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

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***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 [1] which recently has accounted for a growing interest in its application to structural connectivity analysis of the brain. This emerging field exploits diffusion MRI (dMRI) data to derive the local axonal structure at each imaging voxel [2] and estimate a whole-brain mapping of fiber tracts represented by trajectories reconstructed from the local information. This comprehensive map of neural connections of the brain is called the *connectome* [3, 4]. The connectome analysis is a promising tool for neuroscience and clinical applications (**FIXME:** why? or references?).

Early dMRI research focused mainly on the improvements of imaging methodologies better understanding the diffusion effect and improving image reconstruction methodologies. Currently, the connectome extraction and analysis relies on a large amount of sophisticated computational techniques [5, 6] including acquisition, reconstruction, modeling and model fitting, image processing, fibre tracking, connectivity mapping, visualization, group studies, and inference. This growing complexity has given rise to challenging issues towards reliable structural information about the neuronal tracts [7, 8, 9], and statistical analysis [10]. Here,we shall address three tasks included within the image processing stage in a unified approach: brain tissue segmentation in diffusion space (subsection I-B), correction of geometrical distortions (subsection I-C), 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.

A. dMRI data overview

VERY brief look into signal generation HERE and cite reconstruction methods.

dMRI data is strongly affected by partial volume effects (PVEs) [11], which appear when several different tissues, or signal emitters, are present in the same imaging unit, producing an averaged intensity. The effect is directly related to the low resolution achievable with dMRI (typically around $2.0 \times 2.0 \times 2.0 mm^3$). An additional complication specific to dMRI is the cerebrospinal fluid (CSF) *contamination* [12], that is a particular PVE in which the signal sensed inside the affected voxel is linear with respect the grey matter (GM) and

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white matter (WM) contributions, but non-linear with respect CSF.

Generally speaking, alongside the difficulty posed by the low resolution, dMRI processing is also challenging due to the *direction dependency* of raw data.

Introduce here what are b0, fa, md, and direction dependency problem.

These low-b (or $b = 0$) volumes are acquired without direction gradient as reference, and present a T2-like contrast.

B. dMRI segmentation

A precise delineation of the CSF, GM and WM interfacing surfaces is required with sub-pixel resolution. The resulting segmentation is necessary to perform the majority of tractography algorithms and it is required 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 on the fractional anisotropy (FA) [13], a well-known scalar map derived from dMRI data which depicts the isotropy of water diffusion inside the brain. Although this methodology was popular among the premier 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 [14], directly on the diffusion raw data [15], or finding alternative diffusion representations [16]. 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 *low-b* volumes of dMRI data was proposed by [17]. Later studies investigated the application of probabilistic frameworks combining mixtures of gaussians, Markov Random Field (MRF) and labeling fusion techniques [18] 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 [19]. Some proposals suggest the use of the raw diffusion data (directionally dependent) to avoid fitting a certain model [20]. In [21], 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 [22].

A number of methods have been proposed using features not directly derived from dMRI data. Segmentation obtained by co-registering structural T1-weighted images will be covered in subsection I-D. Some other works delay the segmentation task after the tractogram is obtained, performing clustering on features derived on the tracts alignment [23], combined tract registration [24] or using tractography atlases [25]. However, methods based on tractography usually address the tractogram segmentation problem, to later combine the solution to answer the whole-brain segmentation problem.

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 [17, 18, 19, 20, 21]. Generally, results obtained with high resolution atlas co-registration (subsection I-D) are more compelling, minimizing the activity on this line which is currently being considered to be included in reconstruction algorithms [26]. *Golden-standard* evaluation frameworks have been proposed for the segmentation validation [27] on the task of lesion detection in visceral organs.

citations

C. Correction for susceptibility distortions

dMRI data are usually acquired with echo-planar imaging (EPI) sequences as they allow for very fast acquisitions, but they are known to suffer from geometrical distortions and artifacts due to, mainly, three sources: the subject motion between direction sampling, the induced *Eddy currents* on the scanner coils and finally distortions caused by the magnetic susceptibility inhomogeneity present at tissue interface. In this paper, we restrict ourselves to the last one, as it accounts for the major impact in the connectome analysis. *Susceptibility distortions* happen along the phase-encoding direction, and are most appreciable in the front part of the brain for the strong air/tissue interface surrounding the frontal sinuses.

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*, a number of methodologies have been developed to correct for the distortion, and are generically named as *EPI-unwarp* techniques [28, 29, 30, 31]. Unfortunately, the availability of the corresponding fieldmap is not always met.

Mention other problems: low precission, unreliability

Some other methodologies do not make use of the fieldmaps, compensating the distortion with non-linear registration from structural MRI [32] (see subsection I-D), or other means [33]. To our knowledge, there exists no study on the impact of the EPI distortion on the variability of tractography results.

D. Structural information co-registration

Therefore, 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. The significant benefits of exploiting the anatomical MRI when segmenting the dMRI data have been demonstrated [34], justifying the use of the shape prior information.

E. Summary

In this paper we propose a novel registration framework to simultaneously solving the segmentation and distortion challenges, by exploiting as strong shape-prior the detailed morphology extracted from high-resolution anatomical MRI. Indeed, hereafter we assume this segmentation problem in anatomical images as a solved by widely used available procedures. Moreover, the shape prior is of very "strong" nature, since it is specific to the particular subject. Also, after global alignment using existing approaches, the remaining spatial deformation between anatomical and diffusion space is due to EPI 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 diffusion weighted (DW) 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 DW 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. Methodological background

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 [35, 36, 37, 38, 39, 40, 41, 42]. These methods generally have a 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. Closely related to this group are atlas-based segmentation methods [43, 44, 45, 46, 47], where the prior imposes consistent voxel-based classification of contiguous regions. Here, the presence of more structures than one unique region of interest (ROI) helps aligning the target image with the atlas in a hierarchical fashion. Finally, the third group generalizes the atlas to actual images, and the contour is to segment simultaneously two different target images, related by a spatial transform to be co-estimated [48, 42].

B. Mumford-Shah Functional derivation from the Maximum A-Posteriori Model

A widely used approach to image segmentation is derived from the Bayes' rule (1), where one seeks for a partitioning of a certain image X in piecewise smooth regions $\Omega = \{\Omega_k, k \in [1..K]\}$, that maximizes the a posteriori probability given the multivariate image $X \in \mathbb{R}^C$, with C being the number of image channels.

$$p(Y \mid X) = \frac{p(X \mid Y)\, p(Y)}{p(X)}. \tag{1}$$

Therefore, Y is a certain realization of the piecewise disjoint region set Ω. $p(X \mid Y)$ is the *likelihood* of the realization of X (the image) given a certain distribution model for each region Ω_k. The second term, $p(Y)$, is the a-priori probability of the partitioning Y. Finally, $p(X)$ is the probability of a certain image realization, and thus, it will remain constant when computing the maximum a posteriori (MAP). Consequently, $p(Y \mid X) \propto p(X \mid Y)\, p(Y)$, and:

$$\underset{Y}{\operatorname{argmax}} \{p(Y \mid X)\} = \underset{Y}{\operatorname{argmax}} \{p(X \mid Y)\, p(Y)\}. \tag{2}$$

An extended assumption is that the feature vector realization X is *i.i.d.*, and thus, it is possible to write the a-posteriori probability $p(X \mid Y)$ as a continuous product with $d\mathbf{x}$ the infinitesimal voxel size:

$$p(X \mid Y)\, p(Y) = \prod_k \prod_{\mathbf{x} \in \Omega_k} p_k(X(\mathbf{x}) \mid Y(\mathbf{x}))^{d\mathbf{x}}, \tag{3}$$

where the prior probability $p(Y)$ is implicitly defined by the regions definition.

A second widely-accepted assumption is the multivariate normal distribution of the different tissues in MRI data. Therefore, the posterior probability of an infinitesimal voxel can be written as:

$$p_k(X(\mathbf{x}) \mid Y(\mathbf{x})) = \frac{1}{\sqrt{(2\pi)^C\ |\boldsymbol{\Sigma}_k|}}\, e^{\left(-\frac{1}{2}\Delta_k^2(\mathbf{X}(\mathbf{x}))\right)}. \tag{4}$$

where we can identify the factor in the exponential, with $\mathbf{f} = X(\mathbf{x})$ as the squared *Mahalanobis distance* with the parameters set $\Theta_k = \{\boldsymbol{\mu}_k, \boldsymbol{\Sigma}_k\}$:

$$\Delta_k^2(\mathbf{f} \mid \Theta_k) = (\mathbf{f} - \boldsymbol{\mu}_k)^T\, \boldsymbol{\Sigma}_k^{-1}\, (\mathbf{f} - \boldsymbol{\mu}_k). \tag{5}$$

Finally, we can turn the MAP problem into a variational

one applying the following log-transform:

$$E(X \mid Y) = -\log\left[p(X \mid Y)\, p(Y)\right] = \\ = -\log\left[\prod_k \prod_{\mathbf{x}\in\Omega_k} p_k(X(\mathbf{x}) \mid Y(\mathbf{x}))^{d\mathbf{x}}\right] = \\ = \sum_k \int_{\Omega_k} -\log\left[p_k(X(\mathbf{x}) \mid Y(\mathbf{x}))\right]\, d\mathbf{x}, \quad (6)$$

and introducing the posterior probability term (4), we can express the functional in terms of $\{\Theta_k, \Omega_k\}$:

$$E(\Theta_k, \Omega_k) = \\ = \sum_k \int_{\Omega_k} -\log\left[\frac{1}{\sqrt{(2\pi)^C\ |\mathbf{\Sigma}_k|}}\, e^{\left(-\frac{1}{2}\Delta_k^2(\mathbf{f})\right)}\right] d\mathbf{x} = \\ = \sum_k \int_{\Omega_k} \left[\frac{1}{2}\log\left((2\pi)^C\ |\mathbf{\Sigma}_k|\right) + \frac{1}{2}\Delta_k^2(\mathbf{f})\right] d\mathbf{x}. \quad (7)$$

Finally, after removing scaling factors and independent constants, we obtain:

$$E(\Theta_k, \Omega_k) = \sum_k \int_{\Omega_k} \left[\log|\mathbf{\Sigma}_k| + \Delta_k^2(\mathbf{f})\right]\, d\mathbf{x}, \quad (8)$$

(**FIXME:** bad explanation) where we have a constant term scaled by the total volume of the partition Ω_k and the determinant of the covariance matrix of the partition $|\mathbf{\Sigma}_k|$, plus an energy term based on the squared *Mahalanobis distance*.

Equation (8) resembles the Mumford-Shah functional including variance, that modifies the original functional in a way that it can deal with more general distributions. This is necessary to avoid the assumption that regions Ω_k have a fixed covariance matrix on their complete domain. One immediate advantage of this functional from the original one is the possibility to distinguish regions with the same mean vector but different covariance matrix [49]:

$$E(\Theta_k, \Omega_k) = \sum_k \int_{\Omega_k} \left[\log|\mathbf{\Sigma}_k| + \Delta_k^2(\mathbf{f})\right]\, d\mathbf{x} \\ + \lambda \int_{\Omega_k - K} (|\nabla\mu|^2 + |\nabla\mathbf{\Sigma}_k|^2)\, d\mathbf{x} + \nu|K|, \quad (9)$$

that is easily identifiable with (8) when we apply the so-called *cartoon limit*, for $\lambda \to \infty$:

$$E(\Theta_k, K) = \sum_k \int_{\Omega_k} \left[\log|\mathbf{\Sigma}_k| + \Delta_k^2(\mathbf{f})\right]\, d\mathbf{x} + \nu|K|. \quad (10)$$

As long as we do not penalize the edge set K length, $\nu = 0$ and the result is dual to (8):

$$E(\Theta_k, K) = \sum_k \int_{\Omega_k} \left[\log|\mathbf{\Sigma}_k| + \Delta_k^2(\mathbf{f})\right]\, d\mathbf{x}. \quad (11)$$

C. Deformation model

The segmentation problem is transformed into a registration one if the initial partition Y is derived from the initial shape-priors in reference space. Introducing a dense deformation field u that maps the original partition to a better fit of the regions in the target coordinate space. Thus, the minimization problem stated in (8) can be expressed so that u is the unknown:

$$E(u(\mathbf{x})) = \sum_k \int_{\Omega'_k} \left[\log|\mathbf{\Sigma}_k| + \Delta_k^2(\mathbf{f}')\right]\, d\mathbf{x} \quad (12)$$

where $\Omega'_k = u(\Omega_k)$ and $\mathbf{f}' = X(u(\mathbf{x}))$.

D. Active contours without edges based segmentation model

Let us denote $\{c_i\}_{i=1..N_c}$ the nodes of a shape prior surface. In our application, a precise WM-GM interface extracted from a high-resolution reference volume. All the formulations can be naturally extended to include more shape priors. On the other hand, we have a number of dMRI-derived features at each voxel of the volume. Let us denote by x the voxel and $f(x) = [f_1, f_2, \ldots, f_N]^T(x)$ its associated feature vector.
The transformation from reference into dMRI coordinate space is achieved through a dense deformation field $u(x)$, such that:

$$c'_i = T\{c_i\} = c_i + u(c_i) \quad (13)$$

Since the nodes of the anatomical surfaces might lay off-grid, it is required to derive $u(x)$ from a discrete set of parameters $\{u_k\}_{k=1..K}$. Densification is achieved through a set of associated basis functions Ψ_k (e.g. rbf, interpolation splines):

$$u(x) = \sum_k \Psi_k(x) u_k \quad (14)$$

Consequently, the transformation writes

$$c'_i = T\{c_i\} = c_i + u(c_i) = c_i + \sum_k \Psi_k(c_i) u_k \quad (15)$$

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 $f(x)$ of the regions defined by the priors in dMRI space. Using Gaussian distributions as region descriptors, we propose an active contours without edges (ACWE)-like, piece-wise constant, variational image segmentation model (where the unknown is the deformation field) [50]:

where R indexes the existing regions and the integral domains depend on the deformation field u. Note that minimizing this energy, $\mathrm{argmin}_u\{E\}$, yields the MAP estimate of a piece-wise smooth image model affected by Gaussian additive noise. This inverse problem is ill-posed [51, 52]. 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 [53, 54]:

$$E(u) = \sum_{\forall R} \{ \int_{\Omega_R} (f - \mu_R)^T \Sigma_R^{-1} (f - \mu_R) dx \} \\ + \alpha \int \|u\|^2 dx + \beta \int \left(\|\nabla u_x\|^2 + \|\nabla u_y\|^2 + \|\nabla u_z\|^2\right) dx \quad (16)$$

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 [55] to better regularize the EPI distortion.

At each iteration, we update the distortion along the steepest energy descent. This gradient descent step can be efficiently tackled by discretizing the time in a forward Euler scheme, and making the right hand side semi-implicit in the regularization terms:

$$\frac{u^{t+1}-u^t}{\tau} = -\sum_{i=1}^{N_c}\left[e(f(c_i'))\hat{n}_{c_i'}\Psi_{c_i}(x)\right] - \alpha u^{t+1} + \beta\Delta u^{t+1} \tag{17}$$

where the data terms remain functions of the current estimate u^t, thus $c_i' = c_i'(u^t)$. For simplicity on notation, we restricted the number of priors to only 1. We also defined $e(f(c_i')) = E_{out}(f(c_i')) - E_{in}(f(c_i'))$, and $E_R(f) = (f-\mu_R)^T\Sigma_R^{-1}(f-\mu_R)$. We applied a spectral approach to solve this implicit scheme:

$$u^{t+1} = \mathcal{F}^{-1}\left\{\frac{\mathcal{F}\{u^t/\tau - \sum_{i=1}^{N_c}\left[e(f(c_i'))\hat{n}_{c_i'}\Psi_{c_i}(x)\right]\}}{\mathcal{F}\{(1/\tau+\alpha)\mathcal{I} - \beta\Delta\}}\right\} \tag{18}$$

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 [56] 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 [57] 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. (**FIXME:** check coil number of 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 [13]. Based on their findings, FA (19) and MD (20) are considered complementary features, and therefore we selected them for the energy model (16) 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:

$$\mathrm{FA} = \sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{{\lambda_1}^2+{\lambda_2}^2+{\lambda_3}^2}} \tag{19}$$

$$\mathrm{MD} = (\lambda_1+\lambda_2+\lambda_3)/3 \tag{20}$$

where λ_i are the eigenvalues of the diffusion tensor associated with the diffusion signal $S(\vec{q})$. 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 [13].

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* [58] to obtain the cortical gray/white boundary from the T1 scan [59]. 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:

[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

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

$$MSE = \sum_{k} \sum_{j}^{M} w_j \left\| \mathbf{x}_j - \hat{\mathbf{x}}_j \right\| \tag{21}$$

  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.

$$WI = \frac{1}{N} \sum_{i}^{N} \left\| \mathbf{d}_i - \hat{\mathbf{d}}_i \right\| \tag{22}$$

  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 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 (**FIXME**: 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.

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

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.

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.

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