

Expectation maximisation classification and Laplacian based thickness measurement for cerebral cortex thickness estimation

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ABSTRACT

We describe a new framework for measuring cortical thickness from MR human brain images. This involves the integration of a method of tissue classification with one to estimate thickness in 3D. We have determined an additional boundary detection step to facilitate this. The classification stage utilizes the Expectation Maximisation (EM) algorithm to classify voxels associated with the tissue types that interface with cortical grey matter (GM, WM and CSF). This uses a Gaussian mixture and the EM algorithm to estimate the position and width of the Gaussians that model the intensity distributions of the GM, WM and CSF tissue classes. The boundary detection stage uses the GM, WM and CSF classifications and finds connected components, fills holes and then applies a geodesic distance transform to determine the GM/WM interface. Finally the thickness of the cortical grey matter is estimated by solving Laplace's equation and determining the streamlines that connect the inner and outer boundaries. The contribution of this work is the adaptation of the classification and thickness measurement steps, neither requiring manual initialisation, and also the validation strategy. The resultant algorithm is fully automatic and avoids the computational expense associated with preserving the cortical surface topology. We have devised a validation strategy that indicates the cortical segmentation of a gold standard brain atlas has a similarity index of 0.91, thickness estimation has subvoxel accuracy evaluated using a synthetic image and precision of the combined segmentation and thickness measurement of 1.54mm using three clinical images.

Keywords: human cerebral cortex, cortical thinning, MRI brain segmentation, Expectation Maximisation, Laplacian, thickness measurement

1. INTRODUCTION

We aim to quantitatively determine brain changes associated with neuro-degenerative diseases, such as schizophrenia. A previous MRI based study by Lieberman¹ indicated structural brain change during early stage schizophrenia. This is thought to be related to reduction of neuronal size² leading to general cortical thinning³ and particularly over the temporal and dorsolateral prefrontal areas.² It is clinically interesting to determine whether there is thinning of the cortical grey matter in the temporal and frontal lobes. The quantification of cortical thickness *in vivo* requires high resolution MR images and accurate image analysis. In this paper we present a technique that can automatically and accurately determine cortical thickness from MR images. First we need to segment the cortex and then compute its thickness. Other studies have already developed techniques to do this. However, the current methods are either inaccurate or computationally expensive (see later), we discuss their disadvantages and our rationale to constitute a new framework. This new strategy introduces problems identifying boundaries in sets of voxels with disjoint ones which we address using geodesic distance transforms. Our validation indicates a subvoxel (0.14mm) accuracy for synthetic spherical shell images and a precision of 1.39mm for clinical images (both $1 \times 1 \times 1$ mm voxels). Finally, we present the results obtained with a small database of serial MR images specifically designed to monitor cortical thickness during the first stages of the disease.

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2. DEFINITIONS AND RELATED WORK

The *cerebral cortex* is the most exterior structure of the brain containing neurons. It is formed by grey matter (GM) and is a very convoluted sheet with white matter (WM) and *cerebrospinal fluid* (CSF) interfaces. The cortex is defined by two boundaries, the GM/WM (inner boundary) and the CSF/GM (outer boundary). We denote these as B_0 and B_1 respectively. Next we present a brief review of the methods to extract the cortex and measure its thickness.

2.1. Cortex segmentation algorithms

The three main constraints of segmentation algorithms are the accuracy, computation time and the degree of automation. Also important is the way that the method deals with Partial Volume Effect (PVE) and intensity inhomogeneities. We classify them into: (a) *boundary based methods* (e.g. level-sets, Zeng et al.,⁴ Goldenberg et al.⁵); (b) *mesh generation techniques* (Dale et al.,⁶ Fischl et al.,⁷ MacDonald et al.⁸); (c) *intensity thresholding methods* (Shan et al.⁹); (d) *mathematical morphology* (Lohmann et al.¹⁰) and (e) *region based methods* (Van Leemput et al.¹¹). Methods (a) and (b) generate a surface model of the cortex (using smoothing and folding constraints), whereas the others generate volumetric image masks. In addition, (a) and (b) impose the topology of a sphere to the reconstructed surface to prevent possible problems in other operations such as surface mapping.^{4,6,8} However, it is computationally very expensive to preserve the initially imposed topology. Except for Lohmann *et al.*,¹⁰ the other methods don't ensure any particular topology of the segmented cortex.

2.2. Thickness estimation algorithms

Because of the highly convoluted cortical geometry manual estimation of a dense thickness field is not viable. Hence we need automatic methods that utilise the 3D nature of the data. Algorithms are based on different definitions of 3D thickness, and the definition of thickness itself is a source of debate.^{12,13} The most common one is the *closest point* distance: each point on a boundary is assigned the distance to the closest point in the other boundary. Jones et al.¹² proposed another definition of thickness as the length of the streamlines that smoothly traverse from one surface to the other.

3. RATIONALE

In this section we present the methods we have used and the rationale behind our choice.

3.1. Segmentation algorithm

We chose to adopt the method described by Van Leemput et al.¹¹ The method¹¹ can segment the GM, WM and CSF. It models the image intensity as a Gaussian mixture and then uses the EM algorithm to estimate the parameters of each distribution. The initialisation is performed using an *a priori* probability map. The algorithm includes bias field estimation and spatial constraints (Markov random fields) in the EM scheme, estimating the bias field at the same time as the segmentation is performed. It can also be applied to multi-sequence MR images. The results of this method have been reported in.¹¹ There are several advantages regarding other methods. It does not construct a surface model for the cortex like boundary based or mesh generation methods, so it does not have their limitations. It is robust to initial parameters, unlike methods based on intensity thresholding or mathematical morphology. In addition, it is computationally efficient, needing only a few minutes on a conventional machine. We also considered the enhanced method designed to model the PVE.¹⁴ However, we decided not to implement because of the tendency of the Ising MRF model to minimise the boundary length between tissues which leads to inaccurate classification near the cortex.¹⁴ The difficulty with using a classification method is that they generate sets of voxels for each tissue class that, in general, are not connected and have disjoint boundaries.

3.2. Thickness estimation

The adopted method is the one described in Yezzi *et al.*,¹⁵ which provides a numerical optimisation of the method described in Jones *et al.*¹² Its innovation resides in the use of Laplace’s equation to determine a set of nested iso-potential surfaces. The normals of these surfaces define streamlines. The trajectory lengths along the streamlines are denoted L_0 from B_0 to B_1 and L_1 from B_1 to B_0 . Thickness is simply the sum of these lengths $L_0 + L_1$. This definition has a number of advantages compared to the other ones. Streamlines are bijective and never cross, see.¹² Hence the method does not present ambiguities in the thickness values, that is each voxel has a unique value of thickness, unlike the other definitions. Additionally, all voxels in the volume are assigned a thickness value and not only those on the surface. Finally, it seems to be closer to the physiological interpretation of the cortical thickness, as shown in.¹³

Other studies have already estimated cortical thickness for neurodegenerative disease patients. However, some use a deficient definition of thickness based on the closest point.^{16,17} This results in local inaccuracies. In addition, they use segmentation through mesh generation, which is inaccurate and slow and in some cases require manual correction.¹⁶ Our framework combines segmentation through classification with thickness estimation based on Laplace’s equation. The Laplace equation is a boundary value problem¹⁸ and therefore requires values of the potential function at the boundaries. Given this initialisation, each point between the inner and outer surfaces can be assigned an iso-potential. However, the EM algorithm generates sets of voxels for each tissue class that, in general, have disjoint boundaries. Hence we need to determine the B_0 and B_1 surfaces required for thickness estimation algorithm. We explain how we do this in the next section.

4. CORTICAL THICKNESS ESTIMATION

This adopted method involves the determination of a layered set of iso-potential surfaces which are the solutions of Laplace’s equation. The inner and outer surfaces, B_0 and B_1 , are assigned different values of the potential function u . Then the value of the potential function at each voxel $u(i, j, k)$ in the cortical volume of interest R , bounded by B_0 and B_1 , is determined using the following finite difference approximation to Laplace’s equation:

$$u_{i+1,j,k} + u_{i-1,j,k} + u_{i,j+1,k} + u_{i,j-1,k} + u_{i,j,k+1} + u_{i,j,k-1} - 6u_{i,j,k} = 0 \quad (1)$$

The tangent field to the iso-potential surfaces \mathbf{T} is simply the normalised gradient $\frac{\nabla u}{|\nabla u|}$. Yezzi¹⁵ provides an efficient numerical solution, where given the tangent field, the trajectory lengths of the L_0 and L_1 along streamlines are determined iteratively. This allows us to determine the trajectory length along the streamlines without needing to calculate the proper streamlines. The thickness is simply the sum $L_0 + L_1$. Fig. 1 illustrates the steps involved in this process.

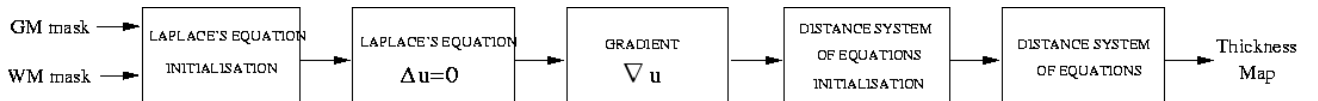


Figure 1. Illustration of the stages of the thickness estimation algorithm. The GM and WM classifications are determined by the EM algorithm. These are transformed into connected volumes during initialisation. Then Laplace’s equation is solved. The gradient gives the tangent field and the streamlines. The streamline equations are solved to give L_0 and L_1 and the thickness map.

The initialisation step involves the detection of the B_0 and B_1 boundaries from the classification masks output from the EM algorithm. As previously stated, these are not necessarily connected and have disjoint boundaries. Given the EM masks, first we find the largest 6-connected component of the GM mask. This ensures the cortex has the same connectivity as that required by Laplace’s equation. Then holes are filled with the method of Soille¹⁹ which uses a 26-connected structuring element. This gives a connected volume for GM, R_{GM} . Voxels of the GM EM mask that are not in the largest 6-connected component are added to the WM EM mask then the largest 26-connected component of this set is determined. This gives a connected volume for WM, R_{WM} . The

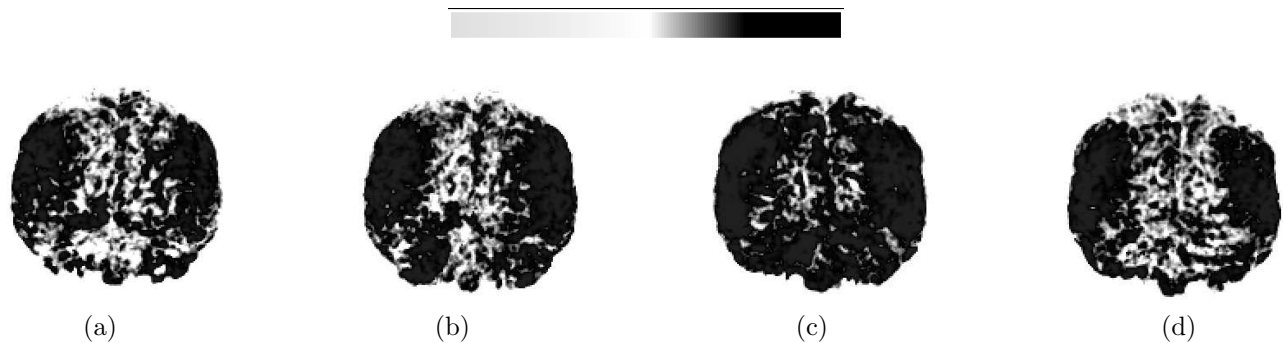


Figure 3. Average population thickness maps for coronal planes. The scale represents thickness (0-5mm, light is thin, dark is thick). (a) controls at baseline; (b) controls at follow-up; (c) patients at baseline; (d) patients at follow-up.

distance measurements. The ground truth was determined analytically by calculating the Euclidean distance from each voxel in the spherical shell to the inner and outer surfaces this gives a gold standard for L_0 and L_1 . We use these to determine the error of L_0 and L_1 estimated by the CTE algorithm. This gave a mean (stdev) absolute error of 0.14mm (0.11mm). We tested for bias in the estimates using a least squares fit of a linear function, this gave a slope and intercept of 0.99 and -0.1 for L_0 and 0.97 and -0.094 for L_1 indicating a small under-estimate of both distances and therefore the thickness.

5.2. Segmentation error

To evaluate the segmentation error of the EM algorithm we used MNI brainweb image (1mm isotropic voxels) with 40% intensity non-uniformity and 4% added simulated Rician noise. Comparing GM segmentations derived using EM with the MNI gold standard gave a sensitivity of 0.93, specificity of 0.88 and a similarity index ($\frac{2N(R_1 \cap R_2)}{N(R_1) + N(R_2)}$ where $N(X)$ is the number of elements of set X) of 0.91. The mean absolute difference (stdev) of thickness measurements between the two segmentations was 0.55mm (0.63mm) for the intersection of segmentations.

5.3. Precision using clinical images

Our strategy is based on determining the precision of thickness measurements using three MR scans of a volunteer with repositioning. To correct for repositioning we rigidly registered the second and third scans to the first, the images were re-sampled using linear interpolation. Then we segmented the three aligned images using the EM algorithm and determined the cortical thickness maps with the Laplacian-based method. We assessed the precision by calculating the mean absolute difference and standard deviation of thickness values. The mean absolute difference (stdev) was 1.39mm (1.54mm).

5.4. Clinical application

We aim to demonstrate how average thickness maps are determined for a population of controls and patients. First we register each image to a common coordinate frame (e.g. baseline image). We use a rigid-body transformation for intra-subject registration and an affine transformation for inter-subject registration. The affine transformation allows for some global shape differences, we plan to use non-rigid to improve on this in the future. The mean thicknesses are shown as grey scale images in the Fig. 3, dark represents thin regions ($< 2mm$ approx) and light represents thick ones ($> 4mm$ approx) Columns (a)-(d) refer to coronal planes through the images. (a), (b) are the baseline and follow-up for the controls; (c), (d) are the baseline and follow-up for the patients. We also produced some color renderings of the volume images and presented these to a clinical psychiatrist for qualitative evaluation. They reported that the renderings indicated more rapid cortical thickness loss in the subjects with first episode schizophrenia in the parieto-occipital area with distinct areas of fronto-temporal thinning were visible. However, these may be initially underestimated due to the scheme used to represent absolute cortical thickness. This is in accordance with volumetric studies that have suggested fronto-temporal cortical volume loss in addition to parietal pathology.

6. DISCUSSION

Our framework has the benefit of using a EM classification technique that is thought to provide sub-voxel accuracy at low computational cost especially compared to surface-based methods. However, a disadvantage is that tissue classifications does not provide preserve the surface boundary which is needed to measure cortical thickness. To address this we have developed a method that uses connected component analysis and geodesic distance transforms. We have designed a validation strategy that measures accuracy using simulation and precision using a small clinical MR image database. Results on synthetic images indicate sub-voxel accuracy (0.14mm, for 1mm isotropic images). However, this test does not reflect the high variability in the curvature of the cerebral cortex. In general, for clinical data, it is difficult to isolate the individual error components (segmentation, registration and thickness estimation). Our results on the brainweb data suggest that segmentation error is just more than half a voxel (mean difference in thickness of 0.55mm, for 1mm isotropic images). The precision results on clinical data indicate that the combined error (segmentation, registration and thickness estimation) is greater than a voxel, mean absolute difference for the three scans was 1.39mm. Given these results it is not possible to claim sub-voxel accuracy for the technique so it could not be used to analyse change over time at the scale of a voxel. However, we would expect errors to average out for a larger region so the technique is likely to be more useful, for instance, to analyze change over a cortical region several voxels in diameter.

In future work we intend to investigate methods of improving the accuracy of the EM classification by modelling the PVE and building more spatial information into the EM algorithm. Further constrains can be built into the thickness estimation algorithm since the normal variation in thickness ranges from 1mm to 5mm.²³

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