This is an Accepted Manuscript of an article published by Taylor & Francis in **CYBERNETICS AND SYSTEMS** on 22.01.2021, available online: https://www.tandfonline.com/doi/full/10.1080/01969722.2020.1871231

Sohail N., Anwar S., Majeed F., Szczerbicki E., Smart Approach for Glioma Segmentation in Magnetic Resonance Imaging using Modified Convolutional Network Architecture (U-NET), CYBERNETICS AND SYSTEMS (2021), pp. 1-23, DOI: 10.1080/01969722.2020.1871231

Smart Approach for Glioma Segmentation in Magnetic Resonance Imaging using Modified Convolutional Network Architecture (U-NET)

Nosheen Sohail[1], Syed M Anwar[2], Farhat Majeed[3], Cesar Sanin[4] and Edward Szczerbicki[5]

[1] *Department of Computer Engineering, University of Engineering and Technology, Taxila, Pakistan*

(nosheen.sohail@students.uettaxila.edu.pk)

[2]*Department of Software Engineering, University of Engineering and Technology, Taxila, Pakistan*

(s.anwar@uettaxila.edu.pk)

[3] *School of Engineering and Built Environment, Griffith University, Nathan, Queensland, Australia.*

(farhat.majeed@griffithuni.edu.au)

[4]*Department of Mechanical Engineering, University of Newcastle, Callaghan, NSW 2308, Australia.*

(cesar.sanin@newcastle.edu.au)

[5]*Faculty of Management and Economics, Gdansk University of Technology, Gdansk, Poland*

(edward.szczerbicki@newcastle.edu.au)

Smart Approach for Glioma Segmentation in Magnetic Resonance Imaging using Modified Convolutional Network Architecture (U-NET)

Abstract:

Segmentation of a brain tumor from magnetic resonance multimodal images is a challenging task in the field of medical imaging. The vast diversity in potential target regions, appearance and multifarious intensity threshold levels of various tumor types are few of the major factors that affect segmentation results. An accurate diagnosis and its treatment demand strict delineation of the tumor affected tissues. Herein, we focus on a smart, automated, and robust segmentation approach for brain tumor using a modified 3D U-Net architecture. The pre-operative multimodal 3D-MRI scans of High-Grade Glioma (HGG) and Low-Grade Glioma (LGG) are used as data. Our proposed approach solves the problem of memory and system resource constraints by robustly applying dense network training on image patches of 3D volumes. It improves the border region artifact detection by applying convolutions at an appropriate phase in the proposed neural network. Multi-class imbalance data are handled by using Categorical Cross Entropy (CCE) loss developed by combining the Weighted Cross Entropy (WCE) with Weighted Multi-class Dice Loss (WMDL) functions, which enables the network to perform smart segmentation of the smaller tumorous regions. The proposed approach is tested and evaluated for the challenge datasets of multimodal MRI volumes of tumor patients. Experiments are performed to compute the average dice scores on BraTS-2019 and BraTS-2020 datasets for the whole tumor region.

Keywords: U-Net, MRI, Semantic, Glioma, Deep learning, Brain tumor, Lesion segmentation

1 Introduction and Background

Sarcoma caused by abnormal over-development of brain cells is considered as tumor, lesion or neoplasia. It is broadly ranked into two categories as primary and metastatic carcinoma. Primary brain tumors arise from supporting brain cells typically termed as astrocytes, ependymal and oligodendroglia cells, which can be benign or noncancerous. Whereas, secondary brain tumors arise from other parts of the body e.g. colon or lungs, which can be cancerous or malignant. These can rapidly spread to the brain through the bloodstream (Lapointe, S., Perry, A., and Butowski, N. A.2018). An average survival rate for 36% of patients diagnosed with a brain tumor is just 5 years (Abdel-Maksoud, Elmogy, and Al-Awadi 2015). Specific causes for a brain tumor are not fully understood; however, most tumors are caused by changes in the DNA cells. The clinical history and symptoms of a patient are considered as key inputs for diagnosis of a brain tumor, which can be performed by using various scan procedures. These scan procedures include computed tomography (CT), angiograms and magnetic resonance imaging (MRI) (Tiwari, Srivastava, and Pant 2020). During the brain MRI procedure, it has been noticed that about 80% of all malignant brain tumors are high-grade glioma (HGG) or low-grade glioma (LGG) and are shown in Figure 1.

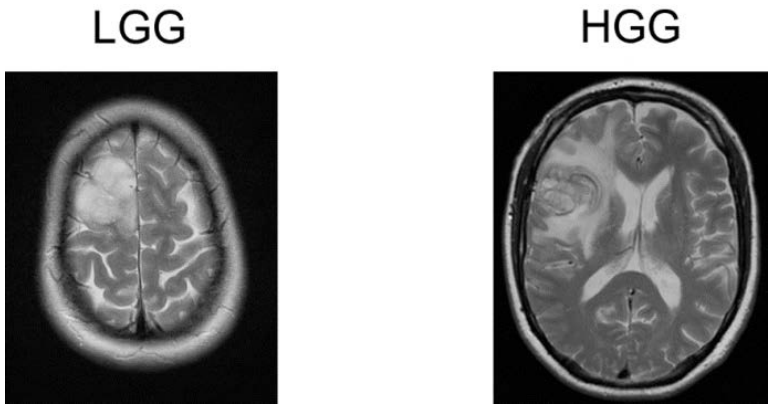


Figure 1: LGG and HGG in brain MRI (van Dellen et al. 2012).

MRI scanning technique is mostly utilized for glioma detection due to its extensively diverse imaging resolution (Amin et al. 2019; Bauer et al. 2013) (Upadhyay and Waldman 2011; Liaqat et al. 2018; Weninger et al. 2018.). It plays a vital role in radiotherapy and surgical planning, where affected regions can be segregated from the healthy tissues. Segmentation analysis is commonly used in MRI scans for delineation of the tumor regions for tumor localization, its volume estimation and surgery planning tasks. Manual segmentation approach is predominant in the present radiological routines. However, more time and clinical practice are required by the radiologists to correctly locate and segment the exact tumorous tissues (Hameurlaine, Messaoud, and Abdelouahab Moussaoui 2019). Furthermore, complexity in glioma features and huge variations among various MRI scanners poses an inescapable challenge for even the expert radiologist to precisely detect tumors through MRI visual examination. In such a scenario, automatic approaches offer effective ways to make the process of diagnosis more efficient and reliable (Fernandes, Steven Lawrence, U. John Tanik, V. Rajinikanth, and K. Arvind Karthik 2020).

In the past few years, deep learning (DL) has played a vital role in the field of medical imaging and many deep network-based techniques are developed for segmenting the brain tumors robustly. Basically, DL methods determine the architecture of the network by integrating multiple layers with multiple abstraction levels (Zhao et al. 2018). Consequently, these techniques have shown promising results in accomplishing segmentation of brain tumor. For example, the contributions made in BraTS 2018 challenge achieved the highest dice scores of 0.91 and 0.94 on the Whole Tumor (WT) (Bakas et al. 2018). The automated tumor segmentation of brain sub-regions has gained a lot of significance in the medical field for diagnosis purpose. In this regard, different approaches have been proposed by using deep convolutional neural network, which is

one of the most popular deep network model (Isensee et al. 2017b; Yang, Ou, and Huang 2017) (Huang et al. 2019).

2D and 3D-variants have been successfully deployed for various biomedical applications (Xie et al. 2016). These variants have achieved competitive results in current biomedical image segmentation challenges (Isensee, Kickingereder, et al. 2018) (Isensee, Petersen, et al. 2018). Similarly, context-aware generative adversarial networks (GAN) are proposed for MRI data synthesis to improve glioma grading and they achieved an accuracy of 89% on the heterogeneous BraTS dataset (Huang et al. 2019). A U-Net based model has been presented by (Hai et al. 2019), which is capable of performing feature mapping in encoding to decoding model by performing successive concatenation (Hai et al. 2019). In multi-network approach, each network is trained separately to segment a tumor sub-type. The biophysical tumor growth modelling has been used by (Pei et al. 2020) to perform longitudinal brain tumor segmentation with better longitudinal tumor prediction. In a recent study, a GAN is proposed to generate segmentation from multi-channel 3D MRI images that penalize unrealistic segmentations generated in the early phases of training (Cirillo, Abramian, and Eklund 2020).

Although, several methods have been presented in literature, but still there exists room to achieve better results and performance in semantic segmentation of gliomas. Therefore, in this research we present a smart approach for segmentation of whole tumor of brain MRI based on datasets of BraTS 2019 and BraTS 2020. Our proposed approach is derived from the famous U-Net architecture by (Ronneberger, Fischer, and Brox 2015), a standard benchmark algorithm in medical segmentation domain. Our main contributions are:

- Development of an improved framework in MATLAB to precisely locate and segment the actual regions of interest by classifying each 3D pixel/voxel in an MR image as background and a whole tumor.

- Enhancing the performance of the model using patch-based segmentation along with dense data augmentation to resolve the issues of over-fitting and lowering error rate.
- Robust training of modified model using a combination of weighted multi-class dice loss and cross entropy loss formulation to resolve the issue of multiclass imbalance. An overlap tile method for test data segmentation is also used to avoid the border region artifacts in output prediction.

The structure of this paper comprises of fundamental concepts in Section 2, which presents the basic concept of use of DL in medical applications, convolutional neural network (CNN) model and description of image dataset. The proposed methodology is explained in Section 3. Experimental Results and discussion are presented in Section 4 followed by concluding remarks in Section 5 respectively.

2 Fundamental Concepts

2.1 Uses of deep learning (DL) in medical applications

In deep learning, a model is being trained with the help of input data along with its corresponding labels, which are termed as ground truths. Ground truths are confirmed and attested by expert radiologists in the medical domain. Currently, many deep network-based techniques are developed for robustly segmenting localized brain tumors. These techniques have shown promising results in performing segmentation of the brain tumor. For instance, the contributions made in BraTS 2018 challenge achieved the highest dice scores of 0.91 and 0.94 on the Whole Tumor (WT) (Bakas et al. 2018).The imaging modalities and ground truth labels of BraTS 2019 dataset are presented in Figure 2.

The terms T1 weighted (T1-w), T2 weighted (T2-w) and T2 Flair are basic radio-frequency pulse sequences in MRI technique, which depict differences in signals based

upon intrinsic relaxation time of various tissues. The T1- weighted image is shown in Figure 2(a), which highlights fat tissues within the body. The T1 post-contrast image in Figure 2(b) represents a T1 image in which a contrast agent/medium is injected intravenously (into a vein) as part of an MRI scan, and eliminated from the body through the kidneys. Such a T1 image is also named as T1 Contrast Enhanced (T1-CE) and is used to enhance the contrast agent sensitive region.

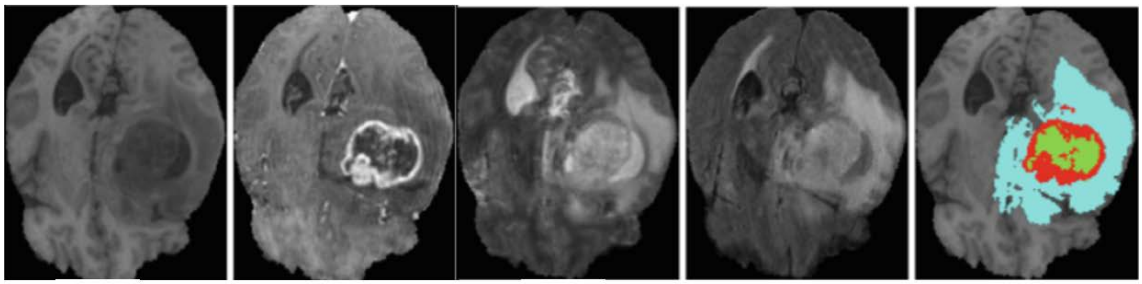


Figure 2: BraTS 2019 dataset imaging modalities and ground truth-labels: (a) T1 weighted, (b) T1 post-contrast, (c) T2 weighted, (d) T2 Flair and (e) T1 labelled image with colors of sub-tumor regions as described in (Bakas et al. 2018).

The most frequently used agent is known as “Gadolinium” or “GD” which is a chemical substance. The timing of radiofrequency pulse sequences used to make T2-weighted images (see Figure 2 (c)) results in images showing fat and water (both) within the body. Moreover, T2 FLAIR and T1 labelled images are shown in Figure 2 (d) and Figure 2 (e) respectively. The T1 labelled image is an expert annotated image with ground truth labels, further elaborating the sub-tumorous regions by distinguishing them with separately labelled colors. For the labels in Figure 2(e), the blue colour indicates the peritumoral edema, green represents the necrotic and non-enhancing tumor, and the red symbolizes the GD enhancing core (B. H. Menze et al.2015).

2.2 Convolutional neural network (CNN) model

The convolutional neural network (CNN) includes several convolutional layers, which are concatenated with pooling layers followed by fully connected (FC) layer to process the high-level input data. CNN technique outperformed conventional approaches in brain lesion segmentation problems (Kamnitsas et al. 2017). A novel technique was proposed for brain tumor segmentation by incorporating a fully connected neural network along with conditional random fields (Zhou et al. 2020). The method was evaluated on BraTS dataset and achieved improved performance as compared to other DL methods. Another CNN based approach with small convolutional kernel for MRI segmentation was proposed in (Yamashita et al. 2018). To study and analyze MRI, a hybrid approach using a combination of clustering and CNN was also proposed in (Abdel-Maksoud, Elmogy, and Al-Awadi 2015). A 3D CNN architecture comprising of 11-layered structure for the classification of healthy/ unhealthy tissues in MRI was employed in (Kamnitsas et al. 2017).

2.3 Description of Image Dataset

In this research, we used the publicly available benchmark dataset from challenges of Brain Tumor Segmentation (BraTS 2019 and BraTS 2020), which is annually organized by Medical Image Computing and Computer Assisted Intervention (MICCAI) conference. After being registered to these online segmentation challenges, the datasets were downloaded and used to train and evaluate the performance of our proposed method. The dataset contains 3D MRI volumes of 335 individuals in total, with 259 HGG and 76 LGG patients. The test volumes were not provided with labels, so we did not use their test data. Instead, we split the 335 volumes into three sub-sets used for training, validation and testing. The size of each multimodal image is 240 x 240 x 155 pixels.

Each multimodal imaging data is provided as Nifti format (.nii.gz) with four sequences/modalities: native (T1), contrast enhanced (T1c), T2-weighted and Fluid Attenuated Inversion Recovery (FLAIR). The pathologically confirmed images are skull-striped, which means non-brain tissues are eliminated from brain MR images for clinical applications. These images are used for analysis and re-sampled to an isotropic resolution with all the four sequences of the same patient already been co-registered. This dataset has been acquired from various scanners with different clinical protocols and obtained from multiple institutions. All the ground truth labels against each case have been denoted by "seg" in the dataset. These labels are obtained from the expert neuroradiologists following the same annotation protocol (Bakas et al. 2018).

3 Proposed Methodology

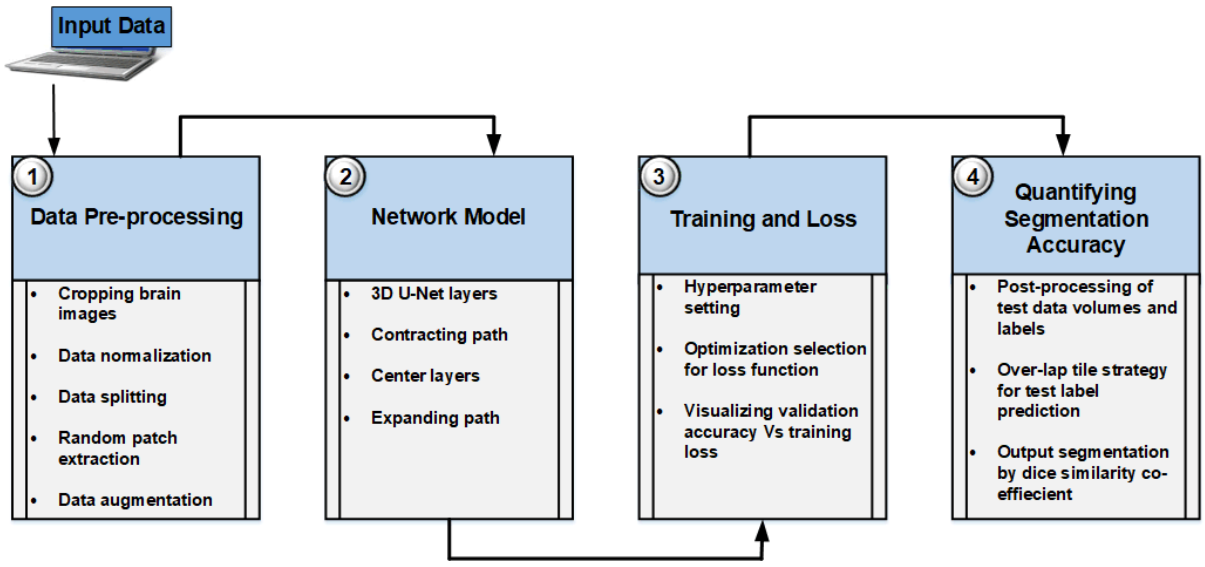


Figure 3: Block diagram of the proposed architecture.

Our proposed approach comprises of four major sections as shown in Figure 3. The first section is about data pre-processing, which makes the input data suitable for feeding the network and initializing the training. Here, the MR slices are grayscale images (black and

white) with gray pixel values and variance is computed by looking at the distribution of pixel values. The training process of a segmentation network having few annotated images requires to have random elastic deformations of the training samples. To cope with this, the smooth deformations are generated by using random displacement vectors and are then sampled from a 'Gaussian Distribution'. The dropout technique is used to prevent the network model from overfitting, whereas implicit data augmentation is achieved by using the drop-out layer at the end of the contracting path.

In the next step, the 3D U-Net layers are set up for the proposed model by using the combination of Weighted Cross Entropy Loss (WCE) and Dice Loss (DL) formulation for smart segmentation. For specifying training options, the optimized hyper-parameters are selected for initializing training from the scratch by using MRI modalities of BraTS 2019 and BraTS 2020 datasets. The final testing was performed using the trained model on the randomly split testing dataset along with its respective ground truth. Testing process took 30 seconds on a single 3D volume. All of the experiments were performed in MATLAB R2019 (b) by using Deep Learning Toolbox, Parallel Computing Toolbox and Computer Vision Toolbox. The working detail of each section of our proposed methodology is explained below.

3.1 Data pre-processing

The input image dataset needs to be pre-processed before sending it to the 3D U-Net network for initiating training process. Therefore, the following pre-processing steps are performed on BraTS 2019 and BraTS 2020 datasets:

- ***Cropping brain images***

Each of the input images is cropped to the tumor region and brain portion. A bounding box is created over the Region of Interest (ROI) for tumor volume and its corresponding labels, respectively. The two vector matrices comprising of tumor rows, columns and

planes are merged to form the cropped tumor volume and cropped tumor label, which are then fed to the next step of data normalization. The size of data is reduced due to cropping, however, useful information part in each MRI volume and each volume's labels is retained.

- ***Data normalization***

The input MRI data contains four modalities, which requires channel-wise pre-processing. This is achieved by normalizing each volume modality of the cropped brain region independently by subtracting the mean and dividing with its standard deviation.

- ***Data splitting***

In this process, the input data is segregated into training, validation and test sets. An approximate value of 82% of the input data is assigned for training, 6% for validation and 12 % for testing purpose.

- ***Random patch extraction***

The random patches are extracted from the input data sets to provide the U-Net model with test data for training and validation purpose. The stored data is maintained by extracting random patches from volumetric images and corresponding pixel label data. Patching technique is very useful for the hardware systems facing memory constraints while performing the dense training on arbitrarily large volumetric images. During the training process of every pair of MR volumes and labels, a patch size of 64 x 64 x 64 voxels is specified, with a mini-batch size of 8 and 16 patches per image from randomly positioned patches.

- ***Data augmentation***

Data augmentation is the last step of the data preprocessing section and is used to augment the training and validation images respectively. This is performed by applying the spatial

elastic transformation after rotating, mirroring and cropping the 3D random patches. These random patches are as per network size requirement i.e., 44 x 44 x44 voxels.

3.2 Network model

The proposed network architecture has been derived from previously proposed '3D U-Net architecture' (Çiçek et al. 2016). In this model, the initial convolutional layers are diffused with max-pooling layers (down-sampling operator), which decreases the input image resolution successively. The output spatial dimensions are kept equivalent to the input by choosing padded convolutions with an input stride of 2 and kernel size of 3 respectively. Leaky rectified linear units with a negatively decaying slope (Isensee et al. 2017a), is used as a non-linearity function (Maas, Hannun, and Ng 2013). The network has 22 convolutional layers. For seamless tiling of the output segmentation map, we selected the input tile size in such a way that all 2x2 max-pooling operations are applied to each layer. These variations in selecting different parameters and empirical values are chosen to be best fit for our network model training. As a result of this, a 3D U-Network by using U-Net Layers is created which specifies dual class segmentation.

- ***3D U-Net layers***

The 3D U-Net layers proposed by (Çiçek et al. 2016) comprises of following layers:

- 3-D input image layer
- 3-D convolutional layer for CNN
- Batch normalization layer
- Leaky rectified linear unit (ReLU) layer
- 3-D max pooling operation layer
- 3-D Transposed/de-convolutional layer
- Softmax output layer
- Concatenation layer

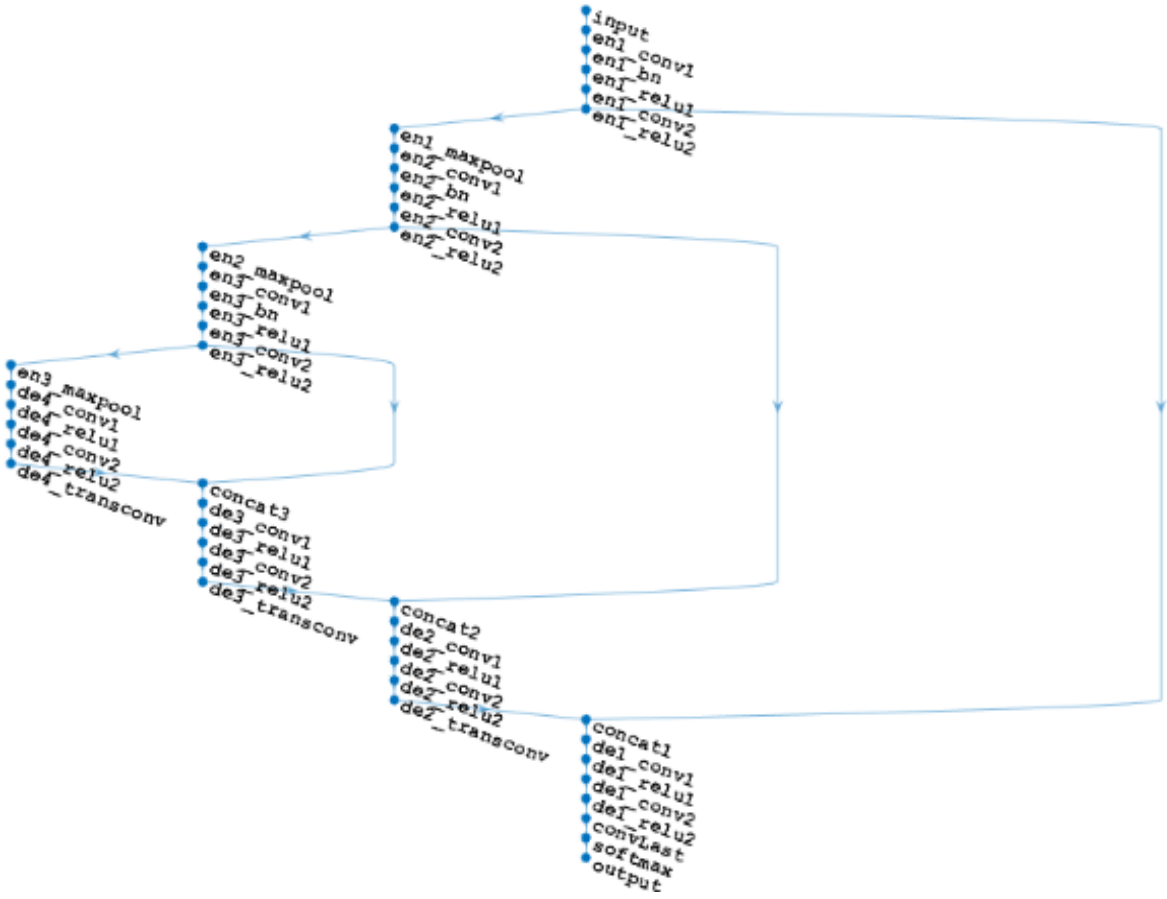


Figure 4: Overall model layers for 3D UNet.

The model layers of 3D U-Network are shown in Figure 4, which is having an image layer followed by contracting path. The contracting path has three encoder modules, which further contains two convolution layers with a filter size of 3x3x3 that doubles the size of total feature maps. The first convolution is followed by a batch of normalization layer. Each encoder ends with a max-pooling layer that halves the image resolution in all dimensions. It is followed by an expanding path in the proposed network. This expanding path comprises of four decoder modules and all of these decoders contain two convolution layers with the filter size of 3x3x3. These convolution layers are aimed to cut half the number of feature maps, while the nonlinear function is activated by using leaky ReLU non-linearity function. The first three decoders terminate with a transposed convolution layer, which upsamples the image by a factor of 2. The final decoder includes a

convolution layer that maps the feature vector of each voxel to each of the two classes (tumor/glioma and background). The custom weighted “dice pixel classification layer” is used as the loss function to increase the impact of the small glioma regions on the dice score. The input layer and encoder modules are concatenated with the fourth decoder module by using concatenation layers. The second ReLU layer of each encoder module is connected with the transposed convolution layer of equal size from a decoder module. Finally, the output of each concatenation layer is connected with the first convolution layer of the decoder module after applying softmax layer.

3.3 Training and loss

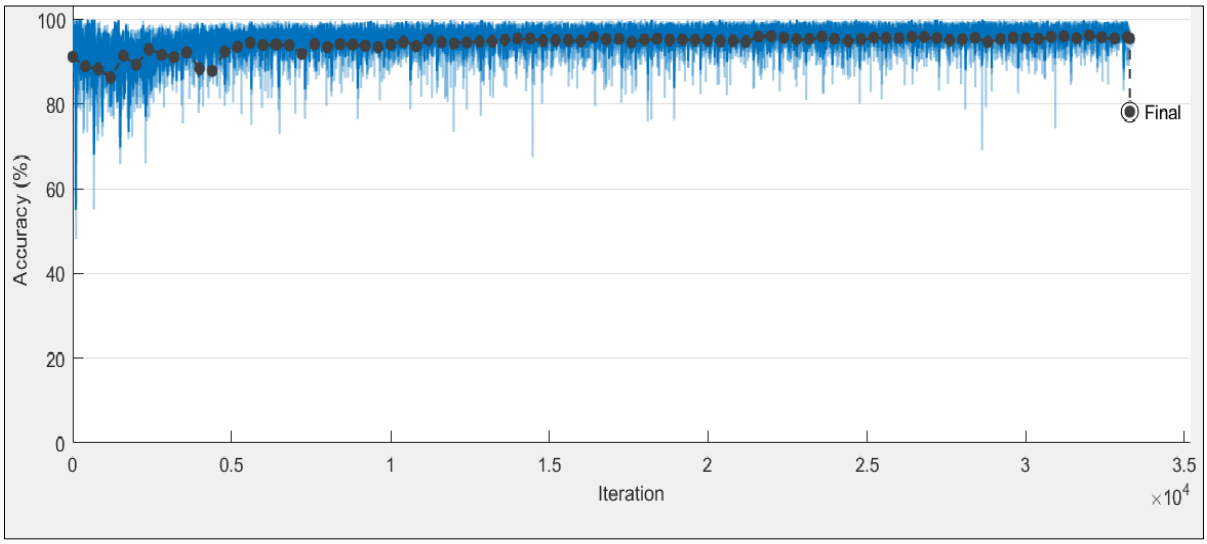
The model is trained from scratch on BraTS 2019 and BraTS 2020 HGG training datasets by using Compute Unified Device Architecture (CUDA) capable NVIDIA GEFORCE GTX 1080Ti GPU with compute capability of 6.0. The optimizers for a neural network can be either selected as stochastic gradient descent (SGD) or ADAM. However, ADAM outperforms with its momentum and the huge amount of impact in reducing error in segmentation problems (Lindsey, Tony, and Jin-Ju Lee 2020). Hence “ADAM” is used as an optimizer for the training of input patches of 64x64x64 in deep learning tool, as shown in Table 1. The initial rate of learning is fixed to $5e^{-4}$ which decreases slowly as the training progresses.

Sr.#	Parameters	Values Set
1	Patch size	64×64×64
2	Patch per image	16
3	Mini-batch size	8
5	Input encoder modules in contracting path	3
6	Convolutional filter size	3×3×3
7	Nonlinear activation function	Leaky ReLU
8	Decoder modules in expanding path	4
9	Upsampling factor	2
10	Number of concatenation layers	3
11	Total U-Net layers	44
12	Max epochs	50
13	Optimizer	ADAM
14	Initial learn rate	5.00E-04
15	Learn rate drop period	5
16	Learn rate drop factor	0.95
17	Validation frequency	200
18	Verbose	FALSE

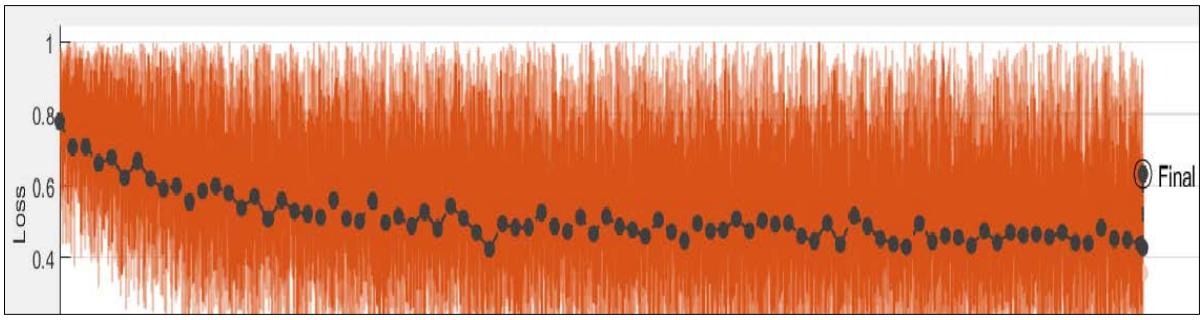
Table 1: Hyper-Parameters setting for network and training.

The summary of selected hyper-parameters for the network and training is shown in Table 1. The training of 44 layered network with 50 epochs took 73 hours on single Nvidia GPU

GTX1080Ti with Intel core i-7(3.60GHz, 24GB RAM). The validation accuracy is 94.8% whereas the training los is 0.4 at the final iteration as shown in Figure 5.



(a)



(b)

Figure 5: Validation accuracy (a) vs. training loss (b).

3.4 Quantifying Segmentation Accuracy

Once the training process for the developed framework was completed, the 3D trained model was saved in the current directory. Quantification was performed on the test dataset that contained the test volumes with its corresponding labels datastore respectively. The central portion of test images and labels were cropped to a window size of 128x128x128 voxels, which is according to the trained model parameters.

For each of the test images, the ground truth image volumes and corresponding labels are added to cell arrays. After this, the technique of overlap-tile strategy for arbitrarily large test volume is applied as shown in Figure 6. Prediction of the segmentation in the yellow area requires image data within the blue area as input, whereas missing input data is extrapolated by mirroring. This technique determines labels against randomly selected overlapped patches and recombines those patches. The predicted labels for each test volume have been obtained with the smart segmentation approach by using the trained network.

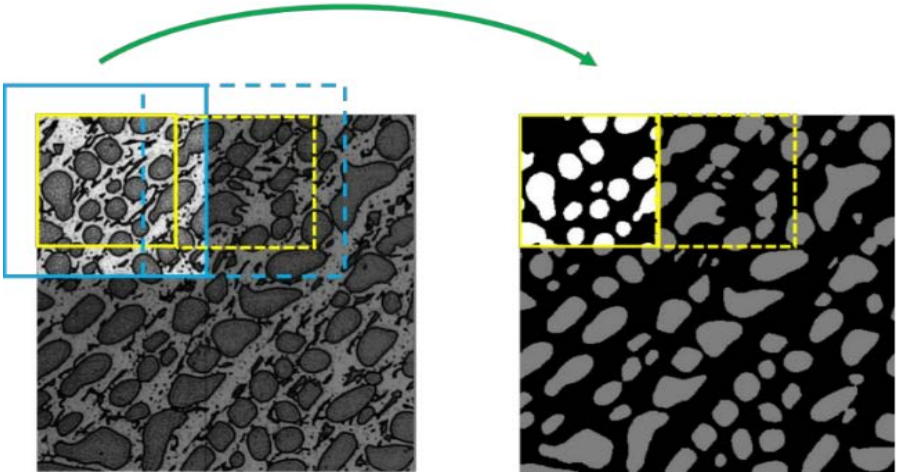


Figure 6: Overlap-tile strategy for seamless segmentation of arbitrary large images.

We used the Dice-Pixel-Classification-Layer instead of plain pixel classification layer to efficiently segment smaller tumor regions thereby, decreasing the effect of larger unnecessary background regions. Minor post-processing of the predicted labels was performed after segmentation. The brain voxels were labelled as ‘1’, and non-rain background voxels as ‘0’. The test images are also used to determine which voxels do not belong to the brain. The predicted labels were cleaned up by the technique of removing islands and filling holes. The filtered labels were cast back to the categorical data type and the original pixel label IDs and class names were specified in order to further clean up the predicted labels.

4 Experimental Results and Discussion

The glioma lies inside the brain cell tissues, therefore some of the brain pixels were made transparent to highlight the tumor portion for better visualization. By doing this, the value of the volume threshold is specified to a range of [0, 1]. Any value below this threshold is considered to be fully transparent. However, to get the context of spatial location of the tumor inside the brain structure, we have to set some of the brain pixels volume threshold intensity to less than '1' (in our case 0.6). The segmentation accuracy of the proposed model is measured by using the weighted multi-class dice function.

The dice similarity coefficient (DSC) between the output predicted volume and ground truth segmentation masks against each test set was calculated. The mean dice similarity coefficient values have been calculated for all test set volumes. Figure 7 shows the output of our network prediction achieving a mean dice score of 0.782 across whole tumor volume on BraTS 2019 challenge dataset. Moreover, the same model also predicted a mean dice score of 0.723 for whole tumor volume on latest released BraTS 2020 challenge dataset. These results show the robustness and generalization capability of the proposed model over a vast variety of clinical data protocols.

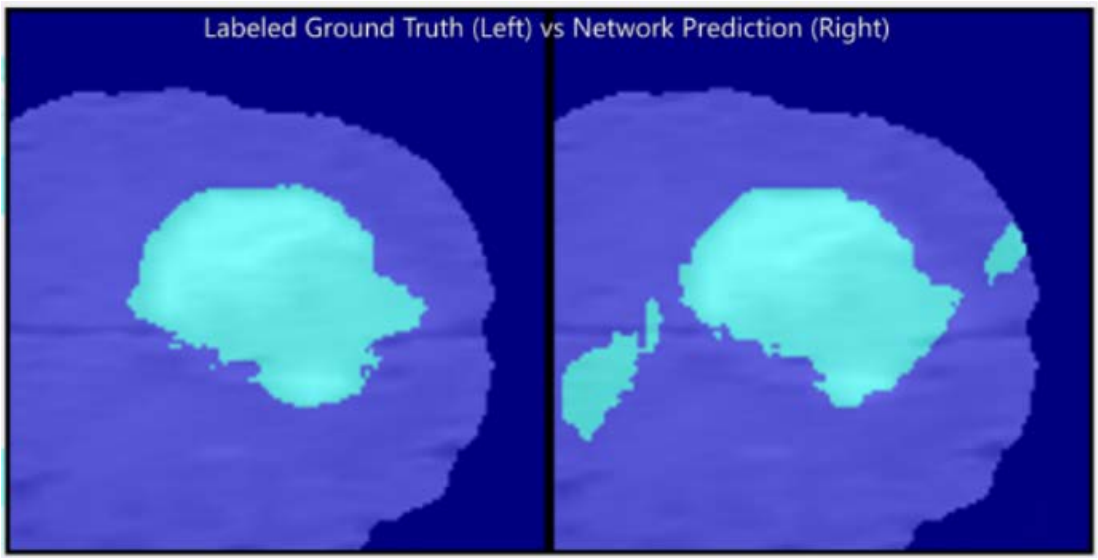


Figure 7: Labeled ground truth Vs output predicted segmentation.

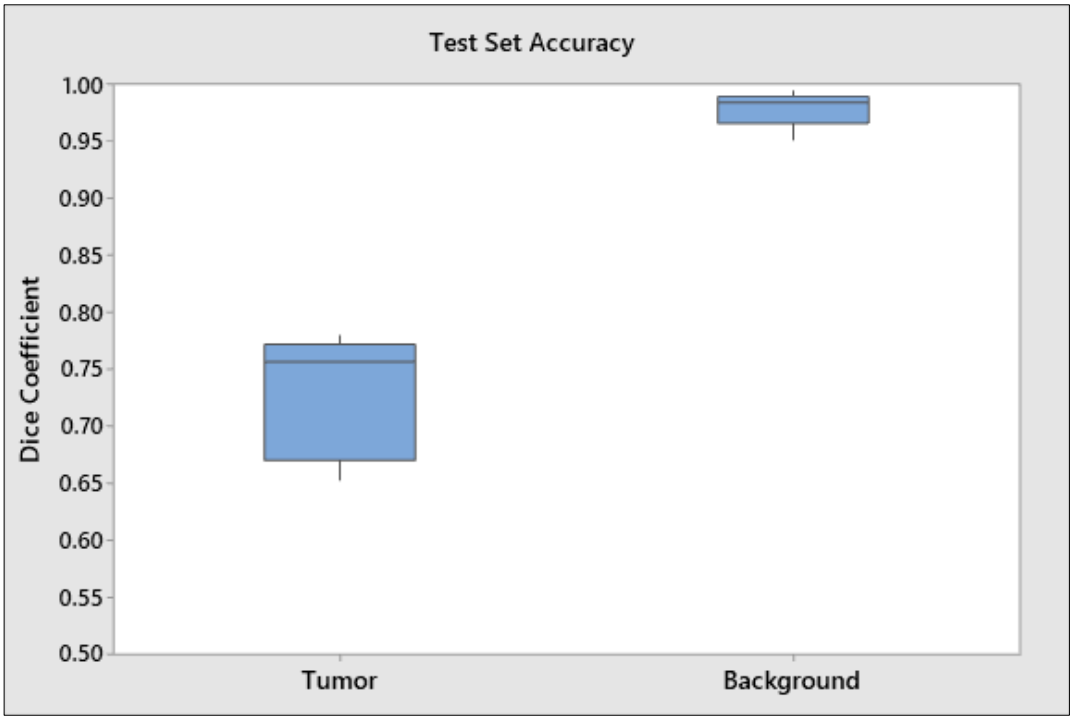


Figure 8: Boxplot of Dice Similarity Coefficient between tumor and background across selected test volumes.

The boxplot for computing test dataset (BraTS 2019) accuracy is shown in Figure 8, which is drawn to statistically monitor the dice similarity coefficient values against the set of selected test volumes and indicates the average dice value for each class labels i.e. background and tumor. It can be seen from the boxplot that extreme data points are not outliers, as they are not laying at an abnormal distance from other values in our obtained data for dice similarity coefficient.

5 Conclusion and Future Work

In this study, we have presented the smart semantic segmentation technique using modified U-net brain lesions (Glioma) by employing a novel seamless approach of data augmentation for robust training. The proposed approach utilizes overlap tile strategy to avoid border artifacts. A combination of the weighted multiclass dice loss function is used to reduce the impact of larger regions on the dice score, which

enables the network to learn the segmentation of smaller tumorous regions. The experimental results obtained on recent data sets released by BraTS 2019 and BraTS 2020 validates the robustness of the proposed approach.

The proposed U-Net based smart method is capable of enhancing the segmentation accuracy for clinical applications by reducing the error rate to a considerable range. This model can serve as a generalized architecture for clinical and experimental databases related to brain abnormalities. In future, it can be further extended for prediction and detection of brain lesions (sub-tumoral regions) in coronal and sagittal views.

References

Abdel-Maksoud, Eman, Mohammed Elmogy, and Rashid Al-Awadi. 2015. "Brain tumor segmentation based on a hybrid clustering technique." *Egyptian Informatics Journal* 16 (1):71-81.

Amin, Javeria, Muhammad Sharif, Mussarat Yasmin, Tanzila Saba, Muhammad Almas Anjum, and Steven Lawrence Fernandes. 2019. "A new approach for brain tumor segmentation and classification based on score level fusion using transfer learning." *Journal of medical systems* 43 (11):326.

Bakas, Spyridon, Mauricio Reyes, Andras Jakab, Stefan Bauer, Markus Rempfler, Alessandro Crimi, Russell Takeshi Shinohara, Christoph Berger, Sung Min Ha, and Martin Rozycki. 2018. "Identifying the best machine learning algorithms for brain tumor segmentation, progression assessment, and overall survival prediction in the BRATS challenge." *arXiv preprint arXiv:1811.02629*.

Bauer, Stefan, Roland Wiest, Lutz-P Nolte, and Mauricio Reyes. 2013. "A survey of MRI-based medical image analysis for brain tumor studies." *Physics in Medicine & Biology* 58 (13):R97.

Çiçek, Özgün, Ahmed Abdulkadir, Soeren S Lienkamp, Thomas Brox, and Olaf Ronneberger. 2016. 3D U-Net: learning dense volumetric segmentation from sparse annotation. Paper presented at the International conference on medical image computing and computer-assisted intervention.

Cirillo, Marco Domenico, David Abramian, and Anders Eklund. 2020. "Vox2Vox: 3D-GAN for Brain Tumour Segmentation." *arXiv preprint arXiv:2003.13653*.

Hai, Jinjin, Kai Qiao, Jian Chen, Hongna Tan, Jingbo Xu, Lei Zeng, Dapeng Shi, and Bin Yan. 2019. "Fully convolutional densenet with multiscale context for automated breast tumor segmentation." *Journal of healthcare engineering* 2019.

Huang, Pu, Dengwang Li, Zhicheng Jiao, Dongming Wei, Guoshi Li, Qian Wang, Han Zhang, and Dinggang Shen. 2019. CoCa-GAN: Common-Feature-Learning-Based Context-Aware Generative Adversarial Network for Glioma Grading. Paper presented at the International Conference on Medical Image Computing and Computer-Assisted Intervention.

Isensee, F, P Kickingereder, W Wick, M Bendszus, and KH Maier-Hein. 2017a. "International MICCAI Brainlesion Workshop." *Cham: Springer*:287-97, 2018. "In International MICCAI Brainlesion Workshop. 287–297." In.: Springer.

Isensee, Fabian, Philipp Kickingereder, Wolfgang Wick, Martin Bendszus, and Klaus H Maier-Hein. 2017b. Brain tumor segmentation and radiomics survival prediction: Contribution to the brats 2017 challenge. Paper presented at the International MICCAI Brainlesion Workshop.

Isensee, Fabian, Jens Petersen, Andre Klein, David Zimmerer, Paul F Jaeger, Simon Kohl, Jakob Wasserthal, Gregor Koehler, Tobias Norajitra, and Sebastian Wirkert. 2018. "nnu-net: Self-adapting framework for u-net-based medical image segmentation." *arXiv preprint arXiv:1809.10486*.

Kamnitsas, Konstantinos, Christian Ledig, Virginia FJ Newcombe, Joanna P Simpson, Andrew D Kane, David K Menon, Daniel Rueckert, and Ben Glocker. 2017. "Efficient multi-scale 3D CNN with fully connected CRF for accurate brain lesion segmentation." *Medical image analysis* 36:61-78.

Liaqat, Amna, Muhammad Attique Khan, Jamal Hussain Shah, Muhammad Sharif, Mussarat Yasmin, and Steven Lawrence Fernandes. 2018. "Automated ulcer and bleeding classification from WCE images using multiple features fusion and selection." *Journal of Mechanics in Medicine and Biology* 18 (04):1850038.

Maas, Andrew L, Awni Y Hannun, and Andrew Y Ng. 2013. Rectifier nonlinearities improve neural network acoustic models. Paper presented at the Proc. icml.

Pei, Linmin, Spyridon Bakas, Arastoo Vossough, Syed MS Reza, Christos Davatzikos, and Khan M Iftekharuddin. 2020. "Longitudinal brain tumor segmentation prediction in MRI using feature and label fusion." *Biomedical Signal Processing and Control* 55:101648.

Ronneberger, Olaf, Philipp Fischer, and Thomas Brox. 2015. U-net: Convolutional networks for biomedical image segmentation. Paper presented at the International Conference on Medical image computing and computer-assisted intervention.

Sudre, Carole H, Wenqi Li, Tom Vercauteren, Sebastien Ourselin, and M Jorge Cardoso. 2017. "Generalised dice overlap as a deep learning loss function for highly unbalanced segmentations." In *Deep learning in medical image analysis and multimodal learning for clinical decision support*, 240-8. Springer.

Tiwari, Arti, Shilpa Srivastava, and Millie Pant. 2020. "Brain tumor segmentation and classification from magnetic resonance images: Review of selected methods from 2014 to 2019." *Pattern Recognition Letters* 131:244-60.

Upadhyay, N, and AD3473894 Waldman. 2011. "Conventional MRI evaluation of gliomas." *The British journal of radiology* 84 (special_issue_2):S107-S11.

van Dellen, Edwin, Linda Douw, Arjan Hillebrand, Irene HM Ris-Hilgersom, Menno M Schoonheim, Johannes C Baayen, Philip C De Witt Hamer, Demetrios N Velis, Martin Klein, and Jan J Heimans. 2012. "MEG network differences between low- and high-grade glioma related to epilepsy and cognition." *PloS one* 7 (11):e50122.

Weninger, Leon, Oliver Rippel, Simon Koppers, and Dorit Merhof. 2018. Segmentation of brain tumors and patient survival prediction: methods for the BraTS 2018 challenge. Paper presented at the International MICCAI Brainlesion Workshop.

Windisch, Paul, Pascal Weber, Christoph Fürweger, Felix Ehret, Markus Kufeld, Daniel Zwahlen, and Alexander Muacevic. 2020. "Implementation of model explainability for a basic brain tumor detection using convolutional neural networks on MRI slices." *Neuroradiology*.

Xie, Long, Laura EM Wisse, Sandhitsu R Das, Hongzhi Wang, David A Wolk, Jose V Manjón, and Paul A Yushkevich. 2016. Accounting for the confound of meninges in segmenting entorhinal and perirhinal cortices in T1-weighted MRI. Paper presented at the International Conference on Medical Image Computing and Computer-assisted Intervention.

Yamashita, Rikiya, Mizuho Nishio, Richard Kinh Gian Do, and Kaori Togashi. 2018. "Convolutional neural networks: an overview and application in radiology." *Insights into imaging* 9 (4):611-29.

Yang, T, Y Ou, and T Huang. 2017. Automatic segmentation of brain tumor from MR images using SegNet: selection of training data sets. Paper presented at the Proc. 6th MICCAI BraTS Challenge.

Zhao, Xiaomei, Yihong Wu, Guidong Song, Zhenye Li, Yazhuo Zhang, and Yong Fan. 2018. "A deep learning model integrating FCNNs and CRFs for brain tumor segmentation." *Medical image analysis* 43:98-111.

Zhou, Chenhong, Changxing Ding, Xinchao Wang, Zhentai Lu, and Dacheng Tao. 2020. "One-pass multi-task networks with cross-task guided attention for brain tumor segmentation." *IEEE Transactions on Image Processing* 29:4516-29.

Bjoern H. Menze, Andras Jakab, Stefan Bauer, Jayashree Kalpathy-Cramer, Keyvan Farahani, Justin Kirby and Yuliya Burren 2015, "The multimodal brain tumor image segmentation benchmark (BRATS)." *IEEE Transactions on Medical Imaging*, vol. 34, no. 10, pp. 1993-2024.

Lapointe, Sarah, Arie Perry, and Nicholas A. Butowski. "Primary brain tumours in adults." *The Lancet* 392, no. 10145 (2018): 432-446.

Hameurlaine, Messaoud, and Abdelouahab Moussaoui. "Survey of Brain Tumor Segmentation Techniques on Magnetic Resonance Imaging." *Nano Biomed. Eng* 11, no. 2 (2019): 178-191.

Fernandes, Steven Lawrence, U. John Tanik, V. Rajinikanth, and K. Arvind Karthik. "A reliable framework for accurate brain image examination and treatment planning based on early diagnosis support for clinicians." *Neural Computing and Applications* 32, no. 20 (2020): 15897-15908.

Lindsey, Tony, and Jin-Ju Lee. "Automated Cardiovascular Pathology Assessment Using Semantic Segmentation and Ensemble Learning." *Journal of Digital Imaging* (2020): 1-6.