Combined magnitude and phase-based segmentation of the cerebral cortex in 7T MR images of the elderly

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Abstract

Cerebral cortex segmentation has been an active research area in medical image processing for several decades. Most automated cortex segmentation methods based on magnetic resonance imaging (MRI) that have been developed so far involve the use of T1 magnitude images which can show poor gray/white matter (GM/WM) contrast in older and diseased populations. We describe a method that makes use of magnitude and phase information obtained from T2*-weighted data to segment the cortex. The method integrates MR phase information in a two steps framework. The first step makes use of K-means clustering on magnitude and phase images to obtain an initial estimation of the cortex. The second step further refines the segmentation within an iterative framework. We evaluate our method by comparing the obtained segmentation with two state-of-the-art methods. The results show a good agreement between our method and these reference methods. Our study suggests that combined magnitude and phase-based method is a good alternative for cerebral cortex segmentation in datasets presenting low GM/WM contrast.

1 Introduction

The cerebral cortex is the thin folded outermost layer of the brain. Its borders are the Cerebrospinal Fluid/Gray Matter (CSF/GM) interface and the Gray Matter/White Matter (GM/WM) interface. As its geometry and texture provide relevant information about the disease stage in various forms of dementia [1] and other diseases such as schizophrenia [2], the cerebral cortex has become an area of great interest for neuroscientists. More particularly, studies have suggested that neurodegenerative diseases such as Alzheimer’s Disease (AD) are associated with abnormal iron deposition within the cortex and basal ganglia [3]. Amyloid-beta plaques, a hallmark of AD found in gray matter, associate with iron and play a major role in the generation of T2* contrast on MR images [4], [5]. As a result, segmentation of the cortex based on the contrasts on T2*-weighted images is a prerequisite for automated methods to assess cortical iron depositions in neurodegenerative disorders in general and AD in particular.

The development of an algorithm for cerebral cortex segmentation on T2* data is of particular interest. A large amount of research has been carried out over the past several decades to develop automated methods making use of T1-weighted data, which often show good GM/WM contrast [6]. Such contrast can however be influenced by age-related and pathological phenomena [7]. Even though existing segmentation methods are not directly applicable to T2* data, one possibility is to apply them to the corresponding T1 data and translate the result to T2* data. However, this approach requires the additional acquisition of T1 data and may suffer from global and local inaccuracies, due respectively to registration and acquisition artifacts, between T1 and T2* data. Furthermore, GM/WM contrast is decreased in T1 and T2* magnitude images at high field MR, especially in the elderly population [7]. This low contrast seriously hampers the efficiency and accuracy of magnitude-based methods.

Because of its higher Signal-to-Noise Ratio, high field MR has enabled the use of phase information, which is obtained together with the magnitude data in the same acquisition. Phase information is sensitive to small differences in tissue susceptibility and appears to present a more consistent GM/WM contrast compared to the magnitude images [8], as shown in Figure 1.

To the best of our knowledge, MR phase information has seldom been used for segmentation purposes. Bourgeat and colleagues have described a method using that information to complement traditional magnitude data in order to segment bones
in the knee. Within that application, they have shown that combining both magnitude and phase yields a significant increase in segmentation accuracy [9].

This paper describes a method which makes use of both magnitude and phase information for cortical segmentation in the context of high-field MR in vivo studies. Contributions of this paper are two-fold: it demonstrates the use of MR phase information to perform cortical segmentation and presents an extensive validation framework that makes use of two state-of-the-art methods as ground truth. In Section 2, we describe our algorithm, as well as the validation framework that we employed. In Section 3 and section 4, we present and discuss the obtained results. Conclusions are presented in Section 5.

2 Materials and methods

2.1 Segmentation algorithm

2.1.1 Overview

The proposed algorithm performs the segmentation of the human brain cortex using T2*-weighted magnitude and phase data acquired at 7T. The algorithm follows the steps depicted in Figure 2. Data are preprocessed before the application of K-means clustering, which is used to extract CSF/GM/WM contrast information from the data. Subsequently, CSF/GM interface (outer boundary) and initial GM/WM interface (inner boundary) are detected, yielding the initial segmentation of the cortex. Refinement based on this initial segmentation results in the final cortex segmentation.

2.1.2 Preprocessing

Preprocessing of the data consists of three main steps: phase unwrapping, non-brain tissue removal, and ventricle segmentation. Phase data originating from the MR scanner is bounded to the $[-\pi, \pi]$ interval. Due to intrinsic inhomogeneity of the magnetic fields applied during acquisition, its actual range is much larger, resulting in phase wraps, i.e. local and rapid transitions from $-\pi$ to $\pi$ and vice-versa. The original phase data must thus be unwrapped before any further processing steps take place. A classic Fourier-based approach was used for this purpose [10]. Non-brain tissue removal is performed as one of the first steps of the segmentation framework. This step consisted of thresholding and connected component analysis on both the magnitude and phase data. Two binary masks were derived by thresholding magnitude and unwrapped phase images using the corresponding standard deviations as thresholds. Connected component analysis on the combination of the masks, retaining the largest component, provided a satisfactory intracranial mask. That mask was subsequently used to remove non-brain tissues from both magnitude and phase image. Finally, segmentation of the ventricle was performed on the T2* magnitude images using a 3D region growing method with a manually selected seed point.

2.1.3 Cortical segmentation

K-means clustering

K-means clustering [11] was applied separately on magnitude and phase images. The magnitude image
was clustered into 4 classes: (1) GM, (2) WM, (3) CSF, and (4) veins/background. Similarly, the unwrapped phase image was clustered into 4 classes: (1) GM, (2) WM/CSF, (3) veins, and (4) background.

**Cortex detection**

**Outer boundary detection**

The input image $B_m$ of outer boundary detection was a binary mask constructed from the results of K-means clustering of both magnitude and phase images. In particular, it was the binary mask of the brain from which the segmentation $B_{CSF, veins}$ of CSF from magnitude and veins from both images were removed, such that:

$$B_{CSF, veins} = \text{Kmeans}_{\text{magnitude}} \cup \text{Kmeans}_{\text{phase}}$$

$$B_m = \text{BrainMask} \cap B_{CSF, veins}$$

Edge detection using Sobel method [12] was performed after noise removal using median filtering and connectivity enhancement using local averaging. 3D connected component analysis on the obtained map resulted in a number of contours which were differentiated by different values.

The segmentations of the ventricle and CSF on magnitude image were used as indicators to retain relevant contours. Assuming that the cerebral cortex is bordered by the outer CSF, contours that were geometrically connected to the outer CSF were considered relevant and retained. Conversely, contours that were geometrically connected to the ventricles were removed. Finally, the mask corresponding to the cortical outer boundary was further refined using a region growing approach. The selected seed point belonged to the region bounded by the retained contours. The detected boundary was the contour of the segmented region.

**Initial inner boundary detection**

The inner boundary was detected based on GM/WM contrast information on the phase image, which was extracted by K-means clustering. We made the hypothesis that cortical thickness can be considered constant as an initial approximation. A minimum cost approach was applied to determine the best contour fitting the global GM/WM interface. The contour was initialized on the outer boundary and subsequently moved by iteratively eroding the outer mask. The cost function was computed based on the number of voxels labeled as GM that belonged to the moving curve. This cost function reached its minima as the curve best fit the boundary of labeled GM/WM or the global GM/WM transition was detected, given the assumption that the cortical thickness is a constant. The thickness $d$ was thus computed as following:

$$\nabla F(d) = \min_n (\nabla F(n))$$

where

$$F = [F_1, F_2, ..., F_i, ..., F_N]$$

$$F_i = \frac{\text{length}(C_i)}{\text{length}(C_o)} \sum_{x, y, z \in C_i} B_p(x, y, z)$$

$n$ being the number of iterations, whose upper bound was set to 4.5mm according to [13], $B_p$ the binary mask of the gray matter classification on phase image, $C_i$ the contour of the eroded mask at iteration $i$ and $C_o$ the contour of the outer mask.

**Refinement of the inner boundary**

Once the initial segmentation was obtained, it was further refined to recover cortex parts being missed due to the lack of CSF/GM information and reflect more accurately local variations in cortical thickness.

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**Figure 2: Flowchart of the presented method**
Considering the initial inner mask $M_i$ as the first region of interest (ROI), the aim was to detect cortex segments contained in the neighboring ROIs. This refinement was carried out using the $B_{GM}$ mask, which combined voxels classified as gray matter on magnitude and phase images. Noise reduction using a median filter and ventricle removal using the segmented ventricle mask were carried out on $B_{GM}$ in advance to the analysis.

Refinement was performed as follows. Given a mask $M_i$ and a cortical segmentation $S_i$ at iteration $i$, $M_{i+1}$ was computed by eroding $M_i$ up to thickness $d$. $ROI$ was constructed as the difference between $M_{i+1}$ and $M_i$. Regions belonging to the intersection of $B_{GM}$ and $ROI$ and connected to $S_i$ were also labeled as cortex, forming together with $S_{i+1}$ the updated segmentation $S_{i+1}$. This iterative process was repeated until no regions were labeled as cortex.

The mask of the recovered regions, computed as $S_{last\ iteration} \cap S_0$, was then filtered using morphological closing (disk-shaped structuring element, radius=3) to remove unwanted discontinuities caused by the noise remaining on the combined gray matter mask.

The final cortex segmentation was obtained after applying area closing (threshold=30 pixels) on the union of the morphological closing result and the initial segmentation $S_0$ to further remove noise while preserving fine details of the cortical boundaries.

### 2.2 Validation framework

#### 2.2.1 Data

The proposed cortical segmentation algorithm was evaluated using in vivo data obtained from 11 elderly patients. A high resolution $T2^*$-weighted gradient echo sequence with a scan duration of 10 minutes (TR/TE/flip angle = 800ms/25ms/45°, voxel size = 0.24x0.24x1mm³, FOV=240x180mm²) was used to acquire 20 axial slices. A navigator echo correction technique (TE=9.5ms) was used to correct for resonance frequency fluctuations. Within the same session, a $T1$-weighted gradient echo sequence was applied to obtain full brain scan (voxel size = 0.7x0.7x0.7mm³, 248 sagittal slices) with scan duration of 9 minutes.

#### 2.2.2 Overview

In order to validate our method, we chose to compare the obtained segmentation masks with those obtained using state-of-the-art methods, FreeSurfer and FSL, on $T1$ images. As a result, three steps were composing our validation framework: segmentation of $T1$-weighted data, registration of $T1$-weighted and $T2^*$-weighted data and comparison of the segmentation results.

### Computation of reference data

As mentioned earlier, cortical segmentation is traditionally performed on $T1$-weighted data. As a result, despite our method using $T2^*$-weighted data, segmentation based on $T1$-weighted data were used for validation purpose. Reference data, i.e. comparable cortical segmentations, were obtained by applying FreeSurfer and FSL on $T1$-weighted images from the same patients.

The segmentation masks obtained from $T1$-weighted data were subsequently linearly registered to $T2^*$ space for comparison. Two registration approaches were investigated: registration based on parameters obtained from the scanner and registration using FSL linear registration tool FLIRT on the segmented masks. Both methods are briefly described in the following paragraphs.

Since $T1$-weighted scan and $T2^*$-weighted scan were acquired in the same session and from the same subject, assuming that the subject did not move between two scans, the scanner parameters contain relevant information about coordinate correspondence. Using information about the voxel size, data size, slab orientation, mid-slab position, and a nearest neighbor interpolator, we registered the $T1$-based segmentations to the corresponding $T2^*$-based segmentations.

Alternatively, we also linearly registered the $T1$-based segmentations to the corresponding $T2^*$-based segmentations using FSL-FLIRT. Because of the acquisition set-up, we chose to limit the registration transform to 6 degrees of freedom (3 translation, 3 rotation). We used the correlation ratio as cost function, and a nearest neighbor interpolator.

### Agreement measurement

The agreement between the segmentation obtained by our method and that obtained by FreeSurfer/FSL was quantified using the Dice Index and direct comparison of the segmentation volumes for each dataset.

The Dice Index, being proportional to the ratio between the overlap and the sum of two volumes, measures the overlap of the volumes.

\[
DI = \frac{2(A \cap B)}{A + B}
\]

The Dice Index is bounded by 0, no overlap, and 1, perfect overlap.

Since the Dice Index does not provide information on the absolute values obtained, we also compared the volumes obtained from the segmentation of $T2^*$-weighted data using our method with those obtained with FreeSurfer and FSL on the corresponding $T1$-weighted datasets.
3 Results

Figure 3 shows an example of segmentation results in which boundaries of the segmented cortex are overlaid on the unwrapped phase, magnitude and corresponding T1-weighted images. The segmentation result obtained using our method seems to reasonably depict the cortical anatomy, even though some errors are observable at the frontal lobe due to the deformation of that region observable on T2* data. Figure 4 presents numerical results depicting the accuracy of our method with respect to FreeSurfer and FSL. Each boxplot in Figure 4(a) shows the following statistics: minimum, first quartile, median (line), mean (plus sign), third quartile, maximum, and outliers (circle). When comparing the segmentation results, both approaches for registration, based on scanner parameters and image-based, were used, resulting in two boxes for each method. Figure 4(b) presents scatterplots showing the agreement of volume measurements between our method and the two reference methods.

Figure 3: Example of cortical segmentation using our method. Cortical boundaries (outer in yellow and inner in green) are overlaid on, respectively, unwrapped phase (left), magnitude (middle), and corresponding T1-weighted image (right). The discrepancy in the right image between the segmented cortex and the underlying T1 image is caused by the susceptibility artifacts on the T2* image due to the frontal sinuses.

Figure 4: (a) Boxplot showing the agreement between our method and FreeSurfer (FS), our method and FSL and FreeSurfer and FSL respectively. One star (*) indicates a registration based on scanner parameters, and two stars (***) image-based registration. (b) Volume comparison between segmentations obtained by our method and those obtained by FreeSurfer/FSL. The dashed line represents y=x.
Several observations can be made based on Figure 4(a). First, the registration method used to align T1-based and T2*-based segmentations has a significant influence on the results. The increased spread observed when using only the scanner parameters could be explained by patient motion and the difference in maximal values seems to statistically indicate that image-based registration will be in any case more accurate. Second, taking into account some disagreement between FreeSurfer and FSL, the agreement between our method and these two state-of-the-art methods on the experimental data showed that our method gave good segmentation results. Moreover, the overall spread is comparable, if not lower, showing that our method is as robust as state-of-the-art methods.

Based on the Bland Altman plots presented in Figure 5, one can make the following observations. Figure 5(a) shows no trend in the volumetric difference between our method and FreeSurfer. However, there is a decreasing trend of the difference as the average increases compared to FSL, as shown in Figure 5(b). The same trend is found between FreeSurfer and FSL, as shown in Figure 5(c), indicating a similar behavior of our method and FreeSurfer compared to FSL. As could be expected from Figure 4(b), our method shows a bias compared to FreeSurfer and FSL, which is higher than the intra-reference bias (FreeSurfer vs. FSL).

4 Discussion

4.1 Method

The method is based on K-means clustering being applied separately on magnitude and phase images, despite K-means clustering being a multi-feature method. We carried out experiments to compare the results obtained using both phase and magnitude information as combined features for the clustering with the presented method. Results were in favor of our method, which can be explained by the different contrast information provided by magnitude and phase: since there is good CSF/GM contrast on magnitude but not on phase image and conversely good GM/WM contrast on phase but not on magnitude image, the quality of the clustering obtained with the multi-feature approach is not as good as expected. Applying K-means separately on phase and magnitude data and combining the results afterwards during the subsequent cortex detection steps seem to make best use of the available information.

In the outer contour detection step, adding vein cluster from phase images to the vein cluster from magnitude images brought added value to the segmentation process. Although both magnitude and phase images contained vein information, the vein cluster obtained from phase images had observably complementary information compared to that obtained from magnitude images, and vice versa.

Magnitude data was not useful in the initial inner contour detection step. This step made use of a minimum cost approach to detect the global GM/WM interface. Due to its low GM/WM contrast, the magnitude data presented unreliable global GM/WM separation information. On the contrary, the phase data did have good GM/WM contrast; and therefore were the subject of this minimum cost approach, yielding a good approximation of the inner cortical boundary.

The subject of the refinement step was the mask combining voxels classified as gray matter on both magnitude and phase images (GM). Since magnitude image presented good local CSF/GM contrast of the cortical segments missing in the initial segmentation, its GM cluster was used to complement for the corresponding information on phase image.

Figure 5: Bland Altman plots for volume measurement of the obtained segmentations. Dashed-dotted lines=Mean, dotted lines=Mean +/- 2SD.
4.2 Validation

The over-segmentation problem observed in the quantitative study comes from two possible sources. First, the refinement step modified the local cortical thickness by increasing it based on $B_{GM}$ mask starting from value $d$ (computed using (3)). Although local cortical thickness smaller than $d$ was not recovered, the results appeared to be fairly accurate and feasible considering that K-means clustering method did not take into account spatial information, resulting in noisy clusters. Second, this over-segmentation can be accounted for by the fact that the overall GM/WM contrast on T1-weighted data is decreased with aging [4], whereas such contrast on phase data seem not to suffer from this effect.

For validation purpose, comparing to manual delineation obtained on T2*-weighted data would be the optimal approach. However, manually segmenting the entire datasets is not only time and labor intensive but also difficult. Validating using a single labeled atlas requires non-rigid registration in order to deform the atlas onto images of other subjects, and consequently would suffer from inter-subject variation as well as registration accuracy.

In summary, our method is capable of providing a good segmentation of the cerebral cortex on challenging data. Results show some disagreement between segmentation obtained using our method with the reference methods. The differences in volumes seem to indicate that our method is not accurate enough to be used for cortical thickness measurements but still provides a good delineation of a region of interest for subsequent, e.g. intensity-based, analysis. The differences in result have to be mitigated by the fact that the T1-weighted images were not presenting an optimal contrast, resulting in possible inaccuracies of the references. Additionally, local distortions due to the different pulse sequences used for T1-weighted and T2*-weighted datasets will intrinsically result in local, sometimes major, differences, such as those observed in the frontal part of the brain. A positive aspect of our method is that it possibly alleviates the need for acquiring a high-resolution T1-weighted dataset when targeting iron deposition in the cerebral cortex. This would result in a shorter acquisition protocol, thus increasing the throughput of the scanner, or in the possibility of performing other types of acquisition.

5 Conclusions

We presented an algorithm which combines magnitude and phase information to segment human brain cortex in 7T MR images. The key idea is to use the contrast information obtained from the phase data that is not present in the magnitude image, especially in data of the elderly population. The detection of initial cortical boundaries is done by means of K-means clustering applied separately on the magnitude and phase images. The inner boundary is further refined using an iterative approach retaining relevant regions based on a combination of magnitude and phase data.

We validated our method by comparing its results to state-of-the-art methods which make use of T1-weighted data. Validation results showed a good overlap agreement between segmentations obtained by our method and those obtained by FreeSurfer/FSL, our method systematically over-estimating the volume of the cerebral cortex. Our study suggests that combined magnitude and phase-based method is a good alternative for cerebral cortex segmentation in datasets presenting low GM/WM contrast.

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References


