Preliminary Report

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Contents

1 Introduction

1.1 Parkinson's Disease

Parkinson's Disease (PD) is a progressive disorder of the central nervous system. This disorder affects several regions of the brain, especially one called the substantia nigra which is responsible for balance and movement.
Parkinson's is a disease is one of the most common neurodegenerative disorders which affects more than 4 million people worldwide and is typically diagnosed by observing physical symptoms such as trembling or shaking of the limbs. Other symptoms include impaired balance and coordination which worsens over time. It is suspected that PD is linked to genetic family history but is not fully understood how genetic changes causes PD. [19] [4]

The Substantia Nigra (SN) is a region in the centre of the brain which contains dopamine producing cells. This region is reduced in area for patients with PD when compared to healthy patients. The true anatomic location of the SN, antero inferolateral (front region of the brain, lower in vertical height) to the red nucleus (part of the mid brain responsible for motor control). This was from a study done by Hirobumi Oikawa et Al. [22]
Hirobumi's study only has 22 patients diagnosed with PD, though these have 22 age and sex matched healthy volunteers to compare to. Also the study involves the use of multiple imaging techniques, primarily focusing on proton density-weighted spin-echo and fast magnetic resonance to determine the precise location of the SN within the brain. They found that SN volume loss is not found in Parkinson's disease, this could be an area to focus on in the process of diagnosing Parkinson's using deep learning.
Hirobumi concluded that there was no significant different observed in hyperintense band. Compared size with averages and st.dev and tested statistical significance (p-value.Therefore it needs more work to determine substructures of SN or MR images (magnetic resonance). No difference reported between Parkinsons patients and healthy.

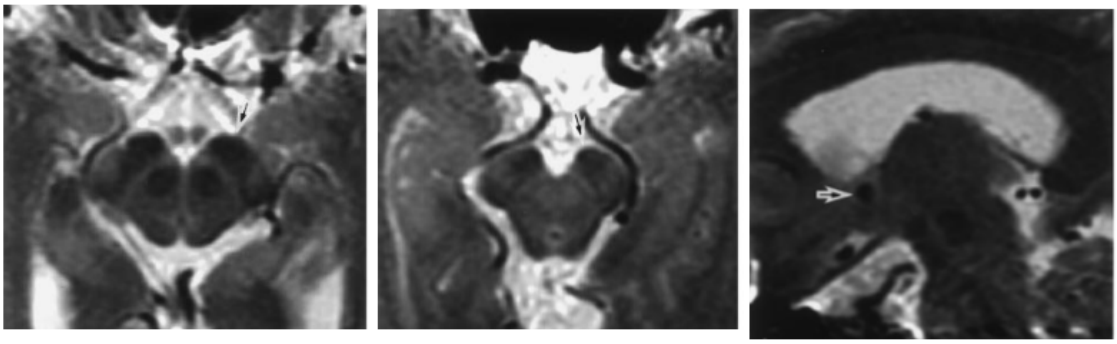


Figure 1: Left: MR weighted image from a control subject, the hypointense area is on the end of the crus cerebi, where the arrow is pointed. Middle: A image from another control subject, the red nucleus is depicted as a round hypointense structure. Right: Sagittal image in a control subject. [22] Sagittal Plane is one which divides the body between left and right (midline); Coronal plane is frontal which divides the body between the torso and back; Axial plane divides the body between the torso and legs.

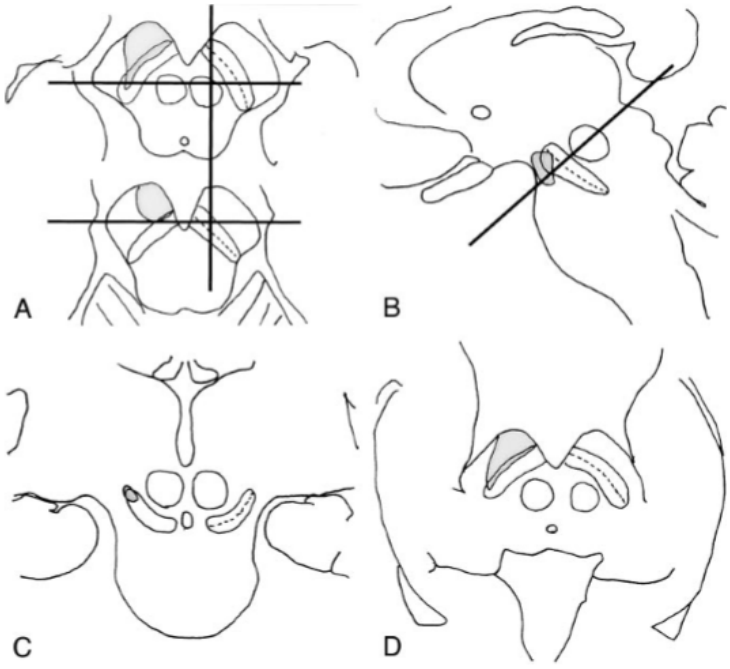


Figure 2: Schematic drawings of the multi-planar localisation of the hyperintense gray matter. A, axial Plane through the upper and lower midbrain. B: Sagittal Plane, C: Coronal Plane, D: Oblique Coronal Plane [22]

1.2 Deep Learning

Deep learning allows computational models composed of multiple processing layers to learn data representations with several layers of abstraction. These methods have been used for to achieve accurate speech recognition, visual object recognition and has been used in drug discovery and genomics.
Deep learning discovers complex structures in large data sets using the backpropagation algorithm to change internal parameters to compute representations of each layer from representations in previous layers. Deep convolutions nets have bought about breakthroughs in image processing, video, speech and audio. [6]

The most common form of machine learning, deep or not is supervised learning. During training, the machine creates a vector of values from an image and assigns this to an output. We want the highest possible score following training, so we have an objective function to measure the error between the output and the desired output. The machine then modifies its adjustable parameters (weights) to train the machine towards the correct answer. A common method used is called stochastic gradient descent where the objective function is incrementally decreased until it can do so no more.

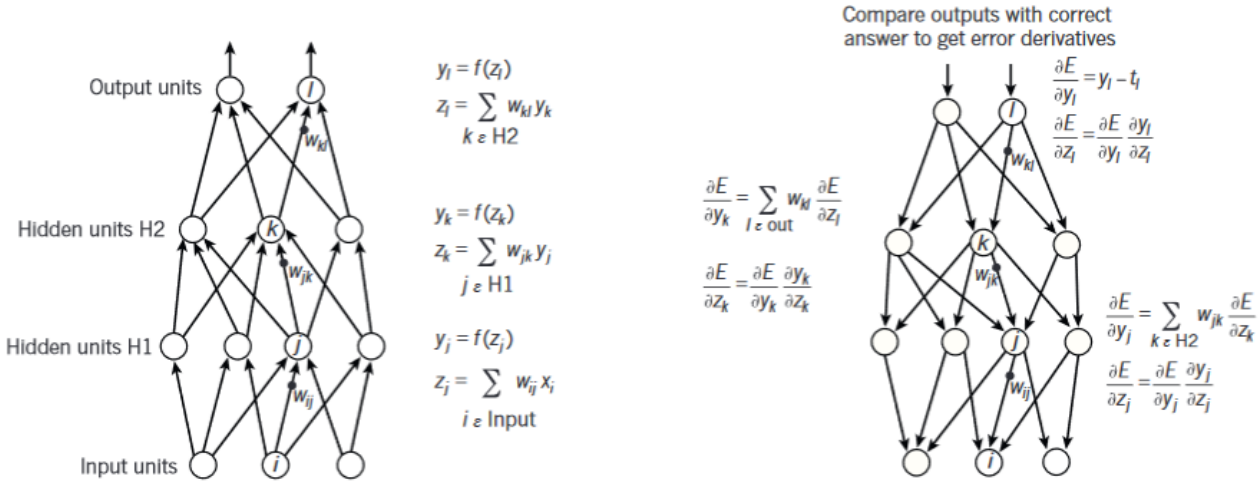


Figure 3: Illustration of a neural network with 2 hidden layers. On the left we have a feed forward layer where the output of each unit is the weighted sum of the inputs which go into a function (such as the sigmoid). And on the right we have the back which propagates the error backwards in order to increment the weights for better classification accuracy
[6]

Convolutional Neural Networks (CNN) is a form of deep learning that is de-

signed to process data that comes in the form of multiple arrays. We can use rectified linear units (ReLU) which are non-linear nonuts in place of the activation function and ultimately accelerates the convergence of gradient descent. [13] In CNN, there is a convolutional layer which slides a filter through the width and height of the input (image) and produces a 2-dimensional activation map. Thereby learning the responses and building the activation map from the filter outputs for visual features such as edges. These activation maps then stack to produce an output volume. [2]
In a CNN, we may have a large volume of weights which becomes cumbersome and unwieldly. If it is not possible to reduce the image by extracting relevant features, we may apply pooling to reduce the image size. Pooling is a technique which passes a filter which scans the multi-dimensional array and applies calculates a metric in each section of the array such as the average value or max value then concatenates these in order to produce an output array with less dimensions. This is typically done after the ReLU function has been applied to normalise the values. By doing this, we keep specific features as well as their relative position to other important features though we may lose exact information on the relative location. [13] [2]

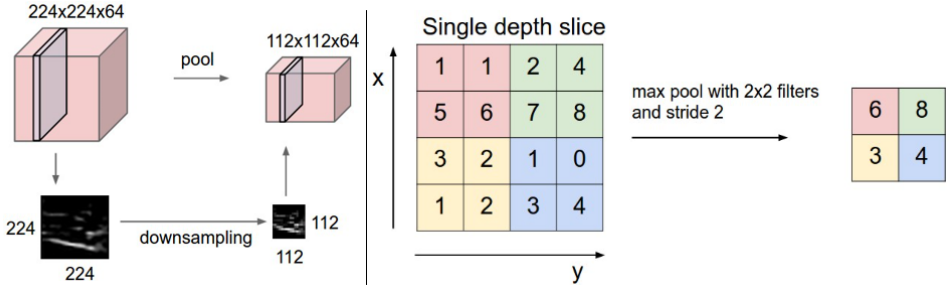


Figure 4: Pooling downsizes the the volume spatially, independent of each depth slice as seen on the left. On the right we see a pooling example where the stride is 2 and max pooling is applied
[2]

At stages within our neural network or between convolution and pooling, one may include 'dropout layers' which removes nodes at random with probability 1-p. The idea behind this is to force the network to remain robust even if neurons are dropped out. This also has the effect of preventing the network from over fitting, a problem whereby the classifier cannot generalise to predict other cases outside the training set of data.

1.3 Literature Review: Current Classifiers in Parkinson's Diagnosis

A lot of recent Convolutional Neural Networks (CNNâĂŹs) can be said to be originally based on Hubel and WieselâĂŹs early work on the catâĂŹs visual cortex imaging [14]. Here convolutional layers apply different kernels in convolution in order to obtain feature maps. Weights are adapted by backpropagation and stacked layers can abstract features even further.
Jie Chang, Luming Zhang et al as an example apply a mix-pooling CNN with a fully connected random field (FCRF) for automatic brain tumor segmentation [34]. Here the usage of efficient CNN with max pooling is compared against CNN with average pooling. 1x1 kernels are used to add non-linear dimensions and a mixture model is applied. This is an instance where MRI scans of brain tumors are used, where T1 brain slices are imaged. Prior to the publication of this paper, a system of classical methods of segmentation involve thresholding, region-based segmentation and pixel classification. This paper finds a non-linear relationship in all the intensities in the image and suggests a two-pathway CNN between max pooling and average pooling, having a slight preference for average pooling.

This is difficult to contextualise as a problem with classical MRI segmentation is a lack of a standardised and quantifiable interpretation of image intensities [21]. As a result, there is no fixed general consensus of interpretation of MRI scans and is relative depending on the scanner method, make and model.

Despite this, Jie Chang et al increased accuracy and sped up training using a non-linear activation function, using hyperbolic tangent. In this a standardised metric was established of measuring the true positive (TP) and false positive (FP) rates as well as positive predictive value and sensitivity. Here the team achieved a sensitivity over 0.9 across all models, showing that average pooling is more important than max pooling for classification of complex brain tissues, though is more subject to noise on the edge of tissues. This finding was significant as it set the grounds for the method of pooling to be used for future CNN pooling methods for complex brain tissue MRI scans.

In contrast to Jie Chang et al, where a CNN is able to identify important features. Hui Ling Chen, Chang-Cheng Huang et al attempted to use a more classical method of supervised learning, fuzzy k-nearest neighbour (KNN) for ParkinsonâĂŹs Disease (PD) diagnosis. Here Hui Ling Chen et al attempted to improve upon the work done by Shahbaba B [32] where an accuracy of 91.4% was achieved in classifying PD with SVM by extracting to another feature space. Using Fuzzy KNN, Hui Ling Chen et al achieved an accuracy of 96.07%, using 10-fold validation to show the reliability of their method. The sensitivity, specificity and area under ROC curve were also measured to show the robustness of their method.
This paper also suggests more complex analysis, whereby points closer to cor-

responding neighbourhood means contribute larger values than those further away. With the highest membership at the end as the winner, utilising fuzzy set theory in the process [15].

Before running a fuzzy KNN model, principal component analysis (PCA) [28] was used to remove redundant features from the feature space, searching for attributes with the largest variation. This was applied to data from the UCI Machine Learning repository, running a sample size of 31 people, 23 of which had PD and 22 different attributes. Here a 10-fold split was utilised to reduce overfitting, whereby 9 was for training and 1 for testing [16]. Like Jie Chang Et al, sensitivity, accuracy and speicificy was used as metrics. Although different numbers of nearest neighbours were tested, with FKNN1 having the highest accuracy of 96.25This was a significant finding as it provided a new model for PD diagnosis, thanks to the high accuracy in discriminating between individuals that are healthy and who may suffer from PD.

Away from PCA, Mohsen Ghafoornian et al [8] use a deep CNN where the location is an input parameter to aid the segmentation of white matter hyperintensities in medical vision. This is very important as it addresses the problem whereby computer vision fails to incorporate the anatomical location of segments in their decision making process, thus hindering success. Here a CNN is used to consider the explicit location of features during training, incorporating basic location information. This is applied on a dataset size of 50 brain scans, providing a dice score of 0.792, similar to the performance of an independent human observer. The difference in accuracy between machine and man was found to be non-statistically significant, thereby demonstrating that CNN segmentation with location inclusion is a powerful method of boosting decision making.
This is another example of where deep NN has been used in many medical imaging domains, including segmentation, detection and registration [17].

In applying CNN to accurately and fully segment white matter hyperintensities, Anouk GW van Norden et al [20] analyse over 500 patients in the Radboud University Nijmegen Diffusion tensor and MRI cohort (RUN DMC) in a baseline study in 2006, with follow-up patient data in 2011/23. Here, the goal is to extract key structures in brain MRI scans and exclude irrelevant structures.
Fast robust automated brain extraction (FSL-BET) on T1 MRI [29] is used. Then the resulting mask is transformed and applied to FLAIR images and corrected for bias due to inhomogenous magnetic fields with FSL-FAST[3]. Finally, this is normalised between [0, 1] and the dataset is split 42/50 for training, using the rest for validation and testing.

Anouk GW van Norden et al. then reduced samples from 128x128 to 32x32 to reduce computational cost. This was achieved by sampling down with convolution layers. Hereby afterward, a variety of CNN models from single-scale to multi-scale late fusion with weight sharing was applied. The goal in ap-

plying many techniques was to reduce overfitting and maximise accuracy, no PCA was required as the network was allowed to learn which features are important. An option of adding the spatial location features was available before or after the responses from the last convolutional layer. Here a Dice score was used for evaluation of standardised segmentation results [7]. Daniel Garcia Lorenzo et al. showed that a significant difference in dice score is observable with p-value < 0.01. Returning back to Anouk GW van Norden et al, it was shown that early fusion had the least improvement against single-scale approach and two late fusion architecture showed good comparable performance. Though late fusion architecture with weight sharing is simpler and has less parameters to learn, therefore one may wish to use this method.
It was also found that adding spatial location features to the first FC layer significantly improves the performance on top of CNN for segmentation.

The scale of PD clinical diagnosis is addressed by Tolosa E [33] where it is found that PD clinical diagnosis is more prone to errors, particularly in early stages where when clinical signs are not entirely evident. And so work is done by C. Salvatore et al in applying machine learning on brain MRI for differential diagnosis of PD and Progressive Supranuclear Palsy (PSP) [25], [18] using T1-weighted MRIâĂŹs and applying PCA for feature extraction. Again these are compared against classical biomarkers [10] in order to see if ML techniques could work as well as classical methods of examining patients. The dataset involved 56 patients, half of which were healthy controls with no history of neurological or psychiatric diseases with normal neurological examinations. The control subjects were also of similar age as both patient groups. Analysis and preprocessing was done on Matlab and with the FSL software [30]. PCA was done using the Fisher Discriminant Ratio as a scoring method for SVM classification in cross-validation. Here the accuracy, sensitivity and specificity were calculated and all found to be above 80%.

So far, effective and accurate diagnosis of PD by means of MRI biomarkers have attracted much attention, with several biomarkers having been shown to be sensitive to the diagnosis of PD. For instance, the morphological abnormalities in the brainstem as well as cerebellar penduncles in medical contexts. [27] [24]. Whereas SVM application to MRI data is not uncommon, the accuracy in detection for individual PD patients achieved 97%, a significant jump [11].

This is important as it discriminates and studies the relevance of brain voxels in the context and respect of classification analysis, allowing identification of regions involved critically in the pathophysiological mechanisms of PD. Thus identifying the midbrain, pons, corpus callosum and thalamus. Furthermore, these findings are highly consistent with typical neuropathological and imaging findings in patients with PSP [31]. This is highly important as PD so far has only been known to exist in patients with certainty in post-mortem examinations upon discovery of lewy body accumulation within the break, a proteic

hallmark of PD as well as consistent damage of the substantia nigra in a consistent and repeated pattern [5] and so is very important as it proves a framework to investigate neurological disorders that affect a distributed network of regions. Thereby offering new avenues for the application of computer-based diagnosis in clinical practice of PD.

2 Project Overview

2.1 Data

The data source is from Parkinson's Progressive Markers Initiative (PPMI) which is an extensive long-term study funded by the Michael J. Fox Foundation for Parkinson's research and industry partners with the goal of identifying one or more of the bio markers of PD progression to aid and develop better treatments for PD. This is a data set available to those who register with the PPMI Data and Publications committee with anonymised patient identities. Within this data set, we will look particularly at the MRI brain scans of patients throughout the US and EU [12].
Our data set consists of over 2200 samples of patients, each identifiable with an ID who are involved with the study who are categorised as such:

- Healthy Controls (HC)
- Parkinson's Disease (PD)
- Showing Early Symptoms (PRODROMA)
- Subjects Without Evidence of Dopaminergic Degeneration (SWEDD)
- GENPD/REGUN/REGPD/GENUN (to be confirmed)
- No Image - We will not include these

There are around 2200 patient samples falling into the categories above. Of which it is estimated about 2/3 of paients have not withdrew or declined imaging, therefore leaving roughly over 1400 samples usable. The data may include screen failures. Additionally, some patients have not completed an MRI scan.

Note that the MRI scans were performed at 8 different imaging sites with different types of MRI machines with different manufacturers and models. so this may need to be accounted for. Also the type of weighting is varied to three different form with the following features [26]:

- T1
    1. Water as well as dense bone and air appear dark
    2. Fats, such as lipids appear bright

3. Pathological processes such as inflammation, increases the water content in tissues, which decreases the signal on T1

- T2
    1. Water, such as the cerebrospinal fluid appears bright, while air appears dark
    2. Fats, such as lipids appear dark
    3. Pathological processes such as inflammation, increases the water content in tissues, which increases the signal on T1
- Proton Density
    1. Water varies in signal, often gray fluids have higher density and air appears dark Fats, such as lipids is relatively bright, though gray matter appears brighter than white matter

So these may need to be accounted for.
There is also other information available regarding patients such as age, sex, build, family history, parkinson's diagnosis etc..
As for the MRI images themselves, there is approximately 42GB worth of image data, these are of three different planes, coronal, saggital and axial such as the images shown in figure 1. Each patient has scans for all three planes, each of which have multiple image slices on equal thickness. An example is displayed below. Figure 5 above is one of 23 slices of the axial plane, each of

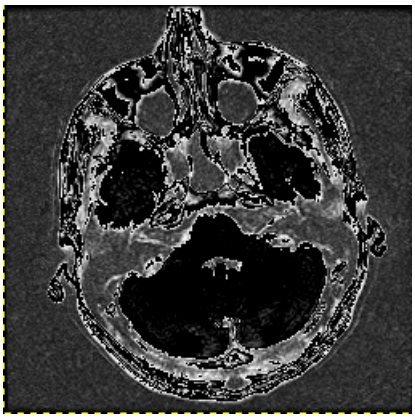


Figure 5: Example patient slice in axial plane
[12]

which is a 256x256 pixel image, therefore making up a 23x256x256 3D representation.This is just for one plane for one patient. Also note the slight tilt in orientation of the patient's skull relative to the vertical, this may need to be accounted for in the processing stage. Each image also comes with tags providing specific details regarding the image such as manufacturer, institution, patient id and so forth.

2.2 Problem Formulation: Aims and Objectives

Aims:

- Low Tier: Achieve a classification accuracy of over 80% using deep learning methods on image data for Parkinson's diagnosis
- Mid Tier: Combine image classification with other patient data to increase diagnostic accuracy to over 95%
- High Tier: Be able to predict Parkinson's disease at early stages to a high accuracy to allow the patient to take preventative action

Objectives / Potential Methodology:

- Preprocessing
    1. Clean up data, remove patients with no image or patients that withdrew from the clinical trial
    2. Categorise data according to imaging plane / manufacturer equipment etc..
    3. Account for rotation/tilt of images
    4. Crop images to take into account the relevant parts only (e.g. Substantia Nigra)
    5. Normalise the data, reducing the function down to a smaller range (perhaps [0, 1]), Perhaps use a Gaussian mask to smoothen after and reduce intensity inhomogenities [23]
    6. Applying a convolutional net filter, consider the batch layers, ReLU and pooling filters, finding a way to segment and account for the white/dark/gray matter regions in the brain [1]
    7. If wanted another model besides deep learning to compare to, could combine more conventional methods such as Random Forest, SVM etc.. with PCA to reduce components to feed into these classifiers
- Build Model
    1. Split data set into training and testing (80% / 20% respectively) and then the training set into training and validation (60% and 40% respectively)
    2. Apply transfer learning model using Matlab's deep learning toolbox with models that are available to use e.g. AlexNet or GoogleNet (start with simple CNN). Could also utilise Google Vizier for parameter tuning, such as Bayesian Optimization [9]
- Test Model
    1. Test accuracy against existing techniques
    2. Go back and tweak parameters to improve classification if required

2.3 Points of Consideration

Things to consider:

- How to work with *.dcm files, perhaps convert these to other image formats
- Which normalisation function to use
- Which method of feature extraction to use
- How to crop each image and which part of slices to take in each plane
- How to segregate the data; plane, manufacturer etc..
- How to account for the imaging tilt, rotate orientation? etc..
- Potential tools required, e.g. Matlab deep learning toolbox, Google Vizier, etc..
- Number of batch/pooling layers or other filters required etc
- How to account for time i.e. how long since diagnosis, if in early stages etc..
- How (and whether to) to select other patient attributes to include in our classifier
- Collaboration with other groups to see how medical professionals examine MRI scans of patients diagnosed with PD
- Things I may have missed in each step..
- The technical details how to achieve the goal. The evaluation process, say, the test platform and procedure, how to present the results, comparisons, etc.

3 Estimated Project Timeline

20/05

- Go through Data Set, filter patients with images available and those who have not withdrew from the clinical trial
- Download information about the respective patient ID's
- Create a list of patient ID's and assimilate a database of relevant image scan details e.g. make, model
- Attach a label to each patient ID, determining whether they are in control group / parkinson's etc..

27/05

- Try and tilt each image to all have same vertical alignment/orientation
- Crop each image to have the relevant features (substantia nigra most likely)

03/06

- Normalise Data
- Smoothen the data
- Split the data into training, test and validation
- Learn tools required to build the model

10/06

- Build, test & tweak deep learning classifier

01/07

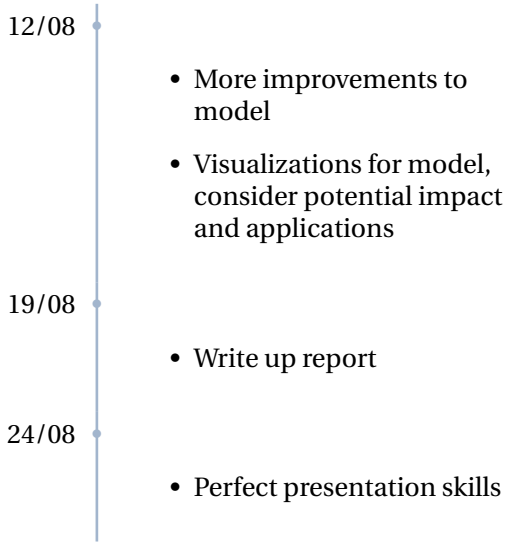
- Write a thorough literature review on techniques, methods and applications
- Review work done so far and document

15/07

- Review of current progress in terms of classification and look for areas of improvement

29/07

- Discuss literature and make improvements to model



Throughout:

- Biweekly meetings with supervisor and PhD student advisors
- Weekly meetings with other MSc students to discuss mutual progress and exchange ideas
- Attempt to get into contact with medical professionals who may be able to provide insight into Parkinson's and improve the strength of the classifier
- Continually research deep learning and optimisation methods (literature, seminars, online videos etc..)

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