Predicting the MGMT Promoter Methylation Status in T2-FLAIR Magnetic Resonance Imaging Scans Using Machine Learning

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Abstract: Glioblastoma is the most common form of brain cancer in adults, and is characterized by one of the worst prognosis, with median survival being less than one year. Magnetic resonance imaging (MRI) plays a key role in detecting and objectively tracking the disease by extracting quantifiable parameters of the tumor, such as its volume or bidimensional measurements. However, it has been shown that the presence a specific genetic sequence in a lesion, being the DNA repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, may be effectively used to predict the patient's responsiveness to chemotherapy. The invasive process of analyzing a tissue sample to verify the MGMT promoter methylation status is time-consuming, and may require performing multiple surgical interventions in longitudinal studies. Thus, building non-invasive techniques of predicting the genetic subtype of glioblastoma is of utmost practical importance to not only accelerate the overall process of determining the MGMT promoter methylation status in glioblastoma patients, but also to minimize the number of necessary surgeries. In this paper, we tackle this problem and propose an end-to-end machine learning classification pipeline benefitting from radiomic features extracted from brain MRI scans, and validate it over a well-established RSNA-MICCAI Brain Tumor Radiogenomic Classification benchmark dataset.

1 INTRODUCTION

Glioblastoma (GBM) stands out as the prevalent malignant brain tumor among adults, and despite extensive research spanning decades, it is still one of the deadliest cancers, primarily attributed to its unfavorable prognosis. Consequently, the precise assessment of therapy response in GBM poses significant challenges and holds immense clinical importance (Qi et al., 2023). Although, multi-modal magnetic resonance imaging (MRI) scans can bring important structural information concerning such brain lesions, their manual analysis of acquired images is time- and cost-inefficient, it lacks reproducibility and suffers from significant inter- and intra-rater disagreement (Xuan et al., 2022; Hu et al. 2022). To automate the tedious process of analyzing MRI scans, various algorithms have been emerging at a steady pace recently. These practical challenges can be effectively tackled by automatic brain lesions detection and segmentation techniques. They may be split into atlas-, image analysis-, machine learning-based, and hybrid techniques. In the atlas-based approaches, we exploit manually-delineated atlases to segment unseen scans, relying on image registration and facing challenges with diverse tumor characteristics that are difficult to capture within an atlas (Xing et al., 2022). Similarly, image analysis-based algorithms, including thresholding and region-growing techniques, are often easy to implement and offer fast operation, but they struggle with heterogeneous tumors and noisy images (Puttagunta et al., 2021; Vadmal et al., 2022). Conventional machine learning approaches offer advantages directly related to their nature (of such methods being data-driven), but they require heavy feature engineering, hence elaborating manually-designed features that would capture intrinsic brain tumor characteristics. Finally, deep learning models encompass a range of network architectures,

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including ensembles (Shi et al., 2021), U-Net (Bukhari et al., 2022), encoder-decoder (Yan et al., 2022), and more (Peiris et al., 2022) that were thoroughly validated over the Brain Tumor Segmentation (BraTS) Challenge throughout the recent years, and established the current state of the art in the field (Baid et al. 2021). Although accurate brain lesion segmentation is of paramount importance in order to objectively assess the tumor progression through extracting its quantifiable characteristics, such as its volumetric or bidimensional measurements (Hu et al. 2022), the structural information concerning the brain may not be enough to fully understand the patient status and benefit from it in planning the treatment (Beyer et al., 2020).

There have been various research efforts indicating that the identification of a particular genetic sequence in a lesion – specifically, the DNA repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation – can serve as an effective predictor of a patient's responsiveness to chemotherapy (Weller et al., 2010). Additionally, the MGMT status has become a stratification parameter of patients with glioblastoma within clinical trials as well. The intrusive nature of examining a tissue sample to confirm the MGMT promoter methylation status is time-intensive and may necessitate multiple surgical interventions in longitudinal studies. Consequently, the development of non-invasive techniques for predicting the genetic subtype of glioblastoma becomes paramount. This not only expedites the overall process of determining the MGMT promoter methylation status in glioblastoma patients but also reduces the need for multiple surgeries such patients would have to undergo. Therefore, developing non-invasive methods for quantifying the MGMT promoter methylation status has been already researched in the literature, e.g., using texture features extracted from T2-weighted MR images and Support Vector Machines (Korfiatis et al., 2016). It was also demonstrated that the use of radiomic features together with machine learning algorithms can enable non-invasive prediction of the MGMT promoter methylation status (Hajianfar et al., 2019) – here, a pipeline of the radiomic feature extraction, feature selection, and classification were employed for each patient. Also, there are deep learning-powered approaches, e.g., exploiting various network architectures (Korfiatis et al., 2017). In their recent work, Saeed et al. 2023 performed an extensive evaluation study of an array of deep learning models for estimating MGMT methylation status from MRI data, and showed that the reliability of the deep learning approaches should be verified using external cohorts before exploiting them in clinical applications. Here, capturing large, heterogeneous and representative datasets that would allow for training large-capacity learners is a practical challenging which may ultimately hamper generalization capabilities of deep learning models.

In this work, we tackle the problem of quantifying the MGMT methylation status based on MRI data, and introduced a classic machine learning algorithm for this task. We hypothesize that the features extracted from the whole brain region scanned using the T2 Fluid Attenuation Inversion Recovery (T2-FLAIR) MR sequence, as such sequences have been designed to suppress the signal from cerebrospinal fluid, providing improved visualization of lesions near cerebrospinal fluid spaces, may be utilized in differentiating the MGMT methylation status (Alpar, 2023). Here, since the lesion segmentation step is skipped in our processing chain, we may not only accelerate the computation, as a single MR sequence is processed, but we can also rely on the widely-established brain extraction (skull stripping) algorithms (Isensee et al., 2019) for removing the skull that are known to be generalizing well over the unseen MR scans. Once the T2-FLAIR sequence is skull-stripped, we extract nearly 120 radiomic-based features that are fed (with or without additional dimensionality reduction) to the classification engine. The generalization capabilities of the proposed technique for quantifying the MGMT methylation status were verified over the RSNA-MICCAI Brain Tumor Radiogenomic Classification benchmark dataset (Baid et al. 2021; Bakas et al., 2017a; Bakas et al., 2017b; Bakas et al., 2017c; Menze et al., 2015). In this study, we frame the problem of assessing the MGMT methylation status as the classification task, with the patients being assigned to unmethylated and methylated classes.

The remainder of the paper is structured as follows. In Section 2, we present the RSNA-MICCAI Brain Tumor Radiogenomic Classification benchmark dataset, and introduce our machine learning pipeline for assessing the MGMT methylation status based on the radiomic-based features extracted from T2-FLAIR MR sequences. In Section 3, we report and discuss the experimental study performed to investigate the generalization capabilities of the algorithms, as well as to verify the impact of various dimensionality reduction techniques on its capabilities (both classic and deep learning-powered, with the latter benefiting from autoencoder architectures). Finally, Section 4 summarized the findings and sheds more light on the

most promising research directions that may emerge from the results obtained in this article.

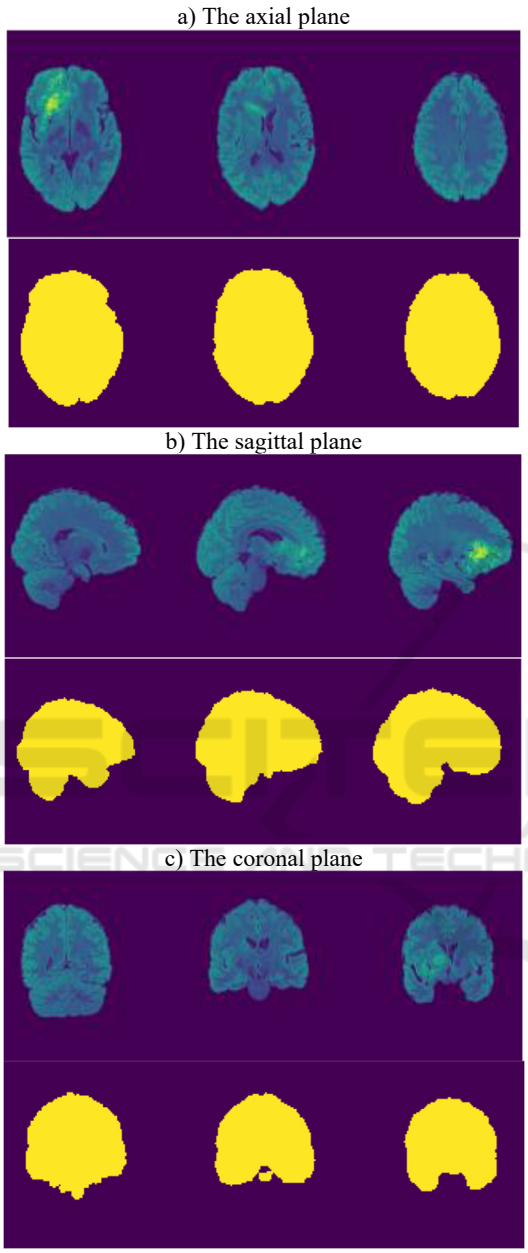

Figure 1: An example of a skull-stripped T2-FLAIR MR frames (visualized in the false-color scheme), together with the corresponding brain regions in the a) axial, b) sagittal, and c) coronal planes.

2 MATERIALS AND METHODS

In this section, we discuss the dataset used in our study (Section 2.1). In Section 2.2, we present the most important steps of our processing chain for classifying the patients into the unmethylated and methylated classes, based on the radiomic features extracted from T2-FLAIR MR sequences.

2.1 The RSNA-ASNR-MICCAI Brain Tumor Segmentation Dataset

In this study, we build upon the RSNA-ASNR-MICCAI Brain Tumor Segmentation (BraTS) benchmark dataset (the 2021 edition, for which the clinical information related to the MGMT promoter methylation status was obtained as well) (Baid et al. 2021; Bakas et al., 2017a; Bakas et al., 2017b; Bakas et al., 2017c; Menze et al., 2015). This dataset contains multi-modal MRI scans captured with different protocols and scanners from multiple institutions, and the BraTS dataset is commonly considered the state-of-the-art benchmark dataset for confronting the brain tumor segmentation algorithms, thanks to its size and heterogeneity. The MRI scans contained within the dataset were interpolated to the same shape (the size of an MRI scan is 240 × 240 × 155, therefore there are 155 images of 240 × 240 MR images, with the voxel size of 1 mm^3). All of the available images are skull-stripped – a set of example T2-FLAIR frames (obtained for a single patient) with the corresponding brain ground-truth segmentation masks are rendered in Figure 1.

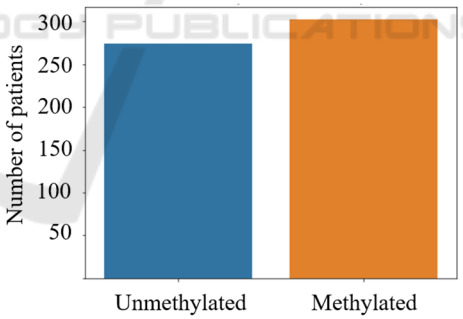

Figure 2: Distribution of the unmethylated and methylated patients in the dataset used in this study.

The MGMT promoter methylation status data was defined as a binary label, corresponding to the unmethylated and methylated patients. The distribution of the methylated and unmethylated patients within the training set of BraTS 2021 (for which the ground-truth labels are known, as they were revealed by the organizers of the challenge) is visualized in Figure 2. Out of all 585 patients, we removed nine patients due to an incorrect registration of their brain segmentation masks and corresponding image data. Therefore, the final dataset included 576

patients with the MRI scans and the corresponding MGMT promoter methylation status. We can observe that the dataset is balanced, and includes a similar number of unmethylated and methylated patients.

2.2 Predicting the MGMT Promoter Methylation Status Using Machine Learning and Radiomic Features

In this work, we introduce an end-to-end processing chain benefiting from classic machine learning classification models (trained in a supervised way) operating over the radiomic features extracted from T2-FLAIR sequences of brain MRI (Figure 3). The feature extraction may be followed by an optional dimensionality reduction step which can play a pivotal role if a very large number of radiomic features are extracted, as it may easily lead to overfitting the model to the training data (Kotowski et al., 2023). Of note, our approach for determining the MGMT promoter methylation status offers a high level of flexibility, and the specific algorithms may be easily updated at each processing step – this flexibility will be further proven in the experimental section of this article.

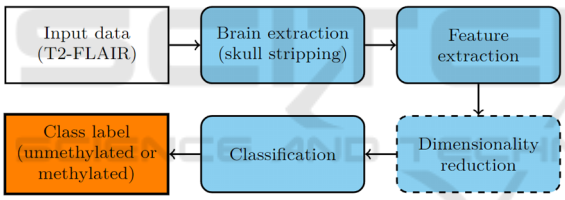

Figure 3: A high-level flowchart presenting the proposed processing chain. The optional step is rendered as a dashed block, whereas the input and output steps are presented as white and orange ones.

The input T2-FLAIR images undergo brain extraction, which might be performed using an array of thoroughly-evaluated state-of-the-art techniques, such as the HD-BET algorithm (Isensee et al., 2019) (note that the scans included in BraTS are already skull-stripped, hence this step was omitted in our study). Afterwards, we extract the following radiomic features (as suggested by van Griethuysen et al., 2017 and by Ponikiewski et al., 2022) from the 3D brain region of the T2-FLAIR scan:

- First Order Statistics (18 features),
- Shape-based (3D) features (14 features),
- Gray Level Co-occurrence Matrix (24 features)
- Gray Level Run Length Matrix (16 features),
- Gray Level Size Zone Matrix (16 features),
- Neighboring Gray Tone Difference Matrix (5 features),
- Gray Level Dependence Matrix (14 features).

The majority of the features are in compliance with the feature definitions as suggested by the Imaging Biomarker Standardization Initiative (Zwanenburg et al., 2020). Overall, we extract 119 features (which were scaled to the unit variance).

Since the number of features is large, especially when confronted with a relatively small number of patients, exploiting all of them while training supervised learners may easily lead to overfitting them to the training set, hence memorizing it – it would render them impossible to generalize over the unseen test patients (Ying et al., 2019). To deal with this issue, we exploit the additional (yet optional) dimensionality reduction step, and employ the following techniques for this task (although we are aware that the hyperparameters of the following data dimensionality methods are tunable, we present them here, rather than in the experimental section in order to make this section self-contained):

- Principal component analysis (PCA), for which the number of principal components (PCs) was selected to explain 98% of the data variance (21 PC were exploited). In Figure 4, we can observe that exploiting just two PCs would make the classification process (i.e., distinguishing the methylated and unmethylated patients) virtually impossible due to heavy overlaps across these two classes in the PC space for 2 PCs.

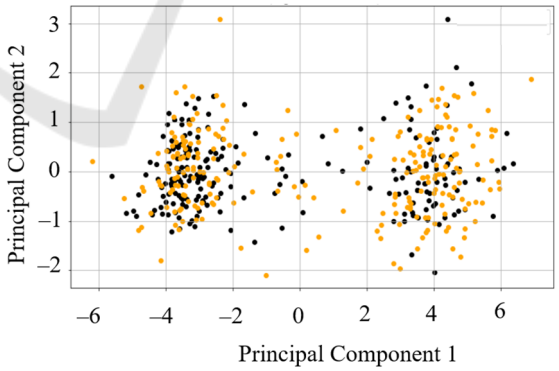

Figure 4: The first two PCs show that discriminating unmethylated (black dots) and methylated (orange dots) patients would be virtually impossible using only two PCs. In this study, we selected 21 PCs to explain 98% variance within the dataset.

- Autoencoder (AE) with a fully-connected architecture with the scaled exponential linear unit activations, containing two encoding and decoding layers (with 50 and 30 neurons), and

elaborating the latent representation of 21 features (to ensure consistency with the number of PCs elaborated by PCA).

- Feature selection (FS), where we selected 21 features with the largest variance (as previously, we ensured consistency with the number of PCs). Such variance-based feature selection might be useful to ensure interpretability of the extracted features (this is not necessarily the case for the radiomic features, as they may be fundamentally challenging to interpret by human readers).

In Figure 5, we render the distributions of the selected features for all dimensionality reduction techniques – these features (extracted by each dimensionality reduction approach) are later fed into the supervised learner for elaborating the predicted class label (i.e., methylated or unmethylated patient).

There are numerous established supervised classification models that could be exploited in our processing pipeline. In this study, we investigated the following machine learning models which have proven their classification capabilities in a range of real-world applications: logistic regression (LR), support vector machines (SVMs), random forests (RFs), *k*-nearest neighbor classifiers (*k*-NN), extreme gradient boosting classifiers (XGBoost), and artificial neural networks (ANNs) with a single hidden layer containing 10 neurons. As for the feature extraction and dimensionality reduction techniques, other machine learning models (also deep learning techniques) can be easily exploited in our approach.

3 EXPERIMENTAL STUDY

In this section, we discuss the results obtained in our experimental study. To quantify the generalization capabilities of the classification engine, we follow the 5-fold cross-validation procedure, where each fold is stratified according to the ratio of unmethylated and methylated patients within the full dataset. The performance of the models was assessed using classic metrics, including precision (Pr), recall (Re), F1 score and the Matthews's correlation coefficient (MCC). All metrics should be maximized, where one indicates the perfect classification (additionally, we tracked accuracy during the ANN training to verify if it started overfitting). The hyperparameters of all investigated machine learning models were fine-tuned using an internal cross-validation procedure performed over the corresponding training set (the test set in the *k*-fold cross-validation approach was never used here).

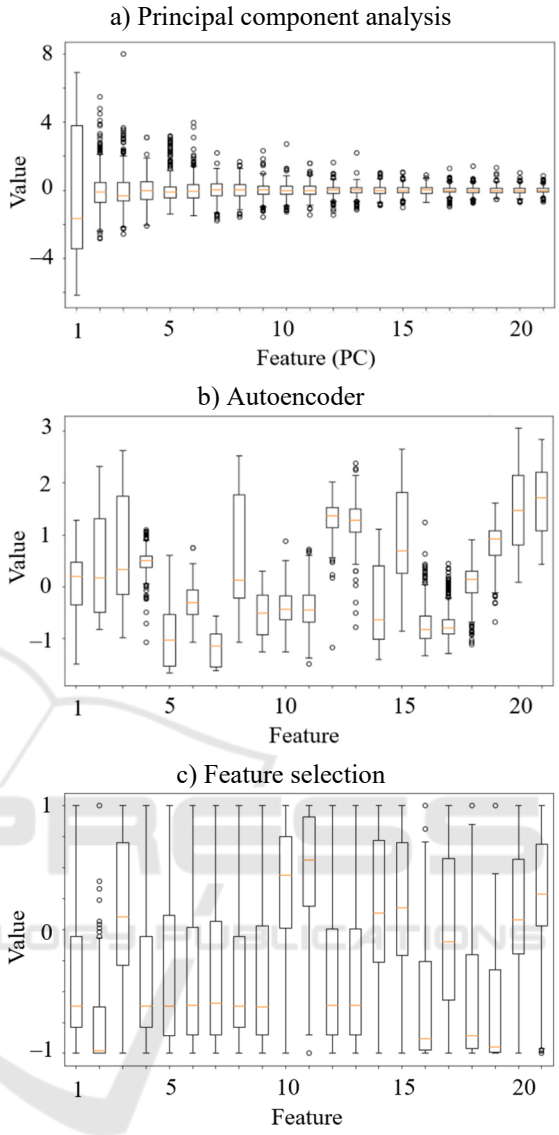

Figure 5: Distribution of the features selected using a) principal component analysis, b) a fully-connected autoencoder, and c) variance-based feature selection.

Finally, to make sure that the processing chain is straightforward to reproduce (the full approach was implemented in Python 3.6), we exploited a well-established *pyradiomics* package to extract radiomic features from the brain areas, and the *scikit-learn* package for the classification models.

In Figure 6, we gather the experimental results (quantified as all above-mentioned quality metrics) obtained for all investigated machine learning models and dimensionality reduction techniques, averaged across all five test folds. We can appreciate that various dimensionality reduction gave consistently similar results for virtually all classification models

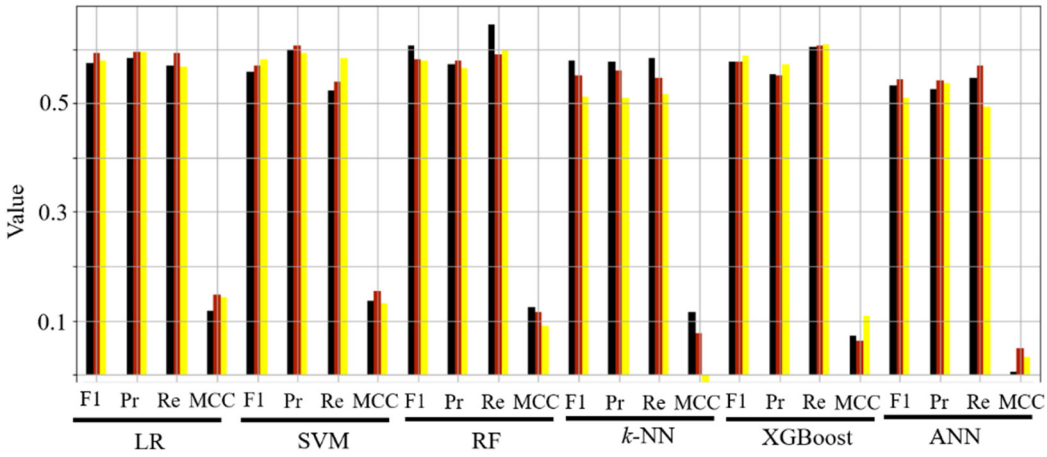

Figure 6: Classification results (averaged across all five test folds) obtained for all investigated machine learning classification models and dimensionality reduction techniques (the black color corresponds to principal component analysis, red to the autoencoder, and yellow to variance-based feature selection).

Table 1: The results obtained using the ANN model without and with regularization techniques applied (averaged across all test sets in the five-fold cross-validation scenario). The best metrics for each dimensionality reduction approach are boldfaced.

Regularization	Metric	PCA	AE	FS
None	F1	0.53	0.54	0.51
	Pr	0.53	0.54	0.54
	Re	0.55	**0.57**	0.49
	MCC	0.01	0.05	0.03
Dropout	F1	0.55	0.49	**0.57**
	Pr	0.54	0.56	0.58
	Re	**0.56**	0.43	0.56
	MCC	0.04	0.06	**0.12**
Dropout and early stopping	F1	**0.56**	**0.56**	**0.56**
	Pr	**0.59**	**0.59**	**0.59**
	Re	0.52	0.54	0.54
	MCC	**0.13**	**0.12**	**0.12**

(the smallest differences between different dimensionality reduction routines were captured for the LR classifier), with PCA outperforming the other methods for RF. Here, this model resulted in the highest recall values which is of paramount clinical significance, as identifying methylated patients may lead to designing their more effective treatment pathways. Of note, it was observable that the ANN model started overfitting the training set – as an example for the PCA dimensionality reduction, the accuracy over the training folds exceeded 0.9, with the corresponding accuracy over the validation set reaching approx. 0.6. This phenomenon was, however, observed for all dimensionality reduction approaches, indicating that the training sample may be too small to elaborate a well-generalizing classifiers. To verify if applying additional regularization techniques could help improve the abilities of the ANN model, we investigated two additional (yet well-established in the field) regularization approaches, being the dropout within the ANN, together with an early stopping routine. The results gathered in Table 1 indeed confirm that applying additional regularization techniques help improve the generalization capabilities of the ANN models.

4 CONCLUSIONS

Glioblastoma is the most common form of brain cancer, and the detailed profiling of patients suffering from this disease is of pivotal importance. We approached this issue, and proposed a machine learning pipeline to predict the MGMT promoter methylation from T2-FLAIR, as it is an important biomarker for the patient prognosis. The experiments indicated that radiomic features extracted from whole-brain scans allow to elaborate classifiers that identify the methylated patients. The generalization of models, thus their clinical utility might be improved by gathering more heterogeneous and representative training sets, as we observed that the models started overfitting, and by explicitly tackling the problem of the dataset imbalance. This issue may be also tackled using model-level regularization which was shown effective in this study.

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