Shape Analysis of Human Brain: A Brief Survey

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***Abstract*— The survey outlines and compares popular computational techniques for quantitative description of shapes of major structural parts of the human brain, including medial axis and skeletal analysis, geodesic distances, Procrustes analysis, deformable models, spherical harmonics, deformation morphometry, as well as other less widely used techniques. Their advantages, drawbacks, and emerging trends, as well as results of application, in particular, for early computer-aided diagnostics, are discussed.**

***Index Terms*—Shape Analysis, Brain, Autism Diagnostics.**

I. Introduction

The human brain belongs to the most complex anatomical structures in the human body. Individual brains vary substantially, and therefore analyzing the brain presents a real challenge. Figure 1 illustrates the complexity of the brain represented in a three-dimensional (3D) mesh format. Computer-aided medical diagnostics calls for quantitative analysis of many structural parts of the brain, such as e.g. its cortex, ventricles, corpus callosum, hippocampus, brain stem, and gyrifications.

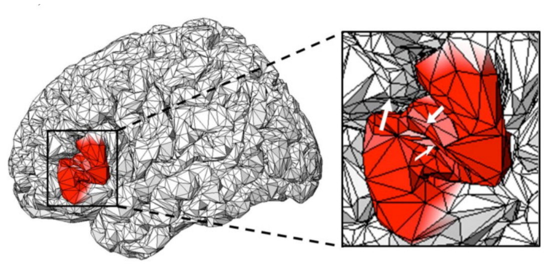

Fig. 1. *3D mesh brain representation (the expanded section details its complexity and variability due to multiple different structures and gyrifications. Courtesy of Barras et al [1]*

This survey focuses primarily on applications of various shape analysis techniques to the human brain. Methods of shape analysis for the human brain include techniques such as medial axis and skeletal analysis, geodesic distances, Procrustes analysis, deformable models, SPHARM, deformation-based morphometry, symmetry-based analysis, Laplace-Beltrami operators, and homologous modeling, among other techniques.

In 1979, Lande [2] proposed to analyze the shape by measuring the brain volume. While the volumetric analysis of brain scans does not arguably yield sound discriminatory features, it was a key starting point for shape analysis related to the brain. Later on, Desimone e.a. [3] and Martin e.a. [4] proposed two more elaborate shape analysis frameworks. The first framework examined color, shape and texture of the cortex, on 2D scans of the brain. The second framework performed a more advanced analysis by examining pre-generated mesh models of the brain ventricles. To more accurately represent the brain, the meshes were decomposed using eigen-vectors, having been obtained in a way similar to conventional Principal Component Analysis (PCA). These early frameworks for examining the shapes of brain constructs did not produce reliable descriptors of brain-related health or behavioral disorders, such as e.g. autism. However, they inspired extensive subsequent research that helped to push the current field of brain shape analysis into the forefront of development for efficient techniques for computer-assisted medical diagnostics.

Generally, shape analysis is applied to digital geometric models of surfaces or/and volumes of objects-of-interest in order to detect similarities or differences between the objects [5]. Typically, it is fully automated or combines automated and manual processing, and is closely paired with some kind of object segmentation. Segmented objects are represented in a variety of digital formats, including volumes, point clouds, and meshes. Most typically, the outer boundary (or surface) of an object, or a manifold representing this object, is examined.[1]

Surface analysis, called surface interrogation in modern computer graphics, and computer-aided design systems, explicitly examine intrinsic and extrinsic geometric properties of surfaces of objects and manifolds, including visual pleasantness, technical smoothness, and geometric constraints [7]. It is often used to detect surface imperfections, analyze shapes, or visualize different forms.

Shape analysis techniques can be primarily classified into first- and second-order types, each containing large numbers of congruency based, intrinsic, and graph based shape descriptors [7]. The first-order methods typically rely on surface normal vectors, inflections, and other intrinsic descriptors, obtained e.g. by the Laplace-Beltrami analysis or the more popular geodesic path analysis. Some congruency methods, such as the shape distribution and symmetry analysis, also fall into this category.

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[1] By Henri Poincare [6], a manifold is the level set of a continuously differentiable function between Euclidean spaces that satisfies the non-degeneracy hypothesis of the implicit function theorem. In a simplified version, it can be thought of as an object with no holes or discontinuities.

Second-order analysis generally is based on the surface curvature and second derivatives. Typical descriptors are produced by moment analysis, spherical harmonics, and Procrustes analysis, being invariant with respect to congruency, and medial axis, skeletal, and Reeb graph analysis, which also heavily rely on the curvature. Importantly, many second-order analysis methods additionally incorporate first-order techniques.

Both categories of shape analysis depend critically on shape interrogation, or extraction of structural characteristics of a shape from its geometric model [7], and re-meshing, i.e. repartitioning of primitive components to fit best the original shape. Most commonly, vertex-vertex or face-vertex methods are used to construct the meshes. The vertex-vertex method deals with a point cloud, where the points relate to critical junctures in an object, while the face-vertex method exploits faces that interconnect vertices in a specific and controlled manner [8]. A widely known example of the latter is Delaunay triangulation, in which every face is a triangle and the final mesh consists of a large number of interconnected triangular faces. While the re-meshing helps to preserve the original shape of the object, it can also be used to enhance some features of the shape. A primitive (such as e.g. a triangle that minimally characterizes the shape) can locally fit any such feature.

Some of the most popular, in application to the human brain, shape analysis techniques are detailed and compared below. These include (*i*) the medial axis and skeletal analysis, which is commonly used for surface (2D) and volume (3D) reconstruction in complex models; (*ii*) geodesic distances to compare different brains in detail by using intrinsic and graph based analysis; (*iii*) Procrustes analysis that can provide accurate and quick statistical evaluation of shapes in rigid objects; (*iv*) deformable models evolving to fit boundaries of complex objects, and (*v*) more recent 3D surface approximation with spherical harmonics in order to analyze the brain shape in detail.

II. Medial Axis and Skeletal Analysis

Medial axes of complex 2D/3D graphical models are widely used for surface reconstruction and dimensionality reduction. A medial axis, or a skeleton of an object is defined as the set of internal points with more than one closest point on the object's surface (see Fig. 2). Generally, it is represented by a polygon or a similar simple construction of concatenated arcs and parabolas that follow the would-be centerline of the object. The medial axis and skeletal graphs facilitate indexing, matching, segmenting, or associating objects with one another. Medial axis analysis has a wide arrange of uses, and can also be used in many anatomical applications outside of the brain, such as e.g. virtual colonoscopies.

The notion of a skeleton of a 2D or 3D shape was first introduced by Blum et al [10], [11]. The underlying idea was to place inside an object a primitive shape, such as a ball, inflate it until reaching the object's surface, and repeat this process until filling the object with the maximum-size primitives. Connected centers of the primitives form the skeleton that represents geometric properties of the object's interior, such as bends and elongations, and reveals the geometric structure, or constituent parts of the object, and gives information about the object's position, orientation, and size.

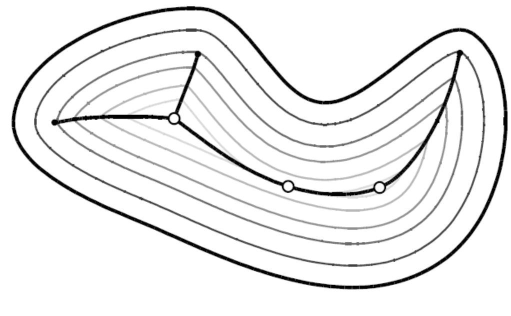


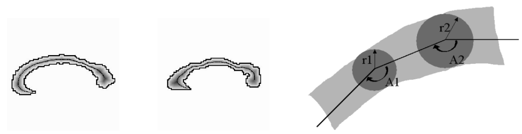
Fig. 2. *Medial axis of a 2D object: the outer black line shows the boundary of the object and the central dark line connecting the open circles is the medial axis. Inner isolines indicate the same distances from the boundary [9].*

TABLE I
AUTOMATED (A) OR SEMI-AUTOMATED (SA) MEDIAL AXIS ANALYSIS: GROUND TRUTH (GT) FROM CLINICIAN (C) OR NON-CLINICIAN (N) EXPERTS; DIMENSIONALITY (DIM) AND SIZES (#) OF EXPERIMENTAL IMAGE DATABASES.

Publication	Year	Mode	Dim	#	GT
Naf et al [12]	1996	A	3D	n/a	N
Golland et al [13]	1999	A	2D	66	C
Pizer et al [14]	1999	SA	2D	20	C
Golland et al [15]	2001	A	3D	30	C
Styner et al [16]	2001	A	3D	20	C
Gorczowski et al [17]	2007	A	3D	70	C
Elnakib et al [18]	2011	A	3D	34	C
Paniagua et al [19]	2013	A	3D	90	C

Table I exemplifies applications of skeletons for human brain analysis, starting from the early and novel at that time proposal by Naf et al [12]. Naf classified various organs, including the brain, after characterizing their structure in 3D images with Voronoi diagrams and skeletons. Excepting [14], all the methods in Table I were used for medical diagnostics or classification.

Golland et al [13] analyzed skeletons of the corpus callosum in 2D images in order to classify cases of schizophrenia. The initial skeletons were refined using snakes, or active contours, which evolved from different randomly chosen starting points. Then the curvature angles and the width of the skeleton shown in Fig. 3 were used as discriminatory features. The angles were calculated between each set of adjacent points along the sampled medial axis, and the width was defined as the radial distance from the medial axis point to the surface boundary. Sampling more points of the skeleton provides finer details, but also increases the analysis time. The approach was tested on clinical datasets for normal and schizophrenic patients. A relatively high accuracy (more than 70% in the best case) was obtained for identifying schizophrenia in patients by statistical shape analysis of the corpus callossum and hippocampus [15] (the accuracy of a linear classifier in determining schizophrenic patients on the training data proved to be consistently higher than the cross validation one).



(a) Example 1 (b) Example 2 (c) Features for classification

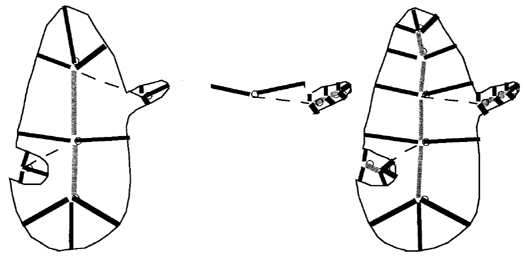
Fig. 3. *Golland's [13] skeleton extraction: gray-coded maps (a,b) of distances from the medial axis to the outer boundary and two features (c) derived from the medial axis for classification, namely, the curvature angle and the shape width.*

As noted in [13], [15], the main advantages and drawbacks of skeletons relates to their compact and intuitive shape representation that can be used for segmentation, tracking, and object recognition, as well as their high sensitivity to noise in the object's boundary, respectively. The complex and spatially variant structure of the brain leads to a large amount of noise along the typical shape boundary. To overcome this challenge, frequently the typical general shapes of the objects are known in advance from segmented training samples, and methods using fixed topology skeletons have been proposed in [13], [15]. The significant benefit of such skeletons is that they can be adjusted to each current object of similar shape and optimized for accuracy.

Pizer et al [14] proposed another method of quantifying object shapes in 2D images that can be used in a variety of applications, including different brain structures. In this case the skeletons were used to register brain shapes and compare the brain ventricles and brain stem. These structures could then be quantitatively described using a combination of the medial axes and distance analysis.

Golland's works [13], [15] dealt primarily with the corpus callosum of the shape that typically features no extending appendages. Contrastingly, Pizer's medial axis analysis was focused on the brain ventricles, shapes of which (and thus their skeletons) often have one or more appendages. The skeletal appendages extend outward to include additional information about the more complex shapes. In Pizer's case, the medial axis analysis was modified to incorporate intersection points where multiple skeletons can be fused together, as e.g. in Fig. 4. The resulting more complex skeletons proved to be useful for solving various problems, including segmentation and image registration [14]. Both Pizer's and Goland's approaches can be easily extended from 2D to 3D objects, at the expense of growing their computational time due to the calculation of 3D distances.

Styner and Gerig [16] expanded Pizer's concepts and analyzed the brain ventricles in 3D ($256 \times 256 \times 128$) images using Voronoi skeletons and principal component analysis (PCA) to obtain discriminatory features of shape changes and locality. Spherical harmonics were used to analyze similarities between the skeletons and compare twin ventricles. Similar to Pizer's implementation, Styner and Gerig's skeletons contain many detailed branches and intersections that represent the shape of the object. To reduce the effect of the noise in the outer object's boundary of the shape, the shape was smoothed by using



(a) (b) (c)

Fig. 4. *Shown is a visual representation of Pizer's [14] medial axis approach. Due to the complexity of the shape, it is initialized with three skeletons (a). These are then individually examined (b) to create a composite skeleton of the parent figure (c).*

PCA to include only dominant characteristics of shapes. After this initial simplification, the Voronoi skeleton was constructed using standard medial axis computation. Then PCA was used once again to "prune" smaller and less important branches of the skeleton.The resulting model reflected the common branching topology of the initial object. Just as with the previous two models, Styner and Gerig's skeleton accurately represented the coarse features of the shape of the brain.

Gorczowski et al [17] used skeletons to analyze shapes and poses of five brain structures in order to classify autism. The mean classification accuracy on the basis of only poses, only shapes, or combined poses and shapes was 56%, 60%, and 64%, respectively, for an image database of 46 autistic and 24 control subjects. Although the combined features gave better results, the overall classification rate was rather low.

Elnakib et al [18] obtained notably better classification accuracy for autistic and control subjects by analyzing the corpus callosum centerline: the study correctly classified 94% autistic and 88% control subjects at the 85% confidence level, 94% autistic and 82% control subjects at the 90% confidence level, and 82% autistic and 76.5% control subjects at the 95% confidence level for the database of 17 autistic and 17 normal subjects.

Paniagua et al [19] used Spherical Harmonics (SPHARM) to calculate the mean latitude axis of ventricles in neonates. While this is not a full medial axis computation, it can be computed in a straightforward manner when using SPHARM. Importantly, Paniagua provides an important fusion of medial axis and SPHARM analysis to achieve a diagnostic classification in neonatal subjects. This is consistent with the modern trend of combining techniques to more accurately achieve results.

In total, the medial axis and skeletal analysis is important for examining basic locations and shapes of structural parts of the brain. Simple representations of and similarity measures for very complex shapes and accurate descriptions of the objects are its main advantages, which are very useful in applications such as object classification and matching of for medical diagnostics or understanding of object structure and construction. The limited use of the object's surface is the major drawback of the skeletal analysis that significantly decreases the usefulness of the medial axes and skeletons in applications dealing with the surface characteristics and/or small variations in shapes.

III. Geodesic Distances

Of primary interest in the analysis of the brain is the ability to make detailed comparisons of different brains. This often requires some form of non-rigid registration of the two surfaces of interest, or surface matching. A popular approach to this shape analysis problem is the use of geodesic distances. Geodesic distance can serve as an important geometric measurement of the brain and can help to provide a means of understanding complex shapes. Geodesic distances can serve to deliver a wealth of information about the surface geometry of a shape [7]. One of the first uses of geodesic distance, as applied to the brain, was by Lewis Griffin [20] in 1994. Griffin proposed the use of geodesic distance to characterize the cortical shape of the brain. This was later expanded on by Khaneja [21] who used geodesic distance to examine the curvature of sulci in the brain.

Geodesic distance is a combination of intrinsic and graph-based analysis. Geodesic distance is defined as the length of the graph of a geodesic between two vertices within an object [22]. It is the shortest path between two points that can be found in a curved space (such as the surface of a sphere) and has a wide array of practical uses. If you have ever boarded a plane to travel between continents, then there is a very high likelihood that you have traveled on a geodesic path, as these are the shortest distances between two points. In the sulci of the brain geodesic paths that connect two points in a single sulcus will often follow the curvature of the sulcus [23]. The detection of geodesic paths is also heavily utilized on the surfaces of meshes for common graphics operations such as mesh segmentation, watermarking, editing, and smoothing [7].

TABLE II
AUTOMATED (A) OR SEMI-AUTOMATED (SA) GEODESIC DISTANCE ANALYSIS: GROUND TRUTH (GT) FROM CLINICIAN (C) OR NON-CLINICIAN (N) EXPERTS; DIMENSIONALITY (DIM) AND SIZES (#) OF EXPERIMENTAL IMAGE DATABASES.

Publication	Year	Mode	Dim	#	GT
Wang et al [23]	2003	A	3D	n/a	N
Pastore et al [24]	2005	SA	2D	200	N
Huang et al [25]	2006	A	3D	36	C
Mio et al [26]	2007	A	3D	14	C
Butman et al [27]	2008	SA	3D	12	C
Hua et al [28]	2008	A	3D	20	N
Liang et al [29]	2008	A	3D	34	C
Joshi et al [30]	2012	A	3D	12	N

Table II exemplifies applications of geodesic distance to the human brain analysis. It includes methods starting with the early application by Wang et al [23] which analyzes individual sulci of the brain. No methods that are primarily based on geodesic distance analysis have been used solely for medical diagnostics or classification.

Geodesic distance can be defined in a number of ways, although the most common calculations are for the Gaussian curvature and the mean surface curvature of an object. These

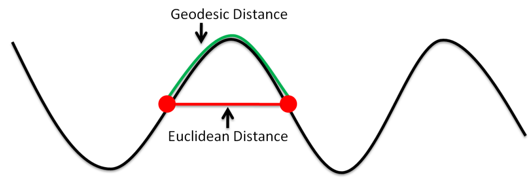
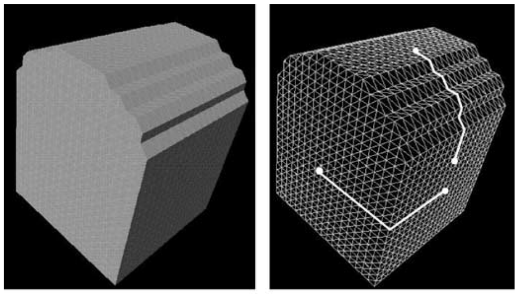


Fig. 5. *A visual representation of a simple geodesic distance. The two points on the curve (shown as red circles) are connected by Euclidean (red straight line) and geodesic (green curved line) distance lines. Note how the geodesic distance follows the arc of the curve.*

metrics allow features of the brain, such as the gyrus and sulcus, to be easily calculated by examining each point. Information about the convex and concave areas of the sulci can be determined by examining the sign of the Gaussian curvature, and if it is greater than or less than the mean surface curvature.

Once points of interest are determined, the geodesic distance can be computed using a number of different proposed methods [31], [32], [33]. One of the most popular methods is the Fast Marching Method proposed by Kimmel and Sethian [33]. This method has gained wide acceptance due to the speed of the calculations, and its easy applicability to a vast array of applications, which include two- and three-dimensional structures. An example of the result of the Fast Marching Method is illustrated on a synthetic surface in Fig. 6.



(a) (b)

Fig. 6. *Illustration showing the calculated geodesic distance between two points on a synthetic surface. (a) The original synthetic surface. (b) The synthetic surface overlayed with geodesic distances between four example points, calculated using the Fast Marching Method [33], [23]*

Wang et al [23] proposed the use of geodesic distance analysis to analyze the sulci and gyral fissures of the brain for matching brains. Locations were classified and compared between subjects. Areas where the sulci and gyri were similar could then be detected in the brain. Their results showed that surface correspondences could be found between brains, and that the fissures could be consistently identified across brains. Pastore et al [24] used geodesic distances to improve the segmentation accuracy (Fig. 7) of the sulci and gyri in the brain. He found that geodesic distances proved to be a precise, efficient and versatile method for segmenting the external boundary of the brain because the gyrifications of the brain have large curvatures, and this feature is carried over into the MRI images.

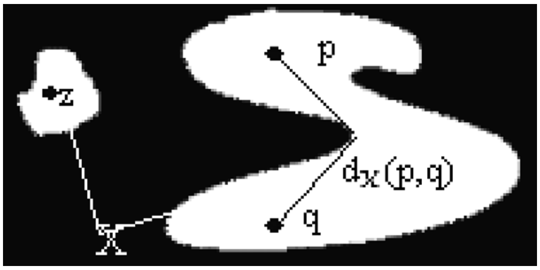


Fig. 7. *Example of a geodesic distance calculation between two points (p and q) on the boundary of a 2D MRI scan [24]. The area has been zoomed and binarized so that the curvature can be clearly seen.*

Huang et al [25] proposed a method for extraction of brain for comparison of contours using geodesic distances. Results they obtained showed that geodesic distances can aid in making extractions consistent across data sets, and the proposed method achieved a tight brain mask around the brain cortex. Mio et al [26] used geodesic distances to compare brains by comparing the decomposed geodesic curvature of each brain. Their work illustrated how geodesic distance can be successfully used to quantify morphological similarity and differences, and to identify particular regions where shape similarity and divergence are the most pronounced.

Butman et al [27] identified the brain ventricles and computed the volume of hydrocephalus in subjects using geodesic distance. Similar to the results of Huang, Butman showed that segmentation results are robust throughout data sets and able to classify hydrocephalus.

Hua et al [28] combined geodesic distances with vector image diffusion, a method of examining intrinsic geometric characteristics (e.g. mean curvatures) using a multi-scale diffusion and scale space, to match brains of different subjects. This method was shown to be superior to anisotropic diffusion and SIFT curvature matching algorithms in finding stable keypoints. Liang et al [29] approximated the curved cingulum bundle using Diffusion Tensor Imaging (DTI) tractography and geodesic distances. Although there were many limitations found, a significant reduction in fractional anisotropy values, within specific anatomical regions, were detected when using geodesic distances.

Joshi et al [30] analyzed the sulcal curvature in the cortex of the human brain using geodesic curvature. They concluded that geodesic curvature showed promising prospects for analyzing the sulcal curvature in case of small temporal lobe lesions. In literature and application, geodesic distances are most often used to examine the curvatures of locations of the brain and to locate key points that can be identified due to their curved nature. Geodesic distances have proven a useful shape analysis tool in segmentation, registration, and analysis and are also unique in that they incorporate aspects of first- and second-order analysis.

Geodesic distances have a large number of applications, but primary advantages are their applications in segmentation and the identification of locations in the shapes of brains. They are also an excellent metric for examining curvature and localized areas of objects, and can provide many discriminatory metrics for classification. Their major drawbacks are their generally localized nature, and the fact that it is difficult to examine large and complex objects that have numerous inflections in their curvature. Three-dimensional analysis of shapes such as the cortex and white matter of the brain would prove more challenging for a solely geodesic analysis.

IV. Procrustes Analysis

Procrustes analysis is a statistical form of congruent shape analysis that primarily focuses on the distributions of sets of shapes. As an interesting aside, Procrustes was a rogue and bandit who was the son of Poseidon in ancient Greek mythology [34]. He was known for either stretching people or cutting off their limbs to force them to fit within a statically sized iron bed. The process of Procrustes analysis thereby refers to shape analysis in which properties such as translation, rotation and scaling are removed so that the shape can be fit into a common reference frame. The process is inherently congruent. Procrustes analysis is most commonly performed by superimposing shapes on top of one another and then applying uniform properties such that geometric transformation of the objects are removed and the shapes can be compared. Procrustes analysis has also served an important role in shape warping, especially as applied to the brain [35].

TABLE III
Automated (A) or semi-automated (SA) Procrustes analysis: ground truth (GT) from clinician (C) or non-clinician (N) experts; dimensionality (Dim) and sizes (#) of experimental image databases.

Publication	Year	Mode	Dim	#	GT
Duta et al [36]	1999	A	2D	28	C
Penin et al [37]	2002	SA	3D	N/A	N
Bienvenu et al [38]	2011	A	3D	144	N

Table III exemplifies applications of procrustes analysis to brain analysis. It includes methods starting with the early application by Duta et al [36] which analyzes the properties of skull structure. Bienvenu et al [38] used Procrustes analysis primarily for medical diagnostics or classification.

Nicolae Duta et al [36] proposed a method for the basis of Procrustes analysis in 2D shape models in medical image analysis. Duta defines the main reasons for the use of Procrustes analysis as a convenient way to compute a prototype (average shape) from a set of simultaneously aligned shapes. Once the point correspondences are found, there exists an analytical or exact solution to the alignment problem.

Mathematically, Procrustes analysis seeks a solution to the following problem: Assume we are given a set of m shape instances where $S_k = (x_i^k, y_i^k)_{i=1\ldots n_k}^{k=1\ldots m}$ that is represented by a set of landmarks or boundary points. This set is partitioned into a set of clusters and for each shape cluster a mean shape, or prototype, must be computed. The set of prototypes can then be used for segmentation or the calculation of other metrics. One such metric is a Procrustes residual, which is defined as a deviation in landmarks on a specific object from the consensus of a group, or the prototypes. Duta illustrated the usage of Procrustes analysis for the segmentation of objects and registration of different objects following segmentation. He also introduced algorithms for global and local similarity measures using Procrustes analysis.

Penin et al [37] proposed a method for the study of the skull of humans and brains as compared to other primates through the use of tri-dimensional Procrustes analysis. In this study, twenty-nine key features were identified as common landmarks between the different skulls and the shapes were defined as Procrustes residuals. A Procrustes residual is a deviation in a landmark from the consensus of a group. One downside that Penin notes is that in Procrustes analysis the size and shape are calculated as independent vectors when using using traditional shape theory, meaning that normalization of objects is often required during pre-processing.

Bienvenu et al [38] proposed a similar method for examining endocranial variations. Bienvenu found that Procrustes analysis was more favorable in examining the skull, as it has less variability than the cortical surface itself, and is therefore less subjective to the noise introduced by the large differences in the cortex. Similar to Penin, Bienvenu selected specific landmarks commonly found on the enocranial surface and generated a prototype. This prototype was then used to examine the differences between males and females of different species. It was found that Procrustes analysis was capable of determining not only the gender, but the species as well due to the large variation in the landmarks of the prototypes.

In a follow up to his previous work, Duta examined the automated construction of shape models using Procrustes analysis [39]. This study determined that the major advantage of Procrustes analysis, as applied to the brain, is that Procrustes analysis is a reliable method of classifying and segmenting anatomical structures in relatively rigid objects including the ventricles and corpus callosum of the brain (Fig. 8). It struggles with more complex structures of the brain, specifically the gray and white matter. Procrustes analysis therefore provides an accurate and fast method of analysis in objects that do not have significant variation. This limits its applicability to only specific cases, however it is a useful measure for examining the shape of the brain and its more rigid structures.

One of the more direct problems related to Procrustes analysis is the method of selecting landmarks on the brain. Because of the variability in sulci and notable landmarks on the brain, this may have an impact on the resulting analysis. Furthermore, the selection of landmarks could introduce a bias into the analysis. If landmarks are not appropriately located, areas may either be over or under-compensated for, adding an additional degree of complication to this form of analysis, and it is likely that this is one of the driving reasons this methodology has only seen moderate modern adoption.

Procrustes analysis, while useful, does not provide as in-depth an analysis of complex objects as some other methods. Discussion of deformable models and spherical harmonics will illustrate examples of some of the more popular techniques for identifying mathematical differences between three-dimensional shapes that the human eye is unlikely to be able to classify.

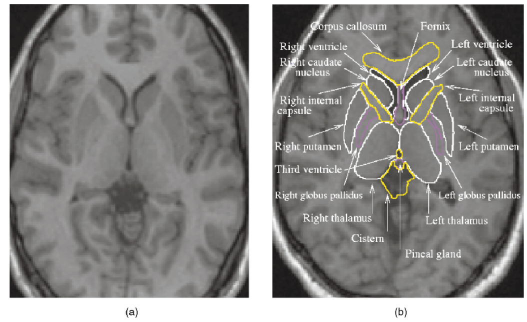


Fig. 8. *Magnetic resonance image (a) of the human brain. Neuroanatomic structures of the brain are highlights by a neuroanatomist (b). Structures shown in yellow are able to be accurately classified by Procrustes analysis. Image courtesy of Duta et al [39].*

V. Deformable Models

Deformable models, also known as active surfaces, are a model-based technique that combines geometry, physics and approximation theory in order to offer a unique and powerful approach to image analysis [40]. Deformable models have proven useful in a variety of applications for the brain including segmentation, shape representation, matching, and motion tracking. Unlike more rigid methods of analysis, deformable models are capable of accommodating for significant variability in shapes (Fig. 9), like the brain, over time and across different individuals. While deformable models were originally used in the field of computer vision, their application to the analysis of complex medical objects, such as the brain, was quickly realized by the scientific community. In their two-dimensional (2D) forms deformable models are often referred to as active contours or snakes [41], [42].

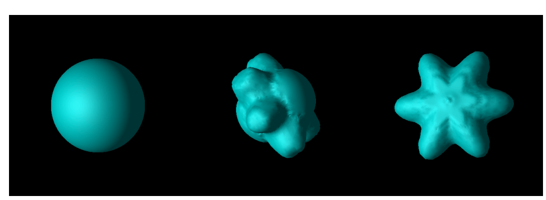


Fig. 9. *Illustration of a 3D deformable model as it contracts on a star-like object [42]. Three frames of progression are shown starting at the left with the original spherical model. The model gradually deforms around the object until it has converged on the star in the center.*

Deformable models have mathematical foundations in geometry, physics and shape approximation theory [40], [41], [42]. Geometry is used to represent an object's shape, and deformable models commonly make use of complex geometric representations, such as splines, that offer flexibility and many degrees of freedom. Physics is applied to impose constraints controlling how that shape can vary, with respect to properties such as space and time. The name "deformable models" is most closely associated with the incorporation of this elasticity theory at a physical level. Therefore, deformable models are most commonly constructed inside a Lagrangian dynamics setting that is able to respond naturally to constraints and applied forces. As a model deforms in the Lagrangian setting, the deformation energy will give rise to internal elastic forces. Potential energy functions for the external model are defined so that the model deforms to fit the data. Through the combination of these two energies, deformable models can be used for many situations. Some of the most common shape analysis applications of deformable models are in the areas of segmentation and volume analysis, along with shape matching and registration.

TABLE IV
AUTOMATED (A) OR SEMI-AUTOMATED (SA) DEFORMABLE MODEL ANALYSIS: GROUND TRUTH (GT) FROM CLINICIAN (C) OR NON-CLINICIAN (N) EXPERTS; DIMENSIONALITY (DIM) AND SIZES (#) OF EXPERIMENTAL IMAGE DATABASES.

Publication	Year	Mode	Dim	#	GT
Davatzikos et al [43]	1996	SA	3D	6	N
Dale et al [44]	1999	A	3D	100	C
Smith [45]	2002	A	3D	45	C
Zhuang et al [46]	2006	A	3D	49	C
Joshi et al [47]	2007	A	3D	6	N
Tu et al [48]	2007	A	3D	28	C
Huang et al [49]	2009	A	3D	36	C
Liu et al [50]	2009	A	3D	38	N
Li et al [51]	2011	A	3D	5	N
Hashioka et al [52]	2012	SA	3D	14	C

Table IV exemplifies applications of deformable model to human brain analysis. It includes methods starting with the early application by Davatzikos et al [43] which was used to identify the central sulci and interhemispheric fissures in the brain. No methods that are primarily based on deformable model analysis have been used primarily for medical diagnostics or classification.

Davatzikos et al [43] proposed one of the earliest methods for analyzing the cortical surface of the brain using deformable models. He used deformable models to identify similar landmarks on different brains for alignment. His results showed that deformable models could be used to to register two different brains with one another, and that they could pick out cortical and subcortical landmarks on the brain cortex.

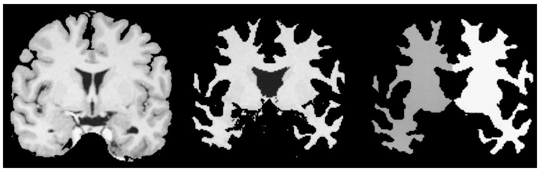


Fig. 10. *Here the results of a deformable model are shown. The goal of the work in this figure is to analyze the volume, and the deformable model proves useful in isolating the voxels that belong to the brain. After identifying the desired portion of the brain with a deformable model, calculating the volume becomes a trivial task [44].*

Dale et al [44] used a simplified deformable model to segment the cortex of the brain (Fig. 10). The algorithm proved to be a robust method of identifying the cortex of the brain with an average accuracy of 96% across a wide variety of subjects. In 2002, Stephen Smith [45] introduced the Brain Extraction Tool (BET). An intensity model is used to initialize the surface model, which is then refined to extract the brain. It was shown to be a fast and accurate method of extraction, having a mean percentage error of about 7% over 45 data sets. Zhuang et al [46] used a model-based level set to perform skull stripping on pediatric and youth brains. The approach showed good accuracy using the DICE metrics, and noteably showed an improvement over the BET proposed several years before by Smith [45].

Joshi et al [47] used deformable models to register sulci in along with a coregistration of brain volume data. Results showed a statistical improvement over the AIR [53], [54] and HAMMER [55], [56] methods. Tu et al [48] use deformable models to aid in segmenting specific locations found in the brain. The discriminative model he developed played a major role in obtaining good segmentations. Additionally, the segmentation could be further improved by adjusting the smoothness of the model, and constraining the shape with a global shape model.

Huang et al [49] proposed the use of deformable models to segment the cortex, gray matter and CSF of the human brain. He showed good results when the data was analyzed using the Dice metric. He concluded that deformable models led to improved segmentation accuracy and robustness when applied using a hybrid approach against, as opposed to using only geometric or statistical features. On real clinical MRI data sets, the hybrid approach demonstrated an improved accuracy over other state-of-the-art approaches.

Liu et al [50] suggested a deformable model driven by radial basis functions to extract the brain. This model proved to be an accurate and fast technique, having a similar accuracy to the BET proposed by Smith [45]. Li et al [51] proposed an alternative method for the automated extraction of the brain using a deformable model. His method was an extension of the human brain extraction tool and was found to more reliably extract brains through the inclusion of a deformable model. Hashioka et al [52] proposed a method that utilized Active Contour Modeling (ACM), also commonly referred to as snakes, for the extraction of the cortex in neonatal children. His results showed a Sensitivity of 98.5% with a false positive ratio of 13.8%. While his results were largely successful when an optimal head contour was present, he noted that a non-optimal contour performed less robustly.

While deformable models may not be in the forefront of diagnosis classifications, they have become an integral element of shape analysis. Their major advantage is in the area of shape segmentation, in which they excel at beyond all other techniques. Deformable models are also very adaptable at isolating complex regions of shapes for further analysis. Deformable models provide useful and accurate ways to identify and segment locations in the brain which is a critical step in analyzing the shape of the brain. The major drawback of using deformable model analysis is that it does not often provide many metrics for directly examining the brain for the purpose of classification or matching.

VI. Spherical Harmonics

Dealing with the orientation of the brain and aligning two brain objects with one another to compare differences in shape can prove challenging and time consuming. Spherical Harmonics, a popular method of shape analysis, can be used to remove these factors. Spherical harmonic analysis [57], [58] considers 3D surface data as a linear combination of specific basis functions. Additionally, spherical harmonics provide a rotation invariant common coordinate system in which shapes can be analyzed. The main goal of spherical harmonics is to decompose a 3D object into concentric, or unit, spheres. This process is what discards the orientation information that primarily accompanies a 3D shape representation of an object. The result is a shape descriptor that is both descriptive and invariant to orientation.

Consideration of the analysis of the entire brain for purposes of identifying differences in shape between different structures is one of the major advantages of spherical harmonics. The volume changes in the brain are intuitive features that can be used to describe illness, disorders and atrophy. One main area volume change fails to address is the structural changes of the surface of the brain. This is an area that spherical harmonics analysis seeks to address. The use of spherical harmonics (SPHARM) applied to brain analysis was first proposed by Gerig et al [57] for the analysis of the lateral ventricles of the brain. SPHARM was originally developed as a technique for model-based segmentation and data storage, however its applications have grown in recent years. One important factor of SPHARM analysis is that it relies on the surface of a shape and manifold properties. Due to this, only shapes without holes or disconnects in their surfaces can be accurately analyzed.

SPHARM is a global based shape analysis technique that is hierarchical in nature. Any shape can be parameterized by a set of basis functions, and these basis functions are the referred to as spherical harmonics. SPHARM is based on Laplace's equation and involves a mathematical solution to the angular components of the equation. They were first discovered by Simon de Laplace in 1782, although it would take several centuries before they were applied to the shape analysis of the brain.

Spherical harmonic basis functions Y_l^m, $-l \leq m \leq l$ of degree l and m are defined on $\theta \in [0;\pi] \times \phi \in [0;2\pi]$ by the following definitions [57]:

$$Y_l^m(\theta,\phi) = \sqrt{\frac{2l+1}{4\pi}\frac{(l-m)!}{(l+m)!}} P_l^m(\cos\theta)e^{im\theta}$$
$$Y_l^{-m}(\theta,\phi) = (-1)^m Y_l^{m*}(\theta,\phi) \quad (1)$$

where Y_l^{m*} denotes the complex conjugate of Y_l^m. P_l^m describes the associated Legendre polynomials given as

$$P_l^m(\omega) = \frac{(-1)^m}{2^l l!}(1-\omega^2)^{\frac{m}{2}} \frac{d^{m+l}}{d\omega^{m+l}}(\omega^2 - l)^l \quad (2)$$

The surface is then decomposed from the cartesian coordinate functions and is represented as $v(\theta,\phi) = (x(\theta,\phi), y(\theta,\phi), z(\theta,\phi))^T$. To express a surface using spherical harmonics the following equation is used:

$$v(\theta,\phi) = \sum_{l=0}^{\infty}\sum_{m=-l}^{l} c_l^m Y_l^m(\theta,\phi) \quad (3)$$

where the coefficients c_l^m are three-dimensional vectors that are typically obtained through solving a least-squares problem for the points. As previously mentioned, these basis functions allow for a hierarchical description of the surface of a shape. The more coefficients are used in the reconstruction, the more detail is present in the final constructed shape.

TABLE V
Automated (A) or semi-automated (SA) spherical harmonic analysis: ground truth (GT) from clinician (C) or non-clinician (N) experts; dimensionality (Dim) and sizes (#) of experimental image databases.

Publication	Year	Mode	Dim	#	GT
Keleman et al [59]	1999	A	3D	21	N
Gerig et al [57]	2001	A	3D	20	C
Chung et al [58]	2007	A	3D	28	C
Uthama et al [60]	2007	A	3D	40	C
Abdallah et al [61]	2008	A	3D	18	C
Chung et al [62]	2008	A	3D	28	C
Uthama et al [63]	2008	A	3D	20	C
Esmaeil-Zadeh et al [64]	2010	A	3D	95	N
Nitzken et al [65]	2011	A	3D	45	C
Nitzken et al [66]	2011	A	3D	30	C
Geng et al [67]	2011	A	3D	5	N
Kim et al [68]	2011	A	3D	n/a	C
Paniagua et al [19]	2013	A	3D	90	C
Hosseinbor et al [69]	2013	A	3D	69	C

Table IV exemplifies applications of Spherical Harmonics (SPHARM) to human brain analysis. It includes methods starting with the early application by Keleman [59], along with notable applications, e.g. Gerig et al [57], which have shown SPHARM as a potential method for classifying neurological disorders. SPHARM has been widely applied as a method for potential diagnosis.

Brechbhler et al [70] demonstrated the usage of SPHARM as a method for parameterizing closed surfaces of 3-dimensional objets. In 1999 Keleman [59] demonstrated the ability of SPHARM to analyze shape deformations in neuro-radiological data. Keleman used training data to compute SPHARM representations of the brain which were than simplified using PCA and applied to segment a cortex. His results showed that SPHARM was a promising technique for improving standard brain segmentations because of the included 3D forces SPHARM offered.

Gerig et al [57] proposed the one of the most significant applications of SPHARM. He used SPHARM to analyze the volume similarity between twin brains and demonstrated that SPHARM shape measures reveal new information in addition to size measurements. He proposed that this information might become relevant for an improved understanding of the structural differences not only in normal populations, but also in comparisons between healthy controls and patients. A sample

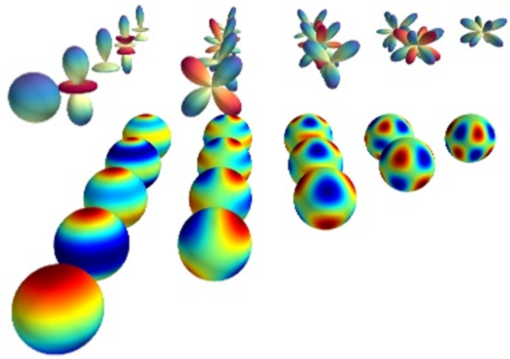


Fig. 11. *Decomposition of an object, as described by Gerig et al [57]. In the foreground the spherical harmonics are plotted overlayed on top of a unit sphere (the traditional method of display). In the rear of the image, the polar plot of the unit spheres are shown to give a more detailed understanding of the actual information contained within each sphere in the foreground.*

example of the deformation of an object is shown in Fig. 11. Styner and Gerig [71] later proposed a framework package based on SPHARM analysis entitled SPHARM-PDM that could be used for analysis of a multitude of brain structures. This SPHARM-PDM package has been used for examining various brain structures, including work by Kim et al [68] on the hippocampus, and by Paniagua et al [19] (previously mentioned) on the lateral ventricles in neonates.

Chung et al [58] proposed a method to analyze the computed SPHARM coefficients to identify autism in subjects. While the SPHARM coefficients did not generate reliable results, his work showed the ability accurately and efficiently encode neurological information using a weighted-SPHARM. Chung et al [62] continued his application and applied his weighted-SPHARM to find statistically significant differences between autistic and control subjects using the coefficients. While his work showed some areas of statistical difference, the locations were largely random. His work did however show that weighted-SPHARM provides better smoothing in cortical applications than other methods.

Uthama et al [60] proposed the analysis of the ventricle geometry using SPHARM between Parkinson's Disease (PD) and control patients. He showed that a statistically significant comparison ($p < 0.05$) of controls and PD subjects could be made using SPHARM and that it was able to detect subtle changes in synthetic and clinical brain ventricle data. Uthama et al [63] also proposed the use of SPHARM to perform fMRI spatial analysis. He was able to demonstrate differences in the way PD patients and healthy controls respond to an increased task demand. The SPHARM analysis illustrated that the inability to respond to task demand was reflected in the failure of PD subjects to increase basal ganglia output, and a reliance on cerebellar and cortical activity to enable successful performance.

Abdallah et al [61] applied a parameterization to meshes before SPHARM application to improve shape detection in ventricles. Results showed that a parameterization of a shape followed by SPHARM analysis can lead to improve comparisons and better shape descriptors.

Esmaeil-Zadeh et al [64] use SPHARM to analyze the hippocampus to classify subjects as either normal or epileptic. His results showed that in an optimum case, a 90.32% rate of classification of left and right anterior temporal lobes could be achieved when validated using the leave-one-out method.

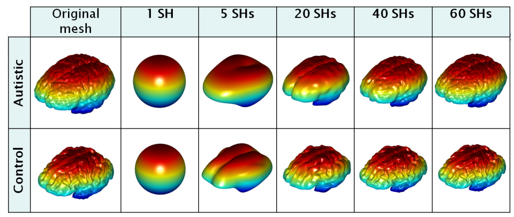


Fig. 12. *Method proposed by Nitzken [65] for the approximation of the 3D brain cortex shape for autistic (A) and normal subjects (C).*

Nitzken et al [65] proposed an alternative use SPHARM by using the SPHARM reconstruction error to classify autism (Fig. 12). Classification accuracies on a test population of 100% could be achieved and illustrates a potentially effective way of classifying autism in subjects. Nitzken et al [66] later expanded this theory to the classification of dyslexia where similar results were achieved.

Geng et al [67] demonstrated the use of SPHARM coefficients to perform nonrigid registration of brain white matter and fiber tracts. This method performed better than standard second order registration methods, although this could also be attributed to the use of higher orders when applying SPHARM. Overall, it was believe that SPHARM provided a notable improvement. In 2013, Hosseinbor et al [69] proposed a further expansion of SPHARM to a 4-dimensional representation of subcortical structures. This new 4D SPHARM is entitled HyperSPHARM and is intended to serve as a method of tracking changes over time using SPHARM. This allows SPHARM to directly compete with applications typically reserved to methods such as Voxel- and Deformation-Based Morphometry.

SPHARM is one of the most beneficial methods of shape analysis for providing meaningful global analyses of objects. SPHARM excels in brain analysis areas that involve large surfaces, such as the cortex and white matter. The major drawbacks to SPHARM analysis are that it can be difficult to localize the analysis to understand select locations. It also struggles with applications such as segmentation and automated identification of objects in two-dimensional images. It's greatest strength comes in it's ability to distinguish between shapes and it's applications such as clinical diagnosis classification.

VII. Voxel- and Deformation-Based Morphometry

Voxel based morphometry (VBM) is another technique for examining the entire brain [80]. VBM is a technique wherein brains between subjects are generally warped, aligned, and normalized to remove large differences between the brains, and a volume is then compared across each brain on a voxel by voxel basis. In VBM smoothed values of the voxels, typically

TABLE VI
AUTOMATED (A) OR SEMI-AUTOMATED (SA) VOXEL- AND DEFORMATION-BASED MORPHOMETRY ANALYSIS: GROUND TRUTH (GT) FROM CLINICIAN (C) OR NON-CLINICIAN (N) EXPERTS; DIMENSIONALITY (DIM) AND SIZES (#) OF EXPERIMENTAL IMAGE DATABASES.

Publication	Year	Mode	Dim	#	GT
Chung et al [72]	2002	A	3D	28	C
Leow et al [73]	2006	A	3D	17	C
Lepore et al [74]	2007	A	3D	30	C
Afzali et al [75]	2010	A	3D	31	C
Wang et al [76]	2012	A	3D	2	C
Yang et al [77]	2012	A	3D	60	C
Fletcher et al [78]	2013	A	3D	285	C
Shi et al [79]	2013	A	3D	35	C

an averaging of a voxel and its neighbors, are used. The major usage for VBM is the detection of differences and similarities for images between two populations or shapes [75]. Deformation-based morphometry (DBM) is a similar form of statistical analysis to VBM, however, instead of measuring the changes between voxels, the changes on the deformation fields are used. The most common variant of DBM in brain shape analysis is Tensor-based morphometry (TBM), which is based on the Jacobian determinants. While DBM, and more specifically TBM, are able to detect more subtle changes between brains, they introduce a significantly higher degree of computational complexity when compared to VBM, as the warping often involves highly non-linear algorithms. Both VBM and TBM are commonly used in measuring cortical thickness measurements as well.

In 2001, Ashburner et al [81] made a case for VBM in response to criticism posed in Dr. Bookstein's article "Voxel-Based Morphometry Should Not Be Used with Imperfectly Registered Images" [80]. He explains that VBM was a method originally intended to explore cortical thickness and benefits from not being affected by volume changes, the major weakness of volumetric analysis. While acknowledging the partial volume effect as a potential issue, Ashburner also details how modern normalization techniques allow for high-resolution image alignments and warping. He also discusses a major benefit in that VBM is not subject to landmark selection that many other methods, such as Procrustes analysis, suffer from. In summary, VBM is a useful and reliable method for examining the volume of the brain and its sub-components, while avoiding the traditional pitfalls associated with volumetric measurements.

Afzali et al [75] explored the differences between using VBM and the tractography of diffusion tensor MRIs for patients with epilepsy. Compared to the tractography methods, VBM showed a consistently accurate performance in analyzing the volume of the hippocampus and frontal lobe of the brain. Afzali does discuss the downside of partial volume effects and an increased statistical analysis complexity for VBM, however, he notes that with modern computing power the second fact becomes increasingly less significant, and modern techniques have greatly reduced partial volume effects.

Chung et al [72] introduced a Tensor-based model for analyzing the brain surface in 2002. Chung applied a diffusion smoothing operator, based on a Laplace-Beltrami operator, to the tensors of the cortex and brain stem to determine local differences. His approach demonstrated that TBM could detect localized regions of differences on the shapes of two clinical groups. Wang et al [76] applied a multivariate TBM to the lateral vents and the hippocampus. Wang demonstrated a straightforward framework for performing TBM operations on sub-components of the brain to be used by other researchers.

Lepore at al [74] applied a generalized TBM method to HIV/AIDs patients to examine differences between the corpus callosum and brain surfaces of individuals. Lepore also explored the use of multivariate tensors and discussed how increasing the number of parameters for these tensors could improve the multivariate statistics. Lepore also comments how TBM is useful in both registration and statistical analysis, illustrating the multiple use cases for many brain analysis applications.

Leow et al [73] proposed using TBM to identify changes in the brains of aging subjects. Leow's results showed that in Alzheimer's patients, there were reliable brain shape changes in the tensors over time relative to baseline controls. Leow also illustrated several methods for correcting distortion in TBM techniques. Fletcher et al [78] combined TBM and boundary-based methods to track longitudinal brain changes in subjects. He compares his method to those that do not involve boundary detection, and demonstrates how the inclusion of boundary parameters helps to correct for noise at the tissue boundaries. His method also helps to remove bias-correction, which may occur from warping algorithms, and adds only a minimal performance degradation. Fletcher, like Leow, also explored the proposition of using TBM to detect Alzheimer's in patients. Yang et al [77] used VBM for the application of Alzheimer's as well. Yang studied the changes of VBM measurements in patients over a 3 year period. The study showed that atrophy clusters in the brain could be detected in patient's who had been diagnosed with Alzheimer's.

Shi et al [79] used TBM to examine the effects of prematurity in the brains of newborns. Different from other methods, Shi registered the surface fluid of the brain, instead of the cortex, and applied a TBM approach to this surface fluid. The statistical analysis showed common clusters of significant difference between the brains of the subjects. Shi also showed that the TBM approach was sensitive enough to measure the largely smooth surface of the surface fluid and discern small, but meaningful differences.

VIII. ADDITIONAL METHODS OF SHAPE ANALYSIS

Table VII details additional applications of shape analysis. It includes additional methods such as graph-matching, symmetry-based analysis, Laplace-Beltrami analysis, and volumetric analysis. Many different methods have been applied as a potential methods of diagnosis or classification.

A. Distance Mapping

Distance mapping is a technique that has similarities to geodesic distance and medial axis analysis, but differs in

TABLE VII
AUTOMATED (A) OR SEMI-AUTOMATED (SA) ADDITIONAL METHODS OF SHAPE ANALYSIS: GROUND TRUTH (GT) FROM CLINICIAN (C) OR NON-CLINICIAN (N) EXPERTS; DIMENSIONALITY (DIM) AND SIZES (#) OF EXPERIMENTAL IMAGE DATABASES.

Method	Publication	Year	Mode	Dim	#	GT
Distance Mapping	He et al [82]	2007	SA	2D	10	N
Entropy-based Particle Systems	Cates et al [83]	2009	A	3D	56	C
Graph Matching	Geraud et al [84]	1995	SA	2D	n/a	N
Graph Matching	Yang et al [85]	2007	A	3D	120	N
Graph Matching	Long et al [86]	2012	SA	2D	60	C
Homologous Model	Yamaguchi et al [87]	2009	A	3D	4	N
Homologous Model	Yamaguchi et al [88]	2010	A	3D	11	N
Laplace-Beltrami	Angenent et al [89]	1999	A	3D	1	C
Laplace-Beltrami	Lai et al [90]	2011	A	2D	32	N
Laplace-Beltrami	Shishegar et al [91]	2011	A	3D	78	C
Laplace-Beltrami	Germanaud et al [92]	2012	A	3D	151	N
Reeb Analysis	Makram et al [93]	2008	A	3D	12	C
Reeb Analysis	Shi et al [94]	2011	A	3D	200	C
Spectral Matching	Lombaert et al [95]	2011	A	3D	36	N
Spectral Matching	Lombaert et al [96]	2013	A	3D	12	N
Symmetry-based	Prima et al [97]	2002	A	3D	250	C
Symmetry-based	Gefen et al [98]	2004	A	2D	232	N
Symmetry-based	Liu et al [99]	2007	A	2D	3	N
Symmetry-based	Feng et al [100]	2008	A	2D	1	N
Symmetry-based	Fournier et al [101]	2011	A	3D	37	N
Volume Analysis	Herman et al [102]	1988	A	3D	n/a	N
Volume Analysis	Wagenknecht et al [103]	2008	A	3D	n/a	N

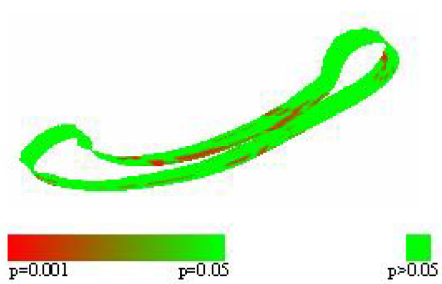


Fig. 13. *Method proposed by He et al [82] using distance mapping to examine areas of significant difference along the outer edge of the corpus callosum.*

that more generalized distance metrics and locations are often measured. He et al [82] proposed a method of brain analysis using distance mapping (Fig. 13). He examined the statistical differences in distances at the border of a segmented corpus callosum in autistic patients. He hypothesized that a statistical mean difference between segmented images could be discovered, however he ultimately concluded that no meaningful statistical difference in shape between subjects could be found using the proposed method.

B. Entropy-based Particle Systems

Cates et al [83] introduced a novel approach to brain shape analysis using an entropy-based system. Points are modeled on the surface of the brain as particles. These particles are then optimized and the negative energy is measured to create a distribution of each unique shape. The technique is applicable in both two and three dimesnions. The computational efficiency of the approach is based on the number of particles used. Cates applied the approach to examination of the hippocampus. The advantages to the technique showed results consistent with many other techniques, while require a minimum amount of parameter tuning and an easy adaption to the brain curvature.

C. Graph Matching

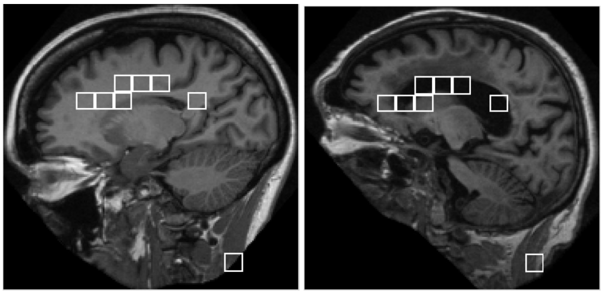


Fig. 14. *Method proposed by Long et al [86]. Showing areas that have been discriminated using a graph matching technique in two subjects.*

Graph matching techniques involve converting more complex information into a more simplified graph-based representation. Similarities in the graphs are then used to identify, segment and analyze the more complex information. Geraud et al [84] proposed a method of graph matching analysis. They utilized a Markovian relaxation on a watershed based adjacency graph to improve segmentation of neighboring structures in the brain. The results showed a good initial approach to the application of graph matching in the area of segmentation and identification.

Yang et al [85] proposed the fact that two graph matching techniques that can be used to constrain a search neighborhood and the genetic algorithms can be used to optimize sulci labeling. They were able to achieve satisfactory identification rates for finding sulci using the proposed graph matching strategy.

Long et al [86] suggested that the brain shape could be decomposed to a graph by subdividing the images into a tree structure containing various properties of the specific brain (Fig. 14). By manually selecting important locations for placing the subdivision structures, the brain could be successfully classified for cognitive impairment due to Alzheimer's disease.

D. Homologous Modeling

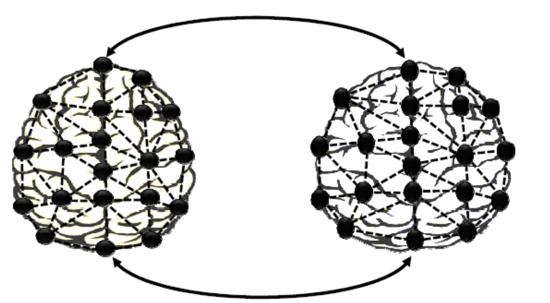


Fig. 15. *Method proposed by Yamaguchi et al [87] illustrating the concept of homologous modeling on two brains.*

Homologous modeling is a mesh based technique in which items having the same number of analysis points in the same locations on two different models can be examined. The technique has been applied to many different applications, but due to implementation complexity is rarely applied to the the whole brain. However, it may also be appropriate for the analysis of other discrete brain structures (e.g. corpus callosum, amygdala, or hippocampus).

Yamaguchi et al [87] demonstrated a method based on a homologous model to calculate a sulcal-distribution index for brains and identify brain fissures (Fig. 15). A mean displacement of $1.3 \pm 0.7mm$ was found. His results suggested that a homologous model could be used to correspond the sulci and gyri among the evaluating brains effectively. Yamaguchi et al [88] proposed a later method to statistically quantify the brain shape using a homologous model. The work examined changes in the frontal and occipital lobes between male and female subjects. A significant difference $(p < 0.05)$ was detected in the sample population and the model was able to successfully detect the locations in the brain that differ significantly.

E. Laplace-Beltrami

Laplace-Beltrami methods comprise any methods that rely heavily on the Laplace-Beltrami operator. The Laplace-Beltrami operator of a smooth function f on a Riemannian manifold M and is defined as $\triangle f = div(gradf)$, where div and $grad$ are the divergence and gradient operators of the manifold M [91]. It is most commonly used in smoothing applications or curvature analysis.

Angenent et al [89] was the first researcher to propose brain analysis using a Laplace-Beltrami model. Angenent hypothesized that a brain could be flattened by using a Laplace-Beltrami operator on the brain surface. The technique was shown to be an efficient method of flattening the brain.

Lai et al [90] used Laplace-Beltrami nodal curves and geodesic curve evolutions to segment to the corpus callosum. In small data tests the method appeared to show positive results and be robust.

Shishegar et al [91] analyzed the first 20 eignevalues of the Laplace-Beltrami spectrum to classify epilepsy. In the best testing results Shishegar acheived a 91.9% true positive rate and a 33.3% false positive rate using out of normal range classifiers and cross-validation, illustrating that while there were issues it was a promising method.

Germanaud et al [92] computed the eigenfunctions of the Laplace-Beltrami operator to decompose meshes for left and right handed subjects. Germanaud was able to detect shallow folds and rare deep folds in the brain which lead to the quantification and classification of brains using the Spangy method.

F. Reeb Graph

A Reeb graph describes the connectivity of the level sets of an object [104]. Visually, a constructed Reeb graph looks similar to a medial axis skeleton. Makram et al [93] suggested a method of using Reeb graph analysis to drive an elastic registration model for the detection of maxilla malformations. The results of detection were deemed satisfactory to a clinician, but not actual values were not reported. The method illustrated the potential for Reeb graph analysis as a registration framework.

Shi et al [94] used reeb graph analysis to isolate, extract, and reconstruct enhanced brain surfaces. The system was able to process cortical surfaces with the accuracy of freesurfer, but at a lower computational cost.

G. Spectral Matching

Lombaert et al [95] proposed a method of spectral correspondence for examining the shape of the brain. He used an eigendecomposition to match brain surfaces between subjects. Initially the spectra are computed for each brain. These spectra are then sorted and aligned. The result allows point locations between two brains to be quickly matched. The method is primarily applicable to brain registration. Lombaert et al [96] proposed an extension of this work for corresponding features on the surface of the brain, entitled FOCUSR. Instead of a generalized matching, surface features of each brain are used to align them. The primary advantage of FOCUSR over competing techniques is the speed required to match the brains to one another. The spectral matching technique required a mere 208 seconds to achieve the same accuracy as FreeSurfer, a commercial brain analysis tool, which required several hours.

H. Symmetry Analysis

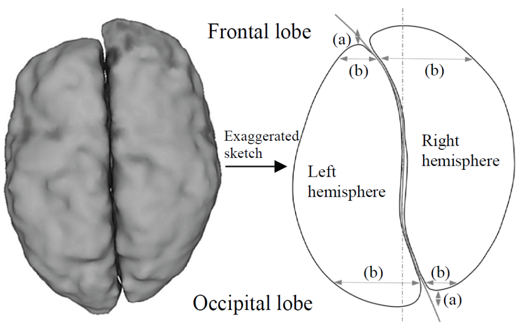


Fig. 16. *As shown by Fournier et al [101], the human brain has a slight asymmetry based on if subjects are right or left-handed.*

Symmetry based techniques exploit the fact that the human brain is largely symmetric along the sagittal plane, and use this information to make observations. Prima et al [97] proposed an early method of symmetry-based brain analysis. Prima analyzed the brain symmetry to automatically compute the mid-saggital plane and obtained sub-voxel accuracy in computing, reorienting and recentering 3D images in a time efficient manner.

Gefen et al [98] aligned individual brain images along their symmetry lines to create more accurate 3D models. Gefen concluded that some regions yielded better restoration in the 3D models than other regions, but overall the alignment results were accurate and consistent.

Liu et al [99] examined the topic of multi-modality brain registration by aligning the symmetry planes of objects using affine transformations. Liu surmised that the test objects were successfully matched and the symmetry planes were accurately computed.

Feng et al [100] used the symmetry properties of the brain to improve brain segmentation algorithms. Feng's algorithm, while effective at determining bilateral symmetry, was limited by only being applicable to 2D images.

Fournier et al [101] examined the asymmetries in brains of humans and chimpanzees and compared left and right handed individuals to search for a difference (Fig. 16). Fournier was able to recover typical global asymmetry patterns and hypothesized that in the future symmetry-based analysis could provide an automated way of comparing individuals.

I. Volumetric Analysis

Volumetric techniques measure the volume of an object. Herman et al [102] proposed a method based on volumetric analysis to use gradient-based boundary tracking to examine the volume between control and Alzheimer's patients. Herman concluded that the gradient-based methods are superior to standard thresholding methods, but did not provide a detailed summary of the diagnostic results.

Wagenknecht et al [103] use another form of volumetric analysis. Wagenknecht used a 3D Live-wire approach to extract volumes of interest from a brain for comparison or identification. An average miscalculation rate less than 0.0039 was reported and the proposed method showed to be accurate and robust for extracting volumes of interest and calculating various properties for them.

IX. Discussion

A. Research Challenges

The brain has long been a topic of research, but utilizing shape analysis with the help of computers enables researchers to examine the shape and texture of the brain. There are several major challenges that shape analysis methods related to the brain or other complex medical structures face going forward. The brain is a complex and very diverse organ. Unlike more rigid and well defined objects that may be simply represented by geometric shapes, the brain suffers from large irregular variabilities. The lack of overall consistency in the brain requires techniques that analyze it to be flexible, and be able to readily adapt to changes in contrast, shape, varying degrees of noise, and abnormality. This illustrates why techniques that rely on pre-determined templates or shape models may suffer from difficulty in brain applications. This problem of consistency and complexity is the driving issue that leads to many of the subsequent challenges. These additional challenges can be summarized as follows:

- Due to the size and complexity of the brain and other medical objects, mesh based approaches often require a significantly large number of nodes or points of reference to perform an accurate surface or shape analysis. Even with modern computing, the large complexity of the brain still poses a computational efficiency challenge.
- Medial axis and other skeleton-based analysis may require a large amount of branches and complex paths to accurately represent all of the distinct locations in the human brain.
- The known shape analysis and diagnosis techniques for the brain largely rely on the accuracy of brain segmentation and the ability to properly determine structures in the brain. Even with the combination and fusion of modern techniques (e.g. active contours, deformable models, SPHARM, geodesic distances), identification and segmentation accuracies still suffer significant errors when applied to large sets of data.
- Computer Aided Diagnostic, or CAD, systems have faced great difficulty in accurately classifying neurological diseases based on shape metrics over the past decades. This is largely due to the lack on inconsistency found across different subjects, but is also due to the difficulty in properly registering and aligning brains so that like areas can be examined.

B. Comparisons and Trends

While there is a high degree of merit in all applications of shape analysis to the brain, some techniques are more suited to specific applications then others. There are four generalized applications of shape analysis techniques to the brain: examination of individual sulci and their curvatures on the brain, examination of the entire human brain and white matter as a whole, registration of brain shapes amongst subjects, and examination of the sub-components of the brain (e.g. corpus callosum, ventricles, hippocampus). Due to the wide variety of shapes and curvatures in the human brain, many techniques can be used in an array of different brain applications. However, it should be highlighted that most of the techniques are more commonly used in one or two areas.

Geodesic distances, medial axis, skeletal analysis, and Laplace-Beltrami methods are the most common methods used for examination of the individual sulci and brain curvature, with geodesic distances between the most prevalent in modern applications. SPHARM, voxel- and tensor-based morphometry, volume analysis, symmetry-based modeling and deformable models are most common for analysis of the brain and white matter, however, SPHARM is generally reserved for mesh-based applications, and deformable models are often preferred for registration and segmentation applications. While having some uses in whole brain shape analysis, Procrustes analysis, homologous modeling, graph matching, and symmetry-based modeling are most commonly used for brain registration and segmentation applications. Voxel- and Tensor-based morphometry, medial axis, skeletal analysis, SPHARM, and distance mapping are the most preferable methods for examination of sub-components of the brain, and while typically not always used exclusively, geodesic distances are often combined with these methods. Voxel- and Tensor-based morphometry and SPHARM also have significant applications in brain shape registration. It should be specifically noted that deformable models have a high degree of applicability to all of the mentioned analysis methods, and are often combined with or frequently used in many forms of brain shape analysis.

To address the aforementioned challenges, recent trends in shape analysis of the brain involve the following aspects:

- Many of the methods discussed were initially applicable to 2-dimensional analysis, but in recent years nearly all methods have evolved for use in 3-dimensional applications.
- Deformable model methods [49], [50], [51] have seen an increase in usage and have additionally taken the place of many segmentation methods in the past five years, leading to an improved accuracy in brain segmentation. These advances will undoubtedly help to push forward new and improved shape analysis techniques.
- More complex techniques such as SPHARM, started by Gerig et al [57], have been further developed by others [61], [64], [62], [65], [66] in recent years have shown great promise in advancing the field for analysis of the cortex and white matter, along with analysis of sub-components of the brain. These methods have illustrated the potential for utilizing methods that are parameter invariant to solve many of the difficult alignment and registration errors that are often associated with the brain.
- Automation has become increasingly important in modern methods, and the rate of semi-automated and manual methods has drastically decreased. Modern methods are generally expected to perform in an automated manner, and the reduction in human interaction has resulted in an increase in the accuracy of newer techniques.
- Methods such as medial axis analysis [18] and geodesic distances [30] are now more frequently combined with other techniques leading to more accurate segmentation, registration and classification of the human brain and its various subcomponents, such as the ventricles and corpus callosum.

X. Conclusion

This survey details the numerous methods for solving the complex problem of brain shape analysis. Early techniques, which suffered from lower accuracies, slow computation times, and significant user input, have given rise to complicated modern techniques that offer high degrees of automation and improved accuracy. Methods such as SPHARM, deformation-based morphometry, and deformable models will likely become the dominant modes of brain shape analysis going forward. Geodesic distances, medial axis, and Laplace-Beltrami operations, among others, will become methods used to support and enhance these dominant modes of brain shape analysis. An amalgamation of techniques opens new opportunities for researchers and engineers to develop more advanced analysis methods. Exciting new opportunities, such as HyperSPHARM and 4-dimensional analysis techniques, give us a look into the future of where modern techniques and amalgamations may be headed. In conclusion, the future of the field of shape analysis for the brain is evolving rapidly, and new techniques will develop and emerge as technology continues to progress.

References

[1] V. Barras, A. S. III *et al.*, “Synthetic Event-Related Potentials: A Computational Bridge Between Neurolinguistic Models And Experiments,” *Neural Networks*, vol. 37, no. 0, pp. 66–92, 2013.

[2] R. Lande, “Quantitative Genetic Analysis of Multivariate Evolution, Applied to Brain: Body Size Allometry,” *Evolution*, vol. 33, no. 1, pp. 402–416, 1979.

[3] R. Desimone, S. Schein *et al.*, “Contour, Color And Shape Analysis Beyond The Striate Cortex,” *Vision Research*, vol. 25, no. 3, pp. 441–452, 1985.

[4] J. Martin, A. Pentland *et al.*, “Shape Analysis Of Brain Structures Using Physical And Experimental Modes,” in *Computer Vision and Pattern Recognition, 1994. Proceedings CVPR ’94., 1994 IEEE Computer Society Conference on*, Jun. 1994, pp. 752–755.

[5] M. Delfour and J.-P. Zolsio, *Shapes and Geometries: Metrics, Analysis, Differential Calculus, and Optimization, Second Edition (Advances in Design and Control)*, 2nd ed. SIAM-Sociecty for Industrial and Applied Mathematics, Dec. 2010.

[6] Poincaré, *Analysis Situs*, 1st ed., ser. Journal de l’Ecole polytechnique IIe sér. Gauthier-Villars, 1895.

[7] L. de Floriani and M. Spagnuolo, *Shape Analysis and Structuring (Mathematics and Visualization)*, 1st ed. Springer, Nov. 2010.

[8] D. Guliato and R. Rangayyan, *Modeling and Analysis of Shape: with Applications in Computer-Aided Diagnosis of Breast Cancer (Synthesis Lectures on Biomedical Engineering)*, 1st ed. Morgan and Claypool Publishers, Jan. 2011.

[9] D. Attali, J. daniel Boissonnat *et al.*, "Stability And Computation Of Medial Axes A State-Of-The-Art Report," in *Mathematical Foundations of Scientific Visualization, Computer Graphics, and Massive Data Exploration*. Springer.

[10] H. Blum, "A Transformation For Extracting New Descriptors Of Shape," *Models For The Perception Of Speech And Visual Form*, vol. 19, no. 5, pp. 362–380, 1967.

[11] ——, "Biological Shape And Visual Science (Part I)," *Journal of Theoretical Biology*, vol. 38, no. 2, pp. 205–287, 1973.

[12] M. Naf, O. Kubler *et al.*, "Characterization And Recognition Of 3D Organ Shape In Medical Image Analysis Using Skeletonization," in *Mathematical Methods in Biomedical Image Analysis, 1996., Proceedings of the Workshop on*, Jun. 1996, pp. 139–150.

[13] P. Golland, W. Grimson *et al.*, "Statistical Shape Analysis Using Fixed Topology Skeletons: Corpus Callosum Study," in *Information Processing in Medical Imaging*. Springer, 1999, pp. 382–387.

[14] S. M. Pizer, D. S. Fritsch *et al.*, "Segmentation, Registration, And Measurement Of Shape Variation Via Image Object Shape," *IEEE Transactions on Medical Imaging*, vol. 18, no. 10, pp. 851–865, Oct. 1999.

[15] P. Golland, "Statistical Shape Analysis of Anatomical Structures," Ph.D. dissertation, Department of Electrical Engineering and Computer Science, Massachusetts Institute Of Technology, Aug. 2001.

[16] M. Styner and G. Gerig, "Three-Dimensional Medial Shape Representation Incorporating Object Variability," in *Computer Vision and Pattern Recognition, 2001. CVPR 2001. Proceedings of the 2001 IEEE Computer Society Conference on*, vol. 2, 2001, pp. II–651 – II–656 vol.2.

[17] K. Gorczowski, M. Styner *et al.*, "Statistical Shape Analysis of Multi-Object Complexes," in *Computer Vision and Pattern Recognition, 2007. CVPR '07. IEEE Conference on*, Jun. 2007, pp. 1–8.

[18] A. Elnakib, M. F. CasaNova *et al.*, "Autism Diagnostics By Centerline-Based Shape Analysis Of The Corpus Callosum," in *Biomedical Imaging: From Nano to Macro, 2011 IEEE International Symposium on*, Apr. 2011, pp. 1843–1846.

[19] B. Paniagua, A. Lyall *et al.*, "Lateral Ventricle Morphology Analysis via Mean Latitude Axis," *Proc Soc Photo Opt Instrum Eng*, vol. 8672, Mar. 2013.

[20] L. D. Griffin, "The Intrinsic Geometry of the Cerebral Cortex," *Journal of Theoretical Biology*, vol. 166, no. 3, pp. 261–273, 1994.

[21] N. Khaneja, M. I. Miller *et al.*, "Dynamic Programming Generation Of Curves On Brain Surfaces," *IEEE Transactions on Pattern Analysis and Machine Intelligence*, vol. 20, no. 11, pp. 1260–1265, Nov. 1998.

[22] M. Berger and B. Gostiaux, *Differential Geometry: Manifolds and Curves and And Surfaces*, ser. Graduate texts in mathematics. Springer-Verlag, 1988.

[23] Y. Wang, B. S. Peterson *et al.*, "3D Brain Surface Matching Based On Geodesics And Local Geometry," *Computer Vision and Image Understanding*, vol. 89, no. 23, pp. 252 – 271, 2003.

[24] J. Pastore, E. Moler *et al.*, "Segmentation Of Brain Magnetic Resonance Images Through Morphological Operators And Geodesic Distance," *Digital Signal Processing*, vol. 15, no. 2, pp. 153–160, 2005.

[25] A. Huang, R. Abugharbieh *et al.*, "MRI Brain Extraction with Combined Expectation Maximization and Geodesic Active Contours," in *Signal Processing and Information Technology, 2006 IEEE International Symposium on*, Aug. 2006, pp. 107–111.

[26] W. Mio, J. C. Bowers *et al.*, "Modeling Brain Anatomy with 3D Arrangements of Curves," in *Computer Vision, 2007. ICCV 2007. IEEE 11th International Conference on*, Oct. 2007, pp. 1–8.

[27] J. A. Butman and M. G. Linguraru, "Assessment Of Ventricle Volume From Serial Mri Scans In Communicating Hydrocephalus," in *Biomedical Imaging: From Nano to Macro, 2008. ISBI 2008. 5th IEEE International Symposium on*, May 2008, pp. 49–52.

[28] J. Hua, Z. Lai *et al.*, "Geodesic Distance-weighted Shape Vector Image Diffusion," *IEEE Transactions on Visualization and Computer Graphics*, vol. 14, no. 6, pp. 1643–1650, Nov. 2008.

[29] X. Liang and J. Zhang, "White Matter Integrity Analysis along Cingulum Paths in Mild Cognitive Impairment - A Geodesic Distance Approach," in *Bioinformatics and Biomedical Engineering, 2008. ICBBE 2008. The 2nd International Conference on*, May 2008, pp. 510–513.

[30] A. A. Joshi, D. W. Shattuck *et al.*, "Geodesic Curvature Flow On Surfaces For Automatic Sulcal Delineation," in *Biomedical Imaging (ISBI), 2012 9th IEEE International Symposium on*, May 2012, pp. 430–433.

[31] R. Kimmel and N. Kiryati, *Finding Shortest Paths On Surfaces By Fast Global Approximation And Precise Local Refinement*. Citeseer, 1994.

[32] R. Kimmel, A. Amir *et al.*, "Finding Shortest Paths On Surfaces Using Level Sets Propagation," *IEEE Transactions on Pattern Analysis and Machine Intelligence*, vol. 17, no. 6, pp. 635–640, 1995.

[33] R. Kimmel and J. A. Sethian, "Computing Geodesic Paths On Manifolds," *Proceedings of the National Academy of Sciences*, vol. 95, no. 15, pp. 8431–8435, 1998.

[34] E. Tripp, *The Meridian Handbook Of Classical Mythology*. PENGUIN USA, 1974.

[35] A. W. Toga and P. M. Thompson, "The Role Of Image Registration In Brain Mapping," *Image Vis Comput*, vol. 19, no. 1-2, pp. 3–24, Jan 2001.

[36] N. Duta, A. K. Jain *et al.*, "Learning 2D Shape Models," in *Computer Vision and Pattern Recognition, 1999. IEEE Computer Society Conference on*, vol. 2, 1999, pp. 2 vol. (xxiii+637+663).

[37] X. Penin, C. Berge *et al.*, "Ontogenetic Study Of The Skull In Modern Humans And The Common Chimpanzees: Neotenic Hypothesis Reconsidered With A Tridimensional Procrustes Analysis," *American Journal of Physical Anthropology*, vol. 118, no. 1, pp. 50–62, 2002.

[38] T. Bienvenu, F. Guy *et al.*, "Assessing Endocranial Variations In Great Apes And Humans Using 3D Data From Virtual Endocasts," *American Journal of Physical Anthropology*, vol. 145, no. 2, pp. 231–246, 2011.

[39] N. Duta, A. K. Jain *et al.*, "Automatic Construction of 2D Shape Models," *IEEE Transactions on Pattern Analysis and Machine Intelligence*, vol. 23, no. 5, pp. 433–446, 2001.

[40] T. McInerney and D. Terzopoulos, "Deformable Models In Medical Image Analysis," in *Mathematical Methods in Biomedical Image Analysis, 1996., Proceedings of the Workshop on*, Jun. 1996, pp. 171–180.

[41] C. Xu and J. L. Prince, "Snakes, Shapes, And Gradient Vector Flow," *Image Processing, IEEE Transactions on*, vol. 7, no. 3, pp. 359–369, 1998.

[42] ——, "Gradient Vector Flow Deformable Models," *Handbook of Medical Imaging*, pp. 159–169, 2000.

[43] C. Davatzikos, "Spatial Transformation and Registration of Brain Images Using Elastically Deformable Models," *Computer Vision and Image Understanding*, vol. 66, no. 2, pp. 207–222, 1997.

[44] A. Dale, B. Fischl *et al.*, "Cortical Surface-Based Analysis: I. Segmentation and Surface Reconstruction," *Neuroimage*, vol. 9, no. 2, pp. 179–194, 1999.

[45] S. M. Smith, "Fast Robust Automated Brain Extraction," *Hum Brain Mapp*, vol. 17, no. 3, pp. 143–155, Nov 2002.

[46] A. H. Zhuang, D. J. Valentino *et al.*, "Skull-Stripping Magnetic Resonance Brain Images Using A Model-Based Level Set," *Neuroimage*, vol. 32, no. 1, pp. 79–92, Aug 2006.

[47] A. A. Joshi, D. W. Shattuck *et al.*, "Surface-Constrained Volumetric Brain Registration Using Harmonic Mappings," *Medical Imaging, IEEE Transactions on*, vol. 26, no. 12, pp. 1657–1669, Dec. 2007.

[48] Z. Tu, K. L. Narr *et al.*, "Brain Anatomical Structure Segmentation by Hybrid Discriminative/Generative Models," *Medical Imaging, IEEE Transactions on*, vol. 27, no. 4, pp. 495–508, Aprilil 2008.

[49] A. Huang, R. Abugharbieh *et al.*, "A Hybrid Geometric Statistical Deformable Model for Automated 3D Segmentation in Brain MRI," *IEEE Transactions on Biomedical Engineering*, vol. 56, no. 7, pp. 1838–1848, Jul. 2009.

[50] J. X. Liu, Y. S. Chen *et al.*, "Accurate And Robust Extraction Of Brain Regions Using A Deformable Model Based On Radial Basis Functions," *Journal of Neuroscience Methods*, vol. 183, no. 2, pp. 255–266, 2009.

[51] J. Li, X. Liu *et al.*, "A Deformable Surface Model Based Automatic Rat Brain Extraction Method," in *Biomedical Imaging: From Nano to Macro, 2011 IEEE International Symposium on*, Apr. 2011, pp. 1741–1745.

[52] A. Hashioka, S. Kobashi *et al.*, "Shape And Appearance Knowledge Based Brain Segmentation For Neonatal MR Images," in *World Automation Congress (WAC), 2012*, Jun. 2012, pp. 1–6.

[53] R. P. Woods, S. T. Grafton *et al.*, "Automated image registration: I. General methods and intrasubject, intramodality validation," *J Comput Assist Tomogr*, vol. 22, no. 1, pp. 139–152, 1998.

[54] ——, "Automated image registration: II. Intersubject validation of linear and nonlinear models," *J Comput Assist Tomogr*, vol. 22, no. 1, pp. 153–165, 1998.

[55] D. Shen and C. Davatzikos, "HAMMER: Hierarchical Attribute Matching Mechanism For Elastic Registration," in *Mathematical Methods in Biomedical Image Analysis, 2001. MMBIA 2001. IEEE Workshop on*, 2001, pp. 29–36.

[56] T. Liu, D. Shen *et al.*, "Deformable Registration Of Cortical Structures via Hybrid Volumetric And Surface Warping," *Neuroimage*, vol. 22, no. 4, pp. 1790–1801, Aug. 2004.

[57] G. Gerig, M. Styner *et al.*, "Shape Analysis Of Brain Ventricles Using SPHARM," in *Mathematical Methods in Biomedical Image Analysis, 2001. MMBIA 2001 IEEE Workshop on*, 2001, pp. 171–178.

[58] M. K. Chung, K. M. Dalton *et al.*, "Encoding Neuroanatomical Information using Weighted Spherical Harmonic Representation," in *Statistical Signal Processing, 2007. SSP '07. IEEE/SP 14th Workshop on*, Aug. 2007, pp. 146–150.

[59] A. Kelemen, G. Székely *et al.*, "Elastic Model-Based Segmentation Of 3D Neuroradiological Data Sets," *IEEE Transactions on Medical Imaging*, vol. 18, no. 10, pp. 828–839, 1999.

[60] A. Uthama, R. Abugharbieh *et al.*, "Invariant SPHARM Shape Descriptors for Complex Geometry in MR Region of Interest Analysis," in *Engineering in Medicine and Biology Society, 2007. EMBS 2007. 29th Annual International Conference of the IEEE*, Aug 2007, pp. 1322–1325.

[61] A. Ben Abdallah, F. Ghorbel *et al.*, "Chapter 9: Shape Analysis of Left Ventricle Using Invariant 3D Spherical Harmonics Shape Descriptors," in *Geometric Modeling and Imaging, 2008. GMAI 2008. 3rd International Conference on*, Jul. 2008, pp. 53–58.

[62] M. K. Chung, K. M. Dalton *et al.*, "Tensor-Based Cortical Surface Morphometry via Weighted Spherical Harmonic Representation," *Medical Imaging, IEEE Transactions on*, vol. 27, no. 8, pp. 1143–1151, Aug. 2008.

[63] A. Uthama, R. Abugharbieh *et al.*, "SPHARM-Based Spatial fMRI Characterization With Intersubject Anatomical Variability Reduction," *Selected Topics in Signal Processing, IEEE Journal of*, vol. 2, no. 6, pp. 907–918, Dec 2008.

[64] M. Esmaeil-Zadeh, H. Soltanian-Zadeh *et al.*, "SPHARM-based Shape Analysis Of Hippocampus For Lateralization In Mesial Temporal Lobe Epilepsy," in *Electrical Engineering (ICEE), 2010 18th Iranian Conference on*, May 2010, pp. 39–44.

[65] M. Nitzken, M. F. Casanova *et al.*, "3D Shape Analysis Of The Brain Cortex With Application To Autism," in *Biomedical Imaging: From Nano to Macro, 2011 IEEE International Symposium on*, Apr. 2011, pp. 1847–1850.

[66] ——, "3D Shape Analysis Of The Brain Cortex With Application To Dyslexia," in *Image Processing (ICIP), 2011 18th IEEE International Conference on*, Sep. 2011, pp. 2657–2660.

[67] X. Geng, T. J. Ross *et al.*, "Diffeomorphic Image Registration of Diffusion MRI Using Spherical Harmonics," *Medical Imaging, IEEE Transactions on*, vol. 30, no. 3, pp. 747–758, Mar. 2011.

[68] H. Kim, T. Mansi *et al.*, "Vertex-Wise Shape Analysis Of The Hippocampus: Disentangling Positional Differences From Volume Changes," *Med Image Comput Comput Assist Interv*, vol. 14, no. Pt 2, pp. 352–359, 2011.

[69] A. Hosseinbor, M. K. Chung *et al.*, "4D Hyperspherical Harmonic (HyperSPHARM) Representation of Multiple Disconnected Brain Subcortical Structures," in *Medical Image Computing and Computer Assisted Intervention (MICCAI), 2013 16th International Conference on*, Sep. 2013.

[70] C. H. Brechbhler, G. Gerig *et al.*, "Parametrization of Closed Surfaces for 3D Shape Description," *Computer Vision and Image Understanding*, vol. 61, no. 2, pp. 154–170, 1995.

[71] M. Styner, I. Oguz *et al.*, "Framework for the Statistical Shape Analysis of Brain Structures using SPHARM-PDM," *Insight Journal*, no. 1071, pp. 242–250, 2006.

[72] M. K. Chung, K. J. Worsley *et al.*, "Tensor-Based Brain Surface Modeling And Analysis," in *Computer Vision and Pattern Recognition, 2003. Proceedings. 2003 IEEE Computer Society Conference on*, vol. 1, 2003, pp. I–467–I–473 vol.1.

[73] A. D. Leow, A. D. Klunder *et al.*, "Longitudinal Stability Of MRI For Mapping Brain Change Using Tensor-Based Morphometry," *NeuroImage*, vol. 31, no. 2, pp. 627–640, 2006.

[74] N. Lepore, C. Brun *et al.*, "Generalized Tensor-Based Morphometry Of HIV/AIDS Using Multivariate Statistics On Deformation Tensors," *IEEE Trans Med Imaging*, vol. 27, no. 1, pp. 129–141, Jan. 2008.

[75] M. Afzali and H. Soltanian-Zadeh, "Comparison Of Voxel-Based Morphometry (VBM) And Tractography Of Diffusion Tensor MRI (DT-MRI) In Temporal Lobe Epilepsy," in *Electrical Engineering (ICEE), 2010 18th Iranian Conference on*, 2010, pp. 18–23.

[76] Y. Wang, T. F. Chan *et al.*, "Shape Analysis With Multivariate Tensor-Based Morphometry And Holomorphic Differentials," in *Computer Vision, 2009 IEEE 12th International Conference on*, 2009, pp. 2349–2356.

[77] H. Yang, W. Liu *et al.*, "Longitudinal change of the grey matter of mild congnitive impairment patients over 3 years by using voxel-based morphometry," in *Biomedical Engineering and Informatics (BMEI), 2012 5th International Conference on*, 2012, pp. 304–308.

[78] E. Fletcher, A. Knaack *et al.*, "Combining Boundary-Based Methods With Tensor-Based Morphometry in the Measurement of Longitudinal Brain Change," *Medical Imaging, IEEE Transactions on*, vol. 32, no. 2, pp. 223–236, 2013.

[79] J. Shi, Y. Wang *et al.*, "Surface Fluid Registration And Multivariate Tensor-Based Morphometry In Newborns - The Effects Of Prematurity On The Putamen," in *Signal Information Processing Association Annual Summit and Conference (APSIPA ASC), 2012 Asia-Pacific*, 2012, pp. 1–8.

[80] F. L. Bookstein, "'Voxel-based morphometry' should not be used with imperfectly registered images," *Neuroimage*, vol. 14, no. 6, pp. 1454–1462, Dec. 2001.

[81] J. Ashburner and K. J. Friston, "Why Voxel-Based Morphometry Should Be Used," *NeuroImage*, vol. 14, no. 6, pp. 1238–1243, 2001.

[82] Q. He, Y. Duan *et al.*, "Statistical Shape Analysis of the Corpus Callosum in Subtypes of Autism," in *Bioinformatics and Bioengineering, 2007. BIBE 2007. Proceedings of the 7th IEEE International Conference on*, Oct. 2007, pp. 1087–1091.

[83] J. Cates, P. T. Fletcher *et al.*, "Shape Modeling And Analysis With Entropy-Based Particle Systems," *Inf Process Med Imaging*, vol. 20, pp. 333–345, 2007.

[84] T. Geraud, J. . F. Mangin *et al.*, "Segmenting Internal Structures In 3D MR Images Of The Brain By Markovian Relaxation On A Watershed Based Adjacency Graph," in *Image Processing, 1995. Proceedings., International Conference on*, vol. 3, Oct. 1995, pp. 548–551vol.3.

[85] F. Yang and F. Kruggel, "Optimization Algorithms for Labeling Brain Sulci Based on Graph Matching," in *Computer Vision, 2007. ICCV 2007. IEEE 11th International Conference on*, Oct. 2007, pp. 1 –7.

[86] S. S. Long and L. B. Holder, "Graph Based MRI Brain Scan Classification And Correlation Discovery," in *Computational Intelligence in Bioinformatics and Computational Biology (CIBCB), 2012 IEEE Symposium on*, May 2012, pp. 335–342.

[87] K. Yamaguchi, S. Kobashi *et al.*, "Brain Shape Homologous Modeling Using Sulcal-Distribution Index In MR Images," in *Systems, Man and Cybernetics, 2009. SMC 2009. IEEE International Conference on*, Oct 2009, pp. 1102–1106.

[88] ——, "Statistical Quantification Of Brain Shape Deformation With Homologous Brain Shape Modeling," in *World Automation Congress (WAC), 2010*, Sept 2010, pp. 1–6.

[89] S. Angenent, S. Haker *et al.*, "On the Laplace-Beltrami Operator And Brain Surface Flattening," *Medical Imaging, IEEE Transactions on*, vol. 18, no. 8, pp. 700–711, Aug. 1999.

[90] R. Lai, Y. Shi *et al.*, "Automated Corpus Callosum Extraction via Laplace-Beltrami Nodal Parcellation And Intrinsic Geodesic Curvature Flows On Surfaces," in *Computer Vision (ICCV), 2011 IEEE International Conference on*, Nov. 2011, pp. 2034–2040.

[91] R. Shishegar, H. Soltanian-Zadeh *et al.*, "Hippocampal Shape Analysis In Epilepsy Using Laplace-Beltrami Spectrum," in *Electrical Engineering (ICEE), 2011 19th Iranian Conference on*, May 2011, p. 1.

[92] D. Germanaud, J. Lefevre *et al.*, "Larger is twistier: spectral analysis of gyrification (SPANGY) applied to adult brain size polymorphism," *Neuroimage*, vol. 63, no. 3, pp. 1257–1272, Nov. 2012.

[93] M. Makram, H. Kamel *et al.*, "3D Elastic Registration Using A Balanced Multi Resolution Reeb Graph : Application For A Detection Of A Maxilla Facial Malformation," in *Computer and Communication Engineering, 2008. ICCCE 2008. International Conference on*, May 2008, pp. 1063–1071.

[94] Y. Shi, R. Lai *et al.*, "Cortical Surface Reconstruction via Unified Reeb Analysis of Geometric and Topological Outliers in Magnetic Resonance Images," *Medical Imaging, IEEE Transactions on*, vol. PP, no. 99, p. 1, 2012.

[95] H. Lombaert, L. Grady *et al.*, "Fast Brain Matching With Spectral Correspondence," *Inf Process Med Imaging*, vol. 22, pp. 660–673, 2011.

[96] ——, "FOCUSR: Feature Oriented Correspondence Using Spectral Regularization–A Method for Precise Surface Matching," *IEEE Trans Pattern Anal Mach Intell*, vol. 35, no. 9, pp. 2143–2160, Sep. 2013.

[97] S. Prima, S. Ourselin *et al.*, "Computation Of The Mid-Sagittal Plane In 3D Brain Images," *Medical Imaging, IEEE Transactions on*, vol. 21, no. 2, pp. 122–138, Feb. 2002.

[98] S. Gefen, Y. Fan *et al.*, "Symmetry-based 3D Brain Reconstruction," in *Biomedical Imaging: Nano to Macro, 2004. IEEE International Symposium on*, Apr. 2004, pp. 744–747Vol. 1.

[99] X. Liu, C. Imielinska *et al.*, "Symmetry Based Multi-modality Registration of the Brain Imagery," in *Signal Processing and Information*

Technology, 2007 IEEE International Symposium on, Dec. 2007, pp. 807–812.

[100] J. Feng, F. Desheng *et al.*, "Brain Image Segmentation Based on Bilateral Symmetry Information," in *Bioinformatics and Biomedical Engineering, 2008. ICBBE 2008. The 2nd International Conference on*, May 2008, pp. 1951–1954.

[101] M. Fournier, B. Combes *et al.*, "Surface-Based Method To Evaluate Global Brain Shape Asymmetries In Human And Chimpanzee Brains," in *Biomedical Imaging: From Nano to Macro, 2011 IEEE International Symposium on*, 30 2011-April 2 2011, pp. 310–316.

[102] G. T. Herman, M. I. Kohn *et al.*, "Computerized Three-Dimensional Volume Analysis From Magnetic Resonance Images For Characterization Of Brain Disorders," in *Biomedical Engineering., Proceedings of a Special Symposium on Maturing Technologies and Emerging Horizons in*, Nov. 1988, pp. 65–67.

[103] G. Wagenknecht and S. Winter, "Volume-Of-Interest Segmentation Of Cortical Regions For Multimodal Brain Analysis," in *Nuclear Science Symposium Conference Record, 2008. NSS '08. IEEE*, Oct. 2008, pp. 4368 –4372.

[104] H. Doraiswamy and V. NataraJan, "Efficient algorithms for computing Reeb graphs," *Computational Geometry*, vol. 42, no. 67, pp. 606–616, 2009.