Deep Diffusion MRI Registration (DDMReg): A Deep Learning Method for Diffusion MRI Registration

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Abstract—In this paper, we present a deep learning method, DDMReg, for fast and accurate registration between diffusion MRI (dMRI) datasets. In dMRI registration, the goal is to spatially align brain anatomical structures while ensuring that local fiber orientations remain consistent with the underlying white matter fiber tract anatomy. To the best of our knowledge, DDMReg is the first deep-learning-based dMRI registration method. DDMReg is a fully unsupervised method for deformable registration between pairs of dMRI datasets. We propose a novel registration architecture that leverages not only whole brain information but also tract-specific fiber orientation information. We perform comparisons with four state-of-the-art registration methods. We evaluate the registration performance by assessing the ability to align anatomically corresponding brain structures and ensure fiber spatial agreement between different subjects after registration. Experimental results show that DDMReg obtains significantly improved registration performance. In addition, DDMReg leverages deep learning techniques and provides a fast and efficient tool for dMRI registration.

Index Terms—Image Registration, Diffusion MRI, Deep Learning, Tractography

1 Introduction

Diffusion magnetic resonance imaging (dMRI) is an advanced neuroimaging technique that measures the random diffusion of water molecules in the brain [1]. dMRI data includes multi-dimensional, orientation-dependent signals that describe not only the strength but also the orientation of water diffusion in brain tissues. As a result, dMRI provides a unique technique to enable in-vivo fiber tracking (tractography) of white matter fiber tracts [2] and to estimate the underlying cellular microstructure of brain tissues [3]. Registration of dMRI data is a crucial step in applications such as population-based analyses of diffusion MRI data in health and disease [4], [5] and construction of brain anatomical atlases [6], [7], [8].

Registration of dMRI data is a challenging task. In traditional neuroimaging data (e.g., T1-weighted or T2-weighted MRI), the images are scalar-valued volumes, representing anatomically meaningful numeric intensity values that are specific to certain brain structures. Registration is performed usually by minimizing the intensity dissimilarity between the volumes to spatially align the corresponding anatomical structures in the brain, such as white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) as well as their subdivisions [9]. dMRI data, however, describe not only the strength but also the orientation of water diffusion. The orientation information encoded in dMRI data is important to reveal the underlying fiber orientation in the white matter. Therefore, dMRI registration should not only spatially align anatomical structures of the entire brain, but also ensure that local fiber orientations remain consistent with the underlying white matter anatomy after image transformations [10], [11], [12], [13].

Many methods have been proposed for dMRI registration, which can be generally categorized based on the input data to the algorithms. The most straightforward approaches use representative scalar images derived from the dMRI data, so that any existing methods developed for traditional imaging data can directly use or easily be adapted for dMRI registration [5], [14]. Currently, the fractional anisotropy (FA) image [3] is the most popular and has been widely used in research studies [5], [14], [15], [16], [17], [18], [19]. Nevertheless, despite the wide usage of scalar images for dMRI registration, this approach does not use water diffusion orientation information contained in the dMRI data and thus discards important information to ensure fiber tract consistency.

A number of approaches for dMRI registration have used input data containing diffusion orientation information. Early work used diffusion tensor imaging (DTI) [11], [20], [21], [22], [23], [24], [25], where each voxel is a 2nd-order Cartesian tensor that can estimate the principal water diffusion direction. However, a known issue is that DTI can not adequately model more complex fiber configurations such as crossing fibers that are prevalent in much of the brain [26]. Consequently, many dMRI registration methods have used more advanced diffusion models that can estimate multiple fiber orientations at each voxel. The widely used models include higher-order diffusion tensor models [27], diffusivity functions [28], Gaussian mixture fields [29], diffusion orientation distribution functions (ODF) [9], spherical harmonics [30], [31] and fiber orientation distributions (FOD) [32], [33], [34]. Registration based on these models has shown to better align brain regions in the presence of crossing fibers. These crossing fibers are often represented as *peaks* (local maxima) of the fiber orientation distribution at

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each voxel. However, these proposed registration methods do not consider to which fiber tract each peak belongs. This can result in the misalignment of peaks from different tracts and affect the geometry of the fibers when performing tractography.

Finally, a number of approaches for dMRI registration have used input data representing white matter fiber tracts. Several methods have been proposed to perform fiber tractography and then register based on fiber streamline trajectory information [35], [36], [37], [38], [39]. Other tractography-based registration methods register volumetric maps computed from the fiber streamlines, such as fiber tract probability (or density) maps [40], [41] and currents (maps computed based on the tangent vector of the streamline trajectory) [42]. These methods have shown good performance to align white matter tracts. Nevertheless, these methods are designed specifically for tract registration, without considering other brain structures.

In terms of methodology, almost all existing dMRI registration methods apply the traditional medical image registration formulation, where the algorithms solve an optimization problem to iteratively align an image pair based on an energy function [43]. Solving a pairwise optimization can be computationally intensive, and hence slow in practice. Recent advances in deep learning techniques have shown not only significantly faster computational speed, but also improved registration accuracy in medical image registration tasks (see [44], [45] for a review). One recent deep learning method improved the registration of T2-weighted images by incorporating DTI information into the loss function during learning [46]. However, no deep learning methods have yet been proposed for dMRI registration.

In this study, we propose a novel deep learning method for registration of dMRI data, which we refer to as the *Deep Diffusion MRI Registration (DDMReg)* method. To the best of our knowledge, this is the first deep-learning-based dMRI registration method. There are several contributions and advantages of our method. First, DDMReg is a fully unsupervised method for pairwise registration. It learns registration between rigidly aligned images and does not require perfectly pre-registered training data. DDMReg enables deformable registration to account for local nonlinear differences of the brains from different individuals. Second, DDMReg contains a novel ensemble learning network architecture, where multiple U-net-based subnetworks for registration are trained on different types of input data derived from dMRI and are subsequently fused for final deformation field estimation. In this way, DDMReg enables good registration of anatomical structures from the entire brain, while ensuring good fiber tract alignment with respect to the underlying white matter anatomy. Third, in order to handle the computational limit due to GPU memory, we propose a novel multi-deformation fusion subnetwork to leverage backbone networks, where weights of a model for registering a certain type of input data can be pretrained.

2 METHODS

The goal of the proposed DDMReg method is to compute a deformation field (ϕ) to register a pair of dMRI datasets, i.e., registering a moving (m) to a target (t) dMRI dataset. Fig. 1 gives an overview of the method. From the raw dMRI data, also known as the diffusion weighted imaging (DWI) data, we first compute input data to our network (Section 2.1). Two types of input data are computed, in which one type (i.e., FA) is generally useful for aligning anatomical structures from the whole brain while the other type (i.e., tract orientation maps proposed in [47]) is useful for aligning fibers of specific anatomical white matter tracts. For each type of input data, a U-net-based registration subnetwork (the same network architecture proposed in [48]) is trained to compute a deformation field that is specific to the input data type. A multi-deformation fusion subnetwork is then used to combine all computed deformation fields to estimate the final deformation field. One of the benefits of the multi-deformation fusion subnetwork is that the different registration subnetworks constrain each other, while cooperating to optimize the entire network. Following that, a spatial transformation subnetwork [49] is used to warp the moving input data into the target subject space (Section 2.2). Given the large number of registration subnetworks (a total of 41 in our study) that is difficult to fit in the GPU at once, we pretrain model weights of the registration subnetworks that are specific for the white matter fiber tracts, and we use them as backbones in our overall network (Section 2.4).

2.1 Network Input

Input data for dMRI registration should be generally descriptive of the different types of anatomical structures in the brain so that it can be used to align the whole brain. Meanwhile, input data should also be useful for describing local fiber orientations to ensure alignment of individual white matter fiber tracts, in particular in the presence of crossing fibers. In our method, we propose to include these two kinds of input images.

For the description of the whole brain, we use the FA image. FA measures the water diffusion anisotropy of the tissues in the brain [3], one of the most important quantitative measures that dMRI can measure. The FA image gives a good contrast for anatomical brain structures such as WM, GM and CSF, and it has been widely used for dMRI registration tasks [5], [14], [15], [16], [17], [18], [19]. (In Supplementary Fig. S1, we also test several other images that have been used for dMRI registration, including diffusion baseline images, diffusion tensor images and FOD peak images. We show that FA generates the best registration performance for our proposed framework.)

For the description of specific white matter tracts, we use tract orientation maps (TOMs) [47]. The TOM contains local fiber orientations of a specific white matter tract (e.g., arcuate fasciculus). At each voxel, a TOM contains one 3D vector (one peak), which represents the local mean fiber streamline orientation of a particular fiber tract. There are several advantages of applying TOMs in our framework. First, each TOM is tract-specific. In the presence of crossing fibers (where voxels contain multiple fiber orientation peaks) the TOM of a tract can identify the orientation peak that is specific to the tract. Second, the TOM is learned using CNNs based on fiber orientation estimated directly from fiber streamlines (see [47] for details). In this case, TOMs encode geometric information of fibers so that registering

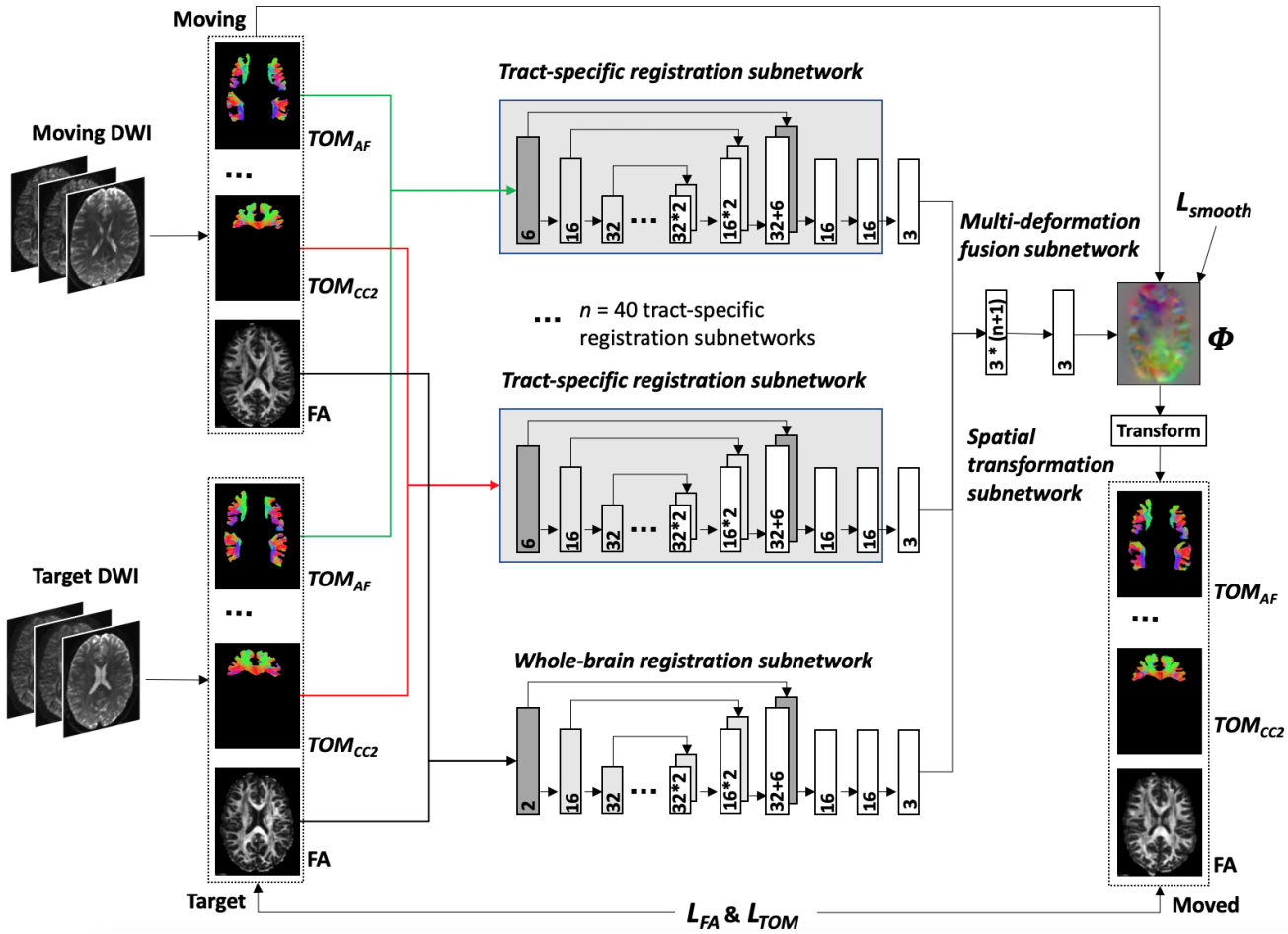

Fig. 1. Method overview of DDMReg. From DWI data of the moving and target subjects, FA and 40 TOM images are computed as input to our network. Whole-brain (n = 1) and tract-specific (n = 40) registration subnetworks are trained to compute deformation fields specific to the input data (FA or TOM). A multi-deformation fusion subnetwork is used to combine all computed deformation fields to estimate the final deformation field. A spatial transformation subnetwork is used to warp the moving input data for loss computation. The model weights of the convolutional layers (gray rectangle) in each tract-specific registration subnetwork are pretrained to reduce computational burden (see Fig. 2).

using TOMs can be helpful to ensure geometric alignment of fiber tracts. Third, computation of TOMs can be done using the GPU, which is time efficient. Fourth, TOMs are stored as volumetric images (a 3D volume with three channels representing the fiber orientation at each voxel), which can be easily used as input to CNNs.

2.2 Architecture

Our proposed network contains four subnetworks: 1) a whole-brain registration subnetwork, 2) n tract-specific registration subnetworks, 3) a multi-deformation fusion subnetwork, and 4) a spatial transformation subnetwork.

The whole-brain registration subnetwork learns a deformation field ϕ_{wb} between the target and moving FA images, i.e., FA(t) and FA(m). We use the Unet-based architecture proposed in VoxelMorph, a popular library for medical image registration [48] (see Fig. 1). Specifically, the subnetwork takes as input a 2-channel 3D volume formed by concatenating FA(t) and FA(m). 3D convolutions are performed in both the encoder and decoder stages using a kernel size of 3, and a stride of 2 (see [48] for other detailed parameter settings). The last layer of this subnetwork is a 3-filter 3D convolutional layer, which outputs a 3-channel 3D volume, i.e., the estimated deformation field ϕ_{wb}.

Each tract-specific registration subnetwork learns a deformation field ϕ^i_{tract} between the target and moving TOM images for a certain white matter tract i, i.e., TOM$^i(t)$ and TOM$^i(m)$. Here, $i \in [1, ..., n]$, where n is the total number of tract-specific registration subnetworks. We use a similar Unet-based architecture as applied in the whole-brain registration subnetwork, but the input is a 6-channel 3D volume formed by concatenating TOM$^i(t)$ and TOM$^i(m)$. The last layer is also a 3-filter 3D convolutional layer that outputs the estimated deformation field ϕ^i_{tract}. In our study, we have a total of $n = 40$ tract-specific subnetworks, corresponding to the number of tract-specific TOMs available in [47] (see Section 3 for details).

The multi-deformation fusion subnetwork combines the whole-brain deformation field and all tract-specific deformation fields to calculate the final deformation field ϕ_{final}. The multi-deformation fusion subnetwork is based on our recently proposed dual-stream network to fuse deformation fields for multimodal image registration [50]. The idea is to concatenate different deformation fields, followed by a 3-filter 3D convolution to estimate the final deformation

field. In our study, the multi-deformation fusion layer takes an input 3D volume with $3 \times (n+1)$ channels formed by concatenating ϕ_{wb} and all n ϕ_{tract}, performs 3D convolution with size $3 \times 3 \times 3$, and outputs a 3D volume with 3 channels, i.e., ϕ_{final}.

The spatial transformation subnetwork warps the moving FA and TOM images into the target subject space using ϕ_{final} for loss computation (see below Section 2.3). This step is done using the spatial transformer network (STN) proposed in [49].

2.3 Loss Function

Our overall loss function L_{final} consists of three components, including: 1) L_{FA} to penalize differences of the whole brain FA, 2) L^i_{TOM} to penalize differences of each tract-specific TOM^i, 3) L_{smooth} to penalize local spatial variations in the deformation fields:

$$\begin{aligned} L_{final}(f, m, \phi) = & \lambda_{FA} L_{FA} + \\ & \lambda_{TOM} \frac{1}{n} \sum_{i}^{n} L^i_{TOM} + \\ & \lambda_{smooth} L_{smooth}(\phi_{final}) \end{aligned} \tag{1}$$

where λ_{FA}, λ_{TOM} and λ_{smooth} are the weighting parameters to denote the relative importance of the three components (see Section 2.5 for detailed settings). For L_{FA} and L^i_{TOM}, we use the widely applied mean squared voxelwise difference, i.e., the mean squared error (MSE) between the moved and target images, that has been shown to be effective for deep learning image registration in VoxelMorph [48]. (In Supplementary Fig. S1, we also test additional difference measures, including normalized cross correlation (NCC) [51] for FA and cosine similarity for TOM [47], where we find that MSE obtains the best performance.) For L_{smooth}, we use an L2-norm of the spatial gradients of the deformation field, as suggested in [48].

2.4 Pretraining Tract-Specific Backbone Subnetworks

Leveraging pretrained network models as backbones has shown to be successful for improving both effectiveness and efficiency in medical image computing tasks [52], [53], [54]. In our work, given the large number of registration subnetworks and the limit of GPU memory, it is difficult to train all U-net models at the same time. To handle this, we propose to pretrain the U-net model for each tract-specific registration subnetwork (as illustrated in Fig. 2). Specifically, given each tract-specific TOM^i, we pretrain the corresponding U-net model with a loss function based on only the TOM data:

$$\begin{aligned} L_{tract}(f, m, \phi) = & \lambda_{TOM} L^i_{TOM} + \\ & \lambda_{smooth} L_{smooth}(\phi^i_{tract}) \end{aligned} \tag{2}$$

where L^i_{TOM}, L_{smooth}, λ_{TOM} and λ_{smooth} are the same as in Eq. (1). These pretrained U-net models are then used as backbones to compute tract-specific deformation fields in our overall network.

For training of the overall network, the model weights of the pretrained tract-specific registration subnetworks (the convolutional layers indicated using the gray rectangles in Figs. 1 and 2) are locked during backpropagation. However, the weights of the whole-brain registration subnetwork are not pretrained, and are updated during backpropagation. In this way, the whole-brain registration subnetwork training can benefit from the local tract alignment information.

2.5 Implementation and Parameter Settings

Our method is implemented using Pytorch (v1.7) [55] based on the existing VoxelMorph implementation[1]. Adam [56] is used for optimization with a learning rate of 10-4 as suggested in VoxelMorph [48]. For the overall network and each tract-specific backbone subnetwork, we train the model using a total of 50,000 batches (sufficient for achieving training and validation loss convergence), where each batch consists of one pair of input volumes. For the weighting parameters, we set $\lambda_{FA} = 1$, $\lambda_{TOM} = 1$, and $\lambda_{smooth} = 0.01$, following the suggested settings for image registration (using MSE) and smoothing weighting parameters in the VoxelMorph package. Our unpublished parameter tuning experiments on a subset of the datasets (10 datasets) confirm that the selected parameter settings give in general the best registration performance.

3 Experimental Datasets

We demonstrate our method using dMRI datasets from 100 subjects (age: 29.1 $\pm$ 3.7 years; gender: 54 females and 46 males) in the Human Connectome Project (HCP) [57]. We split the dataset into three parts: 50 subjects for training, 20 subjects for validation, and 30 subjects for testing.

The dMRI data acquisition parameters are TE = 89.5 ms, TR = 5520 ms, phase partial Fourier = 6/8, voxel size = 1.25 $\times$ 1.25 $\times$ 1.25 mm^3, and matrix = 145 $\times$ 174 $\times$ 145. A total of 288 images were acquired for each subject, including 18 baseline images and 270 diffusion weighted images evenly distributed at three shells of b = 1000/2000/3000 s/mm^3. The dMRI data provided by HCP was processed following the well-designed HCP minimum processing pipeline [57], which includes brain masking, motion correction, eddy current correction, EPI distortion correction, and rigid registration to the MNI space. We cropped each dMRI dataset to 128 $\times$ 160 $\times$ 128 voxels to fit to our network input size, while ensuring coverage of the entire brain.

From each dMRI dataset, we compute the following data that is needed as input to our proposed method as well as other comparison methods (see Section 4). We first compute diffusion tensor images using a least squares estimation, followed by computation of the FA image from the tensor image, using the SlicerDMRI extension[2] [58], [59] in 3D Slicer[3]. We also calculate multi-shell multi-tissue constrained spherical deconvolution (CSD) data, followed by FOD peak extraction with a maximum number of three peaks per voxel, using MRtrix[4] [60], [61]. The extracted FOD peaks are subsequently provided to TractSeg[5] to compute TOMs of 72 white matter tracts [47]. In our method, to

1. https://github.com/voxelmorph/voxelmorph
2. dmri.slicer.org
3. www.slicer.org
4. www.mrtrix.org
5. github.com/MIC-DKFZ/TractSeg

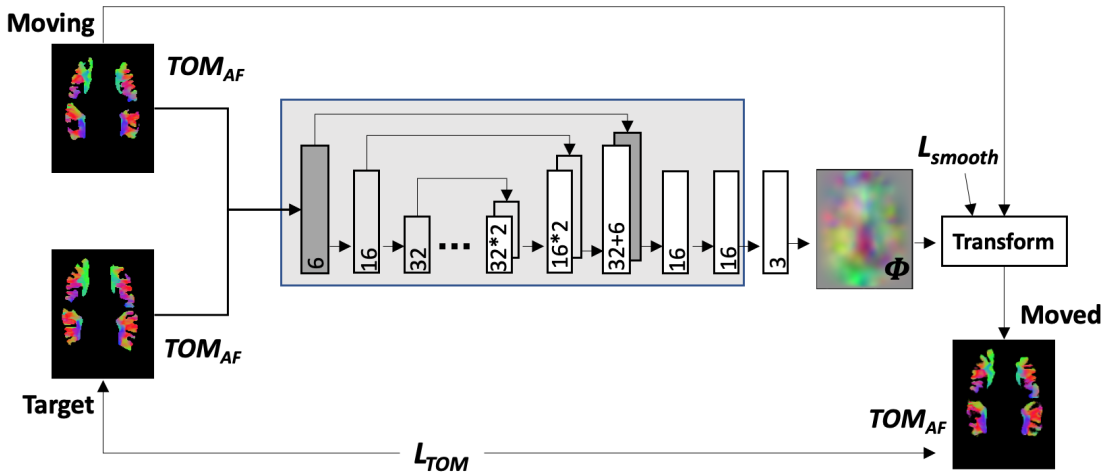

Fig. 2. Pretraining tract-specific backbone subnetwork. After pretraining, the weights of the convolutional layers (in gray rectangle) are directly used in the overall network (Fig. 1) as a backbone to compute the tract-specific deformation field.

reduce the number of TOMs while keeping all fiber orientation information, we combine bilateral tracts (e.g., the left and right arcuate fasciculus tracts) into one TOM. In total, this produced 40 TOMs (see Supplementary Table S1 for the list of TOMs).

For evaluation purposes (see Section 4.1 for details of the evaluation metrics), we compute the binary segmentation mask of each white matter tract [62]. We also perform tractography on the TOMs to compute fiber streamlines for each tract [47]. The masks and streamline tractography are computed using TractSeg with the default parameters suggested by the software. In addition, we also compute a tissue segmentation of the entire brain into WM, GM and CSF from the dMRI data using a deep learning method [63].

4 Experimental Comparisons and Evaluation Metrics

We perform two experimental evaluations. First, we assess the effectiveness of the proposed dMRI registration framework. Second, we compare the proposed method to four state-of-the-art dMRI registration methods. In the rest of the section, we introduce evaluation metrics used in these experiments (Section 4.1), followed by the details of the experimental comparisons (Sections 4.2 and 4.3).

4.1 Evaluation Metrics

We first evaluate the dMRI registration methods by assessing their performance on aligning anatomically corresponding brain structures across different subjects. To this end, we quantify the volumetric overlap of segmented brain structures between moved and target subjects (currently one of the most widely used evaluation metrics in medical image registration tasks [48], [50]). The volumetric overlap is computed using the well-known Dice score [48], [50], [64], which ranges from 0 to 1; a higher value means better overlap. First, we evaluate the volume overlap of each white matter tract by computing the Dice overlap score of the binary tract segmentation masks between the moved and target subjects. Next, we evaluate the volume overlap of the tissue segmentations (i.e., GM, WM, and CSF) of the entire brain. The Dice overlap score is computed for each tissue type to evaluate the performance. In the rest of the paper, we refer to these two metrics as *tract Dice score* and *tissue Dice score*.

Finally, in order to assess fiber spatial alignment, we include an evaluation using the geometric distances between fiber streamlines after registration. We use a metric based on pairwise fiber streamline distances, as proposed in several other studies on dMRI registration [11], [14], defined as follows:

$$\frac{1}{|M|+|T|}\Big(\sum_{f_m \in M} \min_{f_t \in T} d(f_m, f_t) + \sum_{f_t \in T} \min_{f_m \in M} d(f_m, f_t)\Big) \tag{3}$$

where M and T are the moved and target fiber tracts, d is the mean closest point fiber distance [7], [65] between two fibers in M and T, $\min_{f_t \in T} d(f_m, f_t)$ is the distance between the fiber f_m and the fiber in T that is closest to f_m, and, similarly, $\min_{f_m \in M} d(f_m, f_t)$ is the distance between the fiber f_t and the fiber in M that is closest to f_t. In the rest of the paper, we refer to this metric as *tract distance*. A lower tract distance represents a better spatial tract alignment.

4.2 Evaluation of the DDMReg Architecture

We first perform several ablation studies [66] to evaluate the effects of inclusion or exclusion of the proposed tract-specific backbone registration subnetworks. We compare the proposed method with two baseline methods that do not use any tract-specific subnetworks. The first method registers only the FA image (referred to as Reg_{FA}). Reg_{FA} uses the same U-net architecture as our whole-brain registration subnetwork, with a loss function that optimizes the MSE of FA and the smoothness of the deformation field (i.e., $L_{FA}(f, m, \phi) = \lambda_{FA} L_{FA} + \lambda_{smooth} L_{smooth}(\phi_{wb})$). The second baseline method uses both FA and TOM images (referred to as Reg_{FA+TOM}). The same U-net architecture as in Reg_{FA} is used, but with a different loss function that includes an additional component to optimize the MSE of TOMs (i.e., $L_{FA+TOM}(f, m, \phi) = \lambda_{FA} L_{FA} +$

$\lambda_{TOM}\frac{1}{n}\sum_i^n L_{TOM}^i + \lambda_{smooth}L_{smooth}(\phi_{final})$). We use the same number of training batches and the same settings of the weighting parameters as our proposed method (see Section 2.5).

We then assess the performance when including different numbers of tract-specific backbone registration subnetworks. In this experiment, we compare DDMReg (40 backbone subnetworks) with three additional methods that include only one randomly selected backbone subnetwork, three randomly selected backbone subnetworks, and twenty randomly selected backbone subnetworks (half of the total number of backbone networks). Here we also compare results to the Reg_{FA} method, which serves as a reference baseline method without any tract-specific backbone subnetworks.

For each of the methods above and each evaluation metric, we report the mean and the standard deviation across all pairs of the 30 testing subjects (thus 435 pairs). A one-way repeated measures analysis of variance (ANOVA) is performed across the three methods for each evaluation metric, followed by a post-hoc paired t-test and effect size analysis (using Cohen's d [67]) between each pair of the methods. In the assessment of different numbers of tract-specific backbones, we also separately report the mean tract Dice score and the mean tract distance for the tracts that are included or not included.

4.3 Comparison to State-of-the-Art Methods

We compare our proposed DDMReg method to four state-of-the-art dMRI registration methods, which are referred to as the *SyN* [51], *DTI-TK* [11], *MRRegister* [33], and *VoxelMorph* [48] methods in the rest of the paper. For parameters involved in each of these compared methods, we use the default values as suggested in their software.

The SyN method performs registration by optimizing a cross correlation similarity measure between scalar images [51] and it has been shown to be successful in several comparative studies [14], [68]. In particular, for dMRI registration, applying SyN on FA images has shown good registration performance (the second-ranked method across six compared methods [14].) In our study, we use the SyN implementation available in Advanced Normalization Tools (ANTs) [69].

The DTK-TK method performs dMRI registration based on the diffusion tensor images, with the aim of optimizing the L2 inner product distance between the tensors [11]. In two comparative studies for dMRI registration [14], [70], DTK-TK achieved the best performance (including the aforementioned study where the SyN method ranked second [14].) In our study, we use the DTK-TK implementation available in the Diffusion Tensor Imaging ToolKit[6].

The MRRegister method is a more recently proposed method that performs dMRI registration using FODs [33]. MRRegister optimizes a diffeomorphic non-linear transformation model based on the mean squared difference and cross-correlation of the FOD spherical harmonic coefficients. In our study, we use the implementation available in MRtrix [71].

6. http://dti-tk.sourceforge.net/pmwiki/pmwiki.php

The VoxelMorph method is a deep learning method that learns a deformation field between pairs of images [48]. VoxelMorph is not designed specifically for dMRI registration and there has been no previous evaluation on dMRI data. Therefore, we test different combinations of inputs (see Supplementary Fig. S1) and choose the best performing input (i.e., FA) for use in this experiment. In addition, it is suggested in [48] that auxiliary information in the form of anatomical segmentations can be used for VoxelMorph registration improvement. (This is done by optimizing the Dice score of the segmentations [48].) For a complete VoxelMorph comparison, we therefore include an additional auxiliary loss for optimizing the Dice overlap score of the segmentations of the 40 white matter tracts. The implementation available in the VoxelMorph package is used.

For experimental comparison, we report the mean and the standard deviation across all testing subject pairs for each evaluation metric. ANOVA, followed by a paired t-test and effect size analysis (using Cohen's d) between each pair of compared methods, are used for statistical comparison. In addition, to evaluate the regularity of the deformation fields, we compute the Jacobian determinant of the deformation field of each testing image pair (as used in multiple related studies [48], [72], [73]), and we report the mean percentage of voxels with a non-positive Jacobian determinant across all testing image pairs for each method. For each compared method, we also report the computational time for data preprocessing to prepare the method input and that for registering the image pair to estimate the deformation field.

We note that our DDMReg is an ensemble learning method, which enables estimation of uncertainty [74] given the deformation fields from the registration subnetworks. Uncertainty estimates can provide intuitive information about the quality of image registration [75]. To quantify registration uncertainty, for each voxel we compute the covariance matrix of the estimated displacement vectors (a 3×3 matrix) across the 40 tract-specific deformation fields. For visualization of the uncertainty, we calculate the mean of the square root of the diagonal values of the covariance matrix for each voxel. A lower value indicates higher agreement across the registration fields and thus high registration certainty.

5 Experimental Results

5.1 Evaluation of the DDMReg Architecture

As shown in Fig. 3, using only FA for registration (i.e., Reg_{FA}) generated the lowest mean tract Dice score, the lowest mean tissue Dice score, and the highest tract distance (0.732, 0.710, and 4.637 mm, respectively) after registration. Adding an additional loss component to penalize differences of the TOMs (i.e., Reg_{FA+TOM}) improved these evaluation metrics (0.755, 0.733, and 4.172 mm, respectively). Further including the tract-specific backbone registration subnetworks ($\text{Reg}_{Proposed}$) achieved the best results (0.772, 0.734, and 3.947mm, respectively). For each of the evaluation metrics, the ANOVA analysis showed a significant difference in the three-method comparison ($p < 0.001$), where $Reg_{Proposed}$ had significantly better results than the other two methods ($p < 0.001$ and Cohen's $d > 1$). See

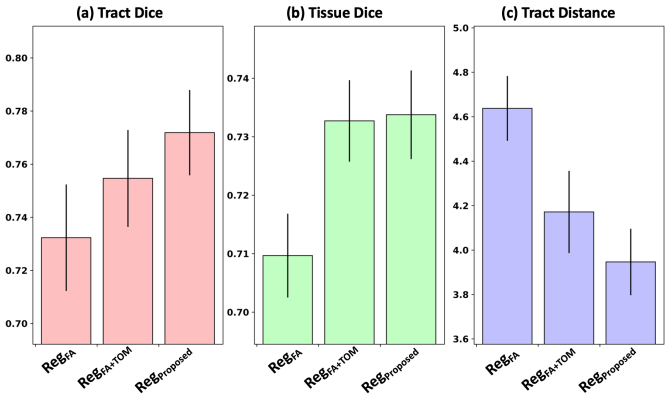

Fig. 3. Comparison between different network inputs and different loss functions.

Supplementary Table S2 for detailed statistical comparison results. The detailed evaluation metrics for each tract and each tissue are provided in Supplementary Fig. S2.

Fig. 4 shows the comparison using different numbers of tract-specific backbone registration subnetworks. From subfigures 4(a) to 4(c), we can observe that including more backbones increased the registration performance. Compared to the method that does not use any backbones, including all backbones (n = 40) increases the tract Dice score by 0.396, the tissue Dice score by 0.241, and decreases the tract distance by 0.691 mm. In addition, from subfigures 4(d) and 4(e), we can observe that including more backbone tracts increased the performance on registering the tracts that were not included during training.

5.2 Comparison to State-of-the-Art Methods

As shown in Fig. 5, for tract-based evaluation metrics (tract Dice score and tract distance), VoxelMorph (0.732 and 4.637 mm) generated the least favored performance, followed by the SyN (0.740 and 4.417), DTI-TK (0.745 and 4.089mm), and MRRegister methods (0.764 and 4.637mm), while the proposed DDMReg method obtained the best results (0.772 and 3.947mm). For the tissue segmentation metric, DDMReg also generated the highest Dice score (0.734), while VoxelMorph (0.710) obtained a better result than the SyN (0.698), DTI-TK (0.682) and MRRegister (0.701) methods. For each of the evaluation metrics, the ANOVA analysis showed a significant difference in the five-method comparison ($p < 0.001$), where DDMReg had significantly better results than the other four compared methods ($p < 0.001$ and Cohen's $d \geq 0.9$). See Supplementary Table S3 for detailed statistical comparison results. The detailed evaluation metrics for each tract and each tissue are provided in Supplementary Fig. S3.

Fig. 6 gives a visualization of registration results for each of the compared methods. All methods generate visually good results to align the two brains, while we can observe differences in local regions. As shown in the inset images that render the anterior part of the anterior thalamic radiation (ATR) tract, VoxelMorph and DDMReg obtain visually more similar results to the target image than the SyN, DTI-TK and MRRegister methods.

Fig. 7 gives a visualization result of the proposed DDMReg method, including the FA images, the estimated deformation field, and the registration uncertainty map. We can observe a good spatial alignment of the FA images after registration. For example, the sizes of the brains (more apparent in the axial view), the shapes of the lateral ventricle (red arrows in the coronal view), and the shapes of the corpus callosum (green arrows in the sagittal view) are highly visually similar between the target and the moved images. The deformation field is visually smooth, showing a regular, smooth displacement after registration. (We refer the readers to Fig. 10 in [48] for a visualization of regular and irregular deformation fields.) The deformation field and uncertainty map show no tract-specific effects (e.g., no particular tract regions showing high uncertainty), even though our tract-specific registration subnetworks register based on individual tracts only. As expected, the uncertainty is generally highest near the cortex, where anatomical variability across subjects is greater, and lowest in the deep white matter.

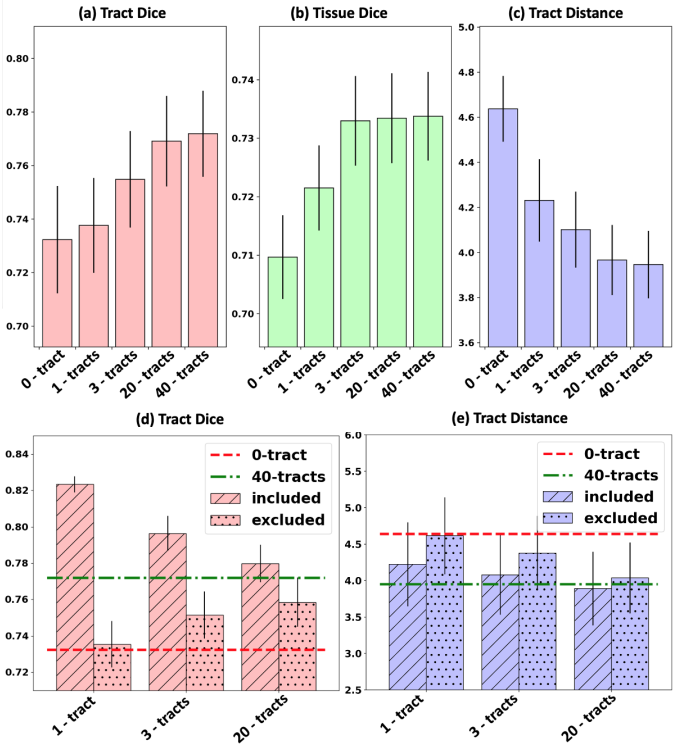

Fig. 4. Comparison across different numbers of backbone tracts.

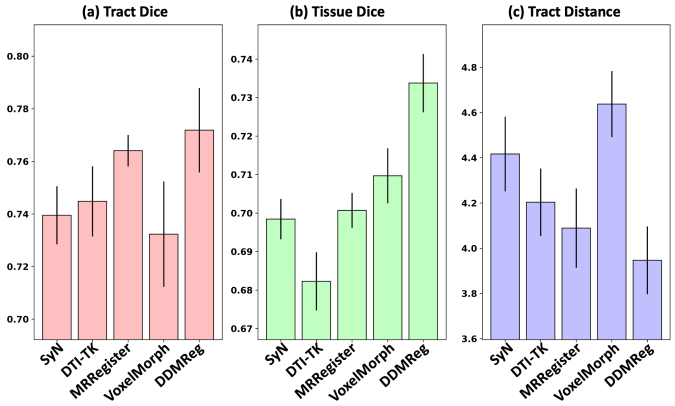

Fig. 5. Comparison to the state-of-the-art methods.

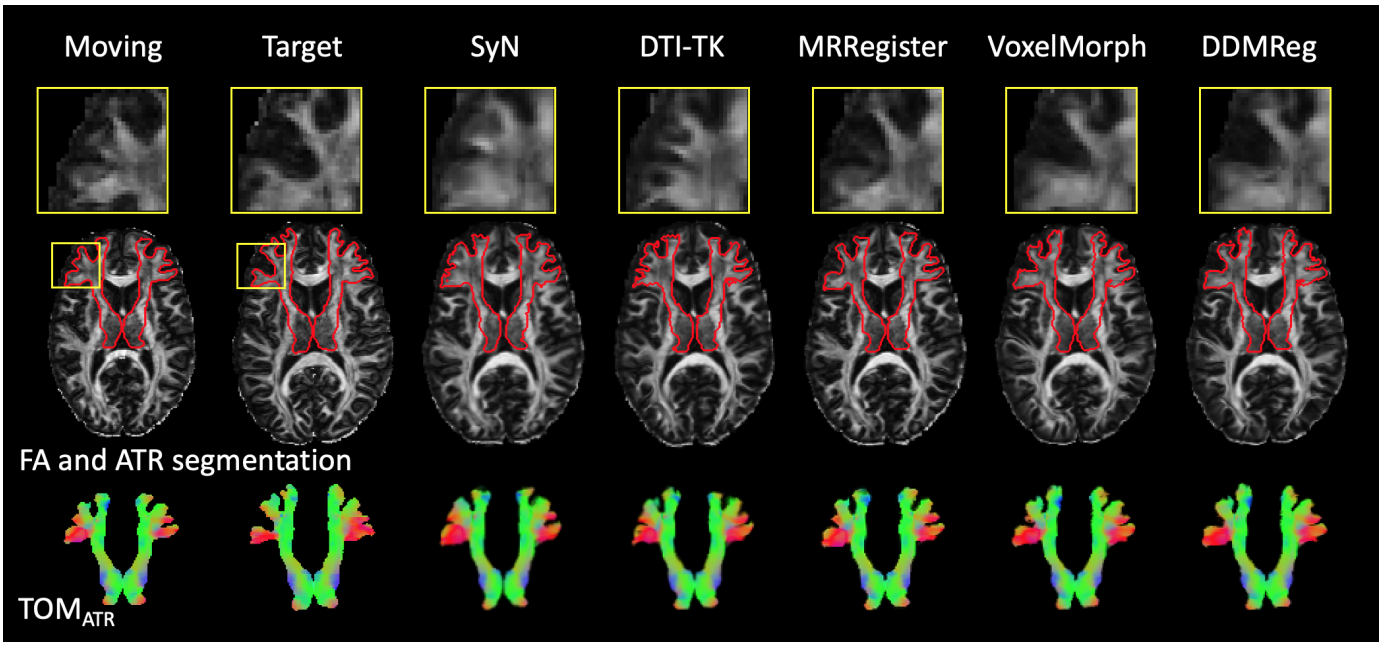

Fig. 6. Visualization of registration results for the compared state-of-the-art and our DDMReg method. One randomly selected example image pair is shown. The whole-brain FA image, plus an insert image that gives a zoomed-in visualization for a part of the Anterior Thalamic Radiation (ATR), are provided. The segmentation of ATR (overlaid on the FA image in red) and the TOM (shown in directionally encoded color [76]) of the entire ATR are also provided.

See Supplementary Fig. S4 for additional visualizations of registration results of the proposed method.

Jacobian determinant: For all methods except SyN, the percentage of voxels with a non-positive Jacobian determinant is 0%. The SyN has a very low percentage of 0.06%. This indicates that all methods produce good deformation regularity.

Runtime: Table 1 gives the computational time for registering a pair of example dMRI datasets for each method. The computation is performed on a Linux workstation, equipped with 8 DIMMs for CPU computation and 4 NVIDIA GeForce GTX 1080 Ti Graphics Cards for GPU computation. For each method, if multi-thread CPU computing is supported, we use 16 threads. The inputs to SyN, DTI-TK and VoxelMorph methods are based on DTI; thus these methods take a small amount of time for computing the input data. The MRRegister and DDMReg methods require the computation of CSD data and FOD peaks, which take a relatively long time. For registering the input data, the SyN, DTI-TK, and MRRegister methods are based on the traditional image registration strategy and can only use CPU computation; thus, they require a relatively long time to register. The VoxelMorph and our proposed DDMReg methods can leverage the GPU, thus highly reducing the computational time. We note that the computational time of VoxelMorph and DDMReg is also small when only using the CPU.

TABLE 1
Computational time (in seconds).

Method	CPU/GPU	Preprocess	Register
SyN	CPU	60s (FA)	350s
DTI-TK	CPU	60s (Tensor)	950s
MRRegister	CPU	1400s (FOD)	350s
VoxelMorph	CPU	60s (FA)	10s
	CPU+GPU		5s
DDMReg	CPU	1800s (FA+FOD+TOM)	80s
	CPU+GPU	1600s (FA+FOD+TOM)	10s

6 Discussion

In this work, we have proposed the first deep learning method for dMRI registration, DDMReg, that enables fast and accurate registration of dMRI data. DDMReg is a fully unsupervised method for deformable registration between pairs of dMRI datasets. We proposed a novel registration architecture that leverages not only whole brain information but also tract-specific fiber orientation information. We compared DDMReg to several state-of-the-art methods, and we showed highly improved registration performance. Below, we discuss several detailed observations about the experimental results.

We designed a novel network architecture for dMRI registration, which enables the ensemble of multiple registration subnetworks trained on different types of input data. Our proposed network is in principle an ensemble learning method, where the outputs of a set of separately trained CNNs are combined to form one unified prediction [77]. Ensemble learning has been shown to be highly successful in many deep learning tasks [78], [79], [80]. In our method, we leveraged the successful U-net-based registration architecture proposed in VoxelMorph [48], which was found to be highly effective for registration of individual types of input data (either FA or TOM). Then, based on our recently

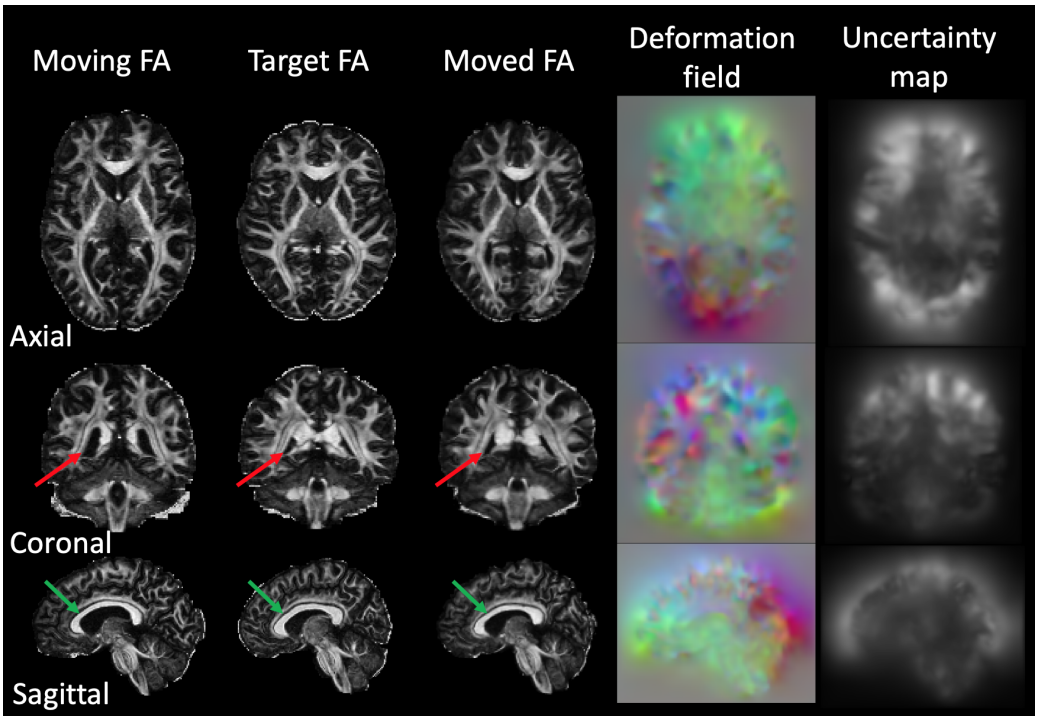

Fig. 7. Visualization of registration results of the proposed DDMReg method, including the FA images, the deformation field and the registration uncertainty map. The red and green arrows indicate the lateral ventricle and the corpus callosum.

proposed dual-stream network that demonstrated success to combine two deformation fields for multimodal image registration [50], our proposed multi-deformation fusion subnetwork combined the outputs of the multiple U-net registration subnetworks. This enabled training the overall network in such a way that the registration subnetworks constrained each other, while cooperating to optimize for a unified registration deformation field. In our experiments, we demonstrated that the ensemble of the whole-brain and the tract-specific registration subnetworks achieved reciprocal advantages to both types of the input data, i.e., improved performance on both whole-brain-wise (tissue Dice score) and tract-specific (tract Dice score and tract distance) evaluation metrics.

We demonstrated advantages by using pretrained backbone registration networks that enabled the usage of multiple registration subnetworks together. Pretrained backbones have been widely used in deep learning for medical image computing tasks and have been shown to improve both effectiveness and efficiency [52], [53], [54]. In our work, we leveraged pretrained backbones to reduce the computational burden, so that we were able to use a large number of U-nets (41 in our study) in the same network. Our results demonstrated that as the number of included pretrained backbones increased, the registration performance kept increasing. We highlight that our proposed pretrained backbone strategy can also enable inclusion of additional inputs, such as T1w, T2w and functional MRI, for registration using multimodal imaging information.

Our method benefited from the unique tract-specific fiber orientation information encoded in the TOM. TOMs have been shown to be successful for tract-specific tractography [47], demonstrating their ability to encode fiber geometric information. Our results showed that including TOMs for dMRI registration greatly improved spatial tract alignment between different subjects after registration. In addition, each voxel in a TOM has only one FOD peak specific to the fiber orientation from a certain white matter tract. Due to this, TOMs are able to unambiguously model crossing fibers (where multiple white matter tracts with different fiber orientations are present within the same voxel). This has two main advantages. First, using TOMs can improve registration in the crossing fiber regions that are widespread in the white matter anatomy. Second, using TOMs can solve the problem that the FOD peak correspondence across subjects is not known when multiple FOD peaks are present in one voxel.

We demonstrated advanced dMRI registration performance compared to several state-of-the-art methods. DTI-TK and SyN are widely used and have been shown to be successful in two comparative studies [14], [68]. The SyN method takes as input the FA, which measures water diffusion anisotropy but not any water diffusion orientation information. DTI-TK uses the tensor map from DTI (from which FA is computed); thus it leverages both water diffusion anisotropy and orientation information. However, its performance is limited due to the fact that DTI can not adequately model the more complex crossing fiber configurations; thus it may be less effective for registration in the presence of crossing fiber regions. The MRRegister method achieves better performance than SyN and DTI-TK. One possible explanation for this improvement is the fact that the FOD data is used as input to MRRegister, which can better capture information about the orientation of multiple fibers in the presence of crossing fibers. VoxelMorph gets unfavorable results compared to SyN, DTI-TK and MRReg-

ister when comparing the two tract-specific metrics, but it overperforms these three methods when measuring the tissue overlap. This is potentially because VoxelMorph is not specifically designed for dMRI registration, but focuses more on the overall alignment of the two brains. The proposed DDMReg generates the best registration performance across all compared methods. On one hand, our method leverages the FA image that is useful to generally describe the whole brain for an overall alignment of the two brains. One the other hand, our method incorporates the TOMs that are effective to describe fiber orientation information, in particular in the presence of crossing fibers.

Potential limitations of the present study, including suggested future work to address limitations, are as follows. First, our proposed method performs a pair-wise registration between dMRI datasets. An interesting future investigation includes extending our method to enable groupwise registration for anatomical template creation. Second, in the present study, we used all TOMs that are available in TractSeg. We demonstrated that as the number of included TOMs increased the registration performance kept increasing. Therefore, it would be interesting to include additional TOMs that are not currently available in TractSeg. Third, currently the computation of a TOM is relatively time-consuming because of the computation of CSD and FOD peaks. A future investigation could include deep learning to perform CSD computation to further improve computational speed [81]. Fourth, currently, we demonstrated our method on HCP data; future investigation could include data from different sources for training and testing.

7 Conclusion

In this paper, we have presented a novel deep learning method to enable fast and accurate dMRI registration, *DDMReg*. Experimental results show that DDMReg achieved significantly improved registration accuracy compared to several state-of-the-art methods. In addition, DDMReg leverages the computational power of the GPU and provides a fast and efficient tool for dMRI registration.

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