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Construction of a neuroanatomical shape complex atlas from 3D MRI brain structures

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ABSTRACT

Brain atlas construction has attracted significant attention lately in the neuroimaging community due to its application to the characterization of neuroanatomical shape abnormalities associated with various neurodegenerative diseases or neuropsychiatric disorders. Existing *shape* atlas construction techniques usually focus on the analysis of a single anatomical structure in which the important inter-structural information is lost. This paper proposes a novel technique for constructing a neuroanatomical *shape complex* atlas based on an information geometry framework. A shape complex is a collection of neighboring shapes – for example, the thalamus, amygdala and the hippocampus circuit – which may exhibit changes in shape across multiple structures during the progression of a disease. In this paper, we represent the boundaries of the entire shape complex using the zero level set of a distance transform function $S(\mathbf{x})$. We then re-derive the relationship between the stationary state wave function $\psi(\mathbf{x})$ of the Schrödinger equation $-\hbar^2\nabla^2\psi+\psi=0$ and the eikonal equation $\|\nabla S\|=1$ satisfied by any distance function. This leads to a one-to-one map (up to scale) between $\psi(\mathbf{x})$ and $S(\mathbf{x})$ via an explicit relationship. We further exploit this relationship by mapping $\psi(\mathbf{x})$ to a unit hypersphere whose Riemannian structure is fully known, thus effectively turn $\psi(\mathbf{x})$ into the square-root of a probability density function. This allows us to make comparisons – using elegant, closed-form analytic expressions – between shape complexes represented as square-root densities. A shape complex atlas is constructed by computing the Karcher mean $\bar{\psi}(\mathbf{x})$ in the space of square-root densities and then inversely mapping it back to the space of distance transforms in order to realize the atlas shape. We demonstrate the shape complex atlas computation technique via a set of experiments on a population of brain MRI scans including controls and epilepsy patients with either right anterior medial temporal or left anterior medial temporal lobectomies.

Introduction

Human brain MRI analysis is an important problem due to its application in the diagnosis and treatment of neurological diseases. In this context, the construction of neuroanatomical atlases of the human brain is of particular interest and its importance has been emphasized in a number of recent studies (Aljabar et al., 2009; Sabuncu et al., 2009; Shattuck et al., 2008; Yeo et al. 2008). In brief, an atlas provides a reference for a population of shapes/images which is useful in numerous applications: (i) statistical analysis of volumetric changes in control and patient populations, (ii) atlas-guided segmentation of structures of interest which is needed in further diagnostic procedures, and (iii) automated detection of disease regions based on shape variations between the atlas and individual subjects. Most existing shape atlases are based on isolated, single anatomical shapes (Fletcher et al., 2004; Liu et al., 2008; Wang et al., 2006) which do not contain any inter-structural information. For example, the spatial relationships among different neighboring structures may change due to the effect of non-uniform volume shrinkage or expansion of neighborhood structures. Furthermore, many neurological disorders are diagnosed by the structural abnormalities (e.g. volume change) ascribed to several brain structures rather than a single structure. Alzheimer's disease is an example of such a neurological disorder—a morphological marker for which is the enlargement of ventricles and the shrinkage of the entorhinal cortex, amygdala and hippocampi (Brice, 2009). Mania, which is most often associated with bipolar disorder serves as another example. In Strakowski et al. (1999), all the brain structures associated with the neural pathways were examined and the authors claimed that patients with mania have a significant *overall* volume difference in the regions including the thalamus, hippocampi and the amygdala. In Seidman et al. (1999), the authors concluded that the structural abnormalities in the thalamus and the amygdala–hippocampus regions represent remarkable anatomical vulnerabilities in schizophrenia subjects. Therefore, a neuroanatomical shape complex atlas which captures anatomical connectivity as well as inter-structural relationships is of primary clinical importance.

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Previous work

In the context of atlas construction for multiple brain structures, most of the efforts in the past were focused on building the full brain *image* probabilistic atlases. For instance, in Joshi et al. (2004), Avants and Gee (2004), Shi et al. (2010), and Xie et al. (2010), several image atlas construction methods for the entire brain were proposed based on the acquisition of 3D brain MR scans. The traditional techniques for image atlas construction usually focus on developing effective image deformation methods to register a population of brain images. Subsequently (or in tandem), the atlas image is estimated as an average over the registered image population. More recent works are based on developing specific techniques for mean computation. For example, in the multi-regional atlas (Shi et al., 2010), the region specific mean is estimated whereas in Xie et al. (2010), the geodesic mean of a population of brain images is computed via an intrinsic averaging method. The brain image atlas has its advantage in general brain analysis. The variations of the entire brain due to aging can be studied (Sabuncu et al., 2009) and the segmentation of brain structures (via registration of the atlas) achieved (Joshi et al., 2004) with the aid of the whole brain image atlas. However, image registration (and hence the analysis based on it) may not be accurate for particular structures of interest due to the misalignment caused by the overall deformation of the convoluted cortex with its gyrencephalic details. Furthermore, it is a non trivial task to extend these techniques to shape atlas construction. Consequently, we will forgo further discussion of image based atlases in this paper and restrict our focus to shape based atlas construction. A shape atlas is of great importance when the analysis is focused on a certain structure or a neural pathway containing several related structures in the brain: examples are the diseases associated with hippocampi and amygdala.

Feature point-sets (or landmarks when specific identities are ascribed to the features) are one of the most common shape representations in the literature. Unbiased atlas construction of hippocampi via groupwise point-set registration of mixture model probability density functions is described in Chen et al. (2010b), Wang et al. (2008), and Chui et al. (2004). While explicit point to point correspondences are recovered in Chui et al. (2004), information-theoretic methodologies are adopted in Chen et al. (2010b) and Wang et al. (2008) resulting in implicit correspondence. In Cootes et al. (2008), a statistical shape model is directly constructed on diffeomorphic deformation fields. Other methods that represent shapes in 2D using parametric curves and in 3D using parametric surfaces have also received considerable attention in the literature (Klassen et al., 2004; Sebastian et al., 2003). Since intrinsic statistical shape analysis in the space of curves/surfaces is in general a non trivial task, methods using this representation have traditionally resorted to computing means etc. of spline parameters. In Styner et al. (2003), a characteristic 3D shape model dubbed the M-rep was proposed, and based on this representation, a mathematical characterization of the space of M-reps was developed. An atlas was then constructed in this space via computation of the geodesic mean of a population of shapes represented by M-reps (Fletcher et al., 2004). Recent work in Liu et al. (2008) describes an interesting model using continuous spherical shapes to analyze the anatomical shape differences in the hippocampus of a control group and blind subjects.

To summarize, in all the techniques discussed thus far, the shape atlas is developed only for an isolated anatomical structure and it is difficult to generalize these methods to multiple connected anatomical structures in a neighborhood. A shape complex analysis algorithm was proposed in Cates et al. (2008), where the shapes are represented by point sets and the correspondences across the shape complexes are optimized via minimizing an entropy based cost function. Although this model leads to straightforward statistical shape analyses, it has to resort to a gradient descent strategy for the optimization. In Gorczowski et al. (2007) and Qiu and Miller (2008) multi-object shape analysis frameworks were presented where each shape of the "multi-object" had an independent representation, and hence extra information on the structural relationships between different shapes needed to be maintained. In Litvin and Karl (2005), a multi-object shape distribution was used as a prior for 2D image segmentation, wherein the distribution of a set of shapes is defined as the average of the distribution corresponding to the individual shapes in the group. This method does extract features from a shape complex but this shape information is lost after averaging.

Before we turn to the actual approach in this work, we briefly describe the role of the correspondence problem in atlas estimation. Groupwise non-rigid registration is used in previous work (Chen et al., 2010b; Wang et al., 2008; Chui et al., 2004) for atlas computation. If explicit point-to-point correspondences can be recovered from groupwise non-rigid registration, then an atlas can be subsequently computed by averaging over corresponding point locations. In contrast, in this work we quotient out an appropriate transformation (rigid, similarity, affine) prior to atlas computation in the space of distance transforms. Consequently, our approach avoids the correspondence problem but the computed atlas now depends on the spatial mapping that is quotiented out. Since distance transforms represent shapes implicitly (rather than explicitly), our approach can be used even in situations where topological differences exist – a common situation in shapes extracted from brain MRI – whereas correspondence-based approaches are notoriously problematic when topological differences are present.

In this paper, we propose a novel technique for constructing the atlas of a neuroanatomical shape complex consisting of multiple neuroanatomical structures where the inter-structural relationships are captured implicitly without any loss of information of any of the constituent structures. In our framework, we first use the zero level set of the distance transform function to represent the boundaries of the entire shape complex and based on the mathematical relationship derived in the section below entitled Shape complex atlas, we then map the distance transform functions to the space of square-root densities where a geodesic mean (atlas) is computed. Finally, the actual shape complex atlas is realized via the inverse map back to the space of distance transforms.

The key contributions of this paper are as follows: (i) We derive a novel relationship between the stationary state wave function $\psi(\mathbf{x})$ of the Schrödinger equation and the eikonal equation $\|\nabla S\| = 1$ for the Euclidean distance transform problem, which serves as a "bridge" that connects the distance transform representation of the shape to the space of square-root-densities. (ii) The inter-structural relationships are well captured in our distance transform representation of the shape complex, which is of great clinical importance for studying the shape variations across multiple structures in both ontogenesis and in various neurological diseases. (iii) We represent shape complexes using square-root densities. Since the manifold of square-root density functions is a unit Hilbertian sphere and its geometry is well understood, it allows us to use intrinsic geometry to compare shape complexes and carry out a statistical analysis of them.

The rest of the paper is organized as follows: In the Shape complex atlas section, we present the details of our shape complex atlas construction methodology. We demonstrate our technique in the Experiments section on a 2D shape complex data set comprising the corpus callosum, brainstem and the cerebellum (taken from the midsagittal plane) and 3D brain structures including left/right hippocampus, entorhinal cortex, amygdala and thalamus. The data are from a population of 46 3D brain MR scans with all the neuroanatomical structures labeled by an expert neurologist.

Shape complex atlas

In this section, we derive the relationship between distance transform function and the square-root density representation, which allows us to model the shape complex in the square-root density space, perform the statistical analysis of the shapes and recover the mean shape back in the distance transform function space.