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Predictive Analytics & Modelling in Parkinson's Disease for Severity Detection

MSc Research Project
Data Analytics

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Predictive Analytics & Modelling in Parkinson's Disease for Severity Detection

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Abstract

Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by a range of motor and non-motor symptoms, significantly affecting patients' quality of life. This research employs predictive analytics and deep learning, with a focus on Long Short-Term Memory (LSTM) networks, to assess the severity of PD using a comprehensive multimodal dataset. The study combines motor and non-motor symptom data, along with genetic data from the Parkinson's Progression Markers Initiative (PPMI), for comprehensive assessment of PD severity detection. The proposed study captures the complex temporal patterns inherent in longitudinal medical data, with LSTM model achieving 91% accuracy in predicting disease severity. The study contributes to the healthcare domain by advancing the understanding of PD through a data-driven approach, highlighting how multimodal approach of integrating diverse modalities for precise severity detection can provide a holistic assessment of PD. The study also underscores the predictive capabilities of LSTM from PPMI data with R2 of 0.88 and RMSE of 0.33.

1 Introduction

Parkinson's disease (PD), primarily affecting individuals over 60, is a neurodegenerative disorder characterized by the loss of dopamine-producing neurons in the substantia nigra (Dumbhare and Gaukar, 2023). Protein accumulation, particularly alpha-synuclein, contributes to neuronal damage. While PD diagnosis relies on clinical symptoms, early detection, and severity detections are crucial for effective management (Bednarz, *et al.*, 2023). PD has a lasting impact on the brain and nerves (central nervous system). It gets worse over time. By the time doctors diagnose PD, people often have trouble moving around. This is because of tremors (shaking), slowness (bradykinesia), stiffness, and balance problems. These issues can make everyday activities like walking, talking, swallowing, and even simple tasks difficult.

On top of these movement problems, PD can also affect thinking, mood, sleep, and digestion. These are called non-motor symptoms and can significantly worsen a person's quality of life. Doctors need to carefully manage these symptoms based on what each person experiences. Interestingly, some non-motor symptoms, like a decreased ability to smell (hyposmia) or acting out dreams during sleep (REM sleep-behavior disorder), can appear years before the movement problems. Other non-motor symptoms, like thinking difficulties,

tend to show up after the movement problems start, indicating the need to detect their severity for better treatments. Parkinson's Foundation estimates that nearly 1 million Americans currently have PD, with that number projected to reach 1.2 million by 2030 (Parkinson's Foundation, 2024). While it can affect anyone, men are more susceptible (Lamba et al., 2021). Early detection is crucial because significant dopamine-producing cells may be lost before symptoms appear. Neuro-digital assessments offer promise for early diagnosis and gauging disease severity. Early diagnosis allows for better management of PD progression. Existing research primarily focuses on motor symptoms for early detection and non-motor symptoms for severity. This study aims to incorporate both types of symptoms, along with genetic data from the PPMI database to improve PD diagnosis and understanding, given the complex interplay of genetic and environmental (Cassotta *et al.*, 2022). The genetic and molecular underpinnings of PD have been uncovered through the application of ML models, analysing complex genetic and transcriptomic data (Balaji *et al.*, 2021). Several studies have employed ML for identifying PD biomarkers from genetic data, including the work of Shamir *et al.*(2017), Calligaris *et al. (*2015), and Dulski *et al.* (2022).

The data utilized for this research is medical longitudinal data which comes with many issues such as missing data points, incomplete variable sets, unevenly spaced observations, and high-dimensional data, and requires careful consideration when processing. Longitudinal studies track the same individuals over time, making the data complex. Repeated measurements from the same person are related, and it's challenging to separate changes within individuals from differences between people (Couronne *et al.*, 2019). Additionally, the measurement process is often subject to varying levels of uncertainty, making the data even more complex to model with traditional machine learning (ML) techniques. These characteristics differentiate longitudinal data from standard time series data and require specialized techniques for analysis such as convolutional neural networks (CNNs), deep neural networks (DNNs), and recurrent neural networks (RNNs). Therefore, this study employs a Long Short-Term Memory (LSTM), a recurrent neural network, to capture the evolving patterns within the selected PPMI dataset for accurately assessing PD severity. LSTM networks are particularly effective at capturing and processing information over extended periods (Yu et al., 2019). Various researchers have successfully utilized LSTM in longitudinal data in domains like natural language processing (NLP) (Mahadevaswamy and Swati, 2023), time series forecasting (Song *et al.*, 2020), anomaly detection (Ergen and Kozat, 2019) and robotics and control systems (Bilal *et al.*, 2022).

1.1 Research Question

The primary research question guiding this investigation is: “How well can deep learning techniques identify the severity of Parkinson's disease using neuro-digital assessment data for risk stratification?”

1.2 Research Objective and Contributions

This research aims to develop a robust deep-learning framework for accurately assessing Parkinson's Disease (PD) severity. By integrating multimodal data encompassing motor, and non-motor symptoms, and genetic information, this study seeks to overcome the limitations of existing research that primarily rely on single data sources. The integration of neuro-digital assessment data will enable the identification of PD severity levels for effective risk stratification. This research will contribute to the field by advancing the understanding of PD progression through a comprehensive data-driven approach and by providing a novel methodology in disease severity detection for improved patient management.

1.3 Project Report Outline / Organisation of the Report

The report is structured as follows: Section 2 provides a critical analysis of existing research on Parkinson's Disease (PD). It examines key studies on PD, highlighting their strengths and weaknesses. By situating the current research within the broader academic context, this section establishes the need for the proposed study and outlines its potential contributions to the field. Section 3 outlines the research design and approach employed in the study. It details the data collection methods, research instruments, and sampling techniques utilized. Additionally, it provides a justification for the chosen methodology and its alignment with the research objectives. Section 4 provides a brief design specification of the developed model for the study, outlining a clear blueprint for the implementation phase. Section 5 covers detailed procedures taken in implementing the model. Section 6 presents the results of the study, assessing the performance of the proposed model. It includes the evaluation of the model’s effectiveness in achieving the research objectives. The results are analysed, interpreted, and discussed in relation to the research questions. Section 7 concludes by summarizing the study’s findings, highlighting key results and their implications. The limitations are also acknowledged and potential avenues for future research that can advance the field of study are outlined.

2 Related Work

Research on Parkinson’s disease has been done in the past and is still ongoing. As highlighted by Dumbhare and Gaukar (2023), a protein called alpha-synuclein plays a starring role in the drama of Parkinson's disease. This protein clumps together abnormally inside brain cells, particularly in an area called the substantia nigra, which is crucial for controlling body movements. This build-up damages the nerve cells and disrupts their production of dopamine, a chemical messenger essential for smooth movement. As a result, Parkinson's disease develops. Researchers from the National Institute of Neurological Disorders and Stroke (NINDS) recently studied that the ability to detect alpha-synuclein could help doctors monitor how much alpha-synuclein is building up over time and use this

information to gauge disease severity.[1] Eventually, this would allow evaluation of the effectiveness of the treatments aimed at lowering alpha-synuclein.

2.1 PD Biomarkers for Severity Detection and Progression

Dinov *et al.* (2016) did a study using a PPMI dataset that combines brain scans, genetic information, patient evaluations, and background details. They built models to classify PD and found that factors like scores from movement assessments and age were consistently important for diagnosis. Brain imaging markers also showed promise, but the link wasn't as stable. They identified specific genetic variations and movement scores as strong predictors using more advanced analyses. AdaBoost outperformed the other models implemented such as Naïve baiyes, SVM, KNN and Decision Tree in different experiments. This study demonstrated the potential of using big data analytics, machine learning, and multimodal data to predict PD diagnosis. But also highlighting that more research is needed to validate and refine the most robust predictive models.

Due to its complexity, PD has been diagnosed using different biomarkers as researchers are constantly trying to find better ways of early diagnosis. In their study, Erdaş and Sümer (2023) explored the use of neuroimaging and deep learning for PD detection and severity prediction. The study utilized 2D and 3D Convolutional Neural Network (CNN) on preprocessed magnetic resonance imaging (MRI) to detect PD achieving an accuracy of (0.9620) and R2 of (0.8372). Complementary work was done on voice data using a multi-task neural network and achieving 99.15% accuracy in classifying severe vs. non-severe Parkinson's disease and predicting disease progression and MSE of 0.15 (García-Ordás *et al.*, 2024). A similar study using telemonitoring vocal data used a machine learning model namely the PCA approach for predicting the severity of PD attaining an R2 of 0.95 accuracy (Pechprasarn *et al.*, 2023). These studies follow the concept of singular modality as opposed to the multimodal proposed in this paper. Sai Kumar (2023) utilized a CNN-LSTM network for classification and severity rating prediction based on gait analysis. The studies show promising results in early diagnosis of PD and progression monitoring but focus on either motor or non-motor symptoms. A full exploration of a combination of motor and non-motor symptoms could present a novel approach to the studies offering potential for improved patient care and management due to better severity detection. PD presents a wide spectrum of motor and non-motor symptoms as noted, impacting the patient's quality of life significantly. The majority of the research focuses on utilizing voice analysis and deep learning techniques to predict disease severity.

While existing research has demonstrated the potential of machine learning and deep learning in PD diagnosis and severity prediction, these studies primarily focus on single

[1] https://www.ninds.nih.gov/current-research/focus-disorders/parkinsons-disease-research/parkinsons-disease-challenges-progress-and-promise

modalities such as neuroimaging, voice analysis, or gait analysis as mentioned. While these approaches have shown promising results, they fall short of capturing the complex interplay between motor and non-motor symptoms and their impact on disease progression. By incorporating a multimodal approach that includes genetic data, this research aims to address this gap and provide a more comprehensive understanding of PD severity.

2.2 Deep Learning on Longitudinal Patient Data in PD and Beyond

The previous and current focus on PD is not only on severity and early detection. Researchers are actively developing algorithms to analyze the complexity of PD from patients' longitudinal records. This is to accelerate the process of finding new drugs or repurposing the existing ones for Parkinson treatment, and to target the root cause of PD beyond movement symptoms. Iwaki *et al*, (2019) employed a meta-analysis of longitudinal genome-wide association studies (GWAS) data to investigate the genetic underpinning of PD progression by analyzing 4093 patients across 12 cohorts. The study provided valuable insights into the genetic heterogeneity of PD progression, paving the way for an improved understanding of disease mechanisms. Similarly, Severson *et al*, (2021) proposed a novel statistical model for PD progression, identifying distinct disease states and complex progression patterns. The incorporation of the medical effects in the model is a significant advancement, however the study's reliance on a specific dataset and its potential limitations in capturing the full spectrum of PD heterogeneity warrants further investigation. While the identification of the disease state in this study is promising, it also indicates the need to further validate the predictive power of the clinical utility of the disease state.

While working with longitudinal data, it is crucial to analyze the relationships and connections between elements within each patient's record sequence. This enables development of more powerful and informative representations of the data. The improved representations can then be used in the clustering stage to effectively group patients with similar characteristics. Recurrent Neural Networks (RNNs) are a powerful tool for capturing the underlying structure within sequential data. Their applications span various fields like speech recognition, text classification, video processing, and natural language processing (Tanveer *et al*., 2022). RNNs excel at capturing the temporal relationships between elements in a sequence. However, traditional RNNs face challenges like vanishing and exploding gradients. To address these limitations, researchers have proposed various RNN variants. Long Short-Term Memory (LSTM) networks are a popular example, known for their ability to handle long-term dependencies between events through a gated architecture. Recent studies in health informatics have shown promising results with LSTM applications. Rizvi *et al.* (2020) proposed deep learning techniques, specifically Deep Neural Networks (DNN) and Long Short-Term Memory (LSTM) networks, for predicting Parkinson's disease (PD) from voice samples. The authors compared the performance of their proposed models with conventional machine learning techniques on the Parkinson Speech Dataset (PSD). The results show that the proposed LSTM model achieved a maximum accuracy of 99.03%, outperforming the DNN model (97.12%) and all previous techniques applied to the PSD dataset. In their study, they highlighted that LSTM is highly effective for PD severity and

early detection due to its ability of handling longitudinal data well as opposed to traditional ML models. In another study related to LSTM on longitudinal data, Hssayeni *et al.* (2021) proposed a deep learning ensemble for continuous UPDRS-III estimation in Parkinson's disease (PD). Notably, the ensemble incorporates a Dual-Channel LSTM model trained on hand-crafted features. LSTMs are particularly well-suited for this task as they can effectively capture the sequential nature of movement data collected from wearable sensors during daily activities. The model was able to learn the temporal dependencies within movement patterns, which are crucial for differentiating the varying motor fluctuations experienced by PD patients. The high accuracy achieved by the ensemble, with LSTM playing a key role, highlighted the potential of this approach for continuous PD monitoring and improved disease management. The limitation of the study is the small dataset used from only 24 patients which makes the model generalizability unclear, therefore further validation on a larger and more heterogeneous cohort is necessary. The proposed study utilizes a larger dataset from more cohorts so that the model's ability to perform well on a more diverse population can be validated.

In general, LSTM achieves the best average accuracy compared to traditional ML models and other deep learning techniques while dealing with longitudinal data. In the study, El-Sayed (2023) proposed a novel CNN-LSTM model for PD classification using handwriting data. They reviewed various existing methods, including CNNs, machine learning, and RNNs with LSTMs. Particularly, LSTMs offer an advantage in capturing the sequential nature of handwriting data, crucial for identifying subtle motor control variations associated with PD. The proposed model leveraged both CNNs for feature extraction and LSTMs for temporal dependencies, which outperformed previous approaches in PD classification accuracy. This existing research demonstrates the potential of LSTM in capturing the complex dynamics of PD progression. However, these studies have limited ability to comprehensively assess the disease severity and identify early markers due to the utilization of either relatively small datasets or single modalities. The proposed study aims to address these limitations by leveraging the LSMT framework on multi-modal datasets. By exploring the intricate relationships between these data types over time, this study seeks to advance the state-of-the-art in PD severity assessment and contribute to improved patient care and management.

2.3 Multimodal Detection – A Study of Different Biomarkers

The research work (Giri *et al.*, 2022) presents a comprehensive approach for remote diagnosis of PD using a combination of motor movements, sketching, pen pressure, and vocal impairment features to develop a Composite Feature Score (CFS). The research used ensemble techniques on the datasets and highlighted that tremors and postural instability are the hallmarks of PD and patients' handwriting and sketching skills are affected, with micrographia being an early indicator. The limitation of the research is that, even though the handwriting and sketching features provide useful information, they are affected by confounding factors and require professional evaluation. This makes them insufficient for accurate detection of PD on their own. In another work with multiple data modalities, Junaid

et al, (2023) proposed a multi-modal time-series framework for PD progression prediction with explainable AI (XAI) techniques, in which the light gradient boosting machines (LGBM) model achieved a 10-fold cross-validation accuracy of 94.89%. While the multi-modal approach and explainability are strengths, the study lacks clinical translation pathways and relies on established algorithms. The approaches used, such as SVM, random forests, and gradient boosting, are well-established in the field of ML. Additionally, ethical considerations regarding AI in healthcare and the limitations of interpretability for non-experts remain unaddressed. The study could be improved by focusing on clinical validation, additional data sources, enhanced explainability for broader audiences, and thorough ethical considerations for responsible AI implementation in PD management. The study provided the pathway into the importance of using multiple modalities for improved accuracy over individual modalities.

Building upon these studies, it is evident that a multi-modal approach is essential for accurate and robust PD diagnosis and progression prediction. Pahuja and Prasad (2022) did a study using CNN to diagnose PD by combining MRI, SPECT, and biological markers (CSF) data. The models achieved 93.33% accuracy using all features and 92.38% after feature reduction. While the model achieved impressive results, there are still limitations including small dataset size, potential overfitting, and complex interpretations. The study is one of the first to utilize deep learning on a heterogeneous dataset that combines neuroimaging and biological markers for PD classification integrating multimodal novelty. CNN has its limitations when it comes to temporal patterns in sequential data. When comparing CNNs and LSTMs for multimodal datasets in PD studies, it's crucial to consider the type of data and the nature of the analysis. CNNs are adept at extracting spatial features from neuroimaging data, making them suitable for identifying structural and functional brain abnormalities. However, they are limited in handling sequential data, such as time-series measurements from biological markers. LSTMs, in contrast, are designed to capture temporal dependencies, making them ideal for analyzing sequential data and longitudinal studies. This study proposes usage of LSTMs which can enhance the understanding of the progression and temporal patterns in multimodal data, offering a more comprehensive view of how different biomarkers evolve over time, which CNNs may not effectively capture.

2.4 Conclusion

The review on PD research highlights the development of diagnostic and prediction tools using machine learning and deep learning. Studies often rely on biomarkers like alpha-synuclein, brain scans, voice signals and gait data for PD assessment. However, many studies focus on individual symptoms rather than combining different types, limiting the understanding of the disease's complexity. While machine learning and deep learning have shown significant progress in PD diagnosis and prediction, research often focuses on individual symptoms as stated. The review indicates the potential of multimodal approaches, especially when combined with LSTM models, to better capture the complex relationships between motor and non-motor symptoms, leading to more accurate PD severity detection and

improved patient care. This study provides a novel approach of utilizing multi-modal approach including genetic information for better PD assessment.

3 Research Methodology

The study adopts a data-driven approach, specifically following the principles of Knowledge Discovery in Databases (KDD). This iterative process emphasizes understanding the data (in this case, Parkinson's disease), defining research objectives, and applying suitable techniques for knowledge extraction. Longitudinal data from the Parkinson's Progressive Markers Initiative (PPMI) is selected for the study. This comprehensive resource provides a wealth of information on Parkinson's disease progression, including clinical assessments (doctor notes and test results), imaging data, and biological samples (blood, spinal fluid, and genetic information). Importantly, PPMI's repository is continuously updated as participants are followed over time, allowing for in-depth analysis of disease trajectory. Other steps in the methodology involve data pre-processing, standardization, transformation, and data mining. The specific steps involved in the research methodology are illustrated in Figure 1 and fully discussed in the following subsections.

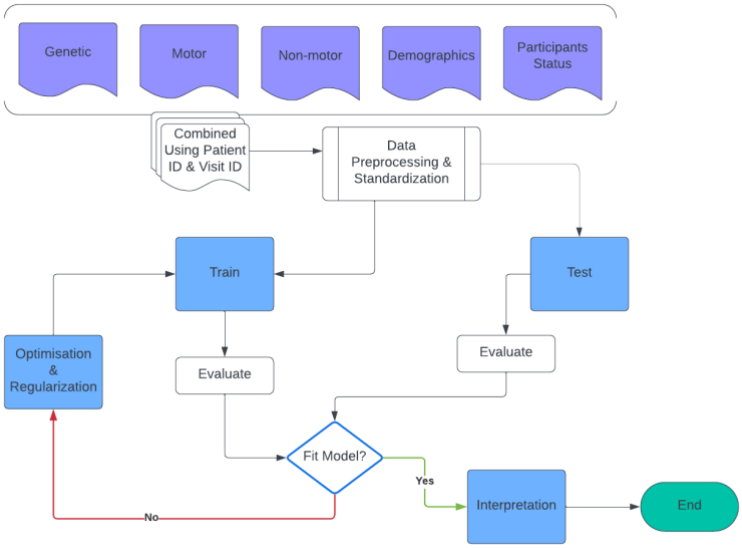

Figure 1: Project Design Specification

3.1 Data Selection and Understanding

The PPMI database contains over 200 datasets for studying PD progression. PPMI has enrolled healthy controls and Parkinson's patients, categorized further based on disease stage and genetics.

Out of a collection of datasets in the repository, 21 were chosen for this study. These datasets encompass various aspects of the patients, including demographics (medical history, sex, age), motor symptoms (rigidity, tremor, gait), non-motor symptoms (sensory

assessments, neurobehavioral), clinical data, and genetic data. The datasets in Figure 2 were selected based on the proposed research on multimodal analysis that involves motor symptoms, non-motor symptoms and genetics data for PD severity detection study.

Data	
CBAR	478593 obs. of 13 variables
Epworth_Sleepiness_Scale	14179 obs. of 16 variables
Gait	65 obs. of 26 variables
GDS	14483 obs. of 22 variables
HVLT	12462 obs. of 20 variables
MDS_UPDRS_Part_I	23537 obs. of 15 variables
MDS_UPDRS_Part_I_PQ	23574 obs. of 16 variables
MDS_UPDRS_Part_II_PQ	23575 obs. of 22 variables
MDS_UPDRS_Part_III	27483 obs. of 62 variables
MDS_UPDRS_Part_IV_MC	8518 obs. of 23 variables
MoCA	13034 obs. of 35 variables
Neuro_QoL__Lower	6371 obs. of 15 variables
Neuro_QoL__Upper	6369 obs. of 15 variables
PAIMPC	789 obs. of 13 variables
Participant_Motor_Function_Questionnaire	5960 obs. of 19 variables
REM	14194 obs. of 29 variables
Research_Biospecimens	20215 obs. of 55 variables
SCOPA_AUT	14158 obs. of 43 variables
Sleep_metrics	106419 obs. of 12 variables
STAI	14464 obs. of 47 variables
TMAB	5944 obs. of 13 variables

Figure 2: PPMI Selected Datasets for Study

To understand the data, a clinical PPMI data dictionary was utilized which is provided in the PPMI repository as shown in Table 1. It was essential in understanding the structure and contents of the datasets facilitating accurate data interpretation and integration. The breakdown of selected datasets was as follows:

3.1.1 Dataset Description

Table 1: Dataset Description

MDS-UPDRS Motor Assessments	**Code**
MDS-UPDRS Part II**:** Patient Questionnaire on Motor Aspects of Experiences of Daily Living (M-EDL)	Evaluates a patient's self-reported motor experiences of daily living, such as speech, handwriting, hygiene, dressing, and walking
MDS-UPDRS Part III**:** Motor Examination	Focuses on a clinician's assessment of motor symptoms such as tremor, bradykinesia (slowness of movement), and rigidity.
Gait Substudy**:** Gait Mobility Assessment and Measurement	Measures gait-related parameters like step length, arm swing, and walking speed in PD patients.
Participant Motor Function Questionnaire**.**	A self-reported questionnaire where participants evaluate their own motor function in daily tasks.
Neuro QoL: Lower Extremity Function (Mobility) - Short Form	Measures mobility and lower extremity motor function, focusing on activities like

	walking, running, and climbing stairs.
Neuro QoL: Upper Extremity Function (Fine Motor, ADL) - Short Form	Evaluates fine motor skills such as gripping, using utensils, or writing.
Roche Smartphone App: Monitoring App v2 data	Collects continuous motor symptom data (e.g, tremor and bradykinesia) through smartphone-based sensors.
Verily Study Watch**:** Ambulatory Derived Data, Step Count Derived Data, Sleep Metrics Derived Data	Provides data on movement, daily step counts, and sleep quality using wearable sensors.
MDS-UPDRS Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	Evaluates non-motor symptoms like cognitive impairment, mood changes, sleep issues, and autonomic dysfunction in PD patients.
MDS-UPDRS Part I Patient Questionnaire: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	Self-reported questionnaire assessing non-motor experiences of daily living, focusing on sleep, cognitive function, mood, and other non-motor domains.
Geriatric Depression Scale (Short Version)	Assesses the presence and severity of depression in older adults, a common non-motor symptom in PD.
State-Trait Anxiety Inventory	Measures anxiety levels, distinguishing between temporary and chronic anxiety in patients.
Hopkins Verbal Learning Test - Revised	Evaluates verbal memory and learning capabilities.
Montreal Cognitive Assessment (MoCA)	A screening tool for mild cognitive impairment and dementia.
Trail Making A and B	Assesses visual attention and task-switching capabilities.
SCOPA-AUT **(**Autonomic**)**	A scale for assessing autonomic dysfunction in PD, including issues related to gastrointestinal, urinary, cardiovascular, and sexual functions.
Epworth Sleepiness Scale	Measures daytime sleepiness, which is often related to sleep disorders in PD.
REM Sleep Behavior Disorder Questionnaire	Evaluates REM sleep disturbances, which are common in PD and linked to disease progression.
Neuro QoL: Cognitive Function - Short Form	Assesses the impact of PD on cognitive abilities, including memory, attention, and problem-solving.
Neuro QoL: Communication - Short Form	Evaluates communication abilities, including speech clarity and comprehension.

3.1.2 Motor Symptoms Datasets

Table 2 shows motor symptoms in Parkinson's Disease which typically involve assessments of motor function and mobility.

Table 2: Motor Symptoms Datasets

MDS-UPDRS Motor Assessments	**Code**
MDS-UPDRS Part II**:** Patient Questionnaire on Motor Aspects of Experiences of Daily Living (M-EDL)	MDS_UPDRS_Part_II_PQ
MDS-UPDRS Part III**:** Motor Examination	MDS_UPDRS_Part_III
Gait Substudy**:** Gait Mobility Assessment and Measurement	Gait
Participant Motor Function Questionnaire**.**	Participant_Motor_Function_Questionnaire
Neuro QoL: Lower Extremity Function (Mobility) - Short Form	Neuro_QoL__Lower
Neuro QoL: Upper Extremity Function (Fine Motor, ADL) - Short Form	Neuro_QoL__Upper

Digital Sensor Data	**Code**
Roche Smartphone App: Monitoring App v2 data	Roche
Verily Study Watch**:** Ambulatory Derived Data, Step Count Derived Data, Sleep Metrics Derived Data	

3.1.3 Non-Motor Symptoms Datasets

Non-motor symptoms in Parkinson's Disease include cognitive, neurobehavioral, autonomic, and sleep disorders as referenced in Table 3.

Table 3: Non-Motor Symptoms Datasets

MDS-UPDRS Non-Motor Assessments:	**Code**
MDS-UPDRS Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	MDS_UPDRS_Part_I
MDS-UPDRS Part I Patient Questionnaire: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	MDS_UPDRS_Part_I_PQ
Neurobehavioral and Neuropsychological Tests	
Geriatric Depression Scale (Short Version)	GDS
State-Trait Anxiety Inventory	STAI

Hopkins Verbal Learning Test - Revised	HVLT
Montreal Cognitive Assessment (MoCA)	MoCA
Trail Making A and B	TMAB
Autonomic and Sleep Disorder Tests:	
SCOPA-AUT **(**Autonomic**)**	SCOPA_AUT
Epworth Sleepiness Scale	Epworth_Sleepiness_Scale
REM Sleep Behavior Disorder Questionnaire	REM
Cognitive and Non-Motor Assessments	
Neuro QoL: Cognitive Function - Short Form	Neuro_QoL_Lower
Neuro QoL: Communication - Short Form	Neuro_QoL_Upper

3.1.4 Genetic Datasets

Genetic data involve analyses of genetic material and testing results. The following datasets were selected:

- Genetic Testing Results (Merge).
- Genetic Testing Results (Online).
- Family History of Parkinson's Disease: 1st Degree Relatives (Online).
- Biospecimen Sample Analysis:
- Current Biospecimen Analysis Results.
- Project 181 Adaptive Immune Markers for Predicting Cognitive Decline in PD.
- Research Biospecimens.

When merging datasets, much of the genetic data was deemed unsuitable for the study and was therefore excluded. The Research Biospecimens dataset was the most significant one included. Additionally, datasets lacking Event_ID, such as TMAB and Roche, were also disregarded, as this feature was crucial for merging the datasets and representing different patient visits.

3.2 Data Cleaning and Pre-processing

There were some variables that were not necessarily required on the datasets and were removed when the datasets were merged. The data dictionary was used for filtering down the variables. The combined dataset had **41847** observations and **251** variables. Cleaned up the observations and variables by filtering visits by Event_ID and removing the ones with low counts (<80). The EVENT_ID (OL070) had mostly one record for most PATNO and therefore was taken out of the study even though its total count was the highest (**12287**). This filtering took the data to (**29471, 199**)

The dataset had a lot of missing values which is a common issue in longitudinal data due to patients not having to attend some visits for the longitudinal data cohorts or dropouts, and this could be a major difficulty when building a model (Cascarano *et al*, 2023). The data is

collected from 2010 up to date. Missing values were calculated and a threshold of 20000 was set to remove features that had missing values more than the threshold. The missing values of the remaining columns were handled using forward fill and backward fill. When longitudinal data are available before and after a missing value, the last observation carried forward (LOCF) method is recommended (Engels and Diehr, 2003).

Researchers use rating scales to assess Parkinson's disease (PD) progression and severity. These scales in Table 4 assign scores to various aspects of a patient's condition, providing insights into their quality of life. Common scales include the Unified Parkinson's Disease Rating Scale (UPDRS) from the Movement Disorder Society, which focuses on non-motor symptoms. Additionally, the UPDRS can be used alongside the Hoehn and Yahr (HY) staging scale and the Schwab and England Activities of Daily Living (ADL) scale to create a comprehensive picture of the disease (Kanagaraj, Hema and Gupta, 2021). For the study, the selected target feature was 'NHY' in the dataset which is based on the severity scale of 0 to 5 from Hoehn and Yahr scale (HY). NHY 101 was also removed from the dataset as it did not provide any insights into the severity scale.

Table 4: Hoehn and Yahr scale

NHY 0	Asymptomatic.
NHY 1	Unilateral movement only.
NHY 101	Unable to Rate
NHY 2	Bilateral involvement without impairment of balance.
NHY 3	Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.
NHY 4	Severe disability; still able to walk or stand unassisted.
NHY 5	Wheelchair bound or bedridden unless aided.

3.3 Data Transformation

PPMI has baseline (BL) and follow-up visits (V#) to track participants' progress. Screening visits (SC) may happen before baseline. Unscheduled visits (U#) are also possible. The exact schedule of tests may vary by participant making the visits random. Therefore, the visits were sorted by count and the visits with less count were disregarded. During data pre-processing, standard scaler normalization was applied. This technique transforms the features to have a zero mean and unit variance making sure that overfitting of the model is minimized (Anisha and Arulanand, 2020).

3.3.1 Label Encoding for Sequence Representation

The patient visits numbers (EVENT_ID) were transformed into an integer by manually assigning an integer to each ID based on the Parkinson's Disease and PD Genetic Schedule of Activities (Years 0 - 13) provided on PPMI. The chronological order is important because the LSTM model learns from temporal patterns and dependencies from the ordered data.

3.4 Data Mining – Long Short-Term Memory (LSTM)

LSTM networks are a type of Recurrent Neural Network (RNN) specifically designed to address the vanishing gradient problem. Unlike standard RNNs, LSTMs incorporate gating mechanisms that control information flow within the network. These gates allow LSTMs to learn and remember information over longer periods, enabling them to capture long-term dependencies in sequential data (Staudemeyer and Morris, 2019).

LSTMs achieve this through memory cells that process both the current input and the information from the previous state. These cells can selectively retain or discard information from the past, ensuring that relevant data persists even over extended sequences (Maalej, Rejab and Nouira, 2023). This functionality makes LSTMs a powerful tool for various tasks involving sequential data, such as speech recognition, machine translation, and time series forecasting. Unlike standard RNNs that struggle with long-term dependencies, LSTMs utilize a cell state for long-term memory, complementing the hidden state's short-term storage. Figure 3 shows an architecture of LSTM model.

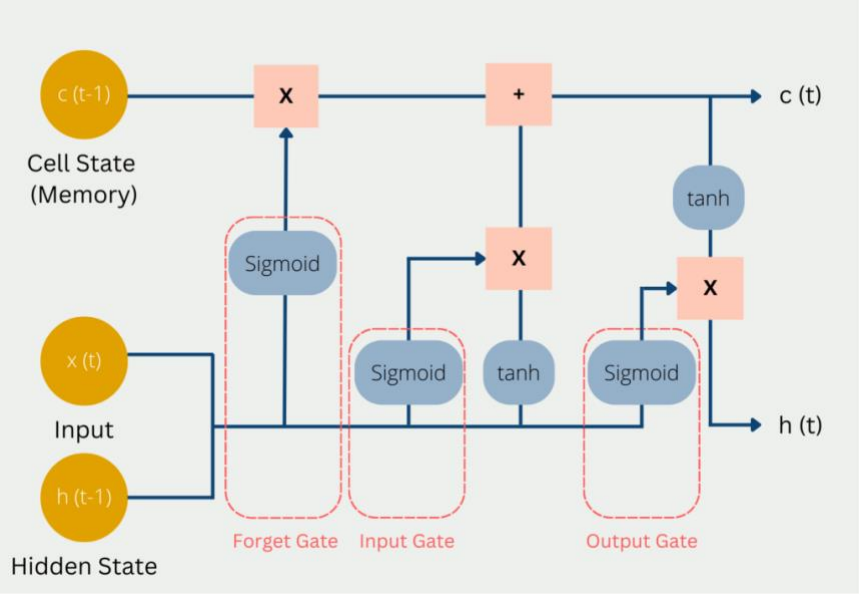

Figure 3: LSTM Architecture

At each step, LSTMs process the current input (x(t)), previous cell state (c(t-1)), and previous hidden state (h(t-1)). These are used by three gates to update the cell and hidden states:

- **Forget Gate (σ):** Determines what information to discard from the cell state and previous hidden state (h(t-1)) using a sigmoid function (σ). Values close to 0 indicate discarding, while 1 indicates retaining information. This output is multiplied by the previous cell state (c(t-1)) to selectively forget.
- **Input Gate (σ):** Decides how much of the current input and previous hidden state (h(t-1)) contributes to the new cell state (c(t)). The information is processed with sigmoid (σ) and combined with the previous cell state using element-wise addition.

- **Output Gate (σ):** Controls the information flow from the cell state (c(t)) to the hidden state (h(t)). It uses a sigmoid (σ) function to select relevant information from the cell state, which is then activated by a tanh function before becoming the new hidden state.

4 Design Specification

This section outlines an overview of how the proposed project was designed and carried out as shown in Figure 4. Majority of the time was spent in modelling the data to get the right dataset for the study. Careful selection of the data, pre-processing, filtering the data, and transformation of the features for LSTM model.

4.1 Techniques and Framework Underlying the Implementation

The primary focus of the literature review was on existing and utilized methods in the research field. Specifically, identifying the merits of an RNN method, namely LSTM, for longitudinal studies and comparing it with Gated Recurrent Units (GRUs) Networks. This comparative analysis aimed to thoroughly evaluate PD severity assessment prediction methods in order to identify patients requiring urgent medical attention for improved PD management.

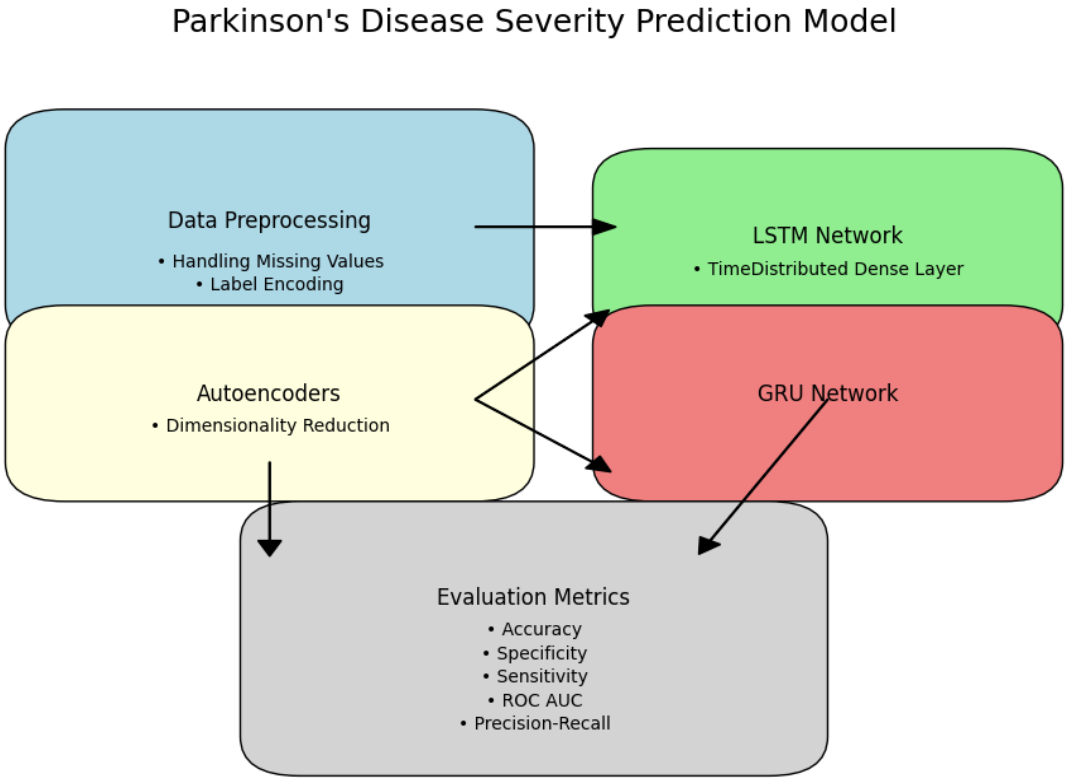

Figure 4: Simplified Proposed Architecture

5 Implementation

In this stage, R studio was used to import the downloaded csv files of the PPMI dataset using R programming language. The tool was also utilised to analyse the data and merge different files creating the combined dataset that was imported into Google Colab to further pre-processing and modeling using Python. The environment was selected as its a free tier of a cloud based Jupyter notebook environment equipped with powerful hardware, specifically GPUs and TPUs. These resources are essential for efficiently handling the project's computationally demanding tasks ensuring scalability and flexibility in model training and evaluation.

5.1 Implementation of Long Short-Term Memory (LSTM)

The processed and normalized data was split into training and testing using 80% and 20% respectively. The model in Figure 5 was built with two LSTM layers, and each was followed by a dropout to prevent overfitting. In the model architecture, the first layer had 64 units with L2 regularization. Additionally, the return sequence was enabled in this layer. The second layer had 32 units also with L2 regularization without returning a sequence. The dropout layers for handling overfitting were 0.4 and early stopping to stop the model training when the validation loss does not improve for several epochs. Moreover, the dense output layer for the model was fully connected with SoftMax activation so that the model could classify the severity into perspective classes based on the input data (Abd El Aal, *et al.*, 2021; Balaji, *et al.*, 2021). To adjust the learning rate during training, the learning rate scheduler was implanted for when the validation loss reaches the state of little or no progress.

Layer (type)	Output Shape	Param #
lstm_8 (LSTM)	(None, 12, 64)	64,000
dropout_8 (Dropout)	(None, 12, 64)	0
lstm_9 (LSTM)	(None, 32)	12,416
dropout_9 (Dropout)	(None, 32)	0
dense_11 (Dense)	(None, 6)	198

Total params: 76,614 (299.27 KB)
Trainable params: 76,614 (299.27 KB)
Non-trainable params: 0 (0.00 B)

Figure 5: Summary of LSTM Model

5.2 Overfitting Reduction

Generally neural networks are prone to overfitting, which is the case whereby the model performs well on training data but performs poorly on unseen data.

5.2.1 L2 Regularization

Regularization is a technique used to mitigate the overfitting issue which occurs when the model becomes overly complex. This was implemented to penalize large weights for minimizing the generalization error of a classifier model (Vidya and Sasikumar, 2022). L2 regularisation also adds weight decay effect to the model where the magnitudes of the weights progressively reduce during training. In the model, the 'kernel_regularizer' is set to `12(0.01). Due to the complexity of the data utilized for the study, this regularization controls the complexity of the model during training. The regularization is as follows:

$$Lregularized(\theta)=L(\theta)+\lambda i\sum\theta i2 \qquad (1)$$

Where L(θ) is the original loss function, θ represents the weights of the model. ∑iθi2 is the sum of the squared weights. λ is the regularization parameter and is (λ=0.01) as per the implementation.

5.2.2 Batch Normalization

This was implemented to add a batch normalization layers that stabilizes and speeds up training by ensuring that the inputs to each layer maintain a consistent distribution throughout the training. Batch normalization layers are added immediately after every LSTM layer. This normalizes the output of the LSTM layer before it passes through the activation function ensuring that the input to the subsequent layers maintain a stable distribution. Incorporation of batch normalization enhances the model's ability to learn intricate temporal patterns from the high-dimensional sequencing data, ultimately improving the accuracy of PD severity prediction (Ahmed, Komeili and Park, 2022).

6 Results and Evaluation

Rigorous analysis of findings was carried out to inform the evaluation made. All the models were implemented on the scaled data over 100 epochs with a batch size of 32. Different experiments were carried out based on different techniques within recurrent neural networks and the following were the results.

6.1 Experiment 1: Building LSTM without Dimensionality Reduction

The best model in Figure 6 attained best accuracy of 91%. This was the best model after different iteration had been done on the model architecture to fine tune it for better performance. The model was evaluated using training and validation loss/accuracy plotted below. The training and validation loss of the model decreases rapidly initially, and this indicates that the model is effectively learning. The divergence between training and validation plots is not substantial indicating that the model is overcoming overfitting.

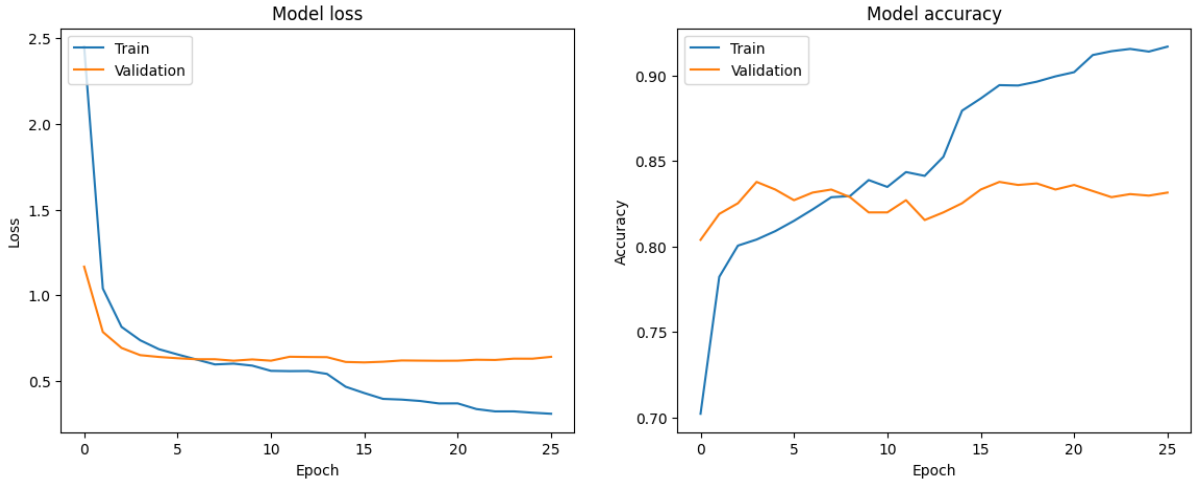

Figure 6: Model 1 Loss and Accuracy Plot

The confusion matrix was created to detail the performance of every class. The performance also reflects the distribution of the imbalanced classes from the data whereby 1,2, and 3 were the majority, and 4 and 5 were the minority. The classes were not balanced so that the model can reflect the true distribution of the classes as shown in Figure 7.

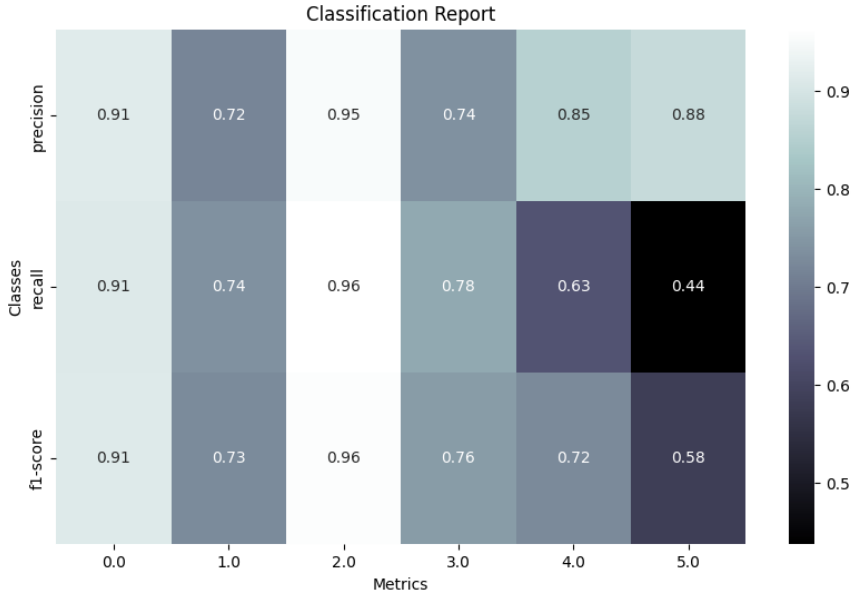

Figure 7: Classification Report

The ROC Curves were implemented to provide insights into the model performance across all thresholds. The results are as below with the lowest being class 1 with 0.088 and highest being class 0 with 0.97.

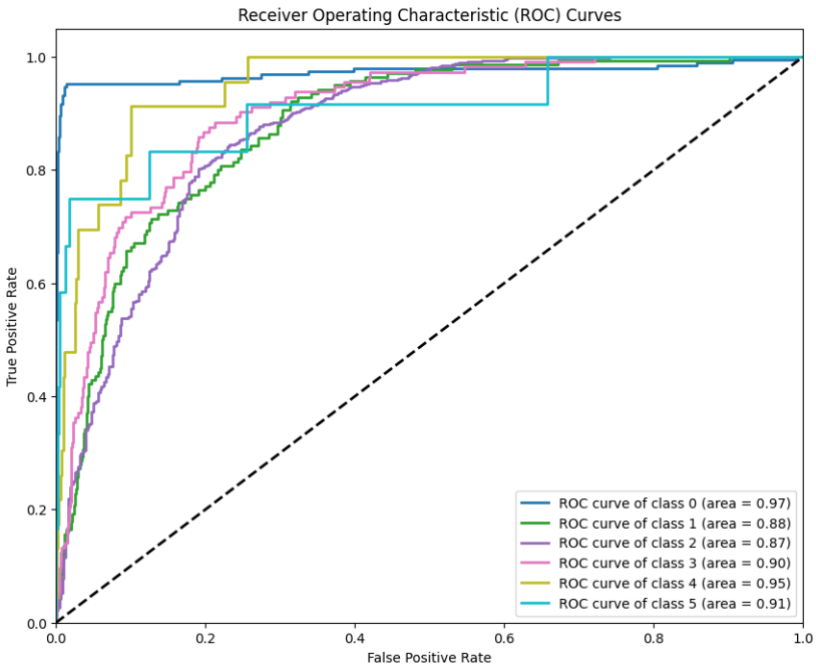

Figure 8: ROC Curve

6.2 Experiment 2: LSTM Model with Time Distributed Dense Layer

The correlation matrix in data pre-processing stage indicated that some features are highly correlated, therefore an experiment for dimensionality reduction was implemented to observe if the model performance will improve as per Figure 9. This was carried out using time-distributed dense layer within the LSTM model. The model had 90% accuracy, which was slightly lower than our best model detailed above. Time distributed layer applies the dense layer to every time step of the LSTM output, effectively reducing the number of features at each step while preserving the temporal structure of the sequence (Quan *et al.*, 2023).

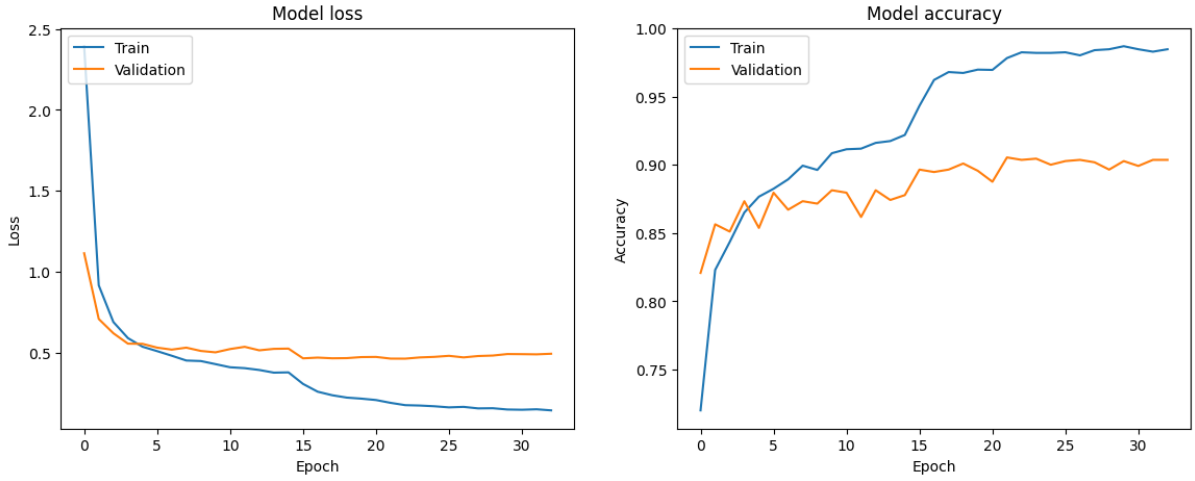

Figure 9: Model 2 Accuracy and Loss Plot

6.3 Experiment 3: LSTM with Autoencoder

The built and trained autoencoder learned a compressed representation of the data. Subsequently, the trained autoencoder was used to transform both the training and test

data into compressed representations. This compressed representation served as the input for the LSTM model, which achieved an accuracy of 87%.

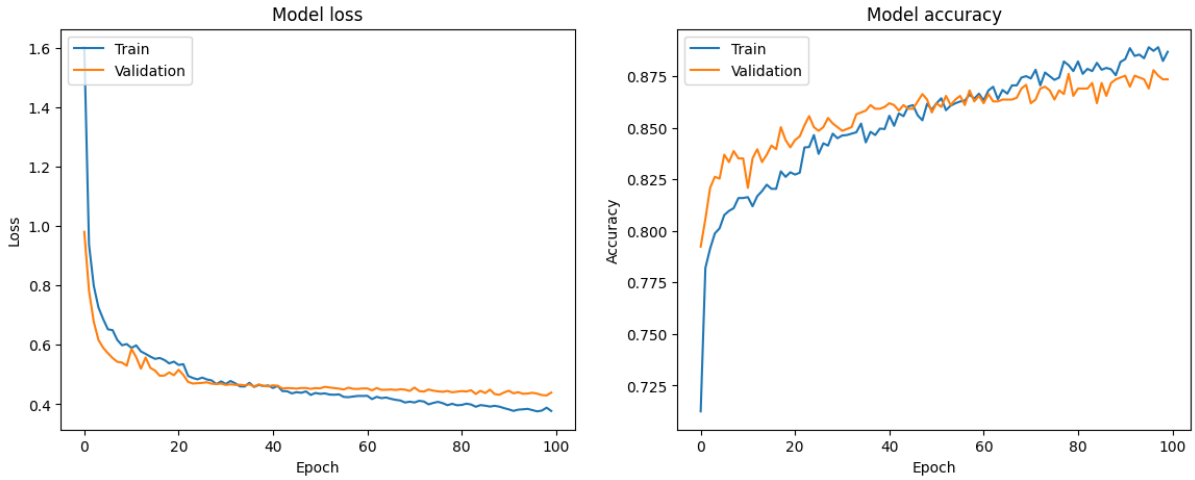

Figure 10: Model 3 Accuracy and Loss Plot

6.4 Experiment 4: GRU Network

GRU model for classification task was implemented in the same way as LSTM model using the same layers, same factors for L2 regularization, early stopping and earning rates reduction.

6.5 Experiment 5: Predictive Modelling

The above experiments are classifications tasks focusing on how effective deep learning techniques can be utilised for PD severity detection. And the second phase of models were regression models for implementing predictive capabilities of the models based on past events for better PD management and predictive modelling for severity detection. Both LSTM and GRU model for comparison were built. The results showed to be predicting close values to the actual values in NHY, which is the severity scale for PD.

	Actual	Predicted
0	2.0	1.948831
1	2.0	1.951219
2	2.0	1.989677
3	2.0	2.310865
4	3.0	2.110927
5	2.0	1.987349
6	0.0	0.028713
7	2.0	1.957208
8	3.0	2.151725
9	2.0	2.887406

Figure 11: LSTM Actual Vs Predicted Values

6.6 Discussion

The study introduced a two-fold evaluation for predictive analytics and modelling of PD severity detection. The novel approach introduced is a multimodal study that combines motor, non-motor symptoms data and genetic data to build a deep learning model. The first fold focused on classification to evaluate how well the LSTM, in comparison to GRU can identify the severity of Parkinson's disease using PPMI data for risk stratification. The second fold looked at the predictive capabilities of this deep learning models by building regression models for both LSTM which is the primary deep learning technique of the study and was compared to GRU as well to support the recommendation of LSTM being the suitable technique for PD severity assessment.

Different iterations of the models were carried out and it was observed that the efforts of dimensionality reduction and hyper parameter optimisation did not improve the final model best model. Table 5 details all the experiments done on classification models for the first fold evaluation and Table 6 details all experiments done on the regression models for the predictive capabilities assessment.

Table 5: Classification Models Results

Model	Accuracy	Precision	Recall	F1-Score
LSTM Best Model	**91%**	**0.907**	**0.907**	**0.905**
LSTM with Time Distributed Dense Layer	90%	0.898	0.901	0.899
LSTM with Autoencoder	84%	0.818	0.837	0.823
LSTM with Keras Classifier Optimization	88%	0.878	0.879	0.878
GRU	82%	0.818	0.837	0.825

Table 6: Regression Models Results

Model	R2	MAE	MSE	RMSE
LSTM	**0.88**	**0.14**	**0.11**	**0.33**
GRU	0.85	0.17	0.16	0.40

7 Conclusion and Future Work

The research was done to study how well can deep learning techniques identify the severity of Parkinson's disease using neuro-digital assessment data for risk stratification. The objective of the study was to develop a robust deep learning framework for accurately assessing PD severity. The main contribution of the research is the proposal of multimodal approach for PD severity detection which is more effective than single modality approach from recent studies. The study will enable better PD management by enabling healthcare providers to detect severity of PD effectively and predict the severity for future visits based on the past events. The severity assessment for PD is evaluated using LSTM model which yielded the best accuracy of 91%.

In the future, an investigation into why the efforts of dimensionality reduction techniques and hyperparameter optimisation did not improve the model. Further fine tuning of GRU models

can also be conducted to advance its classification capabilities. More advanced architecture of the LSTM model can be explored by using memory augmented networks such as Neural Turing Machines (NTMs) and Differentiable Neural Computers (DNCs). These architectures are complex and typically require custom implementations or specialized libraries.

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