Estimation of neurite density from an isotropic diffusion model

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Target audience: Researchers with an interest in diffusion imaging, diffusion-MR method development, and mapping of brain cytoarchitecture.
Purpose: It is well appreciated that the brain shows a remarkable degree of plasticity in both health and disease. This remodeling is continuously active and works at many different levels. At the structural level, pruning and outgrowth of neurite branches are central mechanisms underlying the adaptation of brain function. However, such processes do not readily lend themselves to scrutiny. One possible probe of neuritic reorganization may come from diffusion weighted MRI combined with biophysical modeling. An example of such a method is the neurite model presented in [1] and validated against histology and stereology in [2]. However, before this model can be used in the living humans, it is necessary to drastically reduce the scan time. One such approach is the NODDI framework [3], which alleviates the massive data requirements of the neurite model by introducing additional assumptions, specifically assuming constant values for all diffusivities and a Watson/Bingham distribution for the fiber orientation distribution function (fODF). Here we present and evaluate an alternative method for mapping neurite density in vivo avoiding additional assumptions compared to the original neurite diffusion model. We demonstrate agreement between ground truth values and fast estimates of neurite density in fixed rat brain.
Theory: In [1] and [2] a model was presented allowing estimation of neurite density, ν, from DW MR data:

$$S(b)/S_0 = \nu S_c(b) + (1-\nu)\exp(-D_{\text{eff}}b) \quad (1)$$

where $S(b)$ is the DW MR signal at diffusion weighting b, $S_0 = S(b=0)$. The 'neurite signal' S_c stems from a distribution $f(\theta,\varphi) = \sum_{l,m} f_{lm} Y_{lm}(\theta,\varphi)$ of cylinders with longitudinal and transverse diffusion constants D_L and D_T, respectively. The last term in eq. (1) models diffusion in the extracellular space and cell bodies as free diffusion with diffusivity D_{eff}. This model has 18 parameters and its data requirement renders routine clinical estimation of neurite density and orientation distribution unfeasible despite the potential clinical value of the cytoarchitectural metrics. Here, we achieve a reduction in the dimensionality of the parameter space by averaging of eq. (1) over all gradient directions on the sphere. Thereby information of the orientation of the neurites is averaged out and an isotropic model is obtained with a much simpler signal expression:

$$S/S_0 = (1-\nu)\exp(-bD_{eff}) + \nu \cdot \text{erf}\left(\sqrt{bD_L}\right)\Big/\sqrt{4bD_L/\pi} \quad (2)$$

In this equation, the remaining parameters (apart from normalization) are neurite density, ν, and extra- and intra-cellular diffusivities D_{eff} and D_L. For analysis with this model, several shells of DW MR data should be obtained, and then the data must be averaged over all encoding directions at each b-value. Eq. (2) can then be fit to the orientationally averaged signal curve, producing estimates of four of the 18 parameters in the full model expression in eq. (1). The remaining parameters can then be estimated in a subsequent linear fit of eq. (1) to the same original signal (i.e. before the averaging) In this manner, an estimate of the full set of model parameters may be obtained from substantially less data than needed for a direct approach based on eq. (1) alone.
Methods: Data was acquired in fixed rat brain using a Bruker Biospec 9.4T (Bruker Biospin, Germany) MRI system equipped with a 15 mm quadrature coil. DWI data acquisition was performed using a standard DW spin echo sequence. A total of 15 b-values ranging from 0-3 ms/μm^2 in steps of 0.2 ms/μm^2 were acquired. At each b-value, data was acquired along 33 gradient directions. These directions were obtained from a 3-dimensional 24-point spherical 7-design [4], in addition to the nine directions identified for fast estimation of mean kurtosis in [5]. In order to compensate variations in effective diffusion weighting due to varying imaging gradient contributions among encoding directions, we recorded each direction in separate scans and manually adjusted the 15 diffusion encoding gradient strengths for each of the 24 directions. In this manner, we ensured identical effective b-values for all 33 encoding directions on each shell. Acquisition of all b-values along a single encoding direction was approximately 7 hours. Imaging parameters were: TE = 23.3 ms, TR = 4 s, δ/Δ = 4/14 ms, 2 averages, resolution was 100 μm x 100 μm x 500 μm.
Results: Fig 1A shows neurite density as estimated in rat brain by fitting eq. (1) to the entire data set. Fig 1B shows the isotropic model estimate of neurite density from data averaged averaged over the 24 spherical design directions (of the 33 in total) at each b-value, resulting in a ν estimate based on 73% of the data used to produce fig1A. Fig 1C shows the correlation of the two estimates (1A and 1B) in a scatterplot. The red line is the identity line. Fig 1D shows a neurite density map produced from fitting the isotropic model to data from averaging 24-direction shells at four b-values. Fig 1E shows the agreement between this estimate and the estimate from the full model using the complete data set (fig 1A). All model parameter estimates from this fit are in good agreement with the ground truth fit of eq. (1) to the entire data set. We then fit eq. (1) to the same small subset of the data (four non-zero b-values, 24 directions per shell, no orientational averaging) with the four shared parameters in eqs. (1) and (2) fixed to the values obtained from the fit of eq. (2) to the orientationally averaged data subset. This produced parameter estimates (up to and including the 2nd order in the fODF) in agreement with the ground truth estimates to within ~20% in the majority of pixels based on approximately 12% of the full data set. The two step approach's ability to robustly estimate the f_{lm} values needed to reconstruct the neurite orientation distribution function $f(\theta,\varphi)$ up to 2nd order is shown in fig 1 bottom row. This serves as a proof of principle for this strategy to bring down data requirements for eq. (1) without introducing additional assumptions.

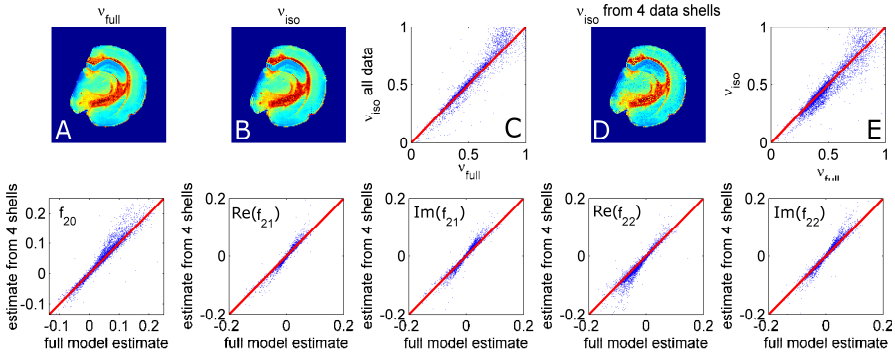

Fig1: Panel A shows full model estimate of neurite density from all data, B shows isotropic model estimate using all b-values. The correlation of the two estimates is shown in C (red line is identity line). D shows neurite density estimated from a small subset of the data using the isotropic model, and E shows this estimate's agreement with the 'ground truth' (A). Bottom row: comparisons of neurite orientation distribution components (flm's) from full model and the two-step modelling strategy.

Discussion and conclusion: We have proposed a modeling strategy based on the model in [1,2] to reduce the data requirement for estimation of neurite density and orientation distribution. The proposed method makes no assumptions about the biophysical properties of tissue beyond the model expression (1) which was validated against gold standards in [2]. The approach thereby avoids fixing diffusion constants or fODFs, which may bias the estimation of model parameters or reduce sensitivity to changes in tissue microstructure/diffusivity. This initial demonstration was performed on data from fixed rat brain where we have demonstrated agreement to neurite density from (1). Our current efforts are directed at determining the minimum data requirement for this strategy and evaluating the method in human brain.
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References: [1] Jespersen et al. NeuroImage 34 2007; [2] Jespersen et al. NeuroImage 49 2010. [3] Zhang NeuroImage 61(4) 2012. [4] Hardin & Sloane: Disc Comp Geo 15 1996. [5] Hansen et al. MRM 69(6) 2013.