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 [5].

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 [6, 7] 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 [8–10], and statistical analysis [11]. 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 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 in between acquiring different sampling directions, 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

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of the brain for the strong air/tissue interface surrounding the frontal 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).

dMRI data is strongly affected by partial volume effects (PVEs) [12], 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 $2.0 \times 2.0 \times 2.0mm^3$). An additional complication specific to dMRI is the cerebrospinal fluid (CSF) *contamination* [13], that is a particular PVE in which the signal sensed inside the affected voxel is linear with respect the grey matter (GM) and white matter (WM) contributions, but non-linear with respect CSF.

Define *raw data*

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 $b = 0$ volumes (also called *EPI baseline*, low-b, or just B0) are acquired without direction gradient as reference, and they 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) [14], 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 [15], directly on the diffusion raw data [16], or finding alternative diffusion representations [17]. 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 [18]. Later studies investigated the application of probabilistic frameworks combining mixtures of gaussians, Markov Random Field (MRF) and labeling fusion techniques [19] 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 [20]. Some proposals suggest the use of the raw diffusion data (directionally dependent) to avoid fitting a certain model [21]. In [22], 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 [23].

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 [24], combined tract registration [25] or using tractography atlases [26]. 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 [18–22]. 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 [27]. *Golden*-standard evaluation frameworks have been proposed for the segmentation validation [28] on the task of lesion detection in visceral organs.

citations

C. 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, [29] 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 [30, 31].

Some other retrospective methodologies do not make use of the fieldmaps, as explicitly modeling the distortion [32], registering with (anatomically correct) T2-weighted MRI [33–36] (see subsection I-D), or acquiring an extra B0 image with reversed phase encoding direction [37].

To our knowledge, there exists no study on the impact of the susceptibility distortion over the subsequent tractography and connectome analyses. However, a comparison of the diverse correction techniques is found in [38]. This study claimed that fieldmap correction methodologies are not entirely accurate and reliable, even though the method is correct in principle. This conclusion was later confirmed by [36]. 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.

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 [39]. The second goal that has justified the applicability of structural images co-registration is susceptibility distortion correction as discussed in subsection I-C. In any case, susceptibility distortion hinders a rigid-registration solution to this end. 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 duality of acquisition procedure. However, parcellation is defined in T1 weighted space, adding an additional registration step missing on the literature due to the novelty of the task. Even though this registration step 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 [33], 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, [34] 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. The basis in the procedure is still the most extended. For instance, [38] also proposed a B-Spline registration providing quantitative comparisons with fieldmap correction methods. Recent approaches take into account the signal loss due to dephasing [35], or introduce more complex variational frameworks [36].

The significant benefits of exploiting the anatomical MRI when segmenting the dMRI data have been demonstrated [40], 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. Summary

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.

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 anatomically correct MRI. Indeed, hereafter we assume this segmentation problem in anatomical images is reliably and accurately solved with readily available tools. After global alignment 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.

(Rewrite) 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 [41**? ? ? ?**]. 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. By including a coordinates mapping, it is possible to perform active contours based registration between timesteps in a time-series or between different images [42–45]. This second group is closely related to atlas-based segmentation methods [46–50], 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

B. From the Maximum A-Posteriori Model to the Mumford-Shah functional

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:

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

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

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

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

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

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

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

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

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

improve this 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 [51]:

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

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

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

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

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

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:

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

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:

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

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):

$$u(x) = \sum_k \psi_k(x) u_k \tag{14}$$

Consequently, the transformation writes

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

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) [52]:

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 [53, 54]. 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 [55, 56]:

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

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 [57] 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:

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

E. Operator splitting

In order to make the Energy minimisation computationally more tractable, we propose the following operator splitting: Let us optimize the data terms and the regularity terms on separate copies of the deformation field, now called u and v, constrained to be equal:

$$\begin{aligned} E(u, v) = & \int_{w'(u)} (f - \mu_w)^T \Sigma_w^{-1} (f - \mu_w) dx \\ & + \int_{g'(u)} (f - \mu_g)^T \Sigma_g^{-1} (f - \mu_g) dx \\ & + \int_{o'(u)} (f - \mu_o)^T \Sigma_o^{-1} (f - \mu_o) dx \\ & + \int v^T A v dx + \int \mathrm{tr}\{(\nabla v^T)^T B (\nabla v^T)\} dx \end{aligned} \tag{19}$$

and now

$$\min_{u,v} \{E\} \quad s.t. \quad u = v \tag{20}$$

In order to take the equality constraint into account, we may make use of augmented Lagrangians (a combination of Lagrangian multipliers and penalty terms on the constraint) [58–60]:

$$AL(u, v, \lambda, r) = E(u, v) + \langle \lambda, u - v \rangle + \frac{r}{2} \|u - v\|_2^2 \tag{21}$$

To solve the constraint minimization problem, we may now optimize the Augmented Lagrangian in an iterative way:

$$\left\{ \begin{array}{lcl} u^{t+1} & = & \mathrm{argmin}_u \, AL(u, v^t, \lambda^t, r) \\ v^{t+1} & = & \mathrm{argmin}_v \, AL(u^{t+1}, v, \lambda^t, r) \\ \lambda^{t+1} & = & \lambda^t + \rho(u^{t+1} - v^{t+1}) \end{array} \right. \quad (22)$$

where typically $0 < \rho < r$. The two subminimization problems will now be much easier to handle than the original complete problem ("divide et impera").

F. Shape gradients

To compute the gradient-descent of the data-term domain integrals with respect to the underlying deformation field, we want to make use of shape gradients [61**?**]. A little bit of theory is therefore in order.

Let Ω be an image domain and ω its boundary. Further, $r(x)$ is an "arbitrary" function over the image domain. We now derive the domain integral w.r.t. the contour evolution parameter τ (time):

$$\frac{\partial}{\partial \tau} \int_\Omega r(x) dx = \int_\Omega \frac{\partial r}{\partial \tau}(x) dx - \int_\omega r(x) \left\langle \frac{\partial \omega}{\partial \tau}, N_\omega \right\rangle dx \quad (23)$$

where $\left\langle \frac{\partial \omega}{\partial \tau}, N_\omega \right\rangle$ is the projection of the boundary movement on the unit inward normal.

G. Min w.r.t. u

The first minimization problem optimizes the data-term. The problem is equivalent to minimizing the following energy:

$$\begin{aligned} E(u) = & \int_{w'(u)} (f - \mu_w)^T \Sigma_w^{-1} (f - \mu_w) dx \\ & + \int_{g'(u)} (f - \mu_g)^T \Sigma_g^{-1} (f - \mu_g) dx \\ & + \int_{o'(u)} (f - \mu_o)^T \Sigma_o^{-1} (f - \mu_o) dx \\ & + \langle \lambda, u - v \rangle + \frac{r}{2} \|u - v\|_2^2 \end{aligned} \quad (24)$$

where we identify three instances of domain integrals of the form $\int_\Omega r(x) dx$. Optimality requires the derivative of this energy with respect to the parameters u to be null. At this point, we may decide to ignore the influence of the boundary shift on the statistics of the regions (i.e. moving the boundary does not significantly impact the μ and Σ descriptors). This means that we can drop the derivative of $r(x)$ w.r.t. contour evolution. What remains, are surface integrals at the two respective domain interfaces, c' (wm/gm) and d' (gm/CSF), plus the Lagrangian and penalty terms:

$$\begin{aligned} \frac{\partial E}{\partial u_k^a} = & \int_{c'} \left[(f - \mu_g)^T \Sigma_g^{-1} (f - \mu_g) - (f - \mu_w)^T \Sigma_w^{-1} (f - \mu_w) \right] \left\langle \frac{\partial c'(s)}{\partial u_k^a}, N_{c'}(s) \right\rangle ds \\ & + \int_{d'} \left[(f - \mu_o)^T \Sigma_o^{-1} (f - \mu_o) - (f - \mu_g)^T \Sigma_g^{-1} (f - \mu_g) \right] \left\langle \frac{\partial d'(s)}{\partial u_k^a}, N_{d'}(s) \right\rangle ds \\ & + \lambda_k^a + r(u_k^a - v_k^a) \\ = & \, 0 \end{aligned} \quad (25)$$

where u_k^a is the a-th component of the parameter u_k, $a \in \{x, y, z\}$, s is the surface parameter, $c'(s)$ and $d'(s)$ the corresponding points on the surfaces c' and d', and $N_{c'}(s)$ and $N_{d'}(s)$ the associated brainwise-inward unit normals. Given the deformation field interpolation stated above, the boundary moves according to

$$\frac{\partial c'(s)}{\partial u_k^a} = \psi_k(c'(s)) e_a \quad (26)$$

where e_a is the unit vector along direction a, and thus

$$\left\langle \frac{\partial c'(s)}{\partial u_k^a}, N_{c'}(s) \right\rangle = \psi_k(c'(s)) N_{c'}^a(s) \quad (27)$$

Now, we will discretize the surface integrals over c' and d' by simply summing over the nodes c_i' and d_i':

$$\begin{aligned} \frac{\partial E}{\partial u_k^a} = & \sum_{i=1}^{N_c} \left[(f(c_i') - \mu_g)^T \Sigma_g^{-1} (f(c_i') - \mu_g) - (f(c_i') - \mu_w)^T \Sigma_w^{-1} (f(c_i') - \right. \\ & + \sum_{i=1}^{N_d} \left[(f(d_i') - \mu_o)^T \Sigma_o^{-1} (f(d_i') - \mu_o) - (f(d_i') - \mu_g)^T \Sigma_g^{-1} (f(d_i' \right. \\ & + \lambda_k^a + r(u_k^a - v_k^a) \\ = & \, 0 \end{aligned} \quad (28)$$

It is straightforward to solve this equation for u_k^a. The optimal distortion u_k is found at each iteration as:

$$\begin{aligned} u_k^{t+1} = & \, v_k^t - \frac{1}{r} \lambda_k^t \\ & - \frac{1}{r} \sum_{i=1}^{N_c} \left[(f(c_i') - \mu_g)^T \Sigma_g^{-1} (f(c_i') - \mu_g) - (f(c_i') - \mu_w)^T \Sigma_w^{-1} (f(\right. \\ & - \frac{1}{r} \sum_{i=1}^{N_d} \left[(f(d_i') - \mu_o)^T \Sigma_o^{-1} (f(d_i') - \mu_o) - (f(d_i') - \mu_g)^T \Sigma_g^{-1} (f(\right. \end{aligned} \quad (29)$$

H. Min w.r.t. v

It is important to realize that here we do not regularize the actual deformation field (i.e. after interpolation), but the underlying raw parameter field.

For the optimization w.r.t. v, the relevant energy writes

$$\begin{aligned} E(v) = & \int v^T A v dx + \int \mathrm{tr}\{(\nabla v^T)^T B (\nabla v^T)\} dx \\ & + \langle \lambda, u - v \rangle + \frac{r}{2} \|u - v\|_2^2 \end{aligned} \quad (30)$$

Let's assume the simplest, homogeneous isotropic case, $A = \alpha/2$ and $B = \beta/2$. The associated Euler-Lagrange equation is found as:

$$\alpha v - \beta \Delta v + r v = r u + \lambda \quad (31)$$

which easily translates into Fourier domain:

$$v^{t+1} = \mathcal{F}^{-1} \left\{ \frac{\mathcal{F}\{ru + \lambda\}}{\mathcal{F}\{(\alpha + r)\mathcal{I} - \beta \Delta\}} \right\} \quad (32)$$

where $\mathcal{I}$ denotes the identity operator.

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

$$\Delta = \mathcal{S}_x^- + \mathcal{S}_x^+ + \mathcal{S}_y^- + \mathcal{S}_y^+ - 4\mathcal{I} \tag{33}$$

where $\mathcal{S}_{x,y}^{\pm}$ stands for the forward $(+)$ and backward $(-)$ shift operator along x or y, respectively, of which the Fourier transform is found easily as

$$\mathcal{F}\{\mathcal{S}_{x,y}^{\pm}\} = e^{\pm i\omega_{x,y}}, \tag{34}$$

where $\omega_{x,y}$ is the normalized pulsation along x- and y-direction. Accordingly, the Fourier transform of the discrete Laplacian is found as

$$\begin{aligned}\mathcal{F}\{\Delta\} &= e^{-i\omega_x} + e^{i\omega_x} + e^{-i\omega_y} + e^{i\omega_y} - 4 \\ &= 2\left(\cos(\omega_x) + \cos(\omega_y) - 2\right)\end{aligned} \tag{35}$$

The remaining transforms are trivial or can be computed using FFT (as in [62]).

I. Lagrangian multiplier update

At each iteration, the Lagrangian multipliers are updated as noted before:

$$\lambda^{t+1} = \lambda^t + \rho(u^{t+1} - v^{t+1}) \tag{36}$$

J. Region descriptor reestimation

In regular intervals, i.e. after n iterations, the parameters μ and Σ of the involved regions need to be reestimated based on the shifted volumetric samples w'_j, g'_j and o'_j.

K. Convergence

In order to "fixate" the evolution when close to convergence, it is advised to slightly increase the penalty weight r at each iteration. Note that as can be seen in the above equations, r governs the step-size or leash-length at each iteration, i.e. the amount by which the new estimate u may move away from the preceding v and vice-versa.

L. Alternative route: Gradient descent

If one absolutely wants to avoid the operator splitting and the augmented Lagrangians, then simple gradient descent may work as well (at least under the same simple model circumstances).

At each iteration, we update the distortion along the steepest energy descent:

$$\frac{\partial u_k^t}{\partial t} = -\frac{\partial E(u)}{\partial u_k^t} \tag{37}$$

At this point, we interpret the parameter field u_k to be a continuous function $u(x)$, sampled at the locations x_k, and determine the gradient-descent equation[1]:

$$\begin{aligned}\frac{\partial u^t}{\partial t} = &-\sum_{i=1}^{N_c}\left[(f(c'_i)-\mu_g)^T\Sigma_g^{-1}(f(c'_i)-\mu_g) - (f(c'_i)-\mu_w)^T\Sigma_w^{-1}(f(c'_i\right. \\ &-\sum_{i=1}^{N_d}\left[(f(d'_i)-\mu_o)^T\Sigma_o^{-1}(f(d'_i)-\mu_o) - (f(d'_i)-\mu_g)^T\Sigma_g^{-1}(f(d'_i\right. \\ &-\alpha u + \beta\Delta u\end{aligned} \tag{38}$$

where we have swapped $\psi_k(c'_i)$ into $\psi_{c_i}(x)$.

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:

$$\begin{aligned}\frac{u^{t+1}-u^t}{\tau} = &-\sum_{i=1}^{N_c}\left[(f(c'_i)-\mu_g)^T\Sigma_g^{-1}(f(c'_i)-\mu_g) - (f(c'_i)-\mu_w)^T\Sigma_w^{-}\right. \\ &-\sum_{i=1}^{N_d}\left[(f(d'_i)-\mu_o)^T\Sigma_o^{-1}(f(d'_i)-\mu_o) - (f(d'_i)-\mu_g)^T\Sigma_g^{-}\right. \\ &-\alpha u^{t+1} + \beta\Delta u^{t+1}\end{aligned} \tag{39}$$

where the data terms remain functions of the current estimate u^t, i.e. all $c'_i = c'_i(u^t)$ and $d'_i = d'_i(u^t)$. Again, we propose a spectral approach to solve this implicit scheme:

$$u^{t+1} = \mathcal{F}^{-1}\left\{\frac{\mathcal{F}\{u^t/\delta - \sum_{i=1}^{N_c}(\ldots) - \sum_{i=1}^{N_d}(\ldots)\}}{\mathcal{F}\{(1/\delta+\alpha)\mathcal{I} - \beta\Delta\}}\right\} \tag{40}$$

It is easily verified, that the same update can be obtained by plugging the AL-update w.r.t. u into the AL-update w.r.t. v, and by identifying $r = 1/\delta$ (the only exception is the distortion on which the data-term is being evaluated).

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 [63] 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 [64] 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

[1]The same assumption was being made above in the minimization of the regularity terms

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 [2] 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 [14]. Based on their findings, FA (41) and MD (42) 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:

$$\mathrm{FA} = \sqrt{\frac{1}{2}} \frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{{\lambda_1}^2+{\lambda_2}^2+{\lambda_3}^2}} \quad (41)$$

$$\mathrm{MD} = (\lambda_1+\lambda_2+\lambda_3)/3 \quad (42)$$

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 [14].

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

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

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* [65] to obtain the cortical gray/white boundary from the T1 scan [39]. 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.

$$MSE = \sum_k \sum_j^M w_j \left\| \mathbf{x}_j - \hat{\mathbf{x}}_j \right\| \quad (43)$$

  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.

$$WI = \frac{1}{N} \sum_i^N \left\| \mathbf{d}_i - \hat{\mathbf{d}}_i \right\| \quad (44)$$

  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 .

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

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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 [3] (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.

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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