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Predicting Parkinson's Disease Severity using Telemonitoring Data and Machine Learning Models: A Principal Component Analysis-based Approach for Remote Healthcare Services during COVID-19 Pandemic

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Abstract

Parkinson's disease (PD) is a progressive and chronic neurological condition that affects about 1% of the world's over-60 population. The COVID-19 pandemic has emphasized the significance of remote healthcare services, such as telemedicine, in managing chronic diseases such as PD. This research intends to construct machine learning (ML) models to predict PD severity utilizing vocal data derived from the UCI database for motor and total Unified Parkinson's disease rating scale (UPDRS) ratings. ML was used to study the association between voice vibration and PD, and PCA and ML models were utilized to minimize model complexity and compare the predictive performance of various statistical models for PD regression. The dataset included 5,875 medical voice records from 42 patients with early-stage PD who participated in a six-month clinical trial. The proposed PCA model simplified the model and achieved a root-mean-square error of 1.78 with an R-squared value of 0.95 for predicting the motor UPDRS and 1.78 with an R-squared value of 0.97 for predicting the total UPDRS. This work can give a framework for developing remote healthcare services for Parkinson's disease and other chronic conditions, which can be helpful during pandemics and other situations where access to in-person care is limited.

Keywords**:** *Parkinson's disease diagnosis; Supervised regression model; machine learning; Principal component analysis; complexity reduced model;, Intelligent diagnostic software; Telemedicine.*

1. Introduction

A chronic and progressive neuro-degenerative disorder, Parkinson's disease (PD) affects 1% of people over 60 worldwide (Marino et al., 2020). It is characterized by the death of dopamine-producing neurons in the substantia nigra area of the brain, which causes non-motor symptoms like depression, anxiety, cognitive decline, and sleep problems (Klockgether, 2004; Pfeiffer, 2016) in addition to motor symptoms like tremors, rigidity, and bradykinesia. Although the precise cause of PD is still unknown, it is widely acknowledged that both genetic and environmental factors (Warner, & Schapira, 2003) contribute to the disease's onset. The loss of dopamine-producing neurons in the substantia nigra and the ensuing drop in dopamine levels in the brain is the root causes of these symptoms (Klockgether, 2004). PD is

associated with non-motor symptoms like autonomous dysfunction in addition to motor symptoms, which can have a big impact on the quality of life.

Recent studies have shown that protein misfolding, aggregation, and dysfunction of the ubiquitin-proteasome system are critical components of the pathophysiology of PD (Dauer, & Przedborski, 2003). Other factors, such as mitochondrial dysfunction, oxidative stress, and inflammation, may also contribute to the progression of the disease (Bhat, Acharya, Hagiwara, Dadmehr, & Adeli, 2018).

Despite its relatively low prevalence compared to other neurodegenerative disorders, PD is the second most common neurodegenerative disorder after Alzheimer's (Jiménez, & Vingerhoets, 2012). This disease can significantly impact a patient's quality of life, as well as the healthcare system and society as a whole.

In recent years, the world has been hit by a global pandemic caused by the novel coronavirus SARS-CoV-2, which has profoundly impacted healthcare systems worldwide. The COVID-19 pandemic has resulted in millions of deaths and has disrupted healthcare services across the globe. In the context of PD, the COVID-19 pandemic has brought new challenges, including difficulties in accessing care and concerns about the potential impact of the virus on PD patients.

Non-motor symptoms often occur in the preclinical and prodromal stages of PD and can precede the onset of motor symptoms by several years (Yahr, Duvoisin, Schear, Barrett, & Hoehn, 1969). These symptoms can be the first signs of PD and significantly impact patients' daily lives.

The COVID-19 pandemic has significantly impacted healthcare services worldwide, with many hospitals and clinics struggling to provide healthcare for patients with chronic diseases such as PD. In addition, there is growing concern about the potential impact of the virus on PD patients.

The International Parkinson and Movement Disorder Society published the Impact on Parkinson's Patients during the Covid-19 pandemic, which suggests that COVID-19 could exacerbate chronic neurological conditions such as PD due to its neurotropic characteristics (Krämer et al., 2019). COVID-19 may exacerbate PD through altered pharmacodynamics and systemic inflammatory responses, worsening motor and non-motor symptoms (Lamotte, Holmes, Wu, & Goldstein, 2019).

Due to age-related comorbidities and disease-related conditions, PD patients are more debilitated than the general population, making them more vulnerable to COVID-19. Advanced PD patients have been found to have a higher mortality rate associated with older age and prolonged disease duration (Simon, Chen, Schwarzschild, & Ascherio, 2007). Furthermore, due to COVID-19, patients with PD have been quarantined at home, making it challenging to access complete treatment (Muqtadar, Testai, & Gorelick, 2012).

PD is a neurodegenerative disorder and a systemic disease that can affect other organ systems, including the cardiovascular system. Cardiovascular failure is a significant non-motor sign in the premonitory stages of PD and can worsen as the symptoms of PD progress (Camargo Maluf, Feder, & Alves de Siqueira Carvalho, 2019).

Oxidative stress, prolonged inflammatory processes, diabetes, obesity, and hypertension are major risk factors for both PD and cardiovascular diseases (Goldstein, & Sharabi, 2019; Prell, Schaller, Perner, Witte, & Grosskreutz, 2020; Shibata, Morita, Shimizu, Takahashi, & Suzuki, 2009). As the population ages, neurodegenerative disorders and cardiovascular diseases are becoming more prevalent, making it essential to examine their relationships and how one condition may affect the other (Organization, 2006).

Changes in the cardiovascular system involve sympathetic denervation, physiological and structural changes, and molecular changes, which can contribute to the progression of PD (Cuenca-Bermejo et al., 2021). Orthostatic hypotension (OH), a common cardiovascular autonomic dysfunction in PD, has been related to parasympathetic dysfunction and sympathetic denervation (Idiaquez, & Roman, 2011).

The COVID-19 pandemic has highlighted the importance of remote healthcare services, including telemedicine, in managing chronic diseases such as PD. Telemedicine has the potential to provide patients with more flexible and convenient access to care, especially for those who are unable to leave their homes due to quarantine or mobility issues (Cruz et al., 2021).

Telemonitoring devices, which allow for remote monitoring of symptoms and vital signs, have been used to manage PD (Polverino et al., 2022). A recent study used a telemonitoring device to collect 5,875 medical voice records from 42 patients with early-stage PD recruited for a six-

month trial (Tsanas, Little, McSharry, & Ramig, 2009). It evaluated the progressiveness of the PD symptom using (1) motor Unified Parkinson's disease rating scale (UPDRS) and (2) total UPDRS. These two UPDRS scales have been standard approaches to assessing PD conditions (Disease, 2003). The study used machine learning models to increase the of UPDRS predictions and compare the performance of different models. The study found that the best method for determining between patients with and without PD is to use unconventional methods in combination with traditional harmonic frequency values, which are suitable for telemonitoring applications (Tsanas et al., 2009).

A popular tool for assessing the severity of Parkinson's disease symptoms is the UPDRS. There are four parts, but here we will concentrate on Part I and Part III because they are the most important. Mentation, Behavior, and Mood, the first section of the study, assesses non-motor symptoms of the illness, including cognitive function, mood, behavior, and daily living activities. In Part III, referred to as the Motor Examination, tasks are used to assess posture, tremors, rigidity, bradykinesia (slowness of movement), and other motor functions.

The severity of the non-motor symptoms is indicated in Part I with scores ranging from 0 to 4. With a score of 4 denoting severe cognitive or behavioral impairment requiring assistance, higher scores indicate greater impairment. Ratings for each item in Part III range from 0 to 4 or 5, depending on the assessment. With a score of 5 denoting complete or nearly complete impairment, higher scores reflect more severe motor symptoms.

Healthcare professionals with management experience for Parkinson's disease administer the UPDRS. To provide an overall evaluation of the severity of the symptoms and the progression of the disease, the scores from Parts I and III are combined with those from the other sections. The objective evaluation of motor function in Part III makes it especially pertinent for research studies. A comprehensive assessment of the overall disease burden, including both motor and non-motor aspects, is provided by the total UPDRS score, which combines scores from all four components (Skorvanek et al., 2017).

In this paper, we utilized the open-source dataset (Tsanas et al., 2009) of the 5,875 medical voice records of Athanasios Tsanas and Max Little of the University of Oxford, downloaded from the University of California Irvine (UCI) Machine Learning Repository and analyzed the data using 26 ML models using MATLAB 2022b to increase the prediction accuracy and compare the performance of different models for predicting motor UPDRS and the total UPDRS. It has been well-established that different ML models are suitable for analyzing a different dataset, and there is no rule of thumb for choosing an appropriate model. Therefore, this research will discuss and explore all the possible ML models available in state-of-the-art data analytic software. Although the dataset has been utilized in several studies reported in the literature (Raundale, Thosar, & Rane, 2021; Sood, & Khandnor, 2019), there was no report computed and compared all the available models. Grover et al. reported the use of deep learning to learn the dataset (Grover, Bhartia, Yadav, & Seeja, 2018; Wan, Liang, Zhang, & Guizani, 2018). Of course, deep learning can provide a higher level of accuracy, however, it does require computing power, such as a graphic computing unit (GPU). It will be shown in the results section later that the ML models can perform sufficiently well compared to deep learning at a much lower required computing capacity. We also reduced the complexity of the model by performing the principal component analysis (PCA) (Panyamit et al., 2022) using the built-in PCA analysis in MATLAB 2022b to identify essential predictors and validate the simplified model using a dataset that was not used during the model training.

The result section will explain and discuss that the proposed PCA model can reduce the complexity and achieve the root-mean-square error of 2.38 with an R-squared value of 0.95 and 2.22 with an R-squared value of 0.94 for predicting the motor UPDRS and the total UPSRS, respectively. The less demanding model can make it more convenient and flexible because it reduces analysis time, computing resources, and cost. This work can provide a framework for developing remote healthcare services for PD and other chronic diseases, which can be beneficial during pandemics and other situations where access to in-person care is limited.

2. Objectives

1. Develop ML models to predict Parkinson's disease severity using vocal information from the UCI database, motor UPDRS, and total UPDRS scales.

2. Investigate the relationship between voice vibration and Parkinson's disease using ML.

3. Use PCA and ML models to reduce model complexity and compare the predictive accuracy of different statistical models for Parkinson's disease regression.

3. Materials and methods

This portion of the paper summarizes the methodology used, including the data source, data curation, and supervised ML training for regression tasks predicting the motor UPDRS and total UPDRS. The machine was trained using the UCI dataset, tested, underwent supervised regression training and PCA computation.

Figure 1 illustrates the process flow of data preparation, data curation, machine learning (ML) training, and validation. The initial step involves downloading the Parkinson Telemonitoring Data Set. Subsequently, the data is curated by eliminating rows and columns containing unnecessary information, resulting in a refined dataset. This refined dataset is then divided into two subsets: the training set and the validation set.

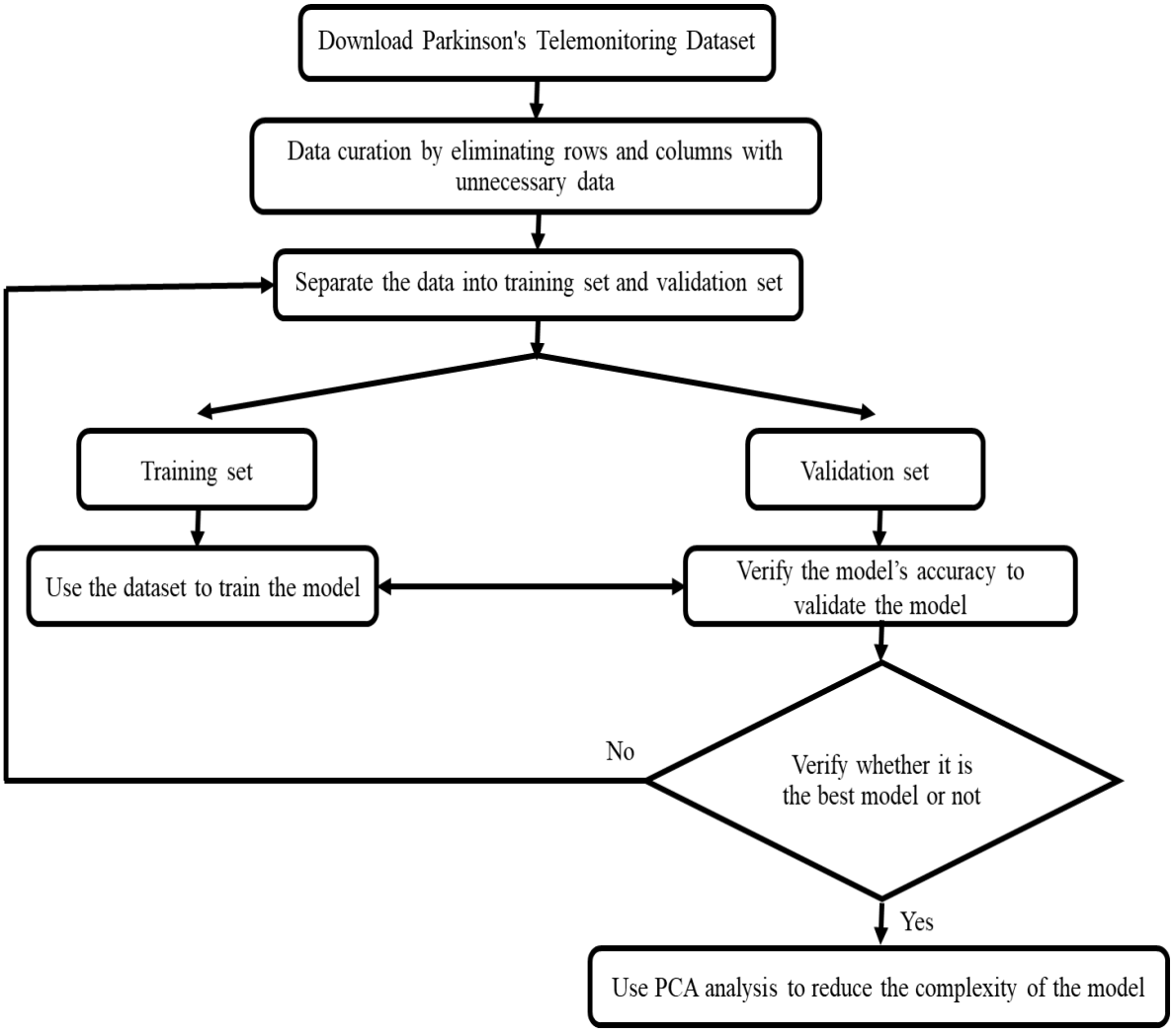

Figure 1 Process flow of data preparation, curation, ML training, and validation in this study.

The training set serves as the dataset used to train the machine learning model, while the validation set is employed to assess the model's accuracy and validate its performance. Following the verification of the model's suitability, the complexity of the model is further reduced using Principal Component Analysis (PCA) analysis. This technique helps to extract the most important features from the dataset, thereby enhancing model efficiency and interpretability.

Three model performance parameters are computed and analyzed to compare the prediction performance of each model.

- Root Mean Square Error (RMSE) is the calculation of the residual which represents the differences between the values predicted by a model and their true values. It is calculated by computing the square root of the mean of the norm of the residual for each data point. As the name suggests, the lower the error, the better the results.

- An R-squared value (R2) indicates the amount of variation of a dependent variable in a regression model is explained by an independent variable. As the value approaches 1, the more efficient the model can be explained by the relationship between the dependent and independent variables.

- Mean absolute Error (MAE) indicates the average magnitude of the errors in predicting the data set. In short, it measures the accuracy of continuous variables. As the value of MAE approaches 0, the more efficient the model will be.

3.1 UCI Data

This analyzed Parkinson's Telemonitoring Data Set was collected from the open-source University of California Irvine (UCI) Machine Learning Repository (Tsanas et al., 2009); assessed on 9November 2022 .A range of biomedical voice measurements of up to 5,875 recordings from 42 patients with early-stage PD was automatically captured in the telemonitoring device in the patient's home. The six-month trial allowed remote monitoring of symptom progression. The database consisted of 19 predictors and 2 UPDRS values, as summarized in Table 1. Note that the patient ID numbers have been excluded from the database in this study.

3.2 Data Curation

The 5,875 data rows covered a linear range of the Motor UPDRS and the Total UPDRS, providing an acceptable unbiased dataset, although there were fewer data rows for the Motor UPDRS greater than the score of 37 and the Total UPDRS greater than 53, as depicted in Figure 2. The two UPDRS curves were then fitted using a linear function, and it found that the R^2 values were 0.9925 and 0.9632 for the Motor UPDRS and the Total UPDRS, respectively.

The variables in Table 1 were treated as 19 predictors and 2 labels for supervised ML training for regression tasks. The 19 predictors and the 2 labels are summarized in Table 2.

3.3 Dataset for training and validation

The 5,875 rows were then divided into 2 datasets: the training dataset (5,288 rows) and the validation dataset (587 rows) at a ratio of 90% to 10%. The training and validation datasets were sparsely selected, ensuring they covered the same range of Motor UPDRS and Total UPDRS data distributions, as shown in Figures 3a and b for the training and validation datasets, respectively.

3.4 Machine Learning Training

MATLAB 2022b's Regression Learner program was used to train 26 supervised machine learning models listed in Table 3 for regression tasks using the training dataset. The multiple models were trained so that their performance on the given dataset could be compared. The performance of regression was assessed using a 5-fold cross-validation computing procedure. Root-mean-square-error (RMSE), R-squared value (R^2), and Mean-absolute-error (MAE) were utilized to determine the difference between the predicted UPDRS values by the models and their corresponding labels. In regression computation, the RMSE and MAE are standard evaluation metrics; they evaluate the difference between the predicted and actual values, and the R^2 is an excellent indicator of the model's correlation. All the training was done using Acer Nitro 7 laptop equipped with a core i7™ CPU, 24 GB RAM, and NVIDIA Geforce GTX 1660 Ti.

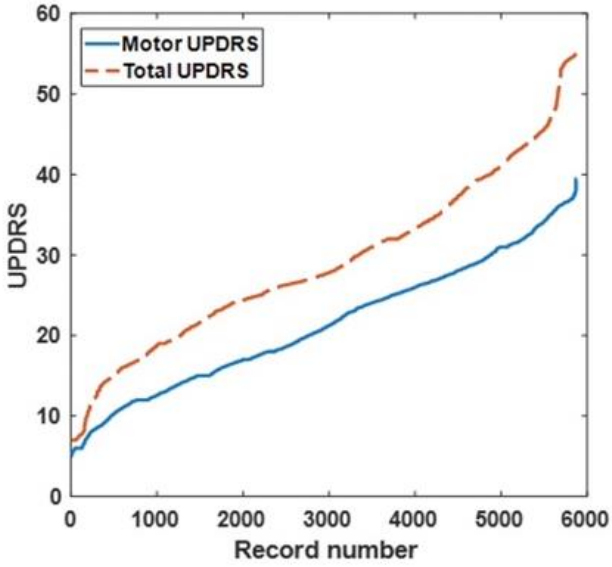

Figure 2 shows the distribution of Motor UPDRS in a solid blue curve and Total UPDRS in a dashed red curve.

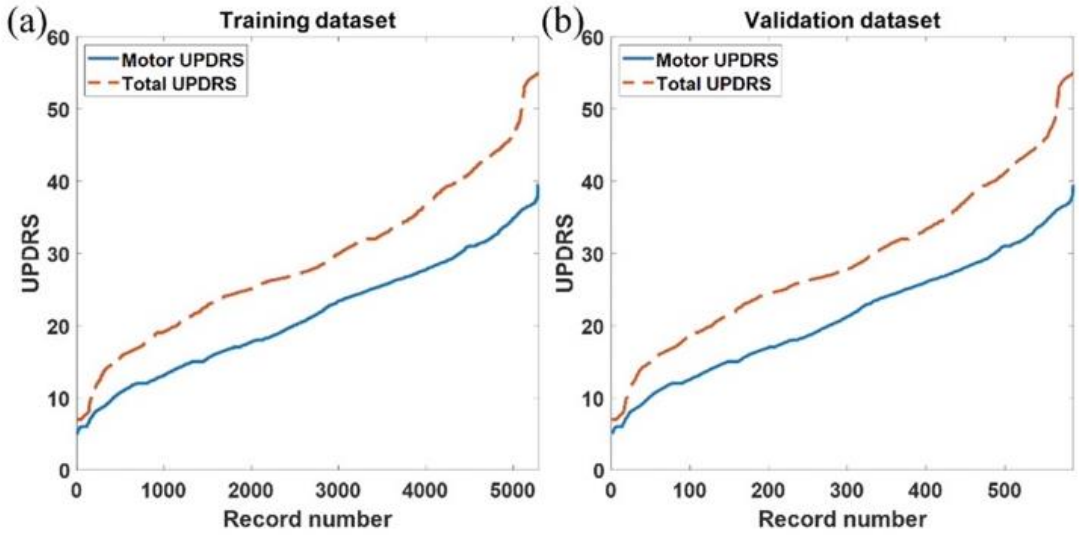

Figure 3 shows the distribution of Motor UPDRS in a solid blue curve and Total UPDRS in a dashed red curve for (a) the training dataset containing 5,288 records and (b) the validation dataset containing 578 records.

3.5 Model complexity reduction approach

Using the built-in PCA analysis tool in MATLAB 2022b, 95% statistical confidence was applied to principal component analysis (PCA) to find essential predictors contributing to model classification accuracy. After identifying crucial predictors, a less complex classification model was trained to demonstrate that with fewer predictors, the classification model may perform comparably to models built with all available predictors. In the section on outcomes, we will also explain how the PCA yields comparable results to other feature section approaches, such as the minimum redundancy maximum relevance (MRMR) algorithm, the f-test, and RreliefF.

Table 1 Predictors and labels obtained from the UCI Parkinson's Telemonitoring dataset.

	Predictors	**Details**	**Values**	**Mean ($\bar{x}$)**	**S.D. (S)**
1	Age	Age in years of the subjects	36-85 years	64.80 years	8.82 years
2	sex	Male gender is defined using the number 0. Male gender is defined using the number 1.	The male of 28 people The female of 14 people	-	-
3	test time	Time since being accepted into the experiment. The integer component represents the number of days since recruiting.	-4.26 - 215.49 days	92.86 days	53.45 days
4	Jitter (%)	Jitter as a percentage can be calculated by the average absolute difference, multiplied by the average time, between two successive periods. It is used as the measurement of fundamental frequency variation.	8.30×10^{-4}-0.10 %	0.0062 %	0.0056 %
5	Jitter (Abs)	Absolute jitter in microseconds can be calculated by the average absolute difference, multiplied by the average time, between two successive periods. It is used as the measurement of fundamental frequency variation.	2.25×10^{-6}-4.46×10^{-4} µs	4.40×10^{-5} µs	3.60×10^{-5} µs
6	Jitter: RAP	Relative Amplitude Perturbation can be calculated by the average absolute difference, divided by the average duration, between a period and the average of that period and its two neighbors, and it is used to measure fundamental frequency variation.	3.30×10^{-4}-0.0575 %	0.0030 %	0.0031%
7	Jitter: PPQ5	Five-point Period Perturbation Quotient can be calculated by the average absolute difference, divided by the average time, between a period and the average of its four closest neighbors. It is used as the measurement of fundamental frequency variation.	4.30e-04 -0.0696 %	0.0033%	0.0037%
8	Jitter: DDP	The term is defined as the average absolute difference between successive differences between successive periods divided by the average period, and it is the measurement of fundamental frequency variation.	9.80×10^{-4}-0.1726	0.0090	0.0094
9	Shimmer	Local shimmer is the average absolute difference, expressed as a percentage, between the average amplitudes of successive periods. It is used as a measurement for change in amplitude.	0.0031-0.2686 %	0.0340%	0.0258 %
10	Shimmer (dB)	The local shimmer in decibels was expressed as the difference between the amplitudes of successive periods' average absolute base-10 logarithm times 20. It is used as a measurement for change in amplitude.	0.0260-2.1070 dB	0.3110 dB	0.2303 dB
11	Shimmer: APQ3	Three-point Amplitude Perturbation Quotient can be defined as the average absolute difference between a period's amplitude and the sum of its neighbors' amplitudes, divided by the period's average amplitude. It is the measurement of change in amplitude.	0.0016-0.1627 %	0.0172 %	0.0132 %

Table 1 Cont.

	Predictors	Details	Values	Mean ($\bar{x}$)	S.D. (S)
12	Shimmer: APQ5	Five-point Amplitude Perturbation Quotient can be calculated by the average absolute difference between a period's amplitude and the sum of its four nearest neighbors' amplitudes, divided by its average amplitude. It is the measurement of change in amplitude.	0.0019-0.1670 %	0.0201 %	0.0167 %
13	Shimmer: APQ11	The 11-point Amplitude Perturbation Quotient was expressed as the average absolute difference, divided by the average amplitude, between the amplitude of a period and the average of the amplitudes of its ten nearest neighbors. It is the measurement of change in amplitude.	0.0025-0.2755 %	0.0275 %	0.0200 %
14	Shimmer: DDA	The term is the average absolute difference between successive variations in period amplitudes, and it is the measurement for change in amplitude.	0.0048-0.4880	0.0515	0.0397
15	NHR	Noise-to-Harmonics Ratio was used as the measurement of the voice's noise-tonal component ratio	2.86×10^{-4}-0.7483	0.0321	0.0597
16	HNR	Harmonics-to-Noise Ratio was used as the measurement of the voice's noise-tonal component ratio	1.6590- 37.8750	21.6795	4.2911
17	RPDE	Recurrence Period Density Entropy	0.1510- 0.9661	0.5415	0.1010
18	DFA	Detrended Fluctuation Analysis	0.5140-0.8656	0.6532	0.0709
19	PPE	Pitch period entropy	0.0220-0.7317	0.2196	0.0915
	Labels	**Details**	**Values**	**Mean ($\bar{x}$)**	**S.D. (S)**
1	Motor UPDRS	Clinician's motor UPDRS score	5.0377-39.5110	21.2962	8.1293
2	Total UPDRS	Clinician's total UPDRS score	7- 54.9920	29.0189	10.7003

Table 2 Regression Model Predictors and Labels

Variables	Type	Variables	Type
age	Predictor	Shimmer: APQ_3	Predictor
sex	Predictor	Shimmer: APQ_5	Predictor
test time	Predictor	Shimmer: APQ_{11}	Predictor
Jitter(%)	Predictor	Shimmer: DDA	Predictor
Jitter(Abs)	Predictor	NHR	Predictor
Jitter: RAP	Predictor	HNR	Predictor
Jitter: PPQ_5	Predictor	RPDE	Predictor
Jitter: DDP	Predictor	DFA	Predictor
Shimmer	Predictor	PPE	Predictor
Shimmer(dB)	Predictor		
Total UPDRS	Label for predicting total UPDRS	Motor UPDRS	Label for predicting motor UPDRS

Table 3 The ML models trained in this study

Model type	Model details
Linear regression	Linear
	Interactions Linear
	Robust Linear
Stepwise Linear Regression	Stepwise Linear
Tree	Fine Tree
	Medium Tree
	Coarse Tree
Support vector machine (SVM)	Linear SVM
	Quadratic SVM
	Cubic SVM
	Fine Gaussian SVM
	Medium Gaussian SVM
	Coarse Gaussian SVM
Ensemble	Boosted Trees
	Bagged Trees
Gaussian Process Regression (GPR)	Squared Exponential GPR
	Matern 5/2 GPR
	Exponential GPR
	Rational Quadratic GPR
Neural Network	Narrow Neural Network
	Medium Neural Network
	Wide Neural Network
	Bi-layered Neural Network
	Tri-layered Neural Network
Kernel	SVM Kernel
	Least Squares Regression Kernel

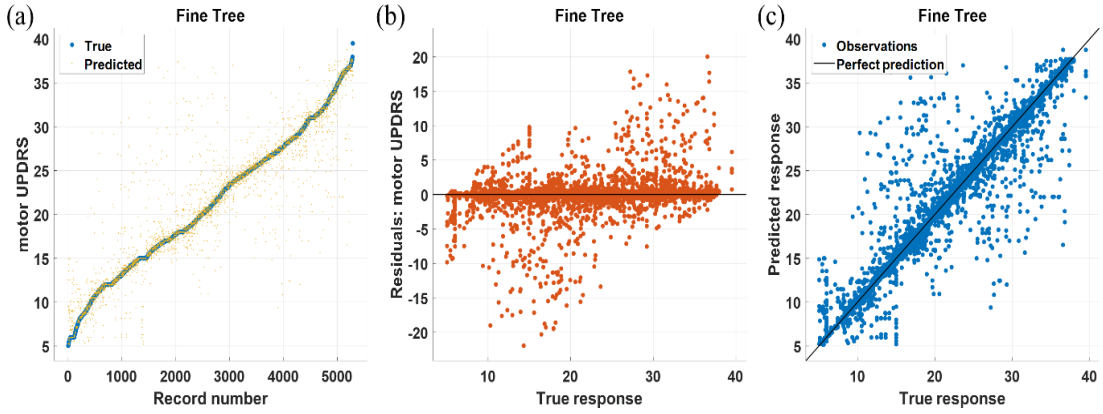

Figure 4 (a) Labels compared to the predicted values from the Fine Tree model for predicting the motor UPDRS, (b) Residual error, and (c) Predicted values plotted against the training labels.

4. Results

4.1 ML models training using 19 predictors

The ML models in Table 3 were first trained using all 19 predictors with the labels to train 2 separated AI for predicting (1) motor UPDRS and (2) total UPDRS using the training dataset Table 1. The regression performance parameters of each model are shown in Table 4 and Table 5 for the motor UPDRS and the total UPDRS, respectively.

Table 4 shows that the top performance model for predicting the motor UPDRS was the Fine Tree model, with an RMSE of 2.55, an R^2 of 0.90, and an MAE of 1.02. Figure 4a shows that most of the predicted motor UPDRS agree well with their corresponding label; however, there are still some discrepancies throughout all the records. The errors of each record are shown in Figure 4b. The errors are randomly distributed, covering positive and negative values. Figure 4c shows the predicted values against their label; the excellent performance model should give the prediction points along the diagonal line of the plot. In this case, most predicted values are in the diagonal line indicating a high-performance model.

Table 4 Regression performance parameters for ML models trained for predicting the motor UPDRS using all 19 predictors.

Model type	Model details	5-fold cross-validation RMSE calculated from the training dataset	5-fold cross-validation R^2 calculated from the training dataset	5-fold cross-validation MAE calculated from the training dataset
Linear regression	Linear	7.51	0.15	6.34
	Interactions Linear	8.57	-0.11	5.83
	Robust Linear	7.61	0.12	6.31
Stepwise Linear Regression	Stepwise Linear	7.25	0.20	5.80
Tree	Fine Tree	2.55*	0.90*	1.02*
	Medium Tree	2.92	0.87	1.49
	Coarse Tree	3.59	0.81	2.28
Support vector machine (SVM)	Linear SVM	7.68	0.11	6.22
	Quadratic SVM	7.40	0.17	5.54
	Cubic SVM	22.70	-6.80	5.28
	Fine Gaussian SVM	4.65	0.67	3.29
	Medium Gaussian SVM	5.69	0.51	4.32
	Coarse Gaussian SVM	7.43	0.16	6.03
Ensemble	Boosted Trees	4.64	0.67	3.77
	Bagged Trees	3.35	0.83	2.54
Gaussian Process Regression (GPR)	Squared Exponential GPR	4.48	0.70	3.20
	Matern 5/2 GPR	4.32	0.72	3.01
	Exponential GPR	4.30	0.72	2.99
	Rational Quadratic GPR	4.30	0.72	2.97

Table 4 Cont.

Model type	Model details	5-fold cross-validation RMSE calculated from the training dataset	5-fold cross-validation R^2 calculated from the training dataset	5-fold cross-validation MAE calculated from the training dataset
Neural Network	Narrow Neural Network	5.39	0.56	4.11
	Medium Neural Network	4.52	0.69	3.27
	Wide Neural Network	4.32	0.72	2.94
	Bi-layered Neural Network	4.11	0.74	2.99
	Tri-layered Neural Network	4.21	0.73	2.84
Kernel	SVM Kernel	7.37	0.18	5.90
	Least Squares Regression Kernel	7.02	0.25	5.81

Table 5 demonstrates that the model with the best performance for predicting the total UPDRS was the Fine Tree model, with an RMSE value of 2.65, an R^2 value of 0.94, and an MAE value of 0.92. Figure 5a demonstrates that the predicted total UPDRS correspond well with their respective labels; however, there is still a slight difference between the labels and the predicted total UPDRS throughout all the records. Each record's error is displayed in Figure 5b, and the errors are dispersed randomly across both positive and negative values. Figure 5c depicts the expected values with their respective labels. Like in the motor UPDRS case, most predicted values lie along the diagonal line, indicating a model with excellent performance.

Table 5 Regression performance parameters for ML models trained for predicting the total UPDRS using all 19 predictors.

Model type	Model details	5-fold cross-validation RMSE calculated from the training dataset	5-fold cross-validation R^2 calculated from the training dataset	5-fold cross-validation MAE calculated from the training dataset
Linear regression	Linear	9.76	0.17	8.07
	Interactions Linear	9.81	0.16	7.52
	Robust Linear	9.79	0.16	8.01
Stepwise Linear Regression	Stepwise Linear	9.38	0.23	7.53
Tree	Fine Tree	2.65*	0.94*	0.92*
	Medium Tree	3.19	0.91	1.49
	Coarse Tree	4.18	0.85	2.49
Support vector machine (SVM)	Linear SVM	9.93	0.14	7.90
	Quadratic SVM	9.56	0.20	7.16
	Cubic SVM	27.71	-5.71	7.08
	Fine Gaussian SVM	6.30	0.65	4.27
	Medium Gaussian SVM	7.85	0.46	5.74
	Coarse Gaussian SVM	9.79	0.16	7.70
Ensemble	Boosted Trees	5.68	0.72	4.54
	Bagged Trees	4.51	0.82	3.32

Table 5 Cont.

Model type	Model details	5-fold cross-validation RMSE calculated from the training dataset	5-fold cross-validation R^2 calculated from the training dataset	5-fold cross-validation MAE calculated from the training dataset
Gaussian Process Regression (GPR)	Squared Exponential GPR	6.10	0.67	4.17
	Matern 5/2 GPR	5.96	0.69	4.03
	Exponential GPR	5.91	0.69	4.00
	Rational Quadratic GPR	5.89	0.70	3.94
Neural Network	Narrow Neural Network	8.04	0.44	5.71
	Medium Neural Network	6.24	0.66	4.26
	Wide Neural Network	5.80	0.71	3.76
	Bi-layered Neural Network	6.06	0.68	4.29
	Tri-layered Neural Network	5.77	0.71	4.19
Kernel	SVM Kernel	9.79	0.16	7.69
	Least Squares Regression Kernel	9.15	0.27	7.43

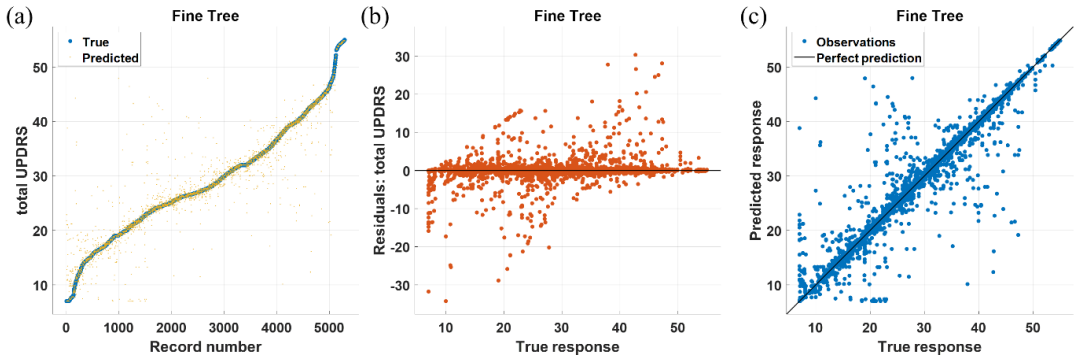

Figure 5 (a) Labels compared to the predicted values from the Fine Tree model for predicting the total UPDRS, (b) Residual error, and (c) Predicted values plotted against the training labels

The top three ML models for predicting both the motor and the total UPDRS were the same, which were the Fine tree was ranked in the top first with RMSE values of 2.55 to 2.65 for two UPRDRS predictions, the medium tree was ranked second with RMSE values of 2.92 to 3.19 for two UPRDRS predictions, and Coarse tree was ranked in the third with 3.59 to 4.18 for two UPRDRS predictions. The list of good performance models for predicting the two UPRDS values is similar, indicating that the two UPDRS data have a similar relationship or trend.

4.2 Validation of the trained models using the validation dataset

The separated validation dataset was then employed to predict the regression outputs from the two Fine tree models for predicting the motor UPDRS and the total UPDRS and compared to their known labels for the 587 validation records. For the motor UPDRS validation, the trained Fine Tree

model had an RMSE of 2.84, an R^2 of 0.87, and an MAE of 0.95. Figure 6a shows the residual error of the predicted motor UPDRS compared to the validation dataset's labels. Figure 6b shows predicted values plotted against the validation dataset's labels. The RMSE, R^2, MAE, and the plots in Figure 6 show slightly worse performance than the training dataset, indicating that the trained model is generalized to predict unseen data.

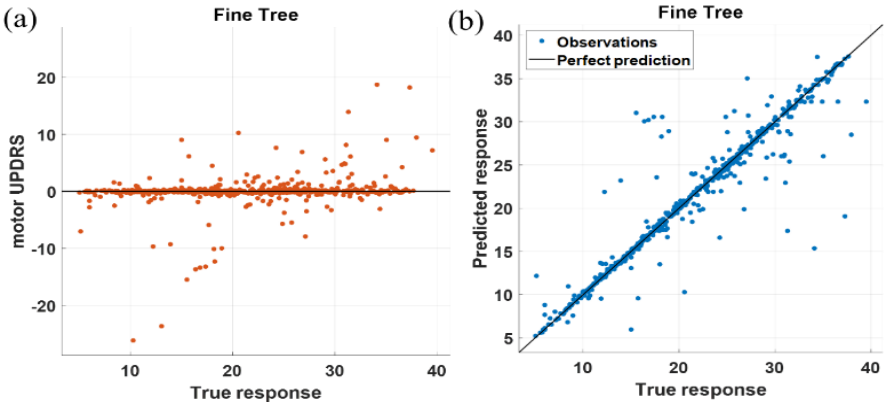

Figure 6 Performance of the trained Fine Tree model for predicting the motor UPDRS when validated using the validation dataset, (a) Residual error, and (b) Predicted values plotted against the training labels

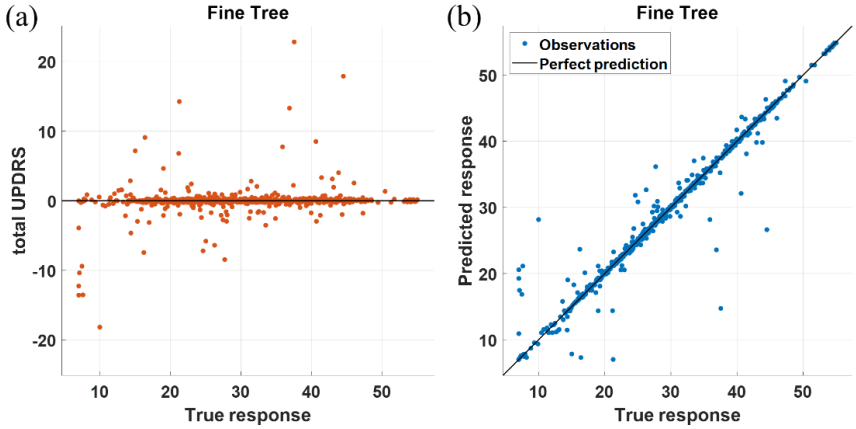

Figure 7 Performance of the trained Fine Tree model for predicting the total UPDRS when validated using the validation dataset, (a) Residual error, and (b) Predicted values plotted against the training labels

For the total UPDRS, the trained Fine Tree model exhibited an RMSE of 2.32, an R^2 of 0.95, and an MAE of 0.73 for total UPDRS validation. Figure 7a depicts the residual error of the predicted motor UPDRS compared to the labels in the validation dataset. Figure 7b depicts regression values displayed against labels from the validation dataset. The RMSE, R^2, MAE, and plots in Figure 7 indicate that the trained model is extended to predict unknown data.

4.3 Model complexity reduction using PCA

In the previous sections, we have demonstrated that regression models can be trained using all the available 19 predictors, which are (1) Age, (2) Test time, (3) DFA, (4) NHR, (5) RPDE, (6) HNR, (7) JitterAbs, (8) PPE, (9) ShimmerdB, (10) JitterDDP, (11) JitterDDP, (12) JitterPPQ5, (13) sex, (14) ShimmerDDA, (15) Jitter, (16) ShimmerAPQ5, (17) Shimmer, (18) JitterRAP, and (19) ShimmerAPQ3 to predict severity of PD. Here, we perform PCA analysis using the built-in Matlab PCA feature, and the coefficients are as shown in Table 6, calculated at 95% confidence compared with other feature selection methods, including MRMR, f-Test, and the RreliFf.

PCA coefficients for training the Fine Tree model for predicting the motor UPDRS and the total

UPDRS using 19 predictors at 95% statistical confidence are shown in Figures 8a and 8b, respectively. The strength of PCA coefficients for each column was then ranked for the two types of UPDRS and listed in Tables 6 and 7. These PCA coefficients are a good indicator for identifying principal components

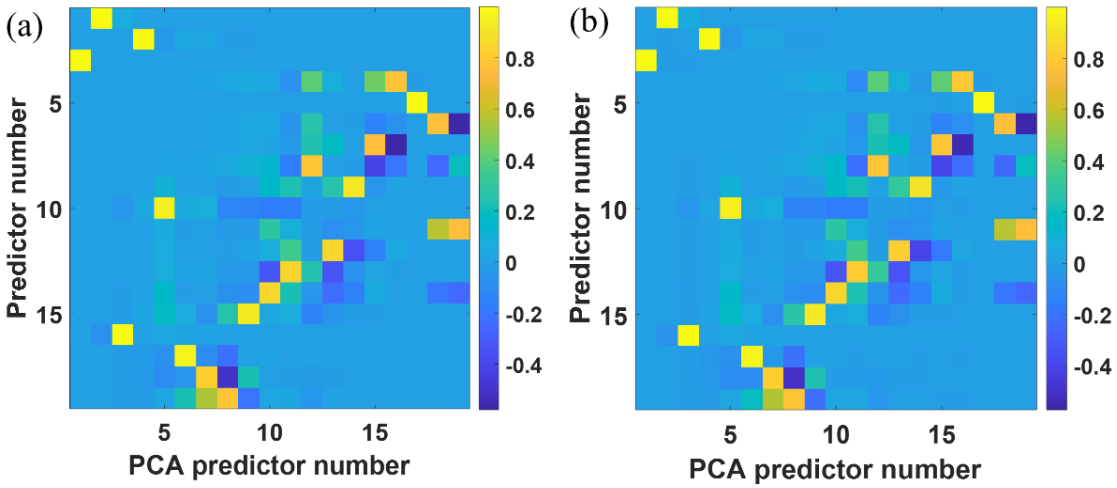

Figure 8 PCA coefficients for training the Fine Tree models for predicting (a) the motor UPDRS and (b) the total UPDRS using 19 predictors at 95% statistical confidence.

There were only 6 predictors that had PCA coefficients more than 0.95, as shown in Tables 6 and 7, which were test time, Jitter (Abs), sex, age, HNR, and RPDE. Like the other feature selection method, only the first 6 to 7 predictors were significant compared to the others. Here, we trained Fine Tree models using a different number of predictors, from 1 predictor to 7 predictors, to determine whether the Fine Tree models trained using only 6 predictors can reach the convergence of RMSE, R^2, and MAE responses, as shown in Tables 8 and 9 for the motor UPDRS and total UPDRS, respectively.

The RMSE, R^2, and MAE values in Tables 8 and 9 show that the Tree models required only 5 variables to reach convergence for predicting the two UPDRS values, although each feature selection method required slightly different predictors. The best method with the lowest RMSE, the lowest MAE, and the highest R^2 was the PCA, which required the following 5 predictors: test time, Jitter(Abs), sex, age, and HNR.

4.4 Validation for the trained Fine Tree models using 5 predictors

In this section, we validated the trained PCA models using 5 predictors to see whether they can perform similarly to the trained models when validated using the separated validation dataset. For the motor UPDRS validation, the trained PCA model can provide an RMSE of 1.78, an R^2 of 0.95, and an MAE of 0.59. For the total UPDRS validation, the trained PCA model can provide an RMSE of 1.78, an R^2 of 0.97, and an MAE of 0.55. These performance parameters indicate that the PCA models can perform similarly to the trained PCA models and are slightly better than those trained using 19 pred ictors. The possible reasons for this are noise in the other predictors, which might not have a solid coloration for the two UPDRS values.

Comparing our findings to related research, a predictive modeling approach based on RNA-Sequence and densely connected deep recurrent neural networks in the field. However, their study reported an RMSE of 6.0 (Ahmed, Komeili, & Park, 2022). Similarly, a deep-learning approach for predicting Parkinson's disease progression, yielded an RMSE of 1.42, an MAE of 0.92, and an R^2 value of 0.97 (Shahid & Singh, 2020). It is worth noting that our results are not only comparable but also tend to be more precise and accurate compared to these prior studies. This can be attributed to our utilization of a diverse range of 26 machine learning models, which allowed for a comprehensive exploration of the data and better prediction accuracy

Table 6 PCA coefficients, MRMR, F Test, and the RreliFf of the 19 predictors for predicting the motor UPDRS

Predictors	MRMR	Predictors	F TEST	Predictors	RRELIFF	Predictors	PCA coefficients
age	1.4112	Age	730.367	age	0.0392	test time	1
test_time	0.8501	HNR	73.1519	DFA	0.0047	Jitter(Abs)	1
DFA	0.0088	PPE	66.2431	JitterAbs	0.0027	sex	0.998
NHR	0.0085	ShimmerAPQ11	62.4847	sex	0.0015	age	0.9978
RPDE	0.0078	DFA	47.654	HNR	0.0014	HNR	0.9966
HNR	0.0062	NHR	44.4732	NHR	0.001	RPDE	0.9725
JitterAbs	0.0061	ShimmerdB	44.0362	JitterRAP	0.0006	Shimmer(dB)	0.9493
PPE	0.0055	Shimmer	43.6371	JitterDDP	0.0006	NHR	0.9243
ShimmerdB	0.0047	RPDE	38.9946	JitterPPQ5	0.0003	Shimmer	0.9008
JitterDDP	0.0046	Jitter	35.9545	Jitter	0.0003	Shimmer: DDA	0.8502
ShimmerAPQ11	0.0045	JitterPPQ5	31.0504	test_time	-0.0002	Shimmer: APQ5	0.8215
JitterPPQ5	0.004	ShimmerDDA	30.132	ShimmerAPQ3	-0.0004	DFA	0.8203
Sex	0.004	ShimmerAPQ3	30.0617	ShimmerDDA	-0.0004	Shimmer: APQ11	0.8147
ShimmerDDA	0.0039	ShimmerAPQ5	29.8136	ShimmerAPQ11	-0.0004	Jitter(%)	0.8028
Jitter	0.0038	JitterDDP	23.3847	PPE	-0.0007	Jitter: PPQ5	0.7815
ShimmerAPQ5	0.0031	JitterRAP	23.0048	ShimmerAPQ5	-0.0008	Jitter: DDP	0.7744
Shimmer	0.0027	JitterAbs	21.9053	ShimmerdB	-0.0009	PPE	0.7742
JitterRAP	0.0023	test_time	12.454	Shimmer	-0.0012	Jitter: RAP	0.7569
ShimmerAPQ3	0.0022	Sex	3.3613	RPDE	-0.0019	Shimmer: APQ3	0.7569

5. Discussion

In Parkinson's patients, a dividend states that if not considered into treatment, it might worsen the symptoms and affect other organ systems, especially cardiovascular systems. This research adds to a backup plan if Parkinson's patients cannot travel to appointments because of another severe illness going into lockdown. Our research is based on an open-source dataset of 19 predictors and 2 UPDRS values. For the motor UPDRS validation (model 1), we have identified 5 predictor variables: test time, Jitter(Abs), sex, age, and HNR by computing PCA analysis which contributes most to the severity in Parkinson patients. As we developed AI, the RMSE of 1.78, an R^2 of 0.95, and an MAE of 0.59 made the model, Fine tree trained using only 5 predictors, sufficient to perform the regression model. For the total UPDRS (model 2), we have identified 5 predictor variables, which are the same as the motor UPDRS case, and as we developed AI RMSE to 1.78, an R^2 to 0.97, and MAE of 0.55, making the model, Fine tree, sufficient enough to track. We found no significant improvement in regression when more than 5 predictor variables were used in ML model training.

Table 7 PCA coefficients, MRMR, F Test, and the RreliFf of the 19 predictors for predicting the total UPDRS

Predictors	MRMR	Predictors	F TEST	Predictors	RRELIFF	Predictors	PCA coefficients
age	1.3614	age	732.9014	age	0.0377	test time	0.9999
HNR	0.5825	HNR	118.2253	DFA	0.0037	Jitter(Abs)	0.9999
DFA	0.5430	Jitter(Abs)	70.7588	Jitter(Abs)	0.0026	sex	0.9980
sex	0.4170	PPE	70.1715	sex	0.0016	age	0.9978
RPDE	0.2262	ShimmerAPQ11	70.0505	HNR	0.0009	HNR	0.9965
ShimmerdB	0.1809	RPDE	66.0790	JitterRAP	0.0005	RPDE	0.9725
PPE	0.1754	DFA	64.3729	JitterDDP	0.0005	Shimmer(dB)	0.9493
ShimmerAPQ11	0.1263	Jitter	62.3868	NHR	0.0001	NHR	0.9243
JitterRAP	0.1170	NHR	61.6483	Jitter	0.0000	Shimmer	0.9008
NHR	0.1104	ShimmerdB	53.9979	JitterPPQ5	0.0000	Shimmer: DDA	0.8502
ShimmerAPQ3	0.0959	Shimmer	53.4228	ShimmerAPQ3	-0.0007	Shimmer: APQ5	0.8215
JitterPPQ5	0.0958	JitterPPQ5	44.3918	ShimmerDDA	-0.0007	DFA	0.8203
Shimmer	0.0846	ShimmerDDA	43.6145	ShimmerAPQ11	-0.0008	Shimmer: APQ11	0.8147
Jitter	0.0828	ShimmerAPQ3	43.3151	ShimmerdB	-0.0012	Jitter(%)	0.8028
ShimmerAPQ5	0.0755	ShimmerAPQ5	38.6322	ShimmerAPQ5	-0.0014	Jitter: PPQ5	0.7815
ShimmerDDA	0.0561	JitterDDP	33.2640	PPE	-0.0016	Jitter: DDP	0.7744
JitterDDP	0.0476	JitterRAP	32.5917	Shimmer	-0.0018	PPE	0.7742
test_time	0.0000	sex	26.4637	RPDE	-0.0018	Jitter: RAP	0.7569
JitterAbs	0.0000	test_time	11.5342	test_time	-0.0018	Shimmer: APQ3	0.7569

This model was trained using MATLAB®, and it only took 2 seconds to train and 2 seconds to make a prediction, saving a significant amount of time compared to a doctor's actual prediction, which would require days to weeks for in-clinic processes and at-home observation, not to mention patient's travel time. Consequently, diagnosis by doctors can be more accurate and delicate. Compared to the deep learning method which generally would take hours to days to train and an average of 6 months in the data collecting period (Grover et al., 2018), the machine learning model is a time-saving method, yet as efficient.

The motor section of the UPDRS is a standardized rating scale that assesses various motor symptoms, such as tremors, rigidity, bradykinesia, and postural instability. The Root Mean Squared Error (RMSE) of 1.78 and R-squared value of 0.95 0indicate that the model fits the data relatively well, while the Mean Absolute Error (MAE) of 0.59 indicates that the model is performing well in predicting the motor UPDRS scores in individuals with Parkinson's disease.

Table 8 shows Fine Tree models for predicting the motor UPDRS trained using a different number of predictors, from 1 predictor to 7 predictors.

MRMR				
No. Predictors	**Predictors**	**RMSE**	**R^2**	**MAE**
1	age	4.93	0.63	3.86
2	age, test_time	2.84	0.88	1.39
3	age, test_time, DFA	3.45	0.82	1.34
4	age, test_time, DFA, NHR	3.19	0.85	1.35
5	age, test_time, DFA, NHR, RPDE	2.96	0.87	1.19
6	age, test_time, DFA, NHR, RPDE, HNR	2.73	0.89	1.06
7	age, test_time, DFA, NHR, RPDE, HNR, JitterAbs	2.50	0.91	0.98
f-test				
No. Predictors	**Predictors**	**RMSE**	**R^2**	**MAE**
1	age	4.93	0.63	3.86
2	age, HNR	5.17	0.60	3.54
3	age, HNR, PPE	5.00	0.62	3.36
4	age, HNR, PPE, ShimmerAPQ11	4.91	0.63	3.21
5	age, HNR, PPE, ShimmerAPQ11, DFA	3.88	0.77	2.52
6	age, HNR, PPE, ShimmerAPQ11, DFA, NHR	3.85	0.78	2.48
7	age, HNR, PPE, ShimmerAPQ11, DFA, NHR, ShimmerdB	3.85	0.78	2.47
RreliefF				
No. Predictors	**Predictors**	**RMSE**	**R^2**	**MAE**
1	age	4.93	0.63	3.86
2	age, DFA	4.34	0.71	2.91
3	age, DFA, JitterAbs	4.14	0.74	2.73
4	age, DFA, JitterAbs, sex	3.06	0.86	2.08
5	age, DFA, JitterAbs, sex, HNR	3.13	0.85	2.08
6	age, DFA, JitterAbs, sex, HNR, NHR	3.07	0.86	2.06
7	age, DFA, JitterAbs, sex, HNR, NHR, JitterRAP	3.18	0.85	2.10
PCA coefficients				
No. Predictors	**Predictors**	**RMSE**	**R^2**	**MAE**
1	test time	4.07	0.75	2.55
2	test time, Jitter(Abs)	7.61	0.12	5.60
3	test time, Jitter(Abs), sex	7.39	0.17	5.23
4	test time, Jitter(Abs), sex, age	1.94	0.94	0.77
5	test time, Jitter(Abs), sex, age, HNR	1.76	0.95	0.66
6	test time, Jitter(Abs), sex, age, HNR, RPDE	1.89	0.95	0.67
7	test time, Jitter(Abs), sex, age, HNR, RPDE, Shimmer(dB)	1.90	0.95	0.69

Table 9 shows Fine Tree models for predicting the total UPDRS trained using a different number of predictors, from 1 predictor to 7 predictors.

MRMR				
No. Predictors	**Predictors**	**RMSE**	**R^2**	**MAE**
1	age	5.89	0.70	4.68
2	age, test_time	3.38	0.90	1.69
3	age, test_time, DFA	4.13	0.85	1.89
4	age, test_time, DFA, NHR	3.63	0.89	1.53
5	age, test_time, DFA, NHR, RPDE	3.83	0.87	1.60
6	age, test_time, DFA, NHR, RPDE, HNR	3.58	0.89	1.45
7	age, test_time, DFA, NHR, RPDE, HNR, JitterAbs	3.42	0.90	1.36
f-test				
No. Predictors	**Predictors**	**RMSE**	**R^2**	**MAE**
1	age	5.89	0.70	4.68
2	age, HNR	6.12	0.67	4.30
3	age, HNR, PPE	5.92	0.69	4.01
4	age, HNR, PPE, ShimmerAPQ11	5.89	0.70	3.95
5	age, HNR, PPE, ShimmerAPQ11, DFA	3.50	0.89	1.35
6	age, HNR, PPE, ShimmerAPQ11, DFA, NHR	4.70	0.81	3.13
7	age, HNR, PPE, ShimmerAPQ11, DFA, NHR, ShimmerdB	4.78	0.80	3.09
RreliefF				
No. Predictors	**Predictors**	**RMSE**	**R^2**	**MAE**
1	age	5.89	0.70	4.68
2	age, DFA	5.35	0.75	3.63
3	age, DFA, JitterAbs	4.54	0.82	3.08
4	age, DFA, JitterAbs, sex	3.82	0.87	2.60
5	age, DFA, JitterAbs, sex, HNR	3.92	0.87	2.60
6	age, DFA, JitterAbs, sex, HNR, NHR	3.96	0.86	2.63
7	age, DFA, JitterAbs, sex, HNR, NHR, JitterRAP	3.88	0.87	2.64
PCA coefficients				
No. Predictors	**Predictors**	**RMSE**	**R^2**	**MAE**
1	test time	5.19	0.76	3.24
2	test time, Jitter(Abs)	10.52	0.03	7.95
3	test time, Jitter(Abs), sex	10.80	-0.02	8.16
4	test time, Jitter(Abs), sex, age	2.53	0.94	1.02
5	test time, Jitter(Abs), sex, age, HNR	2.41	0.95	0.86
6	test time, Jitter(Abs), sex, age, HNR, RPDE	2.54	0.94	0.90
7	test time, Jitter(Abs), sex, age, HNR, RPDE, Shimmer(dB)	2.59	0.94	0.93

The total UPDRS is a standardized rating scale used to assess various aspects of Parkinson's disease, including motor symptoms, activities of daily living, and cognitive function. It is divided into four parts: non-motor symptoms, motor symptoms, motor examinations, and complications of therapy. The total UPDRS score is the sum of all four parts, with a maximum score of 176. The R-squared value of 0.97 indicates that the model explains 95% of the variance in the total UPDRS

scores, while the MAE measures how well the model fits the data. The MAE is 0.55 points away from the actual scores, suggesting that the AI model performs well in predicting the total UDPRS scores in individuals with Parkinson's disease. However, it is crucial to validate the performance of any AI model before using it for clinical or diagnostic purposes.

The RMSE of 1.78 is considered a low chance of error and is sufficient to be deployed for UPDRS predictions. The R-squared of 0.95 and 0.97 shows that the model fits the data relatively well. The MAE of 0.55 and 0.59 also show the model has a sufficiently low error.

Our findings will enable clinicians to pay particular attention to these 5 critical predictors when assessing Parkinson's patient diagnosis. Moreover, the PCA-based framework we have used here is not limited to the Parkinson Telemonitoring dataset; it is equally applicable to other datasets that contain potentially predictive variables. Our approach will facilitate the elimination of unknown variables, reducing the time and cost required to collect patient data. However, the fact that we have not collected actual data from Parkinson's patients by ourselves contributed to this project's limitation. The PCA model shows that Parkinson's severity depends on test time, NHR, Jitter (Abs), sex, and age. A relationship between voice vibration and level of Parkinson's severity was found since two of the predictor variables are Jitter (Abs) which is the voice's vibration magnitude and HNR Harmonics-to-Noise Ratio was used as the measurement of the voice's noise-tonal component ratio.

6. Conclusion

This research aims to construct machine learning (ML) models for predicting the severity of Parkinson's disease using vocal information and to analyze the association between voice vibration and Parkinson's disease using ML. Also, we intended to employ PCA and ML models to reduce model complexity and assess the predicted accuracy of various statistical models for Parkinson's disease regression.

We collected 5,875 medical voice records from the University of California Irvine Machine Learning Repository to achieve our goals. We analyzed the data using 26 machine learning (ML) models in MATLAB 2022b to increase prediction accuracy and compare the performance of different models for predicting the motor UPDRS and total UPDRS. In addition, we decreased the model's complexity by doing PCA analysis to identify critical variables and validated the simpler model using a dataset not utilized during model training.

The suggested PCA model may reduce complexity and attain an RMSE of 1.78 with an R-squared value of 0.95 and an RMSE of 1.78 with an R-squared value of 0.97 when predicting the motor UPDRS and total UPDRS, respectively. The less demanding model can make it more practical and adaptable, decreasing analysis time, computing resources, and expenses.

This work can give a framework for developing remote healthcare services for Parkinson's disease and other chronic conditions, which can be helpful during pandemics and other situations where access to in-person care is limited. In addition, our study underlined the significance of telemedicine in managing chronic diseases such as PD and the possibility of telemonitoring equipment to offer patients more flexible and accessible access to care.

In conclusion, this study demonstrates the potential of machine learning and principal component analysis in predicting the severity of Parkinson's disease using voice input and minimizing model complexity. These findings allow future research to establish remote healthcare services and enhance patient care.

7. Acknowledgements

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8. References

Ahmed, S., Komeili, M., & Park, J. (2022). Predictive modelling of Parkinson's disease progression based on RNA-Sequence with densely connected deep recurrent neural networks. *Scientific Reports, 12*(1), 21469. https://doi.org/10.1038/s41598-022-25454-1

Bhat, S., Acharya, U. R., Hagiwara, Y., Dadmehr, N., & Adeli, H. (2018). Parkinson's

disease: Cause factors, measurable indicators, and early diagnosis. *Computers in Biology and Medicine, 102*, 234-241. https://doi.org/10.1016/j.compbiomed.2018.09.008

Camargo Maluf, F., Feder, D., & Alves de Siqueira Carvalho, A. (2019). Analysis of the relationship between type II diabetes mellitus and Parkinson's disease: a systematic review. *Parkinson's Disease, 2019*. https://doi.org/10.1155/2019/4951379

Cruz, M. J., Nieblas-Bedolla, E., Young, C. C., Feroze, A. H., Williams, J. R., Ellenbogen, R. G., & Levitt, M. R. (2021). United States medicolegal progress and innovation in telemedicine in the age of COVID-19: a primer for neurosurgeons. *Neurosurgery*. https://doi.org/10.1093/neuros/nyab185

Cuenca-Bermejo, L., Almela, P., Navarro-Zaragoza, J., Fernández Villalba, E., González-Cuello, A.-M., Laorden, M.-L., & Herrero, M.-T. (2021). Cardiac changes in Parkinson's disease: Lessons from clinical and experimental evidence. *International Journal of Molecular Sciences, 22*(24), 13488. https://doi.org/10.3390/ijms222413488

Dauer, W., & Przedborski, S. (2003). Parkinson's disease: mechanisms and models. *Neuron, 39*(6), 889-909. https://doi.org/10.1016/s0896-6273(03)00568-3

Disease, Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease (2003). The unified Parkinson's disease rating scale (UPDRS): status and recommendations. *Movement Disorders, 18*(7), 738-750. https://doi.org/10.1002/mds.10473

Goldstein, D. S., & Sharabi, Y. (2019). The heart of PD: Lewy body diseases as neurocardiologic disorders. *Brain research, 1702*, 74-84. https://doi.org/10.1016/j.brainres.2017.09.033

Grover, S., Bhartia, S., Yadav, A., & Seeja, K. (2018). Predicting severity of Parkinson's disease using deep learning. *Procedia computer science, 132*, 1788-1794. https://doi.org/10.1016/j.procs.2018.05.154

Idiaquez, J., & Roman, G. C. (2011). Autonomic dysfunction in neurodegenerative dementias. *Journal of the neurological sciences, 305*(1-2), 22-27. https://doi.org/10.1016/j.jns.2011.02.033

Jiménez, M. C., & Vingerhoets, F. J. (2012). Tremor revisited: treatment of PD tremor. *Parkinsonism & related disorders, 18*, S93-S95. https://doi.org/10.1016/S1353-8020(11)70030-X

Klockgether, T. (2004). Parkinson's disease: clinical aspects. *Cell and tissue research, 318*, 115-120. https://doi.org/10.1007/s00441-004-0975-6

Krämer, H. H., Lautenschläger, G., de Azevedo, M., Doppler, K., Schänzer, A., Best, C., . . . Birklein, F. (2019). Reduced central sympathetic activity in Parkinson's disease. *Brain and behavior, 9*(12), e01463. https://doi.org/10.1002/brb3.1463

Lamotte, G., Holmes, C., Wu, T., & Goldstein, D. S. (2019). Long-term trends in myocardial sympathetic innervation and function in synucleinopathies. *Parkinsonism & related disorders, 67*, 27-33. https://doi.org/10.1016/j.parkreldis.2019.09.014

Marino, B. L., de Souza, L. R., Sousa, K., Ferreira, J. V., Padilha, E. C., da Silva, C. H., . . . Hage-Melim, L. I. (2020). Parkinson's disease: a review from pathophysiology to treatment. *Mini reviews in medicinal chemistry, 20*(9), 754-767. https://doi.org/10.2174/1389557519666191104110908

Muqtadar, H., Testai, F. D., & Gorelick, P. B. (2012). The dementia of cardiac disease. *Current cardiology reports, 14*, 732-740. https://doi.org/10.1007/s11886-012-0304-8

Organization, W. H. (2006). *Neurological disorders: public health challenges*: World Health Organization.

Panyamit, T., Sukvivatn, P., Chanma, P., Kim, Y., Premratanachai, P., & Pechprasarn, S. (2022). Identification of factors in the survival rate of heart failure patients using machine learning models and principal

component analysis. *Journal of Current Science and Technology, 12*(2), 336-348.

Pfeiffer, R. F. (2016). Non-motor symptoms in Parkinson's disease. *Parkinsonism & related disorders, 22*, S119-S122. https://doi.org/10.1016/j.parkreldis.2015.09.004

Polverino, P., Ajčević, M., Catalan, M., Bertolotti, C., Furlanis, G., Marsich, A., . . . Manganotti, P. (2022). Comprehensive telemedicine solution for remote monitoring of Parkinson's disease patients with orthostatic hypotension during COVID-19 pandemic. *Neurological Sciences, 43*(6), 3479-3487. https://doi.org/10.1007/s10072-022-05972-6

Prell, T., Schaller, D., Perner, C., Witte, O. W., & Grosskreutz, J. (2020). Sicca symptoms in Parkinson's disease: association with other nonmotor symptoms and health-related quality of life. *Parkinson's Disease, 2020*. https://doi.org/10.1155/2020/2958635

Raundale, P., Thosar, C., & Rane, S. (2021). *Prediction of Parkinson's disease and severity of the disease using Machine Learning and Deep Learning algorithm.* Paper presented at the 2021 2nd International Conference for Emerging Technology (INCET). https://doi.org/10.1109/INCET51464.2021.9456292

Shahid, A. H., & Singh, M. P. (2020). A deep learning approach for prediction of Parkinson's disease progression. *Biomedical Engineering Letters, 10*, 227-239. https://doi.org/10.1007/s13534-020-00156-7

Shibata, M., Morita, Y., Shimizu, T., Takahashi, K., & Suzuki, N. (2009). Cardiac parasympathetic dysfunction concurrent with cardiac sympathetic denervation in Parkinson's disease. *Journal of the neurological sciences, 276*(1-2), 79-83. https://doi.org/10.1016/j.jns.2008.09.005

Simon, K. C., Chen, H., Schwarzschild, M., & Ascherio, A. (2007). Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. *Neurology, 69*(17), 1688-1695. https://doi.org/10.1212/01.wnl.0000271883.45010.8a

Skorvanek, M., Martinez-Martin, P., Kovacs, N., Rodriguez-Violante, M., Corvol, J. C., Taba, P., …, Foltynie, T. (2017). Differences in MDS-UPDRS scores based on Hoehn and Yahr stage and disease duration. *Movement disorders clinical practice, 4*(4), 536-544. https://doi.org/10.1002/mdc3.12476

Sood, T., & Khandnor, P. (2019). *Classification of parkinson's disease using various machine learning techniques.* Paper presented at the Advances in Computing and Data Sciences: Third International Conference, ICACDS 2019, Ghaziabad, India, April 12–13, 2019, Revised Selected Papers, Part I 3. https://doi.org/10.1007/978-981-13-9939-8_27

Tsanas, A., Little, M., McSharry, P., & Ramig, L. (2009). Accurate telemonitoring of Parkinson's disease progression by non-invasive speech tests. *Nature Precedings*, 1-1. https://doi.org/10.1038/npre.2009.3920.1

Wan, S., Liang, Y., Zhang, Y., & Guizani, M. (2018). Deep multi-layer perceptron classifier for behavior analysis to estimate Parkinson's disease severity using smartphones. *IEEE Access, 6*, 36825-36833. https://doi.org/10.1109/ACCESS.2018.2851382

Warner, T. T., & Schapira, A. H. (2003). Genetic and environmental factors in the cause of Parkinson's disease. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 53*(S3), S16-S25. https://doi.org/10.1001/archneur.1969.00480160015001

Yahr, M. D., Duvoisin, R. C., Schear, M. J., Barrett, R. E., & Hoehn, M. M. (1969). Treatment of parkinsonism with levodopa. *Archives of neurology, 21*(4), 343-354. https://doi.org/10.1001/archneur.1969.00480160015001