Purpose and Research Questions

Purpose

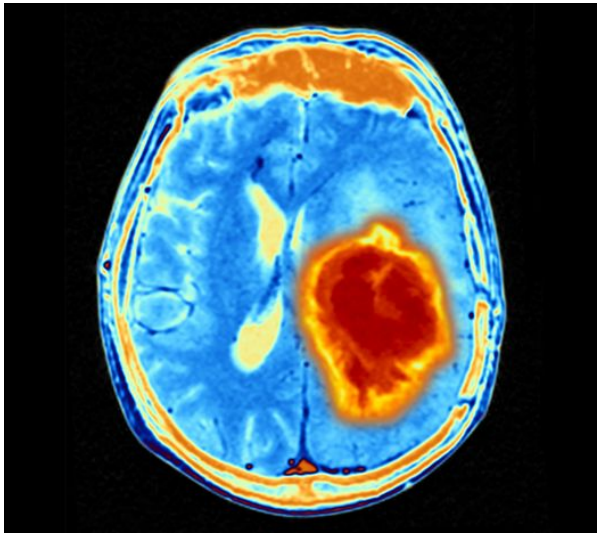
- To develop an automated deep-learning application that applies neural networks to predict **prognosis** and **targeted therapy** for glioblastoma from brain-biopsy whole-slide images more quickly and accurately than traditional pathology.

Research Questions

- How can neural networks predict glioblastoma **prognosis** by analyzing digital brain-biopsy tissue to detect tumor features, molecular subtypes, MGMT methylation, and EGFR amplification?
- How can biomarkers like genetic factors be determined from brain-biopsy whole-slide images and be utilized to effectively determine **targeted therapy?**
- How can the deep-learning software become **globally available and accessible,** especially in regions that lack pathologist expertise?

Background: Glioblastoma

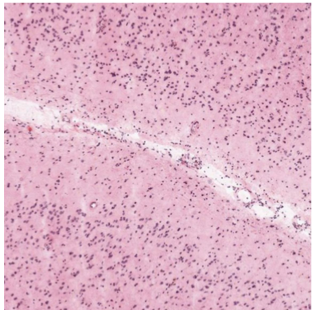
- Glioblastoma is the most aggressive and deadly brain cancer, having a five-year survival rate of only 7%. However, early detection and classification can greatly **improve patient prognosis** and **guide targeted treatment.**
- While many studies analyze MRI and CT scans, biopsy-tissue analysis is the **gold standard** for diagnosis. Traditionally, pathologists analyze brain-biopsy tissue manually to diagnose cancer. However, manual examination requires **days for comprehensive diagnosis** and varies depending on expertise. Many regions of the world also lack trained experts needed for comprehensive diagnosis.
- **Few automated systems exist** using WSIs to determine prognosis and targeted therapy. However, whole-slide images indicate tumor morphology, reveal digital biomarkers, and provide **elaborate tumor detail** when compared with other imagery methods.
- In GlioBLAST, **neural networks** are used to predict glioblastoma prognosis and determine targeted therapy for patients. These neural networks analyze whole-slide images and extract detail about **tumor features and biomarkers**.



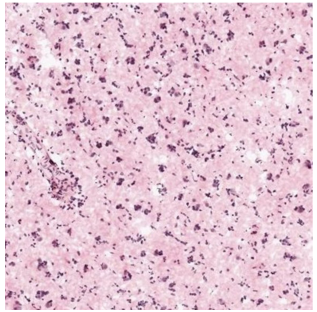
https://www.thetimes.co.uk/article/nhs-boosts-brain-tumour-survival-rates-hqccdpfc5

Background: Tumor Features and Molecular Subtypes

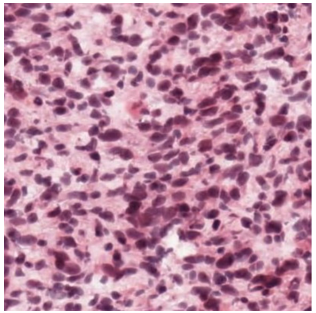
- **Histological Tumor Features:** Histological features are tumor regions with identifiable cellular characteristics. Pathologists utilize tumor-feature analysis **to comprehensively classify glioblastoma** and **to plan targeted therapy** for patients.
    - Leading Edge, Infiltrating Tumor, Cellular Tumor, Perinecrotic Zone, Pseudopalisading Cells, Pseudopalisading Cells Around Necrosis, Hyperplastic Blood Vessels, Microvascular Proliferation, and Necrosis.
- **Molecular Subtypes:** Molecular subtyping classifies cancers according to **biomarkers like informative genes.** Molecular-subtype classification holds **prognostic value,** since subtype clusters exhibit different patient outcomes, and **therapeutic value,** since treatment effectiveness varies between subtypes.
    - Classical, Mesenchymal, Proneural, and Neural.



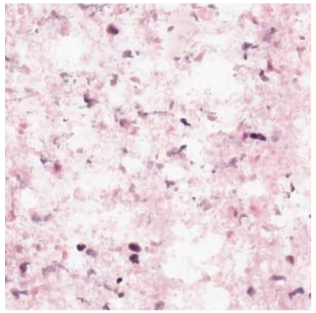
Leading Edge



Infiltrating Tumor



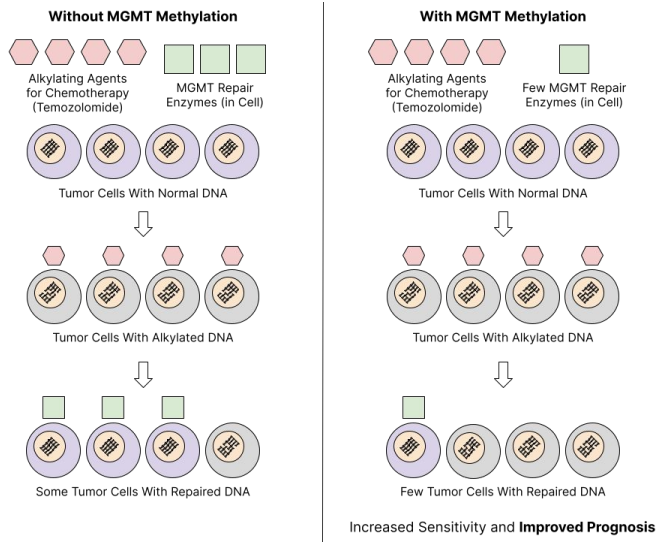
Cellular Tumor

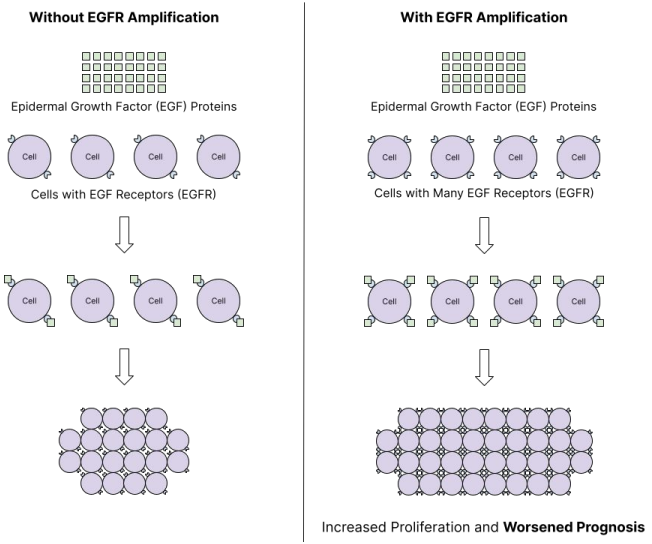


Necrosis

https://glioblastoma.alleninstitute.org

Background: MGMT Methylation and EGFR Amplification



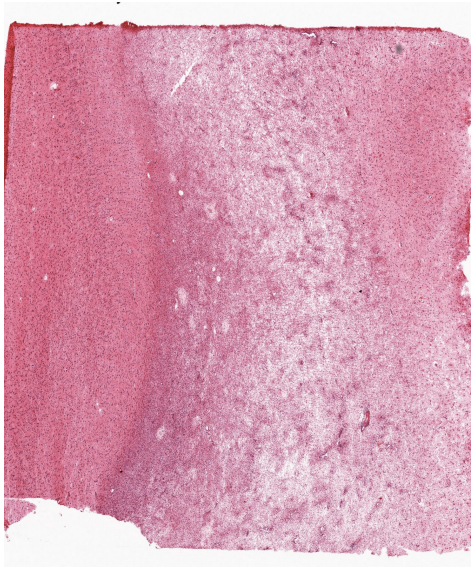


MGMT Methylation: The MGMT gene repairs damaged DNA and thus protects tumor cells from certain chemotherapy agents. MGMT methylation reduces these repair enzymes, **increasing the effectiveness of these drugs.** Thus, MGMT methylation aids **prognosis** and helps doctors determine **targeted therapy** for patients.

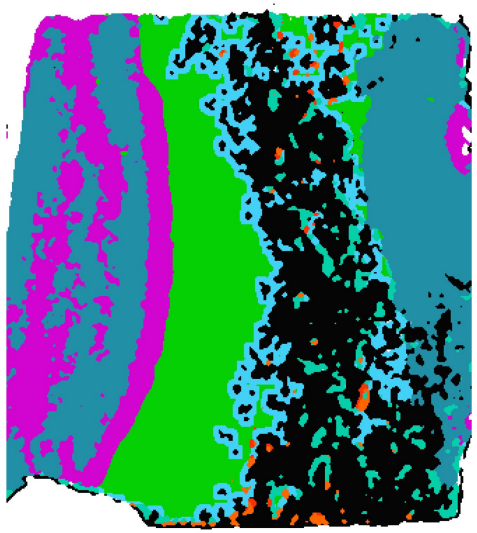
EGFR Amplification: The EGFR gene encodes receptors to the EGF proteins, which stimulate cell growth and proliferation. EGFR amplification increases the prevalence of these receptors, **intensifying tumor proliferation.** Thus, EGFR amplification aids **prognosis** by indicating aggressive tumors and encourages **targeted therapy** for the EGFR gene.

Data: Brain-Biopsy Whole-Slide Images

- Whole-slide images (WSIs) are **large scans of tissue slices** removed from tumor blocks after a resection surgery. Each WSI reveals elaborate details of a tumor, enabling accurate analysis with computers.
- The segmentation and classification models were trained with WSIs from the Ivy GAP (Glioblastoma Atlas Project) dataset, which includes over 11,000 WSIs from 41 different glioblastoma patients.
- The dataset also includes annotations (masks) of the ten tumor features for each WSI, which were used for training the tumor-feature model.
- For each WSI, the dataset includes the corresponding molecular subtype, MGMT-methylation, EGFR-amplification values.
- These images are extremely large, with thousands of pixels on each axis, making them unwieldy in data processing. GlioBLAST employs a novel and unexplored tiling system to analyze these images.



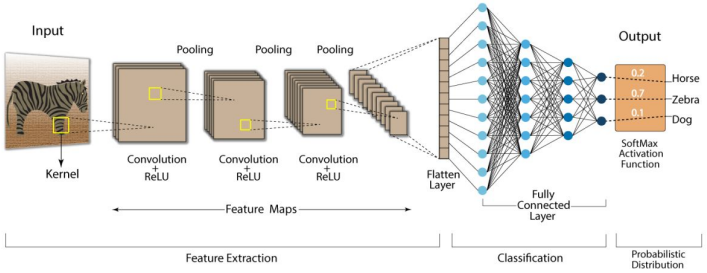
Whole-Slide Image



Tumor-Feature Mask

https://glioblastoma.alleninstitute.org

Framework: Convolutional Neural Networks

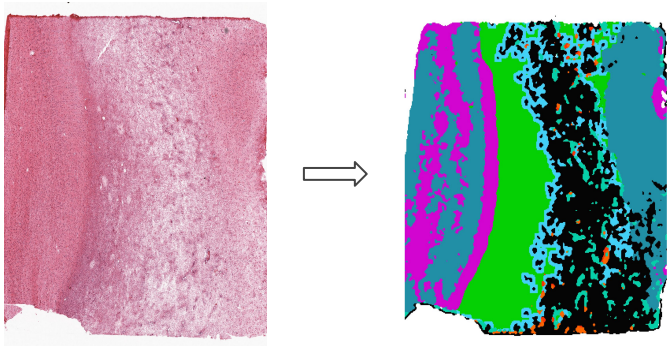


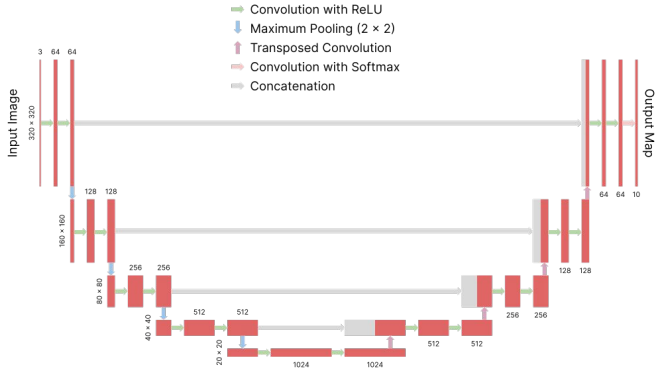
https://neptune.ai/blog/how-to-build-a-light-weight-image-classifier-in-tensorflow-keras

- Neural networks are computational models that make predictions on data after learning from examples through deep learning. These models have spearheaded modern computational advances, from spam detection to autonomous driving.
- Convolutional neural networks (CNNs) are extensively applied to image classification and segmentation tasks. These models consists of *convolutional layers* which progressively extract *features* from images. The initial convolutional layers typically extract simple features such as curves and lines, while the later ones detect composite features like cells.
- Due to widespread use, many CNN varieties exist that solve different image-analysis tasks. Image segmentation involves assigning each pixel to one class, whereas image classification involves assigning the entire image to one class.
- In GlioBLAST, the UNet CNN architecture performs segmentation for tumor features, and the VGG16 CNN architecture performs classification for molecular subtypes, MGMT methylation, and EGFR amplification.

Framework: Segmentation with the UNet Architecture

- Image segmentation involves assigning **each image pixel to a class.** The segmentation model was built for **locating histological tumor features** (ten different classes) within the whole-slide images. For each tile, the tumor-feature model produces a heatmap **indicating the predicted class for every pixel.**
- The model was built using the **UNet architecture,** a convolutional neural network designed for **"biomedical image segmentation."**
- The architecture consists of the encoder layers, which convert the image into feature representations, and the decoder layers, which convert the feature representations into a segmentation map.
- The strength of the UNet architecture for segmentation lies in **the concatenation and convolution layers** used within the decoder blocks. By combining high-resolution features from the encoder block with upsampled features from the decoder block, the later convolution layers can assemble a "precise output."
- For the tumor-feature model, the whole-slide images and masks **were tiled into 320-pixel patches.** The tumor-feature model was then trained on the tile pairs (80% for training, 20% for validation) with the Adam optimizer, the categorical-cross-entropy loss function, a batch size of 1, a learning rate of 0.00001. A central dropout layer was employed to limit overfitting.

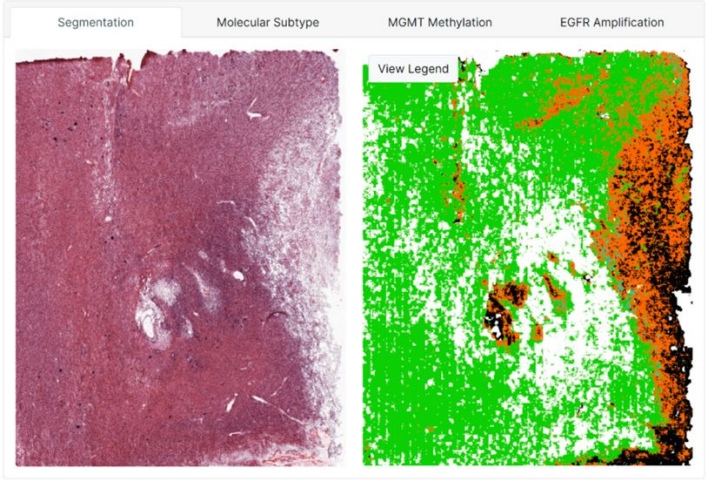


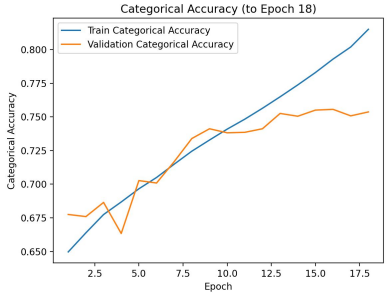


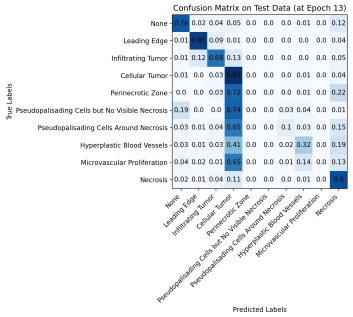
Results: Tumor-Feature Segmentation Model

- The tumor-feature model achieved **a categorical accuracy of 82%,** adjusted for the minor classes (such as "hyperplastic blood vessels" and "microvascular proliferation") which were correctly classified as cellular-tumor regions.
- The confusion matrix exhibits strong performance across the four major classes (the leading-edge, infiltrating-tumor, cellular-tumor, and necrosis regions).
- My model provides **improved speed and precision** when compared with **traditional analysis** of tumor features and **other studies** in glioblastoma segmentation, exhibiting the potential of whole-slide images **to enhance prognosis and targeted therapy.**

Model	Categorical Accuracy
FC DenseNet (Tiramisu) on Resized WSIs [26]	0.70
My UNet Convolutional Neural Network on Tiled WSIs	**0.82**

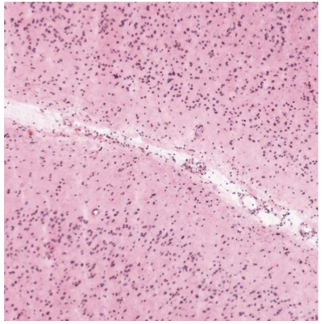






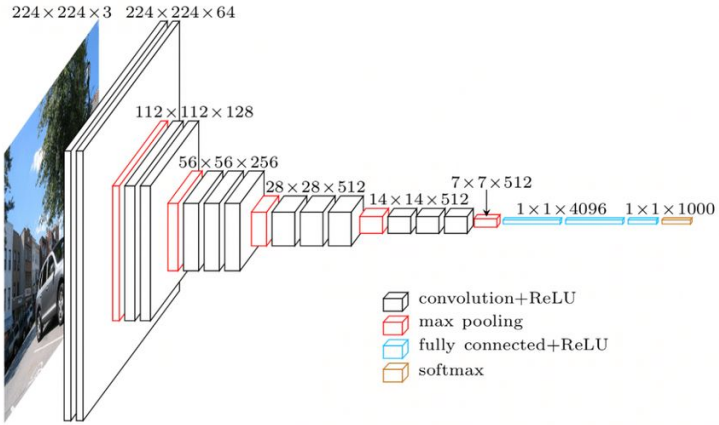
Framework: Classification with the VGG16 Architecture

- Image classification involves assigning **the entire image to a class.** The classification models were built for detecting molecular subtypes, MGMT methylation, and EGFR amplification within whole-slide-image tiles. For each tile, the three models produce a probability or probability distribution for the given factor.
- The classification models were built using the **VGG16 architecture,** a convolutional neural network designed for broad image classification.
- The architecture consists of **initial convolutional blocks,** which extract features from the image, and then **fully-connected dense layers,** which convert the features into a probability classification.
- The classification models were trained with **fine-tuned transfer learning,** where the pretrained weights were used for the VGG16 layers while custom weights were learned for the final dense layers, enabling rapid training progress and improved final performance.
- For the classification models, the whole-slide images and masks **were tiled into 160-pixel patches.** The classification models were then trained on the pairs of tiles and labels (80% for training, 20% for validation) with the Adam optimizer, the cross-entropy loss function, a batch size of 32, a learning rate of 0.0001. Dropout layers were appended to the network to reduce overfitting.



MGMT Methylation: 5%
EGFR Amplification: 93%

Classical: 85%
Mesenchymal: 5%
Proneural: 0%
Neural: 10%



https://towardsdatascience.com

Results: Molecular-Subtype and Genetic-Factor Classification Models

Molecular-Subtype Model

- The molecular-subtype model was trained for 10 epochs, and achieved **98% accuracy** (at epoch 9). The corresponding confusion matrix exhibits strong performance across all classes.

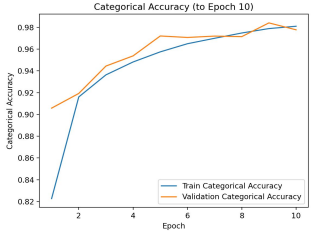
MGMT-Methylation Model

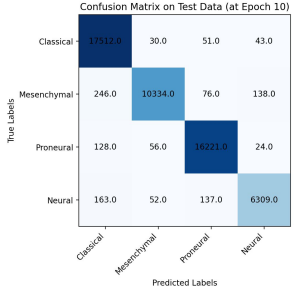
- The MGMT-methylation model was trained for 20 epochs, and achieved **94% accuracy** (at epoch 20). The corresponding confusion matrix exhibits strong performance across both classes.

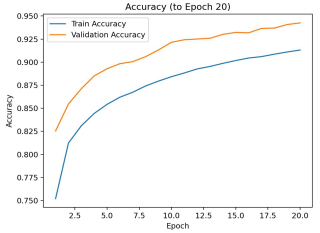
EGFR-Amplification Model

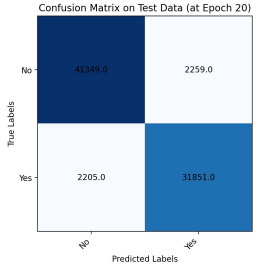
- The EGFR-amplification model was trained for 30 epochs, and achieved **97% accuracy** (at epoch 30). The corresponding confusion matrix exhibits strong performance across both classes.

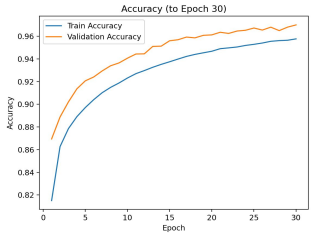
My models provide **improved speed and accuracy,** enabling efficient prognosis and precise targeted therapy using genetic biomarkers like MGMT methylation.

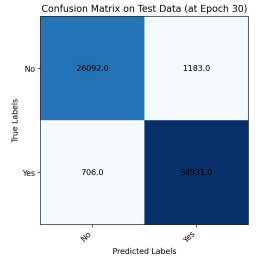




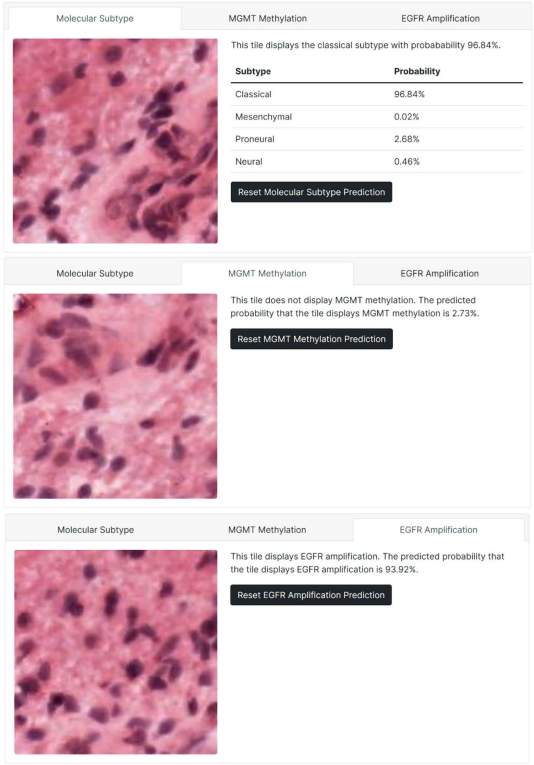


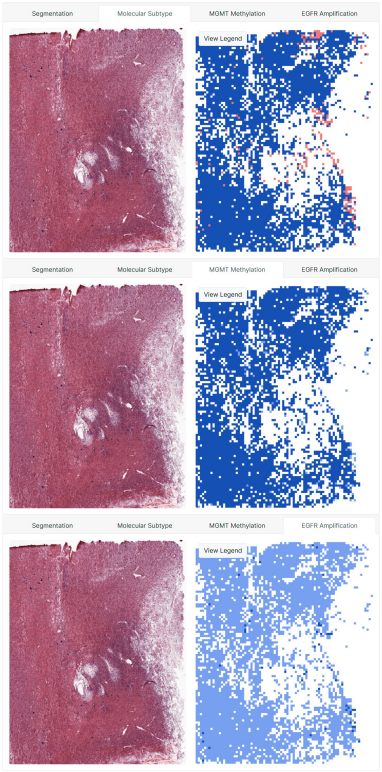






Results: The GlioBLAST Web Application





- The GlioBLAST web application makes the segmentation and classification models accessible to medical professionals worldwide.
- The application hosts the models using an Amazon Web Services (AWS) server, which provides a user interface where users can interact with the models.
- Medical professionals can create patient records and then upload patient images (either whole slide images or tiles from whole slide images) to receive the corresponding predictions or heatmaps after the server runs the models on the provided images.
- These records, predictions, and heatmaps are securely stored within a database and on the file system, allowing medical professionals to return and review or download the results generated earlier.

Conclusion

- GlioBLAST is a novel deep learning system that identifies histological tumor features, molecular subtypes, MGMT methylation, and EGFR amplification in glioblastoma tumors.
- Deep learning has spearheaded advancements in medicine, and this work illustrates that deep learning unlocks improved diagnosis and prognosis for glioblastoma patients.
- The lack of similar research indicates that segmentation for glioblastoma whole-slide images has not been explored thoroughly. This paper addresses the potential benefits of segmentation with deep learning for glioblastoma prognosis.
- The proposed models, utilizing transfer learning to extend modern image-analysis architectures, outperform other deep learning applications and traditional pathologist analysis. This allows timely and precise glioblastoma diagnosis and prognosis, reducing unnecessary costs and the side effects of aggressive therapy by enabling targeted treatment.
- This research also presents the GlioBLAST web application, which complements and enhances traditional glioblastoma treatment. Through the application, physicians can perform analysis and prediction on uploaded image data with the models.
- The publicly accessible application addresses the shortage of pathologist expertise in many regions through precise diagnosis and prognosis without trained experts or costly systems.
- **With global availability and reliable automation, the GlioBLAST system and web application represent an advancement in applying artificial intelligence to healthcare.**