Structural Brain MRI Segmentation Using Machine Learning Technique

Amirreza Mahbod, Chunliang Wang, Örjan Smedby

STH Medical Imaging and Visualization Group
KTH Royal Institute of Technology
Stockholm, Sweden

Abstract. Segmenting brain MR scans could be highly beneficial for diagnosing, treating and evaluating the progress of specific diseases. Up to this point, manual segmentation, performed by experts, is the conventional method in hospitals and clinical environments. Although manual segmentation is accurate, it is time consuming, expensive and might not be reliable. Many non-automatic and semi automatic methods have been proposed in the literature in order to segment MR brain images, but the level of accuracy is not sufficiently comparable with the one of manual. The aim of this project is to implement and make a preliminary evaluation of a method based on machine learning technique for segmenting gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) of brain MR scans using images available within the open MICCAI grand challenge (MRBrainS13).

The proposed method employs supervised artificial neural network based auto-context algorithm, exploiting intensity-based, spatial-based and shape model-based level set segmentation results as features of the network. The obtained average results based on Dice similarity index were 96.98%, 95.35%, 80.95%, 88.36% and 84.71% for intracranial volume, brain (WM + GM), CSF, WM and GM respectively. This method achieved competitive results with considerably shorter required training time on MR-BrainsS13 challenge.

Keywords: MRI, Machine Learning, Brain Image Segmentation

1 Introduction

Rapid development of non-invasive imaging techniques over the last few years has had undeniable effects on our knowledge and understanding about anatomy and function of the brain. Among different imaging modalities, magnetic resonance imaging (MRI) is the most widely used imaging technique for accessing brain diseases and exploring brain anatomy due to its high tissue contrast. The recent development of the MRI imaging techniques, has significantly improved the image quality and resolution. Besides the advances in imaging techniques, medical doctors also need more automated quantitative image analysis tools to help them diagnosis and evaluate brain diseases, as conventional qualitative image interpretation based on visual evaluation is prone to errors and insensitive to subtle brain structure changes [1].

Brain segmentation in MR is often a central piece of such quantitative image analysis system, because it delivers quantitative volume measurement of different brain structures and provides context information to further lesion detection and quantification. Segmentation of the brain could be used for different clinical applications such as evaluation brain atrophy, delineating multiple sclerosis (MS) lesions, analyzing brain development progress in different ages and image guided surgery. [1,2,3,4].

Manual segmentation is often seen as the "gold standard" method for distinguishing different brain tissues. However, it is a tedious and complex procedure that is not practical for analyzing large amount of MRI datasets in clinical practice. Moreover the manual approach also suffers from bad reproducibility due to large intra- and inter-observer variation [1,5].

Diversity of clinical applications and difficulties with manual segmentation led to development of various segmentation methods with different level of accuracy and complexity. A large number of methods have been proposed in the literature to supplant manual segmentation [1]. One set of conventional methods for segmentation are intensity-based algorithms that use the intensity of each pixel/voxel to judge their membership. Examples of this type of methods include thresholding [1], fuzzy clustering [1] and region growing [6]. Usually these methods are not very accurate and many preprocessing steps are needed before using them. Another set of methods is atlas-based methods which use template or reference images as prior knowledge for image segmentation. The segmentation is done by warping the reference images with known structure labels to the unseen image. Due to anatomical variation, these methods often require a large number of reference images and repeat the registration step many times [7,8]. Contour-based methods are also widely used for image segmentation. These deformable models use closed parametric or non-parametric curves for determining boundedness between different regions. The propagation of the closed surfaces is driven by the external forces (controlled by image attributes) and internal forces which keep the region smooth throughout the deformation. Active contours and level set are examples of this kind of models [9,10,11]. Apart from the aforementioned methods, machine learning-based segmentations algorithms[1] are also popular choices for brain segmentation. In a recent brain segmentation challenges, they have been proved to be superior to the purely intensity or gradient driven conventional segmentation methods [1,3]. In addition to the voxel intensity, machine learning methods also look at some other local image features, such as local mean, gradient, outputs of filter bank and entropy, etc. The learning

[1] For more details about machine learning based algorithms for image segmentation please read the appendix (state of the art chapter)

methods are then trained to classify these high dimensional features to different tissue types. Most machine learning based image segmentation methods do not take the global shape information into account when classifying the individual points, except in some cases the coordinates of the voxels are used as image feature for training, which can be seen as using the shape information implicitly. In many conventional methods, the prior knowledge of the structure's shape has been proven to be essential for the algorithms to deliver accurate segmentation results. This motivated us to explore the possibilities of incorporate the shape prior knowledge into the machine learning based image segmentation pipeline. In this project, an algorithm based on artificial neural networks (ANN), which uses the output of a statistical shape model guided level set method as the context information and also auto context model for training, has been implemented for brain tissue segmentation. In addition, other conventional spatial-based and intensity-based features were used which made the the whole algorithm as hybrid model for brain tissue quantification. The implemented method is applied on MRBrainS13 [3] and provides relatively accurate results compared to the segmentation done by clinical experts and other segmentation algorithms.

2 Method

The goal of brain image segmentation is dividing the image into meaningful, homogeneous and non overlapping regions with corresponding attributes. The proposed segmentation method for this project consists of several parts which are shown in Fig. 1. While the main structure of the algorithm is similar to most automatic segmentation methods (see Fig. 6 for more details), it slightly differs regarding the classifier. The classifier consists of two layers of neural network, level set segmentation part and context information which are fed to the network. In the following, the details of different parts of the algorithm are discussed in detail.

2.1 Image Data and Ground Truth

In this project, data from MRBrainS13 were used which contained twenty 3T MR brain exams from twenty different patients. All subjects were above 50 years old with diabetes and matched control with varying degree of atrophy and white matter lesions. Each exam consists of 3 series of MRI images, T1-weighted, T1-weighted inversion recovery and T2-FLAIR. All these series has been aligned with each other using a deformable registration method. The voxel size of provided data were 0.95 $mm \times 0.95$ $mm \times$ 3.0 mm. Each MRI volume (for each patient) contains $240 \times 240 \times 48$ voxels. From the twenty available datasets, five cases were provided with manual segmentation (ground truth) for training purpose. The labels for the remaining 15 datasets are kept away from the participant for evaluating the performance of each proposed methods. Manual segmented images consist of nine classes in total including cortical gray matter, basal ganglia, white matter, white matter lesions (WML), cerebrospinal fluid in

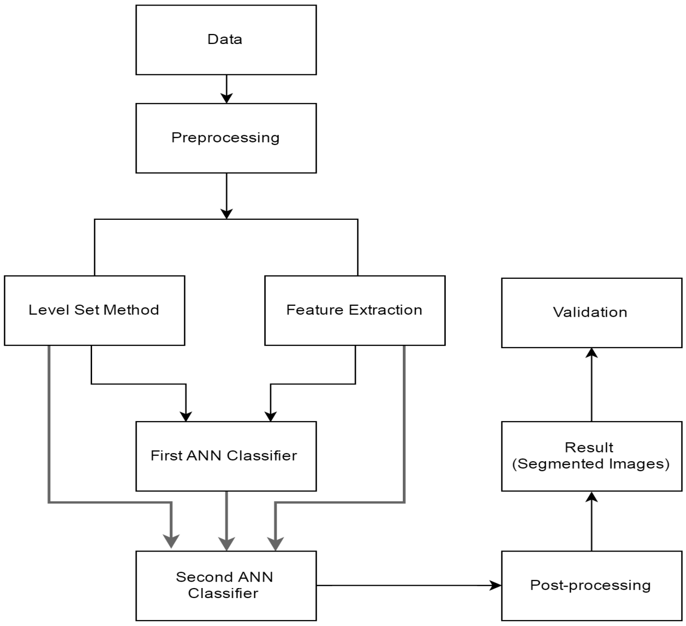

Fig. 1: Flow chart of proposed method for brain tissue segmentation

the extracerebral space, ventricles, cerebellum, brainstem and background. However, for the evaluation, only three classes, GM, WM and CSF are considered, in which Cortical GM and basal ganglia are both considered as GM, and WM and WML are both considered as WM [3]. Thus, cerebellum, brainstem were excluded when evaluating the segmentation accuracy.

2.2 Preprocessing

Preprocessing stage might have significant influence on the accuracy of segmentation results. However, it mainly depends on the input data. The aim of preprocessing is preparing data in suitable way to be fed to the classifier. Proper preprocessing will lead to similar scale, bias, brain tissue and spatial coordinates of all training and testing data. In this project, the following preprocessing steps were applied on data before sending them to classifiers respectively.

- **Histogram matching**: In this step histogram of all datasets were matched to the first dataset. This step is important for preventing network from being confused by different histogram shapes. Histogram matching was performed using Insight Segmentation and Registration Toolkit (ITK) [12].
- **Bias field correction**: Intensity inhomogeneity artifact was removed using ITK [12] . However, this step is not of high importance for datasets used in this project since they were already corrected.

- **Non-brain tissue stripping**: Since non-brain tissues such as skull have major effect on segmentation results, it was reasonable to remove them to increase the accuracy of segmentation algorithm. Skull stripping was performed in two steps. First, a mask was created using a model-based level set on T1-weighted inversion recovery images based on [10,11] for training data. Then a binary ANN-based classifier was trained in order to remove skull from test data. The network in this step had 150 neurons in hidden layers and two output, which represented background and the whole brain tissue. After applying skull stripping, any voxels outside of the brain were mapped to zero as background. Fig. 2 shows the effect of this step for a sample slice.

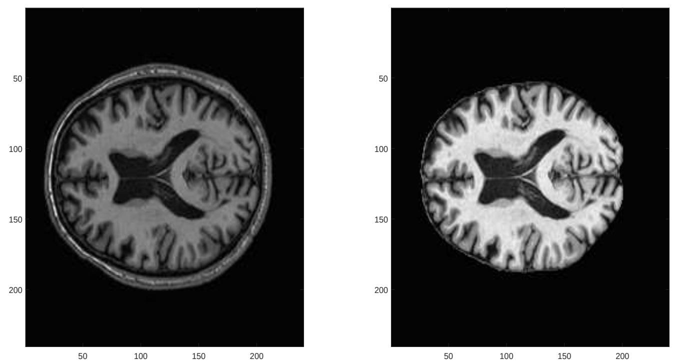

Fig. 2: Non-brain tissue removal for sample slice (25th) from first dataset on T1-weighted scan: Raw image on the left and skull-stripped image on the right

- **Removing extreme high and low intensity values from training and testing dataset**: Outlier intensity might have an adverse impact on the segmentation results. Therefore, 4th percentile and 96th percentile of each datasets were calculated as boundaries and all voxels below and above these calculated values were clipped off and mapped to derived boundaries. Fig. 3 shows how this step affected a sample slice.
- **Normalizing data** : Since intensities from different channels within a patient and also intensities of same channels for different patients could have large variability, normalization is a critical step to be applied on data. Table 1 shows this variation for one sample training channel of dataset (after applying previous preprocessing techniques). Therefore, in this project all images were normalized with zero mean and standard deviation of one.

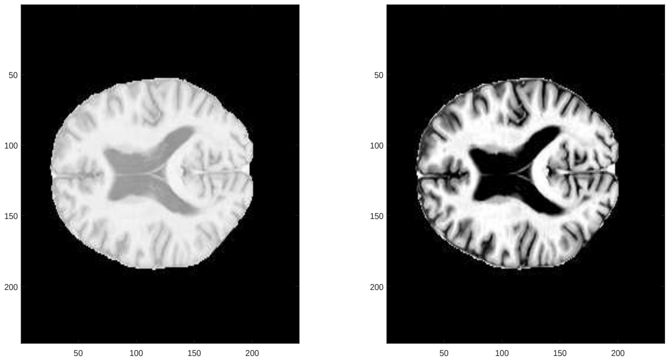

Fig. 3: Removing extremely high and low values for a sample slice (25th) from first dataset on T1-weighted inversion recovery scan: On the left raw image and on the right image after this preprocessing step. (T1-IR shows the effect of this preprocessing step clearly since variation of the intensity values of this channel was significant)

Table 1: Variation of intensity for differnt pattient (T1-weighted channel)

Dataset	**Min.**	**Max.**	**Mean.**
1	19	230	40.98
2	19	196	39.45
3	25	243	48.39
4	16	238	37.92
5	18	222	41.41

2.3 Feature Extraction

As the input of networks (both layers), features were extracted via two separate approaches.
One set of features were conventional intensity-based and spatial-based features. Same features as [13] were extracted from images which are described as following:

- Intensities of different channels (T1-weighted, T1-IR and T2-FLAIR)
- The intensity after convolution with a Gaussian kernel with $\sigma = 1, 2, 3\ mm^2$ (both in 2D and 3D manner)
- The gradient magnitude of the intensity after convolution with a Gaussian kernel with $\sigma = 1, 2, 3\ mm^2$ (both in 2D and 3D manner)
- The Laplacian of the intensity after convolution with a Gaussian kernel with $\sigma = 1, 2, 3\ mm^2$ (both in 2D and 3D manner)

- Spatial information of all voxels (x, y, z) which were divided to length, width, and height of the brain respectively.

Other features such as Gabor filter bank, Haar features , histogram based features (e.g. histogram equalization and contrast-limited adaptive histogram equalization) were extracted from datasets. However, their impact on the results was not significant. Thus in final implementation, they were not utilized. Moreover, T1-IR channel was not used as a direct feature since it had large variability which degraded the segmentation results. Totally, 32 features were extracted and used from this stage of the method.
Another important set of features, used in this project as extra channels, was results from level set method. These features were extracted based on MiaLab framework [10,11]. Brain ventricles, basal ganglia, cortical gray matter, cortical white matter and cortical surface regions were made using a variation of the conventional statistical model-based level set method on T1-weighted images. These five extra features as well as the features obtained previously were sent to the network.

2.4 Classification

Artificial Neural Networks were uses as main classifier of propose algorithm. Several ANN-based algorithms [2] including support vector machine (SVM), multi layer perceptron (MLP), radial basis function (RBF), learning vector quantization (LVQ) and convolutional neural networks (ConvNets) were implemented in the frame of this project. However, the results from MLP were relatively accurate and also training time was considerably shorter compared to other methods. Thus, this network was chosen for this project.
The proposed network consisted of one hidden layer with 100 hidden nodes. The learning rule for updating weights was generalized delta rule which calculated the weight updates from output to input layer (error back-propagation)[14].
In order to exploit of context information, outputs of first network which were discriminative probability (or classification confidence) were convolved with Gaussian filters with kernel size of 0.5 mm and 1 mm and then were sent to the second network as extra features along with all other obtained features. The structure of the second network was identical as with the first one. Each classifier was trained on a total of 40000 samples from training dataset which were randomly selected within the brain excluding the cerebellum and the brain stem. The output of second network contained the information of the voxel classes (totally 6 classes in this stage including WML, WM, Cortical GM, basal ganglia,ventricles and CSF).

2.5 Post-processing

Networks were trained with six labeled classes, thus the network results also included six classes. However, these six classes had to be merged to form fi-

[2] Thorough explanation about these networks can be found in appendix chapter

nal three segmentation parts (i.e. WM, GM and CSF). Procedure for merging different classes can be found on [3].

2.6 Accuracy Analysis

Segmentation results were compared to ground truth based on Dice similarity index and absolute volume different (AVD) similarity index. [3]. While Dice represents the general accuracy of the method, AVD shows the sensitivity of the method to segmentation noises. Background, cerebellum and the brain stem were excluded from validation.

3 Results

The results represented here are based on five training datasets using leave-one-out method (training with four datasets and testing one the other dataset) which are provided by manual segmentation.
Result for testing datasets (the resting fifteen datasets) will be published by MRBrainS13 ($http://mrbrains13.isi.uu.nl/results.php$).
All experiments were performed on a desktop computer with NVIDIA GTX 980 4GB , 32 GB installed memory and Intel Xeon E5-2630 2.40 GH CPU. Main implementation of the algorithm was done with MATLAB (version 2016a). The runtime of implemented algorithm for training networks and testing on a volume was five minutes approximately.
Table 2 shows comparison between three implemented methods. As it is illustrated, MLP achieved better performance with acceptable training time. Therefore, this method was chosen as final choice of ANN structure.

Table 2: Comparison of differnt ANN- based algorithms using leave-one-out method applied on training data to choose the best algorithms. For SVM 15 support vectors were trained and for CNN same sturucture as Fig. 10 was used (The results presented here for SVM and CNN were obtained without context layer).

Method	**Dice(%) ICV**	**Dice(%) Brain**	**Dice(%) CSF**	**Dice(%) WM**	**Dice(%) GM**
MLP	97.73	95.09	83.88	87.39	84.62
SVM	97.73	94.94	83.73	87.17	84.32
CNN	97.73	90.01	76.94	77.33	67.00

In addition in order to investigate the reliability of proposed method, the whole leave-one-out method was executed five times with exactly same parameters and structure. The mean value and standard deviation of Dice index and ADV index are shown in Table 3.

Table 3: Investigating reliability of proposed method using MLP network

Structure	**Mean Dice(%)**	**Std.dev**	**Mean ADV(%)**	**Std.dev**
GM	84.86	1.19	6.39	3.58
WM	87.68	3.13	8.69	6.46
CSF	84.64	0.86	9.45	4.01
Brain	95.19	0.21	4.89	1.41
ICV	98.09	0.14	1.70	0.61

As Table 3 shows the results of segmentation are relevantly accurate. Specially, this can be seen in brain (GM +WM) segmentation since it is almost related to segmentation algorithm and not to skull stripping part. However, AVD index has large variation from data to data. Indeed, AVD is very sensitive to segmentation noises which makes it very challenging to minimize.
Fig. 4, shows final results after segmentation with proposed algorithms for three sample slices for visual inspection. As it is demonstrated in Fig. 4, proposed method provided relatively accurate results compared to manual segmentation. Most of the segmentation errors within the brain occurred in the border of different brain tissues.
In addition, results shows that skull stripping is another source of error. To investigate how much it could affect the results, one test was executed with proposed skull stripping algorithm and one test was executed by using manual segmentation for skull striping (i.e. perfect mask). The results of this approach suggests that approximately 2% of the error for ICV and 5 % of the error for CSF was related to skull stripping. It had very small effect on GM segmentation and almost no effect on WM segmentation.

4 Discussion

Brain image segmentation in this project was performed by combining neural network based method with level set and auto-context model. Therefore, it can be considered as a hybrid model.
The most challenging part of the project (usually for all ANN-based methods) was optimizing network structure and parameters. The aim of this optimization was to minimize the backpropogation error and also avoid over fitting at the same time. It can be inferred from the results that optimization for MLP and SVM was acceptable. However, for CNN more tuning is needed since according to literature CNN has shown better performance compared to other conventional neural network models. Optimization for CNN can be achieved by tuning several parameters of the network including number and structure of convolutional layers, patch size of the images, filter size and number of filters.
While testing, for one of the dataset (patient 2), Dice index of WM was considerably smaller compared to other datasets. After further investigation on this

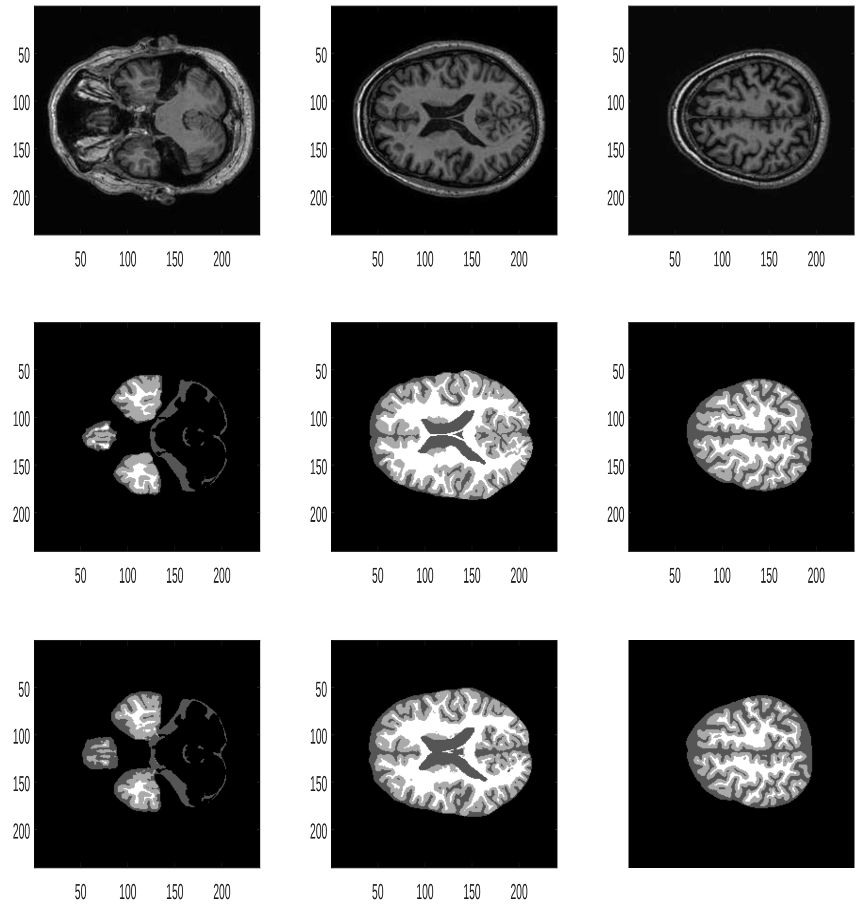

Fig. 4: Example segmentation result for three slices (10, 25, 35) for 5th dataset. First row shows the raw T1-weighted scan, second row shows the manual segmentation and the third row shows the result from proposed method.(Note: Cerebellum and brainstem were removed manually using ground truth)

specific dataset, it was revealed that this 3D volume consisted of a greater fraction of WML compared to other datasets. Therefore, it can be concluded that the size of WML might have an impact on the system performance for segmenting WM. However, since only one of the dataset had this problem, further investigation is needed for approving this hypothesis.
As comparison to other methods which are applied on same dataset [3], training

time of the proposed method (less that 5 min) is considerably shorter compared to most of other methods in the challenge. However, direct comparison is not applicable since algorithms were executed on different systems.
In the proposed algorithm, removing auto-context layer will not affect the accuracy significantly. It can be inferred that context information are derived from level set results so auto-context information may not play an important role for final results. However, the effect of increasing number of auto-context layers could be very interesting to be investigated with varying size of Gaussian filters. Undoubtedly, this will lead to slower system, but it perhaps increases the accuracy. Due to limitation of system installed memory, further increase of auto-context layer was not applicable in this study.
As it was shown in Table 3, the results are not perfectly reproducible and they changed slightly after each execution. One possible reason behind this variation, might be the random selection of training data. Increasing size of training data can lead to smaller standard deviation with the cost of slower system.
The main contribution of this study is proposing a new segmentation algorithm which is the combination of ANN-based model and statistical shape model based on level set method. The combination of both models has better performance compared to each of them individually. Also compared to auto-context models [4,15] it needs fewer number of iterations with almost same accuracy.
Many possible extension could be considered as further development of this study. Principle component analysis (PCA) can be applied on features to firstly reduce size of features and probably increase the performance. This step could be highly beneficial in case of extracting more features. However, there would be no guarantee for improvement of the result if more features are extracted. In addition, using the results from other conventional methods could affect the results and create a new hybrid system. Finally, cross validation could be performed on training data for determining the best parameters of the network which needs sufficient time and also a powerful system for running the program.

5 Conclusion

Segmenting brain MR images is a time consuming and complex task for clinicians. In addition, proposing an automatic and accurate method for segmentation task is challenging. In this project, a fully automatic method has been proposed for segmenting WM, GM and CSF of the brain. Results of the segmentation performed by proposed method were relatively accurate with acceptable standard deviation while the training and testing time were considerably shorter compared to other conventional methods . Further investigation is needed for developing current method to improve the accuracy. Moreover, the generalization power of the proposed algorithm in other field of medical imaging segmentation is open for further studies.

Appendix

State of The Art

This chapter includes brief theoretical background about medical image segmentation and explanation about the most new techniques for brain image segmentation with learning based approaches. It also describes the common preprocessing and post processing methods for MRI scans to enhance the accuracy and efficiency of final segmentation results.

A Background

Image segmentation refers to techniques for partitioning digital images to multiple homogeneous and non-overlapping areas which represents the image in a way to be analyzed visually or computationally for different applications. In medical applications, image segmentation could be highly beneficial for studying anatomical structures of the body, determining region of interests (e.g locating tumors), measuring tissue volume, surgery planning before radiation therapy, image-guided interventions, post-surgical assessment, virtual surgery simulation, etc [2],[16,17].
Among different applications, brain image segmentation is one the most important diagnostic tools for detecting and predicting many brain related diseases and abnormalities such as small vessel disease, Alzheimer disease, dementia, focal epilepsy, Parkinson and also for analyzing brain development [2,3,1]. Segmented areas or different classes on brain scan could include different tissue types. However, the most three important parts of the brain are usually gray matter (GM), white matter (WM) and Cerebrospinal fluid (CSF). Fig. 5 shows theses different areas on two T1-weighted sample slices from 3D MR scans.
Magnetic resonance imaging (MRI) and computed tomography (CT) are the most common non-invasive methods for analyzing the anatomical structure of the brain [17]. While CT is usually used for detecting bleeding, brain damage and skull fractures in patients, MRI is preferable for brain image segmentation application. MR in general has excellent contrast and signal to noise ratio (SNR) for soft tissue imaging and also it is more sensitive for detecting brain diseases in early stage for instance for detecting tumors or white matter diseases. In addition, it is less harmful compared to CT [17]. By using different pulse sequences and changing imaging parameters in MRI which are related to longitudinal relaxation time (T1), and transverse relaxation time (T2) and also signal intensities, different image types could be acquired. Each of these image types with different level of contrast could have applications for analyzing specific tissue in brain. Common MR imaging acquisition protocols are T1- weighted scans, T2-weighted scans, proton density (PD), T1-weighted inversion recovery scans and fluid attenuated inversion(FLAIR)recovery scans [17],[3].

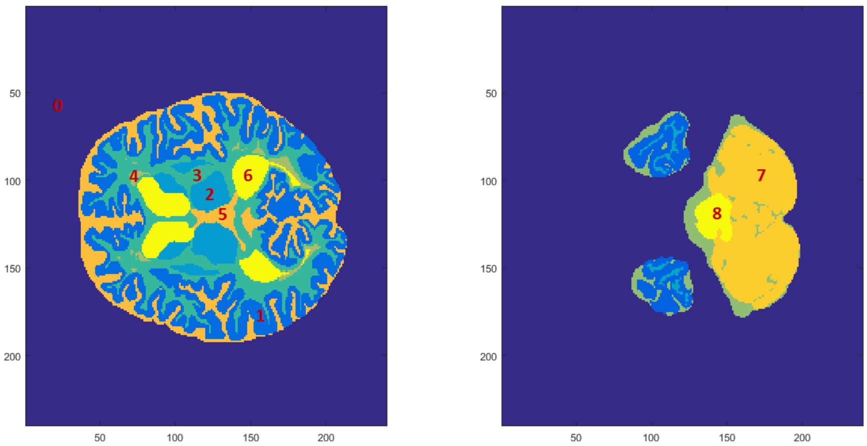

Fig. 5: Two sample T1-weighted MR images which are manually segmented by three experts (Data adapted from http://mrbrains13.isi.uu.nl/).(Left image from middle part of the brain and right image from down part of the brain).The segmented areas are written on the images as area 0 is background, area 1 is Cortical gray matter, area 2 is Basal ganglia, area 3 is White matter, area 4 is White matter lesions, area 5 is Cerebrospinal fluid in the extracerebral space, area 6 is Ventricles, area 7 is Cerebellum and finally area 8 is Brainstem. In case of segmenting to only four areas (background, GM, WM and CSF) area 1 and 2 can be merged as GM, areas 3 and 4 can be merged as WM and areas 5 and 6 can be merged as CSF. Areas 7 and 8 should be excluded from segmentation evaluation.

B Brain Image Segmentation

Currently, the most accurate method for segmenting MR scans is manual segmentation. Manual segmentation is usually performed in dark room with optimal viewing condition by expert physicians and clinicians [3]. Indeed, most of the time even for evaluation of other segmenting methods, their results will be compared with manually segmented images as ground truth. Physical or computational phantoms are also used for validating segmentation methods, but usually they do not provide a realistic representation of anatomical structures. Basically, brain atlases are formed by these manually manipulated images [18]. It should be noted that manual segmentation is complex and tedious task for clinicians [1]. Manual segmentation is typically performed slice by slice even for 3D volume. Therefore, manual segmentation, although accurate, is very time consuming. In addition, this method is subjective (e.g. related to experience and skill of the operator) and very difficult to be reproduced [1],[19].

A number of softwares such as ITK-Snap [20] show different views of the brain (i.e. sagittal, coronal, and axial).Thus, it could be very helpful for expert to conduct better and more accurate manual delineation.

Many other semi-automatic and non-automatic computer aided algorithm are proposed in the literature for brain image segmentation including intensity based methods (including thresholding, region growing), atlas-based methods (using prior knowledge), surface-based methods (including active contours and surfaces, and multiphase active contours)[1]. The common problem of all these methods is accuracy. They may perform well for specific data, but they are not reliable for another dataset.

However, they could be used as part of learning approaches in automatic segmentation methods [17]. Indeed there are new approaches that try to combine different methods to avoid their disadvantages and limitations and at the same time get the best out of each of them.They are generally called "Hybrid segmentation methods "[1].

Because of all mentioned problems, the need for fully automatic and reliable methods for brain image segmentation has emerged. Although, automatic methods have different performance (e.g. in terms of complexity, accuracy, computational speed, etc), most of them are based on learning approaches and share a common structure. The main scheme of these approaches is shown in Fig. 6
.

As Fig. 6 shows the main components of the flowchart are:

- Data
- Pre-processing
- Learning approaches based on feature extraction or Deep learning
- Post-processing
- Validation of results

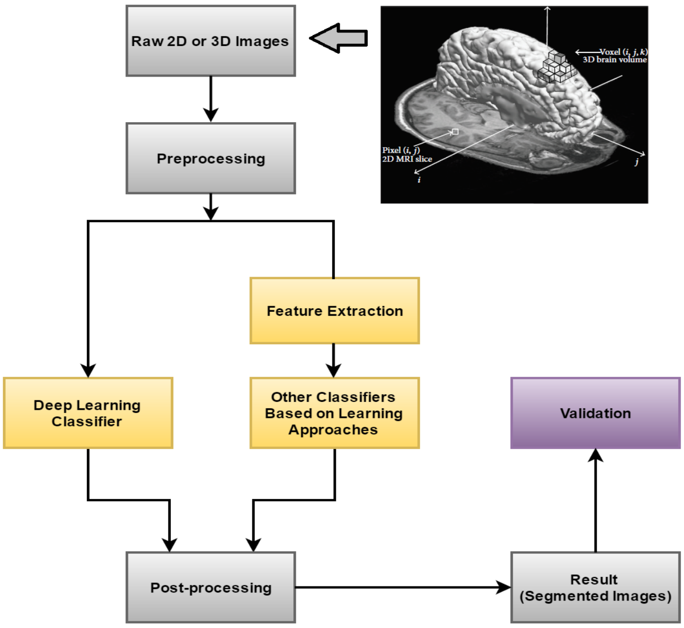

Fig. 6: Generic flow chart of automatic segmentation algorithms

In the following parts of this chapter each of these sections will be described and the state of the art methods for each part will be explained.

B.1 Data

Usually, MR scans are presented as 2D images (pixel-based) or 3D volume (voxel-based). The value of each pixel or voxel represents the intensity of signal which is related to magnetic resonance characteristics of corresponding tissue. Actual pixel/voxel size depends on parameters such as imaging parameters, magnet strength, etc, but usually it is around 1-2mm [1].

It is recommended to use common and reliable data (e.g from previous challenges and online sources such as Internet Brain Segmentation Repository (IBRS)[21], MRBrainS [3] and Alzheimers Disease Neuroimaging Initiative (ADNI) [22]). These datasets provide manual segmented images as ground truth which can be used for both training and evaluation of segmentation algorithms. In addition, using these datasets makes it possible to compare results with other implemented segmentation algorithms on the same data.
In order to estimate the segmentation method error at the end, data usually are divided to two groups. One group for training the segmentation algorithms and the other group for testing the algorithms. Since data are valuable and sometimes insufficient, advance methods are introduced for dividing train and

test data including holdout, re-substitution, cross-validation, leave-one-out and boot-strapping.

B.2 Pre-processing

Preprocessing is one the most important parts that must be done before applying segmentation algorithms. Different artifacts can corrupt MRI scans such as image noise,motion artifact, partial volume effect and bias field effect. One should remove these artifacts in order to improve the final segmentation results. Beside these artifacts, non brain tissue should be removed from images since it degraded segmentation result dramatically [1].

Different methods for noise reduction in MRI scan can be applied. Some MRI de-noising methods are linear filtering methods, nonlinear filtering methods, Markov random field (MRF) models and wavelet transform [2].

Bias field effect (also called intensity inhomogeneity) refers to smooth signal intensity variation within the same tissue.This artifact arises from spatial inhomogeneity of the MRI device. This artifact is correlated with magnetic field (negligible in 0.5T and high in 3T magnetic field) [1]. This artifacts can be modeled as low-frequency component and can be removed by low-pass filtering [23]. However, low-pass filtering may also remove low frequency components in true image. Therefore, more advanced algorithms are proposed in literature for removing that such as minimizing the image entropy [24], maximizing the high-frequency components of the image [25]. Also some software such as SPM8[26] and FSL [27] could do this preprocessing step.

Another preprocessing technique specially in case of using multi dataset or multi-modal images (e.g., MRI, CT, PET, and SPECT), is registration. Registration is the process of finding the transformation between images with corresponding features and aligning images spatially. It is very important when there is motion artifact(e.g patient movement) in the images. Rigid and affine transformation are two typical methods for performing registration[28].In addition some software such as Elastix [29] can be used for image registration. It should be noted that in general registration task becomes more challenging when brain images include lesions or diseases since it is more difficult to align healthy and abnormal tissues[1].

Partial volume effect (PVE) is another artifact that degrades the segmentation result. It refers to loss of small tissue regions because of the poor resolution of the MRI scanner[1]. Indeed when two or more tissues affect one pixel or voxel, the result image will be blurred specially at the boundaries between tissues [17]. One good solution to deal with this problem is soft segmentation which means each pixel can belong to several classes according to specific criteria (see B.4) [17].

As mentioned previously another important step in preprocessing is removing non brain tissue. Non brain tissue includes skull, scalp, dura mater, fat, skin, muscles, eyes and bones[1]. One way for removing non brain tissue is using mask which is generated according to prior knowledge (e.g. brain atlases)[30]. However, this method is not very precise. Alternative method is using brain extraction tools (BET) which is part of free FSL software[27]. This software tries to find center of gravity of the brain and then inflate the sphere until it reaches the boundary. It has shown acceptable performance for T1-weighted and T2-weighted images.

Based on need and input images, other preprocessing steps such as normalization (usually with zero mean and unit standard deviation) and range-scaling can be applied data before feature extraction and classification [31].

Hopefully, after all preprocessing steps, histogram of the image should have three main peaks which represents WM,GM and CSF. Fig. 7 shows a sample preprocessed T1 MR histogram for an adult[1] (Peaks are not that separable for Neonates). As Fig. 7 shows, there is overlap between different parts and overlap between GM and WM is more that overlap between GM and CSF. However, researches show adding additional MRI sequences (e.g T2-weighted) can be helpful and eventually improve segmentation results[1].

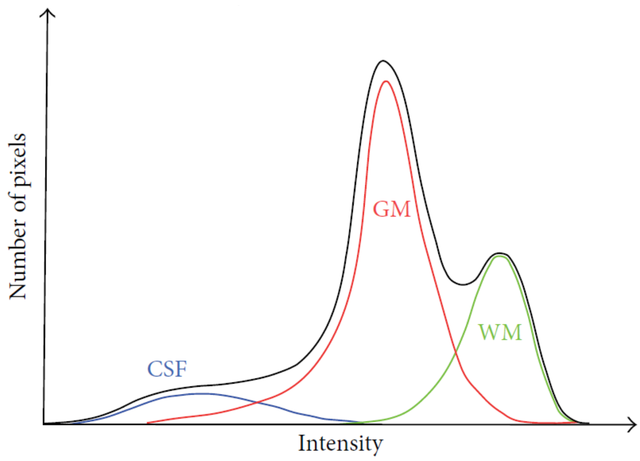

Fig. 7: Histogram of a T1-Weighted MRI of an adult brain (Adapted from http://www.hindawi.com/journals/cmmm/2015/450341/)

B.3 Features

Most of learning based methods for image segmentation are based on features that are extracted from images. Therefore it is worthy to know more about these features. Generally, features are extracted from images by numerical measurements and with aid of them it is possible to discriminate between regions of interest and their background. Appropriate feature selection and feature extraction plays important role in final segmentation results [1].

One set of conventional features that are used for MRI classification are statistical features. Statistical features are based on first and second order statistics of intensities in images. First order statistical features can be derived from image histogram and includes intensity, mean, median, and standard deviation(SD) of images. First order features are useful for image segmentation when background and object of interests have different intensities in large scale [1]. Second order statistical features are usually used for describing image texture and can be extracted from Co-occurrence matrix of images [32]. Energy, contrast, entropy and correlation are some of the features that are used as second order features for brain image segmentation [33]. First and second statistical features are usually called appearance features in literature.

Another popular feature for image segmentation is edge (i.e boundaries in the image when there is a sharp change in intensities value)[1]. Edges in general are sensitive to noise so de-noising must be performed in preprocessing stage for proper edge detection. Edge detection is usually based on gradient (derivative) function. It could be first order (e.g.Prewitt, Sobel, Roberts) or second order derivative (e.g.Laplacian). In literature, Gaussian-scaled gradient magnitude and Gaussian-scaled laplacian of intensity have been used along with intensity and Gaussian-scaled intensity for brain image segmentation[31]. Also more advanced methods are proposed in literature for edge detection such as phase congruency method [34] and Canny edge detection [35]. Gabor filter is another linear filter for edge detection. This filter is sensitive to orientation and frequency in the edges and it has been found particularly appropriate for for texture discrimination in the image. Gabor filters have been used for brain image segmentation along with other features [36].

Haar-like features are also could be used for medical image segmentation. They have been used successfully for face recognition in literature [37]. In this method adjacent rectangular regions are considered in certain location in the detection window. Then sum of pixel intensities in these rectangular areas are calculated and the difference between these sums are derived. The difference could be used to differentiate different areas in the original image. Since Haar-like feature is a weak classifier a large number of Haar-like features are needed to segment the image properly. This feature has been used for brain image segmentation in literature [36].

Spatial information (i.e. x, y, z coordinates of voxels) also can be used as an extra feature. However, this feature should be used carefully if images are not aligned properly. Some studies could use this feature for improving brain image segmentation result[31].

B.4 Learning approaches

Probably the most important part of the flowchart in Fig. 6, is segmentation method. Segmenting MRI scans could be very complicated task since images are imperfect and corrupted with different kind of artifacts (even after preprocessing). Therefore, many image processing techniques have been proposed in literature for medical image segmentation. However, between them learning based approaches (considered as automatic segmentation methods in this report) have shown better performance. In general, they can be divided to supervised learning approaches (i.e training with labeled data as ground truth) and unsupervised learning approaches (i.e train themselves with unlabeled input data). In the following ,the most important techniques with acceptable performance are described briefly.

KNN Classifier : In nearest neighbor classifier each element (pixel or voxel) is classified as the same class of training datum with closest intensity. K-nearest classifier is the generalized version which each element is classified based on majority votes of the closest training data. This method was used in literature for MRI brain segmentation[38],[39]. In those studies,beside intensity,spatial localization of brain structure was used as an additional feature.

Bayesian Classifier : This classifier tries to model the relationship between feature sets and class variables and then use this model to estimate the class of unknown samples[40]. Expectation maximization (EM) segmentation methods are based on Bayesian classifier and have been used in many software packages such as SPM[41], FreeSurfer[42] and FAST[43].

K-means Clustering or Hard C-means : This is an unsupervised iterative method which starts segmentation by putting input data to K different classes. Then in each iteration, it computes the mean intensity (called centroid) for each class and classifies each element into the closest centroid. K-means clustering is known as hard classifier since it force each element to belong to a class in each iteration[44]. Soft version of this method is Fuzzy C-means Clustering (FCM)[45] which let the elements belong to multiple classes based on certain membership value.

Artificial Neural Network Approaches : There are some approaches for image segmentation with promising results that uses artificial neural network (ANN)[3] in their main structures. Generally, these networks consists of input layer (the number of input nodes shows the feature dimension that are extracted from MR images), nodes (building block of the network), activation functions (which affects output of each node), learning rule (depends on the algorithms

[3] In this report all methods which use artificial neurons (nodes) as their building blocks are considered as ANN

it could change such as perceptron learning rule, delta rule, generalized delta rule and Kohonen learning rule), topology (connection between different nodes, input and output layer) and output layer (only for supervised approaches). Fig. 8 shows the topology of ANN.

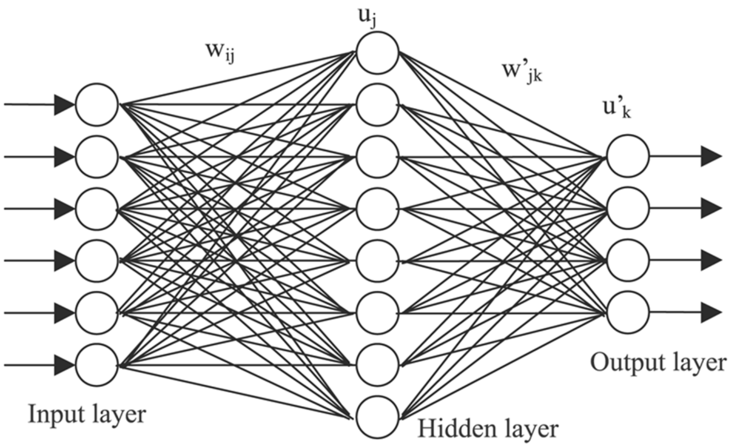

Fig. 8: Generic topology of ANN. W_{ij} shows the weights between input and hidden layer and W_{jk} shows the weights between hidden and output layer. ANN could have more than one hidden layer

Here, most important algorithms of ANN that can be used for segmentation are explained.

- **Multi Layer Perceptron (MLP):** MLP is a feed-forward network with general structure as it is shown in Fig. 8. It is combined of several linear classifiers (each perceptron) that can be together used for non linear classification problem. The weights of network are randomly initiated at first and then in each iteration they will be updated according to generalized delta rule in order to minimize the error function (difference between network output and real output). The method for updating is called back propagation (BP) since updating weights are performed from output layer toward input layer. This method uses gradient descend for minimizing the error function so it may get stuck in local minima [14]. For implementing this method some parameters has to be tuned such as number of nodes in hidden layer, number of hidden layers, number of iterations (trade off between bias and variance), etc. For tuning these parameters some proposed solutions are cross validation and early stopping rule [33],[14]. This method has been used in literature for brain image segmentation [33] and also outdoor image segmentation [46] with promising results.

- **Radial Basis Function (RBF):**RBFs are sets of networks that try to map nonlinear input space to linear feature space and then classify it linearly [14]. For mapping, euclidean distance is used in activation functions. Like MLP network, here again gradient descend approach is used for minimizing error function. The generic architecture of RBF is shown in Fig. 9 . RBF network can be used for brain image segmentation alone[47] or as part of other approaches. For instance SVM, SOM and LVQ use RBF neurons for classification.

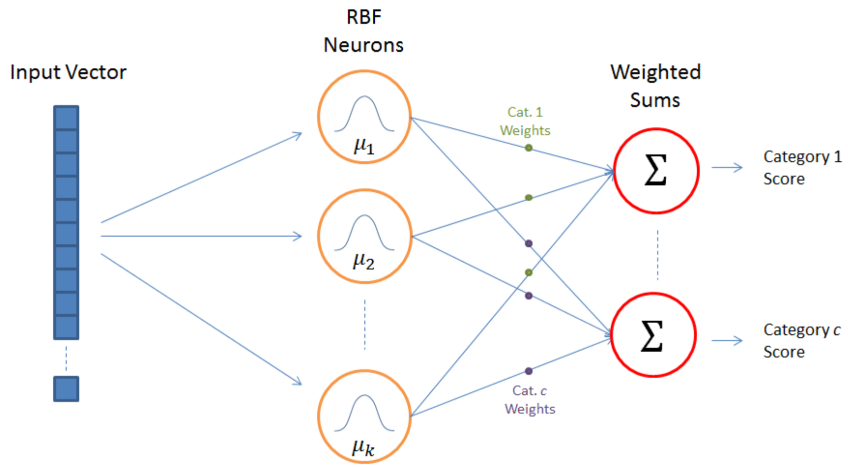

Fig. 9: Generic Architecture of RBF network for two classes classification.$\mu_1, \mu_2 ... \mu_k$ are activation functions based on euclidean distance.

- **Support Vector Machine (SVM):** SVM is a nonlinear binary classifier that can be used for supervised learning. It takes input labeled data from two classes and updates the network for classifying unlabeled data [48]. The weights in this network are updated in order to optimize two terms: maximize the border around decision function and minimize the number of training samples that are wrongly classified. Further information about this algorithm can be found in [49]. Basically SVM is a binary classifier, but it can be used for multi classification as well by one-versus-one approach [31]. This method showed promising result for brain image segmentation but computationally expensive[31]. For reducing the training and testing complexity,the size of original dataset can be reduced by using certain properties e.g discrete wavelet transform[48].

- **Self Organizing Maps (SOM):** This is an unsupervised clustering method that was introduced by Kohonen in 1982 for the first time. SOM network consists of input layer and competitive layer (hidden layer in Fig. 8). Number of nodes in input layer shows number of features and number of nodes in competitive layer shows number of classes (e.g. four nodes for segmenting background, WM, GM and CSF in brain MRI scans). The algorithms can be divided to three phases. Competitive, cooperation and adaptive phase.In Competitive phase, for each input sample, one neuron will be specified as winner neuron. This node has the minimum euclidean distance from the input data. In cooperation phase neighbors of the winning neuron are specified. Generally, neighborhood is specified by a Gaussian function (winning node in the center of Gaussian function and other nodes will be distributed on Gaussian function). Final phase is adaption phase which weights of winning node will be updated. Weights of the neighbor nodes also will be updated, but with less strength (according to Gaussian distribution in cooperation phase). Updating weights is done based on Kohonen learning rule and move the winning node and its neighbors toward the input data. In the other word, SOM network learn the distribution and topology of input data in each iteration and finally classify the input data to different clusters [2]. This method has been used for image segmentation in literature for instance for tumor detection [50].

- **Learning Vector Quantization (LVQ):** This method can be considered as supervised version of SOM. LVQ network consists of three layers: input layer, competitive layer and output layer. In competitive layer input data are classified corresponding to SOM method. Thus, here again the winner neuron is specified based on the euclidean distance between the node and input data and the weights of winning node will be updated. The output layer maps the competitive layer classes to target classes. Indeed, the learning process in each iteration in LVQ method is related to updating winner node weights. When winning node is determined by competitive layer, then it will be checked if it is correctly classified (according to labeled training data). If it is classified correctly, the weights will be updated to move closer to input data and if it is wrongly classified, then it moves away from input data[2]. Several algorithms are proposed in the literature for LVQ network with slight implementation differences. LVQ1, QLVQ, LVQ2.1 and LVQ 3 are some of these learning approaches. Practical experiences show that it is good to initiate the network with LVQ1 and then switch to other algorithms (e.g. LVQ2.1) in further iterations.

Deep Learning: Deep learning is a relatively new branch in machine learning which tries to model high-dimensional input data by multilayer processing neural layers[51]. This approach consists of many architectures, but one which has high potential for image recognition is convolutional neural networks(CNN or ConvNet). For image segmentation, CNN analyses the neighborhood around each voxel (pixel) and tries to classify it. In CNN there is no need for feature extraction and this is the main difference between CNN and other learning approaches. Instead, in CNN middle layers consist of kernels (some already established filter banks) which are convolved with input data. Generally, for classifying each element (pixel od voxel) in CNN, first a small patch from the original image is chosen with the desired element (the pixel or voxel to be classified) in center of patch. Then this patch will be convolved with kernels in middle layer or layers and create feature maps in output. Usually, the final layer is fully connected conventional MLP which creates the final classification output. In literature, CNN has been used for anatomical brain segmentation with promising results [52],[53],[54] . Fig. 10 shows one of the implemented CNN architecture for brain image segmentation to GM, WM, CSF and Background [54].

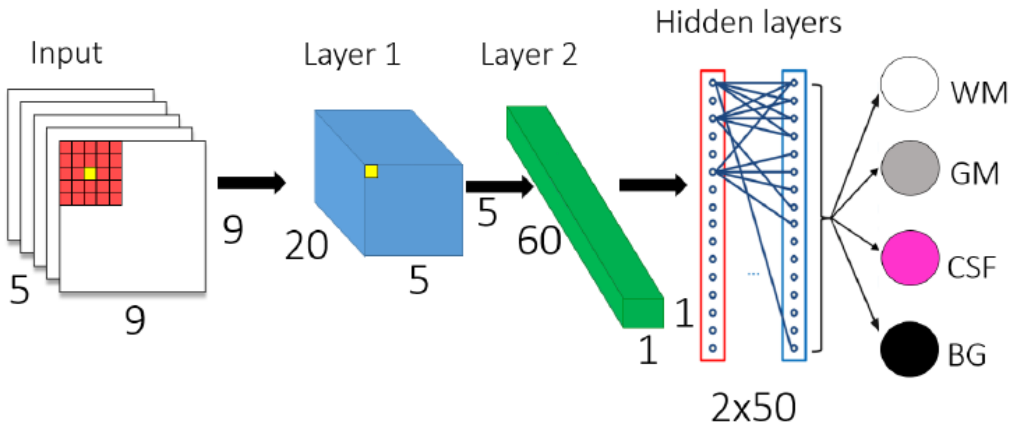

Fig. 10: Brain image segmentation using CNN architecture applied on IBRS data[54]. In left side, a patch is chosen from the 3D volume (with size of $9 \times 9 \times 5$). Then it convolved with filter banks in middle layers (layer one consist of 20 feature maps and layer 2 consists of 60 feature maps). The output of layer to is send to fully concted hidden layer which finally classified the voxel.(Adapted from http://www.diva-portal.org/smash/record.jsf?pid=diva23A814233dswid=-6865)

B.5 Post-processing

Different post-processing techniques could be applied on classifier output. Post-processing part mainly depend on the techniques that are used in previous parts. For instance, if 2D slices were used for segmentation, then combing these slices to form 3D volume could be a post-processing task [1]. Another post processing step could be fusing voxel values of segmented result to reduce number of classes (see Fig. 5)

B.6 Validation methods

Probably one of the conventional problem for medical image segmentation is quantitative comparison and validation. For proper comparison, a gold standard or ground truth is needed. Unfortunately, there is no real ground truth for in vivo brain analysis. Thus, ground truth is made by one or more experts after image acquisition as manual segmentation. As mentioned earlier, this method needs to be critically considered, but so far it is the most reliable approach for evaluation of segmentation algorithms.
For quantifying the overlap between manual segmentation and different segmentation methods, several measures are proposed in the literature.

One of the most popular similarity indexes which determines the spatial overlap is Dice similarity index (DI). It can be be calculated as following:

$$DI\% = \frac{2|A_i \bigcap B_i|}{|A_i| + |B_i|} \tag{1}$$

where i stand for tissue types (e.g. WM, GM, CSF), A stands for manual segmentation (ground truth) and B for MRI segmentation algorithm. It has the range from 0 (the worst result) to 100 (the best result if A and B are completely identical).

Another similarity index (again for spatial overlap) which has been used in literature [33] is Jaccard similarity index (also called as Tanimoto coefficient) which can be derived as following:

$$JI\% = \frac{|A_i \bigcap B_i|}{|A_i \bigcup B_i|} = \frac{|A_i \bigcap B_i|}{|A_i| + |B_i| - |A_i \bigcap B_i|} \tag{2}$$

where i, A and B have the same definition as in Dice index.

Hausdorff distance also can be used as validation methods which is sensitive to segmentation boundaries. Hausdorff distance measures the distance of two subsets of a metric space. Conventional Hausdorff distance is very sensitive to outliers so 95th-percentile of the Hausdorff distance could be used instead. It can be calculated as following:

$$H_{95}(A, G) = K^{th}_{a \in A} min||g - a|| \tag{3}$$

where $K^{th}_{a \in A}$ is the th ranked minimum Euclidean distance, A is set of boundaries points of segmentation result and G is set of boundaries points of ground truth.

A simpler validation method [3] is absolute volumetric differences measurement which is defined as:

$$AVD\% = \frac{|V_a - V_g|}{|V_g|} \times 100 \tag{4}$$

where V_a is volume of segmentation result and V_g is volume of manual segmentation.

All these measurement can be used for different brain structure including GM, WM, CSF, brain(GM+WM) and intracranial volume (GM+WM+CSF).

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