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An Improved Model – Based Segmentation Approach and its Application to a Volumetric Study of Subcortical Structures on MRI Brain Data

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Abstract

We introduce a segmentation approach for brain MR images focusing on the following subcortical brain structures: caudate nucleus, thalamus, putamen, globus pallidus, thalamus, lateral ventricle and third ventricle. The overall image registration and segmentation approach consists of two phases. The first phase is registration of MR images to a standard coordinate and segmentation of brain into three types of tissue. In the second phase, an improved model – based segmentation method for subcortical structures of interest is applied to tissue segmentation result using a set of manually segmented structures as models. The approach first uses the model voxel centroid to locate the structure location, and the distances between valid boundary voxels of both model and incoming image are calculated to perform the structure model selection and matching operations, and finally the model boundary is used to bridge or fill the boundary to obtain the final segmentation result. An improved algorithm introducing direction property to distance calculation in model selection is proposed. A different segmentation approach is applied to lateral ventricle.

Experiments to compare the performance of the original and modified algorithm are carried out. An extensive validation process has been performed with positive results on 11 structures as well. DICE similarity index and modified DICE criterion are used as performance evaluators. The approach is then applied to volumetric study of 11 structures in 113 healthy subjects. The age effect on these structures is investigated and volumes of caudate nucleus, thalamus as well as putamen decrease with aging.
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Chapter 1

Introduction

In this chapter, we first introduce magnetic resonance imaging (MRI) images, then introduce 3 types of tissues in human brain briefly and illustrate the spatial location and shape of 6 subcortical structures in the brain, describe their functions and pathology. At last, we discuss the importance of volumetric as well as cross-sectional study of brain structures.

1.1 Brief introduction to MRI brain images

The basic idea of MRI is to calculate the signal change of the protons by utilizing their interaction with the external magnetic field and radio frequency signal. When a person is placed in a strong magnetic field, the protons in the human body align themselves to the direction of the external magnetic field (z-direction). A radio frequency (RF) pulse is transmitted to the protons. After absorbing the transmitted energy, the protons are forced to the direction perpendicular to...
the z direction. Then, protons start to realign themselves back to the z direction and the energy absorbed by the protons is then released in the form of radio frequency signals. A RF receiver is used to receive these signals which are used to reconstruct the final images.

- **T1 weighted MRI images**

  T1 – weighted images are obtained by comparing the T1 relaxation times of the different tissues. T1 relaxation time measures the time that the protons take to release the absorbed energy to their adjacent tissues and realign to the z-direction.

- **High magnetic field MRI**

  The units for measuring the strength of the magnetic field are Tesla. Majority of MRI scanners used for clinical diagnosis are 1.5 Tesla scanners. MRI scanners with magnetic field larger than 3.0 Tesla are considered as high field MRI. High-field MRI has higher signal-to-noise ratio and better spatial resolution. However, it also causes severe RF intensity inhomogeneity that degrades the image quality and makes the automatic segmentation of brain structures challenging. In this thesis, MRI scanner used is a 4.0 Tesla high field scanner.

- **Three image planes**

  In MRI, the images are generally acquired in three planes: the sagittal plane, the coronal plane, and the axial plane (also called horizontal plane). Figure 1.1 illustrates these three planes.
1.2 Introduction to human brain and subcortical structures

We will first introduce 3 types of tissue in the human brain and then illustrate the spatial location and shape of 6 subcortical structures in the brain, describe their functions and pathology, respectively.

1.2.1 Three types of brain tissue

Human brain consists of three main tissue types: gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). GM and WM are two major components of the central nervous system (CNS).

GM mainly consists of neuronal cell bodies, neuropil and capillaries. In the living body, GM has a gray brown color which comes from capillary blood vessels and neuronal cell bodies. Gray matter is distributed at cerebral cortex and cerebellar cortex, as well as in the depths of the cerebrum, cerebellum, brainstem and spine. The function of GM is to route sensory or motor
stimulus to inter-neurons of the central nervous system in order to create a response to the stimulus. GM structures, both cortex and subcortical structures, process information originating from the sensory organs as well as other GM regions [40].

In contrast to GM, WM is composed of myelinated nerve cell processes (called axons). The white appearance of WM arises mainly from the whiteness of myelin which surrounds axons. WM forms the deep parts of the brain and the superficial parts of the spinal cord. The function of WM is to connect all kinds of GM areas together, where nerve cell bodies locate, and relay nerve impulses among neurons. GM structures are spread within the WM [41].

CSF is clear bodily fluid that circulates throughout the CNS. It resides between the midst of the skull and the layer of the meninx nearest to the brain as well as the ventricular system around and inside the brain. CSF protects the brain tissue from injury when jolted or hit, acting like a cushion or buffer and the circulation of CSF delivers nutrients to the structures of the nervous system and removes wastes from the brain and spinal cord [42].

The following figure illustrates these three types of tissue in T1-weighted MRI image. In T1-weighted images, CSF is dark, WM has bright intensity and GM’s intensity is between CSF and WM. In this thesis, we are interested in the following GM structures: caudate nuclei, putamen, thalamus and globus pallidus plus the following CSF structures: lateral ventricle and third ventricle. These structures will be introduced in details in the next section.
1.2.2 Physical, functional and pathological information of subcortical structures

Subcortical structures are essential elements of the human nervous system. Each structure is responsible for specific functions. Our research is concentrated on the following structures: the caudate nucleus, thalamus, putamen, globus pallidus, lateral ventricle and third ventricle due to their significance in clinical diagnosis. Subcortical brain structures are located inside the cerebral cortex and in the medial aspect of the brain.

Figure 1.3 displays 3D structure of thalamus and basal ganglia. The basal ganglia consists of the caudate nuclei, putamen, and globus pallidus [1]. Figures 1.4 to 1.7 illustrate the spatial location of the caudate nucleus, putamen, globus pallidus and thalamus in 4.0 Telsa MRI T1-weighted images.
Caudate nuclei:

The caudate nucleus is found approaching the core of the brain, locating astride thalamus. Both left and right brain hemisphere have a caudate nucleus inside, respectively. It looks like a C-shape structure with a larger head, narrowing to a body as well as a tail. The caudate nucleus constitutes some of the lower boundary of the anterior horn of the lateral ventricle. The body of caudate nucleus moves backward and its tail bends back toward the front, composing the upper boundary of the inferior horn of the lateral ventricle. It is parted from globus pallidus and putamen by the anterior limb of the internal capsule [1].

The caudate nucleus is primarily involved with control of voluntary movement. It is able to exert modulatory effects on motor activity and facial gestural posture and expression, and aids in the maintenance of selective motoric attention, like standing still and observing. It has been demonstrated that the caudate is also highly involved in learning and memory [2], particularly in
the feedback processing [3]. The left caudate in particular has been suggested to have a relationship with the thalamus that governs the comprehension and articulation of words as they are switched between languages.

It has been theorized that the caudate nucleus may be dysfunctional in persons with obsessive compulsive disorder (OCD), in that it may perhaps be unable to properly regulate the transmission of information regarding worrying events or ideas between the orbitofrontal cortex and thalamus. A neuroimaging study found that the right caudate nucleus has the large change after patients had been treated with paroxetine [4].

Axial view

Sagittal view

Coronal view

Figure 1.4 Boundary of caudate nucleus in axial, sagittal and coronal views, respectively
**Putamen:**

The putamen has a round shape and sits at the bottom of the forebrain. Both left and right brain hemisphere have a caudate nucleus inside. It is the outer most portion of the basal ganglia and lies lateral to the internal capsule, ventrolateral to the caudate, medial to the external medullary lamina, and is separated from the caudate nucleus by the fibers of the internal capsule for most of its length [1]. Nerve pathways connect the putamen together with the globus pallidus.

Because putamen is linked against some other GM structures anatomically, it acts together with them to control all kinds of motor skills, including motor preparation, motor performance and exercises [5] and specification of movement’s magnitudes[6]. Putamen also plays a role in the process of reinforcement and implicit learning. Reinforcement learning means interaction with the surrounding situations and behaving accordingly to maximize the effect. In contrast, implicit learning is a relatively passive. People are exposed to the environment and thus obtain knowledge and take action.

It is clear that the putamen also plays an important role in Parkinson’s Disease[8]. Parkinson’s Disease is the result of neurons’ loss in the substantia nigra area. And putamen is connected with the substantia nigra as well as globus pallidus. The activity in the pathways to interior globus pallidus (GPi) declines while activity in the pathways to external globus pallidus (GPe) rises which jointly leads to extreme restraint of the thalamus, so patients with Parkinson have difficulty conducting motor planning and voluntary movements.
**Globus pallidus:**

The globus pallidus locates at the base of the forebrain. There is a globus pallidus within each hemisphere of the brain. It is a pale appearing spherical area and separated from putamen by lateral medullary lamina. The globus pallidus is traversed by the numerous myelinated axons that give it the pale appearance from which it was named. Globus pallidus is further divided into two segments. The medial segment of the globus pallidus is called internal globus pallidus (GPi), and lateral division is called external globus pallidus (GPe).
Globus pallidus is involved in the regulation of voluntary movements at a subconscious level together with other basal ganglia structures, since it attains input information from the putamen and caudate and projects to the sub-thalamic nucleus. It also constitutes a high-frequency autonomous pacemaker. Autonomous pacemakers are neurons capable of periodic spiking in the absence of synaptic input which are important participants in a wide array of neural circuits [9]. Cells within the globus pallidus may be preferentially damaged and perish in hypotension, carbon monoxide poisoning, barbiturate intoxication, hydrogen sulfide poisoning, and Wilson disease.

Figure 1.6 Boundary of globus pallidus in axial, sagittal and coronal views, respectively
Thalamus:

The thalamus is a midplane paired symmetrical structure within the brain, locating between the cerebral cortex and midbrain. There are two thalami in human brain. The thalamus is a bulb-shape structure, sitting at an angle of 30 degrees and symmetrically on right and left side of the third ventricle. It lies dorsal to the hypothalamic sulcus, a shallow groove on the lateral wall of the third ventricle. The lateral and caudal parts of the thalamus are enlarged and overlie midbrain structures [10].

The thalamus has multiple functions, including carrying motor signals to the cerebral cortex, besides regulation of the states of sleep and wakefulness [11]. It acts as a relay between various subcortical and cortical areas. In each sensory system, thalamus accepts sensory signal and dispatches it to the corresponding cortical area. Taking the human visual system as example, inputs from the retina are sent to the thalamus, and then thalamus dispatches the signal to the visual cortex in the brain. Thalami have intense mutual junctions with the cerebral cortex, that plays a role in consciousness.

Thalamic syndrome possibly burns sensation on either half of human body [12]. Korsakoff's syndrome origins from lesions in mammillothalamus or thalamus. Also, it is likely that injury of thalamus can result in permanent coma.
Axial view

Sagittal view

Coronal view

Figure 1.7 Boundary of thalamus in axial, sagittal and coronal views, respectively

Lateral ventricle and third ventricle are CSF structures. Figure 1.8 (from syweb.com/Brain/Bimages/) displays 3D view of CSF ventricular system in brains. Figures 1.9 to 1.10 illustrate the spatial location of the lateral ventricle and third ventricle in 4.0 Telsa MRI T1-weighted images.
Lateral ventricle:

The lateral ventricles are part of the ventricular system. They are curved-shape structures that form the shape of each hemisphere. Each lateral ventricle consists of three horns: anterior horn, posterior horn and inferior horn. Anterior horn is in the front of the lateral ventricle connecting the lateral ventricles with the third ventricle. Above the anterior horn is the corpus callosum which is a bulk of nerve fibers connecting two hemispheres and making them communicate with each other. The head of the caudate nucleus is inferior to the anterior horn. The posterior horn locates in the back of the lateral ventricle, extending into the occipital lobe in the back of brain. The central body and the cella media form the central section of the lateral ventricle. Below that are regions of the caudate nucleus, the choroid plexus, the thalamus, and the fornix cerebri. The inferior horn sits in the bottom of lateral ventricle, also referred as the temporal horn [13]. Lateral ventricles protect the brain from trauma and provide pathway for the
circulation of cerebrospinal fluid [14]. Choroid plexuses appear in lateral ventricles, which produce cerebrospinal fluid. If its production is bigger than resorption or its circulation is blocked, the enlargement of the ventricles may appear and cause a hydrocephalus.

### Axial view

![Axial view](image)

### Sagittal view

![Sagittal view](image)

### Coronal view

![Coronal view](image)

Figure 1.9 Boundary of lateral ventricle in axial, sagittal and coronal views, respectively

#### Third ventricle

The third ventricle is a fluid-filled cavity comprising the ventricular system. There is only one third ventricle within the human brain. It is a median cleft between the two thalami, and
continuous caudally with the cerebral aqueduct, which runs though the midbrain. It communicates with the lateral ventricles through a small opening (interventricular foramina) at the anterior end of the third ventricle and with fourth ventricle posteriorly by the cerebral aqueduct. Third ventricle has similar functions as lateral ventricles, like providing pathway for circulation of cerebrospinal fluid (CSF). It plays a homeostatic role in the maintenance of CSF electrolytes [15].

Axial view

Sagittal view

Coronal view

Figure 1.10 Boundary of third ventricle in axial, sagittal and coronal views respectively
1.3 Importance of volumetric study of brain structures

Volumetric and shape studies of subcortical brain structures are of great importance in clinical diagnosis. It has been shown that the changes of volume and shape of subcortical structures often are indications of the existence of various types of disorders listed as below.

Schizophrenia: significant volume reductions are found bilaterally in the thalamus and amygdala - hippocampal region in comparison to control subjects and marginal differences are noted in the globus pallidus, putamen, third ventricle, fourth ventricles and cerebellum [16]. It is also reported that lateral ventricles are enlarged and medial temporal lobe structures have reduced volumes in schizophrenia patients [17, 20].

Huntington’s disease: patients with Huntington's disease exhibit significant brain atrophy resulting from volume reductions in both cortical and subcortical grey matter. The caudate nucleus and putamen were strikingly reduced and this atrophy correlated with the severity of disease [18].

Obsessive compulsive disorder (OCD): A voxel-based morphometry study comparing OCD patients with healthy subjects found OCD patients to have enlarged grey matter and some of them extend into the caudate nuclei [19].

1.4 Review of cross-sectional studies of brain structures

Cross-sectional studies form a class of research methods that involve observation of some subset of a population all at the same time, in which, groups can be compared at different ages with respect to volumes of brain structures. The fundamental difference between cross-sectional and longitudinal studies is that cross-sectional studies take place at a single point in time and that a longitudinal study involves a series of measurements taken over a period of time. Cross-
sectional study of healthy subjects can serve as control group for that study in patients with disorders. It can be used to clarify the volume change of structures is caused by aging or all kinds of disorders, thus important to clinical diagnosis.

There is a consensus that in healthy elderly subjects (age > 50 years old), the volumes of lateral ventricle and third ventricle are significantly increased with age [21, 22]. Age related volume loss in caudate and putamen are also reported [25, 26]. However, age effect in thalamus and globus pallidus is not very clear. No relationship between age and the volumes of thalamus has been observed in some papers [25, 27]. However, thalamic age decline has been reported in other samples [28, 29]. It is reported that mild bilateral age-related shrinkage of the globus pallidus was observed in men. [30], but others did not report such shrinkage [31, 32].

For young and mid-aged subjects, there is also conflicting evidence regarding age effects on subcortical structures. Pieperhoff [24] conducted volume analysis on 51 healthy male subjects (age: 18-51 years old) and found volume of both left and right thalamus reduces with age. However, [33] analyzed volume change in 30 healthy subjects (age: 20 – 41 years old) and observed that only right thalamus decreases over age but left thalamus does not. Also, Pieperhoff found right putamen shrink but left putamen does not shrink significantly. But Patrice observed both right and left putamen has significant volume reduction during this age range [33]. Patrice reported right and left caudate nucleus do not have significant reduction, however, Khader [23] did experiment on 33 healthy subjects (age: 19-59) and reported caudate volume decreased rapidly with age. Third ventricle and left lateral ventricle show widening with age increasing while right lateral ventricle does not have the widening significantly [24]. But for age younger than 50 years old subjects, no age related change was observed in [31]. Globus pallidus does not have significant reduction [32, 33, 34].
Chapter 2

Research Problem, Objective and Organization

In this chapter, research problem is presented in Section 2.1 followed by research objective stated in Section 2.2. Section 2.3 introduces the overview of the automatic subcortical segmentation approach. At last, Section 2.4 describes the organization of the thesis.

2.1 Research Problem

Volumetric study of subcortical brain structures is of great importance in clinical diagnosis. It has been shown that the changes in volume and shape of subcortical structures often are indications of the existence of various types of disorders. In the volumetric study of brain structures in patients, healthy subjects serve as a control group to be compared with patients. Because the volume of brain structures could change with age, the study of effect on brain structures in healthy subjects is needed to clarify whether volume change in patients is caused by
Six subcortical structures were selected as research interest due to their importance in clinical diagnosis. They are caudate nuclei, putamen, globus pallidus, thalamus, lateral ventricle and third ventricle. As stated in literature review, volume change of these structures is not very clear, especially in young and mid-aged subjects using high field 4 Tesla MRI scanning. Different papers reported conflicting results. The thesis focused on age effect on these six subcortical structures in healthy young and mid-aged subjects, ranging from 11 years old to 45 years old.

The magnetic resonance imaging (MRI) produces the high quality 2D/3D images of human anatomic tissues by using the interaction of protons with a strong external magnetic field and radio frequency. It is superior to other imaging techniques, such as CT, ultrasound and X-ray in the area of clinical diagnosis of human brains. Segmentation of subcortical structures in MR images is challenging due to intensity inhomogeneity, low intensity contrast among adjacent GM structures, structure topological variation among people, and random noise. Intensity inhomogeneity is inevitable in the MR imaging mainly due to imperfect radio-frequency coils and the bulk magnetization susceptibility variability of different tissues. In MR brain images, this intensity inhomogeneity can be more than 30% variations of image intensity for the same brain tissue [Meyer 1995], and it is even more severe in the high – field MR images. Another difficulty is the low intensity contrast which makes the boundaries between the adjacent GM structures blurry and in some cases even invisible and thus presents a problem for the accurate segmentation of these structures.

The manual segmentation by trained experts working through one slice at a time of the MRI volume remains the golden standard for the segmentation of subcortical brain structures.
Not only it is time-consuming and error-prone, but it also suffers from the low intra-rater and inter-rater consistency. With the rapidly growing use of MRI technique, an automatic segmentation method is desired to maintain performance consistency and save time.

A model-based automatic segmentation method proposed by Cai was proven to be able to obtain acceptable segmentation results and have potential clinical applicability. The approach consists of two steps: first align input MR image to the model image and segment brain into GM, WM and CSF tissues. Second step: use the GM, WM, and CSF tissue segmentation results of the incoming image as input, model selection and matching operation is applied, and a final segmentation result is built. In this thesis, some modifications were made to further improve the segmentation result. And the modified method was applied to healthy subjects to get volumes of brain structures. Last, in a cross-sectional study, statistic analysis was needed to study of age effect on volume changes of brain structures.

2.2 Research Objective

The main research objective of the thesis is to study the relationship between volume of brain structures and age in healthy young and mid-aged subjects. Accurate segmentation of structures is crucial in order to fulfill the main research objective. Based on the main research objective, we have the detailed itemized research tasks as following:

1). Modify existing tissue segmentation method to get better GM, WM and CSF segmentation result which is the fundamental to the model-based segmentation result.

2). Modify the model-based segmentation method for putamen and ventricles.

3). Validate the model-based method by comparing segmentation results with manually segmented results.
4). Apply segmentation approach to a large number of MR brain data to segment 6 subcortical structures and obtain volume values.

5). Conduct statistical analysis to study the correlation between volume change and age.

2.3 Overview of Subcortical Structure Segmentation Algorithm

Cai’s subcortical segmentation approach [46] consists of two parts. First part is to align incoming MR images to standard coordinate and accurately segment MR image into 3 types of tissue (GM, WM, CSF). Second part is to use tissue segmentation result from part 1 as well as a set of manually segmented model structures as input, and a model-matching algorithm is applied to tissue segmentation. A best matching model is selected based on a closeness measure and further segment out subcortical structures. These two parts are separated which enables the incorporation of better segmentation method in either part in the future to improve performance. Also, two parts of the approach are introduced in two chapters respectively.

2.4 Thesis Organization

The thesis is organized as follows: Chapter 1 introduces human brain, subcortical structures, and importance of volumetric study of brain structures in clinical diagnosis. Research problem and objective are presented in Chapter 2. Chapter 3 introduces the first part of the segmentation method --- registration and tissue segmentation in detail including some modifications and post processing. In Chapter 4, the concepts and procedure of the proposed model – based approach are discussed. Limitation of this approach is analyzed and modification is proposed. Chapter 5 presents the results of the validation experiments as well as experiments in a large-scale practical MR data. In Chapter 6, we present the conclusions.
Chapter 3

MR Image Registration and Tissue Segmentation

In this chapter, MR image registration is introduced and illustrated in Section 3.1 and principles of tissue segmentation, its modification and post processing are presented in Section 3.2.1, 3.2.2 and 3.2.3 respectively.

3.1 3D Image registration of MRI brain volumes

During the acquisition of MR images, locations of different subjects’ heads with respect to the MRI scanner can not be exactly the same. Also, subjects might not keep their head upright all the time during the scanning. Thus, image registration which aligns images is necessary in order to be able to locate the rough position of subcortical structures for any segmentation purpose.
Image registration is the process of transforming the different images into one coordinate system which is defined by the template image. Template image is supposed to be stationary and moving images are transformed to align with the template image. General image registration framework consists of four parts: transformation, objective function, optimization and interpolation. The objective function is used to measure the similarity between the template image and moving image. The image registration is indeed an iterative optimization process of trying to find the best transform parameters which maximize or minimize the objective function. Interpolation is a further refinement process to interpolate the transformed image grid to template image grid. In this thesis, the registration algorithm was provided by the widely used Statistical Parametric Mapping (SPM) software package [35].

The 3D image registration used in SPM is a multi-modality image registration method based on information theory [36]. The objective function used is normalized mutual information which computes the mutual information between image A and B [37]. Mutual information measures the amount of information one random variable (image intensity in one image) provides about another random variable (image intensity in the other image). The optimization algorithm is Powell optimization [38]. The transformation matrix is represented as a 3D affine transform with 12 parameters. The interpolation used is trilinear interpolation which is a 3D linear interpolation process. Other input parameters needed in SPM registration are separation, tolerance, and histogram smoothing parameters. Separation is the average distance between sampled points. It can be a vector to allow a coarse registration followed by increasingly fine ones. Tolerance is the accuracy for each parameter. The iteration stops when the difference between successive estimates is less than the required tolerance. Histogram Smoothing is the standard deviation of Gaussian smoothing which is applied to the joint histogram. The result is
the registered MR image and a voxel-to-voxel transformation matrix.

The following figure illustrates rotation and translation effect of image registration. (a) is slice 110 in template brain. (b) is slice 110 in unregistered brain which is totally different from the same slice in template and (c) is slice 98 in unregistered brain which actually corresponds to the slice 110 in template. And (d) is slice 110 in the registered brain. From (b) and (d), we can see registration process translates brain volume in Z-axis by 12 slices to make slice 110 in both template and moving image look alike. Also as shown from (c) and (d), registration rotates the brain by about 5 degrees so that it is as upright as the template image. Without registration, we cannot locate the position of brain structure by simply superimposing structure in the template to the incoming data.

Template volume (slice 110)  Unregistered volume (slice 110)  Unregistered volume (slice 98)

Registered volume (slice 110)
3.2 Tissue segmentation of brain volume

Tissue segmentation is to segment brain images into three main tissue types: GM, WM, and CSF. The principle of tissue segmentation in SPM is introduced first, the deficiency of default SPM probability map is presented and finally, the new map is built to obtain better segmentation result. At last, post-processing operation is introduced.

3.2.1 Principles of tissue segmentation in SPM

The tissue segmentation is a challenging task mainly due to intensity inhomogeneity and partial volume effect. Intensity inhomogeneity means the same brain tissue at different spatial locations may display different intensity values and different brain tissues at different spatial locations may have similar intensities. Partial volume effect is an artifact caused by the insufficient spatial resolution of MR scanners. It refers to the situation that the intensity of a voxel in MR volumetric images is determined by the signals generated from more than one type of tissue. In this thesis, the widely used SPM software package is selected to accomplish tissue
segmentation task because it can well handle intensity inhomogeneity as well as partial volume effect.

SPM’s tissue segmentation is based on the maximum a posteriori (MAP) probability framework. The probability of each voxel being GM, WM or CSF is iteratively calculated using class intensity distributions and class spatial information. Class intensity distributions are modeled with Gaussian distributions. The number of Gaussians used to represent the intensity distribution for each tissue class can be greater than one which could overcome intensity inhomogeneity and partial volume effect to some extent. Class spatial information is modeled with a modified Gaussian Mixture model. The prior spatial probability of each voxel being GM, WM or CSF called tissue prior probability maps is predefined. An iterative approach is used to estimate the intensity parameters with the prior probability atlas being used as the initial starting point. The segmentation result is the one when the iterative process converges. The SPM result is three probability maps, one for each tissue.

3.2.2 Modification of tissue prior probability maps

The default tissue prior probability maps in SPM are modified versions of the International Consortium for Brain Mapping (ICBM) Tissue Probabilistic Atlas [39]. The original data are derived from 452 T1-weighted scans, which were aligned with an atlas space, corrected for scan inhomogeneities, and classified into GM, WM and CSF. These data were then affine registered to the MNI (Montreal Neurological Institute) space and downsampled to 2mm resolution.

The deficiency of the default tissue prior probability maps is those voxels in the location of GM structures globus pallidias (GP) and part of thalamus (TH) has higher probability for WM than GM. Since the intensity of GP and part TH is brighter than average GM intensity, based on
intensity only, they could be easily misclassified as WM during the iteration. So class spatial information is crucial to the successful segmentation of the part of GM. Tissue prior probability maps should provide correct spatial information thus a good starting point for the iteration to avoid wrong local optima.

Manually segmented tissue results available at [http://www.cma.mgh.harvard.edu/ibsr/](http://www.cma.mgh.harvard.edu/ibsr/) [IBSR] provide correct spatial information. Both IBSR and default SPM maps are resized to have the same dimensions and resolutions as incoming data and SPM maps are registered to IBSR heads so that these two can be added. New prior probability maps are constructed by weighted averaging IBSR and default SPM maps. Specifically, new maps = 0.8* IBSR + 0.2*SPM.

Figure 3.2 demonstrates the deficiency of default probability maps. GM probability is very low in the location of GP and TH. Thus in the GM segmentation result, all GP and large part of TH is totally missing, with GM probability close to 0. Even part of putamen is missing as well because GM probability is less than WM probability in that area.

(a) Original image  (b) Default GM probability map  (c) segmentation result (prob.)

Figure 3.2 illustration of deficiency of SPM segmentation using default probability map
The following figure demonstrates the result of modified probability maps. In modified GM probability map, GM probability is high in the location of GP and TH. In the GM result, we can see TH has larger than 0.5 probability and is preserved as GM structures. GP is preserved as GM if appropriate threshold is selected, which will be discussed in the next section.

(a) Original image     (b) Modified GM probability map     (c) segmentation result(prob.)

![Figure 3.3 SPM segmentation result using modified spatial probability map](image)

3.2.3 Post-processing segmentation results

Post-processing segmentation results include two parts. The first part is selection of one appropriate GM threshold to get good deterministic tissue segmentation result for globus pallidus. The other is the correction of CSF segmentation result.

- **Different deterministic tissue segmentation result for globus pallidus**

As stated before, the SPM result is three probability maps, one for each tissue. The deterministic segmentation result is obtained by classifying voxel to the tissue type with highest probability. It works very well for most structures except for GP. In the experiment, we found
part of GP has probability from 0.25 to 0.5 and thus is classified as GM. We set a GM threshold of 0.25 for GP. As long as GM probability is larger than 0.25, it is GM in the final result. Other structures cannot use GP’s tissue segmentation result because GM is overestimated in the location of these structures, some GM/WM boundary (like lateral boundary of putamen) are blurred which has negative effect on subcortical segmentation.

- **Correction of CSF segmentation result**

  The variation in volume and shape of CSF is large among individual brains. CSF spatial prior probability map is not suitable for all brains. For example, CSF in some brains is much smaller than that in prior probability map. Segmentation result could possibly misclassify some GM as CSF. An example is illustrated as below: in the original segmentation result, some GM in caudate is misclassified as lateral ventricle. Correction of CSF segmentation result is needed.
Correction of CSF segmentation is a pixel-wise thresholding method purely based on intensity. Because third ventricle is small and less variation among different individuals, correction of CSF is for lateral ventricle. Also, only caudate has lots of boundaries with lateral ventricle. So correction of CSF is only applied in caudate and its surrounding CSF instead of whole brain. Find the rough location of caudate by its location in template brains, establish a cube which is region of interest (ROI) to contain the caudate, threshold only in this cube. For each slice, the steps below are followed.

1. Calculate standard deviation of CSF intensity in ROI
2. If the standard deviation is smaller than a threshold: STD_threshold, it means the CSF intensity is mostly uniform and no misclassification occurred. So segmentation result keeps unchanged. The STD_threshold is preset to be 16 after parameter tuning in experiments.

3. If the standard deviation is larger than the STD_threshold, it means highly likely some GM is misclassified as CSF. Pixel-wise threshold is applied to correct segmentation.

The threshold CSF_GM_threshold used to separate CSF and GM is automatically found using Otsu's method, which chooses the threshold to minimize the intra-class variance of the thresholded black and white pixels. Set voxel with intensity value smaller than CSF_GM_threshold as CSF, others as GM.

The corrected tissue segmentation result is the input for the following model-based subcortical structure segmentation method.
Chapter 4

Model – Based Approach for the Segmentation of Subcortical Brain Structures and its Improvements

In this chapter, we introduce Cai’s model – based approach for the segmentation of the subcortical GM and CSF structures. The concepts of this approach are introduced in Section 4.1, followed by detailed description of the procedure in Section 4.2. Disadvantage is analyzed and improvement is proposed in Section 4.3. Modified segmentation for CSF structures are shown in Section 4.4. Last, implementation of algorithm is explained in Section 4.5.
4.1 Basic ideas of the model – based approach

The basic idea of the approach is valid boundary voxels of both the model and incoming data are used to perform the structure model selection and matching operations and then, the model boundary is used to bridge or fill the boundary between rather blur regions to complete our segmentation process and obtain the final segmentation result (Valid boundary voxels are the GM boundary voxels with adjacent WM and/or CSF voxels for GM structure segmentation. Valid boundary voxels are the CSF boundary voxels with adjacent GM and/or WM voxels for CSF structure segmentation).

A more detailed description of the model based approach is as below.

Data requirement:

- A set of manually labeled subcortical brain structures are available as models. The valid boundary voxels of the structure are also identified.
- GM, WM and CSF tissue segmentation results of incoming data are available as the input data.

Conceptual procedure:

- Use of each model structure centroid voxel to locate the structure location.
- Valid boundary voxels identification of both the input tissue segmentation and the model subcortical structures.
- Best matching model selection for the structure of interest by calculating the minimal average distance between valid boundary voxels of the model and the valid boundary voxels of incoming data.
- Voxel matching operation to extract the 3 different structure regions (see Figure 4.1) between the input and model structures.
• Recombination of these non-overlapping regions into a single contiguous subcortical structure as the segmented result for the input brain image. The selected model and incoming GM are then combined to form the final segmentation result by using the model boundary to bridge the indistinguishable boundary of the interested structure.

**Fundamental supports for Cai’s model based approach [46]:**

1. The WM, GM, and CSF tissue segmentation is an easier task and results are fairly accurate using the SPM segmentation. This is important to the results since our model based approach depends heavily on the accurate identification of valid boundary voxels of the structures.

2. For MRI brain volumes after non-deformable registration, it is possible to find a set of representable MRI brain models where the incoming MR brain image can closely resemble one of these models. The closeness measure can be established to select best matching model. To segment two adjacent GM regions with a very blur boundary (voxel intensities of GM in adjacent regions may be visually indistinguishable), a closely matched model can be used to bridge or fill the boundary gap.

3. It is experimentally proved by Cai that the voxel centroids of the subcortical structures of interest remain at almost the same location with standard deviation of no more than 2 voxels after image registration [46]. This fact has been established by processing the known segmentation results of the 18 brain samples provided by the Harvard Medical School [50]. This fact confirms that the use of model voxel centroid as the subcortical structure locator reduces the possibility of mis-matching and selecting erroneous subcortical structures in our segmentation process.
4. DICE and related matching performance indexes are acceptable measures to evaluate volume overlapping. It has been reported in the literatures [48] that a DICE value over 70% is considered a good match.

This method can provide the following advantages:

- Suitable for the high – filed MR images with severe intensity inhomogeneity
- Applicable to data obtained from both the control subjects and subjects with atrophies.
- Applicable to large amount of data in the clinical settings
- Computationally efficient.

4.2 Detailed Cai’s Segmentation algorithm [46]

The overall model based segmentation algorithm consists of the following steps:

1. Match the input brain structure to each of the model structures using the following procedure:

   a) Superimpose structure voxel centroids of the input data and model.

   b) Create a cubical 3D region of 120% of the size of the model structure with the centroid as the center voxel.

   c) Search inside the cubical region for all GM voxels, and identify all valid GM boundary voxels for GM structures. For CSF structures (ventricles), search for CSF voxels and identify valid CSF boundary voxels.
d) Match all the identified valid boundary voxels obtained in 1.c. with the valid boundary voxels of the same type provided by the model using the minimum average distance as the index of structure model selection. The minimum average distance is the average of minimum distance of each valid boundary voxel of the model structure to all the valid boundary voxels of the input data.

e) Select the model structure with the minimum average distance over a 3 by 3 by 3 data translations centered at the model structure centroid as the matching model structure to the input structure.

2. Determine all the 3 matching disjoint regions

a) Within the cubical region, for GM structures, determine all the GM voxels of the input structure; for CSF structures, determine all CSF voxels.

b) Determine all the 3 disjoint regions:

** Region A - GM structures: all GM voxels found in both model and input.

** Region B - GM structures: all GM voxels found in the input but not in the model.

** Region C - GM structures: all GM voxels found in model but not in the input.

For CSF structures, determine the same 3 regions using CSF voxels. A 2D illustration of the resulting segmented region is shown in Figure 4.1.
3. Construct the total structure region

A. Establish acceptance or rejection for voxels in Region B.

a) Identify of valid boundary voxels of the model which are in Region A. These voxels form model boundary voxel set. Identify of valid boundary voxels of the input which are in not Region A. These voxel form input boundary voxel set.
b) For each voxel in region B, compute the minimum distance between the voxel with the model boundary voxel set. The voxel in the set with the minimum distance to current Region B voxel is called corresponding model voxel. The minimum distance is called minimum model distance.

c) Perform voxel inclusion using the following rules:

I. If the minimum model distance is greater than T, then exclude this voxel.

II. If the minimum model distance is less than or equal to T, then go to the next steps.

Threshold T is set as follows:

\[ T = \text{mean (Min\_Dist)} + \text{Coeff.} \times \text{std(Min\_Dist)} \]  

(4.1)

Min\_Dist: distances of each voxel in the selected model to its closest voxel in input data. Coeff. is 1 for GM structures and 2 for third ventricle.

III. Compute the minimum distance between the voxel with the input boundary voxel set obtained in (a). The voxel in the set with the minimum distance to current voxel is called corresponding input voxel, and the minimum distance is called minimum input distance.

IV. Compute the distance D between corresponding model voxel and corresponding input voxel.

If both minimum model distance and minimum input distance are smaller than D, then include the voxel. Otherwise, exclude the voxel.

Steps III and IV are needed to exclude other nearby structure of the same tissue type. As shown in Figure 4.2, there is another structure to the left of the structure of interest. The white
circle in the figure represents one of its voxels close to input boundary. This voxel is close to the valid boundary of model (white triangle) and its minimum model distance would be less than the threshold T in step II, thus would be included in the segmentation result wrongly. However, with step IV, the minimum model distance would be greater than the distance D (distance between the square and triangle).

Figure 4.2 illustration of rejection of voxel in Region B.

B. Form the segmented structure region which includes Region A and all voxels in Region B satisfying condition 3.A.c.

4. Final selection of the constructed structure

Only the DICE value equal to or greater than 0.7 is considered acceptable. If DICE value less than the threshold, the segmentation result is presented to human for further visual check to decide whether to accept or reject.

Figure 4.3 illustrated the final segmentation and its relationship with both the input data
and the model. Notice that indistinguishable boundary between two GM regions of the input is represented by the matching model’s boundary.

4.3 Disadvantage and Improvement of Cai’s Model-based Segmentation Algorithm

There is deficiency in selection of best matching model based on minimum average distance between valid boundary voxels in model and those in incoming data which leads to error in segmentation of putamen. We first discuss the disadvantage and then propose the
modification to improve the performance.

- **Disadvantage of the Algorithm**

  For each valid boundary voxel in the model, we find the valid boundary voxel in the input with minimum distance and consider these two voxels as corresponding voxels. But this correspondence could be wrong under the circumstance below.

  As shown in Figure 4.4, both voxel A and B are valid GM boundary voxels in the input, but voxel A is in the structure we want to segment out and voxel B is in other GM area. Voxel C is the valid GM boundary in the model. The correct average distance between model and input should be calculated based on distance from voxel C to voxel A. However, the current algorithm calculates the distance from voxel C to voxel B because the distance from voxel B to C is smaller than that from A to C and consider voxel B and C are corresponding voxels wrongly. Because distance from C to B is small, the average distance between this model to the input is small as well. It is highly likely that this model is selected as best matching model, however, we can clearly see from the figure that this model does not overlap with the structure of interest well.

  ![Diagram](image)

  Figure 4.4 illustration of wrong correspondence between input and model

  Figure 4.5 showed the wrong segmentation of putamen as result of this deficiency in
algorithm. There is a very narrow (1 or 2 voxel wide) WM gap between putamen and other lateral GM structure, thus it is possible to mis-match boundary voxel in putamen model to other GM structure. Also, another GM structure globus pallidus is interior to putemana and there is no valid boundary between GM structures, thus most valid boundary voxels for putamen are along the exterior edge against WM. Mis-match of this edge could easily lead to wrong model selection and the final segmentation is way wrong. For other GM structures, this problem does not exist in our experiments, because the WM gap to separate them from other structures is wider, like WM gap between globus pallidus and thalamus. Moreover, caudate and thalamus also have valid boundary against CSF, not only WM.

![Image](image.png)

Figure 4.5 illustration of wrong segmentation for putamen

- **Proposed Improvement**

  In the original algorithm, correspondence of valid boundary voxels is only based on the distance. Now, another property--- direction is incorporated into corresponding boundary voxel selection. Since the problem of putamen segmentation is caused by GM/WM boundary, the direction property only takes GM / WM boundary into consideration.

  During step 1.d in Section 4.2: selection of closest model, distance between voxel in the
model and input can be only calculated between valid boundary voxels with the same direction. For example, in Figure 4.4, voxel A and C have the same direction: GM is on the left and WM is on the right. Voxel B has different direction: GM on the right and WM on the left. Thus, for voxel C, only voxel A can calculate its distance from C which correctly reflect the correspondence of the model and input data.

We only consider 4-neighborhood voxels for simplicity and thus the following 8 directions. (1) GM left, WM right. (2) WM left, GM right. (3) GM bottom, WM top. (4) GM top, WM bottom. (5) GM left bottom, WM right top. (6) GM left top, WM right bottom. (7) GM right top, WM left bottom. (8) GM right bottom, WM left top. Any other direction does not fall into these 8 categories is considered as one type: no direction. Voxel with no direction in the model can only select voxel with no direction in the input as correspondence.

Figure 4.6 Possible directions of GM/WM boundary
Figure 4.7 shows the putamen segmentation after modification. Correct model is selected after modification of algorithm.

![Figure 4.7 the putamen segmentation after modification.](image)

### 4.4 Modified segmentation of CSF structures

In Cai’s proposal [46], the model-based algorithm is only applied to GM structures. CSF structures are segmented by Narrow Band Level Set Method and a spatial varying Gaussian mixture and markov random field (SVGM-MRF). But the DICE values (explained in Chapter 5.2) for third ventricle segmentation are not high in both methods: 63.29% for level set method and 64.50% for SVGM-MRF method. Also DICE values for lateral ventricle are not very satisfactory. Level set method has 75.32% and 71.0% for right and left lateral ventricle, respectively. SVGM-MRF outperforms the narrow band level set method for the segmentation of the lateral ventricle. The results are a DICE of 78.00% and 75.54% for the right and left lateral ventricle, respectively.

- **Third ventricle**

  Third ventricle (TV) has small absolute volume (generally below 2 cm$^3$) and less variation of volume and shape than lateral ventricle, thus given a set of models, average minimum distance between selected model and input data is still small, so model-based approach
is also applicable to TV. But compared with GM structures, variance of volume of TV is larger, and that requires to set threshold value $T$ to a higher value. In Formula 4.1, for TV, the coefficient before standard deviation is set to be 2 instead of 1 for GM structures.

Higher threshold value could sometimes include part of lateral ventricle wrongly into the segmentation result as illustrated in Figure 4.8 (a). Tip of right lateral ventricle is included. So a clean-up procedure is conducted to get final segmentation. As TV is one region which resides in the middle of brain, the mean of its voxels’ column indices should be around the mid-plain of the brain. However, the mean of right or left lateral ventricles’ column indices is not close to the mid-plain. So the clean-up procedure is:

1. For each slice in axial view, calculate the average column indices for each subregion.
2. If the distance between mid-plain and average column index is larger than a threshold, the subregion is rejected. Otherwise, it is included. The threshold is set to be 4 pixels. The column index of mid-plain is simply half of the brain dimension since brain data has been aligned.

Figure 4.6 (b) shows tip of lateral ventricle is cleaned up from result.

(a)       (b)

Figure 4.8 Segmentation of third ventricle before and after the clean-up procedure
• Lateral ventricle

The reason that model-based approach is not applicable to lateral ventricle (LV) is LV has large absolute volume and large variance among different individuals. The coefficient in threshold in Formula 5.1 needs to be very high to include all the ventricles in the result, but that clearly includes some undesirable structures as well. The following figure shows segmentation results under different coefficient settings. None of them are good. When coeff. is 1 in Figure 4.9(a), lots of LV are missing. When coeff. is 10 in (b), part of right LV is missing. When coeff. is increased to 25 in (c), tip of right LV is still missing and some non-LV structures appear in the result. It demonstrates the model based algorithm is not suitable to LV segmentation no matter how to tune the parameter.

(a) coeff. = 1  
(b) coeff. = 10  
(c) coeff. = 25

![Figure 4.9 undesireable result of applying model-based approach in lateral ventricle](image)

Rationale of LV segmentation:

Subcortical CSF only includes LV, TV, and fourth ventricle, but fourth ventricle is far away in the inferior part of brain and does not cause problem in LV segmentation. Also CSF has already been segmented out in tissue segmentation. If we can identify the subcortical CSF area,
and segment TV out using model based algorithm first, then we simply exclude TV from subcortical CSF area and the rest is LV. Right LV and left LV is separated by the mid-plane.

The detailed procedure is as follows:

1. Locate LV: Find the best matched model using the same procedure in model-based algorithm, set up a cubical 3D region 150% of the cube defined by the model structure as interested subcortical area.

2. Superimpose the model to input data. In each slice in the axial view, for every isolated CSF region, select a CSF seed voxel which is both in the model and input, and make it grow to the CSF boundary. Although it is a 2D process, it uses CSF boundary as LV’s boundary while CSF tissue segmentation is done in 3D, so it does not cause non-smoothing problem in the other two views. For top/bottom slices which are inside the cube but not in the model, select the seed from the uppermost/lowermost slice in the model and let the seed grow in 3D to CSF boundary confined by the cube.

3. In some slices where LV is connected to TV or right LV and left LV are connected together, the seed grows to TV and LV of the other hemisphere. Exclude TV using TV segmentation from result obtained in step 2 and exclude the other half of LV using the mid-plane.

It is faster than step 3 in model based algorithm and does not include some far-away CSF as shown in Figure 4.10. Figure. 4.10 (a) is Figure. 4.9(c) using model –based algorithm and (b) is using the current seed grow algorithm. (b) includes the tip of Right LV and does not have non-LV CSF.
Figure 4.10 segmentations of LV using model-based and modified algorithm respectively

4.4 Implementation of the Improved Model-based Algorithm

The improved model-based algorithm is implemented in Matlab and C++. To reduce the computation time, the most time consuming part: identification of valid boundary voxels, and calculate average distances between model and input data are implemented in C++.
Chapter 5

Experimental Results

Experimental results are shown in this chapter. Information about experimental data is
given in Section 5.1 as well as how to construct a set of models. In Section 5.2, quantitative
analysis of superior performance of improved algorithm is shown and validation experiments for
11 structures are conducted with results. Age effect on volume changes in healthy subjects are
investigated in Section 5.3.

5.1 Experimental Data and Construction of Model Set

In this section, we will introduce information about our experimental data and how to
build a set of models as required by the model-based algorithm.
5.1.1 Experimental Data

In order to illustrate the applicability of our method on the high-field MR images, we applied our approach to the images obtained from a 4-Tesla MR scanners. These images are provided by the Center for Imaging Research (CIR) at the University of Cincinnati. Each data is a T1-weighted volumetric data with the dimension of $192 \times 256 \times 192$ (X×Y×Slice), voxel size of $1\text{mm} \times 1\text{mm} \times 1\text{mm}$.

The data set consists of 113 MR brain images of healthy subjects. The CIR also provides the information related to the age and gender for all brain images. The age of subjects range from 11 years old to 45 years old, and we divide them into 7 age groups with the interval of 5 years. The age and gender information of the test data set is listed below.

<table>
<thead>
<tr>
<th>Age range (years old)</th>
<th>Num of Females</th>
<th>Num of Males</th>
<th>Total num in the age range</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-15</td>
<td>10</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>16-20</td>
<td>11</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>21-25</td>
<td>17</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>26-30</td>
<td>10</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>31-35</td>
<td>10</td>
<td>4</td>
<td>14</td>
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<tr>
<td>36-40</td>
<td>13</td>
<td>5</td>
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</tr>
<tr>
<td>41-45</td>
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<td>4</td>
<td>11</td>
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<tr>
<td>Total num</td>
<td>78</td>
<td>35</td>
<td>113</td>
</tr>
</tbody>
</table>

Table 5.1 Age and gender information for test data

5.1.2 Construction of a Set of Models

A set of manually segmented subcortical structure models is needed to perform the
segmentation. And these models need to be a good representation of the test data, thus we select and build 7 models with one model for each age group. These 7 models are not part of the 113 test data set. Except for used as models, these manual segmented subcortical structures are assumed to be correct and are considered as the ground truth of segmentation results for these 7 volumetric brain data which will be used in Section 5.2 for validation of structure segmentation. Each model is a T1-weighted volumetric data with the dimension of 192×256×192 (X×Y×Slice), voxel size of 1mm × 1mm × 1mm.

Age and gender information for 7 models is listed in Table 5.2.

<table>
<thead>
<tr>
<th>Model index</th>
<th>Age</th>
<th>Gender</th>
</tr>
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<tbody>
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<td>14</td>
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</tr>
<tr>
<td>2</td>
<td>30</td>
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</tr>
<tr>
<td>7</td>
<td>38</td>
<td>male</td>
</tr>
</tbody>
</table>

Table 5.2 Age and gender information for models

To manually segment structures on a stack of 2-D images, 7 brain volumes are registered to one template brain volume first, and then boundaries of 11 structures are traced manually and last tissue around structures are manual segmented as well. The detailed construction procedure is stated below:

1. Registration of 7 brain data to standard coordinate space.
Center for Morphometric Analysis at Massachusetts General Hospital provides 18 brain volumes positionally normalized with Talairach coordinate system [43]. They are available at [http://www.cma.mgh.harvard.edu/ibsr/](http://www.cma.mgh.harvard.edu/ibsr/) [IBSR 2004]. One of them is selected to be the template volume in the registration. Its dimension is $256 \times 256 \times 128$ and voxel size is $1 \text{mm} \times 1 \text{mm} \times 1.5 \text{mm}$, so it is resized and interpolated to have the same dimension and voxel size as the 7 models before registration (7 models have the same dimension and voxel size). Image registration is completed using SPM.


Manual segmentation is done using software 3D Slicer version 2.6, available at [http://www.slicer.org/](http://www.slicer.org/). All 11 structures are first traced in axial view from slice to slice and then switch to sagittal view and coronal view to make sure that boundary outlined in axial view is also smooth in the other two views. The guidelines for tracing these structures are available in [44].

3. Manual segmentation of tissues surrounding structures of interest

Since we need to identify valid boundaries of models to calculate distance between models and input data, also in putamen segmentation, direction property of each valid boundary voxel is required, so tissues surrounding structures of interest need to be manually segmented. It is done using 3D Slicer as well, following the same procedure as structure segmentation. GM, WM, CSF voxels are classified mainly based on their intensities.

Cai has experimentally proved that the same subcortical structure in different brains remain at almost the same location after image registration of brain data [46]. To validate image registration using SPM successfully aligns brain data, an experiment to compute the mean
centroids of 9 structures and their standard deviations using the set of 7 hand drawn models was

carried out. These 9 structures are right caudate nuclei (RCN), left caudate nuclei (LCN), right
putamen (RPU), left putamen (LPU), right globus pallidus (RGP), left globus pallidus (LGP),
right thalamus (RTH), left thalamus (LTH), and third ventricle (TV). Right lateral ventricle (RLV)
and left lateral ventricle (LLV) are excluded because of large variance of volume and shape
among individuals. Table 5.3 shows the coronal, sagittal, and axial coordinates of the mean
centroids for 9 structures. The standard deviations (STD) of centroid coordinates are shown as
well. The overall mean STD of all three coordinates is 1.015 (a little more than 1 voxel) with the
maximum STD of 2.06. This experiment shows that the same structures in different individual
brains are overlapping with their centroids varying about a voxel after registration process using
SPM. As a result, the use of the model centroids as a locator for the input structure data does not
locate erroneous structures.

<table>
<thead>
<tr>
<th></th>
<th>Mean Center Row</th>
<th>Mean Center Col</th>
<th>Mean Center Slice</th>
<th>STD Center Row</th>
<th>STD Center Col</th>
<th>STD Center Slice</th>
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</thead>
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<td>1.744</td>
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</tr>
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<td>2.061</td>
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<td>1.170</td>
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<td>102.57</td>
<td>1.579</td>
<td>1.033</td>
<td>0.714</td>
</tr>
<tr>
<td>LPU</td>
<td>116.55</td>
<td>73.38</td>
<td>103.20</td>
<td>1.603</td>
<td>0.807</td>
<td>0.702</td>
</tr>
<tr>
<td>RTH</td>
<td>135.77</td>
<td>104.98</td>
<td>106.46</td>
<td>0.917</td>
<td>0.900</td>
<td>0.525</td>
</tr>
<tr>
<td>LTH</td>
<td>135.97</td>
<td>87.76</td>
<td>106.62</td>
<td>0.742</td>
<td>0.877</td>
<td>0.546</td>
</tr>
<tr>
<td>RGP</td>
<td>120.96</td>
<td>114.62</td>
<td>101.02</td>
<td>1.289</td>
<td>0.724</td>
<td>0.568</td>
</tr>
<tr>
<td>LGP</td>
<td>121.60</td>
<td>77.90</td>
<td>101.48</td>
<td>1.497</td>
<td>0.618</td>
<td>1.009</td>
</tr>
<tr>
<td>TV</td>
<td>141.88</td>
<td>96.08</td>
<td>106.65</td>
<td>1.780</td>
<td>0.640</td>
<td>0.975</td>
</tr>
</tbody>
</table>

Mean:  1.468  0.776  0.802
Max:   2.061  1.033  1.170
Table 5.3: Centroids for 9 interested subcortical brain structures and their standard derivations

<table>
<thead>
<tr>
<th></th>
<th>Min:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.742</td>
<td>0.580</td>
<td>0.525</td>
</tr>
</tbody>
</table>

Row: Coronal Orientation, Posterior to Anterior

Col: Sagittal Orientation, right to left

Slice: Axial Orientation: Inferior to Superior

5.2 Performance evaluation

We first compare performance of the improved model-based algorithm with the original algorithm for putamen in Section 5.2.1. After that, experiments to validate the segmentation for 11 subcortical structures are carried out and results are shown in Section 5.2.2.

5.2.1 Performance evaluation for improved model-based algorithm

- Performance evaluation using model set

The experimental data is the 7 brain volumes used as models. For current brain volume, we take out the current model structure and the selected model is from a collection of the rest 6 structure models that closely match the input structure. The segmentation result is compared with the manual segmentation. This validation procedure is called “take-one-out” procedure.

For data with manual segmentation available, we chose DICE similarity index [45] as our quantitative error measurement:

\[
D(A, B) = 2|A \cap B|/(|A| + |B|) \times 100\%
\]  
(5.1)
where $A$ denotes the area of the gold standard and $B$ denotes the area of the segmentation result obtained from our algorithms. $|A \cap B|$ denotes the number of voxels in the intersection of the gold standard and our segmentation result, $|A|$ and $|B|$ denote the number of voxels in the gold standard and our segmentation results, respectively.

The improved model-based algorithm is applied to putamen segmentation only. The DICE comparison of the original algorithm and the improved algorithm is listed as below. It is also shown in the table that whether the improved algorithm selects the same best-matching model as the original algorithm. 3 structures among 14 structures select a different best matching model in improved and original algorithms. DICE values for those 3 structures are all improved. Especially, LPU of 2nd brain has improved DICE value by 6.8% and RPU of the 6th brain improves DICE value by 4.4%. It demonstrates that after introducing direction property into the model selection, the algorithm avoids selecting a non-matching model which could lead to undesirable result. If the same best-matching model is selected, the performances of two algorithms are comparable, because the difference in performance is only introduced by thresholds which are only slightly different due to different minimum average distance calculations. The mean of DICE value enhancement for all 14 structures is 1%.
| Model Index |  |  |  |  |  |  |
|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|  | Original RPU | New RPU | Different model selected | Original LPU | New LPU | Different model selected |
| 1 | 0.873 | 0.874 | No | **0.889** | **0.891** | Yes |
| 2 | 0.831 | 0.842 | No | **0.786** | **0.854** | Yes |
| 3 | 0.852 | 0.860 | No | 0.912 | 0.905 | No |
| 4 | 0.859 | 0.857 | No | 0.885 | 0.875 | No |
| 5 | 0.871 | 0.869 | No | 0.834 | 0.835 | No |
| 6 | **0.835** | **0.879** | Yes | 0.891 | 0.899 | No |
| 7 | 0.841 | 0.847 | No | 0.853 | 0.874 | No |
| Mean | 0.852 | 0.861 | 0.865 | 0.876 |
| STD | 0.017 | 0.014 | 0.043 | 0.025 |
| Min | 0.831 | 0.842 | 0.786 | 0.835 |

Table 5.4 Performance comparison of improved algorithm with the original algorithm

Figure 5.1 shows segmentation results of LPU in the 2nd model brain using original and improved algorithm respectively in axial view. In the result of original algorithm, part of GM to the left of LPU is included in LPU segmentation wrongly, this wrong inclusion exists from slice 101 through slice 109. But in the result of the improved algorithm, this error is corrected due to a better-matching model selection.
Figure 5.1 segmentation results of LPU in the 2nd model brain using original and improved algorithm respectively.

- **Performance evaluation using test data set**

  In order to evaluate the performance of our algorithm for the test data set that do not have the segmentation ground truth for structures, we use the following modified dice index as the performance measurement, replacing the manual segmentation result with selected model.

  $\text{DICE} (\text{Model}) = \frac{2|M \cap B|}{(|M| + |B|)} \times 100\% \quad (5.2)$
where $M$ denotes the area of model structure and $B$ denotes the area of segmentation result obtained from our algorithm. $|M \cap B|$ denotes the number of voxels in the intersection of model and the segmentation result, $|M|$ and $|B|$ denote the number of voxels in model structure and our segmentation results respectively.

Cai justified the use of modified DICE as performance indicator and modified DICE value larger than 0.7 is considered as acceptable segmentation result [46]. Improved algorithm shows its superiority only when wrong model is selected by the original algorithm which leads to obvious error, so only segmentation results with modified DICE value less than 0.7 are listed in Table 5.5. Using original algorithm, there are 9 heads (8 are RPU and 1 is LPU) with modified DICE value smaller than 0.7. and mean value is 0.649. Using the modified algorithm, the mean DICE value is improved to 0.731 by 8.2%.
<table>
<thead>
<tr>
<th>Brain Index</th>
<th>DICE (model) of Original algo.</th>
<th>DICE (model) of Improved algo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1_RPU</td>
<td>0.618</td>
<td>0.753</td>
</tr>
<tr>
<td>2_RPU</td>
<td>0.694</td>
<td>0.784</td>
</tr>
<tr>
<td>3_RPU</td>
<td>0.610</td>
<td>0.694</td>
</tr>
<tr>
<td>4_RPU</td>
<td>0.683</td>
<td>0.778</td>
</tr>
<tr>
<td>5_RPU</td>
<td>0.656</td>
<td>0.705</td>
</tr>
<tr>
<td>6_RPU</td>
<td>0.561</td>
<td>0.712</td>
</tr>
<tr>
<td>7_RPU</td>
<td>0.645</td>
<td>0.675</td>
</tr>
<tr>
<td>8_RPU</td>
<td>0.692</td>
<td>0.774</td>
</tr>
<tr>
<td>9_LPU</td>
<td>0.680</td>
<td>0.700</td>
</tr>
<tr>
<td>mean</td>
<td>0.649</td>
<td>0.731</td>
</tr>
</tbody>
</table>

Table 5.5 performance comparison of original and improved algorithm using test data

### 5.2.2 Validation experiments for segmentation of 11 structures

For each of the 11 subcortical structures, we used the same take-one-out procedure as that used in Section 5.2.1 using set of models as input data. DICE Values of 11 subcortical structures in 7 model brains are listed in the Table 5.6.

<table>
<thead>
<tr>
<th>Model Index</th>
<th>RCN</th>
<th>LCN</th>
<th>RPU</th>
<th>LPU</th>
<th>RTH</th>
<th>LTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.906</td>
<td>0.903</td>
<td>0.874</td>
<td>0.891</td>
<td>0.892</td>
<td>0.879</td>
</tr>
<tr>
<td>2</td>
<td>0.886</td>
<td>0.850</td>
<td>0.842</td>
<td>0.854</td>
<td>0.907</td>
<td>0.899</td>
</tr>
</tbody>
</table>
### Table 5.6 (a) Segmentation Performance for CN, PU and TH in 7 model brains

<table>
<thead>
<tr>
<th>Model Index</th>
<th>RGP</th>
<th>LGP</th>
<th>RLV</th>
<th>LLV</th>
<th>TV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.790</td>
<td>0.853</td>
<td>0.935</td>
<td>0.950</td>
<td>0.919</td>
</tr>
<tr>
<td>2</td>
<td>0.879</td>
<td>0.903</td>
<td>0.945</td>
<td>0.935</td>
<td>0.967</td>
</tr>
<tr>
<td>3</td>
<td>0.868</td>
<td>0.884</td>
<td>0.954</td>
<td>0.969</td>
<td>0.820</td>
</tr>
<tr>
<td>4</td>
<td>0.714</td>
<td>0.819</td>
<td>0.947</td>
<td>0.906</td>
<td>0.847</td>
</tr>
<tr>
<td>5</td>
<td>0.798</td>
<td>0.771</td>
<td>0.930</td>
<td>0.918</td>
<td>0.915</td>
</tr>
<tr>
<td>6</td>
<td>0.842</td>
<td>0.812</td>
<td>0.955</td>
<td>0.957</td>
<td>0.857</td>
</tr>
<tr>
<td>7</td>
<td>0.709</td>
<td>0.725</td>
<td>0.956</td>
<td>0.939</td>
<td>0.952</td>
</tr>
<tr>
<td>Mean</td>
<td>0.800</td>
<td>0.824</td>
<td>0.946</td>
<td>0.939</td>
<td>0.900</td>
</tr>
<tr>
<td>STD</td>
<td>0.068</td>
<td>0.062</td>
<td>0.010</td>
<td>0.022</td>
<td>0.056</td>
</tr>
<tr>
<td>Min</td>
<td>0.709</td>
<td>0.725</td>
<td>0.930</td>
<td>0.935</td>
<td>0.820</td>
</tr>
</tbody>
</table>

### Table 5.6 (b) DICE values for GP, LV and TV in 7 model brains

<table>
<thead>
<tr>
<th>Model Index</th>
<th>RGP</th>
<th>LGP</th>
<th>RLV</th>
<th>LLV</th>
<th>TV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.875</td>
<td>0.932</td>
<td>0.860</td>
<td>0.905</td>
<td>0.866</td>
</tr>
<tr>
<td>2</td>
<td>0.878</td>
<td>0.878</td>
<td>0.857</td>
<td>0.875</td>
<td>0.840</td>
</tr>
<tr>
<td>3</td>
<td>0.863</td>
<td>0.801</td>
<td>0.869</td>
<td>0.835</td>
<td>0.877</td>
</tr>
<tr>
<td>4</td>
<td>0.900</td>
<td>0.859</td>
<td>0.879</td>
<td>0.899</td>
<td>0.876</td>
</tr>
<tr>
<td>5</td>
<td>0.822</td>
<td>0.868</td>
<td>0.847</td>
<td>0.874</td>
<td>0.903</td>
</tr>
<tr>
<td>Mean</td>
<td>0.876</td>
<td>0.869</td>
<td>0.861</td>
<td>0.876</td>
<td>0.880</td>
</tr>
<tr>
<td>STD</td>
<td>0.026</td>
<td>0.037</td>
<td>0.014</td>
<td>0.025</td>
<td>0.023</td>
</tr>
<tr>
<td>Min</td>
<td>0.822</td>
<td>0.801</td>
<td>0.842</td>
<td>0.835</td>
<td>0.840</td>
</tr>
</tbody>
</table>
Figure 5.2 illustrates segmentation of 11 subcortial structures in the 1st model brain. Results are shown in 3 views.

<table>
<thead>
<tr>
<th>View 1</th>
<th>View 2</th>
<th>View 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN_axial</td>
<td>CN_sagittal</td>
<td>CN_coronal</td>
</tr>
<tr>
<td>PU_axial</td>
<td>PU_sagittal</td>
<td>PU_coronal</td>
</tr>
</tbody>
</table>

[Images of brain segmentation in different views]
We further evaluated the performance of segmentation using the 113 test data. Since manual segmentation for this 113 test data is not available, we used the DICE (model) as evaluation criterion. Because LLV, RLV, TV have large individual variance, modified DICE which compares segmentation result with selected model is not a good indicator for these ventricle segmentation. Table 5.7 lists mean values and standard deviations of modified DICE for 8 GM structures.
Table 5.7, DICE (model) values of GM structures in 113 test data set

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>STD</th>
<th>Min.</th>
<th>Num. of heads with DICE less than 0.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCN</td>
<td>0.833</td>
<td>0.072</td>
<td>0.670</td>
<td>5</td>
</tr>
<tr>
<td>LCN</td>
<td>0.837</td>
<td>0.065</td>
<td>0.674</td>
<td>1</td>
</tr>
<tr>
<td>RPU</td>
<td>0.840</td>
<td>0.060</td>
<td>0.660</td>
<td>3</td>
</tr>
<tr>
<td>LPU</td>
<td>0.840</td>
<td>0.053</td>
<td>0.676</td>
<td>2</td>
</tr>
<tr>
<td>RTH</td>
<td>0.870</td>
<td>0.054</td>
<td>0.672</td>
<td>2</td>
</tr>
<tr>
<td>LTH</td>
<td>0.881</td>
<td>0.041</td>
<td>0.763</td>
<td>0</td>
</tr>
<tr>
<td>RGP</td>
<td>0.841</td>
<td>0.081</td>
<td>0.637</td>
<td>6</td>
</tr>
<tr>
<td>LGP</td>
<td>0.880</td>
<td>0.083</td>
<td>0.652</td>
<td>2</td>
</tr>
</tbody>
</table>

If modified DICE value is smaller than 0.7, segmentation result needs to be visually checked to decide whether to be accepted or rejected.

5.3 Study of age effect on volumes of subcortical structures

Raw volumes of each structure were obtained from segmentation result. To eliminate individual differences in head size, absolute volumes were normalized by head size. The strength of association between age and volumes of structure were measured using P-value of Pearson's linear correlation coefficient. The significance threshold of P-value was set to be 0.05. If P-value of certain correlation between two variables is less than 0.05, it means there is a significant correlation between these two variables.

The following table shows P-value for 11 structures in all subjects, females and males. Correlations between age and volumes of RCN, LCN, RPU, LPU, RTH and LTH have P values
less than 0.05, meaning significant correlations between volumes changes with age. Volumes of these 6 structures decline with aging. RGP, LGP, RLV, LLV and TV have P values larger than 0.05, meaning insignificant correlation with age. Gender effect is not obvious in volumes change. Significance of correlation with age in females and males are almost the same except LPU in male subjects with P value of 0.0509. Figure 5.3 -5.13 illustrate the correlation between age and volumes. A linear regression trend line is shown in figures as well.

Our experiment shows volume of caudate decreases with age. It is consistent with Khader’s work [23] which studied the age effect on volumes of structure in 33 healthy subjects (age: 19-59 years old), but conflicts against Patrice’s report which showed both left and right caudate do not shrink with age [33]. Patrice analyzed volume change in 30 healthy subjects (age: 20-41 years old). We observed volumes of both left and right putamen decrease with age which is the same as Patrice’s observation. But Pieperhoff, conducting volume analysis on 51 healthy male subjects (age: 18-51 years old), found right putamen shrink but left putamen does not shrink significantly [24]. Our result agrees with Pieperhoff’s work, in volume decrease of left and right thalamus against age. However, Patrice’s work observed that only right thalamus decreases with age but left thalamus does not. Our work shows no significant volume reduction in globus pallidus which is consistent with others’ [32,33,34]. For subjects younger than 50 years old, no age related change of third ventricle, left and right ventricle was observed in [31] and right lateral ventricle does not significantly change with age observed in [24], which is the same as our result. But in [24], third ventricle and left lateral ventricle show widening with age increasing.
<table>
<thead>
<tr>
<th>P value</th>
<th>All</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCN</td>
<td>0.0025</td>
<td>0.0354</td>
<td>0.0006</td>
</tr>
<tr>
<td>LCN</td>
<td>0.0012</td>
<td>0.0130</td>
<td>0.0045</td>
</tr>
<tr>
<td>RPU</td>
<td>0.00004</td>
<td>0.0017</td>
<td>0.0026</td>
</tr>
<tr>
<td>LPU</td>
<td>0.0002</td>
<td>0.0018</td>
<td>0.0509</td>
</tr>
<tr>
<td>RTH</td>
<td>0.0052</td>
<td>0.0220</td>
<td>0.0132</td>
</tr>
<tr>
<td>LTH</td>
<td>0.0011</td>
<td>0.0311</td>
<td>0.0007</td>
</tr>
<tr>
<td>RGP</td>
<td>0.459</td>
<td>0.528</td>
<td>0.292</td>
</tr>
<tr>
<td>LGP</td>
<td>0.929</td>
<td>0.944</td>
<td>0.375</td>
</tr>
<tr>
<td>RLV</td>
<td>0.216</td>
<td>0.374</td>
<td>0.389</td>
</tr>
<tr>
<td>LLV</td>
<td>0.785</td>
<td>0.760</td>
<td>0.911</td>
</tr>
<tr>
<td>TV</td>
<td>0.161</td>
<td>0.208</td>
<td>0.589</td>
</tr>
</tbody>
</table>

Table 5.8 correlation of age and volumes
Figure 5.3 age effect on volumes of LCN
Figure 5.4 age effect on volumes of RCN
Figure 5.5 age effect on volumes of LPU
Figure 5.6 age effect on volumes of RPU
Figure 5.7 age effect on volumes of LTH
Figure 5.8 age effect on volumes of RTH
Figure 5.9 age effect on volumes of LGP
Figure 5.10 age effect on volumes of RGP
Figure 5.11 age effect on volumes of LLV
Figure 5.12 age effect on volumes of RLV
Figure 5.13 age effect on volumes of TV
Chapter 6

Conclusions

Our objective is to investigate the age effect on volumes of subcortical structures in MRI brain data. Subcortical structures of interest are caudate nucleus, thalamus, putamen, globus pallidus, lateral ventricle and third ventricle. An automatic subcortical segmentation algorithm [46] was applied to 113 MRI brain data of healthy subjects with age from 11 years old to 45 years old. The algorithm consists of two parts: tissue segmentation part and model-based subcortical structure segmentation part. The separation of two parts has the advantage that the incorporation of better tissue segmentation methods in the future to improve performance is straightforward.
In the tissue segmentation, first image registration was applied to align brain volume to standard coordinate space, and then a classification method based on MAP was used in registered brain volume to segment brain into GM, WM and CSF. Both registration and segmentation were done by software SPM [35]. A new tissue probability map which provides prior spatial information was constructed to replace the default one in SPM, and better segmentation of GM in the globus pallidus, putamen and thalamus area was achieved. And also a post processing to correct overestimated CSF was proposed and result was illustrated.

The model-based algorithm uses the tissue segmentation results from the first part as input and also a set of model structures. It matches the model to the input data and selects the best-matching model based on average minimum distance between valid boundary voxels in the model and input data. The boundary of the matching model is then used to bridge or fill the boundary gap of incoming image to obtain the final segmentation result. In this thesis, a direction property of each boundary voxel was proposed to be incorporated into the model selection part to avoid wrong correspondence between model and input data. Also, a modified segmentation was proposed for lateral ventricle.

DICE similarity index was used to measure the performance of the algorithm when manual segmentation is available. A modified DICE replacing the manual segmentation with the selected model was used when manual segmentation was not available in clinical. Comparative experiments using DICE as measurement show that the improved algorithm incorporating direction property outperforms the original one by avoiding selecting wrong model. Modified segmentation for ventricles also shows better DICE values. Segmentation results of all structures were also validated using DICE and modified DICE.

The volumes of structures were obtained from the segmentation results and pearson linear
correlation was conducted between age and these structures. Caudate nucleus, putamen and thalamus in both hemispheres have significant volume decrease over the age range. While globus pallidus, lateral ventricle in both hemispheres as well as third ventricle do not show significant volume change with age.
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