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

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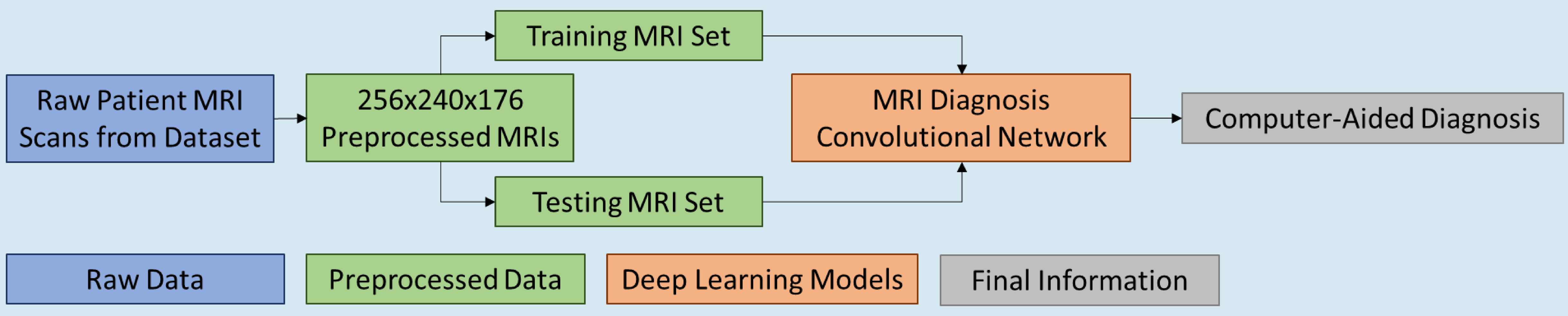
First Iteration Prediction Framework



Model Selection and Creation

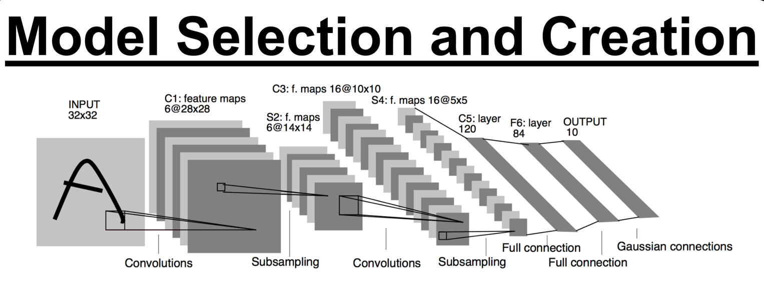


Figure 6: LeNet model architecture (Source: Medium)

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

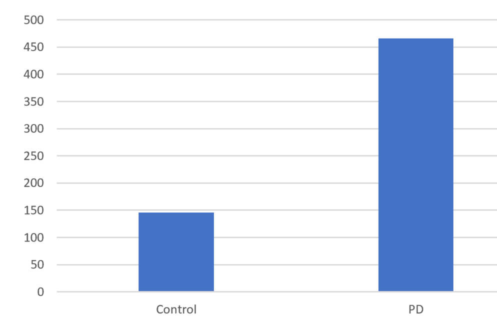


Figure 7: Data split between PD and Control.

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

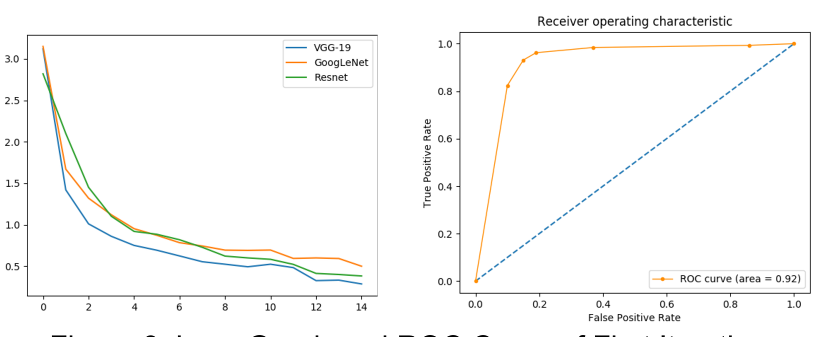


Figure 8: Loss Graph and ROC Curve of First Iteration.

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.

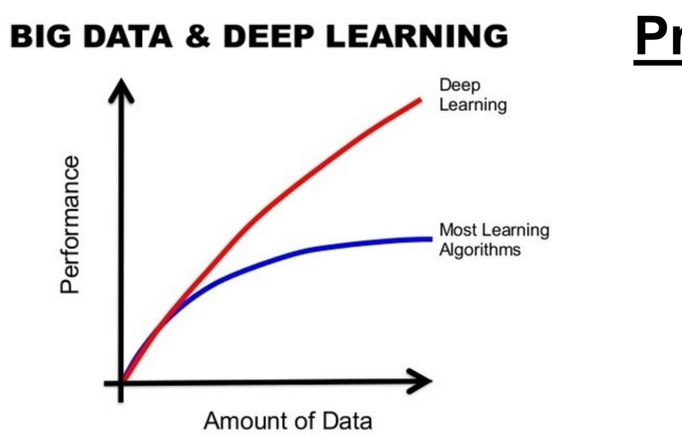


Figure 9: Graph depicting the performance of algorithms as the amount of data grows (Gibson).

Problem: Lack of Available Training Data

As evidenced by the graph to the left, data is important to the performance of a machine learning model, and because the PDGAN system only had access to under 1000 images, the performance was capped at a certain limit purely because of the amount of data.

Unfortunately, no outside source could remedy this, as the LONI Image Data Archive was the largest corpus of Parkinson's MRI scans. The only way, then, to fix this would be to artificially generate new test samples in lieu of a originally large amount of cases.

Second Iteration Generative Framework

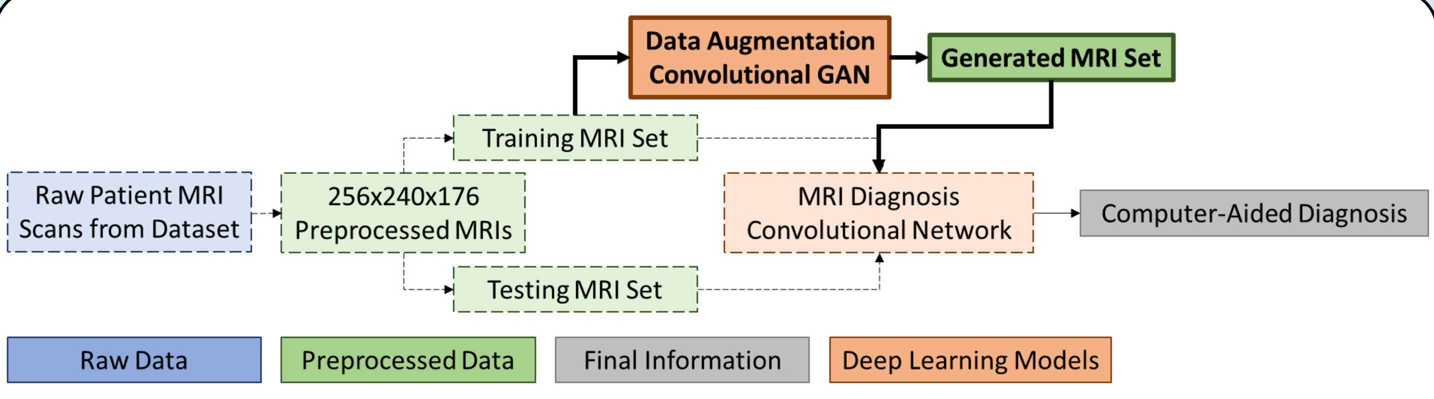


Figure 10: Data Flow through the Second Iteration of the Predictive Model

Generative Adversarial Networks

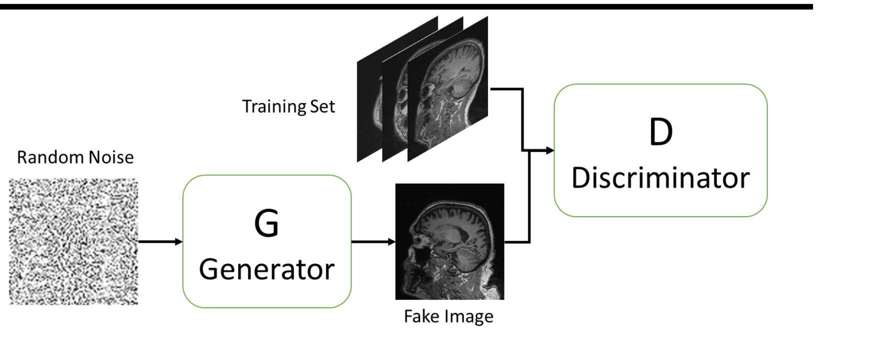


Figure 11: Pipeline for Generation of Images. The Generator generates images and the Discriminator determines if they are real or fake.

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

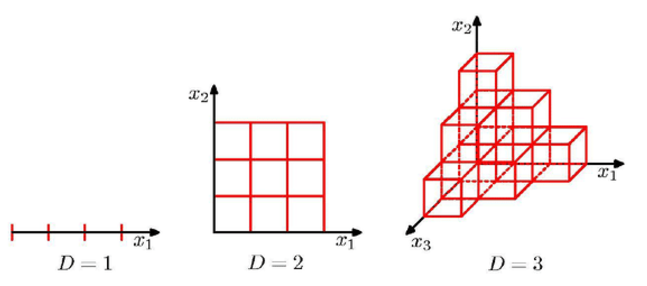


Figure 13: Image Depicting the Stretch of Additional Dimensions. (Source: Hadoux)

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

Addition 1: 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 14: 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

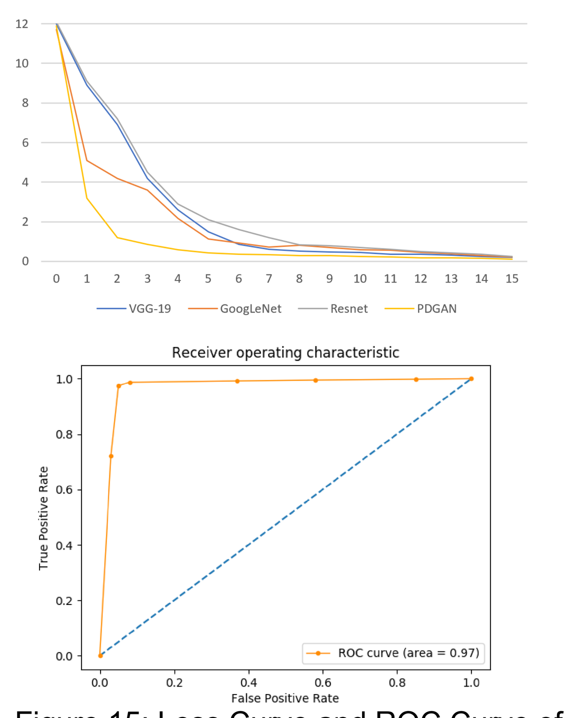


Figure 15: Loss Curve and ROC Curve of Second Training Data

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).

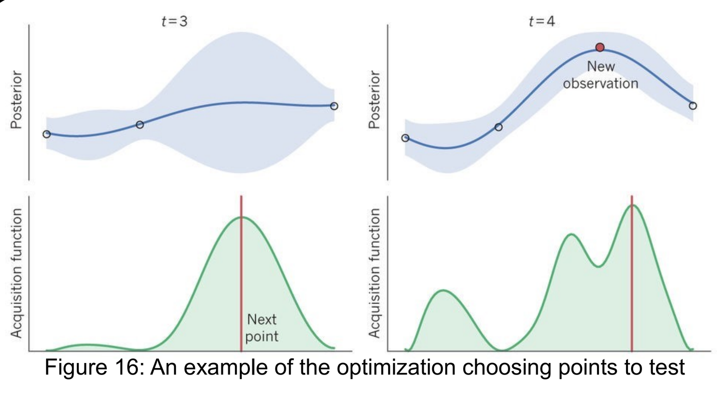


Figure 16: An example of the optimization choosing points to test (Source: MachineLearningWorks)

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 17: Few of the various parameters passed through the Spearmint optimizer.

Addition 3: Sparsely Connected Networks

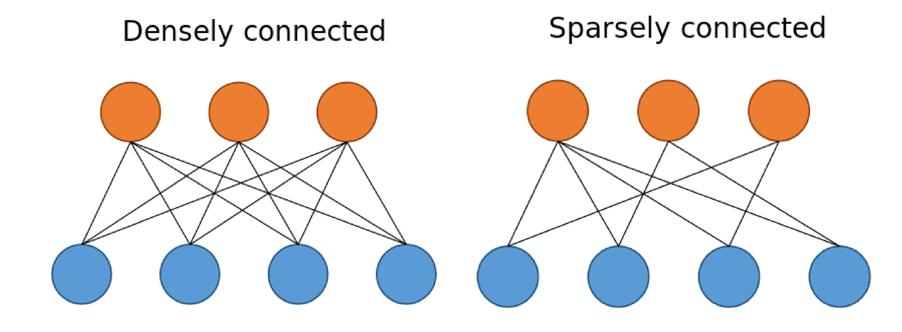


Figure 18: Depicting the difference between Dense and Sparse Networks. (Source: Klear)

Sparsely connected networks allow the machine learning model to sacrifice small amounts of performance for tremendous time saving, as well as a potential fix to overfitting. Using sparsely connected networks reduced training time by up to **19.2%**.

Addition 4: Residual Learning

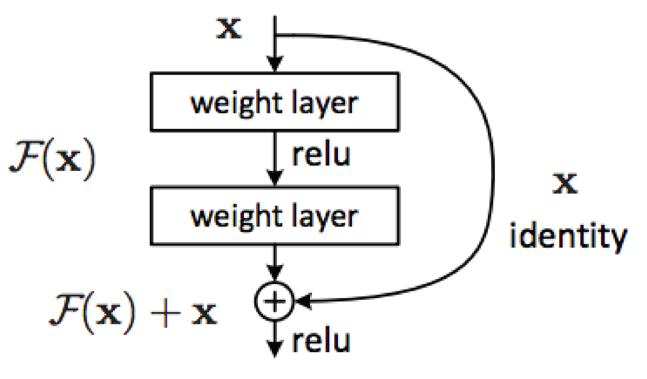


Figure 19: Image Depicting the concept of Residual Learning. (Source: He et. al)

Residual Learning is a solution to the traditional vanishing/exploding gradient problem of stacking layers. As more layers are added, the residual learning is capable of decreasing training error, increasing training speed, and easing optimization for the network. Resnets work by mapping the identity function on top of the network.

Validation: Confirming Generated Brain Border Unity

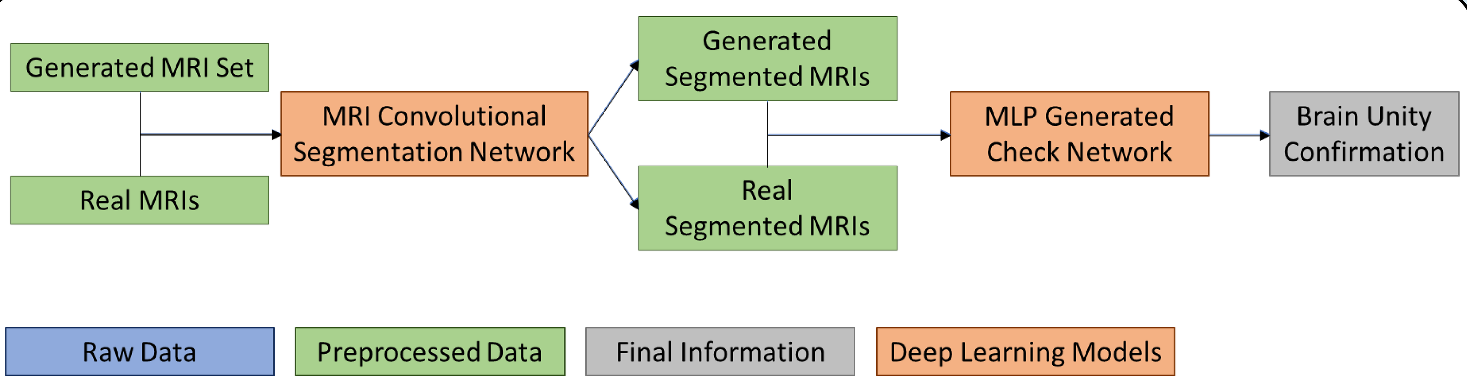


Figure 20: Data Flow through the Validation Segmentation Framework

Reasoning

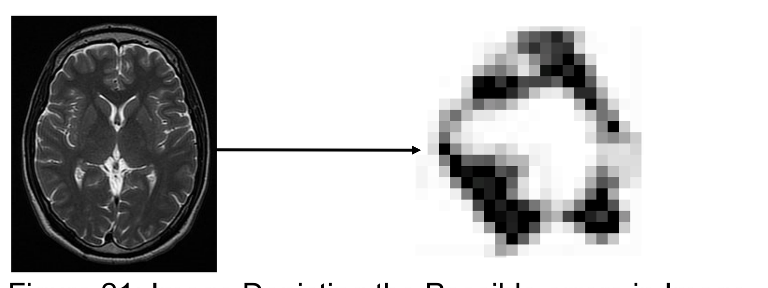


Figure 21: Image Depicting the Possible errors in Image Generation (Source: Medium)

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

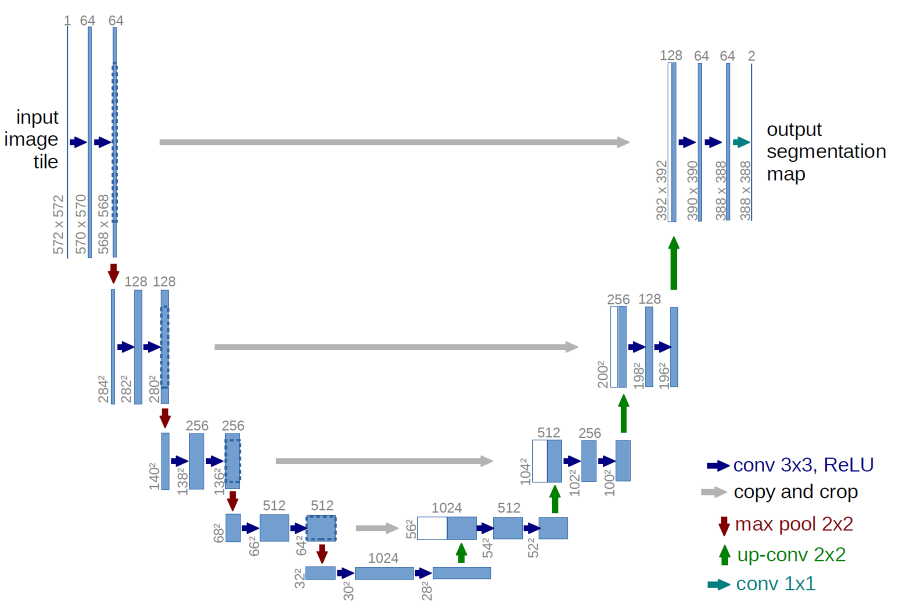


Figure 22: Image Depicting the U-Net Design

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. The U-Net was trained to look for borders of the brain tissue. Segmentation models generate new images where the white part is what it believes is the border, and the rest is black.

Multiple 3-D models were written to verify the accuracy in PyTorch, Keras, and Tensorflow. The models were all used to generate images for the training of the Multilayer Perceptron.

Multilayer Perceptron Framework

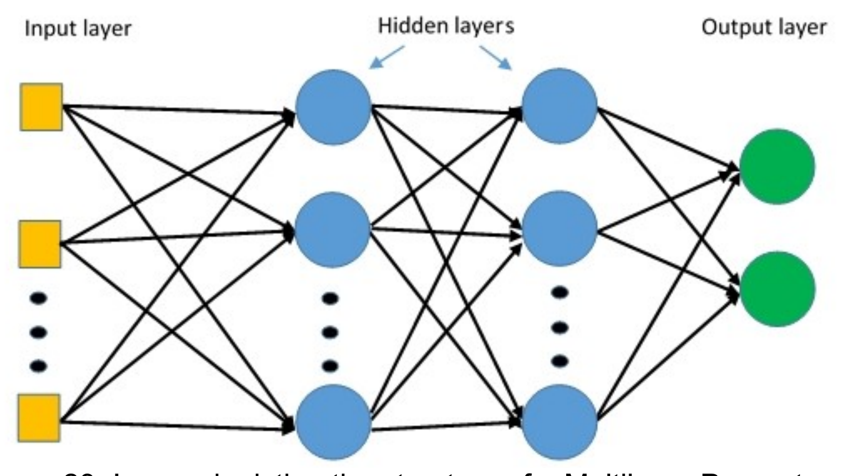


Figure 23: Image depicting the structure of a Multilayer Perceptron (Source: O'Reilly)

The Multilayer Perceptron (MLP) was used to determine if the segmented brain border is connected. The MLP was chosen for this fairly easy task because of its scalability and quickness to train.

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.

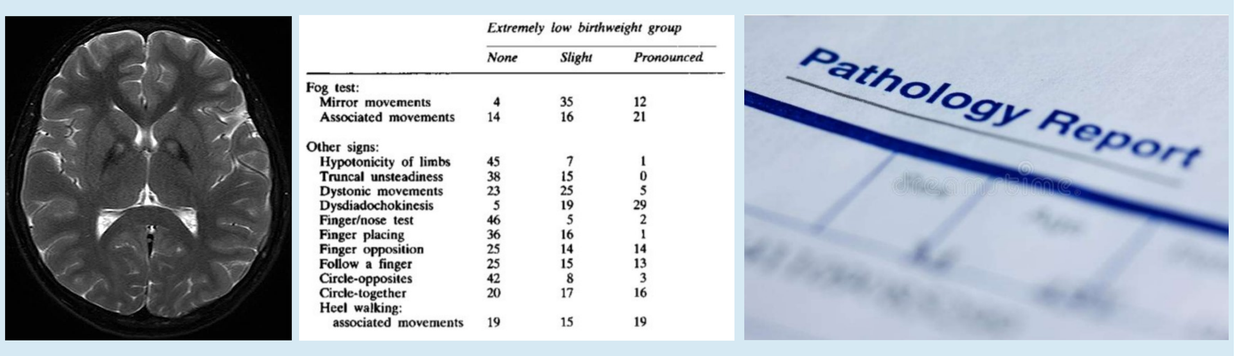


Figure 1: Diagnosis pipeline for Parkinson's Disease. (1) Collection of neurological data including MRI scan, (2) Numerical data from neurologists is also included. (3) A pathologist analyzes the data and determines a diagnosis for the disease (Source: NIH)

Diagnosis Challenges

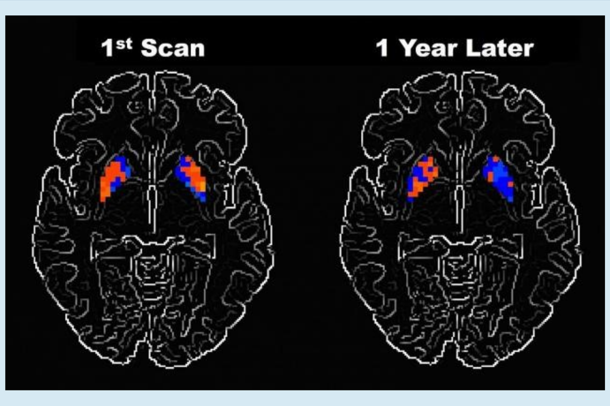


Figure 2: Potential ways to detect Parkinson's Disease through an MRI. (Source: PBS)

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. There are changes in the brain resulting from the substantia nigra failing to produce dopamine. These physical changes, if recognized in an anatomical MRI, could lead to the early detection of Parkinson's Disease.

Problem Definition

Current Treatment Challenges	Potential Solutions
• Post-Symptomatic: Testing to determine for the presence of symptoms must occur after the symptoms are present • Efficiency: Current testing takes 10+ days • Accuracy: Sometimes all the symptoms are not present or are a part of a different disease • Accessibility: Current computational methods are only specific to one MRI scanner type	• Low-cost method is vital • Computational diagnoses are favorable: • Standardized, objective treatment • Should be modular and accept different sizes of MRI scans • Solution to properly handle low amounts of data • The framework requires self-validation to ensure it is justified in the decisions it makes

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.

Overview of Solution

There are four major parts of this project, as categorized as part of the solution and as part of the testing process.

1. **Classification Algorithm:** Multiple state-of-the-art Neural Networks were trained on a corpus of images to analyze anatomical MRI scans for the presence of Parkinson's Disease.
2. **Generation System:** To increase the robustness of the classifier, images were generated using a Generative Adversarial Network. The GAN was trained on the same set of images as the classifier and the performance of the classifier was tested with and without the generated images to see the difference.
3. **Biological Validation System:** As an additional check on the generated images, various biological validators were put in place, including a brain-border validation algorithm which checked if a proper border was established around the generated brain.
4. **Virtual Application:** To increase accessibility for this system, an executable application was created that allows users to evaluate anatomical MRI scans for the presence of Parkinson's Disease.

Technical Background

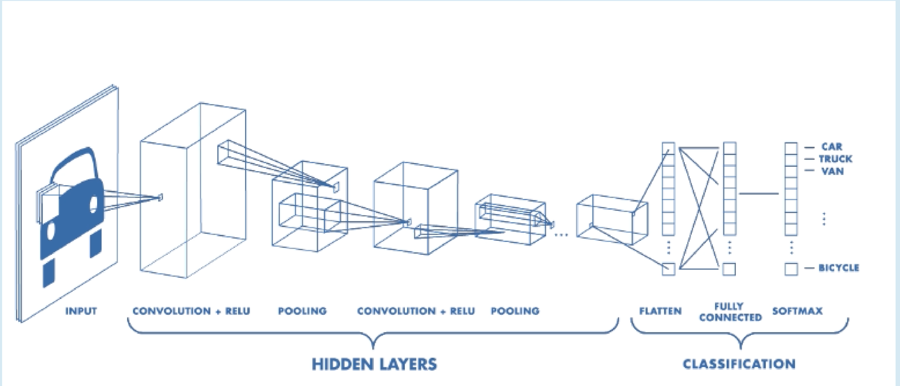


Figure 4: Simple Demonstration of a Convolutional Neural Network (Source: Medium)

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. These networks are powerful in their ability to mathematically learn complex hierarchical patterns through the convolution of weighted, adaptable filters with input data and spatially-correlative features to classify unseen cases.

Image Preprocessing

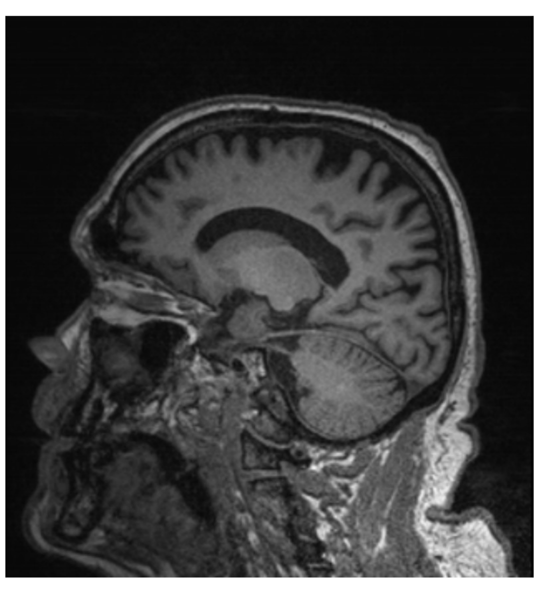
Figure 5: Showing the Asymmetries of the Brain and the importance of **not** rotating the images fed into the network (Watkins).

Because MRI images are already black&white, minimal preprocessing steps were done. Due to the diversity of the dataset many of the images had differing sizes, a size was chosen (256x240x176) and the rest of the images were scaled to that size.

Most image preprocessing also contain steps of rotating images to augment the dataset. However, because MRI images are inherently directional, flipping/rotating images could give misleading and incorrect information to the classifier. Thus, every image was only fed once into the network. Traditional normalization was done as well.

Results

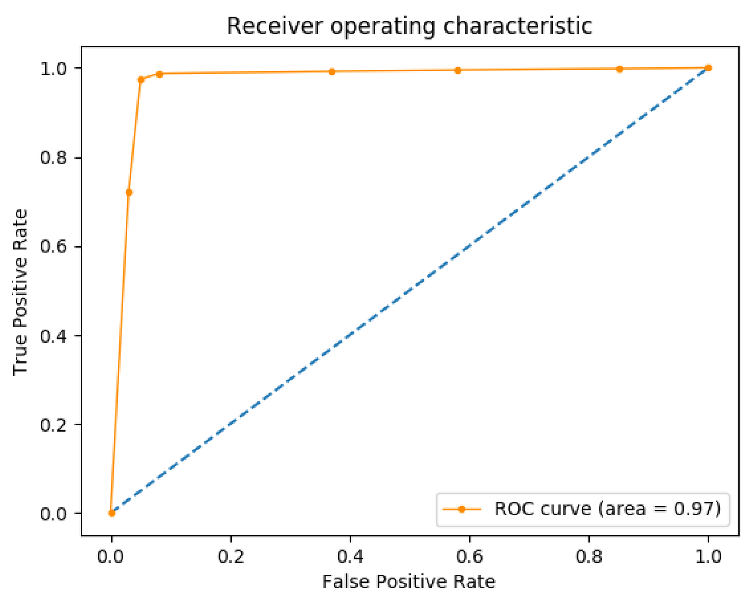
GAN Training Results



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.

Figure 24: Example Slice of Generated Image. Around 80 new images were generated by the GAN and added to the training dataset.

Classifier Predictive Results



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%**

Figure 25: Various final evaluation metrics of all the models. The bolded results indicate metrics when adding additional data.

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 26: 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.

Sharable Application

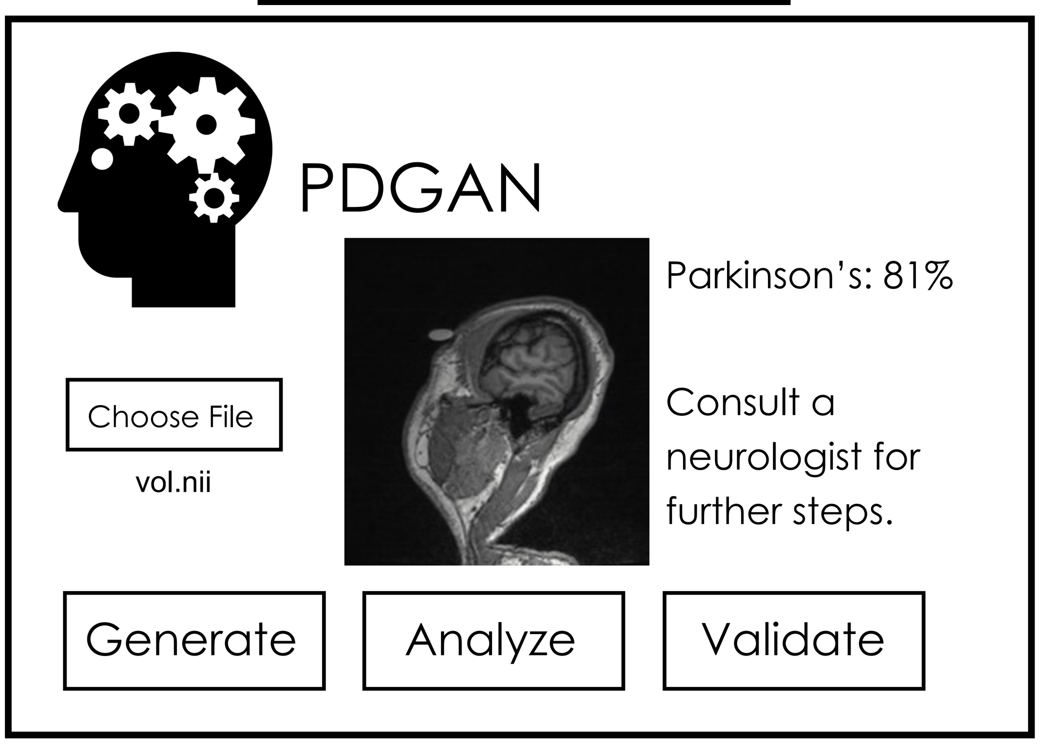


Figure 27: Image depicting the application and its features.

An application was made to facilitate the model's performance on a server. The API is meant to be user-friendly and can perform all of the tasks of the application.

The application is able to take .nii and a directory of .png files as input. It is currently hosted locally but has the capability to be hosted remotely on a website for everyone to use.

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:

1. 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.

2. 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.

3. 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 28: 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
Pereisa 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.

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