A variational framework for distortion correction, segmentation and cortical parcellation of diffusion MRI

Oscar Esteban*, Alessandro Daducci, Meritxell Bach-Cuadra, Jean-Philippe Thiran, Andrés Santos, and Dominique Zosso

***Abstract*—In whole-brain connectivity analysis of diffusion MRI (dMRI) data, an accurate delineation of the white-matter and grey-matter interfaces is required. While high-standard segmentation is readily available for structural MRI, dMRI typically present significant cerebrospinal fluid contamination effects, mainly derived from its typical low resolution, and severe geometrical distortions. We propose a segmentation-registration variational framework that exploits the detailed anatomy extracted from structural MRI as shape-prior. We use an "active contours without edges"-like model to search for a deformation field that optimally maps the shape prior on multivariate dMRI-derived data in diffusion space, registering structural and diffusion coordinate spaces and implicitly segmenting dMRI data. The approach proven the intrinsic coupling of segmentation and distortion correction and we evaluate its results on a digital simulated phantom and real datasets. Therefore, precise and consistent cortical parcellation on dMRI is straightforward by projection from T1 space, avoiding additional registration, segmentation and/or surface matching steps.**

***Index Terms*—diffusion MRI, susceptibility distortion, segmentation, registration, parcellation, shape-prior.**

I. Introduction

DIFFUSION magnetic resonance imaging (MRI) is a widely used family of MRI techniques [58] which accounts for a growing interest in its application to structural connectivity analyses of the brain at the macro-scale [14]. This emerging field exploits diffusion MRI (dMRI) data to derive the local axonal structure at each imaging voxel [**?**] and estimate a whole-brain mapping of fiber tracts [27, 35] represented by trajectories reconstructed from the local information. This comprehensive map of neural connections of the brain is called the *connectome* [26, 56]. The connectome analysis is a promising tool for neuroscience [45] and for the clinical application [23] as well.

Manuscript received XXX XX, 2013; revised XXX XX, 2013. This study is supported by: the Spain's Ministry of Science and Innovation (projects TEC2010-21619- C04-03, TEC2011-28972-C02-02, CDTI-CENIT AMIT and INNPACTO PRECISION), Comunidad de Madrid (ARTEMIS) and European Regional Development Funds; the Center for Biomedical Imaging (CIBM) of the Geneva and Lausanne Universities and the EPFL, as well as the Leenaards and Louis Jeantet foundations. *Asterisk indicates corresponding author*.

*O. Esteban is with the Biomedical Image Technologies (BIT), ETSI Telecomunicación, Universidad Politécnica de Madrid and CIBER-BBN, Madrid, Spain, and the Signal Processing Laboratory (LTS5), École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland (e-mail: phd@oscaresteban.es).

A. Daducci is with the Signal Processing Laboratory (LTS5), École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland.

M. Bach-Cuadra and JP. Thiran are with the Signal Processing Laboratory (LTS5), École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, and Dept. of Radiology, University Hospital Center (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland.

A. Santos is with the Biomedical Image Technologies (BIT), ETSI Telecomunicación, Universidad Politécnica de Madrid and CIBER-BBN, Madrid, Spain.

D. Zosso is with the Department of Mathematics, University of California, Los Angeles (UCLA), Los Angeles, CA, US and is supported by the Swiss National Science Foundation (SNF) under grant PBELP2-137727.

A. DMRI data overview

dMRI data are usually acquired with echo-planar imaging (EPI) schemes as they allow for very fast acquisition of large sets of slices each acquired after a single excitation [47, 55]. EPI volumes are collected in sequence and each one represents one probed diffusion direction.

EPI are known to suffer from geometrical distortions and artifacts due to, mainly, three sources: the subject motion in between acquiring different sampling directions, the induced *eddy currents* on the scanner coils due to the gradient switching [50], and, finally, distortions caused by the magnetic susceptibility inhomogeneity present at tissue interface. *Susceptibility distortions* happen along the phase-encoding direction, and are most appreciable in the frontal part of the brain due to the air/tissue interface located around the sinuses. Two implications are associated to this artifact: the signal loss caused on highly distorted regions, and a significant added difficulty in registering with structural images (e.g. T1-weighted).

After correcting for artifacts, the difficulty of performing analyses directly on the *directionally dependent* raw data is not affordable. Thus, dMRI data is reconstructed using one of a numerous set of readily available algorithms. The outcome is a voxel-wise model of diffusion shape (in [**?**] there is available a comprehensive review of state-of-art methodologies). On top of the chosen model, some scalar maps describing tissue features are generally computed (e.g. fractional anisotropy (FA), and apparent diffusion coefficient (ADC)).

FIX ref

Alongside distortions and direction dependency, dMRI data is strongly affected by partial volume effects (PVEs) [1] that appears when several different tissues are present in the same imaging unit, producing an averaged intensity. The effect is directly related to the resolution, typically around $2.0 \times 2.0 \times 2.0 mm^3$ for dMRI.

B. Correction for susceptibility distortions

One approach to correcting the susceptibility distortions was proposed with the earliest EPI sequences used in functional MRI, and relies on the acquisition of extra MRI data. Generally, a gradient echo sequence (GRE) is used to obtain a map of magnitude and phase of the actual magnetic field inside the scanner. Based on this *fieldmap* and the theory underlying the distortion, [**?**] proposed a correction methodology. A number of forked and improved methodologies have been developed to correct for the susceptibility distortion and received the generic name of "fieldmap correction" techniques [31**?**].

Some other retrospective methodologies do not make use of the fieldmaps, as explicitly modeling the distortion [2], registering with (anatomically correct) T2-weighted MRI [40, 42, 57, 60], or acquiring an extra B0 image with reversed phase encoding direction [3, 30].

A comparison of the diverse correction techniques is found in [66]. This study claims that fieldmap correction methodologies are not entirely accurate and reliable, even though the method is correct in principle. The conclusion was later confirmed by [60]. Additional concerns regarding fieldmap correction are the requirement of an extra acquisition (that is not always met or it is impractical), or the accuracy of the measured fieldmap that is sensitive to various effects (such us respiration, blood flow, etc.). All these factors have turned susceptibility distortion in EPI sequences an active field of research for the last 10 years.

C. DMRI segmentation

A precise delineation of the cerebrospinal fluid (CSF), grey matter (GM) and white matter (WM) interfacing surfaces is required with sub-pixel resolution, because whereas tractography algorithms are very good at estimating the location of bundles in deep WM, they are not god (yet) at identifying where the tracts project into the GM (limitations on the termination criteria, [14, 32]). Thus, a WM segmentation is required by most of the available tractography algorithms to *filter* the resulting tractogram. The GM-WM interface is necessary to locate the starting and ending points of the detected fiber bundles, and CSF-WM surface is critical for pruning spurious and discontinued fiber bundles.

A number of methodologies have been proposed for dMRI segmentation, ranging from intensity thresholding to atlas-based segmentation. The first approach is performed simply thresholding the FA map. Although this methodology was popular among the pioneer tractography studies, they were generally limited to certain regions or significant fiber tracts, and thus, it cannot be applied in whole-brain tractography. Early approaches to dMRI segmentation include level set formulations using scalar maps of direction invariants derived from the tensor model [70], directly on the diffusion raw data [54], or finding alternative diffusion representations [36]. Even though this latter case was restricted to the extraction of the corpus callosum from a real dataset, the density of the components of the diffusion tensor are approximated by multivariate Gaussians for first. Iterative clustering performed on the B0 volumes of dMRI data was proposed by [25]. Later studies investigated the application of probabilistic frameworks combining mixtures of gaussians, Markov Random Field (MRF) and labeling fusion techniques [43] using as features widely-used dMRI-derived scalar maps as FA or mean diffusivity (MD). A similar framework combining co-registered structural information (T1 weighted) with *independent orthogonal invariants* derived from the dMRI tensor model was proposed by [4]. Some proposals suggest the use of the raw diffusion data (directionally dependent) to avoid fitting a certain model [44]. In [28], graph-cuts voxel-based techniques are proposed using the most common diffusion tensor derived features. Further developments of the probabilistic approach have been proposed adding more scalar maps as features and a more detailed treatment of PVE [38].

None of the presented methods have claimed for definite results, mainly due to the lack of a *gold-standard* evaluation methodology. Most of them are tested only on certain regions, or do not provide sub-pixel resolution results [4, 25, 28, 43, 44]. Generally, results obtained with high resolution atlas co-registration (subsection I-D) are more compelling, limiting the activity on dMRI segmentation. However, recently [39] proposed to include this task within reconstruction algorithms. Finally, some *golden*-standard evaluation frameworks for task-based validation have been proposed for the segmentation results (e.g. lesion detection in visceral organs [34]).

reference to a summary table

D. Structural information co-registration

The last addressed task in the image processing stage of the studied connectivity analysis pipelines is the structural information co-registration. The need for this registration step is mainly raised when defining the nodes of the connectivity matrix. This definition step is named *cortical parcellation* as it imposes the regions that will be considered to cluster the fiber bundles reaching the WM-GM surface. The common procedure to accomplish this clustering is using a predefined parcellation in a high-resolution structural T1-weighted atlas (e.g. [22]). The second goal that has justified the applicability of structural images co-registration is susceptibility distortion correction as presented in subsection I-B. In any case, susceptibility distortion hinders a rigid-registration solution to this problem. Additionally, when applying non-linear intensity-based registration algorithms, other difficulties have to be addressed as the significant PVE in the WM-GM layer, or the inherent inadequacy of the B0 contrast (the only *directionally independent* existing in the raw dMRI data) due to the almost null difference in intensity between WM and GM pixels. Early registration methods appeared targeting the distortion correction. They quickly standardized the choice of T2 as anatomically correct source to be registered against the B0 in dMRI. B0 images have a very similar contrast to T2 weighted due to the parallelism of acquisition sequences. However, parcellation is defined in T1 weighted space, adding an additional registration step is generally overlooked by existing literature. Even though this processing stage has a very low complexity compared to the remaining tasks of the pipeline process, it is one additional source of inconsistency and unreliability.

One of the first proposals is [40], where the deformation field is modeled with B-Splines, the cost function is least squares and optimized in a multi-resolution gradient descent strategy. Their method is evaluated in both synthetic and real 2D images. Similarly, [57] proposed a spline-based deformation but including a weighting factor proportional to the Jacobian of the transform to correct the intensity of the undistorted data. They also use the $\log$ of the signal to enhance the low-signal regions, and optimize with a gradient descent algorithm the mutual information of the mapping. This framework set the basis for the following works. For instance, [66] also proposed a B-Spline registration providing quantitative comparisons with fieldmap correction methods. Recent approaches take into account the signal loss due to dephasing [42], or introduce more complex variational frameworks [60].

The significant benefits of exploiting the anatomical MRI when segmenting the dMRI data have been demonstrated [71], justifying the use of the shape prior information. To our knowledge, there is no study simultaneously taking advantage from segmentation or distortion correction tasks to be applied to the co-registration problem.

E. Proposed model

All the available dMRI-derived models and scalar maps are very sensitive to distortions, PVE, noise and axonal dispersion [32], what yields numerous challenges in the processing tasks (artifact correction, segmentation, registration and parcellation). Finally, as a result a vast number of challenges and pitfalls emerge regarding accuracy (correctness) and precision (reproducibility) of tractography-based analyses [37] and connectome analyses.

Moreover, the problems of precise segmentation in dMRI-space and the spatial mapping between these contours and the corresponding surfaces in anatomical images bear significant redundancy. Once the spatial relationship between T1-weighted (T1) and dMRI space is established, the contours which are readily available in T1 space can simply be projected on to the dMRI data. Conversely, if a precise delineation in dMRI space was achieved, the spatial mapping with T1-space could be derived from one-to-one correspondences on the contours. However, neither segmentation nor registration can be performed flawlessly, if considered independently.

Here, we shall address three tasks included within the image processing stage in a unified approach: brain tissue segmentation in diffusion space (subsection I-C), correction of geometrical distortions (subsection I-B), and structural image registration to diffusion coordinate space (subsection I-D). These tasks are generally solved independently, or combined in pairs. However, there exist fundamental coupling relationships that can be exploited to obtain a simultaneous solution to the three problems. This joint approach satisfactory impacts the downstream outcomes of the whole pipeline with the increase of the internal consistency.

In this paper we propose a novel registration framework to simultaneously solving the segmentation, distortion and cortical parcellation challenges, by exploiting as strong shape-prior the detailed morphology extracted from high-resolution and anatomically correct MRI. Indeed, hereafter we assume this segmentation problem in anatomical images is reliably and accurately solved with readily available tools (e.g. [18]). After global alignment with T1 using existing approaches, the remaining spatial mismatch between anatomical and diffusion space is due to susceptibility distortions. Finally, we need to establish precise spatial correspondence between the surfaces in both spaces, including the tangential direction for parcellation. Therefore, we can reduce the problem to finding the differences of spatial distortion in between anatomical and dMRI space. We thus reformulate the segmentation problem as an inverse problem, where we seek for an underlying deformation field (the distortion) mapping from the structural space into the diffusion space, such that the structural contours segment optimally the dMRI data. In the process, the one-to-one correspondence between the contours in both spaces is guaranteed, and projection of parcellisation to dMRI space is implicit and consistent.

We test our proposed joint segmentation-registration model on two different synthetic examples. The first example is a scalar sulcus model, where the CSF-GM boundary particularly suffers from PVE and can only be segmented correctly thanks to the shape prior and its coupling with the inner, GM-WM boundary through the imposed deformation field regularity. The second case deals with more realistic dMRI data stemming from phantom simulations of a simplistic brain data. Again, we show that the proposed model successfully segments the dMRI data based on two derived scalar features, namely FA and MD, while establishing an estimate of the dense distortion field.

The rest of this paper is organized as follows. First, in section II we introduce our proposed model for joint multivariate segmentation-registration. Then we provide a more detailed description of the data and experimental setup in section III. We present results in section IV and conclude in section V.

II. METHODS

A. Related work

We suggest clustering the current methodologies of template-based segmentation methods into three groups. The first group typically adds a shape prior term to the energy functional of an evolving active contour [8, 9, 11, 15, 19]. These methods generally have an explicit description of the expected relative boundary locations of the object to be delineated, and some even model the statistical deviations from this average shape. By including a coordinates mapping, it is possible to perform active contours based registration between timesteps in a time-series or between different images [5, 51, 64, 67, 69]. A summary of these second set of techniques is performed in [16], proposing two different approaches to applying the Mumford-Shah [48] functional in joint registration and segmentation. Finally, a derivation of the latter groups is composed by atlas-based segmentation methods [20, 21, 52, 53, 65], where the prior imposes consistent voxel-based classification of contiguous regions. A comprehensive summary of the active contours without edges (ACWE)-derived methodologies with special attention to joint

registration-segmentation methods is found in [21]. ACWE and level-set based formulations have been widely applied in image processing, as reviewed in [59].

The first joint "morphing"-segmentation approach (it was not a proper registration method) was proposed in [5]. The first registration framework is presented by [68] where the energy functional is defined simultaneously in the moving and target images with an affine transformation supporting the coordinates mapping ("2 PDEs approach"). [64] proposed the first atlas-based registration based on the level set framework and using only one PDE. [63] extended the idea of [5, 68] for non-linear registration with a dense deformation field as mapping function. [16] combining ideas from both branches and proposed the propagation of the deformation field from the contours to the whole image definition. Finally, [21] present a comprehensive generalization of the methodologies.

Even though the historical evolution of joint segmentation and registration procedures is strongly linked to the level sets approximation, our work is based in derivations of the ACWE framework [10], and related to [41]. The main diverging points with respect to [21] are: 1) there is no need for an explicit level set function Φ_G, as we replace the level set gradient computation N_{Φ_G} with shape gradients [29, 33]; 2) regularization is also based on linear diffusion smoothing [61], but we replace the Gaussian filtering by other constraints studied in [49] to better the problem; 3) optimization is applied in the spectral domain, observing anisotropic and inhomogeneous mappings along each direction. With respect [41], the main differences are the distance function, and the spectral solution to the optimization updates, as we shall cover in subsection II-C.

The previous paragraphs in red color are marked by Dominique as "to rework", and I totally agree

B. Proposed model

In this paper we formulate the joint registration-segmentation problem as follows. We look for a spatial mapping (with, typically, $n = 3$ for the 3-dimensional case):

$$\begin{aligned} U : T \subset \mathbb{R}^n &\rightarrow D \subset \mathbb{R}^n \\ \mathbf{x} &\mapsto \mathbf{x}' = \mathbf{x} + u(\mathbf{x}), \end{aligned} \tag{1}$$

such that the known contours in anatomical space T optimally segment the diffusion space D.

In a Bayesian framework, different such mappings U between "T1-" and "dMRI-" spaces are evaluated based on their posterior probability given the observed data F. Using the Bayes' rule, this posterior *likelihood* can be computed as:

$$P(U \mid F, \Gamma_{l,m}) = \frac{P(F \mid U, \Gamma_{l,m})\, P(U)}{P(F)}, \tag{2}$$

where $P(F \mid U, \Gamma_{l,m})$ is the data-likelihood, and $\Gamma_{l,m}$ are a set of contours in T1-space that correspond to two interfacing regions Ω, such that $\Gamma_{l,m} = \partial\Omega_l \cap \partial\Omega_m$.

We are interested in a mapping $\hat{U}$ which maximizes this posterior probability (maximum a posteriori (MAP) estimate, [7]):

$$\begin{aligned} \hat{U} &= \underset{U}{\operatorname{argmax}} \left\{ P(U \mid F, \Gamma_{l,m}) \right\} \\ &= \underset{U}{\operatorname{argmax}} \left\{ P(F \mid U, \Gamma_{l,m})\, P(U) \right\}. \end{aligned} \tag{3}$$

First, we assume independence between pixels, and thus break down the global data likelihood into a product of pixel-wise conditional probabilities:

$$P(F \mid U, \Gamma_{l,m}) = \prod_{\mathbf{x} \in \Omega} P\left(F(\mathbf{x}') \mid U(\Gamma_{l,m})\right). \tag{4}$$

Further, within each region Ω_l defined by the contours Γ trough duality, we assume the features to be i.i.d.:

$$P\left(F(\mathbf{x}') \mid U, \Gamma_{l,m}\right) = p_l(F(\mathbf{x}')) \quad \forall \mathbf{x} \in \Omega_l. \tag{5}$$

For convenience, and because this has been shown to be an appropriate approximation [7], each such region is modeled by a multivariate normal distribution with region descriptors $\Theta_l = \{\boldsymbol{\mu}_l, \boldsymbol{\Sigma}_l\}$:

$$p_l(F(\mathbf{x}')) = \mathcal{N}\left(F(\mathbf{x}') \mid \Theta_l\right). \tag{6}$$

Thus, defining the feature observed as $\mathbf{f} = F(\mathbf{x})$ and the squared *Mahalanobis distance* of $\mathbf{f}$ with respect of the descriptors of region l as

$$\mathcal{D}_M^2(\mathbf{f} \mid \Theta_l) = (\mathbf{f} - \boldsymbol{\mu}_l)^T\, {\boldsymbol{\Sigma}_l}^{-1}\, (\mathbf{f} - \boldsymbol{\mu}_l), \tag{7}$$

I modified this slightly

we write:

$$\begin{aligned} P(F \mid U, \Omega) &= \prod_l \prod_{\mathbf{x} \in \Omega_l} \mathcal{N}(\mathbf{f} \mid \boldsymbol{\mu}_l, \boldsymbol{\Sigma}_l) \\ &= \frac{1}{\sqrt{(2\pi)^C\ |\boldsymbol{\Sigma}_l|}}\, e^{\left(-\frac{1}{2}\mathcal{D}_M^2(\mathbf{f}' \mid \Theta_l)\right)}. \end{aligned} \tag{8}$$

We choose a Thikonov regularization prior as follows:

$$P(U) = \prod_{\mathbf{x}} p(u(\mathbf{x}))$$

with further:

$$\begin{aligned} p(u(\mathbf{x})) &= p_0(u(\mathbf{x}))\, p_1(u(\mathbf{x})) \\ p_0(u(\mathbf{x})) &= \mathcal{N}(u(\mathbf{x}) \mid 0, A^{-1}) \\ p_1(u(\mathbf{x})) &= \mathcal{N}(Du(\mathbf{x}) \mid 0, B^{-1}), \end{aligned}$$

that consider that the distortion and its gradient have zero mean and variance governed by A and B. Since the anisotropy is technically aligned with the imaging axes, these can be simplified:

$$\begin{aligned} p_0(u(\mathbf{x})) &= \sum_{\mathbf{x}} \mathcal{N}(u(\mathbf{x}) \mid 0, (\boldsymbol{\alpha}^{\circ\frac{1}{2}}\, \mathbf{I}_n)^{-1}) \\ p_1(u(\mathbf{x})) &= \sum_{\mathbf{x}} \mathcal{N}(\nabla \cdot u(\mathbf{x}) \mid 0, (\boldsymbol{\beta}^{\circ\frac{1}{2}}\, \mathbf{I}_n)^{-1}) \end{aligned} \tag{9}$$

Finally, we can turn the MAP problem into a variational one applying the following log-transform:

$$\begin{aligned} E(F \mid U) &= -\log \prod_l \prod_{\mathbf{x}\in\Omega_l} p_l(\mathbf{f}')\, p_0(u(\mathbf{x}))\, p_1(u(\mathbf{x})) \\ &= C + \sum_l \sum_{\mathbf{x}\in\Omega_l} \mathcal{D}_M^2(\mathbf{f}' \mid \Theta_l) \\ &+ \sum_{\mathbf{x}\in\Omega} \boldsymbol{\alpha}\cdot u(\mathbf{x})^{\circ 2} + \sum_{\mathbf{x}\in\Omega} \boldsymbol{\beta}\cdot(\nabla\cdot u(\mathbf{x}))^{\circ 2}, \end{aligned} \quad (10)$$

that is the dual expression to the energy functional corresponding to a discrete ACWE framework [10] with anisotropic regularization as studied in [49].

Using the region descriptors derived in subsection II-B, we propose an active deformation field (ADF)-like, ACWE-based, piece-wise constant, image segmentation model (where the unknown is the deformation field) [10] with the energy functional obtained in (**??**). This inverse problem is ill-posed [6, 24]. In order to account for deformation field regularity and to render the problem well-posed, we include limiting and regularization terms into the energy functional [46, 62]:

$$\begin{aligned} E(u) &= \sum_l \int_{\Omega_l'} \mathcal{D}_M^2(\mathbf{f} \mid \Theta_l)\, d\mathbf{x} \\ &+ \int \mathbf{u}^T A\, \mathbf{u}\, d\mathbf{x} + \int \mathrm{tr}\{(\nabla\mathbf{u}^T)^T B(\nabla\mathbf{u}^T)\} d\mathbf{x} \end{aligned} \quad (11)$$

These regularity terms ensure that the segmenting contours in dMRI space are still close to their native shape. The model easily allows to incorporate inhomogeneous and anisotropic regularization [49] to better regularize the EPI distortion.

this last paragraphs in red color were located a bit further, but I think we can keep some of the refs and still reproduce the continuous version of the energy functional

C. Numerical Implementation

Let us denote $\{\mathbf{c}_i\}_{i=1\ldots N_c}$ the nodes of one or several shape-prior surface(s). In our application, precise tissue interfaces of interest extracted from a high-resolution, anatomically correct reference volume. On the other hand, we have a number of dMRI-derived features at each voxel of the volume. Let us denote by $\mathbf{x}$ the voxel and $F(\mathbf{x}) = [f_1, f_2, \ldots, f_N]^T(\mathbf{x})$ its associated feature vector.

1) Deformation field: The transformation from "T1-" into "dMRI-" coordinate space is achieved through a dense deformation field $u(\mathbf{x})$, such that:

$$\mathbf{c}_i' = U\{\mathbf{c}_i\} = \mathbf{c}_i + u(\mathbf{c}_i), \quad (12)$$

where U is defined in (1). Since the nodes of the anatomical surfaces might lay off-grid, it is required to derive $u(\mathbf{x})$ from a discrete set of parameters $\{\mathbf{u}_k\}_{k=1\ldots K}$. Densification is achieved through a set of associated basis functions ψ_k:

$$u(\mathbf{x}) = \sum_k \psi_k(\mathbf{x})\mathbf{u}_k \quad (13)$$

In our implementation, ψ_k is chosen to be a tensor-product B-Spline kernel of degree 3 (B_3). Then, introducing (13) into (12) and replacing ψ by the actual kernel function, the transformation writes

$$c_i' = c_i + \sum_k \left[\mathbf{u}_k \prod_{x,y,x} B_3(c_{i,d} - \mathbf{x}_{k,d}) \right]. \quad (14)$$

Based on the current estimate of the distortion u, we can compute "expected samples" within the shape prior projected into the dMRI. Thus, we now estimate region descriptors of the dMRI features $\mathbf{f}'$ of the regions defined by the priors in dMRI space.

2) Gradient descent: To find the minimum of the energy functional (10), we propose a gradient-descent approach with respect to the underlying deformation field through the following partial differential equation:

$$\frac{\partial u(\mathbf{x},t)}{\partial t} \propto -\frac{\partial E(u)}{\partial u}, \quad (15)$$

with t being an artificial time parameter of the contour evolution, included to express the iterative character of the approach. Now, we can introduce (10) in (15):

$$\begin{aligned} \frac{\partial E(\mathbf{u})}{\partial \mathbf{u}_k} &= \frac{\partial}{\partial \mathbf{u}_k}\Big\{ C + \sum_l \sum_{\mathbf{x}\in\Omega_l} \mathcal{D}_M^2(\mathbf{f}' \mid \Theta_l) \\ &+ \sum_{\mathbf{x}\in\Omega} \boldsymbol{\alpha}\cdot u(\mathbf{x})^{\circ 2} + \sum_{\mathbf{x}\in\Omega} \boldsymbol{\beta}\cdot(\nabla\cdot u(\mathbf{x}))^{\circ 2} \Big\}. \end{aligned} \quad (16)$$

Whereas related ADFs introduced in subsection II-A make use of explicit level-set formulations to solve (16), we alternatively use *shape-gradients* [29, 33]. Let $r(\mathbf{x})$ be an "arbitrary" function over the image domain, and Ω a certain image region with $\Gamma_{l,m}$ its corresponding outer boundary as defined in subsection II-B. We now derive the domain integral w.r.t. t:

$$\frac{\partial}{\partial t}\int_\Omega r(\mathbf{x}')d\mathbf{x} = \int_\Omega \frac{\partial}{\partial t} r(\mathbf{x}')d\mathbf{x} - \int_{\Gamma_{l,m}} r(\mathbf{x}') \left\langle \frac{\partial \Gamma_{l,m}}{\partial t}, N_{\Gamma_{l,m}} \right\rangle d\mathbf{x}$$

where $\left\langle \frac{\partial \Gamma_{l,m}}{\partial t}, N_{\Gamma_{l,m}} \right\rangle$ is the projection of the boundary movement on the unit inward normal $N_{\Gamma_{l,m}}$. Assuming that the region descriptors Θ_l vary slowly enough, we can consider that $\frac{\partial}{\partial t} r(\mathbf{x}') = 0$ and thus:

$$\frac{\partial}{\partial t}\int_\Omega r(\mathbf{x}')d\mathbf{x} = -\int_{\Gamma_{l,m}} r(\mathbf{x}') \left\langle \frac{\partial \Gamma_{l,m}}{\partial t}, N_{\Gamma_{l,m}} \right\rangle d\mathbf{x} \quad (17)$$

Therefore, we can apply a discretized interpretation of (17) to compute the data term in (16) as follows:

$$\begin{aligned} \frac{\partial E_{data}(u)}{\partial \mathbf{u}_k} &= \sum_l \frac{\partial}{\partial u_k^d} \{ \sum_{\mathbf{x}\in\Omega_l} \mathcal{D}_l^{2^2}(\mathbf{f}') \} \\ &= \sum_{l,m} \sum_{\mathbf{c}'\in\Gamma_{l,m}} \left[\Delta_i^2(\mathbf{f}') - \Delta_j^2(\mathbf{f}') \right] \left\langle \frac{\partial \mathbf{c}'}{\partial u_k^a}, \mathbf{n_i}' \right\rangle, \end{aligned} \quad (18)$$

in this case, the formulation has been adapted to the non-binary case, l, m being any pair of neighboring regions, and $\Gamma_{l,m}$ the contour separating them such that $\mathbf{x}' = \mathbf{c}' \in \Gamma_{l,m} \iff \mathbf{x} \in \partial\Omega_i \cap \partial\Omega_j$ and $\mathbf{n_i}'$ is the unit inward normal to the contour at c_i'.

Finally, we can compute:

$$\frac{\partial}{\partial \mathbf{u}_k{}'}\mathbf{c}_i{}' = \frac{\partial}{\partial u_k^{a\prime}}\{c_i + \sum_k \psi_k(\mathbf{c}_i)\mathbf{u}_k\} = \psi_k(\mathbf{c_i})\,\hat{\mathbf{e}}^a \quad (19)$$

where $\hat{\mathbf{e}}^a$ is the unit vector along direction a. Projecting this gradient onto the surface normal, $\left\langle \frac{\partial \mathbf{c}'}{\partial u_k^{a\prime}}, \mathbf{n_i}' \right\rangle = \psi_k(\mathbf{c_i})\,\hat{\mathbf{n}}_i^a$, the full gradient evolution equation (16) yields:

$$\frac{\partial E(u)}{\partial \mathbf{u}_k} = \sum_{l,m}\sum_{\mathbf{c}'\in\Gamma_{l,m}} \left[\Delta_i^2(\mathbf{f}') - \Delta_j^2(\mathbf{f}')\right]\psi_k(\mathbf{c_i})\,\hat{\mathbf{n}}_i^a \\ 2\sum_{x,y,z} a_d u_{k,d}^a - 2\sum_{x,y,z} b_d \nabla u_{k,d}^a, \quad (20)$$

3) Semi-implicit Euler-forward optimization: It is necessary to discretize t in order to obtain a numerical implementation of the equation (20):

$$\frac{u^{t+1}-u^t}{\tau} = -\sum_{l,m}\sum_{\mathbf{c}'\in\Gamma_{l,m}} \left[\Delta_i^2(\mathbf{f}') - \Delta_j^2(\mathbf{f}')\right]\psi_k(\mathbf{c_i})\,\hat{\mathbf{n}}_i^a \\ - 2\sum_{x,y,z} a_d (u_{k,d}^a)^{t+1} + 2\sum_{x,y,z} b_d \nabla (u_{k,d}^a)^{t+1}. \quad (21)$$

The associated Euler-Lagrange equation is found as:

$$(\tau^{-1} + 2\,a_d - 2\,b_d\nabla)\,(u_{k,d}^a)^{t+1} = \tau^{-1}(u_{k,d}^a)^t - \frac{\partial E_{data}(u)}{\partial u_k^d}, \quad (22)$$

that is a linear system that we translate into Fourier domain, to obtain the next deformation field $(u_{k,d}^a)^{t+1}$:

$$(u_{k,d}^a)^{t+1} = \\ \mathcal{F}^{-1}\left\{ \frac{\mathcal{F}\{\tau^{-1}(u_{k,d}^a)^t - \sum_{l,m}\sum_{\mathbf{c}'\in\Gamma_{l,m}} \left[\Delta_i^2(\mathbf{f}') - \Delta_j^2(\mathbf{f}')\right]\}}{\mathcal{F}\{(\tau^{-1} + 2\,a_d)\mathcal{I} - 2\,b_d\Delta)\}} \right\} \quad (23)$$

Here, we rewrite the Laplacian as a linear combination of the identity and shift operators:

$$\Delta = \sum_d \mathcal{S}_d^- + \mathcal{S}_d^+ - 2\mathcal{I} \quad (24)$$

where $\mathcal{S}_d^{\pm}$ stands for the forward $(+)$ and backward $(-)$ shift operator along coordinates axis d, of which the Fourier transform is found easily as

$$\mathcal{F}\{\mathcal{S}_d^{\pm}\} = e^{\pm i\omega_d}, \quad (25)$$

where ω_d is the normalized pulsation along d-direction. Accordingly, the Fourier transform of the discrete Laplacian is found as

$$\mathcal{F}\{\Delta\} = \sum_d e^{-i\omega_d} + e^{i\omega_d} - 2 = \sum_d (2\cos(\omega_d) - 2) \quad (26)$$

The remaining transforms are trivial or can be computed using the fast fourier transform (FFT) as in [**?**].

4) Region descriptor reestimation: In regular intervals, after certain number of iterations, the parameters Θ_l of the regions can be reestimated based on the shifted volumetric samples $\mathbf{x}' = \mathbf{x_0} + u(\mathbf{x})$.

discuss choice of τ, Courant-Friedrichs-Lewy (CFL) condition, etc.

5) Convergence:

6) Efficient field densification: As long as the dense deformation field is iteratively interpolated from the same set of control points that define the $L-1$ contours, it is possible to pre-cache all the $\psi_k(c_i)$ weights into a sparse matrix for fast densification. As well, we achieve a diffeomorphic transform by

III. Data and Experiments

A. Image Data

1) Simulated digital phantom: The lack of a widely accepted *gold*-standard in the application field has been addressed by several authors [13] In this work, we use one of the most complete, and publicly available, digital phantoms (http://hardi.epfl.ch/static/events/2013_ISBI/testing_data.html). The phantom is a spherical volume containing a set of fiber bundles, that connect one area of a "cortex" to another. The model accounts for PVE using a similar approach to [12] and for CSF contamination as well.

2) Real MRI datasets: We used image data from XX healthy volunteers with no history of neurological conditions (ages XX±XX, X female) to illustrate the applicability of our approach. All the subjects were scanned in a 3T MR Scanner (Siemens Magnetom TrioTim, Siemens, Erlangen, Germany) with a standard 12-channel head coil.

check coil # channels

Subjects were scanned twice with the same protocol, described hereafter. After being scanned the first time, each subject exited the scan room for a short break and then reentered for an identical scan session. To note, there was a full repositioning of the volunteer, coils, blankets and pads before each scan and re-scan session. The scan session protocol was as follows:

1) Triplanar survey (Localizer).
2) Field Mapping: field mapping using GRE sequence was performed before dMRI acquisition for susceptibility correction purposes.
3) DTI: dMRI were acquired with axial in-plane isotropic resolution $2mm$, slice thickness $2mm$, $XXX \times XXX \times XXX$ image matrix, TR= XXXX ms, TE = XX ms, NEX = X, BW = XXXX Hz/pixel, GRAPPA acceleration factor 2. The series included images acquired with diffusion weighting along 30 non-collinear directions (b=700sm^{-2}) sampled twice for averaging, and 5 interleaved images acquired without diffusion weighting ($b = 0$).
4) Field Mapping (same as before DTI)
5) Structural T1: An MPRAGE T1-weighted acquisition, sagittal GRE sequence, in-plane isotropic resolution 1.0 mm, slice thickness 1.2mm $XXX \times XXX \times XXX$ image matrix, TR=2300 ms, TE=2.98 ms, FA= 9, NEX=X, BW= 240 Hz/pixel.
6) Structural T2: A T2-weighted acquisition, oblique axial TSE sequence, in-plane isotropic resolution 1.0 mm, slice thickness 1.2mm $XXX \times XXX \times XXX$ image

matrix, TR=3200 ms, TE= 408 ms, NEX=X, BW= 751 Hz/pixel.

B. Image preprocessing and shape-prior generation

Regardless the dataset type (simulated or real), all dMRI datasets were processed using the standard diffusion tensor imaging (DTI) reconstruction methods provided by FSL [1] to fit the tensor model and produce scalar maps of the required features. The properties of the reconstructed tensors and derived scalar maps have been studied by [17]. Based on their findings, FA (27) and MD (28) are considered complementary features, and therefore we selected them for the energy model (11) in driving the registration-segmentation process. Whereas FA informs mainly about the *shape* of diffusion, the MD is more related to the *magnitude* of the process:

$$\mathrm{FA} = \sqrt{\frac{1}{2}} \frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{{\lambda_1}^2+{\lambda_2}^2+{\lambda_3}^2}} \quad (27)$$

$$\mathrm{MD} = (\lambda_1+\lambda_2+\lambda_3)/3 \quad (28)$$

where λ_i are the eigenvalues of the diffusion tensor associated with the diffusion signal $S(\mathbf{q})$. There exist two main reasons to justify their choice. First, they are well-understood and standardized in clinical routine. Second, together they contain most of the information that is usually extracted from the dMRI-derived scalar maps [17].

Preprocessing differed between simulated and real datasets in the shape-prior surfaces generation, as we describe hereafter.

1) Simulated digital phantom: A description goes here: surfaces extraction, synthetic susceptibility artifact generation.

2) Real MRI data: We used a standard automated method available in *FreeSurfer* [18] to obtain the cortical gray/white boundary from the T1 scan [22]. Parcellations used to evaluate the repeatability of the method are also obtained from *FreeSurfer*.

C. Experiments and evaluation

1) Validation on the simulated digital phantom: We firstly evaluated our approach on the simulated data, using the distorted data with a deformation field similar to the susceptibility artifact that affects real dMRI data. To this end, we report the following indices:

- Surface error (SE), a distance between the one-to-one corresponding vertices, weighted by their respective Voronoi area.

$$MSE = \sum_k \sum_j^M w_j \left\| \mathbf{x}_j - \hat{\mathbf{x}}_j \right\| \quad (29)$$

  where $\mathbf{x}_j$ are the locations of the M vertices of the k priors, $\hat{\mathbf{x}}_j$ are the corresponding locations recovered, and w_j the weighting factor as the relative surface of the Voronoi area.

- Warping index (WI), L2-distance between the theoretical and the recovered deformation field.

$$WI = \frac{1}{N} \sum_i^N \left\| \mathbf{d}_i - \hat{\mathbf{d}}_i \right\| \quad (30)$$

  where $\mathbf{d}_i$ is the theoretical displacement vector at position i and $\hat{\mathbf{d}}_i$ is the recovered one at the same index position.
- Parcellation agreement, the SE averaged by defined region of interests (ROIs) between the theoretical and the recovered parcellations.
- number of fibers (NoF) agreement, between the fibers recovered on the original data and the processed data.

Additionally, the entropy of data is studied in both original and recovered datasets to draw another possible basis for the assessment of the real datasets. We also report the same indices for the outcome of a widely-used methodology that combines field-map susceptibility correction and T1-T2-dMRI registration .

I suggest to give it a compact name and define it in the pre-processing section or even before in the intro

2) Evaluation on real datasets: For the real datasets there is no published *gold*-standard to validate results. Thus, visual results are provided to let compare the performance with the NICEACRONYM standard methodology. Additionally, cross-comparison of repeatability results are provided. In this second evaluation strategy, all the indices defined in subsubsection III-C1 are reported.

IV. Results and Discussion

Please! Write me ASAP.

V. Conclusion

A novel application for the ACWE framework is proposed, with the aim at recovering the displacement field underlying the EPI geometrical distortions. Exploiting the segmentation properties of the ACWE and optimizing the displacement field, we describe a registration-segmentation methodology that simultaneously segmented and restored the distortion on dMRI-like synthetic data. Visual results and quantitative results are provided.

We implemented the methodology upon the widely used Insight Registration and Segmentation Toolkit [2] (ITK) for its computational benefits, the standardized code, and with the aim at making the procedure publicly available when ready for sharing with the research community.

Once proven the aptness of the methodology to the application with simplistic synthetic data, in further studies we will cover the actual performance on real images and the benefits of overcoming the described challenges (segmentation and EPI distortion correction) in one single step. Additional research lines regard with the use of more adequate optimization schemes and the use of an energy model better adapted to the specific nature of the dMRI data.

[1] DTIFIT, included in the FMRIB's Software Library (FSL), http://fsl.fmrib.ox.ac.uk/fsl/fsl-4.1.9/fdt/fdt_dtifit.html

[2] http://www.itk.org

We conclude recalling the importance of tackling with the numerous challenges that exist on the dMRI data processing in order to achieve reliable results on the whole-brain connectivity analysis.

ACKNOWLEDGMENT

The authors gratefully acknowledge V. Estellers for critical discussions at early stages of this project, A. Griffa for acquiring the real datasets used in this work, K. O'Brien for his discussions and clarifications regarding distortions and their foundations in dMRI, E. Caruyer for providing us with the simulated digital phantom, and L. Vese for her generous support.

REFERENCES

[1] A. L. Alexander, K. M. Hasan, M. Lazar, J. S. Tsuruda, and D. L. Parker. Analysis of partial volume effects in diffusion-tensor MRI. In *Proc. Intl. Soc. Mag. Reson. Med. 9 (ISMRM 2001)*, volume 45, pages 770–780, Glasgow, Scotland, UK, 2001.

[2] J. L. Andersson, C. Hutton, J. Ashburner, R. Turner, and K. Friston. Modeling geometric deformations in EPI time series. *NeuroImage*, 13(5):903–919, 2001.

[3] J. L. Andersson, S. Skare, and J. Ashburner. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *NeuroImage*, 20(2):870–888, 2003.

[4] S. Awate, H. Zhang, T. Simon, and J. Gee. Multivariate segmentation of brain tissues by fusion of MRI and DTI data. In *5th IEEE International Symposium on Biomedical Imaging: From Nano to Macro (ISBI 2008)*, pages 213–216, Paris, France, 2008.

[5] M. Bertalmio, G. Sapiro, and G. Randall. Morphing active contours. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 22(7):733–737, 2000.

[6] M. Bertero, T. A. Poggio, and V. Torre. Ill-posed problems in early vision. In *Proceedings of the IEEE*, volume 76, page 869–889, 1988.

[7] C. M. Bishop. *Pattern recognition and machine learning*, volume 4. Springer Science+Business Media, LLC, 2006. ISBN 978-0387-31073-2.

[8] X. Bresson, P. Vandergheynst, and J. P. Thiran. A variational model for object segmentation using boundary information and shape prior driven by the mumford-shah functional. *International Journal of Computer Vision*, 68 (2):145–162, 2006.

[9] T. Chan and W. Zhu. Level set based shape prior segmentation. In *IEEE Computer Society Conference on Computer Vision and Pattern Recognition (CVPR 2005)*, volume 2, page 1164–1170, San Diego, CA, USA, 2005.

[10] T. F. Chan and L. A. Vese. Active contours without edges. *IEEE Transactions on Image Processing*, 10(2): 266–277, 2001.

[11] Y. Chen, H. D. Tagare, S. Thiruvenkadam, F. Huang, D. Wilson, K. S. Gopinath, R. W. Briggs, and E. A. Geiser. Using prior shapes in geometric active contours in a variational framework. *International Journal of Computer Vision*, 50(3):315–328, 2002.

[12] T. G. Close, J.-D. Tournier, F. Calamante, L. A. Johnston, I. Mareels, and A. Connelly. A software tool to generate simulated white matter structures for the assessment of fibre-tracking algorithms. *NeuroImage*, 47(4):1288–1300, 2009.

[13] M.-A. Côté, G. Girard, A. Boré, E. Garyfallidis, J.-C. Houde, and M. Descoteaux. Tractometer: Towards validation of tractography pipelines. *Medical Image Analysis*, 2013.

[14] R. C. Craddock, S. Jbabdi, C.-G. Yan, J. T. Vogelstein, F. X. Castellanos, A. Di Martino, C. Kelly, K. Heberlein, S. Colcombe, and M. P. Milham. Imaging human connectomes at the macroscale. *Nature Methods*, 10(6): 524–539, 2013.

[15] D. Cremers, S. J. Osher, and S. Soatto. Kernel density estimation and intrinsic alignment for shape priors in level set segmentation. *International Journal of Computer Vision*, 69(3):335–351, 2006.

[16] M. Droske, W. Ring, and M. Rumpf. Mumford–Shah based registration: a comparison of a level set and a phase field approach. *Computing and Visualization in Science*, 12(3):101–114, 2009.

[17] D. B. Ennis and G. Kindlmann. Orthogonal tensor invariants and the analysis of diffusion tensor magnetic resonance images. *Magnetic Resonance in Medicine*, 55 (1):136–146, 2006.

[18] B. Fischl. FreeSurfer. *NeuroImage*, 62(2):774–781, 2012.

[19] M. Gastaud, M. Barlaud, and G. Aubert. Combining shape prior and statistical features for active contour segmentation. *IEEE Transactions on Circuits and Systems for Video Technology*, 14(5):726–734, 2004.

[20] S. Gorthi, V. Duay, N. Houhou, M. Bach Cuadra, U. Schick, M. Becker, A. S. Allal, and J.-P. Thiran. Segmentation of head and neck lymph node regions for radiotherapy planning using active contour-based atlas registration. *IEEE Journal of Selected Topics in Signal Processing*, 3(1):135–147, 2009.

[21] S. Gorthi, V. Duay, X. Bresson, M. Bach Cuadra, F. J. Sánchez Castro, C. Pollo, A. S. Allal, and J.-P. Thiran. Active deformation fields: dense deformation field estimation for atlas-based segmentation using the active contour framework. *Medical Image Analysis*, 15(6): 787–800, 2011.

[22] D. N. Greve and B. Fischl. Accurate and robust brain image alignment using boundary-based registration. *NeuroImage*, 48(1):63–72, 2009.

[23] A. Griffa, P. S. Baumann, J.-P. Thiran, and P. Hagmann. Structural connectomics in brain diseases. *NeuroImage*, In press, 2013.

[24] J. Hadamard. Sur les problèmes aux dérivées partielles et leur signification physique. *Princeton University Bulletin*, 13:49–52, 1902.

[25] A. Hadjiprocopis, W. Rashid, and P. S. Tofts. Unbiased segmentation of diffusion-weighted magnetic resonance images of the brain using iterative clustering. *Magnetic Resonance Imaging*, 23(8):877–885, 2005.

[26] P. Hagmann. *From diffusion MRI to brain connectomics*. PhD. thesis, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, 2005.

[27] P. Hagmann, P. E. Grant, and D. A. Fair. MR connectomics: a conceptual framework for studying the developing brain. *Frontiers in Systems Neuroscience*, 6: 43, 2012.

[28] D. Han, V. Singh, J. Lee, E. Zakszewski, N. Adluru, T. Oakes, and A. Alexander. An experimental evaluation of diffusion tensor image segmentation using graph-cuts. In *31st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC 2009)*, page 5653–5656, Minneapolis, Minnesota, USA, 2009.

[29] A. Herbulot, S. Jehan-Besson, S. Duffner, M. Barlaud, and G. Aubert. Segmentation of vectorial image features using shape gradients and information measures. *Journal of Mathematical Imaging and Vision*, 25(3):365–386, 2006.

[30] D. Holland, J. M. Kuperman, and A. M. Dale. Efficient correction of inhomogeneous static magnetic field-induced distortion in echo planar imaging. *NeuroImage*, 50(1):175, 2010.

[31] Y.-C. Hsu, C.-H. Hsu, and W.-Y. Tseng. Correction for susceptibility-induced distortion in echo-planar imaging using field maps and model-based point spread function. *IEEE Transactions on Medical Imaging*, 28(11):1850–1857, 2009.

[32] S. Jbabdi and H. Johansen-Berg. Tractography: Where do we go from here? *Brain Connectivity*, 1(3):169–183, 2011.

[33] S. Jehan-Besson, M. Barlaud, and G. Aubert. DREAM2S: deformable regions driven by an eulerian accurate minimization method for image and video segmentation. *International Journal of Computer Vision*, 53(1):45–70, 2003.

[34] A. K. Jha, M. A. Kupinski, J. J. Rodríguez, R. M. Stephen, and A. T. Stopeck. Task-based evaluation of segmentation algorithms for diffusion-weighted MRI without using a gold standard. *Physics in Medicine and Biology*, 57(13):4425, 2012.

[35] H. Johansen-Berg and M. F. Rushworth. Using diffusion imaging to study human connectional anatomy. *Annual Review of Neuroscience*, 32(1):75–94, 2009.

[36] L. Jonasson, X. Bresson, J. Thiran, V. Wedeen, and P. Hagmann. Representing diffusion MRI in 5-d simplifies regularization and segmentation of white matter tracts. *IEEE Transactions on Medical Imaging*, 26(11): 1547–1554, 2007.

[37] D. K. Jones, T. R. Knösche, and R. Turner. White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. *NeuroImage*, 73:239–254, 2013.

[38] S. Kumazawa, T. Yoshiura, H. Honda, F. Toyofuku, and Y. Higashida. Partial volume estimation and segmentation of brain tissue based on diffusion tensor MRI. *Medical physics*, 37(4):1482–1490, 2010.

[39] S. Kumazawa, T. Yoshiura, H. Honda, and F. Toyofuku. Improvement of partial volume segmentation for brain tissue on diffusion tensor images using multiple-tensor estimation. *Journal of Digital Imaging*, pages 1–10, 2013.

[40] J. Kybic, P. Thevenaz, A. Nirkko, and M. Unser. Unwarping of unidirectionally distorted EPI images. *IEEE Transactions on Medical Imaging*, 19(2):80 –93, 2000.

[41] C. Le Guyader and L. A. Vese. A combined segmentation and registration framework with a nonlinear elasticity smoother. *Computer Vision and Image Understanding*, 115(12):1689–1709, 2011.

[42] Y. Li, N. Xu, J. Fitzpatrick, V. Morgan, D. Pickens, and B. Dawant. Accounting for signal loss due to dephasing in the correction of distortions in gradient-echo EPI via nonrigid registration. *IEEE Transactions on Medical Imaging*, 26(12):1698–1707, 2007.

[43] T. Liu, H. Li, K. Wong, A. Tarokh, L. Guo, and S. T. Wong. Brain tissue segmentation based on DTI data. *NeuroImage*, 38(1):114–123, 2007.

[44] C.-F. Lu, P.-S. Wang, Y.-C. Chou, H.-C. Li, B.-W. Soong, and Y.-T. Wu. Segmentation of diffusion-weighted brain images using expectation maximization algorithm initialized by hierarchical clustering. In *30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC 2008)*, pages 5502–5505, Vancouver, Canada, 2008.

[45] J. L. Morgan and J. W. Lichtman. Why not connectomics? *Nature Methods*, 10(6):494–500, 2013.

[46] V. A. Morozov. Linear and nonlinear ill-posed problems. *Journal of Mathematical Sciences*, II(6):706–736, 1975.

[47] P. Mukherjee, S. W. Chung, J. I. Berman, C. P. Hess, and R. G. Henry. Diffusion tensor MR imaging and fiber tractography: Technical considerations. *American Journal of Neuroradiology*, 29(5):843–852, 2008.

[48] D. Mumford and J. Shah. Optimal approximations by piecewise smooth functions and associated variational problems. *Communications on Pure and Applied Mathematics*, 42(5):577–685, 1989.

[49] H.-H. Nagel and W. Enkelmann. An investigation of smoothness constraints for the estimation of displacement vector fields from image sequences. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, PAMI-8(5):565–593, 1986.

[50] K. O'Brien, A. Daducci, N. Kickler, F. Lazeyras, R. Gruetter, T. Feiweier, and G. Krueger. 3D residual eddy current field characterisation: applied to diffusion weighted magnetic resonance imaging. *IEEE Transactions on Medical Imaging*, Early Access Online, 2013.

[51] N. Paragios. A level set approach for shape-driven segmentation and tracking of the left ventricle. *IEEE Transactions on Medical Imaging*, 22(6):773–776, 2003.

[52] K. M. Pohl, J. Fisher, J. J. Levitt, M. E. Shenton, R. Kikinis, W. E. L. Grimson, and W. M. Wells. A unifying approach to registration, segmentation, and intensity correction. In J. S. Duncan and G. Gerig, editors, *8th International Conference of the Medical Image Computing and Computer-Assisted Intervention (MICCAI 2005)*, volume 3749 of *Lecture Notes in Computer Science*, page 310–318, Palm Springs, CA, USA, 2005. Springer Berlin

Heidelberg.

[53] K. M. Pohl, J. Fisher, W. E. L. Grimson, R. Kikinis, and W. M. Wells. A bayesian model for joint segmentation and registration. *NeuroImage*, 31(1):228–39, 2006.

[54] M. Rousson, C. Lenglet, and R. Deriche. Level set and region based surface propagation for diffusion tensor MRI segmentation. In *Computer Vision and Mathematical Methods in Medical and Biomedical Image Analysis*, volume 3117 of *Lecture Notes in Computer Science*, pages 123–134, Prague, Czech Republic, 2004. Springer Berlin Heidelberg.

[55] J. M. Soares, P. Marques, V. Alves, and N. Sousa. A hitchhiker's guide to diffusion tensor imaging. *Frontiers in Brain Imaging Methods*, 7:31, 2013.

[56] O. Sporns, G. Tononi, and R. Kötter. The human connectome: A structural description of the human brain. *PLoS computational biology*, 1(4):e42, 2005.

[57] C. Studholme, R. Constable, and J. Duncan. Accurate alignment of functional EPI data to anatomical MRI using a physics-based distortion model. *IEEE Transactions on Medical Imaging*, 19(11):1115–1127, 2000.

[58] P. C. Sundgren, Q. Dong, D. Gómez-Hassan, S. K. Mukherji, P. Maly, and R. Welsh. Diffusion tensor imaging of the brain: review of clinical applications. *Neuroradiology*, 46:339–350, 2004.

[59] J. Suri, K. Liu, S. Singh, S. Laxminarayan, X. Zeng, and L. Reden. Shape recovery algorithms using level sets in 2-d/3-d medical imagery: a state-of-the-art review. *IEEE Transactions on Information Technology in Biomedicine*, 6(1):8–28, 2002.

[60] R. Tao, P. T. Fletcher, S. Gerber, and R. T. Whitaker. A variational image-based approach to the correction of susceptibility artifacts in the alignment of diffusion weighted and structural MRI. In J. L. Prince, D. L. Pham, and K. J. Myers, editors, *21st Information Processing in Medical Imaging (IPMI)*, volume 5636 of *Lecture Notes in Computer Science*, pages 664–675, Williamsburg, VA, USA, 2009. Springer Berlin Heidelberg.

[61] J.-P. Thirion. Image matching as a diffusion process: an analogy with maxwell's demons. *Medical Image Analysis*, 2(3):243–260, 1998.

[62] A. N. Tichonov. Solution of incorrectly formulated problems and the regularization method. *Soviet Mathematics*, 4:1035–1038, 1963.

[63] G. Unal and G. Slabaugh. Coupled PDEs for non-rigid registration and segmentation. In *IEEE Computer Society Conference on Computer Vision and Pattern Recognition (CVPR 2005)*, volume 1, pages 168–175, San Diego, CA, USA, 2005.

[64] B. Vemuri and Y. Chen. Joint image registration and segmentation. In *Geometric Level Set Methods in Imaging, Vision, and Graphics*, page 251–269, New York, 2003. Springer-Verlag.

[65] F. Wang, B. C. Vemuri, and S. J. Eisenschenk. Joint registration and segmentation of neuroanatomic structures from brain MRI. *Academic radiology*, 13(9):1104–11, 2006.

[66] M. Wu, L.-C. Chang, L. Walker, H. Lemaitre, A. S. Barnett, S. Marenco, and C. Pierpaoli. Comparison of EPI distortion correction methods in diffusion tensor MRI using a novel framework. In D. Metaxas, L. Axel, G. Fichtinger, and G. Székely, editors, *11th International Conference of the Medical Image Computing and Computer-Assisted Intervention (MICCAI 2008)*, volume 5242 of *Lecture Notes in Computer Science*, pages 321–329, New York City, NY, USA, 2008. Springer Berlin Heidelberg.

[67] P. P. Wyatt and J. Noble. MAP MRF joint segmentation and registration of medical images. *Medical Image Analysis*, 7(4):539–552, 2003.

[68] A. Yezzi, L. Zollei, and T. Kapur. A variational framework for joint segmentation and registration. In *IEEE Workshop on Mathematical Methods in Biomedical Image Analysis (MMBIA), Proceedings*, page 44–51, Kauai, Hawaii, USA, 2001. IEEE Comput. Soc.

[69] A. Yezzi, L. Zöllei, and T. Kapur. A variational framework for integrating segmentation and registration through active contours. *Medical Image Analysis*, 7(2): 171–185, 2003.

[70] L. Zhukov, K. Museth, D. Breen, R. Whitaker, and A. Barr. Level set modeling and segmentation of DT-MRI brain data. *Journal of Electronic Imaging*, 12(1): 125–133, 2003.

[71] L. Zöllei, A. Stevens, K. Huber, S. Kakunoori, and B. Fischl. Improved tractography alignment using combined volumetric and surface registration. *NeuroImage*, 51(1): 206–213, 2010.