NeuroImage 45 (2009) 867–879

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Registration based cortical thickness measurement

Sandhitsu R. Das [a,*], Brian B. Avants [a], Murray Grossman [b], James C. Gee [a]

[a] *Penn Image Computing and Science Laboratory (PICSL), Department of Radiology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA*
[b] *Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA*

ARTICLE INFO

Article history:
Received 24 July 2008
Revised 1 November 2008
Accepted 8 December 2008
Available online 25 December 2008

Keywords:
Cortex
Thickness
Diffeomorphism
Euclidean distance
Deformable models
Longitudinal
FTD

ABSTRACT

Cortical thickness is an important biomarker for image-based studies of the brain. A diffeomorphic registration based cortical thickness (DiReCT) measure is introduced where a continuous one-to-one correspondence between the gray matter–white matter interface and the estimated gray matter–cerebrospinal fluid interface is given by a diffeomorphic mapping in the image space. Thickness is then defined in terms of a distance measure between the interfaces of this sheet like structure. This technique also provides a natural way to compute continuous estimates of thickness within buried sulci by preventing opposing gray matter banks from intersecting. In addition, the proposed method incorporates neuroanatomical constraints on thickness values as part of the mapping process. Evaluation of this method is presented on synthetic images. As an application to brain images, a longitudinal study of thickness change in frontotemporal dementia (FTD) spectrum disorder is reported.

Introduction

A number of methodologies for cortical thickness measurements have appeared in neuroimaging literature over the past decade (Zeng et al., 1999; Miller et al., 2000; Jones et al., 2000; Fischl and Dale, 2000; Lohmann et al., 2003; Srivastava et al., 2003; Yezzi and Prince, 2003; Thompson et al., 2004; Lerch et al., 2005; Barta et al., 2005; Scott and Thacker, 2005; Hutton et al., 2008). Nonetheless, no *gold standard* has emerged that one can evaluate a measurement against. One reason is the difficulty of manually measuring thickness values in 3D images, unlike tissue segmentation where voxel-by-voxel manual marking can serve as a gold standard. Thickness measured directly using post-mortem brains is also not considered an absolute metric because of possible tissue shrinkage. What complicates matters more is the lack of a consistent definition of cortical thickness. Some methods require explicit point associations between the white matter (WM)/gray matter (GM) surface and the GM/cerebrospinal fluid (CSF) surface. Some of these methods also require explicit construction of surface meshes (Fischl and Dale, 2000; MacDonald et al., 2000), typically using the extracted WM surface as a model that is fit to the GM surface by deformation, thus establishing node-to-node associations. Alternatively, definitions of thickness based on nearest point (Miller et al., 2000; Fischl and Dale, 2000) and distance along the surface normal (Das et al., 2007) do not require explicit point associations. However, regardless of whether a given method requires *a priori* correspondence maps or not, eventual computation of thickness is always based on some measure of distance between two points. This range of work points to a common definition of thickness that is based on two components: first, a *principled point correspondence* and, second, a *distance measure* between the points. Theoretical distinctions between algorithms occur in the definition of correspondence and/or the distance measurement between corresponding points. Practical differences usually occur in the underlying data representation.

Some researchers have argued that methods that require explicit surface extraction may suffer from inaccuracies due to surface generation (Srivastava et al., 2003; Thompson et al., 2005). One popular class of methods that establishes *a priori* point-to-point correspondence, without an explicit surface representation, is the gamut of PDE based methods (Jones et al., 2000; Yezzi and Prince, 2003; Rocha et al., 2007). Jones et al. (2000) models the cortical mantle as a dielectric and solves Laplace's equation to compute electric field lines through the cortex in order to establish correspondence. There are still other image-based methods that rely on image operations such as morphological filters (Lohmann et al., 2003), geodesic distance transform (Srivastava et al., 2003), edge detection (Scott and Thacker, 2005) or explicit geometric modeling of the cortical sheet (Barta et al., 2005). The method introduced here is also image-based, but uses diffeomorphic image registration based point-to-point correspondence.

One important feature of computational methods in neuroanatomy is the ability to include prior knowledge about the anatomy of interest. Such constraints increase reliability and performance in the presence of noise and when image resolution is sub-optimal. von Economo (1929) reported cortical thickness to be between 1.2–4.5 mm from *ex vivo* measurements, and ≈5 mm is generally reported to be the maximum observed value from *in vivo* measurements (Fischl and

* Corresponding author. 3600 Market Street, Suite 370, Philadelphia, PA 19104, USA.
E-mail address: sudas@seas.upenn.edu (S.R. Das).

1053-8119/$ – see front matter
doi:10.1016/j.neuroimage.2008.12.016

Dale, 2000; Kabani et al., 2001; Hutton et al., 2002). Some surface reconstruction based methods employ proximity constraints on the distance between two surfaces to ensure thickness lies within an anatomic range (Zeng et al., 1999; MacDonald et al., 2000). However, many methods, including Jones et al. (2000), provide no inherent anatomically motivated constraints on the computation of thickness. Note that the method based on solving Laplace's equation within the cortical sheet provides thickness metrics based on curved paths. Such thickness values cannot be directly related to existing post-mortem knowledge, as provided by von Economo and others. Furthermore, straight-line/Euclidean distances are more easily interpreted in terms of a sheet-like model, as relevant for the cortex. Thus, the majority of thickness definitions use Euclidean distances that are consistent with what might be measured post-mortem. For these clinically relevant reasons – and for the purpose of using clinically motivated priors – we also focus on Euclidean distance as a thickness metric, though our technique applies as easily to curved thickness.

A related anatomical problem in thickness computation is the presence of *buried cortex*, which refers to the parts of the cortical surface hidden within the deep sulci. Within these sulci, thin strands of CSF are often mislabeled as GM due to partial volume effects, limited resolution and noisy tissue intensity levels. This mislabeling may lead to overestimation of thickness. Note that we use the terms *buried cortex* and *buried sulci* to refer to these regions of unresolved CSF, as has been used by other studies of cortical thickness (Kim et al., 2005; Hutton et al., 2008), as opposed to referring to the cortex in deep sulcal regions in general (with CSF separating the sulcal banks resolved or not) that is termed buried rather than cortex *visible on the outer surface*, as described in Van Essen et al. (1998); Rettmann et al. (2006). Several existing approaches explicitly address this problem: by image enhancement (Jones et al., 2000) to recover CSF, using morphological processing (Lohmann et al., 2003), stochastic modeling (Barta et al., 2005) and explicit image-based labeling of sulcal points (Hutton et al., 2002). The ACE method in Han et al. (2004) uses a level set based framework that corrects for buried sulci using fuzzy CSF membership information. Our own prior work introduced a novel topology preserving segmentation method (Das et al., 2007) that is able to recover some deep sulci. A similar method that does not preserve topology uses the Laplacian to measure thickness on segmentations with digitally recovered sulci (Hutton et al., 2008).

This paper introduces a new method, which we call Diffeomorphic Registration based Cortical Thickness (DiReCT). DiReCT reduces the problems of buried cortex and unconstrained thickness measurement by using a prior-constrained estimate of the distance between the gray/white interface and the gray/cerebrospinal fluid interface. This strategy, in essence, assigns a distance between opposing faces of a thin, sheet-like structure, here, the cortical mantle. Our approach begins with a hypothetical, infinitesimally thin, cortical mantle with ε thickness that lies along the white matter/gray matter interface. The initial model thus has "open" sulci. This thin cortical mantle is then allowed to expand under a one-to-one, differentiable and invertible map (a diffeomorphism) toward the edges of the data-derived gray matter probability. This mapping gives a correspondence field that allows an estimate of the gray/CSF tissue interface, and thus thickness. An overview of this process is depicted in Fig. 1.

The correspondence problem that we solve is made well-posed by the diffeomorphic constraint, which seeks a minimally deforming solution (Dupuis et al., 1998). The topology preservation provided by diffeomorphisms, along with explicit thickness priors, provide shape guidance to this mapping that prevent sulci from unfolding and neighboring banks of gray matter from intersecting. Thus, a maximum a posteriori estimate of the location of buried sulci is gained. Additionally, our thickness measures are guaranteed to stay within a range that is set by user-defined, spatially varying prior constraints. This shape-constrained mapping is able to represent buried sulci as infinitesimally close, opposing banks of gray matter, in the continuous domain, thus yielding sub-voxel resolution. Further, each gray matter bank is connected diffeomorphically to a unique white matter bank.

In summary, the advantage of our approach, relative to prior work, is that we directly use standard probabilistic segmentation maps – with no further processing – to make a continuous, sub-voxel estimate of cortical thickness, constrained by thickness priors and accurate within buried sulci, within a single algorithmic framework.

The rest of the paper is organized as follows. The Materials and methods section is divided into several subsections. First, various terminologies are introduced and the method for thickness computation

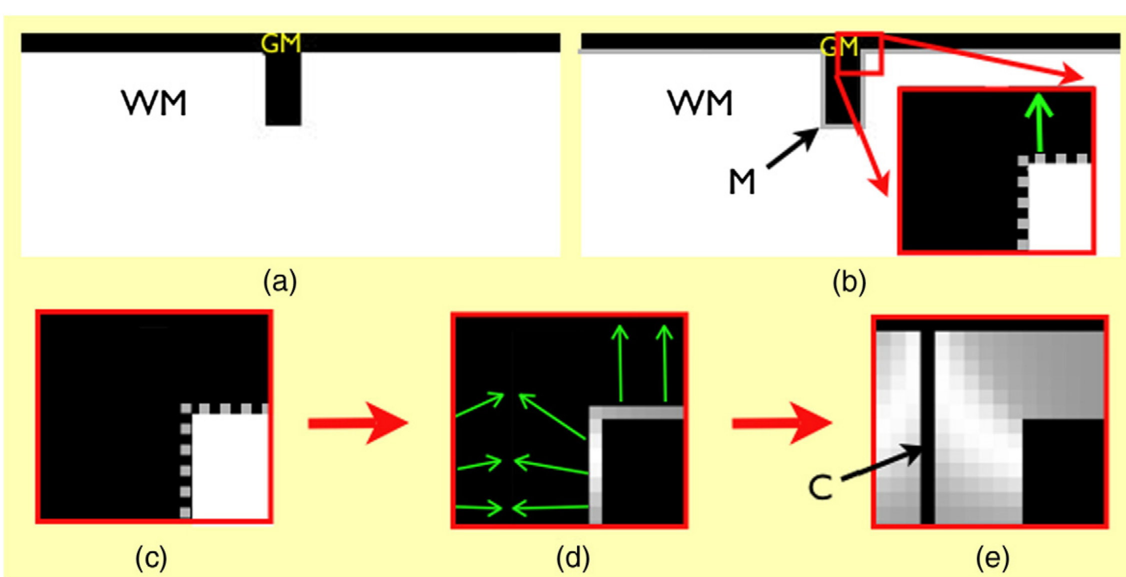

Fig. 1. Overview of proposed methodology. The original gray matter and white matter images are shown in (a). In (b), *M* is the initial cortical model, a thin (one voxel thick) sheet, with the inner edge at the gray/white interface, and the outer edge within gray matter. The region enclosed in red is zoomed in to show the initial model (also in (c)), in which *M* is represented as a gray dotted line. Panel (d) shows how the initial model is deformed to find the estimated gray/CSF interface, and establish point-to-point correspondences (green arrows). Gray levels at the gray/white interface denote the distance between corresponding points, which is the measure of thickness. The thickness values are propagated to the GM volume to generate the volumetric thickness map shown in (e), where *C* denotes the estimated location of gray/CSF interface.