Chapter 1

Introduction

In this chapter, we will briefly introduce the brain structures, the magnetic resonance imaging, computer-aided diagnosis and statistical pattern recognition. Magnetic resonance imaging is a non-invasive method to observe the inside of human body. Computer-aided diagnosis is an automatic system to diagnose diseases by using computerized analysis of medical images. A popular approach to help these systems make decisions is statistical pattern recognition. Our goal is to establish an automatic diagnosis system with statistical pattern recognition techniques.

1.1 Brain Structures and Magnetic Resonance Imaging

The brain is vital to human existence. It not only influences our voluntary movements like raising hands but also regulates involuntary activities such as heartbeat and breathing. The most important function of the brain is to control human consciousness, for instance, memory, thought and feeling. Briefly, the brain dictates the behaviors that allow us to survive.

Before the 20th century, scientists discovered the complex workings of the brain by anatomizing human body. There are three parts of the brain. First is the brain stem, which plays a vital role in basic attention, arousal, and consciousness. It is a bridge to connect information between the brain and our body. Second is cerebellum, involved in the coordination of voluntary motor movement, balance and muscle tone. It is located just above the brain stem and toward the back of the brain. Third is cerebrum, which can be divided into left and right cerebral hemispheres with corpus callosum connecting both of them. Each hemisphere is segmented into four lobes: frontal lobe, involved in motor function, problem solving, memory, language and judgment behaviors, parietal lobe, which involves sensation and perception, temporal lobe, involved in hearing ability, memory acquisition and categorization of objects, and occipital lobe, the center of our visual perception system. Figure 1.1 shows above-mentioned human brain structures.

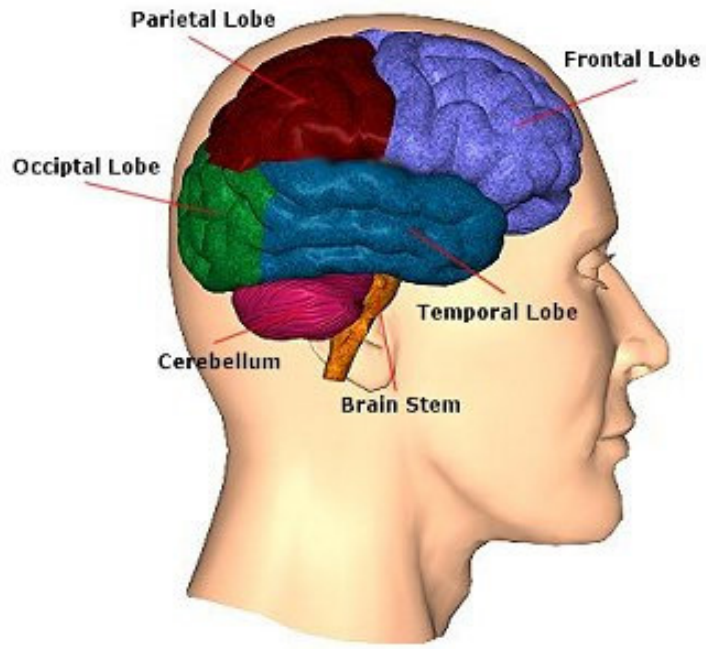

Figure 1.1: **Main human brain structures.** There are three parts of the brain, which are cerebrum, cerebellum, and brain stem. Cerebrum can also be divided into left and right hemispheres, each consists of four lobes: frontal lobe, parietal lobe, temporal lobe and occipital lobe. (Figure source: http://www.neuroskills.com/)

On the other hand, the brain can be divided into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) in terms of the type of brain tissues. Closely packed neuron cell bodies form the grey matter of the brain, involved in muscle control, sensory perceptions, such as seeing and hearing, memory, emotions and speech. Neuronal tissue containing mainly long and myelinated axons is known as white matter, involved in the relay of sensory information from the rest of the body to the cerebral cortex, as well as in the regulation of unconscious functions such as body temperature, heart rate and blood pressure. Cerebrospinal fluid is a fluid within the brain and the subarachnoid space of the spinal cord that cushions the brain inside the skull and protects the spinal cord from mechanical shocks. Figure 1.2 shows distributions of three tissue types in the brain.

In clinical diagnosis, it is impossible to open a living one's skull and see inside of

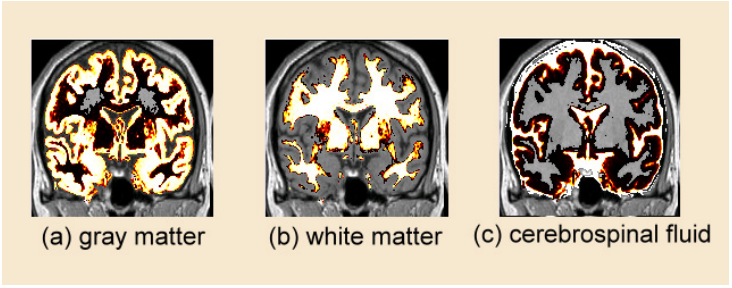

Figure 1.2: **Distributions of GM, WM and CSF in the brain.** According to the type of tissues, the brain can be divided into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). (a) Grey matter forms the exterior part of the brain. (b) White matter situates between the brainstem and cerebellum, and forms the interior part of the brain. (c) Cerebrospinal fluid fills ventricles and surrounds the brain and the spinal cord. (Figure source: The subject is one of our study groups. FAST segmentation tool is applied to extract three tissues and then MRIcro software is used for visualization.)

his brain because human brain is so complicated that even a little influence will make it injured. Fortunately, scientists have developed many neuroimaging techniques along with progress of science and technology. Today, it is achievable and convenient to observe brain structures and brain activities on living beings with neuroimaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), X-ray computer tomography (CT) and magnetic resonance imaging (MRI). In this work, we used magnetic resonance imaging as experimental materials.

In 21st Century, magnetic resonance imaging (MRI) is a modern and popular imaging modality used in medical studies. It is based on the principles of nuclear magnetic resonance (NMR), a spectroscopic technique to obtain microscopic chemical and physical information about molecules, to produce high quality images of the inner of an alive human body. The technology was first discovered by Paul Lauterbur in 1973 [1]. Later, in 1975, Richard Ernst proposed magnetic resonance imaging using phase and frequency encoding, and the Fourier Transform. These techniques are the basis of current MRI techniques. Figure 1.3 shows a simple flowchart of MRI technology. The device contains a main magnet which generates a uniform magnetic field to polarize nuclear spins in an object. Moreover,

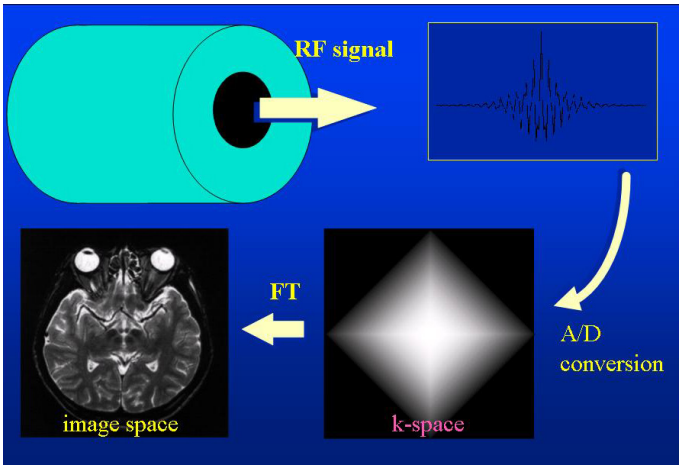

Figure 1.3: **Simple flowchart of magnetic resonance imaging.** There are a main magnet, radio frequency (RF) coils and gradient coils to produce a gradient magnetic field. Image information are observed by the nuclear transition of nuclear spins in an object. After the signals conversion, images in spatial domain are obtained. (This figure is made by Ken Buckwalter, M.D.. It can be found in the website, http://www.indyrad.iupui.edu/public/lectures/mri/iu_lectures/mri_homepage.htm)

there are radio frequency (RF) coils to rotate the net magnetization in a pulse sequence and gradient coils to produce the gradients for signal localization in the magnetic field. Therefore, we detect signals of nuclear transition, the transverse and longitudinal magnetization of nuclear spins. Once observing these signals, we transform this information into frequency domain and gain images in spatial domain by applying the Fourier transform. In short, magnetic resonance imaging is an imaging technique used to construct pictures of the NMR signal from the hydrogen atoms in an object.

MRI has lots of advantages such as non-invasive, safe properties and high resolution of images. MRI detects insides of a living human without a surgical operation so that people will not bear pains caused by invaders. Also, there is no injury report that it is harmful to people who take inspections by MRI scanners until now. Most importantly, because of high contrast resolution, the quality of MR images is good enough to be used in medical diagnosis and pathological studies. With these techniques, doctors can diagnose

abnormalities of subjects by observing their MR images and study the pathology of kinds of diseases. Shortly, MRI assists doctors in clinical diagnosis.

1.2 Statistical Pattern Recognition

We take the abilities for granted to recognize a face, understand spoken words and read handwritten characters. But it is obviously difficult to teach a robot to do the same things. Pattern recognition (PR) is the study of how machines can observe the environment, learn to distinguish patterns of interest from their background, and make sound and reasonable decisions about the categories of the patterns [2]. Watanabe [3] defines a pattern "as opposite of chaos; it is an entity, vaguely defined, that could be given a name." For example, a pattern could be a human face, a speech signal, a DNA sequence and so on.

Pattern recognition encloses subdisciplines such as feature extraction and selection, supervised classification (e.g., discriminant analysis), unsupervised classification (e.g., cluster analysis) and error estimation. It is usually used in image analysis, speech analysis, data mining, man and machine diagnostics, and biometrics. The design of a PR system can be divided into three parts, data acquisition and preprocessing, data representation and decision making. Most PR systems make decisions by learning from a known set of examples, called as training set. There are four well-known approaches for pattern recognition: template matching, statistical classification, syntactic matching and neural networks. In this work, we chose statistical pattern recognition as our method for classification.

In statistical pattern recognition (SPR), a pattern is represented as a d-dimensional feature vector which contains d measurements and is viewed as a point in a d-dimensional space. The recognition system is involved in two modes: learning (training) mode and classification mode. Figure 1.4 draws the macroscopic process of SPR [2]. Training patterns, inputs of the training mode, are examples set we have known and test patterns, inputs

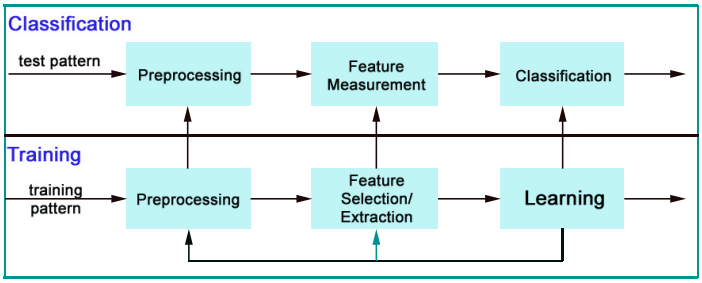

Figure 1.4: **Model for statistical pattern recognition.** Statistical pattern recognition is operated in two modes: the training mode and the classification mode. Given data is as training patterns and unknown data, test patterns, is going to be classified into one of the pattern classes. In the training mode, the feature extraction/selection module is to find more useful attributes to represent the training patterns. In the learning module, a classifier is trained to partition the feature space and is used in classification module to classify unknown samples. The feedback paths will lead the system to optimize the efficiency. (Figure source: Statistical Pattern Recognition: A Review, IEEE Trans. January 2000.)

of the classification mode, are contrarily examples set we do not know. The function of preprocessing module is to retrieve representation of patterns in a compact way. In the training mode, the feature extraction and selection module reduces dimensionalities of patterns and looks for more useful attributes of patterns used to train classifiers in the following learning module. In the classification mode, the classification module is to assign unknown test patterns based on observed attributes to one of the pattern classes with decision rules.

A dichotomy of decision rules in statistical pattern recognition is geometric approach whose decision boundaries are obtained directly and probabilistic density-based approach in contrast to the former [2]. The geometric approach creates the decision boundaries directly from optimizing certain cost functions. On the other hand, the probabilistic density-based approach is more complex. It needs to estimate density function of training patterns and construct the discriminant functions that determine decision boundaries. However, the probability density functions of test patterns conditioned on the pattern classes are unknown in practice and must be learned from the training patterns. There are two ways to find the class-conditional densities of test patterns. One is parametric decision method and the other

is nonparametric decision method. Parametric decision method is used when we know the form of the class-conditional densities but do not know some parameters of the densities. If we do not know the form of the class-conditional densities, we may use some density estimation function strategies to estimate densities such as Parzen windows approach and k-nearest neighbor (kNN) rule. In this work, we used Parzen window approach to estimate the class-conditional density and Bayesian decision rule to classify test patterns. More detailed interpretation of these techniques will be introduced in Chapter 3.

1.3 Computer-Aided Diagnosis

Along with changes in computer technology, there is an enormous influence on medical imaging like existence of CT and MRI. Today, doctors can diagnose medical conditions and disorders of subjects through these modalities. However, this diagnosis is subjective to doctors' judgments and costs much time for subjects to obtain results. Moreover, even an experienced physician has trouble distinguishing subtle differences between normal images and abnormal ones. Therefore, it could be expected to use an objective and convenient method implemented by modern digital computers for interpretation of MR images. The research area is called Computer-Aided Diagnosis (CAD).

Initially, studies in medical images were seen as applications of pattern analysis and computer vision techniques with another interesting dataset. Later in 1970s, some researchers formed a small group, titled Information Processing in Scintigraphy, and made efforts in treating medical and biomedical image analysis as a unique information processing problem. The technology of pattern recognition, signal processing and computer vision plays an important role in solving this problem. As time goes by, the field is developed vigorously and the small research group, renamed Information Processing in Medical Imaging (IPMI), still makes contributions to the issue [4].

Computer analysis of medical images is involved in many potential topic areas such as image acquisition, image reconstruction, image enhancement, image compression and storage, image analysis and image-based visualization [4]. The purposes of these research fields could be divided into two portions. One is to produce high quality of medical images like MRI mentioned in section 1.1 and the other is to interpret computerized analysis of medical images by computers. Image analysis is the extraction of meaningful information from digital images by means of digital image processing techniques. As many morphometric analysis methods are proposed, computers can detect differences of MR images. Therefore, these detected features could be used to construct a classifier that categorizes an observation as normal or abnormal with pattern recognition technology.

There are many well-known applications in CAD area, for instance, chest radiography, breast mammogram, schizophrenia, Alzheimer's disease, bipolar disorder and other psychotic disorders. Materials, features extraction and classification methods they used may be different from each other. Table 1.1 shows a simple comparison of recent CAD systems. The CAD1 system is a study of classification of adolescent psychotic disorders including schizophrenia and bipolar disorder, which used both medical images and neuropsychological tests of subjects as materials and applied linear discriminant analysis (LDA) with eight neuropsychological test variables and four brain structural variables [5]. Furthermore, they provided a tree-type decision to distinguish three groups. The purpose of the CAD2 system was not to classify a test subject into a normal group or an abnormal group but to lateralizate seizure focus in temporal lobe epilepsy [6]. They manually applied a VOI on materials including brain concentration and brain volume and then principal component analysis (PCA) and LDA were adopted to complete the classification. The CAD3 system is a study of classification in schizophrenia which made use of a surface-based approach to extract cortical thickness of subjects instead of 3D volume data as materials [7]. They presented a new procedure for 3D surface object classification that combined a shape description method with suitable pattern classification techniques. Through the high dimensional

landmark representation, the distance between two landmarks could be computed and was represented as the cortical thickness of the position. ROI selection, PCA and support vector machine (SVM) were applied in order to establish the system in a high dimension space. The study of CAD4 system is about the classification of schizophrenia with grey matter concentration [8]. Initially, a voxel-based morphometric (VBM) method and a multivariate linear model (MLM) were used to find an eigenimage. Discrimint function analysis with the eigenimage was then applied to distinguish a test subject into a normal group or an abnormal group. Moreover, the classification is built up in a one dimensional space with an absolute decision. Besides, another study of schizophrenia and Alzheimer's disease classification put emphasis on brain asymmetry features of medical images [9].

All of them, however, built up a computer-aided diagnosis system with absolute decisions which represent that an unknown MR image of a test subject would be either normal or abnormal definitely. Besides, the CAD1 system which study of bipolar disorder is the same as ours made use of behavior data and brain structural data as materials. Thus, in our work, we also followed the basic concepts in establishing a computer-aided diagnosis system but only used MR images of subjects with ROIs selection. Furthermore, the system would provide probabilistic diagnosis of test subjects. Namely, a test subject can know how much probability he or she has to be abnormal.

1.4 Thesis Scope and Organization

In this thesis, our goal is to establish an automatic and fuzzy computer-aided diagnosis system with computerized medical images. As we mentioned in the previous section, the interpretation of medical images by human intelligence will depend on physicians' professional skills. So, it is limited by physicians' subjective judgments and costs a lot of time for people who want to know their diagnosis result. Besides, most of existent CAD systems provide absolute predictions of test subjects. To improve this problem, we proposed a sim-

Table 1.1: Comparisons of four CAD systems.

System	CAD1(2006)	CAD2(2005)	CAD3(2006)	CAD4(2007)
Disease	schizophrenia, bipolar disorder	temporal lobe epilepsy	schizophrenia	schizophrenia
Amount	N=8, S=10, B=10	N=152, E=127	N=52, S=53	N=30, S=30(training) N=16, S=16(testing)
Feature	brain volume, Neuropsychological test	brain concentrations, brain volume	cortical thickness	GM concentration
Method	linear discriminant analysis 12 variables (8:test,4:volume) tree-type decision	VOI(manual) principal component analysis linear discriminant analysis	ROI(lobe) principal component analysis support vector machine high dimensional space	voxel-based morphometry multivariate linear model discriminant function analysis one dimensional space
Boundary	absolute	absolute	absolute	absolute
Accuracy	96%	≥96%	≥88%	≥90%(training) ≥80%(testing)

ple and highly correct classification method that provides an objective way to determine the probability of unknown subjects to be healthy or ill. The system will lighten loads of doctors and let subjects not wait so many days but know the diagnosis in a few minutes. In other word, we built up an automatic and fuzzy MRI evaluation system to help people have a simple examination. To our knowledge, the proposed system is the first fuzzy classifier in this field instead of a hard classifier.

Figure 1.5 is a macro view of the entire system. The whole system was established with many parallel classification models which were corresponding to particular diseases individually. To construct each model in our work, brain T1-weighted MR images of healthy and mentally defective people were collected as experimental materials. GM, WM and CSF of each individual were extracted from each 3D volume data according tissue-based segmentation approaches. After that, all of the same tissues of each subject were normalized into a standard space for comparisons. Moreover, it had been proven that many diseases like psychiatry were highly correlated with brain volume. Therefore, different tissues' volume in patients' brain structures might be larger or smaller than that in healthy brain structures. Thus, tissues' volume in every position of individuals' brain was computed in order to proceed with the following voxel-based statistical analysis. Through morphometric analyses like the voxel-based morphometry analysis, different brain structures between healthy people and patients were found with statistical significance.

Voxels, more significant than others, were considered as better attributes to tell the normal group and the patient group apart. Those better features might belong to GM, WM or CSF respectively. We took those better features as the training data to train three tissue-based classifiers with Bayesian theory. Finally, a leave-one-out cross-validation method is used for the robustness of this procedure. Once the classifier is promoted, it could be applied to a new, unknown test image and make a prediction of it. Figure 1.6 is an overview of each classification model to diagnose new test subjects.

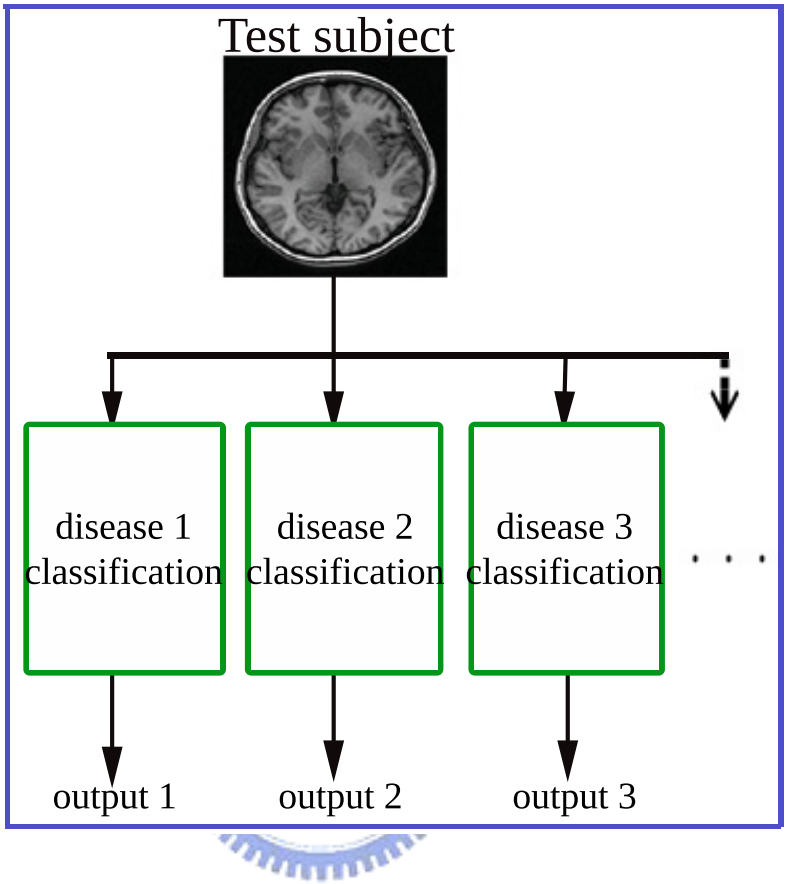

Figure 1.5: **Parallel diagnosis system.** For a specific disease, there is a corresponding classification model to examine whether a test subject is attacked by this illness or not. Thus, the whole system can be viewed as many collateral classification models. Moreover, a new classification model for a new disease can be established by repeating the methods introduced in our thesis and connects with existent models.

In the following chapters, we will bring up our algorithm, experiment results and some discussions. The methods of ROI selection and feature selection will be introduced in Chapter 2. A framework of classification system construction is proposed in Chapter 3. In Chapter 4, we will show our experiment results of applications. Then, we will have discussions in Chapter 5 and conclusions in Chapter 6.

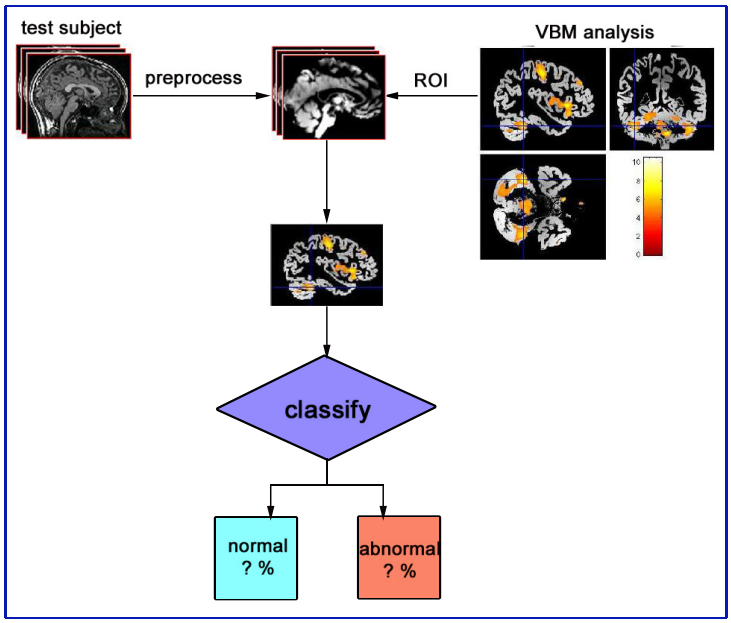

Figure 1.6: **Thesis Overview.** A list of preprocessing like segmentation, normalization, modulation is applied to an unknown image. After these, we select some regions of interest (ROI) of the test subject which are found in known dataset by morphometric analysis. Then, the classifier we established takes these extracted features as input and makes a diagnosis on this unknown sample.