Robust Cortical Thickness Measurement with LOGISMOS-B

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Abstract. Cortical thickness (CT) is an important morphometric measure that has implications for psychiatric and neurologic processes. We propose a novel approach for automatically computing CT in an accurate and robust manner using LOGISMOS-B: Layered Optimal Graph Image Segmentation of Multiple Objects and Surfaces for the Brain. LOGISMOS-B is a cortical surface segmentation method based on LOGISMOS graph segmentation and generalized gradient vector flows. We evaluate our method on two different datasets ($n = 83$ total). The results show that LOGISMOS-B is more accurate than the popular FreeSurfer (FS) method and provides more reliable thickness measurements across a variety of challenging images. LOGISMOS-B accurately recovers known CT patterns, both across cortical lobes and locally, such as between the banks of the central sulcus, in healthy subjects and MS patients. Manual landmarks indicate a signed surface distance of $0.081 \pm 0.447\text{mm}$ for WM and $0.018 \pm 0.498\text{mm}$ for LOGISMOS-B, compared to $0.263 \pm 0.452\text{mm}$ for WM and $-0.167 \pm 0.556\text{mm}$ for GM for FS, highlighting the surface placement accuracy of LOGISMOS-B. Finally, a regresion study shows that LOGISMOS-B provides strong correlation with age and plausible annual thinning rates across the cortex, with locally discerning thinning patterns, in agreement with the literature.

Keywords: LOGISMOS, cortical thickness, optimal multi-surface segmentation, cortical reconstruction, generalized gradient vector flow.

1 Introduction

Cortical thickness (CT) is an important morphometric measure used to describe the local thickness of the layers of the cerebral cortex. It has been implicated in many diseases and disorders, such as autism, schizophrenia and Huntington's disease. The longitudinal trajectory of CT in healthy development and aging is also of interest.

Despite its considerable significance in neuroscience, measurement of CT from in vivo MRI data is challenging. Manual CT measurements are time-consuming and often inaccurate and irreproducible, given the intrinsically 3-D nature of the CT measure and the highly folded anatomy of the human cerebral cortex. Volumetric and surface-based approaches have been developed for automated thickness analysis [1]. Volumetric approaches such as ANTS [16], Laplacian methods [6,13] and GAMBIT [17] often suffer from partial voluming effects. Surface-based approaches such as FreeSurfer (FS) [3], CLASP [8] and CRUISE [4] have to address the difficult and computationally expensive problem of resolving topological inconsistencies. Given the lack of a gold standard, validation of CT algorithms has to rely on either imperfect independent standards such as

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slice-based manual measurements, postmortem measurements and synthetic datasets, or indirect measures such as stability and power analysis.

One of the most common CT analysis tools is FreeSurfer. The cortical reconstruction in FS is based on a surface deformation method using a spring-like term for regularization and an intensity-based term for attracting the boundary to the desired intensity profiles [3]. Gradient descent is used for optimizing this deformation energy along with adaptive step sizes to avoid self-intersections. Once the white and gray matter (WM/GM) surfaces are reconstructed, the CT measurement is based on symmetric closest point matching. In particular, for each GM vertex v, the CT is given by:

$$Thickness(v) = \frac{d(v, f(v)) + d(f(v), g(f(v)))}{2}, \tag{1}$$

where $f(v)$ is the closest WM vertex to GM vertex v, $g(v)$ is the closest GM vertex to WM vertex v, and $d(a, b)$ is Euclidean distance between two points.

We propose a novel CT analysis approach based on the LOGISMOS graph segmentation framework [19] and its more recent LOGISMOS-B[1] variant for accurate cortical reconstruction [11], followed by Laplacian-based thickness measurement. LOGISMOS-B is an accurate and computationally efficient cortical segmentation approach that relies on generalized gradient vector flows for handling the complex geometry of the cortical surface. Paired with the theoretically appealing Laplacian-based thickness measurement method, our pipeline offers a robust CT analysis approach.

2 Methods

Our CT measurement pipeline consists of 3 main steps: 1) accurate cortical reconstruction using LOGISMOS-B, 2) thickness computation using the Laplace equation, and 3) atlas-based cortex parcellation for regional analysis.

2.1 Cortical Reconstruction with LOGISMOS-B

LOGISMOS-B is a recently reported [11] cortical reconstruction algorithm. The input consists of a single T1w image. This image is used for atlas-based tissue classification and bias-field correction using the BRAINSABC suite [7]. The tissue classification results are used for skullstripping. The brain is then split into hemispheres by detecting the plane of maximal symmetry. The WM tissue segmentation is topologically corrected by removing handles and holes, including subcortical structures, ventricles and artifacts.

This initial WM segmentation is used to build a properly-ordered multicolumn graph. The mesh representation of the WM segmentation forms the base graph in the LOGISMOS framework [19]. From each vertex of this base graph, a column is built to represent the local search space. The choice of the method for column construction is crucial for determining the behavior of the segmentation. Starting at each vertex of the base graph, LOGISMOS-B follows the streamlines of the generalized gradient vector flow (GGVF) [18] computed on the gradient f of the bias-corrected T1w image.

The GGVF field $\tilde{\mathbf{v}}$ is given by the equilibrium solution of $\mathbf{v_t} = g(|\nabla f|)\nabla^2\mathbf{v} - h(|\nabla f|)(\mathbf{v} - \nabla f)$. The smoothing term produces a smoothly varying vector field while

[1] B for Brain.

the data term penalizes against large deviations from the input. The weighting functions g and h are chosen to allow reduced smoothing near strong gradients, as in [18].

The WM and GM surfaces are treated as mutually interacting surfaces of the same object. In the LOGISMOS framework, this is represented by two copies of the same graph that are connected together. There are three types of arcs in this composite graph: the intra-column arcs provide the appropriate graph structure for the minimum-cost closed set algorithm, the inter-column arcs enforce surface smoothness constraints and inter-surface arcs enforce inter-surface separation constraints.

As an important extension of the original LOGISMOS-B approach [11], we newly incorporate regionally-dependent parameters in the form of anatomy-derived minimum surface separation constraints. For the regions that are known a priori to have thin cortices, we allow for a reduced minimum surface separation. In particular, for the visual cortex and the postcentral sulcus, among the thinnest in the cortex [2], the minimum inter-surface separation constraint was set to $2\mathrm{mm}$, while it was set to $2.5\mathrm{mm}$ for the rest of the brain. The definitions of regions for this purpose is obtained using an atlas-based approach. The atlas mapping created during the BRAINSABC tissue classification is used to carry the atlas labels to the subject space. Each graph column is assigned a label by considering the label at the pre-segmentation mesh vertex. If this point falls outside the cortex, then the label of a second node that corresponds to the minimum separation constraint between the two surfaces is considered. Any graph columns still without assigned labels are labeled via majority voting from neighboring columns.

Once the graph construction is complete, $s - t$ cut graph optimization is used for finding the minimum-cost closed set of this graph, which within the LOGISMOS framework is equivalent to optimal multi-surface segmentation. The cost functions reflect the gradient magnitude of the bias-corrected and smoothed T1w image for the WM surface, and a weighted sum of the first and second order gradients for the GM surface. Finally, the brainstem and cerebellum are removed using a mask mapped from the atlas.

2.2 Laplacian-Based Cortical Thickness Computation

When cortical surfaces are known, thickness computation methods based on the Laplace equation [6] proved both popular and relevant. In this volumetric approach, the Laplace equation is set up using the input WM and GM surfaces as boundary conditions ($u(x) = 1$ and $u(x) = -1$, respectively), such that $\nabla^2 u(x) = 0$. The smooth gradient of u, $v = \frac{\nabla u}{||\nabla u||}$ is used to compute streamlines, which are guaranteed to not intersect each other and provide a one-to-one correspondence between the two surfaces. The length of each streamline is reported as the thickness measurement.

In particular, we use an implementation of the approach described in [13], which uses a boundary element method (BEM) approach for improved accuracy. We scan-convert the final LOGISMOS-B surfaces, with the brainstem and cerebellum intact, to high-resolution ($0.5\mathrm{mm}$) images to use as input for this purpose. The CT measurements are pulled back to the final surfaces (after the removal of the brainstem and cerebellum) by looking up thickness values at the GM mesh vertex locations; in case these vertices fall outside the valid domain (due to discretization), the corresponding WM mesh vertex is used instead. Keeping the brainstem and cerebellum in place for the thickness computation prevents any topological defects or sharp features at the removal site and provides a more stable thickness measurement for the cortical areas in this region.

2.3 Regional Parcellation

In order to facilitate regional CT measurements, we create a parcellation of the cortex into regions of interest (ROI's), again using the atlas ROI's mapped to the subject space. While a coarse parcellation is previously computed during the graph construction, this is done in the absence of the final surface reconstructions and is therefore prone to errors. After the LOGISMOS-B segmentation is finalized, cortical parcellation labels are improved by considering the final WM and GM vertices for label assignment.

3 Experimental Methods

Datasets. The first dataset from Johns Hopkins University (JHU)[2] [15] has an isotropic resolution of $(1\text{mm})^3$ for the healthy controls ($n = 5$) and $(0.83\text{mm})^3$ for the MS patients ($n = 5$). Manual landmarks are identified by 2 independent raters in 7 clusters on both WM and GM surfaces. Each cluster (calcarine, central sulcus, cingulate, parieto-occipital, sup. frontal, sup. temporal, Sylvian fissure) has 30 landmarks per hemisphere. A total of $7\ \text{clusters} \times 2\ \text{hemispheres} \times 2\ \text{surfaces} \times 30\ \text{landmarks} \times 2\ \text{raters} = 1680$ landmarks are available per subject, or 16,800 landmarks total. The second dataset consists of 73 healthy subjects from the publicly available IXI[3] database, collected at the IoP in London. These images have a resolution of $0.937 \times 0.937 \times 1.2\text{mm}^3$.

Manual thickness. We compute closest-point matching between the WM and GM landmarks. Points that have multiple matches are discarded to avoid inaccurate thickness measurements. Euclidean distance between remaining pairs serves as manual CT. Note that this is far from being a gold standard. The landmarks were chosen for a cortical reconstruction validation study; as such, they are not meant to provide accurately paired points for CT measurement. This may cause over- or under-estimation of CT.

LOGISMOS-B surface reconstruction and Laplacian CT measurement. The same cortical reconstruction parameters as presented in [11] are used. The atlas in the BRAINS package was used for tissue classification and regional parcellation, including 70 cortical ROI's. $20,000$ graph columns per hemisphere were used, each containing 120 nodes, with a node spacing of 0.1mm. The step size is 0.015625 for solving the Laplace equation and 0.125 for the transport equation, which allow for a stable solution [13]. The transport equation is run for 100 iterations (50 backward and 50 forward).

FS surface reconstruction and thickness measurement. FS currently represents the most commonly used approach for CT analysis; version 5.1 was used.

Symmetric closest point (SCP) thickness on LOGISMOS-B surfaces. To separate the effect of cortical reconstruction accuracy from thickness measurements, we also report the thickness measures computed using Eqn. 1 on the LOGISMOS-B surface reconstructions. We refer to this method as LOGISMOS-B + SCP.

Evaluation Strategy. The LOGISMOS-B surface reconstruction and positioning algorithm was previously validated [11]; therefore, in this manuscript, we focus on the evaluation and validation of the thickness measurements given the surfaces.

[2] `http://www.iacl.ece.jhu.edu/Cortical_data/`
[3] `http://biomedic.doc.ic.ac.uk/brain-development`

Table 1. Left, Mean ± std. deviation of whole-brain CT. Right, Mean and std. dev. of distance between manual landmarks and reconstructed surfaces (JHU). * indicates statistical significance.

	JHU		IXI	
	Left	Right	Left	Right
FreeSurfer	3.154 ± 0.798	3.038 ± 0.760	2.824 ± 0.987	2.853 ± 0.996
LOGISMOS-B	2.626 ± 1.151	2.700 ± 1.168	2.946 ± 1.259	2.998 ± 1.255
LOGISMOS-B + SCP	2.232 ± 0.654	2.276 ± 0.662	2.315 ± 0.799	2.363 ± 0.810

	LOGISMOS-B	FreeSurfer
Signed WM	*0.081 ± 0.447	0.263 ± 0.452
Signed GM	*0.018 ± 0.498	-0.167 ± 0.556
Unsigned WM	*0.579 ± 0.264	0.611 ± 0.302
Unsigned GM	0.681 ± 0.298	0.703 ± 0.331

First, we use the JHU dataset to compare the automated CT measurements to the Manual thickness per landmark cluster. We also use the landmark locations, which represent the gold standard for surface placement, to assess the error and bias for each method; signed distance to the landmarks measures surface placement bias, whereas unsigned distance measures bulk error in placement.

Next, we compare the automated CT measurements on both datasets to known patterns from the literature. Specifically, the post-central gyrus is markedly thinner than the pre-central gyrus [10]. The frontal and temporal lobes are thicker than the occipital lobe. MS patients have thinner cortices overall, and in particular in the frontal and temporal lobes, compared to healthy subjects [14]. The brain is relatively symmetric, but asymmetric regions are known to exist such as the superior temporal gyrus [9].

Next, we present the regression of CT against subject age in the large IXI dataset. Similar to [16], we normalize the CT measurements by brain size, estimated by the volume of the skullstrip mask. We compare the findings to known patterns from literature: it is well established that the frontal, insular, temporal and parietal GM shrinks throughout healthy aging, whereas the occipital cortex is largely spared and remains relatively stable across the lifespan (e.g., [12] and the many references therein). Hutton et al. [5] report a CT decrease of up to $0.02\mathrm{mm/yr}$. in select regions of the cortex, especially in frontal and temporal areas, with the whole-brain average thinning of $0.009\mathrm{mm/yr}$.

4 Results

Tab. 1 summarizes the whole brain CT measurements. Two-tailed paired t-tests reveal that all pairs of methods are significantly different from each other (for JHU, $p << 0.001$ for all pairs; for IXI, $p = 0.05$ between LOGISMOS-B + SCP and Laplacian, $p << 0.001$ for all other pairs). Tab. 1 also summarizes the landmark errors for the JHU dataset. LOGISMOS-B surface placement is significantly more accurate than FS.

Tab. 2 shows the average CT measurements per cluster and the amount of asymmetry in CT measurements for each method for the JHU dataset. Overall, most clusters show high symmetry; however, the superior temporal sulcus (ST) is found to exhibit a strong asymmetry with the LOGISMOS-B approach, consistent with literature [9].

Table 2. Left, average CT per cluster (JHU). Right, asymmetry in CT measurements computed as the difference between left and right hemisphere CT. All units are mm.

CT	Manual	FreeSurfer	LOGISMOS-B	LOGISMOS-B + SCP
CALC	2.432	2.281	2.068	1.535
CING	3.356	3.441	3.049	2.267
CS	2.796	2.964	2.270	2.157
PO	2.665	2.877	2.300	2.072
SF	2.782	3.143	2.906	2.557
ST	3.193	3.352	3.116	2.671
SYL	3.083	3.359	2.965	2.415

Asymmetry	Manual	FreeSurfer	LOGISMOS-B	LOGISMOS-B + SCP
CALC	0.020	-0.061	-0.196	0.003
CING	0.053	-0.063	-0.053	0.054
CS	0.169	0.162	-0.003	-0.004
PO	-0.220	0.236	0.024	0.009
SF	-0.346	0.070	-0.231	-0.154
ST	-0.041	0.099	-0.206	-0.111
SYL	0.240	0.062	-0.067	-0.020

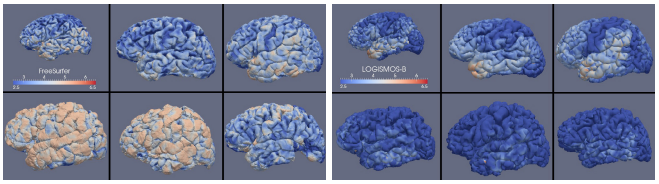

Fig. 1. FS and LOGISMOS-B CT(JHU). Top row, healthy, bottom, MS patients.

LOGISMOS-B reports lower CT measurements in the postcentral gyrus (2.1mm for JHU, 2.2mm for IXI) than in the precentral gyrus (2.4mm for both JHU and IXI), consistent with literature. Tab. 3 compares the healthy and MS groups. The FS measurements disagree with the known fact that MS patients exhibit cortical thinning ([14] and references therein). LOGISMOS-B, in contrast, follows this expected pattern. In fact, in addition to the diffuse overall thinning in the whole brain, LOGISMOS-B reports a marked focal thinning in the frontal and temporal lobes, in close agreement with [14].

Fig. 1 shows representative FS and LOGISMOS-B CT results in the JHU dataset for qualitative evaluation. We observe that the FS surface reconstruction is less than ideal especially for the MS patients; note the missing chunk of tissue for the rightmost subject near the inferior temporal gyrus, as well as the fused appearance of the gyri throughout the brain for all MS subjects, especially in comparison to the LOGISMOS-B surfaces.

Tab. 4 presents the summary statistics per lobe for the IXI dataset. In Tab. 3 and 4, consistent with the literature, the LOGISMOS-B CT measurements are higher in the frontal and the temporal lobes than in the occipital lobe. In Tab. 4, FS reports a low cingulate thickness, by as much as 2mm. Note that the 1.6mm CT reported by FS is not very credible, considering the cingulate CT of over 3mm reported in many in vivo studies (e.g., [16]) and $2.7 - 3.0\text{mm}$ in postmortem specimen [2], which is expected to be lower than in vivo MRI measurements due to shrinkage during fixation of the brain. LOGISMOS-B reports a cingulate thickness of 3.4mm, consistent with the literature.

Tab. 4 presents the regression analysis of CT against subject age. Overall, LOGISMOS-B reports a more rapid thinning per year (as indicated by the slope) and a stronger correlation with age than FS. In particular, LOGISMOS-B reports average thinning of 0.022mm/yr. in the frontal lobe, but a low correlation and only 0.002mm/yr. thinning in the occipital lobe, closely matching the literature. FS-reports only 0.008mm/yr. thinning in the frontal lobe and 0.005mm/yr. thinning and a rather strong correlation in the occipital lobe. The similarity of these two rates and its mismatch with published literature indicate that FreeSurfer is either overestimating occipital thinning or underestimating frontal thinning, or, likely, both.

Table 3. Lobar CT (JHU). Mean ± std. deviation are reported in mm.

	Healthy			MS		
	FreeSurfer	LOGISMOS-B	LOGISMOS-B + SCP	FreeSurfer	LOGISMOS-B	LOGISMOS-B + SCP
Cingulate	3.273 ± 0.742	3.250 ± 1.057	2.460 ± 0.916	3.467 ± 0.747	2.755 ± 2.909	2.081 ± 0.860
Frontal	3.037 ± 0.624	3.271 ± 0.905	2.694 ± 0.611	3.439 ± 0.821	2.502 ± 0.787	2.259 ± 0.505
Insular	3.298 ± 0.971	3.121 ± 0.990	2.368 ± 0.893	3.451 ± 1.015	2.515 ± 2.324	1.956 ± 0.775
Occipital	2.575 ± 0.686	2.326 ± 1.735	1.918 ± 0.541	2.672 ± 0.789	2.089 ± 0.535	1.757 ± 0.506
Parietal	2.674 ± 0.683	2.603 ± 0.755	2.278 ± 0.480	3.152 ± 0.842	2.216 ± 0.458	2.076 ± 0.401
Temporal	3.314 ± 0.735	3.133 ± 1.290	2.496 ± 0.798	3.381 ± 0.815	2.502 ± 1.081	2.103 ± 0.651
Whole brain	2.939 ± 0.737	2.929 ± 1.180	2.414 ± 0.692	3.246 ± 0.864	2.381 ± 1.068	2.085 ± 0.574

5 Discussion

We observe that SCP underestimates thickness. The LOGISMOS-B + SCP measurements are consistently lower than the Laplacian measurements on the same surfaces and lower than the manual measurements (Tab. 1-2), by as much as 15% on average. Despite this bias, the FS pipeline reports a higher CT than LOGISMOS-B in the JHU dataset (Tab. 1-2), suggesting that the FS surface reconstruction must be over-compensating. This is also supported by Tab. 1, which shows bias in FS surface placement. Clearly, over-estimating in one module and under-estimating in another is not an ideal way for reliable measurement. LOGISMOS-B has excellent surface reconstruction accuracy [11], which should inevitably lead to higher accuracy for *any* meaningful thickness measurement approach. The Laplacian method is one such approach.

The inaccurate FS reconstruction for MS subjects, especially the artificially enlarged GM segmentation (Fig. 1), leads to higher reported CT in the MS patients compared to healthy subjects (Tab. 3). The robust LOGISMOS-B accurately captures the thinning in MS patients, both diffusely and focally.

The FS cingulate measurements in Tab. 4 are inconsistent with literature, unlike LOGISMOS-B findings. The LOGISMOS-B + SCP results represent the midway point between the two methods. This indicates that the SCP measurement bias is only partially responsible for the observed cingulate CT discrepancy. This suggests that the LOGISMOS-B surface placement is superior to FS in the IXI dataset, just like for JHU.

LOGISMOS-B findings regarding age effects on CT (Tab. 4) are closely consistent with the literature, unlike FS results. LOGISMOS-B also shows a greater range of these age effects on thickness, which should translate into higher statistical power in studies compared to FS, which report relatively homogeneous thinning rates.

The improved accuracy in LOGISMOS-B is largely due to its graph-based segmentation which guarantees a globally optimal solution and is therefore extremely robust to local image artifacts. LOGISMOS-B used the same parameters on both datasets, indicating its robustness against different acquisition parameters and a large variety of subjects, including healthy volunteers and MS patients and a large age range. Furthermore, while the current experiments used only T1w images for a fair comparison with FS, it is straightforward to extend LOGISMOS-B to use additional images such as T2w scans by simply adapting the cost function, which may further improve the accuracy.

It is also important that the CT is measured along non-intersecting paths. The Laplacian-based methods inherently guarantee this. The closest-point matching in the FS approach often leads to intersecting paths in the tightly folded cortex.

Table 4. Left, Mean ± std. deviation of CT. Right, CT vs. age regression (IXI).

Lobar CT	FreeSurfer	LOGISMOS-B	LOGISMOS-B + SCP
LCingulate	1.526 ± 1.668	3.429 ± 1.116	2.675 ± 0.913
LFrontal	3.037 ± 0.693	3.296 ± 1.269	2.622 ± 0.804
LInsular	3.326 ± 0.997	3.196 ± 1.937	2.323 ± 0.920
LOccipital	2.549 ± 0.790	2.274 ± 1.342	1.803 ± 0.574
LParietal	2.763 ± 0.686	2.605 ± 0.877	2.074 ± 0.589
LTemporal	3.283 ± 0.821	3.166 ± 1.155	2.423 ± 0.838
RCingulate	1.703 ± 1.676	3.359 ± 1.182	2.519 ± 0.955
RFrontal	3.073 ± 0.702	3.337 ± 1.404	2.649 ± 0.830
RInsular	3.157 ± 1.243	3.126 ± 1.689	2.211 ± 0.916
ROccipital	2.626 ± 0.818	2.311 ± 0.968	1.869 ± 0.565
RParietal	2.775 ± 0.691	2.653 ± 0.853	2.146 ± 0.586
RTemporal	3.339 ± 0.813	3.325 ± 1.184	2.556 ± 0.860

	LOGISMOS-B		FreeSurfer	
Regression	Correlation	Slope	Correlation	Slope
LCingulate	-0.219	-0.006	-0.418	-0.003
LFrontal	-0.710	-0.022	-0.570	-0.007
LInsular	-0.575	-0.017	-0.421	-0.006
LOccipital	-0.164	-0.002	-0.436	-0.005
LParietal	-0.639	-0.012	-0.568	-0.006
LTemporal	-0.586	-0.013	-0.541	-0.007
RCingulate	-0.364	-0.011	-0.350	-0.003
RFrontal	-0.716	-0.023	-0.581	-0.008
RInsular	-0.702	-0.019	-0.500	-0.009
ROccipital	-0.230	-0.002	-0.422	-0.005
RParietal	-0.671	-0.013	-0.553	-0.007
RTemporal	-0.504	-0.011	-0.435	-0.006

6 Conclusion

The reported cortical thickness measurement algorithm, using LOGISMOS-B cortical reconstruction and Laplacian-based thickness measurement, is based on a highly accurate cortical reconstruction by extending the LOGISMOS graph segmentation framework using generalized gradient vector flows. Compared to the current state-of-the-art, LOGISMOS-B offers improved accuracy and robustness in cortical thickness studies.

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