

Original Article**An Investigation into the Performance of Adaptive Neuro-Fuzzy Inference System for Brain Tumor Delineation Using Expectation-Maximization Cluster Method; a Feasibility Study**Leila Ghorbanzadeh^{1,*}; Ahmad Esmaili Torshabi¹

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A B S T R A C T

Purpose- In brain MRI analysis, image segmentation is commonly used for measuring and visualizing the brain's anatomical structures, for analyzing brain changes, delineating pathological regions, and image-guided interventions. Since manual segmentation is time-consuming and prone to variable errors, it makes automatic techniques more demanding.

Method- This paper describes a framework for automatic segmentation and tumor border estimation of both normal and abnormal anatomy from medical images based on Adaptive Neuro-Fuzzy Inference System (ANFIS) which is applicable to different types of tumors. The segmentation framework is comprised of five stages: first, median filter is applied to remove or reduce the noise of images; second, it is followed by EM clustering to segment it into different parts with various intensities which is used for feature extraction in the third step. At the fourth stage, extracted features besides ground truth are utilized as ANFIS training dataset. Lastly, the level set is adopted for a precise detection of abnormal tissues for detected abnormal sections either edema or tumor core.

Results- This method was applied for 15 High-Grade (HG) and 15 Low-Grade (LG) simulated brain tumor images. The proposed model provided satisfactory outcomes in which, for the segmentation of whole tumor including both edema and tumor core, the dice index was recorded 0.936 ± 0.04 and 0.921 ± 0.02 for HG and LG dataset respectively; however, the tumor core were recorded 0.899 ± 0.04 and 0.902 ± 0.05 in the mentioned groups.

Conclusion- The results of this study prove the robustness of fuzzy inference systems and neural networks in clinical image analysis and tumor evaluation for brain cancers.

1. Introduction

Generally, magnetic resonance images have been proven a valuable tool to detect brain tumors surrounded by normal tissues that is highly applicable in many diagnosis and treatment fields such as external beam radiotherapy. Manual tumor border delineation is

highly influenced by miscalculations due to inter-observer variability and human error in addition to being time-consuming. In the ideal form, an automatic or semi-automatic segmentation and border detection model would be highly welcome as it decreases the dependency on the human observation that may causes non-negligible errors.

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For medical images segmentation with different sort of tumors, there is not any ubiquitous algorithm. Since tumor and surrounding edema tissues have possible overlapping distributions with nearby normal tissues, various border delineation strategies were proposed at different literatures using two region-based and contour-based techniques [1, 2]. Mostly, they are devoted to full-enhanced tumors or specific types of tumors, and cannot apply to more general types. Furthermore, experiments based on fuzzy clustering algorithms are also proposed in the literature [3-5]. Prastawa *et al.* [6] proposed a method based on learning process using the atlas which considered the tumor as outliers of the normal voxels distribution. The limitation of this method is for large deformations of brain structures, and when such deformations occur, the use of the brain atlas may result in incorrect learning. As an alternative, another method [7] based on the combination of model-based techniques and graph-based affinity, is proposed which uses multi-channel MR images and needs a learning procedure for parameters estimation. In Capelle *et al.* [8], the proposed method works by an evidential segmentation scheme of multi-echo MR images for brain tumors detection. They showed that for the processing of redundant and complementary data of MR images, a modeling by the use of evidence theory is appropriate.

Moreover, automated segmentation methods, based on artificial intelligence techniques, were also proposed in the literature [9, 10], in which none of them used intensity enhancements, provided by the means of contrast agents. However, its application is limited since the input images are restricted to T1, T2, and PD MR Image channels.

Generally, apart from the already mentioned limitations of each method, region-based methods only depend on local information for each voxel rather than the combination of global shape and boundary restraints. Considering contour-based methods, Lefohn *et al.* [11] have introduced a semi-automatic method for tumor segmentation by an application of level sets. For segmentation initialization, the user must first select the tumor region and then according to a visual examination of the results, the level set parameters are set by a

repetitive process. The major handicaps of contour-based deformable models are the difficulties in the definition of the initial contours, the tuning parameters and leakage in ill-defined edges.

Our method presented in this study combines EM clustering strategy with the robustness of fuzzy inference system and neural networks for the definition of tumor and edema simultaneously, relying on the information provided in the T2 image channel. However, other image channels are also implementable in our strategy. Among our dataset that includes 15 High-Grade (HG) and 15 Low-Grade (LG) simulated brain tumor images, only T2 image channels are utilized. High-grade gliomas are attributed to those with the more aggressive form of the disease that have a life expectancy of two years or less and demand immediate treatment [12, 13]. In contrast, low-grade variants, such as low-grade astrocytomas or oligodendrogliomas, come with an average survival rate of several years, so an aggressive treatment is often postponed as long as possible. For both groups, intensive neuro-imaging protocols are used before and after treatment to evaluate the progression of the disease and the success of a chosen treatment strategy [14]. At a glance, the proposed strategy is the investigation the performance of ANFIS for tumor border detection by using EM data cluster algorithm and a level-set deformable model.

The ultimate goal of applying such a system is to reach a precise insight into an image such as pixel greyness ambiguity, geometrical segmentation of the image and the uncertain interpretation of a scene [15].

The final analyzed results of this study demonstrate that the proposed technique can detect edema and tumor core with high accuracy for both high-grade and low-grade dataset.

2. Materials and Methods

The automated segmentation method that we have developed is composed of five major stages, as shown in Figure 1. First, a median filter is applied to the image for noise reduction and making it smoother; after the pre-processing stage, the intensity values are divided into five clusters with varied intensity characteristics using EM data clustering algorithm. EM has a strong statistical

basis besides being robust to outliers and a fast performance. The function of EM is separating different areas with variable densities for feature extracting of labeled tissues. In addition to initial segmentation of image, by means of EM clustering, the complexity of the process that can be reduced as abnormal tissues are in high densities fashion. To be more precise, all clusters are not essentially necessitated to be considered for abnormality detection. In this work, three clusters that are susceptible to contain lesion regions were analyzed. Then, the extracted features with ground truth are used for ANFIS training. Fuzzy logic represents an applicable approach to comprehend and manually influence the mapping behavior. Fuzzy inference (reasoning) is the actual process of mapping from a given input to an output using fuzzy logic [16, 17]. Since there are some small areas with similar intensity to tumor core or edema and a size fewer than 35 pixels, an image erosion as well as

small objects removal were utilized to remove these sections, which also reduced processing complexity. This was followed by applying Gray Level Co-occurrence Matrix (GLCM) method for the labeled image in order to extract features such as entropy, contrast, maximum intensity, minimum intensity, etc. In the fourth step, the extracted features with the real state of each segment according to the ground truth are adopted to ANFIS as input and output dataset, taken into account that k-fold cross validation is selected for validation of the proposed method. However HG and LG images are trained and assessed separately since the intensity was different for each group. In the last stage, having the estimates for tumor and edema intensity parameters obtained, the level set technique is applied to the extracted abnormal parts in order to approach an accurate definition of the tumor tissues. The details of each stage are discussed in the following subsections.

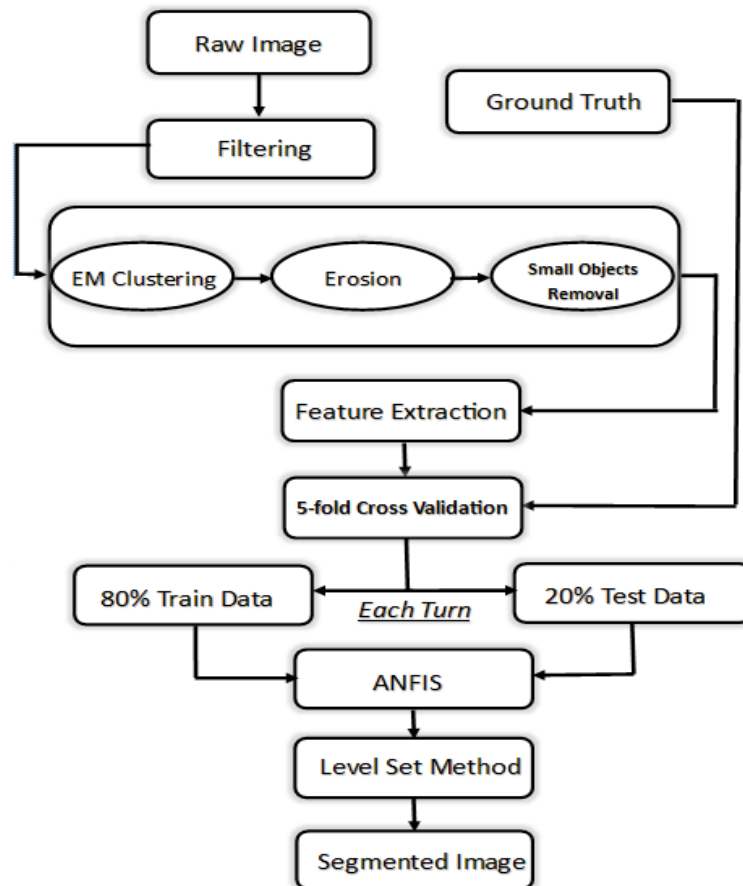


Figure 1. Proposed segmentation model flowchart.

2.1. Image Filtering

Noise removal is the first step of image analysis and is necessary to apply an efficient to redress for such data corruption. In this work, a non-linear common filter namely median filter with a 3x3 square window was adapted to the images as it preserves edges and useful details under certain conditions while removing the noise. It replaces the pixel value with the median of neighboring pixel values.

2.2. Initial Segmentation

2.2.1. Segmentation Using EM Clustering

The Expectation Maximization (EM) algorithm is the most applicable and efficient technique for estimating the mixture model parameters, where the data are supposed to exist as a mixture of densities [18]. The algorithm relies on the maximum likelihood estimations of parameters when the data model depends on certain latent variables [19, 20].

It should be noted that the clustering methods can also be implemented to partially labeled data or data with other types of algorithms known as semi-supervised clustering methods that use both labeled and unlabeled data, accordingly. Among different data clustering algorithm for tumor border detection, K-means cluster method can be taken into account to be modified and the semi-supervised clustering is then emerged. K-means clustering is one of the most common available methods that are implemented to database while all the variables are quantitative and the distance

between observations is calculated by means of a squared euclidean distance. Apart from the K-means algorithm, a few semi-supervised hierarchical clustering methods have also been introduced. This is partly due to the fact that the problem must be formulated differently for hierarchical clustering. In some conditions, the cluster assignments emerged from medical images dataset may be known for some subset of the data. The objective is to classify the unlabeled observations in the data to the appropriate clusters using that cluster assignments determined for this subset of the data. In a certain sense, this problem is equivalent to a supervised classification problem, while the objective is to develop a model to assign observations in a data set to one of a finite set of classes based on a training set where the true class labels are known. However, traditional supervised classification methods may be inefficient when only a small subset of the data is labeled. For these types of problems, conventional supervised classification methods may be inefficient and typically do not use unlabeled data to build the classification algorithm. In these situations, one can often build more accurate classification rules by combining both labeled and unlabeled data that is known as semi-supervised approach [21-26].

Figure 2 demonstrates clustering results using EM algorithm with five clusters besides original image and ground truth. Only three clusters including abnormal regions have been represented in this figure.

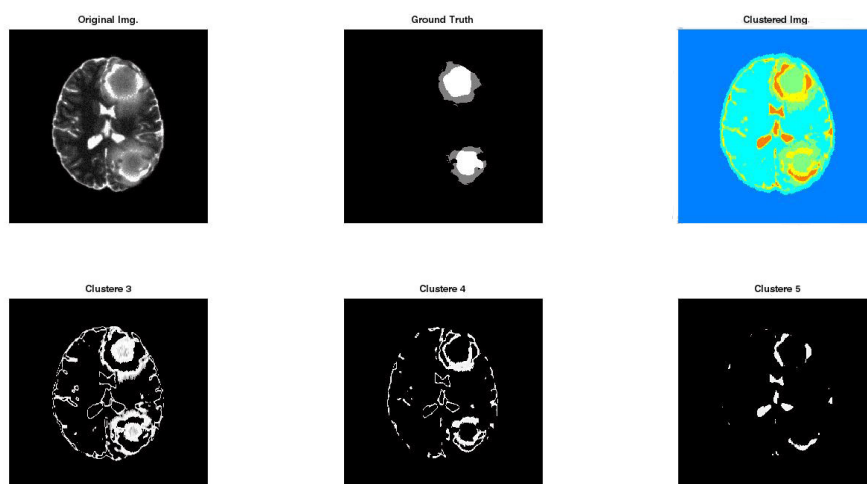


Figure 2. Top: Original image, ground truth and clustered image; Bottom: Three clusters of the image with abnormal regions

2.2.2. Image Erosion

Erosion is one of the basic operator in the area of mathematical morphology, which is used to erode away the boundaries of regions of foreground pixels (*i.e.* white pixels, typically) [27]. Thus, areas of foreground pixels shrink in size, and holes within those areas become larger. Figure 3 shows eroded version of our typical image from skull base section.

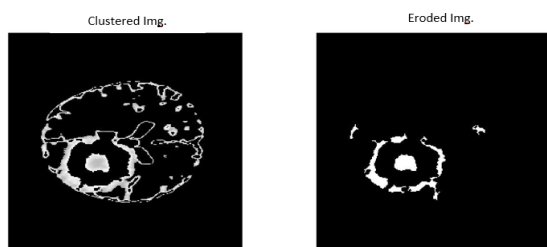


Figure 3. Third cluster of an image and corresponding eroded image.

2.2.3. Small Objects Removal

The intensity of skull section and also some parts of the brain are analogous to tumor areas intensity; to neglect these sections and increase the processing speed, after image erosion implementation, all connected components (objects) that have fewer pixels than the threshold value which is 35 in this work, were removed from a binary image (as displayed in Figure 3). This has increased the processing speed and avoided any potential misinterpretations in model training [28]. This operation is known as an area opening.

2.2.4. Image Labeling

After separating candidate areas, each connected pixels in the extracted candidate matrix is numbered so that each connected candidate pixels got the same label. Thereafter, the properties of each label will be detected and given to the classifier.

2.3. Feature Extraction

To feed the classifier for classification purposes, we need to extract mathematical measurements (features) from that object. Two categories of features were used in this work: 1) shape (features of the shape's geometry captured by both the boundary and the interior region) and 2) texture

(features of the grayscale values of the interior) [29]. The list of features used in this research and also what they measure are as follows:

2.3.1. Shape

Shape feature is an important property to describe an image. Firstly, the shape often links to the target, which has a certain semantic meaning. So shape feature can be a higher level feature than the color and texture feature. A few of the property options used in this study are Diameter, Perimeter and Euler Number [30].

2.3.2. Texture

Gray-Level Co-occurrence Matrix (GLCM) is the statistical method of examining the textures that considers the spatial relationship of the pixels. The GLCM functions characterize the texture of an image by calculating how often pairs of pixel with specific values and in a specified spatial relationship occur in an image, creating a GLCM, and then extracting statistical measures from this matrix. Textural features used as input for model training at this study consist of contrast, Entropy, Homogeneity, Autocorrelation, Variance and Cluster Prominence [31].

2.4. Neuro-fuzzy Based Classification

Neuro-fuzzy systems which use local learning techniques to learn fuzzy sets and fuzzy rules have been recently attracted in research and application. Conventional approaches of pattern classification, fuzzy classification assume that the boundary between two neighboring classes as a continuous and overlapping area within which an object is not allocated to one cluster exclusively and has limited membership in each class. The theory of fuzzy logic provides a mathematical strength to capture the non-statistical uncertainties associated with human cognitive processes, such as thinking and reasoning [32].

2.4.1. ANFIS Architecture

A neuro-fuzzy approach as a combination of neural networks and fuzzy logic has been introduced to overcome the individual weaknesses and to offer more appealing features. Neural networks can only

be taken into account if the problem is expressed by adequate amount of observed examples that are used to train the black box. On the contrary, a fuzzy system demands linguistic rules instead of learning examples as prior knowledge. In the case of incomplete, faulty or inconsistent attained knowledge, fuzzy system must be adjusted in a heuristic way. A suitable method for fuzzy system adaptation is an automatic adaptation procedure like neural networks.

In the present study, a class of adaptive networks that act as a fundamental framework for ANFIS is employed. The process of developing a fuzzy inference in combination with adaptive neural networks is called an ANFIS.

The structure of ANFIS developed in this study consists of 11 inputs indicating mentioned features of candidate regions and one output which means that we consider one neuron in outer layer and we learn the system so that the output of this neuron show the class of regions in classification procedure.

Our dataset consists of two categories: 15 HG and 15 LG brain tumor images. K-fold cross validation is employed for the definition of the model training and testing dataset. In k-fold cross-validation, the original sample is randomly partitioned into k equal size sub-samples. Of the k sub-samples, a single sub-sample is retained as the validation data for testing the model, and the remaining k - 1 sub-samples are used as training data. The cross-validation process is then repeated k times (the folds), with each of the k subsamples used exactly once as the validation data. The k results from the folds can then be averaged (or otherwise combined) to produce a single estimation. The advantage of this method over repeated random

sub-sampling is that all observations are used for both training and validation, and each observation is used for validation exactly once. In this study, k was equal to five. In addition, the training samples are clustered into three different regions namely normal and two abnormal groups including edema and tumor-core regions. Cluster center of the tumor region for all classes are observed and stored. In the testing process, features are extracted and matched with the best possible solution.

There are several training algorithms for feed forward networks of which we implemented hybrid learning algorithm. Hybrid learning algorithm proposed by Jang, Sun and Mizutani [33] uses a fusion of Steepest Descent and Least Squares Estimation (LSE) strategies.

2.5. Extraction of Whole Tumor Region Boundary

As described in section 2.3, for small objects removal, segmented parts of the image are eroded. Moreover, due to overlapping vicissitudes which happens among edema, tumor core and healthy tissues while image clustering, as a compensatory strategy, a level set deformable model [34] in the context of active contours is applied for a precise extraction of tumor region boundary.

Figure 4 shows the ground-truth image and result-tumor region boundary without and with various level set models with $\sigma = 1$, $\lambda = 6$, $\nu = 2$, $\mu = 0.1$ after approximately 250 iterations. It should be noted that the σ is smoothed Dirac approximation value, μ is the level set regularization value and λ and ν are constant values. As it is clear from the figure, results obtained by applying level set is more accurate and reliable.

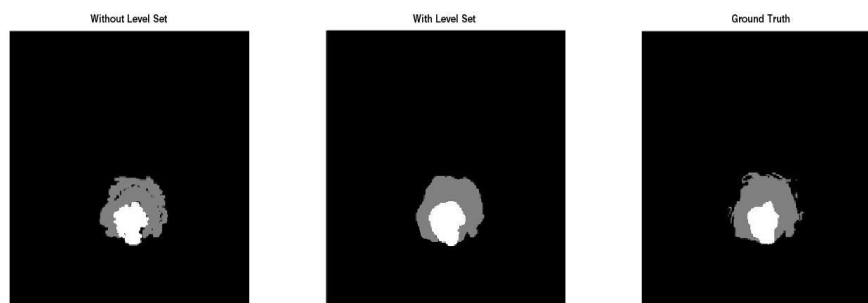


Figure 4. Segmentation results with and without level set and ground truth.

3. Results

The validation of the segmentation results is very important, especially for medical images as any significant disagreement between the detected results and the real targets might lead to severe damages in clinical activities.

Our segmentation procedure is evaluated on 30 simulated cases (15 HG gliomas, 15 LG gliomas) including manual expert annotations. We performed the labelling of each image of the training set, in a 5-fold cross validation framework. The dataset is publicly available through the MICCAI 2013 Brain Tumor Segmentation challenge [37].

We obtained 2D segmented tissues using EM algorithm and adaptive neuro-fuzzy inference systems. Overall, the results suggest comparatively higher score for complete tumors than tumor core. Two different categories namely tumor core and complete tumor, consisting of both edema and tumor core, were considered for the evaluation.

Several metrics were applied for results and model evaluation including Dice, Jaccard, Sensitivity and Specificity indexes.

The Jaccard index, also known as the Jaccard similarity coefficient was represented by Paul Jaccard, is a statistic used for measuring the similarity and diversity of an automatic binary segmentation by a specific method in comparison to its ground truth (where B is the ground truth of the tumor pixels, and A is the set pixels classified as tumor by the automatic method) (see Figure 5):

$$J(A, B) = \frac{A \cap B}{A \cup B} = \frac{t_p}{t_p + f_p + f_n} \quad (1)$$

The Jaccard score will be 1 if the segmentations are identical, while for completely dissimilar segmentations it will approach 0.

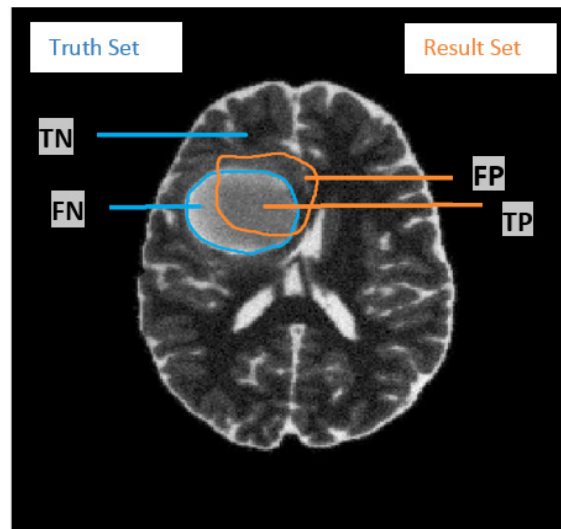


Figure 5. Regions used for calculating evaluation metrics. FN is the true lesion area (outline blue), TN is the remaining normal area, FP is the false predicted lesion area and TP is the true predicted lesion area.

FP and TP are the areas predicted to be lesion by an algorithm (outlined orange), of course unlike TP, FP is not lesion area in reality.

Like the Jaccard similarity index, the Dice coefficient also measures set agreement [35]. In this case, the measure is given by the formula:

$$D(A, B) = \frac{2(A \cap B)}{(|A| + |B|)} = \frac{2t_p}{(t_p + f_p) + (f_n + t_p)} \quad (2)$$

More simply, this formula represents the size of the union of 2 sets divided by the average size of the two sets.

A summary of quantitative overlap scores using Dice and Jaccard metrics for HG and LG dataset are presented in Table 1.

Table 1. Evaluation results of two regions for both HG and LG dataset.

Case No.		Dice		Jaccard	
		Whole Tumor	Tumor Core	Whole Tumor	Tumor Core
1	HG	0.949	0.938	0.902	0.883
	LG	0.918	0.946	0.848	0.897
2	HG	0.927	0.899	0.865	0.817
	LG	0.878	0.879	0.782	0.785
3	HG	0.936	0.829	0.879	0.708
	LG	0.864	0.864	0.761	0.761
4	HG	0.887	0.943	0.797	0.892
	LG	0.924	0.901	0.858	0.820
5	HG	0.968	0.937	0.939	0.882
	LG	0.921	0.936	0.854	0.879
6	HG	0.958	0.905	0.920	0.826
	LG	0.899	0.957	0.817	0.917
7	HG	0.946	0.899	0.897	0.816
	LG	0.937	0.927	0.881	0.863
8	HG	0.970	0.938	0.942	0.883
	LG	0.931	0.807	0.871	0.676
9	HG	0.956	0.935	0.916	0.878
	LG	0.958	0.918	0.920	0.848
10	HG	0.835	0.837	0.717	0.720
	LG	0.913	0.913	0.839	0.839
11	HG	0.928	0.913	0.865	0.840
	LG	0.935	0.795	0.877	0.660
12	HG	0.910	0.877	0.834	0.781
	LG	0.932	0.853	0.872	0.743
13	HG	0.921	0.841	0.854	0.725
	LG	0.924	0.908	0.859	0.831
14	HG	0.940	0.889	0.888	0.800
	LG	0.921	0.817	0.854	0.690
15	HG	0.878	0.87	0.783	0.769
	LG	0.921	0.902	0.854	0.822

Table 2. Median and standard deviation of evaluation indexes for two regarded groups.

		Dice		Jaccard		Sensitivity		Specificity	
		Whole Tumor	Tumor Core	Whole Tumor	Whole Tumor	Whole Tumor	Tumor Core	Whole Tumor	Tumor Core
Median	HG	0.936	0.899	0.879	0.817	0.962	0.983	0.997	0.997
	LG	0.921	0.902	0.854	0.822	0.896	0.891	0.998	0.999
STD	HG	0.037	0.039	0.062	0.064	0.044	0.071	0.003	0.003
	LG	0.023	0.051	0.039	0.081	0.056	0.012	0.002	0.003

According to Table 2 and considering the Dice index the median is 0.936 ± 0.0 and 0.921 ± 0.02 for HG and LG dataset, respectively. Hence, the model has represented an accurate execution for both groups in detection of abnormality; however, the level of preciseness in the former group was slightly higher than the latter. On the one hand, the results reveal that the proposed method performed more accurate in detection of tumor core for LG than HG, on the other hand it was reverse in the detection of edema.

In medical image processing, other common criteria such as sensitivity and specificity were also taken into account for gauging and evaluation of models performances [36]. Sensitivity or true positive rate evaluates the ability of the model to identify abnormal tissues correctly.

$$\text{Sens} = \frac{\text{Number of true positive Marks}}{\text{Number of Lesions}} = \frac{t_p}{(t_p + f_n)} \quad (3)$$

Specificity or true negative rate examines model execution in identification of healthy areas accurately.

$$\text{Spec} = \frac{\text{Number of true Negative Marks}}{\text{Number of Normal tissues}} = \frac{t_n}{(f_p + t_n)} \quad (4)$$

Table 3 represents the overall quantitative of the mentioned assessment tools for two HG and LG dataset. From the results of the Table 3, it can be seen that the proposed model performance for abnormality detection in the former group with 0.962 ± 0.04 was superior to the latter with 0.896 ± 0.06 in sensitivity; even though the noticeable disparity relates to the identification of tumor core with sensitivities at the points of 0.983 ± 0.07 and 0.891 ± 0.01 respectively; which presents the higher success of the method in HG than LG group. Both dataset had high and close outcomes of specificity, the accuracy of normal tissues detection, in two regarded regions.

Table 3. Average results of sensitivity and specificity criteria for all cases.

		Sensitivity		Specificity	
		Whole Tumor	Tumor Core	Whole Tumor	Tumor Core
Median	HG	0.962	0.983	0.997	0.997
	LG	0.896	0.891	0.998	0.999
STD	HG	0.044	0.071	0.003	0.003
	LG	0.056	0.012	0.002	0.003

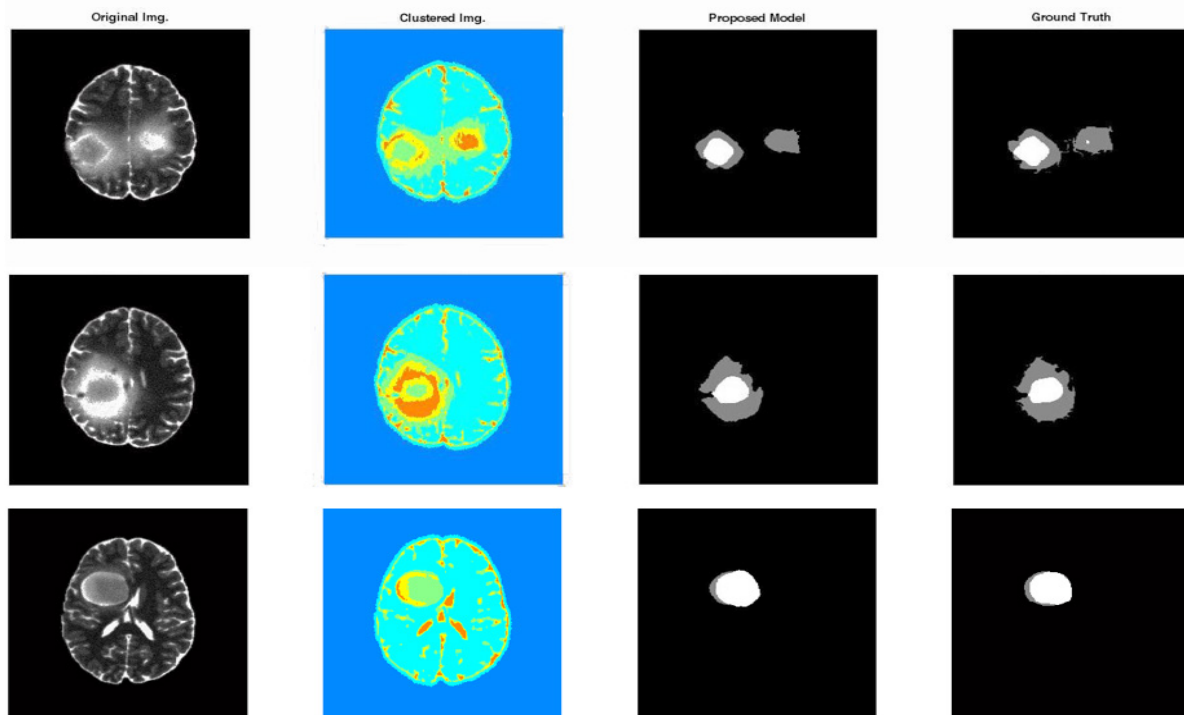


Figure 6. Visual result of image segmentation a) Original image; b) Clustered image; c) Segmentation by proposed model; d) Ground truth.

In Figure 6, as a visual assessment of the model performance, segmentation results of three dataset have been represented in addition to their ground truths and corresponding clustered images.

4. Discussion

An automatic segmentation method based on ANFIS in combination with EM algorithm may process a wide variety of tumors located at different sites of patient body. Number of clusters are very crucial for model performance. In this specific study, the operation of segmentation algorithm with less than four or more than five cluster numbers becomes unsatisfactory especially in the definition of edema due to the similarity between brain structure and this area.

The proposed method segments the whole brain including healthy tissues, and then identifies edema as a target for surgical planning and also a definition proper treatment planning system as the main component at radiotherapy. Moreover, the proposed process works automatically with less computational complexity due to the intrinsic robustness of EM clustering and ANIFS model.

Testing the proposed method on 15 HG and 15 LG dataset showed that the segmentation process is satisfactory and reliable according to the ground truth dataset. In addition to the visual validation, several quantitative measures such as Jaccard and Dice were performed for tumor segmentation quality estimation. At HG dataset, the median of Jaccard factor for whole tumor was 0.879 ± 0.06 while this value was 0.854 ± 0.04 for LG dataset.

5. Conclusion

In this paper we proposed an automatic tumor segmentation method which integrates EM clustering method, adaptive neuro-fuzzy inference system, and boundary extraction based on a level set deformable model. The proposed method was quantitatively assessed with two-labeled (edema and tumor core) brain tumor taken with an MR imaging system. Future studies aim at tumor segmentation of real database in three dimensions and dividing tumor core into three categories namely non-enhancing solid core, active core and non-solid core.

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