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# Unified Statistical Approach to Cortical Thickness Analysis

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## Introduction

We present a unified image processing and analysis framework for cortical thickness in characterizing a clinical population. Due to the convoluted non-Euclidean surface geometry, data smoothing and analysis on the cortex are inherently difficult. When measurements lie on a curved surface, it is natural to assign kernel smoothing weights based on the geodesic distance along the surface rather than the Euclidean distance. We present a new data smoothing framework that addresses this problem implicitly without computing the geodesic distance.

## Cortical thickness

The two surfaces that bound the gray matter in the human brain are extracted from magnetic resonance images (MRI). The distance between the two surfaces is usually referred as the *cortical thickness* (Figure 1). The details of extracting the cortical surfaces can be found in [2, 3, 4].

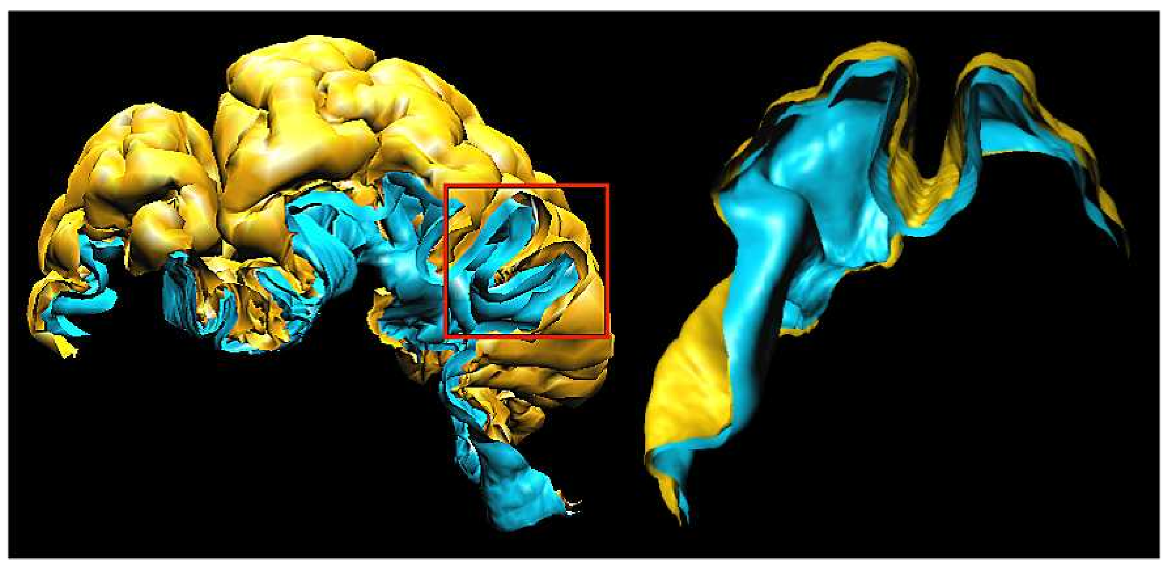

Figure 1: Left: part of the cortex showing the outer and inner surface that bound gray matter. Right: enlargement of the boxed region. The cortical thickness measures the distance between outer and inner surfaces.

## Surface registration

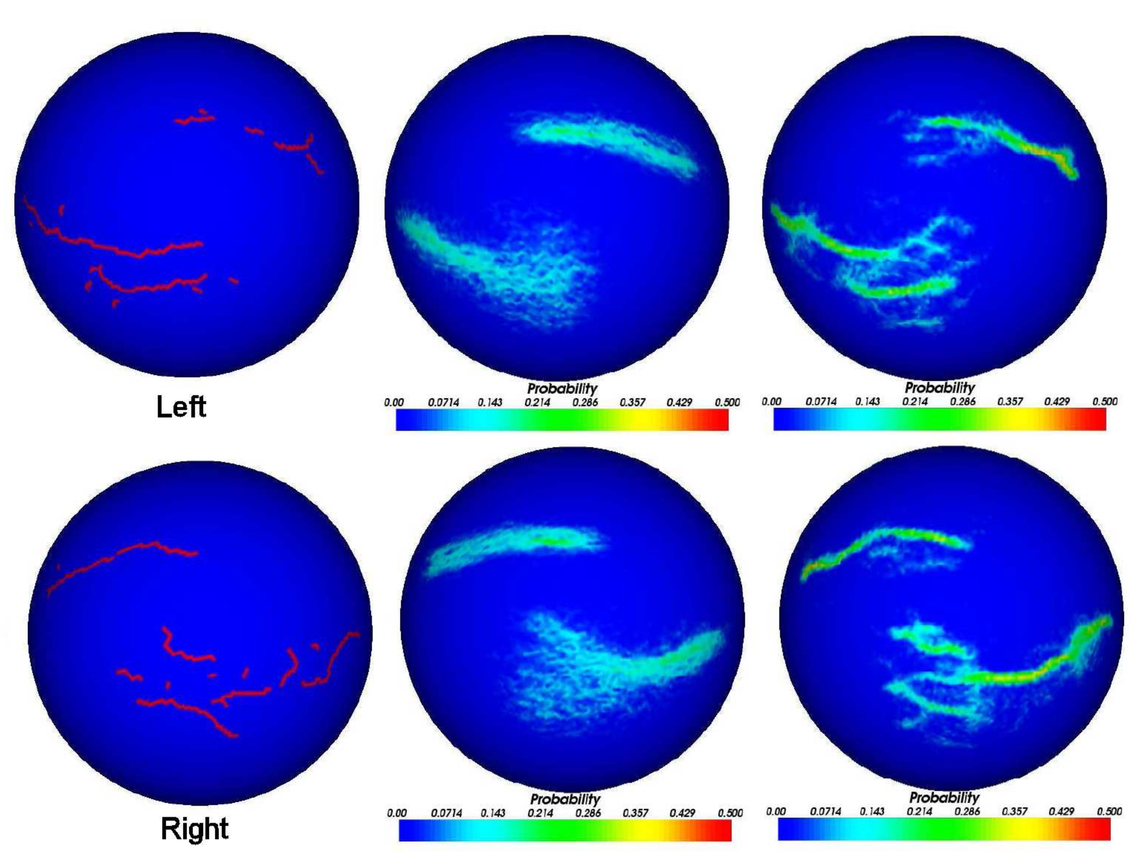


Figure 2: Demonstration of surface registration. Automatically generated traces of the central and superior temporal sulcal fundi are normalized on the unit sphere [2]. The first column shows the traces generated for the template surface. The second column shows the probability of sulcal matching based on 149 normal subjects before any surface normalization. The third column shows the probability after surface normalization.

Spatial normalization of the surfaces is necessary to facilitate vertex-by-vertex inter-subject thickness comparison. The surface deformation field from one surface to the template surface is obtained by minimizing an objective function that measures the global fit of two surfaces, while maximizing the smoothness of the deformation in such a way that the pattern of gyral ridges are matched smoothly. The detail can be found in [2].

## Heat kernel smoothing

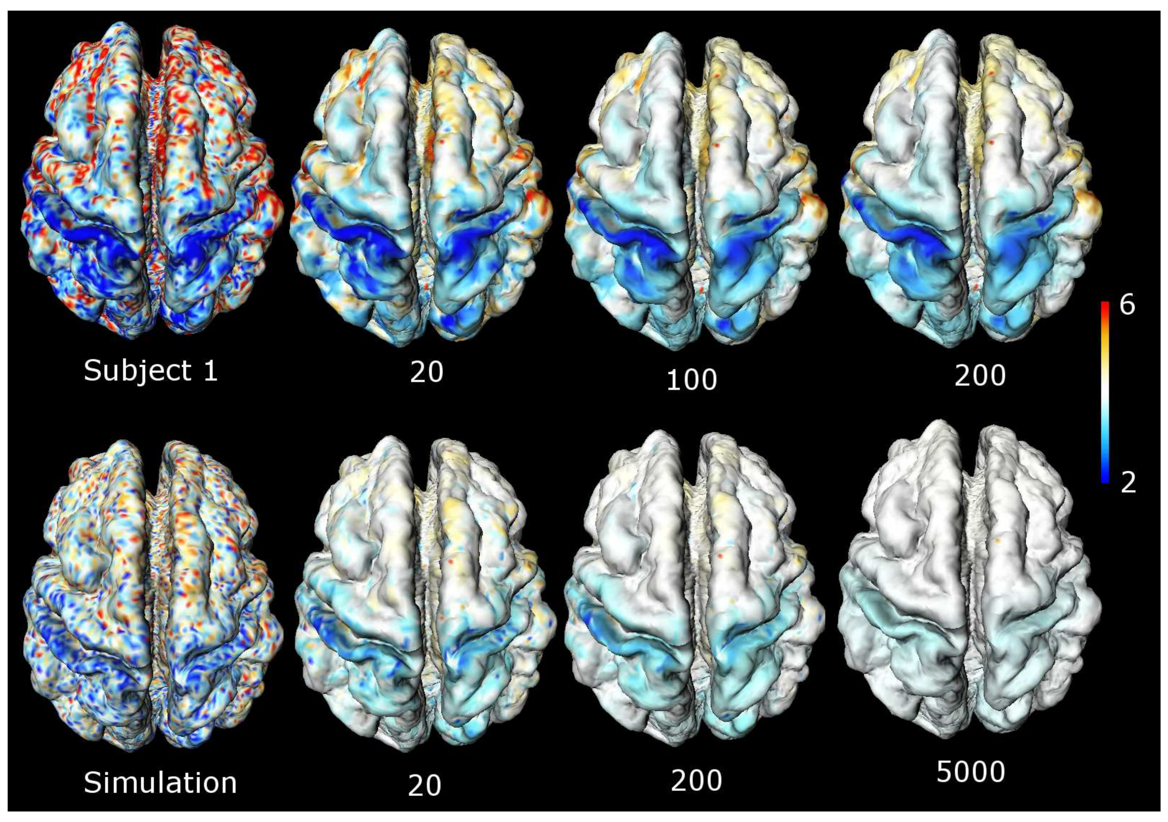


Figure 3: Top: Heat kernel smoothing of cortical thickness with $\sigma = 1$ and $k = 20, 100, 200$ iterations. Bottom: Heat kernel smoothing on simulated data with $\sigma = 1$ and $k = 20, 200, 5000$ iterations.

The cortical thickness measurements are always contaminated with noise. In order to increase the signal-to-noise ratio, new surface-based smoothing called *heat kernel smoothing* is developed [2]. Observations $Y$ measured on the cortex $\partial\Omega$ is assumed to follow the additive model of true signal $\theta$ plus noise $\epsilon$:

$$Y(p) = \theta(p) + \epsilon(p), p \in \partial\Omega.$$

Then we estimate $\theta$ using *heat kernel smoothing*:

$$\widehat{\theta}(p) = K_\sigma * Y(p) = \int_{\partial\Omega} K_\sigma(p,q) Y(q)\, d\mu(q),$$

where $\mu(q)$ is the surface measure and $K_\sigma$ is the heat kernel with bandwidth $\sigma$ [2]. This is a more efficient technique than *diffusion smoothing* [1, 3, 4]. In the diffusion smoothing formulation, the isotropic diffusion equation

$$\frac{\partial f}{\partial t} = \nabla f, f(p,0) = Y(p)$$

is solved via the finite element method on the cortex [3, 4]. $K_\sigma * Y$ is the solution of the diffusion equation after time $t = \sigma^2/2$.
For small $\sigma$ we approximate $K_\sigma$ by the *parametrix expansion* [5]:

$$K_\sigma(p,q) = \frac{1}{(2\pi\sigma)^{1/2}} e^{-\frac{d^2(p,q)}{2\sigma^2}} \big[u_0(p,q) + O(\sigma^2)\big],$$

where $d(p,q)$ is the geodesic distance between $x$ and $y$ and $u_0(p,q) \to 1$ as $p \to q$.

For large $\sigma$, the smoothing is performed by iteratively with a smaller bandwidth:

$$K_{\sqrt{k}\sigma} * Y = \underbrace{K_\sigma * \cdots * K_\sigma}_{k \text{ times}} * Y.$$

The MATLAB implementation can be found in http://www.stat.wisc.edu/ ~mchung/hk/hk.html.

## Statistical inference on manifolds

As an illustration, we have applied the method in detecting the regions of abnormal cortical thickness in 16 high functioning autistic children. We set up a general linear model (GLM) on cortical thickness $Y_j$ for subject $j$:

$$K_\sigma * Y_j(p) = \lambda_1(p) + \lambda_2(p)\cdot \mathtt{age}_j + \lambda_3(p)\cdot \mathtt{volume}_j + \beta(p)\cdot \mathtt{group}_j + \epsilon_j,$$

where $\mathtt{group}_j$ is 1 for an autistic subject and $0$ for a normal subject. $\mathtt{volume}_j$ is the total gray matter volume and $\mathtt{age}_j$ is the age. Then we test the group difference by performing a hypothesis testing:

$$H_0 : \beta(p) = 0 \text{ for all } p \in \partial\Omega$$

v.s.

$$H_1 : \beta(p) \neq 0 \text{ for some } p \in \partial\Omega.$$

Based on $F$ random field $F(p)$, the test statistic $\sup_{p\in\partial\Omega} F(p)$ is used to compute the $p$-value corresponding to the above multiple hypotheses.

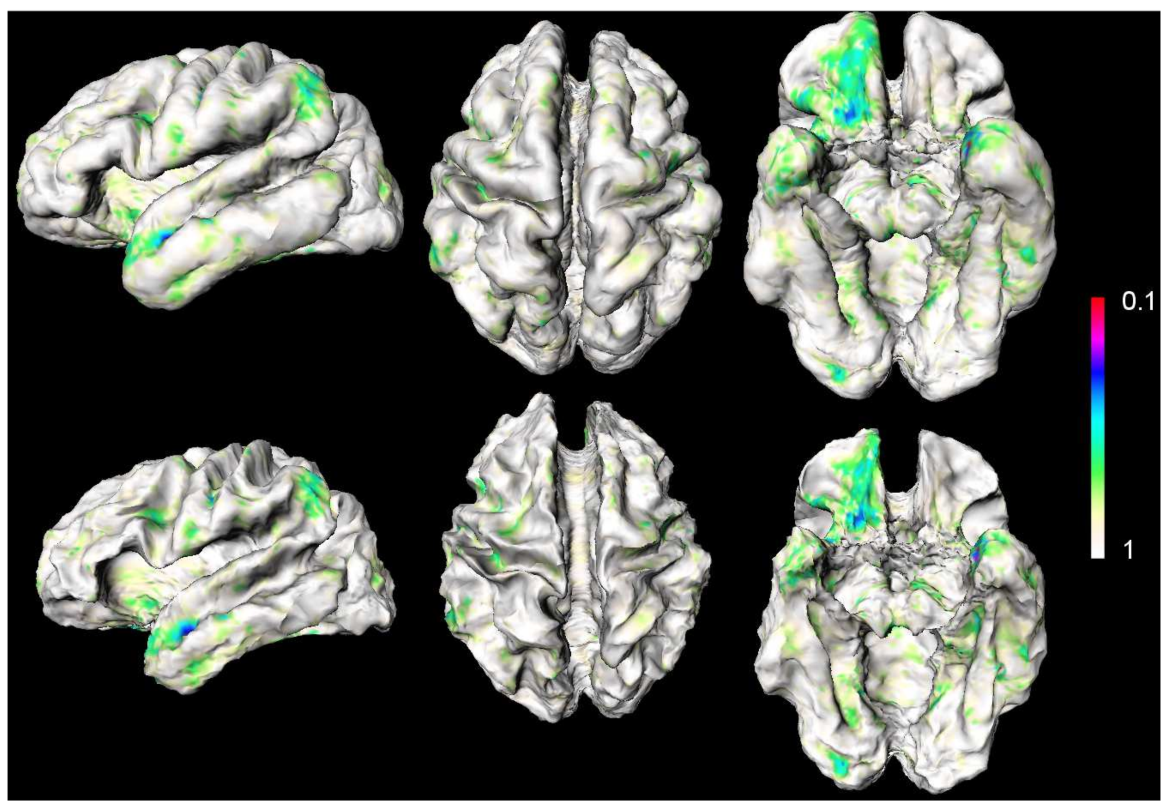


Figure 4: Corrected $p$ value maps of $F$-test removing the effect of age and relative gray matter volume difference projected onto the average outer (top) and inner surfaces (bottom). It shows relatively asymmetric thickness difference between two groups.

## References

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