STATISTICS OF POPULATIONS OF IMAGES AND ITS EMBEDDED OBJECTS: DRIVING APPLICATIONS IN NEUROIMAGING

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ABSTRACT

Work in progress towards modeling shape statistics of multi-object complexes is presented. Constraints defined by the set of objects such as a compact representation of object shape relationships and correlation of shape changes might have advantages for automatic segmentation and group discrimination. We present a concept for statistical multi-object modeling and discuss the major challenges which are a reduction to a small set of descriptive features, calculation of mean and variability via curved statistics, the choice of aligning sets of multiple objects, and the problem of describing the statistics of object pose and object shape and their interrelationship. Shape modeling and analysis is demonstrated with an application to a longitudinal autism study, with shape modeling of sets of 10 subcortical structures in a population of 20 subjects.

1. INTRODUCTION

Statistical shape modeling is concerned with the construction of a compact and stable description of the population mean and variability. A fundamental difficulty is the high dimensionality of the set of features with a relatively small sample size, typically in the range of 20 to 50 in neuroimaging studies. This problem is even more evident for modeling sets of multiple objects, for example the set of subcortical brain structures. Statistical modeling of multi-object complexes with their inherent correlations has significant advantages for deformable-model segmentation, as nicely demonstrated by Tsai et al. [1] and by Yang et al. [2]. The joint modeling of object shapes defines constraints that significantly help to stabilize the segmentation process. Whereas these two papers describe statistical object modeling by level-sets, we propose explicit shape modeling with sampled medial mesh representations. We further discuss the use of curved statistics with modeling of major modes of deformations via principle geodesic analysis (PGA), a nonlinear extension of PCA.

Clinical applications favor a statistical shape modeling of multi-object complexes rather than shape analysis of single anatomical structures represented out of their embedding complex. Neuroimaging studies of mental illness and neurolocal disease, for example, are interested in describing group differences and change due to neurodevelopment or neurodegeneration, processes that most likely affect multiple structures rather than single anatomical objects. A description of the change of the set of objects might help to explain underlying neurobiological processes affecting brain circuits.

This paper summarizes work in progress towards an efficient and compact modeling of sets of objects. We choose a sampled medial representation (M-rep) and a statistical framework based on Riemannian metrics. Driving application is a neuroimaging study where sets of anatomical objects have been segmented using highly reliable user-supervised tools.

2. METHODOLOGY

This research is driven by the challenge to describe the shape statistics of a set of 3-D objects. Whereas analysis of single shapes is well advanced and has been described extensively using a variety of shape parametrization techniques, extension to multi-object complexes still represent significant challenges. Although it might be straightforward to assume that the shape of abutting objects embedded in volumetric images are strongly correlated, the research community does not yet have access to tools for statistical modeling and analysis of sets of objects.

2.1 Statistics of embedded multi-object shape models:

Construction of atlases is a key procedure in population-based medical image analysis. Problems of blurring and eventual bias through the choice of a tempalte can be overcome by nonlinear processing via large deformation registration and population-based simultaneous nonlinear averaging of sets of images [3, 4]. Figure 1 top illustrates the construction of an atlas of a population of 14 3-D MRI images of pediatric subjects at age two using the method developed by Josi et al. Sets of user-guided segmentations of subcortical structures are available for each pediatric 3D MRI. The set of nonlinear

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registrations resulting from unbiased atlas building can thus be applied to the segmented objects to construct a non-linear multi-object average. In our prelimary test, we chose four populations with a total of 20 cases (autistic and healthy subjects at ages of 2 and 4 years). Sets of transformed objects are integrated, and the mean level set was defined as the average object (see Fig. 1 bottom). Please note that *homology* across the sets of objects is defined via the nonlinear deformation maps, linking the atlas uniquely to each subject. A comparison between nonlinear and linear multi-object averaging is discussed in Xu et al. [5].

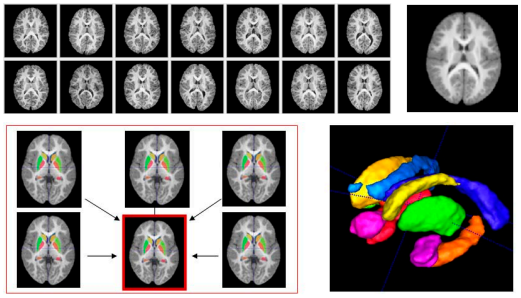

Fig. 1. Unbiased atlas building (top) and calculation of the mean multi-object model (bottom) by applying the set of nonlinear transformations to the segmented brain objects. Qualitatively, the shape and mutual relationship of the structures are preserved in the mean multi-object complex.

2.2 Estimating variability of multi-object complexes:

In linear space, variability of parametrized objects can be described by principle component analysis (PCA) of spherical harmonics [6] or point distribution models (PDM) [7]. The point to point correspondence established via object and parameter space alignment in the spherical harmonic concept or minimum description length optimization in the PDM models guarantees a diffeomorphic mapping. However, the linear principal component analysis (PCA) cannot describe object rotations and the modeling cannot be extended to model points and normals, e.g. Extension to non-linear modeling is achieved by principle geodesic analysis (PGA), developed by Fletcher et al. [8]. PGA extends linear PCA into nonlinear space using "curved statistics" and is a natural generalization of PCA for describing the variability of geometric data that are parametrized as curved manifolds. To recall, the intrinsic mean of a collection of points $x_1, \cdots, x_N$ on a Riemannian manifold M is the Fréchet mean $\mu = argmin \sum_{i=1}^{N} d(x, x_i)^2$, where $d(.,.)$ denotes Riemannian distance on M. Whereas PCA in $\mathbb{R}^3$ generates linear subspaces that maximize the variance of projected data, geodesic manifolds are images of linear subspaces under the exponential map and are defined as the manifolds that maximize projected variance. Principle geodesics can be found by a recursive gradient descent. In practice, an approximation of the true solution can be calculated by the log map and a linear PCA in the tangent space of the mean (please see [9] for details). Important is the fact that PGA is not limited to linear statistics of surface points but can be extended to shape parametrization schemes that include point locations, length parameters and angles.

2.3 Object representation by a medial mesh:

Medial representations represent an alternative to parametrization of 3-D objects via surfaces. Medial axis representations incorporate the notion of symmetry axis or manifolds, where the representation is decomposed into the shape and structure of the skeletal sheet but also the width function as a local attribute. Changes in terms of local translation, bending and widening can be more naturally expressed by medial than by surface representations. Pizer et al. [10, 11] developed an object representation by a mesh of medial atoms. Each atom is characterized as a tuple with position, radius, and the normal vectors to the boundary: $m = \{\mathbf{x}, r, \mathbf{n_0}, \mathbf{n_1}\} \in \mathcal{M}$, with $\mathcal{M} = \mathbb{R}^3 \times \mathbb{R}^+ \times \mathcal{S}^2 \times \mathcal{S}^2$. The object surface can be interpolated from endpoints of the sets of medial atoms, but this representation also allows a continous interpolation of the whole object interior and a rim exterior to the object boundary. Furthermore, unlike many surface representation schemes, this representation encodes not only sample points at the boundary but also normals to the boundary. Since the parameter vector of medial atoms includes position, length and angle (between normals), mean and variability of a population of object shapes is calculated via the Fréchet mean and PGA framework as discussed before.

2.4 Modeling of sets of objects with M-reps:

This paragraph summarizes the sequence of steps for building statistical shape models, for shape parametrization of the set of multiple objects, and for statistical analysis of groups of objects. Details of the various procedures are found in associated papers and PhD theses.

Segmentation of anatomical objects: Anatomical structures of interest, including left and right hippocampus, amygdala, putamen, caudate, pallied globe and lateral ventricles, have been segmented by trained experts using semi-automated procedures. Most structures were segmented with our ITK-SNAP tool, which includes implicit level-set evolution and manual editing functions (free download at www.ia.unc.edu/dev). Our experts went through an extensive training, which is reflected by a very high intra- and inter-reliability [1].

Statistical shape modeling: The segmented objects are represented as binary voxel objects (see Fig. 1). The lateral ventricles had to be excluded due to topology differences. We have applied our shape processing pipeline which includes parametrization by spherical harmonic representations [12], point distribution modeling (PDM) with homology obtained via subdivision sampling, object pose alignment, and alignment of surface parametrizations via the ellipsoid of the first harmonics[7, 13]. We then used the modeling scheme devel-

[1] See http://www.psychiatry.unc.edu/autismresearch/mri/roiprotocols.htm) for a detailed description of protocols and reliability results.

oped by Stner et al. [14] to construct sampled medial models from populations of objects. An explicit error term ϵ defines the maximum distance of each object to the model, and the same error term is used to determine the minimum sampling of each medial mesh model. As a result, the five left and right subcortical structures (hippocampus, amygdala, putamen, pallied globe, caudate) are modeled as compact medial mesh structures (see Fig. 2).

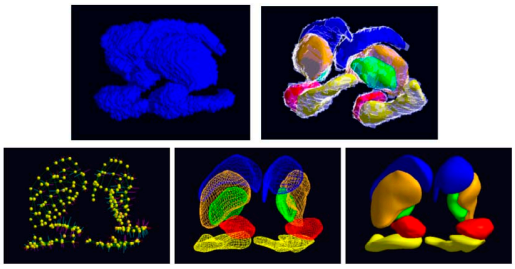

Fig. 2. Multi-object shape parametrization with M-rep's: Top: Binary voxel objects (left) and overlay of parametrized surface (right). Bottom: Mesh of medial atoms (left), implied surface mesh (middle) and implied solid surface (right).

M-rep shape parametrization based on deformable model: The M-rep models are deformed into each anatomical object using the "Binary Pablo" tool developed by Pizer et al.[11]. Driven by a local image match function at object boundaries, M-rep models are deformed to optimally fit the binary voxel segmentations. This process is applied individually to each of the 10 anatomical object in each of the 20 image datasets.

3. RESULTS

3.1 Motivation and clinical data: Driving clinical problem is the need for a joint analysis of the set of subcortical structures. There is strong evidence that the morphology and size of anatomical shapes might show a strong correlation between objects that are part of a circuit or share common functionality. The image data used in this paper is taken from an ongoing clinical pediatric autism study. This study includes autistic subjects (AUT) and matched typically developing healthy controls (TYP) with baseline at age 2 and follow-up at age 4. Through this longitudinal design, we can not only study cross-sectional differences between groups but also growth and even group differences between growth patterns. For the preliminary analysis shown here, we have selected 5 subjects each from the TYP and AUT groups. For eight of these subjects, we had longitudinal data with successful scans at 2 and 4 years of age.

3.2 Principle Geodesic Analysis: We applied the principle geodesic analysis method to the whole set of objects and combined all the subject groups, which ensures projection into the same geometric domain for each subject. Whereas the analysis of single shapes usually follows the typical sequence of linear alignment, correcting for individual object pose and analysis of the residual shape change, a processing of sets of objects might require an extended concept. The individual objects within object complexes can have different relative positions, e.g. they can slide against each other or even show relative rotation. Current research is addressing the questions of aligning sets of objecs and separating shape changes from pose differences.

In our preliminary experiment, the sets of objects are aligned by a global process which is similar to Procrustes fit, but extended to accomodate the atom mesh representation of M-reps. This global alignment includes global translation, rotation and scaling in the three spatial directions. PGA is applied to the aligned sets of objects and results in the mean and the major modes of variations (see Fig. 3).

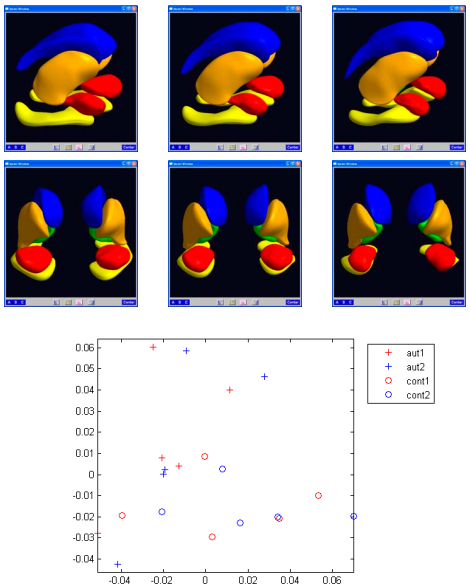

Fig. 3. Eigenmodes of deformation by principle geodesic analysis (PGA). The top images show the first eigenmode with minus 3 stdev, mean and plus 3 stdev for sagittal and coronal views. Bottom: Subject groups projected into the space of the first two PGA eigenmodes.

3.3 Dimensionality Reduction: PGA performs a compression of the multi-object shape variability to a small set of major eigenmodes of deformation. We assume that the first few modes describes most of the shape variability whereas the reminder might mostly represent individual noise. The quality of this compression can be evaluated with the criteria compactness, sensitivity and specificity as discussed in [14]. As a preliminary test, we followed the standard procedure of projecting the multi-object complexes into the space of the eigenmodes: $\mathbf{m}_j = \overline{\mathbf{m}} + \mathbf{P}\mathbf{b}_j$, where $\mathbf{b}_j = \mathbf{P}^T(\mathbf{m}_j - \overline{\mathbf{m}})$. The

columns of $\mathbf{P}$ represent the eigenvectors and the vectors $\mathbf{b}_j$, which are weights in eigenvector space, describe the deviation of individual shapes $\mathbf{m}_j$ from the mean shape. The weight vector represents a descriptor for each multi-object complex. Figure 3 bottom illustrates a projection of the 4 groups (controls and autistic subjects at age 2 and 4) into the space of the first two eigenmodes. Although the plot indicates a possible separation between the TYP and AUT groups characterized by $+$ and $\circ$, it would be premature to draw any conclusions. PGA, similarly to PCA, is selecting a subspace based on maximum common variability but not maximum separation. An extension of independent component analysis (ICA) to curved space or supervised training of a subspace of maximum separation will be explored in our future research.

4. DISCUSSION

We have discussed work in progress towards extending statistical analysis of anatomical shape from single structures to multi-object complexes. In regard to the driving applications in neuroimaging, a *joint* analysis of size, shape and pose of objects and their interrelationships seems superior than single object analysis. This might answer questions about correlation among objects, for example objects that are part of brain circuits or are known to be functionally connected. Key issue addressed in this paper are the extraction of a small set of key features representing the set of objects and calculation of mean and variability via Riemannian metric. The joint analysis of multiple objects even amplifies the fundamental problem of small sample size and high dimensionality of features.

Important open issues remain and need to be addressed not only by our group but by the international research community. The study of object pose, interrelationship between abutting objects, shape changes, and correlation of changes of shape and pose within sets of objects offers challenging but exciting research projects. The relationship between unbiased volumetric atlas building and statistical shape modeling requires further analysis. Whereas the former assumes and maintains a diffeomorphism, it is known that sets of anatomical objects might not be fully described by diffeomorphic transformation to an atlas, for example if objects slide against each other. In regard to the M-rep object parametrization as used here, we still need to demonstrate the quality and stability of correspondence and the robustness, sensitivity and specificity of PGA-based compression of features. Applications in neuroimaging further require hypothesis testing schemes that will have to combine shape features with clinical variables, and which have to properly address the problems of nonlinear modeling and multiple comparison testing. Encouraging progress is shown by recent work of Terriberry et al. [15].

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