Application of Statistical Shape Models in Biomedical Research: Review

Sophie Mei Lin Whikehart

1 Introduction

The topic I have been investigating is the use of statistical shape models [SSMs] for 3D medical image analysis. The literature I have read provides potential applications that SSMs have for implementation in the medical field as well as automating the creation of SSMs. Current research is focused on investigating different approaches used when constructing SSMs in order to leverage the quality of SSMs that can be attached to the availability of training data through different algorithms. Much of the literature I have been reviewing are research publications that present different medical pathologies or structural deformities, and through their research they are able to explain how SSMs can be used to analyze these defects. SSMs are also implemented for sample data analysis as well as creating databases that house training data to be made available to other researchers. Using SSMs as a diagnostic tool in medical research is an important topic because of the vast number of potential applications that SSMS have. It is important to further explore SSMs in order to refine and target solutions to current and future biomedical image analysis challenges especially as technology continues to expand.

2 Overview of Statistical Shape Models

In recent years, statistical shape models (SSMs) have become one of the most widely used tools in medical imaging. A research publication by Heimann and Meinzer (2009) gives an overview on understanding how SSMs are created, the various methods used to achieve creation, and what some of the future applications of SSMs are. Because of the tedious and time consuming nature of creating SSMs, many researchers are proposing ways to semi-automate or fully automate the process. While manual annotation may obtain plausible and accurate segmentation results, an automatic approach or semi-automatic approach saves time and allows for increased availability of training data which makes SSMs more accurate and powerful (Heimann *et al.*, 2009).

2.1 Landmarks

The training data for SSMs usually come from segmented volumetric images and the most generic and simple method used to represent shapes is a set of points that are distributed across the surface. These points are known as landmarks or semilandmarks and are used extensively for the statistical study of biological shape. When landmarks are used as the basis of a SSM they can referred to as **point distribution models (PDMS)**(Cootes *et al.* 1992).

2.2 Shape model construction

To understand the potential applications that SSMs have in the future of biomedical imaging, one must also understand how shape models are constructed. Constructing a SSM is essentially **extracting the mean shape** and **number of modes of variation from a collection of training samples** (Heimann *et al.*, 2009). This is first done by aligning all training samples in a common coordinate frame using the popular method known as **generalized procrustes alignment GPA**. After alignment the next step is to reduce the dimensionality of the training set usually through **principal component analysis PCA** with the final steps being **shape correspondence** and **appearance models**.

2.2.1 Shape correspondence

There are various methods used for **shape correspondence** from *mesh-to-mesh registration, mesh-to-volume registration, volume-to-volume registration, parameterization-to-parameterization registration, or population based optimization.* The three measures to evaluate the general quality of an SSM are the generalization ability, specificity, and compactness (Heimann *et al.*, 2009).

2.2.2 Appearance models

Finally, **appearance models** and **search algorithms** can be classified between *active appearance models, active shape model searche, active apperance model search* as well as other algorithms that have the possibilities to fit a SSM to new data such as

volumetric shape models that use statistical deformation models SDMs. SDM statistical analysis is not conducted using point coordinates but by using volumetric deformation fields between mean image atlas and training samples. The results are then used to constrain registration of atlases to new images, reducing search space considerably (Heimann *et al.*, 2009). In terms of **search algorithms** there should be an incorporation of user interaction in the case of failure of automatic segmentation in which users should be able to correct results by moving a limited number of incorrectly placed landmarks to their true positions (Heimann *et al.*, 2009). It is important to note the large variation of methods used in the construction of shape models as different research teams will utilize the best fit method of their interest.

3 Landmark free SSMs

As noted by Heimann, when landmarks are used as a basis of a SSM they are referred to as **point distribution models PDMS** and that variability is based on a set of training shapes through **principal component analysis PCA**. However, in the literature I am about to review next, the authors Mendonza *et al.*(2014) argue that there are downfalls to PDMs and challenges the typical approach with a different method he proposes in his paper. Mendonza *et al.*(2014) utilize SSMs through a **landmark free approach** in order to represent volumetric cranial shapes to build a SSM of normal anatomy. As an alternative to PDMs, landmark-free SSMs have been explained in other literature as *representing the shape of labeled regions over the whole domain of labeled images which can be regarded as dense as PDMs in which all pixels in the image domain implicitly become a landmark* (Mendoza *et al.* 2014). It is an important trend in landmark free SSMs to represent shape by **deformation fields**. Land-mark free SSMs can also be created from **signed distance functions (SDFs)** or level sets of shape and these representations are appropriate when dealing with limited shape variation.

3.1 Using SSMs for a personalized assessment of craniosynostosis

In a research publication presenting a technique for computational analysis of craniosynostosis from CT images, Mendoza *et al.* (2014) found that you can use SSMs to produce diagnostic features tailored to the anatomy of the subject. Craniosynotosis is the congenital condition characterized by premature fusion of cranial sutures and has multiple cosmetic and functional consequences that can result in limited brain growth, elevated intra-cranial pressure and respiratory and visual impairments (Mendoza *et al.* 2014). It is usually diagnosed using CT scans and these scans are essential for preoperative diagnosis to allow for surgical planning as well as post-surgical assessment.

3.1.1 Results

Mendoza *et al.* (2014) used data in this study from subjects with non-syndromic craniosyntosis ages 0-12 months between the years of 2005-2012. Head CT image of the healthy subjects (the template) was used to define a reference post. On this template, a set of manual landmarks were selected on structures at the base of the cranium. The surface model generation of each volume containing the cranium of the subject was represented as a surface model or mesh of the outer interface of the cranial bones (Mendoza *et al.* 2014). A computational anatomy approach was used to measure shape abnormality in the terms of closest case from a multi-atlas of normal cases. The research results obtained from this study showed that the best results came from comparing the morphology of abnormal subjects with the closest normal subject from a multi-atlas in a PCA transformed space. From each subject data was collected on:

1. Index from cranial suture fusion

2. Deformation and curvature discrepancy averages across five cranial bones and six suture regions

3. The significant differences between normal and craniosyntotic cases obtained from these characteristics

The best results were found by comparing abnormal subjects with closest normal subject from multi-atlas in PCA transformed shape space (Mendoza *et al.* 2014). The research team also found that establishing a cranial shape reference from average does not produce the best results and could possibly by due to the inability of reference shapes to adapt to the normal shape variation across subjects which could be due to various factors such as ethnicity (Dean *et al.*, 1998).

3.1.2 Related findings

The ultimate goal of this research is to assist in surgical planning as it is crucial to characterize dysmorphology in per bone basis. The researchers also found that the automation of diagnosis and its potential applications have the ability to reduce the variability of traditional diagnosis that employ non-automated methods, enable analysis of large numbers of subjects, aid in elucidating epidemiological characteristics of disease, enable correlation with genetic factors and compare subjects anatomy before and after surgical correction in terms of desirable morphology by providing an objective assessment of the success of the procedure (Mendoza *et al.* 2014). Findings related to this work are by Dean *et al.* (1998) that look at the importance of ethnicity and sex in clinical craniofacial research.

4 Studying 'normative' 3D tomography surface images of the skull

In research done by (Dean *et al.* 1998), the authors want to determine the effect of using sex and ethnicity specific adult average 3D skull images for comparisons with patient images at various stages of craniofacial surgical management [ex - diagnosis, treatment planning, prosthetic design, image-guided operative procedures, and outcome assessment] (Dean *et al.* 1998). The research team also proposes that craniofacial surgical reconstruction for abnormal patterns of development, cancer resection or trauma are also likely to benefit from these comparisons.

4.1 Data collection and methods

In order to morphometrically test the significance of separating normative 3D skull data by sex and ethnicity the research team collected 52 3D anatomical landmarks from 3D computer tomography scans of skulls from:

1. 20 Americans of European ethnicity

2. 20 Americans of primarily African ethnicity

One study compared shape of skull in healthy person with that of patient population with Crouzon syndrome and the other study compared the shape of the cerebral ventricles in healthy persons with that of schizophrenia.

4.1.1 Procrustes-based morphometric analysis

Procrustes based morphometric analysis of shape was able to detect 1.2 times as much inheritance variance as intersex variance (Dean *et al.* 1998). In the past the traditional methods used to measure skill differences were cephalometric analyses of linear distances, indices and angles. These methods were used widely in the first three quarters of the 20th century (Dean *et al.* 1998). Nowadays, procrustes analysis is able to provide a new basis for landmark based whole image comparisons and this is what is used in this study.

4.2 Results

4.2.1 Ethnic dimorphism

The results of this study provide only moderate support to claims that in comparison with Europeans and Northern Eurasians, African Americans appear to demonstrate wider upper face, wider inter-orbital spacing and the following soft tissue correlation of wider inter-pupillary distance as well as larger and more protruding oculi (Dean *et al.* 1998).

4.2.2 Sexual dimorphism

The study also shows that their results showed observations of ethnic dimorphism 1.2 times more than for sexual dimorphism (Dean *et al.* 1998). Despite the small sample size however, the researchers' results are still significant (P - 0.001 overall) for both of the main factors of sex and ethnicity separately (Dean *et al.* 1998).

4.3 Related findings

Dean *et al.* (1998) mentions that average 3D craniofacial landmark data is already used clinically, however because the image base samples are so small there are barely any "normative" image data that is able to inform a diagnosis. One of the biggest obstacles for current surgical simulation procedures is the scarcity of the available normative 3D data that is needed to help create a diagnosis to be useful in treatment planing. It should be noted then that the images obtained should be seen more as 'treatment -images rather than a treatment 'norm', 'standard', or 'ideal'. The authors note that a study done on largest samples will inform them more precisely as to how individual features weather by age, sex or ethnic groups are able to co vary between the two groups they have studied in their research. Related to findings to this is Mendoza *et al.* (2014) and the use of SSMs as a diagnostic tool.

5 Methods for liver segmentation based on SSMs prior and enforced local statistical feature

In a different study, Zheng *et al.* (2017) present a novel variation semi-automatic liver segmentation method. This method uses **signed distance functions (SDFs)** to represent pattern shapes to build SSMs. Like Mendoza's research for personalized assessment of craniosyntosis, this research also utilizes a landmark free-approach. Then, a **global gaussian fitting energy** and enforced local feature fitting energy is established to guide the PCA based on **topological transformation**. Experiments are conducted on two publicly available data sets in order to demonstrate that the proposed liver segmentation method achieves competitive results and are state of the art.

5.1 Medical image segmentation

Medical image segmentation is the separation of an interested object from other organs or tissues in a given image (Zheng *et al.* 2017). Manual segmentation is known to be quite time consuming and tedious, so the authors in this paper propose different methods of liver segmentation to be researched such

as an automatic, semi-automatic, gray level or models based on texture information. Each method has its own benefits and downfalls but the paper focuses mainly on a novel variational semi-automated liver segmentation method based on SSMs and enforced local statistical feature.

5.1.1 Proposed segmentation method

The proposed segmentation method is a SDF-based SSM. In order to incorporate statistical shape information into the liver segmentation, the researchers applied a PCA on SDF representing set of training instances. The shape model is based on the PCA that determined the best orthonormal basis to capture the main variations of the training set. In creation of the segmentation model the researchers propose the segmentation model based on the statistical shape prior to the global gaussian fitting energy and local statistical consistency energy in order to drive the contours towards the real boundaries of the liver (Zheng *et al.* 2017).

5.2 Results

The authors have found that the proposed model in this paper is efficient because it is able to incorporate unconstrained shape coefficients as well as global and statistical information into the segmentation process. Experiments done on two publicly available data sets show that utilization of shape prior and statistical image intensity information can lead to robust and competitive results (Zheng *et al.* 2017).

6 Registration of statistical shape models for unsupervised pathology annotation

In a more recent paper, Rahbani *et al.* (2019) are presenting a method to automatically label pathologies in volumetric medical data. This method relies on using healthy SSMs to label pathologies in a novel target during model fitting. The importance of this method is that it is able to detect pathologies with higher accuracy than standard robust detection algorithms and can be used to automate diagnosis or as a pre-processing step to accurately label large amounts of biomedical data (Rahbani *et al.* 2019). The authors argue that automatic labeling of biomedical data is a necessity whether for diagnosis in health care or for image annotation in data sets and this is especially true in the case of pathology labeling in volumetric data sets such as in CT or MR images.

6.1 Application of SSMs

The research done by Rahbani *et al.* (2019) shows how SSMs built from healthy anatomies can be exploited to perform pathology labeling in novel images. Pathology labeling is used as an outlier detection step in a proposed robust non-rigid algorithm. Outliers are defined as all SSM points without a corresponding point in target image and vise versa (Rahbani *et al.* 2019). The main goal of this research is to create an unsupervised learning and probabilistic approach to label surfaces extracted from biomedical images as healthy or pathological as well as using a robust registration algorithm for fitting SSMs to pathological data.

6.1.1 Approaches used to handle outliers

Registration with missing or added data as non-rigid points with outliers have been addressed in extension to robust point matching and in coherent point drift. Outlier detection for SSMs is a pre-processing step for building or fitting and SSMs have also been used in pathology segmentation form fitting errors. The method used in this research does not rely on manual segmentation or reference topology (Rahbani *et al.* 2019). In addition, the method based on this research is to extend standard SSM fitting formulation with additional segmentation of outliers.

6.2 Results

The researchers found that SSMs are able to perform a detection given on a target surface without any further assumptions of user annotations. The pipeline is non-specific to pathology type or imaging domain and can be used to point out regions of interest to clinicians or as a pre-processing step for training end-to-end classifiers (Rahbani *et al.* 2019). Potential future work and applications of this research could be to investigate other probabilistic metric that can work alongside distance based one as well as further testing of method on current biomedical image segmentation's challenges.

7 Statistical deformation models

In the beginning of this paper I reviewed the difference between using landmarks in SSMs and non landmark approaches. I will now cover the subject of **statistical deformation models SDMs** over **statistical shape models SSMs** as proposed in Rueckert *et al.* (2003). SDMs were also briefly mentioned in Heimann et al. (2009) as an alternative algorithm to fit SSM to new data. Rueckert *et al.* (2003) argue that SDMs can be used for the construction of average models of anatomy and their variability and are built by performing statistical analysis of the deformations required to map anatomical features in one subject onto the corresponding features of another subject. SDMs of anatomical variability are a complementary approach to building SSMs which capture statistical information about shapes

across a population but offer several distance advantages over SSMs. SDMs are also closely related to the rapidly developing discipline of **computation anatomy** which is pioneered work of Grenader and Miller (Rucejert *et al.* 2003).

7.1 Advantages of SDMs over SSMs

Rueckert *et al.* (2003) informs that SDMs can be constructed directly from images such as MR or computer tomography volumes without the need for segmentation which is usually a prerequisite for the constructions of SSMs. Instead it is proposed that a nonrigid registration algorithm based on free-from deformations and normalized mutual information is used to compute the deformations required to establish dense correspondences between the reference subject and the subjects in the population class under investigation (Rueckert *et al.* 2003). SDMs allow for the construction of an atlas of the average anatomy as well as its variability across a population of subjects. SDMs also take the 3D nature of underlying anatomy into account by analyzing dense 3D deformation fields rather than only information about the surface shape of anatomical structures. The correspondences that are obtained by the nonrigid registration are then evaluated using anatomical landmark locations. Finally, SDMs can be constructed in order to minimize the bias towards a chosen reference subject (Rueckert *et al.* 2003).

7.1.1 Atlas-based approaches

According to Rueckert *et al.* (2003), because of the significant inter-subject variability of anatomy and function, interpretation of medical images is a challenging task. Therefore atlas-based approaches address this problem by being able to define a common reference space. Mapping data sets into this common reference space not only accounts for the anatomical and functional variations of individual subjects but it also offers a powerful framework to facilitate the comparison of anatomy and function over time, between subjects and between groups of subjects across multiple sites (Rucejert *et al.* 2003). In recent reviews of nonrigid registration techniques it can be noted that traditional medical atlases contain information about anatomy and function from a single individual that usually focuses primarily on the human brain. Even though the individuals for these selected atlases may be considered normal, they also represent an extreme of normal distribution. In order to address this problem, the research team in this paper have developed various probabilistic and statistical approaches which include information from a group of subjects therefore making them more representative of the population under investigation (Rucejert *et al.* 2003).

7.2 Method

Traditionally, landmarks are anatomical characteristic points that can be uniquely identified across a set of individuals (Rucejert *et al.* 2003). The method used in this paper consisted of the researchers performing a PCA on compact parameterization of the deformation fields required to map the anatomy of one subject onto the anatomy of another subject. Non rigid registration was employed because in practice, anatomical variability between subjects cannot be sufficiently explained by affine transformation which only accounts for differences due to position, orientation and overall size of anatomy (Rucejert *et al.* 2003). In order to capture anatomical variability it was necessary in this study to employ nonrigid transformations using a nonrigid algorithm which had previously been applied successfully to a number of difference registration tasks. 25 brain MR images from different subjects with schizophrenia were used to construct SDMs of the brain.

7.3 Results

The main goal of this paper is that the proposed method enables automatic construction of statistical models in both 2D and 3D and can be applied to other anatomical structures such as the heart and liver (Rucejert *et al.* 2003). In this paper, the researchers demonstrated how a nonrigid registration algorithm based on free form deformation (FDM) and normalized mutual information can be used for automatic construction of SDMs of the brain. The results showed that a nonrigid registration algorithm leads to good correspondences. The resulting models can be used to build an atlas of average anatomy as well as its variability which was achieved by performing PCA of control points of FDM required to map the anatomy of reference subject to all other subjects in population. Researchers also found that statistical modeling of deformations in a natural was of constructing statistical models which take in the variability of the entire anatomy (or multiple structures) into account.

7.4 Related findings

At the end of the paper, the authors state that they are currently in the process of building a SDM of the brain using more than 100 normal subjects which is expected to help improve the statistical significance of the principles modes of variation. The research done in this paper hopes to investigate in the future whether SDMs can be applied and used as a deformation based morphometric tool to characterize shape differences between groups of normal and schizophrenic subjects. In a related finding by Fonseca *et al.* (2011) The Cardiac Atlas Project CAP has been able to establish a large-scale database of cardiac imaging examinations and associated clinical data in order to develop a shareable, web acces-

sible, structural and functional atlas of the normal and pathological heart for clinical, research and educational purposes.

8   Cardiac Atlas Project

The original paper written by Fonseca *et al.*, (2011) is about the Cardiac Atlas Project CAP that incorporates the integrative role that SSMs of cardiac anatomy and physiology have in understanding cardiac disease phenotypes and planning therapeutic strategies as well as the availability of imaging data sets. The article emphasizes that the accuracy and predictive power of SSMs in biomedical imaging is dependent upon the breadth and depth of noninvasive imaging datasets (Fonseca *et al.*, 2011). Therefore, CAP has established a large scale database of cardiac imaging examinations and associated clinical data in order to develop a shareable, web accessible, structural and functional atlas of the normal and pathological heart for clinical, research and educational purposes. The goal of CAP is to facilitate collaborative statistical analysis of regional heart shape as well as wall motion and characterize cardiac function among and within population groups.

8.1   Methods

The imaging and clinical data in CAP employ MRI because it is noninvasive, well tolerated and safe and can provide high quality functional information in any plane and direction (Fonseca *et al.*, 2011). In this project to date (2011), all CAP imaging data has come from MRI as the tomographic nature of MRI data lends itself to 3D atlas building techniques. CAP must also obey a variety of legislative and local Institutional Review Board (IRB) requirements because it is an international, multi-institutional collaborative project. In CAP, all data must be de-identifiable by the contributors before being uploaded into the database.

8.2   Results

The research objectives of CAP are to:

1. Create a database of cardiac imaging examinations that consist of de-identified image files together with associated clinical data

2. Create an open source software for the analysis of cardiac morphology that include

    (a) Visualization of images in 3D over time

    (b) Interactive construction of mathematical cardiac models from the images

3. Develop standard protocols for the contribution, curation, archival, classification and sharing of cardiac image data and derived analysis which also include labeling the images and

models in the CAP database with ontological terms (Fonseca *et al.*, 2011).

To this date (2011), CAP currently holds 3000 cardiac MRI studies as well as functional analyses and associated participant data.

8.3   Related findings

The data in CAP can be used for a variety of different purposes. Some of the use cases for CAP data are, *image analysis, clinical evaluation, clinical trials, and education* (Fonseca *et al.*, 2011). A related finding to this work is the Kids First Project Proposal in which researchers are attempting to construct an accessible, open-source tool for comparing individual knockout strain specimens to models that are normally developed. Both of these studies deal with creating collaborative tools that can be used for more future research opportunities.

9   Kids First Proposal

In a research proposal written in 2022, researchers are hoping to understand the genetic basis of asymmetry and its relationship to disease susceptibility in order to help unravel complex genetic and environmental factors and the interactions that increase the risk of developmental disorders. Asymmetry is a key feature of developmental disorders and major structural birth defects as well as neurological disorders. The proposal hopes incorporate data from the KOMP2 project as well as tissue expression data from the GTEx project.

9.1   Use of SSMs in proposal

This proposal will use statistical models of normal anatomy as well as asymmetric anatomy from KOMP2 fetal imaging data. It will also employ open source software to produce detailed phenotypic descriptions from dense mrophometric analysis of 3D images from KOMP2 data set.

9.1.1   Specific aims

The specific aims of the study are to implement an open-source workflow to quantify abnormal asymmetry of structures and segmented organs from 3D fetal imaging of KOMP2 knockout mouse models as well as identify variants on candidate genes selected in the first aim in oral facial cleft cohorts that may indicate a link between asymmetric phenotype and increased disease risk.

9.1.2   Hypothesis

The hypothesis of the first aim is that knockout mouse strains with abnormally asymmetric phenotype may indicate genes associated with disruption in normal asymmetry. The second hypothesis is

that uncommon variants on genes with demonstrated links to asymmetry are more common in OFC populations and may contribute to the multi factorial risks for these disorders.

9.2 Methods

9.2.1 Computational anatomy

Similar to Mendoza *et al.* (2014), a computational anatomy approach will be used to assess asymmetry in 3D images and apply insights to genetic studies of developmental disorders in humans. The proposed computational anatomy (CA) approach will help identify knock out strains with increased asymmetry compared to wild type controls. The CA approach will use average anatomical templates (atlases) to provide a least-biased coordinate system to study structure-function relationships.

9.2.2 Software

The program used in this research will be a 3D slicer platform to construct statistical models of shape and asymmetry and develop a 3D slicer extension to quantify the asymmetry and morphological abnormality of individual knockout strain specimens. Dense systematically shaped pseudo-landmarks will be placed on the external surface of atlas images and segmented regions using an automated approach. Each control embryo will then be aligned and deformably registered to the atlas. Point wise asymmetry will be calculated as well as construction of models to show asymmetry and morphological abnormality.

9.3 Related findings

This proposal draws on many similarities of the literature that has been reviewed in this paper such as Heimann et al. (2009) for use of SSMs, Mendoza *et al.* (2014). for use of computer aided diagnosis, Rahbani *et al.* (2019) for use of an automatic labeling system and outlier detection, Ruecejert *et al.* (2003) for use of atlas based approach, Zheng *et al.* (2014) for use of medical image segmentation and Fonseca *et al.* (2011) on constructing open source databases for the research community.

10   Conclusion

In biomedical image analysis, the incorporation of SSMs is a growing disciplinary in the medical field. 3D SSMs have many potential applications to medical image analysis but they are not limited to being 100% full proof just yet. The biggest strength to SSMs is the sheer amount of applications that SSMs have that include but are not limited to, segmentation with the focus on brain and cardiac structures, liver segmentation for soft tissue structures that have historically been harder for shape modeling, assistance in surgical planning, creation of nonrigid registration algorithms and the integration of open source shareable databases to enhance the amount of training data that is available to researchers.

Some of the weaknesses that SSMs have in general is that in many medical image applications, shape instances are represented as labeled objects in 3D. It is often difficult to establish meaningful landmark correspondences without tedious and time consuming expert work (Mendoza et al., 2014). Even though a number of strategies have been proposed to automatically create landmark corresponds through registration there still have more limitations to SSMs such as numerical instability, inability to accurately capture high curvature locations, and difficult handling topological change. This is why other research studies propose alternatives to SSMs through landmark free approaches or SDMs to work around the downfalls that SSMs have. However with so many different and changing options it can be hard to keep track of all the small nuances and the sheer amount of variability that SSMs have,.

The power and accuracy of SSMs relies on the availability of training data and according to the research I have read, large databases of training data is limited due to the time consumption of non-automated methods to create these training data sets. Next steps in research could be expanding the data cohorts that are being used in training sets as well as making sure that the data available is in an openly accessible platform for researchers. The implementation of redefining automated methods can help in enables analysis of a large number of subjects that researchers can use in their research.

References

[1] Heimann, T. Meinzer, H. P. Statistical shape models for 3D medical image segmentation: A review. Med. Image Anal. (2009) doi:10.1016/j.media.2009.05.004.

[2] Mendoza, C. S. et al. Personalized assessment of craniosynostosis via statistical shape modeling. Med. Image Anal. (2014) doi:10.1016/j.media.2014.02.008.

[3] Rahbani, D., Morel-Forster, A., Madsen, D., Lüthi, M. Vetter, T. Robust registration of statistical shape models for unsupervised pathology annotation. in Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics) (2019). doi:10.1007/978-3-030-33642-4-2.

[4] Rueckert, D., Frangi, A. F. Schnabel, J. A. Automatic construction of 3-D statistical deformation models of the brain using nonrigid registration. IEEE Trans. Med. Imaging (2003) doi:10.1109/TMI.2003.815865.

[5] Zheng, S. et al. A novel variational method for liver segmentation based on statistical shape model prior and enforced local statistical feature. in Proceedings - International Symposium on Biomedical Imaging (2017). doi:10.1109/ISBI.2017.7950515.

[6] Dean, David PhD; Bookstein, Fred L. PhD†; Koneru, Suresh MD†; Lee, Jae-Hak DDS, MSD§; Kamath, Janardhan M Eng; Cutting, Court B. MD¶; Hans, Mark DDS, MSD§; Goldberg, Jerold DDS Average African American Three-Dimensional Computed Tomography Skull Images, Journal of Craniofacial Surgery: July 1998 - Volume 9 - Issue 4 - p 348-358

[7] Carissa G. Fonseca, Michael Backhaus, David A. Bluemke, Randall D. Britten, Jae Do Chung, Brett R. Cowan, Ivo D. Dinov, J. Paul Finn, Peter J. Hunter, Alan H. Kadish, Daniel C. Lee, Joao A. C. Lima, Pau MedranoGracia, Kalyanam Shivkumar, Avan Suinesiaputra, Wenchao Tao, Alistair A. Young, The Cardiac Atlas Project—an imaging database for computational modeling and statistical atlases of the heart, Bioinformatics, Volume 27, Issue 16, 15 August 2011, Pages 2288–2295, https://doi.org/10.1093/bioinformatics/btr360