

# Large Deformation Diffeomorphic Registration of Diffusion-Weighted Imaging Data

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## Abstract

Registration plays an important role in group analysis of diffusion-weighted imaging (DWI) data. It can be used to build a reference anatomy for investigating structural variation or tracking changes in white matter. Unlike traditional scalar image registration where spatial alignment is the only focus, registration of DWI data requires both spatial alignment of structures and reorientation of local signal profiles. As such, DWI registration is much more complex and challenging than scalar image registration. Although a variety of algorithms has been proposed to tackle the problem, most of them are restricted by the diffusion model used for registration, making it difficult to fit to the registered data a different model. In this paper we describe a method that allows *any* diffusion model to be fitted after registration for subsequent multifaceted analysis. This is achieved by directly aligning DWI data using a large deformation diffeomorphic registration framework. Our algorithm seeks the optimal coordinate mapping by simultaneously considering structural alignment, local signal profile reorientation, and deformation regular-

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ization. Our algorithm also incorporates a multi-kernel strategy to concurrently register anatomical structures at different scales. We demonstrate the efficacy of our approach using *in vivo* data and report detailed qualitative and quantitative results in comparison with several different registration strategies.

*Keywords:* diffeomorphism, diffusion-weighted imaging, image registration, signal profile reorientation, explicit orientation optimization

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## 1. Introduction

Diffusion-weighted imaging (DWI) is widely used to non-invasively study white matter microstructure and fiber tracts in the human brain. The information provided by DWI is helpful for identifying pathological damages associated with brain diseases (*e.g.*, stroke [1], Alzheimer’s disease [2, 3, 4, 5], and schizophrenia [6]) and brain changes associated with normal development [7].

To quantify white matter changes, a common space is required where images of patients and healthy controls can be spatially normalized and compared. Image registration is used to build such space and to spatially normalize the images by warping them to the space.

Traditional scalar image registration techniques are not directly applicable to diffusion-weighted images. When diffusion-weighted images corresponding to different diffusion gradient directions are put together, each voxel location encodes a vector-valued signal profile that provides information on the segment of the fiber bundle that traverses the voxel. As such, registration of diffusion-weighted images requires not only the spatial alignment of anatomical structures, as in scalar image registration, but also the reorientation of signal profiles with respect to the surrounding anatomical structures, which is not considered in scalar image reg-

istration. DWI registration is thus much more complicated and challenging than scalar image registration.

A common approach to registering diffusion-weighted images is to fit some diffusion model to the images to estimate angular quantities, such as orientation distribution functions (ODFs), and then incorporate such information into a registration algorithm for structural alignment. There are a number of choices of diffusion models as well as registration algorithms, leading to a variety of DWI registration methods.

Early work uses the relatively simple diffusion tensor model [8, 9, 10, 11, 12, 13]. Alexander *et al.* [8] introduced the preservation of principal direction (PPD) algorithm for the reorientation of diffusion tensors during image alignment. Instead of PPD, Yeo *et al.* [10] used a finite strain reorientation strategy [8] together with a diffeomorphic demons algorithm [14] for registration. Zhang *et al.* [13] broke down the image into uniform regions and estimated an affine transformation for each region by explicitly optimizing tensor orientation within that region. Cao *et al.* [9] proposed a large deformation diffeomorphic metric mapping (LDDMM) algorithm [15] to tackle large-deformation non-linear registration of directional vector fields.

However, the diffusion tensor model can only characterize one principal fiber direction at each voxel and thus is unable to handle complex fiber configurations such as crossings. It has been found that at least one third of voxels in white matter have complex fiber configurations [16]. Obviously, failure to reorient the signal profiles in those voxels will lead to misalignments of microstructure.

To deal with crossing fibers, a number of researchers [17, 18, 19, 20, 21, 22, 23] attempted to use more complicated diffusion models. Geng *et al.* [17] aligned ODFs

represented by spherical harmonics (SHs) using an elastic registration algorithm. Du *et al.* [18] integrated a similarity metric for the ODFs, which is defined in a Riemannian manifold, into a variant of LDDMM algorithm [24]. Yap *et al.* [21] extracted coarse-to-fine features from the ODFs for hierarchically refined alignment. Instead of using ODFs, Hong *et al.* [19] performed registration with the help of  $T_2$ -weighted images and subsequently reoriented the fiber orientation distribution (FOD). Raffelt *et al.* [20] registered DWI data by mapping the FODs through a subject-template-symmetric diffeomorphic framework.

However, the aligned data generated by the above approaches are not in the form of diffusion-weighted images. The ability to produce diffusion-weighted images as final registration outcome is important for common-space analysis using diffusion models without well-defined warping and reorientation methods.

To overcome this problem recent studies propose to register DWI data directly in the  $Q$ -space [22, 23]. Dhollander *et al.* [22] tackled the problem by virtue of an SH-based reorientation algorithm together with a diffeomorphic demons algorithm [14]. In [23] we achieved a similar goal by using a set of diffusion basis functions (DBFs) [25] and a geodesic shooting algorithm simplified reported in [26]. Both methods regard spatial alignment and local signal profile reorientation as two separate components, and perform optimization by alternating between (i) computing the spatial mapping without considering reorientation, and (ii) reorienting the data using the resulting mapping. Although this strategy is simple, it ignores the crucial role reorientation plays in correspondence establishment.

As shown in [10], a better but more complicated strategy is to integrate the two components into a single cost function and explicitly take into account reorientation during registration. In this paper we describe a method that is able to

register DWI data in the  $Q$ -space in a single framework where image matching, data reorientation, and deformation regularization are considered simultaneously. Part of this work has been reported in our recently published conference paper [27]. Herein, we provide additional derivations, implementation details, and experimental results that are not available in the conference version. Compared with [27], the current work uses a more general symmetric tensor model, instead of Watson distribution, as the DBFs [25]. In addition, the cost function is reformulated such that the solution satisfies the Euler-Lagrange equation.

## 2. Outline of the Approach

Our method consists of two components: (1) DWI data reorientation (Section 3) and (2) an LDDMM-based registration algorithm (Section 4). The first component achieves reorientation in the  $Q$ -space while the second one provides a registration framework where alignment and reorientation are considered simultaneously.

The first component is realized based on the work of Yap and Shen [25], where reorientation is achieved by three steps: (i) decomposing the diffusion signal profile into a set of weighted DBFs; (ii) reorienting each DBF independently using a local transformation; (iii) recomposing the reoriented DBFs to obtain the desired profile. Compared with the SH-based reorientation scheme as used in [22], this strategy avoids the computational complexity of SHs as well as the loss of sharp directional information when the maximum order of the SH basis functions is insufficient (see [25] for detailed discussion).

The second component involves the LDDMM algorithm [15]. Based on the spatial mapping estimated by the LDDMM algorithm, a Jacobian matrix can be computed at each voxel location and used for DBF reorientation. The interaction

between the two components is mathematically expressed as a single cost function (Section 4) and, during optimization, spatial alignment and local reorientation are considered simultaneously.

To simultaneously register anatomical structures at different scales we use a multi-kernel strategy [28]. This is to introduce a natural multi-resolution property to our registration algorithm and to provide an intuitive way of parameter tuning based on the desired scales that should be captured by the registration. Details are given in Section 5.1.

This work has three major contributions. First, we propose a non-rigid registration algorithm for direct registration of DWI data. This allows *any* diffusion model to be fitted to the aligned data for subsequent multifaceted analysis. Second, we incorporated spatial alignment and local reorientation into a single cost function. In contrast to [22] and [29], our method does not rely on multi-shell data, which require long acquisition time. Last but not least, we derive the gradient of the cost function and describe in detail the numerical implementation.

### 3. Reorientation of DWI Data

We now briefly review the major concepts involved in reorientation using DBFs [25].

#### 3.1. Decomposition of Signal Profile

Let  $S(\mathbf{q}_i)$  be the diffusion signal measured in direction  $\mathbf{q}_i$  ( $i = 1, \dots, M$ ). It can be represented by a set of  $N$  DBFs:

$$S(\mathbf{q}_i) = w_0 f_0 + \sum_{j=1}^N w_j f(\mathbf{q}_i | \lambda_1, \lambda_2, \boldsymbol{\mu}_j),$$

where  $f(\mathbf{q}_i|\lambda_1, \lambda_2, \boldsymbol{\mu}_j)$  is the  $j$ -th DBF,  $w_j$  is the associated weight, and  $f_0$  is a constant component representing isotropic diffusion. Specifically, the  $j$ -th DBF is defined by

$$f(\mathbf{q}_i|\lambda_1, \lambda_2, \boldsymbol{\mu}_j) = \exp(-b\mathbf{q}_i^T \mathbf{D}_j \mathbf{q}_i), \quad (1)$$

where  $b$  is the diffusion weighting and  $\mathbf{D}_j = (\lambda_1 - \lambda_2)\boldsymbol{\mu}_j\boldsymbol{\mu}_j^T + \lambda_2\mathbf{I}$  is a symmetric diffusion tensor.  $\lambda_1$  and  $\lambda_2$  control the shape of the tensor,  $\{\boldsymbol{\mu}_j\}$  is a pre-defined set of tensor principal directions and  $\mathbf{I}$  is an identity matrix representing an isotropic tensor. We generated  $\{\boldsymbol{\mu}_j\}$  via spherical tessellation by subdividing the faces of an icosahedron.

If  $\lambda_1 \gg \lambda_2$ ,  $\mathbf{D}_j$  can be approximated by  $\lambda_1\boldsymbol{\mu}_j\boldsymbol{\mu}_j^T$ . Then, we have

$$f(\mathbf{q}_i|\lambda_1, \lambda_2, \boldsymbol{\mu}_j) \approx \exp\left(-b\lambda_1(\boldsymbol{\mu}_j^T \mathbf{q}_i)^2\right),$$

which is essentially the p.d.f. of the Watson distribution [30]. This simplified model has been used in our previous work [23, 27]. In this work we use the more general model (1).

Let  $\mathbf{S}$  be the signal vector, then we have  $\mathbf{S} = \mathbf{F}\mathbf{w}$ , where  $\mathbf{S} = [S(\mathbf{q}_1), S(\mathbf{q}_2), \dots, S(\mathbf{q}_M)]^T$ ,  $\mathbf{w} = [w_0, w_1, \dots, w_N]^T$ , and

$$\mathbf{F} = \begin{bmatrix} f_0 & f(\mathbf{q}_1|\lambda_1, \lambda_2, \boldsymbol{\mu}_1) & \cdots & f(\mathbf{q}_1|\lambda_1, \lambda_2, \boldsymbol{\mu}_N) \\ \vdots & \vdots & \ddots & \vdots \\ f_0 & f(\mathbf{q}_M|\lambda_1, \lambda_2, \boldsymbol{\mu}_1) & \cdots & f(\mathbf{q}_M|\lambda_1, \lambda_2, \boldsymbol{\mu}_N) \end{bmatrix}.$$

Since typically,  $M < N + 1$ , this is a set of under-determined linear equations, which can be solved by an  $L_1$ -regularized least-squares solver with a non-negative constraint (see [25] for details).

### 3.2. Reorientation of Signal Profile

At each voxel, a local affine transformation  $\mathbf{A}$  is used to reorient the directions of the DBFs, *i.e.*  $\boldsymbol{\mu}'_j = \mathbf{A}\boldsymbol{\mu}_j / \|\mathbf{A}\boldsymbol{\mu}_j\|$ .  $\mathbf{A}$  is estimated locally from a typically non-linear mapping and hence varies spatially. The reoriented DBF matrix,  $\mathbf{F}'$ , is calculated based on  $\boldsymbol{\mu}'_j$  as follows

$$\mathbf{F}' = \begin{bmatrix} f_0 f\left(\mathbf{q}_1 \left| \lambda_1, \lambda_2, \frac{\mathbf{A}\boldsymbol{\mu}_1}{\|\mathbf{A}\boldsymbol{\mu}_1\|} \right. \right) \cdots f\left(\mathbf{q}_1 \left| \lambda_1, \lambda_2, \frac{\mathbf{A}\boldsymbol{\mu}_N}{\|\mathbf{A}\boldsymbol{\mu}_N\|} \right. \right) \\ \vdots \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \ddots \qquad \qquad \qquad \qquad \qquad \qquad \qquad \vdots \\ f_0 f\left(\mathbf{q}_M \left| \lambda_1, \lambda_2, \frac{\mathbf{A}\boldsymbol{\mu}_1}{\|\mathbf{A}\boldsymbol{\mu}_1\|} \right. \right) \cdots f\left(\mathbf{q}_M \left| \lambda_1, \lambda_2, \frac{\mathbf{A}\boldsymbol{\mu}_N}{\|\mathbf{A}\boldsymbol{\mu}_N\|} \right. \right) \end{bmatrix}.$$

The orientation-rectified signal profile is then computed as  $\mathbf{S}' = \mathbf{F}'\mathbf{w}$ . Note that the isotropic component is not reoriented.

## 4. LDDMM-based DWI Registration

LDDMM techniques [15, 31, 32, 26] are designed for diffeomorphic registration when the object of interest undergoes large shape variation. Initially formulated for scalar image registration [15], it was later extended for registering vector fields [33]. In this work, we further extend it for DWI registration.

Let  $I_0$  be the source image and  $I_1$  be the target image. The goal of the LDDMM algorithm is to minimize the following cost function

$$E(\mathbf{v}) = \frac{1}{2} \int_0^1 \|\mathbf{v}_t\|_V^2 dt + \frac{1}{\sigma^2} \|I_0 \circ \phi_{1,0} - I_1\|_{L^2}^2, \quad (2)$$

where  $\mathbf{v}_t$  is a time-dependent velocity field that needs to be estimated,  $\sigma > 0$  is a regularization constant, and  $\phi_{s,t}$  is a mapping induced by  $\mathbf{v}_t$ , transforming a voxel from its position at time  $s$  to its position at time  $t$  (*e.g.*,  $\phi_{1,0}(\mathbf{x})$  transforms a voxel at position  $\mathbf{x}$  at time 1 to its position  $\mathbf{y} = \phi_{1,0}(\mathbf{x})$  at time 0).  $\|\mathbf{v}_t\|_V^2 = \langle L^\dagger L \mathbf{v}_t, \mathbf{v}_t \rangle_{L^2}$ ,



where  $V$  is a Hilbert space in which the velocity field resides, *i.e.*  $\mathbf{v} \in L^2([0, 1], V)$  and  $L$  is a proper differential operator which, when appropriately chosen, guarantees a diffeomorphic solution [15]. Instead of realizing  $L$  directly, diffeomorphism can be achieved by defining a smoothing kernel  $K = (L^\dagger L)^{-1}$ . Here we use a multi-Gaussian kernel scheme [28] for simultaneous multi-scale registration.

Since our focus is on DWI registration, we further assume that  $I$  is a vector-valued image representing diffusion signal vector  $\mathbf{S}$  at each position  $\mathbf{x}$ , *i.e.*  $I(\mathbf{x}) \equiv \mathbf{S}(\mathbf{x})$ . We denote the  $i$ -th element of  $I(\mathbf{x})$  as  $I^i(\mathbf{x})$ . We define the action of a mapping  $\phi$  on  $I$  as

$$I \circ \phi = F_\phi W \circ \phi, \quad (3)$$

where  $W$  is a vector-valued weight image associated with  $I$ , containing a sparse weight vector  $\mathbf{w}$  at each  $\mathbf{x}$ , *i.e.*  $W(\mathbf{x}) \equiv \mathbf{w}(\mathbf{x})$ , and  $F_\phi(\mathbf{x})$  is a matrix-valued image containing the reoriented DBFs, with the voxel at  $\mathbf{x}$  given by

$$F_\phi(\mathbf{x}) = \begin{bmatrix} f_0 & f\left(\mathbf{q}_1 \middle| \lambda_1, \lambda_2, \frac{(D\phi(\mathbf{x}))^{-1}\boldsymbol{\mu}_1}{\|(D\phi(\mathbf{x}))^{-1}\boldsymbol{\mu}_1\|}\right) & \cdots & f\left(\mathbf{q}_1 \middle| \lambda_1, \lambda_2, \frac{(D\phi(\mathbf{x}))^{-1}\boldsymbol{\mu}_N}{\|(D\phi(\mathbf{x}))^{-1}\boldsymbol{\mu}_N\|}\right) \\ \vdots & \vdots & \ddots & \vdots \\ f_0 & f\left(\mathbf{q}_M \middle| \lambda_1, \lambda_2, \frac{(D\phi(\mathbf{x}))^{-1}\boldsymbol{\mu}_1}{\|(D\phi(\mathbf{x}))^{-1}\boldsymbol{\mu}_1\|}\right) & \cdots & f\left(\mathbf{q}_M \middle| \lambda_1, \lambda_2, \frac{(D\phi(\mathbf{x}))^{-1}\boldsymbol{\mu}_N}{\|(D\phi(\mathbf{x}))^{-1}\boldsymbol{\mu}_N\|}\right) \end{bmatrix},$$

where  $D\cdot$  is the Jacobian operator. From (3), we can see that  $\phi$  spatially transforms the sparse weights and reorients the DBFs via  $F_\phi(\mathbf{x})$ .  $W$  is computed by fitting the DBFs to the DWI data as described in Section 3.

To reflect reorientation, we rewrite the cost function (2) as

$$E(\mathbf{v}) = \frac{1}{2} \int_0^1 \|\mathbf{v}_t\|_V^2 dt + \frac{1}{\sigma^2} \|F_{\phi_{1,0}} W_0 \circ \phi_{1,0} - I_1\|_{L^2}^2, \quad (4)$$

where  $W_0$  is the weight image associated with  $I_0$ . By computing the variation of

$E(\mathbf{v})$  w.r.t.  $\mathbf{v}$ , the gradient of (4) can be obtained as

$$\begin{aligned}
(\nabla_{\mathbf{v}} E)_t = \mathbf{v}_t - \frac{2}{\sigma^2} K & \left( \int_{\Omega} |D\phi_{t,1}^{\mathbf{v}}| \sum_i^M (I_0^i \circ \phi_{t,0}^{\mathbf{v}} - I_1^i \circ \phi_{t,1}^{\mathbf{v}}) \times \right. \\
& \sum_j^N w_j \circ \phi_{t,0}^{\mathbf{v}} \text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) \times \left( \nabla_{\tilde{\boldsymbol{\mu}}_j} \left[ \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right] (D\phi_{t,1}^{\mathbf{v}} D((D\phi_{t,0}^{\mathbf{v}})^{-1})) \boldsymbol{\mu}_j \right)^{\text{T}} \mathbf{q}_i \, d\mathbf{x} \\
& + \frac{2}{\sigma^2} DK \left( \int_{\Omega} |D\phi_{t,1}^{\mathbf{v}}| \sum_i^M (I_0^i \circ \phi_{t,0}^{\mathbf{v}} - I_1^i \circ \phi_{t,1}^{\mathbf{v}}) \times \right. \\
& \sum_j^N w_j \circ \phi_{t,0}^{\mathbf{v}} \text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) \times \left( \nabla_{\tilde{\boldsymbol{\mu}}_j} \left[ \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right] (D\phi_{t,1}^{\mathbf{v}} (D\phi_{t,0}^{\mathbf{v}})^{-1}) \boldsymbol{\mu}_j \right)^{\text{T}} \mathbf{q}_i \, d\mathbf{x} \\
& \left. - \frac{2}{\sigma^2} K \left( \int_{\Omega} |D\phi_{t,1}^{\mathbf{v}}| \sum_i^M (I_0^i \circ \phi_{t,0}^{\mathbf{v}} - I_1^i \circ \phi_{t,1}^{\mathbf{v}}) \mathbf{b}_i^{\text{T}} D(W_0 \circ \phi_{t,0}^{\mathbf{v}}) \, d\mathbf{x} \right), \quad (5)
\end{aligned}$$

where

$$\begin{aligned}
\tilde{\boldsymbol{\mu}}_j &= (D\phi_{t,0}^{\mathbf{v}})^{-1} \boldsymbol{\mu}_j, \\
\text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) &= \exp \left\{ -b \left[ (\lambda_1 - \lambda_2) \left( \left( \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right)^{\text{T}} \mathbf{q}_i \right)^2 + \lambda_2 \right] \right\} \left( -2b(\lambda_1 - \lambda_2) \left( \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right)^{\text{T}} \mathbf{q}_i \right), \\
\mathbf{b}_i &= [f_0, b_{i1}, \dots, b_{iN}]^{\text{T}}, \\
b_{ij} &= f \left( \mathbf{q}_i \mid \lambda_1, \lambda_2, \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right),
\end{aligned}$$

$\Omega$  is a bounded domain in  $\mathbb{R}^d$  and  $\mathbf{x} \in \Omega$ . The detailed derivation is given in Appendix A.

Apart from  $\mathbf{v}_t$ , there are three other terms in (5). If no reorientation is involved, the first two terms will vanish and it is easy to show that (5) is equivalent to the gradient for scalar image registration as given in [15]. When reorientation is in effect, the first two terms contribute to updating  $\{\mathbf{v}_t\}$  by using mappings<sup>1</sup> estimated

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<sup>1</sup>The mappings at each iteration are generated by integrating  $\{\mathbf{v}_t\}$  over time. See Section 5.2 for details.

in the preceding iterations to reorient the directions of the DBFs. This reveals how spatial alignment and reorientation interact with each other. In contrast, spatial alignment and reorientation are regarded as two separate components in [22, 23].

## 5. Numerical Implementation Details

We now describe the numeric implementation details of our algorithm, including multi-Gaussian kernel, mapping computation, and gradient descent optimization.

### 5.1. Multi-Kernel Scheme

Instead of defining  $L$ , we follow the approach proposed by Risser *et al.* [28] to define a multi-Gaussian kernel  $K$  to achieve the desired smoothness. Specifically,  $K$  is realized by a set of weighted Gaussian kernels

$$K = \sum a_l \mathcal{N}(\mathbf{0}, \Sigma_l),$$

where  $a_l$  is the weight of the  $l$ -th Gaussian kernel and  $\Sigma_l$  is a diagonal covariance matrix defined by a scale factor  $\sigma_l$ , *i.e.*  $\Sigma_l = \sigma_l \mathbf{I}$ , where  $\mathbf{I}$  is an identity matrix.

To estimate  $a_l$  we need to perform a pre-registration step to estimate the maximum update of  $\mathbf{v}$  at each position  $\mathbf{x}$ , *i.e.*  $\tau_l = \max(\{\|\delta\mathbf{v}\| \mid \delta\mathbf{v} \text{ at } \forall \mathbf{x} \in \Omega\})$ , where  $\delta\mathbf{v}$  can be computed via (5) by setting  $\phi_{t,0} = \phi_{t,1} = \text{id}$ , where  $\text{id}$  is an identity mapping,  $\mathbf{v}_t = \mathbf{0}$ , and  $K = \mathcal{N}(\mathbf{0}, \Sigma_l)$ . Then  $a_l$  is calculated as the reciprocal of  $\tau_l$  and normalized such that  $\sum a_l = 1$ .

### 5.2. Mapping Computation

Suppose the time interval is  $[0, 1]$ , there are  $n$  time points  $\{t_p \mid p = 1, 2, \dots, n\}$  evenly distributed in this interval, *i.e.*  $t_p = p/n$  and the time point 0 is denoted by  $t_0$ .

To update the gradient using (5), we have to compute the forward mappings  $\{\phi_{t_p,1}\}$  and backward mappings  $\{\phi_{t_p,0}\}$  at each time point  $t_p$ . This can be obtained via a backward integration by assuming that  $\phi_{t_n,1} = \phi_{t_0,0} = \text{id}$ . Specifically, the forward mapping  $\phi_{t,1}$  and backward mapping  $\phi_{t,0}$  can be computed by concatenating a set of small mappings [26], *i.e.*

$$\begin{aligned}\phi_{t_p,1} &= \left(\text{id} + \frac{1}{n} \mathbf{v}_{t_{n-1-p}}\right) \circ \phi_{t_{p+1},1}, \\ \phi_{t_p,0} &= \phi_{t_{p-1},0} \circ \left(\text{id} - \frac{1}{n} \mathbf{v}_{t_{p-1}}\right),\end{aligned}$$

where  $\{\mathbf{v}_{t_p}\}$  is a series of velocity fields.

### 5.3. Gradient Descent

Once we have computed the gradient using (5), we can use any gradient descent algorithm to solve (4). In this work we use line search for gradient descent. A summary of the algorithm is given in Algorithm 1.

## 6. Experiments

DWI data were acquired from 11 adults using a Siemens 3T TIM Trio MR Scanner with an EPI sequence. Diffusion gradients were applied in 120 non-collinear directions with diffusion weighting  $b = 2000 \text{ s/mm}^2$ . The imaging matrix was  $128 \times 128$  with a field of view of  $256 \times 256 \text{ mm}^2$ . 80 contiguous slices with thickness of 2 mm covered the whole brain. A diffusion tensor model was fitted to the signal vector at each voxel, leading to a field of diffusion tensors. The eigenvalues corresponding to the principal eigenvectors were then computed for each tensor. By using a region of interest (ROI) defined at the corpus callosum, which is known to contain coherent single-orientation fiber bundles, we computed  $\lambda_1$  by averaging the eigenvalues

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**Algorithm 1** LDDMM-based DWI Registration

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**Input:**  $I_0, I_1, \{\mu_j\}, \{q_i\}, \lambda_1, \lambda_2, b, n, \{\sigma_l\}$  and  $\{\alpha\}$  (step size)

**Initialization:**  $\{\mathbf{v}_{t_p} | \mathbf{v}_{t_p} \leftarrow \mathbf{0}, \forall p\}$

1: estimate kernel weights  $\{a_l\}$

2: **repeat**

3:     **for each**  $p$  **do**

4:          $\phi_{t_p,1} \leftarrow (\text{id} + \frac{1}{n} \mathbf{v}_{t_{n-1-p}}) \circ \phi_{t_{p+1},1}$

5:          $\phi_{t_p,0} \leftarrow \phi_{t_{p-1},0} \circ (\text{id} - \frac{1}{n} \mathbf{v}_{t_{p-1}})$

6:     **end for**

7:     compute current energy  $E$  using (4)

8:     **for each**  $p$  **do**

9:         compute gradient  $(\nabla_{\mathbf{v}} E)_{t_p}$  using (5)

10:     **end for**

11:      $(E', \alpha) \leftarrow \text{LINESEARCH}(E, \{\mathbf{v}_{t_p}\}, \{\alpha\}, \{(\nabla_{\mathbf{v}} E)_{t_p}\})$

12:     **if**  $E' < E$  **then**

13:         **for each**  $p$  **do**

14:              $\mathbf{v}_{t_p} \leftarrow \mathbf{v}_{t_p} - \alpha(\nabla_{\mathbf{v}} E)_{t_p}$

15:         **end for**

16:     **end if**

17: **until**  $E' \geq E \vee \alpha = \inf\{\alpha\} \vee$  maximum number of iterations

18: **function**  $\text{LINESEARCH}(E, \{\mathbf{v}_{t_p}\}, \{\alpha\}, \{(\nabla_{\mathbf{v}} E)_{t_p}\})$

19:     **for each**  $\alpha$  **do**

20:         **for each**  $p$  **do**

21:              $\mathbf{v}'_{t_p} \leftarrow \mathbf{v}_{t_p} - \alpha(\nabla_{\mathbf{v}} E)_{t_p}$

22:         **end for**

23:         **for each**  $p$  **do**

24:              $\phi_{t_p,1} \leftarrow (\text{id} + \frac{1}{n} \mathbf{v}'_{t_{n-1-p}}) \circ \phi_{t_{p+1},1}$

25:              $\phi_{t_p,0} \leftarrow \phi_{t_{p-1},0} \circ (\text{id} - \frac{1}{n} \mathbf{v}'_{t_{p-1}})$

26:         **end for**

27:         compute current energy  $E'$  using (4)

28:         **if**  $E' < E$  **then**

29:             **return**  $E', \alpha$

30:         **end if**

31:     **end for**

32:     **return**  $E, \inf\{\alpha\}$

33: **end function**

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corresponding to the first principal directions. We then computed  $\lambda_2$  as the mean of the eigenvalues corresponding to the second and third principal eigenvectors.

We randomly chose an image as the target image and used the rest as source images. For each image, we fit the DBFs, with 321 directions uniformly distributed on a unit sphere, to estimate the associated weight image, which was then used to obtain a reconstructed version of the image. A set of affine transformations was estimated between the target image and each source image using their anisotropy images computed from the reconstructed data. We then reconstructed each source image again using the associated weight image by taking into account the affine transformation (see (3)). The resulting reconstructed source images were used for both DWI and diffusion tensor imaging (DTI) registration. We compared our method (Section 4), which we will refer to as LDDMM-DWI, with the following registration strategies:

- (1) *Naïve LDDMM-DWI* [23]: This is a registration scheme that iteratively (1) warps and reorients the source and target images based on an estimated mapping; (2) estimates a new mapping that further aligns the two resulting images via a geodesic shooting algorithm; (3) concatenates the estimated mapping with the one estimated in the previous iteration. The source image is reconstructed using the composite mapping together with an affine transformation, whereas the target is reconstructed without any transformation. At each stage the reconstruction is done by using an increasing number of diffusion directions.
- (2) *DTI Registration*: For each image we computed a DT image by fitting the diffusion tensor model to the reconstructed data. We then registered each source DT image to the target DT image using DTI-TK [13].

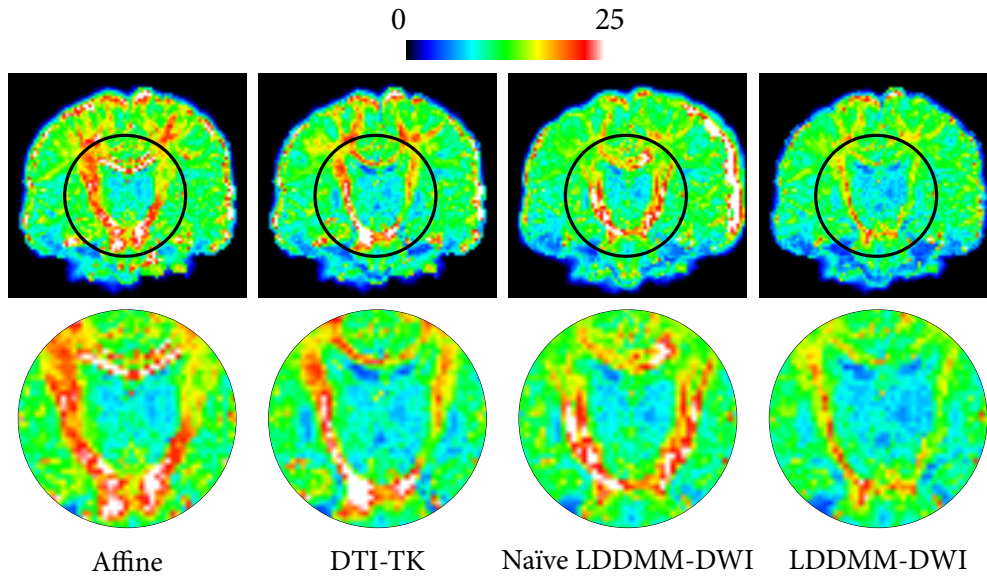


Figure 1: The mean RMS error images (top) and the close-ups of regions marked by black circles (bottom). Note that the images were not sliced for left-right symmetry.

For LDDMM-DWI, we ran line search for 30 iterations. For naïve LDDMM-DWI [23], we performed the registration in 6 stages: 30 iterations in the first two stages, 20 in the middle stages, and 10 and 5 in the last two stages. In each stage, the number of diffusion directions was 1, 6, 21, 81, 120, and 321, respectively. The default parameters provided on the DTI-TK website<sup>2</sup> were used for DTI registration.

To quantify the comparison, we computed the voxel-wise root mean square (RMS) error between the target image and each of source image, warped and re-oriented using the estimated affine and non-linear mapping. Averaging the resulting RMS error images across subjects for each method leads to the mean images shown in Fig. 1. For reference, we also show the mean RMS error image of source

<sup>2</sup><http://dti-tk.sourceforge.net/pmwiki/pmwiki.php>

Table 1: Statistics of the mean RMS error images given by various registration strategies.

Method	Mean±s.d.	Median	90%-ile	$p$ -value
Affine	14.7±6.3	13.4	21.4	$p < 10^{-6}$
DTI-TK	13.3±6.1	12.2	19.6	$p < 0.01$
Naïve LDDMM-DWI	12.9±5.4	11.9	18.3	$p < 0.05$
LDDMM-DWI	<b>11.7±4.5</b>	<b>11.3</b>	<b>16.5</b>	–

images warped and reoriented using affine transformations alone. For each mean RMS error image we computed its statistics (*i.e.*, mean, standard deviation, median, and the 90-th percentile) over all voxels and report the results in Table 1. For each method, we also computed the mean intensity value of the RMS error image associated with each subject and used these means to perform two-tailed student’s  $t$ -tests using LDDMM-DWI as the baseline. The results, given in the same table, indicate that the performance differences are statistically significant.

From Fig. 1, it is clear that LDDMM-DWI significantly improves the alignment of white matter structures, such as the internal capsule. Affine registration and naïve LDDMM-DWI do not take into account reorientation in the optimization process and are hence less effective in white matter alignment. Although DTI-TK explicitly considers reorientation during optimization, it can only handle one principal fiber direction per voxel and thus ambiguity will occur where fiber configuration is complex. The quantitative results given in Table 1 show that LDDMM-DWI outperforms the other methods and reduces overall mismatching error (*e.g.*, smaller median).

To further demonstrate the efficacy of LDDMM-DWI, we compared the similarity of ODFs (for high-anisotropy voxels) computed from the target image and



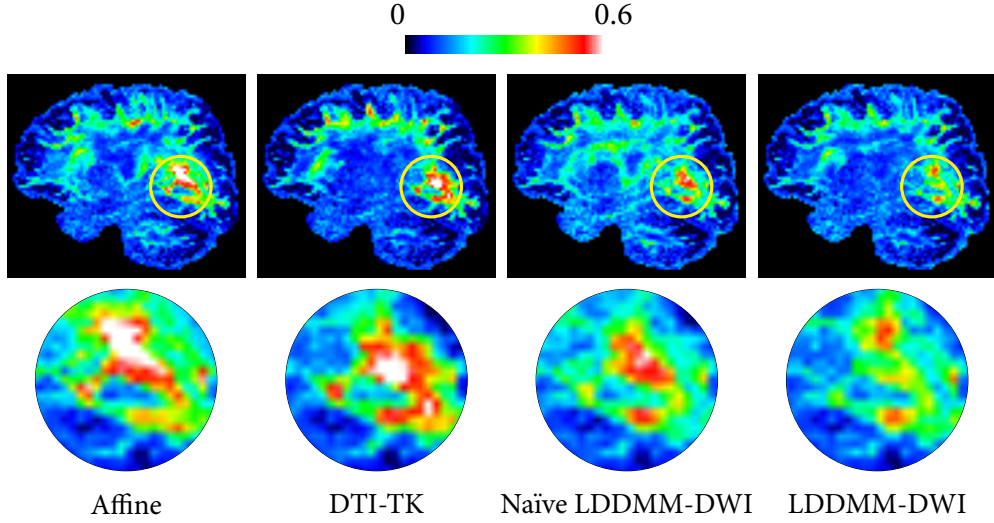


Figure 2: The mean sKL divergence images (top) and the close-ups of regions marked by yellow circles (bottom). Note that the low-anisotropy regions were not masked out for display purpose.

each source image using the symmetrized Kullback-Leibler (sKL) divergence [34]

$$\text{sKL}(\mathbf{p}_1, \mathbf{p}_2) = \int_{\mathbf{s} \in \mathbb{S}^2} \mathbf{p}_1(\mathbf{s}) \log \frac{\mathbf{p}_1(\mathbf{s})}{\mathbf{p}_2(\mathbf{s})} d\mathbf{s} + \int_{\mathbf{s} \in \mathbb{S}^2} \mathbf{p}_2(\mathbf{s}) \log \frac{\mathbf{p}_2(\mathbf{s})}{\mathbf{p}_1(\mathbf{s})} d\mathbf{s},$$

where  $\mathbf{p}_1$  and  $\mathbf{p}_2$  are the ODFs and  $\mathbf{s}$  is a vector defined on the unit sphere  $\mathbb{S}^2$ . The mean sKL divergence images resulting from each method are given in Fig. 2 and the statistics of the mean images are given in Table 2. Similarly, we can see that LDDMM-DWI works much better than other registration methods and reduces white matter misalignment.

Figure 3 shows the anisotropy images of the target image and the mean of the aligned source images, from which we can see that LDDMM-DWI registers all main structures reasonably well. ODFs computed from the target image and the LDDMM-DWI mean image are shown in Fig. 4. It can be observed that the results produced by LDDMM-DWI are in close agreement at voxel level with the

Table 2: Statistics of the mean sKL divergence images given by different registration strategies.

Method	Mean±s.d.	Median	90%-ile	$p$ -value
Affine	0.22±0.10	0.21	0.35	$p < 0.01$
DTI-TK	0.21±0.10	0.20	0.36	$p \approx 0.01$
Naïve LDDMM-DWI	0.21±0.08	0.21	0.32	$p < 0.05$
LDDMM-DWI	<b>0.19±0.09</b>	<b>0.19</b>	<b>0.31</b>	–

target image. This is important for applications such as white matter tractography [35, 36], which is sensitive to errors in local fiber orientations.

## 7. Conclusion and Discussions

We have described a method for directly registering the DWI data under large deformation. This is achieved by incorporating a DWI data reorientation technique [25] into an LDDMM algorithm [15], optimizing spatial alignment and local reorientation simultaneously. Unlike most of the existing methods, our approach eventually results in a set of diffusion-weighted images, thus allowing the fitting of any diffusion model for subsequent analysis. Experimental results indicate that our method significantly outperforms several other registration strategies as well as the method proposed in our earlier work [23], which does not explicitly consider reorientation during optimization. In the future, to overcome the large computation cost of our method, general-purpose computing on graphics processing units (GPGPU) can be employed to significantly speed up the computation of the parallelizable portion of the algorithm.

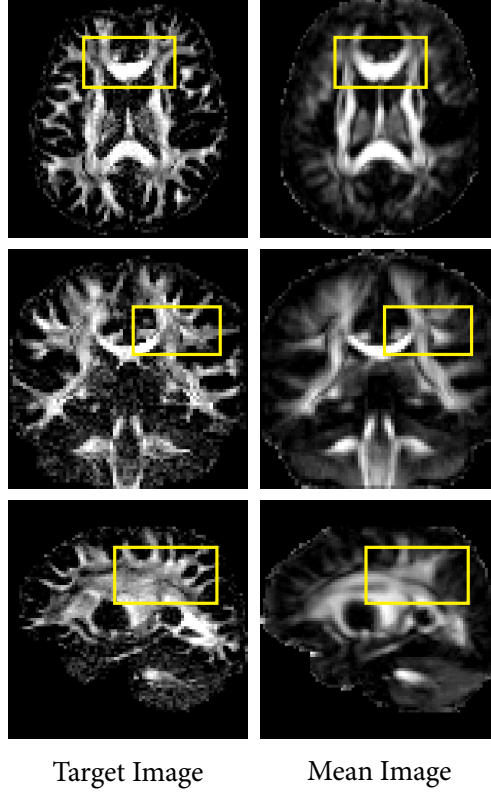


Figure 3: Anisotropy images of the target image and the mean of the align source images. The ODFs in regions marked by yellow rectangles are shown in Fig. 4.

### Appendix A. Derivation of the Gradient of the Cost Function

To minimize the cost function (4), we consider a small perturbation of  $\mathbf{v} \in L^2([0, 1], V)$  along direction  $\mathbf{h} \in L^2([0, 1], V)$ . The variation of energy functional  $E(\mathbf{v})$  w.r.t  $\mathbf{v}$  can be obtained as

$$\partial_h E(\mathbf{v}) \equiv \left. \frac{d}{d\epsilon} E(\mathbf{v} + \epsilon \mathbf{h}) \right|_{\epsilon=0} \equiv \int_0^1 \langle (\nabla_{\mathbf{v}} E)_t, \mathbf{h}_t \rangle_V dt,$$

where  $\partial_h E(\mathbf{v})$  is the Gâteaux derivative of  $E$  and  $\nabla_{\mathbf{v}} E$  is the Fréchet derivative of  $E$ .

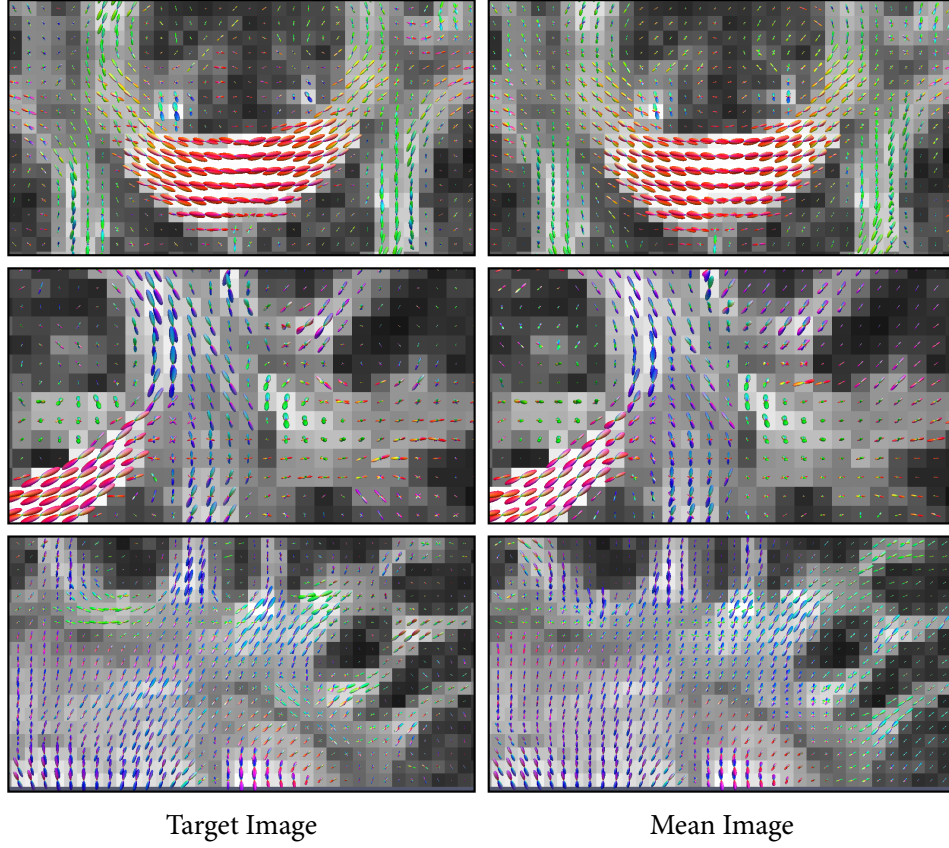


Figure 4: ODFs in the regions marked by yellow rectangles in Fig. 3. The target anisotropy image is used as the background.

The variation of  $E_1(\mathbf{v}) = \frac{1}{2} \int_0^1 \|\mathbf{v}_t\|_V^2 dt$  can be obtained easily as follows

$$\partial_h E_1(\mathbf{v}) = \frac{d}{d\epsilon} \left( \frac{1}{2} \int_0^1 \|\mathbf{v}_t\|_V^2 dt \right) \Big|_{\epsilon=0} = \int_0^1 \langle \mathbf{v}_t, \mathbf{h}_t \rangle_V dt. \quad (\text{A.1})$$

Now focusing on the variation of  $E_2(\mathbf{v}) = \frac{1}{\sigma^2} \|F_{\phi_{1,0}} W_0 \circ \phi_{1,0} - I_1\|_{L^2}^2$ , we have

$$\begin{aligned} \partial_h E_2(\mathbf{v}) &= \frac{d}{d\epsilon} \left( \frac{1}{\sigma^2} \|F_{\phi_{1,0}^{\mathbf{v}+\epsilon h}} W_0 \circ \phi_{1,0}^{\mathbf{v}+\epsilon h} - I_1\|_{L^2}^2 \right) \Big|_{\epsilon=0} \\ &= \frac{d}{d\epsilon} \left( \int_{\Omega} \frac{1}{\sigma^2} \|F_{\phi_{1,0}^{\mathbf{v}+\epsilon h}} W_0 \circ \phi_{1,0}^{\mathbf{v}+\epsilon h} - I_1\|_{L^2}^2 d\mathbf{y} \right) \Big|_{\epsilon=0} \\ &= \frac{2}{\sigma^2} \int_{\Omega} \left( I_0 \circ \phi_{1,0} - I_1, \frac{\partial}{\partial \epsilon} F_{\phi_{1,0}^{\mathbf{v}+\epsilon h}} \Big|_{\epsilon=0} W_0 \circ \phi_{1,0}^{\mathbf{v}} + F_{\phi_{1,0}^{\mathbf{v}}} \frac{\partial}{\partial \epsilon} (W_0 \circ \phi_{1,0}^{\mathbf{v}+\epsilon h}) \Big|_{\epsilon=0} \right)_{L^2} d\mathbf{y}, \end{aligned}$$

where  $\Omega$  is a bounded domain in  $\mathbb{R}^d$  and  $\mathbf{y} \in \Omega$ .  $\frac{\partial}{\partial \epsilon} F_{\phi_{1,0}^{\mathbf{v}+\epsilon h}} \Big|_{\epsilon=0}$  at  $\mathbf{y}$  is given by

$$\begin{bmatrix} 0 & \frac{\partial}{\partial \epsilon} f \left( \mathbf{q}_1 \Big| \lambda_1, \lambda_2, \frac{(D\phi_{1,0}^{\mathbf{v}+\epsilon h})^{-1} \boldsymbol{\mu}_1}{\|(D\phi_{1,0}^{\mathbf{v}+\epsilon h})^{-1} \boldsymbol{\mu}_1\|} \right) \Big|_{\epsilon=0} & \cdots & \frac{\partial}{\partial \epsilon} f \left( \mathbf{q}_1 \Big| \lambda_1, \lambda_2, \frac{(D\phi_{1,0}^{\mathbf{v}+\epsilon h})^{-1} \boldsymbol{\mu}_N}{\|(D\phi_{1,0}^{\mathbf{v}+\epsilon h})^{-1} \boldsymbol{\mu}_N\|} \right) \Big|_{\epsilon=0} \\ \vdots & \vdots & \ddots & \vdots \\ 0 & \frac{\partial}{\partial \epsilon} f \left( \mathbf{q}_M \Big| \lambda_1, \lambda_2, \frac{(D\phi_{1,0}^{\mathbf{v}+\epsilon h})^{-1} \boldsymbol{\mu}_1}{\|(D\phi_{1,0}^{\mathbf{v}+\epsilon h})^{-1} \boldsymbol{\mu}_1\|} \right) \Big|_{\epsilon=0} & \cdots & \frac{\partial}{\partial \epsilon} f \left( \mathbf{q}_M \Big| \lambda_1, \lambda_2, \frac{(D\phi_{1,0}^{\mathbf{v}+\epsilon h})^{-1} \boldsymbol{\mu}_N}{\|(D\phi_{1,0}^{\mathbf{v}+\epsilon h})^{-1} \boldsymbol{\mu}_N\|} \right) \Big|_{\epsilon=0} \end{bmatrix}.$$

Note that we drop  $\mathbf{y}$  for simplicity, *i.e.*  $\phi_{1,0}^{\mathbf{v}+\epsilon h}(\mathbf{y}) \rightarrow \phi_{1,0}^{\mathbf{v}+\epsilon h}$ .

The differentiation of each non-zero element in the above matrix yields

$$\begin{aligned} & \frac{\partial}{\partial \epsilon} f \left( \mathbf{q}_i \Big| \lambda_1, \lambda_2, \frac{(D\phi_{1,0}^{\mathbf{v}+\epsilon h})^{-1} \boldsymbol{\mu}_j}{\|(D\phi_{1,0}^{\mathbf{v}+\epsilon h})^{-1} \boldsymbol{\mu}_j\|} \right) \Big|_{\epsilon=0} \\ &= \text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) \times \left( \nabla_{\tilde{\boldsymbol{\mu}}_j} \left[ \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right] \frac{\partial}{\partial \epsilon} (D\phi_{1,0}^{\mathbf{v}+\epsilon h})^{-1} \Big|_{\epsilon=0} \boldsymbol{\mu}_j \right)^{\text{T}} \mathbf{q}_i \\ &= -\text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) \times \left( \nabla_{\tilde{\boldsymbol{\mu}}_j} \left[ \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right] \left( (D\phi_{1,0}^{\mathbf{v}})^{-1} \frac{\partial}{\partial \epsilon} (D\phi_{1,0}^{\mathbf{v}+\epsilon h}) \Big|_{\epsilon=0} (D\phi_{1,0}^{\mathbf{v}})^{-1} \right) \boldsymbol{\mu}_j \right)^{\text{T}} \mathbf{q}_i. \end{aligned}$$

Note that now  $\tilde{\boldsymbol{\mu}}_j = (D\phi_{1,0}^{\mathbf{v}})^{-1} \boldsymbol{\mu}_j$ . According to the proof given in[15],

$$\frac{\partial}{\partial \epsilon} \phi_{1,0}^{\mathbf{v}+\epsilon h} \Big|_{\epsilon=0} = D\phi_{1,0}^{\mathbf{v}} \int_1^0 (D\phi_{1,t}^{\mathbf{v}})^{-1} \mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}} dt.$$

Hence,  $\frac{\partial}{\partial \epsilon} (D\phi_{1,0}^{\mathbf{v}+\epsilon h}) \Big|_{\epsilon=0}$  can be obtained by simply taking differentiation w.r.t  $\mathbf{y}$  on both sides of the above equation, *i.e.*

$$\frac{\partial}{\partial \epsilon} (D\phi_{1,0}^{\mathbf{v}+\epsilon h}) \Big|_{\epsilon=0} = \int_1^0 (D_{\phi_{1,t}^{\mathbf{v}}}^2 \phi_{t,0}^{\mathbf{v}}) \cdot (\mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}}) (D\phi_{1,t}^{\mathbf{v}}) dt + \int_1^0 (D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}}) (D_{\phi_{1,t}^{\mathbf{v}}} \mathbf{h}_t) D\phi_{1,t}^{\mathbf{v}} dt,$$

where  $D_{\mathbf{y}} \cdot$  is the value of  $D \cdot$  at  $\mathbf{y}$ ,  $D^2 \cdot$  is the Hessian operator,  $D_{\mathbf{y}}^2 \cdot$  is the value of  $D^2 \cdot$  at  $\mathbf{y}$ , giving a vector-valued matrix. For instance,  $D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}} \equiv D\phi_{t,0}^{\mathbf{v}}(\phi_{1,t}^{\mathbf{v}}(\mathbf{y}))$  represents the Jacobian  $D\phi_{t,0}^{\mathbf{v}}$  at position  $\phi_{1,t}^{\mathbf{v}}(\mathbf{y})$ . Then we have

$$\begin{aligned} & (D\phi_{1,0}^{\mathbf{v}})^{-1} \left. \frac{\partial}{\partial \epsilon} (D\phi_{1,0}^{\mathbf{v}+\epsilon \mathbf{h}}) \right|_{\epsilon=0} (D\phi_{1,0}^{\mathbf{v}})^{-1} \\ &= (D\phi_{1,0}^{\mathbf{v}})^{-1} \left[ \int_1^0 (D_{\phi_{1,t}^{\mathbf{v}}}^2 \phi_{t,0}^{\mathbf{v}}) \cdot (\mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}}) (D\phi_{1,t}^{\mathbf{v}}) dt + \int_1^0 (D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}}) (D_{\phi_{1,t}^{\mathbf{v}}} \mathbf{h}_t) D\phi_{1,t}^{\mathbf{v}} dt \right] (D\phi_{1,0}^{\mathbf{v}})^{-1}. \end{aligned}$$

We now deal with the two terms in the above equation one by one:

$$\begin{aligned} & (D\phi_{1,0}^{\mathbf{v}})^{-1} \left[ \int_1^0 (D_{\phi_{1,t}^{\mathbf{v}}}^2 \phi_{t,0}^{\mathbf{v}}) \cdot (\mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}}) (D\phi_{1,t}^{\mathbf{v}}) dt \right] (D\phi_{1,0}^{\mathbf{v}})^{-1} \\ &= \int_1^0 (D\phi_{1,0}^{\mathbf{v}})^{-1} (D_{\phi_{1,t}^{\mathbf{v}}}^2 \phi_{t,0}^{\mathbf{v}}) \cdot (\mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}}) (D\phi_{1,t}^{\mathbf{v}}) (D\phi_{1,0}^{\mathbf{v}})^{-1} dt \\ &= \int_1^0 (D\phi_{1,t}^{\mathbf{v}})^{-1} (D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}})^{-1} (D_{\phi_{1,t}^{\mathbf{v}}}^2 \phi_{t,0}^{\mathbf{v}}) \cdot (\mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}}) (D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}})^{-1} dt \\ &= \int_0^1 (D\phi_{1,t}^{\mathbf{v}})^{-1} D((D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}})^{-1}) \cdot (\mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}}) dt \\ &= \int_0^1 D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,1}^{\mathbf{v}} D((D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}})^{-1}) \cdot (\mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}}) dt, \end{aligned}$$

and

$$\begin{aligned} & (D\phi_{1,0}^{\mathbf{v}})^{-1} \left[ \int_1^0 (D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}}) (D_{\phi_{1,t}^{\mathbf{v}}} \mathbf{h}_t) D\phi_{1,t}^{\mathbf{v}} dt \right] (D\phi_{1,0}^{\mathbf{v}})^{-1} \\ &= \int_1^0 (D\phi_{1,0}^{\mathbf{v}})^{-1} (D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}}) (D_{\phi_{1,t}^{\mathbf{v}}} \mathbf{h}_t) D\phi_{1,t}^{\mathbf{v}} (D\phi_{1,0}^{\mathbf{v}})^{-1} dt \\ &= - \int_0^1 (D\phi_{1,t}^{\mathbf{v}})^{-1} (D_{\phi_{1,t}^{\mathbf{v}}} \mathbf{h}_t) (D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}})^{-1} dt \\ &= - \int_0^1 D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,1}^{\mathbf{v}} (D_{\phi_{1,t}^{\mathbf{v}}} \mathbf{h}_t) (D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}})^{-1} dt, \end{aligned}$$

where we have used  $D\phi_{1,0}^{\mathbf{v}} = D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}} D\phi_{1,t}^{\mathbf{v}}$  and  $D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,1}^{\mathbf{v}} D\phi_{1,t}^{\mathbf{v}} = \mathbf{I}$  for simplification.

Hence, we have

$$\begin{aligned} & (D\phi_{1,0}^{\mathbf{v}})^{-1} \left. \frac{\partial}{\partial \epsilon} (D\phi_{1,0}^{\mathbf{v}+\epsilon \mathbf{h}}) \right|_{\epsilon=0} (D\phi_{1,0}^{\mathbf{v}})^{-1} \\ &= \int_0^1 D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,1}^{\mathbf{v}} D((D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}})^{-1}) \cdot (\mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}}) dt - \int_0^1 D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,1}^{\mathbf{v}} (D_{\phi_{1,t}^{\mathbf{v}}} \mathbf{h}_t) (D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}})^{-1} dt. \end{aligned}$$

Also, we have

$$\begin{aligned}
& \left. \frac{\partial}{\partial \epsilon} (W_0 \circ \phi_{1,0}^{\mathbf{v}+\epsilon \mathbf{h}}) \right|_{\epsilon=0} = DW_0 \circ \phi_{1,0}^{\mathbf{v}} \left. \frac{\partial}{\partial \epsilon} \phi_{1,0}^{\mathbf{v}+\epsilon \mathbf{h}} \right|_{\epsilon=0} \\
& = DW_0 \circ \phi_{1,0}^{\mathbf{v}} \left( -D\phi_{1,0}^{\mathbf{v}} \int_0^1 (D\phi_{1,t}^{\mathbf{v}})^{-1} \mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}} dt \right) \\
& = - \int_0^1 D(W_0 \circ \phi_{1,0}^{\mathbf{v}}) (D\phi_{1,t}^{\mathbf{v}})^{-1} \mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}} dt.
\end{aligned}$$

Now we are ready to compute  $G = \left. \frac{\partial}{\partial \epsilon} F_{\phi_{1,0}^{\mathbf{v}+\epsilon \mathbf{h}}} \right|_{\epsilon=0} W_0 \circ \phi_{1,0}^{\mathbf{v}} + F_{\phi_{1,0}^{\mathbf{v}}} \left. \frac{\partial}{\partial \epsilon} (W_0 \circ \phi_{1,0}^{\mathbf{v}+\epsilon \mathbf{h}}) \right|_{\epsilon=0}$ , where  $G$  is a vector-valued image and the  $i$ -th element of its voxel at  $\mathbf{y}$  is given by  $G^i(\mathbf{y})$ . We have

$$G(\mathbf{y}) = \begin{bmatrix} 0 & a_{11} & a_{12} & \cdots & a_{1N} \\ 0 & a_{21} & a_{22} & \cdots & a_{2N} \\ \vdots & \vdots & \ddots & \vdots & \\ 0 & a_{M1} & a_{M2} & \cdots & a_{MN} \end{bmatrix} \begin{bmatrix} w_0 \\ w_1 \\ \vdots \\ w_N \end{bmatrix} \circ \phi_{1,0}^{\mathbf{v}} + \begin{bmatrix} f_0 & b_{11} & b_{12} & \cdots & b_{1N} \\ f_0 & b_{21} & b_{22} & \cdots & b_{2N} \\ \vdots & \vdots & \ddots & \vdots & \\ f_0 & b_{M1} & b_{M2} & \cdots & b_{MN} \end{bmatrix} \left( - \int_0^1 D(W_0 \circ \phi_{1,0}^{\mathbf{v}}) (D\phi_{1,t}^{\mathbf{v}})^{-1} \mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}} dt \right),$$

where

$$\begin{aligned}
a_{ij} & = - \int_0^1 \text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) \times \left( \nabla_{\tilde{\boldsymbol{\mu}}_j} \left[ \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right] (D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,1}^{\mathbf{v}} D((D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}})^{-1}) \cdot (\mathbf{h}_t \circ \phi_{1,t}^{\mathbf{v}})) \boldsymbol{\mu}_j \right)^{\text{T}} \mathbf{q}_i dt \\
& \quad + \int_0^1 \text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) \times \left( \nabla_{\tilde{\boldsymbol{\mu}}_j} \left[ \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right] (D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,1}^{\mathbf{v}} (D_{\phi_{1,t}^{\mathbf{v}}} \mathbf{h}_t) (D_{\phi_{1,t}^{\mathbf{v}}} \phi_{t,0}^{\mathbf{v}})^{-1}) \boldsymbol{\mu}_j \right)^{\text{T}} \mathbf{q}_i dt,
\end{aligned}$$

$$b_{ij} = f \left( \mathbf{q}_i \left| \lambda_1, \lambda_2, \frac{(D\phi_{1,0}^{\mathbf{v}})^{-1} \boldsymbol{\mu}_j}{\|(D\phi_{1,0}^{\mathbf{v}})^{-1} \boldsymbol{\mu}_j\|} \right. \right) \text{ and } [w_0, \dots, w_N]^{\text{T}} \text{ is the sparse weights of } W_0 \text{ at po-}$$

sition  $\mathbf{y}$ . Let  $\mathbf{b}_i = [f_0, b_{i1}, \dots, b_{iN}]^T$ , we can then compute  $G^i(\mathbf{y})$  as

$$\begin{aligned}
G^i(\mathbf{y}) &= \sum_j^N a_{ij} w_j \circ \phi_{1,0}^v - \int_0^1 \mathbf{b}_i^T D(W_0 \circ \phi_{1,0}^v) (D\phi_{1,t}^v)^{-1} \mathbf{h}_t \circ \phi_{1,t}^v dt \\
&= - \int_0^1 \sum_j^N w_j \circ \phi_{1,0}^v \text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) \times \left( \nabla_{\tilde{\boldsymbol{\mu}}_j} \left[ \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right] (D_{\phi_{1,t}^v} \phi_{t,1}^v D((D_{\phi_{1,t}^v} \phi_{t,0}^v)^{-1}) \cdot (\mathbf{h}_t \circ \phi_{1,t}^v)) \boldsymbol{\mu}_j \right)^T \mathbf{q}_i dt \\
&\quad + \int_0^1 \sum_j^N w_j \circ \phi_{1,0}^v \text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) \times \left( \nabla_{\tilde{\boldsymbol{\mu}}_j} \left[ \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right] (D_{\phi_{1,t}^v} \phi_{t,1}^v (D_{\phi_{1,t}^v} \mathbf{h}_t) (D_{\phi_{1,t}^v} \phi_{t,0}^v)^{-1}) \boldsymbol{\mu}_j \right)^T \mathbf{q}_i dt \\
&\quad - \int_0^1 \mathbf{b}_i^T D(W_0 \circ \phi_{1,0}^v) (D\phi_{1,t}^v)^{-1} \mathbf{h}_t \circ \phi_{1,t}^v dt.
\end{aligned}$$

Now we can rewrite  $\partial_h E_2(\mathbf{v})$  as

$$\partial_h E_2(\mathbf{v}) = \frac{2}{\sigma^2} \int_{\Omega} \langle I_0 \circ \phi_{1,0} - I_1, G \rangle_{L^2} d\mathbf{y} = \frac{2}{\sigma^2} \int_{\Omega} \sum_i^M (I_0^i \circ \phi_{1,0} - I_1^i) G^i d\mathbf{y}.$$

Let  $\phi_{1,t}^v(\mathbf{y}) = \mathbf{x}$ , then  $\mathbf{y} = \phi_{t,1}^v(\mathbf{x})$  and  $d\mathbf{y} = |D\phi_{t,1}^v(\mathbf{x})| d\mathbf{x}$ . By changing the variable, we have

$$\begin{aligned}
\partial_h E_2(\mathbf{v}) &= -\frac{2}{\sigma^2} \int_0^1 \int_{\Omega} |D\phi_{t,1}^v| \sum_i^M (I_0^i \circ \phi_{t,0}^v - I_1^i \circ \phi_{t,1}^v) \times \\
&\quad \sum_j^N w_j \circ \phi_{t,0}^v \text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) \times \left( \nabla_{\tilde{\boldsymbol{\mu}}_j} \left[ \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right] (D\phi_{t,1}^v D((D\phi_{t,0}^v)^{-1}) \cdot \mathbf{h}_t) \boldsymbol{\mu}_j \right)^T \mathbf{q}_i d\mathbf{x} dt \\
&\quad + \frac{2}{\sigma^2} \int_0^1 \int_{\Omega} |D\phi_{t,1}^v| \sum_i^M (I_0^i \circ \phi_{t,0}^v - I_1^i \circ \phi_{t,1}^v) \times \\
&\quad \sum_j^N w_j \circ \phi_{t,0}^v \text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) \times \left( \nabla_{\tilde{\boldsymbol{\mu}}_j} \left[ \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right] (D\phi_{t,1}^v D\mathbf{h}_t (D\phi_{t,0}^v)^{-1}) \boldsymbol{\mu}_j \right)^T \mathbf{q}_i d\mathbf{x} dt \\
&\quad - \frac{2}{\sigma^2} \int_0^1 \int_{\Omega} |D\phi_{t,1}^v| \sum_i^M (I_0^i \circ \phi_{t,0}^v - I_1^i \circ \phi_{t,1}^v) \mathbf{b}_i^T D(W_0 \circ \phi_{t,0}^v) \mathbf{h}_t d\mathbf{x} dt,
\end{aligned}$$

where now  $\tilde{\boldsymbol{\mu}}_j = (D\phi_{t,0}^v)^{-1} \boldsymbol{\mu}_j$ . As  $\mathbf{v}, \mathbf{h} \in V$ , we have the following two equations (see [33] for details on the property of the reproducing kernel Hilbert space)

$$\langle \mathbf{v}, \mathbf{h} \rangle_{L^2} = \langle K\mathbf{v}, \mathbf{h} \rangle_V,$$

$$\langle \mathbf{v}, D\mathbf{h} \rangle_{L^2} = \langle DK\mathbf{v}, \mathbf{h} \rangle_V.$$



Hence, the variation of  $E_2(\mathbf{v})$  is given by

$$\begin{aligned}
\partial_{\mathbf{h}} E_2(\mathbf{v}) = & -\frac{2}{\sigma^2} \int_0^1 \left\langle K \left( \int_{\Omega} |D\phi_{t,1}^{\mathbf{v}}| \sum_i^M (I_0^i \circ \phi_{t,0}^{\mathbf{v}} - I_1^i \circ \phi_{t,1}^{\mathbf{v}}) \times \right. \right. \\
& \left. \left. \sum_j^N w_j \circ \phi_{t,0}^{\mathbf{v}} \text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) \times \left( \nabla_{\tilde{\boldsymbol{\mu}}_j} \left[ \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right] (D\phi_{t,1}^{\mathbf{v}} D((D\phi_{t,0}^{\mathbf{v}})^{-1})) \boldsymbol{\mu}_j \right)^{\text{T}} \mathbf{q}_i \, d\mathbf{x} \right), \mathbf{h}_t \right\rangle_V dt \\
& + \frac{2}{\sigma^2} \int_0^1 \left\langle DK \left( \int_{\Omega} |D\phi_{t,1}^{\mathbf{v}}| \sum_i^M (I_0^i \circ \phi_{t,0}^{\mathbf{v}} - I_1^i \circ \phi_{t,1}^{\mathbf{v}}) \times \right. \right. \\
& \left. \left. \sum_j^N w_j \circ \phi_{t,0}^{\mathbf{v}} \text{const}(\mathbf{q}_i, \tilde{\boldsymbol{\mu}}_j) \times \left( \nabla_{\tilde{\boldsymbol{\mu}}_j} \left[ \frac{\tilde{\boldsymbol{\mu}}_j}{\|\tilde{\boldsymbol{\mu}}_j\|} \right] (D\phi_{t,1}^{\mathbf{v}} (D\phi_{t,0}^{\mathbf{v}})^{-1}) \boldsymbol{\mu}_j \right)^{\text{T}} \mathbf{q}_i \, d\mathbf{x} \right), \mathbf{h}_t \right\rangle_V dt \\
& - \frac{2}{\sigma^2} \int_0^1 \left\langle K \left( \int_{\Omega} |D\phi_{t,1}^{\mathbf{v}}| \sum_i^M (I_0^i \circ \phi_{t,0}^{\mathbf{v}} - I_1^i \circ \phi_{t,1}^{\mathbf{v}}) \mathbf{b}_i^{\text{T}} D(W_0 \circ \phi_{t,0}^{\mathbf{v}}) \, d\mathbf{x} \right), \mathbf{h}_t \right\rangle_V dt.
\end{aligned} \tag{A.2}$$

Since  $\mathbf{h}$  is arbitrary in  $L^2([0, 1], V)$ , we obtain the gradient as given in (5) by combining results (A.1) and (A.2).

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