Machine Learning Methods for Optimal Prediction of Outcome in Parkinson's Disease

M. R. Salmanpour, M. Shamsaei, A. Saberi, S. Setayeshi, E. Taherinezhad, I. S. Klyuzhin, J. Tang, V. Sossi, A. Rahmim

ABSTRACT-In the present work, we systematically probe a range of predictor machines (11 machines), and aim to find the best combinations of features to result in improvements in prediction of outcome in PD. First, we created 32 combinations of 18 conventional features experimentally and selected 4 arrangements of 204 PD subjects. The combinations were applied to the various predictor machines), thereby absolute error of the best combination reached 4.3 (in prediction of MDS-UPDRS-III motor performance in year 4). This is in comparison to previous works that attained errors of around 9. In second part, subset selector machines were used for selecting the best combinations between all features, and GA and ACO selector machines selected the best combinations, further lowering error when combined with LOLIMOT for prediction. Selected features by GA and ACO (UPDRS I-Year 1, UPDRS III-Year 1, left putamen Uptake-Year 1, Age, Gender) had positive effect on prediction of outcome and mean absolute error reached 4.15. Moreover, other subset selector machines also reached acceptable results; mean absolute errors in some predictor machines were below 4.7. Overall, LOLIMOT was seen as the best predictor machine, and GA and ACO as the best feature subset selector machines. Furthermore, MDS-UPDRS III-years 0 and 1, MDS-UPDRS II- year 1, MDS-UPDRS I- years 0 and 1, age and DAT SPECT putamen as well as caudate uptake - year 1 were seen as most important predictors of outcome.

I. INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder after Alzheimer's disease, affecting over 1% of individuals over the age of 60 [1]. PD is a progressive, degenerative movement disorder, characterized by neuronal loss in the substantia nigra with the loss of dopaminergic terminals in the basal ganglia [2,3,4]. It is characterized by a series of motor and non-motor symptoms such as resting tremor, rigidity, bradykinesia, postural instability and autonomic dysfunction [5]. There is not any proven disease modifying therapies for PD, hence, there is an essential need to establish biomarkers of disease progression is vital [6] e.g. an aim of the Parkinson's Progressive Marker Initiative (PPMI) [7]. Furthermore, there is significant interest in prognostication of disease outcome, to properly adapt and power clinical trial studies, as applied to appropriate patients. Stratification of PD based on expected prognosis would allow better designs of disease modifying trials, with greater power to ascertain efficacy [8,9]. There is increasing research into prediction of outcome in PD [8,10,11,12,13,14] in order to properly adapt and power clinical trial studies of novel disease modifying therapies. An aim is to identify and utilize the most relevant features to predict outcome [15].

In the present work, we aim to utilize longitudinal information for improved prediction of outcome as well as identification of optimal combinations of features. We aim to predict motor assessment (MDS-UPDRS-III) at year 4 from data at baseline (year 0) and year 1, by optimal combination of machine learning methods, including static machines, dynamics machines and subset-selector machines [16].

II. MATERIALS AND METHODS

Data were extracted from the PPMI database (www.ppmi-info.org/data) [17]. The movement disorder society unified Parkinson's disease rating scale (MDS-UPDRS) – part III (motor) in year 4 was used as outcome. We considered 18 features as predictors: (1-6) MDS-UPDRS, parts I, II and III in year 0 and 1, (7-8) demographics (age, sex), (9-16) DAT SPECT images (putamen as well as caudate uptake, both left and right) in years 0 and 1, and (17-18) disease duration (DD), taken with respect to time of diagnosis (DD-diag.) as well as time of appearance of symptoms (DD-sympt.). For consistency, we only included patients that were off drug. These selection criteria resulted in 204 PD subjects (149 males, 55 females; average age in year 67.58±10.03, range [39, 91]), with widely distributed year 4 outcome UPDRS-III: 31.4±10.6; range [8,77]. For better consistency, MDS-UPDRS scores were averaged if within ±6 months.

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M. R. Salmanpour is with Amirkabir University of Technology (Tehran Polytechnic), Iran (e-mail: m.salmanpoor66@gmail.com, mohamad91@aut.ac.ir).

M. Shamsaei is with Amirkabir University of Technology (Tehran Polytechnic), Iran (e-mail: pysham@aut.ac.ir).

S. Setayeshi is with Amirkabir University of Technology (Tehran Polytechnic), Iran (e-mail: setayesh@aut.ac.ir).

A. Saberi is with Central Tehran Branch, Islamic Azad University, Iran (e-mail: saberimanesh62@gmail.com).

E. Taherinezhad is with Kharazmi University, Tehran, Iran (e-mail: elahefereshte20@gmail.com).

Ivan S. Klyuzhin is with the University of British Columbia, Vancouver, Canada (e-mail: ivansk@physics.ubc.ca).

J. Tang is with Oakland University, Rochester, USA. (e-mail: jingtang@gmail.com).

V. Sossi is with the University of British Columbia, Vancouver, Canada (e-mail: vesna@phas.ubc.ca).

A. Rahmim is with the University of British Columbia, Vancouver, Canada (e-mail: arman.rahmim@ubc.ca).

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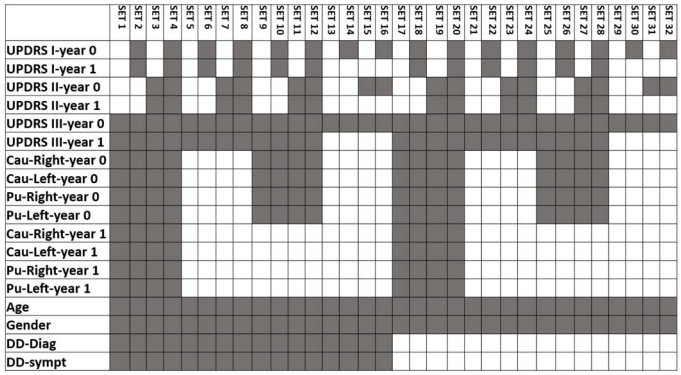
To derive optimal feature combinations, we pursue two approaches, as elaborated next.

A. Making the combinations manually

First, 32 combinations of the 18 features were experimentally created (Table 1), and each combination was assessed using different predictor machines. In this work, a range of predictor algorithms were selected amongst various families of learner and regressor algorithms including: 1) LOLIMOT (Local Linear Model Trees) [18,19], 2) RBF (Radial Basis Functions) [20], 3) MLP-BP (Multilayer perceptron-Backpropagation) [21,22], 4) LASSOLARs (Least Absolute Shrinkage and Selection Operator- Least Angle Regression) [23,24], 5) Random Forest Algorithm [25,26], 6) RNN (Recurrent Neural Network) [27,28,29], 7) BRR (Bayesian Ridge Regression) [30,31], 8) DTC (Decision Tree Classification) [32,33], 9) PAR (Passive Aggressive Regressor) [34,35,43], 10) Thiel-Sen Regressor [36,37,38,39], and 11) ANFIS (Adaptive neuro fuzzy inference system) [40,44].

Overall, 65% of all data were used for training, 5% for validation and 30% for testing. Four different randomized arrangements of the original data were generated. Thus each combination was run four times in order to train and plot the mean absolute errors and their standard deviation. Q-learning (a reinforcement learning technique) was used in most machines so that machine parameters were automatically optimized [45].

Table 1. various combinations between eighteen features



B. Selecting features through feature selector machines

Alternatively, we used systematic feature selection prior to prediction. Specifically, 6 subset selector machines were employed and assessed. All machines aimed to minimize error by selecting the best combination, while NSGAII also aimed to reduce number of features in the set. The machines used for feature subset selection were: 1) GA (Genetic Algorithm) [46,47], 2) ACO (Ant Colony Optimization algorithm) [48,49], 3) PSO (Particle Swarm Optimization algorithm) [50,51], 4) SA (Simulated Annealing) [52,53], and 5) DE (Differential Evolution algorithm) [54,55], and 6) NSGAII (Nondominated sorting genetic algorithm) [56,57].

Subsequently, the selected features were tested on the 11 predictor machines.

III. RESULTS AND DISCUSSION

In our first efforts (A), 32 manual combinations were experimentally created and were applied to the predictor machines. Results are shown in Fig. 1 (ANFIS was excluded for use as predictor machine because it is appropriate for combinations with lower number of features). As shown in Fig. 1, LOLIMOT resulted in best performance over a wide range of combinations. The best results for LOLIMOT were achieved for sets 18, 21 and 22, and some machines also reached similar results for those sets, but were less consistent when including other range of features. Overall, in prediction of year 4 MDS-UPDRS-III (outcome range [8-77]), absolute errors as low as 4.32 were achieved. Such prediction performance far exceeds results in other prior works where absolute errors of the order of 9 were obtained when using similar features [8]. Best results were observed when features MDS-UPDRS I (year 0 and 1), MDS-UPDRS-III (years 0 and 1), putamen as well as caudate uptake (both left and right; years 0 and 1), age and gender were in the sets. Conventional DAT SPECT images were seen to have some (but not large) effect. Some combinations such as sets 1, 3, 6, 7, 8, 19, 20, 23 and 24 also had good results, although they were less consistent than sets 18, 21 and 22.

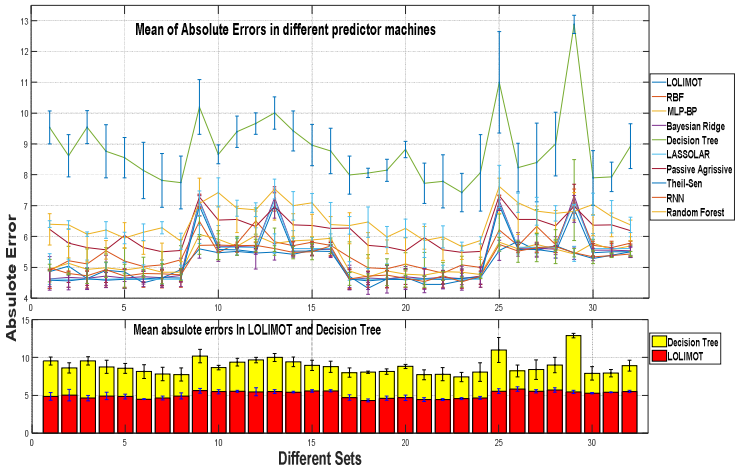


Fig. 1. (Top) Absolute errors in prediction of outcome from 10 predictor machines, each from 32 combinations shown in Table 1. ANFIS was excluded from results due to significantly poorer performance. (Bottom) Amongst the 10 machines, the best and worst performers are shown as bar plots.

Fig. 2 shows one of fitting curves of LOLIMOT results (one of 4 arrangements) where the Y axis is the predicted outcome and X axis reflects the true outcome. Overall, LOLIMOT was seen as the best predictor machine.

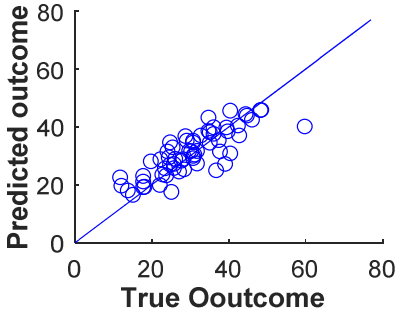


Fig. 2. Plot of outcome prediction from LOLIMOT making use of features in set 18.

In the second set of our efforts (B), we utilized preprocessing, using 6 feature subset selector algorithms. The features selected through these different machines are shown in Table 2.

Table 2. Selected features via different subset selector machines

Selectors	Feature 1	Feature 2	Feature 3	Feature 4	Feature 5
GA	UPDRS I-Year one	UPDRS III-Year one	Left putamen uptake-Year one	Age	Gender
ACO	UPDRSI-Year one	UPDRSIII-Year one	Left putamen uptake-Year one	Age	Gender
PSO	UPDRSII-year zero	UPDRSIII-Year one	Left putamen uptake-Year one	DD-diag	Gender
SA	UPDRSII-year zero	UPDRSIII-Year one	Left putamen uptake-year zero	DD-diag	Gender
DE	UPDRSII-year zero	UPDRSIII-Year one	Left putamen uptake-Year one	DD-diag	Gender
NSGAII	UPDRS II- year zero	UPDRS III-year one	Age	Gender	----------

These featured combinations selected via the selector machines were then applied to the 11 predictor machines as mentioned in Sec. II-A. The results are plotted in Fig. 3. Features selected by subset feature selector machines enabled slightly better results than obtained in the previous section. Most subset feature selector machines selected combinations leading to prediction errors less than 5.

The performances were best for features selected by GA and ACO (UPDRS I-Year one, UPDRS III-Year one, Left putamen uptake -Year one, Age, Gender). In the case of LOLIMOT predictor machine, lowest mean absolute error of 4.15 was reached, though other machines such as LASSOLAR, Bayesian Ridge, Theil Sen Regressor and RNN also performed well. Plot of the results of GA and ACO as applied to LOLITMOT are shown in Fig. 4. Overall, GA and ACO were seen to perform as best feature subset selector machines.

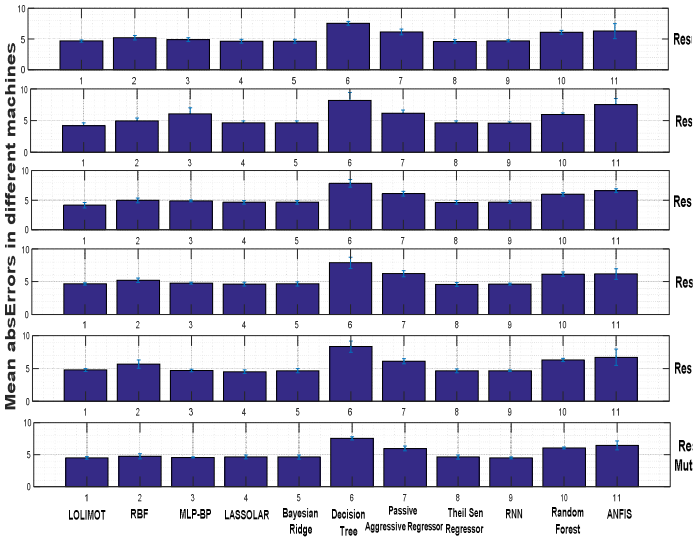


Fig. 3. 11 predictor machines applied to features selected by 6 selector machines.

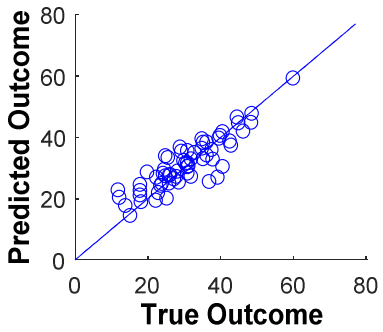


Fig. 4. Plot of outcome prediction by LOLIMOT with features selected by GA or ACO.

Importantly, we saw that not using imaging information lowers performance to around 4.5 (in prediction error), which is likely not a clinically significant degradation. In our other investigations we also found that conventional imaging measures do not correlate well with clinical measures [58] nor improve prediction [8]. However, radiomics analysis of DAT SPECT images, going beyond conventional imaging measures, was seen to provide significant improvements in both tasks. Further, in our recent ongoing efforts involving deep learning based prediction of outcome [59,60], significant improvements were observed, involving implicit discovery of patterns in images. In other words, our present research indicates that there is a need to move beyond conventional imaging metrics for improved prediction of outcome.

IV. CONCLUSIONS

This work explored a range of predictor machines and also aimed to find the best combinations of features to result in improvements in prediction of outcome in PD. Overall, we demonstrated that for our patient studies, absolute errors of the order of ~ 4 could be reached in prediction of motor outcome (UPDRS-III), in comparison to prior works reaching errors of the error of 9 when using readily available features, underlining the importance of optimization (e.g. using Q learning and appropriate feature selection as pursued in this work).

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