A NEW REGISTRATION METHOD BASED ON LOG-EUCLIDEAN TENSOR METRICS AND ITS APPLICATION TO GENETIC STUDIES

Caroline Brun[1]*,Natasha Leporé*[1]*, Xavier Pennec*[2]*, Yi-Yu Chou*[2]*, Agatha D. Lee*[1]*,*
Grieg de Zubicaray[3]*, Katie McMahon*[3]*, Margie Wright*[4]*, Marina Barysheva*[1]*,*
Arthur W. Toga[1]*, Paul M. Thompson*[1]

[1] Laboratory of Neuro Imaging, Department of Neurology, UCLA Los Angeles, CA 90095, USA
[2] Asclepios Research Project,INRIA, 06902 Sophia-Antipolis Cedex, France
[3] Centre for Magnetic Resonance, University of Queensland
[4] Genetic Epidemiology Lab, Queensland Institute of Medical Research,Queensland 4029, Australia

ABSTRACT

In structural brain MRI, group differences or changes in brain structures can be detected using Tensor-Based Morphometry (TBM). This method consists of two steps: (1) a non-linear registration step, that aligns all of the images to a common template, and (2) a subsequent statistical analysis. The numerous registration methods that have recently been developed differ in their detection sensitivity when used for TBM, and detection power is paramount in epidemological studies or drug trials. We therefore developed a new fluid registration method s the mappings and performs statistics on them in a consistent way, providing a bridge between TBM registration and statistics. We used the Log-Euclidean framework to define a new regularizer that is a fluid extension of the Riemannian elasticity, which assures diffeomorphic transformations. This regularizer constrains the symmetrized Jacobian matrix, also called the deformation (or strain) tensor. We applied our method to an MRI dataset from 40 fraternal and identical twins, to revealed voxelwise measures of average volumetric differences in brain structure for subjects with different degrees of genetic resemblance.

***Index Terms*—** Registration, Brain Imaging, MRI, Genetics, Statistical analysis

1. INTRODUCTION

Nonlinear registration of MRI images is challenging subject with a broad range of applications, such as multimodality registration for diagnosis and surgical planning, tracking brain development or degeneration over time, or alignment of multi-subject functional or structural images to detect systematic differences between populations.

More particularly, for analysis of brain structure, Tensor Based Morphometry (TBM) [8, 21, 2] is an increasingly used method that non rigidly registers a set of brain images to a common template, from which vector fields are obtained and statistically analyzed to detect morphometric differences in disease, development or drug trials. The two crucial steps in TBM are the registration process and the statistical analysis. TBM studies generally compute a similarity term between a target and a deforming image and introduce the gradient of this term as a driving force in continuum mechanical equations, considering the deforming image as an elastic [9] or viscous fluid medium [7]. These mechanical equations regularize the deformation, enforcing desirable properties such as smoothness, invertibility and inverse-consistency. The similarity term may be a simple summed squared intensity difference (L^2-norm) between two images, or may involve cross-correlation or information-theoretic measures, such as the mutual information or Jensen-Rényi divergence [6]. Although regularizers for template matching were first developed by analogy with mechanical theory, many approaches incorporated statistical information in the deformation process.

Early registration work regarded the regularizer as an energy density or Gibbs prior distribution on the space of mappings, whose parameters could be learned empirically [10] or based on smoothness or stability considerations (as in Tikhonov regularization). In [11], a Bayesian model was used that incorporated a statistical prior distribution on the deformation embodied in stochastic partial differential equations (PDEs). Later, this work was integrated into the large deformation diffeomorphic metric mapping model [16] that computes energies from the velocity fields of the deformation, their extrema being geodesics in groups of diffeomorphisms matching anatomies.

In [17], Pennec *et al.* developed a new elastic registration method in which the regularizer was computed using Log-Euclidean metrics [1]. This prior regularizes anisotropic deformations (i.e., ones with a preferred direction locally) as well as volumetric gains and losses, as it penalizes the whole deformation (or strain) tensor, $\Sigma = (\nabla\vec{(u)})^T \nabla\vec{u}$, where $\vec{u}$ is the displacement. The deformation matrices, Σ, are sym-

metric positive-definite matrices and form a cone in the space of 3x3 real-valued matrices. The Log-Euclidean framework of [1] allows simple computations to be made intrinsically on this manifold. The Log-Euclidean Riemannian elasticity was thus chosen to replace the standard elastic prior based on Hooke's law (*Saint-Venant Kirchhoff elasticity*)

$$Reg_{SVKE}(\vec{u}) = \int \frac{\mu}{4} Tr((\Sigma - Id)^2) + \frac{\lambda}{8} Tr(\Sigma - Id)^2$$
$$Reg_{RE}(\vec{u}) = \frac{1}{4} dist^2_{Eucl}(\log(\Sigma), \log(Id)) = \frac{1}{4} \int ||\log(\Sigma)||^2$$

Here we extend this elastic registration method proposed in [17] to a 3D fluid version, that allows for large deformation while preserving diffeomorphic properties (i.e., a smooth invertible map; see [7]). Instead of regularizing Σ, we apply the Riemannian prior to the velocity field $\vec{v}$ (derivative of $\vec{u}$). A 2D version of the algorithm was first implemented in [4], where we showed that, in 2D, the fluid Riemannian prior was more sensitive than the Euclidean prior in a subsequent multivariate analysis on the deformation tensors $\sqrt{J^T J}$, where J is the Jacobian matrix of the transformation (see [14], for more insight on the statistical method). In this paper, we developed a fast and optimized 3D Log-Euclidean fluid code to register 40 brain MR images from a dataset of 10 pairs of fraternal twins (DZs) and 10 pairs of identical twins (MZs) to a common template. The resulting vector fields were analyzed to map genetic influences on regional brain volumes. In ongoing work, spatial maps are being developed to understand the differential influences of genes versus environment on brain shape and morphology [20]. For example, total brain volume is under strong genetic control [**?**]. In [23] we mapped genetic influences on brain structure, revealing the heritability of gray matter volumes in the frontal lobes (see also [13]) and in language-related areas. Once identified, heritable patterns of brain structure may be used to create image-derived measures for discovering specific genetic polymorphisms that influence human brain morphology.

2. METHOD

2.1. Subjects

3D T1-weighted images were acquired from 10 pairs of monozygotic twins (MZ) and 10 pairs of same-sex dizygotic twins (DZ) (4 male pairs and 6 female pairs per group; age range $22 - 25$ years) on a 4 T Brucker Medspec whole body scanner (CMR, Brisbane, Australia). DNA tests were performed to confirm zygosity. An MP-RAGE 3D T1-weighted sequence was used ($TR = 2500ms$, $TE = 3.83ms$, $TI = 1500ms$, pulse angle = 15^o, coronal orientation, FOV $230x230x230mm^3$). The study was approved by the Institutional Review Boards at the University of Queensland and at UCLA; each subject signed a formal consent.

2.2. Registration Method

In elastic registration, a force (i.e., the gradient of the similarity term between two images, with respect to the local displacment field) is computed at each voxel and is embodied in a Navier-Lamé equation through which the displacement field $\vec{u}$ is iteratively computed. For small displacements, the deformation remains smooth and invertible because of the presence of restoring (regularizing) forces. Fluid registration, on the other hand, preserves the one-to-one mapping even for large deformations. A velocity field $\vec{v}$ is computed at each time step (for example through a Navier-Poisson equation [7]) and (in a so-called greedy algorithm) is integrated over time to get the displacement field $\vec{u}$. Other velocity-based approaches such as LDDMM [16] and symmetric normalization [3] either regularize using a velocity norm on the full space-time path to generate a deformation that is globally optimal in time, or they use an approach known as geodesic shooting [16]. The simplest Log-Euclidean version of this regularizer is the Isotropic Riemannian Elasticity $Reg_{RE}(\vec{u})$, that measures the deformation of Σ from the identity. Likewise, we constrain the fluid-like deforming image through $(\nabla\vec{v}+Id)^T(\nabla\vec{v}+Id)$. The velocity at each voxel is given by the force from the similarity constraint and the regularizer:

$$\frac{d\vec{v}(\vec{x},t)}{dt} = \vec{F} + \nabla Reg_{Riem}(\vec{v},t)$$

where

$$Reg_{Riem}(\vec{v},t) = \int \frac{\mu}{4} Tr(\log((\nabla\vec{v}+Id)^T(\nabla\vec{v}+Id))^2) + \frac{\lambda}{8} Tr(\log((\nabla\vec{v}+Id)^T(\nabla\vec{v}+Id)))^2$$

with λ and μ are the Lamé coefficients and

$$\vec{F}(\vec{x},\vec{u}(\vec{x},t)) = -[T(\vec{x}-\vec{u}(\vec{x},t)) - S(\vec{x})]\nabla T|_{\vec{x}-\vec{u}(\vec{x},t)}$$

the similarity term based on the squared-intensity difference (here we choose the L^2-norm as our images have comparable intensity distributions).

2.3. Analysis

We tested our implementation of the Riemannian Fluid method on an MRI dataset from monozygotic (MZ) and dizygotic (DZ) twin pairs. Each image was registered to a common template. We used a specific subjects image rather than a Mean Deformation Template (MDT) as the sharper features in an individual brain image may allow for a more accurate registration, which may in turn improve detection power. In [6], the template from an individual control subject outperformed the average ICBM53 atlas brain as a registration target image for TBM [6]. For each subject, we obtained the displacement fields and computed the Jacobian matrices at each voxel. Two values were derived: the determinant of the

Jacobian matrix (commonly called the Jacobian), which measures volume expansion and shrinkage, and the tangent of the geodesic anisotropy, which measures the local anisotropy of the structural differences (i.e., whether the relative elongation or contraction of anatomy is more pronounced in any specific direction). For these two quantities det and tGA, we computed the average differences among MZ pairs and among DZ pairs, to determine whether the resemblance in brain structure between individuals depends on their degree of genetic relatedness. It will also be possible in future, as in our past studies, to compute heritability estimates [23], i.e., maps of the genetic contribution to the variance in a population, for measures such as regional volumes of brain structures (here derived from TBM). In this initial study of N=40 twins, we preferred to create maps of average intrapair differences as these are fairly intuitive and converge in small samples; we will fit full structural equation models once more twins are available; variance components and genetic parameter estimates depend on ratios of variances from nested models, and are known to be highly unstable in samples of only 10 pairs of each zygosity [23].

3. RESULTS

Figure 1 shows a typical result from registering an individual image to the common template; the difference image shows minimal differences between the warped reference and target images. This suggests registration accuracy is good, although further formal verification with anatomical landmarks is necessary. Figure 2 shows that the algorithm is also recovering morphometric differences that have substantial face validity. The average difference in brain structure volumes between MZ twins would be expected to be less that that between DZ twins, as the MZ twins are genetically identical. This is the case, based on maps of the mean absolute difference in the Jacobians of the mappings, averaged across 10 twin pairs per group. In additional there is substantial anatomical detail in the mean maps, as shown in the white matter tracts that thread into the occipital lobes, and in the internal capsules, which are clearly visible as white matter tracts running through the basal ganglia. Overall, these maps appear sensitive to true differences in anatomy. Although there is no independent ground truth as to what the true differences in anatomy are across large numbers of subjects, it is consistent with genetic hypotheses that differences would be less, on average, in identical than fraternal twins, and this is visually confirmed by the maps. Future studies in large samples will evaluate this hypothesis using structural equation models to test for additive genetic effects at each image voxel.

4. DISCUSSION

This work unifies two emerging directions in computational anatomy: (1) Log-Euclidean methods, which have been proposed for performing statistics on tensors using a metric adapted to the tensor manifold geometry; and (2) diffeomorphic image registration, in which a template velocity field is regularized to ensure that mappings across subjects have no folds or tears (positive Jacobian property). TBM methods have typically plotted maps of the Jacobian determinant (which encode volume changes), but morphometric differences are more powerfully detected by analyzing the full deformation tensor in a Log-Euclidean space [14], which is sensitive to directional or anisotropic effects. Given this, it is logical to regularize the deformation energy in a Log-Euclidean space, to be consistent with the subsequent multivariate statistical analysis. This paper does this in a large-deformation setting, which also ensures that mappings are diffeomorphic. Future directions include: (1) extension to an LDDMM or geodesic shooting framework, where the paths are optimal in time, rather than only at each iteration, and form geodesics on the space of diffeomorphisms; (2) inclusion of empirical statistics on the local strain; and (3) comparison of priors for tracking disease progression and factors that modulate it in clinical studies.

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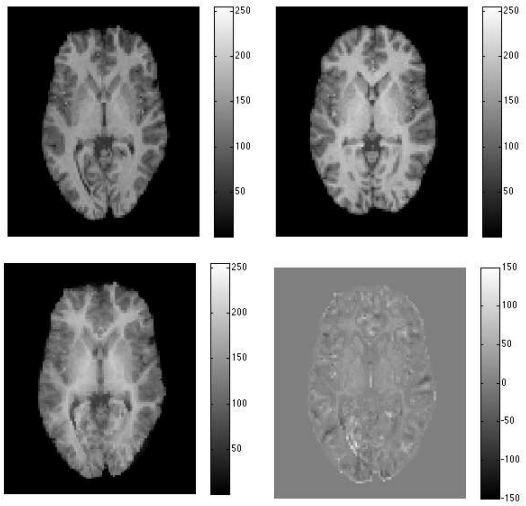

Fig. 1. Registration of a typical healthy subjects brain MRI **top left** to that of another subject **top right**. Axial sections through the warped image **bottom left** and the difference image after registration **bottom right** indicate the registration accuracy.

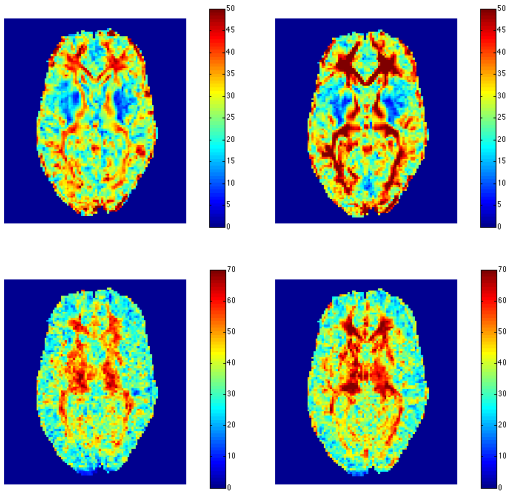

Fig. 2. Images of the mean absolute difference in regional volumes (based on the Jacobian determinant) in the 20 MZ twin pairs **top left** and 20 DZ twin pairs **top right** show that MZ twins resemble each other to a great extent in regional volumes of brain substructures, especially in the deep white matter. Red colors in the deep white matter of the DZ group show that volumes vary by up to 50% between DZ twins for some regions. The lower mean absolute difference in volumes for MZ twin pairs fits with our prior expectation that their genetic affinity leads to greater structural resemblance (this requires formal testing and verification in a larger sample). Corresponding images for the tGA, a measure of the anisotropy of volumetric differences, are more similar for MZ and DZ pairing, perhaps suggesting that this more abstract parameter is under lesser genetic control.