Unraveling intravoxel tissue composition via diffusion MRI

CENIIT – Final report

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Magnetic resonance imaging (MRI) is an indispensable diagnostic tool with proven sensitivity to numerous pathologies as well as to processes such as development and aging. As a powerful characterization tool, magnetic resonance (MR) techniques are also employed for determining the microstructure of porous materials, which is critical for inferring their physical characteristics. For these reasons, MR has been employed by several industries in need of reliable characterization tools. The goal of this project was overcoming the resolution limitation of MRI by exploiting the sensitivity of the MR signal to translational diffusion of spin-bearing particles. The latter provides information on the microstructure of the specimen being examined.

During the course of the project, we made a number of contributions, fundamental [3, 6, 14, 22] as well as application-oriented. We studied the restriction-induced effects which are naturally occurring for multi-compartment environments like tissues and integrated such effects into frameworks developed to characterize tissue heterogeneity [4, 19, 23, 30]. We studied the disentanglement of anisotropy from microstructure information obtained via orientational averaging of the diffusion MR signal [17, 23, 28]. Perhaps most importantly, we incorporated recent developments in applied optimization for strictly enforcing necessary physical and mathematical constraints into our estimation routines in various diffusion MRI methods [21, 26, 32]. Doing so proved particularly beneficial, making the data acquisition feasible within clinically-acceptable times [25]. We disseminated a software package to the research community [29]. Our techniques were also integrated into the Dipy (Diffusion Imaging in Python) software package.

One PhD student (Deneb Boito), one postdoctoral researcher (Cem Yolcu), and two faculty members (Magnus Herberthson and Evren Özarslan) at Linköping University were partially supported by the CENIIT funding. Deneb Boito successfully defended his PhD dissertation in 2024. Evren Özarslan obtained docentship in biomedical engineering sciences in 2018 and was promoted to senior associate professor in 2023.

The project leader served as the examiner for the following three master's thesis projects:

- Shan Cai: Thesis titled "Diffusion-based MR methods for measuring water exchange," completed in Spring 2022.
- Alfredo Miguel Ordinola Santisteban: Thesis titled "MRI based measurement of diffusion and water exchange — Study with a benchtop MR scanner," completed

in Spring 2021.

- Iulian Emil Tampu: Thesis titled "Morphological characterization of neural tissue microstructure using the orientationally-averaged diffusion MRI signal," completed in Spring 2019.

All three students are currently pursuing PhD studies at Linköping University.

Evren Özarslan also co-supervised the following PhD dissertations:

- Xuan Gu: Thesis titled "Advanced analysis of diffusion MRI data," completed in 2019.
- Jens Sjölund: Thesis titled "Algorithms for magnetic resonance imaging in radiotherapy," completed in 2018.

During the CENIIT project, the project team collaborated with other researchers at LiU including Hans Knutsson, Carl-Fredrik Westin, and Anders Eklund who leads the CENIIT project titled "Bayesian methods for fMRI informed brain tumour treatment planning". Anders Eklund is a co-supervisor of Deneb Boito while I have co-supervised David Abramian. Both of these PhD students played crucial roles in the respective CENIIT projects.

The project team was involved in various collaborative projects with the Swedish companies: CR Development, Elekta, Inovia, Synthetic MR, Eigenvision, Raysearch Laboratories, Scaleout Systems and Spectronic. Other projects that made the industrial collaborations possible were funded by ITEA/VINNOVA. These projects are: IMPACT (Intelligence Based Improvement of Personalized Treatment and Clinical Workflow Support) and ASSIST (Automation, Surgery Support and Intuitive 3D visualization to optimize workflow in IGT SysTems, 2021-01954).

The CENIIT project provided a steady support for the research group at the Department of Biomedical Engineering led by Evren Özarslan and was extremely helpful in raising additional funding. The projects IMPACT and ASSIST mentioned above provided 8,1 MSEK to the research group. In addition, a project supported by Analytic Imaging Diagnostics Arena (AIDA) facilitated a collaboration with clinicians at Region Östergötland. Another ongoing project supported by The Swedish Foundation for International Cooperation in Research and Higher Education (STINT) facilitates international exchange and mobility. Evren Özarslan was also granted support by the Swedish Research Council for a four year project. He has been co-applicant on a number of other grants. He leads a well-connected group and is actively collaborating with scientists in USA, China, and UK. He is currently the main supervisor of two PhD students, and co-supervisor of three PhD students. He is the examiner and responsible for the TBMT02 Medical Imaging course and has teaching roles in two other undergraduate courses. Evren Özarslan has also designed two PhD courses.

List of publications

33. A. Ordinola, S. Cai, R. Bai, and E. Özarslan, "Characterizing structure and diffusion exchange: Comparing subsampling strategies," in *Magnetic Resonance in Porous Media Book of Abstracts*, 15, Hangzhou, China, 2022.

32. D. Boito, M. Herberthson, T. C. J. Dela Haije, I. Blystad, and E. Özarslan, "Diffusivity-limited q-space trajectory imaging," *Magnetic Resonance Letters*, *in press*.

    ⋆ This work was also presented at the Annual Meeting of the ISMRM and an abstract was published in *Proc Intl Soc Mag Reson Med*, 30, London, 2022, p. 1866.

31. M. Afzali, T. Pieciak, D. K. Jones, J. E. Schneider, and E. Özarslan, "Cumulant expansion with localization: A new representation of the diffusion MRI signal," *Front Neuroimaging*, vol. 1, 958680, 2022.

    ⋆ This work was also presented at the Annual Meeting of the ISMRM and an abstract was published in *Proc Intl Soc Mag Reson Med*, 30, London, 2022, p. 3294.

30. D. Boito, C. Yolcu, and E. Özarslan, "Multidimensional diffusion MRI methods with confined subdomains," *Front Phys*, vol. 10, 830274, 2022.

29. D. Boito, M. Herberthson, T. C. J. Dela Haije, and E. Özarslan, "Applying positivity constraints to q-space trajectory imaging: The QTI+ implementation," *SoftwareX*, vol. 18, 101030, 2022.

28. M. Afzali, H. Knutsson, E. Özarslan$^{\diamond}$, and D. K. Jones$^{\diamond}$, "Computing the orientational-average of diffusion-weighted MRI signals: A comparison of different techniques," *Sci Rep*, vol. 11, 14345, 2021.

    ◇ These authors share last authorship.

    ⋆ This work was also presented at the Annual Meeting of the ISMRM and an abstract was published in *Proc Intl Soc Mag Reson Med*, 29, Virtual meeting, 2021, p. 3642.

27. A. De Luca, A. Ianus, A. Leemans, M. Palombo, N. Shemesh, H. Zhang, D. C. Alexander, M. Nilsson, M. Froeling, G. J. Biessels, M. Zucchelli, M. Frigo, E. Albay, S. Sedlar, A. Alimi, S. Deslauriers-Gauthier, R. Deriche, R. Fick, M. Afzali, T. Pieciak, F. Bogusz, S. Aja-Fernandez, E. Özarslan, D. K. Jones, H. Chen, M. Jin, Z. Zhang, F. Wang, V. Nath, P. Parvathaneni, J. Morez, J. Sijbers, B. Jeurissen, S. Fadnavis, S. Endres, A. Rokem, E. Garyfallidis, I. Sanchez, V. Prchkovska, P. Rodrigues, B. A. Landman, and K. G. Schilling, "On the generalizability of diffusion MRI signal representations across acquisition parameters, sequences and tissue types: Chronicles of the MEMENTO challenge," *NeuroImage*, vol. 240, 118367, 2021.

    ⋆ This work was also presented at the Annual Meeting of the ISMRM and an abstract was published in *Proc Intl Soc Mag Reson Med*, 29, Virtual meeting, 2021, p. 1728.

26. M. Herberthson, D. Boito, T. C. J. Dela Haije, A. Feragen, C. F. Westin, and E. Özarslan, "Q-space trajectory imaging with positivity constraints (QTI+)," *NeuroImage*, vol. 238, 118198, 2021.

    ⋆ This work was also presented at the Annual Meeting of the ISMRM and an abstract was published in *Proc Intl Soc Mag Reson Med*, 29, Virtual meeting, 2021, p. 2610.

25. D. Boito, M. Herberthson, T. Dela Haije, and E. Özarslan, "Enforcing positivity constrains in Q-space Trajectory Imaging (QTI) allows for reduced scan time," in *Proc Intl Soc Mag Reson Med*, 29, Virtual meeting, 2021, p. 0404.

    ⋆ Accepted ***magna cum laude*** for an oral presentation.

24. M. Afzali, T. Pieçiak, S. Newman, E. Garifallidis, E. Özarslan, H. Cheng, and D. K. Jones, "The sensitivity of diffusion MRI to microstructural properties and experimental factors," *J Neurosci Meth*, vol. 347, 108951, 2021.

23. C. Yolcu, M. Herberthson, C. F. Westin, and E. Özarslan, "Magnetic resonance assessment of effective confinement anisotropy with orientationally-averaged single and double diffusion encoding," in *Anisotropy across fields and scales*, ed. E. Özarslan, T. Schultz, E. Zhang, and A. Fuster, Cham: Springer Nature, p. 203–223, 2021.

22. M. Herberthson, E. Özarslan, and C. F. Westin, "Variance measures for symmetric positive (semi) definite tensors in two dimensions," in *Anisotropy across fields and scales*, ed. E. Özarslan, T. Schultz, E. Zhang, and A. Fuster, Cham: Springer Nature, p. 3–22, 2021.

21. T. C. J. Dela Haije, E. Özarslan, and A. Feragen, "Enforcing necessary non-negativity constraints for common diffusion MRI models using sum of squares programming," *NeuroImage*, vol. 209, 116405, 2020.

20. M. Afzali, T. Pieciak, F. Bogusz, S. Aja-Fernandez, E. Özarslan, D. K. Jones, MRI White Matter Reconstruction Challenge, in *Proc. of IEEE International Symposium on Biomedical Imaging: Nano to Macro*, 17, 2020.

⋆ Winner in "Subchallenge 1: The signal forecast" of the MRI White Matter Reconstruction Challenge.

19. D. Boito, C. Yolcu, and E. Özarslan, "Compartment-specific diffusivity: A new dimension in multidimensional diffusion MRI?" in *Proc Intl Soc Mag Reson Med*, 28, Virtual meeting, 2020, p. 4442.

⋆ Selected for the "ISMRM Highlights Session on Diffusion MRI" of the annual meeting of the ISMRM.

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17. M. Herberthson, C. Yolcu, H. Knutsson, C. F. Westin, and E. Özarslan, "Orientationally-averaged diffusion-attenuated magnetic resonance signal for locally-anisotropic diffusion," *Sci Rep*, vol. 9, 4899, 2019.

16. X. Gu, A. Eklund, E. Özarslan, and H. Knutsson, "Using the wild bootstrap to quantify uncertainty in mean apparent propagator MRI," *Front Neuroinform*, vol. 13, 43, 2019.

15. C. Liu and E. Özarslan, "Multimodal integration of diffusion MRI for better characterization of tissue biology," *NMR Biomed*, vol. 32, e3939, 2019.

14. C. Yolcu, M. Herberthson, C. F. Westin, and E. Özarslan, "Dynamics of the phase-position ensemble in magnetic resonance," ISMAR EUROMAR Joint Conference, Berlin, Germany, 2019.

13. M. Herberthson, C. Yolcu, H. Knutsson, C. F. Westin, and E. Özarslan, "MR signal for powdered specimens," 15$^{\text{th}}$ International Conference on Magnetic Resonance Microscopy, Paris, France, 2019.

12. E. Özarslan, "Influence of structural heterogeneity and curvilinear diffusion on MR diffusion measurements," Workshop on Diffusion MRI and Stochastic Geometry, Sønderborg, Denmark, 2019.

11. E. Özarslan, "Neurite morphology and the orientationally-averaged diffusion MR signal," Dagstuhl Seminar No. 18442: Visualization and Processing of Anisotropy in Imaging, Geometry, and Astronomy, Schloss Dagstuhl, Wadern, Germany, 2018.

10. T. D. Haije, E. Özarslan, and A. Feragen, "Non-negative mean apparent propagators using sum-of-squares optimization: MAP+," in *Proc Intl Soc Mag Reson Med*, 27, Montreal, Canada, 2019, p. 557.

9. H. Knutsson, E. Özarslan, F. Szczepankiewicz, and C. F. Westin, "Restoring rotation invariance of diffusion MRI estimators in the presence of missing or corrupted measurements," in *Proc Intl Soc Mag Reson Med*, 27, Montreal, Canada, 2019, p. 4521.

8. C. Yolcu, M. Herberthson, H. Knutsson, C. F. Westin, and E. Özarslan, "Insights into the diffusion MR signal via an extended Bloch-Torrey equation," Machine and Other Intelligence in Applied Mathematics and Information Technology Conference, Norrköping, Sweden, 2018.

7. J. Sjölund, A. Eklund, E. Özarslan, M. Herberthson, M. Bånkestad, and H. Knutsson, "Bayesian uncertainty quantification in linear models for diffusion MRI," *NeuroImage*, vol. 175, p. 272–285, 2018.

6. E. Özarslan, C. Yolcu, M. Herberthson, H. Knutsson, and C. F. Westin, "Influence of the size and curvedness of neural projections on the orientationally averaged diffusion MR signal," *Front Phys*, vol. 6, 17, 2018.

5. H. Knutsson, F. Szczepankiewicz, E. Özarslan, C. Yolcu, M. Herberthson, M. Nilsson, and C. F. Westin, "Planar quadrature waveforms and b-value independent pore size estimation," Diffusion Workshop 2018: Free gradient waveforms, q-trajectories, and fat b-tensors, Mölle, Sweden, 2018.

4. E. Özarslan, C. Yolcu, M. Herberthson, C. F. Westin, and H. Knutsson, "Effective potential for magnetic resonance measurements of restricted diffusion," *Front Phys*, vol. 5, 68, 2017.

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2. S. Shakya, N. Batool, E. Özarslan, and H. Knutsson, "Multi-fiber reconstruction using probabilistic mixture models for diffusion MRI examinations of the brain," in *Modeling, Analysis, and Visualization of Anisotropy*, ed. I. Hotz, E. Özarslan, and T. Schultz, Berlin: Springer-Verlag, Cham: Springer International Publishing, p. 283–308, 2017.

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