Exploring Diagnostic Models of Parkinson's Disease with Multi-Objective Regression

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***Abstract*—Parkinson's disease is a prevalent condition, and is becoming a significant social and economic problem in countries with aging populations. An important issue is the ability to provide an accurate diagnosis and prognosis for Parkinson's sufferers, a disease that is only partially understood, and for which there are few expert practitioners relative to the size of the patient population. In this work, we explore the potential for using objective, automated methods based around a simple figure copying exercise administered on a graphics tablet. In particular, we use a multi-objective evolutionary algorithm to explore a space of regression models, where each model represents a combination of features extracted from a patient's digitised drawing. The objectives are to accurately predict clinical measures of the patient's motor and cognitive deficit. Our results show that both of these can be predicted, to a degree, and that certain sub-sets of features are particularly relevant in each case.**

I. Introduction

In this work we investigate and describe the use of multi-objective evolutionary techniques to explore predictive models that can differentiate individuals that suffer from Parkinson's disease (PD) from healthy controls. Each subject was asked to trace a pre-defined shape using a digitising tablet. Various features were then extracted from the digitised drawings, and a multi-objective evolutionary algorithm (MOEA) was used to explore the space of linear and non-linear regression expressions in order to identify combinations of features that are predictive of clinical measures. We focus on two target measures: UPDRS, which is a measure of motor dysfunction in PD, and MoCA, which is a measure of cognitive decline in both PD and other neurodegenerative conditions. Motor aspects of PD are well recognised; however, cognitive aspects are becoming an increasingly important area of research [1], [2]. Many patients will experience cognitive decline during the course of the disease, and some will develop full-blown dementia akin to Alzheimer's disease. It is important to be able to measure the degree of deficit in both motor and cognitive ability in order to target treatment and to provide an informed prognosis. It is also desirable to increase general understanding of how to accurately diagnose PD, given that some estimates place the misdiagnosis rate at 25% [3].

This paper is organised as follows: Section II gives a brief introduction to PD and its clinical assessment. Section III reviews related work. Section IV summarises the materials and methods used in this work. Section V presents results. Section VI concludes.

II. Parkinson's Disease

PD is a neurodegenerative condition, meaning that sufferers experience a loss of neurones over the course of time. PD particularly affects neurones that produce dopamine (the neurotransmitter required for movement) and hence the disease initially presents as a movement disorder in most cases. However, it also affects neurones more generally, and in many cases patients will also experience a decline in their cognitive abilities. Medical understanding of PD is incomplete [4]; for instance, its underlying cause is still unknown, and curative therapies are not yet available. Indeed, it is possible that PD is not one but many diseases with overlapping symptoms. PD is often split into sub-categories. In this paper, we consider ideopathic PD, where there is no known cause and a patient presents with motor symptoms, PD with dementia (PDD), where a patient develops full-blown dementia, and PD with mild cognitive impairment (PD-MCI) where a patient may or may not go on to develop dementia.

Accurate diagnosis of PD can be challenging, particularly amongst non-specialists where high misdiagnosis rates have been reported [3], [5]. The current clinical standard for diagnosis involves a review of a patient's history, followed by administration of standardised tests such as the Unified

Parkinson's Disease Rating Scale (UPDRS). The motor section of the UPDRS, in particular, is commonly used to follow the progression of a patient's symptoms, and involves a clinician filling in a multiple-choice form based upon observation of a patient's abilities during clinical examination. This process is known to be subjective, with considerable variance amongst clinicians [6]. It is also labour intensive, which is problematic given the poor availability of PD specialists in many countries [7]. This motivates our focus on objective tests that can provide accurate measures of a patient's motor and cognitive deficit, yet be administered simply and cost-effectively in a primary care setting.

III. Related Work

Figure copying tests, such as clock drawing [8] and the Rey-Osterrieth complex figure [9], have long been used in the assessment of cognitive deficit in neurodegenerative conditions. In most cases, a patient's drawing is assessed by a clinician using a standardised procedure that considers, for example, the placement and sizing of different figure elements. Automating this process is challenging, given that a patient's drawing may be quite different from the original template [10]. Nevertheless, there has been some success. Notably, Souillard-Mander et al. [11] used machine learning techniques to analyse the elements of digitised clock drawings, achieving reasonable discrimination between PD patients and age-matched controls.

A more effective approach may be to use figures that are amenable to computational analysis. An example of this is our previous work with the pentagon spiral figure, a relatively simple drawing template that is nevertheless designed to amplify the clinical symptoms of PD (if present) by requiring the subject to repeatedly accelerate and decelerate. We have previously had some success with applying evolutionary algorithms to these recordings, by using them to train classifiers that respond to over-represented patterns of acceleration [12]. However, a limitation of this approach is interpretability, since it is challenging to understand how these evolved classifiers reach a decision. This is important, since a classifier can only be useful as a decision support tool if a clinician has confidence in the basis of its decision.

The idea of automated, objective diagnosis for PD has also been explored in the context of voice signals. For instance, Tsanas et al. [13] recorded the speech of a number of PD patients and control subjects. They, and others, have since used various machine learning algorithms to build predictive models that discriminate between the vocal patterns of PD patients and controls. However, this system is yet to be used in practice, perhaps due to the relatively small number of recordings in the corpus and the frequent use of black box models.

In this work, we are not aiming to generate a specific predictive model. Rather, we are using MOEAs to explore a space of models, with the intention that these models will be used to inform diagnosis and prognosis of PD more generally. As such, we focus on relatively simple regression models which are interpretable and also widely understood by clinicians. The results reported in this paper build upon an earlier feasibility study [14].

IV. Materials & Methods

A. Pentagon Spiral Figure

Following [12], we used the pentagon spiral figure (see Fig. 1a) as a means of capturing information about a subject's physiological state. This figure copying task involves a subject repeatedly copying a pentagon shape whilst moving steadily outwards from a central point. Repeated movements are known to cause fatigue in PD patients, and continual acceleration and deceleration emphasises the presence of bradykinesia, a general slowing of movement whose presence is one of the cardinal signs considered in clinical assessment of PD. As well as providing a measure of motor dysfunction, the pentagon spiral figure also tests a subject's visuospatial abilities. The decline of this faculty is closely associated with cognitive variants of PD.

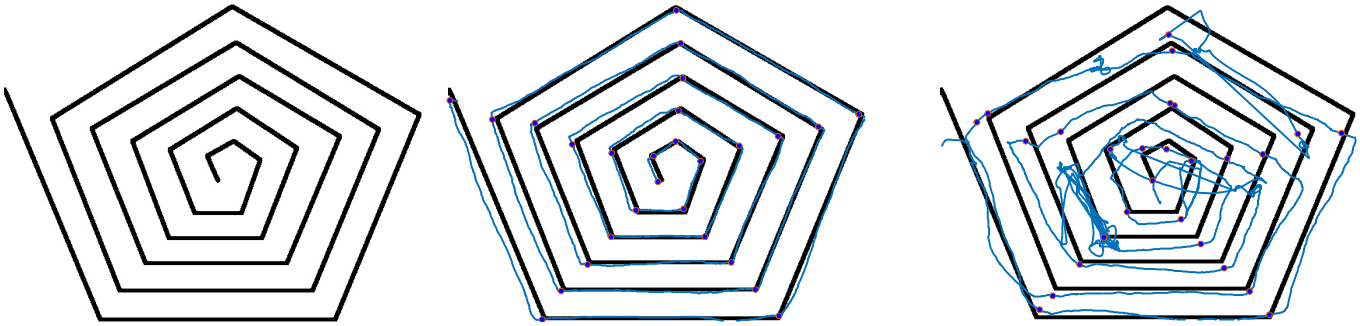
B. Assessment Scores

We use two clinical assessment scores in this work: the motor section of the Movement Disorder Society sponsored revision of the UPDRS [15] and the Montreal Cognitive Assessment [16], [17], or MoCA, which measures cognitive ability. Both are composite scores that result from a series of tasks and observations administered by a clinician, each of which is scored separately. UPDRS scores have a composite value between between 0 and 132, with higher scores indicating motor dysfunction. Composite MoCA scores are ranged between 0 and 30, with lower scores indicating cognitive dysfunction. MoCA scores below 26 are an indication of clinically-significant cognitive impairment, though extra assessments are required to reach a diagnosis of PD-MCI or PDD.

C. Data Collection

After obtaining full ethical approval, 58 PD patients and 29 age-matched healthy controls were recruited at the Leeds General Infirmary. Each subject first underwent a standard clinical assessment, during which their UPDRS and MoCA scores were calculated. Of the PD patients, 22 were assessed as having normal cognition (labelled PD), 26 had impaired cognition (PD-MCI) and 10 had dementia (PDD). Of the controls, 19 had normal cognition, and 10 had impaired cognition (MoCA$<$ 26).

The subjects were then asked to trace over a template of the pentagon spiral figure on an A4-sized Wacom digitising tablet using an inking stylus. As they carried out the drawing, their movements were digitised and stored to a disk file as a time series of $< x, y >$ coordinates, alongside associated pen pressure and orientation information (not currently used in this study). The sampling frequency of the tablet was set at 200Hz. Each subject was asked to repeat the tracing process three times using their dominant and non-dominant hands in turn.



(a) The drawing template

(b) Example of a control subject's spiral pentagon drawing overlaid on the template

(c) In this case, the concentric lines of the pentagon and the corners are challenging to distinguish

Fig. 1: The pentagon spiral figure. On the left is the template presented to a subject. The other two images show digitised recordings by study subjects overlaid on the template: the first from a control, the second a difficult case from a patient.

D. Feature Extraction

Table I summarises the list of features that were retrieved from each drawing. These features were all selected in consultation with PD experts, taking into account the PD literature and insights from other standard clinical tests like finger tapping, studies on grasp control and the gold standard clinical definition of bradykinesia.

Most of the features, with the exception of 1 and 2, were extracted automatically from the tablet recordings with the use of a set of custom-written Matlab scripts. The data extraction started with the automatic alignment of each drawing with respect to the template (Fig. 1a), focusing especially on finding the corners with the use of the minimum eigenvalue method [18]. In some cases the proper assignment of corners was problematic even if the task was done manually (see Fig. 1c), and this is likely to introduce some error during feature extraction.

E. Polynomial Regression

Regression modelling is one of the most widely used tools for classification of samples and feature selection. The method allows the identification of statistical associations and causal relationships and may provide greater understanding of the underlying data generating process. In multivariable regression, a single dependent variable that is the outcome is inferred with the use of multiple independent variables or predictors. The formulation of a basic linear regression model can be described as follows:

$$y = \alpha + \beta x + \epsilon \tag{1}$$

where y is the dependent variable, x the independent one, α is the intercept, β is the predictor and ϵ is the error. This model can be extended in order to include more than one predictor. Then it is called multivariable regression modelling:

$$y = \beta_0 + \beta_1 x_1 + \cdots + \beta_n x_n + \epsilon \tag{2}$$

where in this case β_0 is the intercept, $\beta_1 - \beta_n$ is a vector of n predictors, $x_1 - x_n$ a vector of independent variables and ϵ the error.

The model can be additionally enriched to include non-linear relationships in order to improve the capability of

TABLE I: Features extracted from the digitised drawings.

ID	Name	Feature Description
1	dominant	Dominant or non-dominant hand used
2	attempts	Repeat number: between 1 and 3 for each hand
3	totalTime	Total time: time taken to trace the entire figure
4	areaError	Area error: Area between the template pentagon and the pentagon drawn by the patient
5	distance	Total distance travelled by the pen
6	leaveSurface	Times the pen leaves the tablet surface: patients are instructed to not remove the pen from the tablet
7	timeContact	Total time the pen was in contact with the tablet
8	zeroVel	Duration of zero velocity during the whole task
9	zeroAcc	Duration of zero acceleration during the whole task
10	peakVel	Maximum peak velocity
11	avgVel	Average velocity
12	distPeakV	Distance to maximum peak velocity
13	timePeakV	Time to maximum peak velocity
14	timePeakV	Maximum peak acceleration
15	peakDesAcc	Minimum peak deceleration
16	avgAcc	Average acceleration
17	avgDes	Average deceleration
18	timePeakA	Time to maximum peak acceleration
19	timePeakD	Time to minimum peak deceleration
20	distPeakA	Distance to maximum peak acceleration
21	distPeakD	Distance to minimum peak deceleration
22	timeAAbs	Time in acceleration. Absolute
23	timeARel	Time in acceleration. Relative (% of movement time)
24	timeDAbs	Time in deceleration. Absolute
25	timeDRel	Time in deceleration. Relative (% of movement time)
26	totalNumPeaks	Total number of peaks in acceleration-deceleration
27	peakP	Number of peaks until maximum peak
28	peakN	Number of peaks until minimum peak
29	covV	Coefficient of variance (COV) in velocity
30	covA	COV in acceleration
31	covD	COV in deceleration

fitting more complex functions. In such a scenario, the final polynomial expression could be formulated as:

$$y = \beta_0 + \beta_1 x_1^{\theta_1} + \cdots + \beta_n x_n^{\theta_n} + \epsilon \tag{3}$$

where $\theta_1 - \theta_n$ depict the exponents to which the predictors β_i and independent variables x_i are raised.

A general characteristic of regression modelling is that the predictors derived using the final selected structure of the regression model parameters are applied globally over the problem under consideration assuming spatial non-stationarity. This could be the major limitation of the technique if local differences among areas of the study are significant.

This work uses a conventional ordinary least squared (OLS) regression analysis. This is a typical metric applied to linear regression problems to assess the suitability of a model. The calculation can be mathematically defined as follows:

$$a = \arg\min_{a} \sum_{j=1}^{n} \Big(y_j - F(x_j) \Big)^2 \tag{4}$$

where y_j is the final score or dependent variable for the i-th training example, x_j is the predictor for the same training example over the model and n is the total number of samples.

F. Pareto Archived Evolution Strategy

Multi-objective optimisation is an active research area, with many options available for algorithm design. The available techniques mainly differ in the details of the selection operator, which determines why one solution is chosen rather than another to be a progenitor of new candidate solutions. While this step is a relatively straightforward decision in single-objective optimisation, the area of multi-objective optimisation is essentially defined in terms of precisely how this process is handled.

Reflecting the variance and complexity of real-world applications, no single MOEA design approach has emerged as dominant in the field. However there is a subset of commonly used MOEAs that tend to perform well across the board. We make the pragmatic decision to choose the Pareto Archived Evolution Strategy (PAES) [19] from this commonly used subset, in part because the application in this paper is relatively compute-intensive, and PAES tends to perform well in terms of the speed/performance trade-off, in part due to its maintenance of a small population of solutions.

The disadvantage of a small population is the lack of diversity, which may lead to premature convergence to a local optimum. To avoid this, the algorithm was run multiple times using the same problem configuration, with the archive of best solutions shared and modified among these executions.

G. Model Training

A regression learning procedure aims at searching for the best set of parameters that fits a determined real function. In cases where a polynomial structure is required to capture the essence of a non-linear system, the selection of the degrees of each term that form the polynomial normally relies on a personal decision. Since this is a crucial feature which influences the effectiveness of the function approximation, a more systematic approach should be considered.

In this regard, the traditional Anderson's procedure [20] proposes the discovery of the optimum degree in a polynomial regression by testing in sequence the entire set of coefficients from its maximum boundary to 0. However, if the system under consideration is known to be non-linear and highly complex, or characterised by a significant number of possible features, an exhaustive search of all plausible combinations quickly becomes infeasible.

Algorithm 1 PAES algorithm

```
Require: Max_iter
  Generate int_sol and set it as Current_sol
  Evaluate fitness values of the Current_sol
  Add Current_sol to archive
  for i = 1 To Max_Iter do
    Randomly select one factor to mutate (power, feature);
    Generate new_sol by mutating Current_sol;
    Evaluate fitness values of the New_sol
    if New_sol dominates Current_sol then
      Set New_sol as Current_sol
      Update archive
    else
      if Current_sol dominates New_sol then
        Discard New_sol
      else  ▷ Current_sol and New_sol do not dominate each other
        Update archive using New_sol
        if New_sol dominates any member of the archive then
          remove them
          add New_sol to archive
        else
          add New_sol to archive
          randomly select a Current_sol among New_sol and Current_sol
        end if
      end if
    end if
  end for
  return Non-dominated solutions
```

An alternative way of discovering the best structure is with the use of metaheuristics like evolutionary algorithms. The use of hybrid methods that merge both technologies were successfully reported in different works [21], [22].

Following this approach, the present work is structured as a two-stage method that searches for a model structure that best fits two scores, UPDRS and MoCA. These scores are conflictive in nature due their applicability to different symptomatology areas of Parkinson's disease, cognitive and motor deficit.

By wrapping both a weighted polynomial regression analysis and the conventional OLS that pursues the minimisation of

a given cost function which computes the difference between the scores and the result of the polynomial solution, the EA approach can provide a successful model to select the most relevant set of features for both aspects of the disease. In this regard, the EA is intended to estimate not only the most significant set of parameters, but also the best structure within the polynomial expression.

In this case this minimisation is multi-objective $(\mathcal{F}_1(x), \mathcal{F}_2(x)) = \mathcal{F}(x)$. The set of optimal solutions, also called the Pareto optimal front, is the set of non-dominant solutions where no further Pareto improvements can be made. The objective is to find a Pareto approximation that is located as closer as possible to the true Pareto front.

The starting point of the process will be the execution of the evolutionary algorithm PAES by the random generation of a single individual solution. This solution, also called a chromosome, represents a model composed by a subset of features each linked with a corresponding degree with a polynomial structure. A polynomial can be defined as an expression consisting of variables and coefficients. Consequently the formal chromosome representation can be characterised by two different vectors represented as follows:

$$f = (f_1, f_2 \ldots, f_8), f_i \in \{1 - 31\} \tag{5}$$

$$a = (a_1, a_2 \ldots, a_8), a_i \in \{1 - 6\} \tag{6}$$

where f is a vector of features and a denotes the vector of exponents/powers of the predictors. If a polynomial evolves to an expression that contains like terms, which means the same features with the same exponent, these terms are not combined.

Every time the algorithm finds a good non-dominated solution, this solution is stored in a repository, called an archive, that for our purpose is defined with unlimited size. The archive represents the current approximation of the Pareto front. For each execution of the algorithm, the candidate solution is evolved for 400 generations using selection and mutation operators.

Mutation is defined twofold. Firstly it can be aimed at producing a disturbance in the exponent value of a single term. This type of mutation has the capability of adding and removing terms in the equation. Secondly the mutation can be intended to modify the feature selected within this formula. Features can be repeated within an equation.

The algorithm is executed for each exponent a number of times until achieving five consecutive runs without finding a new non-dominated solution. These executions cover all the range of exponents investigated in this work. Finally the algorithm returns the solutions allocated in the archive with the best prediction using the root-mean-square metric.

H. Model Validation

In order to assess the adequacy of a given model and to avoid overfitting this work uses a division of the data into three subsets: a training and validation set that are used to fit each individual optimisation execution, and a hold-out test that is used to measure the generalization error of the final model [23]. Concretely, from the 50 subjects in the dataset, 35 of them are used to train the regression model, and 15 are assigned to the hold-out set used for testing.

V. Results

One wide-spread method used in the multi-objective community to evaluate the performance of the evolutionary algorithm is the hypervolume indicator [24]. This indicator allows the transformation of the problem into a single objective by mapping a set of points into a scalar. This scalar is the result of calculating the volume covered by the approximation of the Pareto front $P \subset \mathbb{R}^d$ and a reference set $R \subset \mathbb{R}^2$. In this work, the dimension of the multi-objective problem is $d = 2$ and the reference set is formed by two points called utopia and anti-utopia $r_u, r_a \subset \mathbb{R}^2, R = \{r_u, r_a\}$. The calculation of the hypervolume is formalised as follows:

$$I(H)_A := \lambda(H(P, R)) \tag{7}$$

where H represents the set of objective vectors that are enclosed in this front and λ depicts the Lebesgue measure.

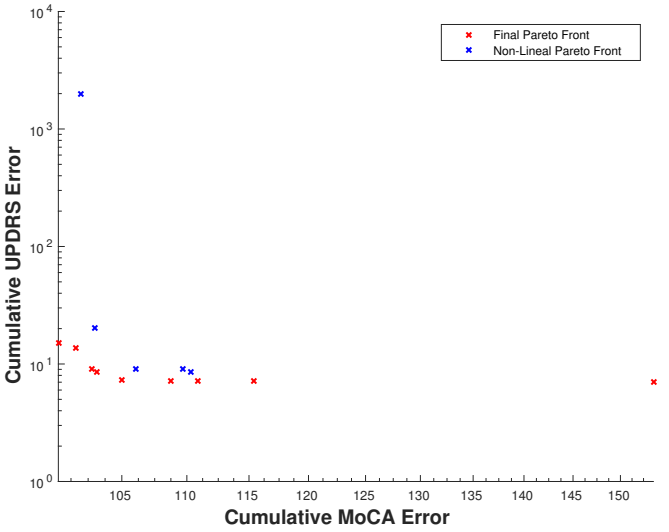


Fig. 2: The set of the non-dominated solutions. Red points show the solutions of the Pareto front, and blue points show the best non-linear regression models. For visualisation purposes, UPDRS errors are shown on a logarithmic axis.

The model training process was repeated for maximum regression exponents from 1 (linear models) to 5. Fig. 2 shows both the overall Pareto front and the front comprised of non-linear models (i.e. those containing exponents greater than 1), showing that the Pareto front is comprised exclusively of linear models. This is further highlighted in Fig. 3, depicting the hypervolumes achieved when using models of different complexity, and showing that runs where only linear models were evolved achieved the highest accuracy. This is perhaps surprising, given the limited expressiveness of linear regression

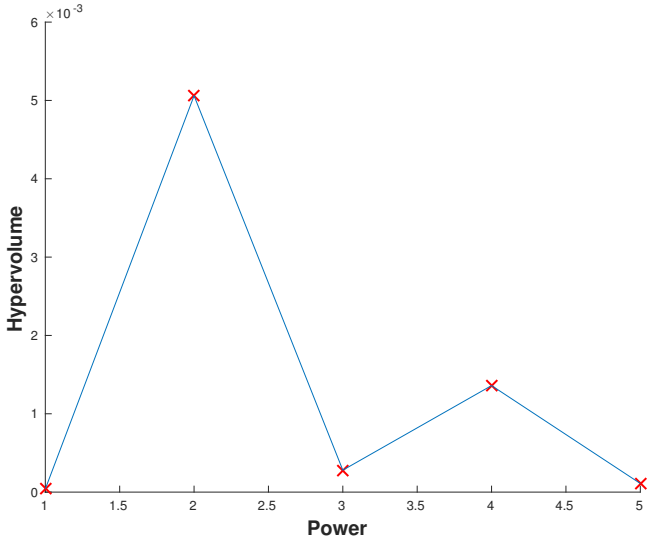


Fig. 3: The relationship between the performance of the MOEA, calculated by means of the hypervolume, and the maximum exponent allowed in the construction of the polynomial regression models.

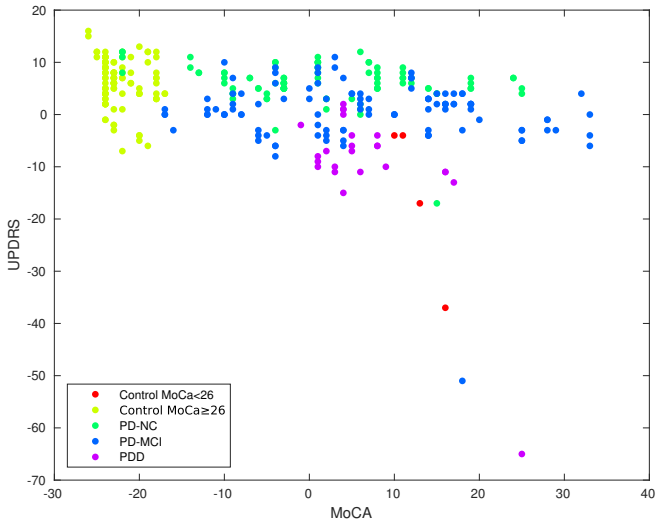


Fig. 4: Visual representation of the residuals resulted from taking the best model found for each of the scores, UPDRS and MoCA, in the archive of best solutions. The scatter plot illustrates regression errors from each subject where colours represent different cognitive conditions that are used to classify the disease: patients without cognitive impairment (PD-NC), mild cognitive impairment (PD-MCI) and patients with dementia (PDD).

models. However, more complex models (i.e. polynomial models in this case) are more likely to overfit data, and this effect is likely to be more pronounced when using a small data set. The instability of higher order solutions is reflected in the non-linear Pareto front, which is relatively sparse, presumably because many solutions decreased in fitness when re-evaluated on the hold-out set. The linear front, by comparison, maintains a reasonable spread of solutions.

Although the regression errors (see Fig. 2) are similar for UPDRS and MoCA, both < 10 on average, when taking into account the MoCA range the errors on this cognitive score are comparatively larger. This may suggest that motor deficit is easier to predict than cognitive deficit. It may also be the case that the drawings contains less cognitive information than motor information, or that MoCA is a less reliable regression target (since clinical scores are subjective and liable to different error rates). Nevertheless, it is apparent from Fig. 4 (which shows the per-subject error rates) that error rates are not uniform across the cohorts. For example, the UPDRS error rate for PDD patients is relatively low. For cognitively-normal controls, UPDRS scores are consistently under-predicted. This may be a limitation of using linear models, since the UPDRS scores for this cohort are much higher than the other cohorts and may be outside the range of the predictor.

Table II and III describe the solutions in the Pareto front. As noted, these are all linear solutions (hence powers of 1 for each feature). It is notable that the solutions include only a subset of the available features, and each has only a small number of terms. Again, this may be required to avoid over-learning in a small data set. However, it is quite advantageous from an interpretability perspective.

The features that are used across all solutions (including both the UPDRS and MoCA ends of the Pareto front) are the area error (f_4), the average rate of deceleration (f_{17}) and the percentage of time spent in deceleration (f_{25}). The use of area error is unsurprising, since the accuracy of the drawing would expect to be lessened with either motor or cognitive impairment. The importance of deceleration is more interesting, and may relate to a recent observation that deceleration and acceleration are not coordinated by the same brain region [25]. Hence, it is possible that PD particularly effects the brain region responsible for control of deceleration, and this could be a potential biomarker. The importance of observing deceleration during diagnosis also reflects our previous work on analysing finger tapping in PD patients, where we identified the closing deceleration of a tap cycle of particularly discriminative between PD patients and controls [26].

The predictors for MoCA additionally make use of the following features: the distance or time along a side until peak deceleration or acceleration (f_{19}, f_{20} and f_{21}), the number of peaks along a side until the peak acceleration on that side (f_{27}), and (to a lesser extent) the duration of time spent at zero acceleration (f_9). This suggests that the presence of multiple bursts of acceleration may particularly be an indicator of cognitive dysfunction. This may further relate to the problem of under-scaling of movements seen in many PD patients, where a subject under-estimates the amount of acceleration required to reach a target (in this case a corner) and consequently must perform further accelerations to compensate. It is quite

	Power	MoCA	UPDRS	Features	Powers
1	1	102.763	9.044	4,9,25,4,21	1,1,1,1,1
2	1	110.893	7.202	17,4	1,1
3	1	100.339	15.005	17,4,27,19	1,1,1,1
4	1	153.575	7.055	17,4,29	1,1,1
5	1	105.010	7.247	25,25,25	1,1,1
6	1	103.129	8.520	25,25	1,1
7	1	115.359	7.106	25	1
8	1	101.589	13.735	20,25	1,1
9	1	108.737	7.216	30,25	1,1

TABLE II: Content of the archive with the non-dominated polynomial regression models gathered from all the sub-archives generated by the different exponents. These solutions constitute the Pareto front approximation. Columns of the table show maximum power/exponent of the polynomial, residual errors for both scores (UPDRS and MoCA), features selected and powers of the corresponding terms.

	Weights UPDRS	Weights MoCA
1	24.219,-0.778,0.098,-0.415,0.195,-0.166	21.329,4.722,3.079,1.505,1.386,1.480
2	24.219,-0.765,-0.225,0.181	21.329,2.915,-3.742,0.937,1.386
3	24.219,-0.790,-0.852,0.181,0.195,-0.162	21.329,3.033,4.864,0.937,1.386,1.516
4	24.219,-0.805,-0.870,0.181,0.195,-0.162	21.329,3.161,5.356,0.937,1.386,1.516
5	24.219,-0.127,-0.137,-0.169	21.329,1.760,1.397,3.494
6	24.219,-0.162,-0.169	21.329,1.397,3.494
7	24.219,-0.143	21.329,1.397
8	24.219,-0.132,-0.169	21.329,1.397,3.487
9	24.219,-0.137,-0.172	21.329,1.286,3.345

TABLE III: The weights of each polynomial depicted in II. During evaluation, each polynomial is fitted separately to each regression target, hence two sets of weights are shown.

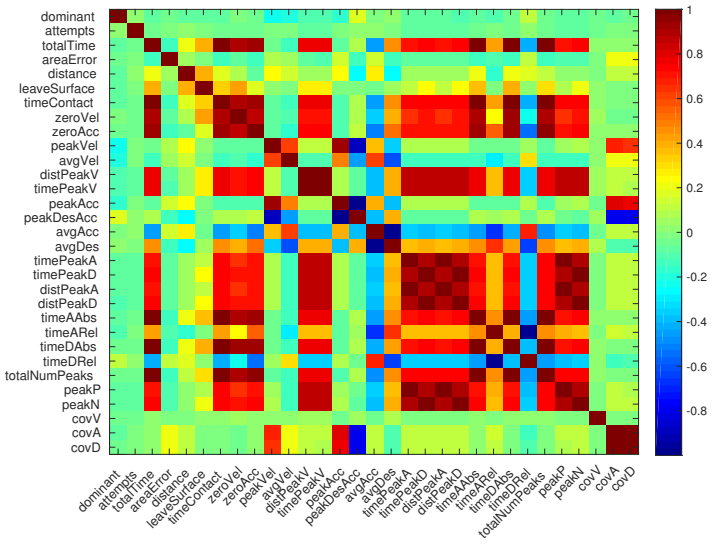


Fig. 5: Visualisation of the Pearson correlation matrix between the extracted features. Positive correlations are displayed in red and negative correlations are shown in blue. Colour intensity is proportional to the correlation coefficients.

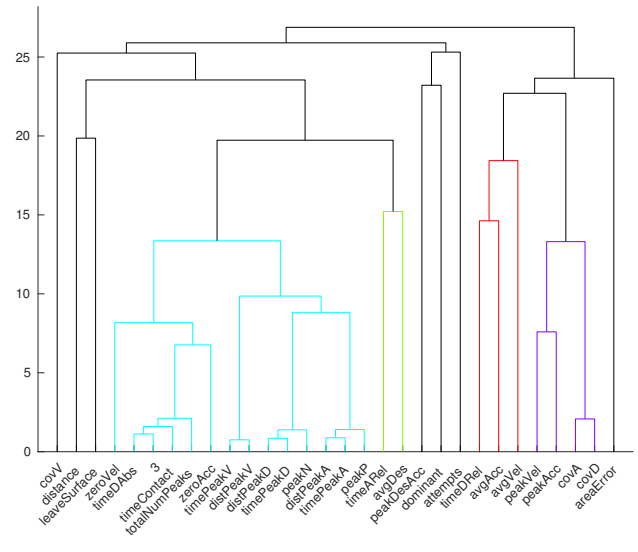


Fig. 6: Clustering dendrogram showing how the different extracted features relate to one another. Smaller distances (y axis) indicate closer relationships. Colours are used to cluster groups of features with significant mutual relationships.

plausible that this behaviour is over-represented in patients with cognitive variants of the disease.

Figs. 5 and 6 depict more general relationships observed between the features, based upon correlation analysis and clustering of the correlation matrix. It can be seen that the 'core' features selected for both motor and cognitive predictors are not correlated with each other. However, the additional features considered in the cognitive predictors are all correlated, and found within the blue cluster marked on the clustering dendrogram. Consequently, the features found in this cluster may all be considered useful indicators of cognitive decline. Some areas of the feature space do not appear to be useful for building predictors: for instance the total distance travelled and

the number of times the subject lifts the pen whilst drawing.

VI. Conclusions

This study aims to use multi-objective evolutionary techniques to explore the space of diagnostic models associated with Parkinson's disease. In this paper, we applied this approach to studying predictive regression models that capture a patient's degree of motor and cognitive dysfunction. Our results suggest that clinical measures of motor and cognitive decline can be predicted, although to varying degree within different patient sub-populations. Analysis of the resulting Pareto front of solutions is informative, suggesting that patterns of deceleration are particularly diagnostically significant. In addition, the presence of multiple bursts of acceleration may be especially significant for predicting cognitive dysfunction. From a modelling perspective, linear models appear to be more predictive, though this may be an indication of their relative stability on small data sets in comparison to polynomial models.

In future work, we aim to look at a wider range of diagnostic objectives, for example the ability to predict the disease in its early stages. It would also be interesting to look at different kinds of predictive model, for example regression trees. More work is also required to fully understand the medical significance of our findings.

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