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A novel cortical thickness estimation method based on volumetric Laplace–Beltrami operator and heat kernel ☆

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ABSTRACT

Cortical thickness estimation in magnetic resonance imaging (MRI) is an important technique for research on brain development and neurodegenerative diseases. This paper presents a heat kernel based cortical thickness estimation algorithm, which is driven by the graph spectrum and the heat kernel theory, to capture the gray matter geometry information from the *in vivo* brain magnetic resonance (MR) images. First, we construct a tetrahedral mesh that matches the MR images and reflects the inherent geometric characteristics. Second, the harmonic field is computed by the volumetric Laplace–Beltrami operator and the direction of the steamline is obtained by tracing the maximum heat transfer probability based on the heat kernel diffusion. Thereby we can calculate the cortical thickness information between the point on the pial and white matter surfaces. The new method relies on intrinsic brain geometry structure and the computation is robust and accurate. To validate our algorithm, we apply it to study the thickness differences associated with Alzheimer's disease (AD) and mild cognitive impairment (MCI) on the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. Our preliminary experimental results on 151 subjects (51 AD, 45 MCI, 55 controls) show that the new algorithm may successfully detect statistically significant difference among patients of AD, MCI and healthy control subjects. Our computational framework is efficient and very general. It has the potential to be used for thickness estimation on any biological structures with clearly defined inner and outer surfaces.

1. Introduction

Alzheimer's disease (AD) is the most common form of cognitive disability in older people. With the population living longer than ever before, AD is now a major public health concern with the number of affected patients expected to triple, reaching 13.5 million by the year 2050 in the U.S. alone (Alzheimer's Association, 2012). It is commonly agreed that an effective presymptomatic diagnosis and treatment of AD could have enormous public health benefits (Sperling et al., 2011). Brain imaging has the potential to provide valid diagnostic biomarkers of AD risk factors and preclinical stage AD (Caselli and Reiman, 2013; Langbaum et al., 2013). Despite major advances in brain imaging used to track symptomatic patients (as reviewed in Chung, 2012), there is still a lack of sensitive, reliable, and accessible brain imaging algorithms capable of characterizing abnormal degrees of age-related cerebral atrophy, as well as accelerated rates of atrophy progression in preclinical individuals at high risk for AD for whom early intervention is most needed.

In AD research, structural magnetic resonance imaging (MRI) based measures of atrophy in several structural measures, including whole-brain (Fox et al., 1999; Chen et al., 2007; Stonnington et al., 2010; Thompson et al., 2003), entorhinal cortex (Cardenas et al., 2011), hippocampus (den Heijer et al., 2010, 2003, 1998, 2004, 2010, 2011, 2013a), and temporal lobe volumes (Hua et al., 2010), as well as ventricular enlargement (Jack et al., 2003;

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Wang et al., 2011) correlate closely with changes in cognitive performance, supporting their validity as markers of disease progression (as reviewed in Braskie and Thompson, 2013). As one of major AD symptoms on clinical anatomy, the partial atrophy in the cerebral cortex of the patients is a biomarker of AD progress (Braak and Braak, 1991). To check and monitor the cortical atrophy, a number of research has been focused on an accurate estimation of cortical thickness (e.g. MacDonald et al., 2000; Fischl and Dale, 2000; Jones et al., 2000; Miller et al., 2000; Kabani et al., 2001; Chung et al., 2005; Kochunov et al., 2012). However, the MRI imaging measurement of cortical thickness, e.g. medial temporal atrophy, is still not sufficiently accurate on its own to serve as an absolute diagnostic criterion for the clinical diagnosis of AD at the mild cognitive impairment (MCI) stage (Frisoni et al., 2010).

According to geometric properties of the measurement tools, the cortical thickness estimation methods can be broadly divided into two categories: based on either surface or voxel characteristics (as reviewed in Clarkson et al., 2011). The measurement methods based on the surface features are aimed to establish triangular mesh models in accordance with the topological properties of the inner and outer surfaces, and then use the deformable evolution model to couple the two opposing surfaces. The thickness is defined as the value of the level set propagation distance between the two surfaces. This measurement accuracy can reach the subpixel level but requires constantly correcting the weights of various evolutionary parameters to ensure the mesh regularity. Sometimes the model cannot work in the highly folding regions such as the sulci. Various approaches were proposed to address this problem and increase the thickness estimation accuracy in the high curvature areas. For example, Mak-Fan and colleagues modeled the sulci regional by adding the cortex thickness constraints (Mak-Fan et al., 2012). Fischl and Dale (2000) proposed to model the middle part of the sulci by imposing the self-intersection constraints. Overall, although better measurement results are achieved, the computation cost is generally high (Dahnke et al., 2013). In contrast, the voxel-based method is the measurement on a three-dimensional cubic voxel grid. The voxel-based measurement acquires the cortical thickness information by solving partial differential equations in the potential field, for example, Jones et al. (2000) first used the Laplace equation to characterize the layered structure of the volume between the inner and outer surfaces and obtained the stream line. This method is known as the *Lagrangian method*. Hyde et al. (2012) proposed the Euler method by solving the one-order linear partial differential equations for thickness calculation which can improve the computation efficiency. The advantages of such an approach include: (1). there is no correction of the mesh topology regularity, so the calculation is simple (Cardoso et al., 2011; Das et al., 2009); (2). the computational model is rigorous and stable. The main disadvantage of the voxel-based estimation method is the computational inaccuracy on the discrete grid. The limited grid resolution affects the accuracy of the thickness measurement (Das et al., 2009). This problem is alleviated only recently. For example, Jones and Chapman (2012) used the boundary topology to initialize a sub-voxel resolution surface and correct the direction of the stream line. This method can increase the measurement accuracy.

From the above discussion, in order to improve the computational efficiency and the degree of automation, one may expect the choice of voxel-based measurement algorithm is more feasible. However, we should overcome the defect of the limited grid resolution which cannot precisely characterize the curved cortical surfaces from MR images. This point will be discussed in Discussion Section. A desired 3D model should achieve a good fitting for the cerebral cortex morphology and facilitate an effective computation on the subvoxel resolution. In this paper, we propose to use tetrahedral mesh (Cassidy et al., 2013) to model the volume between inner and outer cortical surface. For thickness estimation, we adopt the tetrahedral mesh based Laplace–Beltrami operator proposed in our prior work (Wang et al., 2004a), which has been frequently adopted by volumetric shape analysis research (Wang et al., 2004b; Li et al., 2007; Tan et al., 2010; Pai et al., 2011; Li et al., 2010; Paillé and Poulin, 2012; Wang et al., 2012a; Xu et al., 2013a; Li et al., 2013). Generally speaking, the tetrahedral mesh access is time consuming. We extend the half-edge data structure (Mäntylä, 1988) to a half-face data structure for an efficient geometric processing.

Based on spectral analysis theory, we further propose to compute a heat kernel (Hsu, 2002) based method to trace the streamlines between inner and outer cortical surfaces and estimate the cortical thickness by computing the streamline lengths. Mathematically speaking, diffusion kernels (Coifman et al., 2005b) express the transition probability by random walk of t steps, $t \geqslant 0$. It allows for defining a scale space of kernels with the scale parameter t. Such heat kernel-based spectral analysis induces a robust and multi-scale metric to compare different shapes and has strong theoretical guarantees. In recent years, surface based heat kernel methods have been widely used in computer vision and medical image analysis (Chung et al., 2005; Sun et al., 2009; Chung, 2012; Joshi et al., 2012; Lombaert et al., 2012; Litman and Bronstein, 2014), such as functional and structural map smoothing(Qiu et al., 2006a; Qiu et al., 2006b; Shi et al., 2010; Shi et al., 2013b), classification (Bronstein and Bronstein, 2011), and registration (Sharma et al., 2012). However, 3D heat kernel methods are still rare in medical image analysis field. Some pioneering work (Raviv et al., 2010; Rustamov, 2011) used regular grids to compute the heat kernel and their work usually suffered numerical inaccuracies along the surface boundaries. Based on the volumetric Laplace–Beltrami operator, our heat kernel computation is more accurate and the estimated cortical thickness is well-defined, and should reflect the intrinsic 3D geometrical structure better than thickness derived from a simple harmonic field (Jones et al., 2000), and hence facilitate consistent cross-subject comparisons.

In our experiments, our pipeline is applied on MR images from Alzheimer's Disease Neuroimaging Initiative (Mueller et al., 2005; Jack et al., 2008, ADNI). Our data set consists of: 51 patients of Alzheimer's disease (AD), 45 patients of mild cognitive impairment (MCI) and 55 healthy controls. We use FreeSurfer software (Fischl et al., 1999a) for preprocessing. We use Student's t test and False Discovery Rate (FDR) (Benjamini and Hochberg, 1995) for performance evaluation. We set out to test whether our proposed method provides a computationally efficient and statistically powerful cortical thickness solution.

Fig. 1 summarizes our overall sequence of steps used to compute cortical thickness. First, from MR images, we used FreeSurfer to segment and build white matter and pial cortical surfaces (the first and second row). We model the inner volume with a tetrahedral mesh with a triangle surface as it boundary (the third row). Then we apply volumetric Laplace–Beltrami operator to compute the harmonic field and build isothermal surfaces on the obtained harmonic field. Between neighboring isothermal surfaces, we compute heat kernel and estimate the streamline by tracing the maximal heat transition probability. The thickness is then measured by the lengths of the streamlines between white matter and pial surfaces (the fourth row). Last, Student's t test is applied to identify regions with significant differences between any two of three groups and false discovery rate (FDR) (Nichols and Hayasaka, 2003) is used to assign global q-values (the fifth row), i.e., all group difference p-maps were corrected for multiple comparisons using the widely-used FDR method. For example, the FDR method decides whether a threshold can be assigned to the statistical map that keeps the expected false discovery rate below 5% (i.e., no more than 5% of the voxels are false positive findings).