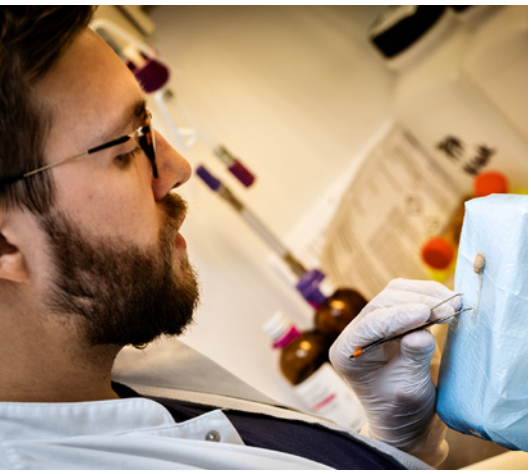
Incorporating the effect of white matter microstructure in the estimation of magnetic susceptibility in ex vivo mouse brain

INTERVIEW BY **CHRISTIAN LANGKAMMER**

EDITOR'S PICK FOR FEBRUARY

This month, we feature an interview with **Anders Dyhr Sandgaard** and **Sune Nørhøj Jespersen** from Aarhus University, Denmark, conducted during the ISMRM Diffusion Workshop in Japan. Their paper was selected for its innovative approach to improving quantitative susceptibility mapping (QSM) by integrating the influence of white matter microstructure. By combining multi-gradient echo and diffusion MRI, they account for orientation-dependent frequency shifts without requiring sample rotations. This advancement enhances the accuracy of susceptibility measurements and paves the way for broader clinical applications.



Anders Dyhr Sandgaard

Sune Nørhøj Jespersen

PHOTOS: TONNY FOGMAR, AUH

MRMH: Could you tell us a bit about your background?

Anders Sandgaard: I studied physics at Aarhus University, initially focusing on accelerator physics with the goal of contributing to particle therapy. My passion has always been applying physics to health sciences. Fortunately, I discovered Sune's neurophysics group, which aligned with my interests by offering a theoretical approach to MRI within health sciences. I completed both my master's and PhD there, and after finishing my PhD, I was able to continue with Sune as a postdoc.

Sune Jespersen: I completed my PhD in theoretical physics and continued with a postdoc in the same field before deciding to return to Denmark. That was quite a few years ago! I remember taking a course in imaging for biological sciences, where MRI was introduced, and it really fascinated me. Then, an opportunity arose, and a mix of luck and interest led me into this field.

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MRMH: Can you tell us about your research group and interests?

Sune: Our group primarily focuses on diffusion MRI and microstructure modeling. We've worked on various projects, including diffusion imaging in the brain, capillary transit time heterogeneity in perfusion, hyperpolarized kinetics, denoising, and more recently, QSM. Our team is based in Aarhus at the Center for Functionally Integrative Neuroscience, a leading brain research center.

MRMH: What motivated you to explore QSM and the microstructural effects in white matter?

Anders: When I joined Sune's group, QSM emerged as an exciting new research direction. The focus was on magnetic susceptibility effects and how microstructure influences white matter MRI signals. Initially, I worked on simulations of microstructure and its effects on the Larmor frequency, extending previous studies to include susceptibility anisotropy. I also had access to 3D microscopy data, which allowed me to examine dispersion effects in more detail. Presenting my first findings at a QSM workshop made me consider the relationship between dispersion and diffusion—and how both modalities might be linked through shared structural information.

Sune: From my perspective, QSM microstructure was a relatively underexplored area in MRI, making it a natural avenue for investigation. I was also familiar with Dmitry Yablonsky and Valerij Kiselev's work, which inspired us to venture into this direction.

MRMH: Can you briefly describe the content of your paper?

Anders: Our ex vivo study builds on a model

we published a year earlier. The aim was to apply this model to ex vivo data, incorporating frequency shifts caused by white matter structural anisotropy. By integrating these shifts into the QSM inversion algorithm—using structural information from diffusion MRI—we were able to estimate only magnetic susceptibility, separating it from microstructural effects.

We analyzed the impact of microstructural frequency shifts on susceptibility values and found that they could alter measurements by up to 25% in the most anisotropic white matter regions. Additionally, we assessed the feasibility of our model by addressing confounding factors such as iron content and validated our approach through simulations. These simulations demonstrated that microstructural frequency shifts could explain susceptibility tensor findings that had previously been attributed to susceptibility anisotropy.

MRMH: Your study used ex vivo mouse MRI data at an extremely high field of 16.4 Tesla. Why did you choose this approach?

Anders: My co-supervisor, Noam Shemesh at Champalimaud Research, had access to these ultra-high-field scanners, primarily used for rodent studies. However, working with such high field scanners allowed us to conduct a highly controlled experiment. Had we started with clinical data, there would have been too many uncontrollable variables. This setup provided a clean, textbook-like acquisition, establishing a solid foundation for future studies.

Sune: Anders was already developing a more comprehensive theory incorporating susceptibility tensors, but it required rotations to be fully explored. Now, we're looking at ways to broaden adoption of this method, as it only requires adding a diffusion MRI scan to standard QSM acquisitions.

MRMH: Is standard DTI sufficient, or do you need higher-order diffusion models?

Anders: Ideally, a high b-value shell with multiple orientations is best. Studies suggest that 15–20 minutes of scanning with b ≈ 5000 and 60 gradient directions provides optimal results. However, to increase accessibility, we are also exploring whether lower b-values—such as those from standard DTI datasets—could approximate the method effectively.

MRMH: Is your model available for download?

Anders: It is currently available upon request, but we are working on making it openly accessible. Our goal is to integrate it into existing toolboxes as an optional module, allowing users to compare results with and without our model. This would help researchers better understand how algorithmic choices influence QSM outcomes.

MRMH: How does your work relate to χ-separation methods?

Anders: The field is moving toward multi-dimensional susceptibility modeling, and our approach could be integrated with χ-separation methods to improve susceptibility estimation by accounting for microstructure-induced frequency shifts. Another exciting direction involves diffusion filtering to extract anisotropic susceptibility information without requiring multiple sample orientations. Inversion problems in QSM are often challenged by division by zero, which can destabilize the process. However, incorporating sub-voxel frequency components introduces non-zero elements along the diagonal of the inversion matrix, which actually helps stabilize the problem.

MRMH: What are the next steps?

Anders: We are conducting validation studies using Monte Carlo simulations on realistic substrates. We recently published the first part, validating our model for the ex vivo study. The next step is to assess how realistic WM microstructure impacts transverse relaxation. We are also performing a validation experiment with pig optic nerve in PBS, similar to Wharton and Bowtell's 2015 MRM study. In our case, we estimate both susceptibility values and measure fiber orientation distribution functions (fODFs). Our model then predicts the unaccounted-for frequency shift from microstructure and we compare it to the residual frequency shift in the tissue, which could not be explained by QSM.

Another promising direction is using diffusion filtering to extract anisotropic susceptibility without acquiring multiple sample orientations, which can be challenging in clinical settings. I am working on integrating my model into the standard model of diffusion in white matter, which describes intra- and extracellular diffusivity at long diffusion times. This framework now accounts for orientation dependent Larmor frequency shifts and transverse relaxation.
Nature has been kind in providing orientation dispersion. When we apply diffusion filtering, we effectively filter axons with different B_0 orientations. By leveraging diffusion gradient filtering, we can selectively target axons based on their orientation relative to B_0, allowing us to modulate anisotropic effects in both Larmor frequency shifts and transverse relaxation.

The key idea is that, even from a single B_0 orientation, we can extract both the anisotropy of the Larmor frequency shifts and transverse relaxation. By combining spin-echo and gradient-echo sequences, we obtain rotation-invariant parameters, meaning the results do not depend on the sample's orientation relative to the scanner.
Sune: Essentially, we are conducting multi-dimensional experiments. We vary both b-value and echo time in gradient or spin-echo sequences. By adding extra dimensions, we can separate effects that would otherwise be indistinguishable. The idea is that a single acquisition could provide complementary information—structural insights from diffusion, magnetic properties from transverse relaxation, and Larmor frequency shifts—all within one protocol.

MRMH: We're conducting this interview while you're attending the Diffusion Workshop in Japan, one of the most successful ISMRM workshops, with almost 400 participants. How has your experience been, and what are your plans afterward?

Sune: The workshop was fantastic! Despite our tight schedule, we managed to explore Kyoto and enjoy some delicious local cuisine. Anders will be staying longer to go hiking in the mountains and visit Osaka and Tokyo before heading back.■