Scan-rescan reproducibility of neurite microstructure estimates using NODDI

Maira Tariq[1]
maira.tariq.11@ucl.ac.uk
Torben Schneider[2]
t.schneider@ucl.ac.uk
Daniel C. Alexander[1]
d.alexander@cs.ucl.ac.uk
Claudia A.M. Wheeler-Kingshott[2]
c.wheeler-kingshott@ucl.ac.uk
Hui Zhang[1]
g.zhang@cs.ucl.ac.uk

[1] Department of Computer Science & Centre for Medical Image Computing
University College London
London, United Kingdom

[2] NMR Research Unit, Department of Neuro-inflammation
UCL Institute of Neurology
University College London
London, United Kingdom

Abstract

In this work we provide a preliminary assessment of the reproducibility of the Neurite Orientation Dispersion and Density Imaging (NODDI), a recent diffusion MRI technique for directly quantifying microstructural indices of neurites *in vivo*, in the human brain. It is important to assess the reproducibility of such a technique to verify the precision of the method, which has implications for translation to clinical studies. NODDI outputs indices which reflect the functional and computational complexity of various regions of the brain and thus can provide useful information, non-invasively, for understanding pathology of the brain. We compare the parameter maps derived from diffusion MRI data acquired using the NODDI protocol from a normal subject, at two separate imaging sessions. We show that the NODDI indices have reproducibility comparable to that of the DTI indices. We additionally show that the clinically feasible NODDI protocol maintains good reproducibility of parameter estimates, comparable to that of a more comprehensive protocol.

1 Introduction

NODDI is a practical diffusion MRI technique, introduced in [15], for estimating the integrity of the axons and dendrites, collectively known as neurites, in the human brain. Dendrites and axons are the extensions from the neural cell bodies, which have a vital role in the communication network of the brain. The morphology and complexity of these structures have been shown to indicate the function as well as pathology of the brain[8, 9, 10]. For example dispersion of dendrites is linked with brain development [6], and their density with ageing [9]. Thus by quantifying the physical characteristics of neurites, promising markers of progression of brain diseases can be obtained and used in the diagnosis, prognosis and treatment of brain disorders.

Neurite density and their *orientation dispersion* are the two microstructural parameters estimated by NODDI. This is in contrast to Diffusion Tensor Imaging (DTI) [4], the standard clinical diffusion MRI technique, which outputs Fractional Anisotropy (FA) and Mean Diffusivity (MD). Although both NODDI and DTI probe microstructure from the diffusion of the water molecules within the brain, DTI is limited in its ability to provide information about the specific changes in microstructure [12]; the indices obtained are affected simultaneously by a number of microstructural changes (e.g. demyelination, inflammation, axonal loss, gliosis), which give rise to the same alterations of their values. NODDI on the other hand estimates the microstructure directly, using an analytical model relating these parameters to the diffusion MRI signal. The NODDI parameters have been shown in [15] to disentangle the microstructural indices which contribute to the changes in FA and thus can provide information about specific changes in microstructure for particular pathologies.

NODDI is underpinned by a multi-compartment signal model of tissue diffusion, which describes analytically how presence of certain structures within the brain affects the diffusion MR signal. Numerous similar techniques exist to infer microstructural features directly (See [3] for a review), but differ from NODDI in the features they model (mostly model only white matter), as well as how they are modelled. But the main limitation of the other models is that they are not clinically feasible. The original work [15] shows results which validate and evaluate the accuracy as well as clinical viability of NODDI, but the precision of the parameters estimated, over multiple imaging sessions, is not explored.

In this work we evaluate the precision of the NODDI by assessing its reproducibility for estimating the microstructural parameters. Such an assessment is important for justifying the use of this technique in clinical and research studies. This is especially true for longitudinal studies since the variability in the parameters needs to be purely due to the changes in brain microstructure.

The paper is organised as follows: Section 2 details the tissue model adapted by NODDI, the data acquisition and the fitting procedure; Section 3 contains the results; Section 4 evaluates and summarises the key findings and discusses future work.

2 Materials and Methods

NODDI combines a three-compartment tissue model with a two-shell high-angular-resolution diffusion imaging (HARDI) protocol, optimised for clinical feasibility. The following sections summarise the NODDI model used to infer the microstructure indices, as well as the protocols used to acquire the images.

2.1 NODDI tissue Model

NODDI is an analytical tissue model, which enables differentiation of three microstructural environments: Intracellular (IC), Extracellular (EC) and CerebroSpinal Fluid (CSF). Each environment affects the diffusion of water molecules within and around them in a characteristic manner and thus contributes distinguishingly to the normalised MR signal, obtained from diffusion imaging. The full normalised signal in a NODDI model is formed from contributions from all of these environments, as shown in the following equation:

$$A = (1 - \nu_{iso})[\nu_{ic}A_{ic} + (1 - \nu_{ic})A_{ec}] + \nu_{iso}A_{iso} \quad (1)$$

The *intracellular* compartment, representing the neurites, has a neurite density given by the volume fraction v_{ic}, and contributing diffusion signal A_{ic}. Axons and dendrites are structurally similar to cylinders, and are modelled for simplicity as sticks, i.e. zero radius cylinders. This reflects the highly restricted diffusion perpendicular to and unhindered diffusion along the length of the structures. The IC diffusion signal also incorporates the orientation dispersion of the neurites, utilising a *Watson Distribution* [11]. Watson distribution is described by κ, which measures the extent of orientation dispersion about μ, the dominant orientation. The *orientation dispersion index* (ODI), output by NODDI, is defined as in equation (2) and ranges from 0, for coherently oriented structures, to 1 for isotropic structures.

$$OD = (2/\pi)\arctan(1/\kappa) \tag{2}$$

The glial cells and, in grey matter, the cell bodies make up the *extracellular* compartment of NODDI. Diffusion of molecules in this compartment is hindered by the presence of neurites, and is thus modelled by Gaussian anisotropic diffusion, i.e. a cylindrically symmetric tensor.

The final compartment models the CSF as isotropic Gaussian diffusion.

2.2 Data Acquisition

Diffusion MR data was acquired on a Philips 3T system with maximum gradient strength of 60mT/m. One healthy volunteer was scanned twice over two sessions separated by 4 weeks. Same imaging protocol was used as the original study [15], which was optimised using the technique described in [1], with a constraint of 30 mins on acquisition time and maximum gradient strength of 60 mT/m. This optimised NODDI protocol consists of a $711 s/mm^2$ shell with 30 gradient directions and a $2855 s/mm^2$ shell with 60 directions, and 9 b=0 measurements. The NODDI protocol is clinically feasible as it takes less than 30 mins to acquire. A more comprehensive 4-shell protocol was utilised to provide a *pseudo-gold-standard* to assess the reproducibility of the NODDI protocol against and determine the effect of acquiring fewer shells on the reproducibility of the parameters estimated. An additional $1000 s/mm^2$ shell of 30 directions and a $2000 s/mm^2$ shell of 60 directions were thus acquired and combined with the NODDI protocol to form this comprehensive protocol. The results from the two protocols were compared to assess the precision in estimation of the indices, when utilising more clinically feasible protocol.

2.3 Processing

The model was fitted to the acquired data using the procedure described in [2], without the MCMC procedure, for computational efficiency [15]. The parameter maps obtained were subsequently aligned using DTI-TK [13] to enable voxel-wise assessment of parameter reproducibility. To assess the parameters' reliably, the maps were segmented into White Matter (WM), Grey Matter (GM) and CSF regions, using MD and *linearity measure* [14] of the diffusion tensor. CSF was segmented as areas where MD was higher than 80%, WM as linearity higher than 0.2 and GM as rest of the brain regions.

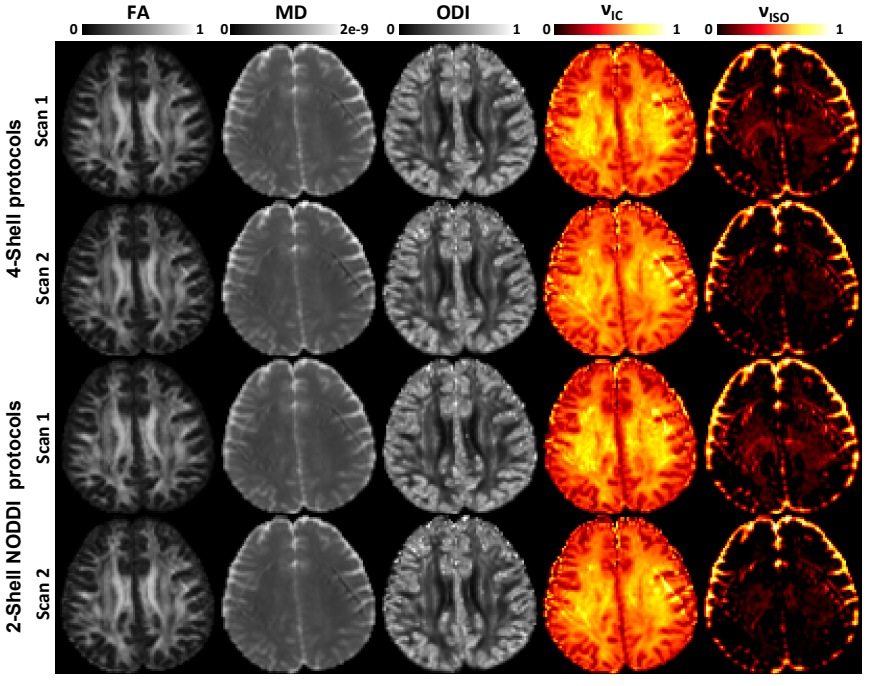

Figure 1: Scan-rescan parameter maps obtained for mid-axial slice, for DTI (first two columns) and NODDI (last three columns), using 4-Shell (first two rows) and NODDI (last two rows) protocols

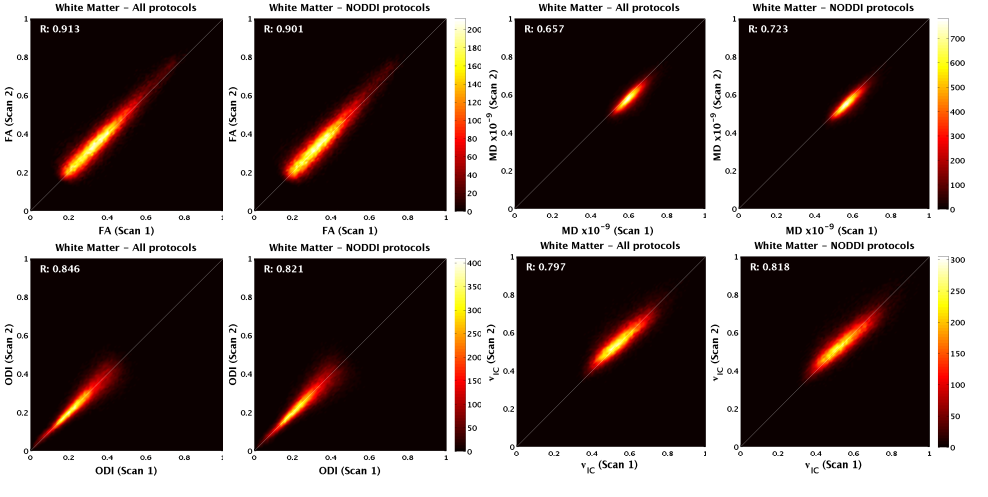

Figure 2: Scatter plots of scan-rescan for WM voxels, for DTI indices (top row) and NODDI parameters (bottom row). R values shown in plots represent the correlation coefficient for the two scans, for each parameter

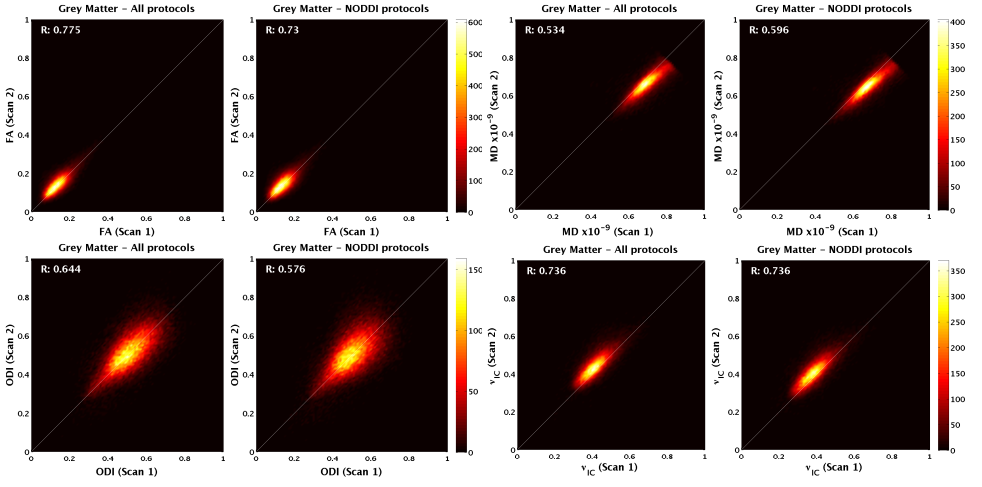

Figure 3: Scatter plots of scan-rescan for GM voxels, for DTI indices (top row) and NODDI parameters (bottom row). R values shown in plots represent the correlation coefficient for the two scans, for each parameter

3 Results

Figure 1, using an exemplar slice, illustrates qualitatively the scan-rescan reproducibility of the NODDI parameters in comparison to the standard DTI indices. The scatter plots in Figures 2 and 3 demonstrate this over the whole brain and separately for WM and GM regions. The quantitative assessment of the reproducibility using the correlation coefficients between the scan-rescan parameters are overlaid on the scatter plots.

These results show that NODDI is able to estimate the microstructure indices of neurites with a high reproducibility, comparable to DTI's ability to reproduce its less specific indices. The comparison with the results from the 4-shell protocol demonstrates additionally that the much more economical NODDI protocol does not result in a loss of the scan-rescan reproducibility, while allowing the acquisition time to be reduced to less than 30 mins.

4 Discussion

We set out to evaluate the reproducibility of NODDI, which is evident from the results presented in this work. We demonstrate that NODDI outputs precise estimates of brain microstructure, utilising the optimised protocol. The accuracy of NODDI parameters, using these protocols, has been established in [15]. Thus NODDI has the potential to help advance the research for understanding brain microstructure and developing normal brain atlases, as well as ones for specific pathologies.

However, just like DTI, NODDI parameters are also affected by drift in the scanner. A slight upward bias in the estimation of v_{ic} can be seen in the scatter plots, by the shift of the data points above the line of equality. This can be attributed to the drift in intensities between the two scans and corresponds to the visible downward bias in the MD scatter plots (lower MD values are associated with IC regions, resulting in a higher v_{ic} in those regions).

The correlation between the two estimates of ODI in GM is particularly low, especially compared to that in WM. This is because the dendrites have a high orientation dispersion, which leads to high ODI values that are more difficult to estimate precisely, as noted in the original work [15].

The acquisition time for NODDI protocol can potentially be reduced to as little as 10 mins by utilising fewer gradient directions in the shells, with no significant loss in accuracy of the estimates (see [15]). The reproducibility of parameters estimates using these NODDI *sub-shells* will be part of a more comprehensive reproducibility study, in future.

The results obtained show tremendous promise for utilisation of NODDI as a technique to accurately and precisely estimate microstructure. However further work is required to establish it as a clinical diagnostic tool. This would include a region based quantification of the error associated with the estimated parameters (similar to [6, 7]), which will determine the ability of the method to distinguish a patient image from that of a normal subject.

4.1 Future work

Future extensions to the work will include a more comprehensive evaluation of reproducibility of the NODDI technique and the optimised protocol, using more subjects. To evaluate the model's use as diagnostic tool for certain brain disorders, it will be important to compare the precision of NODDI parameters, with the expected differences between normal and patient brain.

The NODDI model currently captures the neurite density by a symmetric Watson model. A more comprehensive Bingham model will be incorporated in NODDI which accounts for more realistic dispersion in orientation of neurites. The NODDI model will also be implemented and available for open access within the Camino framework.

4.2 Acknowledgements

This work is supported by the future and emerging technologies (FET) program of the EU FP7 framework through the CONNECT consortium, and the MS society of Great Britain and Northern Ireland, the ISRT and the CBRC. DCA is additionally funded by ESPRC under grant EP/E007748.

References

[1] D. C. Alexander. A general framework for experiment design in diffusion MRI and its application in measuring direct tissue-microstructure features. *Magnetic Resonance in Medicine*, 60:439–448, 2008.

[2] D. C. Alexander, P. L. Hubbard, M. G. Hall, E. A. Moore, M. Ptito, G. J. M. Parker, and T. B. Dyrby. Orientationally invariant indices of axon diameter and density from diffusion MRI. *NeuroImage*, 52:1374–1389, 2010.

[3] Y. Assaf and Y Cohen. Inferring microstructural information of white matter form diffuion MRI. In H. Johansen-Berg and T. E. J. Behrens, editors, *Diffusion MRI: from quantitative measurement to in vivo neuroanatomy*, pages 127–146. Academic Press, 2009.

[4] P. J. Basser, J. Matiello, and D. Le Bihan. MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, 66:259–267, 1994.

[5] D. Bonekamp, L. M. Nagae, M. Degaonkar, M. Matson, W. M. A. Abdalla, P. B. Barker, S. Mori, and A. HorskĞ. Diffusion tensor imaging in children and adolescents: Reproducibility, hemispheric, and age-related differences. *NeuroImage*, 34(2):733–742, 2007.

[6] J. L. Conel. *The postnatal development of the human cerebral cortex*. Harvard University Press, Cambridge, USA, 1939.

[7] L. E. Danielian, N. K. Iwata, D. M. Thomasson, and M. K. Floeter. Reliability of fiber tracking measurements in diffusion tensor imaging for longitudinal study. *NeuroImage*, 49(2):1572–80, 2010.

[8] J.C. Fiala, J. Spacek, and K.M. Harris. Review: Dendritic spine pathology: Cause or consequence of neurological disorders. *Brain Research Reviews*, 39:29–54, 2002.

[9] B. Jacobs, L. Driscoll, and M. Schall. Life-span dendritic and spine changes in areas 10 and 18 of human cortex: A quantitative golgi study. *Journal of comparative neurology*, 386:661–680, 1997.

[10] B. Jacobs, M. Schall, M. Prather, E. Kapler, L. Driscoll, S. Baca, J. Jacobs, K. Ford, M. Wainwright, and M. Treml. Regional dendritic and spine variation in human cerebral cortex: a quantitative golgi study. *Cerebral Cortex*, 11:558–571, 2001.

[11] K.V Mardia and P.E Jupp. Directional statistics. *Wiley series in probability and statistics*, 1990.

[12] C. Pierpaoli, P. Jezzard, P. J. Basser, A. Barnett, and G. Di Chiro. Diffusion tensor MR imaging of the human brain. *Radiology*, 201:637–648, 1996.

[13] Diffusion Tensor Imaging ToolKit. January 2012. URL http://dti-tk.sourceforge.net.

[14] C. F Westin, S. E. Maier, H. Mamata, A. Nabavi, F. A. Jolesz, and R Kikinis. Processing and visualization for diffusion tensor MRI. *Medical Image Analysis*, 6(2):93–108, 2002.

[15] H. Zhang, T. Schneider, C.A. Wheeler-Kingshott, and D.C. Alexander. NODDI: Practical *in vivo* neurite orientation dispersion and density imaging of the human brain. *NeuroImage*, 61:1000–1016, 2012.