POLITECNICO OF TURIN

Master Degree in Biomedical Engineering

Gait assessment in Parkinson's disease using waist-mounted smartphone

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Abstract

Parkinson's disease (PD) is the second neurodegenerative disorder, expressed by motor and non-motor symptoms. One of the primary motor symptoms is gait impairment, that occurs with episodic (freezing of gait and festination) and continuous disturbances, characterized by reduction of step length and gait velocity and increase in stride-to-stride variability, that with postural instability intensifies fall risk. Currently, to assess motor condition and gait impairment progress, subjective and qualitative clinical evaluations are used, which may have negative effects on diagnosis, follow-up and treatment. Therefore, gait analysis systems (laboratory-based or laboratory-free) have been developed, providing objective and additional information to neurologists. The aim of this study was to carry out the assessment of PD walking, by the construction of a systems capable to detect steps, identify initial (heel-strike) and final (toe-off) contacts of gait cycle and discriminate them between left and right, in order to prove the feasibility of a simple and low cost system for home monitoring of gait impairment in PD subjects. Data acquisition was executed with a waist-mounted smartphone, which includes several inertial sensors. A total number of 75 participants took part in the study, divided into three gropus, consisting of neurological healthy people and two composed of PD subjects, respectively. Data processing of acceleration signals was executed offline: wavelet transform has been applied to vertical and anteroposterior components, and autocorrelation function of vertical acceleration was computed. Spatio-temporal parameters and symmetry indices have been extracted and then correlated with subject age, disease duration, UPDRS items and H&Y scores. Significance tests between different groups have been also performed. Results were promising, with 95.3% of total steps detected and over 85% of the parameters values in physiological ranges. The high correlation coefficients and parameters trends are well in line with results found in literature. The alghorithm showed good sensitivity to gait variability, expressed by step and stride variability and symmetry indices. Given the promising results, togheter with ADL-like data aquisition, the proposed alghorithm could be used for remote monitoring of PD patients clinical (e.g. disease progression) and therapeutic (e.g. on/off state) condition, also in free-living environments.

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Chapter 1

Parkinson's disease

Parkinson's disease (PD) is a devastating neurodegenerative pathology related to age, with a multifactorial etiology. It owes its name to James Parkinson who wrote in 1817 a monograph entitled 'Essay on the Shaking Palsy'. He described with extreme details the apparent clinical signs of some patients in which an imbalance is created between the inhibitory and excitatory mechanisms, in favor of the latter. Excitatory (cholinergic) innervation prevails over inhibitory innervation, progressively causing a series of symptoms, such as resting tremor, hypertonia with rigidity, akinesia, postural instability, speech and writing disorders, and also anxiety-depressive symptoms. To date, no therapy has been found for PD, which is cured only with symptomatic treatments.

1.1 Pathology and pathogenesis

PD always show pathological hallmarks.The most important is the preferential, as massive and progressive, degeneration of dopaminergic nigrostriatal neurons, whose cell body is located at the level of the Substantia Nigra pars compacta (SNpc), while the projections mainly branch towards the putamen and partly into the caudate. The SNpc takes its name from the presence of neurons containing neuromelanine, a dark pigment consisting of dopamine polymers (DA) embedded in a glyco-lipid matrix. Macroscopically, the degeneration of these neurons results in the depigmentation of the SNpc (Fig.1.1) [20][11][18][1]. The ventrolateral cell groups (or

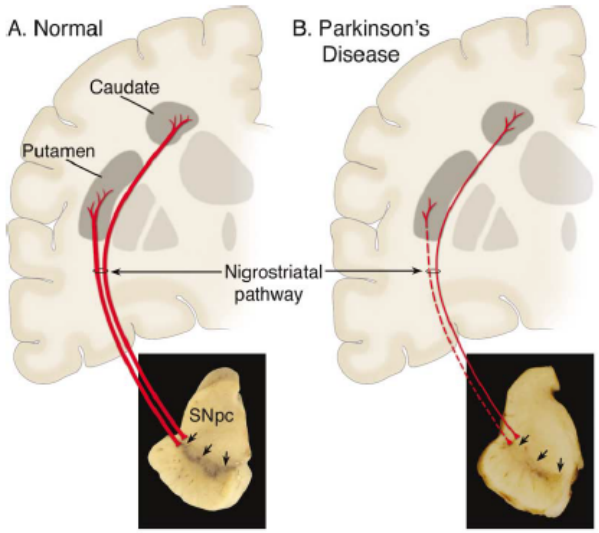

Figure 1.1: Neuropatholofy of Parkinson's disease. a)Schematic representation of the nigrostriatal (red) pathway with normal pigmentation of the SNpc. b)Nigrostriatal pathway (dashed red) in PD, with marked loss of dopaminergic neurons and depigmentation of SNpc.[20].

nigrostriatal pathway) are most vulnerable due to calcium transients, leading to cellular stress, homeostasis interruption, and death. Cell death is associated with the disruption of the cell membrane and the release of pro-aggregating nuclear factors that could trigger the α-synuclein aggregation, a small highly conserved presynaptic protein [5][6]. Loss of dopaminergic neurons in this area starts before the onset of disease motor symptoms, probably leading to the genesis of two of these, namely bradykinesia and rigidity, due to the corresponding decrease in dopamine [18][3]. At the onset of symptoms, about 60% of SNpc dopaminergic neurons have already been lost. However, neuronal loss in PD also occurs in many other brain regions [11][20].

Another hallmark is Lewy pahology, caused by aggregation of intracytoplasmatic abnormally folded proteins, in particular α-synuclein, parkin and ubiquitin. In a misfolded state, these proteins become insoluble and give rise to "Lewy bodies (LBs)" and "Lewy neurites", intracellular inclusions within the cell body and processes (mostly axonal) of neurons, respectively [11][5]. LBs have a diameter of about 15μm, and their accumulations can be caused by mutations and multiplication of SNCA, the gene encoding α-synuclein, by impairment of the ubiquitin-proteasome

system (UPS) and by corruption of the lysosomal autophagy system (LAS) [14], which are very important for intracellular proteolysis [4][18][7][30]. Initially, α-synuclein misfolds in a small number of cell, than gradually engages more brain region with disease progression [14].
In PD patients brain other types of protein aggregations than α-synuclein were also found. They synergise with Lewy pathology and contribute to the clinical expression of Parkinson's disease. Some of these are β-amyloid plaques and tau-containing neurofibrillary tangles, the protein inclusions typical of Alzheimer's disease [11], that seems to be a key factor for the cognitive decline in PD [19].
Oxidative stress is another important features of PD pathogenesis, which implicates the release of oxydoradicals, eliciting the aggregation of α-synuclein and UPS system failure [18][7]. Also mitochondrial dysfunction play a key role, leading to both reduced ATP production and accumulation of electrons that aggrave oxidative stress, with the final outcomes of apoptosis and cell death [18][14][7].
The last phenomen implicated with pathogenesis of PD is neuroinflammation, manifesting with an active inflammatory response in the brain, mediated primarily by resident astrocytes and microglia, producing cytokines that augment apoptosis, and promoting α-synuclein misfolding (Fig.1.2) [18][14][11].

1.2 Risk factors

Although the etiology of PD has not yet been fully clarified, the hypothesis of a multifactorial origin in which environmental and genetic components are involved is now accepted.
Several studies have shown that numerous factors can increase the risk of developing the disease, or even seem to decrease it. About environmental factors, pesticide exposure, prior head injury, rural living, β-blocker use, agricoltural occupation, well-water ingestion, middle-age obesity and lack of excercise could increase the risk. Also use of antypsychotics might enhance risk of developing PD, but additional studies are needed to confirm this associations. Instead, tobacco smoking, coffee drinking, non-steroidal anti-inflammatory drug use, calcium channel blocker use, and alcohol consumption seems to decrease it [11][19][4][3][7].
Regarding genetic factors, in about 95% of cases there is no correlation with

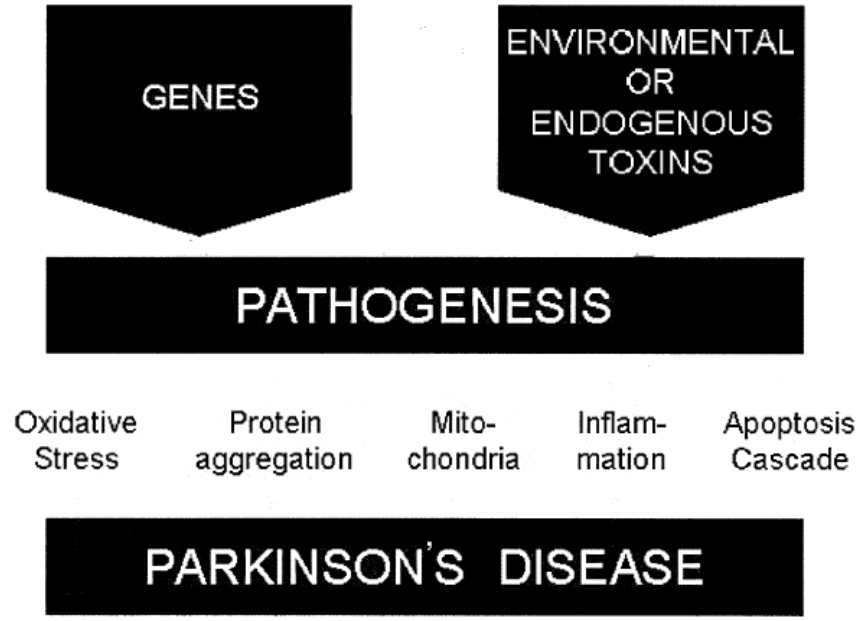

Figure 1.2: Diagram of the concept of the etiology and pathogenesis of Parkinson's disease, [18].

them, and PD is defined as 'idiopathic' or 'sporadic'. The remaining 5% is attributed to inherited genetic mutations and PD is called 'familial'. They are characterized by mutations, and the most important occurs in GBA, which encodes β-glucocerebrosidase. As already mentioned, SNCA mutation, that encodes α-synuclein protein, leads to its aggregation and is assocated with inherited Parkinson's disease. Also mutations in LRRK2 and parkin cause this type of PD, dominantly and recessively respectively, and mutations in PARK7 are related to early onset of the disease [11][15][11][19][14].
So, the risk of developing Parkinson's disease is clearly multifactorial, and a futher understanding of risk factors and their interactions is expected to have broad implications for the elucidation of pathogenic mechanism and individualisation of treatment [11].

1.3 Epidemiology

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer. It is mainly an illness of later life, so is more common in developed

countries where people live longer [7]. The estimated prevalence of PD in industrialized countries is 0.3% in the general population, 1.0% in people older than 60 years, and 3.0% in those aged 80 years and older, with incidence rates of 8 to 18 per 100000 person-years [8]. In Europe the prevalence at age between 85 and 89 has been reported as 3.5% [9] and in Italy the estimated average prevalence is 157,7/100000 [10]. Both incidence and prevalence increase nearly exponentially with advancing age [11]. So with an aging population and rising life expectancy worldwide, the number of people with PD is expected to increase by more than 50% by 2030 [12]. Moreover, the incidence seems to vary within subgroups definded by race and ethnicity. In particular it seems be greater in Hispanics, followed by non-Hispanic Whites, Asians and Blacks [13]. Regarding the patient's gender, in most population PD incidence and prevalence are 1.5 to 2.0 times higher in men than in women [14](Fig.1.3), and age at onset is 2.1 years later in women than in men [8]. Clinical signs emerge in a wide age range, including the young, even if it occurs infrequently under 40 years of age [15]. The median age of onset is 60 years; the mean duration of the disease from diagnosis to death is 15 years, although patients can live for decades with PD [8].

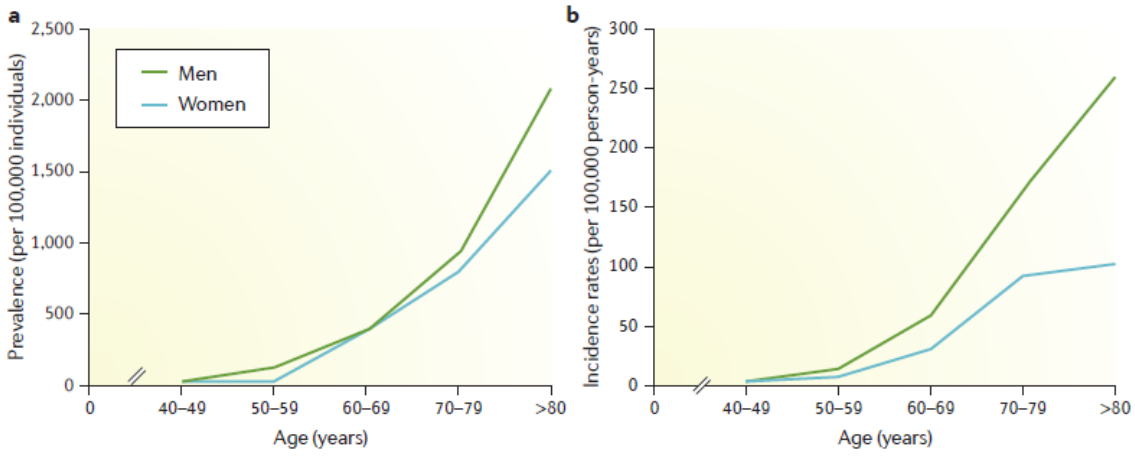

Figure 1.3: Incidence and prevalence of Parkinson's disease. a)Prevalence of Parkinson's disease in men and women per 100000 individuals. b) Incidence rate of Parkinson's disease per 100000 person-years,[14].

1.4 Diagnosis

The evaluation of PD is difficult because the expression of the disorder varies from patient to patient (intra-patient variability), and is also significantly influenced by emotional state, response to drugs, and other variables [17]. Hovewer, the diagnosis of PD is still largely a clinical one, as there is no definitive test able to confirm the diagnosis during life [15][16]. From a practical perspective, the first step for the diagnosis of PD is a careful analysis of patient's history. In particular, in-depth investigations must be carried out, trying to define emerged symptoms and their sequence (such as premotor symptoms), to analyze if patient is exposed to environmental risk factors, to record past and present medical impairments and to examine possible neurological disorders in other family members [15]. At this point, careful clinical examination follows. The disease is clinically defined by presence of bradykinesia and at least one additional cardinal motor feature (rigidity and/or rest tremor), additional supporting and exclusionary criteria, and response to levodopa. The latter is very helpful, indicating presynaptic dopamine deficiency with intact postsynaptic dopamine receptors, features typical of PD [18]. The clinical findings are usually asymmetrical and remain the same throughout the disease, with gait and balance affected later [15][18][4][14][19][16][11].
There are no practical diagnostic laboratory tests for PD, and in most cases, the diagnosis is made only with these clinical examinations, but in specific circumstances, other ancillary investigations are needed. Imaging techniques are used to differentiate Parkinson's disease with motor symptoms from disorders without presynaptic dopaminergic terminal deficiency [11]. Positron emission tomography (PET) with fluorodopa (FDOPA) is one of the available technologies, that measures levodopa uptake into dopamine nerve terminals, but the costs and limited accessibility make it difficult to use [15][18]. Dopamine transporter (DAT) imaging with single photon emission computed tomografy (SPECT) is also a very useful approach, because it is sensitive for the detection of presynaptic dopaminergic neuron degeneration in the striatum [11][15]. Brain structural imaging, either by computed tomography (CT) or magnetic resonance imaging (MRI) can be performed, where the latter is preferred [15]. Standard MRI has a marginal role in PD diagnosis, but high and ultra-high-field MRI combined with advanced techniques are used to

enhance diagnostic accuracy for Parkinson's disease versus other types of degenerative parkinsonism [11][14].
Genetic testing is not part of the routine diagnostic process, except in patients in whom there is a specific suspicion for a possible genetic cause (for example suggestive family history and early onset) [14][11]. Although several studies have assessed α-synuclein and other proteins concentrations in cerebrospinal fluid (CSF), there is currently no clinically useful CSF-based diagnostic test for PD. This is also true for blood biomarkers, although associations of different serum or plasma parameters with disease progression have been described [14][11].

1.5 Clinical Features

The clinical expressions of Parkinson's disease can be divided into two categories: motor symptoms and non-motor symptoms.
The onset of motor symptoms is usually unilateral and asymmetry persists throughout the disease, even in advanced stage. From this standpoint, PD is characterized by four cardinal features [14][7]:

- *Bradykinesia*. It is the most characteristic clinical feature of PD, and it refers to slowness of movement. It may be manifested by a delay in the initiation of a movement and by slowness of its execution. Other aspects include a delay in arresting movement, amplitude and speed decrementing of repetitive movements, and inability to execute simultaneos or sequential actions. In addition to whole body slowness and impairment of fine motor movement, other manifestations of bradykinesia involve drooling due to impaired swallowing of saliva, monotonous dysarthria, loss of facial expression (hypomimia), reduced arm swing when walking (loss of automatic movement), micrographia, reduced amplitude of voice and decreased stride length during walking. Its clinical assessment is carried out by globally observing the patient's spontaneous movements while sitting or walking, and asking him to perform some repetitive movements in a wide and fast way, such as opening and closing the hand, tapping the foot on the ground. During these tasks the examiner looks for a possible decrease or loss in the amplitude.[15][16][17][18][20][7].

- *Rest tremor*, that is the most common and easily recognised symptom of PD.

It is defined as a rythmic oscillatory involuntary movement that comes about when the affected body part is relaxed. It is unilateral, but over time it can affect both sides. Characteristically, rest tremor disappears or decreases its intensity as soon as a finalized movement is performed to execute a certain actions, and during sleep [15][16]. Commonly, this motor symptom manifests as a resting "pill-rolling" hand tremor, that is a supination-pronation tremor which might be evident when the patient is asked to do fine finger movements with the other hand or to walk. Occasionally it involves legs, jaw and tongue, whereas head tremor is not typical of PD [9][15][19]. It occurs at a frequency between 4 and 6 Hz, and can be intermittent at the beginning, being present only in stressful and anxious situations, but with the progression of the disease it tends to be present most of the time and worsen in amplitude with stress or excitement [18][7]. In clinical practice, tremor is observed when the limb muscles are relaxed, elicited by patient's focus on a particular mental task, such as countdown with eyes closed [15].

- *Rigidity.* It indicates an increase in muscle tone at rest or during movement, and is characterized by an increase in resistance during passive mobilization of an extremity, independent of direction and velocity of movement [48]. Rigidity can affect limbs, neck and trunk and appears in several daily activities, like dressing, writing and turning in bed. Typically, during examination of a segment, it is increased by voluntary movement of other body parts (Froment's maneuver) [15][16][7].

- *Postural and gait impairment.* They include postural instability and parkinsonian gait. Postural instability occurs mainly in advanced stages of PD and is caused by a reduction in straightening reflexes, so that subject is not able to spontaneously correct imbalances or to maintain an upright posture. Therefore the patient is more subject to falls (often resulting in hip fractures) which can occur in all directions even if more frequently forward. As the disease progresses, the subject assumes a stooped posture, in which the trunk is bent forward, arms are kept close to trunk and bent, as knees. In the later stages it is also possible to appreciate permanent curvature of neck and back. Clinically, it is evaluated by the pull test: the examiner stands behind the patient and applies a pull in order to assess the ability to regain balance.

Parkinsonian gait is slow and hypokinetic, occurs on a narrow base, and is characterized by short shuffling steps and reduced step length, which gives the observer the impression that the patient is chasing own center of gravity. Another gait disturbance than shuffling is motor blocking, that is called freezing of gait[9][15][17].

There are many other motor findings in PD, most of which are directly related to one of cardinal signs [17].
Although the motor symptoms of PD dominate the clinical picture, parkinsonian subjects also present several non-motor symptoms (Fig.1.4). These include sensory complaints, cognitive impairment, psychiatric symptoms, sleep disorders, autonomic dysfunction, pain and fatigue [11][16][18]. Frequently, some of these can anticipate the onset of classic motor symptoms by years or even decades [15][14][7], such as impaired olfaction, constipation, depression, excessive daytime sleepiness (EDS), and rapid eye movement sleep behavior disorder (RBD)(Fig.1.5). This period is called premotor or prodromal phase [11], and its features vary from patient to patient [9]. With the disease progression, worsening of motor features occurs, and there is an emergence of complications related to long-term symptomatic treatment, including motor and non-motor fluctuations, dyskinesia (abnormal involuntary movement) and psychosis [11]. Severity of bradykinesia, rigidity, gait and balance progress similarly, while tremor severity appears to be rather stable over time, possibly indicating different underlying pathophysiological processes [7].

1.5.1 A focus on gait impairment

Gait disorders in PD is caused by imbalance of cortical and subcortical activities with inhibition of the primary motor cortex, putamen, and cerebellum, which are replaced by overactivation of non-typical brain areas. Some factors that contribute to damage gait are a decrease in the senses of proprioception, discrimination, and position.
Gait impairments can be divided into two types: continuous and episodic. *Episodic disturbances* have a random, intermittent and unpredictable nature. These include freezing of gait (FOG), festination gait (FSG), and start hesitation. FOG occurs most often in PD patient who are in an advanced state of the disease. It is a form of akinesia (loss of movement) and consists of a sudden and transient inability

Neuropsychiatric features
Apathy
Anxiety, panic attacks
Mood disorders, especially depression
Hallucinations, illusions, delusions
Cognitive deterioration, ranging from mild impairment to dementia
Dysautonomia
Orthostatic hypotension
Constipation
Urinary dysfunction (urgency, retention)
Sexual dysfunction
Excessive sweating
Seborrhea
Sialorrhea (i.e., drooling, also attributable to decreased swallowing movements)
Sleep disorders
Insomnia
REM behavior disorder
Restless legs syndrome
Periodic limb movements in sleep
Excessive daytime sleepiness
Sensory dysfunction
Hyposmia (i.e., loss of sense of smell)
Decreased visual contrast and color discrimination
Decreased visual motion perception
Abnormal sensations, such as paresthesias (i.e., tingling)
Pain
Fatigue

Figure 1.4: Non-motor features of Parkinson's disease, [15].

to start or continue a movement. Patients report the feeling that their feet are glued to the ground, expecially when turning or walking through narrow passages, crossing streets or approaching a destination. FOG episodes can be provoked by asking the subject to turn around, giving rise to 'turning hesitation'. FSG is an intermittent episode of few seconds in which patients bend the trunk forward and have an uncontrollated propulsion, where steps become progressively smaller and more rapid. In this case, they report the feeling that were pushed from behind.
Continuous disturbances, instead, refer to the alterations of walking pattern that are evident even after a first analysis, persist (and worsen) during the disease progression and are almost always evident. These include slow ambulation (partly

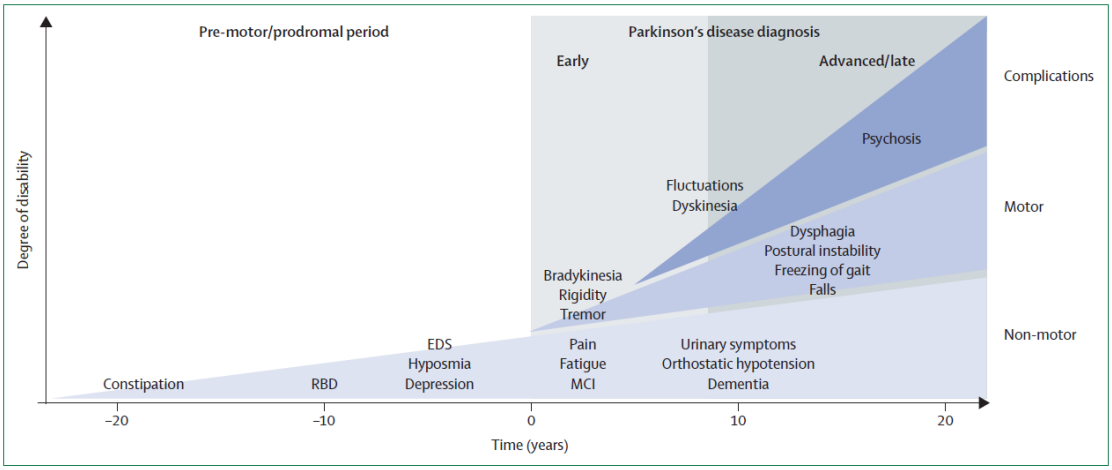

Figure 1.5: Clinical symtoms and time course of Parkinson's disease progression,[11].

manifestation of bradykinesia), absence or reduction of arm swing, longer double support, and impaired postural control. The subject also has a loss in the ability to generate sufficient stride length, causing a reduction in gait velocity and an increased time with the feet on the ground. Moreover, higher stride-to-stride variability is also a characteristic feature of gait in PD[34][15][17][31][33][32].
From a clinical standpoint, it is possible to divide gait disorders and its progression in four stages [31]:

- Stage 1: Initial gait disturbances. In this phase patient starts to manifest some disturbances, like decreased gait speed, decreased arm swing, bradikynesia, shortened steps and increased stride-to-stride variability. However, they do not predominantly affect patient's quality of life [31].

- Stage 2: Mild to moderate functional gait disturbances. It is characterized by shuffling and hypokinetic gait; steps are shorter and lower limb decreases the muscular force applied to employ the foot push-off or hip pull-up. Impairments begin to be more present and mainly disturb the patient. Flexed joints and stooped trunk are also manifested [31].

- Stage 3: Significant functional gait disturbances. In addition to events already mentioned in the previous phases, at this stage episodic walking disorders take place, ie FOG and FSG. Both of them occur in an uncontrolled and

unpredictable way, and have a temporal duration of seconds, rarely exceeding 30s.

- Stage 4: Appearance of falls on the background of other gait disturbances. Both episodic and continuous disturbances work together to intensify the risk of falls in PD. Indeed, falls are one of the main consequences of motor impairments, and with disease progression they become more present and debilitating. Many of these result from sudden changes in posture, in particular turning movements of the trunk, rising from chair or bed, or when trying to perform more than one activity simultaneously with walking or balancing. About 50% of patients report recurrent falls during a year (Fig.1.6), and these could cause injuries, hip fractures, fear of falling, a restriction in daily activities, loss of independence, increased mortality. Patients do not have capacity to produce adequate toe lift and foot pitch, causing greater energy expenditure. In addition, in this advanced stage of PD subjects tend to have bent knees when standing and walking on tiptoe [31][32][34].

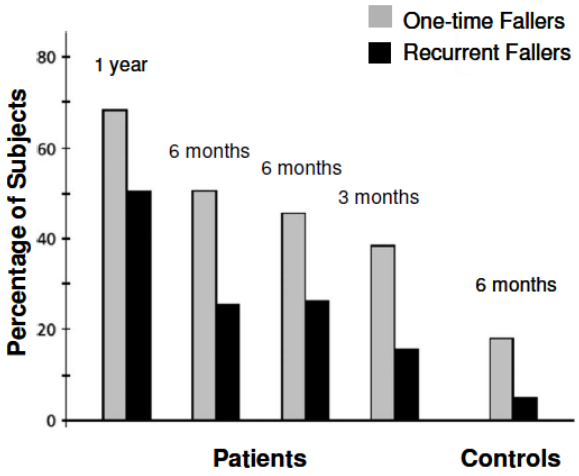

Figure 1.6: Fall rates in PD compared to age-matched controls in different duration of follow-up,[34].

1.6 Rating Scale

In assessing the motor and non-motor symptoms, signs and disabilities of PD, rating scale are used to quantify the impairment and assign a value to a particular features or symptom in question [17][16][2]. Motor scales are the best-known and most widely used, but non-motor symptom scales are equally important. Combined with a motor scale, these give a more balanced picture of how a person is affected by disease [2].

1.6.1 Hoehn-Yahr scale

A method to staging PD is Hoehn-Yahr scale (H&Y). This (Tab.1.1) is simple and of easy application, and used to compare groups of patient with PD and to provide gross assessment of disease progression, raging from stage 0 to stage 5. It does not give precise information about the patient's motor state, nor does it take into account non-motor symptoms. Furthermore it is not useful for monitoring individual responses of a subject to therapy [17][16].

Table 1.1: Hoehn-Yahr Scale.

Point	Observation
0	Asymptomatic
1	Unilateral involvement only
2	Bilateral involvement without impairment of balance
3	Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test
4	Severe disability; still able to walk or stand unassisted
5	Wheelchair bound or bedridden unless aided

1.6.2 UPDRS

The Unified Parkinson's Disease Rating Scale (UPDRS) is used to track the progression of disease, and it is the most well established scale for assessing disability and impairment[17][16][11]. It is made up of four part:

- Part I: Evaluation of mental activity, behaviour and mood.
- Part II: Self-evaluation of activities of daily living.
- Part III: Evaluation of motor function.
- Part IV: Evaluation of complications of therapy.

Each part involves several items to appointing a value to a particular features. The UPDRS testing is carried out by a healthcare professional. Points assigned to every item are based on the person's response, as well as observation and physical examination, and range from 0 to 4. The total cumulative score ranges from 0 (no disability) to 199 (total disability). The scale was introduced in 1987 and has since been updated by specialists from the Movement Disorder Society (MDS) to include new assessments of non-motor symptoms [2]. The UPDRS is often used with H&Y scale, and the Schwab and England Activities of Daily Living (ADL) Scale. Relating to Part III of UPDRS scale, items more inherent to this document are:

- 'Leg Agility (3.8)', Tab.1.2.
- 'Arising from Chair (3.9)', Tab.1.3.
- 'Gait (3.10)', Tab.1.4.
- 'Freezing of gait (3.11)', Tab.1.5.
- 'Postural Stability (3.12)', Tab.1.6.
- 'Posture (3.13)', Tab.1.7.

1.6.3 Other scales

The Schwab and England ADL Scale is a means of measuring ability to perform daily activities in terms of speed and independence through a percentage figure. High percentages indicate a high level of independence while low percentages indicate dependence [2].
There are also many scales, such as the Parkinson's Disease Questionnaire-39 (PDQ-39) and the Parkinson's Disease Quality of Life Questionnaire (PDQL), that attempt to assess the overall health related quality of life[17].

Table 1.2: Leg Agility, item 3.8

Initially it consists in placing the patient's feet on the ground in a comfortable position, and then ask him to beat them 10 times, with the greatest amplitude and as quickly as possible.	
Point	Observation
0: Normal	No problems.
1: Slight	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task.
2: Mild	Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task.
3: Moderate	Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap.
4: Severe	Cannot or can only barely perform the task because of slowing, interruptions or decrements.

Table 1.3: Arising from chair, item 3.9

It consists in having the patient sit on a chair, with the back resting well on the seatback. He is asked to cross his arms over his chest and stand up.	
Point	Observation
0: Normal	No problems. Able to arise quickly without hesitation.
1: Slight	Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair.
2: Mild	Pushes self up from arms of chair without difficulty.
3: Moderate	Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help.
4: Severe	Unable to arise without help.

Table 1.4: Gait, item 3.10

The patient is asked to walk at least 10 meters to evaluate both the right and the left side. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing.	
Point	Observation
0: Normal	No problems.
1: Slight	Independent walking with minor gait impairment.
2: Mild	Independent walking but with substantial gait impairment.
3: Moderate	Requires an assistance device for safe walking (walking stick, walker) but not a person.
4: Severe	Cannot walk at all or only with another person,Äôs assistance.

Table 1.5: Freezing of gait, item 3.11

The presence of fog episodes during the walk, the possible start hesitation and the interruptions of the movements (expecially when turning and reaching the end of the task) is evaluated.	
Point	Observation
0: Normal	No freezing.
1: Slight	Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking.
2: Mild	Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking.
3: Moderate	Freezes once during straight walking.
4: Severe	Freezes multiple times during straight walking.

1.7 Treatment

To date, PD is an incurable progressive disease, and there is no available treatment that stops its progression [9][19]. Therefore, the management deals with reducing and alleviating motor and non-motor symptoms. So, it is a symptomatic treatment.

Table 1.6: Postural Stability, item 3.12

It consists of a retropulsion test, called a pull-test, that takes place while the patient is in an upright posture, with open eyes and feet, and applying a rapid traction force on his shoulders so that the patient must take at least one step back to recover his posture.	
Point	Observation
0: Normal	No problems: Recovers with one or two steps.
1: Slight	3-5 steps, but subject recovers unaided.
2: Mild	More than 5 steps, but subject recovers unaided.
3: Moderate	Stands safely, but with absence of postural response; falls if not caught by examiner.
4: Severe	Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.

Table 1.7: Posture, item 3.13

Posture and postural reflexes are evaluated while the patient is standing after getting up from a chair and while walking.	
Point	Observation
0: Normal	No problems.
1: Slight	Not quite erect, but posture could be normal for older person.
2: Mild	Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so.
3: Moderate	Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient.
4: Severe	Flexion, scoliosis or leaning with extreme abnormality of posture.

Several therapies are adopted, which can be divided into three groups:

- *Pharmacological treatment.* It is chiefly a dopamine (DA) replacement therapy. DA is a neurotransmitter of neurons affected during PD. So, deficency of dopamine result in alteration at the downstream nuclei, that can be restored with this treatment. A variety of dopaminergic agents are available. The most powerful and effective drug is levodopa (L-DOPA), a DA precursor introduced

in therapy at the end of the 60s. It is usually administered with two inhibitors: a decarboxylase inhibitor to prevent 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 [18]. However, after some years, the use of L-DOPA is complicated by the evolution of shorter duration of response to individaul doses (wearing off symptoms), alternative phases with good and poor response to medication (on-off symptoms), drug-induced involuntary movement of the head, trunk or limbs (dyskinesias), and psychosis [14] [18][19][15][9][11].

A very advantageous approach to maintain constant levodopa plasma concentrations is the administration of a levodopa-carbidopa concentrate in the duodenum (known as Duodopa) through a percutaneous endogastric tube connected to a portable infusion pump. This pump allows adjustment of the drug dose according to the patient's condition. This approach has partly reduced the dyskinesias typical of the advanced stages of PD. Furthermore, even a subcutaneous infusion of apomorphine (a powerful antagonist of DA) leads to an improvement in motor fluctuations.

Moreover, in the last few months, a new drug has been marketed: Ongentys, also known as Opicapone. This is an inhibitor of COMT enzymes that degrade L-DOPA at the peripheral level. Therefore it allows to increase the amount of absorbed L-DOPA, reducing motor fluctuations at the end of the dose. So, it is administered only to patients already treated with L-DOPA.

Other drugs used in treating PD symptoms are dopamine agonists. They have good efficacy, and compared to L-DOPA are less likely to produce motor complications, but are more likely to cause hallucinations, confusion and psychosis, and provide less symptomatic benefit. So, thery are not recommended to elderly over age of 70 years [18][15][14]. Subjects with PD also use dopamine releaser, like amantadine, that relieves symtoms (also dyskinesia) but produces mental effects, and monoamine oxidase type B (MAO-B) inhibitors [18][14]. The efficacy of each of these drugs, as well as their adverse-event, need to be fully explained to the patient when treatment options are being considered, and seems to be also influenzed by placebo response [19].

There are also nondopaminergic agents that are useful to treat L-DOPA resistant ("non-dopaminergic") features (treatment-resistant tremor, freezing of

gait, postural instability, falls, swallowing and speech disturances), but also non-motor features, like cognitive and psychotic defects [18][14].

- *Surgical treatment*. It is characterized by stereotaxic deep brain stimulation (DBS), that can be unilateral and bilater. It is made up of a neurostimulator, that is placed subcutaneously in the anterior and superior region of the thorax, and an electrode positioned in the brain. Once the system is in loco, electrical impulses sent from the generator into the brain reduce abnormal electrical signals and alleviate PD motor symptoms. It is used when patient have advanced PD with an excellent L-DOPA response but also motor complications due to long-term medical treatment. The average time to surgical treatment is about after 10-13 years after diagnosis of PD, and location needs to be individualized for each patient. However, treatment of subthalamic nucleus (STN) reduce bradykinesia and levodopa dosage, and therefore dyskinesia severity [18] [15][9][11]. It can also alleviate gait impairment and postural instability, improving asymmetry of gait and joints range of motion, and increasing step length and velocity [31]. Moreover, targeted gene therapy and cell transplantation are also included in this group [11].

- *Exercise-based treatment*, which seem to improve symptoms that do not respond to pharmacological and surgical therapies, like mobility, postural control and balance. This consist of physical therapy with cueing to improve gait, excercise to improve balance, training to build up muscle power and increase joint mobility [19][14].

Chapter 2

Gait Analysis

2.1 Gait Cycle

Walking can be defined as "a method of locomotion involving the use of the two legs, alternatly, to provide both support and propulsion". Formally, walking uses a ripetitious sequence of limb motion to move the body forward while simultaneosuly maintaing stance stability [21].
Human walking is identified by gait cycle cyclical sequence. Gait cycle (GC) is characterized by so-called gait events, that are defined on the basis of feet contact with the ground. They are:

- Heel Strike (HS): the impact of the heel on the ground, ie represents the beginning of load phase, also referred as initial contact (IC). However, for a pathological gait it is possible that either the toe, side of a foot or even the whole foot first touches the ground rather than heel [44].

- Toe-Strike (TS): the impact of the toe on the ground and it represents the end of load phase.

- Heel-Off (HO): the detachment of the heel from the ground; it starts the push phase.

- Toe-Off (TO): the detachment of the toe from the ground; it concludes the push phase, also referred as final contact (FC).

GC is the time interval between two successive and repetitive events of ipsilateral foot (on the same side of the body). It is considered to begin from the contact of one foot with ground (IC) and to finish with next same foot contact. So, gait cycle consists of two steps: left and right. The step begins with the contact of ipsilateral foot and ends with that of contralateral (other side of the body) foot. The sequence of the steps (left-right or right-left) depends on the person's first step.
It is divided in two phases: stance phase and swing phase (Fig.2.1), that are defined by gait events. The stance indicates the period during which the foot of considered lower limb lies on the ground, so begins with the heel-strike (IC) and ends with the toe-off (FC) . The swing, on the contrary, refers to the period in which foot is in the air for the limb advancement, begins with TO and ends with a new heel-strike. Usually, during normal walking, their physiological values are about 60% and 40% of GC, for stance phase and swing phase respectively. However, these vary according to walking speed: if velocity increases, stance becomes smaller and the swing increases [47]. Moreover, GC can be divided in two other phases: single support and double support. The first occurs when leg is in swing phase and the other is in stance, therefore body weight is supported by a single limb. It starts with toe-off of the contralateral foot and ends with a heel strike of the same. The second takes place when both limbs rest on the ground, begins with contralateral limb heel strike and finishs with the toe off of the limb in question. Physiologically, a healthy walking has a single support around 80% and double support around 20% of GC.

2.2 Gait Parameters

The detection of gait events mentioned above allows to obtain several spatio-temporal parameters, that produce a quantitative description of gait. Therefore they reflect the ability of subject and provide information about movement pattern changes. The parameters of greatest relevance with this document are listed below.

- Temporal Parameters
  - Stride Time [s], time between two consecutive HS of the same foot. For healthy person it is on average about 1.03s [44].
  - Stride Frequency [Hz], considered as the reciprocal of stride time.

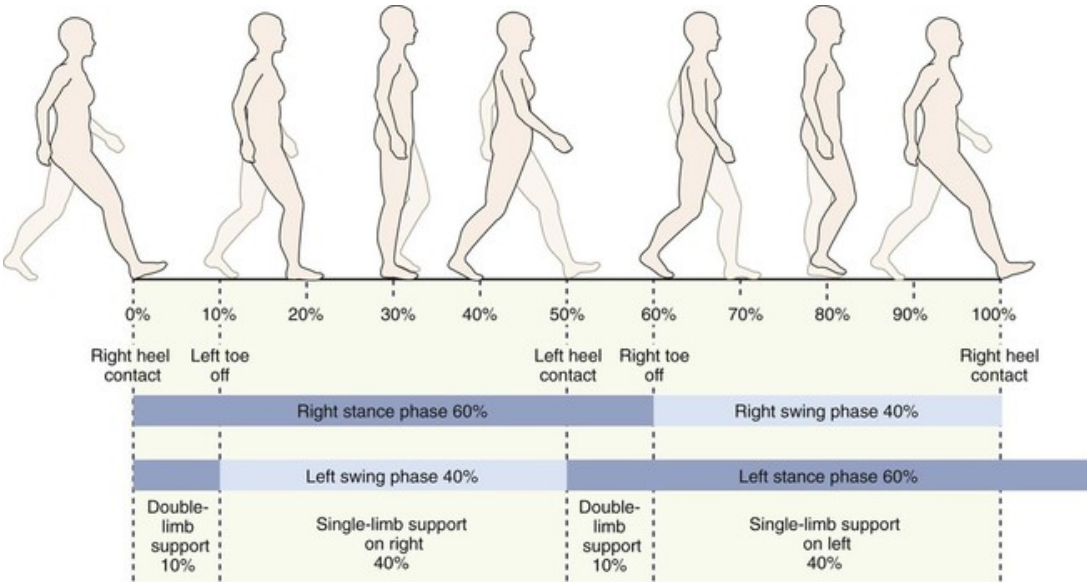

Figure 2.1: Gait cycle phases, [22].

  - Step Time [s], time between HS of ispilateral foot and HS of controlateral foot. Is considered as half of stride time.
  - Step Frequency [Hz], considered as the reciprocal of step time.
  - Stance Time [s], time between HS and TO of the same foot.
  - Stance Duration [%GC], stance time as percentage of the gait cycle.
  - Swing Time [s], time between TO and HS of the same foot.
  - Swing Duration [%GC], swing time as percentage of the gait cycle.
  - Double Support Time [s], time between HS of one foot and TO of the controlateral.
  - Double Support Duration [%GC], double support time as percentage of gait cycle.
  - Single Support Time [s], time between TO of foot and HS of the controlateral.
  - Single Support Duration [%GC], single support time as percentage of gait cycle.

- Spatial Parameters

  - Step Length [m], distance between HS of ispilateral foot and HS of controlateral foot. It is the displacement occuring during step time.

- Spatio-Temporal Parameters

  - Gait Velocity [m/s], velocity during gait cycle. It is the average displacement in unit time.
  - Cadence [N.step/min], measured as the number of steps taken in certain time, usually as the number of steps per minute. It is inversely proportional to time cycle and related to leg length.

2.3 Gait analysis

Gait analysis is commonly referred to the quantitative description of all mechanical aspects of walking [56]. It consists of gait parameters calculation and their evaluation. It can have several purposes. Certainly, the most common applications are clinical, sport and rehabilitation. Depending on area of interest, it takes into account a greater or lesser number of parameters. In particular, clinical application is that in which the greatest number of parameters are calculated to assess the degree of disease or its progress. Gait analysis can be classified into two groups: laboratory-based and laboratory-free. The two categories are discussed below.

2.3.1 Laboratory-based gait analyis

A standard gait laboratory, usually located in a hospital or a research center, frequently have four systems for evaluating gait:

1. A motion-capture system, which digitally tracks the patient's movement and captures the three-dimensional movements of the body. It is made up of synchronized cameras, marker placed over the skin of one or more anatomical segments, and computer software that acquires and processes marker position during walking. In particular, it allows to reconstruct the marker 3D-trajectory from 2D images offered by cameras. This system allows to estimate gait spatio-temporal parameters, but its potential goes beyond this aspect, since they are thought for 3D kinematics measurements. [25][27].

2. A video system, which records images of the patient while walking, and provide a degree of quality control of the motion-capture data. It permits to view the patient movement from different and multiple angles simultaneously, leading to a complete understanding of its pattern. Furthermore, from this system is possible to obtain basic gait parameters, like stride length, speed and cadence.

3. Force platform and pressure platform, where gait is measured by pressure or force sensors and moment transducers when the subject walks on them. The first measures force trasmitted to the floor when walking (Ground Reaction Force GRF), the second find the evolution of foot pressure on the floor in real time, that may reach up to 120%-150% of the patient's body weight in his maximum expression, when the heel touches the floor (HS). If used individually, these devices are basic, and can be used to obtain a general idea of gait problems a patient may have, but when integrated with the motion-capture system they allow to assess the mechanism of movement.

4. An EMG system, which is used to record muscle activity during gait, a process referred to as 'dynamic EMG'. If gait is altered, then also the muscular activity during the same will be altered. EMG is a very useful non-invasive technique used to understand the changes in gait function and gait phase detection [28].

Some examples of optoelectronic systems used in gait analysis are Vicon, Qualisys Motion Analysis or OptoTrack. In particular, Vicon system provides a clinically validated solution in any gait analysis or rehabilitation environment, and can be used to measure or give real-time feedback on the movements of the whole body or a single part, including hands, face, feet and spine, across different applications, like stroke rehabilitation, posture analysis, and balance studies. For these reasons, it is the most commonly and widely choosen (Fig.2.2) [45][53]. To date, analysis with these systems is widely accepted as 'gold standard' for gait analysis, because it is very good in measuring position, and produces well-quantified and accurate results over short distances. On the other hans, it requires that markers always must be seen by cameras, therefore needing the right environmental conditions; presents very long set-up times to position markers adequately, leeding to expensive and cumbersome equipment attached to the body; and has a limitated workspace for the patient's movement, so only a narrow number of consecutive strides can be measured [23][25][26][27][55].

Figure 2.2: Example of marker positioning with Vicon system, [45].

2.3.2 Laboratory-free gait analysis

This type of analysis does not require the use of bulky or permanently localized devices in a laboratory, thus allowing to detect and quantify gait in any place and at any time. It is carried out using different devices:

1. Inertial measurement unit (IMU), that aggregates different type of MEMS sensors, such as accelerometers, gyroscopes and magnetometers, individually or combined. It measures and reports on object's velocity, acceleration, orientation, and gravitational forces. Accelerometer is the most common type of inertial sensor, and its ability to measure changes along its sensitive axis makes it suitable for measuring motion status in human gait; instead gyroscope is an angular rate sensor that measure the angular velocity of the feet or legs while walking. IMU can be located on several parts of the body, such as feet, knees, thighs or waist, individually or combined, so they are weareable system (WS). The sufficient number of IMU to be used to obtain a relevant and complete

analysis is under investigation, but certainly the complexity of the measurements is linked to the number of sensors worn by the subject. Moreover, the miniaturization of IMU allows the possibility of integrating them on instrumented insoles for gait analysis. They are ultra-small size, portable, low cost and pratical useful for longer and natural movements. Furthermore, they do not require a specific laboratory, but they can be used everywhere, and have a theorically unlimited workspace. So, IMU can be successfully used for accurate, non-invasive, and ambulatory motion tracking. 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 [25][24][26][28][23][55]. However, the measurements of inertial systems can be compared to optoelectronic systems (like Vicon), which to date represent the gold standard, to assess validity, reliability and accuracy [59][55], Fig.2.3.

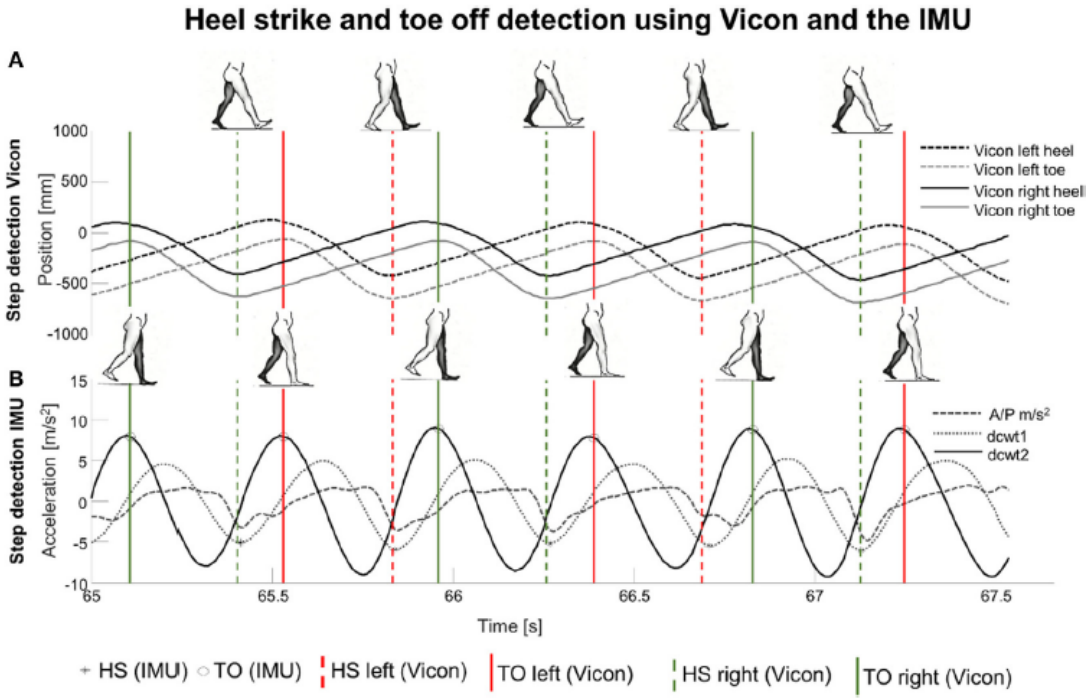

Figure 2.3: Example of IMU measurements compared to Vicon system, representing heel strike and toe off detection, [58].

2. Smartphone, for the purpose of data collection in daily life. This use is becoming increasingly popular thanks to its easy transport and rich sensing abilities. It is equipped with accelerometers, gyroscopes and magnetometers that allow it to be employed in an ever increasing number of fields of application, such as tracking and positioning, activity recognition, health monitoring, telemedicine and telerehabilitation. It is a cheaper and user-friendly alternative to IMUs [49][26][50], which can be used by practically everyone. Indeed, nowadays, any subject belonging to all age groups has one.

3. Goniometers, ie sensors used to measure the angles of human joints, as anklees, knees, hips, ecc. They can be various (strain gauge-based, inductive or mechanical), and are usually fitted in intrumented shoes to measures ankle to foot angles [28][24]. Also force-plate sensors can be embedded into footwear for this type of analysis [25].

A complete view on the advantages and disadvantages of both categories is shown in Tab.2.1.

2.4 Gait analysis in Parkinson's disease

Since it is necessary to evaluate the motor symptoms of PD and their progress during disease, many clinical assessments have been developed, where the most common include the Timed up and Go test and the postural instability and gait disability score derived from the UPDRS. These assessments are easy to accomplish in clinical setting, because they require little equipment, and also provide immediate outcomes that can be reported to the patient. However, these tests show poor sensitivity and specificity for identifying prospective fallers in PD population, and may not be sufficiently sensitive to detect changes in balance and walking in people who have mild to moderate disease severity, like motor fluctuations, FOG, falls [52]. This happens because they are subjective and qualitative measurements, which have a negative effect on the diagnosis, follow-up and treatment of pathology [23][24][60]. They only offer biased evaluations taken over short periods of time, do not take into account the long-term patient mobility, but only indicate the condition at the moment. Moreover, the assessment is dependent on clinician's expertise and individual training [27]. So, it would be helpful for clinicians to be reliably

Table 2.1: Comparison between advantages and disadvantages of laboratory-based and free systems.

Type of system	Advantages	Disadvantages
Laboratory-based	• Repeatability and less external factor interference due to controlled environment • Widely accepted as 'gold standard' • Good at measuring position • Well-quantified and accurate results over short distances	• Long set-up time • Requires adequate environmental conditions • Expensive and cumbersome equipment • Limited workspace • Limited number of measured stride • Impossible monitoring natural movement during real life • Poor at measuring acceleration
Laboratory-free	• Low cost • Useful to monitor longer and natural movement • Employment in any place, not needing controlled enviroment • Possibility of being wireless that enhace usability • Promotes autonomy and active role of patient • Unlimited workspace • Non invasive • Good at measuring acceleration (IMU and smartphone)	• Power consumption restrictions due to limited battery duration • Complex alghoritms needed to estimate parameters (IMU and smartphone) • Susceptibility to noise and interference of external factors • Amplification of measurement error during integration of acceleration signal • Poor at computing precise position, due to baseline drift

and objectivelly informed about several aspects, such as severity of gait disorder, progression of gait disability, therapeutic effects of applied interventions, in order to quantify the real degree of the disease, and based on it, to optimize treatment, and help to reduce different rating strategies [52][25][27][28].

Therefore, several approaches are utilized to overcome these problems, and to improve the objectivity of measures, in order to track symptoms progression and evaluate patient risks, resulting in more efficient measurement and providing specialists with a large amount of reliable information. In particular, gait analysis allows to detect changes in gait that produce key information about patient's quality of life, reducing the error margin caused by subjective techniques [23][24].
A large number of useful gait parameters can be evaluated by both gait categories previous discussed, to improve the sensitivity, accuracy, reproducibility, and feasibility of measurements about changes in motor behaviours [61][27][28]. Laboratory-based systems surely represent the gold standard in gait analysis, but considering the clinical application to Parkinson's disease, they exhibit several problems. In fact, a disadvantage is that the monitoring process is carried out in a controlled enviroment in which the patient feels safe, but many subjects experience the most severe episodes of impaired gait, FSG and FOG (that present episodic and unpredictable nature) while at home [25]. Moreover, their limited workspace does not allow the acquisition of a lot information. So, for these reasons, they result partly inadequate for this application.
Instead, ambulatory gait analysis can provide valuable systems for anywhere-anytime monitoring of PD individual's motor behavior [26][49][54]. In fact, this type of analysis allows to evaluate fluctuating events in response to medication, to capture falls or FOG episodes, and to assess all physical activities in everyday life, that occur over long periods and outside the clinical examination room [61][27]. In particular, a significant number of literature studies supports the use of wearable system, that have recently shown good reliability for assessing individuals with PD, especially for acceleration-based measures calculated in the time domain. They are able to assess standing balance and walking differences for different subgroups of subjects, like PD fallers and non-fallers, people with PD and controls, people with different PD subtypes, and also contribute to the diagnosis beetween idiopatich PD and drug-induced parkinsonim [23][26][28]. Latt et al. [29] used two inertial sensors (accelerometers, Fig.2.4) located in two different body zones (head and sacrum) to detect and evaluate differences between fallers and non fallers in elderly people with PD and controls. Their results show significant differences between analyzed groups (reduced walking speed and step length and increased step time variability),

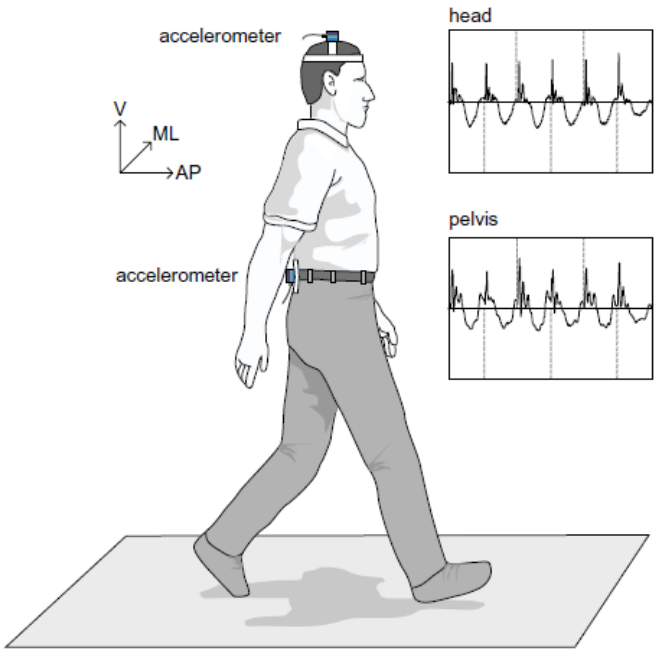

Figure 2.4: Use of two wereable sensors: accelerometers on head and sacrum,[29]

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confirming the reliability of these sensors. Also Weiss et al. [35][36][88] used 3D accelerometer on lower back to compare PD and controls, PD freezers and non-freezer, and PD fallers with non-fallers. Yang et al. [37] make use of 3D accelerometer located on lateral pelvis to investigate PD and controls. Instead Van Emmerik et al. [38] used 1D accelerometer on shank to valuate stride timing variability during gait between PD and control. In their study, Hubble et al. [23] report an overview of wearable sensors types for PD gait analysis to assess standing balance or walking stability, used by other studies published between January 1994 and December 2014. The results (Fig.2.5) demonstrate that the most common sensor used is three-dimensional accelerometer. Nevertheless, in the last few years a large number of studies used smartphone. The figure 2.6 shows exponential growth over the years in the use of wearable sensors, but above all smartphones, in neurological studies. Pepa et al.[39] used it on waist for freezing of gait detection in PD, showing very good sensitivity and specificity (89% and 97% respectively); also Capecci et al. [40] used smartphone for the same purpose; Vezočnik and Juric [41] estimate average step length; Ellis et al. [42] assess gait variability; Arora et al. [43]

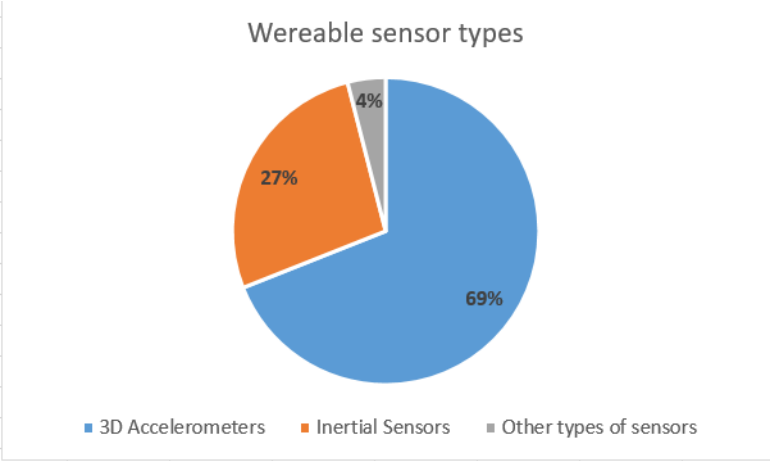

Figure 2.5: Types of wereable sensors used in PD gait analysis,[23]

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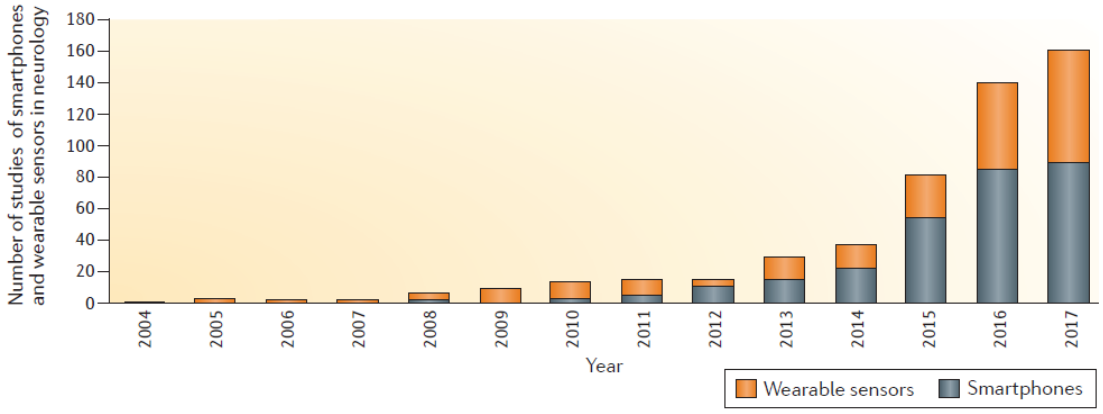

Figure 2.6: Number of studies of smartphones and wearable sensors in neurology in the last 15 years,[46].

differentiate PD subject by healty controls with high accuracy. All these studies highlight that smartphone-based gait analysis can be an alternative to conventional gait analysis methods, particularly when those are cost-prohibitive, cumbersome, or inconvenient.

Hubble et al. [23] also reported the location on patient's body where the sensor is placed, and the most suitable position that provide adequate information for gait analysis is lumbar or sacral region of the trunk (Fig.2.7)[44][51]. This location, although centered, has previously shown to reflect lower extremity movement during

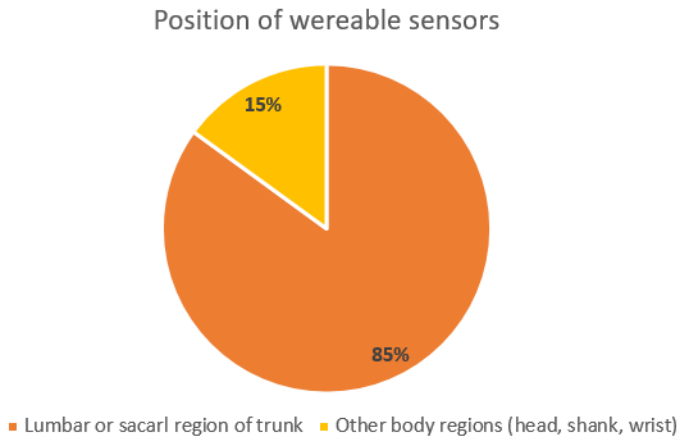

Figure 2.7: Position of wereable sensors used in PD gait analysis,[23]

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walking [36], and it is useful for step detection. In fact, if the device is placed on the left lateral side of waist, signals from the left leg are more prominent than those from the right leg and vice versa, as shown in Fig.2.8, causing several problems. Maetzler et al. [60] report that collection of disease-relevant gait data may even

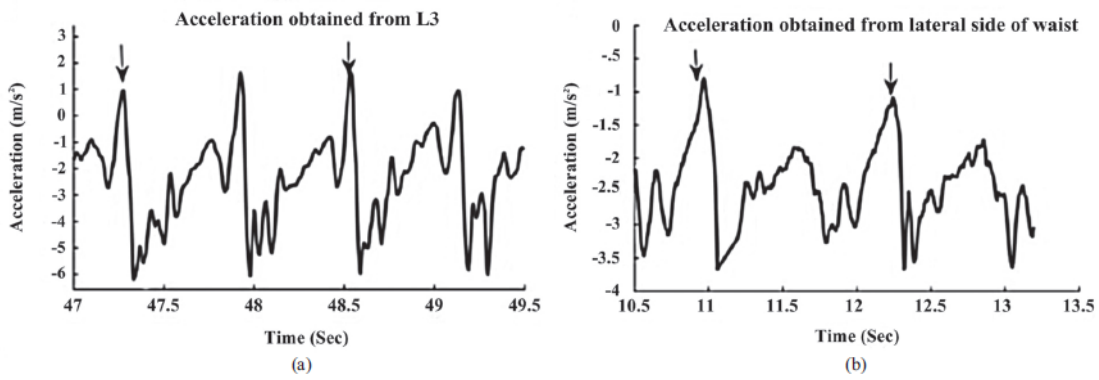

Figure 2.8: Acceleration obtained from two positions of sensor- a)Acceleration obtained from L3. b) Acceleration obtain from lateral side of waist,[44]

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be possible using a single wereable sensor worn at the lower back, through acceleration signal of the vertical axis that allows to assess gait variability computing stride-to-stride variability. This is very useful to predict the risk of future falls.

Furthermore, always using a sensor at the lower back, differences of anticipatory postural adjustament between untreated PD patients and control individuals were found, and this is very important because it is a parameter related to increased risk of FOG and falling [60]. Also falls, which are sporadic and episodic events that require long monitoring, balance impairment and mild postural sway abnormalities can be detected by single sensor with triaxial accelerometer worn at the lower back, like smartphone [60]. Therefore, the best operational solution for gait analysis in PD seems to be the use of a 3D accelerometer (as a single inertial sensor or using the one present in smartphone), positioned at lower waist.
In conclusion, wearable sensors 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 [23]. This will enable patients with movement disorders to benefit from an analysis that has been limited to academic laboratories and state-of-the-art medical centers [27].

Chapter 3

Gait assessment

This chapter describes materials and methods that have been used to extracting and analyzing measured signals. Different spatio-temporal parameters were calculated both in PD subjects and in elderly controls. All calculations and signal processing were performed using Matlab R2018b software.

3.1 Materials

3.1.1 Smartphone sensors characteristics

Before proceeding with the acquisition and elaboration of signals, smartphone sensors characteristics have been evaluated, in particular sampling frequency, range and resolution, to understand if these were suitable for conducting gait analysis.

- Sensors *sample frequency* has to respects the Nyquist theorem, according to which this must be at least twice the maximum useful frequency of the signal to be acquired. Human activity acceleration signal lie in the 0-20 Hz band [63], therefore a frequency of at least 40 Hz must be set. Anyhow, the 3-5 Hz has been defined as 'locomotor band' [40], and it has also been observed that normal walking has a principal frequency around 2Hz [62].

- Acceleration signal *amplitude range* depends on considered direction, location of sensor and body weight. Considering a waist-mounted sensor, acceleration amplitude during walking lies in the range $\pm$1g, with g being the gravitational acceleration.

The Tab.3.1 shows the characteristics of smartphone sensors, demonstrating that it is an adequate device for data acquisition.

Table 3.1: Smartphone sensors characheristics

	Range	**Resolution**	**Sample Frequency**
Accelerometer	± 2 g	$4 \cdot 10^{-3}$ g	200 Hz
Gyroscope	± 34.9 rad/s	$1.1 \cdot 10^{-3}$ rad/s	200 Hz
Orientation	360°	1°	200 Hz

Sensor data were collected by an application called 'Sensor Log' and exported in CSV format. This application is just one of many available that can acquire signals. It is simple to use: the user has to click a button to start recording, and press it again to stop it. So, signals are stored and appear as a database in the history section of the app, which can then be imported to a software, like Matlab.

3.1.2 Sample characteristics

The sample involved in this study consists of 75 individuals, divided into three main groups: one consisting of neurological healthy people, and so utilized as controls, and two composed of PD subjects, called Phase 1 and Phase 2. Control data have been collected at the "Orfanelle" nursing home - Chieri (To) while PD data have been taken from Center of Parkinson and Movement Disorder - "Molinette" Hospital (To). In this case, neurologists selected subjects to be included in the study, and provided information on their disease status. This study was conducted in accordance with the declaration of Helsinki, and patients have been informed about the purpose of the study and gave their consent.
Regarding controls, collected informations concern age, gender and possible use of walking aids. In Phase 1 the presence of FOG episodes and disease duration are also evaluated. For patients in Phase 2, scores for some items of the UPDRS scale provided by neurologists have been collected. Tables 3.2, 3.3 and 3.4 provide a complete picture of all information about the three groups.

Table 3.2: Control group caractheristics

Number	**Gender(% Male)**	**Age (years)** (Mean±SD)	**Gait Assistance (%)**
14	28.6	84.9±7.7	35.7

Table 3.3: Phase 1 group caractheristics

PD subjects - Phase 1	
Number	36
Gender (% Male)	64.4
Age (years) (Mean±SD)	64.9±9.3
Gait Assistance (%)	16.7
Disease Duration (years) (Mean±SD)	9.5±5
FOG Episodes (%)	
Yes	11.2
Hesitation	16.7

3.1.3 Positioning and protocol

In order to acquire data, smartphone has been positioned on the waist, at lower back level, for the following reasons:

- It is a comfortable position, if compared with the others (head, ankle, shank);
- It is close to body center of mass, typically 5th lumbar vertebrae (L5), providing global informations about motor control of walking [64][66];
- It also allows to monitor other symptoms of PD, such as bradykinesia, dyskinesia and FOG;
- It permits to discriminate different groups, such as fallers and non-fallers, controls and PD subjects, PD with no FOG episodes and PD with FOG, etc., as previously discussed.

A belt has been used to fix smartphone on the participants waist, equipped with an elastic band that guaranteed adherence to the body (Fig.3.1). The used experimental protocols are two: one for the controls and PD subjects of Phase 1, and the other for PD subjects of Phase 2. In particular, the first is the six-minute-walking-test, which consists of walking participants back and forth along a hallway during this time interval. It has gained clinical acceptance due to its ease of setting

Table 3.4: Phase 2 group caractheristics

PD subjects - Phase 2	
Number	25
Gender (% Male)	40
Age (years) (Mean±SD)	73.6±8
Disease Duration (years) (Mean±SD)	6.1±4.6
H&Y (Mean±SD)	2.3±1
Item Arising Chair (Mean±SD)	1.7±1
Item Gait (Mean±SD)	1.4±0.8
Item FOG	
Mean	0.5
Range	0 to 2
Item Postural Stability (Mean±SD)	1.5±1.2
Item Posture (Mean±SD)	1.4±0.7
Mean Item Leg Agility (Mean±SD)	1.2±0.6
Average Score (Mean±SD)	1.1±0.6

Figure 3.1: Smartphone belt, smartphone position and reference axes.

up, administration, patient tolerance, reproducibility and similarity to normal daily activities [65]. Participants quit the test if not able to continue. Indeed, the second is represented by the protocol used by neurologists to perform the evaluation of motor functions as required in Part III of the UPDRS scale. Therefore, in this case, the data is acquired in semi-supervised conditions. Different of other studies present in literature, no video recording has been performed, but a chronometer was used, that started when the subject is wearing the smartphone belt. In case of Phase 1 patients, annotations of any noteworthy events (such as hesitations, FOG episodes) have been made, while in Phase 2 the time instants in which the

different UPDRS tasks are performed have been recorded. Furthermore, in order to analyze and apply a gait assessment method to acquired signals, these have been previously labeled offline based on the activity carried out by the subject. In particular, a Matlab interface has been used, that employs a vector of the same signal length and containing different numbers (1 for walking, 2 for turn, etc.) associated with each sample. This allows to easily distinguish and identify walking windows between the various activities performed by the subject.

3.2 Methods

After an initial pre-processing phase of the acquired signals, gait events have been identified (in particular HS and TO), that allows to calculate several spatio-temporal parameters, also differentiated between right and left steps. This is followed by calculation of correlation coefficients and statistical analyses.

3.2.1 Pre-processing

First of all a pre-processing phase was considered necessary. It consists of mean capture of the values by each axis, that are later subtracted from corresponding axes, in order to eliminate offsets and misalignment. Then, a passband filter was applied to the input signals, in order to remove the gravitational component and high frequency noise. The choice of cut-off frequency is very important: it has to take into account the frequency content of the walking signal, and make a choice that does not distort it too much and has no impact on the analysis. Therefore, noting that human activity acceleration signals lie in the 0-20 Hz band, locomotor band is up to 3-5Hz, and literature studies usually make use of cut-off frequencies between 15-20 Hz [66][69], the selection of bandpass filter upper frequency fell back to 20 Hz, and lower frequency has been set to 0.5 Hz. The type of filter is an IIR Butterworth of order 3. Fig. 3.2 shows its frequency response. Furthermore, the anteroposterior (AP) acceleration was further filtered with an order 3 IIR Butterworth low-pass filter with cut-off frequency of 5 Hz. As previously described, through offline labeling all the windows corresponding to the walking activity for each subject have been extracted.

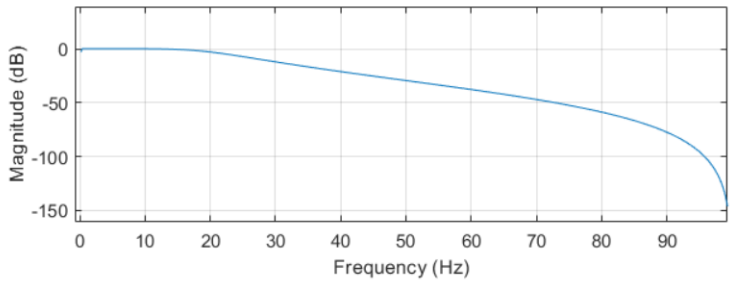


Figure 3.2: Frequency response of designed IIR Butterworth filter.

3.2.2 Trunk acceleration pattern

The selected position to placing the smartphone (waist at the level of the lower back) allows to obtain information about the movement of both limbs and to define a pattern of trunk acceleration. Although there is a inter-subject variation and small asymmetries between right and left steps, it can be considered similar for different subject and speed [68][69].

- *Antero-posterior (AP) acceleration pattern.* AP acceleration increases during single support phase when, after mid-stance, the body is falling forward and downward. Instead, during the transition from single to double support (ie after controlateral foot contact) it decreases because the forward fall of the body changes into an upward movement. Thus, foot contact (IC) coincides with the peak of AP acceleration (Fig.3.3, AP5), which occurs at 0% and 50% of the stride cycle. Furthermore, in some subjects additional peaks or indentations superposed on the basic pattern can be identified, corresponding to the beginning or the end of swing phase, or to forefoot loading (Fig.3.3 AP3, AP4 and AP6 respectively), and which vary from cycle to cycle and also with walking speed. AP3 and AP4 peaks are caused by hip flexion-extension movements, developed to perform the swing phase, which act on the pelvis, affecting trunk acceleration. AP1 represents the minimum reached value [68][69].

- *Vertical (V) acceleration pattern.* Also vertical acceleration has a pattern characterized by increasing and decreasing phases, due to support moments generated in ankle, knee and hip joints. The peak of this acceleration (Fig.3.3, V3) is

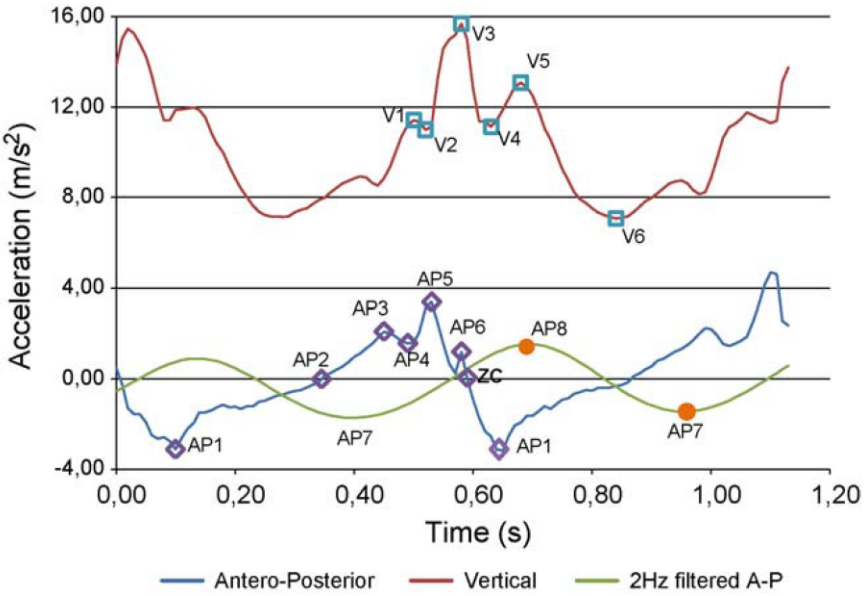


Figure 3.3: Pattern of lower trunk vertical (top) and antero-posterior (bottom) accelerations,[68].

reached very quickly after foot contact (IC, Fig3.3:V2). The indentation immediately after this peak (FC, Fig.3.3:V4) represents toe-off instant (contralateral FC), generated by the leg movement during this gait event [68][69][70][71]. V3, V5 and V6 represent foot flat, mid-stance and initial push off respectively.

- *Mediolateral (ML) acceleration pattern.* Left-right acceleration has small amplitude compared to V and AP accelerations and is related to subsequent left and right foot placements. Peaks are found around the istants of foot contact, both left and right, and they seems to be related to its medially directed impact. Moreover, it shows a more variable pattern from subject to subject and due to this it is less studied [68][69].

Generally, these acceleration patterns maintain the same structure even at different walking speeds, but as the latter increase, they enhance in amplitude and become more pronounced. This is especially true for V and AP accelerations [69][72].

3.2.3 Identification of gait events: Wavelet transform

In order to calculate typical gait spatio-temporal parameters, it is necessary to first identify two fundamental gait events: heel-strike and toe-off, which correspond respectively to initial contact and final contact of gait cycle [73]. The IC is represented in AP acceleration pattern by more prominent peak (AP5) and FC by the first indentation after the greater amplitude peak of V acceleration (V4). Nevertheless, it is not easy to identify these moments, since in this study signals have been collected by smartphone, but above all they derive from elderly or PD-affected subjects, which therefore do not present a standard gait. In fact, both groups are expected to have slower gait pattern, the first due to age and reduced muscle strength, while in the case of PD subjects, due to disease progression. This produces either a reduced amplitude of peaks and indentations of acceleration signals or even disappearance of some of these, making their identification and interception difficult if not impossible by standard methods, as the application of a threshold. So, for these reasons, it has been decided to not identify gait events directly on the acquired signals but to apply the Wavelet transform, as already performed by other studies [68][74][73][67][75][76][77].

Wavelet transform

The Wavelet transform yields a time frequency decomposition of a signal which may separate individual signal components more effectively than short-time Fourier transform (STFT). It can be mainly divided into discrete and continuous forms. The latter decomposed a continuous time signal into wavelets. The Continuous Wavelet Transform (CWT) of a signal x(t) is given as:

$$CWT(a,b) = \frac{1}{\sqrt{a}} \int_{-\infty}^{+\infty} x(t)\, \Psi^*\Big(\frac{t-b}{a}\Big)\, dt \tag{3.1}$$

where $\Psi^*(t)$ is the complex conjugate of the wavelet function $\Psi(t)$, $a > 0$ is the dilation parameter (scale) and $b \in \mathbb{R}$ is the location parameter (time shift). $\Psi(t)$, usually called as mother wavelet function, must satisfy certain mathematical criteria like finite energy to be admissible. Moreover, since wavelets must have zero mean, their transform is the frequency response of a passband filter. Wavelet transform

allows to preserve all information without down-sampling, which makes it appropriate for tasks like peak detection and pattern matching [73][74]. Indeed, this technique removes extraneous signal fluctuations while preserving the underlying frequency variation, thus allowing proper detection of time related features present in the original signal. CWTs are particularly effective in noise suppression, baseline drift correction, and overlapping peaks resolution. So, it allows to accurately determine the timing of events that may otherwise be concealed within irregular acceleration patterns [67].
From a practical point of view, CWT compares signal to shifted and compressed or stretched versions of mother wavelet $\Psi(t)$. Stretching or compressing a function is collectively referred to as dilation or scaling and corresponds to the physical notion of scale. The scale a is inversely proportional to the spectral components: the smaller the scale factor, the more compressed the wavelet. Conversely, the larger the scale, the more stretched the wavelet. So, low scales or high frequencies provide more local information while high scales or low frequencies provide relatively more global information about the signal. To summarize, the general correspondence between scale and frequency is:

- Small scale $a \longrightarrow$ Compressed wavelet $\longrightarrow$ Rapidly changing details $\longrightarrow$ High frequency.

- Long scale $a \longrightarrow$ Stretched wavelet $\longrightarrow$ Slowly changing, coarse features $\longrightarrow$ Low frequency.

This multi-resolution property of CWT makes it appropriate for gait analysis [73]. Nevertheless, even if there is a general relationship between scale and frequency, there is not a direct relationship. It is customary to refer to a pseudo-frequency corresponding to a scale, according to the following equation:

$$F_{\mathrm{sc}} = \frac{F_{\mathrm{c}}}{a \cdot \Delta} \tag{3.2}$$

where F_{c} represents the center frequency of the wavelet (approximation of the leading dominant frequency), a is the scale, Δ represents the sampling period and F_{sc} is the pseudo-frequency [58].

Mother wavelet function and scale choice

It is necessary to choose the most appropriate scale and mother wavelet function to perform the wavelet transform. In the CWTs there are different families and several mother wavelets. Depending on signal features to be detected, one has to be selected. In particular, the wavelet shape should resemble the form of the signal to analyze in order to extract the features that allow the characterization of gait. It has been chosen to use two different mother wavelets, one applied to AP acceleration and the other to V acceleration, since they have different patterns.

- For AP acceleration, the gaussian wavelet of type 1 (Gaus1), shown in Fig.3.4, has been chosen, ie the first derivative of the Gaussian function. It follows the decreasing evolution of AP acceleration which is found after the peak corresponding to the HS, Fig.3.8.

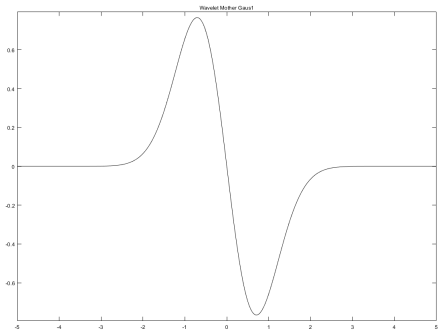


Figure 3.4: Mother Wavelet for AP acceleration: Gaus1.

- For V acceleration, the gaussian wavelet of type 2 (Gaus2), shown in Fig.3.5, has been selected, ie the second derivative of the Gaussian fuction, also known as the "mexican hat". It has a shape comparable to the analyzed signal: a peak flanked by two valleys. In Fig.3.9 it is reported as Gaus2 intercepts the features of vertical acceleration.

Regarding the scale, by varying values of the parameter a and the position parameter b, it is possible to obtain the CWT coefficients C(a,b). These coefficients illustrate how well a wavelet function correlates with a specific signal. Thus greater the correlation, the higher will be the CWT coefficients and vice-versa. In this way

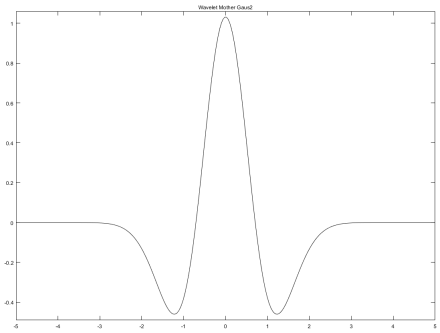
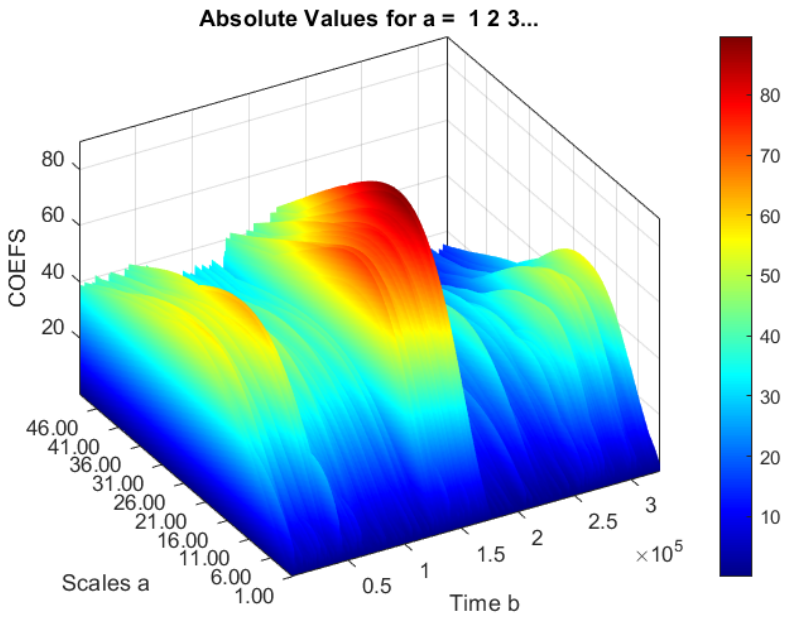


Figure 3.5: Mother Wavelet for V acceleration: Gaus2.

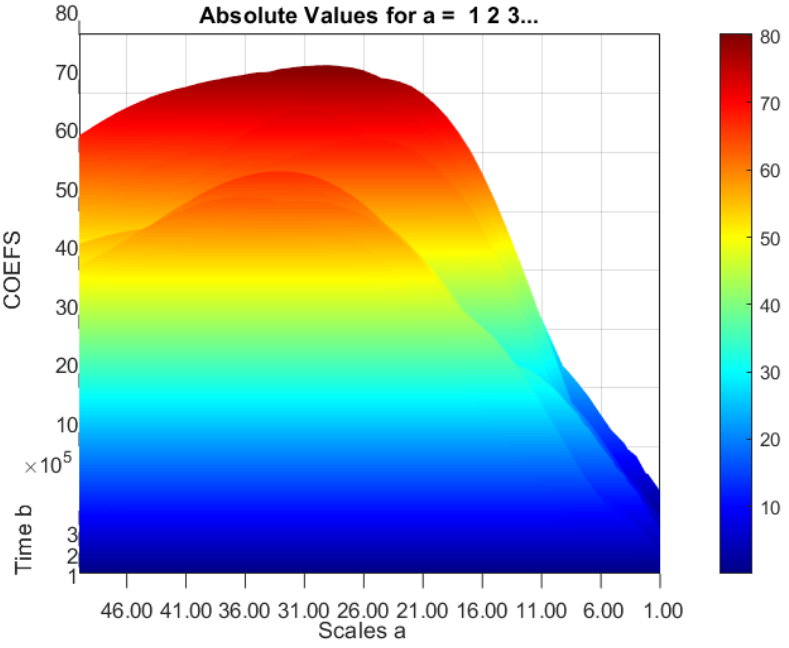
it is possible to select the most suitable scale. For this reason, all walking windows detected by offline labeling and related to each subject have been connected together, obtaining for each analyzed group a vector constituting the AP acceleration and another relative to the vertical component. The wavelet transforms of these vectors have been carried out by varying the scale parameter from 1 to 50, and focusing attention on obtained coefficients, being representative of matching quality.

- For AP acceleration, looking at Fig.3.6, it is possible to observe how the maximum value of coefficients (between 50-80) is reached for scales from 16 to 41 and only in some vector parts. Therefore, in order to perform a satisfactory wavelet transform of the AP acceleration in its entirety, a scale of 14 was chosen. This allows to obtain good coefficients (in a range of 20-40) but above all to carry out analysis with higher frequency resolution compared to larger scales, which is essential to intercept local informations of AP acceleration patterns. So, a=14 is the first scale that intercepts rapidly changing details.

- For V acceleration, it is even more important to use a low value of dilation parameter, since the primary purpose is matching the valley immediately after the peak, corresponding to toe-off instant, ie the contralateral final contact. Therefore high frequency resolution is required. Fig.3.7 highlights that, compared to AP acceleration case, the scales which allow to obtain the highest coefficients are shifted towards low values (range 2-20). Therefore a=6 has been selected, as it enables to obtain high coefficients values and at the same time guarantees an adequate high frequency resolution.

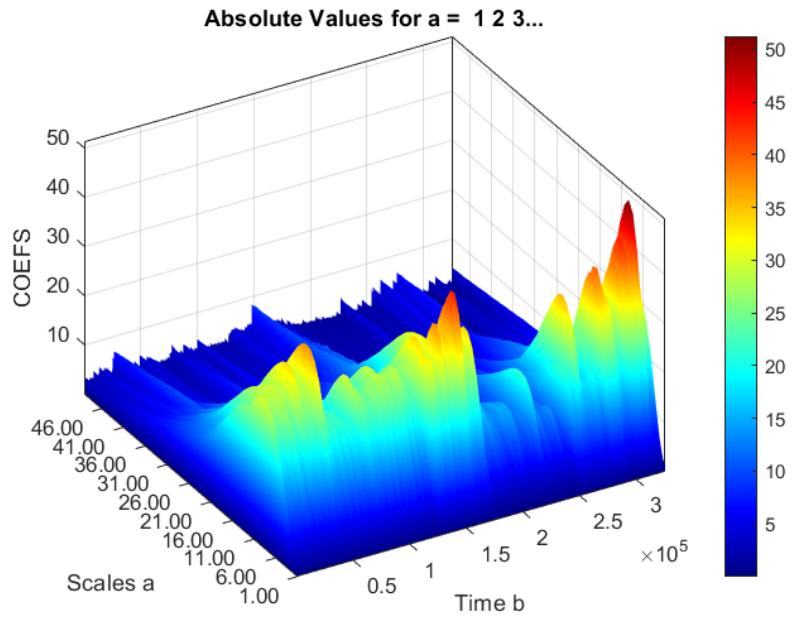


(a) Global wiev.

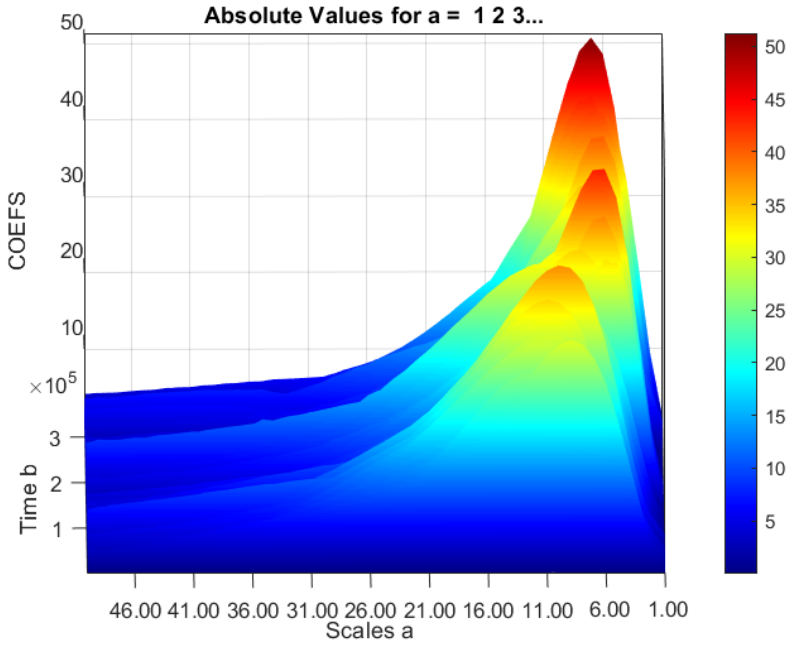


(b) Coefficient-scale detail.

Figure 3.6: Wavelet transform 3D representation of AP acceleration in terms of parameters a, b, and coefficients.



(a) Global wiev.



(b) Coefficient-scale detail.

Figure 3.7: Wavelet transform 3D representation of V acceleration in terms of parameters a, b, and coefficients.

Regarding frequency resolution, as reported in equation (3.2), the pseudo-frequency value is connected to selected dilation parameter, and will be higher for vertical acceleration, having used a smaller scale. Tab.3.5 shows these values and summarizes the implemented choices.

Table 3.5: Mother wavelet and scale choice.

Acceleration Component	**Mother Wavelet**	F_c	**Scale**	Δ	F_{sc}
Anteroposterior	Gaus1	0.2 Hz	14	0.005	2.86 Hz
Vertical	Gaus2	0.3 Hz	6	0.005	10 Hz

The selected mother wavelets, as well as the picked scale values, allowed to adequately intercept the desired local informations of the signal, as shown in Fig.3.8 and 3.9. Therefore, the next step consists in the identification of the IC and FC

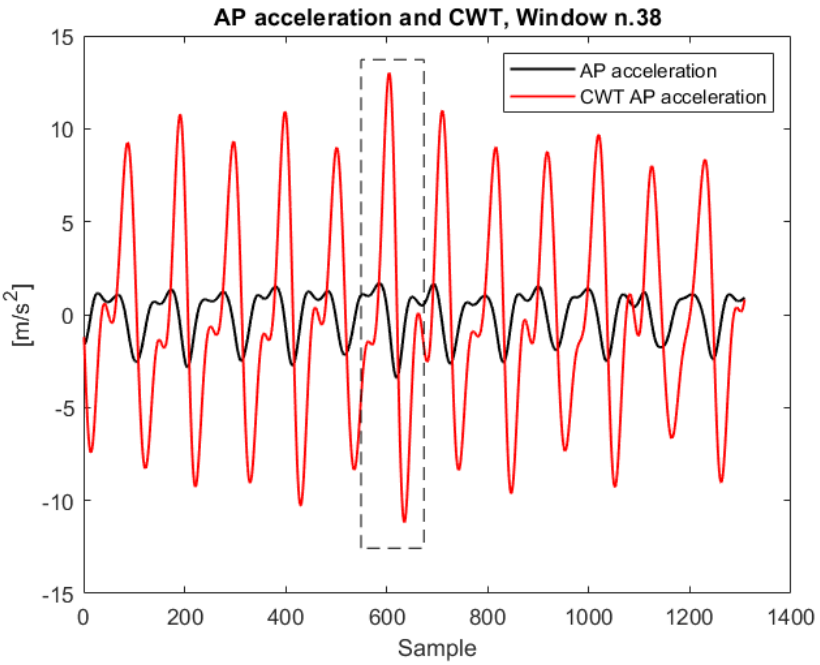


Figure 3.8: Application of 'Gaus1' with a=14 to AP acceleration pattern. The rectangle shows how the chosen mother wavelet and scale intercept very well the decreasing AP acceleration pattern.

instants on the newly calculated wavelet transforms of each participant walking window. So, the Matlab *findpeaks* function has been used, which allows to detect

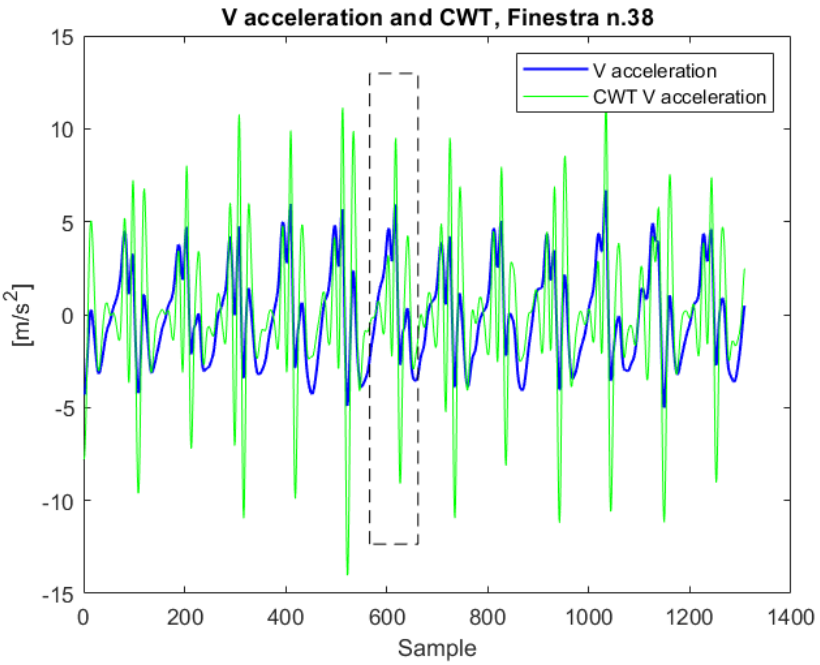


Figure 3.9: Application of 'Gaus2' with a=6 to V acceleration pattern. The rectangles show how the chosen mother wavelet and scale intercept very well the local informations of V acceleration.

all the peaks above a certain threshold, set to 0.35 times the standard deviation of the window signal for CWT AP acceleration, and to 0 for the CWT vertical component. In addition, only the peaks that are distant at least 76 samples are identified, that (with a sampling frequency of 200 Hz) corresponds to a time interval of 0.38s. Fig.3.10, 3.11 and 3.12 show the obtained results, where obviously the contralateral FCs always occur after the ICs. For the following analyses and for calculation of the spatio-temporal parameters, only walking windows in which the number of detected ICs is greater or equal to 5 have been considered (ICs$\geq$5). This is considered as the minimum number of steps executed by a participant that may identify the walking pattern.

3.2.4 Autocorrelation function

In order to compute parameters related to gait symmetry, the autocorrelation function of vertical acceleration has been evaluated. This component was previously

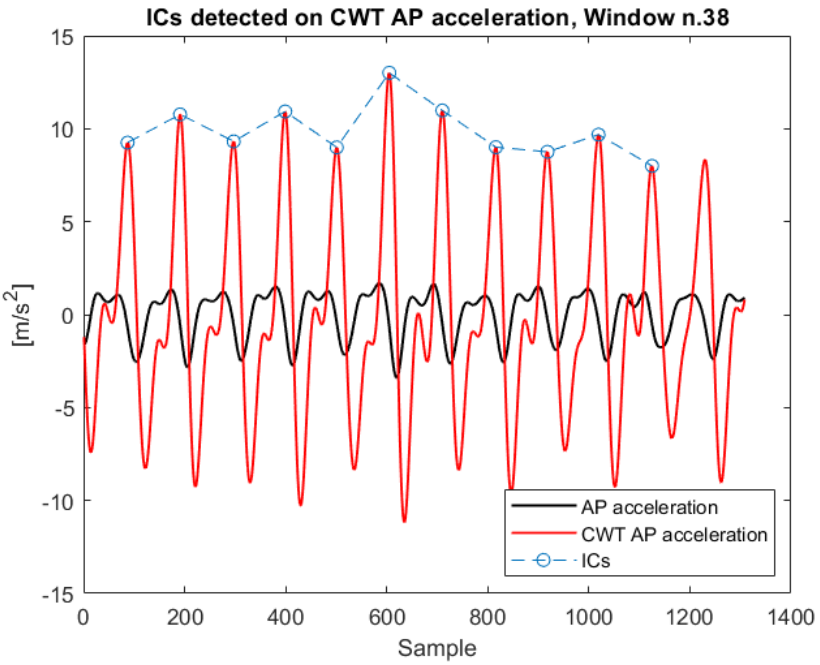


Figure 3.10: Inital contact instants detected on AP acceleration wavelet transform.

filtered by a 4th-order Buttherworth filter with cut-off frequency of 3 Hz. The autocorrelation function will be also used to evaluate the performance of step detection algorithm.

An estimate of autocorrelation function is represented by a sequence of autocorrelation coefficients over increasing time lags. A raw autocorrelation coefficient (A) is the sum of the products of a time series x_{i} (i=1, 2, ..., N) multiplied by a time-lagged replication of the time series ($x_{\mathrm{i+m}}$), where the lag parameter m is the phase shift in number of samples:

$$A(m) = \sum_{i=1}^{N-|m|} x_i x_{i+m} \tag{3.3}$$

Both biased and unbiased estimates can be calculated. In this study the Matlab *xcorr* function has been used to calculate the unbiased autocorrelation estimate. In particular, this alternative is produced by dividing the raw autocorrelation coefficient by the number of samples representing the overlapping part of the time series

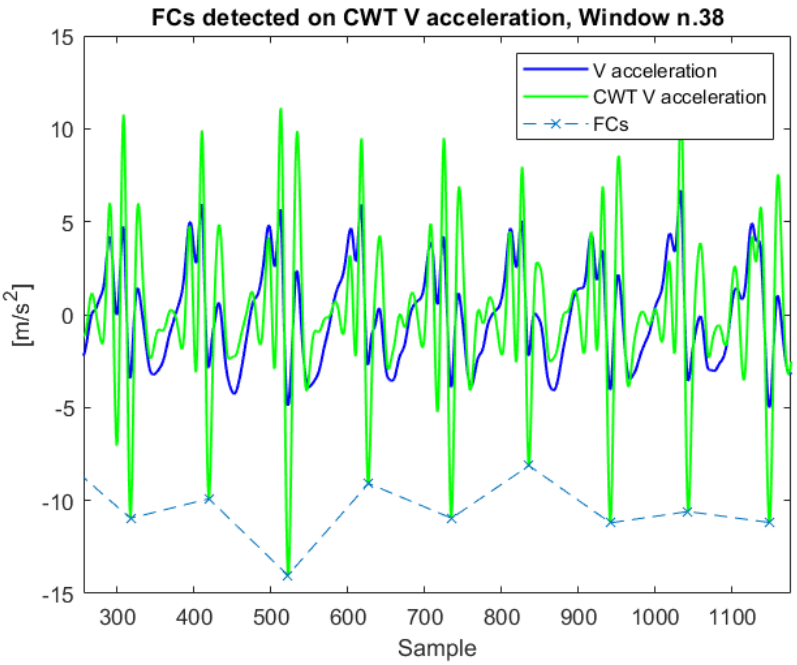


Figure 3.11: Final contact instants detected on V acceleration wavelet transform.

and the time-lagged replication:

$$A(m)_{unbiased} = \frac{1}{N - |M|} \sum_{i=1}^{N-|m|} x_i x_{i+m} \tag{3.4}$$

Since a real signal produces real and also even autocorrelation, its plot is conventionally organized symmetrically with the zero shift located centrally, corresponding to the maximum of the function, and also normalized. Moreover, a cyclic signal produce autocorrelation coefficients with peak values for lags equivalent to the periodicity of the signal, called dominant periods. So, the plot of autocorrelation estimate can be used to inspect the structure of a cyclic component within the time series. For trunk acceleration during walking the coefficients can thus be produced to quantify first and second dominant period, representing phase shift equal to one step and one stride respectively, and associated peaks values [78]. Fig.3.13 shows an example of autocorrelation function and its associated dominant periods, *d1* and *d2*. Therefore, for all walking window belonging to each subject, the autocorrelation function of the vertical acceleration component has been calculated.

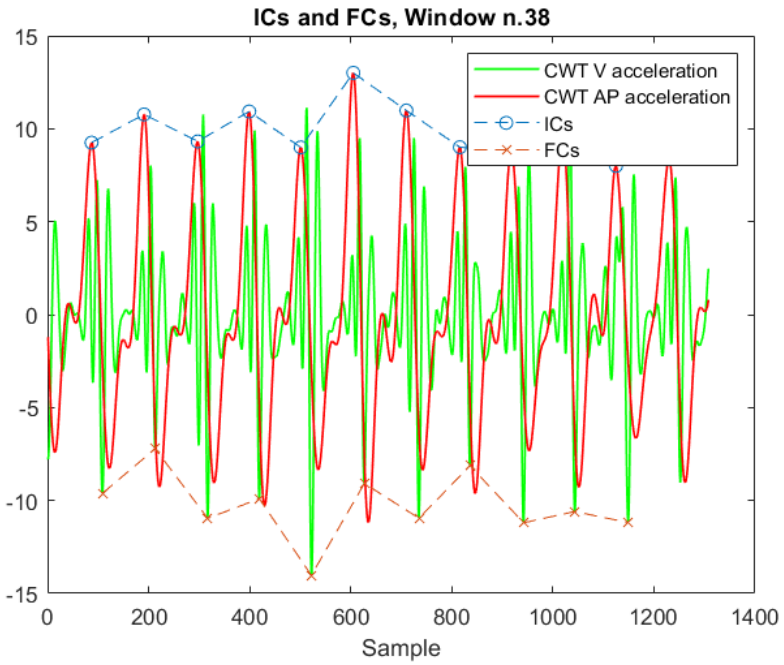


Figure 3.12: Superposition of anteroposterior and vertical acceleration wavelet transforms with detected initial and final contact instants.

The, from each of them the dominant period *d1* has been extracted, corresponding to the window step time. The number of executed steps by each subject has been computed according to the following equation:

$$N_{step} = \sum_{i=1}^{W} \frac{L_i}{d1_i} \tag{3.5}$$

where L_i is the i-th window length, $d1_\mathrm{i}$ is the i-th window step time, and W corresponds to the total number of window. N_step was obviously rounding off to the nearest whole number.

Since no video recording was performed, but only a chronometer has been used to note the istants of most significant events, the number of steps completed by the participants is unknown at first glance. Therefore the number of step in (3.5) calculated by autocorrelation function together with the offline labeling windows, allow to have a rough idea about the walking pattern quantity. Tab.3.6 shows the

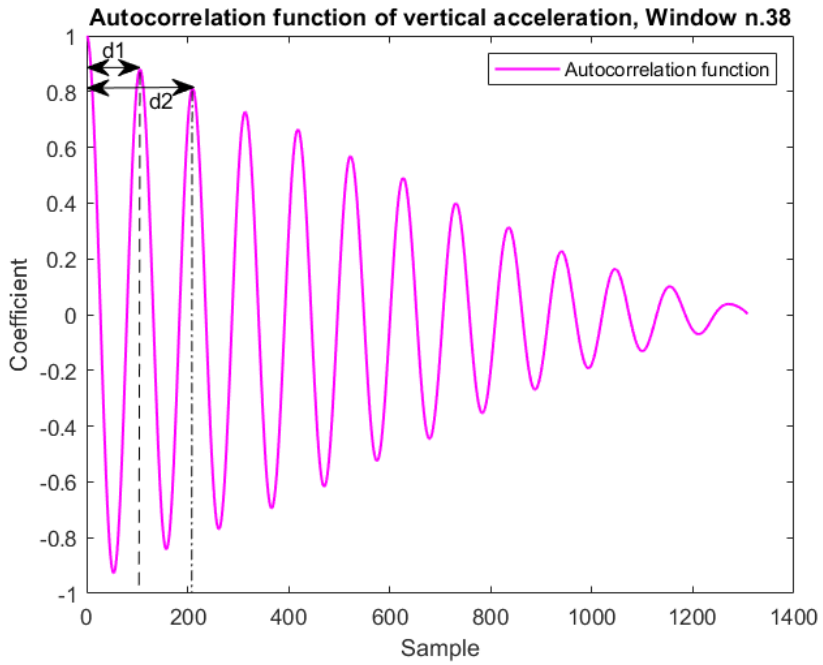


Figure 3.13: Autocorrelation function of vertical acceleration, where *d1* is the first dominant period representing phase shift equal to steps and *d2* is the second dominant period corresponding to stride phase shift.

average number of detected walking windows for each subject belonging to the different groups and the average number of steps in each of them.

Table 3.6: Quantification of the walking pattern.

	Mean Windows Number for Subject	**Mean Step Number for Window**
Control	12	23
Phase 1	12	18
Phase 2	4	11

3.2.5 Calculation of spatio-temporal parameters and symmetry/regularity indices

From the identification of the IC and FC gait events, a different number of spatio-temporal parameters have been calculated, which allow to make assessments about

the quality of walking in the different groups of participants. They are computed as Mean±SD (Standard Deviation) for each walking window and then mediated for each subject. These are:

- Cadence [N.step/min]:

$$Cadence = \frac{N_{ICs} \cdot 60}{\frac{L_i}{f_s}} \tag{3.6}$$

  where N_{ICs} is the number of ICs in a window, L_{i} the i-th window length and f_{s} the sampling frequency.

- Stride Time [s], as the time interval between two non-consecutive ICs (belonging to the same foot), representative of the gait cycle:

$$StrideTime = IC_{j+2} - IC_j \tag{3.7}$$

- Step Time [s], as the time interval between two consecutive ICs (belonging to different foot):

$$StepTime = IC_{j+1} - IC_j \tag{3.8}$$

- Swing Time [s], as the difference between IC and the previous FC:

$$SwingTime = IC_{j+1} - FC_j \tag{3.9}$$

- Swing Phase [%GC], swing expressed as percentage of gait cycle.

- Stance Time [s], as the difference between FC and the previous IC:

$$StanceTime = FC_{j+1} - IC_j \tag{3.10}$$

- Stance Phase [%GC], stance expressed as percentage of gait cycle.

- Single Support Time [s], as:

$$SingleSupportTime = (IC_j - FC_{j-1}) + (IC_{j+1} - FC_j) \tag{3.11}$$

- Single Support Phase [%GC], expressed as percentage of gait cycle.

- Double Support Time [s], as:

$$DoubleSupportTime = (FC_j - IC_j) + (FC_{j-1} - IC_{j-1}) \tag{3.12}$$

- Double Support Phase [%GC], expressed as percentage of gait cycle.

- Step Length [m], estimated using the upward and downward movements of the trunk. Zijlstra et al. [79] have demonstrated that three-dimensional displacements of the lower trunk during walking are well predicted by an inverted pendulum model of the body's centre of mass (COM) trajectory. Assuming a compass gait type, COM movements in the sagittal plane follow a circular trajectory during each single support phase. In this model, changes in height of COM depend on step length. Thus, when changes in height are known, this parameter can be predicted from geometrical characteristics as:

$$StepLength = 2 \cdot \sqrt{2lh_j - h_j^2} \tag{3.13}$$

  where h_{j} is equal to the change in height of the COM, and l is pendulum length. Changes in vertical position have been calculated by a double integration of vertical acceleration through *cumtrapz* function and then *detrend* function to remove integration drift. The amplitude of changes in vertical position (h_{j}) has been determined as the difference between highest and lowest position during a step cycle. Instead, the pendulum lenght l is represented by leg length. Since this value for each subject has not been annotated, a unique value has been selected for all participants that could be representative for both women and men. This is 0.85 m. So, from these data, step length has been estimated [69].

- Gait Velocity [m/s], computed as the ratio between step length and step time:

$$GaitVelocity = \frac{StepLength_j}{StepTime_j} \tag{3.14}$$

- The variation coefficient (CV) has been also calculated for some of the parameters just described, as:

$$CV = \frac{SD_{parameter}}{Mean_{parameter}} \cdot 100 \tag{3.15}$$

since it is another way to express the variability of a parameter.

Some of these parameters are reported in Fig.3.14. Moreover the algorithm removes the parameters value of stride time, swing and stance (and subsequently of double and single support) not belonging to specific ranges:

1. The average stride time is considered to be around 1.03s, but in particular cases it can decrease to 0.67s (for young subject)[81], or significantly increase due to a very slow pattern, reaching values close to 1.18s [35]. So it has been chosen to remove stride time values lower than 0.7 s, as this study does not include young subjects, but only elderly controls and PD partecipants.

2. Regarding swing, PD subjects may not have physiological values but lower ones, even around 33% of GC. To maintain a certain security level due to inter-subject variability, it has been decided to remove swing values lower than 29.5%. As for the upper limit, 45.5% has been set, because excessive swing values (and consequently too small stance values) are only typical at high walking speeds, and this is not the considered case [47].

3. About stance, the discussion is reciprocal to the swing, so the lower limit has been set at 55.5% and the upper limit at 70.5%.

Moreover, symmetry/regularity indices have also been calculated in addition to spatio-temporal parameters. In particular these were obtained from the previously implemented autocorrelation function [78], as shown in Fig.3.15. They are:

- Step Regularity *Ad1*: it is the autocorrelation coefficient corresponding to the first dominant period *d1* that represents a phase shift of one step. So, it is an expression of the regularity of vertical acceleration signal between neighboring steps. It ranges between 0 and 1: if it assumes low values, this demonstrates low regularity between steps; on the contrary values around 1 indicate more rythimc, consistent and stable walking pattern.

- Stride regularity *Ad2*: it is the autocorrelation coefficient corresponding to the second dominant period *d2* that represents a phase shift of one stride. So, it is a measure of the regularity between neighboring strides. As well as *Ad1*, it ranges between 0 and 1, with the same meaning.

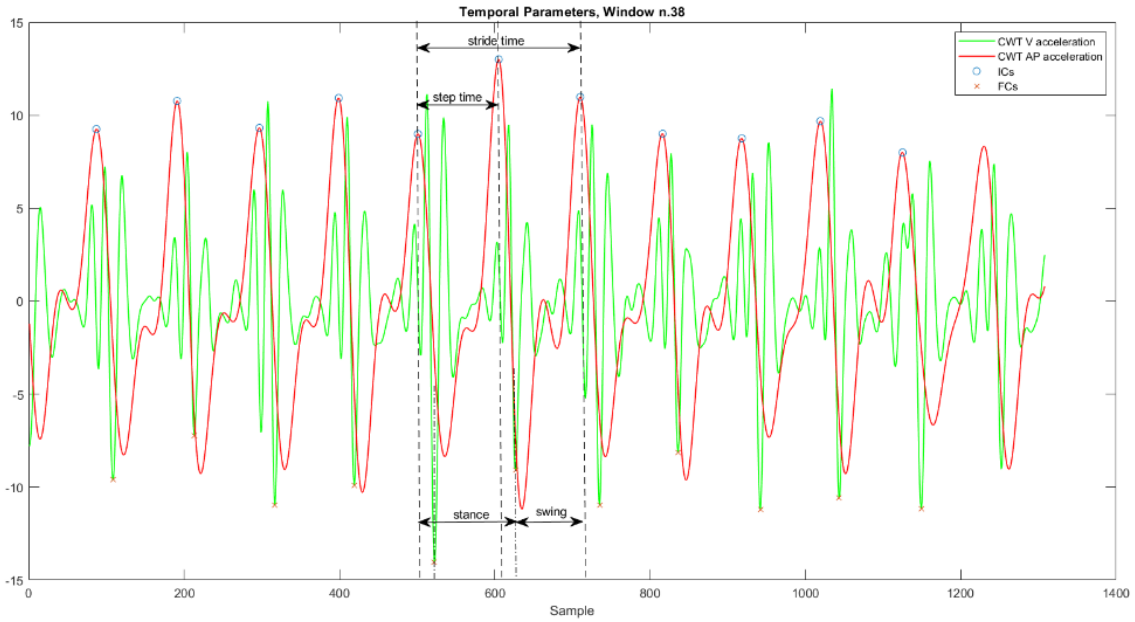


Figure 3.14: Some of temporal parameters: stride time, step time, stance and swing.

- Symmetry, computed as the ratio between step regularity and stride regularity:

$$Symmetry = \frac{Ad1}{Ad2} \tag{3.16}$$

  A ratio closer to 1 represents greater symmetry between left and right steps, while values closer to 0 indicate poorer symmetry.

3.2.6 Identification of right and left steps

Once 'global' parameters have been calculated, it has been decided to subdivide the identified steps (ICs) into right and left ones, in order to obtain extra symmetry indices that can provide additional information on the gait of control group but, above all, of PD subjects.
Discrimination between left and right steps was based upon an analysis of mediolateral movements of the lower trunk. Experimental data and model predictions have shown that the COM, and consequently also the lower trunk, describes an approximately sinusoidal path between the medial borders of the feet during subsequent

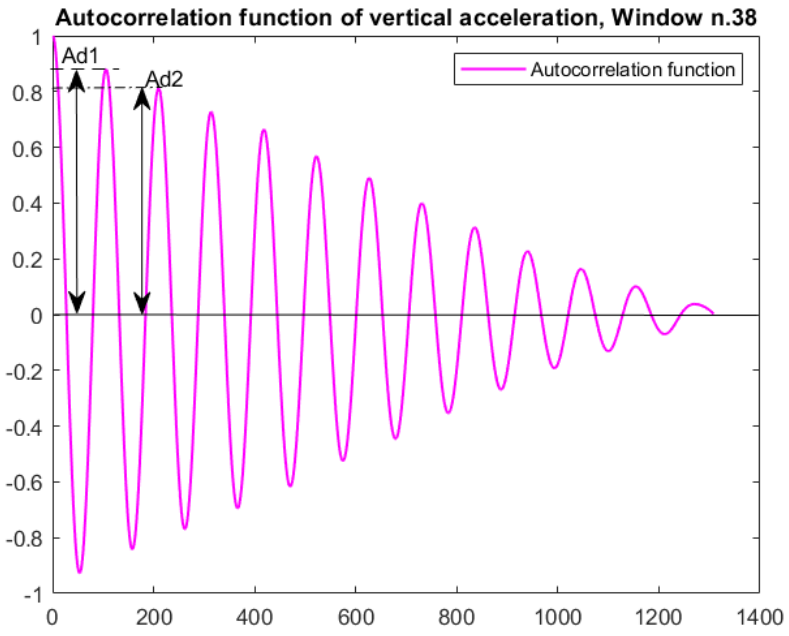


Figure 3.15: Autocorrelation function of vertical acceleration, where *Ad1* is the autocorrelation coefficient representing step regularity and *Ad2* is the autocorrelation coefficient corresponding to stride regularity.

foot placement. During single support, the COM reaches its maximum lateral position towards the stance leg. Hence, discrimination of left and right foot contacts can possibily be based on mediolateral acceleration or position data [69]. It has been decided to employ acceleration rather than position data to avoid integration problems. First, ML acceleration has been subjected to a recalibration process. Secondly, it was low-pass filtered with 3-th Butterworth with cut-off frequency of 1Hz. Finally, it has been used to implement two methods that allow to distinguish right and left steps.

Recalibration process

While vertical and anteroposterior accelerations did not require this step since the applied wavelet transform corrects the baseline drift, working directly on the ML acceleration requires to remove the contribution of the gravitational acceleration acting on the mediolateral axis, due to incorrect positioning of the smartphone.

A common source of error with a waist-mounted smartphone is the resting device angle due to waist girth, clothing, or the device's holster [80]. The recalibration method corrects accelerometer axis orientation by applying a quaternion rotation transformation to the device's raw data. It involves constructing the quaternion rotation matrix by way of the axis-angle representation. A rotation matrix describes a coordinate system orientation with respect to another orientation. A vector $\vec{V}$ in the initial reference frame F can be transformed into a vector $\vec{V}$' in a rotated frame F' by multiplication of $\vec{V}$ with the rotation matrix between F and F'. Rotation matrices are orthogonal, square and invertible:

$$R^T = R^{-1}, detR = 1. \tag{3.17}$$

First, the axis vector is produced by taking the cross product of the initial orientation gravitational vector with the desired orientation gravitational vector. Then, the dot product is used to solve for the rotation angle α, which is then used with axis vector as input to build the quaternion rotation matrix. Finally, all raw accelerometer data thereafter are multipilied by the rotation matrix to achieve the corrected orientation. It is desired to have the gravitational component application only along the vertical axis, ie in X direction. The initial vector $\vec{V_i}$ contains the mean acceleration values along the three axes, obtained from the walking window which for each subject had the greatest length:

$$\vec{V_i} = X\hat{i} + Y\hat{j} + Z\hat{k} \tag{3.18}$$

Instead, the final vector $\vec{V_f}$ is:

$$\vec{V_f} = X'\hat{i} + Y'\hat{j} + Z'\hat{k} = [-9.81, 0, 0] \tag{3.19}$$

Considering the initial vector $\vec{V_i}$ and the desired vector $\vec{V_f}$, it is possible to express the following equation:

$$\vec{V_f} = R\vec{V_i} \tag{3.20}$$

To construct the set of quaternions that yield the required rotation, it is necessary to first produce an axis-angle pair. The axis vector $\vec{A}$ can be found from the cross-product bewteen $\vec{V_i}$ and $\vec{V_f}$:

$$\vec{A} = \vec{V_i} \times \vec{V_f} = (9.81Z)\hat{j} + (-9.81Y)\hat{k} \tag{3.21}$$

The axis vector $\vec{A}$ from (3.21) can then be normalized by dividing the magnitude of $\vec{A}$:

$$\vec{A}_{norm} = \left(\frac{Z}{\sqrt{Y^2 + Z^2}}\right)\hat{j} - \left(\frac{Y}{\sqrt{Y^2 + Z^2}}\right)\hat{k} \tag{3.22}$$

The angle between vectors can be expressed as the cosine from the dot product. Using initial vector $\vec{V_i}$ and vector $\vec{V_f}$ we obtain:

$$\vec{V_i} \cdot \vec{V_f} = \|\vec{V_i}\|\|\vec{V_f}\| \cos(\alpha) = XX' + YY' + ZZ' \tag{3.23}$$

Since Y' and Z'=0, and the magnitude of $\vec{V_f}$ equals X', the equation becomes:

$$\alpha = \arccos\left(\frac{X}{\|\vec{V_i}\|}\right) \tag{3.24}$$

Therefore, since the axis-angle pair was obtained, it can be use to build the quaternion rotation matrix as:

$$R(q_0, q_1, q_2, q_3) = \begin{bmatrix} 1 - 2(q_2^2 + q_3^2) & 2(q_1q_2 - q_0q_3) & 2(q_0q_2 + q_1q_3) \\ 2(q_1q_2 + q_0q_3) & 1 - 2(q_1^2 + q_3^2) & 2(q_2q_3 - q_0q_1) \\ 2(q_1q_3 - q_0q_2) & 2(q_0q_1 + q_2q_3) & 1 - 2(q_1^2 + q_2^2) \end{bmatrix} \tag{3.25}$$

where q_0,q_1,q_2,q_3 are:

$$q_0 = \cos(\alpha/2) \tag{3.26a}$$
$$q_1 = \sin(\alpha/2)A_{norm,x'} \tag{3.26b}$$
$$q_2 = \sin(\alpha/2)A_{norm,y'} \tag{3.26c}$$
$$q_3 = \sin(\alpha/2)A_{norm,z'} \tag{3.26d}$$

So, multiplying the raw acceleration by the rotation matrix in equation (3.25), the revision of orientation has been obtained [80].

Distinction's methods

After the recalibration process, the ML acceleration is used to divided the previously detected ICs in right and left steps. Two different methods have been implemented:

- *Method 1*: evaluation of the ML acceleration sign at the time instants defined by the ICs;
- *Method 2*: sign evaluation of the ML acceleration area between zero-crossing points of the AP acceleration wavelet transform.

Fig.3.16 and 3.17 show these methods, where positive sign corresponds to a left step, while the negative one to the right. These methods have been applied to all three

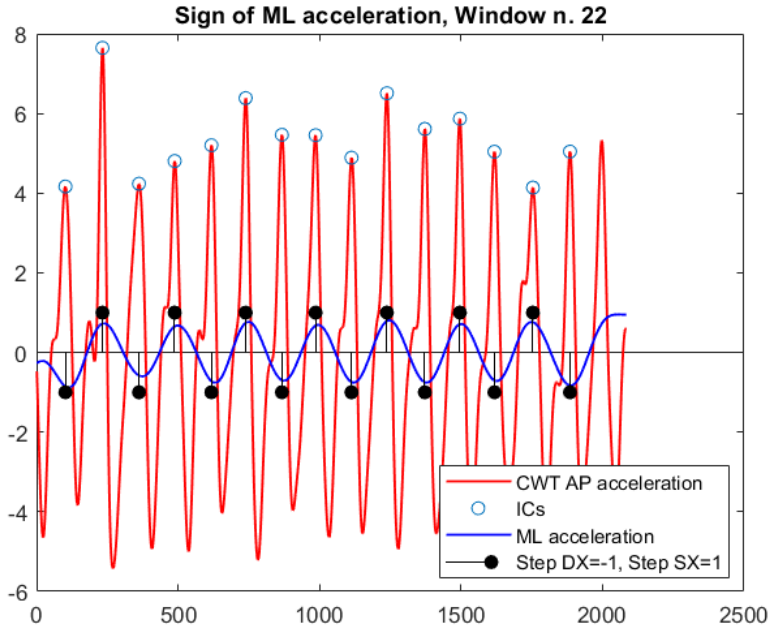


Figure 3.16: First method to divide steps into left and right: ML acceleration sign at ICs istants.

groups, providing errors in some cases, ie the physiological alternation between right and left step was failed. The following table (Tab.3.7) shows them and highlights how the first method is more precise in the steps differentation for Phase 1 and Phase 2 groups, while the second has provided a smaller error for controls. Therefore no method out performs the other one, as they have different performances for each

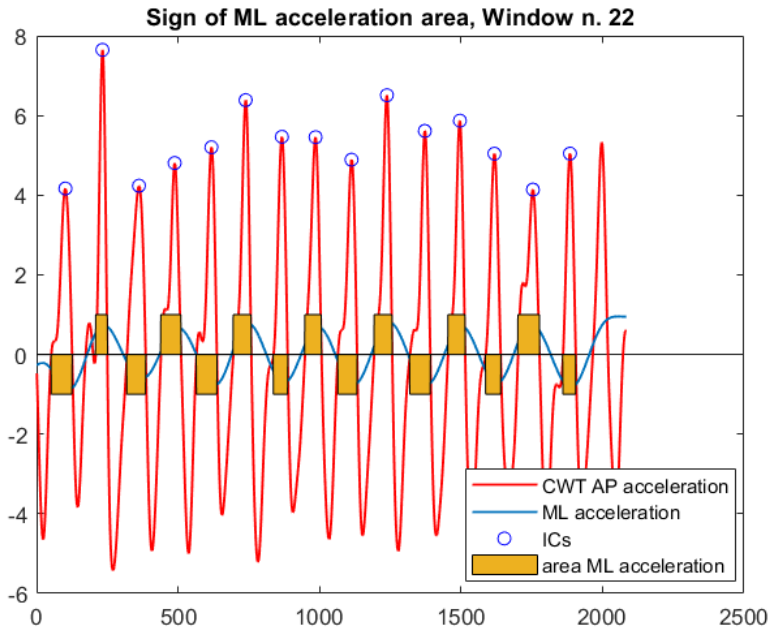


Figure 3.17: Second method to divide steps into left and right: sign of ML acceleration area between zero-crossing of CWT AP acceleration.

Table 3.7: First differentiation errors between left and rigth steps.

Mean Error %			
	Controls	**Phase 1**	**Phase2**
Method 1	10.3	13.1	7.4
Method 2	5.6	28.4	8.5

group. To solve this problem and globally reduce the error that may have a negative impact on variability and asymmetry results, it has been decided to combine their action: first of all, it has been chosen to consider and analyze only walking windows in which both methods provided an error less than 20%; then, for each considered window the method that returned the minor error was selected. In this way it has been possible to obtain a significant improvement: the error is less than 5% for all groups, as shown in Tab.3.8. However, for the subsequent calculations, incorrectly subdivided steps have not been taken into account.

Table 3.8: Final differentiation errors between left and right steps.

Mean Error %		
Controls	**Phase 1**	**Phase2**
2.7	4.4	2.1

3.2.7 Calculation of extra symmetry indices

After steps differentiation into right and left, in order to have a more complete picture of gait, it is possible to compute new symmetry indices, different from those obtained with the autocorrelation function, and relative to previously calculated spatio-temporal parameters, both for mean and standard deviation. The used equation is:

$$IndexLR = \left| \frac{Parameter_{left} - Parameter_{rigth}}{max(Parameter_{left}, Parameter_{right})} \right| \tag{3.27}$$

These indices have lower limit equal to 0, which occurs when the numerator difference is null, but does not have an upper limit. In fact, the greater the difference of the considered parameter between right and left, the greater the asymmetry will be. To have a complete view, Tab.3.9 lists all parameters and indexes that have been calculated in this report.

3.2.8 Computation of Correlation Coefficients

To conduct gait assessment, the next step has been to investigate the of correlation between the previously calculated spatio-temporal parameters and symmetry indices and the variables characterizing the two groups of PD subjects, listed in Tab.3.3 and 3.4. In particular, for Phase 1 the correlation between 56 parameters and the variables gender, age, gait assistance, disease duration and FOG episodes have been evaluated, while for Phase 2 between the same 56 parameters and scores of UPDRS tasks (gait, FOG, postural stability, arising from chair, posture, mean leg agility and scores average). In addition, the correlation with the H&Y score has been also calculated. It has been decided to calculate two types of correlation coefficients: Pearson product-moment (r) and Spearman's rank (ρ) correlation coefficients, to measure the linear correlation, both with a significance level of 0.05. These evaluations have been carried out by *corrocoef* and *corr* Matlab functions.

Table 3.9: Summary of computed spatio-temporal parameters and symmetry indices.

Spatio-temporal parameters	**Symmetry Indices**
Cadence [N.step/min] (Mean±SD)	Step Regularity *Ad1* (Mean±SD)
Stride Time [s] (Mean±SD)	Stride Regularity *Ad2* (Mean±SD)
Step Time [s] (Mean±SD)	Symmetry (Mean±SD)
Swing Time [s] (Mean±SD)	LR Stride Time (Mean & SD)
Swing Phase [%GC] (Mean±SD)	LR CV Stride Time
Stance Time [s] (Mean±SD)	LR Swing Time (Mean & SD)
Stance Phase [%GC] (Mean±SD)	LR CV Swing Time
Single Support Time [s] (Mean±SD)	LR Stance Time (Mean & SD)
Single Support Phase [%GC] (Mean±SD)	LR CV Stance Time
Double Support Time [s] (Mean±SD)	LR Single Support Time (Mean & SD)
Double Support Phase [%GC] (Mean±SD)	LR CV Single Support Time
Step Length [m] (Mean±SD)	LR Double Support Time (Mean & SD)
Gait Velocity [m/s] (Mean±SD)	LR CV Double Support Time
CV Cadenza	LR Swing GC (Mean & SD)
CV Stride Time	LR CV Swing GC
CV Swing GC	LR Stance GC (Mean & SD)
CV Stance GC	LR CV Stance GC
CV Single Support GC	LR Single Support GC (Mean & SD)
CV Double Support GC	LR CV Single Support GC
CV Step Length	LR Double Support GC (Mean & SD)
CV Gait Velocity	LR CV Double Support GC
	LR Step Length (Mean & SD)
	LR CV Step Length

3.2.9 Statistical analysis: significance tests

Some tests have been performed to assess statistically significant differences between examined groups. Three comparisons have been accomplished, using only 27 parameters:

- Comparison 1: between elderly controls group and PD subjects group (joining Phase 1 and Phase 2);
- Comparison 2: PD subject of Phase 2 have been divided into different groups according to their H&Y score and the comparisons have been carried out only between adjacent score groups.
- Comparison 3: Phase 1 and Phase 2 have been connected and then patients

have been divided into subjects that manifest FOG episodes (YFOG), do not show these episodes (NFOG) or have hesitation (HES). Then comparisons between all groups have been accomplished.

Depending on the data distribution of each parameter, different strategies have been performed:

1. If the parameter at hand had normal distributions for both groups indipendent *T-test* was carried out, through Matlab *ttest2* function with significance level of 0.05. The distributions have been investigated by *lillietest* Matlab function and also by a visual inspection, as this function does not take into account skewness.

2. If the parameter had non-normal but continuos distributions for both groups or if one distribution was normal and the other non-normal but continuos, the *Wilcoxon test* has been accomplished through Matlab *runksum* function with significance level of 0.05.

3. If parameter has at least one discontinuos distribution, no test has been conducted.

Chapter 4

Results

This chapter includes results related to algorithm performance, correlation coefficients and significance tests previously carried out.

4.1 Algorithm performance

First of all, the number of steps (represented by ICs number) detected by the algorithm has been compared with N_{step} in (3.5), calculated from autocorrelation function. So, it has been considered as a 'standard value'. This comparison provides an estimate of the implemented wavelet-based method reliability. Tab.4.1 shows the number of steps in each group detected both by the wavelet transforms and autocorrelation methods. It can be seen that for all three groups the algorithm

Table 4.1: Reliability of implemented method.

	Autocorrelation Method (#)	**Wavelet Method(#)**	**Wavelet Method (%)**
Control	3068	2955	96.3
Phase 1	7545	7182	95.2
Phase 2	1145	1071	93.5
Total	11758	11208	95.3

detects more than 90% of the steps. The lower value is obtained for PD subjects belonging to Phase 2, justified by the fact that these participants have fewer walking windows for patient and also a smaller number of steps in them (Tab.3.6), ie the walking pattern may not be completely developed as in the other two groups, since

the initiation strides profoundly alter the pattern. Over all, the wavelet method is able to detect 95.3% of the performed steps, therefore it shows good reliability and gives greater importance to the subsequent analyzes.
Secondly, since only a smartphone has been used on waist and parameters and indices have not been extracted directly from acceleration signal but from its wavelet transform, an error is expected. The dominant period *d1* extracted from the autocorrelation function allows to evaluate the error executed by the algorithm in the calculation of step time. Indeed, *d1* corresponds exactly to the time employed by the subject in each walking window to make a step, and it is considered as the standard. Therefore the computation error of step time has been first evaluated for each partecipant walking window, then mediated for each of them, and finally mediated for each group in the study. Tab.4.2 shows these mean values for each groups, highlighting an almost constant difference around 15ms. Phase 2 has the largest difference and this could occurs for the same reasons as before: a not completely developed acceleration pattern.

Table 4.2: Difference between step time from autocorrelation function and wavelets method.

Error [s]		
Controls	**Phase 1**	**Phase 2**
0.015	0.015	0.018

Finally, the algorithm has a good detection rate of physiological values. Indeed, as summarized in Tab.4.3, in all cases both for controls and PD subjects it found stride time greater than 0.7s; for swing and stance %GC the obtained physiological values are always greater than 85%, ie 93% and 87% for controls and PD subjects respectively. This confirms that despite having a slight delay in the ICs identification, the algorithm can be used to carry out an adequate gait analysis.

Table 4.3: Detected physiological values

	Stride Time (>0.7s)	**Swing & Stance (>29.5% & <45.5%) & (>55.5% & <70.5%)**
Controls	100%	93%
PD Subjects	100%	87%

4.2 Correlation Coefficients - Phase 1

As for phase 1, the correlation coefficients obtained between 56 parameters and the variables gender, age, gait assistance, disease duration, FOG episodes have been analyzed. The most significant values are shown in the following tables, where the parameter related to the considered variable, the correlation coefficient, the significance level (p-value) and the type of correlation (Pearson or Spearman) are indicated. The parameters not present in the tables have significance levels greater than 0.05.

Age

With advancing age an increase in stance and a corresponding decrease in swing, with reducted single support and increased double support, have been found. Therefore PD subjects keep for longer both feet on the ground during gait cycle. Also a growth in single and double support variability has been detected. However, the greatest correlation coefficient has been discovered for the mean step length (r =-0.62 and p <0.001). Also mean gait velocity decreases (reflecting slower walking pattern), and it is more variable, as reported in Tab.4.4.

Table 4.4: Correlation coefficients - Phase 1, Age.

Age (p<0.05)			
Parameter	**r**	**p**	**Type**
Swing %GC Mean	-0.45	0.019	Spearman
Stance %GC Mean	0.47	0.014	Spearman
Single Support %GC SD	**0.49**	**0.01**	Spearman
Double Support %GC SD	**0.49**	**0.01**	Spearman
Single Support %GC Mean	-0.40	0.043	Spearman
Double Support %GC Mean	0.40	0.043	Spearman
Step Length Mean	**-0.62**	**<0.001**	Spearman
CV Gait Velocity	0.40	0.039	Spearman
Gait Velocity Mean	-0.40	0.043	Pearson

Gait Assistance

If PD subjects make use of walking aid, a raising in swing stance, single support and double support variability, expressed as SD and CV, has been identified. However,

the distinctive parameters for this variable are the swing and stance symmetry indices: significant differences between values corresponding to right and left limbs are highlighted. The Tab.4.5 summaryzes coefficients.

Table 4.5: Correlation coefficients - Phase 1, Gait Assistance.

Gait Assistance (p<0.05)			
Parameter	**r**	**p**	**Type**
Swing %GC SD	0.49	0.01	Pearson
Stance %GC SD	0.47	0.014	Pearson
CV Swing %GC	0.40	0.039	Pearson
Single Support %GC SD	0.40	0.04	Pearson
Double Support %GC SD	0.40	0.04	Pearson
CV Double Support %GC	0.43	0.026	Pearson
LR Swing Time Mean	0.46	0.016	Spearman
LR Stance Time Mean	0.50	0.007	Spearman
LR Swing %GC Mean	**0.46**	**0.016**	Spearman
LR Stance %GC Mean	**0.50**	**0.009**	Spearman

Disease Duration

As the disease progress, a general increase in parameters variability has been detected. Indeed, stance, swing, single support, gait velocity and step length are all more variable. Nevertheless, the most relevant parameter in the correlation of disease duration is certainly stride time variability, expressed indistinctly as SD or CV. It is a distinguishing feature of PD gait, and increased falls risk is associated to it. The Tab.4.6 shows obtained coefficients.

Gender

In order to perform this type of correlation, men were assigned score 0 and women 1. It has been found that women spend more time to stride, but at the same time they have more regularity than men. For the latter, less variability in stance time has been also recorded, as shown in Tab.4.7.

FOG Episodes

To carry out this correlation, score 0 has been assigned to patients that do not usually show FOG episodes, 1 to those who manifest them. Increases in swing,

Table 4.6: Correlation coefficients - Phase 1, Disease Duration.

Disease Duration (p<0.05)			
Parameter	**r**	**p**	**Type**
Swing %GC SD	0.45	0.018	Spearman
Stance %GC SD	0.44	0.02	Spearman
CV Swing %GC	0.56	0.002	Spearman
CV Stance %GC	0.47	0.014	Spearman
CV Single Support %GC	0.57	0.002	Pearson
Stride Time SD	**0.49**	**0.01**	Pearson
CV Stride Time	**0.53**	**0.005**	Pearson
Gait Velocity SD	0.51	0.007	Spearman
CV Gait Velocity	0.5	0.008	Spearman
Step Length SD	0.42	0.031	Spearman

Table 4.7: Correlation coefficients - Phase 1, Gender.

Gender (p<0.05)			
Parameter	**r**	**p**	**Type**
Stride Time Mean	0.39	0.044	Pearson
LR Stance Time SD	0.55	0.003	Pearson
LR Stance Time CV	0.44	0.02	Pearson
Stride Regularity *Ad2* Mean	0.46	0.016	Pearson

stance, single support and double support variability have been found. On the other hand, step length decreases, just like symmetry index of stride time variability. This means that the difference between the variability of right and left stride time tends to be less. This may be due to reduction in step regularity, ie subjects with FOG have an intrinsically variable walking pattern at each step. Tab.4.8 shows correlation coefficients.

4.3 Correlation Coefficients - Phase 2

A linear correlation between previously calculated parameters and indices of the 25 patients belonging to Phase 2 and UPDRS task scores has been sought. Relations have been detected only for items of gait, postural stability, FOG, arising from chair and also H&Y score. Tab.4.9 shows their groups cardinality. Only parameters for which a correlation with a significance level lower than 5% has been found are reported in the following tables, that include also root-mean-square-error (RMSE).

Table 4.8: Correlation coefficients - Phase 1, FOG Episodes.

FOG Episodes (p<0.05)			
Parameter	**r**	**p**	**Type**
Swing %GC SD	0.40	0.04	Pearson
CV Swing	0.49	0.01	Spearman
Stance %GC SD	0.42	0.028	Pearson
Cv Stance	0.48	0.012	Spearman
Single Support %GC SD	0.44	0.021	Pearson
CV Single Support	0.50	0.009	Spearman
Double Support %GC SD	0.44	0.021	Pearson
Step Length Mean	-0.40	0.036	Spearman
LR Stride Time SD	-0.49	0.01	Spearman
LR Stride Time CV	-0.49	0.01	Spearman
LR Single Support %GC Mean	0.43	0.027	Pearson
Step Regularity *Ad1* Mean	**-0.50**	**0.009**	Spearman

Table 4.9: Groups cardinality for each analized UPDRS item.

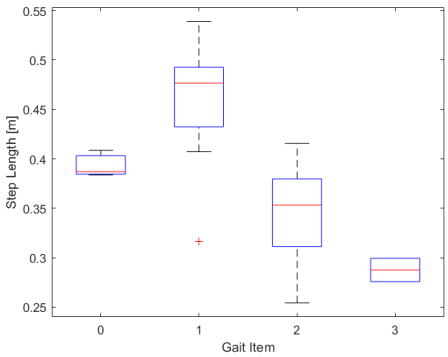
	0	**1**	**2**	**3**	**4**	**NaN**
Gait	3	11	9	2	-	-
Postural Stability	6	7	5	7	-	-
FOG	15	6	3	-	-	1
Arising Chair	6	11	4	3	-	1
H&Y	2	3	6	11	1	2

Gait Item

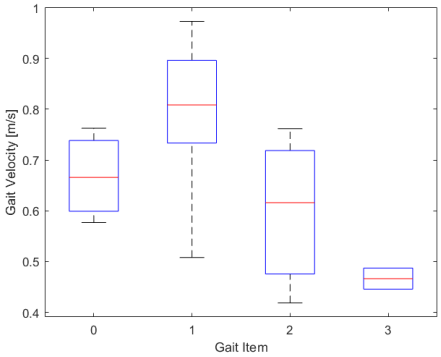
Tab.4.10 underlines that step length and gait velocity parameters are optimally correlated with gait item score. In particular, as this score increases, there is a clear reduction in the two parameters, confirming that PD subjects have a slower walking pattern. Decreases in step regularity and symmetry have also been found. Fig.4.1 shows the boxplots of stride length and gait velocity relating to PD subjects divided according to gait item score, while Fig.4.2 exhibits step regularity and symmetry trends. As previously explained by correlation coefficients, all these parameters have a decreasing trend with non-overlapping boxplots. However, group with zero score does not respect this trend.

Table 4.10: Correlation coefficients - Phase 2, Gait Item.

Gait Item (p<0.05)				
Parameter	**r**	**p**	**RMSE**	**Type**
Step Length Mean	**-0.72**	**0.002**	**0.068**	Pearson
Gait Velociy Mean	**-0.68**	**0.005**	**0.015**	Spearman
Step Regularity *Ad1* Mean	-0.54	0.032	0.152	Spearman
Symmetry Mean	-0.58	0.022	0.176	Pearson



(a) *Step Length as a function of UPDRS gait item score.*



(b) *Gait Velocity as a funcion of UDPRS gait item score.*

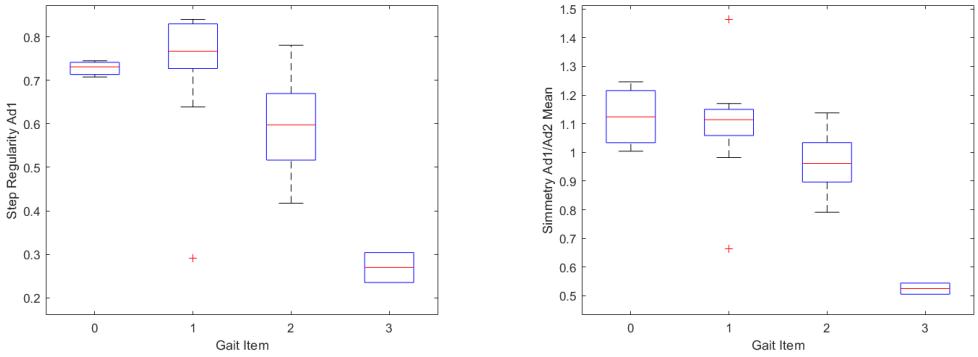
Figure 4.1: Step Length and Gait Velocity as functions of UPDRS gait item score.

Postural Stability Item

From this calculation (Tab.4.11), decreases of step regularity and step length have been identified. On the contrary, increases in swing, stance, but above all stride time variability have been found. Since the latter is highly associated with falls risk, subjects with greater postural instability are also more likely to fall. Fig. 4.3 exhibits parameters tendency.

FOG Item

As for FOG item, the most correlated parameter is cadence, which increases its variability, both expressed as SD and CV (Tab.4.12). In fact, subjects that manifest these episodes do not have a regular walking pattern, especially when the episodes also occur on a linear way and not only in narrow spaces or during turning. Moreover, a decrease in symmetry indices of single and double support variability has



(a) *Step Regulrity as a function of UPDRS gait item score.*

(b) *Symmetry as a funcion of UDPRS gait item score.*

Figure 4.2: Step Regularity and Symmetry as functions of UPDRS gait item score.

Table 4.11: Correlation coefficients - Phase 2, Postural Stability Item.

Postural Stability Item(p<0.05)				
Parameter	**r**	**p**	**RMSE**	**Type**
Swing %GC SD	**0.55**	**0.032**	**0.887**	Spearman
CV Stance	0.52	0.046	2.258	Spearman
Step Length Mean	-0.53	0.041	0.069	Pearson
Stride Time SD	0.53	0.043	0.034	Spearman
CV Stride Time	**0.58**	**0.024**	**2.828**	Spearman
Step Regularity	-0.55	0.032	0.149	Spearman
Symmetry	-0.52	0.047	0.186	Spearman

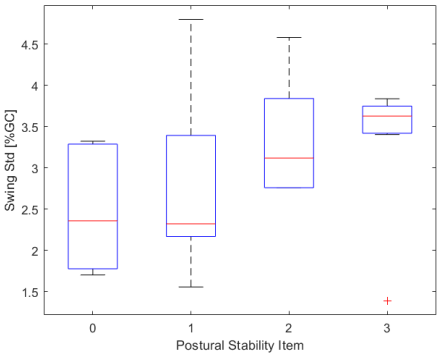
been detected. Fig.4.4 shows trend of correlated parameters to the change of FOG item score.

Arising from chair item

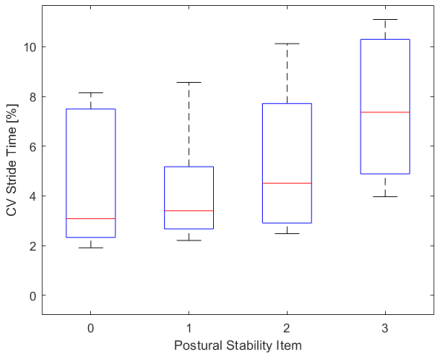
The correlation with "arising from chair" item did not yield very significant results: only increases in swing and stance variability have been found. Tab.4.13 shows these values, while Fig.4.5 illustrates their trends.

H&Y

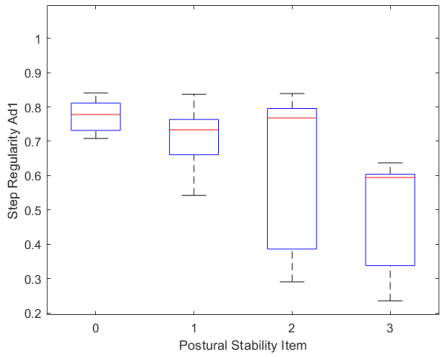
The correlation with H&Y score produced good results: clear decreases in step regularity (-0.73), symmetry (-0.75), step length (-0.64) and gait velocity (-0.53) have



(a) *Swing %GC SD as a function of UPDRS postural stability item score.*



(b) *CV Stride Time as a function of UPDRS postural stability item.*



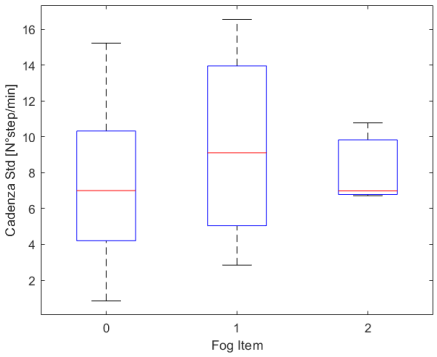
(c) *Step Regularity as a function of UPDRS postural stability item.*

Figure 4.3: Swing %GC SD, CV Stride Time, Step regularity as functions of UPDRS postural stability item score.

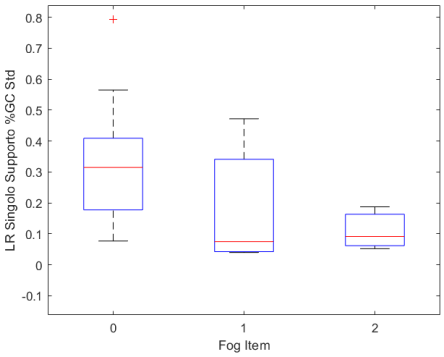
Table 4.12: Correlation coefficients - Phase 2, FOG Item.

FOG Item(p<0.05)				
Parameter	**r**	**p**	**RMSE**	**Type**
Cadence SD	**0.69**	**0.005**	**4.339**	Spearman
Cadence CV	0.63	0.011	5.675	Spearman
LR Single Support %GC SD	-0.57	0.025	0.185	Spearman
LR Double Support %GC SD	-0.57	0.025	0.185	Spearman

been found, which show a worsening of walking pattern as the disease progresses. Tab.4.14 shows the obtained values, and Fig.4.6 shows their trend.



(a) *Cadence SD as a function of UPDRS FOG item score.*



(b) *LR Single Support %GC SD as a function of UPDRS FOG item.*

Figure 4.4: Cadence SD and LR Single Support %GC SD as functions of UPDRS FOG item score.

Table 4.13: Correlation coefficients - Phase 2, Arising Chair Item.

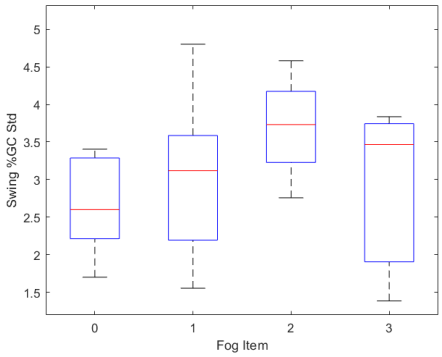
Arising Chair Item(p<0.05)				
Parameter	**r**	**p**	**RMSE**	**Type**
Swing %GC SD	0.55	0.032	0.969	Spearman
CV Stance	0.58	0.024	2.452	Spearman

4.4 Significance Tests

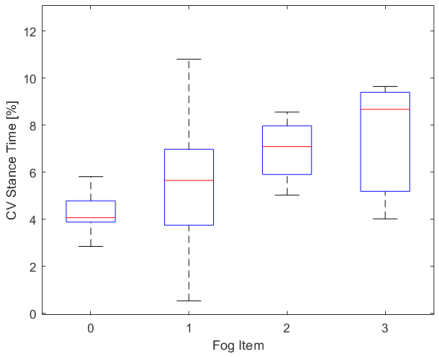
The following subsections describe results acquired by significance tests carried out between various groups. For all comparisons only parameters for which groups were statistically different are shown in tables , along with the corresponding p-value.

4.4.1 Comparison 1: Controls vs PD subjects

The first comparison has been accomplished between elderly controls groups and PD subjects group (joining Phase 1 and Phase 2). From significance test (Tab.4.15) it results that controls have a slower walking pattern (reduced swing, greater stance and reduced speed) and also greater variability in terms of single support, double support and stide time. Instead, PD subjects exhibit for greater variability in cadence, less step regularity and symmetry. This happens because the groups are not well stratified by age.



(a) *Swing %GC SD as a function of UPDRS Arising Chair item score.*



(b) *CV Stance as a function of UPDRS Arising Chair item.*

Figure 4.5: Swing %GC SD and CV stance as functions of UPDRS FOG item score.

Table 4.14: Correlation coefficients - Phase 2, H&Y.

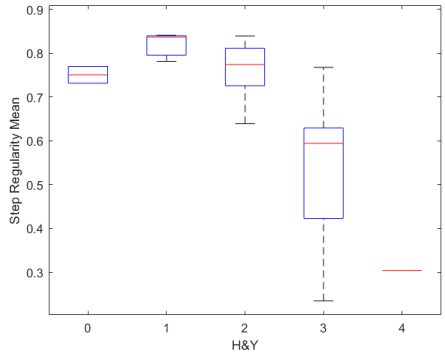
H&Y(p<0.05)				
Parameter	**r**	**p**	**RMSE**	**Type**
Step Regularity *Ad1*	**-0.73**	**0.002**	**0.153**	Spearman
Symmetry	**-0.75**	**0.001**	**0.193**	Spearman
Step Length	**-0.64**	**0.010**	**0.080**	Spearman
Gait Velocity	-0.53	0.044	0.166	Spearman

4.4.2 Comparison 2: PD Phase 2 according to H&Y

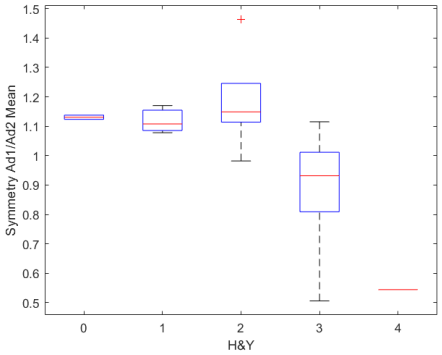
For this comparison (Tab.4.16, 4.17, 4.18, 4.19) PD subjects of Phase 2 have been included. They have also been divided in different groups, according to their H&Y score. Only groups with adjacent H&Y score have been analysed.
The attention has been mainly focused on stride regularity and simmetry. In this regard, these parameters showed significant differences between groups with H&Y stages 2-3 and 3-4, therefore in the most advanced stages of disease, showing a clear reduction. More generally, the most significant differences between parameters have been found always in comparison of these groups.

4.4.3 Comparison 3: PD subjects YFOG, NFOG, HES

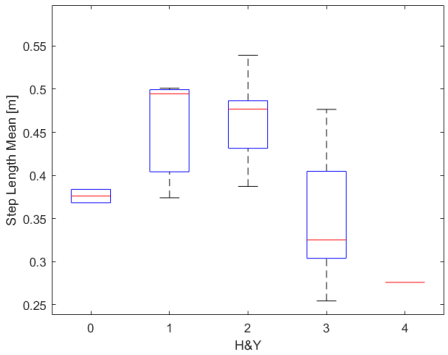
In this comparison PD subjects of Phase 1 and Phase 2 have been included and divided into three groups: those presenting FOG episodes, not presenting and



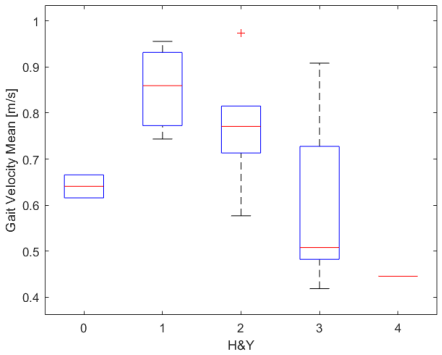
(a) *Step Regularity Ad1 as a function of H&Y.*



(b) *Symmetry as a function of H&Y.*



(c) *Step Length as a function of H&Y.*



(d) *Gait Velocity as a function of H&Y.*

Figure 4.6: Step Regularity, Symmetry, Step Length and Gait Velocity as functions of H&Y.

expressing hesitation. Significant differences between all groups have been sought, in order to evaluate informations about continuos walking pattern. A large number of these have been found in the comparison between NFOG and HES (Tab.4.21), and NFOG and YFOG (Tab.4.22), while between HES and YFOG (Tab.4.20) the differences were smaller.

Table 4.15: Comparison 1: Controls vs PD subjects.

Comparison 1(p<0.05)			
Parameter	**Controls (Mean ± SD)**	**PD (Mean ± SD)**	***p-value***
Cadence SD	**3.62±1.25**	**5.72±2.30**	**0.0008**
Swing %GC Mean	38.95±2.65	39.45±1.73	0.038
Stance %GC Mean	61.22±2.53	60.70±1.71	0.026
Single Support %GC SD	2.51±1.34	2.17±1.40	0.003
CV Single Support	5.13±2.35	4.37±2.32	<0.0001
Double Support %GC SD	2.51±1.34	2.17±1.40	0.003
CV Double Support	11.86±5.66	10.78±7.03	0.008
Stride Time SD	0.042±0.02	0.033±0.02	<0.0001
CV Stride Time	3.31±1.47	2.91±1.53	0.007
Step Time Mean	0.63±0.05	0.56±0.05	<0.0001
Step Time SD	0.039±0.017	0.033±0.018	0.001
Gait Velocity Mean	0.69±0.10	0.77±0.16	<0.0001
Gait Velocity SD	0.073±0.026	0.082±0.035	0.049
Step Regularity *Ad1*	**0.83±0.06**	**0.77±0.14**	**0.0002**
Symmetry	**1.08±0.07**	**1.01±0.13**	**<0.0001**

Table 4.16: Comparison 2: PD group with H&Y=0 vs PD group with H&Y=1.

Comparison 2: H&Y=0 and H&Y=1(p<0.05)			
Parameter	**PD H&Y=0 (Mean ± SD)**	**PD H&Y=1 (Mean ± SD)**	***p-value***
Stride Time Mean	1.17±0.04	1.07±0.06	0.017
Step Time Mean	0.59±0.02	0.54±0.03	0.030
Gait Velocity Mean	0.64±0.03	0.85±0.11	0.004

Table 4.17: Comparison 2: PD group with H&Y=1 vs PD group with H&Y=2.

Comparison 2: H&Y=1 and H&Y=2(p<0.05)			
Parameter	**PD H&Y=1 (Mean ± SD)**	**PD H&Y=2 (Mean ± SD)**	***p-value***
Stride Time Mean	1.07±0.06	1.25±0.10	0.002
Step Time Mean	0.54±0.03	0.62±0.05	0.002

Table 4.18: Comparison 2: PD group with H&Y=2 vs PD group with H&Y=3.

Comparison 2: H&Y=2 and H&Y=3(p<0.05)			
Parameter	**PD H&Y=2 (Mean ± SD)**	**PD H&Y=3 (Mean ± SD)**	***p-value***
Stride Time Mean	1.25±0.10	1.14±0.10	0.003
Step Time Mean	0.62±0.05	0.57±0.05	0.004
Step Length Mean	**0.45±0.06**	**0.35±0.07**	< 0.0001
CV Step Length	10.94±5.59	15.70±5.73	0.009
Step Regularity *Ad1*	**0.79±0.06**	**0.60±0.12**	< 0.0001
Symmetry	**1.16±0.08**	**0.96±0.13**	< 0.0001

Table 4.19: Comparison 2: PD group with H&Y=3 vs PD group with H&Y=4.

Comparison 2: H&Y=3 and H&Y=4(p<0.05)			
Parameter	**PD H&Y=3 (Mean ± SD)**	**PD H&Y=4 (Mean ± SD)**	***p-value***
Stride Time Mean	1.14±0.10	1.30±0.09	0.011
Stride Time SD	0.055±0.040	0.132±0.098	0.027
CV Stride Time	4.66±3.22	9.89±6.67	0.042
Step Time Mean	0.57±0.05	0.65±0.04	0.005
Step Time SD	0.051±0.039	0.109±0.066	0.020
Step Length Mean	**0.35±0.06**	**0.27±0.02**	**0.012**
Gait Velocity Mean	0.63±0.15	0.43±0.05	0.008
Step Regularity *Ad1*	**0.60±0.12**	**0.30±0.12**	**0.001**
Symmetry	**0.96±0.13**	**0.54±0.22**	**0.001**

Table 4.20: Comparison 3: PD HES vs PD YFOG.

Comparison 3: PD HES vs PD YFOG			
Parameter	**PD HES (Mean ± SD)**	**PD YFOG (Mean ± SD)**	***p-value***
Swing %GC Mean	39.66±1.17	38.95±2.21	0.014
Cv Swing	10.93±2.49	8.77±3.70	0.0001
CV Stance	7.60±2.31	5.83±2.63	0.0001
CV Single Support	7.84±3.11	5.93±2.94	0.0026
Stride Time Mean	1.24±0.14	1.14±0.10	0.0001
CV Stride Time	6.11±2.96	3.51±1.67	< 0.0001
Step Time Mean	0.62±0.07	0.57±0.05	0.0005
Gait Velocity Mean	0.61±0.10	0.68±0.15	0.034
Symmetry	0.82±0.23	0.97±0.16	< 0.0001

Table 4.21: Comparison 3: PD NFOG vs PD HES.

Comparison 3: PD NFOG vs PD HES			
Parameter	**PD NFOG (Mean ± SD)**	**PD HES (Mean ± SD)**	***p-value***
Swing %GC SD	2.06±1.05	3.31±0.80	< 0.0001
CV Swing	6.06±2.63	10.93±2.49	< 0.0001
Stance %GC SD	2.00±0.97	3.14±0.80	< 0.0001
CV Stance	4.01±1.93	7.60±2.30	< 0.0001
Single Support %GC SD	1.80±1.23	2.70±0.92	< 0.0001
CV Single Support	3.62±1.78	7.84±3.11	< 0.0001
Double Support SD	1.80±1.23	2.70±0.92	< 0.0001
CV Double Support	8.98±6.18	12.54±4.59	0.0001
Stride Time Mean	1.11±0.08	1.24±0.14	< 0.0001
Stride Time SD	0.027±0.013	0.079±0.044	< 0.0001
CV Stride Time	**2.42±1.13**	**6.10±2.96**	< 0.0001
Step Time Mean	0.56±0.04	0.62±0.07	< 0.0001
Step Length Mean	0.45±0.07	0.37±0.03	< 0.0001
Step Length SD	0.035±0.017	0.051±0.017	< 0.0001
CV Step Length	8.27±4.83	13.69±4.23	< 0.0001
Gait Velocity Mean	0.81±0.14	0.61±0.10	< 0.0001
CV Gait Velocity	9.47±4.87	15.98±5.83	< 0.0001
Stride Regularity *Ad2*	**0.81±0.06**	**0.67±0.19**	**0.0002**
Symmetry	**1.05±0.07**	**0.82±0.23**	< 0.0001

Table 4.22: Comparison 3: PD NFOG vs PD YFOG.

Comparison 3: PD NFOG vs PD YFOG			
Parameter	**PD NFOG (Mean ± SD)**	**PD YFOG (Mean ± SD)**	***p-value***
Swing %GC Mean	39.64±1.48	38.95±2.21	0.003
Cv Swing	6.06±2.67	8.77±3.70	< 0.0001
Stance %GC Mean	60.45±2.63	61.27±2.07	0.0002
CV Stance	4.01±1.93	5.83±2.63	< 0.0001
Single Support %GC Mean	79.79±2.68	78.74±4.82	0.033
CV Single Support	3.62±1.78	5.93±2.94	< 0.0001
Double Support %GC Mean	20.21±2.68	21.26±4.82	0.035
CV Double Support	8.98±6.18	15.45±9.19	< 0.0001
Stride Time Mean	1.11±0.08	1.14±0.10	0.005
CV Stride Time	**2.42±1.13**	**3.51±1.67**	< 0.0001
Step Time Mean	0.56±0.04	0.57±0.05	0.0016
Step Length Mean	0.45±0.07	0.39±0.08	< 0.0001
CV Step Length	8.29±4.82	13.16±4.61	< 0.0001
Gait Velocity Mean	0.81±0.14	0.68±0.15	< 0.0001
CV Gait Velocity	9.47±4.87	14.65±4.53	< 0.0001
Stride Regularity *Ad2*	**0.81±0.06**	**0.69±0.12**	< 0.0001
Symmetry	**1.05±0.07**	**0.97±0.16**	< 0.0001

Chapter 5

Discussion

The correlations for PD subjects of Phase 1 mainly provide general information on the disease, both regarding continuous and episodic motor disturbances. In particular, correlations with subject age and disease duration are of considerable interest for continuous impairment. As for age, a large number of PD walking features have been detected: a definite reduction in step length and gait velocity has been observed, followed by increase in stance at swing expense. These results clearly indicate the presence of a slower and compromised, non-rhythmic walking pattern, since gait velocity increases its variability. Increases in single and double support variability have been also identified. Therefore, globally, it is possible to conclude that, with age progression, motor symptoms related to gait impairment tend to worsen, where the reduced and shorter step length (which has the greatest correlation coefficient, -0.62) could be the triggering cause of the other gait distubances, as reduced gait velocity and increased time with the feet on the ground. These results agrees with those present in literature, as Schlachetzki et al. [82] that exposes the same parameters trends.

The PD gait motor disturbances also include features that are not always easily identifiable during routine clinical observation, but which can be detected by gait analysis systems. One of these is the loss of ability to produce a steady gait rhythm, resulting in higher stride time variability, that is a characteristic feature of gait in PD, closely associated with risk of falls. The correlation with disease duration shows this feature trend, both expressed as SD and CV, where their magnitude tends to increase (0.53), as also reported by Hausdorff [34]. Stride time variability

is a manifestation of a general gait variability, which is also expressed by detected increase in variability of other parameters, such as swing, stance, gait velocity and step length.
For episodic disturbances, correlation with FOG episodes provide some useful informations. First of all, reduction in step regularity has been detected (-0.50), ie patients that manifest these episodes show a less rhytmic and consistent walking pattern. Moreover, similar to correlation with age and disease duration, increase in general gait variability has been found, expressed by CV or SD growth of swing, stance, single support and double support, but also by a reduction in symmetry indices of stride time variability. This means that gait variability is a general feature, and not primarily focused on a specific lower limb.
Correlations with gait assistance and gender provide information not related to the general disease, but more specific to the examined cases: if PD subject uses a walking aid, there is a difference between right and left stance/swing, as expressed by relative symmetry indexes and as it is reasonable to expect. About gender, women seem to have a greater stride time but at the same time a higher gait regularity, and therefore greater stability.
The UPDRS Part III is a means widely used by neurologists to evaluate motor functionality of PD subjects, but it is affected by inter and intra rater variability. Indeed, clinicians do not always assign the same score for an item to a given patient. This can occur because the entries pertaining to a particular score of a specific item are not sufficiently clear, but allows for further interpretation by neurologists. Therefore, the need to quantify the UPDRS items has been felt, in order to provide more precise and objective information that can be used by clinicians, in addition to their experience, to assign a given score.
According to the definition of UPDRS gait item, is given a score to gait by observing mainly changes in step length and velocity. The high detected correlation values correspond to clinician's gait rating: they underline that step length and gait velocity are significantly reduced (-0.72 and -0.68, respecively) in patients who have substantial gait impairment compared to those who have a lower score (minimal or absent damage). The reduction of step regularity (-0.54) also confirms the typical and highly variable gait pattern, while increase of asymmetry agrees with the unilateral nature of the disease.
The performance in pull test determines score assigned by neurologists to postural

stability item. In particular, more are the steps performed by the subject to recover posture and balance or if these are totally absent and subject falls if not supported, higher the score will be. In addition to pull test observation, the extracted correlation coefficients provide a useful supplementary information: the increase in gait variability, expressed by swing and stance variability, step regularity and stride time variability. The latter is related to an increased falls risk, confirming that postural instability is highly related to these events, endangering patients and worsening their quality of life. Instead, the reduction of step length means that the subject takes smaller steps, transferring body weight between limbs more frequently.
Patients in a moderate stage of the disease (H&Y stage 3) show a clear reduction of most the identifying gait parameters: step length (-0.64) and velocity (-0.53). Also step regularity and symmetry are significantly reduced (-0.73 and -0.75, respectively). The first one agrees with the fact that as the H&Y score increases, the patient is more affected by disease and gait impairment, thus showing a greater general gait variability. On the other hand, symmetry is partially in contrast with H&Y scale entries. According to these, score 1 indicates unilateral involvement and 2 a bilateral. However, in patients belonging to these two groups approximately the same symmetry value has been found, and a distinct reduction comes from score 2 onwards. This can be explained by the fact that, although the disease initially reveals itself in a unilateral way and subsequently tends to affect both sides, nevertheless it keeps a unilateral nature, ie there will be always a more affected side.
The results of gait, postural stability and H&Y correlations are consistent with those achieved from other studies: Schlachetzki et al. [82] found PD gait characheristics including short steps, shuffling gait and postural instability features, using inertial sensors units attached laterally to both shoes and comparing parameters to UPDRS gait score; Das et al.[83] obtained mean speed correlation coefficient of -0.51 with UPDRS gait task using motion capture data; Salarian et al.[86] reported high negative correlations between stride length and velocity with UPDRS gait item having use of body-attached gyroscopes.
However, in this work, it has been found that subjects with scores equal to 0 do not respect trend parameters correlated with these UPDRS item, and this may depend on two reasons: a low population in this group or a non-precise distinction of subjects with scores 0 and 1 by neurologists.
Regarding arising chair item, only increases in swing and stance variability have

been found, while about FOG item the noteworthy result is the correlation with cadence SD that significantly intensifies (0.69). Also reduction in symmetry variability indices of single and double support has been detected. This means that there is a tendency to have the same degree of variability on both lower limbs.
The general comparison between controls and PD subjects shows contrasting results compared to those in literature. Schlachetzki et al.[82] reported reduction of stride length and increase of stride time, ie manifestations of a pattern with reduced cadence and gait velocity, reflecting typical bradykinetic characteristics of gait in PD; Wahid et al.[84] obtained higher cadence and smaller step length in PD subjects than in controls; Sofuwa et al.[85] found lower walking velocity and stride length, Salarian et al.[86] reported significantly different gait parameters (like reduced velocity and stride length) between PD subject and controls.
However, in the present work, the opposite has been noted. Controls have a much slower walking pattern than PD subjects: they show a greater swing and a lower stance (keeping feet more time on the ground); have greater variability in single and double support expressed as SD or CV; spend longer time to make a stride with even greater variability (having greater falls risk), and also gait velocity and its variability are reduced. Nevertheless, these results have a specific cause: controls group has a mean age of 84.9 years, significantly higher than the PD subjects group age (70.1). Therefore, it is reasonable that these participants, having an advanced age and a reduced muscular strength, manifest a much slower walking pattern than subjects with a distinctly inferior age, even if with PD. However, these evidences highlight a notheworhty aspect of PD walking: despite controls have slower pattern, PD patients exhibit statistically significant differences concering cadence variability, step regularity and symmetry. In particular, the greater cadence variability is confirmed as one of gait PD features, as well as highest variability to make steps, exposing subject to greater falls possibilities. Instead, about symmetry, this has been found significantly lower than controls, confirming again the asymmetric manifestation of the disease motor symptoms.
About comparison 2, executed between groups with adjacent H&Y scores, results confirm what has been obtained with correlation coefficients. There is a decreasing trend of step regularity and symmetry, but this occurs only in the most advanced stages of disease, confirming that groups with H&Y equal to 0, 1 and 2 are not well differentiated. Therefore, even highlighting this problem, it is possible to claim

that most advanced stages of PD are characterized by a more variable, less stable and non-rhythmic walking pattern and by asymmetry that continues to manifest itself, even if the motor symptoms are widespread on both lower limbs. Also reductions of step length and gait velocity have been found only in these advanced stage, while other parameters, although presenting significant differences between various groups, have a variable trend, like stride time and step time.
Regarding the last comparison (number 3), it shows that it is possible to clearly discriminate subjects that not usually manifest FOG episodes from those who manifest them or express hesitations, while the other two groups appear to be closer and less distinguishable. Indeed, NFOGs express a less compromised walking pattern than HESs: gait variability, expressed by swing, stance, single support, double support, stride time, step length and gait velocity SD or CV is significantly lower; mean values of stride time and step time are smaller (and therefore velocity is greater), and finally even the rhythm of stepping and symmetry have higher values. Also compared to YFOG group, the NFOGs have a better and faster walking pattern: in addition to a lower gait variability, a lesser swing time (and consequently greater stance), higher speed, better stride regularity and higher symmetry have been also found. Instead, as for comparison between YFOGs and HESs, the latter seem to have most compromised gait: they manifest greater variability, higher step time and stride time, and reduced velocity and symmetry. However, this comparison should be further investigated, also increasing HES group population which is lower compared to the other two groups.
Therefore, based on this, we can claim that the most significant comparison is between NFOGs and YFOGs. It represents a further demonstration of results previously observed in Phase 1 and Phase 2 correlations: subjects that manifest FOG episodes have an evident and growing arrhythmicity of stepping, short steps, and a marked increase in gait variability, expressed by swing, stance, double support, single support. In addition, they spend more time with both feet on the ground, as shown by increased stance and double support phases and by corresponding decrease of swing and single support. Also raised stride time variability has been found, emphasizing that FOG, together with postural instability, contribute to exposing subject to a greater risk of falls. All these results about comparison between NFOG and YFOG are consistent with literature: Shah et al. [87] reported same parameters trend using pressur sensor impregnated mat and Weiss et al. [88] found

that freezers had decreased stride regularity compared with non-freezers.

Chapter 6

Conclusions

The application of wavelet transform to vertical and anteroposterior acceleration components allows to detect 95.3% of steps perfomed by participants and to obtain parameter values in physiological ranges. Their trend follows clinically relevant patterns and confirms what is present in literature: reduced swing in favor of stance, reduced gait velocity and step length, asymmetry, but especially increase of gait variability. The trend of this feature has been found in all performed analyses: correlations with age, disease duration, UPDRS item score, H&Y score, comparison between controls and PD, and also between NFOG and YFOG. It is mainly represented by an increase of stride time variability and by a reduction of step/stride regularity. Therefore, PD subjects have a less consistent, arrhythmic and less stable walking pattern, especially in advanced stages of disease.
This work has shown that it is possible to adequately and satisfactorily perform gait assessment in PD through wearable systems, such as a single waist-mounted smartphone, which has the capability to detect changes of some spatio-temporal parameters that are difficult to appreciate during a routine clinical examination. To implement this, it is not necessary for subjects to walk long distances, as demonstrated by Phase 2 group, whose data have been acquired in ADL-like conditions, which makes this approach usable also in a domestic environment. It allows to describe current motor state of PD subject, and can be also extremely useful to monitor the progress of gait impairment, providing in this regard additional and objective informations (also about UPDRS item) that can be employed by neurologists to modify appropriately and specific for each patient the pharmacological

treatment. Furthermore, expressing good sensitivity towards the detection of gait variability, it is also possible to predict and control the risk of falls associated with it and postural instability, that compromise patient quality of life. Finally, having demonstrated good performance for PD subjects with gait impairment, it can be also used in rehabilitation environment to monitor the improvement of subject motor conditions, or to evaluate healthy subjects gait.

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