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A Survey and Analysis on Automated Glioma Brain Tumor Segmentation and Overall Patient Survival Prediction

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Abstract Glioma is the most deadly brain tumor with high mortality. Treatment planning by human experts depends on the proper diagnosis of physical symptoms along with Magnetic Resonance(MR) image analysis. Highly variability of a brain tumor in terms of size, shape, location, and a high volume of MR images makes the analysis time-consuming. Automatic segmentation methods achieve a reduction in time with excellent reproducible results. The article aims to survey the advancement of automated methods for Glioma brain tumor segmentation. It is also essential to make an objective evaluation of various models based on the benchmark. Therefore, the 2012 - 2019 BraTS challenges database evaluates state-of-the-art methods. The complexity of tasks under the challenge has grown from segmentation (Task1) to overall survival prediction (Task 2) to uncertainty prediction for classification (Task 3). The paper covers the complete gamut of brain tumor segmentation using handcrafted features to deep neural network models for Task 1. The aim is to showcase a complete change of trends in automated brain tumor models. The paper also covers end to end joint models involving brain tumor segmentation and overall survival prediction. All the methods are probed, and parameters that affect performance are tabulated and analyzed.

Keywords Deep Learning · Medical Image Analysis · Brain Tumor Segmentation · Magnetic Resonance Imaging · Overall Survival Prediction

1 Introduction

From the days the medical images are captured through the imaging devices and digitally preserved, researchers have started to build computerized automated and semi-automated analysis techniques to address a variety of problems like detection, segmentation, classification, and registration. Till 1990s, medical image analysis was done with pixel processing techniques to detect edge/line with filters, regions based on the similarity of pixels or fit mathematical models to detect lines/elliptical shapes. Afterwards, shape models, atlas models and probabilistic models had become successful for medical image analysis, where from the observations(training data) the model learns to predict the unseen data. This trend had moved towards the machine learning models where features are extracted from the data and fed into the computer to make it learn the underlying class/pattern as per the input features and prediction of unseen data is made in the future. This approach has changed the trend of human-dependent system to machine dependent system where the machine learns from the example data. Such algorithms works very well with the high dimensional feature space to find the optimal decision boundary. Here the only thing which is not done by computer is the feature extraction, which leads to the era of deep learning where the computer learn the optimal set of features for the problem at hand. The deep learning models transform the input data from image/audio/video/text to output data which is location/presence/spread and incrementally learns high di-

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mensional features with the help of set of intermediate layers between input and output layers. Medical image analysis has reached the extent where such algorithms play a significant role in the early detection of the disease based on the initial symptoms leading to better treatments. The deadly disease like cancer (Glioma-the cancerous brain tumor), if detected in the early stage, can increase the life expectancy.

1.1 Brain Tumors and Their Types

When the natural cycle of the tissues in the brain breaks and growth becomes uncontrollable, it results in a brain tumor[56]. The brain tumor is of two types, (1) primary and (2) secondary. The primary tumor starts with the brain tissues and grows within the brain, whereas secondary tumor spreads in the brain and from the other cancerous organs[24]. More than 100 types of brain tumors are named based on the tissue and the brain part where it starts to grow. Out of all these tumors, Glioma is the most life-threatening brain tumor. It occurs in the glial cells of the brain. The severity grades of the Glioma tumors depends on[115].

- the tumorous cell growth rate.
- blood supply to the tumorous cells.
- presence of necrosis (dead cells at the center of the tumor).
- location of the tumor within the brain.
- confined area of the tumor.
- its structural similarity with the healthy cells.

Grade I and II, are known as Low-Grade Glioma (LGG), which are benign tumors. Grade III and IV are known as High-Grade Glioma (HGG), which are malignant tumors. When symptoms like nausea, vomiting, fatigue, loss of sensation or movement, difficulty in balancing, persist for the longer duration, it is advisable to go through the imaging screening to know the internal structural changes in the brain due to tumor.

1.2 Brain Imaging Modalities

Various imaging techniques are used for brain tumor screening which includes positron emission tomography (PET), Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). In PET, the radioactive tracer is injected in the body, which captures the high level of chemical activities of the disease infected body part. In CT, the X-ray tube rotates around the patient's body and emits a narrow X-ray beam, which is passed through the patient body to generate cross-sectional images of the brain. MRI uses a strong magnetic field

around the patient's body, which aligns the protons in the body to the generated magnetic field, which is followed by the passing of radiofrequency signals to the body. When the current is off, the protons emit the energy and tries to align with the magnetic field. The emitted energy form an image which records the response of various tissues of the brain. There are two types of MRI: 1) fMRI (Functional MRI): It measures the brain activities from the change in the blood flow, 2) sMRI (Structural MRI): It captures the anatomy and pathology of the brain. The proposed article uses the sMRI as the focus to deal with the pathology in the brain. Various modalities of sMRI captures responses of the tissues which leads to distinct biological information in the images. Various modalities of sMRI are:

- **Diffusion Weighted Image (DWI) MRI:** MR imaging technique measuring the diffusion of water molecules within tissue voxels. DWI is often used to visualize hyperintensities.
- **FLAIR MRI:** an MRI pulse sequence which suppresses the fluid (mainly cerebrospinal fluid (CSF)) and enhances edema.
- **T1w MRI:** basic MRI pulse sequence that captures longitudinal relaxation time (time constant required for excited protons to return to equilibrium) differences of tissues.
- **T1Gd MRI:** a contrast enhancing agent, Gadolinium is injected into the body and after that T1 sequence is acquired. This contrast enhancing agent shortens the T1 time which results in bright appearance of blood vessels and pathologies like tumor.
- **T2w MRI:** basic MRI pulse sequence that captures transverse relaxation time (T2) differences of tissues.

In general for brain tumors, CT and MRI are the commonly used techniques. Both the imaging techniques are essential, and the differences between CT and MRI are listed in Table 1. Fig. 1 shows the imaging difference between CT and MRI, along with its various modalities. Healthy brain tissues are of three classes: 1) Gray Matter (GM), 2) White Matter (WM), and 3) Cerebrospinal Fluid (CSF). Such soft tissue detailing is captured clearly in MRI compared to CT.

Further different MRI modalities capture responses of various brain tissues differently. The tumor adds one more tissue class in the brain. Fig. 2 shows the difference in the appearance of tumor in CT and MRI.

Table 2 shows the intensity variation of the tumor in different MRI modalities. The tumor class overlaps the normal tissue intensities, e.g., in T1 MR images GM, CSF, and tumor appear to be dark, whereas, in T2 GM, CSF and tumor appear to be bright. It is desirable to use the combination of various modality MRI images for

Table 1: Difference between CT and MRI[93].

Advantages and Disadvantages	
CT	MRI
Non-invasive.	Non-invasive.
Fast.	Accurate.
Cheap.	Expensive.
Less accurate.	More accurate.
Coarse tissue details.	Fine tissue details.
Single modality	Various modalities to record the reaction of different tissues differently (T1, T2, T1c, T2c, FLAIR, DWI).
Generates 3D images.	Generates 3D images.
Images can be in axial, coronal and sagittal views.	Images can be in axial, coronal and sagittal views.
Risks	
CT	MRI
Harms unborn babies.	Reacts with the metals in the body due to magnetic field.
A small dosage of radiation.	The loud noise of the machine causes hearing issues.
Reacts to the use of dyes.	Increases body temperature when exposed for a longer duration.
	Imaging difficulties in case of claustrophobia.

Fig. 1: Imaging modalities[55] a) CT b) T1 MRI c) T2 MRI and d) DWI MRI.

Fig. 2: Appearance of Tumor in a) CT and b) MRI[66].

the analysis purpose[4]. The rest of the article focuses on the methods based on MR images.

Table 2: The appearance of Normal Brain Tissues and Tumor in various MRI modalities.

	GM	WM	CSF	Tumor
T1	Dark	White	Dark	Dark
T2	Light	Dark	White	Bright
T1c	Dark	White	Dark	Bright
FLAIR	Light	Dark	Dark	Bright

The availability of the benchmark dataset has boosted the research in the area of computer-assisted analysis for brain tumor segmentation. Various types of methods for the segmentation task includes semi-automated and automated methods. The semi-automated methods require user input to initiate the process. Circular automata and other random field methods require seed point, diameter, or rough boundary selection for further computation. Atlas-based methods try to fit the pathological image with a healthy image to locate the abnormal brain area. Pathological atlas creation is another approach to determine the abnormality in the brain. Expectation maximization methods iteratively refine the categories of the brain voxels from the input of Gaussian Mixture Models or atlas. The automated methods include machine learning methods, which use the features of the image for voxel classification. Later on, the deep learning methods, specifically Convolution Neural Network(CNN) based methods, have shown success in the field of semantic segmentation, and such methods are adopted widely for brain tumor segmentation. The CNN methods with various architectures as well as ensemble approaches have proven to be the best methods for the segmentation task. In addition to the segmentation task, the survival prediction task predicts the survival days of patients. The contribution of the paper is as follows:

1. It is the most exhaustive review covering brain tumor imaging modalities, challenges in medical image analysis, evaluation metrics, BraTS dataset evolution, Pre-processing and post processing methods, segmentation methods, proposed architecture, hardware and software for implementation, overall survival predictions, and limitations.
2. It exhaustively traces the development in brain tumor segmentation by covering the models based on handcrafted features to deep neural networks. It helps to understand state-of-the-art development more comprehensively.
3. A fair comparison among models is made by covering BraTS benchmark dataset. The methods are classified, their parameters tabulated and analyzed for performance.
4. The paper also covers a survey on end to end methods for brain tumor segmentation and overall survival prediction. It helps to understand the impact of segmentation on overall survival prediction.

The flow of the article is as follows: section 2 covers the challenges for computer-aided medical image analysis. Section 3 covers the problem statement, dataset, and evaluation framework. In contrast, section 4 includes segmentation methods using hand-crafted features with limitations, section 5 covers segmentation and OS prediction using CNN methods, section 6 covers the limitations of tumor segmentation and OS prediction methods followed by a conclusion and discussion in section 7.

2 Challenges in Medical Image Analysis

Volumetric brain MRI images are analyzed and interpreted by human experts (neurologists, radiologists) to segment various brain tissues as well as to locate the tumor. This analysis is time-consuming. Besides, this type of segmentation is non-reproducible. Accuracy of brain tumor segmentation, which is desirable to plan proper treatment like medication or surgery, highly depends on the human expert with utmost precision. The computer-aided analysis helps a human expert to locate the tumor in less time as well as it regenerates the analysis results. The intended analysis by computerized methods requires appropriate input with correct working methods. Input to the method may face the following challenges:

1. Low signal to noise ratio (SNR) and artifacts in raw MRI data are mainly due to electronic interferences in the receiver circuits, radiofrequency emissions due to thermal motion of the ions in the patient body, coils, and electronic circuits in MRI scanners. This random fluctuation reduces the image contrasts due to signal-dependent data bias[49].
2. Non-uniformity is an irrelevant additional intensity variation throughout the MRI signal. Possible causes of non-uniformity are radio-frequency coils, acquisition pulse sequence, the geometry and nature of the sample.
3. The unwanted information acquired by the MR machines along with the brain images like skull, fat, and skin.
4. The intensity profile of MR images may vary due to the variety of MRI machine configuration.
5. Publicly available brain tumor images for computer-aided analysis are very less. The collection of MR images from various hospitals has privacy or confidentiality related issues.
6. The class imbalance problem is another major issue in medical image analysis. The images for the abnormal class might be challenging to find because the abnormal classes are rare compared to the normal classes.

3 Glioma Brain Tumor Segmentation

The focus on the methods to solve medical related issues has increased since the late 1990s, which is apparent by looking at the gradual increase in semi-automated or automated methods for tumor segmentation, as shown in Fig. 3. By considering the same, the main focus of the article is on the Glioma brain tumor segmentation. An additional task is about the survival prediction techniques of the patients suffering from Glioma.

Fig. 3: Papers on PubMed with keywords ‘Brain Tumor Segmentation’.

3.1 Brain Tumor Segmentation(BraTS) Challenge Dataset

The literature proposes various methods for brain tumor segmentation. All the methods claim its superiority and usefulness in some way. Initially, all such methods work on the images taken from some hospitals or the radiology laboratories, which are private, and disclosure of those images to the other researchers was not allowed. It did not allow comparison of different methods. The publicly available dataset and evaluation framework¹ compares and evaluates the methods on the same measure. The BraTS challenge dataset[13],[11],[12] has the following characteristics:

- It contains multi-parametric MRI pre and post - operative scans in T1, T1Gd, T2, and T2-FLAIR volumes(The post operative scans were omitted since 2014);
- The dataset contains images with different clinical protocols(2D or 3D) and various scanners from multiple institutions(1.5T or 3T);
- The dataset set includes the images with preprocessing for their harmonization and standardization without affecting the apparent image information;
- It has co-registration to the same anatomical template, interpolation to a uniform isotropic resolution ($1mm^3$), and skull-stripping.

Initially, the clinical images in the dataset were very less and it was challenging to compare methods based on the results on such a small number of images. The comparison is possible with increase in number of sample images and accurate generation of the ground truth images. The ground truth is generated based on the evaluation by more than one expert to avoid inter-observer variability. The growth of the dataset from its inception is as shown in Table 3.

Four different types of intra-tumoral structures are useful for ground truth generation: edema, enhancing core, non-enhancing(solid) core, and necrotic(or fluid-filled) core as shown in Fig 4. An annotation protocol was used by expert raters to annotate each case manually. Then the segmentation results from all raters were fused to obtain a single unanimity segmentation for each subject as the ground truth. The validation of the segmentation methods is based: 1) Whole Tumor (WT): all intra-tumoral substructures, 2) Tumor Core(TC): enhancing tumor, necrosis, and non-enhancing tumor substructures and 3) Enhancing Tumor(ET): includes only enhancing substructure.

Fig. 4: Intra-tumoral structures appearance on three imaging modalities with manual annotations. (a) Top: whole tumor (yellow), Bottom:FLAIR, (b) Top: tumor core (red), Bottom:T2, (c) Top: enhancing tumor structures (light blue), surrounding the cystic/necrotic components of the core (green), bottom:T1c, (d) Fusion of the three labels [100].

3.1.1 Overall Survival Prediction

On account of sufficient dataset availability, the additional task of overall survival(OS) prediction is introduced in BraTS Challenge since 2017. This task focuses on the OS prediction of HGG patients. The dataset includes age, survival days, and resection status: Gross Total Resection (GTR) or Sub-Total Resection (STR) information for HGG patients in addition to the images. The task is to classify the patients in: long-survivors(>15 months), mid-survivors(between 10 to 15 months), and short-survivors(<10 months). The detailed description of OS prediction task is given in Table 4. In 2019, the additional task included the quantification of uncertainty prediction in segmentation. This task focuses on the uncertainty prediction in the context of glioma tumor segmentation.

3.2 Evaluation Metrics for Brain Tumour Segmentation and OS prediction

The standard evaluation framework for tumor segmentation and OS prediction includes the following metrics.

1. Dice Similarity Coefficient (DSC) (or F1 measure): It is the overlap of two objects divided by the total size of both the objects. True Positive(TP) is the outcome where the model correctly predicts the positive class. In contrast, False Positive(FP) is the outcome where the model incorrectly predicts the negative class to be positive. False Negative(FN) is the outcome where the model incorrectly predicts the positive class to be negative.

$$DSC = \frac{2TP}{2TP + FP + FN} \quad (1)$$

¹ IPP - ipp.cbica.upenn.edu

Table 3: Growth of the BraTS dataset[13],[11],[12].

Year	Total Images	Training Images	Validation Images	Test Images	Tasks	Type of Data
2012	Clinical:45, Synthetic:65	Clinical data: 30(20HGG + 10LGG), Synthetic data: 50(25HGG + 25LGG)	N/A	Clinical data:15 Synthetic data:15	Segmentation	Pre and post operative scans
2013	65	Clinical data from BraTS 2012	N/A	Leaderboard: Clinical:25 (15 from BraTS 2012 + 10 new) Challenge: 10	Segmentation	Pre and post operative scans
2014	238	200	N/A	38	Segmentation, Disease Progression	Pre-operative, Longitudinal
2015	253	200	N/A	53	Segmentation, Disease Progression	Pre-operative, Longitudinal
2016	391	200	N/A	191	Segmentation, Disease Progression	Pre-operative, Longitudinal
2017	477	285	46	146	Segmentation, Survival Prediction	Pre-operative, Longitudinal
2018	542	285	66	191	Segmentation, Survival Prediction	Pre-operative, Longitudinal
2019	626	335	125	166	Segmentation, Survival Prediction, Uncertainty Prediction	Pre-operative, Longitudinal

Table 4: The distribution of BraTS dataset[13],[11],[12] features in survival classes.

Year	# records	Features	Short survivors (<10 months)			Long survivors (between 10 and 15 months)				Long Survivors (>15 months)		
			count	Age ($\mu \pm \sigma$)	OS days ($\mu \pm \sigma$)	count	Age ($\mu \pm \sigma$)	OS days ($\mu \pm \sigma$)		count	Age ($\mu \pm \sigma$)	OS days ($\mu \pm \sigma$)
2017	163	Age	65	65.44 $\pm$ 10.68	147.44 $\pm$ 83.08	50	58.70 $\pm$ 11.26	394 $\pm$ 49.32		48	55.11 $\pm$ 12.19	826.23 $\pm$ 370.91
2017	163	Age	65	65.44 $\pm$ 10.68	147.44 $\pm$ 83.08	50	58.70 $\pm$ 11.26	394 $\pm$ 49.32		48	55.11 $\pm$ 12.19	826.23 $\pm$ 370.91
2019	212	Age, Resection status	82	66.66 $\pm$ 11.42	150.21 $\pm$ 84.72	54	59.14 $\pm$ 10.98	377.43 $\pm$ 40.44		76	57.16 $\pm$ 11.84	796.38 $\pm$ 354.32

2. Jaccard Similarity Coefficient: It is known as the intersection over the union of two different sets.

$$Jaccard = \frac{TP}{TP + FP + FN} \quad (2)$$

3. Sensitivity: It is a measure that correctly identifies tumorous voxels.

$$Sensitivity = \frac{TP}{TP + FN} \quad (3)$$

4. Hausdorff distance: It measures how far two subsets of a metric space are from each other. If x and y be two non-empty subsets of a metric space (M, d) , then their Hausdorff distance $d_H(x, y)$ can be defined by

$$d_H(x, y) = \max\left\{\sup_{x \in X} \inf_{y \in Y} d(x, y), \sup_{y \in Y} \inf_{x \in X} d(x, y)\right\} \quad (4)$$

Where *sup* represents the supremum and *inf* the infimum.

5. The OS prediction is measurable with accuracy, which is defined to be the quality of being precise.

As DSC is the most commonly used evaluation metric, this article compares all the methods based using DSC unless specified explicitly.

3.3 Image Pre-processing

Medical image preprocessing plays a significant role in the appropriate input to the computer-assisted analysis techniques. The preprocessed images help to get the accurate outputs as such images show proper voxel relationships. As mentioned in section 3.1, the dataset has images with different clinical protocols and scanners; the variability is to standardize, and it is necessary to put all the scans on a single scale. In addition to the image registration, uniform isotropic resolution, and skull-stripping, following preprocessing further improve the image input:

- Bias Field Correction(BFC): Bias field is a multiplicative field added in the image due to the magnetic field and radio signal in the MR machine. Authors in [139] have suggested a bias field correction technique.
- Intensity Normalization(IN): Different modality images have a separate intensity scale. They must map to the same range. Standardization of all the scans considers zero mean and unit variance.
- Histogram Matching(HM): Due to the different configuration of MR machines, the intensity profile of the acquired images may vary. Intensity profiles are to be brought to the same scale using the histogram matching process.

- Noise Removal(NR): Noise in MR image at the time of acquisition is due to the radio signal, or the magnetic field. Various noise filtering techniques are useful for the removal of noise.

3.4 Image Post-processing

The segmentation output generated by computer-assisted methods may contain false segmentation in the image due to improper or incorrect feature selection. The segmentation improves by applying post-processing techniques like:

1. Connected Component Analysis (CCA): CCA groups the voxels based on the connectivity depending on the similar voxel intensities values. The connected components which are very small are excluded from the result as such components are considered to be false positives due to spurious segmentation results.
2. Conditional Random Field(CRF): The classifier predicts the voxel class based on the features related to that voxel, which does not depend on the neighbouring relationship of that voxel with other nearby voxels. CRF takes this relationship into consideration and builds a graphical model to implement the dependencies between the predictions.
3. Morphological Operations: Such operations are applied to adjust the voxel value based on the value of the other voxels in its neighborhood according to the size and shape.

4 Segmentation Methods using Handcrafted Features

The methods in this section are divided into two categories: interactive and non-interactive. The interactive methods require user input in form of tumor diameter, boundary or seed point selection. Random field based methods belong to this category. Non-interactive methods do not require user input. First group of this category detects abnormality. In atlas based methods, the abnormal image is non-linearly mapped to the normal/input specific atlas to identify the abnormality which in general is the area of the image where the atlas mapping fails. The other approach is Expectation Maximisation(EM), where the normal and abnormal voxels intensity distribution is learnt with Gaussian Mixture Models(GMM) or probabilistic atlases. The second group of this category is machine learning approaches. The clustering approach groups the voxels in numbers of clusters such that one of these clusters will result in tumorous voxels group. In random forest(RF) and neural network(NN) approaches, high dimensional features

of the images are given for training. The trained model later classifies the unseen voxels. The detailed description of all these approaches is covered in the following sub-sections.

4.1 Random Field Based Methods

Authors in [52] took user input for the largest possible tumor diameter from HGG images to find Volume of Interest (VoI) for tumor and background from T1C MRI images, followed by Cellular Automata (CA) to obtain the probability maps for both the regions. The level set surface was further applied to those probability maps to get the final probability maps. They had further extended their approach in [51], which considered multimodal images (T1C and FLAIR images) to segment tumor, edema as well as LGG images as well.

The semi-automatic method in [50] took the rough tumor region boundary as user input and fine-tuned it with the global and local active contour-based model. The tumor region breaks into sub-regions with adaptive thresholding based on a statistical analysis of the intensities of various tumor regions to separate edema from active tumor core. The process repeats for all the slices of a patient. In [35], the main contribution was to incorporate soft model assignments into the calculations of model-free affinities, which were then integrated with model-aware affinities for multilevel segmentation by weighted aggregation algorithm.

In [145], Random Walk (RW) based interactive as well as an iterative method was applied to fine-tune the tumor boundary. RW was applied as an edge-weighted graph in the discrete feature space based on the variation of the distribution density of the voxels in the feature space. The user made an initial tumor seed selection for tumors as well as edema. Afterward, RW was applied to feature space as well as on the image. If the user did not approve the results, then the segmentation process is reinitiated.

In [42], Hidden Markov Random Field (HMRF) based model was used with modified Pott's Model to panelized the neighboring pixels belonging to different classes. In [137], various modality intensity images along with its neighborhood voxel intensities fed into the map-reduce Hidden Markov Model (HMM), and the model was corrected iteratively based on the class labels.

In [131], Gabor filter bank based Bayesian classification follows by MRF classification. Initially, each voxel divides into its constituent class by applying the Gabor filter bank to the input vector (made up of intensities of four modalities at a voxel) to classify the voxel in five different classes (GM, WM, CSF, tumor, and edema).

Next, MRF based classifier applies to the tumor as well as edema classes. It uses voxel intensity and spatial intensity differences over the neighbor voxels. The [38], uses the Non-Negative Matrix to find voxel clusters, which shows the tumor and level set methods to fine-tune the region boundary.

4.2 Atlas Based Methods

Authors in [112], initially identified the abnormal brain tissues by registering the tumorous brain image with healthy tissues brain atlas. This step was followed by identifying the presence of edema using T2 images, and finally, geometric and spatial constraints were applied to detect the tumor and edema regions. Authors in [36] applied an affine transformation to the atlas image to globally match the patient. The lesion was segmented using the Adaptive Template Moderated Spatially Varying statistical Classification (ATM SVC) algorithm. This atlas was then manually seeded by an expert with a single voxel placed on the estimated origin of the patient's lesion, which was followed by the non-linear demons registration algorithm with the model of lesion growth to deform the seeded atlas to match the patient. Four volumes of the contrast-enhanced agent with meningioma implement the model.

The paper [78] applied the semi-automatic method, which required user input to give the seed point for tumor, radius for each tumor, and seed point for each regular tissue class. The random walk generates tumor priors using initial tumor seeds. The patient-specific atlas was modified to accommodate tumor classes, using a tumor growth model. Empirical Bayes model used the EM framework to update the posterior of tumor, growth model parameters as well as a patient-specific atlas. This work was then extended in [10], where instead of single seed point for various labels, multiple seed points were taken into consideration to find the intensity mean and variance of a specific label. This work focused on preoperative MRI scans. Whereas, it was further extended in [148] to include post-operative scans along with additional features to the GMM. Here the need for manual selection of seed point was also omitted.

4.3 Expectation Maximisation Based Methods

The [99], uses spatially varying probability prior (atlas) to label healthy tissues in the brain. The latent probabilistic atlas 'alpha' finds the probability of having a tumor at that voxel. Gaussian distribution for healthy tissue classes, as well as tumorous tissue class,

was taken into consideration to identify the tumorous tissues in the image by expectation maximization. For the spatial tumor regularization, latent atlas alpha used MRF using channel-specific regularization parameters. In contrast, authors in [118] used probability priors to predict voxel probability using the EM algorithm, followed by the level set framework with a gradient descent approach for parameter estimation.

The authors in [149], applied Gaussian Mixture Model with EM to divide the data into five probable classes. Afterward, the snake method finds the subtle boundary between the tumor and edema based on the snake method. In [138], the Bayesian intensity tissue model uses the expectation-maximization problem using a trimmed likelihood estimator (TLE), which was robust against the outliers. This step was followed by a graph cut algorithm to differentiate between tumorous tissues as well as false positives.

The [150], selects super voxels using Simple Linear Iterative Clustering (SLIC) 3D based on the color and proximity of the voxels. Graph cut on MRF was implemented for initial segmentation, followed by histogram construction, histogram matching, and likelihood estimation applied to predict the probability of voxel. In [110], the Posterior probability using the Bayes theorem was calculated, which was followed by Super voxel partitioning using the SLIC algorithm.

4.4 Clustering Based Methods

In [34], from all the images, D patches of size 3x3x3 are selected in the database. A single patch of this small cube uses all the four modalities. Once the database is ready, from the test dataset, the same size patches are extracted and mapped with the database patches with k-nearest neighbors where $k = 5$. These five nearest neighbors generate the test patch label.

The [32], uses the knowledge-based multispectral analysis on the top of the unsupervised clustering technique. The rule-based expert system then extracted the intracranial region. The training was performed on three T1, Proton Density(PD), and T2 images, whereas the test on thirteen such volumes. The [122], uses the rough-set approximation to fine-tune the prediction done by k-means clustering.

In [116], initially, the enhanced probabilistic fuzzy C-means clustering was applied to get the rough estimation of the tumor region. This estimation and cluster centroid is given to the gradient-vector-flow snake model to refine the tumor boundary. The [126], learns a Sparse dictionary of size 4x4 for different tissue types using four image modalities followed by logistic regres-

sion for the tissue classification. This initial stage classifies the image voxels in various classes. This step was followed by k-means clustering, which uses a very high dimensional feature vector as input to find the classification of the tumor as well as the edema region as an overlap of the output of the previous step.

4.5 Random Forest Based methods

The [95] implements a generative- discriminative model. The generative model estimates tissue probability using density forest (similar to GMM). The discriminative model implements classification forest, which took as an input 51 features (gradient information first-order texture features and symmetry-based features, prior tissue probabilities based on the density forest) to generate the probability of the tissue. This probability was then supplied to the CRF to fine-tune the result.

Authors in [155] use context-aware spatial features, along with the tissue appearance probability generated by Gaussian Mixture Model, to train decision forest. The [17], works on Random forest classification with CRF regularization to predict the probability of tissue in the multiple class, i.e., GM, WM, CSF, Edema, Necrotic core and enhancing tumor. 28-dimensional feature vector (includes the intensity of each modality along with first-order statistics like mean, variance, skewness, kurtosis, energy, and entropy computed from local patches around each voxel in each modality).

In [47], each voxel was characterized by signal modality as well as spatial prior. The averaging across a 3x3x3 cube removes the noise. The random forest trains using local features (intensity or priors), as well as context-specific features (region-based features or symmetry-based features). The forest was made up of 30 trees with a depth of 20 for each tree and trained on the synthetic data.

The [156], uses a discriminative multiclass classification forest. It uses spatially non-local context-sensitive high dimensional features along with the prior probability for the tissue to be classified. Prior probability is available to the GMM. It classifies in three classes, i.e., background, edema, and tumor. Three types of features train 40 tree with a depth of 20 each, and such features were intensity difference, intensity mean difference, and intensity range on a 3D line to check for structural changes. 2000 combination was selected to design the decision trees. The [46], trains the random forest of 50 trees each of depth 25 on 120000 samples with 324 features comprises of intensity, neighborhood information, context information, and texture information.

In [119], Random Forest classifier used intensities, the difference of intensities (T1 - T2, T1- Flair, T1 - T1c), and the texture-based features such as fractal and texton to train RF using three-fold cross-validation. They further extended their work in [120] for the post-processing, where the connected component analysis removes tiny regions in the 3D volume, and holes in between the according to the neighboring region.

In [48], Extremely Randomized Trees(ExtraTrees) were used, which introduces more randomness at the time of training. The classifier was trained on 208 features extracted from all the four modalities, which include intensity values, local histograms, first-order statistics, second-order statistics, and basic histogram-based segmentation. In the paper, the ExtraTrees trains with the best threshold rather than the threshold derived from the individual features. In [75], pixel classification was done with ten random forests with ten trees each, which are trained in parallel to reduce the training time and finally merged into a single forest with Gini impurity. One thousand samples for tumorous class and 1000 samples for the non-tumorous class trains the RF. Classification forest in [96] used 237 features which included appearance specific features (image intensities, first-order texture features, and gradient features), context sensitive features (ray feature, symmetry intensity difference features). Authors in [88], [97], [82], [98], [43], [129], [80], [109] had used random forest classifier with combination of various intensity based features, gradient based features, texture based features, rotation invariant features.

In [19], tensor features were extracted along with mean, entropy and standard deviation features. Authors in [123] extracted features for supervoxels from multi scale images and created sparse feature vectors to segment whole tumor. Sub-regions of tumor were then separated using CRF.

4.6 Neural Network Based methods

In [20], Grouping Artificial Immune Network(GAIN) takes as an input voxel intensity from 2D as well as 3D slices, statistical features and texture features for training as well as segmentation of brain MRI images. Information is in the form of bits from various image modalities. In [2], Convolutional Restricted Boltzmann Machine trains GMM and spatial tissue priors.

Table 5 summarizes the methods for the type of pre-preprocessing, dataset, the number of images used as well as the DSC achieved. The DSC is shown for the various tumor sub-regions which includes WT, ET, TC and Edema(ED) for training, validation and test datasets.

The DSC comparison of different methods for tumor segmentation is shown in Fig. 5. The atlas and RF-based methods performed well compared to all other approaches.

Random field methods, atlas-based methods, expectation maximization methods, and clustering methods do not use any post-processing techniques. Random forest based methods, authors in [46], [120] and [75] used connected component analysis, [96], [97], [129] applied spatial regularization and authors in [88] and [43] applied morphological operations to refine the segmentation output.

Table 5: Summarization of segmentation methods using handcrafted features.

Ref.	Pre-processing	Dataset	# images	DSC Mean
Random Field methods				
[52]	-	Custom	29	Training TC:0.89 Test TC:0.80
[51]	-	BraTS 2012	30	TC:0.69,ED:0.37
[50]	-	BraTS 2013	30	TC:0.82
[35]	IN	Custom	20	Training TC:0.70,ED:0.66 Test TC:0.66,ED:0.61
[145]	NR	BraTS 2012	30	TC:0.53,ED:0.25
[42]	-	BraTS 2013	30	HGG WT:0.84,TC:0.54, ET:0.67 LGG WT:0.81,TC:0.54, ET:0.11
[131]	-	BraTS 2012	28	TC:0.66,ED:0.56
[137]	BFC	BraTS 2013	30	HG TC:0.62,ED:0.59
Atlas Based Methods				
[78]	BFC, IN	BraTS 2014	200	Validation WT:0.86,TC:0.79, ET:0.59 Test WT:0.88,TC:0.83, ET:0.72

Table5 – continued ...

Ref.	Pre-processing	Dataset	# im-ages	DSC Mean
[10]	BFC, IN	BraTS 2015	186	Training WT:0.88,TC:0.77, ET:0.68
[148]	NR, HM	BraTS 2016	200	WT:0.89,TC:0.77, ET:0.67
Expectation Maximisation Based Methods				
[99]	-	BraTS 2012	30	HGG TC:0.55,ED:0.57 LGG TC:0.24,ED:0.42
[118]	-	BraTS 2012	30	HGG TC:0.58,ED:0.60 LGG TC:0.32,ED:0.36
[149]	-	BraTS 2012	30	TC:0.31,ED:0.35
[138]	-	BraTS 2012	30	TC:0.43,ED:0.55
[150]	IN	BraTS 2013	30	HGG WT:0.83,TC:0.74, ET:0.68 LGG WT:0.83,TC:0.58, ET:0.51
[110]	-	BraTS 2015	200	Training WT:0.74,TC:0.55, ET:0.54
Clustering Based Methods				
[34]	-	BraTS 2013	30	HGG WT:0.79,TC:0.60, ET:0.59 LGG WT:0.76,TC:0.64, ET:0.44
[122]	-	BraTS 2013 BraTS 2015	200	WT:0.82,TC:0.71, ET:0.72
[116]	-	Custom	15	TC:0.82
[126]	-	BraTS 2012	30	TC:0.30,ED:0.39
Random Forest Based Methods				
[95]	-	BraTS 2013	30	HGG WT:0.80,TC:0.69, ET:0.69 LGG WT:0.76,TC:0.58, ET:0.20
[155]	-	Custom	40	TC:0.85,NC:0.75, ET:0.80
[17]	BFC, IN, HM	BraTS 2012	30	HGG-real TC:0.62,ED:0.61 LGG-real TC:0.49,ED:0.35

Table5 – continued ...

Ref.	Pre-processing	Dataset	# im-ages	DSC Mean
[47]	HM	BraTS 2012	30	HGG-real TC:0.68,ED:0.56 LGG-real TC:0.52,ED:0.29
[156]	BFC	BraTS 2012	30	HGG-real TC:0.71,ED:0.70 LGG-real TC:0.62,ED:0.44
[46]	BFC, HM	BraTS 2013	30	HGG WT:0.83,TC:0.70, ET:0.75 LGG WT:0.72,TC:0.47, ET:0.21
[119]	BFC, HM	BraTS 2013	30	HGG WT:0.92,TC:0.91, ET:0.88 LGG WT:0.92,TC:0.91, ET:0.88
[120]	-	BraTS 2014	200	Training WT:0.81,TC:0.66, ET:0.71
[48]	BFC, HM	BraTS 2013	208	WT:0.83,TC:0.71, ET:0.68
[75]	HM, IN	BraTS 2014	200	Training WT:0.84,TC:0.68, ET:0.72 Valid/Test WT:0.87,TC:0.76, ET:0.64
[96]	NR, IN, BFC	BraTS 2013	30	Training WT:0.83,TC:0.66, ET:0.58 Challenge WT:0.84,TC:0.73, ET:0.68
[88]	BFC, IN	BraTS 2015	252	WT:0.75,TC:0.60, ET:0.56
[97]	-	BraTS 2015	65	WT:0.83,TC:0.69, ET:0.63
[82]	BFC, NR, IN	BraTS 2013	30	WT:0.87,TC:0.88
[98]	-	BraTS 2013	30	Valid WT:0.79,TC:0.75, ET:0.66 Challenge WT:0.83,TC:0.76, ET:0.71
[43]	BFC, HM	BraTS 2016	200	WT:0.80,TC:0.72, ET:0.73
[129]	IN	BraTS 2015	274	Training WT:0.87,TC:0.72, ET:0.75

Table5 – continued ...

Ref.	Pre-processing	Dataset	# images	DSC Mean
[80]	IN	BraTS 2015	274	Training WT:0.84,TC:0.72, ET:0.71
[109]	BFC	BraTS 2017	285	Training WT:0.64,TC:0.49, ET:0.47 Test WT:0.63,TC:0.41, ET:0.42
[19]	IN, HM	BraTS 2017	285	Validation WT:0.79,TC:0.67, ET:0.61 Test WT:0.77,TC:0.61, ET:0.50
[123]	-	BraTS 2018	285	Validation WT:0.80,TC:0.63, ET:0.57 Test WT:0.73,TC:0.58, ET:0.50
Neural Network Based Methods				
[20]	-	BraTS 2013	30	WT:0.73,TC:0.59, ET:0.63
[2]	-	BraTS 2015	200	Test WT:0.81, TC:0.68, ET:0.65

The limitations associated with the methods working on handcrafted features are as follows:

1. Identifying tissue probability classes: tumor tissue intensities overlap with that of the healthy tissues, as mentioned in Table 1; in such a case identifying the probable class for tumorous tissue is quite challenging.
2. Atlas matching (healthy or tumorous atlas): Usually, the brain atlas contains the normal brain tissue distribution map. Due to the deformation of the healthy tissue by the tumor, the atlas matching of a tumorous brain may result in the wrong map
3. Manual seed point identification for the tumor or its subparts: Almost all semi-automated methods require some initial selection for the tumorous voxel, its diameter, or its rough outer boundary. The selection depends on the expert. Its repetition over all the slices of the brain is a time-consuming task.
4. Feature extraction from the images: RF training depends on the features extracted from the brain images. All the MRI modalities contain different biological information. This variation in the information complicates the task of feature extraction as well as selection to training RF.

5. Discontinuity: The results generated by such methods are spurious, which increases the chances of false positives. The proper post-processing techniques are required to fine-tune the generated results.

5 Deep Neural Network

Deep Neural Network(DNN) is an artificial intelligence function which mimics the human brain working for data processing and pattern creation in decision making. There are mainly four reasons contributing to their success:

1. The DNN models solved the problem in an end-to-end manner. The models learn the features from the data automatically with help of various functions. The feature learning improves from simple features at initial layers to complex features at deeper layers of the model. The automatic feature learning has eliminated the need of domain expertise.
2. The computational capabilities of the hardware in terms of GPU and efficient implementation of the model on GPU with various open source libraries have made the training of the DNN 10 to 50 times faster than CPU.
3. Efficient optimization techniques for robust learning contribute to the success of DNN for optimal network performance.
4. The availability of benchmark datasets allow training and testing of various deep learning models to be implemented successfully.

The exponential growth of the usage of DNN techniques to solve the variety of problems is shown in Fig. 6. A similar growth pattern is identified for solving the brain tumor segmentation problem, which is as shown in Fig. 7.

The general block diagram of any deep learning technique is as shown in Fig 8. The crucial task is to get the labeled data set. After the availability of the dataset, it is divided into training and validation sets, followed by appropriate pre-processing techniques as per the task on hand. Actual DNN applies to the training data, which makes the network learn the network parameters. The output of DNN is spurious at some brain area, and post-processing fine-tunes the segmentation result. And at last, the evaluation framework measures the performance of the network.

5.1 Evolution of DNN

In medical image analysis, the semantic segmentation task is common, e.g., segmentation of organ, lesion.

Fig. 5: Comparison of segmentation methods using hand-crafted features (DSC for validation/Test for Tumor/WT of all images/HGG).

Fig. 6: The growth rate of research papers with the keyword 'deep learning' on PubMed.

Fig. 7: The growth rate research papers with the keywords 'deep learning' and 'brain tumor segmentation' on PubMed.

The Convolutional Neural Network(CNN), specific type of DNN architecture gained its popularity from 1990 with the architecture of LeNet[81], which was two layers of architecture. After the availability of fast GPUs and other computing facilities, over fifteen years later,

AlexNet was proposed by authors in [77] with five convolutional layers. The CNNs are designed with variety of layers (like convolution layers, non-linearity layers, pooling layers, fully-connected layers), regularization, optimization and normalization, loss functions, as well as network parameters initializations. Authors in [18] have nicely explained the architectural elements of CNN which are as follows:

Convolution layer: extracts representative features from the input. It achieves: 1)weight-sharing mechanism, 2)exploits local connectivity of input, and 3) provides shift invariance at some extent.

Non-linearity layer: provides sparse representation of input space which achieves data variability invariance and computationally efficient representation. Types of non-linearity layers are Rectified Linear Unit(ReLU), Leaky ReLU(LReLU), Parametric ReLU (PReLU), S-shaped ReLU(SReLU), Maxout and its variants, Exponential Linear Unit(ELU) and its variants.

Pooling/subsampling layer: extracts prominent features from non-overlapping neighborhood. It is used to 1) reduce no. of parameter, 2) reduce over-fitting, and 3) achieve translation invariance. Commonly used pooling techniques are max pooling and average pooling.

Fully connected layer: converts 2D features to 1D feature vector. It helps to predict input image class label.

Loss functions: improves learning process by improving within class similarity and between class separability.

Regularizations: deals with over-fitting issues. Commonly used regularization techniques are L1 and L2 regularizations, dropout, early stopping, batch normalization.

Fig. 8: Generalize DNN network.

Optimization: used for proper updates of network parameters during backpropagation. Various techniques of optimization includes Nesterov accelerated gradient descent, adaptive gradient algorithm (Adagrad), Root Means Square Propagation (RMSProp)

Weight initialization and normalization: boosts the learning process by helping the weight update with proper initial values.

The convolution layers extract features from the input by applying kernels to it. The output feature map depends on the type of kernel and its size. At the initial layers simple features are extracted from the input like edge or lines. The gradual increase of the network depth requires higher number of feature maps to extract complex shapes[5]. The activation function is applied to the feature maps to learn the non-linear relationship within the data and allows the errors to backpropagate to the initial layers for accurate parameter updates. Increase in the network depth exponentially increases the network parameters, which is highly computationally expensive. To balance the growth of the network parameters, pooling layers are introduced to down sample the input feature maps and reduce its spatial size by considering only the prominent features. The fully connected layers at the end of the network flatten the result of the input layers before actual classification. The loss function at the classification layer calculates the error in the prediction. Based on this error, the network parameters are updated using the gradient descent methods by backpropagation. Commonly used loss functions are:

- Cross Entropy loss function:

$$J = -\frac{1}{N} \left(\sum_{voxels} y_{true} \cdot \log \hat{y}_{pred} \right) \quad (5)$$

- Dice Loss function:

$$J = 1 - \frac{2 \sum_{voxels} y_{true} y_{pred} + \epsilon}{\sum_{voxels} y_{true}^2 + \sum_{voxels} y_{pred}^2 + \epsilon} \quad (6)$$

Here, N = Number of voxels, y_{true} = ground truth label, and y_{pred} = network predicted label.

The CNNs, with convolution layers followed by fully-connected layers, classifies entire image in a single category. GoogleNet(Inception)[134] and InceptionV3[135] networks have introduced the inception module which implements the kernels of different sizes to reduce network parameters. ResNet[136] has introduced the residual connection between the convolution layers such that it learns the identity function which allows effective training of deeper networks. In DenseNet[61] layers are very narrow and adds very less number of feature maps to the network which again allows to design deeper architectures and training is efficient as each layer has direct access to the gradient of the loss function.

For semantic segmentation, the CNN can simply be used to classify each voxel of the image individually by presenting it with several patches extracted around the particular voxel. Each voxel of the image is classified with the same process, resulting in the segmentation of the entire image. This ‘sliding-window’ approach repeats the convolution operations for adjacent patches of neighboring voxels. The improvement to this approach is the replacement of fully-connected layers with convolution layers, which generates the probability map of the entire input image rather than generating output for a single voxel. Such networks are known to be Fully Convolutional Neural Networks(FCNN). FCN[85] is a type of FCNN where skip connections are introduced to reconstruct the high resolution image. U-Net[121], a very known highly adapted network architecture for tumor segmentation has taken the encoder - decoder

approach where every encoding layer is connected with its peer decoding layer with skip connection to reconstruct the dimension as well to get the particular spatial information from the encoding layer. SegNet[8] and DeepLab[28] are the other type of FCNN architecture adopted to solve the problem of brain tumor segmentation.

5.2 Handling Class Imbalance Problem

In medical image analysis, finding the number of abnormal images as compared to the normal images is difficult as abnormality like the tumor is rare. This problem is called ‘class imbalance’. All images in this article are of the tumor; the class imbalance issue persists because, in the single brain volume, the proportion of the tumor is less compared to average brain volume. Even on a single brain slice, the area of the tumor is small compared to the brain part, which leads to a class imbalance problem. The proportion of the brain volume (BV) and back ground volume (BGV) with respect to tumor volume for BraTS 2019 dataset is as shown in Table 6.

Table 6: The proportion of non tumor brain volume (NTBV) and non tumor background volume (NTBGV) vs. tumorous volume(TV).

	% NTBV	% Necrosis	% Edema	% ET
BV	75.75	0.7	17.78	5.77
BGV	99.11	0.03	0.65	0.21

The following approaches address data imbalance problem.

- Patch sampling: The patch sampling-based method can mitigate the imbalanced data problem. The sampling process includes the equiprobable patches from all the tumorous regions as well as the non-tumorous region.
- Improvement in loss functions: Some of the loss functions, when used in its raw form, may not suit the tumor segmentation task, as they consider balanced datasets. These functions adopt imbalanced dataset with modifications as:
 1. The weighted cross-entropy loss function: The voxel-wise class prediction averaged for all voxels may lead to error if the class is imbalanced in the image. The issue is in a weighted cross-entropy function where the weight is associated

with all the voxels prediction. Since the background regions dominate the training set, it is reasonable to incorporate the weights of multiple classes into the cross-entropy such that more weight given to the voxels of the positive class.

$$Loss_{WCE} = \sum_{voxels} \sum_{classes} y_{true} \cdot \log \hat{y}_{pred} \quad (7)$$

2. Generalized Dice Loss Function: Authors in [132] proposed to use the class rebalancing properties of the generalized dice. It provides a robust and accurate deep-learning loss function for unbalanced tasks.

$$Loss_{GDL} = 1 - 2 \frac{\sum_{classes} w \sum_{voxels} y_{true} y_{pred}}{\sum_{classes} w \sum_{voxels} y_{true} + y_{pred}} \quad (8)$$

3. Focal Loss Function: The detection task uses focal loss. It encourages the model to down-weight easy examples and focuses training on hard negatives. Formally, the focal loss defines a modulating factor to the cross-entropy loss and a parameter for class balancing [84].

$$Loss_{FL}(p_t) = -\alpha_t(1 - p_t)^\gamma \log(p_t)$$

$$p_t = \begin{cases} p_t & \text{if } y_i = 1 \\ 1 - p_t & \text{otherwise} \end{cases} \quad (9)$$

where $y \in \{1, -1\}$ is the ground-truth class, and $p_t \in \{0, -1\}$ is the estimated probability for the class with label $y = 1$. The weighting parameter α deals with imbalanced dataset. The focusing parameter γ smoothly adjusts the rate at which easy examples are down-weighted. Setting $\gamma > 0$ can reduce the relative loss for well-classified examples. It places the focus on hard and misclassified examples; the focal loss is equal to the original cross-entropy loss when $\gamma = 0$.

- Augmentation techniques: Most of the time, a large number of labels for training are not available for several reasons. Labeling the dataset requires an expert in this field, which is expensive and time-consuming. Training large neural networks from limited training data causes the over-fitting problem. Data augmentation is a way to reduce over-fitting and increase the amount of training data. It creates new images by transforming (rotated, translated, scaled, flipped, distorted, and adding some noise such as Gaussian noise) the ones in the training dataset. Both the original image and created images are input to the neural network. For example, a large variety of data augmentation techniques include random rotations, random scaling, random

elastic deformations, gamma correction augmentation, and mirroring on the fly during training.

5.3 CNN Methods Classification for Tumor Segmentation

The classification of CNNs for tumor segmentation uses the combination of the design aspects as shown in the Fig. 9.

Input type: The network may take 2D/3D input in form of patches or images. The CNN with fully-connected layers classify the centre voxel of the patch whereas FCNN predicts multiple or all voxels of the patch/image. The network may take multi-scale patches to extract coarse and fine details of the input.

Output Type: The output of the network depends on the problem to solve. It predicts single output for the classification problem and multiple voxel output for the semantic segmentation problem.

Type of network: The CNN approach indicates the convolution network with fully-connected layers at the end whereas FCN indicates the network with all convolution layers.

Ensemble Approach: Ensemble approach can be classified into serial and parallel approaches. In the serial approach multiple networks combine in series to fine tune the end output. The input of one network depends on the output of the other. In the parallel approach multiple networks work in parallel and take the same/different input to gather the comprehensive details from the input. The final output of the network is decided based on the majority voting or averaging of all the network output.

The evolution of CNN based methods for the tumor segmentation is as shown in Fig. 10. Some of well-known CNN architectures for brain tumor segmentation are represented in Fig. 11, Fig. 12, Fig. 13 and Fig. 14.

The architecture of [54] is a two pathway CNN which takes 2D multi-resolution input patches, applies the convolution operations and concatenate the output of both the pathways. The deepmedic[70] also follows two pathways with 3D multi-resolution input patches and incorporates the residual connections and predicts the output for multiple voxels at a time.

U-net[121] is an encoder-decoder architecture with skip-connections between the peer layers of analysis and synthesis path. This architecture has gained most popularity. Anisotropic[142] architecture followed the serial ensemble approach. The first network segments whole tumor, second segments tumor core and considers the

output of first network and finally third network segments enhancing tumor with help of second network output.

Initially, shallow CNN performs the voxel-based image segmentation. The authors in [54] proposed voxel-wise classification using CNN multipath way architecture. One pathway uses 2D patches of size 32x32, and the other uses fully-connected input of 5x5 patch size having center pixel same as 32x32 patch. Patch selection was made such that the labels are equiprobable. L1 and L2 regularizations overcome overfitting. In [140], voxel-wise class probability prediction uses separate 3D CNNs for HGG and LGG images. The final probability classified the voxel into the six classes. In [157], five layers deep 2D CNN architecture performs voxel-wise classification.

Gradually the depth of CNN had increased to accommodate more layers in the network. In [108], 2D deep CNN with fully connected output layers separates HGG and LGG. This approach was further extended by [117] with the two-phase process along with a weighted loss function-initially, the network trains using equiprobable patches that follow actual patch training without the class imbalance problem. In [53], authors had designed 2D InputCascadedCNN, which took the output of TwoPathCNN to train other 2DCNN with the input images. After the successful implementation of FCN by the authors in [85], authors in [70] proposed two pathway architecture, where both pathways included residual connections and trained on the different input patch sizes. As the network was fully convolutional, multiple voxels of the input patch label at a time.

The [151], uses the 2D FCNN approach along with CRF. The FCNN trains on patches and CRF on slices. In [26], cascaded encoder-decoder like FCNNs along with residual connections. The first FCNN segments the whole tumor, followed by the internal tumor regions by the second FCNN. Authors in [90] had proposed encoder-decoder FCNN based architecture to segment various tumor sub-regions. In [21], authors had proposed three different FCNN architecture and showed that the architectures with multi-resolution features performed better compared to single-resolution architecture. Authors in [86] implemented Dilated Residual Network for patch based training where equiprobable patches were supplied to the network for training.

Authors in [41] adopted U-net architecture for brain tumor segmentation. Authors in [44] modified the U-net, which took 3D input, and the depth of the network reduces to three. Authors in [63], had optimized the training of the network proposed in their previous work [62]. In [27], authors had proposed novel encoder-

Fig. 9: Design aspects of CNN architectures.

Fig. 10: Variational growth of CNN for tumor segmentation.

Fig. 11: TwopathwayCascadedCNN Architecture[54].

Fig. 12: Deep Medic Architecture [70].

Fig. 13: U-net architecture[121].

Fig. 14: Anisotropic Cascaded Architecture[142].

decoder architecture that had worked well on multiple biomedical image segmentation problems. Various other CNN based approaches where single CNN was used for segmentation task were [107], [64], [124], [111], [23], [74], [22], [67], [58], [89], [102], [94].

The ensemble of CNNs performs better compared to single CNN, as in [71], where authors had implemented an ensemble of seven networks using DeepMedic, FCN, and U-net along with variations of those three networks. They also tried different three approaches for pre-processing on all these networks. The output of individual networks with all the pre-processing generates the final label. Authors in [91] had extended their work proposed in [90] where the dense module and dilated module were introduced in the encoder decoder cascaded architecture of two networks. The pooling layers were replaced with dilated convolution layers.

The authors in [101] had implemented the ensemble of ten encoder-decoder based architectures, which included the auto-encoder stream to reconstruct the original image for additional information and regularization purpose. Authors in [92] extended their approach proposed in [69]. They used a combination of U-net and Densenet with U-net like architecture containing dense

blocks of dilated convolution. The network of [151] was extended in [152] to create an ensemble of three networks which were trained on three image views. Two network cascaded path was used in [33], where Coarse Segmentation Network segmented WT and Fine Segmentation Network segmented the sub-regions of the network. Both the networks used 3D U-net with four level deep architecture.

Authors in [142] used three networks (WNet, TNet, and ENet) to prepare the cascaded path. The multi-scale prediction averages for the private network. These networks train on three-views of images (axial, coronal, sagittal), and results from averages to generate the final segmentation output. In [153], the cascaded network was proposed, which initially segmented the whole tumor followed by tumor core, and enhancing tumor segmentation refinement. In [79] authors had proposed cascaded UNet with three networks. The network processed downsampled input and generated output was passed to the next network in the cascaded sequence. Authors in [146] proposed multi-scale mask 3D U-nets with atrous spatial pyramid pooling layers, where WT segmentation generated by first networks was passed to the second for TC generation, which in sequence passed

to the final network to generate ET output. Other ensemble based CNN approaches were explained in [87], [73], [60], [143], [7], [31], [25], [147].

The comparison of the methods summarized in Table 8 is based on the pre-processing techniques, DNN architecture, activation function, loss function, post-processing, and DSC achieved. The pre-processing techniques considered for the comparison are:

1. Intensity Clipping: 1 % of highest and lowest frequencies are clipped.
2. Bias Field Correction.
3. Z-score normalization: $Z = (x - \mu)/\sigma$.
4. Histogram matching: Histogram of all the images is match with the reference histogram.
5. Image normalization: Min-max normalization.
6. Intensity standardization with Nyul approach [104].
7. Image denoising: applies noise filtering for e.g. Gaussian noise filtering.
8. Intensity rescaling : rescaling the intensity range between some specific limits.

The post-processing techniques used for segmentation result improvement are:

1. Connected Component Analysis: Analyse the connected components and removes the component with the volume below some threshold.
2. Conditional Random Field.
3. Morphological Operators to remove false positives and fill the holes
4. relabelling the output label: Enhancing tumor labels below some threshold are relabelled as necrosis.

Fig. 15 shows the pictorial representation of the DSC of various CNN methods for whole tumor segmentation. The average DSC of CNN is 0.86, deep CNN and FCN is 0.87, and for ensemble approach is 0.89. The ensemble of the CNNs/FCNNs learns the robust features from the input.

5.4 Hardware and Software for DNN

Hardware: DNN methods have gained its popularity after availability of the Graphical Processing Units (GPU). Nowadays efficient parallel processing for manipulation of large amount of data is applicable with help of General Purpose GPU(GPGPU). The computing libraries like CUDA and OpenGL allows the efficient implementation of the processing code on GPU. The performance of the GPU highly depends on GPU computing cores (CUDA cores), Tensor processing cores, Thermal Design Power (TDP), and on board GPU memory. Various types of GPUs used for the implementation of the CNN methods for segmentation task are as shown

in Table 7. As the computing capacity of the GPU increases, it allows more complex networks with higher number of network parameters to be trained with less time.

Table 7: GPU specifications[103].

Year	GPU Type	CUDA Cores	Tensor Cores	TDP (Watts)	RAM (GB)
2016	Tesla K80	2496	N/A	300	12
2016	GeForce GTX 980 Ti	2816	N/A	165	6
2016 - 2017	GeForce GTX 1080 Ti	3584	N/A	250	11
2017	GTX Titan X	3072	N/A	240	12
2018	Quadro P4000	1792	N/A	105	8
2018	Quadro P5000	2560	N/A	180	16
2018	Titan Xp	3840	N/A	250	12
2018	Tesla P100	3584	N/A	250	16
2018	Tesla V100	5120	640	300	16/32
2018	DGX-1	40960 (8xV100)	5120	3500	128(16 per GPU)

Software: The open software library packages provide implementation of various neural network operations like convolution. Most popular python library packages used for DNN method implementations are Caffe[68], Tensorflow[1], Theano[16], and PyTorch[106]. Some of the third-party packages which work on the top of these networks are Keras[30], Lasagne[39], and TensorLayer[40].

Table 8: Summarization of Segmentation methods using CNN architectures.

Ref.	Pre-processing	Input Modality + Augmentation	Patch/Image	Input view	Network Architecture	# works	Net-works	Ensemble Type	Loss Function	Post-processing	Dataset	DSC Mean
CNN												
[140]	5	T1, T2, T1c, FLAIR	3D patches	axial	3D CNN	1	-	-	Softmax	1	BraTS 2013	Challenge WT:0.87,TC:0.77,ET:0.73
[157]	2,downsampling	T1, T2, T1c, FLAIR	2D patches	axial	2D CNN	1	-	-	Softmax	-	BraTS 2013	Training WT:0.84,TC:0.74,ET:0.69
Deep CNN												
[108]	2, 6	T1, T2, T1c, FLAIR, Rotation at certain angles	2D patches	axial	2D CNN	2	-	-	Categorical Cross-Entropy		BraTS 2015	WT:0.87,TC:0.73,ET:0.68
[53]	1,2,3	T1, T2, T1c, FLAIR	2D multiscale patches	axial	2D CNN	4	-	cascaded, parallel	Softmax	1	BraTS 2013	Test Set WT:0.88,TC:0.79,ET:0.73
[117]	1,2,3	T1, T2, T1c, FLAIR, horizontal and vertical flipping	2D patches	axial	2D CNN	2	-	-	Weighted cross-entropy with L1 and L2 regularization	1	BraTS 2016	Test Set WT:0.87,TC:0.75,ET:0.71
FCNN												
[70]	3	T1, T2, T1c, FLAIR + with flipping around a midsagittal plane	3D multiscale patches	axial	3D FCNN	2	-	parallel	-	2	BraTS 2015	Without residual connections WT:0.90,TC:0.75,ET:0.72 With residual connection WT:0.90,TC:0.76,ET:0.72
[151]	1, 5	T1c, T2, FLAIR	2D multiscale patches	axial	2D FCNN	2	-	cascaded	-	1	BraTS 2013	Challenge: WT:0.87,TC:0.83,ET:0.76 Leaderboard: WT:0.86,TC:0.73,ET:0.62

Table8 – continued ...

Ref.	Pre-processing	Input Modality + Augmentation	Patch/Image	Input view	Network Architecture	# works	Net-works	Ensemble Type	Loss Function	Post-processing	Dataset	DSC Mean
[26]	5	T1, T2, T1c, FLAIR, Rotation at 45 degree, bias field corrected images, Additional Images	2D patches	axial	2D FCNN	2		cascaded	Softmax with L2 regularization	-	BraTS 2016	Challenge: WT:0.89,TC:0.83,ET:0.78
[90]	-	T1, T2, T1c, FLAIR	2D patches	axial	2D FCNN	1		-	sigmoid	-	BraTS 2012	Training WT:0.87,TC:0.69,ET:0.56
[21]	-	T1, T2, T1c, FLAIR	3D multiscale patches	axial	3D FCNN	2		parallel	Softmax	-	BraTS 2015	Training 3Dnet1 WT:0.90,TC:0.77,ET:0.63 3DNet2 WT:0.92,TC:0.70,ET:0.74 3DNet3 WT:0.92,TC:0.84,ET:0.77
[86]	5	T1, T2, T1c, FLAIR	2D patches	axial	2D FCNN	1		-	Dice Loss	-	BraTS 2017	Validation set: WT:0.78,TC:0.69,ET:0.57 Test set: WT:0.69,TC:0.61,ET:0.51
[107]	4	T1, T2, T1c, FLAIR	2D Images	axial	2D FCNN	1		-	Softmax	-	BraTS 2017	Validation set: WT:0.82,TC:0.63,ET:0.58 Test: WT:0.78,TC:0.58,ET:0.50
[64]	-	T2, FLAIR	2D Images	axial	2D FCNN	1		-	-	-	BraTS 2017	Validation: WT:0.88,TC:0.76,ET:0.69 Test: WT:0.86,TC:0.70,ET:0.62
[124]	3	T1, T2, T1c, FLAIR	2D Images	axial	2D FCNN	1		-	Dice loss + cross entropy	1,2	BraTS 2017	Validation set: WT:0.87,TC:0.68,ET:0.65 Test set: WT:0.83,TC:0.65,ET:0.65
[111]	2,4	T1, T2, T1c, FLAIR	2D Images	axial	2D FCNN	1		-	-	3,1	BraTS 2017	Validation set: WT:0.86,TC:0.60,ET:0.69 Test set: WT:0.80,TC:0.55,ET:0.55
[41]	3	T1, T2, T1c, FLAIR	2D Images	axial	2D U-net	1		-	Dice loss	-	BraTS 2015	Training: WT:0.86,TC:0.86,ET:0.65
[44]	1,2,3	T1, T2, T1c, FLAIR	3D patches	axial	3D U-net	1		-	-	-	BraTS 2017	WT:0.84,TC:0.75,ET:0.66
[67]	3	T1, T2, T1c, FLAIR	3D Images	axial	3D FCNN	1		-	Multi scale weighted loss	-	BraTS 2017	Validation set: WT:0.90,TC:0.75,ET:0.71 Test set: WT:0.86,TC:0.78,ET:0.71

Table8 – continued ...

Ref.	Pre-processing	Input Modality + Augmentation	Patch/Image	Input view	Network Architecture	# works	Net-works	Ensemble Type	Loss Function	Post-processing	Dataset	DSC Mean
[63]	3	T1, T2, T1c, FLAIR	3D patches	axial	3D FCNN	1	-	-	Weighted Dice loss + Cross-Entropy Loss	4	BraTS 2018	Validation set WT:0.91,TC:0.86,ET:0.81 Test set WT:0.88,TC:0.81,ET:0.78
[27]	-	T1, T2, T1c, FLAIR	2D Images	axial	2D FCNN	1	-	-	Cross-entropy loss	-	BraTS 2017	Training set WT:0.83,TC:0.73,ET:0.65
[73]	1,3	T1, T2, T1c, FLAIR	2D Images	axial	2D FCNN	1	-	-	Weighted cross entropy loss + generalized dice loss	-	BraTS 2018	Validation set: WT:0.87,TC:0.81,ET:0.78 Test set: WT:0.81,TC:0.73,ET:0.65
[130]	-	T1, T2, T1c, FLAIR	2D Images	axial	2D FCNN	1	-	-	Dice loss	-	BraTS 2018	Validation set: WT:0.90,TC:0.85,ET:0.79 Test set: WT:0.88,TC:0.79,ET:0.78
[57]	-	T1, T2, T1c, FLAIR	3D Images	axial	3D U-net	1	-	-	Cross-Entropy	-	BraTS 2018	Validation set: WT:0.86,TC:0.77,ET:0.72
[102]	5	T1, T2, T1c, FLAIR	3D Images	axial	3D FCNN	1	-	Softmax	-	BraTS 2018	Test set: WT:0.85,TC:0.68,ET:0.67	
Ensemble of CNNs												
[54]	1, 2 on (T1,T1c), 3	T1, T2, T1c, FLAIR	2D multiscale patches	axial	2D CNN	3	-	cascaded, parallel	softmax with L1 and L2 regularization	-	BraTS 2013	Training HGG/LGG WT:0.79,TC:0.68,ET:0.57 WT:0.81,TC:0.75,ET:0.54
[71]	3,2,5 and its different combination	T1, T2, T1c, FLAIR	3D multiscale patches	axial	3D FCNN	7	-	Parallel	-	1	BraTS 2017	Validation set WT:0.90,TC:0.80,ET:0.74 Test set WT:0.87,TC:0.79,ET:0.73

Table8 – continued ...

Ref.	Pre-processing	Input Modality + Augmentation	Patch/Image	Input view	Network Architecture	# works	Net-works	Ensemble Type	Loss Function	Post-processing	Dataset	DSC Mean
[152]	1, 5	T1c, T2, FLAIR	2D Images	axial, coronal, sagittal	2D FCNN	3		Parallel	-	1	BraTS 2017	Validation set: WT:0.89, TC:0.79, ET:0.75 Test set: WT:0.88, TC:0.75, ET:0.76
[101]	3, intensity scale, intensity shift, flip	T1, T2, T1c, FLAIR	3D Images	axial	3D FCNN	1		-	A weighted average of L2, Dice, KL	-	BraTS 2018	Validation Set WT:0.91, TC:0.87, ET:0.82 Test set WT:0.88, TC:0.82, ET:0.77
[92]	3 on the individual volume	T1, T2, T1c, FLAIR	2D Images	axial, coronal, sagittal	2D FCNN	3		Parallel	-	-	BraTS 2018	Validation set WT:0.90, TC:0.85, ET:0.80 Test set WT:0.89, TC:0.80, ET:0.73
[142]	3	T1, T2, T1c, FLAIR	3D patches	axial, coronal, sagittal	2D FCNN	3		Parallel of cascades	Dice Loss	-	BraTS 2017	Validation set WT:0.90, TC:0.83, ET:0.78 Test set WT:0.87, TC:0.77, ET:0.78
[153]	-	-	3D multi scale patches	axial	-	7		parallel	-	1, 4	BraTS 2018	Validation set ET:0.81, WT:0.91, TC:0.87 Testset ET:0.78, WT:0.88, TC:0.80
[79]	3,1	T1, T2, T1c, FLAIR	2D images	axial	2D FCNN	3		cascaded	Mean Dice Loss	-	BraTS 2018	Validation set WT:0.91, TC:0.84, ET:0.77
[146]	2,3	T1, T2, T1c, FLAIR	3D patches	axial	3D FCNN	3		cascaded	Cross entropy	-	BraTS 2018	Validation set WT:0.90, TC:0.83, ET:0.80
[91]	3	T1, T2, T1c, FLAIR	2D images	axial	2D FCNN	2		cascaded	Sigmoid	1	BraTS 2017	Validation set: WT:0.88, TC:0.76, ET:0.71 Test set: WT:0.86, TC:0.71, ET:0.71
[33]	5,3	T1, T2, T1c, FLAIR	3D patches	axial	3D FCNN	2		cascaded	Dice loss	-	BraTS 2017	Validation set: WT:0.86, TC:0.69, ET:0.66 Test set: WT:0.82, TC:0.67, ET:0.60
[23]	5	T1, T2, T1c, FLAIR	2D multiscale patches	axial	3D CNN	4		parallel	Softmax	-	BraTS 2017	Validation set: WT:0.88, TC:0.68, ET:0.71 Test set: WT:0.86, TC:0.67, ET:0.65
[74]	-	T1, T2, T1c, FLAIR	2D Images	axial, coronal, sagittal	2D U-Net	3		parallel	Dice Loss	-	BraTS 2017	Validation set: WT:0.88, TC:0.73, ET:0.75 Test: WT:0.86, TC:0.73, ET:0.72

Table8 – continued . . .

Ref.	Pre-processing	Input Modality + Augmentation	Patch/Image	Input view	Network Architecture	# works	Net-works	Ensemble Type	Loss Function	Post-processing	Dataset	DSC Mean
[22]	-	T1, T2, T1c, FLAIR	3D Images	axial	3D V-net	2		cascaded	weighted Dice + cross entropy	-	BraTS 2017	Validation set: WT:0.88, TC:0.64, ET:0.71
[58]	5	T1, T2, T1c, FLAIR	2D Patches	axial	2D U-Net	4		parallel to cascaded	Dice loss	-	BraTS 2017	Validation set: WT:0.85, TC:0.70, ET:0.65 Test set: WT:0.81, TC:0.69, ET:0.55
[89]	-	T2, FLAIR	2D Images	axial	2D U-Net	2		cascaded	Dice loss	-	BraTS 2018	Validation set: WT:0.90, TC:0.81, ET:0.75 Test set: WT:0.86, TC:0.73, ET:0.65
[87]	3,4,5	T2, FLAIR	3D Images	axial	3D FCNN	3		parallel to cascaded	Dice loss	-	BraTS 2018	Validation set: WT:0.87, TC:0.77, ET:0.74 Test set: WT:0.81, TC:0.73, ET:0.65
[143]	3	T1, T2, T1c, FLAIR + transformation and noise blurring	3D Images	axial	3D FCNN/Test time augmentation)	3		cascaded	Dice loss	-	BraTS 2018	Validation set: WT:0.90, TC:0.86, ET:0.80 Test set: WT:0.88, TC:0.80, ET:0.75
[7]	3	T1, T2, T1c, FLAIR	3D Patches	axial	3D FCNN	4		parallel	Dice loss	-	BraTS 2018	Validation set: WT:0.88, TC:0.78, ET:0.77 Test set: WT:0.85, TC:0.74, ET:0.72
[31]	8	T1, T2, T1c, FLAIR	2D Images	axial, coronal, sagittal	2D FCNN	18		parallel	-	-	BraTS 2018	Validation set: WT:0.88, TC:0.79, ET:0.71
[59]	5	T1, T2, T1c, FLAIR	2D Images	axial, coronal, sagittal	2D FCNN	3		parallel	-	-	BraTS 2018	Validation set: WT:0.88, TC:0.74, ET:0.69 Test set: WT:0.85, TC:0.72, ET:0.66
[94]	3, 8	T1, T2, T1c, FLAIR	3D Images	axial	3D U-net	5		parallel	weighted categorical cross entropy loss	-	BraTS 2018	Validation set: WT:0.91, TC:0.83, ET:0.79 Test set: WT:0.87, TC:0.77, ET:0.71

Table8 – continued ...

Ref.	Pre-processing	Input Modality + Augmentation	Patch/Image	Input view	Network Architecture	# works	Net-works	Ensemble Type	Loss Function	Post-processing	Dataset	DSC Mean
[25]	4	T1, T2, T1c, FLAIR	3D Images	axial	3D V-net	3	dice loss	parallel	generalized2 dice loss		BraTS 2018	Validation set: WT:0.90, TC:0.81, ET:0.77 Test set: WT:0.83, TC:0.73, ET:0.62
[147]	T1, T2, T1c, FLAIR	3D Images	axial, coronal, sagittal 3D FCNN	3	parallel	dice loss	-		BraTS 2018	Validation set: WT:0.88, TC:0.81, ET:0.78 Test set: WT:0.86, TC:0.77, ET:0.72		
[29]	2,4,8	T1, T2, T1c, FLAIR	3D Images	axial, coronal, sagittal	3D FCNN	3		parallel	multi class dice loss		BraTS 2018	Validation set: WT:0.89, TC:0.83, ET:0.75 Test set: WT:0.84, TC:0.78, ET:0.69
[113]		T1, T2, T1c, FLAIR	3D Images	axial	3D FCNN	2		parallel	categorical cross entropy		BraTS 2018	Validation set: WT:0.90, TC:0.77, ET:0.76 Test set: WT:0.86, TC:0.75, ET:0.69
[76]	3	T1, T2, T1c, FLAIR	2D Images + 3D multi resolution patches	axial	3D FCNN	3		parallel	-	2,1	BraTS 2018	Validation set: WT:0.89, TC:0.76, ET:0.76 Test set: WT:0.83, TC:0.72, ET:0.69

5.5 Proposed Architecture for Tumor Segmentation

The authors of the article have adopted 2D U-net architecture with three layers[3]. Each encoder layer is replaced with a dense module as shown in Fig 16. In the first phase, the network is trained for whole tumor for 50 epochs with dice loss function. Further the network parameters are initialized with whole tumor weights to train the network for necrosis, enhancing and edema subregions. The inductive transfer learning approach [105] for parameter initialization has reduced the false positives and boosted the network training convergence. In the second phase, these subregion weights are used as initial parameters to train the networks again for the same subregions using focal loss function. The network training continues for 50 epochs for each subregions. From the BraTS 2019 training dataset, 85% of the images are given for training and 15% are kept for validation. The input to the network is 2D slices of 240x240 size from all the four modalities. The blank slices of the dataset are removed as it does not contain any meaningful information. The following are the updates applied to the network:

- The bounding box is applied around the brain to reduce the input which contains zero intensity (blank) voxels.
- The convolution layer is added in the dense module.

The results for the network are in Table 9, which includes minor variations in the network, different input image sizes, different loss functions, and the number of images in training. The network is trained on 85% of the total image and validated on the remaining 15% images of the BraTS 2019 dataset. The online tool provided by the organizer generates the evaluation metric for the training set as well as a separate validation set in addition to the training set.

The DSC comparison of training and validation sets for these variations are as shown in Fig. 17. The segmentation results show that the method overfits the training data and does not generate good results for the unknown validation set. The segmentation results of the sample images from the training set for correct as well as incorrect segmentation are shown in Fig. 18 and Fig. 19. The network does not distinguish between the subregions where the tumor appearance is homogeneous for all its subregions and intensity is same as the normal brain tissues.

5.6 End to End methods for tumor segmentation and OS prediction

Since 2017, the second task of survival prediction was introduced in the challenge. Some of the methods had participated in end-to-end solutions in the challenge, i.e., segmentation followed by survival prediction.

In [125], an ensemble of RF and CNN segments the tumor and random forest regressor(RFR) was used to predict the overall survival days using 240 features out of 1366 different features (Kaplan-Meier was used to find the relevant and useful features). Authors in [69] had modified U-net with Full Resolution Residual Network(FRRN) and Residual Unit(RU) units along with weight scaling dropout. The survival prediction ANN worked with linear activation function on four selected features.

The variant of U-net was used in [62], which took 3D input and included context module and localization module in each level of the architecture. The segmentation result was generated based on the element-wise summation of the output from the decoder layers. Survival prediction was the average of RFR and multilayer perceptron(MLP). RFR trains on 517 features extracted from three tumor sub-regions using the radiomics package[141]. The output of RFR and MLP averages 15 MLPs design with three hidden layers, each with 64 neurons.

Authors in [9] implemented 3D U-net with three stages of encoder-decoder architecture. Regression model based radiomics features selection trains MLP for OS prediction. Whereas in [144], two 3D U-nets uses four-stage encoder-decoder architecture, the first network segmented the whole tumor, and the second one segmented the tumor sub-region. In addition to four conventional modalities, they used the additional image as an input, which is the T1c-T1 subtracted image. This image provides additional information for the tumor core region. They used only the age feature was used to predict OS using linear regressor. The approach presented in [83] used FCNN named FCRN-101, which derives from pre-trained SegNet and U-net architecture. Three path network combines the result of three views, i.e., axial, coronal, and sagittal. The OS prediction used SPNet, the fully-connected CNN, which took four modalities and the network segmentation result as input to predict the probability of OS prediction.

The [45], uses an ensemble of six 3D U-net type networks with variation in the input size, number of encoding/decoding blocks, and feature maps at every layer. The OS prediction uses linear regression with ground truth image volume, surface area, age, and resection status. Features were input to the network after z-score

Fig. 15: DSC comparison for whole tumor segmentation of CNN methods.

Fig. 16: Three stage U-net architecture [3].

normalization. Authors in [114] had implemented FCN and generated results for three axes and used majority voting to generate the final segmentation results. For OS prediction, ten features (focusing on necrosis and active tumor) from the segmentation results were generated, and mean PCA and standard deviation PCA to train RF on the GTR images.

In [133] an ensemble of three networks (U-net[121], DFKZNet[62], and CA-CNN[142]) was used, and majority voting applied for final segmentation. The OS prediction used RF with 14 radiomics features selected from various modality images, Laplacian of Gaussian Images and wavelet decomposed images. Authors in [6] had implemented 2D U-net architecture with three stages for tumor segmentation and age, volumetric, and shape features of the whole tumor were used to predict OS.

All the approaches did not use the location-based information of the tumor and its sub-regions. In contrast, [72], uses twenty-one brain parcellation regions as an input along with the four MR modalities. It emphasizes the number of tumor regions in those specific parcellation areas. Those twenty-five input channels were given as input the ensemble of 3D U-net as well as the ensemble of DeepMedic architectures with different kernel and input patch sizes. Tractographic features from network segmented regions trains SVM classifiers with the linear kernel to predict OS. Authors in [3] implements 2D U-net of three stages with dense blocks at every encoder level, and the feature set of [6] of necrosis tumor sub-region for OS prediction.

The authors in [128] combines the features from VGG16 based FCN and texton maps to generate the features and supply them to RF classifier to generate the segmentation result. RF is also used for OS pre-

Table 9: Comparison of model variations of [3].

Model	Architectural change	Input Modalities	# Feature maps	Input image size	Loss function	DSC Training Set	DSC Validation Set
1	Original	T1, T1c, T2, FLAIR	32, 64, 128, 64, 32	240 x 240	Dice Loss	WT:0.90 TC:0.86 ET:0.75	WT:0.72 TC:0.63 ET:0.55
2	Original	T1, T1c, T2, FLAIR	32, 64, 128, 64, 32	156 x 200	Dice Loss	WT:0.90 TC:0.86 ET:0.75	WT:0.72 TC:0.63 ET:0.55
3	dense module + convolution layer	T1, T1c, T2, FLAIR	32, 64, 128, 64, 32	156 x 200	Dice Loss	WT:0.89 TC:0.84 ET:0.71	WT:0.71 TC:0.61 ET:0.56
4	dense module + convolution layer	T1, T1c, T2, FLAIR	32, 64, 128, 64, 32	156 x 200	Focal Loss	WT:0.93 TC:0.90 ET:0.83	WT:0.75 TC:0.65 ET:0.60
5	dense module + convolution layer	T1c, T2, FLAIR	32, 64, 128, 64, 32	156 x 200	Dice Loss	WT:0.87 TC:0.81 ET:0.67	WT:0.71 TC:0.58 ET:0.51
6	dense module + convolution layer	T1c, T2, FLAIR	32, 64, 128, 64, 32	156 x 200	Focal Loss	WT:0.92 TC:0.89 ET:0.79	WT:0.76 TC:0.66 ET:0.60

(a)

(b)

(c)

Fig. 17: DSC comparison for training and validation set
a) whole tumor b) tumor core c) enhancing tumor.

diction using volumetric as well as age feature of the patient.

Authors in [154], [60], [65], [37] attempts the end-to-end segmentation approach.

Table 10 compares the segmentation results of end-to-end methods. The approaches for pre-processing and post-processing techniques are as specified in section 5.3 and Table 11 provides details related to the survival prediction.

Fig. 18: Training set image, correct segmentation a) Original FLAIR image b) ground truth segmentation c) model 1 d) model 2 e) model 3 f) model 4 g) model 5 h) model 6.

Fig. 19: Training set image, incorrect segmentation a) Original FLAIR image b) ground truth segmentation c) model 1 d) model 2 e) model 3 f) model 4 g) model 5 h) model 6.

Table 10: End-to-end Methods, Task 1: Brain Tumor Segmentation.

Ref.	Pre-processing	Input Modality + Augmentation	Patch/Image	Input view	Network Architecture	# Net-works	Ensemble Type	Loss Function	Post-processing	Dataset	DSC Mean
[83]	6	T1, T2, T1c, FLAIR	2D Images	axial	2D FCNN	3	Parallel	Weighted Focal Loss	-	BraTS 2017	Validation ET:0.75, WT:0.88, CT:0.71 Test set ET:0.69, WT:0.88, TC:0.71
[62]	3 followed by clipping and scaling	T1, T2, T1c, FLAIR	3D patches	axial	3D FCNN	1	-	Weighted Dice loss	-	Brats 2017	Validation set WT:0.90, CT:0.80, ET:0.73 Test set WT:0.86, TC:0.78, ET:0.65
[125]	2,3	T1, T2, T1c, FLAIR	2D Patches	axial	2D CNN + Random Forest	1	-	Softmax	-	BraTS 2017	HG Testset ET:0.73, WT:0.83, TC:0.72
[69]	-	T1, T2, T1c, FLAIR	2D Images	axial	2D FCNN	1	-	-	-	BraTS 2017	Validation set WT:0.90, TC:0.79, ET:0.75 Test set WT:0.87, TC:0.74, ET:0.67
[128]	1,3,4	T1, T2, T1c, FLAIR	2D Images	axial	2D FCNN	1	-	-	-	BraTS 2017	Validation: ET:0.66, WT:0.86, TC:0.78 Test ET:0.67, WT:0.85, TC:0.69
[154]	4,5	T1, T2, T1c, FLAIR	2D + 3D Patches	axial	2D FCNN	5	cascaded to parallel	-	1,4	BraTS 2017	Training: ET:0.73, WT:0.88, TC:0.72
[45]	2,7	T1, T2, T1c, FLAIR, Random Flip	3D Patches	axial	3D FCNN	6	parallel	Weighted Uniform Loss	-	BraTS 2018	Validation set WT:0.91, TC:0.84, ET:0.79
[114]	8	T1, T2, T1c	2D Images	axial	FCNN	1	-	Softmax	3	BraTS 2018	Training set WT:0.82
[133]	3, random flipping, gaussian noise	T1, T2, T1c, FLAIR	3D Images	axial	FCNN	3	parallel	-	-	BraTS 2018	Validation set ET:0.81, WT:0.91, TC:0.85 Test set ET:0.72, WT:0.88, TC:0.80

Table 10 – continued ...

Ref.	Pre-processing	Input Modality + Augmentation	Patch/Image	Input view	Network Architecture	# works	Net-works	Ensemble Type	Loss Function	Post-processing	Dataset	DSC Mean
[9]	2,3	T1, T2, T1c, FLAIR	3D Patches	axial	3D FCNN	1	-	-	-	1,3, false positives removal	BraTS 2018	Validation set ET:0.75, WT:0.88, TC:0.83 Test set ET:0.67, WT:0.85, TC:0.77
[144]	3	T1, T2, T1c, FLAIR, (T1c-T1)	3D patches	axial	3D FCNN	2	-	cascaded	Dice loss	-	BraTS 2018	Validation set ET:0.71, WT:0.89, TC:0.76 Test set ET:0.62, WT:0.84, TC:0.73
[72]	-	T1, T2, T1c, FLAIR, 21 binary brain parcellation images	3D patches	axial	3D FCNN	26	-	parallel	-	-	BraTS 2018	Validation set ET:0.79, WT:0.91, TC:0.81 Test set ET:0.75, WT:0.88, TC:0.79
[60]	2,4,8	T1, T2, T1c, FLAIR	3d Images	axial	3D FCNN	5	-	parallel to cascaded	Focal loss	1	BraTS 2018	Validation: ET:0.77, WT:0.90, TC:0.84 Test: ET:0.74, WT:0.87, TC:0.80
[14]	-	T1, T2, T1c, FLAIR	2D Images	axial, coronal, sagittal	2D FCNN	3	-	parallel	Weighted cross entropy + generalized dice loss	-	BraTS 2018	Validation: ET:0.77, WT:0.88, TC:0.80 Test: ET:0.74, WT:0.87, TC:0.80
[65]	3	T2, T1c, FLAIR	2D Images	axial	2D FCNN	1	-	-	-	-	BraTS 2018	Validation: ET:0.77, WT:0.90, TC:0.83 Test: ET:0.70, WT:0.87, TC:0.77
[37]	1,3	T1, T2, T1c, FLAIR	3D Images	axial	2D FCNN	9	-	parallel	confusion loss + multi class dice loss	1,3	BraTS 2018	Validation: ET:0.81, WT:0.91, TC:0.85 Test: ET:0.74, WT:0.87, TC:0.79
[6]	3	T1, T2, T1c, FLAIR	2D Images	axial	2D FCNN	1	-	-	Dice	-	BraTS 2018	-
[3]	3	T1, T2, T1c, FLAIR	2D Images	axial	2D FCNN	1	-	-	Focal loss	-	BraTS 2019	Validation set ET:0.59 WT:0.73 TC:0.63

Table 11: End-to-end Methods, Task 2: OS Prediction.

Ref.	Method	# features/type of network	Dataset	Accuracy (%)
[83]	2D CNN	-	BraTS 2017	Valid:55 Test:45
[62]	RFR and MLP	66	BraTS 2017	52.6
[125]	RFR	240	BraTS 2017	Valid:66.7 Test:57.9
[69]	ANN	4	BraTS 2017	Valid:42.4 Test:56.8
[45]	Linear Regression Model	9	BraTS 2018	Valid:32.1
[114]	PCA + RF	10	BraTS 2018	Test:61
[133]	RF	14	BraTS 2018	Valid:46.4 Test:61 Second Rank
[9]	MLP	468	BraTS 2018	Valid:57.1 Test:55.8
[144]	Linear Regressor	1	BraTS 2018	Valid:50 Test:55.8
[72]	SVM with linear kernel	-	BraTS 2018	Valid:35.7 Test:41.6
[6]	RF	13	BraTS 2018	59
[3]	RF	13	BraTS 2019	Valid:58.6 Test:57.9
[128]	RF	4	BraTS 2017	Valid:48.5 Test:41.1
[154]	CNN+XBoost	183 CNN features +	BraTS 2017	Training:63.3
[60]	ensemble of Xboost, SVM, MLP, DT, RF, LDA	900	BraTS 2018	Test:51.9
[14]	MLP	83	BraTS 2018	Valid:54
[65]	ANN	50	BraTS 2018	Valid:67.9 Test:46.8
[37]	Xboost	195	BraTS 2017	Valid:50

6 Limitations of tumor segmentation and OS prediction

The tumor segmentation result depends on the architectural design (from shallow CNN to the ensemble/cascaded

CNN), amount of training data, input pre-processing, type of input(2D/3D), network optimization as well as post-processing of the generated output. Still, the DL methods have certain limitations, which include:

- Over-fitting: The common problem of the DNN based approach is over-fitting. It may occur due to the unavailability of the ample amount of labeled training data for brain tumor segmentation, which refers to a model that has an excellent performance on the training dataset but does not perform well on new data. The over-fitting problem can be handled either by reducing the network complexity (in terms of network layers and parameters) or by generating an ample amount of training data using image augmentation techniques. The augmentation techniques produce new images by performing data transformations and the corresponding ground truth that includes operations of scaling, rotation, translation, brightness variation, elastic deformations, horizontal flipping, and mirroring.
- Class imbalance: Class imbalance is another issue in tumor segmentation where the background class dominates the foreground class(tumor). Class imbalance can be handle by proper training data sampling, improved loss functions, and augmentation techniques.

The highest reported accuracy for the survival prediction task does not exceed 63% [45]. It is due to the dependency on the extraction of the features on the segmentation results. The incorrect segmentation results in wrong feature extraction for survival prediction. The biological importance of the extracted features also plays an important role. If the relevance of the features is not known correctly, the survival prediction cannot be accurate. Besides, the importance of tumor sub-regions plays a role in feature extraction. The dataset includes all the pre-operative scans and does not give any other information like the success of tumor removal, post-operative treatments to the patients, and the response of the patients to such treatments. Chances of tumor reoccurrence are high if the patient is exposed to the radiation environment. Features related to it may further improve the OS prediction.

7 Discussion and Future Direction

The availability of benchmark dataset(BraTS) has grown the field of computer-assisted medical image analysis for brain tumor segmentation. The article covers detailed literature survey for brain tumor segmentation techniques. The tumor segmentation is approached with various techniques like semi-automated and automated

methods. The semi-automated methods works on the input provided by user. Such methods suffer from limitations like manual seed point selection, atlas creation. Methods were gradually improved to include machine learning techniques like clustering, RF, ANN. The limitation of such methods is the selection of the features for training, which requires the knowledge of biological information of the image. The need of domain knowledge is removed by CNNs - deep neural network. CNN extracts high level features at deeper layers successively from the low level features from the preceding layers. This feature learning has improved the performance of CNN for tumor segmentation. The improvements to CNN are its variants, FCNN and ensemble of CNN/FCNN. The detailing of all the methods along with pre-processing, post-processing, prominent highlight of the methods and evaluation measure is given in Table 5, Table 8, Table 10 and Table 11.

The ensemble generates robust segmentation results as well as improvements in the accuracy of the network. All these methods generate spurious segmentation results, which improves with the help of post-processing techniques like connected component analysis, spatial regularization and morphological operations to fine-tune the output. The class imbalance is the primary concern in the training of CNN for medical image analysis. The balanced input selection and loss function for a positive class will resolve the issue. Due to the unavailability of less amount of data for training, it may be possible that the network overfits the training data. The regularization and dropout resolve such issues. Moreover, as Bayesian CNN[127] handles epistemic and aleatoric uncertainties in the presence of limited data and knowledge, such type of network is useful for semantic segmentation. Adaptive loss[15], approximates varieties of loss functions with single latent variable. This function can further be thought of to solve the problem of semantic segmentation. Despite the popularity such methods have following limitations:

- computational efficiency
- memory requirement: As the depth of the network increases, the number of network parameters increases. This increase in the parameter requires additional memory as well as time to tune those on each epoch.
- Ample amount of annotated training data requirement: The annotated data generation is itself a challenge as this process is very time consuming and the annotation results may change depending on variability of the expert. In addition specific annotation tools are required by the expert for proper delineation and annotation purpose. In place of voxel annotation, image labeling for presence/absence of tumor is less time consuming, does not require much

expertise and specialized annotation tool. Use of these image labeling in addition to the voxel labeling may help the network to learn relevant features for segmentation with less annotated data.

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