Predicting MGMT Promoter Methylation in Brain Tumors

Project-II (EC47007) report submitted to

Indian Institute of Technology Kharagpur

in partial fulfilment for the award of the degree of

Bachelor of Technology

in

Electronics and Electrical Communication Engineering

by

Gunda Venkata Shanmukha Sainath

(19EC10026)

Under the supervision of

Professor Jayanta Mukhopadhyay

IIT Kharagpur

Computer Science and Engineering

Indian Institute of Technology Kharagpur

Autumn Semester, 2022-23

April 13, 2023

DECLARATION

I certify that

(a) The work contained in this report has been done by me under the guidance of my supervisor.

(b) The work has not been submitted to any other Institute for any degree or diploma.

(c) I have conformed to the norms and guidelines given in the Ethical Code of Conduct of the Institute.

(d) Whenever I have used materials (data, theoretical analysis, figures, and text) from other sources, I have given due credit to them by citing them in the text of the thesis and giving their details in the references. Further, I have taken permission from the copyright owners of the sources, whenever necessary.

Date: April 13, 2023 (Gunda Venkata Shanmukha Sainath)
Place: Kharagpur (19EC10026)

COMPUTER SCIENCE AND ENGINEERING
INDIAN INSTITUTE OF TECHNOLOGY KHARAGPUR

CERTIFICATE

This is to certify that the project report entitled "**Predicting MGMT Promoter Methylation in Brain Tumors**" submitted by **Gunda Venkata Shanmukha Sainath** (Roll No. 19EC10026) to Indian Institute of Technology Kharagpur towards partial fulfilment of requirements for the award of degree of Bachelor of Technology in Electronics and Electrical Communication Engineering is a record of bona fide work carried out by him under our supervision and guidance during Autumn Semester, 2022-23.

Date: April 13, 2023
Place: Kharagpur

Professor Jayanta Mukhopadhyay
Computer Science and Engineering
Indian Institute of Technology Kharagpur

Abstract

Name of the student: **Gunda Venkata Shanmukha Sainath** Roll No: **19EC10026**

Degree for which submitted: **Bachelor of Technology**

Department: **Computer Science and Engineering**

Thesis title: **Predicting MGMT Promoter Methylation in Brain Tumors**

Thesis supervisor: **Professor Jayanta Mukhopadhyay**

Month and year of thesis submission: **April 13, 2023**

It has been demonstrated that the presence of a certain genetic sequence in the tumor known as MGMT promoter methylation is a positive prognostic factor and a reliable indicator of treatment response. In this work, we explored Deep Learning (Integrating Segmentation and Classification task), Radiomics (Radiomics feature extraction followed by feature selection and classification), and Ensemble (utilizing feature vectors of both Deep Learning and Radiomics methods) approaches. We used [17] Segmentation model for the Deep Learning approach and explored different feature selection methods and classifier models for the Radiomics approach. All the proposed methods are trained and evaluated on the RSNA-ASNR-MICCAI BraTS 2021 challenge dataset and submitted our predictions to the challenge.

Acknowledgements

I would like to thank my supervisor, Prof. Jayanta Mukhopadhyay, for allowing me to work under his guidance, who gave me constructive advice throughout the course of my B.Tech project. He was always understanding and helpful. I would like to thank Mr. Surajit Kundu, Ph.D. scholar who helped me in this project whenever I was stuck, it would not have been possible to do this project without him.

I would also like to give my warmest thanks to my family and friends at IIT Kharagpur for their constant support and motivation throughout the course of my work.

Contents

List of Figures

List of Tables

Chapter 1

Introduction

Glioblastoma is the most frequent malignant primary tumor in the brain, constituting 60% of adult brain tumors [34]. It has a very poor prognosis, with a median survival of less than a year. The current standard of care entails alkylating chemotherapy with temozolomide, radiation, and surgical resection. A DNA repair enzyme is called MGMT (O[6]-methylguanine-DNA methyltransferase). Chemotherapy resistance to alkylating drugs is caused by this enzyme's ability to protect tumor cells from harm caused by alkylating agents. Reduced MGMT protein expression from epigenetic silencing of the MGMT gene caused by promoter methylation may boost therapeutic sensitivity.

Surgery is necessary to remove a tissue sample for genetic analysis of malignancy. The process of identifying the tumor's genetic makeup can thereafter take many weeks. Depending on the outcomes and the initial therapy method used, more surgery may be required. The number of procedures and the type of therapy needed may both be reduced if a reliable approach for predicting the genetics of cancer by imaging (radiogenomics) alone could be created. Patients with methylated MGMT promoters have a median survival rate of 21.7 months, as opposed to 12.7 months

for those with unmethylated MGMT. Glioma molecular and genetic abnormalities are typically discovered by invasive techniques like biopsy or open surgical resection. This requires a lot of the caregiver's time and work and also increases the infection risk from a patient level.

The Medical Image Computing and Computer Assisted Intervention Society (the MICCAI Society) and the Radiological Society of North America (RSNA) have partnered to enhance glioblastoma patient diagnosis and treatment planning. The RSNA-ASNR-MICCAI BraTS 2021 challenge [5] contains two tasks: Tumor segmentation and the MGMT methylation prediction from preoperative magnetic resonance (MR) images. The challenge organizers have released a large dataset with the goal of facilitating comparison between methods and advancing state-of-the-art methods in these domains. In this paper, we focus on the prediction task and show how segmentation task output can be utilized for the MGMT Methylation prediction task.

We proposed the following methods for this task:

- **Deep Learning**: Combining both segmentation and classification tasks by adding Classification functionality to the existing Segmentation model. We used [17] for this method.
- **Radiomics**: Extracting radiomics features from different segmentation parts of the Tumor using the pyradiomics library [37] which are then filtered out using several feature selection techniques. These features are then used to train various Machine Learning Classifier algorithms.
- **Ensemble**: Feature vectors from the above 2 methods are concatenated and a Machine Learning Classifier is trained on them to predict the MGMT Promoter methylation presence.

Chapter 2

Related Work

There are many ways of detecting the presence of MGMT Promoter Methylation. Two broadly used techniques are reviewed in this study.

- **Radiomics Features Based Approach**: Extracting shape-based and various texture-based features [37] like GLCM, GLRM, GLDM, GLSZM using segmentation mask and one of the four modalities (more about this in Chapter 3). Later these features are used to train a Machine Learning model.
- **Deep Learning Approach**: Each modality can be considered as a 3D image. State-of-the-art CNN models like VGG [32], ResNet [18], and EfficientNet [33] can be used in 3D image regime to solve this binary classification task. Some of the approaches first perform tumor segmentation and classification sequentially.

2.1 Radiomics Features

Korfiatis et al. [23] used a semi-automatic way to generate tumor segmentation masks from T1CE which are reviewed using ITKsnap [39] software. All shape and texture-based features were extracted and used to train SVM [19] and Random Forest [6] Classifiers. Zhi Cheng Le et al. [24] introduced the idea of a multi-centric approach where radiomics features are extracted from multiple tumor subregions. Mann-Whitney U test [27] was used to select the most important features. Yiping Lu et al. [25] used radiomics features extracted from T1CE and Visually Accessible Rembrandt Images (VASARI) features to train Machine Learning Model. Daniel Alber et al. [2] used DeepBraTumIA software to obtain a segmentation mask which is used to generate radiomics features from different possible sub-regions of tumors. Duyen Thi Do et al, [11] used a two-stage feature selection process using the XGBoost [8] feature selection model followed by a genetic algorithm (GA)-based wrapper model.

2.2 Deep Learning

Deep Learning has shown success in the field of Radiology. Tasks like Segmentation, Classification in the healthcare sector have used Deep Learning approaches which have shown incredible improvement and are used in production. Xin Chen et al. [9] used VAE-type architecture where both segmentation and VAE tasks used the same decoder and finally used decoder and segmentation outputs for the classification task. Yogananda et al. [38] introduced MGMT-net which performs voxel-wise classification of MGMT Promoter status. This generates two volumes which are then combined using the Dual Volume Fusion method on which a majority voting

technique is applied to predict MGMT Promoter methylation. Aleksandr Emchinov [13] used 3D ResNet and Quoc-Huy Trinh et al. [35] used 3D EfficientNet to solve the MGMT Promoter Methylation prediction task. Walia Farzana et al. [14] introduced the idea of Bayesian Optimization to tune hyperparameters of 3D CNN architecture. Numan Saeed et al. [31] experimented with different 3D CNN architectures like ResNet [18], DenseNet [20], EfficientNet [33] and Vision Transformers [12]

2.3 Ensemble

There are few approaches that used both Radiomics features and Deep Learning approaches. Sveinn Palsson et al. [29] combine the use of radiomics with shape features learned by a variational autoencoder (VAE), implemented with deep neural networks. Training the VAE on tumor segmentations will help to extract complex tumor shape features that radiomics does not include. Siman Doran et al. [26] used 3D EfficientNet to extract features from MRI which are then concatenated with Radiomics features. These concatenated features are used to classify the MGMT Promoter status.

Chapter 3

Data Analysis

3.1 BraTS Challenge

Brain Tumor Segmentation (BraTS) challenge is an annual competition conducted by Medical Image Computing and Computer-Assisted Intervention Society (MICCAI Society) to assess state-of-the-art machine learning methods used for brain tumor image analysis in Multi-parametric Magnetic Resonance Imaging (mpMRI) scans. BraTS 2021 was jointly conducted by The MICCAI Society, the Radiological Society of North America (RSNA), and the American Society of Neuroradiology (ASNR) and had two tasks. Task 1 focuses on the Segmentation problem, segmenting heterogeneous brain glioblastoma sub-regions in mpMRI scans. Task 2 focuses on evaluating methods predicting MGMT Promoter methylation status.

3.2 Data

The organizers of the BraTS 2021 challenge has released two separate datasets for the 2 tasks.

3.2.1 Segmentation task

The dataset of the segmentation task is divided into training, validation, and testing data. Each independent case has a dedicated folder containing four mpMRI scans in nii.gz format. Only training data has an extra segmentation label with the same extension. Validation data is released publicly to allow participants to obtain preliminary results on unseen data. Final rankings are given based on the performance of the approach on unseen testing data which is not available publicly. Training data has mpMRI scans of 1262 patients, validation data has scans of 219 patients, and 570 cases for the final testing.

3.2.2 Classification Task

The dataset of the classification task has the same structure as that of the segmentation task but all the mpMRI scans are in DICOM format. There are no segmentation labels provided for any data type. Training data has mpMRI scans of 585 patients and validation data has scans of 87 patients. It is mentioned that the final ranking is done on data which 5x times that of validation data. Training and Validation data of the classification task are subsets of corresponding datasets of the Segmentation task.

3.3 Sample Analysis

Each scan folder has 4 mpMRI scans which are known as modalities T1, T2, T1CE, and FLAIR. These modalities capture characteristics of the underlying anatomy and all these modalities differ in contrast and function. Each modality provides

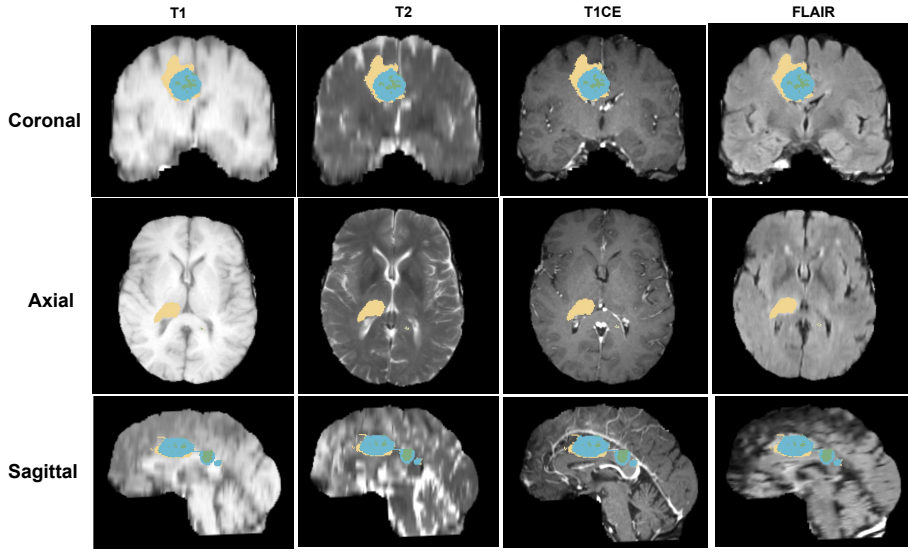

FIGURE 3.1: Sample mpMRI scan. Each row represents different views and each column represents one modality highlighting tumor regions

an intrinsic view of MR parameters. These images were rigidly registered, skull-stripped, and resampled to $1 \times 1 \times 1$ mm isotropic resolution with an image size of $240 \times 240 \times 155$. Each modality can be viewed in different planes: Axial (across 3rd channel), Coronal (across 2nd channel), and Sagittal (across 1st channel).

Four distinct tumoral subregions are present in a mpMRI sequence: the enhancing tumor (ET), which corresponds to the area of relative hyperintensity in the T1CE with respect to the T1 sequence; the non-enhancing tumor (NET) and the necrotic tumor (NCR) which are both hypo-intense in T1CE when compared to T1 and the peri-tumoral edema (ED) which is hyperintense in the FLAIR sequence. These homogeneous subregions (almost) can be clustered together to compose three meaningful tumor subparts: ET is the first cluster, and the addition of ET, NET, and NCR represents the "tumor core" (TC) region and the addition of ED to TC represents the "whole tumor" (WT). The dataset provided by BraTS contains these segmentation clustered labels. Figure 3.1 shows a sample scan in different views and highlights different segments of the tumor.

Chapter 4

Proposed Methodology

4.1 Deep Learning

In Chapter 2 we can see that the majority of Deep Learning approaches uses a model only for the classification task. In this work, we investigated whether an existing segmentation model can help solve both BraTS classification and segmentation tasks in one go without affecting segmentation performance. We used [17] for this approach.

Swin UNEt TRansformers (Swin UNETR) reformulated the task of 3D brain tumor semantic segmentation as a sequence-to-sequence prediction problem wherein multi-modal input data is projected into a 1D sequence of embedding and used as an input to a hierarchical Swin transformer as the encoder. The Swin transformer encoder extracts features at five different resolutions by utilizing shifted windows for computing self-attention and is connected to an FCNN-based decoder at each resolution via skip connections. We used MONAI's [7] SwinUNETR implementation for our task.

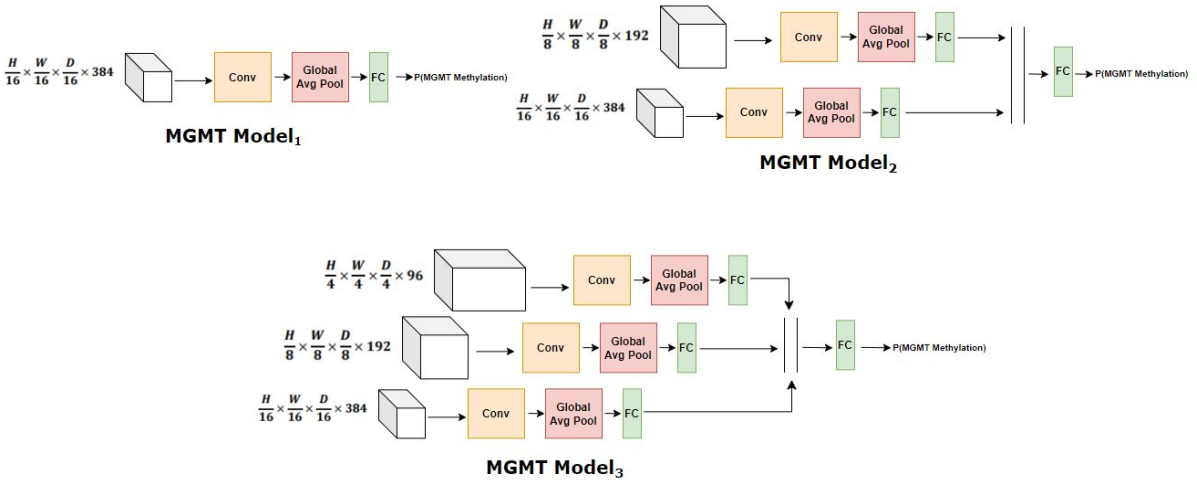

FIGURE 4.1: MGMT Models Architecture

We have added a Convolutional layer followed by Global Average Pooling and a Fully connected layer on top of the Swin Transformer encoder. This is denoted as *MGMT model*. Different MGMT Model architectures experimented on are shown in figure 4.1. For architecture with more than one MGMT model, we concatenate their outputs and add a Classifier layer on top of them. Figure 4.2 shows the model architecture of **SwinUNETR + MGMTModel$_3$**. We have added Dice Loss from the segmentation task and Cross Entropy Loss from the classification task using a hyperparameter α. The loss function is as follows:

$$L_{DL} = \alpha * L_{BCE} + (1 - \alpha) * L_{Dice} \tag{4.1}$$

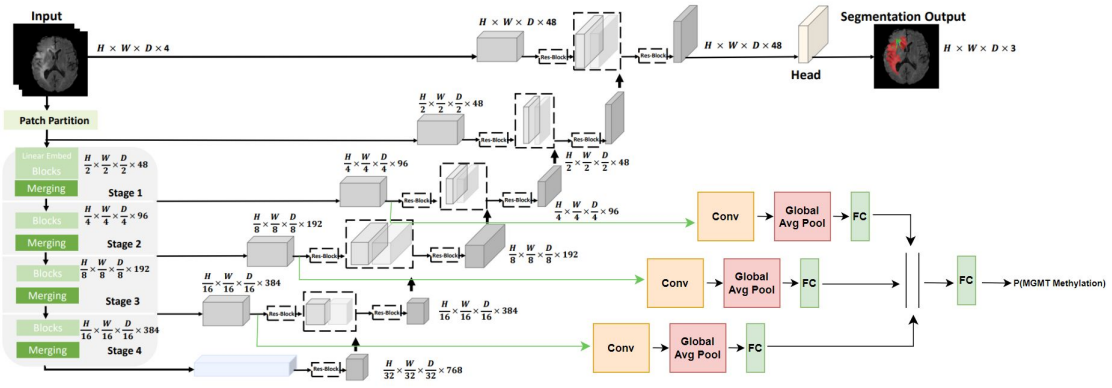

FIGURE 4.2: Deep Learning Approach (SwinUNETR + MGMTModel_3)

4.2 Radiomics

4.2.1 Feature Extraction

Radiomics features are hard-coded engineered features that are obtained based on expert domain knowledge. In the case of the Brain mpMRI scan features are broadly divided into 7 types: shape descriptors, first-order statistics, gray-level co-occurrence matrix (GLCM), gray-level size zone matrix (GLSZM), gray-level dependence matrix (GLDM), gray-level run length matrix (GLRLM), and neighboring gray-tone difference matrix (NGTDM). We use pyradiomics [37], an open-source python library to extract features from mpMRI scans. Given any modality scan and segmentation mask, pyradiomics gives all the features mentioned above as output. For each pair of segmentation labels, modalities 120 features are generated, of which 75 are numeric and relevant. These 75 features are extracted for all the 16 possible pairs and features that are constant over all the patient scans are removed. Figure 4.3 shows the overview of feature extraction implementation. For validation data, we used pre-trained 3D-ESPNet [28] to obtain segmentation masks.

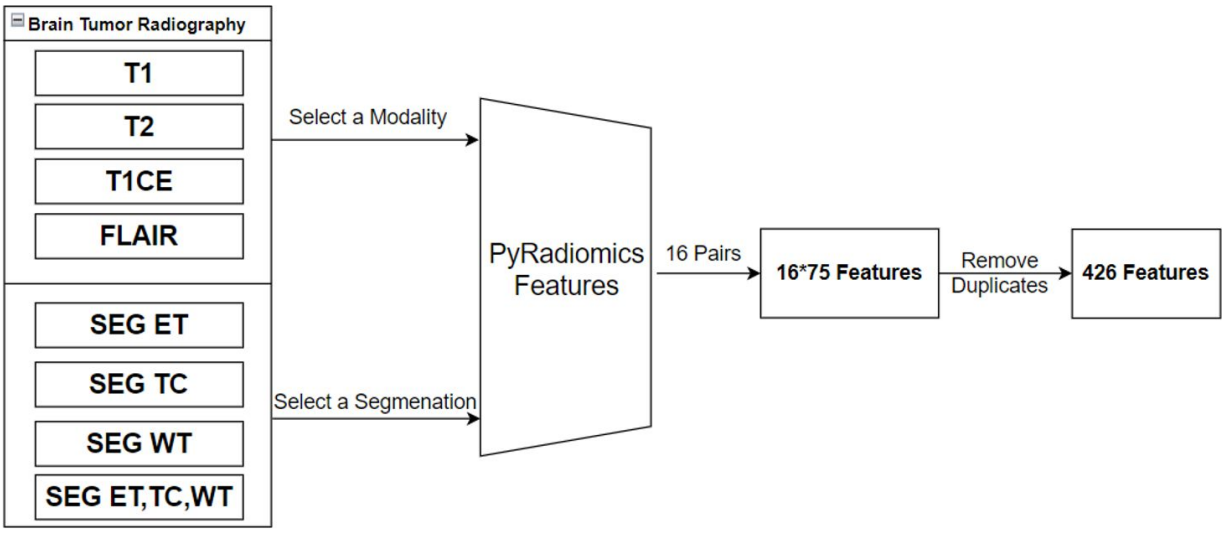

FIGURE 4.3: Feature Extraction Pipeline

4.2.2 Feature Selection

Feature selection plays an important role when solving the MGMT Methylation status task using Radiomics features. From 2 we can see that previous works that used Radiomics features mostly focused on the feature selection step and have used different techniques. In this work, we have experimented with several preprocessing techniques such as chi-square, correlation matrix, PCA, XGBoost feature importance), and several other methods. Recently a new FRUFS [15], an unsupervised Feature selection algorithm, and PyImpetus [16], a Markov Blanket-based feature selection algorithm was introduced which were widely used in several Tabular data competitions on Kaggle. We also tried out these methods on our dataset.

4.2.3 Classification

After finalizing the features, we perform preprocessing on all the features. Standard Scaling is applied for continuous features and Label Encoding is used for categorical features. A stratified 7 Fold cross-validation split is done to perform the validation

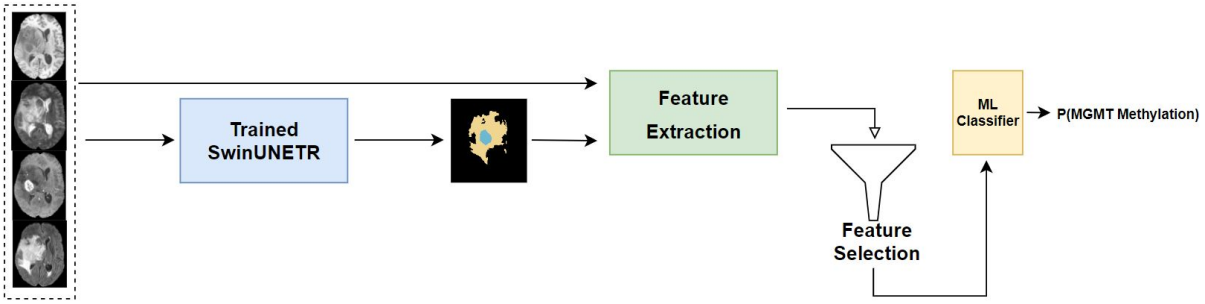

FIGURE 4.4: Radiomics Approach

step and make the model more generalizable. The competition ranks our method based on ROC AUC score on test data, so we use the same metric for ranking our methods. We experimented with several Machine Learning algorithms starting from Logistic Regression and different boosting algorithms like XG Boost [8], Light GBM [22], and Cat Boost [30]. For each method, average predictions of test data across all the folds are submitted for final scoring on the leaderboard. We used Optuna [3] to tune the hyperparameters of ML models and analyzed the performance of each model in detail using the PyCaret AutoML [4] library.

4.3 Ensemble

In the Ensemble approach, we use knowledge from both Radiomics and Deep learning approaches. Firstly trained SwinUNETR is used to extract segmentation masks and feature vectors. Outputs of FC layers of MGMT Models are considered feature vectors. The segmentation mask is then used to obtain radiomics features which undergo a feature selection process as same as the Radiomics approach. Finally, these two sets of features are concatenated and passed to the Classifier model. Figure 4.5 shows the architecture diagram of the Ensemble approach

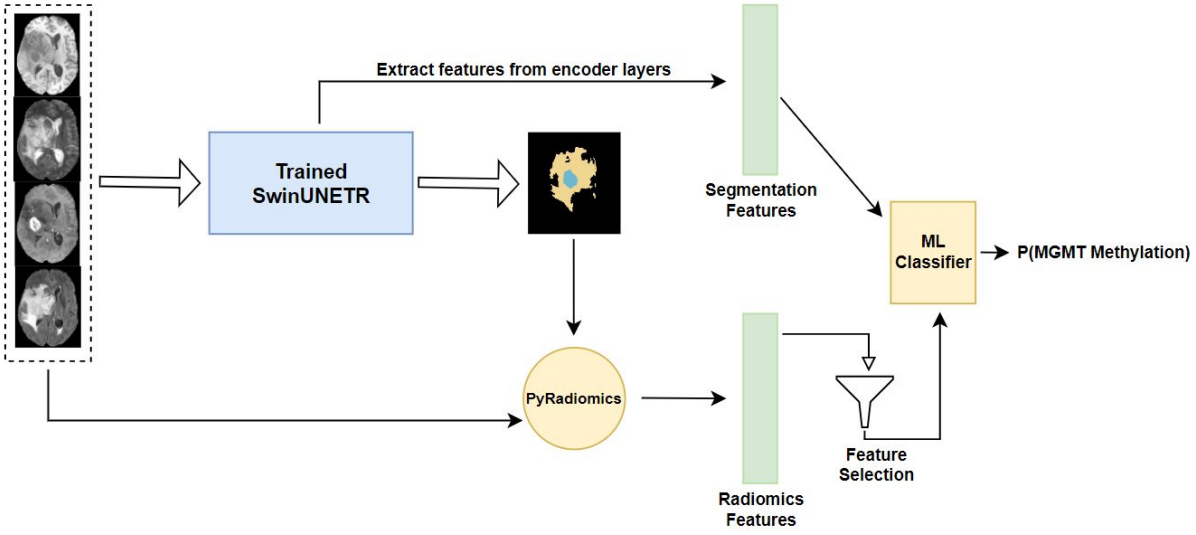

FIGURE 4.5: Ensemble Approach

Chapter 5

Results and Observations

5.1 Quantitative Results

Table 5.1: Comparison of the proposed approach with existing approaches

Method	Type	Leaderboard Score
Abler Daniel et al. [2]	Radiomics	0.524
Aleksandr Emchinov et al. [13]	Deep Learning	0.583
Walia Farzana et al. [14]	Deep Learning	0.477
Quoc-Huy Trinh et al. [35]	Deep learning	0.602
Sveinn Palsson et al. [29]	Ensemble	0.598
Siman Doran et al. [26]	Ensemble	0.603
Our best method	**Ensemble**	**0.609**

We have compared our proposed approach with all the works mentioned in International MICCAI Brainlesion Workshop 2021 (BrainLes) [10], [1]. Table 5.1 shows the list of existing approaches and their performance on test data (Public Leaderboard). The best results were obtained with the ensemble method where MGMT Model_3 and FRUFS Feature selection method selected the 30 most important Radiomics features followed by the LightGBM model for classification [SwinUNETR + MGMT Model_3 + FRUFS (30) + LightGBM]. We outperformed all the existing approaches that were published in the Brainlesion Workshop 2021.

5.2 Ablation Study

5.2.1 Deep Learning

Table 5.2: Variation of Validation AUROC, Dice score with Alpha and MGMT Model of SwinUNETR for Deep Learning Approach

MGMT Model	Alpha	AUROC	Dice WT	Dice TC	Dice ET	Mean Dice
MGMT $Model_1$	0	-	0.932	0.935	0.899	0.922
MGMT $Model_1$	0.1	0.627	0.922	0.929	0.890	0.913
MGMT $Model_1$	0.5	0.689	0.889	0.919	0.885	0.897
MGMT $Model_1$	0.9	0.718	0.741	0.854	0.782	0.792
MGMT $Model_2$	0	-	0.941	0.939	0.901	0.927
MGMT $Model_2$	0.1	0.634	0.928	0.935	0.896	0.919
MGMT $Model_2$	0.5	0.698	0.896	0.922	0.876	0.898
MGMT $Model_2$	0.9	0.735	0.791	0.875	0.795	0.820
MGMT $Model_3$	0	-	0.939	0.935	0.897	0.923
MGMT $Model_3$	0.1	0.657	0.918	0.925	0.897	0.913
MGMT $Model_3$	0.5	0.703	0.897	0.915	0.880	0.897
MGMT $Model_3$	0.9	0.746	0.776	0.867	0.798	0.814

Table 5.2 shows the Validation AUROC along with Dice scores for individual segmented masks as well as the average Dice score. for the Deep Learning approach. We selected four alpha values 0, 0.1, 0.5, and 0.9 which cover all the cases. While the Average dice score decreased with increasing alpha, the Validation AUROC score increased. This can be inferred in general that giving more weight to Dice Loss makes the segmented model learn better. Alpha 0 means there is learning happening in MGMT Model.

5.2.2 Radiomics

Figure 5.1 shows the variation in validation data performance (AUROC) with the number of features selected using different methods using different classifier models. We've experimented with 3 best performing Boosting models: LightGBM, CatBoost, and XGBoost, each figure shows the performance variation corresponding to each model mentioned. FRUFS, Chi-Square, PCA, and PyImpetus feature selection methods were used for the feature selection step. For all the experiments peak

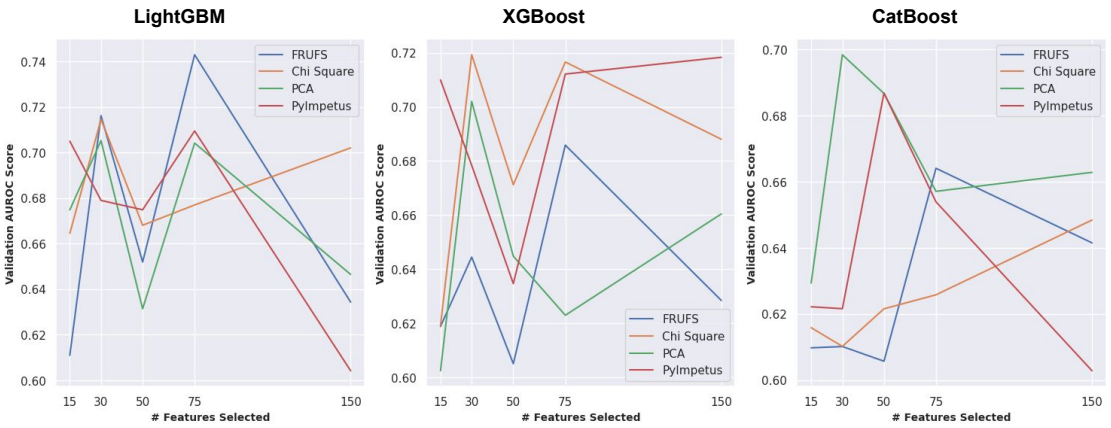

FIGURE 5.1: Variation of Validation AUROC with different feature selection methods and Classifier Models

performance was not uniformly observed but mostly can be seen at 30, 50, and 75 features.

5.2.3 Ensemble

TABLE 5.3: Variation of Validation AUROC with Feature selection and Classifier model for Ensemble approach

MGMT Model	Alpha	Feature Selection	No of Features	Classifier	AUROC
MGMT $Model_1$	0.9	FRUFS	30	LightGBM	0.751
MGMT $Model_2$	0.9	FRUFS	15	LightGBM	0.742
MGMT $Model_1$	0.9	Chi Square	30	LightGBM	0.739
MGMT $Model_3$	0.8	Chi Square	30	CatBoost	0.731
MGMT $Model_2$	0.9	Corr Matrix	30	CatBoost	0.729
MGMT $Model_3$	0.5	PCA	50	XGBoost	0.719
MGMT $Model_1$	0.5	FRUFS	30	XGBoost	0.711
MGMT $Model_2$	0.9	PyImpetus	75	LightGBM	0.708

Table 5.3 lists out the top 8 high-scoring experiments based on the Validation AUROC score. For all the experiments alpha value was above or equal to 0.5. The number of selected features ranged from 15 to 75.

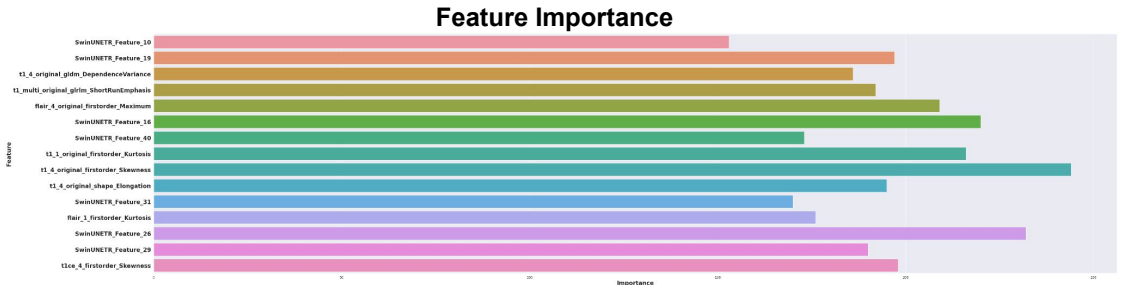

FIGURE 5.2: Feature Importance for Best Performing Experiment

5.3 Qualitative Results

Figure 5.2 shows the top 15 important features of the best-performing approach mentioned in the Quantitative Results section. seven out of 15 features are extracted from the MGMT Model of the Deep Learning Approach. Other radiomics features belong to first-order statistics from different modalities, segmentation labels, and mainly skewness.

tSNE [36] is an algorithm used to visualize high-dimensional data. Figure 5.3 shows the tSNE plot of features obtained from the best experiment of each approach. tSNE is applied to features selected using the FRUFS algorithm. We can see clear clustering in all the approaches. While the learned features are very informative, Feature selection using FRUFS further helped to select the most important features that can differentiate the samples with and without MGMT Promoter Methylation. Figure 5.4 shows the mpMRI scan with a predicted mask using the best-performing approach.

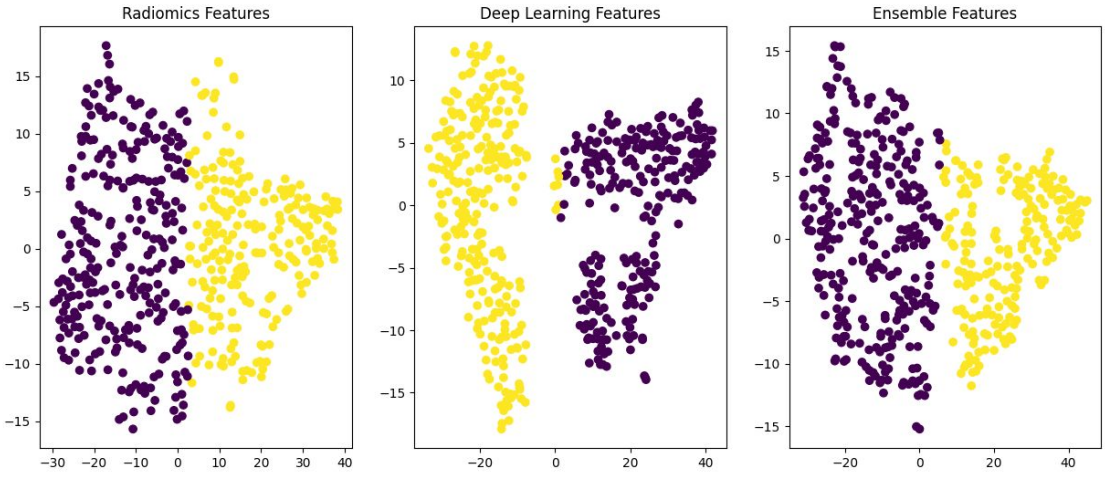

FIGURE 5.3: tSNE plots with and without feature selection for Deep Learning, Radiomics and Ensemble approaches

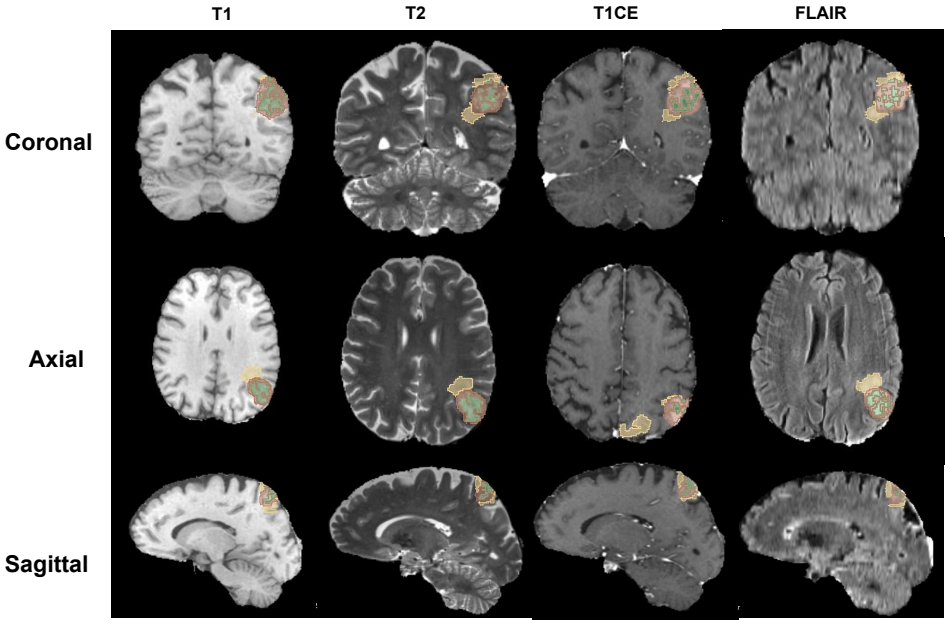

FIGURE 5.4: Sample Segmented Mask of a mpMRI (ID 00021) using Our Best Method

Chapter 6

Summary

In this work, we solved the problem of MGMT Promoter Methylation through three different approaches: Deep Learning, Radiomics, and Ensemble. We explored various models on top of the SwinUNETR segmentation model for the Deep Learning approach, different feature selection techniques, and classifier models for the radiomics approach. Finally, the ensemble approach uses features from the above 2 approaches and adds a classifier model on top of them. The best-performing method is the Ensemble approach with the following structure: **SwinUNETR + MGMT Model$_3$ + FRUFS (30) + LightGBM** which gave a 0.609 AUROC score on the test dataset.

Chapter 7

Future Scope

From the results (6) it is clear that the ensemble approach is giving good results taking advantage of both Deep Learning and Radiomics approaches. While the Radiomics approach mostly depends on Feature selection and classification models, we can explore other existing methods. For the Deep Learning approach, we can modify MGMT Model and change the training procedure by the modifying loss function. We can also explore other existing SOTA Brain Tumor Segmentation models such as [21].

Bibliography

[1] (2021). *Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries: 7th International Workshop, BrainLes 2021, Held in Conjunction with MICCAI 2021, Virtual Event, September 27, 2021, Revised Selected Papers, Part II*, Berlin, Heidelberg. Springer-Verlag.

[2] Abler, D., Andrearczyk, V., Oreiller, V., and Bakas, S. (2022). Comparison of mr preprocessing strategies and sequences for radiomics-based mgmt prediction. In *Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries*, pages 367–380, Cham. Springer International Publishing.

[3] Akiba, T., Sano, S., Yanase, T., Ohta, T., and Koyama, M. (2019). Optuna: A next-generation hyperparameter optimization framework. *CoRR*, abs/1907.10902.

[4] Ali, M. (2020). *PyCaret: An open source, low-code machine learning library in Python*. PyCaret version 1.0.0.

[5] Baid, U., Ghodasara, S., Bilello, M., Mohan, S., Elliott, J., and Bakas, S. (2021). The RSNA-ASNR-MICCAI brats 2021 benchmark on brain tumor segmentation and radiogenomic classification. *CoRR*, abs/2107.02314.

[6] Breiman, L. (2001). Random forests. *Machine Learning*, 45(1):5–32.

[7] Cardoso, M. J., Li, W., Brown, R., Ma, N., Kerfoot, E., Wang, Y., Murray, B., Myronenko, A., Zhao, C., Yang, D., Nath, V., He, Y., Xu, Z., Hatamizadeh, A.,

Zhu, W., Liu, Y., Zheng, M., Tang, Y., Yang, I., Zephyr, M., Hashemian, B., Alle, S., Zalbagi Darestani, M., Budd, C., Modat, M., Vercauteren, T., Wang, G., Li, Y., Hu, Y., Fu, Y., Gorman, B., Johnson, H., Genereaux, B., Erdal, B. S., Gupta, V., Diaz-Pinto, A., Dourson, A., Maier-Hein, L., Jaeger, P. F., Baumgartner, M., Kalpathy-Cramer, J., Flores, M., Kirby, J., Cooper, L. A., Roth, H. R., Xu, D., Bericat, D., Floca, R., Zhou, S. K., Shuaib, H., Farahani, K., Maier-Hein, K. H., Aylward, S., Dogra, P., Ourselin, S., and Feng, A. (2022). MONAI: An open-source framework for deep learning in healthcare.

[8] Chen, T. and Guestrin, C. (2016). Xgboost: A scalable tree boosting system. In *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, KDD '16, pages 785–794, New York, NY, USA. ACM.

[9] Chen, X., Zeng, M., Tong, Y., Zhang, T., Fu, Y., Li, H., Zhang, Z., Cheng, Z., and Jiang, X. (2020). Automatic prediction of MGMT status in glioblastoma via deep Learning-Based MR image analysis. *Biomed Res Int*, 2020:9258649.

[10] Crimi, A. and Bakas, S., editors (2022). *Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries - 7th International Workshop, BrainLes 2021, Held in Conjunction with MICCAI 2021, Virtual Event, September 27, 2021, Revised Selected Papers, Part I*, volume 12962 of *Lecture Notes in Computer Science*. Springer.

[11] Do, D. T., Yang, M.-R., Lam, L. H. T., Le, N. Q. K., and Wu, Y.-W. (2022). Improving mgmt methylation status prediction of glioblastoma through optimizing radiomics features using genetic algorithm-based machine learning approach. *Scientific Reports*, 12(1):13412.

[12] Dosovitskiy, A., Beyer, L., Kolesnikov, A., Weissenborn, D., and Houlsby, N. (2020). An image is worth 16x16 words: Transformers for image recognition at scale. *CoRR*, abs/2010.11929.

[13] Emchinov, A. (2022). A deep learning approach to glioblastoma radiogenomic classification using brain mri. In Crimi, A. and Bakas, S., editors, *Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries*, pages 345–356, Cham. Springer International Publishing.

[14] Farzana, W., Temtam, A. G., Shboul, Z. A., and Iftekharuddin, K. M. (2022). Radiogenomic prediction of mgmt using deep learning with bayesian optimized hyperparameters. In Crimi, A. and Bakas, S., editors, *Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries*, pages 357–366, Cham. Springer International Publishing.

[15] Hassan, A. (2022). Frufs: Feature relevance based unsupervised feature selection. `https://github.com/atif-hassan/FRUFS`.

[16] Hassan, A., Paik, J. H., Khare, S., and Syed, A. H. (2021). PPFS: predictive permutation feature selection. *CoRR*, abs/2110.10713.

[17] Hatamizadeh, A., Nath, V., Tang, Y., Yang, D., Roth, H. R., and Xu, D. (2022). Swin unetr: Swin transformers for semantic segmentation of brain tumors in mri images. In *Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries: 7th International Workshop, BrainLes 2021, Held in Conjunction with MICCAI 2021, Virtual Event, September 27, 2021, Revised Selected Papers, Part I*, pages 272–284. Springer.

[18] He, K., Zhang, X., Ren, S., and Sun, J. (2015). Deep residual learning for image recognition.

[19] Hearst, M., Dumais, S., Osuna, E., Platt, J., and Scholkopf, B. (1998). Support vector machines. *IEEE Intelligent Systems and their Applications*, 13(4):18–28.

[20] Huang, G., Liu, Z., and Weinberger, K. Q. (2016). Densely connected convolutional networks. *CoRR*, abs/1608.06993.

[21] Isensee, F., Jaeger, P. F., Full, P. M., Vollmuth, P., and Maier-Hein, K. H. (2020). nnu-net for brain tumor segmentation.

[22] Ke, G., Meng, Q., Finley, T., Wang, T., Chen, W., Ma, W., Ye, Q., and Liu, T.-Y. (2017). Lightgbm: A highly efficient gradient boosting decision tree. *Advances in neural information processing systems*, 30:3146–3154.

[23] Korfiatis, P., Kline, T. L., Coufalova, L., F., I., Carter, R. E., Buckner, J. C., and Erickson, B. J. (2016). Mri texture features as biomarkers to predict mgmt methylation status in glioblastomas. *Medical Physics*, 43(6Part1):2835–2844.

[24] Li, Z.-C., Bai, H., Sun, Q., Li, Y., Chen, Y., Liang, C., and Zheng, H. (2018). Multiregional radiomics features from multiparametric mri for prediction of mgmt methylation status in glioblastoma multiforme: A multicentre study. *European radiology*, 28(9):3640—3650.

[25] Lu, Y., Patel, M., Natarajan, K., Ughratdar, I., Sanghera, P., Jena, R., Watts, C., and Sawlani, V. (2020). Machine learning-based radiomic, clinical and semantic feature analysis for predicting overall survival and mgmt promoter methylation status in patients with glioblastoma. *Magnetic Resonance Imaging*, 74:161–170.

[26] Mun, T. S. H., Doran, S., Huang, P., Messiou, C., and Blackledge, M. (2022). Multi modal fusion for radiogenomics classification of brain tumor. In Crimi, A. and Bakas, S., editors, *Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries*, pages 344–355, Cham. Springer International Publishing.

[27] Nachar, N. (2008). The mann-whitney u: A test for assessing whether two independent samples come from the same distribution. *Tutorials in Quantitative Methods for Psychology*, 4.

[28] Nuechterlein, N. and Mehta, S. (2019). 3d-espnet with pyramidal refinement for volumetric brain tumor image segmentation. In Crimi, A., Bakas, S., Kuijf,

H., Keyvan, F., Reyes, M., and van Walsum, T., editors, *Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries*, pages 245–253, Cham. Springer International Publishing.

[29] Palsson, S., Cerri, S., and Van Leemput, K. (2022). Prediction of mgmt methylation status of glioblastoma using radiomics and latent space shape features. In Crimi, A. and Bakas, S., editors, *Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries*, pages 222–231, Cham. Springer International Publishing.

[30] Prokhorenkova, L. O., Dorogush, A. V., and Gulin, A. (2018). Catboost: unbiased boosting with categorical features. In *NeurIPS*, pages 6639–6649.

[31] Saeed, N., Hardan, S. E., Abutalip, K., and Yaqub, M. (2022). Is it possible to predict MGMT promoter methylation from brain tumor MRI scans using deep learning models? In *Medical Imaging with Deep Learning*.

[32] Simonyan, K. and Zisserman, A. (2014). Very deep convolutional networks for large-scale image recognition.

[33] Tan, M. and Le, Q. V. (2019). Efficientnet: Rethinking model scaling for convolutional neural networks.

[34] Taylor, O. G. (2019). Glioblastoma multiforme: An overview of emerging therapeutic targets. *Frontiers in oncology*.

[35] Trinh, Q.-H., Mau, T.-H. N., Zosimov, R., and Nguyen, M.-V. (2022). Efficientnet for brain-lesion classification. In Crimi, A. and Bakas, S., editors, *Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries*, pages 249–260, Cham. Springer International Publishing.

[36] van der Maaten, L. and Hinton, G. (2008). Visualizing data using t-SNE. *Journal of Machine Learning Research*, 9:2579–2605.

[37] van Griethuysen, J.M., J., Fedorov, A., Parmar, C., Hosny, A., and Aerts, H. J. (2017). Computational radiomics system to decode the radiographic phenotype. *Cancer Research*, 77.

[38] Yogananda, C. G. B., Shah, B. R., Nalawade, S. S., Murugesan, Patel, T. R., Fei, B., Madhuranthakam, A. J., and Maldjian, J. A. (2021). MRI-Based Deep-Learning method for determining glioma MGMT promoter methylation status. *AJNR Am J Neuroradiol*, 42(5):845–852.

[39] Yushkevich, P. A., Piven, J., Hazlett, H. C., Smith, R. G., Ho, S., Gee, J. C., and Gerig, G. (2006). User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage*, 31(3):1116–1128.