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New Models for Rigidity and other Parkinson's Disease Symptoms' Monitoring with Wearable Devices

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Abstract

Parkinson's disease (PD) is a progressive neurological disease. To date, it has no cure, so its treatment focuses on the symptoms' management. Due to the irregularity of the disease's progression, the scarce number of medical appointments make it insufficient to maintain treatment adjusted to the patient's condition.

The need for a closer follow-up of the patients with PD has moved the scientific community to create technical solutions for symptoms monitoring. However, the number of existing solutions is still reduced and few of them provide an objective quantification of the symptoms. This dissertation aims at introducing a paradigm shift with the development of quantification models for all motor symptoms of Parkinson's disease.

A clinical study on PD symptoms' monitoring was submitted and authorized by the Ethics Comitee (Internal Review Board) of Centro Hospitalar Universitário de São João. The iHandU system, which incorporates a wearable device with an inertial sensor and a mobile application, was the data source of the study and our development of new disease severity estimation models.

A protocol of testing-exercises to assess and collect the inertial signals of 4 different PD symptoms (Rigidity, Gait, Bradykinesia and Tremor) was defined in collaboration with the Neurology clinicians. The severity of the symptoms was classified by doctors according to the MDS-UPDRS semi-quantitative scale (rating between 0 and 4 the different motor symptoms), since clinicians expect that models quantify symptoms according to this scale.

Data from 15 patients and 5 healthy subjects were acquired and a multi-subject dataset was created for each of the 8 test-exercises defined in the protocol. The signals were cropped and pre-processed for the extraction of features. The ability to distinguish different levels of disease severity by each of the extracted features was studied statistically, achieving some promising results.

Subsequently, we tried to explore several machine learning (ML) classification approaches with the acquired new 15 patients PD symptoms datasets and with a previously acquired large dataset of rigidity symptom test-exercises (23 patients and 268 rigidity evaluations with corresponding clinical label) performed during Deep Brain Stimulation surgeries. Although some combinations of extracted features and ML approaches achieved promising results, as already expected the overall results' tendency was to obtain low class separability models for the new 15 patient datasets, probably due to the current small sample size and its class unbalance (much more low severity class samples than higher severity ones). Regarding the exploration of the 23 patients rigidity dataset, the engineering of new features and testing of different ML approaches did not support the development of any model with a better performance than the model previously established in the reference literature.

Resumo

A doença de Parkinson (DP) é uma doença neurológica progressiva. Até à data não tem cura, pelo que o seu tratamento se foca no controlo dos sintomas. Devido à irregularidade da progressão da doença, o acompanhamento médico num número reduzido de consultas torna-se insuficiente para que seja mantido um tratamento ajustado à condição do doente.

A necessidade de um seguimento mais próximo dos pacientes com doença de Parkinson tem movido a comunidade científica no sentido de criar soluções técnicas para a monitorização dos sintomas. Contudo, o número de soluções existentes é reduzido e poucas permitem realizar uma quantificação objetiva dos sintomas. Esta dissertação introduz uma mudança de paradigma com o desenvolvimento de modelos de quantificação de todos os sintomas motores da doença de Parkinson.

Um estudo clínico de monitorização de sintomas da DP foi submetido e autorizado pela Comissão de Ética do Centro Hospitalar Universitário de São João. O sistema iHandU, que incorpora um dispositivo wearable com um sensor inercial e uma aplicação móvel, foi a fonte de dados para o estudo e desenvolvimento de novos modelos de predição da severidade da doença.

Um protocolo de exercícios para a avaliação e recolha dos sinais inerciais de 4 sintomas da DP (Rigidez, Marcha, Bradicinesia e Tremor) foi definido com os clínicos de Neurologia. A severidade dos sintomas foi classificada pelos médicos segundo a escala semi-quantitativa MDS-UPDRS, já que os médicos pretendem que os modelos quantifiquem os sintomas segundo esta escala.

Dados de 15 pacientes e de 5 indivíduos saudáveis foram adquiridos e foi criado um dataset para cada um dos 8 exercícios definidos no protocolo. Os sinais foram cortados e pre-processados para a extração de características. A capacidade de distinção dos níveis de severidade da doença por cada uma das características foi estudada estatisticamente, revelando resultados promissores.

Posteriormente, foram exploradas várias abordagens de aprendizagem computacional para classificações com os novos datasets adquiridos dos sintomas de 15 doentes e com um dataset mais extenso de rigidez (23 pacientes e 268 sinais da evolução da rigidez com a respetiva classificação médica), previamente adquirido em cirurgias de Estimulação Cerebral Profunda. Apesar da combinação de características extraídas e das várias abordagens mostraram resultados promissores, tal como esperado, no geral os resultados revelaram uma tendência de fraca separação das classes pelos modelos nos novos datasets com 15 pacientes, o que provavelmente se deve à reduzida dimensão da amostra e ao desequilíbrio entre classes (mais amostras de severidade reduzida do que de severidade elevada). Quanto ao dataset de rigidez de 23 pacientes, a criação de novas características e a aplicação de diferentes abordagens de aprendizagens computacional não suportaram o desenvolvimento de um modelo com uma performance superior em relação ao modelo estabelecido na literatura de referência.

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“Only from the heart can you touch the sky.”

Rumi

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Abbreviations

A	Acceleration
ApEn	Approximate Entropy
BLE	Bluetooth Low Energy
BRAIN	Biomedical Research and INnovation
CHUSJ	Centro Hospitalar Universitário de São João
DBS	Deep Brain Stimulation
FIR	Finite Impulse Response
FO	Foot-Off
FoG	Freeze of Gait
IC	Initial Contact
IMU	Inertial Measurement Unit
KNN	K-Nearest Neighbours
LOO	Leave-One-Out
M	Mean
MCU	Microcontroller Unit
Med	Median
MDS-UPDRS	Movement Disorder Society - Unified Parkinson's Disease Rating Scale
MoMo	Motion Mote
PD	Parkinson's Disease
PDQ	Parkinson's Disease Quality of life questionnaire
PSD	Power Spectrum Density
RMS	Root Mean Square
ROM	Range Of Motion
SNC	Substantia Nigra pars compact
std	Standard deviation
SVM	Support Vector Machine
W	Angular velocity

Chapter 1

Introduction

1.1 Context

Parkinson's disease (PD) is a neurodegenerative disorder and the second most common after Alzheimer's [1]. With no cure to date, the existing treatments focus on reducing the limitations caused by the symptoms [2]. Levodopa based therapies are the standard treatment and can be combined with enzyme inhibitors and Deep Brain Stimulation (DBS) [1, 2].

The progression of the disease is very irregular, uncertain, and varies immensely between patients. Associated with the levodopa treatment, motor complications come up over time, requiring a detailed understanding, so that doctors can make adjustments and control these problems [1, 2]. The complexity of the disease, together with the reduced number of annual medical appointments with each patient, constitute a limitation for medical follow-up [3]. Moreover, regarding the methods to assess the symptoms, the existent medical rating scales are subjective, depending on the experience and perception of each doctor [4]. At the same time, the descriptions that patients make of their daily condition are usually inaccurate and biased [3].

To tackle these issues, Biomedical Research and INnovation (BRAIN) Laboratory, at IN-ESCTEC, is studying and developing a system to quantify, in real-time, PD motor symptoms to monitor patients at home and support the medical assessments in appointments. The presented thesis is within the scope of this investigation and aims to develop models to quantify PD motor symptoms, with a close collaboration with Centro Hospitalar Universitário de São João (CHUSJ).

1.2 Motivation

PD is the neurological disease with the highest prevalence in the world, expected to affect 12 million individuals globally by 2040 [5, 6]. The limitations in the treatment of this expanding disease require a change in the treatment paradigm, by providing a more frequent, closer and personalized follow-up to these patients [7].

The existing solutions for PD monitoring are insufficient for the patients and physicians' needs. The BRAIN laboratory solution aims to address those needs and enhance PD treatment. It will make possible to assess and register quantitative scores of all cardinal symptoms of PD. This will equip doctors with the necessary tools to assess their patients' condition more frequently and objectively. With a more controlled symptomatology, patients will certainly have a higher quality of life, may participate more actively in society.

As a future Biomedical Engineer, the participation and contribution to this line of research is of my great interest; this thesis facilitates unique experiences such as contacting directly with medical and hospital realities.

The quantification of Parkinson's disease motor symptoms explored in the scope of this thesis is an engaging challenge to my technical and soft skills. The possibility of contributing to the advancement of a new therapeutic approach and the integration of monitoring and quantification systems as a standard in the treatment of PD is a great opportunity, responsibility, privilege, and propels my determination to achieve good progress.

1.3 Objectives

The main objective for this thesis was to expand the iHandU to the monitoring and quantification of PD motor symptoms. To achieve this final goal, the following smaller objectives were defined:

- Support the adaptation of the existent iHandU system to make it suitable to the clinical practice and provide a user-friendly interface;
- Prepare the necessary documentation to start a clinical study;
- Formulate an appropriate protocol for the collection of motion data of PD assessment exercises in the hospital environment;
- Study the PD symptoms and their rating scales in order to understand how to quantify them accordingly to the scales;
- Collect data as specified by the protocol and structure them into datasets;
- Design and extract relevant features;
- Explore a statistical analysis of the determined features to comprehend their ability to distinguish different levels of symptom severity;
- Develop quantification models for different PD motor symptoms based on clinical labeled datasets of PD patients' motion data collected at the hospital's Neurology outpatient clinic.

1.4 Contributions

Monitoring Parkinson's disease is a growing area that still requires the investment of more time and resources to be established as a standard procedure. This work brings what could be the basis for much further development. Its contributions are:

1. Creation of a clinically exploitable motion data gathering protocol of a sequence of PD motor symptoms assessing exercises;
2. Collection of 8 clinically labelled datasets from motor assessment exercises in 15 patients and 5 healthy individuals;
3. The design and development of computational models from collected motion signal processing to quantify the different PD motor symptoms.

1.5 Document Structure

This document has six more Chapters after the introduction.

Chapter 2 sustains the basic understanding of Parkinson's disease, the review of motor symptom monitoring algorithms and the description of the iHandU system.

Chapter 3 depicts the environment in which the work was conducted, the ethics process, the collection of requirements and the creation of the collection protocol that preceded the fieldwork and developments. It also includes a description of the datasets built from the data collected at the hospital.

In Chapter 4 the pre-processing and the processing of the collected motion data for feature extraction are discriminated. The acquired features are also described.

Chapter 5 statistically explores the separability of symptoms severity by each computed feature.

Chapter 6 details the development of the models to quantify the PD motor symptoms as well as their results.

Chapter 7 presents a synthesis of this work's main conclusions and ideas, directing to future possibilities for its continuation.

Chapter 2

State of the Art

2.1 Parkinson's disease

2.1.1 Pathophysiology

Parkinson's disease is characterized by the progressive propagation of Lewy bodies and by the accumulation of alpha-synuclein protein in the nervous tissues [8]. The exact structure where Parkinson's has origin is uncertain, however, it is known that the disease's progression is promoted by the spread of the problem to different areas of the central nervous system [9]. Namely, in the substantia nigra pars compacta (SNc), the death of dopaminergic cells leads to the depletion of striatal dopamine, to the constant excited state of the motor pathways and consequently to the characteristic motor limitations of PD [1]. Figure 2.1 depicts the differences between the SNc structure and the synaptic transmission of healthy individuals and PD patients.

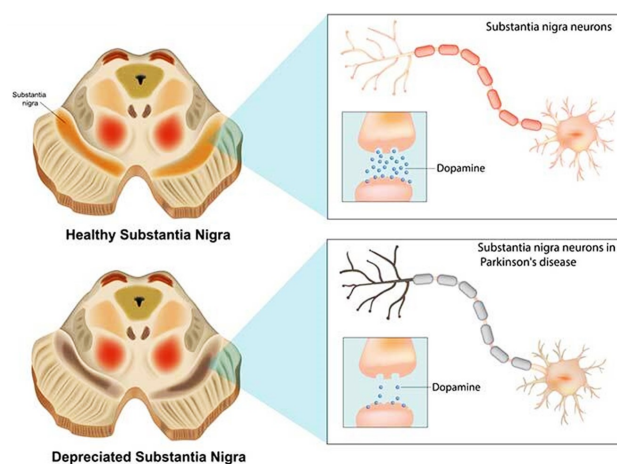


Figure 2.1: Distinction of substantia nigra pars compacta and synapses in healthy people and Parkinson's disease patients. Adapted from Shutterstock ¹.

¹<https://www.shutterstock.com>

2.1.2 Diagnosis

The diagnosis of Parkinson's disease is based on physical examination and gathering of the patient's comprehensive history [2]. The history assessment covers possible symptoms and family history, while the examination verifies the presence of bradykinesia, in addition to rest tremor or rigidity, to confirm a positive diagnosis of PD [10, 11].

The positive response to dopaminergic therapy underpins, in many cases, the diagnosis of PD. However, when there is no direct conclusion, doctors can call upon the observation of nigrostriatal degeneration with single-photon emission computed tomography to confirm the presence or absence of the disease [1, 11].

2.1.3 Symptoms

Parkinson's disease debilitates patients both at motor and non-motor levels. Bradykinesia, tremor, rigidity and postural instability, defined in Table 2.1.3, are the disease's characteristic motor symptoms [2, 10, 11]. Although non-motor symptoms are not mandatory for a diagnosis, many PD patients present these type of manifestations and they tend to become even more prevalent during the disease course. These include hyposmia (olfactory loss), sleep disorders, psychiatric problems (such as depression and anxiety), autonomous dysfunction (including urinary dysfunction and gastrointestinal issues), as well as cognitive impairment (like dementia and hallucinations) [2, 11, 12].

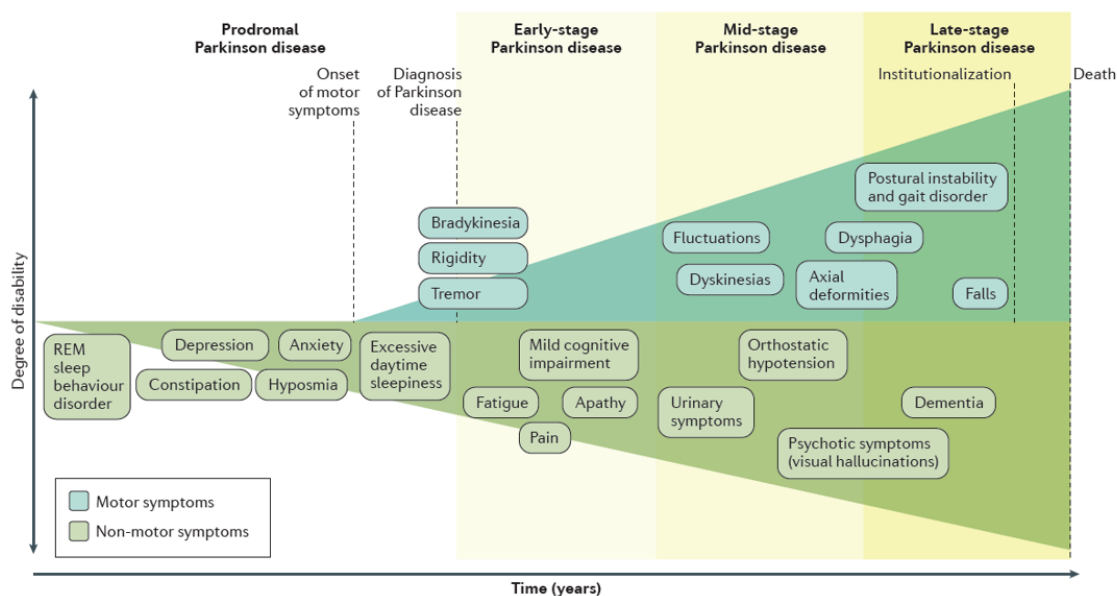


Figure 2.2: Symptoms over the progression of Parkinson's disease. Adapted from [13].

Although PD progression differs from patient to patient and, even for the same person, its rate alternates over the course of the disease, the unfolding of PD has a characteristic profile as presented in Figure 2.2. The diagnosis is usually preceded by a prodromal phase where non-motor symptoms prevail, and diagnosis specific symptoms are not evident. After this period, which may

take from years up to decades, motor symptoms start to show up in an early stage of the disease. In an overall picture, the increasing burden of non-motor, motor and drug-induced symptoms (these last will be addressed in Section 2.1.4.1) leads to the progressive impairment of PD patients going through the middle and late stages of the disease.

Table 2.1: Parkinson's disease cardinal motor symptoms.

Bradykinesia	Progressive speed decrease of movements when performing a repetitive task. Many times associated with the decline of movements amplitude – hypokinesia [2, 14].
Tremor	Rhythmical and oscillatory involuntary movement. Rest tremor has a characteristic frequency between 4 and 6 Hz, while the frequencies of the action tremors, postural and kinetic, are typically between 4 and 9 Hz [15, 16].
Rigidity	Muscle resistance to passive movement of a joint [17].
Postural instability	Imbalanced posture and gait, which reflects in great difficulties to start walking or keeping still. This symptoms can have associated moments of Freezing of Gait (FoG) which is a sudden disruption of the gait [18, 19].

2.1.4 Therapeutics

The first efficient drug used as PD therapeutic was levodopa (dopaminergic treatment), which appeared in 1993 and is, so far, still the most effective treatment [1]. Other pharmacological intervenors such as dopamine agonists, monoamine oxidase-B inhibitors and catechol-O-methyl transferase inhibitors are often prescribed to help control and reduce motor impairment [2, 13].

In more advanced stages of the illness, the decline of the patient's condition requires alternative approaches. Fitted to each patient, intestinal gel infusions of levodopa, subcutaneous apomorphine infusions or DBS surgery are the primary solutions [1, 13].

Despite motor symptoms are the major cause of concern, the treatment of non-motor symptoms has an enormous impact on improving the quality of life of people affected with PD. Likewise, physical exercise is a complement of utmost importance [2]. After all, as there is no treatment for the disease, the best strategy is to manage patients' physical and mental issues, allowing them to maintain the best quality of life possible.

2.1.4.1 Motor complications

Levodopa is strongly associated with the development of motor fluctuations. Nearly half of the patients on this therapeutic show motor complications after four to six years since the start of the treatment, and their prevalence tends to increase over time. Motor complications are not direct symptoms of the disease, but of its medication treatment. Nonetheless, motor fluctuations are as important to manage as PD symptoms [20].

As can be observed in Figure 2.3, with the disease's progression, the response to levodopa decreases and higher and more frequent doses need to be administered. Also, the therapeutic

window, which corresponds to the period when the medication lightens the symptoms, narrows over time.

The most predominant motor fluctuations are the following [21]:

- **Wearing-off:** Is the most common fluctuation among PD patients. It is characterised by the comeback of symptoms a few hours after the intake of medication, when a dose is ceasing to actuate;
- **Unpredictable "off" periods:** Are periods of "off" state (symptoms reemergence after medication intake) with any understood correlation with the time of levodopa's administration;
- **Failure of the "on" response:** "on" state is the period of good response after levodopa intake. This motor fluctuation corresponds to the absence of response or delayed response after an administration of levodopa. This phenomenon may happen due to poor intestinal absorption;
- **Akinesia:** Consists in the sudden lack of response to the medication, followed by a long period (might be days) of akinesia with poor response to the antiparkinson medication;
- **Freezing of gait:** Occurs when patients halt the gait, even if they intend to progress forward. This symptom is very debilitating, as it can lead patients to fall;
- **Dyskinesia:** Is more common in higher doses of levodopa and can be described by the execution of involuntary movements. It is a very limiting complication as it interferes heavily with patients' daily activities.

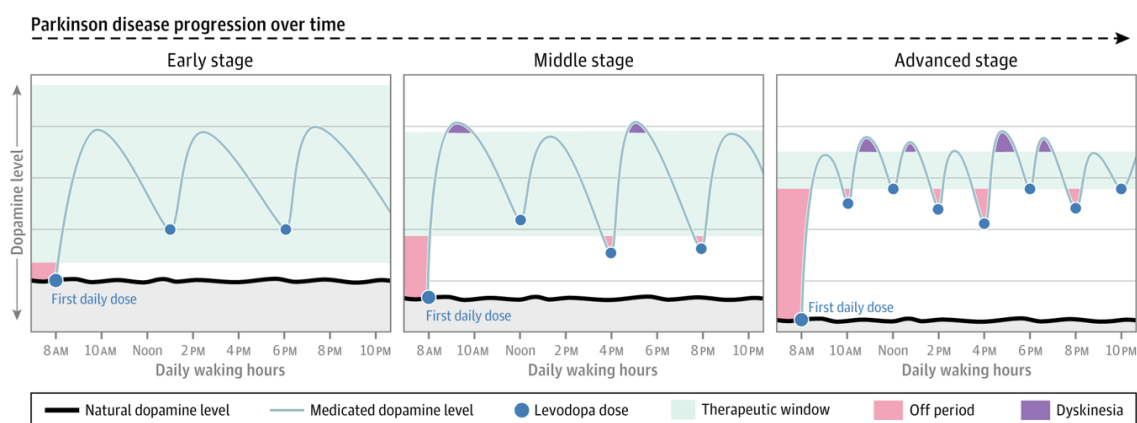


Figure 2.3: Relation between levopoda dosing, wearing-off and dyskinesias, along PD stages [2].

2.2 Clinical assessment and follow-up

The progress of Parkinson's disease is very uncertain. Among the patients, the symptoms that each one presents are variable, the progression of the disease is not constant, and motor oscillations

may arise, resulting from the levodopa treatment. For these reasons, PD requires regular clinical appointments to allow doctors to identify the illness stage, adjust the medications or the stimulation parameters in the case of DBS, and optimize the person's condition.

The follow-up of these patients consists of regular clinical assessments, where the physician will check the progression of the disease, both physically and mentally, since the last appointment. For this assessment of PD impairments, a wide range of rating scales are available for medical use. However, these are not always adopted, due to being time-consuming.

Beyond the patients' recall considered to complement the assessment with out-of-clinic information, diaries are often a useful tool in the patients' follow-up to support the transmitted information in a less biased way. Nevertheless, patients have difficulty describing accurately what they feel and show poor compliance with this demanding task [22–24]. Apart from these diaries, there is no common practice of using other tools to monitor patients outside the clinic.

2.2.1 Rating scales

Rating scales are crucial to standardise assessment, evaluation and detection of PD features. Usually used in the clinical environment by physicians, scales point to a probable disease stage and provide orientation for the treatment choice.

There is a large number of Parkinson's disease scales, standing out the ones for staging, quality of life, impact on activities of daily living and evaluation of symptoms of the disease [25, 26]. Regarding PD motor symptoms scales, the most used ones are:

- **Hoehn & Yahr scale:** Was created in 1967, by Melvin Yahr and Margaret Hoehn. The scale goes from one to five and is used to stage the motor impairment and describe the disease progression [27];
- **Parkinson's Disease Quality of Life Questionnaire:** Contains thirty-nine questions regarding the influence of PD on the patients' quality of life and, for this reason, is known as PDQ-39. The score for each question goes from 0 to 4, and the final score is transformed into a percentage [28].

PDQ-8 is a shorter version of PDQ-39, where only the most significant questions of each addressed area are presented, namely mobility, activities of daily living, emotional well-being, stigma, social support, cognitions, communication and bodily discomfort [29];

- **Schwab & England ADL:** Refers to the abilities of patients with PD in their activities of daily life (ADL). The scale goes from 0 % to 100 % in 10 % increments, with 100 % equating to total independence and 0 % bedridden, without bladder and bowel functioning [30];
- **MDS-Unified Parkinson's Disease Rating Scale:** Is a reviewed version of Unified Parkinson's Disease Rating Scale (UPDRS), by the Movement Disorder Society (MDS), and aims to evaluate the disease's symptoms. It is rated within five points, from zero to four and has

four parts, namely, Part I: Non-motor experiences of daily living; Part II: Motor experiences of Daily living; Part III: Motor examination; Part IV: Motor complications [31].

A greater focus will be put on the MDS-UPDRS scale, the one used more recurrently, and of greatest relevance to this work. Figure 2.4 presents a score sheet of this scale. As mentioned above, the scale is divided into five parts, covering the most differentiated areas of PD concerns.

_____ Patient Name or Subject ID	_____ Site ID	_____ (mm-dd-yy yy) Assessment Date	_____ Investigator's Initials
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MDS UPDRS Score Sheet

1.A	Source of information	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.3b	Rigidity– RUE	
			3.3c	Rigidity– LUE	
Part I			3.3d	Rigidity– RLE	
1.1	Cognitive impairment		3.3e	Rigidity– LLE	
1.2	Hallucinations and psychosis		3.4a	Finger tapping– Right hand	
1.3	Depressed mood		3.4b	Finger tapping– Left hand	
1.4	Anxious mood		3.5a	Hand movements– Right hand	
1.5	Apathy		3.5b	Hand movements– Left hand	
1.6	Features of DDS		3.6a	Pronation- supination movements– Right hand	
1.6a	Who is filling out questionnaire	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.6b	Pronation- supination movements– Left hand	
1.7	Sleep problems		3.7a	Toe tapping– Right foot	
1.8	Daytime sleepiness		3.7b	Toe tapping– Left foot	
1.9	Pain and other sensations		3.8a	Leg agility– Right leg	
1.10	Urinary problems		3.8b	Leg agility– Left leg	
1.11	Constipation problems		3.9	Arising from chair	
1.12	Light headedness on standing		3.10	Gait	
1.13	Fatigue		3.11	Freezing of gait	
Part II			3.12	Postural stability	
			3.13	Posture	
2.1	Speech		3.14	Global spontaneity of movement	
2.2	Saliva and drooling		3.15a	Postural tremor– Right hand	
2.3	Chewing and swallowing		3.15b	Postural tremor– Left hand	
2.4	Eating tasks		3.16a	Kinetic tremor– Right hand	
2.5	Dressing		3.16b	Kinetic tremor– Left hand	
2.6	Hygiene		3.17a	Rest tremor amplitude– RUE	
2.7	Handwriting		3.17b	Rest tremor amplitude– LUE	
2.8	Doing hobbies and other activities		3.17c	Rest tremor amplitude– RLE	
2.9	Turning in bed		3.17d	Rest tremor amplitude– LLE	
2.10	Tremor		3.17e	Rest tremor amplitude– Lip/jaw	
2.11	Getting out of bed		3.18	Constancy of rest tremor	
2.12	Walking and balance			Were dyskinesias present?	☐ No ☐ Yes
2.13	Freezing			Did these movements interfere with ratings?	☐ No ☐ Yes
3a	Is the patient on medication?	☐ No ☐ Yes		Hoehn and Yahr Stage	
3b	Patient's clinical state	☐ Off ☐ On	Part IV		
3c	Is the patient on levodopa?	☐ No ☐ Yes	4.1	Time spent with dyskinesias	
3.C1	If yes, minutes since last dose:		4.2	Functional impact of dyskinesias	
Part III			4.3	Time spent in the OFF state	
3.1	Speech		4.4	Functional impact of fluctuations	
3.2	Facial expression		4.5	Complexity of motor fluctuations	
3.3a	Rigidity– Neck		4.6	Painful OFF-state dystonia	

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Figure 2.4: MDS-UPDRS score sheet with discrimination of the parts and items of the scale. Adapted from [32].

MDS-UPDRS Part III assesses motor symptoms, including one or more exercises for each symptom. More specifically, exercise 3.3 evaluates the rigidity, for bradykinesia evaluation are used from 3.4 to 3.8 together with 3.14; concerning the gait, it is analysed with the tests from 3.9 to 3.13, and tremor is divided into three types, postural tremor assessed in exercise 3.15, kinetic tremor in 3.16 and rest tremor in 3.17. As for speech, facial expression and constancy of rest tremor considered in 3.1, 3.2 and 3.3, respectively, they cover very characteristic symptoms of the disease, that do not require concrete exercises, but are analysed in the normal course of the medical appointment.

Each item of MDS-UPDRS must be rated from 0 to 4, according to the criteria indicated in the scale, with 0 corresponding to the absence of the symptom and 4 to the maximum impairment. Ultimately, an overall score is extracted from the sum of all items.

2.3 Algorithms to monitor and assess Parkinson's disease motor symptoms

Scales aim to support physicians in the assessment of PD symptoms and support their clinical decisions. However, they are many times left apart due to their subjectivity and time-consuming use [33]. Another argument that may lead doctors to leave scales like MDS-UPDRS out of their clinical practice is their limited analysis nature that does not allow a fully confident use of the scales. The fact that scales include several characteristics (speed, amplitude, hesitations, slow-downs, and others) makes medical assessment difficult and demands expertise. Therefore, the scales become subjective to the perception of each doctor [34].

Alongside, the isolated use in clinical evaluations, either in “on” or “off” states, does not provide doctors with a realistic vision of the burden that symptoms have on daily life [4, 35]. PD diaries that could be seen as an alternative to rating scales are often called in to complement information on patients' conditions, but their accuracy and reliability limitations are far too numerous [36]. Therefore, it is essential to find alternatives to evaluate more effectively and objectively the motor symptoms of PD patients.

The use of digital tools to assess PD motor symptoms has begun to be studied, and efforts have been made to start developing such systems. Wearables are ideal to be integrated into these solutions, as they allow the non-invasive record of vital and motion signals, often wirelessly, and give physicians real-time feedback [37].

Thus, the main benefits of wearable monitoring technologies are:

- Objective and reliable assessment of PD motor symptoms [35];
- More information on patients' status is available, providing more complete insights to doctors about symptoms at home [4];
- Broader overview of the disease progression and its documentation [4, 35];

- Support for the treatment optimisation, be it medication or DBS [33]; Accessible channel to translate patients' conditions to healthcare providers [35];
- Patients self-monitoring and empowering in the disease management [38].

Aiming to acknowledge and understand the existing technologies for PD motor symptoms assessment, a research was made of the existing studies and systems in this area, at least as recent as 2018. Their selection prioritised a non-excessive number of sensors, working with inertial signals and having explicit the applied processing. Tables 2.2, 2.3, 2.4 and 2.5 summarise the reviewed papers for the monitoring of tremor, bradykinesia, gait and rigidity, focusing on the performed exercises, which sensors were used and where they were placed on the body, in addition to the processing, extracted features, employed algorithms and the final conclusions of each study.

The most prevalent factors in the presented studies and systems of each symptom will be listed below:

- In what concerns the systems to quantify tremor (Table 2.2), the performed exercises vary, but all correspond to one of the three types of tremor also evaluated in MDS-UPDRS, rest, postural and kinetic tremor. Based on the table, it can be seen that in most cases the movement signals are gathered in the superior limbs with Inertial Measurement Units (IMUs). The pre-processing of these signals primarily involves noise and movement baseline filtering, in order to collect accurate features. These last features relate mainly to the signal amplitude, frequency and entropy and show good correlations with tremor scoring;
- Bradykinesia quantification experiments, presented in Table 2.3, involve from the standard exercises of the movement rating scales to day-to-day activities like talking, walking and shaking a bottle. IMUs or single accelerometers or gyroscopes were placed on the fingertips, hands and wrists for the movement analysis. Along the same lines, signal filtering was an essential step, frequently complemented by the selection of signal windows (maximum of 5 s). Then, proceeding to the features extraction, they refer to amplitude, hesitation, velocity, decrement and energy characteristics. The studied features had a good correlation to the symptom scores, and the developed algorithms from these features also showed good predictive capability;
- Looking at the gait quantification systems in Table 2.4, though the number of studies and products is inferior, the methods to assess this so important symptom together with FoG vary a lot from one another. By recording walk with an inertial sensor, gait signals are measured in areas as diverse as the back, the knees and the wrists. Nevertheless, after signal filtering, the extracted features are very similar, including cadence, movement speed, stance and stride length. Once more, the results demonstrated the relevance of the obtained features, and the engineered algorithms present high predictive ability;
- A passive flexion and extension movement must be executed for rigidity assessment on the chosen joint. These manoeuvres were applied by others than the patient or even by

the system itself. Since this symptom is denoted by muscle stiffness, force sensors and mechanomyographies, alongside IMUs, were placed in the joints of the patients' upper limbs. In this case, the results of the studies presented in Table 2.5 are not as positive as the previous ones. Although the detection of the symptoms is done successfully, the distinction between its different stages and correlation with "on" and "off" states have unsatisfactory results;

- In an overall view of the employed algorithms, they were divided in machine learning and statistical approaches. Machine learning methods have framed deep learning approaches and various supervised algorithms. Whereas the statistical methods investigated both the correlation and the significant separation of the values under analysis.

Efforts are being made to evolve and improve PD treatment and decelerate its progression as much as possible with the aid of systems that objectively quantify symptoms. However, this process is still in a phase of exploring the wearables to use, the products' usability, considering the users' limitations, the analysis made on the data, and many other important details. Major progress can be noted with regard to tremor and bradykinesia, whereas the measurement of gait and rigidity are still in a more preliminary stage and with unsound solutions.

Table 2.2: Systems/studies for tremor assessment and quantification.

Authors	Exercises	Sensors	Body part	Pre-processing	Signal features	Algorithms	Results
de Oliveira Andrade et al. (2020) [39]	Rest and postural tremor	IMU: accelerometer, gyroscope and magnetometer	Dorsum of hand and forearm of the most affected arm	-Selection of 15 s windows from 3 axis of the 3 sensors -Elimination of spikes, with TRMS - Detect low frequencies not related to tremor -Removal of nonlinear component -RMS and PSD calculation	-Amplitude -Bandlimited signal energy	Spearman's rank correlation coefficient with a significance level of 5%	-Higher correlation of rest tremor scores with hand accelerometer metrics ($r=0.72$) -Equal correlation of postural tremor with hand accelerometer or gyroscope metrics ($r=0.85$)
Pierleoni et al. (2019) [40]	Rest, postural and kinetic tremor	IMU and 3 axis digital compass	Both wrists	-FIR filter of bandwidth 3-12 Hz -RMS -Calculation of FFT -Evaluation of fundamental frequency -PSD execution -Frequency related features extraction	-Frequency -Intensity -Central frequency -Frequency dispersion	Classification of tremor according to UPDRS scale (no more specifications on the used algorithm)	Accuracy = 97.7%
Kim et al. (2018) [41]	Rest tremor	Accelerometer and gyroscope	Wrist and finger, tested in both hands	-Selection of middle 50 s window of each signal -Filter of baseline with 1Hz HP -FFT determination -Alignment of 3 axis transformed signals from both sensors to construct an input for the algorithm	-2D structure of transformed signals	Convolutional neural network	Accuracy = 85 %
Lušys et al. (2018) [42]	Postural and, and kinetic tremor	IMU	Hand, forearm and arm of both limbs	-1st order Butterworth 1 Hz HP filter -Elimination of gravity component from accelerometer signal -Calculation of PSD and dominant frequency -Signal RMS -Approximate entropy	-Dominant frequency -Root mean square -Approximated entropy	One-way ANOVA to test the null hypothesis that the tremor metrics were equal in the PD group and the control	Statistically significant differences were present for: -Acceleration and angular velocity entropies of kinetic tremor - Angular velocity entropy of postural tremor -Angular velocity RMS of kinetic tremor - Acceleration dominant frequency of postural tremor

IMU inertial measurement unit, TRMS turkey's running median smoothing, RMS root mean square, PSD power spectrum density, FIR finite impulse response, FFT fast fourier transform, HP high-pass

Table 2.3: Systems/studies for bradykinesia assessment and quantification.

Authors	Exercises	Sensors	Body part	Pre-processing	Signal features	Algorithms	Results
Mahadevan et al. (2020) [43]	Conversation, kinetic tremor, hand pronation/supination, bottle shake and gait	Accelerometer	Wrist	-4th order Butterworth IIR 0.25-3.5 Hz filter -Selection of 3 s nonoverlapping windows of acceleration -Determination of RMS and rate of change of acceleration	-Amplitude of movements - Smoothness - Percentage of time spent with no hand movement -Average time without movement	Longitudinal mixed effects regression model	Correlation of 0.67 between medical score and prediction of bradykinesia score
Bobic et al. (2019) [44]	Finger tapping	Gyroscope	Fingernails of index and thumb	-Adjustment of coordinates system in relation to index -Extraction of dominant axis component -Integration of this component -CWT calculation and coefficients	-Tapping amplitude -Amplitude decrement -Hesitations and freezes -Tapping speed	-Decision support system (group of criteria for the features)	Accuracy = 88.16 %
Lin et al. (2018) [45]	Hand open/close	IMU	Index fingertip	-Application of Kalman filter to gyroscope signal -Determination of dominant frequency -Orientation angle calculation -Extraction of mean of peak to peak of hand grasping range	-Speed of movement -Hand grasping angle -Grasping amplitude	-KNN -Multiclass SVM model	-KNN accuracy = 83.72 % -SVM accuracy = 95.349 %

(continuation of Table 2.3)

Authors	Exercises	Sensors	Body part	Pre-processing	Signal features	Algorithms	Results
Lonini et al. (2018) [46]	Walking; finger to nose, alternating hand movements (clinical activities); drawing, typing on computer (fine motor activities); other	Accelerometer and gyroscope	Back of hand	-Selection of 5 s windows, overlapping 50% -Removal of limb positioning, in acceleration, with 0.5 Hz HP filter -Use of 3 Hz LP filter in both signals	From acceleration and angular velocity, in the 3 axis: -Range -Skew -Kurtosis -Cross-correlation peak -Cross-correlation lag -Dominant frequency -Relative magnitude -Moments PSD -Moments of Jerk magnitude -Sample entropy	Random forest and convolutional neural network	-AUC in walking = 0.771 -AUC in fine motor activities = 0.758 -AUC in clinical activities = 0.730
Juanjuan et al. (2020) [47]	Finger tapping, hand open/close, hand flip and hand pronation/supination	IMU to place in the wrist and 2 inertial sensors (with accelerometer and gyroscope) to place in the finger	Fingers (index and thumb) and wrist	-Eliminate noise -Analysis of signals at time and frequency levels	-Extraction of 35 features. Some of them are: -Acceleration, angular velocity and angular RMS -Approximate entropy -Sample entropy -Main frequency -Total energy statistics -Coefficient of variation -Others	-Neural network multi-layer perceptron model, with hyperbolic tangent as hidden layer activation function, and Softmax as output layer activation function -Reduction of feature dimension to 14	-Y-axis acceleration RMS, combined angular velocity RMS, coefficient of variation, X-axis acceleration peak power and Y-axis acceleration peak power, have a significant correlation with UPDRS scores. -Prediction of having Parkinson's or not has an accuracy of 90 %

IIR infinite impulse response, *CWT* continuous wavelet transform, *KNN* k-nearest neighbours, *SVM* support vector machine, *LP* low-pass, *AUC* area under the curve

Table 2.4: Systems/studies for gait assessment and quantification.

Authors	Exercises	Sensors	Body part	Pre-processing	Signal features	Algorithms	Results
Zago et al. (2018) [48]	Walk straight for 10 meters	IMU	At L5 level	-Acquired signals were filtered with a 4th order Butterworth LP 5 Hz -Use of mean and standard deviation of gait cycles information, provided by embedded software -Estimation of support phase, from acceleration -Determination of step length and velocity based on double integration of acceleration	-Cadence -Velocity -Stride length -Stride duration -Step length -Stance -Swing -Double support duration	-The statistical similarity between the two systems was analysed with Wilcoxon Signed rank test -Spearman correlation was used to compare IMU extracted features to optoelectronic motion capture system	-Gait velocity was statistically different in the two acquisition systems -High correlation was identified for cadence, velocity, stride duration and stride length
Aich et al. (2018) [49]	Walk straight for 6 meters	Accelerometer	Both knees	-Triaxial horizontal to vertical correction to eliminate misalignments -4th order Butterworth LP 15 Hz filter -Signal smooth with integration - Calculation of gaussian continuous wavelet transform, to determine heel initial contact	-Step time -Stride time -Step length -Stride length -Walking speed	-SVM -K-NN -NB -DT	SVM was classifier with the highest accuracy to detect the presence of freeze of gait or not Accuracy (SVM) = 91.42%
Burq et al. (2022) [50]	Stand up and go	Accelerometer and gyroscope	Wrist	-Norm of x and y accelerations (arm swing acceleration) -Rate of change of x-axis acceleration (arm swing forward acceleration) -Peak frequency in PSD (cadence) -Peak magnitude in PSD in walking frequencies, under 2.5 Hz (peak arm swing energy)	-Arm swing acceleration -Arm swing forward acceleration -Peak arm swing energy -Cadence	-Spearman rank correlation between in-clinic extracted features and expert consensus rating -Intra-class week and monthly correlation -Mean difference between measures in on and off state	-Correlation between median lateral acceleration and expert consensus = -0.46 -Mean difference of feature in on and off state = -0.80 -Week and monthly, intra-class correlation, respectively = 0.43 and 0.75

NB naive bayes, *DT* decision tree

Table 2.5: Systems/studies for rigidity assessment and quantification.

Authors	Exercises	Sensors	Body part	Pre-processing	Signal features	Algorithms	Results
Huo et al. (2020) [51]	Wrist and elbow rigidity	Force sensor, IMU and MMG	Upper arm and forearm, of the most affected limb	-MMG's signals were filtered with 4th order Butterworth 10-100 Hz filter -Rectified -Filtered with 4th order Butterworth LP 5H filter -Force and angular velocity signals were used directly	-Torque's mean and standard deviation -Mean angular velocity -MMG's mean and standard deviation	Voting classifier model, using 3 out of 13 classifiers and individual classifiers	-Wrist rigidity (with voting classifier) = 88.4 % -Elbow rigidity (with KNN(K=1)) = 92.7%
Raiano et al. (2020) [52]	Wrist rigidity (passive movement applied by the device)	Force sensors	Right wrist	-Identification of passive perturbations -Averaging of angle and torque of three middle repetitions -Stiffness was determined in the linear portion the torque and angle regression	-Stiffness in extension -Stiffness in flexion	Applied algorithm not specified	-Rigidity score has equal correlation with stiffness measured in "on" or "off" condition
Perera et al. (2019) [53]	MCP rigidity (flexion/extention applied by the device)	Force transducer and electronic sensor	MCP joint of the third finger	-Of 15 continuous gathered cycles, the first five were discarded -Baseline was removed -Slope of force and force per degree -Maximum force -Total area under current signal	-Force Rate -Peak force -Charge -Work estimate	Multiple linear regression	RMSE = 0.712

MMG mechanomyography sensors, *MCP* metacarpophalangeal, *RMSE* root mean square error

2.4 The iHandU system

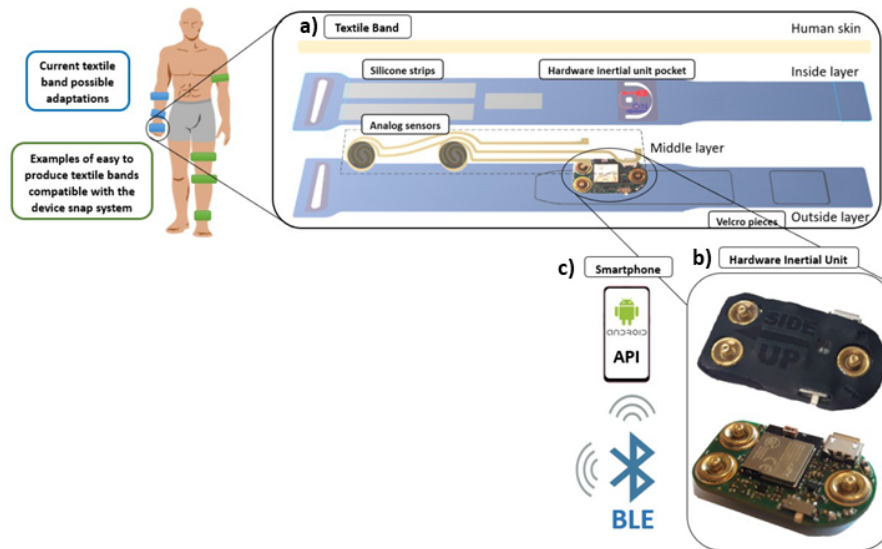


Figure 2.5: iHandU components and its connectivity: **(a)** Textile band to place iHandU with embedded analogue force sensors. **(b)** iHandU hardware. **(c)** Smartphone to which iHandU connects and transmits data via Bluetooth. Adapted from [54].

The iHandU system has been developed in the last years to enable a real-time monitoring of PD symptoms and to support clinicians in appointments and follow-up of their patients. The system comprises a wearable, iHandU, a mobile application and a dashboard for clinical use [55].

The wearable is formed by a comfortable, light and adjustable band that can be easily adapted to the hand, wrist, arm, foot, ankle and leg, even for patients with motor limitations, such as PD patients (Figure 2.5.a). It has two analogue force sensors embedded in the band and also has a 9 degrees of freedom IMU with an accelerometer, a gyroscope and a magnetometer (Figure 2.5.b).

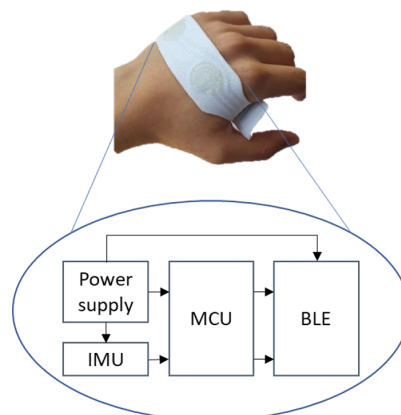


Figure 2.6: Schematic of the iHandU architecture. Adapted from [54] and [56].

The data gathered with the mentioned sensors are transmitted to a Bluetooth Low Energy (BLE) module that integrates the Microcontroller Unit (MCU) and from this to the mobile application (Figure 2.5.c) [54]. The same data is simultaneously available in a medical dashboard for clinicians to consult and keep updated with their patients' state. Figure 2.6 schematises the connection within the hardware elements of the wearable.

Throughout the years, the wearable's hardware suffered some improvement iterations, two of them will be relevant in Subsection 6.1.1, which are Motion Mote (MoMo) version that had a sampling frequency of 28 Hz and Snapki, the more recent version that samples data at 50 Hz [57]. Relevant information on the specifications of the sensors are presented in Table 2.6.

Table 2.6: Sensitivity specifications of gyroscope, accelerometer and magnetometer sensors. [54, 58]

Parameter	Typical	Units
Gyroscope sensitivity		
Full-Scale Range	± 1000	dps
Gyroscope ADC Resolution	16	bits
Sensitivity Scale Factor	32.8	LSB/(dps)
Accelerometer sensitivity		
Full-Scale Range	± 4	g
Accelerometer ADC Resolution	16	bits
Sensitivity Scale Factor	8.192	LSB/g
Magnetometer sensitivity		
Full-Scale Range	± 4800	μT
Magnetometer ADC Resolution	16	bits
Sensitivity Scale Factor	0.15	LSB/ μT

Regarding the mobile application, it presents a list of exercises for the patients' assessment. Three different modes of the application were created (represented in Figure 2.7). One for doctors to measure their patients' symptoms in appointments, another for patients to use at home and a third specific for clinical studies, as is the case of this dissertation, in which data collection has to be done anonymously and safely.

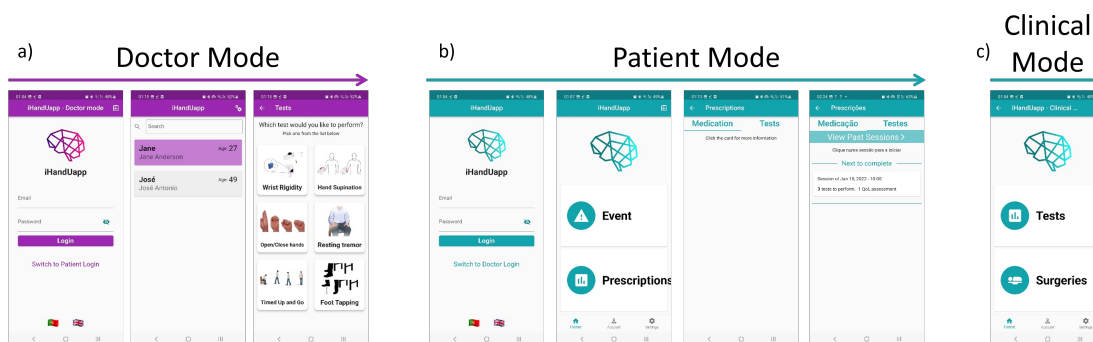


Figure 2.7: iHandU application modes: (a) doctor mode, (b) patient mode and (c) offline mode. Adapted from [59].

In addition, a dashboard was developed for the exclusive use of clinicians. A clinician can consult the page of each patient, as shown in Figure 2.8. General information about the patient, what medications are being taken, the results of the quantification exercises and possible events, when the patient was feeling "off", fell or others are all presented. Other than the patient's data history, the clinicians can adjust exercises and medication's prescriptions and contact remotely with the patients [55, 59].

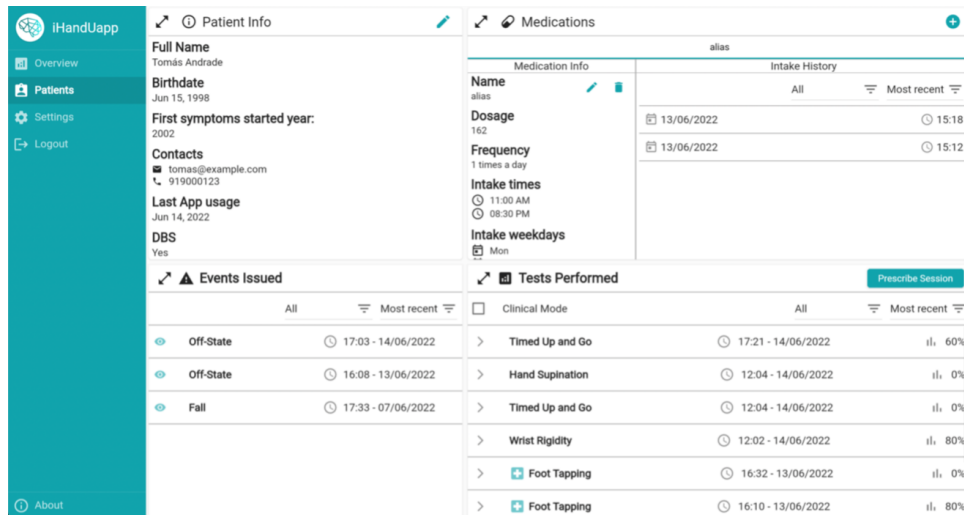


Figure 2.8: Dashboard in patient profile.

2.5 The iHandU system in DBS surgeries

Deep brain stimulation is an alternative treatment to medication when it no longer has the desired effect and no longer allows the control of symptoms. This stimulation supports a greater control of the disease's motor symptoms with a decreased dopaminergic therapy, thus providing patients with a better quality of life [60]. DBS surgery is carried out to implant an electrode in the structures of the basal ganglia, in the *subthalamic nucleus* or the *internal globus pallidus* [61].

The optimized position of the electrode and its respective stimulation parameters are evaluated by testing the improvement of the rigidity, a common symptom in the majority of PD patients [62]. Moreover, rigidity is frequently assessed in the wrist joint rather than in any other articulation, as it allows a good perception of cogwheel. Nevertheless, this evaluation is very subjective and prone to the perception of each physician. Therefore, it is essential to increase the procedure's success by having a solution that objectively quantifies the evolution of rigidity, and for this very reason, the iHandU was firstly developed, prior to its application in symptoms monitoring.

The solution comprised iHandU wearable to capture the rigidity in the patients' wrist and a mobile application where the signal and quantification were displayed. Figure 2.9 shows the utilization of the solution system in a DBS surgery environment.

A dataset was created with the motion data of the passive flexion and extension of patients' wrist by doctors during DBS surgeries. It comprises 268 inertial signals of flexion and extension

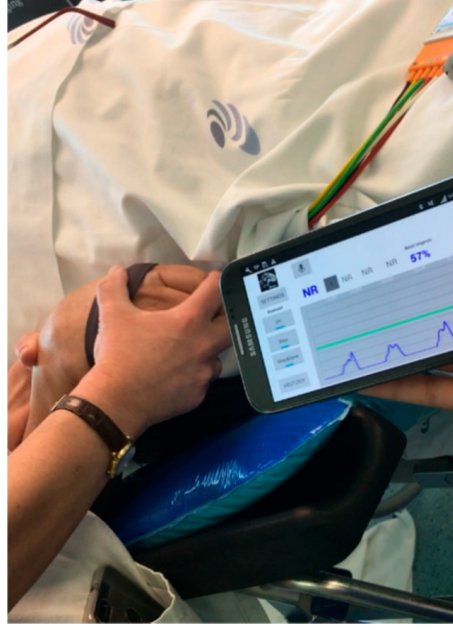


Figure 2.9: iHandU and mobile application for wrist rigidity improvement quantification in a DBS surgery.

movements, each with 200 samples (collected with MoMo hardware) and the respective medical labelling of the rigidity improvement. The improvement of the rigidity was classified as 0, 40, 50, 60, 70 and 80 %.

The angular velocity signals on the y-axis of the flexion-extension movements collected with a iHandU on the patients' hands were filtered with a 4-sample moving average filter, and only the flexion portion of the signal was considered. From this pre-processed signal, the descriptor feature, ϕ_y , is computed with the average angular velocity, μ_{ω_y} , and the average peak, μ_{p_y} , according to Equation 2.1 [57].

$$\phi_y = \sqrt{\mu_{\omega_y} \cdot \mu_{p_y}} \quad (2.1)$$

A second-order polynomial regression model developed with the descriptor feature classifies the improvement of rigidity with a prediction accuracy of 83.9 %. The classification of rigidity improvement (y) is calculated according to the following Equation 2.2 [57]:

$$y = -0.6081\phi_y^2 + 19.6222\phi_y - 75.7418 \quad (2.2)$$

The device and the classification algorithm are patented in Canada, European Unit, Japan, People's Republic of China, United States and Republic of Korea [56,57].

Chapter 3

PD Symptoms Motion Capture Protocol for Data Collection in Hospital Environment

The large number of articles focusing on the quantification of PD symptoms, the need to create remote follow-up solutions brought by the COVID-19 pandemic and the evidence that these are equally or more efficient than the standard methodology emphasise the need to monitor more closely and objectively the disease's motor symptoms [63].

This dissertation is inserted in the further development of the iHandU system. The development and the inclusion of quantification models in the system have its beginning in this dissertation. Thus, the existing system detailed in Section 2.4 which comprehends the iHandU and the mobile application was the main tool for this work. Although the final goal of the system is to be used in home and clinical monitoring, we will only focus on clinical monitoring, since it is a more controlled environment for data collecting.

In order to create a solution that effectively responds to the needs of doctors and PD patients, direct contact with clinicians was kept throughout the process of developing the system. Requirements for the application and dashboard were gathered, and feedback was received to optimise the multiple iterations. Regarding the quantification of symptoms, it was also inquired what information is relevant to the clinical practice, as well as which are the most appropriate scale, motor symptoms and exercises to assess the stage of the disease. Furthermore, to collect PD patients' inertial movements, a protocol and study were submitted to the Ethical Committee of Centro Hospitalar Universitário de São João. All these processes are explored in the following Sections.

3.1 Contributions to the evolution of the iHandU app user interface

The digital interfaces were developed in a dissertation inserted in the PD monitoring project [59]. The involvement in this work was very important to understand in depth what will be the framework for the implementation of the algorithms and also to make explicit what would be crucial to support the quantifications.

Confirmed the need for objective quantification by the consulted clinicians, was underlined the importance of detailing the context of the evaluation to enable a further thorough analysis, namely whether the patients took medication, if so, what the dosage and whether they were in "on" or "off" state. It was also acknowledged the possibility of providing movement metrics, indicative of the assigned classification with the intent to give more complete information that can help improve medical insight.

Despite the great focus on motor symptoms, because they are the easiest to measure and quantify, non-motor symptoms and patients' quality of life are relevant indicators in physicians' daily practice. Given this, doctors agreed that the PDQ-8 scale would be an essential addition to iHandU app and an appropriate choice for screening the quality of life of individuals with PD in a concise way, with only eight questions.

The evolution of the iHandU app was centred in corresponding to the clinical needs and still maintaining it simple for patients' usability. As previously mentioned, specific modes were created for patients and clinicians and a third for clinical studies. In addition, the dashboard was improved in order to maximize the relevant information for the clinicians, keeping an user-friendly display.

3.2 Ethical process

A set of documents were prepared to have the authorization of the Clinical Direction, the Ethical Committee and the Data Protection Officer of Centro Hospitalar Universitário de São João for the study of new methods of monitoring motor symptoms in Parkinson's disease patients with m-Health, machine learning and wearable sensors.

The redacted documents presented the study, its objectives, concepts, relevance, benefits and risks. They equally included a solution proposal for the anonymity of the patients and the collected data. Furthermore, a request to use the collected data in research and development work was also added. Acceptance was stamped at the sixth of May of 2022 by the Clinical Direction. A compilation of the approved documents can be found in [Appendix A.1](#)

Two more patients' informed consent documents were prepared, accordingly to the Declaration of Helsinki. They can be revised in [Appendices A.2](#) and [A.3](#).

The involvement with the CHUSJ made it possible to move forward with the project and collect data that is the input for the development of classification models.

3.3 Gathering of requirements for symptoms' quantification

There is a broad span of scales to quantify PD symptoms, however, MDS-UPDRS part III was the one recommended to assess motor symptoms, since it focuses exclusively on the motor symptoms and doctors are very acquainted with it. Among the symptoms that figure in the scale, some, such as speech and facial expression, were put aside, due to the impossibility of assessing them with iHandU. Whereas rigidity, gait, bradykinesia and tremor were contemplated. For these symptoms have been chosen the exercises which are best depicted in movement signals and can be easily performed at home or in appointments. In Table 3.1 are the selected exercises associated with the symptoms they intend to evaluate and their respective MDS-UPDRS item number.

Table 3.1: Selected exercises to quantify Parkinson's disease motor symptoms and their respective items on MDS-UPDRS scale [31]

Symptom	Exercises	MDS-UPDRS item
Rigidity	Wrist rigidity	3.3
Gait	Walk, turn around and return	3.10
Bradykinesia	Open - close movements	3.5
	Pronation - supination movements	3.6
	Leg agility	3.8
Tremor	Rest tremor	3.17
	Postural tremor	3.15
	Kinetic tremor	3.16

Insights into the symptoms, the exercises and the details that are analysed in each were got not only in the beginning, but throughout the entire period of going to the Neurology appointments. The participation in these appointments allowed the author to be acquainted with the characteristics that physicians look for and on which they base themselves to make subject quantifications of the symptoms. This is a fundamental starting point to later extract from the signals these same characteristics that physicians focus on, but in objective numbers.

3.4 Protocol design

A protocol was designed to gather data from the assessing exercises in PD patients' appointments in CHUSJ. For the data acquisition was used iHandU and iHandU offline mode app, specific for clinical studies. Therefore, for each exercise, the protocol distinguishes three different steps: the iHandU positioning, the preparation of the exercise and the indications given by the doctor to perform the exercise.

The protocol presented below resulted from a collective effort with the doctor who followed the work more closely. The protocol was based on the MDS-UPDRS Part III indications, and there was a great concern to make it executable in a hospital environment and adapted to the established clinical practice.

Moreover, the procedure had to be adapted in some cases because the hospital's conditions differed from those idealised or because patients had restrictive disabilities. For example, the hospital chairs had no arms so that patients could lay their hands during the resting tremor exercise, so another support surface had to be devised, as well, the advanced state of the disease made it impossible for some patients to complete the minimum distance in the gait exercise. Follows the created protocol:

A) Wrist rigidity exercise - Figure 3.1

This exercise must be performed by the physician.

1. Place the band below the fingers, with the box in the interior facing the hand palm.
2. Explain to the patient to go as limp as possible as you test for rigidity.
3. When the exercise gets started, the helper must do slow passive movements of the wrist joint.

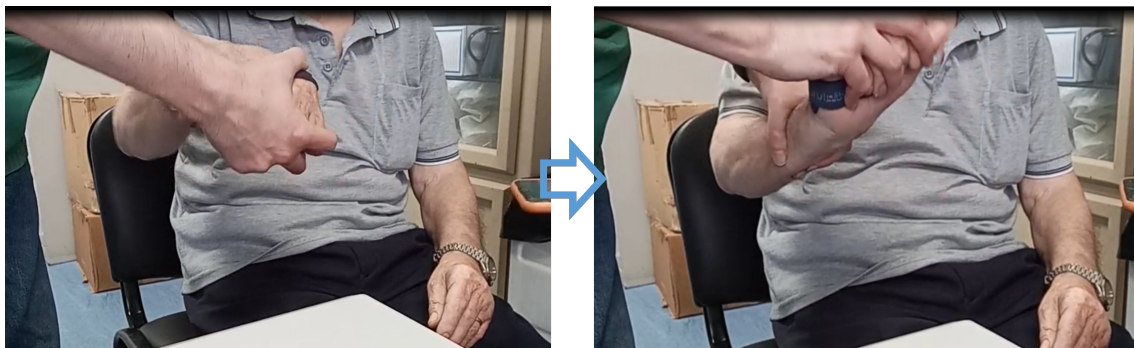


Figure 3.1: Example of rigidity exercise.

B) Gait exercise - Figure 3.2

1. Place the band on the ankle, with the box in the interior to the outer side of the ankle.
2. To get prepared for the test, the patient must be in a wide corridor where it is possible to walk forward and return.
3. When the exercise gets started, the patient must walk at least 5 meters and turn around to return to the initial point.

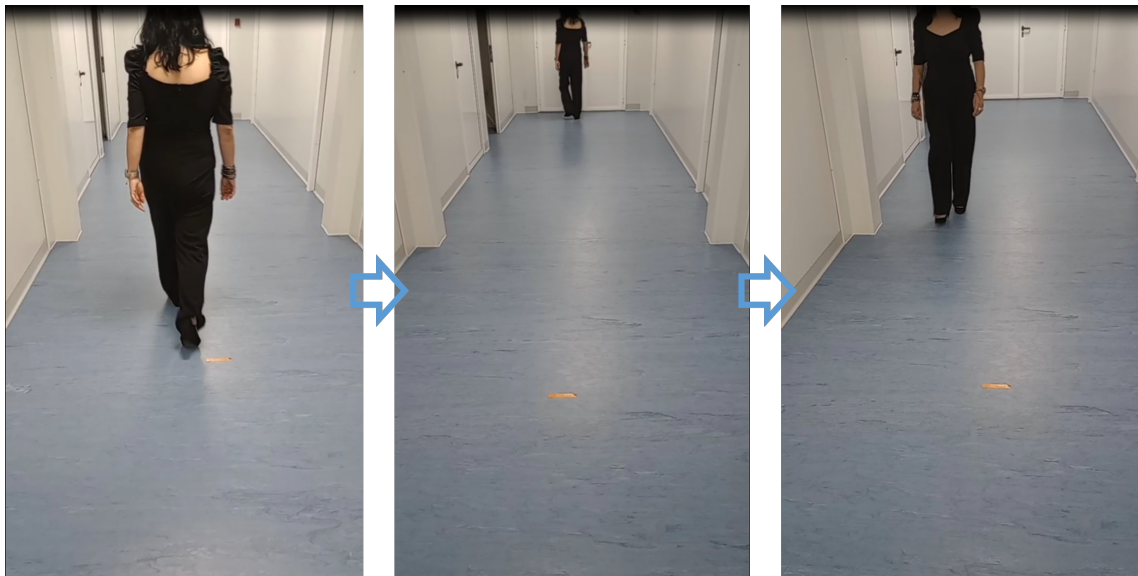


Figure 3.2: Example of gait exercise.

C) Hand open-close movements exercise - Figure 3.3

1. Place the band around the fingers, with the box in the interior facing the hand palm.
2. To get prepared for the test, the patient must extend the arm out in front of the body with the palms down.
3. When the exercise gets started, the patient must close and open the hand at least 10 times as quickly and as fully as possible.



Figure 3.3: Example of hand open-close exercise.

D) Hand pronation-supination movements exercise - Figure 3.4

1. Place the band below the fingers, with the box in the interior facing the hand palm.
2. To get prepared for the test, the patient must extend the arm out in front of the body with the palms down.

3. When the exercise gets started, the patient must turn the palm up and down alternately at least 10 times as fast and as fully as possible.

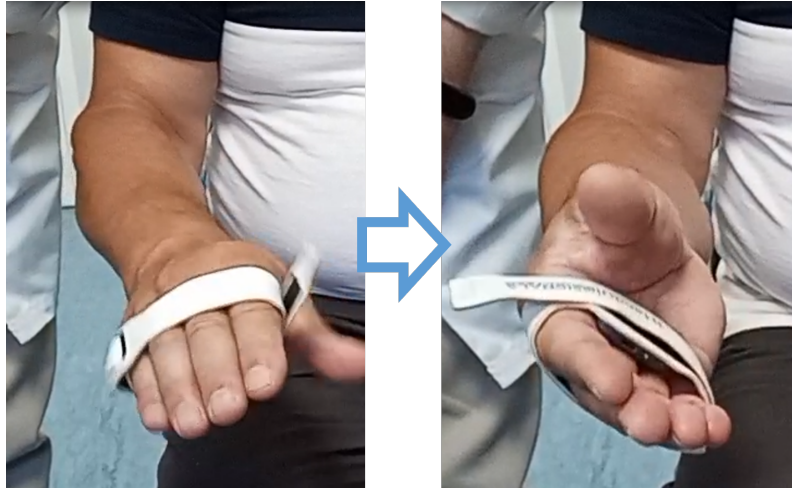


Figure 3.4: Example of hand pronation-supination exercise.

E) Leg agility exercise - Figure 3.5

1. Place the band on the ankle, with the box in the interior to the outer side of the ankle.
2. To get prepared for the test, the patient must sit in a straight-backed chair with arms, with both feet comfortably on the floor.
3. When the exercise gets started, the patient must raise and stomp the foot on the ground at least 10 times as high and as fast as possible.



Figure 3.5: Example of leg agility exercise.

F) Rest tremor exercise - Figure 3.6

1. Place the band around the fingers, with the box in the interior facing the hand palm.
2. To get prepared for the test: Sit quietly in a chair with the hands placed on the arms of the chair.
3. When the exercise gets started, keep this posture for at least 10 seconds.



Figure 3.6: Example of rest tremor exercise.

g) Postural tremor exercise - Figure 3.7

1. Place the band around the fingers, with the box in the interior facing the hand palm.
2. To get prepared for the test, the patient must stretch the arms out in front of the body with palms down. The wrist should be straight.
3. When the exercise gets started, the patient must keep this posture for at least 10 seconds.



Figure 3.7: Example of postural tremor exercise.

H) Kinetic tremor exercise - Figure 3.8

1. Place the band around the fingers, with the box in the interior facing the hand palm.
2. To get prepared for the test, the patient must place the arm in an outstretched position with the palm down.
3. When the exercise gets started, the patient must get the finger to the nose's tip and stretch it fully again, at least 3 times. It is not necessary to do the exercise too quickly.

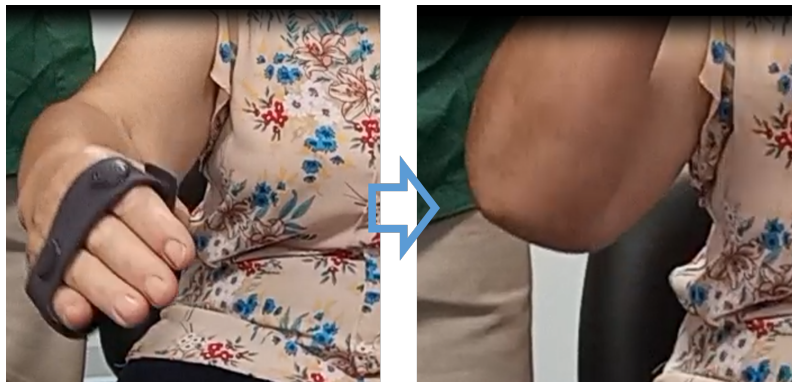


Figure 3.8: Example of kinetic tremor exercise.

3.5 Hospital setup and datasets collection



Figure 3.9: Example of hospital setup for data collection.

In the Neurology appointments at the CHUSJ, a collaborative approach was made between the author and the attending physician for the data acquisition regarding each of the exercises of the designed protocol (Subsection 3.4).

Beforehand, a camera was set for recording the execution of the exercises. Then, to each exercise, the iHandU band would be placed on the patient according to the protocol instructions. Completed that step, the doctor would give the exercise guidelines to the patients. After the execution of the exercise, the doctor would classify the severity of symptom, and it would be recorded on the application.

The physician gives a discrete score from 0 to 4, accordingly to the MDS-UPDRS scale, with 0 corresponding to no impairment and 4 to the symptom maximum severity.

Figure 3.9 shows the normal setup adopted for data collection in the hospital. For rigidity assessment, in this case, already with the band on the patient's hand, the physician performs the manoeuvre, while the author registers the motion data of the exercise and the medical rating.

3.5.1 Datasets construction

For each one of the eight exercises a dataset was created. The collected data were cropped, accordingly to the steps in Figure 3.10, so they were prepared for further processing and development of severity quantification models.

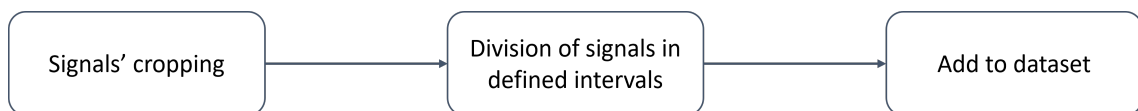


Figure 3.10: Schematisation of steps for datasets preparation.

Firstly, videos of the exercises were reviewed and confronted with the recordings with the signals. Then, the signals' portions in which the task might have been performed erroneously or in which the exercise was not performed were eliminated. In a last step, the signals were divided into intervals, the majority equivalent to the minimum number of repetitions imposed on MDS-UPDRS scale. In Table 3.2 are listed the intervals retained for each exercise, as well as the number of crops extracted from each signal. The reasons behind the defined cropping intervals and number of repetitions per signal are enumerated in the following points. Moreover, divergent situations are also stated.

- In the recording of the gait exercise, some patients only managed to perform a shorter version of the route, and there were also individuals who, due to the still early stage of the disease, repeated the task. In the latter case, the repetitions were separated and recorded individually.
- In the case of bradykinesia, ten movements of the exercises were cut out, following the indications of the MDS-UPDRS scale. However, only one repetition of the ten movements per signal was considered for the datasets since the assessment of this symptom considers the amplitude, speed and progression over time. Thus, a second repetition of the moves could reveal a greater disability than the real one.

- Concerning the tremor exercises, they also followed the number of movements stated in the scale, three finger-to-nose movements in kinetic tremor and ten seconds of rest and postural tremor. In the case of this symptom, its assessment focuses only on the presence of tremor and its amplitude, but not on its temporal progression, therefore, if it exists, the several repetitions along the signal were recorded.
- In the rigidity exercise, when rigidity is not detected, an activation manoeuvre is applied in the opposite arm to the tested one to distinguish between level 0 and 1. This way, a dataset was created from the rigidity signals under the activation manoeuvre, if they represent a level 1, and of the standard wrist manipulation, for all the other levels. A sliding window of three consecutive flexions was run to select, in each signal, the flexions with the most constant amplitudes.

Table 3.2: Intervals and number of repetitions per signal considered to crop various exercises' signals.

Symptom	Exercises	Interval	Repetitions/signal
Rigidity	Wrist rigidity	Three wrist flexion movements	One
Gait	Walk, turn around and return	Walk, turn and return	As many intervals as are contained in the signal
Bradykinesia	Open - close hand movements	Ten open-close movements	One, starting in the first movement
	Pronation - supination movements	Ten pronation-supination movements	
	Leg agility	Ten foot tapping movements	
Tremor	Rest tremor	Ten seconds	As many intervals as are contained in the signal
	Postural tremor	Ten seconds	
	Kinetic tremor	Three finger-to-nose movements	

The rigidity's manoeuvre of flexion and extension of the wrist must be performed, imposing the same amount of strength along the exercise duration. However, it is very difficult to be maintained and guaranteed by the person doing the manoeuvre. In this manner, by the centrifugal force equation, presented in Equation 3.1, with a constant mass, m , and radius, r , by assuring a constant angular velocity, ω , it is possible to ensure that the applied strength, F , is constant too. For this reason, the movements with the lowest standard deviation of angular velocity were selected to provide a constant applied force.

$$F = m.\omega^2.r \quad (3.1)$$

On the other hand, the force measured on the analogue sensors, which could provide more direct insight into the movements, proved inconclusive due to a misuse of the sensors. The force of the movement was not always placed on the sensors, and individuals with larger hands had to be tested with a prototype band without force sensors. Whereby the inclusion of force analysis was not taken further.

3.5.2 Datasets collected at the hospital

The data contained in the datasets were collected from fifteen patients and five healthy individuals (all considered zero stage for the medical label). In an overall view and exemplified in Figure 3.11, the datasets are made up of:

- The name of the CSV document in which the signals were exported.
- The side on which the exercise was performed, having not been performed only on both sides due to lack of time in consultations.
- The medical label, from 0 to 4, given by the doctor according to the MDS-UPDRS scale criteria.
- Three-axis data from the accelerometer, the gyroscope and the magnetometer.
- Data from the two force sensors.

name	side	medLabel	ax	ay	az	wx	wy	wz	mx	my	mz	f1	f2
'1654790189558'	'right'	0	419x1 dou...	419x1 dou...	419x1 dou...	419x1 dou...	419x1 dou...	419x1 dou...	419x1 dou...	419x1 dou...	419x1 dou...	419x1 dou...	419x1 dou...

Figure 3.11: Example of a dataset line.

Examples of cropped acceleration and angular velocity signals of the different exercises are presented in Appendix B. Acceleration (A) and angular velocity (W) are the signals used in this work. In the following Chapter, these raw signals will be pre-processed and characteristics of the symptoms will be extracted from them.

Table 3.3: Number of signals per severity level, from 0 to 4, collected in the datasets of each exercise.

MDS-UPDRS score	0	1	2	3	4	Total
Rigidity	3	8	10	3	0	24
Gait	5	15	4	0	1	25
Leg agility	3	7	6	1	0	17
Open-close	4	3	7	2	0	16
Pronation-supination	7	6	6	0	0	19
Rest tremor	11	5	0	1	0	17
Postural tremor	8	6	0	0	0	14
Kinetic tremor	13	6	0	0	0	19
Total	54	56	33	7	1	151

The total number of signals after cropping differs from the number of participants, as seen in Table 3.3. Steps such as excluding signals smaller than the intervals considered or where exercises were not performed correctly decreased the number of signals. At the same time, the selection of as many repetitions per signal as possible added more signals.

Table 3.4: Characterisation of the data level of severity for each exercise by its weighted average and standard deviation.

Severity level	Weighted mean	Weighted standard deviation
Rigidity	1.54	0.88
Gait	1.08	0.86
Leg agility	1.29	0.85
Open-close	1.44	1.03
Pronation-supination	0.95	0.85
Rest tremor	0.47	0.80
Postural tremor	0.43	0.51
Kinetic tremor	0.32	0.48

The symptoms severity of the analysed population are more concentrated in the lower stages, as can be read in Table 3.4. This is a consequence of the involved patients having their symptoms well controlled with the therapies in use and being in "on" state at the time of acquisition.

The unbalanced distribution of the severity levels among the participants and the existence of many levels which do not have representative signals denote a limitation for the development of robust models to quantify PD symptoms. Due to the strong possibility of the models being seriously impacted by the limited datasets, other analysis methods, namely statistical methods, were used and presented in Chapter 2 to ascertain the potential of the data.

Chapter 4

PD Motor Symptoms Data Processing and Features Extraction

Following the collection of motion data of PD motor symptoms in the hospital and the preparation of datasets, the next step is to extract features. To achieve this goal, a set of processes were conducted. First, were studied which were the most relevant signals that translate the core of the movement of each exercise. Then, the direction of the axes of these signals was envisioned with their change along the movements and on different points on the body to link each portion of the signal to a motion segment.

After defining the approach to have with each signal, a pre-processing pipeline was outlined based on the literature and tailored to the existing data. From these pre-processed signals, were extracted features capable of defining the symptom and translating details which were identified during hospital appointments as the focus of physicians for the assessment of symptoms severity.

The quantification of rigidity improvement in DBS surgeries will also be considered in this thesis as an additional contribution and a possibility to analyse and understand in more depth the rigidity symptom. In this way, the processing and feature extraction regarding the rigidity in DBS will also be presented in this Chapter. All the processes explained in this Chapter were done using MATLAB R2020a.

4.1 Gait

The gait evaluation with MDS-UPDRS focuses on the level of impairment present during the exercise execution [31].

Signal pre-processing

The gait analysis was based on the z-axis of the gyroscope for the evaluation of the stride cycle, on the x-axis of the gyroscope to determine the reversal of gait direction, on the vertical axis of

acceleration, x-axis, to infer the height of the steps and on the y axis to infer on their length.

Starting with the gyroscope z-axis signal, W_z , for its processing, the signal was firstly inverted when the wearable was used on the left ankle. With the data acquired on the left and right sides uniformed, a fourth-order low-pass Finite impulse response (FIR) filter with a 20 Hz cutoff frequency was applied to reduce the frequencies above the range of motion, as well as an 8 samples window moving average filter to remove noise from the higher frequencies which could still be present.

In regard to the x-axis gyroscope signal, W_x , it did not need to be inverted, since its direction change can result either from turning to the left or the right, and this will not be relevant information to retain. The same filters were applied as in the previously discussed signal. The processing steps of gyroscopic signals used for gait analysis are schematised in Figure 4.1.

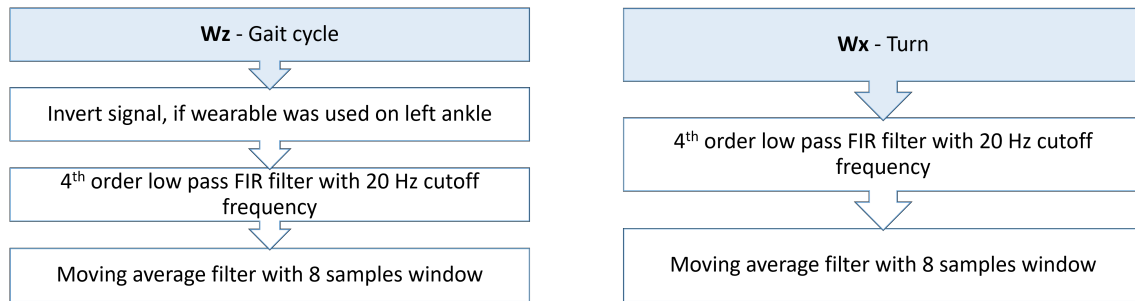


Figure 4.1: Processing steps of the W_z and W_x gait signals.

The height and size of the steps are very important in gait assessment. Thus, the vertical and horizontal acceleration signals, A_x and A_y , respectively, were processed in order to draw more insights. In both signals, a fourth-order low-pass FIR filter with 20 Hz cutoff frequency was applied to reduce the non-relevant high frequencies. In addition, a moving average with only 3 samples window was applied to prevent the signal's decrease in amplitude, which will be necessary for the to be performed analyses.

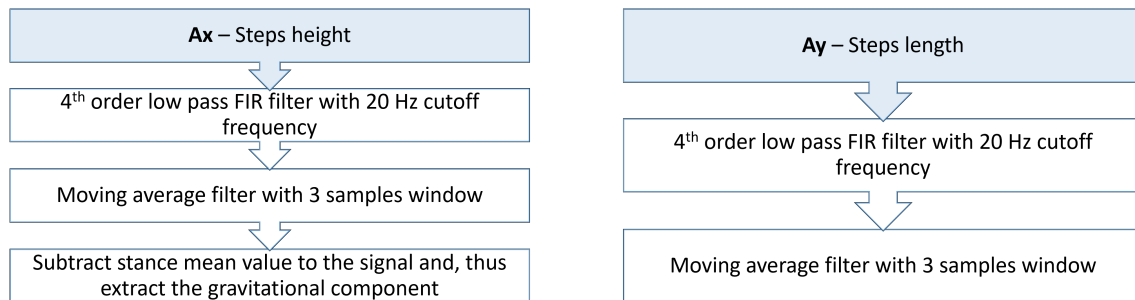


Figure 4.2: Processing steps of the A_x and A_y gait signals.

The vertical portion of acceleration contains a gravitational component. In this way, an approximate value of this component was determined and removed from the total signal, in order to obtain an acceleration as close to the true gait acceleration as possible. That approximate value was

deduced from the average acceleration only on stance periods (when the foot with the wearable is on the floor) [64]. Figure 4.2 schematises the acceleration's processing steps.

Features extraction

The gait segmentation into steps is fundamental for the determination of gait parameters. To perform this segmentation, an algorithm was developed, whose result is presented in Figure 4.3.a. It starts by detecting the positive peaks that correspond to mid-swing points in the W_z signal. The Foot-Off (FO) event, when the foot leaves the floor, is identified as the negative peak prior to the mid-swing peak. As for the foot's Initial Contact (IC) with the floor, it coincides with the negative peak following the mid-swing peak [64].

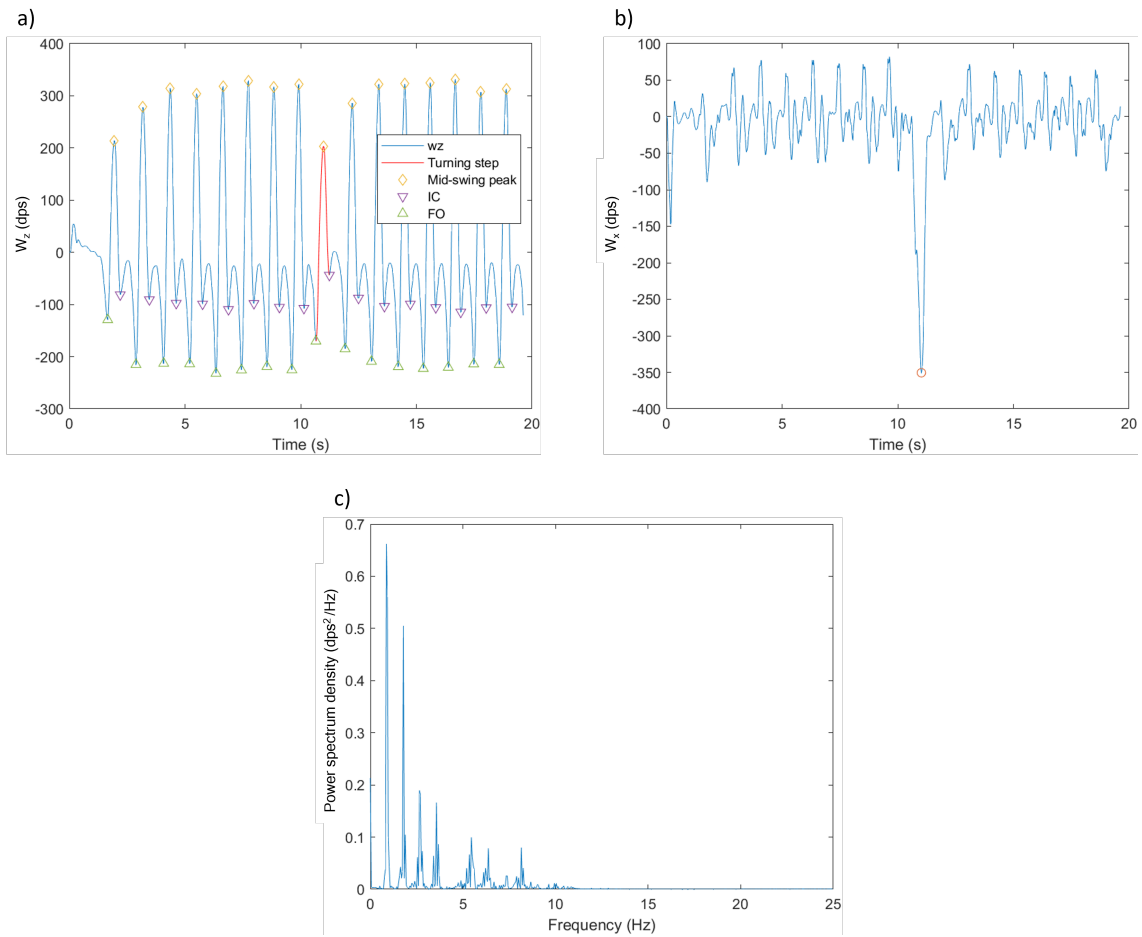


Figure 4.3: Examples of gait processing to determine: **(a)** the mid-swing peaks, the initial contact and the foot-off points and consequently segment the steps, **(b)** the more prominent rotation point from W_x maximum point and **(c)** the number of cogwheel points and the A_y power spectrum density.

From the W_x signal, the maximum peak was detected, that is, the point where the greatest lateral rotation of the foot occurs, shown in Figure 4.3.b. This point was then associated with a step in order to identify the turning step (see Figure 4.3.a). In spite of being recognised as a turning

step, this may not correspond to the only step of the turn, but the most accentuated one. This occurs because the turn may require several steps in individuals with more pronounced disease.

Furthermore, an interpreted at the frequency level was made. To this end, the A_y power spectrum density was calculated, as represented in Figure 4.3.c. The steps and turn segmentation, and the frequency analysis were the starting point for the extraction of gait features.

For each step was determined its swing time (period off the floor) and the following stance time (period on the floor), the latter corresponding to the swing time of the foot opposite to the one with the wearable. The ratio between stance and swing time was calculated up to the second-to-last step, to ensure that each swing has a corresponding stance. The average of these ratio values was used as a metric of gait balance. On the other hand, excluding the turning step that differs from the straight stride, the consistency of the gait was estimated, from the calculus of the standard deviation of the swing periods. Another consistency extracted feature was the number of steps per minute (with both feet).

Regarding the turn analysis, a binary characteristic referring to the non-detection of turning was created (1 if it is not detected, 0 if it is), which may be indicative of a more advanced stage of the disease. In addition, the rotation angle of the turning step was also calculated from the integration of this step over time.

The acceleration signals were equally used to calculate characteristics, namely the average of an approximate height and length of the steps. The first measure was obtained through the double integral of the acceleration of each step, which matches the vertical upward displacement of the foot, divided by two to consider only the elevation. The latter was obtained directly by double integrating the acceleration of each step.

The last two extracted features derived from the frequency analysis, being them the sum of immobilisation moments density and the sum of freeze of gait density. Immobilisation moments where considered to happen in the frequencies below 0.5 Hz and freeze of gait events to occur, according to the literature, from 3 to 8 Hz [65]. The list of gait features can be found in Table 4.1.

Table 4.1: List of gait features.

Gait features	Units
Gait balance	-
Gait consistency	-
Steps per minute	steps/min
Turn not detected	-
Rotation angle	degrees
Steps' mean height	-
Steps' mean length	-
Immobilized	dps^2/Hz
FoG	dps^2/Hz

4.2 Bradykinesia

Bradykinesia is evaluated in three exercises: leg agility, open-close and pronation-supination movements. But regardless of that, their medical labelling stands in the observation of the same conditions: the movement amplitude, velocity, their decrease along time and the presence of interruptions [31].

4.2.1 Leg agility

Signal pre-processing

The leg agility exercise involves tapping the most affected foot on the floor. This does not require any rotation, thus, the analysis of this exercise's signal was centred only in the movement acceleration in A_x .

The steps taken for the signal processing are schematised in Figure 4.4. Given the superposition of the gravitational force, the signal is predominantly negative. For a more straightforward interpretation and manipulation, the signal's absolute value was calculated. Few or virtually no developments exist around the quantification of leg agility exercise to have per base, so the filters that were applied were those that seemed most appropriate for the majority of the dataset signals. A sixth-order FIR low-pass filter with 20 Hz cutoff frequency was applied, followed by a fourth-order high-pass filter with 1 Hz of cutoff frequency and a moving average filter of 3 samples windows to reduce high frequencies, but keep the signals' amplitude resembling the original as much as possible to later calculate the foot displacement as accurately as possible from this signal.

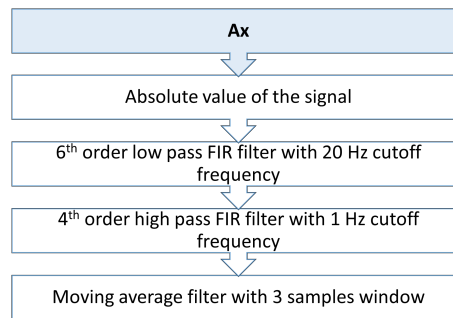


Figure 4.4: Processing steps of the A_x leg agility signal.

Features extraction

For the extraction of features, each repetition of leg raising and lowering was segmented. For that, the minimum peaks of the double derivative of the A_x signal were detected, which correspond to the sudden decrease of acceleration that occurs when the foot hits the ground. In Figure 4.5.a is represented an example of a leg agility signal with the detected events of foot-on-floor pointed out in diamond shape.

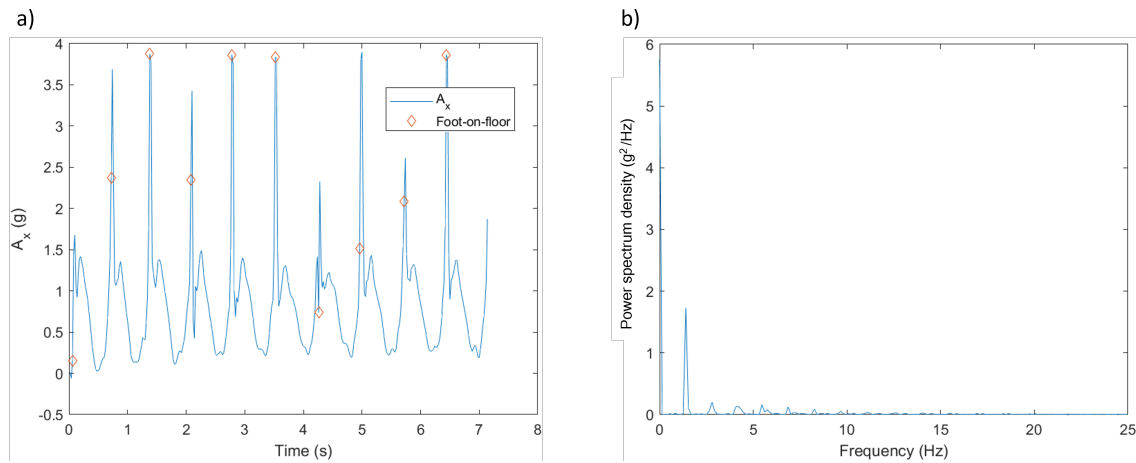


Figure 4.5: Examples of leg agility processing to determine: **(a)** the A_x corresponding to foot-on-floor events and **(b)** the A_x power spectrum density.

The Approximate Entropy (ApEn) of the ten repetitions was extracted as a measure of the regularity of patterns over time [66], based on the method developed by Juanjuan et al. [47]. Furthermore, the total signal power, i.e., the energy involved in the exercise, was calculated as the integral of the PSD curve [67]. Alongside, the density of immobilisation moments (frequency < 0.5 Hz) was summed. The PSD graph can be observed in Figure 4.5.b.

Having per base the duration of each exercise repetition, the average value from the ten repetitions was extracted. The standard deviation of the repetitions' duration was also calculated, as an indirect reference of the consistency of the exercise. Moreover, for each signal, the evolution of the exercise's duration at each repetition was translated by the slope of the linear regression line, m , [67].

The same parameters of mean, standard deviation and slope were determined for the foot elevation's height. The elevation height was calculated by double integrating the acceleration of each raising and lowering and dividing it by two to refer only to the raising height. An overview of the leg agility extracted features is shown in Table 4.2.

Table 4.2: List of leg agility features.

Leg agility features	Units
A_x ApEn	-
Total power	g^2
Immobilized	g^2/Hz
Mean duration	s
Mean height	-
m duration	s/repetition
m height	-
Duration consistency	s
Height consistency	-

4.2.2 Open-Close

Signal pre-processing

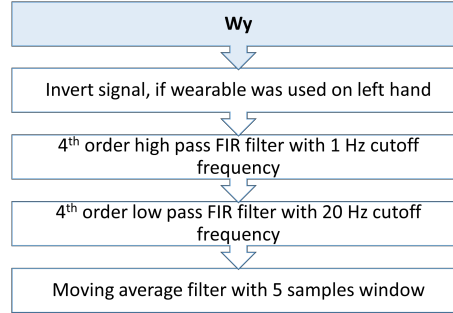


Figure 4.6: Processing steps of the W_y open-close signal.

The open-close hand movement is predominantly rotary around the gyroscope's y-axis. Thus, the W_y signal was processed, following the steps presented in Figure 4.7. Firstly, if the signal was acquired on the left hand, it was inverted so that the close movements were always positive. Following, a sixth-order FIR low-pass filter with 20 Hz cutoff frequency and a fourth-order high-pass filter with 1 Hz of cutoff frequency were implemented, the same way as in the leg agility. To reduce the higher frequencies even more, was used a moving average filter with a 5 sample window, which best fit the majority of the signals.

Features extraction

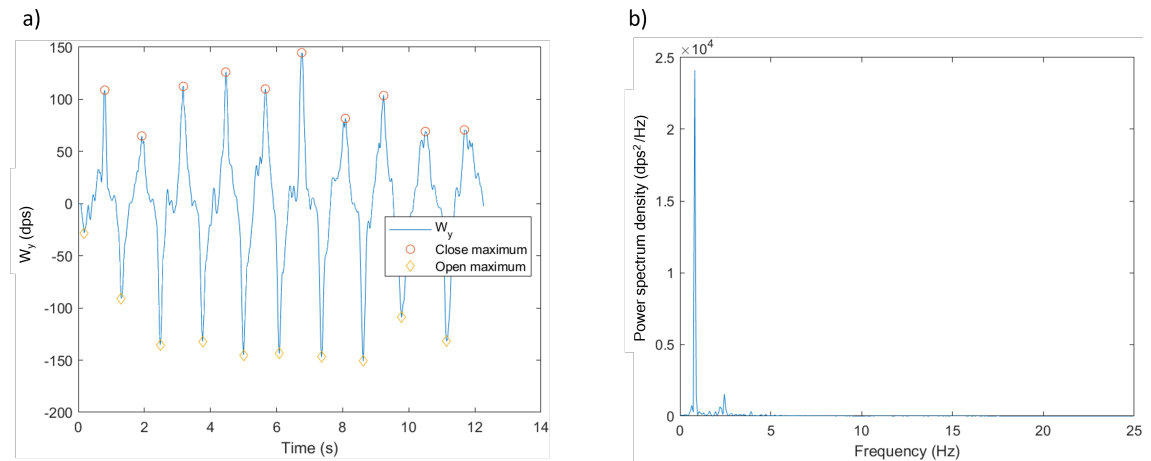


Figure 4.7: Examples of open-close processing to determine: **(a)** the points corresponding to open and close maximum speed and **(b)** the W_y power spectrum density.

Observing the W_y signal in Figure 4.7.a, is notorious the periodicity of the signal that reflects the repetition of opening and closing of the fist. The positive part represents the hand closing, with the maximum peak indicating the maximum speed of the movement, the zero on the left

indicating the beginning and the one on the right indicating the end of the movement. The negative portion of the signal corresponds to the opening of the hand, which is always followed by a closing movement. Likewise, the peak value characterises the maximum speed of the opening and the zeros delimit the movement.

Therefore, for the movements' segmentation, the maximum and minimum peaks were identified. An algorithm was implemented to ensure that the points had been correctly identified, checking if between two repetitions of the same movement, there was one and only one point of the opposite movement. If there is more than one movement, the point with the higher absolute value is kept, which has a higher probability of being an absolute peak and not a misidentified relative peak. In case there is not any point between two movements, the movement with the higher absolute value is kept once more.

Once the peaks were identified, as pointed out in Figure 4.7.a, the open and close intervals were segmented accordingly to the zeros that limited them. The features extracted from the open-close signal are similar to the ones calculated for leg agility, since the same symptom is assessed. The approximate entropy of W_y signal was calculated, as well as the total power and immobilised density, the last two from the power spectrum density (Figure 4.7.b).

The angle of each hand opening movement was further determined through the angular velocity integral with respect to time, along with the velocity peak-to-peak value and the duration of each open-close repetition (based on [67]). These parameters were estimated to try to gauge their linearity, consistency and mean value, over time. The total group of features extracted for the open-close exercise is presented in Table 4.3.

Table 4.3: List of open-close features.

Open-close features	
W_y ApEn	-
Total power	dps^2
Immobilized	dps^2/Hz
Mean duration	s
Mean amplitude	dps
Mean angle	degrees
m duration	s/repetition
m amplitude	dps/repetition
m angle	degrees/repetition
Duration consistency	s
Amplitude consistency	dps
Angle consistency	degrees

4.2.3 Pronation-Supination

Signal pre-processing

The pronation-supination movement is equally a rotational movement, but around the gyroscope's x-axis. Therefore, the W_x sign is inverted, if the wearable is worn on the left, so that pronation corresponds to the positive part. Once more, the signal underwent a sixth-order FIR low-pass filter

with 20 Hz cutoff frequency, a fourth-order high-pass filter with 1 Hz of cutoff frequency and a moving average filter with 3 samples window. Figure 4.8 schematises the pre-processing stages.

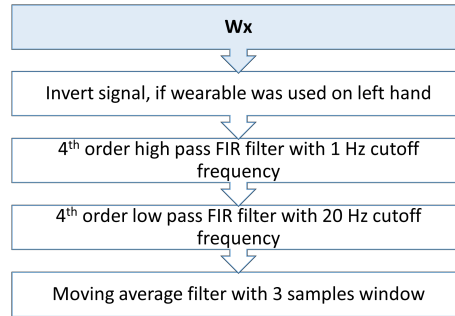


Figure 4.8: Processing steps of the W_x pronation-supination signal.

Features extraction

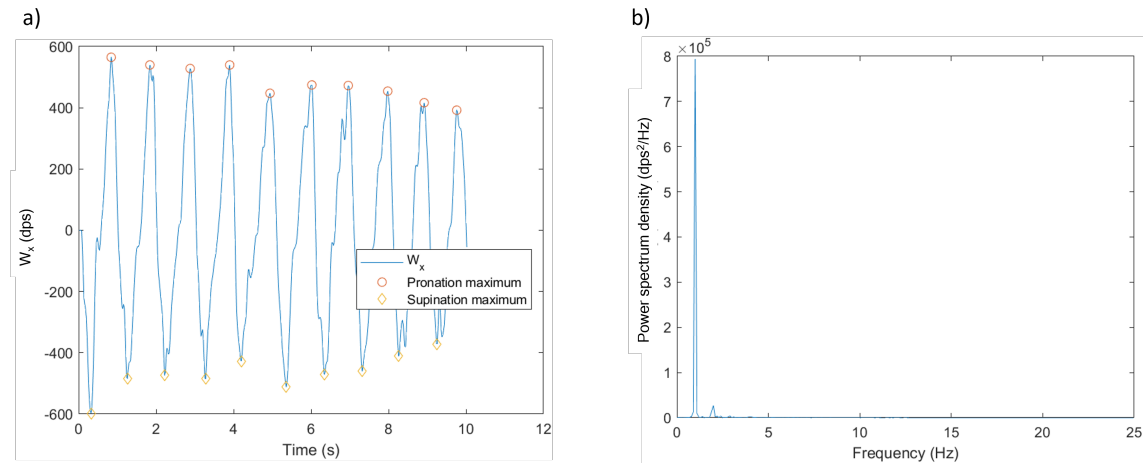


Figure 4.9: Examples of pronation-supination processing to determine: **(a)** the points corresponding to pronation and supination maximum speed and **(b)** the W_x power spectrum density.

The pronation-supination signals, exemplified in Figure 4.9.a, are very similar to the open-close ones; the maximum peaks correspond to the maximum velocity reached in pronation and the minimum peaks to the maximum velocity in supination. The peaks were then identified, eliminated the points that could have been wrongly detected (with the same process previously detailed process for open-close) and the intervals were segmented in line with the zeros that precede and proceed each peak.

The obtained characteristics followed the path established so far for bradykinesia. The pronation angle (integrating the portion of the signal referring to this movement), the peak-to-peak value from pronation to supination and the duration of each exercise repetition were calculated. The mean, the m value and the standard deviation of each one of the determined parameters were used as a measure of the exercise. Even more, from the power spectrum density graph, in Figure

4.9.b, total power and immobilised characteristics were extracted. The approximate entropy of the W_x signal was also extracted. Table 4.4 exhibits all pronation-supination features.

Table 4.4: List of pronation-supination features.

Pronation-supination features	Units
W_x ApEn	-
Total power	dps^2
Immobilized	dps^2/Hz
Mean duration	s
Mean amplitude	dps
Mean angle	degrees
m duration	s/repetition
m amplitude	dps/repetition
m angle	degrees/repetition
Duration consistency	s
Amplitude consistency	dps
Angle consistency	degrees

4.3 Tremor

In MDS-UPDRS, three types of tremor are assessed: rest, postural and kinetic tremor. Although there are three different exercises, the presence of tremor and its amplitude are commonly evaluated parameters [31].

Signal pre-processing

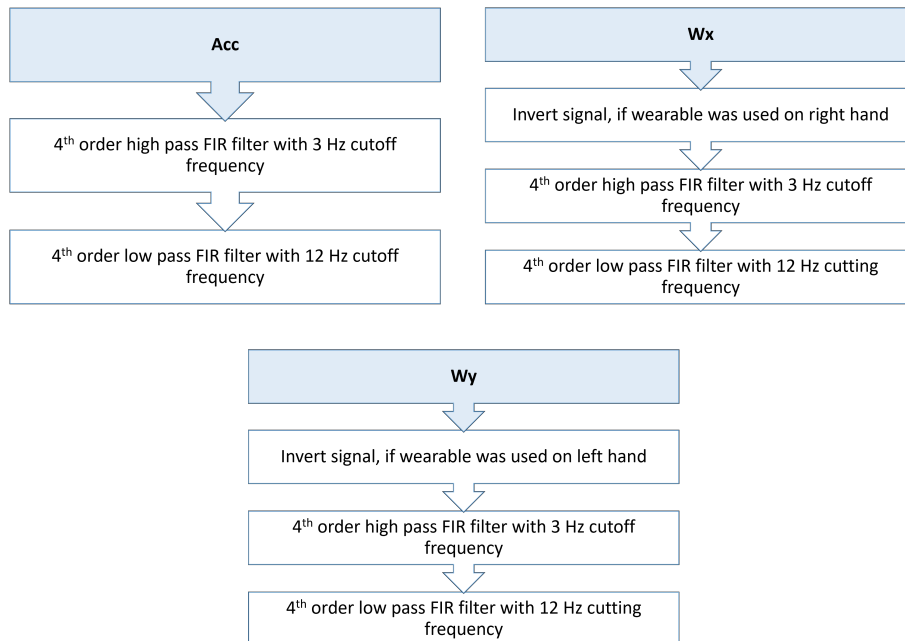


Figure 4.10: Processing steps of the Acc , W_x and W_y tremor signals.

In the kinetic tremor exercise, the finger-to-nose movement has a lower frequency than the tremor. In this way, tremor, usually, only becomes evident in moments of complete extension or flexion of the arm, with it stopped. On the other hand, the rest and posture exercises are static positioning exercises, so if it exists, the tremor will be present throughout the whole task.

Observing acceleration, the tremor may be present in the various axes, so, the three axes were conjugated and was determined the magnitude of the total acceleration vector, Acc . As well, tremor can lead to lateral, vertical or even mixed rotation. Therefore the W_x and W_y signals were considered for the extraction of characteristics.

Acceleration and x and y axes' angular velocity were pre-processed, following the steps schematised in Figure 4.10. A fourth-order high-pass FIR filter with a cutoff frequency of 3 Hz was implemented to reduce movements unrelated to tremor, along with a fourth-order low-pass FIR filter with 12 Hz of cutoff frequency, based on the literature [40]. W_x was inverted when collected on the right side, W_y when used on the left side and both signals were filtered with the same two filters applied to acceleration.

Features extraction

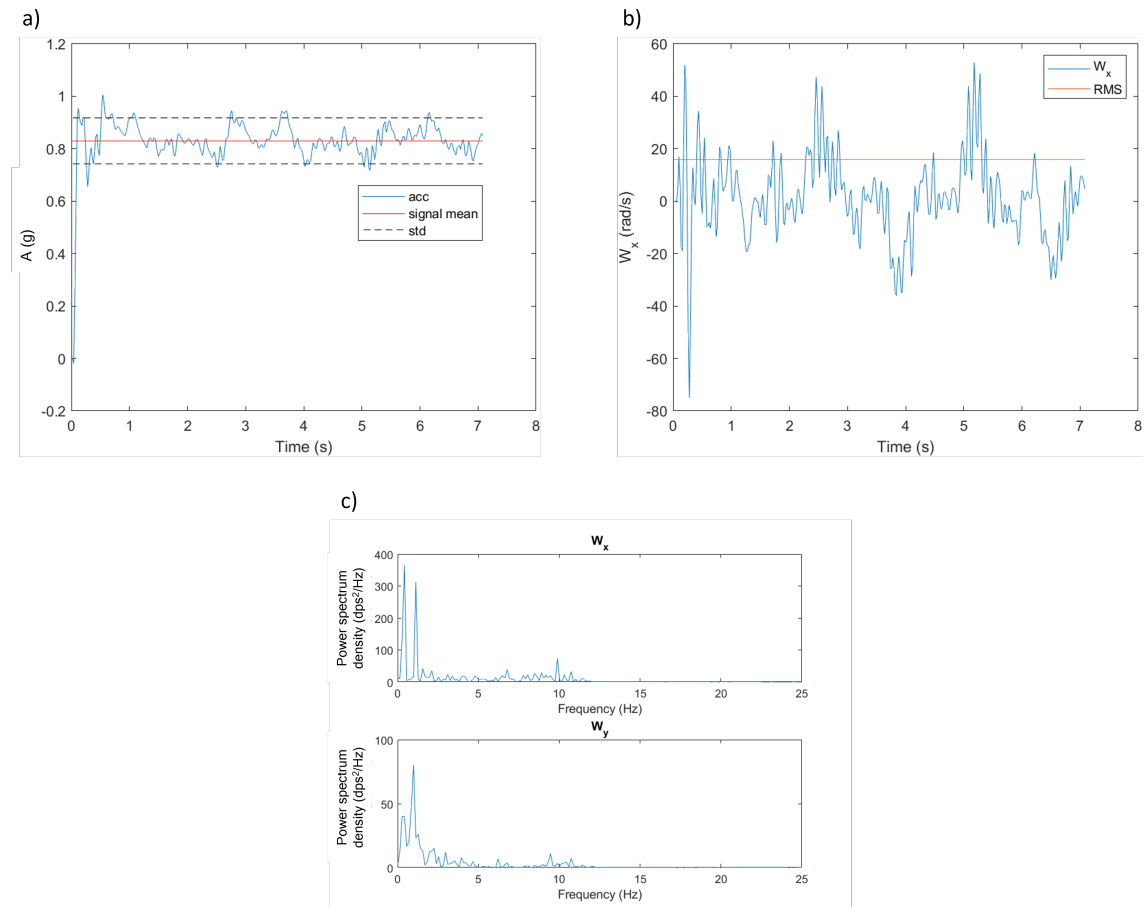


Figure 4.11: Examples of tremor processing to determine: (a) the Acc standard deviation, (b) the W_x root mean square value and (c) the W_x and W_y power spectrum density.

Having these three signals per base, the same characteristics were extracted for each tremor exercise. Following Lušys et al. [42], the approximate entropy was calculated for all considered signals. Moreover, the RMS (based on [42] too) and the standard deviation (std) values of the three signals were determined, both in an attempt to report the amplitude of the tremor. Ultimately, the density of each tremor's characteristic frequencies was assessed in the angular velocity signals, as only these revealed the tremor frequencies. The range of rest tremor stands between 4 and 6 Hz, while the postural and kinetic tremor's frequencies are placed within 4 and 9 Hz [16]. Standard deviation, RMS and PSD of some of the kinetic tremor signals are exemplified in Figure 4.11. Graphs of all the features collected for the three tremor types can be found in Appendix C. Withal, Table 4.5 presents all features extracted in tremor.

Table 4.5: List of tremor features.

Tremor features	
Acc ApEn	-
W_x ApEn	-
W_y ApEn	-
Acc std	g
W_x std	dps
W_y std	dps
Acc RMS	g
W_x RMS	dps
W_y RMS	dps
W_x tremor frequency	dps^2/Hz
W_y tremor frequency	dps^2/Hz

4.4 Rigidity

The assessment of rigidity with the MDS-UPDRS scale acknowledges the detection of rigidity. If it is not noticed, the exercise is done with a complementary activation manoeuvre. When rigidity is detected, it is evaluated after the movement range of motion [31].

Signal pre-processing

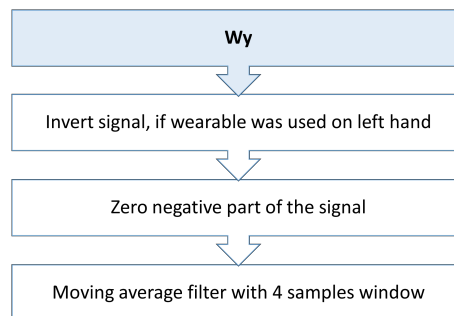


Figure 4.12: Processing steps of the W_y rigidity signal.

Wrist flexion is reflected as a rotation around the y-axis, so the W_y signal was used for rigidity interpretation. Its processing followed the steps reported by Lopes et al. [57]. The signal was inverted when the wearable was used on the left hand, so the flexion motion is always positive. The negative part of the signals is then zeroed, since it is not intended to be considered. As a last step, a four samples window moving average was applied to remove noise of higher frequencies. This pre-processing flow is structured in the scheme in Figure 4.12.

Features extraction

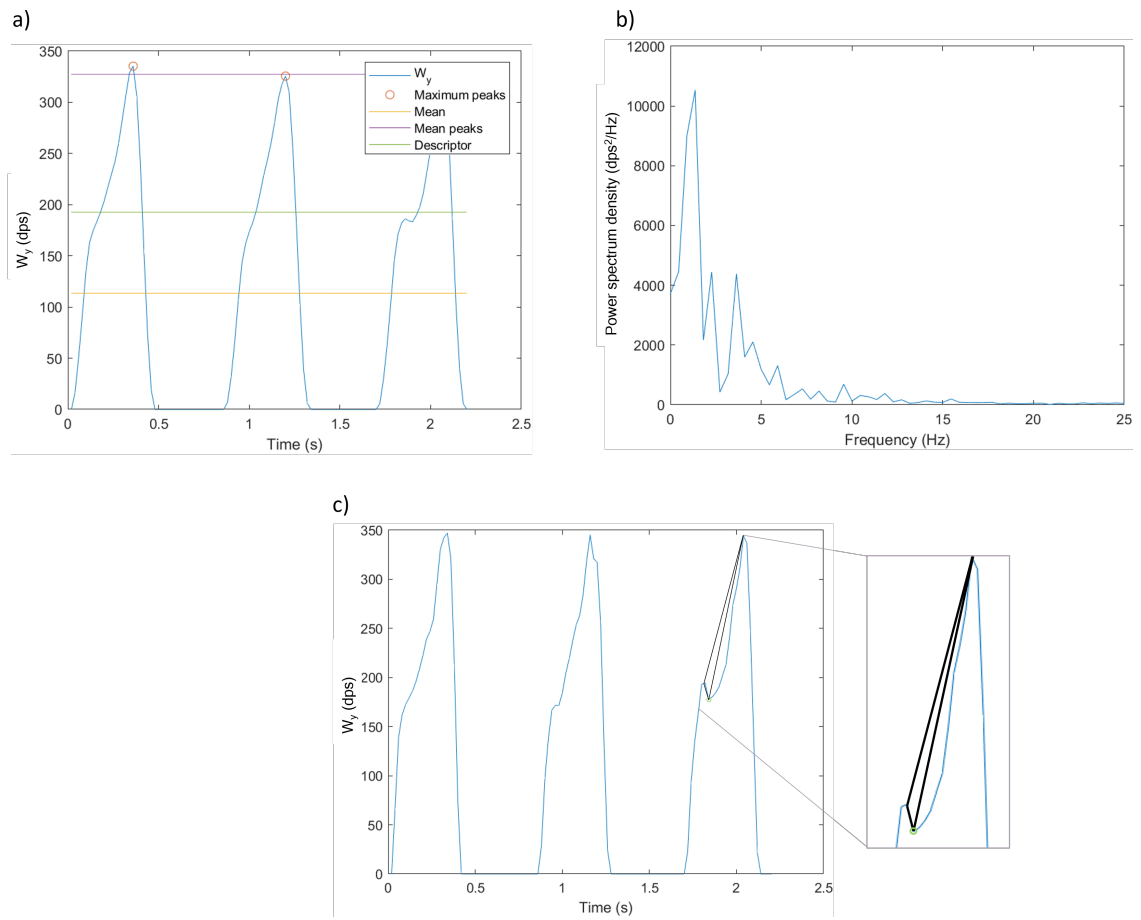


Figure 4.13: Examples of rigidity processing to determine: **(a)** the mean signal, the mean peaks and the descriptor, **(b)** the W_y power spectrum density and **(c)** the number of cogwheel points and the triangles drawn at each point.

Making use of the three arcades' signal, including the zero spacing between them, was extracted the mean signal, by averaging all points. Mean peaks was calculated by averaging the maximum peak of each arcade. Descriptor resulted from the combination of these last two features, according to the Equation 2.1 presented in Subsection 2.5 (features illustrated in Figure 4.13.a. Also from the entire signal, the power spectrum density was calculated (see Figure 4.13.b).

From it, the dominant frequency of the movement was inferred, i.e., the frequency with the highest intensity.

For a cogwheel and range of motion (ROM) centred study, the approach focused only on the arcades was taken. In the cogwheel evaluation, for each arcade, the maximum and minimum points were identified. When a minimum point exists in an arcade, that point is considered a cogwheel event. In this way, the points of each arcade were counted and the cogwheel number feature was created from its average value in the arcades.

Still in the same matter, based on Costa et al. work [62], considering that when there is a minimum cogwheel point, there are two adjacent maximum points, those three points were connected, forming a triangle. In Figure 4.13.c, is exemplified a signal in which the third arcade presents a cogwheel point, and the triangle formed by the extrema points is delimited. With a strong probability that the area of the triangles is indicative of the level of rigidity, this value was calculated (with Heron's formula [68]), the total area for each arch was summed, and the average for the three arcades was established as the cogwheel area characteristic.

Regarding the range of motion of the movement in wrist flexion, it is reflected in the angle that the hand makes over the wrist joint. This angle was calculated from the integration of the flexion arcades with respect to time. The ROM feature was calculated as the average value of the three arcades, as well as the ROM std, which is a measure of the rigidity consistency.

Table 4.6: List of rigidity features.

Rigidity features	
Mean	dps
Mean peaks	dps
Descriptor	dps
Frequency	Hz
Cogwheel number	-
Cogwheel area	dps^2
ROM	degrees
ROM std	degrees

4.4.1 DBS rigidity

Rigidity is assessed during deep brain stimulation surgeries by a clinician, who passively flexes the patient's wrist joint and scores its improvement. This improvement is rated relatively to the baseline at the beginning of surgery, with the patients refrained from any medication at least twelve hours previous [57]. As an additional contribution, pre-existing data of rigidity improvement in DBS surgeries were processed and analysed the same way as the data collected in the hospital.

Signal pre-processing

The rigidity signals acquired in DBS surgeries followed the same processing steps as those obtained at Neurology appointments, listed in Figure 4.12.

Features extraction

Two lines of feature design were taken using DBS rigidity data. In the first line, the descriptor's feature (described in Section 2.4) was calculated. For the second, the features were determined not from the complete signals but only from the arcades, discarding the continuity of zeros between arcs.

Focusing on the second approach, a large set of features was compiled. Starting with mean, presented in Figure 4.14.a, it is determined by summing the three arcades' points and dividing the outcome by the number of points constituting them. The value of mean peaks, exemplified in Figure 4.14.b, results from averaging the arcades' maximum peaks. The descriptor characteristic was assembled from the mean and mean peaks' values and added to the features list.

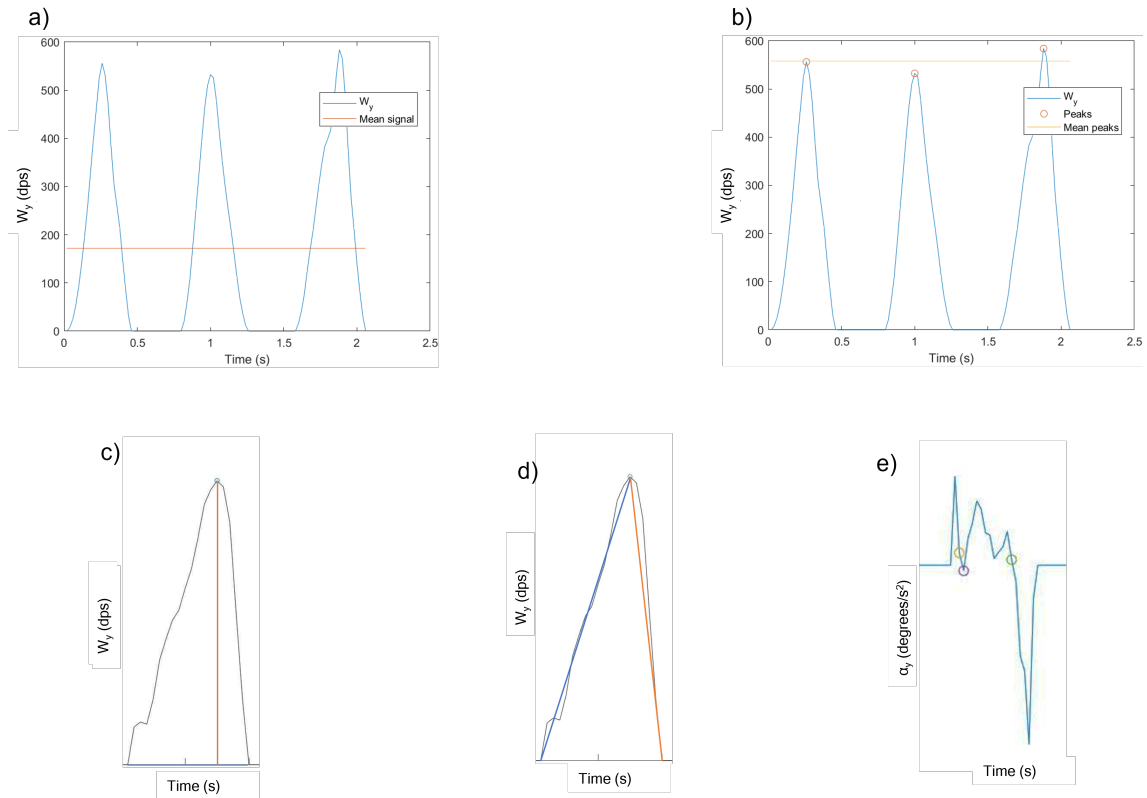


Figure 4.14: Examples of DBS rigidity processing to determine: **(a)** the mean value of the signal, **(b)** the peaks' mean value, **(c)** the arcade's amplitude and duration, **(d)** the lines that connect the arcade's limits to its peak and **(e)** the inflexion points from the derivative signal.

The ratio between each arcade's peak amplitude and its duration was determined, and the mean value of the ratio for the three arcades constitutes the ratio feature. Figure 4.14.c shows the detection of an arcade peak, vertically, and its number of samples, on the basis. A measure of the arcades' tilt was extrapolated from the lines that unite the arcades' limits to their maximum peak, exemplified in Figure 4.14.d. For both sides, was calculated the division between the peak amplitude and the number of samples between the peaks' abscissa and one of its ends. This

measure, which will be as bigger as more prominent the slope is, originated the left and right side relative hypotenuse features from the mean value of three arcades.

A feature regarding the absolute hypotenuse value was also extracted. The left side absolute hypotenuse equals the average value of the distance between the start of the arcades and their maximum peaks. On the other hand, the right side absolute hypotenuse is the average distance between the arcades' peaks and their end. Moreover, a feature was created from the arcade's error to the triangle formed by the two hypotenuse lines. The error triangle feature results from the average difference between the lines' and the arcades' points.

Finally, the average percentage of inflexion points in the arcades was determined to verify the signals' regularity. The first derivative of the arcade is determined to detect the inflexion points, and is imposed the condition that the multiplication of a point by its following point must have a negative result (points with opposite signs) for it to be an inflexion. A case of the second derivative of an arcade with its respective inflexion points is displayed in Figure 4.14.e.

The features extracted from DBS rigidity are reported in Table 4.7.

Table 4.7: List of DBS rigidity features.

DBS rigidity features	
Mean	dps
Mean peaks	dps
Descriptor	dps
Ratio	-
Right side relative hypotenuse	-
Left side relative hypotenuse	-
Right side absolute hypotenuse	dps
Left side absolute hypotenuse	dps
Error triangle	dps
Percentage of inflexion points	percentage

The extraction of features from DBS rigidity and the rigidity collected in appointments was done at different times. The DBS rigidity data was analysed and processed before the appointment data were collected. With the results obtained with the DBS rigidity (in Section 6.1), features that indicated less promise were excluded and other new ones were explored.

4.5 Final extracted features for PD motor symptoms analysis

Table 4.8 shows the list of all extracted features in the different exercises. These features will be used in the following Chapters. In Chapter 5, the features' potentiality and capability to distinguish between the severity levels of the symptoms with statistical significance will be studied. In Chapter 6, features will be explored and selected to develop models to quantify the severity of PD motor symptoms.

Table 4.8: List of features extracted in the different exercises.

Gait	Leg agility	Open-close	Pronation-supination	Tremor	Rigidity	DBS Rigidity
Gait balance	A_x ApEn	W_y ApEn	W_x ApEn	Acc ApEn	Mean	Mean
Gait consistency	Total power	Total power	Total power	W_x ApEn	Mean peaks	Mean peaks
Steps per minute	Immobilized	Immobilized	Immobilized	W_y ApEn	Descriptor	Descriptor
Turn not detected	Mean duration	Mean duration	Mean duration	Acc std	Frequency	Ratio
Rotation angle	Mean height	Mean amplitude	Mean amplitude	W_x std	Cogwheel number	Right side relative hypotenuse
Steps' mean height	m duration	Mean angle	Mean angle	W_y std	Cogwheel area	Left side relative hypotenuse
Steps' mean length	m height	m duration	m duration	Acc RMS	ROM	Right side absolute hypotenuse
Immobilized	Duration consistency	m amplitude	m amplitude	W_x RMS	ROM std	Left side absolute hypotenuse
FoG	Height consistency	m angle	m angle	W_y RMS		Error triangle
		Duration consistency	Duration consistency	W_x tremor frequency		Percentage of inflexion points
		Amplitude consistency	Amplitude consistency	W_y tremor frequency		
		Angle consistency	Angle consistency			

Chapter 5

Motor Symptoms Features Statistical Analysis for PD Severity Classification

The creation of new datasets was very beneficial for this work, as it allowed to know its contents well and to have confidence in it. However, the small size of the datasets is very limiting when it comes to developing prediction models. The existing data may not be sufficient to train the classification models appropriately, and it will still be difficult to infer which features are the most descriptive and enriching for each exercise.

Consequently, statistical analysis emerges as a tool to take the investigation of the extracted features further. This method is also limited by the small amount of data, but may open a larger window to understand which features are most relevant, how classes differ and their applicability in quantification models.

This study investigated the features' power to differentiate the symptoms' classes of severity, between 0 and 4. Since it was impossible to do so in the presence of groups with only one element, all classes containing only one event were eliminated. The DBS rigidity dataset was not studied in this Chapter as it was not considered relevant, given its considerable dimensions. Similarly, the nominal features were left out of this study.

First, the data's normal distribution was tested with Shapiro-Wilk test, due to the reduced number of participants. After that, if the data has a normal distribution, the discrimination between classes is accessed in two ways: independent-samples t-test, if there are only two classes of data for the feature in question, or One-way between-groups ANOVA, when there are more than two classes. In the latter case, the post-hoc Tukey test was used to understand which classes the feature allows to be distinguished [69].

For the features whose data has a non-normal distribution, was applied the non-parametric Kruskal-Wallis test (can be used between two or more groups [70]). In case there is a significant difference between the groups, the Mann-Whitney U test was applied to discriminate between

which groups this difference exists [69]. All the statistical analysis presented in this Chapter were performed with IBM SPSS Statistics 27.

Figure 5.1 summarises in a decision tree chart all these described steps to analyse the distinction between classes of each feature.

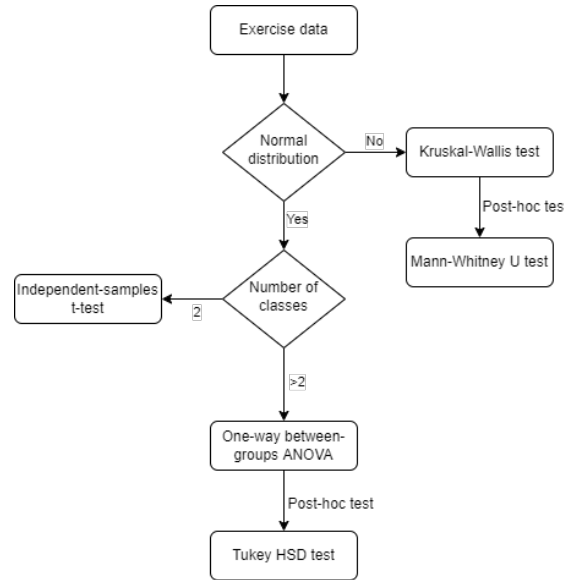


Figure 5.1: Steps to analyse the classes' discrimination in each feature. Based on [69].

5.1 Rigidity

Results

ANOVA analysis was performed to understand the capacity of the extracted features to distinguish the different rigidity stages. The evaluated characteristics belong to levels 0, 1, 2 and 3. A statistically significant difference ($p < 0.05$) was recorded for mean peaks ($F(3,20) = 3.145$, $p = 0.048$) and descriptor ($F(3,20) = 3.123$, $p = 0.049$).

Tukey HSD post-hoc test in mean peaks characteristic points out that the average value for class 0 ($M = 461.283$, $std = 101.046$) has significantly different from class 3 ($M = 287.607$, $std = 58.634$, with $p = 0.040$, represented in Figure 5.2. Classes 1 ($M = 336.064$, $std = 66.762$) and class 2 ($M = 343.978$, $std = 73.797$) do not show any significant different from the remaining.

Although not pointed in the ANOVA test, the post-hoc analysis of mean shows a significant differentiation of the average values of classes 0 ($M = 159.047$, $std = 12.146$) and 3 ($M = 100.528$, $std = 13.481$) (Figure 5.3), with $p = 0.038$. Classes 1 ($M = 127.868$, $std = 26.946$) and 2 ($M = 126.823$, $std = 26.195$) does not present any distinction from the other groups.

Regarding the descriptor feature, post-hoc indicates a significant separation between the average value of classes 0 ($M = 270.053$, $std = 37.397$) and 3 ($M = 169.907$, $std = 28.397$), with $p = 0.033$, but non for classes 1 ($M = 207.231$, $std = 42.066$) and 2 ($M = 208.733$, $std = 43.076$). This is shown in Figure 5.4. On the other hand, the Kruskal-Wallis test applied to the features

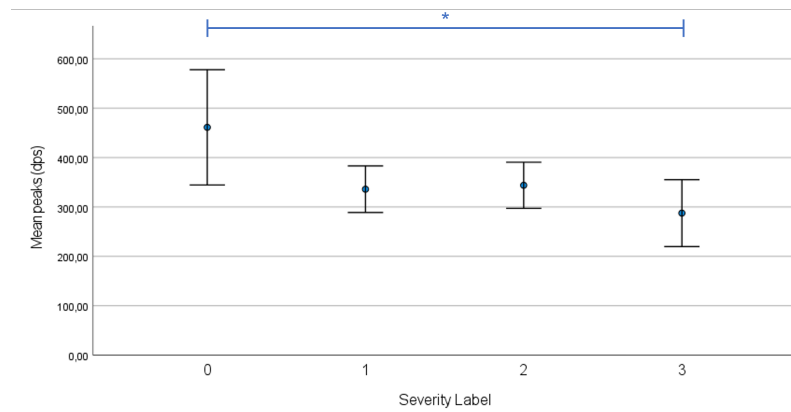


Figure 5.2: Average rigidity mean peaks of classes 0, 1, 2 and 3. *p < 0.05.

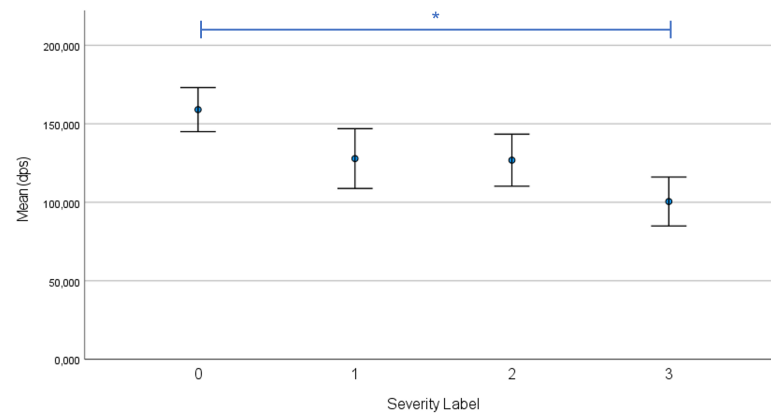


Figure 5.3: Average rigidity mean of classes 0, 1, 2 and 3. *p < 0.05.

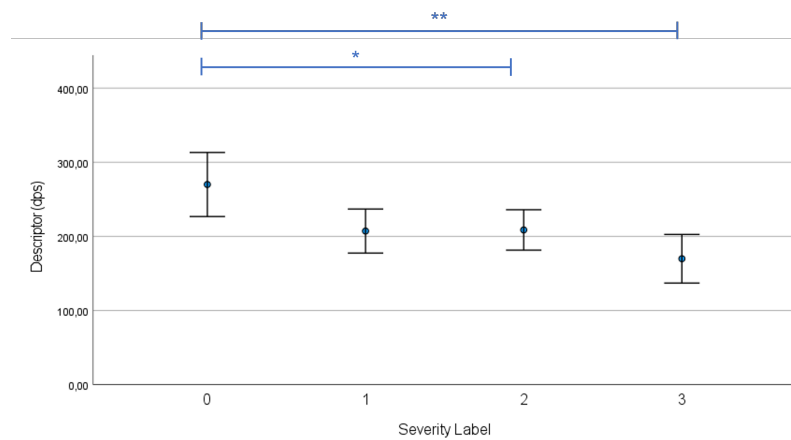


Figure 5.4: Average rigidity descriptor of classes 0, 1, 2 and 3. *p < 0.05, **p < 0.01.

with a non-normal distribution revealed that these are not able to discriminate rigidity stages. In Appendix D.1 are presented all the data obtained in the statistical analysis of rigidity.

Discussion

The descriptor feature separates the more classes, distinguishing 0 and 3 as the mean and mean peaks, and is the only feature to differentiate 0 and 2. Likewise, the separation of 0 and 3 has a higher significance using the descriptor. These results highlight a great difficulty of the features in translating the differences between adjacent levels.

5.2 Gait

Results

The ANOVA test showed that the measurement of the rotation angle and the steps mean length characteristics allowed a distinction between degrees 0, 1 and 2 of gait limitation, with statistical significance ($F(2,21) = 5.271$, $p = 0.014$ and $F(2,21) = 5.726$, $p = 0.010$, respectively).

The post-hoc evaluation of rotation angle reveals that the average value of class 2 ($M = 43.687$, $std = 18.459$) differs significantly from classe 1 ($M = 90.376$, $std = 27.650$), with $p = 0.012$, and class 0 ($M = 88.825$, $std = 25.141$), with $p = 0.044$. The described differences are represented in Figure 5.5.

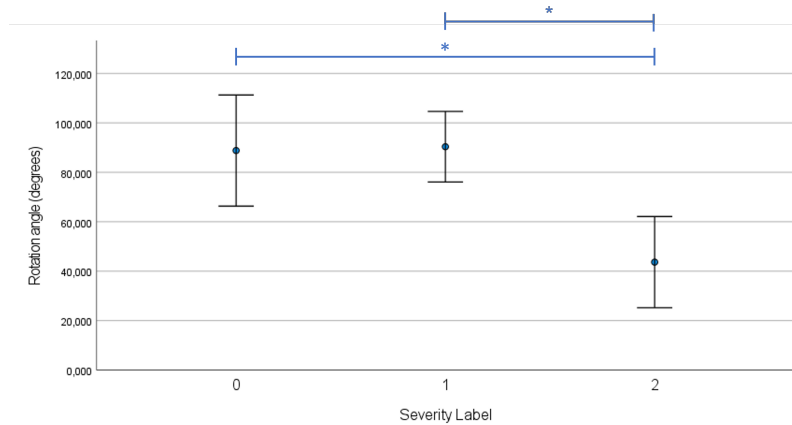


Figure 5.5: Average gait rotation angle of classes 0, 1, and 2. * $p < 0.05$.

As for steps mean length, as shown in Figure 5.6, post-hoc test suggests a significant differentiation between the average value of class 0 ($M = 0.070$, $std = 0.015$) and classes 1 ($M = 0.054$, $std = 0.012$), with $p = 0.048$, and 2 ($M = 0.044$, $std = 0.009$), with $p = 0.009$.

In contrast, the non-parametric test indicated that the analysed features do not significantly differentiate the gait's impairment stages. Appendix D.2 gathers all statistics drawn from gait.

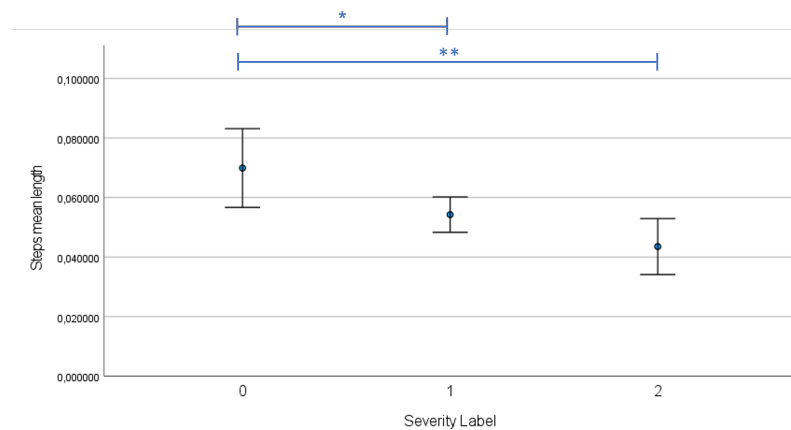


Figure 5.6: Average gait steps mean length of classes 0, 1, and 2. * $p < 0.05$, ** $p < 0.01$.

Discussion

In the assessment of gait features, both the rotation angle and the steps mean length enable distinguishing between classes 0 and 3. However, the steps mean length makes a more significant separation. Furthermore, each of them allows for a further distinction. The steps mean length differentiates class 0 from 1 and the rotation angle, class 1 from 2. Envisioning the creation of models, it can be concluded that their combination would lead to the creation of a model with a better performance.

5.3 Bradykinesia

5.3.1 Leg agility

Results

Among the features with normal distribution, only total power can differentiate the classes 0, 1 and 2 that characterize the leg agility data ($F(2,13) = 8.352$, $p = 0.005$). The Tukey HSD test suggests a significant separation of classe 0 ($M = 0.701$, $std = 0.098$) from class 1 ($M = 0.526$, $std = 0.082$), with $p = 0.014$, and from class 2 ($M = 0.484$, $std = 0.057$), with $p = 0.004$ (Figure 5.7).

Once again, the non-parametric test showed that the features evaluated by it do not have enough information to separate the existing classes. Appendix D.3 contains all data from the evaluation of leg agility.

Discussion

From the set of features drawn from the leg agility exercise data, only total power was found to differentiate between the existing classes, which may be due to a complex translation of the bradykinesia symptoms in this exercise. Total power distinguishes class 0 from classes 1 and 3, the latter with an even greater significance. This again shows a good distinction of the boundary

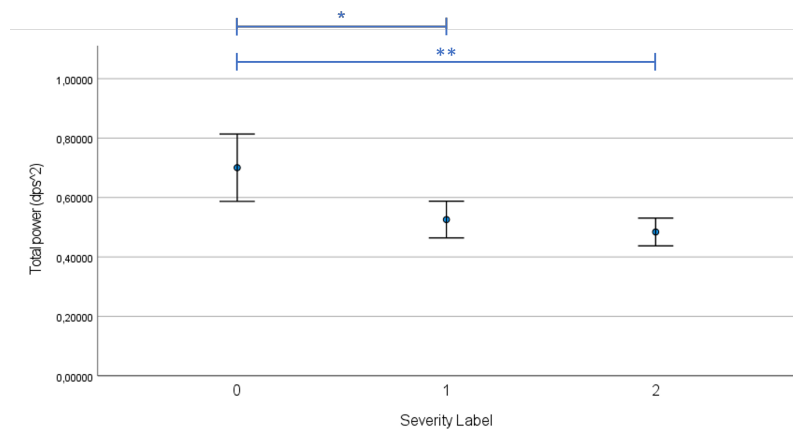


Figure 5.7: Average leg agility total power of classes 0, 1, and 2. * $p < 0.05$, ** $p < 0.01$.

classes, but a greater challenge in adjacent classes. With only one discriminative feature, which does not distinguish class 1 from class 2, it would be challenging to develop a model that could separate them.

5.3.2 Open-close

Results

In the dataset of the open-close exercise, all classes are present except for class 4, and by the ANOVA test, there is a distinction between them, using mean angle ($F(3,12) = 4.386$, $p = 0.027$), mean duration ($F(3,12) = 9.386$, $p = 0.002$) and mean amplitude ($F(3,12) = 4.278$, $p = 0.029$).

The mean angle measure allows a significant dissociation, shown in Figure 5.8, between the average values of class 0 ($M = 64.840$, $std = 26.789$) and class 2 ($M = 34.541$, $std = 8.036$), only, with $p = 0.042$. Classes 1 ($M = 57.874$, $std = 10.395$) and 3 ($M = 30.316$, $std = 14.519$) are not subject to any distinction.

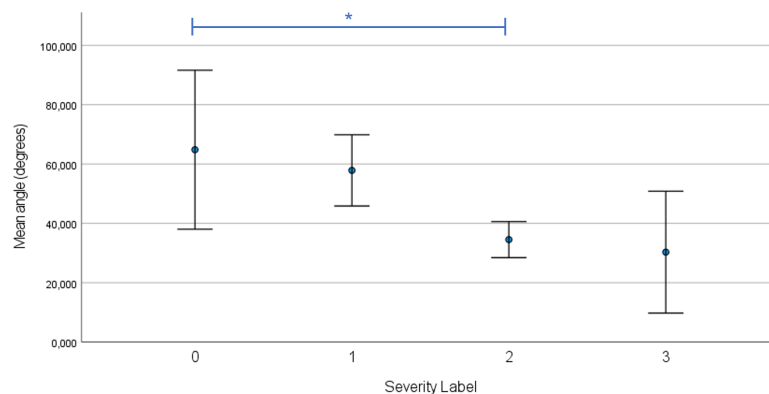


Figure 5.8: Average open-close mean angle of classes 0, 1, 2 and 3. * $p < 0.05$.

In what concerns mean duration, pos-hoc indicates a significant differentiation of the average values of class 0 ($M = 13.900$, $std = 1.635$) and all other classes: for class 1 ($M = 21.467$, $std = 3.961$), with $p = 0.032$, for class 2 ($M = 23.450$, $std = 3.496$), with $p = 0.002$ and for class 3 ($M = 24.300$, $std = 0.636$), with $p = 0.010$. The differences between average values are represented in Figure 5.9.

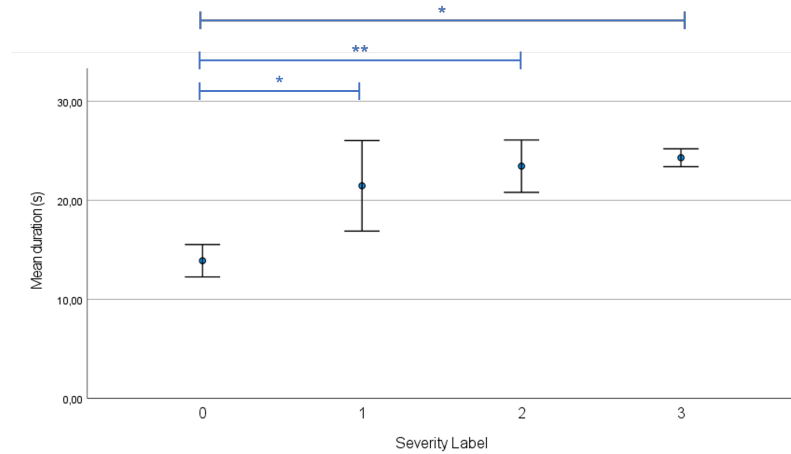


Figure 5.9: Average open-close mean duration of classes 0, 1, 2 and 3. * $p < 0.05$, ** $p < 0.01$.

As for mean amplitude, separates with significance class 0 ($M = 84.417$, $std = 43.604$) and class 2 ($M = -4.669$, $std = 36.395$), with $p = 0.018$ exhibit in Figure 5.10, but not classe 1 ($M = 18.071$, $std = 36.873$) and class 3 ($M = 31.251$, $std = 52.671$).

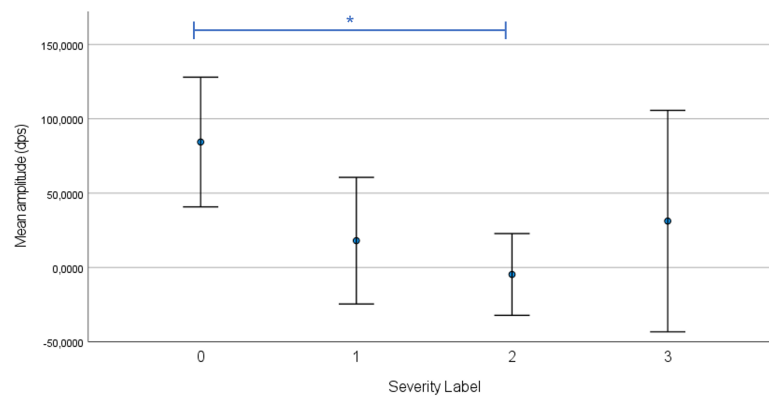


Figure 5.10: Average open-close mean amplitude of classes 0, 1, 2 and 3. * $p < 0.05$.

Contrary to the analyses seen so far, Kruskal-Wallis test revealed a significant difference for the total power feature ($\chi^2(3, n = 11.264)$, $p = 0.010$). In order to identify which classes total power is able to discriminate, Mann-Whitney test was administered. Its result lead to the conclusion that with total power measure it is possible to distinguish class 1 ($Md = 3.22E+5$, $n = 3$) from class 2 ($Md = 7.39E+3$, $n = 7$), with $U = 1.000$, $z = -2.165$ and $p = 0.030$. Classes 0 ($Md = 1.12E+5$, n

= 4) and 3 ($Md = 7.33E+3$, $n = 2$) are not distinguishable using this feature. The average values differences are shown in Figure 5.11. Appendix D.4 compiles all results of the statistical analysis of open-close.

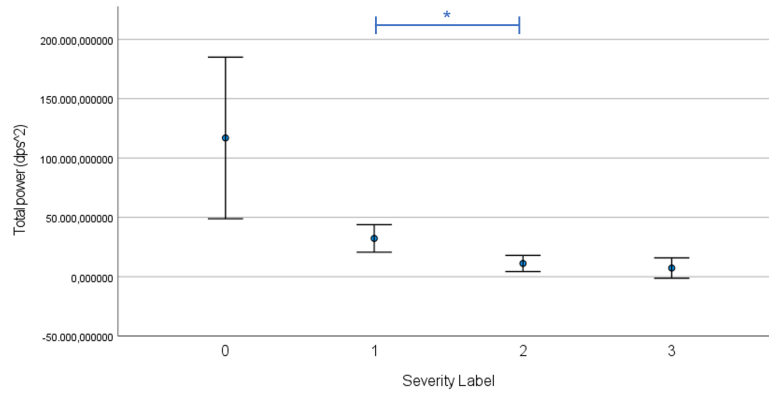


Figure 5.11: Average open-close total power of classes 0, 1, 2 and 3. * $p < 0.05$.

Discussion

The mean duration feature is the one that makes the distinction between the largest number of groups, namely distinguishing class 0 from all the others. All the features with normal distribution distinguish class 0 from 2, being mean duration the one that does it with more significance. Moreover, total power is the only one that distances class 1 from 2. It reinforces the facility to separate the boundary classes. With the variety of classes that each feature can distinguish, in this case, a classification algorithm of the open-close exercise would certainly benefit from the combination of features.

5.3.3 Pronation-supination

Results

The ANOVA test revealed W_y approximate entropy and mean angle as the features capable of distinguishing between the represented classes, 0, 1 and 2 ($F(2,16) = 3.822$, $p = 0.044$ and $F(2,16) = 9.030$, $p = 0.002$, respectively).

Analysing with the post-hoc test, W_y approximate entropy distinguishes significantly class 0 ($M = 0.404$, $std = 0.033$) from class 2 ($M = 0.516$, $std = 0.091$), with $p = 0.043$, while class 1 ($M = 0.485$, $std = 0.095$) is not separable (Figure 5.12). Regarding mean angle, it is possible to conclude that it allows distinguishing with statistical significance classes 0 ($M = 173.653$, $std = 23.349$) from class 1 ($M = 140.350$, $std = 12.143$), with $p = 0.040$, and class 2 ($M = 122.321$, $std = 27.818$), with $p = 0.002$ (Figure 5.13).

Kruskal-Wallis revealed that total power can distinguish the bradykinesia impairment assessed with pronation-supination task ($\chi^2(2, n = 7.814)$, $p = 0.020$). Going further in analysing which

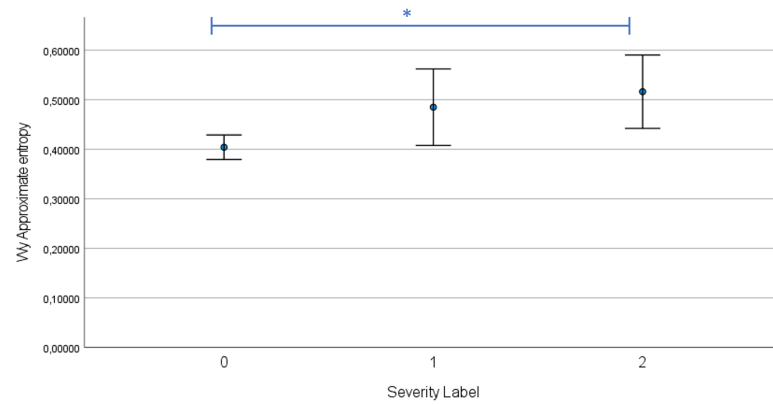


Figure 5.12: Average pronation-supination W_y approximate entropy of classes 0, 1, and 2. * $p < 0.05$.

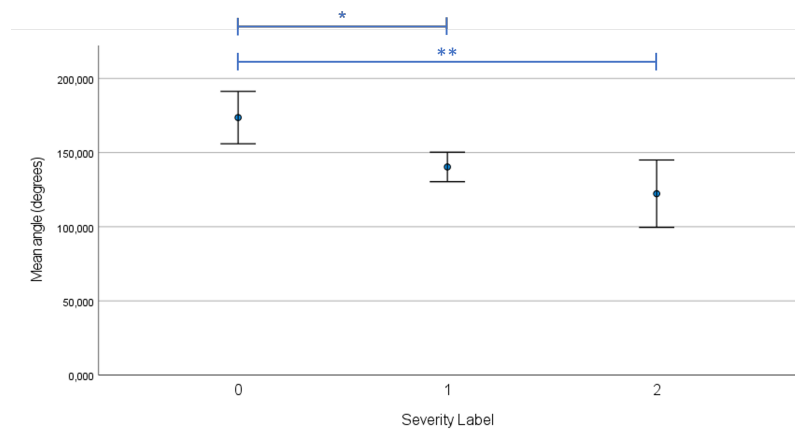


Figure 5.13: Average pronation-supination mean angle of classes 0, 1, and 2. * $p < 0.05$, ** $p < 0.01$.

groups it is possible to distinguish, Mann-Whitney tests indicate a significant separation of the average value of class 0 ($Md = 3.08E+5$, $n = 7$) and 2 ($Md = 1.19E+5$, $n = 6$), with $U = 2.000$, $z = -2.714$ and $p = 0.007$. Concerning class 1 ($Md = 1.80E+5$, $n = 6$), it is not possible to segment. Figure 5.14 shows the average values of total power.

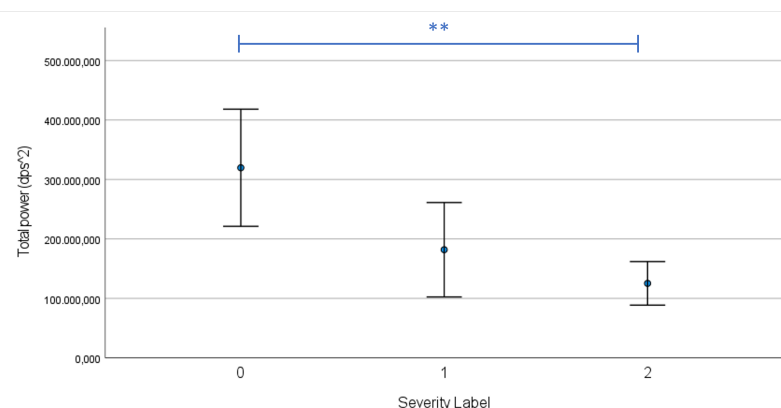


Figure 5.14: Average pronation-supination total power of classes 0, 1, and 2. $**p < 0.01$.

Appendix D.5 includes all results from the statistical analysis of pronation-supination.

Discussion

As for the W_y approximate entropy, mean angle and total power, all distinguish class 0 from class 2. Mean angle still separates class 0 from class 1. The poor ability to separate intermediate classes 1 and 2 would constrain performance if a bradykinetic classification model were created with the pronation-supination exercise data.

Observing the results obtained in the three bradykinesia exercises, it can be noted that total power is able to separate classes for all cases, which implies that it transversally captures the elements of bradykinesia that differentiate classes. In the same way, the number of significant features in the open-close exercise is higher. Therefore this task may reflect more evidently in its data those that are the evaluation parameters of bradykinesia. This point would be important to investigate further if one ever wanted to choose only one exercise for each symptom.

5.4 Tremor

5.4.1 Rest tremor

Results

The tremor exercises only have data of impairments 0 and 1, so the t-test is the tool used for their analysis. In the case of rest tremor, none of the extracted features were able to differentiate with statistical significance the data of the two classes. The statistic values obtained for rest tremor are presented in Appendix D.6.

Discussion

The inexistence of features that differentiate between classes of rest tremor impairment may have several underlying reasons. It may be related to the reduced dimension of data, the design of features that do not accurately translate the symptom or even to the MDS-UPDRS scale, which has very close levels.

5.4.2 Postural tremor

Results

Of the postural tremor features analyzed with the t-test, non differentiate the two classes. Concerning the features evaluated with Kruskal-Wallis, W_x standard deviation (Figure 5.15), W_x RMS (Figure 5.16) and W_x frequency (Figure 5.17) showed to be able to differentiate the average values of class 0 from class 1. The first separates class 0 (Md = 1.42, n = 8) from class 1 (Md = 4.76, n = 6), having $\chi^2(1, n = 6.017)$, $p = 0.014$, the second separates class 0 (Md = 1.48, n = 8) from class 1 (Md = 4.79, n = 6) with exactly the same parameter values and the third separates class 0 (Md = 7.81, n = 8) from class 1 (Md = 198.58, n = 6), with $\chi^2(1, n = 6.667)$, $p = 0.010$. In Appendix D.7 are exhibit all the results obtained for postural tremor.

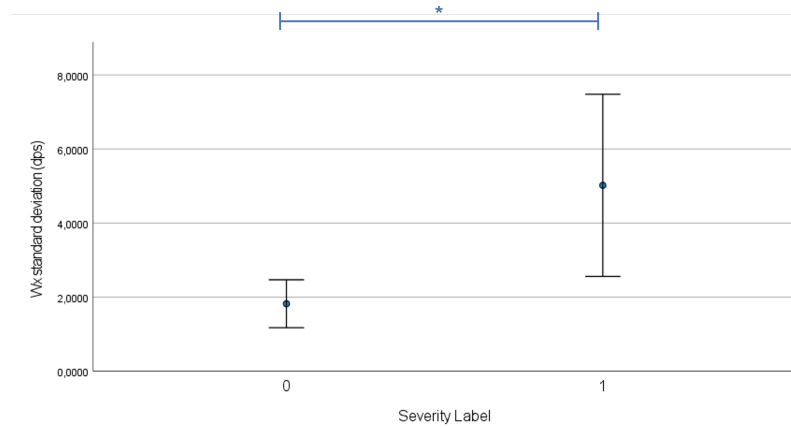


Figure 5.15: Average postural tremor W_x standard deviation of classes 0 and 1. * $p < 0.05$.

Discussion

In tremor, there are only data from classes 0 and 1, so the features were only tested to distinguish these two. It should be underlined that all features capable of differentiating the classes derive from the W_x signal, thus it is possible to conclude that this is the one that retains relevant information regarding postural tremor.

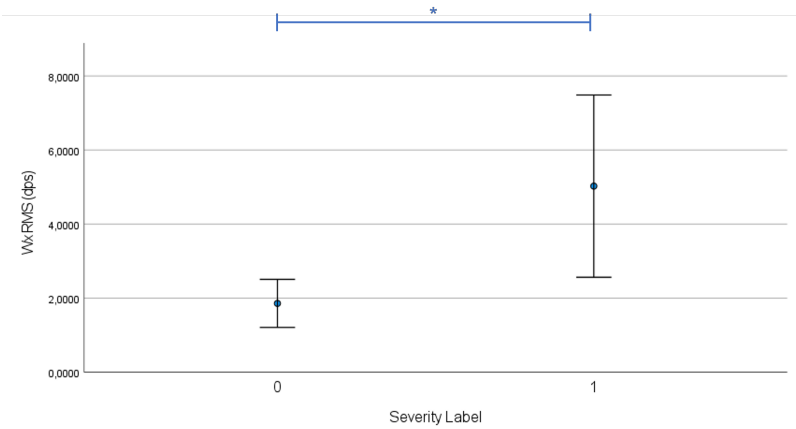


Figure 5.16: Average postural tremor W_x RMS of classes 0 and 1. * $p < 0.05$.

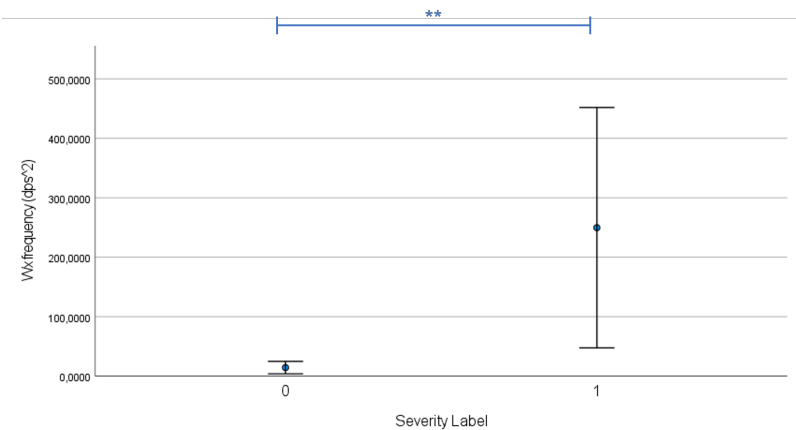


Figure 5.17: Average postural tremor W_x frequency of classes 0 and 1. ** $p < 0.01$.

5.4.3 Kinetic tremor

Results

On kinetic tremor exercise, the analysis performed with ANOVA test revealed acceleration approximate entropy as the only feature capable of differentiate significantly the average value of class 0 ($M = 0.693$, $std = 0.111$) and class 1 ($M = 0.50$, $std = 0.147$), with $t(17) = -2.582$, $p = 0.019$ and assuming equal variances (Levene's test: $p = 0.784$). Figure 5.18 shows the average values of Acc approximate entropy. In Appendix D.8 are shown all results from the statistical analysis of kinetic tremor data.

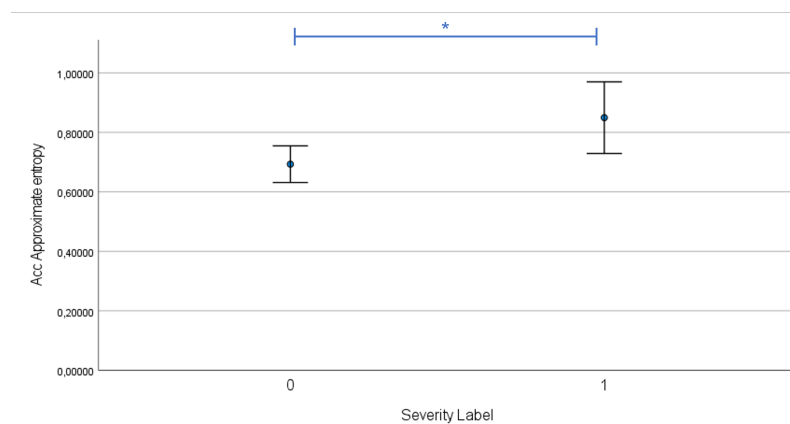


Figure 5.18: Average kinetic tremor Acc approximate entropy of classes 0 and 1. $*p < 0.05$.

Looking to the Kruskal-Wallis test results, only acceleration RMS distinguishes the average value of class 0 ($Md = 0.79$, $n = 13$) and class 1 ($Md = 0.75$, $n = 6$), with $\chi^2(1, n = 4.431)$ and $p = 0.035$. The average values of ACC RMS are displayed in Figure 5.19.

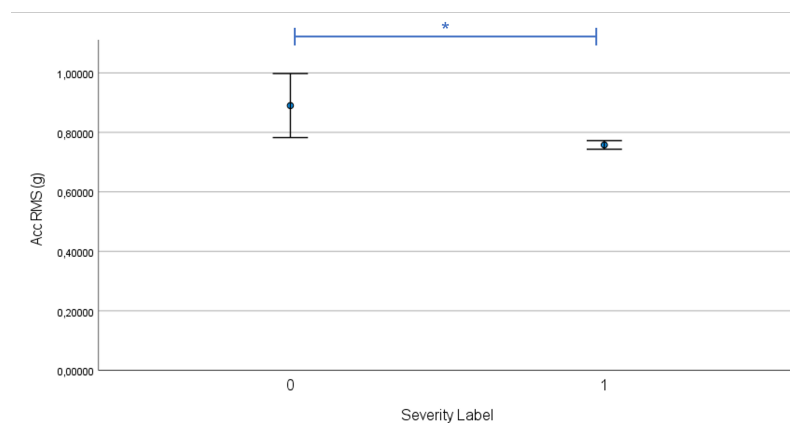


Figure 5.19: Average kinetic tremor Acc RMS of classes 0 and 1. $*p < 0.05$.

Discussion

At last, acceleration approximate entropy and acceleration RMS were the features that were proved to differentiate between classes 0 and 1. It can be verified that acceleration was at the base of these two features. However, as an exercise that demands constantly moving of the hand, it is possible that these features capture the movement's dynamics, distinguishing the classes by the presence of bradykinesia and not the tremor itself. In addition, it can be seen that the RMS measurement proved to be efficient in both postural and kinetic tremor.

5.5 Results summary and discussion

The employed statistical tests allowed as intended to understand the separation of the classes by each feature. Features from all exercises, with the exception of rest tremor, are able to distinguish between classes with statistical significance. Even more, there was generally less power to distinguish between close classes. This statistical analysis highlights the relevant features capable of distinguishing between different severity classes, even if the quantification models to be discussed in the next Chapter do not evidence this power.

In a summarized way, Table 5.1 presents, for each exercise, the percentage of features that express a significant distinction between classes. Similarly, for each of these features, is displayed the percentage of distinctions between classes relative to the total number of distinctions.

Table 5.1: Percentage of significant features ($p < 0.05$), and percentage of classes distinction that each is able to recognize.

Exercise	Percentage of significant features over all extracted	Significant features	Percentage of classes distinction
Rigidity	3/8 → 37.50%	Mean peaks	1/6 → 16.67%
		Mean	1/6 → 16.67%
		Descriptor	2/6 → 33.33%
Gait	2/9 → 22.22%	Rotation angle	2/3 → 66.67%
		Steps mean length	2/3 → 66.67%
Leg agility	1/9 → 11.11%	Total power	2/3 → 66.67%
Open-close	4/12 → 33.33%	Mean angle	1/6 → 16.67%
		Mean duration	3/6 → 50.00%
		Mean amplitude	1/6 → 16.67%
		Total power	1/6 → 16.67%
Pronation-supination	3/12 → 25.00%	Wy ApEn	1/3 → 33.33%
		Mean angle	2/3 → 66.67%
		Total power	1/3 → 33.33%
Rest tremor	0/11 → 0.00%	-	-
Postural tremor	3/11 → 27.27%	Wx std	1/1 → 100.00%
		Wx RMS	1/1 → 100.00%
		Wx frequency	1/1 → 100.00%
Kinetic tremor	2/11 → 18.18%	Acc ApEn	1/1 → 100.00%
		Acc RMS	1/1 → 100.00%

Chapter 6

Motor Symptoms Machine Learning Analysis for PD Severity Classification

In this Chapter is presented the ultimate goal of this dissertation, the development of models to quantify the severity of PD symptoms. First the DBS rigidity dataset was explored, testing various tools and approaches in order to improve the performance of the model of the reference literature.

Following, models to quantify PD motor symptoms in follow-up were built from the data collected during the hospital appointments. The extracted features were combined and applied to the development of different models for the quantification of severity. The models resulting from this analysis are unlikely to be viable, due to the limited data. They may also indicate the direction to head for the models' improvement. All the processes presented in this Chapter were implemented in Python 3.10.

6.1 DBS rigidity improvement classification

6.1.1 Classification of DBS rigidity data with descriptor feature

Goals

The potentiality of the descriptor feature (see Subsection 2.4) for the classification of DBS rigidity was explored. To this end, goals were outlined to reproduce the patented regression, to optimize the classification with different algorithms and class balancing techniques, and also, replicate all the previews steps with a uniform dataset in accordance with Snapki data.

Methodology

The rigidity dataset acquired in deep brain stimulation surgeries which originated the patented polynomial regression and described in Subsection 2.5 was explored in this work. Recalling the dataset details, rigidity improvement was labeled within six discrete percentages, namely, 0 %, 40

%, 50 %, 60 %, 70 % and 80 %. Nevertheless, class 0 % is not represented in this dataset, seeing that many of these signals were mislabeled.

The different versions of the iHandU hardware have set distinct sampling frequencies, as already mentioned in Subsection 2.6. The latest version, Snapki, samples at 50 Hz, while MoMo samples at 28 Hz. With this sampling, MoMo's signals have a lower definition and show some glitches.

The MoMo signals were then resampled with the Snapki frequency, and the isolated peaks corresponding to glitches were eliminated. This signal transformation had the purpose of correcting the errors present in the signals and standardizing all the data that will be worked on. The transformation process was applied to all DBS rigidity data, originating a new dataset containing the modified data, whose signals have 356 samples.

The two datasets were divided into 80 % and 20% for train and test, respectively, for all the employed algorithms. Starting with the regression reproduction, a second-order polynomial regression was implemented [71, 72]. The training set was divided using Leave-One-Out (LOO) [73], a polynomial regression was fitted for the entire training data except the one left out and thus, the final coefficients resulted from the average values of all iterations.

Knowing that the regression is a continuous function, its output had to be limited in order to match the discriminated classes. Thereby, all values below 0 % were considered 0 %, all values above 85 % were considered 84.9 % and all classes were given an uncertainty of 5 %, this means, all values above or below 5 % of the central value of the class were considered to belong to it. KNN was also applied, given its use and success rate in the quantification of symptoms of the systems and studies reviewed in Section 2.3. For the KNN classification, the k neighbour value was optimized for the k with the lowest test error and the higher accuracy.

The classes' dispersion is unbalanced, with a higher prevalence in the higher classes, as it is in these that physicians have more focus on verifying the optimisation of the parameters and stimulation position. Having this in view and expecting to balance the datasets, an oversampling technique, Synthetic Minority Oversampling Technique (SMOTE) [74], that equals all classes to the size of the larger one, to fifty-seven signals, is applied to the data. Undersampling is also tested by reducing all classes to the size of the smaller one, to twenty-six signals. In Figure 6.1 is schematised the used methodology.

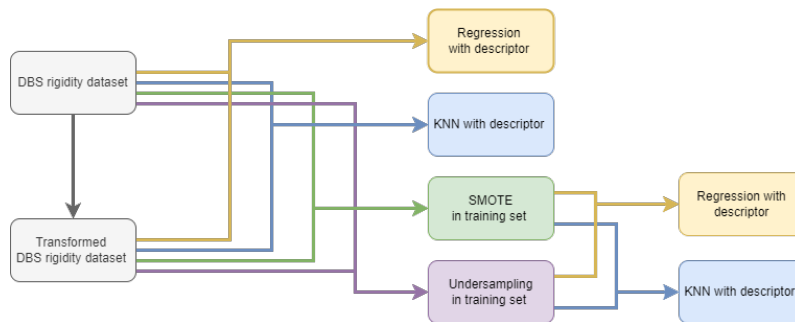


Figure 6.1: Schematisation of the development process of DBS rigidity algorithms from descriptor feature.

Results

In Figure 6.2 are displayed the various testing lines, followed by the obtained test accuracy and the k value, if it is a KNN. The regression reproduction has an accuracy superior to the verified in the literature, due to a distinct implementation of LOO. Regarding the regression and KNN classification with the transformed dataset, both show lower accuracy values in comparison with the same algorithms developed using the original data.

As for the use of SMOTE, it has a very heterogeneous effect on the various classifications, improving the classification of the original's database and the KNN of the transformed data, maintaining the same quality in the KNN of the original and worsening it in the regression using the transformed data. Finally, the use of undersampling technique transversely worsens the accuracy of the classifications, both with the original dataset and with the transformed one.

Overall, the best accuracy achieved is 87.27 % for four algorithms, KNN (k=29), regression with SMOTE, KNN with SMOTE (k=6) and KNN with SMOTE and transformed data (k=12).

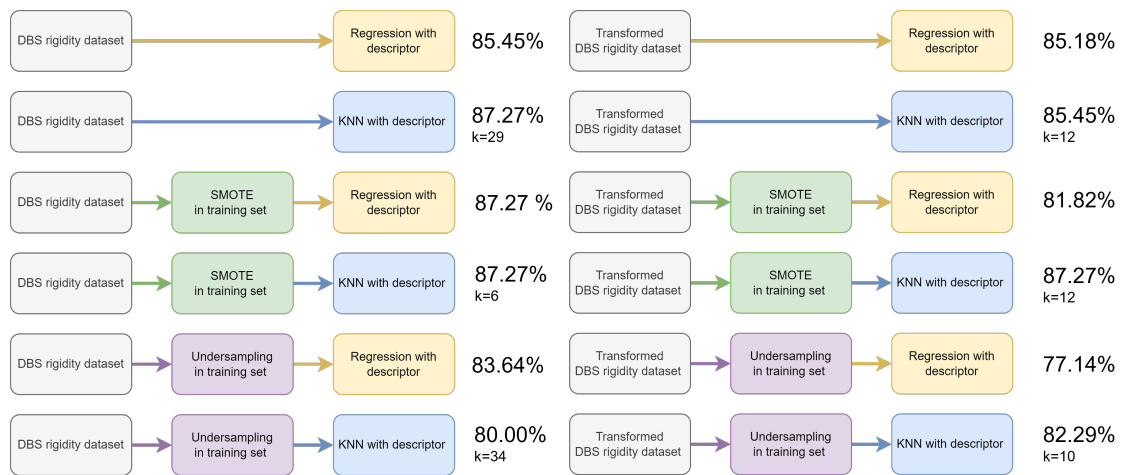


Figure 6.2: Result of algorithms, using descriptor feature.

6.1.2 Classification of DBS rigidity data from arcades' descriptor and conjugated features

Goals

In continuation of the research presented in the previous Section, the use of only three arcades of each signal was tested, as was their positioning in different portions of the signal, in order to assess their impact on classification. Furthermore, with the same aim, in addition to the descriptor, new features were introduced.

Methodology

In Figure 6.3 is schematised the methodology explored in this Section. Six datasets were created, three of them from three arcades of the original data, namely the first, the middle and the final

three. The remaining datasets follow the arcades selection logic, but with the transformed data.

In an initial step, second order regression and KNN algorithms were developed from the descriptor feature and an 80/20 test-train split, like previously. In a next phase, the development of the same two types of algorithms was continued, but with more features. In order to achieve that, sets of two and three features were selected for each dataset, using the mRMR algorithm [75], which prioritises the selection of features with minimum redundancy and maximum relevance.

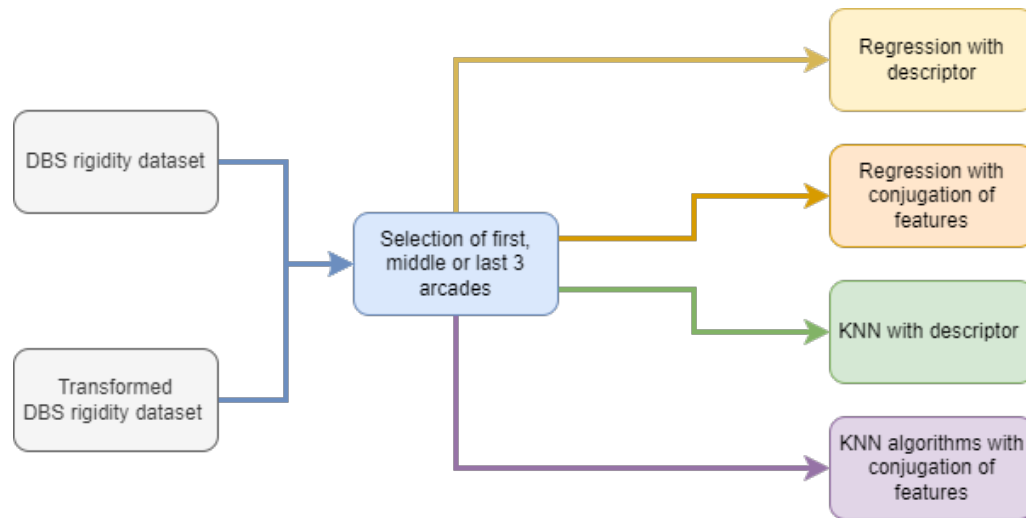


Figure 6.3: Schematisation of the development process of DBS rigidity algorithms from arcades.

Results

The results for the algorithms using the descriptor feature are presented in Figure 6.4. Focusing on the data transformation, it was both an improving and worsening effect on the classification, within the different arcades' selections.

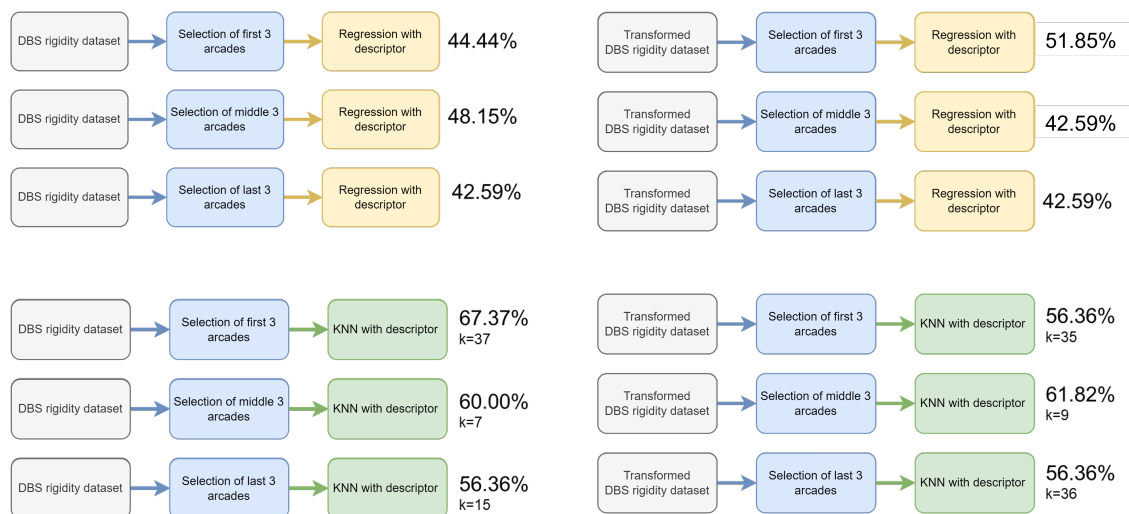


Figure 6.4: Result of algorithms, using arcades and descriptor feature.

The most accurate classification, using the original data is achieved with the middle arcades, for regression, and with the first three in the case of KNN. Turning to the transformed data, the best results are obtained, in both algorithms, with the first three arcades. The best regression obtained then has an accuracy of 48.15 % and is obtained using the three middle arcades of the original signals, while the best KNN algorithm has an accuracy of 67.37 %, obtained with the first three arcades of the original data and optimised with k equal to thirty-seven.

The features selection of two features, used in the regression and the KNN, for each one of the databases are presented in Table 6.1. The results of the classifications obtained with these characteristics are also shown in Figure 6.5.

Table 6.1: Two features selection.

Dataset	Arcades	Regression	KNN
DBS rigidity dataset	First	Descriptor Mean peaks	Descriptor Mean peaks
	Middle	Descriptor Mean	Descriptor Mean
	Last	Descriptor Left side absolute hypotenuse	Descriptor Right side absolute hypotenuse
Transformed DBS rigidity dataset	First	Mean peaks Descriptor	Mean peaks Descriptor
	Middle	Mean peaks Descriptor	Mean peaks Descriptor
	Last	Right side relative hypotenuse Descriptor	Mean peaks Descriptor

Looking to the accuracy values obtained for the original data and to the ones obtained with the transformed data, once again, there is not a consistent improvement or worsening, in both classification algorithms. Comparing the behaviour of the algorithms developed with the arcades for the different positions, the most exact regression algorithms were the ones developed with the first three arcades and the most exact KNN algorithms were the ones developed with the last three arcades, in both cases for the original and transformed data. In a global vision, the best regression has an accuracy of 65.45 %, and was built from the three first arcades of the transformed dataset, with the descriptor and mean peaks characteristics. Meanwhile, the best KNN has an accuracy of 53.74 %, was built from the three last arcades of the original dataset, with descriptor and right side absolute hypotenuse characteristics, and optimised with six neighbour.

The feature selection was also performed for three features and the respective results are presented in Table 6.2. Moreover, the results for the algorithms developed with three features are exhibit in Figure 6.6.

The transformation of the dataset was mirrored in a random quality of the regressions and a worsening for all KNN. It can also be observed that in regressions the best results are reached with the first three arcades, while in KNN the best results are reached with the last three arcades, the same that happens with two features classification. Lastly, the the best regression's accuracy result was achieved for the three first arcades of original data, corresponding to 61.82 %, using

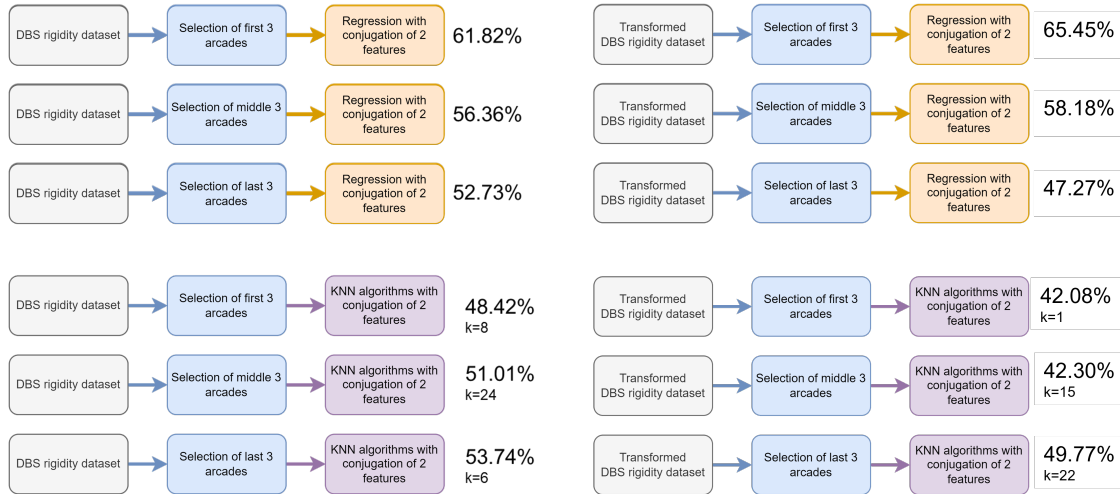


Figure 6.5: Result of algorithms, using arcades and two conjugated features.

Table 6.2: Three features selection.

Dataset	Arcades	Regression	KNN
DBS rigidity dataset	First	Mean peaks Descriptor Mean	Descriptor Mean peaks Mean
	Middle	Mean Descriptor Left side absolute hypotenuse	Descriptor Mean Right side absolute hypotenuse
	Last	Mean Descriptor Left side absolute hypotenuse	Descriptor Mean Right side absolute hypotenuse
Transformed DBS rigidity dataset	First	Mean Descriptor Mean peaks	Mean Descriptor Mean peaks
	Middle	Mean Descriptor Mean peaks	Mean Descriptor Mean peaks
	Last	Mean Descriptor Right side relative hypotenuse	Mean Descriptor Mean peaks

the descriptor, mean peaks and mean features. With respect to KNN, 57.42 % was the best accuracy achieved, with the last three arcades of original data, descriptor, mean and left side absolute hypotenuse, and yet optimised for k equal to nine neighbours.

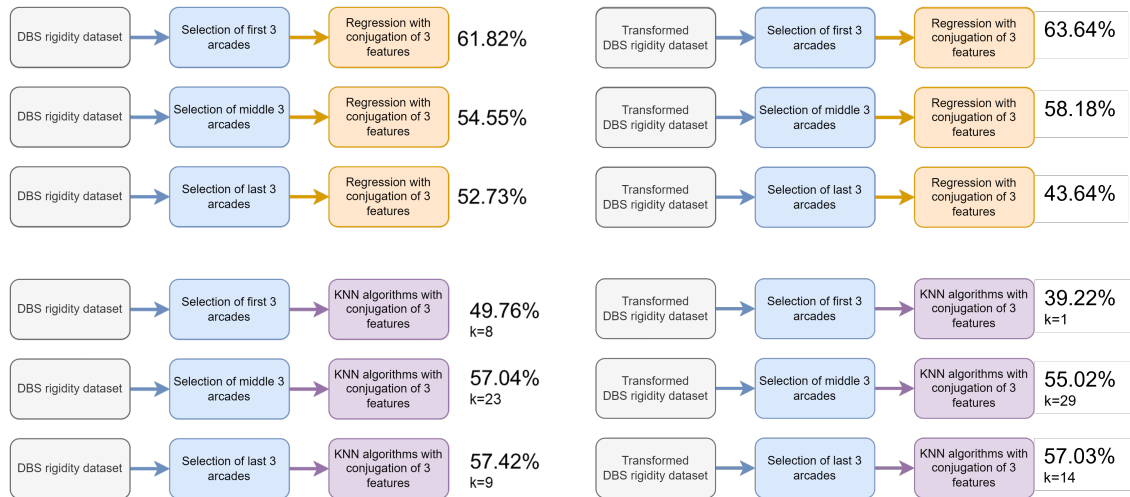


Figure 6.6: Result of algorithms, using arcades and three conjugated features.

6.1.3 Discussion

The data transformation does not have a linear impact on the algorithms' accuracy, contrary to what one would expect, since signal errors, such as glitches, have been eliminated.

Regarding the analysis on Subsection 6.1.1, the use of SMOTE is favourable to the improvement of performance, in most cases, so its application proved to be positive. On the other hand, undersampling has a negative influence on the success of the classifications, so it should not be used to balance the datasets at stake.

Among the algorithms with the highest accuracy, if one had to be chosen to put into practice, regression would be the best option, since it has the advantage of being able to distinguish the 0 % class even without it being trained, unlike the other KNN algorithms.

Moving on to the analysis of Subsection 6.1.2, the selection of the first and last arcades is shown to be more significant in most cases. What is more, the selection of three features, compared to the selection of two, only led to an improvement of the algorithms in half of the cases.

The best result obtained for the regression came from the conjugation of the descriptor and the mean peaks, extracted from the transformed signals of the first three arcades, having an accuracy of 65.45 %. This algorithm presents the benefit of knowing the class 0 %, however it results from the conjugation of two redundant features, since the descriptor is calculated using the mean peaks.

As for KNN, its best results are obtained only from the descriptor feature extracted from the first three arcades of the original signals. It presents an accuracy of 67.37 %. Despite not knowing class 0 %, it is optimised for thirty-seven neighbours, a value superior to the dimension of classes 40 % and 50 %, which may result in overfitting.

Putting into perspective the algorithms with the descriptor from complete signals and of arcades, in Figures 6.2 and 6.4, respectively, it can be seen that the results of the latter are significantly lower than the former. This allows to infer that three arcades are not enough to extract the necessary information or even that the spacing between arcades present in the complete signals contains relevant information for classification.

6.2 Motor symptoms quantification for PD monitoring

The data collected and statistically analysed were used in the development of algorithms for quantifying motor symptoms of PD. The latter is reported throughout this Section. To this end, a pipeline was established and applied to the data of all exercises.

The first step was to consider only those classes that include more than one element, since they were an obstacle to the feature selection that will be further addressed. From these data, a stratified division was made of 80 % for the train set and 20 % for the test set. The stratified division made it possible to keep the proportion of classes in the two sets, which is important to ensure a good training of the models, considering the small dimensions of the created datasets.

The machine learning algorithms selected were a second-order polynomial regression, because it was used previously with rigidity and defined a good model. KNN and SVM were also chosen, since its use on the systems reviewed in Section 2.3 showed positive results. From the several features extracted, the sets of 2 and 3 features with less redundancy and maximum relevance were selected with the mRmR algorithm [75]. mRmR groups the features differentially for regression and classification, SVM and KNN included. The reduced number of features to select was meant to avoid a high computational cost when implementing the model, but still guarantee sufficient information for a clear distinction of the classes.

Three types of algorithms were trained with the selected features: second-order polynomial regression, KNN and SVM. The regression has a continuous output, therefore, to cross them with the discrete labels, its results were rounded to the unit and considered zero if below zero and four if above it. In addition, the parameters of KNN and SVM were optimised for each model created.

To evaluate the model, the classification accuracy of the model for the training and test sets was determined. Furthermore, its confusion matrix was presented to better understand the model's performance in each class.

6.2.1 Rigidity

The features selected for regression and rigidity classifications are displayed in Table 6.3. Part of them corresponds to those which distinguish between classes. Others were also considered, like the range of motion and its standard deviation.

Table 6.3: Groups of two and three features selected for regression and classification of rigidity.

	Regression	Classification
2 features	Mean ROM std	Mean peaks ROM std
3 features	Mean ROM std Descriptor	Mean peaks ROM std ROM

Table 6.4: Train and test accuracy of the rigidity models.

	Regression		KNN		SVM	
	2 features	3 features	2 features	3 features	2 features	3 features
Train accuracy	47.37 %	57.89 %	26.32 %	100.00 %	42.11 %	42.11 %
Test accuracy	20.00 %	20.00 %	60.00 %	20.00 %	40.00 %	40.00 %

The training and testing accuracy values of the trained models are shown in Table 6.4, as well as their confusion matrices in Figure 6.7. The test accuracy values are low, showing KNN from two features the highest. The higher training accuracy values indicate an overfitting in the polynomial regression and the KNN with three features. The two-feature KNN model shows a large discrepancy between training and testing, which may indicate an underfitting of the model. This could also result from a data imbalance, however, with the same data, the SVM models achieved a very similar performance in the training and testing sets.

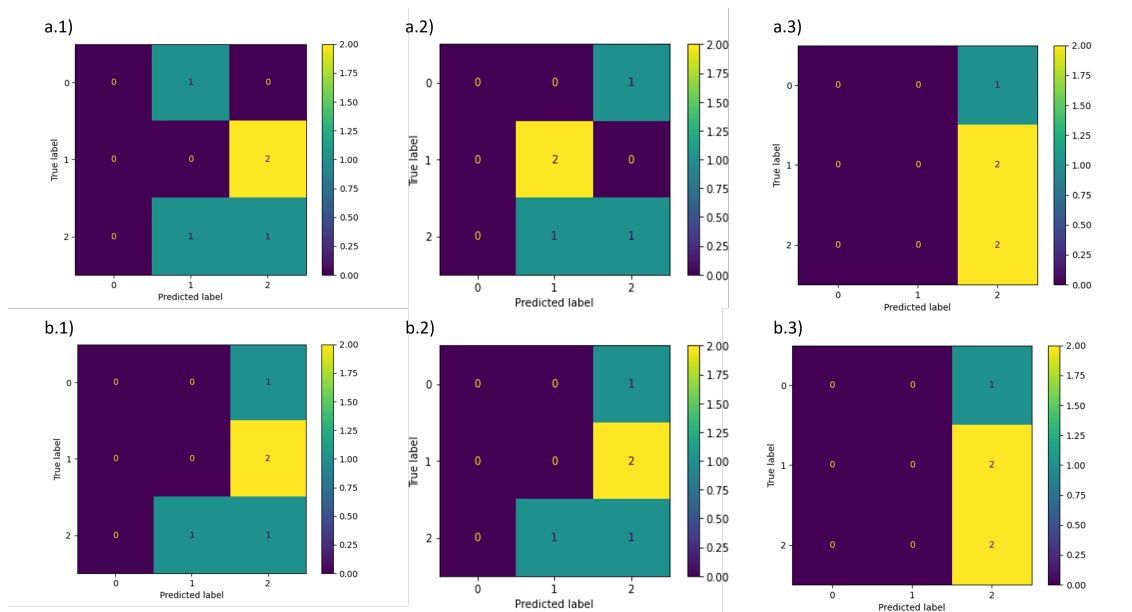


Figure 6.7: Confusion matrix of rigidity (a.1) second-order polynomial regression, (a.2) KNN and (a.3) SVM models from two features; (b.1) second-order polynomial regression, (b.2) KNN and (b.3) SVM models from three features.

Looking at Figure 6.7, the confusion matrices of the various models implemented in the test

set, it can be verified that the regressions and KNN classified the data between classes 1 and 2, not considering class 0, and the SVM only considered the data as class 2. The confusion matrices allow inferring that there was a weak learning in the training of the models.

6.2.2 Gait

Table 6.5: Groups of two and three features selected for regression and classification of gait.

	Regression	Classification
2 features	Steps mean length Steps mean height	Steps mean length Rotation angle
3 features	Steps mean length Steps mean height Rotation angle	Steps mean length Steps mean height Rotation angle

The selected feature groups for gait data are presented in Table 6.5. All of them contain the steps mean length, which has been found to separate the classes significantly. The other significant feature, rotation angle, is included in all but two feature set for the regression. The third feature included in the groups is the steps mean height.

Table 6.6: Train and test accuracy of the gait models.

	Regression		KNN		SVM	
	2 features	3 features	2 features	3 features	2 features	3 features
Train accuracy	89.47 %	78.95 %	100.00 %	100.00 %	73.68 %	73.68 %
Test accuracy	80.00 %	80.00 %	100.00 %	100.00 %	80.00 %	80.00 %

Turning the attention to Table 6.6, it can be noted that the developed models have a good performance in the classification of the test data, namely an accuracy of 80.00 % in the polynomial regressions and the SVM models, and of 100.00 % in the case of the KNN ones.

Both KNN models have the same training and testing accuracy. As for the SVM models, there is a subtle difference, with the training accuracy being lower, which suggests a possible weakness in the model training. In what concerns regression, the model developed from two features has a higher training accuracy than the testing accuracy, so the first model is slightly overfitted.

By analysing the confusion matrices of the models in Figure 6.8, as expected, the classification of KNN is successful for all classes. Meanwhile, in the regression models, classes 0 and 1 are accurately classified, but data from class 2 were classified as 1. the same happens with SVM models, but involving different classes. The models classify well data from classes 1 and 2, but data from class 0 were considered as being from class 1.

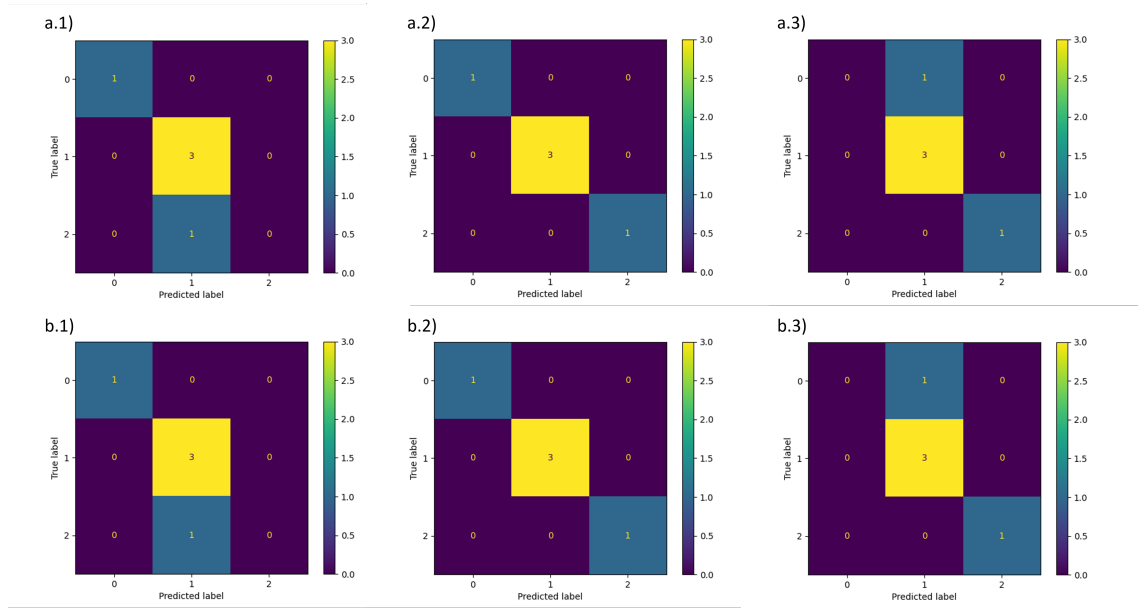


Figure 6.8: Confusion matrix of gait (a.1) second-order polynomial regression, (a.2) KNN and (a.3) SVM models from two features; (b.1) second-order polynomial regression, (b.2) KNN and (b.3) SVM models from three features.

6.2.3 Bradykinesia

6.2.3.1 Leg agility

Leg agility has only one statistically differentiating feature, total power. This is among the selected ones, together with m duration and mean duration. Moreover, in this case, the selected features are the same for regression and classification (Table 6.7).

Table 6.7: Groups of two and three features selected for regression and classification of leg agility.

	Regression	Classification
2 features	Total power m duration	Total power m duration
3 features	Total power m duration Mean duration	Total power m duration Mean duration

The accuracy metrics calculated and presented in Table 6.8 are very heterogeneous across the various models. In all, the training accuracy values are higher than the test ones. This difference is accentuated in KNN models, and the one developed with three features showed a test accuracy of 0.00 %. The second-order polynomial regression model implemented with three features is the one that seems to have a better performance, given the little difference in the values of training and test accuracy, and its accuracy of 75.00 % in the test set.

Table 6.8: Train and test accuracy of the leg agility models.

	Regression		KNN		SVM	
	2 features	3 features	2 features	3 features	2 features	3 features
Train accuracy	66.67 %	83.33 %	58.33 %	100.0 %	58.33 %	58.33 %
Test accuracy	50.00 %	75.00 %	25.00 %	0.00 %	50.00 %	50.00 %

The classifications of the test set data performed with the various models are reported with confusion matrices in Figure 6.9. The regression from two features correctly classified the data from class 0, some from class 1 with errors and the data of class 2 as 1. On the other hand, the model from three features classified agreeably the data from classes 0 and 1, but considered the data from class 2 as being from class 1. As for the KNN, the model from two features considered all data as being from class 0, and the one created from three features performed a random classification. Finally, both SVM models classified all data as class 1.

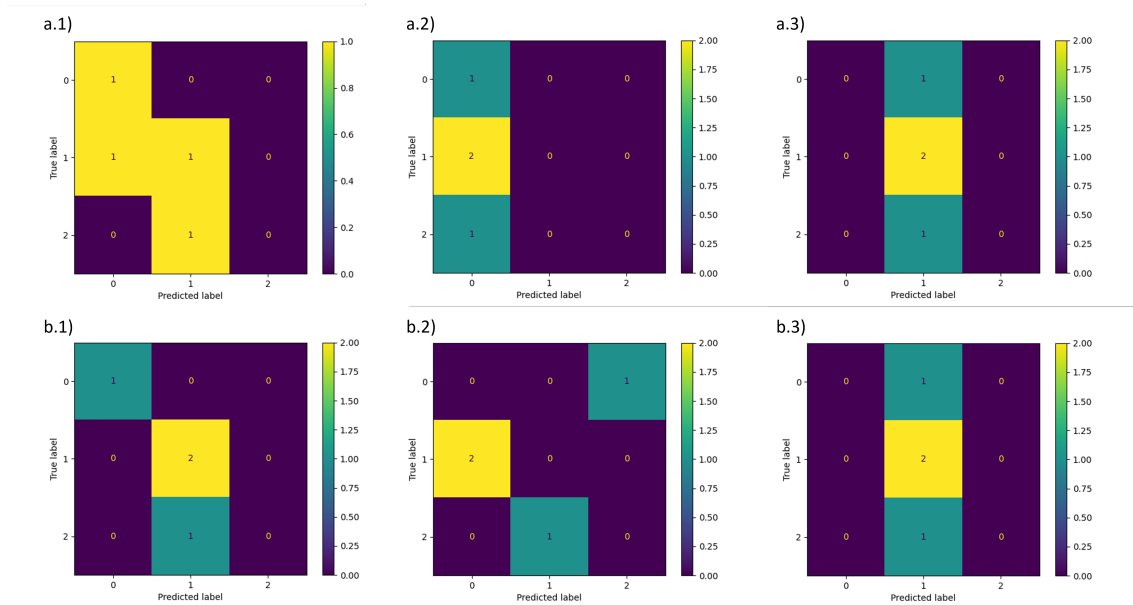


Figure 6.9: Confusion matrix of leg agility (a.1) second-order polynomial regression, (a.2) KNN and (a.3) SVM models from two features; (b.1) second-order polynomial regression, (b.2) KNN and (b.3) SVM models from three features.

6.2.3.2 Open-close

The features selected for the open-close exercise are shown in Table 6.9. The feature mean duration, capable of significantly distinguishing classes, is found in all selected groups. With the same capability, total power is present in both regression groups and is the third element of the classification. The third feature of the regression is the mean angle, also considered significant, contrarily to the third feature of the classification, W_y ApEn, which does not significantly distinguish classes.

The test and training accuracy values are reported in Table 6.10. Polynomial regressions and KNN have low test accuracy values, lower than the training values, which is indicative of an

Table 6.9: Groups of two and three features selected for regression and classification of open-close.

	Regression	Classification
2 features	Mean duration Total power	Mean duration W_y ApEn
3 features	Mean duration Total power Mean angle	Mean duration W_y ApEn Total power

overfitting of the models to the training data. In what concerns the SVM models, these show a test accuracy of 75.00 %, considerably higher than the remaining. Nevertheless, both have training accuracy values lower than the test accuracy, which reflects a weak model training.

Table 6.10: Train and test accuracy of the open-close models.

	Regression		KNN		SVM	
	2 features	3 features	2 features	3 features	2 features	3 features
Train accuracy	91.67 %	100.0 %	75.00 %	75.00 %	66.67 %	58.33 %
Test accuracy	25.00 %	0.00 %	25.00 %	25.00 %	75.00 %	75.00 %

Observing the confusion matrices presented in Figure 6.10, it is possible to understand that the classifications of the models are quite random for the various classes. Specifically, the two-feature regression model classified data from classes 0 and 1 as class 4. Even more, the three-feature KNN and both SVM did not classify any value as being class 2, which may suggest a poor training of this class to the model.

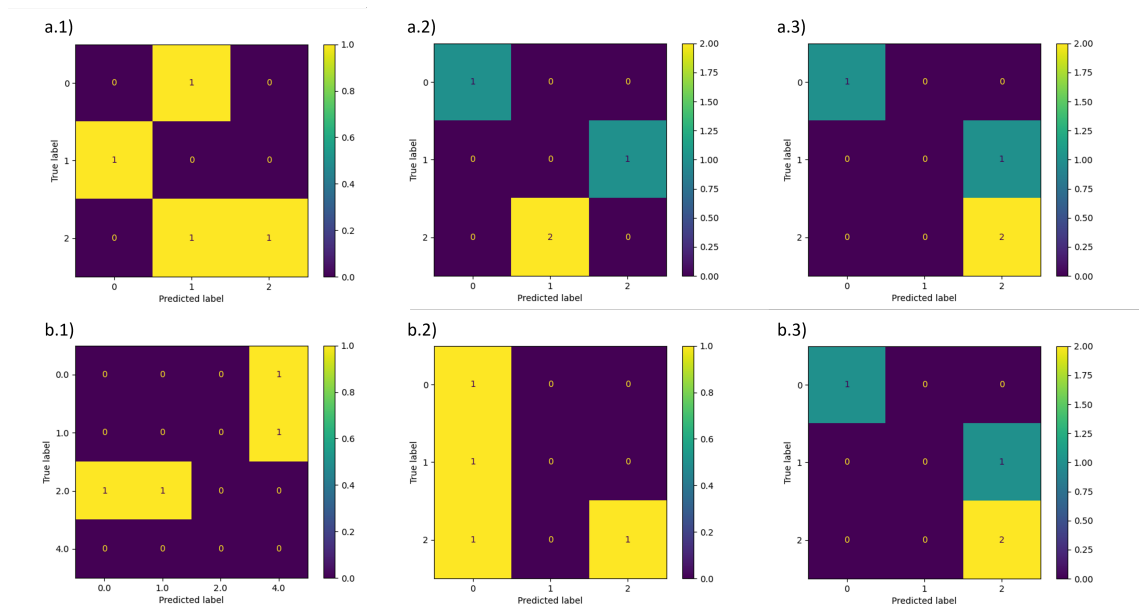


Figure 6.10: Confusion matrix of open-close (a.1) second-order polynomial regression, (a.2) KNN and (a.3) SVM models from two features; (b.1) second-order polynomial regression, (b.2) KNN and (b.3) SVM models from three features.

6.2.3.3 Pronation-supination

Table 6.11 lists the groups of two and three features selected for the regression and classifications. Of the features that in the statistical analysis revealed to be able to discriminate between levels of the symptom, the mean angle is present in all groups, the total power in the regression ones and the W_y ApEn in the group of regression with three elements. In the classification are also found the feature m angle and, in the group with three features, the m amplitude too.

Table 6.11: Groups of two and three features selected for regression and classification of pronation-supination.

	Regression	Classification
2 features	Mean angle Total power	Mean angle m angle
3 features	Mean angle Total power W_y ApEn	Mean angle m angle m amplitude

From these features, were developed second-order polynomial regression, KNN and SVM algorithms, whose training and testing accuracy metrics are exposed in Table 6.12. Except for the regression from three features and the SVM from two features, all models present higher testing accuracy than training accuracy, which is a sign of bad training of the models. The regression from three features also presents a higher training accuracy than testing accuracy, possibly due to model overfitting. In addition, the SVM from three features has a training accuracy of 73.33 % and a testing accuracy of 75.00 %, very close values, which makes this model the one with the most balanced behaviour towards different sets.

Table 6.12: Train and test accuracy of the pronation-supination models.

	Regression		KNN		SVM	
	2 features	3 features	2 features	3 features	2 features	3 features
Train accuracy	66.67 %	93.33 %	86.67 %	86.67 %	86.67 %	73.33 %
Test accuracy	75.00 %	50.00 %	100.00 %	100.00 %	75.00 %	75.00 %

The confusion matrices of the pronation-supination classification models are shown in Figure 6.11. The regression with two features correctly classified data of classes 0 and 1, having classified data of class 2 as being of class 3. As for the regression with three features, it also correctly classified class 0, but classified data of class 1 as being of class 3 and data of class 2 as being of class 0, having a random behaviour that does not follow the increasing progression of the classes. The KNN models made an utterly correct classification of the test data, as seen earlier, despite the limitations of the models. As for the SVM models, both correctly classify classes 0 and 2, but class 1 is not distinguished, being considered as class 2.

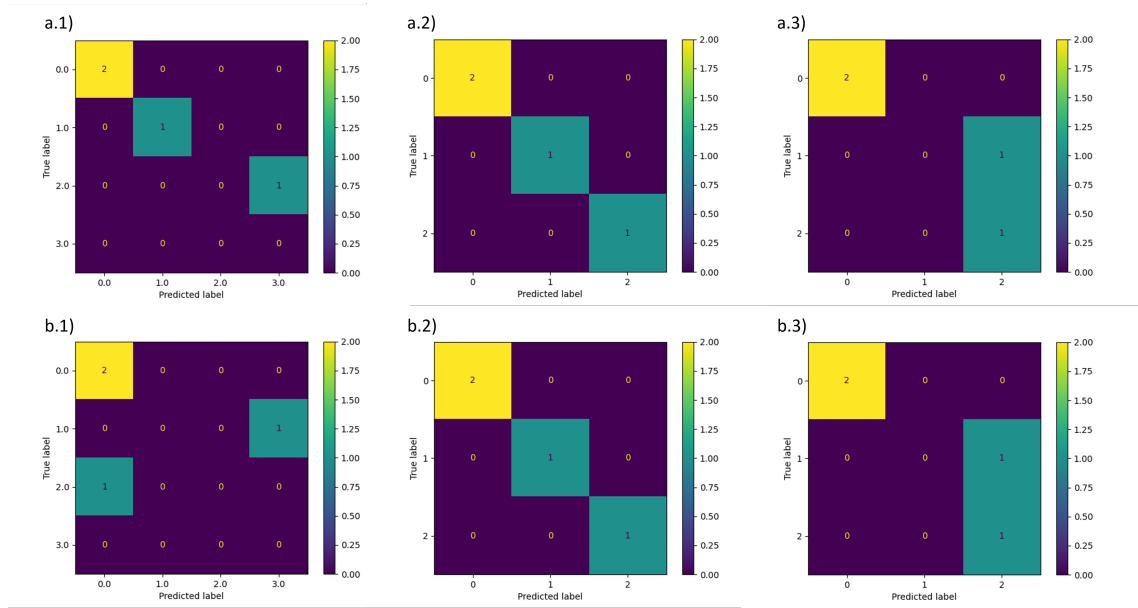


Figure 6.11: Confusion matrix of pronation-supination (a.1) second-order polynomial regression, (a.2) KNN and (a.3) SVM models from two features; (b.1) second-order polynomial regression, (b.2) KNN and (b.3) SVM models from three features.

6.2.4 Tremor

6.2.4.1 Rest tremor

The tremor rest exercise did not present any feature that differentiated level 0 from level 1 of the symptom (the only ones present in the data) with significance. Based on minimum redundancy and maximum relevance, the algorithm used selected, both for regression and classification, the features Acc RMS, Acc ApEn and, as a third feature, Acc standard deviation. The selected features' groups are exhibited in Table 6.13.

Table 6.13: Groups of two and three features selected for regression and classification of rest tremor.

	Regression	Classification
2 features	Acc RMS	Acc RMS
	Acc ApEn	Acc ApEn
3 features	Acc RMS	Acc RMS
	Acc ApEn	Acc ApEn
	Acc std	Acc std

The training and testing accuracy values obtained for models are displayed in Table 6.14. All KNN and SVM models classified the test data with an accuracy of 50.00 %. However, their accuracy is higher for the training data, which is suggestive of an overfitting of the models. Regression, in contrast, performs perfectly with the two models and both for training and testing. In the case of deploying one of them, the model with two features would be preferable because of the lower computational cost of fewer features.

Table 6.14: Train and test accuracy of the rest tremor models.

	Regression		KNN		SVM	
	2 features	3 features	2 features	3 features	2 features	3 features
Train accuracy	100.00 %	100.00 %	100.00 %	100.00 %	83.33 %	83.33 %
Test accuracy	100.00 %	100.00 %	50.00 %	50.00 %	50.00 %	50.00 %

The behaviour of the models can be analysed class by class in Figure 6.12. First of all, it turns out that the classification behaviour with two or three features was the same, whatever the model. Moreover, the regression models correctly classified the training set, as previously ascertained. However, for the KNN and SVM models, class 1 were all correctly positioned, while some data corresponding to class 0 were misclassified.

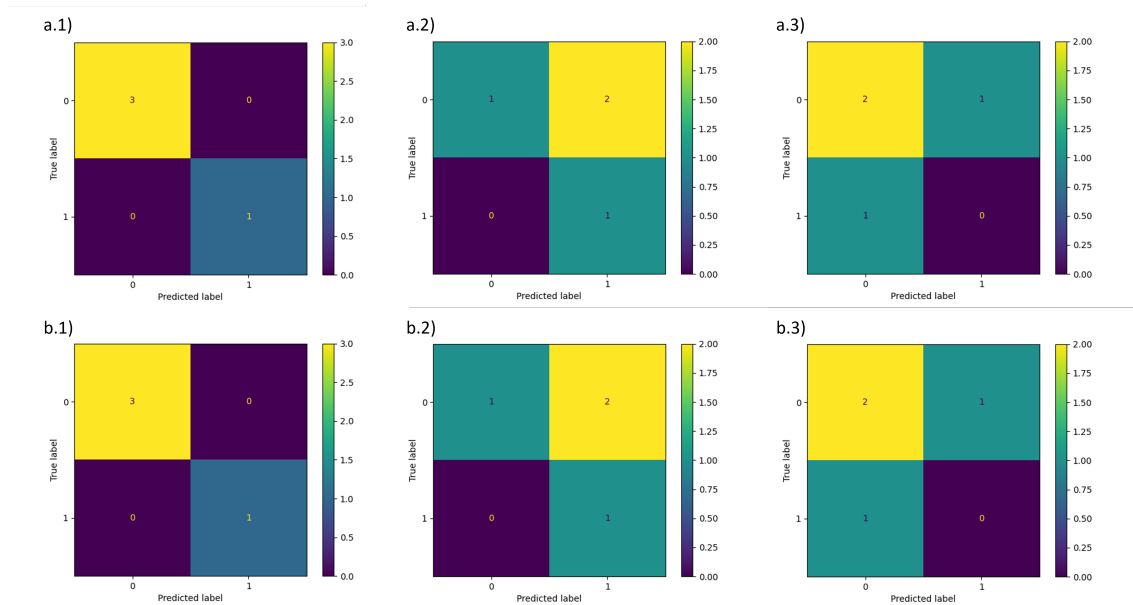


Figure 6.12: Confusion matrix of rest tremor (**a.1**) second-order polynomial regression, (**a.2**) KNN and (**a.3**) SVM models from two features; (**b.1**) second-order polynomial regression, (**b.2**) KNN and (**b.3**) SVM models from three features.

6.2.4.2 Postural tremor

Table 6.15: Groups of two and three features selected for regression and classification of postural tremor.

	Regression	Classification
2 features	W_x std W_x RMS	W_x std W_x RMS
3 features	W_x std W_x RMS W_x tremor frequency	W_x std W_x RMS W_x tremor frequency

The groups of features selected to be used in regression and classification are presented in Table 6.15. The selected features are exactly the same ones that distinguish the classes with statistical significance. The groups thus include W_x standard deviation, W_x RMS and, as the third feature, W_x tremor frequency.

Table 6.16: Train and test accuracy of the postural tremor models.

	Regression		KNN		SVM	
	2 features	3 features	2 features	3 features	2 features	3 features
Train accuracy	81.82 %	100.00 %	72.73 %	72.73 %	72.73 %	81.82 %
Test accuracy	100.00 %	66.67 %	100.00 %	100.00 %	100.00 %	100.00 %

Table 6.16 shows the metrics evaluated for each model. All models, except the three-feature regression, revealed much higher test accuracy than training accuracy, which puts into question the learning of the models. On the other hand, the regression with three features has a training accuracy of 100.00 %, but a lower test accuracy of 66.67 %, which shows that the model possibly was overfitting.

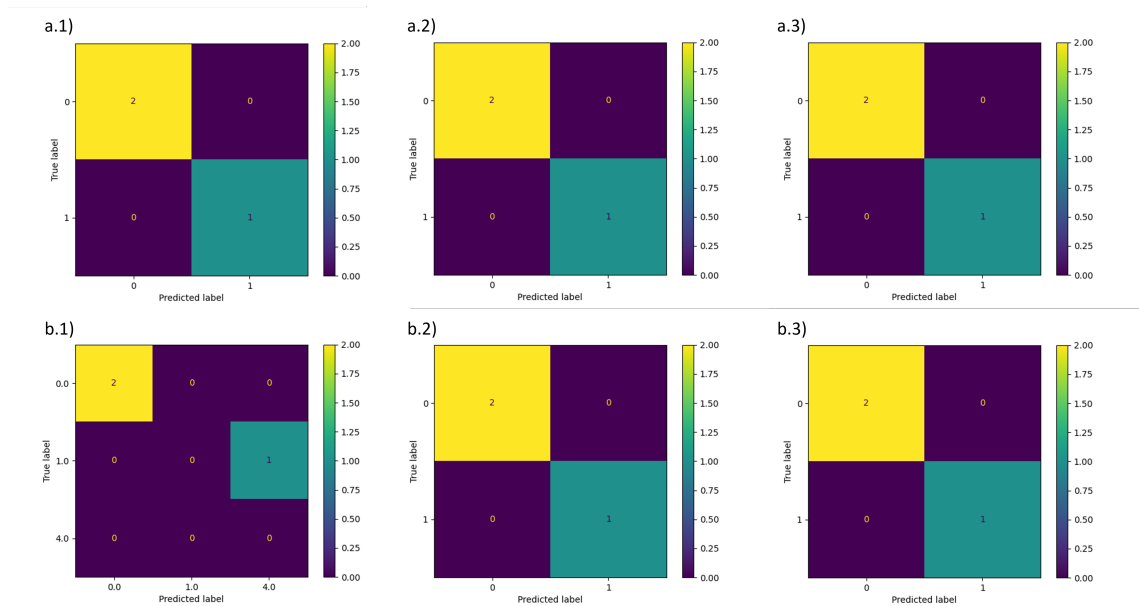


Figure 6.13: Confusion matrix of postural tremor (a.1) second-order polynomial regression, (a.2) KNN and (a.3) SVM models from two features; (b.1) second-order polynomial regression, (b.2) KNN and (b.3) SVM models from three features.

Observing the confusion matrices in Figure 6.13, the only model that did not classify with complete accuracy the test set was the regression model from three features. It can be seen that this model classified correctly the elements of class 0, but failed in class 1, assuming them to be class 4.

6.2.4.3 Kinetic tremor

Table 6.17: Groups of two and three features selected for regression and classification of kinetic tremor.

	Regression	Classification
2 features	Acc ApEn W_x tremor frequency	Acc ApEn W_x tremor frequency
3 features	Acc ApEn W_x tremor frequency Acc RMS	Acc ApEn W_x tremor frequency Acc RMS

Table 6.17 shows the groups of features selected for kinetic tremor. Among the various features, Acc ApEn and Acc RMS are the only ones that differentiate the symptom classes with statistical significance. The W_x tremor frequency is the other considered feature. Among all models, SVM models have the lowest discrepancy and a moderate test performance of 75.00 %.

Table 6.18: Train and test accuracy of the kinetic tremor models.

	Regression		KNN		SVM	
	2 features	3 features	2 features	3 features	2 features	3 features
Train accuracy	93.33 %	93.33 %	100.00 %	100.00 %	86.67 %	86.67 %
Test accuracy	75.00 %	50.00 %	50.00 %	50.00 %	75.00 %	75.00 %

Overall, all models have training accuracy values higher than the test ones, as shown in Table 6.18, which is indicative of overfitting.

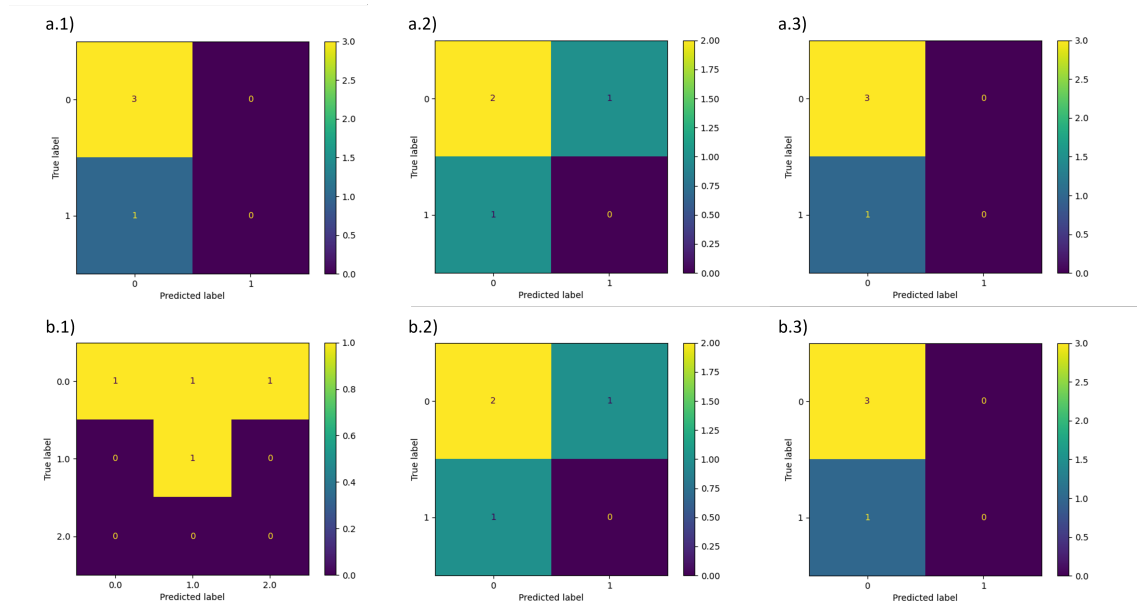


Figure 6.14: Confusion matrix of kinetic tremor (a.1) second-order polynomial regression, (a.2) KNN and (a.3) SVM models from two features; (b.1) second-order polynomial regression, (b.2) KNN and (b.3) SVM models from three features.

The confusion matrices of the various models are presented in Figure 6.14. The regression model with two features classified class 0 and class 1 data as class 0. On the other hand, the three-feature regression placed the class 0 elements in several classes, showing an incapability to distinguish this class. As for the KNN models, both misclassify elements of the two classes. Meanwhile, the SVM models misclassified all class 1 elements as 0, demonstrating difficulty differentiating the two classes.

6.2.5 Results summary and discussion

The collected results, the models' performance and the influence of the datasets and employed features will be further discussed in this Subsection.

Starting with rigidity, regression and KNN models are either underfitted or overfitted. At the same time, SVM models show a balanced performance between training and test sets, but do not enable a distinction between the three classes. Of the features that were shown to make significant distinctions, the mean and mean peaks showed a significant separation between classes 0 and 3, however, class 3 is not represented in the test set to assess whether this distinction also occurs in the models. Regarding descriptor, only employed in the regression with three features, it distinguishes class 0 from class 3 as from class 2. However, any of these clear distinctions are reflected in the model. Simultaneously, class 0 is proportionally less represented and coincides with numerous errors in its recognition by the various models.

In gait, the regression with three features and the KNN models show good performances, especially KNN, which achieved a correct distinction of all classes in the test set. Concerning the features, steps mean length, used in all models, distinguishes between class 0 and classes 1 and 2. The rotation angle is also found in all models, except for the regression with two features, and distinguishes between classes 0 and 2 and between classes 1 and 2. Looking at the regression with three features, it correctly separated data from classes 0 and 1. However, it did not distinguish between classes 1 and 2, as did the regression with two features, which shows that the rotation angle feature did not enhance the separation of these classes. In the case of SVM, a correct differentiation can be noted between classes 1 and 2, but not between 0 and 1, demonstrated by the feature steps mean length. These observations suggest that the imbalance of the dataset negatively impacts the training of the models.

All leg agility models are under or overfitted to the data. The regression with three features, the model less overfitted, is the only one that followed the distinction of classes according to feature total power. Recalling, this is the only feature that showed significance, namely distinguishing class 0 from classes 1 and 2. On the other hand, class 0 is the least represented in the dataset, but this is not directly reflected in a lower recognition of it by the models.

Regarding the open-close models, none show a good performance. Looking at the class-by-class results, KNN and SVM with two features, such as mean duration (feature used in the models), failed to distinguish between classes 1 and 2. Simultaneously, SVM with three features, even incorporating the total power, which separates classes 1 and 2, maintained the same error. KNN with three features, like total power, was able to separate between 1 and 2, but not between

0 and 1, neither 0 and 2. As for the regressions, the one with three features, although it has the mean duration and mean angle able to do so, the model did not distinguish class 0 from classes 1 and 2. Likewise, it did not correctly separate classes 1 and 2, which the embedded total power distinguishes. In the same way, regression with two features did not allow the distinction between the classes present in the test set. Turning to the class distribution, class 2 is the one in the greatest proportion; indeed, there is a large percentage of elements from other classes misclassified as class 2.

Among the pronation-supination models, only the SVM with three features showed consistency over the different sets. This model, similarly to the mean angle, separated correctly class 0 from classes 1 and 2, but failed to distinguish between classes 1 and 2. Despite the worse performance with the training set, the SVM with two features showed the same ability to separate features in the test set as the SVM with three features. As for KNN models, the correct distinction of all test elements does not reflect the model's accuracy. In the case of regression with two features, in the same way as the mean angle, it separated class 0 from classes 1 and 2. As for the regression with three features, even though it distinguished classes 0 and 1, it failed to distinguish classes 0 and 2, even including the mean angle, total power and W_y ApEn features that allow this distinction. Although classes are balanced, in SVM, there is a greater tendency for misclassification as class 2.

Concerning rest tremor, the same features were used in the three algorithms, but only regression distinguished the classes. Even though no feature proved statistically significant in differentiating the classes, those selected for the classifications were effective when applied to regression. Class 0 has a higher proportion than class 1 in the dataset, but this imbalance is not directly reflected in the results.

The models presented of postural tremor do not show much promise. Of all, only the regression with three features does not perform perfectly in the test set. As with the features W_x standard deviation, W_x RMS and W_x tremor frequency, the model correctly distinguished between classes 0 and 1. As it is a regression, a continuous function, it allowed the classification of classes not represented in the dataset, which was verified. As regards the dataset, this is balanced in the same way as the classification made by the models.

In terms of the kinetic tremor models, all are overfitted to the training data and unable to distinguish between classes 0 and 1 of test set, even though part of the features on which the models are based do make this separation. The dataset for this exercise has considerably more data from class 0, to which tends the classifications performed with the two-feature regression and SVM models.

In general, the classification models do not perform well. This is quite reasonable, given the small size of the datasets used and the imbalance of some of them. A larger dataset could be a step to avoid the under and overfit of the models, which was observed. The mirroring in the models of the features' capacity to distinguish the symptoms, verified in some cases, evidences the need to employ and search for features that translate relevant information.

Chapter 7

Conclusions and future work

To fulfil this thesis' main objective of developing algorithms for Parkinson's disease motor symptoms quantification, several steps and approaches were taken, all of which will be recalled in this Chapter. The conclusions of the various research stages and the future work that is foreseen as a continuation of this project are also outlined.

Only with the study approval, the gathering of requirements for the iHandU system and the creation of a hospital adapted protocol was it possible to collect data and then begin the development part of the work. The collected data was structured in datasets and pre-processed. From these processed signals a set of features that translate the various symptoms were extracted. The features were applied both in statistical analysis and for the development of models.

In the statistical analysis, except for rest tremor, for all exercises, features showed to be capable of distinguishing the different levels of the symptom in question with statistical significance. The creation of features capable of making this distinction is supported by a correct processing and understanding of the fundamental aspects of symptom quantification.

Before developing quantification algorithms from the newly created datasets, a rigidity dataset acquired in the context of DBS surgery was explored to better study the symptom and try to improve the existing model. Despite not outperforming the model presented in the literature, the use of different features seemed positive. However, the poor results of the selection of three arcades lead to the conclusion that the information contained in these arcades is not equivalent to the total signal, and this conditioned the test of the new features.

The new datasets were used to create symptoms' severity quantification models. The developed models do not present good performances, with some exceptions, proving to be too under or overfitted to the data. This turns out to be normal, given the small dimension of the created datasets.

The data were collected in a hospital context, in the Parkinson's disease appointments at the Centro Hospitalar Universitário de São João, which played a key role in this work, beyond being the source of data. This experience enabled an insight into the reality of the patients, the exercises

they may perform, how to optimise the system for their use. In the same way, it was possible to understand the details that doctors look at when quantifying symptoms, the aspects that concern them the most in their patients and how they manage the disease. Overall, the appointments provided a deeper understanding of the disease and consequently a greater sensitivity to the translation of symptoms.

The results obtained are very interesting and promising, but they mark only the beginning of a long path that has to be taken to achieve really reliable models to be applied in the daily life of patients and clinicians. Based on the work done, there are some logical steps to explore next, which will be listed below.

First, it is essential to collect more data, in quantity and from all classes, to support the correct training of algorithms. To overcome the features' difficulty to separate the closest levels of the symptoms, more features should be studied.

Focusing on rigidity, the various approaches applied to the signals, acquired both in surgery and in consultations, point out that three arcades are not representative of the whole signal and rigidity therefore. For this reason, in the future it could be explored what is the minimum number of features that allows the models to achieve the same accuracy as with the full signal considered in the reference literature model.

Appendix A

Ethical Process Documents

A.1 Study approval



n.º 01 / 2022

DIREÇÃO CLÍNICA
2022, 5, 06

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração
do Centro Hospitalar de São João

Nome do Investigador Principal:
João Paulo Cunha

CONSELHO DE ADMINISTRAÇÃO - REUNIÃO DE
Presidente do Conselho de Administração

(Prof. Doutor Fernando Araújo)

Diretora Clínica	Coordenador de Ensino	Vogal Executivo	Vogal Excecutivo
(Prof. Doutora Maria João Ractzina)	(Enf. Filomena Cardoso)	(Dr. Luís Pinto Gomes)	(D. Sofia Leal)

Título da Investigação:

Novos métodos para acompanhamento de doentes com doença de Parkinson baseados em sistemas m-Health e na quantificação de sintomas motores através da combinação de sensores têxteis inerciais e técnicas de machine learning.

Pretendendo realizar no(s) Serviço(s) de:

Neurologia

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/Promotor

Porto, 15 de Dezembro de 2021.



Encarregado
de Proteção de Dados
Data Protection Officer

Entrad

Centro de Epidemiologia Hospitalar

25/2/2022

Parecer da Comissão de Ética do

Centro Hospitalar Universitário de São João / Faculdade de Medicina da Universidade do Porto

Título do Projeto: Novos métodos para acompanhamento de doentes com doença de Parkinson baseados em sistemas m-Health e na quantificação de sintomas motores através da combinação de sensores têxteis inerciais e técnicas de machine learning

Nome do Investigador Principal: Prof. Doutor João Paulo Cunha (FEUP e INESC TEC)

Onde decorre o Estudo: No Serviço de Neurologia. Apresentou declaração Prof.^a Doutora Elsa Azevedo. O profissional de ligação será o Dr. João Massano.

Objetivos do Estudo:

O presente projeto pretende contribuir para o desenvolvimento de um sistema baseado em novas tecnologias wearable e mobile para o acompanhamento e monitorização de sintomas motores de doentes com a doença de Parkinson. Pretende-se recolher dados com o sistema de forma a evoluir a sua interface, assim como os modelos que estão a ser desenvolvidos para quantificar sintomas tais como a rigidez e bradicinesia. Os dados recolhidos pelos sensores wearable têm como objetivo serem utilizados em modelos de machine learning de forma a investigar diferentes modelos para obter uma quantificação destes parâmetros que permita uma fácil avaliação, assim como uma melhor e quantificada comparação ao longo da doença de cada doente em específico. Este conceito pretende avançar com a área da saúde personalizada em doentes com doença de Parkinson permitindo também o seu follow-up dentro e fora do ambiente hospitalar através de uma aplicação móvel e uma interface para uso clínico. Este estudo pretende também analisar o uso deste sistema pelos doentes fora do ambiente hospitalar de forma a obter um sistema m-Health capaz de fazer o acompanhamento durante todo o ciclo da doença de Parkinson.

Conceção e Pertinência do estudo:

A Doença de Parkinson (DP) é uma doença neurodegenerativa que afeta a mobilidade. É caracterizada pela perda progressiva das células dopaminérgicas da substância nigra e pelos sintomas motores resultantes do constante estado de excitação dos neurónios motores.

O diagnóstico clínico foca-se maioritariamente nos sintomas motores, como a bradicinesia (característica fundamental), a rigidez, o tremor de repouso ou alterações posturais e da marcha. Não existe até à data cura para a DP, contudo o uso de terapêuticas dopaminérgicas ou a estimulação cerebral profunda permitem reduzir as limitações causadas pelos sintomas e melhorar a qualidade de vida dos doentes com DP.

Até à data, o diagnóstico e acompanhamento dos doentes com a doença de Parkinson dá-se em consultas hospitalares que recorre a escalas qualitativas para avaliar o estado do doente no momento da consulta. Há, no entanto, a necessidade e a abertura a outros tipos de acompanhamento, nomeadamente à telemedicina, para complementar as consultas presenciais, bem como para quantificar as complicações motoras diárias dos doentes, permitindo assim os médicos terem informação mais completa quanto à progressão da doença para um melhor e mais personalizado acompanhamento de cada doente.

O sistema iHandUapp pretende expandir o sistema que já está a ser utilizado recorrentemente no serviço de neurocirurgia durante as cirurgias de estimulação cerebral profunda (denominado de iHandU) para fora do

bloco operatório, permitindo o seu uso nas consultas de rotina e no acompanhamento dos doentes com e sem implantação do sistema de neuro-estimulação.

As manifestações clínicas da doença de Parkinson são diferentes de doente para doente e o seu progresso incerto. A complexidade da doença, aliada ao número reduzido de consultas anuais com cada doente constituem uma limitação para o acompanhamento médico. Desta forma, é essencial dar resposta a este problema, dando as ferramentas necessárias aos médicos para estes avaliarem frequentemente possíveis alterações na progressão da doença dos seus doentes e, consequentemente, melhorar a qualidade de vida dos últimos, já que a sua condição será devidamente controlada.

O projeto de investigação apresentado pode ser categorizado em quatro linhas de investigação (LI) principais, que apresentam métodos de análises de dados distintas:

LI 1 – Quantificação de sintomas motores de doentes com doença de Parkinson durante consultas de acompanhamento

LI 2 - Quantificação de sintomas motores dos doentes com doença de Parkinson em casa

LI 3 – Estudo de interatividade e usabilidade das Interface web&mobile para acompanhamento do doente e realização de testes

LI 4 - Estudo longitudinal sobre o impacto do sistema no acompanhamento da doença e na redução dos sintomas motores.

Benefício/risco:

Não são esperados riscos pela participação neste estudo.

Este estudo não irá afetar diretamente a saúde da população em estudo sendo que tem como objetivo apoiar os clínicos na decisão de terapia, não atuando sobre o doente. Numa fase inicial este sistema irá apenas ser utilizado para recolha de dados e desenvolvimento de novos modelos de quantificação de sintomas, sendo que apenas depois é que irá ser validado clinicamente para possivelmente depois ser usado como apoio à decisão clínica.

Confidencialidade dos dados:

O participante não será identificado (por exemplo, nome, número de identificação civil) em nenhuns relatórios ou publicações deste estudo

Algumas medidas serão tomadas para proteger a identidade individual, nomeadamente: a) a cada participante será atribuído um código; b) todos os dados recolhidos serão guardados num servidor local do INESC TEC/Universidade do Porto (instituição acolhedora do projeto) com acesso restrito e limitado apenas aos membros do grupo de investigação envolvidos; c) qualquer vídeo ou fotogramas contendo imagens que identifiquem os participantes serão guardados de forma segura e apenas é permitido o seu acesso a investigadores autorizados. Os vídeos e fotogramas que eventualmente sejam escolhidos para constar de apresentações, publicações e outras atividades de I&D e de educação serão sempre anonimizados e não irão conter imagens da cara (e.g. cara será tapada/desfocada), nem qualquer forma de identificar mantendo assim a absoluta confidencialidade. Os dados anonimizados podem ser partilhados com investigadores de outros centros de I&D para trabalhos científicos e de educação.

Não serão realizadas consultas de registos já existentes, não sendo por isso necessário o pedido de Reutilização de Registos Clínicos para Investigação e Desenvolvimento (I&D).

Apresentou a 'avaliação sobre o impacto da proteção de dados' para o EPD.

Respeito pela liberdade e autonomia do sujeito de ensaio:

Dispõe de uma adequada informação ao participante e modelo de CI do CHUSJ.

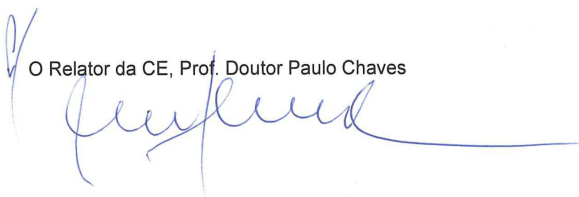
Curriculum do investigador: Adequado à investigação.

Data previsível da conclusão do estudo: dezembro de 2026

Conclusão: Proponho um parecer favorável à realização do estudo.

Porto, 21 de janeiro de 2022

O Relator da CE, Prof. Doutor Paulo Chaves





Comissão de Ética Centro Hospitalar São João /
Faculdade de Medicina da Universidade do Porto

n.º _____ / _____

Questionário para submissão de Investigação

Exmo. Sr. Presidente da Comissão de Ética do Centro Hospitalar de São João /
Faculdade de Medicina da Universidade do Porto,

Pretendo realizar a investigação infracitada, solicito a V. Exa., na qualidade de Investigador, a sua apreciação e a elaboração do respetivo parecer. Para o efeito, anexo toda a documentação requerida.

IDENTIFICAÇÃO DO ESTUDO

Título da investigação: Novos métodos para acompanhamento de doentes com doença de Parkinson baseados em sistemas

Nome do investigador: João Paulo Cunha

Endereço eletrónico: joao.p.cunha@inesctec.pt

Contacto telefónico: 222094000

Caracterização da investigação:

☐ Estudo retrospectivo

☒ Estudo observacional

☒ Estudo prospetivo

☐ Inquérito

☐ Outro. Qual? _____

Tipo de investigação:

☐ Com intervenção

☒ Sem intervenção

Formação do investigador em boas práticas clínicas (GCP): ☐ Sim ☒ Não

Promotor (se aplicável): _____

Nome do orientador de dissertação/tese (se aplicável): _____

Endereço eletrónico: joao.p.cunha@inesctec.pt

Local/locais onde se realiza a investigação: Centro Hospitalar de São João

Data prevista para início: 01 / 01 / 2022

Data prevista para o término: 31 / 12 / 2026

PROTOCOLO DO ESTUDO

Síntese dos objetivos:

O presente projeto pretende contribuir para o desenvolvimento de um sistema baseado em novas tecnologias wearable e mobile para o acompanhamento e monitorização de sintomas motores de doentes com a doença de Parkinson. Pretende-se recolher dados com o sistema de forma a evoluir a sua interface, assim como os modelos que estão a ser desenvolvidos para quantificar sintomas tais como a rigidez e bradicinesia. Os dados recolhidos pelos sensores wearable têm como objetivo serem utilizados em modelos de machine learning de forma a investigar diferentes modelos para obter uma quantificação destes parâmetros que permita uma fácil avaliação, assim como uma melhor e quantificada comparação ao longo da doença de cada doente em específico. Este conceito pretende avançar com a área da saúde personalizada em doentes com doença

Fundamentação ética (ganhos em conhecimento/ inovação; ponderação benefícios/riscos):

Introdução:

A Doença de Parkinson (DP) é uma doença neurodegenerativa que afeta a mobilidade. É caracterizada pela perda progressiva das células dopaminérgicas da substância nigra e pelos sintomas motores resultantes do constante estado de excitação dos neurónios motores.

O diagnóstico clínico foca-se maioritariamente nos sintomas motores, como a bradicinesia (característica fundamental), a rigidez, o tremor de repouso ou alterações posturais e da marcha. Não existe até à data cura para a DP, contudo o uso de terapêuticas dopaminérgicas ou a estimulação cerebral profunda permitem reduzir as limitações causadas pelos sintomas e melhorar a qualidade de vida dos doentes com DP [1].

Até à data, o diagnóstico e acompanhamento dos doentes com a doença de Parkinson dá-se em consultas hospitalares que recorre a escalas qualitativas para avaliar o estado do doente no momento da consulta. Há, no entanto, a necessidade e a abertura a outros tipos de acompanhamento [2], nomeadamente à telemedicina, para complementar as consultas presenciais.

CONFIDENCIALIDADE

De que forma é garantida a anonimização dos dados recolhidos de toda a informação?

Exceto no que se refere aos investigadores do estudo, os registos médicos e do estudo de investigação serão mantidos em sigilo, a menos que autorize a sua publicação ou que os ditos registos sejam exigidos por decisão judicial. Não será

O investigador necessita ter acesso a dados do processo clínico? ☐ Sim ☒ Não

Está previsto o registo de imagem ou som dos participantes? ☒ Sim ☐ Não

Se sim, está prevista a destruição deste registo após o sua utilização? ☐ Sim ☒ Não

CONSENTIMENTO

O estudo implica recrutamento de:

Doentes: ☒ Sim ☐ Não Voluntários saudáveis: ☐ Sim ☒ Não

Menores de 18 anos: ☐ Sim ☒ Não

Outras pessoas sem capacidade do exercício de autonomia: ☒ Sim ☐ Não

A investigação prevê a obtenção de Consentimento Informado: ☒ Sim ☐ Não

Se não, referir qual o fundamento para a isenção:

Existe informação escrita aos participantes: ☒ Sim ☐ Não

PROPRIEDADE DOS DADOS

A investigação e os seus resultados são propriedade intelectual de:

☐ Investigador ☐ Promotor ☒ Ambos ☐ Serviço onde é realizado

☐ Não aplicável

Outro: _____

BENEFÍCIOS, RISCOS E CONTRAPARTIDAS PARA OS PARTICIPANTES

Benefícios previsíveis:

Este estudo vai permitir desenvolver novos modelos de processamento de sinal e sua classificação para quantificar sintomas motores de doentes com a doença de Parkinson. Este estudo vai permitir estender o conhecimento que foi adquirido no estudo da rigidez em ambiente operatório para o acompanhamento do doente em consultas. Este estudo certamente poderá resultar em diversas publicações científicas em que a equipa clínica envolvida também será envolvida na autoria das mesmas. A nível

Riscos/incómodos previsíveis:

Não são esperados riscos pela participação neste estudo.

Este estudo não irá afetar diretamente a saúde da população em estudo sendo que tem como objetivo apoiar os clínicos na decisão de terapia, não atuando sobre o doente. Numa fase inicial este sistema irá apenas ser utilizado para recolha de dados, desenvolvimento de novos modelos de quantificação de sintomas, sendo que apenas depois é que irá ser validado.

São dadas contrapartidas aos participantes:

- pela participação ☐ Sim ☐ Não ☒ Não aplicável
- pelas deslocações ☐ Sim ☐ Não ☒ Não aplicável
- pelas faltas ao emprego ☐ Sim ☐ Não ☒ Não aplicável
- por outras perdas e danos ☐ Sim ☐ Não ☒ Não aplicável

CUSTOS / PLANO FINANCEIRO

Os custos da investigação são suportados por:

☒ Investigador ☐ Promotor ☐ Serviço onde é realizado

☐ Não aplicável

Outro: _____

Existe protocolo financeiro? ☐ Sim ☐ Não

LISTA DE DOCUMENTOS ANEXOS

- ☒ Pedido de autorização ao Presidente do Conselho de Administração do Centro Hospitalar de São João (se aplicável)
- ☐ Pedido de autorização à Diretora da Faculdade de Medicina da Universidade do Porto (se aplicável)
- ☒ Protocolo do estudo
- ☒ Declaração do Diretor de Serviço onde decorre o estudo
(sendo um estudo na área de enfermagem deve anexar também a concordância da chefia de enfermagem)
- ☐ Profissional de ligação
- ☐ Informação dos orientadores
- ☒ Informação ao participante
- ☐ Modelo de consentimento
- ☒ Instrumentos a utilizar (inquéritos, questionários, escalas, p.ex.): Descrito no protocolo de estudo
- ☐ Curriculum Vitae abreviado (máx. 3 páginas)
- ☐ Protocolo financeiro
- ☒ Outros:

Pequena nota: não serão realizadas consultas de registos já existentes, não sendo por isso necessário o pedido de Reutilização de Registos Clínicos para Investigação e Desenvolvimento (I&D).

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (1960 e respetivas emendas), e da Organização Mundial da Saúde, Convenção de Oviedo e das "Boas Práticas Clínicas" (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CES o relatório final da investigação, assim que concluído.

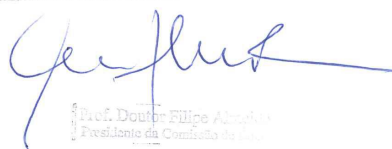
Porto, 15 de Dezembro de 2021
Nome legível: João Paulo Cunha


assinatura

Parecer da Comissão de Ética do Centro Hospitalar de São João/FMUP

Emitido na reunião plenária da CE de 21 / 01 / 2022

A Comissão de Ética para a Saúde
APROVA por unanimidade o parecer do
Relator, pelo que nada tem a opor à
realização deste projecto de investigação.


Prof. Doutor Filipe Albuquerque
Presidente da Comissão de Ética

01-22



SÃO JOÃO

RESPONSÁVEL PELO ACESSO À INFORMAÇÃO

**Pedido de Reutilização de Registos Clínicos
para Investigação e Desenvolvimento (I&D)**

Exmo. Senhor
Responsável pelo Acesso à Informação
(Artigo 9.º da Lei n.º 26/2016, de 22 de agosto)
Dr. Rui de Vasconcellos Guimarães

Número do Pedido
212101171212
(A preencher pelo Gabinete de Apoio ao RAI)



SÃO JOÃO

AUTORIZADO
RAI - Responsável pelo Acesso
à Informação - Centro
Hospitalar de São João
(Art. 9.º, Lei 26/2016, de 22/8)

08.02.2022

1. Identificação do(s) Investigador(es) Preenchimento Obrigatório

1.1. Investigador Principal No caso de haver mais do que um investigador mencionar nas observações

Nome **João Paulo Cunha**

Contacto telefónico **2 2 2 0 9 4 0 0 0**

Endereço eletrónico **jp Cunha @inesctec.pt**

1.2. Investigador(es) Associado(s)

Número Total: **5**

Nome **Duarte Filipe Dias**

Contacto telefónico **9 1 9 1 8 2 9 3 3**

Endereço eletrónico **duarte.f.dias @inesctec.pt**

Nome **Elodie Múrias Lopes**

Contacto telefónico **9 1 8 0 1 6 0 8 5**

Endereço eletrónico **elodie.m.lopes @inesctec.pt**

Nome **Patrícia Valcarcel Lopes**

Contacto telefónico **9 1 3 7 0 0 7 7 5**

Endereço eletrónico **patricia.lopes @insignals-neurotech.com**

1.3. Afiliação Institucional do Investigador Principal

1.3.1. Grupo Profissional

☐ Médico(a) ☐ Enfermeiro(a) ☒ Docente ☐ Estudante

☐ Outro. Qual? _____

1.3.2. Documento de identificação pessoal ou profissional

☐ Cartão de Cidadão ☐ Bilhete de Identidade ☐ Cédula Profissional

☒ Cartão de Docente ☐ Cartão de Estudante ☐ Outro. Qual? _____

Número de Documento **5 0 6 3 3 7**

2. Enquadramento e Identificação do Trabalho de Investigação e Desenvolvimento Preenchimento Obrigatório

2.1. Enquadramento da investigação

☒ Projeto ou trabalho académico de investigação e desenvolvimento:

☐ Não conferidor de grau

☐ Conferidor de grau: ☐ Licenciatura ☐ Mestrado ☐ Doutoramento



SÃO JOÃO

Gabinete
de Apoio ao RAI

Recebido em
01.02.2022

A funcionária
TE

pág. 1/3

RAI-0002-0

2.2. Entidade(s) que tutela(m) a investigação☒ Centro Hospitalar de São JoãoServiço: Neurologia☒ Universidade do PortoFaculdade / Instituto: INESC TEC - Instituto de Engenharia de Sistemas e Computadores, Tecnologia e Ciência☐ Outra Instituição. Qual? _____**Há alguma parceria entre instituições?**☐ Não☒ Sim. Qual(is)? Centro Hospitalar de São João - INESC TEC; Insignals Neurotech Lda - INESC TEC**2.3. Orientador** *Se Aplicável*Contacto telefónico

Endereço eletrónico _____ @ _____

2.4. Título provisórioNovos métodos para acompanhamento de doentes com doença de Parkinson baseados em sistemas m-Health e na quantificação de sintomas motores através da combinação de sensores têxteis inerciais e técnicas de machine learning.*Deverá posteriormente indicar o título definitivo para emissão do Certificado de Reutilização pelo RAI - Data REUse Certificate for Research - DARE através dos contactos disponíveis no fim deste formulário.***2.5. Acesso requerido**☒ Ficheiro*Descrição do património informacional a que pretende ter acesso, identificando a informação a obter, i.e. nome, morada, diagnóstico, idade, códigos dos distritos, entre outros.*

Para efeitos de estudos retrospectivos, poderá ser necessário recolher os registos anteriores às consultas relativos à severidades dos sintomas motores analisado pelo médico. Não será recolhida nenhuma informação pessoal, apenas registos relativos à avaliação dos sintomas motores.

☐ Consulta de processos clínicos em ambiente papel:☐ Bloco☐ Consulta Externa☐ Hospital de Dia☐ Internamento☐ MCDT☐ Urgência*Deverá anexar ficheiro(s) contendo a identificação do pretendido, i.e. números de processos, episódios, números de utente, entre outros.*[Anexar ficheiro no ato de envio](#)☐ Consulta de registos clínicos eletrónicos*Especificar os Sistemas de Informação:*Data previsível de fim de utilização das credenciais de acesso - - ☒ Outro Acesso. Qual?

Participação e recolha de dados e indicadores clínicos durante consultas de acompanhamento de doentes com doença de Parkinson em fase de medicação ou que foram submetidos a cirurgia para implantação de neuroestimulador.

2.3. Pareceres e Autorizações☐ Autorização da Hierarquia☐ Protocolo Científico Aprovado¹☐ Parecer da Comissão de Ética para a Saúde (CES)¹☐ Parecer do Centro de Epidemiologia Hospitalar¹*Deverá anexar ficheiro(s) contendo cópia dos documentos referentes às opções selecionadas.*[Anexar ficheiro no ato de envio](#)¹ Obrigatório quando aplicável.

3. Observações Preenchimento Facultativo

Para além dos 3 investigadores associados irão existir mais dois que irão também fazer parte do estudo, sendo que estes são alunos que estão a realizar tese de Mestrado no âmbito deste projeto.

4- Adriana Guedes Arrais; 932090590; adriana.g.arrais@inesctec.pt

5- Eduardo Ferreira Campos; 919094959; eduardo.f.campos@inesctec.pt

4. Aceitação dos Termos e Condições da Reutilização

Cumulativamente com as obrigações decorrentes da lei já citada (n.º 2 e 3 do art.º 21 e o n.º 1 e 2 do art.º 12, ambos da Lei n.º 26/2016, de 22 de Agosto) ao submeter o presente pedido concordo e fico ainda vinculado, juridicamente, aos seguintes termos e condições:

- Comprometo-me a manter confidencial toda a informação à qual vou ter acesso;
- Após explicação do RAI do CHUSJ, embora a Lei 26/2016, de 22 de agosto, imponha como requisito a anonimização sem possibilidades de reversão, tal desiderato, é não só uma impossibilidade matemática já comprovada, como ainda resulta num prejuízo para a investigação, face à quantidade e qualidade da informação a retirar à fonte, razão pela qual, concordando com o RAI, assumimos como compromisso a pseudo anonimização, o que impõe uma avaliação e gestão do risco, num quadro ético-jurídico que aceitamos e nos comprometemos a colaborar;
- Não vou elaborar registos, suscetíveis de identificar ou tornar identificável a identidade das pessoas a quem os mesmos dizem respeito;
- Comprometo-me a consultar os processos clínicos nos termos e locais que me forem indicados para o efeito;
- Além do presente pedido para reutilizar registos clínicos, dirigido ao RAI, comprometo-me a obter os necessários pareceres quer do Encarregado da Proteção de Dados, quer da Comissão de Ética do Hospital, quer ainda do Centro de Epidemiologia Hospitalar;
- Comprometo-me a citar as fontes, sempre que publicitar o trabalho de investigação, independentemente de requerer a Certidão de Reutilização (DataREUseCertificate for Research – DARE).
- Tomei conhecimento, que a violação de qualquer dos compromissos aqui assumidos, resultará no apuramento de responsabilidades disciplinares, civis e penais e ainda, à impossibilidade futura de aceder a informação de saúde para fins de investigação.

5. Decisão do investigador sobre requerer a DataREUse Certificate for Research – DARE Preenchimento Obrigatório

☒ Pretendo desde já requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em <http://portal-chsj.min-saude.pt/pages/710>.

☐ Não pretendo requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em <http://portal-chsj.min-saude.pt/pages/710>.

Na circunstância do requerente não indicar nenhuma opção, presumimos que pretende requerer o DARE.

6. Assinatura

Nota 1: Se o presente pedido for submetido eletronicamente ou faz assinatura digital qualificada, ou posteriormente vem ao Centro Hospitalar de São João exibir o seu documento de identificação pessoal, ou no âmbito do seu espaço de liberdade e como manifestação expressa do seu consentimento envia cópia do referido documento, neste caso, concluído o processo ser-lhe-á devolvida ou eliminada a cópia do documento de identificação pessoal, conforme as indicações que dá.

Nota 2: Se o presente pedido for entregue presencialmente, assina e exibe o documento de identificação a quem recebe o pedido.

Data 2021 - 12 - 23


Investigador Principal

Em caso de dúvida no preenchimento contacte através dos endereços eletrónicos
rai.reutilizacao.id@chsj.min-saude.pt ou ruiguimaraes@chsj.min-saude.pt
ou pelos números de telemóvel 962 204 194 ou 918 880 299

SUBMITER



ENCARREGADO DE PROTEÇÃO DE DADOS (EPD)
CENTRO HOSPITALAR UNIVERSITÁRIO DE S. JOÃO, EPE

Paulo Alexandre Mota da Silva
 Encarregado de Proteção de Dados do CHUSJ
epd@chsj.min-saude.pt

Ref.º CES CHUSJ: 01 / 2022

Título do Projeto	Novos métodos para acompanhamento de doentes com doença de Parkinson baseados em sistemas m-Health e na quantificação de sintomas motores através da combinação de sensores têxteis inerciais e técnicas de machine learning.		
Responsável pelo tratamento	João Paulo Cunha		
Instituição	Centro Hospitalar Universitário de São João (CHUSJ)		
Investigador	Interno	☒ Externo	
Contacto telefónico	222094000	Endereço Electrónico	joao.p.cunha@inesctec.pt
Profissional de Ligação	João Massano (Assistente Hospitalar Graduado de Neurologia)		
Amostra	30 (p/ano)		
Análise de Risco	Tolerável	☒ Baixo	Elevado Muito Elevado

Parecer do EPD:

Data: 24/02/2022

Finalidade: contribuir para o desenvolvimento de um sistema baseado em novas tecnologias wearable e mobile para o acompanhamento e monitorização de sintomas motores de doentes com a doença de Parkinson. Pretende-se recolher dados com o sistema de forma a evoluir a sua interface, assim como os modelos que estão a ser desenvolvidos para quantificar sintomas tais como a rigidez e bradicinesia. Os dados recolhidos pelos sensores wearable têm como objetivo serem utilizados em modelos de machine learning de forma a investigar diferentes modelos para obter uma quantificação destes parâmetros que permita uma fácil avaliação, assim como uma melhor e quantificada comparação ao longo da doença de cada doente em específico. Este conceito pretende avançar com a área da saúde personalizada em doentes com doença de Parkinson permitindo também o seu follow-up dentro e fora do ambiente hospitalar através de uma aplicação móvel e uma interface para uso clínico. Este estudo pretende assim também analisar o uso deste sistema pelos doentes fora do ambiente hospitalar de forma a obter um sistema m-Health capaz de fazer o acompanhamento durante todo o ciclo da doença de Parkinson.

Licitude: fundamento previsto no artigo 6(1)(a) e 9(2)(a) do RGPD.

Categorias de dados pessoais: variáveis identificadas com detalhe na AIPD, datada de 09/02/2022, ponto 13 e protocolo de investigação, tendo presente o princípio da minimização dos dados.

Conservação: os dados serão alvo de pseudonimização, armazenados em local seguro, em área restrita com acesso limitado ao profissional de ligação e Investigador Principal, com acesso a ficheiros protegido por palavra-passe, efetuando-se a conservação até a conclusão da investigação, durante o prazo máximo de dez (10) anos. Os dados recolhidos serão destruídos após a finalização do estudo.

Comunicação de Dados: não há partilha de dados pessoais.

Faça ao exposto, e observadas as recomendações, entende-se que a presente AIPD apresenta os elementos necessários para assegurar que o tratamento é realizado em conformidade com o RGPD.

Recomendações:

- Sempre que o consentimento do titular for o fundamento de legitimidade adequado para o tratamento de dados, dever-se-á assegurar que o mesmo é válido nas condições legalmente exigíveis: **uma manifestação de vontade livre, específica, informada e inequívoca**. Neste contexto, o consentimento deverá ser objeto de reflexão por parte do participante fora do ambiente hospitalar, devendo para tal, existir a possibilidade de o mesmo remeter o consentimento por correio em envelope RSF.
1. Reforçar as medidas de segurança previstas para a conservação dos documentos em formato de papel que impeçam o acesso à informação a pessoas não autorizadas, bem como o seu manuseamento indevido;
 2. Garantir medidas de segurança adicionais no transporte dos dados com recurso a dispositivos electrónicos de armazenamento, nomeadamente através de medidas de cifragem e autenticação;

4. Em caso de necessidade de extensão de prazo e/ou de qualquer alteração dos pressupostos atinentes ao presente parecer o Investigador Principal deverá solicitar a reapreciação do projeto de investigação junto do EPD.

Revisão AIPD:☐

Data da próxima revisão: __/__/__

☒

Não carece de revisão.

Anexos:

1. Processo CES n.º 01/2022
2. Parecer CES (21/01/2022)
3. AIPD (09/02/2022)
4. Consentimento Informado e Informação ao Participante
5. Protocolo de Investigação

Assinado por: **PAULO ALEXANDRE MOTA DA SILVA**Num. de Identificação: 12061004
Data: 2022.02.24 10:52:51+00'00'**CARTÃO DE CIDADÃO**
• • • • •

A.2 Informed consent to the participant

Informação ao Participante

Projeto: Novos métodos para acompanhamento de doentes com doença de Parkinson baseados em sistemas m-Health e na quantificação de sintomas motores através da combinação de sensores têxteis inerciais e técnicas de machine learning.

Investigadores Responsáveis: João Paulo Cunha, Professor Associado com agregação na Faculdade de Engenharia da Universidade do Porto e Investigador sénior INESC TEC.

Objetivo geral do estudo: O serviço de Neurologia do Centro Hospitalar Universitário de São João (CHUSJ) e o Instituto de Engenharia de Sistemas e Computadores, Tecnologia e Ciência (INESC TEC), Porto, estão a colaborar mutuamente no desenvolvimento de um sistema que combina tecnologia móvel, dispositivos *wearable* e Inteligência Artificial (IA), capaz de inferir quantitativamente os sintomas motores dos doentes com doença de Parkinson.

Procedimentos: Se fizer parte deste estudo, terá que autorizar a partilha de informação médica como registos de movimento através de sensores inerciais, adquirida no âmbito hospitalar com a equipa de investigadores. Em alguns momentos, poderá ser pedido que permaneça em repouso por alguns minutos, durante os registos, assim como que execute alguns movimentos, habitualmente efetuados em testes clínicos. Ser-lhe-á também solicitado que apresente vários dados de natureza clínica e demográfica, que serão recolhidos no decorrer das consultas normalmente agendadas no decurso do seu seguimento médico regular.

Possíveis Riscos: Não são esperados riscos pela participação neste estudo.

Benefícios: Não existe um benefício imediato para si, financeiro ou de qualquer outra natureza, devido à participação neste estudo. A sua participação neste estudo será importante para o progresso que está a ser feito em relação ao tratamento e acompanhamento dos doentes com doença de Parkinson.

Compensações e/ou custos: Não há qualquer compensação financeira, nem custos associados à participação neste estudo.

Confidencialidade de Relatórios Médicos e da Investigação: Exceto no que se refere aos investigadores do estudo, os registos médicos e do estudo de investigação serão mantidos em sigilo, a menos que autorize a sua publicação ou que os ditos registos sejam exigidos por decisão judicial. Não será identificado (por exemplo, nome, número de identificação civil) em nenhuns relatórios ou publicações deste estudo.

Gestão dos dados: Algumas medidas serão tomadas para proteger a sua identidade individual, nomeadamente: a) a cada participante será atribuído um código; b) todos os dados recolhidos serão guardados num servidor local do INESC TEC/Universidade do Porto (instituição acolhedora do projeto) com acesso restrito e limitado apenas aos membros do grupo de investigação envolvidos; c) qualquer vídeo ou fotogramas contendo imagens que identifiquem os participantes serão guardados de forma segura e apenas é permitido o seu acesso a investigadores autorizados. Os vídeos e fotogramas que eventualmente sejam escolhidos para constar de apresentações, publicações e outras atividades de investigação e de educação serão sempre anonimizados e não irão conter imagens da sua cara (e.g. cara será tapada/desfocada), nem qualquer forma de o identificar mantendo assim a absoluta confidencialidade. Os dados anonimizados podem ser partilhados com investigadores de outros centros de I&D para trabalhos científicos e de educação.

Direitos do Titular dos Dados: Enquanto titular dos dados, a lei reconhece-lhe os seguintes direitos: Informação, Acesso, Retificação, Apagamento, Oposição e Portabilidade. No caso de desistência não há prejuízo no tratamento de dados recolhidos até então, sendo estes tornados totalmente anonimizados.

Pontos de contacto: O contacto preferencial para o exercício de direitos deverá ser realizado através do Dr. João Massano. Caso tenha dúvidas sobre a forma como os seus dados pessoais são tratados, para saber mais sobre os seus direitos no âmbito da proteção de dados, pode entrar em contacto com o Encarregado de Proteção de Dados (EDP) do CHUSJ através do endereço de email: epd@chsj.min-saude.pt

Reclamações: Caso considere que os seus dados não estão a ser objeto de tratamento legítimo, pode, a todo o momento, apresentar uma reclamação junto da autoridade competente, a Comissão Nacional de Proteção de Dados (www.cnpd.pt).

CONSENTIMENTO INFORMADO, LIVRE E ESCLARECIDO

Considerando a "Declaração de Helsínquia", da Associação Médica Mundial

(Helsínquia 1964; Tóquio 1975; Veneza 1983; Hong Kong 1989; Somerset West 1996; Edimburgo 2000)

Projeto: Novos métodos para acompanhamento de doentes com doença de Parkinson baseados em sistemas m-Health e na quantificação de sintomas motores através da combinação de sensores têxteis inerciais e técnicas de machine learning.

Eu, abaixo-assinado (nome completo do doente adulto ou do voluntário)

declaro não estar a participar em nenhum outro projeto de investigação neste momento. Recebi o texto de *Informação ao Participante* relativo ao procedimento que concordei em efetuar. Compreendi a explicação que me foi fornecida pelo investigador que assina este documento. Foi-me ainda dada oportunidade de fazer as perguntas que julguei necessárias, e de todas obtive resposta satisfatória. Tomei conhecimento de que, de acordo com as recomendações da Declaração de Helsínquia, a informação ou explicação que me foi prestada versou os objetivos, os métodos, os benefícios previstos, os riscos potenciais e o eventual desconforto. Além disso, foi-me afirmado que tenho o direito de recusar a todo o tempo a minha participação no estudo, bem como pedir a imediata eliminação de todos os meus dados recolhidos no âmbito do estudo, sem que isso possa ter como efeito qualquer prejuízo na assistência que me é prestada. Por isso, consinto de forma livre e esclarecida que me seja aplicado o método, o tratamento ou o inquérito proposto pelo investigador.

Assinatura do doente ou voluntário: _____

Data: __/__/__

Nome e Assinatura do Investigador responsável:

Data: __/__/__

Anulação do Consentimento Informado

Declaro que recebi a *Informação ao Participante* relativo ao estudo / projeto de investigação em questão, que me foi proposto pelo investigador que assina este documento e **pretendo anular** o consentimento dado na data __/__/__.

Assinatura do doente ou voluntário: _____

Data: __/__/__

Assinatura do Investigador responsável: _____

Data: __/__/__

Nota: Fornecimento obrigatório de cópia ao participante

A.3 Hospital informed consent to the participant



CONSENTIMENTO INFORMADO, ESCLARECIDO E LIVRE

PARA INVESTIGAÇÃO CLÍNICA

Considerando a "Declaração de Helsínquia" da Associação Médica Mundial (Helsínquia 1964; Tóquio 1975; Veneza 1983; Hong Kong 1989; Somerset West 1996; Edimburgo 2000; Seul 2008; Fortaleza 2013)

Designação do Estudo (em português)

Novos métodos para acompanhamento de doentes com doença de Parkinson baseados em sistemas m-Health e em novos métodos para quantificar sintomas motores através da combinação de sensores têxteis inerciais e técnicas de machine learning.

Confirmo que expliquei ao participante/ representante legal, de forma adequada e compreensível, a investigação referida, os benefícios, os riscos e possíveis complicações associadas à sua realização.

Informação escrita em anexo: ☐ Não ☒ Sim (Nº de páginas 3)

O Investigador responsável

Nome: João Paulo Cunha

legível

assinatura

Identificação do participante

Nome: _____

BI/CC n.º: _____

Participante/ Representante legal

- Compreendi a explicação que me foi facultada acerca do estudo que se tenciona realizar: os objetivos, os métodos, os benefícios previstos, os riscos potenciais e o eventual desconforto.
- Solicitei todas as informações de que necessitei, sabendo que o esclarecimento é fundamental para uma boa decisão.
- Fui informado da possibilidade de livremente recusar ou abandonar a todo o tempo a participação no estudo, sem que isso possa ter como efeito qualquer prejuízo na assistência que é prestada.
- Declaro não ter sido incluído em nenhum outro projeto de investigação nos últimos três meses.

Concordo com a participação neste estudo, de acordo com os esclarecimentos que me foram prestados, como consta neste documento, do qual me foi entregue uma cópia.

Data: ____ / ____ / ____

assinatura

Nome (Pais/Representante legal): _____

BI/CC n.º: _____

Grau de parentesco: _____

Data: ____ / ____ / ____

assinatura

Appendix B

Motion Raw Signals Collected from Protocol Exercises

B.1 Rigidity signals

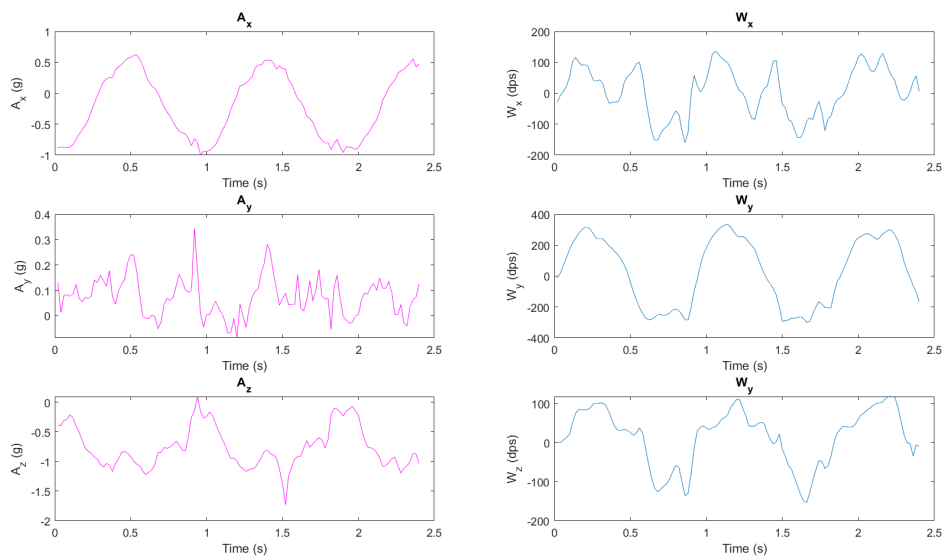


Figure B.1: Example of accelerometer and gyroscope signals from a rigidity acquisition.

B.2 Gait signals

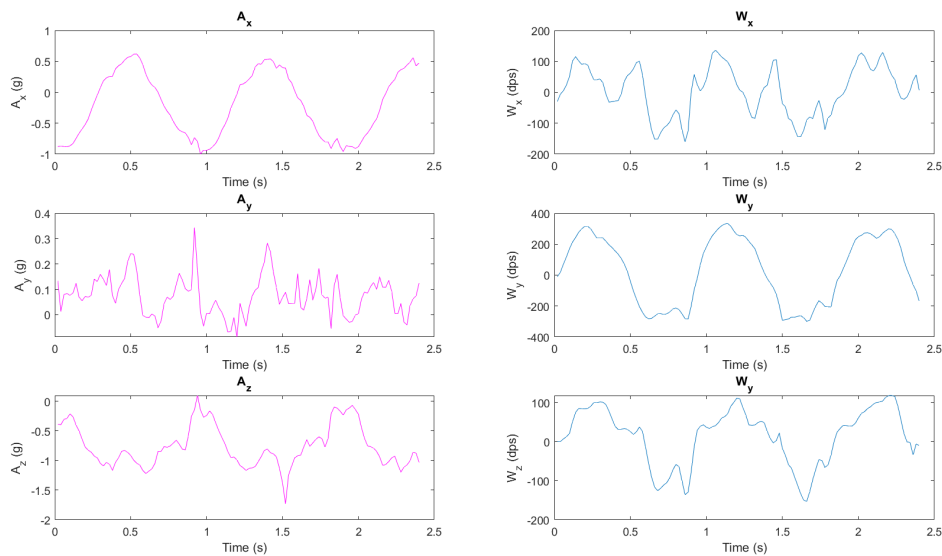


Figure B.2: Example of accelerometer and gyroscope signals from a gait exercise acquisition.

B.3 Leg agility signals

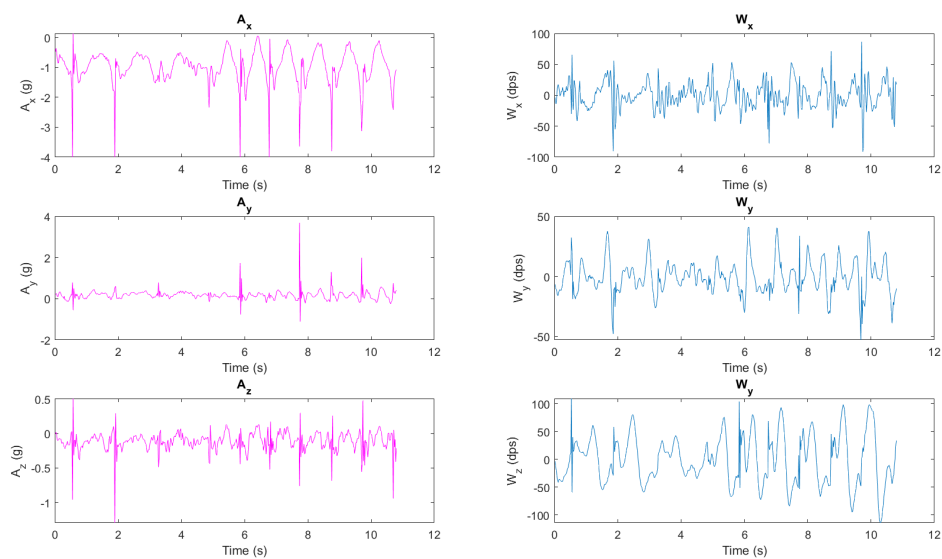


Figure B.3: Example of accelerometer and gyroscope signals from a leg agility exercise acquisition.

B.4 Open-close signals

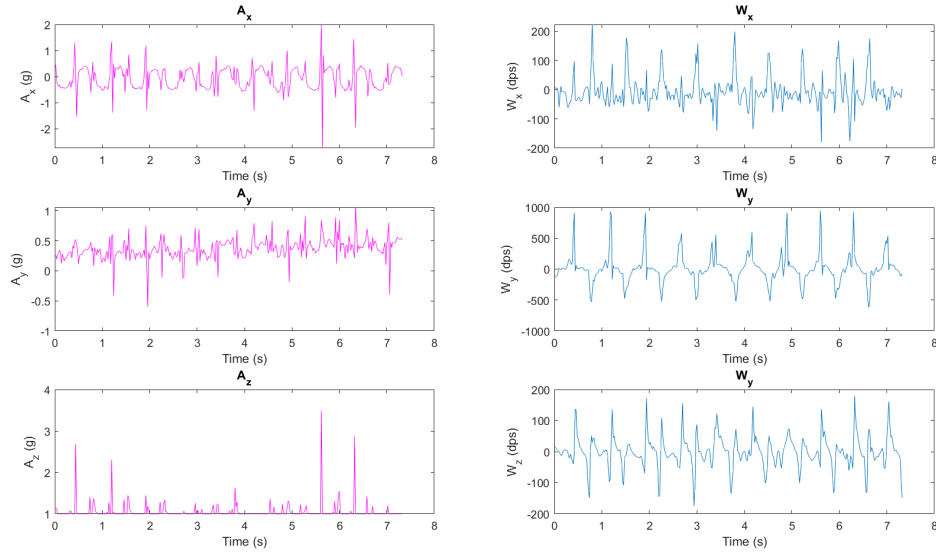


Figure B.4: Example of accelerometer and gyroscope signals from a open-close exercise acquisition.

B.5 Pronation-supination signals

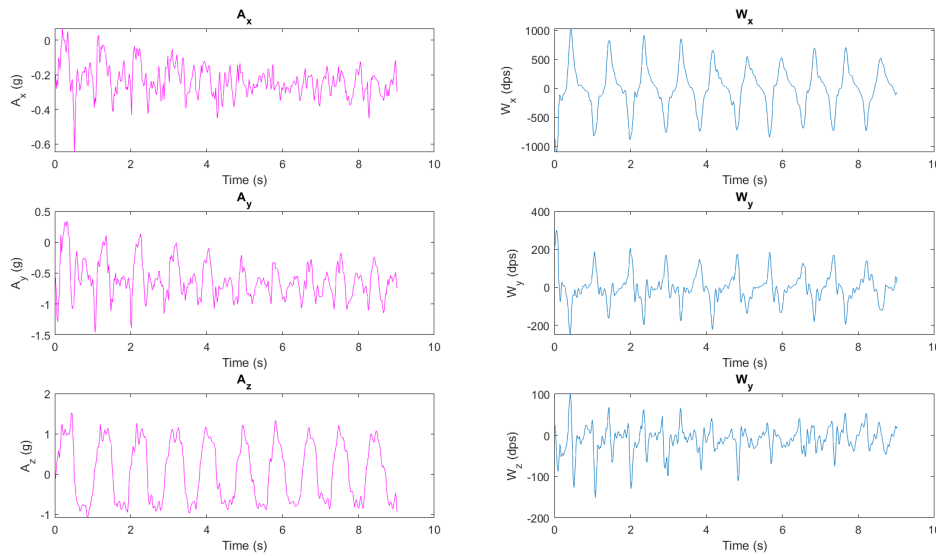


Figure B.5: Example of accelerometer and gyroscope signals from a pronation-supination exercise acquisition.

B.6 Rest tremor signals

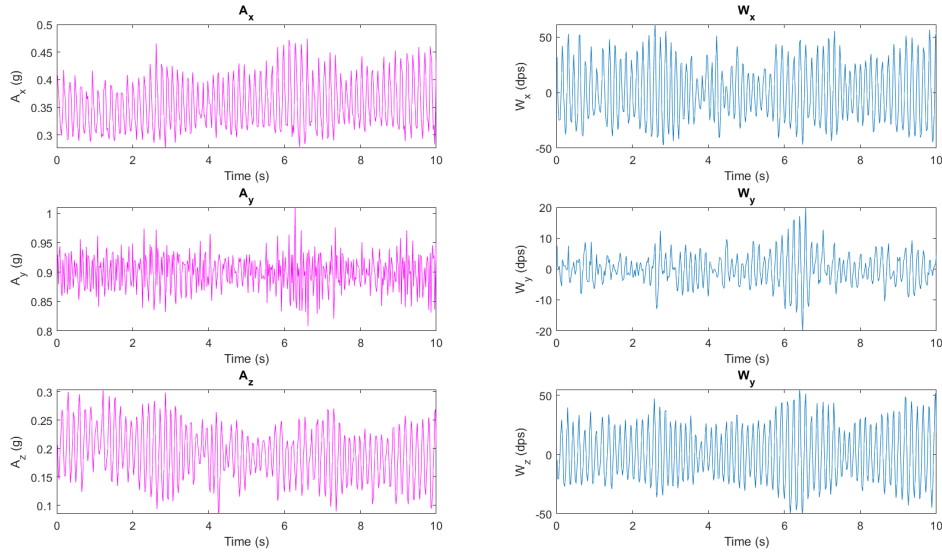


Figure B.6: Example of accelerometer and gyroscope signals from a rest tremor exercise acquisition.

B.7 Postural tremor signals

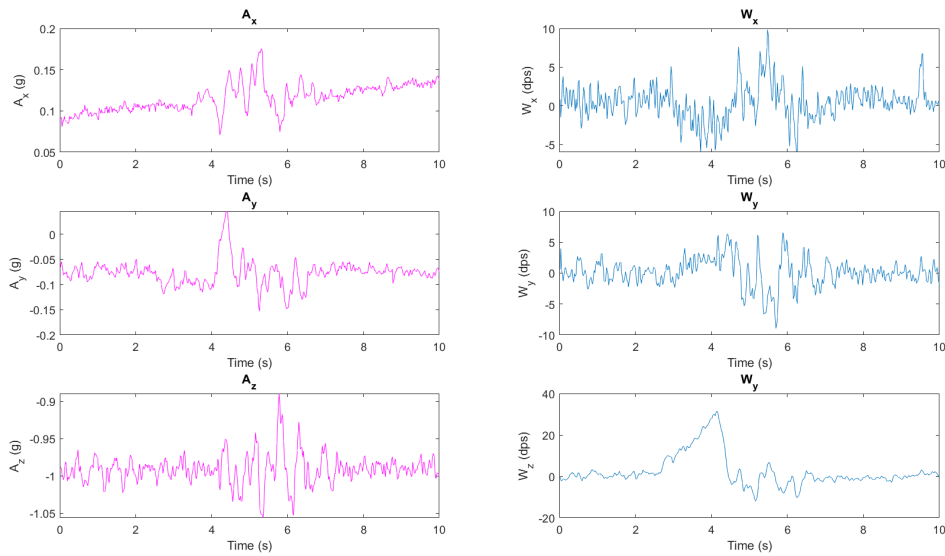


Figure B.7: Example of accelerometer and gyroscope signals from a postural tremor exercise acquisition.

B.8 Kinetic tremor signals

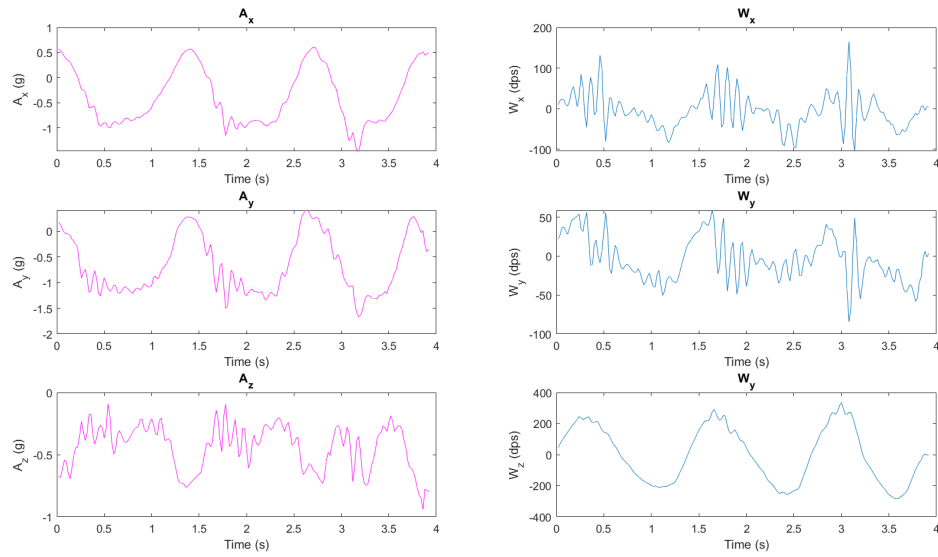


Figure B.8: Example of accelerometer and gyroscope signals from a kinetic tremor exercise acquisition.

Appendix C

Tremor processing

C.1 Rest tremor processing

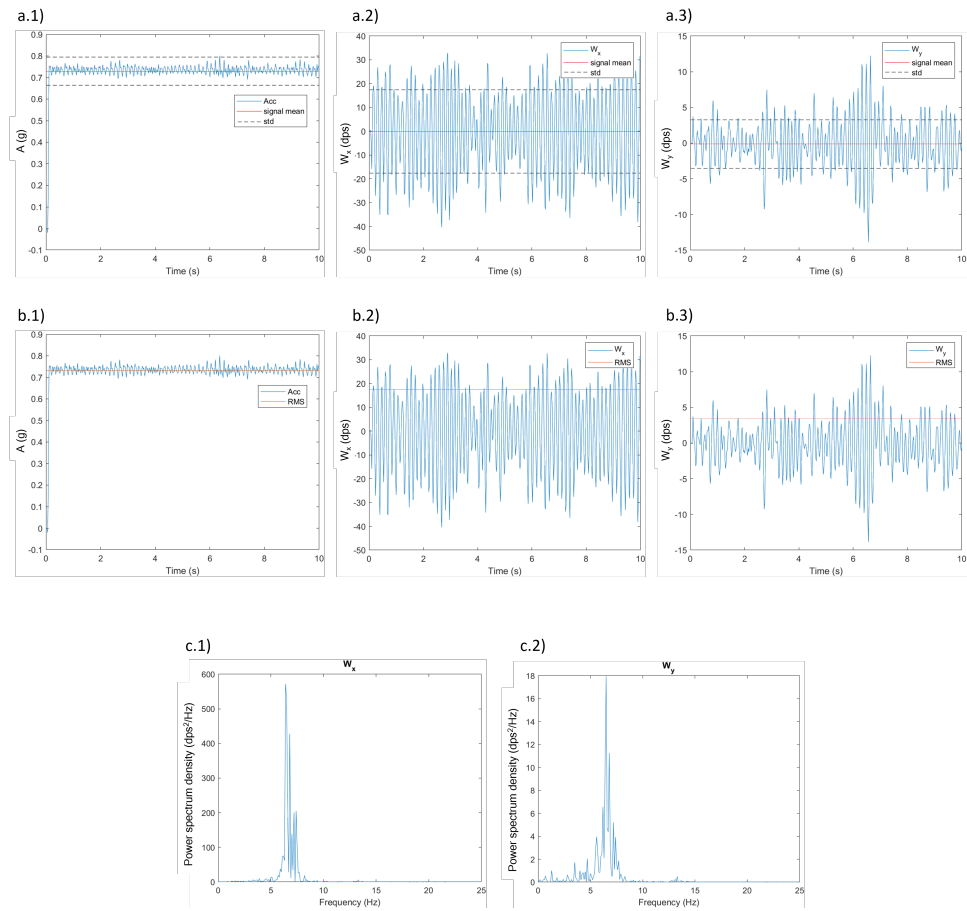


Figure C.1: Examples of rest tremor processing to determine: **(a.1)** A , **(a.2)** W_x and **(a.3)** W_y standard deviation; **(b.1)** A , **(b.2)** W_x and **(b.3)** W_y root mean square value; **(c.1)** W_x and **(c.2)** W_y power spectrum density.

C.2 Postural tremor processing

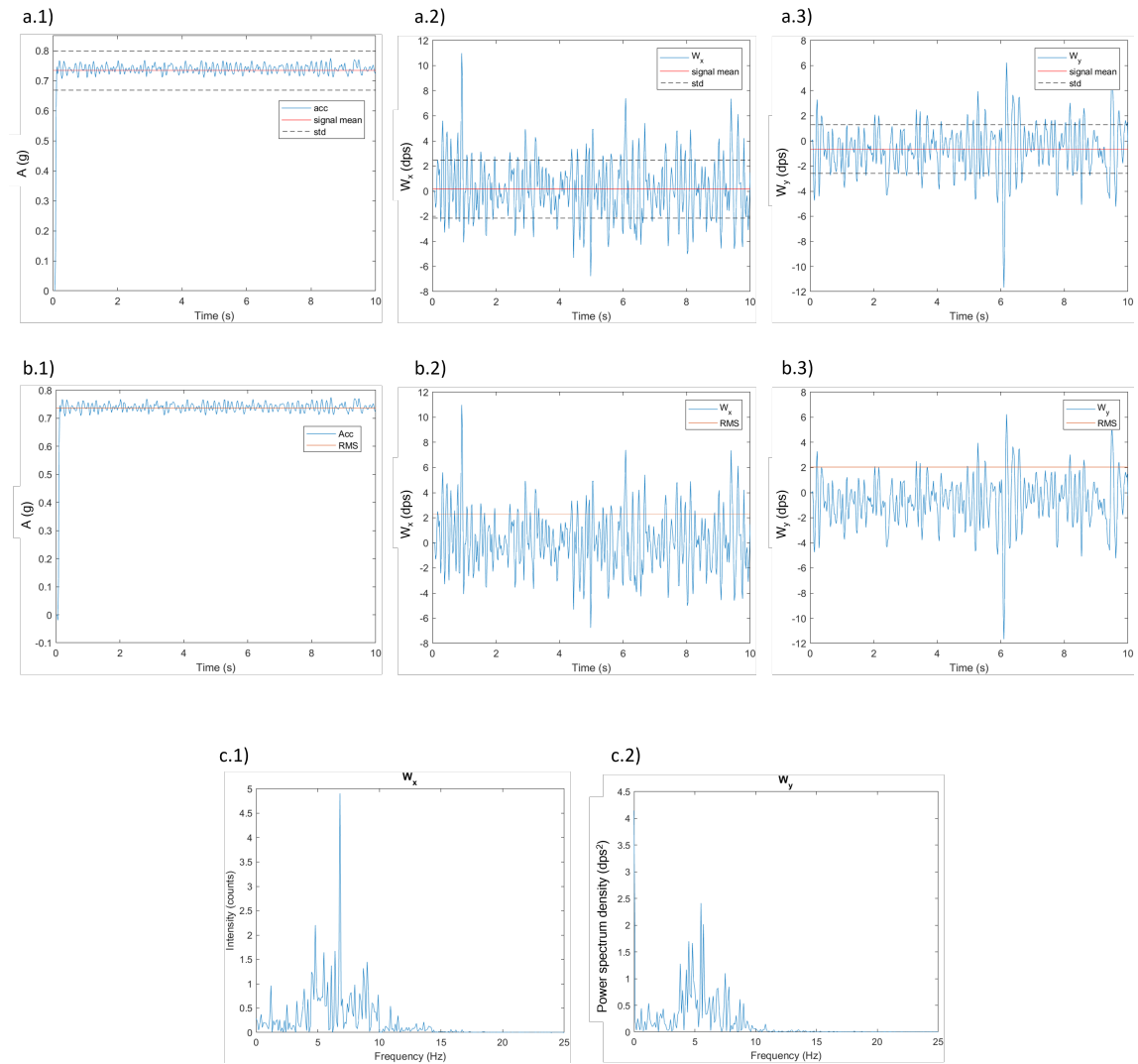


Figure C.2: Examples of postural tremor processing to determine: **(a.1)** A, **(a.2)** W_x and **(a.3)** W_y standard deviation; **(b.1)** A, **(b.2)** W_x and **(b.3)** W_y root mean square value; **(c.1)** W_x and **(c.2)** W_y power spectrum density.

C.3 Kinetic tremor processing

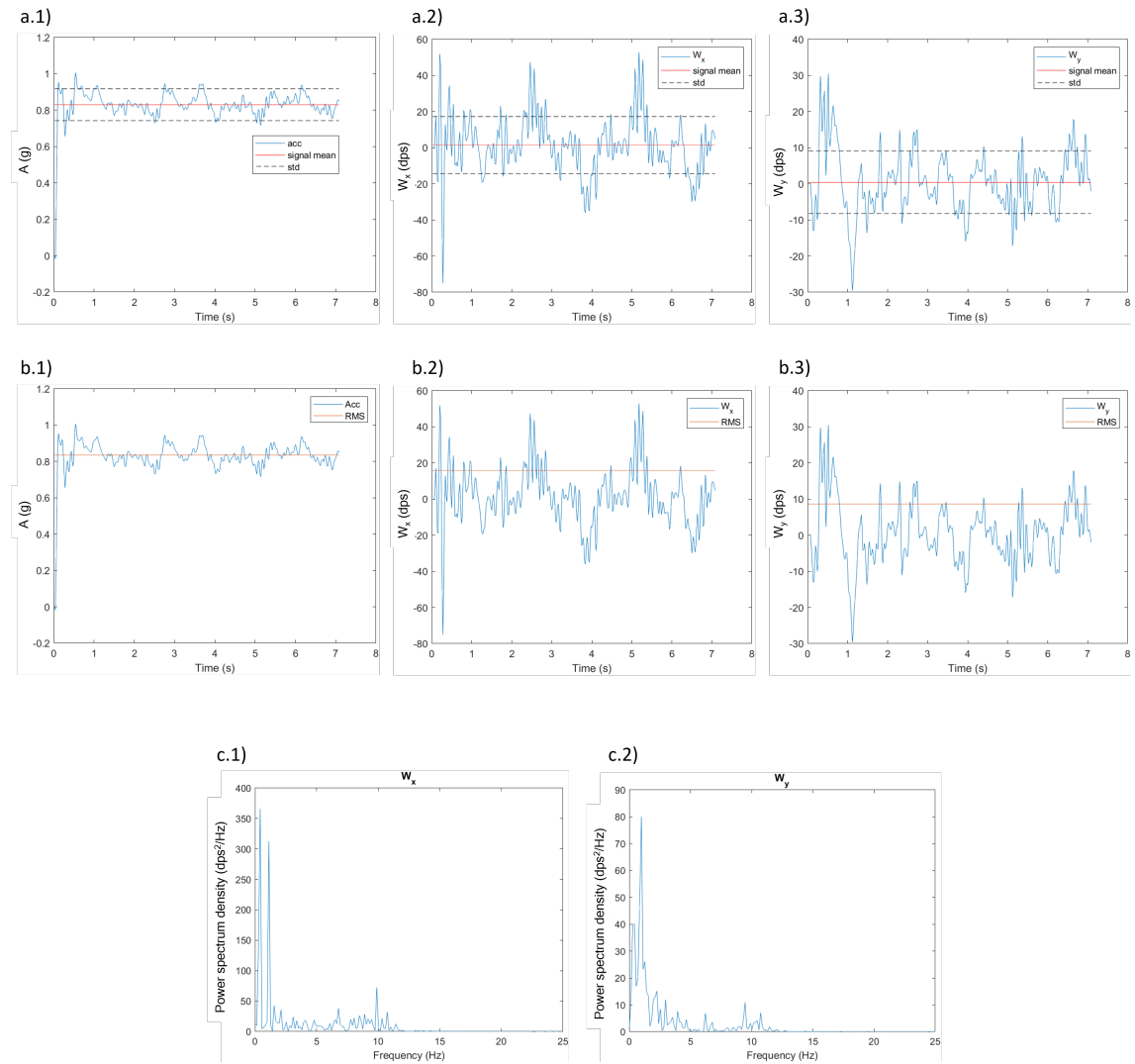


Figure C.3: Examples of kinetic tremor processing to determine: **(a.1)** A , **(a.2)** W_x and **(a.3)** W_y standard deviation; **(b.1)** A , **(b.2)** W_x and **(b.3)** W_y root mean square value; **(c.1)** W_x and **(c.2)** W_y power spectrum density.

Appendix D

Statistic Analysis Extra Tables

D.1 Rigidity

Tests of Normality						
	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
mean_peaks	,155	24	,139	,963	24	,512
mean	,093	24	,200 [*]	,969	24	,648
descriptor	,087	24	,200 [*]	,984	24	,953
frequency	,277	24	<,001	,795	24	<,001
ROM	,094	24	,200 [*]	,940	24	,160
ROM_std	,205	24	,011	,895	24	,017
cogwheel_area	,222	24	,003	,773	24	<,001
cogwheel_number	,199	24	,015	,878	24	,007

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Figure D.1: Kolmogorov-Smirnov and Shapiro-Wilk normality tests applied to rigidity features.

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
mean_peaks	Between Groups	50720,997	3	16906,999	3,145	,048
	Within Groups	107510,868	20	5375,543		
	Total	158231,866	23			
mean	Between Groups	5168,929	3	1722,976	2,892	,061
	Within Groups	11916,514	20	595,826		
	Total	17085,443	23			
descriptor	Between Groups	15692,849	3	5230,950	3,123	,049
	Within Groups	33496,042	20	1674,802		
	Total	49188,890	23			
ROM	Between Groups	2418,259	3	806,086	2,111	,131
	Within Groups	7636,453	20	381,823		
	Total	10054,712	23			

Figure D.2: One-way between-groups ANOVA applied to normally distributed rigidity features.

Multiple Comparisons

Tukey HSD

Dependent Variable	(I) medicalLabel	(J) medicalLabel	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
mean_peaks	0	1	125,21958	49,63659	,087	-13,7101	264,1492
		2	117,30533	48,26388	,103	-17,7822	252,3929
		3	173,67667*	59,86398	,040	6,1212	341,2321
	1	0	-125,21958	49,63659	,087	-264,1492	13,7101
		2	-7,91425	34,77783	,996	-105,2552	89,4267
		3	48,45708	49,63659	,764	-90,4726	187,3867
	2	0	-117,30533	48,26388	,103	-252,3929	17,7822
		1	7,91425	34,77783	,996	-89,4267	105,2552
		3	56,37133	48,26388	,653	-78,7162	191,4589
	3	0	-173,67667*	59,86398	,040	-341,2321	-6,1212
		1	-48,45708	49,63659	,764	-187,3867	90,4726
		2	-56,37133	48,26388	,653	-191,4589	78,7162
mean	0	1	31,178667	16,525337	,265	-15,07470	77,43203
		2	32,193867	16,068327	,220	-12,78036	77,16809
		3	58,518333*	19,930307	,038	2,73468	114,30199
	1	0	-31,178667	16,525337	,265	-77,43203	15,07470
		2	1,015200	11,578462	1,000	-31,39218	33,42258
		3	27,339667	16,525337	,373	-18,91370	73,59303
	2	0	-32,193867	16,068327	,220	-77,16809	12,78036
		1	-1,015200	11,578462	1,000	-33,42258	31,39218
		3	26,324467	16,068327	,381	-18,64976	71,29869
	3	0	-58,518333*	19,930307	,038	-114,30199	-2,73468
		1	-27,339667	16,525337	,373	-73,59303	18,91370
		2	-26,324467	16,068327	,381	-71,29869	18,64976

Figure D.3: Tukey HSD test for multiple comparisons applied to normally distributed rigidity features.

Dependent Variable	(I) medicalLabel	(J) medicalLabel	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
descriptor	0	1	62,82208	27,70591	,140	-14,7250	140,3692
		2	61,32033	26,93970	,137	-14,0822	136,7228
		3	100,14667*	33,41459	,033	6,6214	193,6720
	1	0	-62,82208	27,70591	,140	-140,3692	14,7250
		2	-1,50175	19,41212	1,000	-55,8350	52,8315
		3	37,32458	27,70591	,545	-40,2225	114,8717
	2	0	-61,32033	26,93970	,137	-136,7228	14,0822
		1	1,50175	19,41212	1,000	-52,8315	55,8350
		3	38,82633	26,93970	,490	-36,5762	114,2288
	3	0	-100,14667*	33,41459	,033	-193,6720	-6,6214
		1	-37,32458	27,70591	,545	-114,8717	40,2225
		2	-38,82633	26,93970	,490	-114,2288	36,5762
ROM	0	1	21,816958	13,228834	,375	-15,20970	58,84362
		2	11,057033	12,862989	,825	-24,94565	47,05972
		3	35,473000	15,954574	,151	-9,18283	80,12883
	1	0	-21,816958	13,228834	,375	-58,84362	15,20970
		2	-10,759925	9,268770	,657	-36,70262	15,18277
		3	13,656042	13,228834	,733	-23,37062	50,68270
	2	0	-11,057033	12,862989	,825	-47,05972	24,94565
		1	10,759925	9,268770	,657	-15,18277	36,70262
		3	24,415967	12,862989	,260	-11,58672	60,41865
	3	0	-35,473000	15,954574	,151	-80,12883	9,18283
		1	-13,656042	13,228834	,733	-50,68270	23,37062
		2	-24,415967	12,862989	,260	-60,41865	11,58672

*. The mean difference is significant at the 0.05 level.

(Continuation of Figure D.3)

Test Statistics^{a,b}

	frequency	ROM_std	cogwheel_ar ea	cogwheel_nu mber
Kruskal-Wallis H	1,537	7,493	,731	2,501
df	3	3	3	3
Asymp. Sig.	,674	,058	,866	,475

a. Kruskal Wallis Test

b. Grouping Variable: medicalLabel

Figure D.4: Kruskal-Wallis test applied to non-normally distributed rigidity features.

D.2 Gait

Tests of Normality						
	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
gait_balance	,112	24	,200 [*]	,974	24	,759
gait_consistency	,155	24	,138	,899	24	,020
rotation_angle	,084	24	,200 [*]	,982	24	,936
steps_per_minute	,155	24	,140	,954	24	,324
steps_mean_height	,201	24	,013	,875	24	,007
steps_mean_length	,190	24	,026	,918	24	,052
immobilized	,252	24	<,001	,739	24	<,001
FoG	,110	24	,200 [*]	,917	24	,051
turn_not_detected	.	24	.	.	24	.

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Figure D.5: Kolmogorov-Smirnov and Shapiro-Wilk normality tests applied to gait features.

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
gait_balance	Between Groups	,015	2	,008	,151	,861
	Within Groups	1,059	21	,050		
	Total	1,074	23			
rotation_angle	Between Groups	7155,021	2	3577,510	5,271	,014
	Within Groups	14253,988	21	678,761		
	Total	21409,009	23			
steps_per_minute	Between Groups	378,140	2	189,070	,996	,386
	Within Groups	3986,845	21	189,850		
	Total	4364,985	23			
steps_mean_length	Between Groups	,002	2	,001	5,726	,010
	Within Groups	,003	21	,000		
	Total	,005	23			
FoG	Between Groups	,288	2	,144	,567	,576
	Within Groups	5,327	21	,254		
	Total	5,615	23			

Figure D.6: One-way between-groups ANOVA applied to normally distributed gait features.

Multiple Comparisons							
Tukey HSD							
Dependent Variable	(I) medicalLabel	(J) medicalLabel	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
gait_balance	0	1	-,00311933	,11594217	1,000	-,2953597	,2891211
		2	-,06987750	,15061330	,889	-,4495089	,3097539
	1	0	,00311933	,11594217	1,000	-,2891211	,2953597
		2	-,06675817	,12634505	,858	-,3852198	,2517034
	2	0	,06987750	,15061330	,889	-,3097539	,4495089
		1	,06675817	,12634505	,858	-,2517034	,3852198
rotation_angle	0	1	-1,550667	13,453737	,993	-35,46176	32,36042
		2	45,138200*	17,476916	,044	1,08640	89,19000
	1	0	1,550667	13,453737	,993	-32,36042	35,46176
		2	46,688867*	14,660870	,012	9,73511	83,64262
	2	0	-45,138200*	17,476916	,044	-89,19000	-1,08640
		1	-46,688867*	14,660870	,012	-83,64262	-9,73511
steps_per_minute	0	1	-1,551333	7,115238	,974	-19,48579	16,38312
		2	-11,686550	9,242965	,430	-34,98409	11,61099
	1	0	1,551333	7,115238	,974	-16,38312	19,48579
		2	-10,135217	7,753650	,407	-29,67884	9,40840
	2	0	11,686550	9,242965	,430	-11,61099	34,98409
		1	10,135217	7,753650	,407	-9,40840	29,67884
steps_mean_length	0	1	,015655400*	,006167564	,048	,00010962	,03120118
		2	,026381750*	,008011901	,009	,00618719	,04657631
	1	0	-,015655400*	,006167564	,048	-,03120118	-,00010962
		2	,010726350	,006720947	,269	-,00621427	,02766697
	2	0	-,026381750*	,008011901	,009	-,04657631	-,00618719
		1	-,010726350	,006720947	,269	-,02766697	,00621427
FoG	0	1	,11192267	,26009610	,903	-,5436678	,7675132
		2	-,18468950	,33787474	,849	-1,0363266	,6669476
	1	0	-,11192267	,26009610	,903	-,7675132	,5436678
		2	-,29661217	,28343315	,557	-1,0110254	,4178010
	2	0	,18468950	,33787474	,849	-,6669476	1,0363266
		1	,29661217	,28343315	,557	-,4178010	1,0110254

*. The mean difference is significant at the 0.05 level.

Figure D.7: Tukey HSD test for multiple comparisons applied to normally distributed gait features.

Test Statistics ^{a,b}			
	gait_consistency	steps_mean_height	immobilized
Kruskal-Wallis H	2,904	3,169	1,537
df	2	2	2
Asymp. Sig.	,234	,205	,464
a. Kruskal Wallis Test			
b. Grouping Variable: medicalLabel			

Figure D.8: Kruskal-Wallis test applied to non-normally distributed gait features.

D.3 Leg agility

Tests of Normality						
	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
ax_ApEn	,159	16	,200 [*]	,898	16	,074
immobilized	,185	16	,147	,940	16	,351
total_power	,150	16	,200 [*]	,933	16	,269
m_height	,352	16	<,001	,452	16	<,001
m_duration	,283	16	,001	,664	16	<,001
mean_height	,295	16	<,001	,649	16	<,001
mean_duration	,150	16	,200 [*]	,939	16	,339
height_consistency	,360	16	<,001	,423	16	<,001
duration_consistency	,296	16	<,001	,592	16	<,001

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Figure D.9: Kolmogorov-Smirnov and Shapiro-Wilk normality tests applied to leg agility features.

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
ax_ApEn	Between Groups	,008	2	,004	,474	,633
	Within Groups	,113	13	,009		
	Total	,121	15			
immobilized	Between Groups	7,502	2	3,751	1,498	,260
	Within Groups	32,559	13	2,505		
	Total	40,061	15			
total_power	Between Groups	,097	2	,049	8,352	,005
	Within Groups	,076	13	,006		
	Total	,173	15			
mean_duration	Between Groups	,159	2	,080	1,909	,188
	Within Groups	,541	13	,042		
	Total	,700	15			

Figure D.10: One-way between-groups ANOVA applied to normally distributed leg agility features.

Multiple Comparisons

Tukey HSD

Dependent Variable	(I) medicalLabel	(J) medicalLabel	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
ax_ApEn	0	1	,02463048	,06429673	,923	-,1451410	,1944019
		2	,06033500	,06588454	,640	-,1136290	,2342990
	1	0	-,02463048	,06429673	,923	-,1944019	,1451410
		2	,03570452	,05183768	,774	-,1011696	,1725787
	2	0	-,06033500	,06588454	,640	-,2342990	,1136290
		1	-,03570452	,05183768	,774	-,1725787	,1011696
immobilized	0	1	-,3693619	1,0920827	,939	-3,252937	2,514214
		2	-1,6456500	1,1190517	,336	-4,600436	1,309136
	1	0	,3693619	1,0920827	,939	-2,514214	3,252937
		2	-1,2762881	,8804652	,346	-3,601101	1,048525
	2	0	1,6456500	1,1190517	,336	-1,309136	4,600436
		1	1,2762881	,8804652	,346	-1,048525	3,601101
total_power	0	1	,17466333*	,05265367	,014	,0356346	,3136920
		2	,21633500*	,05395396	,004	,0738730	,3587970
	1	0	-,17466333*	,05265367	,014	-,3136920	-,0356346
		2	,04167167	,04245075	,601	-,0704169	,1537602
	2	0	-,21633500*	,05395396	,004	-,3587970	-,0738730
		1	-,04167167	,04245075	,601	-,1537602	,0704169
mean_duration	0	1	-,05247333	,14083015	,927	-,4243265	,3193798
		2	-,23886833	,14430796	,259	-,6199044	,1421678
	1	0	,05247333	,14083015	,927	-,3193798	,4243265
		2	-,18639500	,11354090	,264	-,4861926	,1134026
	2	0	,23886833	,14430796	,259	-,1421678	,6199044
		1	,18639500	,11354090	,264	-,1134026	,4861926

*. The mean difference is significant at the 0.05 level.

Figure D.11: Tukey HSD test for multiple comparisons applied to normally distributed leg agility features.

Test Statistics^{a,b}

	m_height	mean_height	mean_duration	height_consistency	duration_consistency
Kruskal-Wallis H	,819	2,668	2,731	1,694	1,711
df	2	2	2	2	2
Asymp. Sig.	,664	,263	,255	,429	,425

a. Kruskal Wallis Test

b. Grouping Variable: medicalLabel

Figure D.12: Kruskal-Wallis test applied to non-normally distributed leg agility features.

D.4 Open-close

Tests of Normality						
	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
wy_ApEn	,147	16	,200 [*]	,936	16	,303
immobilized	,281	16	,002	,623	16	<,001
total_power	,303	16	<,001	,696	16	<,001
m_angle	,173	16	,200 [*]	,932	16	,259
m_duration	,115	16	,200 [*]	,978	16	,942
m_amplitude	,109	16	,200 [*]	,974	16	,895
mean_angle	,237	16	,017	,902	16	,088
mean_duration	,155	16	,200 [*]	,951	16	,505
mean_amplitude	,108	16	,200 [*]	,973	16	,891
angle_consistency	,281	16	,001	,780	16	,001
duration_consistency	,283	16	,001	,731	16	<,001
amplitude_consistency	,253	16	,007	,870	16	,027

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Figure D.13: Kolmogorov-Smirnov and Shapiro-Wilk normality tests applied to open-close features.

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
wy_ApEn	Between Groups	,031	3	,010	1,520	,260
	Within Groups	,082	12	,007		
	Total	,113	15			
m_angle	Between Groups	8,251	3	2,750	,661	,592
	Within Groups	49,915	12	4,160		
	Total	58,166	15			
m_duration	Between Groups	,673	3	,224	1,317	,314
	Within Groups	2,042	12	,170		
	Total	2,715	15			
m_amplitude	Between Groups	258,921	3	86,307	1,860	,190
	Within Groups	556,951	12	46,413		
	Total	815,871	15			
mean_angle	Between Groups	3253,963	3	1084,654	4,386	,027
	Within Groups	2967,378	12	247,281		
	Total	6221,341	15			
mean_duration	Between Groups	265,431	3	88,477	9,386	,002
	Within Groups	113,117	12	9,426		
	Total	378,547	15			
mean_amplitude	Between Groups	20475,986	3	6825,329	4,278	,029
	Within Groups	19145,102	12	1595,425		
	Total	39621,088	15			

Figure D.14: One-way between-groups ANOVA applied to normally distributed open-close features.

Multiple Comparisons							
Tukey HSD							
Dependent Variable	(I) medicalLabel	(J) medicalLabel	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
wy_ApEn	0	1	,09843167	,06321439	,437	-,0892456	,2861089
		2	-,02242357	,05187700	,972	-,1764413	,1315941
		3	,01334500	,07167838	,998	-,1994610	,2261510
	1	0	-,09843167	,06321439	,437	-,2861089	,0892456
		2	-,12085524	,05711470	,203	-,2904231	,0487127
		3	-,08508667	,07555565	,681	-,3094039	,1392306
	2	0	,02242357	,05187700	,972	-,1315941	,1764413
		1	,12085524	,05711470	,203	-,0487127	,2904231
		3	,03576857	,06636129	,948	-,1612515	,2327887
	3	0	-,01334500	,07167838	,998	-,2261510	,1994610
		1	,08508667	,07555565	,681	-,1392306	,3094039
		2	-,03576857	,06636129	,948	-,2327887	,1612515
m_angle	0	1	-2,156254250	1,557701966	,532	-6,78091736	2,46840886
		2	-1,012754250	1,278330933	,857	-4,80799239	2,78248389
		3	-,588194250	1,766268008	,987	-5,83206932	4,65568082
	1	0	2,156254250	1,557701966	,532	-2,46840886	6,78091736
		2	1,143500000	1,407396037	,847	-3,03491967	5,32191967
		3	1,568060000	1,861809955	,834	-3,95946966	7,09558966
	2	0	1,012754250	1,278330933	,857	-2,78248389	4,80799239
		1	-1,143500000	1,407396037	,847	-5,32191967	3,03491967
		3	,424560000	1,635246423	,994	-4,43032494	5,27944494
	3	0	,588194250	1,766268008	,987	-4,65568082	5,83206932
		1	-1,568060000	1,861809955	,834	-7,09558966	3,95946966
		2	-,424560000	1,635246423	,994	-5,27944494	4,43032494

Figure D.15: Tukey HSD test for multiple comparisons applied to normally distributed open-close features.

Dependent Variable	(I) medicalLabel	(J) medicalLabel	Mean	Std. Error	Sig.	95% Confidence Interval	
			Difference (I-J)			Lower Bound	Upper Bound
m_duration	0	1	-,205050333	,315099850	,913	-,14055063	,73044996
		2	-,233765429	,258587261	,803	-,100148544	,53395458
		3	-,709087000	,357289646	,247	-,176984463	,35167063
	1	0	,205050333	,315099850	,913	-,73044996	1,14055063
		2	-,028715095	,284695204	1,000	-,87394701	,81651682
		3	-,504036667	,376616355	,558	-,162217339	,61410005
	2	0	,233765429	,258587261	,803	-,53395458	1,00148544
		1	,028715095	,284695204	1,000	-,81651682	,87394701
		3	-,475321571	,330785936	,502	-,145739231	,50674916
	3	0	,709087000	,357289646	,247	-,35167063	1,76984463
		1	,504036667	,376616355	,558	-,61410005	1,62217339
		2	,475321571	,330785936	,502	-,50674916	1,45739231
m_amplitude	0	1	-5,82319167	5,20326744	,685	-21,2711782	9,6247949
		2	-9,39932500	4,27007082	,178	-22,0767431	3,2780931
		3	-10,35383000	5,89995070	,340	-27,8702003	7,1625403
	1	0	5,82319167	5,20326744	,685	-9,6247949	21,2711782
		2	-3,57613333	4,70119325	,870	-17,5335112	10,3812446
		3	-4,53063833	6,21909410	,884	-22,9945138	13,9332371
	2	0	9,39932500	4,27007082	,178	-3,2780931	22,0767431
		1	3,57613333	4,70119325	,870	-10,3812446	17,5335112
		3	-,95450500	5,46229295	,998	-17,1715127	15,2625027
	3	0	10,35383000	5,89995070	,340	-7,1625403	27,8702003
		1	4,53063833	6,21909410	,884	-13,9332371	22,9945138
		2	,95450500	5,46229295	,998	-15,2625027	17,1715127

(Continuation of Figure D.15)

Dependent Variable	(I) medicalLabel	(J) medicalLabel	Mean	Std. Error	Sig.	95% Confidence Interval	
			Difference (I-J)			Lower Bound	Upper Bound
mean_angle	0	1	6,966583	12,010309	,936	-28,69084	42,62400
		2	30,299536*	9,856282	,042	1,03721	59,56186
		3	34,524750	13,618410	,104	-5,90696	74,95646
	1	0	-6,966583	12,010309	,936	-42,62400	28,69084
		2	23,332952	10,851409	,193	-8,88381	55,54971
		3	27,558167	14,355065	,271	-15,06060	70,17693
	2	0	-30,299536*	9,856282	,042	-59,56186	-1,03721
		1	-23,332952	10,851409	,193	-55,54971	8,88381
		3	4,225214	12,608198	,986	-33,20728	41,65771
	3	0	-34,524750	13,618410	,104	-74,95646	5,90696
		1	-27,558167	14,355065	,271	-70,17693	15,06060
		2	-4,225214	12,608198	,986	-41,65771	33,20728
mean_duration	0	1	-7,56667*	2,34494	,032	-14,5286	-,6048
		2	-9,55000*	1,92438	,002	-15,2633	-3,8367
		3	-10,40000*	2,65891	,010	-18,2940	-2,5060
	1	0	7,56667*	2,34494	,032	,6048	14,5286
		2	-1,98333	2,11867	,787	-8,2735	4,3068
		3	-2,83333	2,80274	,746	-11,1544	5,4877
	2	0	9,55000*	1,92438	,002	3,8367	15,2633
		1	1,98333	2,11867	,787	-4,3068	8,2735
		3	-,85000	2,46167	,985	-8,1585	6,4585
	3	0	10,40000*	2,65891	,010	2,5060	18,2940
		1	2,83333	2,80274	,746	-5,4877	11,1544
		2	-,85000	2,46167	,985	-6,4585	8,1585
mean_amplitude	0	1	66,3461500	30,5067976	,185	-24,225516	156,917816
		2	89,0859071*	25,0354585	,018	14,758106	163,413708
		3	53,1660000	34,5914570	,447	-49,532615	155,864615
	1	0	-66,3461500	30,5067976	,185	-156,917816	24,225516
		2	22,7397571	27,5631327	,842	-59,092458	104,571973
		3	-13,1801500	36,4625972	,983	-121,433996	95,073696
	2	0	-89,0859071*	25,0354585	,018	-163,413708	-14,758106
		1	-22,7397571	27,5631327	,842	-104,571973	59,092458
		3	-35,9199071	32,0254662	,684	-131,000350	59,160535
	3	0	-53,1660000	34,5914570	,447	-155,864615	49,532615
		1	13,1801500	36,4625972	,983	-95,073696	121,433996
		2	35,9199071	32,0254662	,684	-59,160535	131,000350

*. The mean difference is significant at the 0.05 level.

(Continuation of Figure D.15)

Test Statistics ^{a,b}					
	immobilized	total_power	angle_consistency	duration_consistency	amplitude_consistency
Kruskal-Wallis H	3,866	11,264	4,163	,203	4,852
df	3	3	3	3	3
Asymp. Sig.	,276	,010	,244	,977	,183

a. Kruskal Wallis Test

b. Grouping Variable: medicalLabel

Figure D.16: Kruskal-Wallis test applied to non-normally distributed open-close features.

Report		
total_power		
medicalLabel	N	Median
0	4	1.123650E+5
1	3	3.219900E+4
2	7	7.387600E+3
3	2	7.326700E+3
Total	16	1.896800E+4

Figure D.17: Group size and median of total power feature of open-close.

					Test Statistics ^a	
Ranks					total_power	
	medicalLabel	N	Mean Rank	Sum of Ranks		
total_power	0	4	5,25	21,00	Mann-Whitney U	1,000
	1	3	2,33	7,00	Wilcoxon W	7,000
	Total	7			Z	-1,768
					Asymp. Sig. (2-tailed)	,077
					Exact Sig. [2*(1-tailed Sig.)]	,114 ^b

a. Grouping Variable: medicalLabel

b. Not corrected for ties.

Figure D.18: Mann-Whitney U test applied to compare classes 0 and 1 in non-normally distributed open-close features.

Ranks					Test Statistics ^a	
	medicalLabel	N	Mean Rank	Sum of Ranks	total_power	
total_power	1	3	8,67	26,00	Mann-Whitney U	1,000
	2	7	4,14	29,00	Wilcoxon W	29,000
	Total	10			Z	-2,165
					Asymp. Sig. (2-tailed)	,030
					Exact Sig. [2*(1-tailed Sig.)]	,033 ^b

a. Grouping Variable: medicalLabel
b. Not corrected for ties.

Figure D.19: Mann-Whitney U test applied to compare classes 1 and 2 in non-normally distributed open-close features.

Ranks					Test Statistics ^a	
	medicalLabel	N	Mean Rank	Sum of Ranks	total_power	
total_power	2	7	5,14	36,00	Mann-Whitney U	6,000
	3	2	4,50	9,00	Wilcoxon W	9,000
	Total	9			Z	-,293
					Asymp. Sig. (2-tailed)	,770
					Exact Sig. [2*(1-tailed Sig.)]	,889 ^b

a. Grouping Variable: medicalLabel
b. Not corrected for ties.

Figure D.20: Mann-Whitney U test applied to compare classes 2 and 3 in non-normally distributed open-close features.

Ranks					Test Statistics ^a	
	medicalLabel	N	Mean Rank	Sum of Ranks	total_power	
total_power	0	4	4,50	18,00	Mann-Whitney U	,000
	3	2	1,50	3,00	Wilcoxon W	3,000
	Total	6			Z	-1,852
					Asymp. Sig. (2-tailed)	,064
					Exact Sig. [2*(1-tailed Sig.)]	,133 ^b

a. Grouping Variable: medicalLabel
b. Not corrected for ties.

Figure D.21: Mann-Whitney U test applied to compare classes 0 and 3 in non-normally distributed open-close features.

D.5 Pronation-supination

Tests of Normality						
	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
wy_ApEn	,175	19	,128	,952	19	,433
immobilized	,416	19	<,001	,466	19	<,001
total_power	,155	19	,200 [*]	,888	19	,030
m_angle	,109	19	,200 [*]	,954	19	,452
m_duration	,150	19	,200 [*]	,947	19	,356
m_amplitude	,154	19	,200 [*]	,978	19	,918
mean_angle	,103	19	,200 [*]	,976	19	,879
mean_duration	,150	19	,200 [*]	,952	19	,425
mean_amplitude	,111	19	,200 [*]	,948	19	,362
angle_consistency	,277	19	<,001	,574	19	<,001
duration_consistency	,181	19	,101	,913	19	,085
amplitude_consistency	,110	19	,200 [*]	,941	19	,273

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Figure D.22: Kolmogorov-Smirnov and Shapiro-Wilk normality tests applied to pronation-supination features.

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
wy_ApEn	Between Groups	,044	2	,022	3,822	,044
	Within Groups	,092	16	,006		
	Total	,136	18			
m_angle	Between Groups	10,546	2	5,273	1,155	,340
	Within Groups	73,045	16	4,565		
	Total	83,590	18			
m_duration	Between Groups	,001	2	,000	1,904	,181
	Within Groups	,003	16	,000		
	Total	,004	18			
m_amplitude	Between Groups	1245,763	2	622,881	2,849	,087
	Within Groups	3497,924	16	218,620		
	Total	4743,687	18			
mean_angle	Between Groups	8892,025	2	4446,013	9,030	,002
	Within Groups	7877,454	16	492,341		
	Total	16769,479	18			
mean_duration	Between Groups	,026	2	,013	,362	,702
	Within Groups	,581	16	,036		
	Total	,607	18			
mean_amplitude	Between Groups	303,190	2	151,595	,014	,986
	Within Groups	174444,880	16	10902,805		
	Total	174748,070	18			
duration_consistency	Between Groups	,004	2	,002	1,065	,368
	Within Groups	,029	16	,002		
	Total	,033	18			
amplitude_consistency	Between Groups	7548,541	2	3774,270	,973	,399
	Within Groups	62077,575	16	3879,848		
	Total	69626,116	18			

Figure D.23: One-way between-groups ANOVA applied to normally distributed pronation-supination features.

Multiple Comparisons							
Tukey HSD							
Dependent Variable	(I) medicalLabel	(J) medicalLabel	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
wy_ApEn	0	1	-,08083690	,04225683	,167	-,1898735	,0281997
		2	-,11213024 [*]	,04225683	,043	-,2211668	-,0030936
	1	0	,08083690	,04225683	,167	-,0281997	,1898735
		2	-,03129333	,04385198	,759	-,1444460	,0818593
	2	0	,11213024 [*]	,04225683	,043	,0030936	,2211668
		1	,03129333	,04385198	,759	-,0818593	,1444460
m_angle	0	1	-,280714095	1,188724661	,970	-3,34801706	2,78658886
		2	1,453731905	1,188724661	,457	-1,61357106	4,52103486
	1	0	,280714095	1,188724661	,970	-2,78658886	3,34801706
		2	1,734446000	1,233597880	,361	-1,44864471	4,91753671
	2	0	-1,453731905	1,188724661	,457	-4,52103486	1,61357106
		1	-1,734446000	1,233597880	,361	-4,91753671	1,44864471
m_duration	0	1	-,0069292452	,0074441201	,629	-,026137538	,012279048
		2	-,0145252119	,0074441201	,157	-,033733505	,004683081
	1	0	,0069292452	,0074441201	,629	-,012279048	,026137538
		2	-,0075959667	,0077251285	,598	-,027529354	,012337421
	2	0	,0145252119	,0074441201	,157	-,004683081	,033733505
		1	,0075959667	,0077251285	,598	-,012337421	,027529354

Figure D.24: Tukey HSD test for multiple comparisons applied to normally distributed pronation-supination features.

Dependent Variable	(I) medicalLabel	(J) medicalLabel	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
m_amplitude	0	1	19,56579524	8,22606713	,073	-1,6601799	40,7917703
		2	7,55311524	8,22606713	,637	-13,6728599	28,7790903
	1	0	-19,56579524	8,22606713	,073	-40,7917703	1,6601799
		2	-12,01268000	8,53659330	,361	-34,0399154	10,0145554
	2	0	-7,55311524	8,22606713	,637	-28,7790903	13,6728599
		1	12,01268000	8,53659330	,361	-10,0145554	34,0399154
mean_angle	0	1	33,302857 [*]	12,344684	,040	1,44949	65,15623
		2	51,331357 [*]	12,344684	,002	19,47799	83,18473
	1	0	-33,302857 [*]	12,344684	,040	-65,15623	-1,44949
		2	18,028500	12,810684	,361	-15,02730	51,08430
	2	0	-51,331357 [*]	12,344684	,002	-83,18473	-19,47799
		1	-18,028500	12,810684	,361	-51,08430	15,02730
mean_duration	0	1	-,030714	,105981	,955	-,30418	,24275
		2	-,089381	,105981	,682	-,36285	,18408
	1	0	,030714	,105981	,955	-,24275	,30418
		2	-,058667	,109982	,856	-,34246	,22512
	2	0	,089381	,105981	,682	-,18408	,36285
		1	,058667	,109982	,856	-,22512	,34246

(Continuation of Figure D.24)

Dependent Variable	(I) medicalLabel	(J) medicalLabel	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
mean_amplitude	0	1	-.9,416714	58,091977	,986	-159,31324	140,47981
		2	-.2,329048	58,091977	,999	-152,22557	147,56747
	1	0	9,416714	58,091977	,986	-140,47981	159,31324
		2	7,087667	60,284893	,992	-148,46730	162,64264
	2	0	2,329048	58,091977	,999	-147,56747	152,22557
		1	-7,087667	60,284893	,992	-162,64264	148,46730
duration_consistency	0	1	,023219952	,023600382	,597	-,03767684	,08411675
		2	-,011845381	,023600382	,871	-,07274218	,04905141
	1	0	-,023219952	,023600382	,597	-,08411675	,03767684
		2	-,035065333	,024491274	,349	-,09826092	,02813026
	2	0	,011845381	,023600382	,871	-,04905141	,07274218
		1	,035065333	,024491274	,349	-,02813026	,09826092
amplitude_consistency	0	1	40,895429	34,654083	,481	-48,52357	130,31443
		2	41,734595	34,654083	,468	-47,68441	131,15360
	1	0	-40,895429	34,654083	,481	-130,31443	48,52357
		2	,839167	35,962241	1,000	-91,95532	93,63365
	2	0	-41,734595	34,654083	,468	-131,15360	47,68441
		1	-,839167	35,962241	1,000	-93,63365	91,95532

*. The mean difference is significant at the 0.05 level.

(Continuation of Figure D.24)

Test Statistics^{a,b}

	immobilized	total_power	angle_consistency
Kruskal-Wallis H	2,577	7,814	,408
df	2	2	2
Asymp. Sig.	,276	,020	,816

a. Kruskal Wallis Test

b. Grouping Variable: medicalLabel

Figure D.25: Kruskal-Wallis test applied to non-normally distributed pronation-supination features.

Report

total_power		
medicalLabel	N	Median
0	7	3.08460E+5
1	6	1.80235E+5
2	6	1.18955E+5
Total	19	2.00800E+5

Figure D.26: Group size and median of total power feature of pronation-supination.

Ranks					Test Statistics ^a	
					total_power	
	medicalLabel	N	Mean Rank	Sum of Ranks	Mann-Whitney U	9,000
total_power	0	7	8,71	61,00	Wilcoxon W	30,000
	1	6	5,00	30,00	Z	-1,714
	Total	13			Asymp. Sig. (2-tailed)	,086
					Exact Sig. [2*(1-tailed Sig.)]	,101 ^b
					a. Grouping Variable: medicalLabel	
					b. Not corrected for ties.	

Figure D.27: Mann-Whitney U test applied to compare classes 0 and 1 in non-normally distributed pronation-supination features.

Ranks					Test Statistics ^a	
					total_power	
	medicalLabel	N	Mean Rank	Sum of Ranks	Mann-Whitney U	12,000
total_power	1	6	7,50	45,00	Wilcoxon W	33,000
	2	6	5,50	33,00	Z	-,961
	Total	12			Asymp. Sig. (2-tailed)	,337
					Exact Sig. [2*(1-tailed Sig.)]	,394 ^b
					a. Grouping Variable: medicalLabel	
					b. Not corrected for ties.	

Figure D.28: Mann-Whitney U test applied to compare classes 1 and 2 in non-normally distributed pronation-supination features.

Ranks					Test Statistics ^a	
	medicalLabel	N	Mean Rank	Sum of Ranks	total_power	
total_power	0	7	9,71	68,00	Mann-Whitney U	2,000
	2	6	3,83	23,00	Wilcoxon W	23,000
	Total	13			Z	-2,714
					Asymp. Sig. (2-tailed)	,007
					Exact Sig. [2*(1-tailed Sig.)]	,005 ^b

a. Grouping Variable: medicalLabel
b. Not corrected for ties.

Figure D.29: Mann-Whitney U test applied to compare classes 0 and 2 in non-normally distributed pronation-supination features.

D.6 Rest tremor

Tests of Normality						
	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
acc_ApEn	,343	16	<,001	,602	16	<,001
wx_ApEn	,157	16	,200 [*]	,925	16	,206
wy_ApEn	,155	16	,200 [*]	,944	16	,396
acc_std	,418	16	<,001	,416	16	<,001
wx_std	,359	16	<,001	,629	16	<,001
wy_std	,408	16	<,001	,370	16	<,001
acc_RMS	,205	16	,071	,809	16	,004
wx_RMS	,359	16	<,001	,630	16	<,001
wy_RMS	,411	16	<,001	,370	16	<,001
wx_frequency	,372	16	<,001	,517	16	<,001
wy_frequency	,502	16	<,001	,291	16	<,001

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Figure D.30: Kolmogorov-Smirnov and Shapiro-Wilk normality tests applied to rest tremor features.

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
wx_ApEn	Equal variances assumed	2,196	,160	,162	14	,874	,02491255	,15419814	-,30580957	,35563466
	Equal variances not assumed			,200	13,132	,844	,02491255	,12448911	-,24375435	,29357944
wy_ApEn	Equal variances assumed	,560	,467	-,204	14	,841	-,02854836	,13962374	-,32801151	,27091479
	Equal variances not assumed			-,218	9,158	,832	-,02854836	,13093704	-,32397123	,26687450

Figure D.31: Independent-samples t-test applied to normally distributed rest tremor features.

Test Statistics ^{a,b}									
	acc_ApEn	acc_std	wx_std	wy_std	acc_RMS	wx_RMS	wy_RMS	wx_frequency	wy_frequency
Kruskal-Wallis H	3,546	,080	1,697	,927	3,083	1,415	1,158	2,698	2,005
df	1	1	1	1	1	1	1	1	1
Asymp. Sig.	,060	,777	,193	,336	,079	,234	,282	,100	,157

a. Kruskal Wallis Test

b. Grouping Variable: medicalLabel

Figure D.32: Kruskal-Wallis test applied to non-normally distributed rest tremor features.

D.7 Postural tremor

Tests of Normality						
	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
acc_ApEn	,206	14	,111	,920	14	,222
wx_ApEn	,204	14	,120	,930	14	,301
wy_ApEn	,141	14	,200 [*]	,919	14	,216
acc_std	,357	14	<,001	,490	14	<,001
wx_std	,228	14	,047	,764	14	,002
wy_std	,318	14	<,001	,516	14	<,001
acc_RMS	,141	14	,200 [*]	,961	14	,734
wx_RMS	,232	14	,040	,765	14	,002
wy_RMS	,315	14	<,001	,518	14	<,001
wx_frequency	,424	14	<,001	,614	14	<,001
wy_frequency	,422	14	<,001	,365	14	<,001

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Figure D.33: Kolmogorov-Smirnov and Shapiro-Wilk normality tests applied to postural tremor features.

Independent Samples Test									
		Levene's Test for Equality of Variances		t-test for Equality of Means					
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower Upper
acc_ApEn	Equal variances assumed	5,664	,035	-2,180	12	,050	-,21093542	,09673986	-,42171347 -,00015736
	Equal variances not assumed			-1,974	6,683	,091	-,21093542	,10683630	-,46600987 ,04413904
wx_ApEn	Equal variances assumed	1,048	,326	2,074	12	,060	,12542458	,06046842	-,00632479 ,25717395
	Equal variances not assumed			1,981	8,865	,079	,12542458	,06330087	-,01810614 ,26895531
wy_ApEn	Equal variances assumed	2,298	,155	,488	12	,634	,03439542	,07050401	-,11921962 ,18801046
	Equal variances not assumed			,548	9,353	,596	,03439542	,06272191	-,10667912 ,17546995
acc_RMS	Equal variances assumed	,318	,583	,671	12	,515	,00098292	,00146567	-,00221051 ,00417635
	Equal variances not assumed			,702	11,999	,496	,00098292	,00140099	-,00206962 ,00403546

Figure D.34: Independent-samples t-test applied to normally distributed postural tremor features.

Test Statistics ^{a,b}							
	acc_std	wx_std	wy_std	wx_RMS	wy_RMS	wx_frequency	wy_frequency
Kruskal-Wallis H	,817	6,017	3,750	6,017	3,750	6,667	6,667
df	1	1	1	1	1	1	1
Asymp. Sig.	,366	,014	,053	,014	,053	,010	,010

a. Kruskal Wallis Test

b. Grouping Variable: medicalLabel

Figure D.35: Kruskal-Wallis test applied to non-normally distributed postural tremor features.

Report				
medicalLabel		wx_std	wx_RMS	wx_frequency
0	N	8	8	8
	Median	1,422050	1,482700	7,813850
1	N	6	6	6
	Median	4,762450	4,786400	198,583500
Total	N	14	14	14
	Median	1,970750	1,972100	23,479000

Figure D.36: Group size and median of W_x std, W_x RMS and W_x frequency features of postural tremor.

D.8 Kinetic tremor

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
acc_ApEn	,119	19	,200 [*]	,972	19	,810
wx_ApEn	,131	19	,200 [*]	,964	19	,645
wy_ApEn	,109	19	,200 [*]	,977	19	,895
acc_std	,212	19	,025	,819	19	,002
wx_std	,284	19	<,001	,743	19	<,001
wy_std	,265	19	,001	,782	19	<,001
acc_RMS	,309	19	<,001	,662	19	<,001
wx_RMS	,275	19	<,001	,744	19	<,001
wy_RMS	,274	19	<,001	,793	19	<,001
wx_frequency	,206	19	,034	,801	19	,001
wy_frequency	,265	19	,001	,773	19	<,001

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Figure D.37: Kolmogorov-Smirnov and Shapiro-Wilk normality tests applied to kinetic tremor features.

Independent Samples Test										
		Levene's Test for Equality of Variances							t-test for Equality of Means	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
acc_ApEn	Equal variances assumed	,077	,784	-2,582	17	,019	-,15653731	,06061816	-,28443045	-,02864417
	Equal variances not assumed			-2,315	7,733	,050	-,15653731	,06761297	-,31339342	,00031881
wx_ApEn	Equal variances assumed	,330	,573	-,921	17	,370	-,07061013	,07665149	-,23233063	,09111038
	Equal variances not assumed			-,848	8,163	,420	-,07061013	,08321920	-,26184799	,12062774
wy_ApEn	Equal variances assumed	2,267	,151	-1,671	17	,113	-,13160833	,07876757	-,29779338	,03457671
	Equal variances not assumed			-1,508	7,838	,171	-,13160833	,08725913	-,33355612	,07033946

Figure D.38: Independent-samples t-test applied to normally distributed kinetic tremor features.

Test Statistics ^{a,b}								
	acc_std	wx_std	wy_std	acc_RMS	wx_RMS	wy_RMS	wx_frequency	wy_frequency
Kruskal-Wallis H	,623	,031	,008	4,431	,031	,000	,769	2,492
df	1	1	1	1	1	1	1	1
Asymp. Sig.	,430	,861	,930	,035	,861	1,000	,380	,114

a. Kruskal Wallis Test

b. Grouping Variable: medicalLabel

Figure D.39: Kruskal-Wallis test applied to non-normally distributed kinetic tremor features.

Report		
acc_RMS		
medicalLabel	N	Median
0	13	,7940500
1	6	,7517700
Total	19	,7660900

Figure D.40: Group size and median of Acc RMS feature of kinetic tremor.

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