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Toward an objective assessment of mobility in clinical and daily activity settings

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In love's great ocean, whose calm-shelter'd shore
Must he for ever leave, whose soul is bound
On farthest quest, life's wonders to explore—
Hafez

Abstract

Quantification of mobility is the key to monitor the progression of mobility disorders as well as the effect of an intervention. Inertial measurement units (IMUs) with dedicated algorithms can quantify postural transitions and gait as the two key aspects of mobility in an objective and continuous manner. IMU-based mobility assessments can be performed by either functional tests in the clinic or through daily activities. Assessments performed in the clinic are more indicative of people's best performance or capacity, while assessments performed at home represent mostly their actual performance. Yet the relationship between these two settings is not fully understood, both due to the existing gaps in technical algorithms as well as challenges in comparing two inherently different domains. To this end, in this thesis, I firstly focused on developing and validating algorithms to quantify mobility in both clinical and domestic environments. The added clinical value of these IMU-based mobility assessments was shown in several populations with mobility impairments. Finally, by proposing novel approaches, I focused to bridge the gap between clinical and daily activity assessments.

The previous approaches to quantify mobility are mostly based on algorithms that are validated only during clinical or lab-based assessments. Opposed to daily activities, lab assessments contain simple and single-task activities. Therefore, it is important to design algorithms robust to the complex context of daily life setting while being unobtrusive to daily activities. A new algorithm was introduced to detect and characterize postural transitions, i.e., sitting and standing. Next, machine-learning-based algorithms were developed to detect walking bouts and estimate gait speed. The proposed postural transition and gait quantification algorithms were based on a single IMU on the lower back which is unobtrusive to daily activities. The novelty of the algorithms is their robustness to sensor placement changes during daily activities. The proposed algorithms demonstrated high performance during both clinical and daily activity assessments whether on healthy individuals or participants with mobility impairments.

Next, through several analyses, I demonstrated how such instrumented mobility assessments can discriminate different patient populations. For instance, IMU-derived mobility parameters could differentiate older adults with and without risk of falls as well as patients with moderate or severe stages of multiple sclerosis. Moreover, the aforementioned parameters were compared between clinical and daily activity assessments. By this comparison, clinicians can have a better understanding of patients' capacity through a remote assessment of mobility. Finally, it was shown how clinical and daily activity assessments can provide complementary information to each other. For instance, by introducing novel approaches to compare gait speed between clinical and daily activity assessments, the effect of the medication in

Parkinson's disease (PD) was traceable during daily activities. The findings can lead to better optimization of the medication dose in PD.

Overall, this thesis provided a framework that can help clinicians with an objective assessment of mobility. Furthermore, the approaches introduced in this thesis can help for better management of intervention and tracking its effects where both clinical and daily activity assessments exist.

Keywords: wearables, digital health, mobility, inertial sensors, postural transitions, gait speed, walking bout, Parkinson's disease, multiple sclerosis, older adults, fear of falling, falls, home vs. lab, clinical assessment, daily activities, capacity, performance, TUG, five-time sit-to-stand test.

Résumé

La quantification de la mobilité est la clé pour surveiller la progression des troubles de la mobilité et l'impact des interventions. À l'aide d'algorithmes dédiés, des centrales inertielles peuvent quantifier les transitions posturales et la marche, deux aspects clés de la mobilité, de manière objective et continue. Les évaluations de la mobilité basées sur des centrales inertielles peuvent être réalisées soit par des tests fonctionnels en clinique, soit dans le cadre des activités quotidiennes. Les évaluations réalisées en clinique sont plus représentatives de la capacité ou des performances optimales des personnes, tandis que les évaluations réalisées à la maison représentent plus fidèlement les performances réelles. Pourtant, la relation entre ces deux contextes n'est pas entièrement comprise, à la fois en raison des lacunes existantes dans les algorithmes techniques et des défis que pose la comparaison de deux domaines intrinsèquement différents. Par conséquent, dans cette thèse, je me suis d'abord concentré sur le développement et la validation d'algorithmes pour quantifier la mobilité dans les environnements cliniques et domestiques. La valeur clinique ajoutée de ces évaluations de la mobilité basées sur les centrales inertielles a été démontrée dans plusieurs populations avec déficit de mobilité. Enfin, en proposant des approches nouvelles, j'ai cherché à combler le fossé entre les évaluations cliniques et les évaluations de l'activité quotidienne.

Les approches précédentes pour quantifier la mobilité sont pour la plupart basées sur des algorithmes qui ne sont validés que dans le cadre d'évaluations cliniques ou en laboratoire. Contrairement aux activités quotidiennes, les évaluations en laboratoire consistent en des activités simples et mono-tâches. Par conséquent, il est important de concevoir des algorithmes robustes au contexte complexe de la vie quotidienne et un dispositif peu invasif. Un nouvel algorithme a été introduit pour détecter et caractériser les transitions posturales, i.e. se lever et s'asseoir. Par la suite, des algorithmes basés sur l'apprentissage automatique ont été développés pour détecter les phases de marche et estimer la vitesse de la marche. Les algorithmes proposés pour la quantification des transitions posturales et de la marche sont basés sur une seule centrale inertielle placée au bas du dos, ce qui n'est pas invasif dans le cadre des activités quotidiennes. La nouveauté apportée par les algorithmes est la robustesse aux changements de placement des capteurs pendant les activités quotidiennes. Les algorithmes proposés ont démontré une performance élevée lors d'évaluations cliniques et dans les activités quotidiennes, aussi bien sur des individus sains que des participants à mobilité réduite.

Par la suite, à travers plusieurs analyses, j'ai démontré comment ces évaluations de la mobilité instrumentées pouvaient permettre de discriminer différentes populations de patients. Par exemple, les paramètres de mobilité extraits avec une centrale inertielle permettent de

distinguer les personnes âgées avec ou sans risque de chute, ainsi que les patients atteints de sclérose en plaques à un stade moyen ou avancé. En outre, les paramètres susmentionnés ont été comparés entre les évaluations cliniques et les évaluations de l'activité quotidienne. Cette comparaison ouvre la perspective, pour les cliniciens, de comprendre la capacité des patients en évaluant leur mobilité à distance. Enfin, il a été démontré que les évaluations cliniques et les évaluations de l'activité quotidienne peuvent fournir des informations complémentaires. Par exemple, en comparant la vitesse de marche dans le cadre des évaluations cliniques et dans l'activité quotidienne, l'effet sur les activités quotidiennes des médicaments contre la maladie de Parkinson a pu être observé. Ces résultats peuvent conduire à une meilleure optimisation de la dose de médicament pour les patients atteints de la maladie de Parkinson.

Dans l'ensemble, cette thèse a fourni un cadre qui peut aider les cliniciens, avec une évaluation objective de la mobilité. De plus, les approches introduites dans cette thèse peuvent permettre une meilleure gestion de l'intervention et un suivi de ses effets lorsque l'on dispose à la fois d'évaluations cliniques et d'évaluations de l'activité quotidienne.

Mots clés: technologie portable, santé digitale, mobilité, capteurs inertiels, transitions posturales, vitesse de la marche, périodes de marche, maladie de Parkinson, sclérose en plaques, personnes âgées, peur de chuter, chutes, domicile vs. laboratoire, évaluation clinique, activités quotidiennes, capacité, performance, TUG, Test du lever de chaise

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In the last few years, I have had quite a journey that when I look back, seems like a typical hike in Switzerland. I took many steps, climbed up the hills, went down the valleys, went up again, till I reached the mountain with the view of the green hills and the lake; the kind of view that you have at Les Rochers-de-Naye. Many lessons have been learned; many experiences have been gained which of course, are mostly owing to the ones who accompanied me in this adventure.

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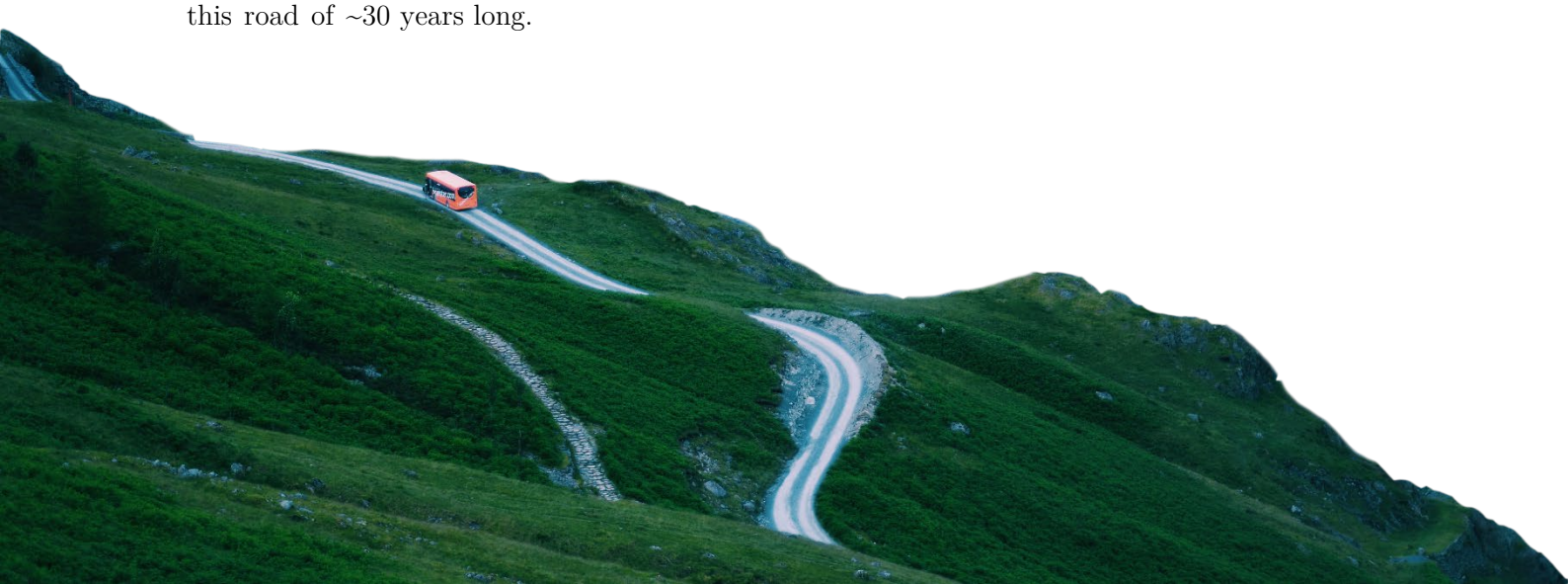

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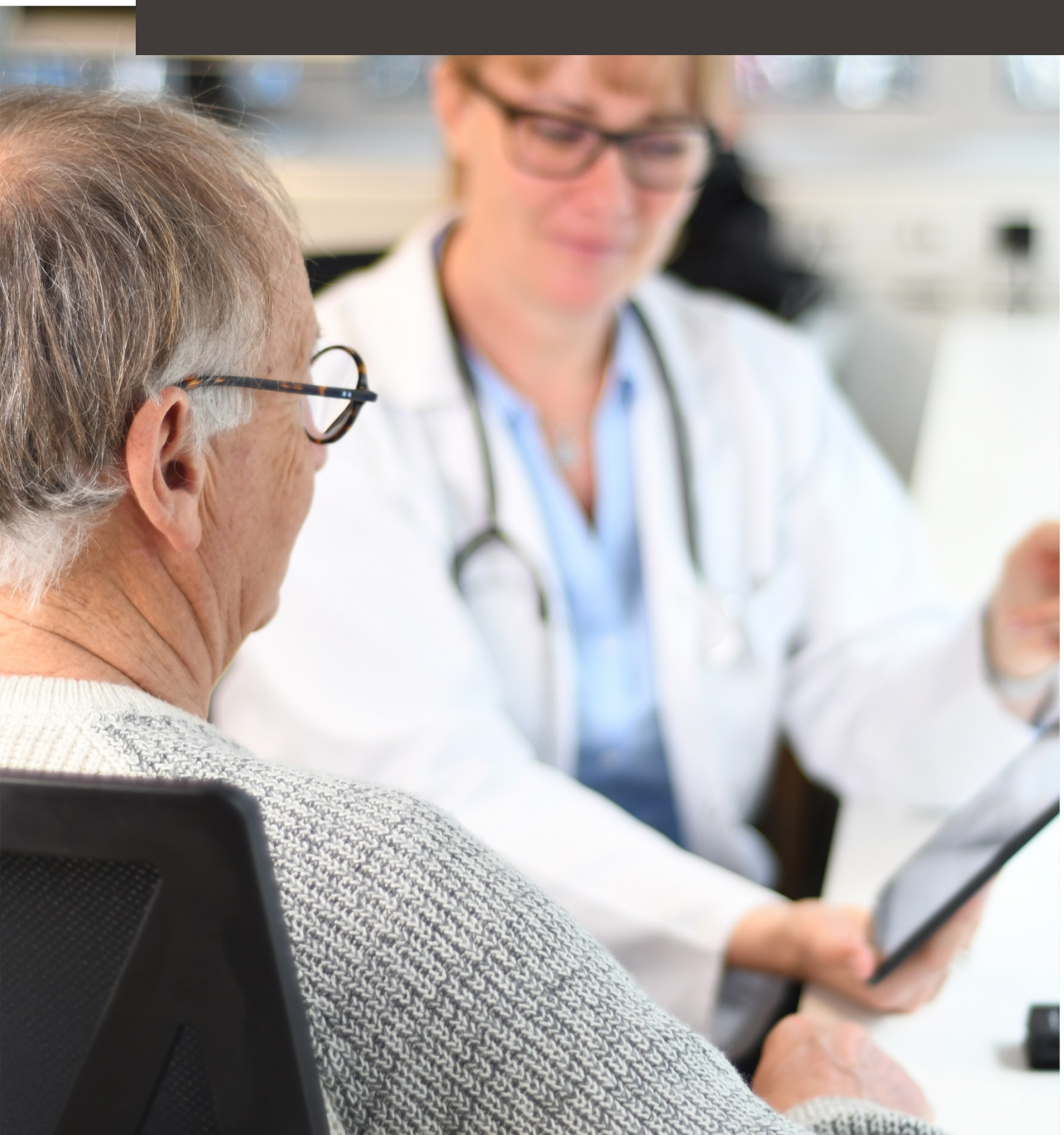
Part I

Introduction and Background



1 Introduction

1.1 Mobility

We humans are always in move to satisfy our needs from the very basic ones, such as walking, to more complex physical activities, such as doing sports. Arduous mobility and physical activities were part of our ancestors' daily life not only for living (finding food, building shelter, etc.) but also for social and cultural events (Manley, 1996). "Paleolithic rhythm" included one or two days of intense activity followed by one or two days of reset and celebration (Eaton, Shostak, & Konner, 1988). Even during the rest days, our ancestors were exerting 10 to 30 kilometres of trips to visit friends and relatives, in addition to dancing and cultural play (Eaton et al., 1988).

Nowadays, however, technological innovation has contributed to a more sedentary life style (WHO, 2020); therefore, maintaining physical activity has become more important than before to prevent diseases such as cardiovascular disease, diabetes, and dementia (I. M. Lee et al., 2012; Schuch et al., 2016; WHO, 2020).

In general, mobility has been defined as the ability to move freely and easily and is one of the four subdomains of physical function, i.e. mobility, dexterity, central function, and complicated daily activities (Dias, 2014; Haskell, Blair, & Hill, 2009; Schalet et al., 2016). Among these sub-domains, mobility has been shown to be associated with the quality of life (Hausdorff & Alexander, 2005), obesity (Bravata et al., 2007), risk of falls (Deandrea et al., 2010), risk of cardiovascular diseases (Murtagh, Murphy, & Boone-Heinonen, 2010), and mortality (Erlichman, Kerbey, & James, 2002).

An independent and active mobility can be impeded by mobility disorders. These disorders are usually caused by aging, neurological or musculoskeletal deficits, and injuries (S. Chen, Lach, Lo, & Yang, 2016) which are reviewed briefly in the following. Among neurodegenerative diseases, Parkinson's disease and multiple sclerosis are common in older adults.

1.1.1 Aging

Older adults undeniably experience higher levels of mobility disorders due to the aging process (Manini, 2013). Between 2015 and 2050, the proportion of adults older than 60 years will double from 12% to 22% (World Health Organization, 2018a). Currently, the world's oldest populations are in Europe with Germany having the largest percentage of older adults (65+) (He, Goodkind, & Kowal, 2016). Older adults' mobility is usually characterized by a slower gait speed (F. Li, Fisher, Harmer, McAuley, & Wilson, 2003; Studenski et al., 2011), having higher risk of falls (F. Li et al., 2003), and an unstable gait (Granata & Lockhart, 2008; Verghese, Holtzer, Lipton, & Wang, 2009).

Falls are among the most serious and common concern of older adults' health (Florence et al., 2018). Approximately, 1 out of 3 adults aged 65 years and older experience falls (Morrison, Fan, Sen, & Weisenfluh, 2012). This incidence can be often injurious and cause restrictions in mobility, daily activities, and quality of life (Ambrose, Paul, & Hausdorff, 2013). On the other hand, reduction of physical activities will lead to muscle strength decay which can create additional balance deficits (Zijlstra & Aminian, 2007). Moreover, falls are associated with fractures, injuries, and mortality (Hadjistavropoulos, Delbaere, & Fitzgerald, 2011). Therefore, the major challenge is to first distinguish older adults at risk of falls and design timely interventions to prevent falls and its related injuries and its consequences.

During clinical assessments, older adults are usually being asked if they have experienced falls during the last 6 or 12 months (Ponti, Bet, Oliveira, & Castro, 2017). Therefore, based on patients' number of falls and their injuriousness, patients are categorized into fallers and non-fallers. For instance, fallers can be identified if they have had one injurious fall or more than one fall whether injurious or not during the last year (Granbom et al., 2019).

On the other hand, fear of falling (FOF) is also prevalent in older adults. FOF is defined as "low perceived efficacy at avoiding falls during essential, nonhazardous activities of daily living" (Tinetti, Richman, & Powell, 1990). For instance, 27% of male and 43% of female older adults have been shown to have FOF (Tomita et al., 2018). While FOF can lead to future falls, it is also associated with decreased quality of life as it can hinder patients' daily activities due to their concerns (Deshpande, Metter, Lauretani, Bandinelli, & Ferrucci, 2009).

FOF is conventionally quantified by questionnaire scales such as Falls Efficacy Scale (FES) (Tinetti et al., 1990). The English version of this questionnaire asks the patients to rate 1 (not at all concerned), 2 (somewhat concerned), 3 (fairly concerned), or 4 (very concerned) to each of the 16 questions asking about the intensity of patients concerns about falling during various types of daily activities (such as preparing food, taking shower, etc.). Therefore, the scale can vary from 16 to 64, with 16 showing a lack of concern and 64 showing the highest

amount of concern about falling. There are established cut-points to categorize patients having low, moderate, and high FOF (Delbaere et al., 2010).

1.1.2 Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease that is named after Dr. James Parkinson that published the details of this disease for the first time in his "An Essay on the Shaking Palsy" in 1817 (Parkinson, 2002). The prevalence of PD is between 1'267 to 1'535 per 100,000 in Europe, the United States, and Australia (Pringsheim, Jette, Frolkis, & Steeves, 2014) which is after Alzheimer, the second most common neurodegenerative disease (Lebouvier et al., 2009). The severity of motor and non-motor symptoms increases with age (Pagano, Ferrara, Brooks, & Pavese, 2016). Moreover, its prevalence is higher among older adults reaching 2.6% in older adults between 85 to 89 years (Pringsheim et al., 2014).

Although the cause of PD is unknown, degeneration of dopaminergic nerve cells is associated with reduced motor function and impaired movement control. Normally, neurons produce a chemical substance called dopamine that is responsible for the communications between nerve cells (neurotransmitters). Due to impairment of neurons in the substantia nigra, the production of dopamine decreases in PD patients, resulting in symptoms such as tremor, stiffness, bradykinesia, and depression. Moreover, PD patients' gait is characterized by reduced amplitude of arm swing (Huang et al., 2012), lower gait speed, reduced step-length, freezing of gait, and impaired balance control (Di Biase et al., 2020).

Currently, PD cannot be cured; therefore, PD treatments focus on the control of motor and non-motor symptoms using dopamine compensation, mainly with Levodopa, and surgical methods such as deep brain stimulation (Iarkov, Barreto, Grizzell, & Echeverria, 2020).

Levodopa also known as L-DOPA is the most effective drug used to compensate dopamine concentration. However, it has some side effects such as dyskinesia (involuntary movement) and motor fluctuations that occur after a long-term use (Pandey & Srivanitchapoom, 2017). Levodopa induced dyskinesia (LID) happens due to maximal benefit from single-dose Levodopa and includes involuntary movements of any body part (Nutt, 1990).

Motor fluctuations can happen in various forms (Figure 1.1). For instance, when the effect of Levodopa wears off, the patients' PD symptoms come back; therefore, they need to take another dose of Levodopa; alternatively, PD patients might experience a delayed response to Levodopa (Pandey & Srivanitchapoom, 2017). Therefore, throughout the day, patients might experience two states, i.e. ON and OFF medication states. In early PD, two or three doses per day can help the patients to manage well their symptoms (Fox & Lang, 2008). However, as PD advances, the response duration to Levodopa can decrease. Thus, the clinicians need

to adapt the amount and timing of medication dose to minimize the motor fluctuations of PD.

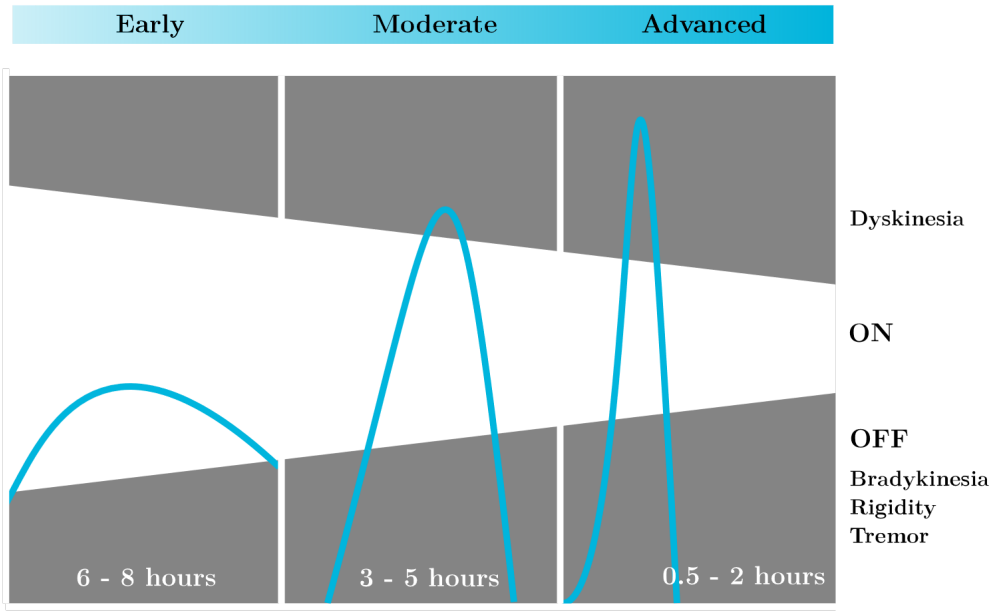


Figure 1.1: Complications of PD medication, Image adapted from (Joseph Jankovic, 2005)

The Unified Parkinson's Disease Rating Scale (UPDRS) was initially developed to monitor PD symptoms and impairment (Fahn, S; Elton, 1987). It was later revised to MDS-UPDRS to cover greater manifestations of PD (Goetz et al., 2008). This scale includes 4 parts: non-motor aspects of experiences of daily living, motor aspects of daily living, motor examination, and motor complications. In the first part, the patients are asked about their non-motor aspects of their daily activities such as depressed mood, sleep problems, etc. in which patients should respond how severe is their symptom (on a scale from 0 to 4). The second part considers motor aspects of the daily living such as speech, eating tasks, etc. During the third part, i.e. motor examination, first, the examiner should note the medication state of the patient, i.e. ON and OFF, at the time of the examination in addition to the time since the last Levodopa intake. Next, the examiner has to engage in patients' motor performance and observe their behaviour and rate the patient accordingly. Finally, the last part, the clinician has to examine two motor complications, i.e. dyskinesia and motor fluctuations. The highest total UPDRS score is 199 which expresses the worst possible disability of PD (Holden, Finseth, Sillau, & Berman, 2018).

In addition to lab-based evaluations, motor diaries can be also used at home in which patients are required to register their motor state every half an hour (Hauser et al., 2000).

To monitor the stage of PD and its progression, the Hoehn and Yahr (H&Y) scale is commonly used (Goetz et al., 2004; Margaret M. Hoehn & Yahr, 1967). The scale goes up from stage 1

with minimal disability to stage 5 which means confinement to bed or wheelchair unless with aid. The rating is based on the evaluation of the patient. In a study on 695 patients, the median number of months to transit from stage 1 to 2, 2 to 2.5, 2.5 to 3 were 20, 62, and 25 months (Y. J. Zhao et al., 2010).

1.1.3 Multiple sclerosis

Multiple sclerosis (MS) is another type of mobility-related disorder that is the most common non-traumatic disease that can affect both younger and older adults (Kobelt, Thompson, Berg, Gannedahl, & Eriksson, 2017). Prior to the 20th century, there were only a few case reports regarding this disease; however, nowadays, this disease has become one of the most frequent reason for neurological ward admissions (Compston, 2005) and has affected around 2.5 million people worldwide (World Health Organisation, 2008).

While the cause of MS is not known, it is considered an autoimmune disease. In fact, the body's immune system wrongly attacks a fatty substance called Myelin that protects our nerve fibers in the brain and spinal cord (Compston & Coles, 2008). When this protective layer is damaged, the communication within the central nervous system is modified or halted. MS includes variety of symptoms such as fatigue, mobility impairments, and pain (Kister et al., 2013; Solaro et al., 2004). Mobility-related problems such as walking difficulty is the main complain of MS patients (R. W. Motl, 2013). Mobility of patients with MS is characterized by reduced amount of activity, a slow gait with poorly coordinated lower limbs, and higher variability of step-length (Cameron & Nilsagard, 2018; Pirker & Katzenschlager, 2017; Zwibel, 2009).

Although MS cannot be diagnosed by a specific and single test, thanks to the recent advancements in the health care system, it can be diagnosed by integrating various medical history and examination such as blood tests, Magnetic resonance imaging (MRI), and spinal tap (Calabresi, 2004). Indeed an early diagnosis of MS helps a better management of the disease and its delayed degenerative progression (Miller, 2004), Disease-modifying therapies (DMTs) that can be injected or taken orally have been designed to slow down the progression of the disease. Although these treatments preserve neurological function, they have side effects and health risks. Therefore, a good understanding of the stage of the disease and benefit-risk profiles of the treatment is required to prescribe the appropriate treatment option (Gajofatto & Benedetti, 2015; Wingerchuk & Carter, 2014).

The Expanded Disease Status Scale (EDSS) is one of the clinical gold standards to measure the disability in MS patients (Kurtzke, 1983). EDSS ranges from 0 to 10 with 0.5 increments; 0 means a normal neurological exam without any functional disability while 10 is death due to MS (Kurtzke, 1983). A score higher than 4.0 is indicative of mobility impairment. For

instance for scales of 4.0, 4.5, and 5.0, the ability of the patient to walk without aid for 500, 300, 200 meters, respectively is asked.

1.1.4 Other mobility-related disorders

Other neurological disorders can include but are not limited to cerebral palsy (CP) and stroke. In CP, early damage to the developing brain can cause motor disorders such as an altered gait (Baxter, 2007). Being the most frequent motor disorder in children, it affects 1.8 out of 1000 live births in Europe (Sellier et al., 2016).

In stroke survivors, walking dysfunction often demonstrates in 80% of the cases which is characterized by gait asymmetry, increased stance time, and hemiplegic gait (S. Li, Francisco, & Zhou, 2018). To recover motor functions, stroke survivors often require an intensive physical rehabilitation (Massé et al., 2015).

Mobility impairments are not limited only to neurological disorders and aging. Injuries and musculoskeletal impairments such as knee osteoarthritis (McClelland, Webster, & Feller, 2007), anterior cruciate ligament (ACL) injury (Gardinier, Manal, Buchanan, & Snyder-Mackler, 2012), and sarcopenia (Perez-Sousa et al., 2019) can also lead to mobility problems such as decrease in mobility, tetraplegia (paralysis of four limbs and torso), and loss of skeletal muscle mass.

1.1.5 Traditional mobility assessment methods

Aging and several disorders such as PD and MS affect the mobility. Mobility reduction is generally assessed in clinics by questionnaires as shortly described earlier. In these questionnaires, patients are rated based on their mobility performance. However, questionnaires can be subjective and dependent on the rater (Benoit Mariani et al., 2010). Moreover, they do not continuously evaluate the patients but often in short snapshots of lab assessment (B. R. Greene et al., 2015). Although there are some questionnaires that evaluate the patients' performance during daily activities, such as the Physical Activity Scale for Individuals with Disabilities (Richards & Olney, 1996), low compliance has been reported in using them (B. R. Greene et al., 2015). Despite their established implementation, some of these scales such as EDSS are not linear or have low sensitivity to the changes in the severity of the disease (Vienne-Jumeau, Quijoux, Vidal, & Ricard, 2020). Finally, patients might have difficulties recalling or differentiating their symptoms (B. R. Greene et al., 2015).

More structured mobility assessment methods require the patients to perform functional tests in the clinic or lab while they are being observed or rated by a specialist. These functional tests usually evaluate the gait and balance performance of the patients as the two key aspects of mobility (Lockhart, Soangra, Zhang, & Wu, 2013). In timed-up-and-go (TUG) test, patients

are asked to stand up from a chair, walk for several meters (normally 3 or 7 meters), turn 180 degrees, walk back to the original position, and sit down on the chair while turning 180 degrees for the second time (Richardson, 1991). The total time taken for the patient to complete the test is measured while a specialist can observe the gait and balance performance of the patient. This test is commonly used to assess frailty and risk of falls (Savva et al., 2013; Thrane, Joakimsen, & Thornquist, 2007). Moreover, freezing of gait, i.e. the failure to initiate or maintaining a gait, can be observed during turning phases of TUG test in PD patients (Mancini, Priest, Nutt, & Horak, 2012). A strong point about TUG test is that it involves several functional tasks that are required to be achieved in a sequence, allowing the examination of motor and executive functions. Indeed the transition phases of this test, e.g. sit-to-walk and turn-to-sit, require a complex coordination of upper and lower limbs.

Other lab-based gait tests measure the time taken to walk a pre-defined distance such as 10 or 20 meters. These tests can also be accompanied by another motor or cognitive task known as dual-task tests (Plummer et al., 2013). For instance, spelling a word backward is one of the cognitive tasks performed during dual-task functional tests (Lowe, MacAulay, Szeles, Milano, & Wagner, 2020). Maintaining balance during dual or multi-tasking is challenging. Thus, these tests require higher attention and considerable balancing skills compared to single task walking tests (Leland et al., 2017).

Other functional tests can focus on balance performance of the individuals. For instance, five-time sit-to-stand (5xSTS) test requires the patients to perform five repetitions of sit-to-stands (mostly as fast as possible but sometimes with their preferred speed) (Csuka & McCarty, 1985). The total time taken to perform this test is measured by a stopwatch. It has been shown that a total time of greater than 15 seconds is associated with recurrent falls in older adults (Buatois et al., 2008).

The total number of sit-to-stands to be performed during 30 seconds can be measured as the 30-second chair rise test (30SCT). Both of the 5xSTS and 30SCT tests have been shown to have good test-retest reliability and are associated with lower extremity strength of the community-dwelling older adults (Bohannon, Bubela, Magasi, Wang, & Gershon, 2010; De Melo et al., 2019; Kuo, 2013).

Despite their predictive power and high reliability, these assessments are only limited to laboratory-based environments and might neglect a large part of the patients' life which is their daily activities. Furthermore, these assessments might not be sensitive enough to detect subtle differences between patient populations (Rob C. Van Lummel et al., 2016).

These are among the dozens of reasons that urge us to consider digital solutions as part of global health strategies (Jandoo, 2020).

1.2 Digital health

1.2.1 Introduction

Digital health has a broad scope that incorporates several domains such as mobile health, health information technology, wearable devices, telehealth, and personalized medicine (C. E. Chen, Harrington, Desai, Mahaffey, & Turakhia, 2019). These domains that lie at the intersection of digital technology and health care have become an essential part of health care infrastructure (Mesko, 2018).

Probably the first emergence of digital health can be traced back to 1990s in two separate and confidential domains: telemedicine and health informatics (André, 2018). The former is defined as the delivery of remote care while the latter is defined as the integration of programmable software into health care (Della Mea, 2001; Lincoln & Builder, 1998).

Today, with the advancements in software, hardware, and communication technology, we are observing a rapid growth of digital solutions in diagnosis and treatment of the patients (World Health Organization, 2018b). In 2019 alone, 7.4 billion dollars have been invested in digital health sector compared to 6 and 4.4 billion dollars in 2017 and 2016, respectively (Mathews et al., 2019; Rodriguez, Clark, & Bates, 2020). Currently, there are more than 3 million mobile health applications with more than 200 apps produced each day (Mathews et al., 2019).

Increasing costs of health care due to longer life expectancy of the population has put a pressure on health systems. Digital health technologies can help to lighten this burden and enhance the efficiency of the health system (Ekman, 2018). For instance, telemedicine can provide a solution to the population in the regions where resources and facilities are not sufficient (Dorsey, Glidden, Holloway, Birbeck, & Schwamm, 2018).

Digital health can also provide solutions for prevention and self management of some of health issues in order to decrease clinical or hospital visits. For instance, the wearables that continuously monitor the level of sugar in blood can help their users to avoid complications associated with diabetes.

Advances in hardware technology allows a rich sources of digital data and biomarkers that are assessed continuously opposed to traditional distinct point measurements in the clinic (Uddin & Syed-Abdul, 2021). The biomarkers collected by the consumer-grade wearable devices can give us the access to a large amount of data in real-world settings. This vast information can be integrated with recent advancements in artificial intelligence (AI) for a more precise diagnosis and treatment of disorders.

Therefore, it is not surprising that the digital health domain has gained attention for research, especially since the last five years (Figure 1.2). Only in 2020, 22'100 scientific articles were

published including the term “digital health” which is the highest number ever. This is probably due to the COVID-19 pandemic that has catalysed the research and interest in digital health.

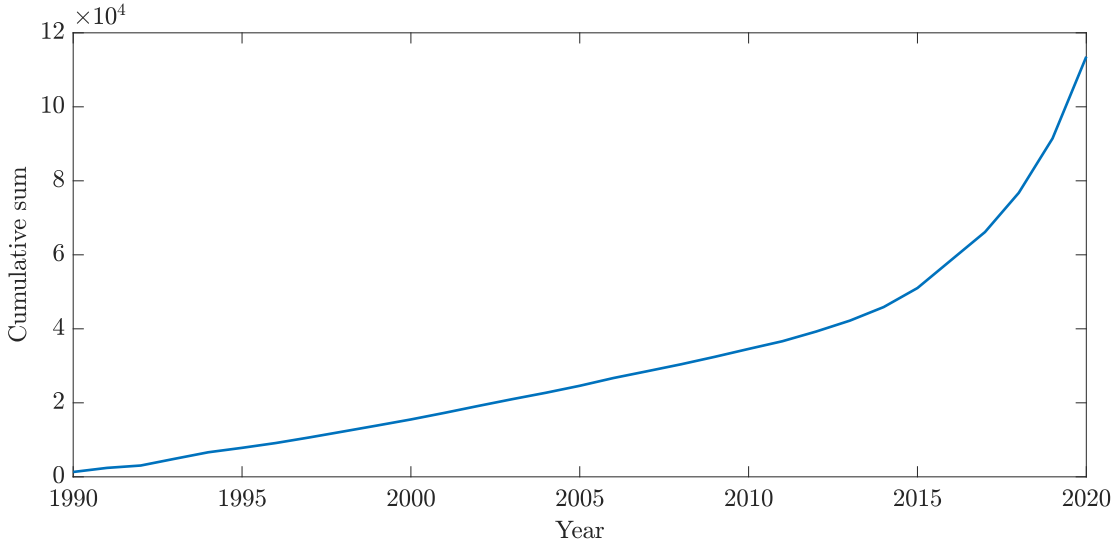


Figure 1.2: Cumulative sum of number of scientific publications involving the term "digital health". Source of data: Google Scholar

1.2.2 Hidden aspects of a global pandemic

On March 11, 2020, the world health organization (WHO) announced COVID-19, a respiratory illness caused by the coronavirus SARS-CoV-2, as a global pandemic (Donald G. McNeil Jr., 2020; Wu et al., 2020). A global crisis that so far has contaminated millions of people and left more than two millions of deceased*, aside from economic recession around the world. So far, there is no effective treatment against this disease and despite a few effective vaccines, the vaccination is going very slowly. Therefore, governments (or at least most of them) have imposed preventive measures to decrease the speed of the propagation and reduce the burden on the health care system (Figure 1.3a).

One of these ordinances is to avoid close and direct contacts as much as possible. People were encouraged to stay at home and practice physical distancing. Therefore, physical activity and mobility were reduced (Figure 1.3b). It is not surprising that WHO changed its physical activity guidelines for the first time in the last 10 years to mitigate the associated health risks (Bull et al., 2020; WHO, 2020).

Indeed, despite its drastic economic, political, and social changes, COVID-19 pandemic had some hidden aspects. One aspect that many people, both specialists and non-specialists, started to discover more during this period was the benefits of digital health (Figure 1.4).

* Until March 17, 2021, 121’370’328 cases and 2’684’236 deaths were declared in the world. Source: worldometers.info

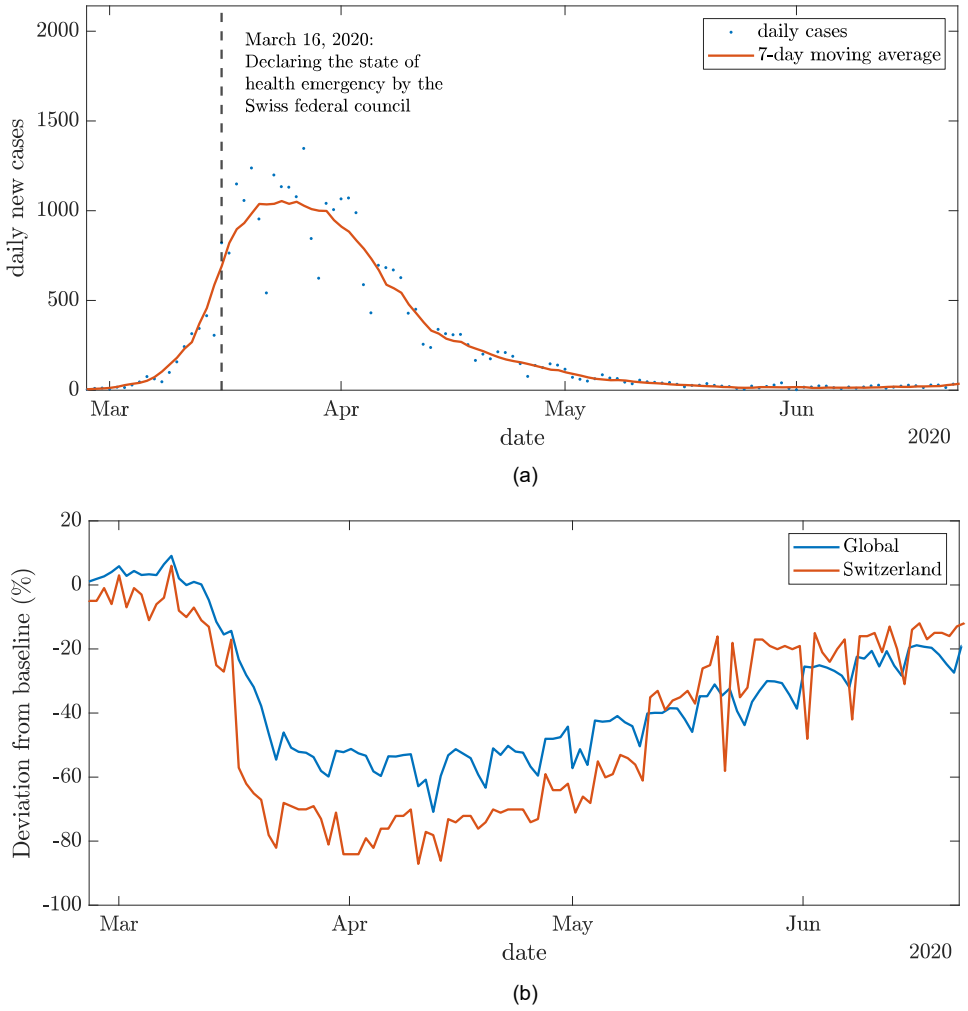


Figure 1.3: (a) Daily cases of COVID-19 during the first wave of the pandemic, data source (Probst, 2020) *and (b) Retail and recreation mobility in the world and Switzerland at the beginning of the COVID-19 pandemic. Data source: Google Mobility*

For instance, during this pandemic, smartphone applications were developed to trace contacts of the infected person (Hernandez-Orallo, Manzoni, Calafate, & Cano, 2020). The people who were in contact (measured by the proximity of Bluetooth) with an infected person during the last days could be informed by these applications. This contact tracing has helped to decrease the contamination of the virus by placing the infected person's contacts into quarantine.

Machine learning (ML) methods have shown the potential to alleviate the workload of the healthcare professionals during the COVID-19 pandemic. For instance, ML-based classifiers can automatically detect COVID-19 with computed tomography (CT) scans (Peiffer-Smadja et al., 2020). Moreover, ML can accelerate the screening for treatment of COVID-19, for instance by selecting an appropriate medicine from a broad range of options by taking into account the patients' and the drugs' characteristics (Peiffer-Smadja et al., 2020). The clusters of virus contamination can be analyzed by artificial intelligence methods to better understand the spread of the virus and effective ways to prevent the contaminations (Alimadadi et al.,

2020). Remote patient monitoring, digital data collection, as well as wearables sensors were among other digital health solutions that existed before but have been appreciated more during COVID-19 pandemic.

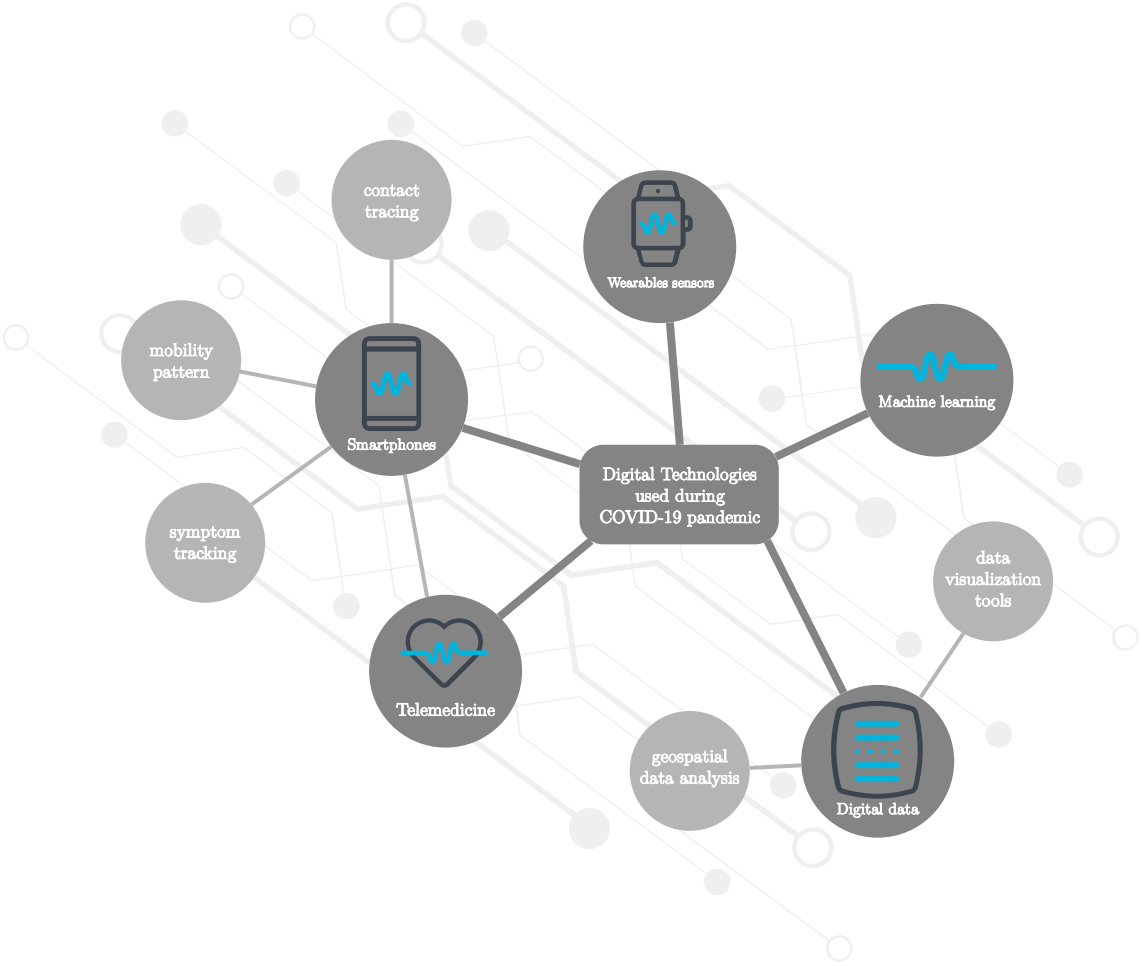


Figure 1.4: Digital health solutions as the response to COVID-19 pandemic. Image inspired from (Budd et al., 2020)

1.2.3 Remote patient monitoring

Despite numerous studies and implementation experiences, the adaptation of remote patient monitoring (RPM) was very slow in many countries (Bashshur, Doarn, Frenk, Kvedar, & Woolliscroft, 2020). However, now as one of the impacts of COVID-19, it has been valorized much faster. RPM helps patients to avoid unnecessary commute to the hospital and consequently, reduces the risk of getting infected for both the patients and other people that might be in contact with them. Furthermore, it reduces the cost of hospitalization, provides an objective assessment of the patients in their natural living condition rather than clinic, and may detect the diseases earlier, to name a few (Malasinghe, Ramzan, & Dahal, 2019).

Reducing the costs of hospitalization can include less occupied beds in the hospitals which reached a critical point in many countries during the COVID-19 pandemic.

Today, the world is realizing the merits of RPM. For instance, in the United States, during the first quarter of 2020, the telehealth visits were increased between 50% to 154% compared to the same period in 2019 (Koonin et al., 2020). With the current acceleration in telehealth growth, it is estimated that $250 billions of the current US health care system have the potential to be spent on telehealth. This is 83 times higher than the current annual revenue of the American telehealth providers (Bestsennyy, Gilbert, Harris, & Rost, 2020).

Particularly in Switzerland, there is a rich infrastructure to operate telemedicine as the technological condition for easy access to digital health is met. 93% of the households had access to the internet and almost 80% of the Swiss population had a smartphone in 2017 (OFS, 2017). Moreover, the four main telemedicine providers in Switzerland (Medgate, Medi24, Monvia, santé24) together record around 2.5 million contacts per year by the patients which is an increasing rate (Zingg, Sojer, & Röthlisberger, 2019).

RPM can include several groups of patients belonging to a specific category of diseases such as cardiovascular and respiratory system related diseases, diabetes, brain and neurological disorders, and mobility related diseases (Malasinghe et al., 2019).

1.2.4 Digital data collection

Digital surveillance in which data is collected from digital records of diseases has shown how using a huge amount of data can help for a better management and earlier detection of the disease (Sun, Chen, & Viboud, 2020). In addition to collecting the data related to a disease, data visualization tools can effectively help for making decisions on interventions. Moreover, these data visualization dashboards along with social media can potentially increase the public awareness about a disorder (Nextstrain, 2021).

With the recent advancements, new sources of data can be processed with innovative tools for a more impactful research. These datasets should come from various sources such as laboratory, real-life settings, and digital devices. Combined with traditional and established methods of data collection, digital health technologies provide a novel insight into the diagnosis and analysis of a disease (Cancela, Charlafti, Colloud, & Wu, 2020).

1.2.5 Wearable sensors

The building blocks of digital data collection are sensors and wearable devices. For instance, these sensors and devices can easily measure the blood pressure and the oxygen saturation in blood, monitor the blood sugar level in people suffering from diabetes, measure the heart rate variability, and monitor people's activity and fitness (Figure 1.5). Integrating some of these

devices (e.g. number of steps tracker, heart rate, and sleep monitoring devices) can take the form of a smart watch that is accompanied by algorithms and a software to interpret the raw data and the results for the user and the clinician. The recovery of a patient and the effectiveness of a treatment can be monitored remotely using the data from these devices. Furthermore, the data collected by these wearables can be used to detect early stages of a disease. For instance, analyzing data from number of daily steps, heart rate, and sleep time can detect 80% of COVID-19 cases 4 to 7 days earlier than the onset of symptoms (Mishra et al., 2020). In another study on around 300 health workers, the participants' heart rate variability was longitudinally measured by Apple Watch (Hirten et al., 2020). Very interestingly, the heart rate variability of the participants that tested positive for COVID-19 (with a PCR test) showed a significant difference 7 days before their COVID-19 test results.

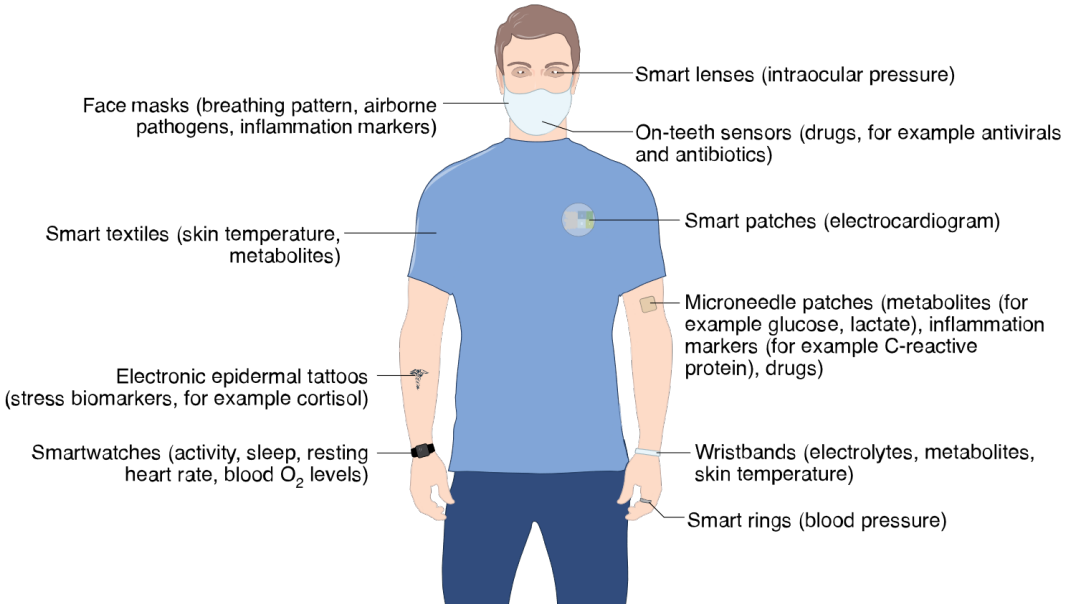


Figure 1.5: The future of wearable devices as depicted by Ates, Yetisen, Güder, & Dincer, 2021. Authorized copy from Springer Nature

The advantage of such an instrumentation with wearables is first to collect huge amounts of data from people and patients in their natural environment. Additionally, it can be used by professionals to get a better evaluation of their patients providing that sufficient quality of the data is available. The wearable sensors can collect the data continuously opposed to lab assessments that occur once in a while. Their data can help the clinicians and the user to have information from all days of the year as people might not remember all of their symptoms and incidents for all periods of the year. Moreover, it can be even used directly by the user and the clinician as soon as the data is interpretable and allows a reliable feedback.

Despite these achievements, the percentage of population who actually use the wearables in real-life remains low. This might be due to the fact that companies producing commercial

devices such as Fitbit, barely disclose the functionality and algorithms inside their products (Mackinlay, 2013). Furthermore, the provided functionality might not fit within the needs of the user. For instance, cadence cannot provide a good feedback for the change in mobility. On the other hand, algorithms developed and validated in the research labs need to be commercialized to promote their reliability and advantages. Moreover, research-based and validated algorithms are mostly based on offline collection and analysis of data rather than cloud-based and remote analysis (Del Din, Kirk, Yarnall, Rochester, & Hausdorff, 2021).

Another issue can be that some of the novel technological methods are more engineering-oriented rather than involving clinicians to solve a clinical problem. Moreover, the usability of the system from both the patients and the clinicians' point of view should be studied (Routhier et al., 2020).

Privacy issues can also raise concerns and doubts in using such wearables. For example, in a study on mobile health apps, only 30% of the apps had a privacy policy (Sunyaev, Dehling, Taylor, & Mandl, 2015).

Finally, digital health tools should pass several steps including regulation to be accepted as digital biomarker devices (Coravos, Khozin, & Mandl, 2019). Some recent projects try to achieve qualification from regulatory agencies such as European Medicines Agency (EMA) for the use of mobility assessment algorithms and devices (Viceconti et al., 2020).

1.2.6 Digital biomarkers of mobility

A biomarker is defined as a characteristic that is measured as an indicator of biologic or pathologic processes, or response to an intervention (Cancela et al., 2020). Therefore, a digital biomarker is a biomarker collected by sensors and computational tools (Coravos et al., 2019).

By comparing digital biomarkers to their normative values or their measurement at the baseline, one can diagnose the state of a disease or monitor the outcome of a treatment (Shah, McNames, Mancini, Carlson-Kuhta, Nutt, et al., 2020). Therefore, quantification of gait, balance, and physical activity as the markers of mobility is the key to understanding the underlying problem of mobility deficits.

Digital biomarkers can be the digital version of a well established clinimetric marker such as the total time of the TUG test measured by a wearable device, or a new metric such as the maximum angular velocity of the trunk during the turn-to-sit transition of the TUG test.

Inertial measurement units (IMUs) can measure the angular velocity and the acceleration of the movement by the gyroscope and accelerometer sensors that have been integrated inside this unit. IMUs are integrated into smartphones, smartwatches, or mobility assessment wearables developed by companies such as Gait Up (CH), Hasomed (GE), Xsens (NL) to

name a few. By fusing the data of these sensors, one can obtain the orientation of the sensor with respect to an earth-fixed global frame (Madgwick, Harrison, & Vaidyanathan, 2011; Angelo M. Sabatini, 2006). These signals have made the building block of the many algorithms that can help us to analyze the kinetic and kinematics of the body movements and extract meaningful biomechanical parameters to evaluate gait and balance of individuals (Figure 1.6).

Recent studies have shown the feasibility of IMUs in extracting mobility-related parameters, and using these parameters in diagnosis stage of a mobility impairment, e.g. to detect early stages of a mobility-related disorder (Del Din et al., 2019), and during treatment phase, e.g. to evaluate the effect of interventions (Pfeiffer et al., 2020).

Among mobility parameters, gait speed is designated as the sixth vital sign (Fritz & Lusardi, 2009) and has been shown to be a reliable measure in diagnosis (Rochester, Burn, Woods, Godwin, & Nieuwboer, 2009; Zwartjes, Heida, Van Vugt, Geelen, & Veltink, 2010) and a marker of functional decline (Brach, VanSwearingen, Newman, & Kriska, 2002; S. M. Kim, Kim, Yang, Ha, & Han, 2018). As it was shown in section 1.1, an altered gait speed is common in most of the mobility impairments. Unsurprisingly, there are currently several research projects such as Mobilise-D European project to introduce and validate gait speed as a digital biomarker of mobility (Rochester et al., 2020). Or for instance, currently, 95th percentile of gait speed measured by a proper wearable device on the shank has received positive feedback from the European Medicines Agency (EMA) in trials of Duchenne muscular dystrophy (EMA, 2019).

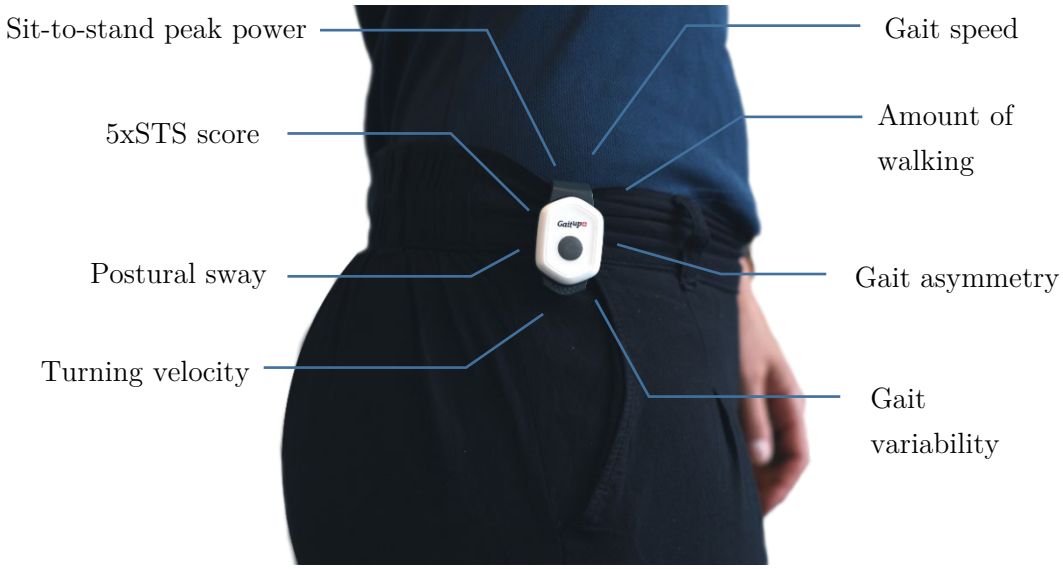


Figure 1.6: An IMU attached to the belt along with some examples of the gait (on the right) and balance (on the left) parameters that can be obtained

Measuring gait parameters by IMUs can also evaluate the effect of a treatment or therapy. For instance, in a group of PD patients, gait speed and stride length were increased after the Automated Mechanical Peripheral Stimulation (AMPS) treatment (Kleiner et al., 2015). This

improvement which had a positive correlation with H&Y stage, ranged from 10% to more than 40%.

Gait asymmetry is another gait parameter that can be measured more sensitively and objectively by an IMU compared to visual observation (S. A. Moore et al., 2017). Gait asymmetry can be obtained by various metrics such as the acceleration signal of the trunk during left and right feet gait cycles (Del Din, Godfrey, & Rochester, 2016) or based on the step length of the left and right feet (K. K. Patterson, Gage, Brooks, Black, & McIlroy, 2010). Gait asymmetry measured by IMUs have high reliability in stroke patients (C. Buckley et al., 2020) and can differentiate PD patients and healthy controls during walking bouts between 30 and 60 seconds of length (Del Din, Godfrey, Galna, Lord, & Rochester, 2016).

Gait variability is defined as the standard deviation or coefficient of variation of a gait parameter (e.g. gait velocity, stride length, or gait cycle time). For instance, gait dysfunction in PD patients is characterized by higher gait variability (Bryant et al., 2011). Therefore, stride length and gait speed coefficient of variation extracted by IMUs have demonstrated high discriminative value between PD patients and healthy controls (Shah, McNames, Mancini, Carlson-Kuhta, Spain, et al., 2020b).

Amount of walking or physical activity during daily activities can predict faller older adults (Brodie, Lord, Coppens, Annegarn, & Delbaere, 2015) or differentiate patients with lower back pain (Anisoara Paraschiv-Ionescu, Perruchoud, Buchser, & Aminian, 2012).

Moving and walking from one place to another are sometimes accompanied by standing up in the beginning and sitting-down at the end. Postural transitions, i.e. sit-to-stands and stand-to-sits are frequently occurred during our daily activities. These mechanically demanding tasks require complicated coordination of lower and upper limbs (Mathiyakom, McNitt-Gray, Requejo, & Costa, 2005) and are associated with balance control of individuals.

Balance control during postural transitions can be evaluated as a stand-alone functional test such as the 5xSTS test. As introduced earlier, this test is used widely in the clinical mobility assessments. Instrumenting such functional tests with IMUs can provide a more detailed analysis of the balance performance of the participants. For instance, it has been shown that the IMU-based 5xSTS test has higher clinical relevance in predicting the physical health of the older adults compared to the traditional stop-watch method (Rob C. Van Lummel et al., 2016). Vertical peak power (maximum value of the multiplication of mass, vertical acceleration and speed of trunk) is one of the kinetic parameters that can be extracted with IMUs during a postural transition. This parameter is indicative of muscle strength (Alcazar et al., 2020) and can predict mobility changes and risk of fall (Regterschot et al., 2014).

Postural sway and turning velocity are among other parameters related to balance performance of the individuals that can be measured by the IMUs. Postural sway which can be measured by the mediolateral displacement of the trunk obtained by an IMU during

tandem walking can manifest vestibular dysfunction (K. J. Kim, Gimmon, Millar, & Schubert, 2019). Turning velocity which can be quantified by the average or peak angular velocity of the trunk during turning can distinguish PD patients from healthy controls (Rehman et al., 2020) as well as PD patients with and without fear of falls (Haertner et al., 2018).

Some mobility parameters like gait speed can be measured simply by a stopwatch or some other parameters like gait asymmetry can be assessed qualitatively by an experienced movement specialist. However, IMUs can measure these parameters more objectively and with higher sensitivity that can detect subtle changes between different groups of the patients. In addition to those parameters, more complex parameters such as gait variability, the sit-to-stand peak power, or turning peak angular velocity can be obtained by the IMUs and dedicated algorithms.

Moreover, being light and relatively inexpensive, IMUs provide flexibility to the environment in which they can be used, whether in the clinic or outside the laboratory.

1.3 Lab vs. Home

IMUs can be employed to assess the mobility of the patients either by functional tests in the clinic (such as TUG test) or by daily activity monitoring at home. However, the International Classification of Functioning Disability and Health (ICF) suggests that there is a difference between these two settings (World Health Organization, 2002). The measurements that are carried out in standardized environments such as the clinic reflect the best performance of the patients or their capacity and the assessments that are carried during daily activities are more representative of the patients' actual performance. In the following section, we will take a look at the differences between clinical and home assessments.

In the literature, different terms are used generally for clinical and daily activity assessments (Figure 1.7). Laboratory or clinical assessments are used interchangeably in the literature. A mobility assessment can be carried out in a motion lab along with conventional clinical assessments such as UPDRS or cognitive tests or can be performed entirely in the clinic. While in the literature capacity is being used mostly for the clinical assessments, it might not be completely accurate. For instance, a walking test that has been performed in the clinic while the participant had been asked to walk with normal speed cannot really be considered as capacity. Therefore, in this case walking as fast as possible can be more representative of the individuals' capacity. The same is also true during daily activity assessments. The patients' maximum gait speed during daily activities might be considered as their capacity during daily activities rather than their performance. Regarding supervised and unsupervised assessment, an assessment can be supervised while being performed at home and vice versa. Therefore, one should be careful about using an accurate terminology. Throughout this thesis, we specified home assessment when we want to refer real-life situation and daily activities that

can happen inside or outside home but definitely they are outside a standardized environment such as a lab or clinic.

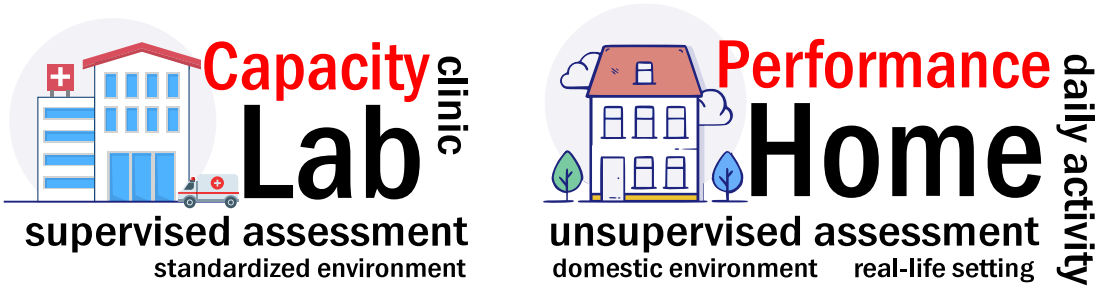


Figure 1.7: Different terms being used for lab and home-based assessments

Earlier we mentioned the benefits of using wearables during daily activities. Particularly, they can obtain rare information such as falls and amount of physical activity that cannot be determined during clinical visits (Warmerdam et al., 2020). Having continuous information from the actual performance of the patients in their household, the clinicians can design and adapt the intervention to improve the patients' performance not only in the clinical environment but also during their daily activities.

As pointed out earlier, the major difference between clinical and home-based assessments is that the former represents more the capacity of the individuals while the latter is representative of actual performance. There are also other sources of difference between those two settings (Bock & Beurskens, 2010; Warmerdam et al., 2020). In the clinic, the individuals are asked to perform the tasks, e.g. walking, by a trigger for the specific task's own sake while during daily activities, our tasks are self-initiated to achieve other goals. During a functional test in the clinic, individuals are more focused on the task itself compared to the daily activities where the individual is confronted with multitasking (e.g. the pedestrian crossing on a road). Actually dual-task walking tests in the lab are more similar to daily living conditions rather than a single task walking test (Hillel et al., 2019). The presence of a clinician or observer that is watching the patient may also have an impact on the performance of the patients in clinical trials. The white-coat effect in which there is a worsening change in a parameter because it is measured at a hospital and the Hawthorne effect which is an improvement in performance when patients are aware of being studied are two well-known effects that might happen in clinical assessments (Warmerdam et al., 2020). The context of the environment might change the patients behaviour. In the clinic, the space might be confined but at the same time there might be less obstacles to perform a walking test. However, at home, there are many obstacles and changes in the context of the environment that the individual needs to adapt their gait which induces higher gait variability compared to the lab. In outdoor activities, the vast space allows to have very long walking bouts while indoor there are mostly shorter walking bouts.

Sometimes the difference can be due to the algorithm being used for the extraction of the parameters from the wearables. Most of the algorithms in the literature have been validated in the laboratory setting rather than during daily activities. For instance, lower accuracy in detecting walking periods has been obtained in home settings compared to the laboratory-based tests by the same algorithm in a study on PD patients (Dijkstra, Kamsma, & Zijlstra, 2010). Sometimes the algorithms have been validated only on healthy young subjects (McCamley, Donati, Grimpampi, & Mazzà, 2012). Thus, employing these algorithms on participants with mobility disorders that have slower gait might lead to inaccurate results. The sensor setup being used during the assessments, specially during the daily living measurements, can have an impact on the performance of the patients. A cumbersome sensor setup on the body can be obtrusive to patients' activities. Indeed by utilizing several IMUs, one can have a more accurate measurement of human movements. By fusing information from IMUs on different locations of the body, e.g., feet, legs, wrist, and trunk, we can have a full assessment of gait, postural transitions, and turns (H. Nguyen et al., 2017). However, despite this exhaustive and more accurate assessment, we cannot expect the patients to wear complex sensor setups and walk or move naturally.

Therefore, algorithm developments should focus more on a single IMU setup, if the goal is to have a comfortable system during patients' daily activities. Among different sensor locations, due to several reasons that will be explained later, foot is a popular placement to attach the IMUs for an accurate gait evaluation (Zrenner et al., 2020). However, with a single IMU on the foot, detecting and characterizing the postural transitions such as sit-to-stands might be challenging if not impossible. Furthermore, an IMU on the foot needs to be attached either by rubber clips on the shoes or by straps to the foot itself, which might not be comfortable for the patients at home. On the other hand, an IMU on the lower back is capable of capturing the postural transition movements as well as gait due to its closeness to the center of mass. Although we may not obtain all the gait parameters that were extractible by foot IMU, lower back placement seems to be a balance between accuracy and a simple sensor setup for daily activities (Storm, Nair, Clarke, Van der Meulen, & Mazzà, 2018). Another technical issue is that most of the algorithms have been designed to be placed on a specific location of the body to track movements such as gait or postural transitions. However, in real-life, one cannot guarantee that the user will fix the sensor always at the same location or attach it as firmly as possible to prevent movement artifacts. Therefore, algorithms should be robust to sensor placement changes.

Finally, the distributions of a parameter within clinical and daily-living measurements are different. For instance, for gait speed, an individual has a very few steps in a functional test in the clinic, while daily activities contain several hundreds of gait cycles. Therefore, at home, we expect to have a wide distribution of gait speed while at the clinic, gait speed would be limited to one value (Figure 1.8). As pointed out by (Warmerdam et al., 2020) there are some

gaps and challenges that should be addressed before we can better take into account long-term daily activity measurements into clinical interpretations.

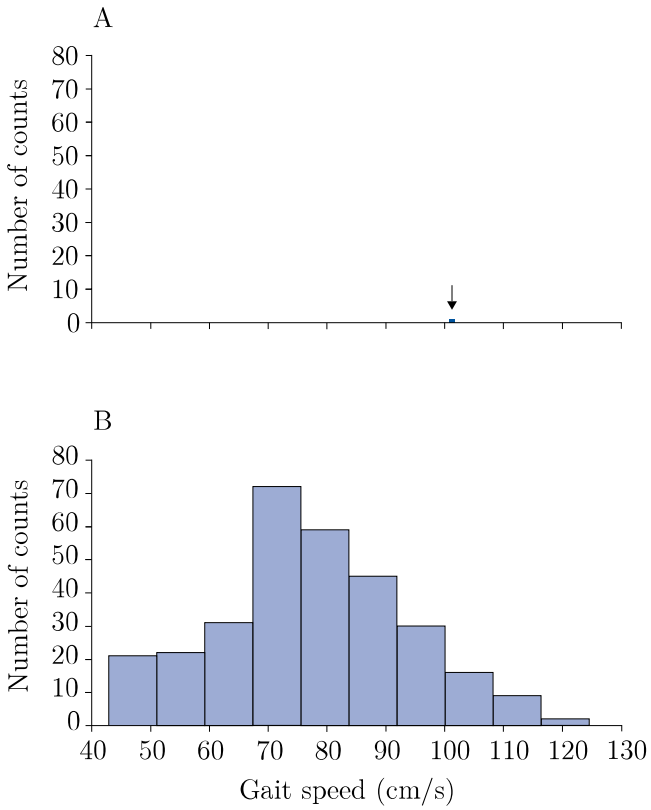


Figure 1.8: Difference between gait speed distribution during clinical assessment (up) and daily activities (down). Image adapted from Elsevier

Focusing on those challenges that are mostly related to the strategy and the data analysis approaches could help us better understand the association between clinical and home-based assessments. The algorithms being used for parameter extraction should be harmonized between lab and home and be validated in both of the settings. While video recordings can be used as a gold standard reference to validate some mobility metrics during daily activities such as number of steps or amount of walking (Hickey, Del Din, Rochester, & Godfrey, 2017), it might raise privacy concerns. An alternative method of validation would be to use "silver standard" reference systems, i.e. a system that has been validated before with a gold standard reference system. For instance, an accurate multiple-IMU system can be used during daily activities to validate a metric such as number of steps obtained by a single IMU on the trunk (Anisoara Paraschiv-Ionescu et al., 2019). An alternative solution can be to simulate real-life settings in the lab and ask the participants to perform simple daily activities while the environment of the lab is designed in a way that it resembles a home environment. This solution can be helpful when we need accurate optical motion tracking systems for validation as they are limited to laboratory settings.

Moreover, the measurement system being used must be as less obtrusive as possible and should be minimized to a single sensor setup in order to have the least influence on the performance of the patients. The algorithms should be designed in a way that they are robust to sensor placement changes. Finally, appropriate comparison and statistical methods need to be employed to compare two aspects that are inherently different.

In addition to the differences between clinical and daily activity measurements mentioned above, a few recent studies have tried to compare these two settings. However, the relationship between the two settings have not yet been well understood. Why are we interested in the relationship between capacity and performance? Performance shows to what extent the capacity of the patients are being used during their daily activities. By having this information, the clinician can design the intervention and medication in a way that helps the patients to use their capacity to a proper extent. Understanding the degree of association between capacity and performance determines if there is a casual relationship between the two. In case of a casual relationship, improving the capacity of patients by measurements in the clinic, one can ensure that the performance of the patients will be also improved.

By comparing each individual's performance to their own capacity we can draw a baseline about a person's best performance. Therefore, a personalized intervention or medication can be designed for the patients in order to optimize their performance. For instance, for PD patients, the optimal dose of Levodopa can be obtained to minimize their motor fluctuations during daily life.

Another reason to justify the importance of capacity and performance comparison is what we mentioned earlier about RPM. If due to some circumstances, the patients are being remotely evaluated in their domestic environment, can the clinician get the information that was possible before during clinical assessment (by measurements performed at home)? Can a functional test performed at home resemble the functional test performed in the clinic? For example, during COVID-19 pandemic, this information can be very helpful if we can keep the older adults safe by performing their mobility assessments in their domestic environment. The contrary can also be of interest. How much information can the clinician obtain about the performance of the patients by assessing the patient only in the clinic? Which functional tests are more representative of patients' performance at home?

Therefore, in this thesis we provide objective tools based on an unobtrusive single IMU for the clinicians to assess the mobility of the individuals. The association between clinical and daily activity measurements is investigated. While we study the impact of mobility impairments on the IMU-derived parameters, we demonstrate how clinical and daily activity measurements can complement each other.

1.4 Objectives of the thesis

This chapter introduced the importance of mobility in health evaluation and its conventional assessments in people with mobility disorders. The benefits of digital health were presented. It was shown how IMU-based digital biomarkers of mobility can help us to have a more in-depth diagnosis of a disorder and a more objective design and evaluation of an intervention. Furthermore, we demonstrated the differences between clinical and daily activity mobility assessment along with the existing challenges in this topic. Finally, the importance of understanding the association between clinical and daily activity assessments was described. The current thesis has been achieved in the framework of a European project called Keep Control which allowed us to have access to a variety of datasets belonging to both healthy people and individuals with mobility impairments collected by other members of the consortium.

As it was mentioned earlier, it is important to develop validated algorithms to assess mobility based on a single IMU setup that is not obtrusive to the users' daily activities. Furthermore, the algorithm needs to be validated during both clinical and daily activity assessments. To this end, the first objective of the thesis is defined as:

i. To design and validate algorithms based on a single IMU on the lower back to extract gait and balance parameters during both clinical and daily activity settings

To achieve our first objective, we developed and validated a postural transition detection algorithm that is based on a single IMU on the lower back. The main goal was to make the postural detection algorithm independent of the location of the IMU around the waist.

Next, we devised and validated a novel approach to detect walking bouts and consequently extract gait speed during walking by a single IMU on the lower back. We showed that by a multiple-sensor setup in the lab, we can train a single-sensor-based model to estimate gait speed during both clinical and daily activity assessments. Our algorithms were validated in patients with multiple sclerosis to show the feasibility of the algorithm in an impaired gait.

In addition to algorithm validation, it would be interesting to know if such an instrumentation with IMUs can help clinicians for an objective diagnosis of the mobility impairments. Thus, the second objective is defined as:

ii. To show how the extracted gait and balance parameters have clinically relevant information in mobility impairment diagnosis

To achieve this objective, the mobility parameters are compared between different populations, i.e. between healthy individuals and participants with mobility disorders, or between patients in moderate and severe stages of a disease such as MS, or between individuals with and without risk of falling. It is demonstrated that which parameters during a clinical or

daily activity assessment have more discriminative power in differentiating patient populations. Furthermore, the effect of medication (Levodopa in PD patients) on the IMU-derived mobility parameters are shown.

Once we are reassured that our methods are technically valid and clinically relevant, we can perform the comparison between clinical and daily activity measurements. Therefore, the third objective is defined as:

iii. To investigate the association between clinical and daily activity assessments in gait and balance field

Particularly, this objective targets to compare capacity and performance through several means. Firstly, considering that the functional tests are performed usually in the clinical environment, it is investigated whether a functional test performed at home achieves similar results to the same functional test performed at the clinic. We explore during which conditions we can find closer association between clinical and daily activity assessments, or when clinical functional tests (i.e. capacity) represent better the performance of the patients in real-life settings. Finally, it is shown how daily activity assessment can complement clinical assessment firstly in determining the effect of medication and secondly in differentiating patient populations.

The methods introduced to achieve this objective provides a framework that can be applied on various patient populations where data from both clinical and daily activity assessments are available.

In the next chapter, the state of the art and the previous works found in the literature are introduced. The existing gaps in the literature are elaborated.

1.5 Outline of the thesis

To explain more clearly the link between the objectives of the thesis and the thesis chapters, we have organized the thesis into four main parts. Each part consists of chapters that accomplish one or more than one of the aforementioned objectives.

Part I - Introduction and Background: The first part introduces the main topic and the state-of-the-art in clinical and daily activity assessments.

- **Chapter 1** which is the current chapter, introduced mobility and some of its conventional assessment methods. Digital health benefits especially in the context of COVID-19 pandemic were explained. It was shown how mobility parameters obtained by the IMUs can provide an objective assessment of mobility. The sources of difference between clinical and daily activity assessments were explained. Based on the existing challenges in the IMU-based mobility assessment in clinical and daily living assessments, the objectives of the thesis were defined.

- **Chapter 2** briefly introduces the biomechanics of gait and postural transitions as the two main components of the mobility considered in this thesis. The existing works regarding the detection and characterization of postural transitions as well as gait detection and speed estimation are reviewed along with their strengths and drawbacks. Finally, the previous studies that compared clinical and daily living assessments are explained and the research questions that have been left unanswered will be formed.

Part II – Algorithm design and validation: In this part, detailed explanation of the methods and algorithms to assess postural transitions and walking speed is provided. Furthermore, the algorithms are validated to show their accuracy and feasibility to be used in clinical and daily activity assessments.

- **Chapter 3** describes a new method to detect and characterize postural transitions based on a single IMU on the waist. By using the vertical acceleration of the trunk in the global frame, we designed an algorithm independent of the location of the sensor in detecting the postural transitions. By validation against reference systems, the accuracy of the detection method is shown in healthy individuals and patients with mobility disorders during simulated real-life measurements. Furthermore, several biomechanical parameters were extracted and compared between healthy and patients populations to show the discriminative power of the parameters extracted by the IMU.

- **Chapter 4** proposes a walking bout detection and gait speed estimation method based on a single IMU on the lower back. In this study, we show that by having a multi-sensor setup in the lab we can train a single-IMU-based model to estimate gait speed during both clinical and daily activity measurements. A machine learning method was employed to develop this model that can detect walking bouts and estimate gait speed. The method was validated in patients with MS as an example to show that the algorithm works for an impaired gait. The gait speed extracted by the IMU on the lower back is shown to have discriminative power between MS patients in moderate and severe stages of the disease. Additional results and applications of these algorithms are provided in two annexes: In the first annex, we investigate the relationship between a functional test performed both in the clinic and at home. In the second annex, the robustness of the developed algorithms of this chapter with respect to sensor placement changes is presented.

Part III - Clinical application: This part presents the clinical and scientific values of this thesis by employing the validated algorithms and helps us for a better understanding of the association between lab and home.

- **Chapter 5** employs the algorithm developed in Chapter 3 to extract temporal, kinematic, kinetic, and smoothness parameters during an instrumented 5xSTS test in more than 450 community-dwelling older adults. The extracted parameters were able to predict prospective fallers while the conventional method based on the total duration of the test measured by a stopwatch failed to do so

- **Chapter 6** introduces two novel approaches to compare gait speed between clinical assessments and daily activities. The first approach is using Gaussian mixture models to quantify the gait speed distribution in the clinic and at home. It compares the two settings and investigates if the patients have the same preferred gait speed in the lab and at home. It demonstrates the clinical walking tests that can better represent daily activities at home. In the second approach, we introduce the Exceptional Strides which later tell us under which conditions during daily activities PD patients reach their capacity in the lab. More importantly, the added value of these comparisons between clinical and daily activity assessments in monitoring the effect of medication in PD is demonstrated.

- **Chapter 7** which employs the algorithms and results obtained by the previous chapters to investigate the effect of fear of falling on the mobility of PD patients as measured during several functional tests in the clinic and also during daily activities performed outside clinic. Moreover, it demonstrates how daily activity assessment can complement clinical assessments to distinguish participants with fear of falling. Furthermore, it demonstrates the association between the same parameters obtained in the clinic and daily activities, i.e. gait speed, sit-to-stan peak power, and turning peak angular velocity.

Part IV - Conclusions: This part summarizes the works that have been done in this thesis and concludes whether gait and balance parameters assessed in the lab are comparable with those collected in domestic environment

- **Chapter 8** as the epilogue of this thesis concludes the works and contributions of this thesis. It provides the discussion around different achievements and paves the way for future research.

The relationship between the thesis chapters are shown in Figure 1.9.

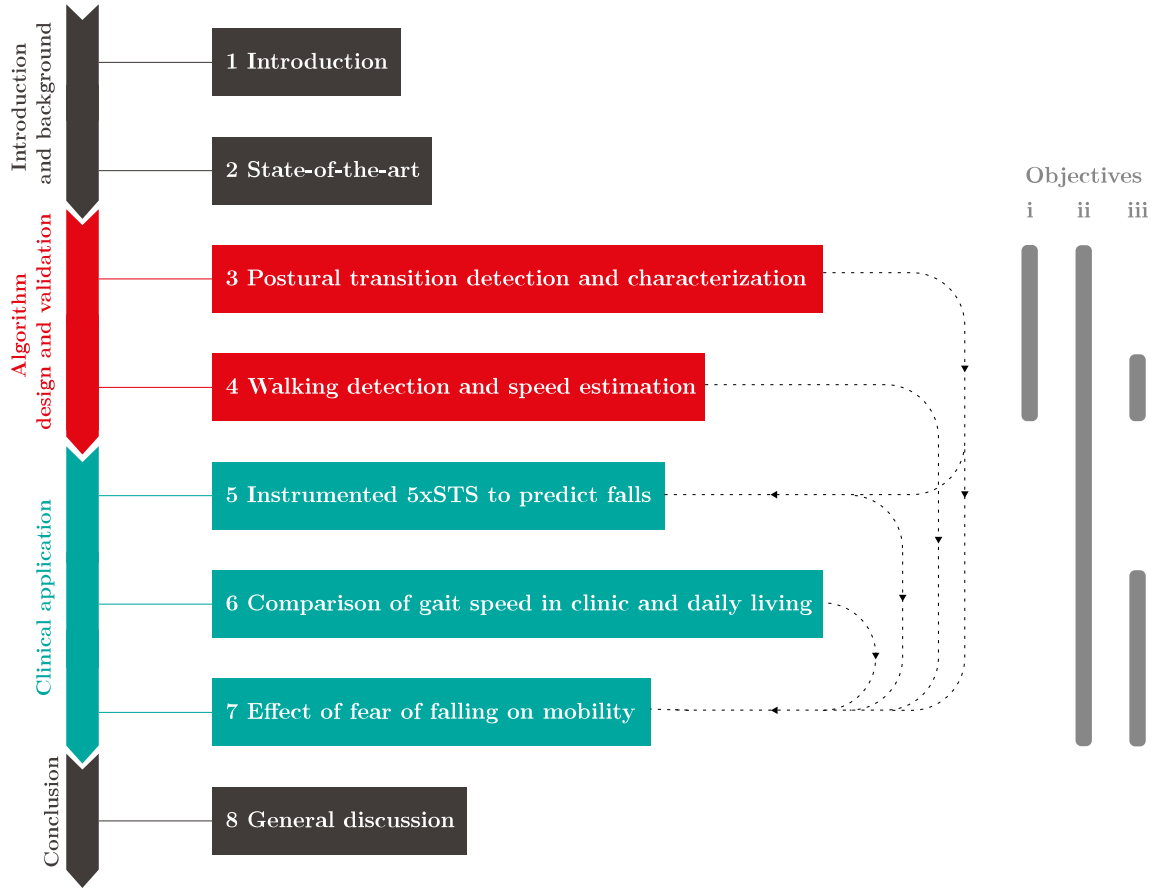


Figure 1.9: Thesis chapters overview, the titles of the parts and chapters may be shortened. The dotted lines represent the methods or results of a chapter that were used in another chapter. For each chapter in Parts II and III, their objectives are labelled on the right. Briefly, the objectives are i: algorithm design and validation, ii: presenting added value in clinical diagnosis, iii: studying relationship between clinical and daily activity assessment

2 State of the art

2.1 Overview

In the previous chapter, the importance and advantages of digital health tools in particular for mobility assessment in daily activities were described. Moreover, I emphasized on postural transitions, i.e. sit-to-stands and stand-to-sits, and gait among the aspects of mobility that occur frequently in daily living. In this chapter, I take a closer look firstly at the biomechanics of postural transitions and gait. Next, I will introduce the conventional semi-objective and objective instruments (with a detailed focus on IMUs) that are used to evaluate postural transitions and gait. The existing methods in the literature to assess those two aspects with IMUs in clinical and home-based measurements will be discussed along with their strengths and drawbacks. Finally, the studies that have focused on the comparison of clinical and daily activity assessments will be reviewed.

2.2 Biomechanics of postural transitions and gait

2.2.1 Biomechanics of postural transitions

The main body postures are lying, sitting, and standing (Vähä-Ypyä, Husu, Suni, Vasankari, & Sievänen, 2018). Standing posture itself can include walking, running, turning, standing still, etc. Therefore, postural transitions can take many forms such as sit-to-walk, sit-to-stand, stand-to-sit, turn-and-sit, and walk-to-sit-to-lie. As the postural transitions can challenge balance and stability, analyzing them can lead to a better understanding of an individual's balance performance.

Among the postural transitions, sit-to-stands and stand-to-sits are inseparable components of daily activities and occur usually more frequently than the others (Rodríguez-Martín, Samà, Pérez-López, & Català, 2012). The number of sit-to-stands per day can vary from 30 to 70 in community-dwelling adults (Figure 2.1) (Bohannon, 2015). Individuals that have a daily sit-to-stand number of less than 45 can have a potential work deficit (Bohannon, 2015).

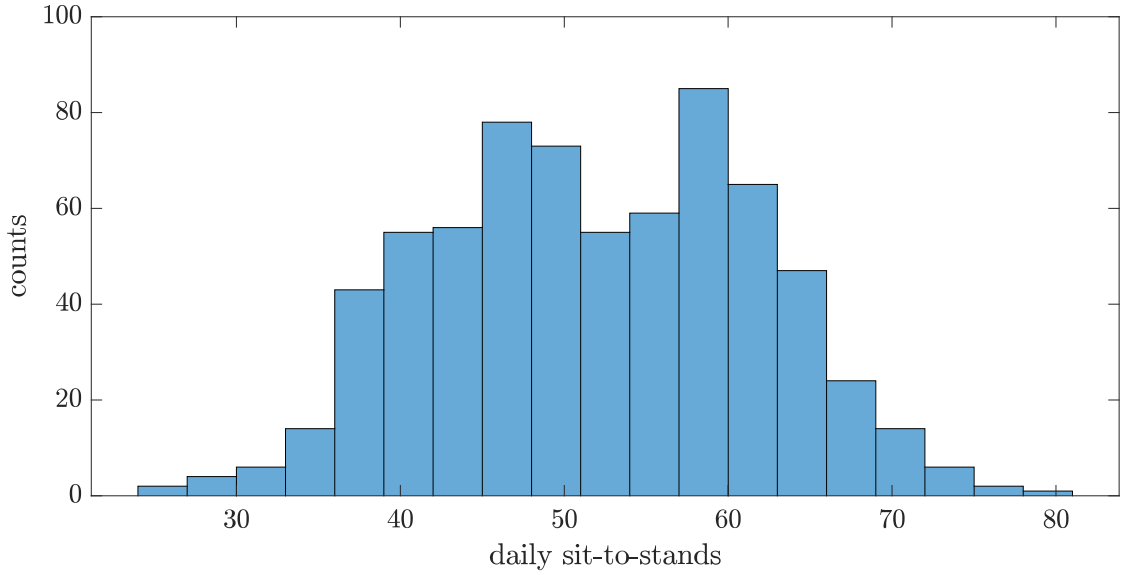


Figure 2.1: The number of sit-to-stands per day in 689 adults measured by tally counters or IMUs. Image generated by the information given by (Bohannon, 2015).

A sit-to-stand requires complicated coordination of lower and upper limbs and is indicative of muscle power and balance control. In fact, a sit-to-stand consists of four phases (Figure 2.2) (Schenkman, Berger, Riley, Mann, & Hodge, 1990):

1. Flexion momentum: Initiates the movement and continues just before the buttocks leave the seat. The flexion of the trunk generates the momentum required for the next phase while the thighs, shanks, and legs are fixed on the ground.

2. Momentum transfer: Begins as the buttocks leave the seat until the ankle dorsiflexion reaches its maximum. The momentum generated during the previous phase is transferred to move the body center of mass (CoM) upward and forward. At the end of this phase, the CoM has its maximum anterior position.

3. Extension: During this phase hip and trunk have an extension movement and the upward motion of the trunk continues to reach its maximum vertical displacement.

4. Stabilization: Finally, the person adjusts their posture as they have stood up completely. This phase has not a clear ending as people continue to have anterior-posterior and lateral sway.

To obtain the stability region of the CoM, the linear and angular momenta can be obtained (Pai & Lee, 1994). Biomechanical models of the sit-to-stand have been developed in the literature to estimate the momenta.

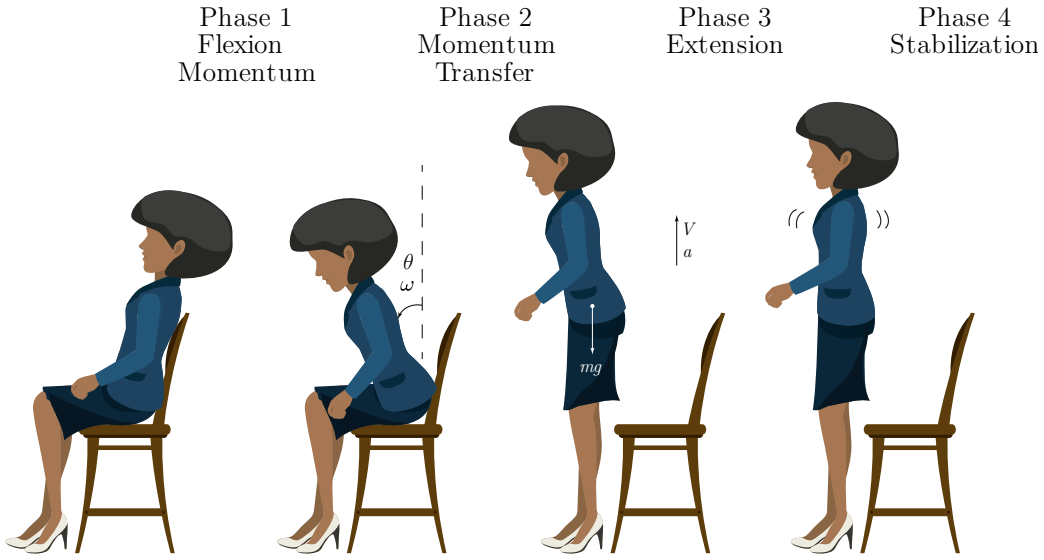


Figure 2.2: Different phases of a sit-to-stand transition, θ is the trunk tilt angle, ω is trunk angular velocity in sagittal plane, V and a are vertical velocity and acceleration, mg is the weight of the subject

For instance, two telescopic inverted pendulums (TIP1 and TIP2) were introduced to model two phases of a sit-to-stand: 1) before seat unloading, 2) after seat-off (Papa & Cappozzo, 1999). Before losing the contact with the chair, only the head, arms, and trunk (HAT) are moving; therefore, the CoM of HAT is attached to the TIP1 which its length increases by a linear actuator acting as trunk muscles that increase or decrease lumbar lordosis (Figure 2.3). TIP1 is hinged at a point between the hips. Right after seat-off, the TIP2 (hinged between the ankles) replaces TIP1, and the whole body is moving instead of HAT. A linear actuator acts as the trunk, hip, and knee flexors which elongates the inverted pendulum. In both TIP1 and TIP2, two rotational actuators (one in sagittal plane and the other in frontal plane) determine stability and rotations in their respective planes. The input of this model is the trajectory of the CoM.

The abovementioned model was further improved to also include the transition between before and after seat-off (Aissaoui, Ganea, & Aminian, 2011). The authors suggested two inverted pendulums, one extendable while the other is rigid.

As in every biomechanical modelling, external forces and moments have an impact on the biomechanics of the movement, sit-to-stand task can also be influenced by the chair settings. For example, raising the seat height, can reduce the biomechanical demand of a sit-to-stand (Arborelius, Wretenberg, & Lindberg, 1992). Therefore, individuals have reported an easier movement from a raised seat (S. H. Chen, Lee, Chiou, & Chen, 2010). More objectively, raising the seat height decreases the trunk, hip, and knee angular velocity and rotation (Kuo, Tully, & Galea, 2010), hip and knee flexion moments (Arborelius et al., 1992), and their muscle activity (Hurley, Rutherford, & Hubley-Kozey, 2016). Using armrests can also decrease

the effort as well as the joint moments when rising up from a chair (Arborelius et al., 1992). Of course the change in effort depends on the strength of the arm muscles compared to those of the legs. Although during clinical assessments, these extrinsic factors (such as armrest and chair height) are controlled, during daily activities, individuals sit on different chairs with various properties.

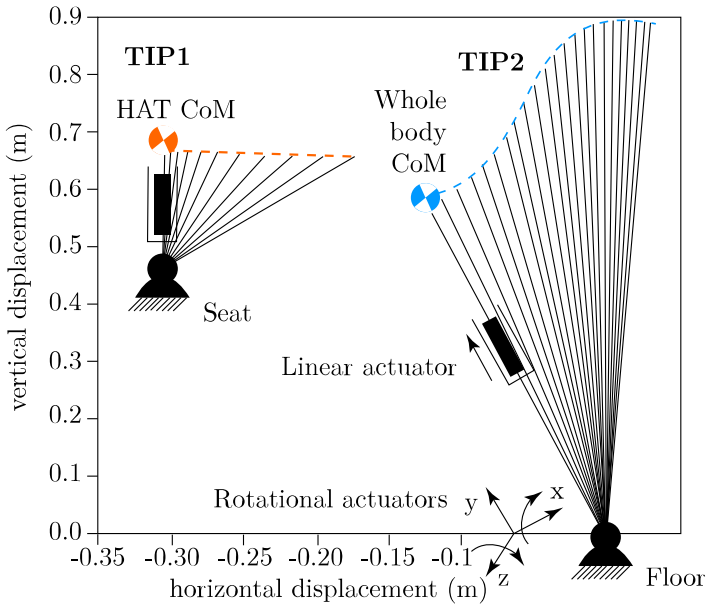


Figure 2.3: The TIP model proposed by (Papa & Cappozzo, 1999) to model the biomechanics of sit-to-stand, Image recreated from (Papa & Cappozzo, 1999)

Other than extrinsic factors, functional deficits can alter the biomechanics of the postural transitions. Several parameters extracted during the postural transitions have been shown to have clinical predictive value. For instance, the maximum angular velocity of trunk is indicative of a successful transition (P. O. Riley, Krebs, & Popat, 1997; Zablotny, Nawoczenski, & Yu, 2003), duration of each sit-to-stand or stand-to-sit changes between younger and older adults (R. C. Van Lummel et al., 2013) or between older adults with a low and high risk of falls (Najafi, Aminian, Loew, Blanc, & Robert, 2002). Peak power which is the multiplication of mass, vertical velocity, and acceleration is associated with muscle strength (W. Zhang, Regterschot, Geraedts, Baldus, & Zijlstra, 2017; Zijlstra, Bisseling, Schlumbohm, & Baldus, 2010).

2.2.2 Biomechanics of gait

Gait bout is an episode of locomotion that is consisted of several gait cycles. Each gait cycle or stride begins with one foot's initial contact with the ground and continues until the next initial contact. The two phases of a stride are stance and swing. During the stance phase, the reference foot is on the ground while in swing phase it is not in contact with the ground and

swings in the air. Kinematic and kinetic modelling of walking enables the understanding of the relation between lower extremity and the movement of the CoM. Inverted pendulum model is the simplest model to analyze CoM displacement during walking (Figure 2.4A). In this model, the whole leg is considered as an inverted pendulum during the stance phase. In this case, the CoM has the largest possible vertical oscillation. There had been some debates over this model as it has been suggested that our body employs some strategies to reduce the vertical displacement of the CoM to decrease the energy expenditure (Charalambous, 2014), an optimal vertical displacement that is "neither too flat nor too bouncy" (Neumann, 2002).

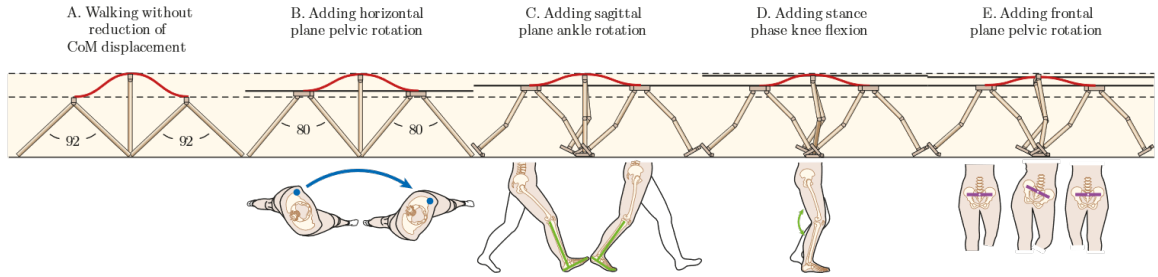


Figure 2.4: The biomechanical models relating the kinematics of lower extremity to the CoM displacement (Neumann, 2002)*, authorised copy from Elsevier*

Firstly, the pelvis horizontal rotation moves the swinging leg forward, reducing the hip flexion and extension rotation to achieve a given step length (Figure 2.4B). Secondly, taking into account the knee and ankle joint rotations leads to a functional elongation of the leg that further reduces the downward vertical displacement of the CoM (Figure 2.4C). Finally, in the fourth and fifth models, the flexion of the knee joint in stance phase as well as the frontal rotation of the pelvis assist reducing the upward vertical oscillation of the CoM (Figure 2.4D and Figure 2.4E).

As lateral stability might be challenged in some neurological or orthopaedic impairments, some of the biomechanical models consider also an inverted pendulum like motion for the lateral oscillation of the CoM during gait (Tesio & Rota, 2019). In the frontal plane, at each step, the CoM oscillates between the supporting leg and the opposite one through an inverted pendulum like motion. Therefore, as proposed by (Tesio, Rota, Chessa, & Perucca, 2010), if we subtract the forward progression of the CoM (e.g. in a treadmill walking), the CoM follows a closed eight-shape trajectory (Figure 2.6). This closed eight-shape trajectory that is also known as bow-tie shape was later confirmed and validated mathematically (Minetti, Cisotti, & Mian, 2011).

The path of CoM has a close relationship with walking velocity; an increase in velocity increases the upward concavity of the bow-tie shape (Figure 2.6). Hence, as walking speed increases, the lateral motion oscillations decrease and the vertical motion oscillations increase (Malloggi et al., 2019; Tesio et al., 2010).

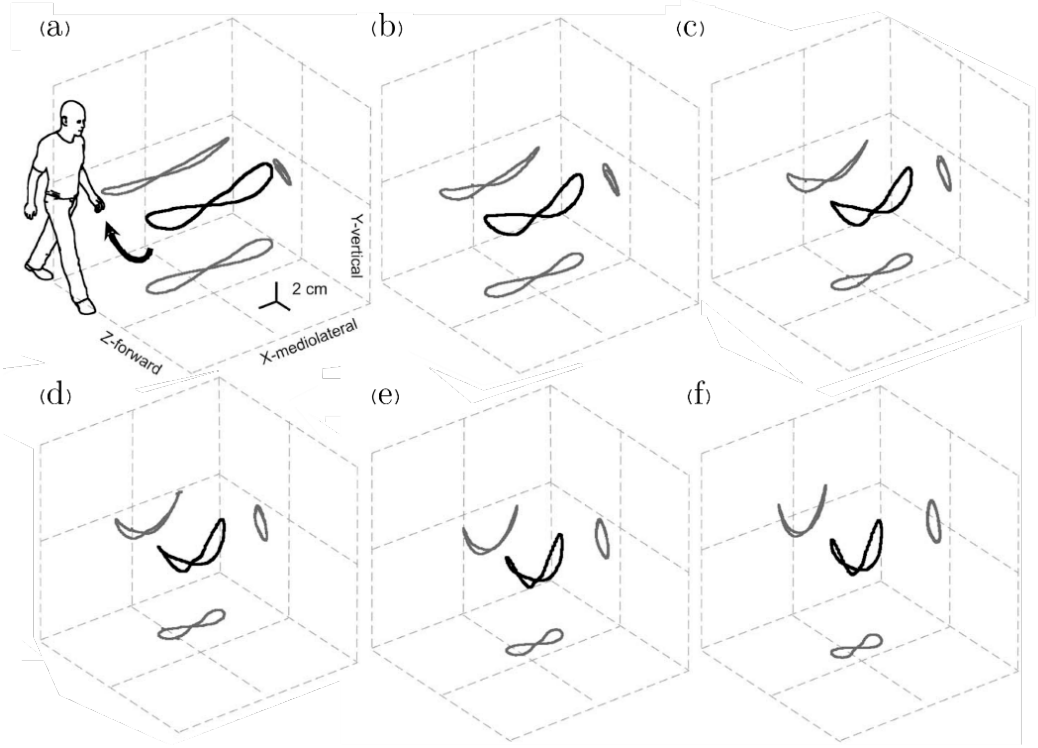
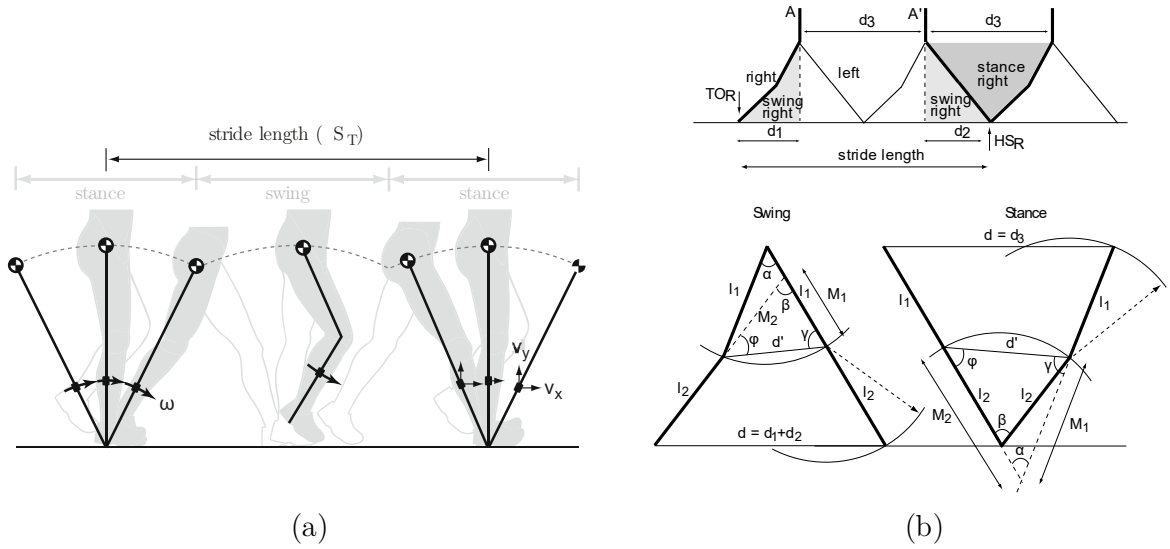


Figure 2.5: The closed eight-shape 3D trajectory of CoM during gait along with its 2D projections on the anatomical planes. The CoM was grand-averaged from 18 young healthy adults. Gait speed varies through each subfigure from 0.3 m/s in (a) to 1.4 m/s in (f). Image adapted from (Tesio et al., 2010), Image used with authorization from Elsevier

These biomechanical models allow the extraction and analysis of gait parameters such as stride length (Figure 2.5). For instance, in the model proposed by (Aminian, Najafi, Büla, Leyvraz, & Robert, 2002), legs are simulated by a double pendulum model during swing phase and by an inverted double pendulum model during stance. By measuring the kinematics of these models, i.e. the length of the pendulums as well as the angles, one can estimate the stride length. Consequently, the stride length is equal to the sum of the distance traversed by the swinging foot and the foot in stance phase ($d_1 + d_2 + d_3$, Figure 2.6b).

Gait parameters can be divided into two categories of temporal and spatial parameters. Temporal parameters characterize the gait in the time domain. For instance, gait cycle time, double support time (in which both of the feet are in stance phase), stance time, and swing time are among the temporal gait parameters. Spatial parameters concern the spatial aspect of the gait. Stride length, step length, pitch angle (the rotation of the foot in the sagittal plane), and swing width (the lateral displacement of foot during swing phase) are some of the spatial gait parameters. Among all the gait parameters, gait speed is a spatiotemporal parameter, involving both spatial (stride length) and temporal (gait cycle time) aspects of gait.



(a) (b)

Figure 2.6: (a) The inverted pendulum model of the shank (Q. Li et al., 2010) (b) The double pendulum models for spatial analysis of gait proposed by (Aminian et al., 2002) , Images used with authorization from Elsevier

For a normal gait, all of these systems need to function properly: locomotor function, balance control, postural reflex, sensory function, musculoskeletal system, cognition, and cardiopulmonary system (Pirker & Katzenschlager, 2017). A disorder in one of the aforementioned functions can alter gait and its parameters. There are several types of abnormal gait, each with their own characteristics. Freezing gait (gait blockage especially during turning), stepping gait (weak foot extensors) and dystonic gait (abnormal leg posture) are among abnormal gaits (Pirker & Katzenschlager, 2017).

In addition to pathologies, environmental factors can also impact gait. Especially during daily walking these factors are not controlled opposed to the laboratory environment that has a less complex context. For example, walking uphill requires more energy than walking on a flat surface (Minetti, Moia, Roi, Susta, & Ferretti, 2002) while walking downhill needs to overcome the acting downward inertial forces (Gottschall & Kram, 2005). In young healthy adults, it has been shown that uphill walking reduces the gait speed, step length, and cadence of the participants while gait coordination parameters such as gait asymmetry and gait variability remain unchanged (Kimel-Naor, Gottlieb, & Plotnik, 2017). Stairs ascent and descent usually causes a less stable gait compared to level walking. Moreover, ascending the stairs can increase the stance and double support time (Demura, Demura, & Shin, 2010). During daily activities, walking is often accompanied by other tasks that require our attention. For instance, cognitive tasks during dual walking tests can decrease our gait speed and increase the double support time (Bowen et al., 2001). Furthermore, outside clinic, there might be obstacles that we need to constantly adapt our gait. For example, gait speed can decrease slightly when walking in a shopping mall compared to a suburban street where there are less perturbations and obstacles (Donovan, Lord, McNaughton, & Weatherall, 2008).

2.3 Objective assessment of postural transitions and gait

In the previous chapter, I highlighted the importance of the objective assessment of mobility as the conventional subjective methods such as questionnaires and rating scales are dependent on the observer. Therefore, some instruments are being used for a more objective assessment of postural transitions and gait. For instance, by stopwatch, one can measure the total time taken by a person to perform the five-time sit-to-stand (5xSTS) test (Csuka & McCarty, 1985). Walking tests are also quantified using a stopwatch. For some of these tests such as TUG test, the outcome of the test can be simply the total time measured by the stopwatch. For some other walking tests, in addition to the total time, gait speed can be obtained by dividing the distance traversed by the participant by the total time measured by the stopwatch. Although these measurements provide good reliability, they are subject to inter-rater and inter-trial effects (Donoghue, Savva, Börsch-Supan, & Kenny, 2019).

Another device that is used to assess speed, is the global navigation satellite system (GNSS) receiver. GNSS receivers make use of triangulation to obtain position and velocity. Therefore, they can be used to obtain gait speed or stride length (Soltani, Dejnabadi, Savary, & Aminian, 2020). However, their use is limited to outdoors as the signals are hampered by solid objects such as buildings (Terrier & Schutz, 2005).

In addition to the stopwatch and GNSS receivers there are other instruments to assess postural transitions and gait. In this section, I briefly review those tools and their application in gait and postural transition assessment in laboratory and home environments (Figure 2.7).

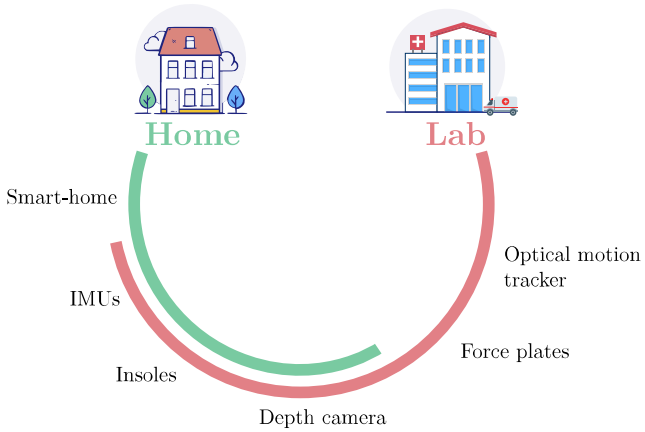


Figure 2.7: Some of the objective assessment tools to evaluate postural transitions and gait in lab and home, red curve marks the assessments used in the lab, green curve marks the instruments used outside the lab or in domestic environments

2.3.1 Optical motion tracker

The optical motion tracking systems often include several cameras that track the motion of reflective markers that can be actively or passively emitting. These systems are mostly used

as a gold standard reference to validate other methods as they have very high accuracy. In human body motion tracking, markers can be either placed at anatomical points or as clusters on body segments to track the movements of each segment of the body. With the information from the kinematics of the body segments, one can have an assessment of full body motion that can be integrated with other sensors such as force plates to also obtain kinetic analysis such as joints forces and moments.

In the early 90s, researchers analyzed the sit-to-stand transitions and define their different phases by optical motion tracking systems (Patrick O. Riley, Schenkman, Mann, & Hodge, 1991; Schenkman et al., 1990). Moreover, by using these systems, it was concluded that there are three different strategies to stand-up from a chair in older adults (Figure 2.8) (Hughes, Weiner, Schenkman, Long, & Studenski, 1994): 1) Momentum transfer: in which individuals use the horizontal momentum generated by the flexion of the trunk to stand up, 2) Stabilization: in which individuals decrease the distance between their CoM and base of support on the ground with little horizontal momentum, and 3) Combined: which is a combination of the two mentioned strategies. Determining the strategy that has been employed by the subject can help the clinicians to evaluate the balance performance of the patients.

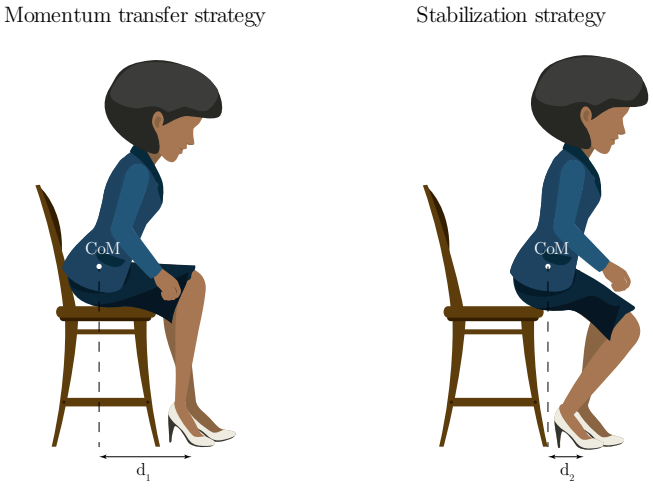


Figure 2.8: Momentum transfer and stabilization strategies to stand up ($d_1 > d_2$)

Regarding gait analysis, by attaching markers on specific bony landmarks, the kinematic features of gait can be obtained by methods such as Plug-in-Gait (Davis, Õunpuu, Tyburski, & Gage, 1991).

In spite of being very accurate, these systems are expensive and are confined to the laboratory environment. Therefore, for example in case of gait analysis, there might not be enough steps to have a steady-state analysis. More importantly, the small space of the laboratory might not represent the real-life situation and the arrangement of a simulated real-life environment might be challenging.

2.3.2 Force plates

Force plates are used in the lab to measure the ground reaction forces, moments, and center of pressure (CoP). These systems generally consist of load cells or triaxial force transducers located at each corner of a rectangular platform. Force plates can be integrated into a treadmill that measure the forces continuously during gait cycles. These systems can overcome the "targeting" problem in which the participants try to adapt their stride length to step over the small area of a force plate (Challis, 2001). However, they can only measure the performance of the participant during straight walking and with constant speed (Tao, Liu, Zheng, & Feng, 2012).

The data obtained by the force plate can be combined with the one from a motion capture system such as optical motion trackers to have a full kinematic and kinetic analysis of movements such as postural transitions (Stevermer & Gillette, 2016) and gait (Ren, Jones, & Howard, 2008). For instance, vertical power during a sit-to-stand transition can be measured by multiplying the vertical velocity of the CoM obtained by the optical motion trackers and the sum of vertical reaction forces measured by the force plates (Baltasar-Fernandez et al., 2021). The vertical power during a sit-to-sand transfer is well correlated with isokinetic muscle strength (Lindemann et al., 2003; Yamada & Demura, 2010).

During gait, by employing the inverse dynamics approach, the internal forces and moments of joints (e.g. hip, knee, and ankle) can be determined by the motion data and ground reaction forces.

2.3.3 Portable depth camera

Cheaper and portable optical-based systems can be used instead of gold standard optical motion trackers but with a less accuracy. These systems are mostly based on the integration of a depth and a normal camera to track the 3D positions of the cloud points in the space.

Some of these systems have built-in models of human skeletal model that can track the movements of human body segments. For instance, Microsoft Kinect has been used in a study to monitor the 5xSTS test performed by community-dwelling older adults in an unsupervised manner in their domestic environment (Ejupi et al., 2015). The system was able to differentiate retrospective fallers and non-fallers. These systems can have an accuracy of above 98% to detect gait cycles and an error of 1 cm/s to estimate gait speed (Rocha, Choupina, Vilas-Boas, Fernandes, & Cunha, 2018). Although being cheap and portable, these systems suffer from occlusion and can reach an error of 10 cm in tracking a human joint (Atrsaei, Salarieh, & Alasty, 2016). Moreover, the depth of field of Kinect is small, limiting the number of steps that can be performed in front of the camera (Ng et al., 2020). Fusing the data of Kinect with other sensors such as IMUs can overcome these problems (Atrsaei et al., 2016).

With recent advances in computer vision methods, a simple RGB video camera without depth images can be used to track the gait trajectory and consequently extract gait parameters (Ng

et al., 2020). However, the video-based methods might raise privacy-related concerns among the individuals.

2.3.4 Insoles

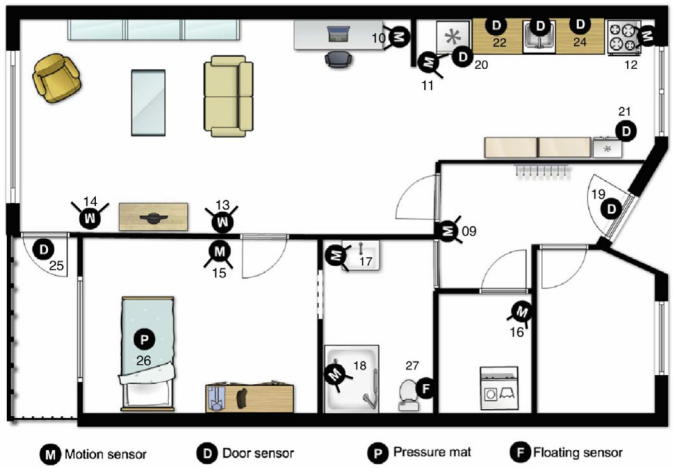
Sensing insoles are a matrix of resistive, capacitive, piezoelectric, or piezoresistive pressure sensors taking the form of a foot insole. Each cell of this matrix measure the pressure exerted upon its small area. Therefore, in addition to the pressure distribution on the foot, the CoP and vertical ground reaction forces can also be obtained. An application of the sensing insoles is to evaluate foot deformity by measuring the pressure distribution obtained by these sensors (Turner & Woodburn, 2008). The sensing insoles are attractive as they can be integrated into shoes that can be used also outside the laboratory environment opposed to the force plates (Q. Zhang et al., 2019). Moreover, they have lower costs compared to the force plates. However, shoe insoles might alter participants' gait performance as they might add additional materials between the feet and the shoes (Debbi et al., 2012). Furthermore, the available shoe insoles might not always match the shoe size of all the participants (Debbi et al., 2012).

These shoe insoles can be combined with inertial measurement units and provide a better detection of activities of daily living (Moufawad el Achkar et al., 2016). For instance, a zero or near zero force measured by the insoles is indicative of lying activity (Moufawad el Achkar et al., 2016). Furthermore, as postural transitions are accompanied by a change in the static vertical ground reaction forces, they can be detected by the insoles (Moufawad el Achkar et al., 2016). However, there are some evidence in the literature that the insoles might not distinguish well the walking and standing activities especially in slow walkers (Fulk & Sazonov, 2011). Therefore, using the information from inertial measurement units for walking detection can be helpful.

The sensing pressure insoles can take the form of instrumented walkways (known also as instrumented mats). These systems provide a spatiotemporal analysis of gait through their matrix of pressure sensors and a dedicated software. As the instrumented walkways measure the pressure of the foot during each contacts, they can measure the gait events (and consequently temporal gait parameters) more precisely than visual detection methods (Cutlip, Mancinelli, Huber, & Dipasquale, 2000).

2.3.5 Smart-home

Another solution for continuously monitoring the activity of the patients would be to use a network of sensors in the domestic environment of the patients. For instance, several ambient, pressure, and door sensors were installed in volunteers' apartments in a study (Aicha, Englebienne, & Kröse, 2018) (Figure 2.9). By extracting a set of features from these sensors and having some information about the localization of the sensors, the authors extracted the walking trajectories as well as their corresponding duration. Consequently, gait speed was calculated during daily activities.



Id	Sensor location	Sensor type	Room (number)
09	Hall	Motion	Hall (3)
10	Desk	Motion	Living room (6)
11	Kitchen	Motion	Kitchen (4)
12	Kitchen hob	Motion	Kitchen (4)
13	Living front	Motion	Living room (6)
14	Living back	Motion	Living room (6)
15	Bedroom	Motion	Bedroom (2)
16	Laundry	Motion	Laundry room (5)
17	Washbasin	Motion	Bathroom (1)
18	Shower	Motion	Bathroom (1)
19	Front Door	Door	Hall (3)
20	Freezer	Door	Kitchen (4)
21	Fridge	Door	Kitchen (4)
22	Cupboard1	Door	Kitchen (4)
23	Cupboard2	Door	Kitchen (4)
24	Cupboard3	Door	Kitchen (4)
25	Balcony	Door	Living room (6)
26	Bed	Pressure	Bedroom (2)
27	Toilet	Floating	Bathroom (1)

Figure 2.9: A network of several sensors installed in a volunteer's apartment to track gait speed (Aicha et al., 2018)*, authorized copy from Springer Nature*

In another study, several infrared sensors were installed on a wall with a known distance. The gait speed was calculated by the time difference when a person was passing in front of the sensors (Chapron, Bouchard, & Gaboury, 2020). A Bluetooth wristband was given to different individuals as a solution for multiple-residents apartments. These systems may not have enough accuracy to estimate the gait speed of the individuals as the angle view of the ambient sensors are wide (Aicha et al., 2018). Furthermore, these sensors give little information regarding the biomechanics of the movement as well as the context of the daily living activities.

Recently, a sensor based on radio signals has been developed that can track the position of the human body based on the distortion that they make in the radio signals of the environment (Hsu et al., 2017; F. Zhang, Chen, Wang, & Liu, 2018). This system that can be attached to the wall in the user's domestic environment can report gait velocity of the subject with an accuracy of above 95% (Hsu et al., 2017).

As these systems provide a continuous and remote assessment of gait speed, they can be used in elderly care applications. For instance, these systems can indicate abrupt changes in gait speed due to stroke for example, or slow decline due to cognitive impairments (Austin, Hayes, Kaye, Mattek, & Pavel, 2011).

2.3.6 IMUs

As mentioned in the first chapter, IMUs consist of accelerometer and gyroscope sensors that measure the acceleration of the motion plus the gravity reaction as well as the angular velocity.

In an ideal world, one can integrate the gyroscope signal to have the orientation of the rigid body to which the IMU is attached; however, as there is noise and bias in the signal, integrating the gyroscope leads to an accumulating error through time which is called drift.

To correct this drift, we can fuse gyroscope data with accelerometer (6D fusion) or accelerometer and magnetometer (9D fusion) signals. In case of a 6D fusion, the orientation of the IMU is specified in a relative global frame in which its vertical axis is aligned with gravity and its horizontal axes are oriented arbitrarily in the horizontal plane. In case of a 9D fusion, the orientation of the sensor is stated with respect to a global frame that is called North-East-Down (NED) coordinate system in which the X axis is pointing to the magnetic north, Y axis is pointing to the east, and Z-axis is vertically downward. Magnetometers that measure the earth magnetic field in the sensor frame can be combined with IMUs (9D fusion) to correct the drift in the azimuth angle (the heading angle with respect to the magnetic north). However, a fusion approach should be employed that rejects the effects of magnetic perturbations (Angelo M. Sabatini, 2006).

The two most well-known methods that are used to fuse the IMU data to estimate its orientation are Kalman (Angelo M. Sabatini, 2006; Vitali, McGinnis, & Perkins, 2021) and Madgwick filters (Madgwick et al., 2011). The former is based on an optimal state estimation method while the latter is based on a gradient descent based method. The two methods have almost the same accuracy (Madgwick et al., 2011) with Madgwick filter performing faster than the Kalman filter (Ludwig & Burnham, 2018). The output of both of the approaches can be a quaternion that transforms any vector in the sensor frame to the global frame.

To track the position of the rigid body to which the IMU is attached, the ideal way would be to double integrate the acceleration data (obtained by the accelerometer sensor and the orientation of the IMU) in the global frame. However, again due to high noise and bias, the obtained position will drift several meters over only a few seconds. Therefore, additional sources of information are needed to obtain a drift-free position (or displacement). This complementary information can come from other sensors such as a depth camera (Atrsaei et al., 2016), GNSS receiver (L. Chen & Hu, 2012), or barometric pressure sensor (Angelo Maria Sabatini & Genovese, 2014). Using each of these sensors alone has its own drawbacks for position tracking. Occlusion for the depth camera, low sampling frequency for GNSS and depth camera, and high noise for barometers to name but a few. However, fusing their information with IMUs can provide a more robust and accurate position tracking approach.

Another source of information can be biomechanical constraints or information. For instance, as it will be explained later, during gait analysis, the velocity and vertical position of the foot that is in motionless period (foot-flat phase during stance), have zero values. Using this information can overcome the drift problem of the velocity and vertical position of the foot obtained by the integration of the acceleration from IMUs (Benoit Mariani et al., 2010). As another example, during the 5xSTS test, the sitting position of the performer can be considered the same over all the sit-to-stand repetitions. Therefore, by updating the vertical velocity and displacement signals to zero, one can correct the drift for these two signals (Figure 2.10).

With IMUs being attached to the human body segments, we can extract features either directly from the gyroscope and acceleration signals or from the orientation or position of the

sensor. These features can be key events to detect a special kind of motion, for instance the beginning and the end of postural transitions (Atrsaei et al., 2020) or biomechanical features that can be fed into a regression model to estimate a parameter like gait speed (Soltani, Dejnabadi, et al., 2020).

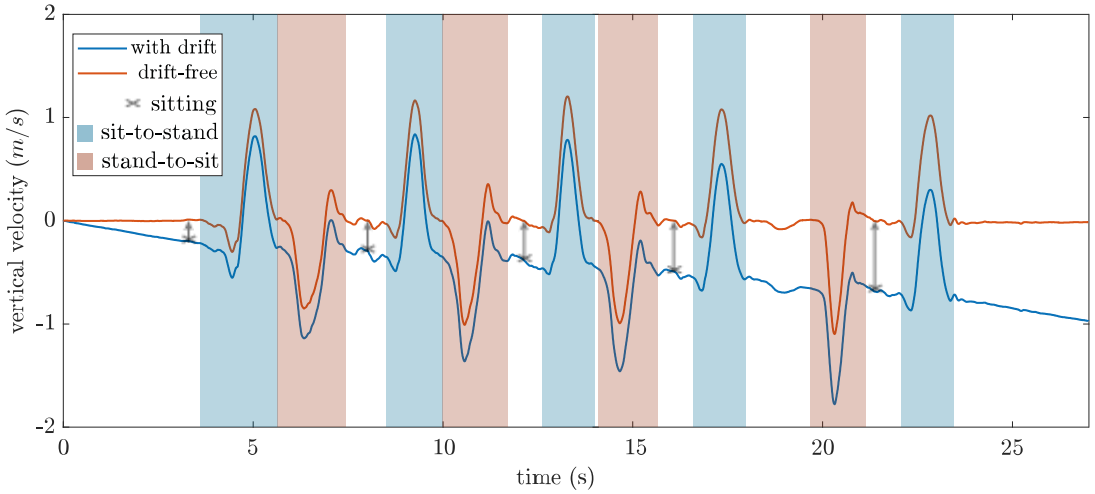


Figure 2.10: The vertical velocity signal before and after drift correction during the 5xSTS test. The signal is measured by an IMU on the trunk on a healthy young subject during the 5xSTS test with preferred speed

The main advantage of the IMUs compared to other tools mentioned in this chapter is the flexibility that they provide to be used in any environment whether in a laboratory, clinic, outdoors, or at home. Furthermore, they are light weight and are less obtrusive to normal movements or daily activities of the individuals.

Depending on the application and the required accuracy, there can be a single or multiple IMU-setup on the body to track the segments' movements. Usually the multi-sensor setup provides more accuracy sacrificing the comfort for the user and complicated setup (Favre, Aissaoui, Jolles, de Guise, & Aminian, 2009). Therefore, the algorithms should consider using a single sensor setup if possible while maintaining an acceptable accuracy compared to the multi-sensor system. In this case, the sensor setup will be more comfortable for both the clinician and the patient and will less hinder the user's daily activities.

As the IMU was the main tool that was used in this thesis to detect and characterize postural transitions and estimate walking bout duration and speed, we review in the following section the existing IMU-based methods and algorithms in those two domains.

While IMUs provide raw data of the acceleration and angular velocity of the body segments, algorithms are needed to pre-process this data through proper filtering (e.g. lowpass filtering, Kalman filtering), to detect events (e.g. initial foot contact during gait, a sit-to-stand transition), and finally to extract meaningful biomechanical parameters (gait speed sit-to-stand peak power).

2.4 Postural transition assessment using IMUs

Inertial sensors can be used in any environment to assess the postural transitions (PTs). In laboratory environment, single PTs such as a single sit-to-stand or the PT during the TUG test have been analyzed with IMUs (Janssen, Bussman, Horemans, & Stam, 2005; Lepetit, Ben Mansour, Boudaoud, Kinugawa-Bourron, & Marin, 2018; Najafi et al., 2002; Witchel et al., 2018). Furthermore, functional tests such as 5xSTS test or 30-second chair rise test (30SCT) have been instrumented by IMUs (Millor, Lecumberri, Gómez, Martínez-Ramírez, Rodríguez-Mañas, et al., 2013; R. C. Van Lummel et al., 2013). Firstly, different events of the PTs were detected by the characteristics of the angular velocity signal, i.e. zero-crossing of this signal for the start and end of each PT. For each PT, several kinematic parameters were extracted that could be used as complementary information to the conventional test score (the total time taken to perform five sit-to-stands for 5xSTS or the total sit-to-stands performed in 30 seconds for 30SCT) to characterize the PTs and detect subtle differences that can exist between populations. It was shown that instrumented 5xSTS has a higher clinical relevance compared to the conventional stop-watch-based method (Rob C. Van Lummel et al., 2016).

Functional tests such as 5xSTS or 30SCT only include PTs opposed to real-life settings in which there are many other activities that can resemble PTs in the signal shape. On the contrary, PTs during real-life settings might not have exactly the same signature as in the lab due to extrinsic factors such as armrest, chair height, etc. Therefore, detecting the true PT events during daily activities can be more challenging than the functional tests and relying solely on the angular velocity signal as proposed by (Millor, Lecumberri, Gómez, Martínez-Ramírez, Rodríguez-Mañas, et al., 2013; R. C. Van Lummel et al., 2013) can lead to detecting false PTs (Figure 2.11).

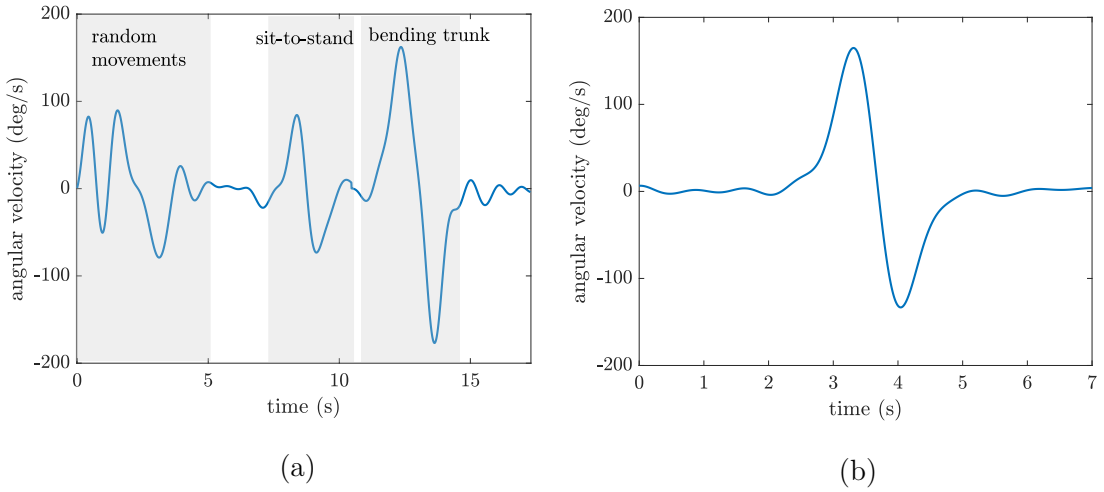


Figure 2.11: The angular velocity of the lower back for a healthy young subject (a) in real-life settings (b) during a sit-to-stand phase of the 5xSTS functional test, both measured by an IMU on the lower back

To overcome this challenge, some studies have used barometric pressure sensor data as an additional source of information to IMUs to detect the PTs during daily activities. With barometric pressure sensor, one can estimate the vertical displacement changes. Several statistical and postural features from accelerometer and barometer sensors integrated into a pendant device were extracted and trained to classify PTs (W. Zhang et al., 2014). The algorithm was tested first in a standard protocol in the lab in which subjects were asked to perform a routine of simple daily activities. After that, the subjects wore the device in their domestic environment during 30 minutes of daily activities. The positive predictive value (PPV) and the sensitivity (SE) of their method were 87% and 85% during the simulated daily activities (first experiment) and 89% and 61% during the real-life daily activities (second experiment). Using continuous wavelet transform (CWT) instead of machine learning to classify PTs showed a higher performance in another study with the same device (Ejupi et al., 2017). Adding the gyroscope data to the accelerometer and barometer data showed promising results in mobility-impaired stroke patients by a sensor on the trunk (Masse, Gonzenbach, Paraschiv-Ionescu, Luft, & Aminian, 2016).

Although using the barometric pressure sensor data in addition to IMU could help us to detect the PTs with a high performance, this sensor is prone to pressure changes and high noise. The pressure changes caused by changing the environment can lead to errors in estimating the vertical displacement. For instance, in (W. Zhang et al., 2014), the sensitivity of the sit-to-stand detection was decreased by 25% in outdoor environments. Therefore, instead of one IMU at a single location, some studies have used multiple IMUs at different locations of body to detect the postural transitions.

As during sit-to-stand (or stand-to-sit) transitions, thighs have an extension (or flexion), they can have a complementary information to the trunk to detect the PTs. Using these multi-sensor setup systems, one can achieve very high accuracy (H. Nguyen et al., 2018; A. Paraschiv-Ionescu, Buchser, Rutschmann, Najafi, & Aminian, 2004). However, using multiple sensors in daily activities can be cumbersome and reduce the comfort for the user.

Therefore, some studies have focused on a single IMU on the trunk or lower back to detect the PTs. The gyroscope and accelerometer signal along with a discrete wavelet transform have been used to obtain the trunk angle and consequently to detect the PTs (Najafi et al., 2003). The vertical acceleration was used to distinguish sit-to-stands and stand-to-sits. In this study, it was shown that the vertical acceleration of the trunk has a specific pattern for sit-to-stands and stand-to-sits: a positive acceleration peak followed by a negative acceleration peak in the vertical direction during sit-to-stand and a negative peak followed by a positive peak during stand-to-sit transitions (Figure 2.10). To lower the power consumption, only the accelerometer data was used in (A. Godfrey, Bourke, Ólaighin, van de Ven, & Nelson, 2011). The trunk tilt angle was obtained by the scalar product of the accelerometer data and gravity vector obtained during a static calibration at the beginning of each measurement. These studies were validated under very controlled conditions that involved sit-to-stand and stand-to-sit movements with a few other activities. Furthermore, since the detection is based on the trunk

angle, the algorithm lead to numerous false positives for the instances that the subjects bend their trunk without standing or during an unsuccessful sit-to-stand attempt.

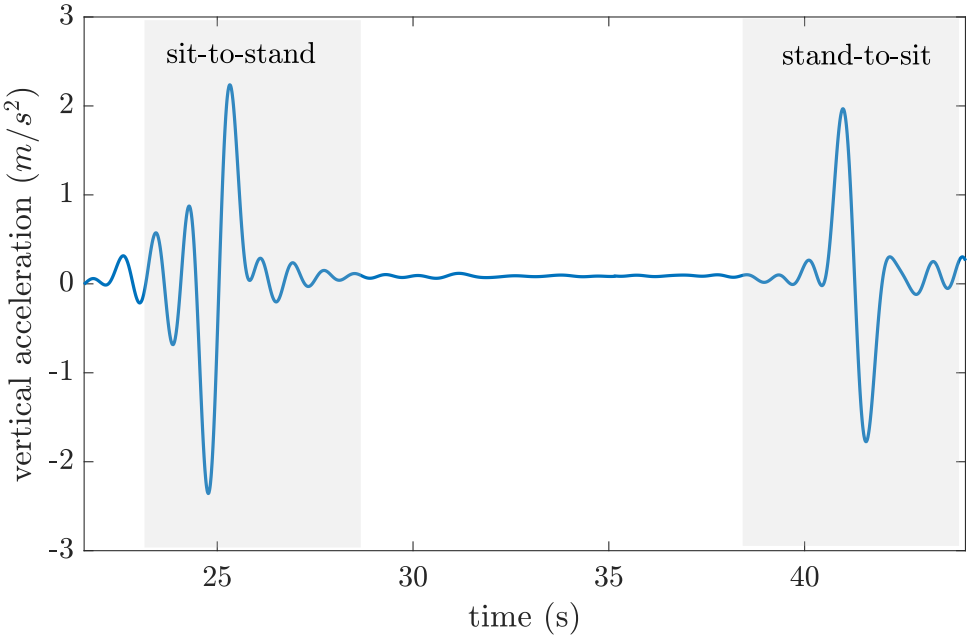


Figure 2.12: The pattern of sit-to-stand and stand-to-sit transitions in a healthy young adult measured by an IMU on the lower back

More daily activities were included in the measurement protocol used by (Salarian, Russmann, Vingerhoets, Burkhard, & Aminian, 2007). To reduce the false positive trunk movements, fuzzy rules were employed to improve the accuracy of PT detection and to separate the periods of sitting and standing based on the information regarding the transitions and the previous and following activities. Although these rules improved the estimation of the duration of sitting and standing periods, a better performance to detect the number of true PTs was not obtained (Raluca Ganea, Paraschiv-Lonescu, & Aminian, 2012). The performance of the PT detection was further improved by employing the dynamic time warping (DTW) method as a template matching technique (Raluca Ganea et al., 2012). In this study, the peaks of trunk angular velocity were detected as the candidates of PTs. To determine which candidate is a true PT, the authors compared the shape of the acceleration norm to the template of a sit-to-stand or stand-to-sit transition by DTW. However, the performance of the detection algorithm was still not sufficient with a PPV and SE of 65% and 68%, respectively. More recently, based on a single IMU on the lower back (Pham et al., 2018) or on the trunk (Nazarahari & Rouhani, 2018), the changes in trunk tilt angle were detected as the candidates of the PTs. The authors filtered out these candidates to get true PTs by obtaining the trunk vertical displacement obtained by integration of vertical acceleration around a PT candidate. All of the studies reviewed above have been summarized in Table 2.1 for their performance as well as their sensor setup and validated population.

Table 2.1: Previous studies on detecting the sit-to-stands during daily activities, PPV is positive predictive value, SP is specificity, and SE is sensitivity

Study	Population	Sensors used	PPV/SP (%)	SE (%)
Pendant device				
(W. Zhang et al., 2014)	21 healthy older adults	acc+baro	87.4	85.3
(W. Zhang et al., 2014)	30 healthy older adults	acc+baro	88.6	85.3
(Ejupi et al., 2017)	25 healthy older adults	acc+baro	89.9	93.1
Multiple IMUs				
(H. Nguyen et al., 2018)	9 PD patients	acc+gyr	99.9	100
(A. Paraschiv-Ionescu et al., 2004)	21 patients with back pain	acc+gyr	100	99.4
Single IMU on the lower back or trunk				
(Masse et al., 2016)	12 stroke patients	acc+gyr+bar	89.9	92.7
(Najafi et al., 2003)	9 healthy older adults	acc+gyr	93.0	82.0
(A. Godfrey et al., 2011)	10 healthy older adults	acc	89.0	83.0
(Salarian et al., 2007)	5 young healthy subjects	acc+gyr	55	80
(Raluca Ganea et al., 2012)	5 young healthy subjects	acc+gyr	65	68
(Pham et al., 2018)	11 healthy older adults and 21 PD patients	acc+gyr	83	89
(Nazarahari & Rouhani, 2018)	10 young healthy subjects	acc	97	98
(Adamowicz et al., 2020)	19 healthy subjects and 20 PD patients[1]	acc	99	90

[1]Validated only during 5xSTS in lab

The major drawback of all of the previous studies concerning the detection of the PTs with a single IMU is that they need the sensor to be attached to a fixed and specific location of the body, either sternum or lower back. However, this requirement cannot be guaranteed during daily activities as the user might detach the sensor and wear it at another location throughout the day. Therefore, a more robust algorithm is needed to detect and characterize the PTs regardless of its placement on the trunk or lower back. A solution can be to use the norm of the accelerometer data as was the case in a very recent study (Adamowicz et al., 2020). In this study, CWT has been used to detect the sit-to-stand transitions. The algorithm showed a good performance (90% sensitivity and 99% precision) during a 5xSTS test in the lab. However, a validation during real-life daily activities is still needed.

2.5 Walking detection and speed estimation using IMUs

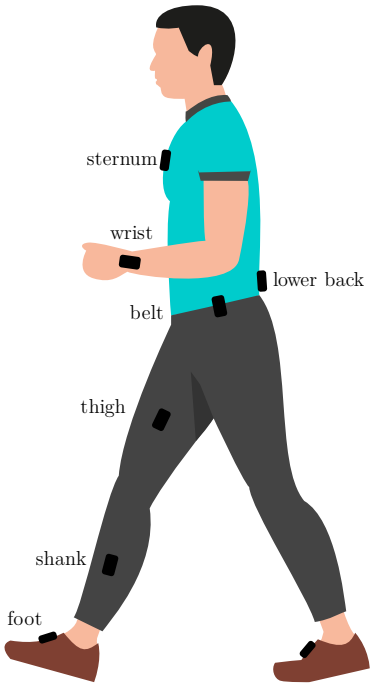


Figure 2.13: The most common locations for IMUs to detect and analyze walking bouts

To detect the walking bouts (locomotion periods) and consequently estimate their duration, the sensor setup, i.e. location and number of IMUs, plays an important role so does the population of interest, e.g. healthy individuals versus patients with mobility impairments. During walking, the whole body, i.e. head, upper limbs and lower limbs are in coordination with each other to have a stable gait (Machado, Darmohray, Fayad, Marques, & Carey, 2015). Therefore, several of our body segments have the potential to detect walking bouts by IMUs. To categorize the previous works in the literature, most of them have placed IMUs on one or a combination of these locations to detect and consequently characterize walking bouts: foot, leg (shank and/or thigh), belt, lower back, sternum, and wrist (Figure 2.13).

For obtaining gait asymmetry based on lower limbs, i.e. the dissimilarity of left and right lower limbs, two IMUs might be needed to be attached to left and right feet or legs.

2.5.1 Based on the lower limbs

Due to the nature of gait, analysing the IMU signals placed on the lower limbs will be more straightforward than other locations. In an unimpaired gait, several features can be observed directly from the angular velocity or acceleration signal of the lower limb (Figure 2.14); therefore, making the detection of gait events such as initial contact and terminal contact possible (Aminian et al., 2002; Kitagawa & Ogihara, 2016; Benoit Mariani, Rouhani,

Crevoisier, & Aminian, 2013; S. T. Moore, MacDougall, Gracies, Cohen, & Ondo, 2007; Rebula, Ojeda, Adamczyk, & Kuo, 2013; Angelo M. Sabatini, Martelloni, Scapellato, & Cavallo, 2005).

For an impaired gait such as in PD, the featured events might not be as distinguishable as of a healthy subject. For example, it was shown that in children with higher disability of CP, the peaks showed in Figure 2.14 could hardly be detected from the IMU on the foot (Carcreff et al., 2018). As in CP, an abnormal gait is more evident in distal segments of the body compared to the proximal segments, using IMUs on the shanks or thighs can provide higher accuracy and robustness in detecting gait events (Carcreff et al., 2018). Other solutions can be to apply more complex rules and algorithms to detect the gait events. For instance, adaptive thresholds have been used to detect mid-swing events in which the foot angular velocity is at its maximum value (Trojaniello et al., 2014). When one foot is in the swing phase, the other foot is definitely in the stance phase. Therefore, once the mid-swing event of one foot is determined, the search interval for initial and terminal contacts of the other foot will be shortened to have a more robust detection algorithm (Trojaniello et al., 2014).

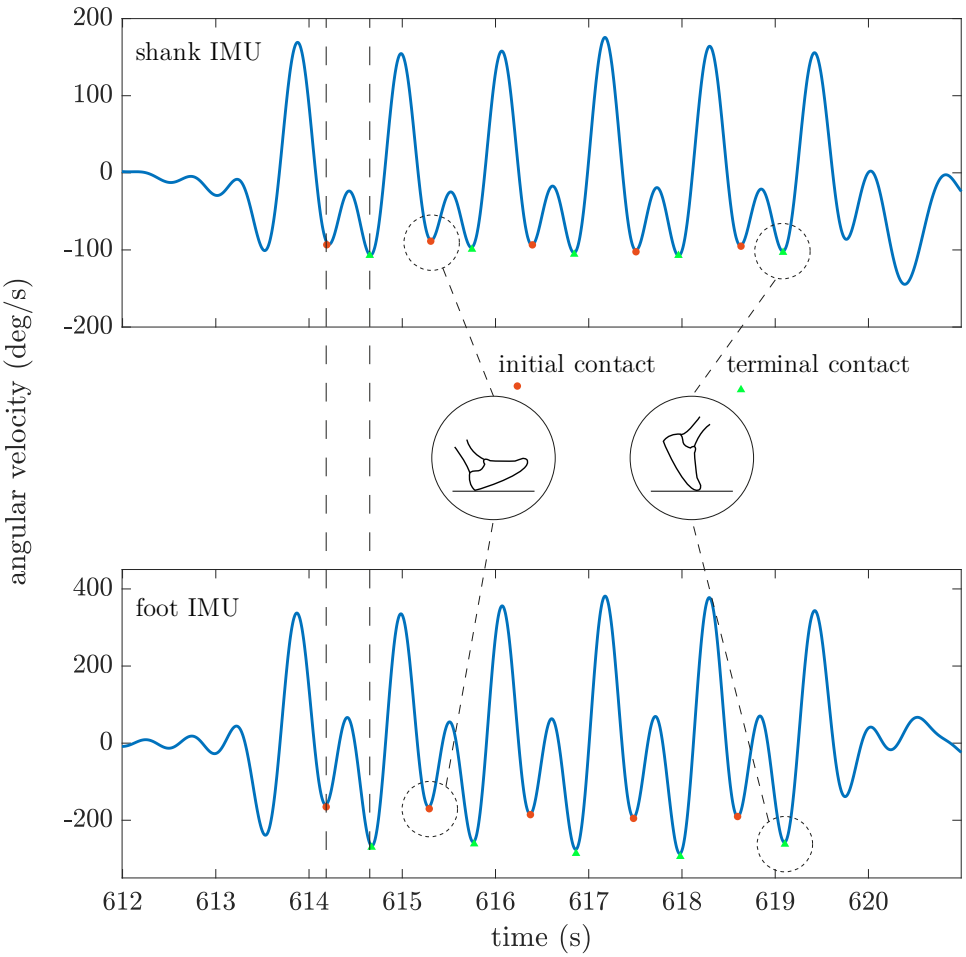


Figure 2.14: The angular velocity of shank (top) and foot (down) along with foot initial an terminal contacts marked directly on the signal (Aminian et al., 2002; Benoit Mariani, Rouhani, et al., 2013)

When the IMU is on the foot, the foot is temporarily in a static position during the stance phase in each gait cycle. This phenomenon which is known as zero-velocity update helps us to correct the drift when integrating the acceleration signal of the foot to gait speed and foot trajectory (Benoit Mariani et al., 2010; Angelo M. Sabatini et al., 2005).

The zero-velocity update will be no longer valid when the IMU is placed on any other location than the foot. Therefore, some other methods are required to perform the spatial analysis of the gait and obtain the gait speed. Placing the IMU on the shank, shank can be modelled as an inverted pendulum during each stance phase (Q. Li, Young, Naing, & Donelan, 2010). The horizontal instantaneous velocity can be updated in each foot flat to be equal to the angular velocity multiplied by the distance of the IMU from the ground. Moreover, the vertical instantaneous velocity can be updated to zero. When the IMU is on the thighs and shanks, gait can be modelled by double pendulum during swing phase and inverted double pendulum during the stance phase (Aminian et al., 2002). These methods could estimate gait speed with an error ranging from 0.6 to 6 cm/s.

Detection of gait events such as initial contact, terminal contact, foot flat, etc. is possible during functional walking tests in which the signal of interest contains only a walking bout. However, this is not the case for long-term monitoring during daily activities in which there are other activities than gait. Firstly, each walking bout should be detected and within that walking bout, the temporal and spatial parameters such as gait speed can be extracted. With sensors on the lower limb there are several methods to detect walking bouts. Based on Figure 2.14, two consecutive negative peaks of the foot pitch angular velocity can be candidates of a gait cycle (Moufawad el Achkar et al., 2016). The candidate gait cycles that did not belong to the normal cadence range of 40 to 160 steps/min were removed. Therefore, the locomotion periods were detected with an accuracy of 98% compared to the recorded video of the subjects as the reference system (Moufawad el Achkar et al., 2016). In another study, DTW was applied to detect the walking bouts by matching the template of a gait cycle acceleration and angular velocity signals (Oudre et al., 2018). The proposed algorithm showed a high performance (recall and precision of over 98%) to detect gait cycles of healthy individuals and patients with neurological disorders.

Although a high accuracy can be obtained by sensors on the lower limb for both walking bout detection and gait speed estimation, other IMU placements such as wrist or belt are preferable during daily activities. Firstly, the sensor instrumentation can be minimized to a single IMU providing comfort for the user and the clinician. Furthermore, these locations will be less obtrusive in daily activities.

2.5.2 Based on the wrist location

For instance, most of the recently developed smartwatches have a built-in IMU. Therefore, by integrating a proper algorithm into the device we can track the activities of the user. However, detecting walking bouts and estimating gait speed will be even more challenging for

the wrist location (Fasel et al., 2017). During walking, arms can have independent movements from walking (Fasel et al., 2017). In this case, machine learning methods have shown a good performance to detect walking bouts (Awais, Chiari, Ihlen, Helbostad, & Palmerini, 2019; Soltani, Paraschiv-Ionescu, Dejnabadi, Marques-Vidal, & Aminian, 2020) and accordingly estimate gait speed (Fasel et al., 2017; Soltani, Dejnabadi, et al., 2020; Zihajehzadeh & Park, 2016b). Several features categorized into intensity, periodicity, and posture of the movement can be extracted from the accelerometer signal of the wrist (Soltani, Dejnabadi, et al., 2020; Soltani, Paraschiv-Ionescu, et al., 2020). Compared to the reference systems, i.e. recorded video and global navigation satellite system, the accuracy of walking bout detection was 97% and the root mean square error of the gait speed estimation was obtained as 14 cm/s (Soltani, Dejnabadi, et al., 2020; Soltani, Paraschiv-Ionescu, et al., 2020).

2.5.3 Based on the lower back or trunk location

Another alternative to wrist location would be to use an IMU on the lower back or on the trunk. In addition to being unobtrusive to daily activities, this location is closer to the CoM of the body therefore less prone to miscellaneous movements compared to the wrist placement. Nevertheless, an IMU placed on the lower back can be loosely attached as the fixation is not directly on a bony segment. Therefore, they can be attached by tapes to the trunk (Germanotta et al., 2021) or to the belt by a rubber clip which is preferrable in long-term measurements. Wavelet transform method can be used to detect gait cycles with an IMU on the lower back (Brodie et al., 2016; Hickey et al., 2017; McCamley et al., 2012). In this method, a wavelet transformation like Gaussian (McCamley et al., 2012) or Daubechies 'db5' (Brodie et al., 2016) is applied to the accelerometer data. Special features of the transformed signal, e.g. the local maxima or local minima can be detected as the initial contact or final contact gait events (Figure 2.15). Although this method can solve the problem of detecting irrelevant peaks directly from the acceleration signal itself, it is accurate mostly in higher gait speeds. In slow walkers, e.g. a gait speed of less than 0.5 m/s, there can be 100% error in detecting the steps (Storm et al., 2018). For an atypical gait, a more complex algorithm such as using an adaptive threshold rather than a fixed threshold is needed (Anisoara Paraschiv-Ionescu et al., 2019). Alternatively, with machine learning methods one can train a model to map biomechanical or statistical features of the acceleration and angular velocity signals to an activity classifier (Awais et al., 2019; Panahandeh, Mohammadiha, Leijon, & Handel, 2013; Rodriguez-Martin et al., 2013).

To estimate gait speed by an IMU on the lower back, the previous works in the literature are based on either integration methods (Alvarez, Álvarez, & López, 2018; Köse, Cereatti, & Della Croce, 2012; Angelo Maria Sabatini & Mannini, 2016), biomechanical models (Hu, Sun, & Cheng, 2013; Q. Zhao et al., 2017; Zijlstra & Hof, 2003) or machine learning approaches (Byun et al., 2019; Keppler et al., 2019; McGinnis et al., 2017; Schimpl, Lederer, & Daumer, 2011; Shammas et al., 2014; Supratak et al., 2018; Vathsangam, Emken, Spruijt-Metz, & Sukhatme, 2010; Zihajehzadeh & Park, 2016a).

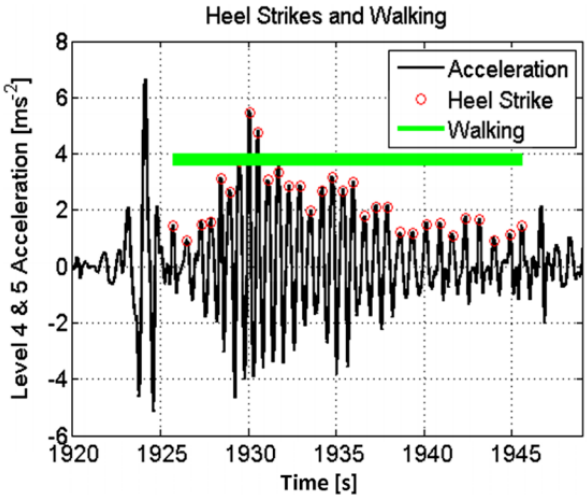


Figure 2.15: Detecting initial contact events by the peaks of level 4 and 5 wavelet transformation of the acceleration signal that have a value of higher than 0.5 m/s^2, authorized copy from Springer Nature (Brodie et al., 2016)

As mentioned before, unlike the foot placement, there is no zero-velocity instant when the IMU is on the lower back. However, in a study, an interesting approach was implemented (Angelo Maria Sabatini & Mannini, 2016). In this approach, instead of integrating directly the accelerometer signal, a Fourier series was fitted upon the cyclic accelerometer signal. Next, the fitted Fourier function was integrated in frequency space rather than a time series numeric integration from a noisy signal. Therefore, there was no drift in the velocity. The root mean square error of their method was around 8 cm/s. Other integration approaches try to integrate the acceleration signal once to get the velocity and twice to get the position (Alvarez et al., 2018). These method assume a cyclic motion during gait; thus, firstly each gait cycle is detected. For each gait cycle, several strategies can be applied to integrate the acceleration signal. For instance, the mean of the acceleration is subtracted from the acceleration signal before the integration to reduce the linear drift to the bias of the acceleration signal (López, Álvarez, González, & Álvarez, 2008). In another study, a high-pass filter was applied to the acceleration signal before the integration to reduce the drift caused by the low-frequency noise (Köse et al., 2012). Next, to obtain the velocity while further reducing the drift, a weighted forward-backward integration was applied. However, in the integration approaches, the estimation of the initial value of speed at the beginning of each gait cycle might be challenging.

In biomechanical models, step length can be modelled with an inverted pendulum model and by detecting gait cycle time with the acceleration signal peaks (Figure 2.16a), gait speed can be obtained (Zijlstra & Hof, 2003). As shown in section 2.2.2, this model can be improved by considering the strategies to decrease the vertical oscillation of the CoM such as pelvis rotation (Hu et al., 2013; Neumann, 2002). These biomechanical models were often validated in healthy individuals with unimpaired gait. Extending them to individuals with mobility impairments can be challenging (McGinnis et al., 2017). Interestingly, based on the inverted pendulum assumption, several studies have derived empirical models for the step length in which the stride length is related to some features of the acceleration signal (e.g. min or max during

each gait cycle) of the lower back (Q. Zhao et al., 2017). The step length has been shown to be related to the acceleration-based features with some coefficients that can be determined by a calibration phase (Q. Zhao et al., 2017). This method opens the idea of machine learning-based approaches to estimate gait speed by the acceleration signal measured by an IMU on the lower back.

Machine learning methods that extract several time-domain and frequency-domain features from the acceleration signal (Figure 2.16b) and map them into gait speed have shown promising results during walking tests in the lab (Byun et al., 2019; Keppler et al., 2019; McGinnis et al., 2017; Schimpl et al., 2011; Shammas et al., 2014; Supratak et al., 2018; Vathsangam et al., 2010; Zihajehzadeh & Park, 2016a). Some of these studies include also some demographic information such as height of the user in the features to improve the accuracy of their model (Byun et al., 2019).

Various reference systems have been used to train such a gait speed estimation model. For instance, walking speed obtained by the instrumented walkways (Byun et al., 2019; McGinnis et al., 2017), electronic perambulators (Keppler et al., 2019; Vathsangam et al., 2010; Zihajehzadeh & Park, 2016a), treadmill (Vathsangam et al., 2010), or measured by a physician over a known distance (Shammas et al., 2014; Supratak et al., 2018) were used for the training sessions.

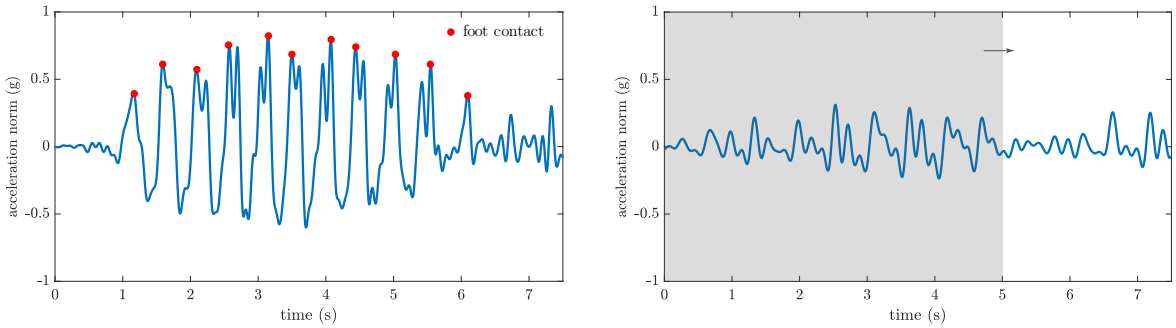


Figure 2.16: The acceleration norm of the IMU on the lower back during walking (a) in a healthy subject (b) in a patient with PD. In (a), peaks of the acceleration can be marked as steps by the method proposed by (Zijlstra & Hof, 2003). In (b), windows of 5 seconds can be defined to extract features for mapping into gait speed (McGinnis et al., 2017)

These methods have been mostly validated in laboratory conditions during which there are only walking episodes in the measurements rather than daily activities that can involve other tasks (Anisoara Paraschiv-Ionescu et al., 2019). Recently, smart-watches and smart-phones have been embedded with algorithms to detect walking bouts and gait speed in daily activities (Figure 2.17). However, their accuracy is in dispute; although there are some unofficial reports in social media (B. Greene, 2020), no validation has been done for some of these commercial devices. Furthermore, aside from being like a black box, these systems might be designed only for their typical users which are healthy adults rather than mobility-impaired patients.

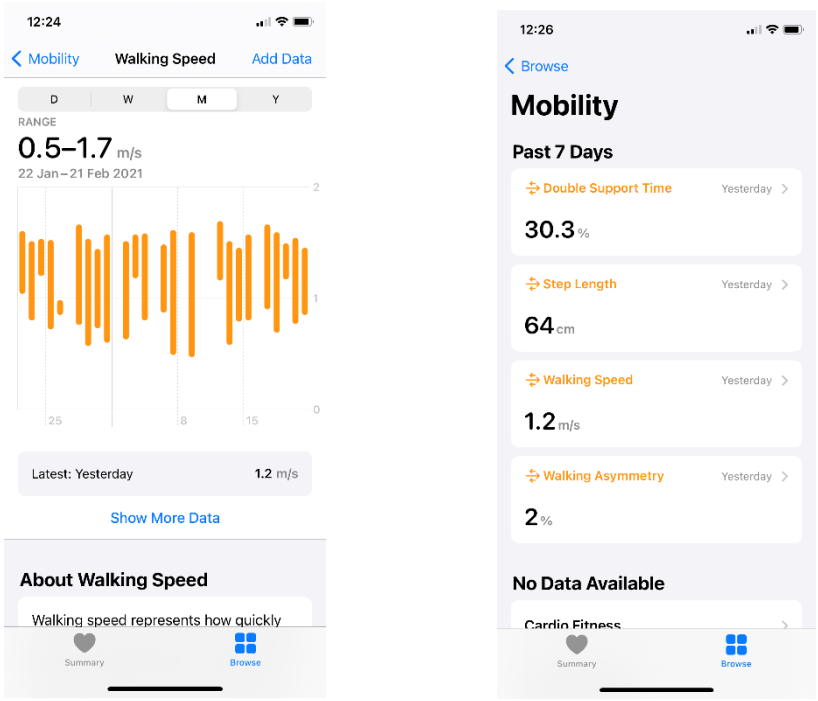


Figure 2.17: The Health app introduced by iOS 14 in iPhone that can measure gait speed and other mobility-related parameters

Another difference between laboratory and daily activity measurements is that during assessments performed at the lab, only walking task exists. However, during daily activities, it is required to first detect the walking bouts and estimate gait speed within each walking bout. Furthermore, by detecting the walking bouts, one can obtain their duration. Knowing the duration of walking bouts during daily activities can provide more detailed insight about the characteristic of gait parameter during walking bouts with different lengths (Del Din, Godfrey, Galna, et al., 2016; Shah et al., 2021).

Therefore, by considering also the patient populations, a validated algorithm is needed to detect the walking bouts and estimate gait speed during both clinical and daily activity assessments. This algorithm shall be preferably designed based on a single IMU on the lower back to make it more comfortable during daily activity measurements.

2.6 Clinical versus daily activity assessments

In the first chapter, I introduced the sources of differences between an assessment performed in the clinic and an assessment performed during daily activities. Moreover, I emphasized why its important to compare these two settings. In this section, I review what has been done in the literature in this topic and what yet remains unknown.

As this topic of lab versus home is quite a new trending topic, there are not so many previous works. PubMed and Google Scholar were searched for articles published in English from January 2014 to December 2020. Keywords were selected as ("supervised" OR "laboratory" OR "clinic") AND ("inertial sensor" OR "IMU" OR "wearables" OR "inertial measurement unit") AND ("unsupervised" OR "daily activity" OR "home" OR "real-life") AND ("gait" OR "balance"). Relevant studies were selected if they had both clinical and daily activity measurements of gait and/or balance. The references of these publications were also explored for additional references. Studies with simulated daily activities in laboratory environment were excluded. Finally, I found 16 key studies in the literature that compared clinical and daily activity assessments. By categorizing these studies, two main objectives were found:

- Obtaining the degree of correlation between parameters extracted at lab and at home
- Analysing how much information from home assessment is explained by lab

By considering these two objectives, the previous studies tried to show how much information can be extracted from the performance of the individuals during daily activities by only functional tests in the lab. Moreover, knowing the degree of correlation between these two settings can reveal how much these two settings are related. It will tell us if by performing remote mobility assessments during daily activities we can have information about the capacity of the patients during lab-based assessments. Furthermore, a casual association between capacity and performance implies that improving capacity also improves the performance.

Regarding the population of the study, community-dwelling older adults were the most studied population (5) followed by PD patients (4), frail older adults (2), children with cerebral palsy (CP) (2), community-dwelling adults (1), MS patients (1), and both PD and MS patients (1).

In community dwelling older adults, by monitoring the activity of the patients at home and comparing the amount of lying, sitting, standing, and walking with functional tests scores in the lab, low correlations were obtained between those measures (Rob C. Van Lummel et al., 2015). A factor analysis revealed that in this study, clinical and daily living assessments were two separate domains. For obtaining the degree of correlation, most of the studies obtained the same parameters in the lab and home and calculated Pearson's correlation coefficient between the two settings (Carcreff, Gerber, Paraschiv-Ionescu, De Coulon, Aminian, et al., 2020; Carcreff, Gerber, Paraschiv-Ionescu, De Coulon, Newman, et al., 2020; Takayanagi et al., 2019; Toosizadeh et al., 2015; Van Ancum et al., 2019). Sit-to-stand duration, stand-to-sit duration, gait speed, and other gait parameters such as gait symmetry and variability were among these parameters. These studies have achieved different conclusions depending on the population and the parameter that they analysed. For instance, children with CP showed a high correlation ($\rho = 0.85$) between lab and home for gait speed while their age-matched typically developed control group showed no significant correlation ($\rho = 0.29$) (Carcreff, Gerber, Paraschiv-Ionescu, De Coulon, Newman, et al., 2020). The authors justified this observation by stating that individuals with lower capacity, e.g. CP children, have more

difficulty adapting to a complex and unpredictable context like home. However, this is in contrast with the findings obtained by (Toosizadeh et al., 2015). In this study, for gait speed for instance, no significant correlation was found between lab and home for PD patients while the age-matched control group had a low correlation between the lab and home assessments ($\rho = 0.36$). Apart from the fact that the populations of these two studies were from different characteristic and age, the reason for this seemingly contradictory result might be due to the selection of the methodology to quantify gait speed distribution at home. As in the CP children study, the authors had selected only the walking bouts that corresponded to the same walking bout length in the lab while in the PD study, the authors had calculated the mean value of gait speed throughout the day which is in fact neglecting the complex gait speed distribution at home. Using the same approach of condensing the gait speed distribution at home to a mean value, in a very large population of healthy older adults, a low correlation coefficient was obtained ($\rho = 0.33$) (Takayanagi et al., 2019).

As I mentioned earlier in the first chapter, gait speed has a wide range during one day of activity monitoring, that can reach 5000 gait cycles or even beyond that. Therefore, limiting this distribution to a mean value may not well represent this vast or even non-Gaussian distribution. In a study, an interesting approach to quantify gait speed distribution at home was introduced (Van Ancum et al., 2019) which was inspired by the same distribution of cadence during daily activities (Brodie et al., 2017). In this study, it was hypothesized that gait speed has a bimodal distribution and this hypothesis was tested in 254 community-dwelling adults and it was observed that 96% had actually a bimodal gait speed distribution. This phenomenon shows that people have two different preferred gait speeds, a lower gait speed and a higher one. The lower preferred gait speed is more related to short walking bouts during daily activities while the higher preferred gait speed happens more during long walking bouts outdoors. In the aforementioned study, the participants were asked to walk 4 meters with their convenient speed. The gait speed obtained during this test was then compared to the two modes of the bimodal gait speed distribution at home as well as several percentiles of this distribution. Significant correlations were found only with higher percentiles of gait speed. Therefore, clinical assessment often lies near the maximum values of the distribution obtained during daily activities. This hypothesis that clinical and daily activity assessments are more associated in patients with mobility impairments rather than healthy individuals was also supported by two other studies (Jansen et al., 2019; Kawai et al., 2020). One of these studies showed frailty moderates the relation between those two settings (Jansen et al., 2019). Lab and home were more associated in frail and pre-frail patients compared to non-frail subjects. The authors justified this finding by the fact that older adults with lower level of disability have more variability during their performance of daily activities which results in lower association between clinical and daily activity measurements. On the contrary, frail older adults perform near their maximal capacity during daily activities; as a consequence, it is not surprising that their performance and capacity are more associated.

Another method to quantify a parameter throughout daily activities is to divide the walking bouts into different groups based on their length. For instance, it has been shown that gait

stride time in short walking bouts could differentiate better patients in mild and severe stage of MS compared to medium and long walking bouts (Storm et al., 2018). Moreover, in this study, it has been shown that continuous walking test in which the patients were asked to walk freely without any predefined trajectory, had comparable cadence variability compared to the short walking bouts at home.

The predictability of home measurements by lab assessments has been studied to investigate how much information we can have about the performance of the patients at home by only clinical measurements. 84 older adults were recruited in a study in which they were evaluated in the lab with the instrumented TUG test and several metrics were extracted from this test (Giannouli, Bock, Mellone, & Zijlstra, 2016). Later, the participants were monitored for active and gait time during their daily activities. The TUG metrics were taken as predictors for daily life measurements. However, only a very small variance of daily life measurements (20%) were explained by TUG-based predictors. In another study in PD patients, this percentage was even less, i.e. 12% (Galperin et al., 2019). In both of these studies, only one gait test with the patients' convenient speed was obtained in the lab.

To conclude, based on the evidence and remarks of the previous studies, we can assume that patients with mobility impairments have more associated clinical and daily activity performance unlike healthy individuals in which the two settings have completely different information. Nevertheless, in both healthy and mobility-impaired individuals a single gait test cannot represent and predict the performance of the people during daily activities. In terms of quantifying the distribution of parameters during daily activities, grouping walking bouts of the same length, bimodal analysis, and acquiring higher percentiles of the distribution showed more meaningful comparison compared to the average value. Finally, people perform better in the lab compared to home. The previous studies have been summarized in Table 2.2.

What is yet remained unknown is that under what conditions during daily activities patients perform similar or even better than their capacity in the lab? Answering this question can help the clinicians to look for specific periods and conditions during daily activities if they want to assess patients' capacity during RPM.

Another question is whether instead of a single walking test in the clinic, can we perform other walking tests to have a more accurate overview or prediction of the patients' performance at home? For instance, it was observed that the faller older adults perform more similar to their daily activities during dual-task walking test at the lab rather than the single-task walk test (Hillel et al., 2019). Walking during daily activities are often accompanied by other motor or cognitive tasks; thus, it is no wonder that more demanding walking tests in the lab such as dual-task tests are closer to our daily activity performance than single walking test.

Functional tests such as TUG or 10-meter walk tests have been often performed in the clinic. But what if we perform these functional tests at home to avoid patients to come to the hospital? Can we expect to obtain the same results? In a very recent study, very high

correlation ($\rho = 0.91$) was reported between clinic and home for the 10-meter walk test in PD patients (Gaßner et al., 2020). However, patients performed significantly faster in the clinic compared to home. More evidence is required to address this question.

Most of the studies have focused on gait tests, but little on comparing postural transitions. How much association exist between sit-to-stand tests performed in the lab and sit-to-stands during daily activities?

The previous studies often considered a normal gait speed distribution at home and compared its mean and standard deviation to those of lab-based assessments. However, as a recent study has shown, gait speed during daily activities can have a more complex distribution such as a bimodal Gaussian distribution (Van Ancum et al., 2019). In another study, only walking bouts with almost the same length as the walking test in the lab was considered from daily activity assessments (Carcreff, Gerber, Paraschiv-Ionescu, De Coulon, Newman, et al., 2020). These studies suggest that novel approaches are needed to quantify the vast distribution of gait speed during daily activities. Can dividing walking bouts into different types based on their duration provide us more information about the performance of the patients at home? Finally, which setting can help us better to classify a specific impairment? For instance, in a very recent study it was shown that gait parameters obtained during daily activities have higher discriminative power in classifying MS or PD patients from their age-matched healthy controls compared to laboratory-based measures (Shah, McNames, Mancini, Carlson-Kuhta, Spain, et al., 2020a). However, it was not shown if the information from both of the settings can improve the classification or not. Do lab and home settings have complementary information to each other?

These are the questions that we will answer in the following chapters.

Table 2.2: Summary of the studies on clinical versus daily activity assessments

							
Study	Population	Parameters	Tests	Parameters	Number of days	Quantification at home	Conclusion
(Rob C. Van Lummel et al., 2015)	49 older adults	Total time and conventional score of functional tests	TUG, 5xSTS, Balance	Duration of 4 main activities, intensity of activities	1 week	Duration of activities	Lab and home associated but two separate domains
(Carcreff, Gerber, Paraschiv-Ionescu, De Coulon, Newman, et al., 2020) (Carcreff, Gerber, Paraschiv-Ionescu, De Coulon, Aminian, et al., 2020)	15 CP children, 14 typically developed children	Several spatio temporal gait parameters	Several trial of 10-meter walk test	Several spatio temporal gait parameters	3 days	Median of walking bouts corresponding to lab	Higher correlation in CP compared to the control group

Table 2.2 (continued): Summary of the studies on clinical versus daily activity assessments





Study	Population	Parameters	Tests	Parameters	Number of days	Quantification at home	Conclusion
(Takayanagi et al., 2019)	1965 older adults	Gait speed	6.4-meter walking test	Gait speed	40 days	Mean	Low correlation
(Van Ancum et al., 2019)	254 adults	Gait speed	4-meter walking test	Gait speed	1 week	Bimodal distribution, percentiles	Two preferred gait speed at home, Low correlation between lab and home
(Brodie et al., 2017)	96 older adults	Conventional test scores	TUG, Cognitive tests, questionnaires	Cadence, gait duration	1 week	Bimodal distribution, short walking bouts	Bimodal cadence for non-fallers, home measures better at identifying fallers
(Jansen et al., 2019)	112 older adults	Gait speed	Walking tests	Active time, steps	2 days	Activity periods	Higher correlation in frail adults
(Kawai et al., 2020).	90 older adults	Gait speed	5-meter walk test	Gait speed	30 days	Mean	Low correlation

Table 2.2 (continued): Summary of the studies on clinical versus daily activity assessments

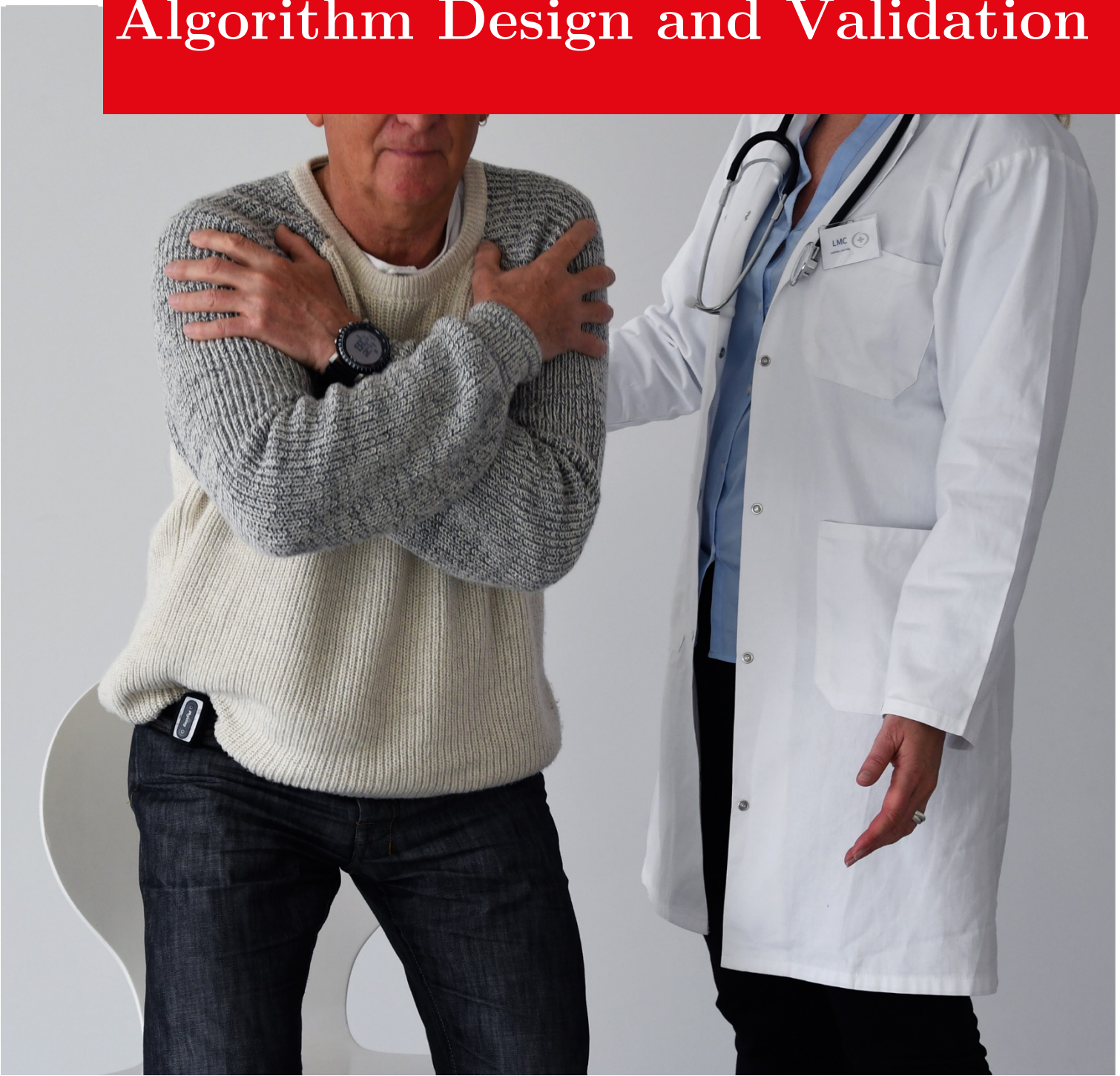
							
Study	Population	Parameters	Tests	Parameters	Number of days	Quantification at home	Conclusion
(Storm et al., 2018)	14 MS patients	Cadence, gait variability	Continuous and straight walk tests	Cadence, gait variability	1 week	Walking bout duration	Short walking bouts closer to continuous walk test in lab
(Giannouli et al., 2016)	84 older adults	Gait speed, cadence	TUG	Active time, life-space	1 week	Activity periods	Lab cannot predict home
(Galperin et al., 2019)	125 PD patients	Gait symmetry	Gait and balance tests	Gait quantity and variability	1 week	Activity periods	Lab cannot predict home
(Haertner et al., 2018)	55 PD patients	Turning parameters	TUG	Turning parameters	12 days	Mean	Lab and home different
(Hillel et al., 2019)	150 elderly fallers	Gait parameters	Single and dual-task gait	Gait parameters	1 week	30-s walking bouts, percentiles	Dual task more correlated to home
(Gaßner et al., 2020)	20 PD patients	Gait parameters	TUG	Gait parameters	-	Mean	TUG at home and lab: High correlation but different

Table 2.2 (continued): Summary of the studies on clinical versus daily activity assessments

							
Study	Population	Parameters	Tests	Parameters	Number of days	Quantification at home	Conclusion
(Toosizadeh et al., 2015)	15 PD patients, 35 control	Several gait and balance parameters	TUG	Several gait and balance parameters and activity duration	1 day	Mean value	No correlation for PD opposed to control; higher effect size of lab compared to home
(Shah, McNames, Mancini, Carlson-Kuhta, Spain, et al., 2020a)	15 MS patients and 16 control, 16 PD patients and 15 control	Several gait parameters and lumbar range of motion	Stand and walk test (Similar to TUG)	The same as lab	1 week	Mean and standard deviation values	Parameters obtained during daily activities can differentiate better PD or MS patients from the control group

Part II

Algorithm Design and Validation



3 Postural transitions detection and characterization in healthy and patient populations using a single waist sensor

Abstract: Sit-to-stand and stand-to-sit transitions are frequent daily functional tasks indicative of muscle power and balance performance. Monitoring these postural transitions with inertial sensors provides an objective tool to assess mobility in both the laboratory and home environment. While the measurement depends on the sensor location, the clinical and everyday use requires high compliance and subject adherence. The objective of this study was to propose a sit-to-stand and stand-to-sit transition detection algorithm that works independently of the sensor location. For a location-independent algorithm, the vertical acceleration of the lower back in the global frame was used to detect the postural transitions in daily activities. The detection performance of the algorithm was validated against video observations. To investigate the effect of the location on the biomechanical parameters, these parameters were extracted during a five-time sit-to-stand test and were compared for different locations of the sensor on the trunk and lower back. The proposed detection method demonstrates high accuracy in different populations with a mean positive predictive value (and mean sensitivity) of 98% (95%) for healthy individuals and 89% (89%) for participants with diseases. The sensor location around the waist did not affect the performance of the algorithm in detecting the sit-to-stand and stand-to-sit transitions. However, regarding the accuracy of the biomechanical parameters, the sensors located on the sternum and L5 vertebrae demonstrated the highest reliability.[*]

[*] Chapter adapted from Atrsaei, A., Dadashi, F., Hansen, C., Warmerdam, E., Mariani, B., Maetzler, W., & Aminian, K. (2020). Postural transitions detection and characterization in healthy and patient populations using a single waist sensor. Journal of NeuroEngineering and Rehabilitation, 17(1), 1-14.
Contributions: performed the study, designed the experiment for Dataset A, developed the algorithm, analysed the data, and drafted the manuscript

3.1 Introduction

Being able to maintain balance during movements is a prerequisite for an independent life. The inability to do so can lead to an increased risk of falls and consequently a dependent and inactive life (Judge, 2003; Shumway-Cook, Gruber, Baldwin, & Liao, 1997; W. Zhang et al., 2014). Balance disorders can lead to problems with postural transitions (PTs), such as the sit-to-stand movements (T. A. Buckley, Pitsikoulis, & Hass, 2008). These challenging PTs require complicated coordination of lower and upper limbs (Mathiyakom et al., 2005) and frequently occur during daily living activities (Moufawad el Achkar et al., 2018; Yamako, Chosa, Totoribe, Fukao, & Deng, 2017). As the sit-to-stand transitions are indicative of lower limb muscle strength and balance control (Bean et al., 2002; Jones, Rikli, & Beam, 1999; Yamako et al., 2017), quantifying these movements is key to understand the underlying problem of balance disorders.

Clinicians conventionally assess the sit-to-stand transitions by either diaries (Bratteby, Sandhagen, Fan, & Samuelson, 1997) and questionnaires (Baecke, Burema, & Frijters, 1982; Washburn, Zhu, McAuley, Frogley, & Figoni, 2002) or functional tests. Standardized assessment tools can provide here valuable additional information.

The five-time sit-to-stand (5xSTS) test which measures the time to perform five sit-to-stand transitions (Csuka & McCarty, 1985; J. M. Guralnik et al., 1994) and thirty-second chair-rise (30SCT) test which includes the numbers of sit-to-stands that can be performed within thirty seconds (Jones et al., 1999; Lord, Murray, Chapman, Munro, & Tiedemann, 2002) are standardized functional tests used in clinical routine to assess the ability to perform, and the quality of transitions. Although these methods have been proven to display discriminative properties for balance disorders (Whitney et al., 2005), subtle differences that may provide further relevant information about the movement are not detectable with these tests (Millor, Lecumberri, Gomez, Martìnez-Ramirez, & Izquierdo, 2014).

For instance, during sit-to-stand transitions, maximum angular velocity has been shown to be associated with inadequate momentum generation and consequently, the success of the PT (P. O. Riley et al., 1997; Zablotny et al., 2003). Moreover, duration of each phase of sit-to-stand transitions changes between young and old adults (R. C. Van Lummel et al., 2013) and between older adults with a low or a high risk of fall (Najafi et al., 2002). Peak power of transition has been reported to be associated with muscle power and strength (W. Zhang et al., 2017; Zijlstra et al., 2010). Therefore, instrumenting these functional tests and extracting meaningful parameters can provide a more in-depth and precise analysis. Sit-to-stand transitions have been studied with optical motion trackers (Patrick O. Riley et al., 1991) and force plates (Mazzà, Zok, & Della Croce, 2005). Although these methods provide very detailed and granular information about the movements, they are limited to the laboratory environment (Millor et al., 2014; Moufawad el Achkar et al., 2018).

The laboratory setting can only assess the performance of the participants in the confined environment (e.g. in-clinic) while individuals demonstrate different behaviour in real-life daily activities (Rob C. Van Lummel et al., 2015; Warmerdam et al., 2020). For example, sit-to-stand duration has been shown to be higher during daily activities compared to the functional test performed in the clinic in older adults and in patients with idiopathic Parkinson's disease (IPS) (Toosizadeh et al., 2015). Thus, it is important to develop methods that can also be used in domestic environments.

Inertial sensors can be applied in almost every environment. Moreover, they have been already used to instrument the 5xSTS (R. C. Van Lummel et al., 2013) or the 30SCT (Millor, Lecumberri, Gómez, Martínez-Ramírez, Rodríguez-Mañas, et al., 2013) tests. Kinematic parameters extracted from such instrumented assessments have been shown to have greater clinical relevance than the conventional clinical approach (Lepetit et al., 2019; Rob C. Van Lummel et al., 2016). Wearable sensors have provided an objective tool to evaluate PTs during daily activities as well. Barometric pressure sensor within the pendant device was used as a complementary source of data to detect the PTs (Ejupi et al., 2017; W. Zhang et al., 2014); however, due to the pressure changes in outdoor environments, the use of the barometric sensor can adversely affect the detection accuracy. For instance, (W. Zhang et al., 2014) showed that the sensitivity of the sit-to-stand detection was decreased by 25% in outdoor environments.

There are some studies on monitoring sit-to-stand transitions with a single inertial sensor on either the sternum or on the lower back. In reference (Najafi et al., 2003), the gyroscope and accelerometer signal along with a discrete wavelet transform have been used to obtain the trunk angle and consequently to detect the PTs. A simpler sensor setup with only a tri-axial accelerometer was used in (A. Godfrey et al., 2011). In this study, the tilt angle of the trunk was estimated by the scalar product of the accelerometer data and gravity vector obtained during a static calibration at the beginning of each measurement. These studies were validated under very controlled conditions that involved sit-to-stand and stand-to-sit movements with a few other activities. More daily activities were included in the measurement protocol used by (Salarian et al., 2007) and to reduce the false positive trunk movements, fuzzy rules have been employed to improve the accuracy of detection based on the previous or next activity. The performance of the PT detection was further improved by employing a template matching technique with dynamic time warping method in (Raluca Ganea et al., 2012). However, the performance of the detection algorithm was still unsatisfying with a positive predictive value and sensitivity of 22% and 50%, respectively. In another study, with a single inertial sensor on the waist, the candidates of the PTs were first detected by detecting the peaks of the tilt angle of the lower back. These were filtered out by double integrating the vertical acceleration and calculating the elevation change of the lower back (Pham et al., 2018).

The drawback of all of these studies (Raluca Ganea et al., 2012; A. Godfrey et al., 2011; Karantonis, Narayanan, Mathie, Lovell, & Celler, 2006; Masse et al., 2016; Najafi et al., 2002,

2003; Pham et al., 2018; Salarian et al., 2007) is that they require the sensor to be attached to a specific and fixed location of the body, which is difficult to maintain during daily activities and may not be achievable by patients themselves without a trained operator, thus limiting its broaden applicability in clinical setting.

This issue has been partially solved through using the signal vector magnitude which is the Euclidean norm of the accelerometer signal (Bidargaddi et al., 2007; Hickey, Galna, Mathers, Rochester, & Godfrey, 2016). The choice of various wavelets and scale approximations were studied in (Hickey et al., 2016) to detect the PTs in a large group of healthy younger and older adults. However, in both of these studies, no method was suggested to distinguish true PTs from movements that can have similar wavelets to PTs. Their algorithms have been validated in measurements involving only sit-to-stand and stand-to-sit movements with rest periods in-between. In a very recent study, the same approach of using wavelet transform on the norm of accelerometer data was used (Adamowicz et al., 2020). Although the authors could achieve high performance (sensitivity of 90% and precision of 99%) in detecting sit-to-stands during a 5xSTS test in the lab, their performance of their method is unknown during daily activities.

To this end, an algorithm which is robust to sensor placement changes and validated in a range of daily activities is desirable. Furthermore, little is known about the transferability of algorithms developed within a certain cohort, to other cohorts (e.g., with different and without diseases). The goal of this study was therefore to evaluate the performance of a new PT detection algorithm in healthy individuals and patients with different diseases that were all equipped with an inertial sensor on different locations around the waist and on the trunk. The new algorithm was validated in both laboratory and daily activity settings. Finally, the effect of the sensors location on the detection performance and extracted parameters was evaluated.

3.2 Methods

3.2.1 Materials and measurement protocol

In this study, two datasets were used to reach the objectives of the study (Table 3.1):

Dataset A: (1) To validate the proposed PT detection method during simple daily activities with inertial sensors on different locations around the waist and on the trunk, (2) to validate the extracted biomechanical parameters against reference systems, and (3) to investigate the effect of sensor location on the biomechanical parameters.

Dataset B: To demonstrate the performance of PT detection algorithm in different healthy and patient populations.

Dataset A was obtained through measurements on 15 young healthy adults. Table 3.1 provides demographic information. Participants wore four inertial sensors (Physilog 5, Gait Up, CH)

at four different locations on the body (Figure 3.1): chest (TR), lower back at the area of L5 (L5), anterior superior iliac spine (ASIS), and an arbitrary position on the right hip (RH). Data from the 3D accelerometer and 3D gyroscope was recorded with a sampling frequency of 128 Hz and was used to test the PT detection algorithm described in the next two sections.

Table 3.1: Demographic data of Datasets A and B

	Population	Participants (female)	Age	Height (cm)	Weight (kg)	Disease scale
Dataset A	Healthy young adults	15 (4)	27 ± 3	172 ± 8	67 ± 14	-
Dataset B	Healthy young adults	21 (9)	29 ± 9	182 ± 8	74 ± 12	-
	Healthy older adults	3 (1)	69 ± 4	178 ± 8	69 ± 13	-
	IPS patients	5 (1)	58 ± 9	176 ± 6	87 ± 13	UPDRS[1]: 22 ± 17
	MS patients	5 (2)	41 ± 17	185 ± 5	73 ± 8	EDSS[2]: 3 ± 2
	Stroke patients	8 (2)	66 ± 13	176 ± 12	79 ± 25	-

[1]Unified Parkinson Disease Rating Scale
[2]Expanded Disability Status Scale

Figure 3.1: The location of inertial sensors for Dataset A

The measurement protocol consisted of two tests. The first test aimed to validate the performance of the PT detection algorithm during 10 minutes recording of daily tasks performed in a fixed order inside a building: sitting on different chairs and sofas with different heights, walking through different offices, bending to pick up objects from the floor, lying, tying shoe laces, picking objects from the fridge, and using stairs and lift. Subjects were free to move outside the lab and between different offices. As the reference events for the PTs, the participants were video recorded during the whole measurement with a camcorder (Sony, JP) with 25 frames per second.

The goal of the second test was to validate the accuracy of the extracted biomechanical parameters and determine the effect of the sensor location on the characterization of the PTs. The participants were asked to perform a 5xSTS test in the lab on a chair without armrest. Regularly, 5xSTS is performed as fast as possible. Here, the test was performed with self-

selected speed as this is in our view, closer to daily life behavior. Two parameters were validated: the trunk tilt angle and the duration of each transition. Trunk tilt was validated by an optical motion capture system (Vicon, UK). Four reflective markers (Figure 3.1) were mounted on the inertial sensors to track the movements of the trunk and lower back. Furthermore, the participants were video recorded and transition durations were validated. All subjects were provided with the informed consent, and the protocol was approved by the Human Research Ethics Committee of École Polytechnique Fédérale de Lausanne (EPFL), HREC No: 038- 2018/ 09.08.2018.

Dataset B was obtained through measurements on 42 participants: 21 healthy younger adults, 3 healthy older adults, 5 patients with multiple sclerosis (MS), 5 IPS patients, and 8 patients who had stroke. Table 1 provides clinical and demographic information. The measurement protocol consisted of a home setting simulation in which subjects performed several simple daily living tasks: Setting a table (including sitting at table, eating and drinking, and cleaning table afterwards), standing up and sitting down multiple times (in open space and at a table), ironing, tooth brushing, and replacing objects from different heights and out of a cabinet. As reference for validation, an observer logged the time when the PTs were performed. All participants gave written informed consent and the study was approved by the ethical committee of the medical faculty at Universitätsklinikum Schleswig-Holstein (UKSH), No: D438/18. Since the objective here was to further validate the transition detection algorithm in various populations, data extracted from the L5 sensor (myoMOTION, Noraxon, USA) was used.

3.2.2 PT detection algorithm

The main idea to make the detection algorithm independent of the sensor location was to use the vertical acceleration in the global frame. This vertical acceleration has a positive acceleration peak followed by a negative acceleration peak in the vertical direction during sit-to-stand and a negative peak followed by a positive peak during stand-to-sit transitions (Najafi et al., 2003). For this purpose, the vertical acceleration in the global frame was obtained first, and then a robust peak detection algorithm was designed to detect the PT candidates. Finally, a fitting model on vertical displacement allowed selecting the actual PTs. The following section describe these different steps. Figure 3.2, illustrates the algorithm flowchart.

Vertical acceleration

Given the measurements from the accelerometer in the sensor frame (a_s), the data can be obtained in the global frame by:

$$a_g = q \otimes [0 \quad a_s] \otimes q^* \tag{3.1}$$

in which q is the quaternion specifying the orientation of the sensor in the global frame and is calculated by fusion of accelerometer and gyroscope (Madgwick et al., 2011). q^* is the

conjugate of the quaternion, $\otimes$ operator is quaternion multiplication, and a_g is the accelerometer data in the global frame.

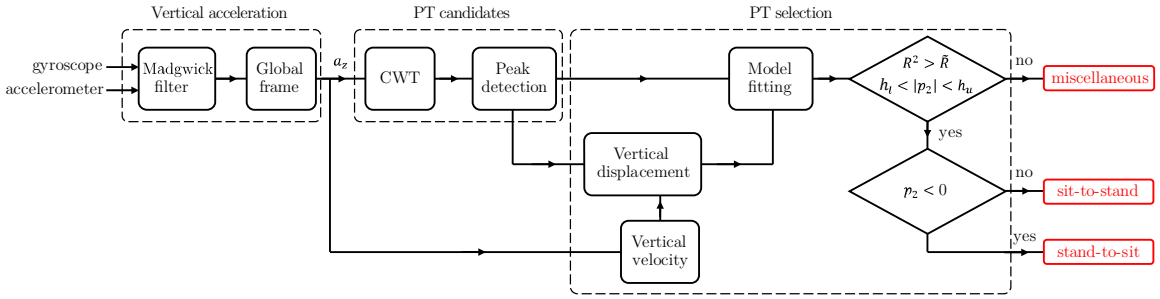


Figure 3.2: The PT detection algorithm flowchart

The acceleration of the movement (a) can be obtained by subtracting the gravity vector from the accelerometer data in the global frame:

$$a = a_g - g \tag{3.2}$$

in which $a = [a_x \quad a_y \quad a_z]$ and a_z is the vertical acceleration. To remove the noise and artifacts included in the signal, a low-pass Butterworth filter of order 12 with a cut-off frequency of 1.3 Hz was used to filter the vertical acceleration. This cut-off frequency was achieved empirically by attenuating other movements than the PTs.

PT candidates

As the first step to detect the candidates of these PTs, the continuous wavelet transform (CWT) was applied to detect the specific sit-to-stand and stand-to-sit patterns in a_z (Ejupi et al., 2017; Najafi et al., 2003). By scaling (frequency localization) and shifting (time localization) of a template signal called mother wavelet, CWT tries to find the patterns through the measured signal similar to the mother wavelet. This will provide us with CWT coefficients ($C_w(a,t)$):

$$C_w(a,t) = \frac{1}{\sqrt{|a|}} \int_{-\infty}^{+\infty} a_z(u) \psi \left(\frac{u-t}{a} \right) du \tag{3.3}$$

in which, a is the scale factor, t is the time, $a_z(u)$ is the vertical acceleration signal, and $\psi(u)$ is the mother wavelet function.

The "bior 1.5" wavelet was chosen as the mother wavelet due to the similarity between this wavelet and the sit-to-stand (or stand-to-sit) vertical acceleration pattern. The coefficients belonging to the scales of 0.5 to 5 seconds (0.2 Hz to 2 Hz) were obtained (Ejupi et al., 2017). The sum of the coefficients was then calculated as:

$$A_w(t) = \sum_a C_w(a,t) \tag{3.4}$$

The wavelet analysis was performed by MATLAB Wavelet Analyzer Toolbox. The peaks of the $|A_w(t)|$ can be chosen as the candidates for the sit-to-stand and stand-to-sit transitions.

In order to make the computation more efficient and to avoid less false positives, we have chosen the peaks that are greater than $\frac{1}{4}\max(|A_w(t)|)$, in which $\max(|A_w(t)|)$ is the maximum value of the entire signal of $|A_w(t)|$. The reason for using this value rather than a fixed threshold is that individuals have different magnitude of acceleration during PTs. Furthermore, we hypothesized that it is unlikely to have two consecutive PTs within two seconds in the real life settings; thus, the peaks of $|A_w(t)|$ should have minimum time distance of 2 seconds.

PT candidate selection

Since not all the detected candidates belong to the true sit-to-stand and stand-to-sit transitions, it is required to filter out these candidates. For each candidate k at time t_k, the velocity signal of the movement in the vertical direction (v_z) was integrated through an interval of ΔT seconds which was set empirically to 4 seconds to get the vertical displacement of the motion throughout the transition:

$$d_{z,k}(t) = \int_{t_k-\Delta T/2}^{t_k+\Delta T/2} v_z(t)dt \tag{3.5}$$

where the vertical velocity (v_z) was obtained by integrating the acceleration signal throughout the whole measurement and applying a 3rd order Butterworth bandpass filter (0.1 – 50 Hz) to remove the drift caused by the integration and the noise and bias in the acceleration signal.

Upon each $d_{z,k}(t)$ signal, a Sigmoid model was fitted:

$$\tilde{d}_k(t) = p_1 t + \frac{p_2}{1+\exp(\frac{p_3-t}{p_4})} \tag{3.6}$$

in which $\tilde{d}_k(t)$ is the fitted model and p_1, p_2, p_3, and p_4 are the model parameters which were calculated by MATLAB "nlinfit" function. In this model, p_1 accounts for the linear drift, p_2 determines the amplitude of the elevation change, p_3 is the time localization of the PT event, and as it will be explained later, p_4 is linearly proportional to transition duration, Figure 3.3.

A PT candidate k is considered as a true sit-to-stand or stand-to-sit if these conditions were satisfied:

- The R-squared (R^2) of the fitting model is above a certain threshold $\tilde{R}$.
- The elevation change ($|p_2|$) is between a lower bound h_l and an upper bound h_u.

The reason for choosing the R^2 of the fitting model as a metric to detect the true transitions is that this parameter corresponds to the quality of the fitting and specifies the degree of similarity between $d_{z,k}(t)$ and $\tilde{d}_k(t)$. The value for $\tilde{R}$ was set empirically to 0.92. The values for h_l and h_u were determined by maximizing the sensitivity and positive predictive value of the detection algorithm based on the L5 location in Dataset A. The same values for the determined parameters were used for other sensor locations in Dataset A and the whole data

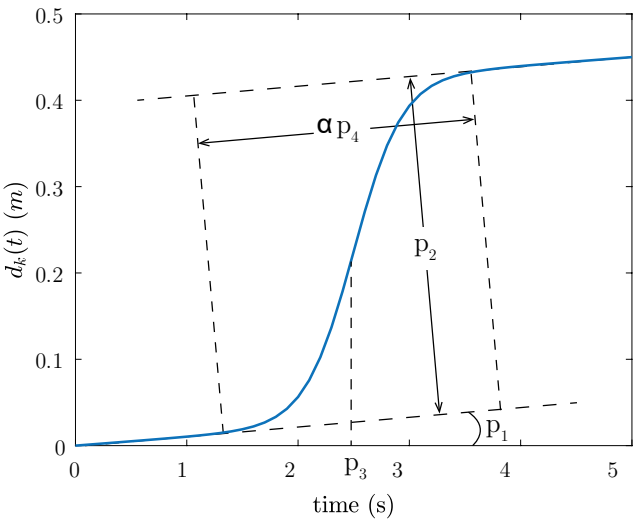


Figure 3.3: The parameters of the estimated displacement during a sit-to-stand defined by Equation 3.6

of Dataset B. A sensitivity analysis was performed to determine the effect of changing the value of these parameters (i.e. $\tilde{R}$, h_l, and h_u) on the performance of the detection algorithm.

3.2.3 Biomechanical features

The following biomechanical features were extracted to characterize the sit-to-stand and stand-to-sit transitions:

Transition duration

Two estimates were used for the transition duration, one based on the angular velocity (TD_ω) and the other based on the vertical acceleration (TD_a). To calculate TD_ω, for each transition, a principal component analysis (PCA) was performed on the gyroscope data, to get the angular velocity of the trunk in the sagittal plane considered as the principal plane for trunk rotation. The start of the transition was defined as the end of the plateau before the negative peak of the angular velocity (forward trunk rotation) and the end of the transition was defined as the start of the plateau after the positive peak of the angular velocity (backward trunk rotation). For (TD_a) estimation, first an approximation of vertical acceleration was obtained by calculating the second derivative of $\tilde{d}_k(t)$:

$$\tilde{a}_k(t) = \frac{d^2}{dt^2}\left(\tilde{d}_k(t)\right) \tag{3.7}$$

Then using the model presented in Equation 3.6 and considering a_0 as the acceleration threshold to define the start and end of plateau, TD_a was obtained by:

$$TD_a = \alpha p_4 \tag{3.8}$$

in which,

$$\alpha = 2\ln\left(\frac{2\beta}{-2\beta + 1 - \sqrt{1-4\beta}}\right) \tag{3.9}$$

$$\beta = \frac{p_4^2 a_0}{p_2} \tag{3.10}$$

p_2 and p_4 are the displacement model parameters introduced by Equation 3.6.

Tilt angle and anterior-posterior angular range

Tilt angle (θ) was calculated by converting the quaternions to the Euler angles (Berger, Sinha, & Roitsch, 2007).

The anterior-posterior angular range ($\Delta\theta_{AP}$) was defined as the change in the tilt angle of the trunk at the beginning and the end of the flexion phase (forward trunk rotation) of the sit-to-stand transition.

Peak power

The power was calculated by the product of the vertical velocity and the vertical force exerted during the PT (Zijlstra et al., 2010):

$$P_k(t) = m\tilde{a}_k(t)\tilde{v}_k(t) \tag{3.11}$$

in which m is the body mass, $\tilde{v}_k(t) = \frac{d}{dt}\left(\tilde{d}_k(t)\right)$ is the estimated vertical velocity, and $\tilde{a}_k(t)$ is calculated by Equation 3.7. The peak power was defined by the maximum power during a transition, i.e. $P_{max} = \max(P_k(t))$.

Peak angular velocity

The peak angular velocity (ω_{max}) was defined as the maximum angular velocity during flexion in a sit-to-stand transition in the sagittal plane.

3.2.4 Validation and statistical analysis

As described before, Dataset A and Dataset B were used for the validation of the PT detection algorithm. The performance of the algorithm was reported by the sensitivity (SE) and positive predictive values (PPV):

$$PPV = \frac{TP}{TP + FP} \times 100 \tag{3.12}$$

$$SE = \frac{TP}{TP + FN} \times 100 \tag{3.13}$$

in which TP stands for true positive, FP for false positive, and FN for false negative.

Furthermore, we compared the results of our method in detecting the sit-to-stands within Dataset B to the recent study that was published after our publication (Adamowicz et al., 2020). Their code is publicly accessible in (Adamowicz & Patel, 2020).

The second test within Dataset A corresponding to the 5xSTS test was used to estimate the accuracy of the relevant biomechanical parameters extracted for the sit-to-stand and stand-

to-sit transitions (i.e., TD_ω, TD_a, θ, and $\Delta\theta_{AP}$) and also to determine the effect of sensor location on the parameters.

For transition duration, two observers logged the durations recorded by the camcorder. The mean of the values determined by the observers was used as the reference. The error was calculated as the difference between the estimated transition duration (TD_ω or TD_a) and the reference value. The relative absolute error was also determined.

For the tilt angle, the tilt angles computed by the marker clusters on the TR sensor and L5 sensor were used as the reference. The error was defined as the difference between the reference and the estimated angle by the inertial sensor.

The errors were represented by the mean and standard deviation (std), and the one-sample Kolmogorov-Smirnov test was used to test the normality of the error.

To determine the associations between the parameters obtained by different sensor locations, Pearson's correlation coefficient (ρ) was used. A correlation coefficient of less than 0.5 was considered as low, between 0.5 and 0.7 as moderate, and above 0.7 as high (Rob C. Van Lummel et al., 2015). To show the statistical differences between two measurements, t-test was used where the data is normally distributed; otherwise, Wilcoxon test was employed.

3.3 Results

3.3.1 Vertical acceleration

Figure 3.4 shows an example of comparing the vertical accelerations (a_z) obtained by Equations 3.1 and 3.2 for data extracted from inertial sensors located at L5, ASIS, RH, and TR, worn by a healthy young participant in Dataset A. The vertical accelerations of the different locations matched almost perfectly. Pearson's correlation coefficients between respective positions were high, i.e. 0.95 between L5 and ASIS, 0.96 between L5 and RH, 0.94 between L5 and TR, 0.98 between ASIS and RH, 0.91 between ASIS and TR and 0.95 between RH and TR. However, when the participant bent his trunk to pick up an object from the ground, conceivably, higher acceleration in TR was observed compared to L5.

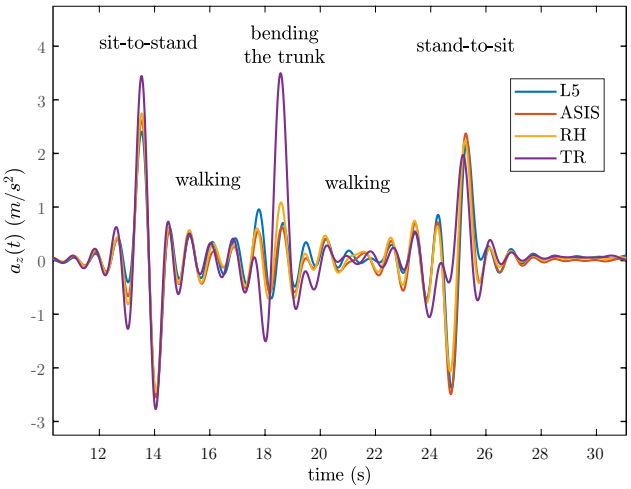
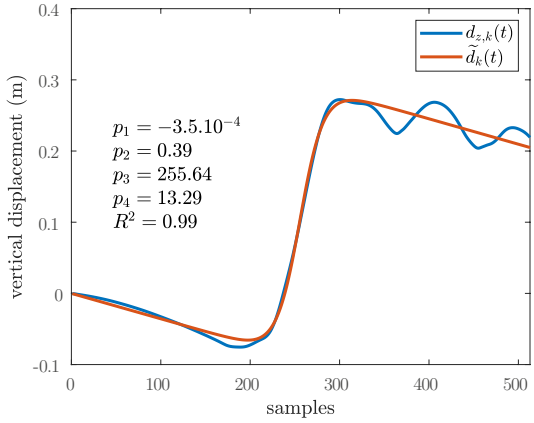
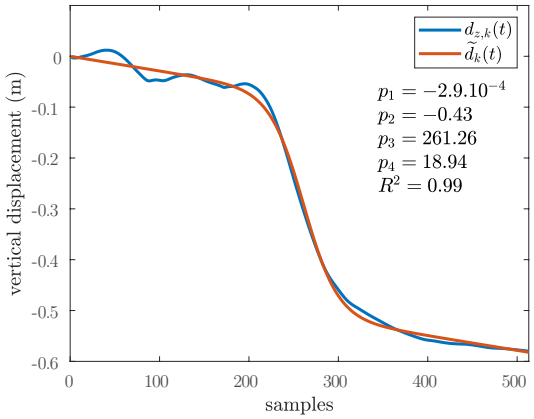


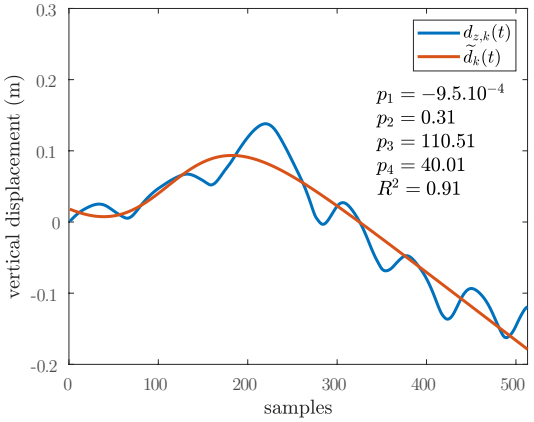
Figure 3.4: The vertical acceleration signal obtained by different locations of the sensor for a healthy young subject



(a)



(b)



(c)

Figure 3.5: The measured $d_{z,k}(t)$ (in blue) and estimated $\tilde{d}_k(t)$ (in red) displacement for PT candidates: (a) sit-to-stand transition, (b) a stand-to-sit transition and (c) a miscellaneous movement

The results of the fitting model for typical sit-to stand and stand-to sit movements were compared with a non-PT transition (miscellaneous movements) and shown on Figure 3.5 along with the model parameters.

For the R^2 and p_2 parameters, the differences between 171 sit-to-stand and stand-to-sit transitions and 35 miscellaneous movements that were detected by the algorithm in Dataset A were shown in Figure 3.6. For both of these parameters, the Wilcoxon rank sum test indicated a significant statistical difference between the true transitions and miscellaneous movements ($p < 0.001$).

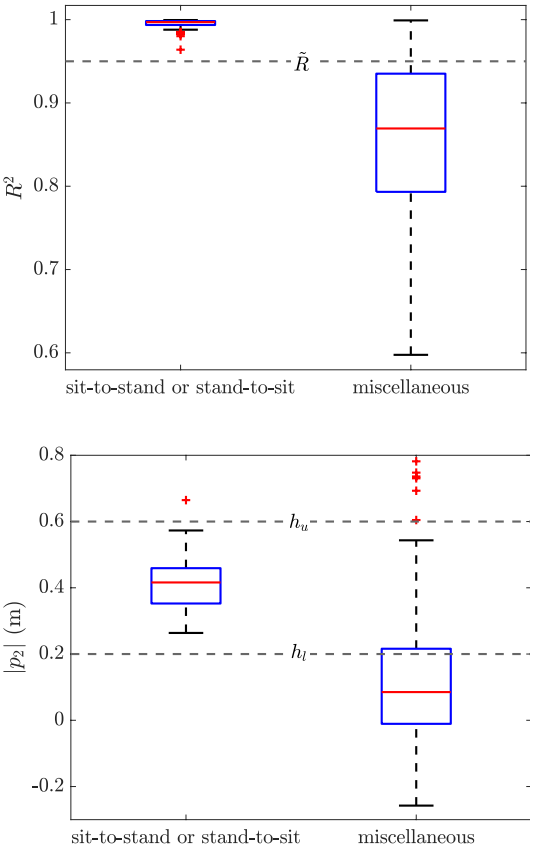


Figure 3.6: The comparison between the true PTs and miscellaneous movements for (a) the R^2 and (b) the p_2 parameters

3.3.2 PT detection

The performance of the algorithm in detecting the sit-to-stand and stand-to-sit transitions during simulated real-life condition were shown in Table 3.2 for different locations of the sensor (Dataset A) and on Table 3.3 among different populations for the L5 sensor (Dataset B). Almost the same performance was achieved for all the locations around the lower back, with the ASIS location showing the best performance. The performance was the lowest for TR, which was driven by low sensitivity for stand-to-sit transitions. PPVs for L5, ASIS and RH were above 93%, indicating that only very few miscellaneous movements were detected as PTs by the algorithm.

Table 3.2: Performance metrics for the PT detection algorithm: Dataset A (different sensor location), 15 young healthy adults

	Sit-to-stand					Stand-to-sit				
	TP	FP	FN	**PPV**	**SE**	TP	FP	FN	**PPV**	**SE**
L5	85	3	5	**97**	**94**	79	6	11	**93**	**88**
ASIS	88	3	2	**97**	**98**	82	6	8	**93**	**91**
RH	81	2	9	**98**	**90**	70	5	20	**93**	**78**
TR	86	14	4	**86**	**96**	68	23	22	**75**	**76**

Table 3.3: Performance metrics for the PT detection algorithm: Dataset B (different population), 21 healthy younger adults, 3 healthy older adults, 5 patients with MS, 5 IPS patients, and 8 stroke patients

	Sit-to-stand					Stand-to-sit				
	TP	FP	FN	**PPV**	**SE**	TP	FP	FN	**PPV**	**SE**
Healthy young adults	133	5	8	**96**	**94**	133	0	14	**93**	**88**
Healthy older adults	15	0	0	**100**	**100**	16	1	1	**94**	**94**
IPS patients	24	6	6	**80**	**80**	21	5	9	**81**	**70**
MS patients	23	2	1	**92**	**96**	23	1	4	**96**	**85**
Stroke patients	48	3	4	**97**	**92**	72	5	18	**94**	**80**

As reported in Table 3.3, the algorithm achieved lower performance among IPS patients while for the other populations the performance was high.

It should be mentioned that the threshold for the R-squared ($\tilde{R}$) was set empirically to 0.92. By the sensitivity analysis, it was observed that a change of ±2% in the value of $\tilde{R}$ will affect the PPV and SE values by ±1%. Furthermore, the h_l and h_u values determined by maximizing the mean of the PPV and SE of the sit-to-stand and stand-to-sit detections were 20 cm and

60 cm, respectively. A change of ±5 cm for these values affect the PPV and SE parameters by ±1%.

The results of a recent study (Adamowicz et al., 2020) on detection of sit-to-stands with only accelerometer data for Dataset B have been shown in Table 3.4. It can be seen that our method had higher performance.

Table 3.4: Performance metrics for the PT detection algorithm by (Adamowicz et al., 2020) within Dataset B (different population)

Algorithm by (Adamowicz et al., 2020)	Sit-to-stand				
	TP	FP	FN	**PPV**	**SE**
Healthy young adults	120	59	21	**67**	**85**
Healthy older adults	13	6	2	**68**	**87**
IPS patients	17	19	13	**47**	**57**
MS patients	16	6	8	**73**	**67**
Stroke patients	40	27	12	**60**	**77**

3.3.3 Biomechanical features

The algorithm detected all PTs correctly that were performed during the 5xSTS test. The biomechanical features defined previously were extracted and compared for different sensor locations; where applicable, the parameters were validated against the reference system.

Transition duration

Regarding the difference between the transition durations, the Wilcoxon rank sum test showed no significant difference between the observers for the sit-to-stand transitions ($p = 0.23$); however, there was a significant difference for the stand-to-sit transitions ($p < 0.05$).

Among the two methods proposed for the estimation of the transition duration, (TD_ω) which was based on the angular velocity had lower errors for all of the locations compared to the method based on vertical acceleration (TD_a). Overall, for both of the methods, the accuracy of the L5 sensor was the highest, followed by the TR sensor; whereas, RH sensor was the least accurate (Table 3.5). The relative absolute error for both of the methods for the L5 location was calculated. The 75th percentile of the relative error for TD_ω was 9.8% and 6.6% for the sit-to-stand and stand-to- sit durations, respectively while these values for TD_a were 18.8% and 24.0%.

Table 3.5: Mean (standard deviation) of the error (in milliseconds) of the transition duration (TD_ω and TD_a) compared to reference values obtained by the observers

	Sit-to-stand				Stand-to-sit			
	L5	ASIS	RH	TR	L5	ASIS	RH	TR
TD_ω	-2 (233)	338 (297)	229 (310)	-20 (229)	-27 (172)	237 (337)	101 (319)	-43 (165)
TD_a	-18 (387)	54 (344)	208 (564)	-21 (318)	224 (275)	160 (352)	312 (539)	80 (281)

Tilt angle and anterior-posterior angular range

The tilt angle during a typical trial of the sit-to-stand and stand-to-sit transitions is shown on Figure 3.7 in which it is observed that the angular range was underestimated by the ASIS and RH sensors.

The error of the total tilt angle signal (θ) and the anterior-posterior angular range ($\Delta\theta_{AP}$) were compared to the references obtained by the optical motion tracker at L5 and TR locations (Table 3.6).

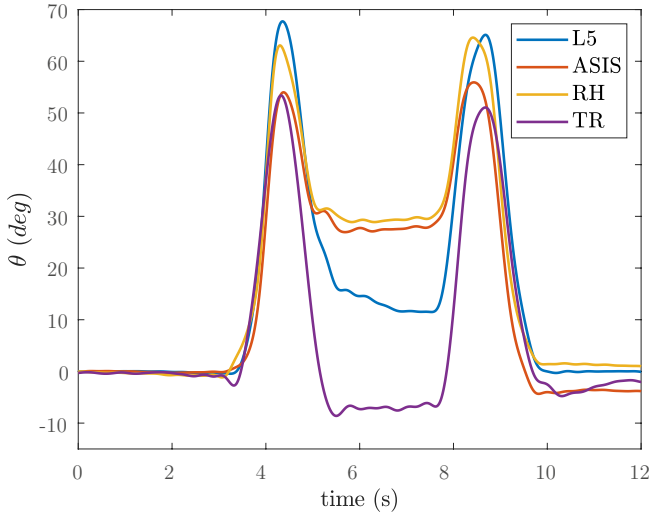


Figure 3.7: The tilt angle of the trunk obtained by the inertial sensors on different locations during one trial of a sit-to-stand and stand-to-sit

θ was obtained during the whole 5xSTS test of all the participants and $\Delta\theta_{AP}$ was calculated for 5 sit-to-stand transitions giving 75 values for all the participants. The lowest errors among the sensors belonged to L5 and TR locations with the 75th percentile relative absolute error of 5.6% and 8.1%, respectively.

Table 3.6: Mean (standard deviation) of the error of the tilt angle (θ) and the anterior-posterior angular range ($\Delta\theta_{AP}$) compared to the reference system in degrees

Location	L5	ASIS	RH	TR
Reference		L5		TR
θ	-0.3 (2.1)	-6.7 (10.7)	-4.8 (6.9)	-1.6 (3.3)
$\Delta\theta_{AP}$	-1.0 (3.2)	-6.1 (9.0)	1.2 (11.8)	-1.5 (3.0)

Peak power

For each subject the peak power was calculated for each of the five sit-to-stand transitions, providing 75 values for each sensor location. The box plot on Figure 3.8a shows these values for different sensor locations. The sensors around the belt had almost the same range while TR sensor shows higher values. High correlations were found between the L5, ASIS, and TR sensors (0.95 between L5 and ASIS, 0.77 between L5 and TR, 0.78 between ASIS and TR). Furthermore, moderate to high correlations were determined between the sensors around the belt (0.65 between L5 and RH and 0.74 between ASIS and RH). The correlation between RH and TR was 0.44.

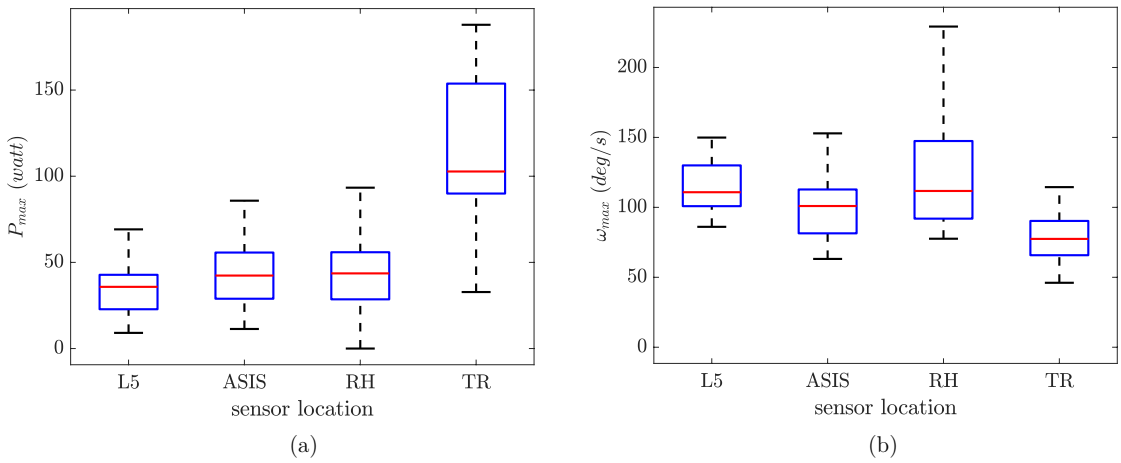


Figure 3.8: (a) The peak power and (b) peak angular velocity calculated by different sensor locations

Peak angular velocity

For each subject the peak angular velocity was calculated for each of the five sit-to-stand transitions, providing 75 values for each sensor location. The box plot for the peak angular velocity calculated by different sensor locations is shown on Figure 3.8b. The peak angular velocity determined by the trunk sensor was the lowest among all the locations. The correlation coefficient values were obtained as 0.71 between L5 and ASIS, 0.52 between L5

and RH, 0.54 between L5 and TR, 0.67 between ASIS and RH, 0.35 between ASIS and TR and 0.47 between RH and TR.

3.3.4 Comparison of biomechanical parameters between populations

The extracted biomechanical parameters from Dataset B (i.e. TD_a, ω_{max}, $\Delta\theta_{AP}$, and P_{max}) were compared between healthy (24 participants) and pathological (18 participants) groups (Figure 3.9). TD_a was significantly lower ($p < 0.05$) in healthy subjects compared to the patient population, while ω_{max}, $\Delta\theta_{AP}$, and P_{max} were significantly higher ($p < 0.05$) for healthy participants. To investigate the effect size, the Cohen's d for TD_a, ω_{max}, $\Delta\theta_{AP}$, and P_{max} were obtained as 0.6, 0.8, 0.2, and 0.8, respectively.

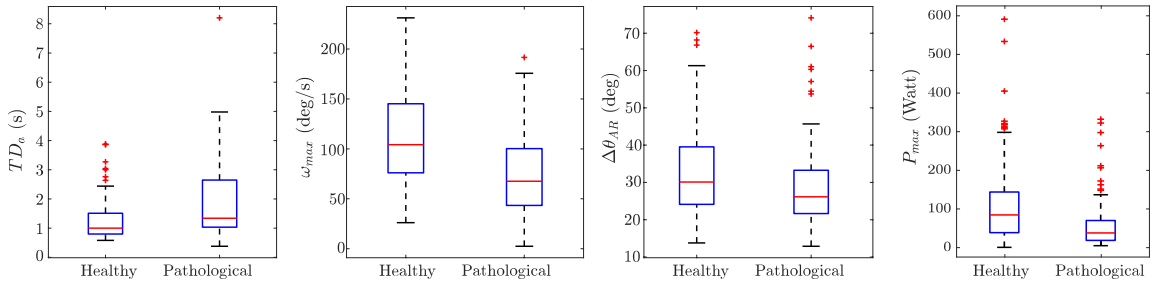


Figure 3.9: Comparison of the biomechanical parameters between the healthy and pathological participants in Dataset B

3.4 Discussion

The goal of this study was to develop and validate an algorithm to detect sit-to-stand and stand-to-sit transitions in healthy individuals and patients and provide useful parameters for functional evaluation. The algorithm is applicable on a single inertial sensor around the waist or on the trunk making the system appropriate for daily and clinical use. The algorithm validated in the lab showed high performance and its use in the field demonstrated little sensitivity to the change between healthy and pathological group.

Utilizing the vertical acceleration in the global coordinate system made the algorithm robust to sensor placement changes. The estimated vertical acceleration in the global frame was actually similar between different locations around the trunk based on high correlations observed between signals that were extracted from different sensors. Therefore, our hypothesis regarding the similarity between the vertical accelerations produced by different sensor locations seems valid even if some discrepancy can be observed in Figure 3.4. Not surprisingly, the ASIS and RH sensor positions which had the closest distance to each other, had the highest correlation values while the sensors at TR and ASIS positions had the lowest correlation, because they were relatively distant from each other.

The performance of the algorithm in detecting the PTs were validated against video observations (Table 3.2 and Table 3.3). The protocol of the test included a broad range of simple activities of daily living rather than only isolated PTs as used by (Bidargaddi et al., 2007; A. Godfrey et al., 2011; Alan Godfrey, Barry, Mathers, & Rochester, 2014; Hickey et al., 2016; Karantonis et al., 2006; Najafi et al., 2002, 2003). The algorithm showed an excellent performance in detecting these transitions with the inertial sensors around the waist (PPV of more than 97% and SE of more than 90%). However the TR sensor, showed lower accuracy. During a PT, the upper back performs more rotation than the lower back area, and because the algorithm was developed based on the lower back displacement model, this aspect may best explain this phenomenon. The differences of rotation values between these body areas were confirmed by calculations with the tilt angle, where the flexion and extension angular ranges were lower in the L5, ASIS and RH positions, than in the TR position (Figure 3.7).

The ASIS position was the most accurate in PT detection (Table 3.2) which probably was due to the rigid attachment of the sensor to this position (Figure 3.1). RH and L5 sensors may be exposed to some artificial motion, occurring, e.g., from soft-tissue movement and less stable positioning on the body.

Compared to previous studies (Ejupi et al., 2017; Raluca Ganea et al., 2012; Pham et al., 2018; Salarian et al., 2007; W. Zhang et al., 2014) with almost the same measurement protocol, our algorithm demonstrated better performance in detecting PTs, with a mean PPV and SE of 98% and 95% for healthy adults and 89% and 89% for participants suffering from diverse diseases. With a pendant device used by 25 community-dwelling older people, the performance of the algorithm used in (Ejupi et al., 2017) had a SE of 93% and a PPV of 90%. Moreover, compared to this study, we did not use the barometric pressure sensor, as the pressure changes from one place to another might affect the accuracy of the algorithm. In studies (Salarian et al., 2007) and (Raluca Ganea et al., 2012) in which a single inertial sensor on chest was used, the SE and PPV assessed through a group of 15 younger adults in a controlled protocol were less than 80% (R. L. Ganea, 2011). Compared to a study in which a single inertial sensor on lower back was used (Pham et al., 2018), our algorithm showed better performance in healthy older adults. In IPS patients without dyskinesias, the former study reached higher PPV and SE than our study. The most probable explanation is that in IPS patients the duration of the PTs may be longer compared to the healthy subjects (Toosizadeh et al., 2015) and our displacement model might not capture the high amount of the drift.

Compared to the study in (Masse et al., 2016), our algorithm had higher SE in sit-to-stand detection but slightly lower SE in stand-to-sit transitions. The lower SE in detecting stand-to-sit movements by our method might be attributed to the fact that sometimes after sitting down, people try to adjust their posture on the chair and perform one or two smaller PTs right after the original stand-to-sit. Therefore, their vertical displacement does not comply with the sigmoid model presented in Figure 3.5b. The reduced accuracy in detecting the stand-to-sit movements has been also observed in (Hickey et al., 2016) in which the authors have

considered the various strategies of individuals in sitting down as the contributing factor. Our hypothesis is in agreement with their statement.

Finally, we compared our method specifically to the method proposed by (Adamowicz et al., 2020) as their code was publicly accessible and they have employed almost similar approach as ours but using only the accelerometer data. Our method showed a higher performance in real-life situation (Table 3.3 and Table 3.4). The reason for this difference can be due to the displacement model, i.e. fitting a sigmoid function, that we used to detect true PTs. Using this model rather than only checking the value of the displacement of the trunk (as was the case with (Adamowicz et al., 2020)) can help to exclude false PTs. The performance of their method was lower in detecting the sit-to-stands compared to the value they reported during the 5xSTS tests in the lab (a drop between 3% to 52%). This shows the importance of validating the algorithms in real-life settings in addition to functional tests in the lab.

In previous works, the inertial sensor was always placed on either TR or L5. We are not aware of any study that investigated PTs using different inertial sensor positions on the human body simultaneously. We investigated the effect of different sensor locations on the biomechanical parameters during the PTs during the 5xSTS test.

In order to estimate transition duration, the angular velocity method (TD_{ω}) showed a better accuracy (34% less error); however, the acceleration-based approach (TD_{a}) is preferable in real-life situations. Because, during the 5xSTS test, only sit-to-stand and stand-to-sit movements with rest periods in between were measured which allows the detection of the angular velocity plateau (Figure 3.10a); however, this is not the case in daily activities as there are additional movements involved, e.g. walking after sit-to-stand movement (Figure 3.10b). In fact, the estimated model of the vertical acceleration ($\tilde{a}_k(t)$), isolates the PT movement from the signal (Figure 3.11), and with the help of the parameters of the fitted model, the transition duration can be determined by Equations 3.8-3.10.

Interestingly, although comparable results were obtained for the sit-to-stand phase, there was a statistically significant difference between the two observers concerning the estimation of stand-to-sit phases. Although we do not have any explanation for this observed difference, we see this result as a further argument for the use of objective measurement techniques, as provided by inertial sensors for instance and the algorithm introduced here.

Compared to the previous studies that validated the transition duration against video observations (Adamowicz et al., 2020; Bidargaddi et al., 2007; Alan Godfrey et al., 2014; Pham et al., 2018; W. Zhang et al., 2014), our algorithm achieved higher accuracy with a bias of 2 (L5 location) and 20 (TR location) milliseconds in sit-to-stand and 27 (L5 location) and 43 (TR location) milliseconds for stand-to-sits. The bias of the error was obtained as 10 to 50 milliseconds for sit-to-stand and 80 to 170 milliseconds for stand-to-sits in (Alan Godfrey et al., 2014; Hickey et al., 2016). (Pham et al., 2018) and (Adamowicz et al., 2020) had an error with a bias of 200 and 100 milliseconds compared to the video observations.

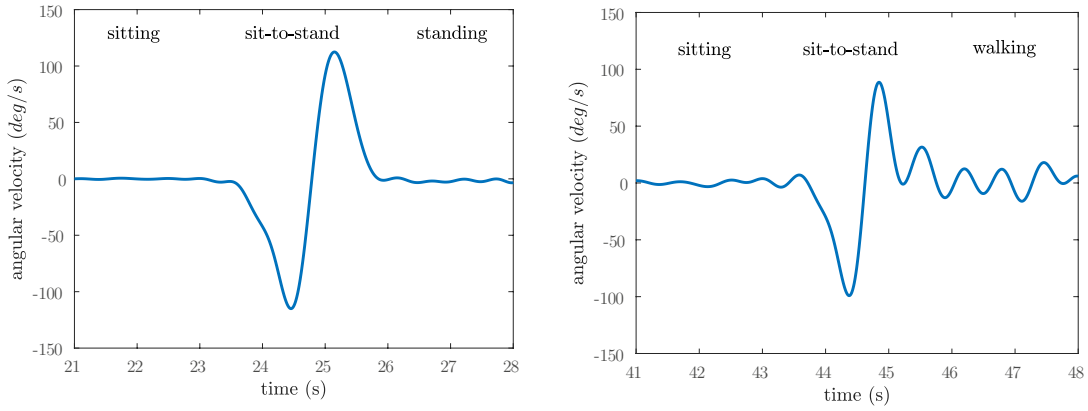


Figure 3.10: The angular velocity of the trunk for a young healthy subject (a) during the 5xSTS test and (b) real life setting

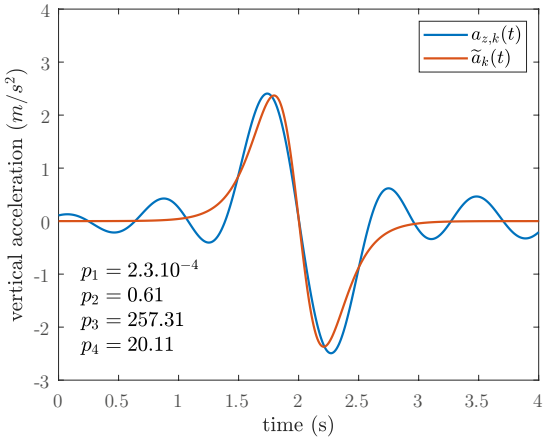


Figure 3.11: The fitted acceleration model for a sit-to-stand transition during daily activities for a young healthy subject, $a_{z,k}(t)$ is the measured acceleration and $\tilde{a}_k(t)$ is the estimated acceleration

The peak power was overestimated by the sensor on the chest compared to the other three placements (Figure 3.8a), as it is at the proximal distance relative to the lower back; therefore, during a rotation, it undergoes higher vertical velocity and acceleration (Equation 3.11). However, in spite of the differences between the upper and the lower back peak power, high correlations were found for all of the locations. Since peak power is based on vertical acceleration and velocity, it can be considered as a metric that is more robust to the changes in sensor location.

Comparing the peak angular velocity for different locations, lower correlations were found for the TR and RH sensors with respect to the other two locations. For the RH sensor as it is hinged to the belt with a rubber clip, the abdominal muscles may push the sensor around the belt, causing artifacts that are not related to the postural movement itself. This also explains the higher range of peak angular velocity calculated by the RH sensor compared to the other

locations (Figure 3.8b). The low correlations with TR sensor, can be explained by different rotational behaviour of upper and lower back.

Finally, the comparison between healthy and pathological participants in the extracted biomechanical parameters showed that our algorithm was able to show the subtle differences between different populations in an objective manner. The Cohen's d values for these parameters revealed that for the peak angular velocity and peak power the difference between the healthy and patient populations were greater than the angular range and duration of the transition. Yet further studies with bigger sample group are needed to investigate in details the association of those parameters with specific disease symptoms.

One limitation of our study is the use of wavelet transform as it is computationally expensive and may not be appropriate for real-time applications. To compare the signal to the PT templates, cross correlation can be used instead of the wavelet transform. Moreover, the use of only accelerometer data rather than the fusion of accelerometer and gyroscope data should be studied in order to decrease the power consumption of the device (A. Godfrey et al., 2011).

As there was a variety of populations performing the PTs in this study, the discriminative power of the biomechanical parameters could be studied. It has been shown in (Lepetit et al., 2019) that the spatiotemporal and biomechanical parameters extracted during sit-to-stand transitions can help clinicians detect individuals with frailty and abnormal functional capacities.

3.5 Conclusion

This study presents a novel algorithm for detecting the sit-to-stand and stand-to-sit transitions in both the simulated home setting and the laboratory environment based on a single inertial sensor. The novelty of this approach is that the algorithm is largely independent of the position of the inertial sensor on the trunk. The algorithm was validated in both healthy subjects and patients suffering from diverse diseases in simulated daily activity situations. This study used a novel approach to estimate the transition duration and peak power, by introducing a fitting model on the vertical displacement of the trunk. The effect of the location of the sensor on the extracted biomechanical parameters was also investigated, and it was shown that the L5 and TR positions are the most accurate locations to evaluate transition duration and tilt angle of the PTs. Further research should now investigate the predictive and discriminative power of the biomechanical parameters from the novel PT detection algorithm, for different aging and diseased populations.

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Abbreviations

Acronyms	Definition
3D	Three dimensional
30CTS	Thirty-second chair rise
5xSTS	Five-time sit-to-stand
ASIS	Anterior superior iliac spine
CWT	Continuous wavelet transform
FN	False negative
FP	False positive
IPS	Idiopathic Parkinson's disease
MS	Multiple sclerosis
PCA	Principal component analysis
PPV	Positive predictive value
PT	Postural transition
RAE	Relative absolute error
TP	True positive
TR	Trunk
SE	Sensitivity
std	Standard deviation

4 Toward a remote assessment of walking bout and speed: application in patients with multiple sclerosis

Abstract: Gait speed as a powerful biomarker of mobility is mostly assessed in controlled environments, e.g. in the clinic. With wearable inertial sensors, gait speed can be estimated in an objective manner. However, most of the previous works have validated the gait speed estimation algorithms in clinical settings that can be different than the home assessments in which the patients demonstrate their actual performance. Moreover, to provide comfort for the users, devising an algorithm based on a single sensor setup is essential. To this end, the goal of this study was to develop and validate a new gait speed estimation method based on a machine learning approach to predict gait speed in both clinical and home assessments by a sensor on the lower back. Moreover, two methods were introduced to detect walking bouts during daily activities at home. We have validated the algorithms in 35 patients with multiple sclerosis that often presents with mobility difficulties. Therefore, the robustness of the algorithm can be shown in an impaired or slow gait. To the best of our knowledge, there are very few studies that have focused on locomotion detection in MS patients, as it can be helpful to understand the amount of activity of the patients at their home. Against silver standard multi-sensor references, we achieved a bias close to zero and a precision of 0.15 m/s for gait speed estimation. Furthermore, the proposed machine learning-based locomotion detection method had a median of 96.8% specificity, 93.0% sensitivity, 96.4% accuracy, and 78.6% F1-score in detecting walking bouts at home. The high performance of the proposed algorithm showed the feasibility of the unsupervised mobility assessment introduced in this study.[*]

[*] Chapter adapted from Atrsaei, A., Dadashi, F., Mariani, B., Gonzenbach, R., & Aminian, K. (2021). Toward a remote assessment of walking bout and speed: application in patients with multiple sclerosis. IEEE Journal of Biomedical and Health Informatics

Contributions: developed the algorithm, analyzed and interpreted the data, and drafted the manuscript

4.1 Introduction

Walking speed is a powerful clinical marker in predicting the functional status of the individuals (Fritz & Lusardi, 2009). It has been shown that gait speed can predict functional decline (Brach et al., 2002), is associated with functional status (Purser et al., 2005), and can track the stages of a mobility-related disease such as multiple sclerosis (MS) (J. A. Cohen et al., 2014).

Mobility impairments are a major concern in patients with MS. Due to progressive nature of the disease, these impairments can gradually lead to a decreased activity and quality of life (LaRocca, 2011). Therefore, it is important to monitor these patients' mobility as it indicates advancing neurological problems (Kesselring, 2010).

Mobility is usually assessed by filling out questionnaires or a clinician's observation of the way the patient walks. For instance, in MS patients, the expanded disability status scale (EDSS) is a well-accepted clinical score that measures the impairments in these patients (Kurtzke, 1983) in which a score higher than 4.0 is indicative of mobility impairments (Freeman, Langdon, Hobart, & Thompson, 1997). However, like other questionnaire-based methods, EDSS assessments can be subjective and may not report the actual performance of the patients during daily routines (Inojosa, Schriefer, Klöditz, Trentzsch, & Ziemssen, 2020). Furthermore, this scale is not sensitive enough to the changes in the severity of the disease (Vienne-Jumeau et al., 2020).

To have a more objective assessment, the measurement of gait speed has been employed through timed walks in the clinic, e.g. 10-meter walk test (10MWT) (Bethoux & Bennett, 2011; R. Motl, Goldman, & Benedict, 2010) by stop-watches, walkways, or sometimes inertial sensors. In patients with MS, It has been shown that gait speed was reduced compared to healthy controls (Martin et al., 2006). Furthermore, gait speed significantly decreased in higher disability levels, i.e. with higher EDSS (Preiningerova et al., 2015).

However, gait speed is often obtained in clinical environments under supervised conditions which may not reflect the performance of the patients in real-life settings (Warmerdam et al., 2020). Moreover, clinical assessments cannot continuously measure the amount of daily activities or more specifically amount of walking bouts. Body worn inertial measurement units (IMUs) coupled with the dedicated algorithms have the potential to overcome these challenges by estimating the walking speed during locomotion periods regardless of the measurement environment.

There are actually numerous previous works on the estimation of gait speed by IMUs on the lower limbs (Aminian et al., 2002; Benoit Mariani et al., 2010; Moon et al., 2017; Rampp et al., 2015; Angelo M. Sabatini et al., 2005). These methods mostly employed the zero-velocity update approach where the drift in the velocity signal caused by the integration of the acceleration is removed by detecting stance phases and updating the velocity to zero (Benoit

Mariani et al., 2010; Angelo M. Sabatini et al., 2005). Although these methods provide high accuracy due to the biomechanical nature of the lower limb during walking, a single sensor placed on trunk or wrist is preferable in free living context where the usability and comfort are better for the users (Fasel et al., 2017; Storm et al., 2018). However, opposed to the lower-limb based methods, zero velocity update approach is challenging when the sensor is placed on the trunk or the wrist because of the lack of motionless instances. Therefore, the methods based on trunk or wrist are mostly based on either biomechanical models (Hu et al., 2013; Zijlstra & Hof, 2003) or machine learning approaches (Byun et al., 2019; Fasel et al., 2017; Keppler et al., 2019; McGinnis et al., 2017; Schimpl et al., 2011; Shammas et al., 2014; Soltani, Dejnabadi, et al., 2020; Supratak et al., 2018; Vathsangam et al., 2010; Zihajehzadeh & Park, 2016a).

In biomechanical models, mostly the step length was modelled by an inverted pendulum and then by detecting the gait cycle events based on the peaks of the acceleration signal, the gait speed was estimated (Zijlstra & Hof, 2003). The model was further improved by considering the rolling of the ankle and the rotation of the trunk affecting the trajectory of the center of mass (Hu et al., 2013; Neumann, 2002). As these biomechanical models are often validated in healthy individuals with unimpaired gait, extending them to individuals with mobility impairments can be challenging (McGinnis et al., 2017). In machine learning approaches, several features were extracted mostly from the acceleration signal, and a prediction model was trained to estimate gait speed. These features often fall into time-domain and frequency-domain categories which represent the intensity, periodicity, and posture of the movement (Soltani, Dejnabadi, et al., 2020). Although in these studies, high accuracy was obtained to estimate the gait speed in supervised conditions such as laboratory environments, little is known about their performance in unsupervised daily activities and in domestic environments.

For instance, in a study on MS patients to estimate the gait speed on the belt, time and frequency-domain features were extracted from both the vertical and horizontal components of the accelerometer signal on the lower back (McGinnis et al., 2017). A model was trained based on a dataset of healthy adults and was tested in patients with MS in a six-minute walk test on the treadmill in the lab. The accuracy of the model was established and it was shown that the estimated gait speed had high correlations with EDSS.

To detect walking bouts based on a single IMU, the existing methods in the literature can be mostly divided into peak detection and machine learning methods. In peak detection algorithms, steps (and consequently walking bouts) can be detected for instance, from the peaks of pitch angular velocity signal of the foot (Moufawad el Achkar et al., 2016), acceleration signal of the trunk (Del Din, Godfrey, & Rochester, 2016; Dijkstra, Zijlstra, Scherder, & Kamsma, 2008; A. Godfrey et al., 2011; Massé et al., 2015; Pham et al., 2017; Zijlstra & Hof, 2003), or the spectrum of the accelerometer signal on the wrist (Fasel et al., 2017). As detecting those peaks require a threshold to be selected, the robustness of the algorithm is affected by inter-individual variability. Furthermore, the pattern of a signal from

an individual with an impaired gait might differ from that of a healthy individual (Anisoara Paraschiv-Ionescu et al., 2019). Enhancing peak detection by using advanced and complicated filters and smoothening functions (Hickey et al., 2017; Anisoara Paraschiv-Ionescu et al., 2019; Storm et al., 2018) or using information from IMUs on another location (Trojaniello et al., 2014) seems to solve the aforementioned issues. In machine learning algorithms, several features from acceleration or angular velocity signals can be mapped into the activity classes (Awais et al., 2019; Gyllensten & Bonomi, 2011; Soltani, Paraschiv-Ionescu, et al., 2020). With reference systems such as video camera (Awais et al., 2019), a classifier can be trained to detect walking bouts.

Lack of validation in daily activities at home also exists in the literature when it comes to locomotion detection (Anisoara Paraschiv-Ionescu et al., 2019). There are some previous works in detecting the walking bouts by a sensor on the trunk (A. Godfrey et al., 2011; Panahandeh et al., 2013; Rodriguez-Martin et al., 2013; Sandroff et al., 2014; M. Zhang & Sawchuk, 2013) but most of them have been validated in laboratory environments or under controlled conditions (A. Godfrey et al., 2011; Panahandeh et al., 2013; Rodriguez-Martin et al., 2013; Sandroff et al., 2014; M. Zhang & Sawchuk, 2013). For instance, (Sandroff et al., 2014) benchmarked two commercial accelerometers in detecting walking periods in the 6-minute walk tests in the lab. In spite of obtaining a good accuracy in the lab for detecting the steps, the performance of the system is not known during daily living activities. As it has been shown in (Dijkstra et al., 2010), lower accuracy in detecting walking periods has been obtained in daily activity settings compared to the laboratory-based tests.

To this end, the goal of this study was to design new algorithms to estimate gait speed and detect the walking bouts using a single IMU on the lower back. The main novelty of the algorithms relied on a training phase at the clinic. The algorithms were then tested and validated both in supervised condition, i.e. at the clinic and unsupervised condition, i.e. at home. It should be mentioned that firstly, we have used a single IMU rather than a network of multiple IMUs on the body to be as less obtrusive as possible during daily activities and reduce the complexity associated with the sensor setup. Furthermore, we focused on the lower back sensor for its closeness to the center of mass compared to the wrist IMU and its ease of use compared to the foot placement.

4.2 Data collection

4.2.1 Participants

The recruitment and clinical measurements were performed in Valens rehabilitation hospital, Valens, Switzerland. The study was approved by the ethical committee of St. Gallen Canton (ethics number: BASEC-ID 2017-01949). 35 participants with MS were recruited in this study. The demographic data was shown on Table 4.1. The inclusion criteria for recruitment were

confirmed diagnosis of MS by the criteria of McDonald 2017 (Thompson et al., 2018), EDSS of 1.0 to 6.5, ability to use smartphones and sensors properly, and having enough space at home to perform 10MWT. Participants were excluded from the study if they had obvious cognitive deficits, or they were pregnant, breastfeeding, or desirous to be pregnant.

Table 4.1: Demographic data of the participants

Number of participants (female)	35 (23)
Age	49.7 ± 13.0 year
Height	172.4 ± 8.6 cm
Weight	72.4 ± 12.7 kg
EDSS	4.7 ± 1.0 (min = 2.5, max = 6.5)

4.2.2 Protocol and sensor setup

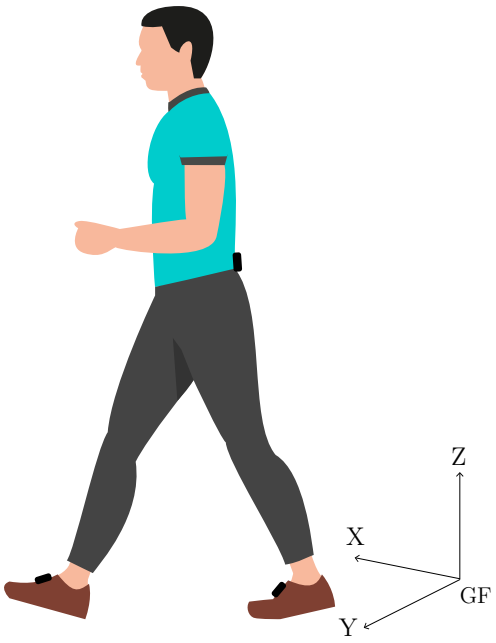


Figure 4.1: The location of IMUs on feet and belt, GF is the global frame in which the Z axis is the vertical axis, and X and Y axes lie on the horizontal plane

During the measurements, participants were equipped with three IMUs (Physilog 5®, Gait Up, CH), one on the belt and two on both feet (Figure 4.1). It was instructed to attach the sensors by a rubber clip to the shoes and to the belt on the middle of the lower back. Each IMU included 3D accelerometer and gyroscope data recorded at a sampling rate of 128 Hz. The sensors on the feet were used to provide reference values for training and validation of waist worn sensor algorithms (see section 4.2.3). Participants were also given a smartphone that could provide the patients with the instructions about performing the tests. Moreover, the smartphone was used to connect to the IMUs by Bluetooth to start and stop the measurements and store the data. The data was then transferred to a secured server through internet by the same app from the smartphone.

The data was collected in two phases. First in the clinic, where the patients were asked to perform the 10MWT in three sessions with their preferred speed. During this test, patients had to walk for 10 meters, turn and walk back to their initial position. Patients were also instructed how to use the three sensors and the smartphone to become ready for the second phase happening in real life conditions. With the instructions given in clinic and also displayed on the phone, half of the patients (18 patients randomly chosen from the 35 patients) were asked to perform the 10MWT at home for 12

sessions, one session per week with their preferred speed. For each 10MWT session at home, the duration of the recorded signal as well as the 3D trajectory of the foot (Benoit Mariani et al., 2010) were checked individually. If the duration of performing the test was too short, e.g. 2 or 3 seconds or patients had performed too many turns, that measurement was discarded due to its contrast to the protocol of the test. If possible, patients were requested to perform their usual daily activities while wearing the IMUs for 6 hours of measurement. They were allowed to go outside and perform their habitual activities.

4.2.3 Reference values of the gait speed and walking bouts

Reference values for gait speed were obtained with a previously validated algorithm using IMUs on the feet of which the error was achieved as 1.4 ± 5.6 cm/s in a study with healthy older and younger adults (Benoit Mariani et al., 2010) or 2.8 ± 2.4 cm/s in another study on patients with Parkinson's disease (Benoit Mariani, Jiménez, Vingerhoets, & Aminian, 2013). The gait speed values obtained by this method were used for training and validation of the speed estimation algorithm using waist sensor.

Throughout the measurements performed during daily activities at home, the aim was to determine the periods in which the participant was walking. Therefore, two classes were considered during daily activities: locomotion and non-locomotion. Foot worn IMUs were used to label the activities by applying a previously validated algorithm with an accuracy of 98% (Moufawad el Achkar et al., 2016).

It should be noted that our reference for gait speed estimation and walking detection algorithms did not depend on the sensor location on the foot. Firstly, because gait speed is determined in the global coordinate system (Benoit Mariani et al., 2010), and in a global coordinate system, the placement and orientation of the attached sensor does not matter. Moreover, the reference algorithms based on the foot IMUs perform an automatic sensor to segment calibration during gait, making the reference values for locomotion periods and gait speed, independent of the sensor placement on the foot.

4.3 Gait speed estimation

4.3.1 Waist vertical acceleration

To suppress the dependency of the algorithm to the orientation of the IMU attached to the belt, the vertical acceleration signal in the global frame (Z axis in Figure 4.1) was chosen to extract the features (Atrsaei et al., 2020). In this way, a need for calibration of the sensor to anatomical frame could be avoided. Therefore, it will maintain reliability as the participants might wear the sensor in different ways throughout the day.

The accelerometer data was transformed from the IMU frame (a_s) to the global frame (a_g) by quaternions.

$$a_g = q \otimes [0 \quad a_s] \otimes q^* \tag{4.1}$$

In which q is the quaternion calculated by the fusion of the accelerometer and gyroscope data with a gradient descent algorithm (Madgwick et al., 2011), q^* is the quaternion conjugate, and $\otimes$ operator is quaternion multiplication.

The vertical acceleration (a) signal was then obtained by subtracting the gravity acceleration (g) from the z axis component of a_g:

$$a = a_{g,z} - g \tag{4.2}$$

4.3.2 Feature extraction

The vertical acceleration signal was low-pass filtered with a third-order Butterworth filter and a cut-off frequency of 3 Hz. The azimuth angle and angular velocity signals were also calculated by the method introduced by (El-Gohary et al., 2014). Next, the three signals (vertical acceleration, azimuth angle, and azimuth angular velocity) were divided into windows of 2 seconds with a one second overlap. For each window k a set of 18 features were extracted. 13 of these features belonged to the low-pass filtered vertical acceleration signal (a_f). These features were chosen based on the existing literature and they reflect the intensity and periodicity of the movement (McGinnis et al., 2017; Zihajehzadeh & Park, 2016b). The remaining 5 features were from the azimuth angular velocity (ω) and azimuth angle (θ). Azimuth angular velocity and rotation were used as they are indicative of turns and people might have different behaviors during turnings (Pham et al., 2017). Each sample is denoted by i and within each window there are N samples. The list of these 18 features has been shown in Table 4.2. Dominant frequency and its amplitude were obtained by computing the fast Fourier transform (FFT) of the signal throughout the window (Frigo & Johnson, 2005). 11 features ($x_{k,1}$ to $x_{k,11}$) were then selected out of 18 features by the backward elimination method according to (Farzin Dadashi, Millet, & Aminian, 2014). All of these 11 features belonged to the vertical acceleration signal and reflect its statistical and frequency properties.

The feature vector $x_k = \{x_{k,1} \quad \cdots \quad x_{k,11}\}^T$ was mapped into the instantaneous gait speed (V_k):

$$V_k = f(x_k) + n \tag{4.3}$$

in which n is a white Gaussian noise with zero mean and covariance σ^2. Gaussian process regression (GPR) was used to build the regression model with MATLAB Regression Learner toolbox (Seeger, 2004). GPR was chosen because of its non-parametric characteristic which makes it a data-driven regression. Furthermore, being a stochastic model, GPR can estimate the uncertainty of the prediction (F. Dadashi, Millet, & Aminian, 2013; Zihajehzadeh & Park, 2016b).

Table 4.2: List of 18 features before selection, features 1 to 11 were selected for gait speed estimation method in section 4.3.2, features 1,2, and 5 were selected for walking bout detection method in section 4.4.2

	Feature	Formula
Vertical acceleration	Mean	$x_{k,1} = \frac{1}{N}\sum_{i=1}^{N} a_{f,i}$
	Standard deviations	$x_{k,2} = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}\left\|a_{f,i} - x_{k,1}\right\|^2}$
	Maximum	$x_{k,3} = \max\left(a_{f,i}\right)$
	Minimum	$x_{k,4} = \min\left(a_{f,i}\right)$
	Sum of absolute values	$x_{k,5} = \sum_{i=1}^{N}\left\|a_{f,i}\right\|$
	Sum of squared values	$x_{k,6} = \sum_{i=1}^{N} a_{f,i}^2$
	Maximum of the vertical velocity	$x_{k.7} = \max\left(\int a_f(i)di\right)$
	Mean of the vertical velocity	$x_{k.8} = \text{mean}\left(\int a_f(i)di\right)$
	Minimum of the vertical velocity	$x_{k.9} = \min\left(\int a_f(i)di\right)$
	First dominant frequency	$x_{k,10} = f_{max,1}$
	Amplitude of the first dominant frequency	$x_{k,11} = A_{f_{max,1}}$
	Second dominant frequency	$x_{k,12} = f_{max,2}$
	Amplitude of the second dominant frequency	$x_{k,13} = A_{f_{max,2}}$
Azimuth angular velocity and angle	Mean	$x_{k,14} = \frac{1}{N}\sum_{i=1}^{N} \omega_i$
	Standard deviation	$x_{k,15} = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}\left\|\omega_i - x_{k,14}\right\|^2}$
	Maximum	$x_{k,16} = \max\left(\omega_i\right)$
	Minimum	$x_{k,17} = \min\left(\omega_i\right)$
	Range	$x_{k,18} = \max(\theta_i) - \min\left(\theta_i\right)$

4.3.3 Cross-validation

To evaluate the performance of the algorithm, leave-one subject-out strategy was used. For a given participant, the 10MWTs performed in the clinic by the rest of the participants were used as the training data for gait speed estimation of the 10MWT at clinic by the given participant. The error was estimated as the root mean square (RMS), median, and inter-quantile range (IQR) of the difference of instantaneous gait speed estimated by the algorithm and reference value. If the participant had also performed the 10MWT and daily activities at home, the error for these two settings were also calculated. In the end, the median (bias) and IQR (precision) of each of the three parameters mentioned before were reported for all the participants. None of the measurements performed at home was used as the training dataset.

Bland-Altman plot (Bland & Altman, 2003) was also used to visualize the performance of the algorithm in each of the three settings, i.e. 10MWT at clinic, 10MWT at home, and daily activities at home. Furthermore, the estimated values and the reference values were compared against each other and Pearson's correlation coefficient was reported to present the degree of agreement between these two values.

To demonstrate the impact of the severity of the disease on the estimated parameters, the patients were divided into two groups of mild (EDSS $\leq$ 4.5) and severe (EDSS $\geq$ 5) stage of the disease (Angelini et al., 2020). The gait speed obtained during the three assessment settings was compared between the two groups. Moreover, we compared the RMS error between the two groups, to investigate if the severity of the disease had an effect on the accuracy of the gait speed estimation algorithm. Wilcoxon rank sum test was used to show if there is a significant difference between the two groups. To assess the discriminative power and the effect size of the algorithm in predicting mild or severe stages of the disease, the Cohen's d value was calculated for the gait speed and the 11 features during the 10MWT:

$$d = \frac{\sqrt{2}(\mu_{mild} - \mu_{severe})}{\sqrt{\sigma_{mild}^2 + \sigma_{severe}^2}} \tag{4.4}$$

in which μ_{mild} and σ_{mild} are the mean and standard deviation values of a parameter from the mild group and μ_{severe} and σ_{severe} belong to the severe group.

According to (D. K. Lee, 2016), a Cohen's d value of 0.8 and higher represents a large effect size while a value smaller than 0.4 shows a small effect size.

4.4 Walking bout detection

We have devised two methods to detect the walking bouts or the locomotion periods: one based on a threshold on the gait speed developed from the previous section (GST Method) and the other by a machine learning approach (ML Method) based on the norm of the acceleration.

4.4.1 GST method

We hypothesized that for gait speed values close to zero, the person is at rest and for higher speeds, the person is walking. Therefore, by applying a threshold (v_0) on the gait speed obtained from the previous part, the periods in which the gait speed is higher than v_0 are considered as locomotion while any other periods are considered as rest or non-locomotion. v_0 was fixed as the optimal threshold from the receiver operating characteristic (ROC) curve in the range of 0 to 3 m/s.

4.4.2 ML method

The gravity acceleration (g) was first subtracted from the norm of the accelerometer data (a_s).

$$a_n = \sqrt{a_{s,x}^2 + a_{s,y}^2 + a_{s,z}^2} - g \tag{4.5}$$

A third-order Butterworth filter with a cut-off frequency of 20 Hz was applied on the a_n signal which was divided further into windows of 1 second. With backward elimination method, 3 features were chosen to be extracted from each window k: Mean ($x_{k,1}$), standard deviation ($x_{k,2}$), and sum of absolute values ($x_{k,5}$).

Several classifiers were used by MATLAB Classification Learner toolbox and the classifier with the highest accuracy and a fast speed for training and test was chosen.

4.4.3 Logical rules

To further improve the accuracy of the walking bout classification, two additional rules have been employed:

1) The non-locomotion periods that have less than 3 seconds duration and are between two locomotion periods, should be converted into locomotion.
2) The locomotion periods of less than 3 seconds should be converted into non-locomotion periods.

The biomechanical reason behind these two rules was that a walking period of less than 3 seconds is assumed to do not be a real walking bout (Moufawad el Achkar et al., 2016). Furthermore, a non-locomotion period of less than 3 seconds between two locomotion periods can be considered as a short negligible pause. These two rules were applied respectively after we had estimations from both GST and ML classification methods.

4.4.4 Cross-validation

We used again the leave-one subject-out strategy to train and test the classifier for the ML method, meaning that for each patient, we used the remaining patients' daily activity data to train the classifier and the classifier was tested on the unseen patient. The procedure was repeated as the same number as the participants. As the GST method has a threshold-based approach, no cross-validation was performed. The output classes of the GST method were directly compared to the reference values for all the participants.

The classification results were compared to the reference system and the confusion matrix was obtained. Furthermore, specificity, sensitivity, accuracy, and F1-score were reported for both of the classification methods:

$$\text{specificity} = \frac{TN}{TN + FP} \times 100 \tag{4.6}$$

$$\text{sensitivity} = \frac{TP}{TP + FN} \times 100 \tag{4.7}$$

$$\text{accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \times 100 \tag{4.8}$$

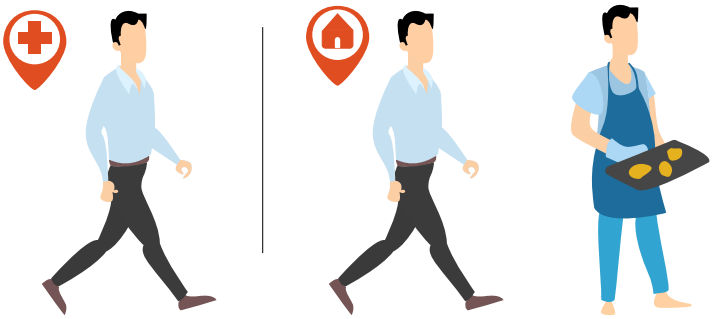
$$\text{F1} - \text{score} = \frac{2TP}{2TP + FN + FP} \times 100 \tag{4.9}$$

In which TP, TN, FP, and FN stand for true positive, true negative, false positive, and false negative, respectively.

4.5 Results

4 out of 18 patients left the study before performing the home assessments. Furthermore, out of 14 patients, only 9 of them performed the daily activity measurements.

For each of the settings, i.e. 10MWT at the clinic, 10MWT at home, and daily activities at home, patients did not perform all the sessions. Therefore, we analysed the data of 49 sessions of 10MWT at the clinic, 96 sessions of 10MWT at home, and 51 sessions of daily activities for all the patients that remained in each setting (Figure 4.2). During daily activities, over 300 hours of measurement were collected from the 9 patients that completed the measurements.



	10MWT	10MWT	DailyActivity
Patients	35	14	9
Sessions	49	96	51

Figure 4.2: The available data for analysis in home and clinical assessments for 10MWT and daily activities. For the 10MWT, there were 35 and 14 patients at the clinic and home, respectively. For the daily activities at home, data from 9 patients was available. Number of sessions shows how many measurements we had in each setting.

4.5.1 Gait speed estimation

The average of the steady-state gait speed, i.e. excluding initiation, termination, and turning of the test for all the 10MWT trials at the clinic and home was shown in Figure 4.3 for the 14 patients that could perform the test also at their home. It can be observed that except patients 11 and 15, all the participants had either a higher gait speed in the clinic, e.g. patients 7, 21, and 27 or a gait speed in the same range as their gait speed at home, e.g. patients 19, 25, and 33.

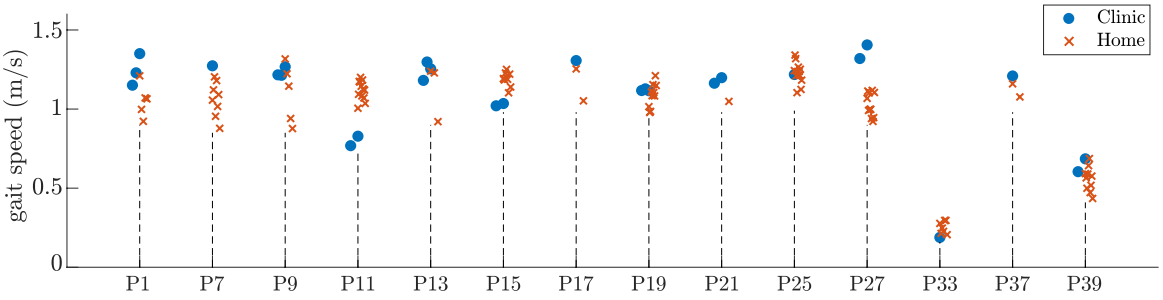


Figure 4.3: Mean values of the gait speed for the 10MWT for participants that could perform the test both at the clinic and home

The vertical acceleration signal along with the corresponding estimated gait speed for the 10MWT at home and also a part of the daily activity is shown in Figure 4.4 for participant number 15 (male, age=43, weight=84 kg, height=184 cm, EDSS=5.5) as an example. It can

be observed that the estimated and reference values are in close agreement (Figure 4.4b and Figure 4.4d). Comparing Figure 4.4b and Figure 4.4d, gait speed has generally higher values during the 10MWT compared to daily activities. The same difference can also be observed in the intensity or the peaks of the vertical acceleration signals (Figure 4.4a vs. Figure 4.4c).

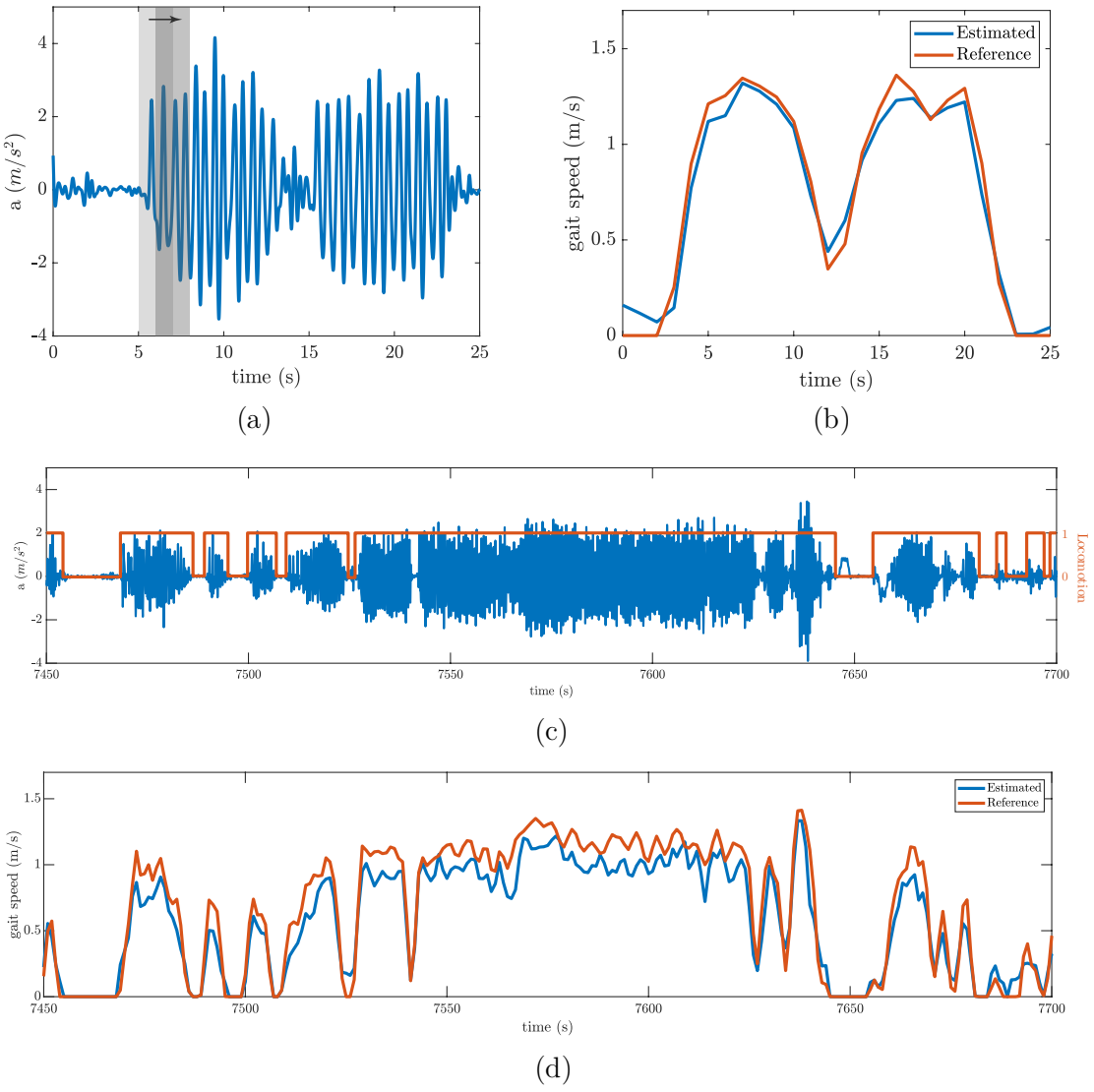


Figure 4.4: Example of the signals for P15 (a) vertical acceleration during 10MWT at home along with two consecutive examples of windows used to extract features. Length of the windows is 2 seconds and they have one second overlap. (b) Estimated versus reference values of gait speed for 10MWT at home (c) Vertical acceleration signal during daily activities with the reference locomotion periods in red. (d) Estimated versus reference values of gait speed for daily activities

Stacking all the participants together, the median and IQR of the error metrics (i.e. RMS, median, IQR) were reported in Table Table 4.3 for three different settings: 10MWT in the clinic, 10MWT at home, and daily activity. For the daily activities, only the walking periods estimated by the reference system were considered. To have an overview of the range of the gait speeds in each setting, the IQR values of the gait speed (V_k) were [0.21, 1.05], [0.24, 1.05], and [0.24, 0.80] m/s for 10MWT in the clinic, 10MWT at home, and daily activities at home, respectively.

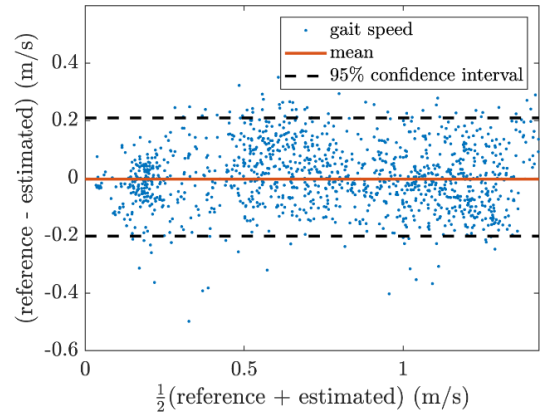
Table 4.3: The RMS, median (bias), and IQR (precision) of the error of the gait speed estimation in m/s. For each of these three parameters the median and IQR values were reported.

	RMS (m/s)		Median (m/s)		IQR (m/s)	
	Median	IQR	Median	IQR	Median	IQR
10MWT at clinic	0.10	[0.08 , 0.12]	-0.01	[-0.04 , 0.03]	0.10	[0.07 , 0.15]
10MWT at home	0.13	[0.11 , 0.14]	-0.02	[-0.06 , 0.04]	0.15	[0.13 , 0.18]
Daily activity	0.15	[0.14 , 0.18]	0.00	[-0.02 , 0.03]	0.15	[0.15 , 0.19]

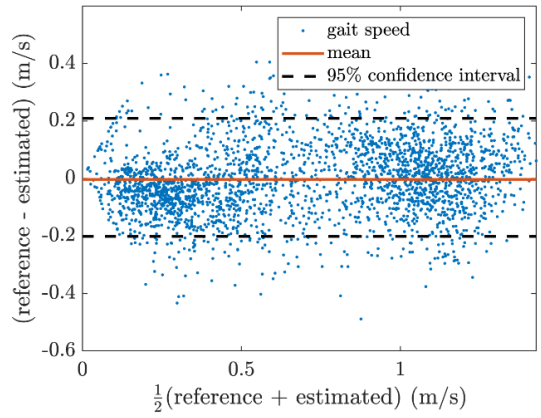
The RMS error of the 10MWT at the clinic was 0.10 m/s and it was increased to 0.13 m/s at home. Furthermore, the RMS error of the predicted values during daily activities at home was 0.15 m/s which was the greatest of the three settings. In general, the IQR of RMS error varied between 0.08 and 0.18 m/s for all the settings and participants. The bias of the estimation error was -0.01, -0.02, and 0.00 m/s for the three settings, respectively. The precision was obtained as 0.10 m/s at the clinic, and 0.15 m/s at home.

The amount of error was illustrated by the Bland-Altman plot (Figure 4.5), stacking all the participants and all the sessions together within each setting. The mean of the error was 0.00, 0.00, and 0.02 m/s for 10MWT at the clinic, 10MWT at home, and daily activities, respectively. Furthermore, the 95% confidence intervals were [-0.20, 0.21], [-0.20, 0.21], and [-0.23, 0.25] m/s, respectively.

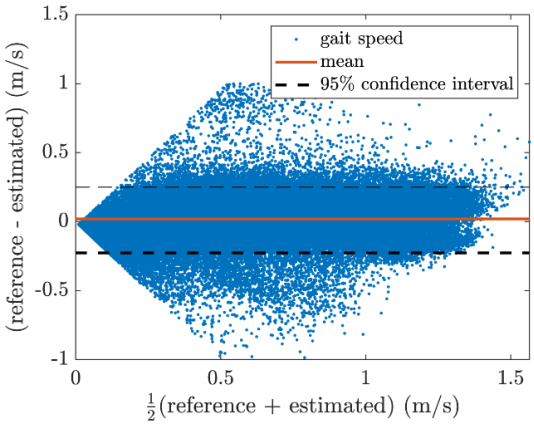
Pearson's correlation coefficients between the estimated values of the gait speed and the reference values were obtained as 0.96, 0.95, and 0.89 for 10MWT at the clinic, 10MWT at home, and daily activities, respectively. It can be noticed that high correlations exist between the predicted and reference values.



(a)



(b)



(c)

Figure 4.5: Bland-Altman plot representing the estimation error of the gait speed in three settings: (a) 10MWT at the clinic, (b) 10MWT at home, (c) Daily activity

After dividing the patients between mild and severe group, their gait speed during the three settings was compared between the two groups (Table 4.4). The Wilcoxon rank sum test showed that the gait speed of the mild group was significantly higher than the severe group for both of the 10MWTs. However, the severe group had a significantly higher gait speed during daily activities at home. Furthermore, the gait speed obtained during the 10MWTs showed a large effect size while the effect size for the daily activities was small (Sullivan & Feinn, 2012).

The RMS error was also compared between the two groups. Wilcoxon rank sum test showed no significant difference between the mild and severe group in none of the settings (10MWT at clinic: p-value=0.31. 10MWT at home: p-value=0.52, Daily activity: p-value=0.90).

To evaluate the discriminative power of the features between mild and severe groups, the Cohen's d value was calculated for each feature and was shown in Figure 4.6. It can be seen that 7 out of 11 features had a large effect size, i.e. a Cohen's d value of 0.8 or higher, according to the criteria given by (Sullivan & Feinn, 2012). Features 5, and 11 ($x_{k,5}$, and $x_{k,11}$) had the highest effect size, while features 8 and 10 ($x_{k,8}$, and $x_{k,10}$) were the lowest among all the features.

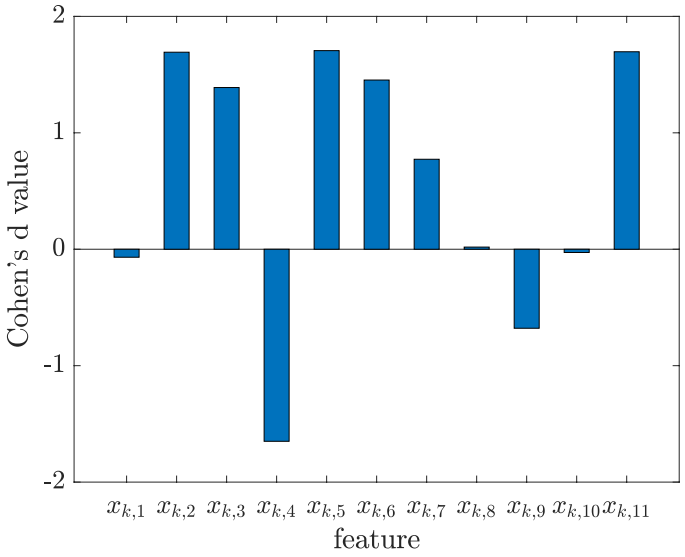


Figure 4.6: The Cohen's d value for each of 11 features chosen for gait speed estimation, the higher the absolute values, the higher the discriminative power of the features between the mild and severe group

*Table 4.4: Comparison of the gait speed estimated by the belt IMU between patients with mild (EDSS≤4.5) and severe (EDSS≥5) stage of the disease, *p-value of less than 0.05 was considered as significant*

	Mild		Severe		Comparison	
	Median (m/s)	IQR (m/s)	Median (m/s)	IQR (m/s)	p-value	Cohen's d
10MWT at clinic	1.20	[1.14 , 1.27]	0.83	[0.58 , 1.02]	<0.001*	1.76
10MWT at home	1.10	[1.00 , 1.21]	1.07	[0.50 , 1.17]	0.007*	1.05
Daily activity	0.50	[0.25 , 0.78]	0.52	[0.24 , 0.86]	<0.001*	-0.16

4.5.2 Walking bout detection

For the GST method, the ROC curve was depicted on Figure 4.7 by varying v_0 from 0 to 3 m/s. The optimal value for v_0 was obtained as 0.11 m/s in which the median sensitivity and specificity were 95.2% and 90.0% respectively. The area under ROC curve (AUC) was 0.98. For $v_0 = 0.11$ m/s, the performance metrics of the detection algorithm for all the subjects were summarized in Table 4.5. The median specificity, accuracy, and sensitivity were above 90% and the median F1-score was 59.3%.

The confusion matrix where the predicted classes of activity (locomotion and non-locomotion) are shown in hours in Table 4.6 for both the reference labels and the predicted labels, demonstrate that out of almost 22.5 hours of locomotion 21.5 hours were detected correctly. However, in addition to those, there were about 25.1 hours that were falsely marked as locomotion. Around 1 hour of locomotion was missed by the GST algorithm.

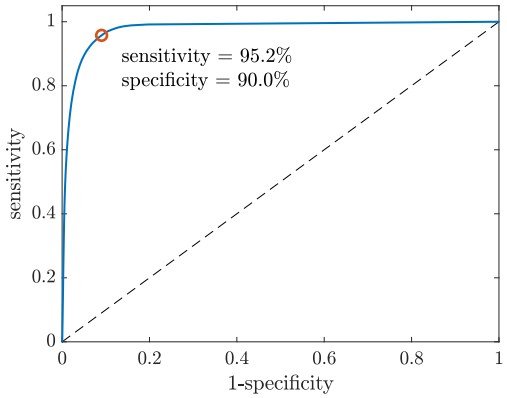


Figure 4.7: The ROC curve for v_0 from 0 to 3 m/s to detect the walking bouts based on the GST method, the optimal value of v_0 was 0.11 m/s

For the ML method, the performance of the several classifiers that were used is shown in Table 4.7. Among these methods, the naïve Bayes classifier was chosen due to its accuracy and computation time. The performance metrics as well as the confusion matrix for the chosen classifier are given in Table 4.5 and Table 4.6, respectively. It can be observed that except the sensitivity, the performance metrics for the ML method were higher than the GST method.

Table 4.5: The performance metrics (in %) of the locomotion detection algorithm for the GST and ML methods

	GST method		ML method	
	Median	IQR	Median	IQR
Specificity	90.0	[86.5 , 96.2]	96.8	[94.1 , 98.8]
Sensitivity	95.2	[94.0 , 95.5]	93.0	[89.2 , 95.7]
Accuracy	90.4	[87.6 , 96.2]	96.4	[94.2 , 98.6]
F1-score	59.3	[56.5 , 64.1]	78.6	[74.2 , 80.5]

Table 4.6: Confusion matrix of the activity classification for the GST and ML methods in hours

		Predicted				Ref.
		Locomotion		Non-locomotion		
		GST	ML	GST	ML	
Ref.	Locomotion	21.5	20.5	1.0	2.0	22.5
	Non-locomotion	25.1	9.2	253.1	269.0	278.2
Predicted		46.6	29.7	254.1	271.0	300.7

Table 4.7: The employed machine learning methods along with their accuracy and processing time for ML method to detect the walking bouts

Method	Accuracy (%)	Training and test time (s)
Decision tree	95.0	48
Linear discriminant analysis	94.6	12
Logistic regression	94.2	35
Naïve Bayes	94.7	16
K Nearest Neighbour (K=10)	95.0	219

4.6 Discussion

The designed algorithm based on a single IMU on the lower back was able to detect walking bouts and predict gait speed in slow and impaired gait such as in MS patients.

We chose the waist location for the IMU, rather than foot or wrist, due to several reasons. As movements during gait concern mostly the lower-limbs, foot or shank can be considered as the most accurate location to attach an IMU for gait assessment. For temporal parameters of gait, e.g. gait cycle time, movements of foot are characterized with features that make the extraction of these parameters more accurate and straight-forward than other locations (Benoit Mariani, Rouhani, et al., 2013). For spatial parameters of gait, e.g. stride length, the existence of zero-velocity update method allows the extraction of these parameters accurately without the drift problem (Benoit Mariani et al., 2010). Therefore, this IMU position can be considered as the most popular placement during lab assessments (Zrenner et al., 2020). However, we need to attach the IMU either by straps around a bare foot or via rubber clips or straps to the shoes. We cannot expect the users to wear their shoes all the time during daily activities. Using straps around their foot might become uncomfortable after some time. Moreover, based on our direct observation by working with patients, sometimes patients are reluctant to wear the IMU on the foot outside the laboratory environment, especially if they intend to go outdoors. Because the sensor might resemble a GPS tracker. To this end, we may sacrifice the accuracy and the number of extracted gait parameters for the sake of comfort of the users and consider wrist or waist placements during daily activities. Wrist IMU has the advantage of being embedded in a smart-watch and might have the least obtrusiveness; however, independent movements of wrist during gait can make the development of the algorithm more challenging (Soltani, Dejnabadi, et al., 2020; Soltani, Paraschiv-Ionescu, et al., 2020). Therefore, the waist placement seems to be a compromise between comfort and accuracy. Because the IMU can be attached easily by a rubber clip to the belt and due to its closeness to the center of mass (Storm et al., 2018; Yang & Hsu, 2010), gait pattern can be captured more accurately than wrist location. Moreover, by using a single IMU on the waist, more information regarding the mobility of the patients can be extracted. For instance, gait

asymmetry (Del Din, Godfrey, & Rochester, 2016) or postural transitions (sit-to-stands or stand-to-sits) (Atrsaei et al., 2020) can be evaluated which might not be possible with wrist IMU for the former and foot IMU for the latter.

In order to estimate the performance of the algorithm, a previously validated wearable system using sensors on feet was used, offering the possibility to validate the new algorithms in supervised (clinic) and unsupervised setting (home and real life conditions).

Gait speed was estimated from the vertical acceleration in the global frame making the algorithm independent of the sensor placement and orientation on the lower back as in practice the sensor placements were done by the patients themselves in unsupervised settings. Two methods were proposed and compared for walking bout detection, one using only the gait speed value and the other based on acceleration norm features and machine learning.

Comparing vertical acceleration signal and its corresponding gait speed revealed the relationship between gait speed and the signal from which the features were derived (Figure 4.4). Higher gait speeds had generally higher intensity in the vertical acceleration obtained by the belt IMU. Gait speed was decreased in the middle of the 10MWT (Figure 4.4b) which shows the moment that the patient reached the marked position (10-meter mark) and had to turn and go back to their original position.

One interesting observation in the vertical acceleration signal during daily activities occurred around the time 7650 s (Figure 4.4c). A pattern of increase, constant, and decreasing positive signal can be seen before the time 7650 s followed by the same pattern in the negative direction after that time. The motion that can be attributed to this pattern is probably being in an elevator in which the acceleration increases to a constant value and decreases back to zero. Please also note that during the first bump (the beginning of the elevator motion), gait speed was estimated as zero despite vertical acceleration signal had some non-zero values when the lift had an acceleration. This shows the efficiency of the frequency-domain features, i.e. $x_{k,10}$ and $x_{k,11}$, as these two features take into account the periodicity of gait. During the second bump (at the end of the elevator motion), the patient has a few steps with low gait speeds inside the elevator.

Using silver standard reference systems, the accuracy of the gait speed estimation algorithm was assessed by several means. The RMS, bias, and precision of the error shown in Table 4.3, indicated that our algorithm could achieve with only a slight decrease in the performance when being validated in home assessments. The RMS error of the estimation was 0.10 m/s in the clinic, and 0.13 and 0.15 m/s at home in 10MWT and daily activities, respectively. Compared to other algorithms (McGinnis et al., 2017) validated in supervised conditions, where the RMS error of the gait speed estimation during treadmill walking in MS patients was 0.12 m/s, our algorithm demonstrated slightly better accuracy. But compared to the reference (Byun et al., 2019), we achieved a lower accuracy as the RMS error of their gait speed estimation was 0.07 m/s. In this study, a model was trained based on a large group of

older adults. Gait speed was obtained by an IMU on the lower back in straight walking tests in the clinic. The authors showed that adding demographic data and anthropometry can reduce the estimation error of gait speed. In (Soltani, Dejnabadi, et al., 2020), an RMS error of 0.05 m/s was achieved based on a personalized algorithm in healthy subjects and in conditions where only walking rather than other activities was included in the protocol. Compared to another study based on an accelerometer on the lower back in which the gait speed in MS patients was overestimated by a bias of 0.12 m/s (R. W. Motl et al., 2012), we achieved a bias of almost zero in all the three settings (Table 4.3).

This was also shown in Bland-Altman plot (Figure 4.5). However, during daily activities, the estimation error was higher for gait speeds lower than 1 m/s (Figure 4.5c). In our opinion, there are two potential explanations for the large errors around the gait speed of 0.5 m/s. One reason can be a lower accuracy of our algorithm during slower walking speeds. While this reason is unlikely as we do not see these large errors around lower gait speeds during clinical assessments, it can be avoided by employing two regression models, one for lower gait speeds, and one for higher gait speeds. For instance, in another study, a low speed-specific model was used for gait speeds of less than 1 m/s to have a more accurate gait speed estimation (Byun et al., 2019). The second reason which is more related to the complex context of the domestic environment, can be due to the slower gait speeds during very short walking bouts, e.g. less than 10 seconds, or activities that involve other tasks rather than gait. During daily activity monitoring, it has been shown in the literature that short walking bouts are generally accompanied by other tasks while longer walking bouts are generally single-task and occur more outdoors (Van Ancum et al., 2019). Furthermore, shorter walking bouts can have slower gait speeds than longer walking bouts (Del Din, Godfrey, Galna, et al., 2016). Therefore, we believe that those large errors around 0.5 m/s can be more related to very short walking bouts that included shuffling or even were wrongly detected as gait. These tasks might potentially affect the accuracy of our silver standard reference as well as the predicted values by the IMU on the belt. To avoid such errors, a constraint on the minimum duration of a walking bout, e.g. 10 or 15 seconds can be set to have a steady-state gait. The funnel shape in Figure 4.5 is because of the instances in which either the reference or the estimated value was close to zero but their difference was slightly higher than zero. Thus, two lines with slopes of ± 2 appeared in this plot. The percentage of the reference and estimated values that were close to zero were 1.5% and 0.2% in Figure 4.5a, 1.1% and 1.4% in Figure 4.5b, and 5.0% and 1.2% in Figure 4.5c.

The correlation analysis between the estimated values and the reference values showed that although there was an excellent agreement between those two, this association decreased in home assessments. This can be due to the different context of the environment at home compared to the clinic, e.g. many obstacles, slopes, turnings in real-life settings.

Several comparisons were performed between the patients with mild (EDSS$\leq$4.5) and severe (EDSS$\geq$5) stages of the disease. Firstly, we noticed that the patients in the mild stage of the

disease had an estimated gait speed higher than the severe group during the 10MWTs (Table 4.4). This states that our method had the potential of predicting the progression of the disease in an objective manner. Decreasing gait speed with the EDSS has also been observed in (McGinnis et al., 2017; Preiningerova et al., 2015; Supratak et al., 2018). The patients in the severe stage of the disease had a higher mean of gait speed during daily activities. This can be because of the small sample size of this setting. Furthermore, large effect size values were observed for gait speed obtained during the 10MWTs performed in clinic and at home, but not for the daily activities. This might be again due to the small number of patients (9) for the daily activity measurements. Analysing the discriminative power of each feature between mild and severe group revealed that features $x_{k,5}$ (sum of absolute values) and $x_{k,11}$ (amplitude of the dominant frequency) had the highest ability in differentiating between the two groups with $x_{k,5}$ being the highest (Figure 4.6). This feature was the sum of absolute values which can be somehow considered as the absolute value of the vertical velocity of the center of mass. Therefore, the gait speed extracted by the IMU along with the features have the potential to help the clinicians monitor the progress of the disease.

Some of the features in Figure 4.6, e.g. $x_{k,4}$ and $x_{k,9}$, had negative Cohen's d values. According to Equation 4.4, a negative Cohen's d value means a higher mean of a feature from the severe group. These two features ($x_{k,4}$ and $x_{k,9}$) belong to the min value of the acceleration and its integration signals. As it can be seen in Figure 4.4, the local minimums of the acceleration signal are negative. Therefore, the severe group of the patients have higher $x_{k,4}$ value and consequently, a lower absolute value than the mild group which is expected as the intensity of the signal is lower for the severe group.

Another interesting observation in Table 4.4 was that for the 10MWT, the severe group had on average higher gait speed in the clinic compared to home. This is in contrast to the moderate group and also to a recent study on patients with Parkinson's disease (PD) that participants had generally higher gait speeds in the 10MWT performed in the clinic (Gaßner et al., 2020). While going into the details of this hot topic of "clinical vs. home assessment" is out of the scope of the current study, there are some explanations for this seemingly contradictory behaviour. The main reason can be due to the fact that individuals behave differently in different settings due to several factors (Warmerdam et al., 2020). Other than sensorimotor system, psychological factors can impact our mobility. For instance, the white-coat effect in which patients perform worse in the clinic is one of these psychological factors (Warmerdam et al., 2020). Sometimes, the presence of an observer might induce stress in the patients causing them to not present their actual capacity. While in the aforementioned study on PD patients (Gaßner et al., 2020), the general trend was a higher gait speed in the clinic, there were a few patients having faster gait speeds at home. It is worth mentioning that in our study, two of the patients, i.e. P11 (EDSS=6.5) and P15 (EDSS=5.5) specifically, were among the severe group that their higher gait speed at home was evident from Figure 4.3. Another probable explanation for this difference can be that the severe group had benefited

more from their rehabilitation in the clinic compared to the moderate group. Because home assessments were performed after the clinical assessments in the rehabilitation center. However, more evidence with a larger dataset is required to confirm this reasoning. Whatever the reasons are for this observation, our method could detect these subtle changes in an objective manner. Furthermore, an unsupervised assessment at home can question the measurements performed in the clinic and help the clinicians have a better insight into the actual capacity of the patients.

For the locomotion detection during daily activities, we introduced two new methods. Both methods showed a specificity, sensitivity, and accuracy of higher than 90% with the ML method being superior in F1-score (78.6% versus 59.3% in GST method). Detecting walking bouts during daily activities can help the clinicians have an objective and more accurate estimation of the activity status of the patients at home. Furthermore, by having the duration of each walking bout, gait speed can be estimated in walking bouts with a specific duration such as the duration that it takes for the patients to perform the 10MWT. When optimizing by the ROC curve, the GST method had higher sensitivity and lower specificity compared to the ML method. One explanation can be that some movements of the lower back can induce a speed for the center of mass; however, these movements might not be actually a walking bout. Therefore, in GST method the predicted walking bouts were almost double the ML method. On the other hand, the GST method depends on the threshold that is being used. For instance, to have a specificity as the same as the ML method, the sensitivity of the GST method drops to 83%.

There are very few previous studies on walking bout detection that validated their algorithms in real-life daily activities. We have achieved comparable sensitivity (93.0% by ML method versus 87.1% in (Soltani, Paraschiv-Ionescu, et al., 2020) and 94.0% in (Anisoara Paraschiv-Ionescu et al., 2019)) and specificity (96.8% by ML method versus 96.7% in (Soltani, Paraschiv-Ionescu, et al., 2020) and 97.0% in (Anisoara Paraschiv-Ionescu et al., 2019)) compared to two studies one on 37 older adults (Soltani, Paraschiv-Ionescu, et al., 2020) and the other on 15 children with cerebral palsy (Anisoara Paraschiv-Ionescu et al., 2019). Regarding the F1-score, we achieved slightly higher performance (78.6% versus 74.9%) compared to the study conducted by (Soltani, Paraschiv-Ionescu, et al., 2020). However compared to another study with 20 older adults (Awais et al., 2019), their proposed method achieved a higher F1-score of 87.1%. One explanation can be using a gold standard system, i.e. camera in their study as the reference system rather than a silver standard reference system as was the case in our study. Having a more accurate reference system can lead to a more accurate classifier. Another explanation for their superior results can be their choice of features as they have used numerous time-domain features from both the accelerometer and gyroscope signal from all the three axes. Although, using features from all the three axes of the sensors may provide additional information about the biomechanics of the movement, it makes the performance of the algorithm dependent to sensor placement changes. Using the

norm of the accelerometer or the vertical acceleration in the global frame (as was the case in our study or in (Soltani, Paraschiv-Ionescu, et al., 2020)) can prevent such dependencies.

The novelty of this work was mainly the method used to train the models to estimate gait speed and detect walking bouts by a single IMU on the lower back. We have used the features stated in the literature while we introduced a novel method to map these features into gait speed and state of activity. This method which is the training by a silver standard reference system, i.e. IMUs on the feet, allowed the estimation of instantaneous gait speed as well as state of activity (locomotion or non-locomotion) by a single IMU on the belt. This new method can have two potential applications: the first one which was shown in this paper, is training of the estimation model in the lab with a multi-sensor system. By having this model, the clinicians can ask the patients to wear only the lower back IMU which is more comfortable and easier to use (due to the reasons mentioned throughout the paper) during assessments at home or outside clinic. The other potential application which can be a future study, is a personalized approach, meaning that patients can be equipped initially with 3 IMUs on the feet and the lower back, and be asked to perform their daily activities while the sensors are recording the data. Once enough walking bouts were measured and a model with a clinically meaningful accuracy was trained, patients can detach the feet sensors and continue their daily activities with only the IMU on the belt. To better clarify the contribution of this study compared to the previous studies with similar machine learning-based algorithms or approaches, we see two main distinctions:

- Our proposed method and algorithms are capable of estimating the instantaneous gait speed rather than a single value gait speed over a trial of walking test as was the case in (Byun et al., 2019; McGinnis et al., 2017; Zihajehzadeh & Park, 2016a, 2016b). This way of gait speed estimation allows the estimation of gait variability during walking tests as well as gait speed distribution during daily activities. Furthermore, opposed to the studies in (Byun et al., 2019; McGinnis et al., 2017; Zihajehzadeh & Park, 2016a, 2016b), we validated our algorithm also during daily activities and walking tests performed in the patients' home.
- Compared to the recent study introduced by (Soltani, Dejnabadi, et al., 2020) which trained their gait speed estimation model by a Global Navigation Satellite System (GNSS) system, we used IMUs on the feet to train the model. Using GNSS signal might face problems related to the strength of the signals received from the satellites, specially, when the patients are indoors, GNSS can have a weak signal acquisition. Moreover, the accuracy of our reference used for gait speed training is higher (an error of 2.4 cm/s from foot IMUs versus an error of 12 cm/s by GNSS).

The first limitation of our study was the small sample size of participants in the daily activity setting. Nevertheless, the dataset was large enough to perform the validation, as we had over 300 hours of daily activity measurements in which 22 hours were locomotion periods. Due to limitations in the materials and equipment as well as the long duration of the home

assessments (12 weeks), half of the patients (18) were given the equipment for the home assessments. From these 18 participants, 4 of them quit the study due to personal and technical issues: one of them got a new job and was not willing to continue the study. Another participant was at a 4-week holiday and decided to stop participating in the study. One of the patients reported a long waiting time for the sensors to be connected to the smartphone by Bluetooth. Therefore, they sent back the system to be repaired. The fourth patient completely forgot to perform the home assessments. Even though text messages had to be sent as reminders to the patients that did not perform the tests on time, sending reminders to this specific patient was overlooked. Furthermore, 5 out of 14 patients did not perform the daily activity part. The fact that this part was not mandatory and patients were asked to perform it in case of possibility can explain the reason.

Among the remaining patients that performed the measurements, some of the sessions were missed or excluded. Around 25% of these sessions belonged to the data that was recorded by the sensors but the protocol of the test was not respected, and 75% of these sessions belonged to missing data. While the exact reason for the missing data is not known to us individually for each session, we assume it can be due to the difficulty of the participants to work with a smartphone other than their own phone, slow connection of Bluetooth, and disruption in data connection to transfer data.

While using a single sensor setup (as was the main goal of this study) rather than a complex multi-sensor system can overcome some of the issues mentioned above, designing a more autonomous system can be helpful. For instance, the IMUs used in this study were being charged through USB cable. A smart charging dock station can be designed instead, to transfer the data from the IMUs memory card to the server automatically while the IMUs are being charged. Moreover, using a faster mean of communication, e.g. WiFi, rather than Bluetooth could improve the connection between IMUs and smartphone. Another problem was that some of the patients did not respect the protocol of the test during the unsupervised assessment. An automated algorithm (e.g. checking the traversed distance or the azimuth angle of the trunk) embedded on the sensors can notify the user immediately if the walking test was not performed correctly. In this case, the user can repeat the test and data loss would be reduced. Finally, recently, there are more and more studies showing the relationship between a walking test performed in the clinic and measurements performed during daily activities. By knowing these relations, clinicians can estimate patients' capacity from daily living assessments without actually performing the clinical gait tests.

While studying the usability of the system was out of scope of the current study, an impartial study can be helpful to investigate the usability and acceptability of such a system among the patients. Because in the end, if we want these wearables to be integrated into clinical assessments of the patients, their usability will have an important role. Another aspect of limitation can be using silver standard methods to validate the algorithms, therefore making the accuracy highly dependent on such methods. To have a more reliable references, walkways

during clinical assessment and annotated videos during daily activities can be used to validate the gait speed estimation and walking bout detection methods, respectively. Finally, we observed relatively large errors around slower gait speeds during daily activities. While we hypothesize these errors can be due to the gait speeds during short walking bouts, more evidence with a larger dataset is required to confirm this assumption and investigate the effect of bout length on the performance of our methods.

In this study, we showed two signals that can be used to make the algorithm independent of the sensor location and orientation when attached to the body as it is important to suppress the need for a functional calibration during daily activities. These two signals were vertical acceleration in the global frame and the norm of acceleration data. The later has the advantage of having less computational and power consumption as it does not use a gyroscope and there is no need to calculate the quaternion. However, in the current dataset, by a quick analysis we obtained higher error for gait speed estimation when we used the norm of the acceleration signal. A more in-depth analysis with a larger dataset is needed to investigate which signal, vertical acceleration or norm of acceleration data has a higher performance in walking speed and duration estimation.

Future work will be focused on the comparison of the gait speed between the clinical and home settings. It would be interesting to see under what conditions during daily activities, the patients can have the same performance as their clinical assessments. This would help us have a deeper understanding of the degree of overlap between supervised and unsupervised assessments.

4.7 Conclusion

This study introduced Gaussian process regression method to estimate the gait speed in clinical as well as home environments using a single IMU at waist. Based on vertical acceleration in global frame, the method was independent on sensor placement on waist. The robustness of the method was guaranteed by dual validation in both supervised gait test and unsupervised daily activities at home. We built a model based on a multi-sensor setup in the clinic, and the model was tested with a simpler sensor setup, i.e. a single lower back IMU at home. Moreover, two methods to detect the walking bouts were presented in which the machine learning-based approach seemed to perform better. This validation study can provide clinicians with an objective tool to assess the mobility performance of the patients in both clinic and home in an unsupervised manner.

Now that an unsupervised assessment of mobility in MS patients seemed feasible, future research is now possible to compare the patients' mobility between supervised and unsupervised settings in both aspects of quantitative, e.g. amount of walking, and qualitative, e.g. walking speed analysis.

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Annex 4.A Gait speed during functional walking test in lab versus home in patients with multiple sclerosis*

4.A.1 Introduction

As we indicated in the first chapter of this thesis, remote patient monitoring (RPM) is gaining more and more attention. RPM can reduce the cost of several hospital visits, saving time for the patients and clinicians. Moreover, RPM can be an alternative option for patients that live in regions with few available specialists. In the main body of Chapter 4, it was observed that some differences exist between the 10-meter walk test (10MWT) performed in the clinic and the 10MWT performed at home. In this annex, we investigate these differences in more details.

10MWT is one of the functional tests that can be performed in the clinic to evaluate mobility or more specifically gait speed of the patients. Inertial measurement units (IMUs) can be used to extract gait speed during this test regardless of the assessment environment. To the best our knowledge, there are not many studies obtaining gait speed during a functional test that is performed both in the clinic and at home. In a study on a group of 47 Parkinson's disease (PD) patients, participants were asked to perform four trials of the 10MWT both in the lab and in the clinic (Gaßner et al., 2020). Comparing gait speed between the two assessments, high correlations were obtained ($\rho = 0.91$). Furthermore, patients generally performed faster in the clinic, i.e. on average 1.14 m/s, compared to home, i.e. on average 1.07 m/s, (p-value=0.004). Therefore, it is important to determine the association between a supervised and unsupervised functional assessment. In this study, we compare the gait speed obtained by a lower back IMU during 10MWTs performed at clinic and at home.

4.A.2 Method

The dataset for this study is the same as the one used in this thesis chapter. 14 of the 35 recruited participants could perform the 10MWT during both clinical and home assessments. The demographic data of these participants have been shown in Table 4.A. 1.

Table 4.A. 1: Demographic data of the participants

Number of participants (female)	14 (8)
Age	51.6 ± 13.3 year
Height	172.8 ± 9.3 cm
Weight	77.2 ± 11.9 kg
EDSS	4.5 ± 1.2 (min = 2.5, max = 6.5)

* Adapted from Atrsaei, A., Mariani, B., & Aminian, K. (2020). Comparison of the gait speed assessed during an instrumented 10-meter walk test at home and clinic in patients with multiple sclerosis. Neurorehabilitation & Neural Repair (NNR) Contributions: developed the algorithm, conducted the data analysis, drafted the manuscript

Participants were equipped with three IMUs (Physilog 5®, Gait Up, CH), one on the waist and two on both feet. Only the IMU on the waist was used for the current data analysis. Each IMU included 3D accelerometer and gyroscope data recorded at a sampling rate of 128 Hz. Participants were also given a smartphone that could provide the patients with the instructions about performing the tests. Moreover, the smartphone was used to connect to the IMUs by Bluetooth to start and stop the measurements and store the data.

By first checking the quality of the data, the measurements that were not recorded completely or the patients did not respect the protocol of the test were removed from data analysis. Next, by the method explained in this chapter, instantaneous gait speed was obtained during each trial of the 10MWT from the belt IMU. For each trial of the test, mean of the steady-state gait speed, i.e. excluding the initiation, termination, and turning within the test was calculated.

For each patient, the mean gait speed of all of their trials for both clinic and home was obtained. Wilcoxon signed rank test was used for a paired comparison between 10MWT at the clinic and 10MWT at home. Moreover, Pearson's correlation coefficient was calculated between the two settings.

4.A.3 Results

For all the patients, the mean of gait speed during 10MWT trials in the clinic and at home is repeated here in Figure 4.A. 1.

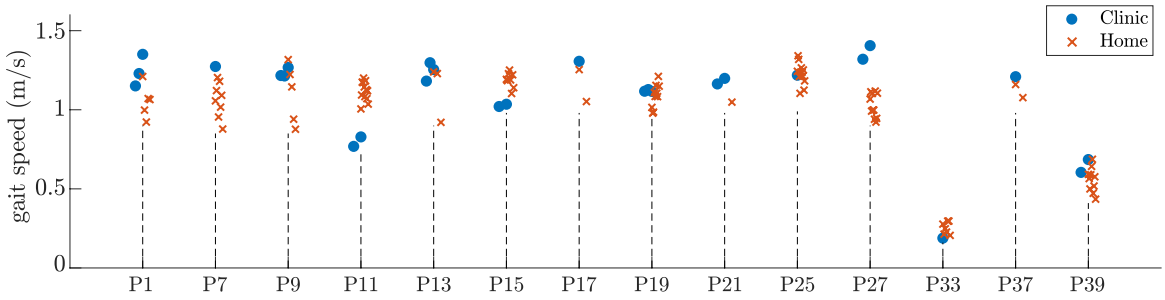


Figure 4.A. 1: Mean values of the gait speed for the 10MWT for participants that could perform the test both at the clinic and home

The mean of 10MWT trials at the clinic versus home is shown for all the patients in Figure 4.A. 2. Generally the trend is toward a faster performance in the lab, except for four participants: P11 (EDSS=6.5), P15 (EDSS=5.5), P25 (EDSS=4.5), and P33 (EDSS=5.5).

Considering all the 14 patients, the Wilcoxon signed rank test showed no significant difference between the two settings (p-value=0.06) Moreover, comparing all the patients, a Pearson's correlation coefficient (ρ) of 0.86 was obtained between clinic and home. These results have been summarized in Table 4.A. 2.

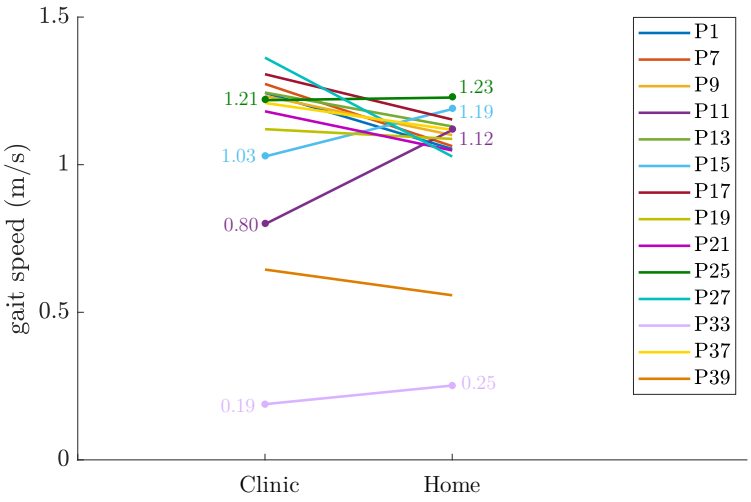


Figure 4.A. 2: Mean of all the trials of 10MWTs performed at clinic and home. In general, most of the patients had a lower gait speed at home.

Table 4.A. 2: Comparison of the gait speed (m/s) obtained during 10MWT performed in the clinic and at home

10MWT at clinic		10MWT at home		Comparison	
Median	IQR	Median	IQR	p-value	ρ
1.21	[1.03 , 1.24]	1.09	[1.05 , 1.13]	0.06	0.86
Fitted line:		$Clinic = 1.04Home + 0.03$			

4.A.4 Discussion

In this study, we compared 10MWT performed in the clinic and at home. By the algorithm developed at the beginning of this chapter, we extracted gait speed during these functional tests. Most of the participants performed faster in the lab and at home. Although, this difference was not significant considering all the patients.

Four participants specifically had on average a better performance (faster gait speed) at home. This supports the fact that environmental and psychological factors can affect the gait performance of the individuals (M. R. Patterson et al., 2014). The reason for a faster gait speed at the clinic might suggest that patients were more focused during their clinical test.

However, this observation did not exist for four of the participants. For participants number 25 and 33, their gait speed at the clinic was almost in the same range as their performance at home (Figure 4.A. 1). As only one trial of the 10MWT at the clinic existed for these two participants (Figure 4.A. 1), further evidence is required for a better conclusion. However, for participants number 11 and 15, their gait speed from all the clinical tests were lower than all

of their tests at home. Several potential reasons can explain this difference. Firstly, as the patients were in the rehabilitation center, these two patients might have benefitted from their rehabilitation program in the clinic. Because the home assessments were performed after the clinical visits. Another explanation can be that these two participants were more cautious in the clinic due to the presence of an observer. Especially that these two participants were in the more severe stage of the MS. Nevertheless, high correlation was obtained between clinic and home ($\rho = 0.86$). This high correlation can also be observed in Figure 4.A. 2 in which the slope of the drop in the gait speed at home is the same for most of the patients. This suggests that nearly the same effect exists for all the patients when they perform the same functional test in an unsupervised manner.

Almost the same findings have been obtained in a similar study on the PD patients (Gaßner et al., 2020); patients performed significantly faster in the lab compared to home while a few of the patients had a higher gait speed at home. Furthermore, high correlation was obtained between these two measures ($\rho = 0.91$). Comparing the fitted line on the clinic-home data, they have obtained almost the same regression line $Clinic = 1.05Home + 0.03$ as ours*. In another study with a different functional test, i.e. the five-time sit-to-stand test measured by a depth camera, high correlation existed between clinical and home assessment of sit-to-stand velocity while participants performed faster in the lab (Ejupi et al., 2015).

Future work should be focused on developing algorithms to automatically check how well the protocol of the test is respected as it is important to consider the factors such as obstacles in the complex context of home environment that can modify the pathway of the patients during the test.

4.A.4 Conclusion

The findings of this study accompanied by the other similar studies suggest that the same functional test in clinic and at home can have a strong correlation while most of the times patients perform better in the clinic compared to home. In spite of this difference, the strong correlation can provide the clinicians with a simple linear regression model to correctly interpret the measurements of the functional tests performed at home. Nevertheless, the data of the participants that does not obey the general trend (like the four participants in our study) can provide additional information. For instance, it can let us know which group of participants are more cautious during clinical tests. Moreover, it might question the assessments performed in the clinic. For example, a patient might not have a good understanding of their true capacity. Therefore, with measurements outside clinical environment, complementary information can be obtained.

* Although the equation of the fitted line has not been explicitly mentioned in their results, digitizing the figure revealed this equation.

Annex 4.B Effect of sensor location on the estimation of walking bout and speed*

4.B.1 Introduction

In the first chapter, we emphasized the importance of having an algorithm that is robust to sensor placement as during the unsupervised assessments, attaching the sensors in the desired way is out of our control. This is an aspect that in the literature has not been heeded when an algorithm for long term monitoring of mobility is developed. There are very few studies evaluating the consistency and agreement between biomechanical parameters when extracted by different locations of the sensors. For instance, (Del Din, Hickey, et al., 2016) extracted several gait parameters from IMUs on chest and waist with an algorithm that had been validated before on an IMU on L5 location. Depending on the parameters being extracted, some had excellent agreement for both of the locations compared to that of the L5 while for some other parameters only one of the two locations, i.e. chest or waist had a good agreement. Very recently, (Tietsch et al., 2020) developed an algorithm to detect steps during walking that is independent of the location of IMU around the waist. They showed that the dominant frequency of the movement during walking can vary between sensor placements especially for the IMUs that are further from the body center of mass.

Therefore, it is necessary to develop algorithms that are ideally independent of the sensor placements, and if not possible, at least evaluate the effect of sensor placement changes to determine the uncertainty of the system when a parameter is extracted. To this end, in this annex, we have studied the effect of changing the location of the sensor on the gait speed estimation and walking bout detection algorithms that were introduced in this chapter.

4.B.2 Method

15 young healthy adults (4 females) were recruited for this study (Dataset A in (Atrsaei et al., 2020)). Participants were 27 ± 3 years old and had 172 ± 8 cm height and 67 ± 14 kg weight. Participants were equipped with four inertial sensors (Physilog 5, Gait Up, CH) at four different locations on the waist and trunk (Figure 4.B. 1): chest (TR), lower back at the area of L5 (L5), anterior superior iliac spine (ASIS), and an arbitrary position on the right hip (RH). Two additional IMUs were attached to both feet to be used as the reference values for gait speed and activity status, i.e. locomotion and non-locomotion. Data from the 3D accelerometer and 3D gyroscope was recorded with a sampling frequency of 128 Hz.

* Some parts of this annex were done under the framework of a semester master project at LMAM (master student Lisa Mareschal).
Contributions: developed the speed estimation and walking bout detection algorithms, collected the data, supervised the project, performed final analysis and interpretation of the results

Barometric pressure sensor from the L5 location was also recording the data with a sampling frequency of 64 Hz.

In the test, 10 minutes recording of daily tasks was performed in a fixed order inside a building: sitting on different chairs and sofas with different heights, walking through different offices, bending to pick up objects from the floor, lying, tying shoe laces, picking objects from the fridge, and using stairs and lift. Subjects were free to move outside the lab and between different offices. The study was approved by the Human Research Ethics Committee of École Polytechnique Fédérale de Lausanne (EPFL), HREC No: 038-2018/09.08.2018 and the subjects were given the informed consent.

Figure 4.B. 1: Location of the IMUs on the waist and trunk

Firstly, to compare the vertical acceleration signal between different sensor placements, the difference between L5 and each of ASIS, RH, and TR positions were calculated. The median and inert-quantile range (IQR) of the differences were calculated for each subject. Moreover, the attenuation coefficient (C_a) was calculated to quantify the differences of the vertical acceleration signals between different placements (Anisoara Paraschiv-Ionescu et al., 2019):

$$C_{a_i} = \left(1 - \frac{\mathrm{RMS}_{a_i}}{\mathrm{RMS}_{a_{L5}}}\right) \times 100 \qquad (4B.1)$$

in which RMS_{a_i} is the root-mean-square of the vertical acceleration at i =ASIS, RH, or TR and $\mathrm{RMS}_{a_{L5}}$ is the root-mean-square of the vertical acceleration signal at L5 location. A negative value for C_a shows the amplification of the signal compared to the L5 location. Furthermore, a close value to zero demonstrates higher similarity between the corresponding location and L5. To investigate the effect of soft tissue artifacts on the differences between sensor placements, the correlation coefficient between C_a and BMI was calculated for all the subjects. We hypothesize that body fat can contribute to higher differences between the signal of the sensors at different locations of the body.

The method described in this chapter was used to estimate gait speed and detect walking bouts. Walking bouts were detected using the ML method described in this chapter. For each

of the 4 sensor placements shown in Figure 4.B. 1, a model was trained to estimate gait speed and detect walking bouts creating 4 different models. Features extracted from the 4 locations were fed into each of the 4 models leading to 16 states. For instance, a model trained by the L5 location was tested on L5 location itself, ASIS, RH, and TR location. The output of the trainings were validated against the reference gait speed values and activity states given by the feet IMUs (Benoit Mariani et al., 2010; Moufawad el Achkar et al., 2016). Leave-one subject-out strategy was used for cross-validation. It has to be mentioned that the periods that included climbing up or down stairs have been removed from training and test as our reference method is not valid during walking on non-flat surfaces. Those periods were recognized by converting the barometric pressure sensor data to altitude changes.

The root mean square error (RMSE) to estimate gait speed as well as F1-score of walking bout detection were calculated for the four models tested on the four sensor locations. F1-score was defined as $(\frac{2\mathrm{TP}}{2\mathrm{TP}+\mathrm{FP}+\mathrm{FN}} \times 100)$ in which TP, FP, and FN stand for true positive, false positive, and false negative, respectively. F1-score was used to be able to fairly compare the results to those obtained in the main body of this chapter about walking detection in the dataset of MS patients. Furthermore, F1-score represents both precision and recall at the same time.

4.B.3 Results

Comparing the vertical acceleration signal between different sensor locations, the median, IQR, and C_a were obtained for each of ASIS, RH, and TR placements compared to L5. For each of these parameters median and IQR were presented (Table 4.B. 1).

Table 4.B. 1: Comparing the vertical acceleration signal of each placement to L5, IQR is the inter-quantile range, C_a is the attenuation coefficient. Median and IQR were calculated from the vertical acceleration signal of the desired location minus the one of L5

Location versus L5	Median (m/s²)		IQR (m/s²)		C_a (%)	
	Median	IQR	Median	IQR	Median	IQR
ASIS	0.00	[0.00 , 0.01]	0.28	[0.23 , 0.33]	-7.21	-[9.23 , 3.81]
RH	0.00	[-0.01 , 0.00]	0.25	[0.21 , 0.30]	-9.13	-[13.15 , 5.57]
TR	0.00	[-0.01 , 0.00]	0.24	[0.21 , 0.29]	-10.5	-[14.40 , 7.44]

The median of the difference between the signals, i.e. the bias, were very close to zero for all the locations while the IQR, i.e. the precision, was in the range of 0.28 for ASIS, 0.25 for RH, and 0.24 for TR location. No statistically significant difference was found for median and IQR between each location (p-value>0.1).

For C_a, all of the values were negative. Although the RH was higher than ASIS and TR was higher than RH values, the difference was not statistically different (Figure 4.B. 2).

The correlation coefficient between C_a and BMI was $\rho = -0.83$ (p-value<0.001) for ASIS, $\rho = -0.87$ (p-value<0.001) for RH, and $\rho = -0.56$ (p-value=0.03) for TR locations (Figure 4.B. 3).

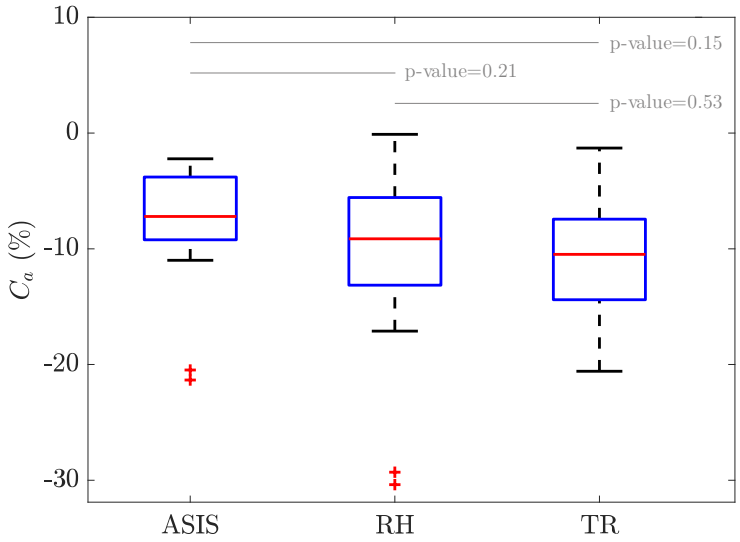


Figure 4.B. 2: The attenuation coefficient (C_a) of vertical acceleration at ASIS, RH, and TR locations with respect to the L5

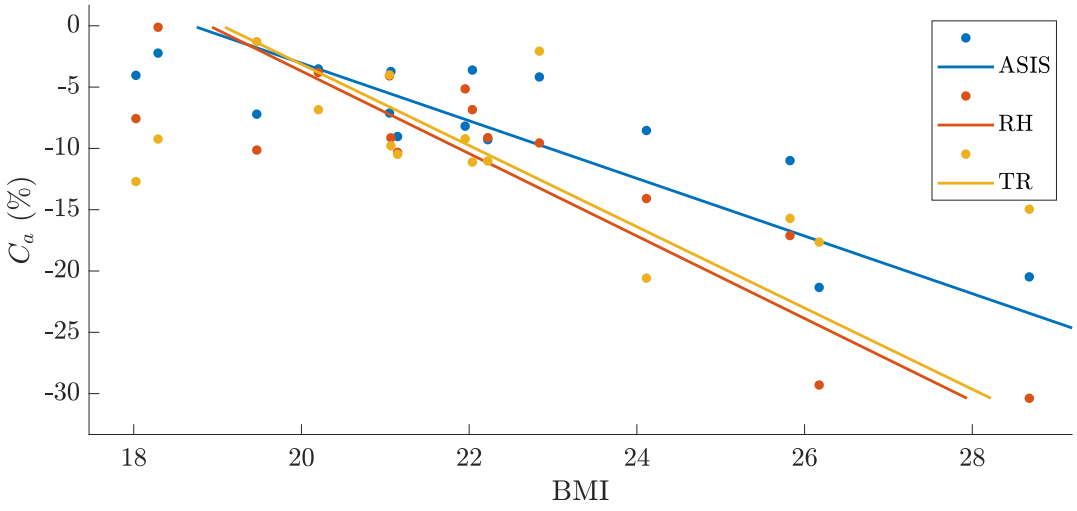


Figure 4.B. 3: The relationship between C_a and BMI for different locations of the sensor

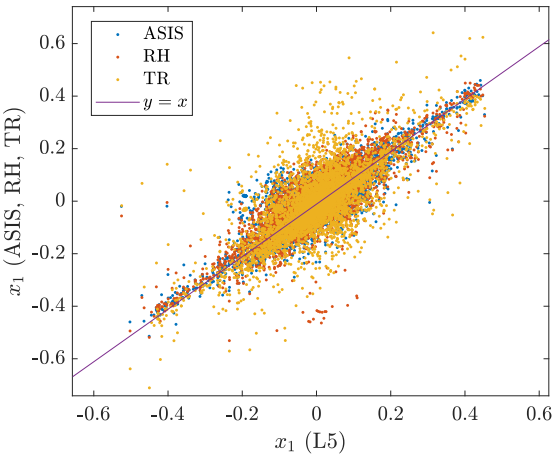


Figure 4.B. 4: Feature 1 (x_1, Table 4.2) from ASIS, RH, and TR versus L5

After removing part of the data that belonged to climbing up and down the stairs and the reference outliers, 1.8 hours of measurement were remained in which 0.8 hours belonged to walking (47%). Comparing the extracted features between different IMU locations high correlations existed between the locations (median ρ of 0.93 and IQR of [0.71 , 0.98]). As an example, the first feature was shown in Figure 4.B. 4 for ASIS, RH, and TR placements compared to L5 location.

The RMSE and F1-score of the models are shown based on testing in different locations in Table 4.B. 2 as well as in Figure 4.B. 5 and Figure 4.B. 6.

For each model, the median of the RMSE varied from -0.02 m/s to 0.03 m/s when the model was tested on a location other than the one by which it had been trained. For instance, for the model that was trained based on RH location, the RMSE was increased to 0.11 when it was tested on other locations and while for ASIS model, the RMSE was decreased to 0.09 when it was tested on RH location. The most accurate training and test belonged to RH location (RMSE 0.09 m/s). Furthermore, when other models belonging to other sensor locations were tested on RH placement they achieved the lowest RMSE. It can be seen from Figure 4.B. 5 that this placement had also the least IQR of error.

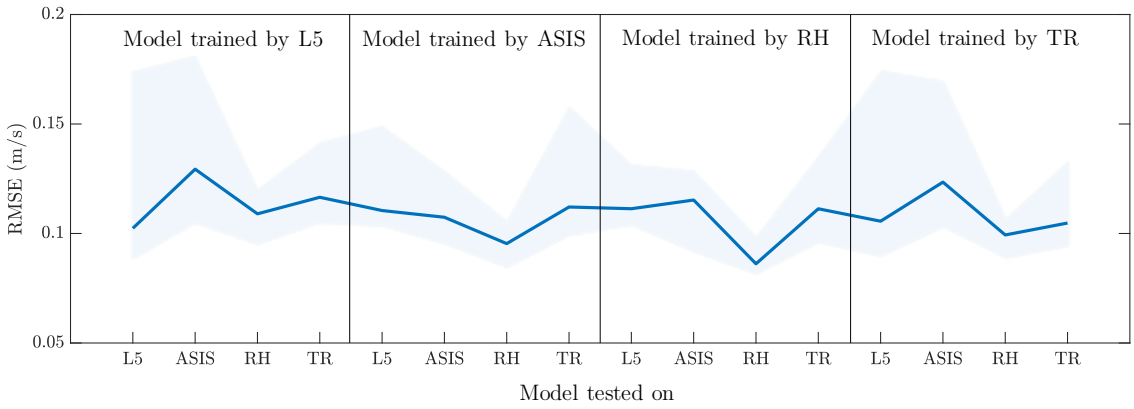


Figure 4.B. 5: Gait speed estimation root-mean-square error (RMSE) based on models on training and testing on 4 different locations of the waist and trunk (Figure 4.B. 1)

Regarding the walking bout detection, the F1-score varied from -3% to 3% when a model was tested for other locations than the one it had been trained with. The highest F1-score belonged to ASIS and RH locations. The most accurate setting was when the model was trained on

ASIS and tested on the same location. The lowest accurate model belonged to TR location. Furthermore, the lowest accurate placement was L5 location regardless of the trained model.

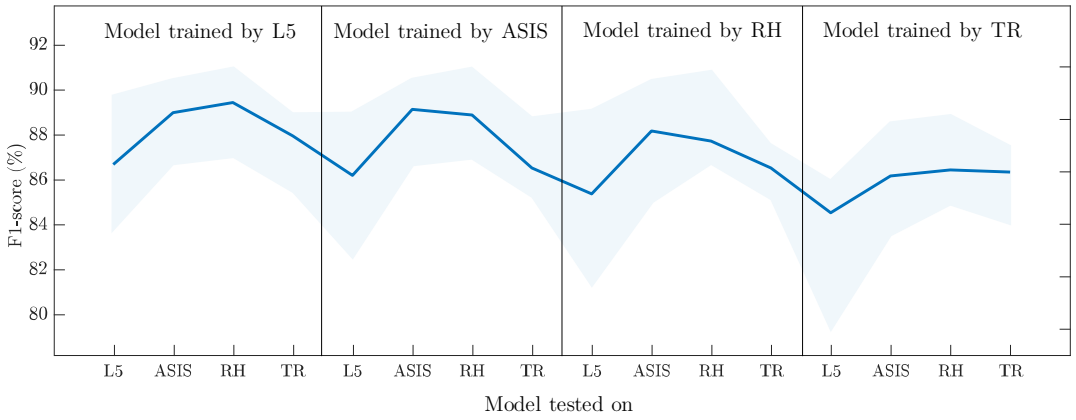


Figure 4.B. 6: F1-score of the walking bout detection based on models on training and testing on 4 different locations of the waist and trunk (Figure 4.B. 1)

Table 4.B. 2: Gait speed estimation root-mean-square error (RMSE) and F1-score of the walking bout detection method based on models on training and testing on 4 different locations of the waist and trunk (Figure 4.B. 1)

		RMSE (m/s)		F1-score (%)	
		Median	IQR	Median	IQR
Model trained by L5 and tested on:	L5	0.10	[0.09 , 0.17]	86.7	[88.8 , 89.7]
	ASIS	0.13	[0.10 , 0.18]	89.0	[86.7 , 90.5]
	RH	0.11	[0.09 , 0.12]	89.4	[87.1 , 90.9]
	TR	0.12	[0.10 , 0.14]	88.0	[85.5 , 88.9]
Model trained by ASIS and tested on:	L5	0.11	[0.10 , 0.15]	86.2	[82.6 , 89.0]
	ASIS	0.11	[0.09 , 0.13]	89.1	[86.7 , 90.5]
	RH	0.09	[0.08 , 0.10]	88.9	[87.0 , 90.9]
	TR	0.11	[0.09 , 0.16]	86.5	[85.3 , 88.7]
Model trained by RH and tested on:	L5	0.11	[0.10 , 0.13]	85.4	[81.4 , 89.1]
	ASIS	0.11	[0.09 , 0.13]	88.2	[85.0 , 90.4]
	RH	0.09	[0.08 , 0.10]	87.7	[86.7 , 90.8]
	TR	0.11	[0.09 , 0.13]	86.5	[85.2 , 87.6]
Model trained by TR and tested on:	L5	0.11	[0.09 , 0.17]	84.5	[79.4 , 86.0]
	ASIS	0.12	[0.10 , 0.17]	86.2	[83.6 , 88.5]
	RH	0.10	[0.09 , 0.11]	86.4	[84.9 , 88.8]
	TR	0.10	[0.09 , 0.13]	86.3	[84.0 , 87.5]

4.B.4 Discussion

Firstly, regarding the comparison of the vertical acceleration signal between different locations, a bias very close to zero was found (Table 4.B. 1), meaning that there was no systematic bias existed between different locations of the trunk compared to L5. However, the IQR was not zero and it was in the range of 0.25 m/s^2.

The attenuation coefficient (C_a) was negative, meaning that all of the ASIS, RH, and TR locations had an amplification compared to the L5 location while this amplification was the lowest for ASIS and the highest for TR, though not statistically significant. This might be because of the closer location of ASIS to L5 and the furthest location of TR to L5. Another reason can be that during gait, the pelvis axial rotation moderates the vertical displacement of the center of mass (Neumann, 2002); thus, pelvis has lower vertical acceleration magnitudes compared to the trunk.

Interestingly, the BMI had a significant correlation coefficient compared to other sensor placements. Having an almost wide range of BMIs in our dataset (Figure 4.B. 3), this shows that the higher the BMI, the higher the absolute value of C_a, and consequently, the lower similarity between the vertical acceleration signals. Therefore, higher body weights can lead to more sensor artifacts and larger distance between the sensors that can lead to larger difference between the acceleration signals. The correlation was high for ASIS and RH locations ($\rho = -0.83$ and $\rho = -0.87$ respectively) while the correlation was medium for TR location ($\rho = -0.56$). This can be due to the fact that while body artifacts can explain the difference between ASIS and L5 or RH and L5, the difference between L5 and TR was more related to the biomechanical modelling of these two locations. The high correlation between BMI and the difference between the signals might suggest that including anthropometric data in machine learning based approaches to estimate gait speed can increase the accuracy of the model.

Extracting the features based on vertical acceleration signal from different IMU locations revealed high correlations between different placements showing high agreement and a potential to estimate the signals between different locations of the trunk.

We trained 4 models based on each IMU placement and as it was shown in Table 4.B. 2, testing the models did not affect the performance of gait estimation and walking bout detection methods introduced in this chapter. A change of maximum 0.03 m/s for gait speed estimation and 3% for walking bout detection was observed in the performance of the proposed algorithm when tested on different locations of the trunk. The most accurate locations to estimate gait speed and detecting walking bouts were the RH and ASIS placements. The reason can be due to the more rigid fixation to the body for these placements (Figure 4.B. 1). Lower F1-score was obtained for L5 and TR locations as L5 IMU was attached by an elastic band to the body of the subjects leading to augmented oscillations during walking. We

hypothesize that the attachment of TR IMU was also not rigid enough resulting in lower performance in detecting the walking bouts.

The performance of our method for gait speed estimation is in the same range as the beginning of this chapter in MS patients' dataset (Table 4.3). Even the RMSE of estimating gait speed in the current annex is less than the results shown in Table 4.3 (0.11 m/s versus 0.15 m/s); the reason might be due to the participants as in the current annex, we used the data of healthy younger adults while the results shown in Table 4.3 belonged to MS patients that had an impaired and slower gait. Furthermore, the protocol of the study in this annex was simpler as the participants were not performing complicated daily activities. On the contrary, the study on participants with MS were carried out in their natural living environment in which the participants could perform more complex daily activities.

The performance of the walking detection method is also higher in this dataset compared to the MS patients' dataset (F1-score of 86.6% versus 78.6%). Beside being healthy, the participants of the current dataset performed a simulation of daily activities rather than natural daily activities. Furthermore, there was a more balanced dataset of locomotion and non-locomotion leading to a better training of the classifier (47% versus 7% locomotion periods).

It should be noted that in addition to the placement of the sensor, its attachment is also important. The attachment of a sensor should be as firm and rigid as possible to avoid movement artifacts. On the other hand, the usability of the system and comfort of the user should not be neglected.

4.B.5 Conclusion

The method that we employed to estimate gait speed and detect walking bouts were robust to sensor placement changes even if there was a high distance between the IMU locations, e.g. sternum (TR) and hip (RH). A maximum drop of 0.03 m/s and 3% in performance was reported to estimate gait speed and detect walking bouts, respectively. This robustness can provide a more accurate and flexible monitoring of gait during unsupervised assessments during daily activities. Indeed providing more flexibility and options for sensor placement is key for applying RPM in real world. Furthermore, we showed that a linear relationship exists between BMI and the similarity between the vertical acceleration signals. This has the potential to better compensate for the errors that are associated with body artifacts and sensor placement changes.

Part III

Clinical Applications

5 Instrumented five-time sit-to-stand test: parameters predicting serious falls beyond the duration of the test

Abstract: Falls are a major cause of injuries in older adults. To evaluate the risk of falls in older adults, clinical assessments such as the five-time sit-to-stand (5xSTS) test can be performed. The development of inertial measurement units (IMUs) has provided the possibility of a more in-depth analysis of the movements' biomechanical characteristics during this test. The goal of the present study was to investigate whether an instrumented 5xSTS test provides additional information to predict multiple or injurious falls compared to the conventional stopwatch-based method. Data from 458 community-dwelling older adults was analysed. The participants were equipped with an IMU on the trunk to extract temporal, kinematic, kinetic, and smoothness movement parameters in addition to the total duration of the test by the stopwatch. The total durations of the test obtained by the IMU and the stopwatch were in excellent agreement (Pearson's correlation coefficient: 0.99) while the total duration obtained by the IMU was systematically 0.52 second longer than the stopwatch. In multivariable analyses that adjusted for potential confounders, fallers had slower vertical velocity, reduced vertical acceleration, lower vertical power, and lower vertical jerk as compared to non-fallers. In contrast, the total duration of the test measured by either IMU or stopwatch did not differ between the two groups. An instrumented 5xSTS test provides additional information that better discriminates among older adults those at risk of serious falls than the conventional stopwatch-based assessment.[*]

[*] Chapter adapted from Atrsaei, A., Paraschiv-Ionescu, A., Krief, H., Henchoz, Y., Santos-Eggimann, B., Büla, C., & Aminian, K. (2021). Instrumented five-time sit-to-stand test: parameters predicting serious falls beyond the duration of the test. Gerontology (under review)
Contributions: developed the postural transition (PT) algorithm, extracted the PT parameters, prepared the results, and wrote the manuscript

5.1 Introduction

Five-time sit-to-stand (5xSTS) test is a well-established test to assess mobility during which the patients are asked to perform five sit-to-stand transitions consecutively (J. M. Guralnik et al., 1994). The test total duration to perform these postural transitions (PTs), traditionally measured by a stopwatch, has been shown to discriminate between patients with and without balance disorders (Whitney et al., 2005). The total duration has also been associated with muscle strength (Lord et al., 2002), as well as an increased risk of future disability and morbidity (Jack M. Guralnik et al., 2000).

The 5xSTS test has also been used to predict the risk of recurrent falls in community-dwelling older adults (Buatois et al., 2008). Falls result from multiple factors, including reduced muscle strength and impaired balance (Ambrose et al., 2013; Bergquist et al., 2019), and occur among one in three people aged 65 years and over (World Health Organization, 2007). Falls prevention has become a major focus as the number of older adults increases worldwide (World Health Organization, 2007). Older adults who perform the 5xSTS test in more than 15 seconds tend to have an increased risk of falls (Buatois et al., 2008). In addition to the total duration of the test, various temporal, kinematic, and kinetic parameters can be extracted from each PT thanks to the inertial measurement units (IMUs) (Atrsaei et al., 2020; Ejupi et al., 2017; A. Godfrey et al., 2011; Lepetit et al., 2019; Najafi et al., 2002; Pham et al., 2018; R. C. Van Lummel et al., 2012; W. Zhang et al., 2017, 2014; Zijlstra et al., 2010). Previous studies have shown that instrumenting the 5xSTS test with IMUs provides more information regarding the health status of the individuals than the traditional stopwatch-based method (Rob C. Van Lummel et al., 2016). Indeed, an instrumented 5xSTS test allows an in-depth analysis of the PTs by knowing their detailed biomechanics (Lepetit et al., 2018; Millor, Lecumberri, Gómez, Martínez-Ramírez, & Izquierdo, 2013; Rob C. Van Lummel et al., 2016). This in-depth analysis is based on the extraction of parameters that lie mostly into temporal, kinematic, kinetic, and smoothness categories (Millor et al., 2014).

The feasibility of such instrumentation has been previously reported (R. C. Van Lummel et al., 2013). Comparing the duration of each PT in younger and older adults, the authors observed that older adults had significantly longer durations in standing up and sitting down. In addition to transition duration, other parameters can be extracted from each PT such as vertical velocity and acceleration (Costantini, Carota, Maccioni, & Giansanti, 2006; R. Ganea et al., 2007), angular range (Atrsaei et al., 2020), angular velocity (Millor, Lecumberri, Gómez, Martínez-Ramírez, & Izquierdo, 2013), jerk (Doheny et al., 2011), and power (W. Zhang et al., 2017). Vertical acceleration is indicative of the upward motion of the trunk; thus, it can be associated with hip extension moment that is required to reach an upright position (Zijlstra et al., 2010). The range of vertical acceleration can differentiate patients with mobility impairments such as stroke from healthy controls (Na, Hwang, & Woo, 2016). Vertical velocity is proportional to the exerted momentum to transfer the body center of mass and can

differentiate successful and unsuccessful attempts of sit-to-stand (Bahrami, Riener, Jabedar-Maralani, & Schmidt, 2000; R. C. Van Lummel et al., 2013). Angular displacement of the trunk determines its range of extension and flexion motion. A low angular velocity of the trunk indicates an inadequate momentum transfer during sit-to-stand transitions (P. O. Riley et al., 1997). For instance, using armrest of a chair as the support can result in lower peak angular velocity during flexion and extension movements (Soangra & Lockhart, 2012). Vertical power as the multiplication of mass, vertical velocity, and vertical acceleration is representative of balance and leg muscle strength (Regterschot et al., 2014; Zijlstra et al., 2010). Finally, jerk, the third derivative of the vertical displacement, characterizes the fluency or smoothness of a movement (Kerr, Pomeroy, Rowe, Dall, & Rafferty, 2013). While it can be an objective measure of coordination and hesitation during a PT, it is associated with aging and risk of falls (Kerr et al., 2013).

It has been shown that frail and non-frail older adults have significant differences in acceleration and angular velocity parameters obtained during repeated sit-to-stand and stand-to-sit transitions (Galán-Mercant & Cuesta-Vargas, 2013). Moreover, several temporal and kinematic parameters extracted during an instrumented 5xSTS test (such as sit-to-stand duration, mediolateral acceleration, and jerk) have been shown to differ between fallers and non-fallers (Doheny et al., 2011, 2013). These studies essentially used mean and coefficient of variation of the temporal and kinematic parameters of all PTs during the 5xSTS test. Another approach would be to see the variation between the first and the last sit-to-stand in the test. This method was evaluated in a recent study where the authors compared the angular velocity of the trunk in the sagittal plane between the first and the last sit-to-stand-to-sit of the 5xSTS test by a dynamic time warping approach. Based on this comparison, they were also able to classify fallers and non-fallers (Ghahramani, Stirling, & Naghdy, 2020).

In previous studies, the added value of an instrumented test has not been directly compared to the stopwatch-based method. For instance, discriminating fallers from non-fallers has not been investigated by the total duration measured by a stopwatch by (Doheny et al., 2013) and (Doheny et al., 2011). It is not yet fully clear which parameters have the most discriminative power to distinguish fallers from non-fallers. Another limitation of these previous studies is that they all used a retrospective assessment of falls rather than a prospective study.

Thus, the present study investigated the added value of instrumenting the 5xSTS test in a large group of older adults with and without prospective falls, i.e. falls that happened after the 5xSTS assessment. Specifically, the total time of the test measured by the IMU was compared to the conventional stopwatch-based method to determine the consistency of these two approaches. Furthermore, the performance of the IMU and stopwatch in differentiating faller and non-faller older adults was compared through several statistical tests.

5.2 Methods

5.2.1 Participants and data collection

Data was obtained from community-dwelling older adults (N=906) who participated in the 2011 follow-up of the ongoing population-based Lausanne cohort 65+ (Lc65+) (Santos-Eggimann et al., 2008). The study was designed as a nested case-control in which the participants underwent the 5xSTS test at their visit to the study center.

The participants were equipped with a Physilog® 3 IMU (Gait Up, CH) that was attached to the sternum. Accelerometer (range ±10g) and gyroscope (range ±900°/s) data were recorded at a sampling rate of 128 Hz. The participants were asked to perform the 5xSTS test as fast as possible. A trained research assistant also measured the total duration of the test by a stopwatch (T_{SW}).

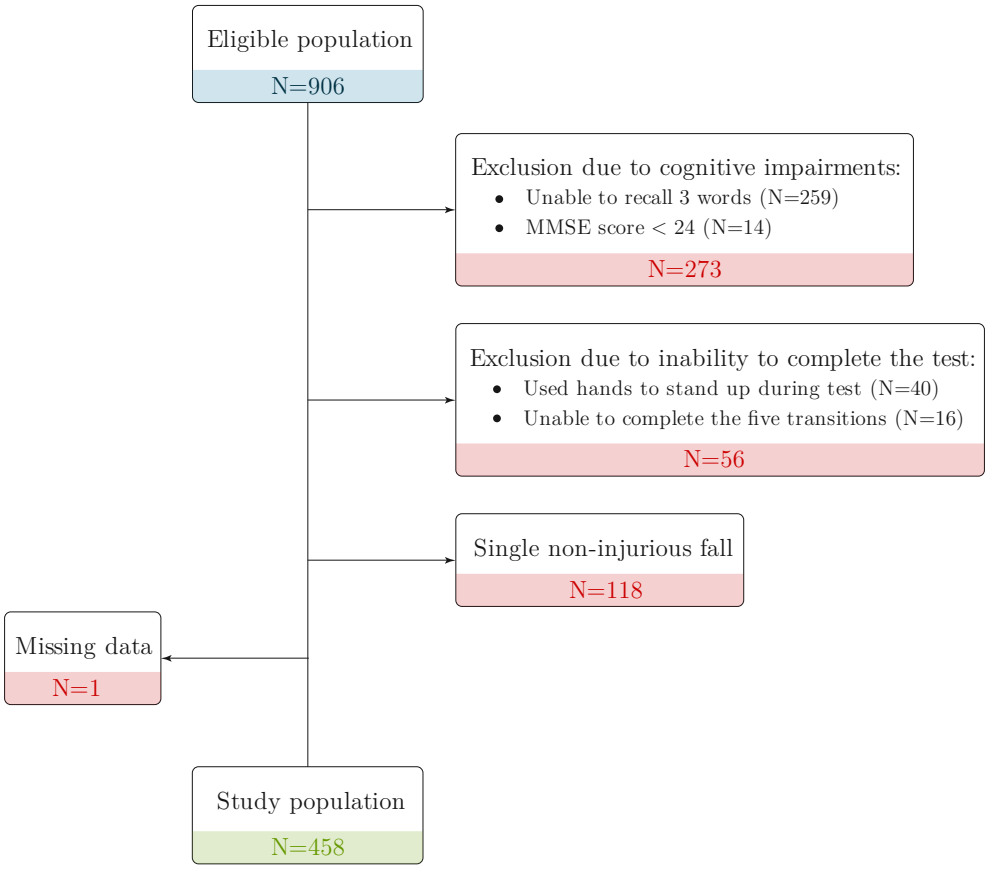


Figure 5.1: Flow diagram of study participants and reasons for exclusion

Falls were assessed prospectively over the 12-month period following the instrumented 5xSTS test. Participants were asked to report their falls and their consequences using a monthly calendar as recommended (Hauer, Lamb, Jorstad, Todd, & Becker, 2006). Fallers were defined

as participants who reported two or more falls or one injurious fall over the 12-month follow-up period (Granbom et al., 2019). Non-fallers were defined as participants reporting no fall. Participants who reported only one fall without injury were excluded (N=118). Participants with cognitive impairment (N=273, defined as a score of less than 24 at the Mini-Mental State Exam (MMSE) or unable to recall 3/3 words from delayed recall domain of MMSE), those unable to perform the 5xSTS test without using their hands (N=40), or unable to complete the 5xSTS test (N=16) were excluded from the analysis. Thus, 458 (50.3%) of the 906 initially eligible participants were included in the analyses (Figure 5.1).

The protocol was approved by the Ethics Committee of the Faculty of Biology and Medicine of the University of Lausanne (Protocol No. 19/04) (Santos-Eggimann et al., 2008). Written informed consent was obtained from the participants. All procedures were in accordance with the 1964 Helsinki declaration and its later amendments.

5.2.2 Signal processing and parameter extraction

Vertical acceleration ($\boldsymbol{a}$) was obtained by transferring the accelerometer data into the global coordinate system and subtracting gravity (Atrsaei et al., 2020). A low-pass Butterworth filter of order 12 with a cut-off frequency of 4.0 Hz was applied to $\boldsymbol{a}$ (Atrsaei et al., 2020). $\boldsymbol{a}$ was integrated to obtain the vertical velocity ($\boldsymbol{V}$). Sit-to-stand and stand-to-sit transitions were detected by the method given by (Atrsaei et al., 2020). Sitting instances were defined as the moments between each stand-to-sit and the next sit-to-stand. During the sitting instances, the vertical velocity can be approximately assumed to be zero. Therefore, the drift of $\boldsymbol{V}$ obtained by integrating $\boldsymbol{a}$ was removed with a linear drift model between two consecutive sitting instance.

As during the 5xSTS test, most of the trunk rotation is around the medio-lateral axis, the principal component analysis (PCA) was applied to the gyroscope data to obtain trunk rotation in the sagittal plane ($\boldsymbol{\omega}$) (Atrsaei et al., 2020). The low-pass Butterworth filter was applied to remove the noise from the $\boldsymbol{\omega}$ signal. A threshold of 7 deg/s was used to determine the beginning and ending of each PT (Atrsaei et al., 2020). The duration of each PT ($\boldsymbol{T_{PT}}$) was obtained by the difference of its start and end (Atrsaei et al., 2020). The mean and standard deviation of the error for this method to estimate $\boldsymbol{T_{PT}}$ are 20 and 229 milliseconds, respectively (Atrsaei et al., 2020).

The total duration of the test by the IMU ($\boldsymbol{T_{tot}}$) was estimated by calculating the difference between the time at the end of the last sit-to-stand and the time at the beginning of the first sit-to-stand. To determine the degree of association between the total duration of the test measured by the IMU and the stopwatch, Pearson's correlation coefficient was obtained. Moreover, to investigate the difference between these two measures (IMU and stopwatch) and its relationship with the total duration of the test, we used the Bland-Altman plot (Bland &

Altman, 2003). The total duration of the rest periods (T_{rest}) that includes four sitting and four standing positions, was calculated as the difference between the total duration of the test and the sum of all the PTs:

$$T_{rest} = T_{tot} - \sum_{i=1}^{N} T_{PT,i} \tag{5.1}$$

in which N is the total number of transitions which is normally 9 (5 sit-to-stands and 4 stand-to-sits).

In addition to T_{SW} and the parameters mentioned above, which were for the whole 5xSTS test (except T_{PT} that was for each PT), several additional parameters were extracted from each PT according to (Atrsaei et al., 2020). The anterior-posterior angular range (θ) was obtained by calculating the change in the tilt angle of the trunk at the start and the end of the flexion phase during a PT (Atrsaei et al., 2020). The error of calculating this parameter is 1.5±3.0 degrees (Atrsaei et al., 2020). The maximum value of ω during each PT was obtained as the peak angular velocity (ω_{max}). The maximum, minimum, and average of the a and V during each PT were also calculated. Power (P) was obtained by multiplying mass (m), a, and V (Atrsaei et al., 2020). Scaled peak power (P_{sc}) was calculated by $P_{sc} = \frac{1000P}{mg\sqrt{gh}}$ in which g is gravitational acceleration and h is the height of the subject. Finally, the derivative of a was obtained as the jerk (j). All of the aforementioned parameters fitted into four categories: temporal, kinematic, kinetic, and smoothness, as summarized in Table 5.1.

Table 5.1: Parameters extracted from IMU within each category

Category	Name of the parameter	Symbol
Temporal	Total duration of the test by IMU (s)	T_{tot}
	Total duration of the rest periods (s)	T_{rest}
	PT duration (s)	T_{PT}
Kinematic	PT anterior-posterior angular range (deg)	θ
	PT peak angular velocity (deg/s)	ω_{max}
	PT maximum vertical velocity (m/s)	V_{max}
	PT minimum vertical velocity (m/s)	V_{min}
	PT average vertical velocity (m/s)	V_{avg}
	PT maximum vertical acceleration (m/s^2)	a_{max}
	PT minimum vertical acceleration (m/s^2)	a_{min}
	PT average vertical acceleration (m/s^2)	a_{avg}
Kinetic	PT maximum vertical power (W)	P_{max}
	PT minimum vertical power (W)	P_{min}
	PT average vertical power (W)	P_{avg}
	PT Scaled peak power	P_{sc}
Smoothness	PT maximum vertical jerk (mm/s^3)	J_{max}

Regarding the parameters extracted for each PT (either a sit-to-stand or stand-to-sit), we discarded the last sit-to-stand transition, thus yielding four sit-to-stand and four stand-to-sit

transitions. This decision was made to cancel the possible effect of misunderstanding the test protocol in some participants that might have performed the last transition with doubt due to the loss of PTs' count.

Next, for four sit-to-stand transitions (and four stand-to-sit transitions) we calculated mean and standard deviation (std). Thus, for all parameters starting with PT in Table 5.1, we had four sub-parameters, two for sit-to-stand and two for stand-to-sit. As a consequence, a total of $3 + 14 \times 4 = 59$ parameters were analysed for each participant. The signal processing and parameter extraction were performed using MATLAB R2019b (MathWorks, US).

5.2.3 Statistical analysis

The goal of the statistical analyses was to show the effect of prospective falls on the parameters extracted by the IMU and the time measured by the stopwatch. For all 59 parameters mentioned above, a bivariate analysis (ANOVA test with Bonferroni correction for multiple comparisons) was performed to determine which parameters differed between fallers and non-fallers. To evaluate the difference, Student's ttest (for normally distributed data) and Wilcoxon rank sum test (for non-normal distributions) were applied. Kolmogorov-Smirnov test was used to check the normality of the distributions. Significance level was set at $p < 0.05$. The Cohen's d parameter was also calculated to obtain the effect size of each parameter in order to evaluate its discriminative power.

A multivariable analysis was performed to adjust for individual characteristics, i.e. sex, height, and body mass index (BMI), that could potentially confound the relationship between each PTs parameter and falling status. A logistic regression model (model A) was applied to determine the odds of being a faller:

$$log\left(\frac{q}{1-q}\right) = c_0 + c_1 x + c_2 sex + c_3 height + c_4 BMI \tag{5.2}$$

in which q is the probability of being a faller; x as a continuous variable is one of the 59 sub-parameters; sex as a categorical variable is "1" if the participant was female and "0" for male; $height$ is a continuous variable concerning the height of the subject; and finally, BMI as a categorical variable is "1" for underweight and normal, "2" for overweight, and "3" for obese (Samuelson, 1997). $c_i, i \in \{0:4\}$ are the model coefficients. It should be noted that in models investigating PTs power parameters (except the scaled peak power), the BMI variable was discarded to avoid collinearity as power already involves the mass of the participant.

Model A (Equation 5.2) tells us if an IMU-derived parameter can differentiate fallers from non-fallers. However, this model does not determine whether it can differentiate fallers and non-fallers that had almost the same total duration of the test measured by the stopwatch. Therefore, we developed an additional logistic regression model (model B) that adjusts for T_{SW} as well as the characteristic confounders. In this way, we can better attempt to isolate

the independent added value of each parameter obtained by the IMU to differentiate between fallers and non-fallers. Within each category of kinematic, kinetic, and smoothness, the parameter with the highest observed effect size was selected. This model (model B) is shown in Equation 5.3.

$$log\left(\frac{q}{1-q}\right) = c_0 + c_1 y + c_2 sex + c_3 height + c_4 BMI + c_5 T_{SW} \quad (5.3)$$

in which y is the parameter from kinematic, kinetic, or smoothness categories obtained by IMU with the highest effect size. The fitted logistic regression model determines whether each of the coefficients in Equation 5.2 or 5.3 are significant or not.

To show the discriminative power of IMU-derived parameters regardless of the total duration of the test, the area under the receiving operating characteristics curve (AUC) was obtained for model B.

Initial selection and extraction of all the parameters of the 5xSTS test within each category was performed by two of the authors who were blind about participants' falling status. Subsequent statistical analyses were performed by a statistician not involved in the initial selection, using Stata 2016 (StataCorp, US).

5.3 Results

A total of 458 participants were included in the data analysis (Figure 5.1). Among these participants, 350 (76.4%) were fallers and 108 (23.6%) were non-fallers. Characteristics of the participants and their comparisons between fallers and non-fallers are shown in Table 5.2. No significant difference was observed in the demographics and anthropometric characteristics in fallers vs. non-fallers.

The trunk angular velocity signal in the sagittal plane (ω) along with the segmentation of the sit-to-stands and stand-to-sits are shown in Figure 5.2. Vertical velocity (V) and acceleration (a) are also shown in Figure 5.2. The velocity obtained by direct integration of a had some drift; however, the drift was removed by assuming linear drift model between sitting periods (Figure 5.2).

The relationship between the total duration of the test estimated by the IMU (T_{tot}) and by the stopwatch (T_{SW}) was investigated in terms of correlation (Figure 5.3a) and difference (Figure 5.3b). T_{tot} and stopwatch T_{SW} were highly correlated (Pearson's ρ of 0.99) as shown by the fitted line in Figure 5.3a. However, a significant average difference of 0.52 second (95% confidence interval -0.33, 1.37) was observed between the two measures (p-value < 0.001), with a longer total duration measured by IMU than by the stopwatch (Figure 5.3b). Overall, 30 participants had a difference larger than 1 second between IMU and stopwatch, more frequently in the direction of a longer duration measured by IMU.

Table 5.2: Characteristics of the participants for fallers and non-fallers

	Population			p-value
	All (N = 458)	Non-faller (N = 350)	Faller (N = 108)	
Number of females (%)	260 (57%)	187 (53%)	73 (68%)	0.009*
Age [years]	74.9 ± 1.4	74.9 ± 1.4	74.7 ± 1.4	0.271
Height [cm]	165.1 ± 8.7	165.5 ± 8.8	163.8 ± 8.2	0.059
Weight [kg]	73.8 ± 14.4	74.2 ± 14.5	72.4 ± 14.3	0.135
BMI	27.0 ± 4.4	27.0 ± 4.3	27.0 ± 4.8	0.684
BMI [number within each class]				
Underweight and normal (%)	156 (34%)	120 (34%)	36 (33%)	0.308
Overweight (%)	200 (44%)	147 (42%)	53 (49%)	
Obese (%)	102 (22%)	83 (24%)	19 (17%)	

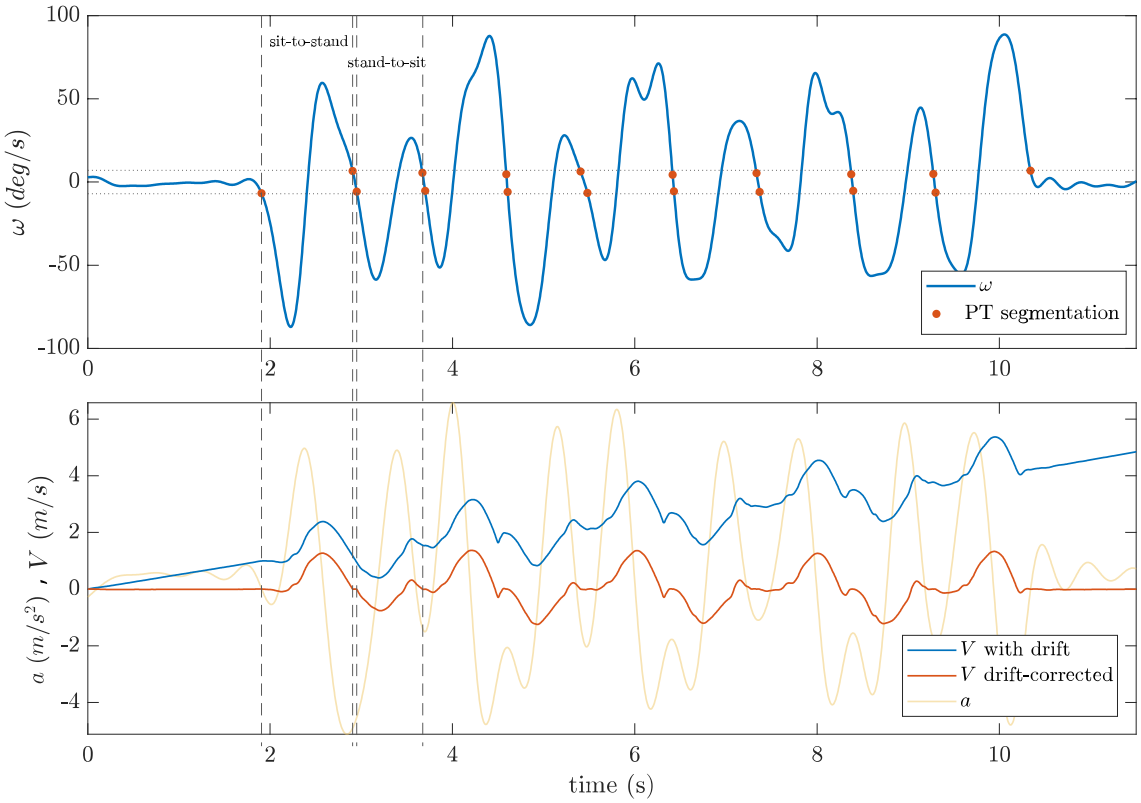
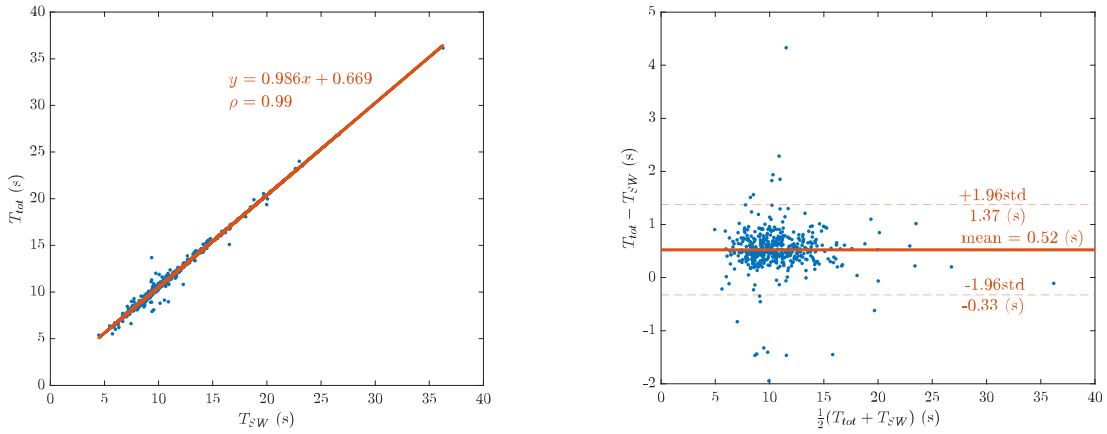


Figure 5.2: The sample IMU signals for one of the participants. The trunk angular velocity in sagittal plane (ω) on the top along with the segmentation of the PTs. The vertical velocity (V) and acceleration (a) are shown on the bottom. The drift from the vertical velocity was removed by linear drift models between each sitting instance.

The difference between the total duration obtained by IMU and stopwatch ($T_{tot} - T_{SW}$) was not different for fallers (mean difference of 0.53 second) and non-fallers (mean difference of 0.52 second), p-value = 0.765.



(a) (b)

Figure 5.3: (a) Correlation between the total duration of the 5xSTS test measured by the IMU (T_{tot}) and stopwatch (T_{SW}) and (b) Bland Altman plot of the differences between the two measures with 95% confidence interval (CI)

The sit-to-stand parameters extracted by the IMU as well as the temporal parameters related to the whole test were compared between fallers and non-fallers in Table 5.3. Table 5.4 presents the same results for stand-to-sit parameters. These tables provide p-values for both bivariate and multivariable (model A, adjusted for sex, height, and BMI) analyses. Cohen's d values for the effect size are also presented for each parameter in these Tables, as well as in Figure 5.4 (in absolute values) to facilitate their comparisons.

Compared to non-fallers, fallers consistently had slower transitions, as measured by all temporal parameters of the whole test, i.e., T_{SW} and T_{tot}, , as well as longer rest time (T_{rest}) (Table 5.3). However, after adjustment for demographic and anthropometric confounders, these differences did not remain significant. The mean duration of sit-to-stand and stand-to-sit transitions (T_{PT}) during the test also did not differ fallers from non-fallers after adjustment.

Regarding the sit-to-stand kinematic parameters, fallers had significantly lower mean of maximum vertical velocity (V_{max}), average vertical velocity (V_{avg}), maximum vertical acceleration (a_{max}), and minimum vertical acceleration (a_{min}) (Table 5.3). After adjustment in multivariable analysis, mean of V_{max}, a_{max}, and a_{min} remained significantly different between the two groups. The variability of a_{min} was significantly lower in fallers.

Table 5.3: Comparisons of parameters extracted by the IMU (for sit-to-stand and the whole test) and stopwatch (T_{SW}) during the 5xSTS test in non-fallers and fallers, with p-values from bivariate and multivariable analyses. For each parameter, the first line shows the mean of the transitions and the second line (in grey) shows their STD.

Category	Par.	Non-Fallers		Fallers		p-value		Effect size
		Median	IQR	Median	IQR	bivar.	multivar.	
Temporal	T_{SW}	9.60	[8.35 , 11.50]	10.55	[9.05 , 11.97]	0.006*	0.296	-0.15
	T_{tot}	10.21	[8.79 , 12.05]	11.30	[9.62 , 12.70]	0.004*	0.275	-0.16
	T_{rest}	0.23	[0 , 0.44]	0.30	[0.16 , 0.51]	0.004*	0.409	-0.10
	T_{PT}	1.11	[0.98 , 1.29]	1.19	[1.04 , 1.34]	0.009*	0.190	-0.19
		0.12	[0.08 , 0.18]	0.12	[0.08 , 0.18]	0.599	0.261	0.11
Kinematic	θ	33.13	[27.48 , 38.94]	32.08	[25.95 , 40.71]	0.533	0.940	0.00
		4.31	[3.07 , 6.217]	4.31	[2.90 , 6.19]	0.507	0.449	0.08
	ω_{max}	60.70	[43.19 , 78.89]	62.54	[47.72 , 89.12]	0.202	0.150	-0.16
		17.88	[11.47 , 25.44]	17.21	[9.79 , 24.94]	0.320	0.434	0.12
	V_{max}	1.12	[0.95 , 1.27]	1.02	[0.90, 1.12]	<0.001*	0.012*	0.36
		0.08	[0.06 , 0.12]	0.07	[0.05, 0.10]	0.040*	0.082	0.20
	V_{min}	-0.09	-[0.14 , 0.05]	-0.14	-[0.17, 0.05]	0.134	0.039*	0.21
		0.04	[0.03 , 0.06]	0.04	[0.03 , 0.06]	0.641	0.918	0.00
	V_{avg}	0.39	[0.32 , 0.49]	0.36	[0.31 , 0.42]	0.009*	0.037	0.30
		0.06	[0.04 , 0.10]	0.06	[0.04 , 0.10]	0.027*	0.124	0.21
	a_{max}	3.80	[2.94 , 4.73]	3.31	[2.54 , 4.26]	<0.001*	0.007*	0.36
		0.39	[0.28 , 0.56]	0.41	[0.25 , 0.55]	0.734	0.521	-0.02
	a_{min}	-4.10	-[3.37 , 4.84]	-3.61	-[3.16 , 4.21]	<0.001*	0.008*	-0.35
		0.48	[0.31 , 0.76]	0.39	[0.26 , 0.58]	0.006*	0.009*	0.18
	a_{avg}	0.05	[-0.04 , 0.16]	0.06	[-0.03 , 0.16]	0.779	0.644	-0.07
		0.06	[0.04 , 0.10]	0.06	[0.04 , 0.09]	0.631	0.854	0.00
Kinetic	P_{max}	189.7	[131.5 , 279.1]	157.2	[108.9 , 206.2]	<0.001*	0.005*	0.41
		30.95	[18.80 , 46.07]	26.92	[18.68 , 38.99]	0.081	0.663	0.15
	P_{min}	-222.6	-[320.4 , 144.1]	-180.6	-[232.2 , 126.0]	<0.001*	0.005*	-0.40
		35.38	[22.78 , 56.18]	26.72	[20.25 , 42.23]	0.004	0.106	0.26
	P_{avg}	2.63	[-0.08 , 5.35]	2.09	[0.17 , 5.29]	0.505	0.637	0.08
		2.10	[1.04 , 3.81]	1.62	[0.94 , 3.68]	0.180	0.607	0.12
	P_{sc}	6.68	[4.71 , 9.26]	5.44	[3.96 , 7.78]	<0.001*	0.004*	0.38
		1.08	[0.68 , 1.60]	1.04	[0.64 , 1.39]	0.230	0.416	0.15
Smoothness	J_{max}	0.50	[0.38 , 0.63]	0.41	[0.34 , 0.53]	<0.001*	0.005*	0.36
		0.09	[0.05 , 0.13]	0.08	[0.05 , 0.13]	0.342	0.374	0.11

Table 5.4: Comparisons of stand-to-sit parameters extracted by the IMU during the 5xSTS test in non-fallers and fallers with p-values from bivariate and multivariable analyses. For each parameter, the first line shows the mean of the 4 transitions and the second line (in grey) shows their STD

Category	Par.	Non-Fallers		Fallers		p-value		Effect size
		Median	IQR	Median	IQR	bivar.	multivar.	
Temporal	T_{PT}	1.09	[0.93 , 1.28]	1.17	[0.98 , 1.36]	0.032*	0.471	-0.11
		0.10	[0.06 , 0.16]	0.10	[0.06 , 0.17]	0.918	0.711	0.02
Kinematic	θ	33.80	[27.70 , 40.55]	33.25	[27.15 , 40.44]	0.507	0.722	-0.02
		4.44	[2.71 , 6.72]	4.11	[2.78 , 5.75]	0.281	0.170	0.15
	ω_{max}	78.67	[65.54 , 94.72]	78.90	[65.30 , 93.84]	0.320	0.817	0.04
		11.03	[7.71 , 15.58]	8.80	[6.42 , 13.70]	0.009*	0.038*	0.23
	V_{max}	0.13	[0.06 , 0.20]	0.15	[0.09 , 0.21]	0.013*	0.005*	-0.32
		0.04	[0.02 , 0.06]	0.05	[0.03, 0.07]	0.0895	0.155	-0.13
	V_{min}	-0.93	-[1.07 , 0.80]	-0.88	-[1.01, 0.74]	0.060	0.221	-0.21
		0.08	[0.06 , 0.13]	0.08	[0.06, 0.12]	0.542	0.622	0.06
	V_{avg}	-0.34	-[0.41 , 0.28]	-0.30	-[0.36, 0.25]	0.001*	0.035*	-0.30
		0.04	[0.02 , 0.06]	0.03	[0.02, 0.06]	0.393	0.320	0.11
	a_{max}	3.64	[2.84 , 4.40]	3.43	[2.69 , 4.13]	0.190	0.494	0.11
		0.46	[0.31 , 0.66]	0.47	[0.33 , 0.69]	0.205	0.235	-0.12
	a_{min}	-3.39	-[2.79 , 4.29]	-3.21	-[2.46 , 3.77]	0.019*	0.08	-0.23
		0.55	[0.31 , 0.85]	0.49	[0.33 , 0.74]	0.361	0.134	0.18
	a_{avg}	0.09	[-0.01 , 0.19]	0.06	[-0.00 , 0.19]	0.682	0.767	0.01
		0.06	[0.04 , 0.12]	0.05	[0.03 , 0.09]	0.004*	0.060	0.22
Kinetic	P_{max}	148.2	[102.9 , 216.2]	125.2	[82.1 , 178.8]	0.012*	0.121	0.28
		31.92	[19.52 , 50.00]	30.01	[19.86 , 46.59]	0.462	0.759	0.11
	P_{min}	-151.8	-[211.9, 106.3]	-136.5	-[177.3 , 92.8]	0.042*	0.476	-0.19
		31.23	[20.18 , 45.45]	29.27	[16.41 , 45.83]	0.244	0.551	0.14
	P_{avg}	-1.49	[-3.90 , 0.80]	-1.10	[-3.54 , 0.68]	0.480	0.560	-0.07
		1.96	[0.91 , 3.70]	1.15	[0.69 , 2.83]	0.003*	0.067	0.25
	P_{sc}	5.50	[3.67 , 6.95]	4.70	[3.08 , 6.46]	0.027*	0.066	0.25
		1.10	[0.71 , 1.62]	1.04	[0.71 , 1.70]	0.648	0.696	0.06
Smoothness	J_{max}	0.67	[0.48 , 0.84]	0.62	[0.41 , 0.77]	0.049*	0.097	0.21
		0.11	[0.07 , 0.16]	0.11	[0.07 , 0.17]	0.672	0.878	-0.02

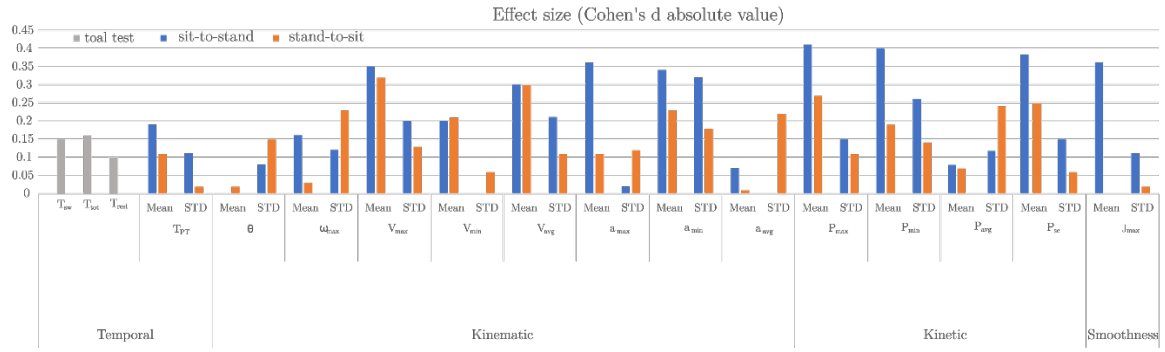


Figure 5.4: Effect size for each parameter extracted from the 5xSTS test

Regarding the stand-to-sit kinematic parameters, fallers had significantly lower variability of peak angular velocity (ω_{max}), including after adjustment in multivariable analysis (Table 5.4). The absolute value of average vertical velocity (V_{avg}) was also significantly lower for fallers by both bivariate and multivariable analyses.

For the kinetic parameters, except the average vertical power, all other kinetic parameters (i.e. mean of P_{max}, P_{min}, and P_{sc}) had significantly lower mean values in fallers in both bivariate and multivariable analyses during sit-to-stand (Table 5.3), but only in bivariate analysis during the stand-to-sit (Table 5.4).

Finally, smoothness measured as the mean of maximum jerk was significantly lower in fallers during both sit-to-stand and stand-to-sit transitions.

Overall, more differences in parameters were observed during sit-to-stand than stand-to-sit transitions across the two groups in both bivariate and multivariable analyses.

According to results presented in Table 5.3, Table 5.4, and Figure 5.4, the mean of the maximum vertical power in sit-to-stand had the highest effect size (Cohen's d = 0.41) among all parameters. Largest effect sizes were observed for the mean maximum vertical acceleration in sit-to-stand (0.36) among kinematic parameters, for the mean maximum vertical power in sit-to-stand (0.41) among kinetic parameters, and for the mean maximum vertical jerk in sit-to-stand (0.36) among smoothness parameters. Therefore, these parameters were used for multivariable model B.

Results of the multivariable model B are presented in Table 5.5. For all three parameters extracted by the IMU, the corresponding coefficients (c_1) were statistically significant whereas the coefficients from the total duration obtained by the stopwatch (c_5) were not. The area under the ROC curve (AUC) is the largest for the mean of maximum vertical acceleration during sit-to-stand in which the sensitivity and specificity were obtained as 56% and 69%, respectively.

Table 5.5: p-values and area under the ROC curve (AUC) for sit-to-stand parameters assessed in the second multivariable analysis (model B)

y	p-value		AUC
	c_1	c_5	
Mean of a_{max} in sit-to-stands	0.010*	0.610	0.63
Mean of P_{max} in sit-to-stands	0.007*	0.569	0.62
Mean of J_{max} in sit-to-stands	0.008*	0.812	0.63

5.4 Discussion

This study investigated whether an instrumented 5xSTS test performed better compared to the conventional stopwatch-based approach in differentiating among faller and non-faller older adults. We defined fallers as those who had serious (i.e., multiple and/or injurious) falls over a 12-month follow-up period. Using a single IMU on the trunk, several temporal, kinematic, kinetic, and smoothness parameters were extracted from the whole test, as well as from each phase of sit-to-stand and stand-to-sit transitions. The algorithm that we employed was based on the angular velocity of the trunk in sagittal plane (ω) to segment the PTs. ω was determined by an automatic PCA applied to the gyroscope signal during the 5xSTS test (Atrsaei et al., 2020). Furthermore, other parameters like V, a, P, and θ were determined from a direct transformation of the IMU signals from the sensor frame to the global frame (Atrsaei et al., 2020; Madgwick et al., 2011). These approaches make the algorithm independent of the orientation and location of the IMU on the chest providing flexibility for the user and the clinician (Atrsaei et al., 2020). Moreover, they eliminate the need for functional calibration as it can be time-consuming and dependent on the performance of the participant's pure movement (Seel, Raisch, & Schauer, 2014; Taetz, Bleser, & Miezal, 2016).

Our results confirm the good performance of the algorithm in detecting the sit-to-stand and stand-to-sit events as the total durations of the test determined by the IMU and by the stopwatch were highly correlated (Pearson's r 0.99, Figure 5.3). Furthermore, the total duration measured by the IMU was consistent with the 12.6-second normative value reported in the literature for a population of older adults between 70 to 79 years old (Bohannon, 2006). Nevertheless, the total duration measured by the IMU was 0.52 second longer than by the stopwatch. Thirty (6.6%) of the 458 participants had a difference over 1 second between IMU and stopwatch. An explanation might likely be the relatively low threshold in detecting trunk motion during PTs using angular velocity (i.e. 7 deg/s according to (Atrsaei et al., 2020)). This makes the system more sensitive compared to a human observer to whom the small movements during the flexion phase of the sit-to-stand might not be perceptible. Similarly, the backward motion of the trunk (extension phase) on the chair when sitting might have been overlooked by the observer. Nevertheless, the difference observed in the current study is well in line with those (0.61 second of IMU-overestimation) reported in another study

(Hellmers et al., 2019). Compared to a very recent study, we achieved better performance, as their IMU-based estimated time obtained a bias of 1.3 s (limits of agreement -2.5, 5.1 s) compared to the stopwatch (C. Park et al., 2021). Furthermore, we used a single IMU rather than 5 IMUs compared to the aforementioned study, providing more comfort and ease for the clinician and the participant.

In the literature, the total time taken to perform the 5xSTS test in fallers has been reported as more than 15 seconds (Buatois et al., 2008; Doheny et al., 2011, 2013; Ejupi et al., 2015; Whitney et al., 2005). In our study, the total time in fallers was 11.30 seconds by the IMU and 10.55 seconds by the stopwatch (Table 5.3). This shorter duration is likely explained by differences in the protocol of the test. For instance, in (Doheny et al., 2011, 2013; Ejupi et al., 2015), from the acceleration signals, it can be seen that their definition of the 5xSTS test included 10 PTs (i.e. 5 sit-to-stands and 5 stand-to-sits). In our study, we defined the protocol with 9 PTs, i.e., one stand-to-sit less. The allowance of rest periods between the PTs can also play a role as in our study, the participants were instructed to stand upright after sitting down and the rest periods were relatively short, i.e. less than 0.5 second in total (Table 5.3).

To compare the IMU and stopwatch in differentiating fallers from non-fallers, we performed several statistical tests. Firstly, the Wilcoxon ranksum test was used to determine the differences between the two groups without adjustments for characteristics and demographics of the participants. Results show that fallers had significantly slower performance than non-fallers when performing the test (T_{tot}=11.30 versus 10.21, p-value=0.004). Cohen's d values that determined the effect size of the parameters revealed that parameters other than the temporal aspect of the test have higher discriminative power. For instance, mean of V_{max} (Cohen's d=0.36), a_{max} (Cohen's d=0.36), P_{max} (Cohen's d=0.41), and J_{max} (Cohen's d=0.36) had higher effect sizes than T_{SW} (Cohen's d=-0.15) or T_{PT} (Cohen's d=-0.19). To isolate the effect of falling from the characteristic and demographics of the participants, we applied a logistic regression model. This multivariable analysis adjusted the model for gender, height, and BMI. Consequently, none of the differences in temporal parameters remained significant after this adjustment. This finding is consistent with previous observations (Doheny et al., 2011) and further highlights the potential interest of using additional parameters beyond the mere duration of the test. Regarding the choice of the potential confounders, it should be noted that the age of the participants were not significant between fallers and non-fallers (Table 5.2). Moreover, our cohort had a quite uniform age (standard deviation of 1.4 years, Table 5.2). Therefore, we did not adjust our model by age. However, gender was significantly different between the two groups (Table 5.2). Height was at the edge of the significance level (p-value=0.059). Furthermore, performance of the individuals during a PT depends on their height and BMI (Baltasar-Fernandez et al., 2021; Bollinger, Walaszek, Seay, & Ransom, 2019). Thus, including gender, height, and BMI in the multivariable model A is reasonable. Nevertheless, we performed the analysis with different combinations of confounders, e.g. gender and height and weight, or gender and height, or gender and BMI.

However, the coefficient of $x = T_{SW}$ in model A (c_1 in Equation 5.2) was not statistically significant in any of these combinations ($p > 0.05$).

A significant contribution of the present study is to provide detailed and mostly original information on other parameters belonging to the kinematic, kinetic, and smoothness categories. Indeed with the help of IMUs and dedicated algorithms, we can extract information from the 5xSTS test that is not possible with a stopwatch. Although a stopwatch has a lower cost than IMU, our results suggest that it might not be sensitive enough to detect subtle differences between groups of participants. Furthermore, as previous studies suggest, while 5xSTS test recorded by a stopwatch has high reliability (Silva, Quintino, Franco, & Faria, 2014), its result can be dependent on the observer's reaction time and experience (Atrsaei et al., 2020; Rob C. Van Lummel et al., 2016). Therefore, using IMU-derived parameters can provide higher reliability and objectivity.

For instance, results of the present study highlight that parameters from sit-to-stand rather than stand-to-sit transitions better discriminate fallers from non-fallers. Compared to non-fallers, fallers had slower vertical velocity, reduced vertical acceleration, lower vertical power, and lower vertical jerk. These findings most likely reflect reduced muscle strength in fallers, as reported in several previous studies (Doheny et al., 2011; Ejupi et al., 2015; Skelton, Kennedy, & Rutherford, 2002), and further highlight the higher need for proper coordination of lower and upper limbs to overcome the gravitational force when standing (Mathiyakom et al., 2005; Watt, Clark, & Williams, 2018). Moreover, results show that the mean of maximum vertical power during sit-to-stand had the best discriminative power (i.e., the highest effect size) in distinguishing fallers from non-fallers among all parameters measured by IMU. This result brings new evidence further supporting a previous observation that muscle strength could be a good marker of falling risk (Pijnappels, van der Burg, Reeves, & van Dieën, 2008). It also extends the findings of another study that compared pre-frail and frail adults and concluded that the peak power had a higher discriminative power compared to velocity and acceleration-based parameters (Millor et al., 2017). However, in that study, the anterior-posterior angular range during the impulse phase of the sit-to-stand had even a higher discriminative impact during the 30-second chair rise test while in our study the effect size of the angular range was almost zero. This suggests that anterior-posterior angular range should be obtained during a specific phase of the sit-to-stand transitions rather than the whole transition as was the case in our study.

The statistical model A adjusted the analysis for gender, BMI, and height as potential confounders. We added the time measured by the stopwatch to this model which resulted in model B. The goal of model B was to isolate the effect of IMU-derived parameters through adjusting the statistical analysis for the total time measured by the stopwatch. In this way, model B treats fallers and non-fallers as if they had the same duration of the test. The coefficient related to the IMU-derived parameters remained significant in model B (c_1 in Table

5.5); therefore, we can conclude that fallers and non-fallers that had the same duration of the test, they could still be significantly differentiated by IMU-based parameters (i.e. a_{max}, P_{max}, and J_{max}). Another conclusion from model B is that opposed to c_1, the coefficient of T_{SW} (c_5) was not significant in any of the three models represented in Table 5.5. This further supports that IMU-based parameters were stronger predictors of falls compared to the total time obtained by the stopwatch.

Despite these encouraging results, the area under the ROC curve (AUC) to discriminate fallers from non-fallers was only 0.63 (sensitivity 56%; specificity 69%) for the mean of maximum vertical acceleration, an unsatisfactory result to apply at an individual level. Yet, this result is still slightly better than those observed with the stopwatch in a previous study (sensitivity 55%, specificity 65%) (Buatois et al., 2008). Another study that used a classification based on IMU-based multiparametric feature selection yielded better sensitivity and specificity (68.7% and 80.0%, respectively) (Doheny et al., 2013). It should be noted that the AUC values in Table 5.5, take only two parameters into account, i.e. the total duration obtained by stopwatch and one of the kinematic, kinetic, or smoothness parameters obtained by the IMU. A combination of IMU-derived parameters could be considered to improve the performance of the model in distinguishing fallers from non-fallers. For instance, in a study of community-dwelling older adults, the AUC value obtained by the sit-to-stand jerk was 0.64 (Qiu, Rehman, Yu, & Xiong, 2018) which is similar to what we have obtained for the same parameter (Table 5.5). The authors of this study improved their classification results by adding other parameters such as sit-to-stand angular velocity, stand-to-sit jerk, and gait speed from the timed-up-and-go (TUG) test. Specificity and sensitivity of around 95% and 93% were obtained by considering all of the mobility parameters obtained by the IMUs during functional tests in the clinic.

Overall, these results emphasize the potential contribution of the instrumented 5xSTS test beyond the temporal parameters to identify serious fallers. Moreover, the observations enhance our current knowledge on transitions' biomechanics and might help to improve training exercises for fall prevention.

Compared to most previous studies (Bergquist et al., 2019; Doheny et al., 2011; R. C. Van Lummel et al., 2013), a clear strength of the present study is the multivariable analysis that adjusted for potential demographic and anthropometric confounders (i.e., sex, height, and BMI) to isolate the independent contribution of each transition parameter. An additional strength is that our study considered only prospective falls whereas most previous studies used retrospective self-reported falls.

Our study has however also some limitations. Our analysis is based on only one measurement at a single time to predict the risk of falls. However, as recent studies suggest, considering other functional tests such as TUG in addition to 5xSTS test can improve the prediction of falls (Qiu et al., 2018). More importantly, the IMUs have the ability to assess the mobility of

the participants also in their living environment which is different than their performance in the clinic (Warmerdam et al., 2020). Therefore, including daily activity mobility assessments provides complementary information to clinical assessments.

Another limitation of the current manuscript is that our analyses mainly focused on parameters based on the vertical displacement of the trunk. Additional parameters such as medio-lateral and anterior-posterior motions during PTs could certainly provide additional information about patients' performance. Finally, we focused on the comparison between recurrent and/or injurious falls as these types of falls put the older adults at even higher risk of subsequent falls (Beauchet, Dubost, Revel-Delhom, Berrut, & Belmin, 2011; Granbom et al., 2019; Pohl, Nordin, Lundquist, Bergström, & Lundin-Olsson, 2014). Therefore, we excluded the participants that had one-time non-injurious falls. The results might slightly differ if we include these participants.

5.5 Conclusion

In conclusion, the instrumented 5xSTS approach presented in this study showed added value over the conventional duration of the test to differentiate older adults with and without prospective serious falls. Among parameters extracted by the IMU, the mean of maximum vertical acceleration, power, and jerk showed the highest effect size but their clinimetric performance remains too limited to be applied at the individual level for clinical decision making. Nevertheless, instrumented 5xSTS provides a more detailed analysis regarding the biomechanics of the patients' movements during the test. Future research can focus on an unsupervised assessment of PTs during daily activities to determine if additional information can be obtained for a better classification of falling risk.

Acknowledgments

The authors would like to thank the people that participated in the data collection of the study. We would also like to thank Hooman Dejnabadi and Lenny Dupourqué for their help in the data acquisition.

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6 Gait speed in clinical and daily living assessments in Parkinson's disease patients: performance versus capacity

Abstract: Gait speed often referred as the 6th vital sign is the most powerful biomarker of mobility. Gait speed can be determined based on data from inertial measurement units and dedicated algorithms either through functional tests in the clinic or during real-life conditions. The goal of this study was to investigate objectively under what conditions during daily activities, patients perform as well as or better than in the clinic. To this end, we recruited 27 Parkinson's disease (PD) patients and measured their gait speed through several walking tests in the clinic as well as their daily activities at home. By fitting a bimodal Gaussian model to their gait speed distribution, we found that on average, patients had similar modes in the clinic and during daily activities. Furthermore, we observed that the number of medication doses taken throughout the day had a significant and moderate correlation with the difference between clinic and home. Performing a cycle-by-cycle analysis on gait speed during the home assessment, overall only about 3% of the strides had equal or greater gait speeds than the respective gait speed assessed in the clinic. These strides were mainly observed during long walking bouts (>1 minute) and happened before noon, around 26 minutes after medication intake, reaching their maximum occurrence probability 3 hours after Levodopa intake. These results open the possibility of better control of medication intake in PD by considering both functional capacity and continuous monitoring of gait speed during real-life conditions.[*]

[*] Chapter adapted from Atrsaei, A., Corrà, MF., Dadashi, F., Vila-Chã, N., Maia, L., Mariani, B., Maetzler , W., & Aminian, K. (2021). Gait speed in clinical and daily living assessments in Parkinson's disease patients: performance versus capacity. npj Parkinson's Disease, 7(1).
Contributions: developed the idea, analyzed the data, performed the statistical analysis, and drafted the manuscript

6.1 Introduction

Motor impairments in Parkinson's disease (PD) are often characterized by tremor, postural instability, and reduced gait speed (J. Jankovic, 2008; Morris, Iansek, Matyas, & Summers, 1998). While the cause of PD is unknown, degeneration of dopaminergic nerve cells is associated with reduced motor function and impaired movement control. Therefore, PD treatments focus on the control of motor and non-motor symptoms using dopamine compensation, mainly with Levodopa, and surgical methods such as deep brain stimulation (Iarkov et al., 2020).

To monitor the progression of disease and symptoms, assessment scales such as the Unified Parkinson's disease Rating Scale (UPDRS) are being used widely by clinicians. Although these scales have been shown to have reliable clinometric characteristics (Ramaker, Marinus, Stiggelbout, & van Hilten, 2002), they cannot be obtained continuously and are dependent on the rater (Heijmans et al., 2019; Ramdhani, Khojandi, Shylo, & Kopell, 2018). More objective assessments can include timed tests in the lab in which gait speed can be calculated by measuring the time taken to traverse a predefined distance by stopwatch, e.g. 20-meter walk test.

With inertial measurement units (IMUs), gait parameters can be obtained accurately providing objective outcome measures (Aminian et al., 2002; Del Din, Godfrey, & Rochester, 2016; A. Godfrey, Del Din, Barry, Mathers, & Rochester, 2015; Benoit Mariani et al., 2010; Zijlstra & Hof, 2003). Based on the IMU signals or derived gait parameters, one can classify early PD (Rehman et al., 2019), investigate subtle differences among PD patients (A. Nguyen et al., 2019), predict freezing of gait (Mancini et al., 2019; Palmerini et al., 2017), monitor PD symptoms (Heijmans et al., 2019), and the Levodopa response (S. T. Moore et al., 2007; Pulliam et al., 2018) in long-term daily activities. Among various gait parameters, gait speed is often considered as the sixth vital sign (Fritz & Lusardi, 2009) and has been shown to be a reliable measure in diagnosis (Rochester et al., 2009) and a marker of functional decline (Brach et al., 2002; S. M. Kim et al., 2018). As this parameter contains both spatial, i.e. stride length, and temporal, i.e. gait cycle time, aspects of gait, it has a strong discriminative power among patient populations (Rehman et al., 2019).

Being wearable, IMUs allow gait to be assessed in both clinical and domestic environments. However, as the International Classification of Functioning Disability and Health (ICF) model suggests, there is a difference between the assessments performed in the clinic which reflects functional capacity and the assessments performed during daily activities, which are more indicative of the actual performance of the individuals (World Health Organization, 2002). For instance, it has been shown that during daily activities, gait speed can decrease by 30% compared to the clinic in PD patients (Toosizadeh et al., 2015). A basic explanation for this different behaviour is that mobility is not only affected by the sensorimotor system but also

by psychological factors (Feltz & Payment, 2005; Kaspar, Oswald, Wahl, Voss, & Wettstein, 2015; Owsley & McGwin, 2004; Warmerdam et al., 2020). Patients are more focused on the task and try to achieve better results in the presence of a clinician than during their actual performance in everyday life (Heijmans et al., 2019). Moreover, the context of the environment is different at home or outdoor where there are multiple obstacles and more complexity compared to the clinical setting (Bock & Beurskens, 2010; Warmerdam et al., 2020). Therefore, unsupervised assessments at home can provide additional information through long-term monitoring (Wuehr et al., 2020). Furthermore, it would also be possible to capture rare incidents such as falls or stage before an injury which may not be measurable during a clinical visit.

Hence, domestic and clinical assessments can be considered as associated but separate domains of physical function (Rob C. Van Lummel et al., 2015). Recent studies have been trying to discover the associations between clinical and home assessments. In a group of PD patients, gait and postural transition parameters were evaluated at the clinic and home (Toosizadeh et al., 2015). It was observed that no significant correlation between clinical and home measurements exists for the patients, even for the same parameter. This study was limited in a sense as for the assessments performed at home, the wide distribution of parameters such as gait speed was condensed to an average value. As a consequence, the large variety of gait speed at home was neglected.

It has been shown that the extreme values of gait or balance parameters of home-based monitoring are more closely associated with the laboratory-based measurements (Rispens et al., 2015; Van Ancum et al., 2019; W. Zhang et al., 2017). In a study, it was observed that the differences between PD patients and healthy older adults become more evident during daily living conditions because of the reduced attentional input in a real-life setting (Del Din, Godfrey, Galna, et al., 2016). However, for some parameters such as gait speed, it has been shown that during free-living conditions, only longer walking bouts could distinguish the two populations. The turning parameters have been also studied in PD patients with and without risk of falls (Haertner et al., 2018). The results of this study suggested that fear of falls affects the turning behaviour of the patients differently in the clinic and at home. The association of the laboratory and home-based measurements with conventional clinical assessments, e.g. the UPDRS, has been also studied. In a large group of PD patients, the authors showed that 46% of the UPDRS variance was explained by the demographic data, clinical and home assessments. From this portion, most of the variance (62%) was explained by daily living measurements (Galperin et al., 2019).

These studies have revealed that there is a difference between the clinical and home assessments even for the same parameter (Warmerdam et al., 2020). The previous studies are mostly based on correlation analysis that showed the association and the difference between clinical and home measurements. Yet, the relationship between these two assessments is not

fully understood. Previous studies have not shown under what conditions these differences between clinic and home are minor. Knowing these conditions, clinicians can have a better estimate of how much extent patients' capacity is being used in real-life.

Therefore, in this study, we aimed towards investigating the conditions in which the clinical and home assessments become closer. More specifically, we focused on the gait speed and we have answered the following two research questions:

1) Do patients with PD have the same preferred gait speed at the clinic and home?

2) Under what condition does the PD patient performance measured by gait speed in free-living conditions reach the capacity measured by gait speed in the clinic?

The novelty of this study is the way we quantified gait speed distribution particularly, during daily activities in PD patients. In previous studies, the distribution has been mostly condensed to one mean and standard deviation values limiting the information we can get from this wide distribution. In this study, by including several walking tests in the clinic rather than a single gait test, we investigated the hypothesis of a bimodal gait speed distribution during both clinical and home assessments. Moreover, we have shown that how the medication state, the time of the day, and the duration of walking bouts can contribute to the difference between capacity and performance. This information can provide a better understanding of the relationship between medication intake and the resulting increase in performance at home compared to the patients' capacity.

6.2 Methods

6.2.1 Participants and study design

A total of 27 participants (11 females, 16 males) diagnosed with PD based on the UK Brain Bank criteria (Daniel & Lees, 1993) were included in the study. Measurements were taken from distinct individuals. Information about demographic data and patients' characteristics was collected from the participants (age: 70 ± 7.7 years, H&Y stage median of 2, disease duration of 7 ± 5 years, the age of disease onset: 63 ± 8.2). UPDRS including the subscales of UPDRS-II and III was obtained during both ON and OFF medication states by a clinician that was not blinded to the medication status of the patients (UPDRS II of 5.6 ± 4.5 during ON medication and 8 ± 5.9 during OFF medication, UPDRS III of 14.3 ± 10 during ON medication and 25 ± 11.8 during OFF medication). The exclusion criteria were being older than 90 years, suffering from dementia or mobility-related health problems other than PD, the inability to walk consecutively for 20 meters, and having a difference of less than 2 between ON and OFF states in the UPDRS-III to take into account minimal clinically significant difference (Shulman et al., 2010). The study was approved by the institutional review board of Centro Hospitalar Universitário do Porto (Porto, Portugal) and was performed in

agreement with the WMA Declaration of Helsinki's Ethical Principles for Medical Research Involving Human Subjects ("World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects," 2014). Written informed consent was collected from all the patients before their participation.

6.2.2 Clinical assessments

Patients were evaluated first at OFF state which occurred at least 12 hours after their last medication intake. The patients were equipped with RehaGait (Hasomed GmbH, DE) with IMUs on each foot. After at least one hour from their medication intake, patients were considered to be in their ON medication state and were evaluated again. During each medication state, they were asked to perform a 20-meter straight walk test at convenient and fast speed as well as circular walking tests (1080° around a circle) at both left and right directions. However, due to the difficulties of the patients to complete the straight walking test at fast speed, this test was skipped during OFF. The clinical gait assessments are summarized in Table 6.1.

Table 6.1: Clinical gait tests

ON state	OFF state
20-meter straight walk test at convenient speed	20-meter straight walk test at convenient speed
20-meter straight walk test at fast speed	
Circular walk test at left direction	Circular walk test at left direction
Circular walk test at right direction	Circular walk test at right direction

6.2.3 Home assessment

The next day, patients came to the hospital again around 9:00 in the morning to be equipped with Physilog® 5 (Gait Up, CH) IMUs on the right foot. The patients were asked to go back home and perform their daily routine activities for one day. It should be noted that patients were allowed to go outside home and perform their usual daily activities. Therefore, "home assessment" can also include daily activities that had been done outside their living space. The sensors were programmed to start recording automatically at 10:00 for 12 hours, i.e. until 22:00. The patients recorded the time of their medication intake in a diary. Based on their diary, we have assumed and defined the ON state periods as starting one hour after taking the medication and lasting for a period of two hours and the OFF state periods starting half an hour before taking the medication and lasting for a period of one hour (Nelson et al., 1989; Rastgardani, Armstrong, Gagliardi, & Marras, 2018).

6.2.4 Gait speed and walking bout extraction

For all of the clinical gait tests mentioned in Table 6.1, the raw data of gyroscope and accelerometer from both of the feet were used. To have a more steady-state gait, the first and last two strides were discarded. With a previously validated algorithm (Benoit Mariani, Jiménez, et al., 2013), gait speed was obtained for each gait cycle by the right foot IMU. Since each of the clinical tests (Table 6.1) contained only one walking bout, no analysis regarding the detection of walking bouts was made as opposed to the home assessment. In addition to the gait speed for each gait cycle, the mean value of the gait speed throughout the test was also calculated.

For home assessments, first, the walking bouts were detected using the angular velocity signal (Moufawad el Achkar et al., 2016). To have enough steps within each walking bout, the walking bouts that had a duration of less than 15 seconds were discarded. This was done to prevent detecting other movements than gait that can wrongly impact our analysis. Furthermore, removing very short walking bouts let us have a more steady-state gait during daily activities. Next, within each walking bout, gait speed was calculated for each gait cycle (Benoit Mariani, Jiménez, et al., 2013). Gait cycles with a speed of less than 0.2 m/s were discarded as these could potentially be a break.

Walking bouts were divided into short (duration between 15 and 30 seconds), medium (duration between 30 and 60 seconds), and long (duration of more than 60 seconds) bouts.

6.2.5 Distribution of gait speed at the clinic and home

To obtain a distribution for the gait speed, all the gait cycles were considered for each clinical and home setting. There is some evidence in the literature for a bimodal Gaussian distribution during daily-life gait speed (Van Ancum et al., 2019) and cadence (Brodie et al., 2017). As in the current study we had performed several clinical gait tests in various conditions, we considered the following bimodal distribution $f(x)$ for each of the clinical and home assessments.

$$f(x) = c_1 \exp\left(-\frac{1}{2}\left(\frac{x-\mu_1}{\sigma_1}\right)^2\right) + c_2 \exp\left(-\frac{1}{2}\left(\frac{x-\mu_2}{\sigma_2}\right)^2\right) \quad (6.1)$$

in which x is the gait speed distribution, c_1 and c_2 determine the amplitude, μ_1 and μ_2 are the means presenting the preferred lower and higher gait speed (Van Ancum et al., 2019), and σ_1 and σ_2 are the standard deviations from each of the means.

MATLAB's fitgmdist function was used to fit the Gaussian models. Ashman's D was calculated to quantify the fitting quality. A value of greater than 2 is indicative of a bimodal distribution (Ashman, Bird, & Zepf, 1994).

The two means and standard deviations were compared together between clinical and home assessments using two-sided ttest for normally distributed data or Wilcoxon sign rank test for data that did not follow a normal distribution. One-sample Kolmogorov-Smirnov test was used to test for the normality of data. Pearson's correlation coefficient with the criteria given in (Mukaka, 2012) for low, moderate, and high correlations was also obtained.

To observe the differences between the preferred gait speeds at clinic ($\mu_{1,clinic}$, $\mu_{2,clinic}$) and at home ($\mu_{1,home}$, $\mu_{2,home}$), we defined two parameters $\Delta_{\mu_1}$and Δ_{μ_2}that represent the percentage of difference between clinic and home for μ_1 and μ_2, respectively.

$$\Delta_{\mu_1} = \frac{2(\mu_{1,clinic} - \mu_{1,home})}{\mu_{1,clinic} + \mu_{1,home}} \times 100 \tag{6.2}$$

$$\Delta_{\mu_2} = \frac{2(\mu_{2,clinic} - \mu_{2,home})}{\mu_{2,clinic} + \mu_{2,home}} \times 100 \tag{6.3}$$

We obtained Pearson's correlation coefficient between number of doses and Δ_{μ_1} and Δ_{μ_2} considering all the patients.

Furthermore, the cumulative distribution function of gait speed at the clinic (CDF_{clinic}) as well as home (CDF_{home}) were determined for each patient. Receiver operating characteristic (ROC) curve was obtained for each patient by considering CDF_{home} as the x axis and CDF_{clinic} as the y axis. Finally, for each patient, the area under the ROC curve (AUC) was calculated. An AUC value close to 0.5 means that the clinical and home assessments have the same gait speed distribution while a value closer to 0 (or 1) means that the probability of having a gait speed less than a specific value is higher at home (or in the clinic).

6.2.6 Capacity vs. Performance (Exceptional Strides)

For each patient, their average gait speed during the 20-meter walk test with fast speed (at ON medication) was obtained and taken as their capacity (V_c). To investigate when patients reach their capacity V_c or go beyond it during daily activities, for each stride k, its gait speed ($V_{h,k}$) was compared to V_c and if it was greater or equal than V_c, it was marked as an Exceptional Stride and the following information was extracted for that stride:

- Time of occurrence (t_k)
- Its time difference compared to the last medication intake ($t_k - t_c$)
- Whether it happened during ON state or OFF state (MED_k)
- The duration of its corresponding walking bout ($T_{WB,k}$)
- Whether it happened during short, medium, or long walking bout (WB_k)

- Its gait speed difference compared to V_c ($V_{h,k} - V_c$)

To correct for measurement errors, a threshold of 0.1 m/s was used when comparing $V_{h,k}$ and V_c to obtain the Exceptional Strides.

The impact of the status of PD on the percentage of Exceptional Strides over the total number of strides for each patient was examined. We calculated the correlation coefficient between the amount of Exceptional Strides and UPDRS-III (at OFF medication) as well as the correlation coefficient between the amount of Exceptional Strides and number of medication intakes during the day.

6.3 Results

6.3.1 Distribution of gait speed at the clinic versus daily activities

The mean gait speed during clinical assessments was compared to the distribution of the gait speed at home for all the patients (Figure 6.1). The average value of the 20-meter walk test with fast speed, considered as the capacity of the patients, were near to or even higher than the maximum values of the gait speed measured at home. Furthermore, the average value of the circular walking tests was lower than the other clinical assessments. The average duration of the straight walking tests for all the patients was 18.5 ± 3.8 seconds.

For a typical patient, the histogram of the gait speed as the probability density function distribution is shown in Figure 6.2 along with the fitted Gaussian mixture models during daily activities and all the clinical assessments. The bimodal distribution of the gait speed at both home and clinic can be inferred from this figure. The patient had two preferred gait speeds, a lower (μ_1) and a higher one (μ_2) during both clinical and home assessments. The standard deviations from these two preferred speeds were denoted by σ_1 and σ_2. For this specific patient, the preferred gait speeds at home (0.44 and 0.83 m/s) were close to the preferred speeds at the clinic (0.45 and 0.90 m/s).

For the clinical measurements, the distribution was also shown coloured with the type of the test. The circular walking tests constructed the left part of the distribution and the straight walking tests constructed the right part of the distribution.

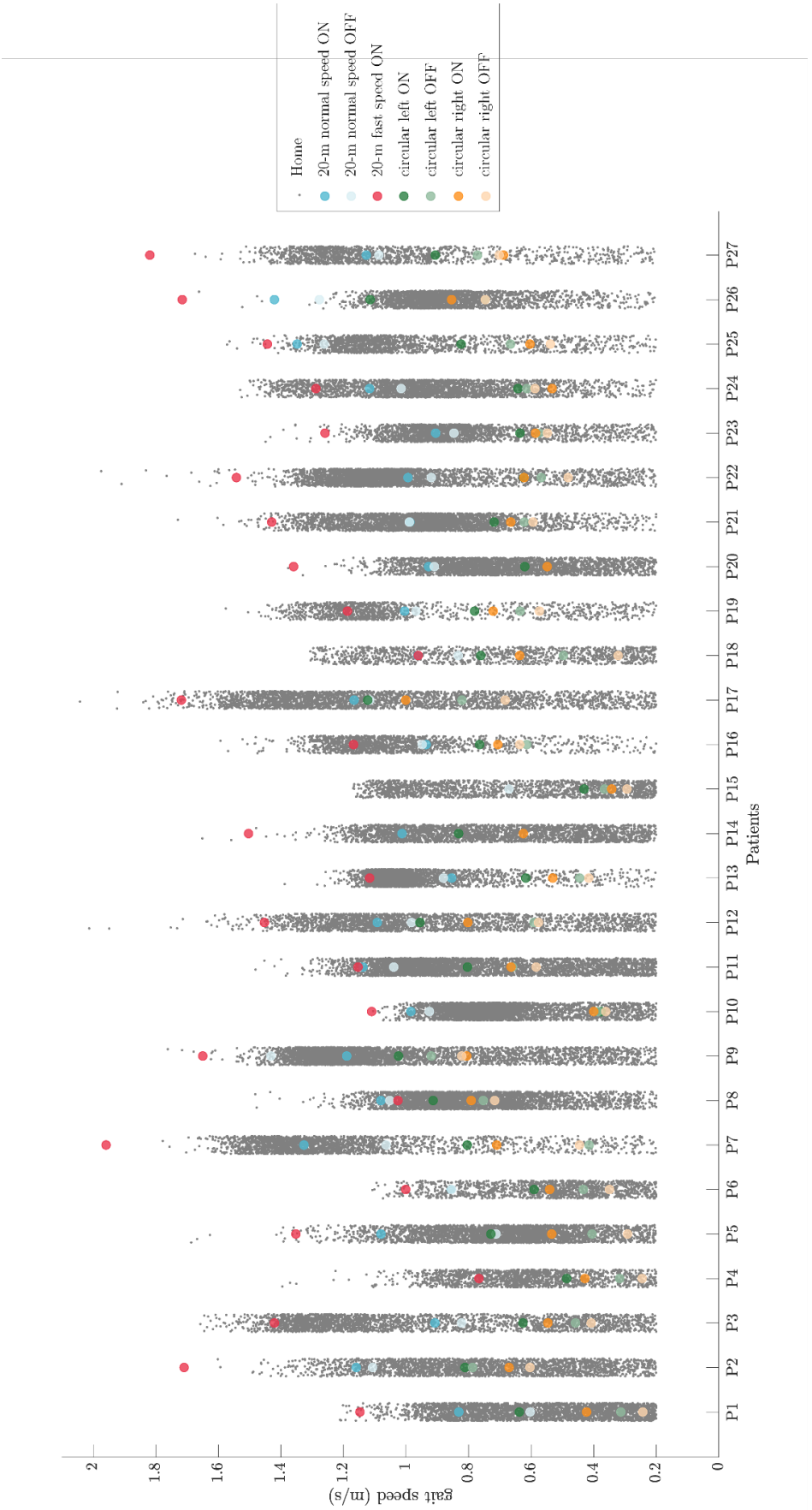
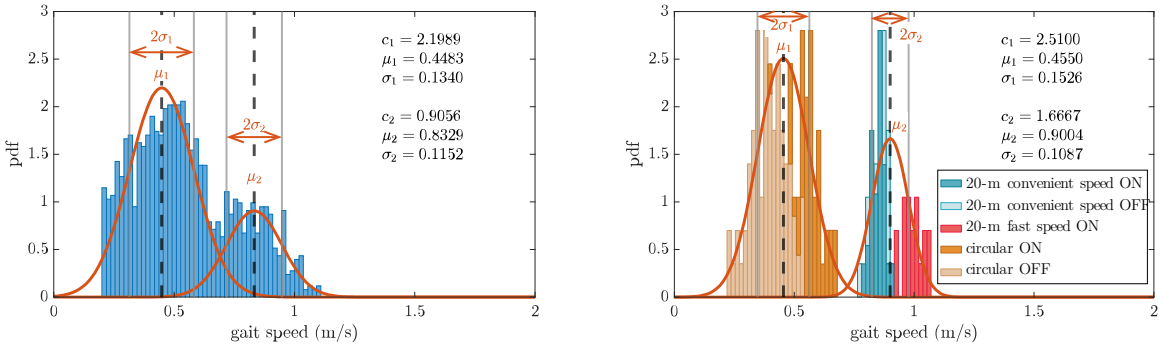


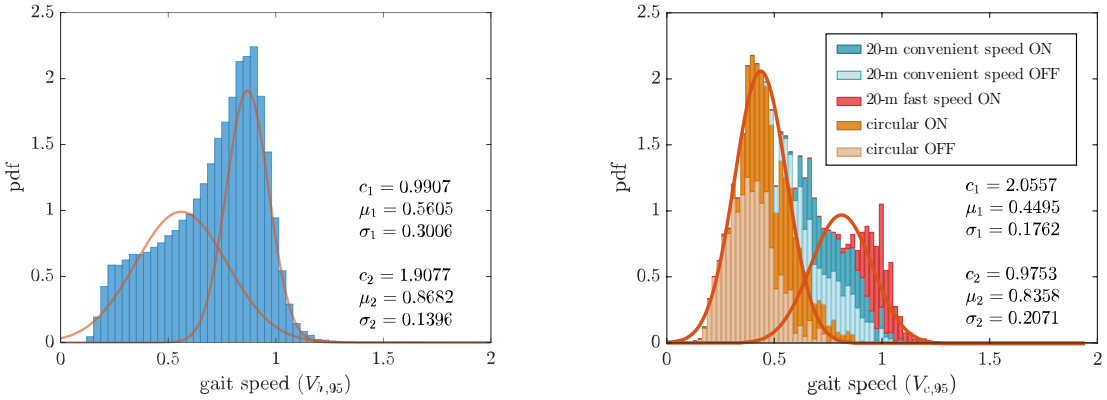
Figure 6.1: Distribution of gait speed at home and the average values of the gait speed for the clinical assessments for each patient



(a) (b)

Figure 6.2: An example of the gait speed probability density function (pdf) for one of the patients (P6) at (a) home and (b) at the clinic. The red fitted curves are the first and second terms of the bimodal Gaussian distribution introduced by Equation 6.1, the parameters c_1, c_2, μ_1, μ_2, σ_1, and σ_2 are the Gaussian mixture model parameters defined in Equation 6.1

To evaluate the existence of bimodal Gaussian distribution in the whole group of the patients, for each patient their gait speed distributions in the clinic and at home were normalized by the 95th percentile of the respective distribution ($V_{c,95}$ for clinical assessment, $V_{h,95}$ for home assessment). The gait speed distributions in both clinic and daily activity are depicted by considering all patients congregated (Figure 6.3). During the clinical assessment, the circular walking tests lay more on the left of the distribution, the straight walking tests with convenient speed were in the middle and the fast walking tests were at the right of the distribution.



(a) (b)

Figure 6.3: The gait speed probability density function (pdf) for all the patients together at (a) home normalized by $V_{h,95}$ and (b) the clinic normalized by $V_{c,95}$, the red fitted curves are the first and second terms of the bimodal Gaussian distribution introduced by Equation 6.1

The fitting quality of the bimodal Gaussian distribution estimated by Ashman's D value was higher than 2 for all the clinical assessments. However, for three patients (P5, P8, and P26),

this value was below 2 during their home assessment, meaning that there was not a clear separation between the modes of gait speed distribution at home. For all the remaining patients, the means (μ_1 and μ_2) and standard deviations (σ_1 and σ_2) were compared between clinic and home with the Wilcoxon test (Table 6.2).

No significant difference was observed between the means (μ_1 and μ_2) and the standard deviation corresponding to the higher preferred gait speed (σ_2) between the clinical and home assessments. However, the standard deviation corresponding to the lower preferred gait speed (σ_1) was significantly higher at home compared to the clinic (p-value < 0.001). These results show that the patients had on average the same preferred gait speeds at the clinic and at home with the same deviation from the higher preferred gait speed. However, their gait speed variation around the lower preferred gait speed was significantly higher during daily activities. A moderate correlation was found for the higher preferred gait speed (μ_2) between clinic and home ($\rho = 0.61$, p-value=0.0015, 95% confidence interval: 0.28 : 0.81). The correlation between the lower preferred gait speed (μ_1) was also moderate ($\rho = 0.52$, p-value=0.0084, 95% confidence interval: 0.15 : 0.77). No significant correlation was found for the standard deviations (σ_1: $\rho = 0.06$, p-value = 0.7897, 95% confidence interval: -0.34 : 0.46 and σ_2: $\rho = -0.02$, p-value = 0.8898, 95% confidence interval -0.32 : 0.48).

Table 6.2: Comparison of the preferred gait speeds along with their corresponding deviations between clinic and home, the significance level (*) was set to 0.05, two-sided Wilcoxon sign rank test, Cohen's d was calculated for effect size

	Home (m/s)		Clinic (m/s)		Comparison		Correlation	
	Median	IQR	Median	IQR	p-value	Cohen's d	ρ	p-value
μ_1	0.47	[0.44 , 0.73]	0.63	[0.47 , 0.71]	0.3173	0.29	0.52	0.0084*
μ_2	1.00	[0.88 , 1.14]	1.02	[0.90 , 1.41]	0.5028	0.39	0.61	0.0015*
σ_1	0.17	[0.13 , 0.26]	0.08	[0.07 , 0.15]	<0.001*	-1.07	0.06	0.7897
σ_2	0.14	[0.11 , 0.16]	0.14	[0.08 , 0.23]	0.6725	0.25	-0.02	0.8898

$\Delta_{\mu_1}$and Δ_{μ_2} as the percentage of the differences for preferred gait speeds between clinic and home were shown in Figure 6.4a. The median values are 6% and 7%, for $\Delta_{\mu_1}$and Δ_{μ_2}, respectively. The 25th and 75th percentiles are less than 23%, and the upper and lower adjacent values can reach up to 60%.

The AUC values that present the similarity of the cumulative distribution functions of clinic and home were shown in Figure 6.4b. The median value was obtained as 0.64 and the 25th and 75th percentiles as 0.51 and 0.68, respectively.

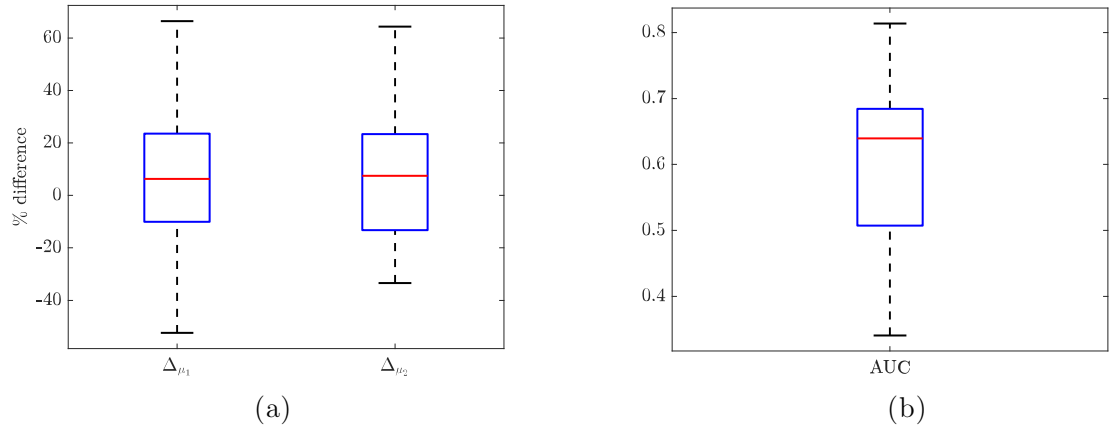


Figure 6.4: The boxplots (a) showing the percentage of difference between clinic and home for preferred gait speeds μ_1 and μ_2, (b) showing the area under the ROC curve (AUC) of CDF_{clinic} versus CDF_{home}: Center line: median; box limits: upper and lower quartiles; whiskers: 1.5 × interquartile range

The correlation between the number of medication doses taken during the course of data recording and Δ_{μ_1} was $\rho = -0.19$ (p-value=0.3649, 95% confidence interval: -0.55 : 0.23). The correlation between number of medication intakes and Δ_{μ_2} was $\rho = -0.50$ (p-value=0.0126, 95% confidence interval: -0.75 : -0.12). Plotting the number of medication doses intake versus Δ_{μ_1} and Δ_{μ_2} in Figure 6.5 revealed that patients with higher number of Levodopa intakes during daily activities performed faster at home ($\Delta_{\mu_2} < 0$) while patients with lower number of Levodopa intakes performed faster in the clinic ($\Delta_{\mu_2} > 0$).

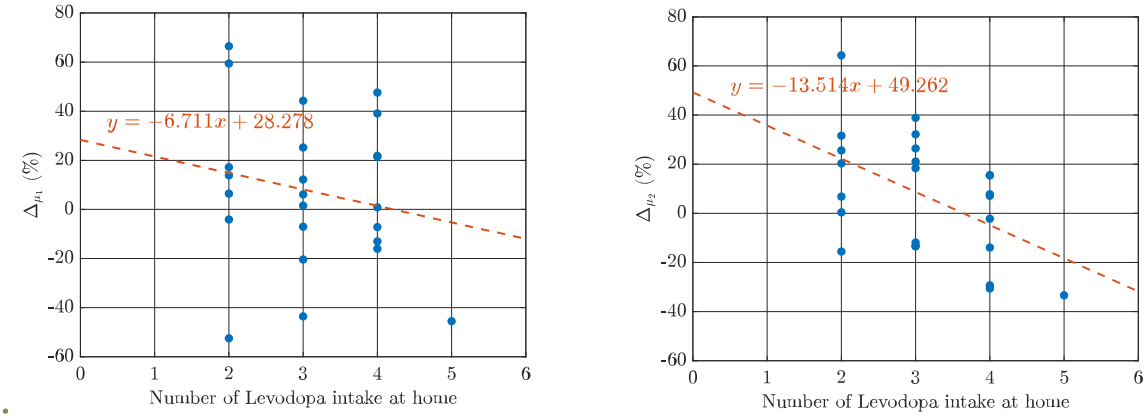


Figure 6.5: The relationship between the number of medication doses taken during the interval of data recording in home assessment and Δ_{μ_1} (on the left) and Δ_{μ_2} (on the right)

6.3.2 Exceptional Strides

Regarding the Exceptional Strides, the information concerning one Exceptional Stride k (section 6.2.6) as an example, is shown for one of the patients (Figure 6.6). This specific Exceptional Stride happened 0.34 hours (20.4 minutes) after the last Levodopa intake at 17:00. Therefore, it happened during the predefined OFF state. Furthermore, this stride belonged to a walking bout with a length of 84.8 seconds considered as a long walking bout. The gait speed of this stride was 0.01 m/s higher than the patient's capacity (V_c).

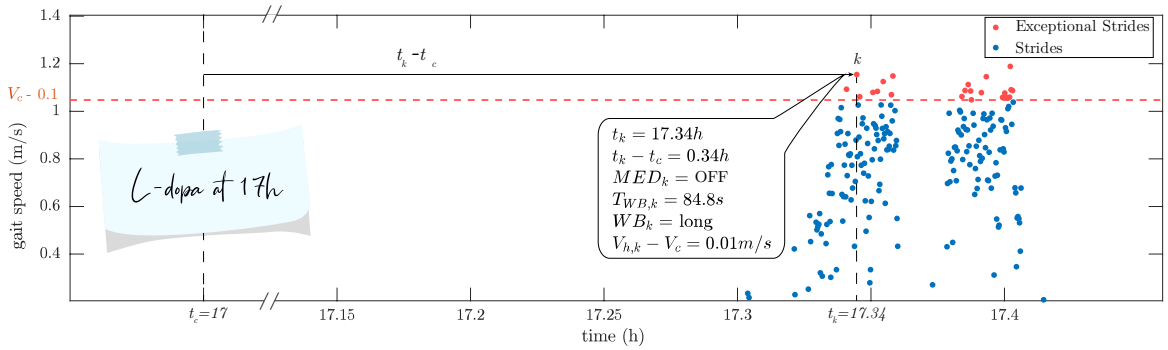


Figure 6.6: The information extracted for Exceptional Stride k for one of the patients as an example. Each blue dot shows the gait speed of a gait cycle at a specific time of the day during daily activities. This patient took Levodopa at time $t_c = 17h$. V_c is the capacity of the patient, i.e. gait speed during fast walking test in the clinic. The Exceptional Strides have been marked with red dots. k is one example of the Exceptional Strides with the information extracted according to section 6.2.6. No walking with a duration of more than 15 seconds occurred before 17.3.

Out of 27 patients, 3 patients did not have any Exceptional Stride in their home assessment (P2, P7, and P27). Furthermore, for one of the patients (P15), no data was present from their 20-m straight walk test with fast speed as depicted in Figure 6.1. Stacking the data from the remaining 23 patients together, the aforementioned parameters were given in Table 6.3.

It can be observed that a median of 104 Exceptional Strides existed from all the 23 patients (see Table 6.3). For each patient, the number of their Exceptional Strides was normalized by their total number of strides. It can be seen that 3.4% of their gait cycles had a speed higher than or equal to their capacity at the clinic.

A negative but insignificant trend was observed between the amount of Exceptional Strides and UPDRS-III ($\rho = -0.10$ p-value=0.6344, 95% confidence interval: -0.47 : 0.30). Moreover, a positive but insignificant relationship was found between the amount of Exceptional Strides and number of Levodopa intakes ($\rho = 0.17$ p-value=0.4144, 95% confidence interval: -0.23 : 0.52).

Exceptional Strides occurred at a median of 11.74 h or a bit before noon (11:44). The 3D histogram plot for the time of occurrence of the Exceptional Strides (t_k) as well as their time difference with regard to their previous medication intake ($t_k - t_c$) is shown in Figure 6.7. In this figure, the yellow bar demonstrates the highest peak of the Exceptional Strides that occurred around 10:00 to 10:30 and had a time difference of approximately 2 hours with their previous medication intake. Therefore, they correspond to the medication doses taken around 8:00 to 8:30. Other peaks can be observed around 12:00 and 17:30.

Table 6.3: The parameters of Exceptional Strides for all the patients except P2, P7, P15, and P27

	Median	IQR
Number of Exceptional Strides	104	[32 , 557]
Normalized number of Exceptional Strides (%)	3.4	[0.9 , 25.1]
t_k (h)	11.7	[10.6 , 14.6]
$t_k - t_c$ (h)	2.80	[2.03 , 3.42]
MED_k = ON (%)	27.4	[3.5 , 75.8]
MED_k = OFF (%)	3.9	[0.2 , 26.1]
$T_{WB,k}$ (s)	46.2	[26.1 , 129.4]
WB_k = short (%)	0.9	[0 , 10.3]
WB_k = medium (%)	7.0	[3.9 , 19.4]
WB_k = long (%)	89.5	[72.8 , 95.1]
$V_{h,k} - V_c$ (m/s)	-0.02	[-0.06 , 0.04]

Regarding the time difference between the Exceptional Strides and their corresponding last medication intake, the median value was 2.80 hours which states that most of the Exceptional Strides happened 2.80 hours after taking Levodopa. The probability distribution function (pdf) of the time differences were plotted in Figure 6.8 along with the fitted kernel density smoothening function. Two peaks can be distinguished from the kernel smoothening function at 0.44 and 2.97 hours. This implies that around half an hour and three hours after taking the medication, there is a high probability of having a gait speed equal or greater than the capacity at the clinic. Moreover, a sharp drop can be observed at approximately one hour after taking the medication. Furthermore, the probability of having an Exceptional Stride during ON state was higher than during OFF state (Table 6.3).

While the median of the walking bout duration in which the Exceptional Strides had occurred ($T_{WB,k}$) was 46.17 seconds, most of the Exceptional Strides happened in long walking bouts, i.e. walking bouts with a duration of more than 60 seconds. 89.5% of the Exceptional Strides belonged to long walking bouts while this amount was reduced to 7.0% and 0.9% in medium and short walking bouts, respectively.

Finally, the median difference between the gait speed of the Exceptional Strides and the capacity ($V_{h,k} - V_c$) was obtained as -0.02 m/s (Table 6.3).

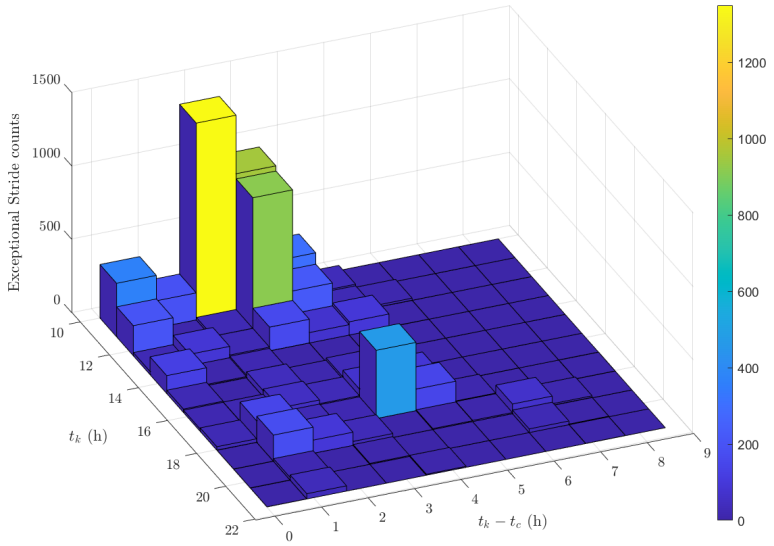


Figure 6.7: 3D Histogram plot of Exceptional Stride time of occurrence (t_k) and their time difference from their corresponding previous medication intake ($t_k - t_c$)

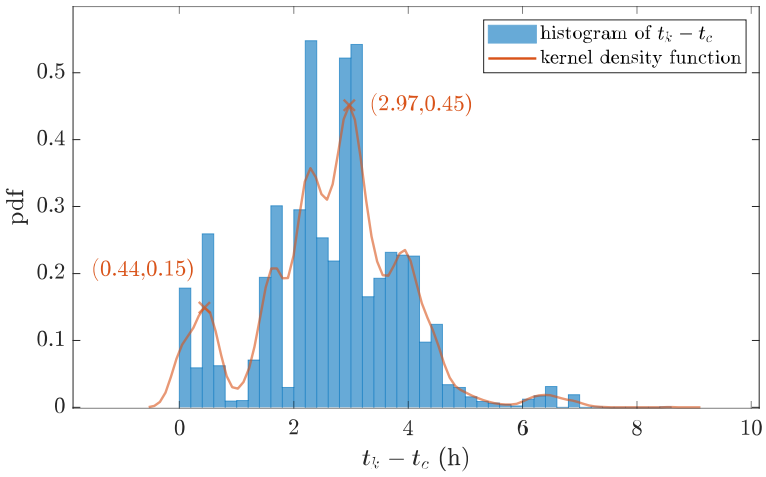


Figure 6.8: The probability distribution function (pdf) of Exceptional Strides in relation to medication intake time (blue) with the fitted Gaussian mixture model (red)

6.4 Discussion

In this chapter, we aimed to investigate under what conditions the clinical and home measurements demonstrate a close association. In previous studies, it had been proven that there are differences even for the same parameter obtained during clinical and home assessments (Carcreff, Gerber, Paraschiv-Ionescu, De Coulon, Aminian, et al., 2020; Carcreff, Gerber, Paraschiv-Ionescu, De Coulon, Newman, et al., 2020; Del Din, Godfrey, Galna, et al., 2016; Jansen et al., 2019; Takayanagi et al., 2019; Toosizadeh et al., 2015; Van Ancum et al., 2019). However, to the best of our knowledge, it has not been investigated under what circumstances the gap between clinical measurements and real-life daily activities becomes smaller.

Gait speed was extracted during functional tests performed at the clinic and during daily activities in real-life settings. Several walking tests were performed at the clinic during both ON and OFF states to capture different aspects of the patients' gait. During daily activities, we discarded the walking bouts with a duration of less than 15 seconds to include walking bouts with a steady-state gait speed. This value is reasonable as the duration of the straight walking tests during the clinical assessment was around 18 seconds making the comparison between clinic and home fairer. It was shown that the 20-m straight walking test with fast speed lay at the extreme end of the gait speed distribution at home (Figure 6.1). This is in line with what has been previously reported in the literature (Hillel et al., 2019; Van Ancum et al., 2019; Warmerdam et al., 2020). Comparing the gait speed obtained during daily activities and a 4-meter walk test at the clinic in community-dwelling participants, one previous study showed that the high percentiles of the gait speed distribution at home had higher correlations with the 4-meter walk test at the clinic (Van Ancum et al., 2019).

Specifically, for three patients, i.e. participants #16, 18, and 19, their fast walking test at the clinic had relatively slower speed compared to their maximal performance at home as there were many gait cycles with a higher speed at home (Figure 6.1). While due to psychological factors people behave differently in different settings (Bock & Beurskens, 2010), we believe that some other reasons can also explain this difference. We checked the assessment data of these patients in more detail, and found that they all performed their walking tests in the clinic formally during best ON medication, i.e., about 90 minutes after their last Levodopa intake. Therefore, we were reassured that the protocol of the test regarding the assessment time after medication intake was respected for these patients. Moreover, their treatment response as defined by the UPDRS-III scores (participant #16: 26 points during OFF, 20 points during ON; participant #18: 31 versus 12; participant #19: 22 versus 8) indicates good Levodopa response. Nevertheless, we believe that the effect of medication can be different for each patient and patients can respond differently to dopaminergic medication especially concerning pharmacodynamic aspects. This, in fact, shows that home assessment can have complementary information to clinical assessment and may give us a better insight about the

actual capacity of the patients. While the reasons for these differences in clinic versus home behaviour remain unclear, our study may stimulate further investigation in this area of research.

The gait speed distribution during both of the clinical assessments and daily activities followed a bimodal distribution for almost all the patients. This indicates that patients had two different preferred gait speeds. During clinical assessment, this phenomenon is because patients were assessed basically under two groups of walking tests, demanding as well as simpler ones. During home assessment, we can assume that the lower preferred gait speed is more attributed to shorter walking bouts that occur more indoors and higher preferred gait speed to the longer walking bouts that might occur more outdoors. Although we did not ask the patients to register the information about their indoor or outdoor activities, having this information could have confirmed our hypothesis. This bimodal phenomenon has been shown in previous studies for gait speed (Van Ancum et al., 2019) and cadence (Brodie et al., 2017) in community-dwelling adults during daily activities. In this study, we have confirmed this phenomenon for the first time in PD patients during daily living measurements. The advantage of such quantification of gait speed distribution is to preserve the information of this wide distribution rather than condensing it to one mean and standard deviation value.

In Figure 6.2 and Figure 6.3, it was shown that the circular walking tests composed the lower scales of the gait speed distribution while the straight walk tests constructed the higher gait speeds. This is not surprising as patients can have a lower gait speed in more demanding tasks. In a study on older fallers, it was shown that the gait speed obtained during dual-task walking tests corresponded better to the daily activities as opposed to the usual walking test (Hillel et al., 2019). This shows that performing more demanding walking tests in the clinic can give a better view of the patients' performance at home and clinicians can adapt or choose the most relevant clinical assessments. In other words, more demanding walking tests such as circular walk tests or dual-task tests represent the patients' lower preferred gait speed and simple walking tests such as straight walk tests represent the patients' higher preferred gait speed during daily activities.

Comparison of the bimodal distribution between clinic and home showed that patients had on average the same preferred gait speeds in both of the settings (Table 6.2). There was a significant difference between the two settings for the variations from the lower preferred gait speed (σ_1) but not from the higher gait speed (σ_2). Patients had higher variability for their lower preferred gait speed at home compared to the clinic. This can be explained by the complex context of the environment in real-life settings, e.g. turns, curved paths, obstacles, which causes people to continuously adapt their gait speed (Carcreff, Gerber, Paraschiv-Ionescu, De Coulon, Newman, et al., 2020). However, the variations around the higher preferred gait speed (σ_2) was not significantly different between real-life and clinical setting. This might be because the higher preferred gait speed expresses the capacity of the patients

which might stay constant between clinic and home. This can also explain the higher correlation for the higher preferred gait speed ($\rho = 0.61$) between lab and home compared to the lower preferred gait speed ($\rho = 0.52$). Another contributing factor can be the use of different vestibular systems when we walk slowly or fast (Dietrich et al., 2020; Jahn et al., 2004).

While the statistical test did not show a significant difference between clinic and home for the preferred gait speeds (μ_1 and μ_2), this lack of significance can be due to lack of power. To this end, we introduced additional parameters ($\Delta_{\mu_1}$and Δ_{μ_2}) to look at the difference between clinic and home more deeply. $\Delta_{\mu_1}$and Δ_{μ_2} showed that for most of the patients, the difference between clinic and home was less than 23% while there were few patients that had a larger difference of up to around 60% between clinic and home (Figure 6.4a). The AUC values that were on average about 0.64 confirmed that the cumulative distribution function of gait speed in clinic and home are comparable (Figure 6.4b).

The reason for this difference between clinic and home was partly explained by the variation in PD as there was a significant and moderate correlation between the number of Levodopa intakes throughout the day and Δ_{μ_2} (Figure 6.5). These results suggest that higher numbers of daily Levodopa intakes have a positive impact on preferred walking speed at home, especially in the "capacity area" (μ_2). However, we should also consider that patients with lower number of Levodopa intakes tend to respond better during clinical assessments. Another similar but independent reasoning can be the rationale behind why certain PD patients may get a little number of daily Levodopa prescribed, e.g. because they may not be able to manage a complex medication regimen. Considering our limited sample size, whatever the reasons are for this observation, such analyses can serve as first steps into a better understanding of the relation between medication intakes and difference between clinical and home assessments.

Therefore, to answer our first research question which was whether patients have the same preferred gait speed in the clinic and at home, we showed that by performing gait assessments under different conditions in the clinic, we can cover a wide range of gait speeds that can reach on average similar bimodal distribution observed in real-life. Nevertheless, daily-life measures can still provide complementary information to the clinical assessments (Rob C. Van Lummel et al., 2015; Warmerdam et al., 2020).

To answer the second research question which was investigating the instances in which the patients' performance reaches their capacity, we introduced and detected the Exceptional Strides for each patient during real-life conditions. These strides express the ability of the patient to reach equal or greater gait speed than the fast speed in the clinic (V_c) considered as the capacity of the patients. We considered a threshold of 0.1 m/s to compensate for the measurement errors. This value can be justified by the error of the employed algorithm (around 5 cm/s) to extract gait speed as shown by (Benoit Mariani, Jiménez, et al., 2013).

Exceptional Strides constituted only 3.4% of the total strides of the patients (Table 6.3). This reveals that in very small part of daily activities patients went beyond their capacity.

Although not significant, a negative relation was found between UPDRS-III and the amount of Exceptional Strides meaning that patients with higher UPDRS-III can have lower number of Exceptional Strides. Moreover, the positive but insignificant relation between the amount of Exceptional Strides and the number of Levodopa intakes taken during the day suggests that patients with higher amounts of Exceptional Strides might have taken higher number of medication doses. However, more evidence with a larger dataset is needed to confirm these findings.

Histogram plot of Exceptional Strides time of occurrence (Figure 6.7) showed that most of the Exceptional Strides happened before noon. This confirms the finding in the literature that PD patients with early or moderate stage of the disease have similar pattern of diurnal activity and are more active in the morning with a late morning peak (Van Hilten et al., 1993). This may be explained by being more active and having more walking bouts that occurred in the morning. These strides decreased in the afternoon reaching a minimum at 13:30 which might be due to a decrease in activity levels after lunch. Exceptional Strides increased again reaching their maximum around 17:00 in the evening which can again be due to the recovered energy before the end of the evening. Moreover, some of the patients were going to work; therefore, coming back from work can be another potential explanation to have Exceptional Strides at 17:00. However, the Exceptional Strides count was still approximately only one third compared to the morning. Having the Exceptional Strides mostly in the morning can also be due to the study design as the patients had to go back home from the hospital; therefore, they might have had more long walking bouts and consequently more Exceptional Strides in the morning.

The effect of Levodopa might be considered as maximum, approximately 3 hours after taking the medication as the Exceptional Strides occurred mostly at this time (Table 6.3). This is in line with a previous study that presented a model for Levodopa medication effect in finger tapping tests (Baston, Contin, Buonaura, Cortelli, & Ursino, 2016). It was shown that the tapping frequency increased around 30 minutes after taking Levodopa and was at its maximum around 180 minutes. In another study, by monitoring the stride length of the patients during daily activities, it was reported that the onset of the medication was 24 minutes. We have obtained almost the same value, as it can be observed in Figure 6.8, there was an increase in the number of Exceptional Strides 0.44 hours or 26 minutes after medication intake. As expected, Exceptional Strides occurred more frequently in ON state periods compared to the OFF state periods (Table 6.3). Our initial assumption of ON state periods in which we considered between 1 hour and 3 hours after taking the medication was generalized to the whole population. However, such a generalization might not be accurate for an individual patient due to different treatment responses. Moreover, the emergence of

Exceptional Strides in less than half an hour for some patients (Figure 6.8) might suggest that the initial assumptions for OFF state periods might not be true. Therefore, having the information about patients' performance during daily activities and comparing it to their capacity in the clinic can provide the potential to determine and monitor the effect of Levodopa in PD patients in a personalized manner. This is again in favour of the complementary aspect of information from daily living measurements.

It was observed that the occurrence of the Exceptional Strides was hardly seen in short walking bouts as only less than 1% of them happened during this type of walking bout. This percentage was increased in medium and long walking bouts with long walking bouts having a large portion of the Exceptional Strides (almost 90%). This can be justified by the fact that shorter walking bouts might occur when there are obstacles in the walking path of the individuals making them pause or stop their gait. Furthermore, shorter walking bouts can occur when people are doing several daily tasks requiring more attention and as a consequence causing the reduction of gait speed. However, for longer walking bouts, people can reach a more steady-state gait speed where it can be expected that the main task of walking is less perturbed by secondary tasks as is the case in the clinical assessment (Bock & Beurskens, 2010). The importance of considering longer walking bouts to predict PD has also been shown in another study (Del Din, Godfrey, Galna, et al., 2016). It was shown that short walking bouts of less than 20 seconds cannot reveal a significant difference between control group and PD patients' gait speed. However, as the duration of the walking bouts increases, the corresponding gait speed difference between the control and PD group becomes larger, reaching its maximum for walking bouts of longer than 2 minutes.

Finally, we observed that the Exceptional Strides' gait speed deviated between -0.06 and 0.04 (Table 6.3). Therefore, the threshold of 0.1 m/s to consider Exceptional Strides seems reasonable as it lay outside these two values. This threshold was considered only due to the error of our gait speed estimation system. However, to take into account also the performance of the patients individually, an adaptive threshold based on each patient's gait speed range can be employed.

The main contribution of the current study was a novel approach to compare clinical and home assessments, firstly, by comparing the bimodal distribution of gait speed between clinic and home, and secondly, by the Exceptional Strides. These approaches could preserve the information regarding the type of walking bouts, the medication effects, the time of the day as well as the complex distribution of gait speed that has been mostly limited in the literature to a unimodal distribution. Thanks to these two approaches, we were able to determine the conditions that lead patients to reach their capacity. In this way, the clinicians can know to what extent the patients' capacity is being used during daily activities, especially if a walking test in the clinic is not possible and patients are being monitored remotely in their domestic environment due to situations such as the COVID-19 pandemic (Rochester et al., 2020).

Looking specifically at the difference between the higher preferred gait speed at home and clinic (Δ_{μ_2}), the 97th percentile of gait speed distribution at home (because we showed Exceptional Strides compose 3% of the gait cycles), walking bouts longer than 1 minute, gait cycles happening in the morning, and gait cycles around 3 hours after taking the medication has the potential to give some information about the capacity of the patients.

Moreover, to the best of our knowledge, this is the first study investigating the effect of medication on the difference between clinical and home assessments of gait speed. The comparison of bimodal gait speed distribution between clinic and home was shown to have the potential to estimate the optimal number of medication doses throughout the day. Moreover, the effect of medication intake can be monitored objectively by comparing capacity and performance. This can help the clinicians to design the optimal dose of the medication for the patients. Yet more evidence in a larger dataset including healthy controls is needed to determine a meaningful relationship between the number of Exceptional Strides and the stage of PD.

The first limitation of our study was that daily activity assessments have been performed only in one day. Several days or a week could be more relevant to capture all the aspects of daily activities as people may have different amounts of activity e.g. on weekdays and weekends (Carcreff, Gerber, Paraschiv-Ionescu, De Coulon, Aminian, et al., 2020).

Another limitation of this study was neglecting very short walking bouts, i.e. walking bouts having less than 15 seconds duration as these very short walking bouts compose most of the walking bouts during daily activities (Del Din, Godfrey, Galna, et al., 2016). These walking bouts could have improved probably the power of calculations. Nevertheless, removing those very short walking bouts made our analysis fairer and also let us obtain a more steady-state gait speed during home assessment.

We did not distinguish curved walking bouts from straight walking bouts during daily activities. An algorithm such as the one introduced by (El-Gohary et al., 2014) can be employed to detect turnings during daily activities and differentiate the walking bouts during curved and straight paths. As this algorithm was designed for an IMU on the lower back, a sensor on the lower back can be useful for this purpose. Furthermore, the effect of the duration of the walking bouts on the comparison between clinic and real-life should also be studied.

Finally, in the current study, we investigated the circumstances in which the clinical and daily living measurements were more associated together. Although the findings can help the clinicians to know which tests in the clinic are better representative of daily living measurements, or vice versa, which conditions during daily living are better indicative of capacity in the lab, they do not concern about the information that is not mutual between clinic and home. Future studies can be focused for instance on metrics from daily living

measurements that are not associated with clinical assessments and still provide us relevant information regarding the mobility of the patients.

6.5 Conclusion

To conclude, this study presented novel insights to investigate when daily activity performance reaches the functional capacity as measured in clinic. By collecting all walking bouts and estimating their speed, we found that PD patients had a bimodal gait speed distribution during real-life conditions with on average similar modes as the gait tests performed in clinic during various conditions and speeds. Further analysis at stride level showed a low percentage of strides (~3%) had a gait speed equal or greater than the maximum speed in clinic considered as patients' capacity. These strides, termed as Exceptional Strides, happened mostly before noon, during ON state, and walking bouts with at least 1-minute duration. There was an increase in the number of Exceptional Strides starting 26 minutes after medication intake reaching the maximum at 3 hours. It was also concluded that by comparing the capacity and performance, one can monitor the effect of medication during daily activities and possibly adapt it to reach a gait speed closer to that of the capacity more frequently. Future research is however necessary to determine the meaningful relationship between the number of Exceptional Strides and the progression of the disease as well as the amount of Levodopa intake.

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7 Effect of fear of falling on mobility measured during lab and daily activity assessments in patients with Parkinson's disease

Abstract: In chronic disorders such as Parkinson's disease (PD), fear of falling (FOF) is associated with falls and reduced quality of life. This inherently subjective symptom is mostly evaluated with questionnaires while the impact of FOF on mobility can be measured objectively. With inertial measurement units (IMUs) and dedicated algorithms, different aspects of mobility can be obtained during supervised tests in the lab and also during daily activities. To our best knowledge, the effect of FOF on mobility has not been investigated in both of these settings simultaneously. To this end, in addition to functional tests in the lab, we evaluated the mobility performance of 26 PD patients by an IMU on the lower back over 14 days of daily activity. Parameters related to gait, sit-to-stand transitions, and turns were extracted from IMU signals in both settings. FOF was assessed using the Falls Efficacy Scale-International (FES-I) and patients were grouped as with (PD-FOF+) and without FOF (PD-FOF-). Mobility parameters between groups were compared using a logistic regression as well as the effect size values obtained by Wilcoxon rank sum test. The peak angular velocity of the turn-to-sit transition of the timed-up-and-go test had the highest discriminative power. Although not significant, PD-FOF+ had a tendency toward lower gait speed at home and lower amount of walking bouts. Classifying patients into PD-FOF+ and PF-FOF- lead to higher accuracy from both lab and daily activity assessments compared to each setting alone. Finally, high correlation existed between lab and daily activity assessments for sit-to-stand peak power and gait speed.[*]

[*] Chapter under review as Atrsaei, A., Hansen, C., Elshehabi, M., Nussbaum, S., Berg, D., Liepelt-Scarfone, I, Maetzler, W., & Aminian, K. Effect of fear of falling on mobility measured during lab and daily activity assessments in patients with Parkinson's disease.
Contributions: developed the gait and postural transition algorithms, extracted the mobility parameters, performed the analyses

7.1 Introduction

Fear of falling (FOF) is one of the most stressful symptoms for patients with Parkinson's disease (PD) (Frazier, 2000; Jonasson, Nilsson, Lexell, & Carlsson, 2018), leading to reduced quality of life and social isolation (Howcroft, Kofman, & Lemaire, 2013). Moreover, it is the strongest predictor currently known for future falls in this population (Lindholm, Hagell, Hansson, & Nilsson, 2015), which indirectly but strongly associates FOF with consequence of falls, such as fractures and other injuries (Allen, Schwarzel, & Canning, 2013; Bloem, Grimbergen, Cramer, Willemsen, & Zwinderman, 2001).

FOF can be assessed by several scales of which the Falls Efficacy Scale-International (FES-I) is the most widely used to evaluate patients' concern about falling during various daily activities (Delbaere et al., 2010). These activities include walking, postural transitions, and turnings during daily activity. Being subjective in nature, FOF can have impacts on mobility that can be measured objectively (Rochat et al., 2010). Therefore, by the assessment of mobility, future falls can be predicted (Delbaere, Crombez, Vanderstraeten, Willems, & Cambier, 2004). Inertial measurement units (IMUs) enable the objective evaluation of mobility performance, both during functional tests in the lab and during daily activities. Instrumenting functional tests such as the timed-up-and-go (TUG) and five-time sit-to-stand (5xSTS) with IMUs provides a more in-depth analysis of gait and balance performance (Salarian et al., 2010; Rob C. Van Lummel et al., 2016). Furthermore, IMUs can help the clinicians to evaluate the patients' performance also during daily activities that has been shown to be often very different from the supervised assessment in the lab and the clinic (Warmerdam et al., 2020).

The feasibility of IMUs to distinguish patients with falls from those without has been shown in the literature (Howcroft et al., 2013). These studies suggest that the most promising mobility parameters to detect increased risk of falling are in the area of gait (B. R. Greene et al., 2010; Marschollek et al., 2009; A. Weiss et al., 2011; Aner Weiss et al., 2013), postural transition (Doheny et al., 2011; Najafi et al., 2002; Narayanan et al., 2008; A. Weiss et al., 2011), and turning (Haertner et al., 2018). However, none of these studies investigated the contribution of FOF to these associations in much detail.

In community-dwelling older adults, it has been shown that IMU-derived TUG parameters, such as total duration, turning velocity, and sit-to-stand duration, have a significant association with the FES-I total score (Williams & Nyman, 2018). Moreover, it has been shown in PD patients that FOF affects turning performance during the TUG test (Haertner et al., 2018). PD patients with FOF had significantly lower turning peak angular velocity, and PD fallers had significantly lower gait speed, compared to non-fallers (Latt, Menz, Fung, & Lord, 2009). A drawback of the previous studies is that the performance of the participants has been studied mostly during assessments performed in the clinic while the association between FOF and performance of the investigated cohorts during daily activities remains

unknown. This is an enormous advantage, as daily activity assessments can provide added value to clinical assessments as mobility is influenced by psychological and environmental factors that cannot be effectively investigated in a supervised environment (Del Din et al., 2021; Evers et al., 2020; Feltz & Payment, 2005; Kaspar et al., 2015; Maetzler et al., 2020; Owsley & McGwin, 2004; Rudman, Friedland, Chipman, & Sciortino, 2006; Shah, McNames, Mancini, Carlson-Kuhta, Spain, et al., 2020a).

Based on these findings, the first goal of this study was to determine whether there exist mobility differences between PD patients with (PD-FOF+) and without FOF (PD-FOF-). For this purpose, we compared IMU-derived gait, sit-to-stand, and turning parameters from respective lab and daily activity assessments. The second goal was to determine whether daily activity assessment can complement lab assessment in differentiating PD-FOF+ from PD-FOF-. The third goal was to investigate the associations between the same parameters obtained during these two assessment settings and study their differences in PD-FOF+ and PD-FOF-.

7.2 Methods

7.2.1 Participants and study cohort

Twenty-six participants with PD were included in the analysis. Inclusion criteria were age between 50 and 85 years, PD based on the UK Brain-Bank Society criteria, and the ability to understand and communicate well with the investigator. Patients with dementia were excluded from the study (Emre et al., 2007). All participants gave their written informed consent and the study was approved by the ethics committee of the Medical Faculty of the University of Tübingen (protocol no. 686/2013BO1) (Haertner et al., 2018).

7.2.2 Lab assessments

Lab assessments were performed during ON medication state, and included the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Goetz et al., 2008) and the Hoehn & Yahr (H&Y) score (M. M. Hoehn & Yahr, 2001). FOF was assessed with the FES-I (Yardley et al., 2005). An FES-I score >19 was defined as presence of FOF (Delbaere et al., 2010).

For the mobility assessments, participants were equipped with Mobility Lab® (APDM, US) IMUs on the lower back and on the two feet. The sampling frequency was set at 128 Hz. For the analysis, accelerometer and gyroscope data were used. All participants performed first a 7-meter TUG test with their convenient speed. The TUG test includes a sit-to-stand movement, a walking phase, a 180° turn, a walking back phase and a turn-to-sit movement. The turn-to-sit transition consists of a simultaneously performed stand-to-sit transition and a

180° turn. Then, the participants performed the 5xSTS test once with their preferred speed and once as fast as possible. Rest periods were given between these three lab mobility tests.

For the analysis of the TUG test, the lower back IMU was used to analyze the sit-to-stand and stand-to-sit postural transitions with a previously validated algorithm (Atrsaei et al., 2020). The beginning of the sit-to-stand ($t_{b,SiSt}$) and the end of the stand-to-sit ($t_{e,StSi}$) times, as well as the sit-to-stand peak power (P_{TUG}) were extracted. The two turns within the TUG were analysed by another validated algorithm, using data from the lower back IMU (Salarian et al., 2010). The end of the second turn ($t_{e,Turn2}$) as well as the maximum angular velocities of each of the two turns ($\omega_{TUG,1}$ and $\omega_{TUG,2}$) were extracted. The total time of the TUG was calculated by subtracting the start of the sit-to-stand from the maximum value between the end of the second turn and the end of stand-to-sit:

$$T_{TUG} = \mathrm{Max}\left(t_{e,StSi}, t_{e,Turn2}\right) - t_{b,SiSt} \tag{7.1}$$

The IMUs on the lower back and feet were used to extract instantaneous gait speed during the TUG test based on the algorithm introduced in Chapter 4. Mean gait speed of the whole test was calculated ($V_{TUG,avg}$).

The 5xSTS tests were analyzed by the algorithm given in (Atrsaei et al., 2020), using data obtained from the lower back IMU. The following parameters were calculated: total time and mean sit-to-stand peak power of the normal ($T_{5xSTS,N}$, $P_{5xSTS,N}$) and the fast 5xSTS ($T_{5xSTS,F}, P_{5xSTS,F}$).

7.2.3 Mobility assessment during daily activities

The participants were equipped with a RehaGait® IMU (Hasomed, DE) in an elastic belt on the lower back and were asked to wear the system over a period of 14 days. Measurement phases of less than 6 hours/day were discarded from the analysis. The following mobility parameters were extracted for each patient.

Gait

Walking bouts were detected by the algorithm introduced in Chapter 4. Instantaneous gait speed, i.e. gait speed at each second was calculated. Instances in which the gait speed was less than 0.2 m/s were not included in walking bouts as these instances can be considered as "non-gait" periods (Atrsaei et al., 2021). Walking bouts of less than 15 seconds were excluded from the analysis, to have a more steady-state gait and prevent non-locomotion movements to be detected. The total duration of walking for each day was obtained and was expressed as the percentage of the respective day's measurement duration. Over all days of measurement, the minimum ($Gait_{ALL,min}$), average ($Gait_{ALL,avg}$), and maximum ($Gait_{ALL,max}$) values of walking percent were calculated. For instance, when a participant was assessed over a period of 5 days,

and walked 5%, 10%, 15%, 20%, and 25% of the entire daily assessment periods, respectively, $Gait_{ALL,min}$, $Gait_{ALL,avg}$, and $Gait_{ALL,max}$ would be 5%, 15%, and 25%, respectively.

Walking bouts were divided into short (between 15 and 30 seconds), medium (between 30 and 60 seconds), and long ones (longer than 60 seconds). Again, minimum, average, and maximum values of walking percentage per day for each type of walking bout were calculated. SWB, MWB, and LWB indices were used to describe short, medium, and long walking bouts.

Over all days of measurement stacked together, the gait speed distribution during all walking bouts (V_{ALL}), as well as during short (V_{SWB}), medium (V_{MWB}), and long (V_{LWB}) walking bouts were obtained separately. For each of these four distributions, the median, and the 95th percentile values were calculated.

There is evidence in the literature that gait speed has often a bimodal distribution during daily activities (Atrsaei et al., 2021; Van Ancum et al., 2019). The first mode represents the participants' lower preferred gait speed while the second mode represents the participants' higher preferred gait speed (Van Ancum et al., 2019). Therefore, we also extracted the first and second modes of V_{ALL} distribution as V_{μ_1} and V_{μ_2}, respectively.

Sit-to-stand transitions

Sit-to-stand transitions were detected during daily activities with a validated algorithm (Atrsaei et al., 2020). For each day, the number of sit-to-stands per hour was obtained. The minimum ($SiSt_{min}$), average ($SiSt_{avg}$), and maximum ($SiSt_{max}$) number of sit-to-stands per hour were calculated over all days of measurement. Furthermore, for each sit-to-stand, the vertical peak power was determined as this parameter is a predictor of prospective falls (Regterschot et al., 2014). The distribution of all the peak power values over all days of measurement stacked together were obtained as P_H. The median of this distribution ($P_{H,P50}$) and its 95th percentile ($P_{H,P95}$) were calculated.

Turns

Turns were detected during daily activities with a validated algorithm (El-Gohary et al., 2014). The number of turns per hour were determined for each day. The minimum ($Turns_{min}$), average ($Turns_{avg}$), and maximum ($Turns_{max}$) number of turns per hour were also calculated over all days of measurement. For each turn, the peak angular velocity around the vertical direction was obtained. The distribution of all the peak angular velocity values over all days of measurement stacked together were obtained as ω_H. The median ($\omega_{H,P50}$) and 95th percentile ($\omega_{H,P95}$) of this distribution were calculated.

7.2.4 Comparison between PD-FOF+ and PD-FOF-

All the mobility parameters extracted from lab and daily activity assessments were compared between PD-FOF+ and PD-FOF-. To exclude the potential differences due to sex and PD stage, the values were adjusted for sex and UPDRS-III with a multivariable logistic regression model. This analysis determines the odds of being PD-FOF+ considering sex (binary value, 0 for male, 1 for female), UPDRS-III (real-valued), and one of the mobility parameters (real-valued) explained in the previous section as independent variables. Moreover, the effect size (r-value) was obtained by dividing the Wilcoxon rank sum test statistics by the square root of the population (Ivarsson, Andersen, Johnson, & Lindwall, 2013). An r value of about 0.1 indicates a small, 0.3 a medium, and 0.5 a large effect size, respectively (J. Cohen, 1992).

7.2.5 FOF classification

To determine the predictive power of the extracted parameters in classifying PD-FOF+ and PD-FOF-, three classifiers based on a decision tree were used. Each classifier was trained based on one of the three sets of features mentioned below:

- $\mathbb{F}1$, Lab and daily activity (selected features): From all the parameters extracted from lab and daily activity measurements, we selected those with an absolute r value of higher than 0.2. A backward elimination method was further applied to select the optimal features (Farzin Dadashi et al., 2014).
- $\mathbb{F}2$, Lab: From the set $\mathbb{F}1$, the parameters from the lab assessment were used.
- $\mathbb{F}3$, Daily activity: From the set $\mathbb{F}1$, the parameters from daily activity assessment were used.

The decision tree approach was used due to its proven performance in classifying patient populations based on mobility biomarkers (Millor et al., 2017; Rehman et al., 2019). For all the three sets mentioned above, the cross-validation was performed based on leave-one subject-out approach. The classification performance was evaluated by sensitivity, specificity, precision, accuracy, and area under the receiver operating characteristic curve (AUC) metrics.

7.2.6 Lab versus daily activity assessment

For each of the two groups, gait speed, sit-to-stand peak power, and peak angular velocity were compared between lab and daily activities. For each parameter, a paired comparison was performed with the Wilcoxon sign rank test, and the significance level was set at $p = 0.05$. The Pearson's correlation coefficient (ρ) was also obtained. A correlation coefficient <0.5 was considered as low, between 0.5 and 0.7 as moderate, and >0.7 as high (Mukaka, 2012).

Moreover, each parameter obtained during daily activities was divided by the same parameter obtained during the lab assessment. The new unitless parameters were compared between PD-FOF+ and PD-FOF- by the Wilcoxon rank sum test.

7.3 Results

7.3.1 Comparison between PD-FOF+ and PD-FOF-

The characteristics of the participants are shown in Table 7.1. From the 26 participants, 9 had an FES-I score >19. The PD-FOF+ showed a trend towards higher UPDRS-III scores, compared to the PD-FOF-.

Table 7.1: Comparison of PD-FOF+ and PD-FOF-.

Parameter	PD-FOF+	PD-FOF-	p-value	ES
Number	9 (9 females)	17 (12 females)	0.083	0.35
Age (year)	65 [62 , 69]	64 [58 , 75]	0.829	0.05
Height (m)	1.78 [1.67 , 1.83]	1.75 [1.69 , 1.79]	0.608	0.11
Weight (kg)	81.0 [77.0 , 86.0]	77 [70.5 , 97.0]	0.935	-0.02
UPDRS-III (0-132)	30 [24 , 34]	22 [18 , 28]	0.053	0.38

The p-value was obtained by Wilcoxon rank sum test. Significance level was set at 0.05. Except the number of participants, the values are shown with Median [IQR]. ES is the effect size obtained by the r-value.

Table 7.2 presents results from the comparison of lab and daily activity mobility parameters between PD-FOF+ and PD-FOF-. Three parameters from the TUG test (i.e. T_{TUG}, $\omega_{TUG,1}$, and $\omega_{TUG,2}$) remained significantly different between the two groups after adjustment for UPDRS-III and sex. PD-FOF+ participants had significantly longer T_{TUG} accompanied by slower $\omega_{TUG,1}$, $\omega_{TUG,2}$, and a slower $V_{TUG,avg}$ which however, did not reach significance.

Nevertheless, several parameters were slightly different between the two populations although the logistic regressions showed no significant difference. For instance, compared to PD-FOF-, PD-FOF+ had on average lower gait speeds during the TUG ($V_{TUG,avg}$) and daily activities (V_{μ_1}), longer $T_{5xSTS,F}$, lower percentages of walking bouts (i.e., $Gait_{ALL,min}$, $Gait_{ALL,avg}$, and $Gait_{ALL,max}$), and lower numbers of sit-to-stands ($SiSt_{max}$) and turns ($Turns_{min}$) per hour during daily activities.

No significant differences were found between the two groups when dividing the walking bouts based on their duration (Table 7.3). However, PD-FOF+ tended to have a lower percentage of short (e.g. $Gait_{SWB,max}$) and long (e.g. $Gait_{LWB,max}$) walking bouts, compared to PD-FOF- (Table 7.3).

Table 7.2: Comparison of the extracted parameter between PD-FOF+ and PD-FOF-

Category	Parameter	PD-FOF+	PD-FOF-	p-value	ES
TUG	T_{TUG} (s)	19.93 [19.29 , 21.43]	17.40 [15.23 , 19.38]	0.044*	0.51
	$V_{TUG,avg}$ (m/s)	1.01 [0.95 , 1.08]	1.13 [1.05 , 1.29]	0.069	-0.47
	$\omega_{TUG,1}$ (deg/s)	124.4 [119.1 , 165.0]	161.6 [149.4 , 202.0]	0.029*	-0.36
	$\omega_{TUG,2}$ (deg/s)	110.2 [103.0 , 132.4]	158.5 [140.2 , 167.3]	0.018*	-0.61
	P_{TUG} (W)	44.11 [16.07 , 49.26]	37.32 [28.61 , 45.08]	0.269	-0.01
Normal 5xSTS	$T_{5xSTS,N}$ (s)	17.02 [15.79 , 21.61]	16.94 [15.05 , 21.11]	0.772	-0.10
	$P_{5xSTS,N}$ (W)	44.86 [32.96 , 51.29]	39.13 [32.47 , 50.02]	0.949	0.33
Fast 5xSTS	$T_{5xSTS,F}$ (s)	14.24 [13.58 , 15.02]	11.48 [11.03 , 16.32]	0.594	0.35
	$P_{5xSTS,F}$ (W)	65.32 [46.86 , 74.92]	49.16 [37.71 , 70.15]	0.373	0.35
Gait at Home	$V_{ALL,P50}$ (m/s)	0.81 [0.79 , 0.93]	0.88 [0.76 , 0.93]	0.660	0.01
	$V_{ALL,P95}$ (m/s)	1.17 [1.11 , 1.33]	1.23 [1.09 , 1.27]	0.822	0.13
	V_{μ_1} (m/s)	0.49 [0.36 , 0.59]	0.63 [0.43 , 0.75]	0.053	-0.31
	V_{μ_2}(m/s)	0.91 [0.82 , 1.00]	0.96 [0.84 , 1.06]	0.447	-0.16
	$Gait_{ALL,min}$ (%)	0.47 [0.43 , 0.83]	0.93 [0.62 , 2.86]	0.122	-0.29
	$Gait_{ALL,avg}$ (%)	3.10 [2.69 , 3.33]	4.28 [2.78 , 5.95]	0.174	-0.24
	$Gait_{ALL,max}$ (%)	6.59 [4.56 , 7.88]	8.05 [6.71 , 13.34]	0.177	-0.33
Sit-to-stand at Home	$P_{H,P50}$ (W)	18.72 [12.62 , 24.33]	19.54 [13.00 , 25.72]	0.291	-0.05
	$P_{H,P95}$ (W)	43.10 [36.69 , 54.54]	43.22 [33.30 , 62.99]	0.239	-0.03
	$SiSt_{min}$ (/h)	1.75 [0.96 , 2.60]	1.75 [0.80 , 3.27]	0.998	-0.05
	$SiSt_{avg}$ (/h)	3.74 [2.80 , 4.60]	4.45 [3.42 , 5.17]	0.670	-0.24
	$SiSt_{max}$ (/h)	5.42 [4.11 , 6.39]	6.27 [5.59 , 8.40]	0.254	-0.33
Turn at Home	$\omega_{H,P50}$ (W)	60.24 [58.67 , 63.78]	63.55 [59.13 , 68.70]	0.638	-0.23
	$\omega_{H,P95}$ (W)	110.6 [107.2 , 123.1]	111.1 [108.1 , 123.4]	0.758	-0.03
	$Turns_{min}$ (/h)	55.71 [48.56 , 68.32]	74.30 [55.86 , 83.79]	0.923	-0.33
	$Turns_{avg}$ (/h)	86.46 [82.02 , 96.16]	102.5 [85.81 , 118.2]	0.578	-0.24
	$Turns_{max}$ (/h)	123.7 [109.4 , 192.1]	142.0 [124.4 , 163.0]	0.553	0.10

The p-value shows the significance of the coefficient of the IMU-based parameter in the logistic regression. P-value<0.05 was considered significant. The values of IMU-based parameters are shown by Median [IQR]. ES is the effect size obtained by the r-value.

Effect sizes of the parameters are shown in Table 7.2 and in Figure 7.1 in descending order. As a general note, lab-extracted parameters showed higher effect sizes than those extracted from the daily activity assessment. $\omega_{TUG,2}$ had the highest effect size, followed by other parameters extracted from the TUG test (except P_{TUG} which had a very small effect size, see also Figure 7.1). $\omega_{TUG,1}$ had a lower effect size than $\omega_{TUG,2}$. Directly after the TUG test parameters ranked the $T_{5xSTS,F}$ and $P_{5xSTS,F}$ from the 5xSTS test with fast speed. The effect sizes of the parameters from the 5xSTS with normal speed ($T_{5xSTS,N}$ and $P_{5xSTS,N}$) were lower

than those from the fast version. $T_{5xSTS,N}$ had a smaller effect size compared to $P_{5xSTS,N}$. $Gait_{ALL,max}$, $SiSt_{max}$, $Turns_{min}$, and V_{μ_1} had the highest effect sizes among the daily activity parameters, and the median gait speed ($V_{ALL,P50}$) the lowest.

Table 7.3: Comparison of the extracted parameter for short, medium, and long walking bouts (WB) between PD-FOF+ and PD-FOF-.

WB	Parameter	PD-FOF+	PD-FOF-	p-value	ES
Short	$V_{SWB,P50}$ (m/s)	0.70 [0.63 , 0.71]	0.71 [0.60 , 0.76]	0.533	0.04
	$V_{SWB,P95}$ (m/s)	1.10 [1.06 , 1.19]	1.07 [1.01 , 1.20]	0.529	0.10
	$Gait_{SWB,min}$ (%)	0.43 [0.39 , 0.49]	0.69 [0.36 , 1.31]	0.187	-0.24
	$Gait_{SWB,avg}$ (%)	1.40 [1.19 , 1.68]	1.72 [1.30 , 2.47]	0.167	-0.26
	$Gait_{SWB,max}$ (%)	2.65 [2.19 , 2.81]	3.15 [2.31 , 4.50]	0.095	-0.23
Medium	$V_{MWB,P50}$ (m/s)	0.83 [0.79 , 0.89]	0.85 [0.78 , 0.92]	0.761	0.09
	$V_{MWB,P95}$ (m/s)	1.12 [1.08 , 1.27]	1.16 [1.06 , 1.24]	0.613	0.12
	$Gait_{MWB,min}$ (%)	0.00 [0.00 , 0.07]	0.00 [0.00 , 0.13]	0.271	-0.19
	$Gait_{MWB,avg}$ (%)	0.51 [0.29 , 0.67]	0.62 [0.52 , 0.92]	0.110	-0.25
	$Gait_{MWB,max}$ (%)	1.38 [0.84 , 1.88]	1.57 [1.24 , 2.35]	0.184	-0.22
Long	$V_{LWB,P50}$ (m/s)	0.92 [0.89 , 1.05]	0.96 [0.89 , 1.07]	0.859	0.03
	$V_{LWB,P95}$ (m/s)	1.24 [1.12 , 1.40]	1.24 [1.11 , 1.32]	0.772	0.15
	$Gait_{LWB,min}$ (%)	0.00 [0.00 , 0.00]	0.00 [0.00 , 0.05]	0.279	-0.16
	$Gait_{LWB,avg}$ (%)	1.08 [0.74 , 1.24]	1.87 [0.78 , 2.70]	0.431	-0.28
	$Gait_{LWB,max}$ (%)	3.24 [2.26 , 5.31]	5.43 [3.94 , 7.08]	0.314	-0.31

The p-value shows the significance of the coefficient of the IMU-based parameter in the logistic regression. P-value<0.05 was considered significant. The values of IMU-based parameters are shown by Median [IQR]. ES is the effect size obtained by the r-value.

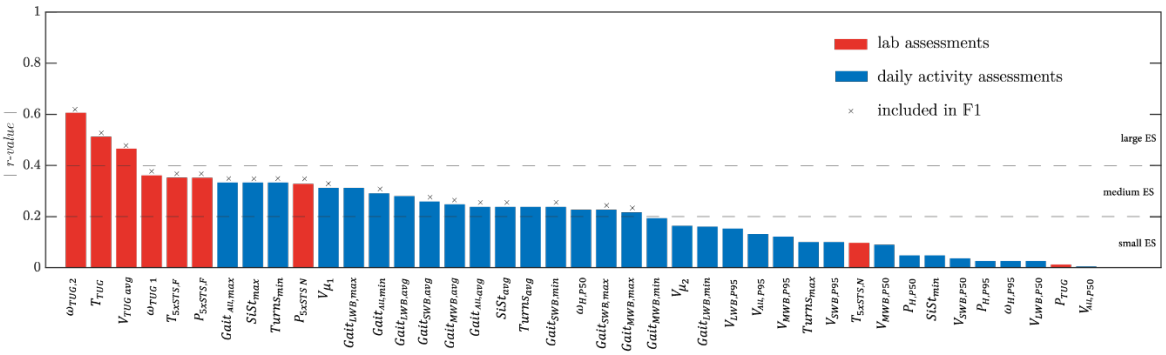

Figure 7.1: Absolute effect size values (r-value) of the mobility parameters extracted from lab (in red) and daily activity assessments (in blue). The features selected for the F1 feature set are marked by a cross (see section 7.3.2).

7.3.2 FOF classification

Out of the 41 mobility parameters, 23 had an effect size >0.2 (Figure 7.1). From these parameters, 19 features (used for machine learning-based classifier; marked with [x] in Figure 7.1) were selected by the backward elimination method and used for the 𝔽1 set.

Based on the 3 sets of features mentioned in the methods section, the results of the classification are shown in Table 7.4. The best performance was achieved based on set 𝔽1 which was a combination of features obtained from the lab and daily activity assessments. The accuracy of this set was higher than when using lab (𝔽2) or daily activity (𝔽3) features alone.

The sensitivity of the classification based on the features from the lab (𝔽2) were higher than that obtained from the daily activity features, while the specificity of the classification based on daily activity features (𝔽3) was higher. Moreover, 𝔽2 features achieved higher accuracy and AUC values, than did the 𝔽3 features.

Table 7.4: The performance metrics of the classification of PD-FOF+ versus PD-FOF-

Feature set	Sensitivity (%)	Specificity (%)	Precision (%)	Accuracy (%)	AUC
𝔽1, Lab and daily activity	55.6	94.1	83.3	80.8	0.75
𝔽2, Lab	57.7	64.7	40.0	65.4	0.68
𝔽3, Daily activity	44.4	76.5	50.0	57.7	0.54

𝔽1: Selected 19 features marked with crosses in Figure 7.1. 𝔽2: 7 lab features from 𝔽1. 𝔽3: 12 daily activity features from 𝔽1

7.3.3 Lab versus daily activity assessment

The results of the paired comparison between lab and daily activity assessments for gait speed, sit-to-stand peak power, and turning peak angular velocity are shown in Table 7.5. In the PD-FOF+ group, no significant correlations were found between lab and daily activity assessments concerning gait speed. Moreover, PD-FOF+ had higher gait speeds at the 95th percentile of their walking speed distributions compared to the lab ($V_{ALL,P95}$, $V_{SWB,P95}$, $V_{MWB,P95}$, and $V_{LWB,P95}$). In the PD-FOF- group, $V_{TUG,avg}$ had a significant but low correlation with $V_{H,P95}$ ($\rho = 0.48$). A high correlation was also observed between $V_{TUG,avg}$ and V_{μ_2} ($\rho = 0.70$). Moderate correlations were observed between $V_{TUG,avg}$ and gait speed of medium ($V_{MWB,P95}$) and long ($V_{LWB,P50}$) walking bouts ($\rho = 0.59$ and $\rho = 0.57$, respectively). PD-FOF- walked significantly faster during the TUG than during their daily activities.

Regarding the sit-to-stand peak power, high correlation was found between P_{TUG} and $P_{H,P95}$ for PD-FOF+ ($\rho = 0.75$). In both groups, $P_{5xSTS,N}$ had a high correlation with $P_{H,P95}$ (PD-

FOF+, $\rho = 0.83$; PD-FOF-, $\rho = 0.70$). No significant correlations were found between the 5xSTS with fast speed and daily activity assessment. Both groups had significantly higher peak power during the 5xSTS tests compared to $P_{H,P50}$ during daily activities. However, $P_{H,P95}$ values were not significantly different from the 5xSTS tests in the lab.

Finally, for turning peak angular velocity, no significant correlations were found between lab and daily activity in any group. For PD-FOF+, there were no significant differences between $\omega_{H,P95}$ and both turns of the TUG. However, PD-FOF- had faster turns in the lab, compared to the home environment.

Table 7.5: Paired comparison of the parameters between lab and home.

Category	Lab	Daily activity	Difference, p-value		Correlation (ρ)	
			PD-FOF+	PD-FOF-	PD-FOF+	PD-FOF-
Gait speed	$V_{TUG,avg}$	$V_{ALL,P50}$	0.023*	<0.001*	-0.34	0.36
		$V_{ALL,P95}$	0.008*	0.836	-0.15	0.48*
		V_{μ_1}	0.008*	<0.001*	0.35	0.44
		V_{μ_2}	0.039*	<0.001*	-0.03	0.70*
		$V_{SWB,P50}$	0.008*	<0.001*	-0.14	0.38
		$V_{SWB,P95}$	0.039*	0.044*	0.20	0.40
		$V_{MWB,P50}$	0.016*	<0.001*	-0.48	0.44
		$V_{MWB,P95}$	0.008*	0.309	-0.04	0.59*
		$V_{LWB,P50}$	0.148	<0.001*	-0.12	0.57*
		$V_{LWB,P95}$	0.008*	0.193	-0.10	0.42
Sit-to-stand peak power	P_{TUG}	$P_{H,P50}$	0.039*	0.001*	0.75*	0.48
		$P_{H,P95}$	0.541	0.006*	0.77*	0.79*
	$P_{5xSTS,N}$	$P_{H,P50}$	0.015*	0.003*	0.83*	0.13
		$P_{H,P95}$	0.578	0.167	0.83*	0.70*
	$P_{5xSTS,F}$	$P_{H,P50}$	0.031*	0.002*	-0.28	0.12
		$P_{H,P95}$	0.312	0.492	-0.34	0.61
Turning peak angular velocity	$\omega_{TUG,1}$	$\omega_{H,P50}$	<0.001*	<0.001*	0.28	0.20
		$\omega_{H,P95}$	0.139	<0.001*	-0.44	0.00
	$\omega_{TUG,2}$	$\omega_{H,P50}$	<0.001*	<0.001*	0.69	0.43
		$\omega_{H,P95}$	0.815	<0.001*	0.57	0.00

*p-value from the Wilcoxon sign rank test and Pearson's correlation coefficient (ρ) describe differences of parameters between lab and daily life. The significance level was set to 0.05 and shown with *. Significant correlation coefficients were marked with *.*

For a better representation of lab versus daily activity parameters, gait speed, sit-to-stand peak power, and turning peak angular velocity are presented in Figure 7.2 as unitless ratios (daily activity parameter divided by the respective lab parameter). Most of the ratios were less than 1 (i.e., lower value of a parameter in the daily life environment). However, a few

parameters, e.g. $\frac{V_{ALL,P95}}{V_{TUG,avg}}$, $\frac{P_{ALL,P95}}{P_{TUG}}$, had values >1, preferentially in the PD-FOF+ group. Moreover, when comparing PD-FOF+ with PD-FOF-, significant differences were found for the ratios $\frac{V_{ALL,P95}}{V_{TUG,avg}}$, $\frac{V_{SWB,P95}}{V_{TUG,avg}}$, $\frac{V_{MWB,P95}}{V_{TUG,avg}}$, $\frac{V_{LWB,P50}}{V_{TUG,avg}}$, $\frac{V_{LWB,P95}}{V_{TUG,avg}}$, $\frac{\omega_{H,P50}}{\omega_{TUG,avg}}$, and $\frac{\omega_{H,P95}}{\omega_{TUG,2}}$, with higher ratios in the PD-FOF+ group.

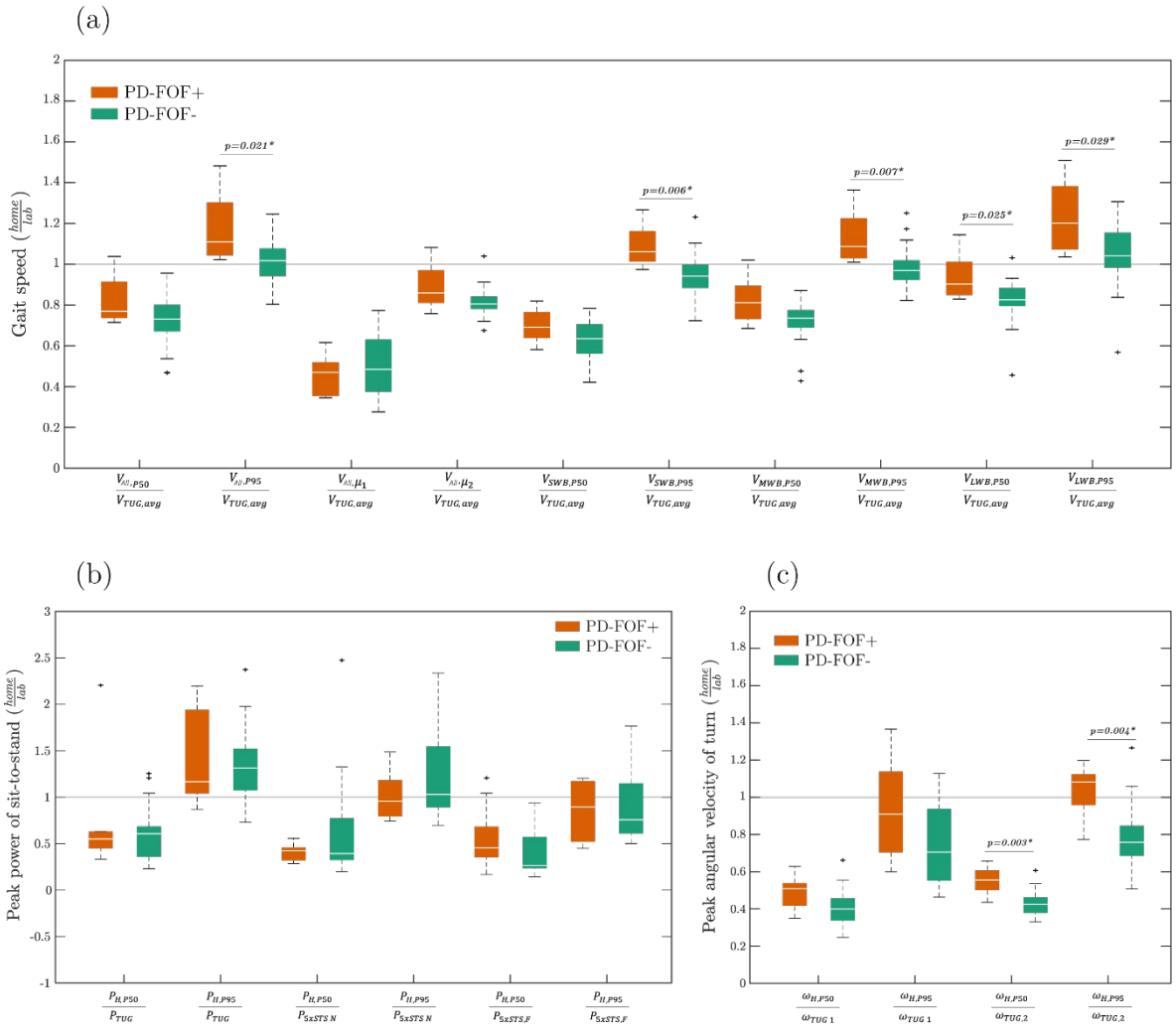

*Figure 7.2: Unitless daily activity divided by lab parameter ratios of (a) gait speed, (b) sit-to-stand peak power, and (c) turning peak angular velocity in PD-FOF+ and PD-FOF-. Differences between the groups were analyzed by Wilcoxon rank sum test. Only significant differences were shown on the plots * p<0.05.*

7.4 Discussion

In this study, several mobility parameters were collected from PD patients with and without FOF, when performing functional tests in the lab and living in their usual environment. Most of the previous studies on this topic that have shown mobility-associated differences between PD-FOF+ and PD-FOF- have investigated their participants only in the lab. In the current

study, thanks to IMUs and dedicated algorithms, we were able to objectively quantify mobility both inside and outside the laboratory environment. Three objectives were defined specifically in this paper: 1) Investigating the effect of FOF on mobility parameters obtained during lab and daily activity assessments, 2) to know whether daily activity assessments can provide a more accurate classification of FOF compared to considering only lab assessment, and 3) exploring the degree of association between lab and daily activity settings for different aspects of mobility.

Regarding the effect of FOF on mobility, PD-FOF+ needed more time to perform the TUG test than the PD-FOF-, which was –at least partly- explained by slower performance of the two turns included in this test (Table 7.2). This supports previous findings (Bryant, Rintala, Hou, & Protas, 2014; Haertner et al., 2018; J. H. Park et al., 2014), and suggests that PD-FOF+ suffer from increased fear especially during turns. This fear may be justified, e.g. through increased dysbalance or other constrains associated with FOF. The larger difference between the two groups in the second turn, which also includes a stand- or walk-to-sit movement, may also argue for different balance capacities between the groups. This argument is further supported by slower peak angular velocity during the second turn compared to the first turn in PD-FOF+.

In contrast to the evidence in the literature (Bryant et al., 2014), we did not observe a significant difference in gait speed between PD-FOF+ and PD-FOF- during the TUG test ($V_{TUG,avg}$). As the r-value showed a large effect size for this parameter in both groups, we hypothesize that PD severity rather than FOF has a particular influence on this parameter. We performed a Wilcoxon rank sum test on $V_{TUG,avg}$ without adjusting for the aforementioned confounders, and obtained a significant difference between the PD-FOF+ and PD-FOF- ($p = 0.021$). Therefore, more evidence with a larger dataset is required to confirm this hypothesis as most of the previous studies did not adjust the statistical analysis for potential confounders.

The 5xSTS tests were performed in two trials, once with the patients' preferred speed, and the other as fast as possible. Although none of these tests could sufficiently discriminate between the PD-FOF+ and PD-FOF-, the fast 5xSTS test presented larger effect sizes than the preferred speed 5xSTS test (Table 7.2 and Figure 7.1). This is an argument to include the fast version, rather than the preferred speed version (Goldberg, Chavis, Watkins, & Wilson, 2012; Whitney et al., 2005), in the assessment panel of clinical protocols. For the 5xSTS with preferred speed, the mean peak power of sit-to-stands ($P_{5xSTS,N}$) had a medium effect size while the effect size for the total duration of the test ($T_{5xSTS,N}$) was low (Table 7.2 and Figure 7.1). This again highlights the usefulness of an instrumented 5xSTS test with IMUs to extract biomechanical parameters beyond the conventionally measured duration of the test (Rob C. Van Lummel et al., 2016). Nevertheless, the IMU-derived sit-to-stand peak power did not differentiate PD-FOF+ from the PD-FOF-. Also the sit-to-stand peak power derived from the TUG test (P_{TUG}) was not significantly different between the groups. An explanation can be

that the PD-FOF+ group might not have particular difficulties in performing postural transitions. However, numerous studies showed the predictive power of the 5xSTS test for future falls (Buatois et al., 2008; Doheny et al., 2013; Duncan, Leddy, & Earhart, 2011; Qiu et al., 2018). Therefore, our results, together with previous results, suggest that the 5xSTS test is associated with aspects of falls that are independent of FOF.

None of the parameters derived from the daily activity assessment could differentiate significantly the PD-FOF+ from the PD-FOF-. However, medium effect size values were observed for several parameters. Interestingly, the effect size for the lower preferred gait speed (V_{μ_1}) was higher than the median or 95th percentile values of gait speed distribution. This shows the importance of a more precise modelling of gait speed distribution, rather than assuming a simple normal distribution of the obviously complex movements that occur in the usual environment (which was done in most of the previous studies, e.g. (Shah, McNames, Mancini, Carlson-Kuhta, Spain, et al., 2020a; Takayanagi et al., 2019; Toosizadeh et al., 2015)). Interestingly, V_{μ_1} showed a higher effect size than V_{μ_2}. It should be noted that V_{μ_1} is assumed to correspond more to shorter walking bouts and V_{μ_2} represents mostly longer walking bouts that are more likely to occur outdoors (Van Ancum et al., 2019). Thus, our results regarding the higher effect size of V_{μ_1} versus V_{μ_2} suggest that shorter walking bouts are more meaningful to describe mobility performance (limitations) of PD-FOF+, and may be an interesting therapeutic target for future trials. It could also be speculated that PD-FOF+ have more problems than PD-FOF- during multitask-walking, as shorter walking bouts have obviously a higher probability to be associated with additional tasks, compared to long walking bouts which have a high probability to reflect e.g. walks without relevant dual-task claim. Therefore, according to Figure 7.1, it is not surprising that the features that remained for the classification included more parameters from short walking bouts ($Gait_{SWB,min}$, $Gait_{SWB,avg}$, and $Gait_{SWB,max}$) than from medium and long walking bouts ($Gait_{MWB,avg}$ and $Gait_{MWB,max}$).

In addition to $Gait_{ALL,max}$, $SiSt_{max}$ and $Turn_{min}$ were among the daily activity parameters with the highest effect sizes. Thus, the amount of various types of activities should also be considered in addition to parameters such as gait speed, sit-to-stand peak power, and turning peak angular velocity that characterize these activities. Although the difference between the two groups for these parameters were not significant, there was a tendency toward a lower amount of activity in PD-FOF+. As the reason might be due to a small sample size, more evidence is required. Nevertheless, the results highlight again the relevance of daily activity monitoring, as the amount of physical activities cannot be measured during clinical assessments (Warmerdam et al., 2020).

After feature selection in section 7.2.6, several parameters from the lab and daily activity assessments remained in the selected features (Figure 7.1). Training three classifiers based on three sets of features, i.e. $\mathbb{F}1$, $\mathbb{F}2$, and $\mathbb{F}3$, revealed that set $\mathbb{F}1$ led to the most accurate

classifier to distinguish the PD-FOF+ from the PD-FOF- group (Table 7.4). This selection, including features from both the lab and daily activity assessments, further supports the usefulness of including daily activity assessments into clinical practice as they have complementary information to the assessments performed in the lab (Maetzler et al., 2020). The more accurate classification of FOF with lab features ($\mathbb{F}2$), compared to daily activity features ($\mathbb{F}3$, Table 7.4), suggests that functional tests in the lab should always be performed for the evaluation in FOF, although the inclusion of environmental context and psychological factors from daily life is a valuable addition and can contribute to increased specificity.

Comparing gait speed between lab and daily activity assessments, significant correlations were found for the PD-FOF- but not the PD-FOF+ (Table 7.5). Interestingly, PD-FOF+ had higher gait speed values in the "capacity" area of their daily activity assessment compared to the lab. For these participants, $\frac{V_{P95}}{V_{TUG,avg}}$, $\frac{V_{SWB,P95}}{V_{TUG,avg}}$, $\frac{V_{MWB,P95}}{V_{TUG,avg}}$, and $\frac{V_{LWB,P95}}{V_{TUG,avg}}$ had values greater than 1 (Table 7.5). One explanation can be that PD-FOF+ might be more cautious in non-familiar environments such as the lab. Moreover, they might have had problems judging their convenient gait speed in the lab. On the contrary, another explanation is that PD-FOF+ might have been less cautious in their daily life. Therefore, their risk of fall can be due to fact that they are not cautious enough during their daily activities.

Another interesting observation was, in our view, that in PD-FOF-, $V_{TUG,avg}$ was significantly correlated with parameters during daily activity assessments that represent mostly the capacity aspects, i.e. $V_{H,P95}$, V_{H,μ_2}, $V_{MWB,P95}$, and $V_{LWB,P50}$. Moreover, the correlation between $V_{TUG,avg}$ and V_{μ_2} was high ($\rho = 0.70$). These findings firstly confirm the relevant association of lab parameters with daily activity parameters that are near the capacity area (Van Ancum et al., 2019; Warmerdam et al., 2020). These results suggest that capacity-associated values obtained during daily activities can indeed predict a participants' capacity in the lab. Furthermore, the high association between $V_{TUG,avg}$ and V_{μ_2} is again in favour of considering a bimodal gait speed distribution during daily activities.

Regarding the sit-to-stand peak power, $P_{H,P95}$ had high correlations with P_{TUG} and $P_{5xSTS,N}$ but not with $P_{5xSTS,F}$ (Table 7.5). This indicates that the 5xSTS test with preferred speed and the sit-to-stand part of the TUG test are most representative for the sit-to-stands performed during daily activities. In fact, in the TUG test, it is more accurate to name the initial postural transition as sit-to-walk rather than sit-to-stand. Since in daily life there is often more sitting-to-walking than sitting-to-standing, the high correlation between P_{TUG} and $P_{H,P95}$ seems reasonable. Therefore, to have a better understanding of patients' sit-to-stand performance during daily activities, clinicians should consider the 5xSTS test with preferred speed and the TUG sit-to-stand movement, rather than the fast 5xSTS test. The high association of sit-to-stand peak power between the lab and daily activity assessments was also observed in a study in community-dwelling older adults (W. Zhang et al., 2017). Nevertheless, as we demonstrated

earlier, the 5xSTS test with fast speed had higher discriminative power for differentiating PD-FOF+ from PD-FOF-.

Our results are comparable to a very recent study on the impact of FOF on mobility parameters in a relatively large population of community-dwelling older adults (Wang, Patriquin, Vaziri, & Najafi, 2021). In that study, FOF led to a poorer mobility performance during both, lab and daily activity assessments. Moreover, and comparable to this study, consideration of both assessments showed the best discriminatory power between presence and absence of FOF (lab assessment, AUC=0.64; lab and daily activity assessment, AUC=0.77). The strengths of our study, compared to the aforementioned study, are that we included postural transition and turning, in addition to walking, and we assessed daily activity over an average period of 12 (and not only 2 days (Wang et al., 2021)).

Our study faces some limitations. First, our sample size might have been small for statistical analyses. This could explain why the parameters obtained during daily activities did not differentiate significantly between PD-FOF+ and PD-FOF-. For instance, V_{μ_1} was at the edge of a statistically significant difference. However, it should be noted that finding participants with a specific impairment that are willing to participate in several clinical assessments as well as two weeks of activity monitoring can be challenging. While in this study, we explored the difference between participants with low and moderate FOF, the difference between participants with low and high FOF might be more evident with mobility parameters obtained during daily activities. Using other questionnaires in addition to FES-I can also be investigated. For example, participants can be asked whether their FOF restrict their activities or not (Rochat et al., 2010).

Another point of limitation can be the turning assessment during daily activities. The turning algorithm considered turns with durations of 0.5 to 10 seconds and angles >45° (El-Gohary et al., 2014). This is a broad range, and future studies should investigate whether more specific definitions for turns that are performed in daily life have higher discriminatory power. Furthermore, the employed algorithm detected turns regardless of their occurrence during walking or sedentary behaviour. Although it might be rare, participants might have been in a sitting position in a moving vehicle that had similar turning to those of a human that walks and turns at the same time. Therefore, further work is required to adapt the algorithm to detect turnings that occur during locomotion.

Based on an algorithm that was developed and validated previously, postural transitions such as sit-to-walk and sit-to-stand were all defined as sit-to-stand movements. An algorithm that differentiates between sit-to-walk and sit-to-stand movements could add relevant information to this research question and beyond. For the distribution of gait speed, sit-to-stand peak power, and turning peak angular velocity, we stacked all the days together to obtain one distribution over the entire daily activity phase per participant. It would be interesting to analyze the distributions of these parameters for each day separately and observe their

variation and reliability for each day of measurement. Another point was that since some of the unitless parameters showed significant differences between the two groups (Figure 7.2), we were curious if adding them to the feature set $\mathbb{F}1$ will improve the classification results in Table 7.4. However, no improvement was observed. The reason might be that the ratio of home-derived mobility parameter divided by the same parameter obtained in the lab did not bring additional information as the information regarding both of the assessment settings were already there. Finally, to keep data accuracy as high as possible, we excluded walking bouts <15 seconds from the analysis. However, these walking bouts contribute to a relevant portion of daily walking (Del Din, Godfrey, Galna, et al., 2016), and removing them might affect the meaningfulness of walking parameters with respect to the actual research question. Nevertheless, most of the participants completed the TUG test in more than 15 seconds making the comparison between lab and daily activity assessments fairer.

7.5 Conclusion

To conclude, the use of the IMU along with the dedicated algorithms allowed an unobtrusive assessment of mobility during daily activities. Although lab-based mobility parameters had generally higher discriminative power in differentiating PD-FOF+ and PD-FOF-, integrating daily activity assessments provided a more accurate classification of these patients. By comparing the same parameters from both settings, we could show for the first time that (i) considering lab and daily activity mobility parameters can lead to a more accurate classification of PD-FOF+ and PD-FOF- compared to each lab and daily activity assessments alone (ii) the PD-FOF+ group performs the lab assessments with a rather cautious gait but used a rather incautious gait pattern in the usual environment; and (iii) the sit-to-stand peak power of the 5xSTS test with preferred speed and of the TUG were more closely associated with sit-to-stand movement in daily life, than was the same parameter obtained from the fast 5xSTS, and (iv) the 5xSTS test with fast speed measured mostly capacity aspects of daily activities. These results provide further insight into the daily life behaviour of PD patients with FOF, can stimulate prevention and treatment strategies, and can serve as a template for further studies using these novel techniques and assessment strategies.

Part IV

Conclusions

8 General discussion and perspective

8.1 Main contributions

The main objective of this thesis was to demonstrate the added value of IMU-based assessment of mobility and to better understand the link between its clinical and daily activity assessments. To achieve this objective, I needed to address some of the existing gaps in the literature especially on the technical side, i.e. the algorithm design. Thus, I dedicated the second part (Part II) of this thesis to algorithm development and validation.

Having reliable algorithms to firstly detect gait and PTs and extract accurately gait speed and biomechanical parameters during PTs, the next step would be to show how these parameters are clinically valuable. In other words, an instrumented mobility assessment with an IMU should be beneficial for the patient, clinician, and the health service to help for a better diagnosis and evaluation of gait and balance (Rochester et al., 2020). To this end, I have also focused on clinical applications which were partly shown in the second part of the thesis and then mainly in the third part.

The clinical applications of the IMU-based mobility assessment were shown in several populations, e.g. patients with PD, older adults, faller older adults, and MS patients. In Part III, I demonstrated these applications during clinical and daily activity assessments. It was shown how different biomarkers of mobility extracted from a single IMU can help us differentiate better patient populations and monitor the effect of intervention such as Levodopa in PD patients. Although community-dwelling older adults and patients with PD were the focus of this part of the thesis, the framework provided in these studies could be applied to any population in which both clinical and daily activity assessments exist.

It is worth mentioning that while wrapping up the conducted studies and writing this thesis, some studies were published that had similar goals and sometimes similar methodology and findings as ours (Adamowicz et al., 2020; Gaßner et al., 2020; Tietsch et al., 2020; Wang et al., 2021). This shows the importance of the current topic and the need for a more in-depth

analysis of mobility. In the following sections, I explain in details the achievements of this thesis alongside the take home messages.

8.1.1 Robustness of the algorithms during real-life settings

The novelty and contribution of our algorithms regarding PT and gait were their robustness to sensor placement changes. This aspect will suppress the need for cumbersome functional calibrations during the measurements and provide more reliable and comfortable measurement system for both the clinicians and the users. Especially, during daily activities or remote assessments where the user attach the sensor themselves without the help of a specialist. Indeed using the vertical acceleration in the global frame made the PT and walking bout detection and gait speed estimation algorithms independent of the location of the sensor around the waist. Being based on a single IMU on the lower back, the proposed methods for PT detection and characterization as well as walking bout detection and speed estimation provide comfort for their users.

The positive predictive value of the PT detection algorithm did not differ between different sensor locations around the waist. Regarding the sensitivity, we observed a difference of 8% and 10% in detecting the sit-to-sand and stand-to-sits, respectively.

Another significant contribution of the PT detection and characterization algorithm was the fitted displacement model. Firstly, this sigmoid model (Equation 3.6) allowed a better filtering of true PTs because of the similarity between the sigmoid model and the displacement of the trunk in a PT. Such modelling can justify why we had a better PT detection performance compared to (Adamowicz et al., 2020; Pham et al., 2018) in which only a constant threshold for displacement was used to filter true PTs. Moreover, our fitted displacement model allowed the isolation of PTs from other movements during daily activities. In fact, by an isolated signal, parameters such as peak power, peak acceleration, and transition duration would be obtained more easily and accurately (Figure 3.11).

Regarding gait, altering the location of the sensor around the waist or even placing the sensor on the trunk lead to a maximum difference of 0.03 m/s in RMS error (annex 4B). This is mainly due to using the vertical acceleration of the trunk (whether lower or upper) as the main signal to extract the features for the gait speed estimation model. As it was shown both in chapter 3 and annex 4B, the vertical acceleration signal is approximately similar through multiple IMU locations on the trunk. Nevertheless, some part of the small differences between different locations were shown to be due to soft tissue artifacts. Interestingly, it was shown that the dissimilarity of the vertical acceleration signals obtained by different IMU locations on the trunk, is directly associated with the body mass index (BMI). The higher the BMI, the more fatty tissue artifacts, and consequently, the higher the difference between the signals of various IMU locations (annex 4B). This is indeed a novel finding as it implies that the effect

of soft tissue artifacts may be removed easily by considering a linear relationship between BMI and the attenuation coefficient of the signal (annex 4B).

Another factor contributing to the small differences between the accuracy of the algorithms (regarding PT and gait) is the fixation of the sensor. By taking a closer look on the fixation of the IMUs to the body, these little differences were attributed to the rigidity of the sensor attachment. Therefore, an important take home message was that fixation in addition to the placement of the IMU to the body plays a major role in the accuracy of an estimated parameter like gait speed or sit-to-stand duration. A rigid fixation can result in a more robust and accurate estimation.

8.1.2 Performance of the algorithms in different populations

Another contribution of the technical part of this thesis was that the algorithms were validated during daily activities in addition to clinical assessments. Both healthy individuals or participants with mobility disorders were included in the algorithm validation providing reliability of the algorithm.

The proposed algorithms demonstrated high performance. For instance, to detect PTs, a mean positive predictive value (and mean sensitivity) of 98% (95%) for healthy individuals and 89% (89%) for participants with mobility impairments were achieved (chapter 3). In the same chapter, I demonstrated the effect of sensor placement changes on the accuracy of the biomechanical parameters extracted by the IMU during PTs. It was shown that L5 and trunk location were the most accurate locations to obtain the transition duration as well as the trunk tilt angle.

To detect walking bouts, a sensitivity of 93%, specificity of 97%, and F1-score of 77% were obtained during daily activities of participants with multiple sclerosis (MS) (chapter 4). Furthermore, during simple daily activities, the F1-score of walking detection for healthy younger adults were obtained as 87% (annex 4B). The performance of PT and walking detection methods did not change considerably by sensor placement changes around the waist.

The gait speed estimation algorithm had a root mean square (RMS) error of 0.15 m/s for MS patients and 0.11 m/s for healthy younger adults (chapter 4 and annex 4B). The high performance of the algorithm introduced in chapter 4 was further supported by a bias of almost zero for estimating gait speed.

8.1.3 Novel machine learning-based gait analysis method

Finally, the novelty of the machine learning-based method introduced in chapter 4 was that the gait speed estimation model can be trained by reference systems. The reference system that is used for training can take the form of a silver standard reference such as a multi-IMU

setup or a gold standard reference such as instrumented walkways. By training the model based on these reference systems we can maintain the reliability of the lower-back IMU in estimating gait speed during daily activities. The gait speed model can be developed for a specific population by a training phase in the lab or even at home (chapter 4). Alternatively, the model can be obtained for the general population by training in a large dataset as well as considering the demographic and characteristic of the participants as the features.

8.1.4 Mobility biomarkers

In almost all of the chapters of this thesis, clinical applications of the IMU-based mobility assessments were demonstrated. The extracted mobility parameters from the IMU could trace the subtle changes between patient populations. Biomechanical parameters extracted from the IMU during PTs differentiated between healthy individuals and patient populations (chapter 3). Furthermore, by instrumenting the five-time sit-to-stand (5xSTS) test with an IMU, the prospective fallers could be predicted (chapter 5). Indeed, extracting parameters in kinematic, kinetic, and smoothness categories characterized the balance performance of a large cohort of community-dwelling older adults (N=458). Therefore, more information rather than a mere duration of the test measured by a stopwatch was obtained which led to a better prediction of risk of falls in community-dwelling older adults.

The predictive power of the IMU-based parameters was not only limited to the PTs. Gait speed demonstrated a high discriminative power and effect size. For instance, gait speed obtained during the 10-meter walk test (10MWT), whether at the lab or home, discriminated MS patients in the moderate and severe stages of the disease. Moreover, maximum turning velocity during the second turn of the timed-up-and-go (TUG) test showed a high discriminative power to distinguish PD patients with fear of falling.

8.1.5 Novel approaches to compare clinical and home assessments and their application in monitoring the effect of medication

The main contribution of this thesis regarding the clinical part was to show how conjoint clinical and daily activity assessments can provide remarkable insights into the mobility of the individuals. Particularly, I introduced a novel approach to compare gait speed of participants with PD during clinical and daily activity assessments (chapter 6). Most of the works in the literature, consider mean and standard deviation values for gait speed distribution. However, sometimes this assumption might not be true, especially during daily activities where the context is more complex. Therefore, I fitted a bimodal Gaussian distribution on the gait speed during both daily activities and a variety of walking tests performed in the clinic (chapter 6). The presentation of a bimodal Gaussian distribution was demonstrated for the first time in patients with PD. By this novel approach, it was concluded

that the participants had on average similar modes of gait speed. This indicates that people may have similar preferred gait speeds in different environments whether in the lab or in the clinic. Such kind of comparison between clinical and daily activity assessment was further exploited to study the effect of medication dose in PD. By comparing modes of gait speed between these two assessments, a significant and moderate correlation was observed between number of medication dose and the difference between clinic and home. The higher number of medication doses at home lead to a higher gait speed at home. Therefore, by comparing the modes of gait speed between clinic and home, the clinician can adjust the number of medication doses throughout the day.

Another novel approach to compare gait speed between clinical and daily activity settings was the Exceptional Strides concept that was introduced for the first time in this thesis. The increase in the number of Exceptional Strides after taking the medication showed the potential to monitor its efficacy. In fact, by the capacity of the patients in the clinic, we can define a baseline to evaluate the patients' performance at home.

Therefore, the bimodal comparison of gait speed can help the clinicians to optimize the number of medication doses while the Exceptional Strides can be analyzed to determine the timing between medication doses. The findings and methods of chapter 6 can contribute for a better monitoring of Levodopa to avoid the motor fluctuations and dyskinesia in PD.

8.1.6 Complementary information of clinical and home assessments

Another aspect that was shown in this thesis was that how daily activity assessments can provide complementary information to clinical assessments. In addition to monitoring the effect of medication, daily activity assessments provide more information to classify different patient populations. For instance, in chapter 7, although mobility parameters obtained in the lab had generally higher effect sizes than the daily activity assessment, considering both of the assessments together improved the classification results. When parameters from both of the settings were considered, an AUC value of 0.75 (versus 0.68 for lab and 0.54 for daily activities) was obtained in classifying the two groups. This shows how daily activity measurements can complement lab-based assessments. Comparing the same parameters between lab and daily activities, we noticed that patients with FOF had been impacted more by the white-coat effect as they had higher gait speeds during daily activities. The same finding was also observed in the Annex 4.B where there were two participants in the severe stage of MS that had higher gait speeds at home compared to the lab. Although further research is required to confirm these findings, they might suggest that patients with a more impaired mobility might not perform their best during clinical assessments. This group of patients might have some concerns during clinical assessments that need to be resolved by being reassured in the clinic.

Finally, our studies concerned also the degree of association between clinical and daily activity assessments. In the literature, most of the times, the functional walking tests such as the 10MWT are being performed in the clinic. However, by performing the 10MWT at home in participants with MS, I studied its association with respect to the same test in the clinic (annex 4A). Although no significant difference was found between these two settings, there was a tendency to a higher gait speed during clinical assessment. Furthermore, high correlation was obtained between gait speed obtained in these two settings. These findings can support the remote assessment of mobility during functional tests in the domestic environments of the individuals as they showed high association with respect to the clinic. This remote assessment can prevent unnecessary commute of the patients to the clinic to save time and costs. Furthermore, it can help the vulnerable in situations such as COVID-19 pandemic. Such assessment can also be obtained during daily activities at home. For instance, in chapter 6, it was shown that Exceptional Strides occurred during longer walking bouts, i.e. walking bouts longer than one minute and during ON medication state, starting 30 minutes after medication intake and reaching their maximum around 3 hours after taking medication. These strides composed 1% to 25% of the overall strides of the patients, meaning that if a clinician wants to have an overview of the patients' capacity during daily activities, they need to extract the higher percentiles of the distribution at home, e.g. between 75th to 99th percentile. On the other hand, if due to some circumstances, the patients cannot be monitored during daily activities, by determining the degree of correlation between clinical and daily activity assessments, the clinician can know which functional tests are better representative of patients' performance in the clinic. As it was demonstrated in chapter 6, demanding tasks (such as circular walking test or straight walking test as fast as possible) rather than a straight walking test with patients' preferred speed should be performed. Regarding the 5xSTS test, the test with participants' preferred speed had high correlation with their sit-to-stand performance during daily activities (chapter 7). However, the same test with as fast speed as possible did not.

8.2 Applications in industry and health care

This thesis has been conducted under the framework of the Keep Control European project as an industrial academic initial training network. Therefore, the algorithms developed in this thesis are the property of Gait Up, a MindMaze Holding Company. To exploit the outcomes of the developed algorithms, turning them into a commercialized product is an important step to solve the problems of the users and improve the quality and robustness of the algorithms. Some of the developed algorithms have been already implemented by my colleagues at Gait Up S.A. on a smart-phone application called Gait Up GO as a medical product (Figure 8.1). The purpose of such a product is to instrument the functional tests based on a single IMU that can be performed anywhere by either the patients or the specialists. For instance, the instrumented 5xSTS test is one of the functional tests included in this application that can

generate a report for the user's feedback (Figure 8.2). Indeed several steps are required to flourish a product from an algorithm coded in MATLAB. Firstly, the algorithm should be optimized in terms of computational costs and be adapted (e.g. the sampling rates and filters) to meet the hardware settings. The codes should be translated into a programming language that is compatible with the hardware. The software that is the interface between the user and the raw signal should be designed in a way that every action of the user is predicted. Because in the end, no matter how perfect and accurate the algorithm is, it should provide usability and adherence for the user. The connection between the IMU and the smartphone is also important during a real-time application. The data should be transferred without any delay with no loss in order to have accurate results.

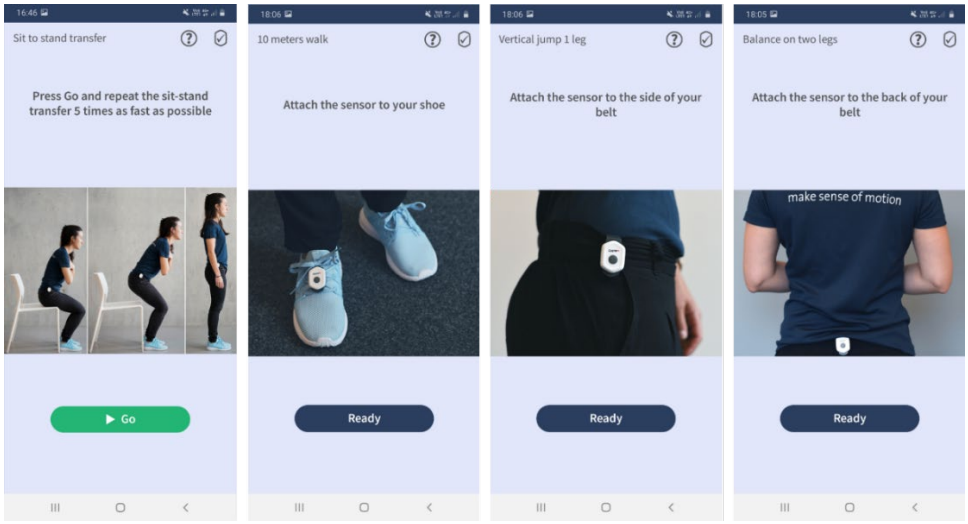

Figure 8.1: A functional test integrated into the app Gait Up GO developed by Gait Up S.A.

8.3 Limitations and challenges

While for each chapter, I explained the limitations of the corresponding study individually, here I summarize the general limitations throughout this thesis.

8.3.1 Algorithm design and validation

Regarding the PT detection algorithm, although the performance of the algorithm was high in general, we had some reduction in the performance when the sensor was placed on the sternum or when the algorithm was validated in PD patients. The source of this lower performance was mostly an inaccurate displacement model due to the drift caused by double integrating the vertical acceleration especially in PD patients that had a longer PT duration. More work is needed to obtain a drift-free displacement signal. A potential solution can be fusing the data of vertical acceleration and barometric pressure sensor data with fusion methods such as Kalman filter.

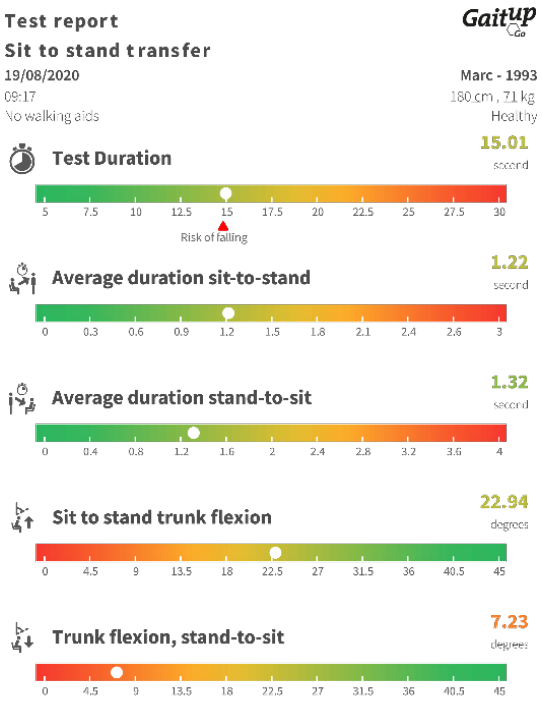

Figure 8.2: The report generated by the Gait Up GO app after performing the 5xSTS test

Another limitation of the PT detection algorithm was its lack of possibility to detect the unsuccessful attempts of rising up from a chair. Adding the number of unsuccessful attempts to the biomechanical parameters extracted during the 5xSTS test in chapter 5 could increase the accuracy of falls prediction (Najafi et al., 2002). Having in mind that failed PTs have generally lower peak vertical velocity of CoM than successful PTs, we could separate those PTs simply by a threshold on the vertical velocity (Zablotny et al., 2003).

In the third chapter, I only focused on the number of PTs but not on the sitting (i.e. between a stand-to-sit and the next sit-to-stand) or standing (i.e. between a sit-to-stand and stand-to-sit when the subject is not walking) periods. Having this information can help us better obtain the activity status of the individuals during the day and separate sedentary from standing periods. Combined with the walking bout detection and gait speed estimation developed in the fourth chapter, we can perform complexity analysis of activity. This could be done through coding the activity to different levels and evaluating the dynamics of code changes, similar to "barcoding concept" proposed by (Anisoara Paraschiv-Ionescu et al., 2012) but with only one IMU instead of three.

In detecting the PTs, I simply grouped all the transitions into sit-to-stands and stand-to-sit. However, during daily activities, the postural transitions are different and they might not be exactly a sit-to-stand or stand-to-sit. For instance, as most of the times, we walk after standing up from a chair, we can expect that most of the sit-to-stands are actually sit-to-walks. Or other transitions can be walk-to-sit, sit-to-lie, etc. Devising an algorithm that can detect all

of these transitions separately can provide us a more detailed information regarding the physical activity of the individuals. For example, when comparing different patient populations, the sit-to-walks might have more discriminative power than sit-to-stands as sit-to-walks are more demanding daily activities.

The developed algorithms regarding walking bout detection and speed estimation were based on machine learning methods making them dependent on the population being trained and tested. Therefore, a model tested on MS patients for example, might not be accurate on the population of healthy adults. This problem can be solved by taking into account the demographics of the individuals and the characteristics of their health status as the features fed into the model. For instance, it was shown that adding demographic data or considering two separate gait speed estimation models for slow and fast walkers can help to improve the performance of the algorithm (Byun et al., 2019). More importantly, by having a larger datasets with a broad range of populations with different characteristics we might have a better model as in any machine learning approach.

Moreover, our approach required a training approach in the lab. Although for patients that perform walking tests in the clinic, providing such a dataset may not be a problem, still a lab session is required to train the gait speed model. An alternative solution can be a personalized approach that is explained in section 8.4.2.

It is worth mentioning that gait is one of the numerous means of locomotion. Although I simplified all the detected locomotion periods as gait, this assumption might not be always true. For instance, individuals might walk or run in different settings such as slopes, stairs, or rugged ground during daily activities. While I supposed that participants were always walking on flat ground, the accuracy of our walking bout detection and gait speed estimation algorithms needs to be obtained during these occasional settings. Furthermore, for participants with mobility disorders, the accuracy of the algorithm during shuffling or other abnormal gaits should be studied and if necessary other algorithms should be devised for these altered gaits.

8.3.2 Clinical application studies

Predicting fall older adults was only limited to the 5xSTS test (chapter 5). While several metrics obtained by the IMU could differentiate between fallers and non-fallers, their effect size was not high to well separate these two groups. This can be due to the fact that more functional tests might be needed to have a more robust evaluation of the patients' physical function. For instance, walking tests such as TUG or 10MWT as well as more balance tests such as Tandem can be added.

In chapters 6, 7, and partly in chapter 4 where we had unsupervised and long-term assessments outside the clinical environment, we faced several challenges during this type of monitoring.

One of these challenges is triggering the data recording. For instance, in chapter 4, we lost a large part of the data due to slow Bluetooth connection between phone and the IMUs used to start the data recording. Because in this study, the patients had been asked to perform the TUG test in addition to the 10MWT. However, after data collection, I noticed that for almost 90% of the measurements the first part of the test, i.e. sit-to-stand transition, was missing and the signal started in the middle of the walking bout. Patients had pressed the start button while they immediately stood up from the chair causing some part of the signal to be lost before the sensors actually start the measurements. This problem was seen only after the analysis of the data had been started. Therefore, as all of the data had been collected, a compensation for the rest of the measurements was not possible. Thus, we had to exclude TUG test from our analysis. This issue could be solved by displaying a countdown from 5 to 1 on the smartphone while the IMUs are recording the data. The patients should be asked to start the test only after the countdown which allows a static phase at the beginning of the test and prevents the loss of data. This in general shows that there should be a thorough thinking and scrutiny about the usability and ergonomics of the product.

Another problem that was raised was charging the IMUs. Because like other electronical devices with battery they need to be charged. We had received several reports that patients had difficulties charging the sensors through a micro USB charger as this was the only mean to charge the IMUs. This caused the sensors to not be charged correctly and the battery life was finished in the middle of daily activity measurements. Furthermore, if the battery finishes, the internal clock of the IMU does not work anymore and the time needs to be readjusted by a computer. Several times we received back some of the sensors that were broken due to misuse. Therefore, as our patients were mostly older adults, we could not expect them to perform all of these steps by themselves. Some part of these problems were solved by my colleagues at Gait Up by upgrading the firmware of the Physilog IMUs and increasing the battery life from 10 hours recording to more than a day. Another idea to potentially solve these issues was to design a smart charging dock station to charge the sensors while their clock can be adjusted and the data can be transferred automatically through internet. Nevertheless, the charging dock might also have its own problems. Therefore, the success rate of such devices might be improved only with more usages. Big companies like Apple or Fitbit can help to grow the market and the usability of such wearables.

These problems affected our measurement in chapter 6 where some of the IMUs, especially the IMU on the lower back could not be charged correctly; therefore, I had to use the IMU on the right foot to extract gait speed. Out of 39 patients enrolled in the daily activity measurements, we had 27 patients with a complete amount of daily activity data with the IMU on the right foot (which I used for the data analysis in chapter 6) and 15 patients with the IMU on the lower back. It has to be mentioned that participants of this study had been equipped with three IMUs on the lower back, right foot, and right wrist during daily activities

and we decided to use only the right foot IMU as the population having complete data with other sensor placements was too small.

Loss of data was not only limited to Physilog IMUs. In chapter 7, where the RehaGait (Hasomed, DE) system was used, almost the same amount of data loss was observed. Originally, 42 patients had participated in the study while only 26 patients had completed daily activity measurements.

The number of participants with complete data was compared between supervised (clinic) and unsupervised (home or daily activities) assessments in Table 8.1 for different chapters of this thesis where we had both the clinical and home assessments. The data loss in the datasets from supervised to unsupervised assessment shows the challenges involved in the unsupervised setting. While the reasons have been discussed extensively in chapter 4 (section 4.6) and in this section, this shows the long road ahead for the integration of the IMUs in real-life and daily activities of the patients. Although the scope of this thesis was mainly robustness and accuracy through algorithm development, an impartial study is required to explore the usability and acceptability of such a system during unsupervised assessments. Nevertheless, we can expect that a single IMU system can provide better usability compared to a multi-IMU setup.

Table 8.1: Comparing the number of participants with existing data between supervised and unsupervised assessments in the chapters that we had both of the assessments

	Number of participants		Percent decrease
	Supervised assessment (clinic)	Unsupervised assessment (home)	
Chapter 4	35	14 (10MWT) 9 (daily activity)	60% (10MWT) 75% (daily activity)
Chapter 6	39	27	31%
Chapter 7	42	26	39%

8.4 Perspective for future studies

Aside from its achievements, this thesis paves the way for future research on unsupervised assessment of mobility. While improving the limitations stated in the previous section can be a starting point, here, I introduce additional points that can be considered as future developments.

8.4.1 Comparison of sit-to-stand pattern between individuals

To characterize the postural transitions, I focused mostly on biomechanical parameters such as peak vertical velocity, peak power, etc. throughout this thesis. However, the pattern of performing the postural transitions can also give us more information about the performance of the individuals. This pattern can be quantified by the trajectory of the CoM obtained by the displacement of the IMU on sacrum in the sagittal plane. For example, for a healthy young adult and a PD patient (from the dataset of chapter 3), the trajectory of the IMU displacement in the sagittal plane during a 5xSTS test is shown in Figure 8.3. The pattern of the two individuals differed substantially. It can be observed that for the young healthy subject, the sit-to-stand strategy is closer to momentum transfer strategy introduced in section 2.3.1 while the PD patient had mostly the stabilization strategy (Figure 2.8). While this example is only for presentation purposes, for a fair comparison, the effect of different chairs and different body heights should also be considered. This kind of comparison has been introduced for the trajectory of the foot and showed a promising performance in distinguishing an activity or a group of patients (Benoît Mariani, 2012). The challenge for performing such analysis will be removing the drift from the displacement signals obtained by the integration of vertical and anterior-posterior velocity signals. Updating the displacement signals to zero for each sitting period would be a potential solution to overcome this challenge.

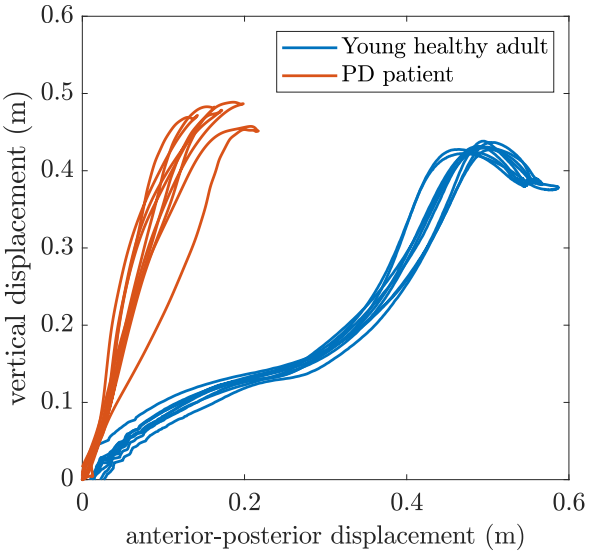

Figure 8.3: Comparing the pattern of the CoM displacement during the 5xSTS test for a young healthy adult and a PD patient (data from the dataset of chapter 3)

8.4.2 Personalized gait speed estimation

As I discussed in chapter 4, our proposed method for gait speed estimation and walking bout detection can also be implemented to develop a personalized model. In this case, there will be

no need for a training phase in the lab. Participants can be asked to wear three IMUs, one on the waist, and two on the feet and perform their usual daily activities. Once, enough data has been gathered to obtain accurate gait speed estimation and walking bout detection models, the user can take off the feet IMUs and continue their daily activities with only the IMU on the waist. In this way, the walking bout detection and speed estimation models will be independent of the population. To have an accurate estimation, the required amount of training in terms of data recording duration should be obtained. For instance, for one of the MS patients that participated in our study in chapter 4, I measured the root-mean-square error (RMSE) of the gait speed estimation during 5 hours of daily activities by varying the duration of data used for training (Figure 8.4). It can be seen that after using around 75 minutes of the daily activities for training the gait speed estimation model, we could reach a steady RMSE of 0.18 m/s that did not improve by increasing the amount of training set. It has to be mentioned that any system with an accurate estimation of gait speed can replace the foot IMU, whether an instrumented walkway, or a markerless camera system that is accurate and reliable.

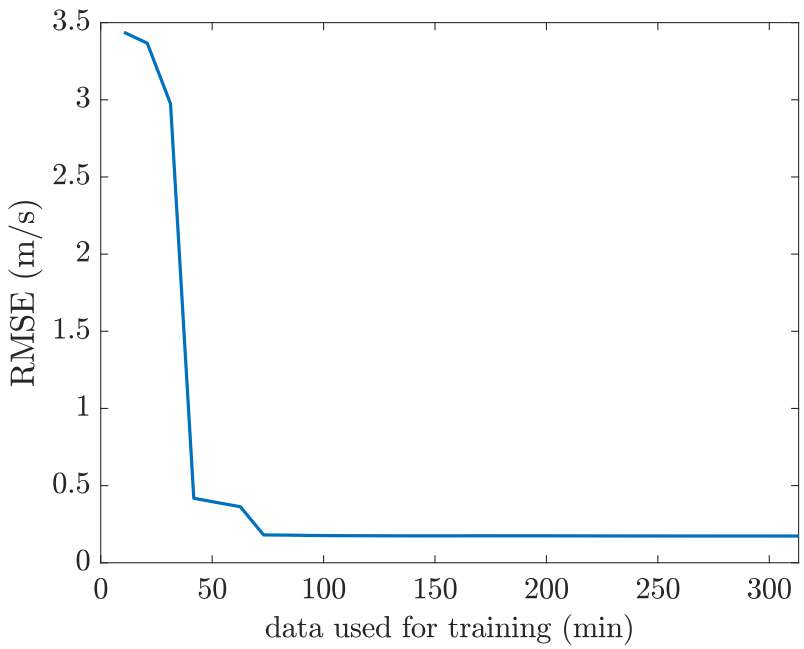

Figure 8.4: Personalized gait speed estimation for an MS patient as an example. The root-mean-square error (RMSE) of the predicted gait speed throughout the measurement (5 hours of daily activities at home) compared to the reference remained unchanged after around 75 minutes of data used for training

8.4.3 Benchmarking commercial devices that estimate gait speed

As introduced in chapter 1, there are emerging wearables such as Apple Watch or iPhone that can estimate walking speed, walking asymmetry, step length, and double support time. To

evaluate the reliability and accuracy of such systems, one can perform several measurements in the lab as well as during daily activities and compare the results to the gold standard reference systems. Such a benchmarking should be done in several populations, whether healthy younger adults or older adults with mobility disorders. This benchmarking can let us know how accurate are the built-in algorithms of this device in obtaining those parameters in different populations. An inaccurate result might suggest the need for an application that can replace the iOS internal mobility assessment app while using the raw data of iPhone or Apple Watch.

8.4.4 Effect of intervention on clinical and home assessments

Although I showed the effect of medication on the difference between clinical and daily activity assessments, I did not study how much an intervention can affect these two settings separately. As the final goal of an intervention such as medication, surgery, or rehabilitation is to improve the daily life of the patients, it would be interesting to see how an intervention affects capacity and performance separately. For instance, imagine a patient that has almost the same capacity as a healthy individual but with lower performance in daily activities. Therefore, to have an optimal effect, the prescribed intervention for this patient can be adapted to improve their performance rather than their capacity.

8.4.5 Amount of walking in patients with MS

In chapter 1, we introduced the EDSS questionnaire that is currently used in the clinic as a scale of the stage of disease in MS. It was also mentioned that a score of 4.0 or higher implies mobility impairment. From this score, the patients are rated based on their daily activity walking, e.g. 500 meters, 200 meters, etc. Therefore, the amount of walking is very important to evaluate the stage of the disease in MS. As our dataset in chapter 4, regarding the daily activity of the patients was too small, we could not analyze accurately the amount of daily walking for the participants. Therefore, in a larger dataset, obtaining the amount of walking per day for MS patients with the algorithm proposed in chapter 4, can reveal the association between an EDSS score and the objective amount of walking obtained by an IMU. It is worth noting that the amount of walking that can be obtained by our algorithm is specified in duration, e.g. 60 minutes of walking. However, due to inter- or intra-individual gait speed variability, it is better to specify the amount of walking in meters. A solution can be to multiply the duration of each walking bout to its average gait speed. By summing the traversed distances of each walking bout, the amount of walking in meters can be obtained in meters per day. An alternative solution would be to estimate stride length rather than gait speed. In this case, the total walking distance would be the sum of all the stride length values.

8.4.6 Best performance through the day or the week

In the literature as well as in this thesis, when the goal was to extract a parameter during the long-term daily activity measurements, the whole duration of the measurement has been considered. For instance, if one week of daily activity assessment has been performed, the distribution of the whole measurement throughout the week has been considered to extract the 95th percentile of gait speed as an example. However, if we look at each of the 7 days individually, we might obtain different values for this parameter (95th percentile of gait speed). It would be interesting to evaluate the reliability of such parameters by calculating their ICC (Intra-class correlation coefficient) values. Furthermore, it should be investigated which value of a parameter (p) can represent better the performance of the patient (p can be any parameter, for instance, the 95th percentile of gait speed):

- Best p_i, in which p_i is obtained during the i^{th} day of the week
- $\frac{1}{7}\sum_{i=1}^{7} p_i$, which is the average of p_i throughout the week
- Or p which is the corresponding parameter over the whole days of the week stacked together.

8.4.7 Using other wearables and technologies

In chapter 1, I introduced IMU-based mobility devices as one of the many wearable devices that are currently available. While these wearables provide us a valuable information about the mobility of the people during the day, the role of other wearable devices should not be neglected in daily activity monitoring. For instance, sleep trackers can quantify the quality of the sleep by several parameters such as total amount of sleep, the sleep efficiency, and amount of waking ups (Dickinson, Cazier, & Cech, 2016; Pigeon et al., 2018). Accelerometers, heart rate and respiration sensors can be used in sleep tracker devices. Therefore, with these devices we can integrate the amount and the quality of the sleep with the physical activity of the patients during the day. Furthermore, heart rate sensors can measure the intensity of a physical activity (Düking et al., 2020). These sensors might have the potential to be fused with the information from the IMUs to estimate gait speed or provide a more accurate information about the intensity of an activity. Nevertheless, the higher number of devices can put their usability at risk. Therefore, a trade-off would be to use a smartwatch in which all of these sensors are integrated.

Rather than wearables, other technologies can also be implemented for a more accurate mobility assessment and more detailed information. For instance, instrumented shoes in which pressure sensors are integrated with IMUs can provide a more accurate classification of daily activities and detection of gait events. Markerless camera systems can also be used with careful consideration of the privacy of the users.

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Curriculum Vitae

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Education

Ecole Polytechnique Fédérale de Lausanne (EPFL), Ph.D. Oct 2017 – May 2021

- Robotics, Control, and Intelligent Systems program (EDRS)
- Laboratory of Movement Analysis and Measurement (LMAM)
- Thesis: "Toward an objective assessment of mobility in clinical and daily activity settings"
- Supervised 4 semester projects and 1 master internship
- Teaching assistant of the courses "Analysis and Modelling of Locomotion" and "Design and Optimization of Internet-of-Things Systems"

Sharif University of Technology, M.Sc. Sep 2014 – Sep 2016

- Mechanical Engineering, Dynamics and Control
- Thesis: "Fusing Kinect and inertial measurement units with unscented Kalman filter to track human arm movements"
- Teaching assistant of the course "Modern Control"

Shiraz University, B.Sc. Sep 2010 – Sep 2014

- Mechanical Engineering
- Thesis: "Design and manufacturing of a cable robot"
- Teaching assistant of the laboratory "Mechanics of Materials"

Professional Experience

Gait Up S.A., Algorithm researcher Oct 2017 – Oct 2020

- Lausanne, Switzerland
- Ph.D. in industry as part of the European project Keep Control, algorithm developer for motion analysis with inertial measurement unit

Saipa Automotive Research and Innovation, Research assistant Jan 2017 – Aug 2017

- Tehran, Iran
- Working on the design and simulation of an engine mounting system to minimize the transferred noise and vibration from the engine to the vehicle's chasis

Institute for Advanced Medical Technologies, Research assistant Oct 2016 – Dec 2016

- Tehran, Iran
- Working on the tracking of the laparoscopic tool in robotics surgery using inertial measurement units

Publications

- **Atrsaei, A.**, Dadashi, F., Mariani, B., Gonzenbach, R., & Aminian, K (2021). Toward a remote assessment of walking bout and speed: application in patients with multiple sclerosis. *IEEE Journal of Biomedical and Health Informatics*.

- **Atrsaei, A.**, Corrà, M., Dadashi, F., Vila-Chã, N., Maia, F., Mariani, B., Maetzler, W., & Aminian, K. (2021). Gait speed in clinical and daily living assessments in Parkinson's disease patients: performance versus capacity. *npj Parkinson's Disease*, 7(1).

- **Atrsaei, A.**, Mariani, B., & Aminian, K. (2021). Comparison of the gait speed assessed during an instrumented 10-meter walk test at home and clinic in patients with multiple sclerosis. *Neurorehabilitation and Neural Repair*. (abstract accepted for publication, based on the oral presentation at the 11th World Congress for NeuroRehabilitation, Lyon, France 2020)

- **Atrsaei, A.**, Dadashi, F., Hansen, C., Warmerdam, E., Mariani, B., Maetzler, W., & Aminian, K. (2020). Postural transitions detection and characterization in healthy and patient populations using a single waist sensor. *Journal of NeuroEngineering and Rehabilitation*, 17, 1-14

- Warmerdam, E., Hausdorff, J. M., **Atrsaei, A.**, Zhou, Y., Mirelman, A., Aminian, K., ... & Maetzler, W. (2020). Long-term unsupervised mobility assessment in movement disorders. *The Lancet Neurology*, 19(5), 462-470.

- **Atrsaei, A.**, Salarieh, H., Alasty, A., & Abediny, M. (2018). Human arm motion tracking by inertial/magnetic sensors using unscented Kalman filter and relative motion constraint. *Journal of Intelligent & Robotic Systems*, 90(1), 161-170.

- **Atrsaei, A.**, Salarieh, H., & Alasty, A. (2016). Human arm motion tracking by orientation-based fusion of inertial sensors and Kinect using unscented Kalman filter. *Journal of biomechanical engineering*, 138(9).

Publications under review

- **Atrsaei, A.**, Paraschiv-Ionescu, A., Krief, H., Henchoz, Y., Santos-Eggimann, B., Büla, C., & Aminian, K. Instrumented five-time sit-to-stand test: parameters predicting serious falls beyond the duration of the test. *Gerontology*

- **Atrsaei, A**., Hansen, C., Elshehabi, M., Nussbaum, S., Berg, D., Liepelt-Scarfone, I, Maetzler, W., & Aminian, K. Effect of fear of falling on mobility measured during lab and daily activity assessments in patients with Parkinson's disease. *Journal of Parkinson's Disease*

- Corrà, M., **Atrsaei, A.**, Sardoreira, A., Hansen, C., Aminian, K., Correia, M., Vila-Chã, N., Maetzler, W., Maia, L. Comparison of laboratory and daily-life gait speed assessment during ON and OFF states in Parkinson's disease. *Sensors*

Honors and awards

- **Best booth award,** together with Ms. Cléo Moulin at the EU Falls Festival 2018, Manchester, UK
- **Silver medal winning,** National scientific Olympiad of mechanical engineering, Tehran, IR
- **Ranked 18th,** in the university entrance exam for master's degree among +24,000 participants, IR
- **Ranked 354th,** in the university entrance exam for bachelor's degree among +277,000 participants, IR