Brain Tumor Classification using Medical Data

A Project Report Submitted to the Faculty of

St. Joseph's University



By

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in partial fulfilment of the requirements for the degree of

Master of Science In Big Data Analytics

June 2024

Dedications

I dedicate this project report to

Almighty God, My Teachers and My Project Guide. [Internship completion letter to be inserted as a full-page image] [If you don't have it yet, leave it blank with the above line only]

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DEPARTMENT OF BIG DATA ANALYTICS CERTIFICATE

This is to certify that this Master of Science thesis entitled "Brain Tumor Classification using Medical Data" is a bon-a-fide work done by Aman Deepak Chhabria bearing roll no [222BDA21] in the 4th semester in St. Joseph's University during the year 2023-2024 in the partial fulfilment of the requirement for the award of Master of Science in Big Data Analytics from St. Joseph's University.

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DECLARATION BY THE CANDIDATE

I do hereby declare that this work entitled "Brain Tumor Classification using Medical Data" that is a project with the help of computer vision, keras and pytorch built a model to classify Brain Tumor(LGG or HGG) which has been originally carried out by me under the guidance and supervision of **Praveen Kumar J**, Guest Faculty, Department of Advanced Computing, St. Joseph's University, Bangalore, India. This work has not been submitted elsewhere for the award of any other degree or diploma certificate.

Bangalore

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1. ABSTRACT

Data is the most crucial part in the data analytics. Data Analytics revolves around the collection, processing and analysis of data and is one of the most interesting domains to deal with. In today's world Data is everything, without meaningful data organisations and Individuals would struggle to make informed decisions and forecast various trends. Hence this Project work is carried out with the motivation to deal with Image Data "Brain Tumor Classification using medical data" the objective is to use image segmentation to segment the Brain tumor and classify them under 2 classes i.e. LGG(Low-grade Gliomas) and HGG(High-grade Gliomas).

2.INTRODUCTION

2.1 Dealing with Medical Data(NIFTI Images):

NIfTI stands for Neuroimaging Informatics Technology Initiative and it provides a file format for neuroimaging data to be useful for fMRI research. For instance, NIfTI was created in order to facilitate inter-operation of various tools and programs through file formats. Before NIfTI, there were several major fMRI analysis software packages, and each of these utilised a different file format. This data exchange format was created for all of these (and other) neuroimaging software packages that were listed above: NIfTI.

One more enhancement with the NIfTI format was to support a single file. It is important to know that ANALYZE format needs two files – a header file with the extension of . hdr extension is required for storing the metadata associated with the image while the image data is contained in . img file. These files had to share the same name before the extension (e.g. g., brain_image. hdr and brain_image. img), as well as doubled the number of files in a folder with picture files, which only made it more messy. NIfTI describes a single image file that has a file extension ending with a . nii extension. In addition, the NIfTI images can be compressed again with a standard and rather accessible format called Gzip in order to decrease the demand for storage space for imaging data. This compression was useful as neuroimaging data files are large in size most of the times. For example to save space 100+ medical images along with their metadata can be stored in one .nii file.

Imported packages

- dicom2nifti: It is used to convert DICOM images into NIfTI format
- NiBabel: It is capable of reading and translating the NIfTI format and other neuroimaging formats such as ANALYZE.

 NiLearn: Originally, the program is aimed at offering statistical analysis and machine learning functions for neuroimaging. But it also contains several tools for reading and writing NIfTI images, and for working with or visualizing data.

But in my project only NiBabel was used to read the medical NIFTI files.

2.2 Computer Vision

Computer Vision is a field of Artificial Intelligence(AI). Computer vision is used to gain meaningful insights on real time visual data around us. By using various algorithms and models, Computer vision can mimic a humans behaviour by analysing and getting insights through data like images or videos which could even be implemented for real time.

Digital Image Processing is a subset of Computer Vision, it deals with enhancing, analysing and understanding images. Image processing can be defined as a task of performing set of operations on an image, analyse and manipulate the contents of an image or the image data.

Key Tasks in Computer Vision

- a. Image Classification
- **b.** Object Detection
- c. Image Segmentation
- d. Facial Recognition
- e. Edge detection

a. Image Classification: Image Classification is one of the most studied topic in the field of computer vision. Image Classification is a quite simple problem statement, given a dataset of a group of images it is our job to classify them in 2 or more classes. For example if we have a dataset of cats and dogs we

can classify them in 2 classes i.e. 1 for cats and the other for dogs by assigning labels to each class.

b. Object Detection: Object Detection is quite self-explanatory; it refers to detecting objects in a particular image by surrounding the objects with bounding boxes. According to the particular problem statement the model tries to detect the object required for the problem statement in an image or a video. Deep Learning models such as YOLO, RCNN are used for object detection.

c. Image Segmentation: Image Segmentation is the division of an image into subparts which can help the machine to receive multiple segments/objects from the same image. Modern-day deep learning architectures like U-Net, SegNet etc are used to perform image segmentation tasks.

d. Facial Recognition: Facial Recognition is a subpart of object detection where the objective is to detect a human face. Facial Recognition performs not only detection, but also recognition of the detected face. Facial recognition is used to find certain features such as eyes, nose etc and classify a face according to the features. Some deep learning algorithms like FaceNet can be used for facial recognition.

e. Edge Detection: Edge detection is the task of detecting boundaries in objects. It is algorithmically performed with the help of mathematical methods that help detect sharp changes or discontinuities in the brightness of the image. Often used as a data pre-processing step for many tasks, edge detection is primarily done by traditional image processing-based algorithms like Canny Edge detection and by convolutions with specially designed edge detection filters.

2.3 Brain Tumor:

Brain tumors are one of the most deadly cancers worldwide. Among these tumors, glioma is the most common type. The average survival time for glioblastoma patients is less than 14 months. Timely diagnosis of brain tumors is thus vital to ensuring appropriate treatment planning, surgery, and follow-up visits. As a popular non-invasive technique Magnetic Resonance Imaging (MRI) produces markedly different types of tissue contrast and has thus been widely used by radiologists to diagnose brain tumors. However, the manual segmentation of brain tumors from MRI images is both subjective and time-consuming. Therefore, it is highly desirable to design automatic and robust brain tumor segmentation tools.

Recently, deep learning-based methods such as convolutional neural networks (CNNs), have become increasingly popular and achieved significant progress in brain tumor segmentation tasks. Unfortunately, a severe class imbalance problem usually emerges between healthy tissue and tumor tissue, as well as between intra-tumoral classes. This problem causes the healthy tissue to be dominant during the training phase and degrades the optimization quality of the model.

2.4 Brain Tumor Classification

A brain tumour is made up of cells, which are believed to be relate to brain or nervous system. Based on cells growth speed and similarity to scenario they grow back again, there are two overall brain tumours categories: malignant and benign. Benign tumours are not cancerous cells, they grow very slowly, also it less likely they will return after treating. On the other hand malignant tumours are nothing but of cancers cell, they have the ability to locally invasion on the tissues or spread to another body parts.

- Grade I is a benign tumour (ie, most curable), and most often found in children.
- Grade II encompasses three tumour types: astrocytomas, oligodendrogliomas, and oligoastrocytoma, which is a mixture of the other two. All three types are adult tumours; however, they have the potential to become high-grade cancers. All low-grade gliomas can potentially become high-grade gliomas in time.
- Grade III lesion may include Anaplastic Astrocytoma, Anaplastic Oligodendroglioma, or Anaplastic Oligoastrocytoma and are more malignant and infiltrating than grade II tumours.
- Grade IV glioma, known as Glioblastoma Multiforme (GBM), is the deadliest tumour in the WHO category.

In general, grades I and II gliomas are low-grade gliomas (LGG), which are benign tumours and can be operated by surgical resection, while grades III and IV are high-grade glioma (HGG) which are malignant tumours that these glioma type cannot be resected by operation conduct due to their invasion scope of tissue of neighbourhood.

2.5 Big Data Analytics

Data is traditionally referred to raw facts. The term 'big data' is used to describe everything we do, say, write, visit or buy leaves a digital trace, the resulting data can be used by us to gain new insights and improve results. Although the term 'big data' will probably disappear as 'big data' becomes plain old data, it is currently considered 'big' because of 4 V's:

- 1. Volume: relating to the vast amounts of data that are being generated every second due to ever utilization of smart technology and constant connectivity.
- 2. Velocity: relating to the speed at which new data is generated and moves around the world.

- 3. Variety: relating to the increasingly different types of data that are being generated from financial data to social media feeds, to photos to sensor data, to video footage to voice recordings.
- 4. Veracity: relating to the messiness of the data being generated analogous to Twitter posts with hash tags, abbreviations, typos, text language and colloquial speech.

Used effectively the 4 V's can also deliver the 5th V - Value.

This is what Analytics is really all about - the use of data to deliver value.

Hence, my focus will narrow down to performing particularly Text Analytics on Contract Data which leads to my problem statement as defined next.

2.6 **Problem Statement**

To perform Brain Tumor Classification with the help of segmentation is the main goal of my project. There are two types of classes in my problem statement i.e. LGG (Low Grade Glioma) and HGG (High Grade Glioma). With the help of segmentation the classification of the brain tumor in the given classes was done by testing on two architecture i.e. UNet and GoogleNet.

2.7 Software Specification

Python 3.9

The list of packages in python used:

nibabel, numpy, matplotlib, Pytorch, sklearn and keras

The details about each of the packages will be discussed in the following sections.

3. Literature Review

3.1 Brain Tumor Classification:

This paper emphasizes on classifying three grades of brain tumors with high accuracy and sensitivity utilizing a Convolutional Neural Network (CNN) and seeking to present a new CNN structure for grading brain tumors through using T1-weighted contrast-enhanced brain MR images.

In the introduction, peer-reviewed articles on medical uses of deep learning are presented with a focus on CNN in brain tumor classification; this demonstrates that the method achieves high levels of accuracy and sensitivity when differentiating between various types of tumors.

T1 weighted and contrast-enhanced brain MRI images of 3064 cases with three kinds of brain tumor were used as the dataset for classification using a CNN architecture of 18 layers. To further divide the dataset the dataset together with a brief methodology of how the CNN was trained is shown below:

The proposed CNN classifier achieved high accuracy and sensitivity for grading brain tumors into three classes: Primary Brain Tumors meaning Tumours arising from the brain are of three types Glioma, Meningioma and Pituitary Tumor.[a]

3.2 Hybrid Deep learning models:

This paper uses transfer learning to develop EfficientNets in precise classification of brain tumor types in order to improve the performance and credibility of MRI scanners in categorizing brain tumors. Contrary to the hypothesis, the experiment systematically compares the fine-tuned EfficientNets with other pre-trained models and yields satisfactory testing accuracy, precision, recall, and F1-factor values. The credibility of the method can be affirmed further by cross-dataset validation with an independent set of images, thereby proving the aptness and applicability of the model for distinguishing brain tumours. The primary objective of the study is to assist

in the enhancement of the classification of brain tumors using Convolutional Neural Networks and Deep Learning algorithms.

The introduction focuses on the role of accurate classification of the types of brain tumor leading to early diagnosis, survival rate of patients with tumor in brain, the significance of medical imaging in the detection of tumor, effectiveness of deep learning and transfer learning techniques and strength of the proposed method via cross-dataset comparison.

The presented methodology includes the fine-tuning of pretrained efficient nets with objectives of multiclass classification of the brain tumor types; the details are provided in the "Materials and methods" Section Afterwards the results and their analysis are presented in the "Experimental results and discussion" Section. In the last section, the performance analysis and comparison with other practices are discussed under the "Conclusion" while the "Future work" section provides further ideas for improvement.

The authors of Baiju Babu Vimala, Saravanan Srinivasan, Sandeep Kumar Mathivanan, Prabhu Jayagopal, & Gemmachis, Teshite Dalu (2023) also note that the proposed method outperforms other methods with high accuracy of deep learning and transfer learning methodology is suggested to diagnose the brain tumor and exploring the potential implications in the medical field.[b]

3.3 Brain Tumor Segmentation:

The paper outlines segmentation of brain tumor from MRI images, the use of four modalities of brain to increase accuracy, benefit of Distance-Wise Attention mechanism, and the efficiency of the proposed model in terms to other models.

The proposed model seems to have performed satisfactorily well on BRATS 2018 dataset and boasts of near perfect dice scores especially for whole tumour, enhancing tumour and tumour core areas. Automated segmentation of the brain tumor can play an important role in disease diagnosis and therapy, as it issues the necessary data for further therapy progress. The Distance-Wise Attention mechanism in the model improves the

segmentation as it focuses on extracting different types of context from the tumor and the brain.

The approach includes the preprocessing, Cascade Convolutional Neural Network, Distance-Wise Attention, four types of brain structures, the combined CNN model of the local and global features.

The limitations are discussed in the subsequent section of the study, such as the need to work with the image of the brain with large tumor volumes, the effectiveness of the Distance-Wise Attention mechanism, the focus on the part of the brain image near the tumor tissue, and the need to develop a special architecture for segmentation of brain tumor using the characteristics of four MRI modalities.[c]

4. Methodology

4.1 About the Data

A data pipeline in computer vision is a path through which the data flows, from collection of the image data to storage which will be further used for model training and deployment

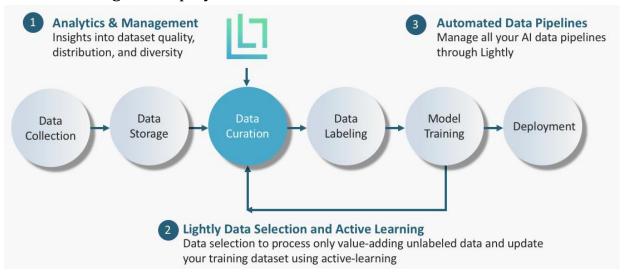


Figure 1: Basic Data Pipeline

 Data Collection: This stage involves gathering and collecting an image dataset to work with. In my problem statement I collected image data of Brain tumor (medical data) which was open source data tht was directly available on Kaggle.

https://www.kaggle.com/datasets/andrewmvd/brain-tumorsegmentation-in-mri-brats-2015

- Data Storage: The data collected is securely stored, this could be stored on the cloud or locally on your system.
- Data Curation/Preprocessing: Raw data might contain inconsistencies or errors in the classes of your dataset. For example in my dataset

there was inconsistency in my 2 classes, as 1 class in my dataset had majority data and in another class I had minority data which caused imbalance in my dataset, thus I had to perform oversampling of the minority class with the help of various preprocessing steps such as Data Augmentation to prevent the unbalance of data.

- Data Labelling: The data most of the time will be manually labelled based on the contents of the image. In my dataset the images were labelled in 2 classes i.e. LGG and HGG. Which was further labelled as 0 for class 0(LGG) and 1 for class1(HGG).
- Model Training: The labelled data is then used to train a model by learning various patterns in my data. Train_test_split was used to train on 80% of the data and test on 20% of the data. In the project 2 models were tested Unet and GoogleNet which will be discussed in detail in the following sections.
- Deployment: The trained model can further then be deployed into production. It could be made into an API so that it can be used to make predictions on new unseen data.

4.2 Class Imbalance

In few papers I read during the course of the project they spoke a lot about class imbalance and how to tackle such a crucial problem. As class imbalance will not allow your model to run how its supposed to and will prove to overfit on the majority class.

Class imbalance has emerged as one of the major challenges for medical image segmentation. The model cascade (MC) strategy significantly alleviates the class imbalance issue via running a set of individual deep

models for coarse-to-fine segmentation. Despite its outstanding performance, however, this method leads to undesired system complexity and also ignores the correlation among the models. Thus is important to handle class imbalance to prevent overfitting and 1 class getting labelled better than the other class.

One of the papers I read said, The issue of class imbalance is commonly encountered in medical image segmentation, especially brain tumor segmentation. To address this problem, many recent studies have adopted the MC strategy to perform coarse-to-fine segmentation. In particular, the common two-model cascaded framework has been widely adopted in many applications, including renal segmentation in dynamic contrast-enhanced MRI (DCE-MRI) images, cancer cell detection in phase contrast microscopy images, liver and lesion segmentation, volumetric pancreas segmentation in CT images, calcium scoring in low-dose chest CT images, etc. Moreover, MC can incorporate more stages to achieve better segmentation performance.

4.3 Over Sampling

In my dataset I had quite an imbalance of data, i.e. 2345 samples in the HGG class and 755 samples in the LGG class. So, I thought of performing data augmentation on my data to over sample the minority class in my dataset by using the package imblearn which has a module called RandomOverSampler. Data augmentation artificially increases the size of the training set by generating many realistic variants of each training instance. This reduces overfitting, making this a regularization technique. The generated instances should be as realistic as possible: ideally, given an image from the augmented training set, a human should not be able to tell whether it was augmented or not. Simply adding white noise will not help; the modifications should be learnable (white noise is not).

For example, you can slightly shift, rotate, and resize every picture in the training set by various amounts and add the resulting pictures to the training set. To do this, you can use Keras's data augmentation layers. This forces the

model to be more tolerant to variations in the position, orientation, and size of the objects in the pictures. To produce a model that's more tolerant of different lighting conditions, you can similarly generate many images with various contrasts. In general, you can also flip the pictures horizontally (except for text, and other asymmetrical objects). By combining these transformations, you can greatly increase your training set size.

Generating random samples to over sample the data with the help of data augmentation is also called synthetic minority oversampling technique.

4.4 Exploratory Data Analysis

- Visualization:
- Sample Images: Sample of Images can be displayed from each class to understand the data and the patterns.

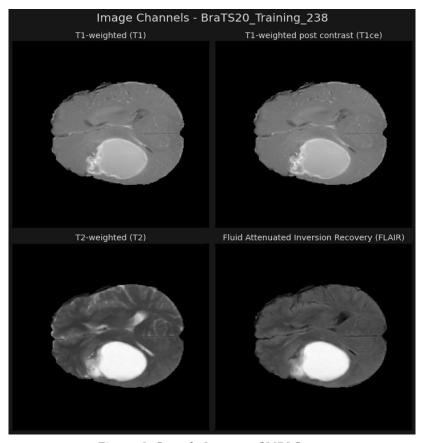


Figure 2: Sample Images of MRI Scans

 Various Plots: To analyse the dimensions and intensity of the images various plots could be incorporated to perform EDA.

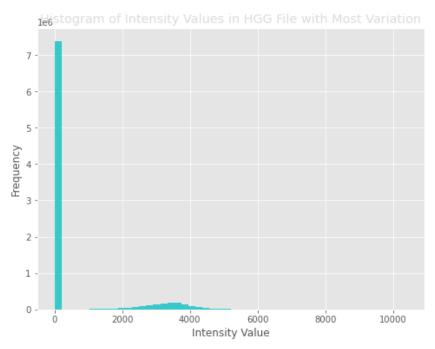


Figure 3: Plot for intensity of an Image

 Heatmaps: It could visualise the pixel intensities across various regions in a particular image. The higher intensities area could show the presence of a tumor.

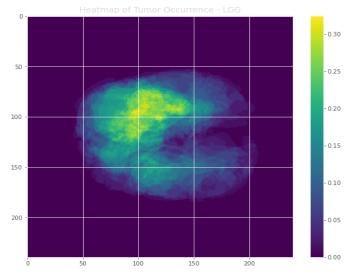


Figure 4: Heatmap of a MRI scan

- Statistical Analysis:
- Class Distribution or Imbalance: It helps in analysing the number of images per class. If there is a class imbalance it could affect the model's performance and be biased towards 1 majority class. In my dataset I had class imbalance so I performed Data augmentation to oversample the minority class so that my model performs without any bias.

4.5 Proposed Models

UNet:

Image segmentation is an important task in Computer Vision, which aims to divide an image into multiple parts to describe various aspects of the image. Segmentation entails the partitioning of an image into various structures signifying elements or components.

UNet was a fully convolutional neural network (FCN) introduced in 2015 by Olaf Ronneberger, Philipp Fischer, and Thomas Brox UNet. UNet is widely used for image segmentation and has received much attention, especially in medical imaging domains thanks to its performance. The unique idea is based on the U-shaped structure that includes the encoder arc (contractor arc) and decoder arc (expander arc).

With the help of this architecture having an 'U' shape UNet retains the most local features as well as long-range context and hence, ultimately gives the most precise results of segmentation. It is also worth noting that UNet does not learn the classification task directly. Generating the probability map for segmentation of a brain tumor is much easier using UNet, but adding a classification layer for the brain tumor requires extra processes. However, UNet is effective in achieving high accuracy for segmentation but challenging for achieving high accuracy in classification alone.

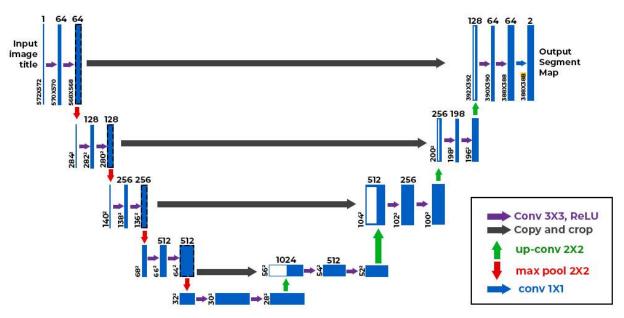


Figure 5: UNet Architecture

GoogleNet:

The proposed deep convolutional neural network model is a 22 layer GoogLeNet or Inception network. Inception-v4 is a network architecture that is derived from a variant of the Inception Network that was conceptualized by researchers from Google. In the "Going Deeper with Convolutions" paper the inception module was revealed as the main module of GoogLeNet. The inception module was the core layer in the GoogLeNet architecture discussed in "Going Deep with Convolutions" paper.

The ILSVRC uses scores from both object detection and image classification to judge models as part of the annual ImageNet Large Scale Visual Recognition competition. GoogleLeNet proved themselves the best in image classification of ILSVRC 2014, beating the VGG Model. Most importantly GoogLeNet had a much lower error rate than the previous ILSVRC chassis which won in 2013 and 2012 the respectively ZF-Net and AlexNet.

The Inception module deals with the issue of extracting features at different scopes but yet has to keep reasonable computational complexity. This it does

by using the convolution filters of different dimensions $(1\times1,3\times3)$ and $5\times5)$ within the same neuron. This architecture enables the network to preserve more details in the results of smaller filters yet simultaneously remain sensitive to more global patterns via larger filters. Moreover, 1×1 convolutions are utilized for feature dimensionality reduction which decreases the number of channels of the formula and also the computation.

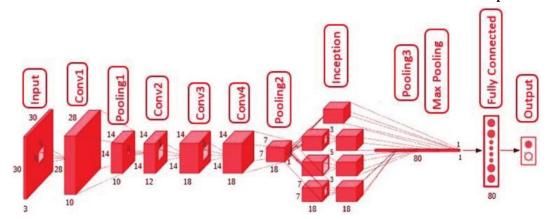


Figure 6: GoogleNet Architecture

4.6 Results

UNet:

Unet is specifically designed for biomedical image segmentation thus I experimented on this architecture, It excels at capturing fine details and the context within medical images due to its unique U-shaped architecture. The model of UNet is mainly used for segmentation tasks for medical images, thus the classification didn't perform so well on my data. I ran it on a total of 20 epochs but the results were not promising.

| Epochs | Train_loss | Train_accuracy | Val_loss | Val_accuracy |
|----------|------------|----------------|----------|--------------|
| Epoch 1 | 0.6891 | 0.5011 | 0.6927 | 0.4957 |
| Epoch 2 | 0.6858 | 0.5051 | 0.7336 | 0.5981 |
| Epoch 3 | 0.6841 | 0.5269 | 0.7947 | 0.5043 |
| Epoch 4 | 0.6835 | 0.5368 | 0.7890 | 0.5341 |
| Epoch 5 | 0.6762 | 0.5650 | 0.6527 | 0.6087 |
| Epoch 6 | 0.6695 | 0.5872 | 0.6595 | 0.5832 |
| Epoch 7 | 0.6669 | 0.5975 | 0.6696 | 0.6354 |
| Epoch 8 | 0.6674 | 0.5941 | 0.7531 | 0.5203 |
| Epoch 9 | 0.6651 | 0.5967 | 0.7604 | 0.4989 |
| Epoch 10 | 0.6629 | 0.6207 | 0.6818 | 0.5139 |
| Epoch 11 | 0.6740 | 0.5861 | 0.7134 | 0.6077 |
| Epoch 12 | 0.6644 | 0.6053 | 0.8090 | 0.5043 |
| Epoch 13 | 0.6642 | 0.6055 | 0.6722 | 0.5437 |
| Epoch 14 | 0.6574 | 0.6213 | 0.6926 | 0.5256 |
| Epoch 15 | 0.6557 | 0.6231 | 0.6644 | 0.5885 |
| Epoch 16 | 0.6545 | 0.6319 | 0.6898 | 0.5064 |
| Epoch 17 | 0.6514 | 0.6381 | 0.8086 | 0.5043 |
| Epoch 18 | 0.6599 | 0.6223 | 0.6758 | 0.5906 |
| Epoch 19 | 0.6540 | 0.6362 | 0.6621 | 0.6503 |
| Epoch 20 | 0.6513 | 0.6447 | 0.6769 | 0.5341 |

Table 1: Results of UNet Architecture

Since the max validation accuracy got was 65% which wasn't so great, thus I went with another model for classification called googlenet

GoogleNet:

GoogLeNet is a deep convolutional neural network known for its efficiency and high performance in image classification tasks. It employs an Inception module that allows the network to capture multi-scale features in a single pass, which enhances its ability to recognize complex patterns within the image.

GoogleNet is a model that works much better as a classification model then UNet. It is much faster then Unet and has faster convergence rate as well. I trained the model using 10 epochs and got a pretty good accuracy with the test data.

| Epochs | Train_loss | Train_accuracy | Val_loss | Val_accuracy | Confusion Matrix |
|---------------|------------|----------------|----------|--------------|-------------------------|
| Epoch 1 | 0.4924 | 0.7992 | 0.2838 | 0.8689 | [[380 85] |
| • | | | | | [18 455]] |
| Epoch 2 | 0.4420 | 0.8640 | 0.4551 | 0.8252 | [[367 98] |
| • | | | | | [67 406]] |
| Epoch 3 | 0.3587 | 0.8628 | 0.2666 | 0.8881 | [[412 53] |
| | | | | | [59 414]] |
| Epoch 4 | 0.4374 | 0.8665 | 0.6008 | 0.6514 | [[219 246] |
| | | | | | [66 407]] |
| Epoch 5 | 0.5768 | 0.6915 | 0.3387 | 0.8731 | [[402 63] |
| | | | | | [41 432]] |
| Epoch 6 | 0.3484 | 0.8631 | 0.3145 | 0.8721 | [[388 77] |
| | | | | | [41 432]] |
| Epoch 7 | 0.3390 | 0.8766 | 0.1600 | 0.9510 | [[441 24] |
| | | | | | [21 452]] |
| Epoch 8 | 0.1601 | 0.9479 | 0.1276 | 0.9552 | [[459 6] |
| | | | | | [38 435]] |
| Epoch 9 | 0.1116 | 0.9578 | 0.2446 | 0.9424 | [[462 3] |
| | | | | | [53 420]] |
| Epoch 10 | 0.3166 | 0.8924 | 0.1914 | 0.9350 | [[431 34] |
| _ | | | | | [18 455]] |

Table 2: Results of GoogleNet Architecture

As you can see the accuracy from the GoogleNet model is more precise and the convergence is also much better for my MRI data compared to the Unet Architecture

5. Conclusion

The Algorithms used in my Project/research work is key in performing image segmentation and classification in computer vision tasks. A lot of learning took place during the complete period of my completion of my project. In future I could use this model in the medical area which would help the doctors to catch the type of tumor without any difficulty and also speed up the process.

6. References

- a) https://arxiv.org/pdf/2001.08844
- b) https://www.nature.com/articles/s41598-023-50505-6
- c) https://www.nature.com/articles/s41598-021-90428-8