# Objective assessment of motor and gait

# parameters of patients with multiple sclerosis

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Karlsruhe, 04.07.2018 Layal Shammas

Abstract

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system. It affects approximately 400.000 individuals in Europe and about 2.5 million worldwide. Clinical symptoms of MS are highly variable and depend on the localization of lesions in the brain and spinal cord. Patients with chronic progressive neurological diseases such as MS typically show a decrease of physical activity as compared with healthy individuals. Approximately 75 to 80 percent of patients with MS (PwMS) experience walking and physical activity impairment in early stages of the disease. Therefore, walking impairment is considered as a hallmark symptom as this may have a significant impact on different daily activities. Moreover, an indirect association between overall MS symptoms and physical activity was found.

Several studies investigated the walking ability and physical activity under free-living conditions in PwMS, as this may provide significant information to predict the patient's health status. Different methods have been used for this purpose, including subjective approaches like self-report, questionnaires or diary methods. Although these methods are inexpensive and can easily be employed preferably in large scale studies, they are prone to error due to memory failure and other kind of misreporting. For many years, laboratory analysis systems have been considered to be the "gold standard" for physical activity and walking ability assessment. Nevertheless, these methods require extensive technical support and are unable to assess unconstrained physical activities in free-living situations. Thus, there is increasing interest in ambulatory assessment methods that provide objective measures of physical activity and gait parameters.

Therefore, this thesis takes a different approach and investigate the usage of an objective monitoring system to early detect the slightly changes in disease-related walking ability and gait abnormality using one accelerometer. Moreover, this work aims to classify the derived acceleration data regarding their response to a certain intervention and treatment. In doing so, first of all, different algorithms were developed to extract activity and gait parameters in time, frequency and time-frequency domain. Then a Home-based system was developed and provided to help doctors monitor the changes in the ambulatory physical activity of PwMS objectively. The developed system was applied in two different studies over long period of time (one year) to assess changes in physical activity and gait behavior of PwMS and to classify their response to medical treatment.

The aim of the first study was to investigate the ability of the developed parameters to objectively capture the changes in motor and walking ability in PwMS. Moreover, the objective was to provide additional evidence from long-term design study that support the association between changes in physical activity and walking ability and disease progression over time.

The aim of the second study was to investigate the effectiveness of the medication treatment using the developed gait parameters and the assessment system developed in this work. The result of the study was compared to those assessed in the clinic. Comprehensive analysis of gait features in frequency and time-frequency domain can provide complementary information to understand gait patterns. Therefore, in this study, the parameters peak frequency and energy concentration were integrated along with time-domain parameters, such as step counts and walking speed.

In case of chronic diseases, such as MS, medical benefit is the main factor to accept new technology. Thus, the developed system should be advantageous for diagnosis and therapy of MS. Moreover, it is important for the physician to be able to get better overview of the medical data about the disease course and health condition of their patients. Therefore, many critical factors regarding medical, technical and user specific aspects were considered in this work while developing the ambulatory assessment system. To assess the acceptance of the system a questionnaire was designed with main focus on two factors; usefulness and ease-of-use. The questionnaire was based on the Technology Acceptance Model (TAM).

As a result, the design, validation and clinical application of Home-based monitoring system and algorithmic methods developed in this thesis offer the opportunity to comprehensively and objectively assess the pattern of behavioral change in physical activity and walking ability using one sensor across prolonged periods of time. The derived information may assist in the process of clinical decision making in the context of neurological rehabilitation and intervention (evaluation of medication or physiotherapy effects) and thus help to eventually improve the patients' quality of life.

In this work the focus was on patients with multiple sclerosis, however the developed and evaluated system can be adapted to other chronic diseases with physical activity disorders and impairment of gait.

# Zusammenfassung

Multiple Sklerose (MS) ist eine chronisch entzündliche Erkrankung des zentralen Nervensystems. Sie betrifft schätzungsweise 400.000 Menschen in Europa und etwa 2,5 Millionen weltweit. Die klinischen Symptome der MS sind sehr unterschiedlich und hängen von der Lokalisation der Läsionen im Gehirn und Rückenmark ab. Patienten mit chronisch fortschreitenden neurologischen Erkrankungen wie MS zeigen üblicherweise einen Rückgang der körperlichen Aktivität im Vergleich zu gesunden Menschen. Circa 75 bis 80 Prozent der Patienten mit MS (PmMS) leiden in frühen Krankheitsstadien an Mobilitäts- und Geheinschränkungen, die erhebliche Auswirkungen auf die alltäglichen Aktivitäten haben können. Aus diesem Grund wird die Gehbeeinträchtigung als ein typisches Symptom der MS gesehen. Darüber hinaus weisen mehrere Studien einen indirekten Zusammenhang zwischen MS-Symptomen und körperlicher Leistungsfähigkeit auf.

Mehrere Studien untersuchten die Gehfähigkeit und die körperliche Aktivität unter alltäglichen Bedingungen bei PmMS, da diese wichtige Informationen zur Vorhersage des Gesundheitszustandes des Patienten liefern können. Dazu wurden verschiedene Methoden eingesetzt, darunter subjektive Ansätze und Methoden wie Fragebögen oder Tagebücher. Diese Methoden eignen sich aufgrund der geringen Durchführungskosten bei gleichzeitig hoher Fallzahl, bergen aber ein Risiko für Verzerrungen der Einschätzungs- und Erinnerungsfähigkeit.

Seit vielen Jahren gelten Laboranalysesysteme als „Goldstandard" für die Bewertung der körperlichen Aktivität und der Gehfähigkeit. Dennoch erfordern diese Methoden einen umfangreichen technischen Support und sind für die breite Anwendung im Alltag nicht geeignet. Daher besteht ein zunehmendes Interesse an ambulanten Bewertungsmethoden, die objektive Informationen über die alltägliche körperliche Aktivität und Gangparameter liefern.

Die vorliegende Arbeit hat das Ziel, ein objektives Aktivitätsmonitoring und ein Mobilitätsanalysesystem zu entwickeln, das minimale Änderungen in der krankheitsspezifischen Gangfähigkeit und -anomalie mit einem Beschleunigungssensor frühzeitig erkennt. Ferner soll die Wirksamkeit einer bestimmten Intervention und Behandlungstherapie anhand der erfassten Beschleunigungsdaten nachgewiesen werden. Zunächst wurden verschiedene Algorithmen zur Extraktion von Aktivitäts- und Gangparametern im Zeit-, Frequenz- und Zeit-Frequenzbereich entwickelt. Darauf aufbauend wurde ein

System zur Erfassung der Bewegungs- und Aktivitätsdaten im häuslichen Umfeld konzipiert und entwickelt. Das System ermöglicht den Ärzten die Veränderungen in dem alltäglichen Aktivitätsverhalten des Patienten objektiv zu erfassen und zu überwachen. Das entwickelte System wurde in zwei Langzeitstudien angewendet, um Veränderungen der physischen Aktivität und des Gangbildes bei PmMS zu messen und den Einfluss auf die medizinische Behandlung zu bestimmen.

Ziel der ersten Studie war es, die entwickelten Parameter auf ihre Eignung zur objektiven Erfassung und Erkennung von Veränderungen der Aktivitäts- und Gangfähigkeiten bei PmMS zu prüfen. Es konnten evidenzbasierte Erkenntnisse einer Langzeitstudie gewonnen werden, die einen Zusammenhang zwischen Gangbild; Aktivitätsfähigkeiten und Krankheitsverschlechterung darstellten.

Das Ziel der zweiten Studie war es, die Wirksamkeit der Medikamentenbehandlung unter Verwendung der entwickelten Parameter und des Assessment-Systems zu untersuchen. Die Studienergebnisse wurden mit denen aus der Klinik verglichen. Eine umfassende Analyse der Gangeigenschaften mithilfe der entwickelten Parameter im Zeit-, Frequenz-, und Zeit-Frequenzbereich bieten ergänzende Informationen zum Verständnis des Gangbildes.

Bei chronischen Erkrankungen wie MS spielt der medizinische Nutzen der neuen Technologie eine große Rolle bei der Akzeptanz. Daher sollte das entwickelte System für die Diagnose und Therapie der MS von Vorteil sein und dafür dienen, dem Arzt einen besseren Überblick über den Krankheitsverlauf und den Gesundheitszustand des Patienten zu verschaffen. Aus diesem Grund wurden bei der Entwicklung des ambulanten Monitoringsystems Faktoren hinsichtlich medizinischer, technischer und anwenderspezifischer Aspekte berücksichtigt. Für die Akzeptanzanalyse wurde ein Fragebogen entwickelt, der sich auf zwei Faktoren konzentriert: Nützlichkeit und Benutzerfreundlichkeit. Der Fragebogen basiert auf dem „Technology Acceptance Model" (TAM).

In dieser Arbeit wurde ein Aktivitätsmonitoring System und Algorithmen entwickelt, die Möglichkeit bieten, Muster der Verhaltensänderung in der körperlichen Aktivität und Gehfähigkeit mit einem einzigen Beschleunigungssensor über längere Zeiträume objektiv zu erfassen. Die gewonnenen Informationen können bei der klinischen Entscheidungsfindung im Rahmen der neurologischen Rehabilitation und Intervention (Bewertung der

Auswirkung der medikamentösen und physiologischen Therapien) helfen und so die Lebensqualität der Patienten verbessern.

In dieser Arbeit lag der Fokus auf Patienten mit multipler Sklerose, jedoch können das entwickelte und evaluierte System und Parameter an andere chronische Erkrankungen mit Aktivitäts- und Geheinschränkungen angepasst werden.

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# 1 Introduction

Gait disorders and physical inactivity are common in patient with chronic diseases such as Multiple sclerosis (MS). Gait impairments are hallmark symptoms as they may have significant impact on patients' quality of life. Assessment of physical intensity and gait parameters are of key importance for choosing the suitable intervention for the patients and help clinicians with just-in-time treatment adjustment. Over the last decades, multiple systems were applied to measure physical activity and walking ability of patients with motor and gait disorders. For many years, laboratory and clinical measures of physical activity and gait parameters have been considered as a gold standard. Nevertheless, these methods require extensive technical support and unable to assess unconstrained motor and gait parameters in everyday life situation. Therefore, in clinical studies and for the aim of continuous monitoring of patient's mobility situation, increased interest in ambulatory assessment methods has been expressed. These methods provide objective measures of activity and walking ability under free-living condition [1]. Portable devices and telemedicine systems can permit this assessment in free-living setting over prolonged periods without inducing an excessive interference with natural daily activity.

Over the past several decades, telemedicine has constituted an important breakthrough in healthcare. The term telemedicine refers to the usage of medical information exchanges from one site to another via telecommunication technology for medical diagnosis, treatment and patient care. Over forty years ago, telemedicine grew rapidly and its use has been widely spread. That is because the usage of telemedicine system can improve not only the access to the patients' information, but it also improves access in secondary care (i.e. access both between and within hospitals). Furthermore, telemedicine helped toward the transfer of healthcare from in-hospital to in-home healthcare. Different factors have contributed to the transform including the nature of the disease, demographic changes, increased healthcare complex equipment and amount of rehabilitation services, increased focus on quality of life and increased demand for healthcare cost containment, to name a few.

Transferring the healthcare from clinic setting to patient's home increases the need for remote monitoring and treatment. In the case of patients with chronic disease, such as MS, the information flow between patient and professional staff becomes complex and challenging. Telemedicine system and IT applications can efficiently improve the information flow and the relationship between patients and healthcare professionals.

Telemedicine can be useful when the system met the following conditions: easy to be used; involves the patients in the management of their disease; and has a direct impact on the fundamental aspects of patient management [2]. Furthermore, in the long-term monitoring, telemedicine could considerably reduce the cost of healthcare and increase efficiency through better management of chronic diseases. The usage of telemedicine systems to monitor patients under free-living conditions over longer period of time can help physicians to track disease progression. Early detection of disease state and health condition can help to earlier intervention and therapy adjustment [3]. Furthermore, telemedicine system can provide a tool to reduce medication and diagnostic errors and increase efficiency during decision making and physician can use these systems to monitor patient's response to a certain treatment [4]

This work illustrates the potential of using telemedicine system to objectively monitor comprehensive motor and gait parameters derived from one triaxial accelerometer in patient with multiple sclerosis (PwMS). The overall aim of the work was to apply IT for objectively data collections, processing and presentation of disease status, health condition and treatment response in PwMS. The main focus was on developing the methods and system for data processing and on the choice of useful motor and walking parameters. The data used for the development and evaluation of the methods consist of repeated measures, which were collected at different times over a long period of time to support the process of clinical decision making in the context of neurological rehabilitation and intervention.

## 1.1 Physical Activity and Gait in PwMS – Background and Motivation

MS is an inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS). MS affects approximately 2.5 million individuals worldwide, of which 400.000 are in Europe and most commonly young adults (20-40 years) [5]. The following figure (Figure 1-1) shows global prevalence of MS.

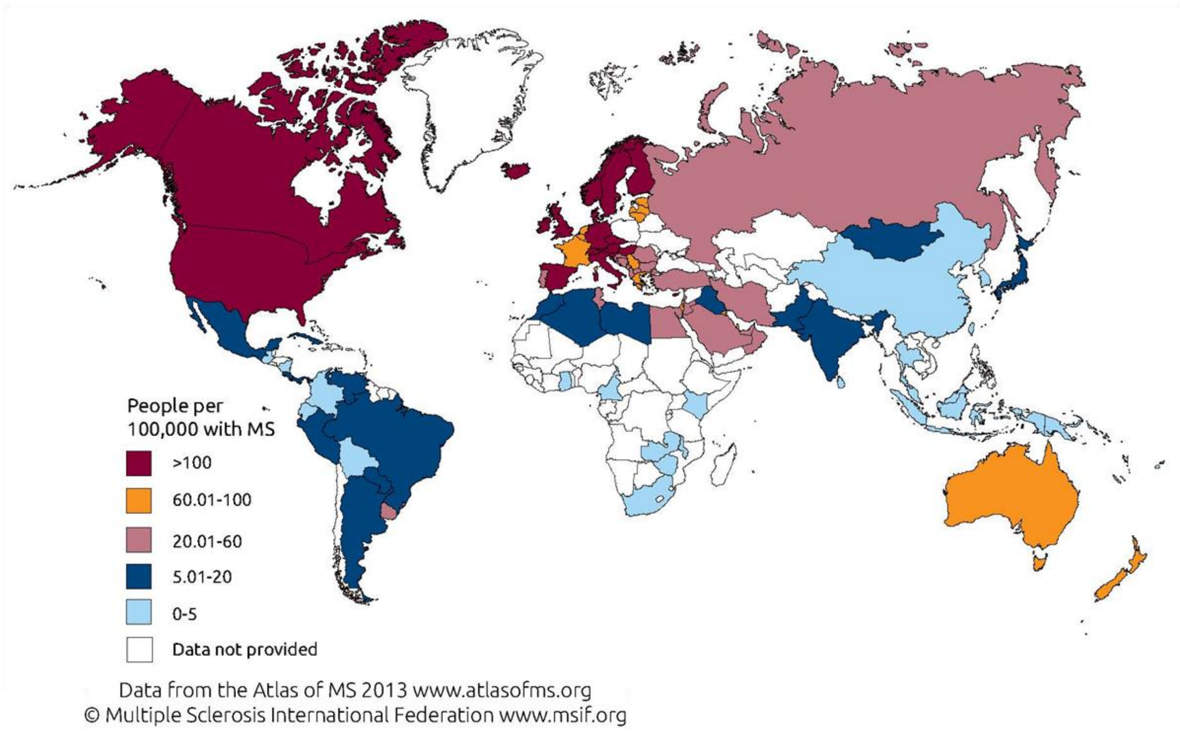



Figure 1-1. Global prevalence of Multiple Sclerosis [6]

MS is resulting in demyelination of the axons which leads to a loss of conduction along certain neural pathways. The reported cortical lesions in frontal brain areas contribute to cognitive dysfunctions and in particular, to motor deficits in MS. Thus, it is not surprising that impaired walking and physical inactivity are one of the most commonly reported symptoms in MS; approximately 85% of PwMS experience walking disability and motor impairment [7]. A meta-analysis suggested that PwMS engage in less physical activity than healthy samples and typically only a small proportion of PwMS achieves the amount of daily moderate-to-vigorous physical activity intensity (MVPA) that has been recommended by health guidelines [8]. Degenerative processes may also result in gait impairment which is considered as key components of disability in PwMS. Thus, physical inactivity and gait disability are considered as a key problem in PwMS as they may incur a loss of personal independence, withdrawal from social life and finally decline on quality of life [9].

The state of the art in the clinical setting is to use the clinical rating scales, such as Expanded Disability Status Scales (EDSS). It includes items that score the degree of neurological impairment in different functional systems yielding total scores that range from 0 to 10 [10]. However, the EDSS has been criticized due to methodological problems associated with predicting the clinical outcome in

MS, such as using an ordinal scale. Furthermore, EDSS is shown to be insensitive to the clinical change which could affect the accuracy of the diagnosis, since it is mainly based on the observations and judgments by physicians [11].

Effective symptom management of PwMS relies on timely diagnosis and classification of disease course. Therefore, early diagnose and in-time treatment optimizations are critical to prevent irreversible neurological deficits and reduce the rate of acute neurological relapses [3]. Moreover, observer-independent measures before and after treatment intervention can cover more aspects of the outcome than the established subjective clinical scales.

Severity of the overall symptoms and the level of neurological impairment have been reported to be significantly correlated with physical activity behavior and walking ability [12]. Moreover, clinical scales that assess the health status of PwMS typically include items pertaining to motor activity. For example, walking ability is a central element of the EDSS [10]. Therefore, physical activity and gait analysis has become a widely used clinical tool to assess ongoing clinical status of the patients and enable accurate diagnosis.

## 1.2 Objective of this work

Physical activity behavioral and gait performance in PwMS have typically been assessed by questionnaires or diary methods. Although these methods are inexpensive and can easily be employed preferably in large scale studies, they rely on correct memory retrieval and an accurate estimation of physical activity. Clinical tests such as 6-Minute Walk Test and the Timed 25-Foot Walk Test, have frequently been employed to assess physical function. However, these movement probes are also limited to the clinical setting and have a poor ecological or real-life validity [13].

Increased recognition has been given to the importance of physical and walking limitations in everyday life of PwMS. Therefore, a regular and objective assessment of physical and motor ability has been considered to be a very useful tool to monitor clinical disease activity and assess the efficacy of rehabilitation therapies.

For many years, laboratory analysis systems have been considered to be the “gold standard” for physical activity and walking ability assessment. Nevertheless, these methods require extensive technical support and are unable to assess unconstrained physical activities in free-living situations. Therefore, there is increasing interest in ambulatory assessment methods that provide objective measures of physical activity and gait parameters.

Various types of wearable sensors and different positions have been used and described in the literature, where accelerometers showed to be the most preferable in term of accuracy, cost and comfortability. Nevertheless, studies applied accelerometer either used multiple sensors attached to different part of the body, or they used it in combination with other sensors. The studies used only one accelerometer, are usually expressed the data as “activity counts”. This value depends on one single regression model, which is not applicable on all typed of activities [14]. More importantly, most of the accelerometers only provide basics gait parameters, such as steps count, walking speed but not gait abnormality (e.g. asymmetry) unless in combination with other types of WS.

Therefore, further research is needed in term of simplified procedures for supporting the diagnosis and assessment of health condition in PwMS under free-living conditions. There is a need for an objective monitoring system with reduced number of sensors that is able to early detect the disease-related changes of activity and gait. Furthermore, this system should be accepted by patients and physicians for everyday use.

Based on the research needs previously raised, this work aims to realize and develop a method that allows a complex and reliable assessment of physical activity and gait disorder in PwMS under free-living conditions. Based on one accelerometer this method should be able to assess comprehensive number of activity and gait parameters to help physicians in monitoring changes in motor ability, thus allowing an early treatment adjustment and optimization. Furthermore, the developed method should provide a valuable tool to evaluate the effectiveness of treatment intervention. The focus of this work is the objectively detection of the slightly changes in disease-related walking ability and gait abnormality using daily acceleration data. Moreover, this work aims to classify the derived data regarding their response to a certain intervention and treatment using time-domain and frequency domain methods.

In order to allow meaningful interpretation of the results and insure the reliability of the assessed data, physical activity and gait parameters should be observed across prolonged period of time.  Therefore, this work also objects to develop a prototypical Home-based assessment system, which should enable the possibility to integrate, manage and analyze the assessed data. This system should be user-friendly, easy to use and provide comprehensive overview of patients on each clinical stage. Moreover, it should be; a) applied in free-living environment of the patients, b) integrated in the clinical setting to support clinicians by the medical decision. Therefore, different technical and usability aspects as well as patients and physicians' requirements were considered for the development of the end-user's software.

The hypotheses of this work are:

H1: It is possible to use one wearable sensor to analyze comprehensive physical activity and gait parameters in order to capture the slightly changes of these parameters in absence of clinical measures.

H2: Accelerometer can be used to significantly differ between different impairment levels.

H3: Accelerometer can provide objective useful tool to monitor and evaluate the intervention effects during rehabilitation process.

H4: The developed system is adapted for long-term monitoring and qualitative and quantitative assessment of motor abnormalities in PwMS during their daily activities with high acceptance rate.

The research approach of the developed methods is illustrated in Figure 1-2. At the lowest level the system should assess comprehensive number of gait parameters under free-living conditions to reach the capacity of the laboratory systems. In neurological healthcare environments, the extracted parameters should provide an insight into mobility and walking behavior of PwMS. The assessment should be done using one accelerometer and the measurements should be performed repeatedly in the patients' homes.  This could enable the detection of gait abnormalities, which may indicate the onset of diseases progression and capturing the slightly changes in mobility behavior in absence of clinical disability.  In the next stage, the data-driven analysis methods should be applied to analysis the relationship between the extracted parameters as independent measures and the dependent outcome which is obtained by the clinical ratings. Finally, the extracted parameters should be evaluated for its reliability and sensitivity. Reliability refers to the extent to which the parameters are free from measurement. Moreover, the extracted parameters should be able to detect the changes over time, which result from treatment intervention as well as from natural disease progression.

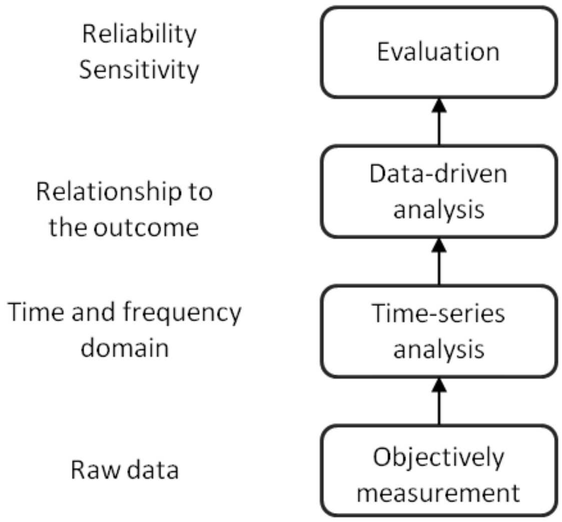



Figure 1-2: Approaches to methods development and evaluation

Gait acceleration is a powerful tool to assess human activity and capture deterioration in gait characteristics. Therefore, it can be a very important source of clinical relevant information and a helpful tool in decision making. Gait analysis system available nowadays usually includes kinematics and kinetics information. However, obtaining this information is complex, time demanding and intrusively. Other systems used several wearable sensors to extract spatio-temporal parameters (e.g. swing and stance phases, steps).

This work presents new methods to extract different gait parameters to reach the capacity of the laboratory systems with only one wearable sensor. In comparison to the However, not only time domain parameters were extracted, but the novelty of this work is its comprehensive analysis of multiple gait features in time, frequency and time-frequency domain in PwMS under free-living conditions. For the first time, it will be possible to objectively obtain the slightly changes in physical and gait parameters such system was applied over long period of time (one year) to assess changes in physical and gait behaviour of PwMS and to classify their response to medical treatment.

## 1.3 Outline of this work

This work is organized in 8 chapters. Chapter 0 (current chapter) introduces the topic of this thesis and outlines the rest of the work. Motivations of the research work are explained with the objectives of the thesis. Chapter 2 presents the basic concepts of the physiological of human physical activity and gait, as well as the general backgrounds of the disease multiple sclerosis. Chapter 3 covers the theoretical background of modern sensor technologies, as well as basic concepts of signal processing and analyzing. Chapter 4 presents the state of the art in the field of physical activity and gait parameters assessment tools, including a short description of the common used clinical reference methods, overview about the various laboratory methods and a review of methods based on wearable technology. This chapter summarizes the advantages and disadvantages of the available methods regarding their usability for the purpose of this work.

Chapter 5 covers the conception of the developed system, where the hardware and the software requirements are presented. This chapter presents the new algorithms developed to assess gait parameters using one accelerometer, throughout temporal and frequency parameters detection. Developing of these parameters is essential tasks for the realization of the system to assess comprehensive gait parameters in free-living environment. Furthermore, the chapter presents the development of the software components of the monitoring systems. Chapter 6 and Chapter 7 presents two different studies where the systems was applied and evaluated for assessing changes in physical activity and gait parameters, determination of the stability of the extracted parameters on free-living environments and finally to evaluate the systems as a clinical tool to measure and monitor the efficiency of the therapy. Chapter 8 summarizes the results finalizes the work with a conclusion and an outlook for future work.

# 2 Basic Concepts – Human physiology and Multiple sclerosis

In this chapter, the most important concepts of physical activity, human gait and the disease of multiple sclerosis will be explained. At first, the physiological background of human physical activity and gait will be described. Then, the basic theoretical understanding of the disease and the physical and gait impairment in patient with multiple sclerosis will be presented.

## 2.1 Human Physical Activity

Physical activity is defined as any movement or force produced by skeletal muscles and results an increase in energy expenditure above the rest [15]. Physical activity can be categorized in various ways. The simplest categorization includes the physical activity that occurs while resting, at work and at leisure [15]. However, leisure physical activity requires voluntary muscular work and can be divided into subcategories, such as sport, household, conditioning exercises (e.g. to improve fitness, enhance mental well-being, promote health).

The description of physical activity is usually done by the following parameter [16]:

- Type of the activity (walking, jogging…etc)
- Duration of the activity in minutes or hours per day or movement unit.
- Frequency of occurrence per day, week or months.
- Intensity; normally classified into mild, moderate and vigorous. The intensity is often quantified in metabolic equivalent (MET). One MET is equivalent to the energy consumption at rest [17].

### 2.1.1 Anatomy of Human movement

The purpose of this section is to present a brief overview of the anatomical principles that apply to movement in exercise and activity. First of all, the planes and the axes of the movement will be presented. The anatomy and the function of the human skeleton are also discussed. Detailed information can be found in [18,19].

The movement of the human body joints takes place about a rotational line. This line is the rotation axis and is perpendicular to the plane in which the movement occurs. Figure 2-1 shows the three different planes of the human body, i.e.

sagittal, frontal and vertical. The Sagittal plane divides the body into left and right parts, whereas the frontal plane divided the body into anterior and posterior parts. The vertical plane divides the body into superior and inferior. The general movements of the body are described by defined terms. Most of these terms are treated in pairs.

**Flexion and extension** describe movements that affect the angle between two parts of the body. Flexion is a bending movement, in which the angel is decreased, such as bending the elbow, sitting down, moving the trunk forward and backward. When the angle between body parts increases the term "extension" is used. Thus, the extension describes the movement in the posterior direction.

**Abduction and adduction** are sideways movements that refer to the motion in the frontal plane and describe the movement away from or toward the body center. The center of the body is defined as the mid-sagittal plane. Abduction is the motion that moves away from the midline of the body, whereas adduction refers to the movement toward the midline.

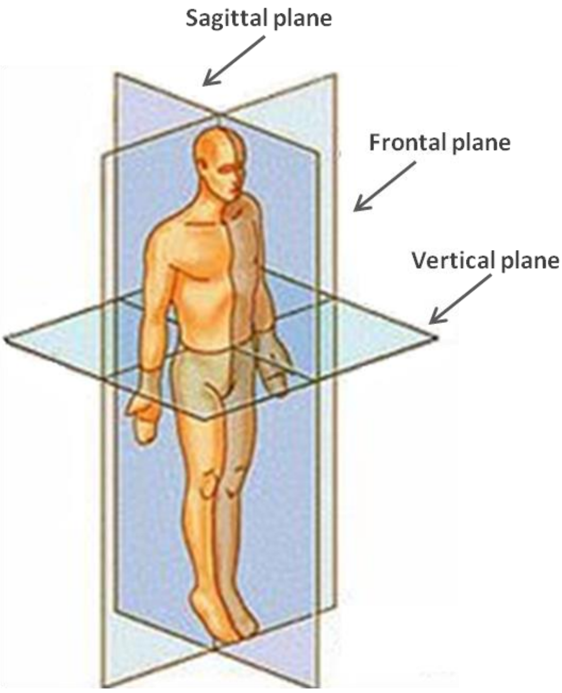



Figure 2-1. Planes of the human body movement ([18] modified)

**Elevation and depression** describe the movement above and below the horizontal. They refer to the motion in the superior and inferior direction, respectively. Other movement such as rotation refers to the rotation towards or away from the center of the body.

**Human skeletal system:** The human skeletal system consists of 206 bones, of which 177 involve in voluntary movement. It consists of bones, membranes that line the bones and cartilage. These bones include connective tissue, nervous tissue and muscle and epithelial tissues. The skeleton shown in Figure **2-2** is divided into axial and appendicular skeleton. The former is mainly protective, whereas the latter is involved in locomotion. Axial skeleton includes skull, vertebrae, ribs, lower jaw, sternum, sacrum and coccyx. The appendicular skeleton is comprised of pelvis gridle, shoulder gridle and upper and lower extremities.

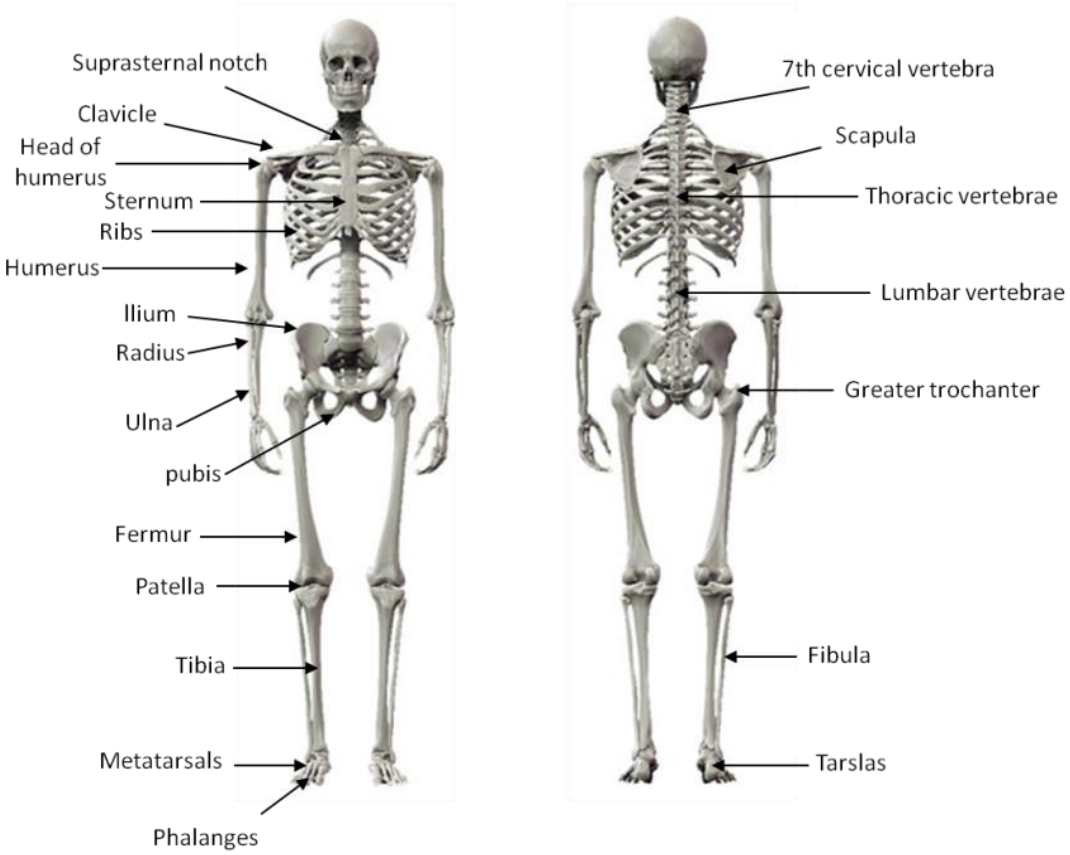



Figure 2-2. Human skeletal system ([19] modified)

One of the most important functions of the skeletal system is to protect soft organs from injury, such as heart and lungs. Furthermore, it provides a supportive framework for the attachment of muscles and other tissues and enables body movements. Bones are considered to be minerals storage, such as calcium and phosphorus which are essential for different cellular activities. Moreover, the adipose cells of the yellow marrow store minerals and lipids (fats). Thus, the skeletal system serves as energy reservoir.

The bones of the skeletal system [19] can be classified according to their shape, size, structure and functional requirements into:

- Long bones: They are bones that are longer than they are wide. They exist mostly in the appendicular skeleton and are responsible for weight-bearing and movement. They consist of a long shaft with two bulky ends or extremities. They are primarily compact bone but may have a large amount of spongy bone at the ends or extremities. Examples of long bones are the humerus, radius and femur.
- Short bones: These bones are small, chunky and irregular in shape with vertical and horizontal dimensions approximately equal. They consist of thin layer of compact bone with relatively large amount of bone marrow. Bones of the hand, foot and tarsal are examples of short bones.
- Flat bones: These bones are thin, strong, flattened and usually curved. Their main function is to protect the vital organs and provide a base for muscular attachment. Sternum, skull, ribs and hip bones are classified as flat bones. In adults, flat bones are also responsible for producing blood cells.
- Irregular bones: Bones with non-uniform shape are classified as irregular bones. They are mainly spongy and covered with a thin layer of compact bone. These bones include vertebrae, sacrum and ilium.
- Sesamoid bones: Patella is an important example of the bones from this category. They usually represent a point of attachment for tendons and ligaments.

**Human skeletal muscle:** Muscles are considered to be the powerhouse of the body movements. They convert chemical energy into mechanical work and heat. Skeletal muscle makes up approximately 40-50% of an adult total body mass, enabling the body to control motor, maintain posture and store energy. Figure **2-3** illustrates the main skeletal muscles. Each skeletal muscle may be made up of hundreds of fibers (or muscle cells) lying parallel to another and bundled together by connective tissue. There are three different layers of connective tissues. Epimysium separates the muscle from its neighbors and surrounding tissues. The surrounding tissue or perimysium surrounds the bundled fibers. The third layer of the connective tissue called endomysium. This layer surrounds each individual muscle cells. Skeletal muscles are voluntary muscles and they are supplied and controlled by blood vessels and nerves of the central nervous system, respectively. Each nerve impulse causes all the fibers to contract fully and simultaneously. Each nerve is accompanied with an artery and at least one vein. These blood vessels are responsible for supplying the skeletal muscles with oxygen and nutrients and for carrying wastes out.

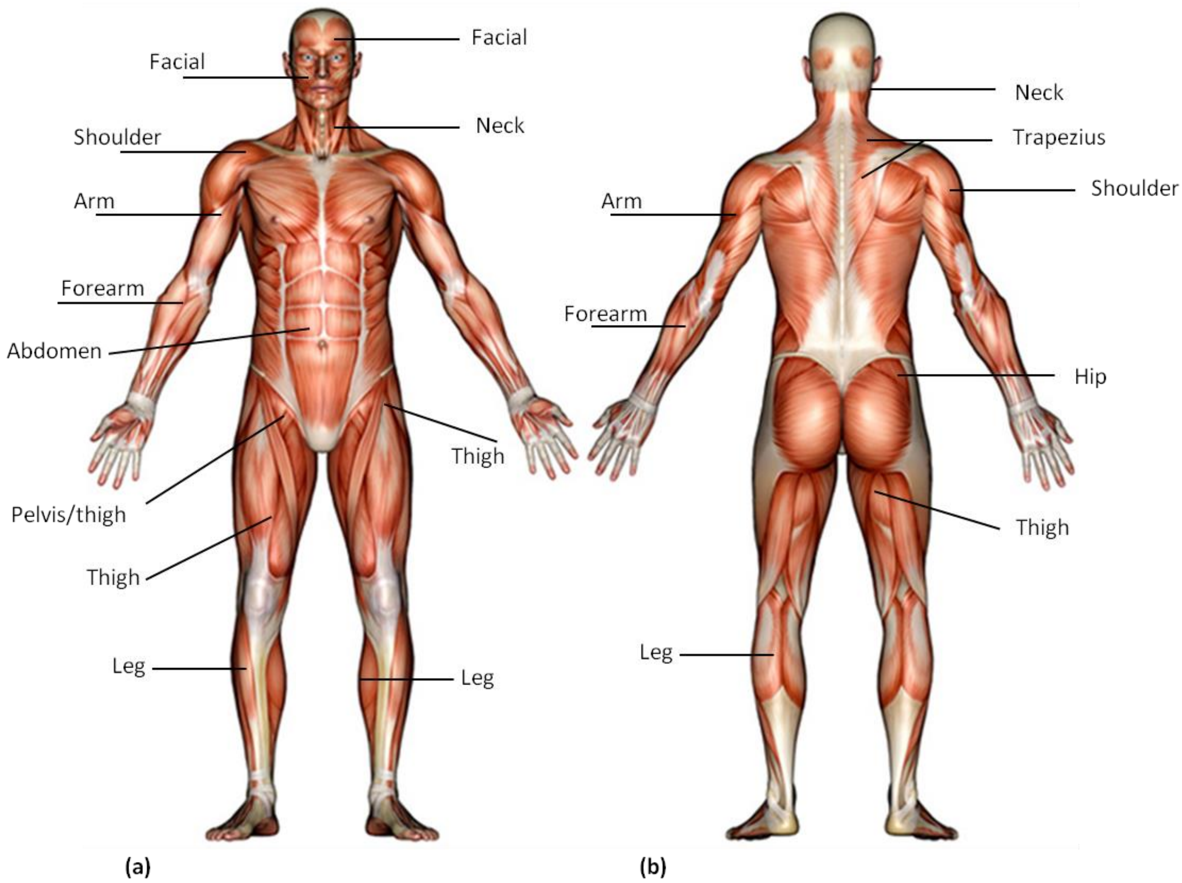



Figure 2-3. Main skeletal muscles - front view (a) and back view (b)( [20]simplified)

The body contains three types of muscle tissues. Their shape, location and responsibilities are summarized in the following table (Table **2-1**).

Table 2-1. Type of body muscles

| Type | Description |
|---|---|
| Cardiac muscles | • Rectangular in shape<br>• Involuntary, striated and rhythmical muscles<br>• Found in the walls of heart<br>• Under control of the autonomic nervous system<br>• Propel blood into heart and through blood vessels |

| | |
|---|---|
| Skeletal muscles | • Fibers are the basic unit<br>• Voluntary, striated muscles<br>• Usually attached to the skeleton<br>• Controlled by peripheral parts of the central nervous system<br>• Responsible for body movement |
| Smooth muscles | • Spindle-shaped<br>• Involuntary, non-striated, slow and rhythmical muscles<br>• Found in the walls of the hollow internal organs, e.g. veins and blood vessels<br>• Under control of the autonomic nervous system |

The structural classification of the muscles and their attachment to the skeletal system and the movement they cause can be found in different physiology and anatomy books. For example [19,20].

#### *2.1.1.1 Nervous System*

The nervous system is made up to three types of organs: the brain, the spinal cord and nerves. The brain and the spinal cord are along the midline of the body; therefore, they are referred to as a central nervous system (CNS). The peripheral portions of the nerves system extend from the central nervous system to the peripheral organs such as muscles and glands. These nerves are referred to as peripheral nerves system (PNS). The major division of the nervous system (i.e. CNS and PNS) and their subdivision are shown in the following Figure **2-4**.

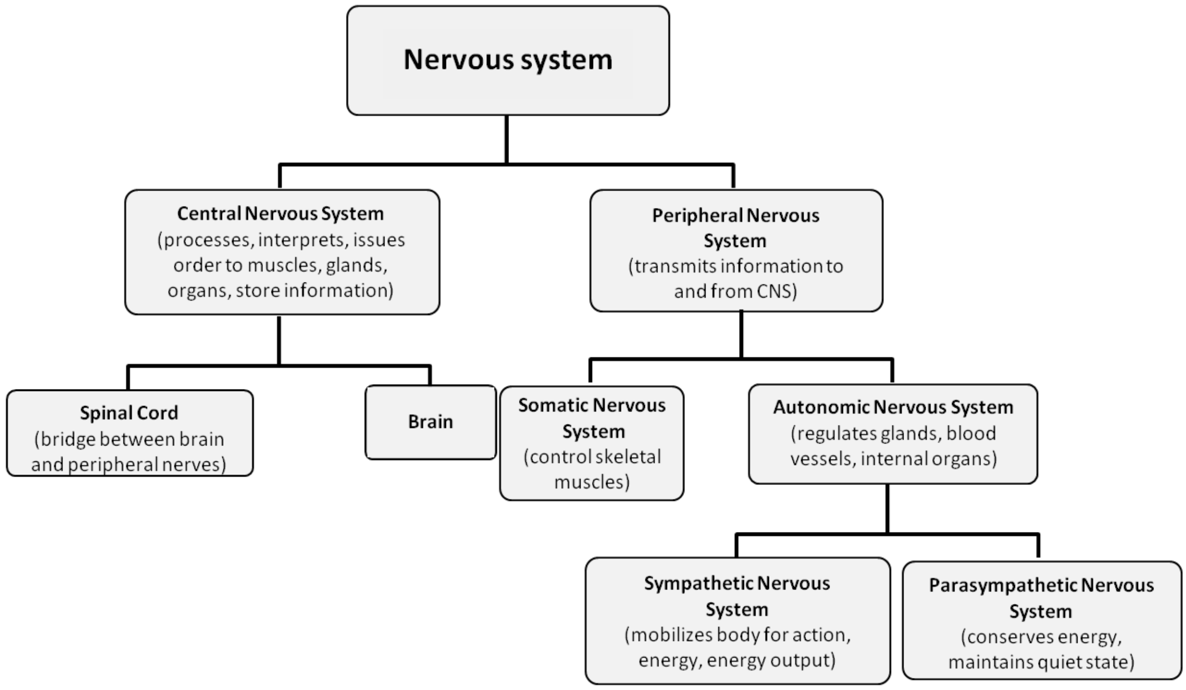



Figure 2-4. Major divisions of the nervous system and their subdivisions ([21] edited)

The nervous system is responsible for communicate, control and regulate the action and reaction of the body in response to the environment stimulus. It controls directly the glands and the voluntary movements of the skeletal muscles. Moreover, the nervous system regulates indirectly the other parts of the body by adjusting, for example, the amounts of the hormones produced by some glands.

Neurons are the core units of the nervous system. Each neuron consists of cell body (soma), one or more dendrite and a single axon (Figure 2-5). The neurons, or nerve cells, conducting the impulses sent by the brain to a certain part of the body (e.g. muscles, glands), and sending messages back to the brain. Functionally, neurons are divided into three categories according to the direction in which they transmit impulses: Sensory neurons, motor neurons and association neurons. Sensory neurons are the nerve cells that transmit impulses from body organ to the CNS, whereas motor neurons carry impulses in the opposite direction, i.e. from the CNS to the effector organs. The third type of neurons called interneuron or association neurons. They are located in the entirely within the CNS forming the connection between sensor and motor neurons.

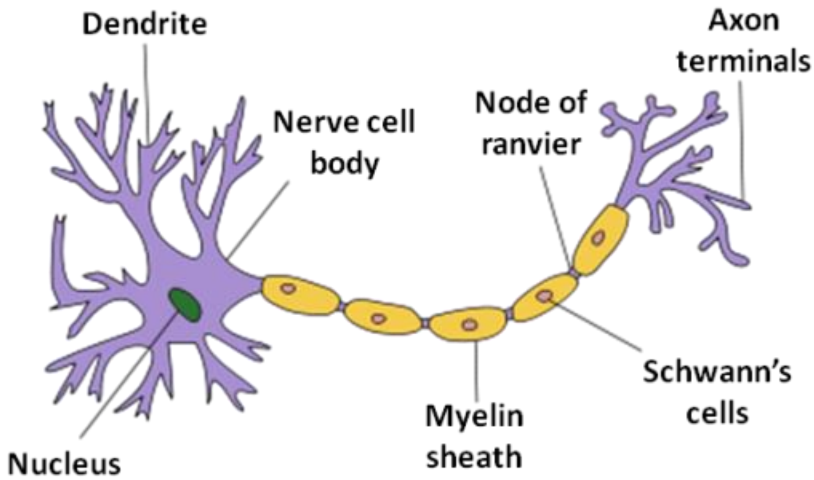



Figure 2-5. Structure of a normal neuron [22]

In relation to physical activity, the motor body functions are controlled by spinal cord and brain. The spinal cord harmonized muscle contractions, whereas the brain triggers action and reaction signals over the spinal cord. Understanding these circuits and the relation between movement and its central control (i.e. the nervous system) is important to be able to understand both normal behavior and the causes of abnormal activity behavior in various neurological diseases, such as multiple sclerosis and Parkinson’s disease. The lower motor neurons in the spinal cord and brainstem are considered as the primary motor neuron. They initiate all movements of the skeletal muscle by innervating the fibers within each single muscle. The neurons innervating the same muscle are grouped together and form a motor neuron pool. The electrophysiological properties of an individual motor neuron are appropriately matched to the contractile properties of the fibers it innervates. The assembly of the motor neuron and the fibers it innervates called motor unit. Figure **2-6** illustrates the distinct and overlapped neural subsystems responsible for the control of movements.

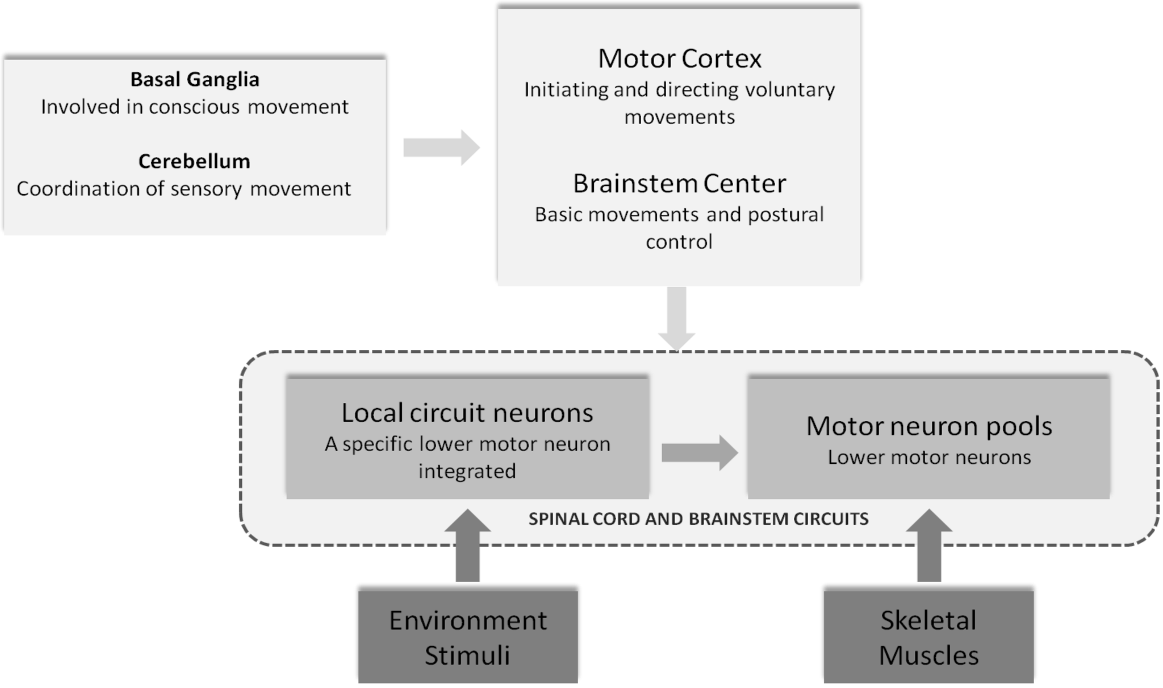



Figure 2-6. Interaction of neural structures involved in the control of the movement ([22] modified)

Local circuit neurons and the lower motor neurons constitute the first subsystems. The neurons of the lower motor neurons are located in the spinal cord and brainstem. They extend their axons out of the spinal cord and brainstem to innervate the muscle fiber of the body and head, respectively. Both reflexive and voluntary movements are eventually transmitted to the muscles by the activation of the lower motor neurons. Lower motor neurons for both head and body are controlled by the upper motor neurons. The neurons of the upper motor neurons are located in the brainstem or cerebral cortex and their axons pass down directly to the synapse of the local circuit neurons or lower motor neurons. Basal ganglia and cerebellum subsystems are complex circuits which are responsible for controlling and regulating the activity of the upper motor neurons.

Further information with more details about motor neurons types, the activity and responsibilities of the neural structures involved in the control of movement can be found in [21,22].

## 2.2 Human Gait

Locomotion is the process by which the human move from one point to another. It consists of basic events; starting, stopping, changing direction and speed. Human locomotion is either voluntary or automated motion, and it is controlled and regulated by feedforward and feedback [23]. Walking is considered as one of the most basic voluntary human movement. Its messages are initiated by the motor and premotor cortex and regulated by brainstem and cerebellum (section 2.1.1.1). This complex coordination between different human systems and body parts results into rhythmic gait.

The ability to stand and walk normally require multiple inputs from different systems, such as visual, vestibular, motor, sensory. Therefore, balance and gait require healthy brain, spinal cord and sensory system. Normal gait refers to the natural and general human walking parameters, whereas, pathological gait refers to abnormal gait affected by factors, such as age, pathology of skeletal muscle or neurological disease [24]. Understanding and analysis of gait has been considered to be an important aspect of assessment, diagnosis of walking disorder in neurological diseases, such as multiple sclerosis.

Gait is a cyclical movement that possesses very rhythmical and periodical events. These repeatable events are referred to as gait cycle. Figure2-7 illustrates the gait cycle with the main two events or phases. As shown in this figure the movement begins and ends with ground contact (heel strike) of the same foot, i.e. reference foot. Thus, a gait cycle consists of two main phases; stance phase and swing phase. During the stance phase the reference foot is on the ground, whereas it is off the ground in the swing phase.

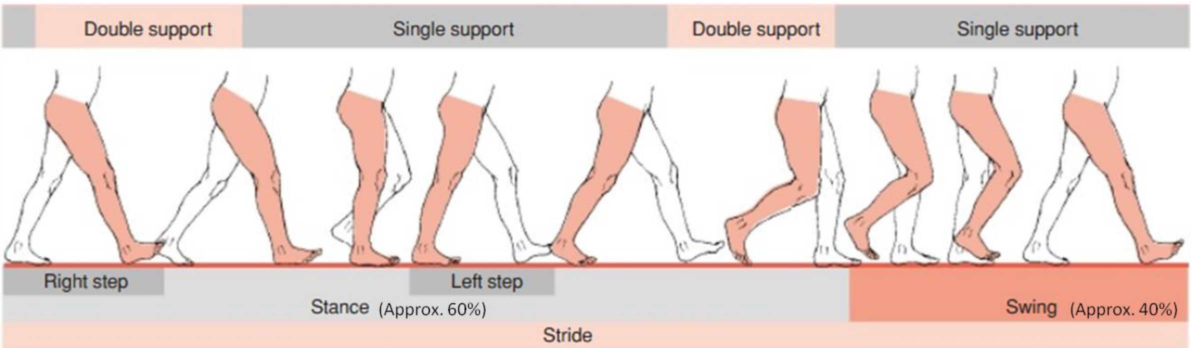



Figure2-7. Phases of the human gait [24]

The stance phase is responsible for stability and weight bearing, shock absorption. It makes up approximately 60% of the gait cycle and can be divided into sub phases or periods. It begins with the **initial contact**, which refers to the time instant when the foot touches the ground. The sub phase where the foot comes to full contact with the ground is referred to as **loading response**. The following sub phase called **mid stance**, it begins when the foot leaves the ground and ends with the trunk glides over the stance limb. Terminal stance or

**heel off** is the period in which the heel leaves the ground and the contra-lateral foot touches the ground. The pre-swing, also known as **toe off**, is the final period of the stance phase (from 50% to 60% of the gait cycle) and characterized by double support. The body's weight in this period the will be loaded to the opposite side. The swing phase can also be divided in three periods, namely initial swing, mid-swing and late swing. **Initial swing**, called also early swing forms the first third of the swing phase and starts when the foot leaves the ground. The maximum flexion of the knee defines the end of the early swing and represents the start of the **mid-swing** period. This period extends till approx. 85% of the gait cycle and terminates when the swing foot passes the opposite fixed foot. The third and ultimate period of the swing phase is the **late swing**. In this period the knee reaches its maximum extension preparing for ground contact.

Kinematics is the motion, independent from the forces, which describes the movement in term of placement, speed and acceleration. Examine and analysis of velocity and acceleration data may provide important and valuable information about gait pathology.

The repetition of the same event for the same foot referred to as stride. On contrary, a step is the movement of a single limb from heel strike of the first foot to the heel strike of the opposite one. A stride can be characterized by multiple temporal parameters stride time, stance and swing time, swing/stance ratio, double support and single support time. Walking speed is also considered as a temporal characteristic of the stride; it is a function of both cadence and step length. These parameters are defined in Table **2-2**. Gait impairments lead to alteration in the temporal parameters, such as decreased walking speed, cadence, decreased single limb support. Different studies showed that, apparently from normal variability, these parameters can be used to distinguish between normal and pathological gait [24]. Therefore, temporal parameters of gait are helpful in assessing and tracking a progress of patient's clinical and health status.

Table 2-2. Temporal parameters of stride

| Parameter | Description |
|---|---|
| Stride length | The distance between heel strike of one foot and the subsequence heel strike of the same foot |
| Step length | The distance between heel strike of one foot and the subsequence heel strike of the contra-lateral foot |
| Walking speed | Distance over time, usually reported in m/sec |
| Cadence | Steps per minute |
| Stance time | Time in seconds where the reference foot is on the ground |
| Swing time | Time in seconds where the reference foot is off the ground |
| Swing/stance ratio | Ratio between stance and swing time |

## 2.3 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic neurological illness which is considered to be the most common inflammatory demyelinating disease of the central nerves system (CNS). The disease typically affects adults between the ages of 20 and 40 with an onset peak age of 30 years [5]. Multiple sclerosis impacts approximately 2.5 million individual worldwide and about 400.000 individuals in Europe with rates go higher farther from equator and occurs in women more often than in men with a ratio of 3.2:1 [6].

MS is considered as an autoimmune disease, that is a condition in which the immune system attacking the individual's tissue. MS cannot be spread from person to person. As described in the previous section (section 2.1.1.1), the CNS consists of nerve cells known as neurons. These neurons are coated by a fatty membrane called myelin sheath, which covered the neurons of brain and spinal cord. This tissue protects the nerves and enables the conduction of the nerve electrical impulses that travel through the body. For unknown reason the immune system treats the myelin sheath as foreign substance and starts to react against it. Thus, MS occurs when the myelin sheath is destroyed. When myelin degrades, the conduction of electrical impulses through neurons is either impaired or lost. Figure **2-8** illustrates the difference between a healthy neuron and MS affected one.

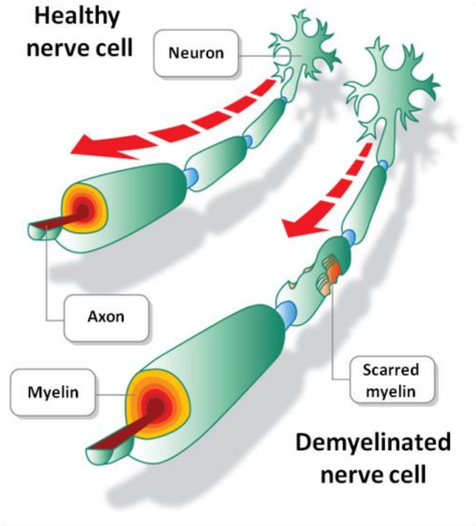



Figure 2-8. Healthy nerve and Multiple Sclerosis affected nerve [5]

### 2.3.1 Causes, diagnose and classification

Normally, the immune system protects the body against foreign substance except in autoimmune diseases such as MS, where the immune system starts to attack its own tissue. Scientists do not considered MS as an inherited disorder but still aren't certain about the causes of this phenomenon. However, one theory believes that a combination of genetic predisposition and environmental or vital factor, such as infections, diet, country of birth and residence, might increase the risk of developing MS. First of all, it is essential to understand that the disease course varies from one patient to another. Typically, patient experiences clinical onset of an acute and sub-acute neurological disturbances, which is known as *clinically isolated syndromes*. The diagnosis of MS is complex and needs to demonstrate dissemination of lesions over time and space and to exclude alternative diagnoses. There are different valuable investigations of MS; magnetic resonance imaging (MRI), evoked potentials and cerebrospinal fluid (CSF) examination [25]. However, the most recently diagnostic method called McDonald's Criteria is known with its high degree of sensitivity and specificity in early diagnosis of MS, thus allowing of better consulting and effective earlier treatment [26].

MS is generally described as a disease with several clinical types, namely four types, which their names describe the course of the disease and the way it acts on the body over time. However, a clear classification of MS is difficult to be made [5]. These four types are:

- **Relapsing-remitting MS (RRMS):** This is the most common type. Approximately 85-90% of patients are diagnosed with RRMS at onset. It is characterized by its relapses period in which symptoms worsen lasts for weeks or months. Relapses are followed by periods of remission.
- **Secondary-progressive MS (SPMS):** It is characterized by its steadily worsening of the disease symptoms. About 50% of the RRMS patients transition this type of the disease within a decade of the onset.
- **Primary-progressive MS (PPMS):** It is not a very common type. Approximately 10% of the patients of MS are diagnosed with PPMS. This type is characterized by its slow and steady worsening of the symptoms from the time of onset with no relapses or remission.
- **Progressive-relapsing MS (PRMS):** This type is relatively rare with about 5% of the MS cases. It is characterized by the steady progression from the initial time of the diagnosis with occasional relapses.

The types of the disease and their frequencies are displayed in Figure **2-9**.

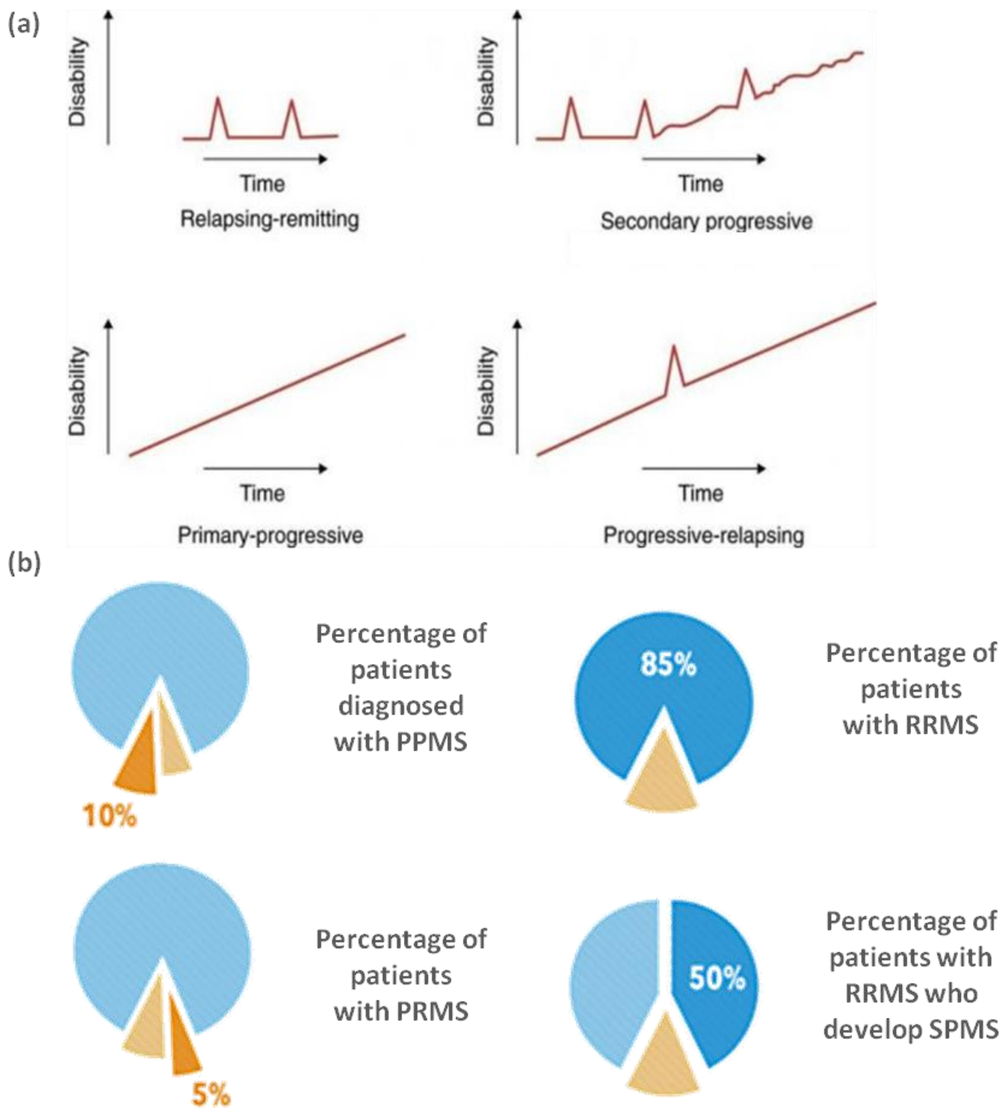



Figure 2-9. a) Different clinical types of the disease MS, b) Frequency of MS types [27]

### 2.3.2 Symptoms and assessment tools

MS has been characterized as an immune-mediated disorder that leads to multifocal demyelinating lesions in the white mater (WM) of the CNS [28]. Clinical symptoms of MS are highly variable and depend on the localization of lesions in the brain and spinal cord. Approximately 45% of patients diagnosed with MS don't have severe symptoms at onset. Given that, the affected places in brain and spinal cord vary from one patient to another; MS patients can experience different symptoms. However, there are common symptoms which are reported by most of the patients. Fatigue, walking and mobility, balance and coordination problems are considered as the most common symptoms with a rate of 80% of patients. Further common symptoms are pain (normally chronic pain) and cognitive dysfunction, where approximately 50% - 55% of MS patients report these symptoms. Problem in speaking and swallowing, hearing, seizures are the less common symptoms.

The traditional concept of MS as a white matter disease has been revised over the past years due to increasing evidence for grey matter lesions. In addition to intracortical lesions in PwMS, a predominant location of plaques was found in the frontal cortex including cortical motor regions. In particular, greater activation was found during motor tasks in the ipsilateral premotor and inferior frontal gyrus of patients with clinically isolated syndromes (CIS), which may be indicative of MS, compared to healthy controls. These changes also imply a previous impairment of the brain motor network of PwMS [28].

Recently, a number of instruments have been developed to measure the clinical severity and functional impairments. These instruments are used as clinical endpoint to assess the effectiveness of therapeutic interventions. The most commonly used disability endpoint is the so called Expended Disability Status Scale (EDSS) [29]. EDSS is developed by the neurologist, John Kurtzke, and considered as a gold standard for evaluating the degree of neurological deficit and disease progress. The EDSS quantifies neurological impairments of eight functional systems (FS): Pyramidal (ability to walk); Cerebellar (coordination); Brain stem (speech and swallowing); Sensory (touch and pain); Bowel and bladder function; Visual; Mental and other. In addition to the isolated syndrome in PwMS, an association of intracortical lesion load with clinical disability scores (EDSS) and the clinical course of MS has been found [28].

The EDSS is an ordinal scale that ranges from 0 to 10 in 0.5 unit increments (when reaching EDSS 1), where 0 described the normal neurological condition and 10 described the mortality due to MS. EDSS scores are summarized in Table **2-3**.

Table 2-3. Expanded Disability Status Scale EDSS

| Score | Description |
|---|---|
| 0 | Normal neurological exam |
| 1 | No disability, minimal sings in one FS* |
| 1.5 | No disability, minimal signs in more than one FS* |
| 2 | Minimal disability in one FS |
| 2.5 | Minimal disability in two FS |
| 3 | Moderate disability in one FS, or mild disability in three or four FS though fully ambulatory |
| 3.5 | Fully ambulatory but with moderate disability in one FS and one or two FS |
| 4 | Fully ambulatory without aid up to 12 hours a day despite relatively severe disability. Able to walk without aid or rest up to 500 meters. |
| 4.5 | Fully ambulatory without aid up to most of the day. However, may have some limitation or require minimal assistance. Able to walk without aid or rest up to 300 meters |
| 5 | Ambulatory without aid or rest for about 200 meters. The disability is severe enough to impair full daily activities |
| 5.5 | Ambulatory without aid for about 100 meters. The disability is severe enough to preclude full daily activities |
| 6 | Assistance (cane, crutch, brace) is required to walk about 100 meters with or without resting |
| 6.5 | Constant bilateral assistance is required to walk up to 20 meters without resting |
| 7 | Unable to walk beyond approximately 5 meters even with aid |
| 7.5 | Restricted to wheelchair. Unable to walk more than a few steps |
| 8 | Restricted to bed or chair but may be out of bed much of the day. However, perambulated wheelchair is required |
| 8.5 | Essentially restricted to bed much of the time, has some effective use of the arm |
| 9 | Helpless, restricted to bed, can communicate and eat |
| 9.5 | Totally helpless bed patient, unable to communicate or eat |
| 10 | Death due to MS |

Instruments that assess the neurological condition of the PwMS typically include items pertaining to motor activity. This also holds for EDSS, where walking ability constitutes the central aspect of this instrument. Despite being the most commonly used scale to assess disease severity, it has been criticized due to methodological problems in predicting the clinical outcomes [30]. The EDSS basically depends on the rates, therefore, it has high variability, i.e. two assessors seldom get the same score when assessing the same patient. It is subjective and does not reflect the walking ability in the customary environments, thus EDSS score can vary depending on the time of the assessment day resulting in poor reliability [31]. EDSS has also been criticized for its usage of an ordinal scale to evaluate symptoms. As a result of this ordinal non-linear scale, patients will progress faster from step one to five than from steps five to seven. Moreover, problems with applying the scale to a patient without ambulation problems as well as insensitivity to clinical change are also considered as weaknesses of the EDSS [32]. Finally, as EDSS assessed by a neurologist, it is cost effective instrument to be used in clinical and research settings.

### 2.3.3 Physical activity and gait impairment in multiple sclerosis

Physical activity has generally been acknowledged to be a health-promoting factor. It may occur in any behavioral setting and can be categorized on the basis of the type or purpose of the gross motor activities (e.g. in the context of occupational or leisure activities) [33]. Over the last decade, many evidences have been gained of the importance of physical activity as a method to improve quality of life. In this section physical activity and gait impairment in PwMS as well as their relation to other MS symptoms will be discussed.

Brain lesions and degenerative processes can elicit motor and gait impairment. Thus, physical activity and motor disorders are among the major problems of PwMS, as they may incur a loss of personal independence, and finally withdrawal from social life. Over the course of their disease, many patients experience a significant decline of mobility and daily life activity [9]. Gait parameters are the hallmark symptoms, and they are particularly reported by approximately up to 90% of PwMS [34]. Although, mobility and gait impairment are more common in patients with further disease level, they are also observed in the early stages of MS. Different studies reported decline in waling speed, distance and stride length in PwMS with mild disability (EDSS $\leq$ 2.5) compared with healthy control [35]. Studies lasted over long period of time (e.g. one year, 2.5 years) documented a significant reduction in physical activity and gait parameters [14,36]. Hence, approximately 50% of PwMS will require mobility aid within 15 years after onset [37]. However, regardless of disease duration or severity, the functions of lower limb were considered to be at high priority of 13 different bodily functions (Figure **2-10**)

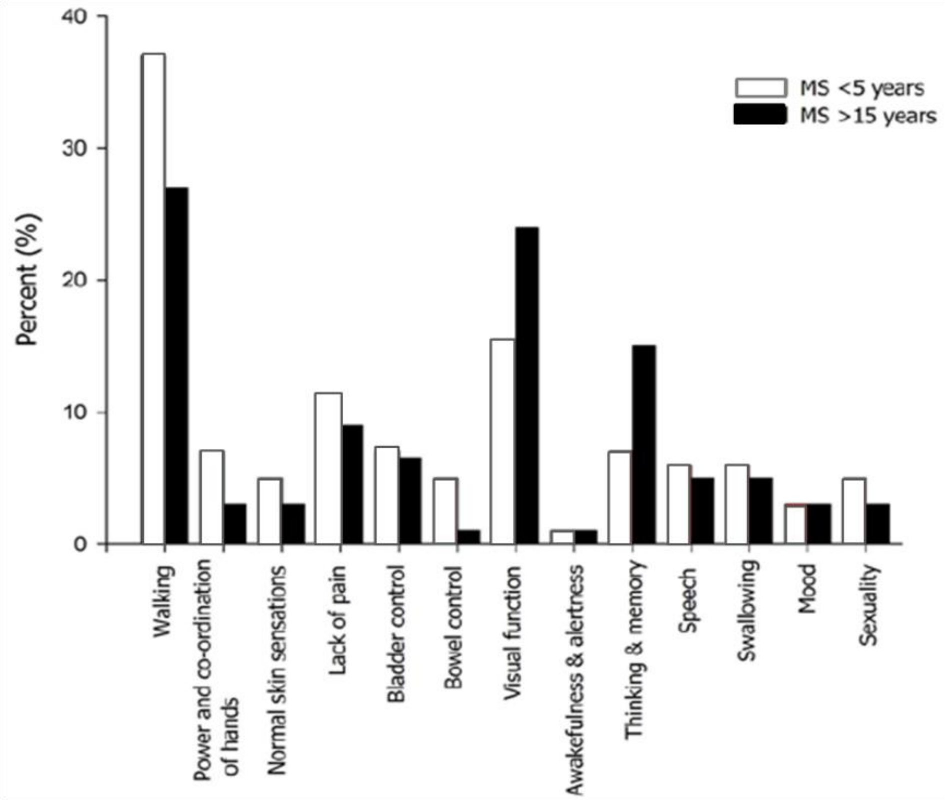



Figure 2-10. Rank of most important bodily functions in early and late MS [37]

Because MS is incurable disease, researchers and clinicians focused on treatments for symptoms management. Clinical symptoms or MS are highly variable and depend on the localization of lesions in the brain and spinal cord. Therefore, they are perceived indicators for the severity of the deficiency in different functional neurological system (e.g. muscle weakness, sensory and vision impairment, degree of instability). However, a significant correlation between the frequency or intensity of the overall symptom and the physical activity has been reported. The study of Molt et al. showed that the worsening of overall symptoms is associated directly or indirectly with lower physical activity [38]. For example, motor symptoms (e.g. arm weakness, balance, coordination impairment) are moderately and inversely associated with activities of daily living (ADL) of PwMS. Secondary analysis of data obtained from 686 PwMS reported that emotional symptoms have moderate and inverse correlation with ADL [39]. Other studies (cf. [12,40]) have also documented a correlation between symptoms of fatigue, depression and pain with physical activity. Moreover, Givon et al. reported significant correlations between different spatio-temporal gait parameter and the level of neurological impairment due to MS [41]. Therefore, researchers have started to consider physical activity and gait impairment as a behavioral correlate of disability progression in PwMS.

These observations highlight the importance of the assessment of the physical activity and walking ability in order to understand the relation between these measures and the symptoms and the progression of the disease. This could enable the early diagnosis of symptoms worsening and thus help with just-in-time treatment adjustment.

# 3 Sensor Technologies and signal analysis

This chapter gives an overview about sensor technology and signal analysis. First of all, basic theoretical knowledge of sensors, which are commonly used to capture physical activity and gait parameters, will be presented. In addition, the concepts of signal analysis methods used in this work will be described.

## 3.1 Microsystem Technologies

Microsystem technology (MST) is the technology used to fabricate microsystem. Microsystems deal with integrated microstructures and signal processing to generate the desire output. MST includes microelectronics, micromechanics and micro-optics components which are fabricated on the same substrate.

This leads to the term Micro-Electro-Mechanical Systems (MEMS), which was generally coined to refer to miniature sensors and actuators operating between electrical and mechanical domains. The first MEMS device appeared in the USA in 1980's. However, the development of MEMS technology was relatively slow due to the complexity of the manufacturing process. Figure 3-1 illustrates some fundamental techniques required to develop MEMS device [42]. Physical dimensions of MEMS devices can range from below one micron to sever millimeters. As well as, the types of MEMS devices can vary from relatively simple structures to extremely complex systems. Some advantages of MEMS are; small size, light weight, on-chip integration of electromechanical systems and their controlling electronic circuitry, high functionality, lower power consumption to name some. These allowed applications to be developed which would otherwise be impossible.

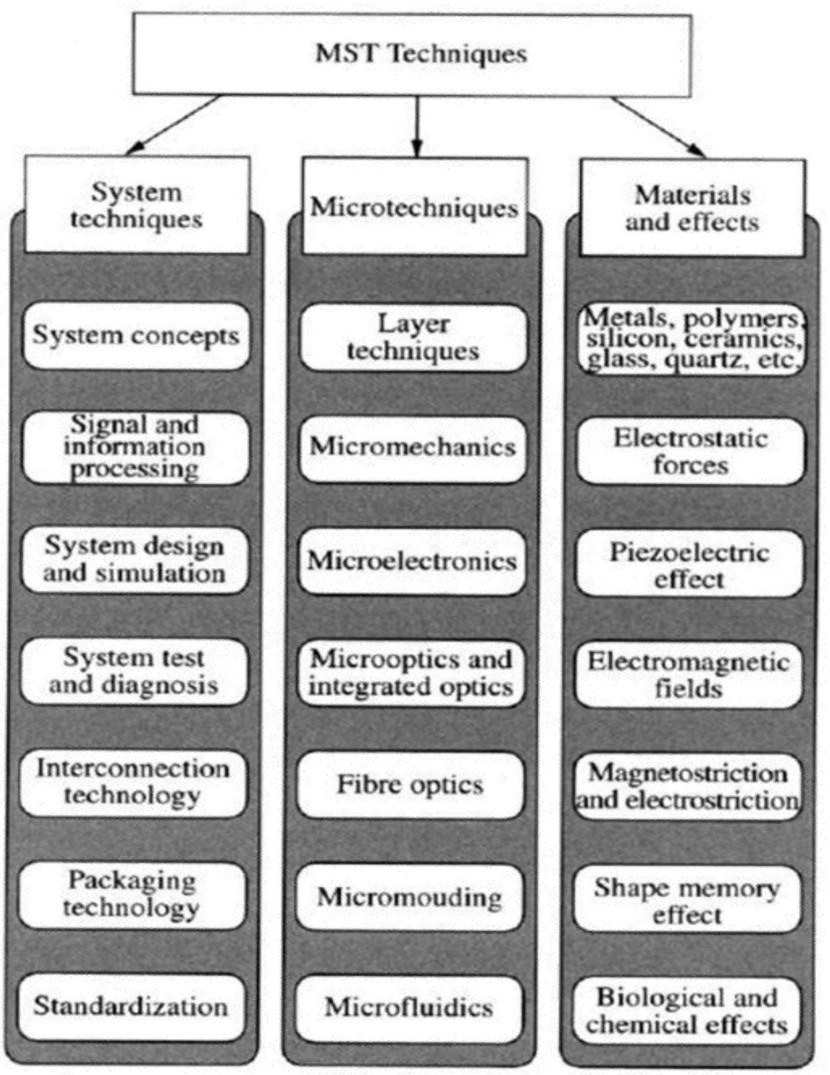



Figure 3-1. Some of the many fundamental techniques required to develop MEMS [42]

### 3.1.1 Applications

There are plenty of applications for MEMS, essentially, where miniaturization is beneficial. The concepts and feasibility of more complex MEMS devices offered a comprehensive penetration in various fields of application such as; microfluidics, aerospace, biomedical, chemical, physical, data storage, wireless communications, etc.[43]. Figure 3-2 illustrates the different functional domains of MEMS applications.

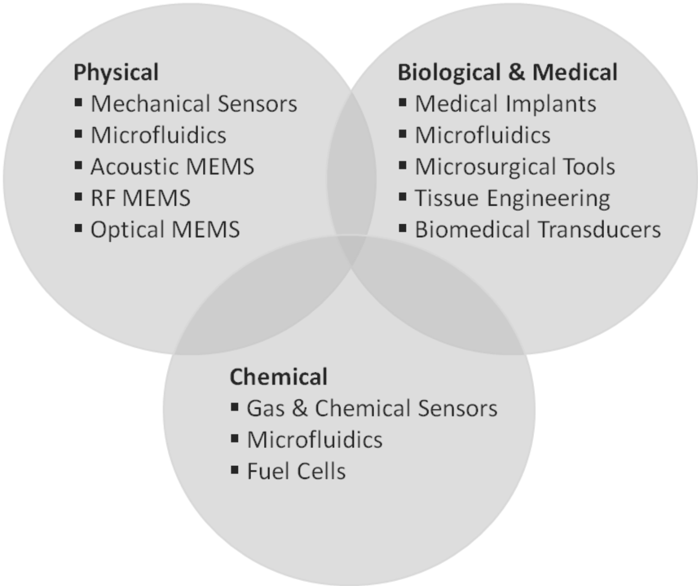



Figure 3-2. Various application domains of MEMS ([43] modified)

Basically, sensors are a major application of MEMS technology in different fields; such as industry (airbag systems, medical blood pressure sensor). The combination between MEMS sensors and other sensors can be implemented in the field of multi-sensing applications. There are three primary types of MEMS sensor; pressure sensors, chemical sensors and inertial sensors (accelerometers, gyroscopes).

## 3.2 Sensor

As definition, sensor is a device that receives and responds to signal stimulus. Generally, they are energy converter which transfers the input signal (stimulus) into an electrical signal. Therefore, the term “sensor” should be distinguished from “transducer”. The former converts the energy from a certain type into an electrical energy, whereas the latter converts any type of energy into another. A sensor is always a part of a larger system (data acquisition system) that may incorporate other detectors, signal conditioners, signal processors, memory devices, data recorders and actuator [44]. Transducer may be part of a complex sensor Figure 3-3. As shown in this figure, the last part of a complex sensor is a direct sensor that produces electrical output. Thus, there are two types of sensors; direct and complex. A direct sensor uses a certain physical effect to directly convert a stimulus into an electrical signal, whereas a complex sensor Figure 3-3 in addition needs one or more transducers of energy before a direct sensor can be employed to generate an electrical output.

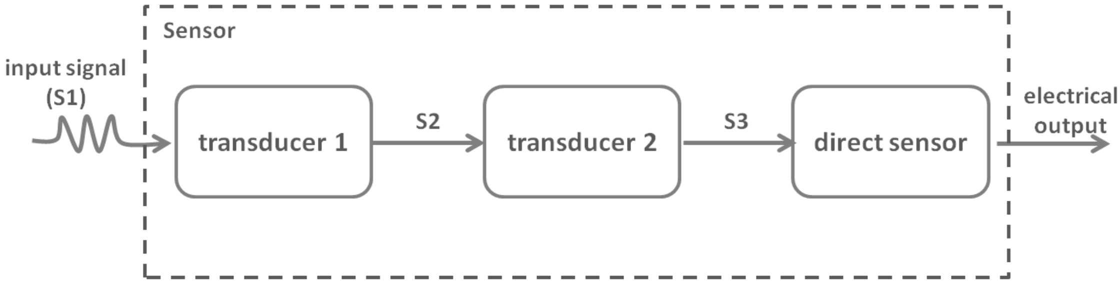



Figure 3-3. Transducer as a part of complex sensor ([44] modified)

Depending on the classification purpose, the sensor classification schemes could range from very simple to complex. Generally, all sensors can be categorized under two categories, either passive or active. Passive sensor can directly generate an electrical output with no need for any additional energy source, e.g. photodiode, piezoelectric sensor. On contrary, the active sensors need external power for their operation, e.g. thermistor, which does not generate electrical signal, but its resistance can be measured by detecting the variations in the output current and/or voltage.

Furthermore, based on the selected criteria, sensors can be classified into absolute and relative. Absolute sensors measure stimulus with respect to their absolute scales, whereas relative sensors generate a signal that relates to a known baseline. Considering their properties, such as sensitivity, accuracy, detection means, material and field of application, sensors can also be further classified into multiple categories.

### 3.2.1 Acceleration Sensor

Accelerometers are one of the most commonly used and commercially successful MEMS sensors. In general, accelerometers are used to measure dynamic force subjected to a moving object, where the former is related to the velocity and the acceleration of the object. They are widely demanded due to their applications in automotive industry, where the acceleration sensors are used in safety systems such as airbags activation. However, due to the small size and low cost of the accelerometers, their applications cover broader spectrum. For example, mobile electronics, hardware protection, biomedical applications, to name a few.

Figure 3-4 illustrates the principle operation of an acceleration sensor. The simplest form of an accelerometer consists of a proof mass suspended by springs attached to fixed frame. The principle operation behind the accelerometer is the Newton’s second law of motion which defined the acceleration by relating it to the mass and force ($F = a \,.\, m$). In other words, a net force ($F$) subjected on an object of mass ($m$) causes the latter to accelerate along its sensitive axis. This acceleration ($a$) is directly proportional to the magnitude of the force and inversely proportional to the mass ($m$) of the object [45].

$$\mathrm{F = a \,.\, m = m \,.\, f + m \,.\, g} \qquad \text{Eq.3-1}$$

As a result of an external acceleration, the support frame will be displaced relatively to the proof mass, which in turn changes the internal stress of the suspension spring. Based on the relative displacement the extension can be used to measure the external acceleration. The accelerometer is insensitive to the gravitational acceleration ($g$) and thus provides an output proportional to the non-gravitational force per unit mass ($f$) to which the sensor s subjected along its sensitive axis.

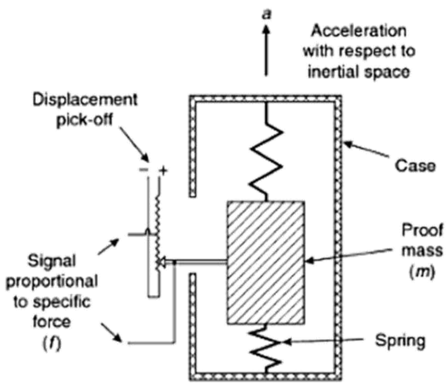



Figure 3-4. A simple acceleration [45]

The total force $F$ is described by the gravitational force and other external forces which cause the mass $m$ to accelerate. Considering the case where an accelerometer falls freely within a gravitational field, the output remains at zero. This because, in the “falling-freely” situation, the accelerometer will fall with acceleration equal to the gravity field ($a = g$), and hence according to the equation above the $f$ will be zero ($f = 0$). Conversely, in the situation where the accelerometer is held stationary ($a = 0$) the accelerometer will measure the force acting to stop it from falling. Following from (Eq.3-1), this force ( $m \,.\, f = -m \,.\, g$) is the specific force required to offset the effect of gravitational attraction. Therefore, having the knowledge about the gravitational field enables the measure of the accelerometer output. Commonly the earth’s gravitational pull is the reference value from which all other accelerations are measured. It is known as $g$ and is approx. equal to 9.8m/s$^2$. MEMS accelerometers are described in more detailed in [45].

Typically, accelerometers are specified by their sensitivity, output range, Dynamic range, Amplitude stability, frequency response, resolution, full-scale nonlinearity, offset, number of axes shock survival and bandwidth [45]. Therefore, the definition of the required specifications is application depended. Furthermore, acceleration sensors are divided in different types according to the way the displacement of the proof mass is sensed. Examples of the device types are capacitive, piezoelectric, piezoresistive, optic, electromagnetic. In the following sections the most common types will be presented.

#### *3.2.1.1 Capacitive*

Capacitive accelerometers measure a change in capacitance across a bridge circuit. They essentially contain at least two components, the first is the fixed plate and the other is a plate attached to the proof mass (Figure 3-5). These plates form a capacitor whose value is a function of a distance $d$ between the plates. Hence, changing the distance between the plates will change the capacity of the system, which can be measured as a voltage output. When an external acceleration is applied the proof mass moves away from or toward a plate, hence the capacitive will decrease or increase, respectively. The change in capacitance is given by the following equation [44]:

$$\Delta C = \varepsilon A\left(\frac{1}{d_0 - x} - \frac{1}{d_0 + x}\right) \xrightarrow{x^2 \ll {d_0}^2} 2\varepsilon A \frac{x}{{d_0}^2} \qquad \text{Eq.3-2}$$

Where; $A$ is the area of the plate and $d_0$is the nominal gap between the plate and the proof mass.

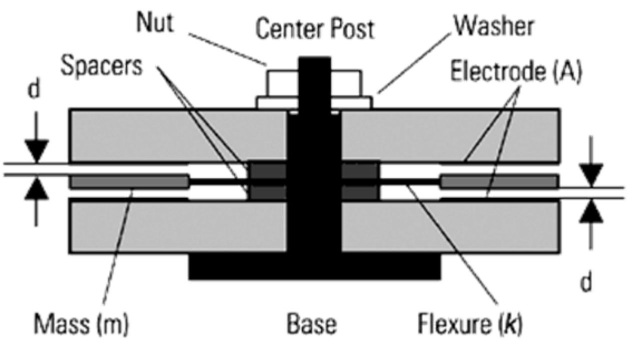



Figure 3-5. Capacitive acceleration sensor [46]

Capacitive accelerometers have several advantages; high sensitivity, high precision, low cost, good noise performance, less prone to variation with temperature, less power dissipation and simple structure. Therefore, they have been applied in a wide range of applications such as; automotive (crash detection and stability control), biomedical (activity monitoring), consumer electronics (portable computers, cellular phones), robotics (control and stability), structural health monitoring and military application.

#### *3.2.1.2 Piezoresistive*

Piezoresistive accelerometers (also known as Strain gauge accelerometers) are one of the first commercialized microaccelerometer (Figure 3-6). These sensors include piezoresistive material that changes its resistance when mechanical stress is applied. These devices can sense accelerations within a broad frequency range (from near DC up to 13 kHz) and can withstand overshock up to 10.000 g, therefore, they are preferred in high shock applications.

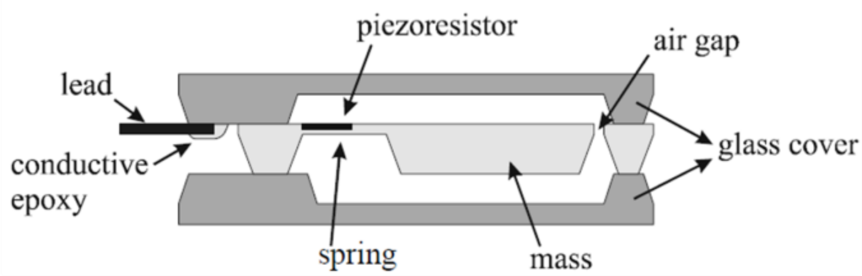



Figure 3-6. Piezoresistors accelerometer [46]

Piezoresistive accelerometer based on piezoresistive effect, which describes the changing in electrical resistive of a semiconductor due to mechanical strain. Hence, when a force is applied to the proof mass, the latter will be displaced and causes stress in the piezoresistive material. This strain extracted from the proof mass change the resistance of this material. Therefore, the strain can be directly correlated with the magnitude and rate of the mass displacement and, subsequently, with an acceleration.

The main advantage of piezoresistive accelerometers is the simplicity of their structure and fabrication process, as well as their readout circuitry, since the resistive bridge generates a low output-impedance voltage. However, they exhibit larger temperature sensitivity, thus an additional temperature compensation circuitry is required. Moreover, they have smaller overall sensitivity compared to capacitive devices, and hence a larger proof mass is preferred for them.

### 3.2.2 Gyroscope

Gyroscopes are devices able to measure the angular rotation rate of a body with respect to the reference frame (gyroscope frame). They consist, generally, of a mass with a free axis or rotation supported by a gimbal, and the latter is supported by a gyroscope frame Figure 3-7. The main concept of the operation is based on the basic principle of the angular momentum conservation. Extensive information can be found in [44].

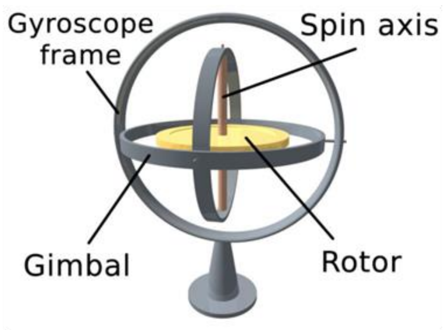



Figure 3-7. A Gyroscope [47]

MEMS gyroscope are gyroscopes miniaturized and packaged with electrical transducers. There are three types of MEMS gyroscopes: rotational, optical and vibrating. Rotational microgyroscopes are similar in design to the traditional gyroscopes. A high-speed rotational component is involved in the design; thus this type is costly in fabrication. Optical gyroscopes are the most accurate type; however, because of the size and the cost of the manufacturing, they are not widely used in industrial applications. The most commonly used type is the vibration microgyroscopes (Figure 3-8 a), which based on the transfer of energy between two vibration modes caused by Coriolis acceleration (Coriolis Effect). Inducing a vibration on the solid mass causes the mass to proceed along its reference axis ($x$) with a velocity ($v$). This, in turn, induces and angular rotation of the mass ($\Omega$) along a direction perpendicular to the velocity's plane, which produces Coriolis acceleration $a_c$ (Figure 3-8 b). This acceleration can be expressed by:

$$a_c = 2v \times \Omega \qquad \text{Eq.3-3}$$

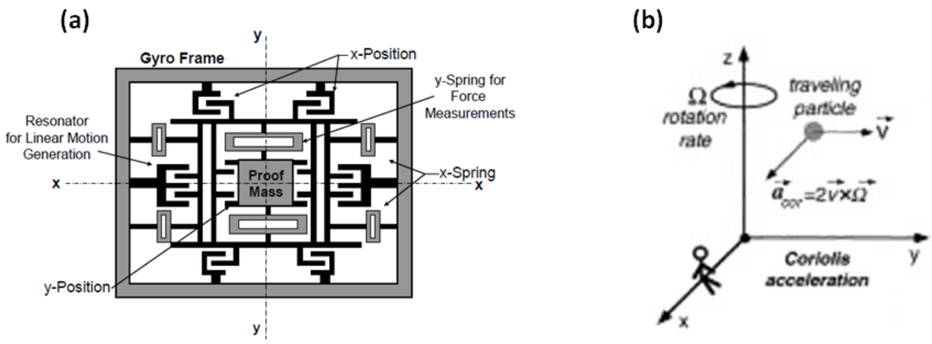



Figure 3-8. Vibration Microgyroscopes (a) [48], Coriolis Effect (b) [49]

Recently, these devices have gained a lot of attention for several applications. For example, using MEMS gyroscopes have been used in companion with MEMS accelerometers to detect heading information for inertial navigation purposes. Furthermore, they are widely used in airplanes, spacecrafts, automobiles consumer electronics (e.g. video-camera stabilization, inertial computer mouse), robotics applications, and wide spectrum of military applications.

### 3.2.3 Pressure Sensor

By definition, the pressure is a force exerted on a surface per unit area. The SI unit of pressure is the pascal ($Pa$): ($1Pa = 1\frac{N}{m^2}$). That is, one pascal is equal to one Newton per meter squared. Pressure sensor is a device that is capable of generating signal related to the pressure. They are complex sensors, that is more than one step of energy conversion is required till an electrical signal is generated. Different measures can be acquired from the pressure, such as speed and altitude.

Two essential elements are required to make a pressure sensor; the membrane (plate) with a known area $A$ and a detector that responds to the applied stress $F$, thus ($p = \frac{dF}{dA}$). Therefore, in most cases the pressure sensors contain deformable elements whose deformations are measured and converted by the displacement into electrical signals related to the pressure value. In pressure sensors, this deformable or sensing element is a mechanical device that undergoes structural changes under strain resulting from applied stress. Generally, the main problems in pressure sensors are in the system packaging and protection of the diaphragm from the contacting pressurized media, which are often corrosive, erosive and at high temperatures.

Pressure sensor can be categorized in different classes depending on the type of pressure the device measures [44] (Figure 3-9):

1. Absolute pressure: These sensors measure the pressure relative to the perfect vacuum pressure. Measurement assessed in absolute pressure use the absolute zero as their reference point. The vacuum has to be negligible compared to the pressure to be measured. Such sensors are used to gas analysis, altimeters, engine air intake performance, to name few.
2. Gauge pressure: This pressure is measured relative to the ambient atmospheric pressure. Thus, the output of the gauge pressure is directly influenced by the changes in weather conditions or altitude. Positive pressure is referred to the pressure higher than the ambient pressure, whereas negative pressure is referred to the pressure lower than the atmospheric pressure. Typical example of the usage of gauge pressure sensor is the measure of tire pressure. These sensors are also used for surgery of emergency applications.
3. Differential pressure: This kind of sensors has two pressure ports, that is, they measure the difference between two pressures applied to the sensing unit.

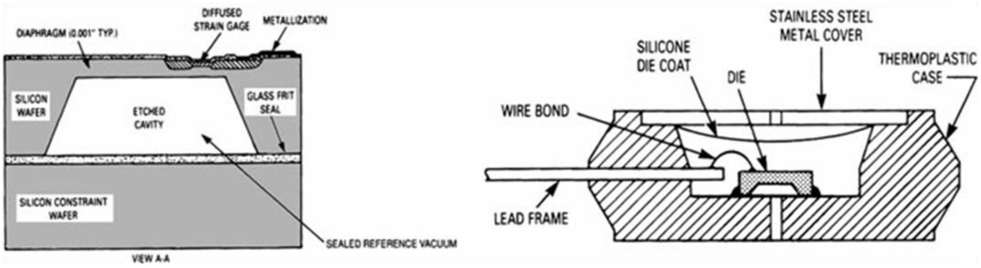



Figure 3-9. Absolute (right) and differential (left) pressure sensor [44]

### 3.2.3.1 MEMS Pressure sensors

MEMS pressure sensors are among the first MEMS devices developed and produced for real world applications. The sensing element in these sensors is made of thin silicon diaphragm with a size that varies from few micrometers to a few millimeters square. MEMS pressure sensor used the principle of mechanical bending of thin silicon diaphragm by the contact medium (liquid or gas) [48]. There are two common types of MEMS pressure sensors that will be presented in this section: piezoresistive and capacitive pressure sensors.

### 3.2.3.1.1 Piezoresistive Pressure Sensor

At the moment, piezoresistive pressure sensors are still the most commonly used. They consist of thin silicon diaphragm and a tiny piezoresistors diffused into the diaphragm (Figure 3-10). Usually, the resistor is connected to the Wheatstone bridge [48].

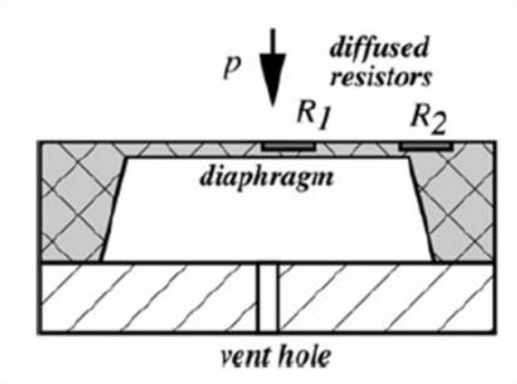



Figure 3-10. Piezoresistors in the silicon diaphragm [44]

When stress applied to a resistor, the latter changes its resistance due to the piezoresistive effect. This change in the resistivity is proportional to the applied stress and thus to the applied pressure. The maximum output of such devices is on the order of several hundred millivolts. Therefore, a conditioner is required in order to have the output in an acceptable format. However, piezoresistive sensors have high temperature sensitivity, thus the conditioner should not include temperature compensations. Further disadvantage of this type of sensors is the low sensitivity of the piezoresistors; therefore, they are not suitable to be used in low pressure measurement application. However, piezoresistive pressure sensors have small size, are simple to be fabricated and have a high linearity between the applied pressure and the output voltage [48].

### 3.2.3.1.2 Capacitive Pressure Sensor

The other way of converting pressure into electrical output is to use the capacitance change measuring principle (Figure 3-11).

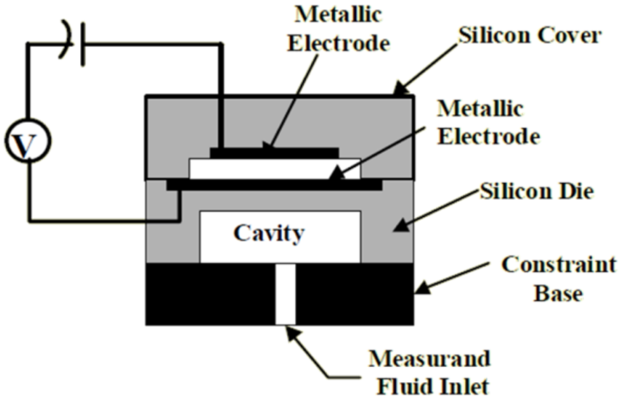



Figure 3-11. Capacitive pressure sensor [48]

In the capacitive-pressure sensor the diaphragm displacement changes the capacitance with respect to the reference plate. This kind of measure is especially suitable for the low-pressure sensors. The diaphragm can be designed to obtain up to 30% capacitance change. Furthermore, these sensors have low power consumption and low temperature sensitivity, which makes them candidates for elevate temperature application. However, they suffer from the non-linearity relation between the input pressure and the measured output.

## 3.3 Signal Processing and Analysis

The following section gives an overview about the basic concepts of the signal processing, classification and statistical analysis methods used in this work.

### 3.3.1 Time, Frequency and Time-Frequency Domain Signal Processing

A signal is a function of an independent variable such as time, distance, position, etc. The signal can be classified into: continuous-time, discrete-time; analog, digital; periodic, aperiodic; causal, anticausal, noncausal; deterministic, random; finite, infinite length signal [50].

The primarily goal of signal processing is to extract features out of the signal, which can be provide underlying information on a specific problem for decision making. Signal processing can be done either in time, frequency or time-frequency domain.

#### *3.3.1.1 Time Domain Representation*

Time domain analysis is the investigation of the physical phenomenon or signal in respect to time, i.e. to record of what happened to the system parameters versus time.

In the time domain, a signal is represented as sequences of numbers, called samples, which denoted as $x[n]$ with $n$ being an integer in the range $-\infty \leq n \leq \infty$. Discrete-time signal is represented by $\{x[n]\}$. This sequence may be also generated by periodically sampling continuous-time signal $x_a(t)$ at uniform intervals of time. The $n$-th sample is given by:

$$x[n] = x_a(t)|_{t=nT} = x_a(nT), n = \cdots, -2, -1, 0, 1, \ldots \qquad \text{Eq.3-4}$$

Where, $T$ is the sampling interval or sampling period.

#### *3.3.1.2 Frequency Domain Representation*

Signals are often represented in frequency domain by their spectrum, frequency, amplitude and phase. Frequency domain representation can be effectively used in measurement of signal parameters, signal transmission, system design, etc.

The most important principle in the frequency domain analysis is the transformation, which is the conversion of the function from time domain to frequency domain and vice versa. Fourier transform allows the characterization of systems in a simple algebraic form instead of differential equations connected to time domain representation.

#### 3.3.1.2.1 Fourier series and Fourier transform

A periodic signal can be decomposed into linear combination of sine and cosine functions. This series is referred to as Fourier series of signals, and it has the following form:

$$u(t) = U_0 + \sum_{k-1}^{\infty} (U_k^A \cos k\omega t + U_k^B \sin k\omega t) \qquad \text{Eq. 3-5}$$

where $\omega = \frac{2\pi}{T}$ ($T$ stands for the period). The coefficients can be calculated using the following equations:

$$U_0 = \frac{1}{T}\int_0^T u(t)dt, U_k^A = \frac{2}{T}\int_0^T u(t)\cos(k\omega t)dt, U_k^B = \frac{2}{T}\int_0^T u(t)\sin(k\omega t)dt \qquad \text{Eq. 3-6}$$

These operations are based on the orthogonality of trigonometric functions on the interval $[0\ldots T]$.

Fourier transform is the extension of Fourier series to periodic and nonperiodic signals. The spectrum of the signal $x(t)$ is defined as:

$$X(j\omega) = \int_{-\infty}^{+\infty} x(t)\, e^{-j\omega t} dt \qquad \text{Eq. 3-7}$$

The signal can be reconstructed from the spectrum $X(j\omega)$ as follows:

$$x(t) = \frac{1}{2\pi}\int_{-\infty}^{+\infty} X(j\omega)\, e^{j\omega t} d\omega \qquad \text{Eq. 3-8}$$

More details about frequency domain representation and Fourier transformation can be found in [50].

### *3.3.1.3 Time-Frequency Domain Representation*

Many signals and systems are generally described by their frequency components, which have infinite duration and change as a function of time. For these certain case of signal, time-frequency analysis is of great interest. That is, because it offers simultaneous interpretation of the signal in both time and frequency domain. The time-frequency representations (TFR) can be classified according to the analysis method. In the first category, the signal is represented by time-frequency function derived a basis function having a definite time and frequency localization. For a signal x(t), the TFR is given by:

$$TF_x(t,\omega) = \int_{-\infty}^{+\infty} x(\tau)\,\phi_{t,\omega}^{*}(\tau)d\tau = \left(x, \phi_{t,\omega}\right) \qquad \text{Eq. 3-9}$$

where $\phi_{t,\omega}$ represents the basis functions and $(*)$ represents the complex conjugate. Short time Fourier transformation, wavelets and matching pursuit algorithms are typical examples in this category.

The second category of TFR based on the time-frequency distributions idea presented in [51], in which the TFR described by a kernel function as follow:

$$TF_x(t,\omega) = \frac{1}{4\pi^2}\int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty} x\left(u+\frac{1}{2}\tau\right)x^{*}\left(u - \frac{1}{2}\tau\right)\phi(\theta,\tau)e^{-j\theta t - j\tau\omega + j\theta u}du\,d\tau\,d\theta \qquad \text{Eq. 3-10}$$

where $\phi(\theta,\tau)$ is the two dimensional kernel function, determining the specific representation in this category, and hence the properties of the representation.

Nowadays, different time-frequency approaches are available for high-resolution decomposition in time-frequency plane, including Short-Time Fourier transformation (STFT), Wigner-Ville transformation, Choi-Williams distribution (CWD), and the continuous wavelet transformation (CWT). In the following section, the most favored tool will be presented, namely CWT.

##### 3.3.1.3.1 Wavelet Transform- Continuous Wavelet Transformation

Within the last two decades, the wavelet transform (WT) has become widely considered as an alternative to the Short-Time Fourier transformation (STFT). The main principle of the CWT based on the convolution of the signal with a set of functions, which are a translated and dilated version of a main function. The main function is a continuous function in time and frequency domain and called mother function, whereas the translated and dilated functions are called wavelet. Mathematically, the CWT of the signal $x(t)$ is given as follow:

$$W(a,b) = \frac{1}{\sqrt{a}}\int x(t)\bar{\psi}\left(\frac{\mathrm{t-b}}{\mathrm{a}}\right)\mathrm{dt} \qquad \text{Eq. 3-11}$$

Where, $b, a$ are the location and the dilation parameter, respectively. $\psi(\mathrm{t})$ is the mother function. On contrary to STFT, CWT allows high localization in time of high frequency signal features. Furthermore, CWT is not limited to using sinusoidal function.

Wavelet transformation is commonly used in image compression application, acoustics processing, pattern recognition, filter design, electrocardiogram analysis. Furthermore, due to its ability of capturing sudden changes in signals like the one measured by an accelerometer, wavelet transformation technique has been often applied in activity recognition and gait analysis methods [52].

### 3.3.2 Statistical Tools for Data Analysis

#### 3.3.2.1 Reliability and Intraclass Correlation

**Reliability:** is the degree to which an assessment tool produces stable and consistent results. There are two types of reliability: relative reliability and absolute reliability. Relative reliability indicates the consistency of an individual's rank position in respect to the other over repeated measurements. Absolute reliability indicates the degree of which repeated measurement vary for the individual, i.e. the absolute difference in the group's mean over identically repeated measurement (e.g. stability) [53]. The reliability is formally given by:

$$reliability = \frac{between\ subjects\ variability}{between\ subjects\ variability + error} \qquad \text{Eq. 3-12}$$

Reliability is usually calculated to assess: the reliability of the measurement device, the reliability of the observer and the stability of the variable being measured.

**Intraclass correlation (ICC):** is a relative measurement of reliability, which has become common choice in reliability studies [54]. ICC is an attempt to overcome some of the limitations of the classic correlation coefficients. Similarly, to other reliability indices, ICC does not have standard acceptable level of reliability. Theoretically, it can vary between 0 and 1.0, where 0 indicates no reliability and 1.0 indicates perfect reliability. As it can be seen in the (Eq. 3-12), if the variability between subjects is sufficiently high, the reliability will obviously be high. Thus, if individuals differ from each other a lot, the ICC magnitude can be large, and if they differ little from each other the value will be small. There are plentiful versions of the ICC with each being suitable for specific situation.

#### 3.3.2.2 Standard Error of Measurement and Minimal Detectable Change

**Standard error of measurement (SEM):** is defined as "the standard deviation of errors of measurement that is associated with the test scores for a specified group of test takers" [55]. If any test were to be applied to individual numerous numbers of times, it would be expected that the responses would vary a little from trial to trial. Therefore, the standard deviation of measurement errors indicates how reliable the measurement test is. Unlike, ICC which is a relative measure of reliability, SEM indicates the absolute reliability and is expressed in the actual units of the measurement, making it easy to be interpreted. SEM can be calculated by multiplying the baseline standard deviation of the values of the measurement response by the square root of one minus the ICC:

$$SEM = SD_{baseline} * \sqrt{1 - ICC} \quad \text{Eq. 3-13}$$

Since that SEM is measure of the precision of an instrument, it is related to the concept of minimal detectable change.

**Minimal detectable change (MDC):** is the smallest alteration in a given measure that indicates a true change. In other words, MDC provides the absolute amount of change necessary to exceed the measurement error of repeated measures at a certain confidence interval (CI). It is a useful tool to operationally determine whether a magnitude of change in the parameter of interest is greater than the amount of change attributable to measurement error [56]. Minimal detectable change can be calculated using the following formula:

$$MDC = SEM * z * \sqrt{2} \quad \text{Eq. 3-14}$$

where $(z = 1.64)$ or $(z = 1.96)$ reflects the 90% or 95% confidence interval (CI), respectively.

### 3.3.3 Classification and Regression Model

This section presents the methods and techniques used in this work for the aim of regression model development and classification.

#### *3.3.3.1 Decision Tree*

Decision tree is a learning algorithm that is widely used in solving classifications problems [57]. Decision trees have increasingly become important classification techniques due to their simplicity and computational efficiency. Their simple structure provides an easily understanding and interpretation of the information, thus easy to be translated into rules. However, the complexity of the tree increases with the amount of data. A decision tree partitions the feature space into a set of disjoint regions and assigns a specific value to each corresponding region. A general graphical representation of a decision tree is shown in **Fehler! Verweisquelle konnte nicht gefunden werden.**.

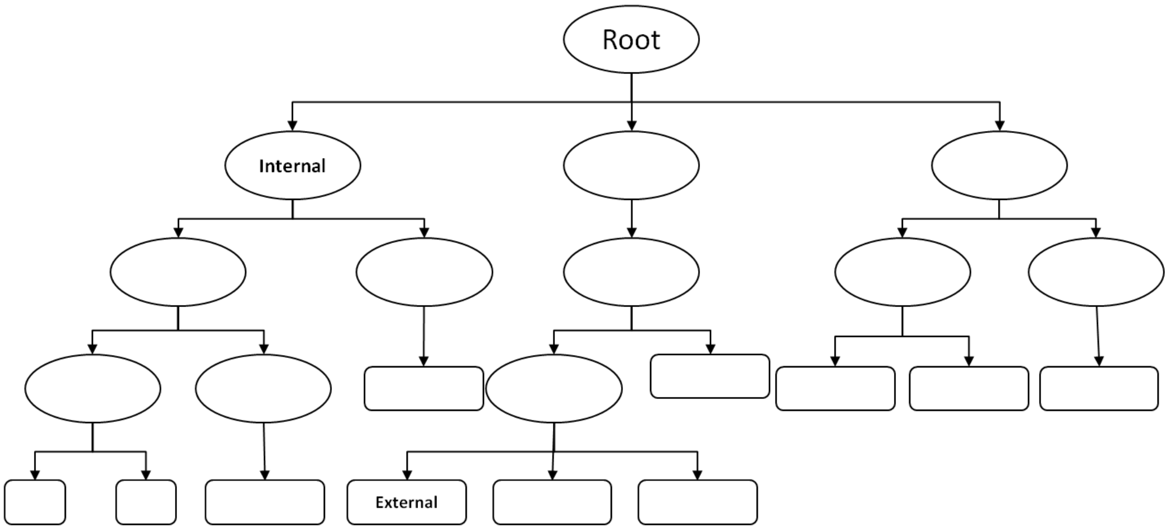



Figure 3-12. General graphical representation of a decision tree

A decision tree consists of nodes connected by branches. There are three types of node:

**Root node:** The first node in the tree that contains all the data. It has no incoming branches and many outgoing branches.

**Internal node:** also called "test node". Each internal node tests an attribute.

**External node/leaf node**: also called "decision node". These nodes present the results of the classification. It has one incoming branch and no outgoing branch.

The basic concept of the decision tree is to partition the input data set (feature space) into smaller segment called terminal nodes. Each terminal node is assigned to a class label. The partitioning process terminates when the resulted subsets cannot be partitioned any further.

The decision tree is called binary tree when each internal node can be partitioned into exact two child node only, such as classification and regression tree (CART). If the internal node can have two or more child node, then the decision tree is called multi-child tree, such as iterative dichotomier 3 (ID3). The CART decision tree is the methods was used in this work and will be briefly presented in the following section.

#### 3.3.3.1.1 Classification and regression tree (CART)

The CART decision tree (Figure 3-13) is a binary recursive partitioning procedure capable of processing and continuous and nominal attributes as predictors [58]. The basic idea of tree building is to choose the split criteria among all possible split criteria at a certain node. In CART algorithm the split criteria depend on the value of only one predictor variable (or feature).

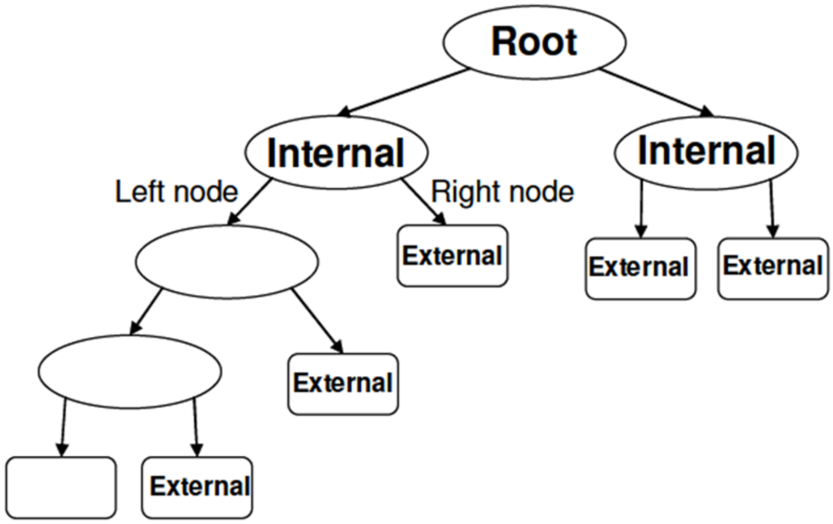



Figure 3-13. Binary decision tree (CART)

The algorithm builds the tree starting from the root node repeatedly using the following step:

1. Find the best split point for each feature that maximizes the splitting criteria when the node is split according to it. The definition of the splitting criteria will be explained later.

2. Find the node's best split. Among the best split points found in the previous step, choose the one that maximizes the splitting criteria.

3. Split the node using its best split found in the step 2 if the stopping rules are not satisfied, restart at step 1.

**Splitting criteria and impurity measurement:**

*Impurity:* Let $i(N)$ denote the impurity of the node then:

$i(N)$ is 0 if the data at this node all belong to the same class.

$i(N)$ is maximum if the classes are equally represented.

There are many different mathematical measures of the node's impurity:

- Entropy: it is calculated as following:

$$i(N) = \sum_j p(C_j) log_2\, p(C_j) \qquad \text{Eq. 3-15}$$

where $p(C_j)$ is the fraction of the data set at node $N$ that belong to the $C_j$

- GINI diversity index: it s given by:

$$i(N) = 1 - \sum_j \left[P(c_j|node)\right]^2 \qquad \text{Eq. 3-16}$$

where $P(c_j|node)$ presents the frequency of the class $j$ in the current node $N$.

<u>*Splitting criteria:*</u> at a certain node $N$ the splitting criteria $\Delta i(s, N)$ corresponds to the decrease in impurity and is given by:

$$\Delta i(s, N) = i(N) - p_L i(N_L) - p_R i(N_R) \qquad \text{Eq. 3-17}$$

Where $s$ is the split condition; $i(N_L)$ and $i(N_R)$ are the impurities of the left and the right child nodes; and $p_L$, $p_R$ are the percentages of the cases in the node $N$ that branch left and right, respectively.

CART decision tree uses GINI diversity index as split criteria. To choose the best split s condition the following calculation takes place for each possible splitting value:

$$GINI_{split} = \sum_{i=1}^{m} \frac{n_i}{n} i(N) \qquad \text{Eq. 3-18}$$

Where, $n_i, n$ are the number of cases in the child node $i$ and the parent node, respectively.

After doing the calculation in equation (GINI split), the CART algorithm will choose the split value that has the least GINI impurity. Depending on this value the node will be split into left and right node. More detailed survey can be found in [58].

### 3.3.3.2 Support Vector Machine

Support Vector Machines (SVMs) are a popular type of binary pattern classification methods which have gained increasing attention since they are first presented by Vapnik [59]. Figure 3-14 illustrates the basic principle of the linear SVM.

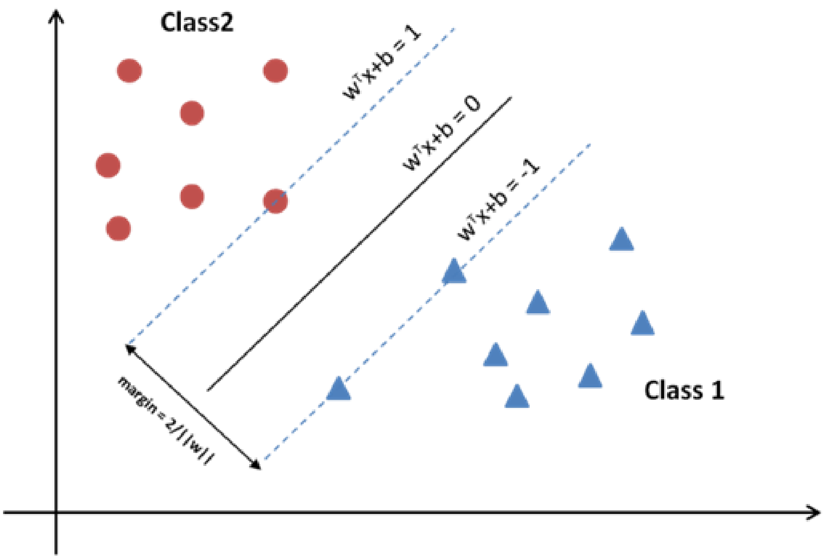



Figure 3-14. Linear Support Vector Machine

Considering the training set D$\{(X_i, y_i)\}_i^l$ ; where $X = \{x_1, \ldots . x_n\} \in \mathfrak{R}^n$ denotes the input vectors and $y_i \in \{-1,1\}$ is the indicator. With the nonlinear data set the input vector $X$ will be mapped into high-dimensional space in which a linear decision surface can be constructed. This transformation is realized by kernel function:

$$K(x_i, x_j) = \Phi(\mathrm{x_i}). \Phi(\mathrm{x_j}) \qquad \text{Eq. 3-19}$$

where, $\Phi$ is a nonlinear function.

The commonly used kernel functions are: Fisher kernel, Graph kernel, Polynomial kernel, RBF kernel and string kernels.

The optimal classifier is obtained by solving the following quadratic problem:

$$\min_{\omega.b.\xi} \left\{ \frac{1}{2} \omega^T \omega + C \sum_{i=1}^{L} \xi_i \right\} \qquad \text{Eq. 3-20}$$

Subject to:

$$y_i\left(\omega^T\Phi(x_i)^T + b\Phi(x_j)\right) \geq 1 - \xi_i \qquad \text{Eq. 3-21}$$

where, $C$ is a regularization coefficient and $\xi_i$ called slack variable and they are introduced to deal with nonlinear feature vectors.

#### 3.3.3.2.1 Support vector regression (SVR)

SVM can be applied also to the case of regression. The main idea of the SVR is to map the input vector $X$ into high-dimensional feature space and then to perform linear regression in the feature space [60]. Same as in SVM this transformation can be realized by the kernel function $K(x_i, x_j)$. The correlation between input and output can be written as following:

$$y = f(x) = \omega . \Phi(x) + b \qquad \text{Eq. 3-22}$$

where, $X \in \mathfrak{R}^n$ is the dimensional input space and $y \in \mathfrak{R}$ is the corresponding output. $\Phi(x)$ is the features of the input variables, and the coefficients $\omega, b$ can be estimated by minimizing:

$$E(\omega) = C\frac{1}{N}\sum_{i=1}^{N}|y_i - f(x_i,\omega)|_\epsilon + \frac{1}{2}\|\omega\|^2 \qquad \text{Eq. 3-23}$$

where, $C \in \mathfrak{R}^+$ determines the trade-off between the empirical risk and the regularization term $\frac{1}{2}\|\omega\|^2$. The empirical risk can be given by the insensitive loss function ($\epsilon$):

$$|x|_\epsilon := \begin{cases} 0 & if\ |x| - \epsilon \\ |x| - \epsilon & else \end{cases} \qquad \text{Eq. 3-24}$$

To reduce the complexity by minimizing $\|\omega\|^2$ the non-negative slack variables $\xi_i, \xi_i^*$ can be introduced to measure the deviation of training sample outside $\epsilon$-insensitive zone. Thus SVR is formulated as following:

$$E(\omega) = C\frac{1}{N}\sum_{i=1}^{N}(\xi_i + \xi_i^*) + \frac{1}{2}\|\omega\|^2 \qquad \text{Eq. 3-25}$$

Subject to:

$$\begin{cases} y_i - f(x_i, \omega) \leq \epsilon + \xi_i \\ f(x_i, \omega) - y_i \leq \epsilon + \xi_i^* \\ \xi_i, \xi_i^* \geq 0 \end{cases} \qquad \text{Eq. 3-26}$$

After transforming the optimization problem into the dual problem, the output model can be given as following:

$$f(x, a) = \sum_{i=1}^{N} (a_i^* - a_i) \, K\left(x_i, x_j\right) + b \qquad ; \; 0 \leq a_i^*, a_i \; \leq C \qquad \text{Eq. 3-27}$$

where, $a_i^*, a_i$ are the Lagrange multipliers.

# 4 Assessment of Physical Activity and Gait Impairment - State of the Art

Physical activity is a complex behavior that can be subdivided into a number of dimensions, such as frequency, duration intensity and type of activity. It has generally been acknowledged to be a health-promoting factor [33]. Hence, an increased effort has been placed in the area of development of population-based interventions. However, patients with chronic progressive neurological disease, such as multiple sclerosis, typically show a decrease of physical activity as compared with healthy individuals [61]. Over the course of their disease, many patients experience a significant decline of mobility and daily life activity [9]. Mobility and gait impairments in PwMS, such as reduced walking, stride length and distance, are associated with increased activity limitations and thus with decreased quality of life [62]. A clearer understanding and assessing of physical activity impairment and gait ability in PwMS is essential for the development of effective interventions to alter the progressive disease course.

As for healthy population, several methods have been used to assess physical activity (activity count, MET level) and walking ability (e.g. velocity, step length, swing time, cadence, symmetry) in PwMS [14,36]. Generally, these methods could be categorized as subjective (e.g. questionnaires, self-reports) and objective (e.g. laboratory system, wearable system). This chapter briefly presents these methods and discusses their advantages and disadvantages.

## 4.1 Questionnaires and Self-Report Assessment Methods

In individuals with physical activity disabilities, physical activity in daily life have typically been assessed by questionnaires or diary methods [63,64]. With self-report methods, individuals are asked to report on their activities, sometimes even from a previous day, week or months. Information such as activity type, frequency, duration and intensity can be also gathered using self-report and questionnaires. Global self-reports are usually used to gather information about the individual’s activity pattern over a long period of time (e.g. one year). Recall questionnaires ask individuals to report on their activity from the previous day or week; they are short and designed to classify activities into groups [65]. Self-report and questionnaires methods have been widely used to assess physical activity in PwMS.

Self-reports and questionnaires methods are well-known for their cost efficiency, user friendliness and suitability to be employed preferably in large scale studies [66]. They also are able to distinguish between physical activity domains, such as occupation, household, leisure time or sport [67,68]. However, the major disadvantage of the questionnaires and self-report methods is that the collected information is subjective and relies on correct memory retrieval [67,69]. Furthermore, these methods rely on accurate estimations of physical activity. Biased responding may result in an under- or overestimation of the actual activity [70]. Most available self-report measures are not sufficiently sensitive to register low levels of activity resulting in floor effect [71]. Moreover, automatic activities with a moderate intensity such as walking are poorly encoded in episodic memory and are thus likely to be underestimated [72]. It has been reported that self-report and questionnaires may also be affected by the "social desirability" theory [73].

## 4.2 Clinical Assessment Methods

In addition to self-report and questionnaires methods, there exists a wired range of clinical assessment instruments that address different walking ability and clinical status. The importance of walking ability lies in the fact that gait disorders affect a high percentage of the population with neurodegenerative diseases such as multiple sclerosis. Usually, clinical assessment methods, also called semi-subjective methods, are carried out under clinical conditions by a specialist. The various gait-related parameters are assessed and evaluated while the patients perform predefined tasks. The following section comprises the most common clinical assessment methods that used to measure the walking ability.

### 4.2.1 Timed 25-Foot Walk test (T25FW)

This method is the first part of Multiple Sclerosis Functional Composite (MSFC). T25FW is one of the most widely standardized measures of gait velocity. The test consists of three parts for use in clinical, and its component can display variable results, especially in patients with slow walking speed [74]. The T25FW measures the time the patient needed to walk the 25 feet (7 and a half meter) distance with self-selected walking speed or fastest safe walking speed. Time may be recorded either manually with a stop watch or via mechanized equipment such as photocells. The output measure of this test is used to differentiate between PwMS with mild disability and those with moderate disability. The T25FW showed high reliability of (ICC = 0.9) [74].

However, the test is not useful for patients with severe disability and cannot walk the 25 feet.

### 4.2.2 Six-Minute Walking test (6-MW)

The 6MW was first validated in 1982 and in the last decade as been increasingly used in neurological populations, such as stroke, Parkinson's disease and multiple sclerosis [75–77]. The outcome measure is the total distance covered for 6 min. Patients are asked to walk for 6 min at maximal speed back and forth in a hallway. Patients may use an assistive device, but rest is not allowed within this 6 min. The 6MW has been validated as a measure for walking ability. The results indicated that the measured distance travelled within 6 min has differed between PwMS and healthy individuals. The test has high intra-rater and inter-rater reliability (ICC = 0.9). Furthermore, it is robust and has improved precision compared with T25FW test [35]. Moreover, it has a sensitivity to change of (MDC = ±92.1m) in patients with mild to moderate disability.

### 4.2.3 12-Item Multiple Sclerosis Walking Scale (MSWS-12)

The 12-Item multiple sclerosis walking scale (MSWS-12) is a self-report measure that assesses 12 parameters, which describe the impact of multiple sclerosis on walking ability in the past 2 weeks [78]. Each item consists of 5 scales, with 1 meaning no limitation and 5 meaning extreme limitation. This instrument has been included in the gait outcome measures recommended by the consensus conference of the Consortium of Multiple Sclerosis Center [79].

### 4.2.4 Timed Up and Go (TUG)

Timed up and go (TUG) is a timed test of dynamic balance. The patients are instructed to stand up from a chair and walk a 3m distance then turn around, walk back to the chair. The output of the test is the time from the moment the pelvis lifts off chair till the moment it reaches the chair again. The time is measured by a stop watch. The TUG has an excellent reliability (ICC = 0.94) and its sensitivity to change is reported to be about; MDC = 4.09 sec, 11 sec for patient with Alzheimer disease and Parkinson's disease, respectively.

Generally, these clinical methods and functional tests have been reported to be useful for discriminating pathology population. However, they prone to error due to specialist's manual measurement and subjectivity. Basically, there are two main sources of subjectivity; clinical subjectivity and patient subjectivity. On the clinical side, the assessment may differ between raters, due to rater's interpretation of the patient's status. Patient subjectivity may occur due to the intra-variability, i.e. the performance of the patient in a certain test might vary from time to time depending on the patient's mood, fatigue, etc. Moreover, in some tests the outcome measure might be unable to assess the little changes within and between patients or between normal and abnormal condition. Finally, these clinical methods usually require a specialist who's able to carry out the test and manual data analysis to obtain the results. A comprehensive description of these and further clinical assessment methods can be found in potter [80].

The complexity and high variability of physical activity and gait makes them difficult to be measured. Nevertheless, it remains of intense public health interest to accurately and reliably assess them. Therefore, several researchers have intended to develop and use different objective systems and devices for measuring and evaluating physical activity and gait parameters. In the following sections an overview about some known and commonly used objective devices will be given.

## 4.3 Objective Assessment Methods – Laboratory Systems

Gait laboratories typically use a system, such as marker-based motion capture and force plates. These systems are considered as gold standard for motion and gait analysis and are known for their ability to provide very accurate description and reliable measurements of the gait pattern. Furthermore, they allow getting quantitative and objective figures of the clinical gait. In the following, some of these systems will be presented.

Optical motion analysis system consists of markers attached to specific locations on the individuals using a set of cameras. Applications of these systems can be classified into gait parameter analysis and gait classification to distinguish between different types of activities [81]. Currently, optical motion systems are the most well-known and precise gait analysis systems. However, they are expensive (60.000-150.000€) and their complexity for preparation and analysis makes them unsuitable to be integrated in the daily routine assessment of gait parameters in patients with severe walking impairment.

Alternative systems to camera-based systems are force plates. These systems measure the ground reaction forces generated by a body standing or moving across them. Force plates systems are used to quantify balance and assess gait kinetic parameters. The platform is about 60 x 60 cm and they can provide accurate temporal parameters such as heel strike and toe off contact signals [82].

Some commercial force plates are: Force plate AMTI series OR6-7 Figure 4-1, Kistler force plates.

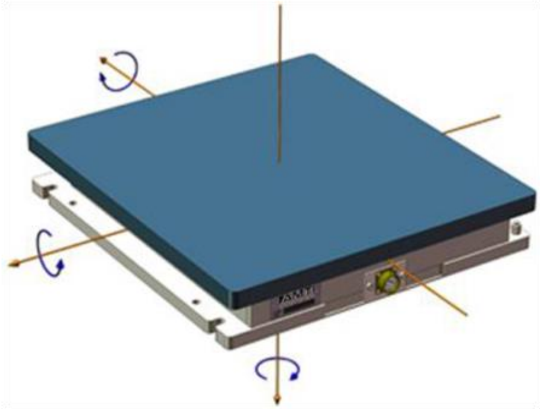


Figure 4-1. Force Platform AMIT force plat [82]

Major disadvantage of the force plates systems is that they can measure the parameter only within one stride. Therefore, for longer distance where several steps are involved, the computerized walking mat GAITRite© Analysis System (CIR System Inc, Clifton, NJ) is used [83]. It is an electronic walkway system that can be connected via serial port to a personal computer. GAITRite© is a carpet of 89 cm wide and 9.75 m long, where the active area is about 61 cm wide and 7.32 m long and contains 16.128 pressure sensors. This system should be differentiated from the force plates, the latter quantifies horizontal and shear components of the applied force, whereas the former can quantify the pressure patterns. Pressure sensors integrated in the walkway system are activated at footfall and deactivated at toe-off, thus they enable a continuous capturing spatio-temporal gait data sampled at 8 Hz. GAITRite© system has been reported to have high reliability (ICC $\geq$ 0.85) and high validity when compared with video-based motion analysis (ICC $\geq$ 0.93) [84]. However, GAITRite© is an expensive system and need to be installed in appropriate rooms. Furthermore, the data capture is restricted to a few steps at a time; therefore, the patient needs to walk many times on the mat in order to obtain statistically valid data.

Recently, instructed treadmill gait analysis system has been proposed as an alternative gait assessment and analysis system. This device enables the capturing of gait parameters over long distance and long period of time under consistent conditions; distance, belt speed and inclination. Most gait parameter captured by this system showed high reliability [85]. The usage of instructed treadmill has several advantages compared to over ground assessment system. First of all, they are not limited to the number of steps per trial as with

GAITRite©. Furthermore, these systems allow the analysis of gait characteristics at different speed including jogging, because while walking on treadmill patients are able to control their speed.

Finally, instructed treadmill enables gait assessment while walking on an inclined surface [86]. However, energy costs have been reported to be higher during walking on treadmill than over ground. Moreover, walking on treadmill may impede individual’s natural gait pattern [87]. Other several non-traditional methods, such as laser technology [88], ultrasound system [89] and magnetic tracking system for gait analysis have been developed. Figure 4-2 illustrates the most widely used gait analysis systems under laboratory condition.

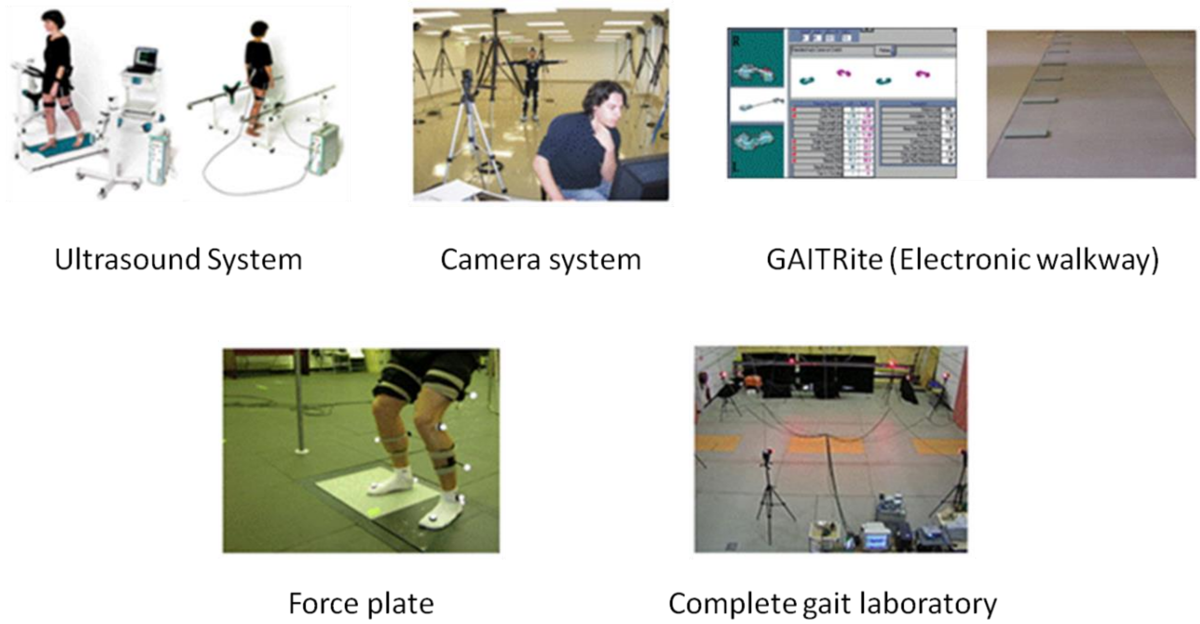



Figure 4-2. Most frequently used gait analysis technologies and systems [82]

However, these systems are expensive, complex and can only be operated by specialist trained person. Moreover, laboratory conditions may influence the natural behavior of the patients. Most importantly, the usage of these systems is time-costly, thus its integration in clinical routine is limited. Therefore, there is an increasingly need for an inexpensive, unobtrusive system, which allows monitoring and evaluating of physical activity and gait parameters continuously outside the lab (i.e. under free-living condition).

## 4.4 Objective Assessment Methods- Wearable Sensors

Recent advances in technology have promoted the development of objective methods based on wearable sensors (WS) to allow continuous monitoring of daily physical activity of multiple populations with gait disorder, such as stroke survivors, Parkinson's disease (PD) and PwMS [90]. Such systems allow capturing and monitoring of gait and physical parameter under customary environments, thus they overcome the limitations of laboratory and clinical subjective methods. WS-based systems use sensors attached to the body to assess and evaluate the different aspects of human activity and gait during the patient's everyday activities under free-living conditions. There are different types of WS have been used in the field of gait and physical activity assessment (Table 4-1). A review of the most common used WS and their application is presented in the following.

Table 4-1. Commonly used wearable sensor to assess physical activity and gait parameter

| **Sensor** | **Usage** |
|---|---|
| Accelerometer | Walking speed, displacement of the body segment |
| Gyroscope | Angular velocity and rotation |
| Pedometer | Steps count |
| Magnetometer | directional vectors of spatial orientation |
| Electromyography | Time and amount of muscles activation |
| Goniometr | Joint angular range of motion |
| Pressure sensing | Stance phase detection |

### 4.4.1 Pedometers

Pedometers are compact, battery operated devices that measure number of step taken by the individual in continuous manner [91]. Some pedometers available nowadays use the number of steps to estimate the travelled distance and energy expenditure (EE). Pedometers have been applied in several applications: to distinguish between individuals based on steps/day, to measure the effect of the intervention on physical activity, to assess and compare time trends in physical activity. These sensors have three principles of mechanism; Spring-levered arm, piezoelectric and magnetic [92] . Spring-levered pedometers (Figure 4-3) use a spring-suspended horizontal arm that moves up and down in response to hip movement while walking or running. The arm opens and closes an electrical circuit with each step and the number of steps is then counted.

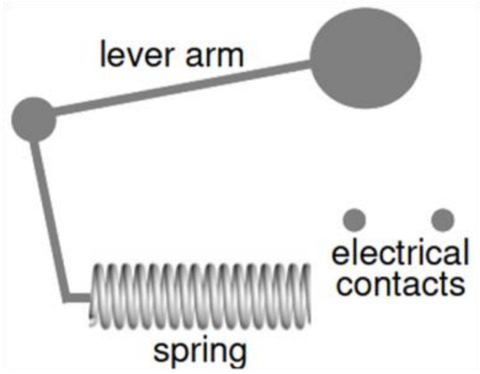



Figure 4-3. Spring-level pedometer

Magnetic reed proximity type also consists of spring-suspended horizontal lever arm and a magnet attached to it. In this mechanism the magnetic field causes the electrical contact of two overlapping metal pieces (magnetic reed proximity) enclosed in a glass cylinder.

Piezoelectric pedometer (Figure 4-4) has an accelerometer with a horizontal beam that compresses a piezoelectric crystal when subjected to movement (e.g. walking). This generates a voltage proportional to the movement. The voltage oscillation is used to record steps [93].

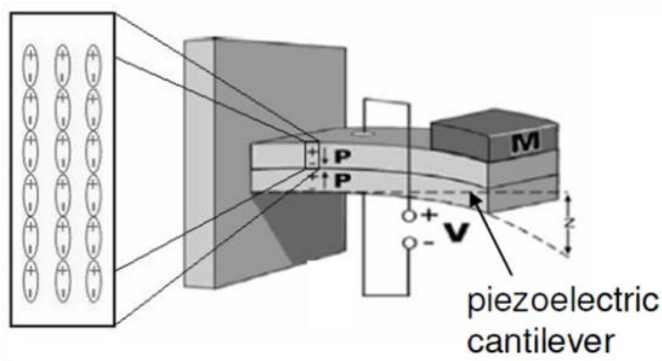



Figure 4-4. Piezoelectric pedometer

Over the last decade a quite variety of pedometers has been introduced; conventional stand-alone pedometers and personal digital devices (Table 4-2).

Table 4-2. Pedometers - Commercial types ([94], modified)

| **Device** | **Model** | **measurement** | **assessment time** | **placement** |
|---|---|---|---|---|
| Omron HJ-720 |  | Steps, aerobic, activity time, distance, calories | 7 days displayed 42 days in memory | Pocket, bag or clip to belt |
| Yamax CW series |  | Steps, distance, calories | 7 days 2weeks total | Clip to belt |
| Sport line 955 |  | Steps, speed, activity time, distance, calorie | 10 days | Wrist |
| Fitbit one |  | Steps, distance, calories, stair climbed, quality of sleep | 5-7days | Clip to pocket, in pocket |
| Nike |  | Step, distance, time, calories | - | iPod OS |
| iPhone |  | Steps | - | iPhone OS X |

Although pedometers only capture steps and limited type of activities [92], they have been used in different healthcare studies and clinical researchers. For example, these devices have been used to detect differences in physical activity between PwMS and healthy individuals, to evaluate their accuracy and reliability, under free-living environment and controlled conditions [95,96]. Pedometers showed high reliability of ICC = 0.93 and ICC = 0.80 for 7-days and 3-days of monitoring, respectively. However, difficulties may arise, especially in populations with neurological disease whereby the gait pattern may be abnormal and asymmetrical [97]. Therefore, the validity of such systems for individuals with gait disorder is questionable.

Although pedometers are inexpensive, simple to use and unobtrusive devices, they have a major drawback: they are unable to reflect the intensity of the patient’s movements, like increases in moderate or vigorous physical activity or reduction in sedentary time [98]. Furthermore, they may suffer from inaccuracy during self-selected and slow walking speed[99]. Moreover, pedometers cannot provide important clinical information about gait quality, such as gait asymmetry.

### 4.4.2 Gyroscopes

Micromachined gyroscopes are based on another working principle, which implies that all body revolves around an axis develops rotational inertia. Typically, a gyroscope can be used to measure the motion and posture of the human body (angular orientation) by measuring the angular rate (i.e. the output of the angular rate sensors) [100]. Gyroscopes must always face the same direction, being used as a reference to detect changes in direction. The advantage of using gyroscopes is that gyroscopes allow angular velocity measurement and short-time estimate of total orientating. The reliability of the gyroscope in detecting gait event (i.e. initial contact and toe of) has been reported to be high (ICC = 0.98) [101]. However, the usage of gyroscope in measuring daily-living activities, where the temperature fluctuation is larger than in the laboratory, results in an offset error affects the gyroscopes signal. A relatively small offset error will introduce large integration errors. Therefore, several studies have used a combination of gyroscope and accelerometer or magnetometer. The gravitational acceleration component could provide inclination information that is useful to correct the drifted orientation estimate from the gyroscopes, whereas the sensitivity of the magnetometer to the earth's magnetic field helps in correcting the drift of the gyroscope about the vertical axis. Furthermore, using gyroscopes will decrease the autonomy of the monitoring system due to their high power consumption [102].

### 4.4.3 Electromyography

Electromyography (EMG) is performed using an electromyograph. EMG measures the electrical activity of the muscles at rest and during contraction. It could be either voluntary or involuntary muscle contraction. The EMG signal can be captured either by surface electrode (Figure 4-5), or with wire or needle electrodes. The outcome signal should be then amplified to yield a suitable format that can be used for further analysis.

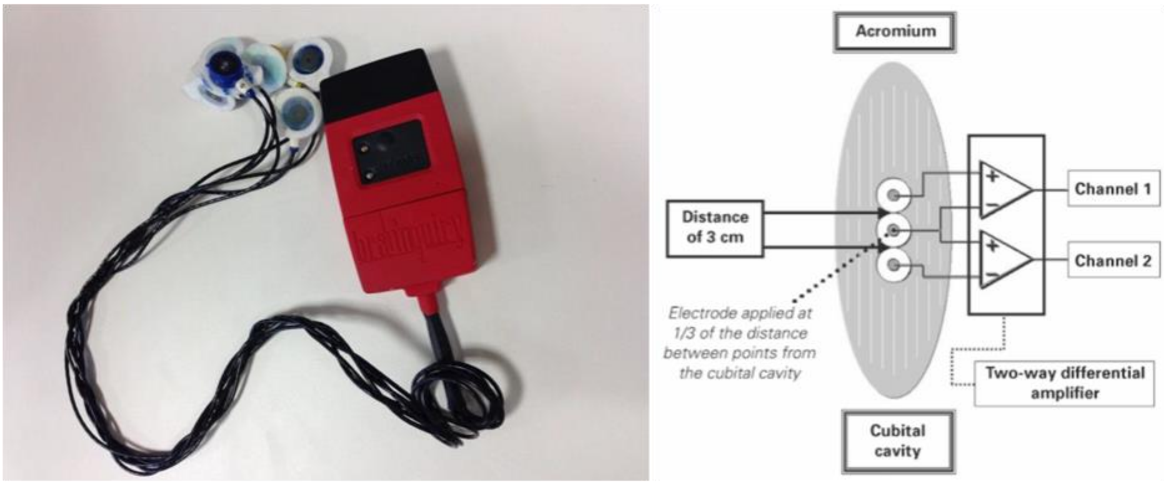



Figure 4-5. Brainquiry Wireless EMG/EEG/ECG system (right [82]), Simplified scheme of the surface electrodes (left [103])

EMG has been widely used in the field of gait analysis as a tool to distinguish between normal and pathological gait in both adults and children. Surface electromyography (SEMG) is a useful tool for the assessment of motor disorder in medical researchers, such as neurology, neurophysiology, orthopedics and rehabilitation. Figure 4-6 illustrates a schematic view of SEMG application within a gait analysis laboratory. Furthermore, EMG signals can be used to assess different gait characteristics which are mainly related to functional and pathophysiological characterization of gait disturbance [104]. For example, EMG signal amplitude increases with increased walking speed, whereas the EMG activity is minimized during comfortable speed.

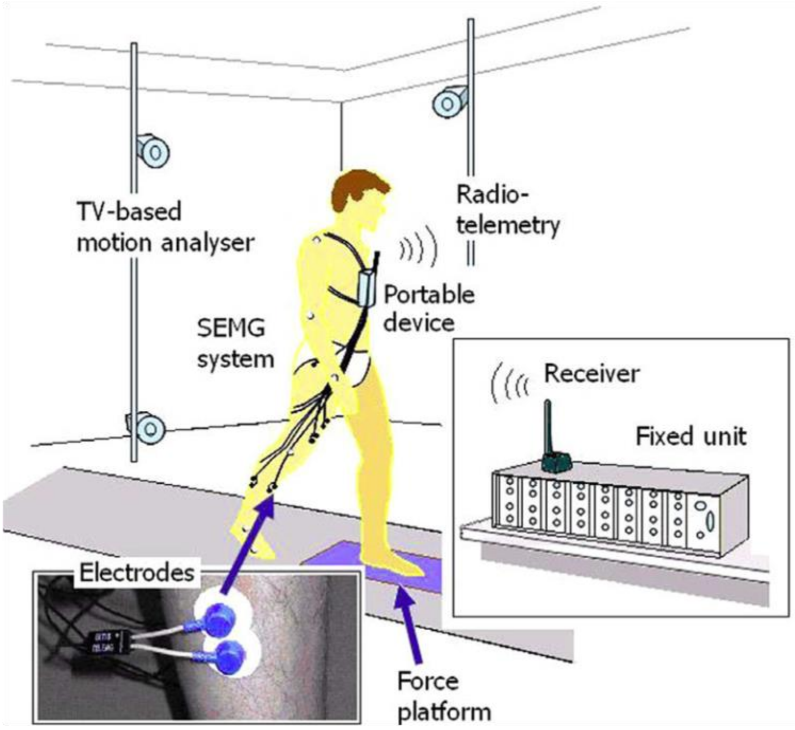



Figure 4-6. Schematic of SEMG System [105]

EMG can be very useful analysis instrument if applied under proper conditions. Basically, SEMG are used when only general information on muscle activity is required. On contrary, wire electrodes will be used if specific information on a particular muscle is needed. In this case, the wire electrode must be integrated into the muscle using a hypodermic needle. However, despite their poor usability and their intrusively, EMG sensors are not suitable for ambulatory application because of the sensitivity to the poor electrode site preparation and placement [106].

### 4.4.4 Accelerometer

Accelerometers are devices that measure the acceleration of person's body while moving. Due to the advances in sensor technology over the past decades, accelerometers become smaller, lighter, cheaper with high user acceptability. Moreover, the new developed accelerometers are able to collect data at high frequency and store it over many days or weeks, have high battery performance and memory capacity [107]. Therefore, they now are the most commonly used objective devices to assess physical activity and gait under free-living conditions in large-scale observational studies. It was also shown that accelerometers have advantages over other devices in assessing human activities, estimating EE and gait velocity as well as detecting gait abnormality.

Accelerometer can measure movement either uniaxial or triaxial. The uniaxial accelerometer measures the acceleration in one plane, usually the vertical plane, whereas triaxial accelerometers measure the acceleration in the vertical, sagittal and lateral planes. However, triaxial have shown to be more sensitive in detecting the variability of the activity in population with gait and movement disorders. Accelerometers can be worn on various body parts, such as waist, chest, ankle, pocket, wrist and shoe. During assessment of physical activity, desire information about intensity, frequency and duration can be captured by applying a suitable time sampling interval. In order to capture the full range of human motions, sampling frequency should fulfill Nyquist criterion “the sampling frequency should be at least twice the highest frequency contained in the signal”. Typically, the frequency of normal physical activity is below 8 Hz (during running), although the upper limit could reach 25 Hz for some arm movements. Therefore, the commercially available accelerometers have a sample frequency between 1 Hz to 64 Hz [108].

There are several devices currently available on the market. In the following the most common devices will be briefly presented. A technical specification and detailed survey are summarized in Table 4-3.

*activPAL:* The activPAL is a uniaxial accelerometer, which can be worn on the thigh. The sensor has been used to classify different free-living activities. In comparison with two pedometers, activPAL revealed an accurate steps-counting and cadence estimation. Moreover, the sensor has been shown to be valid and reliable tool in measuring cadence and steps (ICC > 0.99 and absolute percentage error < 1.11 %) [109].

*SenseWear:* The SenseWear is an activity monitor device worn on the upper limbs. Consists of combines multiple sensors; triaxial accelerometer, skin temperature, heat flux and galvanic skin response. The output measures of SenseWear are: total EE, METs, total number of steps and sleep duration. The SenseWear revealed an accurate performance in estimating EE during slow and normal walking, but showed underestimation of EE during increased walking speed [110].

*ActiGraph:* There are two different models available on the market, namely GT1M and GT3X. The GT1M is a uniaxial accelerometer and measures acceleration at 30 Hz. It can be worn on the waist to measure activity counts, step counts and EE. It can be used for sleep monitoring purpose. Multiple studies have reported its reliability and validity [111].The new model of ActiGraph is the GT3X. It is a tri-axial sensor and can be worn on a belt on the right hip. Several clinical studies have mainly used GT3X to assess physical activity and activity count. The sensor has been evaluated in many studies and the results that GT3X accurately measures physical activity when compare to oxygen consumption, whereas the estimation of EE depends strongly on the sample population and the type and intensity of physical activity [112].

*StepWatch:* The StepWatch is an ankle-worn sensor for gait measurement. It records steps and cadence in different gait speed and styles. The accuracy of StepWatch in counting steps has been investigated in several studies under different conditions. The sensor showed overestimated step counting during a 24 hour monitoring [113]. The validity of the sensor was also reported in population of widely varying impairment levels, such as PD and MS [114].

Table 4-3. Summarizes of different accelerometer types ( [115], modified)

| Sensor | ActiGraph GT1M | ActiGraph GT3X | ActiGraph ActiTrainer | actibelt Trium Analysis | Biotel 3DNX | Tracmor$_D$ Philips | RT3 Stayhealthy | MoveII Movisens | Step Watch | activPAL | SenseWear | IDEEA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Size (mm) | 53x51x22 | 38x37x17 | 50x40x15 | 91x43x17 | 54x54x18 | 32x32x5 | 71x56x28 | 50x36x17 | 75x50x20 | 53x35x7 | 88x56x24 | 70x54x 17 |
| Weight (g) | 27 | 27 | 45 | 53 | 70 | 12.5 | 65 | 17 | 38 | 15 | 45.4 | 59 |
| Number of axis | 1 | 3 | 1 | 3 | 3 | 3 | 3 | 3 | 2 | 1 | 3 | 2 |
| Sampling rate (Hz) | 30 | 30-100 | 30 | 100 | 20 | - | 1 | 64-128 | 32 | 10 | 32 | 32 |
| Sensitivity range | 0.05-2.5 | 0.05-2.5 | 0.05-2.5 | 0.01 | 0.2-20 | - | 2-10 | 0.04 | - | 2g | 2g | 5g |
| Battery life | 20 days | 20 days | 20 days | 20 days | 21 days | 3 weeks | 30 days | 7 days | - | 10 days | 7 days | 60 h |
| Output measures | Activity counts, steps, MET, intensity level | Activity counts, steps, MET, intensity level | Activity counts, steps, MET, intensity level, heart rate | Activity counts, steps, MET, gait speed, distance travelled, changes in altitude | EE | EE | Activity intensity, EE, MET | EE, Activity type, steps, body position | Gait characteristics | Sedentary and upright time, steps, cadence, MET, EE | EE, activity duration, sleep duration | Activity type, gait type, EE |

## 4.5 Commercialized Systems for Physical Activity and Gait Analysis

There are several commercial systems for physical activity and gait analysis on the market. These systems are either wearable or non-wearable and usually use a combination of different aforementioned sensors and technologies. Some examples of these systems will be presented in this section. BTS GAITLAB system provides quantitative and objective information about possible gait, postural dysfunction and muscular insufficiency. The system was used in the study of Bello et al. [116] to measure the effects of intervention training program on gait in PD. Tempol clinical gait analysis is also used for multiple clinical purposes, such intervention control, rehabilitation, pre- and post-comparison [117]. One of the widely used WS systems for gait analysis is Xsens MVN [118]. It consists of 17 inertial sensors placed on chest, upper and lower limb. The data are captured via wireless communicated suit (Figure 4-7).


Figure 4-7. Xsens-Motion tracking system [119]

Another commercial system is the wireless M3D gait analysis system. The system uses motion sensors on the lower leg, the thigh, the waist and the back and wearable force plates on the toes and the heels. M3D includes an accelerometer, a triaxial gyroscope sensor and a triaxial geomagnetic sensor [120].

Commercial wearable systems with in-shoe integrated pressure (Figure 4-8), such as in-shoe based foot plantar pressure sensor F-Scan® System by Tekscan [121], have also been commonly used in clinical studies to assess and analyze gait disorder.

Figure 4-8. In-shoe plantar pressure analysis system [121]

A comprehensive review about commercial systems for physical activity and gait assessment can be found in [82].

## 4.6 Summary

The previous sections highlighted the most commonly used methods and systems for capturing physical activity and gait in both healthy individuals and patients with gait disorder (such as PD and PwMS). These methods are categorized as subjective (self-report, clinical instruments) and objective (Laboratory system and WS). A comprehensive review of clinical research literatures revealed that self-report and clinical instruments are widely used in population with gait disorders. Although these subjective methods have been reported to be valid and less expensive, they rely on recall and can only offers biased evaluation taken over short period of time, as previously discussed in section 4.1 and section 4.2. To overcome these disadvantages, several researchers tended to apply objective method to assess physical activity and gait parameters. Laboratory systems enable a simultaneous analysis of multiple gait parameters captured from different approaches, are highly accurate and allow more precision measurement when complex systems are applied. Therefore, they have been widely applied for physical activity and gait assessment, especially in patients with gait disorders. However, they are very complex, expensive, and cannot monitor free-living gait outside the controlled environment. Particularly, in the field of neurological diseases, there is increasingly need for constant observation of patients' mobility and walking ability in their free-living conditions over a long period of time. Considering the advantages of WS systems in measuring and evaluating physical activity and human gait, several researchers applied these systems for clinical gait and mobility observations. Table 4-4 summarizes different clinical studies that used wearable sensors to assess physical and gait parameters. Among all WS accelerometers are considered to be the most suitable sensor for measuring physical activity and gait under free-living conditions. They provide more precise information regarding physical activity and their battery life is assured for several days. Moreover, they are unobtrusive so that individuals are unrestricted during their daily-living activities. Therefore, accelerometer was used in this work.

Table 4-4. Summary of clinical studies that used wearable sensor to assess physical activity and gait

| Study | Population | Type of WS | Placement | Experimental setup | Outcome measure |
|---|---|---|---|---|---|
| [61] | MS | Triaxial accelerometer | Trunks and legs | Free-living (24 hours) | Daily activity (walking, sitting, standing and lying) |
| [36] | MS | Triaxial accelerometer | Waist | Free-living (6 occasions of 7 days each separated by 6 months) | Activity count |
| [122] | MS | Pedometer, triaxial accelerometer | Waist, leg | Free-living (7 days) | Activity count, activity temperature, steps count |
| [123] | MS | Triaxial accelerometer | Waist | Free-living (7 days) | Steps count |
| [124] | MS | Uniaxial accelerometer | Waist | Free-living (7 days) | Activity count |
| [125] | Stroke | Force-sensitive resistors and 3 accelerometers | Shoe-based WS | Laboratory environment | Spatio-temporal parameters |
| [126] | PD | Accelerometer | Waist | Predefined walkway | Temporal parameters |
| [127] | Vestibular disorder | Pressure | Foot | Laboratory environment | Temporal parameters |
| [128] | Stoke | Triaxial accelerometer | Both ankles | Indoor/outdoor predefined walkways | Speed, bouts of walking, Activity type |
| [129] | PD | Two uniaxial gyroscopes, 3 | Shanks, wrist, | Predefined walkways at | Stride length, stride velocity, |

| | | | | | |
|---|---|---|---|---|---|
| | | biaxial gyroscopes, triaxial accelerometer | chest | laboratory and at home | cadence, arm angular velocity and turning velocity |
| [130] | Stroke | Two triaxial accelerometer | Both ankles | Free-living (8 hours) | Walking bouts, total walking time, speed, steps count, gait asymmetry, cadence |
| [131] | MS | Uniaxial accelerometer | Waist | Free-living (7 days at baseline and 6 months later) | Activity count |
| [132] | PD | Triaxial accelerometer, biaxial gyroscope | thigh and shank | Predefined walkway | Freezing of gait (FOG) |
| [133] | PD | IMU | Both ankles | Laboratory environment | Gait asymmetry |
| [134] | MS | Uniaxial accelerometer | Waist | Free-living (7 days) | Activity count |
| [135] | MS | Triaxial accelerometer | Waist | Free-living (4 days) | Activity count |
| [136] | Vertigo and vestibular disorder | Pressure | Foot | Laboratory environment | Temporal parameters |
| [137] | PD | Triaxial accelerometer | left and right ankle | Laboratory | Gait events (initial and end contact) |
| [138] | Stroke | Five biaxial accelerometer | Chest, thighs, each forefoot | Timed short-distance walk | Gait cycle events, cycle duration, step and stride length, speed |
| [139] | PD | Gyroscope | Forearms, thighs and shanks | Laboratory | Gait cycle, spatio-temporal parameters |

# 5 Conception and Implementation of a home-based system to objectively assess comprehensive gait parameter for PwMS

The main aim of a clinical motor and gait analysis system is the identification of health status and altering pathological movement pattern. In neurological diseases such as MS, motor and gait analysis may help in diagnose and treatment determination. However, neurological disorders generally involve a variety of symptoms that lead to considerable functional impairments in daily life. Therefore, the assessment of physical activity and gait parameters should include a reference of daily life, as such be a more effective way to monitor the actual physical activity and walking behavior. Consequently, this daily monitoring may be a sensitive tool to influence clinical decision-making in intervention and rehabilitation. However, the quantitative assessment of daily physical activity and gait parameters requires an objective, comprehensive, reliable and easy to use technique to be applied in free-living situation. This chapter presents the procedure and workflow conception and the algorithms developed and applied to achieve the above mentioned goals. In the first part the hardware and software requirements are presented and discussed. In the second part of this chapter the developed algorithms are presented.

## 5.1 Is-Process and To-be-Process

As it was mentioned in section 2.3, MS is an incurable autoimmune disease of the CNS with unpredictable symptoms that can vary in every individual depending on the location of the affected nerve fibers. Therefore, the treatment of MS should be individually determined and strongly based on the symptoms. Furthermore, the adjustment of the therapy depends on the disease progression and patient’s health status. Particularly, regular check-ups and physician visits are carried on in order to monitor the condition of the patients and their response to the treatment (determination of EDSS and MSFC). During the basic examinations in the clinic, patients go through several clinical re-tests (e.g. T25FWT, standing with eyes closed). Besides these tests, physicians perform interviews with the patients in order to find out more detailed information about their daily routine, difficulties by mobility and other functional areas. However, this approach suffers from the following problems:

- The intervals between the tests are large (each 6 months), so that an exact determination of the health status and disease course is not possible.

Moreover, because of the long intervals the deterioration could be too late noticed and treated.
- The clinical tests are prone to error due to the subjective assessment of the disease-related information, and due to the poor evaluation of everyday situation based on momentary estimation and impression of the disease course.
- The physicians do not have sufficient feedback on the effect of the treatment on the health situation (e.g. mobility).
- The observations are very time consuming and affected by patients and physicians' intra-variability.

Nowadays, the determination of an adequate therapy and medication basically depends on the aforementioned assessed information. Thus, it is desirable to improve and objectify the assessment methods, so that the physicians learn more about everyday occurrences in the time between two successive clinical visits. Hence the disease progression and health state of the patient can be evaluated more precisely. This might help in the early detection of disease deterioration, which in turn may intend to reduce the stationary stay and the error rate in the determination of the therapy and medication. Therefore, it is of great importance and need to develop a technical monitoring system that enables objective, ambulatory and continuous assessment of the health status over a long period of time. Figure 5-1 illustrates the steps that should be considered while developing such a system:

1. Define the factor parameters that are important and relevant to measure disease progression and clinical state: In the developing of such a system, the main focused should be on could this system provide a great support for both physicians and PwMS. The first step is then to determine what parameters play an important role in disease progression. Furthermore, the effects of these parameters on patient's health condition and quality of life should be considered.
2. The distribution of the disorder of the specific parameters should be considered, that there will be more sense to consider the symptoms that occur in a big proportion of patients.
3. If the considered parameters are measurable, the next step will be to define which technology should be chose or developed to assess them objectively under everyday life condition.

4. Once the parameters and the technology were defined, data collection and analysis should be considered. Mainly, the focus here is on the comprehensively analyze of the parameters to extract clinically important and relevant information.

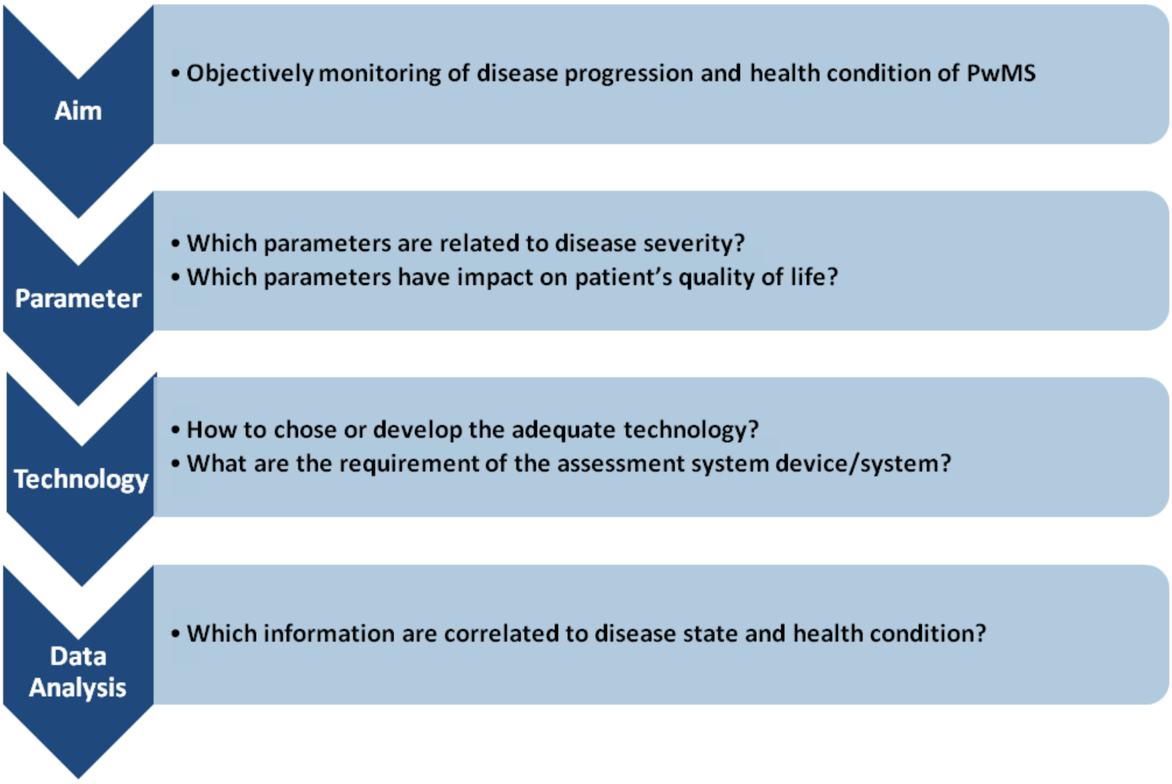



Figure 5-1: Main steps of an objective monitoring system of health condition of PwMS

For the selection of the parameters relating to MS, it is crucial to understand which symptoms are particularly common in MS and mostly influence the quality of life of PwMS. According to the World Health Organization, impairment is defined as an abnormality of body or organ structure of function whereas disability is defined as a global health picture related to a reduction of a person's ability to perform a basic task [140]. In MS, approx. 80 % of the patients suffer from fatigue and muscle weakness and spasticity at the early stage of the disease. These symptoms have been considered to be the underlying causes of patient's disability to perform their normal daily activity and to tend to be less active than people without MS. This inactivity considered to be an important factor that negatively affects the patient's quality of life. Multiple studies showed that the patient's quality of life is hardly affected by motor and coordination disturbance and reported a high correlation between activity and gait parameters and EDSS score. Hence, physical activity and walking ability can be considered as an important source of clinical relevant information. Therefore, the observation and quantifying of these parameters might provide an important tool to draw conclusions on patient's health condition and support in clinical decision making. Thus, the monitoring system should be able to derive and analyze the daily activity and gait data.

In addition to data acquisition and processing, which is essential for extracting the important information, an adequate visualization of the information to the end-users is highly required in order to reveal insight and knowledge about the overall fluctuation and progression of the disease. Therefore, the daily collected data must be transmitted to a platform where the analysis is automatically performed and a report about the daily activity and gait information is generated. Using this report the physician should be able to obtain a comprehensive picture about patient's health condition and disease course. Consequently, deterioration can be early detected and signaled to the physicians, who in turn can adjust and optimize the therapy. Most people diagnosed with MS known very well about their disease and are interested in their current health condition and disease progression. Therefore, besides physicians, patients are also interested in having feedback about their daily activity and walking behavior. Taking all the above mentioned points into account, the following principle system component were determined (Figure 5-2)

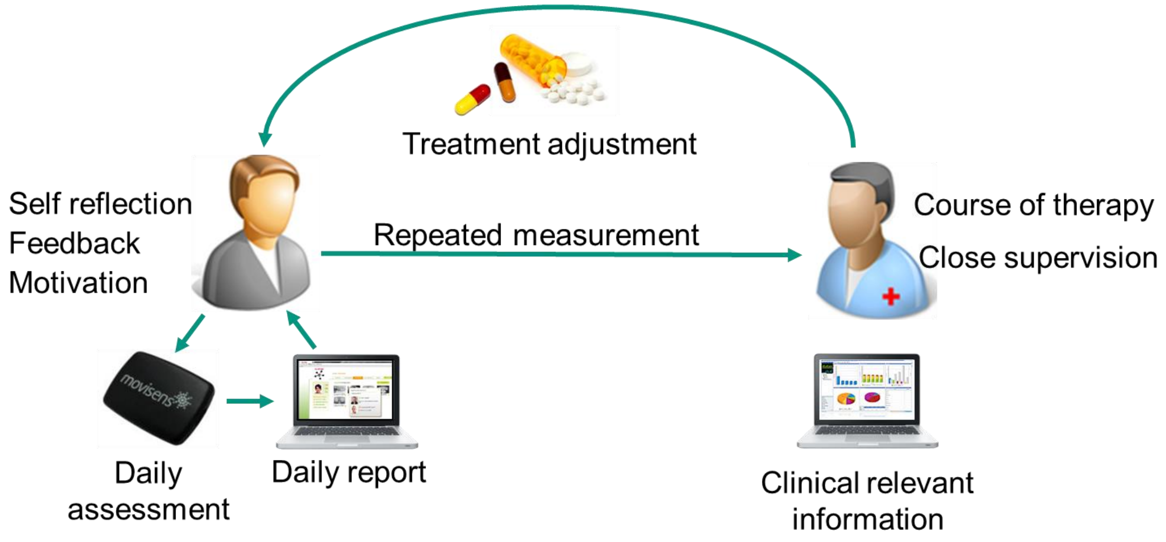



Figure 5-2: Principle system component

The system components illustrated in the figure are:

- Motion sensor: To assess data related to activity and walking behavior of the patients in their free-living environment.
- Data processing: The daily data collected should be daily transferred into PCs and saved. Comprehensive algorithms for feature and parameter extraction should be implemented.
- Visualization: The extracted parameters should be presented and visualized to the physician to provide them with an insight into mobility and walking behavior of the patients. They should enable recovery process assessment, detection of gait abnormalities that may indicate the onset of diseases progression and capturing of the slightly changes in mobility behavior in absence of clinical disability. This could help to develop an appropriate treatment intervention.
- Feedback: Patients should be able to receive feedback on their current measurements. This feedback should give them an overview on their daily activity and motivate them to contribute in the management of their MS by staying active or become more active.

## 5.2 Requirements of the Measurement System

The system is to be used for the aim of daily assessment of physical activity and gait parameters in PwMS who are able to walk without assistance (EDSS 1-5). In the medical field not only medical and technical requirements should be taken into account, but also ease of use and efficiency aspects have to be considered.

The two main end-users of this system are: a) patients with restricted mobility and walking ability, b) physicians who aim to objectively monitor and support the patients in their free-living environment and response, when necessary, in a timely manner. Therefore, the requirements of the patients and the physicians had to be analyzed. Workshops and interviews were conducted with patients and professional staff in the neurological clinic of Bad Neustadt, Germany. Feedback from patients and physicians was captured and analyzed. The following requirements were then determined:

- The motion sensor must not interfere or disturb users while carrying out their free-living activities. Furthermore, the usage of the sensor should be possible without much effort.
- For the diagnosis, no immediate data analysis is required and thus no immediate data transfer is needed. Therefore, the trade-off between online data transmitting and battery life of the sensor reveals that the battery life should be considered as an essential requirement. The battery life should be adequate for the ambulatory assessment scenario. That means, the motion sensor should be able to capture data as long as possible with no need to be recharged, which ensure the comfortable usage of the sensor.
- In order to get reliable activity and gait information, data from at least 4 days have to be collected. However, in ambulatory scenarios it is important to assess data from weekdays as well as weekends; therefore, the sensor should be able to capture data for long period of time (> 1 week).
- For offline analysis a flash (non-voltage) memory, i.e. SD cards allow stand-alone operation and thus there will be no need for a host system or online data transmission. This is very important in term of battery life increment.
- The data should be comprehensive analysed and detailed information about activity intensity, walking ability and abnormalities must be provided. Furthermore, the relationship between the extracted parameters and the health score should be analyzed.
- Even if the sensor is able to capture data over long time, the system should allow daily data storage to ensure the availability of these data. Sensor management charging should be taken into account while developing a long term monitoring system. The physicians should be able to monitor and manage all patients' measurements with less time consumption and technical effort. Therefore, for the aim of data

collecting, managing and analyzing two different end-user software should be developed.

**Motion sensor:** Several motion sensors were analyzed. Different technologies can be used in health care scenarios to capture activity and gait parameters. However, the choice of the adequate device should take several factors into account. First of all, the device should be able assess information about overall human activity, deterioration in gait characteristics and to detect gait abnormality. Additionally, it must be possible for the patient to use the device easily by oneself at home, thus the device should have high usability. Power consumption is an important factor while considering the fact that the system should realize long term observation. The system should be used in an ambulatory home care scenario and should be able to collect information about free-living activities of the patients. Therefore, the motion sensor needs to be wearable without disturbing patient during their everyday activities. Table 5-1 summarize the different main technologies for ambulatory gait analysis.

Table 5-1. Comparison of main technologies for ambulatory gait analysis

| Device | Activity Score | Usability | Power consumption | Wearability |
|---|---|---|---|---|
| Pressure sensor | + | - | + | + |
| Gyroscopes | + | + | - | + |
| Electorgoniometers | - | - | + | - |
| Accelerometers | + | + | + | + |

According to this analysis, accelerometer appears to be the best choice for objectively movement assessment and analysis of PwMS.

**End-user software:** Regarding the developed software, the interviews with physicians and patients revealed how the data from new patients as well as the ongoing measurement should be processed. Which type of information should be delivered to and/or assessed in the clinic. Thus, the following requirements were derived from the professional staff:

- Provide clear overviews on the patients are monitored, with clear indication about how long he/she has been monitored.
- Provide a visual representation of where each patient is in the measurement process, determine which tests are ordered and when.

- Recode which measurement is reported, and which contains critical results.
- Ability to provide reports about each day of each measurement. Furthermore, a complete report about the whole measurement of each patients.

Questionnaires and Feedback from patients were analyzed and the following system requirements were revealed:

- Provide overview about the process and information about their measurement.
- System should provide them with feedback about their daily activity. This feedback was considered as a motivation factor.
- The system should be robust and easy to use without any special technical experiences. Furthermore, problem with the motion sensor should be clearly signaled.

By choosing an adequate accelerometer, develop comprehensive activity and gait analysis algorithms and design an appropriate assessment system it will be possible to realize the aimed home-based measurement system that fulfill the above mentioned requirements.

## 5.3 Concept and Implementation

This section presents the conception of the developed Home-based monitoring system. This system provides to clinical staff a powerful decision support tool and to patients a robust health evaluation and monitoring system, which feedback them with their medical and health information. The main contributions of the systems are:

1. A comprehensive activity and gait monitoring system to recognize disease progression and detect changes in health status.
2. Robust and simple mechanism, which inform patients about their actions and motivate them to active contribute in the management of their disease.
3. An objective monitoring and health care tool, which assist physicians to design patient-specific treatment and to optimize this treatment when needed.

The system consists of three subsystems: the motion sensor, Patient-Unit and Physician-Unit.

The motion sensor attached to the patient's body. It enables the gathering of patient's daily physical activity and gait parameters through the continuous recording of the acceleration signals. The selection of the adequate accelerometer is discussed in section 5.3.1. The Patient-Unit consists of an EeePC on which the Patient-Software is installed. This software is mainly responsible for the raw data storage, sensor recharging and feedback daily reports generating. The Physician-Unit is located at the Physician's office or the clinic. It consists of personal computer Physician-PC, on which the Physician-Software is installed. This Unit is responsible for all patients' data processing and assisting the physicians in capturing the slightly changes in the health status and classifying the responses of the patients to the intervention. Patients' data are restored on the Physician-PC and further knowledge and parameters are generated so that the physicians are informed about abnormal situation and patient's health condition. Thus, in case of abnormalities the physicians will be able to modify the treatment or trigger alarm situation. The main components of this unit are:

a) Patients' record management.

b) Measurement management.

c) Comprehensive data analysis and reports generating.

### 5.3.1 Accelerometer Selection

There are different types of accelerometer on the market section 4.4.4. These devices differentiate from each other in term of their technical specifications. One of the important specifications is the number of the axes. The sensor should be able to sense the components of the body movement in the all three directions. Therefore, a triaxial acceleration sensor was chosen.

One of the key points to measure human acceleration is to understand the motion of the human body and to define which physical property is wished to be measured. This is necessary to choose the right accelerometer placement. The signal of an acceleration sensor attached to the human body consists of three base components: the static acceleration of gravitational field, the acceleration component due to bodily motion and spurious accelerations; such as artifacts due to vibration caused by other sources. However, the first two components are connected directly to the physical activity and gait, whereas the third component presents noise in the signal and can be minimized by using the right signal filtering and through carefully chosen sensor placement. Various sensor placements have been used to assess gait over the years (e.g., [12], [13]).

The position at which an accelerometer is placed in the body is an important consideration in the measurement of body movement. The placement position has large variety including and not limited to chest, fore head, ankle, hip, thigh, wrist. Normally the sensors will be attached to the part of the body whose movement is being studied. For example, to investigate the movement of the leg during walking the sensor is attached to the ankle and shin. The sensor in this work was used to assess the patient's physical activity and gait data in their free-living environment, and thus the placement of the sensor should not interfere with the patients' everyday activity. Measures of trunk acceleration have shown to be sensitive to age- and disease-related gait changes [141]. Therefore, the trunk sensor position has been considered as an indicator of the motor control of walking. Hip placement showed in different studies higher accuracy and user acceptance in ambulatory activity monitoring and best performance predicting speed in Comparison with wrist, thigh and ankle placement [142]. Therefore, the placement position on the hip was chosen.

To measure the human everyday activity and gait, the measurement system employed must be able to measures up to the desired frequency. Generally, acceleration signals were found to increase in magnitude from the head to the ankle. The frequencies of the human free-living activities, such as; walking, running, climbing stairs range between 0.25 Hz and 20 Hz [143]. Similar as for the frequency, the amplitudes of the signal involved in locomotion are lower at the head in comparison with the signal measured at the low back. The amplitude of the acceleration signal assessed at the ankle has the highest value. For example, during jumping the absolute vertical peak accelerations measured at the head ranges between 3.0-5.6 g, whereas it varies between 3.9-6 g at the low back and between 3.0-7.0 g at the ankle. This leads to the conclusion that, if the sensor is to place on the hip the measurement range of ±6g should be sufficient. However, experimental data suggest safe amplitude limits for the sensor hardware that is used to capture acceleration data during running and similar type of application. For a sensor attached at the torso or hip a range of ±8g is recommended.

*Move II* was the only acceleration sensor on the market which fulfills the previous mentioned requirements (e.g. number of acceleration axes, battery life, data transfer and storage). The measurement unit consists of a tri-axial acceleration sensor (adxl345, Analog Device) with a measurement range of ±8 g, a sample rate up to 128 Hz and a resolution of 12 bit, and an air pressure sensor (BMP085, Bosch GmbH) with a sample rate of 8 Hz and a resolution of 0.03 hPa. The sensor weights 32 g has the dimensions of 3 cm × 5 cm × 2 cm, and can be carried at different body positions (hip, wrist or chest). The acceleration signal can be recorded up to 30 days and saved on a 2 GB micro SD card. The recorded raw data can be transferred to a computer by USB 2.0 interface. Figure 5-3 shows the block diagram of the measurement unit.

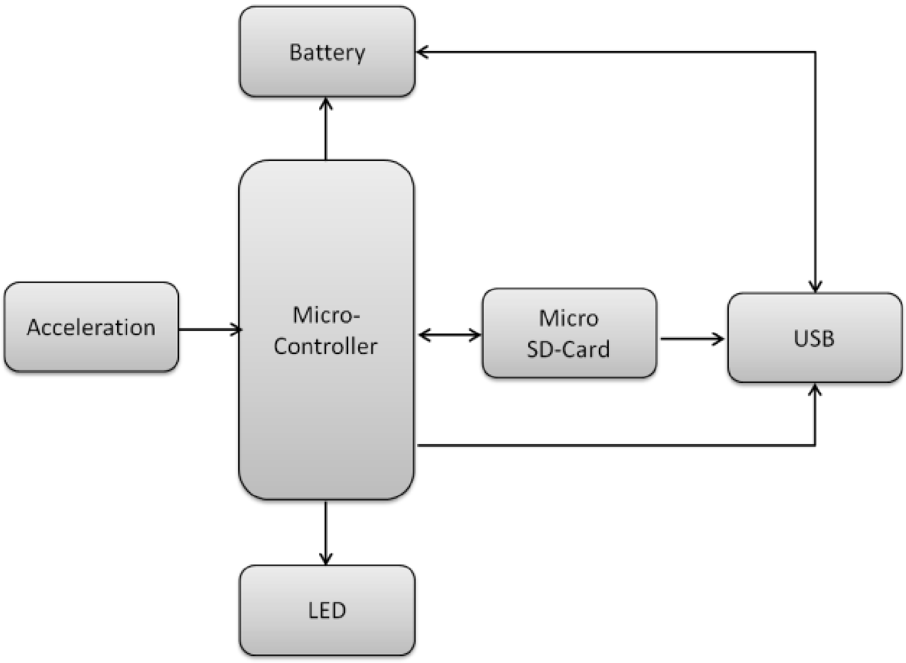



Figure 5-3. Block diagram of the triaxial acceleration sensor (*move II*) (modified)

The acceleration raw data assessed by the measurement unit (acceleration sensor) were transmitted via the USB interface to a local laptop or computer. As illustrated in Figure 5-4 Matlab was used for the aim of data pre-processing, analysis and development and evaluation of the algorithms.

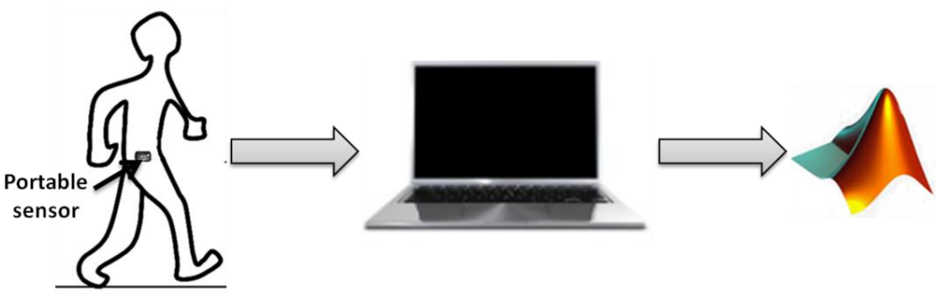



Figure 5-4. Data collection and processing

### 5.3.2 System Architecture and End-User Software

To realize the daily data assessment and analyzing over a long period of time a corresponding software platform was developed for Physician-Unit and Patient-Unit. This section introduces the system architecture and the software framework. The requirement according easy use with no especial technical skills was highly considered during the development.

System activity diagram shown in Figure 5-5, gives an overview about the usage process of the system. A measurement carried out with this system consists of three phases; Begin Phase, Measurement Phase and End Phase. In the *Begin Phase*, measurement's parameters will be determined (e.g. measurement time) and the measurement will be started. Based on the measurement time, the life cycle (measurement begin and measurement end) of each measurement will be defined. *Measurement Phase* is the core phase in the daily acceleration data are generated and collected. These data are collected over a period of time that is defined in the *Begin Phase* (measurement time). The *End Phase* is the last phase of the measurement cycle in which the system is returned, data are transferred to the physicians PC, comprehensive analysis of the data is performed and a report about the activity behavior is visualized.

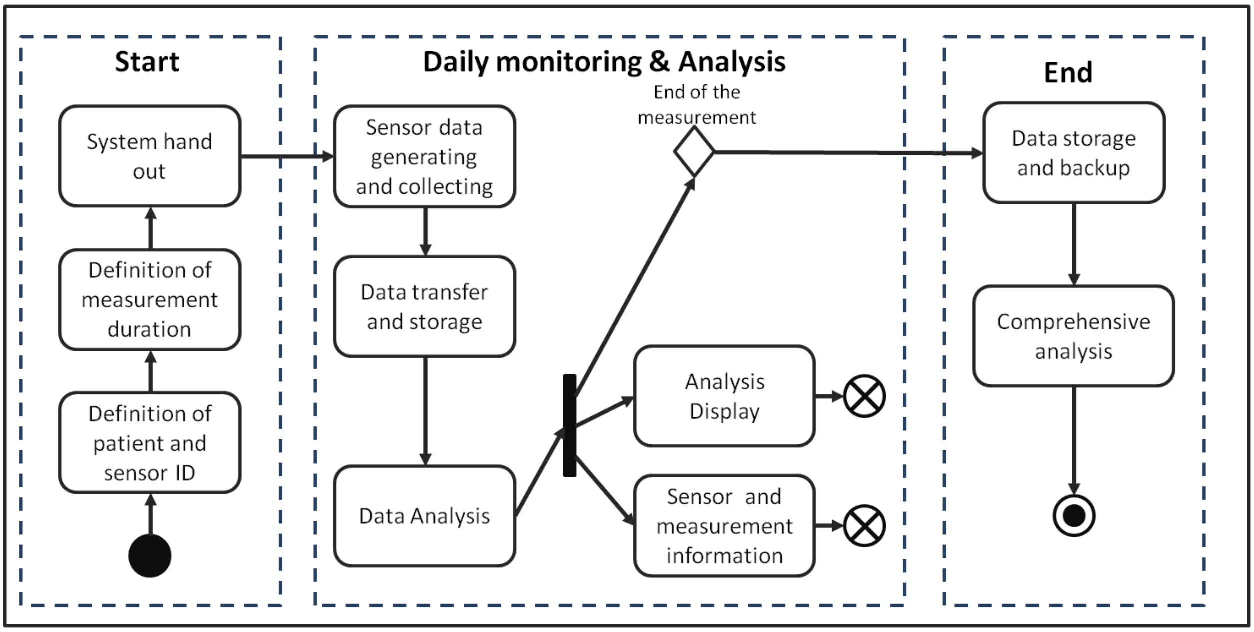



Figure 5-5. System activity diagram

**Measurement Configuration and Process:** Configuration process started by the physician, where the Sensor-ID and Patient-ID are interred and connected to each other (Figure xx). Sensor will be configured, in which the start and end time of the measurement are defined. Furthermore, sensor will be attached to the

EeePC so that the latter will be assigned to this specific sensor along the measurement time, i.e. the sensor is assigned to the EeePC. Based on this assignment system will control the sensor attached to the EeePC, and in case of differences, no data transfer will be possible. This information (i.e. Sensor-ID, EeePC-ID and Patient-ID) are saved in the measurement configuration. EDSS-value of the patient will be captured and stored for the analysis.

*Measurement data*: Is the event where the Sensor-ID, Patient-ID and EeePC-ID are given and saved in the system. Furthermore, the measurement time is defined.

*Sensor attached to the EeePC*: Is the event where the measurement time and Sensor-ID are automatically configured on the EeePC.

*Measurement start:* After having measurement time and Sensor-ID configured on the EeePC, the daily measurement can be started. During this event, the Patient-Software transfers the data to the EeePC and generates a daily report. When achieving the end time, the measurement will be ended and the configuration of the EeePC are automatically reset and wait for the new measurement configuration.

Data collected using the above-described system were analyzed, filtered and processed to derive clinically related information associated with activity and gait characteristics of PwMS.

**System Architecture**: As it was aforementioned, there are two different end-user software; Patient-Software (Figure 5-6) and Physician-Software (Figure 5-8)

Patient-Software is installed on the EeePC and consists of three components *Patient Interface*, *Patient Controller* and *Patient Model*.

Patient Interface: This component is responsible for the display of measurement information (i.e. checking measurement schedule, how long did the measurement last) as well as sensor-related information (e.g. sensor data will be copied, senor will be recharged). This information will be passed to this component from Patient Controller component. Furthermore, this interface is dedicated to display the daily activity report. The analyzed data will be also passed from the Patient Controller component.

Patient Controller: This component is dedicated for the measurement and sensor control. It is the intermediate between the motion sensor and the Patient-Software. A Subcomponent of the Patient Controller is the Sensor Manager, which enables the access to the sensor device. For the very first time when the sensor attached to the EeePC Sensor Manager reads the main measurement configuration, i.e. sensor-ID and measurement duration. This information will be automatically passed to the Patient Controller. Hence, in the successive times when the sensor is attached, this information will be checked by the Sensor Manager. This ensures that the right patient's activity data are saved on the right EeePC. Furthermore, the Sensor Manger reads sensor data and passes it to the Storage Manager to be saved on the SD card. Another subcomponent is the Config Manager, which is dedicated to store sensor and measurement configuration data. The third subcomponent is the Analysis Manager. This component accesses the raw data and performs the analysis. Patient Controller component passes the analyzed data to the Patient Interface. Furthermore, it informs the Patient Interface component about the loading state of the sensor as well as the measurement state.

Storage Manager: As it was mentioned before, the sensor is able to capture data for 1 week, however, the sensor might be defect or the memory could be full. Therefore, the data should be daily stored on the EeePC and deleted from the sensor. The component Storage Manager is responsible for the raw data save on the SD card of the EeePC. When the data are saved, this component deletes it from the sensor. As soon as the data have been transferred to the SD card Storage Manager informs the Analysis Manager component, so that the latter can perform the analysis.

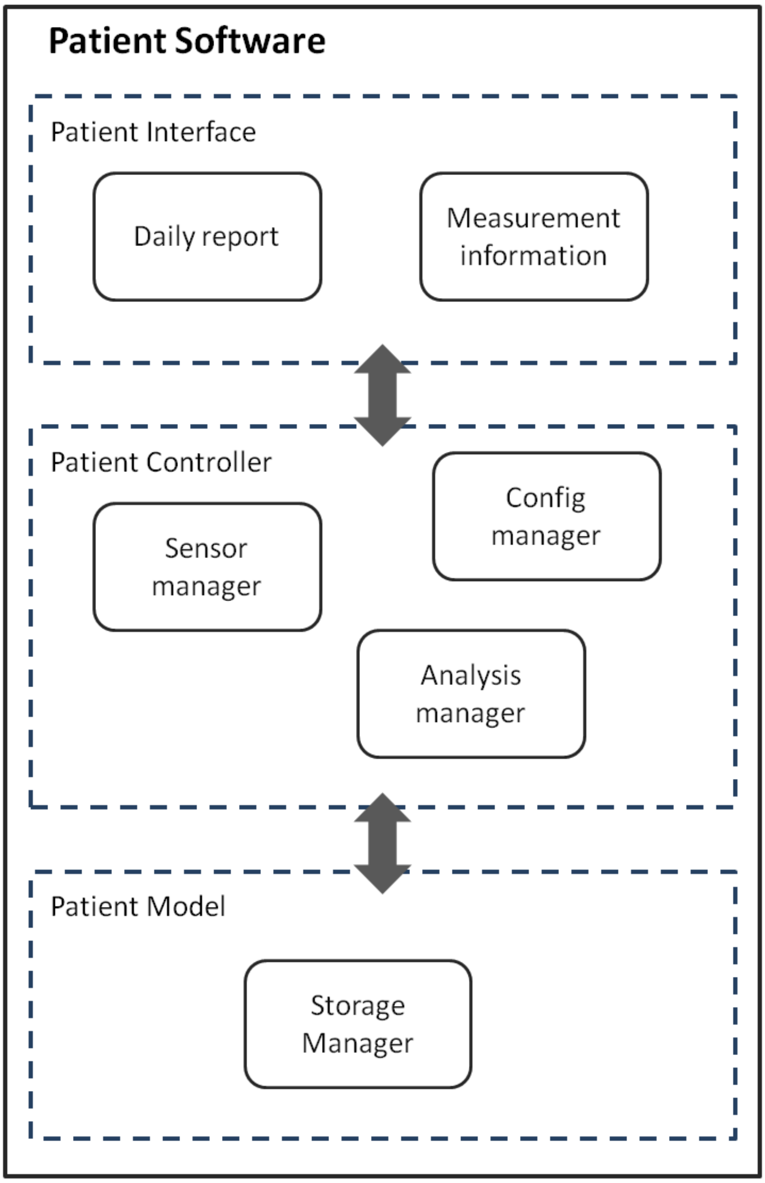



Figure 5-6. System architecture- Patient-Software

The Patient Graphical User interface is developed to be simple without interaction of the patient. The designed interface starts automatically when the EeePC is turned on. As soon as the EeePC is turned, the Patient-Software will automatically start. After having the sensor attached, data will be automatically transferred and saved on the SD card, and the sensor will be recharged. Patients can use this interface to get their feedback about their daily activities. The main functionalities of the patient interface are:

a) Display the measurement's information and measurement's schedule.

b) Illustrate information about sensor and data storage status.

c) Display the analysis results.

The EeePC is automatically shut down as soon as the data are saved, analysed and the sensor is fully recharged.


Figure 5-7. User Interface - Patient-Software

For the physician a Physician-Software was developed and installed on the Physician-PC. This software is dedicated to assess the physician in monitoring patient's activity and walking behavior in their free-living environment. Similarly, to Patient-Software, Physician-Software consists of three main components:

Physician Interface: This component gives the information about patients, measurements and sensors (in use and available). Furthermore, Physician Interface is responsible for the analysis display of the completed measurements. Patient-related information (e.g. name and EDSS) as well as measurement-related information (begin and end) will be passed from this component to the Physician Controller.

Physician Controller: It can be considered as a core component of the Physician-Software. Physician Controller is responsible for measurement configuration. This can be done via the subcomponent Sensor Manager, which allows the access to the sensor, where the measurement duration and configuration will be saved. Sensor Manager Component passes the sensor-ID to the Physician Controller and the latter assign this ID and the measurement configuration to the patient-ID. Physician Interface component can then request this information from the Physician Controller. Moreover, Physician Controller component checks if the correct sensor is attached, then it transfers the data from the SD card and passes it to the Storage Manager. Otherwise, the transfer will not be possible, and an error message will be displayed. After having the data saved, the access to the Analysis component will be allowed, and analysed data will be passed to the Physician Interface to be displayed as well as to the Storage Manager to be saved.

Storage Manager: All captured data will be saved on the Physician-PC in order to have more detailed analysis and better assessment of the patient's motor and health status. Storage Manager is responsible for data storage on Physician-PC. This component gets the assignment information from the Physician Controller so that the right sensor data will be saved and assigned to the right patient. Furthermore, this component is responsible for store all patient-related, measurements and analysis information.

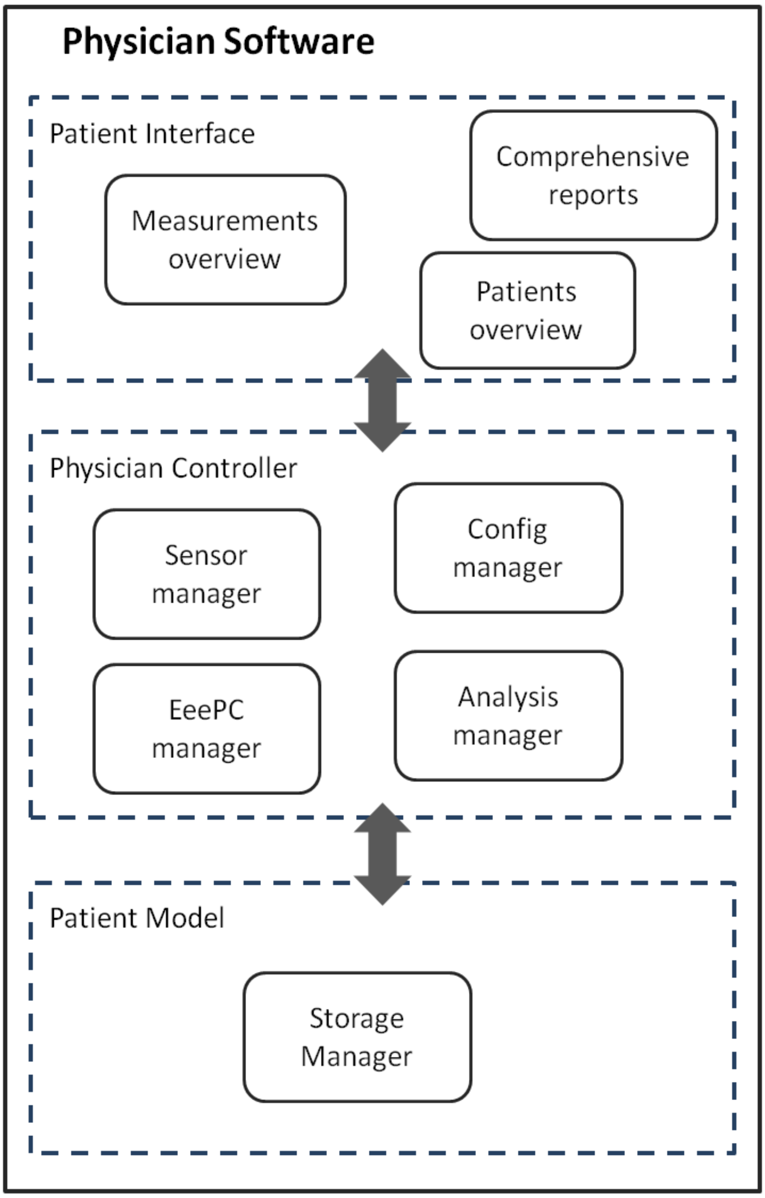
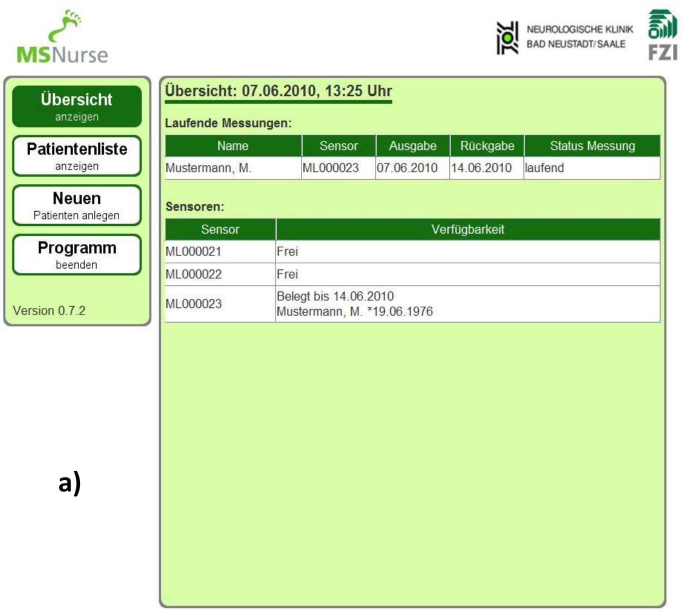



Figure 5-8. System architecture- Physician-Software

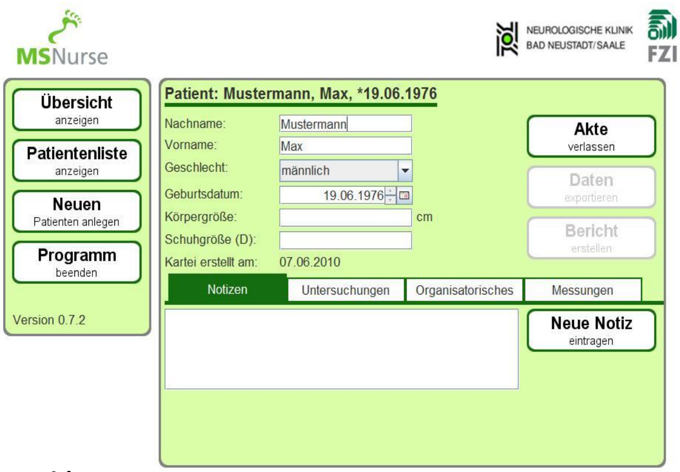
The physician user interface was developed to help physicians for manage and monitor patients' daily measurements. The key functionalities of this interface are:

- Patients Overview: This view displays all running measurements and the sensors (the one in use and the available one) (a)
- Adding new patient: Before the new measurement can be started, a new patient record should be generated. This functionality allows the physicians to inter patient-related information, define measurement configuration and assign a certain sensor to the specific patient. If the patient already exist, then the patient record can be opened and a new measurement can be started. (b)

- Starting new measurement: In this step the Patient-ID, Sensor-ID will be defined. Measurement configurations will be determined and the EDSS Scale of the patients will be captured and saved. (c).
- Open and requesting information from a certain patient: This functionality allows the physicians to search for a certain patient in the patient database and e.g. measurement process and/or analysis information of a specific measurement day. Furthermore, the ongoing measurement can be stopped or canceled. The 10-meter test shown in the figure was especially developed to collect reference data for developing the algorithms of activity and gait parameter (e.g. asymmetry)
- End measurement: to terminate the ambulatory measurement.
- Extracting sensor data and Analysis: After terminating the measurement, sensor data will be transferred to the Physician-PC, and then the analysis will be performed. Physician can display information and report about each measurement day as well as a complete report about the whole measurement. (d). Example of the extracted report is shown in (e)




a)

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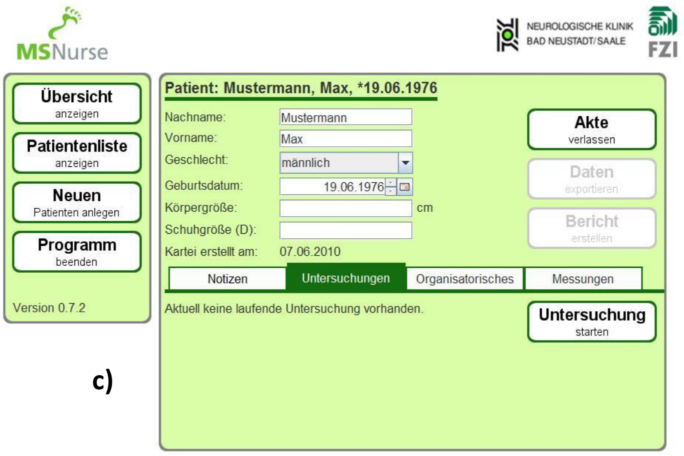

MSNurse
NEUROLOGISCHE KLINIK BAD NEUSTADT/SAALE
FZI
Übersicht anzeigen
Patientenliste anzeigen
Neuen Patienten anlegen
Programm beenden
Version 0.7.2
Patient: Mustermann, Max, *19.06.1976
Nachname: Mustermann
Vorname: Max
Geschlecht: männlich
Geburtsdatum: 19.06.1976
Körpergröße: cm
Schuhgröße (D):
Kartei erstellt am: 07.06.2010
Akte verlassen
Daten exportieren
Bericht erstellen
Notizen
Untersuchungen
Organisatorisches
Messungen
Aktuell keine laufende Untersuchung vorhanden.
Untersuchung starten

c)


MSNurse
NEUROLOGISCHE KLINIK BAD NEUSTADT/SAALE
FZI
Übersicht anzeigen
Patientenliste anzeigen
Neuen Patienten anlegen
Programm beenden
Version 0.7.2
Patient: Mustermann, Max, *19.06.1976
Nachname: Mustermann
Vorname: Max
Geschlecht: männlich
Geburtsdatum: 19.06.1976
Körpergröße: cm
Schuhgröße (D):
Kartei erstellt am: 07.06.2010
Akte verlassen
Daten exportieren
Bericht erstellen
Nachricht
Die Daten wurden erfolgreich übertragen.
Die Speicherkarte wurde geleert.
OK
Messungen
Beginn:
Ende:
Gewicht:
Gleichgewichtstest: ---
MSFC: ---
EDSS: ---
Motorik (Ashworth): ---
Fatigue: ---
Ambulationsindex: ---
10m-Gehen Messung neu starten
Alltagsaktivität Messung neu starten
Untersuchung beenden
Untersuchung abbrechen
Messungen:
10 10 10 A A A
07.06.10 07.06.10 07.06.10 06.04.10 08.04.10 08.04.10

d)

e)

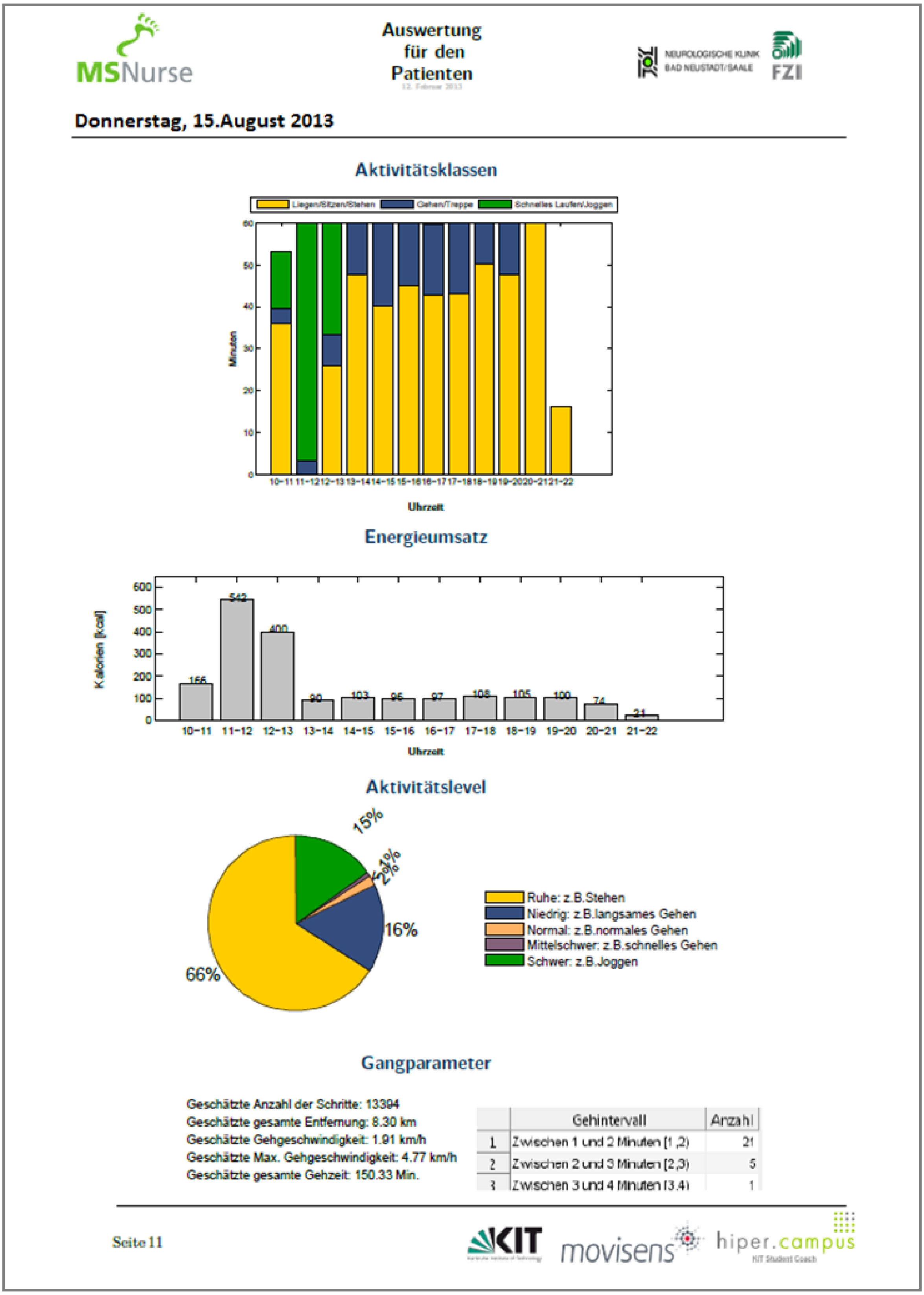



Figure 5-9. User Interface- Physician-Software

## 5.4 Development of gait parameters in time, frequency and time-frequency domain

As previously discussed in section 2.3, activity and gait disturbance are the most common symptoms in patients with multiple sclerosis. In this work, features in time, frequency and time frequency domains were explored.

Walking speed and cadence are widely considered in healthcare researches as a predictor of e.g. disability and falls. Daily steps count has been shown to be related to different clinical measures; such as balance, fatigue. Therefore, gait parameters such as walking speed and steps count were investigated in this work to capture the changes in health status of the PwMS. Furthermore, Increasing disability and symptoms may prevent PwMS from participating in physical activity and different studies include patients with mild, moderate and sever disability showed that increased level of disability is associated with decreased level of physical activity performance (metabolic equivalent [MET]) [144]. Typically, the symptoms of MS are likely to be dominant on one side. Thus, gait asymmetry can be a direct consequence of abnormality and could be increased as result of degeneration of health status.

Moreover, comprehensive analysis of gait feature in frequency and time-frequency domain can provide complementary information to understand gait patterns and can possibly be used to identify changes in gait parameters. Therefore, additional parameters such as; peak frequency and energy concentration were investigated in this thesis. Figure 5-10 illustrates the approaches along with the gait features were extracted and analyzed.

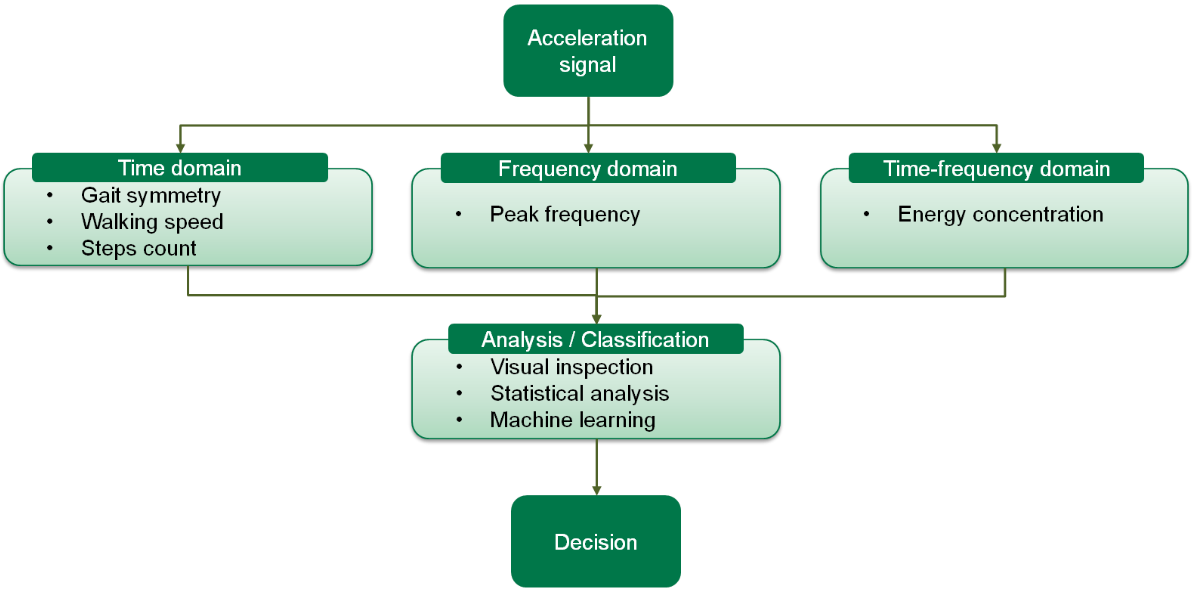



Figure 5-10. Approaches for gait features extraction and analysis

The assessed parameters were used to objectively capture the slightly changes in gait characteristics and classify the response to medical therapy. In the following the algorithms developed to extract different signal features in time, frequency and time-frequency domain will presented.

### 5.4.1 Walking speed

Walking speed is widely reported measures in clinical setting. It is a reliable, valid measure and considered to be a good indicator of gait performance. Therefore, it is often included in clinical research studies. The objective here is to develop a system to capture walking speed of PwMS in their everyday life using one tri-axial accelerometer placed on the hip. In this work a support vector machine (SVM) was implemented. Unlike other methods (e.g. activity count, neural network) SVMs can deal large-scale training data without a large amount of learning time, they are less prone to over fitting and needs less memory to store the predictive model. Furthermore, they are less sensitive to between-subject biomechanical. Based on the developed algorithm the changes in daily walking speed of multiple sclerosis patients were assessed.

Different studies used accelerometer to extract walking speed in free-living environments. Some of those systems used multiple accelerometer devices attached to chest, thigh and forefoot to capture walking speed [145]. However, such systems have low user's acceptance and therefore are not suitable for long-term monitoring. The most common method to estimate walking speed from accelerometers is the measure of activity counts (ACs). Due to its sensitivity to between-subjects biomechanical this method suffers from poor accuracy. Machine learning methods, such as artificial neural network (ANN), have been also applied to detect walking speed. The main drawback of the ANN-based methods is their dependency on large amounts of training time and data and the complexity. Other researchers decided to use predefined human gait model. This method does not require subject-specific training phase. Nevertheless, the accuracy in such methods depends on the validity of the model. Furthermore, subject-specific anthropometry must be measured in order to build the model, which requires additional efforts.

#### *5.4.1.1 Dataset*

Data from two different studies were used to train and evaluate the gait speed estimation model (Indoor and Outdoor studies) [145]. In the indoor scenario 17 individuals were asked to carry out different activities (sitting, standing, walking, etc.). During all the activities an accelerometer (section 5.3.1) was attached to the hip. The raw data captured with sample rate of 128 Hz. For the development of walking speed estimation algorithms, activities as walking and jogging were considered. Individuals walked along a predefined walkway in a circular indoor track at three different walking speed; normal (NWS), fast (FWS) and Jogging (JOG) (approx. 1.33 m/s, 1.55 m/s and 2.22 m/s), respectively. They walked 3 minutes for each speed. The speed was controlled using an audible signal to set up the walking speed rhythm. Furthermore, participants walked on treadmill where the speed was defined for each activity. In the outdoor study twenty individuals have participated. In order to simulate situations similar to those in the free-living environments participants were constructed to walk an outdoor predefined distance at three self-selected walking speed (NWS, FWS and JOG). The distance in the case of NWS and FWS was 415 m and for JOG was 830 m and the time needed for the individual to cover the distance was noted. The acceleration signal in were also captured via accelerometer (section 5.3.1) attached to the hip and with sample rate of 64 Hz. Individuals' characteristics are shown in the table below (Table 5-2).

Table 5-2. Individuals' characteristics

| | Males (N=24) | Females (N=13) | All subjects (N=37) |
|---|---|---|---|
| Age (yrs.) | 31.63 ± 9.67 | 31.00 ± 8.51 | 31.41 ± 9.29 |
| Height (m) | 1.79 ± 0.07 | 1.67 ± 0.04 | 1.75 ± 0.08 |
| Weight (kg) | 82.70 ± 12.06 | 65.09 ± 9.00 | 76.51 ± 13.91 |
| BMI (kg.m-2) | 25.83 ± 3.04 | 23.36 ± 2.99 | 24.96 ± 3.24 |

#### *5.4.1.2 Development of the SVR estimation model*

The only input of the algorithm is the acceleration signal captured from the sensor attached to the hip. Walking speed cannot be simply estimated by integrating the acceleration signals. First of all, the acceleration signal consists of not only from body acceleration but also of static acceleration of gravitational field and artifacts acceleration. Secondly, the accelerometer drift grows proportional to the square of the time resulting in large inaccuracies in the estimation. Therefore, both gravity acceleration and noise were eliminated with a Butterworth high-pass filter (cut-off 0.2 Hz) and Butterworth low-pass filter (10 Hz), receptively. For the analysis the vertical axis was extracted. Then the overlapping sliding windows, each of 3 seconds interval, was performed. (Figure 5-11).

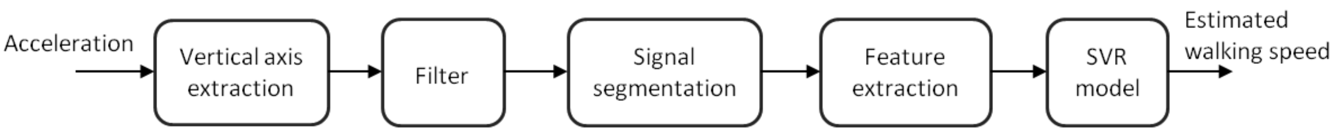



Figure 5-11. SVR estimation model

Each segment was then presented as a vector of different features. These features were used to train and evaluate the SVR regression model. First of all, the feature signal energy ($e$) was calculated. This feature contributes significantly and has a good correlation with walking speed. Therefore, this work considers this feature as the main feature and combined it with other features to increase the accuracy. After that, the variance ($var$) of the vertical axis and the difference between the minimum and the maximum acceleration ($Amp$) of the vertical axis were calculated for each segment. In time domain features extraction, the variance is a good measure of the spread of the signal around its mean. However, this feature could be affected by the number of steps were taken, therefore, for the 3 seconds segment the variance for each 0.1s was derived and the mean value was calculated. The feature $Amp$ of the vertical axis is known to be strong correlated with the walking speed (Figure 5-12) and also is independent from the number of steps within the considered segment. Furthermore, Fast-Fourier-Transformation was applied to determine the maximum signal frequency and its corresponding position in time domain. Due to small windows interval of 3 seconds (Figure 5-13), zero-padding was performed so that more precise frequency localization will be possible.

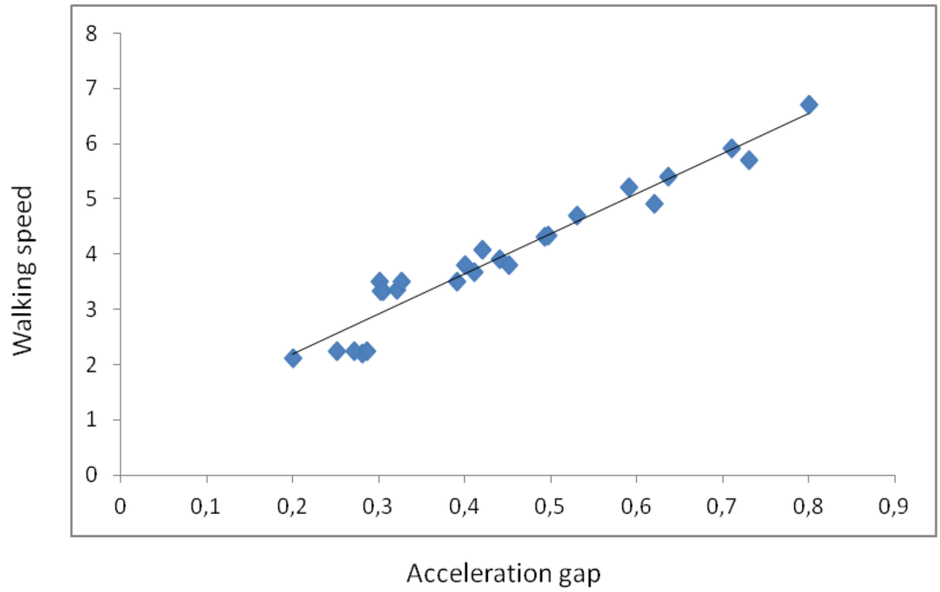



Figure 5-12. Correlation between acceleration gap and walking speed

The following features have been extracted:

**Energy** $(e)$: Is the signal energy for all three axes; where $(x_i, y_i\ and\ z_i)$ are the three axes of the $i^{th}$ segment:

$$e = \frac{1}{N}\sum_{i=1}^{N}\sqrt{x_i^2 + y_i^2 + z_i^2} \quad \text{Eq.5-1}$$

**Variance** $(var)$: The variance of the vertical axis $(y)$

$$var = \frac{1}{N}\sum_{i=1}^{N}\left(y_i - mean\ (\vec{y})\right)^2 \quad \text{Eq.5-2}$$

**Frequency** $(freq)$: The maximum frequency component of the vertical axis $(y)$; where $fft(y)$ is the Fourier transform of the vertical axis and $f_s$ is the sample rate.

$$freq = fft(\vec{y});\ f_s \coloneqq \left|Y(f_s) = \max\left(\vec{Y}\right)\right| \quad \text{Eq.5-3}$$

**MinMaxDiff** $(Amp)$: The amplitude of the vertical axis

$$Amp = max(\vec{y}) - min(\vec{y}) \quad \text{Eq.5-4}$$

**SteplengthTimesFreq** $(v)$: step length multiplied by step frequency

$$v = steplength * stepfrequency \quad \text{Eq.5-5}$$

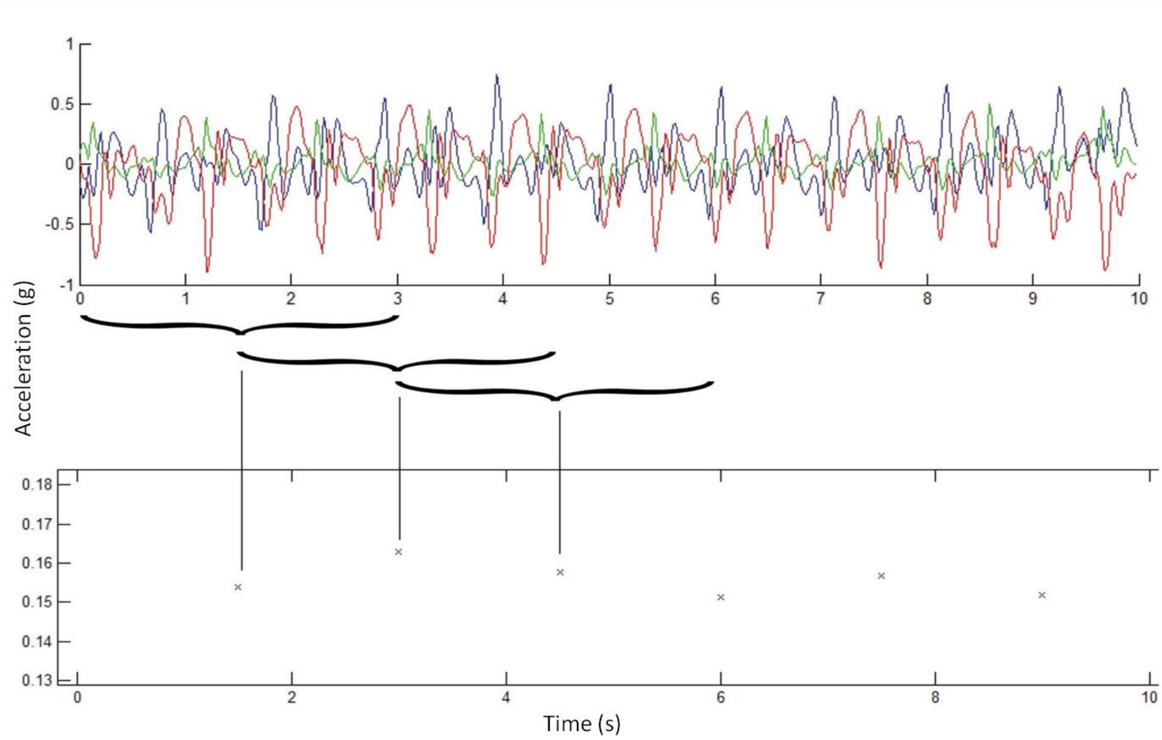



Figure 5-13. Example of feature extraction (energy) for 3 seconds acceleration signals

RBF-Kernel function will be used and this function is spherically symmetric, the extracted featured were normalized as follow:

$$v\vec{f}_{norm} = \frac{\vec{f} - \min(\vec{f})}{\max(\vec{f}) - \min(\vec{f})} \qquad \text{Eq.5-6}$$

where, $\vec{f}$ is the features vector

Three model parameters $(C, \gamma, \epsilon)$ are determined so that the test error is minimal. In this work these parameters are optimized by greedy search and cross validation procedures. From the three parameters 27 different combinations of $(C, \gamma, \epsilon)$ determine possible solutions to be tested. Figure 5-14 illustrates the entire process to select the best feature and model parameters were determined. For each feature combination value of the $(C, \gamma, \epsilon)$ parameters were found. Greedy search approach was used to optimize the model parameters. Greedy search method works in stages. At each step one input value of $(C, \gamma, \epsilon)$ parameters is considered. This particular input will be evaluated and decided whether it gives the optimal solution or not. The optimal solution is the one with minimum square error. After that, the estimation model was build and trained with this set of feature combination and characteristic parameters. Then the model was tested using leave-one-subject out approach.

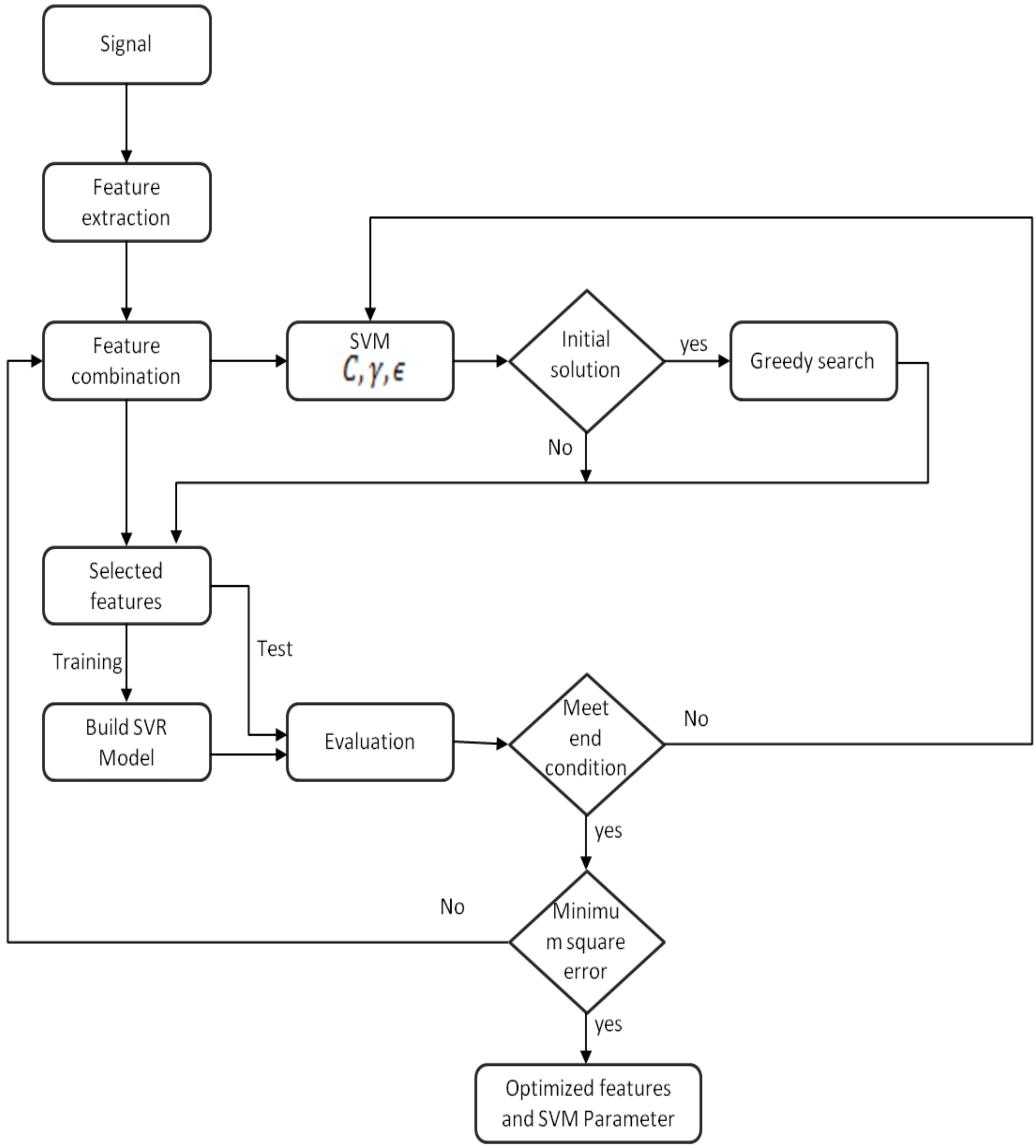



Figure 5-14. Entire process to select features and model parameters

The dataset used in this work includes treadmill walking activity and ground walking activity. Since the walking on treadmill differs from walking on ground the SVR model was trained for the dataset with and without treadmill.

Moreover, two separate SVR models (one for slow and fast walking and one for jogging/running) were trained. The results showed that when using the general estimation model, the mean square error is lower when the complete dataset was included; i.e. dataset with treadmill (RMSE (m/s) = 0.0432) and without treadmill (RMSE (m/s) = 0.0467). Therefore, the complete dataset was used for the evaluation of the speed prediction models (Table 5-3).

Table 5-3. Estimation error of different datasets

| Dataset | RMSE m/s |
|---|---|
| Complete | 0.0432 |
| Complete without treadmill | 0.0467 |
| Jog | 0.0884 |
| Jog without treadmill | 0.0975 |
| Walking | 0.0092 |
| Walking without treadmill | 0.0116 |

Using different estimation models (i.e. general, Jog/running and walking slow/fast models) several features' combinations were tested to determine the best combination with minimum mean square error. The results showed that the feature energy can provide lower mean square error with acceptable svRatio (the number of support vectors divided by the number or training samples) in comparison with all other features combinations (energy: RMSE = 0.043 m/s; svRatio 0.11) (Table 5-4). Therefore, in the forthcoming analysis the feature energy was used.

Table 5-4. Mean square error and svRatio of different feature combinations (General model, Jogging Model and Walking model)

| **Feature** | **RMSE m/s** | **svRatio** |
|---|---|---|
| **General Model** | | |
| $e$ | 0.043 | 0.15 |
| $e\ var$ | 0.045 | 0.13 |
| $e\ steplength$ | 0.046 | 0.14 |
| $e\ Amp$ | 0.049 | 0.13 |
| $e\ freq\ steplengthvar$ | 0.05 | 0.11 |

| | | |
|---|---|---|
| $e\ freq$ | 0.053 | 0.09 |
| $steplength$ | 0.055 | 0.08 |
| $e\ freq\ var$ | 0.06 | 0.11 |
| **Jogging Model** | | |
| $e$ | 0.08 | 0.15 |
| $e\ var$ | 0.11 | 0.22 |
| $e\ steplength$ | 0.116 | 0.21 |
| $e\ Amp$ | 0.108 | 0.22 |
| $e\ freq\ steplengthvar$ | 0.11 | 0.21 |
| $e\ freq$ | 0.12 | 0.21 |
| $steplength$ | 0.21 | 0.19 |
| $e\ freq\ var$ | 0.12 | 0.28 |
| **Walking Model** | | |
| $e$ | 0.009 | 0.07 |
| $e\ var$ | 0.010 | 0.09 |
| $e\ steplength$ | 0.011 | 0.03 |
| $e\ Amp$ | 0.012 | 0.06 |
| $e\ freq\ steplengthvar$ | 0.012 | 0.08 |
| $e\ freq$ | 0.013 | 0.03 |
| $steplength$ | 0.022 | 0.05 |
| $e\ freq\ var$ | 0.014 | 0.04 |

#### 5.4.1.2.1 Validation

Cross validation technique was used to validate the developed SVR model. Leave-one-subject out approach was applied, which is a particular case of leave-p-out subject where p=1. This method involves one observation out of the dataset as validation set and the remaining observations as training set. To quantify the accuracy of the method, the RMSE was calculated as well as the RMSE %. Table 5-5 summarizes the results of the three models (general, jogging and walking) for both indoor and outdoor studies. Both walking and jogging data from both studies were used as input for the general SVR model.

Best results was seen when estimating fast walking speed for both indoor and outdoor studies (RMSE = 0.07m/s, RMSE% = 4.66 and RMSE = 20.04m, RMSE% = 4.82%, respectively) in comparison to jogging (RMSE = 0.22m/s, RMSE% = 10.2; $p < 0.01$ and RMSE = 90 m, RMSE% = 10.8%; $p < 0.01$) and slow walking (RMSE = 0.16m/s, RMSE% = 12.3; $p < 0.01$ and RMSE = 48.4

m, RMSE% = 10.2%; $p < 0.01$) activities. However, using slow/fast model showed higher RMSE and RMSE% values in estimation fast walking speed when compared with the general methods, whereas the results observed for slow walking was better in the outdoor study. The general model showed better results for jogging activity in comparison with jogging SVR estimation model for outdoor study; where as the result for indoor study was better when using the jogging model.

The values of RMSE in the outdoor study using jogging and slow/fast walking model were 78.57m and 23.96m, respectively. In the comparison of speed, the average speed error was 0.16 m/s when using the general model and 0.27 m/s and 0.07 m/s when using the jogging model and slow/fast walking speed model, respectively. The jogging model showed larger absolute and percentage error in comparison to the general and slow/fast walking speed model.

Table 5-5. Mean square error and percentage mean square error of the estimation models

| Dataset | Error | General model | | | Jogging model | Slow/fast model | |
|---|---|---|---|---|---|---|---|
| | | jog | slow | fast | | slow | fast |
| Outdoor study | RMSE (m) | 90 (7.31) | 48.42 (8.7) | 20.04 (3.67) | 78.57 (3.22)$^{**}$ | 23.95 (0.53)$^{**}$ | 26.95 (0.9)$^{*}$ |
| | RMSE % | 10.85 (0.88) | 10.18 (2.1) | 4.82 (0.88) | 9.47 (0.38) | 5.77 (0.12) | 6.49 (0.2) |
| Indoor study | RMSE (m/s) | 0.22 (0.07) | 0.16 (0.12) | 0.07 (0.01) | 0.27 (0,02)$^{**}$ | 0.07 (0.01)$^{**}$ | 0.07 (0.02) |
| | RMSE % | 10.22 (0.4) | 12.3 (9.3) | 4.66 (0.5) | 12.36 (0.79) | 5.5 (0.09) | 4.55 (0.03) |

*Note*: Mean and SD were given. Jog = jogging, slow = slow walking speed, fast = fast walking speed

$^{*}$ = $p < 0.05$, $^{**}$= $p < 0.01$

***Validation with Data from PwMS***: This algorithm was developed to be used for walking speed estimation in PwMS. However, gait pattern and parameters may differ in PwMS from those of healthy individuals. Therefore, the estimation accuracy of the algorithm was evaluated using dataset collected from PwMS. The data was collected from 11 PwMS during the 10-meter walking test where the patient walked along a 10 meter flat walkway forth and back one time at their comfortable speed and the other time at fastest (as fast as possible) but safe walking speed (section 6.1.1.2). Number of steps and the step length were assessed by the clinical staff and the actual distance the patient walked was calculated. Using the walking speed developed algorithm these walking distances were estimated and both RMSE (m) and RMSE% were calculated (0.24 and 0.02%), respectively (Figure 5-15)

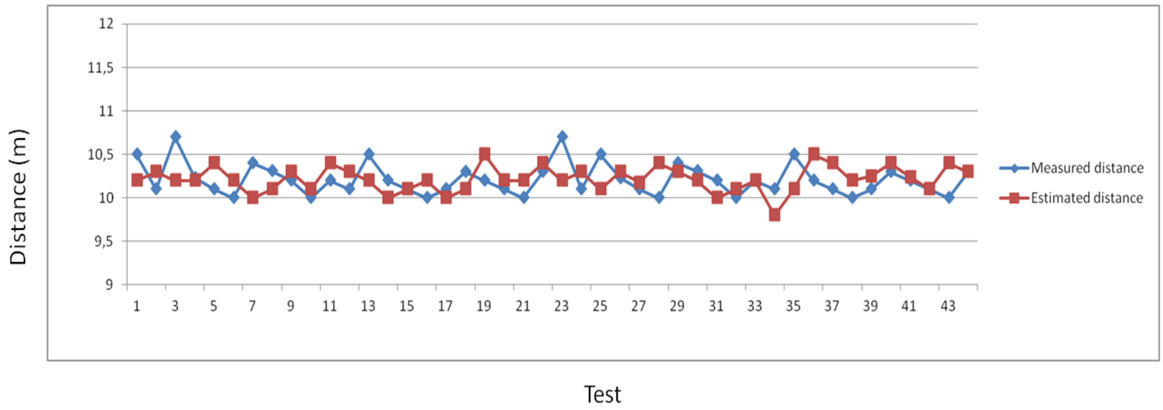



Figure 5-15. Walking speed estimation in PwMS - Clinical test

### 5.4.2 Steps count

#### 5.4.2.1 Related work

There are different methods for step detections used in the previous studies such as; peak detection, flat zone. Step detection typically used peak detection method, which is sensitive to noise and greatly affected by individual walking speed, producing a high rate of false positive. Flat zone detection using acceleration differential is not suitable if only one sensor will be used and the flat zone of the signal will not be detected if the sensor is attached to the waist or hip.

Neural network has been also used for the aim of step detection. This method is accurate especially when it used to differentiate between walking activity and other similar activities. However, it is hardly affected by walking speed, thus in order to get high detection accuracy a big training data for each possible walking speed is needed. Step detection using pressure sensor is considered to be very accurate. Nevertheless, such methods are not appropriate for purpose of ambulatory assessment because a separate sensor integrated in the shoe sole is required. Detection methods based on smart phone have also been proposed, however with limited accuracy of step detection.

Other studies used frequency-based methods such as Fast Fourier Transformation or Lomb-Scargle periodogram.  However, in contrast to time-based methods the frequency-based methods are highly affected by different speed and therefore show low accuracy at low walking speed [146].

#### 5.4.2.2 Development

In this work a step detection algorithm using zero-crossing was used. Using these algorithm steps taken by individuals in their everyday life was detected and the cadence was extracted. Furthermore, using the detected steps the step length were assessed and gait asymmetry was investigated (section 5.4.3). Figure 5-16 illustrates the developed algorithm.

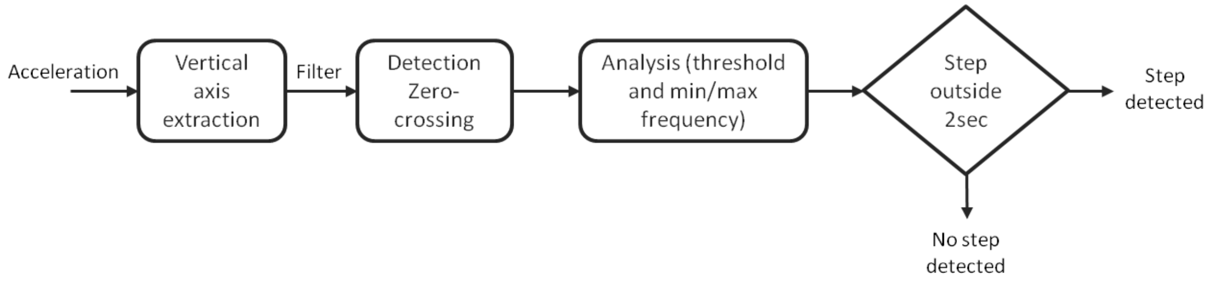



Figure 5-16. Step detection algorithm- Flowchart

First of all, the vertical axis was considered for the analysis. The noise was filtered, and the offset was removed using Butterworth high-pass (0.2 Hz) and low-pass filters (3.5 Hz), respectively. The filter process was performed twice with inverse direction for the second time. This ensures that the detected zero crossing points will not be shifted in time by the effect of the filter's phase response. This is an important step especially in the analysis of gait asymmetry (section 5.4.3). After having signal filtered and the time delay compensated (Figure 5-17 a ,b), a threshold of -0.02g was determined and every oscillation around zero bigger than -0.02g was excluded from the analysis, otherwise, it was considered as zero-crossing and included in the further analysis as corresponding peaks. The zero crossing points in the positive direction correspond to a positive peak. Furthermore, since the frequency of walking activity range between 0.5-4Hz, the frequency of two consecutive points is examined if it is in the acceptable range (2 seconds). In this case a potential step between the first and third zero crossing points was defined. Within this potential step the minimum, whose amplitude exceeds a certain threshold was searched, after that the time different between this potential steps and the previous was investigate. If the time difference was in the interval of ±2 second then the step was recognized as such, otherwise no step was detected (Figure 5-17 c).

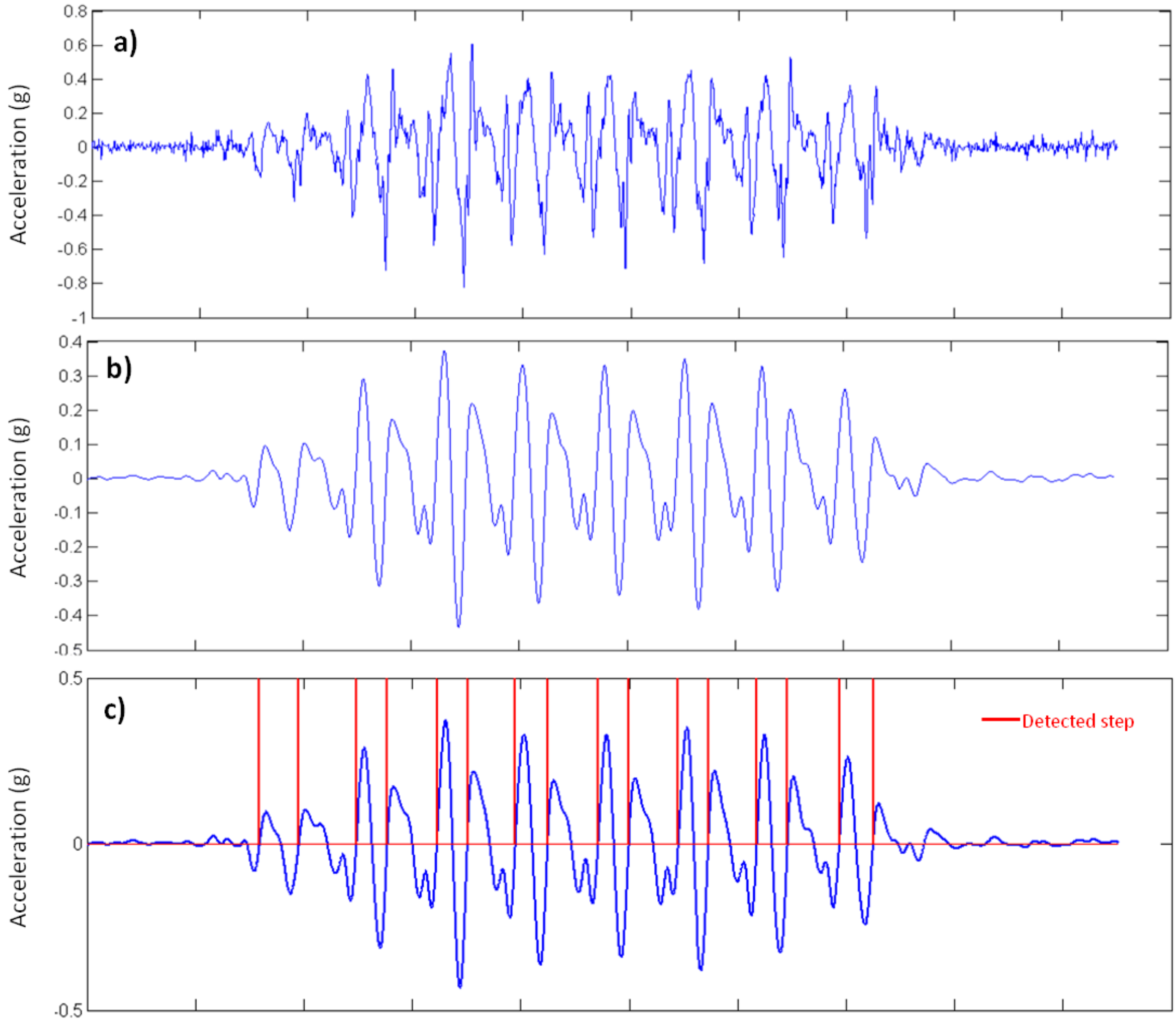



Figure 5-17. a) Raw acceleration signal, b) Filtered signal, c) Detected steps

To evaluate the step detection algorithm, dataset form the previous mentioned study was used (section 5.4.1.1). Sensitivity and positive predictive value were calculated (Table 5-6). Results showed high sensitivity (99.97 %) for both walking and jogging activity. The detected steps were then used to investigate gait asymmetry in PwMS (section 5.4.3).

$$Sensitivity\ (SE) = \frac{TP}{TP + FN} \qquad \text{Eq.5-7}$$

$$Positive\ predictive\ value\ (PPV) = \frac{TP}{TP + FP}$$

Table 5-6. Sensitivity and positive predictive value of step detection - walking and jogging activities

| Activity | step | FP | FN | TP | SE | PPV |
|---|---|---|---|---|---|---|
| Slow and fast | 22291 | 5 | 11 | 22280 | 99.95% | 99.97% |
| Jogging | 16981 | 6 | 12 | 16969 | 99.92% | 99.96% |

*Note:* slow and fast = slow and fast walking speed

### 5.4.3 Gait Asymmetry

#### *5.4.3.1 Related work*

Gait symmetry has been defined as the prefect function agreement between left and right limb. Movement asymmetry is associated with motor and gait dysfunctions and it is commonly observed in related with decline in health status. Patients with chronic diseases, such as Multiple sclerosis, may exhibit very asymmetrical gait [147]. Therefore, the reduction of asymmetry is clinically addressed by rehabilitation therapists and considered to be important parameter in gait evaluation and clinical decisions especially in patients with residual stroke or neurological chronic disease such as multiple sclerosis.

The term "gait symmetry" can be applied when the right and the left sides of the body behave identically. Therefore, the typical symmetry measures aimed to compute this similarity using either discrete or continuous methods.

*Discrete methods:* are the most common. They require simple temporal of spatial gait measurements or featured extracted from the movement signal. Usually, the simple symmetry index is used.

$$SI_{simple} = \frac{X_L}{X_R} \quad \text{Eq.5-8}$$

However, the symmetry index requires the choice of a reference value. This is the major disadvantage of this method because the reference value is not always clear and can lead to inconsistent results. Other studies used the symmetry angel to investigate gait asymmetry. This method is not affected by the choice of reference value. However, the system needed to capture angel symmetry consists of different markers attached to the upper and lower limbs and 6-camera systems [148]. Gyroscopes and pressure sensors have been also used to define the swing phase of each gait cycle and to calculate the asymmetry. As it mentioned before (chapter 4), the main limitation of such systems is their high power consumption or low user acceptance, respectively.

*Continuous methods:* based on the similarity comparison between two continuous signals, such as EMG or angular displacement. Continuous methods might be considered to be more informative in compare to discrete method. However, in order to get high accurate results multiple sensors should be attached to different body position (e.g. both legs, arms and legs).

The unique opportunity to use only one accelerometer to capture gait asymmetry under controlled and free-living condition is presented in this work.

#### 5.4.3.2 Development of gait asymmetry

Data from PwMS was collected during the 10-meter walking test (age = 41±9.3; height = 170±8.1; weight = 72±16.7; EDSS = 3.6±1.66). Patients were asked to walk forth and back at different walking speed. Detailed information is in (chapter 6).

Acceleration signals were assessed using 3 acceleration sensor attached to the right side hip. Gait symmetry/asymmetry index ($SI$) was defined using two different parameters; step time and swing phase ratio.

Step time ($T$): is the time between the two consecutive ground contacts (heel strike) of the same foot. This time was calculated for the right and the left foot, $T_R and\ T_L$, respectively (Figure 5-18).

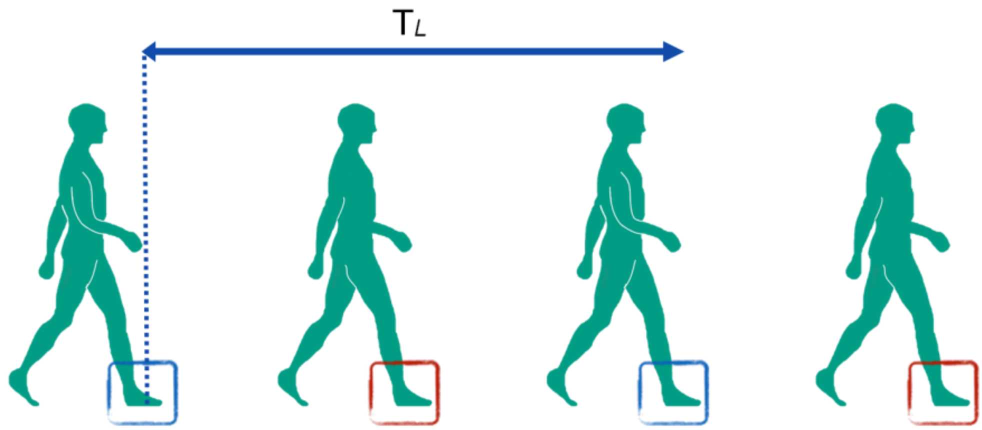



Figure 5-18. Step time for left (blue) and right (red) foot

Heel strike is one of the clearest points in the signal. Therefore, the time between two consecutive heel strikes was calculated to determine the step time ($T$). This time is defined as:

$$T_n = T_{HS_{n+1}} - T_{HS_n} \qquad \text{Eq.5-9}$$

where, $T_{HS_n}$ is the step time of the $n$th ground heel strike.

Step time $T$ for each foot was defined and the value of the difference between both times, i.e. $T_L$and $T_R$ , determines the $SI$.

Different phases compose the gait cycle (section 2.2). That means each step time of each foot consists of different phases, namely swing phase and stand phase (Figure 5-19).

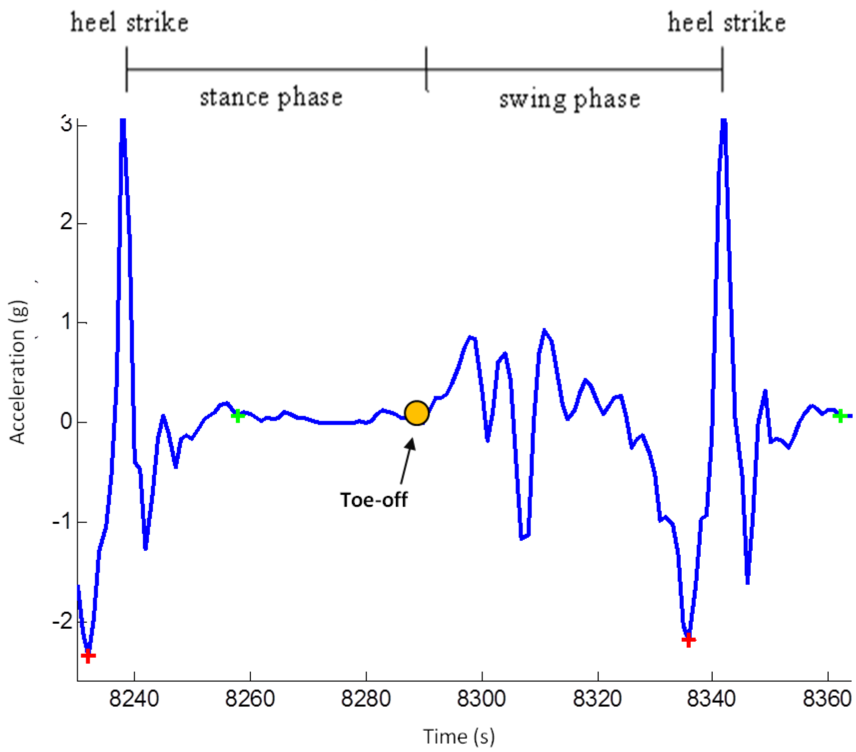



Figure 5-19. Gait phases in acceleration signal [149]

Therefore, in order to determine the ratio of the swing phase to the total step time, two main distinctive time stamps should be defined. Those are; the beginning of the swing phase (Toe off) and the end of this phase (heel strike). Swing phase ratio can be then defined as:

$$\emptyset_{swing} = \frac{T_{swing}}{T_n} \qquad \text{Eq.5-10}$$

$$T_{swing} = T_{HS_n} - T_{TO_n}$$

where; $T_{swing}$ is the time between the toe off time $T_{TO_n}$ (foot leaves the ground) and the consecutive heel strike of the same foot $T_{HS_n}$ (Figure 5-20).

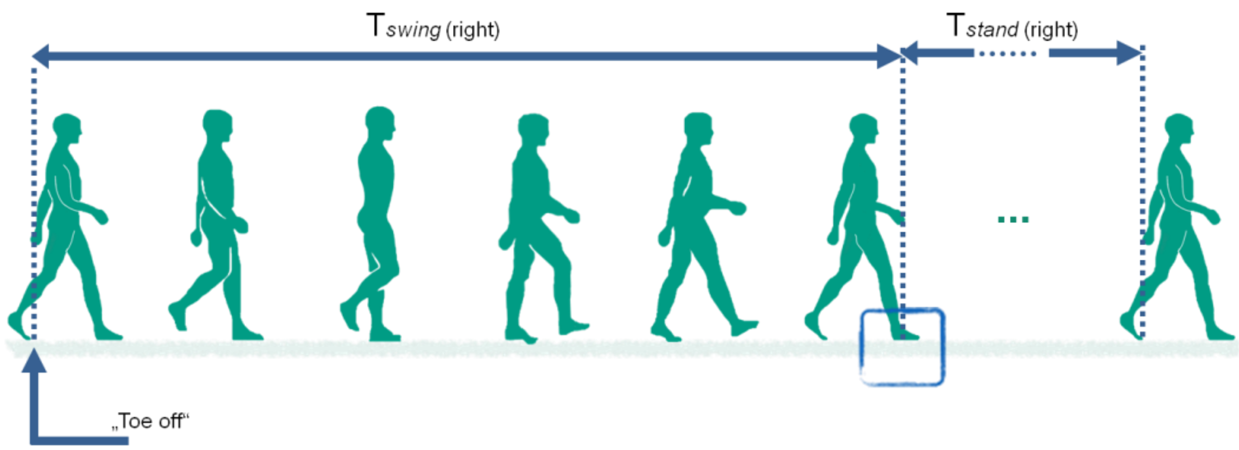



Figure 5-20. Swing and Stand time - right foot

The following figure (Figure 5-21) shows the process of the gait asymmetry algorithm.

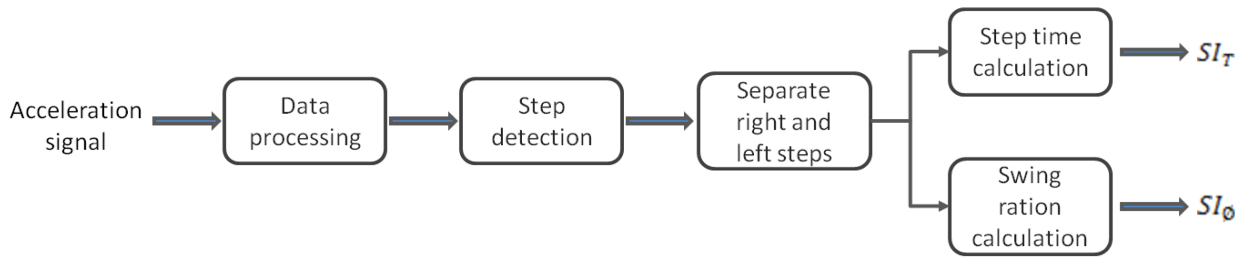



Figure 5-21. Calculation of the gait asymmetry indices

The vertical axis was separated and filtered using Butterworth high-pass and low-pass filter. Then step detection algorithm (section 0) was applied and the timestamp of each step were determined.  In order to calculate the above mentioned parameter, the steps taken by the right foot had to be separated from the ones taken by left foot. Therefore, the major peak had to be determined. The major maximum represents the step of the right foot, whereas the smaller maximum represents the step of the left feet. This assumption is due to the fact that the senor is attached to the right side hip. Thus, the forces that actually act on the left foot will be attenuated due to the biomechanical differences. After having the major peak determined, it can be assumed that this is a step of the right foot. Since the steps are alternating occurred thus they can be easily separated and assigned to their corresponding foot (Figure 5-22).

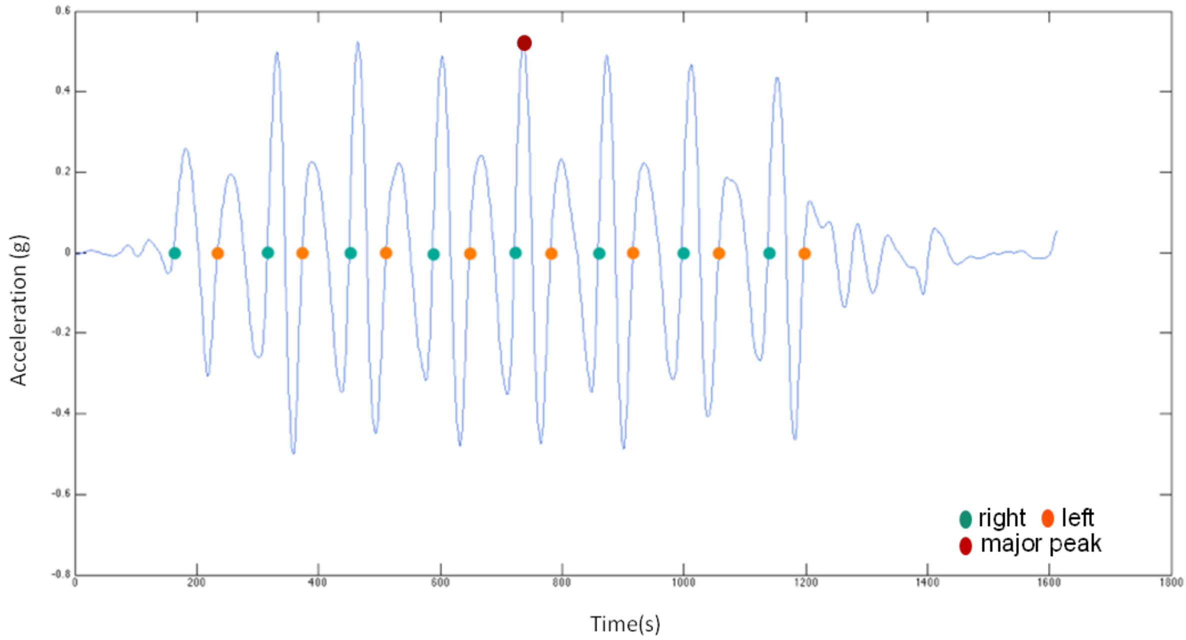



Figure 5-22. Identification of left and right steps

Having the step separated the calculation of step time and swing ration and the corresponding $SI$ index can be determined. $SI_T$ is the defined as (Figure 5-23):

$$SI_T = 100\%.\frac{|\bar{T}_L - \bar{T}_R|}{\max(\bar{T}_L, \bar{T}_R)} \qquad \text{Eq.5-11}$$

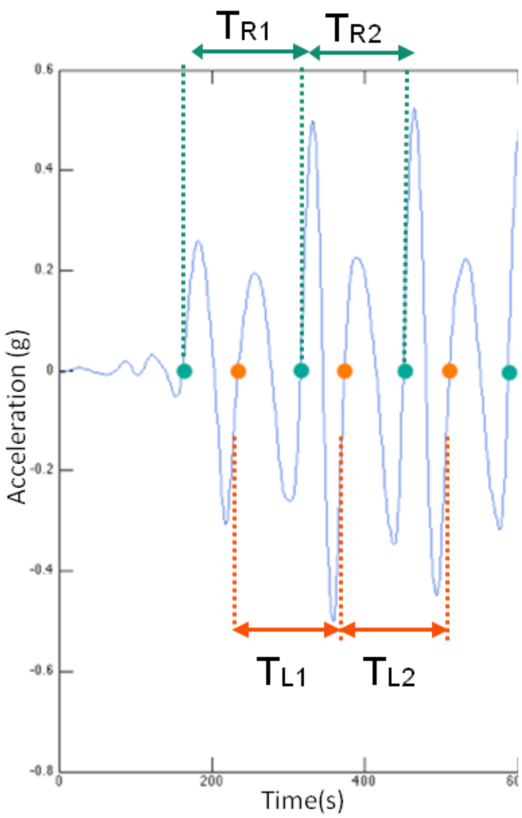



Figure 5-23. Determination of step time asymmetry index

The calculation of the swing ratio depends basically on the determination of the toe off/heel off time stamp. However, in the acceleration signal of the sensor attached to the hip, this determination is not quite possible, due to the attenuation of the signal. Therefore, the ratio of the double support time to the total step duration (5%-10%) was considered. Based on this consideration the time stamp of the left foot toe off ($T_{TO_L}$) was defined and the swing phase ratio was calculated (Figure 5-24). The $SI_{\emptyset}$ was defined as:

$$SI_{\emptyset} = 100\%.\frac{\left|\overline{\emptyset}_{swingL} - \overline{\emptyset}_{swingR}\right|}{\max(\overline{\emptyset}_{swingL}, \overline{\emptyset}_{swingR})} \qquad \text{Eq.5-12}$$

where, $\overline{\emptyset}_{swingL}$ and $\overline{\emptyset}_{swingR}$, are the swing phase ratio of left and right foot, respectively.

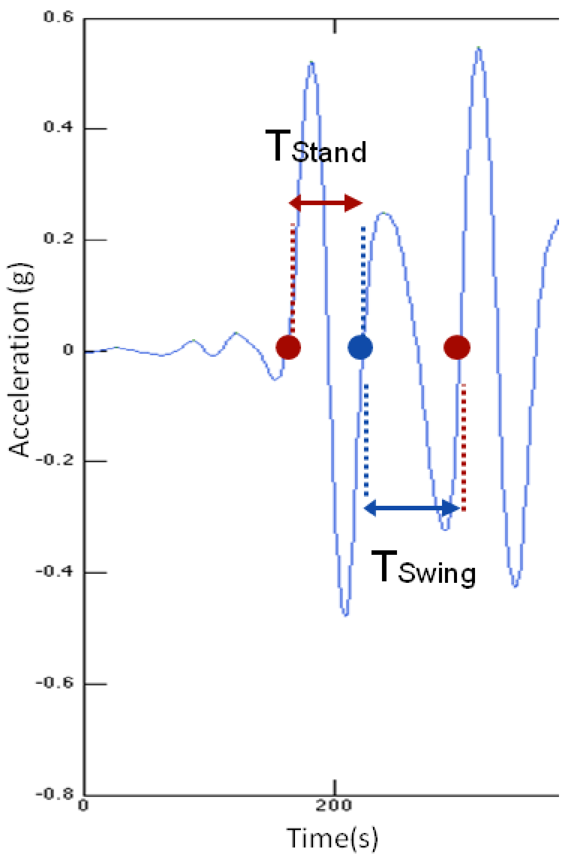



Figure 5-24.Determination of swing phase ratio asymmetry index

#### 5.4.3.3 Evaluation

Differences between right and left foot were investigated in PwMS for step time and swing ratio. Step time showed no significant difference between both feet (1030 ±165 ms, 1027±168 ms, p = 0.5), whereas swing time illustrates significant difference (54.24±1.8%, 43.61±1.9%; p<0.05), respectively. Furthermore, asymmetry indices $SI_T, SI_\emptyset$ of PwMS were compared with those of healthy control groups (Table 5-7)

Table 5-7. Characteristics of patient and healthy control groups

| | PwMS | Control |
|---|---|---|
| Age | 41 (±9.3) | 28.2 (±3.35) |
| Height | 170 (±8.1) | 171.8 (± 9.65) |
| Weight | 72 (± 16.7) | 63.2 (±15.8) |
| EDSS | 3.6 (± 1.66) | - |

Student t-test was used to investigate the differences between PwMS and healthy control. The results showed that in general, PwMS have less symmetry gait in comparison with healthy control group (Figure 5-25 and Figure 5-26). Both asymmetry indices $SI_T, SI_\emptyset$ were significantly higher in PwMS ($p < 0.01$). This indicates that PwMS have low similarity between body sides compared to healthy control (

Table 5-8).

Table 5-8. Gait asymmetry differences between PwMS and healthy control

| | PwMS | Control | p-value |
|---|---|---|---|
| Step time asymmetry ($SI_T$) | 2.61 ± 3.4 | 0.9 ± 0.5 | < 0.01 |
| Swing phase asymmetry ($SI_{\emptyset}$) | 12.11 ± 7.6 | 7.6 ± 6.1 | < 0.01 |

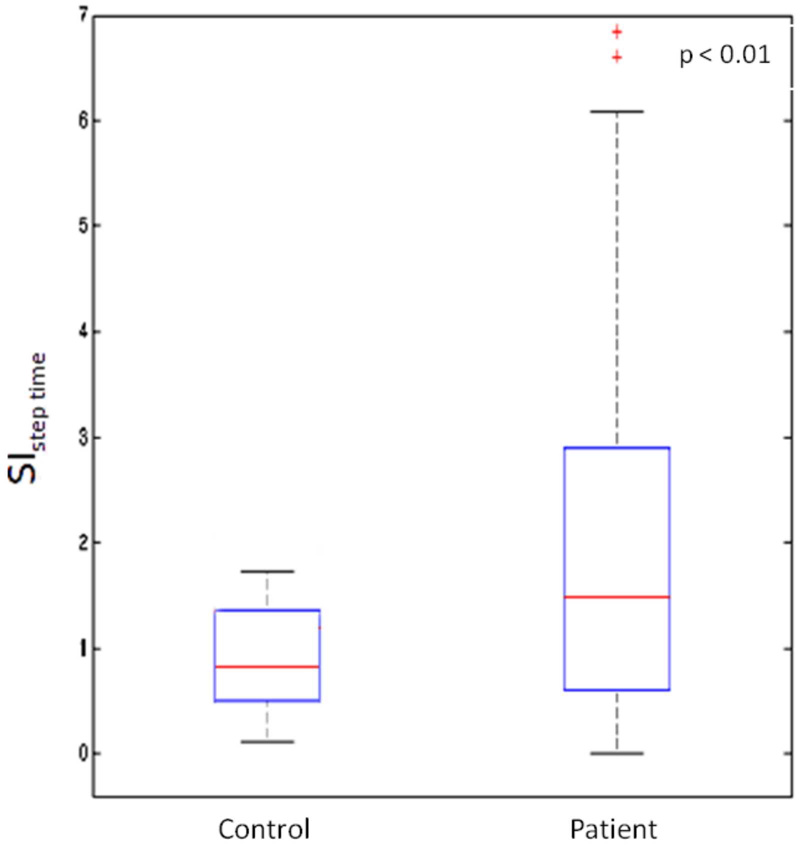



Figure 5-25. Step time asymmetry index in PwMS and healthy control

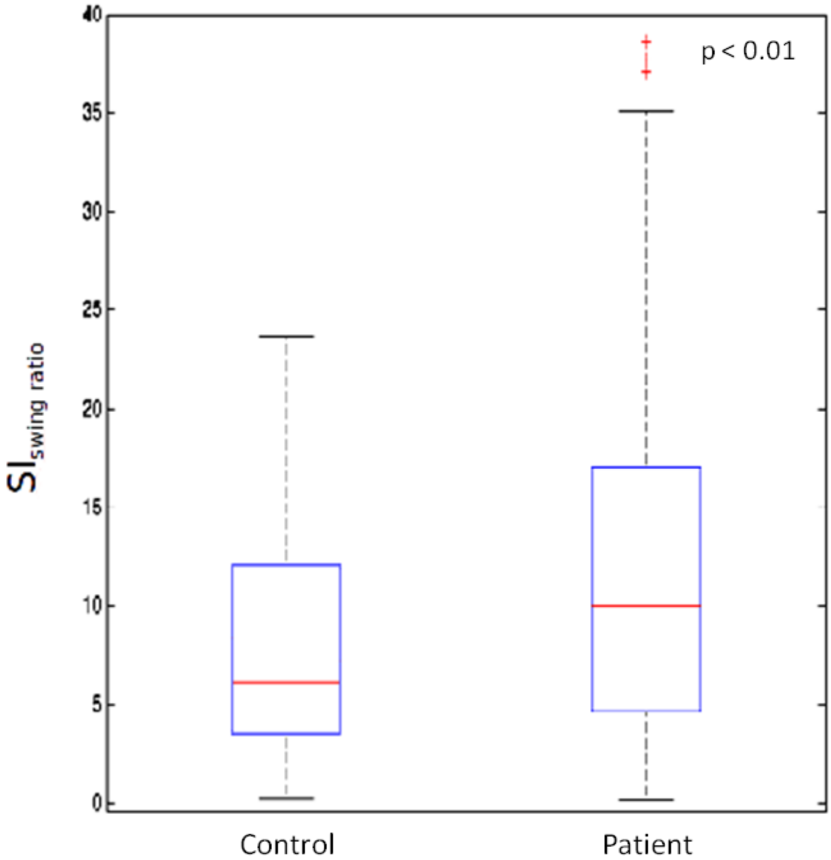



Figure 5-26. Swing time ratio asymmetry index in PwMS and healthy control

### 5.4.4 Peak Frequency and Energy Concentration

#### *5.4.4.1 Related work*

The acceleration data are considered to be a most useful tool for gait analysis when features are not interpreted in isolation but together. The gait features discussed above are time-domain features. Since walking is periodic activity, the frequency transformation of feature time series is worth investigated. Therefore, in this work additionally to the time-domain feature presented before, features in frequency and time-frequency domain were developed and analysed. This may provide a comprehensive picture into the motor control of walking activity.

Frequency domain analysis has been previously used to assess normal and disordered gait. This analysis has been considered to be a powerful tool to identify changes in gait due to age- and disease-related impairments especially when such changes are not obvious in time domain. The main objective of using time-frequency analysis is to determine the energy concentration along the frequency axis at a certain time instant. Furthermore, the use of wavelet as analysis and feature extraction tool in gait analysis has gained considerable attention.

Multiple studies have investigated gait features in frequency and time-frequency domain. Some of these studies extracted the gait features using smart mat (GAITRite) or force platform. These systems provide rich information, on the other hand are restricted to laboratory and clinical environment. Other studies used either gyroscope in combination with accelerometer or multiple accelerometers attached to different body position. Such systems are not feasible to be used in medical researchers.

#### *5.4.4.2 Development of peak frequency und energy concentration*

**Peak Frequency:** First of all, the segments of the signal that are corresponding to movement activity were separated and included in the processing, whereas, signals corresponding to sitting, standing and lying activities were excluded. Peak frequency and energy concentration features were extracted from the medial-lateral axis of the acceleration signal from the sensor attached to the right-side hip.

Fourier transformation is an important tool for analyzing signals with periodic repetition. Gait signals can be considered as quasi periodic; thus, it is possible to perform a spectral analysis on this signal. The qualitative analysis of the signal in the frequency domain allows identifying different spectrums that could be associated to gait impairment. One main parameter associated with a spectrum is the peak frequency ($PF$). Peak frequency ($PF$) denotes the frequency at which the maximum spectral power occurred. In other words, it presents the highest peak in the frequency space to which the acceleration signal was converted.

$$f_p = argmax_{f\epsilon|0,f_{max}|} \, |F_x(f)|^2 \qquad \text{Eq.5-13}$$

$PF$ $f_p$ was detected in the frequency space and had the highest peak around the $PF$ candidate. $F_x(f)$ is the Fourier transform of the signal and $f_{max}$ is the sampling frequency.

Figure 5-27 illustrates the extracted process. First of all, the offset in the signal was eliminated by subtracting the mean and then the signal was smoothened using a Butterworth low-pass filter (cut-off 3.5 Hz) in order to decrease the effect of the high-frequency noise that accompanies $PF$ detection. Then the hamming window was applied. The size of the window is dynamically adapted to the signal length. Gait signal can be considered as a quasi-periodic, i.e. the start and the end of the signal might not match with each other. This could result in the so called leakage effect. Therefore, windowing the data ensures that the ends of the signal match up, which remarkably reduces the spectral leakage and leads to better and reliable $PF$ analysis .The next step is to transfer the signal into frequency space where finally the frequency with the highest power spectrum can be extracted.

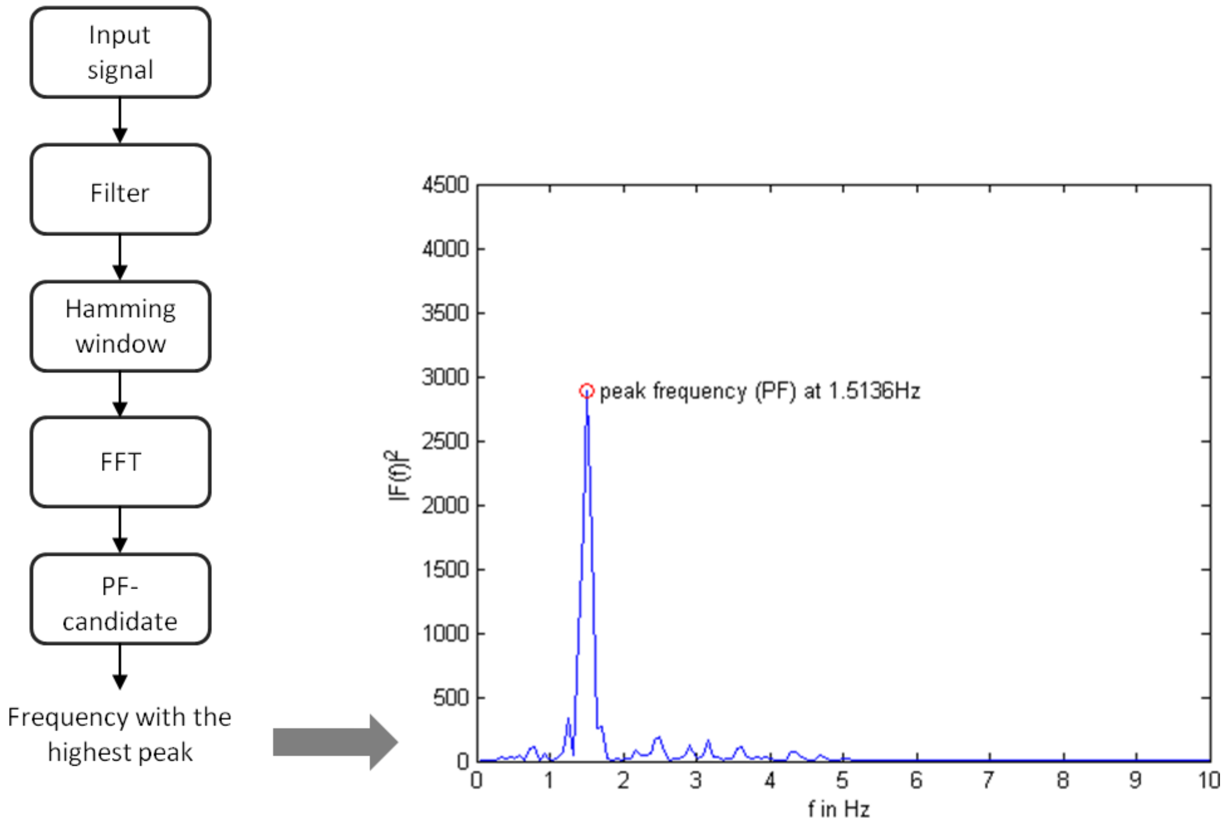



Figure 5-27. Peak frequency extraction algorithm

**Energy Concentration:** Wavelet transformation was utilized to extract the relative energy concentration $EnC$ of the signal in a specific frequency band. The idea behind Wavelet methods is to analyze the behavior of the energy distribution at a certain time instance or frequency band. In this work it was particularly used to analyze the distribution of the energy concentration in different frequency bands of the time-frequency domain. The analysis of energy concentration can provide a useful tool to reveal more information from gait signal for diagnostic purposes. Figure 5-28 illustrates the extraction process.

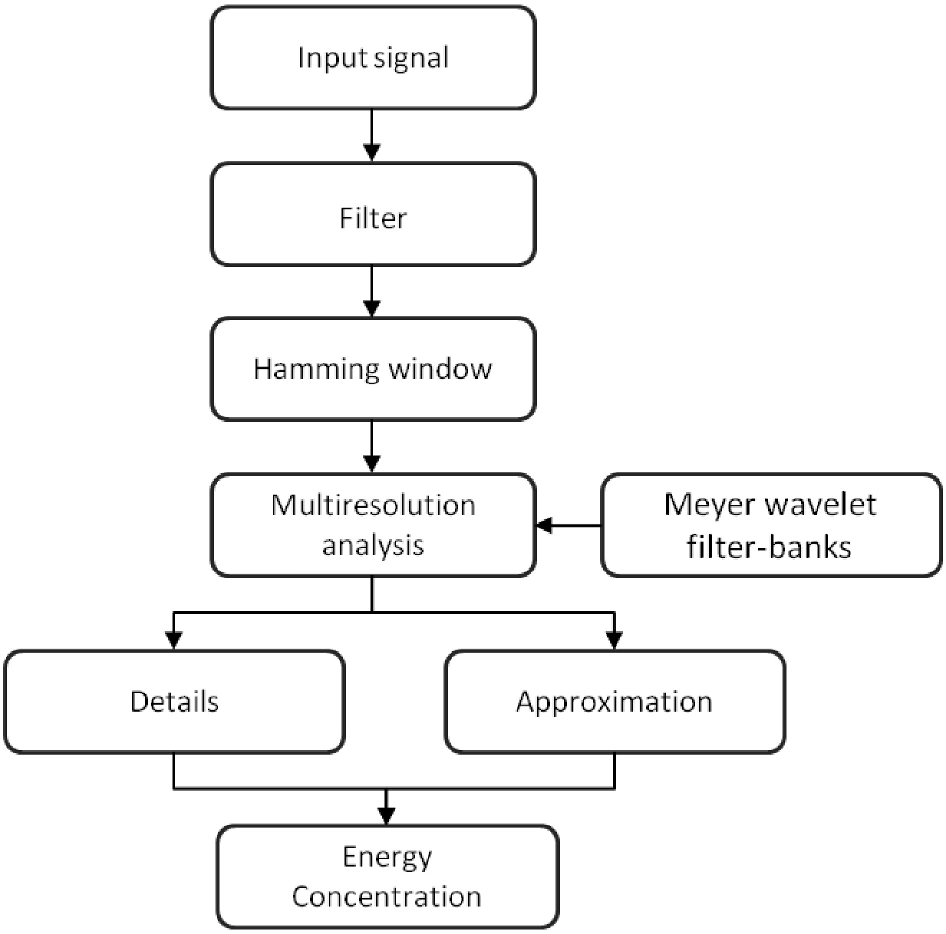



Figure 5-28. Energy concentration extraction algorithm

The input signal was filtered using the same cut off frequencies as for $PF$. Then the filtered signal was multiplied with a hamming window equally. After the preprocessing, a multi-resolution analysis (MRA) until the 10th level was performed using Meyer wavelet filter-banks. The multi-resolution analysis is a common tool to perform wavelet decomposition on time-discrete signals. Each step of the MRA develops a set of detail coefficients $d_k$ and a set of approximation coefficients $a_k$ according to the model in Figure 5-29. As it shown in this figure the signal goes through a high-pass and a low-pass filter.

The output signals of both filters are down sampled to avoid redundancy in the data. The result signal is detail and approximation coefficients. The complete 10-level Meyer wavelet decomposition procedure by using MRA is illustrated in

Figure 5-30.

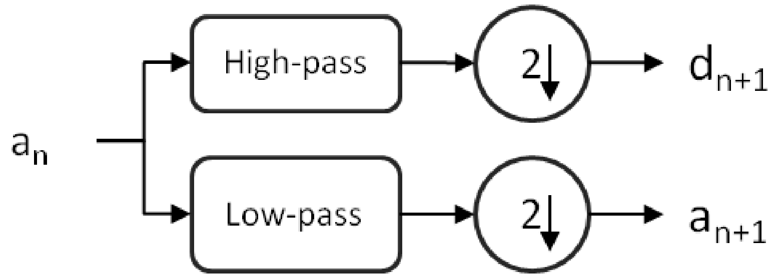



Figure 5-29. One step wavelet decomposition - d is details and a is approximations

To develop the relative energy concentration $EnC(k)$ in one of the 10 frequency bands, each set of detail coefficients have to be calculated and its energy using the formula:

$$\mathrm{E}_{\mathrm{d,k}} = \|\mathrm{d_k}\|^2, \mathrm{k} \in \{1, 2, \dots, 10\} \qquad \text{Eq.5-14}$$

The energy of the approximation coefficients set at the 10th level is equally needed to extract the relative energy $EnC(k)$.

$$\mathrm{E}_{\mathrm{a10}} = \|\mathrm{a}_{10}\|^2 \qquad \text{Eq.5-15}$$

where, $\|.\|$is the Euclidean norm and $\mathrm{a}_{10}$ represents a vector

Therefore, the relative energy $EnC$ is calculated by the quotient "detail energy at k" to the energy of the complete signal "approximation energy at 10" plus the sum of the detail energy from 1 to 10.

$$EnC_k = \frac{\mathrm{E}_{\mathrm{dk}}}{\mathrm{E}_{\mathrm{a10}} + \sum_{\mathrm{k}=1}^{10} \mathrm{E}_{\mathrm{dk}}} ; \mathrm{k} \in \{1,2, \dots 10\} \qquad \text{Eq.5-16}$$

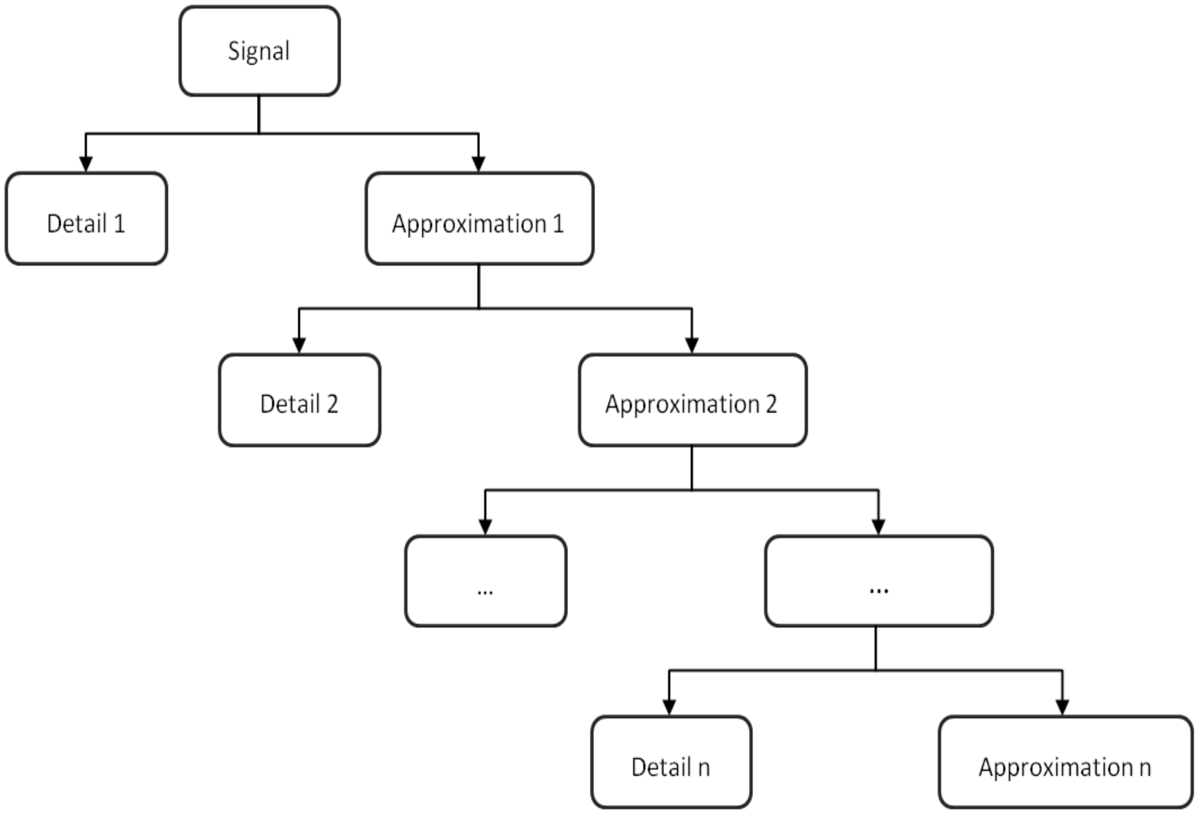
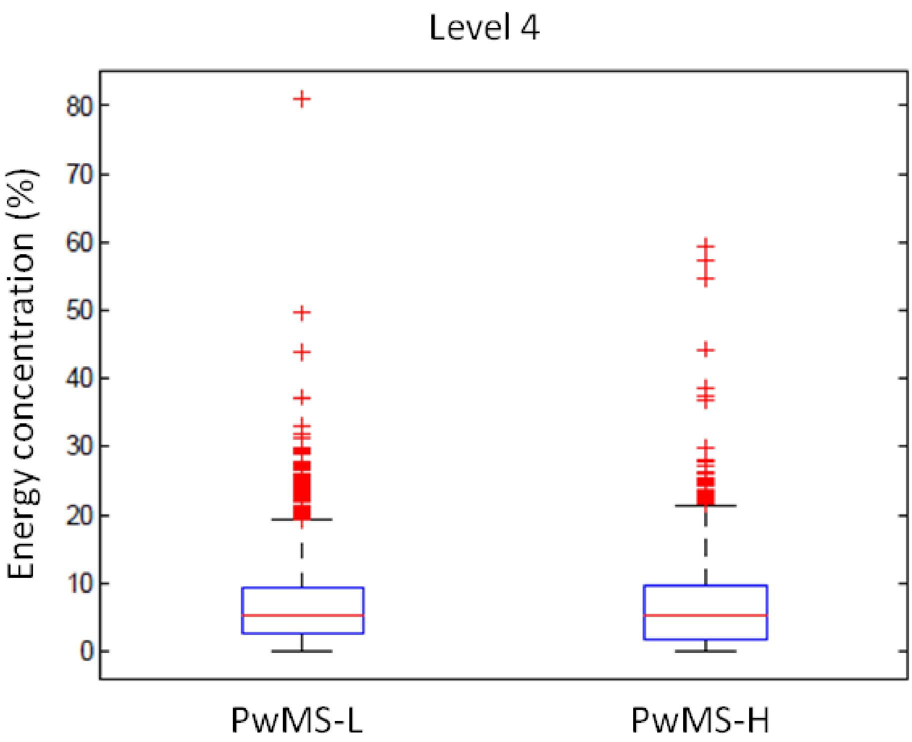
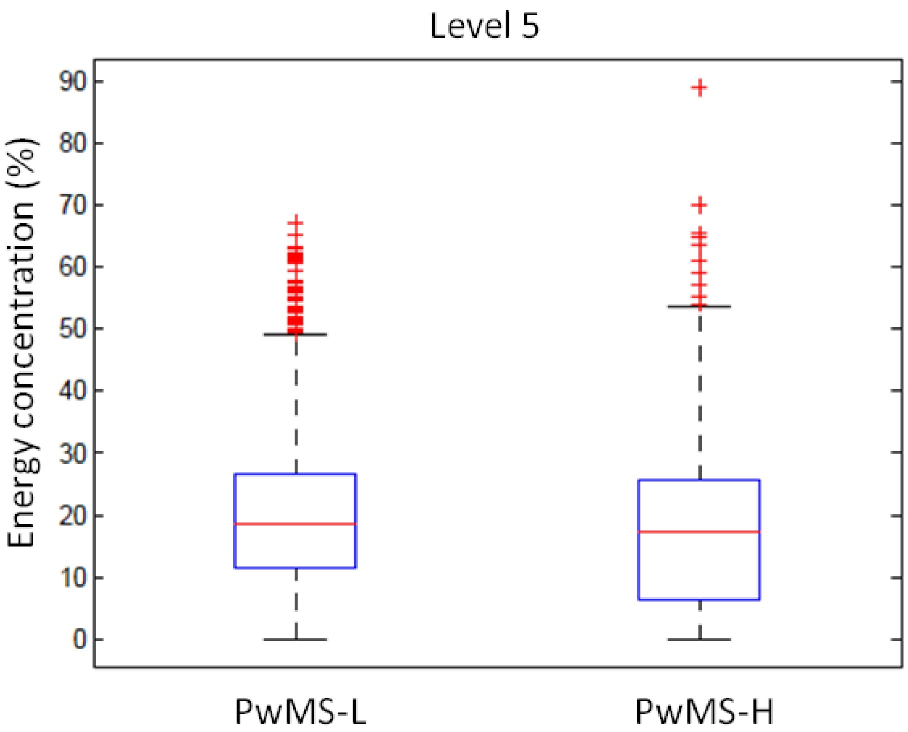



Figure 5-30. Ten level wavelet decomposition tree

Energy concentration was tested at different level (from 1 to 10). However, as it can be seen in Figure 5-31, energy concentration at level 6 showed significant difference between patient groups with mild and moderate disability, whereas other level showed no significant differences between both groups.



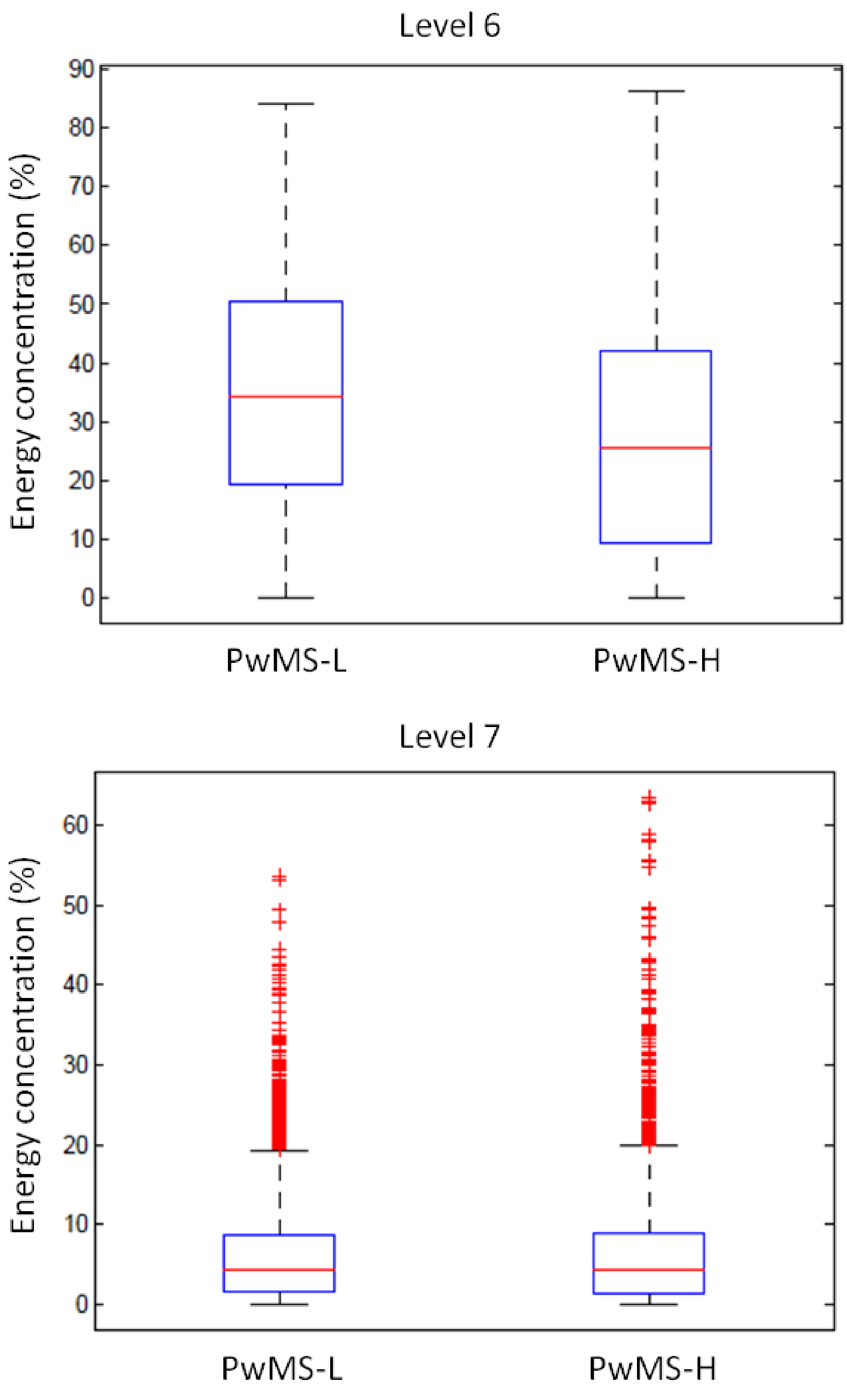



Figure 5-31. Comparison of different decomposition level

$EnC$ feature showed significant differences between both PwMS subgroups (PwMS-L: EDSS = 1-2.5; PwMS-H: EDSS = 3- 5) (Figure 5-31). Patients with mild disability showed significantly higher energy concentration (35.63 ± 20.19) at level 6 ($EnC$ 6) in comparison to patients with moderate disability (31.67± 18.41). Student t-test was used to compare both subgroups ($p < 0.05$). Figure 5-32 illustrates the differences between both subgroups regarding peak frequency. Peak frequency showed marginal significant difference between both subgroups ($p = 0.08$). Peak frequency can be hardly affected by signal fluctuation, which could be a possible explanation of the results. However, these features were tested and evaluated by using bigger sample size (Chapter 7). Table 5-9 summarizes the differences between both subgroups.

Table 5-9. Comparison between both patients' subgroups regarding energy concentration and peak frequency (mean, SD and p-value)

| | PwMS-L | PwMS-H | p-value |
|---|---|---|---|
| Energy concentration (%) | 35.63 ± 20.19 | 31.67 ± 18.41 | < 0.05 |
| Peak frequency (Hz) | 1.54 ± 0.61 | 1.39 ± 0.68 | 0.08 |

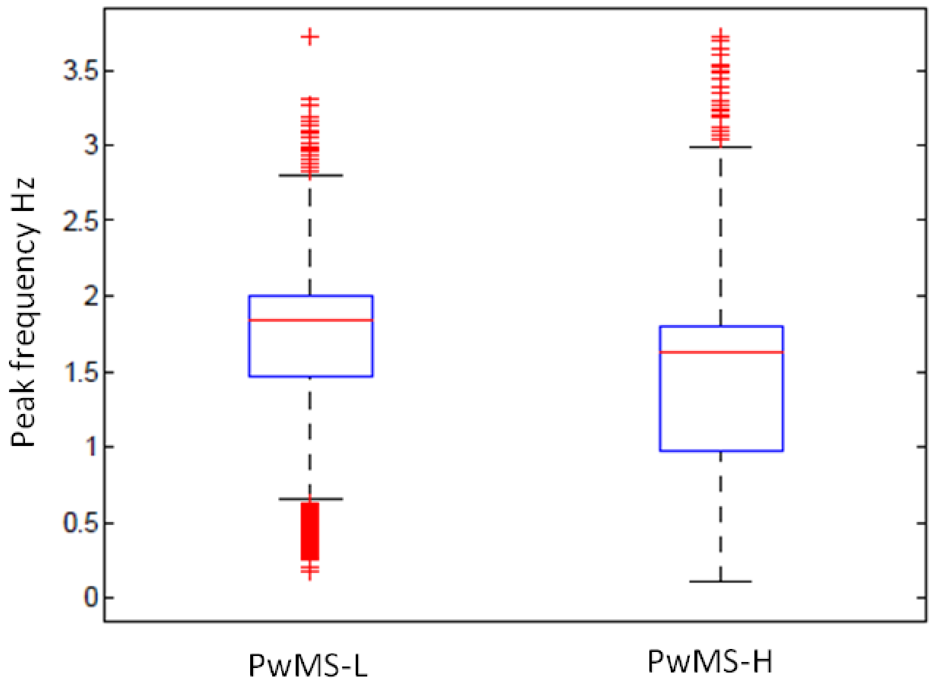



Figure 5-32. Peak frequency comparison between mild and moderate subgroups

# 6 Ambulatory assessment of neurobehavioral alteration and gait impairments in PwMS

As it was mentioned in section 2.3walking impairment is one of the most ubiquitous features of MS. It can have impactful effect on the independence and activities of daily life. Assessment of motor and gait disability in PwMS requires continuous evaluation. This continuously is essential to monitor the course of the disease, to understand the development of the health status which may help in early treatment optimization. Moreover, the assessment of the variability of motor and gait parameters in free-living environment may provide significant information to predict the health status of the PwMS. Repeated measurements of this variation might also provide useful indicators of activity and walking ability change that is unlikely to be due to error in measurement.

## 6.1 Study Design and Data Fusion

The following study was carried out as a part of the project MS Nurse and in contribution with the hospital of neurologic acute and rehabilitation medicine in a rural area in Northem Bavaria, Germany.

Study design, measurement system and participants characteristics will be presented in the following.

### 6.1.1 Study Design

The aim of this study was to determine the ability of the developed parameters to objectively capture the slightly changes in motor and walking ability in PwMS. Moreover, the objective was to provide additional evidence from long-term design study that support the association between changes in physical activity and walking ability and disease progression over time. This can be accomplished by collecting observations or data at more than one point of time. This could also allow investigating the correlation between the changes and the disease severity. Variations and differences between patients with mild and moderate disease severity and within a patient should be captured in order to assess the disease dynamic. Furthermore, the stability and sensitivity of these parameters were measured, and the amount of the clinically meaningful change was determined.

These measures were collected four times (four phases), each lasting 10 days with an interval of three months between each phase. Person-specific data were collected at the beginning of the study. Move II accelerometer is the only sensors on the market that fulfill the hardware requirements discussed in Chapter 5. The study was divided into clinical measures and ambulatory measures. The developed system presented in Chapter 5 was applied for the assessments.

#### 6.1.1.1 Participants

Over a period of one year, 11 PwMS (females = 7, males = 4; age: 41 ± 9.3 year; height: 170 ± 8.12 cm; weight: 72 ± 16.77 kg; disease duration: 12.18 ± 10.67) were recruited in the hospital for neurologic acute and rehabilitation medicine in a rural area in Northern Bavaria, Germany. Participants had to meet the following inclusion and exclusion criteria:

a) definite diagnosis of MS [26].
b) EDSS score below 5 (3.6 ± 1.66), which indicates the ability to walk at least 200 m without assistive devices [29].
c) a completed and signed an informed consent. Eight patients had relapsing-remitting multiple sclerosis, one patient had primary progressive multiple sclerosis and two patients had secondary progressive multiple sclerosis.

The procedure of this study was approved by the ethics committee of the Bavarian Medical Association, Germany. The study lasted one year and consisted of clinical measures and ambulatory activity measures.

#### 6.1.1.2 Clinical measures and pre-test assessment

The clinical measurement took place in the clinic at the beginning of each phase. These measures were:

1. *10-meter walking test* was used for initial calibration, in which patients were instructed to wear the *move II* (one on the right side hip and two sensors on the right and left ankle) and to walk along a 10 meter flat walkway. Since gait pattern of PwMS differ in various walking speed patients were asked to walk back and forth once at their comfortable walking speed and once again at fastest walking speed. Information about stride length, time and number of steps were recorded by the physician and as raw acceleration data from the *move II* (Figure 6-1). This information was used to develop gait asymmetry algorithm (chapter 5.4.3).

2. *Expanded Disability Status Scale EDSS (Chapter 2.x.x)* patients who score at or less than 5.5 are considered to be able to walk at least 100 m

without aid or rest. Patients with score between 6.0 and 8.0 are considered to be ambulatory with limitations. Patients with EDSS score more than 8.0 considered to be totally dependent. Patients' disease severity and clinical symptoms were assessed using EDSS by an experienced neurologist. EDSS score was evaluated quarterly and at the beginning of each measurement.

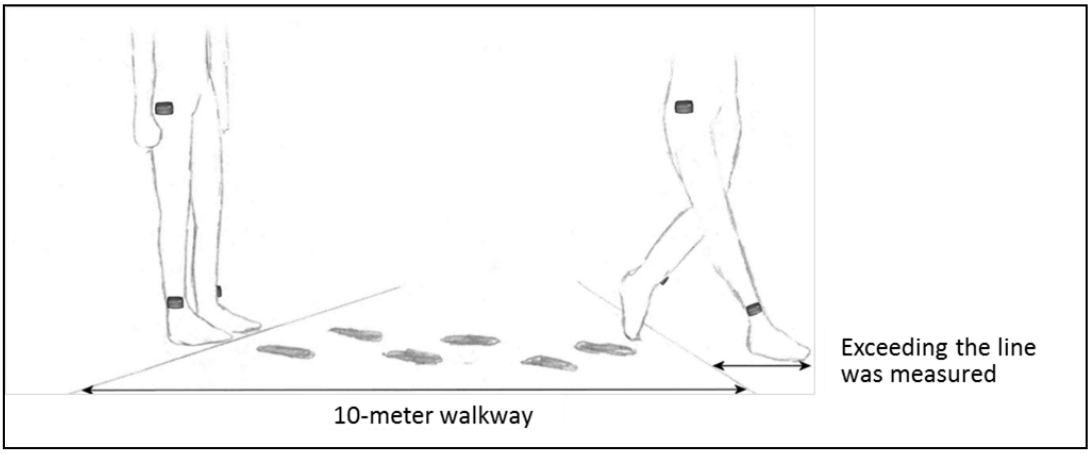



Figure 6-1. 10-meter clinical walking test

#### *6.1.1.3 Ambulatory measures*

Based on the challenges of PwMS previously described (section 2.3), the scenario for applying activity and gait analysis in MS treatment can be drawn up as follows. Typically, PwMS who lives at home on their own, live and work as usual and consult their physician once every three months for their basic physical examinations (EDSS). In the three months between the check-ups they wear a device, which continuously monitors their movement during daily-life activities. At the next regular physician's visit, the sensor data will be transferred and analysed using the Physician-Software described in section 5.3. In contrast to the usual check-up, the analysis results not only provide information about the momentary health status, but also about the development over the last months.

The activity monitoring system (*move II* and the pre-configured EeePC) was given to the patient at the time of the clinical measurements. Participants were asked to carry the *move II* sensor on the right side hip (see Figure 6-2) up to ten days while carrying out their usual daily activities. They were asked to start carrying the sensor early morning as soon as they get up until they go to bed again (except while swimming, showering and bathing). Furthermore, they were asked to attach it to the notebook via USB before going to sleep. The raw sensor data were transferred automatically and stored on the SD card and the patients got feedback about their activity pattern. This feedback should encourage them to maintain their activity level. The developed software for sensor management and physical activity report was presented previously (Patient-Software). After ten days, the participants returned the system to the clinic, the data were downloaded to the computer and the participants received a report of their physical activity of the past ten days. Figure 6-3 illustrates the measurement's process.

Figure 6-2. Sensor position

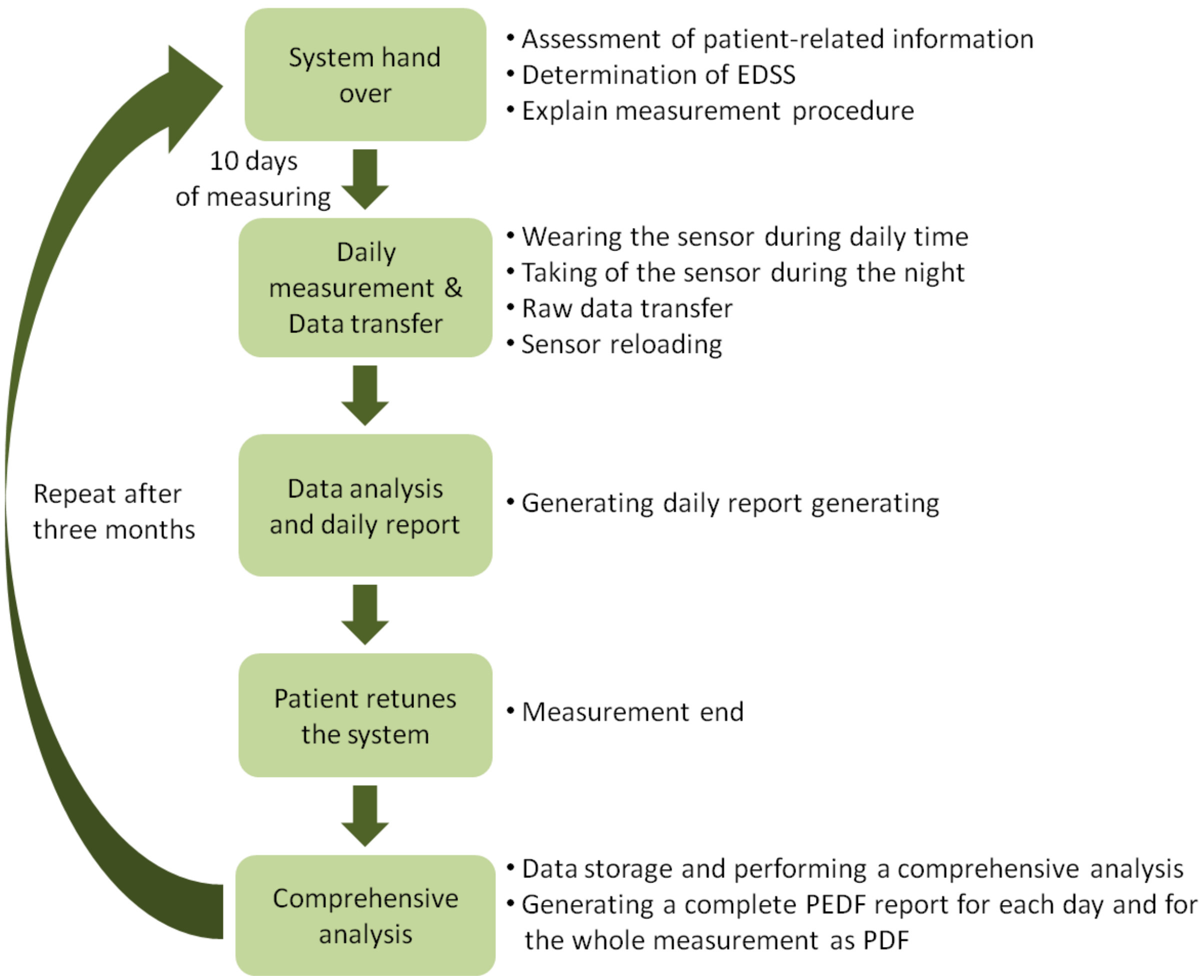



Figure 6-3. Measurement process

## 6.2 Activity and Gait parameters

To understand the changes in physical activity characteristics in PwMS, the following parameters were examined: a) number of steps calculated over the day (number of awake hours), b) mean and maximum walking speed, c) physical activity level in terms of MET level (light and moderate to vigorous MVPA MET level) which is the ratio of the associated metabolic rate for the specific activity divided by the resting metabolic rate (RMR). These values can be obtained from published tables [17]. To assess the impact of the disability on ambulatory activity behavior, the participants were separated according to their disease severity into two subgroups; mild ambulatory limitation (PwMS-L: EDSS = 1–2.5) and moderate ambulatory limitation (PwMS-H: EDSS = 3–5). Subgroups were determined based on the categorization published in [35] (Table 6-1).

Table 6-1. Patients' characteristics

| | PwMS | PwMS-L (EDSS 1-2.5) | PwMS-H (EDSS 3-5) |
|---|---|---|---|
| Age | 41 (±9.3) | 36.14 (±10.53) | 46.64 (± 1.68) |
| Height | 170 (±8.1) | 165.83 (±6.08) | 176 (±6.96) |
| Weight | 72 (± 16.7) | 65.33 (±14.04) | 79.72 (±17.76) |
| EDSS | 3.6 (± 1.66) | 1,75 (±0,82) | 4,40 (±0,89) |
| Men | 4 | 1 | 3 |
| Women | 7 | 5 | 2 |
| Total | 11 | 6 | 5 |

*Note: mean ± SD was calculated*

## 6.3 Data Reduction and Data Analysis

As the devices were handed out to the patients at different hours of the first day, this day was excluded from the analysis. All participants accepted to wear the sensor for 9 days and at least 10 h per day. The number of steps per measurement as well as the mean walking speed was calculated as an overall average of all days in each measurement. For the activity depended MET level estimation, the activity of the patients was classified and each activity was categorized as light or MVPA according to [17]. Based on the detected activity class, the energy expenditure was estimated, and the MET level value was calculated with the following formula (MET = EE / BMR). Having both information (activity class and its corresponding calculated MET value) the MET categories of our patients' group were defined.

Mean value and standard deviation for MVPA and gait parameters were calculated. Differences in all these parameters between two consecutive phases were calculated for each patient. In addition, the differences between the first phase and the follow-up fourth phase for each parameter were assessed non-parametrically by using the Wilcoxon test. To analyze the differences between both subgroups the nonparametric Mann–Whitney *U* test was used. Wilcoxon test and Mann-Witney *U* tests were used due to the small sample size.

Differences with $p \leq 0.05$ were noted as significant. Moreover, bivariate correlation between EDSS and gait parameters (number of steps, mean walking speed, max walking speed and MET level) was analyzed. Values between 0.00 and 0.25 was considered as no correlation, values between 0.70 and 0.89 as high correlation and values between 0.90 and 1.00 as very high correlation [150]. Spearman Rho was used for this analysis.

Repeated measurement of the variations in MVPA and gait parameters might provide useful indicators of activity change that is unlikely due to error in measurement. The standard error of measurement (SEM) which is closely related to minimal detectable change (MDC), has been used to quantify the *within-subject* variability. The MDC is a useful tool to operationally determine whether a magnitude of change in the parameter of interest is greater than the amount of change attributable to measurement error. This determination may support the process of clinical treatment evaluation and decision making. In order to calculate MDC the stability of the parameter should be calculated. Therefore, the response reliability was investigated by calculating the intra-class correlation coefficient (ICC; two-way mixed, single measures) for all patients across all days (day1 to day9) within the first measurement of the whole sample size. The ICC value represents the consistency and ranges from 0 to 1. An ICC below 0.04 indicates poor stability, ICCs from 0.60 to 0.74 suggest good stability and ICCs from 0.75 to 1.00 suggest excellent stability [54].

Moreover, standard errors of measurement (SEM) were calculated as follows: in a first step, ICCs for *between-session* reliability were computed between data from the first measurement (M1, baseline) and each of the follow-up measurements (M2, M3 and M4) separately (two way mixed, single measures). Again, the model testing for consistency was used. The SEM, which estimates the measurement error across repeated measurement, was calculated by multiplying the baseline standard deviation of the samples for each parameter by the square root of one minus the ICC ($SEM = SD_{baseline} * \sqrt{1 - ICC}$). This value indicated the amount of error that must be considered when interpreting individual test results.

As it was discussed in (chapter 3.3.2.2) MDC provides the absolute amount of change necessary to exceed the measurement error of repeated measures at a certain confidence interval (CI). This information may be used to distinguish between true performance change and an observed change due to measurement error. In this work the MDC was calculated at 95% CI ($MDC = SEM * 1.96 * \sqrt{2}$). Furthermore, to investigate MDC independently from the unit of the parameter, the MDC% was calculated:

$$MDC\% = \left(\frac{MDC}{\bar{X}}\right) * 100 \qquad \text{Eq.6-1}$$

where, $\bar{X}$ is the mean value of the parameter for all measurements.

## 6.4 Results

While EDSS score did not change throughout the study's phases in all patients, the physical activity parameters showed differences between each two consecutive phase in both subgroups.

### 6.4.1 Decline of MVPA and gait parameters in PwMS-L and PwMS-H

In this section the descriptive and statistical analysis of the changes in PwMS will be presented. PwMS-L showed a slightly increases in steps/day between the first phase and the follow-up second phase. Remarkably, these changes in steps/day were combined with slightly increases in mean and maximum walking speed (1.8% and 1.13%), respectively. Only one patient showed decline between these two phases (~292) (Figure 6-4).

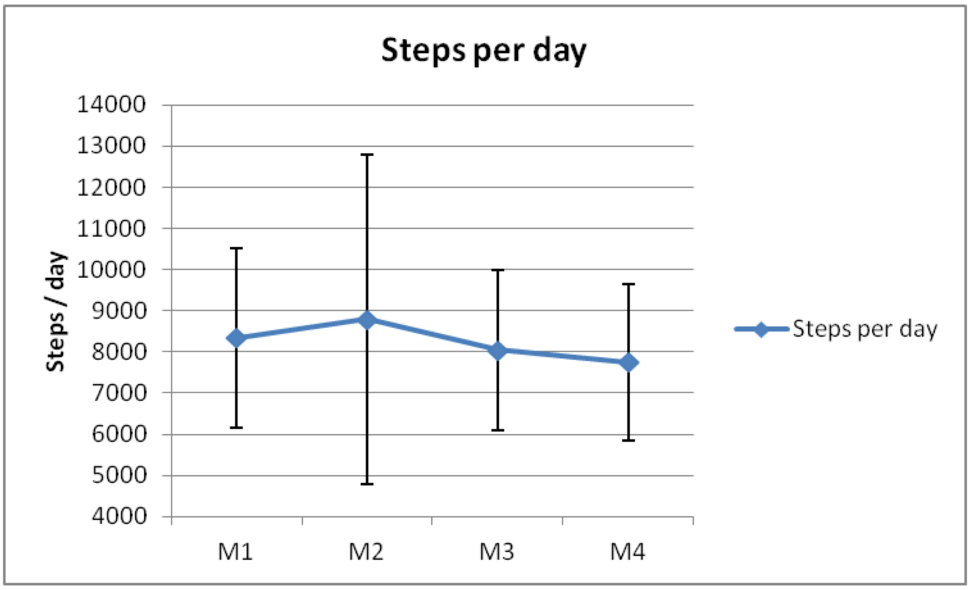



Figure 6-4. Changes in steps /day in PwMS (exemplified for one patient)

In average, PwMS-L showed a decline in all parameters between the second the third phase as well as between the third and the fourth phase. However, in comparison to baseline, they showed decline in steps/day (~1683), mean walking speed and maximum walking speed (-0.12 Km/h, -0.16 Km/h), respectively (Figure 6-5 and Figure 6-6). MVPA did not show significant change between the first and the follow-up measurement. Patients of the group PwMS-H showed a decline in all parameters between each two consecutive phases. In comparison to the baseline, PwMS-H showed decline in steps/day (~1673), a slightly decline in mean and maximum walking speed (8.7%, 2.6%), respectively and in MVPA (-1.4%) between first and the follow-up fourth measurement.

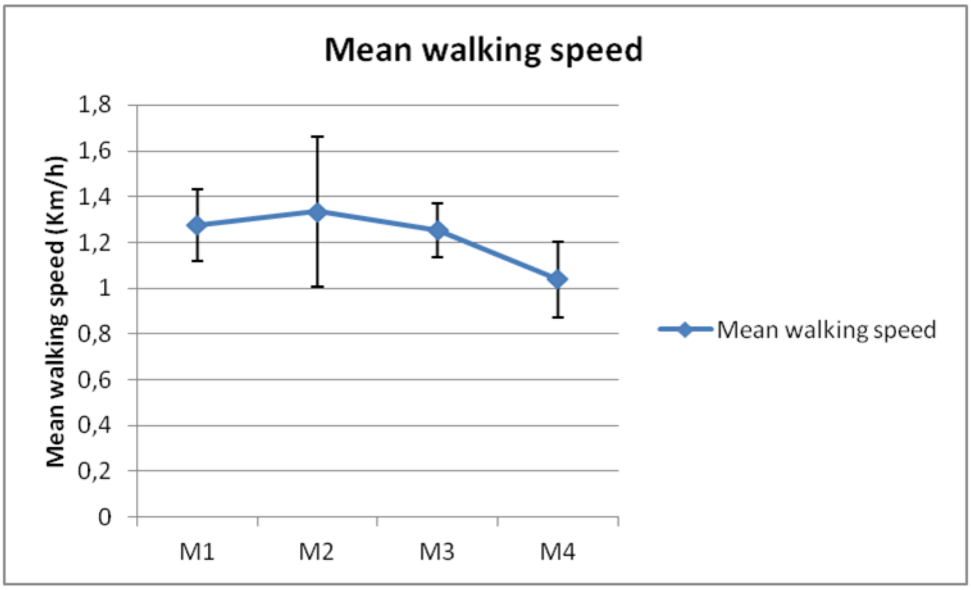



Figure 6-5. Changes in mean walking speed in PwMS (exemplified for one patient)

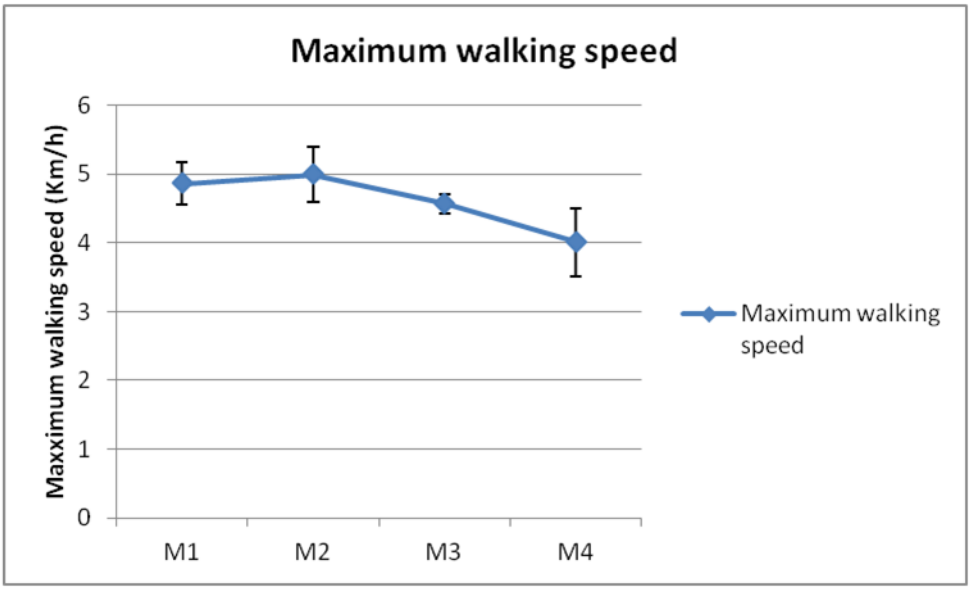



Figure 6-6. Changes in maximum walking speed in PwMS (exemplified for one patient)

Furthermore, the differences in MVPA and gait parameters were investigated in all patients combined. In comparison to baseline, 81% of the patient showed a significant decline in the steps/day ($p = 0.008$) as well as in MVPA ($p = 0.03$), 63% showed significant reduction in maximum walking speed ($p = 0.02$) between first phase and the follow-up fourth phase. Mean walking speed did not demonstrate a significant decline ($p = 0.75$) (Table 6-6).

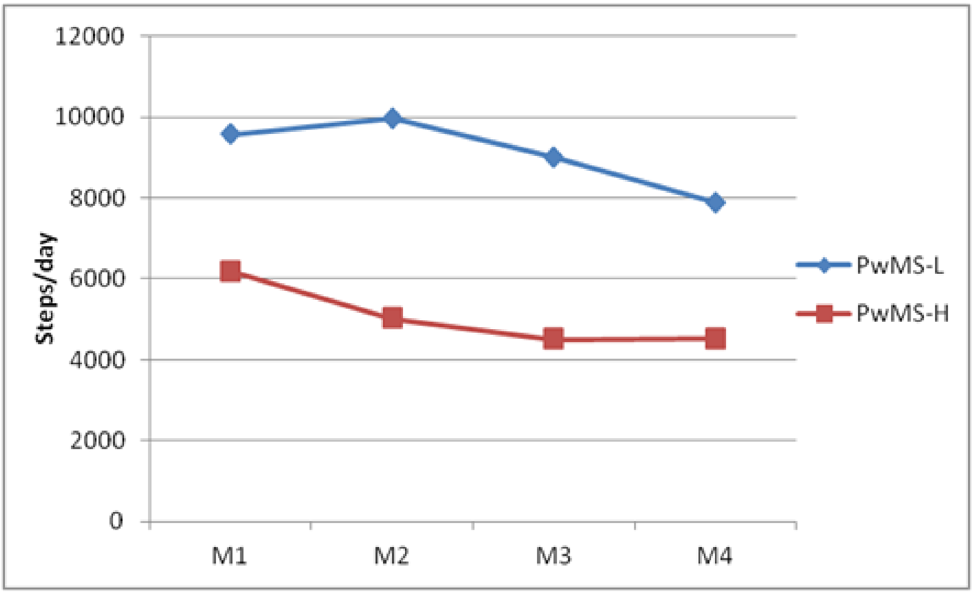
### 6.4.2 Between groups differences

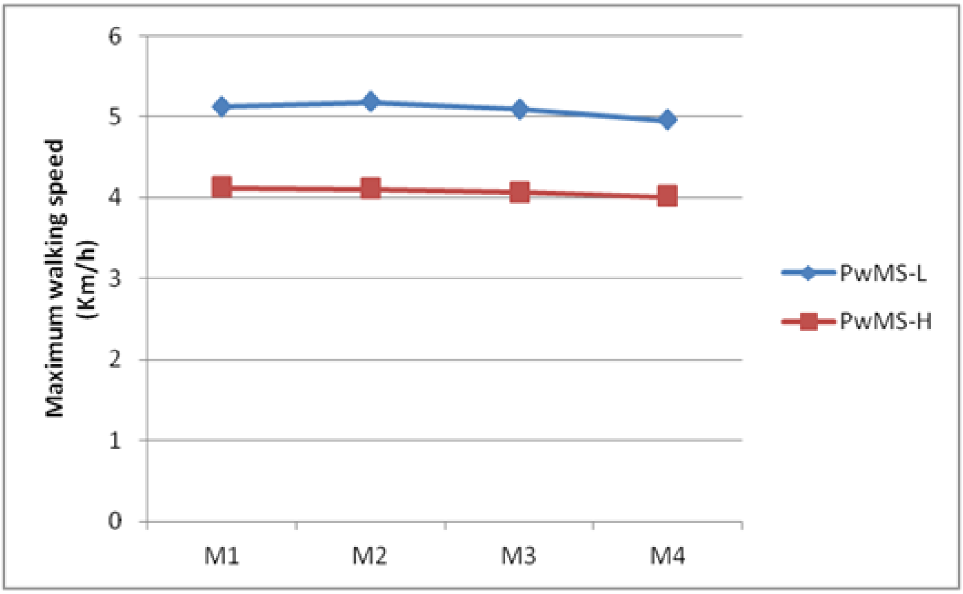
To understand the impact of MS disease on mobility and walking ability the differences between PwMS-L and PwMS-H were investigated. on average of overall measurements, mild affected MS accumulated significantly more steps, and had faster mean walking speed compared to moderated affected MS (9287.33 ± 1976.25 vs. 5043 ± 2849.75, $p < 0.005$; 1.49 ± 0.2 vs. 1.13 ± 0.44, $p = 0.03$), respectively. Furthermore, a marginal difference between the subgroups in maximum walking speed was noticed (5.09 ± 0.6 vs. 3.84 ± 1.03, $p = 0.08$). On contrary, MVPA demonstrated non-significant differences between both MS groups (11.6 ± 4.37 vs. 7.79 ± 5.19; $p = 0.1$) (Table 6-2, Figure 6-7). As discussed in section 5.4 significant differences was also noticed in energy concentration ($p < 0.05$) whereas marginal differences was shown in peak frequency ($p = 0.08$).

Table 6-2. Differences between disability subgroups

| | PwMS-L (EDSS: 1-2.5) | PwMS-H (EDSS: 3-5) | p-value |
|---|---|---|---|
| **Steps per day** | 9287.33 ± 1976.25 | 5043 ± 2849.75 | 0.005* |
| **Maximum walking speed** | 5.09 ± 0.6 | 3.84 ± 1.03 | 0.08§ |
| **Mean walking speed** | 1.49 ± 0.2 | 1.13 ± 0.44 | 0.03* |
| **Energy concentration (%)** | 35.63 ± 20.19 | 31.67 ± 18.41 | < 0.05 |
| **Peak frequency (Hz)** | 1.54 ± 0.61 | 1.39 ± 0.68 | 0.08 |
| **MET Level % (MVPA)** | 11.6 ± 4.37 | 7.79 ± 5.19 | 0.1 |

*Note*: * Statistically significant ($p < 0.05$), § Statistically marginal significant


12000
10000
8000
6000
4000
2000
0
Steps/day
M1
M2
M3
M4
PwMS-L
PwMS-H


6
5
4
3
2
1
0
Maximum walking speed
(Km/h)
M1
M2
M3
M4
PwMS-L
PwMS-H

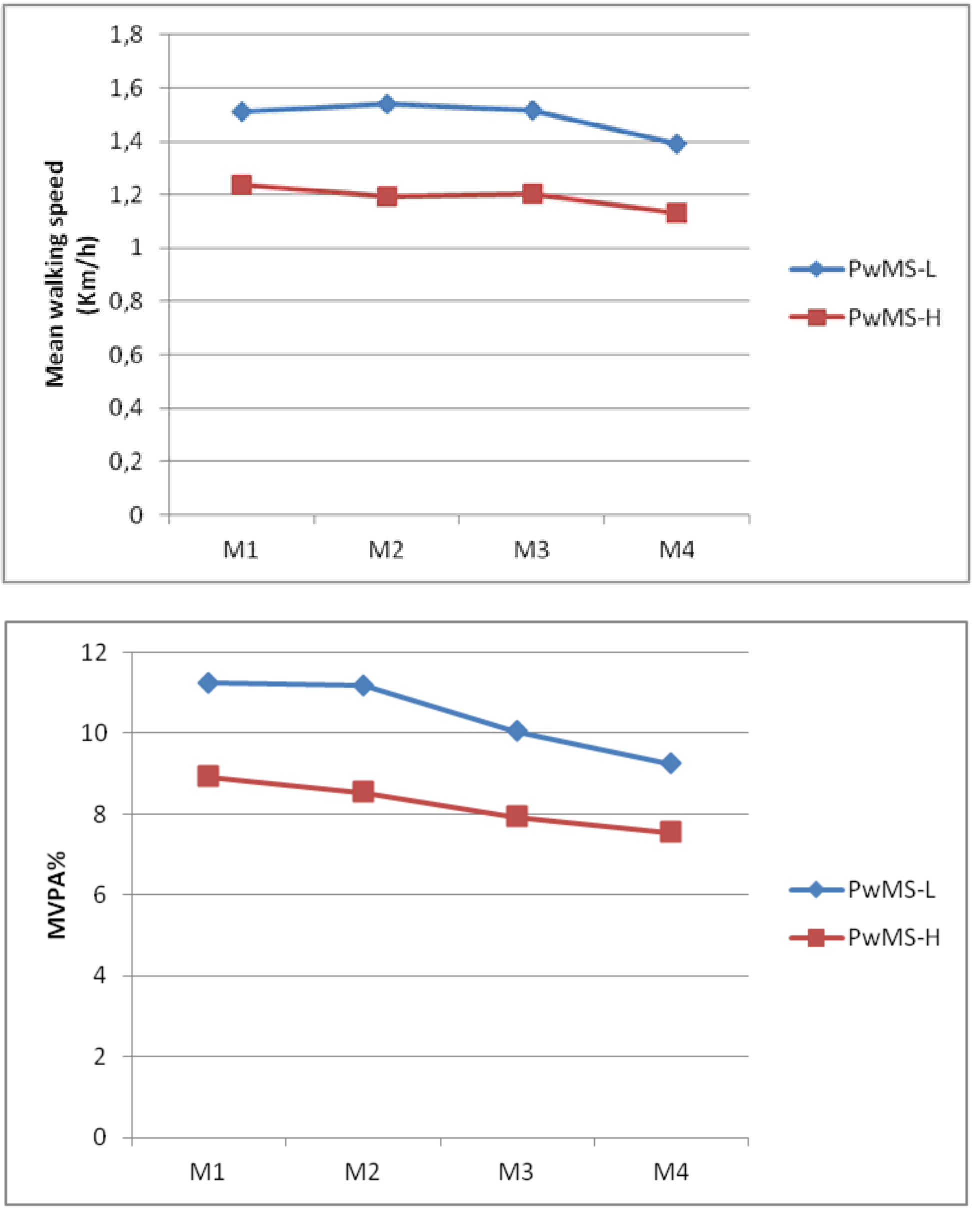



Figure 6-7. Difference between PwMS-L and PwMS-H

Correlation between Relatively weak correlation was found between the total number of steps and the EDSS score ($r = -0.54$, $p = 0.08$). High inverse correlation was notices between Walking speed and EDSS score ($r = -0.71$, $p = 0.01$), whereas maximum walking speed did not show a maximum correlation with EDSS score ($r = -0.37$, $p = 0.2$). Gait asymmetry also showed marginal significant correlation with the EDSS score ($r = -0.522$, $p < 0.05$). Both energy concentration and peak frequency showed significant correlation with EDSS score ($r = - 0.63$, $p < 0.05$; $r = - 0.751$, $p < 0.01$), respectively Table 6-3 illustrates the correlation coefficient between gait parameters and EDSS.

Table 6-3. Bivariate relationships between ambulatory parameters and EDSS

| | **Steps/day** | **Walking speed** | **Gait asymmetry** | **Peak frequency** | **Energy concentration** | **EDSS** |
|---|---|---|---|---|---|---|
| **Steps per day** | 1 | 0.758* | 0.727* | 0.636* | 0.55* | -0.541§ |
| **Walking speed** | | 1 | 0.782* | 0.327 | 0.376 | -0.706** |
| **Gait asymmetry** | | | 1 | 0.325 | 0.265 | -0.522§ |
| **Peak frequency** | | | | | 0.357 | -0.63* |
| **Energy concentration** | | | | | | -751* |
| **EDSS** | | | | | | 1 |

*Note* : * Statistically significant ($p < 0.05$), § Statistically marginal significant

It was also of interest to compare the physical activity and gait parameters between PwMS and healthy individuals. Therefore, the data from a healthy population study [151] was used. To investigate the differences regarding activity and gait parameters between the healthy population and the MS subgroups, Cohen's d and effect sizes r was calculated for the parameters MVPA and steps per day during baseline and the first follow-up measurement (after three months). The effect sizes ranged from 0.4 to 0.9.At baseline, the difference between PwMS-L and PwMS-H in MVPA showed medium to large effect sizes ($d = 5.5$; $r = 0.6$), similar to the differences between PwMS-L and healthy group ($d = 2.9$; $r = 0.8$). The difference between PwMS-H and the healthy group was small ($d = 1$; $r = 0.4$). For the second follow-up measurement, the differences between PwMS-L and PwMS-H in MVPA showed medium effects sizes ($d = 1.54$; $r = 0.61$) as was the case for the difference between

PwMS-Hand healthy group (d = 1.17; r = 0.5).The difference between PwMS-L and healthy group had a large effect size (d = 4.2; r = 0.9).

### 6.4.3 Precision and minimal detectable change

As it is aforementioned in the section of data analysis, the first step before investigating SEM and MDC is to calculate the stability (ICC) of the measure. The calculated ICC values for MVPA and gait parameters revealed a fair stability for mean walking speed (0.49 (0.27, 0.76)), steps/day (0.5 (0.35, 0.75)), and MVPA (0.47 (0.25, 0.75)). The ICC value of maximum walking speed indicated high intra-individual stability of this parameter (0.84 (0.69, 0.94)).

***Patients with MS***: Table 6-4 shows the values of ICC calculated between the first (baseline) measurement and the second ($M_{1,2}$), third ($M_{1,3}$) and fourth ($M_{1,4}$) follow-up measurements. The SEM and clinically important change index (MDC) for the overall sample are also given. The range of ICC values for all parameters across three months was 0.86 to 0.96, across six months 0.8 to 0.95 and across nine months 0.67 to 0.96. The ICC value across all measurements was calculated. Based on this ICC value we determined the overall SEM.

The SEM provides an indicator of measurement precision and should be considered together with overall mean values. The maximum walking speed showed the best precision estimates. The overall SEM for maximum walking speed was 0.23 m/s, where the mean value was 4.54 m/s, indicating that the change of 0.23 m/s may be due to measurement error. Mean walking speed showed a lower precision (SEM= 0.19 m/s, mean = 1.38 m/s). In comparison, the SEM for steps per day was 1588 steps per day (where the mean value was 7358 steps per day) indicating that a change of up to 1588 steps per day may be due to measurement error. The MVPA MET level showed the lowest precision (SEM = 2.59, mean = 9.88). The maximum walking speed showed the lowest MDC and MDC% values between baseline and follow-up measurements, whereas mean walking speed showed a greater MDC. MVPA and steps per day had the largest estimate of MDC and MDC% values.

Table 6-4. ICC, SEM, MDC and MDC % for ambulatory parameters of overall patients' group

| Parameter | ICC | | | SEM | | | MDC | | | MDC% | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $M_{1,2}$ | $M_{1,3}$ | $M_{1,4}$ | $M_{1,2}$ | $M_{1,3}$ | $M_{1,4}$ | $M_{1,2}$ | $M_{1,3}$ | $M_{1,4}$ | $M_{1,2}$ | $M_{1,3}$ | $M_{1,4}$ |
| max WS (m/s) | 0.96 | 0.95 | 0.96 | 0.06 | 0.07 | 0.06 | 0.18 | 0.2 | 0.17 | 3.9 | 4.7 | 3.9 |
| mean WS (m/s) | 0.87 | 0.82 | 0.71 | 0.09 | 0.11 | 0.14 | 0.26 | 0.31 | 0.4 | 19.5 | 23.3 | 30.31 |
| Steps (per day) | 0.9 | 0.81 | 0.87 | 824 | 1150 | 937 | 2285 | 3189 | 2597 | 28.3 | 42.55 | 36.03 |
| MVPA (%) | 0.86 | 0.81 | 0.67 | 1.3 | 1.5 | 2.1 | 3.73 | 4.43 | 8.82 | 35.34 | 46.13 | 59.51 |

*Note:* max WS = maximum walking speed; mean WS = mean walking speed; MVPA = moderate to vigorous MET level

***Disability subgroups***: ICC, SEM and MDC% for PwMS disability subgroups are given in

Table 6-5. The ICC estimation indicated that maximum walking speed and steps per day were stable across all measurements for both groups (ICC > 0.8). Considering steps per day in the group of moderate disability, the stability between baseline and third measurement ($M_{1,3}$) (ICC = 0.6) was lower than the one noticed in the other two follow-up measurements (ICC > 0.8). Furthermore, the ICC values were greater for mean walking speed and MVPA MET level in the moderate disability group between baseline and the second and third follow-up measurement (ICC range = 0.9– 0.98).However, the ICCs for these parameters in the moderate disability groups were lower but still acceptable for the fourth follow-up measurement. The ICC values for maximum walking speed as well as for steps per day showed greater reliabilities between baseline ($M_1$) and all follow-up measurements ($M_2$, $M_3$, $M_4$) in the group of mild disability. ICC value for mean walking speed indicated acceptable reliabilities for all follow-up measurements (ICC range = 0.6– 0.7). MVPA MET level showed high reliabilities between baseline $M_1$ and $M_2$ and $M_3$. However, the ICC value was lower in $M_4$. Maximum walking speed showed the best precision estimates across time, whereas mean walking speed and steps per day showed a poorer, but still acceptable precision. The MDC% values for maximum and mean walking speed were lower in both groups than for steps per day and MVPA MET level. However, the MDC% values for physical activity and gait parameters were greater in PwMS-L than in PwMS-H. This result indicates that the variability of the measurements might be sensitive to the level of disease severity.

## 6.5 User Acceptance

For successful integration of new technologies in healthcare scenarios issues of acceptability and acceptance should be taken into account. In the development of an ambulatory assessment system, many critical factors regarding medical, technical and user specific aspects should be considered. The present system was developed for an ambulatory environment to collect information about ADLs of PwMS. Therefore, it had to be easy to use and wearable without disturbing patients in their daily routine. Furthermore, it must be possible for the patients to use the system easily by themselves at home. To assess the acceptance of the system a questionnaire was designed with main focus on two factors; usefulness and ease-of-use of the system. The questionnaire was based on the Technology Acceptance Model (TAM). The TAM is a technology adoption model that considers user acceptance of information system.

In medical studies usefulness is the most important factor of user acceptance for all involved parties. For chronic patients, such as PwMS, the crucial condition to accept new technology is to have medical benefit, i.e., the developed methods should be advantageous for diagnosis and therapy of MS. Furthermore, it is important for the patient that the physician and healthcare staff will be able to get better overview of the medical data about their disease course and health condition. Thus, the usefulness factor mainly considers the question; whether the patient believes that the technology could enhance the access and improve the understanding of his/her health condition. Furthermore, the delivered daily report and feedback about individual's activity information could influence the activity level of the patients and integrate them in the management of their disease. Therefore, the designed questionnaire also considered the importance and usefulness of the daily feedback provided to the patient was investigated.

Usability and ease-to-use factors certainly influence user acceptance. Usability is the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use (ISO 9241).Therefore, it should be hardly considered because a problem with the usability could influence the medical usefulness and thus the user acceptance and attitudes towards the system. During the development of the system the adoption of patient's abilities and life condition was considered. Therefore, the difficulty for the patient to operate and interact with the system and to handle the sensor presents an important factor of the usability and ease-to-use.

In order to better predict, explain and increase the usage of IT, it is importance to understand the antecedents of patients' technology adoption and their IT-background. This background can affect the acceptance of the system. Appendix xx illustrates the questionnaires was used in this work.

To evaluate the acceptance of the system and whether it was sufficiently easy to handle, patients who were monitored by the system (n = 11) completed a separate acceptance questionnaire at the end of the first ambulatory measurement phase. The aim was to investigate how acceptable is the developed system in term of completion by the participants, does it represent a burden and is it easy to administer and process. The questionnaires contain questions regarding:

a) The usage of technical equipment in general and especially the overall acceptance of IT-technology as a treatment and therapy support tool, e.g. “I always willing to test new intervention forms”
b) Patient’s health condition and to which level they are interested in having detailed information about the disease and to use new technology to manage their MS, e.g. “I always search for new information about MS”
c) Patients’ expectation from the developed system and its usefulness, e.g. “The system gives my doctor objective information about my health status”
d) System operation and feedback, e.g. “The operation of the system is complex”, “The daily feedback motivates me”.

### 6.5.1 Results:

The questionnaires were rated on five-point Likert scale, which is the commonly used scale in survey research. It measures the individuals’ attitudes by asking the extent to which they agree or disagree. The typical scale is (1 = strongly agree, 2 = agree, 3 = neutral, 4 = disagree, 5 = strongly disagree).

In general, most of the patients are well informed about the disease (mean = 1.6; SD = 0.5) and always looking forward get more detailed information. “I always try to keep my knowledge to my illness up to date” (mean = 2.1; SD = 1.1). The results showed that PwMS are interested in testing new treatment and intervention methods. “I always looking for a new treatment methods” (mean = 1.9; SD =1.2), “I am ready to test new treatments” (mean = 1.9; SD = 0.8). Only two patients reported fewer tendencies towered new interventions. Figure 6-8 illustrates the results regarding patients’ tendency towards new treatment’s form (Set 1).

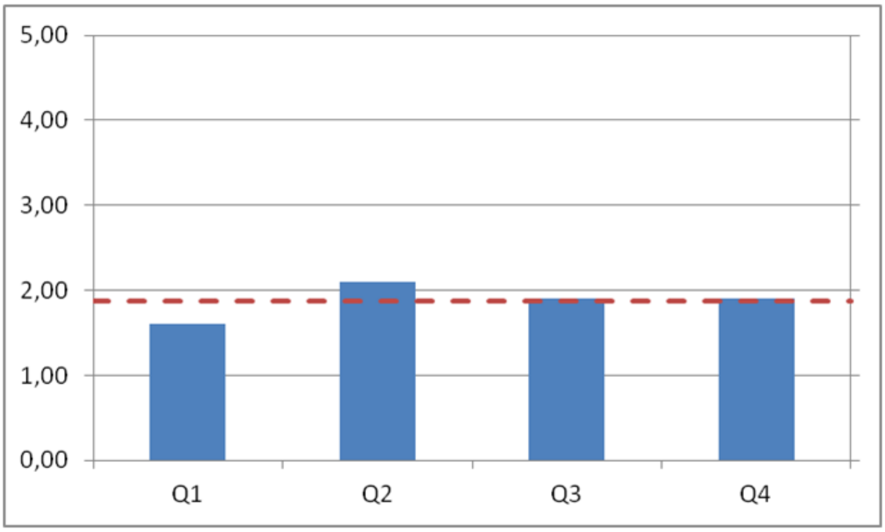



Figure 6-8. Mean values of the questionnaires' results - Set 1

Moreover, patients in general showed an open-minded attitude towards the integration of the technology (sensor and software) in the treatment and monitoring process. The results reported (mean = 2.1; SD = 1.2) as a response to the questions “I have positive attitude towards modern technology”. Regarding the usage the systems, the results showed that the patients in general have positive perceptions and do not have problems using new technology (sensor). This has been confirmed by the responses to the question “I have no problem with using the telemedicine technology” (mean = 1.35; SD = 0.6), and to the question “I will not feel overstrained using the new technology” (mean = 1.2; SD = 0.4). Moreover, PwMS did not expect to need extra effort in order to deal with the system, as the results to the question “I won’t need to put out extra effort and I will accept the system” showed (mean = 1.2; SD = 0.4). Figure 6-9 illustrates the results regarding patients’ attitudes towards telemedicine technology (Set 2)

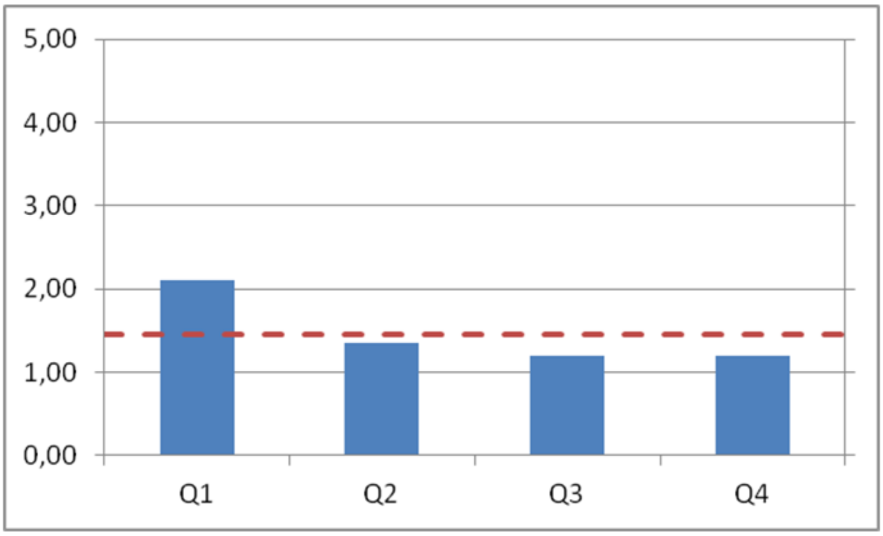



Figure 6-9. Mean values of the questionnaires' results - Set 2

Long-term objective data of patient's daily physical activity and gait parameters are considered to be essential to objectify the assessment of their motor and walking ability. Therefore, patients hoped that the developed technology will provide more up to dated and detailed information about their conditions and also hope that such a system will improve the documentations of their medical history. The acceptance analysis showed that most PwMS believe that the employed system was a positive technical development that could be useful for patients with chronic illness and improve medical care. Moreover, patients showed positive expectation (mean = 1.2; SD = 0.4) as response to the question "The system will provide my physician with objective overview", as well as to the question "The objective documentation will help to improve my health status" (mean = 1.6; SD = 1.2). However, the acceptance of most patients is linked to their satisfaction with information and support given by their physicians. This was confirmed by the question "The acceptance of my physician is important" (mean = 1.3; SD = 0.4), and the question "I would like to be indicated to me from my physician" (mean = 1.3; SD = 0.5). Figure 6-10 illustrates the results regarding the usefulness system (Set 3).

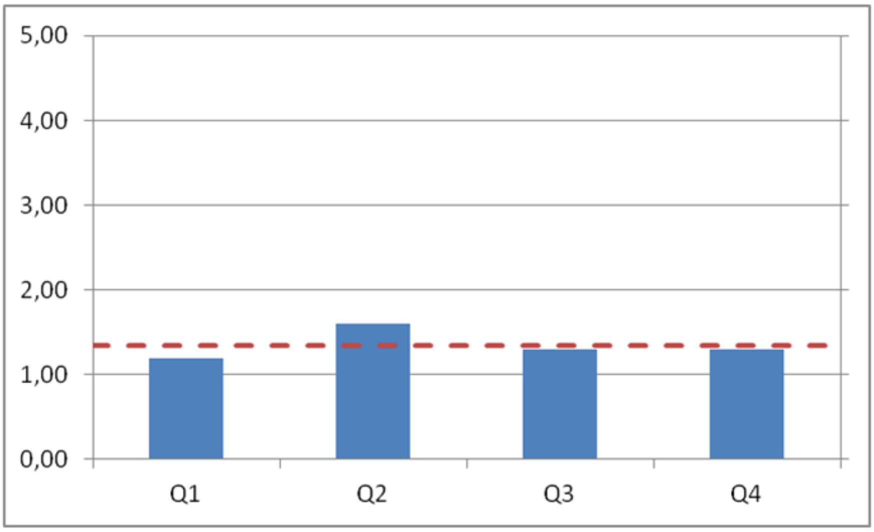



Figure 6-10. Mean values of the questionnaires' results - Set 3

The system was generally well accepted by the patients. "I got along with the sensor well" (mean = 1.2; SD = 0.4). Furthermore, the sensor data were read out automatically via the developed end-user software and IT skills were not required and the patients reported high satisfaction with the easy-to-use and efficiency of the system. This was confirmed by the responses to the questions: "was the system easy to handle?"(mean = 1.4; SD = 0.4), "There is no need for me to get more interaction with the software" (mean = 2.9; SD = 1.3). Figure 6-11 illustrate the general user acceptance analysis of the system and ease-of-use (Set 4).

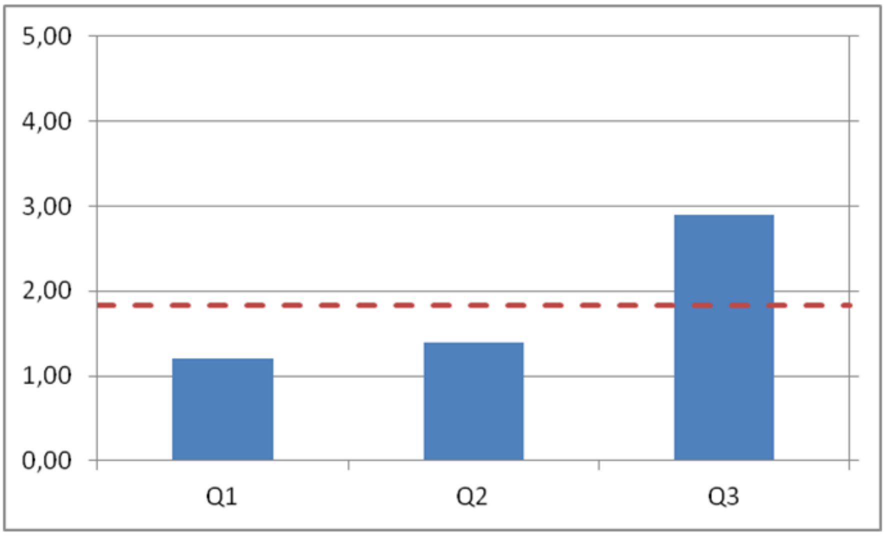



Figure 6-11. Mean values of the questionnaires' results - Set 4

An important aspect of perceived usefulness was the experience of individual feedback and the patients express that, without getting any information about their daily situation is the usefulness and the personal benefit of the system doubtful. Patients also reported positive results regarding to be informed about their condition at home and not only at physician visit “I would prefer to receive the analysis also at home and only at the physician’s office” (mean = 2.5; SD = 1.5). Furthermore, the daily feedback about their physical activity has motivated the patients to patients to stay active: “The daily feedback motivates me” (mean = 2.1; SD = 1.2). Additionally, they were interested in having more detailed and comprehensive information about their activity analysis during the measurement: “I want to get more information about the data during the measurement” (mean = 2.1; SD = 1.5). Figure 6-12 illustrates the results regarding the daily feedback (Set 5).

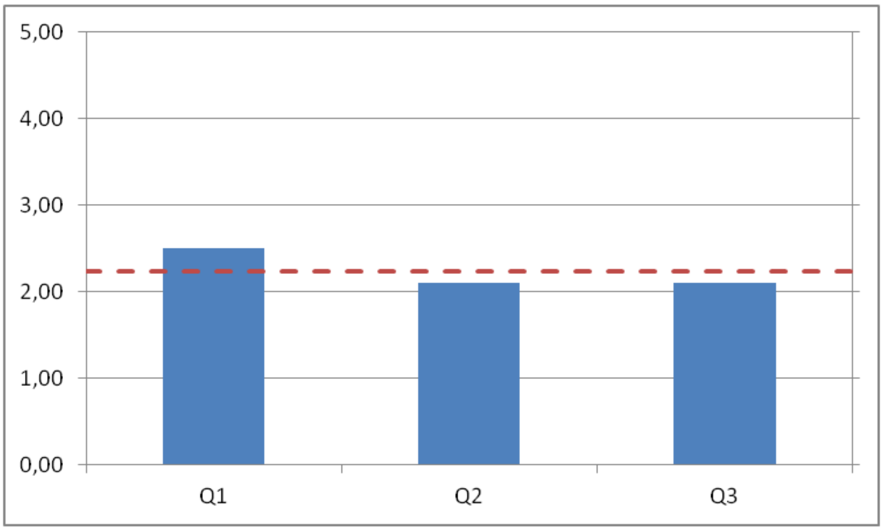



Figure 6-12. Mean values of the questionnaires' results - Set 5

## 6.6 Summary

A simple triaxial accelerometer was applied to assessed slightly changes in physical and gait behavioral in PwMS over a long period of time. Results showed that the ambulatory captured parameters are more sensitive and responsible to slight disability changes than the clinical measures. Acceptable to excellent reliabilities were observed for all activity and gait parameters. Differences were found for precision and minimal delectable change between baseline and follow-up measurements. The MDCs values are clinically useful because they might help to determine necessary amount a repeated measurement would need to differ from the initial value in order to be considered as a true change. Therefore, MDCs value reported in this study may also be incorporated into clinical decision making. In general, all parameters showed lower MDCs in first than in the follow-up measurements. This information could be useful for the interpretation of activity and gait measures in PwMS within three months, six months to one year. Long-term activity and gait monitoring of activity and gait parameters thus offers the opportunity to comprehensively assess the pattern of behavioral change across prolonged periods of time. This information may assist in the process of clinical decision making in the context of neurological rehabilitation and intervention and thus help to eventually improve the patients' quality of life.

The results of the acceptance analysis indicated that the acceptance of the developed method and system was high and the compliance to use the system was acceptable. Moreover, the results showed that most of the patients have an open-minded attitude towards the sensor and the developed software. Almost all the queried patients believe that technologies are positive technical development and they appreciated the daily feedback pertaining to their activity pattern and reported that this was a factor that encouraged them to maintain their activity level.

Table 6-5. ICC, SEM, MDC and MDC % for ambulatory parameters of patients' subgroups. Comparison of changes from baseline (M1) to follow-up measurements.

| Parameter | Group | ICC | | | SEM | | | MDC | | | MDC% | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $M_{1,2}$ | $M_{1,3}$ | $M_{1,4}$ | $M_{1,2}$ | $M_{1,3}$ | $M_{1,4}$ | $M_{1,2}$ | $M_{1,3}$ | $M_{1,4}$ | $M_{1,2}$ | $M_{1,3}$ | $M_{1,4}$ |
| max WS | PWMS-L | 0.84 | 0.86 | 0.9 | 0.15 | 0.15 | 0.11 | 0.41 | 0.43 | 0.32 | 8.09 | 8.51 | 6.3 |
| (m/s) | PWMS-H | 0.94 | 0.92 | 0.94 | 0.06 | 0.07 | 0.06 | 0.18 | 0.22 | 0.17 | 4.6 | 5.1 | 4.6 |
| mean WS | PWMS-L | 0.7 | 0.6 | 0.63 | 0.17 | 0.2 | 0.2 | 0.48 | 0.56 | 0.53 | 32.1 | 37.2 | 37.1 |
| (m/s) | PWMS-H | 0.9 | 0.9 | 0.75 | 0.06 | 0.06 | 0.1 | 0.17 | 0.17 | 0.27 | 15.1 | 15.1 | 24 |
| Steps | PWMS-L | 0.86 | 0.85 | 0.81 | 1224 | 1263 | 1445 | 3394 | 3501 | 4005 | 33.4 | 37.5 | 46.3 |
| (/day) | PWMS-H | 0.95 | 0.6 | 0.8 | 413 | 1218 | 844 | 1145 | 3378 | 2340 | 20.4 | 63 | 43.7 |
| MVPA | PWMS-L | 0.88 | 0.61 | 0.31 | 1.56 | 2.77 | 3.71 | 4.31 | 7.68 | 10.28 | 34.6 | 68.5 | 90.1 |
| (%) | PWMS-H | 0.96 | 0.91 | 0.53 | 0.51 | 0.81 | 1.87 | 1.43 | 2.22 | 5.19 | 17.3 | 27.7 | 64.6 |

*Note:* PwMS-L = group of mild disability, PwMS-H = group of moderate disability

Table 6-6. Gait parameters and MVPA MET level in patients with MS and disability subgroups

| Parameter | PwMS-overall | | | | PwMS-L (mild disability) | | | | PwMS-H (moderate disability) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M1 | M2 | M3 | M4 | M1 | M2 | M3 | M4 | M1 | M2 | M3 | M4 |
| Steps(/day) | 8059±4183 | 8087±4583 | 6354±3510 | 6931±3784* | 9628±3856 | 7872±3305 | 10647±4257 | 9002±3648 | 6177±3798 | 4533±2840 | 5014±2691 | 4448±2070 |
| maxWS(m/s) | 4.5±0.9 | 4.4±1.04 | 4.5±1.2 | 4.02±0.7* | 5.13*±0.61 | 4.96*±0.8 | 5.18*±0.63 | 5.1*±0.56 | 3.92*±0.97 | 3.82*±0.97 | 3.89*±1.2 | 3.85*±1.13 |
| meanWS(m/s) | 1.36±0.5 | 1.35±0.4 | 1.2 ±0.3 | 1.34± 0.5 | 1.52§±0.33 | 1.54±0.33 | 1.49±0.28 | 1.52±0.3 | 1.18§±0.55 | 1.08±0.4 | 1.13±0.5 | 1.13±0.53 |
| MVPA (%) | 10.18±5.5 | 9.03±4.5 | 10.1±5.5 | 9.3±4.7* | 11.5±4.9 | 10.4±3.8 | 13.5±4.7 | 11±4.1 | 8.65±5.98 | 7.42±4.91 | 7.82±4.95 | 7.42±4.91 |

*Notes: Means and SD are given. Max WS = maximum walking speed; mean WS = mean walking speed; MVPA = moderate to vigorous MET level; *: significant p-value; §: marginal p-value*

# 7 Ambulatory assessment system to evaluate the effect of pharmacological intervention

Usually, the investigation of the motor and gait ability in response to physical or medical treatment bases on stationary assessed parameters. However, this method is time costly and unable to reflect patients' activities in real conditions. Therefore, the aim of this study was to objectively investigate the effectiveness of the medication treatment (Fampridine) using the gait parameter assessment system developed in this work and to compare the results with those assessed in the clinic. Comprehensive analysis of gait features in frequency and time-frequency domain can provide complementary information to understand gait patterns. Therefore, in the following study, the parameters peak frequency and energy concentration were integrated along with the previous discussed parameters (time-domain parameters) (chapter 6).

## 7.1 Study Design, Data Fusion and Reduction

The following study was carried out in contribution with MS Center, Dresden University of Technology, Germany. In this study the activity and gait parameters were assessed using the accelerometer for evaluating the changes of these parameters under fampridine-therapy. 26 patients (mean age: 49.6 years, mean EDSS score: 5.6) were recruited in the study. Initial investigation (phase1) was followed by fampridine therapy for 14 days (phase2). Quantitative and qualitative gait parameters (T25FW, 2-MWT, MSWS-12) were assessed in both phases to investigate fampridine response on walking impairment of PwMS. Based on the clinical tests patients were classified as responder and non-responder. Patients of responder group (R) (mean age = 48,1, mean EDSS = 5,8) showed an improvement in gait performance during phase 2 (after Fampridine intake), whereas the patients of the non-responder group (NR) (mean age = 56 year, mean EDSS = 4) did not show any improvement or had a decline during phase 2.

The system used for the ambulatory assessment was the one described in chapter 5. Patients were asked to carry *move II* during their normal daily activities. As Detailed information about the system usage can be found in chapter 6. In phase 1 patient carried the sensor for 8 days on average and in phase 2 for 10.7 days on average. The sensor was carried for 13.3h on average per day.

The patient was excluded from the analysis if she/he did not wear the sensor for at least 5 days a’ 8h or 10 days a’ 8h, before and after fampridine intake, respectively. Furthermore, if the data from phase 1 or phase 2 are missing the patient was excluded. The total number of patients included in the analysis was 22 patients.

## 7.2 Data Analysis and Classification

The first step before developing the classification method is to extract gait parameters. The input signals were assessed during every day activities, thus in contains different types of physical activity including sitting, standing and lying. However, the parameters of interest are those that occur during move activities, such as walking and jogging. Therefore, the physical activity algorithms developed in [152] was firstly applied. The segments of signal correspond to the move activities were then separated for the analysis. After that the segments were transformed in a parameter vector. For walking speed estimation 3s signal overlapping was used, whereas for all the other parameters the extraction was done over 1s segment (Figure 7-1). Detailed information about parameter extraction and developing were presented and discussed in chapter 5.

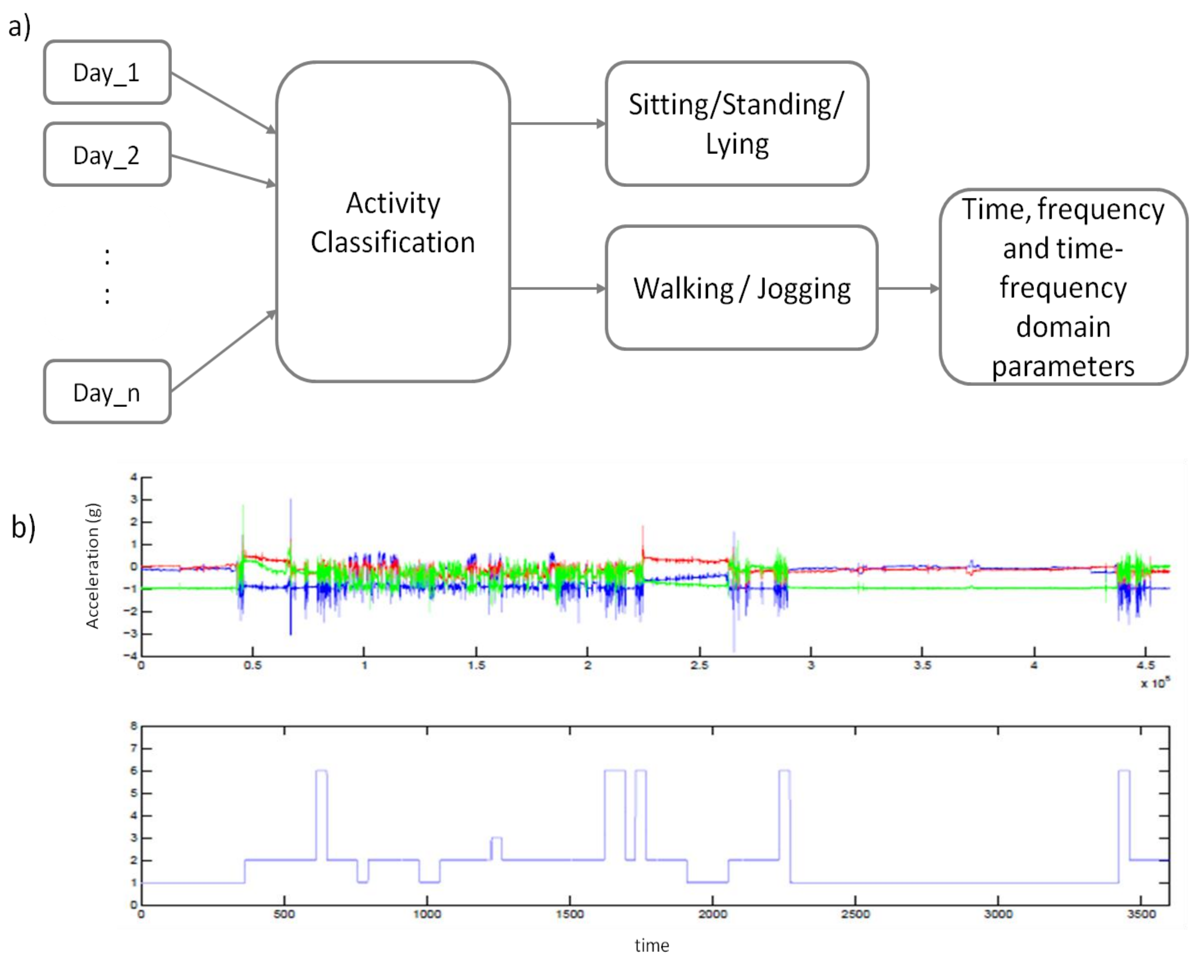



Figure 7-1. Process of gait parameters extraction (a); Example of signal segment with activity classification (b)

### 7.2.1 Parameter Selection

The hypothesis was that the developed system and parameters should be able to determine whether the patients show an improvement in gait parameters in phase2 in comparison to phase1 or not. Therefore, before starting with the classification the parameters were tested using box plot method. The investigation based on the clinical determination of R and NR. Patients in R group showed improvement in phase2 in comparison to phase1 (Figure 7-2). The paired sample *t-test* was used to investigate the improvement statistically. Significant improvements were shown in steps/day: $p = 0.001$, asymmetry: $p < 0.05$, step length: $p < 0.05$, walking speed: $p = 0.01$, energy concentration: $p < 0.05$ and peak frequency $< 0.05$. However, they showed marginal significant improvement in cadence $p = 0.08$. On contrary, patients in NR groups did not show any positive response to the fampridine treatment (Figure 7-3).

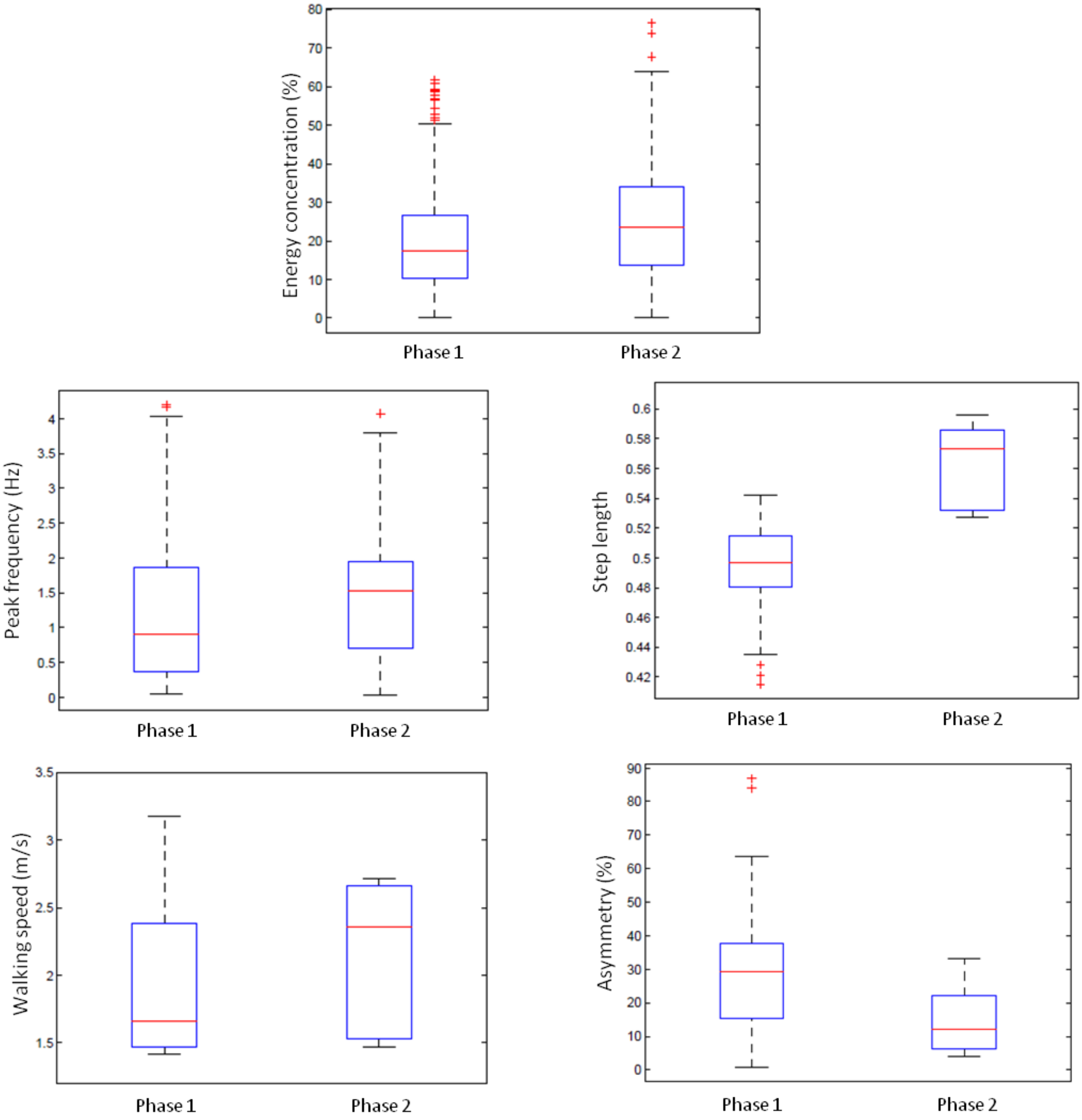



Figure 7-2. Gait parameters in response to the treatment (Responder)

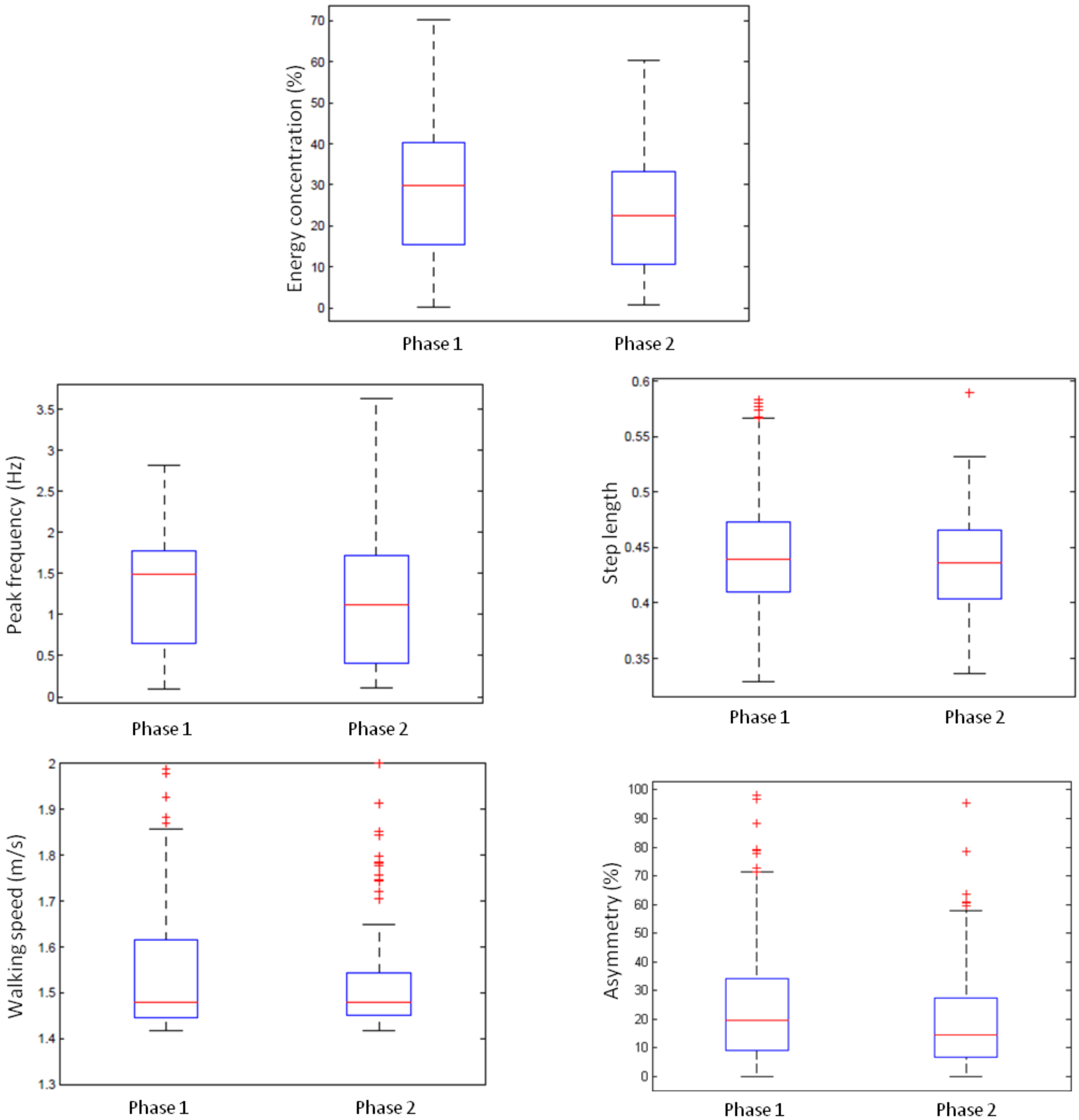



Figure 7-3. Gait parameters in response to the treatment (Non-Responder)

### 7.2.2 Classification

As it was mentioned above, the purpose of the analysis is to investigate the possibility to discriminate between two output response of fampridine-treatment, namely R or NR. The classification is based on the aforementioned gait parameters, which were assessed objectivity under free-living condition. Therefore, the main aim here was to use machine learning method for developing models to predict patients' response to treatment. After having the parameters of phase 1 and phase 2 extracted the classifier is to be constructed.

Using gait parameters as input data the classifier should give one output which is corresponding to the treatment response (i.e. responder or non-responder)

In this work, two different classification methods were used and investigated; decision tree and Support Vector Machine (SVM). Decision tree requires relatively little effort from users for data preparation especially when there are few decisions and outcomes included in the tree. Furthermore, decision tree need no assumptions of linearity in the data. SVM is considered to be stable method. It showed better accuracy over neural network methods in classifying individuals based on their gait pattern. Furthermore, SVM is able to model complex nonlinear decision boundaries and are much less prone to over fitting than other algorithms such as k-Nearest Neighbor and Naïve Bayes [153].

The Classification and Regression Tree (CART) was used in this work to generate the classification tree. Classification tree is built through the binary recursive partitioning process. SVM classifier with Gaussian Radial Basis kernel function (GRB) was used to build the classifier to identify responders and non-responders for fampridine-treatment. The classifier was evaluated using repeated random sub-sampling (RRS) with the ratio of 50%/50% of training/testing sub-dataset. This procedure was repeated several times with different sub-sets, which were randomly split based on RRS methods. (Figure 7-4) illustrates the whole process of the classification approach. The evaluation of the classifier includes the three performance measure:

$$Sensitivity\ (SE) = \frac{TP}{TP + FN} \qquad \text{Eq.7-1}$$

$$Specificity\ (SPC) = \frac{TN}{TN + FP}$$

$$F_{Factor} = \frac{2TP}{2TP + FN + FP}$$

$$Positive\ predictive\ value\ (PPV) = \frac{TP}{TP + FP}$$

Sensitivity, also called true positive rate or recall rate, is a statistical measure of how well a classification method correctly identifies a condition. Specificity, also called true negative rate, is a statistical measure of how well a classification method correctly identifies the negative cases. Accuracy is defined as a number or correct classification to the number of all cases. Positive predictive value, also called precision, is a statistical measure of the test performance. F_Factor is a statistical measure of performance on the test; it is a harmonic mean of precision and recall.

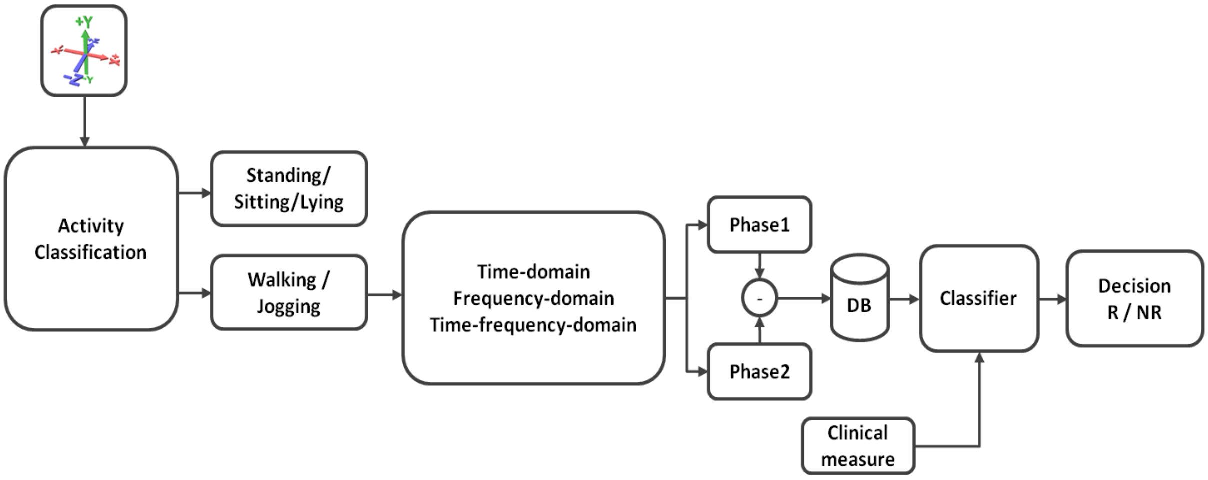



Figure 7-4. Process of the classification approach

Based on the results in section 7.2.1, whole parameters were included in the classification. However, different parameters combinations were investigated to determine the best combination that contains large amount of information regarding changes in walking ability in response to the treatment. Table 7-1 and Table 7-2 summarize the 5 best combinations of SVM and CART methods, respectively. Based on RRS validation, the best classification performance was achieved by applying SVM on a set of 2 parameters with sensitivity rate ranges from 71.2% to 78.2% and specificity rate ranges from 62.7% to 77.3%. Figure 7-5 illustrates the accuracy of the SVM classifier with different parameter combination.

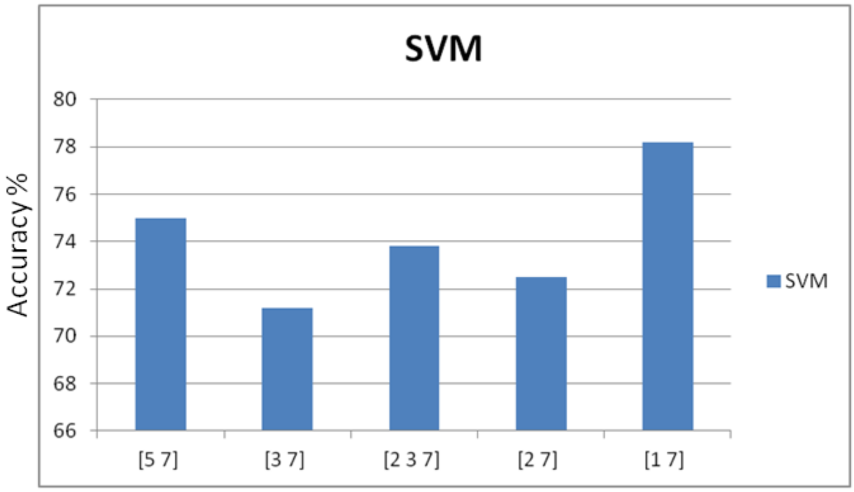



Figure 7-5. Classification of responder and non-responder patients using SVM classifier

CART classifier showed better sensitivity (82.7% - 85%) on set of 4 parameters. However, the specificity of CART classifier varies from 29.2% to 32%. Figure 7-6 illustrates the accuracy of the SVM classifier with different parameter combination.

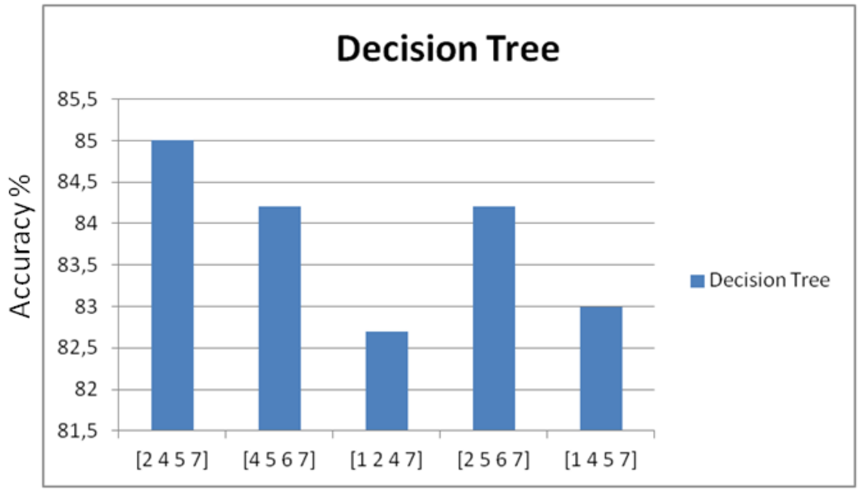



Figure 7-6. Classification of responder and non-responder patients using CART classifier

However, both classifiers showed high positive predictive value (PPV). For Decision tree the values of PPV range from 84.9% to 85.5% and for SVM the PPVs range from 91.1% to 93.7%. Based on these results, SVM with GRB kernel function can be used to objectively predict the responders to the treatment.

The results indicate that an intelligent classifier built by SVM and with an averaged sensitivity of 74% and average specificity of 72% can be applied to provide objective suggestion for patient's responses to therapy.

Table 7-1. Classification results using SVM with different parameters' combinations

| Parameters combination | Sensitivity (%) | Specificity (%) | PPV (%) | F_Factor (%) |
|---|---|---|---|---|
| [5 7] | 75% | 77.3% | 93.7% | 77.8 % |
| [3 7] | 71.2% | 76.8% | 93.5% | 75.5 % |
| [2 3 7] | 73.8% | 70.3% | 91.6% | 72.7 % |
| [2 7] | 72.5% | 72.9% | 91.1% | 71.5 % |
| [1 7] | 78.2% | 62.7% | 91.1% | 71.2% |

*Note:* 1 = steps, 2 = asymmetry, 3 = cadence, 4 = step length, 5 = velocity, 6 = energy concentration, 7 = peak frequency

Table 7-2. Classification results using CART with different parameters' combinations

| Parameters combination | Sensitivity (%) | Specificity (%) | PPV (%) | F_Factor (%) |
|---|---|---|---|---|
| [2 4 5 7] | 85% | 32% | 85.5% | 50% |
| [4 5 6 7] | 84.2% | 30.5% | 85.1% | 50% |
| [1 2 4 7] | 82.7% | 29.7% | 85.1% | 49.7% |
| [2 5 6 7] | 84.2% | 29.2% | 85.3% | 48.7% |
| [1 4 5 7] | 83% | 29.2% | 84.9% | 48.3% |

*Note:* 1 = steps, 2 = asymmetry, 3 = cadence, 4 = step length, 5 = velocity, 6 = energy concentration, 7 = peak frequency

## 7.3 Summary

In this chapter, the usage of machine learning algorithm to objectively assess the response of the medication treatment was discussed. From the result it can be concluded that the presented methods provide safe, unobtrusive, inexpensive and objective possible to classify the patients according to their response to the treatment with high sensitivity and specificity. Moreover, the WS-based technique used in this work will help to overcome the disadvantages of the single or multiple snapshot assessments in current clinical practice.

# 8 Discussion and Outlook

## 8.1 General Discussion

As highlighted in chapter 2, impairments of physical activity and gait are important neurobehavioral consequences of MS that may affect the patients' quality of life. Several tools have been employed to assess activity and walking ability in PwMS [36]. As discussed in chapter 4, contemporary methods to assess activity and gait impairment are regular clinical observations and laboratory assessment systems. These methods were found to be subject to a range of limitations, potentially limiting the capacity of assessing these impairments under free-living condition. Other researchers used wearable sensors to capture motor and walking disability. However, the assessment was either in clinical environment with short discrete motor tasks or over short period of time (e.g. 7 days). As such, the primary objective of this thesis was to design and develop a Home-based system capable to extract comprehensive gait parameters to help doctors monitor the changes of activity and walking ability objectively in customer environment. This system can be used in applications involving the monitoring of degenerative or improved health conditions. The common goal and consideration of the assessment system was to make the system as simple to use as possible. For example, the pre-subject calibrations were avoided in the development of the gait parameters' algorithms. Furthermore, especial software for data gathering and analyzing were designed to be completely automatic in *push-button* style interface (chapter 5). Moreover, the algorithms had to be developed using only one measurement device, i.e. wearable sensor, which is suitable for free-living data assessment. There are many types of sensors that can be used for the aim of this thesis. Due to methodological problems of assessment devices, such as gyroscopes, pedometers and pressure sensors, accelerometers have increasingly been considered as the "new gold standard" to measure free-living activities. Triaxial accelerometers have been proven to be more sensitive to detect differences of physical activity in patients with mobility and walking impairments such as PwMS. Therefore, in this work triaxial accelerometer was applied. The contribution of this work was the development of comprehensive gait parameters using one triaxial accelerometer.

The most challenging part of the thesis was to develop several new methods and algorithms to detect and quantify various motor and gait abnormalities while the patients were performing their daily activity. The methods developed in this thesis were able to assess several gait parameters in time, frequency and time-frequency domain using one triaxial accelerometer attached to the hip. Recent studies on MS have increasingly assessed gait parameters, such as walking speed and number of steps as it is believed to be an indicator of disability and progression of neurological disease. Therefore, this work aimed to develop algorithms for walking speed estimation and step detection. Walking speed estimation algorithm was realized using SVR regression methods. Different models were developed; model for jogging activity, model for walking slow and fast and the third model was a general model for jogging and walking activities. The accuracy of the algorithm was investigated using the data from healthy control as well as data from PwMS. The average speed error using data from healthy control was 0.16m/s when using the general model and 0.29m/s and 0.07m/s when using the jogging and slow/fast model, respectively. Using the data collected from PwMS during 10-meter walking test, the accuracy of the algorithm was reported to be 0.24m (0.02%). Step detection algorithm was based on zero-crossing method was developed and the sensitivity (SE) and positive predictive value (PPV) were calculated. On average, the algorithm has high SE and PPV of 99.93% and 99.95%, respectively for slow/fast walking, jogging and walking up-downhill.

Asymmetric gait is commonly observed in conjunction with a decline in walking ability. Therefore, it is considered to be one of the important gait characteristic that is increasingly reported by PwMS. The main research gap related to gait asymmetry analysis in PwMS were investigated from two perspectives; objectivity of the analysis system in general, the ability of applying the system in every-day life for a long time (chapter 5). Therefore, one of the key aims of this work was to develop an algorithm able to capture gait asymmetry in PwMS in their free-living environment using one triaxial acceleration sensor. Two different parameters were used to build $SI$, namely step length and swing time. PwMS showed differences between both foot ($p<0.05$). Furthermore, in comparison with healthy control PwMS showed less gait symmetry in both indices ($p<0.01$).

Frequency and time-frequency domain gait parameters have been considered as a powerful tool to identify and analyze gait changes. Several researches have investigated gait parameters in frequency and time-frequency domain, however, either with complex, costly demand laboratory-based system or with WS-based system with multiple sensors attached to the body. The contribution of this work was the development of an algorithm to extract parameters such as, peak frequency and energy concentration using an accelerometer attached to the hip. Patients with moderate disability showed significantly low energy concentration in compare to patient of mild disability group ($p<0.05$), whereas, peak frequency showed significantly marginal differences between both groups ($p=0.08$).

Using the Home-based measurement system and the algorithms developed in this work, many daily activity measurements of PwMS have been performed. As a result, rich 902 days with daily-activities of PwMS were collected in two different studies. First of all, the system was employed in a long-term study of one year period of time. In this study, motor and gait parameters were collected to objectively investigate the ability of the developed system in capturing the minimal change in activity behavior of PwMS even in absence of clinical signs. Therefore, the parameters were assessed in four follow-up measurements phases with three months intervals. This frequency is important to be able to capture the early slightly changes and hence help in just-in-time treatment adjustment and optimization. The results showed that motor and gait parameters of PwMS assessed during their daily-activities are more responsive to the slight disability changes than the clinical measures. The PwMS demonstrated significant decline in ambulatory parameters at follow-up measurements. This was, for example, revealed by lower number of steps and slower walking speed, -23.20%, -5.3%, respectively. Furthermore, the results showed that there is correlation between EDSS score and gait parameters (number of steps: $r=-0.54$; walking speed: $r=-0.71$; asymmetry: $r= -0.53$; energy concentration: $r=-0.71$; Peak frequency: $r=-0.63$). These correlations provide evidence that physical and gait parameters measured by the Home-base system can be used to monitor the patient's clinical status.

After the usage of the developed parameters was investigated for its ability to capture the changes of motor and gait behavioral under free-living condition, the stability and precision of these parameters had to be studied. This leaded to determine the amount of change necessary to infer a clinically meaningful change in follow-up assessments. Reliability represents the stability of a measure in the absence of changes. Intra-class correlations of the baseline data with subsequent measurements were calculated across a period of nine days. Number of steps, MVPA and walking speed showed high stability with ICC > 0.8. The SEMs showed slightly increased over time from baseline to the follow-up measurements in the total MS group as well as in each disability subgroups. PwMS-L showed larger SEM than the PwMS-H subgroup, which could be associated with the greater variability of activity performance in patients with mild disability compared to the patients with moderate disability. The SEM-based precision estimates showed in general acceptable to great precision. MCDs and MCD% of physical and gait parameters showed that maximum walking speed required the smallest change in comparison to mean walking speed, number of steps and MVPA. *Between-phases* MDCs for walking speed was 0.2m/s for overall sample, and 0.5m/s, 0.3m/s for PwMS-L and PwMS-H, respectively. Moreover, MCD% showed that a change between 32% and 37% represents a meaningful change in PwMS-L, whereas, the meaningful change in PwMS-H ranges from 15% to 24%. These results suggest the consideration of walking speed to measure responsiveness to change over time because of useful MDC scores in PwMS. Greater changes were found in number of steps and MVPA. Between-phases MDC% ranged from 28% to 42% (number of steps) and from 35% to 46% (MVPA) when considering all patients. Similar to walking speed, MDC% of number of steps were greater in PwMS-L compared to PwMS-H. The MDCs values are clinically useful because they might help to determine necessary amount of change a repeated measurement would need to differ from initial value in order to be considered as a true change. Therefore, the MDCs value reported in this work may also be incorporated into clinical decision making. Long-term monitoring of motor and gait parameters offers the opportunity to comprehensively assess the pattern of behavioral change across prolongs periods of time. This information may assist in the process of clinical decision making in the context of neurological rehabilitation and intervention and thus help to eventually improve the patient’s quality of life.

Observations and findings from the first study shed a light on using the accelerometer as a tool to determine the benefit of medical treatments and interventions. While currently no other objective ambulatory system exists to detect the response to treatment, the home-based system and algorithms developed in this work were employed to classify PwMS as responder (R) or non-responder (NR) according to the changes in their gait pattern and physical behavior in response to fampridine treatment. Parameters were collected in two phases; pre-treatment and post-treatment. Pre-treatment phase lasted for one week, whereas, post-treatment phase lased for 2 weeks. In total, data of 21 days of free-living activities of 22 PwMS were gathered. First of all, the developed algorithms were applied on the data of the pre- and post-treatment phase (phase1 and phase2, respectively) and the resulted parameters were analyzed. Then, the effect of the treatment on each parameter was investigated. In this work, two different machine learning algorithms were applied to investigate the response to the treatment. Differences in gait parameters between phase1 and phase2 in both R and NR groups were tested. Significant improvement in all gait parameters was observed in R group; $p<0.05$ for asymmetry, step length, energy concentration and peak frequency, whereas walking speed and number of steps had significant value of $p\leq0.01$. In comparison to R group, gait parameters in NR group did not report any significant differences between phase1 and phase2. Decision tree and SVM classifiers were then applied to classify the patients based on the changes in their gait parameters. The results showed that it is possible to reach a high sensitivity (80%) and specificity (75%) using ambulatory assessment of changes in motor and gait parameters.

User acceptance analysis showed that there is a possibility to apply telemedicine technologies in real world. Telemedicine technology can also have a positive impact on the patient's behavior (e.g. stay active) when it is feasible, reliable and easy to use. Therefore, factors like usefulness and easy-to-use do influence the acceptance of the new technology.

The general result of this dissertation can be concluded as: The design, validation and clinical application of Home-based monitoring system and algorithmic methods for objectively monitoring and quantifying changes in motor and walking ability with wearable sensors. Walking ability was quantified and analyzed by extracting relevant gait parameters in individuals who suffer from activity and gait disorder while performing their daily activities. In this work the focus was on patients with multiple sclerosis.

## 8.2 Outlook and Future Work

The measurement system developed in this work can be used as a tool capable to record, assessed and analysed the main and important changes in walking ability due to disease progress or even as response to a certain treatment. The next logical step is to perform the analysis online, to collect high number of data in order to improve the accurate of the detection of treatment effect.

### 8.2.1 Adherence

One main challenging problem in PwMS is the long-term adherence to therapy. As emphasized by the World Health Organization (WHO), "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of population than any improvement in specific medical treatments". Multiple benefits are associated with treatment adherence that extend beyond a lower risk of relapses and reduced disability progression. Adherence reduces the hospitalization and absences from work. These factors can significantly affect patient's quality of life.

To promote adherence, healthcare provider should assess patients' needs and lifestyles in order to choose the appropriate therapy for each individual patient. Moreover, an individualized treatment increased patient's adherence as they will be motivated by the positive effect of the treatment.

Basically, medication treatment improves patient's mobility. Additionally, by staying active patients will be able to strengthen the immune system so that their body can better handle the disease. Therefore, the combination between medication and physical therapy can increase patient's quality of life. Based on the proposed algorithms and methods developed in this work an adherence index can be developed. The functionality of the system can be described as follow: Based on the current situation and needs, and the aimed to-be situation of the patient, physicians can determine an individual treatment program. Beside medication treatment an activity program can be also determined and agreed (e.g. certain number of steps per week). Based on the ambulatory and online continuously monitoring of the daily motor and walking data the adherence of the patient can be assessed and analysed, with the aim to keep the patient in the green zone (Figure 8-1) and to offer him/her the best possible treatment and hence improve his/her quality of life.

| Medication Adherence | Activity Adherence |
|---|---|
| No | No |
| Yes | No |
| No | Yes |
| Yes | Yes |

Figure 8-1. Adherence monitoring system

### 8.2.2 Fall Detection

Fall is a common health concern in multiple sclerosis. While it is not a symptom of MS per se, it has been found to be associated with disease progress and quality of life. Because of its frequently in PwMS and the injury it may cause, fall detection should be included in the ambulatory monitoring system. During this work, an algorithm for fall detection using one accelerometer attached to the hip was developed. Data from 16 healthy individuals were collected. Different types of daily activity were performed, and fall was manipulated. Certain thresholds for both acceleration and angel were determined. The signal event was defined as fall when a high acceleration within 0.5 sec as well as changes in body posture was detected. The developed algorithm showed a SE of 93.75% and PPV of 83.33%.

Evaluation of the patient’s risk of falling is required to provide adapted assistance and prevention methods. Normally, this risk is evaluated by using questionnaires, which have drawbacks such as subjectivity and prone to recall. Risk can be also evaluated by clinical tests. However, an objective method for measuring the risk through the monitoring of motor and walking ability is of great importance. Moreover, the number of fall occurrence has been considered to be an important indicator for disease degeneration. Therefore, a development of a reliable system that is capable to automatically report the fall events and to send automatic alarm when help is needed is very important in clinical research. Therefore, based on gait parameters and fall detection algorithms developed in this work risk of fall can be investigated and applied in application for fall prevention in PwMS.

# 9 List of Figures

# 10 List of Tables

# 11 References

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# 12 List of Publications


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# 13 List of Supervised Student Theses

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