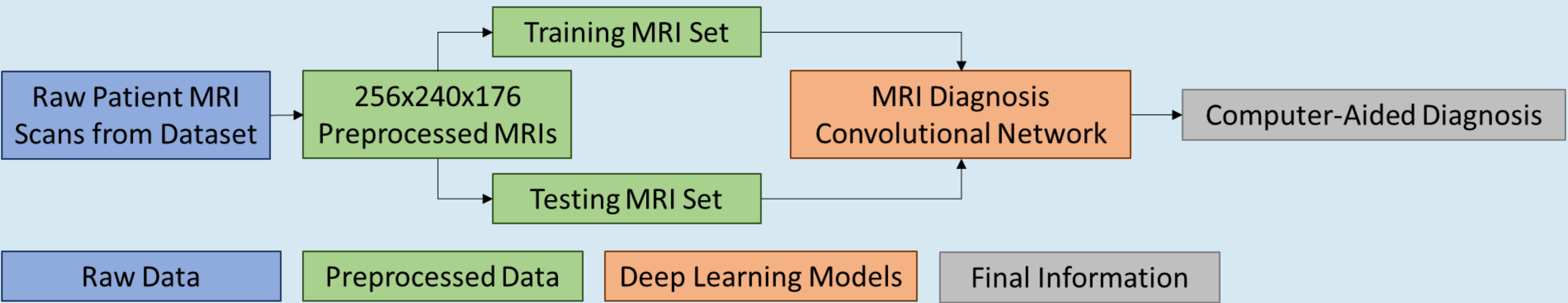


MRI Image Synthesis for the Diagnosis of Parkinson's Disease using Deep Learning

Neeyanth Kopparapu

First Iteration Prediction Framework



Model Selection and Creation

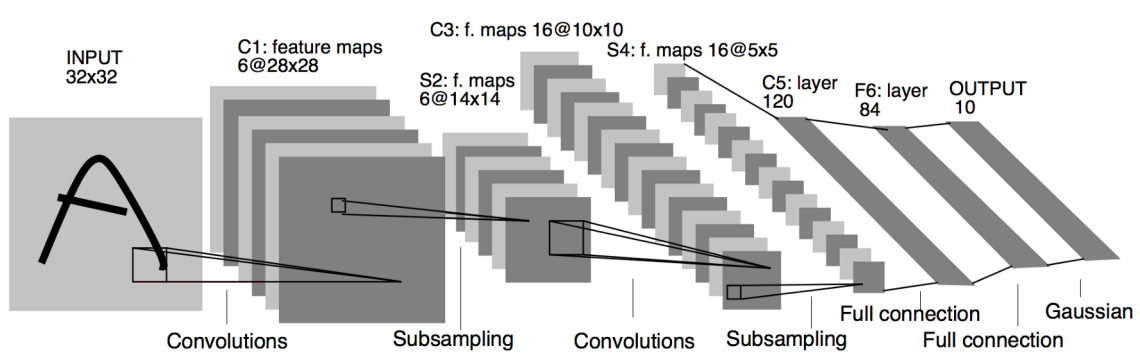


Figure 7: LeNet model architecture (Source: Medium)
3 models (LeNet, VGG-19, Resnet-50) were tested for accuracy, sensitivity, and specificity through 15 epochs of training, each lasting around 8 hours on a NVIDIA Tesla K80 GPU.

These models were chosen because of their high performance in the ImageNet challenge, showing capability to see patterns in images.

Medical Dataset

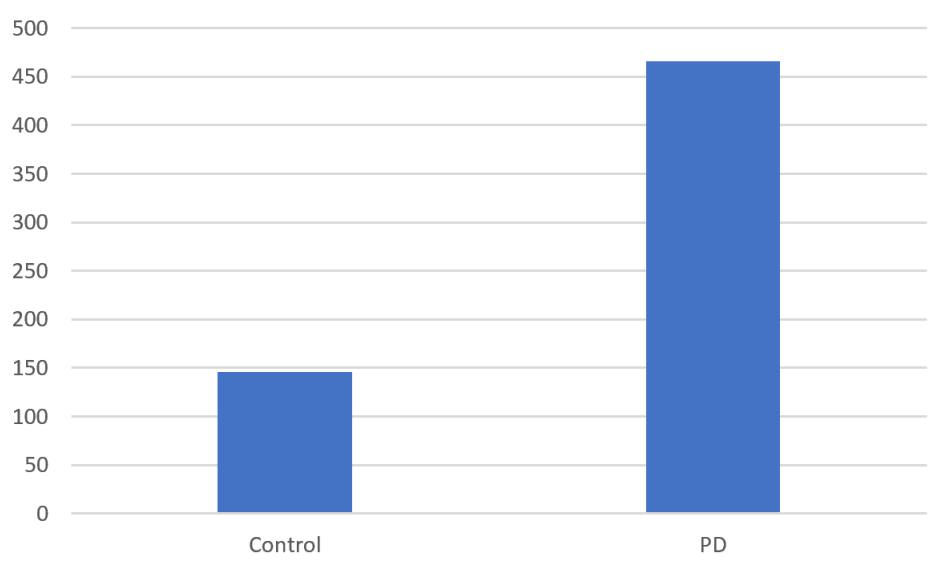


Figure 8: Data split between PD and Control.

The data, acquired from the LONI Image Data Archive, contained 612 scans of the correct size, 466 in the PD Group and 146 from the Control Group.

Initial Training Results

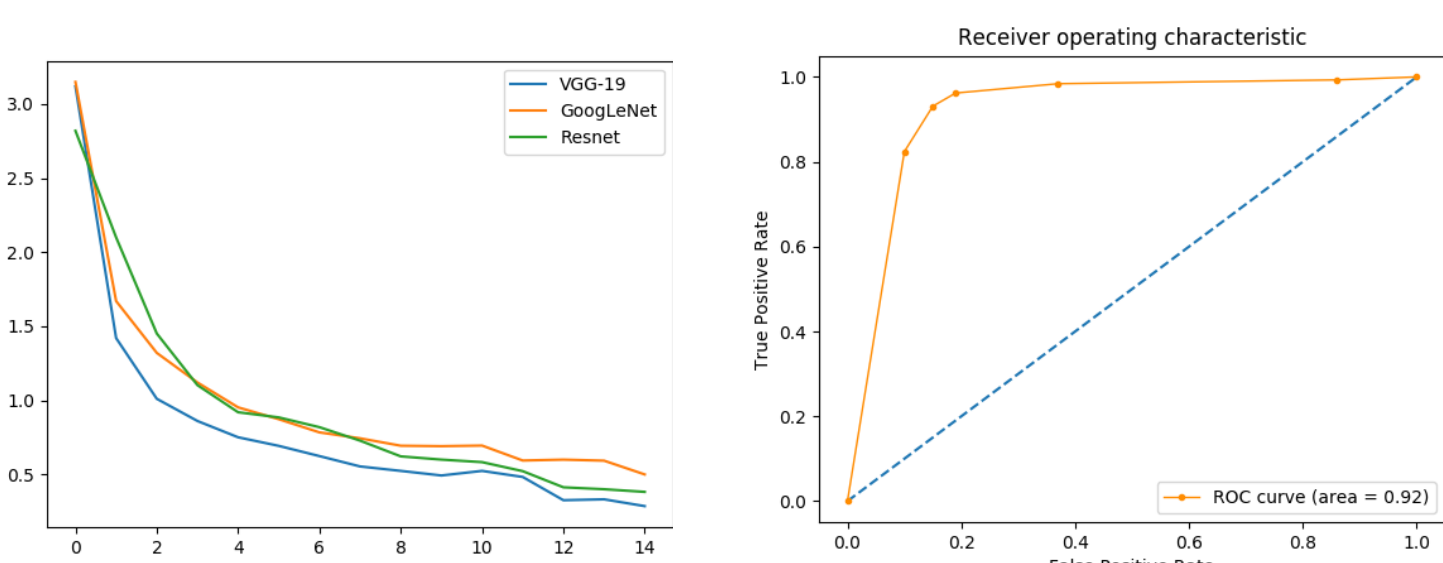


Figure 8: Loss Graph and ROC Curve of First Iteration.

The final model had a highest accuracy of 90.2% and lowest loss of 0.148. Although this accuracy was an increase compared to clinical settings, the loss and accuracy stopped improving after 15 epochs, signaling the performance can be improved.

Second Iteration Generative Framework

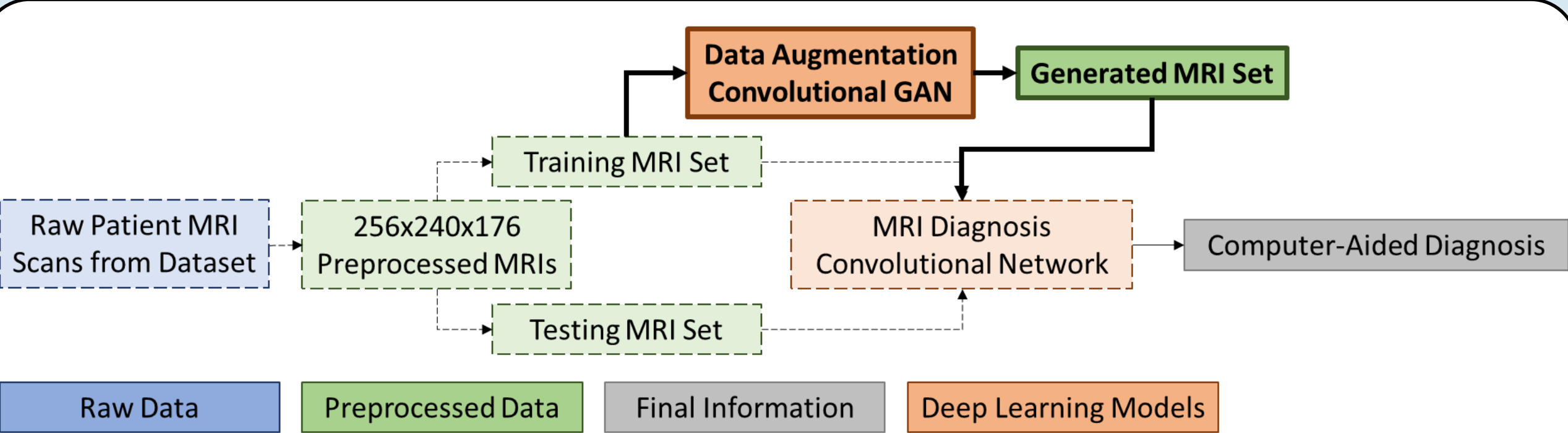


Figure 9: Data Flow through the Second Iteration of the Predictive Model

Generative Adversarial Networks

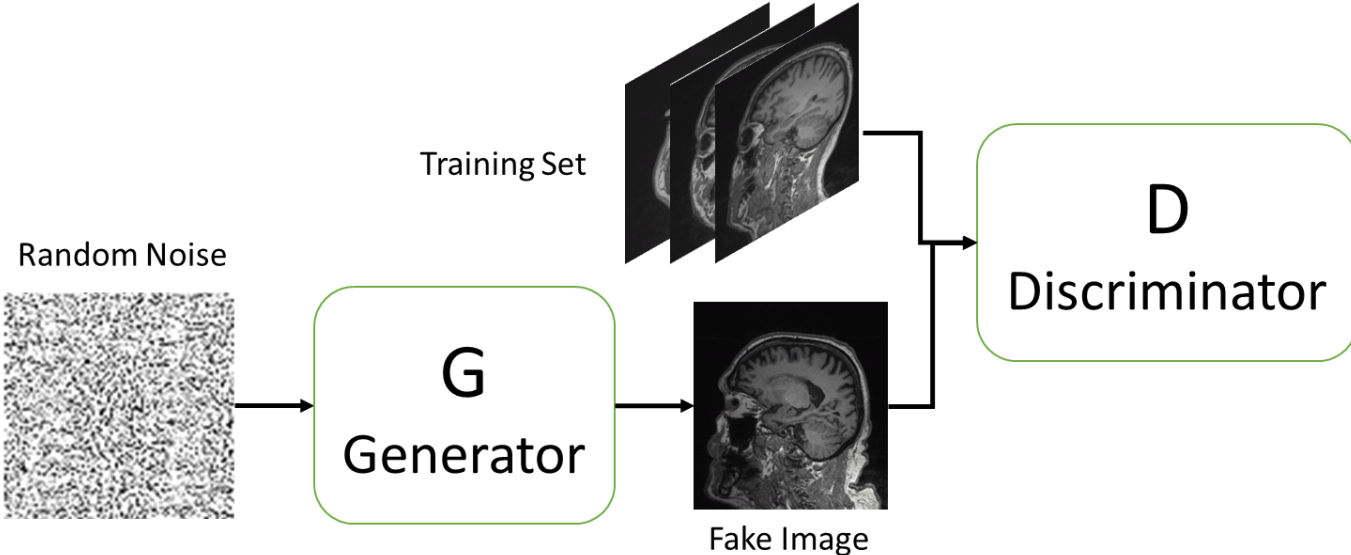


Figure 10: Pipeline for Generation of Images. The Generator generates images and the Discriminator determines if they are real or fake.

Challenge 1: Vanishing Gradient

$$\mathcal{E}_l = ((\omega^{l+1})^T \mathcal{E}_{l+1}) \odot \sigma'(z^l)$$
$$\omega_l \rightarrow \omega_l - p \sum_x \mathcal{E}_{x,l} (a^{x,l-1})^T$$

Figure 12: Equations Related to the Back-propagation Algorithm.
With deep neural networks, the number of layers limits the changing of weights to very small amounts, which forces training to take hundreds of epochs.

Challenge 2: Curse of Dimensionality

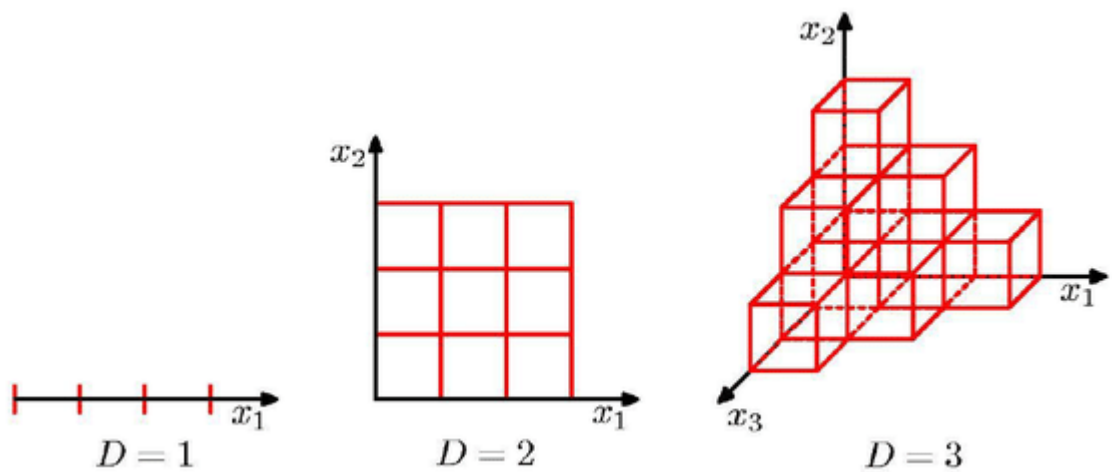


Figure 13: Image Depicting the Stretch of Additional Dimensions. (Source: Hadoux)

With over 10 million dimensions, it is very easy to overfit because of the lack of sample training images.

Addition: PDGAN Model

Convolutional Network Configuration
Convolutional 3D (512) x 3 Layers
Max-Pooling 3D (4x4x4)
Convolutional 3D (128) x 4 Layers
Max-Pooling 3D (4x4x4)
Convolutional 3D (16) x 4 Layers
Max-Pooling 3D (2x2x2)
Convolutional 3D (8) x 2 Layers
Global Averaging 3D (2x2x2)
FC - 512
FC - 16
Softmax

Figure 11: PDGAN Model Architecture

To solve some of the problems, a new PDGAN model was designed to be smaller to combat the vanishing gradient problem, but still capable of analyzing complex MRI-specific problems.

Final Training Results

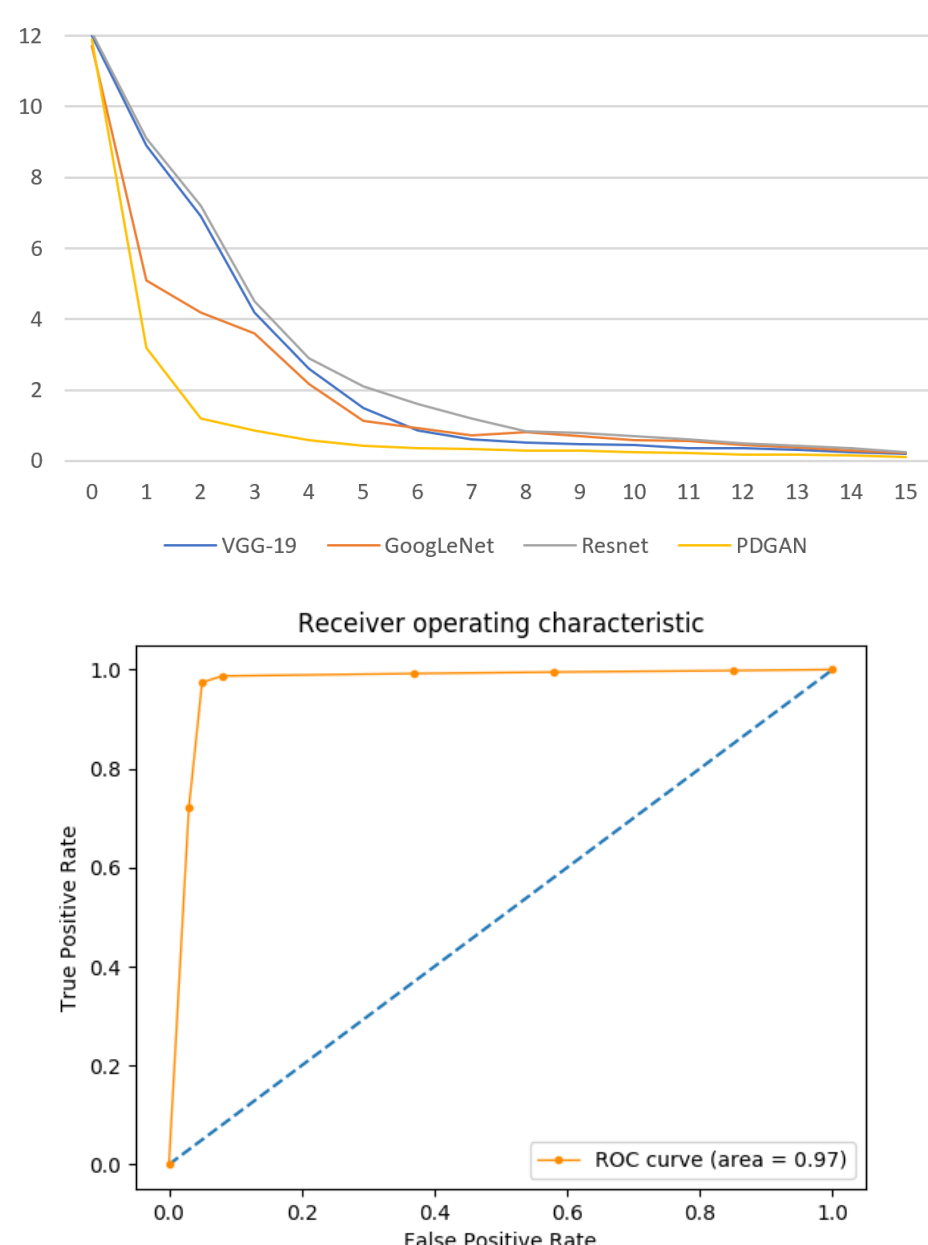


Figure 14: Loss Curve and ROC Curve of Second Training Data

Evidently, the ROC curve score of 0.97 is higher than the first attempt, which was at 0.92. Additionally, the final training loss of 0.112 was less than the first iteration (0.148).

Addition 2: Bayesian Optimization

To increase the accuracy of the model further, the hyperparameters of the model were tuned using Bayesian Optimization. This was done using the Spearmint package, optimizing under the number of filters per layer, learning rate, and other related quantities.

```
variable {
  name: "conv"
  type: INT
  size: 3
  min: 1
  max: 64
}

variable {
  name: "dense"
  type: INT
  size: 1
  min: 4
  max: 256
}

variable {
  name: "optimizer"
  type: ENUM
  size: 4
  options: "adam"
  options: "adagrad"
  options: "nadam"
  options: "sgd"
}
```

Figure 16: Few of the various parameters passed through the Spearmint optimizer.

Validation: Confirming Generated Brain Border Unity

Reasoning

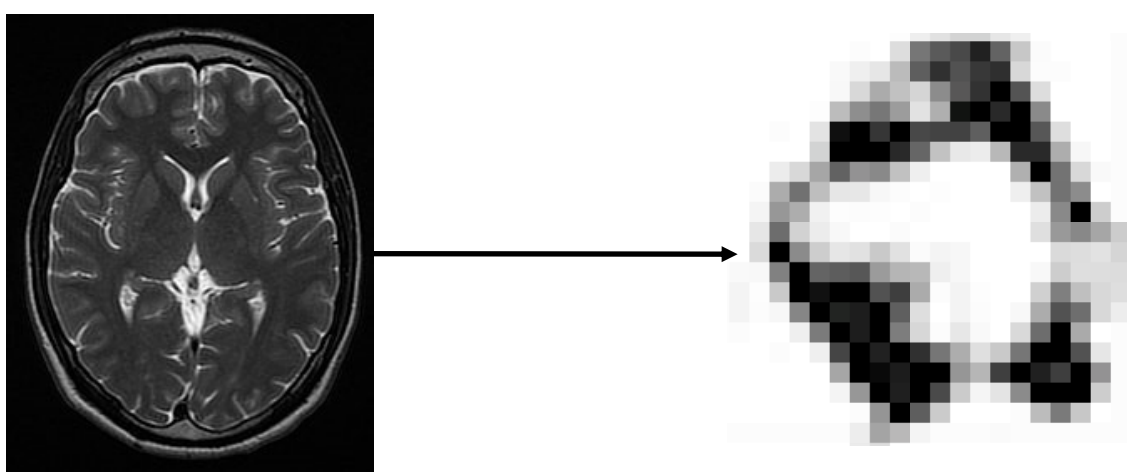


Figure 17: Image Depicting the Possible errors in Image Generation (Source: Medium)

Because the images that are generated may not actually be correct brain images, a brain-border segmentation model was trained to ensure the boundary of the brain in generated remained intact. This was to potentially avoid the problem above, that wouldn't give any useful information or better data.

Brain Border Segmentation Framework

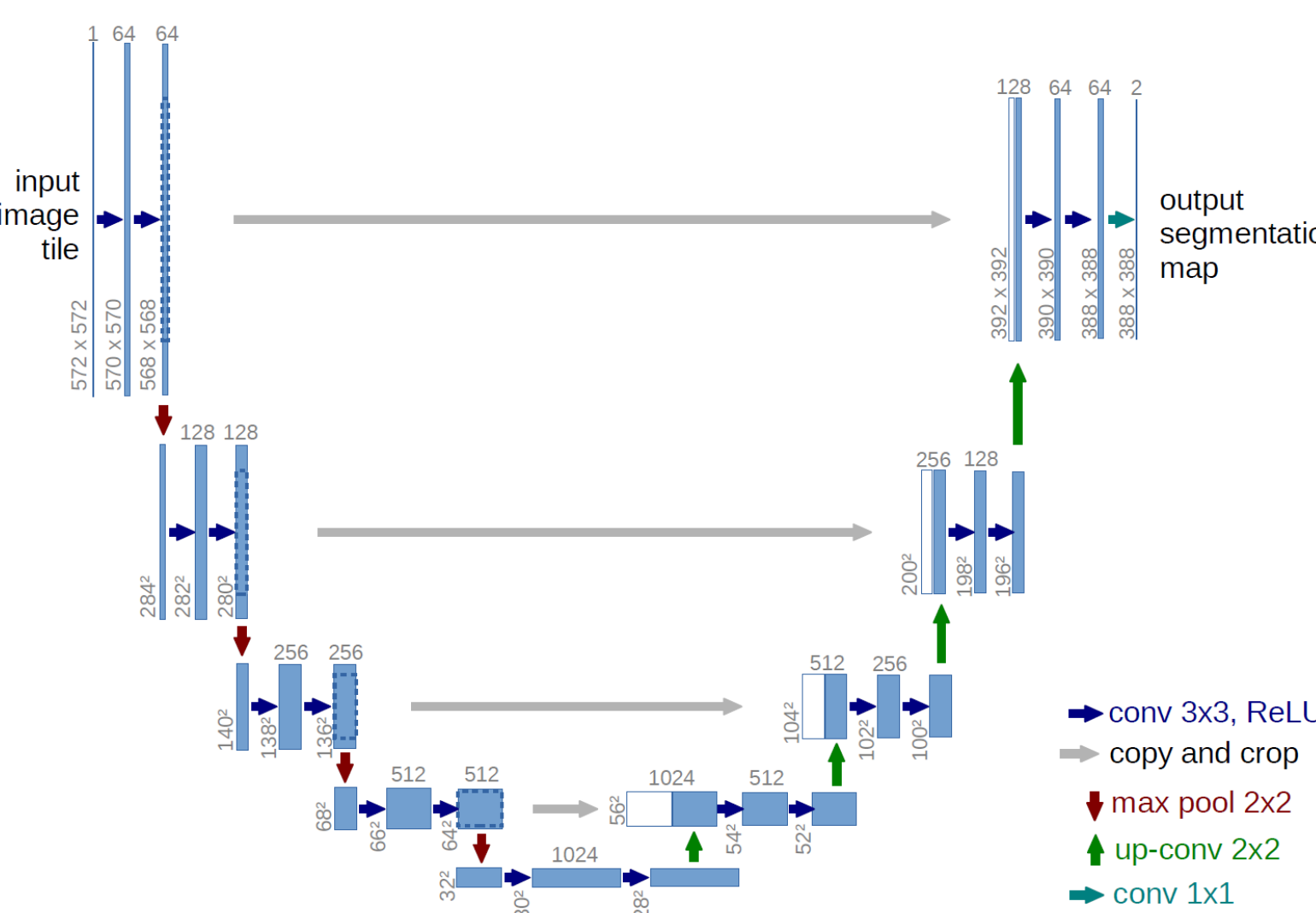


Figure 18: Image Depicting the U-Net Design

A 3-D model based off the U-Net architecture was used for the image segmentation. The U-Net was designed specifically for the task of image segmentation, and has been used frequently in the field of medical informatics.

Multiple 3-D models were written to verify the accuracy in PyTorch, Keras, and Tensorflow.

Parkinson's Disease

Parkinson's Disease (PD):

- Is the **second most prevalent neurodegenerative disease**, affecting approximately 1% of the population above the age of 65.
- average life expectancy **decreases by 16 years**.
- contains many **irreversible** symptoms including bradykinesia, cognitive problems, **hallucinations**, **paralysis**, and tremors.

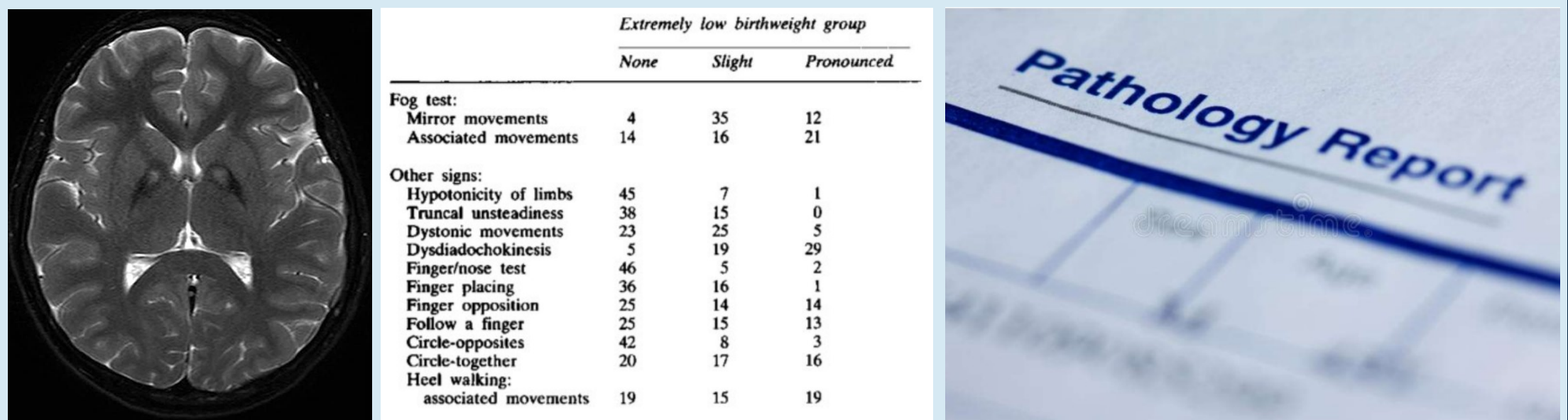


Figure 1: Diagnosis pipeline for Parkinson's Disease. (1) Collection of neurological data including MRI scan, (2) Numerical data from neurologists is also included. (3) A pathologist

Diagnosis Challenges

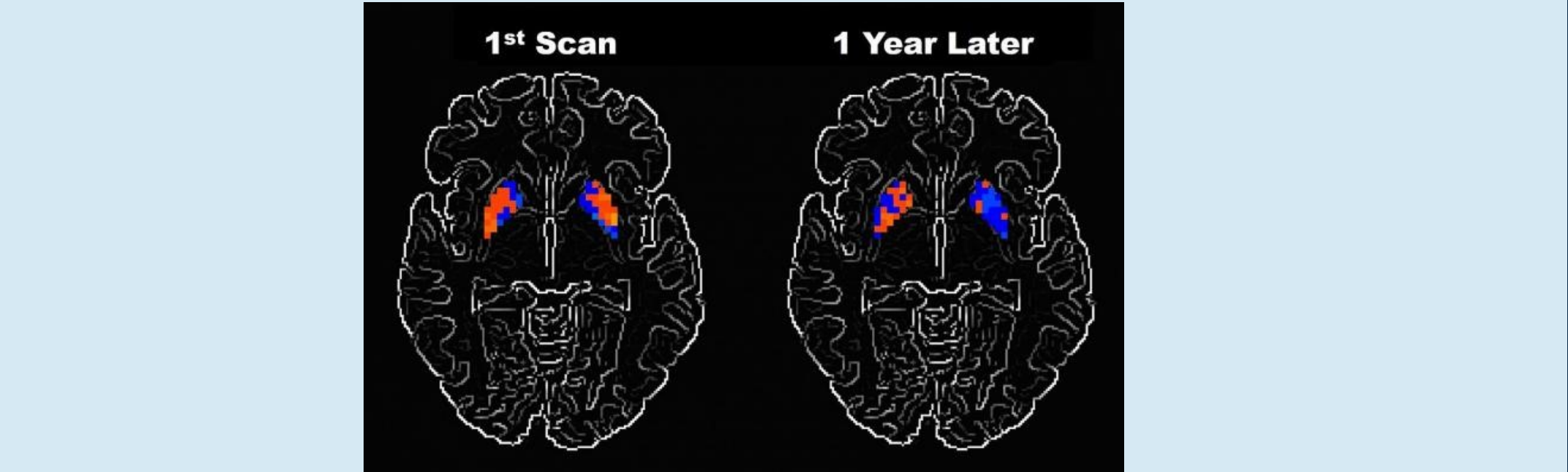


Figure 2: Potential ways to detect Parkinson's Disease through an MRI. (Source: PBS)

From the data collected, diagnoses made by pathologists is purely from knowledge of the prevalence of supposed symptoms. This leads to many diagnoses being incorrect, as either symptoms have not appeared yet, or the symptoms are of another disease, culminating in a clinical diagnosis accuracy of 80.6% (Rizzo, 2016).

Many scientists believe that an MRI scan can reveal details about the development of Parkinson's Disease. As Figure 2 shows, there are changes in the brain resulting from the substantia nigra failing to produce dopamine.

Problem Definition

Current Treatment Challenges	Potential Solutions
<ul style="list-style-type: none">Post-Symptomatic: Testing to determine for the presence of symptoms must occur after the symptoms are presentEfficiency: Current testing takes 10+ daysAccuracy: Sometimes all the symptoms are not present or are a part of a different disease	<ul style="list-style-type: none">Low-cost method is vitalComputational diagnoses are favorable:<ul style="list-style-type: none">Standardized, objective treatmentShould be modular and accept different sizes of MRI scansSolution to properly handle low amounts of data

A method to predict information from a MRI scan would enable greater effectiveness of treatments administered earlier in the disease cycle.

Objectives

- Create models to:
 - Efficiently and accurately **automatically predict a diagnosis** of an subject with or without Parkinson's Disease based off of an MRI scan.
 - Determine the best forms of models capable of being modular and accurate without losing information.
- Overcome many medical informatics problems including the lack of a large enough dataset to produce reasonable predictions.

Methods

Dataset: With a medical contract, the PPMI database of Parkinson's data was obtained for the purpose of this research. This database contains genetic data, image collections, motor assessments, and more data related to Parkinson's Disease.

Pipeline Overview: To analyze images, a feedforward set of neural networks will be used to analyze and predict information based on the data.

MRI Predictive Framework: To predict the prognosis of Parkinson's Disease based off of MRI images, 3D-convolutional networks and other image processing techniques were used to gather conclusions based off of the data.

Patent-Pending: PDGAN is provisionally patented as a method to generate whole MRI slides to improve classification performance.

Technical Background

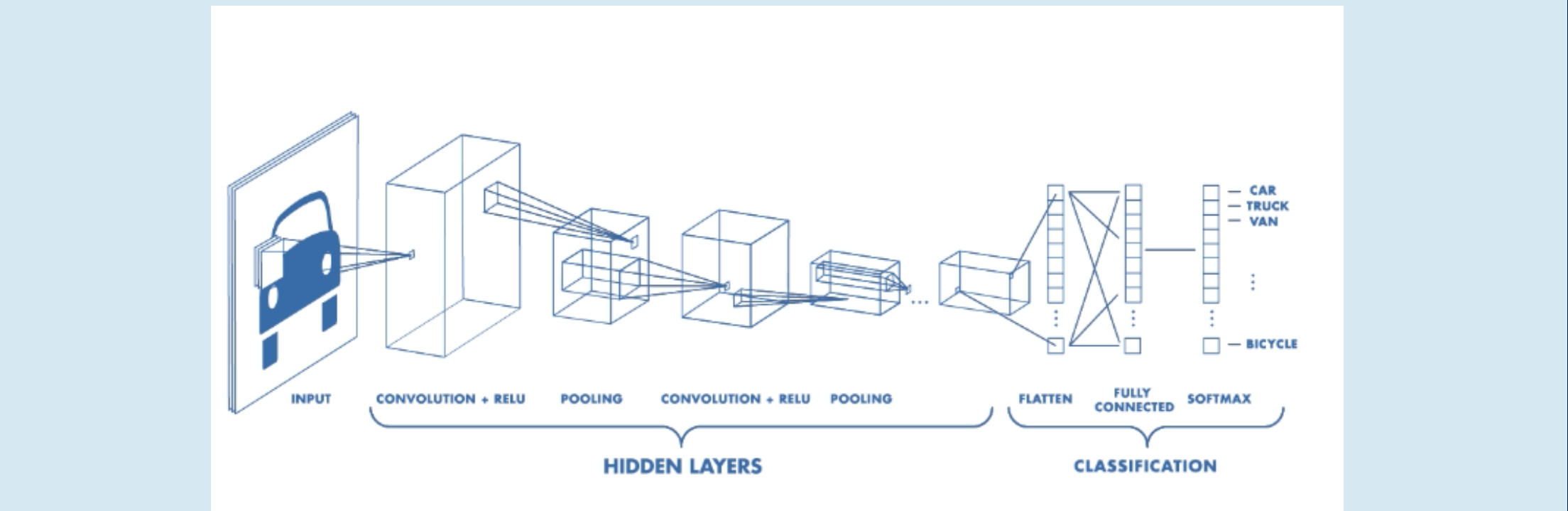


Figure 4: Simple Demonstration of a Convolutional Neural Network (Source: Medium)

This project utilizes various deep learning techniques and models to classify, annotate, and generate images. An example is the Convolutional Neural Network (CNN) which specializes in image processing.

Results

GAN Training Results

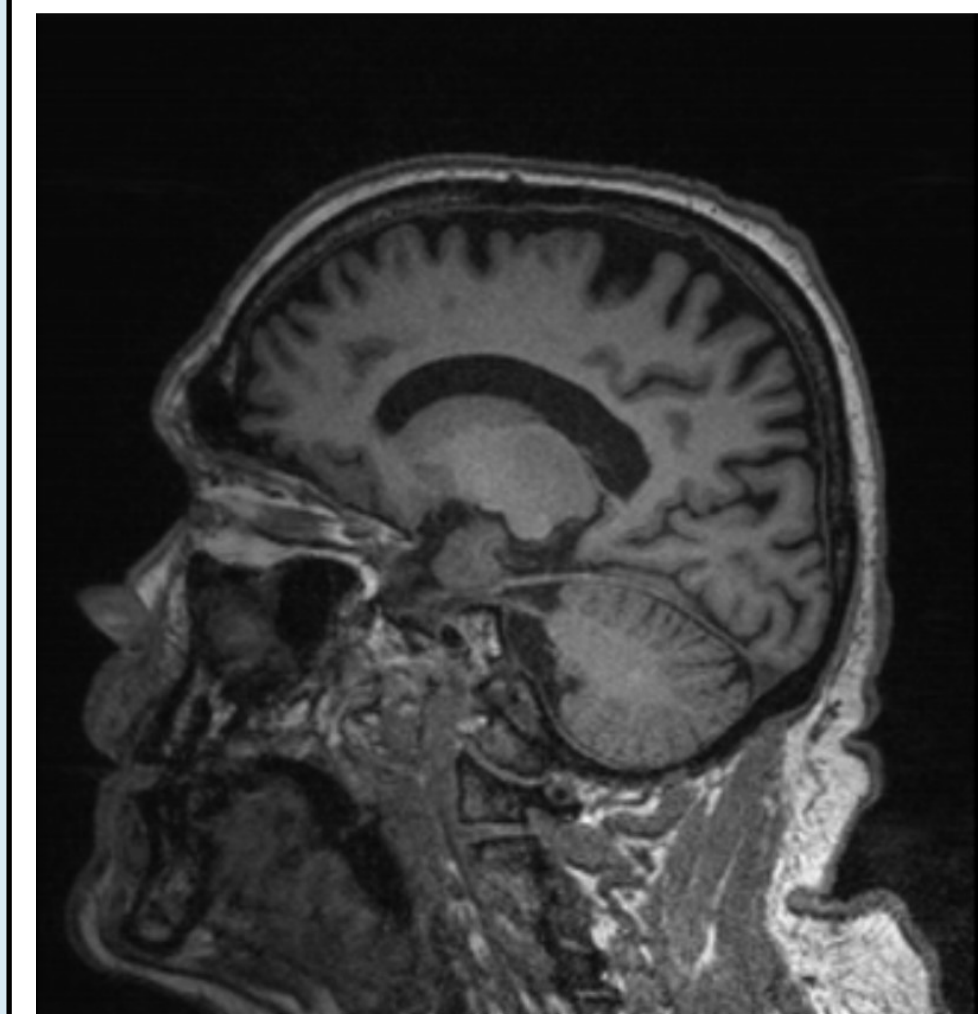


Figure 19: Example Slice of Generated Image. Around 80 new images were generated by the GAN and added to the training dataset.

After 148 epochs, the GANs training loss was less than 10^{-7} . The 80 generated images added were only appended to the training set, to ensure that the model was only being evaluated on pure images and not generated ones. This means the increase in accuracy on the test set actually improved the analysis model on real data.

Classifier Predictive Results

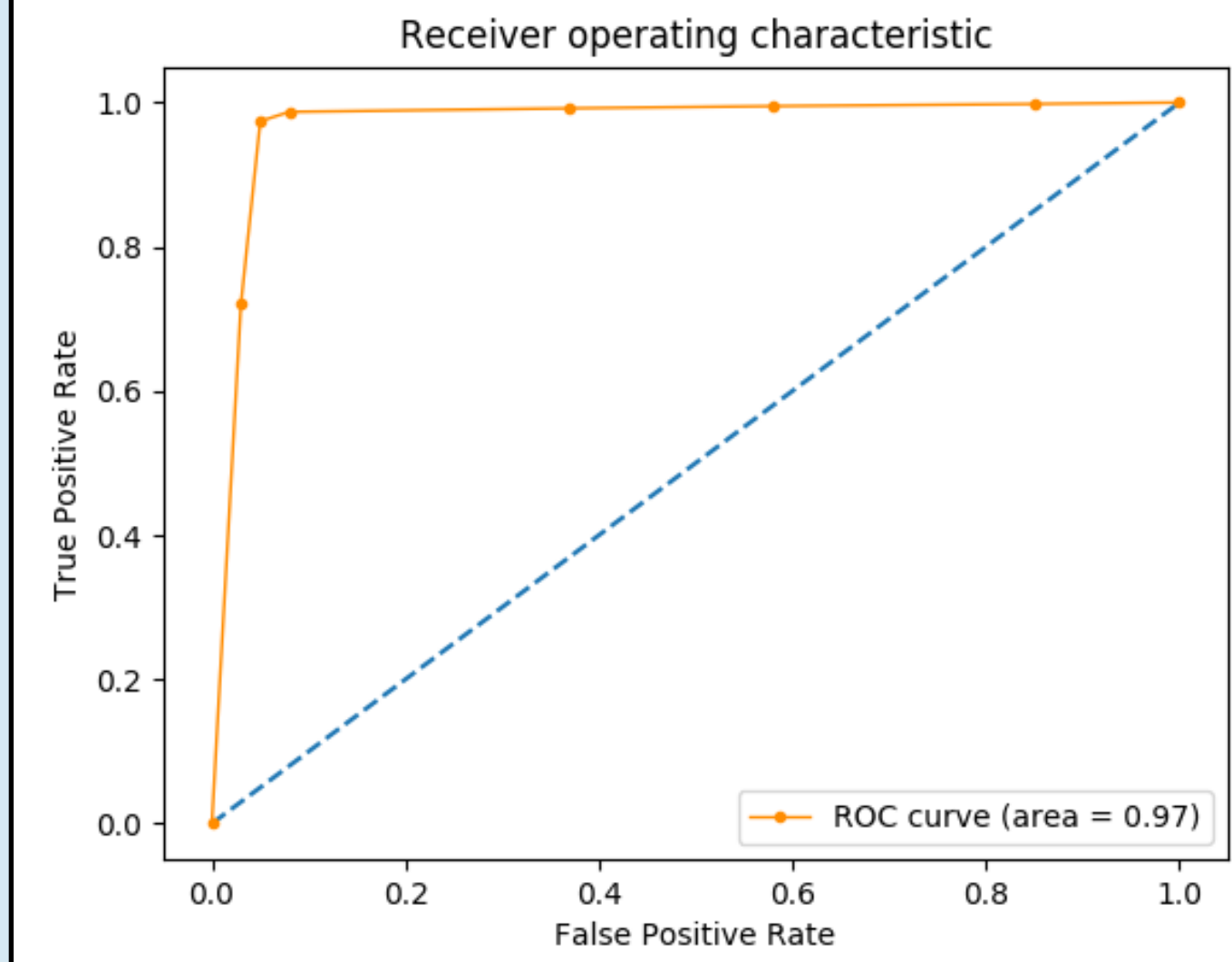


Figure 20: Various final evaluation metrics of all the models. The bolded results indicate metrics when adding additional data.

Model	Accuracy	Sensitivity	Specificity
PDGAN	96.62%	97.41%	94.59%
VGG-19	94.12%	94.83%	91.89%
VGG-19	94.12%	94.83%	91.89%
GoogLeNet	84.97%	86.21%	81.08%
GoogLeNet	91.50%	92.24%	89.19%
Resnet-50	88.89%	92.24%	78.38%
Resnet-50	89.54%	87.93%	94.59%

The Classifier did significantly better with the introduction of more data. The AUROC increased from 0.92 to 0.97, and the accuracy of the best model increased from 94.12% to 96.62%. This final accuracy is 16% higher than the empirical accuracy of diagnosing Parkinson's disease based off symptoms.

The 2.5% increase in accuracy is statistically significant with a $p < 0.01$ through the T Test for Independent Means.

Brain Segmentation Results

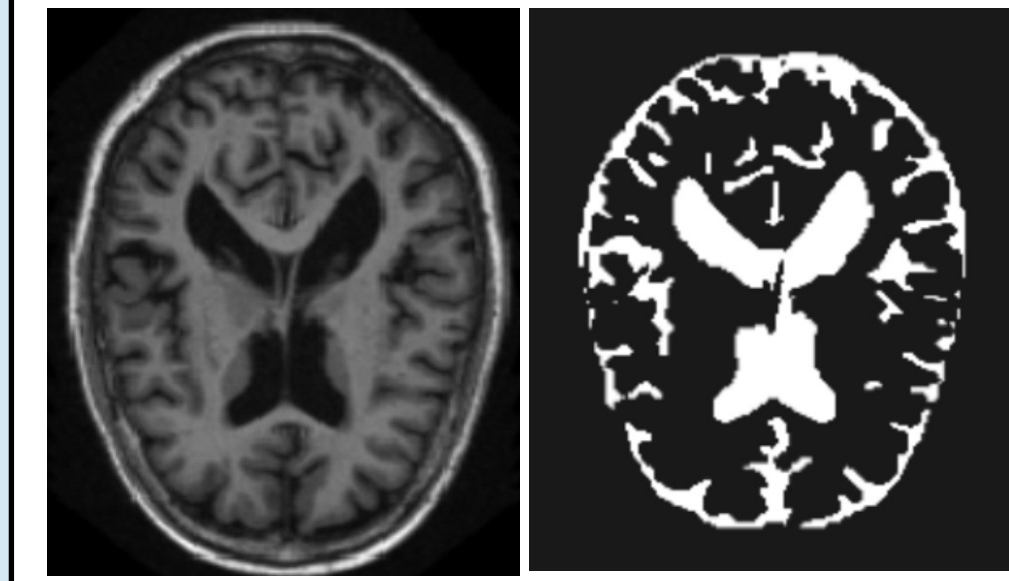


Figure 21: Example Segmented Image.

The Segmentation based model achieved an accuracy of 81%, sensitivity of 96%, and specificity of 78% on the test set.

The Segmentation model trained at a loss of less than 10^{-5} . The model filtered generated images into the training set.

Discussion

The primary objective of the work was to improve on the current diagnosis system for PD and increase the chance for early diagnosis among patients. As evidenced by the research, PDGAN's generation ability is able to improve its performance by bypassing the problem many medical applications face of having a low amount of data. Combined with other machine learning optimization techniques, PDGANs general accuracy showed major improvements compared to other computational models.

PDGAN offers several major improvements over existing experimental and computational methods:

- Segmentation Task: A Check on the Generated Images**
 - Checking to ensure that generated images have proper shape before inputting them into the training set ensures that the generated images have actual meaning to the classifier.
- Modularity of Input Shape: More Accessible for every MRI Scan**
 - Using special layer flavors and models, the PDGAN model in specific is able to accommodate various input shapes from different MRI scanners, giving it unparalleled accessibility.
- Generated Images: Solve to Problem Regarding Little Data**
 - Many studies, including Chen 2013 and Adams 2017 were able to diagnose Parkinson's Disease with an accuracy of ~90%, but had access to tens of thousands of samples. The Generated Images in PDGAN provide the robustness to solve the problem of low-data if it is encountered.

Figure 22: Summary of Related Literature

Study	Description	Input Data	Methodology	Accuracy	Difference between study
Chen, 2013	FKNN – based Diagnosis	Voice Measurements	Fuzzy K-Nearest Neighbors	91.07%	Had thousands of sample data
Frid-Adar et al.	Liver Lesion Classification	Liver Lesion Images	GANs, CNNs	88.4%	Used GANs but with a different classifier – low accuracy
Gil et al.	MLP – based Diagnosis	Voice Measurements	MLP and SVM	88.31%	Had thousands of sample data
Adams, 2017	Typing based Diagnosis	Typing Movements	Various Machine Learning Models	90.1%	Had thousands of sample data
Pereira et al.	Writing and Medical Exam Diagnosis	Handwriting, Medical Exam Information	Computer Vision Processing, CNNs, MLP	67%	Low accuracy, used a combination of tests.

Conclusions

CONTRIBUTIONS: PDGAN is a data-driven approach of diagnosing Parkinson's Disease using cutting-edge machine learning technology to offset many problems that occur in traditional medical informatics solutions. PDGAN's combination of generative and classification networks allows it to be robust in the environment of the problem it solves.

APPLICATIONS: The unique, integrative approach requires no expensive equipment, other than the common MRI machine. Additionally, the flavor of PDGAN model can be used in similar problems that could use an MRI scan to predict a patients' prognosis.

FUTURE WORK:

- Incorporating several different modalities of pathological and radiological imaging and techniques to improve accuracy.
- Looking for connection between genetic traits and MRI scans to determine if early detection of Parkinson's before symptoms even begin to appear is possible.
- Apply the PDGAN model to different informatics problems for validation.