Journal of Advanced Research in Applied Sciences and Engineering Technology

Journal homepage:
https://semarakilmu.com.my/journals/index.php/applied_sciences_eng_tech/index
ISSN: 2462-1943

Development of Prediction Models to Detect the Presence of MGMT Promoter Methylation for Prognosis of Brain Tumor

Musaab Nabil Ali Askar[1], Azian Azamimi Abdullah[1,*], Md Altaf-Ul-Amin[2], Shigehiko Kanaya[2]

[1] Biomedical Electronic Engineering Programme, Faculty of Electronic Engineering and Technology, Universiti Malaysia Perlis, 02600 Arau, Perlis, Malaysia
[2] Graduate School Information Science, Nara Institute of Science and Technology, 8916-5 Takayama-cho, Ikoma, Nara 630-0192, Japan

ABSTRACT

Methylation of the MGMT promoter is a molecular marker of predictive relevance in brain tumors. Methylation of the MGMT promoter is related to an improved prognosis and may influence therapy decisions. According to the most recent Malaysian National Cancer Registry Report (MNCRR) for 2012–2016, there were 2097 cases of brain tumors in Malaysia overall, with 1117 cases involving men and 908 cases involving women. This research aims to create prediction models for detecting MGMT promoter methylation in brain tumors. So, a dataset from the BraTS (Brain Tumor Segmentation) challenge, which included MRI scans and clinical data for patients with brain tumors, was utilized and explored using Exploratory Data Analysis (EDA) and data visualization techniques. The dataset has 306 methylation cases identified as "1" and 276 unmethylated cases identified as "0". The average number of scans of train data for modality per patient is between 127 and 171, which provides a wealth of information for pattern learning while the average number of scans of test data for modality per patient is between 124 and 165. In both sets, FLAIR has the least number of files while T2w has the highest number of files among them. Two models of deep learning approaches, ResNet50 and EfficientNetV2, were used to construct and form the prediction models. Various criteria were employed to evaluate the performance of the models. The T2w modality consistently achieved the highest validation accuracy, precision, recall, and F1-score for both the ResNet50 and EfficientNetV2 models. Specifically, the T2w modality achieved a validation accuracy of 0.9453 and a validation loss of 0.2417 for ResNet50. Furthermore, the brain tumor diagnosis interface utilized DICOM images from MRI scans to identify MGMT methylation status, aiding in therapy effectiveness prediction. Pre-trained ResNet50 model on T2w images was used for classification. The interface displayed the original MRI image, predicted state, and treatment effectiveness indication, while promptly notifying users of invalid or inadequate data for accurate analysis.

Keywords:
Brain tumor diagnosis; MGMT; deep learning; MRI scans; TMZ; chemotherapy

* *Corresponding author.*
E-mail address: azamimi@unimap.edu.my

https://doi.org/10.37934/araset.61.1.1022

1. Introduction

According to the Malaysian National Cancer Registry Report (2012-2016), 2097 Malaysians were diagnosed with brain tumors, with 1117 samples involving men and 908 samples involving women. Glioblastoma (GBM) is a form of brain tumor distinguished by molecular heterogeneity and methylation of genes [1]. Early detection is critical for successful therapy and patient recovery. Biopsies and computed tomography (CT) scans are frequently employed for diagnosis, while MRI is useful for visualizing the central nervous system (CNS) and vascular architecture [2]. Surgical removal may cause delays in making crucial therapy choices and might be affected by intra-tumoral heterogeneity [3, 4]. Given that the human skull is a hard and volume-limited shell, any unanticipated development may impact a person's function depending on the portion of the brain implicated [5].

DNA methyltransferase O6-Methylguanine (MGMT) is a DNA repair enzyme discovered in cells of glioblastoma that can repair alkylating chemical damage. Its presence or absence determines glioblastoma chemoresistance because it prevents both normal and malignant cells from dying [6]. GBM cells are less able to repair damage when the MGMT gene promoter is methylated, making them more vulnerable to alkylating therapy. The unmethylated MGMT gene promoter permits GBM cells to repair damage, limiting the efficacy of alkylating therapy [7, 8]. It is critical to develop non-invasive image-based diagnostic techniques for determining MGMT promoter methylation status in brain tumors to minimize invasive procedures and minimize dangers. A meta-analysis of MRI characteristics discovered that methylated MGMT promoters were linked with decreased edoema, increased ADC, and decreased perfusion in glioblastoma [9].

With the advancement of artificial intelligence (AI) in the medical field [10], and other domains [11-15], there is an opportunity to more process of gathering all the quantitative information contained within the MR images, which may enable the classification and estimation of the genetic traits of glioma, which play such an important role in treatment management and prognosis [16]. Deep learning (DL) is a subset of Machine learning (ML) and AI in which image feature selection and classification procedures occur concurrently in one algorithm, obviating the requirement for human interaction during training. In general, it is end-to-end machine learning [17].

Some researchers have conducted their studies on detecting the status of MGMTp methylation using CNN. Chang *et al.,* [18], obtained the images from the Cancer Imaging Archives for 259 patients. The performance evaluation of his model reaches an accuracy of (0.76 – 0.88). While Chen *et al.,* [19], applied the CNN on a total of 106 GBM patients collected from The Cancer Imaging Archive with an accuracy of 0.827. Han *et al.,* [20], proposed a similar method using CRNN on 159 unique patients' MRI scans acquired in 3 modalities from The Cancer Genome Atlas Glioblastoma Multiforme (TCGA-GBM) project and got an accuracy of 0.62.

Chen *et al.,* [21], investigated 111 patients with diffuse gliomas who participated in the retrospective review (56 with MGMT promoter methylation and 55 with MGMT promoter unmethylation) and achieved an AUC of 0.9 using a Resnet50-18 that was fed Radiomics characteristics. Kim *et al.,* [22], examined a ResNet50 on FLAIR and T1wCE with an AUC of 0.65 on the BraTS 2021 dataset with a dataset from Seoul National University Hospital (SNUH).

Yogananda *et al.,* [9], applied Voxelwise classification and 3D-dense-UNets on 247 subjects from The Cancer Imaging Archive and The Cancer Genome Atlas using only T2WI and reach an AUC of 0.93. Lu *et al.,* [23] investigated a total of 181 patients enrolled from their institution using the random survival forest (RSF) and obtained an AUC of 0.962. Lastly, Le *et al.,* [24] used Binary classification on patients with GBM from the TCGA-GBM project, which included preoperative multimodal MRI (mMRI) scans from 262 participants with an accuracy of 0.887.

Deep learning algorithms and MRI images will be used in this project to predict the existence of MGMT promoter methylation in brain tumors. The study intends to discover where the methylation status emerges most frequently by analyzing the four modalities of MRI separately. Furthermore, this study aims to provide a user-friendly interface for forecasting MGMT promoter methylation, which is time-consuming and potentially prone to mistakes process at the moment.

2. Methodology

This section outlines the steps to develop and validate prediction models for detecting MGMT promoter methylation in brain tumors. The methodology includes data acquisition, image pre-processing, deep learning models and evaluation, and Graphical User Interface (GUI) development.

The flowchart in Figure 1 shows the steps of loading the data from the BraTS dataset to be used for applying the visualization technique to the image pre-processing. The data is pre-processed to handle missing values, deal with outliers, and transform variables as needed. The next step is to develop prediction models using appropriate deep learning algorithms. These models are then evaluated using appropriate metrics such as accuracy, precision, recall, and F1 to assess their performance. Based on the evaluation results, the models may be refined and optimized by adjusting model hyperparameters, trying different image pre-processing techniques, or different algorithms. If the models do not need to be refined and optimized, they are validated using the testing set and any additional validation datasets. Once the models have been validated, the best model can be used to predict the MGMT promoter methylation status of brain tumors and a GUI to predict the value of MGMT promoter for brain tumor prognosis.

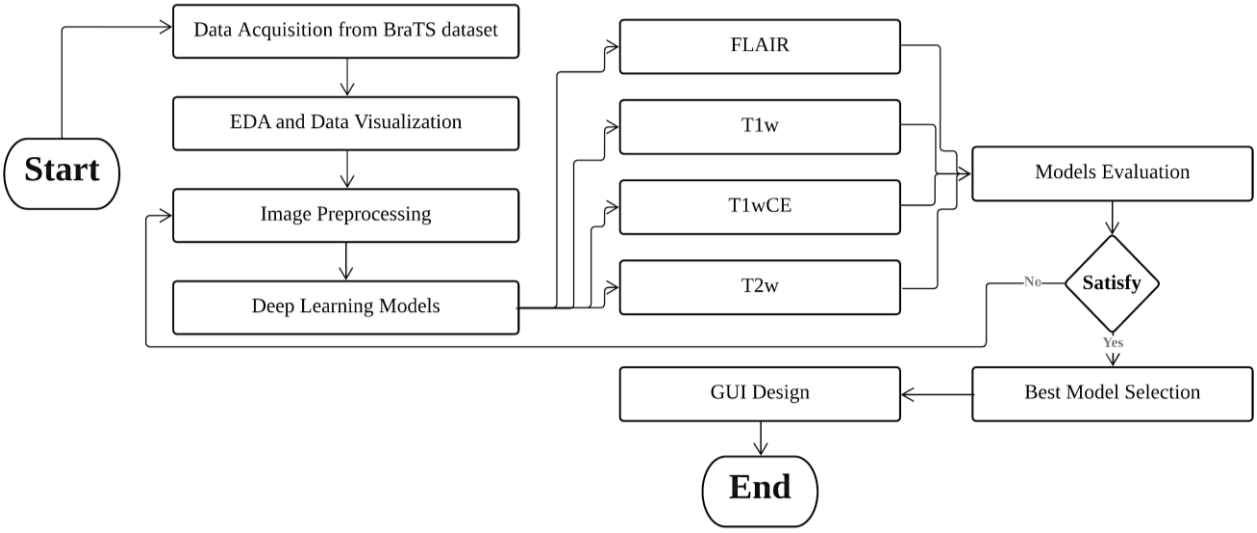

Fig. 1. Research flowchart

The BraTS dataset was built up of retrospective MRI scans of brain tumors acquired from several institutions, each with its own imaging equipment and methodologies, resulting in a range of picture quality reflecting real-world clinical practice. The dataset contains 585 labeled patient samples, each of which contains T1w, T2w, T1Gd, and FLAIR imaging sequences. The sample sizes differ, and each corresponds to one of the four modalities. However, due to image errors stated by the host, three individuals (IDs 00109, 00123, and 00709) were eliminated from the collection, leading to a total of 582 samples. The folder's structure is shown in Figure 2.

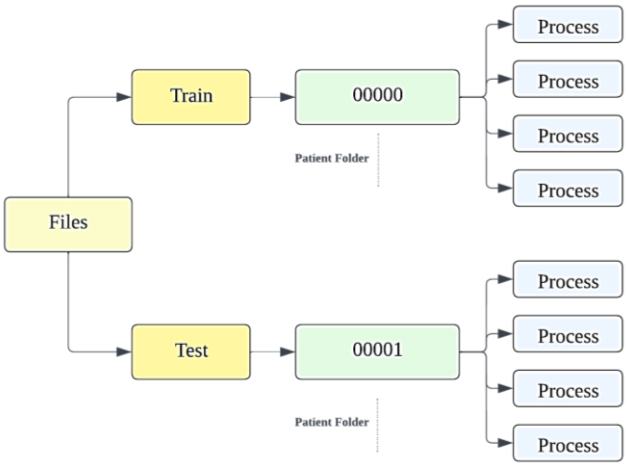

Fig. 2. Folder structure of BraTS dataset

2.1 Exploratory Data Analysis and Data Visualization

Exploratory Data Analysis (EDA) and Data Visualization are essential tools for understanding the patterns and trends in a dataset. By analyzing and visualizing the data, we can uncover insights and relationships that may not be apparent at first glance, which can then inform further analysis and decision-making. The MGMT promoter methylation value can be represented using EDA and visualization as a 0 or 1. Due to the binary nature of the MGMT promoter methylation value, the data can be represented in a pie chart as 0: unmethylated and 1: methylated. Using correlation assumptions prior to data analysis through the EDA process enables the explicit articulation of the link between data or characteristics. It may be advantageous to explore, describe, and comprehend the significance of the data before selecting an acceptable analysis method to develop a prediction model.

2.2 Image Pre-Processing

Image pre-processing is the process of preparing images for further analysis or processing. It involves a series of steps to enhance the quality of the images, remove noise and artifacts, and adjust the images to a format that is more suitable for the intended application. Various techniques can be used for image pre-processing, depending on the application's specific requirements and the images' characteristics. Some common techniques include image resizing, cropping, rotation, color space conversion, enhancement, and denoising. Image pre-processing is an essential step in the analysis of medical images, such as those used to predict the presence of MGMT promoter methylation for the prognosis of brain tumors. Medical images often contain noise, artifacts, and other inconsistencies that can affect the accuracy and reliability of the analysis. Therefore, it is important to apply appropriate image pre-processing techniques to improve the quality of the images and remove any distractions that may interfere with the analysis. Image normalization, value of interest lookup table (VOI LUT) application, image type conversion, and image resizing are the proposed techniques for this study.

2.3 Deep Learning Models

Deep learning is a subset of machine learning that mimics the brain’s neural networks. It processes data and makes judgments without explicit programming by utilizing artificial neural

networks. It can extract patterns and relationships from big datasets. Deep learning has been used successfully for a variety of tasks, including image recognition and healthcare applications. However, it necessitates significant data and computer resources, and overfitting can be an issue.

ResNet is a convolutional neural network developed by Microsoft Research in 2015 to address the issue of vanishing gradients in deep neural networks. It introduces skip connections to allow an easier flow of gradients through the network and improve learning and performance [25]. EfficientNetV2 is a convolutional neural network (CNN) architecture that researchers developed at Google as an improvement over the original EfficientNet architecture [26]. It is designed to be more efficient and perform better on a wide range of image classification tasks while using fewer resources such as computational power and memory.

2.4 Performance Evaluation

The confusion matrix will be used as a reference to evaluate the performance of the models. Evaluating the efficacy of a model is a vital step. Accuracy, Precision, Recall, and F1 are used to assess the proposed model's performance and can be calculated. Additionally, performance evaluation is used to assess how well the test dataset's MGMT value predictions are performed.

In the context of a prediction model for MGMT methylation in tumors, true positives (TP) refer to cases where the model correctly predicts that a patient has MGMT methylation. On the other hand, true negatives (TN) are cases where the model accurately predicts that a patient does not have MGMT methylation. False positives (FP) occur when the model incorrectly predicts that a patient has MGMT methylation. False negatives (FN), on the other hand, are instances where the model incorrectly predicts that a patient does not have MGMT methylation.

For accuracy, it is the proportion of correctly identified samples to the total number of samples.

$$\text{Accuracy} = \frac{\text{TN}+\text{TP}}{\text{TN}+\text{FN}+\text{TP}+\text{FP}} \tag{1}$$

Precision is expressed as the number of correctly identified positive samples divided by the total number of samples that were identified as positive.

$$\text{Precision} = \frac{\text{TP}}{\text{TP}+\text{FP}} \tag{2}$$

The recall is calculated as the ratio between the number of positive samples correctly classified as Positive to the total number of positive samples.

$$\text{Recall} = \frac{\text{TP}}{\text{TP}+\text{FN}} \tag{3}$$

F1 Score is needed when you want to seek a balance between precision and recall.

$$\text{F1 Score} = \frac{2\times\text{Precision}\times\text{Recall}}{\text{Precision}+\text{Recall}} \tag{4}$$

2.5 Graphic User Interface Development

A graphical user interface (GUI) allows users to interact with a computer or other device using visual elements such as icons, buttons, and windows. GUI applications provide a more intuitive and

user-friendly way for users to interact with the computer than command-line interfaces or text-based interfaces, which require users to enter commands or data using text-based commands.

3. Results

This section summarizes the associated results for data acquisition, exploratory data analysis (EDA) and data visualization, image pre-processing, deep learning models, performance evaluation of the model, and GUI for prediction of MGMT promoter methylation value.

3.1 Data Acquisition

During imaging, each modality in which the scan type specifies a focus. FLAIR, for example, captures the effect of cerebrospinal fluid (CSF) suppression, in which liquid signals like water are suppressed to highlight other parts. T2-weighted imaging, on the other hand, emphasizes differences in lateral tissue relaxation, and the combination of effects provides a comprehensive description of the lesion from multiple perspectives. Each sample in the dataset is represented by a quadruple of these four imaging modalities. Each Modality has two classes: methylated and unmethylated. Figures 3 and 4 show the difference between methylated and unmethylated MGMT.

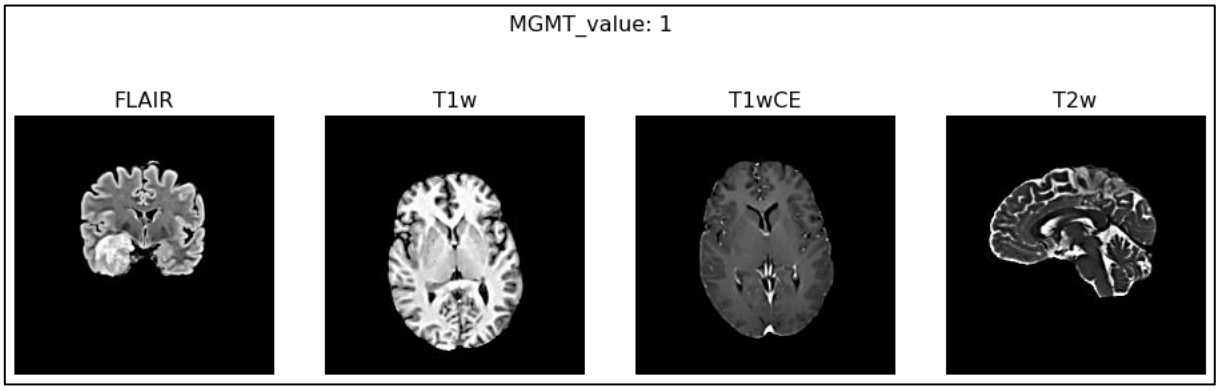

Fig. 3. Methylated sample from the dataset

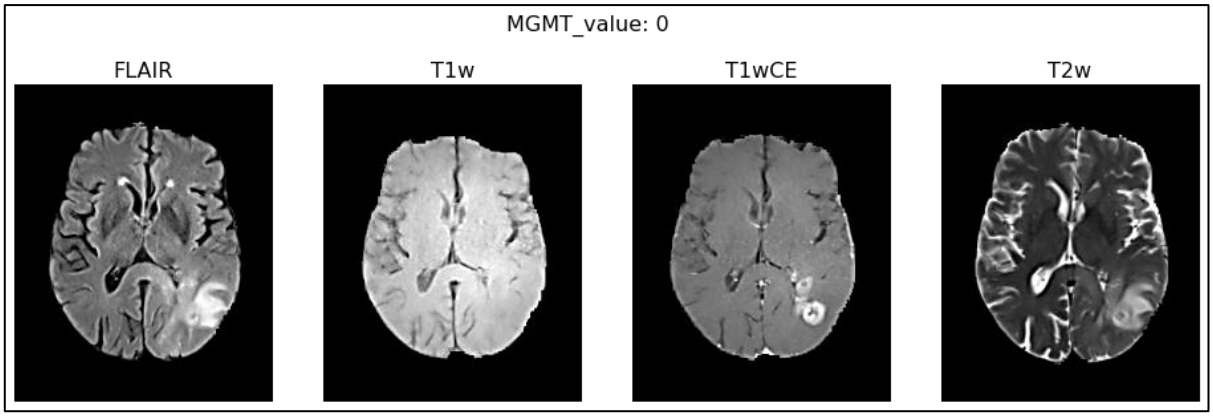

Fig. 4. Unmethylated sample from the dataset

3.2 Exploratory Data Analysis and Data Visualization

Patients are separated into two groups, those with methylated MGMT and those without. The images are in DICOM format with a header comprising clinical data such as modality, orientation, and

MRI-specific data. The dataset has 306 methylation cases identified as "1" and 276 unmethylated cases identified as "0", making it balanced.

Figure 5 shows the Kernel density estimation (KDE), and Table 1 shows the number of MRI scans for each modality of train data after excluding some images due to issues. The average number of scans for modality per patient is between 127 and 171, which provides a wealth of information for pattern learning.

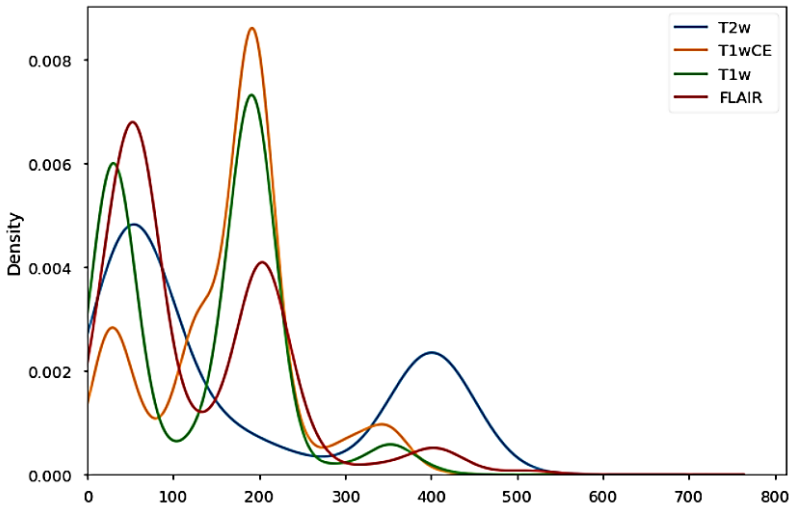

Fig. 5. Kendal density of train set

Table 1
Number of files for each modality in the training set

Scan Type	FLAIR	T1w	T1wCE	T2w
Files	74,010	77,128	96,368	99,774
Average Files per Case	127	133	165	171
Min Files in a case	15	19	19	19
Max Files in a case	514	400	400	472

Figure 6 shows the Kernel density estimation (KDE), and Table 2 shows the number of MRI scans performed for each test data modality. The average number of scans for modality per patient is between 124 and 165, which provides a wealth of information for pattern learning.

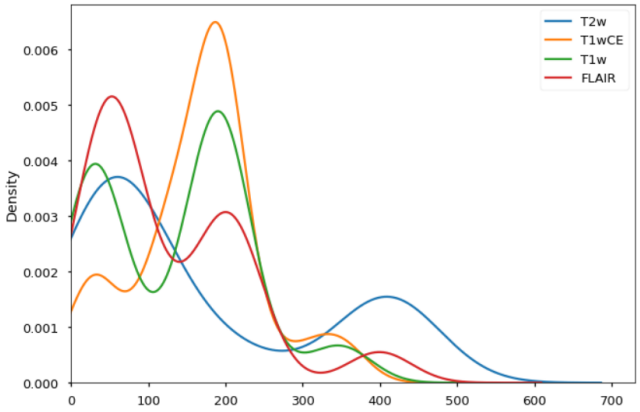

Fig. 6. Kendal density of test set

Table 2
Number of files for each modality in the testing set

Scan Type	FLAIR	T1w	T1wCE	T2w
Files	10,816	26,276	14,378	14,381
Average Files per Case	124	137	165	165
Min Files in a case	19	20	23	20
Max Files in a case	412	352	352	464

3.3 Image Pre-Processing

In the beginning, black images must be removed. It has several effects on the model's performance. It reduces dataset noise by eliminating photos with little to no visual content. As a result, the dataset becomes cleaner and more concentrated, allowing the model to focus on essential patterns and attributes.

Then, two essential operations are conducted during preprocessing: VOI LUT application and normalization. The VOI LUT is used to increase the contrast and visibility of regions of interest within the DICOM image. It converts the original pixel values to a new range, allowing for enhanced visualization and analysis. In addition, the normalization procedure ensures that the pixel values are uniform and standardized throughout the image. Normalizing the intensity values reduces differences in luminance and contrast between DICOM images, allowing for more precise comparisons and subsequent analysis. These preprocessing operations optimize the visual quality, uniformity, and interpretability of radiographic images of brain tumors, thereby augmenting the efficacy of subsequent image-based analysis and decision-making processes.

The int16 format in DICOM images can store positive as well as negative numbers due to its greater range of values. Since it uses 16 bits per pixel, it requires more storage space and more RAM to operate. However, uint8, which uses 8 bits per pixel and expresses only positive numbers, is easier on storage space and more suited to visual representation. Converting to uint8 ensures that images will work with a wide range of image processing techniques and applications that typically work with uint8 images.

Typically, MRI images have high resolution and large dimensions, such as 512x512 pixels. Nonetheless, processing such large images can be computationally and memory-intensive, particularly when working with enormous amounts of data. This can present difficulties for inference and training on devices with limited resources. To overcome these obstacles, images have been resized to 64x64 pixels. This operation substantially reduces the image's dimensions, resulting in decreased memory usage and computational complexity. By decreasing the scale of an image, the data can become more manageable, allowing devices to perform processing tasks more efficiently.

3.4 Image Classification

Image classification was performed on a dataset of Brain Tumor MRI images using the ResNet50 and EfficientNetV2 architectures. The goal was to accurately classify the images into two categories: methylated and unmethylated for each sequence. The dataset consisted of a total of 202,285 images for training, evenly distributed for all MRI sequences between classes, and 50,573 images for validation. Here's a comparison table summarizing the class counts (Table 3).

Table 3
MRI sequences comparison of methylated and unmethylated counts in training and validation sets after preprocessing

MRI	Methylated		Unmethylated	
Sequences	Training set	Validation set	Training set	Validation set
FLAIR	25,063	6,212	17,820	4,509
T1w	24,324	6,043	22,142	5,574
T1wCE	30,497	7,547	26,031	6,586
T2w	33,544	8,410	22,864	5,692
Total	113,428	28,212	88,857	22,361

The model training method employed the use of MRI image slices as individual images within a specified directory structure. This technique in medical imaging analysis treats each slice of an MRI image as an individual image and allocates it to its corresponding class. This method enables more detailed analysis because each slice may have unique traits or patterns that contribute to the classification process.

For each MRI sequence, two common architectures, ResNet50 and EfficientNetv2, were used to train the models, yielding a total of eight models for evaluation. The adoption of these models for each sequence of MRI shows insight into the performance and applicability of various architectures for the classification task at work. This method allows for a thorough examination of the models' performance and aids in determining the most effective architecture for each MRI sequence.

ResNet-50 & EfficientNetV2 models are implemented with the deep learning application programming interface (API) known as “Keras”. Moreover, “sigmoid” function is used as the activation function in the output layer. The sigmoid function is a frequent activation function in ANN. It converts input values to a range of 0 to 1, making it useful for tasks requiring probability prediction. It is formally defined as $f(x) = 1 / (1 + \exp(-x))$, where x is the input. The sigmoid function is important for applications like binary classification, which requires us to divide inputs into two separate classes: ‘’methylated'' and ''unmethylated''.

The micro average is used to compare the precision, recall, and F1-score values of different models' classification reports as shown in Table 4. The micro average is a statistic that computes these scores by aggregating all classes, taking the average values for each class. We gain a thorough assessment of the overall performance of the models by using the micro average, which considers the aggregate performance across all classes. The table provides a detailed examination of the performance metrics for ResNet50 and EfficientNetV2 models across various modalities such as FLAIR, T1w, T1wCE, and T2w. Accuracy, loss, precision, recall, and F1-score are among the measures assessed.

Table 4
Classification Report of the Models

	ResNet50				EfficientNetV2			
Metrics	FLAIR	T1w	T1wCE	T2w	FLAIR	T1w	T1wCE	T2w
Accuracy	0.9276	0.9172	0.9423	0.9453	0.8646	0.8922	0.8975	0.9097
Loss	0.3284	0.3510	0.2583	0.2417	0.6777	0.4688	0.3980	0.4576
Precision	0.93	0.92	0.94	0.95	0.86	0.89	0.90	0.91
Recall	0.93	0.92	0.94	0.95	0.86	0.89	0.90	0.91
F1-Score	0.93	0.92	0.94	0.95	0.86	0.89	0.90	0.91

Both ResNet50 and EfficientNetV2 perform well across all modalities. ResNet50 routinely outperforms EfficientNetV2 in accuracy. ResNet50 achieves accuracies ranging from 0.92 to 0.95 across all modalities, while EfficientNetV2 scores a bit lower, ranging from 0.86 to 0.91. This shows

that ResNet50 generalizes better to new data and performs better in classifying validation samples. ResNet50 consistently has lower losses than EfficientNetV2. This shows that ResNet50 can make more accurate predictions and minimize mistakes on the validation dataset.

The T2w modality consistently produces the highest validation accuracy, precision, recall, and F1-score for both the ResNet50 and EfficientNetV2 models, as shown in the Table 4. The T2w modality highlighted in the Table 4 has a validation accuracy of 0.9453 for ResNet50, suggesting that the model properly identifies 94.53% of the samples from this sequence. Similarly, T2w has the highest precision, recall, and F1-score among all sequences for both ResNet50 and EfficientNetV2. This implies that the T2w sequence for the ResNet50 algorithm contains significant features and patterns that enable the models to generate more accurate predictions. T2-weighted pictures are important in a variety of medical imaging activities because they provide essential information concerning fluid accumulation, edema, and lesions. The models' outstanding performance on T2w images demonstrates their capacity to successfully learn and apply the unique aspects of this modality.

The BraTS RSNA-MICCAI Brain Tumor Radiogenomic Classification study did not release its results of the testing set, limiting comparing and measuring the accuracy of prediction outcomes with the actual results. As a result, a validation set has been utilized to analyze and evaluate the performance of estimations as discussed earlier.

3.5 Graphic User Interface Development

The brain tumor diagnosis interface uses DICOM images of MRI to determine MGMTp methylation status, which is an important biomarker for predicting the efficacy of Temozolomide (TMZ) alkylating treatment. When a DICOM file of a brain tumor is uploaded, the interface makes predictions using a pre-trained ResNet50 model of T2w. The model analyses the image, employs relevant preprocessing techniques, and determines whether the MGMTp methylation status is unmethylated. Based on the classification outcome, the user is shown the original MRI image, the estimated state, and an indicator of the efficiency of TMZ treatment as shown in Figure 7. This interface was designed using the library ‘Gradio’.

If the model suggests that the brain tumor has MGMTp methylation in the case of a "methylated" classification. This shows that Temozolomide (TMZ) alkylating treatment is more likely to be effective. This classification result will be presented to the user, allowing them to potentially enhance patient outcomes. If the model suggests that a brain tumor is classified as "unmethylated". This indicates a decreased likelihood of a good response to TMZ alkylating therapy. This classification result will be presented to the user, allowing them to investigate other treatment options and make well-informed judgments based on the expected unmethylated status. The last case is when the interface recognizes "black images” as incorrect images in this scenario. It will show that the uploaded image is inappropriate for analysis since there is insufficient valid data. The user will be notified of the problem by an error message "Invalid Image". This message makes the user aware of the mistaken image and allows them to take relevant measures, such as re-uploading a genuine MRI scan for proper analysis.

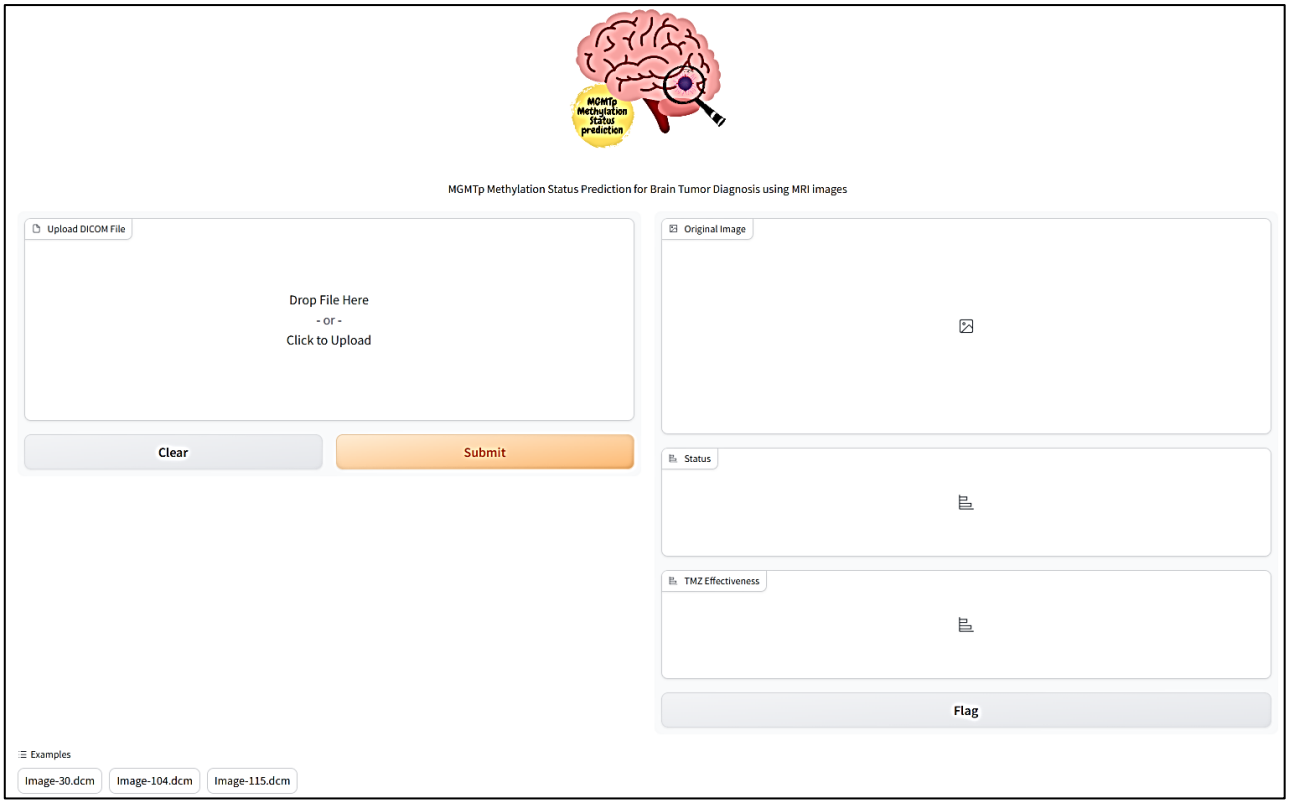

Fig. 7. Graphical user interface

4. Conclusions

This study aimed to develop GUI to classify brain tumor images based on methylation status. A balanced dataset of DICOM images, consisting of methylated and unmethylated cases, was used. Image pre-processing techniques were applied to enhance the dataset's quality and computational efficiency. The ResNet50 and EfficientNetV2 models were employed, with the T2w modality consistently demonstrating superior performance, which achieved the best validation accuracy of 0.9453 and a validation loss of 0.2417 for ResNet50. A user-friendly interface was created for easy image upload, analysis, and prediction of methylation status using it. The interface provides feedback on the predicted state and treatment effectiveness. In the case of invalid data, an error message prompts the user to provide accurate MRI scans.

Considering the current context, exploring brain tumor data from Malaysia would be valuable. Analyzing data from the local population can provide insights into the unique characteristics, prevalence, and treatment outcomes of brain tumors in Malaysia. This localized approach can help in tailoring diagnostic and treatment strategies to the specific needs and demographics of the Malaysian population.

Acknowledgement

This research was funded by Universiti Malaysia Perlis.

References

[1] Zhang, Yu-Hang, Zhandong Li, Tao Zeng, Xiaoyong Pan, Lei Chen, Dejing Liu, Hao Li, Tao Huang, and Yu-Dong Cai. "Distinguishing glioblastoma subtypes by methylation signatures." *Frontiers in genetics* 11 (2020): 604336. https://doi.org/10.3389/fgene.2020.604336

[2] Fahmi, Fahmi, Fitri Apriyulida, Irina Kemala Nasution, and Sawaluddin. "Automatic detection of brain tumor on computed tomography images for patients in the intensive care unit." *Journal of Healthcare Engineering* 2020, no. 1 (2020): 2483285. https://doi.org/10.1155/2020/2483285

[3] Huang, Huan, Fei-fei Wang, Shigang Luo, Guangxiang Chen, and Guangcai Tang. "Diagnostic performance of radiomics using machine learning algorithms to predict MGMT promoter methylation status in glioma patients: a meta-analysis." *Diagnostic and Interventional Radiology* 27, no. 6 (2021): 716. https://doi.org/10.5152/DIR.2021.21153

[4] Lara-Velazquez, Montserrat, Rawan Al-Kharboosh, Stephanie Jeanneret, Carla Vazquez-Ramos, Deependra Mahato, Daryoush Tavanaiepour, Gazanfar Rahmathulla, and Alfredo Quinones-Hinojosa. "Advances in brain tumor surgery for glioblastoma in adults." *Brain sciences* 7, no. 12 (2017): 166. https://doi.org/10.3390/brainsci7120166

[5] Sultan, Hossam H., Nancy M. Salem, and Walid Al-Atabany. "Multi-classification of brain tumor images using deep neural network." *IEEE access* 7 (2019): 69215-69225. https://doi.org/10.1109/ACCESS.2019.2919122

[6] Kirstein, Anna, Thomas E. Schmid, and Stephanie E. Combs. "The role of miRNA for the treatment of MGMT unmethylated glioblastoma multiforme." *Cancers* 12, no. 5 (2020): 1099. https://doi.org/10.3390/cancers12051099

[7] Kamson, David O., and Stuart A. Grossman. "The role of temozolomide in patients with newly diagnosed wild-type IDH, unmethylated MGMTp glioblastoma during the COVID-19 pandemic." *JAMA oncology* 7, no. 5 (2021): 675-676. https://doi.org/10.1001/jamaoncol.2020.6732

[8] McAleenan, Alexandra, Claire Kelly, Francesca Spiga, Ashleigh Kernohan, Hung-Yuan Cheng, Sarah Dawson, Lena Schmidt et al. "Prognostic value of test (s) for O6-methylguanine–DNA methyltransferase (MGMT) promoter methylation for predicting overall survival in people with glioblastoma treated with temozolomide." *Cochrane Database of Systematic Reviews* 3 (2021). https://doi.org/10.1002/14651858.CD013316.PUB2

[9] Yogananda, C.G.B., B.R. Shah, S. S. Nalawade, G.K. Murugesan, F.F. Yu, M.C. Pinho, B.C. Wagner, Mickey, B., Patel, B., Fei, A.J., Madhuranthakam, and Maldjian, J.A. "MRI-based deep-learning method for determining glioma MGMT promoter methylation status." *American Journal of Neuroradiology* 42, no. 5 (2021): 845-852. https://doi.org/10.3174/ajnr.A7029

[10] Muthu, Shanmuga Pillai Murutha, and Sellappan Palaniappan. "Categorization of Early Detection Classifiers for Gastric Carcinoma through Data Mining Approaches." *Journal of Advanced Research in Computing and Applications* 32, no. 1 (2023): 1-12. https://doi.org/10.37934/arca.32.1.112

[11] Din, Roshidi, Nuramalina Mohammad Na'in, Sunariya Utama, Muhaimen Hadi, and Alaa Jabbar Qasim Almaliki. "Innovative machine learning applications in non-revenue water management: Challenges and future solution." *Semarak International Journal of Machine Learning* 1, no. 1 (2024): 1-10. https://doi.org/10.37934/sijml.1.1.110

[12] Morshidi, Azizan, Noor Syakirah Zakaria, Mohammad Ikhram Mohammad Ridzuan, Rizal Zamani Idris, Azueryn Annatassia Dania Aqeela, and Mohamad Shaukhi Mohd Radzi. "Artificial intelligence and Islam: A bibiliometric-thematic analysis and future research direction." *Semarak International Journal of Machine Learning* 1, no. 1 (2024): 41-58. https://doi.org/10.37934/sijml.1.1.4158

[13] Ong, Siew Har, Sai Xin Ni, and Ho Li Vern. "Dimensions affecting consumer acceptance towards artificial intelligence (AI) service in the food and beverage industry in Klang Valley." *Semarak International Journal of Machine Learning* 1, no. 1 (2024): 20-30. https://doi.org/10.37934/sijml.1.1.2030

[14] Shatnawi, Hashem, and Mohammad N. Alqahtani. "Delving into the revolutionary impact of artificial intelligence on mechanical systems: A review." *Semarak International Journal of Machine Learning* 1, no. 1 (2024): 31-40. https://doi.org/10.37934/sijml.1.1.3140

[15] Zulkefli, Nor Atirah Izzah, Yeak Su Hoe, and Nor Afifah Hanim Zulkefli. "Fuzzy predator-prey systems by extended runge-kutta method with polynomial interpolation technique." *Semarak International Journal of Machine Learning* 1, no. 1 (2024): 11-19. https://doi.org/10.37934/sijml.1.1.1119

[16] Zlochower, Avraham, Daniel S. Chow, Peter Chang, Deepak Khatri, John A. Boockvar, and Christopher G. Filippi. "Deep learning AI applications in the imaging of glioma." *Topics in Magnetic Resonance Imaging* 29, no. 2 (2020): 115-00. https://doi.org/10.1097/RMR.0000000000000237

[17] Davenport, Thomas, and Ravi Kalakota. "The potential for artificial intelligence in healthcare." *Future healthcare journal* 6, no. 2 (2019): 94-98. https://doi.org/10.7861/futurehosp.6-2-94

[18] Chang, Peter, J. Grinband, B. D. Weinberg, M. Bardis, M. Khy, G. Cadena, M-Y. Su et al. "Deep-learning convolutional neural networks accurately classify genetic mutations in gliomas." *American Journal of Neuroradiology* 39, no. 7 (2018): 1201-1207. https://doi.org/10.3174/ajnr.A5667

[19] Chen, Xin, Min Zeng, Yichen Tong, Tianjing Zhang, Yan Fu, Haixia Li, Zhongping Zhang, Zixuan Cheng, Xiangdong Xu, Ruimeng Yang, Zaiyi Liu, Xinhua Wei, and Xinqing Jiang. "Automatic prediction of MGMT status in glioblastoma via

deep learning-based MR image analysis." *BioMed research international* 2020, no. 1 (2020): 9258649. https://doi.org/10.1155/2020/9258649

[20] Han, Lichy, and Maulik R. Kamdar. "MRI to MGMT: Predicting methylation status in glioblastoma patients using convolutional recurrent neural networks." In *Pacific Symposium on Biocomputing 2018: Proceedings of the Pacific Symposium*, pp. 331-342. 2018. https://doi.org/10.1142/9789813235533_0031

[21] Chen, Sixuan, Yue Xu, Meiping Ye, Yang Li, Yu Sun, Jiawei Liang, Jiaming Lu et al. "Predicting MGMT promoter methylation in diffuse gliomas using deep learning with radiomics." *Journal of clinical medicine* 11, no. 12 (2022): 3445. https://doi.org/10.3390/jcm11123445

[22] Kim, Byung-Hoon, Hyeonhoon Lee, Kyu Sung Choi, Ju Gang Nam, Chul-Kee Park, Sung-Hye Park, Jin Wook Chung, and Seung Hong Choi. "Validation of MRI-based models to predict MGMT promoter methylation in gliomas: BraTS 2021 radiogenomics challenge." *Cancers* 14, no. 19 (2022): 4827. https://doi.org/10.3390/cancers14194827

[23] Lu, Yiping, Markand Patel, Kal Natarajan, Ismail Ughratdar, Paul Sanghera, Raj Jena, Colin Watts, and Vijay Sawlani. "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 (2020): 161-170. https://doi.org/10.1016/j.mri.2020.09.017

[24] Le, Nguyen Quoc Khanh, Duyen Thi Do, Fang-Ying Chiu, Edward Kien Yee Yapp, Hui-Yuan Yeh, and Cheng-Yu Chen. "XGBoost improves classification of MGMT promoter methylation status in IDH1 wildtype glioblastoma." *Journal of personalized medicine* 10, no. 3 (2020): 128. https://doi.org/10.3390/jpm10030128

[25] He, Kaiming, Xiangyu Zhang, Shaoqing Ren, and Jian Sun. "Deep residual learning for image recognition." In *Proceedings of the IEEE conference on computer vision and pattern recognition*, pp. 770-778. 2016. https://doi.org/10.1109/CVPR.2016.90

[26] Soundarya, C., A. Kalaiselvi, and J. Surya. "Brain Tumor Detection Using Transfer Learning." *J. Signal Process* 9, no. 1 (2023): 33-42. https://doi.org/10.46610/JOSP.2023.v09i01.004