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Morphometry of anatomical shape complexes with dense deformations and sparse parameters

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ABSTRACT

We propose a generic method for the statistical analysis of collections of anatomical shape complexes, namely sets of surfaces that were previously segmented and labeled in a group of subjects. The method estimates an anatomical model, the *template complex*, that is representative of the population under study. Its shape reflects anatomical invariants within the dataset. In addition, the method automatically places control points near the most variable parts of the template complex. Vectors attached to these points are parameters of deformations of the ambient 3D space. These deformations warp the template to each subject's complex in a way that preserves the organization of the anatomical structures. Multivariate statistical analysis is applied to these deformation parameters to test for group differences. Results of the statistical analysis are then expressed in terms of deformation patterns of the template complex, and can be visualized and interpreted. The user needs only to specify the topology of the template complex and the number of control points. The method then automatically estimates the shape of the template complex, the optimal position of control points and deformation parameters. The proposed approach is completely generic with respect to any type of application and well adapted to efficient use in clinical studies, in that it does not require point correspondence across surfaces and is robust to mesh imperfections such as holes, spikes, inconsistent orientation or irregular meshing.

The approach is illustrated with a neuroimaging study of Down syndrome (DS). The results demonstrate that the complex of deep brain structures shows a statistically significant shape difference between control and DS subjects. The deformation-based modelingis able to classify subjects with very high specificity and sensitivity, thus showing important generalization capability even given a low sample size. We show that the results remain significant even if the number of control points, and hence the dimension of variables in the statistical model, are drastically reduced. The analysis may even suggest that parsimonious models have an increased statistical performance.

The method has been implemented in the software Deformetrica, which is publicly available at www.deformetrica.org.

Introduction

Non-invasive imaging methods such as magnetic resonance imaging (MRI) enable analysis of anatomical phenotypic variations over large clinical data collections. For example, MRI is used to reveal and quantify effects of pathologies on anatomy, such as hippocampal atrophy in neurodegenerative diseases or change in neuronal connectivity in neurodevelopmental disorders. Subject-specific digital anatomical models are built from the segmentation and labeling of structures of interest in images. Inneuroanatomy, these structures of interest are often volumes whose boundaries take the form of 3D surfaces. For a given individual, the set of such labeled surfaces, which we call an *anatomical complex*, is indicative of the shape of different brain objects and their relative position. Our goal is to perform statistics on a series of such anatomical complexes from subjects within a given population. We assume that the complex contains the same anatomical structures in each subject, so that interindividual differences are not due to the presence or absence of a structure or a split of one structure into two. The quantification of phenotypic variations across individuals or

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populations is crucial to find the anatomical substrate of neurologic diseases, for example to find an early biomarker of disease onset or to correlate phenotypes with functional or genotypic variables. Not only the *quantification*, but also the *description* of the significant anatomical differences is important in order to interpret the findings and drive the search for biological pathways leading to pathologies.

The core problem is the construction of a computational model for such shape complexes that would allow us to measure differences between them and to analyze the distribution across a series of complexes. Geometric morphometric methods make use of the relative position of carefully defined homologous points on surfaces, called landmarks (Bookstein, 1991; Dryden and Mardia, 1998). Landmark-free methods often use geometric characteristics of the surfaces. They therefore need to make strong assumptions about the topology of the surface, for example limiting analysis to genus zero surfaces (Boyer et al., 2010; Chung et al., 2003) or using medial representations (Bouix et al., 2005; Gorczowski et al., 2010; Styner et al., 2005) or Laplace–Beltrami eigenfunctions (Reuter et al., 2006). Such methods can rarely be applied to raw surface meshes resulting from segmentation algorithms since such meshes may include small holes, show irregular sampling or split objects into different parts.

More importantly, such methods analyze the intrinsic shape of each structure independently, therefore neglecting the fact that brain anatomy consists of an intricate arrangement of various structures with strong interrelationships. By contrast, we aim at measuring differences between shape complexes in a way that can account for both the differences in shape of the individual components and the relative position of the components within the complex. This goal cannot be achieved by concatenating the shape parameters of each component or by finding correlations between such parameters (Gorczowski et al., 2010; Tsai et al., 2003), as such approaches do not take into account the fact that the organization of the shape complex would not change, and in particular, that different structures must not intersect.

One way to address this problem is to consider surfaces as embedded in 3D space and to measure shape variations induced by deformations of the underlying 3D space. This idea stems from Grenander's group theory for modeling objects (Grenander, 1994), which revisits morphometry by the use of 3D space deformations. The similarity between shape complexes is then quantified by the "amount" of deformation needed to warp one shape complex to another. Only smooth and invertible 3D deformations (i.e., diffeomorphisms) are used, so that the internal organization of the shape complex is preserved during deformation since neither surface intersection nor shearing may occur. The approach determines point correspondences over the whole 3D volume by using the fact that surfaces should match as a soft constraint. The method is therefore robust to segmentation errors in that exact correspondences among points lying on surfaces are not enforced. In this context, a diffeomorphism could be seen as a low-passfilter to smooth shape differences. In this paper, it is our goal to show that the deformation parameters capture the most relevant parts of the shape variations, namely the ones that would distinguish between normal and disease.

Here, we propose a method that builds on the implementation of Grenander's theory in the LDDMM framework (McLachlan and Marsland, 2007; Miller et al., 2006; Vaillant et al., 2007). The method has 3 components: (i) estimation of an average model of the shape complex, called the template complex, which is representative of the population under study; (ii) estimation of the 3D deformations that map the template complex to the complex of each subject; and (iii) statistical analysis of the deformation parameters and their interpretation in terms of variations of the template complex. The first two steps are estimated simultaneously in a combined optimization framework. The resulting template complex and set of deformations are now referred to as an *atlas*.

Previous attempts to estimate template shapes in this framework offered little control over the topology of the template, whether it consists in the superimposition of a multitude of surface sheets (Glaunès and Joshi, 2006) or a set of unconnected triangles (Durrleman et al., 2009). The topology of the template may be chosen as one of a given subject's complex (Ma et al., 2008), but this topology then inherits the mesh imperfections that result from an individual segmentation. In this paper, we follow the approach initially suggested by Durrleman et al. (2012), which leaves the choice of the topology of the template with the number of connected components to the user. This method estimates the optimal position of the vertices so that the shape of the template complex is an average of the subjects' complexes. Here, we extend this approach in order to guarantee that no self-intersection could occur during the optimization.

The set of deformations that result from warping the template complex to each subject's complex captures the variability across subjects. The deformation parameters quantify how the subject's anatomy is different from the template, and can be used in a statistical analysis in the same spirit as in Vaillant et al. (2004) and Pennec (2006). We follow the approach initiated in Durrleman et al. (2011, 2013), which uses control points to parameterize deformations. The number of control points is fixed by the user, and the method automatically adjusts their position near the most variable parts of the shape complex. The method therefore offers control over the dimension of the shape descriptor that is used in statistics, and thus avoids an unconstrained increase with the number of surfaces and their samplings (Vaillant and Glaunès, 2005). We show that statistical performance is not reduced by this finite-dimensional approximation and that the parameters can robustly detect subtle anatomical differences in a typical low sample size study. We postulate that in some scenarios, the statistical performance can even be increased, as the ratio between the number of subjects and the number of parameters becomes more favorable.

An important key element of the method is a similarity metric between pairs of surfaces. Such a metric is needed to optimize the deformation parameters that enable the best matching between shape complexes. We use the varifold metric that has been recently introduced in Charon and Trouvé (accepted for publication). It extends the metric on currents (Vaillant and Glaunès, 2005) in that it considers the *non*-oriented normals of a surface instead of the oriented normals. The method is therefore robust to possible inconsistent orientation of the meshes. It also prevents the "canceling effect" of currents, which occurs if two surface elements with opposite orientation face each other, and which may cause the template surface to fold during optimization. Otherwise, the metric inherits the same properties as currents: it does not require point-correspondence between surfaces and is robust to mesh imperfections such as holes, spikes or irregular meshing (Durrleman et al., 2009; Vaillant and Glaunès, 2005).

This paper is structured as follows to give a self-contained presentation of the methodology and results. We first focus on the main steps of the atlas construction, while discussing the technical details of the theoretical derivations in the appendices. We then present an application to neuroimage data of a Down syndrome brain morphology study. This part focuses on the new statistical analysis of deformations that becomes possible with the proposed framework, and it also presents visual representations that may support interpretation and findings in the context of the driving clinical problem. The analysis also includes an assessment of the robustness of the method in various settings.

Mathematical framework

Kernel formulation of splines

In the spline framework, 3D deformations ϕ are of the form $\phi(x) = x + v(x)$, where $v(x)$ is the displacement of any point x in the ambient 3D space, which is assumed to be the sum of radial basis functions K located at control point positions $\{c_k\}_{k=1,\dots,N_{cp}}$:

$$v(x) = \sum_{k=1}^{N_{cp}} K(x, c_k)\alpha_k. \quad (1)$$