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An Optimized Transfer Learning Based Framework for Brain Tumor Classification

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ABSTRACT- Brain Tumor (BT) categorization is an indispensable task for evaluating Tumors and making an appropriate treatment. Magnetic Resonance Imaging (MRI) modality is commonly used for such an errand due to its unparalleled nature of the imaging and the actuality that it doesn't rely upon ionizing radiations. The pertinence of Deep Learning (DL) in the space of imaging has cleared the way for exceptional advancements in identifying and classifying complex medical conditions, similar to a BT. Here in the presented paper, the classification of BT through DL techniques is put forward for the characterizing BTs using open dataset which categorize them into benign and malignant. The proposed framework achieves a striking precision of 96.65%. The proposed framework can be employed to assist physicians and radiologists in validating their initial screening for brain tumor classification.

Keywords: Deep Learning, Artificial Intelligence, Image Processing, Transfer Learning.

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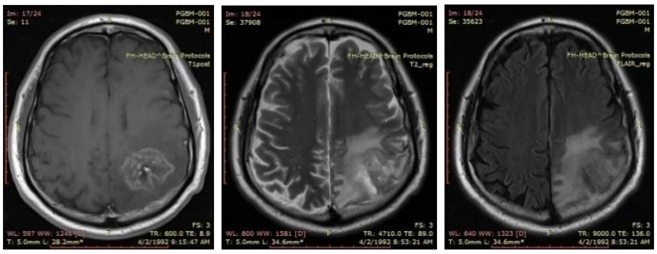
1. INTRODUCTION

Tumor of brain may be portrayed as anomalous as well as uncontrolled growth of cells in the neural structure. Any alarming growth in the brain might affect the human ability; additionally, it may grow into other parts of the body [1]. As per WHO BT signifies below 2% of human cancer [2]. The size of tumor its category along with its position in brain is pivotal in deciding the treatment. Generally, brain surgery is considered as a routine method of handling BT [3]. The most oftentimes happening BTs falls into Glioma categories that consolidate roughly 30% of all Tumors in brain and around 80% of all damaging BTs [4]. In the midst of different clinical developments, MRI produces information about the locale and tumor size. Its function is based on proton activity confined in the magnetic field by varying frequency of radio waves and retrieve their normal state [5] To unequivocally isolate fragile tissues with high exactness MR modality is quite proficient and is progressively receptive to alteration in strength of tissues. The MR modality classify images into T1-weighted (T1-w) which are employed for non-intrusive brain studies as they depict elevated contrast. While, T2-weighted (T2-w) MR images are acceptable for observing the image periphery [6]. The vital pitfall of these images is that BT, Grey Matter (GM) as well as cerebrospinal fluid (CSF) are tied together. Medically, the use of such MR modalities is pivotal in pinpointing tumors nevertheless it may pose some difficulties in sorting out tumorous zones [7]. Consequently, for evaluating the periphery of tumorous tissues counter to a non-tumorous one, use of T1 and T2 weighted contrast modes are important. Tumors of brain are at times mystified for the reason that they continue to be unaltered even with the improvement in their contrast. Successively, the FLAIR images are employed alongside T2-w for showing the non-enhanced BTs [8]. The various MR image types are presented in *figure 1*.



(a) (b) (c)
Figure 1: MRI images (a) to (c) - T1, T2, and FLAIR

DL is a kind of Artificial Intelligence method that copies the working of a human mind for processing information as well as producing model valuable in settling on appropriate decisions. Deep Learning utilize different layers of non-linear type that are efficient for extrication of image features. The result of each organized layer is the commitment of the accompanying one, and that helps in deliberating data as we jump inside the framework [9]. Convolutional Neural Network (CNN) belongs to the family of DL and the essential interesting point in CNNs are its capability to grasp features and to provide precise exactness instead of customary AI methods by augmenting the training samples and thus prompts to a much robust and exact system [10]. The essential commitment of this proposed work is to present a powerful and robust DL framework utilizing Transfer Learning (TL) strategies for identifying and categorizing BTs by extricating crucial features on a universal image set and then, to explore DL techniques like GoogleNet, ResNet50, and ResNet101 using BT images and apply TL approach on the standard image set to advance a comprehensive performance assessment of features critical for fine tuning of pretrained frameworks. Conclusively to evaluate the correlation among these deep learning networks utilizing different parameters critical for detection of BTs. Rest of this paper is planned as; *section 2* presents the various state of the art, succeeding *section 3* describes the methods employed. *Section 4* is given to the results and its discussion which id than tracked by *section 5* which concludes the paper.

2. STATE OF ART

Deep Convolutional Neural Network was first utilized when a DL network 'LeNet" was used for detection of documents in the year1998. Years after, a significant rise is seen while a Deep Learning network was used to distinguish images by utilizing a pretrained network called AlexNet [11]. It exhibited striking results when contrasted against other frameworks of that time. Afterward, its success incited consecutive victories of CNNs in the field of DL. In CNNs, the features are extricated by filters and as we plunge in depth, considerably additional complicated features are extracted. Feature extrication happens by convolving filters of small size with the input configurations for finding most idiosyncratic features for network classification. In [12] SVM and k-Nearest Neighbour techniques is set forward to distinguish glioma. They accomplished an exactness of 85% for manifold classification and 88% precision is acquired for binary detection.

In [13] author tried to distinguish 80 images of BT which include both anomalous and normal using technique of Discrete Wavelet Transform (DWT) for extrication of features, for reduction of features PCA is employed, and subsequently Artificial Neural Network (ANN) and k-NN is utilized with an exactness of 97% and 98% separately. In [14] a method is introduced for the upgradation BT detection utilizing image dilation and subsequently separating them into sub-areas. Author used three different techniques for extrication of features; Bag of Words (BOW), intensity histogram as well as Gray Level Co-occurrence Matrix (GLCM) and achieved the best accuracy of 91.28%. In [15] Convolutional Neural Networks is used to recognize high and low grades of glioma and gained precision of 71 and 96 percent respectively. In [16] author, for training, used transverse images of BT and used CNN for the purpose of detection thus achieved the most extreme precision of 91.43%. Author in [17] presented a capsule network called CapsNet that summarizes brain MR images with the coarse tumor margins to describe the type of BTs and acquired an accuracy of 90.89%.

Author in [18] presented a framework to distinguish MR images of BT utilizing Genetic Algorithms and Convolutional NN. They accomplished an exactness of 90.9% and 94.2% in recognizing glioma and its evaluations individually. In [19] author proposed a Wavelet-based Auto Encoder using ANN that stalls the image into low resolution images for categorization. For reducing the computational complexity these images are than passed on as an input to CNN without influencing the accuracy. A technique was put forward in [20] in which the weighted fuzzy framework was used to isolate BTs images and kernel matrix was used to augment the process of segmentation. In [21] a fruitful framework based on NN for BT detection was proposed which focused on the brain tissue division and gave ideal precision.

In [28], authors proposed the Densenet201 Pre-Trained Deep Learning Model is fine-tuned and later trained using a deep transfer of imbalanced data learning. The features of the trained model are extracted from the average pool layer, which represents the very deep information of each type of tumor. In [29], three different CNN models are proposed for three different classification tasks. Brain tumor detection is achieved with 99.33% accuracy using the first CNN model. The second CNN model can classify the brain tumor into five brain tumor types as normal, glioma, meningioma, pituitary and metastatic with an accuracy of 92.66%. The third CNN model can classify the brain tumors into three grades as Grade II, Grade III and Grade IV with an accuracy of 98.14%. All the important hyper-parameters of CNN models are automatically designated using the grid search optimization algorithm.

3. PROPOSED METHODOLOGY

We are here investigating three extraordinary Deep Learning systems like GoogLeNet, ResNet50, and ResNet101 using BT images and applying Transfer Learning (TL) strategies on the given image set. These PTNs are used to do TL to extract features that are outwardly recognizable and pivotal. And at last, the feature characterization is completed using the softmax layer. The proposed strategy of this work is introduced in *figure 2*. It starts by collecting MR image set of brain which is organized into malignant and benign slices. The proposed methodology contains supplementary stages which includes pre-processing, augmentation, and data division followed by TL based extrication of features and ultimately the classification of tumor types.

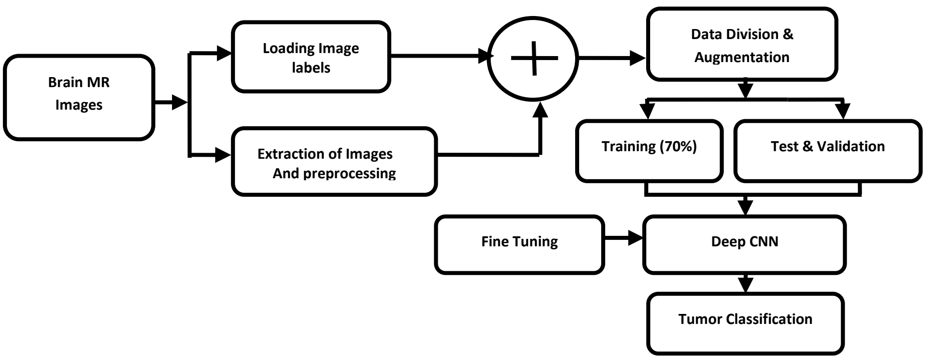


Figure 2: The proposed Deep Learning system structure

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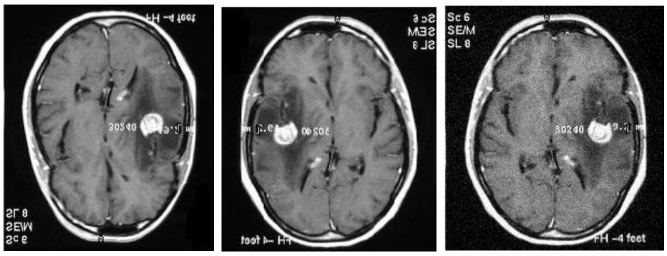
3.1 Imageset

MR image set of brain for the purpose of assessment of the presented work is obtained from TCIA, a public repository [22]. This image set comprises of an assorted image sets of 20 patients with freshly spotted glioblastoma. We here choose to use T1-w image sets as shown below in *figure 3*. This image set consist of 696 images of MR type, out of these 472 are malignant and 224 are benign. The dimensions of each image are set to 225x225 in JPG/JPEG format.

3.2 Preprocessing

Sooner than passing the imageset into the projected arrangement, they are preprocessed. These images are essentially downsized to 225x225x1 pixels to decrease dimensionality computations and backing the framework to show accurate results in substantially short time. By then, jumbling of the dataset is done prior to image separation so that the system works on the dataset which is unarranged. Thereafter imageset is parted into three sections: testing, training and validation with 15% for testing and validation separately while 70% is kept for training. Finally, augmentation of image is done with mirroring and flipping to make sufficiently large amount of imageset for the system to be trained upon so as to avoid overfitting and enhance its sturdiness [23]. Alongside augmenting the image, a little salt and pepper noise is also included for a grayscale distortion of the imageset. In *figure 3* below the preprocessed image is shown with flipped, mirrored, and pepper and salt noise image.



(a) (b) (c)

Figure 3: (a) Image flipping (b) Image Mirroring (c) Pepper and Salt Noise

3.3 Feature Extraction by Transfer Learning Using Pretrained Networks

Adjusting a PTN with TL is typically much speedier and less complex than beginning from scratch. Using pre-trained deep learning frameworks aids the systems to learn new tasks quickly. Different researchers and experts believe that TL as a viable instrument that can accelerate our advancement in the direction of AI [24]. Ordinary learning is disengaging and takes place on a specific task and for training of independent models over them. Not a bit of the information is retained that may be used from one in hand task to the other. While in TL, one may utilize data from the previously trained model and can take care of things like having little data for the newer assignment. Deep Learning systems learn different features at different steps. These steps are then eventually connected to the final fully connected layer to produce the desired results. These layered arrangements allow us to utilize a PTN like GoogLeNet, ResNet, and so on, devoid of its final layer as an extractor of features for various tasks [25].

3.4 Optimization Techniques

Most of the deep learning techniques use optimization methods for either minimizing or maximizing the function $f(x)$ by changing x. Such functions are called as an objective function. Nevertheless, when the minimization of function is done it is termed as the error function or the cost function. For the optimization of the function $J(\theta)$, called as the objective function, gradient descent is used, which is classified by a model's restriction $\theta \in \mathbb{R}^d$ by amending it in the opposite direction to the function $\nabla_\theta J(\theta)$ with respect to the parameters. The size of the step used to attain the (local) minimum is the rate of learning and is denoted by 'η'. For quickening the slope in a suitable direction and for reducing its oscillations, SGDM is used in which 'γ' of the past stage is added to the current vector.

$$\left.\begin{aligned} v_t &= \gamma v_{t-1} + \eta \nabla_\theta J(\theta) \\ \theta &= \theta - v_t \end{aligned}\right\} \quad (1)$$

4. RESULTS AND DISCUSSION

The Transfer Learning algorithms are evaluated in the presented paper for distinguishing BTs into malignant and benign types. The training of this presented framework is done through distinctive DL networks like ResNet101, ResNet50 and GoogLeNet to get to the finest precision. The identification of image is completed by utilizing softmax layers of the PTNs by features finetuning. In this work the features which are visually recognizable are tuned in accordance to the objective imageset and categorization of BTs is completed using the softmax layer by instating the neurons quantity to the two classes. Such modified parameters are not trained by itself, and thusly it is essential to set the parameters which are optimized in accordance to the result of trained MRI imagesets for enhanced performance. This proposed system is trained repeatedly for all the mentioned PTNs utilizing SGDM to achieve the most ideal precision. Training progress and loss of the proposed three PTNs are presented in *figure 4*.

4.1 Confusion Chart

This matrix is a diagram that is often used to portray how the given network is working as classifier on the imageset used for testing for which the results are known. Performance consolidation of the network for categorization of BTs is shown in *figure 5*. The articulation for Sensitivity, Specificity, Exactness and Accuracy etc. is presented in *table1* while *table 2* enlist the parameter values for GoogLeNet. In *table 3* the results of network training for various PTNs used in this study along with the time to train utilizing the SGDM optimizer is presented. The results tabulated shows that the PTN GoogLeNet presents the utmost exactness of 96.65% when contrasted with the remainder of the PTNs used.

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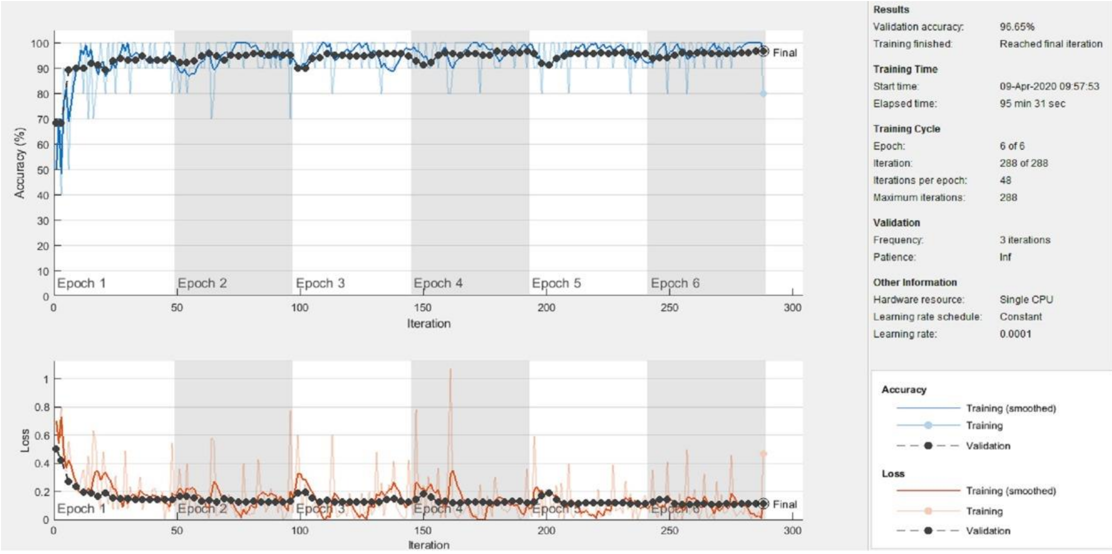
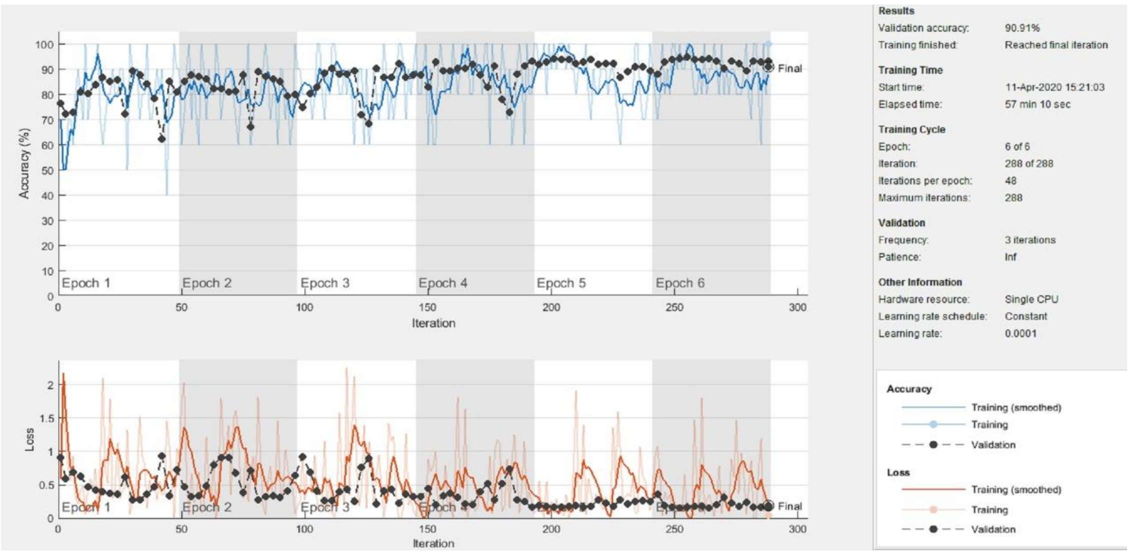
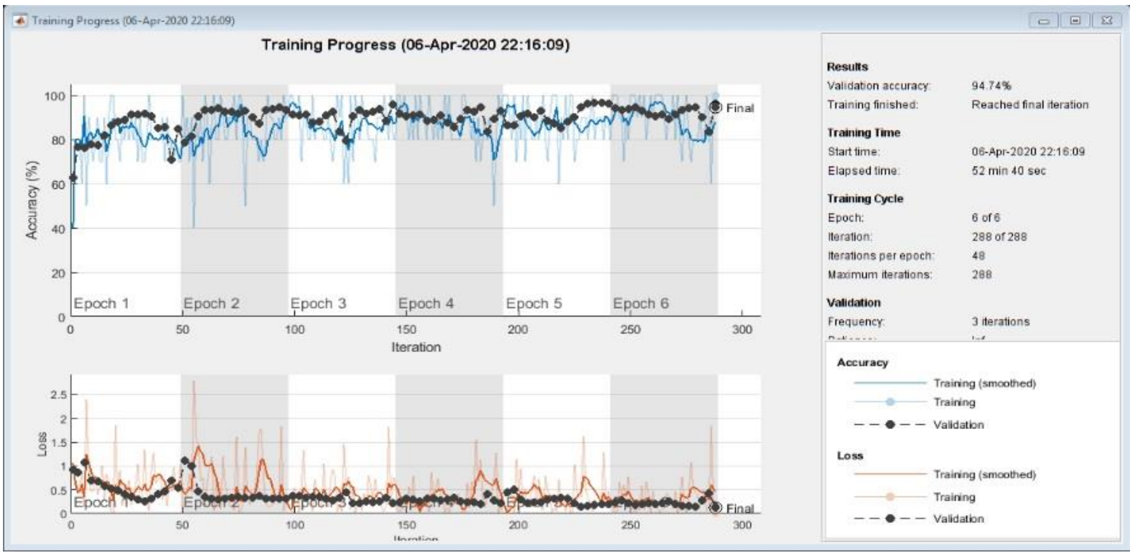


(a) Fine-tuned GoogLeNet



(b) Fine-tuned ResNet50



(c) Fine-tuned ResNet101

Figure 4: Results of training and loss for various PTNs using SGDM

Table 1: **Parameters for classification of Image**

Parameters	Expressions
Specificity	$\frac{TN}{TN+FP}$
Accuracy	$\frac{TP+TN}{TP+TN+FP+FN}$
Sensitivity	$\frac{TP}{TP+FN}$
Precision	$\frac{TP}{TP+FP}$
MCC	$\frac{TP.TN-FP.FN}{\sqrt{(TP+FP)(TP+FN)(TN+FP)(TN+FN)}}$
Error Rate	$\frac{FP+FN}{TP+TN+FP+FN}$
F1 Score	$\frac{2*(Precesion*Specificity)}{(Precesion+Specificity)}$

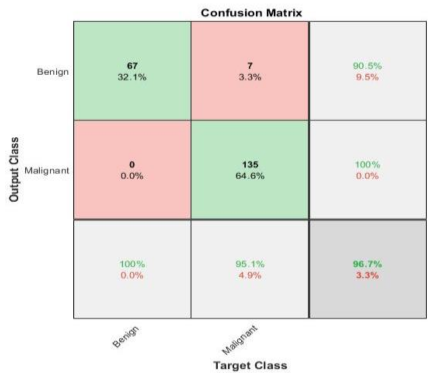


Figure 5: Confusion Matrix for GoogLeNet

Table 2: Parameters of Confusion Matrix for GoogLeNet

Model Parameter	**Proposed System**	
Tumor Types	Benign	Malignant
TP	67	135
TN	135	67
FP	7	0
FN	0	7
Error rate	0.03349	0.03349
F1-score	0.92722	1
MCC	0.92777	0.92777
Specificity	0.95070	1
Sensitivity	1	0.95070
Accuracy	0.96650	0.96650
precision	0.90540	1
Overall Accuracy	**96.65%**	

Table 3: Training results of pre-trained DL network

Algorithms	Optimizer	Accuracy	Benign Acc	Malignant Acc	Training Time
ResNet 101		94.74%	96.70%	94.00%	52m 40s
ResNet 50	SGDM	90.91%	96.20%	89.20%	57m 10s
GoogleNet		**96.65%**	90.50%	100%	95m 31s

4.2 Fine-tuning of Network and Optimization of Hyper Parameters

Here, different settings embroiled in planning the finest framework are presented. *Table 4* presents distinct parameters attempted prior to showing up at the calibrated framework that gives the most excellent result.

Table 4: Finetuning of parameters for obtaining the utmost accuracy

Factors	Values
Conv.+ RLU Layer	1,3,4
Dropout	1,2,3
Max Iterations	80,150,288
Pooling Layer Types	Max. & Avg. Pooling
Optimizer Employed	SGDM
PTNs tested	ResNet50, ResNet101, GoogLeNet
Mini Batch	4,8,10,12,16
Learning level	0.01, 0.001, 0.0001
drop factor	0.1, 0.2, 0.3,0.5
Max. Epoch	5,6,7,8

4.3 Evaluation against the state-of-the-Art

In this research work, a network architecture is proposed for choosing the PTN for applying TL to categorize BTs into malignant and benign types. 225x225 image size is used here in JPG/JPEG format. MATLAB 2018a platform is employed for the execution of the proposed work and GoogLeNet gave the utmost exactness of 96.65% among z5 different associated State of the Art (SoA) is given and *figure 6* gives the portrayal of SoA in graphical form.

Table 5: State of the Art

Authors	Techniques Used	Accuracy
J. Cheng et al. [14]	SVM and KNN	91.28%
J. S. Paul et al. [16]	CNN	91.43%
Anaraki et al. [18]	GA-CNN	94.20%
Bahadure et al. [7]	BWT+SVM	95.00%
Sultan et al. [26]	CNN	96.13%
A. Kumar et al. [27]	GWO+M-SVM	95.23%
M. Imran Sharif [28]	InceptionV3	95.20%
Emrah Irmak[29]	ResNet-50	92.79%
Proposed System	PT-CNN (GoogLeNet)	**96.65%**

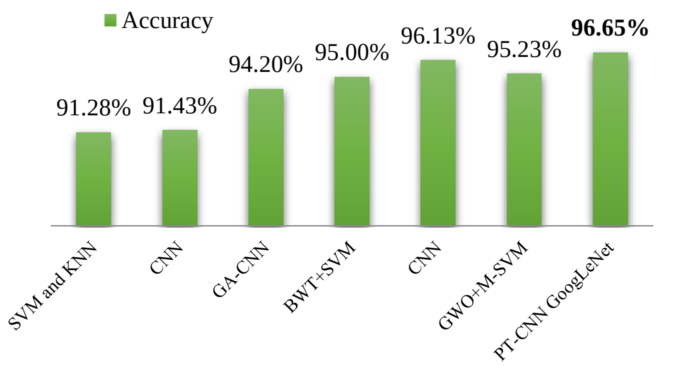


Figure 6: Evaluation against the State of the Art

In the proposed system, efficient automatic brain tumor detection is performed by using convolution neural network. Simulation is performed by using python language. The accuracy is calculated and compared with all other state of arts methods. The training accuracy, validation accuracy and validation loss are calculated to find the efficiency of proposed brain tumor classification scheme.

5. CONCLUSION

This research explores different PTNs for enhancing classification of the image MRI for BTs utilizing TL approach. Considering the execution results of the proposed system, it is apparent that TL using GoogLeNet gives the most extreme exactness of 96.65% among other PTNs utilized. Despite the fact that the imageset isn't sufficiently huge, augmented images used has done genuinely well to give exceptional results. Work on bigger imageset may be done in future to additionally enhance the precision and attempting to limit the training time by utilizing sophisticated processors.

Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study

REFERENCES

[1] DeAngelis, L. M. (2001). Brain tumors. New England journal of medicine, 344(2), 114-123.

[2] Stewart, B. W., & Wild, C. P. (2014). World cancer report 2014. IARC. IARC Nonserial Publ: Lyon, France, 630.

[3] E. Aarthi, S. Jana, W. Gracy Theresa, M. Krishnamurthy, A. S. Prakaash, C. Senthilkumar, S. Gopalakrishnan (2022), Detection and Classification of MRI Brain Tumors using S3-DRLSTM Based Deep Learning Model. IJEER 10(3), 597-603. DOI: 10.37391/IJEER.100331.

[4] Goodenberger, M. L., & Jenkins, R. B. (2012). Genetics of adult glioma. Cancer genetics, 205(12), 613-621.

[5] Pereira, S., Pinto, A., Alves, V., & Silva, C. A. (2016). Brain tumor segmentation using convolutional neural networks in MRI images. IEEE transactions on medical imaging, 35(5), 1240-1251.

[6] Zimny, A., Neska-Matuszewska, M., Bladowska, J., & Sąsiadek, M. J. (2015). Intracranial lesions with low signal intensity on T2-weighted MR images–review of pathologies. Polish journal of radiology, 80, 40.

[7] Bahadure, N. B., Ray, A. K., & Thethi, H. P. (2017). Image analysis for MRI based brain tumor detection and feature extraction using biologically inspired BWT and SVM. International journal of biomedical imaging, 2017.

[8] Jalab, H. A., & Hasan, A. (2019). 'Magnetic resonance imaging segmentation techniques of brain tumors: A review. Arch. Neurosci, 6.

[9] Deng, L., & Yu, D. (2014). Deep learning: methods and applications. Foundations and trends in signal processing, 7(3–4), 197-387.

[10] Litjens, G., Kooi, T., Bejnordi, B. E., Setio, A. A. A., Ciompi, F., Ghafoorian, M., & Sánchez, C. I. (2017). A survey on deep learning in medical image analysis. Medical image analysis, 42, 60-88.

[11] Krizhevsky, A., Sutskever, I., & Hinton, G. E. (2012). Imagenet classification with deep convolutional neural networks. In Advances in neural information processing systems (pp. 1097-1105).

[12] Zacharaki, E. I., Wang, S., Chawla, S., Soo Yoo, D., Wolf, R., Melhem, E. R., & Davatzikos, C. (2009). Classification of brain tumor type and grade using MRI texture and shape in a machine learning scheme. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine, 62(6), 1609-1618.

[13] El-Dahshan, E. S. A., Hosny, T., & Salem, A. B. M. (2010). Hybrid intelligent techniques for MRI brain images classification. Digital Signal Processing, 20(2), 433-441.

[14] Cheng, J., Huang, W., Cao, S., Yang, R., Yang, W., Yun, Z., ... & Feng, Q. (2015). Enhanced performance of brain tumor classification via tumor region augmentation and partition. PloS one, 10(10), e0140381.

[15] Ertosun, M. G., & Rubin, D. L. (2015). Automated grading of gliomas using deep learning in digital pathology images: A modular approach with ensemble of convolutional neural networks. In AMIA Annual Symposium Proceedings (Vol. 2015, p. 1899). American Medical Informatics Association.

[16] Paul, J. S., Plassard, A. J., Landman, B. A., & Fabbri, D. (2017). Deep learning for brain tumor classification. In A. Krol & B. Gimi (Eds.), Medical Imaging 2017: Biomedical Applications in Molecular, Structural, and Functional Imaging (Vol. 10137, p. 1013710). SPIE. https://doi.org/10.1117/12.2254195

[17] Afshar, P., Plataniotis, K. N., & Mohammadi, A. (2019, May). Capsule networks for brain tumor classification based on MRI images and coarse tumor boundaries. In ICASSP 2019-2019 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP) (pp. 1368-1372). IEEE.

[18] Anaraki, A. K., Ayati, M., & Kazemi, F. (2019). Magnetic resonance imaging-based brain tumor grades classification and grading via convolutional neural networks and genetic algorithms. Biocybernetics and Biomedical Engineering, 39(1), 63-74.

[19] Chen, T., Lin, L., Zuo, W., Luo, X., & Zhang, L. (2018, April). Learning a wavelet-like auto-encoder to accelerate deep neural networks. In Thirty-Second AAAI Conference on Artificial Intelligence.

[20] Shalini, R., Muralidharan, V., & Varatharaj, M. (2014). MRI brain tumor segmentation using kernel weighted fuzzy clustering. Int. J. Eng. Res. Technol., 3(4), 121-125.

[21] Damodharan, S., & Raghavan, D. (2015). Combining tissue segmentation and neural network for brain tumor detection. International Arab Journal of Information Technology (IAJIT), 12(1).

[22] Clark, K., Vendt, B., Smith, K., Freymann, J., Kirby, J., Koppel, P., & Tarbox, L. (2013). The Cancer Imaging Archive (TCIA): maintaining and operating a public information repository. Journal of digital imaging, 26(6), 1045-1057.

[23] Wong, S. C., Gatt, A., Stamatescu, V., & McDonnell, M. D. (2016, November). Understanding data augmentation for classification: when to warp?. In 2016 international conference on digital image computing: techniques and applications (DICTA) (pp. 1-6). IEEE.

[24] Sarkar, D. (2018). A Comprehensive Hands-on Guide to Transfer Learning with Real-World Applications in Deep Learning.

[25] V. Sanjay and P. Swarnalatha (2022), A Survey on Various Machine Learning Techniques for an Efficient Brain Tumor Detection from MRI Images. IJEER 10(2), 177-182. DOI: 10.37391/IJEER.100222.

[26] Sultan, H. H., Salem, N. M., & Al-Atabany, W. (2019). Multi-classification of brain tumor images using deep neural network. IEEE Access, 7, 69215-69225.

[27] Harendra singh and Roop Singh Solanki (2021), Classification & Feature extraction of Brain tumor from MRI Images using Modified ANN Approach. IJEER 9(2), 10-15. DOI: 10.37391/IJEER.090202.https://ijeer.forexjournal.co.in/archive/volume-9/ijeer-090202.html

[28] Sharif, M.I., Khan, M.A., Alhussein, M. et al. A decision support system for multimodal brain tumor classification using deep learning. Complex Intell. Syst. 8, 3007–3020 (2022). https://doi.org/10.1007/s40747-021-00321-0

[29] Irmak, E. Multi-Classification of Brain Tumor MRI Images Using Deep Convolutional Neural Network with Fully Optimized Framework. Iran J Sci Technol Trans Electr Eng 45, 1015–1036 (2021). https://doi.org/10.1007/s40998-021-00426-9.