



# **Deep-Quantitative Medical Image Analysis Methods Applied on Brain Tumor Diagnosis**

**Aref Safari** <sup>1\*</sup>

<sup>1</sup>Department of Computer Engineering, Rasht Branch, Islamic Azad University, Rasht, Iran.

Received: 25-Oct-2020, Revised: 23-Dec-2020, Accepted: 23-Dec-2020.

## **Abstract**

Solving medical image diagnosis and image analysis problems has long been thought of in many research types in the last decades. Mostly the interpretations of medical data are being made by a medical expert. In terms of image interpretation by a human expert, it is entirely limited due to its subjectivity, complexity, extensive variations across different interpreters, and fatigue. After the success of deep learning in other real-world applications, it provides exciting solutions with reasonable accuracy for medical imaging and is seen as a critical method for future applications in the health sector. This study proposed the deep learning approach based on soft-max activation function to obtain more reliable medical image diagnosis results properly. The proposed model evaluated a brain tumor (MRI) medical dataset, alongside an assessment in terms of accuracy, MSE, and RMSE, as a qualitative analysis of the learned features and practical commendations. This research should help improve the application and refinement of the evaluated approaches in the future.

**Keywords:** Deep Learning, Medical Image Analysis, Machine Intelligence.

---

## **1. INTRODUCTION**

Machine Learning (ML) and Artificial Intelligence (AI) have progressed rapidly in recent years. ML and AI techniques have played an important role in the medical field like medical image processing, computer-aided diagnosis, image interpretation, image fusion, image registration, image

segmentation, image-guided therapy, image retrieval, and analysis. Techniques of ML extract information from the images and represent information effectively and efficiently. The ML and AI facilitate and assist doctors in diagnosing and predicting accurately and faster the risk of diseases and preventing them in time. These techniques enhance researchers' abilities to understand how to analyze the generic variations that

---

\*Corresponding Authors Email:  
safari.aref@gmail.com

will lead to disease. These techniques are composed of conventional algorithms without learning like Support Vector Machine (SVM), Neural Network (NN), Fuzzy Clustering Means (FCM) and, K-Means. and deep learning algorithms such as Convolutional Neural Network (CNN), Recurrent Neural Network (RNN), Long Short-term Memory (LSTM), and Generative Adversarial Networks (GANs). Former algorithms are limited in processing the natural images in their raw form, time-consuming, expert knowledge, and requiring much time for tuning the features. The later algorithms are fed with raw data, automatic features, learner, and fast. These algorithms learn multiple levels of abstraction, representation, and information automatically from a large set of images that exhibit the desired behavior. Although automated detection of diseases based on conventional medical imaging methods has been shown significant accuracy for decades, new advances in machine learning techniques have ignited a boom in deep learning. Deep learning-based algorithms showed promising performance and speed in different domains like speech recognition, text recognition, lips reading, computer-aided diagnosis, face recognition, and drug discovery. In machine learning, the typical goal is to map input patterns to an output value. For instance, we have images of objects as input data (represented by pixel intensity values) and correct labels (one for every type of object) as corresponding output values. the algorithm aims to learn this mapping (from the samples to the output value) to predict the correct output of a new input sample. Machine learning is used in the medical imaging field,

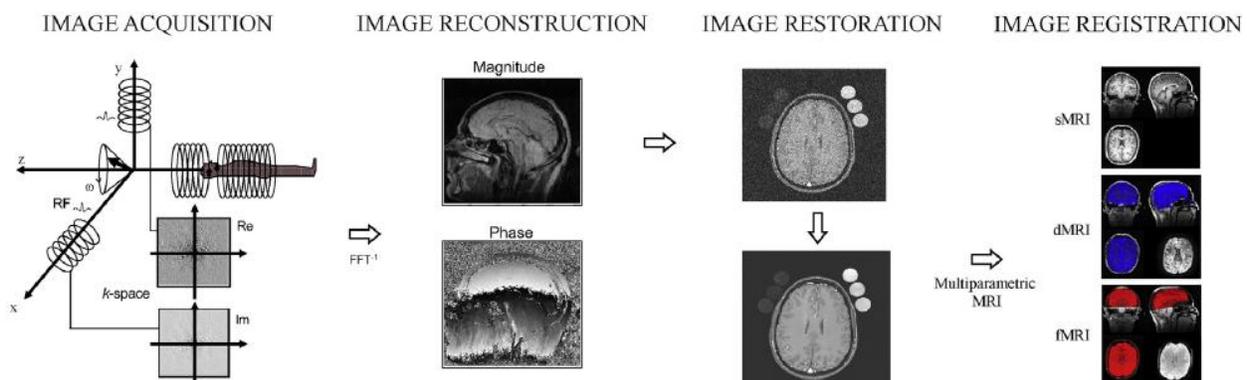
including computer-aided diagnosis, image segmentation, image registration, image fusion, image-guided therapy, image annotation, and image database retrieval. This means that there are multiple medicine areas where machine learning methods can be applied and can help improve patients' health care Computer-aided diagnosis (CAD) has become one of the major research subjects in medical imaging and diagnostic radiology [1]. For instance, machine learning methods can be used to detect breast cancer [2]. One particular task that can be addressed with machine learning approaches is classification, where objects are classified (e.g., abnormal or normal, benign or malign) based upon input features [3,4]. The classification of lung diseases in computed tomography scans is one example of applying machine learning methods to this task [5]. Deep learning methods are algorithms in machine learning, which learn multiple representations and abstraction levels that help make sense of data [6]. Higher-level abstractions are defined from lower-level ones, so more complex functions can be learned. In particular, if a deep architecture can compactly represent a function, the same function could require an extensive architecture if the depth of this architecture is made shallower [7]. Furthermore, this brief overview validates that algorithmic literature offers a great variety of deep learning methods. In [8], knowledge mining in medical systems is based on Differential Evolutionary (DE) Analysis and k-NN. They proposed an enormous repository of data so that analysis based on this historical information can be made. They focused on computing the probability of occurrence of a

particular disease from the medical data by mining it using a unique algorithm that increases the accuracy of such diagnosis by linking the key points of neural networks, large memory storage and retrieval, k-NN, and differential diagnosis all integrated into one single algorithm. In [9] deliberated disputes in medical diagnosis based on computational techniques. They emphasize several methods offered by researchers for medical diagnosis, and their performance issues are discussed. Research has been carried out to diagnose medical images using Classification, Association Rule Mining, Clustering, or algorithms. In [10] studied Super Vector Machines (SVM) based classification of Soft tissues in brain CT images based on wavelet-based dominant gray level run length texture features. They focused on medical CT imaging procedures as one of the widely applied and reliable techniques used to recognize and position pathological changes efficiently. Their study aimed at the methods of classifying and segmenting soft tissues in brain CT images. In [11], the authors introduced an improved

pre-processing system with an image mining methodology for medical image classification. In their proposed method, they isolate the looked-for object from the image. On the other hand, they try to apply association rule mining techniques to solve feature selection problems and try to extract a small-size feature subtype acceptable for classification tasks. They applied the decision tree as the main classification technique for their learning classifiers.

## 2. METHODS AND MATERIALS

There are different machine learning settings and disciplines illustrated in Figure 1 and explained below. The characteristics of the data set and the specific task determine the algorithm type, as described in the following. Accurate diagnoses of the disease depend upon image acquisition and image interpretation. Image acquisition devices have improved substantially over the recent few years, i.e., currently, we are getting radiological images (X-Ray, CT, and MRI scans) with much higher resolution.



*Fig.1. Steps of medical image analysis [16].*

However, we just started to get benefits for automated image interpretation. One of the best machine learning applications in computer vision, though traditional machine learning algorithms for image interpretation rely heavily on expertly crafted features, i.e., lung tumor detection requires structure features to be extracted. Due to the extensive variation from patient-to-patient data, traditional learning methods are not reliable. Machine learning has evolved over the last few years by shifting through complex and big data.

### ***Supervised Learning***

The supervised learning problem is a classic machine learning setting. The training data is made up of tuples  $(x_i, y_i)$ , where  $x_i$  is the input and  $y_i$  the corresponding target vector [8]. The case in which the target value is discrete, such as the digit recognition problem, where the images are mapped to a finite number of discrete categories, is called a classification problem. If the target value is continuous, the task is called the regression problem. An example of a regression problem would be predicting the price of a house (continuous output value), where the input variables are the number of rooms and the living area.

### ***Unsupervised Learning***

The training data comprises examples of the input vectors without any corresponding target values in unsupervised learning problems. There are different objectives in unsupervised learning problems, such as clustering, density estimation, and

visualization. The goal of clustering is to discover groups of similar examples based on measured or perceived similarities between the examples. To determine the distribution of the data within the input space is the purpose of density estimation. The data is projected down for visualization, from a high-dimensional space to two or three dimensions [8].

### ***Semi-Supervised and Self-Taught Learning***

There are two approaches: using unlabeled data in supervised learning tasks and, therefore, halfway between supervised and unsupervised learning. The possibility of having algorithms learn from unlabeled data and the challenge to get (enough) labeled data for supervised learning tasks motivate these approaches [9]. The main idea is to give the algorithm large amounts of unlabeled data to learn a good feature representation of the input and then feed the labeled data to the algorithm to solve the supervised task based on the learned feature representation.

### ***Reinforcement Learning***

Reinforcement learning (RL) is concerned with the problem of how to interact with the environment. It is choosing suitable actions in a given situation in order to maximize the reward. In contrast to supervised learning, there are no examples with an optimal output given, but instead, the algorithm should learn which actions to execute in a specific situation by interacting with the environment [9].

### ***K-Nearest Neighbors***

The K-nearest neighbor approach is one of the approaches for classification, which is intuitive and straightforward to understand but works very well in practice. In the classification problem, as shown in Figure 2.4, a new (unlabeled) data point is classified according to the k nearest neighbors [11]. The classification of a new point can now be divided into two steps: First, the k nearest neighbors have to be determined. There are different techniques to compute the distance between two examples (e.g., Euclidean distance, Manhattan distance), and the performance of this algorithm depends on the used distance metric to identify the nearest neighbors. Secondly, the new data point class has to be determined, corresponding to the labels of the k nearest neighbors, which have been identified in the previous step. There are various ways to calculate the final class from the k nearest neighbors, besides the simple majority vote. In contrast to SVMs or Random Forests, the K-nearest neighbor algorithm has no, or only a minimal, explicit training phase. Instead, the whole training set is used to predict a new data sample (in contrast to the sparse representation' in SVM, where only the support vectors are used for prediction). Though the K-nearest neighbor algorithm's primary focus is on classification, the regression problem can be solved with this approach. The target value is then computed of the values of the k nearest neighbors. Further, this method can be used for density estimation too. For a given position  $x$ , the density  $p(x)$  can be calculated in Equation (1):

$$P_{(x)} = \frac{K}{VN} \quad (1)$$

where  $V$  is the volume of the sphere (centered at  $x$ , and the radius of the sphere is allowed to grow until it contains precisely  $K$  data points), and  $N$  is the number of observations in the training set.

### ***Deep Artificial Neural Networks***

The main focus of deep learning is to discover abstractions from low-level features to high-level representations automatically. Ideally, this learning procedure is done with as little human effort as possible without hand-engineering features. There are several motivations and advantages of deep architectures. There are abstraction and representation levels in deep architectures, which allow modeling high-dimensional, non-linear data such as images, audio, and text. Here, abstractions can be understood as categories or as features (a mapping of input data), where features can be discrete (e.g., input pixel is 'bright' or 'dark', depending on the intensity value) or continuous (e.g., the size of an object in the input image). The backpropagation algorithm allows to compute the gradient of various error functions, and the gradient descent method uses these gradients to perform parameter updates. The objective of this training procedure is to find a parameter configuration that minimizes the given error function. Neural networks are made up of single neurons connected and therefore form the neural network. A neuron is the basic building block of a neural network and can be seen as a simple model. A neural network model consists of neurons, which are connected. The output of one neuron can be the input of another neuron, as shown in the simple example for a neural network model

shown in Figure 4. This model is an example for a small neural network also known as a perceptron, in which the neurons are grouped into layers, each layer is fully connected to the next one (each neuron of a layer is connected with each neuron of the subsequent layer), and the connections do not form any closed directed cycles. ANN and deep learning methods are increasingly used to improve clinical practice, and the list of examples is long, growing daily

### 3. RESEARCH METHODOLOGY

Poisson image editing is a popular gradient-domain compositing technique for seamless image composition. The underlying principle of this method is that, given the boundary values and the Laplacian of a scalar function's interior values, it is possible to find a unique solution to the values of the function across the entirety of its domain using the Poisson equation. Similarly, the boundary values along the insertion area of a target image can

be interpolated inwards under the guidance of the source image's gradient field to obtain a seamless blending of a source object within the domain of a target image. More formally, let  $\Omega$  be a region in the image with boundary  $\partial\Omega$ . Denoting the source and target images as  $f_s$  and  $f_t$ , respectively, the composite image over the interior of  $\Omega$  can be found by solving the following Equation as the gradient operator as follows:

$$\min_f \iint_{\Omega} |\nabla f - \nabla f_s|^2; \text{ with } f|_{\partial\Omega} = f_t|_{\partial\Omega} \quad (2)$$

Since the choice of the error function is interrelated with the selection of the output layer activation function and therefore the problem setting, the choice of the activation function  $\sigma_i$  is discussed too. Although the choice of the error function, concerning the particular activation function  $\sigma_i$ , can be problems, the output-layer activation function is the identity  $\sigma_x = x$ , which is also

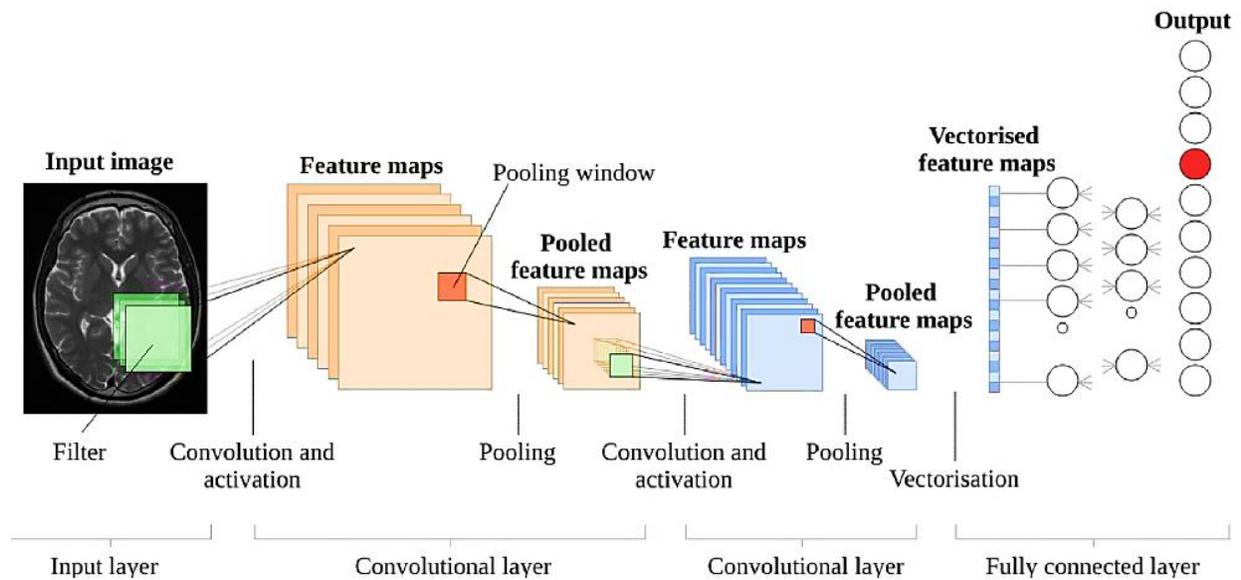
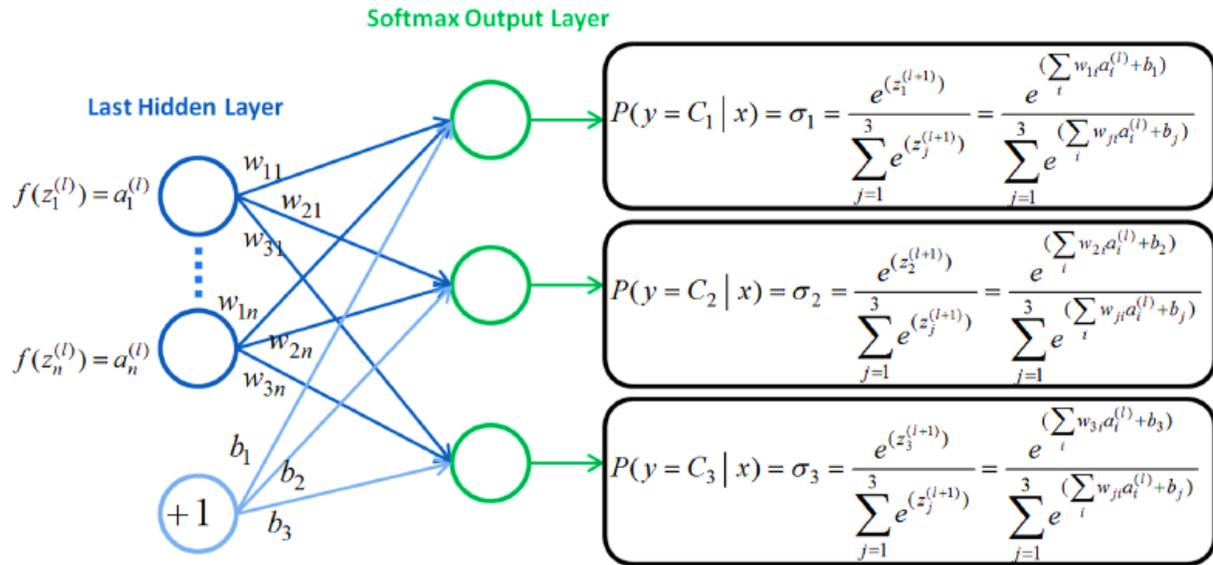


Fig. 2. Building blocks of a typical CNN [11].



**Fig. 3. Illustration of a network using the SoftMax activation function  $\sigma_i$  in the last layer.**

statistically motivated, a statistical discussion is omitted because this would go beyond the scope of this work. Statistical issues can be found in [13]. For standard regression called the linear activation function, because the output is then a simple linear combination of the inputs.

For two-fold classification problems, the activation function of the output unit is chosen to be the logistic sigmoid function in Equation (2):

$$\sigma_x = \frac{1}{1 + e^{-x}} \quad (3)$$

where the two classes are denoted as  $\{0,1\}$  If  $y = 1$  is defined as a label for the class  $C_1$  and  $y = 0$  denotes class  $C_2$ , then the output  $h_w, b(x)$  can be interpreted as the class membership probability for  $C_1$ . The class membership probability for  $C_2$  is then given as  $1-h_w, b(x)$ . Since a network can have more than one output-unit, this activation function

can be used for every output unit to deal with multiple binary classification problems. In this case, each output unit can be seen as a binary class label. In multiclass classification problems, each input example is assigned to precisely one of the  $k$  classes. Since every output unit is associated with one class, in a  $k$ -class classification problem, the network has  $k$  output units. Because each output unit is assigned to a specific class, and the network outputs are interpreted as the class membership probabilities.

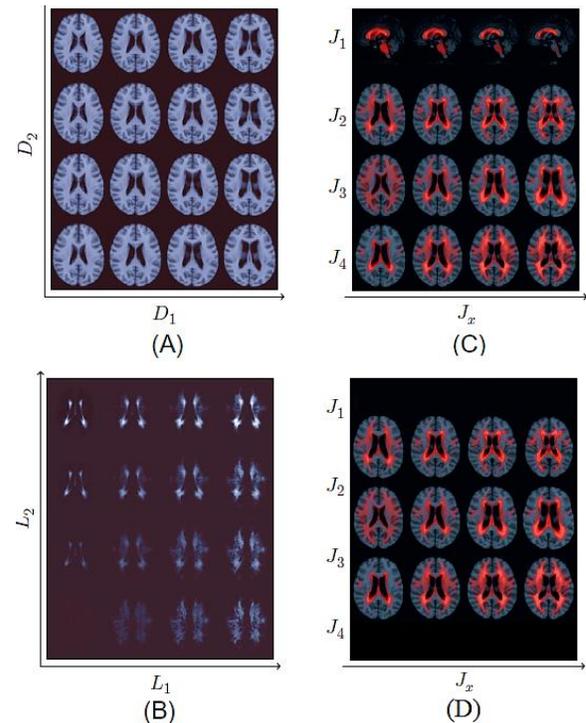
### 3.1. Datasets of This Study

In order to evaluate the reliability and accuracy of the proposed model, a well-known MRI brain tumor dataset has been applied. The extraction of a single or multiple anatomical meaningful regions of interest (ROI) from a subject's brain magnetic resonance (MR) image is essential for computer-aided diagnosis and therapy

planning, as well as for the extraction of clinically useful biomarkers (e.g., in clinical trials). The process of subdividing an image into distinct regions is referred to as segmentation. Once a brain MR image is segmented into its anatomical components, volumes or shape-related measures can be readily quantified. Also, anatomical regions' microstructure tissue properties can be accessed via multi-modal imaging, for example, diffusion-weighted MR imaging. The process of semantic segmentation refers to the labeling of pixels or voxels into anatomically meaningful regions. In the context of the segmentation of brain MR images, this often includes tissue segmentation and the parcellation of tissues into distinct regions. For example, gray matter (GM) may be subdivided into cortical GM and subcortical GM. The cortical GM may be further subdivided into the temporal lobe, occipital lobe, parietal lobe, and frontal lobe. Each lobe can be further subdivided in line with knowledge from anatomical or cytoarchitectonic brain atlases such as the Brodmann atlas [11].

Similarly, subcortical GM can be further differentiated into structures such as the thalamus, putamen, and basal ganglia. Semantic segmentation depends heavily on a priori knowledge about the location and relationship of different anatomical structures in the brain. In most cases, this knowledge is represented in the form of atlases of the human brain. It is comprised of 120000 28-by-28 patches in total, which have been sampled from 128 Computed tomography (CT) volumes of the thorax. An example for one slice of a volume and its corresponding annotation can be seen in

Figure 5. The slices have a size of 512-by-512, where one volume comprises about 500 slices (the number of slices varies). The pixel values lie in the range of [2000; 4095]. Since this work aims to compare machine learning methods in terms of classification, an appropriate dataset has to be defined [14,15]. Therefore 28-by-28 patches are cut out from the three-dimensional volumes, where the patches are lying in the axial plane. For each volume, 3000 patches are selected randomly per class, so 384000 patches are created for each class. The volumes are annotated by



**Fig. 4. Slices from generated volumes from the (A) morphology, (B) lesion, and (C) joint models. The morphology model captured ventricular enlargement (D1) and a decrease in brain size (D2) as the main modes of variation. For the lesion model, L1 captured an increase in lesion load throughout the WM, while L2 captured primarily periventricular lesion load variations.**

expert radiologists and contain six different classes, which are demonstrated in Table 1. Pulmonary arterial hypertension is a common and potentially fatal complication of scleroderma that may involve inflammatory and autoimmune mechanisms.

#### 4. PERFORMANCE ANALYSIS AND EXPERIMENTS

The confusion matrix can be used to determine the performance of the proposed method. Here, two classification algorithms, Naive Bayesian and Decision Tree for learning procedure and FCM for the handling uncertainty associated with MRI images, have been implemented. This matrix describes all possible outcomes of prediction results in a table structure. The possible outcomes of a two-class prediction, be represented as True Positive (TP), True negative (TN), False Positive (FP), and False Negative (FN). The normal and abnormal images are correctly classified as True Positive and True Negative, respectively. A False Positive is when the outcome is incorrectly classified as positive when it is negative. False Positive is the False alarm in the classification process. A false negative is when the outcome is incorrectly predicted as negative when it should have been positive. TP= Number of Abnormal images correctly classified, TN= Number of Normal images correctly classified, FP= Number of Normal images classified as Abnormal, FN= Number of Abnormal images classified as Normal.

$$\text{Precision} = \frac{TP}{(TP + FP)} \times 100\% \quad (4)$$

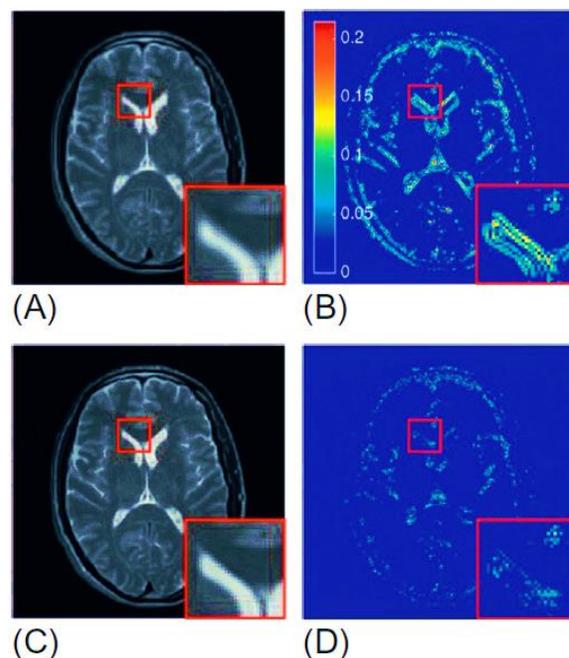
$$\text{Recall} = \frac{TP}{(TP + FN)} \times 100\% \quad (5)$$

$$\text{Accuracy} = \frac{(TP + TN)}{(TP + FP + FN + TN)} \quad (6)$$

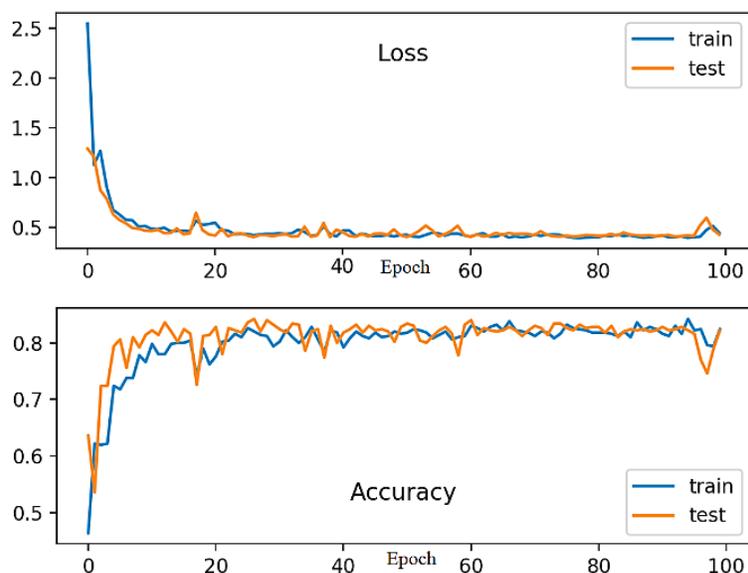
Concerning the general performance of the methods, it can be stated that the stacked sparse auto-encoder, the stacked denoising auto-encoder, and the Deep-FCM achieved the highest accuracy among all evaluated approaches on both datasets. Simultaneously, these three methods exhibit the highest training time among all evaluated approaches on both datasets. Therefore, these methods are preferable if the available computational resources allow them to use them. In contrast, the K-Means approach and the FCM exhibit the shortest training time on both datasets but achieve a more insufficient accuracy than the approaches mentioned above. Since the results suggest that the K-Means algorithm fails to solve more complicated classification tasks, the Deep-FCM is preferable in addressing medical classification tasks if the computational cost is essential. Although the K-means deep learning algorithm helps to improve the performance of the extremely randomized trees on the PULMO dataset, it is not clear if this is also true for other medical datasets, in particular, because the K-means deep learning algorithm worsens the generalization performance of the extremely randomized trees on both datasets. Besides these findings concerning accuracy and runtime, the results suggest that the K-means deep learning algorithm, the stacked sparse auto-encoder, and the stacked denoising auto-encoder are all successful in learning problem-specific features. The perfusion studies, both with CT and or MRI, considered by recent studies, can be used for preoperative grading of the gliomas, in

particular for the differential diagnosis of low and high-grade astrocytoma's because these technologies can provide complementary information about tumor hemodynamics, not available with conventional CT or MR. Elastography is a non-invasive method in which stiffness or strain images of soft tissue are used to detect or classify tumors. A tumor or a suspicious cancerous growth usually is 5 to 28 times stiffer than typical soft tissue background. When a mechanical compression or vibration is applied, the tumor deforms less than the surrounding tissue. i.e., the strain in the tumor is less than the surrounding tissue.

Table 1 shows the Training results for Deep and Counterpart methods, where Table 2 reveals the Test results for Deep and Counterpart methods in terms of following metrics: The Mean Absolute Error (MAE) and Root Mean Square Error (RMSE) metrics have been applied in the proposed model as follows:



**Fig. 5. Sparse-coded approximations of a brain MR image using a DCT dictionary: (A, B) and a trained dictionary (C, D) with a sparsity index  $S = 3$ . Error maps show absolute value differences for the original image. The region of interest (ROI) in the red rectangle (dark gray in print versions) is enlarged for better visualization.**



**Fig. 6. the average training and testing accuracy and error rate (loss) for the proposed model.**

**Table 1. Training results for Deep and Counterpart methods.**

Method	Accuracy	inputs	Layers	RMSE	MAE
K-Means	84%	5	Fixed	0.199	0.191
Deep K-Means*	<b>91%</b>	6	Fixed	<b>0.059</b>	<b>0.029</b>
FCM	79%	2	Adaptive	0.145	0.172
Deep-FCM*	<b>97%</b>	2	Adaptive	<b>0.056</b>	<b>0.096</b>

**Table 2. Test results for Deep and Counterpart methods.**

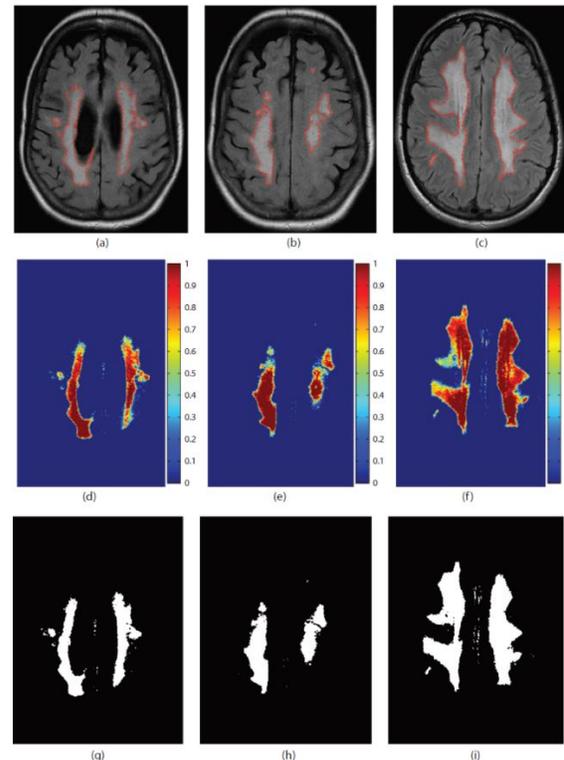
Method	Accuracy	Inputs	Layers	RMSE	MAE
K-Means	89%	5	Fixed	0.324	0.198
Deep K-Means*	<b>93%</b>	6	Fixed	<b>0.041</b>	<b>0.132</b>
FCM	81%	2	Adaptive	0.201	0.167
Deep-FCM*	<b>95%</b>	2	Adaptive	<b>0.038</b>	<b>0.171</b>

$$RMSE = \sqrt{\frac{\sum_1^n d_i^2}{n}} \quad (7)$$

$$MAE = \frac{1}{n} \sum_1^n |y_i - y'_i| \quad (8)$$

## 5. CONCLUSION

Besides a general introduction to machine learning and deep learning, four different methods have been described, implemented, and evaluated on two different medical datasets. Two of these methods (K-Means and FCM) can be categorized as conventional approaches, whereas the other four approaches (Deep K-Means and Deep-FCM) can be characterized as deep learning methods. The significant findings of this work are summarized, and areas of further investigation are indicated. The results of the



**Fig. 7. Segmentation and Diagnosis on the Brain MRI input images.**

applied dataset indicate that the hyperparameters for the first layer are the most important parameter of this method since Soft-Max of the first layer exhibits the most substantial influence on the accuracy, the runtime, the number of group members in the first layer, and the number of group members in the second layer. Experiments are conducted on brain MR images to investigate the proposed method's effectiveness in segmenting brain tumors. The Deep K-Means and Deep-FCM are compared to explore the efficiency and accuracy of the proposed method.

## REFERENCES

- [1] Hervé Abdi and Lynne J Williams. Principal component analysis. *Wiley Interdisciplinary Reviews: Computational Statistics*, 2(4):433–459, 2010.
- [2] Erin L Allwein, Robert E Schapire, and Yoram Singer. Reducing multiclass to binary: A unifying approach for margin classifiers. *The Journal of Machine Learning Research*, 1:113–141, 2001.
- [3] Telmo Amaral, Luís M Silva, Luís A Alexandre, Chetak Kandaswamy, Jorge M Santos, and Joaquim Marques de Sá. Using different cost functions to train stacked auto-encoders. In *12th Mexican International Conference on Artificial Intelligence (MICAI)*, pages 114–120. IEEE, 2013.
- [4] Safari, A. (2019). MCSM-DEEP: A Multiclass Soft-Max Deep Learning Classifier for Image Recognition. *Journal of Advances in Computer Research*, 10(4), 1-10.
- [5] Graham Bath and Judy McKay. *Praxiswissen Softwaretest: Test-Analyst und technical Test-Analyst*. dpunkt-Verlag, 2010.
- [6] Arivazhagan S, Ganesan L. Texture classification using wavelet transform. *Pattern Recognit Lett* 2003; 24: 1513-1521.
- [7] Yoshua Bengio. Learning deep architectures for ai. *Foundations and trends in Machine Learning*, 2(1):1–127, 2009.
- [8] A Rezaeian, S Homayouni, A Safari, Segmentation of Polarimetric SAR Images Using Wavelet Transformation and Texture Features, *The International Archives of Photogrammetry, Remote Sensing and Spatial Information Sciences*, vol 4, issue 1, page 613.
- [9] Yoshua Bengio. Practical recommendations for gradient-based training of deep architectures. In *Neural Networks: Tricks of the Trade*, pages 437–478. Springer, 2012.
- [10] Yoshua Bengio, Pascal Lamblin, Dan Popovici, Hugo Larochelle, et al. Greedy layer-wise training of deep networks. *Advances in neural information processing systems*, 19:153, 2007.
- [11] Safari, A. (2020). A Novel Transformation Watershed Image Segmentation Model in Digital Elevation Maps Processing. *Journal of Modern Processes in Manufacturing and Production*, 9(3), 13-22.
- [12] Fathizad H., Safari A., Bazgir M., Khosravi Gh, Evaluation of SVM with Kernel method (linear, polynomial, and radial basis) and neural network for

- 
- land use classification, Iranian Journal of Range and Desert Research 2017, Volume 23, Number 4; Page(s) 729 To 743.
- [13] Klemens Burg, Herbert Haf, Friedrich Wille, and Andreas Meister. Vektoranalysis, volume 2. Springer, 2012.
- [14] Aref Safari, Danial Barazandeh, Seyed Ali Khalegh Pour. A Novel Fuzzy-C Means Image Segmentation Model for MRI Brain Tumor Diagnosis. J. ADV COMP ENG TECHNOL, 6(1) Winter 2020: 19-2
- [15] Tae-Yun Kim, Jaebum Son, Kwang-Gi Kim, Recent Progress in Quantitative Medical Image Analysis for Computer Aided Diagnosis Systems, Healthc Inform Res. 2011 September;17(3):143-149.
- [16] Nie K, Chen JH, Yu HJ, Chu Y, Nalcioglu O, Su MY. Quantitative analysis of lesion morphology and texture features for diagnostic prediction in breast MRI. Acad Radiol 2008; 15: 1513-1525.