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Dynamic handwriting analysis for the assessment of neurodegenerative diseases: a pattern recognition perspective

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***Abstract*— Neurodegenerative diseases, as for instance Alzheimer's Disease (AD) and Parkinson's Disease (PD), affect the peripheral nervous system, where nerve cells send the messages that control muscles in order to allow movements. Sick neurons cannot control muscles properly. Handwriting involves cognitive planning, coordination and execution abilities. Significant changes in the handwriting performance are a prominent feature of AD and PD. This work addresses the most relevant results obtained in the field of on-line (dynamic) analysis of handwritten trials by AD and PD patients. The survey is made from a pattern recognition point of view, so that different phases are described. Data acquisition deal not only with the device, but also with the handwriting task. Feature extraction can deal with function and parameter features. The classification problem is also discussed along with results already obtained. The paper also highlights the most profitable research direction.**

***Index Terms*— On-line Handwriting Analysis, Kinematics, AD assessment, PD assessment, Task analysis, Motor control.**

I. INTRODUCTION

Neurodegenerative disorders, such as Parkinson's disease (PD) and Alzheimer's disease (AD), affect the structure and functions of certain brain regions resulting in a progressive cognitive, functional and behavioural decline. Changes in the brain result in degradation of the performance of motor skills.

A special role in the context of neurodegenerative disease assessment can be covered by handwriting. Cerebral cortex, basal ganglia and cerebellum are involved in learning and performing handwriting [92]; it is a complex activity entailing cognitive, kinaesthetic and perceptual-motor components. Handwriting problems can be related to the disease as well as to its severity, so changes in writing can be considered a prominent biomarker. For example, it is well-known that micrographia (an abnormal reduction in writing size) is typically associated with PD and it can be easily detected by conventional pen-and-paper tasks [40]. Dysgraphia (a progressive disorganization and degeneration of the various components of handwriting) has been observed in patients presenting mild to moderate AD levels [51], [21], [27].

Several advances have already been made in the offline (static) domain [96] but, nowadays, online (dynamic) systems can be adopted. In this case, the trait is represented as a sequence $\{S(n)\}_{n=0, 1,\dots,N}$, where S(n) is the signal value sampled at time $n\Delta t$ of the writing process ($0 \le n \le N$), Δt being the sampling period. The online case concerns the treatment of a spatio-temporal representation (see Fig. 1).

Fig. 1. Dynamic handwriting ("♦" : pen-down; "•" : pen-up)

The main advantage of on-line acquisition devices is their ability to acquire kinematics (dynamics) of the writing process which are lost in off-line systems. More specifically, dynamic features are: position (x,y), pressure over the writing surface (pad in the following), azimuth (i.e. angle of the pen in the horizontal plane) and altitude (i.e. angle of the pen with respect to the vertical axis). The movement of the pen can be recorded not only while the pen is on the writing surface (on-pad movements), but also when the pen is in the proximity of the surface, i.e. in-air movements (see Fig. 2). The max height at which the pen tip is detected is typically in the range of 0.6-1.0 cm depending upon the specific device adopted.

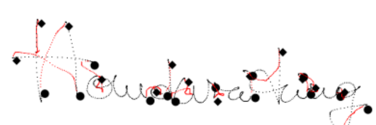

Fig. 2. Dynamic acquisition ("♦" : pen-down; "•" : pen-up; black dots: on pad samples; red dots: on air movement samples)

Studies on fine motor control in healthy and unhealthy people have been available so far, so that a growing research interest has arisen towards the possibility to automatically discriminate between impaired subjects and healthy controls (HC), based on the kinematic features [69]. The aim is to develop research in the direction of a Computer Aided Diagnosis (CAD) system. It must be underlined that these systems are not intended to replace doctors or to perform a self-diagnosis, but rather to provide a set of additional evidences to the medical staff to support the diagnosis.

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This paper points out the most relevant research results related to the application of on-line handwriting analysis to the assessment of PD and AD disorders. The review is principally organized from a Pattern Recognition perspective, typically based on data acquisition, feature extraction and data analysis and classification. Therefore, the paper intends to:

- Provide details about data acquisition, feature extraction and recognition applied to AD as well to PD;
- Point out and discuss the main findings from the two different diseases;
- Discuss open issues.

The paper is organized as follow. Section II presents the main aspects related to the on-line data acquisition and Section III discusses the pre-processing and feature extraction phase. Section IV describes research activities concerning the data analysis and the classification phase and presents the main results. Promising research directions are reported in Section V, and the summary of the paper in Section VI.

II. DATA ACQUISITION

Different issues must be taken into account: participant recruiting, choice of the acquisition device and identification of the most appropriate handwriting tasks. Once all these steps have been completed samples can be collected within a dataset: currently available databases are described at the end of this section.

A. Participant recruiting

Three aspects can be typically addressed:

1. Patients: severity of the illness in accordance with standard clinical test scores must be taken into account. The Unified PD Rating Scale (UPDRS) is the most commonly used scale in case of PD. It is based on interview and clinical observations most concerning motor evaluation [47]. Standard assessments of AD include cognitive and functional tests such as Mini-Mental State Examination (MMSE). It consists in a 30-point questionnaire including questions and problems in many areas ranging from orientation to time and place to registration recall [22].
2. Patients: whether the patient is ON/OFF medication. For example, studies involving PD have shown handwriting changes based on the level of treatment [20], [84].
3. Healthy Controls (HC): a set of healthy people (controls) must be enrolled. In general elderly controls (EC) and young controls (YC) can be taken into account; however a fair comparison should consider demographic as well as educational characteristics.

B. Acquisition Device

A wide set of devices for data acquisition is available. In some situations the use of an electronic pen on a digital screen could be unusual or unfamiliar to patients, so writing with an ink pen on paper fixed to the tablet may be an option [69], [92]. Some “training” task to let the user familiarize with the tool can be also considered [88]. The main attributes acquired depends upon the specific tool, however, typically acquired parameters are: (x-y)coordinates of the pen position, time stamps, pen orientation (azimuth and altitude) and pressure. In air movements can be also considered taking into account the so-called button status, which is a binary variable (0) for pen-up state (in-air movement) and (1) for pen-down state (on-surface movement).

Electronic (smart) pens have been adopted as an alternative to tablets. In this case active sensors are within the pen and are able to capture position, acceleration and tilt angle of the pen, as well as pressure and vibration (generated in the refill during writing or drawing on a pad) and the pressure of the fingers holding the pen [55], [86].

C. Writing Tasks

The writing process involves a complex feedback system and implicates the participation of several cognitive and motor processes. Acquisition tasks can be classified as follow.

1. *Simple Drawing tasks.* Straight lines, spirals, meanders and circles have been frequently used for the evaluation of the motor performance in both PD and AD [20], [56], [72], [12]. In general all simple drawings have been used for trajectory, tremor, dimension (size), velocity and acceleration evaluations.
2. *Simple Writing tasks.* Non-sense words containing one or more character repetitions have been used, see table 1 for details. Such characters are easy to write in a recursive and continuous way. Moreover, to better address the motor processes, their use minimizes the linguistic-comprehension processes. The “*e*” and “*l*” characters both contain an up- and a down- velocity stroke. According to the Delta-Lognormal Kinematic Theory [62] of the handwriting process which “*describes a stroke velocity profile as the output of a system made up of two neuromuscular systems, one agonist (acting in the direction of the movement) and the other antagonist (acting in the opposite direction)*”, the “*e*” as well the “*l*” characters are constituted by just two velocity strokes. Moreover, the use of “*l*” and “*e*” involves the handwriting of the same character scaled in amplitude. In addition, simple words and short sentences have been also widely adopted (see table 1). Typically, words/sentences used in these tasks are chosen based on their simple orthography and easy syntax. In some situations the sentence contains words having a common “core” (e.g. “*The leveler leveled all levels*” [88]) in order to verify how a common pattern is modified with or without a prefix or a suffix. Sentences have been built by including words with ascendant and descendent traits (e.g. “*g*” and “*l*”). A sentence requires a high degree of simultaneous processing and may have a higher neuro-motor programming load than a sequence of identical cuttings. It also offers the possibility to better evaluate the motor-planning activity between a character and the following one (in general a hesitation or pause between two characters or words could point out the necessity to re-plan the writing activity, while fluid writing can reveal the presence of an anticipated motor planning). A sentence allows the capturing of a large number of in-air movements between words [18], conversely a word could also be written without lifting the pen tip from the pad. It has been observed that AD patients, in order to proceed with the writing of a part of the word or of a new

word, need to come back on the previously written one and to "re-write" it, to some extent, in the air again. This aspect is important to evaluate patients with both the sequential programming engine and the competing processes altered [35]. Moreover, a sentence composed of more than one word allows the recording of the effect of fatigue during writing [16], [17]. Handwritten signatures have been taken into account [59], [3] since a signature conveys a lot of information about the signer related not only to the representation of the name and surname of the signer, but also to the writing system [58], [29]. Variations have been observed on global parameters (e.g. signature size) and on local ones related to longitudinal compression [95].

3. *Complex tasks.* In this case the handwriting task is part of a more complex task involving motor, cognitive and functional issues (see table 2). Van Gemmert et al. [88] were among the first to verify that PD patients are more vulnerable to a secondary task load than elderly or young controls. The handwriting task has been coupled with a simultaneous hearing and tone counting [8]. When a functional writing task, such as copying the details of a bank check into the appropriate places, is considered, the patient should be able to read the source field, locate the target field to be filled in and write the correct content there. These tasks are typically applied for the analysis of AD more than PD, since AD is primarily characterized by cognitive deficits. Very recently the Clock Drawing Test (CDT) has also been used [6], [25], [48]. CDT is able to reveal visual-spatial deficits: in some cases of dementia the deficit is evident from the early stages. CDT, as well as many other complex tasks, involves various neuro-psychological functions: auditory perception, auditory memory, abstraction capacity, visual memory, visual perception, visual-space functions, programming and execution capacity. Similarly, constraints on time (duration) and stroke dimension have been investigated [87], [89], as well as the use of visual feedback, in order to reach specific targets while writing [23], [83]. Verbal feedback (reminders to write bigger) have also been investigated [50].

D. Datasets

Most research has been conducted on reduced sets of patients and HC. A brief description of the most consistent ones is here reported (see table 3).

The Parkinson's Disease Handwriting Database (PaHaW) consists of multiple handwriting samples from 37 Parkinsonian patients and 38 age- and gender-matched controls [14]. Tasks include words written in Czech (the native language of the participants). The main characteristic of the selected words is that they can be written without lifting the pen above the surface. A tablet was overlaid with a white template paper and a conventional ink pen was used.

The original HandPD dataset comprises handwritten/drawn trials from healthy and PD people and was primarily designed for static analysis. The dataset was further extended for dynamic analysis and it contains data from 66 individuals (35 healthy controls and 31 PD patients). The new extended version is simply called NewHandPD [55]. Handwritten dynamics were captured by means of a smart pen (BiSP).

The ParkinsonHW [32] consists of 62 PD patients and 15 HCs. Three types of handwriting tasks were considered: the Static Spiral Test (SST), the Dynamic Spiral Test (DST) and the Stability Test on a Certain Point (STCP). In addition, the images of the spirals drawn by the PD patients are included. In the SST test, three wound Archimedean spirals are displayed on the tablet screen and patients are asked to retrace the same spiral. In the DST test, the Archimedean spiral appears and disappears at certain time intervals. In the STCP, a red point is displayed in the middle of the screen and subjects are asked to hold the pen on the point without touching the screen.

TABLE I
SIMPLE WRITING TASKS

Pattern	Reference
"eeee"	Cobbah et al. [10]; Contreras-Vidal et al. [11]; Poluha et al. [64]
"elel"	Gangadhar et al. [24]; Smits et al. [77]
"ellhell"	Teulings et al. [83]
"hello hello"	Caligiuri et al. [9]
"l" "le" "les"	Drotár et al. [13]; [14], [15], [16], [17], [18]
"lilili"	Van Gemmert et al. [87]
"lll"	Bidet-Ildei et al. [5]
"*llll*"	Cobbah et al. [10]; Contreras-Vidal et al., [11]; Oliveira et al. [50]; Poluha et al. [64]; Slavin et al. [75]; Teulings et al. [82]; Ünlü et al. [86]; Van Gemmert et al. [87], Senatore et al. [73];
"lln"	Bidet-Ildei et al. [5]; Van Gemmer et al. [89]
"Die Wellen schlagen hoch"	Siebner et al. [74]
"Ein helles grelles Licht"	Lange et al. [41]; Tucha et al. [84]
"en liesje leerde loesje lopen"	Ponsen et al. [65]
"lektorka" "nepopadnout" "porovnat"	Drotár et al. [13], [14], [15], [16], [17], [18]
"mamma"	Impedovo et al. [31]
"The leveler leveled all levels"	Van Gemmert et al. [88]
"Tramvaj dnes už nepo-jede"	Drotár et al. [13], [14], [15], [16], [17], [18]
writing own name	Rosenblum et al. [69]
Handwritten Signature	Pirlo et al. [59], Zhi et al. [95]

TABLE II
COMPLEX TASKS

Task	Reference
"*The leveler leveled all levels*" written under four different conditions	Van Gemmert et al. [88]
Adapt the size of a drawing to a given (displayed) input	Fucetola et al. [23]; Teulings et al. [83]
Constraints on time (duration) and stroke dimension	Van Gemmert et al. [89]; Van Gemmert et al. [87]
Loop drawing while tone-counting	Broeder et al. [8]
Bank-check field copying	Rosenblum et al. [69]; Werner et al. [92]
Address, phone number, grocery list, details of a check, the alphabet sequence and paragraph copying	Rosenblum et al. [69]; Werner et al. [92]; Garre-Olmo et al. [25]
Clock Drawing	Garre-Olmo et al. [25]; Müller et al. [49]

The ISUNIBA [59] dataset contains handwritten trials collected from 41 people: 12 HC and 29 AD patients. Each participant was requested to write the word *"mamma"* (i.e. Italian of “mom”) over different recording sessions. The choice of the word mom, identical to all the authors, is related to the importance of this word, and to the figure associated with it. This word, in addition to being often one of the first words spoken by individuals, is also repeated with high frequency by subjects in an advanced state of AD.

EMOTHAW (EMOtion recognition from HAndWriting and draWing) has been recently developed to investigate emotional states. It does not involve PD and/or AD patients, but tasks adopted are typically used in studies devoted to PD and AD [43]. The dataset could be useful for comparison aims.

TABLE III
DATASETS

Dataset Name	Size	Acq. Device	Tasks	Reference
PaHaW	37 PD 38 ED	Wacom Intuos 4M	Spiral drawing, repetition of *“l”, “le”, “les”, “lektorka”, “porovnat”, “nepopadnout”, “Tramvaj dnes už nepo-jede”*	Drotár et al. 2013 [14]
NewHandPD	31 PD 35 ED	BiSP	Spiral and meander drawing	Pereira et al. 2016 [55]
ParkinsonHW	62 PD 15 ED	Wacom Cintiq 12WX	Spiral drawing and stability test	Isenkul et al. 2014 [32]
ISUNIBA	29 AD 12 ED	Wacom Intuos Touch 5	Repetition of *“Mamma”*	Impedovo et al. 2013 [31]
EMOTHAW	129 HP	Wacom Intuos 4	Copying of: pentagons, house drawing; writing four words; loop drawing; CDT; writing of a sentence	Likforman-Sulem et al. 2017 [43]

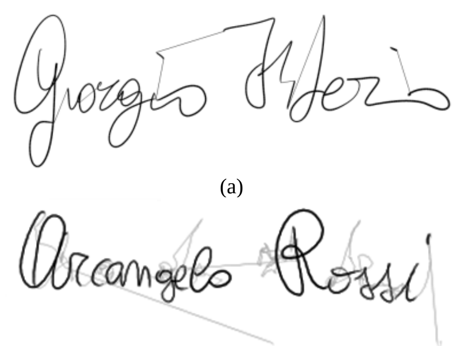
III. PRE-PROCESSING AND FEATURE EXTRACTION

Raw data acquired by the device are generally enhanced by means of standard signal processing algorithms: filtering, noise reduction and smoothing. Well-known techniques could be applied, however, their use must be circumstantial. In fact they could result in the loss of important information. For example, the normalization of the duration of the signal (in order to have all S(n) sequences of the same length) is sometimes applied for signature verification [28]. However, in this domain it would lead to the loss of information related to the time spent by each participant in performing a specific task (that is a discriminative feature). Given this consideration, it is quite usual to not adopt pre-processing steps (e.g. [92]).

Two types of features can be considered: function features and parameter features. When function features are used the handwritten trials are characterized in terms of a time function whose values constitute the feature set. When parameter features are used the trial is characterized as a vector of elements, each one representative of the value of a feature. In the latter case the indexes of vector are not referred to a time sequence.

A. Function Features

The most common function features are: position in terms of (x,y) coordinates, time stamp, button status, pressure, azimuth, altitude, displacement, velocity and acceleration. Some of these features are directly conveyed by the acquisition device, whereas others are numerically derived (see Table 4 for details). It is not surprising to note that the most used are velocity (speed) and acceleration: the former conveys information related to the slowness of PD and AD movements, while changes on the acceleration profile are able to reveal tremor. Displacement, Velocity and Acceleration can be computed as reported in table IV, as well as they can be computed along the x or y direction. In order to evaluate in-air-based features, coordinates, azimuth, altitude, velocity, acceleration, azimuth and altitude can be considered for timestamps having the button status b(t)=0. It has been recently demonstrated that in-air features conveys very useful information [48], [49]. In fact it has been showed that the in-air time in writing is related to functional decline, as well as to difficulties in planning an activity [68]. In order to have an idea of the potentialities of in-air movements see fig. 3: handwriting fluidity is much more evident in in-air movements than on-the-pad ones.



(a) (b)

Fig. 3. On-pad (black) and in-air (gray) movements. (a) belongs to a HC, (b) belongs to a suspected case. Both users were required to write an invented signature.

B. Parameter Features

In this case the trait is characterized as a vector of elements, each one representative of the value of a feature. Parameter features are obtained by means of transformations upon the function features (see Table 5 for details). To some extent also features used in the off-line domain could be used [54].

Some parameters have been specifically inspected and/or designed with the aim of performing AD and PD analysis. Amongst others two interesting parameters are the total time of the pen movement in-air and on-the-pad while performing a task. In fact, it has been observed that these values increase, as task length and difficulty increase while other values (e.g. pressure) remain constant. When a copy task is considered, the in-air time reflects the hesitations of AD patients.

Parameters can be evaluated at global (task level) or even at local level (typically at stroke level). Although a formal definition of the velocity stroke has been reported in the above, in AD and PD works, stroke is generally considered as

Fig. 4. On-pad strokes of the word in fig. 2.

TABLE IV
FUNCTION FEATURES

Feature Name	Source	Description	Disease	Reference
Position	Device	Position in terms of s(x,y)	AD, PD	Drotár et al. [13], [14], [15], [16], [17], [18]; Pereira et al. [55]; Rosenblum et al. [69]; Werner et al. [92]
Button Status	Device	Movement in the air: b(t)=0 Movement on the pad: b(t)=1	AD, PD	Drotár et al. [13], [14], [15], [16], [17], [18]; Rosenblum et al. [69]; Werner et al. [92]
Pressure	Device	Pressure of the pen on the pad (levels of pressure depend upon the acquisition device and are generally normalized [0,1])	AD, PD	Drotár et al. [13], [14], [15], [16], [17], [18]; Garre-Olmo et al. [25]; Ünlü et al. [86]; Rosenblum et al. [69],
Azimuth	Device	Angle between the pen and the vertical plane on the pad	AD, PD	Drotár et al. [13], [14], [15], [16], [17], [18]; Rosenblum et al. [69]; Ünlü et al. [86]; Werner et al. [92]
Altitude	Device	Angle between the pen and the pad plane	AD, PD	Drotár et al. [13], [14], [15], [16], [17], [18]; Rosenblum et al. [69]; Ünlü et al. [86]; Werner et al. [92]
Displacement	Calculated	It can be computed as $d_i = \begin{cases} \sqrt[2]{(x_{i+1}-x_i)^2+(y_{i+1}-y_i)^2}, & 1 \le i \le n-1 \\ d_n - d_{n-1}, & i = n \end{cases}$	PD	Lange et al. [41]
Velocity	Calculated	It can be computed as $v_i = \begin{cases} \frac{d_i}{t_{i+1}-t_i}, & 1 \le i \le n-1 \\ v_n - v_{n-1}, & i = n \end{cases}$	PD, AD	Broderick et al. [7]; Broeder et al. [8]; Caligiuri et al. [9]; Cobbah et al. [10]; Eichhorn et al. [20]; Fucetola et al. [23]; Garre-Olmo et al. [25]; Impedovo et al. [31]; Kotsavasiloglou et al. [38]; Oliveira et al. [50]; Pirlo et al. [59]; Ponsen et al. [65]; San Luciano et al. [70]; Schröter et al. [72]; Slavin et al. [75]; Smits et al. [77]; Tucha et al. [84]; Werner et al. [92]; Yu et al. [94]
Acceleration	Calculated	It can be computed as $a_i = \begin{cases} \frac{v_i}{t_{i+1}-t_i}, & 1 \le i \le n-1 \\ a_n - a_{n-1}, & i = n \end{cases}$	PD, AD	Broderick et al. [7]; Cobbah et al. [10]; Eichhorn et al. [20]; Fucetola et al. [23]; Garre-Olmo et al. [25]; Oliveira et al. [50]; Tucha et al. [84]; Van Gemmer et al. [89]

TABLE V
PARAMETER FEATURES

Feature Name	Description	Disease	Reference
Task duration	Total time duration of the performed task	AD	Schröter et al. [72]; Werner et al. [92]; Yan et al. [93]
		PD	Cobbah et al. [10]; Drotàr et al. [13]; Smits et al. [78], Teuligngs [81]
Dimension	Length and/or height of the trait in terms of samples or pixels both at task and at stroke level	AD	Werner et al. [92]
		PD	Drotàr et al. [13], [16], [17];Smits et al. [78] Rosenblum et al. [69]
in-air time	Total time of the pen in-air movements while performing a task	AD	Schröter et al. [72]; Werner et al. [92]; Yan et al. [93]
		PD	Drotár et al. [15]; Rosenblum et al. [69]
Normalized Time in-air	Time in-air normalized on the total task duration	PD	Drotár et al. [18]
On-the-pad time	Total time of the pen on-pad	AD	Schröter et al. [72]; Yan et al. [93], Werner et al. [92]
		PD	Drotár et al. [15], [17], [18]
Normalized Time on-the-pad	Time on-the-pad normalized over the total task duration	PD	Drotár et al. [15], [18]
In-air/on-the-pad ratio	Ratio of the total time of the pen in-air movements over the on-the-pad movements	AD	Yan et al. [93]
		PD	Drotár et al. [15], [17]
Stroke Number	Number of strokes within a task	AD	Schröter et al. [72];
NCV	Number of changes of velocity. (NCV has also been normalized on the duration of the task/stroke)	AD	Yan et al. [93]
		PD	Cobbah et al. [10]; Drotár et al. [13], [15], [16], [17], [18]
NCA	Number of changes of acceleration. (NCA has been also normalized on the duration of the task/stroke)	AD	Yan et al. [93]
		PD	Cobbah et al. [10]; Drotár et al. [13], [15], [16], [17], [18]
NCP	Number of changes of pressure. (NCP has been also normalized on the duration of the task/stroke)	PD	Drotár et al. [17], [18]
Entropy	Shannon or Rény operators applied on (x,y)	PD	Drotár et al. [16], [17]; López et al [45]
Energy	Teager-Kaiser energy or conventional energy	PD	Drotár et al. [16], [17];
NLOGnorm	Number of log-normal components	AD	Impedovo et al. [31], Pirlo et al. [59], Van Gemmert et al. [91];
EMD	Empirical mode decomposition	PD	Drotár et al. [16]

a single component of the handwritten trait which is connected and continuous: a stroke is the sequence of samples between two consecutive pen-downs and pen-ups on the pad (see fig. 4). The number of strokes per second can be considered to be representative of the handwriting frequency: in AD patients a significantly low writing frequency has been observed [35].

Jerk (which characterizes PD) can be measured in terms of Number of Changes in Acceleration (NCA) over time per stroke and it is often taken into account with the Number of Changes in Velocity (NCV). These features are also typically normalized on a per-feature basis. In order to obtain complete statistical representation of the available function features, max, min, means, standard deviation, range and median have been considered (e.g. v_{max}, p_{range}, etc.).

Tremor and irregular muscle contractions introduce randomness to the movements: entropy and energy have the potential to describe “noise” in the handwriting process. Entropy- and energy- based features have been calculated starting from the (x,y) coordinates, adopting well-known Shannon and Rény operators. Recently a metric named Normalized Velocity Variability (NVV) has been introduced [38]: low-level control of opposing muscular systems occurs in terms of milliseconds, while conscious control of movement cannot be at the same frequency. Similarly, Empirical Mode Decomposition decomposes a signal within finite and a small number of components able to reveal information regarding the most oscillating (high-frequency) part of the signal [16]. it is quite evident that although there are many other frequency analysis techniques (e.g. Fourier and all the related discrete transforms, etc.), these do not seem to have been still investigated within this field.

Features based on the kinematic theory of rapid human movement have also been considered by adopting the Sigma-Lognormal model to represent the information of both the motor commands and timing properties [59]. This model has also been adopted to study and model children’s movement [19] and to differentiate between children of different school levels [21], as well as for synthetic handwritten gesture generation [2].

Many of the above reported parameters have been normalized, based on the total time duration of the task or stroke.

Finally, in order to reduce data dimensionality and to select the most discriminating features, well known feature selection schema have been adopted: Mann-Whitney U-test [16] and Relief algorithm [16], [95].

IV. Data Analysis and Classification

The aim of this section is to point out relations between the tasks, features and main findings observed in the literature. For the sake of simplicity and clarity the results are discussed separately for PD and AD

A. Parkinson’s Disease

1) Handwriting and PD: insight

PD is usually diagnosed by the first motor synptoms : in particular slowness [7], [9], [65], [77], [83], [88], [57], reduction in amplitude of repeated actions (bradykinesia) and micrografia [8], [23], [46], [56], [65], [77], [87], [89], [44], [90], [89], tremor and rigidity are observed [7], [38], [56], [79], [88], [12], [42]. PD patients, if compared to controls, write smaller letters, apply less pressure and require more performance time.

Phillips et al. [56] adopted a simple zig-zag drawing: results revealed that patients had more difficulties in producing smooth movements rather than in controlling stroke length or duration. This result is confirmed by the one obtained in [83], where users were asked to produce handwriting modifying speed and dimension. Similar results (reduced length, velocity and height) have been mostly observed also in other different tasks [5], [10], [65], [77]. However it must be underlined that not all the mentioned characteristics (micrographia, slowness, longer time duration, etc.) have been simultaneously observed during any task. Just for instance [5] did not observe micrographia or reduction in letter size. However, in the latter case, the result could be related to the reduced length of the adopted pattern (*“lll”* and *“lln”*), in fact micrographia have been generally observed over longer words or within signatures or sentences [89]. In this direction, a unique result has been obtained on non-western languages (that can be written horizontally as well as vertically from top to bottom): a decrease in size was observed only in the horizontal direction [46]. Regarding micrographia, two recent studies [5], [46], seem to confirm it may be tied to the control of the extension of the wrist. Moreover, the *“Λ”* drawing task was considered [7]: the drawing of the shape was requested to be performed from left to right and vice versa. This specific task requires movements in four directions: PD patients showed significantly lower mean velocity, lower acceleration, and higher jerk scores than controls.

Handwriting in PD patients seems to be mainly impaired in force amplitude [80], [83]. Constrains on time (duration) and stroke dimension have been investigated by imposing different dimension targets while writing [87], [89]: a matching to the imposed targets has been observed only to a certain extent, inadequate matching to the required target (in time and dimension) has been related to acceleration inefficiencies.

Visual feedback has been taken into account [23], [83], in order to inspect the capability of adjusting the size of a drawing given an input. In PD patients, the effect was particularly pronounced when they were requested to draw smaller than normal, even if, with practice, improvements were observed. Overall, these findings support the opinion that PD patients may have specific difficulty adjusting to a change in gain (or discrepancy) between visual and kinaesthetic feedback. Visual (target points or examples) and verbal feedback (reminders) have been used to verify whether micrographia could migrate to normal amplitude [50], as well as to study perception and its usage [82]. It has been shown [50] that the stroke dimension can be improved and that improvements persist also shortly afterwards in free handwriting (without feedback), however, the increase in the amplitude obtained is due more to an increase in movement time rather than in peak velocity. Practice can help PD patients to partly overcome bradykinesia and to improve the control of repetitive forces [80].

Anticipation can be referred to the ability of the handwriting motor system to plan forthcoming strokes of the writing sequence while the movement of the current stroke is being executed [34]. The anticipation capability has been investigated observing that patients are able to write the pattern without pauses between characters [5], [41]. On the other hand, in different and more complex tasks (involving not only handwriting), difficulties in anticipating the upcoming component of the movement have been observed [76].

The effects of medication (levodopa, dopamimetic and/or neurostimulation) on handwriting have also been investigated. The evidence is that kinematic handwriting analysis is useful for monitoring the effect of medication [20] in terms of parameter changes as well as tremor reduction. It has been observed [11], [64] that handwriting changes across the medication cycle [10], [41], [84]. The velocity measure was able to distinguish drug-induced PD patients from HC with a high level of accuracy [10]. High-frequency neuro stimulation of the subthalamic nucleus has been considered: during stimulation handwriting movements became faster and smoother, moreover a reduction in micrographia has been observed [67], [74].

Even if PD mainly affects the motor system, also cognition, planning and execution impairments can be observed in the early stages and, in some situations, prior to diagnosis [33]. So far, it has been positively tested the hypothesis that PD patients are more vulnerable to a moderate level of secondary task load than elderly or young controls [88]. Different conditions were considered: PD patients had increased movement duration, increased total pause duration and increased jerk. More recently similar results have been observed by combining the writing task with (simultaneous) tone counting [8].

The use of an electronic biosensor pen named BiSP [86] highlighted that, amongst the other, the most discriminating feature is based on the difference between the controlled writing pressure in *x-y* direction and the tilt tremor of the pen.

2) Handwriting and PD: the challenge of a CAD

Although studies on the correlation of handwriting and PD have been available for a while, only in the last 5-6 years this evidence has been applied to obtain a Computer Aided Diagnosis (CAD) system. These studies have also highlighted new findings. Comparing results obtained by different researchers is quite difficult due to the different datasets used and the different experimental set ups adopted.

The first result to be pointed out deals with a task to be used for assessment. It has been verified that, on the PaHaW dataset, the use of all tasks gives better classification performance (PD vs. healthy) in terms of accuracy, if compared to the use of a single writing task [13]. The use of only some specific tasks has also been investigated. In particular the Archimedean spiral drawing seems to be useful for discrimination purposes due to tremor evaluation. Similarly, on another dataset, the use of just this task was able to achieve a sensitivity of 0.86 [70]. Very recently also the use of a simple horizontal line drawn at a constant velocity has been inspected: accuracy of 88.63% was achieved [38]. An excellent accuracy (97.50%) has been obtained in the following two tasks: writing one's own name and copying an address [69].

Although an in-air feature set seems, under certain conditions, to outperform an on-surface one [14], better results can be achieved by combining both according to a feature selection scheme [15], [69].

Among the other on-surface features, pressure has been demonstrated to be very useful [18], [70]. It has been shown that pressure-based features outperform other kinematic features [18]. However, it must be underlined that there is not a specific feature set able to clearly outperform the other independently of the considered writing task.

In addition to conventional kinematic handwriting measures, entropy, signal energy and EMC gave the best accuracy in the PaHaW dataset [16].

For classification purpose, Support Vector Machine – SVM with a Radial Basis Function Kernel [13], [14], [15], [16], [17], [18], Discriminant Analysis [69], Convolutional Neural Network [55] and Naïve Bayes [38] have been successfully used. Table 6 summarizes the results.

Finally, as well as feature selection, it has been observer that a specific task could be better than another for discrimination aim. This has been the case of the guided spiral drawing which has provided the best classification results if compared to other tasks [95]. This result suggest to combine feature selection along with task selection.

Figure 5 shows a timeline of the milestones in the PD CAD development.

B. Alzheimer's Disease

1) Handwriting and AD: insight

AD firstly results in cognitive rather than motor degradation. In fact, handwriting tasks have generally been coupled with cognitive ones [72], [75], [92], [94]. So far it has been observed that in the mild phase of the disease there are few possible lexico-semantic problems in the speaking process which worsen with the progression of the disease. A similar trend can be observed in written tasks: AD is associated with deterioration in fine motor control and coordination [63], [93]. This result has been confirmed also in different writing tasks. The popular *"llll"* pattern under different writing conditions (including visual feedback) has been considered: AD patients' strokes had a less consistent length, duration and peak velocity than the controls [75]. A similar result has also been obtained in the circle drawing task: movements of AD patients have been observed to be significantly less automated, accurate and regular than the controls [72].

The use of the delta-lognormal [62] and the sigma-lognormal [52] representation of handwriting generation showed that the maximum speed value is almost regular in healthy persons while it is greatly reduced at the beginning of the disease and completely lost in the advanced stage [31]. A similar result has been achieved taking into account a wide set of tasks dealing with fine movements (straight lines, cursive-connected loops, a single circle, continuous circle drawing). Results showed that slowness and irregularity of movement of AD patients were not present in all tasks [94]. Impairment was not found in the straight lines and cursive-connected loop tasks. AD patients exhibited difficulties in drawing due to a reduced ability in wrist and finger coordination.

In general, AD patients produce slower, less smooth, less coordinated and less consistent handwriting movements than their healthy counterparts.

2) Handwriting and AD: the challenge of a CAD

Werner et al. [92] adopted a discriminant analysis to determine which feature would be the best predictor of group membership (AD vs. EC). Temporal measures (especially in-air time) were higher in the AD patients group, while the mean pressure was lower. Although velocity and pressure remained relatively stable across the different tasks, the temporal and spatial measures increased with the difficulty of the task: the increase was reflected mainly in the in-air measures.

Handwritten signatures have been demonstrated to be useful. Velocity-based features related to the sigma-lognormal model of the kinematic theory of rapid human movement have been adopted [59]. In this case, a Bagging CART (classification and regression tree) classifier was able to achieve an EER (Equal Error Rate) of 3%.

Garre-Olmo et al. [25] were among the first to adopt copying tasks (including two and three dimensional figures) and the CDT. Several kinematic features were used in order to classify participants (by means of a discriminant analysis). Additionally, energy and complexity were also considered. Classification performance was strictly dependent on the task considered. Moreover, function features were able (in general) to provide better accuracy results. Regarding the CDT, it has been shown that in-air features are the most consistent for discrimination purposes [49].

Müller et al. [48] referred to the copying of a three-dimensional house. A Receiver Operating Characteristic curve (ROC) and logistic regression analyses were used. Once again, in-air time was significantly different between the groups (AD patients vs. Controls), as well as on-surface time and total time (i.e., in-air plus on-surface time).

Details are reported in table 7. Figure 6 shows a timeline of the milestones in the AD CAD development.

TABLE VI
PD CAD SYSTEMS
ABBREVIATIONS: T = TABLET; ST = SHEET OF PAPER FIXED ON THE TABLET; EP = ELECTRONIC PEN: AUC = AREA UNDER THE ROC; ACC=ACCURACY

Reference	Participants	Device	Tasks	Features	Classifier	Results
Drotár et al. 2013 [13]	Dataset PaHaW			On-surface features	SVM Radial Basis Function	ACC = 79.4%
Drotár et al., 2013 [14]				16 In-air selected features	SVM Radial Basis Function	ACC = 80.09%
Drotár et al. 2014 [15]				On-surface features + in-air features	SVM Radial Basis Function	ACC = 85.61%
Drotár et al., 2015 [16]				Entropy, signal energy, empirical mode decomposition (on-surface) + feature selections	SVM Radial Basis Function	ACC = 88.1%
Drotár et al., 2015 [17]				Stroke height/width, duration, writing length, NCP, Entropy, Energy	SVM Radial Basis Function	AUC = 89,09%
Drotár et al., 2016 [18]				Kinematic and pressure features + feature selection	SVM Radial Basis Function	ACC = 82,5%
Rosenblum et al., 2013 [69]	20 PD 20 EC	ST	Name writing, copying an address	On-surface + in-air features	Discriminant Analysis	ACC = 97.5%
Pereira et al., 2016 [55]	14 PD 21 EC	EP	Spiral and meander drawing	Pressure, grip pressure, refill pressure, tilt and acceleration	Convolutional Neural Networks	ACC = 87.14%
Kotsavasiloglou et al., 2017 [38]	24 PD 20 EC	T	Line drawing	Position, Normalized Velocity Variability, Velocity's Standard Deviation, Mean Velocity, Entropy	Naïve Bayes	ACC = 88.63%
Zham et al. [95]	31 PD 31 EC	T	Sentence and characters writing, Archimedean guided spiral	Displacement, pressure, average speed,, Rate at which pen tip changes position and velocity, max acceleration, + feature selection	Naïve Bayes	AUC = 93,3% Archimedean guided spiral

TABLE VII
AD CAD SYSTEMS
ABBREVIATIONS: T = TABLET; ST = SHEET OF PAPER FIXED ON THE TABLET;

Reference	Participants	Device	Tasks	Main features	Classifier	Results
Werner et al., 2006 [92]	22 AD 41 EC	ST	Copying: a phone number, a grocery list, the details of a check, the alphabet sequence and a paragraph	Size, duration (on-paper time and the in-air), pressure, mean velocity, mean pressure	Discriminant Analysis	ACC = 72%
Pirlo et al., 2015 [59]	29 AD 30 EC	T	Handwritten Signature	Velocity profiles	Bagging CART	EER= 3%
Garre-Olmo et al., 2017 [25]	23 AD 17 EC	ST	Dictated sentence writing, free sentence writing, two and three dimension drawing, clock drawing	Pressure, time, velocity, acceleration, energy, complexity	Discriminant Analysis	ACC = from 63.5% to 100% depending on the task
Müller et al., 2017 [48]	20 AD 20 EC	T	Three-dimensional house copying	in-air time, on-surface time, total time	Logistic Regression	ACC = 0.925
Müller et al., 2017 [49]	20 AD 20 EC	T	Clock drawing test	in-air time, on-surface time, total time	Logistic Regression	ACC = 87.2%

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Fig. 5. Timeline of the milestones in the PD CAD development.

Fig. 6. Timeline of the milestones in the AD CAD development.

V. Future research directions

Much evidence linking PD and AD to handwriting/drawing is available. Although some specific open issues have been already pointed out, in the following the most relevant are briefly discussed.

A. Dataset

Many researchers have adopted databases/datasets built by collecting data themselves. These datasets are different in tasks, size (in general very reduced), acquisition devices, etc.. The lack of a big dataset involving a statistically significant number of patients, as well as, a set of significant tasks, greatly limits research development. None of the datasets currently available provide meta-data that could be useful to perform a deep analysis and to support CAD development establishing stage of the disease, the medical treatment (if any), educational information as well as many other factors (risk factors, contour conditions, etc.). It must be underlined that there is the lack of research on non-western languages, on the other hand this would be of great interest since scripts have many pictorial elements could convey useful information [85].

Acquisition sessions should be repeated over time in order to study the evolution of the disease and its effects on the handwriting (the task should be repeated ideally every 6-9 months).

Datasets should also include "suspected" patients.

Unfortunately, developing such a benchmark database is a time-consuming and expensive process. It involves not only scientific and technical issues, like those related to acquisition devices and protocols as well as the statistical relevance of the population of the individuals involved, but also legal aspects related to data privacy and intellectual property rights.

B. Multi modalities

Acquisition tasks should include not only handwriting and/or drawing but also finger taps [36], [53]. Just think of the daily use of smartphones and the connected potentialities. From this point of view a new research direction could be the investigation of the evolution of keystroke and touch dynamics. The combination of handwriting with other biometrics should be also considered, since it has been showed the possibility to have diseases diagnosis by means of speech [71], [39], gait [1], eye movements [4], [66] and gesture. This will reinforce the overall accuracy. In order to include gesture, the use of a camera or a kinect could be considered during the writing phases [27]. This would result in a system in which the two modalities are referred to the same action. The recording of the voice would require the use of a microphone and the assessment of some specific tasks designed for the aim.

The use of multiple modalities would result within a complete CAD framework.

C. Features

Many features have been considered to date. Some of them are directly conveyed from the handwriting recognition task, some others are able to better describe tremor or other characteristics connected to the diseases. Even if a set of more than two hundred features has been in general evaluated, there is a wide number of well-known features still not considered: Fourier-based and more in general transform based. At the same time some new specifically devoted features could be also designed and based on a specific task, as for instance a distance metrics for the guided spiral drawing task [95].

Feature selection has been considered taking into account different "general purpose" strategies [16], [18], [95]: e Mann-Whitney U-test, Relief algorithm, etc.. Also in this case there is a plethora of other well-known techniques could be considered, as well as, specifically designed schema. It is our opinion that feature selection should be coupled with task selection, in fact many researchers have found, in other application fields, that a set of features is better than another for a specific task [29]. Feature evaluation/selection could also be moved to a per-user or per-class (to be defined) or per-zone perspective. In other words, given a specific task, a set of features could be used in order to distinguish healthy vs. non-healthy, another one to classify stages of the disease. The situation could be completely different if another handwriting task would be considered.

D. Classification

It is worth noting that up to date the classification problem has been considered as a binary one [14], [15], [16], [17], [18], [49], [92]: i.e. healthy vs. non-healthy. This is quite restrictive. The classification challenge should consider different stages of the disease. The subsequent steps would be the one in which HC are classified between healthy and those that have a certain probability to be exposed to the disease risk. To this aim, stability/complexity analysis could be considered, in order to reveal the most relevant regions of the patterns [58], [29].

Even if multiple task are available, up to date, the classification has been performed on a lumped feature vector containing features belonging to the whole set of tasks. More sophisticated (and probably performing) schema could be investigated and based on multiple classifiers [37] also considering feedback learning [30], [61]. In the case of measurement level fusion, score normalization must be considered [60].

E. Implementation

The main advantage of a CAD system based on dynamic handwriting analysis is probably it is a non-invasive methodology so that it has a very high acceptability by final users. Nevertheless its implementation can be considered to be low cost in terms of hardware since just a professional tablet is required. The system could make available to doctors at hospital, however also at home use could be considered. This last scenario has sense if we consider some handwriting task to be performed for "rehabilitation" or exercise purposes. In this case the system would be able to trace the course of the disease. Finally, if we consider the development of an app able to work with keystroke and touch dynamics more than handwriting, then probably it could be in the next generation of our mobile devices.

VI. Summary

Handwriting is a good candidate as a biomarker for the assessment of AD and PD. From this point of view, this paper has provided a comprehensive overview of the literature dealing with the application of on-line handwriting analysis to the assessment of the mentioned diseases from a pattern recognition perspective based on data acquisition, feature extraction, data analysis and classification. The main findings have been pointed out and discussed and many more research efforts have been made on PD, so that many findings are quite clear. Promising research has been developed on AD.

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