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# Neurite density imaging versus imaging of microscopic anisotropy in diffusion MRI: A model comparison using spherical tensor encoding

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ABSTRACT

In diffusion MRI (dMRI), microscopic diffusion anisotropy can be obscured by orientation dispersion. Separation of these properties is of high importance, since it could allow dMRI to non-invasively probe elongated structures such as neurites (axons and dendrites). However, conventional dMRI, based on single diffusion encoding (SDE), entangles microscopic anisotropy and orientation dispersion with intra-voxel variance in isotropic diffusivity. SDE-based methods for estimating microscopic anisotropy, such as the neurite orientation dispersion and density imaging (NODDI) method, must thus rely on model assumptions to disentangle these features. An alternative approach is to directly quantify microscopic anisotropy by the use of variable shape of the *b*-tensor. Along those lines, we here present the 'constrained diffusional variance decomposition' (CODIVIDE) method, which jointly analyzes data acquired with diffusion encoding applied in a single direction at a time (linear tensor encoding, LTE) and in all directions (spherical tensor encoding, STE). We then contrast the two approaches by comparing neurite density estimated using NODDI with microscopic anisotropy estimated using CODIVIDE. Data were acquired in healthy volunteers and in glioma patients. NODDI and CODIVIDE differed the most in gray matter and in gliomas, where NODDI detected a neurite fraction higher than expected from the level of microscopic diffusion anisotropy found with CODIVIDE. The discrepancies could be explained by the NODDI tortuosity assumption, which enforces a connection between the neurite density and the mean diffusivity of tissue. Our results suggest that this assumption is invalid, which leads to a NODDI neurite density that is inconsistent between LTE and STE data. Using simulations, we demonstrate that the NODDI assumptions result in parameter bias that precludes the use of NODDI to map neurite density. With CODIVIDE, we found high levels of microscopic anisotropy in white matter, intermediate levels in structures such as the thalamus and the putamen, and low levels in the cortex and in gliomas. We conclude that accurate mapping of microscopic anisotropy requires data acquired with variable shape of the *b*-tensor.

## 1. Introduction

Axons and dendrites, collectively referred to as neurites, are thought to exhibit anisotropic water diffusion (Beaulieu, 2002; Jespersen et al., 2007; Tournier et al., 2011). Diffusion magnetic resonance imaging (dMRI) thus holds promise to non-invasively infer information on these structures. Diffusion tensor imaging (DTI) can be used to quantify diffusion anisotropy on the voxel level (Basser et al., 1994). However, voxel-level anisotropy is determined not only by the microscopic anisotropy in neurites, but also by the level of orientation dispersion that they exhibit (Kroenke et al., 2004; Oouchi et al., 2007; Vos et al., 2011; Szczepankiewicz et al., 2015). Quantification of neurite properties from dMRI must thus separate effects of microscopic anisotropy from orientation dispersion (Kroenke et al., 2004).

Conventional dMRI, based on single diffusion encoding (SDE), inherently entangles microscopic anisotropy and orientation dispersion with intra-voxel variance in isotropic diffusivity (Mitra, 1995; Westin et al., 2016). Microscopic anisotropy was nevertheless estimated with

*Non-standard abbreviations:* DTD, diffusion tensor distribution; LTE, linear tensor encoding; PTE, planar tensor encoding; STE, spherical tensor encoding; DIVIDE, diffusional variance decomposition; CODIVIDE, constrained diffusional variance decomposition

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good accuracy from SDE data by Jespersen et al. (2010), who also demonstrated dMRI-based neurite density maps in good agreement with myelin-stained histology slides. However, the acquisition was performed on fixed tissue, took 15 h and featured $b$-values markedly higher than what is clinically feasible (up to 15 ms/μm$^2$). The analysis also used an extensive model with up to 23 free parameters to capture both microstructure and orientation information. Even so, the neurite orientation dispersion and density imaging (NODDI) method was suggested to enable quantification of neurite density from a 10-minute only acquisition (Zhang et al., 2012). To achieve this acceleration, NODDI relies on a much smaller dataset together with model constraints that connect microscopic anisotropy to diffusional properties of different water components.

A different approach to imaging microscopic diffusion anisotropy is to go beyond SDE and use diffusion encoding with variable shape of the $b$-tensor (Westin et al., 2016). While conventional SDE yields linear tensor encoding (LTE), other shapes can be obtained using non-conventional gradient waveforms. For example, the double diffusion encoding (DDE) sequence (Cory et al., 1990) yields planar tensor encoding (PTE), and a number of approaches exist for spherical tensor encoding (STE) (Wong et al., 1995; Eriksson et al., 2013; Sjölund et al., 2015). Importantly, STE is sensitive only to the intra-voxel variation in isotropic diffusivity, and insensitive to anisotropy and orientation dispersion (Eriksson et al., 2013; Lasič et al., 2014).

Estimation of microscopic anisotropy through this approach has been performed previously by combining LTE and PTE from DDE (Özarslan and Basser, 2008; Jespersen et al., 2013; Lawrenz and Finsterbusch, 2013). More recent work has shown that data acquired with variable shape of the $b$-tensor can be used to estimate the full diffusion tensor distribution (DTD) (de Almeida Martins and Topgaard 2016), or as in another approach, just the mean diffusion tensor and the tensor covariance of this DTD (Westin et al., 2016). The tensor covariance naturally separates variance due to microscopic anisotropy and intra-voxel variance in isotropic diffusivity (Westin et al., 2016). These variance components can also be estimated directly by joint analysis of LTE and STE data (Lasič et al., 2014), using an approach we now refer to as 'diffusional variance decomposition' (DIVIDE) (Szczepankiewicz et al., 2016a). Here, we introduce a novel method that we refer to as 'constrained diffusional variance decomposition' (CODIVIDE). CODIVIDE is based on the DIVIDE approach (Lasič et al., 2014), but is more similar to NODDI since it employs a model that features three distinct components. However, the joint analysis of LTE and STE data allows CODIVIDE to rely on fewer assumptions and estimate additional parameters compared to NODDI.

NODDI arguably offers a simple method to quantify the neurite density, and thus the level of microscopic anisotropy, already from conventional LTE data. However, the model constraints that make this possible have not been validated experimentally, and the interpretation of the NODDI parameters has been called into question (Jelescu et al., 2016). Yet, NODDI has been applied in clinical studies (Kamagata et al., 2015; Wen et al., 2015; Surova et al., 2016), which have sometimes rendered unintuitive results. For example, Wen et al. (2015) cautioned against interpreting their finding of a neurite density contrast within gliomas as actually due to neurites. Since the interpretation of NODDI-based studies rests on the validity of the model constraints, it is of utmost importance to investigate them in detail. One way of doing so is to use data obtained with variable shape of the $b$-tensor. Since a correct model should be fairly invariant to acquisition parameters, the NODDI constraints may be validated by testing whether NODDI results are consistent between e.g. LTE and STE data.

In this work, we compared imaging of neurite density via NODDI with imaging of microscopic anisotropy via joint analysis of LTE and STE data using CODIVIDE. Both NODDI and CODIVIDE were applied to data acquired in the healthy brain and in glioma brain tumors, and the resulting parameter maps were compared. Furthermore, we investigated the NODDI model constraints by testing whether the NODDI analysis can be extended to and predict STE data. Finally, we simulated the response in the NODDI and CODIVIDE parameters to variations in the underlying DTD that may not conform to the model constraints.

## 2. Theory

### 2.1. Multi-component modeling of diffusion

Quantitative dMRI uses models that parameterize the diffusion-weighted MR signal in terms of biophysically relevant features, which are then estimated as the solution to an inverse problem (Nilsson et al., 2013a). NODDI and CODIVIDE belong to a class of methods that model the dMRI signal by separate components with Gaussian diffusion. The diffusion in the components are described by axially symmetric diffusion tensors with axial and radial diffusivities $d_{||}$ and $d_{\perp}$, respectively. Here, we characterize these tensors by their isotropic diffusivity, $d_{\mathrm{I}}=1/3d_{||}+2/3d_{\perp}$, and their anisotropy, $d_{\Delta}=(d_{||}-d_{\perp})/(d_{||}+2d_{\perp})$, according to the formalism of Eriksson et al. (2015).

We define a multi-component signal model common to both NODDI and CODIVIDE as

$$S = \sum S_k A_k(b, b_{\Delta}, d_{\mathrm{I};k}, d_{\Delta;k}), \tag{1}$$

where, for component $k$, $S_k$ is the non-diffusion attenuated signal intensity and $A_k$ is the diffusion attenuation given by the properties of the encoding tensor ($b$, $b_{\Delta}$) and the diffusion tensor ($d_{\mathrm{I};k}$, $d_{\Delta;k}$). The concept of describing the diffusion encoding by a tensor with a user-defined size ($b$) and anisotropy ($b_{\Delta}$) is relatively recent (Eriksson et al., 2015; Westin et al., 2016), and arose due to the use of novel diffusion sequences that vary the gradient direction between excitation and image readout (Eriksson et al., 2013; Sjölund et al., 2015; Westin et al., 2016). For clarity, we note that the conventional $b$-factor ($b$) is given by the trace of the $b$-tensor, while the anisotropy $b_{\Delta}$ takes values between −0.5 for a planar tensor and 1 for a stick (or linear) tensor (Eriksson et al., 2015). We assume axially symmetric $b$-tensors, whose shapes are fully described by $b$ and $b_{\Delta}$.

In our model, we neglect the orientation distributions of anisotropic components. Rather than to model and estimate these, we employ the concept of 'powder averaging', in which the data is arithmetically averaged across all encoding directions. This procedure has been applied frequently in the context of estimating microscopic anisotropy (Jespersen et al., 2013; Lawrenz and Finsterbusch 2013; Lasič et al., 2014). It induces complete orientation dispersion, and thus an orientation invariant signal, provided that a sufficient number of directions are employed (Szczepankiewicz et al., 2016b). After powder averaging, the signal attenuation in Eq. 1 is given by

$$A_k(b, b_{\Delta}, d_{\mathrm{I}}, d_{\Delta}) = \exp(-bd_{\mathrm{I};k}[1-b_{\Delta}d_{\Delta;k}])g(3bd_{\mathrm{I};k}b_{\Delta}d_{\Delta;k}), \tag{2}$$

where

$$g(\alpha) = \int_0^1 \exp(-\alpha x^2)\mathrm{d}x = \sqrt{\frac{\pi}{4\alpha}}\,\mathrm{erf}\,(\sqrt{\alpha}), \tag{3}$$

and erf($x$) is the error function (Lindblom et al., 1977; Callaghan et al., 1979; Kroenke et al., 2004; Eriksson et al., 2015).

### 2.2. Overlapping constraints

Several models for diffusion in brain tissue include separate components for water with microscopically anisotropic diffusion (e.g. neurites) and water with more isotropic diffusion (e.g. the extracellular space) (Assaf et al., 2004; Jespersen et al., 2007; Fieremans et al., 2011). NODDI and CODIVIDE additionally include an isotropic component (a 'ball') with fixed diffusivity to separate cerebrospinal fluid (CSF) from tissue. Furthermore, NODDI and CODIVIDE assume that the anisotropic component is described by a linear diffusion tensor (a 'stick'), since the small diameters of compartments with anisotropic