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Harmonizing 1.5T/3T Diffusion Weighted MRI through Development of Deep Learning Stabilized Microarchitecture Estimators

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Abstract

Diffusion weighted magnetic resonance imaging (DW-MRI) is interpreted as a quantitative method that is sensitive to tissue microarchitecture at a millimeter scale. However, the sensitization is dependent on acquisition sequences (e.g., diffusion time, gradient strength, etc.) and susceptible to imaging artifacts. Hence, comparison of quantitative DW-MRI biomarkers across field strengths (including different scanners, hardware performance, and sequence design considerations) is a challenging area of research. We propose a novel method to estimate microstructure using DW-MRI that is robust to scanner difference between 1.5T and 3T imaging. We propose to use a null space deep network (NSDN) architecture to model DW-MRI signal as fiber orientation distributions (FOD) to represent tissue microstructure. The NSDN approach is consistent with histologically observed microstructure (on previously acquired ex vivo squirrel monkey dataset) and scan-rescan data. The contribution of this work is that we incorporate identical dual networks (IDN) to minimize the influence of scanner effects via scan-rescan data. Briefly, our estimator is trained on two datasets. First, a histology dataset was acquired on three squirrel monkeys with corresponding DW-MRI and confocal histology (512 independent voxels). Second, 37 control subjects from the Baltimore Longitudinal Study of Aging (67-95 y/o) were identified who had been scanned at 1.5T and 3T scanners (b-value of 700 s/mm², voxel resolution at 2.2mm, 30-32 gradient volumes) with an average interval of 4 years (standard deviation 1.3 years). After image registration, we used paired white matter (WM) voxels for 17 subjects and 440 histology voxels for training and 20 subjects and 72 histology voxels for testing. We compare the proposed estimator with super-resolved constrained spherical deconvolution (CSD) and a previously

presented regression deep neural network (DNN). NSDN outperformed CSD and DNN in angular correlation coefficient (ACC) 0.81 versus 0.28 and 0.46, mean squared error (MSE) 0.001 versus 0.003 and 0.03, and general fractional anisotropy (GFA) 0.05 versus 0.05 and 0.09. Further validation and evaluation with contemporaneous imaging are necessary, but the NSDN is promising avenue for building understanding of microarchitecture in a consistent and device-independent manner.

Keywords

DW-MRI; Harmonization; Deep Learning; Null Space; Fiber Orientation Distribution; Spherical Harmonics; Dual Network

INTRODUCTION

Diffusion-weighted magnetic resonance imaging (DW-MRI) is a non-invasive imaging modality that can provide information about microarchitecture of the brain at a millimetric scale [1-3]. Multiple DW-MRI approaches have been proposed to model the DW-MRI signal to estimate the 3D microstructure [4]. A common approach is diffusion tensor imaging (DTI) which can capture a single fiber population per voxel [5-7]. Although DTI has been established as reproducible and characterizes the DW-MRI signal well, it is limited that it cannot capture complex fiber microstructure like fanning, crossing, kissing fibers [8, 9]. Advanced approaches fall under the nomenclature of high angular resolution diffusion imaging (HARDI) methods [10]. HARDI methods are routinely applied to DW-MRI acquisition with more than 45 gradient volumes [10], as reviewed in [4]. While HARDI methods are quite reproducible (>0.7) in terms of fiber counts within a scanning protocol on a single device, but quite different across methods [11-13]. Challenge studies depict a similar story [4]. In the context of DW-MRI signal the measurements are affected by different scanners and HARDI method reconstruction is impacted due to these effects [14]. Hence, harmonization is a critical problem where the microarchitecture reconstruction is impacted by protocol effects, scanner effects, and site effects (Fig 1).

Harmonization has been pursued at for DTI using COMBAT to harmonize the metrics of fractional anisotropy (FA) and mean diffusivity (MD) [15]. While COMBAT is a method of harmonizing the metrics directly, [16] was proposed to harmonize the DW-MRI signal using rotational invariant spherical harmonic (RISH) features [16, 17]. Previously meta-analysis techniques have been used to quantify group differences for e.g., FA [18, 19]. Statistical covariates have been used to characterize site differences as well [20]. Recently, an approach to harmonize the microstructure was recently proposed to harmonize the microarchitecture directly in the space of spherical harmonics [31]. However, this approach relied on scanners of the same manufacturer and similar field strength and only relied on just an extra L2 loss for harmonization. The time separation between acquisitions were within ~2 weeks. This approach was built on the basis of sequential DNN approach [30]. Herein, we extend the approach to inter-field strength harmonization and evaluate in a rather extreme case of 4 years mean separation. Moreover, we introduce a modification to loss function to improve consistency of scalar metric consistency while maintaining FOD consistency.

The NSDN approach is based on using a dataset where corresponding DW-MRI and ground truth FOD of microstructure was reconstructed using histology [21]. The dataset consists of white matter (WM) voxels from three squirrel monkeys. A deep neural network (DNN) regression model could learn the histology using the inputs of DW-MRI on a voxel by voxel basis [30]. The proposed NSDN approach takes paired inputs of voxels of 17 subjects (1.5T and 3T scanners). The hypothesis is that when predicted/estimated their outcome should be the same, this has been modelled using a custom loss function and with the help of identical dual networks. A total of 37 subjects from the Baltimore Longitudinal Study of Aging (BLSA) were identified with paired acquisitions on 1.5T and 3T scanners. 20 subjects were completely withheld for testing of the proposed approach. CSD and DNN as baseline.

DATA & METHODS

Squirrel Monkey Data Acquisition

Three squirrel monkeys ex-vivo acquisition were acquired on a Varian 9.4T scanner [21]. A total of 100 gradient volumes were acquired using a diffusion-weighted EPI sequence at a b-value of 6000 s/mm². Voxel resolution was set at 0.3 mm. Once acquired the tissue was sectioned and stained with fluorescent dil and imaged on a LSM710 Confocal microscope with procedures outlined in [21]. The ground truth histological FOD (HFOD) was extracted with 3D structure tensor analysis. A total of 513 histological voxels were processed with corresponding DW-MRI after quality control. 100 random rotations were applied to each voxel thus augmenting the dataset to 51,813 voxels. A withheld set of 7,272 voxels were maintained for validation. The DW-MRI signal and HFOD were both represented in spherical harmonic (SH) coefficients of the 6th order using a regularized linear least square fit. 44,541 voxels were used for training DNN and NSDN.

BLSA Data Acquisition

37 control subjects were imaged after informed consent and institutional review board approval and retrieved in deidentified form from the BLSA based on paired acquisitions on 1.5T and 3T scanners [22]. All acquisitions were extracted with their corresponding MPAGE. All scans were processed with topup and eddy for correction of susceptibility distortion and eddy currents [23, 24]. Skull stripping was performed using FSL on all scans [25]. Multi-atlas segmentation was done on the MPAGE using BrainCOLOR protocol [26]. The segmented image and the diffusion image were all coregistered using flirt [27]. The DW-MRI was limited to only WM of the brain using the segmented image. All DW-MRI voxels were transformed to 6th order SH coefficients using a regularized linear least square [28] fit for training and testing the NSDN. A total of ~750,000 WM voxels were extracted from the 17 training subjects. 44,541 WM voxels were randomly selected from the BLSA ~750,000 WM voxels to down sample the unpaired training data for NSDN.

Null Space Deep Network

The NSDN architecture is built upon the base network of the DNN (Fig 2). The base network is composed of all fully connected dense layers with 28, 400, 66, 200 and 28 neurons per layer. The first three layers were activated using 'ReLU' while the remaining two outer layers were linearly activated to ensure that negativity as a SH coefficient

prediction can be negative. Inputs to DNN are 6th order DW-MRI SH Coefficients and outputs are 6th order FOD SH Coefficients. Both are 1D vectors of 28 coefficients.

NSDN is inspired by linear algebra null spaces where the motivation is that the network must be constrained in such a way that the outcome is left unaffected. A similar architecture was first proposed for person re-identification problem [29]. The novelty in this approach is that paired unlabeled data is used to drive the training of the network where it learns to ignore features of scanner noise and inter-scanner bias which would otherwise lead the network differentiate between the data. The NSDN architecture follows the DNN structure and has an identical dual network of the DNN. This implies the core network to have shared weights where it can learn and ignore potential scanner bias features. NSDN takes 3 inputs of 6th order DW-MRI SH coefficients where the first comes from the histology data and the other two are a corresponding/pair of voxels of the same subject from 1.5 Tesla and 3 Tesla scanners. The output of NSDN is a 6th order FOD SH coefficient.

The NSDN uses a custom loss function which is an additive combination of three L2 losses and all are governed by their individual hyper-parameters (1). The first is the L2 loss between the network's FOD prediction and the ground truth with the hyper-parameter ' α '. The second is the L2 loss between the paired voxels which has an expectation of 0 and the hyper-parameter is ' λ '. The third is the L2 loss between the GFA of the paired voxels which also has an expectation of 0 and the hyper-parameter is ' β '. The GFA is defined by $\text{std}(\psi)/\text{rms}(\psi)$ where ψ is a set of SH Coefficients. GFA describes the anisotropic nature of the expansion of SH coefficients. The hyper-parameter ' α ' was set to 2.75 in an ad-hoc manner. This was done to balance the relative energies of the other two loss function terms.

$$L = \frac{1}{m} \sum_{i=1}^m \alpha(y_{true_i} - y_{pred_i})^2 + \lambda(P_{a_i} - P_{b_i})^2 + \beta(GFA(P_{a_i}) - GFA(P_{b_i})) \quad \dots(1)$$

All methods were evaluated using ACC (2), MSE and difference in GFA. ACC is a metric for calculating correlations of functions of all directions over a spherical harmonic expansion. It provides an estimate of how closely two FOD's relate to each other, 'u' and 'v' are the two sets of expansions of SH for corresponding voxels in all analysis. A value of '1' for ACC describes high correlation.

$$ACC = \frac{\sum_{j=1}^{\infty} \sum_{m=-j}^j u_{jm} v_{jm}^*}{\left[\sum_{j=1}^{\infty} \sum_{m=-j}^j |u_{jm}|^2 \right]^{0.5} \cdot \left[\sum_{j=1}^{\infty} \sum_{m=-j}^j |v_{jm}|^2 \right]^{0.5}} \quad \dots(2)$$

RESULTS

The ACC of the NSDN has the most skewed distribution towards '1' as compared to both the baseline approaches (Fig 3A). DNN has the highest variance of MSE distribution with CSD having a lower variance and NSDN as the lowest (Fig 3B). CSD and NSDN show an equally controlled distribution for difference in GFA while DNN having a higher variance as compared to the other two (Fig 3C). The median diff in GFA in terms of absolute values for

CSD, DNN and NSDN are 0.05, 0.09 and 0.05. The median value of MSE for CSD, DNN and NSDN are 0.0037, 0.0326 and 0.0011. The median ACC of CSD, DNN and NSDN are 0.28, 0.46 and 0.81. Non-parametric signed rank test for all pairs of distributions were found to be $p < 0.001$.

The mean ACC of CSD, DNN and NSDN are 0.28, 0.36 and 0.74 (Fig. 4A, 4B & 4C orange and blue lines). CSD has the highest ACC variance while ACC variance decreases for DNN and is the most constrained for NSDN (Fig 4A, 4B, & 4C). The difference in GFA for pairs of WM voxels per subject has a similar constricted spread for CSD and NSDN while DNN has the widest variance (Fig 4D, 4E & 4F). The distribution of MSE for all pairs of WM voxels per subjects shows that the DNN variance is the highest with CSD having quite a constrained distribution while NSDN having an even narrower one.

Figure 5 presents a qualitative comparison of spatial maps of ACC across four random subjects. Figure 6 examines the frontal lobe matter where we see low correlation for CSD, increased ACC with DNN, and the highest correlation with NSDN. Figure 7 presents a harmonized perspective of the subject presented in Figure 1.

DISCUSSION

The NSDN architecture simultaneously (1) learns a mapping from ex vivo DW-MRI to a histology FOD, (2) ignores in vivo scanner effects that occur between 1.5T and 3T, and (3) enforces consistency of GFA. This effort is a first attempt at direct harmonization of the estimated microstructure (FOD) through manipulation of data-driven tissue models. We believe this framework will be useful for harmonization of the microstructure in situations where scan-rescan data are available and have shown its efficacy in an extreme situation of non-contemporaneous 1.5T and 3T imaging. More broadly, the NSDN architecture could be applied for other machine learning problems in different domains where there is paired unlabeled data.

Despite the success of the NSDN, there are limitations of this study and additional validation is needed. First, the scan-rescan data were not contemporaneously acquired. Second, only two scanners / protocols were used, and these scanners were the same manufacturer. Third, subjects were all older than 67 years old. In terms of generalizability, NSDN has yet to be evaluated across scanners within a field strength, across b-values, or across gradient sample schemes.

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Figure 1:

A) Middle axial slice on a 1.5T scanner depicting CSD FOD's across the WM. B) Middle axial slice on a 3T scanner depicting CSD FOD's across the WM. C) Angular Correlation Coefficient of the FOD's which is calculated on corresponding voxels of 1.5T and 3T scanner. Annotations 1,2 and 3 depict low correlation regions of the brain on the left side, same can be observed on the right side.

Figure 2:

The base regression neural network is depicted in the center which describes the parameters of the fully connected dense layers with respective activation functions. The plot at left: Depicts three inputs where the center input comes from corresponding DW-MRI with histology. The other two are pairwise inputs from corresponding voxels of scanner 1.5T and 3T. The plot at right: Depicts the loss function which uses the hypothesis that the outcome/ prediction should be same irrespective of the scanner gradient strength.

Figure 3:

A) Shows ACC between 1.5T and 3T scanner acquisitions across all WM voxels of 20 withheld subjects for the three methods CSD, DNN and NSDN. B) Shows MSE between 1.5T and 3T scanner acquisitions across all WM voxels of 20 withheld subjects for the three methods CSD, DNN and NSDN. C) Shows difference in GFA between 1.5T and 3T scanner acquisitions across all WM voxels of 20 withheld subjects for the three methods CSD, DNN and NSDN.

Figure 4:

A, B and C) Depict the individual distribution per subject of ACC across WM voxels between 1.5T and 3T scanners. The blue and orange lines depict the mean and median of ACC across all 20 subjects. D, E and F) Depict the individual distribution per subject of difference in GFA across WM voxels between 1.5T and 3T scanners. G, H and I) Depict the individual distribution per subject of MSE across WM voxels between 1.5T and 3T scanners.

Figure 5:

Row-wise spatial maps of ACC for the middle axial slice of the brain are depicted for the three methods per columns. ACC improves from left to right with NSDN achieving the highest across all four subjects.

Figure 6:

A & B) Depicts CSD FOD's with underlay of ACC on Scanner 1.5T and Scanner 3T data. C & D) Depicts DNN FOD's with underlay of ACC on Scanner 1.5T and Scanner 3T data. E & F) Depicts NSDN FOD's with underlay of ACC on 1.5T and 3T. G) The region of interest being observed is the left side frontal lobe WM.

Figure 7:

A) Middle axial slice on a 1.5T scanner depicting NSDN FOD's across the WM. B) Middle axial slice on a 3T scanner depicting NSDN FOD's across the WM. C) ACC of the FOD's which is calculated on corresponding voxels of 1.5T and 3T scanner. Annotations 1,2 and 3 depict higher correlation regions of the brain on the left side, same can be observed on the right side as compared to Figure 1.