Microstructural neuroimaging using spherical convolutional neural networks

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Abstract

Diffusion-weighted magnetic resonance imaging is sensitive to the microstructural properties of brain tissue. However, estimating clinically and scientifically relevant microstructural properties from the measured signals remains a highly challenging inverse problem. This paper presents a novel framework for estimating microstructural parameters using recently developed orientationally invariant spherical convolutional neural networks and efficiently simulated training data with a known ground truth. The network was trained to predict the ground-truth parameter values from simulated noisy data and applied to imaging data acquired in a clinical setting to generate microstructural parameter maps. Our model could estimate model parameters from spherical data more accurately than conventional non-linear least squares or a multi-layer perceptron applied on powder-averaged data (i.e., the spherical mean technique, a popular method for orientationally invariant microstructural parameter estimation). Importantly, our method is generalizable and can be used to estimate the parameters of any Gaussian compartment model.
1 Introduction

Neuroimaging enables non-invasively measuring functional and structural properties of the brain, and it is of crucial importance in modern neuroscience. Diffusion-weighted magnetic resonance imaging (dMRI), the most commonly used imaging modality for quantifying microstructural properties of the brain, is sensitive to the displacements of water molecules at the microscopic level and thus sensitive to tissue microstructure. dMRI has been used to localize microstructural alterations associated with, for example, learning [1], healthy development [2], ageing [3], neurodevelopmental disorders [4], and neurodegenerative diseases [5]. However, accurately inferring clinically and scientifically relevant properties of tissue microstructure (e.g., cell morphology or distribution of cell types) from the measured signal remains a highly challenging inverse problem [6]. Most dMRI data analysis methods are based on signal models that express the measured signal as a function of parameters of interest and can be fit to data by numerically minimizing an objective function [7].

An important requirement for microstructural neuroimaging methods is orientational invariance (i.e., estimated parameters should not depend on how the subject’s head is oriented in the scanner). Furthermore, it is often desirable for the parameter estimates not to depend on the orientation distribution of the microscopic structures (e.g., an estimate of neurite density should not depend on whether the neurites are aligned or crossing). These two requirements are often achieved by averaging over the acquired diffusion encoding directions, a method known as “powder averaging” like in the field of solid-state nuclear magnetic resonance (NMR). Fitting signal models to powder-averaged signals is often referred to as the "spherical mean technique" (a term introduced by Kaden et al. [8]). While it enables the estimation of various microstructural parameters [8–13], a significant amount of information is lost during averaging.

In recent years, parameter estimation using supervised machine learning has received significant attention as a potential solution to some issues with conventional model fitting such as slow convergence, poor noise robustness, and terminating at local minima [14–24]. In the context of microstructural neuroimaging, a particularly promising development in the field of deep learning has been the invention of spherical convolutional neural networks (sCNNs) [25–27]. sCNNs are SO(3)-equivariant artificial neural networks (ANNs) that enable orientationally invariant classification and regression, making them potentially well-suited for estimating microstructural parameters from dMRI data.

This paper presents a novel framework for estimating microstructural parameters from dMRI data using the sCNN architecture by Esteves et al. [26] and efficiently simulated training data. We trained an sCNN to estimate the parameters of a constrained 2-compartment model by Kaden et al. [11] which is regularly used in neuroscience to study white matter [28–32]. The sCNN could estimate apparent neurite density and diffusivity from spherical data more accurately than conventional non-linear least squares (NLLS) or a multi-layer perceptron (MLP) applied to powder-averaged data. To demonstrate that our method is applicable to any Gaussian compartment model, the network was also trained to estimate the parameters of a constrained 3-compartment model by Gyori et al. [18] that enables the estimation of apparent neural soma density using tensor-valued diffusion encoding [33].
2 Method

2.1 Spherical harmonics

Signals and orientation distribution functions (ODFs) were represented in the spherical harmonics domain to efficiently simulate training data and perform spherical convolutions with learnable zonal (i.e., symmetric with respect to the z-axis) filters.

Any square-integrable function on the sphere $f : S^2 \rightarrow \mathbb{C}$ can be expanded in the spherical harmonic basis:

$$f(x) = \sum_{l=0}^{b} \sum_{m=-l}^{l} \hat{f}_l^m Y_l^m(x),$$

(1)

where $x$ is a point on the sphere, $b$ is the bandwidth of $f$, $l$ is the order of the spherical harmonic, $m$ is the degree of the spherical harmonic, $\hat{f}_l^m$ is an expansion coefficient, and $Y_l^m$ is a spherical harmonic defined as

$$Y_l^m(\theta, \phi) = \sqrt{\frac{2l+1}{4\pi}} \frac{(l-m)!}{(l+m)!} P_l^m(\cos \theta)e^{im\phi},$$

(2)

where $\theta \in [0, \pi]$ is the polar coordinate, $\phi \in [0, 2\pi]$ is the azimuthal coordinate, and $P_l^m$ is the associated Legendre function.

The expansion coefficients are given by

$$\hat{f}_l^m = \int_{S^2} d\mathbf{x} \ f(x)Y_l^m,$$

(3)

which can be evaluated exactly as a finite sum using the sampling theorem by Driscoll and Healy [34]. Considering that diffusion encoding directions do not usually follow the sampling theorem, we used the least-squares solution by Brechbühler et al. [35] to compute the expansion coefficients.

Since the reconstructed dMRI signals are real-valued and antipodally symmetric, the following basis was used:

$$S_l^m = \begin{cases} 
0 & \text{if } l \text{ is odd} \\
\sqrt{2} \Im(Y_l^{-m}) & \text{if } m < 0 \\
Y_l^0 & \text{if } m = 0 \\
\sqrt{2} \Re(Y_l^m) & \text{if } m > 0 
\end{cases}$$

(4)

2.2 Spherical convolution

Convolution of a spherical signal $f$ by a spherical filter $h$ is defined as

$$(f * h)(x) = \int_{\mathbb{R}^{SO(3)}} d\mathbf{R} \ f(\mathbf{R}\hat{\mathbf{e}_z})h(\mathbf{R}^{-1}x),$$

(5)

where $\hat{\mathbf{e}_z}$ is a unit vector aligned with the z-axis. If $f$ and $h$ are band-limited, the above equation can be efficiently evaluated as a point-wise product in the spherical harmonics domain [34]:

$$(f * h)_l^m = 2\pi \frac{4\pi}{2l+1} \hat{f}_l^m \hat{h}_l^0$$

(6)
2.3 Simulations

Compartment models represent the measured signal as a sum of signals coming from different microstructural environments (e.g., intra-neurite diffusion). For details, see [7]. Here, we focus on models with Gaussian compartments. The signal along $\hat{n}$ is expressed as

$$S(\hat{n}) = \int_{R \in SO(3)} dR \text{ODF}(R\hat{e}_3)K(R^{-1}\hat{n}),$$  

(7)

where $K$ is the microstructural kernel response function:

$$K(\hat{n}) = \sum_{i=1}^{N} f_i \exp(-b : D_i),$$  

(8)

where $N$ is the number of compartments, $f_i$ is the signal fraction of the $i$th compartment, $b$ is the b-tensor corresponding to $\hat{n}$ and a b-value equal to $\text{Tr}(b)$, $: \text{ denotes the generalized scalar product (} b : D = \sum_{i=1}^{3} \sum_{j=1}^{3} b_{ij}D_{ij} \text{)}$ [36], and $D_i$ is a diffusion tensor aligned with the z-axis corresponding to the $i$th compartment.

We simulated training data by evaluating Equation 7 in the spherical harmonics domain. The response function values were evaluated along 768 directions uniformly distributed over the surface of the sphere according to the HEALPix sampling scheme [37, 38] and expanded in the spherical harmonics domain with spherical harmonics until order 8.

Rician noise was added to the simulated signals:

$$S_{\text{noisy}} = \sqrt{(S + X)^2 + Y^2},$$  

(9)

where $S$ is the simulated signal without noise and $X$ and $Y$ were sampled from a normal distribution with zero mean and standard deviation of $1/\text{SNR}$, where SNR is the signal-to-noise ratio. SNR was chosen to match the SNR in the imaging experiments.

2.4 Network architecture

Our network consisted of three spherical convolution layers with 16, 32, and 64 output layers followed by three fully connected layers with a hidden layer size of 128. The number of input channels was equal to the number of shells in the data and the number of outputs was equal to the number of predicted parameters. Each spherical convolution layer was followed by a rectified linear unit (ReLU) applied in the signal domain. Each hidden fully connected layer was followed by batch normalization [39] and a ReLU. Global average pooling was applied in the signal domain after the final spherical convolution layer to obtain a 64-dimensional orientationally invariant feature vector that was passed to the first fully connected layer. There were 38,562 trainable parameters in the network predicting the 2-compartment model parameters and 39,300 in the network predicting the 3-compartment model parameters.

3 Experiments

We trained our sCNN to estimate the parameters of two microstructural models and applied the trained network to imaging data acquired in a clinical setting to generate microstructural parameter maps. The
sCNN was compared to NLLS using the software by Kaden et al. [11] and to an MLP similar to the ones used by Gyori et al. [18,23]. The MLP had three hidden layers with 256 nodes each and was trained to predict the model parameters from powder-averaged data. Each hidden layer was followed by batch normalization and a ReLU. The MLP for predicting the 2-compartment model parameters had 134,402 trainable parameters and the MLP predicting the 3-compartment model parameters had 136,452 trainable parameters. The MLP went through the same training as the sCNN.

3.1 Imaging data

The brains of four healthy adult volunteers were scanned on a Siemens Magnetom Prisma 3T (Siemens Healthcare, Erlangen, Germany) at Great Ormond Street Hospital, London, United Kingdom. Data was denoised [40] using MRtrix3 [41] and distortion/motion corrected using FSL [42,43]. SNR was estimated as the inverse of the standard deviation of the normalized signals without diffusion-weighting.

3.1.1 High-angular resolution diffusion imaging

Three volunteers were scanned using a standard clinical two-shell high-angular resolution diffusion imaging (HARDI) protocol with two non-zero b-values of 1 and 2.2 ms/µm² with 60 directions over half a sphere each. Other relevant scan parameters were the following: diffusion time (Δ) = 28.7 ms; diffusion encoding time (Δ) = 16.7 ms; echo time (TE) = 60 ms; repetition time (TR) = 3,050 ms; field of view (FOV) = 220 × 220 ms; voxel size = 2 × 2 × 2 mm³; slice gap = 0.2 mm; 66 slices; phase partial Fourier = 6/8; multiband acceleration factor = 2. Fourteen images were acquired without diffusion-weighting, one of which had the phase encoding direction reversed. The total scan time was 7 minutes. SNR was 30. Fibre ODFs were estimated with multi-tissue constrained spherical deconvolution [44]. Spherical harmonics until order 8 were included when expanding signals in the spherical harmonics domain.

3.1.2 Tensor-valued diffusion imaging

One volunteer was scanned using a prototype spin echo sequence that enables tensor-valued diffusion encoding [45]. Data was acquired using numerically optimized [46] and Maxwell-compensated [47] gradient waveforms encoding linear and planar b-tensors. The acquisitions with linear b-tensors were performed with b-values of 0.5, 1, 2, 3.5, and 5 ms/µm² with 12, 12, 20, 20, and 30 directions over half a sphere, respectively. The acquisitions with planar b-tensors were performed with b-values of 0.5, 1, and 2 ms/µm² with 12, 12, and 20 directions over half a sphere, respectively. Other relevant scan parameters were the following: TE = 82 ms; TR = 4.2 s; FOV = 220 × 220 ms; voxel size = 2 × 2 × 2 mm³; slice gap = 0.2 mm; 66 slices; phase partial Fourier = 6/8; multiband acceleration factor = 2. Fourteen images were acquired without diffusion-weighting, one of which had the phase encoding direction reversed. The total scan time was 12 minutes. SNR was 20. When expanding the signals in the spherical harmonics domain, we included spherical harmonics until order 4 for shells with 20 or more directions and 2 otherwise.

3.2 2-compartment model

The so-called ”standard model” of diffusion in white matter consists of a one-dimensional compartment representing diffusion inside neurites and a coaxial axially symmetric extra-cellular compartment. We used
Figure 1: Loss during training of the networks for estimating the 2-compartment model parameters. The sCNN required more training but achieved smaller loss than the MLP.

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3.2.1 Training

Training was done over $10^5$ batches of simulated data generated during training. Each batch contained signals from $10^3$ microstructural configurations produced by random sampling. ODFs were sampled from one of the volunteer scans, normalized, and randomly rotated. $f \sim U(0,1)$ and $d \sim U(0,3 \, \mu m^2/\text{ms})$. Validation and test datasets were constructed similarly, except that they contained $10^5$ and $10^6$ microstructural configurations, respectively, and the ODFs were sampled from different subjects. The network was trained with ADAM [48] and an initial learning rate of $10^{-3}$, which was reduced by 90% at batches $5 \cdot 10^4$ and $7 \cdot 10^4$. Mean squared error (MSE) was used as the loss function, and $d$ was scaled by $\frac{1}{3}$ so it would range from 0 to 1 like $f$. Training the sCNN took 7 h on NVidia’s Tesla T4 graphical processing unit (GPU) with 16 GB of memory. Loss during training is shown in Figure 1.

3.2.2 Results

The sCNN outperformed NLLS and the MLP (Table 1). Figure 2 shows the estimated values against the ground-truth values. In 16% of the test dataset, the NLLS fit failed and estimated $f$ to be within $10^{-3}$ of the lower or upper bound (this can cause highly inaccurate black voxels to appear in white matter in maps of $f$). In cases where the NLLS fit failed, the mean ground-truth value of $f$ was 0.66. In 39% of these cases, the MLP predicted $f$ to be within 0.05 from 0.6, failing to make meaningful predictions. The sCNN did not suffer from this issue. The sCNN was the most accurate method even when evaluated on the test dataset.

a constrained version of the standard model [11] that enables model parameters to be estimated from powder-averaged data using NLLS. The model contains two parameters: intra-neurite signal fraction $f$ and intra-neurite diffusivity $d$. Axial and radial diffusivities of the extra-cellular compartment are $d$ and $(1 - f)d$, respectively.
\begin{tabular}{|l|l|l|}
\hline
\textbf{Method} & \textbf{MSE}(d) & \textbf{MSE}(f) \\
\hline
sCNN & $0.76 \cdot 10^{-2}$ & $0.52 \cdot 10^{-2}$ \\
NLLS & $3.01 \cdot 10^{-2}$ & $3.75 \cdot 10^{-2}$ \\
MLP & $1.54 \cdot 10^{-2}$ & $1.27 \cdot 10^{-2}$ \\
\hline
\end{tabular}

\textit{Table 1: Mean squared error of the 2-compartment model parameter estimates on the test dataset. Values of $d$ are in the units of $\mu m^2/ms$.}

\textit{Figure 2: Estimated 2-compartment model parameters against the ground-truth values of the test dataset. Values of $d$ are in the units of $\mu m^2/ms$.}
after removing the datapoints where the NLLS fit failed. The sCNN generated whole-brain maps of $d$ and $f$ (Figure 3) within seconds on the GPU.

Since the sampling errors occurring when moving between the signal and spherical harmonics domains can be significant, and the non-linearity applied in the signal domain can make the signal not band-limited, the orientational variance of the sCNN was evaluated. We simulated signals from $10^4$ randomly selected microstructural configurations of the test dataset rotated over 729 Euler angles given by the sampling theorem by Kostelec and Rockmore [49]. No noise was added to the signals to exclude the effects of noise. The mean coefficient of variation (CV = $\sigma/\mu \cdot 100\%$) was 0.04% for $d$ and 0.06% for $f$, showing that the neural network architecture is nearly orientationally invariant.

### 3.3 3-compartment model

Palombo et al. [16] added a spherical compartment representing neural soma to the standard model to make it more suitable for gray matter. We used the 3-compartment model by Gyori et al. [18] that uses tensor-valued diffusion encoding to make neural soma imaging more feasible without custom high-performance gradient hardware. The model contains four parameters: intra-neurite signal fraction $f_i$, spherical compartment signal fraction $f_{sph}$, intra-neurite diffusivity $d_i$, and spherical compartment diffusivity $d_{sph}$. Axial and radial diffusivities of the extra-cellular compartment are $d_i(1 - f_i - f_{sph})^{1/2}f_{sph}/(f_{sph} + f_i)$ and $d_i(1 - f_i - f_{sph})(1/2f_{sph} + f_i)/(f_{sph} + f_i)$, respectively.

#### 3.3.1 Training

Training done the same way as with the 2-compartment model. $f_i \sim U(0, 1)$, $f_{sph} \sim U(0, f_i)$, $d_i \sim U(0, 3 \mu m^2/ms)$, and $d_{sph} \sim U(0, \max(d_i, 0.5 \mu m^2/ms))$. The upper limit of $d_{sph}$ was chosen to correspond to a sphere with a diameter of 25 $\mu$m using the Monte Carlo simulator Disimpy [50].

#### 3.3.2 Results

Table 2 summarizes the performance of the sCNN and MLP. The sCNN performed better than the MLP. Figure 4 shows the parameters estimated by the sCNN against the ground-truth values. As expected based
Table 2: Mean squared error of the 3-compartment model parameter estimates on the test dataset. Values of $d_i$ and $d_{sph}$ are in the units of $\mu m^2/\text{ms}$.

| Method | MSE($d_i$) | MSE($d_{sph}$) | MSE($f_i$) | MSE($f_{sph}$) |
|--------|------------|----------------|------------|----------------|
| sCNN   | $7.52 \cdot 10^{-2}$ | $0.83 \cdot 10^{-2}$ | $0.83 \cdot 10^{-2}$ | $1.59 \cdot 10^{-2}$ |
| MLP    | $10.20 \cdot 10^{-2}$ | $0.94 \cdot 10^{-2}$ | $1.89 \cdot 10^{-2}$ | $2.29 \cdot 10^{-2}$ |

Figure 4: 3-compartment model parameters estimated by the sCNN against the ground-truth values of the test dataset. Values of $d_i$ and $d_{sph}$ are in the units of $\mu m^2/\text{ms}$.

on previous work [16, 18, 51], estimation of $d_{sph}$ and $f_{sph}$ was difficult, especially for low $f_{sph}$. However, the modelling details are outside the scope of this work. Figure 5 shows whole-brain maps that the sCNN generated from preprocessed dMRI data within seconds on the GPU.
Figure 5: 3-compartment model parameter maps generated by the sCNN.
4 Discussion

The primary purpose of this study was to investigate if sCNNs can improve the accuracy of microstructural parameter estimation from noisy dMRI data. We focused on a constrained 2-compartment model widely used in neuroscience research to study human white matter in vivo. Our sCNN was able to estimate the ground-truth parameter values from simulated noisy spherical data more accurately than NLLS or an MLP applied on powder-averaged data. In neuroimaging studies, effect sizes are often small, and acquiring data is expensive, making it essential to optimize methods proven to be sensitive to clinically relevant microstructural alterations. However, parameter estimates must be interpreted cautiously as broken model assumptions and training data distribution can reduce their accuracy [23,52–54]. To demonstrate the generalizability of our method, we trained the sCNN to predict the parameters of a recently developed 3-compartment model and found an improvement compared to an MLP applied on powder-averaged data. Previous studies on apparent neural soma imaging predicted model parameters from powder-averaged data [16,18].

To our best knowledge, only a few studies have used sCNNs to analyze dMRI data previously. Sedlar et al. [22] trained an sCNN to estimate the parameters of a constrained 2-compartment model from subsampled data and showed an improvement in accuracy compared to NLLS and previously used ANNs. Goodwin-Allcock et al. [55] showed that sCNNs can improve the robustness of diffusion tensor estimation from data with just a few directions. Furthermore, sCNNs have been used to estimate ODFs [21] and [20]. This study is the first time sCNNs have been trained to predict microstructural parameters from simulated training data with a known ground truth. Although we implemented spherical convolution layers as described by Esteves et al. [26], other architectures also exist and warrant investigation in the context of microstructural neuroimaging. For example, the sCNNs by Cohen et al. [25] use cross-correlation and learnable non-zonal filters, Kondor et al. [56] developed efficient quadratic non-linearities in the spherical harmonics domain, and the graph-based sCNN by Perraudin et al. [27] is suitable for spherical data with very high angular resolution. Besides optimizing network architecture, future studies should also focus on optimizing hyperparameters, acquisition protocols, microstructural models, and other aspects outside the scope of this study.

In conclusion, our work demonstrates that sCNNs can improve the accuracy of microstructural neuroimaging and provide a compelling alternative to estimating parameters from powder-averaged data.
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