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Ambulatory gait analysis for the assessment of Parkinson's disease

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Summary

Parkinson's disease (PD) is the second most common neurodegenerative disease affecting dopaminergic neurons in the substantia nigra, a region of the brain. Patients with Parkinson's disease (PwPD) suffer from non-motor problems such as neuropsychology, perceptual, and sleep difficulties, in addition to some common motor disorders like bradykinesia, tremor, stiffness, and postural instability. PD results in impairments in the subject's gait, such as asymmetrically reduced arm swing, increased stance time, increased stride-to-stride variability, reduced swing time, and reduced step length and gait speed. A variety of technologies, based either on wearable or non-wearable sensors can be employed to measure gait parameters. Inertial measurement units (IMU) are wearable devices that are widely used for human gait analysis because of their small size and portability, so they do not require a specific laboratory environment. Most literature studies have compared gait temporal parameters (TP) of healthy subjects and PwPD. However, few studies have compared the gait parameters of PwPD in different gait tasks. The objective of this thesis is to assess the TP of PwPD completing four motor tasks and examine any statistical variations in parameter estimation caused by different sensor placements. Thirteen PwPD in the OFF state (i.e. not under dopaminergic therapy), were recruited from the Regional reference center for PD and movement disorders, Molinette Hospital, Turin, Italy. In this study, three inertial sensor units (MPU9250), one on each ankle and one on the trunk, were used for data collection. Four motor tasks were performed by each patient, including the Time Up and Go test, a simple walk back and forth task, and two additional tasks including an obstacle and a cognitive task. Gait events (i.e. Heel strike and Toe off) were identified, and the following temporal characteristics were computed: stride time, step time, stance time, swing time, single support time, and double support time. TP, collected by IMUs on the ankles and the trunk, were compared using the Mann-Whitney U-test. For each motor task under investigation, it is noticed that for almost all patients examined, stride and step time did not reveal any significant variations ($p > 0.05$) between the sensors on the ankles and the trunk. This suggests that gross temporal gait parameters such as step and stride time can be determined by using a single IMU on the trunk. Instead, for each motor activity under consideration, finer TP such as stance time, swing time, and single and double support time consistently differ ($p < 0.05$) between the IMUs at the ankles and that at the trunk. Furthermore, it is discovered that while the TP do not appear to change between some tasks, they significantly differ in the presence of a motor-cognitive dual task. The results of this work confirm the hypothesis

that when a motor activity becomes more complex, PwPD tend to lengthen the time their feet are in contact with the ground (stance/double support phase). The outcomes of this thesis demonstrate how the use of a single sensor may be sufficient for monitoring some temporal characteristics (i.e. step and stride time) and their changes as the motor task's difficulty increases.

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Chapter 1

Parkinson's disease

Parkinson's disease (PD) was described for the first time as a neurological syndrome by James Parkinson, an English doctor, in his famous treatise "An Essay on the Shaking Palsy", published in 1817. PD is the second most common neurodegenerative disorder after Alzheimer's disease and it is a complex neurodegenerative disorder that presents different motor and non-motor features [20]. Bradykinesia, rest tremor, and rigidity are the main motor features that are mainly ascribed to the loss of dopaminergic neurons, furthermore also posture, balance, and gait contribute to impairment and disability in advanced PwPD. Non-motor features result from multiple neurotransmitter deficiencies in the central and peripheral nervous system and include psychiatric (depression, apathy, hallucinations, and delusions) and autonomic (constipation, orthostatic hypotension, and urinary and genital disturbances) features, cognitive impairment (involvement of executive functions, memory, and visuospatial functions up to dementia), sleep disorders, olfactory dysfunction, and pain that together contribute to worsening the quality of life of Parkinson's people [25]. To date, there is no cure for Parkinson's; only few treatments are available to control symptoms.

1.1 Pathogenesis

PD is a complex neurodegenerative disease involving an array of molecular pathways, all of which may be implicated in the neuropathophysiology of the disease. The progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which project to the striatum (the nigrostriatal pathway), results in the loss of dopaminergic function in individuals with PD. The substantia nigra, also known as Sommering's black substance, belongs to those anatomical structures that together constitute the basal ganglia. The term substantia nigra comes from the fact that this area is darker than the surrounding brain area and such coloration, in particular, is related to the presence in the cells of a pigment, called neuromelanin. Due to the slow and considerable death of dopaminergic neurons containing neuromelanin, less brownish discoloration has been observed in such areas of patients' brains as observed in Fig. 1.1. The basal ganglia, thalamus, and cerebral cortex all become severely dysfunctional as a result of the striatum's inability to release dopamine. Motor and non-motor disorders, including tremor, rigidity, bradykinesia, and loss of balance, depend on these alterations. It was long considered that 50–70% of SNpc dopaminergic neurons have died by the time clinical motor symptoms become evident. Apart from the SNpc, widespread cell loss can be found in several subcortical nuclei, including the locus coereleus, the nucleus basalis of Meynert, the dorsal motor nucleus of the vagus nerve, the pedunculopontine nucleus, the raphe nuclei, and also the hypothalamus and the olfactory bulb [23]. A hallmark of PD is the presence of Lewy bodies (LBs), named after the neurologist F.H. Lewy who identified them in 1912, which accumulate particularly in the substantia nigra. LBs are intracytoplasmic inclusions consisting of a granular and fibrillar core with a surrounding halo and their size can vary from 5 to 30 µm in diameter. The primary structural component of LBs is filamentous α-synuclein, a protein ubiquitously expressed in the brain. Lbs are also made of proteins responsible for proteolyses, such as ubiquitin, alpha-crystallin, and microtubule protein tau. In PD, α-synuclein has a β-sheet-rich amyloid-like structure and misfolded α-synuclein is found within LBs as 5–10 nm long filaments [23]. Unfolded monomers, soluble oligomers, protofibrils, and high molecular weight insoluble fibrils are the different species of α-synuclein in the PD brain. Oxidative stress and mitochondrial dysfunction are important features to describe PD pathogenesis. Oxidative stress represents one of the main pathogenetic mechanisms of neuronal death in PD: in fact, damage to SN neurons originates as a consequence of the overproduction of free radicals in the course of the oxidative metabolism of dopamine. The increased production of free radicals contributes to increased aggregation of synuclein and other misfolded proteins. Reduced ATP production and increased electron concentration result from mitochondrial dysfunction,

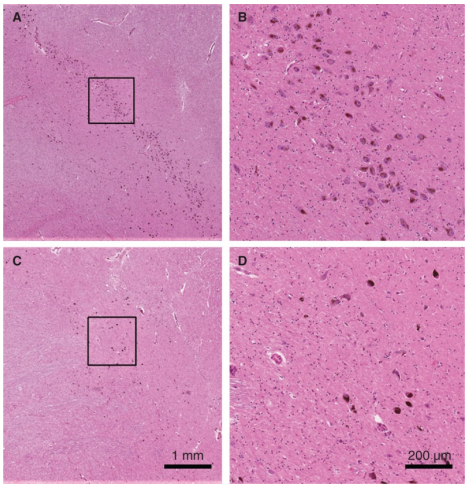

Figure 1.1. Coronal section at the level of the SNpc in a control (A and B) and a PD brain (C and D) stained by hematoxylin and eosin. In both sections, the dark brown cells are the dopaminergic (DA) neurons containing neuromelanin. Dopaminergic cell loss is evident in the SNpc of the PD brain. The squared areas in A and C are magnified in B and D, respectively, to show a closer view of the darkly pigmented DA neurons [23].

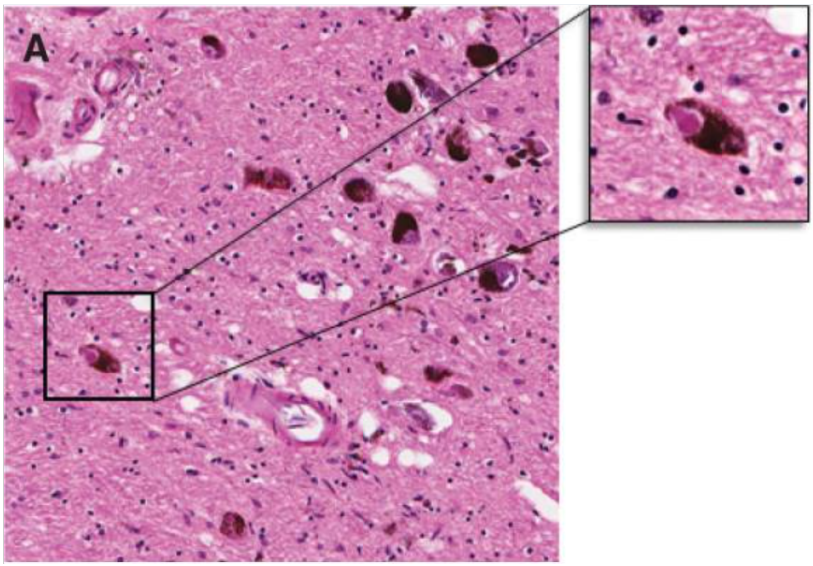

Figure 1.2. Typical brainstem Lewy body inside a neuromelanin-containing DA neuron in routine hematoxylin and eosin histological staining [23].

which increases oxidative stress resulting in the degeneration of dopaminergic neurons [14]. Neuroinflammation is another factor in the pathogenesis of Parkinson's.

It is a brain inflammation or rather an inflammatory reaction mediated by the brain's immune cells (microglia) with production of inflammatory cytokines such as TNF-α, Interleukin-6 and Iinterleukin-1 and promoting α-synuclein misfolding.

1.2 Epidemiology and Risk Factors

PD is the second most common neurodegenerative disease (after Alzheimer's disease) , with median age-standardised annual incidence rates in high-income countries of 14 per 100 000 people in the total population, and 160 per 100 000 people aged 65 years or older [18]. Globally, disability and death due to PD are increasing faster than for any other neurological disorder. The prevalence of PD has doubled in the past 25 years. Global estimates in 2019 showed over 8.5 million individuals with PD. Current estimates suggest that, in 2019, PD resulted in 5.8 million disability-adjusted life years, an increase of 81% since 2000, and caused 329 000 deaths, an increase of over 100% since 2000. In Italy, according to the latest data from the Ministry of Health, there are about 230,000 people affected by PD, of whom about 5 percent are under the age of 50, while 70 percent are over the age of 65. Due to the increasing aging of the general population, the number of cases is expected to double by 2030. Although the etiology of PD has

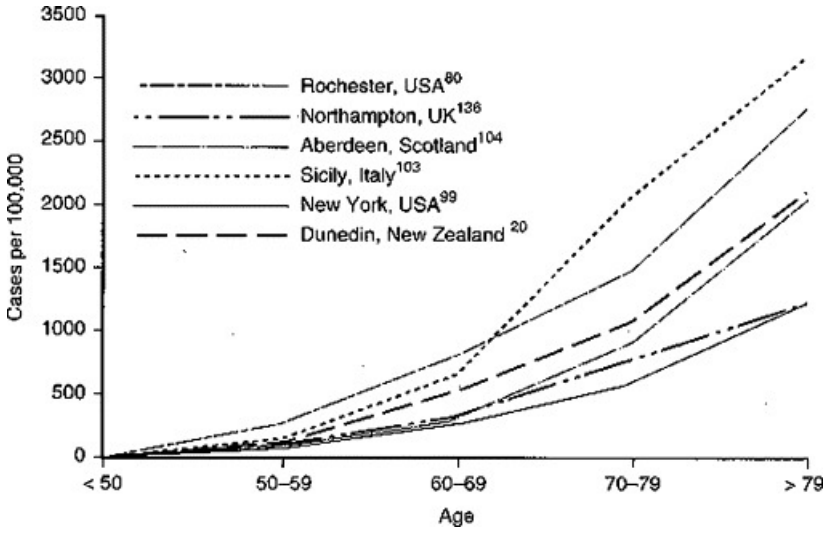

Figure 1.3. PD age-specific prevalence [37].

not yet been fully clarified, several studies have shown that numerous factors can increase the risk of developing the disease, or even seem to decrease it. Regarding genetic factors, in about 95% of cases there is no correlation with them, and PD is defined as 'idiopathic' or 'sporadic'. The remaining 5% is attributed to inherited

genetic mutations and PD is called 'familial'. The genes that have been found to potentially cause PD are assigned a "PARK" name in the order they are identified. To date, 23 PARK genes have been linked to PD. Mutations in the PARK genes demonstrate either autosomal dominant (e.g., SCNA, LRRK2, and VPS32) or autosomal recessive inheritance (e.g., PRKN, PINK1, and DJ-1) [34]. Several risks factors has been proposed through the years [4] :

- Environmental exposure (industrial chemicals and pesticides)
- Traumatic brain injury
- Blood cholesterol and hypertension
- Average age of onset of PD approximately 50 to 60 years
- Gender:there is a ratio male-to-female of about 3:2
- Dairy products
- Melanoma

Although there are also factors related to a decreased risk, as instance:

- Tobacco smoking
- Coffee drinking
- Calcium channel blocker use
- Physical activity
- Urate

1.3 Diagnosis

The diagnosis of PD remains predominantly clinical and is based on the presence of the characteristic triad extrapyramidal rigidity, tremor and bradykinesia. Furthermore, diagnosis is supported by a good response to dopaminergic therapy and asymmetric limb involvement at onset [22]. Dopamine transporter single-photon emission computed tomography (DaT SPECT) identifies the presynaptic dopamine neuronal dysfunction present in PD and other neurodegenerative parkinsonisms by demonstrating reduced uptake of a radioactive tracer that binds to dopamine transporters in the basal ganglia. DaT scans are generally useful only when the presence of parkinsonism is uncertain on examination. If a patient has unequivocal parkinsonism, the scans are typically positive and add little to the diagnostic assessment.

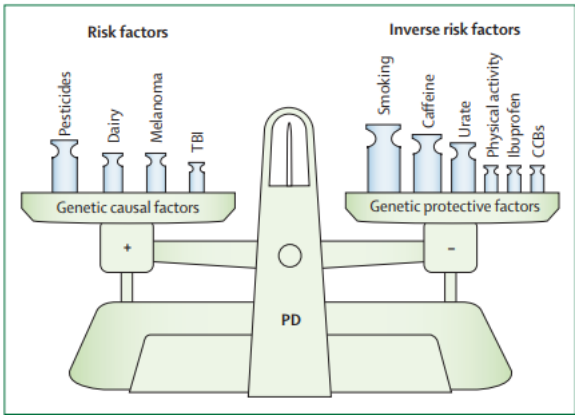

Figure 1.4. The balance of genetic and environmental factors that underlie Parkinson's disease occurrence [4].

They cannot differentiate between PD and other parkinsonisms (eg, multiple system atrophy, progressive supranuclear palsy). It is also possible to measure the lack of dopamine synthesis and storage in pre-synaptic striatal nerve terminals using functional brain imaging with positron emission tomography (PET) and the radiotracer 18-fluorodop (FDOPA). Therefore, FDOPA-PET allows the diagnosis of PD in early disease stages and the differentiation of clinically unclear cases from other movement disorders, e.g. essential tremor. Additionally, FDOPA-PET imaging permits the follow-up of disease progression, the assessment of medical and surgical PD therapy strategies with possible neuroprotective properties and the detection of pre-clinical disease in subjects at risk for the disorder [3]. Biochemical, clinical, pathological, imaging, and genetic biomarkers are among the numerous ones that have been discovered for examination. As observed in Fig. 1.5 different biomarkers can be identified to diagnose PD.

1.4 Clinical features

The typical motor disorders of PwPD include bradykinesia, tremor, stiffness, and postural instability, in addition to non-motor disorders such neuropsychology, perceptual disorder, and sleep problem.

1.4.1 Motor features

The main motor symptoms are:

- Tremor: it is a rhythmic, involuntary, oscillatory movement of a body part. It is distinguished basically into resting or action forms. The patient with PD

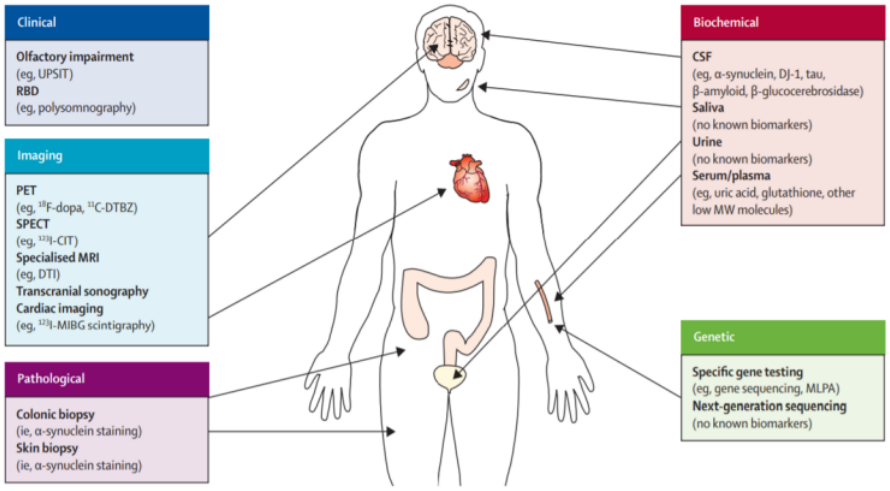

Figure 1.5. Biomarkers useful for PD diagnosis [22].

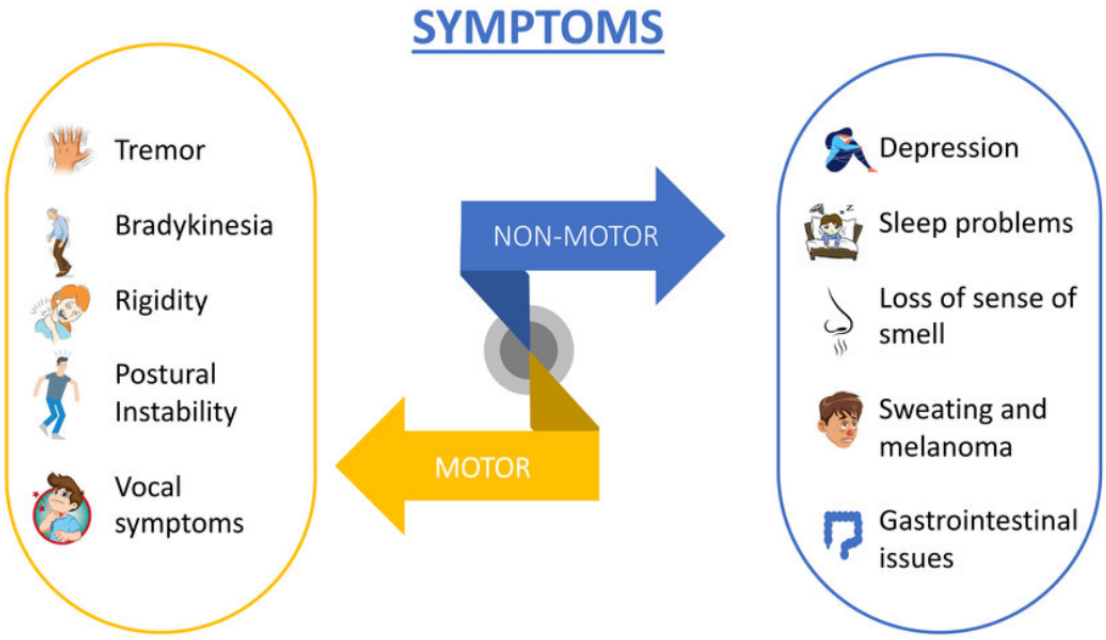

Figure 1.6. Motor and Non-motor symptoms in PD [35].

typically presents with a resting tremor with a frequency of 3-6 Hz (69-100% of cases). In 65% of cases it constitutes the first symptom of the disease, preceding even by years the manifestation of the other cardinal symptoms. Primarily localized to the extremities of the upper limbs , it can also affect the lower limbs, neck, lips, face and tongue. It manifests at rest and stops with movement. Its duration is intermittent and irregular; it disappears during sleep and gets worse under stressful or anxious circumstances. In the advanced stages of the disease it may reduce until it disappears.

- Rigidity: it is an involuntary increase in muscle tone. Stiffness can be the first symptom of PD; it often begins on one side of the body, but many patients do not feel it. It can occur in the limbs, neck, and trunk. Reduced pendular oscillation of the upper limbs during walking is a sign of rigidity, associated with slowness of movement [25].

- Bradykinesia: the term bradykinesia refers to slowness of movement, that is, an increase in the time taken to perform the movement. In the upper limbs, bradykinesia manifests early with a reduction in the patient's manual dexterity and gestures. Patients complain of difficulty performing simple tasks, completing small, precise movements, such as buttoning clothes, typing, tying shoelaces. In the lower limbs, bradykinesia appears with a slowing of gait and a reduction in stride width; steps become shorter and smaller. Progressive loss of spontaneous movements (commuting of limbs during walking) and gestures is also common, and body language that normally accompanies the emotional tone of verbal communication (amimia, facial expressionlessness) is reduced, and speech undergoes significant changes, such as hypophonia, stuttering with major difficulties in communication. Bradykinesia is the feature of PD that most appears to be correlated with a decrease in dopamine levels. This has been demonstrated through techniques of PET imaging that show that decreased fluorodopa uptake in the striatum is proportional to the degree of bradykinesia [1].

- Postural instability (impaired balance and coordination): a person with postural instability may assume a hunched posture, with the head bowed and shoulders slumped. The trunk may bend forward or backward, and the person may suffer falls that result in injury. In some cases normal walking can be interrupted by events such as festination, in which the patient undergoes acceleration of walking by performing a rapid succession of small steps, or by freezing of gait (FOG), during which the which the patient undergoes motor freezing, especially in the presence of obstacles or directional changes.

1.4.2 Non motor features

The main non motor symptoms are:

- Depression: the association between depression and PD is very common, in at least 40% of cases there is a depressive episode. Characteristic is the observation of their grouping into two stages distinct stages of the disease: early and late. Neurobiological and pharmacological evidence suggest that depression may be an integral part of the Parkinsonian syndrome, linked to a dysfunction of mesocortical and prefrontal dopaminergic projections underlying the neuropsychological processes of motivation and gratification.

- Sleep disorders: are frequent and can involve up to 70% of patients. They occur both at the onset of disease and during its course. Manifestations are multiple, determined by the underlying pathology and the medications used. Sleep disorders include: insomnia, excessive daytime sleepiness and behavioral disturbance in the sleep (REM) phase.

- Olfactory disorders: many patients report disturbances of the sense of smell (the ability to sense odors), which begin even many years before the first motor manifestations. Olfactory dysfunction persists over time and does not seem to change with drug therapy.

- Cognitive and neurobehavioral problems: some PwPD experience cognitive decline as the disease progresses. It is estimated that individuals diagnosed with PD have a 6-fold higher risk higher than healthy individuals of developing dementia [12]. The patient's quality of life can be significantly impacted by cognitive deficiencies in a variety of areas, including memory, language, and attention.

1.5 Parkinson's disease evaluation

During the neurological examination to evaluate PD, the physician makes a record of the clinical signs found. They may be given a numerical score through the use of a rating scale. The most commonly used rating scales for PD motor symptoms are Hoehn and Yahr (HY) and Unified Parkinson's Disease Rating Scale (UPDRS). One of the most widely used scales to assess PD is the UPDRS (Unified PD Rating Scale) which was first proposed in 1980 and has become the most widely used method for assessing the status of PwPD. In 2001 it was revised by the Movement Disorder Society (MDS), it is made up of four sections: Section I (Non-motor experiences of daily living), Section II (Motor experiences of daily living), Section III (Motor examination), Section IV (Motor complications) [15]. Section I is itself

divided into two sections, the first of which involves an assessment, carried out by the physician, related to behavioral aspects, based on information obtained from the patient and caregiver, while the second is completed by the patient, without the intervention of the physician. The aspects that are investigated in this first part are cognitive and behavioral. Part II is presented in the form of a self-administered questionnaire, and allows assessment of motor aspects such as speaking, dressing, and other normal gestures of daily life. In addition, this section assesses walking and the presence of freezing of the gait. Part III is based on a motor examination, which involves instructions that the physician can provide to the patient, and a questionnaire, which will be completed by the physician. At this stage, the physician should indicate whether the patient is on levodopa therapy and the time since the last administration. In the case the patient is on therapy, it is necessary to indicate whether at the time of the visit, he is in the ON phase, that is, under the effect of medication, or in the OFF phase, typical of patients with poor response to therapy medication. The examination involves the physician's observation of motor symptoms, for example:

- Limb stiffness
- Facial expressions
- Posture
- Bradykinesia
- Tremor at rest

Simple motor tests are also performed, which include:

- Hand and finger movements
- Leg agility
- Getting up from a chair
- Walking, with possible assessment of the presence of gait freezing
- Retropulsion testing to assess postural stability

Part IV involves the evaluation of two motor complications: dyskinesias, random movements involuntary, and motor fluctuations, or variability in response to medication. In this phase, the information is collected by a questionnaire submitted by the physician to the patient. Each of the tasks in the four parts of the assessment is assigned a score, with a numerical value ranging from 0 to 4, where 0 means that the symptom is not present and 4 means that the symptom is severe. The Hoehn

and Yahr scale is commonly used to describe the symptoms of PD progression. It was originally published in 1967 in the journal Neurology by Melvin Yahr and Margaret Hoehn and included stages 1 to 5. Since then, a modified scale has been proposed, with the addition of stages 1.5 and 2.5, which describe the intermediate course of the disease. The main advantage of the HY scale is its ease of use, but it is a classification scale and not a rank order [2].

Stage	Modified Hoehn and Yahr Scale
1	Unilateral involvement only
1.5	Unilateral and axial involvement
2	Bilateral involvement without impairment of balance
2.5	Mild bilateral disease with recovery on pull test
3	Mild to moderate bilateral disease;some postural instability;physically independent
4	Severe disability, still able to walk or stand unassisted
5	Wheelchair bound or bedridden unless aided

Table 1.1. Modified Hoehn and Yahr scale.

1.6 Treatments

The primary goal of therapy for PwPD is to alleviate their symptoms in order to maintain the highest quality of life possible. There is currently no known cure for the PD. [21]. There are 3 main therapies:

- Pharmacological treatment: most people with PD need a medication called levodopa. It is absorbed by the nerve cells in your brain and turned into the chemical dopamine, which is used to transmit messages between the parts of the brain and nerves that control movement. Other medications can be used in combination with levodopa: carbidopa that prevents formation in the peripheral tissues and catechol-O-methyltransferase inhibitor to extend its plasma half-life and to prolong the duration of action of each dose. A serious problem with this type of therapy is that when it is administered long term, it causes side effects that aggravate symptoms already present due to the disease, leading, for example, to the appearance or aggravation of dyskinesias, caused by the intermittent stimulation of dopamine receptors. Pharmacological studies highlight how such side effects depend on both the dose of levodopa administered and by the patient's level of neuronal loss at the time of treatment initiation [33]. The so-called "wearing off" effect is another important problem with the treatment. Levodopa's effect can, in fact, gradually lose effectiveness over time, necessitating a rise in dose, which leads to an increase

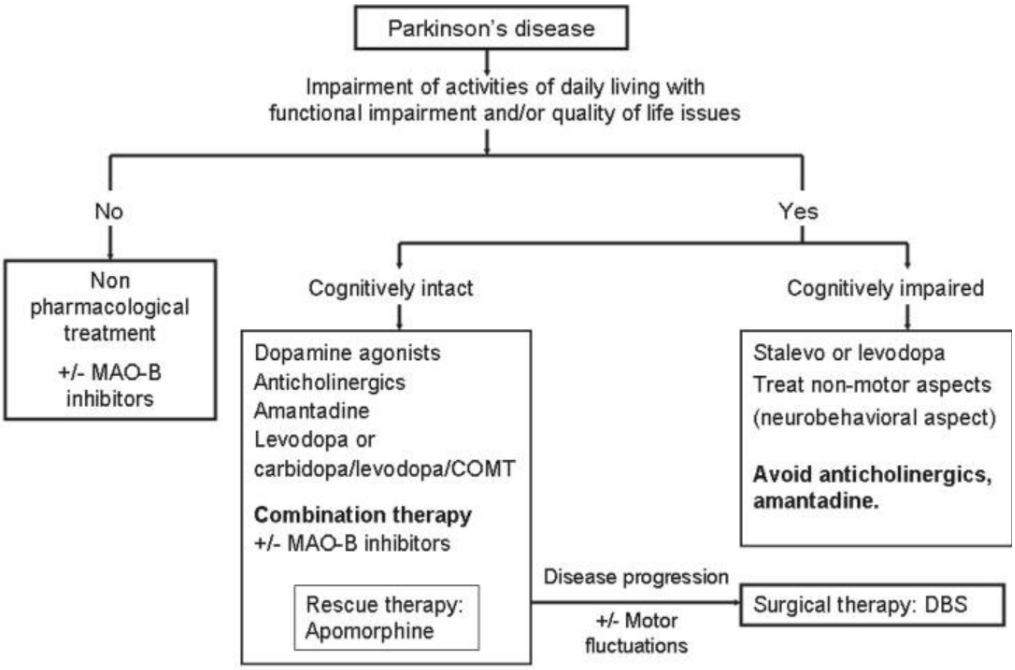

Figure 1.7. Treatment guidelines for the progressive stages of PD.

in the motor difficulties caused by the drugs. An innovative and cost-effective approach to maintain constant plasma levodopa concentrations is the administration of a levodopa-carbidopa concentrate into the duodenum (known as Duodopa) through a percutaneous endogastric tube connected to a portable infusion pump. This adjusts the drug dose through this pump according to the patient's condition. This method makes it possible to reduce the dyskinesias typical of the advanced stages of PD [16]. Another therapeutic method used consists of the administration of dopamine agonist drugs. They are molecules that can mimic the action of dopamine (an endogenous neurotransmitter) by binding to its receptors and activating them. The advantage of this therapy is to achieve good improvement in the symptomatic aspect of the condition, and secondly to delay the introduction of levodopa, and consequently the motor effects caused by the same. Dopamine agonist drugs are more likely to cause hallucinations, confusion and psychosis, and provide less symptomatic benefit [30]. PwPD also use dopamine releaser, like amantadine, that relieves symtoms (also dyskinesia) but produces mental effects, and monoamine oxidase type B (MAO-B) inhibitors. Three monoamine oxidase type B (MAO-B) inhibitors are used in the treatment of PD (PD): selegiline, rasagiline, and

safinamide. All three drugs are effective in reducing motor fluctuations in patients undergoing prolonged treatment with levodopa (L-DOPA) due to their inhibitory activity on dopaminergic metabolism. Whatever drug is used, the patient receives the therapy in small doses at first to evaluate its effectiveness and any adverse effects, and then the doses are gradually increased until the patient receives the complete regimen.

- Surgical treatment: this surgical therapy is offered to patients in advanced stages of the disease with significant dyskinesias and motor blocks that can no longer be controlled by drug therapy. Deep brain stimulation (DBS) is the surgical therapy most used for PD. DBS involves the insertion of an electrode into a specific area of the brain, connected to a neurostimulator (a kind of pacemaker) placed in the upper chest area or abdomen. The pacemaker will send electrical impulses to the brain, aimed at reducing the symptoms of the specific condition. Commonly, the area stimulated to reduce bradykinesias, tremor and stiffness is the nucleosubthalamic. Subjects who can undergo this therapy make up about 10% of the population with PD. They are relatively young and healthy subjects (age limit of 70 years), with severe side effects given by the drug therapy used to control the disease. Intact cognitive, mental function and normal neuroradiological imaging are required [17]. Side effects that the patient may experience following stimulation are:
  - apathy
  - hallucinations
  - compulsive gambling
  - hypersexuality
  - cognitive dysfunction and depression
  - dysarthria
  - paresthesias

  Treatment can be reversible: in fact, DBS can be turned off at any time. The majority of patients do not feel stimulation; in a few rare instances, however, a tingling sensation or paresthesias may be felt as soon as the device is turned on. It is also appropriate to inform the patient that this intervention technique does not cure the neurological condition but does allow for symptom reduction.
- Complementary and supportive therapies, such as diet, exercise, physical therapy, occupational therapy, and speech therapy

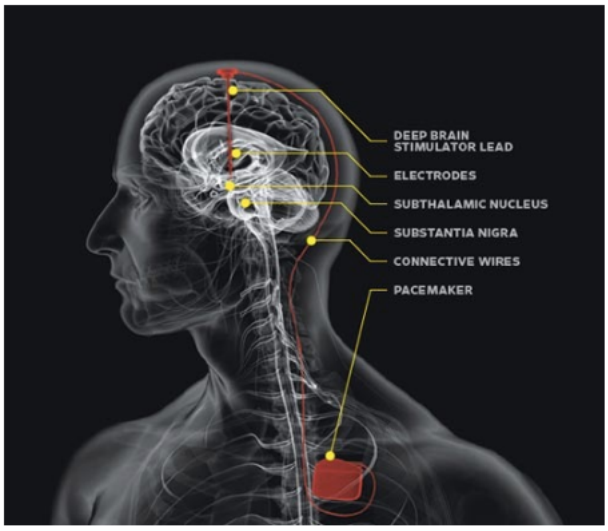

Figure 1.8. DBS for PD.

Chapter 2

Gait analysis

2.1 Gait cycle

Gait is given by a cyclic succession of alternating rhythmic movements in what is called the gait cycle. The "gait cycle" can be considered the unit of measurement of the gait. The pattern of movement recognized as human walking is the result of the interaction between three systems: the central nervous, the peripheral nervous, and the musculoskeletal effector. The gait cycle is measured from the moment the heel of the observed leg makes contact with the ground (initial contact or heel strike) until the next contact of the same heel. The gait cycle is divided into two periods:

- stance phase: represents the interval during which the foot remains in contact with the ground. It begins with the heel strike (HS), ends with the toe off (TO), and represents about 60% of the entire gait cycle.
- swing phase: represents the interval during which the foot is not in contact with the ground. It begins from the toe off, ends when the foot rests on the ground, and lasts about 40% of the cycle.

Actually, each of these two phases is in turn divided into other sub-phases whose combination fulfills three basic tasks: cushioning the impact of the heel on the ground; ensure limb stability; enabling the coordinated progression in the regular rhythm of the steps. The stance phase consists of :

- Initial contact, from 0 to 2% of the gait cycle, consists of the initial contact of the foot with the ground that occurs with the heel (heel strike)
- Loading response, from 2% to 10% of the gait cycle, is the phase in which the body rests on both lower limbs (double limb stance) and ends at the moment when the contralateral limb comes off the ground

- Mid-stance, from 10% to 30% of the gait cycle, starts with the toe off of the contralateral leg and it ends when the weight is supported by the metatarsal heads and toes of the foot of interest.
- Terminal stance, from 30% to 50% of the gait cycle, ends when the contralateral limb touches the ground
- Pre-swing, from 50% to 60% of the gait cycle, corresponds again to the double stance phase and ends with the detachment of the toes from the ground.

The swing phase consists of:

- Initial Swing, from 60% to 73% of the gait cycle, the leg, lifted off the ground, begins to move forward
- Mid-swing, from 73% to 87% of the gait cycle, this is the phase in which the observed limb moves from a posterior position to an anterior position relative to the trunk
- Terminal swing, from 87% to 100% of the gait cycle, this is the phase that marks the end of the gait cycle and corresponds to the moment when the heel rests back on the ground.

2.2 Gait parameters

There are many spatial and temporal parameters that can be used to quantitatively analyze the gait cycle of a human subject. Spatio-temporal parameters allow for reflecting changes in the movement. Thus, they can help clinicians in deciding about the progress of the rehabilitation process and choose the best rehabilitation protocol [8]. In order to compute the spatio-temporal parameters, it is necessary to identify the gait events (GEs), defined on the basis of the contact of the feet with the ground during the stance phase, as showed in Fig. 2.2 [26]. The identified GEs are:

- Heel strike: it is the impact of the heel on the ground
- Toe strike: it is the impact of the toe on the ground
- Heel off: it is the detachment of the heel from the ground
- Toe off: it is the detachment of the toe from the ground

The space-temporal parameters extracted are:

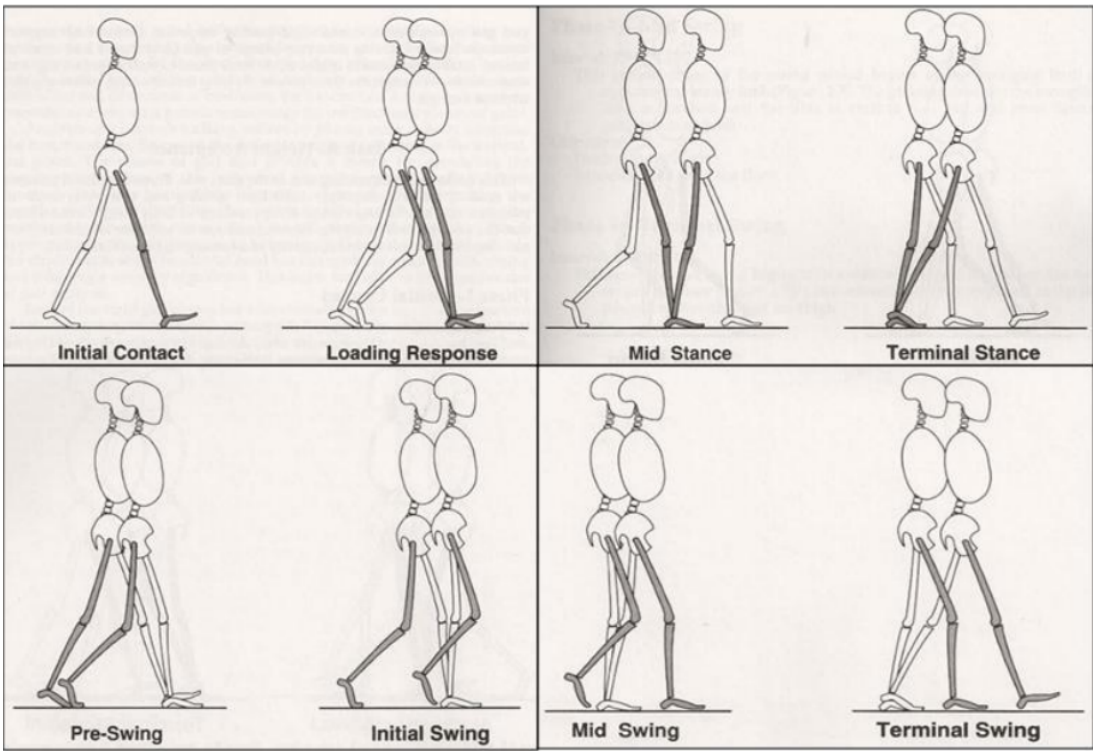

Figure 2.1. Phases of gait [29].

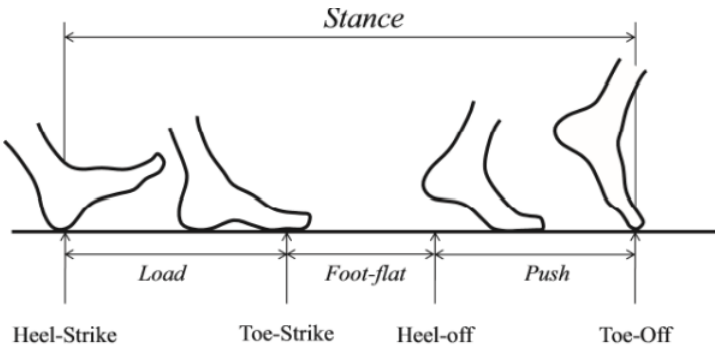

Figure 2.2. GEs during stance phase [26].

- Stance time: it starts from heel contact and ends with the release of the toes of the same foot. Thus, it is the elapsed time between the first and last contact of two consecutive supports on the same foot

- Swing time: it begins when the toe of the foot leaves the ground and ends

with heel contact. Thus, it is the elapsed time between the last contact of the foot stance and the first contact of the next stance

- Step time: it is the elapsed time from the first contact of one foot to the first contact of the opposite foot
- Stride time: it is the time between two consecutive heel strikes of the same foot
- Single support time: it is the time when only one foot is in contact with the ground. In walking, this is equal to the swing phase of the other limb
- Double support time: the period during which both feet are in contact with the support surface during one gait cycle
- Limp index: it is the ratio of the stance times of the two feet
- Cadence: number of steps per minute
- Step Length: distance from the heel of one foot-strike to the heel of the opposite foot-strike
- Stride length: distance of two consecutive heel strike of the same foot.

The values of these parameters change when there are motor disorders resulting from various causes. A quantitative examination of the gait is specifically required in these situations in order to understand the true cause of such variations or to come up with a potential solution to the problem.

2.3 Technologies Used in gait analysis

Gait analysis can be useful in evaluating the progress of rehabilitation therapies and in the diagnosis of conditions that are not identified by other examinations. Therefore, gait analysis allows for the detection of:

- hip abnormalities (such as coxarthrosis)
- muscle contractures
- hallux rigidus
- ankle joint abnormalities
- knee problems
- neurological disorders

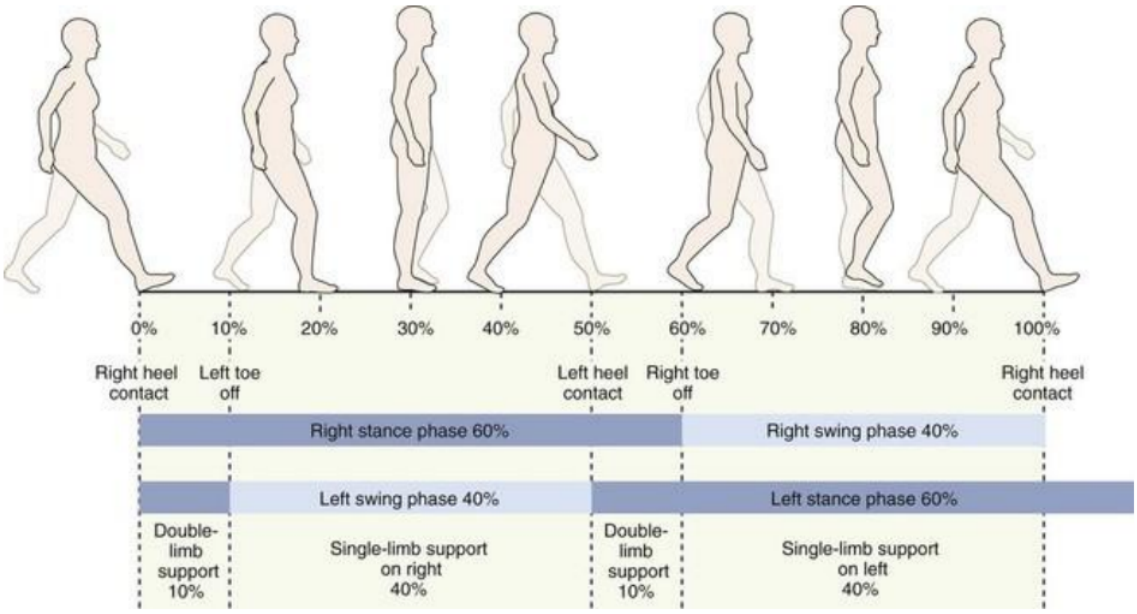

Figure 2.3. Phases of gait useful to detect the spatio-temporal parameters [10].

Various technologies can be used to quantify gait parameters and can be divided into technologies based on non-wearable sensors (NWS) or on wearable sensors (WS). NWS generally provide the most sensitive and accurate gait data, yet require dedicated laboratory environments and are expensive compared to wearable systems.

2.3.1 Non wearable technologies

Three main NWS are [35]:

- Optical motion capture systems are made up of a variable number of cameras (typically 2 to 6), whose video camera system is stimulated by an infrared light source to illuminate a set of markers, reflective material elements that are placed on the patient's body in accordance with established protocols at specific repair points. The reflection of the marker is captured by the cameras of the optoelectronic system that is responsible for calculating the three-dimensional (XYZ) coordinates of the markers themselves. Given the three-dimensional coordinates of the markers, it is possible to calculate the main kinematic variables kinematics such as the velocity and acceleration of the body segments and determine the trajectories of the main joint angles

rather than calculating gait parameters.Vicon, Qualisy, Motion Analysis or OptoTrack are the most common known optical motion systems and they are considered a gold standard for gait analysis. These systems have three disadvantages: they are very expensive, require for a specialized lab, and can only record a certain number of subsequent steps.

Figure 2.4. Motion Analysis Laboratory.

- force platforms consist of steel blocks equipped with straing gauge or piezo-electric transducers. Force platforms return the forces exchanged with the ground, in contrast to pressure platforms that measure pressure changes over time under one foot. They are generally expensive and require dedicated laboratory environments and skilled technical personnel to operate. However, they can be used in conjunction with motion capture and EMG systems to provide joint kinetics (moments, power, and forces applied by each joint when braking or propelling) [35].

- instrumented walkway mats are portable mats a few meters in length. They have sensors to identify foot contacts. The most used instrumented walkway mat is GAITRite and it is able to obtain spatio-temporal measures of gait (including walking speed; step and stride lengths; base of support; step, stride, swing, stance, single support, and double support times; and toe in/out angle) with high sensitivity for detecting pathology-related changes [40].

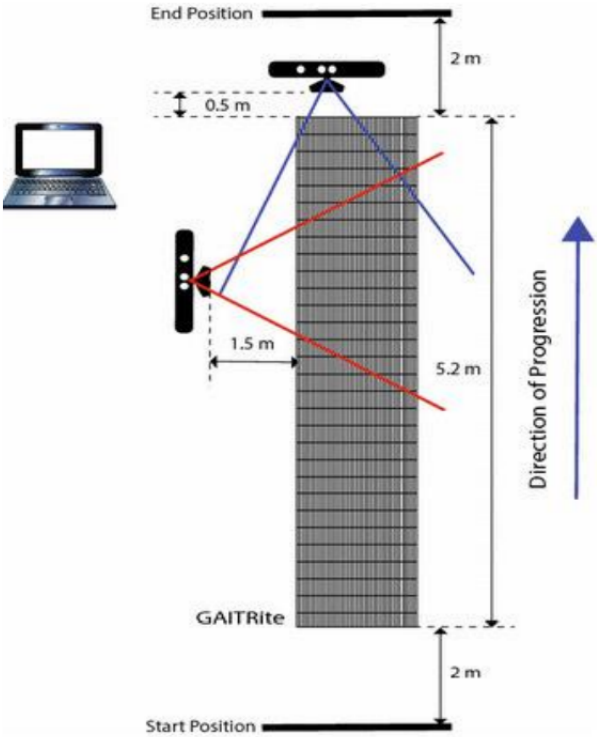

Figure 2.5. GAITRite Walkway [28].

NWS, as described above, return kinematic paramenters accurately and reliably even in the early stages of the disease. On the other hand these systems are more expensive and are not usable in environments where everyday actions are performed.

2.3.2 Wearable technologies

WS are placed on various parts of the patient's body such as the feet, knees, or hips to measure characteristics of the human gait. The most popular WS are:

- pressure sensors are insoles instrumented or integrated into the shoe to measure pressure changes between the foot and the ground. Pressure sensors use plantar pressure measurements to calculate spatio-temporal gait variables, including gait phases (e.g. stance time and swing time and stride time).
- Inertial measurement units (IMUs) are a combination of MEMS sensors such as tri-axial accelerometer, tri-axial gyroscope, and tri-axial magnetometer.

Tri-axial sensors can capture spatio-temporal and 3D kinematic data including joint and segment angles. Accelerometers measure proper acceleration with respect to the sensitive axis, rotational speed can be detected using one or more gyroscopes, and direction through magnetometers. The accelerometers, most commonly used in gait analysis, are piezoresistive and capacitive as they allow high stabiliy. The working principle of accelerometers is as follows: it is based on detecting the inertia of a mass when it is subjected to acceleration. The mass is suspended from an elastic element, while some kind of sensor detects its displacement relative to the fixed structure of the device. In the presence of acceleration, the mass (which has its own inertia) moves from its rest position in a manner proportional to the detected acceleration. The sensor converts this displacement into an electrical signal that can be acquired by modern measurement systems. The operating principle of the gyroscope is based on the Coriolis force, which is an apparent force. The Coriolis force induces a secondary vibration orthogonal to the original direction of vibration of the mass contained within the sensor. By measuring the deformation due to the secondary vibration it can determine the angular velocity. Lastly, magnetometer is a device that measures changes in the orientation of a body with respect to magnetic north (the vertical axis in the case of path analysis) by exploiting the magnetoresistive effect. IMUs can be integrated into insoles making them highly suitable for gait analysis but they can also be attached to other parts of the body such as on a belt or the wrist as illustrated in Fig. 2.6. They are also integrated in smart devices such as phones and watches. The advantages of using IMUs are small size, low cost, portable, and most importantly, they do not require to be used in the laboratory. However, they allow to estimate temporal and spatial parameters, but the integration of acceleration signals is subject to drift, leading to measurement errors. In addition, where the magnetometers are present, they are influenced by the surroundings and so they limit the settings for the analysis [39].

- goniometers can be used to measure angles in the sagittal or frontal planes of joints such as ankle, knee and hip. They can be various (strain gauge-based, inductive or mechanical), and are usually fitted in intrumented shoes to measures ankle to foot angles [5].
- Electromyography sensors are capable of acquiring the electrical signal associated with muscle activity by means of surface electrodes or with wire or needle electrodes. EMG is a very useful non-invasive technique used to understand the changes in gait function and gait phase detection [39].

The main advantages and disadvantages of the two technologies (WS and NWS)

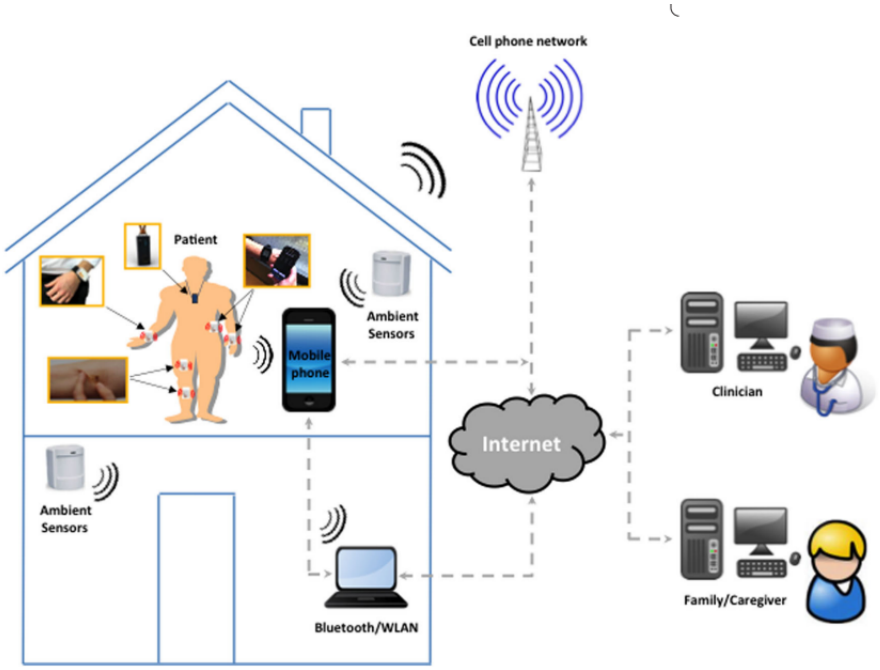

Figure 2.6. Schematic representation of a subject undergoing monitoring in the home setting using wearable and ambient sensors. The technology shown includes a wireless unit strapped around the wrist, Band-Aid-like sensors attached to the lower limbs, a wearable camera worn as a pendant, a smart watch, and a mobile phone clipped on the belt used as gateway to relay the data to the cloud to assess specific functions (using its embedded sensors) as well as to communicate with the patient (using customized apps). Ambient sensors and computer technologies are used in the home settings to gather additional information or replace WS when WS cannot be used [13].

are summarized in the Fig. 2.8.

2.4 Assessing gait in Parkinson's disease

PD diagnosis is made by a medical specialist using the UPDRS scale, but this implies that the outcome of the diagnosis will depend on the doctor's skill in recognizing the symptoms. One solution might be to supplement current diagnostics with the use of technology in the PwPD home environment so as to collect useful data for a more accurate diagnosis. PD is characterized by a hypokinetic gait,

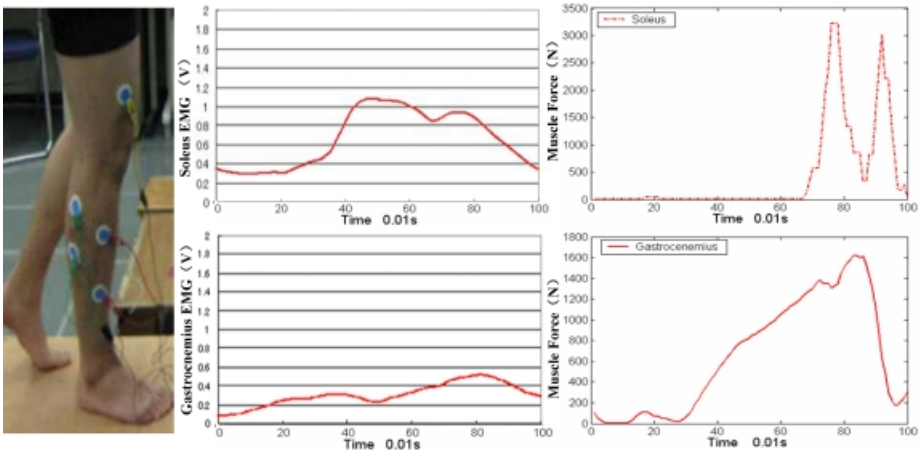

Figure 2.7. Diagram of EMG application in human gait [38].

with slow and shuffling steps, as well as an asymmetrically reduced arm swing. This hypokinetic gait usually improves with dopaminergic medication and with deep brain stimulation (DBS) [24]. Two typical phenomena that manifest PwPD during gait analysis are: FOG and fall events. The first phenomenon is normally transitory characterized by the sudden impossibility of moving, taking a step, turning around, or crossing narrow spaces such as a door. During an episode FOG, one has the feeling that the feet are glued to the ground. However, while the feet remain in place, the torso can have a forward momentum, which can cause a fall. Gait freeze can occur when mobility is impaired with a poor response to dopaminergic therapy (status called "off ") or also during the patient's states of good mobility in response to dopaminergic therapy (state called "on"). It is usually more common and severe in the off state. Detecting FOG is difficult in environments such as hospitals as they are spacious and free of obstacles while it is easier for it to manifest itself during the patient's daily activities. The development of IMUs for monitoring people with PD has focused mainly on the motor aspects of the disease (e.g., tremor, bradykinesia, gait disturbances, and dyskinesias). Some disadvantages of using these IMUs relate to the fact that their resolution depends from the area of the body on which they are applied and the fact that sensors from different manufacturers return differentiated results. To understand how much the use of these sensors is to consider that 32% of users stop using IMUs after 6 months and 50% after just over a year [13]. A very important choice is represented by the best position and the appropriate number of the IMUs to extract the parameters during the gait analysis, according to a literature review the most used set-up is with a single IMU and it is frequently worn on the lower back. In 41.7% and 30.6% of the items analyzed, IMUs are also placed on both ankles (or tibias) and on

System	Advantages	Disadvantages
NWS	- Allows simultaneous analysis of multiple gait parameters captured from different approaches - Non restricted by power consumption - Some systems are totally non-intrusive in terms of attaching sensors to the body - Complex analysis systems allow more precision and have more measurement capacity - Better repeatability, reproducibility and less external factor interference due to controlled environment. - Measurement process controlled in real time by the specialist.	- Normal subject gait can be altered due to walking space restrictions required by the measurement system - Expensive equipment and tests - Impossible to monitor real life gait outside the instrumented environment
WS	- Transparent analysis and monitoring of gait during daily activities and on the long term - Cheaper systems - Allows the possibility of deployment in any place, not needing controlled environments - Increasing availability of varied miniaturized sensors - Wireless systems enhance usability - In clinical gait analysis, promotes autonomy and active role of patients	- Power consumption restrictions due to limited battery duration - Complex algorithms needed to estimate parameters from inertial sensors - Allows analysis of limited number of gait parameters - Susceptible to noise and interference of external factors not controlled by specialist

Figure 2.8. Comparison between WS and NWS systems.

both feet. Furthermore in some papers they are also worn on the wrist or chest [6].

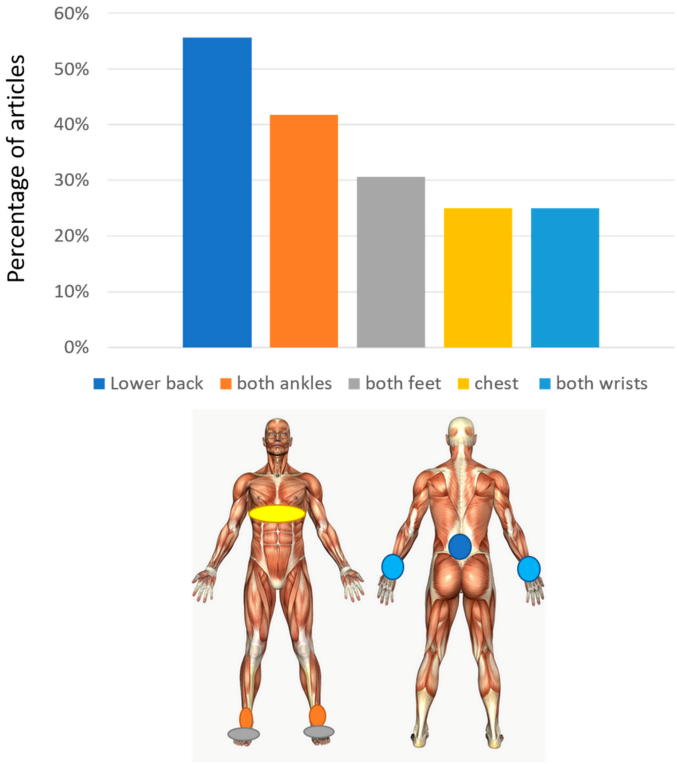

Figure 2.9. Sensor placement. At the top, the percentage of studies involving a sensor on different positions is reported. At the bottom, the corresponding position of sensors with respect to the body is reported [6].

Moreover, from the various studies in the literature it has also emerged that the most used IMUs for PwPD are triaxial-accelerometers as shown in Fig. 2.10. In conclusion, IMUs provide a light-weight, portable and affordable alternative to more expensive three-dimensional motion analysis systems and are effective for detecting changes in standing balance and walking stability among people with PD [19].

2.5 Algorithms for the gait events estimation with IMUs

Several methods have been developed to estimate the GEs (HS and TO) of the gait cycle using IMU data, taking into account the IMU's position and whether it is used in combination with another IMU or alone. Methods for estimating GEs using

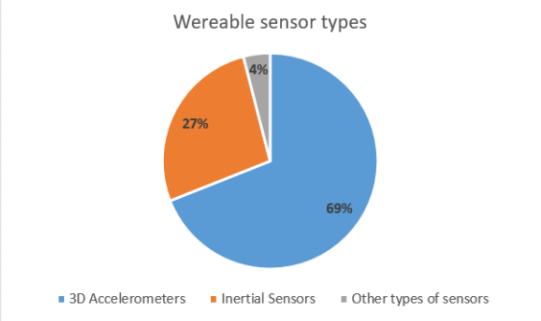

Figure 2.10. Types of wearable sensors [19].

IMUs are often based on thresholds or peak identification. Time-frequency analysis techniques (i.e., wavelet-based methods) have also been employed and in recent years, solutions based on machine learning (i.e., artificial neural network, hidden markov models, etc.) are also implemented. It is evident that the pathological subjects, in this case affected by PD, show patterns of IMU data that are not very clear, therefore the identification of the GEs is still an open question. Starting with the use of a single IMU at the trunk, it is possible to detect GEs from the antero-posterior acceleration. In detail, the maximum peaks of this signal are identified as foot contact events (HS) with the ground, as suggested by Zijlstra and Hof. [42] while the minimum peaks of the same signal are identified as foot detachment events (TO), as proposed by Bugane´ et al. [7]. Another algorithm used for the trunk is the one proposed by McCamley [27], who searched the GEs after applying a first order Gaussian (gaus1) continuous wavelet transform to the vertical acceleration. In particular, HS events are detected as the local minima of the CWT (findpeaks). A further differentiation resulted in the local maxima being defined as the TO events. When two IMUs are used, such as on the ankles or knee, the algorithm proposed by Salarian et al. is used to detect the subject's GEs [32]. This algorithm is applied to the identification of GEs from the medio-lateral angular velocities of the two shank/ankles-IMUs. HS events are identified as the peaks following the upward concaves, while TO events are identified as the peaks preceding the upward concaves. Using a single inertial sensor takes into account the movement of the pelvis and trunk, the setup will be minimal and less cumbersome but there will be more difficulty in finding the GEs. On the other hand, using two inertial sensors take into account the movement of feet, the setup will be more complex but the detection will be easier.

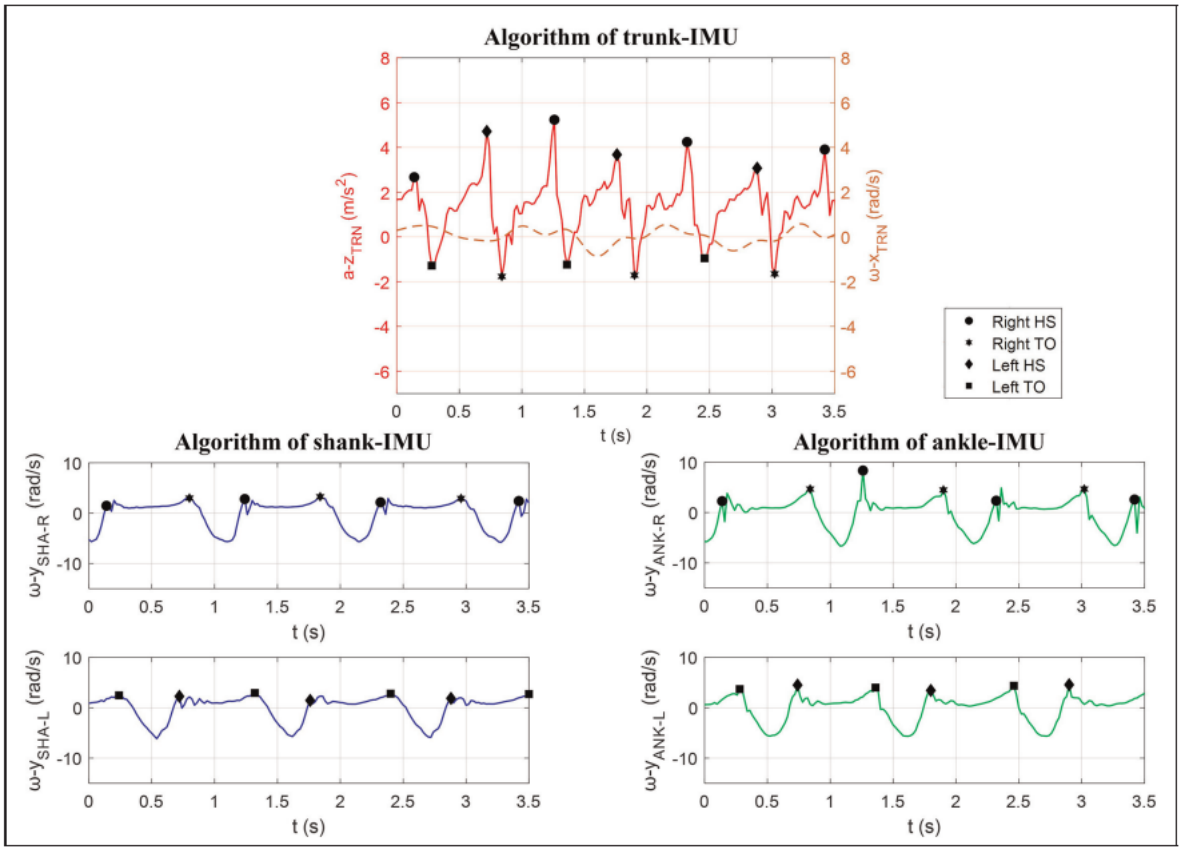

Figure 2.11. Algorithm for the identification of GEs from signals of IMUs on: (a) trunk, (b) right shank, (c) left shank, (d) right ankle, and (e) left ankle [9].

Chapter 3

Material and Methods

This chapter describes the research protocol adopted and the methods implemented to calculate the temporal parameters (TP) in PD subjects. All calculations and signal processing are performed using Matlab R2022b software.

3.1 Subjects

Fifteen PwPD, during OFF state, are recruited from the Molinette Hospital in Turin. Neurologists assessed the clinical picture of PwPD through some standardized reference scales: Hoehn and Yahr scale (HY), Unified PD rating scale (UPDRS) part I-III, FOG questionnaire (FOG-Q), and FES questionnaire (FES-1). The demographic and clinical characteristics of the patients are shown in Tab. 3.1 and Tab. 3.2. All patients gave their consent to carry out the study which is conducted following the Declaration of Helsinki.

Patients (Male)	Age (Years)	Disease duration (Years)	HY
15 (8)	69.8 ±7.9	10.9 ±6.8	2.7 ±0.6

Table 3.1. Demographic and clinical features of patients enrolled in the present study (mean ± standard deviation).

3.2 Instruments

Three Nordic Thingy:52 sensors and a smartphone are used to record patients' walking. The Nordic Thingy:52™ is a compact, power-optimized, multi-sensor device designed for collecting environmental data of various type. This multi-sensor is based on the NRF52832 Bluetooth 5 SoC developed by Nordic Semiconductor.

TOTUPDRS I	TOTUPDRS II	TOTUPDRS III	FOG-Q	FES-1
17.3 ±5	20.6 ±7.9	38.4 ±14.6	20.2 ±4.5	47.7 ±28.6

Table 3.2. Standardised scales and scores of patients enrolled in the present study (mean ± standard deviation). TOTUPDRS I-III: Unified PD rating scale (UPDRS) part I-III; FOG-Q: Freezing Of Gait questionnaire; FES-1: Falls-Efficacy Scale.

Thingy connects to Bluetooth-enabled devices and sends data from its sensors and actuators to an application or the cloud. This sensor can detect motion, orientation, temperature, humidity, air pressure and quality, light and color. This device features a Lithium-Ion battery with a capacity of 1440 mAh. Thingy includes MPU9250 9-axis motion IMU. This device combines a 3-axis gyroscope, 3-axis accelerometer, 3-axis magnetometer, and a Digital Motion Processor. Tab. 3.3 describes the features of the IMU utilized in the study. The smartphone is used to record patients' walking.

Figure 3.1. Nordic Thingy:52.

3.3 Protocol and Data Acquisition

To collect data, 3 IMUs are placed on patients' body according to the configuration showed in Fig. 3.2: two IMUs are located on the ankles and one at the trunk (lumbar aerea). IMUs are attached to the subject ankles with X, Y, and Z axes pointing in vertical, antero-posterior, and medio-lateral directions. Whereas X, Y, and Z axes on the trunk correspond to vertical, medio-lateral, and antero-posterior directions. Raw data from IMUs are sent in real-time to the smartphone via the Bluetooth module, and saved as files in CSV format. Data are sampled at 60Hz.

	Range	Resolution	Sample Frequency
Accelerometer	$\pm 2g$	16 bit	60 Hz
Gyroscope	$\pm 250°/sec$	16 bit	60 Hz
Magnetometer	360°	16 bit	60 Hz

Table 3.3. MPU9250 9-axis motion IMU features.

In order to evaluate each patient's motor skills, the clinical protocol created by neurologists required to 15 PwPD to complete 4 different motor-cognitive tasks. The 4 tasks performed are :

1. TUG (Time Up And Go): is a simple test to measure a person's level of mobility.It measures the time it takes a person to get up from a chair, walk 10 meters, turn 180 degrees, return to the chair and sit down again.
2. Walk: the subject walk back and forth for 10 meters.
3. Walk+obstacle: the subject walk back and forth for 10 meters, with an interposition of two chairs (narrowing of the hallway).
4. Walk+cognitive dual task: the subject walk back and forth for 10 meters, counting from 100 to 0 with steps of 7.

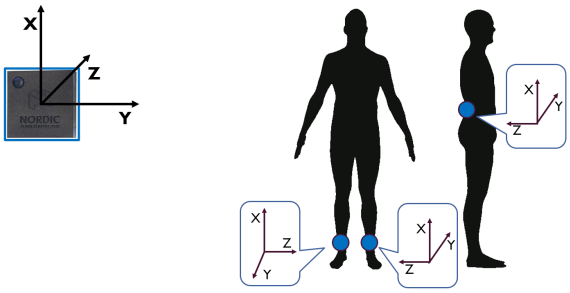

Figure 3.2. Position of IMUs on the patient's body.

3.4 Processing

The diagram, shown in 3.4, represents the algorithm used in this study for the gait analysis. The dataset selection phase is followed by the filtering of the trunk and ankle signals. Subsequently the initial and final contact instants are calculated separately for the trunk and ankles, then the turning events for each IMU are

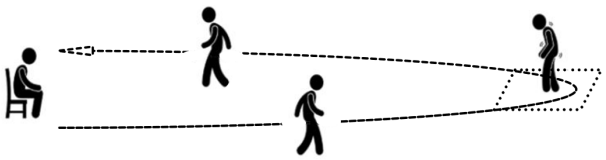

Figure 3.3. TUG test.

removed. At the end, TP are calculated for the trunk and ankles, and a statistical analysis is performed to note the differences between the various motor tasks and between the IMUs worn by the patients.

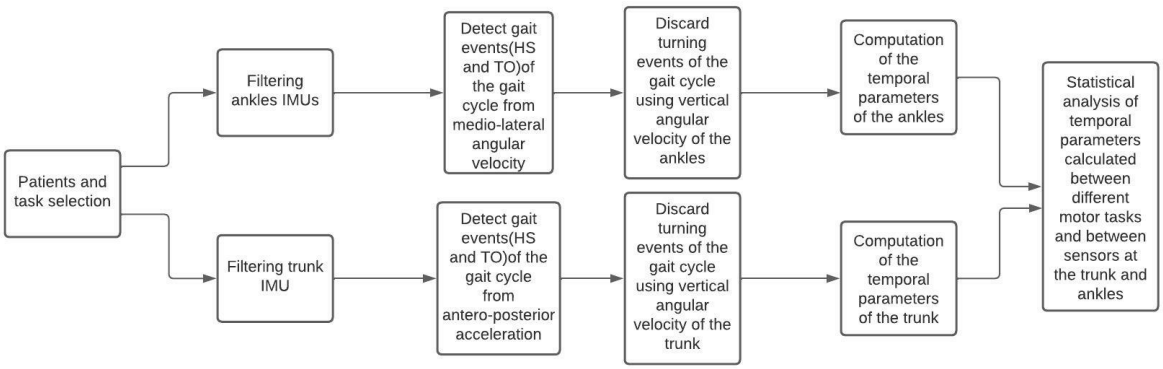

Figure 3.4. Algorithm block-diagram.

3.4.1 Data analysis

First of all, it has been necessary to define the number of patients, tasks and IMUs that have been chosen for the gait analysis. 2 patients from 15 are excluded from the analysis because they conducted all motor tasks with the aid of foldable walker. Therefore, the parameters obtained would have been insignificant. All 4 motor tasks performed and all sensors worn are considered in this study. At this point, raw data collected from the IMUs at the ankles and trunk are processed.

3.5 Ankles

This section describes the methods implemented for the identification of GEs (HS/TO). For the two ankles, angular velocity signals, acquired by the gyroscope along the 3 axes, are used for gait analysis. The techniques described in this section are applied both for the right and left ankle.

3.5.1 Filtering

Angular velocities recorded by gyroscope are filtered to reduce noise components and artifacts recorded during acquisition. This filtering step allowed for a more accurate estimation of the time parameters. A passband IIR Butterworth filter of order 5 is applied to medio-lateral angular velocity (w_z) and antero-posterior angular velocity (w_y). The bandpass filter's upper frequency has been set to 5 Hz, while the lower frequency has been set to 0.5 Hz. Furthermore, vertical angular velocity (w_x) is filtered with an order 5 IIR Butterworth low-pass filter with a cut-off frequency of 1 Hz. Since the GEs are derived from the component w_z, it is therefore important to preserve by filtering its shape. In Fig. 3.5 and Fig. 3.6 it is possible to observe the post-filtering results.

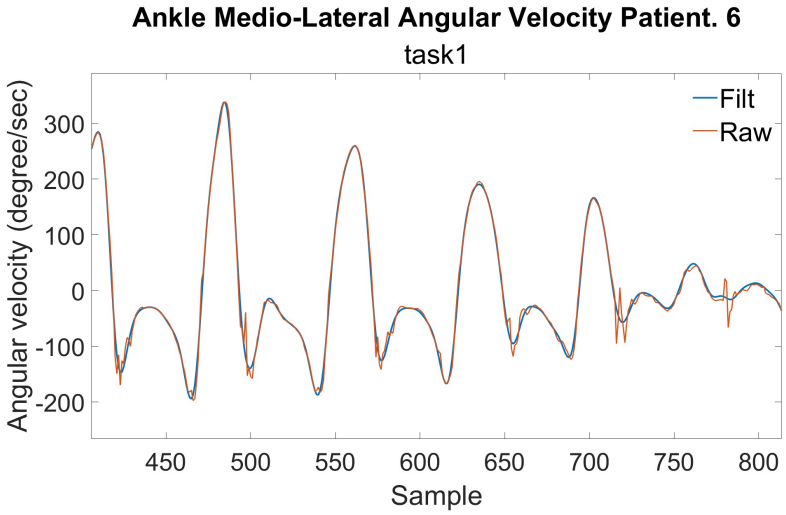

Figure 3.5. Filtering w_z applying a passband IIR Butterworth filter of order 5 with upper frequency set to 5 Hz, while lower frequency set to 0.5 Hz. Orange=Raw w_z, Blue= Filter w_z.

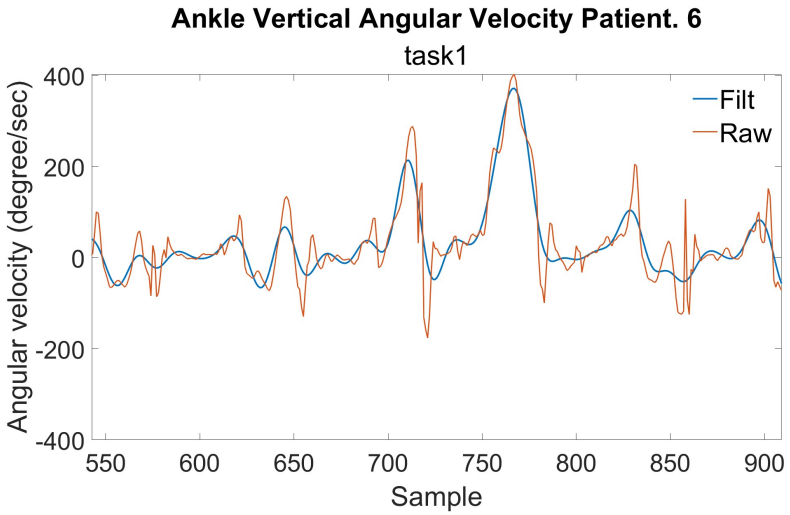

Figure 3.6. Filtering w_x applying a low-pass Butterworth filter of order 5 with cut-off frequency of 1 Hz. Orange=Raw w_x, Blue= Filter w_x.

3.5.2 Detection of gait events

After filtering the gyroscope signals, GEs are identified to subsequently calculate the TP. Specifically, the instants of initial contact, HS, and final contact, TO, of the gait cycle are detected using the medio-lateral angular velocity of the two ankles. Time events, corresponding to the midswing instants during the gait cycle, are first identified. These time events are computed using findpeaks function in Matlab. Peaks height greater than the standard deviation of the medio-lateral angular velocity are considered to be the midswing instants (MS) of the gait, as shown in Fig. 3.7. If multiple adjacent peaks within a maximum distance of 500 ms are detected, the peak with the highest amplitude is selected and the others are discarded [32]. MS are used as a reference to identify the corresponding instants of HS and TO. Each positive peak is accompanied by two negative peaks (or minima) on either side which indicate the reversal of leg velocity direction. TO event is detected as the negative peak (NP) preceding the positive peak (MS) while the negative peak (NP) after the positive peak (MS) is marked as HS, as shown in Fig. 3.8. Fig. 3.7 and Fig. 3.8, show respectively the instants of midswing, heel strike and toe off during gait cycle.

3.6 Trunk

This section describes the methods implemented for the identification of GEs (HS/TO) related to the IMU on the trunk.

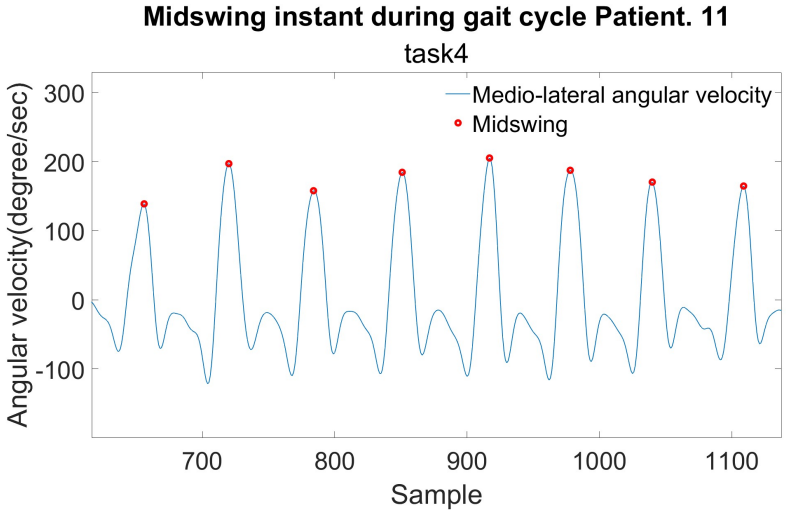

Figure 3.7. Detection midswing instants as peaks height greater than the standard deviation of the medio-lateral angular velocity. Blue=w_z, Red=midswing instants.

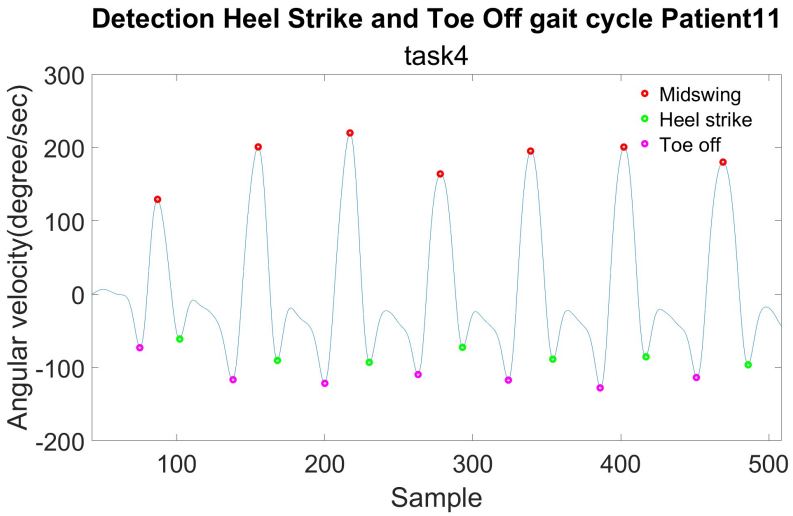

Figure 3.8. Detection heel strike and toe off instants at the ankles as described in [32]. Blue=w_z, Red=midswing instants, Green=heel strike instants, Magenta= toe off instants.

3.6.1 Filtering

The choice about type of filter and cutoff frequency for the trunk is based on the following assumption: human activity acceleration signals are in the 0-20 Hz

band, while the locomotor band is up to 3-5 Hz. For this reason, a passband IIR Butterworth filter of order 5 is applied to antero-posterior acceleration (a_z) to remove the gravitational component and high frequency noise. The upper cutoff frequency has been set to 5 Hz while the lower cutoff frequency has been set to 1 Hz. Furthermore, the vertical angular velocity (w_x) is low-pass filtered with a 1.5 Hz cutoff frequency Butterworth filter of order 3 to remove the high frequency components.

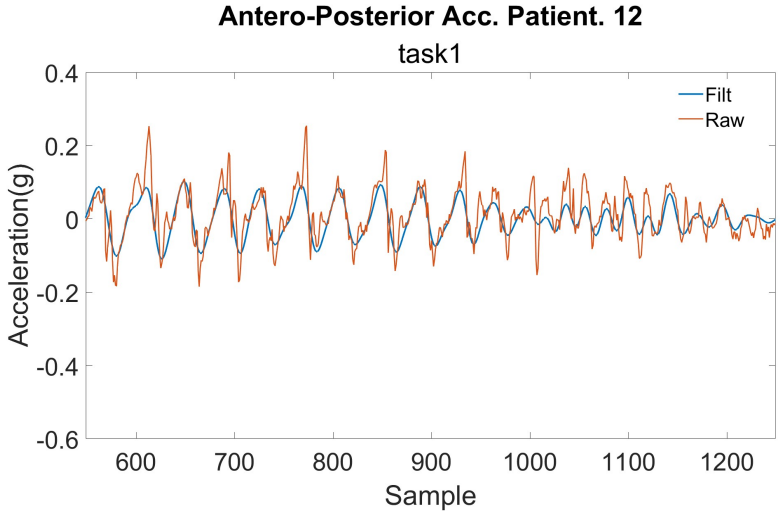

Figure 3.9. Filtering a_z applying passband IIR Butterworth filter of order 5 with upper cutoff frequency set to 5 Hz while lower cutoff frequency set to 1 Hz. Orange=Raw a_z, Blue=Filter a_z.

3.6.2 Detection of gait events

Vertical acceleration is often used in the literature to detect heel strike and toe-off but in this case, these events are searched using antero-posterior acceleration. In this case, the antero-posterior acceleration is considered to identify the GEs during gait cycle. Firstly, the peaks of the antero-posterior acceleration signal are detected using the findpeaks function in Matlab. The conditions for detecting these peaks, imposed in findpeaks function, are that their height must be greater than the standard deviation of the signal and that the distance between peaks must be at least 400 ms. The peaks detected by this method represent the HS events of the gait detected by the IMU at the trunk as as demonstrated in [42]. The minimum peaks at each heel strike represent the instants of TO. Initial (HS) and final contacts (TO) obtained are reported in Fig 3.11 and Fig. 3.12. It is also interesting to compare the GEs - HS and TO - detected wearing two IMUs

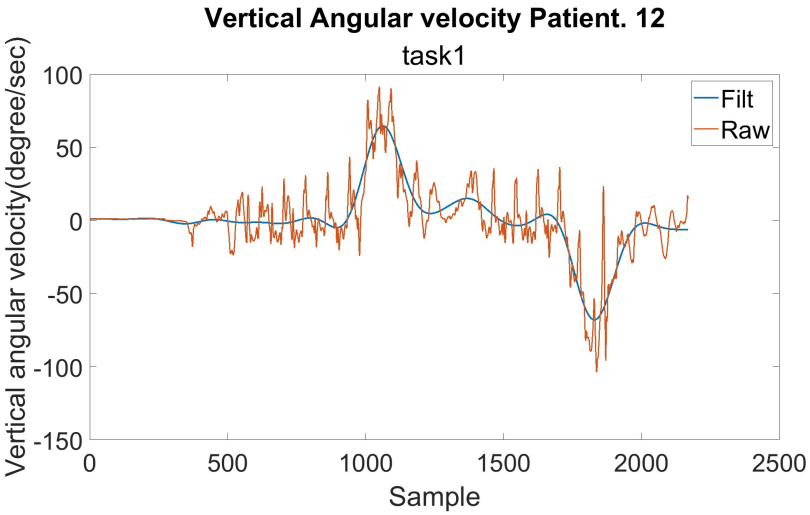

Figure 3.10. Filtering w_x applying a low-pass Butterworth filter of order 3 with a cut-off frequency of 1.5 Hz. Orange=Raw w_x, Blue=Filter w_x.

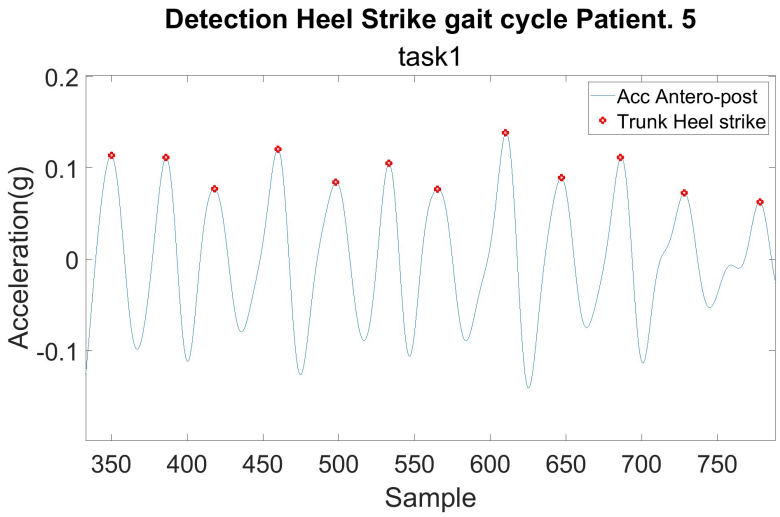

Figure 3.11. Detecion heel strike instants at the trunk as peaks height greater than the standard deviation of the antero-posterior acceleration. Blue=a_z, Red=heel strike instants.

at the ankles and the one at trunk as shown in Fig. 3.13 and Fig. 3.14. The two figures 3.13 and 3.14 show that there is a strong correlation between the gait events detected with the IMU at the trunk and the IMUs at the ankles.

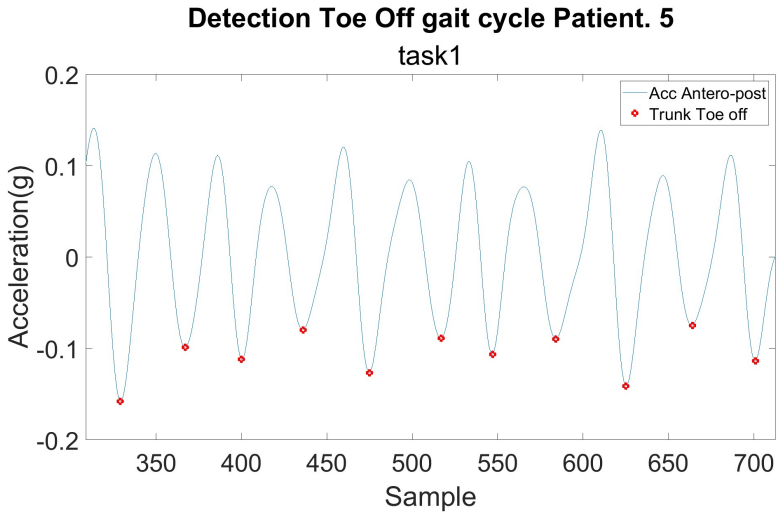

Figure 3.12. Detection toe off at the trunk as minimum peaks in the antero-posterior acceleration. Blue=a_z, Red=toe off instants.

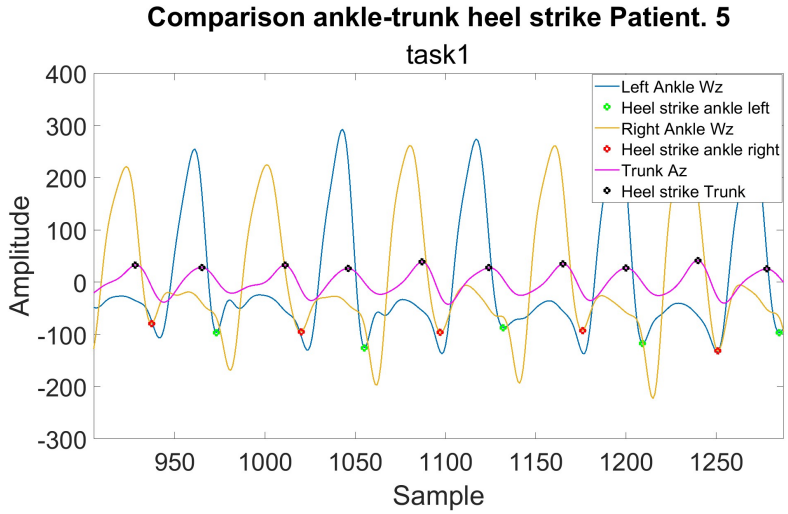

Figure 3.13. Comparing heel strike detected by ankles' IMU and trunk's IMU. Blue=Left ankle w_z [degree/sec], Green=Heel strike left ankle, Orange=Right ankle w_z [degree/sec], Red=Heel strike right ankle, Magenta=Trunk a_z [g], Black=Heel strike trunk.

3.7 Turning events

Turning problems are very common in PwPD during gait cycle. In fact, upper body movements during rotation are more rigid and to make a rotation are necessary

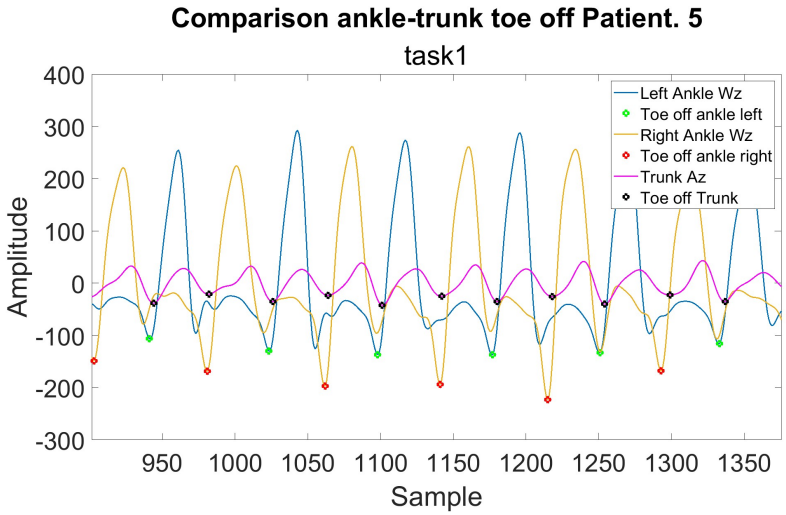

Figure 3.14. Comparing toe off detected by ankles' IMU and trunk's IMU. Blue= Left ankle w_z [degree/sec], Green=Toe off left ankle, Orange=Right ankle w_z [degree/sec], Red=Toe off right ankle, Magenta=Trunk a_z [g], Black=Toe off trunk.

more steps. PwPD show a lack of dissociation, that is, a lack of coordination of segments, in the rotation of the head, pelvis and feet. Difficulty turning in people with PD is associated with clinical outcomes, such as falls, fear of falling, disease severity, freezing of gait and cognitive impairment. Various algorithms have been implemented to identify turns using IMUs: peak detection, angular displacement thresholds and zero-crossing. It is fundamental to identify the beginning and end of each identified rotation. Both for trunk and ankles, vertical angular velocity (w_x) is used to detect the turns. In this study, all motor tasks also had a turning phase in which patients turned 180 degrees to return to the starting position. Time instants in which patients made a 180-degree rotation, during walking, are discarded in the calculation of TP. The motor tasks, performed by the PD patients in the hospital, involved multiple turning phases, but in this study only the back-and-forth walking of each task is analyzed.

3.7.1 Ankles turning events

The method described is applied for both ankles. To identify the turning phases, the angular velocity w_x is considered. First the peaks of vertical angular velocity are identified using the findpeaks function then they are compared with the matching peaks on medio-lateral angular velocity. The subject made a rotation when either of these two conditions occurs:

- height of vertical angular velocity's peak is greater than the height of medio-lateral angular velocity's one.

- ratio between height of the vertical angular velocity's peak and the height of the medio-lateral angular velocity's one is greater than 40%.

Thus, the peaks identified as the subject's turning step aren't considered in the gait analysis, so excluding respective HS and TO events. Thereby, only straight walking is analyzed for all PD patients.

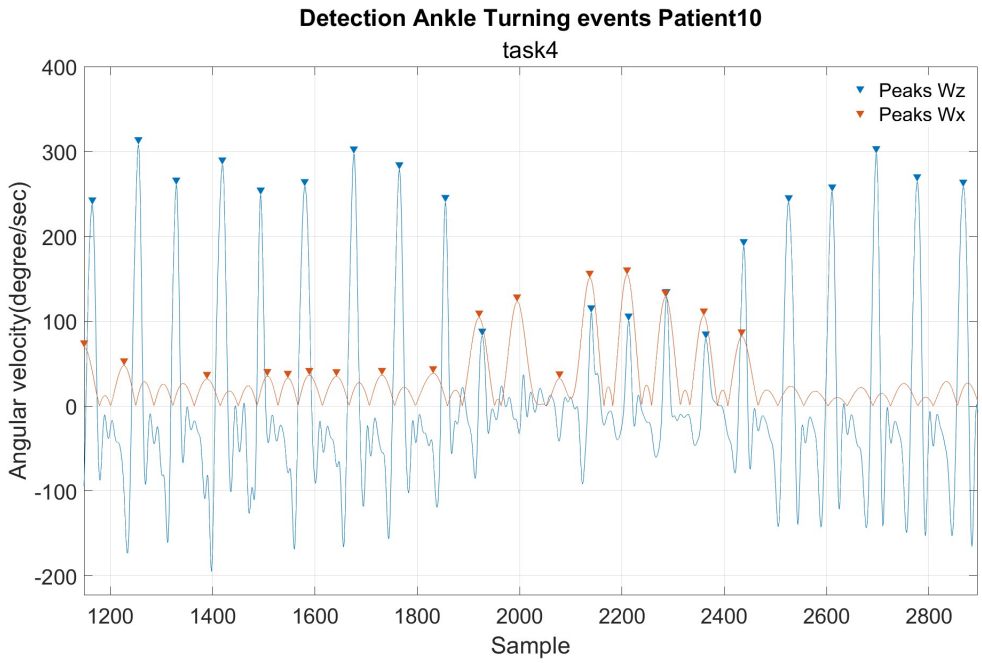

Figure 3.15. Turn phase identified comparing w_z and w_x using IMU on left or right ankle, subject makes a rotation if height of vertical angular velocity's peak is greater than the height of medio-lateral angular velocity's one or if ratio between height of the vertical angular velocity's peak and the height of the medio-lateral angular velocity's one is greater than 40%.

3.7.2 Trunk turning events

An IMU on the lower back most closely reflects the movement of the center of mass and is commonly used for turn detection. As already done for ankles, the intervals, at which the subject turns, should be removed from the gait analysis. The method

implemented to remove these intervals is based on the algorithm proposed by El-Goharay [11]. The turning instants are identified as the peaks of the filtered vertical angular velocity greater than a threshold set at 15°/s. The beginning and end of each turn are set to the point at which the filtered vertical angular velocity falls below 5°/s within the peak range considered. An additional condition imposed is that only turns with period between 0.5 s and 10 s are accepted.

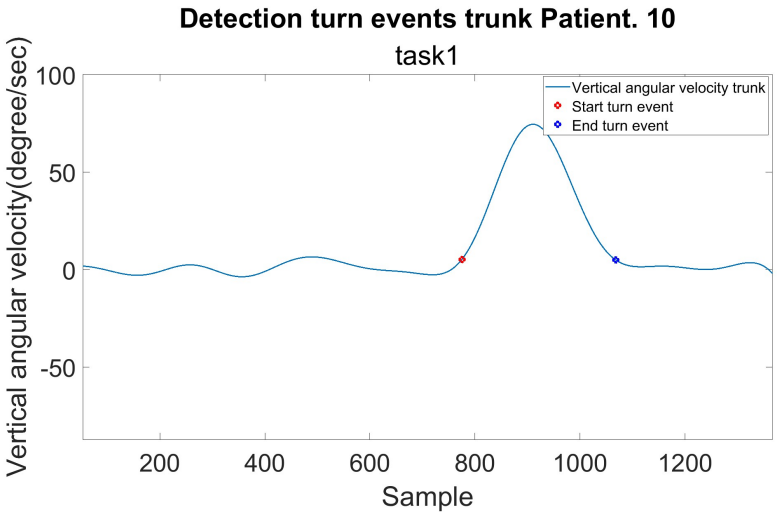

Figure 3.16. Detection start and end of turn event using IMU on trunk, algorithm for turning instants are described in [11]. Red=Start turn event, Blue=End turn event.

3.8 Temporal parameters

After detection of HS and TO, each gait cycle must have, for example, the following time sequence of events to be considered valid: initial contact of right foot, terminal contact of left foot, initial contact of left foot and terminal contact of right foot. The next time event is next initial contact of right foot that it also represents the beginning of the next gait cycle. Therefore, after GEs (HS and TO) are identified, TP are calculated for trunk and ankles. They are calculated for each patient and for each task they perform. Temporal parameters are:

- Stride time [s]: HS_{i+2} - HS_i
- Step time [s]: HS_{i+1} - HS_i
- Swing time [s]: HS_{i+1} - TO_i

- Swing phase [%]: expressed as percentage of gait cycle
- Stance time [s]: TO_{i+1} - HS_i
- Stance phase [%]: expressed as percentage of gait cycle
- Single support time [s]: HS_i - TO_{i-1} + HS_{i+1}-TO_i
- Single support phase [%]: expressed as percentage of gait cycle
- Double support time [s]: TO_i - HS_i + TO_{i-1} - HS_{i-1}
- Double support stance [%]: expressed as percentage of gait cycle

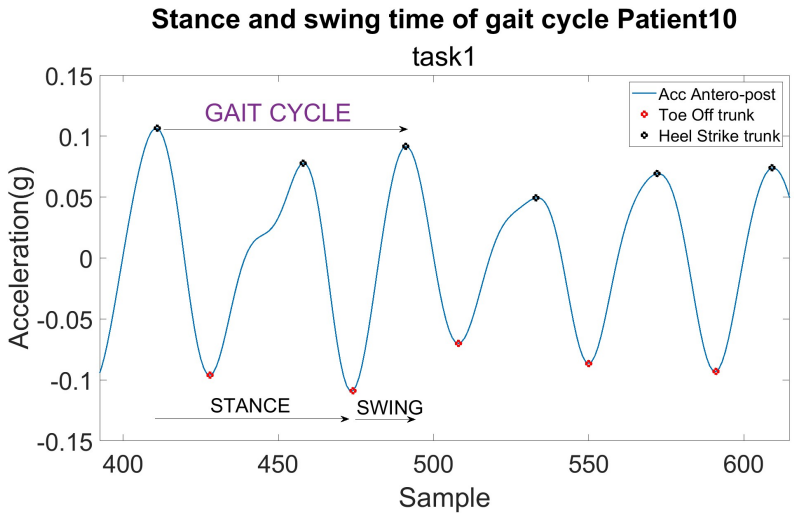

Figure 3.17. Temporal parameters: stance and swing time of a gait cycle.

3.9 Statistical analysis

After all time parameters are obtained, a statistical analysis was performed to evaluate the differences between the IMUs at the ankles and IMU at the trunk and between the various motor tasks. First of all, the mean and standard deviation of all TP for each IMU are calculated. Then, the Wilcoxon non-parametric statistical test is used to compare in each patient:

- TP obtained from the IMUs at the ankles and IMU at the trunk for each task
- TP for different motor tasks obtained from the IMUs at the ankles

- TP for different motor tasks obtained from the IMU at the trunk

Wilcoxon test is implemented in Matlab using the ranksum function with a significance level of 0.05.

Chapter 4

Results

This chapter shows the results of the statistical analysis of TP of the gait.

4.1 Trunk-ankle comparison

This section shows the statistical results achieved by comparing the IMUs at the ankles with the one at the trunk. In particular, the Wilcoxon test is conducted for each patient by comparing the TP that are calculated for the ankles and trunk. Tab. 4.1 below has on the rows the motor tasks (tasks 1,2,3) performed by patients while on the columns are the TP. Specifically in Tab. 4.1 is reported, for each motor task, the percentage of patients who showed no significant variations between the TP calculated at the ankles and those at the trunk. For each motor task taken into consideration, it is observed that for almost all patients examined, the TP of stride and step did not reveal any significant variations (p-value>0.05) between IMUs at the ankle and IMU at the trunk. On the other hand, the other TP were statistical different between ankles' IMUs and trunk's IMU for all patients.

TASK	STANCE	SWING	STRIDE	SS	STEP	DS
1	0	0	**87.5**	0	**87.5**	0
2	0	0	**100**	0	**100**	0
3	0	0	**100**	0	**75**	0

Table 4.1. Percentage of patients who showed no significant variations between the TP calculated using ankles' IMU and trunk's IMU. SS: single support; DS: double support.

4.2 Ankles' motor tasks

This section shows the statistical differences in TP, computed using ankles' IMUs, between the various motor tasks for each patient. Tables 4.2, 4.3, 4.4, 4.5 reported the comparison between different motor tasks, in detail on the rows are the IDs of the PwPD while on the columns are the TP. The p-values for all TP, for each patient, are reported in all tables comparing the various motor tasks. P-values greater than 0.05 showed that there was no significant variation in the TP among the motor tasks considered. Except for patient 5 during task 2-3, not many meaningful statistical differences existed between tasks 1-3 and 2-3 in terms of the TP as observed in Tab. 4.2 and Tab. 4.3. Instead, it is observed in Tab. 4.3 that patient 5 showed significant changes in the TP of stride, step and single support between tasks 2 (simple walking) and 3 (walk+obstacle). The mean and standard variation of the above TP are reported: stride time for task 2 was 1.21 ± 0.047 s while for task 3 was 1.33 ± 0.102 s, step time for task 2 was 0.629 ± 0.062 s while for task 3 was 0.689±0.070 s, single support duration for task 2 was 46 ± 3.72 % of gait cycle while for task 3 was 42 ± 2.92 % of gait cycle. The most significant statistical differences are noted between tasks 2-4 and 3-4 for patients 3, 7 and 9 as showed in Tab. 4.4 and Tab. 4.5. A statistical variation in all TP is observed for patient 9 between tasks 2-4. The mean and standard deviation of the following time parameters are reported: stance duration for task 2 was 56 ± 1.72 % of gait cycle while for task 4 was 60 ± 2.62 % of gait cycle, swing duration for task 2 was 44 ± 2.43 % of gait cycle while for task 4 was 36 ± 3.09 % of gait cycle, double support duration for task 2 was 10 ± 2.56 % of gait cycle while for task 4 was 25 ± 4.01 % of gait cycle. For tasks 2-4, the statistical variations of single and double support for patient 3 are also presented: single support duration for task 2 was 37 ± 5.2 % of gait cycle while for task 4 was 32 ± 4.7 % of gait cycle, double support duration for task 2 was 28 ± 4.1 % of gait cycle while for task 4 was 33 ± 6.1 % of gait cycle.

TASK 1-3

IDs	STANCE	SWING	STRIDE	SS	STEP	DS
4	0.407	0.501	**p<0.001**	0.583	**p<0.001**	0.396
5	0.054	0.435	0.379	0.454	0.406	0.118
6	0.908	0.817	0.116	0.794	0.684	0.884
10	0.294	0.199	0.078	0.117	**0.002**	**0.002**
11	0.480	0.760	0.758	0.473	0.731	0.905

Table 4.2. P-values for all TP, for each patient, comparing motor task 1-3 using ankles'IMU. SS: single support; DS: double support.

TASK 2-3

IDs	STANCE	SWING	STRIDE	SS	STEP	DS
3	0.318	0.190	**p<0.001**	0.618	0.709	0.314
5	0.691	0.730	**0.016**	**0.043**	**0.026**	0.108
6	0.544	0.707	0.246	0.664	0.839	0.907
7	0.772	0.600	0.908	0.672	0.798	0.809
9	0.511	0.755	0.393	0.755	0.711	0.986
10	0.964	0.659	0.798	0.378	0.732	0.894
11	0.466	0.301	0.067	0.324	**0.01**	0.840

Table 4.3. P-values for all TP, for each patient, comparing motor task 2-3 using ankles'IMU. SS: single support; DS: double support

TASK 2-4

IDs	STANCE	SWING	STRIDE	SS	STEP	DS
3	0.320	0.290	0.295	**0.003**	0.1	**0.009**
7	0.984	0.604	**p<0.001**	0.776	**p<0.001**	0.979
9	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**

Table 4.4. P-values for all TP, for each patient, comparing motor task 2-4 using ankles'IMU. SS: single support; DS: double support.

4.3 Trunk's motor tasks

This section shows the statistical differences in TP, computed using trunk's IMU, between the various motor tasks for each patient. Tables 4.6, 4.7, 4.8, 4.9 referred to the comparison between different motor tasks, in detail on the rows are the IDs of the PD subjects while on the columns are the TP. The p-values for all TP, for each patient, are reported in all tables comparing the various motor tasks. P-values greater than 0.05 showed that there was no significant variation in the TP among the motor tasks considered. Even in this comparison using IMU at

TASK 3-4

IDs	STANCE	SWING	STRIDE	SS	STEP	DS
3	0.077	0.098	**0.0052**	**0.04**	0.320	0.451
4	0.452	0.525	0.054	0.897	**0.011**	0.755
7	0.835	0.835	**p<0.001**	0.955	**p<0.001**	0.552
9	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**

Table 4.5. P-values for all TP, for each patient, comparing motor task 3-4 using ankles'IMU. SS: single support; DS: double support.

the trunk demonstrated that statistical changes in TP were more evident between tasks 2 and 4 and tasks 3 and 4 in patients 3, 7, 9 as observed in Tab. 4.8 and Tab. 4.9. Stride and step times were TP that exhibited statistic differences in this analysis.

TASK 1-3

IDs	STANCE	SWING	STRIDE	SS	STEP	DS
4	0.246	0.746	**p<0.001**	0.746	**0.0071**	0.102
5	0.589	0.237	0.546	0.237	0.505	0.395
6	0.863	0.503	0.084	0.503	0.349	0.449
10	0.281	0.453	0.089	0.453	0.307	0.734
11	0.620	0.417	0.920	0.417	0.656	0.874

Table 4.6. P-values for all TP, for each patient, comparing motor task 1-3 using trunk's IMU. SS: single support; DS: double support.

TASK 2-3

IDs	STANCE	SWING	STRIDE	SS	STEP	DS
3	0.333	0.173	**0.031**	0.173	0.172	0.676
5	0.189	0.093	**0.037**	0.093	0.107	**0.013**
6	0.886	0.241	0.132	0.241	0.943	0.286
7	0.873	0.804	0.461	0.804	0.835	0.854
9	0.660	0.536	**0.047**	0.536	**0.028**	0.453
10	0.385	0.519	0.906	0.519	0.962	0.622
11	0.249	0.548	0.168	0.548	0.297	0.738

Table 4.7. P-values for all TP, for each patient, comparing motor task 2-3 using trunk's IMU. SS: single support; DS: double support.

TASK 2-4

IDs	STANCE	SWING	STRIDE	SS	STEP	DS
3	0.602	0.308	0.479	0.308	0.401	0.847
7	0.822	1	**0.006**	0.431	**0.025**	0.685
9	0.122	0.214	**p<0.001**	0.215	**p<0.001**	0.187

Table 4.8. P-values for all TP, for each patient, comparing motor task 2-4 using trunk's IMU. SS: single support; DS: double support.

TASK 3-4

IDs	STANCE	SWING	STRIDE	SS	STEP	DS
3	0.589	0.604	**0.002**	0.604	**0.041**	0.868
4	0.256	0.914	**0.028**	0.914	0.420	0.136
7	0.635	0.798	**p<0.001**	0.798	**0.011**	0.812
9	0.236	0.142	**p<0.001**	0.142	**p<0.001**	**0.04**

Table 4.9. P-values for all TP, for each patient, comparing motor task 3-4 using trunk's IMU. SS: single support; DS: double support.

Chapter 5

Discussion

Most publications in the literature compare healthy and PwPD gait and, consequently, TP between these two groups. According to numerous papers, there are some differences between the two groups. Specifically, the gait of PwPD shows reduced stride length, reduced speed, reduced swing phase, and increased stance phase and double support phase [31, 36, 41]. However, there are few articles inherent to the analysis of TP as motor tasks vary, thus this thesis aims to address this topic. The objective of this thesis was to assess the TP of PwPD completing four motor activities and examine any statistical variations in parameter estimation caused by different IMUs placements. The results obtained for each patient, in particular, allowed us to study the differences in TP based on the location of the IMU for each motor task, and also the variation of TP both for the trunk and for the ankles as the motor activities performed varied.

In particular, the TP measured by two distinct IMUs — one at the trunk and two at the ankles — are compared. This comparison enabled us to determine whether we could achieve comparable outcomes with just one IMU as opposed to two. For each motor task taken into consideration, it was observed that for all patients examined (100%) as described in Tab. 4.1, the TP of stride and step did not reveal any significant variations (p-value>0.05) between the ankle and trunk IMUs. This showed how accurate time metrics like step and stride time could be determined with a simple IMU setup—in this case, just one inertial sensor at the trunk. Using a single IMU, the setup will be minimal and less cumbersome. Instead, it could be seen that for each motor activity under consideration, the other TP, such as stance, swing, single support, and double support, consistently differed (p-value<0.05) across the two IMUs in all patients as described in Tab. 4.1. According to the results, there was no significant variance between the step and stride characteristics since the heel strike instants computed by the two distinct IMUs were comparable to one another. On the other hand, the various ways in

which the two IMUs under examination detected the toe off instants of the gait could be used to explain variations in the other TP.

It was also useful to compare how the TP change for each patient as the motor task performed varies. The statistical variations of the TP acquired from the ankle IMU are showed in Tables 4.2, 4.3, 4.4 and 4.5. It is discovered that while the TP did not appear to change for task 1 (TUG) and task 3 (walk+obstacle) and for task 2 (walk) and task 3 (walk+obstacle), in the presence of a motor-cognitive task there was a change in the TP as reported in Tab. 4.4 and Tab. 4.5. It became evident that some time parameters varied consistently between patients who performed tasks 2 (walk) and 4 (walk+cognitive dual task), as well as tasks 3 (walk+obstacle) and 4 (walk+cognitive dual task). Due to the complexity of the task 4, for example, patient 3 double support phase lasted longer (28% in task 2 vs 33% in task 4) because the patient probably wanted to remain in this more stable condition for a longer period of time with both feet on the ground. Additional evidence for the aforementioned was provided by patient 9, who performed task 4 in comparison to task 3 with an increase in the stance phase (56% in task 2 vs 60% in task 4), double support phase (10% in task 2 vs 25% in task 4) and a decrease in the swing phase (44% in task 2 vs 36% in task 4). Regarding the TP of the trunk, it could be seen that, also in this case, tasks 2-4 and 3-4 presented the largest statistical differences as showed in Tab. 4.8 and Tab. 4.9. Additionally on the trunk, it should be noticed that a motor-cognitive task, as task 4, had different TP than simpler motor tasks (task 2 or 3). The variations of the TP in this case mostly affected the stride and step times rather than the other temporal factors. This may be explained by the trunk's IMU better ability to detect these TP than the others. The results back up the theory that Parkinson's patients tend to extend the period during which feet are in contact with the ground (stance/double support phase) and shorten the period during which foot is not in contact with the ground (swing phase) as the difficulty of the motor task increases. The patient will feel more steady but will still exhibit a pathological gait.

Chapter 6

Conclusions and future work

The purpose of this thesis has been to estimate the TP during walking of PwPD completing 4 motor tasks utilizing IMUs at the ankles and at the trunk. For PwPD, who frequently exhibit distinct gait changes (slowdowns, hesitations, blocks), as well as a decreased capacity for multitasking, gait analysis acquires a significant clinical relevance.

Thirteen Parkinson's patients without treatment (OFF state) are enrolled in this study at the Molinette Hospital in Turin, where they performed four different motor tasks. Three inertial sensors (MPU9250) are utilized in this study, two on each ankle and one on the trunk, to collect signals of acceleration and angular velocity in all directions. Initial and final contact are found for the IMU at the trunk and the IMUs at the ankles, moreover, steps that were part of the instants of gait rotation are excluded from the study. Subsequently, TP for various motor tasks were computed for all patients using the ankle and trunk IMUs. The statistical analysis revealed that, while the other TP varied between the two inertial sensors, the stride and step time could be calculated with just one IMU at the trunk. The setup will be simpler and more manageable if only one IMU is used. Furthermore, the effects of performing various motor tasks on time parameters are examined, with notable outcomes. The results of this work confirm the hypothesis that when a motor activity becomes more complex, PwPD tend to shorten the time a foot is not in contact with the ground (swing phase) and lengthen the time feet is in contact with it (stance/double support phase).

The study under consideration had some limitations, such as the small number of patients who completed all 4 motor tasks and the fact that not all IMUs (at

the ankles and trunk) are employed to record signals for every motor tasks. Furthermore, some patients utilized walking stick thus obtaining TP that were not very indicative of their actual motor condition. The use of inertial sensors for gait analysis could not only be limited to the clinical setting but would offer the possibility of continuous monitoring of his pathology in the home. According to the results of our study, it is important to note that for home monitoring not all TP can be accurately detected by a single IMU. Moreover, future research may be interested to investigate the connection between temporal factors and increasing motor task complexity in PD patients because most published papers do not focus on this topic.

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