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Abstract. Parkinson's Disease (PD) is a chronic and progressive illness that affects hundreds of thousands of people worldwide. Although it is quite easy to identify someone affected by PD when the illness shows itself (e.g. tremors, slowness of movement and freezing-of-gait), most works have focused on studying the working mechanism of the disease in its very early stages. In such cases, drugs can be administered in order to increase the quality of life of the patients. Since the beginning, it is well-known that PD patients feature the micrography, which is related to muscle rigidity and tremors. As such, most exams to detect Parkinson's Disease make use of handwritten assessment tools, where the individual is asked to perform some predefined tasks, such as drawing spirals and meanders on a template paper. Later, an expert analyses the drawings in order to classify the progressive of the disease. In this work, we are interested into aiding physicians in such task by means of machine learning techniques, which can learn proper information from digitized versions of the exams, and them recommending a probability of a given individual being affected by PD depending on its handwritten skills. Particularly, we are interested in deep learning techniques (i.e. Convolutional Neural Networks) due to their ability into learning features without human interaction. Additionally, we propose to fine-tune hyper-arameters of such techniques by means of meta-heuristic-based techniques, such as Bat Algorithm, Firefly Algorithm and Particle Swarm Optimization.

Keywords: Convolutional Neural Networks, Parkinson's Disease, Machine Learning, Meta-heuristics

1 Introduction and Motivation

Parkinson's Disease (PD) is a chronic, progressive and neuron-degenerative illness that affects people worldwide. Firstly described by James Parkinson [1] in 1817, PD is often related to the slowness of movement, tremors and muscle stiffness. Other side effects concern changes in speech, writing and the well-known freezing-of-gate. According to the Parkinson's Disease Foundation, approximately $60,000$ Americans are diagnosed with PD [2]. The problem gets worse, since thousands of potential individuals may not be properly diagnosed, or even remain uncovered by exams or any sort of clinical diagnosis.

Computer-assisted PD diagnosis has been the foremost research in the last decades, since mathematical models are more appropriate to detect subtle changes in a number of symptoms related to the disease. As a matter of fact, the main concern is related to the detection of PD first symptoms, i.e. to detect the side effects at the very early stages of the disease, where the treatment can increase the quality of life of a given patient.

Machine learning-driven tools are the most likely approaches to succeed when dealing with automatic diagnosis of Parkinson's Disease, since they can be fed with labeled data for further learning the non-linear mapping between input data and the real diagnosis (ground-truth) given by the expert. In the last years, deep learning techniques (DL), a branch of machine learning research field, have arisen as a powerful tool to help the task of unsupervised feature learning by means of a series of layers that are in charge of extracting different information on each [3]. Convolutional Neural Networks (CNNs) [4], Deep Belief Networks (DBNs) [5], and Deep Boltzmann Machines (DBMs) [6] are among the most used techniques based on deep learning. Given an input image, DL-based approaches aim at performing a series of similar tasks in order to obtain a high-dimensional representation of that input data, which can be further used to feed a supervised pattern classifier.

Therefore, instead of handcrafting features, deep learning techniques can be used to learn proper information about the problem without human intervention. However, in health-related applications, we usually do not have sufficient training samples, where automatic approaches may fail. In such circumstances, we still need the doctor-in-the-loop [7,8]. Another major drawback related to DL techniques concerns their parameters, which can reach hundreds of thousands depending on the complexity of the model. Therefore, the task of finding such parameters can be model as an optimization problem, where the fitness function is the classification error over a training/validating set. Particularly, we are interested in meta-heuristic-based techniques, since they can provide an elegant solution and easy implementations to a number of distinct problems [9].

This work concerns two main contributions: (i) to use CNNs to learn features from handwriting exams in order to aid PD diagnosis, and (ii) to use meta-heuristic-based optimization techniques to fine-tune CNN hyper-parameters. To the best of our knowledge, some of the techniques used in this paper have never been used to optimize CNN parameters to date, such as Bat Algorithm [10], Particle Swarm Optimization [11] and Firefly Algorithm [12]. The reasons for using such techniques concern their swarm-based behaviour, as well as they are considered state-of-the-art techniques in the related field.

1.1 Glossary and Key Terms

Deep learning: a branch of machine learning that aims at studying techniques that learn features in an unsupervised fashion [3].

Convolutional Neural Networks (CNNs): technique composed of a series of layers (e.g. convolution and pooling) that aim at learning specific features on each. Usually, such networks output a high-dimensional feature vector given an input image, which is used to feed a supervised pattern recognition technique [4].

Optimization: it usually refers to the task of finding the minimum/maximum value of a function given some input values (decision variables) [9].

Meta-heuristics: techniques used to solve problems (heuristics) in general. They are often used to handle optimization-oriented problems [9].

Parkinson's Disease: is a chronic, progressive and neuron-degenerative illness, which is often related to the slowness of movement, tremors, muscle stiffness, and the freezing-of-gate [1].

Micrography: usually featured by Parkinson's Disease patients, it concerns the decreasing ability in the writing, which may become smaller as the illness progresses.

Handwritten exam: usually a piece of paper used to assess the handwritten skills of a given individual. Such exam requires the user to perform some predefined tasks, such as drawing spirals, circles and meanders to asses its handwritten skills.

Handwritten trace: drawing done by the patient when performing a handwritten exam.

Handwritten template: template printed out in the form to be completed by the patient.

Bat Algorithm (BA): optimization algorithm based on the behavior of bats when hunting down their preys [10].

Firefly Algorithm (FA): optimization algorithm based on the flashing lighting mechanism of fireflies, which is used for matting partners [12].

Particle Swarm Optimization (PSO): optimization algorithm based on swarms of livings beings [11].

2 State-of-the-Art in Computer-Aided Parkinson's Disease Diagnosis

Spadotto et al. [13] introduced the Optimum-Path Forest (OPF) [14,15] classifier to aid the automatic identification of Parkinson's Disease, and later on the same group of authors proposed an evolutionary-based approach to select the most discriminative set of features that help improving PD recognition rates [16]. The OPF classifier seemed to be a suitable tool, since it is parameterless and easy-to-manage.

Das [17] presented a comparison of multiple classification methods for the diagnosis of PD, among them Neural Networks, and Regression and Decision Trees. Several evaluation methods were employed to calculate the performance of that classifiers, being the experiments conducted in a dataset composed of a range of biomedical voice measurements from 31 people, in which 23 diagnosed with Parkinson's disease. The best results were obtained by Neural Networks (around 92.9% of PD recognition rate). In 2014, Weber et al. [18] used a biometric pen together with Support Vector Machines to learn handwritten dynamics from PD patients.

In the work conducted by Zhao et al. [19], five patients and seven healthy individuals were used to recognize Parkinson's disease by means of the voice analysis. In order to fulfil this purpose, the individuals' voice were recorded using an Isomax EarSet E60P5L microphone, being the recording sessions lasting around 25 minutes each, and a total of 50 pre-recorded prompts consisting of emotional sentences spoken by a professional actress. Tsanas et al. [20] evaluated different algorithms based on dysphonia measures aiming at PD recognition. A total of 132 acoustic features were initially used for further feature selection, and the authors concluded the dysphonia information together with existing features end up helping PD recognition. Harel et al. [21] claimed that PD symptoms are detectable up to five years prior to clinical diagnosis, and symptoms presented in speech include reduced loudness, increased vocal tremor, and breathiness. In their work, the authors used a dataset of the National Center for Voice and Speech, which comprises 263 phonations from 43 subjects (17 females and 26 males, being 10 healthy controls and 33 diagnosed with PD).

Since one of the first manifestation of Parkinson's Disease is the deterioration of handwriting, the micrography is another information widely used for the diagnosis of Parkinson's disease [22]. This technique is considered an objective measure, since a PD patient possibly features the reduction of calligraphy size, as well as the hand tremors. Nowadays, this procedure is often conducted by filling out some specific forms. Rosenblum et al. [23] suggested that writing exams can be used to distinguish PD patients from healthy individuals. The authors employed the following methodology to support their assumption: 20 PD patients and 20 control individuals were asked to write their names and addresses in a piece of paper attached to a digital table. Further, for each stroke, the mean pressure and velocity were measured in order to compute spatial and temporal information. The authors presented very good recognition rates, being 97.5% of the participants classified correctly (100% of the control individuals, and 95% of

PD patients). Later on, Drotár et al. [24] claimed that movement during handwriting of a text consists not only from the on-surface movements of the hand, but also from the in-air trajectories performed when the hand moves in the air from one stroke to the next. The authors demonstrated the assessment of in-air hand movements during sentence handwriting has a higher impact than the pure evaluation of on surface movements, leading to classification accuracies of 84% and 78%, respectively.

Recently, Pereira et al. [25] proposed to extract features from writing exams using visual features learned from drawings the patients were asked to do. The authors also designed and made available a dataset called "HandPD" with all images and features extracted from the handwriting exams[4]. Pasluosta et al. [26] focused on PD as a representative disease model by evaluating the Internet-of-Things (IoT) platform in the context of healthcare. The authors considered the potential of combining wearable technology with the IoT in the healthcare scenario, as well as the engagement of patients in the assessment of symptoms, diagnosis, and consecutive treatment options. Zhao et al. [27] also analyzed E-health support in PD, but now with smart glasses.

Khobragade et al. [28] applied a Large-Memory Storage and Retrieval neural network for the prediction of onset of tremor in PD patients. The work demonstrated a fully automated deep brain stimulation system that can be applied on-demand, i.e. only when it is needed, since the usual treatments apply that stimulation continuously. Navarro et al. [29] proposed to employ an augmented reality-based approach that has been widely used in the field of rehabilitation to aid PD patients. The experiment was tested on 7 PD individuals, and showed that VR is a simple and suitable tool that should be encouraged to be used in PD patients.

Geldenhuys et al. [30] presented the use of a novel video-based paradigm for analyzing the gait of patients with Parkinson's disease. The idea was to consider the locomotor kinematics, which is capable of detecting subtle changes in gait and analyze the results in a gender-specific manner. In their experiments, a male mice group showed a statistically significant higher propensity towards gait changes than the female mice, suggesting that gait deficits in female-treated mice might be subtler.

Kim et al. [31] proposed a novel smartphone-based system using inertial sensors to detect freezing-of-gate symptoms in an unconstrained way. Several motions such as ankle, trouser pocket, waist and chest pocket, were evaluate. Data obtained and pre-processed via discriminative features extracted from accelerometer and gyroscope motion signals of the smartphone were used to classify freezing-of-gate episodes from normal walking using AdaBoost.M1 classifier with sensitivity of 86% at the waist, and 84% and 81% in the trouser pocket and at the ankle, respectively.

Another contribution of this work is to optimize CNN hyper-parameters by means of meta-heuristic techniques. As far as we are concerned, only a few and very recent works have employed such optimization models to fine-tune

[4] http://wwwp.fc.unesp.br/~papa/pub/datasets/Handpd/

hyper-parameters of deep learning techniques [32,33,34,35,36,37]. Usually, such optimization models are based on evolutionary/bio-inspired/meta-heuristic techniques, since they offer easy and elegant solution to a number of problems in the literature. Roughly speaking, such techniques start placing possible solutions (the so-called agents) at random positions in the search space. At each iteration, the solutions move onto the search space according to some specific dynamics (bat's behaviour in Bat Algorithm and fireflies in Firefly Algorithm, among others). However, as any optimization technique, the main idea is to converge to some global optimum when it exists. The reader can refer to the work of Holzinger et al. [38] for an interesting overview of these techniques.

3 Open Problems

The main challenges in computer-assisted Parkinson's Disease diagnosis include:

- Different data sources
- To detect PD at the very early stages of the disease
- To monitor the patient at home
- To obtain digitized versions of pretty old exams.

Bellow, we briefly discuss some of the most important problems we usually face when dealing with PD diagnosis.

Problem 1. **It is quite difficult to identify the first symptoms of the disease in its early stages.** Pereira et al. [25] showed the handwritten exam of a healthy individual and an early-stage patient can be the much similar to each other. Such situation poses a big challenge when using images acquired from handwritten exams only.

Problem 2. **Datasets with different modalities concerning the data source are rare.** As aforementioned, using only images from handwritten exams may not be enough to accurately identify PD patients at the very early stages of the disease, since subtle information may not be observed by either humans and machines. Therefore, complimentary information from sensors can be helpful to provide a more reliable decision-making model. One example concerns using "smart pen" to detect the handwritten dynamics, for instance.

Problem 3. **To obtain digitized versions of quite old exams.** There might be a number of handwritten exams in the hospitals and clinics that can be of extreme importance to identify the behaviour of PD patients. However, as stated by Pereira et al. [25], there is a need for specific protocols concerning the image acquisition of the exams, their pre-processing and feature extraction.

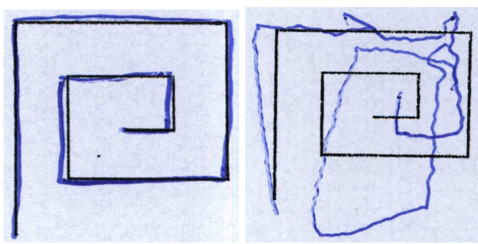
Problem 4. **Technology is not available to everyone.** Although in-home tools are quite efficient to monitor PD patients (e.g. tablets to asses handwritten skills, on-body sensors to detect freezing of movements and virtual reality), they are expensive and most of time not available for those who need care.

4 Methodology and Experiments

4.1 HandPD Dataset

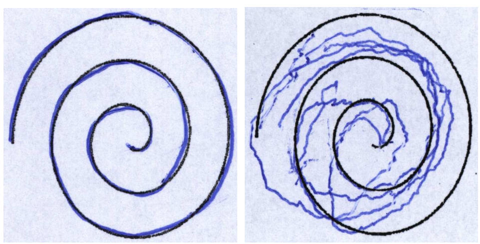
The HandPD dataset[5] was collected at the Faculty of Medicine of Botucatu, São Paulo State University, Brazil, being composed of images extracted from handwriting exams of individuals divided into two groups: (i) healthy people and (ii) PD patients [25]. The dataset comprises 35 individuals, being 14 patients (10 males and 4 females) and 21 control (healthy) individuals (11 males and 10 females). Each person is asked to fill out a form starting from inward to outward. This activity concerns the analysis of the movement provided by spirals and meanders drawings, which quantify the normal motor activity in a healthy individual, as well as the dysfunction of PD patients.

Figures 1 and 2 illustrate some drawing images concerning meanders and spirals, respectively. One can observe the different patterns between spiral and meander images, as well as different patterns between the same sketch of healthy and PD patients.



(a) (b)

Fig. 1. Meander samples from: (a) control and (b) PD patient.



(a) (b)

Fig. 2. Spiral samples from: (a) control and (b) PD patient.

[5] http://wwwp.fc.unesp.br/~papa/pub/datasets/Handpd/

4.2 Modelling CNN Hyper-parameter Optimization

We propose to model the selection of suitable hyper-parameters as an image recognition task by means of CNNs. The learning step has three main hyper-parameters: the base learning rate η, penalty parameter (momentum) α and weight decay λ. Therefore, we have a three-dimensional search space with three real-valued variables. Roughly speaking, the proposed approach aims at selecting the set of CNN hyper-parameters that minimizes the loss function of the images from the validation set. After that, the selected set of hyper-parameters is thus applied to classify images from the test set.

4.3 Experimental Setup

In this work, we classified meanders and spirals images drawn by the control group and PD patients using a CNN-based approach. Three different meta-heuristic techniques were employed to fine-tune CNN hyper-parameters: BA, PSO and FA. Also, to serve as a baseline for comparison purposes, we employed a standard CNN without optimization[6] and a Random Search (RS)[7]. Also, the hyper-parameters of each optimization technique were set empirically.

We divided the experiments into two datasets: (i) the meanders and the (ii) spirals. Both datasets are composed of 264 images (256×256 pixels), being 124 PD patients and 140 control group samples. In addition, we employed 30% of the dataset for training, 20 % for validation and 50% for testing purposes. In order to provide a statistical analysis by means of Wilcoxon signed-rank test [40] with significance of 0.05, we conducted a cross-validation with 10 runnings. We employed 15 agents over 25 iterations for convergence considering all techniques. This configuration leads us to $15 \times 25 = 375$ evaluations of the fitness function for each technique. If one decides to use a near-exhaustive search over three parameters, we could adjust the number of evaluations to be close to 375 for a fair comparison. In this case, we would be allowed to consider a range of 7 possible values for each hyper-parameter, since $7^3 = 343$. However, the hyper-parameters are real-valued, and we believe only seven values would not be enough for a good evaluation of the search space. Table 1 presents the hyper-parameter configuration for each optimization technique[8].

In regard to the source-code, we used the well-known Caffe library[9] [39], which is developed under GPGPU (General-Purpose computing on Graphics Processor Units) platform, thus providing more efficient implementations. Each meta-heuristic technique was evaluated by the same CNN architecture provided by Caffe, using $1,000$ training iterations with mini-batches of size 12. We have set each CNN hyper-parameter according to the following ranges: $\eta \in [0, 0.01]$,

[6] The CNN hyper-parameters in this case are the default values given by Caffe [39].
[7] A random search means an aleatory initialization of hyper-parameters between the range bounds.
[8] Notice these values have been empirically setup.
[9] http://caffe.berkeleyvision.org

Table 1. Hyper-parameter configuration.

Technique	Hyper-parameters
BA	$f_{min} = 0$, $f_{max} = 2.0$ $A = 0.5$, $r = 0.5$
PSO	$c_1 = 1.7$, $c_2 = 1.7$, $w = 0.7$
FA	$\gamma = 1.0$, $\beta_0 = 1.0$ $\alpha = 0.2$

$\alpha \in [0, 1]$ and $\lambda \in [0, 0.001]$. Finally, the best hyper-parameters found by the meta-heuristic techniques were evaluated again.

Regarding the architecture used on this experiment, we used the one proposed by Krizhevsky et.al [41]. Briefly speaking, such CNN is composed of 5 convolution layers, 5 pooling layers and 2 normalization layers. It is also constituted by 7 ReLU layers, 3 inner product layers, 2 dropout layers, 1 accuracy layer and 1 softmax loss layer for testing purposes.

4.4 Experimental Results

This section aims at presenting the experimental results concerning the CNN-based Parkinson's Disease identification, as well as its hyper-parameter fine-tuning effectiveness. As aforementioned in Section 4.3, we compared three distinct meta-heuristic techniques among with a baseline network without optimization and a random initialization of hyper-parameters considering both meander and spiral datasets. Notice the overall accuracy is computed using the standard formulation, i.e., $(1 - \frac{errors}{dataset\ size}) * 100$. Additionally, we provided the accuracy per class, i.e. "Control" and "PD". Tables 2 and 3 present the average results concerning meanders and spirals, respectively, and the best set of hyper-parameters (average) found by each technique. The most accurate results according to Wilcoxon signed-rank test are in bold.

	Accuracy (%)			Best Hyper-parameters		
	Overall	Control	PD	η	α	λ
Standard	**78.18%**	74.14%	**82.74%**	0.001	0.9	0.0005
RS	72.50%	80.14%	63.87%	0.0048	0.4233	0.0005
BA	**79.62%**	75.43%	**84.35%**	0.0008	0.6437	0.0007
FA	69.85%	**93.71%**	42.90%	0.0009	0.3594	0.0003
PSO	**75.76%**	85.00%	**65.32%**	0.0009	0.5144	0.0004

Table 2. Average accuracies and best hyper-parameters over the test set considering meander dataset.

Once can observe FA obtained the best results concerning "Control" (healthy individuals) class for meander dataset, but it has performed poorly when dealing with PD patients. This situation has led FA to the worst overall result with

69.85%. Considering the RS, it was also one of the worst techniques, mainly due its randomness and its lack of exploitation ability. The most accurate techniques were BA, PSO and the standard set of hyper-parameters defined by the library, although BA obtained the best recognition rate.

In regard to the spirals (Table 3), BA, PSO and the standard set of hyper-parameters obtained the best results once again. Nevertheless, RS was able to almost obtain similar results. In this case, BA and PSO can be considered similar to each other concerning the PD class, while standard performed better in "Control" class. By taking into account both exams, i.e. meanders and spirals, the latter are more discriminative and effective to distinguish healthy individuals from PD patients. Since meanders feature straight lines only (Figure 1), we believe it is more difficult (for those affected by Parkinson's Disease) to follow the complex pattern of spirals when performing the exams.

	Accuracy (%)			Best Hyper-parameters		
	Overall	Control	PD	η	α	λ
Standard	**89.55%**	**93.71%**	84.84%	0.001	0.9	0.0005
RS	86.67%	**92.43%**	80.16%	0.0038	0.5343	0.0005
BA	**87.20%**	84.14%	**90.65%**	0.0036	0.3972	0.0008
FA	83.79%	82.29%	85.48%	0.01	0.4522	0.0006
PSO	**88.33%**	85.00%	**92.10%**	0.0026	0.2733	0.0004

Table 3. Average accuracies and best hyper-parameters over the test set considering spiral dataset.

In order to provide a deeper experimental section, we executed one extra round of experiments (10 runnings with randomly generated sets) using the best set of hyper-parameters found out by each optimization technique (notice the standard results are the same). Tables 4 and 5 present such results concerning meanders and spirals, respectively. Since in the previous experiment we used training and validating sets (30% and 20%, respectively), in this extra round of experiments we merged them into a single training set.

	Accuracy (%)			Best Hyper-parameters		
	Overall	Control	PD	η	α	λ
Standard	78.18%	74.14%	82.74%	0.001	0.9	0.0005
RS	78.18%	76.86%	79.68%	0.003856	0.472675	0.000388
BA	**83.11%**	70.43%	**97.42%**	0.000143	0.923070	0.000929
FA	74.39%	**81.14%**	66.77%	0.000448	0.387494	0.000079
PSO	77.65%	**84.14%**	70.32%	0.000675	0.729715	0.000884

Table 4. Average accuracies using the best hyper-parameters found over the test set considering meander dataset.

Considering meander images, BA obtained the best overall accuracy so far, followed by the standard set of hyper-parameters, RS and PSO. This very good result was pushed up by the BA best recognition rate over PD class (i.e. 97.42%). With respect to spirals, standard, BA and PSO obtained similar results concerning the overall recognition rates, tough BA achieved the highest accuracy.

	Accuracy (%)			Best Hyper-parameters		
	Overall	Control	PD	η	α	λ
Standard	**89.55%**	**93.71%**	84.84%	0.001	0.9	0.0005
RS	86.97%	**95.29%**	77.58%	0.002717	0.322419	0.000856
BA	**90.38%**	89.29%	**91.61%**	0.001843	0.266447	0.001
FA	83.86%	80.86%	**87.26%**	0.01	0.096975	0.001
PSO	**89.62%**	86.00%	**93.71%**	0.003552	0	0.000210

Table 5. Average accuracies using the best hyper-parameters found over the test set considering spiral dataset.

5 Conclusion and Future Outlook

In this paper, we dealt with the problem of Parkinson's Disease identification by means of features learned from handwritten exams. The features were extracted by Convolutional Neural Networks fine-tuned by meta-heuristic-based optimization techniques, which obtained the best results for meanders, tough being similar to the standard set of parameters defined by the library with respect to spiral images (which we believe were hand-tuned). The experiments highlighted spirals as the most discriminative drawing, since it appears to be more difficult to perform such exam than meanders, which are composed of straight lines only.

In regard to future works, we intend to combine the results of the different optimization techniques, since they seem to disagree with respect to both "Control" and "PD" classes, being probably complementary to each other. Also, we aim at evaluating other meta-heuristic techniques, such as Cuckoo Search and Genetic Programming.

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