NEUROPHYSICS 2020-2021

by Sune Nørhøj Jespersen

Introduction

Progress in the diagnosis and treatment of neurological diseases is severely hampered by the lack of a noninvasive imaging technology with sensitivity and biological specificity on the cellular scale. MRI is currently limited to providing a range of differently "weighted images" with millimeter resolution and contrast reflecting physical properties with no clear biological relevance. Indeed, when brain abnormalities are first noticed with MRI, the biological underpinnings are often obscure, and neurodegenerative diseases have advanced too far to be effectively treated or even managed. But by harnessing the versatility of MRI, combined with validated biophysical modeling of its relation to tissue structure on the micrometer scale (microstructure) both enhanced sensitivity and biological specificity on the cellular scale can be achieved, effectively enabling *in-vivo*, MRI based, super-resolution microscopy. The development and validation of the necessary biophysical models, as well as the translation to clinical application, is the overarching goal of the Neurophysics group.

As a testimony to the excitement about this line of research, microstructure took a central stage at the 2021 annual meeting of the International Society for Magnetic Resonance in Medicine, which typically attracts more than 6000 attendees. In a plenary session entitled "Microstructure: Richness of Scales & Contrasts", the capacity for MRI to quantify tissue microstructure from multiple different types of MRI contrast was explored. The neurophysics group is active in two the areas covered, namely diffusion and susceptibility based contrast and the plenary talk on diffusion, "Probing the Micrometer Scale with Diffusion" was delivered by Sune Jespersen. Briefly, diffusion is sensitive to microstructure because the water molecules giving rise to the signal explore their environment on the scale of ~10 micrometres during the diffusion acquisition, and in this way they can essentially be used as endogenous tracers. Susceptibility based contrast, on the other hand, depends on microstructure because the local perturbation of the magnetic field is sensitive to the organization of e.g. myelin and iron. In turn, the local perturbation of the magnetic field affects both the phase and magnitude of gradient echo MRI signals.

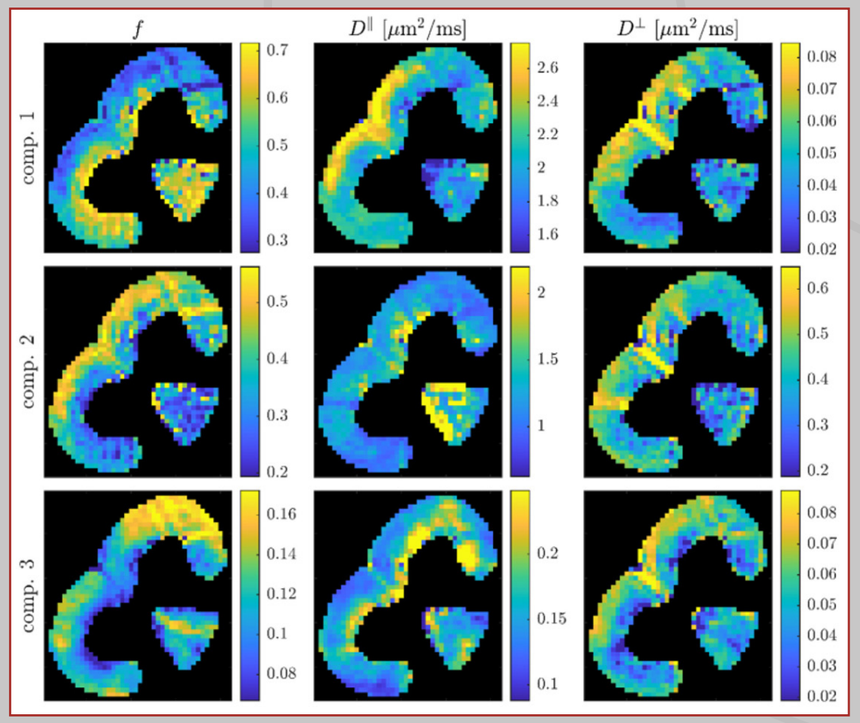

Figure 1
Maps of compartmental volume fractions (f), intracompartmental axial $D^{\parallel}$ and radial diffusivities $D^{\perp}$ in rat spinal cord, from[8]. Compartment 1 (comp. 1) is the intra-axonal compartment, comp. 2 the extra-axonal, and comp. 3 the new slow diffusing compartment, possibly related to other cell types or subcellular compartments. Adapted with permission under the CC BY-NC-ND license.

Research Output

As mentioned above, achieving biological specificity on the micrometer scale with MRI depends on biophysical models. Neurophysics has contributed to a widely used framework for modeling diffusion in the white matter in the regime typically probed by clinical scanners[2-4]. This so-called "Standard Model" (with a tongue-in-cheek reference to high-energy physics) of diffusion in white matter has now reached a stage where it can be applied on clinical scanners with a robustness and precision on par with Diffusion Tensor Imaging (DTI)[5] – i.e., on the level of 10% variability. However, with more sensitive experimental scanners, it is possible to probe deviations from the standard model, or "physics beyond the Standard Model". Such observations drive the development of more advanced models for more accurate and complete microstructural characterization.

One such study was undertaken by PhD student Jonas Olesen, by adopting advanced diffusion pulse sequences to acquire a comprehensive diffusion data set from fixed rat spinal cords at a 16.4T (ultrahigh field) MRI scanner with cryogenic coils. This unique data set combined with sophisticated data analysis allowed Olesen to identify an additional tissue compartment for water molecules with slow and approximately isotropic diffusion, see Figure 1. Further research is necessary to establish the biological identity of the

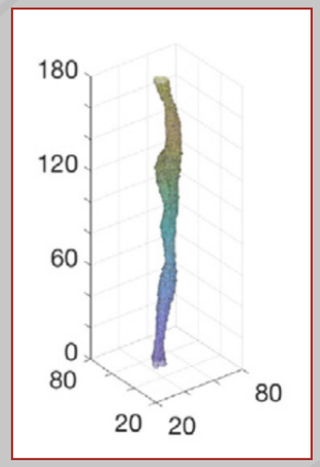

Figure 2
Real axons show both cross-sectional variation and undulations. A digitially reconstructed from 3d electron microscopy. Adapted with permission under the CC BY-NC-ND license from[6].

FACTS

Group members, students and collaborators:

- Sune N. Jespersen (group leader, Professor)
- Jonas Lynge Olesen, (PhD stud. 2019-2022)
- Anders Dyhr Sandgaard, (PhD stud. 2019-2023)
- Nicoline Hummelmose (MSc. 2019-2020)
- Kristian Kortegaard (MSc. 2020-2021)
- Anders Bak-Nyhus (MSc. 2021-2022)

Conferences and meetings:

- ISMRM annual meeting: August 8-14 , 2020, Online. (Presentations by Jonas L. Olesen, Anders Dyhr Sandgaard)
- ISMRM annual meeting: May 15-20, 2021, Online. (Presentations by Jonas L. Olesen, Anders Dyhr Sandgaard and Sune Jespersen)

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- "Helga og Peter Kornings Fond"

Invited talks:

- 2020 "Quantifying brain microstructure with diffusion MRI". Invited Plenary talk for Mexican Neuroscientific meeting "XXII Reunión de Neuroimagen" http://neuroimagen2020.eventos.cimat.mx/ Held online due to Covid-19.
- 2021 "Probing the Micrometer Scale with Diffusion". Invited Plenary talk at the annual meeting of the International Society for Magnetic Resonance in Medicine.

compartment, but in the meantime, his results may explain some inconsistencies in the literature.

In another study led by Hong-Hsi Lee, the limitations of approximating axons as cylinders, as done in the Standard Model, was explored in detail with theory and numerical simulations[6]. Among other things, it was quantified how caliber variations (or cross-sectional variance) and undulations cause axonal diameters to be overestimated by up to a factor of two, even when discarding extra-axonal space which is known to further confound diameter quantification[7]. This clearly calls for caution when attempting to estimate axon diameters based on diffusion MRI.

A more agnostic (but less specific) approach to diffusion MRI is embodied by diffusion kurtosis imaging (DKI). Briefly, DKI is an extension of DTI taking into account deviations from Gaussian diffusion, due to heterogeneous properties of diffusion across the microdomains within the voxel[9, 10]. However, kurtosis parameters are often less robust to estimate in vivo, sometimes resulting in the so-called “black voxels”. In a collaboration led by Rafael Neto-Henriques and Jelle Veraart, we developed a method for more robust estimation combining theory with machine learning[11].

Diffusion kurtosis metrics depend on the pulse sequence used to acquire the images. Often, this is a kind of trivial dependence that is not informative with respect to microstructure, but we realized that using so-called (asymmetric) double diffusion encoded sequences (DDE)[12], novel microstructural contrast could be achieved. While double diffusion encoded sequences were reviewed by us in[13], 2020-2021 saw 2 papers published on the new method dubbed Correlation Tensor Imaging (CTI). In the first paper[1], the method was presented and examined with numerical simulations and experiments in both ex vivo and in vivo rat brains. It was demonstrated how CTI can separate kurtosis sources (sources of diffusion heterogeneity) due to either anisotropic variance, isotropic variance, or microscopic kurtosis. The novel step here was the quantification of microscopic kurtosis, which is due to restricted diffusion in cellular environments or exchange. In the second paper[14], a more systematic investigation of microscopic kurtosis was undertaken in rat brains, highlighting in particular how neglecting (as normally done) it can severely bias other parameters. We are currently working to apply CTI in subacute stroke, where we believe CTI can potentially be used to inform treatment via more accurate characterization of stroke subtypes.

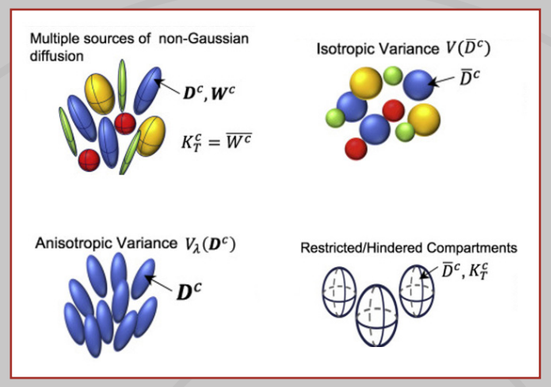

Figure 3
Kurtosis sources arise from heterogeneity of diffusion properties across microenvironments. Net kurtosis (upper left) has contributions from variations in size (mean diffusivity, upper right), anisotropy (lower left), and also microscopkuc kurtosis from restrictions and exchange (lower right). Adapted with permission under the CC BY-NC-ND license from[1].

We have previously developed ultra-fast protocols for imaging kurtosis metrics[15, 16]. In a collaboration with Yury Shtyrov, these methods enabled Nicola Vukovic to detect microstructural changes occurring in the human brain only 40 minutes after language learning[17].
Read more about this study in the NeDComm contribution to the annual report.

Finally, in a collaboration with Trevor Owens group, former PhD student Andrey Chuhutin combined DKI with biophysical modeling in the experimental autoimmune encephalomyelitis mouse model of multiple sclerosis (MS). He demonstrated that the biophysical parameters detected changes in normal appearing white matter that correlated strongly with disability. These findings lend hope of resolving the so-called clinico-radiological paradox that conventional MRI abnormalities do not explain the clinical symptoms of MS patients very well.

Several of the projects mentioned above are outcomes of our very fruitful and long-standing collaboration with Dr. Noam Shemesh, a world-renowned preclinical MRI scientist at the Champalimaud Centre for the Unknown in Lisbon.

References

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17. Vukovic, N., et al., Rapid microstructural plasticity in the cortical semantic network following a short language learning session. PLoS Biol, 2021. 19(6): p. e3001290.

FACTS

Teaching and outreach:

- MR physics, graduate course in spring 2021 Department of Physics, Aarhus University.
- Lectures for high school classes about MRI
- Interdisciplinary Summer School on Neuroimaging Summer 2021
- Introduction MATLAB with examples from Health Science.
- Calculus Beta, Department of Physics, Aarhus University.
- Mechanics and Thermodynamics, Department of Physics, Aarhus University.

Collaborators:

- Noam Shemesh, Rafael Neto-Henriques and Andrada Ianaus, Champalimaud Research, Champalimaud Centre for the Unknown, Lisbon, Portugal
- Dmitry Novikov, Els Fieremans, and Santiago Coelho, Center for Biomedical Imaging, NYU Langone, New York, USA.
- Hong Hsi Lee, Massachusetts General Hospital, Boston, USA
- Mark Does, Biomedical Engineering, Vanderbilt University.
- Valerij Kiselev, Freiburg University Hospital, Freiburg, Germany.
- Brian Hansen, CFIN, Aarhus University.
- Leif Østergaard, CFIN, Aarhus University.
- Simon Eskildsen, CFIN, Aarhus University.
- Sarang Dalal, CFIN, Aarhus University.
- Lau Møller Andersen, CFIN, Aarhus University.
- Tamas Minarik, CFIN, Aarhus University.
- Yury Shtyrov, CFIN, Aarhus University.
- Torben Lund, CFIN, Aarhus University.
- Kristian Sandberg, CFIN, Aarhus University.
- Jens Randel Nyengaard, Section for Stereology and Microscopy, Aarhus University.
- Erhard Trillingsgaard Næss-Schmidt, Hammel Neurorehabilitation Centre and University Research Clinic, Hospital Midt, Denmark.
- Jesper Folsted Kallehauge Danish Centre for Particle Therapy -Department of Clinical Medicine, Aarhus University Hospital.
- Lars Næsby Hvid & Ulrik Dalgas, Department of Public Health - Sport Science, Aarhus University.
- Trevor Owens, Department of Molecular Medicine, University of Southern Denmark.