Quasi-conformal Statistical Shape Analysis of Hippocampal Surfaces for Alzheimer Disease Analysis

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Abstract Alzheimer's Disease (AD) is a no-cure disease that frustrates scientists for many years. Analyzing the disease has become an important but challenging research topic. The shape analysis of the sub-cortical structure of AD patients has been commonly used to understand this disease. In this paper, we assess the feasibility of using shape information on the hippocampal (HP) surfaces to detect some sub-structural changes in AD patients. We propose a quasi-conformal statistical shape analysis model, which allows us to study local regional shape differences of the HPs amongst normal control (NC) and AD groups. A shape index defined by the quasi-conformality and surface curvatures is used to characterize region-specific shape variations of the HP surfaces. Feature vectors can be extracted for each HPs, with which a classification model can be built using the machine learning methods to classify HPs between NC and AD subjects. Experiments have been carried out on 99 normal controls and 41 patients with AD. Results demonstrate the proposed quasi-conformal based model is effective for classifying HPs into NC and AD groups with high classification accuracy (with highest overall classification accuracy reaches up to 87.86% in a leave-one-out experiment).

Keywords Alzheimer's Disease, Beltrami Coefficient, Hippocampus, Machine Learning, P-value, Shape Classification, Surface Registration.

1 Introduction

The Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by a decline in cognitive functions. The cause of AD is poorly understood. It usually starts slowly, gets worsen over time and eventually leads to death. Early detection of AD is thus an important but challenging task.

Amongst the various subcortical structures, the hippocampus (HP) has demonstrated pronounced shape changes in the early stage of AD. For example, the hippocampal atrophy has been recognized to be more aggressive in AD in comparison with the normal aging [1,2,3,4,5,6]. The HP surface is therefore amongst the most important biomarker for the early diagnosis of the disease.

HP shape analysis has usually been carried out by studying its global and local shape changes. For global shape analysis, the overall HP volumes are usually evaluated to study global shape differences amongst AD patients. It is believed that HP volumetric decline is correlated to the memory lost [7]. Tissue

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losses in the HP have also been found in the AD [8]. As a matter of fact, HP volumetry on MR images has been widely used and found helpful for the diagnosis of AD.

Although the HP volume can provide significant information to discriminate AD from normal control subjects, significant regional shape changes in the HP have been observed in the neurodegenerative process of AD [9,10]. For example, neuron loss has commonly been found in CA1 and subiculum subfields [11,12, 13]. In view of this, the examination of the local regional shape changes in the HPs is expected to provide better information to analyze the disease and classify HPs between AD and NC groups. Besides, another potential limitation of the global shape analysis approach is that geometric differences between AD and NC groups may only occur at some specific local regions. Taking into account of the overall shape change of the whole HP volume may average out or diminish the discriminative power of the geometric differences amongst the normal and diseased group, which hinders the shape analysis accuracy. It is therefore desirable to design local shape analysis model that can measure regional shape changes effectively.

In order to analyze the localized pattern of HP shape changes, surface-based morphometry can be employed. A shape index that quantifies regional shape changes is often defined, with which statistical shape analysis can be performed for the HP classification. In this work, we propose a quasi-conformal based shape analysis approach, which allows us to study local regional shape differences of the HP amongst NC and AD groups. A shape index based on the quasi-conformality and surface curvatures is applied to characterize region-specific shape variations of the HP surfaces amongst different subjects. The shape index is a positive real-valued function defined on every vertices of the HP. Feature vectors for each HP can be extracted from their shape indices using statistical methodologies. A classification model can then be built using the extracted feature vectors. The proposed quasi-conformal based model is found to be an effective approach to classify HPs into NC and AD groups.

Our experiments are performed on 99 normal controls and 41 patients with AD. The data is obtained using 1.5T magnetic resonance imaging (MRI) scanner. Using our method, we can accurately achieve a high accuracy of classification between NC and AD groups.

The rest of the paper is organized as follows. In Section 2, we review some previous literatures closely related to this work. Our proposed quasi-conformal shape analysis model will be described in details in Section 3. Experimental results will be shown in Section 4 and 5. The paper is concluded in Section 6, in which possible future works are discussed.

2 Previous Works

The shape analysis of the HP for the disease analysis of AD has been widely studied by various research groups. Different approaches have been developed. For global shape analysis, HP volume has been used for classifying AD subjects and AD diagnosis [5,6,14,15,16,17]. In particular, by studying the HP volumes, [18] has reported the classification result between AD and cognitively normal subjects with a success rate about 72-74% over an Alzheimer's Disease Neuroimaging Initiative (ADNI) database. To further improve the accuracy for the analysis of AD, local shape changes in the HP have been taken into account. Surfacebased morphometry of the HP surfaces has been extensively studied. The spherical harmonic (SPHARM) representation of the HP surface has been exploited to extract shape features to quantify shape changes caused by AD [18,19,20,21,22]. Longitudinal approaches which study the HP atrophy rates over times have been proposed for AD classification problems [23,24]. These approaches can often achieve higher classification accuracy than the volumetric approaches (e.g. 82% on 568 images of the ADNI dataset by Wolz et al. [24]). Younes et al. [25] applied the large deformation diffeomorphic metric mapping method for HP surface registration and successfully detected the changing point that indicated the AD. Wang et al. [26] proposed the tensor-based surface morphometry on the HP to analyze shape changes in HPs of AD subjects. To better examine the regional shape changes of the HP, algorithms which segment subfields of the HP has been proposed to detect the local atrophy pattern [27,28]. Lui et al. [29] also proposed to obtain HP registration using Beltrami holomorphic flow. Using the registration, vertex-wise shape changes can be detected and statistical significance map (p-map) can be computed to visualize the regions with significant shape differences.

Statistical shape analysis methods to analyze AD has also drawn much attention recently. For instance, Miklossy et al. [30] used the Koch's and Hill's criteria in finding the AD. The analysis of the reviewed data following Koch's and Hill's postulates shows a probable causal relationship between neurospirochetosis and AD. Comelli M et al.[31] combined the univariate tests and logistic regression in proposing a therapy for AD. Thompson et. al [32] used the statistical region-of-interest method in assessing the twelve-month metabolic declines in probable AD and Amnestic Mild Cognitive Impairment. It is noteworthy that both the statistical analysis and surface mapping take an important role in human brain analysis especially for the study of AD. Recently, multidimensional classification methods have been widely used for disease classification [19,33,34,35,36,37].

In order to perform local shape analysis, surface registration that captures the one-to-one vertexwise correspondence between different HP surfaces is crucial. Harmonic surface registration has been widely used [38,39], which produces smooth surface mapping by simply solving a elliptic PDE. Landmarkmatching optimized harmonic map has also been proposed to obtain an optimal harmonic map that matches corresponding landmark features [40,41,42,43].

Quasi-conformal theory will be applied in this work. Computational quasi-conformal mapping has been studied recently and applied successfully in the medical imaging field. Lui et al. proposed to obtain quasiconformal surface registration using the Beltrami holomorphic flow method [29]. The method has been applied to compute HP surface registration [44]. Quasi-conformality has also been utilized to quantify non-isotropic deformations, which can be used to detect abnormal growth or deformation [45]. To deal with higher genus surfaces, different methods have been developed to compute quasi-conformal mappings of surfaces with general topologies [46,47]. Landmark-based surface quasi-conformal registration has also been investigated [46,48].

3 Quasi-conformal Statistical Shape Analysis model

In this section, we will describe our proposed quasi-conformal statistical shape analysis model in details. Suppose we are given a collection of hippocampal (HP) surfaces of normal controls (NC) and diseased subjects suffering from the Alzheimer disease (AD). Our goal is to learn a classification model using their shape information, with which a new input HP surface can be classified into either normal or diseased subject. This can potentially assist physicians for the diagnosis of the AD. For this purpose, we propose to combine quasi-conformal theories and statistical tools to develop a shape classification machine. Shape deformation measurement are firstly obtained through quasi-conformal theories, which provide accurate measurement of local geometric differences amongst subjects. A shape classification model can then be learnt through statistical tools and machine learning procedures.

Denote the collection of HP surfaces of m normal controls and n diseased subjects by $N = \{S_i^t\}_{i=1}^m$ and $\tilde{A} = \{S_i^t\}_{i=m+1}^{m+n}$ respectively, where t = 0 or 1. The HP surface of each subject was captured at the base-time t = 0 and after one year t = 1. Their surfaces are denoted by S_i^0 and S_i^1 respectively. Our proposed quasi-conformal statistical shape analysis can be summarized as follows, which consists of five main steps.

- 1. Surface registration: For each subject *i*, the deformation $f_i : S_i^0 \to S_i^1$ of subject *i* is obtained. Also, surface registrations $g_{ij} : S_i^0 \to S_j^0$ are computed. These registrations give point-wise correspondence between subjects for further shape analysis.
- 2. Shape deformation measurement: For each subject *i*, measure the shape deformation at each vertex of the HP from t = 0 to t = 1 using quasi-conformal theories. A shape index $E_{shape}^i : S_i^0 \to \mathbb{R}^+$ is obtained that measures the degree of deformation at each vertex.
- 3. Extraction of statistical significant regions: Statistical significant p-map is obtained based on the shape index computed for each subject. A statistical significant region Ω can be extracted to obtain more accurate classification results.
- 4. Extraction of feature vector: The shape index E_{shape}^i together with the statistical significant region Ω give rise to a discriminative feature vector $\tilde{\mathbf{c}}_i$ for each subject. A mean feature $\tilde{\mathbf{c}}_{mean}^{NC}$ amongst the normal control group can also be extracted. Distance d_i between each feature vector $\tilde{\mathbf{c}}_i$ and the mean feature vector $\tilde{\mathbf{c}}_{mean}^{NC}$ can be computed, which can be used to build the shape classification machine.
- 5. Building the classification model: Using the discriminative feature vector, a classification model is to be built to classify a new input subject into either NC group or AD group.

We will now explain each steps in details.



Fig. 1: Infinitesimal behaviour of quasi-conformal map

3.1 Surface registration

Registration between HP surfaces must be computed to obtain point-wise correspondences between surfaces. With the registration, vertex-wise geometric difference between subjects can be measured and local shape analysis can be carried out. In this work, we apply the radial registration about the centerlines of the HP surfaces to obtain the surface registration. Given two HP surfaces S_i^0 and S_j^0 , the centerlines of each surfaces are computed. From the centerlines, corresponding radial loops on each surfaces can be extracted. The radial loops can be parameterized using the angular parametrization, with which point-wise correspondences of each pair of corresponding loops can be computed. Combining the registrations of every pairs of radial loops, the surface registration $g_{ij}: S_i^0 \to S_j^0$ between S_i^0 and S_j^0 can be obtained. Similarly, the surface registration $f_i: S_i^0 \to S_i^1$ between the HP surfaces of a subject measured at different times can be computed. For details of the registration algorithm, we refer the readers to [19].

3.2 Shape deformation measurement

The surface registration $f_i : S_i^0 \to S_i^1$ for each subject allows us to analyze the shape deformation at each vertex of the HP surface. It is believed significant shape deformations (atrophy) occur on HP surfaces of patients suffering from AD [2,11,12,13,14,15]. Understanding the shape deformation pattern of the HP surface over time can possibly provide information to classify HP surfaces into normal and AD groups. To quantitatively measure the degree of shape deformation, we compute a shape index using the quasi-conformality and curvatures to measure subtle deformation of the HP surface. Given the surface registration $f_i : S_i^0 \to S_i^1$, the shape index $E_{shape}^i : S_i^0 \to \mathbb{R}^+$ is a positive real-valued function on S_i^0 . In practice, HP surfaces are represented discretely by triangular meshes. E_{shape}^i is defined on each vertex \mathbf{v}_i^j of S_i^0 as follows.

Definition: (Shape index) Given the surface registration $f_i: S_i^0 \to S_i^1$, the shape index $E_{shape}^i(\mathbf{v}_i^j)$ at the vertex \mathbf{v}_i^j of S_i^0 is defined as:

$$E_{shape}^{i}(\mathbf{v}_{i}^{j}) = \gamma |\mu(f_{i})(\mathbf{v}_{i}^{j})| + \alpha |H_{0}(\mathbf{v}_{i}^{j}) - H_{1}(f_{i}(\mathbf{v}_{i}^{j}))| + \beta |K_{0}(\mathbf{v}_{i}^{j}) - K_{1}(f_{i}(\mathbf{v}_{i}^{j}))|$$
(1)

where α , β and γ are real positive scalar parameters. $|\mu(f_i)(\mathbf{v}_i^j)|$ is the complex dilation defined by:

$$|\mu(f_i)(\mathbf{v}_i^j)| = |\frac{\partial f_i}{\partial \bar{z}}(\mathbf{v}_i^j)| / |\frac{\partial f_i}{\partial z}(\mathbf{v}_i^j)|.$$
(2)

 H_1 and H_2 are the mean curvature on S_i^0 and S_i^1 respectively. K_1 and K_2 are the gaussian curvature on S_i^0 and S_i^1 respectively.

The complex dilation $|\mu(f_i)(\mathbf{v}_i^j)|$ measures the conformality distortion of the deformation at the vertex \mathbf{v}_i^j . Intuitively, a general deformation maps an infinitesimal circle at \mathbf{v}_i^j to an infinitesimal ellipse at $f_i(\mathbf{v}_i^j)$. The distortion from the small circle to the small ellipse can be measured by $|\mu(f_i)(\mathbf{v}_i^j)|$. More specifically,

the maximal stretching and shrinkage can be measured by $1 + |\mu(f_i)(\mathbf{v}_i^j)|$ and $1 - |\mu(f_i)(\mathbf{v}_i^j)|$ respectively (see Figure (1)). In particular, the deformation is conformal or locally isotropic at \mathbf{v}_i^j if $|\mu(f_i)(\mathbf{v}_i^j)| = 0$. The partial derivatives $\frac{\partial f_i}{\partial z}(\mathbf{v}_i^j)$ and $\frac{\partial f_i}{\partial z}(\mathbf{v}_i^j)$ are defined using the coordinate charts of S_i^0 and S_i^1 . Let $\phi_j : U_j \subset S_i^0 \to \mathbb{C}$ and $\varphi_j : V_j \subset S_i^1 \to \mathbb{C}$ be coordinate charts of S_i^0 and S_i^1 around \mathbf{v}_i^j and $f_i(\mathbf{v}_i^j)$ respectively. The partial derivatives can be defined as:

$$\frac{\partial f_i}{\partial \bar{z}}(\mathbf{v}_i^j) := \frac{\partial \varphi_j \circ f_i \circ \phi_j^{-1}}{\partial \bar{z}}(\phi_j(\mathbf{v}_i^j)); \quad \frac{\partial f_i}{\partial z}(\mathbf{v}_i^j) := \frac{\partial \varphi_j \circ f_i \circ \phi_j^{-1}}{\partial z}(\phi_j(\mathbf{v}_i^j)), \tag{3}$$

where $\frac{\partial}{\partial \bar{z}} = \frac{1}{2} \left(\frac{\partial}{\partial x} + i \frac{\partial}{\partial y} \right)$ and $\frac{\partial}{\partial z} = \frac{1}{2} \left(\frac{\partial}{\partial x} - i \frac{\partial}{\partial y} \right)$. This shape index has been used to formulate an energy functional over all possible surface mappings

This shape index has been used to formulate an energy functional over all possible surface mappings to solve the geometric matching surface registration problem [44]. Note that E^i_{shape} is a complete shape index measuring different kinds of distortions of the deformation. A different combination of parameters gives rise to different shape indices measuring different kinds of distortions, which can be summarized as below:

- $-\alpha = \beta = 0$ and $\gamma \neq 0$: E_{shape}^{i} measures the conformality distortion of the deformation. In other words, $E_{shape}^{i} \equiv 0$ if the deformation is locally isotropic everywhere.
- $-\alpha = 0, \ \beta \neq 0$ and $\gamma \neq 0$: E_{shape}^{i} measures the isometric distortion of the deformation. An isometric deformation preserves the metric (both length and angle). In other words, $E_{shape}^{i} \equiv 0$ if the deformation deforms the shape while keeping the length and angle structure of the shape.
- $-\gamma = 0, \alpha \neq 0$ and $\beta \neq 0$: E_{shape}^{i} measures the curvature deviation of the deformation.
- $-\alpha \neq 0, \beta \neq 0$ and $\gamma \neq 0$: E_{shape}^{i} measures all kinds of distortion of the deformation. In particular, $E_{shape}^{i} \equiv 0$ under the deformation f_{i} if and only if S_{i}^{0} and S_{i}^{1} are equal up to a rigid motion.

In this work, we set $\alpha \neq 0$, $\beta \neq 0$ and $\gamma \neq 0$ to measure all kinds of distortions of the deformation. The shape index functions can be computed for every subjects. A feature matrix can then be built to learn a classification machine. Since all HP surfaces are registered, we assume all HP surface meshes have the same number of vertices and connectivity. Suppose the vertices of S_i^0 are ordered and denoted by $\{v_i^1, v_i^2, ..., v_i^N\}$. Without loss of generality, we may assume v_i^k and v_j^k correspond to each others for every $1 \leq k \leq N$. Using the shape index function E_{shape}^i , a feature vector \mathbf{c}_i can be computed for each subject:

$$\mathbf{c}_{i} = (c_{i1}, c_{i2}, ..., c_{ij}, ..., c_{iN}) \tag{4}$$

where $c_{ij} = E_{shape}^{i}(\mathbf{v}_{i}^{j})$. Combining all feature vectors, we obtain a feature matrix C, which can be used to study the geometric difference of the HP deformations and build the classification model:

$$C = \begin{pmatrix} \mathbf{c}_1 \\ \vdots \\ \mathbf{c}_i \\ \vdots \\ \mathbf{c}_{m+n} \end{pmatrix} = \begin{pmatrix} c_{11} & c_{12} & \dots & c_{1j} & \dots & c_{1N} \\ \vdots & \vdots & \ddots & \vdots \\ c_{i1} & c_{i2} & \dots & c_{ij} & \dots & c_{iN} \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ c_{m+n,1} & c_{m+n,2} & \dots & c_{m+n,j} & \dots & c_{m+n,N} \end{pmatrix}$$
(5)

Without loss of generality, we may assume the first m rows of C are the feature vectors of the HP surfaces from the normal control group. The last n rows are the feature vectors of the HP surfaces from the AD group. Each column of C captures the degrees of distortions of the HP deformations at a particular (corresponding) vertex of all subjects. Since AD is believed to be related to the shape changes of the HP, the feature matrix provide full information of the shape deformation of the HP and hence can be used to develop a classification model.

3.3 Extraction of statistical significant regions

The feature matrix C gives full information about the shape deformation at every vertices of the HPs. In real situation, AD may have effect only on some particular regions or positions of the HP. Utilizing the full information of the deformation at every vertices to build the statistical model may hinder the classification accuracy. To solve this issue, we propose to extract significant regions and analyze their shape deformations to enhance the classification accuracy. More specifically, we proceed to look for a set of vertices $\{\mathbf{v}_i^{j_1}, ..., \mathbf{v}_i^{j_k}, ..., \mathbf{v}_i^{j_l}\}$, whose shape deformations give the most important information for the classification of the HPs. Each column j of C captures the degree of distortions of the HP deformation at a particular vertex. To determine the importance of the shape deformation information at this vertex, we quantitatively measure its statistical significance. We perform a t-test on each column to get a p-value p_j at the vertex j. p_j reports the probability of the geometric difference in the deformation at vertex j occurring from the same distribution by chance. The smaller p_j is, the higher the probability that the shape deformation at vertex j can distinguish between the normal and AD groups.

In order to stabilize and advance the discriminative power of the selected feature points, we make use of the famous bagging predictors [49]. We compute P_{ij} , the p-value computed at vertex j, using all the m + n subjects from the database except for the i^{th} one. Then we assign

$$\widetilde{p}_j = \min_{i=1,\dots,m+n} P_{ij} \tag{6}$$

to the vertex j. Hence, we obtain a p-map $\tilde{p}: \tilde{S} \to [0,1]$, where \tilde{S} is a template mesh having the same number of vertices and connectivity as the HP dataset, such that $\tilde{p}(v_j) = \tilde{p}_j$.

From the p-map \widetilde{p} , the statistical significant regions can be extracted:

$$\Omega := \bigcup_{j \in I_{sig}} \{ \widetilde{\mathbf{v}}^j \} \subseteq \widetilde{S},\tag{7}$$

where $\widetilde{\mathbf{v}}^{j}$ is the j^{th} vertex of the surface mesh \widetilde{S} and the index set I_{sig} is defined as:

$$I_{sig} = \{j_1, j_2, ..., j_l : \tilde{p}_{j_k} \le p_{cut} \text{ for } 1 \le k \le l\}.$$
(8)

Here, p_{cut} is some constant threshold. In other words, we extract all vertices having p-value less than or equal to p_{cut} as statistical significant regions for our investigation.

3.4 Extraction of discriminative feature vectors

Once the statistical significant region Ω is extracted, the shape deformations at statistical significant vertices can be analyzed and build the classification model. The discriminative feature vector $\tilde{\mathbf{c}}_i$ can be computed for each subject *i* as follows:

$$\widetilde{\mathbf{c}}_i = (c_{ij_1}, \dots, c_{ij_k}, \dots, c_{ij_l}).$$
(9)

Combining discriminative feature vectors of all subjects together gives the discriminative feature matrix \widetilde{C} defined as:

$$\widetilde{C} = \begin{pmatrix} c_{1j_1} & c_{1j_2} & \dots & c_{1j_k} & \dots & c_{1j_l} \\ \vdots & \vdots & & \vdots & & \vdots \\ c_{ij_1} & c_{ij_2} & \dots & c_{ij_k} & \dots & c_{ij_l} \\ \vdots & \vdots & & \vdots & & \vdots \\ c_{m+n,j_1} & c_{m+n,j_2} & \dots & c_{m+n,j_k} & \dots & c_{m+n,j_l} \end{pmatrix}$$
(10)

The discriminative feature matrix captures distortions of HP deformations at vertices which provide the most significant information to classify HP surfaces into normal and AD groups. The mean discriminative feature vectors of the normal group can also be constructed:

$$\widetilde{\mathbf{c}}_{mean}^{NC} = \sum_{i=1}^{m} \frac{1}{m} \widetilde{\mathbf{c}}_i \tag{11}$$

3.5 Building the classification model

The discriminative feature vectors can be used to build a classification machine. In this work, both for simplicity and efficiency, we use a simple L^2 classification model, which is based on the mean discriminative feature vector $\tilde{\mathbf{c}}_{mean}^{NC}$ of the NC group. For each subject *i*, we compute the distance of $\tilde{\mathbf{c}}_i$ from $\tilde{\mathbf{c}}_{mean}^{NC}$ to get:

$$d_i = ||\widetilde{\mathbf{c}}_i - \widetilde{\mathbf{c}}_{mean}^{NC}||_2. \tag{12}$$

We make the assumption that the deformation patterns of the HPs in the normal group are similar to each others. Thus, d_i is assumed to be small if subject *i* is in the NC group. We proceed to search for a parameter δ to classify the HP surfaces into either NC or AD groups. More specifically, we conclude the HP is from the NC group if the distance of its discriminative feature vector from $\tilde{\mathbf{c}}_{mean}^{NC}$ is less than δ . Otherwise, we conclude the HP comes from the AD group.

Our goal is to search for the optimal classification parameter δ^{opt} that yields the best classification accuracy. We first rearrange the distances d_i 's in ascending order:

$$d_{i_1} \le d_{i_2} \le \ldots \le d_{i_{m+n}}.\tag{13}$$

For each δ , we can obtain the true positive set (TPS(δ)) and true negative set (TNS(δ)) with respect to δ as follows:

$$TPS(\delta) = \{S_i^0 : S_i^0 \text{ is classified as a normal subject and } 1 \le i \le m\};$$

$$TNS(\delta) = \{S_i^0 : S_i^0 \text{ is classified as an AD subject and } m+1 \le i \le m+n\}.$$
(14)

The true positive rate $(\text{TPR}(\delta))$ and the true negative rate $(\text{TNR}(\delta))$ with respect to δ can be defined as follows:

$$\text{TPR}(\delta) = |\text{TPS}(\delta)|/m; \quad \text{TNR}(\delta) = |\text{TNS}(\delta)|/n$$
 (15)

The optimal classification parameter δ^{opt} can then be computed by solving the following optimization problem:

$$\delta^{opt} = \operatorname{argmax}_{\delta} \{ \frac{|\operatorname{TPS}(\delta)| + |\operatorname{TNS}(\delta)|}{m+n} \}$$
(16)

In practice, the number of HP surfaces are finite. Therefore, the optimization problem (16) above is optimized over a finite set. More specifically, we define:

$$P = \{ \widetilde{\delta} : \widetilde{\delta} = \frac{d_{i_j} + d_{i_{j+1}}}{2} \text{ for some } j \text{ such that } d_{i_j} < d_{i_{j+1}} \}.$$

$$(17)$$

Then, P is a finite set and the optimization problem (16) can be formulated as:

$$\widetilde{\delta}^{opt} = \operatorname{argmax}_{\widetilde{\delta} \in P} \{ \frac{|\operatorname{TPS}(\widetilde{\delta})| + |\operatorname{TNS}(\widetilde{\delta})|}{m+n} \}.$$
(18)

It becomes an optimization problem over a finite set, which can be solved by maximizing amongst all possible choices.

Once the optimal classification parameter is computed, the classification model can be built. Suppose a new input HP surface S is given, S will be registered to the template surface \tilde{S} . The discriminative feature vector \tilde{c}_S of S will be constructed. The distance between $\tilde{\mathbf{c}}_S$ and $\tilde{\mathbf{c}}_{mean}^{NC}$ will then be computed: $d_S = ||\tilde{\mathbf{c}}_S - \tilde{\mathbf{c}}_{mean}^{NC}||_2$. If $d_S \leq \tilde{\delta}^{opt}$, we conclude S belongs to the NC group. Otherwise, we conclude S belongs to the AD group.

Apart from the simple L^2 classification, we can also use other clustering method, like the K-mean clustering and the Support Vector Machine (SVM) clustering.

If we turn to use K-mean clustering, then after applying p-value test to select feature points, we split those NC HP into K_{NC} sub-groups and those AD HP into K_{AD} sub-groups, by packing those with similar shape index on the statistical significant region together. A mean discriminative feature vectors of each sub-group is built. Whenever a new subject is imported, we compute its distance from all the $K_{NC} + K_{AD}$ sub-groups similarly as (12). If the smallest distance is recorded to any sub-group of NC HP models, we classify the new subject as NC. Otherwise we classify it as AD.

This K-mean clustering is more advanced than the simple L^2 classification since we have in total $K_{NC} + K_{AD}$ sub-groups instead of just one for each class. However, we should note that firstly, the number

 K_{NC} and K_{AD} must be selected carefully. Too few sub-groups may have only limited help to boost up the classification accuracy of our algorithm, while too many sub-groups will induce over-determining effect and hence causing inaccuracy. Also, the proportion between the two class of data is important. Unbalanced proportion of data will significantly induce bias to our algorithm and hence limit its performance.

On the other hand, we can also choose to use the famous SVM clustering to replace the simple L^2 classification above. In SVM clustering, we compute a hyperplane which best separates the NC HPs and the AD HPs into zones concerning the shape index E_{shape} on the region Ω . When a new subject is imported, we compute E_{shape} on this subject and see which zone, NC or AD, it belongs to, so as to classify it.

3.6 Overall algorithm

The overall algorithm can be described as follows.

Algorithm 1: Quasi-conformal statistical shape analysis

Input: Training data: NC HP $\{S_i^t\}_{1 \le i \le m, t \in \{0,1\}}$; AD HP $\{S_i^t\}_{m+1 \le i \le m+n, t \in \{0,1\}}$. Input surface S to be classified.

Output: Classification value $C(S) = \begin{cases} 0 & \text{if } S \text{ is NC} \\ 1 & \text{if } S \text{ is AD} \end{cases}$

Step 1: Compute the deformations $f_i: S_i^0 \to S_i^1$ and the pairwise registrations $g_{ij}: S_i^0 \to S_j^0$.

Step 2: For each S_i , compute E_{shape}^i that measures the distortion of the shape deformation of S_i^0 .

Step 3: Extract the statistical significant region Ω .

Step 4: Compute the discriminative feature vector $\tilde{\mathbf{c}}_i$ for each S_i^0 and the mean discriminative feature vector of the normal control group $\tilde{\mathbf{c}}_{mean}^{NC}$.

Step 5: Compute $d_i = ||\widetilde{\mathbf{c}}_i - \widetilde{\mathbf{c}}_{mean}^{NC}||_2$ for $1 \leq i \leq n + m$. Compute the optimal classification parameter δ^{opt} .

Step 6: Compute the discriminative feature vector $\tilde{\mathbf{c}}_S$ of S. Compute $d_S = ||\tilde{\mathbf{c}}_S - \tilde{\mathbf{c}}_{mean}^{NC}||_2$ If $d_S \leq \delta^{opt}$, set $\mathcal{C}(S) = 0$. If $d_S > \delta^{opt}$, set $\mathcal{C}(S) = 1$.

Remark: Step 5 and Step 6 can be replaced by other classification models such as the K-mean clustering or the support vector machine (SVM) clustering. In this work, we use a simple L^2 thresholding classification model, which can be computed efficiently. We have found that even with such a simple model, the classification accuracy is reasonably good. We have also compared this simple classification model with the K-mean clustering and the SVM clustering in Section 5.

4 Experimental Results

In this section, we focus on analyzing the accuracy of our proposed algorithm via different experiments. We have altogether 99 NC HP models and 41 AD HP models (140 models in total). To evaluate the accuracy of our algorithm, we employ the Leave-one-out test. In each experiment we will perform 140 sub-experiments, and in the i^{th} sub-experiment, we input the i^{th} model as the input surface, and the remaining 139 models as training data into Algorithm 1 stated in section 3.6. Then we count the TPR, TNR and the classification accuracy over all the 140 sub-experiments.

There are several parameters in our algorithm. The first three are α , β and γ , the weighting function of shape index. We will test the effect of each of them on the accuracy of our model. By normalizing the shape index we can always assume $\gamma = 1$ if complex dilation is included and $\gamma = 0$ if not. The next parameter is the threshold cutting p_{cut} in the p-Value test, we will also check its contribution.

Among all experiments, our fundamental setup is:

$$\alpha = 3.05, \quad \beta = 0.35, \quad \gamma = 1.00, \quad p_{cut} = 0.03$$

In each experiment, we will vary each parameter one-by-one and show the above setup generates the best accuracy. By a set of 'good' parameters we mean the one that gives high TPR, TNR and total accuracy simultaneously, so that our algorithm is clinically effective.

Not only those parameters stated above may affect the effectiveness of our algorithm, but the total number of HP surfaces and the ratio of NC HP surfaces to AD HP surfaces may also be crucial factors. So the variation of the number of subjects used will also be included as one of our experiments.

After that, we plot the template mesh \tilde{S} with colors indicating the p-value at each vertex. This may help us further understand the geometric region being included in Ω by the p-value test.

Lastly, to further validate the accuracy of our algorithm (with the optimal parameters), we perform an evaluation of our model, which will be explained in detail in the corresponding sub-section.

4.1 The Energy Model Test

To begin with, we show the importance of each element in the shape index. The result is reported in table (1):

α	β	γ	TPR	TNR	Total accuracy
0	0.35	1.00	0.8687	0.7805	0.8429
3.05	0	1.00	0.8990	0.7805	0.8643
3.05	0.35	0	0.8586	0.5610	0.7714
3.05	0.35	1.00	0.9091	0.8049	0.8786

Table 1: Importance of each energy element (0 for excluding the corresponding element)

From the above, we see that including all three elements gives the highest accuracy. Among the three elements, the complex dilation plays the most important role in the classification model as without it, the accuracy drops the most significantly. The mean curvature and the Gaussian curvature are not that important but still helps to give a higher accuracy.

Our next goal is to investigate the effect of varying the weighting of each element. As discussed before, we always assume $\gamma = 1$ since this normalization of the shape index does not affect the algorithm. The result is reported in table (2) and (3). The graph of TA (total classification accuracy) versus alpha and versus beta are plotted in Figure (2).

α (mean curvature)	β (Gaussian curvature)	TPR	TNR	Total accuracy
0.00		0.8687	0.7805	0.8429
0.35		0.8687	0.7805	0.8429
0.80		0.8485	0.7561	0.8214
1.25		0.8586	0.7561	0.8286
1.70	0.35	0.8384	0.8049	0.8286
2.15		0.8586	0.7561	0.8286
2.60		0.8990	0.8049	0.8714
3.05		0.9091	0.8049	0.8786
3.50		0.8687	0.7805	0.8429

Table 2: Classification results with different α

α (mean curvature)	β (Gaussian curvature)	TPR	TNR	Total accuracy
	0.00	0.8990	0.7805	0.8643
	0.35	0.9091	0.8049	0.8786
	0.80	0.8990	0.8049	0.8714
	1.25	0.8889	0.8049	0.8643
3.05	1.70	0.8889	0.8049	0.8643
	2.15	0.8788	0.8049	0.8571
	2.60	0.8889	0.8049	0.8643
	3.05	0.8889	0.8049	0.8643
	3.50	0.8687	0.7805	0.8429

Table 3: Classification results with different β



Fig. 2: Plot of TA (total accuracy) versus α and β

From the results we see that $\alpha = 3.05, \beta = 0.35, \gamma = 1.00$ give rise to the best overall performance.

4.2 The Threshold Test

It now comes to the investigation of p_{cut} . By setting $\alpha = 3.05$, $\beta = 0.35$, $\gamma = 1.00$, we vary p_{cut} evenly with step size 0.01 and perform leave-one-out experiment each time. Note that smaller p_{cut} means a stricter decision that less vertices are included in Ω . And on the contrary if p_{cut} is large, more vertices can be included Ω but too many feature points may weaken the significance of those critical vertices. Therefore, a balance is needed and this is the role of p_{cut} .

The result is recorded in table (4).

p_{cut}	TPR	TNR	Total accuracy	p_{cut}	TPR	TNR	Total accuracy
0.01	0.8788	0.8049	0.8571	0.11	0.9192	0.5366	0.8071
0.02	0.8586	0.8049	0.8429	0.12	0.9293	0.5122	0.8071
0.03	0.9091	0.8049	0.8786	0.13	0.9293	0.5366	0.8143
0.04	0.8788	0.7805	0.8500	0.14	0.9293	0.5366	0.8143
0.05	0.8788	0.7317	0.8357	0.15	0.9192	0.5366	0.8071
0.06	0.8687	0.6829	0.8143	0.16	0.9192	0.5366	0.8071
0.07	0.8586	0.5610	0.7714	0.17	0.9192	0.5366	0.8071
0.08	0.9192	0.5854	0.8214	0.18	0.9192	0.5366	0.8071
0.09	0.9596	0.5854	0.8500	0.19	0.9394	0.5366	0.8214
0.10	0.9596	0.5854	0.8500	0.20	0.9697	0.5366	0.8429

Table 4: Classification results with different p_{cut}



Fig. 3: Plot of TA versus different p_{cut}

From the table we see that choosing $p_{cut} = 0.03$ gives the best accuracy. Therefore p_{cut} is set to be 0.03. This means that any vertex on a registered HP surface must have p-value \tilde{p}_j less than or equal to 0.03 so that it is extracted as feature points under the p-value test. About 1,600 vertices out of total 6,002 vertices are selected as feature points under the setting $p_{cut} = 0.03$. Also, from the graph in Figure (3), we record a gradual decline in overall performance of our algorithm in increasing p_{cut} , declaring more points to be feature points. Hence, a loose restriction on feature points selection does worsen the accuracy. Nevertheless, a very strict restriction may also have negative effect, as shown in Figure (3).

We also validate the importance of this threshold cutting. If we do not perform p-value test and take every vertex as feature points, under the experiment with the same setting, TPR=0.9495, TNR=0.4390, and total accuracy=0.8000. Clearly the accuracy of our algorithm when employing feature selection dominates that when all points are included in the significant region Ω . In particular, TNR falls sharply to less than 0.5. Therefore, the threshold cutting is necessary to our algorithm.

4.3 The Database Test

In all of the above tests, we note that TNR is always lower than TPR. While TPR can often pass through 0.85 under different parameters setting, TNR seems to face resistance getting over 0.80. To evaluate this observation, we note that on one hand, we have near 100 NC HP subjects, but on the other hand we do not even have 50 AD HP subjects. We believe that this great bias in our pool of models is the most contributing factor. So to validate our assertion, we are going to test the effect of this proportion to the classification accuracy of our model. Since we have just a few AD HP models, we will vary the size of NC HP models from 10 to 90 with step size 10 each time, and finally the whole database is used. The ratio of NC HP models to AD HP models varies from around 1:4 to around 2:1, and the total number of models involved varies from 51 to 140. The result is recorded in table (5).

No. of NC HP	No. of AD HP	TPR	TNR	Total accuracy
10		0.6000	0.9756	0.9020
20		0.5500	0.9512	0.8197
30		0.7333	0.8049	0.7746
40	41	0.7750	0.8049	0.7901
50		0.8800	0.8293	0.8571
60		0.8500	0.8293	0.8416
70		0.9000	0.8049	0.8649
80		0.8625	0.7805	0.8347
90		0.8556	0.7561	0.8244
99		0.9091	0.8049	0.8786

Table 5: Classification results with different numbers of HP models used



Fig. 4: Plot of TA versus different number of HP models used

From the result, two conclusions can be made. Firstly, the ratio of the two types of HP models used is crucial to the performance of our algorithm. When the number of AD HP models is far more than that of NC HP models, TPR is significantly lower than TNR, which is almost 1.00. Another conclusion is that the total number of models used also affect much. As the total number of models used increases, the performance of our algorithm comes better and more stable. The result shows that if more sample models are available, the total accuracy of our algorithm can be further boosted up.

4.4 The p-value region

In this sub-section, we want to understand the locations of feature points being chosen in our classification model. We plot the template mesh \tilde{S} with colors indicating the p-value at the corresponding vertex in Figure (5).



(c) Feature points highlight (front view)

(d) Feature points highlight (back view)

Fig. 5: Color-map of HP surface indicating p-values at each vertex

Figure 5(a) and (b) shows a smooth color plot of the p-value at each vertex from the front view and back view respectively. (c) and (d) shows the highlighting (in red) showing vertices with p-values less than 0.03 from the front view and back view respectively.

4.5 Evaluation of our model

In this section, we want to further evaluate the classification accuracy of our algorithm. Recall that we have altogether 140 subjects in our database. We perform 140 experiments, and in the *i*-th experiment, we remove the *i*-th subject out of our database, and use the remaining 139 subjects to do a leave-one-out test. So ultimately we would have done 140 leave-one-out testes. We compute the statistical distribution of these 140 classification accuracy values. Figure (6) shows the histogram of the 140 values. The mean, median and standard deviation are 0.8720, 0.8777 and 0.0081 respectively and the 95% confidence interval is (0.8707, 0.8734).



Fig. 6: Histogram of the classification accuracy of our algorithm under the optimal parameters

5 Comparison with other classification models

In our work, a simple L^2 classification model is applied to classify the HPs into NC and AD groups. In this section, we investigate the classification accuracies when other classical classification models are used, namely, 1. K-mean clustering and 2. Support Vector Machine (SVM) clustering.

5.1 K-mean Clustering

In this subsection, we modify our algorithm using the K-mean clustering, and compare this with our original algorithm.

Now, with $\alpha = 3.05$, $\beta = 0.35$, $\gamma = 1.00$ and $p_{cut} = 0.03$, we set $K_{NC} = 2$ and $K_{AD} = 2$. The accuracy varies the size of NC HP data is recorded in table (6) and in Figure (7).

From the result, the K-mean clustering method is worse than the L^2 classification model only when large number of NC HP models are included. However, as discussed above, this may probably be caused by the unbalanced data size. When the size of two data set are more balanced, the overall performance of the modified algorithm is significantly better than the original one. This motivates us to use the K-mean clustering instead of the simple L^2 classification when a large balanced data set is available.

No. of NC HP	No. of AD HP	TPR	TNR	Total accuracy
10		0.9000	0.9756	0.9608
20		0.8500	0.9268	0.9016
30		0.8333	0.8293	0.8310
40	41	0.8750	0.8537	0.8642
50		0.9200	0.8537	0.8901
60		0.8833	0.8049	0.8515
70		0.8714	0.8293	0.8559
80		0.8750	0.6585	0.8017
90		0.8444	0.6829	0.7939
99		0.8687	0.6829	0.8143

Table 6: Classification results with different numbers of HP models used (K-mean clustering)



Fig. 7: Plots of TA versus different numbers of HP models using L^2 classification and K-mean clustering

5.2 SVM clustering

In this sub-section, we tried to apply the famous SVM clustering to modify our algorithm.

As in the above, we set $\alpha = 3.05$, $\beta = 0.35$, $\gamma = 1.00$ and $p_{cut} = 0.03$ and this yields the following results in table (7) when we vary the size of our database.

No. of NC HP	No. of AD HP	TPR	TNR	Total accuracy
10		0.8000	0.9756	0.9412
20		0.8500	0.9024	0.8852
30		0.8667	0.8293	0.8451
40	41	0.9000	0.8780	0.8889
50		0.8800	0.8293	0.8571
60		0.8667	0.8293	0.8515
70		0.8429	0.7073	0.7928
80		0.8625	0.6829	0.8616
90		0.8556	0.6341	0.7863
99		0.8687	0.6585	0.8071

Table 7: Classification results with different numbers of HP models used (SVM clustering)

From the result, we see that SVM clustering allows our algorithm to reach higher total accuracy when the database has quite balanced data. When the number of NC HP models used are closed to the number of AD HP models used, the total accuracy generated by employing the simple L^2 classification is generally worse than that using SVM clustering. As the size of the database increases, the accuracy using SVM



Fig. 8: Plots of TA versus different numbers of HP models using L^2 classification and SVM clustering

clustering method seems to decline, but this is more likely to be a drawback of the unbalanced database instead of a defect or limitation of the SVM clustering. Therefore, similar as in the situation using the K-mean clustering, we are motivated by this result to replace the simple L^2 classification method by the more advanced SVM clustering method, provided once again we have a larger and balanced data size.

6 Conclusion and Future Work

In this paper, we proposed a quasi-conformal based statistical shape analysis model on hippocampal surfaces to study Alzheimer disease. Given a set of HP surfaces as training data, our algorithm computes the shape index, which measures local regional geometric changes including quasi-conformality and curvatures, on each vertex of the surface. Based on the shape index, an automatic algorithm is then built, using machine learning methods, to classify any newly imported HP surface into either NC or AD group. Experimental results show that, in particular, the quasi-conformality plays a crucial role in the classification accuracy of our proposed model. According to the results, the maximal total classification accuracy of our algorithm is 87.86%. In addition, the results show there is a possibility to further boost up the classification accuracy of our algorithm using more advanced clustering methods, provided that the database is balanced and large enough.

There are several directions which are still under investigation. Firstly, our current algorithm fixes the parameters, such as α and β in defining E_{shape}^i and p_{cut} . In the future, we aim to develop an algorithm to simultaneously search for the optimal parameters in our classification model. Secondly, the current classification algorithm utilizes a simple L^2 threshold clustering model. While this simple model together with the quasi-conformality gives reasonably satisfactory classification accuracy, a more advanced classification model may further boost up the classification accuracy. One of our future works will be to investigate more classification models and combine them into our current model to improve the performance of our method. Finally, we will examine our method on a larger and more balanced dataset.

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