POLITECNICO DI TORINO

Master Degree Course in Biomedical Engineering

Master Degree Thesis

The phenomenon fatigue in patients with multiple sclerosis treated with 4-aminopyridine: an experimental setting able to quantify the possible improvement of the symptom.

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July 2018

Sommario

to my family

INTRODUCTION

Multiple Sclerosis is a multifactorial disease still argument of much research and studies. At present, there is no therapy and treatment able to cure the disease. For this reason, many drugs are still experimental and a continuous and constant monitoring of patients is needed to evaluate the effectiveness of the therapy. Multiple Sclerosis causes different symptoms among which fatigue is one of the most annoying and debilitating symptom. One way to monitor the patients' conditions, besides the analysis of magnetic stimulations, is to analyze the gait through a Six Minute Walking Test (6MWT).

The purpose of this work is to find an appropriate arrangement in order to pick up the walking test signals and implement an automatic algorithm able to quantify fatigue. The study was performed on 3 patients (2 men and 1 woman) with different levels of severity of the disease, subject to a treatment with the Fampyra® drug at the San Luigi Gonzaga University Hospital of Orbassano (TO) and 2 people healthy as a reference. In addition, 18 healthy elderly people are analyzed only with some age problem in order to verify the effectiveness of the algorithm.

First of all, a simple and non-invasive arrangement is developed that can detect and record signals related to the walk using smartphone's sensors. Then, the signals are transmitted on the laptop for further processing. Several methods have been implemented and evaluated in order to provide parameters to quantify the phenomenon of fatigue and to support doctors in monitoring patients. The desired future developments will be to improve an easy to use application by patients, enabling remote physiological and functional monitoring and assessment of individuals in their homes. Subsequently the data may be available to the doctor who, after the subsequent processing of the algorithm, will be able to evaluate the progression of the patients' disease.

The following work of thesis is articulated in five chapters:

- In the first chapter the characteristics of multiple sclerosis are exposed with particular attention to the symptom that will be the subject of this study, i.e. fatigue.
- In the second chapter the state of art of the techniques used to collect and process the signals related to the walking analysis is presented in detail.
- The third chapter describes the arrangement used for acquisition of the signals and the methods implemented and tested on the signals to quantify the fatigue.
- In the fourth chapter, the selected parameters to analyze the fatigue and the obtained results are presented.
- In the fifth chapter, the acquisition system and the results obtained on elderly subjects are treated.
- The Thesis ends, in sixth chapter, with conclusions and future developments.

CHAPTER 1: MULTIPLE SCLEROSIS

1.1 GENERAL ASPECTS

Multiple Sclerosis (MS) is a chronic inflammatory and neurodegerative disease of the central nervous system [1]. The name Multiple Sclerosis derives from the presence of scars, also called 'plaques', in different areas of the central nervous system with a preference for the optic nerves, cerebellum and bone marrow.

Numerous clinical and experimental studies show that MS is caused by an adverse reaction of the immune system against myelin causing its damage and loss, and against specialized cells, the oligodendrocytes, which produce it. The myelin sheath is an insulating covering that encases the axons responsible for the transmission of electrical signals, the action potentials, by nerve cells. Damage to the myelin sheath, therefore, leads to an ineffective transmission of the signals [2].

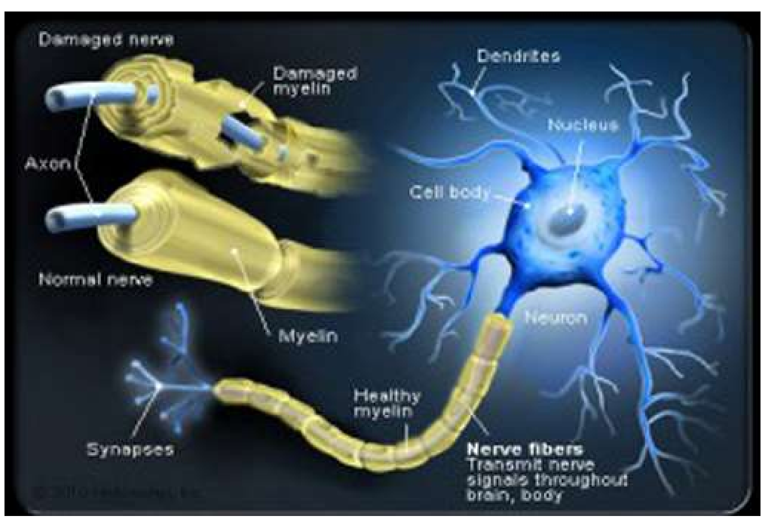


***Figure 1**: Demyelination in multiple sclerosis [3].*

MS affects about 2.5-3 million people, including 600.000 in Europe and 118.000 in Italy, with a greater diffusion in the areas far from the equator, while a progressive reduction is observed with the approach of the equator. The disease is diagnosed mainly in adults between 20 and 40 years and for women twice as much as men [4].

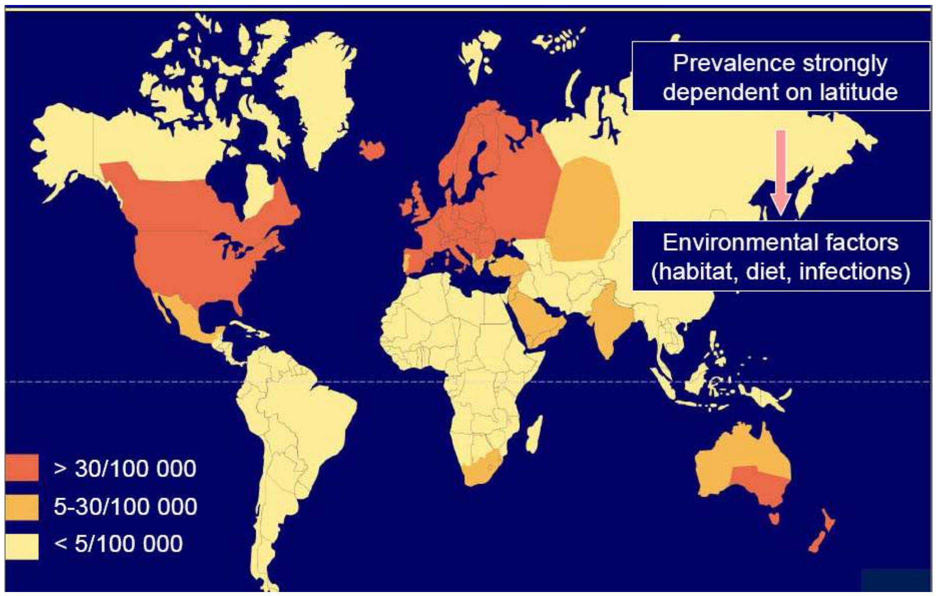


Figure 2*: Distribution of Multiple Sclerosis [5].*

The causes of multiple sclerosis are still research topic, but the main suspected factors are:

- the environment and ethnicity (temperate climate, latitude, Caucasian origin, toxic agents, low levels of vitamin D);
- exposure to infectious agents (viruses, bacteria) especially during the first years of life;
- a genetic predisposition: it is not transmitted from parents to children but there is a greater frequency of the disease in components of the same family nucleus.

1.2 TYPES OF MS

It is possible to distinguish different kinds of disease:

- *Benign MS*: is characterized by one or more relapses with complete remission [2].
- *Relapsing-remitting (SS)*: is the most common disease course (about 85% of people are initially diagnosed with this course of disease). It is characterized by attacks with new or increasing neurologic symptoms. These attacks, also called relapses, are followed by periods of partial or complete recovery (remissions). During remissions, all symptoms may disappear, or some symptoms may continue and become permanent. However, there is no progression of the disease during the period of remission [6].

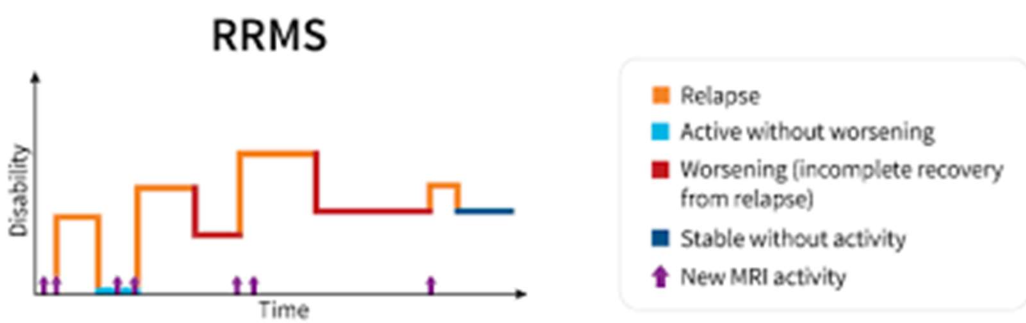


***Figure 3**: Multiple sclerosis with relapsing-remitting course (RRMS) [6].*

- *Secondary progressive (SP)*: follows the relapsing-remitting course because there is a progressive worsening of neurologic function (accumulation of disability) over time [6].

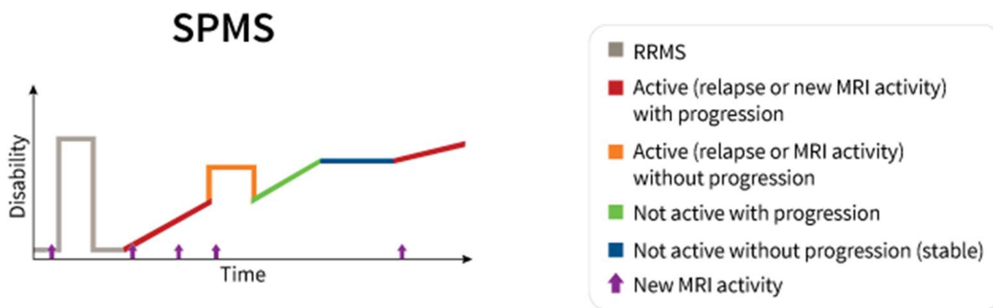


Figure 4: *Multiple sclerosis with Secondary progressive course (SPMS) [6].*

- *Primary progressive (PP)*: is characterized by worsening neurologic function (accumulation of disability) from the onset of symptoms, without early relapses or remissions [6].

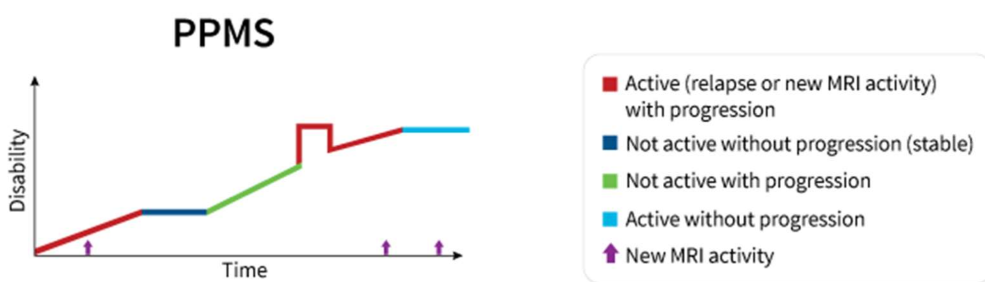


Figure 5: *Multiple sclerosis with Primary Progressive course (PPMS) [6].*

- Progressive-Relapsing (PR): it is characterized by progressive worsening of the disease from the onset of the disease and between a relapse and the other [2].

1.3 DIAGNOSIS AND TREATMENT

The diagnosis of MS can be formulated by physician only through a set of exams and a prolonged clinical observation. The main elements considered are the symptoms reported by the patient, the neurological examination and the instrumental (magnetic resonance, evoked potentials) and biological analysis (blood and cerebrospinal fluid) [4].

The therapies used, to date, are not able to cure the disease but can reduce relapses and their severity (corticosteroids) and prevent relapse and prevent or delay the progression of the disease (Disease Modifying Therapy, DMT, treatments that modify the disease) [4].

1.4 MS FATIGUE

MS is characterized by the accumulation of numerous neurological symptoms based on the different possible location of lesions in the central nervous system. The most frequent symptoms in MS are: fatigue, sensitivity disorders, visual disturbances, pain, intestinal disorders, cognitive disorders, depression, coordination disorders (ataxia, tremor), language disorders (dysarthria) [3]. Among these, fatigue is considered by 78% of MS patients one of the most disabling symptom, and it can occur at all stages of the disease, alters quality of life, influences work performance and affects social and family interactions.

The Multiple Sclerosis Council for clinical practice describes fatigue as ‘a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities’ [1].

It is possible to distinguish fatigue in ‘primary’ and ‘secondary’. The primary fatigue is directly related to the state of the disease and damage of central nervous system. It causes a sensation of persistent tiredness. The secondary fatigue is mostly related to the emotional state such as depression and anxiety but also to other factors such as an infection, fever or sleep disorder. Different drugs can have effects of weakness and sleepiness or worsen fatigue. Another important classification of fatigue is ‘chronic fatigue’ and ‘acute fatigue’. Chronic fatigue is present at every moments of the day, while the acute fatigue is a significant and unexpected sense of tiredness that can also be associated with relapse [5].

Some characteristics of fatigue are that it proves to be independent of physical activity, is sensitive to heat as climatic changes and is subjective both by type and by the time in which it appears.

To assess the extent of the symptom, in addition to the common (clinical and instrumental) examinations and the clinical history of the person with MS, there are scales and questionnaires that allow subjective evaluations, based on individual perceptions and objective assessments. Questionnaires are related to the reduction of muscle strength, energy consumption and the time needed to perform certain activities [4]. The main questionnaires are:

- *FSS (Fatigue Severity Scales):* it is a questionnaire focused on physical aspects of fatigue. The questionnaire consists of 9 questions, each of which can be answered with a score from 1 (strongly disagree) to 7 (strongly agree). The result is obtained by adding all the answers and dividing the sum by the number of questions (9). The final score has a range between 9 to 63 [1].

Fatigue Severity Scale (FSS)

During the past week, I have found that	Disagree ⟷ Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my 3 most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7
Total Score							
FSS mean score = total score for 9 items divided by 9. Mean Score							

***Figure 6**: Fatigue severity scale (FSS) [7].*

- *MFIS (Modified Fatigue Impact Scale)*: it is a questionnaire focused on cognitive, physical and psychosocial aspects of fatigue. The questionnaire consists of 21 questions, each of which can be answered with a score by 0 (never) to 4 (almost always). The result is obtained by adding all the answers and the final score has a range between 0 to 84 [1].

Cognitive subscale	*Never*	*Rarely*	*Sometimes*	*Often*	*Almost always*
1. I have been less alert	0	1	2	3	4
2. I have had difficulty paying attention for long periods of time	0	1	2	3	4
3. I have been unable to think clearly	0	1	2	3	4
4. I have been forgetful	0	1	2	3	4
5. I have had difficulty paying attention for short periods of time	0	1	2	3	4
6. I have had difficulty making decisions	0	1	2	3	4
7. I have been less motivated to do anything that requires thinking	0	1	2	3	4
8. I have had trouble finishing tasks that require thinking	0	1	2	3	4
9. I have had difficulty organizing my thoughts when doing things	0	1	2	3	4
10. My thinking has been slowed down	0	1	2	3	4
11. I have had trouble concentrating	0	1	2	3	4
				Cognitive subscale score ______	

Physical subscale	*Never*	*Rarely*	*Sometimes*	*Often*	*Almost always*
12. I have had to pace myself in my physical activities	0	1	2	3	4
13. I have been less motivated to do anything that requires physical effort	0	1	2	3	4
14. I have trouble maintaining physical effort for long periods	0	1	2	3	4
15. I have trouble maintaining physical effort for short periods	0	1	2	3	4
16. I have been physically uncomfortable	0	1	2	3	4
17. I have been less able to complete tasks that require physical effort	0	1	2	3	4
18. I have needed to rest more often or for longer periods	0	1	2	3	4
				Physical subscale score______	

Psychosocial subscale	*Never*	*Rarely*	*Sometimes*	*Often*	*Almost always*
19. I have avoided/eliminated certain tasks, activities and lifestyles	0	1	2	3	4
20. I have been less motivated to participate in social activities	0	1	2	3	4
21. I have been limited in my ability to do things	0	1	2	3	4
				Psychosocial subscale score______	
				Total MFIS-SCI score = ______	

***Figure 7**: Modified Fatigue Impact Scale (MFIS) [8].*

- *VAS (Visual Analogue Scale)*: it is a question that allows users to directly indicate the score that reflects the severity of fatigue. It can be answered with a score of 0 (absence of fatigue) to 10 (severe fatigue) [1].

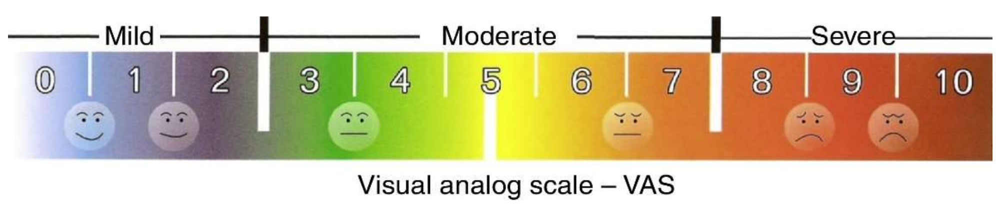


***Figure 8**: Visual Analog Scale (VAS) [9].*

- *EDSS (Expanded Disability Status Scale)*: it is a score ranging from 0 (no disability) to 10 (death due to MS) assigned by physician based on two factors: walking ability and scores for eight functional systems (pyramidal, cerebellar, brainstem, sensitive, sphincter, visual, cerebral and others) [10].

Figure 9: *Expanded Disability Status Scale (EDSS) [11].*

Correct fatigue management is essential to reduce its impact in everyday life and to save as much energy as possible. In this regard, there are strategies such as:

- learn how to balance activities and rest
- plan the activities to be carried out every day in order of priority
- recognize signs of fatigue and learn to stop before reaching full exhaustion
- make work and home environment more comfortable in order to reduce energy expenditure
- use of relaxation techniques that allow patient to make the most of moments of rest

Because MS fatigue is a multifactorial problem, the multidisciplinary approach seems necessary and highly recommended. For this reason, there is no drug that completely removes the effects of fatigue, but there are pharmacological and not-pharmacological techniques that can reduce the intensity of symptom and improve quality of life.

CHAPTER 2: STATE OF ART

2.1 Six-Minute Walk Test (6MWT)

In a healthcare environment, the six-minute walk test (6MWT) is a common clinical tool to measure a patient's residual functional capacity, to understand a person's current state and evaluate improvement in rehabilitation [12]. Furthermore, the walking test is a quick and inexpensive measure to assess the ability to perform normal daily activities or, conversely, the degree of functional limitation of the subject. The 6MWT is easy to implement, well tolerated, safe, and does not require special equipment. For the walking test, the patient is invited to walk at maximum speed as possible for six minutes, in a corridor with a well-defined path and without obstacles.

There are established threshold values and ranges of meters traveled to define the functional capacity of the healthy patient. These values are shown in table 1.

	Good functional capacity	*Poor functional capacity*
healthy subjects <70 years	400 – 700 meters	< 400 meters
healthy subjects >70 years	300 – 400 meters	< 300 meters

Table 1: *threshold values and ranges of meters of the functional capacity [13].*

2.2 Monitoring system

Normal smartphones are equipped with sensors such as accelerometer, gyroscope and orientation. For this reason, many works use the smartphone as wearable device because a simple arrangement of this is possible with minimal additional setup and immediately providing useful data for gait analysis. In clinical environment, wearable devices allow a person to walk freely and naturally, which is more representative of daily life [12].

Various arrangement strategies are possible for recording data with smartphone sensors. In the work of Sculte et al. [14] a client-server application has been implemented. The client part consists of patient and mobile application and the server part formed by the carer and server application. Patients wear appropriate body sensors (heart rate on the chest, $Sp0_2$ in the finger, and a 3-axis sensor on the patient's hip for detecting motion) and the mobile device to interact with the server side. The mobile application is performed on the mobile device to record sensor data and the patient begins the walking test. The carer is equipped with a laptop to monitor the walking test and the patient undergoing the test. In this way, the server application interacts with the mobile application to obtain monitored data. The figure 10 shows the used arrangement:

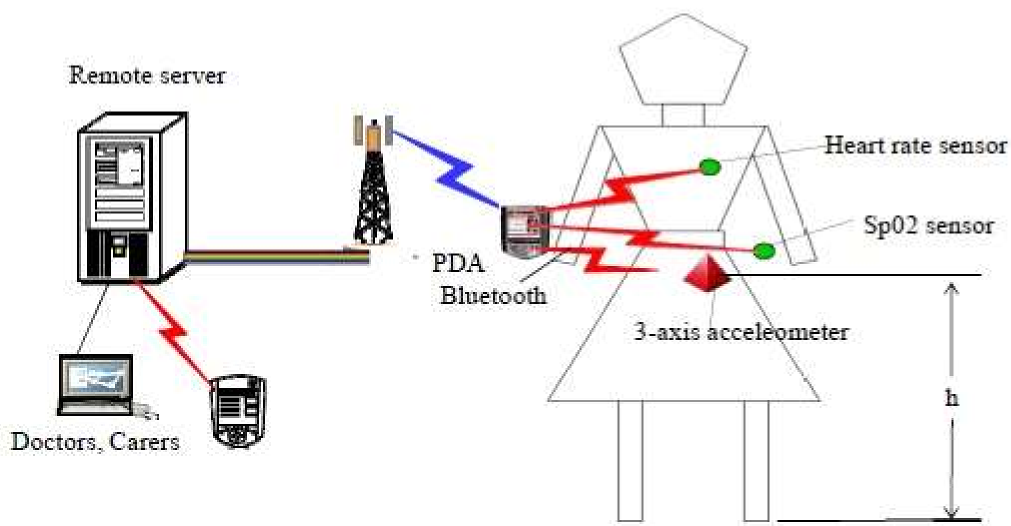
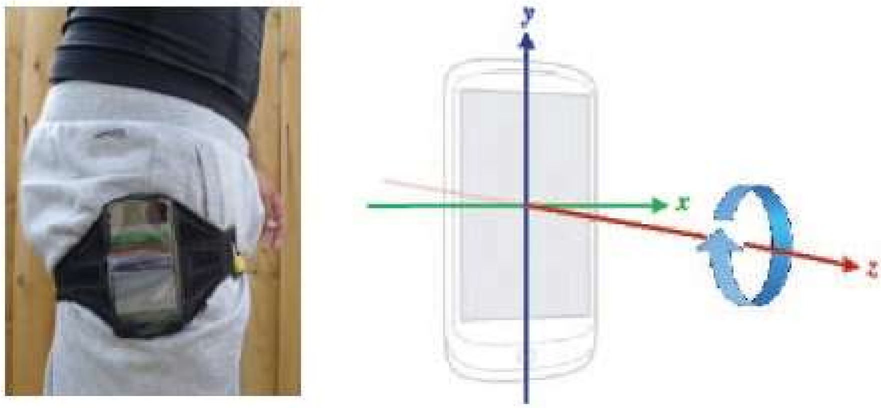


Figure 10: *The remote 6MWT configuration [14].*

The work by Le Moing and Stengel [15] shows the possibility of recording sensor data even without the use of body sensors. In fact, in their work, patients wear a leg band (figure 11a) containing the smartphone that allows the recording sensor data directly present in the smartphone (figure 11b).



(a) (b)

Figure 11: (a)"Leg band" (Side view) and ***(b)*** Smartphone axis (Android, 2014) [15].

2.3 General parameters

In the work of Schulte et al. [14] the developed smartphone app is able to show different parameters in application interface such as time elapse, distance walked, steps taken, heart rate, and SpO_2 level as showed in figure 12.

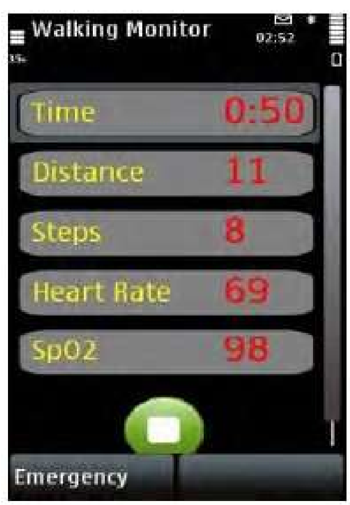


Figure 12: *The 6MWT user interface [14].*

To determine a walking distance, it was noted that, during walking, the vertical acceleration varies above and below a normal value. Using this fact, the algorithm counts the number of steps identifying each step when the vertical acceleration exceeds the normal value. The distance per step can be calculated in two ways:

1. Integrating acceleration over a certain period of time
2. Using average speed for each step and the time taken to complete the step

To determine the walking distance, a standard basic algorithm is applied in their work:

$$v = \sqrt{h\ (g - a_{vmin})}$$

$$l = v\left(T_{1,step(n+1)} - T_{1,step(n)}\right)$$

$$d = \sum_{i=2}^{n} l_{i-1} = \sum_{i=2}^{n} v_{i-1}\left(T_{1,step(n+1)} - T_{1,step(n)}\right)$$

where *h* is effective length of the leg, *g* the gravitational acceleration, T_1 the time step below a set vertical acceleration, a_{vmin} the minimum of a measured acceleration within a stride, *v* is the walking speed, *l* the length of a single step and *d* the distance walked.

Other parameters were obtained such as:

- Cadence: number of steps per minute (steps min^{-1}) [16].
- Step length: distance between two consecutive heel contacts of the same foot (m) [17].
- Step time: time spent between two consecutive heel contacts of the same foot (s) [17].

2.4 Walking speed

In Qureshi et al. [18], the average gait speed for j^{th} minute has been set as follows:

$$S_j = \frac{F_s N_j}{|B_j|} = \frac{F_s}{\overline{B_j}}$$

Where F_s is a sampling frequency, N_j is a number of gait cycles completed in minute j, B_j is a gate time series obtained from minute j and $\overline{B_j}$ is a number of samples in a gait cycle in minute j. In the study of Goldman et al. [18], the average speed of 20 healthy people and 40 people suffering from multiple sclerosis is calculated. The result graph is shown below:

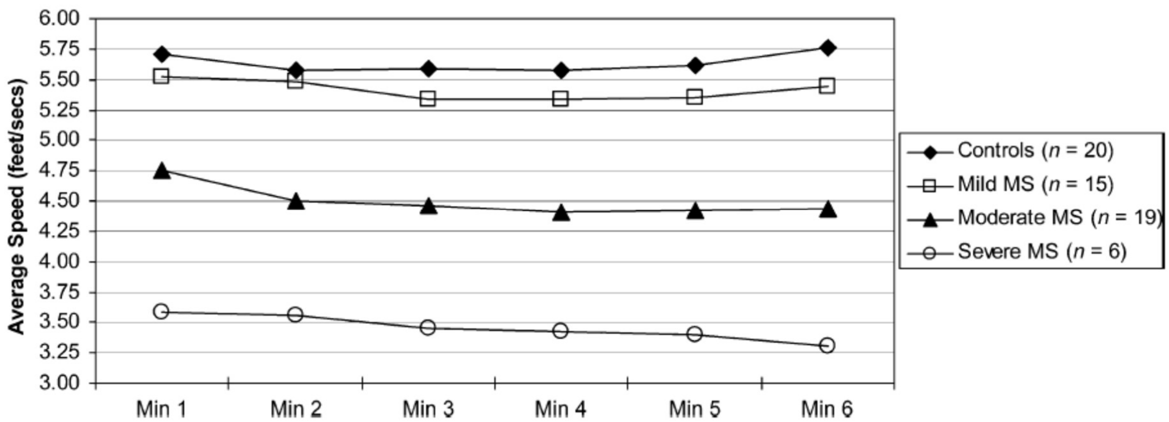


***Figure 13**: 6MWT average speed in 1 min epochs in MS subjects and controls [18].*

In their work, as the graph shows (figure 13), they observed that, on average, healthy patients slow down after the first minute and tend to accelerate at the last minute until they reach the initial speed or overcome it. Patients with MS show a similar behavior, but they accelerate less in the last minute and conclude the 6-minute test with a final speed lower than the initial one. Furthermore, it can be seen that increased disease progression leads to a lower final patient acceleration.

2.5 Dynamic Time Warping (DTW)

The DTW algorithm is a method of determining the optimal alignment between two signal sequences of the same subject and allows to provide a measure of similarity between two temporal sequences [20]. In the work of Dandu et al. [20], the gait cycles are aligned using the DTW algorithm to obtain two different measures: DTW score and Warp score. The DTW distance summarizes the degree of similarity between sequences after alignment. The Warp score summarizes the number of repetitions or sample needed to achieve the optimal alignment. Given two sequences of equal length:

$$P = \left[p_1, p_2, p_3, \ldots, p_n\right]$$

$$Q = \left[q_1, q_2, q_3, \ldots, q_n\right]$$

Where p_i and q_i are 3-dimensional vectors with x, y and z acceleration values respectively. The outputs of DTW algorithm will be the corresponding aligned sequences P^w and Q^w:

$$P^w = \left[(p_1)^{a_1}, (p_2)^{a_2}, (p_3)^{a_3}, \ldots, (p_n)^{a_n}\right]$$

$$Q^w = \left[(q_1)^{b_1}, (q_2)^{b_2}, (q_3)^{b_3}, \ldots, (q_n)^{b_n}\right]$$

Where $(.)^k$ means k repetitions of a given sample.

The DTW distance between P and Q is the Euclidean distance between P^w and Q^w. The warping length (Warp score) may be computed by follows:

$$\text{Warping Length} = \sum_{i=1}^{n} a_i = \sum_{i=1}^{n} b_i$$

For each subject all the cycles collected in the second minute are compared with those collected in the last minute and a matrix containing these values is created. Subsequently the matrix is reduced in order to obtain a single value that summarizes the DTW-based calculations. To obtain a significant value, the matrix is reduced with the following steps:

1. Each row and each column of the matrix is reduced to their minimum value.

2. The row and column obtained are reduced to their median value.
3. Finally, the two values obtained from the row and the column are summed or averaged to obtain the final value.

This process is illustrated in figure 14:

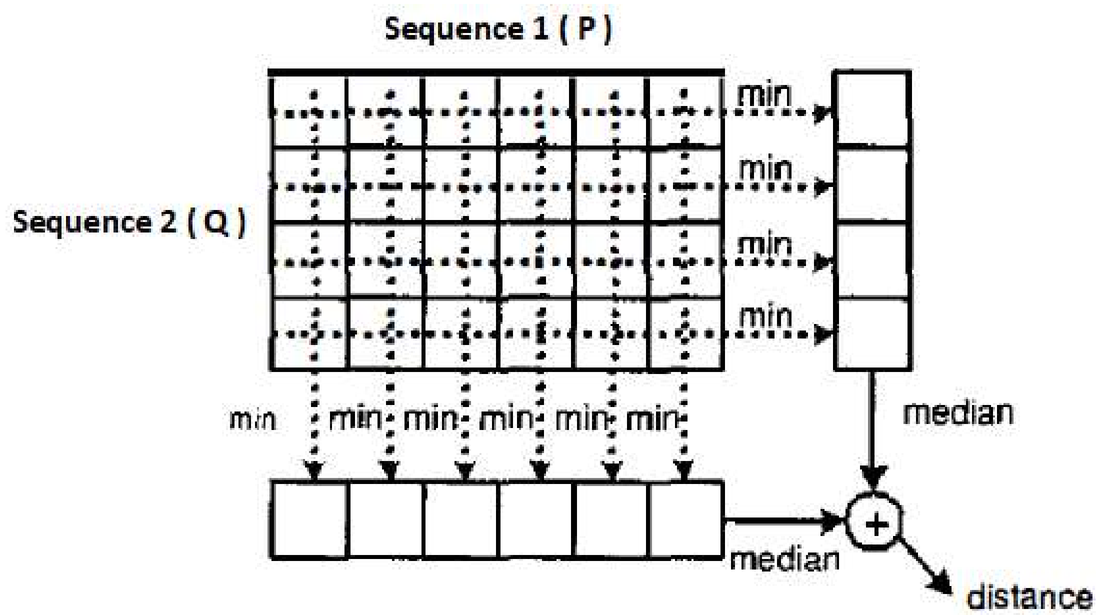


Figure 14: *Graphical representation of the proposed distance calculation process [21].*

In this way, for each subject we obtain a value of dtw score and a value of warp score.

Engelhard et al. [22], applying this method, observed that the best results are obtained using the Warp score. Figure 15 shows the result obtained:

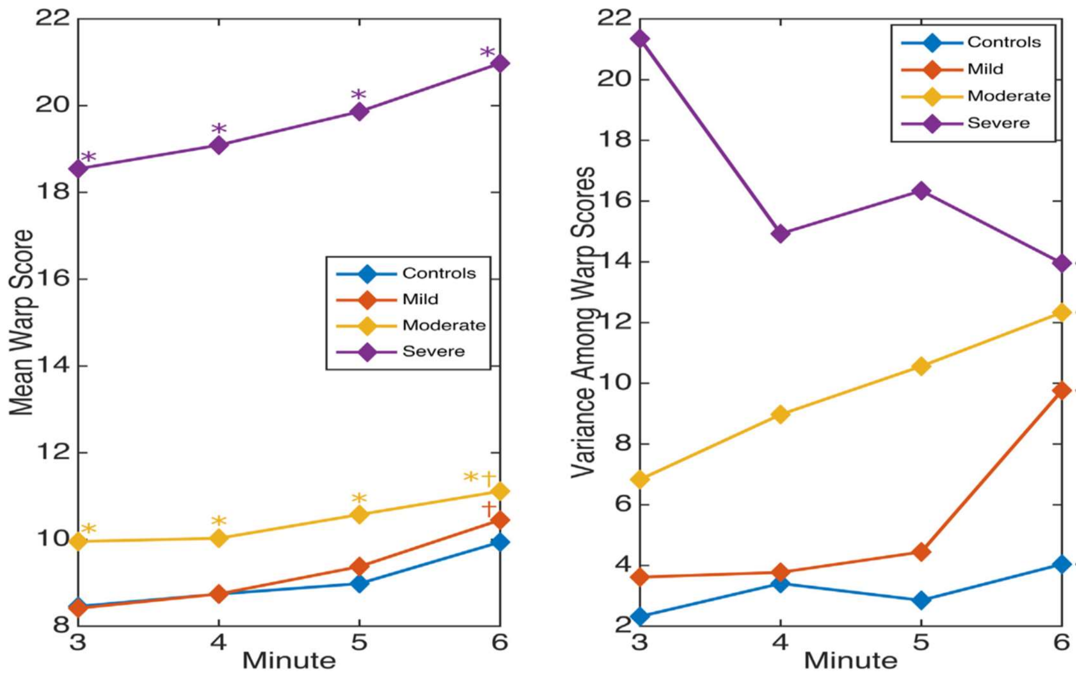


***Figure 15**: Warp score mean (left) and variance (right) in MS subjects and controls [22].*

It can be noted that severe subjects (EDSS> 4.5) have a warp score higher than the other groups of people observed. Warp scores in moderate subjects (EDSS=3-4.5) are higher than controls and mild subjects (EDSS=0-2.5), which tend to be very similar to each other. Furthermore, variance decreased over time in the severe group, but increased in other groups.

2.6 Kernel density estimation (KDE)

Kernel density estimation is a standard, non-parametric statistical method to estimate the probability density of a random variable using a given finite data sample. The random variable is X and has an unknown density function $f_X(x)$. Using n random observations of X (x_1, x_2, …, x_3), KDE counts observations within the distance of the points of interest x, assigning weights that diminish with distance from x, where h>0 is the smoothing parameter or bandwidth. The kernel estimator can be defined as:

$$\hat{f}_X(x)=\frac{1}{n}\sum_{i=1}^{n}K_h(x\text{-}x_i)$$

Where $K_h(x)=\frac{1}{h}K\left(\frac{x}{h}\right)$, and K(x) is a non-negative kernel function which assigns the weights to the neighbors of x [23]. The KDE method is applied in the study of Qureshi et al. [23], where the typical densities of MS and control subjects are studied, as shown in figure 16:

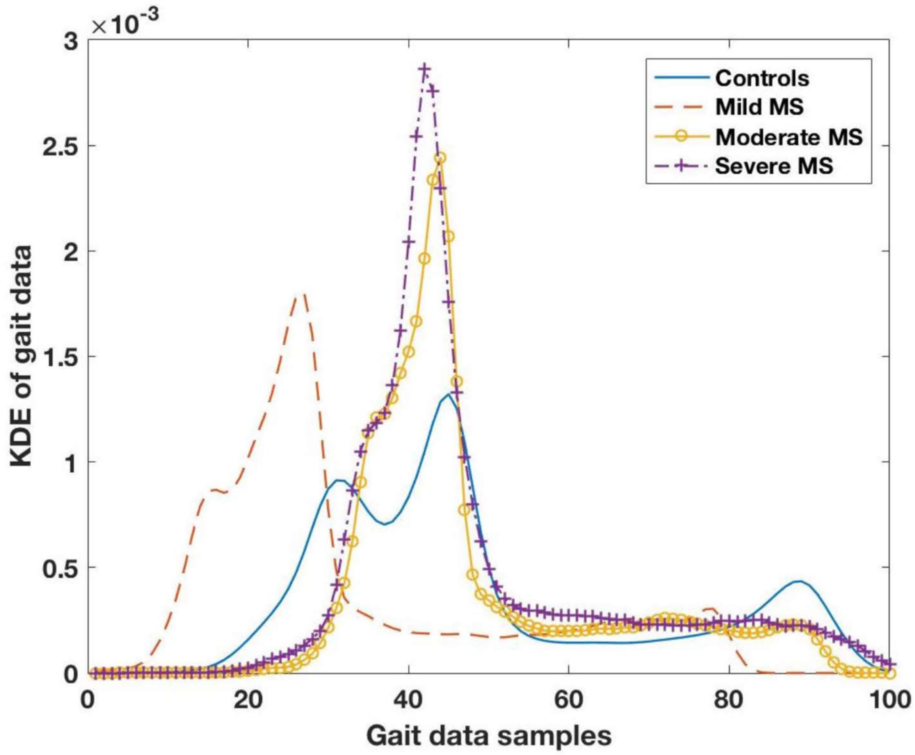


Figure 16*: Typical gait densities of MS and control subjects [23].*

The control subjects produce a bimodal pattern of KDE and a smaller peaks compared to most of the estimates of the density of MS subjects. The MS subjects produce a unimodal pattern of KDE with a high peaks values and concentrated peaks around smaller range of amplitude, indicating less variability in walk.

CHAPTER 3: MATERIALS AND METHODS

3.1 Introduction

This chapter describes all the materials and methods used in this study to verify the efficacy of the drug Fampyra® in patients with multiple sclerosis.

In this work to test the effectiveness of the drug, the patients of the San Luigi Gonzaga University Hospital in Orbassano (TO), in addition to electrical stimulation, are subjected to the 6-minute walking test. The 6MWT runs on a corridor with a well-defined path of 25 feet (7.62 meters) and without obstacles.

All the methods described are designed also to monitor and quantify the phenomenon of fatigue. For this reason, in addition to the comparison tests between the parameters obtained on the tests carried out on the patients before and after the administration of the drug, comparative tests were performed between the parameters obtained at the beginning and at the end of the 6MWT carried out by the patient. Moreover, the methods described are applied to all 3 components of the signal separately to evaluate the possibility of finding different details for each of them.

In this way, the effectiveness of the drug is tested both in terms of patient performance and in terms of constancy of performance.

3.2 Materials

3.2.1 Fampyra®

Fampyra® is a drug available as a tablet containing a slow-release formula of 4-aminopyridine, which is a blocker of potassium channels on the surface of nerve fibers. By blocking the potassium channels, ionic current dispersion is reduced through these channels, thus prolonging the phenomenon of repolarization and increasing the formation of action potential in demyelinated axons and neurological functions. It is believed that this facilitates the walk.

Two studies were conducted on patients treated with Fampyra® from 9 to 14 weeks compared to placebo (a substance with no effect on the body). Patients were expected to respond to treatment if, at least three times out of four, their walking speed was higher than the maximum speed recorded before treatment. Fampyra® was effective in improving walking speed: in fact, in the first study about 35% of patients treated with Fampyra® responded to treatment compared to 8% of subjects treated with placebo.

The recommended dose is one 10 mg tablet taken orally, twice a day, 12 hours apart (one tablet in the morning and one in the evening). In particular, the initial prescription should be limited to 2 weeks of therapy because generally the clinical benefits should be identified within 2 weeks of starting treatment with Fampyra®. If the treated persons do not report and have no benefit the treatment will be stopped.

3.2.2 Equipment of the monitoring system

At the beginning of the project, the monitoring system consists of a smartphone, an ankle strap and a laptop. The smartphone used is equipped with the main sensors (almost all smartphones are provided), among which the accelerometer, the gyroscope and magnetometer are used. Furthermore, the Matlab app is installed on the smartphone, which allows connection, via Wi-Fi, with the Matlab (Matlab R2018a) software installed on the laptop for data transfer. The walk test is executed by performing the following steps:

- the correct connection between smartphone and laptop occurs;
- the ankle strap containing the smartphone is positioned on the patient's ankle;
- the Matlab code used to record the sensor signals on the laptop is started

At this point, the 6MWT can start and, once finished, you can remove the ankle strap from the patient and close the application on the smartphone. In this way, the accelerometer, gyroscope and magnetometer data are directly available on the laptop, in an appropriate format, for further processing.

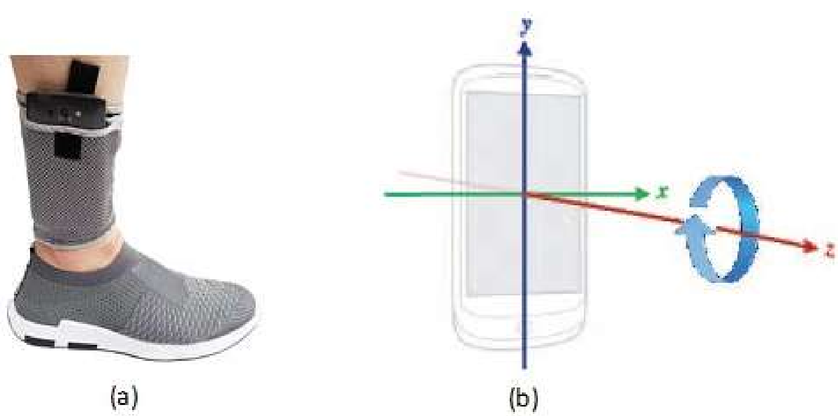


Figure 17: (a) *ankle strap and* ***(b)*** *smartphone axis.*

The walk analysis on patients with multiple sclerosis is performed as described above. A different acquisition system, instead, is used for the 2 healthy subjects, consisting only of a smartphone in which an app is installed that can be downloaded easily from the smartphone app store that allows the recording of sensor data in .csv format. A suitable algorithm will allow the conversion of data into the appropriate format for the subsequent processing of data on Matlab.

3.2.3 Data Patients

As described in paragraph 1.4 "MS fatigue", there are some questionnaires that allow to obtain subjective evaluations of the fatigue phenomenon. For this reason, at the end of the test, questionnaires are provided to hospital patients asking them to take a few minutes to fill them out. This was done because, even although these questionnaires are subjective, they can provide an idea of the patient's feeling related to the improvement of fatigue or worsened during the study. The aforementioned questionnaires are the main fatigue scales that are MFIS, FSS and VAFS.

Also the EDSS score is also provided but this is only assessed once by the clinician because it should not change in two weeks (this is the period between the pre-medication administration and post). Table 2 shows patient data:

				MFIS	*FSS*	*VAFS*	*EDSS*
Patient	*Gender*	*Age (years)*		0-84	9-63	0-10	0-10
1	*F*	*50*	*Pre*	33	41	6	*1*
			post	35	46	6	
2	*M*	*28*	*Pre*	37	57	3	*3*
			post	25	37	7	
3	*M*	*37*	*Pre*	59	60	8	*3*
			post	45	54	3	

Table 2: *Fatigue scale values for each patient for the clinical trial.*

Moreover, during the 6MWT the doctor takes into account the meters traveled by the patient. These data are shown in table 3 below:

Patient		*Walked meters (m)*
1	*pre1*	394.6
	pre2	397.7
	Post	389.4
2	*pre1*	213.3
	pre2	203.6
	Post	212.8
3	*pre1*	364
	pre2	391
	Post	440.8

Table 3: *Walked meters by each patient in the six-minute walking test.*

3.3 Methods

3.3.1 Signal Processing

In this work, for the analysis of the walk test, it was decided to use only the signal taken from the gyroscope because it seems the one that best represents the progress of the walk. The signal used is therefore the angular velocity around a specific axis and it consists of three components along the three axes x, y and z and an associated time vector of the same length.

In particular,

- The x component of the angular velocity describes the left and right swing of the foot and then a lateral deviation from the patient's rectilinear path;
- The y component of the angular velocity describes the rotation around itself of the patient;
- The z component of the angular velocity describes the forward and backward oscillation of the feet and therefore the trend of the step.

The following figure shows an enlargement of the signal in order to highlight all the components of the signal:

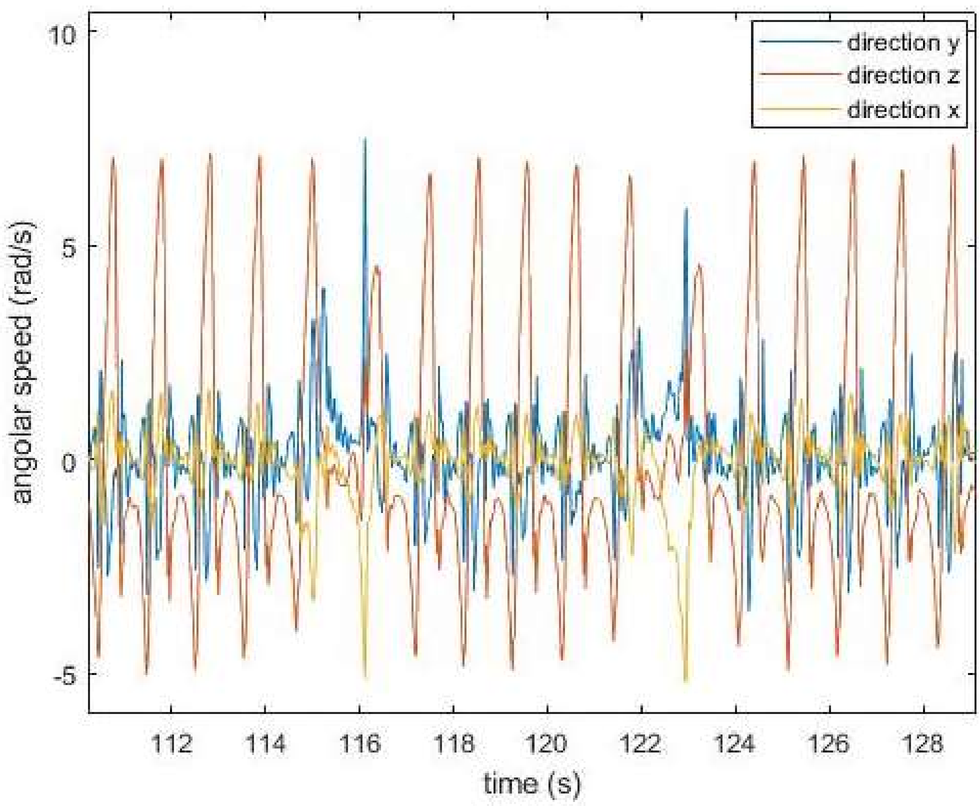


Figure 18: *Signal acquired by the gyroscope characterized by three x, y and z components.*

A Matlab program was developed for the signal processing. First, the signal has been aligned to identify the main angular component of the step, thus allowing to compensate, on the overall signal, the incorrect positioning of the smartphone on the patient's ankle. Secondly, the initial step and the final step of the walk are identified by setting a minimum threshold value to eliminate the signal noise. The figure below show the obtained result of these simple operations:

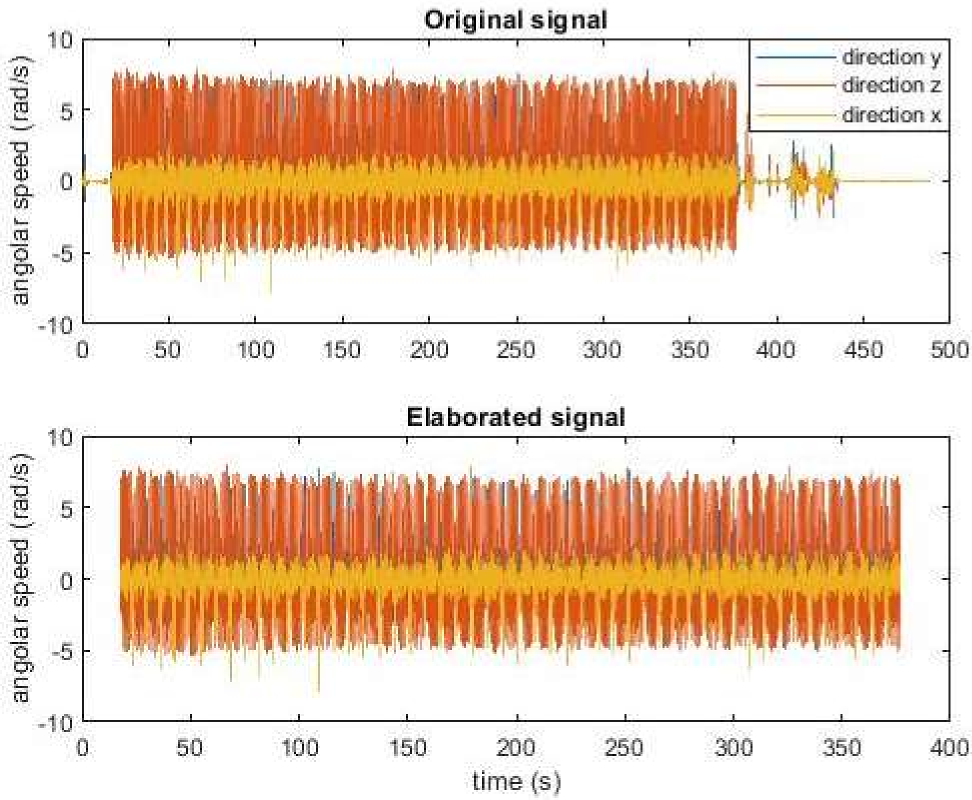


Figure 19: The same signal before and after signal processing.

Third, the signal is segmented in different ways to apply various techniques on different segments of the signal. This approach was chosen to compare different results of the analysis of the fatigue phenomenon during the walk test and to be able to choose the methods that best quantify fatigue.

The segmentation techniques used are described below:

1. *Minutes*: the six minute signal is divided minute by minute. Every minute is identified by defining two vectors searching, within the signal timing vector, the indices corresponding to the time that characterize the beginning and the end of the minute. For example, the first minute starts at the second 0 and ends at the second

60, the second minute starts at the second 61 and ends at the second 120 and so on. Once the indices are found, it is possible to divide the signal minute by minute. A matrix is created with 6 rows (each row represents one minute) and a variable number of columns based on the length of minutes in the different signals taken. The figure 20 shows the result:

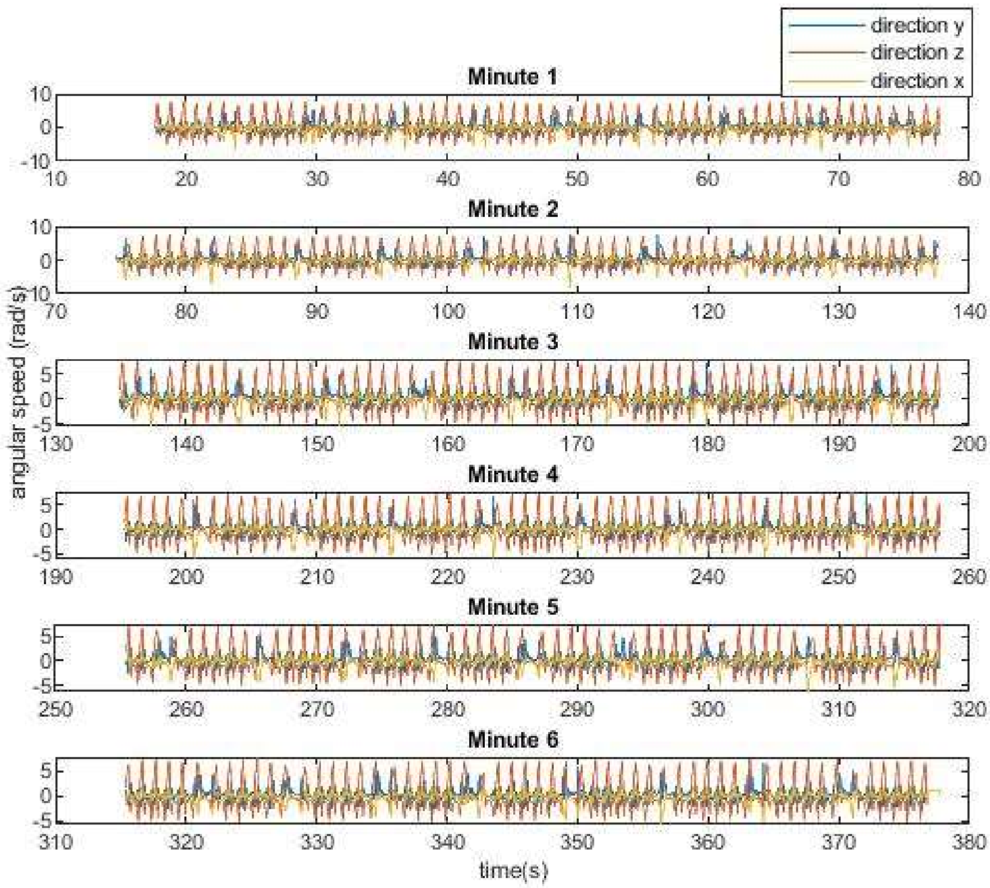


***Figure 20**: Segmentation of the signal minute by minute.*

2. *Walking cycles*: each cycle is defined with the following protocol: forward, U-turn and return. The patient then travels 25 feet, after which he makes a 180 ° rotation and traces another 25 feet. The rotation of the patient, as can be seen from figure 17, causes a decrease in the amplitude of the signal in the z-direction and an increase in the amplitude of the other two directions, and in particular of the y-direction.

Using these observations, each 25-foot tract is identified by looking for indices corresponding to the patient's peak of rotation. Two thresholds are defined for this research: the first is used to set the minimum peak width and the second is used to set the minimum distance between one peak and the next. These thresholds were assigned by observing the signals. Once the indeces have been found, it is possible to divide the signal into walking cycles, considering that one cycle corresponds to two 25-foot sections and therefore using only one index every two. A matrix is created with a variable number of rows based on the number of walking cycles in each selected signal and a variable number of columns based on the length of the walking cycles in the different signals taken. The figure 21 shows the first two walking cycles as example:

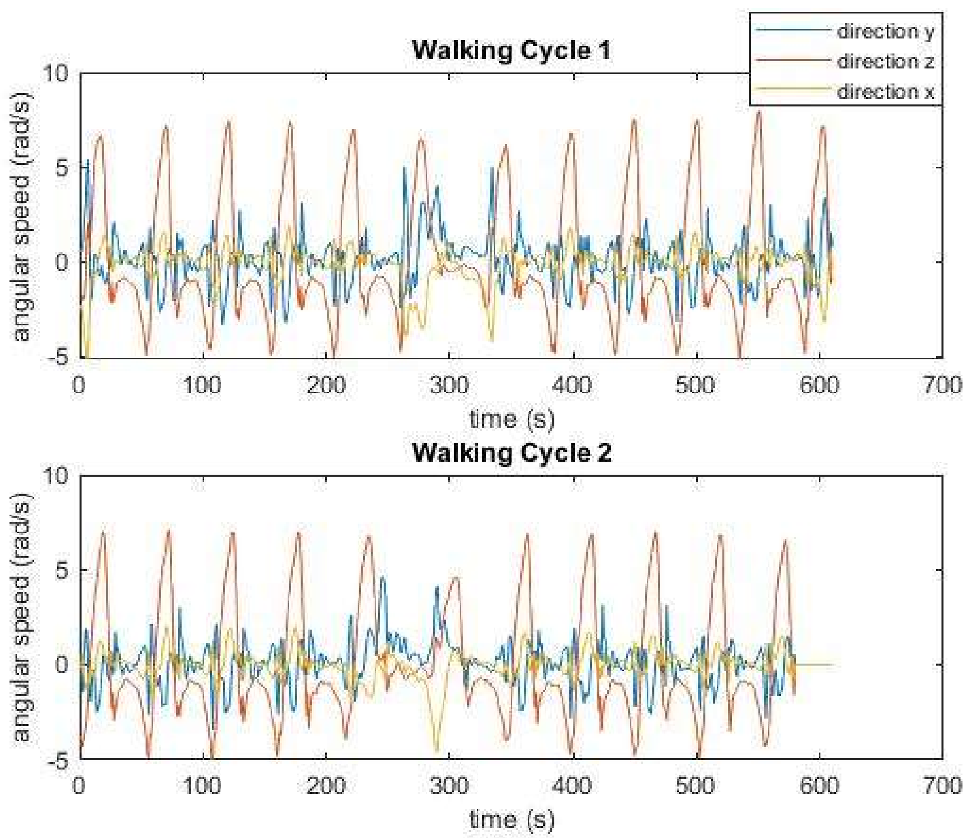


***Figure 21**: Segmentation of the signal in walking cycles.*

3. *Averaged step within minutes:* each step taken is identified and mediated with the other steps identified within the same minute. This procedure is repeated for all the minutes of the signal in order to obtain a trend of the average step of each minute. As can be seen from figure 22, the step is characterized by two minimums at the beginning and at the end of it.

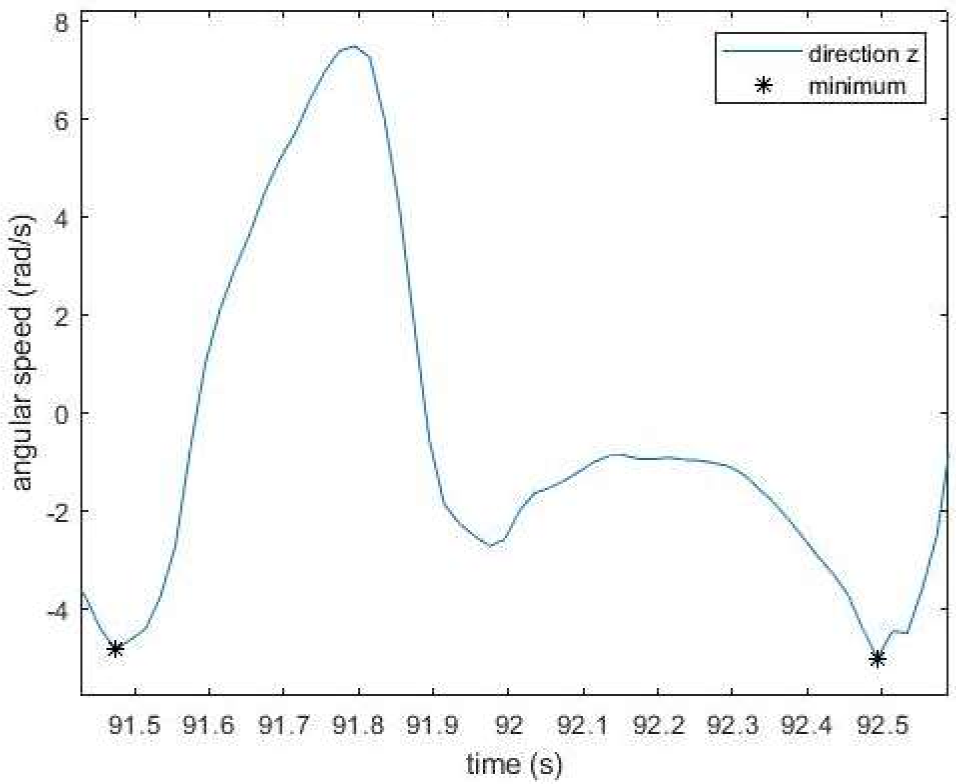


Figure 22*: representation of a step delimited by two minima.*

By exploiting this observation, the indices corresponding to these minima are searched through the setting of two thresholds: the first imposes the maximum amplitude of the peak and the second imposes a minimum distance between two minima in order not to make mistakes in the search. Once the indices are found, for every minute, the signal is divided into segments containing the step trend and then an average of these segments is performed to obtain the mean step within each minute. A matrix is created with 6 rows (each row represents one minute) and a variable number of columns based on the step length in the different signals taken. The figure 23 shows the average step of the first two minutes as an example:

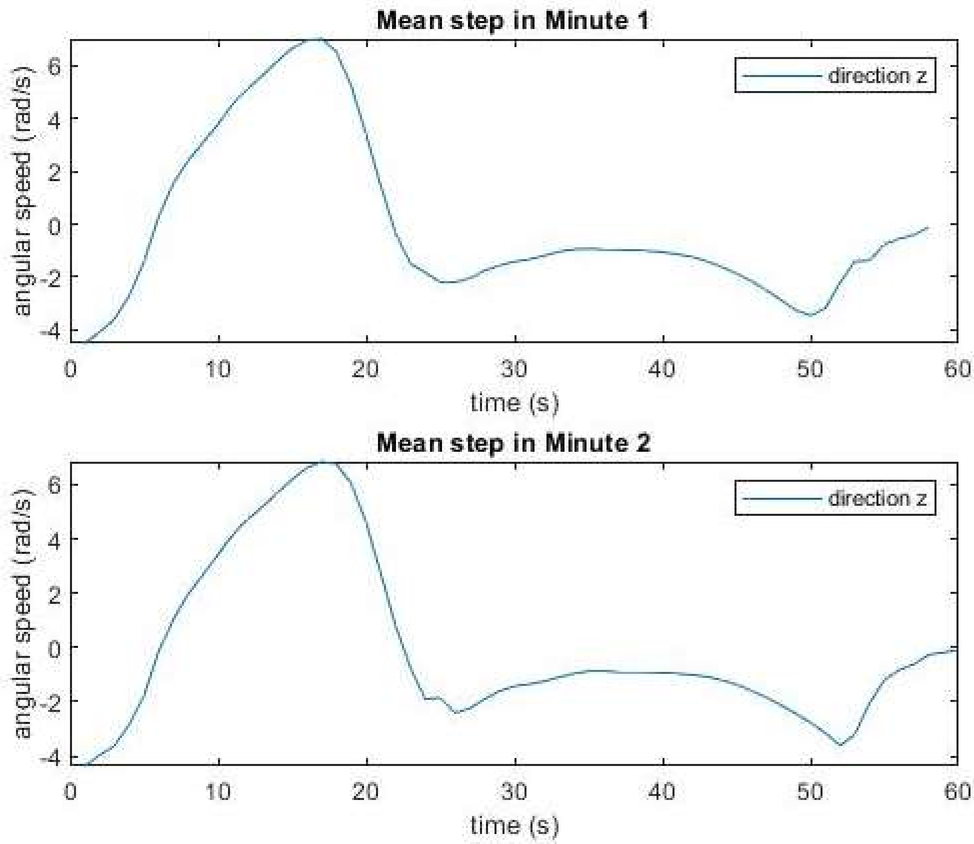


Figure 23: *Mean step in the first two minutes.*

4. *Averaged step within walking cycles:* each step taken is identified and mediated with the other steps within the same walking cycle. This procedure is repeated for all the walking cycles of the signal in order to obtain a trend of the average step of the walking cycle. The procedure used is the same as described in the previous segmentation method. In this case, having a shorter signal than before, the segment of the step corresponding to the rotation of the subject is eliminated in order to obtain a more accurate average of the step. In the following figure is shown the mean step of the first two walking cycles:

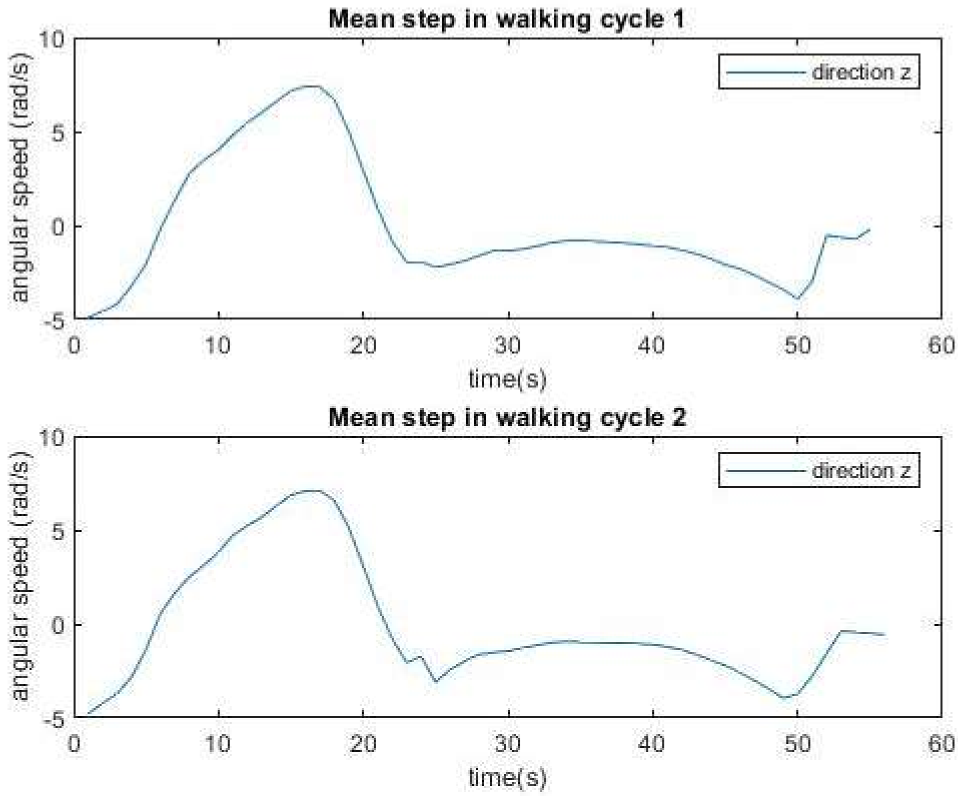


Figure 24: *Mean step in the first two walking cycles.*

3.3.2 General Parameters

From the signal, it is possible to extrapolate simple parameters that provide important information on the patient's walk. The parameters obtained are the following:

1. *Meters walked:* total distance traveled by the patient in 6MWT. Although this information was recorded by the doctor during the test, it was calculated to evaluate the possibility, in the future, to eliminate the need for a medical contribution during the test and to be able to perform the test directly at home. To determine the walked meters, the number of patient rotation peaks is calculated, which occurs when a 25-foot tract ends. As a result, the total number of peaks of rotation are

multiplied by the length of the tract or 25 feet to obtain the total distance meters multiplies the total peaks of rotation peaks.

2. *Steps taken*: total number of steps taken by the patient during the 6MWT. First of all, the number of steps made every minute are calculated, obtaining the information easily from the segmentation carried out with the “Averaged step within minutes” method previously described (paragraph 3.3.1 “Processing signals”), in which the signal is been segmented step by step. Next, the number of steps taken in each minute is added together to obtain the total number of steps performed in the 6MWT.
3. *Average step length*: average of the segments corresponding to the meters traveled to make a step (m). The figure 25 shows a representation of the step length.

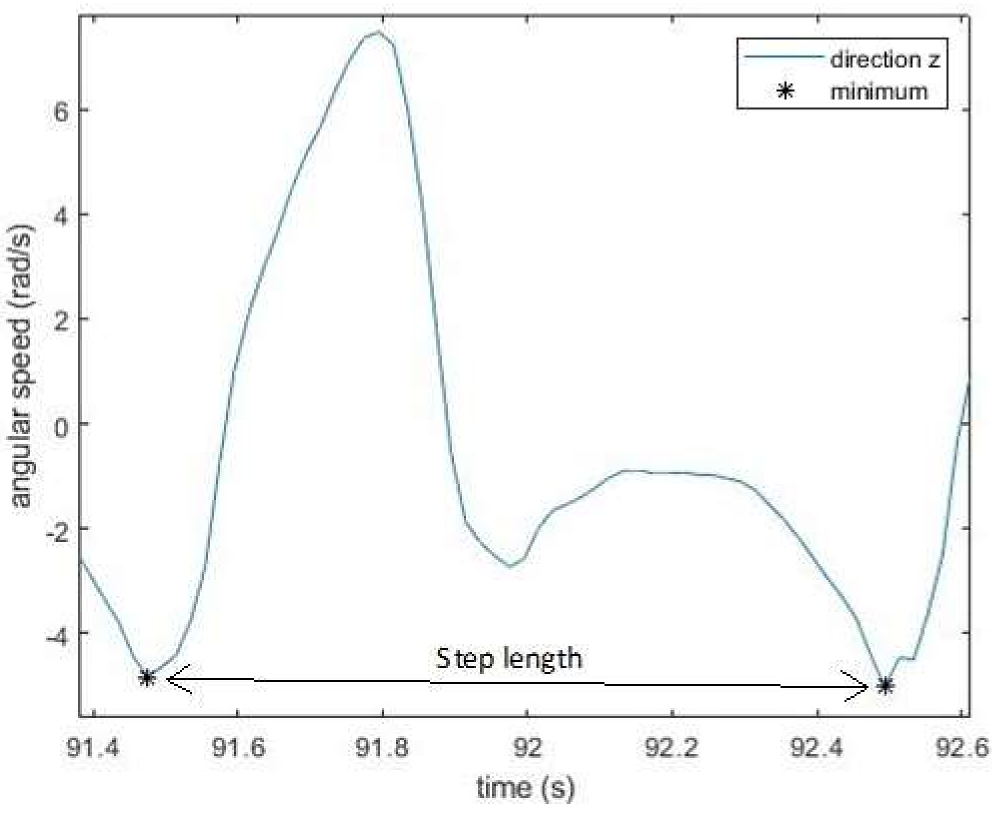


Figure 25: *Representation of step length.*

For each step, the distance between the indices corresponding to the characteristic minimums of the step is calculated and then the average of the obtained distances for each minute and for the entire 6MWT is calculated.

In this way, the obtained results are expressed in samples and it is therefore necessary to obtain a conversion factor capable of converting the samples into meters. The conversion factor is derived, for each signal, by making a proportion between the samples present between a rotation peak and the next, which we know to be a 25-foot tract, and the samples of the step length we want know the meters.

4. *Average step time:* average of the segments corresponding to the time spent to make a step in seconds. For each step, the difference between the times related to the indices corresponding to minima characteristic of the step is calculated and then an average of the differences obtained for each minute and for the whole 6MWT is calculated.

3.3.3 Walking speed

A very important parameter is the speed that allows to evaluate the rapidity with which the patient moves in different phases of the 6MWT. In this work, the speed is calculated in two different ways as described below:

1. *Walking speed expressed in meters per second*. To obtain this walking speed, the following formula has been applied:

$$\mathrm{v_{ms}} = \frac{\text{walked meters} - 7.62}{\Delta \mathrm{t}}$$

Where *walked meters* are the meters obtained as described in the previous paragraph 3.3.2 “General parameters” and *Δt* is the time interval between the time corresponding to the index of the last rotation peak and the time corresponding to the first peak of rotation. By calculating the time interval as described, the first 25-feet section is neglected, which is why 7.62 meters are subtracted in the meters used for speed calculation. The walking speed is obtained for each minute and the average of the values obtained for the six minutes and the variance is also obtained.

2. *Walking speed expressed in steps per second*. To obtain this walking speed, the following formula has been applied:

$$v_{ss} = \frac{1}{t_s}$$

Where t_s is the step time, obtained as described in the previous paragraph 3.3.2 "General parameters", before calculating the average on each step performed during the minute. Consequently, at each step (1 to the numerator) the time corresponding to divide is associated. Finally, the average of the speeds obtained is calculated to find the average walking speed for each minute with relative standard deviation and, from these, the average walking speed of the entire 6MWT with relative standard deviation.

Through this analysis, a graph is then obtained for each type of speed. In order to summarize each graph, a value Δv_{16} is calculated showing the quantitative difference between the speed obtained at the first minute and that obtained at the sixth minute.

3.3.4 Dynamic Time Warping (DTW)

The DTW technique is used, in this work, as a measure of similarity between two temporal sequences. In particular, through this technique, two parameters can be obtained:

1. DTW score: it summarizes the degree of similarity between sequences after alignment [20]. The DTW score is easily obtained as output of the Matlab DTW function to which the two time sequences which it wishes to align are given as input.
2. Warp score: summarizes the number of repetitions or sample needed to achieve the optimal alignment [20]. The Warp score is obtained by exploiting the other two outputs of the DTW function that contain the indices to the elements of the

corresponding sequence that are repeated the necessary number of times to get the alignment of the same sequence. Thus the substitution of these indices to the initial sequence gives the sequence distorted and aligned with the other. By exploiting this information, the warp score is obtained by making a difference between the signal obtained after the distortion and the initial signal.

This method has been applied to all the segmentation methods described in the paragraph 3.3.1 “Signal processing” in order to compare all the results obtained and to verify which was the most representative to quantify the fatigue phenomenon.

For each test category described in details then, we obtain:

- a value of DTW score and Warp score useful to represent the whole signal obtained by reducing the matrix of values as described in paragraph 2.5 “Dynamic Time Warping (DTW)” and illustrated in figure 14. Furthermore, an example of the complete process applied to our work is shown in Figure 26.

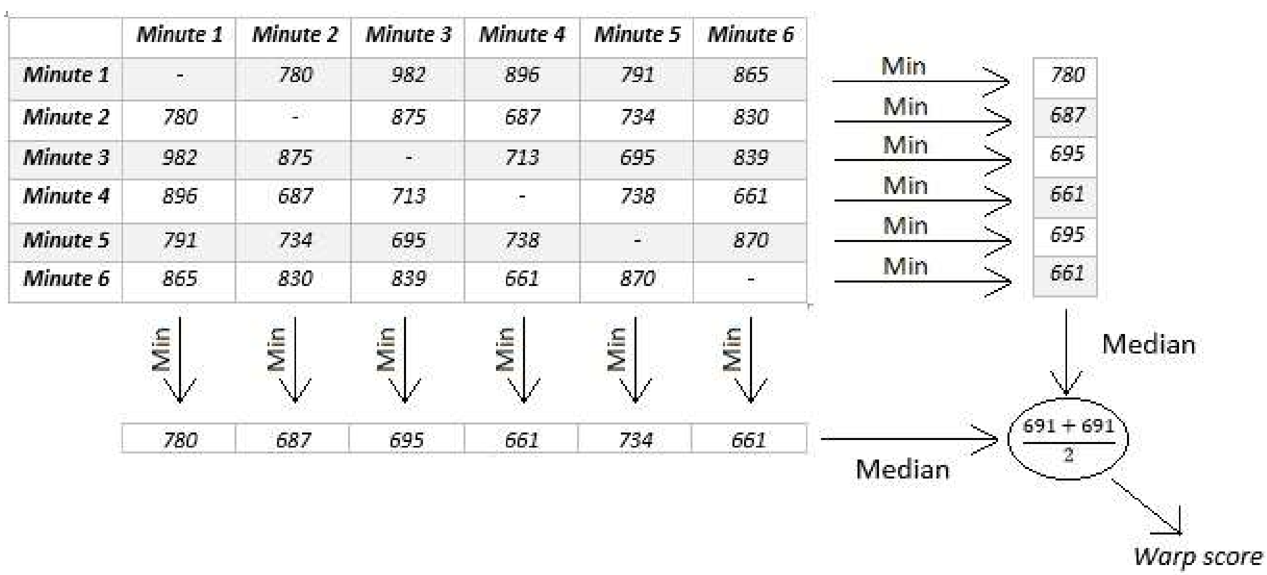


__Figure 26__: example of Warp score calculation process.

- a percentage value of DTW score and warp score useful to quantify the fatigue presented by the patient inside the signal obtained with a normalization between the value obtained at the end of 6MWT and that obtained at the beginning of 6MWT. The formula below shows the normalization described:

$$\Delta W_{\%} = \frac{Warp\ score_{end} - Warp\ score_{start}}{Warp\ score_{start}}$$

Below, the test categories are described in detail:

1. *DTW in minutes*: DTW technique applied to the segmented signal minute by minute. Each minute represents a time segment to be used in the DTW technique. All minutes are aligned to each other and a 6x6 matrix is thus obtained.

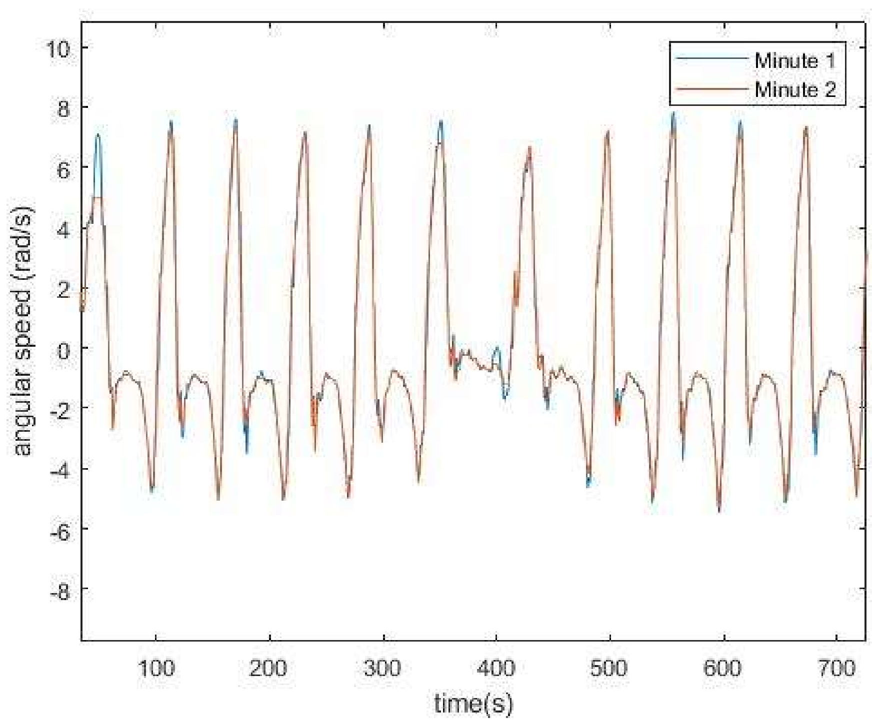


Figure 27*: example of application of the DTW technique on minute 1 and 2.*

2. *DTW in walking cycles*: DTW technique applied to the segmented signal in walking cycles. Each walking cycle represents a time segment to be used in the DTW technique. All walking cycles are aligned to each other and we thus obtain a matrix with number of rows and columns equal to the number of walking cycles obtained in each signal.

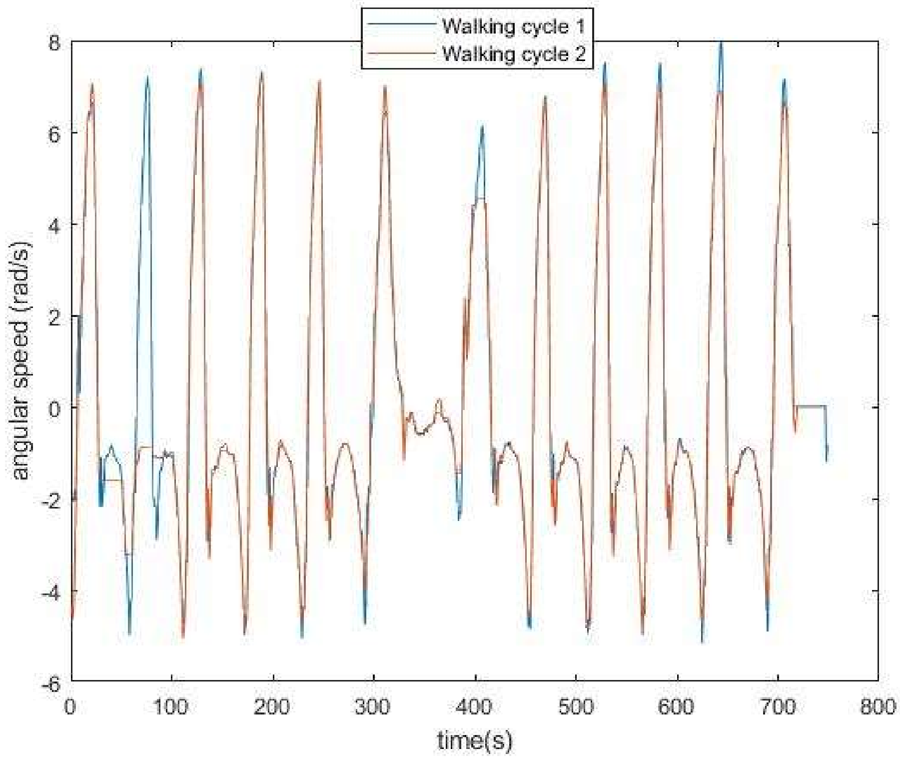


Figure 28*: example of application of the DTW technique on walking cycle 1 and 2.*

3. *DTW in average step within minutes:* DTW technique applied to the segmented signal in average step within minutes. Every average step represents a time segment to be used in the DTW technique. All average step obtained are compared to each other and a 6x6 matrix is thus obtained.

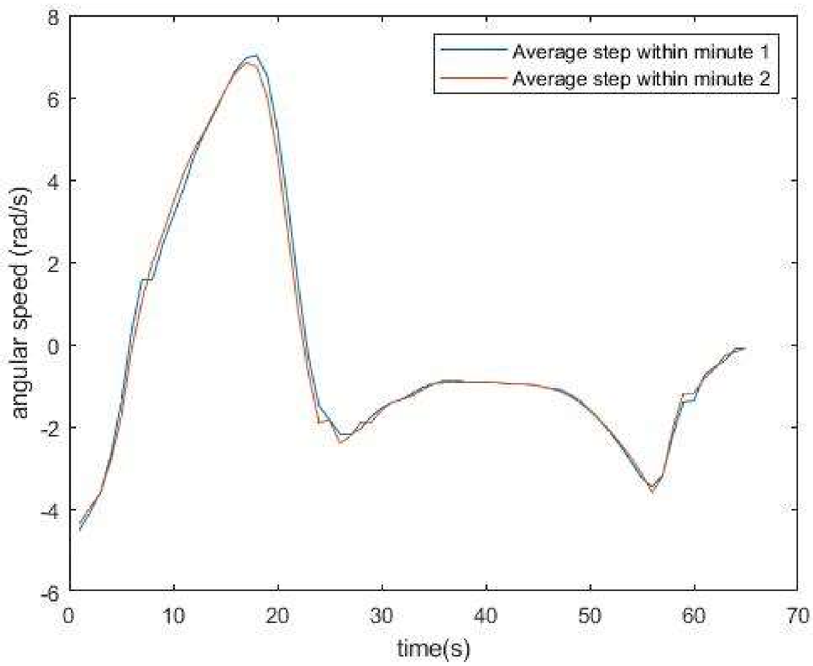


Figure 29: *Example of the application of the DTW technique on average step within minute 1 and 2.*

4. *DTW in average step within walking cycle:* DTW technique applied to the segmented signal in average step within walking cycles. Each average step represents a time segment to be used in the DTW technique. In this case, to avoid considering all the walking cycles, representative of the signal ones 6 are considered, that are the first, the second, the fourth, the eighth, the penultimate and the last. In this way, a 6x6 matrix is obtained.

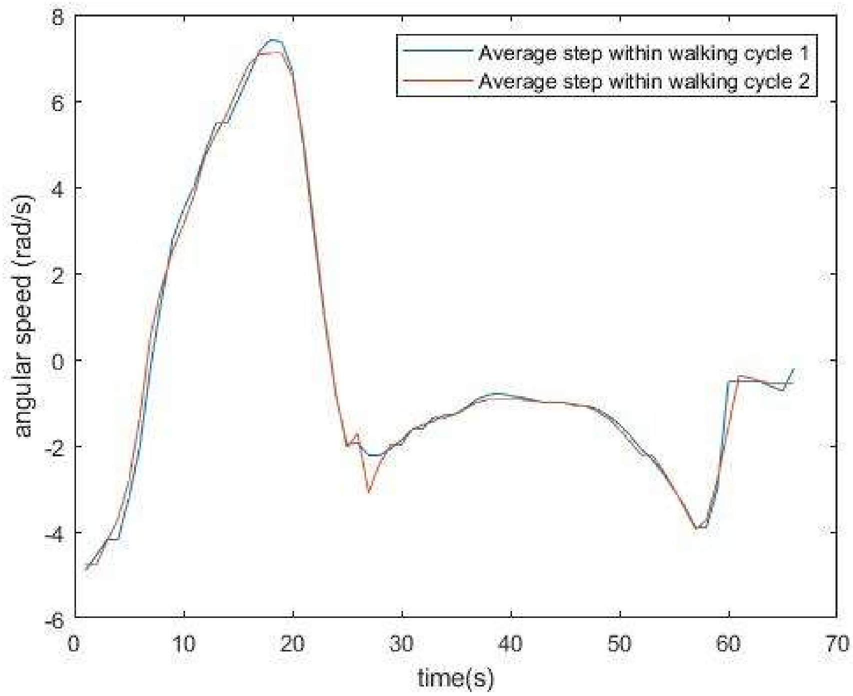


Figure 30: *Example of the application of the DTW technique on average step within walking step 1 and 2.*

3.3.5 Kernel density estimation (KDE)

This method was used to verify a different representation of the disease depending on the severity of the disease. This parameter can be easily obtained by applying the function present in Matlab called "ksdensity" which requires as input the time sequence to which the technique is applied and provides the KDE function as output. The maximum value, the minimum value and the standard deviation are then derived from the KDE function.

The technique is applied for each minute obtaining a graph like the one shown in figure 31 and for the first, second and last walking cycle obtaining a graph like the one shown in figure 32.

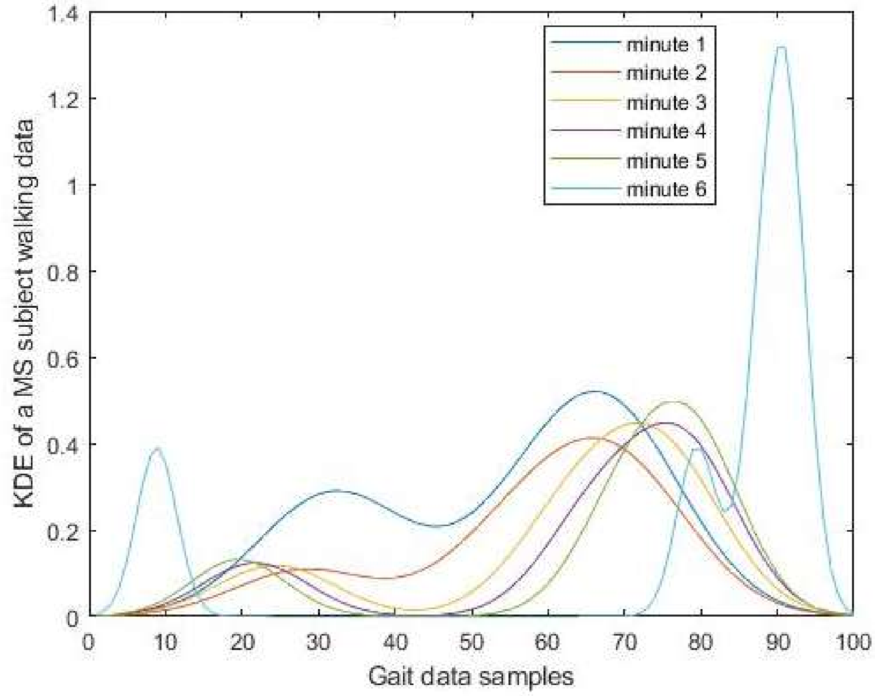


***Figure 31**: example of KDE of each minute of the 6MWT data for an MS subject.*

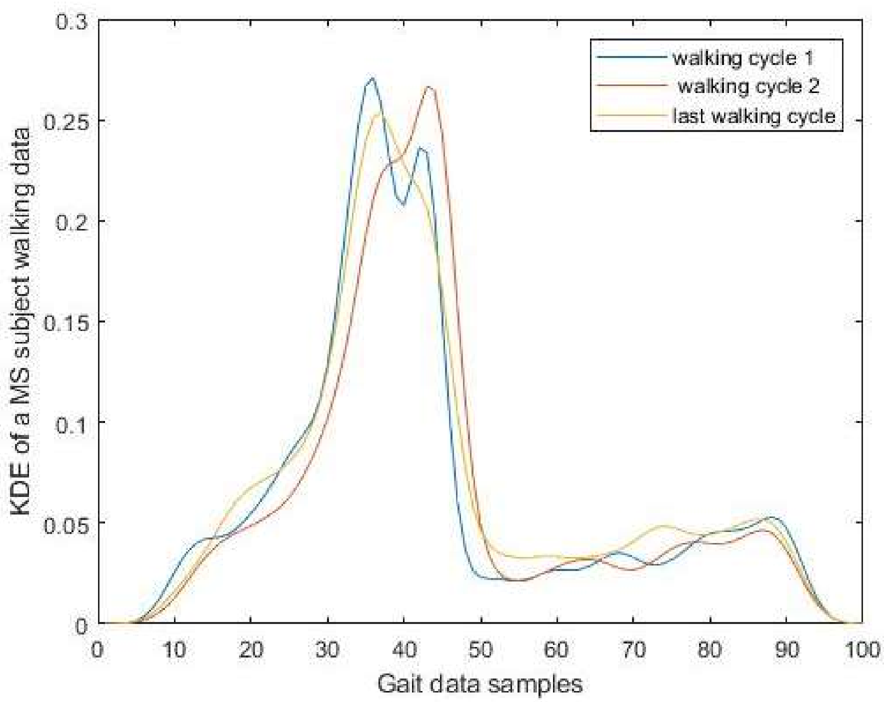


***Figure 32:** example of KDE of the first, second and last walking cycles of the 6MWT data for an MS subject.*

CHAPTER 4: RESULTS

4.1 Introduction

Firstly, this chapter aims to describe the choice of appropriate parameters in order to quantify the phenomenon of fatigue and monitor the patient's condition before and after the administration of the drug.

The results obtained for patients with multiple sclerosis and healthy subjects will be analyzed in detail. In particular, patients treated with Fampyra® at the San Luigi Gonzaga University Hospital of Orbassano (TO) are two men and a woman while healthy subjects are two women.

4.2 Selected parameters

Among the parameters described in chapter 3, they are selected only to optimally quantify the phenomenon of fatigue and monitor the patient's condition based on the patients studied in the present work.

The selected parameters are:

- *Data patient:* these are the values resulting from the questionnaires and the evaluation of the clinician and they are:

1. *MFIS (Modified Fatigue Impact Scale)*
2. *FSS (Fatigue Severity Scale)*
3. *VAFS (Visual Analogue Scale)*
4. *EDSS (Expanded Disability Status Scale)*

5. *Walked meters:* meters recorded by the doctor during 6MWT. Despite the results obtained by the algorithm was quite accurate, in this work we chose to consider the meters traveled calculated by the doctor during the test. The reason for this is that the calculation carried out by the algorithm can not take into account the last tract since the 6 minutes may have been completed in the middle of it and since at the end of the tract the patient does not perform the rotation as the test is completed.
6. Δm: the difference between the meters traveled after the administration of the drug and before the administration of the drug.
7. Δv_{16}: the quantitative difference between the walking speed obtained at the first minute and that obtained at the sixth minute. Between the two walking speeds obtained we chose to use the speed expressed in meters per second as the results obtained were very similar to each other.

Between the DTW score and the Warp score, the Warp score is the parameter that best describes the results obtained. Furthermore, the segmentation mode has been chosen in minutes as it produces more significant results and allows to analyze longer segments of the signal. Furthermore, the warp score turns out to be the most significant parameter among all and for this reason a more detailed analysis was carried out reporting the values obtained for all the components of the signal separately and selecting the following parameters:

8. *Warp score:* DTW technique applied to the segmented signal minute by minute. You get a value of Warp score that represents the whole signal.
9. $\Delta W_{pre\text{-}post}$: Percentage value obtained with normalization between the value of warp score obtained after administration of the drug and that obtained before administration of the drug.
10. *Warp score 1-6:* DTW technique applied to the first and second minute and then it is applied to the first and last minute.

11. ΔW_{16}: Percentage value obtained with normalization between the value of warp score obtained at the first and last minute of 6MWT and this obtained at the first and second minute of 6MWT.

The results obtained with the kernel density estimation (KDE) method did not show significant results for the quantification of fatigue in patients suffering from multiple sclerosis.

4.3 Healthy subjects

<table>
<tr><th></th><th></th><th colspan="4">Subject 1</th><th colspan="4">Subject 2</th></tr>
<tr><td>5</td><td>Walked meters (m)</td><td colspan="4">403.86</td><td colspan="4">358.14</td></tr>
<tr><td>6</td><td>Δm (m)</td><td colspan="4">-</td><td colspan="4">-</td></tr>
<tr><td>7</td><td>Δv_{16}</td><td colspan="4">-0.073</td><td colspan="4">0.0362</td></tr>
<tr><td rowspan="2">8</td><td rowspan="2">Warp score</td><td>x</td><td colspan="2">y</td><td>z</td><td>x</td><td colspan="2">y</td><td>z</td></tr>
<tr><td>2493.5</td><td colspan="2">2334</td><td>1790</td><td>2534</td><td colspan="2">2643</td><td>1870.5</td></tr>
<tr><td rowspan="2">9</td><td rowspan="2">$\Delta W_{pre-post}$</td><td colspan="3">x</td><td colspan="2">y</td><td colspan="3">z</td></tr>
<tr><td colspan="3">-</td><td colspan="2">-</td><td colspan="3">-</td></tr>
<tr><td rowspan="2">10</td><td rowspan="2">Warp score 16</td><td colspan="2">1-2</td><td colspan="2">1-6</td><td colspan="2">1-2</td><td colspan="2">1-6</td></tr>
<tr><td colspan="2">1919</td><td colspan="2">1974</td><td colspan="2">1885</td><td colspan="2">1856</td></tr>
<tr><td>11</td><td>ΔW_{16}</td><td colspan="4">2.86%</td><td colspan="4">-1.54%</td></tr>
</table>

Table 4: *Selected parameters for the healthy subjects.*

The meters traveled by the two subjects are close to 400 meters, which is considered the established threshold value of functional capacity.

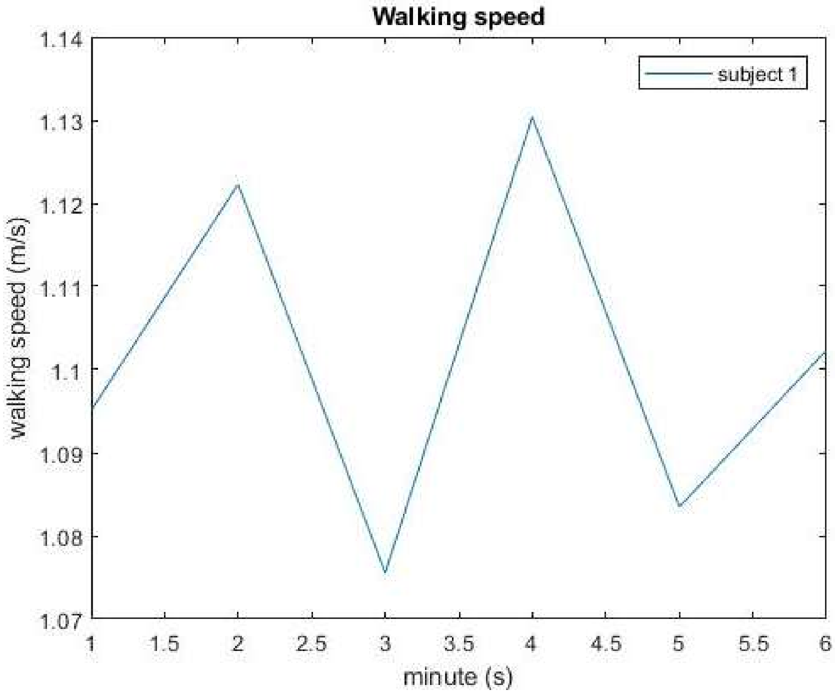


Figure 33: *Walking speed of the subject 1.*

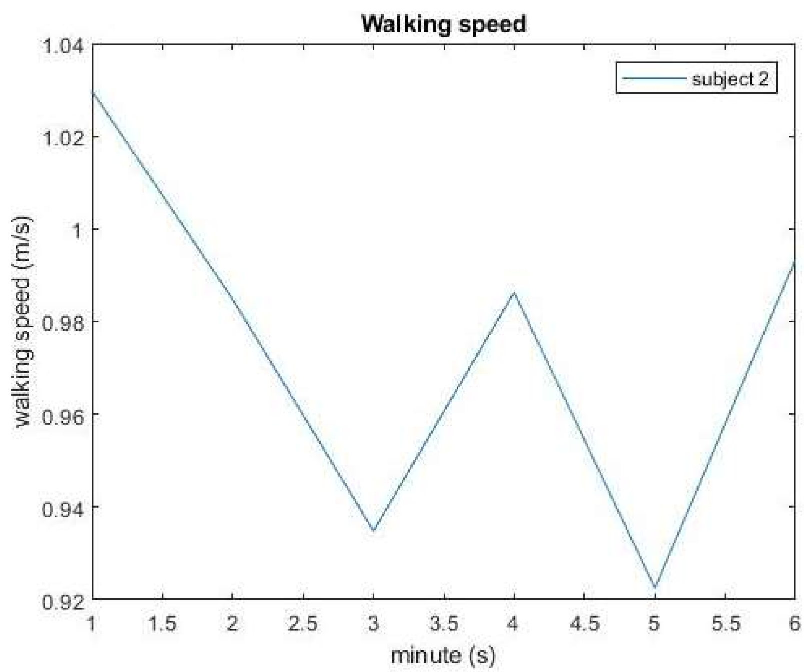


Figure 34: *Walking speed of the subject 2.*

The parameter concerning the speed, Δv_{16}, and the figure 33 and figure 34 allow to evaluate the phenomenon of fatigue within the signal itself: as you can see, subject 1 and subject 2 show a very constant speed from the beginning to the end of 6MWT. In particular, subject 1 shows a slight increase in speed in the last minute while subject 2 shows a slight decrease in speed in the last minute.

It is recalled that:

- The x component of the angular velocity describes the oscillation to the left and right of the foot and then a lateral deviation from the patient's rectilinear path;
- The y component of the angular velocity describes the rotation around itself of the patient;
- The z component of the angular velocity describes the oscillation forward and backward of the feet and then the trend of the step.

From this information and analyzing the results of the Warp score it can be deduced that the Warp score for the x component and y component is very similar while for the z component it is lower than the other two components. Regard to the occurrence of the phenomenon of fatigue analyzed for the z component, it can be seen that the values of warp score are very similar to each other and differ only by a few percentage.

In conclusion, it can be observed that all the parameters obtained from subject 1 and subject 2 show a constant trend throughout the 6MWT and without fatigue symptoms.

4.4 Patient 1

		Pre1	*Pre2*	*Post*
1	*MFIS (0-84)*	33	33	35
2	*FSS (9-63)*	41	41	46
3	*VAFS (0-10)*	6	6	6
4	*EDSS (0-10)*	1	1	1
5	*Walked meters (m)*	394.6	397.7	389.4
6	*Δm (m)*			-5.2
7	Δv_{16}	0.099	0.036	0.1

Table 5: *Selected parameters for the patient 1.*

From an analysis of the clinical parameters it can be seen that patient 1 describes a fatigue disorder higher than the mean value for the FSS and VAFS questionnaires, while slightly lower than the mean value for the MFIS questionnaire. After the administration of the drug, the patient 1 observes a very slight worsening of the disturbance due to fatigue. The clinical evaluation of the patient 1 is very low (equivalent to 1) because the patient has very few signs of disability.

The meters traveled by patient 1 are slightly below 400 meters which is considered the established threshold value of functional capacity. Also for this parameter there is a slight deterioration in the patient's performance after administration of the drug.

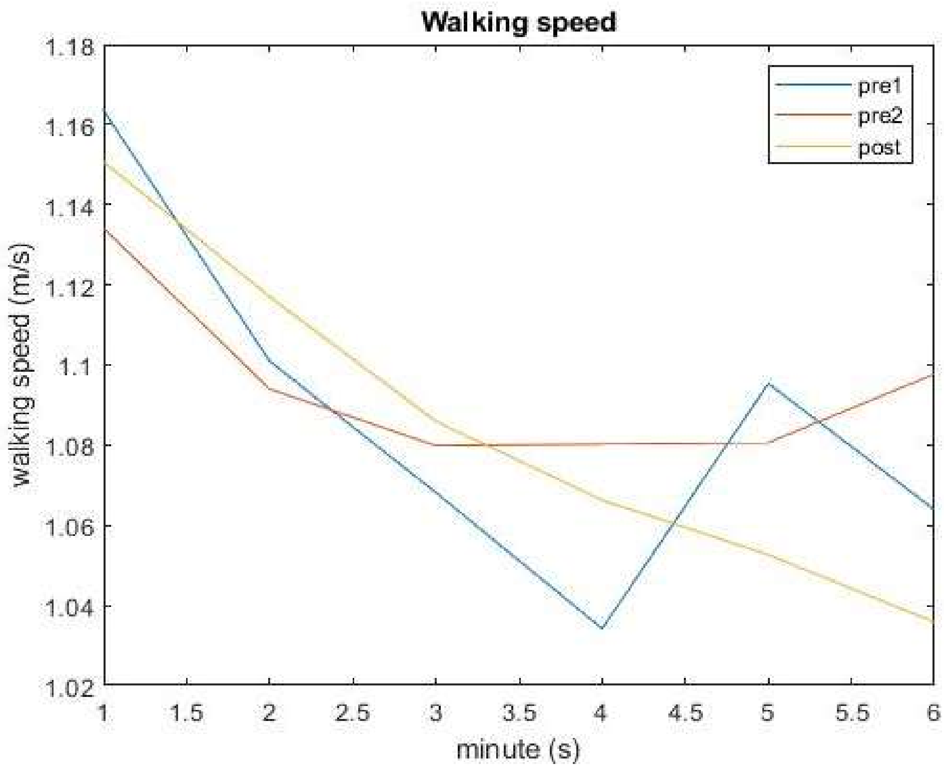


Figure 35: *Walking speed of the patient 1.*

The parameter concerning the speed, Δv_{61}, and the figure 35 allow to evaluate the phenomenon of fatigue within the signal itself: as you can see, the patient 1 shows a slight decrease in performance in the last minute due to multiple sclerosis, according to the literature. However, this decrease is not excessive due to the fact that the patient has very few signs of physical disability confirmed by the EDSS value. Despite this, also the Δv_{61} parameter is slightly higher after the administration of the drug, in accordance with the previous parameters analyzed.

		Pre1			*Pre2*			*Post*		
8	*Warp score*	***x***	***y***	***z***	***x***	***y***	***z***	***x***	***y***	***z***
		981.5	897	691	1012.5	1050	641	1147	998.5	760
9	$\Delta W_{pre\text{-}post}$	***x***			***y***			***z***		
		16.86%			*11.32%*			*9.99%*		
10	*Warp score 16*	***1-2***	***1-6***		***1-2***	***1-6***		***1-2***	***1-6***	
		780	865		797	718		875	960	
11	ΔW_{16}	*10.9%*			*-9.91%*			*9.71%*		

***Table 6**: Selected parameters of the Warp score of the patient 1.*

By the results of the warp score, it can be deduced that the Warp score before and after the administration has higher values for the x component, intermediate for the y component and lower for the z component. The values of all components after administration of the drug are higher than before the administration of the drug so there is a deterioration in patient performance of about 10%. Also with regard to the occurrence of the phenomenon of fatigue analyzed for the z component, it can be seen that in absolute values the values of the warp score are higher after the administration of the drug. The phenomenon of fatigue seems to improve slightly compared to before the administration of the drug, but the percentage is still very close to 10%.

In conclusion, it can be observed that the patient 1 shows a slight worsening of the performances of about 10% after the administration of the drug, as all the selected parameters are in agreement with this. Although this percentage is higher than that obtained with healthy patients, it is still low and, for this reason, the patient can be considered stationary.

4.5 Patient 2

		Pre	Post
1	*MFIS (0-84)*	37	25
2	*FSS (9-63)*	57	37
3	*VAFS (0-10)*	3	7
4	*EDSS (0-10)*	3	3
5	*Walked meters (m)*	203.6	212.8
6	*Δm (m)*		9.2
7	Δv_{16}	0.042	-0.044

Table 7: *Selected parameters for the patient 2.*

From an analysis of the clinical parameters it can be observed that patient 2 describes a fatigue disorder smaller than the mean value for the MFIS and VAFS questionnaires, while slightly higher than the mean value for the FSS questionnaire. In general, after the administration of the drug, the patient observes a slight improvement of the disturbance due to fatigue. The clinical evaluation of the patient 2 is equivalent to 3 because the patient has a moderate physical disability.

The meters traveled by patient 2 are below 400 meters which is considered the established threshold value of functional capacity and consequently this confirms a poor functional capacity of the patient. But, in this case, for this parameter there is an improvement after the administration of the drug because the patient travels almost 10 meters more than the 6MWT carried out before the administration of the drug.

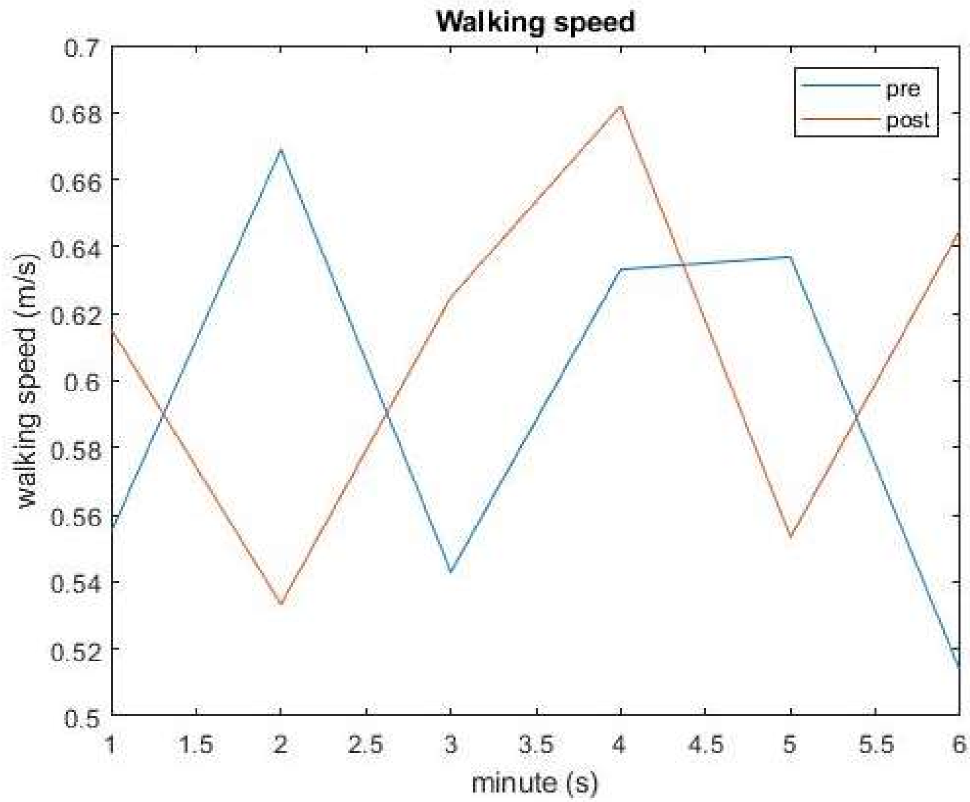


Figure 36*: Walking speed of the patient 2.*

The parameter concerning the speed, Δv_{16}, and the figure 36 allow to evaluate the phenomenon of fatigue within the signal itself: in accordance with the previous parameters analyzed, the Δv_{61} parameter also shows an improvement in patient performance.

<table>
<tr><td></td><td></td><td colspan="3">Pre</td><td colspan="3">Post</td></tr>
<tr><td rowspan="2">8</td><td rowspan="2">Warp score</td><td>x</td><td>y</td><td>z</td><td>x</td><td>y</td><td>z</td></tr>
<tr><td>1291.5</td><td>1493</td><td>1225.5</td><td>1206</td><td>1516</td><td>1213</td></tr>
<tr><td rowspan="2">9</td><td rowspan="2">ΔW_{pre-post}</td><td colspan="2">X</td><td colspan="2">y</td><td colspan="2">z</td></tr>
<tr><td colspan="2">-6.6%</td><td colspan="2">1.54%</td><td colspan="2">-1.02%</td></tr>
<tr><td rowspan="2">10</td><td rowspan="2">Warp score 16</td><td colspan="2">1-2</td><td>1-6</td><td colspan="2">1-2</td><td>1-6</td></tr>
<tr><td colspan="2">1360</td><td>1342</td><td colspan="2">1346</td><td>1258</td></tr>
<tr><td>11</td><td>ΔW₁₆</td><td colspan="3">-1.32%</td><td colspan="3">-6.56%</td></tr>
</table>

Table 8: *Selected parameters of the Warp score for the patient 2.*

The Warp score before and after the administration of the drug has higher values for the y component, intermediate for the x component and lower for the z component. The values of all components after administration of the drug are lower than before the administration of the drug, except for the y component, so there is a little improvement in patient performance, except for its rotation capacity, which is slightly worse. Also with regard to the occurrence of the phenomenon of fatigue analyzed for the z component, it can be seen that in absolute values the values of the warp score are lower after the administration of the drug. The phenomenon of fatigue seems to improve slightly compared to before the administration of the drug, but the percentage is still very small.

In conclusion, it can be observed that the patient 2 shows a slight improvement of the performances after the administration of the drug, as all the selected parameters are in agreement with this. Although this, the percentage is still low and, for this reason, the patient can be considered stationary.

4.6 Patient 3

		Pre	*Post*
1	*MFIS (0-84)*	59	45
2	*FSS (9-63)*	60	54
3	*VAFS (0-10)*	8	3
4	*EDSS (0-10)*	3	3
5	*Walked meters (m)*	391	440.8
6	*Δm (m)*		49.8
7	Δv_{16}	-	0.085

Table 9: *Selected parameters for the patient 3.*

Unfortunately, on this patient we could not take the signal before the drug was administered because the present study started after this date. For this reason, the current data of the patient 3 before the administration of the drug is only the data recorded by the doctor.

From an analysis of the clinical parameters it can be observed that patient 3 describes a fatigue disorder higher than the mean value for the MFIS, FSS and VAFS questionnaires. After the administration of the drug, the patient observes an improvement of the disturbance due to fatigue. The clinical evaluation of the patient 3 is equivalent to 3 because the patient has very a moderate physical disability.

The meters traveled by patient 3 are slightly under 400 meters before the administration of the drug and slightly above 400 m after the administration of the drug which is considered the established threshold value of functional capacity. Also for this parameter, there is an improvement after the administration of the drug because the patient travels almost 50 meters more than the 6MWT carried out before the administration of the drug.

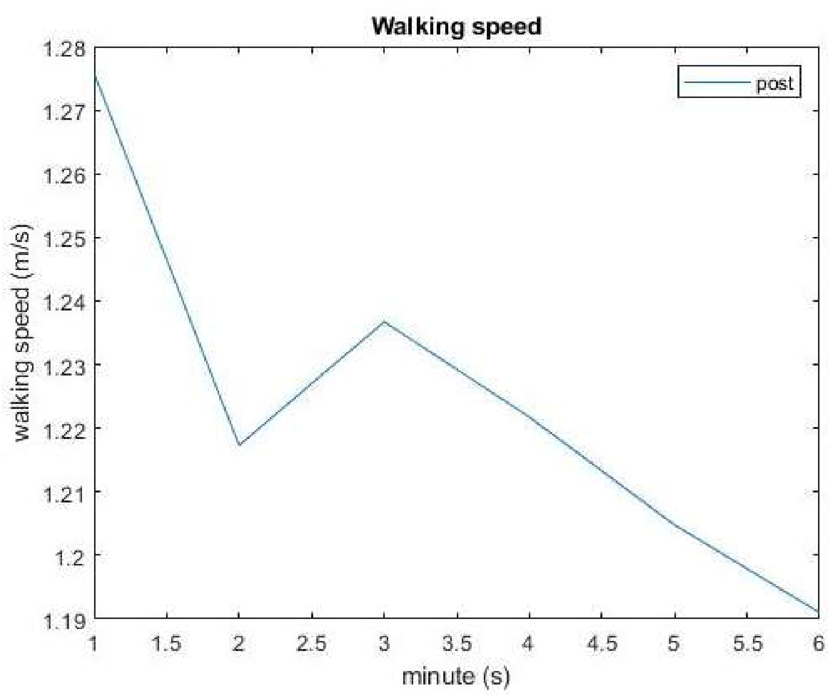


Figure 37: *Walking speed of the Patient 3.*

The parameter concerning the speed, Δv_{16}, and the figure 37 allow to evaluate the phenomenon of fatigue within the signal itself: as you can see, the patient shows a slight decrease in performance in the last minute due to multiple sclerosis, according to the literature.

		Post		
8	Warp score	***x***	***y***	***z***
		111.5	1007	587
9	$\Delta W_{pre\text{-}post}$	***x***	***y***	***z***
		-	-	-
10	*Warp score 16*	***1-2***		***1-6***
		767		797
11	ΔW_{16}	3.91%		

Table 10*: Selected parameters for the Warp score for the patient 3.*

The Warp score before and after the administration of the drug has higher values for the x component, intermediate for the y component and lower for the z component. Also with regard to the occurrence of the phenomenon of fatigue analyzed for the z component, it can be seen that in absolute values the values of the warp score are higher after the administration of the drug. The phenomenon of fatigue is very low with a percentage of 3.91 indicating a very slight phenomenon of fatigue in the last minute compared to the beginning.

In conclusion, it can be observed that the patient 3 shows a slight improvement of the performances after the administration of the drug. However, the available data are too few to be able to carry out a complete analysis.

4.7 Comparisons between patients

It can be seen that the meters traveled by the patient 1 and patient 2 are only very similar around 400 meters, slightly greater for the patient 3. While the patient 2 is able to travel a lot less meters than the other two patients. The walking speeds also reflect these observations compared to the three patients.

Although not particularly significant, an analysis of the absolute values of the warp score shows how they are very similar to each other for patient 1 and patient 3, recording values around 1000 and slightly less than 1000 for patient 1, while patient 2 has values higher than these, around 1300 (these values have been obtained using the same acquisition system described in the paragraph 3.2.2 “Equipment of the monitoring system”).

Furthermore, it can be observed that despite the patient 2 and the patient 3 have the same EDSS value, their performances are very different, in fact the patient 2 shows less physical performance but a little less fatigue during the 6MWT while the patient 3 shows greater physical performance but also greater fatigue during the 6MWT.

CHAPTER 5: ELDERLY SUBJECTS

The 18 elderly subjects are subjected to 6MWT on a 10-meter corridor without obstacles. The acquisition system consisting in a smartphone in which an app is installed that can be downloaded easily from the smartphone app store that allows the recording of sensor data in .csv format. A suitable algorithm will allow the conversion of data into the appropriate format for the subsequent processing of data on Matlab. In this case, the strap is placed in the basin.

For each subject are available, in addition to personal data, also indications such as the need for medical support during the test or medical observations both on the performance of the walking test. These data is shown in the table 11:

Subject	*Gender*	*Age (years)*	*Gait assistance*	*Other info*
1	*F*	*88*	No	skidding
2	*F*	*90*	No	
3	*F*	*90*	No	
4	*M*	*98*	Right stick	Balance disorders
5	*F*	*98*	Right stick	
6	*F*	*90*	Right crutch	
7	*F*	*86*	Right stick	
8	*F*	*91*	Right stick	
9	*M*	*80*	Left crutch	
10	*F*	*79*		
11	*F*	*88*		
12	*M*	*88*		
13	*M*	*80*	Left crutch	
14	*F*	*79*		
15	*F*	*88*		
16	*M*	*88*		
17	*M*	*83*		
18	*F*	*74*		

Table 11: *Data elderly subjects.*

Table 12 shows the results of the selected parameters applied to elderly patients.

<table>
<tr><th rowspan="2">Subject</th><th rowspan="2">Walked meters(m)</th><th rowspan="2">Mean speed (m/s)</th><th rowspan="2">Δv₁₆</th><th colspan="3">Warp score</th><th colspan="2" rowspan="2">Warp score 16</th><th rowspan="2">ΔW₁₆</th></tr>
<tr><th>X</th><th>y</th><th>z</th></tr>
<tr><td rowspan="2">1</td><td rowspan="2">380</td><td rowspan="2">1,08</td><td rowspan="2">-0,053</td><td rowspan="2">6912</td><td rowspan="2">7137</td><td rowspan="2">6831</td><td>1-2</td><td>1-6</td><td rowspan="2">3,26%</td></tr>
<tr><td>7089</td><td>7320</td></tr>
<tr><td rowspan="2">2</td><td rowspan="2">110</td><td rowspan="2">0,66</td><td rowspan="2">0,027</td><td rowspan="2">5828</td><td rowspan="2">7045</td><td rowspan="2">6555</td><td>1-2</td><td>1-3</td><td rowspan="2">-0,86%</td></tr>
<tr><td>6612</td><td>6555</td></tr>
<tr><td rowspan="2">3</td><td rowspan="2">240</td><td rowspan="2">0,67</td><td rowspan="2">0,053</td><td rowspan="2">6640</td><td rowspan="2">6492</td><td rowspan="2">5713</td><td>1-2</td><td>1-6</td><td rowspan="2">8,26%</td></tr>
<tr><td>5773</td><td>6250</td></tr>
<tr><td rowspan="2">4</td><td rowspan="2">200</td><td rowspan="2">0,71</td><td rowspan="2">0,049</td><td rowspan="2">6665</td><td rowspan="2">7263</td><td rowspan="2">6950</td><td>1-2</td><td>1-6</td><td rowspan="2">5,40%</td></tr>
<tr><td>7061</td><td>7442</td></tr>
<tr><td rowspan="2">5</td><td rowspan="2">40</td><td rowspan="2">0,38</td><td rowspan="2">0,038</td><td rowspan="2">7366</td><td rowspan="2">7659</td><td rowspan="2">7548</td><td colspan="2">1-2</td><td rowspan="2">-</td></tr>
<tr><td colspan="2">7548</td></tr>
<tr><td rowspan="2">6</td><td rowspan="2">120</td><td rowspan="2">0,50</td><td rowspan="2">-0,043</td><td rowspan="2">6746</td><td rowspan="2">7476</td><td rowspan="2">7198</td><td>1-2</td><td>1-4</td><td rowspan="2">1,08%</td></tr>
<tr><td>7393</td><td>7473</td></tr>
<tr><td rowspan="2">7</td><td rowspan="2">60</td><td rowspan="2">0,46</td><td rowspan="2">0,009</td><td rowspan="2">7242</td><td rowspan="2">7773</td><td rowspan="2">7261</td><td colspan="2">1-2</td><td rowspan="2">-</td></tr>
<tr><td colspan="2">7261</td></tr>
<tr><td rowspan="2">8</td><td rowspan="2">90</td><td rowspan="2">0,39</td><td rowspan="2">0,038</td><td rowspan="2">6555</td><td rowspan="2">6834</td><td rowspan="2">6605</td><td>1-2</td><td>1-4</td><td rowspan="2">0,17%</td></tr>
<tr><td>6599</td><td>6610</td></tr>
<tr><td>9</td><td>40</td><td>0,86</td><td></td><td colspan="3"></td><td colspan="2"></td><td></td></tr>
<tr><td>10</td><td>70</td><td>1,22</td><td></td><td colspan="3"></td><td colspan="2"></td><td></td></tr>
<tr><td>11</td><td>80</td><td>1,37</td><td></td><td colspan="3"></td><td colspan="2"></td><td></td></tr>
<tr><td>12</td><td>90</td><td>1,30</td><td></td><td colspan="3"></td><td colspan="2"></td><td></td></tr>
<tr><td>13</td><td>50</td><td>0,88</td><td></td><td colspan="3"></td><td colspan="2"></td><td></td></tr>
<tr><td>14</td><td>60</td><td>1,16</td><td></td><td colspan="3"></td><td colspan="2"></td><td></td></tr>
<tr><td>15</td><td>80</td><td>1,37</td><td></td><td colspan="3"></td><td colspan="2"></td><td></td></tr>
<tr><td>16</td><td>90</td><td>1,30</td><td></td><td colspan="3"></td><td colspan="2"></td><td></td></tr>
<tr><td rowspan="2">17</td><td rowspan="2">60</td><td rowspan="2">0,55</td><td rowspan="2">0,039</td><td rowspan="2">2542</td><td rowspan="2">3329</td><td rowspan="2">2820</td><td colspan="2">1-2</td><td rowspan="2">-</td></tr>
<tr><td colspan="2">2820</td></tr>
<tr><td rowspan="2">18</td><td rowspan="2">60</td><td rowspan="2">0,38</td><td rowspan="2">0,071</td><td rowspan="2">3148</td><td rowspan="2">3775</td><td rowspan="2">3245</td><td colspan="2">1-2</td><td rowspan="2">-</td></tr>
<tr><td colspan="2">3245</td></tr>
</table>

Table 12: *Selected parameters for the elderly subjects.*

As it was noted from the data in Table 12, unfortunately not all the subjects were able to carry out all the 6MWT. In some cases, however, the signals were not completely acquired due to interference problems and, for this reason, only part of the signal was available for analysis. For these reasons, Δv_{16} and ΔW_{16} parameters are calculated as described in paragraph 3.3.3 “Walking speed” and paragraph 3.3.4 “Dynamic Time Warping (DTW)” but applied to the first minute and last minute available in the signal, while the reported walked meters are calculated by the algorithm as described in the paragraph 3.3.2 “General Parameters”.

The results show very low and negligible Δv_{16} values. The ΔW_{16} parameter, instead, shows an increasing percentage with the increase in the length of the signal for which the patients who performed the test entirely have a higher value than those who did not complete the test. These observations therefore suggest that the subjects did not stop because of a feeling of affliction, but because of other problems linked perhaps to the age of the subjects. Furthermore, it can be noted that the subject 3 has been more tired than the subject 1 and the subject 4 for the same duration of the walk test. Subject 2, subject 6 and subject 8, on the other hand, even if they did not complete the walk test, would seem to have not tired themselves.

CHAPTER 6: CONCLUSIONS

6.1 Observations and conclusions

The aim of this work is to find an appropriate arrangement in order to pick up the walking test signals and implement an automatic algorithm able to quantify fatigue in patients with multiple sclerosis before and after the administration of the drug Fampyra®.

For this analysis, four different segmentations of the gyroscope signal to which to apply parameters were studied in order to evaluate which segmentation and which parameters could best quantify fatigue. In addition, an analysis is performed of both the signals before and after the administration of the drug and within a signal to quantify the patient's affection during the walk test.

From the results obtained, small improvements or worsening of patient performance can be observed, but they are also present in healthy patients because small variations can be considered physiological and not a symptom of improvement or worsening of the patient.

The number of patients available for analysis was very limited and this is why this thesis contains an observational study on the selected parameters. It will be necessary to repeat the measures on more patients in order to have a sufficient case study to draw conclusions statistical.

In general, we can see how these parameters, also in the case of elderly subjects, allow us to provide an excellent analysis of the progress of patients during the test and this can certainly support the doctor in monitoring the patient's condition.

6.2 Future developments

In the first place it would be important to study the parameters analyzed in this work to a larger number of patients so as to be able to validate their effectiveness and be able to implement improvements on the techniques used. A further possible future development could be to provide quantitative intervals of these parameters in order to give each of them indicative ranges on the severity of the disease and on the EDSS.

Furthermore, in the present work we have chosen to work on the signals obtained from the gyroscope because they showed a better representation of the progress of the path. A possible future development could be to study also the accelerometer and magnetometer signals as they are sensors easily available in any smartphone.

In conclusion the desired future development would consist in implementing an easy-to-use application by patients, allowing remote physiological and functional monitoring and evaluation of people in their homes so that the data are subsequently available to the doctor who, after the subsequent processing of the algorithm, will be able to evaluate the progress of the patients' disease.

BIBLIOGRAPHY

[1] Samar S. Ayache, Moussa A. Chalah. *Fatigue in multiple sclerosis – insights into evaluation and management.* Neurophysiologie Clinique/ Clinical Neuropysiology (2017) 47, 139-171.

[2] https://it.wikipedia.org/wiki/Sclerosi_multipla.

[3]https://www.medimagazine.it/nuove-intuizioni-sulla-causa-della-sclerosi-multipla/

[4] https://www.aism.it/index.aspx?id_area=3&codpage=la_sm.

[5] http://www.la-sclerosimultipla.net/.

[6] https://www.nationalmssociety.org/What-is-MS/Types-of-MS.

[7]https://gardenrain.wordpress.com/2009/10/06/the-universal-fatigue-assessment-scale/.

[8] http://s3.amazonaws.com/snoreguide/ms-fatigue-impact-scale.html.

[9]http://www.allwidewallpapers.com/ramsey-pain-scale/cmFtc2V5LXBhaW4tc2NhbGU/.

[10] http://www.sclerosimultipla-e.it/capire/scala-edss.shtml.

[11] https://hsctindia.com/edss.php.

[12] Nicole A. Capela-IEEE Member, Edward D. Lemaire-IEEE Member, and Natalie C. Baddour-IEEE Member. *A Smartphone Approach for the 2 and 6-minute Walk Test.*

[13]http://www.siditalia.it/pdf/lazio-congresso-nov-2016/presentazione%20test%20del%20cammino_%20Forte-Buonocore.pdf.

[14] Jurgen Schulte, Nguyen Anh Duc, Doan B.Hoang, Doug Elliott, Sharon McKinley and Priyadarsi Nanda. *A Remote Sensor-Based 6-Minute Functional Walking Ability Test.*

[15]Josselyn Le Moing and Ingo Stengel. *The Smartphone as a Gait Recognition Device: Impact of selected Parameters on Gait Recognition.*

[16] Massimiliano Pau, Silvia Caggiari, Alessandro Mura, Federica Corona, Bruno Leban, Giancarlo Coghe, Lorena Lorefice, Maria Giovanna Marrosu, Eleonora Cocco. *Clinical assessment of gait individuals with multiple sclerosis using wearable inertial sensors: Comparison with patient-based measure.* Multiple Sclerosis and Related Disorders 10 (2016) 187-191.

[17] Alon Kalron. *Gait variability across the disability spectrum in people with multiple sclerosis*. Journal of the Neurological Sciences 361 (2016) 1-6.

[18] Asma Qureshi, Maite Brandt-Pearce and Myla D. Goldman. *Relationship between Gait Variables and Domains of neurologic Dysfunction in Multiple Sclerosis Using ix-minute Walk Test.*

[19] Myla D. Goldman, Ruth Ann Marrie and Jeffrey A Cohen. *Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls*. Multiple Sclerosis 2008; 14:383-390.

[20] Sriram Raju Dandu, Matthew M Engelhard, Asma Qureshi, Jagi Gong, John C Lach, Maite Brandt-Pearce, and Myla D Goldman. *Understanding the Physiological Significance of Four Inertial Gait Features in Multiple Sclerosis*. Journal of biomedical and health informatics, special issue, 2017.

[21] Nikolaos V.Boulgouris, Konstantinos N. Plataniotis, and Dimitrios Hatzinakos. *Gait Recognition Using Dynamic Time Warping*. 2004 IEEE 6th Workshop on Multimedia Signal Processing.

[22] Matthew M. Engelhard , Sriram Raju Dandu, Stephen D. Patek, John C. Lach and Myla D. Goldman. *Quantifying six-minute walk induced gait deterioration with inertial sensors in multiple sclerosis subjects.* Gait & Posture 49 (2016) 340-345.

[23] Asma Qureshi, Maite Brandt-Pearce, Matthew M. Engelhard and Myla D. Goldman. *Relationship between Kernel Density Function Estimates og Gait Time Series and Clinical Data.* 2017 IEEE.