Statistical Properties of Jacobian Maps and the Realization of Unbiased Large-Deformation Nonlinear Image Registration


Abstract—Maps of local tissue compression or expansion are often computed by comparing magnetic resonance imaging (MRI) scans using nonlinear image registration. The resulting changes are commonly analyzed using tensor-based morphometry to make inferences about anatomical differences, often based on the Jacobian map, which estimates local tissue gain or loss. Here, we provide rigorous mathematical analyses of the Jacobian maps, and use it to motivate a new numerical method to construct unbiased nonlinear image registration. First, we argue that logarithmic transformation is crucial for analyzing Jacobian values representing morphometric differences. We then examine the statistical distributions of log-Jacobian maps by defining the Kullback–Leibler (KL) distance on material density functions arising in continuum-mechanical models. With this framework, unbiased image registration can be constructed by quantifying the symmetric KL-distance between the identity map and the resulting deformation. Implementation details, addressing the proposed unbiased registration as well as the minimization of symmetric image matching functionals, are then discussed and shown to be applicable to other registration methods, such as the inverse consistency registration. In the results section, we test the proposed framework, as well as present an illustrative application mapping detailed 3-D brain changes in sequential magnetic resonance imaging scans of a patient diagnosed with semantic dementia. Using permutation tests, we show that the symmetrization of image registration statistically reduces skewness in the log-Jacobian map.

Index Terms—Biomedical imaging, image matching, image registration, information theory, magnetic resonance imaging.

I. INTRODUCTION

NONLINEAR image registration is a well-established field in medical imaging with many applications in functional and anatomic brain mapping, image-guided surgery, and multimodality image fusion [1]–[6]. The goal of image registration is to align, or spatially normalize, one image to another. In multi-subject studies, this serves to reduce subject-specific anatomic differences by deforming individual images onto a population average brain template.

The deformations that map each anatomy onto a common standard space can be analyzed voxel-wise to make inferences about relative volume differences between the individuals and the template, or statistical differences in anatomy between populations, such as patients with Alzheimer’s disease and healthy elderly normal subjects [7]. Similarly, in longitudinal studies it is possible to visualize structural brain changes that occur over time by deforming subjects’ baseline scans onto their subsequent scans, and using the deformation map to quantify local changes [8]–[10]. This general area of computational anatomy has become known as tensor-based morphometry [11]–[15].

To construct a deformation that is smooth, one-to-one, and differentiable [6], [16]–[18], we must impose a regularizing constraint. Thus, the problem of image registration is often cast as a minimization problem with a combined cost functional consisting of an image matching functional and a regularizing constraint $R$ on the deformation. Common choices of image matching functional include squared intensity difference, cross correlation [19], and (normalized) mutual information or other divergence-based or information-theoretic measures [20]–[23], while choices of regularization usually involve differential operators inspired by thin-plate spline theory, elasticity theory, fluid dynamics and the Euler–Poincaré equations [1], [2], [17], [24].

II. THEORY-CONSTRUCTING UNBIASED DEFORMATION

One could not study nonlinear image registration without closely examining Jacobian maps. The Jacobian map is the determinant of the Jacobian matrix of a deformation field, and encodes the local volume difference between the source and target image (a value of 0.9 denotes 10% tissue loss, while 1.1 a 10% tissue increase). Log-transformation of a Jacobian field has become standard in most tensor-based morphometry papers [25], [26]. The Jacobian determinant of a diffeomorphic
map is bounded below by zero but unbounded above. Thus, the statistical distribution of Jacobian values would be a better fit to a symmetric distribution if we apply the logarithmic transform. This is important, for example, when testing for the presence of mean structural change in a multisubject experiment. In this case, one might want to employ classical statistical approaches and test the null hypothesis of zero mean change, at each voxel, using standard parametric statistics. A second argument in favor of logarithmic transform is that it symmetrizes the Jacobian distribution by considering halving or doubling of volume to be equally likely a priori, i.e., assigning equal probabilities to expansions and shrinkages that are reciprocals of each other. This is a reasonable requirement as the correspondence field should be the same regardless of the order of the two images that are matched; if mappings in both directions are considered, compressions or expansions are equally likely.

Thus, the logarithmic transform is crucial in analyzing Jacobian determinant values, and in this paper we argue that all pertinent statistical analyses should be conducted in this space. Of note, a related approach is taken by Pennec et al. [29], where the Cauchy-Green strain tensor [27], [28] of a deformation mapping is logarithmically transformed and used as a term in a penalty functional that is integrated over the image domain to regularize the deformation.

### A. Detecting No Change in the Absence of Real Change as a Necessary Criterion for Proper Registrations: Realizing Unbiased Test Statistics

In this section, we wish to derive some basic principles that any registration algorithm should satisfy in order to be applicable in real applications. To this end, we can construct cases in which we have a priori knowledge of the true Jacobian distribution, to which we can then compare the computed Jacobian maps. For example, consider nonlinearly registering one image to another image, with their only difference being noise. In this case, we expect the resulting log-Jacobian field to realize a null distribution as well. Thus, we argue that a necessary condition for any registration algorithm to be unbiased is to yield log-Jacobian maps that imply zero-change, when no difference other than noise is present between two registered images. We refer to this principle as the principle of realizing unbiased test statistics under null distribution.

Suppose $T$ (target) and $S$ (source), both defined on a computational domain $\Omega$, are the two images to be registered. Let us also assume, without loss of generality, that the volume of this domain is 1, i.e., $|\Omega| = 1$. We seek to estimate a deformation $h$ such that $h$ is nonlinearly mapped to $T$ when deformed by $h$ (i.e., $S(h(x))$). In this paper, we will restrict this mapping to be differentiable, one-to-one, and onto from the image domain onto itself (in practice/implementation, the one-to-one and onto property can be achieved by enforcing Neumann/Dirichlet boundary conditions or by extending the boundary towards infinity.

We will use the notation $u = (u_1, u_2, u_3)$, the displacement vector field away from the identity map, to represent the transformation $h$ (i.e., $h(x) = x + u(x)$). The inverse map $h^{-1}$ of $h$ (i.e., $h^{-1}(h(x)) = x$ for all $x$), thus, maps the target to the source image. We will also use the notation $\epsilon^{-1}$ to denote the displacement field of the inverse map $h^{-1}$. Let us denote the Jacobian matrix of $h$ as $Dh$ (with the $(i,j)$th element $\partial h_i/\partial x_j$). The Jacobian map can, thus, be defined as the determinant of the Jacobian matrix $|Dh(x)|$. Notice that this map estimates the local volume percentage difference of the source with respect to the target image. As a result, we consider the Jacobian map of $h$ to reside in the target reference frame, while we consider the Jacobian map of $h^{-1}$ to reside in the source reference frame (thus preserving the overall density integrated over the image domain)

$$\int_\Omega |Dh(\xi)| d\xi = \int_\Omega dy = 1 \quad \int_\Omega |Dh^{-1}(\xi)| d\xi = \int_\Omega dx = 1. \quad (1)$$

Here, $y$ and $x$ reference the target and source frame respectively. Given the preservation of density in (1), we can associate three probability density functions to the identity mapping ($id$) as well as the deformation $h$ and its inverse

$$pdf_h(\xi) = |Dh(\xi)|$$
$$pdf_{h^{-1}}(\xi) = |Dh^{-1}(\xi)|$$
$$pdf_{id}(\xi) = 1. \quad (2)$$

Let us also derive the following inverse matrix relationship by differentiating the identity $h^{-1}(h(x)) = x$ on both sides. We obtain

$$\text{Let } y = h(x) \text{ then}$$
$$Dh^{-1}(y) \cdot Dh(x) = Id$$

or

$$|Dh^{-1}(y)| \cdot |Dh(x)| = 1. \quad (3)$$

As discussed in previous sections, we consider log-Jacobian the natural test statistic when analyzing Jacobian maps. Now, let us integrate this test statistic on the whole image domain. The following calculation reveals that this simply computes the negative of the Kullback–Leibler (KL) distance between the probability density functions of identity map and $h$, and is always nonpositive

$$\int_\Omega \log |Dh(x)| \, dx = \int_\Omega \log \left(\frac{1}{|Dh(x)|}\right) \, dx$$

$$= \int_\Omega pdf_{id} \log pdf_{id} \, dx \quad \int_\Omega \log pdf_h \, dx \quad \int_\Omega pdf_h^{\epsilon^{-1}} \log pdf_{id} \, dx$$

$$= - \text{KL}(pdf_{id}, pdf_h) \leq 0. \quad (4)$$

Here, KL, the nonnegative asymmetric K-L distance, between two PDF’s $X$ and $Y$, is defined as

$$\text{KL}(X,Y) = \mathbb{E}_X [\frac{X}{Y}] = \int_X X \log \frac{X}{Y} \, dx \geq 0;$$
\[ \text{KL}(X,Y) \neq \text{KL}(Y,X); \]

\[ \text{KL}(X,Y) = 0 \iff X \equiv Y. \quad (5) \]

Thus, the equality in (4) holds if and only if the Jacobian map of \( h \) takes the constant value 1, or \( h \) is locally volume preserving everywhere. Interestingly, the KL distance in (4) has skew-symmetry with respect to \( h \) and its inverse

\[
\text{KL}(\text{pdf}_{id}, \text{pdf}_{h^{-1}}) = -\int_{\Omega} \log |Dh^{-1}(y)| dy \\
\quad y = h(x) \\
\quad = \int_{\Omega} \text{pdf}_h \log \frac{\text{pdf}_h}{\text{pdf}_{id}} dx \\
\quad = \text{KL}(\text{pdf}_h, \text{pdf}_{id}).
\]

Similarly, we have

\[
\text{KL}(\text{pdf}_{id}, \text{pdf}_h) = \int_{\Omega} -\log |Dh(x)| dx \\
\quad = \text{KL}(\text{pdf}_{h^{-1}}, \text{pdf}_{id}) \\
\quad = \int |Dh^{-1}(y)| \log |Dh^{-1}(y)| dy. 
\]  

(7)

To further show the close relationship between the KL-distance and Jacobian maps, we can also attach geometric meaning to the integral in (4), (6), (7). For example

\[
\text{KL}(\text{pdf}_{id}, \text{pdf}_{h^{-1}}) = -\int_{\Omega} \log |Dh^{-1}(y)| dy \\
\quad = \int_{\Omega} (\log |Dh(\xi)|)_{\xi = h^{-1}(y)} dy. 
\]

(8)

Here, the right-hand side simply computes the integral of the pulled-back (by the inverse of \( h \)) Jacobian map of \( h \).

To summarize, we conclude that symmetrizing KL distance is equivalent to considering both the forward and backward mapping in image registration. As a result, the skew-symmetry in (6) and (7) is closely related to the asymmetric nature of KL distance. In [30], the authors proposed integrating with respect to the square root of the Jacobian determinant, in order to remove this skew-symmetry. Interestingly, this approach has an equivalent in information theory, namely, the Bhattacharyya distance \( B \), another well-known measure [31]

\[
B(\text{pdf}_{id}, \text{pdf}_h) = \int |Dh(x)|^{1/2} dx \\
\quad = \int |Dh^{-1}(x)|^{1/2} dx \\
\quad = B(\text{pdf}_{h^{-1}}, \text{pdf}_{id}).
\]

(9)

Here, the Bhattacharyya distance, though not defined in the logarithmic space, is symmetrical with respect to its two arguments, as well as inverse-consistent. To further connect the KL-distance and Bhattacharyya distance, one can also consider the geodesic linking of the two PDFs: \( P(\cdot, t) \), parameterized by time \( t \)

\[
P(x, t) = \frac{\text{pdf}_{id}^t(x)^t \text{pdf}_h(x)^{1-t}}{N} \\
N = \int \text{pdf}_{id}^t(x) \text{pdf}_h(x)^{1-t} dx.
\]

(10)

The Bhattacharyya distance corresponds to the arbitrary choice of \( t = 1/2 \), while a generalization of the above leads to the Chernoff distance in information theory [32].

B. Realizing Unbiased Deformation in the Logarithmic Space Using Symmetrized KL-Distance

Before developing formulations to construct unbiased deformations in the logarithmic space, we generalize (4) to the case of mapping regions of interest (ROIs). Assuming we have a priori knowledge that one ROI is mapped to another [e.g., mapping ventricular changes in Serial magnetic resonance imaging (MRI) images], we again would like to recover a mapping that is unbiased in the logarithmic space. Intuitively, without further knowledge other than overall ROI mapping, the resulting Jacobian map should take a constant value inside the ROI.

This can again be achieved using the proposed formulations. Indeed, given any deformation \( g \) mapping domain \( A \) in the source (with volume \( a \)) to domain \( B \) in the target (with volume \( b \)), we have the following \( \int_A \log |Dg(x)| dx/a \leq \log b/a \), with equality obtained if and only if the Jacobian map of \( g \) takes a constant value (i.e., \( b/a \)). This generalization can be shown by observing that the logarithmic mapping is a convex mapping: \( \sum_i \log(x_i) \leq n \log(\bar{x}); \bar{x} = (1/n) \sum_i x_i \).

With the above generalization, one can see that, assuming the only constraint being an ROI mapping from \( A \) to \( B \), the unbiased mapping under the logarithmic operation has an evenly distributed Jacobian field, which is also intuitively correct (as there is no reason to assume nonuniformity of the Jacobian field inside the ROI).

C. Un-Biased Nonlinear Image Registration in the Logarithmic Space via KL Divergence

Given (4) and its generalization, we now propose to quantify the distance between any given deformation and the identity map by computing the symmetric KL distance through their density functions. Due to the above mentioned skew-symmetry, this distance takes the following several equivalent forms

\[
\text{KL}(\text{pdf}_h, \text{pdf}_{id}) + \text{KL}(\text{pdf}_{h^{-1}}, \text{pdf}_{id}) \\
= \text{KL}(\text{pdf}_h, \text{pdf}_{id}) + \text{KL}(\text{pdf}_{id}, \text{pdf}_h) \\
= \text{KL}(\text{pdf}_{id}, \text{pdf}_{h^{-1}}) + \text{KL}(\text{pdf}_{id}, \text{pdf}_h) \\
= \text{KL}(\text{pdf}_{id}, \text{pdf}_{h^{-1}}) + \text{KL}(\text{pdf}_{id}, \text{pdf}_h) \\
= \int (|Dh(x)| - 1) \log |Dh(x)| dx \\
= \int (|Dh^{-1}(y)| - 1) \log |Dh^{-1}(y)| dy.
\]

(11)
Given an image matching function, we argue that one achieves unbiased deformation by seeking, among all deformations minimizing this image matching functional, the deformation with minimal distance as given in (11).

To see why this approach leads to unbiased deformation in the logarithmic space, we observe that this integrand in (11) is always nonnegative, and only evaluates to zero when \( h \) is volume-preserving everywhere (Jacobian of \( h \) is 1 everywhere), thus, by treating it as a cost, we recover zero-change by minimizing this cost when we compare images differing only in noise. Second, this approach is also unbiased for mapping ROIs in the logarithmic space, due to the above generalization of (4).

Under this framework, constructing deformations can be viewed as quantifying the symmetric KL-distance between the identity map and the resulting deformation [or the inverse deformation due to the equivalence in (11)]. Moreover, this framework embeds statistical analyses into the construction of deformations, penalizing deformations that skew the distribution of test statistics. A second interpretation of (11) is that it simply calculates the mean log-Jacobian for \( h \) and its inverse inside the domain, thus computing the integral effect of the test statistics on the whole image domain as well.

To further link this approach to other branches of mathematics, optimization problems involving Jacobian operator are commonly encountered in grid generation [33] and in continuum mechanics, where the Hencky tensor arises in modeling very large deformations. However, we believe that the logarithmic transform has not been formally introduced in the grid generation literature and may also be useful there.

III. PRACTICAL IMPLEMENTATION CONCERNS

Here, we detail how this framework can be implemented. Given an image matching functional \( C \), as discussed in previous sections, we seek, among all deformations minimizing this matching cost, the deformation with minimal symmetric KL-distance from the identity as in (11). In practice, a numerical implementation can be achieved using the following combined minimization problem

\[
\arg\min_{h \in H} C(T, T \circ h^{-1}, S, S, \partial h) + \mu \mathbb{L}(\nabla \text{pdf}_i \nabla \text{pdf}_d) + \mathbb{L}(\text{pdf}_i \text{pdf}_d), \tag{12}
\]

Here, \( \mu \) is a weight parameter (or Lagrange multiplier), and \( H \) is the solution space. Often, the solution is numerically obtained by recursive smoothing or regularization applied to the force field. We, therefore, need to find the gradient descent direction contributed by the symmetric KL-distance term, via its Euler-Lagrange equation. To this end, let us denote \( \text{Co}_{ij} \) the matrix cofactor for the \((i, j)\)th component of the Jacobian matrix \( Dh \), we then obtain its Euler-Lagrange equation, using standard calculus of variations (see, for example, [34]) with respect to the \( j \)th coordinate as follows

\[
\sum_j \frac{\partial}{\partial f_{ij}} \left\{ (1 + \log |Dh(x)| - 1/|Dh(x)|) \text{Co}_{ij}(x) \right\} = 0
\]

\[
(Dh(x))^{-1} = \left( \text{Co}_{ij}(x) \right)^T / |Dh(x)|. \tag{13}
\]

A. Symmetrization of the Image Matching Functional—The Method of Equivalent Perturbation

In this section, we introduce the method of equivalent perturbation, an algorithm necessary for numerically solving the minimization of the symmetric image matching functional in (12) as well as other registration methods requiring optimization in both the forward and backward direction.

To motivate this method, we notice that to date all image matching functions available are unidirectional, while a completely symmetric formulation in (12) would require a symmetric image matching function as well. Nevertheless, any given unidirectional matching cost function \( C(T, S(h(x))) \) can be symmetrized as follows—similar to the step in (11) first-order

\[
C(T, S(h(x))) + C(S, T(h^{-1}(x))) \tag{14}
\]

However, this complicates numerical implementations. Unlike the symmetric KL-distance term in (12) that can be optimized in either forward or backward direction due to the equivalence relations in (11), minimizing (14) usually requires optimizing \( h \) and the inverse of \( h \) separately. This same dilemma was encountered in the pioneering paper on inverse consistency [35] (also see [36] for an earlier approach), where the authors propose the following minimization, similar to (14), with any given regularization penalty \( R(h) \) first-order

\[
E(T, S) = \underbrace{\int |S(h(x)) - T(x)|^2 \, dx}_{E_1} + \underbrace{\int |T(h^{-1}(x)) - S(x)|^2 \, dx}_{E_2} + \lambda R(h) \tag{15}
\]

Here, \( \lambda \) is a positive scalar weighting for the regularizers.

To solve (15) numerically, the authors separately considered the mappings in the forward and backward directions in (15) and solved for \( h \) and \( g \) separately with an additional inverse consistency constraint (weighted by \( \rho \)) so that \( g \) numerically realizes \( h^{-1} \).

\[
E_h(T, S) = \int |S(h(x)) - T(x)|^2 \, dx + \lambda R(h)
\]

\[
+ \rho \int \| h - (g)^{-1} \|^2 \, dx \tag{16}
\]

\[
E_g(T, S) = \int |T(g(x)) - S(x)|^2 \, dx + \lambda R(g)
\]

\[
+ \rho \int \| g - (h)^{-1} \|^2 \, dx. \tag{16}
\]

This splitting-up principle is also applicable to minimizing the general formulation in (14), but may not be optimal. Equation (16) is essentially a two-step strategy and creates a lag in estimating \( h \) and \( g \). Either \( h \) or \( g \) has to be alternately fixed (i.e., the
two maps are not estimated simultaneously). Moreover, an extra weighting parameter for the inverse consistency constraints has to be considered and was tuned case-by-case.

Here, we propose a more natural numerical algorithm, the method of equivalent perturbation, to solve minimization problems such as (14) and (15), instead of the modified 2-step approach in (16).

Given any infinitesimal perturbation $\xi$ applied to the inverse mapping, the method of equivalent perturbation seeks to solve for $\eta$, the perturbation in the forward mapping that preserves the fact that $h$ and $h^{-1}$ must be inverses of each other first-order

\[
give perturbation \quad h^{-1}(x) \rightarrow h^{-1}(x) + \varepsilon \xi(x)
\]

Solve $\eta(x)$ such that

\[
\lim_{\varepsilon \to 0} \frac{(h^{-1} + \varepsilon \xi) \circ (h + \varepsilon \eta)(x) - x}{\varepsilon} = 0
\]

or

\[
(h^{-1} + \varepsilon \xi) \circ (h + \varepsilon \eta)(x) = (h^{-1}(y) + \varepsilon \xi(y))|_{y=h(x)+\varepsilon \eta(x)} = x + O(\varepsilon^2).
\]

(17)

Here, $\varepsilon$ is an infinitesimally small positive number. Using this method of equivalent perturbation, we can, thus, combine all body forces in only the forward direction and solve (14) and (15) unidirectionally without explicitly involving the inverse mapping $h^{-1}$.

To solve for $\eta$, we expand (16), collect first-order terms of $\varepsilon$, and obtain the following equality:

\[
Dh^{-1}(y)|_{y=h(x)} \cdot \eta(x) = -\xi(h(x)).
\]

(18)

Recalling the inverse matrix relationship in (3), we obtain $\eta$ as a function of $\xi$ first-order

\[
\eta(x) = -D(h(x)) \cdot \xi(h(x)).
\]

(19)

In (19), the forward equivalent of a body force in the backward direction is computed using only the forward mapping $h$ (without involving $h^{-1}$), allowing us to circumvent the inherent numerical errors incurred when performing numerical inversion operations to go between $h$ and $h^{-1}$.

IV. RESULTS

A. Image Matching Using the Method of Symmetric KL Distance

In this section, we implement the proposed un-biased non-linear registration in Section II-C. To compute a numerical solution, we minimize the combined cost function as in (12).

To address the solution space $H$ in (12), we used the numerical scheme proposed in [20], which essentially is a fast solver and approximates the well-known viscous fluid registration model pioneered by Christensen et al. in [16]. The deformation fields were computed using adaptive time stepping, with maximal change in displacement of 0.1 allowed in each iteration. In order to obtain a fair comparison between the proposed and the viscous fluid method, re-gridding was not employed. Of note, re-gridding is essentially a memory-less procedure, as how images are matched after each re-gridding is independent of the final deformation before the re-gridding, rendering the comparison of final Jacobian fields and cost functionals problematic. Moreover, we consider the strategy of re-gridding, through the relaxation of deformation fields over time, to be less rigorous from a theoretical standpoint.

In Figs. 1–3, we show the results of matching two 2-D binary images (each of size 289 × 289), representing midline corpus callosum contours of two control subjects. Both the viscous fluid registration method without regridding (D’Agostino’s algorithm) and the proposed method generated a close match between the deformed image and the target (Figs. 1 and 2). Here, we used the sum of squared difference as the image matching functional, and optimal matching was considered achieved once the overall cost functional stopped decreasing. The weight $\psi t = 1,000$ was used in (12) for the proposed method. However, as seen in Fig. 2, the proposed method more evenly distributes deformation inside the corpus callosum. Indeed, given only binary images depicting corpus callosal contours (without other information inside the contour), one can argue that the Jacobian field should be evenly distributed. Fig. 2(c) and (d) illustrates that the Jacobian field of the proposed method is more evenly distributed inside corpus callosum. The histograms of the Jacobian field inside the ROI are shown in Fig. 2(e) and (f) (the histogram for the proposed method is noticeably sharper). Fig. 3(a) plots the standard deviation of the Jacobian field inside the contour as a function of iteration number. For the viscous fluid method, the standard deviation increased with the number of iterations, since the grid became less regular. On the other hand, the proposed method generated a grid with smaller standard deviation which

![Fig. 1. Corpus callosum example. (a) subject 1; (b) subject 2; (c) subject 1 is deformed to subject 2 using the viscous fluid method; (d) subject 1 is deformed to subject 2 using the proposed method.](image-url)
Finally, we implemented the proposed method in 3-D and tested it on the original 3-D MRI volumes (see next section as well as Fig. 8 for details; the initial scan and the 6-year follow-up scan of a patient with semantic dementia were used), with \( w_{fl} = 500 \). In Fig. 7(a) and (c), the 3-D Jacobian map generated using the viscous fluid method is visually very noisy with extreme values along the boundaries of the brain as well as in the background, masking the real change over the right temporal area. In contrast, as shown in Fig. 7(b) and (d), right temporal atrophy (RT) and ventricular enlargement (V) are easily visualized in the Jacobian map generated using the proposed method, demonstrating its theoretical and practical advantages.

**B. Applying the Method of Equivalent Perturbation to Inverse Consistent Mapping**

Three-dimensional T1-weighted MRI of a 57-year-old male patient diagnosed with semantic dementia were obtained using a gradient echo acquisition (TR 25 ms, TE 5 ms, slice thickness 1.5 mm, FOV 24 × 18 cm, flip angle 40°, no gaps). Four serial scans were obtained (baseline scan in 02/1993; follow-up scans in 10/1994, 02/1996, and 08/1999). The baseline (target) and the final follow-up (source) scans were used to evaluate the proposed approach. The two scans were first rigidly aligned and re-sliced to an isotropic volume of size 180 × 180 × 180 (a \( \text{voxel} = 1 \text{mm}^3 \)). We then tested the method of equivalent perturbation by applying it to compute an inverse consistent registration deforming the source back to the target. Instead of using SSD as the matching cost functional as in [35], we maximized the mutual information (MI), now considered one of the most versatile matching functionals, between the deforming source and target image. For the regularization, we followed the formulations in [35] with the following linear elasticity operator:

\[
\hat{R}(u) = \int \left| -\Delta u - \beta \nabla (\nabla \cdot u) \right|^2 \mathrm{d}x, \tag{20}
\]

Here, \( \Delta \) is the Laplacian and \( \alpha \) and \( \beta \) are the Lamé constants (both set to be 1.0). As in [35], the Fast Fourier transform technique (FFT) is applied to parameterize the displacement field. A multiresolution minimization scheme can then be implemented in the frequency domain.

This spatial normalization of scans over time allowed local tissue change to be estimated as was previously mentioned. A multiresolution scheme starting from the \( 32 \times 32 \times 32 \) FFT resolution was used (\( \lambda = 10^{-4} \); time step = \( 3 \times 10^{-6} \)), and numerical convergence was checked every 20 iterations (convergence criteria was met when the MI failed to increase by 0.001 after one iteration). 40 iterations were computed in each FFT resolution before the resolution was increased by a factor of 2 (with the time step decreased to one-tenth) in each dimension. Fig. 8 plots three orthogonal views of the four Serial MRI scans, showing prominent left temporal lobe atrophy (L), as well as a relative preservation of the right temporal lobe (R). However, closer inspection of the Jacobian map (Fig. 9) shows more active atrophy in the right temporal lobe, as well as bilateral tissue loss in the caudate (RC, LC), putamen (RP, LP), and thalamus (RT, LT), while less active atrophy was detected in the left temporal area.
Fig. 3. Corpus callosum example. (a) Standard deviation of Jacobian values inside corpus callosum per iteration. (b) Symmetric KL distance. For the viscous fluid method (dashed blue), both standard deviation and symmetric KL distance increase, whereas for the proposed method (solid red), both standard deviation and symmetric KL distance decrease and stabilize.

Fig. 4. Two-dimensional serial MRI example. (a) initial scan (02/1993, refer to Fig. 8); (b) follow-up scan (08/1999, refer to Fig. 8); (c) initial is deformed to follow-up using the viscous fluid method; (d) initial is deformed to follow-up using the proposed method.

lobe during the same time period. Fig. 10 plots the values of the MI term and the regularizer versus iterations in the forward and backward direction using the proposed inverse consistent approach in (15), and an inconsistent approach [minimizing only the term $E_1$ in (15)]. Here, the consistent mapping achieved not only higher MI values, but also lower regularizer values.

To show the reduction of inverse consistency errors, we compared the deformation with that obtained by switching the order of source/target. Ideally, the deformation should not depend on the order of the input images and, thus, inverse consistency can be assessed by examining the difference (Table I) in the deformation pair. For comparison, the corresponding errors using

Fig. 5. Two-dimensional serial MRI example. The top row shows results obtained using (a) the viscous fluid method and (b) the proposed method. Blue, yellow and red contours represent the boundaries of the ventricles in initial, follow-up, and deformed initial, respectively. Note that for both methods, yellow contour is essentially invisible due to a very close match. However, the resulting grid of the proposed method is visually more regular. The middle row shows the visualization of the Jacobian maps of the deformations for (c) the viscous fluid method and (d) the proposed method. The bottom row shows histograms of Jacobian values of the deformations inside ventricles for (e) the viscous fluid method and (f) the proposed method.
Fig. 6. Two-dimensional serial MRI example. (a) Standard deviation of Jacobian values inside the ventricle per iteration. (b) Symmetric KL distance. For the viscous fluid method (dashed blue), both standard deviation and symmetric KL distance increase, whereas for the proposed method (solid red), both standard deviation and symmetric KL distance stabilize.

Fig. 7. Three-dimensional serial MRI example. Jacobian maps are superimposed with the deformed volumes for the viscous fluid method (a) and (c) and the proposed method (b) and (d). Right temporal atrophy (RT) and ventricular enlargement (V) are easily visualized in the Jacobian map generated using the proposed method, while the viscous fluid method generated a very noisy map.

The inconsistent algorithm are also reported. The proposed algorithm yielded smaller errors in all aspects, and on average decreased the mean error to about one-seventh compared to the inconsistent algorithm.

Next, we examined the statistical properties of the log-Jacobian values. Recall in Section II, we discussed that the symmetrization of registration often reduces left skewness in the corresponding Jacobian distribution as it evenly penalizes compression/expansion of the same factor (also refer to [37] for a detailed discussion on why compressions are easier to achieve). We aimed to test if this reduction in skewness can be statistically confirmed using this dataset. Here, we used the standard measure of skewness in statistics, i.e., the third moment about the mean divided by the third power of the standard deviation.

To test the hypothesis of symmetry around zero, we employ permutation testing to generate samples statistically equivalent, under the null hypothesis, to the two log-Jacobian distributions. When testing whether any given distribution is symmetric...
around zero, we generate 10000 samples by randomly flipping the sign of the log-Jacobian value at each voxel, as under the null hypothesis that the observed distribution is symmetric around zero, each value is equally likely to be positive or negative. The next step involves picking a suitable test statistic, in this case the mean value of the re-sampled distribution (under the null hypothesis, the mean value is simply zero). To compute a $p$-value, we then rank the observed test statistic relative to the re-sampled test statistics.

For example, if the observed mean log Jacobian value ranks at 50 percentile among all re-sampled test statistics using samples generated from the observed Jacobian map, then the $p$-value is 0.5 and, thus, we cannot reject the null hypothesis at a conventional threshold level of 0.05 (see [10], [38], which describe the benefits of permutation testing for performing inferences in brain imaging).

In the case of the log Jacobian distribution generated using inverse consistent matching, no null re-sampled test statistic (the mean log Jacobian value) (maximum $7.67 \times 10^{-5}$; minimum $-8.23 \times 10^{-5}$) was as extreme as the observed statistic of $-0.0011$, thus allowing us to reject the null hypothesis with statistical significance ($p < 0.0001$). Similarly, the null hypothesis that the log Jacobian distribution generated using the inconsistent matching is symmetric around zero was also rejected ($p < 0.0001$). We then relaxed the null hypothesis and tested if the two Jacobian distributions were symmetric around their corresponding mean values (without assuming the mean is zero) using another permutation test (random flipping around the observed mean) with skewness as the test statistic. Fig. 11(c) shows the histogram of the re-sampled statistics. In the case of inverse consistent matching, the one-sided $p$-value is 0.067 and, thus, the null hypothesis (of symmetry around its mean) cannot be rejected at the 5% significance level. By contrast, a similar skewness permutation test performed on the log Jacobian distribution under the inconsistent mapping yielded a $p < 0.0001$, thus detecting a statistically significant skewness.

Thus, using this single subject example, we were able to detect a statistically significant left skewed log Jacobian distribution in the case of inconsistent matching, but not in the case of inverse consistent matching.

Finally, by directly comparing these two log-Jacobian distributions, we formally tested the presence of statistically significant differences in these two distributions. As discussed in Section II, one would argue that, by more equally penalizing compression and expansion (easier to achieve expansions of the same magnitude compared to unidirectional approach) a symmetrized method would shift the mean log Jacobian value rightward (i.e., it would become less negative). We formally tested the statistical significance of this shift using a third permutation test Fig. 11(d). The test statistic in this case was the difference of the mean log Jacobian values between consistent and inconsistent mappings, with the observed statistic $6.066 \times 10^{-4}$. 10000 samples of this test statistic were calculated by generating two re-sampled distributions using random shuffling of each element in the two observed distributions (under the null hypothesis that the two distributions are the same, we can randomly assign each element to either distribution). Again, not a single re-sampled test statistic ($\max 9.44 \times 10^{-5}$, $\min -8.73 \times 10^{-5}$) was as extreme as the observed and, thus, a statistically significant difference was detected between the two observed distributions.

To summarize, we showed, in this section, that symmetrization of a unidirectional registration method changes the distribution of the corresponding Jacobian values. Namely, the symmetrized registration method in general achieved a less left-skewed log Jacobian distribution, making it more symmetric around its mean value, as well as shifted the mean value rightward (less negative). Moreover, these effects can be confirmed.

**TABLE I**

<table>
<thead>
<tr>
<th>Forward mapping (inverse consistent)</th>
<th>$u_{c,b}$</th>
<th>$u_{c,b}^{*}$</th>
<th>$u_{c,b}$</th>
<th>$h_{b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum</td>
<td>0.3893</td>
<td>0.8290</td>
<td>0.4345</td>
<td>0.8616</td>
</tr>
<tr>
<td>Mean</td>
<td>0.0047</td>
<td>0.0071</td>
<td>0.0049</td>
<td>0.0115</td>
</tr>
<tr>
<td>Backward mapping (inverse consistent)</td>
<td>$u_{c,b}$</td>
<td>$u_{c,b}^{*}$</td>
<td>$u_{c,b}$</td>
<td>$h_{b}$</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.2751</td>
<td>0.8009</td>
<td>0.4145</td>
<td>0.8107</td>
</tr>
<tr>
<td>Mean</td>
<td>0.0048</td>
<td>0.0071</td>
<td>0.0047</td>
<td>0.0115</td>
</tr>
<tr>
<td>Forward mapping (inverse inconsistent)</td>
<td>$u_{c,b}$</td>
<td>$u_{c,b}^{*}$</td>
<td>$u_{c,b}$</td>
<td>$h_{b}$</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.8499</td>
<td>0.9009</td>
<td>0.9884</td>
<td>0.9579</td>
</tr>
<tr>
<td>Mean</td>
<td>0.0322</td>
<td>0.0288</td>
<td>0.0362</td>
<td>0.0674</td>
</tr>
</tbody>
</table>

**Fig. 9.** Three-dimensional Jacobian map of the brain changes recovered in the semantic dementia patient shows active right temporal lobe atrophy (lower panel axially cut through the temporal lobes) and deep nuclear involvement (upper panel; see text). Here, LP and RP denote the left and right putamen; LC and RC the left/right caudate head; LT and RT the left/right thalamus.
to be statistically significant in real applications. The implication of these experiments can be far reaching in that registration methods/regularizers, often regarded as simply matters of choice, may be more influential than they seem. They deserve rigorous mathematical and theoretical explorations in order to fully understand their impacts when interpreting brain imaging results.

V. DISCUSSIONS

Over the past decade, a few studies have investigated the influence of regularization techniques and the logarithmic transformation on Jacobian fields. For example, Ashburner et al. [26] reported an important innovation in which they defined a logarithm-type deformation penalty on triangles in a 2-D image domain. For each triangle in 2-D, the penalty is defined as: \( \lambda [1 + \text{det}(J)] \), \( \log s_{11} + \log s_{22} \)/2, where \( \lambda \) is a Lagrange multiplier on the regularizer, \( J \) is the Jacobian determinant, and \( s_{11} \) and \( s_{22} \) are the eigenvalues of the deformation tensor. The term \( 1 + \text{det}(J) \) integrates the cost with respect to the undeformed lattice, and the final term penalizes logarithmically-transformed eigenvalue deviations in the local deformation tensor but not rotations. This cost per triangle can be summed over the image domain and thought of as a cost functional that integrates the deviation of the eigenvalue distribution from log-normal. Following a similar rationale, a variational penalty could be formulated to penalize deformations whose Jacobian PDFs deviate from log-normal. For

---

**Fig. 10.** (a) and (b) The mutual information and (c) and (d) the regularizer, calculated using (20) are plotted against the iteration number (x axis) in both (a) and (c) the forward and (b) and (d) backward direction. The transient increase of the values around iteration 40 is due to the upsampling of the displacement FFT parameterization.
example, using tensor computation in the log-Euclidean space, a Riemannian elasticity regularizer was recently proposed [29] that calculates the integral of the trace of $(\log \Sigma)^2$ on the image domain. Here, $\Sigma$ is the Cauchy-Green tensor, defined as the Jacobian matrix left-multiplied by its transpose. Of note, this Riemannian elasticity regularizer has a very similar form to the proposed formulations in this paper.

More recently, a new approach termed “large-deformation diffeomorphic metric matching,” or LDDMM [17], was proposed by regularizing a velocity field that integrates to the displacement, allowing for arbitrarily large deformation as well as automatic inverse consistency. A formulation based on momentum of deformation maps and “geodesic shooting” is proposed to introduce a metric on the group of diffeomorphic mappings. Though extremely powerful, this approach is computationally expensive, as it requires integration of the velocity field in time. Moreover, this approach does not address the statistical analysis of resulting deformation maps at a voxel level, which becomes relevant in brain mapping applications.

VI. CONCLUSION

In this paper, we characterized the statistical properties of the Jacobian maps that arise in deformation-based morphometry, both empirically and theoretically, by applying the KL distance to the set of material density functions in both target and source coordinates. We then proposed a framework for constructing unbiased deformation fields. Details on implementing this framework were discussed, along with the development of a numerical algorithm tackling minimization problems in the presence of body forces from both the forward and backward directions. This is commonly encountered in newer nonlinear image registration methods (e.g., the inverse consistent approach), where the symmetrization of registration often requires minimization in both directions. We then tested the proposed framework, and showed that it simplified the implementation of inverse consistent matching.

Finally, the statistical theory of these distributions has strong ties with information theory. Our conclusion has important consequences when performing statistical tests on maps of tissue change in both longitudinal and inter subject/group studies. As interest increases in tensor-based morphometry for clinical and basic neuroscience studies, there is a growing need to rigorously evaluate various aspects of the process. Ongoing work is also focusing on the optimal filtering of the Jacobian fields, using approaches analogous to sigma-filtering [39] and on the modeling the null distributions for features such as suprathreshold clusters and volumes in tensor-valued and vector-valued random fields [40]–[42].

REFERENCES

Statistical Properties of Jacobian Maps and the Realization of Unbiased Large-Deformation Nonlinear Image Registration


Abstract—Maps of local tissue compression or expansion are often computed by comparing magnetic resonance imaging (MRI) scans using nonlinear image registration. The resulting changes are commonly analyzed using tensor-based morphometry to make inferences about anatomical differences, often based on the Jacobian map, which estimates local tissue gain or loss. Here, we provide rigorous mathematical analyses of the Jacobian maps, and use it to motivate a new numerical method to construct unbiased nonlinear image registration. First, we argue that logarithmic transformation is crucial for analyzing Jacobian values representing morphometric differences. We then examine the statistical distributions of log-Jacobian maps by defining the Kullback–Leibler (KL) distance on material density functions arising in continuum-mechanical models. With this framework, unbiased image registration can be constructed by quantifying the symmetric KL-distance between the identity map and the resulting deformation. Implementation details, addressing the proposed unbiased registration as well as the minimization of symmetric image matching functionals, are then discussed and shown to be applicable to other registration methods, such as the inverse consistency constraint. In the results section, we test the proposed framework, as well as present an illustrative application mapping detailed 3-D brain changes in sequential magnetic resonance imaging scans of a patient diagnosed with semantic dementia. Using permutation tests, we show that the symmetrization of image registration statistically reduces skewness in the log-Jacobian map.

Index Terms—Biomedical imaging, image matching, image registration, information theory, magnetic resonance imaging.

I. INTRODUCTION

Nonlinear image registration is a well-established field in medical imaging with many applications in functional and anatomic brain mapping, image-guided surgery, and multimodality image fusion [1]–[6]. The goal of image registration is to align, or spatially normalize, one image to another. In multi-subject studies, this serves to reduce subject-specific anatomic differences by deforming individual images onto a population average brain template.

The deformations that map each anatomy onto a common standard space can be analyzed voxel-wise to make inferences about relative volume differences between the individuals and the template, or statistical differences in anatomy between populations, such as patients with Alzheimer’s disease and healthy elderly normal subjects [7]. Similarly, in longitudinal studies it is possible to visualize structural brain changes that occur over time by deforming subjects’ baseline scans onto their subsequent scans, and using the deformation map to quantify local changes [8]–[10]. This general area of computational anatomy has become known as tensor-based morphometry [11]–[15].

To construct a deformation that is smooth, one-to-one, and differentiable [6], [16]–[18], we must impose a regularizing constraint. Thus, the problem of image registration is often cast as a minimization problem with a combined cost functional consisting of an image matching functional and a regularizing constraint $R$ on the deformation. Common choices of image matching functional include squared intensity difference, cross correlation [19], and (normalized) mutual information or other divergence-based or information-theoretic measures [20]–[23], while choices of regularization usually involve differential operators inspired by thin-plate spline theory, elasticity theory, fluid dynamics and the Euler–Poincaré equations [1], [2], [17], [24].

II. THEORY-CONSTRUCTING UNBIASED DEFORMATION

One could not study nonlinear image registration without closely examining Jacobian maps. The Jacobian map is the determinant of the Jacobian matrix of a deformation field, and encodes the local volume difference between the source and target image (a value of 0.9 denotes 10% tissue loss, while 1.1 a 10% tissue increase). Log-transformation of a Jacobian field has become standard in most tensor-based morphometry papers [25], [26]. The Jacobian determinant of a diffeomorphic
map is bounded below by zero but unbounded above. Thus, the statistical distribution of Jacobian values would be a better fit to a symmetric distribution if we apply the logarithmic transform. This is important, for example, when testing for the presence of mean structural change in a multisubject experiment. In this case, one might want to employ classical statistical approaches and test the null hypothesis of zero mean change, at each voxel, using standard parametric statistics. A second argument in favor of logarithmic transform is that it symmetrizes the Jacobian distribution by considering halving or doubling of volume to be equally likely a priori, i.e., assigning equal probabilities to expansions and shrinkages that are reciprocals of each other. This is a reasonable requirement as the correspondence field should be the same regardless of the order of the two images that are matched; if mappings in both directions are considered, compressions or expansions are equally likely.

Thus, the logarithmic transform is crucial in analyzing Jacobian determinant values, and in this paper we argue that all pertinent statistical analyses should be conducted in this space. Of note, a related approach is taken by Pennec et al. [29], where the Cauchy-Green strain tensor [27], [28] of a deformation mapping is logarithmically transformed and used as a term in a penalty functional that is integrated over the image domain to regularize the deformation.

A. Detecting No Change in the Absence of Real Change as a Necessary Criterion for Proper Registrations: Realizing Unbiased Test Statistics

In this section, we wish to derive some basic principles that any registration algorithm should satisfy in order to be applicable in real applications. To this end, we can construct cases in which we have a priori knowledge of the true Jacobian distribution, to which we can then compare the computed Jacobian maps. For example, consider nonlinearly registering one image to another image, with their only difference being noise. In this case, we expect the resulting log-Jacobian field to realize a null distribution as well. Thus, we argue that a necessary condition for any registration algorithm to be unbiased is to yield log-Jacobian maps that imply zero-change, when no difference other than noise is present between two registered images. We refer to this principle as the principle of realizing unbiased test statistics under null distribution.

Suppose $T$ (target) and $S$ (source), both defined on a computational domain $\Omega$, are the two images to be registered. Let us also assume, without loss of generality, that the volume of this domain is 1, i.e., $|\Omega| = 1$. We seek to estimate a deformation $h$ such that $S$ is nonlinearly mapped to $T$ when deformed by $h$ (i.e., $S(h(x))$). In this paper, we will restrict this mapping to be differentiable, one-to-one, and onto from the image domain onto itself (in practice/implementation, the one-to-one and onto property can be achieved by enforcing Neumann/Dirichlet boundary conditions or by extending the boundary towards infinity.

We will use the notation $u = (u_1, u_2, u_3)$, the displacement vector field away from the identity map, to represent the transformation $h$ (i.e., $h(x) = x + u(x)$). The inverse map $h^{-1}$ of $h$ (i.e., $h^{-1}(h(x)) = x$ for all $x$), thus, maps the target to the source image. We will also use the notation $u^{-1}$ to denote the displacement field of the inverse map $h^{-1}$. Let us denote the Jacobian matrix of $h$ as $Dh$ (with the $(i,j)$th element $\partial h_i / \partial x_j$). The Jacobian map can, thus, be defined as the determinant of the Jacobian matrix $[Dh(x)]$. Notice that this map estimates the local volume percentage difference of the source with respect to the target image. As a result, we consider the Jacobian map of $h$ to reside in the target reference frame, while we consider the Jacobian map of $h^{-1}$ to reside in the source reference frame (thus preserving the overall density integrated over the image domain)

$$
\int_{\Omega} |Dh(\xi)|^{y=b}\left(\xi\right) dx = 1
\int_{\Omega} |Dh^{-1}(\zeta)|^{x=b}\left(\zeta\right) dx = 1.
$$

(1)

Here, $y$ and $x$ reference the target and source frame respectively. Given the preservation of density in (1), we can associate three probability density functions to the identity mapping $(id)$ as well as the deformation $h$ and its inverse

$$
pdf_{h}(\xi) = |Dh(\xi)|
pdf_{h^{-1}}(\zeta) = |Dh^{-1}(\zeta)|
pdf_{id}(\xi) = 1.
$$

(2)

Let us also derive the following inverse matrix relationship by differentiating the identity $h^{-1}(h(x)) = x$ on both sides. We obtain

$$
\frac{\partial y}{\partial x} = h^{-1}(h(x)),
$$

then

$$
Dh^{-1}(y) \cdot Dh(x) = Id
$$
or

$$
[Dh^{-1}(y)] \cdot [Dh(x)] = 1.
$$

(3)

As discussed in previous sections, we consider log-Jacobian the natural test statistic when analyzing Jacobian maps. Now, let us integrate this test statistic on the whole image domain. The following calculation reveals that this simply computes the negative of the Kullback–Leibler (KL) distance between the probability density functions of identity map and $h$, and is always nonpositive

$$
\int_{\Omega} \log |Dh(x)| dx = -\int_{\Omega} \log \left( \frac{1}{|Dh(x)|} \right) dx
= \int_{\Omega} pdf_{id} \log pdf_{id} dx
\int_{\Omega} pdf_{h} \log pdf_{h} dx
= -\text{KL}(pdf_{id}, pdf_{h}) \leq 0.
$$

(4)

Here, KL, the nonnegative asymmetric K-L distance, between two PDF’s $X$ and $Y$, is defined as

$$
\text{KL}(X, Y) = \mathbb{E}_X \left[ \frac{X}{Y} \right] = \int_{\Omega} X \log \frac{X}{Y} dx \geq 0;
$$
\[ \text{KL}(X,Y) \neq \text{KL}(Y,X); \]
\[ \text{KL}(X,Y) = 0 \iff X \equiv Y. \] (5)

Thus, the equality in (4) holds if and only if the Jacobian map of \( h \) takes the constant value 1, or \( h \) is locally volume preserving everywhere. Interestingly, the KL distance in (4) has skew-symmetry with respect to \( h \) and its inverse

\[ \text{KL}(\text{pdf}_{id}, \text{pdf}_{h^{-1}}) = -\int_{\Omega} \log |Dh^{-1}(y)| \, dy \]
\[ = \int_{\Omega} |Dh^{-1}(y)| \log |Dh^{-1}(y)| \, dy. \] (6)

Similarly, we have

\[ \text{KL}(\text{pdf}_{id}, \text{pdf}_{h}) = \int_{\Omega} -\log |Dh(x)| \, dx \]
\[ = \text{KL}(\text{pdf}_{h^{-1}}, \text{pdf}_{id}) \]
\[ = \int_{\Omega} |Dh^{-1}(y)| \log |Dh^{-1}(y)| \, dy. \] (7)

To further show the close relationship between the KL-distance and Jacobian maps, we can also attach geometric meaning to the integral in (4), (6), (7). For example

\[ \text{KL}(\text{pdf}_{id}, \text{pdf}_{h^{-1}}) = -\int_{\Omega} \log |Dh^{-1}(y)| \, dy \]
\[ = \int_{\Omega} \log |Dh(\xi)| \exp_{h^{-1}}(y) \, dy. \] (8)

Here, the right-hand side simply computes the integral of the pulled-back (by the inverse of \( h \)) Jacobian map of \( h \).

To sumarize, we conclude that symmetrizing KL distance is equivalent to considering both the forward and backward mapping in image registration. As a result, the skew-symmetry in (6) and (7) is closely related to the asymmetric nature of KL distance. In [30], the authors proposed integrating with respect to the square root of the Jacobian determinant, in order to remove this skew-symmetry. Interestingly, this approach has an equivalent in information theory, namely, the Bhattacharyya distance \( B \), another well-known measure [31]

\[ B(\text{pdf}_{id}, \text{pdf}_{h}) = \int |Dh(x)|^{1/2} \, dx \]
\[ = \int |Dh^{-1}(x)|^{1/2} \, dx \]
\[ = B(\text{pdf}_{h^{-1}}, \text{pdf}_{id}). \] (9)

Here, the Bhattacharyya distance, though not defined in the logarithmic space, is symmetrical with respect to its two arguments, as well as inverse-consistent. To further connect the KL-distance and Bhattacharyya distance, one can also consider the geodesic linking of the two PDFs: \( P_{\alpha}(t) \), parameterized by time \( t \)

\[ P(x,t) = \frac{\text{pdf}_{id}^t(x) \text{pdf}_{h}^{1-t}}{N} \]
\[ N = \int \text{pdf}_{id}^t(x) \text{pdf}_{h}^{1-t} \, dx. \] (10)

The Bhattacharyya distance corresponds to the arbitrary choice of \( t = 1/2 \), while a generalization of the above leads to the Chernoff distance in information theory [32].

B. Realizing Unbiased Deformation in the Logarithmic Space Using Symmetrized KL-Distance

Before developing formulations to construct unbiased deformations in the logarithmic space, we generalize (4) to the case of mapping regions of interest (ROIs). Assuming we have a priori knowledge that one ROI is mapped to another [e.g., mapping ventricular changes in Serial magnetic resonance imaging (MRI) images], we again would like to recover a mapping that is unbiased in the logarithmic space. Intuitively, without further knowledge other than overall ROI mapping, the resulting Jacobian map should take a constant value inside the ROI.

This can again be achieved using the proposed formulations. Indeed, given any deformation \( g \) mapping domain \( A \) in the source (with volume \( a \)) to domain \( B \) in the target (with volume \( b \), we have the following \( \int A \log |Dg(x)| \, dx / a \leq \log b / a \), with equality obtained if and only if the Jacobian map of \( g \) takes a constant value (i.e., \( b/a \)). This generalization can be shown by observing that the logarithmic mapping is a convex mapping: \( \sum_{i} \log(x_i) \leq n \log(\Sigma_i x_i) ; \Sigma_i x_i = (1/n) \Sigma_i x_i \).

With the above generalization, one can see that, assuming the only constraint being an ROI mapping from \( A \) to \( B \), the unbiased mapping under the logarithmic operation has an evenly distributed Jacobian field, which is also intuitively correct (as there is no reason to assume nonuniformity of the Jacobian field inside the ROI).

C. Un-Biased Nonlinear Image Registration in the Logarithmic Space via KL Divergence

Given (4) and its generalization, we now propose to quantify the distance between any given deformation and the identity map by computing the symmetric KL distance through their density functions. Due to the above mentioned skew-symmetry, this distance takes the following several equivalent forms

\[ \text{KL}(\text{pdf}_{h}, \text{pdf}_{id}) + \text{KL}(\text{pdf}_{h^{-1}}, \text{pdf}_{id}) \]
\[ = \text{KL}(\text{pdf}_{id}, \text{pdf}_{id}) + \text{KL}(\text{pdf}_{i}, \text{pdf}_{id}) \]
\[ = \text{KL}(\text{pdf}_{id}, \text{pdf}_{id}) + \text{KL}(\text{pdf}_{id}, \text{pdf}_{h^{-1}}) \]
\[ = \text{KL}(\text{pdf}_{id}, \text{pdf}_{id}) + \text{KL}(\text{pdf}_{id}, \text{pdf}_{h}) \]
\[ = \int (|Dh(x)| - 1) \log |Dh(x)| \, dx \]
\[ = \int (|Dh^{-1}(y)| - 1) \log |Dh^{-1}(y)| \, dy. \] (11)
Given an image matching function, we argue that one achieves unbiased deformation by seeking, among all deformations minimizing this image matching functional, the deformation with minimal distance as given in (11).

To see why this approach leads to unbiased deformation in the logarithmic space, we observe that this integrand in (11) is always nonnegative, and only evaluates to zero when \( h \) is volume-preserving everywhere (Jacobian of \( h \) is 1 everywhere), thus, by treating it as a cost, we recover zero-change by minimizing this cost when we compare images differing only in noise. Second, this approach is also unbiased for mapping ROIs in the logarithmic space, due to the above generalization of (4).

Under this framework, constructing deformations can be viewed as quantifying the symmetric KL-distance between the identity map and the resulting deformation [or the inverse deformation due to the equivalence in (11)]. Moreover, this framework embeds statistical analyses into the construction of deformations, penalizing deformations that skew the distribution of test statistics. A second interpretation of (11) is that it simply calculates the mean log-Jacobian for the identity map and the resulting deformation [or the inverse of \( h \) everywhere], thus computing the integral effect of the test statistic. A second interpretation of (11) is that it deforms, penalizing deformations that skew the distribution of test statistics. A second interpretation of (11) is that it simply calculates the mean log-Jacobian for the identity map and the resulting deformation [or the inverse of \( h \) everywhere], thus computing the integral effect of the test statistic.

To further link this approach to other branches of mathematics, optimization problems involving Jacobian operator are commonly encountered in grid generation [33] and in continuum mechanics, where the Hencky tensor arises in modeling very large deformations. However, we believe that the logarithmic transform has not been formally introduced in the grid generation literature and may also be useful there.

### III. PRACTICAL IMPLEMENTATION CONCERNS

Here, we detail how this framework can be implemented. Given an image matching functional \( C \), as discussed in previous sections, we seek, among all deformations minimizing this matching cost, the deformation with minimal symmetric KL-distance from the identity as in (11). In practice, a numerical implementation can be achieved using the following combined minimization problem

\[
\arg\min_{h \in H} C(T, T \circ h^{-1}, S, S, \text{ch}) + \omega t (KL(pdfs_h, pdfs_u) + KL(pdfs_{u, p} pdfs_h)), \tag{12}
\]

Here, \( \omega t \) is a weight parameter (or Lagrange multiplier), and \( H \) is the solution space. Often, the solution is numerically obtained by recursive smoothing or regularization applied to the force field. We, therefore, need to find the gradient descent direction contributed by the symmetric KL-distance term, via its Euler-Lagrange equation. To this end, let us denote \( C_{o_{ij}} \), the matrix cofactor for the \((i, j)\)th component of the Jacobian matrix \( Dh \), we then obtain its Euler-Lagrange equation, using standard calculus of variations (see, for example, [34]) with respect to the \( j \)th coordinate as follows

\[
\sum_j \frac{\partial}{\partial e_j} \left\{ (1 + \log |Dh(x)| - 1/|Dh(x)|) C_{o_{ij}}(x) \right\} = 0
\]

\[ (Dh(x))^{-1} = (C_{o_{ij}}(x))^T / |Dh(x)|. \tag{13} \]

### A. Symmetrization of the Image Matching Functional—The Method of Equivalent Perturbation

In this section, we introduce the method of equivalent perturbation, an algorithm necessary for numerically solving the minimization of the symmetric image matching functional in (12) as well as other registration methods requiring optimization in both the forward and backward direction.

To motivate this method, we notice that to date all image matching functions available are unidirectional, while a completely symmetric formulation in (12) would require a symmetric image matching function as well. Nevertheless, any given unidirectional matching cost function \( C(T, S(h(x))) \) can be symmetrized as follows—similar to the step in (11) first-order

\[
C(T, S(h(x))) + C(S, T(h^{-1}(x))) \tag{14}
\]

However, this complicates numerical implementations. Unlike the symmetric KL-distance term in (12) that can be optimized in either forward or backward direction due to the equivalence relations in (11), minimizing (14) usually requires optimizing \( h \) and the inverse of \( h \) separately. This same dilemma was encountered in the pioneering paper on inverse consistency [35] (also see [36] for an earlier approach), where the authors propose the following minimization, similar to (14), with any given regularization penalty \( R(h) \) first-order

\[
E(T, S) = \int_{\Omega} \left[ S(h(x)) - T(x) \right]^2 dx + \lambda R(h) \bigg|_{\Omega} \bigg|_{E_1} + \int_{\Omega} \left| T(h^{-1}(x)) - S(x) \right|^2 dx + \lambda R(h^{-1}) \bigg|_{\Omega} \bigg|_{E_2} \tag{15}
\]

Here, \( \lambda \) is a positive scalar weighting for the regularizers.

To solve (15) numerically, the authors separately considered the mappings in the forward and backward directions in (15) and solved for \( h \) and \( g \) separately with an additional inverse consistency constraint (weighted by \( \rho \)) so that \( g \) numerically realizes \( h^{-1} \).

\[
E_h(T, S) = \int_{\Omega} \left[ S(h(x)) - T(x) \right]^2 dx + \lambda R(h) \bigg|_{\Omega} + \rho \int_{\Omega} \left| h - (g)^{-1} \right|^2 dx \bigg|_{E_3}
\]

\[
E_g(T, S) = \int_{\Omega} \left[ T(g(x)) - S(x) \right]^2 dx + \lambda R(g) \bigg|_{\Omega} + \rho \int_{\Omega} \left| g - (h)^{-1} \right|^2 dx. \tag{16}
\]

This splitting-up principle is also applicable to minimizing the general formulation in (14), but may not be optimal. Equation (16) is essentially a two-step strategy and creates a lag in estimating \( h \) and \( g \). Either \( h \) or \( g \) has to be alternately fixed (i.e., the
two maps are not estimated simultaneously). Moreover, an extra weighting parameter for the inverse consistency constraints has to be considered and was tuned case-by-case.

Here, we propose a more natural numerical algorithm, the method of equivalent perturbation, to solve minimization problems such as (14) and (15), instead of the modified 2-step approach in (16).

Given any infinitesimal perturbation \( \xi \) applied to the inverse mapping, the method of equivalent perturbation seeks to solve for \( \eta \), the perturbation in the forward mapping that preserves the fact that \( h \) and \( h^{-1} \) must be inverses of each other first-order

\[
give perturbation \quad h^{-1}(x) \rightarrow h^{-1}(x) + \varepsilon \xi(x)
\]

Solve \( \eta(x) \) such that

\[
\lim_{\varepsilon \to 0} \frac{(h^{-1} + \varepsilon \xi) \circ (h + \varepsilon \eta)(x) - x}{\varepsilon} = 0
\]

or

\[
(h^{-1} + \varepsilon \xi) \circ (h + \varepsilon \eta)(x) = (h^{-1}(y) + \varepsilon \xi(y)) |_{y=h(x)+\varepsilon \eta(x)} = x + O(\varepsilon^2).
\]

(17)

Here, \( \varepsilon \) is an infinitesimally small positive number. Using this method of equivalent perturbation, we can, thus, combine all body forces in only the forward direction and solve (14) and (15) uni-directionally without explicitly involving the inverse mapping \( h^{-1} \).

To solve for \( \eta \), we expand (16), collect first-order terms of \( \varepsilon \), and obtain the following equality:

\[
Dh^{-1}(y)|_{y=h(x)} \cdot \eta(x) = -\xi(h(x)).
\]

(18)

Recalling the inverse matrix relationship in (3), we obtain \( \eta \) as a function of \( \xi \) first-order

\[
\eta(x) = -D(h(x)) \xi(h(x)).
\]

(19)

In (19), the forward equivalent of a body force in the backward direction is computed using only the forward mapping \( h \) (without involving \( h^{-1} \)), allowing us to circumvent the inherent numerical errors incurred when performing numerical inversion operations to go between \( h \) and \( h^{-1} \).

IV. RESULTS

A. Image Matching Using the Method of Symmetric KL Distance

In this section, we implement the proposed un-biased non-linear registration in Section II-C. To compute a numerical solution, we minimize the combined cost function as in (12).

To address the solution space \( H \) in (12), we used the numerical scheme proposed in [20], which essentially is a fast solver and approximates the well-known viscous fluid registration model pioneered by Christensen et al. in [16]. The deformation fields were computed using adaptive time stepping, with maximal change in displacement of 0.1 allowed in each iteration. In order to obtain a fair comparison between the proposed and the viscous fluid method, re-gridding was not employed. Of note, re-gridding is essentially a memory-less procedure, as how images are matched after each re-gridding is independent of the final deformation before the re-gridding, rendering the comparison of final Jacobian fields and cost functionals problematic. Moreover, we consider the strategy of re-gridding, through the relaxation of deformation fields over time, to be less rigorous from a theoretical standpoint.

In Figs. 1–3, we show the results of matching two 2-D binary images (each of size 289 × 289), representing midline corpus callosum contours of two control subjects. Both the viscous fluid registration method without regridding (D’Agostino’s algorithm) and the proposed method generated a close match between the deformed image and the target (Figs. 1 and 2). Here, we used the sum of squared difference as the image matching functional, and optimal matching was considered achieved once the overall cost functional stopped decreasing. The weight \( w_{fl} = 1,000 \) was used in (12) for the proposed method. However, as seen in Fig. 2, the proposed method more evenly distributes deformation inside the corpus callosum. Indeed, given only binary images depicting corpus callosal contours (without other information inside the contour), one can argue that the Jacobian field should be evenly distributed. Fig. 2(c) and (d) illustrates that the Jacobian field of the proposed method is more evenly distributed inside corpus callosum. The histograms of the Jacobian field inside the ROI are shown in Fig. 2(e) and (f) (the histogram for the proposed method is noticeably sharper). Fig. 3(a) plots the standard deviation of the Jacobian field inside the contour as a function of iteration number. For the viscous fluid method, the standard deviation increased with the number of iterations, since the grid became less regular. On the other hand, the proposed method generated a grid with smaller standard deviation which

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![Fig. 1. Corpus callosum example](image-url)
Finally, we implemented the proposed method in 3-D and tested it on the original 3-D MRI volumes (see next section as well as Fig. 8 for details; the initial scan and the 6-year follow-up scan of a patient with semantic dementia were used), with \( wIF = 500 \). In Fig. 7(a) and (c), the 3-D Jacobian map generated using the viscous fluid method is visually very noisy with extreme values along the boundaries of the brain as well as in the background, masking the real change over the right temporal area. In contrast, as shown in Fig. 7(b) and (d), right temporal atrophy (RT) and ventricular enlargement (V) are easily visualized in the Jacobian map generated using the proposed method, demonstrating its theoretical and practical advantages.

B. Applying the Method of Equivalent Perturbation to Inverse Consistent Mapping

Three-dimensional T1-weighted MRI of a 57-year-old male patient diagnosed with semantic dementia were obtained using a gradient echo acquisition (TR 25 ms, TE 5 ms, slice thickness 1.5 mm, FOV 24 x 18 cm, flip angle 40°, no gaps). Four serial scans were obtained (baseline scan in 02/1993; follow-up scans in 10/1994, 02/1996, and 08/1999). The baseline (target) and the final follow-up (source) scans were used to evaluate the proposed approach. The two scans were first rigidly aligned and re-sliced to an isotropic volume of size 180 x 180 x 180 (a voxel = 1 mm³). We then tested the method of equivalent perturbation by applying it to compute an inverse consistent registration deforming the source back to the target. Instead of using SSD as the matching cost functional as in [35], we maximized the mutual information (MI), now considered one of the most versatile matching functionals, between the deforming source and target image. For the regularization, we followed the formulations in [35] with the following linear elasticity operator:

\[
\hat{R}(u) = \int \| -\Delta u - \beta \nabla (\nabla \cdot u) \|^2 dx, \tag{20}
\]

Here, \( \Delta \) is the Laplacian and \( \alpha \) and \( \beta \) are the Lamé constants (both set to be 1.0). As in [35], the Fast Fourier transform technique (FFT) is applied to parameterize the displacement field. A multiresolution minimization scheme can then be implemented in the frequency domain.

This spatial normalization of scans over time allowed local tissue change to be estimated as was previously mentioned. A multiresolution scheme starting from the 32 x 32 x 32 FFT resolution was used (\( \lambda = 10^{-4}; \) time step = \( 3 \times 10^{-6} \)), and numerical convergence was checked every 20 iterations (convergence criteria was met when the MI failed to increase by 0.001 after one iteration). 40 iterations were computed in each FFT resolution before the resolution was increased by a factor of 2 (with the time step decreased to one-tenth) in each dimension. Fig. 8 plots three orthogonal views of the four Serial MRI scans, showing prominent left temporal lobe atrophy (L), as well as a relative preservation of the right temporal lobe (R). However, closer inspection of the Jacobian map (Fig. 9) shows more active atrophy in the right temporal lobe, as well as bilateral tissue loss in the caudate (RC, LC), putamen (RP, LP), and thalamus (RT, LT), while less active atrophy was detected in the left temporal...
Fig. 3. Corpus callosum example. (a) Standard deviation of Jacobian values inside corpus callosum per iteration. (b) Symmetric KL distance. For the viscous fluid method (dashed blue), both standard deviation and symmetric KL distance increase, whereas for the proposed method (solid red), both standard deviation and symmetric KL distance decrease and stabilize.

Fig. 4. Two-dimensional serial MRI example. (a) initial scan (02/1993, refer to Fig. 8); (b) follow-up scan (08/1999, refer to Fig. 8); (c) initial is deformed to follow-up using the viscous fluid method; (d) initial is deformed to follow-up using the proposed method.

lobe during the same time period. Fig. 10 plots the values of the MI term and the regularizer versus iterations in the forward and backward direction using the proposed inverse consistent approach in (15), and an inconsistent approach [minimizing only the term $E_1$ in (15)]. Here, the consistent mapping achieved not only higher MI values, but also lower regularizer values.

To show the reduction of inverse consistency errors, we compared the deformation with that obtained by switching the order of source/target. Ideally, the deformation should not depend on the order of the input images and, thus, inverse consistency can be assessed by examining the difference (Table I) in the deformation pair. For comparison, the corresponding errors using...
Fig. 6. Two-dimensional serial MRI example. (a) Standard deviation of Jacobian values inside the ventricle per iteration. (b) Symmetric KL distance. For the viscous fluid method (dashed blue), both standard deviation and symmetric KL distance increase, whereas for the proposed method (solid red), both standard deviation and symmetric KL distance stabilize.

Fig. 7. Three-dimensional serial MRI example. Jacobian maps are superimposed with the deformed volumes for the viscous fluid method (a) and (c) and the proposed method (b) and (d). Right temporal atrophy (RT) and ventricular enlargement (V) are easily visualized in the Jacobian map generated using the proposed method, while the viscous fluid method generated a very noisy map.

Next, we examined the statistical properties of the log-Jacobian values. Recall in Section II, we discussed that the symmetrization of registration often reduces left skewness in the corresponding Jacobian distribution as it evenly penalizes compression/expansion of the same factor (also refer to [37] for a detailed discussion on why compressions are easier to achieve). We aimed to test if this reduction in skewness can be statistically confirmed using this dataset. Here, we used the standard measure of skewness in statistics, i.e., the third moment about the mean divided by the third power of the standard deviation.

To test the hypothesis of symmetry around zero, we employ permutation testing to generate samples statistically equivalent, under the null hypothesis, to the two log-Jacobian distributions. When testing whether any given distribution is symmetric...

Fig. 8. This figure shows the serial MRI scans obtained at 4 different time points for a patient diagnosed with semantic dementia. Visual inspection shows atrophied right temporal (R) and left temporal (L) lobes, as well as ventricular dilation.
around zero, we generate 10,000 samples by randomly flipping the sign of the log-Jacobian value at each voxel, as under the null hypothesis that the observed distribution is symmetric around zero, each value is equally likely to be positive or negative. The next step involves picking a suitable test statistic, in this case the mean value of the re-sampled distribution (under the null hypothesis, the mean value is simply zero). To compute a $p$-value, we then rank the observed test statistic relative to the re-sampled test statistics.

For example, if the observed mean log Jacobian value ranks at 50 percentile among all re-sampled test statistics using samples generated from the observed Jacobian map, then the $p$-value is 0.5 and, thus, we cannot reject the null hypothesis at a conventional threshold level of 0.05 (see [10], [38], which describe the benefits of permutation testing for performing inferences in brain imaging).

In the case of the log Jacobian distribution generated using inverse consistent matching, no null re-sampled test statistic (the mean log Jacobian value) (maximum $7.67 \times 10^{-5}$; minimum $-8.23 \times 10^{-5}$), was as extreme as the observed statistic of $-0.0011$, thus allowing us to reject the null hypothesis with statistical significance ($p < 0.0001$). Similarly, the null hypothesis that the log Jacobian distribution generated using the inconsistent matching is symmetric around zero was also rejected ($p < 0.0001$). We then relaxed the null hypothesis and tested if the two Jacobian distributions were symmetric around their corresponding mean values (without assuming the mean is zero) using another permutation test (random flipping around the observed mean) with skewness as the test statistic. Fig. 11(c) shows the histogram of the re-sampled statistics. In the case of inverse consistent matching, the one-sided $p$-value is 0.067 and, thus, the null hypothesis (of symmetry around its mean) cannot be rejected at the 5% significance level. By contrast, a similar skewness permutation test performed on the log Jacobian distribution under the inconsistent mapping yielded a $p < 0.0001$, thus detecting a statistically significant skewness.

Thus, using this single subject example, we were able to detect a statistically significant left skewed log Jacobian distribution in the case of inconsistent mapping, but not in the case of inverse consistent mapping.

Finally, by directly comparing these two log-Jacobian distributions, we formally tested the presence of statistically significant differences in these two distributions. As discussed in Section II, one would argue that, by more equally penalizing compression and expansion (easier to achieve expansions of the same magnitude compared to unidirectional approach) a symmetrized method would shift the mean log Jacobian value rightward (i.e., it would become less negative). We formally tested the statistical significance of this shift using a third permutation test Fig. 11(d). The test statistic in this case was the difference of the mean log-Jacobian values between consistent and inconsistent mappings, with the observed statistic $6.066 \times 10^{-4}$. 10,000 samples of this test statistic were calculated by generating two re-sampled distributions using random shuffling of each element in the two observed distributions (under the null hypothesis that the two distributions are the same, we can randomly assign each element to either distribution). Again, not a single re-sampled test statistic (max $9.44 \times 10^{-5}$, min $-8.73 \times 10^{-5}$) was as extreme as the observed and, thus, a statistically significant difference was detected between the two observed distributions.

To summarize, we showed, in this section, that symmetrization of a unidirectional registration method changes the distribution of the corresponding Jacobian values. Namely, the symmetrized registration method in general achieved a less left-skewed log Jacobian distribution, making it more symmetric around its mean value, as well as shifted the mean value rightward (less negative). Moreover, these effects can be confirmed.

### Table I

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<th>$u_{\text{L}}-u_{\text{R}}$</th>
<th>$u_{\text{L}}+u_{\text{R}}$</th>
<th>$u_{\text{L}}-u_{\text{R}}$</th>
<th>$h-h^*$</th>
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<tbody>
<tr>
<td><strong>Forward mapping (inverse consistent)</strong></td>
<td>Maximum 0.3893 0.8290 0.4345 0.8616</td>
<td>Maximum 0.2751 0.8009 0.4145 0.8107</td>
<td>Mean 0.0048 0.0071 0.0049 0.0115</td>
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<tr>
<td></td>
<td>Minimum 0.0047 0.0071 0.0049 0.0115</td>
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<th>$h-h^*$</th>
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<tr>
<td><strong>Backward mapping (inverse consistent)</strong></td>
<td>Maximum 0.8343 0.8894 0.9616 0.9617</td>
<td>Maximum 0.8499 0.9009 0.9884 0.9579</td>
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<tr>
<td></td>
<td>Minimum 0.0223 0.0297 0.0360 0.0965</td>
<td>Minimum 0.0223 0.0297 0.0360 0.0965</td>
<td>Mean 0.0223 0.0297 0.0360 0.0965</td>
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**Fig. 9.** Three-dimensional Jacobian map of the brain changes recovered in the semantic dementia patient shows active right temporal lobe atrophy (lower panel; see text). Here, LP and RP denote the left and right putamen; LC and RC the left/right caudate head; LT and RT the left/right thalamus.
to be statistically significant in real applications. The implications of these experiments can be far reaching in that registration methods/regularizers, often regarded as simply matters of choice, may be more influential than they seem. They deserve rigorous mathematical and theoretical explorations in order to fully understand their impacts when interpreting brain imaging results.

V. DISCUSSIONS

Over the past decade, a few studies have investigated the influence of regularization techniques and the logarithmic transformation on Jacobian fields. For example, Ashburner et al. [26] reported an important innovation in which they defined a log-type deformation penalty on triangles in a 2-D image domain. For each triangle in 2-D, the penalty is defined as: \( \lambda [1 + \det(J)] \cdot \log \left[ \frac{1}{2} \left( \log s_{11}^2 + \log s_{22}^2 \right) \right] / 2 \), where \( \lambda \) is a Lagrange multiplier on the regularizer, \( J \) is the Jacobian determinant, and \( s_{11} \) and \( s_{22} \) are the eigenvalues of the deformation tensor. The term \( 1 + \det(J) \) integrates the cost with respect to the undeformed lattice, and the final term penalizes logarithmically-transformed eigenvalue deviations in the local deformation tensor but not rotations. This cost per triangle can be summed over the image domain and thought of as a cost functional that integrates the deviation of the eigenvalue distribution from log-normal. Following a similar rationale, a variational penalty could be formulated to penalize deformations whose Jacobian PDFs deviate from log-normal. For
example, using tensor computation in the log-Euclidean space, a Riemannian elasticity regularizer was recently proposed [29] that calculates the integral of the trace of \((\log \Sigma)^2\) on the image domain. Here, \(\Sigma\) is the Cauchy-Green tensor, defined as the Jacobian matrix left-multiplied by its transpose. Of note, this Riemannian elasticity regularizer has a very similar form to the proposed formulations in this paper.

More recently, a new approach termed “large-deformation diffeomorphic metric matching,” or LDDMM [17], was proposed by regularizing a velocity field that integrates to the displacement, allowing for arbitrarily large deformation as well as automatic inverse consistency. A formulation based on momentum of deformation maps and “geodesic shooting” is proposed to introduce a metric on the group of diffeomorphic mappings. Though extremely powerful, this approach is computationally expensive, as it requires integration of the velocity field in time. Moreover, this approach does not address the statistical analysis of resulting deformation maps at a voxel level, which becomes relevant in brain mapping applications.

VI. CONCLUSION

In this paper, we characterized the statistical properties of the Jacobian maps that arise in deformation-based morphometry, both empirically and theoretically, by applying the KL distance to the set of material density functions in both target and source coordinates. We then proposed a framework for constructing unbiased deformation fields. Details on implementing this framework were discussed, along with the development of a numerical algorithm tackling minimization problems in the presence of body forces from both the forward and backward directions. This is commonly encountered in newer nonlinear image registration methods (e.g., the inverse consistent approach), where the symmetrization of registration often requires minimization in both directions. We then tested the proposed framework, and showed that it simplified the implementation of inverse consistent matching.

Finally, the statistical theory of these distributions has strong ties with information theory. Our conclusion has important consequences when performing statistical tests on maps of tissue change in both longitudinal and inter subject/group studies. As interest increases in tensor-based morphometry for clinical and basic neuroscience studies, there is a growing need to rigorously evaluate various aspects of the process. Ongoing work is also focusing on the optimal filtering of the Jacobian fields, using approaches analogous to sigma-filtering [39] and on the modeling the null distributions for features such as suprathreshold clusters and volumes in tensor-valued and vector-valued random fields [40]–[42].

REFERENCES


