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# Domain Adaptive Federated Learning for Multi-institution Molecular Mutation Prediction and Bias Identification

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## ABSTRACT

Deep learning models have shown potential in medical image analysis tasks. However, training a generalized deep learning model requires huge amounts of patient data that is usually gathered from multiple institutions which may raise privacy concerns. Federated learning (FL) provides an alternative to sharing data across institutions. Nonetheless, FL is susceptible to a few challenges including inversion attacks on model weights, heterogenous data distributions, and bias. This study addresses heterogeneity and bias issues for multi-institution patient data by proposing domain adaptive FL modeling using several radiomics (volume, fractal, texture) features for O6-methylguanine-DNA methyltransferase (MGMT) classification across multiple institutions. The proposed domain adaptive FL MGMT classification inherently offers differential privacy (DP) for the patient data. For domain adaptation two techniques e.g., mixture of experts (ME) with a gating network and adversarial alignment are used for comparison. The proposed method is evaluated using publicly available multi-institution (UPENN-GBM, UCSF-PDGM, RSNA-ASNR-MICCAI BraTS-2021) data set with a total of 1007 patients. Our experiments with 5-fold cross validation suggest that domain adaptive FL offers improved performance with a mean accuracy of 69.93% $\pm$ 4.8 % and area under curve of 0.655 $\pm$ 0.055 across multiple institutions. In addition, further analysis of probability density of gating network for domain adaptive FL identifies the institution that may bias the global model prediction due to increased heterogeneity for a given input. Our comparison analysis shows that the proposed method with bias identification offers the best predictive performance when compared to different commonly employed FL and baseline methods in the literature.

**Keywords:** Federated Learning (FL), Domain Adaptation (DA), Radiomics, Fractal texture, MGMT, Magnetic Resonance Imaging (MRI), Classification, Differential Privacy (DP).

## 1. DESCRIPTION OF PURPOSE

Glioblastoma (GB) is a malignant brain tumor, affecting 50% of all brain gliomas.[1] Standard treatment includes surgical resection, radiation therapy, and temozolomide (TMZ) and Novo-TTF.[2] Epigenetic variations and actionable mutations are found in GB cases.[3] In one-third GB cases, MGMT is epigenetically silenced by promoter hypermethylation,[4] improving survival and favorable response to TMZ.[5]

Several prior studies[6–8] demonstrate that deep learning (DL) models can predict MGMT methylation status from pre-operative magnetic resonance imaging (MRI), but centralized data aggregation for DL model training raises privacy concerns. Federated learning (FL) offers a promising approach, where participating institutions train local models on their own data without forwarding it to a server or central node.[9] While FL has shown significant advancements in medical domain, the overall challenges associated with FL are privacy, security, data heterogeneity, and bias.[10]

Despite the promising aspects of FL, adversaries can decrypt DL model weights, revealing patients' information with high accuracy.[11] To alleviate disclosure of patient information from the model weights, differential privacy (DP)[12] has been proposed. DP works by minimizing individually identifiable information while maintaining the global statistical distribution of the data set. DP can be implemented by adding noise to shared model weights in FL.[13]

A common challenge in the medical domain, including GB research, is the domain shift in MRI data distributions across institutions, affecting the generalization of models trained on quantitative features.[14] Domain adaptation techniques, e.g., mixture of experts (ME) with a gating network and adversarial domain alignment[15,16]within the FL framework can improve global model performance. Recently, Li et al.[17] demonstrated the potential of

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domain-adaptive FL in medical settings. Given their success with functional MRI (fMRI) data, we hypothesize that this approach may also work well for structural MRI, which exhibits similar challenges with data heterogeneity, bias, and privacy.

Acknowledging the data heterogeneity across institutions, it becomes crucial to explore how the global model performs for various local (private) institutions and identify potential biases in decision-making. The gating network[15] within ME identifies the contribution of private and global models for patient cases. Further, the associated distribution of gating network outputs across each institution (private domain) may assist to identify the institution that may contribute to biased decision-making in the global model.

Consequently, this study aims to address issues of heterogeneity and bias in FL for multi-institutional patient data. Our proposed approach involves a domain-adaptive FL model using selected radiomics (volume, fractal, texture) features for O6-methylguanine-DNA methyltransferase (MGMT) classification across multiple institutions.

## 2. METHODOLOGY

In addressing the challenges of privacy, security, data heterogeneity, and bias outlined in the introduction, our methodology is designed to not only contribute to improved prediction performance but also to tackle these challenges. The subsequent sections detail how each aspect of our methodology directly addresses these critical challenges.

### 2.1 Patient Data

To address the challenge of data heterogeneity, patient data from three distinct institutions were meticulously curated, and a comprehensive mapping strategy was employed to avoid overlap. This approach ensures the robustness and generalizability of our model across diverse institutional dataset. In this study, we collect data from 3 different institutions that are publicly available in the Cancer Imaging Archive (TCIA). The data set is comprised of UPENN-GBM,[18] UCSF-PDGM,[19] RSNA-ASNR-MICCAI BraTS-2021.[20,21] We use the pre-operative scans of GB patients, which include four sequences of MRI scans: pre-contrast T1-weighted (T1), post-contrast T1-weighted (T1Gd), T2-weighted (T2) and T2 Fluid Attenuated Inversion Recovery (FLAIR). The status of MGMT methylation is provided for each patient within the data set. Appropriate mapping is conducted to avoid patient data overlap across institutions. All scans are co-registered, and skull stripped. The data set from 3 institutions includes the expert annotated tumor sub-regions of GB: enhancing tumor (ET), edema (ED), necrosis (NC), and non-enhancing tumor (NCR/NET). The distribution of patients across three sites is presented in Table 1.

Table 1: Summary of patient data across three institutions

| | **UPENN-GBM** | **UCSF-PDGM** | **BraTS-2021** | **Overall Total** |
|---|---|---|---|---|
| **Total Patient Case** | 262 | 169 | 576 | 1007 |
| **Patient with Methylated Status** | 111 | 122 | 300 | 533 |
| **Patient with Unmethylated Status** | 151 | 47 | 276 | 474 |
| **Total number of MRI scans** | 1048 | 676 | 2304 | 4028 |

### 2.2 Feature Extraction and Selection

Given the inherent data heterogeneity, our feature extraction process is designed to capture relevant information from multi-sequence MRI. The subsequent in-house feature selection algorithm ensures that the chosen features are not only informative but also contribute to addressing the challenge of extracting meaningful insights from diverse dataset.We extract multi-resolution fractal texture features[22–24] and conventional radiomics features from multiple sequence MRI (mMRI) for each institution. The features represent histogram-based statistics,

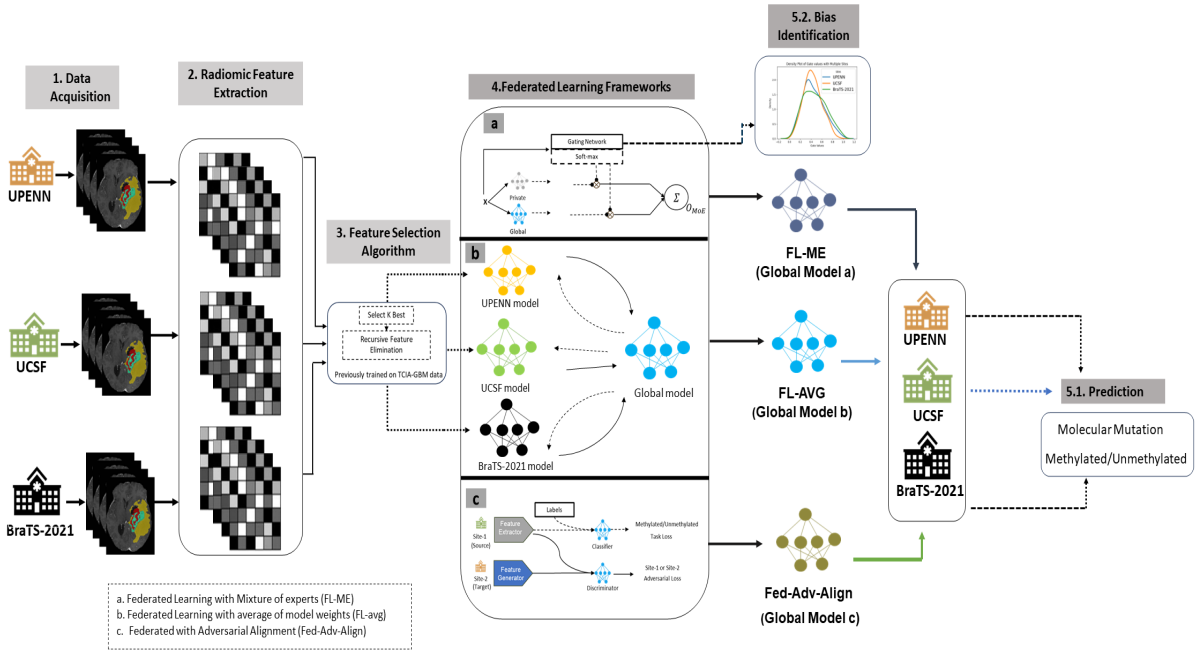



Figure 1: The overall FL pipeline for MGMT status prediction across multiple institutions.

volumetric, area, and textural properties of the tumor and its subregions. Total 1723 radiomics features are extracted from mMRI, and an in-house feature selection algorithm[25] is applied on the extracted features. The final number of features is 222 for each institution.

## 2.3 Federated Learning Frameworks

To ensure privacy and security, we employ a Federated Learning (FL) framework with three distinct configurations. FL-avg addresses bias concerns by averaging weights and introducing Laplacian noise, FL-ME adapts the global model to each institution, mitigating bias through a dynamic mixture of experts, and Fed-Adv-Align combats domain-specific biases by aligning feature distributions across institutions.
A deep feedforward neural network (FNN) 222-64-8-2 (corresponding to 222 nodes for first layer, 64 nodes followed by 8 nodes for hidden layer and 2 nodes as the output) is utilized to classify MGMT methylation status. We use ReLU activation in the hidden layers followed by batch normalization.Each institution has its own local model that outputs the class-wise probabilities for the given input features.We use the Adam optimizer (initial learning rate of 1e-3, lowered by 0.5 every 20 epochs) to train for 100 epochs with the categorial cross entropy loss.Each of the local models and the global model have the same FNN structure.Three different model configurations are applied within the FL framework, with details provided in the following sub-sections.

### 2.3.1 Federated Learning with average of model weights (FL-avg)

In the FL-avg framework (shown in Fig.1 [4.b]), The central node averages the weights of local models, and the weights from global model ($G_{fed}$) are sent back to update the local models. Random noise using Laplacian mechanisms[17] is added to ensure differential privacy.

### 2.3.2 Federated Learning with Mixture of Experts (FL-ME)

The global model $G_{fed}$ trained under the privacy preserving FL framework is adapted to each institution. Under FL-ME configuration, the global (general) model and private (institution) models are trained jointly to yield the

output for a given input (shown in Fig.1 [4.a]).
Let $M_{Gfed}$ be the general model with parameters $\theta_{Gfed}$ and $\hat{y}_{Gfed} = M_{Gfed}(x, \theta_{Gfed})$ be the predictive probability of the positive class by $M_{Gfed}$.The private model $M_{Pi}$ for $i^{th}$ institution has parameters $\theta_{Pi}$ and $\hat{y}_{Pi} = M_{Pi}(x, \theta_{Pi})$. The predicted output for institution $i$ is:

$$\hat{y}_i = \alpha_i(x) M_{Gfed}(x, \theta_{Gfed}) + (1 - \alpha_i(x)) M_{Pi}(x, \theta_{Pi}) \tag{1}$$

where, $\alpha_i(x)$ is the gating function and defined as the non-linear layer,[15] $\alpha_i(x) = \sigma(w_i^T x + b_i)$ , where $\sigma$ is the sigmoid function and $w_i^T, b_i$ are model weights.

### 2.3.3 Federated Learning with Adversarial Domain Alignment (Fed-Adv-Align)

As shown in Fig.1 (4.c), source and target sites have respective feature extractors, $G_S$ and $G_T$. For a source-target pair, discriminator $D_S$ is trained to classify the domain from which a sample is taken. Meanwhile, $G_S$ and $G_T$ are trained in opposition to $D_S$, effectively aligning the source and target feature distributions. The process repeats for each institution so that all institutions' feature distributions are aligned.

### 2.3.4 Bias Identification from Gating Network

The gating network plays a crucial role in identifying and mitigating bias within the FL-ME configuration. By dynamically weighing the contributions of global and private models based on input, it serves as a tool for detecting and addressing biases within specific institutional dataset, a key challenge outlined in the introduction. The gating function $\alpha_i(x)$ in equation (1) learns the contribution of global and private (institution) models over the training process. If the value of $\alpha_i(x)$ is small for a particular institution, the overall contribution of the private model will be higher compared to the global model. Hence, the probability density analysis of the gating values indicate the presence of an unusual domain distribution within a particular institution,[26] which cause bias in the global model.

## 3. RESULTS

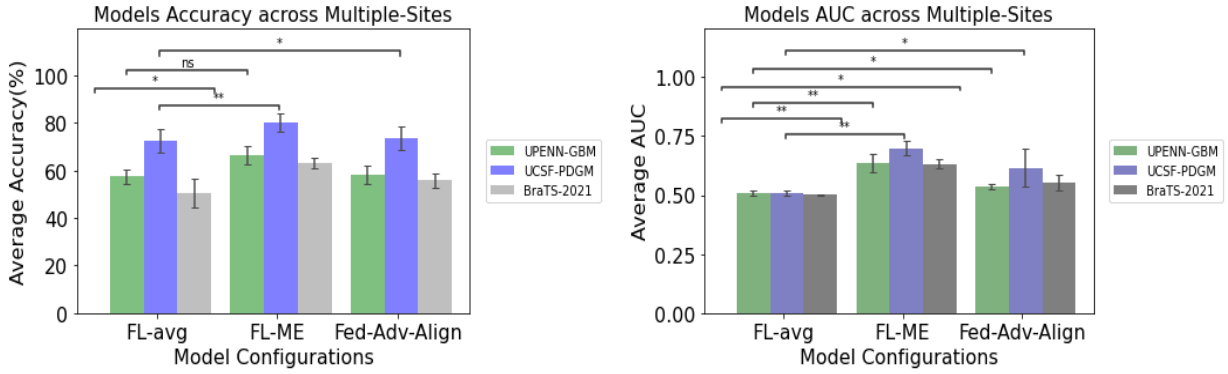
In this work, we evaluate the efficacy of domain adaptation within the FL framework for MGMT methylation classification across multiple institutions using FL-avg, FL-ME, and Fed-Adv-Align models. The performance of the model is evaluated using 5-fold cross validation within individual institutions.The baseline method indicates when the model is trained and tested on the same institution data. For instance, the baseline model with the same FNN architecture is trained and tested on UPENN-GBM data with 5-fold cross validation.

Table 2: Mean Test Accuracies(%) across multiple institutions for 5-fold cross validation

| Model Configurations | UPENN-GBM | UCSF-PDGM | BraTS-2021 | Average |
|---|---|---|---|---|
| **Baseline** | 42.3± 3.9 | 71.8 ± 5.4 | 51.8 ± 1.9 | 55.3± 3.7 |
| **FL-avg** | 57.6± 3.9 | 72.4 ± 5.6 | 50.5 ± 0.6 | 60.2 ± 3.4 |
| **FL-ME** | 66.4 ± 4.9 | 80.2 ± 6.5 | 63.2 ± 2.9 | **69.93 ± 4.8** |
| **Fed-Adv-Align** | 58.3 ± 4.1 | 73.6 ± 5.4 | 55.9 ± 3.7 | 62.60 ± 4.4 |

Table 3: Mean Test Area Under Curve (AUC) across multiple institutions for 5-fold cross validation

| Model Configurations | UPENN-GBM | UCSF-PDGM | BraTS-2021 | Average |
|---|---|---|---|---|
| **Baseline** | 0.5± 0.0 | 0.496 ± 0.008 | 0.498 ± 0.003 | 0.498 ± 0.003 |
| **FL-avg** | 0.508± 0.010 | 0.510 ± 0.016 | 0.501 ± 0.003 | 0.507 ± 0.010 |
| **FL-ME** | 0.635 ± 0.040 | 0.698 ± 0.097 | 0.633 ± 0.026 | **0.655 ± 0.055** |
| **Fed-Adv-Align** | 0.537 ± 0.012 | 0.616 ± 0.088 | 0.553 ± 0.033 | 0.569 ± 0.044 |

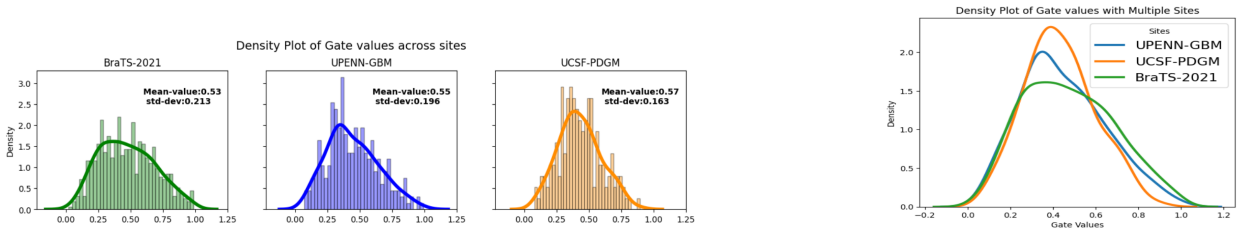



(a) Model Accuracy on Test Data (b) Model AUC on Test Data

Figure 2: (a) Mean Accuracies for 5-fold cross validation with 3 different model configurations. (b) Mean AUC for 5-fold cross validation with 3 different model configurations. Error bars show the standard deviation. A '*' depicts a significant difference (p-value¡0.05) between two groups, and 'ns' denotes a non-significant difference between two groups.

The inclusion of domain adaptation (ME) in FL modeling improves cross-validation accuracy and AUC to 69.93% and 0.655, respectively. Significant differences (ANOVA test, p-value $< 0.05$) exist across institutions with different model configurations as shown in Figure 2.

The gating values for each institution are the output of the gating network as shown in Fig.1. The institution with smaller gating value and probability density gives more weight to the private model's decision compared to the global model. As shown in Figure 3(a) the mean with standard deviation for BraTS-2021 is 0.53±0.213 while that of UCSF-PDGM is 0.57±0.163. Moreover, there is a significant difference (p-value=0.04) between the probability density distribution of UCSF-PDGM and BraTS-2021.We observe low performance of global models (FL-ME, FL-Avg, Fed-Adv-Align) in BraTS-2021 when compared to UCSF-PDGM, UPENN-GBM as shown in Table 2 and Table 3. Therefore, if the contribution of global and private model is not regulated, the global model performance may be biased when adapted to unusual domains like BraTS-2021.BraTS-2021 is considered as an unusual domain (heterogeneous) since it comprises 576 patient data curated from different institutions,[27] when compared to the other two data sets from single institution (e.g., UPENN-GBM and UCSF-PDGM) only.




(a) (b)

Figure 3: (a) The mean and standard deviation of gating values for each institution (BraTS-2021, UPENN-GBM, and UCSF-PDGM), (b) Probability density of gating values across three institutions.

The performance comparison of our FL models with deep learning in Table 4 shows that the proposed FL-ME performs better than other approaches. It is evident from the comparison that other deep learning-based methods does not consider the differential privacy within FL and bias identification for multi-institutional data.

## 4. NOVEL CONTRIBUTION

The contributions of this study are two-folds. First, this work addresses the challenge posed by data heterogeneity and bias across multiple institutions with domain adaptive FL modeling to improve accuracy and generalizability

Table 4: Performance comparison between our method and other MGMT predictive DL methods.

| **Methods** | **Data** | **Total number of patients** | **Validation Method** | **MRI Sequence** | **Accuracy (%)** | **AUC** | **FL with Differential Privacy** | **Bias Identification** |
|---|---|---|---|---|---|---|---|---|
| B. H. Kim et al.[6] (2022) | SNUH, BraTS-2021 | 985 | SNUH as test data | FLAIR, T1, T1Gd, T2 | 49.3 ± 1.3 | 0.516 ±3.8 | ✘ | ✘ |
| N. Saeed et al.[6](2023) | BraTS-2021 | 585 | 5-fold CV | FLAIR, T1, T1Gd, T2 | – | 0.63 ±0.01 | ✘ | ✘ |
| Atef et al.[28] (2022) | BraTS-2021 | 672 | External Validation Data | FLAIR, T1, T1Gd, T2 | – | 0.6152 | ✘ | ✘ |
| FL-avg **(Ours)** | UPENN-GBM, UCSF-PDGM, BraTS-2021 | 1007 | 5-fold CV | FLAIR, T1Gd, T2 | 60.2 ±0.034 | 0.507 ±0.010 | ✓ | ✓ |
| FL-ME **(Ours)** | UPENN-GBM, UCSF-PDGM, BraTS-2021 | 1007 | 5-fold CV | FLAIR, T1Gd, T2 | **69.93 ±0.048** | **0.655 ±0.055** | ✓ | ✓ |
| Fed-Adv-Align**(Ours)** | UPENN-GBM, UCSF-PDGM, BraTS-2021 | 1007 | 5-fold CV | FLAIR, T1Gd, T2 | 62.60 ±0.044 | 0.569 ±0.044 | ✓ | ✓ |

of MGMT classification across institutions for 1007 patients with a total of 4028 MRI scans. Second, analysis of probability density of gating network outputs with domain adaptive FL provides insights into which institution may be contributing to bias the global model prediction. This offers better understanding of diagnostic reliability of the global FL model for MGMT classification in this study.

## 5. CONCLUSION

This work proposes a comprehensive and generalized privacy preserving domain adapted FL model to handle heterogenous data distributions and bias from multiple institutions (UPENN-GBM, UCSF-PDGM, RSNA-ASNR-MICCAI BraTS-2021) for MGMT classification in GB patients. The experimental results suggest that the domain adaptive module within the FL framework provides the best predictive performance when compared to other relevant state-of-the-art FL approaches. We further perform rigorous statistical analysis of gating network outputs to identify the institution that may bias predictions from the global model. The outputs of gating network regulate the contribution of private and global model across each institution. Therefore, as observed

from the experimental results, the predictive performance of gating network outputs for BraTS-2021 (and consequently for the global model) are lower when compared to UCSF-PDGM and UPENN-GBM. Since BraTS-2021 dataset encompasses patient cases from different institutions, it is more heterogenous and hence exhibits an unusual domain distribution that can lead to bias in the predictive performance of global model. In the future, we plan to study the cause of bias in the global model due to private model data distribution. We further plan to identify the underlying imaging biomarker(s) and survival analysis of patient cases across multiple institutions with the domain adaptive FL model.

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