AMBULATORY MONITORING OF MOTOR FUNCTIONS IN PATIENTS WITH PARKINSON´S DISEASE USING KINEMATIC SENSORS

THÈSE N^{O} 3475 (2006)

PRÉSENTÉE LE 17 MARS 2006

À LA FACULTÉ SCIENCES ET TECHNIQUES DE L'INGÉNIEUR

Laboratoire de mesure et d'analyse des mouvements

SECTION DE GÉNIE ÉLECTRIQUE ET ÉLECTRONIQUE

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

POUR L'OBTENTION DU GRADE DE DOCTEUR ÈS SCIENCES

PAR

Arash SALARIAN

M.Sc. in Computer Engineering, Sharif University of Technology, Iran
et de nationalité iranienne

acceptée sur proposition du jury:

Prof. J. R. Mosig, président du jury
Dr K. Aminian, directeur de thèse
Dr P. Burkhard, rapporteur
Prof. R. Moe-Nilssen, rapporteur
Prof. D. Thalmann, rapporteur

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Lausanne, EPFL
2006

To my parents, Susan and Kamal-al-din

Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease in the general population. Cardinal symptoms of Parkinson's disease are resting tremor, rigidity, akinesia and bradykinesia and in advanced stages, gait impairments, postural instability and complications of chronic treatment with levodopa such as motor dysfunctions and dyskinesia. Multitude and complexity of these motor symptoms and their variability over the time have made assessment of them a difficult task. Moreover, following the fluctuations of motor performance (ON/OFF fluctuations) of the PD patients throughout their daily activities by quantifying their motor symptoms is a major challenge.

The aim of this thesis was to design and validate a portable ambulatory movement analysis system for long-term monitoring and qualitative and quantitative assessment of motor abnormalities of PD patients during daily activities.

We have designed a new measurement system consisting of five independent, lightweight, autonomous sensing units based on kinematic sensors that can continuously record body movements during daily life. Using this system and by performing several clinical studies, both in controlled conditions and on free moving patients, we have prepared a database of different movement patterns of PD patients. This database was the basis to design several new algorithms for the analysis of tremor, bradykinesia, gait and posture.

An accurate algorithm based on spectral estimation has been proposed to detect and quantify tremor during daily activities of PD patients with a resolution down to three seconds using gyroscopes attached to the forearms.

By quantifying the speed, range and the frequency of the movements, we have proposed a new method to assess the bradykinesia and tested it both in controlled and free conditions. We found out that in the free moving patients, the outcomes of this algorithm show significant and good correlation to the established clinical scores.

Regarding the detection and analysis of gait, we have developed and tested a method based on four sensors attached to the lower limbs that provided spatio-temporal parameters of gait with good accuracy. We further improved our method using a new biomechanical model that could predict the movements of thighs from the movements of

shanks during walking. This way we could reduce the number of sensor sites on the body while keeping the same accuracy in estimation of the spatio-temporal parameters of gait.

By combining a statistical classifier, to detect transitions between sitting and standing postures, and a fuzzy classifier, to detect the basic body postures, we have developed an algorithm to classify basic body posture allocations both in PD patients and aged matched healthy subjects.

Finally, while currently no other objective ambulatory method exists to accurately detect the periods of ON and OFF in PD patients, by combining the outcomes of the above algorithms (tremor, gait, bradykinesia and posture) using a statistical approach, we have proposed a method to detect periods of these two states with a resolution of 10 minutes in free moving patients.

We believe that the proposed system has a high potential both for the clinical applications and research purposes related to the patient with Parkinson's disease and possibly other neurological movement disorders.

Keywords: Parkinson's disease, Body-fixed sensors, Ambulatory system, Tremor, Bradykinesia, Gait analysis, Physical activity, Kinematic sensors, Biomedical signal processing.

Résumé

La maladie de Parkinson est la deuxième maladie neurodégénérative affectant l'être humain. Ces symptômes les plus importants sont les tremblements de repos, la rigidité, l'akinésie et la bradykinésie. Dans les cas plus avancés, cette maladie engendre également une dégradation de la marche, une instabilité posturale, et des complications aux traitements chroniques avec la Levodopa, comme des troubles moteur et de la dyskinésie. La multitude et la complexité, de ces symptômes moteur, associé à leur variation au cours du temps en rendent l'évaluation difficile. De plus, le suivi des changements des performances moteur (état ON/OFF) des patients atteints de la maladie de Parkinson au cours de leurs activités quotidiennes par quantification des symptômes moteur est un challenge de taille.

L'objectif de ce travail de thèse était la conception et la validation d'un système d'analyse longue durée du mouvement, à la fois ambulatoire et portable, permettant une évaluation qualitative et quantitative des disfonctionnements moteur des patients atteints de la maladie de Parkinson durant leurs activités journalières.

Un nouveau système de mesure composé de cinq unités indépendantes et autonomes a été conçu. Ces unités, de faible poids, peuvent enregistrer continuellement les mouvements du corps aux cours des activités quotidiennes. Par l'emploi de ce système lors de plusieurs études cliniques, en environnement contrôlé et en conditions libres, nous avons constitué une banque de données riche de différents patrons de mouvements de patients parkinsoniens. Cette banque de données a servit à la conception de plusieurs nouveaux algorithmes pour l'analyse des tremblements, de la bradykinésie, de la marche et de la posture.

Un algorithme précis, utilisant des gyroscopes fixés sur les avant-bras, et basé sur une analyse spectrale a été proposé pour détecter et quantifier les tremblements durant les activités quotidiennes des patients avec une résolution de trois secondes.

Par la quantification de la vitesse, de l'amplitude, et de la fréquence des mouvements, une nouvelle méthode d'évaluation de la bradykinésie a été proposée et testée en environnement libre et contrôlé. Une corrélation bonne et significative a été montrée entre les

résultats de cet algorithme et les tests cliniques reconnus, lors d'activités en environnement libre.

Concernant la détection et l'analyse de la marche, une méthode basée sur quatre capteurs fixés sur les membres inférieurs a été proposée et testée. Cette méthode fournit les paramètres spatiaux-temporels de la marche avec précision. De plus, cette méthode a été améliorée à l'aide d'un nouveau modèle biomécanique capable de prédire les mouvements des cuisses pendant la marche à partir de ceux des jambes. Cette amélioration diminue le nombre de capteurs fixés sur le corps tout en maintenant identique la précision de l'estimation des paramètres spatiaux-temporels de la marche.

Par la combinaison d'un classificateur statistique détectant les transitions entre les positions assises et debout avec un classificateur flou détectant les postures basiques, nous avons développé un nouvel algorithme ouvert pour déterminer la répartition des postures de base tant chez les patients atteints de la maladie de Parkinson, que chez des sujets sains de même âge.

Finalement, alors qu'actuellement aucune autre méthode objective et ambulatoire ne permette la détection précise des états ON et OFF des patients atteints de la maladie de Parkinson, par la combinaison des précédents algorithmes (tremblement, marche, bradykinésie et posture) au travers d'une approche statistique, une méthode pour détecter les états ON et OFF avec une résolution de 10 minutes en environnement libre a été proposée.

Nous pensons que le système proposé a un fort potentiel tant pour les applications cliniques que pour la recherche en relation avec les patients atteints de la maladie de Parkinson et éventuellement, également pour d'autres troubles neurologique du mouvement.

Motes-clés: Maladie de Parkinson, Capteur emarqué, Système ambulatoire, Tremblement, Bradykinésie, Analyse de la marche, Activité physique, Capteur cinématique, Traitement des signaux biomédical.

Acknowledgements

A Ph.D. thesis, especially in applied fields, is never a solo undertaking: combined efforts of a team are needed to realize the concepts and ideas. As such, first of all I would like to thank Dr. Kamiar Aminina, the director of the thesis, for his continuous support and guidance during past few years.

I would also like to express my gratitude to the members of my jury, Prof. R. Moe-Nilssen, Dr. P. R. Burkhard, Prof. D. Thalmann and Prof. J. Mosig who took time to read and examine my this thesis and provided me with valuable feedbacks.

Most of the ideas that shaped this thesis came from regular meetings of our working group for the last five years. I would like to thank all present members of this group, Dr. P. R. Burkhard, Prof. F. J. G. Vingerhoets, Dr. K. Aminian. Also I would like to thank previous members of our group, Dr. Y. Blanc and Dr. C. Dehollain. Mz Special thanks go to Dr. H. Russmann who shared with me lots of ideas and co-authored all of the publications we had during this period.

The design and implementation of the measurement systems, sensors and firmwares were done by our two ingenious engineers J. Graminger (Fredo) and P. Morel, to whom I send my outmost gratitude.

All the invaluable clinical data that was gathered to make this thesis possible were registered in CHUV and HUG. From CHUV I would like to thank Prof. F. J. G. Vingerhoets, Dr. H. Russmann, Dr. C. Wider, Dr. C. Cereda, Dr. V. Rey and the two never tiring, ever smiling nurses, B. Robert and M. Roberge. From HUG I would like to thank Dr. P. R. Burkhard, Dr. Y. Blanc, Dr. S. Catalano and Dr. B. Christe.

I would also like to thank H. Coley and P. Pakzad for the time they spent reading and editing my thesis, which I'm sure at times drove them crazy with the large number of typos I tend to make. J. Favre was so kind as to translate the abstract of the thesis to French that I hereby express my gratitude.

My espical thanks goes to B. Najafi that apart from recommending me to Dr. Aminian in the first place, has been a true friend and big support during last 15 years. My outmost gratitude goes to all my colleagues and friends in LMAM, D. Alvarez, V. Besson, B. Coley,

H. Dejnabadi, A. Ionescu, T. Knezovic, for providing a dynamic and stimulating environment, insightful discussions and the good time we had together. I would also like to thank the all colleagues of the old MET laboratory under supervision of Prof. P. Robert and NAM laboratory under supervision of Prof. O. Martin, the secretaries M. Noè and P. Pirerrette and my friends D. Alasia, J. Besson, F. Brifford, A. Desmangles, M. Gonzalez, S. Le Floch, G. Lévêque, M. Mattiello, A. Nesci for the great time we had during these years.

All these would be impossible without care, patience and love of my wife, Marjan, who was besides me in all the sunny and cloudy days. I would also like to thank my parents, Susan and Kamal-al-din who teach me that there is no bigger joy in life than seeking knowledge.

Finally I'd like to thank Swiss National Science Foundation that supported this project by grants #3152-062006 and #3152A0-103933.

Contents

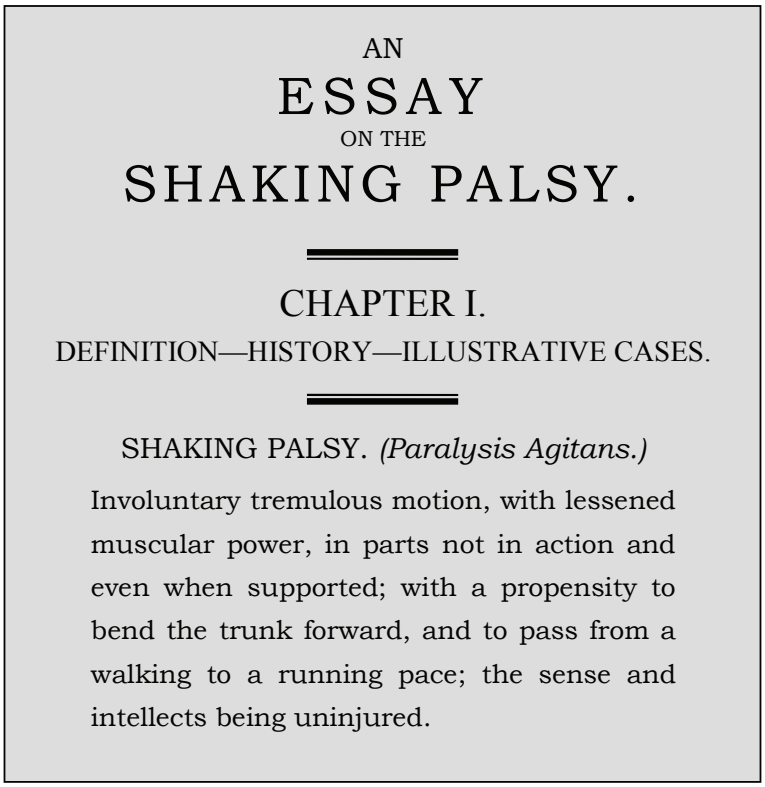
List of figures

List of tables

Chapter 1 Introduction

1.1 Parkinson's disease

Parkinson's disease (PD; paralysis agitans) is a neurodegenerative disease of the substantia nigra (an area in the basal ganglia of the brain, which controls voluntary movements and helps to regulate mood). Dr. James Parkinson discovered this disease and documented its syndromes in his famous monograph *An Essay on the Shaking Palsy* published in 1817 (Parkinson 1817).



AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace; the sense and intellects being uninjured.

Figure 1-1. James Parkinson's classical essay on shaking palsy.

After Alzheimer's, Parkinson's disease is the second most common neurodegenerative disease. According to the United Nations, at least four million people worldwide have it. It is estimated that the prevalence and incident rates of Parkinson's disease in Europe is approximately 108 to 257/100,000 and 11 to 19/100,000 per year, respectively. In the older age groups (i.e. > 60 years) the rates of prevalence and incidence are much higher:

1280 to 1500/100,000 and 346/100,000, respectively (Von Campenhausen, Bornschein *et al.* 2005). It is expected that its prevalence and the anticipated social and economical burden related to it, increase in the next few decades as a result of both increased longevity and multiplication of effective therapies despite the two to five times higher mortality than age-matched controls (Lang and Lozano 1998a; b).

Parkinson's disease occurs when certain neurons of the brain, mostly in the substantia nigra die or become impaired. The symptoms of Parkinson's disease result from the loss of these dopamine-secreting (dopaminergic) cells and subsequent loss of melanin, secreted by the same cells, in the pars compacta region of the substantia nigra (also known as black substance). This leads to inhibition of the direct pathway of movement and activation of the indirect pathway of movement. Since the direct pathway facilitates movement and the indirect pathway inhibits movement, the loss of these cells leads to a hypokinetic movement disorder. The lack of dopamine results in an excessive inhibition of the thalamus, leading to hypokinesia (Lang and Lozano 1998a; b).

1.2 Major Symptoms of the Parkinson's disease

PD affects mainly the motor system and its cardinal symptoms are tremor, rigidity, akinesia, postural abnormalities and gait impairment (Lang and Lozano 1998a; b; Petit, Allain *et al.* 1994). In addition to the motor symptoms, mental disorders like depression or psychosis, and autonomic and gastrointestinal dysfunction may occur; all of which considerably impair the quality of life of the patients (Schrag, Jahanshahi *et al.* 2000).

Tremor in PD has a number of characteristics that make it easy to differentiate from other causes of tremor: it is slow with frequency of 4 to 6Hz and affects asymmetrically upper and lower limbs (Deuschl, Bain *et al.* 1998; Hallett 1998).

Rigidity or increased stiffness of the muscles, frequently associated with cogwheeling, is a plastic, lead-pipe form of hypertonia that affects many muscles of the limbs and the trunk and is responsible for the typical stooped posture of the PD patients.

Akinesia (lack of movement) is perhaps the most disabling symptom of PD and includes many features such as delayed motor initiation and slow performance of voluntary movements (bradykinesia), insufficiency of motion (hypokinesia), difficulty in reaching a target with a single continues movement, rapid fatigue with repetitive movements, inabilities to execute simultaneous actions and inability to execute sequential actions (Delwaide and Gonce 1998).

Gait can also be altered in PD. Akinesia is particularly obvious during gait where it is responsible for the short, shuffling steps, reduced arm swing, hesitations in start, turning-around and sometimes leading to freezing phenomena (Delwaide and Gonce 1998).

Various combinations of PD symptoms, their severity, location and variability over the time in a particular patient generate a significant functional disability that tends to increase as the disease progresses (Hoehn and Yahr 1967).

Apart from the complex and constantly evolving pattern of these motor changes, there is considerable interpersonal heterogeneity of PD, making comparisons between individual patients a difficult task. Therefore, measuring the effect of therapeutic interventions on the symptoms of PD is a major challenge.

1.3 Treatments of PD and ON/OFF fluctuations

Currently the principle treatments include medications that mimic dopamine, compounds used to create dopamine in the brain (such as levodopa) and drugs that inhibit the breakdown of dopamine. Among the others, levodopa is the most important and commonly used.

However, a major disabling symptom of chronic levodopa (LD) therapy is dyskinesia (Nutt, Carter *et al.* 1995). Dyskinesia generally occurs at the maximal benefit from a single LD dose (peak-dose dyskinesia) that can involve any body part with choreic or dystonic movements. As dyskinesia is a side effect of the levodopa therapy, it is often referred to as levodopa-induced dyskinesia (LID) (Nutt 1990). The actual emergence of dyskinesia during the day depends on timing and quantity of each individual does of levodopa and also to a lesser extent, depends on stress, food and many other factors (Nutt 1990). Other chronic levodopa therapy related motor manifestations that may develop are motor fluctuations such as wearing-off, early-morning dystonia, delayed ON or no-ON response and eventually ON-OFF phenomena (Marsden, Parkes *et al.* 1981; Petit, Allain *et al.* 1994).

Two important and commonly used terms regarding the parkinsonian state of the patients are *ON* and *OFF* states. During the ON state, the medication (in particular levodopa) is active and motor performance of the patient is improved. OFF state is the period that starts when the effects of the medications wear off and PD symptoms re-emerge.

Many of PD patients start to fluctuate between the ON and OFF states. Moreover, during the ON state patients may suffer from dyskinesia. Figure 1-2 shows a schematic of these ON/OFF fluctuations during the day. The physicians constantly need to adjust the dose

and the time between each intake of the medications to maximize the period of ON state and minimize the periods of OFF and dyskinesia. Over the time the response to a fixed dose of the levodopa therapy decreases and as a result, the dose or the time between each intake needs to be adjusted. Clearly, to optimally adjust the treatments, knowing the exact periods of ON and OFF state during the day is invaluable to the physicians.

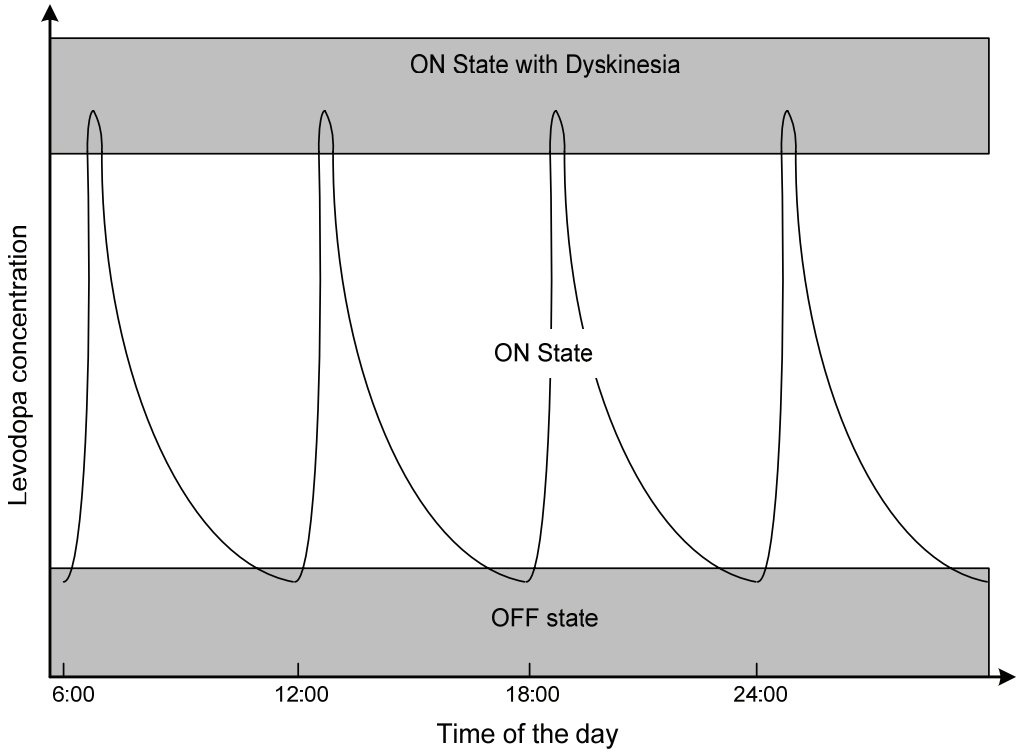


Figure 1-2 A schematic view of the levodopa fluctuations in the patients with PD.

1.4 Sub-Thalamic Nucleus, Deep Brain Stimulation

Recently *Deep Brain Stimulation* (DBS) in the *sub-thalamic nucleus* (STN) has been introduced as a treatment in patients with pharmacoresistent fluctuations (Benabid, Benazzouz *et al.* 1998): In a surgical procedure, through a small opening in the skull an electrode is implanted into the basal ganglia (see Figure 1-3). Electrical stimulation through the electrode interferes with neural activity in the target area which can alleviate parkinsonian signs.

After the surgery is completed, an expert calibrates the unit in order to maximize its effectiveness. The calibration includes setting the frequency, voltage and duty cycle of the square wave oscillator inside the neurostimulator. The neurostimulator is a pacemaker like device that contains a battery and circuitry to generate the electrical signals that through the electrode stimulates the targeted area in the brain. Currently *Medtronic Inc.* is the leader in producing neurostimulators and other components of the STN-DBS.

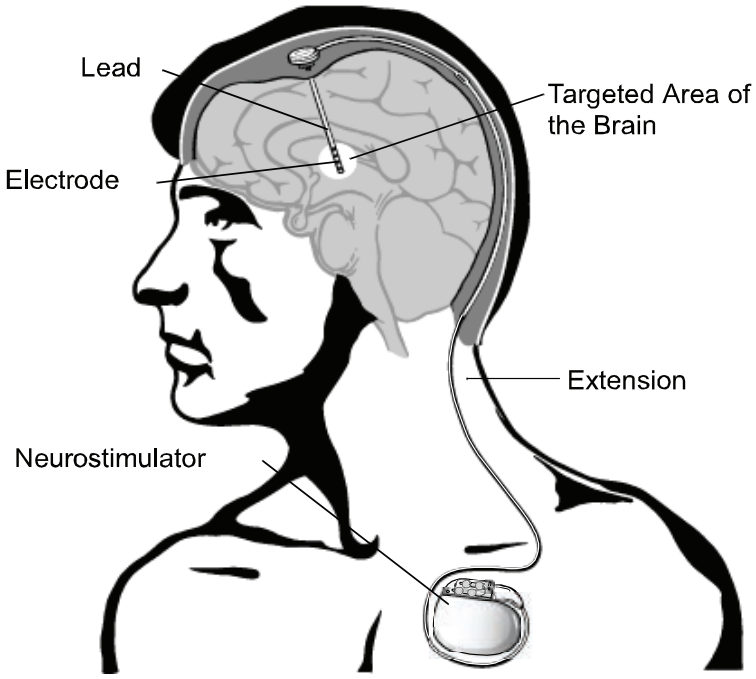


Figure 1-3. Components of the STN-DBS stimulation system.

STN-DBS results in a significant reduction of the needed medication and in some cases patients can completely stop taking them (Vingerhoets, Villemure *et al.* 2002); which in turn eliminates the problem of wearing-off with the levodopa therapy and can stop fluctuations and the dyskinesia.

The programming of the neurostimulator can take up to a year to achieve an optimal setting. Sometimes DBS is performed unilaterally on the side of the brain opposite to the side of the body most affected by the disease, but in many cases it is performed bilaterally in a single operation.

During the thesis, we had a chance of close collaboration with the departments of neurology of *Centre Hospitalier Universitaire Vaudois* (CHUV) (the largest center of STN-DBS therapy in Switzerland) and *Hôpitaux Universitaires de Genève* (HUG). Through our collaboration with these two centers, we had access to both PD patients with STN-DBS implantations and those following therapies based on medications.

1.5 Common clinical assessment methods of PD

Currently, motor assessment in PD is mainly based on historical information, home diaries and neurological examination during visits to the clinic. These methods clearly suffer from many drawbacks: data from these sources can be highly subjective, they rely on the patient's memory and perception of his own symptoms and they depend on the physician's experience in the field. Moreover, most of the patients may not be aware of

mild tremor or dyskinesia. They may not necessarily understand medical terminology. They may unconsciously exaggerate or attenuate symptoms' severity. Finally, short-term memory can be affected by PD (Brown, Maccarthy *et al.* 1989; Lang and Fahn 1989; Scholz and Bacher 1995).

In an attempt to solve these problems and to find more objective assessments, several rating scales have been designed and used (Larsen, LeWitt *et al.* 1983; Martinez-Martin 1993). Among them, the *Unified Parkinson's Disease Rating Scale* (UPDRS) is the most widely used (Fahn, Elton *et al.* 1987). This rating scale tries to quantify selected symptoms and signs of parkinsonism in a 5-points scoring system (with 0 for no sign and 4 for a marked severity of the sign).

Unfortunately, the UPDRS like any other semi-objective rating scale has limitations like intra and inter-observer inconsistencies, can be time consuming and can be biased by subjectivity issues related to historical information. Moreover, the pattern and severity of PD symptoms may vary considerably during the day, while clinical rating scales only provide moment-to-moment assessments; and finally, measurements of motor functions made in the clinic may not accurately reflect the actual functional disability experienced by the patients in their daily life (Kiani, Snijders *et al.* 1997).

In addition to rating scales, akinesia and gait are sometimes evaluated by means of timed motor performance test (Giovannoni, van Schalkwyk *et al.* 1999), Purdue pegboard test (Desrosiers, Hebert *et al.* 1995; Reddon, Gill *et al.* 1988), pronation-supination test, hand movement between two points (Zappia, Montesanti *et al.* 1994), finger dexterity (Boraud, Tison *et al.* 1997), stand-walk-sit test (Watts and Mandir 1992) or tremor amplitude (Norman, Edwards *et al.* 1999). Also, objective methods have been suggested to quantify rigidity (Patrick, Denington *et al.* 2001). While these methods are quantitative, again they only provide information limited to the setting of the clinic.

1.6 Ambulatory monitoring of PD motor symptoms

The ideal assessment method should provide objective, quantitative and long-term data that could be easily translated into simple and useful information. For this purpose an instrumental method is undoubtedly more appropriate. A limited number of movement analysis systems (MAS) have been described for the ambulatory measurement of the various aspects of movement disorders in PD.

Electromyography (EMG) techniques provide detection and monitoring of electrical muscle activities by attaching surface electrodes on the belly of the selected muscles. EMG does not directly measure movements and a large number of electrodes may be

needed to study complex movements. EMG has been used for a long time to study tremor in PD and several ambulatory, long-term EMG recording systems have been described (Andreeva, Ivanova-Smoielnskaya *et al.* 1985; Bacher, Scholz *et al.* 1989; Boose, Spieker *et al.* 1996; Foerster and Smeja 1999; Scholz, Bacher *et al.* 1988; Spieker, Boose *et al.* 1998). Also, ambulatory EMG recording has been used to detect basic body postures (Ng, Sahakian *et al.* 2000). And finally, EMG has been used to study gait in PD (Albani, Sandrini *et al.* 2003; Cioni, Richards *et al.* 1997; Dietz and Colombo 1998; Mitoma, Hayashi *et al.* 2000), though not in ambulatory conditions.

An ambulatory approach to analyze gait is based on special footwear with foot-switches or other pressure sensitive devices inside (Lackovic, Bilas *et al.* 2000; Pataky, Faravel *et al.* 2000). However, using special footwear is not always possible and may also hinder subject's normal gait. Moreover, PD patients may tend to shuffle while walking, making the initial and terminal contact detection difficult. In these cases, the gait temporal parameters may not be calculated precisely. In addition, the foot-switch techniques do not provide spatial parameters.

Recent developments in microelectronics have led to design and production of a new generation of small, cheap and robust sensors that can be used to measure kinematic parameters of the movements of the body segments. These developments have breathed a new life in design of ambulatory systems for long-term monitoring of body movements. Accelerometers and gyroscopes have been used to detect and quantify tremor (Burkhard, Langston *et al.* 2002; Frost 1978; Hoff, Wagemans *et al.* 2001; Smeja, Foerster *et al.* 1999; Van Someren, Vangool *et al.* 1993; Van Someren, Vonk *et al.* 1998), bradykinesia and hypokinesia (Dunnewold, Jacobi *et al.* 1997; Ghika, Wiegner *et al.* 1993; Katayama 2001; Van Someren, Vonk *et al.* 1998) in PD patients. Ambulatory gait analysis systems has been design based on accelerometers (Aminian, Rezakhanlou *et al.* 1999; Moe-Nilssen and Helbostad 2004; Sabatini, Martelloni *et al.* 2005; Selles, Formanoy *et al.* 2005) and gyroscopes (Aminian, Najafi *et al.* 2002; Aminian, Trevisan *et al.* 2004) for healthy subjects, elderly and pathological cases. These sensors have been used as activity monitor (Bussmann, Reuvekamp *et al.* 1998; Bussmann, Martens *et al.* 2001; Fujikane, Yokota *et al.* 1995; Mochio, Oka *et al.* 1997; Veltink, Bussmann *et al.* 1996b) or to classify different body postures (Dunnewold, Hoff *et al.* 1998; Najafi, Aminian *et al.* 2002; Najafi, Aminian *et al.* 2003; Paraschiv-Ionescu, Buchser *et al.* 2004). Also recently kinematic sensors has been used in detection and quantification of dyskinesia (Burkhard, Shale *et al.* 1999; Hoff, Wagemans *et al.* 2001; Keijsers, Horstink *et al.* 2003a; b; Manson, Brown *et al.* 2000).

Today, especially regarding assessment of PD, none of the abovementioned techniques are perfect or sufficiently investigated and overall there is little experience with them. Long-term quantification has only rarely been achieved. These methods are yet young and none of them has been used in large scale nor has reached consensus as a gold standard in the scientific and clinical community. Moreover, each system only either addresses one or few of the major PD motor dysfunctions. Finally, available ambulatory methods can not yet detect periods of ON and OFF state in individual PD patients with acceptable accuracy (Hoff, Van Der Meer *et al.* 2004).

1.7 Objectives

The primary objective of this thesis was:

- To design and validate a portable ambulatory movement analysis system for long-term monitoring and qualitative and quantitative assessment of motor abnormalities of PD patients during their daily activities.

Additional goals of this thesis were:

- To use available sensors to identify body movement patterns that are specific to motor changes in PD including tremor, bradykinesia, gait impairments and physical activity.
- To design and test new sensors and to identify their optimal configuration for the purpose of the detection of the described motor phenomena.
- To determine and standardize the most convenient number and location of sensors as well as the best recording parameters of the final movement analysis system (MAS).
- To use the optimized MAS in clinical studies on the free moving PD patients and to characterize fluctuations in their motor performance.
- And finally, to use the objective parameters provided by the MAS to detect motor states (ON and OFF states) in the free moving PD patients.

In this thesis, we have mostly focused on the PD patients with bilateral STN-DBS implantation. Patients participated in our studies had optimally tuned STN-DBS and showed no signs of dyskinesia during the ON state. By switching the stimulation on and off, we could mimic severe motor fluctuations normally occurring in levodopa treated PD patients. The biggest advantage of working with these patients for our study was the possibility to record the body movement patterns particular to the OFF and ON states in the *same* patient, within the limited time we had with them. Detection and quantification of

dyskinesia which is the side effect of the levodopa therapy and not a PD symptom per se, however, was not in the scope of this thesis.

1.8 Outline of the thesis

The thesis is organized in nine chapters.

The first (current) chapter, *Introduction*, introduces the basic ideas, provides a short review of the literature and discusses about the objectives of the thesis.

The second chapter, *Clinical studies*, presents the clinical measurement protocols used throughout the different studies in the thesis, the information about the patients participated in the measurements and the results of the clinical tests that they have done.

The third chapter, *Movement Analysis System*, focuses on the architecture and the design of the measurement systems used in the different studies. The engineering and clinical decisions and compromises that finally led to the design of our new MAS are presented in this chapter.

The fourth chapter, *Quantification of tremor and bradykinesia*, presents our new algorithms to detect and quantify these two important parkinsonian symptoms. Two clinical studies with STN-DBS on an off, one in controlled conditions and one on free moving PD patients had been performed and the methods and results are presented.

The fifth chapter, Analysis of physical activity, describes the method to detect four basic human body postures (i.e. sitting, standing walking and lying) in the case of PD patients with STN-DBS on an off. Presence of motor abnormalities of PD makes the task of detection of these postures a notoriously difficult job for this specific group of patients.

The sixth chapter, *Gait assessment*, presents our proposed gait analysis method and the results of the gait analysis of a group of PD patients and control subjects in a controlled study, again in both states of on and off.

The seventh chapter, *Gait analysis of free moving patients*, takes our gait analysis method to a next step and presents a new gait analysis method with half of the number of the sensors of previous method, with similar accuracy. The new method has been used to analyze gait in free moving PD patients while the state of the stimulation was being changed.

The eighth chapter, *Detection of the periods of ON and OFF*, presents a statistical approach to use the outcomes of the all of the algorithms discussed in the preceding chapters to detect periods of ON and OFF in group of free moving PD patients.

The ninth and the final chapter, *Conclusions*, summarizes the contributions of this thesis and presents the perspectives of the future studies.

All chapters of the thesis follow a similar structure. Each chapter starts with a short abstract, including some backgrounds, a summary of the objectives, methods, major results and the main contribution. Afterwards an introduction is presented to bring the subject of the chapter into focus and it is followed by the details of the method, results and conclusions.

At the end of the thesis, in the bibliography section, all of the referenced articles, books and our resources used throughout the thesis are listed.

Chapter 2 Clinical studies

Abstract

Background—Our study was primarily based on data analysis, visualization, several iterations of finding and applying ideas, and finally testing them on real world data, i.e. *clinical situations*.

Objectives—Protocols of measurements should be designed and used in clinical studies to provide needed data in each of the phases of pilot works, design, test and application of the methods.

Method—With collaboration of neurology groups of HUG and CHUV, protocols of the measurements were developed and their respective sensor configurations were determined. The measurement protocols were designed according to the needs of each phase of the thesis. Four groups of clinical studies have been performed during this research, each with progressively more improved version of MAS, to provide a database of movement patterns of PD patients and healthy controls.

Results—In summary, 41 PD patients and 10 healthy control subjects participated in more than 65 sessions and 118 hours of measurements. The database of normal and abnormal movement patterns alongside the measurement logs, videos and reports provided an invaluable resource for design and development of algorithms to detect and quantify PD movement disorders.

Main contributions—A rich database of movement patterns of PD patients and control subjects has been gathered that includes a large spectrum of normal and abnormal patterns of movement in both controlled and ambulatory conditions.

2.1 Introduction

During the course of the thesis, a series of measurements and studies were performed with close collaboration between our laboratory and neurology departments of Centre *Hospitalier Universitaire Vaudois* (CHUV) and *Hôpitaux Universitaires de Genève* (HUG). These measurements provided the necessary *real-world* data to design the architecture of

the movement analysis system (MAS), to design and test the algorithms and to do feasibility studies to test the whole system within the clinic.

As the data gathered in these studies was used repeatedly in several following chapters, they are all presented in this chapter to avoid unnecessary repetition.

The measurements can be divided into four groups:

1. *Pilot study*, where the basic structure of MAS, typical patterns of the abnormal movements and practical limits of the system were studied.
2. *Controlled study,* where under a fully controlled and documented approach, the core algorithms and the measurement system were designed and in some cases tested.
3. *Transition study,* which was performed when the second prototype of the MAS was ready. As the architecture of the MAS was radically changed between the first and the second prototype, this study was performed to ensure that the two systems provide similar outcomes using our analysis algorithms.
4. *Long-term study,* where the system was used for monitoring ambulatory patients for several hours.

In the following sections, for each of these studies the issues of measurement system and its configuration, selection of the patients and the measurement protocol are discussed.

Patients diagnosed with probable PD according to widely used clinical criteria were selected in HUG and CHUV neurology departments to be enrolled in the studies. In short, the selection criteria included:

- *Inclusion criteria*
    - Probable PD according to UKPDSBB diagnostic criteria (Gibb and Lees 1988; Hughes, Daniel *et al.* 1992).
    - Improvement in UPDRS score part III of 30% or more following a regular morning dose of levodopa.
    - Presence of motor manifestations of sufficient magnitude to justify neurophysiological assessment.
    - Interest in the study and adequate availability.
- *Exclusion criteria*

- Any conditions that may significantly interfere with motor function outside PD, such as ophthalmologic, orthopedic or rheumatologic illnesses.
- Cognitive impairment or psychiatric manifestations that may prevent acceptable understanding of the study requirements.

Moreover, a group of neurologically intact subjects, matched for age and gender were used as controls to find the *normal* values in the controlled study. The studies were submitted to the local *Ethics Committees* (Neuclid in HUG, Internal Medicine in CHUV) and the participants had signed the usual informed consent before the measurements.

2.2 Pilot study

At the beginning of the thesis, during the period of May to November 2001, a pilot study was performed. This study was used as a test bed for completion of the design of clinical protocols and also to test and to establish the configuration of the MAS. During the period of this study, the configuration of the MAS and also clinical protocols were continuously changed and polished to prepare a foundation for the later studies.

2.2.1 Objectives

The pilot study was performed with several objectives in mind. The data from these series of measurements were used:

- To identify movement patterns that are specific to motor changes in PD, including tremor, bradykinesia, gait impairments and postural abnormalities, using available sensors.
- To design and development of a new portable MAS, supportable by PD patients.
- To determine and standardize the most convenient number and location of sensors to be used, as well as the best recording parameters of the MAS.

2.2.2 Subjects and measurement setup

Following the general inclusion/exclusion criteria, eight PD patients participated in the pilot study. They included six males and two females. Three PD patients participated in the study during the OFF state and the other five patients did the test in ON state. Also, one healthy, normal subject did several tests in this study. The setup and the number of sensors were varied from subject to subject. As the study progressed, the setup became more complete.

To record tremor, a pair of 3D gyroscopes attached on the forearms were used. To record gait patterns, a set of four uni-axial gyroscopes were attached on the lower limbs. One or two Physilog® data-loggers were used to record the signals.

The last six measurements included a sensor setup similar to the *controlled study* and four of them were fully recorded by video. For more details about the measurement system used in this study, see section 3.2.

2.2.3 Measurement protocol

The first two patients participated in several separate recordings, including periods of tremor in hands and feet and several walking trials. In six tremor recordings, each time only one 3D gyroscope sensor was attached on either the forearm or the feet. Signals were recorded for 60 seconds. Two walking trials were performed by each subject at their preferred, normal speed in a 20m pathway and subjects were instructed to walk in a straight line.

The only healthy normal subject participated in this study performed several walking trials at slow, normal and fast speeds in the same 20m pathway. He also did several walking trials trying to mimic the festinating gait of PD patients.

Six PD patients participated in a protocol of 16 typical daily activities. These activities included tasks like: writing, eating, drinking, walking, climbing the stairs, etc. The exact number, order, type and period of each task were changed several times till the satisfactory measurement protocol was agreed upon. This protocol was later used in the *controlled study*, (details in section 2.3.3).

2.3 Controlled study

Following the pilot study, the configuration of the MAS and the details of the clinical protocol of this study were determined. The measurements were performed during the period of February to June 2002.

The data recorded in these series of measurements formed a very important database of PD movement abnormalities patterns that served as the basis of the design and validation of most of the different algorithms developed during the course of the thesis.

All details of the study were carefully documented, either on video or in written logs and participants followed a clearly defined, timed protocol including standard tasks selected from typical daily activities.

The data recorded in this study has been used in the design and/or test of the methods presented in chapters 4, 5, 6 and 7.

2.3.1 Objectives

Several objectives were persuaded with the controlled study. This study was done:

- To prepare a database of the signatures of PD gait, tremor, bradykinesia and postural abnormalities.
- To make a database of the signatures of the movement abnormalities of PD patients while they were performing typical daily activities.
- To prepare a database of the signatures of the movements of healthy subjects, performing the same tasks as the PD patients.
- To have a series of movement recordings in both PD patients and healthy controls where the exact type, intensity and period of each activity were precisely recorded.
- To design algorithms to detect and analyze gait, tremor, body posture and bradykinesia.
- To find the statistical performance (sensitivity and specificity) of detection algorithms for gait, tremor and posture transitions.
- To compare the outcomes of the mentioned algorithms to the established clinical scores.
- To compare the performance of the same PD patients between the ON and OFF states, as reflected in the changes in different objective parameters evaluated by our analysis methods.
- To compare the respective objective parameters between PD patients and healthy controls.

2.3.2 Subjects and measurement setup

In this study, two groups of participants were enrolled. The first group consisted of ten PD patients, 20 ± 3 months after implantation of bilateral STN-DBS (Vingerhoets, Villemure *et al.* 2002) including five males and five females with an average age of 61.5 years (max = 75.1, min = 48.7, S.D. = 7.8) who agreed to participate in a Stim-off procedure and to carry our MAS. Ten healthy control subjects (5 men, 5 women, 63.6 ± 10.5 years old) were also enrolled in the study.

All patients had dopa-responsive PD, without atypical signs on examination (O'Sullivan, Said *et al.* 1998), no dementia (following International Classification of Diseases-10 definition of dementia) and no depression. The control subjects had no neurologic disease or medical condition associated with tremor. They didn't take tremorogenic medication

and they didn't have orthopedic or arthritic conditions on the upper limbs limiting the recordings (Burkhard, Langston *et al.* 2002).

To record the signals, the first prototype of MAS, a system including two Physilog® data-logger and kinematic sensors on seven sites on the body was used. The details of the measurement system can be found in section 3.3.

2.3.3 Measurement protocol

Subjects carried the first prototype of measuring system and followed a protocol of 17 typical daily activities (Table 2-1). It took up to 45 minutes for each subject to complete the protocol.

Table 2-1 shows the list of the activities used in the measurement protocol of this study. All activities were videotaped and video segments were later examined to prepare a log of all activities including the time of the start and end of each period of tremor in hands, periods of each of the four basic body postures (sitting, standing, walking and lying) and the exact time of the transitions between sitting and standing.

	Activity	Minimum time
1	Sitting with no movement	30s
2	Sitting and talking	60s
3	Sitting, counting in inverse starting from 100 each time subtracting 7	60s
4	Sitting, holding the 2 hand in 90°	30s
5	Sitting, alternate movement of the right hand	30s
6	Sitting, alternate movement of the left hand	30s
7	Standing, followed by walking round 2m toward a table and sitting behind it	120s
8	Sitting, writing the date, name and a series of standard phrases	60s
9	Sitting, eating and drinking	120s
10	Standing, followed by walking toward the lavatory	60s
11	Standing, brushing the teeth	60s
12	Standing, combing the hair	60s
13	Walking from the lavatory to the corridor and sitting on the chair	120s
14	Standing, walking for 20m with normal speed, turning back and sitting on the chair	120s
15	Standing, climbing the stairs, turning back and sitting on the chair	120s
16	Standing, walking for 20m with fast speed, turning back and sitting on the chair.	120s
17	Lying in the bed	60s

Table 2-1. The list of the activities used in the measurement protocol of the controlled study.

Before each measurement, patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS), motor section III (Fahn, Elton *et al.* 1987). Each patient performed the protocol twice: once during Stim ON (i.e. when both stimulators were turned on) and once during Stim OFF (i.e. when both stimulators have been turned off). The Stim OFF measurement was recorded between 120 to 180 minutes after turning STN-DBS off (Temperli, Ghika *et al.* 2003).

Four patients did not need to take any medication; the others took dopaminergic medication consisting of levodopa and/or a dopamine agonist. All medications were discontin-

ued prior to the test (Vingerhoets, Villemure *et al.* 2002). Table 2-2 and Table 2-3 show the UPDRS motor section scores of the PD patients participated in this study.

Patient	1		2		3		4		5	
Stimulation	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
UPDRS Part III sub-scores										
18. Speech	2	2	2	2	1	2	1	1	0	1
19. Facial Expression	1	3	1	4	2	4	1	2	1	2
20. Tremor at Rest										
20.a Face	0	0	1	2	1	2	0	0	1	2
20.b Upper Extremity R, L	0, 1	4, 4	1, 0	3, 1	0, 0	1, 1	0, 0	3, 1	0, 0	1, 1
20.c Lower Extremity R, L	0, 0	0, 0	1, 0	3, 0	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0
21. Action or Postural Tremor (R, L)	1, 1	4, 4	0, 1	2, 1	1, 1	1, 1	0, 0	3, 1	0, 0	0, 1
22. Rigidity										
22.a Neck	1	4	1	4	2	4	1	4	1	1
22.b Upper Extremity R, L	1, 1	4, 4	1, 0	4, 2	2, 2	3, 4	0, 0	4, 4	0, 0	1, 0
22.c Lower Extremity R, L	0, 1	2, 3	0, 1	3, 3	2, 2	3, 4	2, 2	3, 4	1, 0	0, 0
23. Finger taps	1, 2	3, 4	4, 2	4, 4	2, 3	3, 4	1, 1	4, 4	0, 0	2, 2
24. Hand Movements R, L	1, 3	4, 4	4, 2	4, 4	2, 3	3, 4	1, 1	3, 4	0, 0	1, 2
25. Rapid Alternate Movements R, L	3, 3	4, 4	4, 3	4, 4	3, 3	4, 4	2, 2	4, 4	0, 0	1, 2
26. Leg Agility R, L	0, 0	4, 4	0, 1	3, 4	1, 2	3, 4	1, 2	3, 3	0, 0	2, 1
27. Arising From Chair	0	4	0	3	3	4	0	1	0	0
28. Posture	1	1	0	0	2	2	1	1	0	0
29. Gait	0	3	2	3	3	4	2	2	0	1
30. Postural Stability	1	4	1	3	3	4	1	1	0	0
31. Body Bradykinesia	1	4	2	4	3	4	1	3	0	1
Total	26	85	35	78	49	77	23	67	4	25

Table 2-2 The UPDRS motor section scores of the patients 1 to 5, participating in the controlled study.

Patient	6		7		8		9		10	
Stimulation	ON	OFF	ON	OFF	ON	ON	OFF	ON	OFF	ON
UPDRS Part III sub-scores										
18. Speech	1	4	2	2	1	1	4	2	2	1
19. Facial Expression	0	2	2	2	1	0	2	2	2	1
20. Tremor at Rest										
20.a Face	1	1	1	1	0	1	1	1	1	0
20.b Upper Extremity R, L	1, 0	4, 4	1, 1	1, 1	0, 0	1, 0	4, 4	1, 1	1, 1	0, 0
20.c Lower Extremity R, L	0, 0	2, 2	0, 0	1, 1	2, 0	0, 0	2, 2	0, 0	1, 1	2, 0
21. Action or Postural Tremor (R, L)	1, 1	2, 2	1, 1	1, 2	1, 1	1, 1	2, 2	1, 1	1, 2	1, 1
22. Rigidity										
22.a Neck	0	2	2	3	2	0	2	2	3	2
22.b Upper Extremity R, L	0, 0	1, 2	2, 2	1, 2	0, 0	0, 0	1, 2	2, 2	1, 2	0, 0
22.c Lower Extremity R, L	0, 0	1, 1	2, 1	2, 2	1, 1	0, 0	1, 1	2, 1	2, 2	1, 1
23. Finger taps	0, 0	2, 3	2, 2	3, 4	1, 1	0, 0	2, 3	2, 2	3, 4	1, 1
24. Hand Movements R, L	0, 0	2, 3	2, 2	4, 4	2, 2	0, 0	2, 3	2, 2	4, 4	2, 2
25. Rapid Alternate Movements R, L	0, 0	1, 2	1, 1	4, 4	2, 2	0, 0	1, 2	1, 1	4, 4	2, 2
26. Leg Agility R, L	0, 0	1, 1	0, 0	0, 1	1, 1	0, 0	1, 1	0, 0	0, 1	1, 1
27. Arising From Chair	0	0	0	0	0	0	0	0	0	0
28. Posture	0	0	1	2	1	0	0	1	2	1
29. Gait	0	0	1	1	2	0	0	1	1	2
30. Postural Stability	0	1	1	2	2	0	1	1	2	2
31. Body Bradykinesia	1	2	0	1	1	1	2	0	1	1
Total	6	48	31	52	28	6	48	31	52	28

Table 2-3. The UPDRS motor section scores of the patients 6 to 10, participating in the controlled study.

2.4 Transition study

In 2003 we had a new architecture for the measurement system and our new sensing units based on this architecture were ready. In the period of May to June 2003, we performed a small study to find out if during the transition from the first prototype to the second prototype that was based on this new architecture, any significant changes could be found in quality of the recorded data and if the same algorithms could provide identical results using any of the two systems.

2.4.1 Objectives

The transition study was performed:

- To test the second prototype of the MAS for the first time on the patients.
- To test the system for any flaws in the hardware or the embedded software of the recording units.
- To find the optimum method of the attachment of the system on the body.
- To compare the outcomes of the analysis methods between the first and second prototype.

2.4.2 Subjects, systems and protocol

Four PD patients with bilateral STN-DBS implantation participated in this study. Their ages were between 55 to 69 years old. The first *and* the second prototype of the MAS (see sections 3.3 and 3.4) were carried by the patients at the same time (see Figure 2-1). Considering the number and complexity of the system, it is clear that it was a difficult task for the patients.

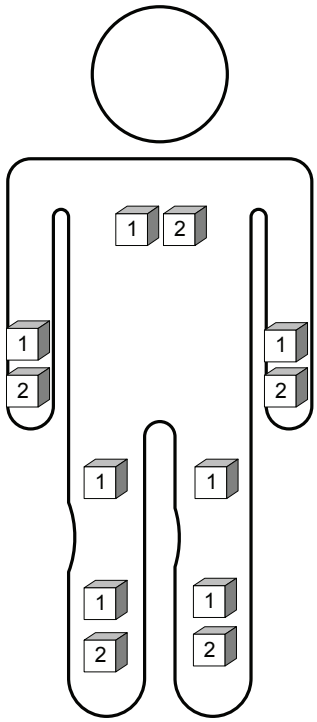


Figure 2-1. The sensors sites on the body in the transitions study. Sensors of the first prototype are marked with number 1 and those of the second prototype are marked with 2.

A series of measurement using the same protocol of the *controlled study* was performed (see section 2.3.3 for the details of the protocol): PD patients performed a protocol of 17 typical daily activities, once during Stim ON and once three hours after turning the STN-DBS off. Each measurement took less than 45 minutes. As the setup was heavy, in the period between the two measurements it was removed from the body. The data was transferred to a personal computer for the analysis.

Patient	1		2		3		4	
Stimulation	ON	OFF	ON	OFF	ON	OFF	ON	OFF
UPDRS Part III sub-scores								
18. Speech	1	2	0	1	2	2	2	2
19. Facial Expression	1	3	1	2	2	2	2	2
20. Tremor at Rest								
20.a Face	0	0	0	0	0	0	0	0
20.b Upper Extremity R, L	0,1	1,4	0,0	0,0	0,0	0,0	0,0	0,0
20.c Lower Extremity R, L	0,0	1,0	0,0	0,0	0,0	2,0	0,0	0,0
21. Action or Postural Tremor (R, L)	0,1	3,4	0,0	0,0	0,0	1,1	0,1	0,1
22. Rigidity								
22.a Neck	1	3	0	3	2	3	0	1
22.b Upper Extremity R, L	0,1	2,4	0,0	1,2	1,2	2,3	1,0	1,1
22.c Lower Extremity R, L	0,1	3,2	0,0	1,2	2,2	2,2	0,0	0,0
23. Finger taps	1,1	2,4	0,1	3,3	2,2	2,2	0,1	1,1
24. Hand Movements R, L	0,1	0,3	0,1	2,3	1,1	2,2	0,1	0,1
25. Rapid Alternate Movements R, L	1,2	2,3	0,1	3,4	3,2	3,3	0,1	0,1
26. Leg Agility R, L	0,0	2,3	0,1	2,3	1,1	1,1	0,1	0,1
27. Arising From Chair	1	2	0	1	0	0	0	0
28. Posture	1	1	0	1	1	1	0	1
29. Gait	1	1	0	1	1	1	1	1
30. Postural Stability	2	2	0	1	1	1	0	1
31. Body Bradykinesia	0	1	0	3	2	3	0	0
Total	15	58	5	42	31	40	11	16

Table 2-4. The UPDRS motor section scores of the patients participating in the transition study.

2.4.3 Data analysis and outcomes

A potential concern was the effect of the higher weight and size of the second prototype's recording units (in comparison to the first one's), on the recorded data: If the attachments were not optimal, during the activities the heavier recording units could move more and produce more artifacts in the recorded signal. Moreover, there were some differences in the amplitude and spectral characteristics of the noise of the two systems. As *peak-detection* was used in some of our analysis algorithms, noise in the recorded signals could potentially change the position of the detected peaks by a few samples.

However, by comparing the estimated parameters using the gait, tremor, bradykinesia and posture analysis algorithms (see chapters 4, 5 and 6) no statistically significant differences between the two systems were found. These results were expected as the types and the ranges of the sensors were identical. Moreover, the gyroscopes placed and aligned to the same axes on the same body segment would measure exactly the same angular velocity as the rate of the rotation on a rigid body is independent of the position. Accelerometers were used only in the sensors on the trunk and as sensors of the two units were attached on the trunk side by side (see Figure 2-1), in the sagittal plane they would record the same acceleration. In summary, all differences in the measured quanti-

ties between the two prototypes where below the ranges of the error or the sensitivity of our algorithms.

This study also helped to solve some small but important problems in the embedded software of the recording units before starting the next study. However, the recorded data was not later used for the design or the test of the analysis algorithm: We decided that because of the weight of the setup and its inconvenience for the patients, the recorded movement data would not be the best representative of *normal* body movement patterns.

2.5 Long-term study

The third study was performed during the period of August 2003 to January 2004. It was focused on the continuous recording of the ambulatory PD patients for relatively long periods of time (several hours), while the state of the stimulation was changed between ON and OFF.

As the periods of the measurements were long, video recording was not possible for the whole period and was limited to specific parts of the protocol. To solve this limitation, an observer performed *visual observation* using a hand-held computer during the recordings to prepare a time-tagged log of the subjects' activities.

The data recorded in this study has been used in the design and/or test of the methods presented in all later chapters 4 to 8. The outcomes of the analysis algorithms have been compared to the clinical scores to see if the objective parameters estimated using our method could follow the changes of the patients' conditions.

2.5.1 Objectives

The objectives of the study were:

- To prepare a database of recordings of gait, tremor, bradykinesia and physical activity movement patterns while the parkinsonian signs fluctuated over a period of few hours.
- To prepare a database of the signatures of body movements of PD patients during daily physical activities, accompanied by accurate observation reports.
- To evaluate the feasibility and ease of use of the second prototype of the MAS in long-term monitoring.
- To provide a test-bed for clinical evaluation of the recording units to improve the hardware/software in the next prototypes.

- To statistically analyze the outcomes of the algorithms of quantification of gait, tremor, bradykinesia and physical activities to see if they could follow the fluctuations of the parkinsonian signs.
- To study the effect of the selection of *window size* on the outcomes of those analysis methods like quantification of bradykinesia, where the values of the estimated objective parameters were dependent on the size of the temporal window.
- To study the possibility of detection of periods of ON and OFF by combining the outcomes of all analysis algorithms.

2.5.2 Subjects and measurement setup

In total 19 PD patients with bilateral STN-DBS implantation participated in this study. The measurement system used in the study was the second prototype of the MAS.

Unfortunately, the recorded data of six subjects was partially corrupted and was not used. The corruptions in the data were mainly because of some software failures (bugs) in the early versions of the firmware of the recording units. The remaining 13 *good* recordings included recordings of seven male and 4 females with an average age of 66.5 years (max=82.3, min = 59.6, S.D. = 6.8). Table 2-5 and Table 2-6 show the results of UPDRS tests in ON and OFF period of these PD patients

Patient	1		2		3		4		5		6		7	
Stimulation	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
UPDRS Part III sub-scores														
18. Speech	2	3	1	2	0	2	2	2	2	2	1	2	1	2
19. Facial Expression	2	3	1	2	1	2	2	3	2	2	1	2	1	2
20. Tremor at Rest														
20.a Face	0	0	0	0	0	0	0	2	0	1	0	0	0	0
20.b Upper Extremity R, L	0,0	0,0	0,0	1,1	0,0	0,0	0,0	4,2	0,1	0.5,0	0,1	1,1	1,0	2,0
20.c Lower Extremity R, L	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	1,0	4,4
21. Action or Postural Tremor R, L	0,0	0,0	0,0	0,0	0,0	1,1	1,1	1,1	0,0	1,1	0,1	0,1	0,0	1,1
22. Rigidity														
22.a Neck	1	3	1	1	1	3	1	3	0	2	1	4	2	4
22.b Upper Extremity R, L	1,1	2,3	0,1	2,2	1,0	2,1	0,0	3,3	0,0	1,1	2,1	4,2	1,1	2,2
22.c Lower Extremity R, L	1,1	3,3	1,0	1,1	0,0	3,2	0,0	2,2	0,0	1.5,1.5	1,0	3,4	2,1	4,2
23. Finger taps R,L	1,1	3,3	2,1	2,3	1,2	4,4	3,3	3,3	2,2	4,3	3,3	4,4	2,2	3,3
24. Hand Movements R, L	0,1	2,3	2,2	2,3	1,0	3,4	3,3	2,3	2,1	4,3	1,1	4,4	1,2	3,3
25. Rapid Alternate Movements R, L	2,2	4,3	2,2	2,3	2,2	4,4	2,2	4,4	2,2	4,4	1,2	4,4	3,2	3,4
26. Leg Agility R, L	2,2	3,4	1,1	2,2	1,1	4,4	1,1	2,2	2,2	4,4	0,0	3,3	1,2	3,4
27. Arising From Chair	1	1	0	0	0	2	0	2	4	4	0	1	0	3
28. Posture	2	2	1	1	1	2	1	2	4	4	1	1	1	3
29. Gait	2	2	1	2	1	3	1	1	4	4	1	1	2	3
30. Postural Stability	2	2	1	1	1	2	1	2	3	3	0	1	2	4
31. Body Bradykinesia	2	3	1	2	1	4	1	3	2	3	1	4	2	3
Total	29	55	22	38	17	61	29	61	37	62.5	23	62	33	72

Table 2-5. The UPDRS motor section scores of the patients 1 to 7, participating in the long-term study.

Patient	8		9		10		11		12		13*	
Stimulation	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
UPDRS Part III sub-scores												
18. Speech	1	2	0	1	2	3	1	1	1	1	2	-
19. Facial Expression	2	2	1	1	1	3	1	1	1	1	2	-
20. Tremor at Rest												
20.a Face	0	0	0	0	0	0	0	0	1	0	1	-
20.b Upper Extremity R, L	0,0	3	0,0	0,0	0,0	0,0	0,0	2,2	0,0	2,3	2,1	-
20.c Lower Extremity R, L	0,0	0	0,0	2,2	0,0	0,0	0,0	0,0	0,0	1,3	3,1	-
21. Action or Postural Tremor R, L	0,0	1	0,0	2,1	0.0	1,1	0,1	2,2	0,0	0,1	1,2	-
22. Rigidity												
22.a Neck	0	2	2	4	3	4	1	4	3	3	0	-
22.b Upper Extremity R, L	1,1	3,1	2,0	3,2	2,0	3,2	2,2	2,3	1,0	2,3	2,1	-
22.c Lower Extremity R, L	0,0	3,0	1,0	3,2	2,0	4,3	2,2	3,4	1,0	2,2	1,1	-
23. Finger taps R,L	0,1	4,1	2,2	3,4	3,2	4,3	2,2	3,3	2,3	3,3	1,0	-
24. Hand Movements R, L	0,1	3,1	1,1	2,3	3,2	4,3	1,1	3,3	1,2	1,2	0,0	-
25. Rapid Alternate Movements R, L	0,0	3,0	0,1	3,3	3,2	4,4	0,1	3,2	2,3	2,3	1,0	-
26. Leg Agility R, L	0,1	3,3	0,1	3,4	4,3	4,4	1,2	3,4	0,0	3,3	1,1	-
27. Arising From Chair	0	0	0	3	2	4	0	2	0	2	0	-
28. Posture	0	1	1	3	3	4	1	2	0	1	2	-
29. Gait	0	0	2	2	3	4	1	2	0	2	2	-
30. Postural Stability	1	2	1	2	4	4	2	2	1	2	0	-
31. Body Bradykinesia	1	3	1	3	3	4	1	2	1	3	2	-
Total	10	41	19	61	47	74	27	60	23	54	30	-

Table 2-6. The UPDRS motor section scores of the patients 8 to 13, participating in the long-term study. The last patient (the 13th patient) could only do the test in ON state.

As a result of feedbacks from the patients during the *controlled study* and the improvements in the gait analysis method (see chapter 7), the number of sensor sites on the body was reduced from seven to five by removing the sensors on thighs. We had a positive feedback on ease of use of the system mainly because of removing the cables and reduction of total weight of the setup. More details about the measurement system are presented in the section 3.4.

2.5.3 Measurement protocol

The protocol of this study was based on continuous recording of activities of the patients for several hours, while the state of the stimulation was being changed. Figure 2-2 shows the timing of the events in this measurement protocol: At the beginning of the measurement, patients did a UPDRS test (U1). The stimulator was then turned off. Every one hour, another UPDRS test was performed (U2, 3, 4, 5). After three hours the stimulator was turned on again (after U4) and finally, measurement was ended after U5. During the periods between the UPDRS tests, patients were moving freely.

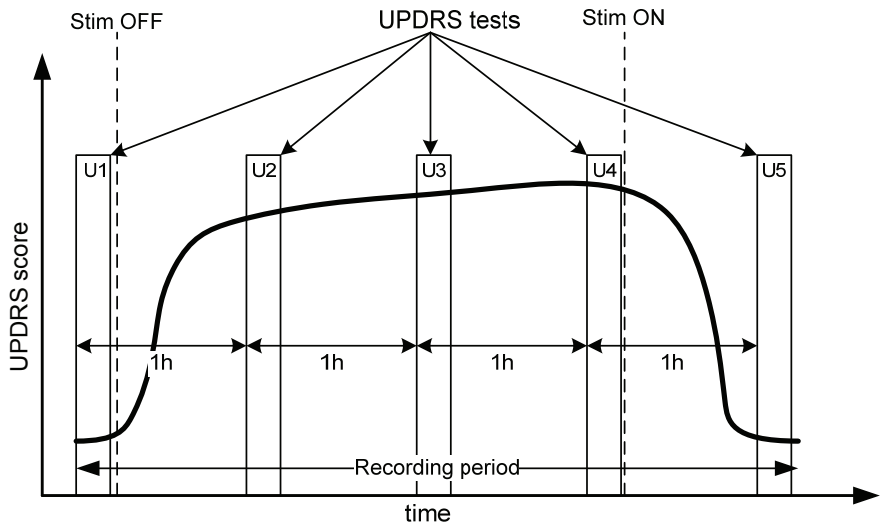


Figure 2-2. Structure of the long-term study's protocol. The thick line shows the UPDRS score of the patient. The square boxes show the period of UPDRS tests.

An interactive program was developed to be used with hand-held computers for logging the activities of the patients. An observer followed the subjects all the time with a *Pocket PC* running the program, preparing time-tagged logs of activities of the patients. Figure 2-3 shows a screenshot of this program. The program featured a button for each of the main body postures (*Sitting, Standing, Walking* and *Lying*) and also provided an easy method to enter time-tagged comments and to give scores to possible tremor and dyskinesia observed during the recordings. As the input method in a hand-held computer is based on touch-screens, the data entry using this approach was fast and simple.

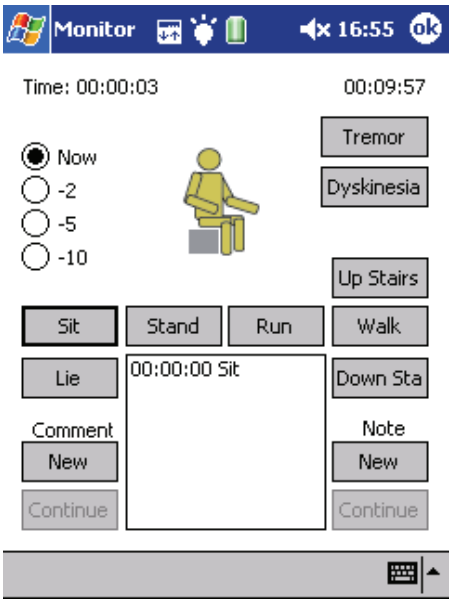


Figure 2-3. A screenshot of the data-logging program ran on hand-held computers to provide accurate reports of the activities of the subjects.

2.6 Conclusion

We have performed a series of measurements on PD patients from the beginning of the thesis to provide needed data for each step of the design, test and application of the algorithms and devices. A *pilot study* gave us insights into the design of the system and the challenges ahead in design of the algorithms. Needed data to design the algorithms and test them under controlled and well-documented situation were provided in a *controlled* study. We performed a *transition study* when the second prototype of the MAS, based on a new concept was first available. Finally, the system was used in real clinical situations for several hours, monitoring PD patients that were free to perform normal activities.

Besides the recorded data, these clinical studies provided valuable and significant insights and feedbacks from the beginning of the thesis to understand the conditions and the needs to use the proposed MAS in real clinical situations. Visual observations as well as video recordings were crucial to understand as an engineer the extents and variety of the movement disorders in PD patients. Based on these experiences, the methods devised in the next chapters where oriented to fulfill clinical needs in the analysis of movement disorders in PD.

Chapter 3 Movement Analysis System

Abstract

Background—Starting from a pilot system based on available sensors and methods, step by step the requirements to design a new Movement Analysis System (MAS) including the recording system, system configuration and sensor sites were considered and addressed.

Objectives—The primary goal was to design a new movement analysis system based on the kinematic sensors suitable for ambulatory recording of body movements of PD patients. Moreover we tried to determine the simplest and most convenient system setup to record movement data for long periods of a day.

Method—A pilot study was started using available components. Based on the results of this study, the initial system configuration was determined and a prototype using new sensors and existing portable data-loggers was designed. In a further step, a prototype of a new architecture for an autonomous sensing unit was prepared and tested in the clinic. Finally, the final system was designed and tested.

Results—We found that to record kinematic data to analyze gait, physical activity, tremor and bradykinesia five sites on the body were enough. A new portable movement analysis system (MAS), based on Autonomous Sensing Unit Recorders (ASUR) was designed and tested inside the clinic. The new system was lightweigth (50g), consumed low power (recording up to 14 hours) and was easy to use for the clinical studies and convenient to carry for the patients.

Main contributions—Design of a new device (MAS) to record body movements of PD patients for long periods of a day without hindering the subjects in their daily activities.

3.1 Introduction

The primary objective in the design of the MAS was to find a minimal number of sensor sites to record adequately the widest possible movement patterns, while making sure that carrying the system for long periods of times (at least up to 12 hours a day) by the patients would not hinder their daily activities. This implied that:

- The size and the weight of the system should be small and the placement of the sensors should be comfortable so that carrying the system would not interfere with the normal movements of the patient during the day.
- The power consumption should be low so that the system could operate for long periods of a day.
- The system should be easy to use, discreet and unobtrusive so that the usage of the system inside the clinic or home would be easy and acceptable for majority of the patients.

Ultimately, the idea was to make such a simple to use system that patients themselves, or by help of their partners, could use the system at home and only submit the data files to clinic for the analysis. This called for a simplified user interface, installation procedure and minimal or no per subject calibration of the system.

3.2 The pilot study

During the *Pilot study* (see section 2.2), a series of measurements were performed to investigate the possible choices for the sensors sites and overall system configuration. As this study was used as a test bed for an iterative, *trial-and-error* based approach, to find the suitable sensor configuration the placements and number of sensors in the system were changed a few times. Moreover, this study helped us to determine the sensor types, needed ranges and sensitivity to record the patterns of the PD abnormalities (like tremor, bradykinesia, dyskinesia…).

3.2.1 Sensors and signals

After a few separate measurements in this study and based on the ideas from previous works, finally seven sensor sites were selected (see Figure 3-1a). To record and analyze gait and based on the method of (Aminian, Najafi *et al.* 2002), four sites on the lower limbs were selected (Figure 3-1b): two sites on the shanks and two sites on the thighs. One site on the trunk (Figure 3-1c) was used to record physical activity based on the method of (Najafi, Aminian *et al.* 2003).

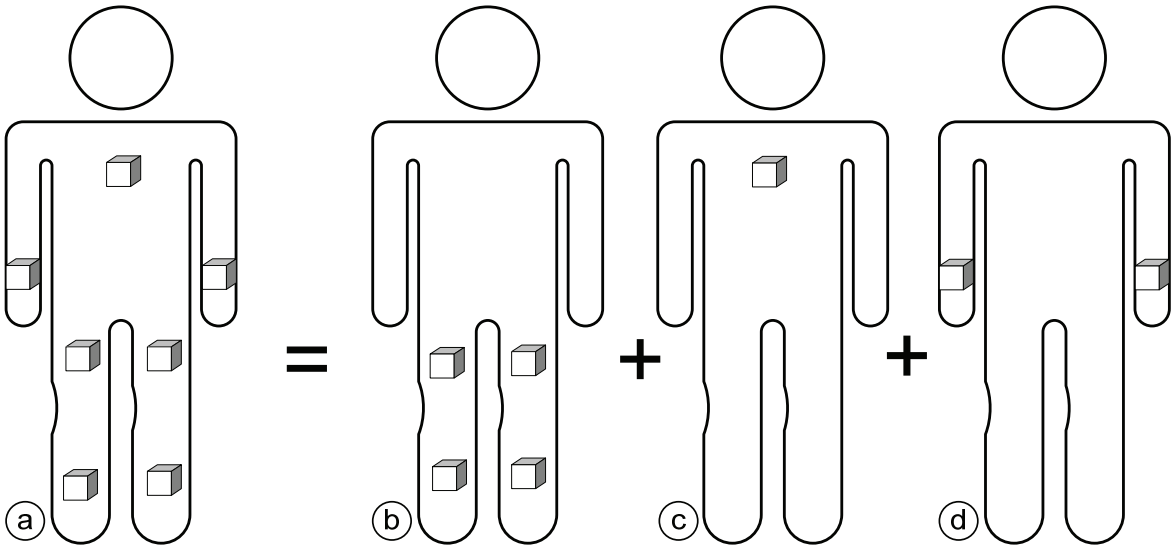


Figure 3-1. a) Sensors sites on the body in the pilot study. The system was a union of three subsystems: b) gait recording system c) physical activity recording system d) tremor and bradykinesia recording system

To record tremor patterns, (Burkhard, Langston *et al.* 2002) used a uni-axial gyroscopes on the dorsum of the hand. We found that this site on hands was not very practical for long-term monitoring as the sensor could receive lots shock due to the impacts to the objects during daily activities. We decided to use a site on the forearm (Figure 3-1d), similar to a watch, which could potentially reduce the risk of impacts and shocks and also would be more discreet. The same sensor was also used for analysis of bradykinesia. The measured and selected range for each of the kinematic sensors in the mentioned sites is presented in Table 3-1.

Sensor site	Sensor type	Signal range	Selected range
Forearms	Gyroscope	±1100°/s	±1200°/s
Shank	Gyroscope	±510°/s	±600°/s
Thigh	Gyroscope	±260°/s	±400°/s
Trunk	Gyroscope	±190°/s	±400°/s
Trunk	Accelerometer(f)	±1.4g	±2g
Trunk	Accelerometer(v)	±1.8g	±2g

Table 3-1. The measured and finally selected range of each kinematic sensor on the body. (f) stands for frontal and (v) stands for the vertical axis.

All sensors used in this study were miniature, solid-state devices. The sensor on the trunk included (see Figure 3-2a) one gyroscope (*Murata, ENC-03J*) in the sagittal plane with a range of ±400°/s and two accelerometers (*Analog Device, ADXL202*) with the range of ±2g, measuring the frontal and vertical accelerations.

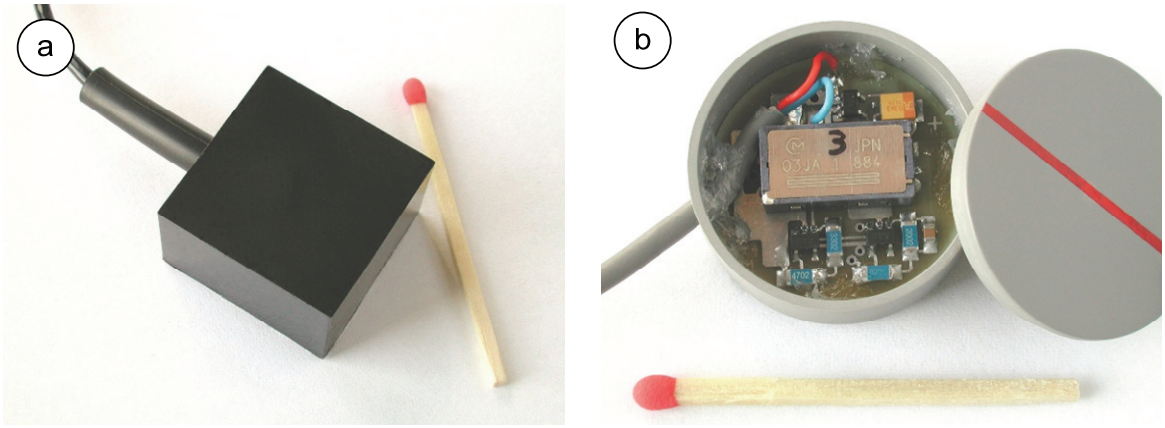


Figure 3-2. a) The trunk sensor used for physical activity monitoring. b) The uni-axial gyroscopes used for the gait analysis.

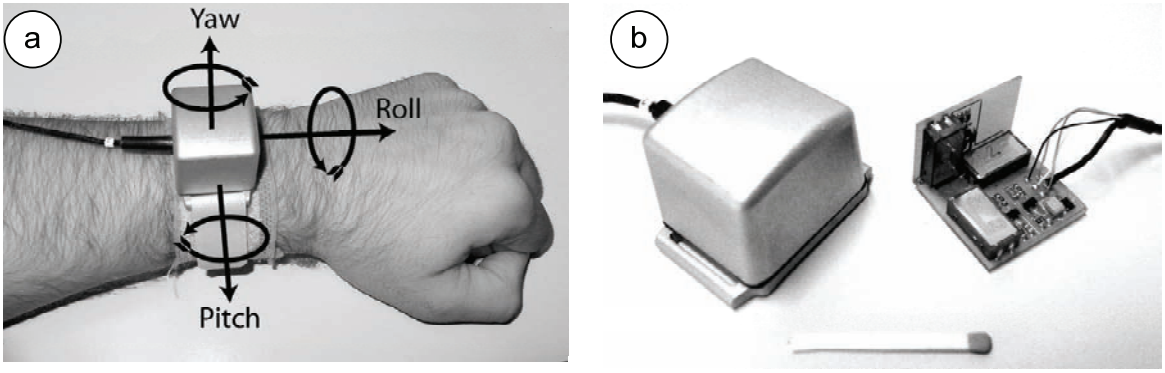


Figure 3-3. The 3D gyroscope used to record the movements of the forearms. a) The sensitive axes of the 3D gyroscope. b) A closer photo of the module and its internals.

To record gait movement patterns, four uni-axial gyroscopes (Murata, ENC-03J) were used (see Figure 3-2b). The sensors on the thighs had a range of ±400°/s and the shanks sensors had a range of ±600°/s.

Movements of the forearms were recorded by 3D gyroscope units (Figure 3-3a). Each module included three uni-axial gyroscopes assembled in the three perpendicular axes of pitch, roll and yaw inside the module (Figure 3-3b). Each gyroscope had a range of ±1200°/s. This large range was selected to cover the possible, very fast movements of the hands during periods of dyskinesia.

To attach the module on the trunk, a self-adhesive patch (Huguenin, CH) was used. On one side, the patch was covered with a silicon based glue to prevent allergic reactions of the skin and on the other side was covered by Velcro. The back of the trunk module also had a small patch of Velcro that fixed the unit on the patch. Silicon based elastic bands (Huguenin, CH) in two different sizes were used to attach the sensors to the thighs and

shanks. Similar to the trunk sensor, between the sensor and the attachment, layers of Velcro were used.

3.2.2 Recording and analyzing the data

All signals were recorded using Physilog® (BioAGM, CH) portable data-logging systems. They converted the analog signals to digital with a 12bits A/D. Each Physilog data-logger could record up to eight channels. As the number of the individual sensors was high (11 gyroscopes and two accelerometers), two *independent* Physilog systems were used at the same time. To store the data, each Physilog was equipped with an 8MBytes memory card. At the beginning, a sampling rate of 40Hz was used but after a few measurements we decided to use a higher sampling rate of 200Hz to increase the temporal resolution.

Subjects carried a small carrying bag to put the Physilogs inside. Cables with round metallic connectors were used to connect the sensors to the Physilog data-loggers.

To record the activities of the subjects some of the measurement sessions were recorded on video. An observer tried to make a log of the activities using a chronometer, pen and paper but it was soon decided that this method was not practical as the observer made numerous mistakes in accurately recording of the activities in real-time. It was decided that for short recordings, the video was more accurate and dependable than the paper based logs. Following this decision, a reviewer prepared the time-tagged logs of the activities *after* the measurement session using the recorded videos.

All of the data-analysis tasks were performed in MATLAB. Several programs were developed to characterize temporal and spectral features of the signals. In this pilot study, to analyze gait the algorithm of (Aminian, Najafi *et al.* 2002) and to analyze physical activities the algorithm of (Najafi, Aminian *et al.* 2003) were used.

We soon realized that the existing gait and posture analysis algorithm were not adequate for our application. Tremor in the trunk and also very slow speed of the movements during transition between body postures of the PD patients, especially in the OFF state made the outcomes of the existing posture analysis very inaccurate: On nearly 40% of the posture transitions in the PD patients were not detected (see chapter 5). The existing gait analysis program had also problems in detection of the gait, especially in presence of tremor or festinating gait. While the reported results in (Aminian, Najafi *et al.* 2002) were very good (nearly perfect gait detection) for the elderly, round 15% of gait cycles were not detected correctly in our PD patients. Clearly, new analysis algorithms were needed.

3.3 First prototype system

Based on the experience gathered in the *pilot study*, the sensor sites and the type of the sensors needed to record movement of the limbs and trunk were chosen. In the *controlled study* (see section 2.3), a system based on two Physilog data-loggers and seven sensors was used (see Figure 3-1a). One major problem with the setup used in the pilot study was the lack of synchronization between the two data-loggers. To solve this problem a marker device was added to the setup. The marker device provided a pulse on the output that was recorded by both data-loggers and could be later used by the analysis algorithms to synchronize the data.

3.3.1 System architecture

The components of the system used in this study are shown in the Figure 3-4.

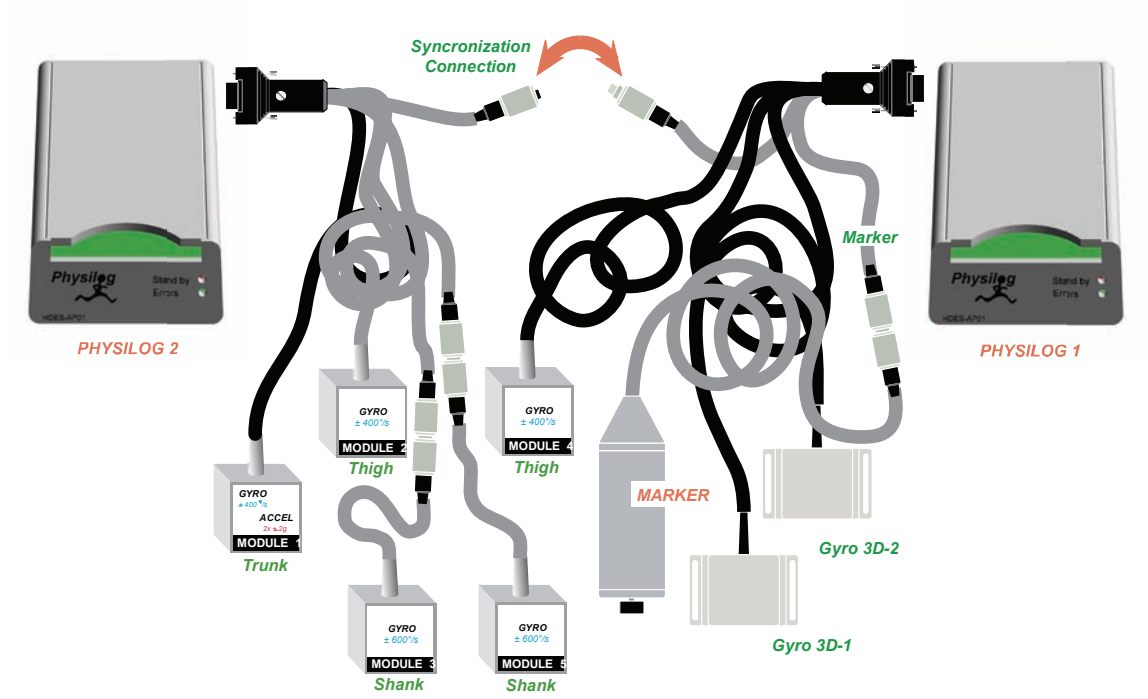


Figure 3-4. The components of the measurement system used in the controlled study.

The two 3D gyroscopes (used for the forearm sites) and one uni-axial gyroscope (used for one of the thigh sites) were connected to the first Physilog. The remaining four sensors, including three uni-axial gyroscopes (used for the two shanks and one remaining thigh site) and the last sensor including two accelerometers and one gyroscope (used for the trunk site) were connected to the second Physilog.

A marker device was also used in this setup. During the measurements, the start and the end of each part of the 17 steps protocol of the measurement (see section 2.3.3) was

marked. By pressing the button on the marker, a 2.5 volts output was activated and by pressing the button again, the output returned back to zero. A red LED and an audio signal reminded the state of the maker device to the operator. Marker was connected to the both Physilog data-loggers and its output was recorded as an input channel of each one of them. Later, a program written in MATLAB was used to synchronize the signals from the two Physilogs based on detection of the rising and falling edges of the recorded marker device signals.

3.3.2 Limitations of the first prototype system

A major limitation of this prototype was the maximum possible period of the measurement. The memory cards used by the Physilog systems had a maximum capacity of only 8Mbytes, so the recording sessions were limited to a little bit more than 55 minutes:

$$8 \text{ channels} \times 1.5 \text{ bytes/sample} \times 200\text{Hz} \times 60 = 144\text{Kbytes/minutes}$$

Moreover, the internal battery of the Physilog was rather small and even with a solution for the memory capacity, Physilog units themselves could not support three or four sensors for more than a few hours.

The second limitation was the weight of the system:

$$\text{Total weight} = 2 \times \text{weight of Physilog} + 7 \times 25\text{g (average weight of sensor)} + \text{weight of the cables, connectors and the small sack to carry the Physilogs}$$

$$\rightarrow \text{Total weight} = 2 \times 300 + 7 \times 25 + 350 = 1125\text{g}$$

The third limitation was the cables used to connect the sensors, marker and the data-loggers (see Figure 3-4). In total more than 10m of thin cable was used in this setup. Although the cables could be run under the cloths and could be fixed using tapes, clearly such a long and complex cabling system could not be easy for the patients to use for measurements longer than one or two hours. Moreover, long cabling could make the system prone to many problems like complex installation procedure, long installation time, broken cables, mistakes in connecting the right connectors, etc.

3.4 Second prototype: autonomous units

To answer the limitations of the first prototype and prepare the system for long-term measurements, a fresh approach and a new architecture for the system was needed. As stated before, main limitations of the approach based on portable data-loggers were the capacity of memory, battery, weight and the cables.

A new architecture was designed for the MAS for the *long-term study*. We called the new units based on this concept the *ASUR* units: Autonomous Sensing Unit Recorders.

3.4.1 Architecture of the ASUR prototype units

The concept of the ASUR system was based on integration of all elements needed for ambulatory recording of kinematic signals in one small box, thus making them independent, avoiding any need to run cables between the units. Each ASUR unit was a complete data-logger integrated with up to four kinematic sensors with enough internal memory and battery to continuously record body movement up to 14 hours.

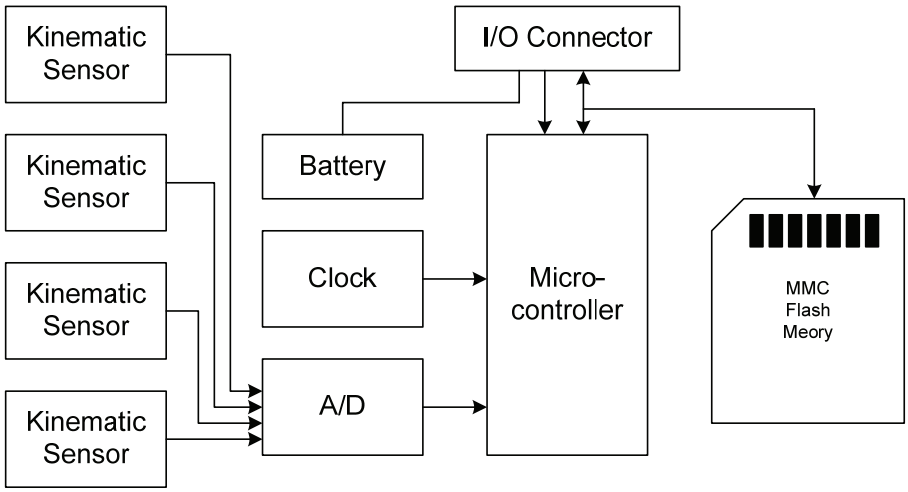


Figure 3-5. Simplified schema of the internal architecture of the prototype ASUR units.

Figure 3-5 shows a simplified block diagram of the ASUR units' architecture. Each unit contains:

- A dedicated rechargeable NiMH battery.
- A flash memory card with a capacity of 64Mbytes.
- A four channels, 16 bits A/D converter with a 200Hz sampling rate.
- A precision, quartz based internal clock.
- An I/O connector.
- One to four kinematic sensors: gyroscopes or accelerometers.
- An 8bits micro-controller.

The first prototype of the ASUR system (see Figure 3-6), was implemented in an aluminum box with a large glass window. An elastic band was used to fix the unit on the body sites. The weight of each unit was less than 80g and after initial start sequence, each

unit operated totally independently. The sensors for different body sites were physically identical and color codes on one side the sensor box were used to differentiate them.

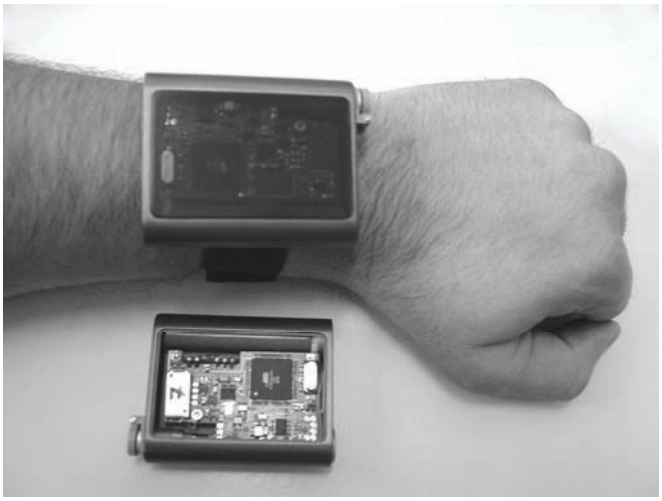


Figure 3-6. First prototype of the ASUR units.

3.4.2 Synchronization and charge unit

As each unit operated independently, a synchronization procedure was needed so that those algorithms using the data from more than one sensor site could function. A controller station (see Figure 3-7) was designed to solve this problem. To better understand the function of this station and method used for the synchronization; let's take a look at the steps taken in a measurement using ASUR prototype units:

- Before the beginning of the measurements, all ASUR prototype units were connected to the controller station.
- The *start* button was pressed on the station. A signal was sent to all units at the same time and they started to record.
- ASUR units were detached from the station, fixed on the body and the measurement session was started. During the measurement the units operated independently.
- At the end of the measurement session, all units were connected again to the controller station. The *stop* button was pressed on the controller station and a signal was sent to all units to stop recording simultaneously.

Despite using high precision quartz crystals in the clock circuits of the units, after several hours of recording the clocks of the different units could go out of synchronization. We observed that this deviation of clocks could be at most in order of few samples per hour at our selected sampling rate of 200Hz: We used five units and performed 13

measurements of round 4 hours on a subject doing daily activity (thus, typical changes in the temperature, variations in power consumption due to functions of gyroscopes and accelerometers, etc.). All modules were started and stopped at the same time. For each measurement, we took the module with the least number of recorded samples and compared the number of recorded sample of the other modules to it (see Table 3-2). We found that on average, the deviation in the number of samples between different units were 1.7 ± 0.9 (mean ± S.D.) samples.

Test	Nr. Extra samples recorded by				Reference	Average
	Unit 1	Unit 2	Unit 3	Unit 4	n. samples	deviation per hour
1	4	8	14	6	2932122	2.0
2	6	11	18	8	3522510	2.2
3	3	6	9	4	1852612	2.1
4	2	7	13	6	3018267	1.7
5	3	11	17	7	3903394	1.8
6	3	7	13	5	3190194	1.6
7	5	9	14	6	3205353	1.9
8	4	8	12	5	2905139	1.8
9	6	9	14	6	3221472	2.0
10	0	5	9	4	2708749	1.2
11	5	9	15	6	3388892	1.9
12	2	5	9	4	2449036	1.5
13	0	2	8	3	2924968	0.8

Table 3-2. Clock deviation of the ASUR units comparing to the slowest unit in each test. The reported values show the deviation in samples.

As all units started and stopped recording of the data at exactly the same time, by assuming a constant frequency of clock inside each unit, the clock deviation between the units could be easily compensated in the data analysis software:

- The number of recorded samples (n_0) of the slowest unit (u_0) was taken as the reference.
- For all other u_i units, the difference $\delta_i = n_i - n_0$ between the recorded samples (n_i) in comparison to u_0 was calculated.
- In the recorded data of each unit, with the assumption of constant clock speed, the last sample of each period of n_i / δ_i were removed.

Besides sending the start and stop commands to the ASUR units, synchronization station performed two more tasks: charging the battery of the units while they were connected to the station and transferring the recorded data to a personal computer using USB connection.

3.4.3 System setup

For the *long-term study*, we used ASUR prototype systems on five body sites. We could reduce two body sites as we developed our gait analysis method further and the new algorithm did not need the two thigh sites anymore (see chapter 7). Also instead of using 3D gyroscopes on hands, 2D gyroscope units were used: By reviewing the results from the *controlled study*, we found that using 2D gyroscopes instead of 3D gyroscopes by eliminating the *yaw axis*, did not significantly affect the performance of the tremor and bradykinesia quantification algorithms (see chapter 4). At the same time, removing the yaw gyroscope could help to reduce the thickness of the units. An additional technical benefit of reduction of one gyroscope was to reduce the power requirements of the unit (thus, the size of the battery) as the gyroscopes were the most energy consuming components of the system (each one needed round 5mA to operate).

Another difference comparing to previous system was the use of 16 bits A/D converters instead of Physilog's 12 bits converters. However, by measuring the level of the noise, we found out that this change could only make a small improvement: The noise level in the Physilog was -65.6dBFS (dB full scale) while in the new system it was -75.4dBFS.

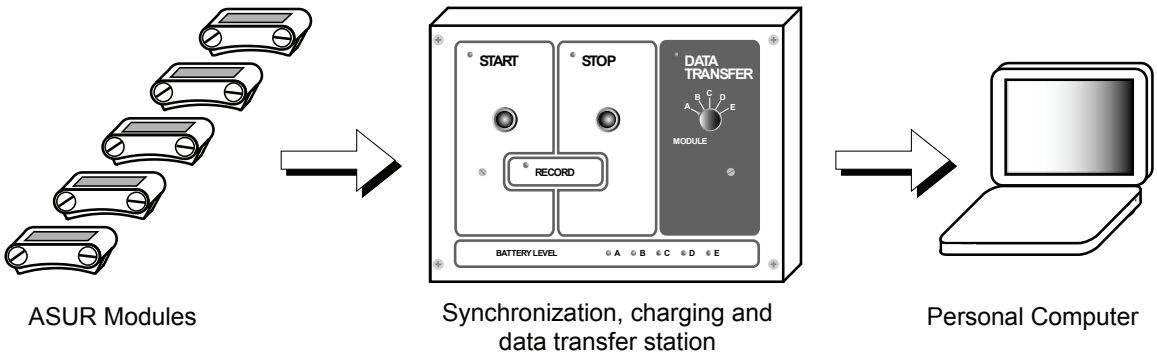


Figure 3-7. Components of the ASUR prototype system.

In summary, we used five units on five body sites (forearms, shanks and trunk). In total seven gyroscopes and two accelerometers were used in this setup and sampling frequency was again 200Hz. The weight of the setup carried by the patients was significantly reduced from 1125g in the first prototype used in the controlled study to 400g (5 × 80g) while at the same time the maximum possible period of recording was increased from 55 minutes to 14 hours. By elimination of all cables and reduction of the weight, we had a very positive feedback from the patients regarding convenience and ease of use of the system.

3.5 Third and final prototype of the MAS

Following the path from the *pilot study* to the *controlled study* and finally the *long-term study*, step by step the architecture and technical aspects of our MAS were refined and matured. The prototype of the ASUR system met almost all of our criteria for a simple to use ambulatory monitoring system. The final version of the ASUR units is now being used in some further clinical studies (see section 9.2, perspectives and further clinical studies).

In order to optimize the final system, few changes were made to the second prototype (ASUR system). The aluminum box of the units was replaced with a plastic one to further reduce the weight of the system (Figure 3-8a). Instead of color codes to designate different sensors, a picture was added the front face of the units to clearly show the sensor site (see Figure 3-8a). The controller unit used in the prototype was divided in to two units: one dedicated to transfer the data to PC and the other one to charge and synchronize the recording units (Figure 3-8b). The new controller could accept one to three ASUR units and provided a connector to be connected to additional controller to synchronize additional units.

Internally, the same architecture as the prototype for the recording units were used but some electronic circuits were redesigned to reduce the electronic noise of the circuits and to replace the Murata gyroscopes with new Analog Device gyroscopes (model ADXRS300) that had lower drift and were much more resistant to the mechanical shocks (max 2000g vs. max 50g). On the downside, after making the needed changes in the power supply circuits, the level of the recorded noise was increased from -75.4dBFS to -71.5dBFS.

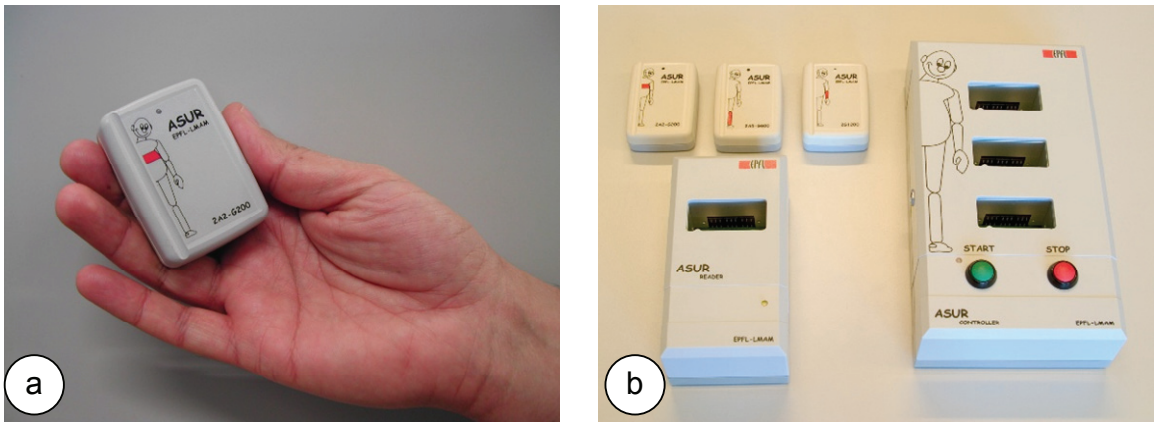


Figure 3-8. a) The ASUR unit. b) Components of the ASUR monitoring system. On top left, the units, on bottom left the data transfer unit and on the right the charge and synchronization unit.

To fix the recording units on the body, on the shanks and forearms, new elastic bands were used. The new bands had a silicon layer on the side facing the skin with soft but bumpy texture. The texture in the silicon layer helped better blood circulation while the silicon based material minimized the risk of allergic response of the skin. The attachment of the trunk unit was similar to the first prototype system and was based on self-adhesive patches.

3.5.1 Architecture of the third prototype

The final ASUR recording unit internally consisted of several sections (Figure 3-9). These sections were:

- The kinematic sensors. Up to two gyroscopes (in the roll and pitch axes) and two accelerometers could be present in each ASUR recording units.
- The analog amplifier and interface circuits.
- Anti-aliasing filters (a RC filter with a cut-off frequency of 17Hz) to limit band-width of the analog signals.
- The digital section that itself included a 16bits, four channel multiplexing A/D converter, a Micro-controller, clock circuits and a 64Mbytes flash memory. This section also included a LED to show the state of the unit: Off when the unit is off. Blinking in green when the unit is recording. Blinking in red in case of errors. Red when being charged and Green when the battery is fully charged.
- A miniature, switching power circuits to provide constant and low noise supply for the digital and analog sections.
- A gold-plated connector to connect the unit to the controller. The connector included pins for the *start* and *stop* commands. It also included an interface to the internal flash memory of the unit, so that the recorded data could be read by the dedicated data transfer unit. It also included a pin to send ON/OFF command to the unit as well as a pin used in charging the internal battery of the unit.

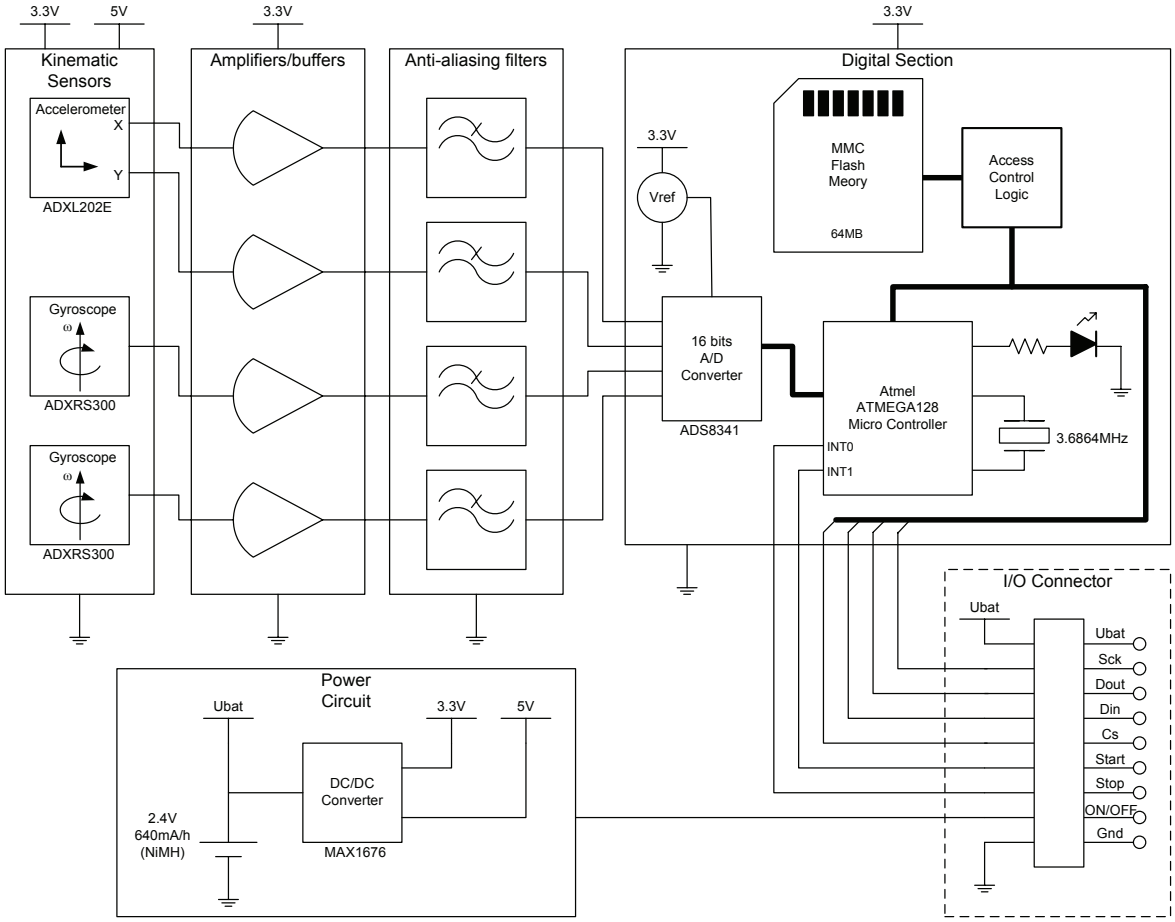


Figure 3-9. Internal architecture of the ASUR units.

The final ASUR unit weighted 50g (i.e. 30g less than the prototype version). This way, the total weight of the system fixed on the body was reduced to 250g. The maximum recording capacity of each unit was 14 hours.

A library of MATLAB functions to calibrate the sensors, access the recorded data and to synchronize the data files from recordings with more than one unit were also developed:

- A MEX[1] function called *BinInfo* to get the number of recorded channels, sampling rate and number of sample in an ASUR data file.
- A MEX function called *BinRead* to read recorded data file and to calibrate the signal (conversion from the volts unit to measurement unit of the sensor) using the information stored in the header of the file.

[1] MEX files are special routines written in C/C++, to be used by MATLAB programs to perform system-level tasks.

- A MATLAB class called *dataset* to link several recorded data files together, perform synchronization and provide access to the calibrated data in selectable time windows.

A stand-alone visualization program written in C++ was also developed to visualize, export and show the header information of the recorded data in the field, using a portable computer (see Figure 3-10).

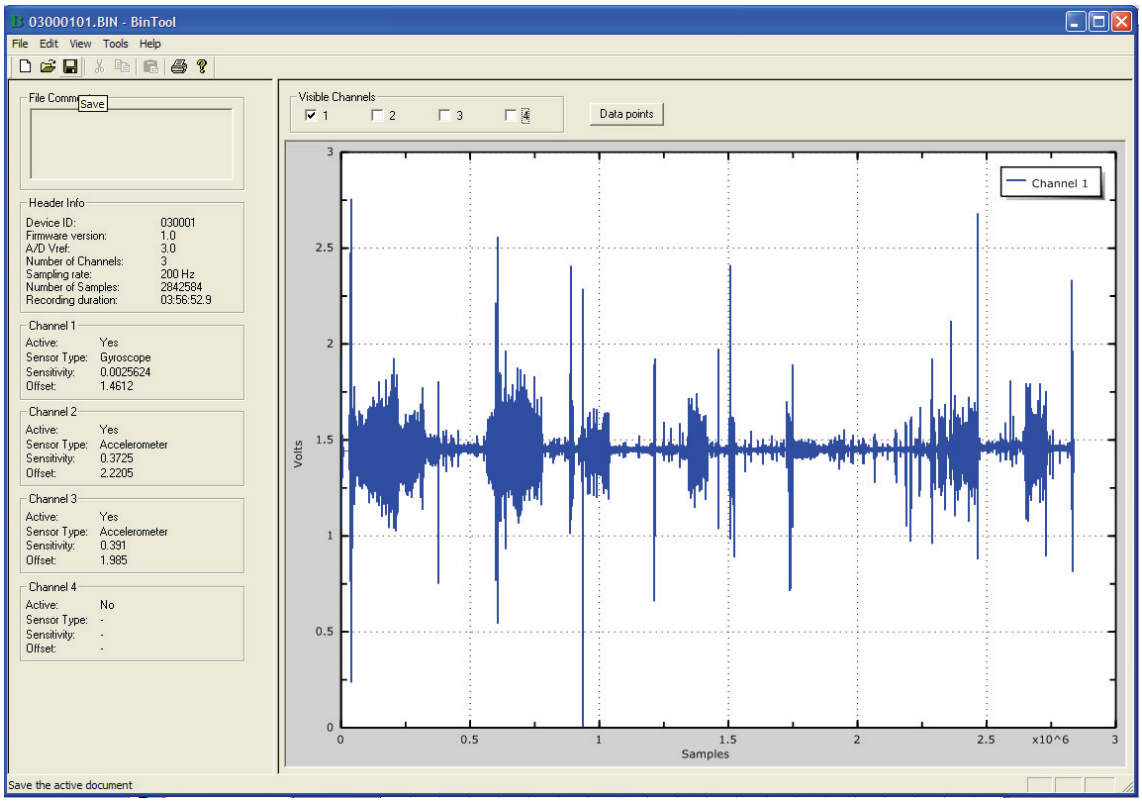


Figure 3-10. A screen shot of the stand-alone data visualization program.

3.6 Conclusion

Using a new architecture for the ASUR system, comparing to the first prototype the total weight of the setup fixed on the body was reduced from 1125g to 250g, the maximum recording period was increased from under one hour to 14 hours and by removing all the cables between units and providing a simple interface to use the system, the time and complexity to setup the system and ease of use for the patients were dramatically enhanced. A comparison of several characteristics of the three systems in presented in the Table 3-3.

In summary, starting from a pilot study, the sensor configuration and recording units used in our final MAS were step by step designed, evaluated and refined. Finally, a

configuration based on five lightweight, autonomous recording units were proposed to record body movement using kinematic sensors during daily activities.

Parameter	First prototype	Second prototype	Third prototype
Number of sites on the body	7	5	5
Number of sensors	13	9	9
A/D resolution	12 bit	16 bits	16 bits
Noise level	-65.6dBFS	-75.4dBFS	-71.5dBFS
Sampling rate	Selectable: 1 ~ 1kHz	Fixed (200Hz)	Fixed (200Hz)
Total memory capacity	8MB	5 × 64MB	5× 64MB
Autonomy (power)	3 hours	14 hours	14 hours
Autonomy (memory)	55 minutes	15 hours	15 hours
Total weight of the setup	1125g	400g	250g
Dimensions of the sensors	25 × 25 × 15mm	60 × 50 × 18mm	61 × 44 × 19mm
Time needed to install the system	15 minutes	5 minutes	5 minutes
Ease of use according to the patients	Poor	Good	Good

Table 3-3. Comparison of the characteristics of the three prototype systems

Chapter 4 Quantification of tremor and bradykinesia

Abstract

Background—Tremor and Bradykinesia are two of the most important movement abnormalities in Parkinson's disease. The presence and severity of tremor and bradykinesia, like other parkinsonian signs, can change during the day and as such, detection, assessment and following the changes of these signs during daily activities are of great interest.

Objectives—Design and validation of an ambulatory system based on kinematic sensors to detect and quantify tremor and bradykinesia in PD patients while the patients were performing daily activities. Accurate detection of the start and end of each period of tremor was of interest. Moreover, investigating the highest possible temporal resolution to estimate bradykinesia related parameters was another objective of this study.

Method—Two studies were performed. In the first study, a group of PD patients and control subjects followed a 45 minutes protocol of typical daily activities while the whole session was recorded on video. Using gyroscopes attached on the forearms, the angular velocity of the movements of the hands was recorded. To detect tremor, a method based on spectral estimation was developed. Using the speed, the range and the frequency of the movements, an algorithm to estimate bradykinesia related parameters was also designed. The obtained parameters to quantify tremor and bradykinesia were compared to the UPDRS score of the subjects. The detected periods of the tremor were compared to the video to find the accuracy of the algorithm.

In the second study, the movements of the hands of a group of PD patients were recorded for several hours while they were free to move on will. The outcomes of the tremor and bradykinesia quantification algorithms were compared to the UPDRS score of the patients. The effect of the selection of the *window size* to estimate bradykinesia related parameters was also studied.

Results—In the first study, tremor detection algorithm showed a sensitivity of 99.5% and a specificity of 94.2%. Estimated tremor amplitude showed a high correlation to the UPDRS tremor sub-score ($r = 0.87$, $p < 0.001$ for the roll axis). Also, high and significant

correlation between the estimated bradykinesia parameters and respective UPDRS sub-score was found ($r = -0.83$, $p < 0.001$ for the roll axis). In the second study, similar results to the first study were obtained with a time window of 45 minutes while bradykinesia related parameter showed significant correlation ($r = -0.74$, $p < 0.01$) even with the smallest window size (5 minutes).

Main contributions—Two new algorithms to quantify tremor and bradykinesia were developed and tested, both in controlled and free conditions. The algorithm to detect tremor showed a high accuracy in detection of tremor even when subjects were performing typical daily activities. Several objective parameters related to bradykinesia were introduced. These parameters showed a high correlation to the UPDRS clinical score. Our study showed the possibility of objective evaluation of tremor and bradykinesia of free moving PD patients during their daily activities.

4.1 Introduction

Tremor and Bradykinesia are among the most important movement abnormalities in Parkinson's disease (Stern and Koller 1993). Tremor appears as a beating or oscillating movement and is regular (4-6 beats per second) (Deuschl, Bain *et al.* 1998; Hallett 1998). As the tremor in PD usually appears when the muscles are relaxed, it is called *resting tremor*. This means that the affected body part trembles when it is at rest and not doing work and often subsides with action (Deuschl, Bain *et al.* 1998). Figure 4-1a shows 10 seconds of recorded tremor using a gyroscope attached to the forearm of a PD patient. The sensitive axis of the gyroscope was the roll axis. Figure 4-1b. shows the frequency spectrum of this signal.

Bradykinesia is the slowing of voluntary movements. In addition to slow movements, a person with bradykinesia would possibly have incompleteness of movement, difficulty in initiating movements, and arrests of ongoing movement. Figure 4-2a shows the angular velocity of the movements of the hands, recorded by a gyroscope in the roll axis, of a PD patient with STN-DBS implantation. The patient was following a protocol of typical daily activities. The stimulator was turned ON in this measurement. Figure 4-2b shows the angular velocity of the same hand of the same patient, this time with the stimulator turned OFF. The patient was following the same protocol of the activities. There is a marked reduction of the amplitude of the angular velocity signal during the whole period of the recording in OFF state.

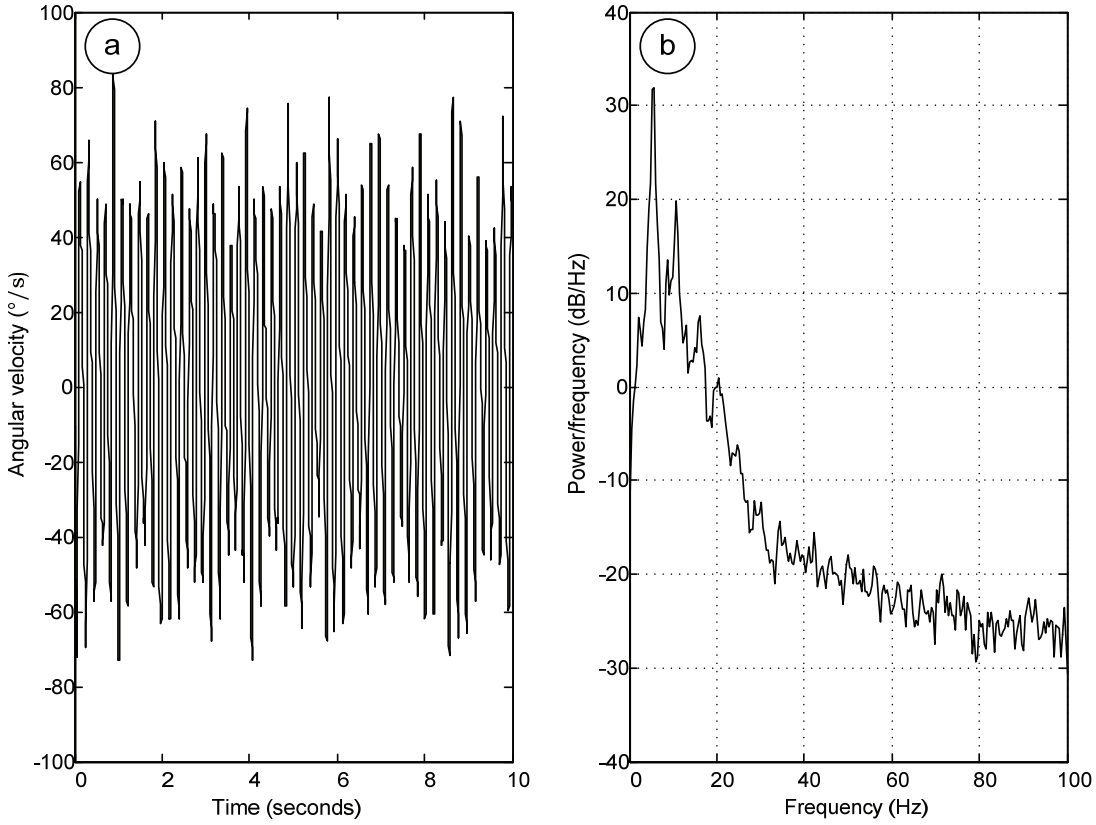


Figure 4-1. a) 10 seconds of the rest tremor recorded by a gyroscope on the forearm of a PD patient. b) The frequency spectrum of this period of tremor. Notice the dominant peak near 5Hz.

Currently assessment of motor abnormalities in PD is mainly clinical, based on different scales. Amongst them, the most widely used rating scale is the Unified Parkinson's Disease Rating Scale (part III) (Fahn, Elton *et al.* 1987). Using various techniques, several groups have proposed objective methods to detect and quantify tremor (Bacher, Scholz *et al.* 1989; Dunnewold, Jacobi *et al.* 1997; Eberhart 1999; Norman, Edwards *et al.* 1999; Scholz, Bacher *et al.* 1988; Spieker, Boose *et al.* 1998) and bradykinesia (Boraud, Tison *et al.* 1997; Giovannoni, van Schalkwyk *et al.* 1999; Katayama 2001). Recently, there has been a growing interest in applications of body-fixed sensors (BFS) and in particular kinematic sensors for long-term monitoring of PD patients. Several groups have used *accelerometers* to detect and quantify tremor (Hoff, Wagemans *et al.* 2001; Smeja, Foerster *et al.* 1999; Van Someren 1997; Van Someren, Vonk *et al.* 1998) and bradykinesia (Dunnewold, Hoff *et al.* 1998; Dunnewold, Jacobi *et al.* 1997; Ghika, Wiegner *et al.* 1993; Katayama 2001), yet, an other type of kinematic sensors, gyroscopes, that can measure angular velocity of the movement of the body segments, has been rarely used but may turn to be even more useful to quantify tremor and bradykinesia (Burkhard, Langston *et al.* 2002).

The objective of the study was to design a new ambulatory system to quantify tremor and bradykinesia during daily activities of the patients. The new system is based on miniature gyroscopes attached on forearms. Two studies have been performed. In the first study, PD patients with bilateral STN-DBS implantations and a control group performed a protocol of typical daily activities. Sensitivity and specificity of a new algorithm to detect tremor and quantify the severity of the tremor and bradykinesia were determined.

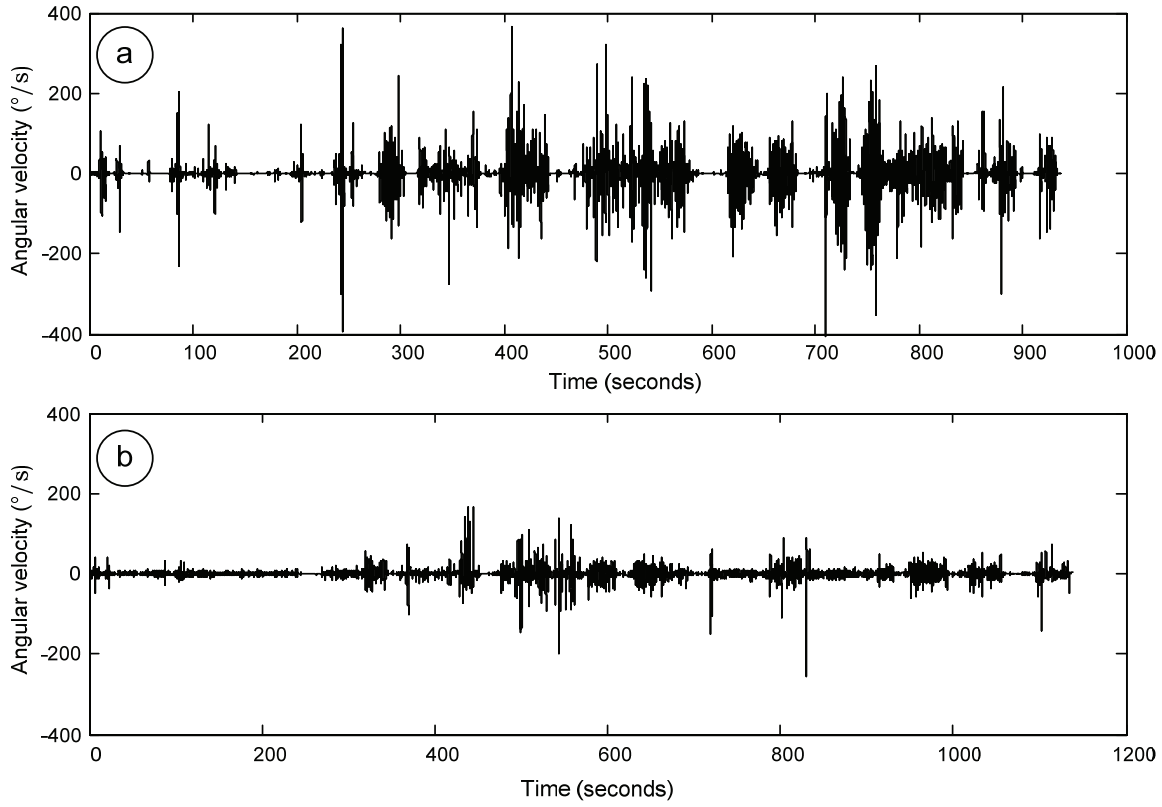


Figure 4-2. a) Angular velocity of the movements of the hands in a PD patient with STN-DBS while the stimulator was turned ON. Patient was following the protocol of the controlled study. b) The angular velocity of the movements of the same hand of the same PD patient, following the same protocol of the movements, this time with the stimulator turned OFF.

During the second study, the method was applied to a group of PD patients that were free to perform daily activities at will during several hours of continuous recording while the state of the stimulation was changed from ON to OFF and back to ON again. We also studied the effect of selection of the window sizes used to calculate the parameters related to the tremor and bradykinesia on the correlation between UPDRS and these parameters.

4.2 Method

4.2.1 Patients and experiment design

The data from two studies has been used. In the first study, two groups of participants were enrolled in this study. A group of ten PD patients and a second group consisted of 10 age and sex-matched normal control subjects participated in this study. A series of measurements was done while the subjects carried the measuring system and followed by a set of typical daily activities like eating, writing, brushing the teeth, several walking trials, climbing the stairs etc. It took about 45 minutes for each subject to complete the protocol. Before each measurement, PD patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS, motor section III, (Fahn, Elton *et al.* 1987)). Each patient performed the protocol twice: once during *Stim ON* and once during *Stim OFF* (i.e. when both stimulators have been turned off). More details about the patients, protocol and the clinical test is provided in section 2.3, the *controlled study*.

Eleven PD patients participated in the second study. They included seven males and four females with an average age of 66.5 years (max=82.3, min = 59.6, STD = 6.8). In this study patients were free to move inside the clinic and to perform activities they wished. Subjects started while the STN-DBS stimulation was ON. Subsequently, the stimulators were turned OFF for three hours and turned ON again. Typically, each measurement took about five hours including one hour during Stim ON, followed by the three hours during Stim OFF and followed by another one hour during Stim ON. An UPDRS test was performed at the beginning of the measurement and was repeated at least every one hour. More detail about patients and experiment protocol can be found in section 2.5, the *long-term* study.

4.2.2 Measurement system

In the first study, a system based on two 3D gyroscopes and a Physilog® data-logger has been used to record the movements of the forearms (see Figure 4-3). In the second study, two ASUR prototype units have been used. The ASUR units included two gyroscopes in the roll and pitch axes. More details about the measurement systems are presented in the sections 3.3 and 3.4.

4.2.3 Detection and quantification of tremor

To detect tremor, the signals from each axis of the sensors were analyzed separately. Figure 4-4.a shows the block diagram of the method. The first step was to remove the drift of the gyroscope signals using a very fast (i.e. low computation time) first degree IIR filter with a cut-off frequency of $fc \approx 0.25Hz$ in the software. To detect tremors, the recorded

angular velocity signal was then divided into three seconds windows. Since we were interested in the analysis of tremor in PD which normally has a duration in the range of at least few seconds after onset, selecting too short window sizes (e.g. less than one seconds) could dramatically increase false-positives and also could make it difficult to compare the outcomes to the video recording that would not be accurate for very short periods. A too large window (e.g. more than ten seconds) would not let us detect short periods of tremor accurately before or after a period of activity as the spectrum of the signal tended to get flat or to include multiple peaks.

For each window the frequency spectrum of the signal was estimated using an all-pole 6th degree AR model by using the Burg (Burg 1975) method (see Figure 4-5). If a dominant peak in the spectrum, i.e. a pole close to the unit circle with an amplitude more than a certain threshold (in this case, a threshold of 0.92 gave us the be best results based only our data-sets), with a frequency between 3.5 and 7.5 Hz was detected, the window was reported as tremor. With the selected window size (3 seconds), we observed that sometimes during the periods that subjects had no tremor, some isolated windows (i.e. with no detected tremor before or after them) were misclassified as tremor while subject performed certain activities (like brushing the teeth). To reduce these kind of false-positives, those isolated windows where removed from the output by marking them as no-tremor. This step reduced false-positives at the risk of potentially reducing true-positives. However, as extremely short periods of PD tremor are unusual, we found that benefits of this method outweighed its drawbacks.

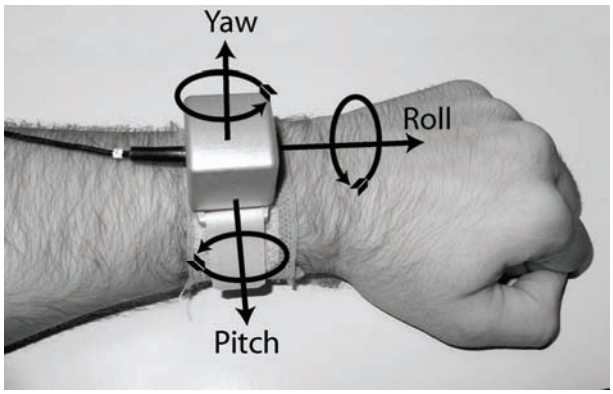


Figure 4-3. The 3D gyroscope used in the first study. The three sensitive axes of the device are shown in the picture.

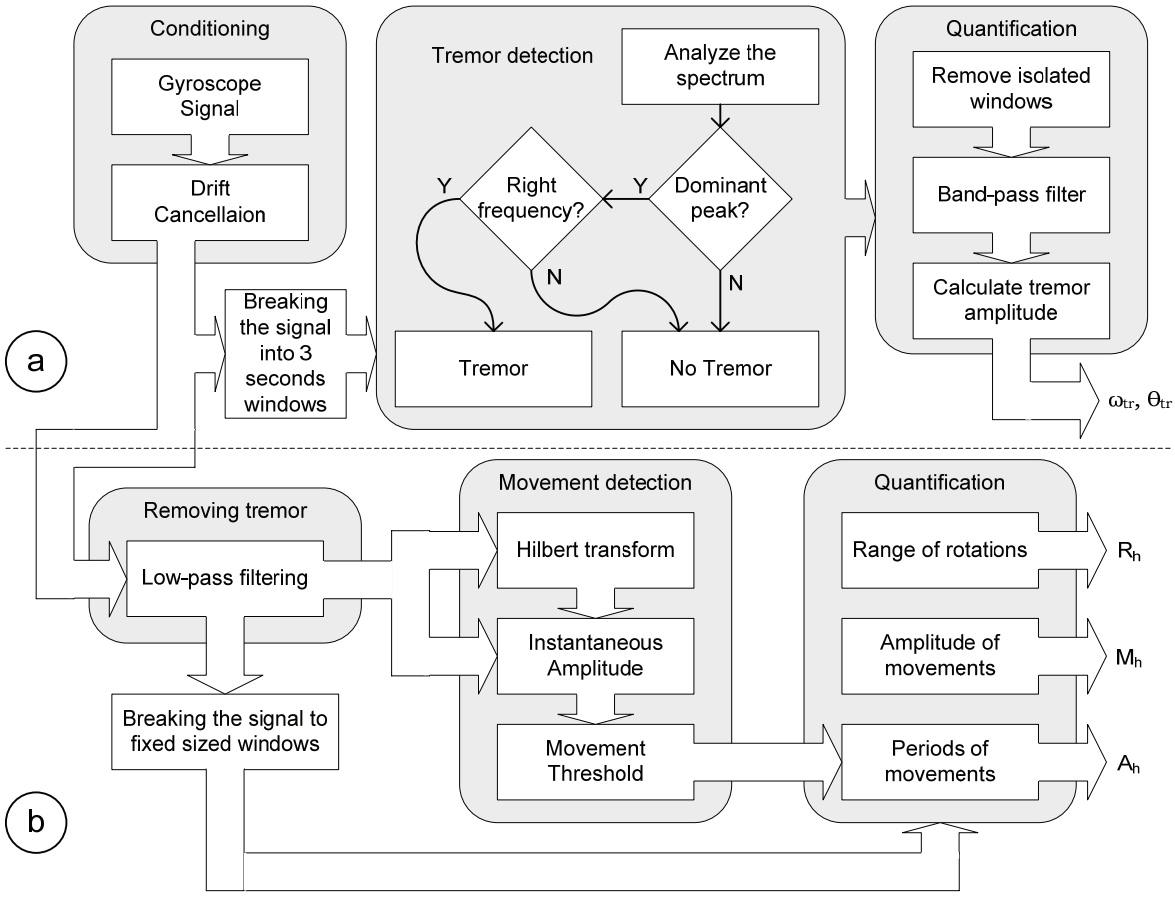


Figure 4-4. The flowchart of the methods. a) The tremor detection and quantification method b) Quantification of the bradykinesia.

The amplitude of the detected tremors in degrees/sec (ω_{tr}) was calculated by taking the *Root Mean Square* (RMS) value of the angular-velocity signal of the gyroscope after filtering using a 280 degrees band-pass FIR filter with cut-off frequencies of 3.5 and 7.5 Hz. The filter was used to reduce the effect of movements of the hands with frequencies outside of the range of the frequencies associated with PD tremor. (Initially an IIR filter with similar cut-off frequencies was considered but finally we found out that this filter introduced too much distortion in the signal so we decided to use a computationally more expensive FIR filter with lower distortion). To calculate the amplitude of the tremor in degrees (θ_{tr}), the filtered signal was integrated over the time and again RMS value was calculated.

By taking ω_p, ω_r and ω_y as the amplitude of the tremor for the pitch, roll and the yaw axes respectively, considering that the sensitive axes of gyroscopes were perpendicular, the amplitude of a combination of axes could be calculated by:

$$\vec{\omega}_{pr} = \vec{\omega}_p + \vec{\omega}_r \Rightarrow \omega_{pr} = \sqrt{\omega_p^2 + \omega_r^2} \qquad (4\text{-}1)$$

$$\vec{\omega}_{py} = \vec{\omega}_p + \vec{\omega}_y \Rightarrow \omega_{py} = \sqrt{\omega_p^2 + \omega_y^2} \quad (4\text{-}2)$$

$$\vec{\omega}_{ry} = \vec{\omega}_r + \vec{\omega}_y \Rightarrow \omega_{ry} = \sqrt{\omega_r^2 + \omega_y^2} \quad (4\text{-}3)$$

$$\vec{\omega}_{pry} = \vec{\omega}_p + \vec{\omega}_r + \vec{\omega}_y \Rightarrow \omega_{pry} = \sqrt{\omega_p^2 + \omega_r^2 + \omega_y^2} \quad (4\text{-}4)$$

where ω_{pr} represents the amplitude of the tremor in combined axes of pitch and roll, ω_{py} stands for the combination of pitch and yaw axes, and ω_{ry} stands for the combination of roll and yaw axes. ω_{pry} stands for the combination of all three axes. With change of the symbols, the same formulas were used for the angle values: θ_{pr}, θ_{py}, θ_{ry} and θ_{pry}. The amplitude of the signal could be influenced by the proximity of the sensor to the clinically mainly affected part of the limb which is in PD patients normally the hand or the fingers.

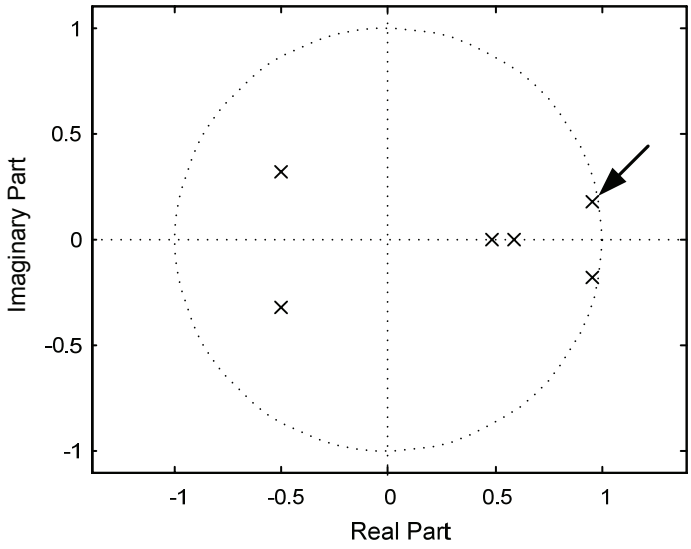


Figure 4-5. Estimated poles for the period of the tremor shown in the Figure 4-1 using Burg's method. The arrow shows the pole that signifies the presence of PD tremor.

4.2.4 Quantification of Bradykinesia

The method to quantify bradykinesia included two steps: identifying periods of movement and calculating parameters related to the movements (see Figure 4-4b). The method was based on estimation of related parameters for each consecutive fixed period of time. In the first study, the parameters related to bradykinesia were calculated for the whole period of measurement (round 45 minutes). In the second study, the periods of the recording were broken into a series of fixed sized windows and the parameters were calculated for each window. Several sizes for the windows (45, 30, 15, 10 and 5 minutes) were considered and the effect of the window size on the ability of the algorithm to follow the fluctuations of the bradykinesia was studied.

To identify periods of movements, after cancelling the drift of the gyroscope (described in the previous section) an IIR low-pass filter of degree eight, with a cut-off frequency of $fc \approx 3.5Hz$ was applied to remove the effects of tremor. To find the *instantaneous amplitude* of the low-pass filtered signal of the gyroscope ($g_{lp}(t)$), an analytical signal was constructed (Oppenheim and Shafer 1998):

$$a(t) = g_{lp}(t) + i.\overline{g_{lp}}(t) \tag{4-5}$$

Where the bar over $g_{lp}(t)$ represents its *Hilbert transform*. The amplitude and phase of this analytical signal at each time t represented instantaneous amplitude and phase of the $g_{lp}(t)$.

The periods of movements of the hands were defined as those periods of time when the instantaneous amplitude of the gyroscope signal was more than five degrees/sec. Movements of the hands slower than this threshold were hardly visible in practice and were very close to the recorded noise or artifacts in our recorded signals. To quantify the movements, three aspects of the movements were considered: the average speed, periods and the average range of the movements. As such, the average value of three parameters were calculated for each time window: The *Mobility of hand*, M_h, represented the average velocity of the hands and was defined as the RMS of the $g_{lp}(t)$ during the periods of movements. *Activity of the hand* or A_h was defined as the percentage of the time that hand was in movement (i.e. when $a(t)$ was more than the selected threshold) during the period of the selected time window. The third calculated parameter was the a*verage Range of rotation of hand* (R_h). To calculate R_h , the range of the rotations of hands (angles) were calculated by integration of the $g_{lp}(t)$ during the period of the movements.

4.2.5 Statistical analysis and comparison to UPDRS

Sensitivity of the tremor detection can be defined as the proportion of the periods of tremor (true-positives) that could be correctly identified. In the same way, specificity of the tremor detection can be defined as the proportion of the periods of no-tremor (true-negatives) that could be correctly identified. We evaluated the sensitivity and specificity of the tremor detection method in comparison to *video recordings* as currently no alternative instrumental method could be used as a gold standard. During the first study, where subjects performed a 45 minutes protocol of typical daily activities, movements of the hands were recorded by video. A reviewer carefully examined the recordings and identified the start and end of each period of visible tremors of the hands of the PD patients, independent of their amplitude or direction. These periods were then compared to the outcomes of the tremor detection algorithm, to calculate the sensitivity of the method for each axis or combination of axes of the gyroscope. The controls participating in this

study, by definition, had no tremor. In order to estimate the specificity, any detected period of the tremor in the gyroscope signals of the control group were considered as false-positives. As obtaining optimal images of the hands from a distance was difficult, this method avoided uncertainties that could arise when the algorithm detected a period of tremor while hands were not completely visible. A similar approach was used by (Van Someren, Vonk *et al.* 1998), where they used the reported periods of tremor in a group of patients with Alzheimer's disease as false-positives. To calculate *overall* sensitivity and specificity for all subjects, total period of false positive/negative were divided by total periods of measurements. This approach let us reduce the effect of very low prevalence of tremor in some patients, while including all of them in the calculation of the overall values.

To study the correlations between UPDRS and the outcomes of the algorithms, two UPDRS sub-scores were used. A sub-score of UPDRS motor section from items 20 and 21 (rest tremor and action tremor) was used to evaluate the results of the tremor quantification. For bradykinesia, the summation of the sub-scores 23, 24 and 25 (finger tapping, hand movement, rapid alternate movements of hand) was used. When comparing the tremor sub-score of UPDRS and outcomes of the algorithm, the logarithms of the parameters were considered. As it was possible that tremors would stop for some periods of time, where an amplitude of zero was reported, instead of directly taking logarithm of the amplitudes, $log_{10}(1+\omega_{tr})$ and $log_{10}(1+\theta_{tr})$ were used in calculations.

During the second study, patients performed a UPDRS test with a frequency of at least one test per hour. For each patient, the period between the second UPDRS test after turning stimulator off and the third test (i.e. between two hours after turning off the stimulator and the third hour) was selected. Using the proposed algorithms, the time windows of 5, 10, 15, 30 and 45 minutes before the end of the period, until the end of the period were used to study the correlation between the UPDRS and the estimated parameters related to bradykinesia and tremor.

Wilcoxon's non-parametric rank-sum test was used to compare different parameters between the normal subjects and PD patients. To compare between the Stim ON and Stim OFF states, Wilcoxon's non-parametric paired test, sign-rank test was used. The correlation between UPDRS sub-scores and different parameters was estimated using Pearson's correlation. For all statistical tests, p-values of more than 0.05 were considered as non-significant.

4.3 Results

4.3.1 First study: Subjects following the test protocol

For each period of 3 seconds, the tremor detection algorithm provided two outputs: presence of tremor and the amplitude of the tremor. Figure 4-6 shows a typical outcome. The periods of the tremor reported by video observations, are also presented.

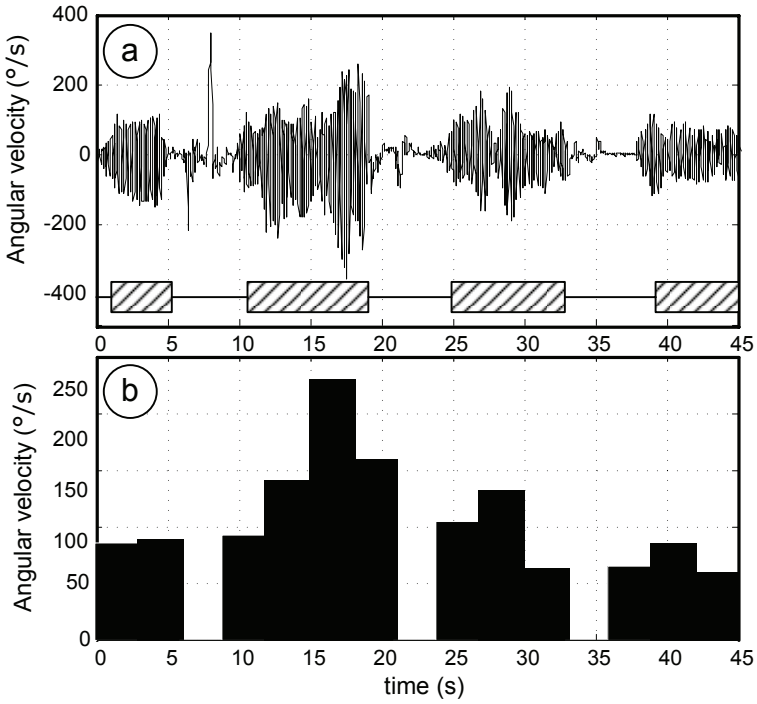


Figure 4-6. A sample of the tremor detection algorithm's output. a) Raw signal from the gyroscope (roll axis). The boxes with hatched patterns signify the periods of tremor detected by visual observation b) Output of the algorithm. Black bars shows the periods marked as tremor and the height of the bar shows the amplitude of the tremor.

Table 4-1 shows the results of estimated sensitivity and specificity of the tremor detection algorithm, for each axis and each possible combination of axes of the gyroscopes. Among the three axes of the sensor, roll axes showed the highest sensitivity and specificity. When combining the outputs of two or three axes, the optimal combination always included the roll axis.

	Subject	Pitch	Roll	Yaw	Pitch+Roll	Roll+Yaw	Pitch+Yaw	All axes	Prevalence
Sensitivity	Patient 1	68.3%	81.8%	71.1%	88.4%	88.8%	83.3%	91.1%	79.6%
	Patient 2	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	10.1%
	Patient 3	49.3%	52.3%	52.3%	81.6%	83.9%	70.0%	98.5%	12.8%
	Patient 4	56.1%	80.3%	45.0%	94.8%	86.6%	71.6%	99.6%	23.7%
	Patient 5	59.0%	0.0%	73.7%	59.0%	73.7%	100.0%	100.0%	1.3%
	Patient 6	45.9%	86.7%	70.4%	88.8%	90.9%	75.0%	92.2%	58.5%
	Patient 7	66.8%	67.4%	68.6%	85.5%	86.7%	89.1%	96.3%	26.6%
	Patient 8	66.3%	70.3%	76.5%	87.0%	95.6%	87.6%	100.0%	31.3%
	Patient 9	88.5%	100.0%	88.5%	100.0%	100.0%	88.5%	100.0%	1.4%
	Patient 10	81.7%	99.1%	45.1%	100.0%	100.0%	87.6%	100.0%	32.4%
	Average	68.2%	73.8%	69.1%	88.5%	90.6%	85.3%	97.8%	27.8%
	Overall	65.2%	82.0%	67.6%	93.4%	94.3%	84.1%	99.5%	31.4%
Specificity	Control 1	99.8%	99.7%	99.4%	99.5%	99.1%	99.1%	98.8%	-
	Control 2	98.5%	98.0%	98.3%	96.5%	96.3%	96.8%	94.8%	-
	Control 3	99.3%	99.5%	99.8%	98.7%	99.3%	99.1%	98.5%	-
	Control 4	95.8%	98.2%	97.5%	94.0%	95.7%	93.3%	91.5%	-
	Control 5	94.9%	97.3%	95.0%	92.2%	92.3%	89.9%	87.2%	-
	Control 6	96.9%	97.2%	96.4%	94.1%	93.5%	93.3%	90.4%	-
	Control 7	100.0%	98.7%	100.0%	98.7%	98.7%	100.0%	98.7%	-
	Control 8	100.0%	97.4%	99.8%	97.4%	97.2%	99.8%	97.2%	-
	Control 9	97.0%	96.9%	96.4%	94.0%	93.4%	93.5%	90.4%	-
	Control 10	96.2%	98.7%	96.5%	94.9%	95.2%	92.7%	91.4%	-
	Average	97.8%	98.1%	97.9%	96.0%	96.1%	95.8%	93.9%	-
	Overall	97.9%	98.2%	98.0%	96.2%	96.2%	95.9%	94.2%	-

Table 4-1. The performance of the tremor detection algorithm comparing to the video reference. Average values signify the mean of the values across the patients. Overall values were calculated by counting the total number of false-positives (or false negatives) and dividing the result by the total period of the measurements.

In the first study, for each subject during whole period of measurement, one value for each of the three bradykinesia related parameters were calculated. Table 4-2 shows these results. The results of the hypothesis test for the equivalence of the mean between the three groups of Stim OFF, Stim ON an controls show that the M_h and R_h had significant differences (except for one case) between the three groups while A_h did not show any significant differences.

Parameter	Axis	OFF	ON	Control	OFF v.s. Control	ON v.s. Control	ON v.s. OFF
Mh (degree/s)	Pitch	26.1±8.0	40.8±12.0	54.5±8.4	0.0002	0.0036	0.0020
	Roll	35.8±9.1	56.9±10.5	74.9±10.7	0.0002	0.0028	0.0020
	Yaw	31.8±8.3	51.3±12.2	79.5±11.6	0.0002	0.0006	0.0020
Rh (degree)	Pitch	3.4±1.4	4.9±1.5	6.2±1.0	0.0022	N.S.	0.0039
	Roll	3.4±1.1	5.2±1.2	6.5±1.1	0.0003	0.0140	0.0020
	Yaw	4.3±1.6	6.6±1.9	9.6±2.5	0.0002	0.0113	0.0020
Ah (%)	Pitch	43.1±6.5	44.8±6.5	49.0±5.3	N.S.	N.S.	N.S.
	Roll	50.6±10.0	49.6±8.5	53.9±5.6	N.S.	N.S.	N.S.
	Yaw	43.9±8.1	44.9±7.6	48.7±3.8	N.S.	N.S.	N.S.

Table 4-2. Bradykinesia related parameters calculated for each axis of the sensors. The values are shown in mean±S.D. format. The three right-most columns show the p-value of the hypothesis test of equivalence of the mean of the parameters in different groups.

To compare the outcomes of the tremor quantification algorithm with UPDRS, correlation between the UPDRS tremor sub-score and logarithm of the tremor amplitude reported by the algorithm was calculated. As each PD patient performed the test both in ON and OFF

state, a partial correlation coefficient was also performed to remove the effect of ON/OFF factor. Table 4-3 shows the results.

Table 4-4 shows the results of the correlation study between UPDRS bradykinesia sub-score and the bradykinesia related parameters (M_h, R_h and A_h) where significant correlations in some case were obtained.

Axis	Pearson correlation				Partial Correlation			
	ω_{tr}		θ_{tr}		ω_{tr}		θ_{tr}	
	r	p	r	p	r	p	r	p
Pitch	0.84	0.0001	0.85	0.0001	0.78	0.0001	0.83	0.0001
Roll	0.87	0.0001	0.86	0.0001	0.81	0.0001	0.84	0.0001
Yaw	0.81	0.0001	0.82	0.0001	0.74	0.0003	0.78	0.0001
Pitch + Roll	0.87	0.0001	0.87	0.0001	0.81	0.0001	0.84	0.0001
Roll + Yaw	0.86	0.0001	0.86	0.0001	0.81	0.0001	0.84	0.0001
Pitch + Yaw	0.82	0.0001	0.87	0.0001	0.76	0.0001	0.85	0.0001
All axes	0.86	0.0001	0.86	0.0001	0.81	0.0001	0.84	0.0001

Table 4-3. The correlation between UPDRS tremor sub-score and the parameters calculated by the algorithm. Partial correlation was performed to remove the effect of ON/OFF factor.

Parameter	Axis	Pearson correlation		Partial Correlation	
		r	P	r	p
M_h	Pitch	-0.54	0.0131	-0.25	N.S.
	Roll	-0.83	0.0001	-0.68	0.0014
	Yaw	-0.76	0.0001	-0.57	0.0105
R_h	Pitch	-0.47	0.0362	-0.32	N.S.
	Roll	-0.70	0.0006	-0.48	0.0380
	Yaw	-0.53	0.0163	-0.44	N.S.
A_h	Pitch	-0.55	0.0123	-0.59	0.0073
	Roll	-0.42	N.S.	-0.53	0.0186
	Yaw	-0.45	0.0466	-0.53	0.0203

Table 4-4. The correlation between UPDRS bradykinesia sub-score and the parameters calculated by the algorithm. Partial correlation was performed to remove the effect of ON/OFF factor.

4.3.2 Second study: Long-term monitoring with free moving subjects

Figure 4-7.b shows a typical result of the outcome of the tremor algorithm when used to monitor a subject for 3 hours. Measurement was started with during Stim-ON, the stimulator was turned OFF (t = 0 min), and again it was turned ON (t = 180 min). During this period, the subject did several UPDRS tests and the values of sub-score related to tremor of hands are shown in Figure 4-7.a. As the resolution of the tremor detection algorithm is much higher than resolution of the UPDRS tests, to make the comparison between the results simpler, a moving average window was run over the tremor amplitude results. Also, the logarithm of the results was calculated. Figure 4-7.c shows this

new graph. It can be observed that the results follow the changes of the UPDRS tremor sub-score.

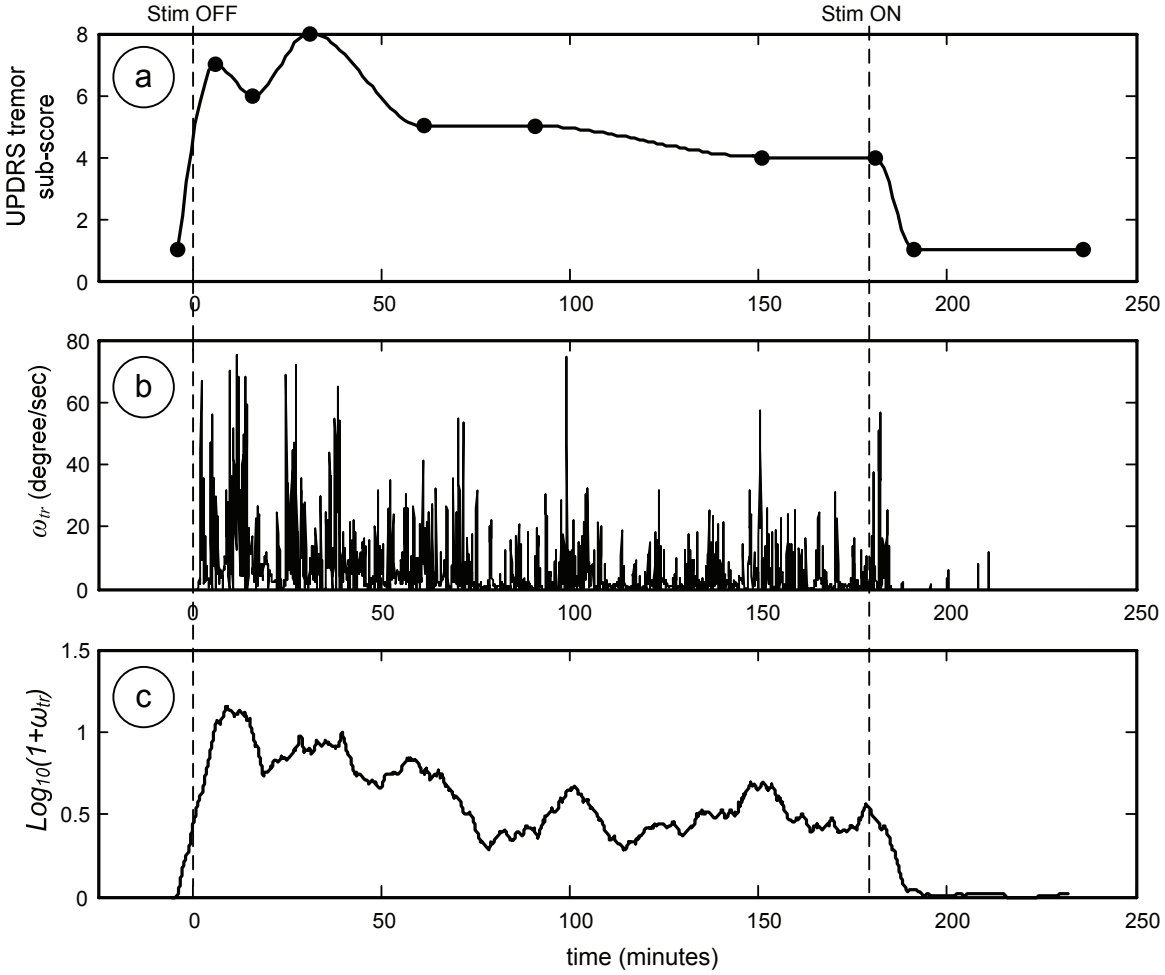


Figure 4-7. a) The tremor sub-score of UPDRS for a typical PD patient. Several UPDRS tests have been performed during the 3 hours period of measurement. Black circles show the results of the tests. b) The primary output of the algorithm for the roll axis. For each period of 3 seconds, if tremor was detected, a bar representing the amplitude of the tremor was drawn. c) Logarithm of the amplitude of the tremor as reported by the algo-rithm. A moving average window with a width of 10 minutes were used to produce this figure (The delay caused by the moving average window has been compensated).

Figure 4-8 shows a typical graph of the output of the algorithm for the bradykinesia. This patient started the measurement during the ON period. At $t = 0min$ stimulator was turned OFF and at $t = 220min$ it was turn ON again. Figure 4-8.a shows the changes in the bradykinesia sub-score of the UPDRS for this patient. Figure 4-8.b, c and d show the M_h, A_h and R_h. In this graph, a window size of 20 minutes was used to estimate these parameters. The first UPDRS was done just before the beginning of the recording and the last one just after the end of the recording. As the patient became more bradykinetic, the

speed of his movements and his level of activity decreased. Round $t = 110min$ he was almost totally inactive ($A_h = 0$). By turning the stimulator ON again, the average mobility of the hands and the level of activity increased again.

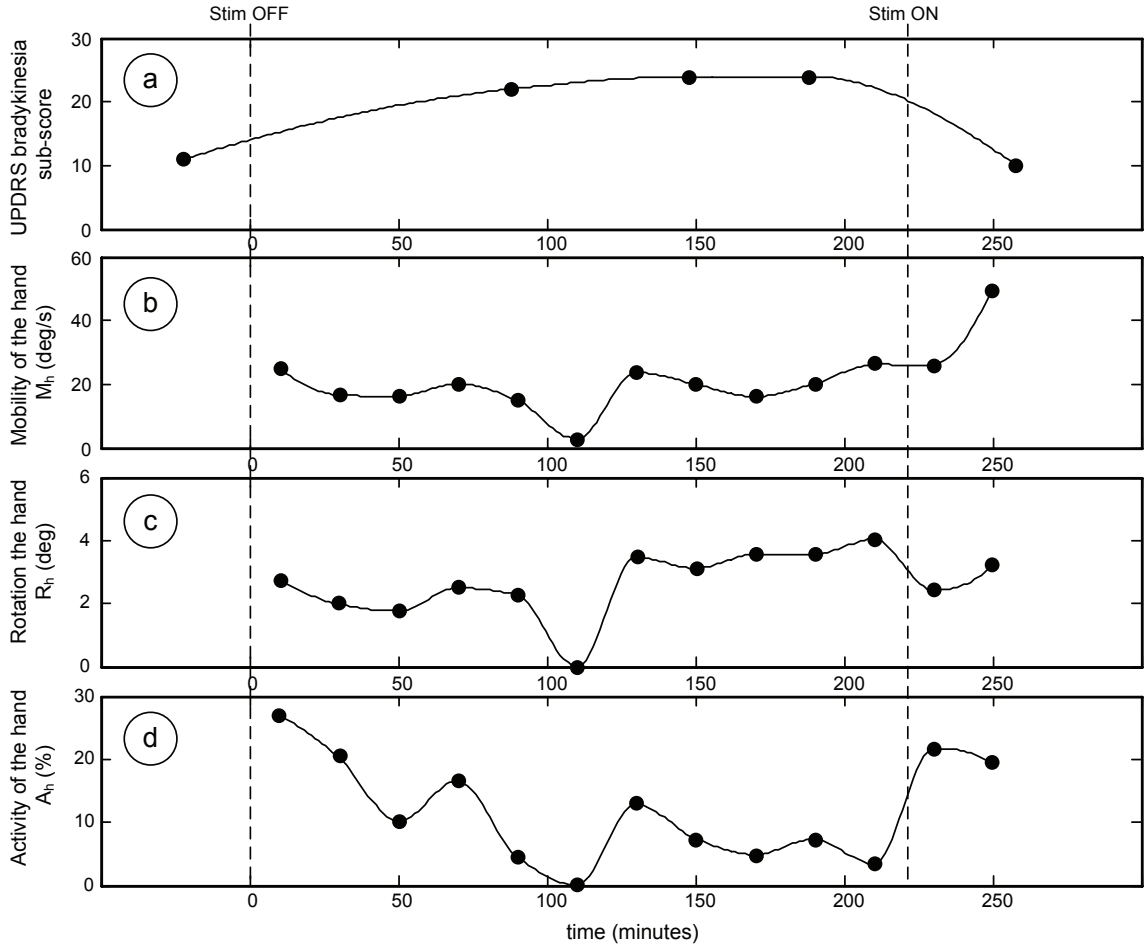


Figure 4-8. a) The UPDRS bradykinesia sub-score of a typical PD patient. Black circles show the results of each UPDRS test. b, c, d) M_h, R_h and A_h estimated for each 20 minutes window.

The effect of the selection of the size of window size on the correlation between UPDRS sub-scores and tremor and bradykinesia related parameters is illustrated in the Figure 4-9 where window size was changed from 5 minutes to 45 minutes. Figure 4-9.a shows the coefficient of the correlation between the UPDRS bradykinesia sub-score and the three bradykinesia related parameters estimated for all patients. Similarly, Figure 4-9.b shows the coefficient of correlation between UPDRS tremor sub-score and the estimated amplitude of the tremor for all patients in function of the window size.

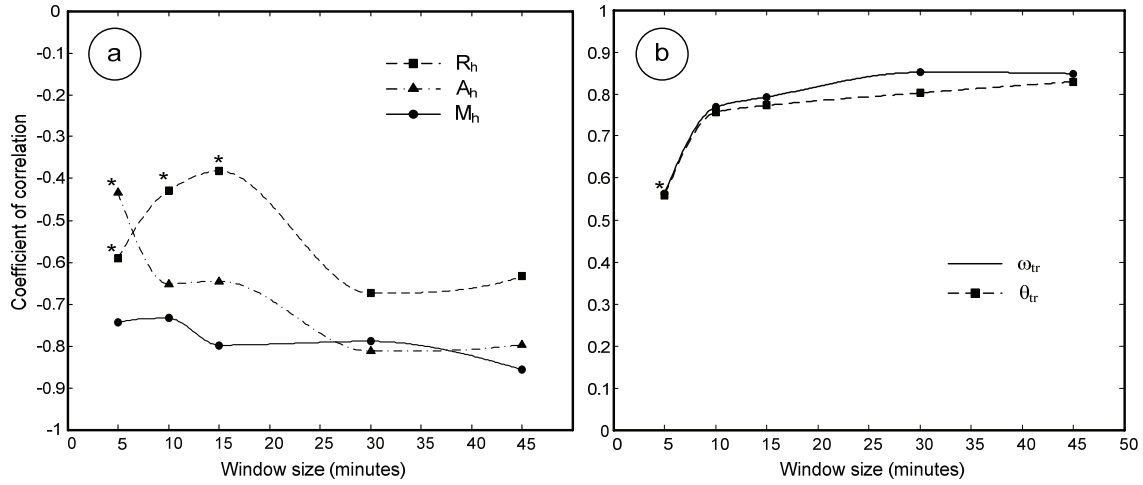


Figure 4-9. a) The effect of the selection of time window in the correlation between the UPDRS bradykinesia sub-score and calculated parameters by the algorithm. b) The correlation between UPDRS tremor sub-score and the average value of the amplitude of the tremor reported by the algorithm. The symbol * shows where correlations were no more significant (i.e. p > 0.05).

4.4 Conclusion and Discussion

4.4.1 Detection and quantification of tremor and bradykinesia

We have found a good overall sensitivity and specificity (99.5% and 94.2% respectively) for tremor detection using a 3D gyroscope (see Table 4-1). The high sensitivity of the algorithm can be partially due to the fact that it could be difficult to notice low-amplitude tremor with the video, a problem also reported by (Van Someren, Vonk *et al.* 1998). By reducing the number of the sensitive axes to two or only one, the sensitivity reduced but specificity increased. The reason of the increase of specificity could be that by combining the sensitive axes together, the false-positives added-up. We notice that the activities that produced most of the false-positives were brushing the teeth and voluntary, rhythmic oscillations of hands.

We found a high correlation between the parameters estimated by our method and UPDRS tremor sub-score (see Table 4-3). For example the estimated amplitude of angular velocity of tremor (ω_{tr}) in the roll axis showed a correlation with $r = 0.87$ ($p < 0.001$) to the UPDRS sub-score. As we had included each subject two times in the calculations of the correlation in Table 4-3, once during ON and once during the OFF state, we performed a partial correlation study demonstrating that the correlation obtained was not solely related to the ON/OFF factor. In this case, by removing the effect of ON/OFF factor (i.e. taking the partial correlation), the correlation reduced only marginally to $r = 0.81$.

We found that M_h and R_h measured in any of the axes of the sensor showed significant differences between PD patients during Stim OFF period and controls ($p \leq 0.002$, see Table 4-2). At the same time, we found significant differences in these two parameters between Stim ON and Stim OFF states ($p \leq 0.004$). While STN-DBS showed a significant improvement of these parameters, in almost all cases (except for the R_h of the pitch axis) the PD patients remained significantly different from the healthy control subjects. We also found highly significant correlation between these parameters (M_h and R_h) and UPDRS bradykinesia sub-score (see Table 4-4). However, using statistical analysis with partial correlation, we found that by removing the effect of ON/OFF factor from our data, only M_h was able to maintain high and significant correlation with the UPDRS ($r = -0.83$ and $r = -0.68$ in roll axis for normal and partial correlation). Bradykinesia refers to the slowness of the ongoing movements. As gyroscopes directly measure the angular velocity of movements and all body movements are in fact rotations around joints, these results are not unexpected. The third parameter calculated by our algorithm, A_h, was not significantly different between the three groups. This result was somewhat expected as all subjects followed the same protocol of timed activities and as such, in practice they had the same level of activity.

4.4.2 Long-term measurements

We evaluated the sensitivity and specificity of the method in the first study while subjects performed a protocol of typical daily activities. However, as continuous video recording for up to five hours of free moving PD patients including clear view of their hands all the time was not possible, we could not evaluate sensitivity during long-term measurement. Instead we only compared the results to the UPDRS score of the patients to see how well the outcomes of the method could follow the changes in the state of tremor score of the patients. Results of the first study showed that the proposed algorithms to quantify tremor and bradykinesia have an excellent correlation with the UPDRS scores. Those results were obtained using a time window of 45 minutes. To find out the effect of the size of the time window on these parameters, we used the data from our second study where subjects were free to perform any activity they preferred. The idea was to assess whether the system could report accurate results independent of the type and intensity of the activities, even with smaller window sizes or not. With a window size of 45 minutes, the correlations of most of the estimated parameters to their respective UPDRS sub-score were similar to those obtained in the first study (see Figure 4-9). This confirms the consistency of the results obtained during the test protocol of the first study. As the

windows size decreased, in general the correlations also started to decrease. With the smallest sizes of the windows in some cases the correlation was no longer significant.

Figure 4-9.b shows the results for the study of the parameters related to tremor amplitude. For all window sizes, by averaging the reported amplitude of the tremor for the three seconds interval, a significant and high correlation to UPDRS was obtained. Only for the smallest window sizes (five minutes) the correlation lost its significance. One explanation could be that the tremor of PD patients can momentarily stop due to activities. The effect of these stops on the *mean value* of the amplitude gets more and more important. As the size of the windows reduces, the average amplitude of tremor can dramatically change from one window to another.

Amongst the parameters related to bradykinesia, M_h showed the highest correlation to UPDRS (Figure 4-9.a), even with the smallest window size of five minutes ($r = -0.74$, $p < 0.01$). In the first, controlled study A_h did not show any correlation to UPDRS while in the second study, where no protocol of activity was involved, this parameter showed a high and significant correlation to UPDRS with large window sizes ($r = -0.81$ and $r = -0.80$ for 30 and 40 minuets windows, $p < 0.003$). This is probably due to the fact that in the first study subjects followed a *fixed* set of activities for a *similar period* of time: A_h that measured the level of activity was very similar for all subjects and did not show any significant differences between control subjects and PD patients in any state. Rather than bradykinesia, A_h could be more related to other symptoms of PD, i.e. *akinesia* and *hypokinesia* which refer to the difficulty to initiate movement and reduction of movement amplitude, respectively. As A_h represents the intensity of the activities during a certain period of time, we expect this parameter to be a good estimator of hypokinesia. Bradykinesia and hypokinesia are intrinsically related and in many cases present at the same time in PD patients. This represents the probable basis for A_h showing some correlation with the UPDRS bradykinesia sub-score. However, finding an objective relationship between hypokinesia and A_h will need further study.

4.4.3 Comparison to the other systems

Several studies have addressed the problem of using kinematics sensors for the ambulatory detection and quantification of tremor (Hoff, Wagemans *et al.* 2001; Spieker, Boose *et al.* 1998; Van Someren, Vonk *et al.* 1998). Hoff et al. reported a good sensitivity and specificity (82% and 93% respectively) comparing to video recordings (Hoff, Wagemans *et al.* 2001). They also reported significant correlation between the duration and intensity of tremor calculated by their method and UPDRS tremor sub-scores in sitting and standing body postures (Hoff, Wagemans *et al.* 2001). Van Someren et. al also reported a good

sensitivity (between 0-5.9% false-positives) in detection of tremor during daily activities (Van Someren, Vonk *et al.* 1998). Comparing to these studies our proposed method shows an even higher sensitivity and specificity (99.5% and 94.2% respectively). Moreover, the reduction of the number of sensors from three to two (like in the ASUR units) reduced the sensitivity by only a small margin (see Table 4-1).

In contrast to tremor, bradykinesia has been studied only rarely in a quantitative way using ambulatory systems. Katayama (Katayama 2001) used a system based on *actigraphy* to study the effects of drugs on hypokinesia and to determine hypokinetic periods during a day. Dunnewold et al. (Dunnewold, Jacobi *et al.* 1997) used a 3D accelerometer to measure the accelerations on the wrist and compared them to Movement Time (MT) and Tap Rate (TR) scores (Zappia, Montesanti *et al.* 1994). They found significant differences between healthy controls and PD patients; however, they found moderate or no correlation to UPDRS.

4.4.4 Conclusion

We propose a new ambulatory monitoring system to simultaneously measure tremor and bradykinesia in PD patients and to provide objective parameters. The system is simple to use and does not hinder the patients, as it consists of only two small and light (50g) sensing units (ASUR units) attached on each forearm while offering continuous, long-term monitoring up to 14 hours. We found a high sensitivity and specificity in detection of tremor while subjects were performing typical daily activities. Also a high correlation between tremor and bradykinesia related parameters and UPDRS sub-scores were found. Finally, our study has shown the possibility of evaluation the bradykinesia during short intervals (as short as 5 minutes) while the patient performs his daily activity.

Chapter 5 Analysis of physical activity

Abstract

Background—Parkinson's disease especially in advanced stages can severely reduce the physical activity of the patients. Also, compared to the ON state, PD patients have more difficulty to perform their daily activities in OFF state. As such, objective assessment of PD patients' physical activity in general, and detecting and following the changes in their performance during a day in particular, is of interest.

Objectives—Design and validation of an ambulatory physical activity monitoring system based on kinematic sensors with high accuracy to monitor the patients during daily activities. The system should detect start and end of basic body postures during the monitoring period and to provide objective parameters related to these activities that could differentiate between the performance of the patients in ON and OFF states.

Method—A new method based on three sensing units attached on the trunk and each shank including a combination of gyroscopes and accelerometers has been developed. A signal processing algorithm was developed to detect several movement patterns related to the basic body postures or changes between postures and to use parameters describing these patterns to classify the postures. The algorithm was validated by comparing the results to the logs prepared by analyzing video recordings of the activities of the subjects. Moreover, the correlation between the obtained objective parameters and UPDRS score has been studied. We also tested the method in a group of free moving patients.

Results—For the control group, the sensitivity and the specificity of classification of body postures were: 99.5% and 99.8% for Sitting, 96.1% and 97.9% for Standing, 99.1% and 99.8% for Walking and 100% and 100% for Lying, respectively. The sensitivity and specificity of classification of body postures for the PD patients were: 86.3% and 98.0% for Sitting, 83.6% and 96.5% for Standing, 98.5% and 97.8% for Walking and 91.8% and 99.8% for Lying, respectively. We also found significant differences in parameters related to Sit-to-Stand and Stand-to-Sit transitions between PD patients and controls and also between the two states of the stimulation.

Main contributions—A new method using statistical classification to detect posture transitions and fuzzy logic to classify basic body posture allocations, has been designed and tested for PD patients. Several objective parameters have been introduced to quantify posture transition pattern. These parameters separated PD patients from controls and showed significant improvements in performance of PD patients using STN-DBS. Significant correlation between these parameters and UPDRS clinical score has been found.

5.1 Introduction

Daily physical activity of a person is a complex phenomenon. The number and variety of the possible activities that human body can perform is very high. The objective of *physical activity monitoring* is to find the *posture allocations* during the period of the monitoring. However, even by focusing on static postures, considering the highly articulated human body anatomy the number of distinct postures is very high. To simplify the problem and bringing the possibility of accurate and objective analysis of the body postures, a simpler model for body postures is desirable. Several authors have used a rather simple model of four basic body postures to classify daily activities (Aminian, Robert *et al.* 1999; Bussmann, Reuvekamp *et al.* 1998; Najafi, Aminian *et al.* 2003; Ng, Sahakian *et al.* 2000; Paraschiv-Ionescu, Buchser *et al.* 2004; Veltink, Bussmann *et al.* 1996a). Figure 5-1 shows this model. The four basic activities that have been considered were: *Lying*, *Sitting*, *Standing* and *Walking*. The activities like *Sitting* and *Standing* can be further divided to low and high active periods.

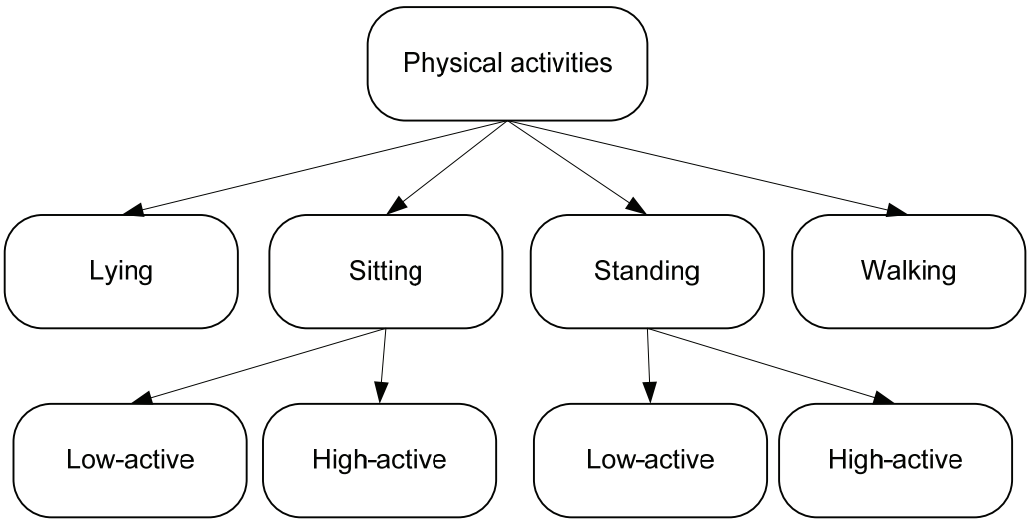


Figure 5-1. Simplified model of daily activities and body postures.

The main objective of this study was to design a new method to find the period of these four basic activities using ambulatory techniques in PD patients. Body fixed sensors such

as accelerometers and gyroscopes have been proposed for the ambulatory monitoring of daily physical activities in normal, elderly and patients with various medical conditions (Aminian, Robert *et al.* 1999; Bussmann, Reuvekamp *et al.* 1998; Najafi, Aminian *et al.* 2003; Ng, Sahakian *et al.* 2000; Paraschiv-Ionescu, Buchser *et al.* 2004; Veltink, Bussmann *et al.* 1996a). However, few studies have applied the technique to PD. For example, Van Someren has proposed a system based on *actigraphy* to determine periods of movements and rest (Van Someren 1997) and Keijsers et al (Keijsers, Horstink *et al.* 2003a) has briefly described a method similar to the Veltink et al's method (Veltink, Bussmann *et al.* 1996a) to classify different physical activity in PD patient but has not reported the performance of this method.

We have designed a new method for the ambulatory analysis of physical activity in PD patients using body fixed sensors. The system is based on a combination of gyroscopes and accelerometers with long-term recording capability, and was used to classify four basic body postures of *Sitting*, *Standing*, *Walking* and *Lying* while patients were performing normal activities. We have proposed a new approach based on statistical classification and fuzzy inference to increase the sensitivity and specificity of body posture detection. The study was carried out in a particular group of PD patients treated with bilateral sub-thalamic nucleus (STN) deep brain stimulation (DBS) (Benabid, Benazzouz *et al.* 1998; Vingerhoets, Villemure *et al.* 2002), in whom the switching the stimulators ON or OFF reproduced the severe motor fluctuations naturally occurring in levodopa treated PD patients.

5.2 Methods

5.2.1 Measurement system

We performed two studies. The system used in both studies, consisted of three sensing units attached on trunk and shanks (see Figure 5-2). The unit on the trunk included two accelerometers and one gyroscope and the shank units included only a single gyroscope.

In the first study, the first prototype of the MAS based on Physilog® data-loggers was used to record the data. More details about the measurement system can be found in the section 3.3. In the second study, we used the second prototype of the MAS based on ASUR units. More details about this system are presented in the section 3.4.

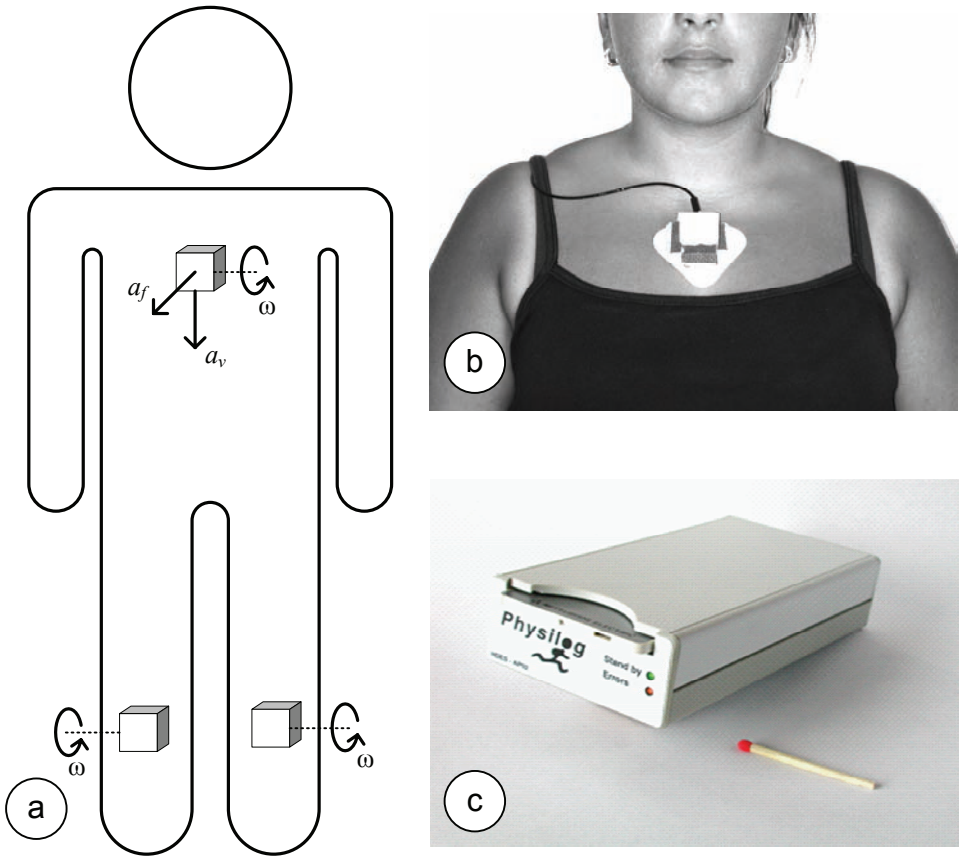


Figure 5-2. a) Sensors sites on the body: one sensor on the trunk and one sensor on each shank b) Sensor on the trunk is attached to the body using adhesive patch c) The Physilog® data-logger

5.2.2 Patients and experimental setup

A group of ten PD patients and a second group consisted of 10 age and sex-matched normal control subjects participated in the first study. A series of measurements was done while the subjects carried the measuring system and followed a protocol of typical daily activities like eating, writing, brushing the teeth, several walking trials, climbing the stairs etc. It took about 45 minutes for each subject to complete the protocol. Before each measurement, PD patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS, motor section III, (Fahn, Elton *et al.* 1987)). Each patient performed the protocol twice: once during *Stim ON* and once during *Stim OFF* (i.e. when both stimulators have been turned off). More details about the patients, protocol and the clinical test is provided in the section 2.3, the *controlled study*.

13 PD patients participated in the second study. They consisted of a group of seven males and six females. Each measurement took three to six hours during ambulatory conditions where patients were free to move and perform activities they liked. An UPDRS

test was performed at the beginning of the measurement and then at least after every one hour.

In the second study, an observer followed the patients all the time and prepared a time tagged log of all their activities. For six measurements, a second independent observer prepared a second log in parallel. This ways it was possible to evaluate the accuracy of visual observation by comparing the two logs prepared in parallel. More detail about the protocol is presented in the section 2.5, the *long-term study*.

5.2.3 Posture analysis

Detection of different body posture was performed in several steps. In each step, the information from one or several body sensors was used. Figure 5-3 shows the flowchart of the whole algorithm.

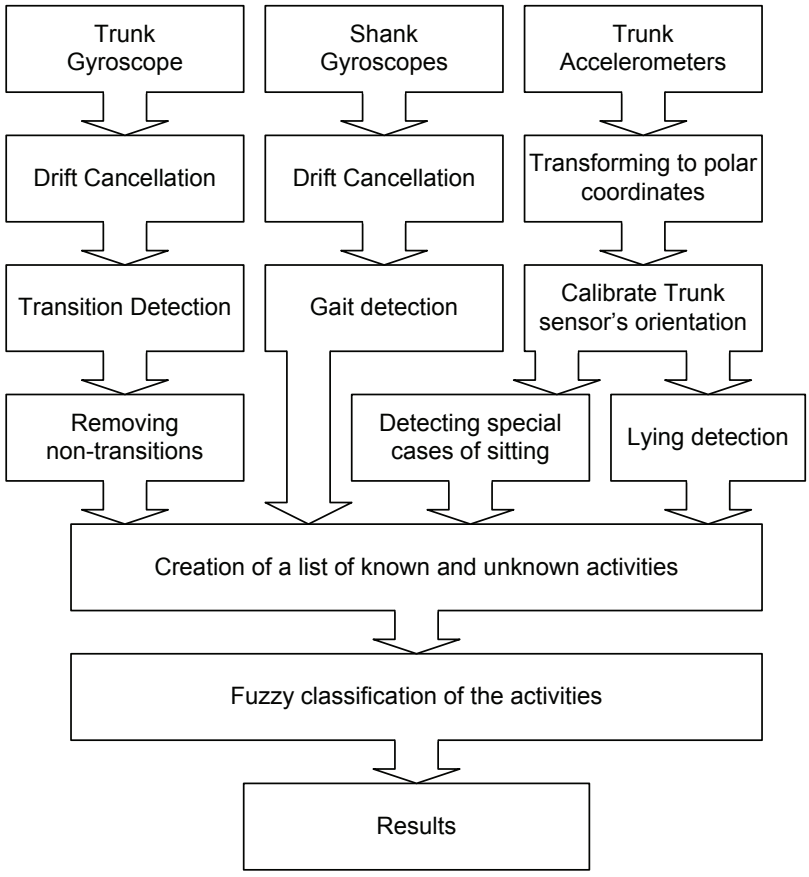


Figure 5-3. Flowchart of posture detection and classification algorithm.

5.2.3.1 Calibration of the trunk acceleration

Taking the vertical axis as the reference, trunk's acceleration in the sagittal plane could be described as a vector with a norm of a_{trunk} and a phase of θ_{trunk}. Due to the anatomy of

the trunk and the physical shape of the sensors module, there could be a bias θ_0 between sensor inclination θ_{biased} and θ_{trunk} (Figure 5-4):

$$a_{trunk} = \sqrt{a_f{}^2 + a_v{}^2} \tag{5-1}$$

$$\theta_{trunk} = \theta_{biased} - \theta_0 \tag{5-2}$$

$$\theta_{biased} = \text{atan}(\frac{-a_f}{a_v}) \tag{5-3}$$

where a_f and a_v are the frontal and vertical acceleration measured by the trunk sensors.

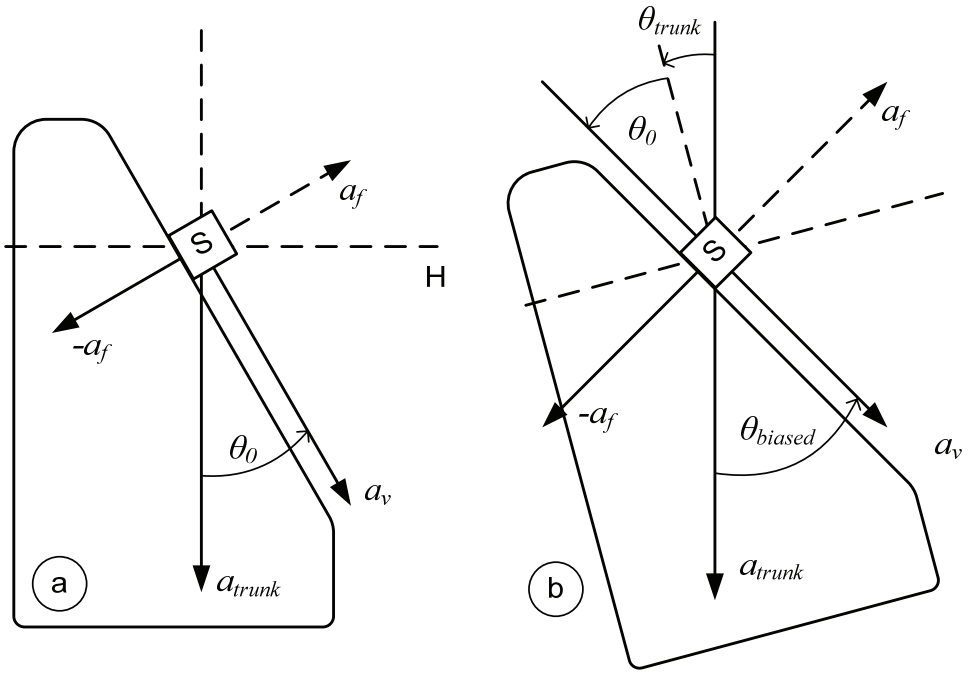


Figure 5-4. a) During up-right standing the sensor box (S) can have an inclination θ_0. b) When trunk has an inclination θ_{trunk}, sensor measures θ_{biased} that can be corrected using the θ_0 measured before.

The trunk inclination during the quiet standing posture has been selected as the reference value for the θ_{trunk}. To find θ_0, θ_{biased} during walking periods was calculated and was filtered using a low-pass FIR filter with a cut-off frequency of $f_c = 1Hz$. The median value of the filtered θ_{biased} was found as a good estimation of θ_0.

During the measurement protocol each subject was asked to stand in up-right position for 20 seconds and the mean value of the θ_{biased} during this period was used for validation of the outcome of the algorithm. The method was based on the fact that the accelerometers in the sagittal plane can be used like an inclinometer in the absence of movement. However, it is possible to have a rather crude estimation of the true trunk inclination (θ_{trunk}) even *with* presence of the low-intensity activities (like lying or low activity sitting or

standing) by removing the high frequency components of the acceleration signal: θ_{trunk} signal was filtered with a low-pass filter with $f_c = 1Hz$ and the average value over windows of one seconds were calculated.

5.2.3.2 Detection of lying and walking periods

Using the trunk's inclination estimated using accelerometers, lying periods can be detected. The method was similar to (Aminian, Robert *et al.* 1999). The periods of at least 30 seconds while any of these two criteria could be met, were considered as a lying periods:

- Lying on back or lying prone detected with the criteria: $\theta_{trunk} < -50°$ or $\theta_{trunk} > 50°$.
- Lying on sides. In this case, the amplitude of the acceleration vector (a_{trunk}) will be less than 1g. By setting a threshold of a lateral inclination of more than $45°$, the selected criteria to detect lying on sides was: $a_{trunk} < 0.7g$.

Using the algorithm described in the chapter 6, walking periods were automatically detected. Walking periods were defined as those periods of alternate movements of the feet during which a total of more than two consecutive gait-cycles (four steps) could be detected.

Putting the periods of walking and lying aside, the remaining periods would correspond to either sitting or standing. Using the acceleration signals of the trunk, two special cases of sitting position were also detected. We hypothesized that:

- It would be highly unlikely for the subject to have a backward inclination of trunk of more than $15°$ for a period of over 30 seconds during standing; therefore these periods were classified as sitting.
- Periods of more than 30 seconds with almost no movement in the trunk (standard deviation of a_{trunk} less than 0.015g) would correspond most likely to sitting.

5.2.3.3 Detection and classification of posture transitions

Besides some special cases like those mentioned before, any inertial (acceleration or angular velocity) signal of the trunk or the shanks during quiet sitting or standing postures were very similar and had no distinctive feature to be used for classification. However, during the *transition* periods between these postures, the recorded signals showed interesting features (Najafi, Aminian *et al.* 2003). As such, the key element to classify sitting and standing periods in our system was to detect posture transitions accurately and with a high sensitivity.

To detect posture transition *candidates*, we used the signal of the gyroscope on the trunk in an algorithm with the following steps:

- Drift of the gyroscope was removed using a filter similar to the one for the shank signals.
- The signal was low-pass filtered using an FIR filter with a cut-off frequency of 0.65Hz.
- Change in the trunk tilt, θ_g, was calculated by integration of the above signal. It is noteworthy that θ_g corresponds to the change of trunk orientation in sagittal plane (relative angle) while θ_{trunk} which was calculated by the accelerometers, shows the absolute orientation of the trunk in (nearly) static conditions.

Transitions from the sitting to standing posture (*SiSt*) and from standing to sitting posture (*StSi*) produced a special pattern in the θ_g signal (see Figure 5-5). (Najafi, Aminian *et al.* 2002) have already shown that the positive peaks of the transition patterns correspond to the start and the end of the posture transitions.

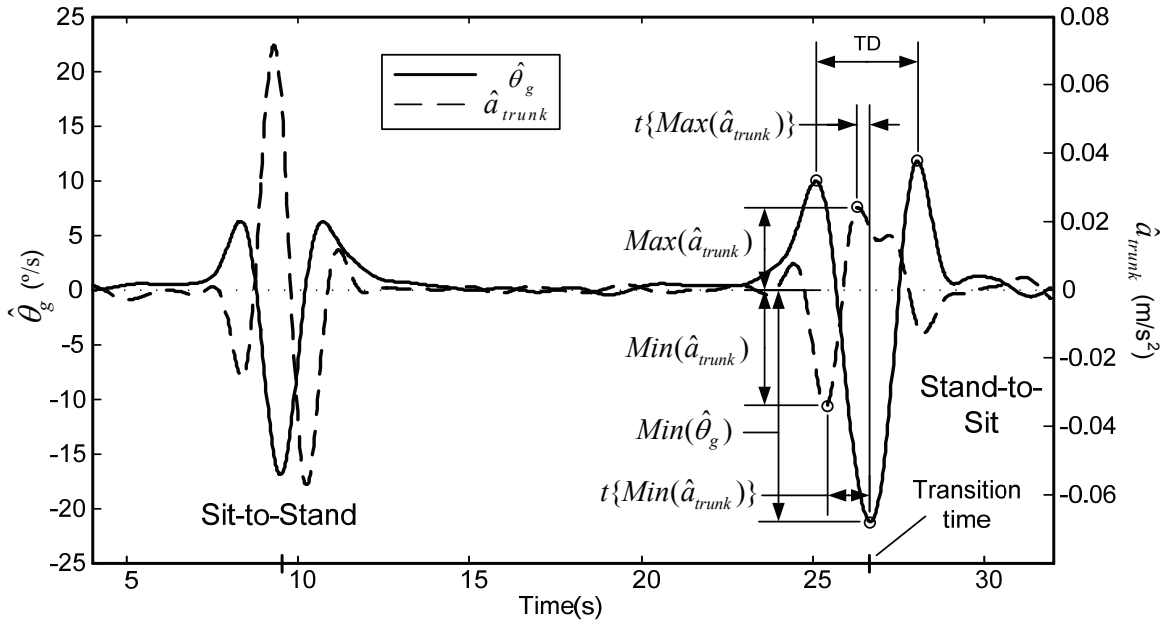


Figure 5-5. A Sit-to-Stand transition followed by a Stand-to-Sit transition. Transitions start and end with two positive peaks and the transition time is defined as the time of the highest negative peak inside the transition period. Notice the relative position of the highest negative peaks in the acceleration and angular velocity signals in these two different types of transitions.

Finally, posture transition candidates were detected using a simple peak-detection in the θ_g signal. Patterns with negative peaks with amplitudes of more than 10° were selected as candidates for the posture transitions. The candidates, however, could also include

spurious peaks resulting from activities or movements other that posture transitions. These peaks and their respective patterns were referred to as *non-transitions*.

To separate true transitions from non-transitions for each candidate pattern, several features were extracted and the corresponding parameters were calculated (see Figure 5-5):

- $Min(\theta_g)$: The amplitude of the negative peak in the θ_g signal, showing the maximal tilt.
- TD: Duration of transition. Defined as the difference between end and start of the transitions.
- cTD: Core of the transition period. Part of the transition period during which θ_g was below zero.
- $Max(\omega_{trunk})$: Peak value of the trunk angular velocity during the core of the transition.
- $\bar{\omega}_{trunk}$: Average trunk angular velocity. Defined as the average value of trunk's gyroscope signal during the core of the transition.
- ROR_{trunk}: Range of antero-posterior tilt of the trunk. To calculate this parameter, the drift of the gyroscope signal was canceled using the same IIR filter as for the shank signals; then the signal was integrated during the time of the transition and its range was calculated.
- $Range(a_{trunk})$: Range of the trunk acceleration signal, a_{trunk}, during the posture transition.
- $Range(\hat{a}_{turnk})$: Range of the low-pass filtered trunk acceleration, $\hat{a}_{trunk}$, during the posture transition. (a FIR filter with a cut-off frequency of 0.65Hz was used.)
- $Max(\hat{a}_{turnk})$ and $Min(\hat{a}_{turnk})$: Maximum and minimum of the filtered trunk acceleration signal, $\hat{a}_{trunk}$, during the posture transition time and also the relative position of this peak to the time of the transition ($t\{Max(\hat{a}_{turnk})\}$ and $t\{Min(\hat{a}_{turnk})\}$).

Considering p_{tr} to be the probability that a posture transition candidate was a real transition, it was convenient to model this probability in terms of the *log odds* of detection, usually called *logit*:

$$\text{logit}(p_{tr}) = \ln\left(\frac{p_{tr}}{1-p_{tr}}\right) \tag{5-4}$$

The *logistic regression model* (Hosmer and Lemeshow 1989) tries to fit the log odds by a linear function of the parameters of the transition (as in multiple regression):

$$\text{logit}(p_{tr}) = \alpha + \sum \beta_i . x_i \tag{5-5}$$

where x_i stands for the calculated parameters of the posture transition. In order to estimate α and β_i coefficients a *training* session was carried out, using the exact time of the transitions found from reviewing the video recordings. The transition candidates from all of the periods of the measurement and for all subjects were sorted in to two groups: transitions and non-transitions. For each group, two subgroups were randomly selected and one subgroup was used to find α and β_i coefficients and the other one was used to evaluate the performance of the classification method.

To classify posture transitions to sit-tand (SiSt) or stand-sit (StSi) transitions, a similar approach was used to calculate another series of α and β_i coefficients to make a function similar to model in (5-5) to estimate the probability (p_{SiSt}) that a transition was of type SiSt or StSi. To find these coefficients half of the real transitions confirmed by the video were used and the other half was used to evaluate the performance of classification.

Finally, for each posture transition candidate the time of the posture transition, p_{tr} and p_{SiSt} were calculated. For instance, to calculate p_{tr} for each posture transition the parameters related to the features of the pattern (x_i) where extracted and using (5-6) the p_{tr} was calculated:

$$p_{tr} = \frac{1}{1 + e^{-(\alpha + \sum \beta_i . x_i)}} \tag{5-6}$$

5.2.3.4 Fuzzy classification of the activities

Using the methods of the previous sections, the periods of walking, lying and some special cases of sitting were detected. Also candidates for posture transitions and their associated p_{tr} and p_{SiSt} were calculated. To classify the remaining periods of the monitoring into *Sitting* or *Standing*, a *mamdani* fuzzy classification system (Mamdani 1977) was used.

Based on the periods of activities detected so far and the time of the transitions, the whole period of monitoring was divided into a list of several smaller periods. Each of these smaller periods could have either an unknown state or a known state. Starting from the first unknown state in the list to the last one, six *fuzzy variables* were passed to the fuzzy classifier to decide the type of the activity:

- *LastState*: the activity immediately before the current activity

- *NextState*: the activity immediately after the current activity
- *CurrTR*: the strength of the transition at the beginning of the current activity
- *NextTR*: the strength transition at the end of the current activity
- *CurrTRtype*: type of the transition at the beginning of the period
- *NextTRtype*: type of the transition at the end of the current period

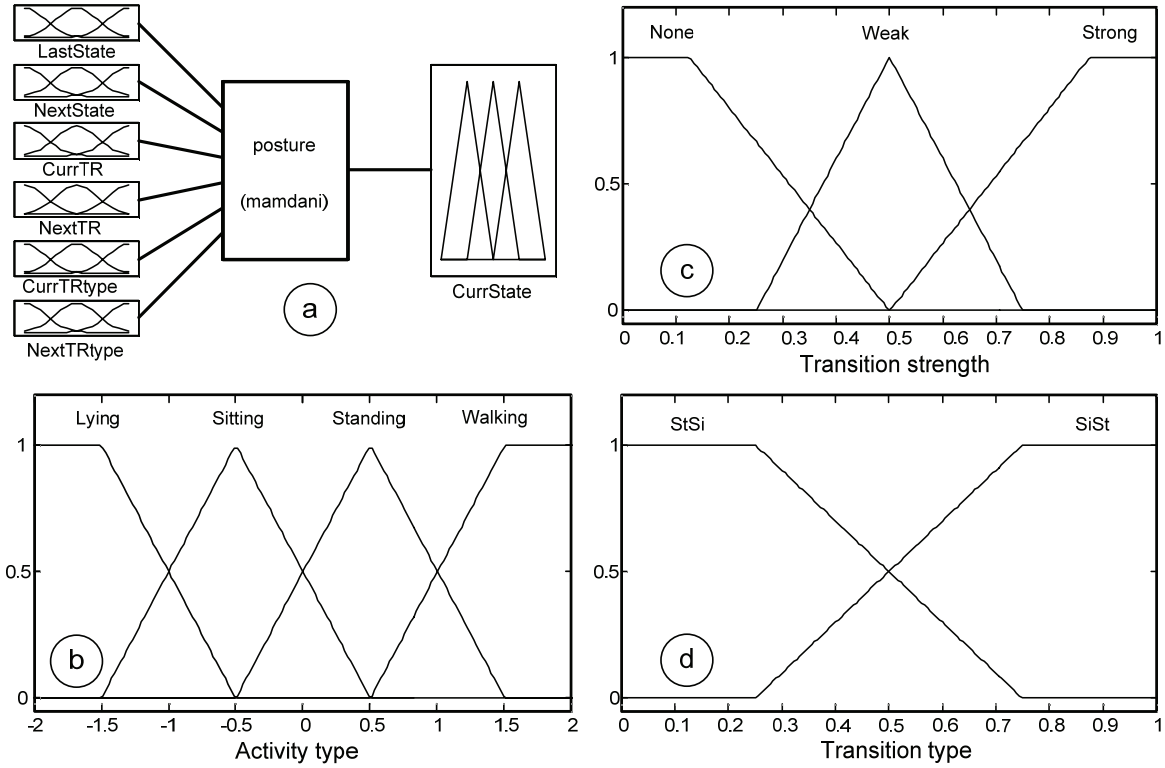


Figure 5-6. a) The inputs and the output of the fuzzy controller b) Membership functions in the activity state variables c) Three levels of strength of the transitions based on the p_{tr} d) Type of the transition

In all fuzzy variables, fuzzy sets from the *trapezoid* family were used. To express the strength of the transition candidates based on p_{tr} three fuzzy sets were considered. *Strong* transition candidates were those with a very *high ptr* and *None* transition candidates were those with a very *low* p_{tr}. Those transition candidates with a p_{tr} round 0.5 were considered as *weak*. Transition candidates with a *low* value of p_{sist} were assigned to the *StSi* fuzzy set and those with a *high* value of p_{sist} were assigned to the *SiSt* fuzzy set.

Two input fuzzy variables (*LastState* and *NextState*) and the single output variable (*CurrState*) expressed the type of the activity (see Figure 5-6.b). In a scale of -2 to 2, in increasing order fuzzy sets has been defined for the *Lying, Sitting, Standing* and *Walking* states with an overlap of 50% between the adjacent sets.

As the output, the fuzzy classifier produced the *CurrState* fuzzy variable. The fuzzy sets used in this method and their membership function are shown in the (Figure 5-6).

For each transition based on the p_{tr}, three levels of strength have been assigned: Strong, Weak, None-transition. A set of 14 fuzzy (see Table 5-1) rules has been used in the fuzzy controller. Rules had weights between 0.25 and 1.0. When all needed information to classify an unknown state was provided, the stronger activated rule would dominate the output and when only partial information was available, only a rule with a lower weight would activate. If for a given period no transitions were detected, a rule with a low weight would get activated to assign *CurrState* either a value of *Sitting* or *Standing*, based on the state of the previous period or next periods.

For example, if in between two standing periods, a period starting with a *strong* StSi transition and ending with a *weak* SiSt transition was given to the classifier, two rules with the weights 1.0 and 0.5 would get activated (rules number 1 and 7 of Table 5-1) and assigned the *Sitting* as the value of the *CurrState*.

Rule Nr.	Rule	Weight
1	If NextTR is Strong and NextTRtype is SiSt then State is Sit	1
2	If NextTR is Strong and NextTRtype is StSi then State is Stand	1
3	If CurrTR is Strong and CurrTRtype is SiSt then State is Sit	1
4	If CurrTR is Strong and CurrTRtype is StSi then State is Stand	1
5	If LastState is (Stand or Walk) and CurrTR is Weak and CurrTRtype is StSi then State is Sit	0.5
6	If LastState is (Sit or Lye) and NextTR is Weak and CurrTRtype is SiSt then State is Stand	0.5
7	If NextState is (Stand or Walk) and NextTR is Weak and NextTRtype is SiSt then State is Sit	0.5
8	If NextState is (Sit or Lye) and NextTR is Weak and NextTRtype is StSi then State is Stand	0.5
9	If LastState is (Sit or Lye) and CurrTR is None then State is Sit	0.25
10	If LastState is (Stand or Walk) and CurrTR is None then State is Stand	0.25
11	If NextState is (Stand or Walk) and NextTR is None then State is Stand	0.25
12	If NextState is (Sit or Lye) and NextTR is None then State is Sit	0.25
13	If LastState is (Stand or Walk) and NextState is (Stand or Walk) and CurrTR is Weak and NextTR is weak and CurrTRtype is StSi and NextTRtype is SiSt then state is Sit	0.75
14	If LastState is (Sit or Lye) and NextState is (Sit or Lye) and CurrTR is Weak and NextTR is weak and CurrTRtype is SiSt and NextTRtype is StSi then state is Stand	0.75

Table 5-1. List of the all fuzzy rules used by the fuzzy classifier to decide between Sitting and Standing states.

5.2.4 Statistical analysis

To compare different parameters between the normal subjects and PD patients Wilcoxon's non-parametric rank-sum test was used. To compare between the Stim ON and Stim OFF states, Wilcoxon's non-parametric paired test, sign-rank test was used. The correspondence between UPDRS sub-scores and different parameters was estimated with the non-parametric, Spearman's rank correlation.

To evaluate the performance of the classification algorithms, when possible, four complementary statistics were calculated: Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV). These statistics were expressed as conditional probabilities:

$$Sensitivity = P(test^{+} \mid ref^{+}) \tag{5-7}$$

$$Specificity = P(test^{-} \mid ref^{-}) \tag{5-8}$$

$$PPV = P(ref^{+} \mid test^{+}) \tag{5-9}$$

$$NPV = P(ref^{-} \mid test^{-}) \tag{5-10}$$

Where $test^{+}$ means positive outcome of the test, ref^{+} means positive observation by the reference, $test^{-}$ means negative outcome of the test and ref^{-} stands for the negative observation by the reference. The values of these probabilities were presented in the form of percentage. In the second study, theses statistics were also calculated by taking the first observer as the reference and the second observer as the test to find out the limits of the accuracy of the observation.

5.3 Results

5.3.1 Automatic calibration of the trunk sensor's inclination

An error of -5.5±3.2 degree (mean ± S.D.) between the estimated θ_0 by the algorithm and mean value of θ_{biased} during the standings periods (identified from the video) was found. The negative value of the mean of the error implies that the subjects tend to walk with slightly bent forward as compared to the up-right standing. However the magnitude of the error for the purpose of the posture analysis algorithm was found to be negligible.

5.3.2 Transition detection and classification

The first step in detecting posture transitions was to identify negative peaks in the θ_g signal (Figure 5-5). The time of these peaks were considered as the potential candidates of the time of the posture transitions. As shown in Table 5-2, for the normal subjects the algorithm could detect posture-transitions with a very high sensitivity (94.4%). In the case of PD patients, the sensitivity was reduced to 83.8% yet in both cases it has been better than the similar algorithm in (Najafi, Aminian *et al.* 2003). However, the downside of having a higher sensitivity was lower *Positive Predictive Value* (PPV) because of more false-positives.

Method	Sensitivity	PPV
Normal (N = 232)		
Proposed method	94.4%	56.4%
Najafi et al. method	91.4%	73.9%
Parkinson (N = 272)		
Proposed method	83.8%	57.3%
Najafi et al. method	62.1%	70.1%

Table 5-2. The performance of the peak-detection algorithm in finding posture-transition candidates. N stands for the number of transitions in each case.

The second step of the transition detection was to use a statistical classifier to separate true posture transitions from the false-positives. To demonstrate the potentials of our approach, the classifier was first applied to the data from the control subjects (see Table 5-3). The results show high sensitivity and specificity (>95%).

For practical application of our method in monitoring both normal subjects and PD patients, α and β_i were calculated by running the training algorithm on a group of randomly selected posture transition candidates from the Control *and* Patient data (see also Table 5-3). The results show that the statistical classifier significantly increased the PPV. Similarly, a second classifier was trained to separate the SiSt and StSi transitions. Table 5-4 summarizes the results obtained using the control data and those obtained using the mixed control and patient data.

		Reference Data (video)- control data			Reference Data (video)- mixed control/patient data		
		Transition	Non-transition		Transition	Non-transition	
Algorithm	Transition	63	2	PPV = 96.9%	107	16	PPV = 87.0%
	Non-transition	3	49	NPV= 94.2%	22	84	NPV= 79.2%
		Sensitivity 95.5%	Specificity 96.1%		Sensitivity 83.0%	Specificity 84.0%	

Table 5-3. Performance of the statistical posture transition classifier trained and applied only on the control data and on the mixed control- patient data

		Reference Data (video)-control data			Reference Data (video)- mixed control/patient data		
		SiSt	StSi		SiSt	StSi	
Algorithm	SiSt	32	1	PPV = 97.0%	61	6	PPV = 91.0%
	StSi	2	32	NPV= 94.1%	6	56	NPV= 90.3%
		Sensitivity 94.1%	Specificity 97.0%		Sensitivity 91.0%	Specificity 90.3%	

Table 5-4. Performance of the SiSt/StSi transition classifier trained and applied using only control data (152 samples for training, 67 samples for evaluation) and using mixed control and patient data (298 samples for training, 129 samples for evaluation)

5.3.3 Classification of the body postures

As an example, Figure 5-7 shows a part of the output of the algorithm of a typical case. Starting from sitting position, subject has stood up, climbed some stairs, paused for a

short while and continued with walking on flat surface followed by a short period of lying down and finally standing up.

Walking periods have been detected using the shank gyroscopes' signals (Figure 5-7.a) and lying periods were detected using θ_{trunk} (Figure 5-7.b). Finally, by detecting SiSt and StSi transitions from θ_g signal (Figure 5-7.c), periods of sitting and standing were detected (Figure 5-7.d).

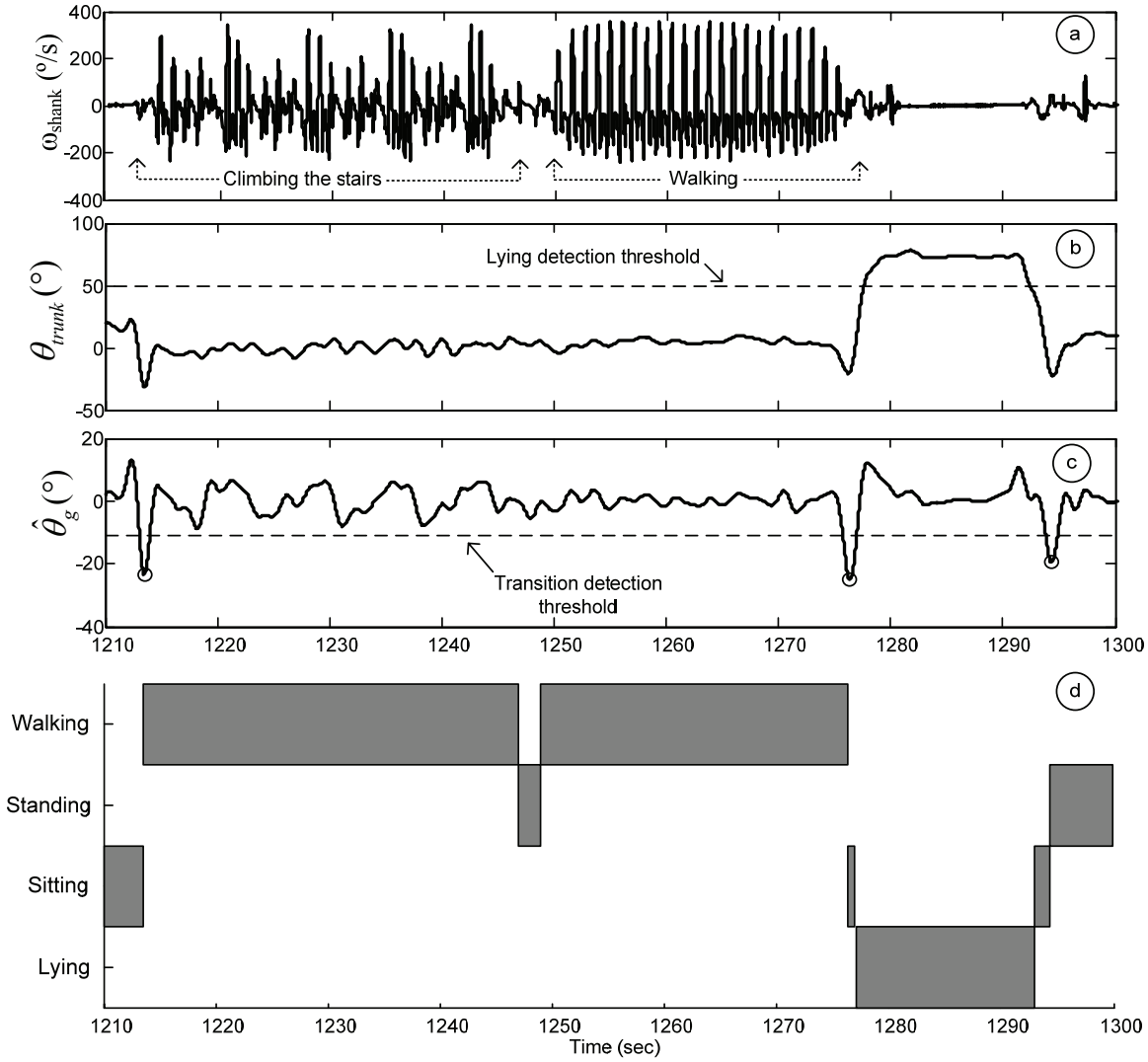


Figure 5-7. a) Right shank's gyroscope signal that together with the left shank's signal was used to detect gait. b) θ_{trunk} is the calibrated trunk's inclination angle and is used to detect lying periods. c) θ_g is the filtered trunk's tilt obtained from the trunk's gyroscope sensor used to detect posture transitions. d) Output of the fuzzy classifier showing periods of the different activities.

	Walking	Standing	Sitting	Lying
		Normal		
Sensitivity	99.1%	96.1%	99.5%	100%
Specificity	99.8%	97.9%	99.8%	100%
PPV	99.0%	90.2%	99.4%	100%
NPV	99.8%	99.2%	99.9%	100%
		PD Patients		
Sensitivity	98.5%	83.6%	86.3%	91.8%
Specificity	97.8%	96.5%	98.0%	99.8%
PPV	98.0%	83.5%	89.6%	92.3%
NPV	98.3%	96.5%	97.3%	99.8%

Table 5-5. performance of the algorithm in classifying four basic body postures.

Table 5-5 summarizes the results of assessment of sensitivity and specificity of the detection of each body posture for the control and patient groups by comparing the outcome of our method and the time tagged logs obtained from reviewing the video tapes.

5.3.4 Posture-transition related parameters

For each subject, the average value of each parameter related to posture transitions were calculated. Results of the PD patient measurement were put into two groups, Stim ON and OFF based on the state of the stimulator. For each group of Control, Stim ON and Stim OFF, the average value of each parameter and its standard deviation was calculated. Each group included ten subjects, hence ten samples. The results are shown in Table 5-6.

	Values for each group (in mean ± S.D.)			p-value for the hypothesis test of the equivalence of the medians		
Parameter	Control	Stim ON	Stim OFF	Control vs. Stim ON	Control vs. Stim OFF	Stim ON vs. Stim OFF
$Max(\omega_{trunk})$ (°/s)	139.7±38.5	109.6±37.7	91.7±27.5	0.0757 (N.S.)	0.0028	0.0371
$\overline{\omega}_{trunk}$ (°/s)	13.12±2.02	9.65±2.29	7.85±2.20	0.0010	0.0002	0.0098
TD (s)	2.82±0.22	3.27±0.42	3.54±0.53	0.0312	0.0058	0.0058
ROR_{trunk} (°)	21.4±4.4	18.9±4.9	16.7±4.8	0.3847 (N.S.)	0.0539 (N.S.)	0.0273
$Max(\hat{a}_{turnk})\,(g)$	1.067±0.009	1.048±0.010	1.036±0.011	0.0006	0.0002	0.0098
$Min(\hat{a}_{turnk})\,(g)$	1.036±0.011	0.960±0.011	0.972±0.009	0.0028	0.0002	0.0020
$Min(\theta_g)$ (°)	-21.7±3.3	-15.9±3.5	-13.5±3.4	0.0007	0.0002	0.0371
$Range(a_{turnk})\,(g)$	0.648±0.114	0.505±0.088	0.456±0.067	0.0113	0.0013	0.3750 (N.S.)
$Range(\hat{a}_{turnk})\,(g)$	0.124±0.018	0.088±0.021	0.064±0.020	0.0017	0.0002	0.0039

Table 5-6. the value of posture transition related parameters for each group of Contorl, Stim ON and Stim OFF and the p-value of the hypotesis tests to compare the median of groups.

We have found significant differences ($p < 0.05$) in many parameters related to the posture transitions between the control group and the PD patients and also between the Stim ON and OFF states.

5.3.5 Detection of basic body postures in the free moving patients

Table 5-7 shows the results of the comparison of the output of the posture analysis algorithm to the time-tagged logs prepared by observation. The results also include the statistics of the comparison of the logs of the second observer to those of the first one.

	Algorithm vs. Observation				Observer 2 vs. Observer 1			
	Walking	Standing	Sitting	Lying	Walking	Standing	Sitting	Lying
Sensitivity	95.0%	56.6%	84.6%	91.1%	93.8%	81.1%	99.5%	80.0%
Specificity	99.8%	94.0%	90.3%	80.3%	99.8%	99.5%	85.0%	100%
Prevalence	5.58%	3.0%	71.4%	20.3%	5.58%	3.0%	71.4%	20.3%

Table 5-7. Accuracy of the posture analysis algorithm in detection of the four basic body postures.

Walking and standing postures had the least prevalence in the measurements. In total, PD patients spent only 8.6% of the time in either of these two positions. Most of the time, they selected a sitting position and over all spent more than 71% of the time in this position. They spent the remaining 20% of the time in a lying position.

The algorithm was most accurate in detecting walking and lying postures. Detection of standing body posture, however, was rather poor. This body posture also had the least prevalence during the measurement period and the two observers showed the least agreement about it.

5.4 Discussion and conclusions

5.4.1 Transition detection and body posture classification

As presented in Table 5-2, the sensitivity of the algorithm to detect posture transition candidates in the normal, control group is very high. The method described in (Najafi, Aminian *et al.* 2003) also show similar, marginally lower sensitivity. However, while our proposed method of transition detection showed almost 10% less sensitivity, the other method had nearly 30% less sensitivity in PD patients. Moreover, in both populations our proposed method had lower Positive Predictive Value (PPV) because of more false-positives (56.4% vs. 73.9% for controls and 57.3% vs. 70.1% for PD patients). Najafi et al method continues to classify the activities at this point while in the new method, in order to improve PPV, we have taken some further steps. Logistic regression was used to separate true-positives from false positives: for each candidate a probability was assigned to state how probable it was that the candidate was true posture transition. This approach also integrated well the fuzzy classifier used in a later stage to classify the body postures and involves useful information hidden in the features of the posture transition pattern. Using this methdo, the PPV of the outcome of the algorithm was significantly enhanced (see Table 5-5).

The sensitivity of detection of *Sitting* in both PD patients and controls was a little bit higher than the sensitivity of detection of posture transition candidates. The reason was that the quality of the output of the fuzzy sitting/standing classifier is not solely based on detection of posture transitions. Some special cases of sitting postures can be detected using only acceleration signals on the trunk. While these cases are particular, they tend to occur during long periods of sitting so their early detection provided an important boost to the quality (sensitivity/specificity) of the output of the algorithm.

In most cases, all unknown states could be classified by running the fuzzy classifier only once from the start to the end of the list. In rare cases, a second run of the classifier was needed to classify all of the unknown states. In those rare cases, by re-running the fuzzy classifier all unknown periods were classified. Running the classifier from start to the end of the list or from the end to the start did not show significant differences.

In the case of PD patients, some limitations increased the error in the classification of the transitions and ultimately body postures. For example tremor, could introduce a lot of noise on the trunk sensor. Also when PD patients are in OFF periods, sometimes they had difficulty performing posture transitions and other activities even with help. The rigidity of muscles in PD patients or external help during posture transitions reduced the trunk movements and distorted the pattern of the trunk tilt signal thus affecting the posture transition detection. Gait detection could also become less reliable when PD introduces abnormalities in the gait pattern.

5.4.2 Posture-transition related parameters

Because subjects followed the same protocol of activities, duration and type of the activities were very similar between them. However the calculated parameters related to posture transitions showed significant differences between control subjects and PD patients (see Table 5-6). During posture transitions, compared to the controls, PD patients in the Stim OFF period, had a significantly longer posture transition times (3.54 vs. 2.82 seconds), less average angular velocity of the trunk (7.85 vs. 13.12 degree/seconds) and showed a marked and nearly significant (p = 0.054) reduction in the range of the rotation of the trunk (16.7 vs. 21.4 degrees). At the same time, PD patients had significantly lower accelerations of the trunk ($Range(\hat{a}_{turnk})$, $Range(a_{trunk})$, $Max(\hat{a}_{turnk})$, $Min(\hat{a}_{turnk})$) compared to the controls.

These altered parameters were likely to be related to a mixture of rigidity and bradykinesia, hypothesis supported by finding that STN-DBS improved significantly most of them. Indeed, during Stim ON, PD patients had significantly shorter posture transition times

(3.27 vs. 3.54 seconds), higher average angular velocity of the trunk (9.65 vs. 7.85 degree/seconds) and higher range of rotation of the trunk (18.9 vs. 16.7 degrees). Three of the four parameters related to the acceleration of the trunk also showed significant improvement during Stim ON compared to the Stim OFF period ($Range(\hat{a}_{turnk})$, $Max(\hat{a}_{turnk})$, $Min(\hat{a}_{turnk})$). Range of the acceleration of the trunk, $Range(a_{trunk})$, was not significantly different between Stim ON and Stim OFF states while the range of low-pass component of a_{trunk} during posture transitions, $Range(\hat{a}_{turnk})$, showed a significant difference between Stim ON and Stim OFF: this is probably due to the removal of noisy, high frequency components of a_{trunk} during the transitions (e.g. the impact produced during sitting).

Although STN-DBS improved most posture transitions related parameters, PD patients still showed significant differences in many of these parameters during Stim ON when compared to the control subjects. They had significantly longer posture transition times (3.27 vs. 2.82 seconds), less average angular velocity of the trunk (9.65 vs. 13.12 degree/seconds) and less $Range(\hat{a}_{turnk})$ (0.088 vs. 0.124 g).

Therefore, our data reported in Table 5-6 show significant differences in most, but not all, parameters in Stim ON patients compared to healthy controls suggesting that the magnitude of improvement provided by STN-DBS, although significant, was by no mean sufficient to *normalize* the posture transitions in PD. This is in agreement with clinical observation that the effects of STN-DBS are more marked on limbs rather than on trunk Parkinsonism features.

5.4.3 Correlation between UPDRS and posture transition

Three different sub-scores defined as U1 to U3 (see Table 5-8) were made based on a combination of different UPDRS III items. Parameters related to the posture transitions where compared to these sub-scores. Table 5-9 shows the coefficient of the non-parametric, rank correlation between the sub-scores and posture transition parameters. The first column shows the correlation coefficient related to the whole UPDRS score.

Sub-score	Related symptoms	UPDRS III sub-scores
U1	Gait	29
U2	Gait & posture	27 + 28 + 29 + 30
U3	Bradykinesia	23 + 24 + 25 + 26 + 31

Table 5-8. UPDRS sub-scores used in calculation of correlation coefficients

Parameter	UPDRS	U1	U2	U3
$Max(\omega_{trunk})$	N.S.	N.S.	N.S.	N.S.
$\overline{\omega}_{trunk}$	-0.49	-0.56	-0.56	-0.45
TD	0.64	N.S.	0.65	0.55
ROR_{trunk}	N.S.	N.S.	N.S.	N.S.
$Max(\hat{a}_{turnk})$	-0.55	-0.67	-0.64	-0.49
$Min(\hat{a}_{turnk})$	0.69	0.72	0.79	0.60
$Min(\theta g)$	N.S.	0.49	0.49	N.S.
$Range(a_{trunk})$	N.S.	N.S.	N.S.	N.S.
$Range(\hat{a}_{turnk})$	-0.65	-0.71	-0.72	-0.59

Table 5-9. Coefficient of rank correlation between UPDRS sub-scores and posture transition parameters. Where the p-value was more than 0.05, the correlation was considered as Not Significant (N.S.).

Several parameters show significant correlation to UPDRS score and/or some of the sub-scores. $Range(a_{trunk})$ showed no significant correlation with the UPDRS score or any of the sub-scores while $Range(\hat{a}_{turnk})$ showed significant correlations to the UPDRS and all sub-scores. Figure 5-8 shows a scatter plot of U3 (posture sub-score) and $Range(\hat{a}_{turnk})$.

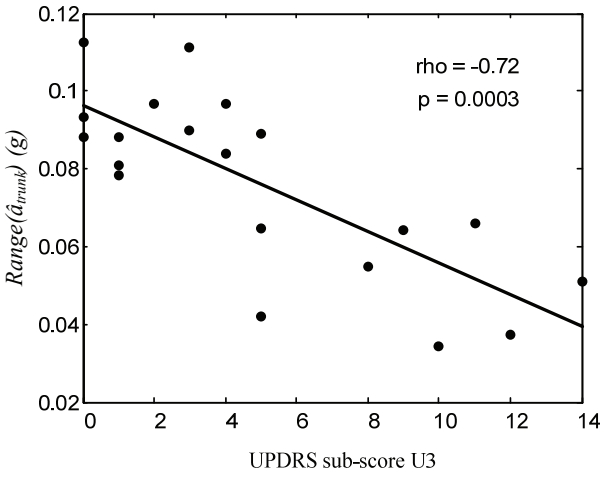


Figure 5-8. Scatter plot comparing UPDRS sub-score U3 and range of filtered trunk acceleration.

5.4.4 Posture analysis results in the free moving patients

The prevalence of walking and standing during the measurements was very small. The posture analysis algorithm had the poorest results in detection of standing periods (see Table 5-7). Part of the problem could be explained by noticing that deciding between very short walking periods and active standing periods depended very much on the subjective preferences of the observers. This also explains why standing was the activity that the two observers had the least agreement about (Sensitivity was 81.1% and PPV was 87.4%).

In the same way, the two observers had a large disagreement in classification of lying periods. The source of the problem was deciding that long periods of leaning backward should be reported as sitting or lying. Detection of lying using accelerometers on the trunk is generally considered highly accurate (Najafi, Aminian *et al.* 2003; Paraschiv-Ionescu, Buchser *et al.* 2004). The algorithm classified long periods of backward inclinations of higher than 45° as lying. Low specificity of the algorithm (80.3%) in detection of lying can be attributed mostly to the subjective decision of the observers as to take how much leaning backward as lying. A very high prevalence of nearly 92% for sitting and lying indicates that although the PD patient were free to move, they either decided to remain inactive or could not do much activity in the hospital.

5.4.5 Comparison to other ambulatory systems

Recently a system based on kinematic sensors with two sensor sites on the body has been reported in (Paraschiv-Ionescu, Buchser *et al.* 2004) and a comparison to several other systems (Bussmann, Reuvekamp *et al.* 1998; Najafi, Aminian *et al.* 2003; Ng, Sahakian *et al.* 2000) has been reported. In Table 5-10 our proposed system has been added to the same comparison list.

System	Fixation sites	Subject/hours	Sensitivity				Specificity			
			Sitting	Standing	Walking	Lying	Sitting	Standing	Walking	Lying
Proposed system	3	10/8 (h)	99.5	96.1	99.1	100	99.8	97.9	99.8	100
		20/15 (p)	86.3	83.6	98.5	91.8	98.0	96.5	97.8	99.8
Paraschiv et. al.	2	21/61	98.2	98.0	97.1	99.2	98.8	98.5	97.9	98.6
Najafi et al.	1	15/30	87.0	87.6	92.3	99.0	89.4	86.7	94.0	98.7
Bussman et al.	3	8/8	94	84	85	86	-	-	-	-
Ng et al.	2	5/5 (h)	98.8	95.8	95.0	97.6	99.3	98.4	98.6	99.6
		20/20 (p)	80.6	94.6	80.3	93.1	98.9	92.8	98.5	93.8

Table 5-10, comparison of the performance of the proposed method with several other methods in controlled conditions (p stands for Patients and h stands for Healthy subjects).

Based on this comparison, our proposed system not only competes very well with the other methods, but also demonstrates that the system is versatile and could be used easily in the clinic for the assessment of movement disorders of neurological origin. Regarding PD patients, Keijsers et al. (Keijsers, Horstink *et al.* 2003c) have also proposed a system with a method similar to (Veltink, Bussmann *et al.* 1996a) to estimate periods of different body postures, but they did not report the classification performance of their algorithm.

5.4.6 Conclusions

We designed and investigated an ambulatory method suitable for the monitoring of daily activities in PD patients. With three sensor fixation sites, the system could accurately and reliably classify basic body postures in both healthy subjects and PD patients.

In addition, we have found significant differences in the parameters related to posture transitions between normal subjects and PD patients even when optimally treated. At the same time, significant and good correlations between some of these parameters and commonly used UPDSR score have been found.

The method presented here provides an effective way of ambulatory monitoring of the physical activities of PD patients with good sensitivity and specificity in detection of the basic body posture and offers the objective quantification of some aspects that improve the assessment of physical mobility not only in PD patients but possibly also in other patients with movement disorders.

Chapter 6 Gait assessment

Abstract

Background—Parkinson's disease can have a dramatic effect on gait. Typically, PD patients' gait is slow and shuffling, stride length is shortened and velocity reduced. A reduced range of motion at the joint level is also present. As the parkinsonian signs can change during the day, gait parameters can also change during the day.

Objectives—Design and validation of a new method of gait analysis of PD patients based on kinematic sensors. The method was needed to automatically detect gait and provide spatio-temporal parameters of the gait. Finding differences in the gait parameters in PD and healthy control subjects and correlations between the gait parameters and clinical scores were additional goals of this study.

Method—A system based on four gyroscopes attached to the lower limbs has been proposed. An algorithm has been designed to detect gait events (initial and terminal contact) with high accuracy. A two-segment model of the gait has been used to obtain stride-length. Using a video recording the sensitivity of algorithm in detection of the PD gait was calculated. The obtained gait parameters in PD patients and control group were statistically compared.

Results—We found significant differences in the gait parameters of PD patients comparing to controls. They had 52% less stride length, 60% less stride velocity and 40% longer gait cycle time. Also they had significantly longer stance and double support (11% and 59% more, respectively) than controls. STN-DBS significantly improved gait parameters. During Stim ON period, PD patients had 31% faster stride velocity, 26% longer stride length, 6% shorter stance and 26% shorter double support. Gait cycle time, however, was not significantly different. Some of the gait parameters had high correlation with UPDRS sub-scores.

Main contributions— A new ambulatory gait analysis method based on kinematics sensors has been proposed and validated that has a better accuracy and time complexity than the previous methods and can detect PD gait with high sensitivity. Using this simple

and relatively inexpensive device, clinical results comparable to more complex methods based on camera based systems used in gait labs has been obtained.

6.1 Introduction

Gait is a particular, semi-automatic motor task which is specifically sensitive to ON-OFF changes of parkinsonian state. When OFF, PD patients tend to walk slowly with short shuffling steps, reduced arm swing, stooped posture and they may present start hesitations and freezing episodes when turning around or facing an obstacle. During ON state, the same patients may walk nearly normally with or without "dancing" steps as a result of the presence of dyskinesia involving the lower limbs. Analysis of gait parameters may therefore constitute a reliable paradigm to assess global motor function over time in PD patients. However, until now there have been a limited number of ambulatory systems to analyze human gait. Some of these systems need special footwear with foot-switches or other pressure sensitive devices inside (Lackovic, Bilas *et al.* 2000; Pataky, Faravel *et al.* 2000). Using special footwear is not always possible and may also hinder subject's normal gait. Moreover, PD patients often tend to shuffle while walking, making the initial and terminal contact detection difficult. In these cases, the gait temporal parameters can not be calculated precisely. In addition, the foot-switch techniques do not provide spatial parameters. An accelerometer which does not need to be fixed under the foot has been used as an alternative (Sekine, Tamura *et al.* 2002; Willemsen, Bloemhof *et al.* 1990). An automated algorithm for gait temporal parameters estimation was proposed by (Aminian, Rezakhanlou *et al.* 1999) and validated on osteo-arthritis patients. More recently, using accelerometers attached to the trunk an original method to estimate mean step length and walking speed was described by (Zijlstra and Hof 2003). However this system was not validated in pathological gait.

Our goal in this part of the thesis was to design and validate a new method for ambulatory gait analysis in PD patients based on body fixed sensors. As PD patients during OFF state quite often walk only for short periods, high sensitivity and specificity in detection of gait was a secondary goal to obtain the most out of all walking periods subjects may have.

6.2 Definition of gait parameters

6.2.1 Introduction

Human gait is a complex movement that includes activities in many muscles and joints of the body. Gait is rhythmic or semi-repetitive in nature. To analyze the gait in an objective manner, the first step is to break the repetitive complex movements of the body

into (more or less) similar blocks, usually referred to as *gait cycles*. Each gait cycle can be characterized by several *spatio-temporal* gait parameters (Giannini, Catani *et al.* 1994; Inman, H.J. *et al.* 1981; Perry 1992), or for short *gait parameters*. To describe these parameters, we rely on the terminology used by GCMAS[1] society (Õunpuu 1994). To identify a gait cycle, we need to find the respective *gait events*. There are two important gait events in this regard:

- Initial Contact (*IC*): The moment in time that the foot touches the ground.
- Terminal Contact (*TC*): The moment in time that the foot leaves the ground.

To have a complete gait cycle, five gait events are needed: $IC_R(k)$, $TC_R(k)$, $IC_L(k)$, $TC_L(k)$ and $IC_R(k+1)$. A complete gait cycle starts from the *IC* of the right foot and ends with the following *IC* of the same foot.

6.2.2 Temporal parameters

Temporal parameters are those parameters of a gait cycle that are related to time. Usually, temporal parameters are defined as a percentage of the total gait cycle time. Figure 6-1 shows a typical gait cycle and the respective temporal parameters.

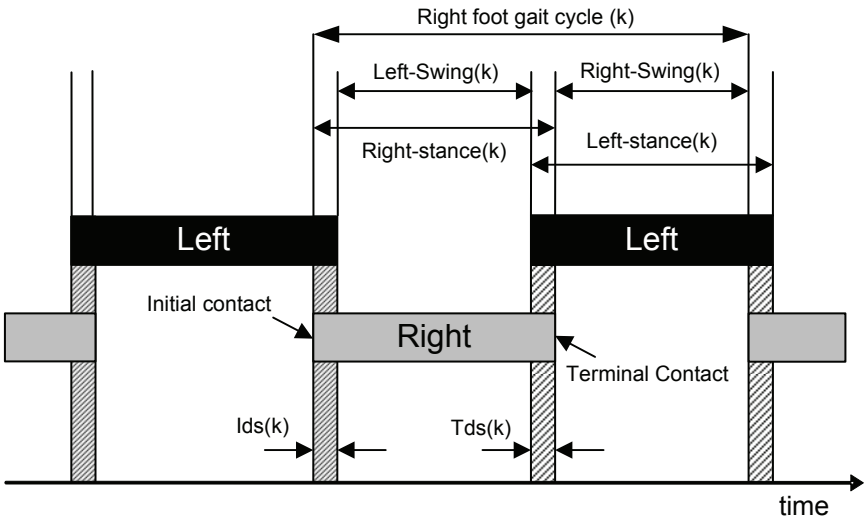


Figure 6-1. Temporal parameters of a gait cycle.

For each gait cycle *k*, the following temporal parameters can be considered:

- Gait Cycle Time (*GCT*): The period of the time between the *IC* of the right foot to the next *IC* of the same foot.

[1] GCMAS: Gait and Clinical Movement Analysis Society.

$$GCT(k) = IC_R(k+1) - IC_R(k) \tag{6-1}$$

- Stance phase (*ST*): The period of the time when the foot is in contact with the ground.

$$ST_R(k) = 100 \times \frac{TC_R(k) - IC_R(k)}{GCT(k)} \tag{6-2}$$

$$ST_L(k) = 100 \times \frac{TC_L(k+1) - IC_L(k)}{GCT(k)} \tag{6-3}$$

- Swing phase (*SW*): The period of the time when the foot is not in contact with the ground.

$$SW_R(k) = 100 \times \frac{IC_R(k+1) - TC_R(k)}{GCT(k)} \tag{6-4}$$

$$SW_L(k) = 100 \times \frac{IC_L(k) - TC_L(k)}{GCT(k)} \tag{6-5}$$

- Double Support (*DS*): The period of time when both feet are in contact with ground. This happens two times during a gait cycle: at the beginning and at the end of the right foot's stance. The first one is called Initial Double Support (*IDS*) and the second one is called Terminal Double Support (*TDS*). The absolute value of the difference of the *IDS* and *TDS* is called the *Limp*. As the asymmetry in gait grows, the value of the Limp also gets higher.

$$IDS(k) = 100 \times \frac{TC_L(k) - IC_R(k)}{GCT(k)} \tag{6-6}$$

$$TDS(k) = 100 \times \frac{TC_R(k) - IC_L(k)}{GCT(k)} \tag{6-7}$$

$$DS(k) = IDS(k) + TDS(k) \tag{6-8}$$

$$Limp(k) = \left| IDS(k) - TDS(k) \right| \tag{6-9}$$

- Cadence: Rate at which a person walks, expressed in steps per minutes.

6.2.3 Spatial parameters

Spatial parameters are those parameters of a gait cycle that are related to the distance and velocity. We have considered the following parameters (see Figure 6-2):

- Stride Length (*SL*): The distance from initial contact of one foot to the following initial contact of the same foot, expressed in meters. Sometimes, this parameter is normalized to the leg-length and is expressed in percentage (Hof 1996).

- Stride Velocity (*SV*): The average linear velocity of foot during the gait cycle, expressed in meters/second (*m/s*). If normalized stride length is used to calculate the stride velocity, the unit will be s^{-1}.

$$SV_R(k) = \frac{SL_R(k)}{GCT(k)} \tag{6-10}$$

$$SV_L(k) = \frac{SL_L(k)}{GCT(k)} \tag{6-11}$$

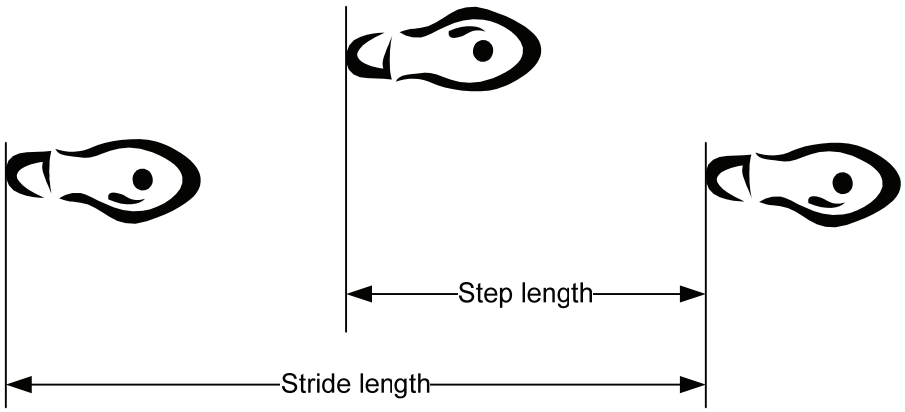


Figure 6-2. Definition of Stride length.

6.2.4 Estimation of spatial parameters: gait model

Human body is a highly articulated structure. For the purpose of gait analysis, even by limiting ourselves only to the segments and joints in the lower limbs, the number of joints and total degrees of freedom are very high. In some applications like computer graphics, with an objective of maximizing the accuracy of the human body models, a large number of joints and segments are considered. For example, in the H-Anim[1] standard (Badler, Phillips *et al.* 1993) a multi-segmented foot, even including the digits is considered. Clearly such complex models are too detailed to be used by a system with a very small number of sensors (or markers).

In our approach, a double pendulum model for swing and an inverse double pendulum model for stance presented in (Aminian, Najafi *et al.* 2002) was used (see Figure 6-3a). In this figure *L1* and *L2* are length of the thigh and shank, respectively. By finding the time of *IC* and *TC* events, swing and stance phases could be detected. The stride length was broken into three different segments, *d1* to *d3*. The value of *d1+d2* was estimated during swing phase and d_3 was estimated during the stance phase. To estimate the stride length for the right foot, *d1+d2* was calculated by calculating α, range of right thigh rotation

[1] H-Anim is becoming an ISO/IEC standard

during swing phase; and β, range of right shank rotation during swing phase. For the same gait cycle, d_3 was estimated by calculating γ, range of left shank rotation during stance and δ, range of left thigh rotation during stance. The details of the calculations are presented in (Aminian, Najafi *et al.* 2002).

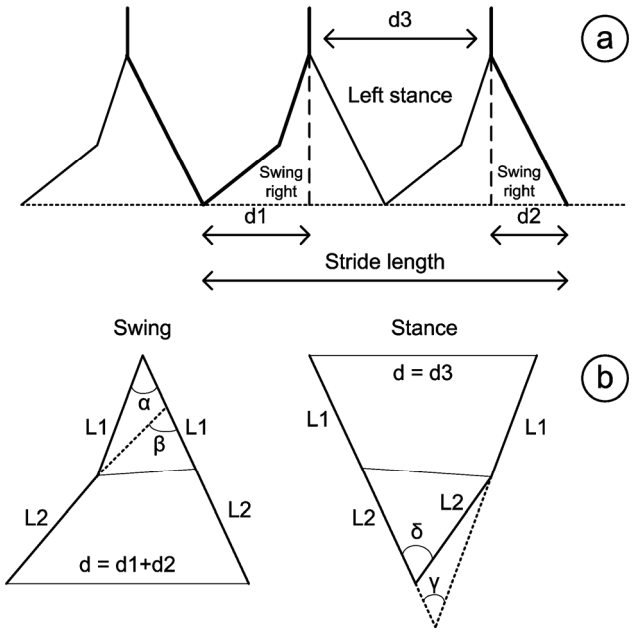


Figure 6-3. Double pendulum model used to estimate gait parameters. (a) Gait cycle starts with Right foot's Initial-Contact. Right foot leaves the ground at *TC* and hits the ground at *IC*. (b) Stride length can be estimated by solving two separate geometries for Swing and Stance phases.

6.3 Methods

6.3.1 Measurement System and experiment setup

In this study, we have used the data from our *controlled study* (see chapter 2.3). As stated before, 10 PD patients and 10 healthy normal subjects participated in this study. During the walking trials, subjects carried a Physilog® (BioAGM, CH) portable data-logger. Gyroscopes that measure the angular rate of the rotations were attached to selected body segments (see Figure 6-4).

All measurement sessions were recorded using a portable video camera. After each session, a reviewer carefully examined the video tape and counted the number of gait cycles in each gait cycle to calculate the sensitivity of the algorithm in gait detection.

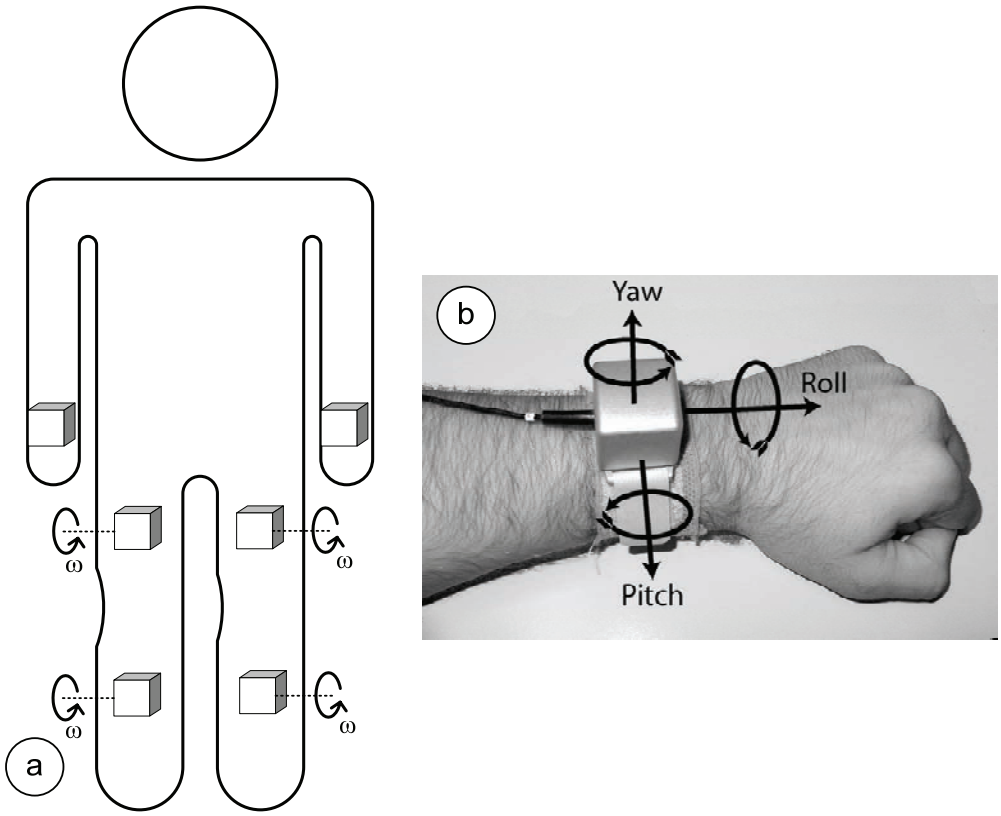


Figure 6-4. a) Attachment of the sensors on the body. Boxes represent sensors: One sensor on each left and right forearms, thighs and shanks. b) Close-up view of sensor on forearm shows its 3 sensitive axes (Pitch, Roll and Yaw).

6.3.2 Pre-recorded database of gait cycles with a reference system

For validation purposes a pre-recorded database of gait cycles has been used (Aminian, Trevisan *et al.* 2004). This database included 229 gait cycles of a group of eigth normal subjects, seven coxarthorosis and six hip-arthoroplasty patients. Each subject had up to 8 walking trials for each of the right and left legs and gait cycles were recorded by Physilog, force-plate and a camera-based system (Elite). Recorded data was verified for potential technical problems like incorrect synchronization between the three devices or cases when subject did not walk over the force plate or both of his feet touched the force plate and finally 229 gait cycles recorded correctly by all three systems were selected.

6.3.3 Temporal parameters estimation

To cancel possible offset and drift of the sensors, resulted from changes in temperature and also possible variations in supply voltage, a high-pass IIR filter was used. The transfer function of this filter was:

$$H(z) = \frac{1 - z^{-1}}{1 - \alpha \cdot z^{-1}} \tag{6-12}$$

To avoid phase distortion, the filter was applied on the input data twice. After filtering in the forward direction, the filtered sequence was reversed and run back through the filter. With α=0.995 the cut-off frequency of the filter was $f_c \approx 0.25$Hz.

Using the signals from shanks, gait cycles and related events were detected and temporal parameters of gait were estimated. The first step was to detect initial and terminal contact of feet with the ground (*IC*, and *TC*). By simultaneously recording the gait signal using Physilog® and force-plate (Kistler, CH), the intervals where these events occurred were determined based on the shank angular velocity (Figure 6-5). The swing phase of a gait cycle is characterized by a positive shank angular velocity reaching its highest values at around Mid-Swing. Prior to swing phase, a negative angular velocity peak can be observed which is associated with *TC*. At the end of the swing period, the *IC* area is characterized by several negative angular velocity peaks. The first negative peak in this area is associated with *IC*. With different populations of normal and pathologic, young and elderly subjects, previous studies confirm the presence of these peaks (Aminian, Najafi *et al.* 2002).

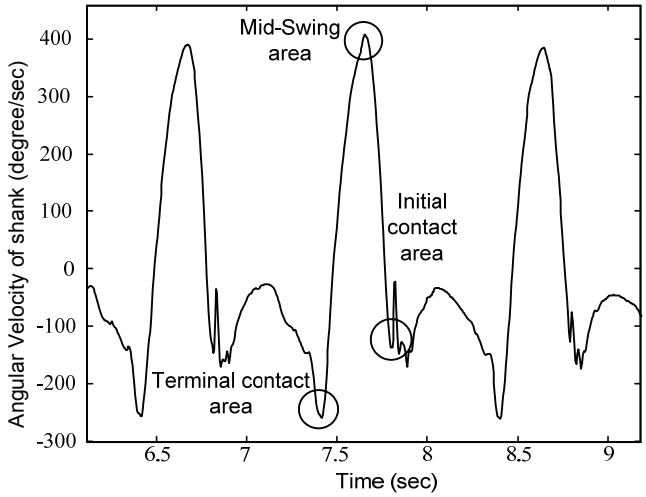


Figure 6-5. Shank angular velocity. Marked areas show where important gait events occur.

Taking advantage of these facts, a new algorithm was developed to extract the precise instances of *IC* and *TC* from right and left shank angular velocity of the respective foot. For the clarity of the explanation, let us consider right shank angular velocity as input. It is obvious that a similar method applies to the signal from the left side. Starting point was the identification of the time events corresponding to the Mid-Swing (t_{ms}) of shank angular velocity. The t_{ms} samples represent approximately the moment of Mid-Swing during a gait cycle however their exact significance is not of interest; they were only used as references in order to select the intervals in which negative peaks reminiscent of *TC*

and *IC* were to be found. First, the local maximum peaks of the signal were detected. Those peaks that were larger than 50 degree/sec were candidates for marking the Mid-Swing area. If multiple adjacent peaks within a maximum distance of 500ms were detected, the peak with the highest amplitude was selected and others were discarded. This prominent peak in the swing area was taken as the Mid-Swing.

In next step, local minimum peaks of shank signal inside interval $[t_{ms} - 1.5s, t_{ms} + 1.5s]$ were searched. The nearest local minimum after t_{ms} was selected as *IC*. As the negative peak associated to *TC* was generally a small peak, to smooth the signal and to get rid of spurious peaks, signal was filtered using a low-pass FIR filter with cut-off frequency of $f_c \approx 30$Hz and pass-band attenuation of less than 0.5dB. The local minima in the signal were searched and for each detected Mid-Swing the minimum prior to t_{ms} with amplitude less than -20 degree/sec was selected as the terminal contact. The -20 degree/sec threshold was used to avoid detecting a wrong peak in the swing area instead of the *TC*. To validate these algorithms, we used the pre-recorded data-base of gait cycles (see section 6.3.1).

After detection of *IC*s and *TC*s, gait cycles were formed to calculate gait temporal parameters. Each complete gait cycle had five associated time events. In order of occurrence: Initial Contact of Right foot (IC_R), Terminal Contact of Left foot (TC_L), Initial Contact of Left foot (IC_L), Terminal Contact of Right foot (TC_R). The fifth time event was the next Initial Contact of Right foot that was also the start of the next gait cycle. This way, the conditions for the time events within k'th gait cycle to be valid were:

$$IC_R(k) < TC_L(k) < IC_L(k) < TC_R(k) \tag{6-13}$$

To form gait cycles conforming to (6-13), for each IC_R a simple algorithm was used to find correct corresponding gait events. In the case a valid gait event could not be detected for a gait cycle, a special *Unknown* value was assigned to it, practically stopping further related calculations on that particular gait cycle. This could happen if any of the following happened:

- Subject suddenly stopped walking, and the started to walk again *with the same* foot he took the last step with.
- Walking was changed to running, i.e. no double-stance period could be detected.
- In rare cases that one or more respective *IC* and *TC* events could not be detected.

Figure 6-6 summarizes different steps taken in calculation of temporal parameters.

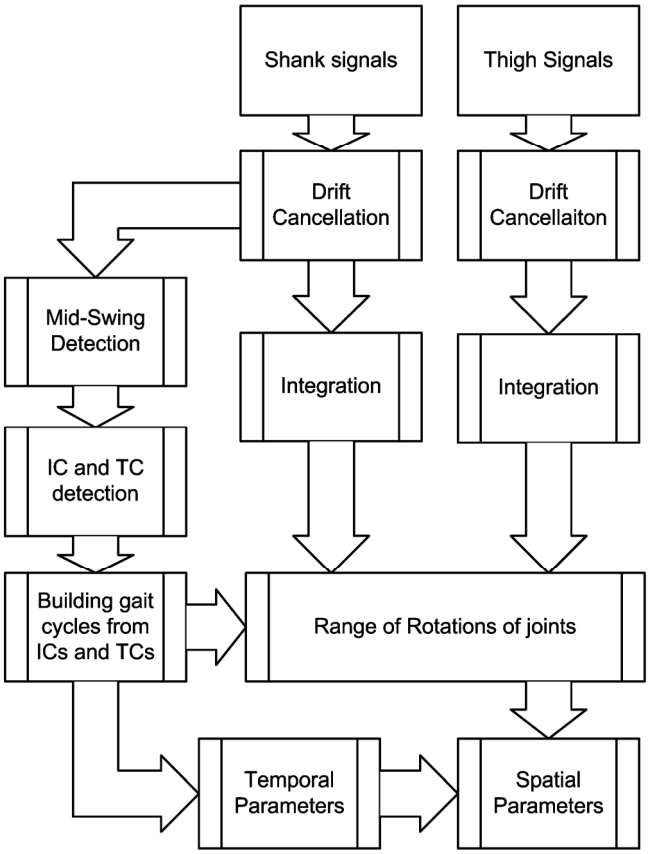


Figure 6-6. Flowchart of spatio-temporal gait parameter estimation algorithm.

6.3.4 Estimating spatial parameters of gait

To find the instantaneous angle of each segment, the angular velocity of that segment was integrated during each gait cycle (see Fig. 3). This way, having discrete values of $\omega[n]$ for each sample and sampling rate of Δ, instantaneous angle $\theta[n]$ of the segment will be:

$$\theta[n] = \theta[n-1] + \frac{\Delta}{2}(\omega[n] + \omega[n-1]) \tag{6-14}$$

In the above equation, the initial condition, $\theta[0]$, is unknown and was assumed zero for the start of each gait cycle. The range of rotation of the segments is:

$$\tilde{\theta}_n = \underset{i=IC_n}{\overset{IC_{n+1}}{\mathrm{MAX}}}(\theta[i]) - \underset{i=IC_n}{\overset{IC_{n+1}}{\mathrm{MIN}}}(\theta[i]) \tag{6-15}$$

where IC_n stands for initial contact of the n'th gait cycle. This value is independent of the $\theta[0]$. Based on the instantaneous segment angles, the calculation of joint angles was trivial. If we have the angle of segments $s1$ and $s2$ making the joint j, then the joint angle for each sample will be:

$$\theta_j[n] = \theta_{s1}[n] - \theta_{s2}[n] + \theta_{j0} \tag{6-16}$$

where again the θ_{j0} or the initial condition is unknown and we took the value as zero for the start of each gait cycle. The range of joint rotations was also calculated in the same way as (6-15). Using this method, the range of rotation of each shank and thigh was calculated. Similarly, for each axis of the sensors on the forearms the range of the rotation during each gait cycle was calculated. To validate the results, the database of pre-recorded gait cycles was used and estimated ranges of angles were compared to those obtained from reference system.

Stride-Length and velocity were then calculated using the range of thigh and shank rotations using a double pendulum model similar to (Aminian, Najafi *et al.* 2002).

6.3.5 Outcomes

Following parameters were finally estimated and reported: spatio-temporal gait parameters including gait cycle time, double support, limp and stance, stride length and velocity; range of rotation of shanks, knees, forearms and peak angular velocity of shanks.

Double support, limp and stance were normalized by gait cycle duration and presented as percentage of it (0-100%). Stride length and velocity were normalized to subject's height and presented as percentage of stature.

Mean and standard deviation of parameters were calculated. To compare variability of the stride-to-stride parameters, the coefficient of variation, CV (Standard Deviation / mean) was calculated. To compare the mean values of different parameters between Stim ON and Stim OFF groups, Wilcoxon's non-parametric paired test, sign-rank test (Wilcoxon 1945) was used and to compare between control group and the PD patients, rank-sum test was used. When needed, Jarque-Bera (Judge, Hill *et al.* 1988) test for goodness-of-fit to a normal distribution was used. To estimate the significance of the correlation coefficients, the Pearson test was used.

6.4 Results

6.4.1 Error in estimation of gait parameters comparing to reference motion-capture systems

Table 6-1 summarizes the error in estimating gait parameters using our new method against the reference motion-capture systems (see 6.3.1). Error was defined as the difference between values for the reference system and the values estimated by our algorithms. Mean and S.D. of this error, across all gait cycles and all subjects were then calculated. Mean of the error in independent parameters (like IC and TC) signifies the presence of a systematic error which can be later corrected and S.D. of the error signifies

the range of the accuracy of the system in comparison to the references. Further, Jarque-Bera goodness of fit test confirms that the error has a normal distribution ($p < 0.0001$).

Error in estimation of parameter	New Method		Previous Method	
	Mean	S.D.	Mean	S.D.
Initial Contact (ms)	8.7	12.5	12.6	14.3
Terminal Contact (ms)	2.9	26.8	-6.6	29.2
Gait Cycle time (ms)	-2.2	23.2	-2.4	24.1
Stance (ms)	-5.9	29.6	-19.2	31.4
Range of Shank rotation (deg)	-0.7	3.3	0.3	3.3
Range of Thigh rotation (deg)	-3.5	4.2	-2.4	4.2
Stride Length (cm)	-3.5	8.5	-0.4	9.6
Stride Velocity (cm/s)	-3.0	7.6	-2.5	8.3
Total execution time (s)	10.5		94.6	

Table 6-1. Error in estimation of gait parameters based on the new method in comparison to the reference motion-capture system. As for comparison, the error of a previous method (Aminian, Najafi *et al.* 2002) is also reported.

6.4.2 Sensitivity of gait cycle and gait event detection

All controls performed the three walking trials. PD patients however were not consistently able to perform all trials and did one to three trials each. For each trial, the first and the last two gait cycles were omitted to avoid the effects of gait initiation and termination.

	PD subjects Stim ON	PD Subjects Stim OFF	Controls
Trials	21	17	30
Total Gait Cycles	274	248	514
True-Positive Gait Cycles	274	247	514
False-Positive Gait Cycles	3	4	0
True-Positive Gait Events	272	239	512
False-Positive Gait Events	1	4	2

Table 6-2. Summary of measured trials and gait cycles.

Table 6-2 summarizes the measured trials and the number of gait cycles eventually obtained for each group. *Total Gait Cycles* comes from the observation based on the video tapes: a reviewer counted the number of gait cycles in each trial. There are two possible types of detection errors: errors in detection of a gait cycle (i.e. error in finding Mid-Swing peak) and errors in finding related gait events (*IC* and *TC*). Based on these values, we had a very high sensitivity in detection of gait cycles (100% for controls and 100% for PD patients during Stim ON and 99.6% during Stim OFF). Also sensitivity in detection of gait events was very high (99.6% for controls and 99.3% for PD patients during Stim ON and 96.4% during Stim OFF). The positive prediction value (PPV) in detection of gait cycles has been 100% for controls, 98.9% for Stim ON and 98.4 for Stim OFF group. PPV for detection of *IC* and *TC* has been 99.6% for controls and 99.6% for Stim ON and 98.4% for Stim OFF group.

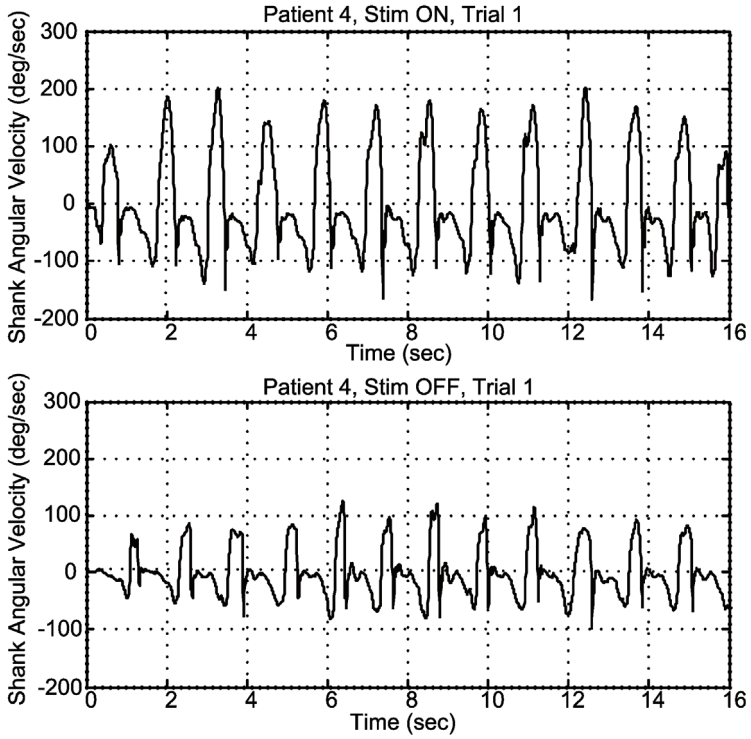


Figure 6-7. A sample of the recorded signal on shanks. A PD patient with and without stimulation shows different pattern of walking.

Figure 6-7 shows a sample of the recorded signal on the shank. As it can be seen here, during the Stim ON, the subject moved his shank significantly faster; however both signals show noticeable variability in the peak speed of the shank.

6.4.3 UPDRS motor score

The UPDRS motor scores and sub-scores for all PD patients during Stim ON and Stim OFF periods are presented in Table 2-2 and Table 2-3. Stimulation significantly improved (decreased) UPDRS motor scores ($p = 0.002$). All UPDRS sub-scores were also significantly improved ($p = 0.042$) but not the sub-scores for Speech and Posture (items 18 and 28)

6.4.4 Gait Parameters

Gait parameters are reported in Table 6-3 for both states of stimulation and also for controls in (mean ± S.D.) format. The results of the statistical hypothesis tests of equivalence of means and also CV of the three groups are also presented. A paired test was used when comparing the Stim ON and Stim OFF groups.

Gait Parameters	Values for each group in mean±S.D.			p-value for the equivalence of mean of parameters			p-value for equivalence of mean of C.V,		
	Stim OFF	Stim ON	Control	ON/OFF paired	ON v.s. Control	OFF v.s. Control	ON/OFF paired	ON v.s. Control	OFF v.s. Control
Gait Cycle Time (s)	1.4± 0.6	1.2±0.2	1.0±0.1	N.S.	0.0312	0.0312	N.S.	0.0211	N.S.
Stance (%)	65.7± 8.6	61.5±4.5	59.4±1.2	0.0488	N.S.	0.0312	N.S.	0.0173	0.0211
Double Support (%)	31.4±17.1	23±9.1	18.7±2.5	0.0488	N.S.	0.0312	N.S.	N.S.	N.S.
Limp (%)	7.2±8.6	4.2±2.2	1.4±0.5	N.S.	0.0010	0.0006	N.S.	N.S.	N.S.
Stride Length (%h)	46.2±19.4	58.6±17.9	77.1±6.5	0.0020	0.0073	0.0004	N.S.	N.S.	0.0017
Stride Velocity (%h/s)	40.5±23.5	53.1±20.2	77.4±9.2	0.0039	0.0022	0.0003	0.0137	N.S.	N.S.
Range of Shank rotation (deg)	45.6±19.5	56.5±18.5	76±5.9	0.0020	0.0022	0.0002	0.0020	0.0113	0.0028
Range of Thigh rotation (deg)	28±8.5	34.4±8.6	34.4±11.8	0.0098	N.S.	N.S.	N.S.	0.0257	0.0028
Range of Knee rotation (deg)	39.4±13.7	45.4±15.8	60.4±7.9	0.0195	0.0113	0.0003	N.S.	N.S.	0.0140
Range of hand rotation, Pitch axis (°)	8.4±5.1	17.8±12.6	20.2±6.4	N.S.	N.S.	0.0013	N.S.	N.S.	N.S.
Range of hand rotation, Roll axis (°)	14±13.3	18.2±6.7	22.9±5	N.S.	N.S.	0.0028	N.S.	N.S.	N.S.
Range of hand rotation, Yaw axis (°)	10.3±5.3	24.6±12.1	47.6±8.4	0.0039	0.0013	0.0002	N.S.	0.0452	N.S.
Peak Shank angular Velocity (°/s)	225±103	275±110	386±40	0.0020	0.0058	0.0003	0.0020	N.S.	0.0452

Table 6-3. Measured gait parameters for Patients during Stim ON and OFF state and Controls. p-values more than 0.05 were considered as Not Significant (N.S.).

6.5 Discussion and conclusion

6.5.1 Spatio-temporal parameters

During Stim OFF, PD patients had significantly (for the p-values and also standard deviations see Table 6-3) less stride velocity than controls (40.5 %h/s vs. 77.4 %h/s) due to significantly shorter stride lengths (46.2 %h vs. 77.1 %h) and significantly longer gait cycle times (1.4s vs. 1.0s). Also, duration of stance (65.7% vs. 59.4%) and double support (31.4% vs. 18.7%) was significantly longer for PD patients as compared to controls. Limp, defined as the difference between initial and terminal double support, was significantly larger in PD patients during Stim OFF than controls (7.2% vs. 1.4%). These results are consistent with the clinical observation of PD gait which is typically characterized by shortened, shuffling steps, reduced speed and difficulty to initiate lower limb movements. These abnormalities are mostly due to the basal ganglia dopamine deficiency-related symptom akinesia, and to a lesser extend rigidity, which are the main determinants of gait impairment in moderate to advanced PD. This is supported by a striking, although incomplete, improvement of these symptoms under levodopa replacement therapy observed in a majority of PD patients, and possibly following STN-DBS, although the latter has been recently the matter of some debate.

Indeed, in this study during Stim ON, STN-DBS significantly improved stride velocity (53.1%h/s vs. 40.5%h/s), stride length (58.5 %h vs. 46.2 %h), stance (61.5% vs. 65.7%) and double support (23.0% vs. 31.4%) but not the gait cycle time which is in agreement with previously reported findings (Ferrarin, Lopiano *et al.* 2002; Krystkowiak, Defebure *et*

al. 2000; Melnick, Radtka *et al.* 2000). Limp, however was not changed significantly. Despite the improvement obtained during Stim ON, all parameters remained significantly different from controls except stance and double support; i.e. gait cycle time (1.2s vs. 1.0s), stride length (58.6 %h vs. 77.1 %h), stride velocity (53.1 %h/s vs. 77.4 %h/s) and limp (4.2% vs. 1.4%). These results confirm that STN-DBS provides a substantial and measurable improvement of most gait parameters. However, according to our data, this benefit appears selective to certain aspects of gait disturbances (stride length and velocity, stance, double support), since other parameters were found unchanged (gait cycle time and limp) between Stim On and Stim OFF situations. These data suggest that these unmodified variables may reflect dopamine-independent features of PD gait, well known examples of which being freezing episodes while ON, festination and kinesia paradoxica.

6.5.2 Segment and joint rotations and angular velocities

On the lower limbs, during Stim OFF, measured parameters showed differences between controls and PD patients. Range of knee flexion (39.4 degree vs. 60.4 degree) was significantly different due to different range of shank rotation (45.6 degree vs. 76.0 degree) but the range of thigh rotation that did not have a significant difference. The reduction of range of knee flexion confirms findings of (Ferrarin, Lopiano *et al.* 2002; Morris, McGinley *et al.* 1999; Zijlmans, Poels *et al.* 1996) and is consistent with the common clinical observation of bent knees in PD patients, which is mostly due to limb rigidity. Also, the peak velocity of shank was significantly lower for the PD patients (225 degree/s vs. 386.3 degree/s). On the upper limbs, PD patients during Stim OFF had a significantly smaller range of rotation of the forearms, namely in yaw axis (10.3 degree vs. 47.6 degree), roll axis (14.0 degree vs. 22.9 degree) and pitch axis (8.4 degree vs. 20.2 degree). This represents the neurophysiological counterpart of the clinical feature of reduced arm swing which is an early sign of akinesia exhibited by PD patients while walking.

STN-DBS improved most of these parameters. During Stim ON, PD patients had a significantly larger range of knee flexion than controls (45.4 degree vs. 39.4 degree) due to both larger thigh and shank rotation. This finding is in agreement with (Ferrarin, Lopiano *et al.* 2002). Peak velocity of the shank was also significantly higher during Stim ON vs. Stim OFF (275 degree/s vs. 225). On the upper limbs however, STN-DBS only significantly improved range of forearm rotation in yaw axis (24.6 degree vs. 10.3 degree). Despite these improvements, PD patients during Stim ON had significantly lower range of knee flexion than controls (45.4 degree vs. 60.4 degree) due to lower thigh and shank rotation which is also in agreement with (Ferrarin, Lopiano *et al.* 2002). Moreover, the peak shank angular velocity is also lower than controls (275.4 degree/s vs. 386.3 de-

gree/s). Also range of forearm rotation in yaw axis was significantly lower in PD patients during ON state compared to the controls (24.6 degree vs. 47.6 degree). However, range of thigh rotation, maximum knee flexion and rotations of forearm in roll and pitch axis was not significantly different from controls during Stim ON.

In summary, based on the data reported in Table IV, it can be inferred from the significant differences found for most, but not all, parameters in Stim ON patients compared to healthy controls that the magnitude of improvement provided by STN-DBS, however significant, is by no mean sufficient to *normalize* the gait in PD.

6.5.3 Correlation between gait parameters and UPDRS

Six different sub-scores defined as u1 to u6 (see Table 6-4) were made based on UPDRS III sub-scores (Table III). Estimated gait parameters were then compared to these sub-scores.

Sub-score	Related symptoms	UPDRS III sub-scores
u1	Bradykinesia	23+24+25+26
u2	Rigidity	22
u3	Tremor	20+21
u4	Gait	29
u5	Gait and Posture	27+28+29+30
u6	Posture	28+30

Table 6-4. UPDRS sub-scores used in calculation of correlation coefficients.

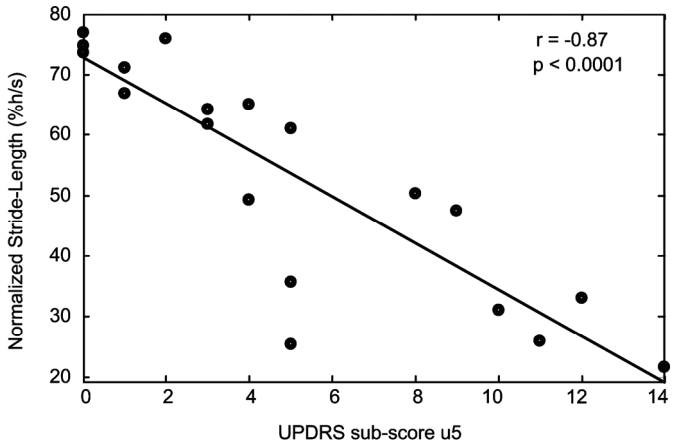


Figure 6-8. Scatter plot comparing UPDRS sub-score u5 and normalized Stride-Length

As seen from Table 6-5, the range of rotation in the Yaw axis of the forearms always has the highest significant correlation with bradykinesia and rigidity sub-scores among the three forearm sensors' axes. Stride-length, stride-velocity and range of shank rotation show a very good correlation with gait sub-score. Figure 6-8 shows a scatter plot of u5 (gait and posture sub-score) and estimated stride-length, where significant and high

correlation was found between a typical estimated outcome and UPDRS. The significance of this correlation was confirmed by using a boot-strapping method (Efron and Tibshirani 1993) where a range of (-0.98, -0.72) was obtained for the 95% confidence interval of correlation coefficient.

Parameter	u1	u2	u3	u4	u5	u6
Gait Cycle Time	N.S.	N.S.	N.S.	0.61	0.65	0.65
Stance	0.48	0.45	N.S.	0.69	0.67	0.64
Double Support	0.48	0.45	N.S.	0.69	0.67	0.64
Limp	N.S.	N.S.	N.S.	0.51	0.49	0.50
Stride Length	-0.68	-0.74	N.S.	-0.90	-0.87	-0.80
Stride Velocity	-0.58	-0.65	N.S.	-0.84	-0.83	-0.79
Shank ROR	-0.64	-0.72	N.S.	-0.88	-0.84	-0.76
Thigh ROR	-0.59	-0.72	N.S.	-0.79	-0.81	-0.78
Range of Knee flexion	N.S.	-0.57	N.S.	-0.68	-0.68	-0.63
Forearm, Pitch axis ROR	-0.47	N.S.	-0.46	N.S.	N.S.	N.S.
Forearm, Roll axis ROR	-0.51	-0.56	N.S.	-0.60	-0.63	-0.55
Forearm, Yaw axis, ROR	-0.71	-0.69	-0.56	N.S.	-0.59	-0.52
Peak Shank angular Velocity	-0.56	-0.63	N.S.	-0.81	-0.78	-0.72

Table 6-5. Coefficient of correlation between UPDRS sub-scores and gait parameters. p-values more than 0.05 were considered as Non Significant (N.S.). ROR stands for *Range of Rotation*

6.5.4 Validations

Two validation studies have been performed. In the first study the sensitivity of the algorithm in detection of gait and temporal parameters has been assessed and in the second one the error of the system in comparison to reference systems has been calculated.

For the first study using portable video camera, after each session a reviewer counted the actual gait cycles in each walking trial. The results were compared to the output of the algorithm. Despite the sever abnormalities during Stim OFF period, the algorithm could detect gait cycles and related gait events (IC and TC) with very high sensitivity (more than 96%) and with PPV more than 98%.

In the second study, we used the data recorded with Physilog® and a reference system based on a motion-capture system (Elite) to find the accuracy of the algorithm in detection of gait temporal and spatial parameters. For this validation, however, we only used the gait data from normal subjects and pathological gait. The estimated error (see Table 6-1), considering the 200Hz sampling rate of the system, was around two samples for *IC* and 5 samples for *TC*. The relative error in estimation of the gait cycle time was 2% and for Stride-Length and Stride-Velocity were less than 8%. These results have been proved

to be accurate enough to show significant differences between Stim ON and Stim OFF states of the PD patients.

6.5.5 Comparison to other ambulatory systems

Our gyroscope based method has several advantages over other ambulatory systems. Unlike some of the foot-switch or other pressure sensitive devices, no special footwear is needed which is more comfortable for long term monitoring. Also the available foot-switch based devices limit the gait analysis to the temporal parameters (Lackovic, Bilas *et al.* 2000; Pataky, Faravel *et al.* 2000) while our method can provide both temporal and spatial parameters. The same thing is true for many of the accelerometry methods as they do not provide spatial parameters (Aminian, Rezakhanlou *et al.* 1999).

The idea of using gyroscopes to assess gait has been also used in different studies (Aminian, Najafi *et al.* 2002; Tong and Granat 1999). Despite the similarities, our new method uses a totally different signal processing approach from (Aminian, Najafi *et al.* 2002): While we kept using the same model and sensors (only sensors on the forearms has been added), more traditional IIR and FIR filters were used instead of the Wavelet approach. The results of the validations show that compared to the previous method, the new method has higher precision (lower S.D. of error in Table 6-1) for spatio-temporal parameters estimation, higher accuracy (mean in Table 6-1) for temporal event detection, while slightly lower accuracy is observed for spatial parameters. In particular, the systematic error in detection of *IC* and *TC* has been reduced by a large margin (31.0% and 56.1% reduction respectively). As a result, the systematic error in detection of stance is now 69.3% smaller. Also, the standard deviation of error in estimation of *IC* is now 12.5%, of *TC* is 8.2% and of stance is 5.7% reduced. Moreover, the standard deviations of errors in estimation of stride length and stride velocity are now reduced by 11.5% and 8.4%, respectively. These improvements have been achieved while the new method performed the analysis almost nine times faster than the pervious method. Also, the new algorithm specifically addresses the cases that *IC* or *TC* can not be correctly detected, in order to prevent the propagation of error to the next gait cycles.

6.5.6 Conclusions

An ambulatory method capable of quantifying a number of parameters related to the gait of PD patients has been introduced. The results can be summarized as follows:

- Using minimal attachment sites and without any need for per-person calibrations, the system could successfully estimate gait parameters with a high degree of accuracy.

- The results confirmed previous findings that were obtained using sophisticated gait analysis methods restricted to gait labs while preserving the possibility of an ambulatory monitoring of the subjects.
- Together, the results form sections 6.5.1 and 6.5.2 support the method described in this study as a sensitive tool to assess subtle changes of gait parameters over time, and to distinguish physiological from parkinsonian gait, even in optimally STN-DBS treated PD patients where the gait is frequently reported as normal.

The method presented here, provides a simple and effective way of ambulatory gait analysis in PD patients. We therefore believe that by using units like ASUR (see section 3.4) instead of Physilog, with increased memory capacity and battery stamina, the proposed system can be used in long-term monitoring; to assess gait in PD patients in their daily life.

Chapter 7 Gait analysis of free moving patients

Abstract

Background—Previously, we have proposed a gait analysis method based on four sensor sites on the lower limbs and had evaluated it in a controlled study. Reducing the complexity of the setup helps to make the system more comfortable to use by PD patients even in advanced stages of the disease. As such, reducing the number of sensor sites needed for gait analysis can improve the ease of use of the system for the patients.

Objectives—Design, validation and clinical evaluation of a gait analysis method based on only two sensor sites on the shanks. The method should be able to estimate all of the gait parameters that the previous method provided, without a significant sacrifice of the accuracy. The system should be evaluated by comparing the outcomes to a reference camera based system and also by using the system to record and analyze the gait of a group of free moving PD patients for several hours.

Method—The angles of the thighs and the shanks were represented using a parametric representation based on Fourier series. The parameters that describe the curve of the thigh angles were estimated using the parameters describing the shank angles. The thigh angle curves were reconstructed from the parametric representation so that the previous gait analysis algorithm that used a two-segment model for gait could be used to estimate the spatial parameters of gait. The accuracy of system was evaluated by comparing the outcomes to those of the previous method and also by comparing to a camera based reference system. The method was used to record and analyze gait on group of free moving PD patients for several hours and the estimated gait parameters are statistically compared to their UPDRS scores.

Results—We have found that by using only six Fourier series harmonics, thigh angles can be reconstructed by our prediction method with good accuracy. The error in estimation of thigh angles comparing to values directly measured by a gyroscope was -2.0 ± 5.0 degrees (mean ± S.D.) for the healthy controls, -0.9 ± 5.1 degrees for the PD patients during ON state and 0.5 ± 6.3 degrees for the PD patients during OFF state. Comparing to the camera based system, the estimated stride-length using the new method had a

slightly higher error than the previous method (*2.4 ± 9.3 cm vs. -3.4 ± 8.5 cm*) while the error was better than a system using three gyroscopes (*2.4 ± 9.3 cm vs. -2.8 ± 10.3 cm*).

For the free moving PD patients, comparing to the visual observation, our system had a sensitivity of 95.0% and a specificity of 99.8% in detection of gait which were close to the limit of the accuracy of the visual observation itself. The estimated gait parameters for the free moving PD patients showed a significant correlation to the UPDRS gait and posture sub-score (e.g. stride-velocity with $\rho = -0.46$ and $p < 0.001$).

Main contributions—A new ambulatory gait analysis system has been proposed that needs only one gyroscope on each shank to estimate spatio-temporal parameters of gait with good accuracy over a large range of different walking speeds. Using this system, gait analysis of PD patients for several hours while they are freely doing daily activities is possible.

7.1 Introduction

In chapter 6, an ambulatory gait analysis system has been introduced and evaluated. That system was based on four sensor sites on the lower limbs (one uni-axial gyroscope on each shank and thigh). In this chapter, a new system is presented that can provide all of the spatio-temporal parameters of gait calculated by the first system with just two sensor sites: one on each shank.

Reduction of the number of sensor sites from four to two had several advantages: reduction of the total weight of the system, reduction of the time needed to install the system on the body and increase in the reliability of the system (by reducing the number of the components of the system). The importance of these improvements becomes more evident by considering that we already have three other sensor sites on the body for other purposes (the sites on the trunk and forearms). Moreover, based on the feedbacks from the patients we noticed that the sensors fixed on the thighs using elastic bands were not exactly the most convenient part of the system for long-term measurements.

The downside of removing the sensors on the thighs was that we no longer could measure the thigh angles during gait that were imperative to estimate the spatial parameters of the gait using our gait model. Gait is rhythmic movement where flexion-extension of lower limbs are limited and controlled both by the neural system and the bio-mechanical limitations of the joints. Therefore we can assume a certain level of *relationship* between the movements of thigh and shank. In our approach, we propose a new method that enables us to *predict* movements of the thighs based on the movements of the shanks.

We have preformed three studies. In the first study, the prediction coefficients needed by the system are calculated and the outcome of the new system is compared to the four sensors system in a small population of PD patients and control subjects. In the second study, the accuracy of the system is evaluated by comparing it to a camera based system and finally in the third study, the system has been used to automatically detect and analyze gait in a group of PD patients moving freely for several hours.

7.2 Methods

7.2.1 Measurement system and experimental setup

The data from three different studies have been used in this chapter. The data from the *controlled study* (see chapter 2.3) was used in the first study to train the thigh predictor and later, to evaluate the error of the algorithm in calculating the thigh angles. 10 PD patients and 10 normal subjects participated in the first study. Subjects carried the first prototype of MAS (see section 3.4). This system included four uni-axial gyroscopes on the lower limbs (see Figure 7-1a). Previously, (Aminian, Najafi *et al.* 2002) has proposed a gait analysis system based on three sensors sites, one on the right thigh and two on the shanks (see Figure 7-1b). The accuracy of these two configurations has been compared to our new proposed configuration (Figure 7-1.c). In the first study, subjects followed a protocol of typical daily activities and performed several walking trials in different speeds (see section 2.3).

In the second study, accuracy of the new method has been evaluated by using a database of pre-recorded gait cycles and comparing to the outcomes of a camera-based reference system (Elite) (Andreeva, Ivanova-Smoielnskaya *et al.* 1985). This database included 229 recorded normal and pathological gait cycles from a group of 15 subjects. More details can be found in the section 6.3.2. The measurement system was similar to the previous study: four uni-axial gyroscopes attached on the shanks and thighs and a Physilog® data-logger.

Finally, 12 PD patients participated in the third study. They consisted of a group of seven males and four females. Each measurement took up to five hours in ambulatory conditions where patients were moving freely and performed activities they liked. An UPDRS test was performed at the beginning of the measurement and then at least once every one hour. Patients started with STN ON, which was subsequently turned OFF for three hours and ON again for the last hour. An observer followed the patients during the measurement and using a portable computer and a data-logging program made a time tagged log of the activities of the patients. These logs were used to assess the sensitivity and speci-

ficity of automatic gait detection. To find the limits of the accuracy of the logs, for six patients two observers prepared two separate logs in parallel that were later compared to each other. More details about patients and experiment protocol can be found in section 2.5, the *long-term* study. The measurement system used in this study was the second prototype of the ASUR system (see section 3.4). Two sensing units were used and each one included a single uni-axial gyroscope.

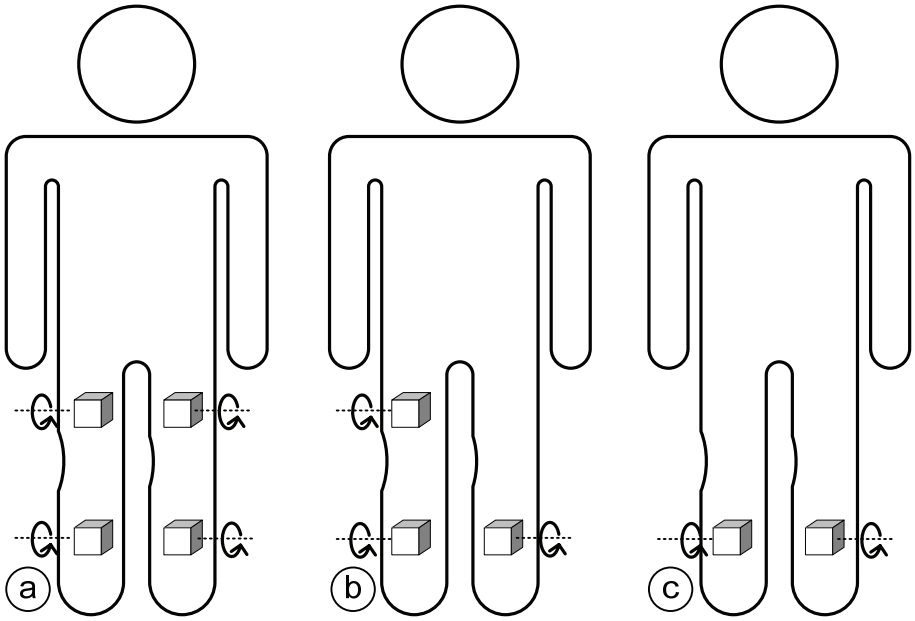


Figure 7-1. The configuration of the sensors. a) Our four sensors gait analysis system included two sensors on the shanks and two sensors on the thighs. b) A three sensors system based on the configuration suggested by Aminian et al (Aminian, Najafi *et al.* 2002) c) The suggested configuration based on using only two sensors on the shanks, in this chapter.

Previously in section 6.4.4, we showed that the estimated gait parameters in a controlled study had a high correlation to the UPDRS motor scores. In this study we investigated to see if in unfavorable conditions (i.e. considering the limitations of the system, gait model and having free moving patients) the estimated gait parameters could yet show any significant correlation to the UPDRS motor score.

7.2.2 Gait model

The biomechanical model of the gait used in this method was the same as to the previous algorithm (see section 6.2.4). It was based on a double pendulum model for the swing and an inverse double pendulum model for the stance period. Figure 7-3 shows the details of this model. The hip was considered as a simple joint, connecting the two thighs. Leg had two rigid segments, shank and thigh. Stride-length was estimated by

calculating the movement of the body during the swing phase of the gait (*d1* + *d2*) and the movement during the stance (*d3*).

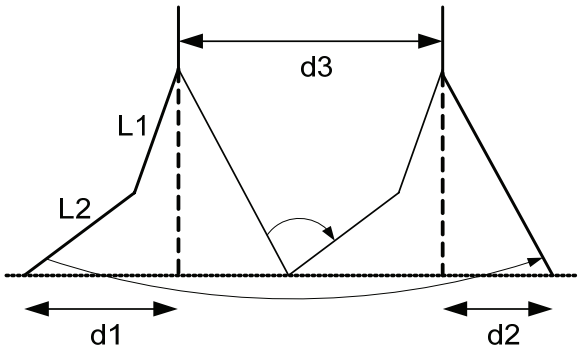


Figure 7-2. Our gait model based on two segments for the lower limbs.

To solve this model, the length of the segments (*L1* and *L2*) and the range of rotation of the shank and thigh segments during swing and stance phases were needed. In our new proposed algorithm, as we only had the shank sensors, the range of rotation of the thigh during swing and stance phases were unknown; hence the model could not be solved. To overcome this problem we used a prediction method to estimate thigh angles based on the shank angles and kept using the existing gait model.

7.2.3 Overview of the method

Figure 7-3 shows the flowchart of the algorithm. Those parts of the algorithm related to the detection of the gait events and estimation of the temporal gait parameters are identical to the previous method (see section 6.3.3 for the details). The important change in the new algorithm was removal of the thigh sensors and instead, prediction of the thigh angles based on the shank angles.

7.2.4 Predicting thigh angles from the shank angles

The main hypothesis behind the method was the possibility of predicting the thigh angles only based on the known shank angles during the gait. The method was based on *parametric representation* of the shank angle curves during *each gait cycle* and to use a transformation matrix, to find the corresponding parameters describing the thigh angle curve.

Figure 7-4a shows a typical angular velocity signal during walking for the case of a PD patient. As mentioned earlier in the section 6.2, a gait cycle is defined as the period of the time between two consecutive Initial Contacts (*IC*) of the right foot. In the Figure 7-4a the start and end of a gait cycle is marked. By integration of this signal, the shank angle

could be found (see Figure 7-4b). The initial value needed for the integration was unknown and as finding absolute angles was not important for our application, a value of zero was used. Next, the curve representing the relative angle of the shanks for each gait cycle was separated (see Figure 7-4c). Finally, by infinite repetition of this pattern, a period signal was made (see Figure 7-4d).

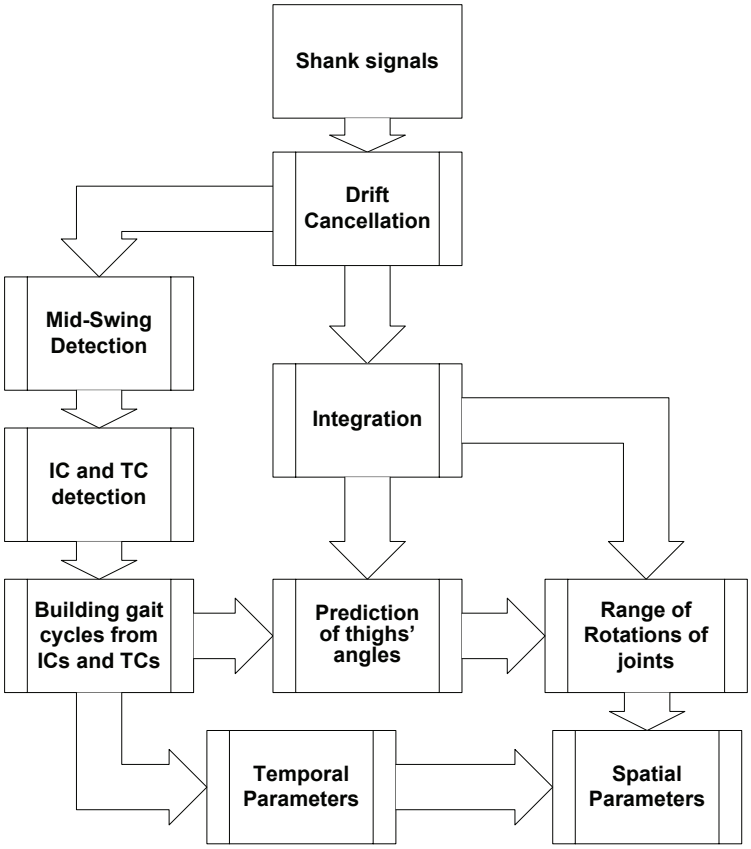


Figure 7-3. The flowchart of the gait analysis algorithm.

This periodic signal, could be parametrically represented using *Fourier series* (Oppenheim and Shafer 1998): calling this *N-periodic* periodic shank angle signal for the right foot θ_{SR}, it could be represented by a linear combination of complex exponential signals

$$e^{j0\omega_0 n} = 1, e^{j\omega_0 n}, e^{j2\omega_0 n}, \cdots, e^{j(N-1)\omega_0 n} \tag{6.17}$$

as

$$\theta_{SR}[n] = \sum_{k=0}^{N-1} a_k e^{jk\omega_0 n} \tag{6.18}$$

where j stands for the square root of *-1* and ω_0 is the *discrete-time fundamental frequency*: $\omega_0 = 2\pi/N$.

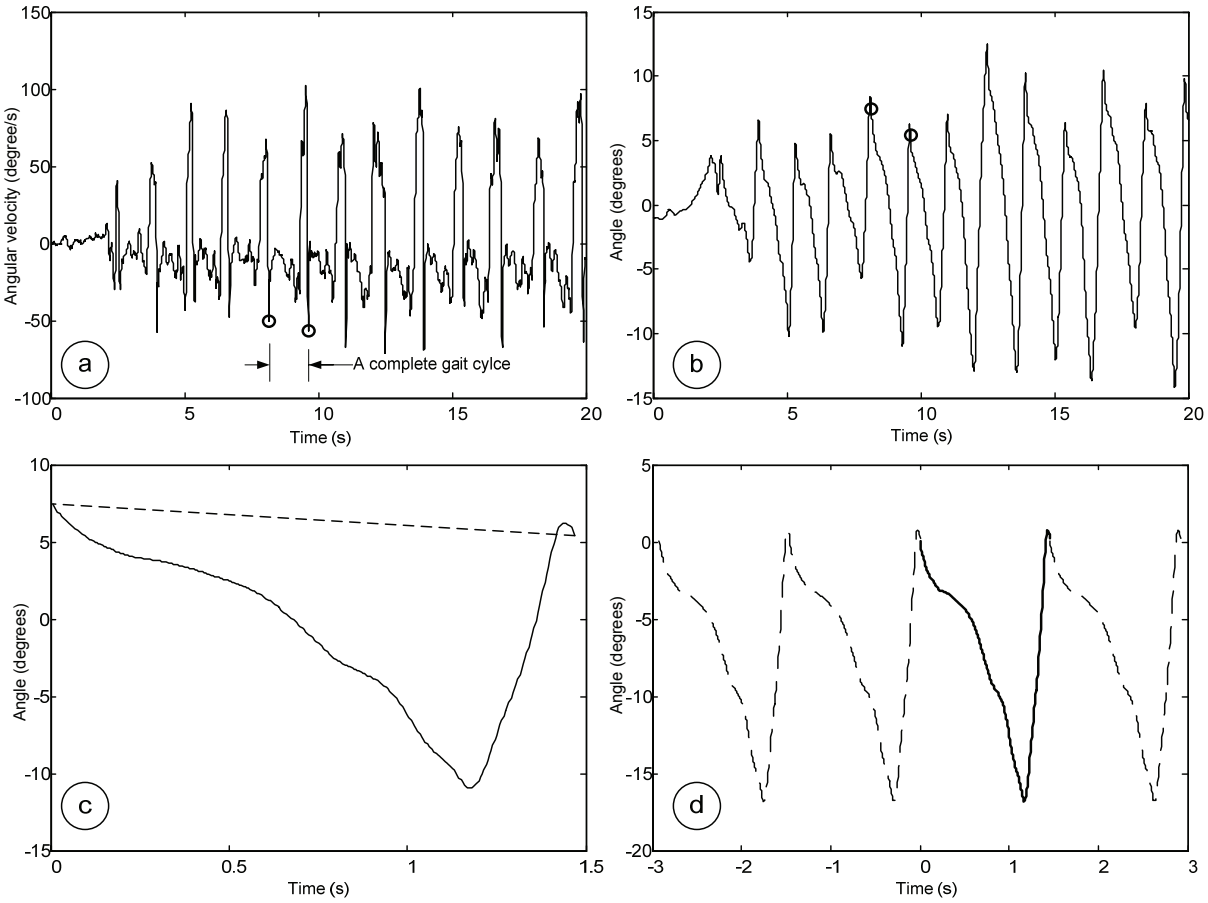


Figure 7-4. a) A typical pattern of the shank angular velocity during a walking trial of a PD patient. The small circles that correspond to two consecutive *Initial Contact* events, designate the start and end of a gait cycle b) Integration of the shank angular velocity, produces the relative angle of the shank. c) The pattern of the gait angle in the designed gait cycle period. Notice the slight tilt of the pattern. d) By repeating the pattern on the two sides, a periodic signal is produced.

The complex coefficients $a_0, a_1, \ldots, a_{N-1}$ could be calculated using this formula:

$$a_k = \frac{1}{N}\sum_{n=0}^{N-1}\theta_{SR}[n]e^{-jk\omega_0 n} \quad ,k = 0,1,\ldots,N-1 \tag{6.19}$$

As shown in the Figure 7-4c, it was possible that the value of the shank angle (or the thigh angle) at the start and end of a gait cycle were not equal. If the curve was repeated with no modifications, the difference between these values would result in a discontinuity at the beginning and end of each period of period signal of Figure 7-4d.

The presence of such discontinuities could produce overshoots or undershoots in the signal reconstructed using the Fourier harmonics due to the famous Gibbs phenomenon (Jerri 1998). To avoid this problem, for each gait cycle, the angle curves were corrected by

removing the trend line passing through the start and the end of the curve (see Figure 7-4c). To *de-trend* the signal, the slope of the trend line was calculated:

$$m_{SR} = \frac{\theta_{SR}[N] - \theta_{SR}[1]}{N-1} \tag{6.20}$$

The offset of the trend line was not important for our application as later we'd only use the range of the rotations and not the absolute values of the angles.

The number of the a_k coefficients needed to fully describe the angle patterns depends on the N, the number of samples in each gait cycle. By keeping only a fixed and small number (n) of the first coefficients and also the slope of the trend line (m_{SR}), an approximation of the curves could be represented using $<a_1, a_2, \dots, a_n, m_{SR}>$ parameters for the right shank. Similar method was used to find the $<b_1, b_2, \dots, b_n, m_{SL}>$ parametric representation of the left shank's angle curve for each gait cycle. As for our application we only needed relative angles and not the absolute angles the mean values (DC component) of the shank angles during the gait cycles, a_0 and b_0 were not needed in our list of the parameters.

In order to predict thigh angles from shank parameters, we considered the prediction matrixes X_R and X_L that were used to predict thigh parametric representation ($<c_i, m_{TR}>$ and $<d_i, m>$ for the right and left thighs, respectively) from the shank parameters. This way, for each gait cycle we could estimate the right thigh parameters from the shank parameters:

$$\langle a_1, a_2, \dots, a_n, m_{SR}, b_1, b_2, \dots, b_n, m_{SL} \rangle \times X_R = \langle c_1, c_2, \dots, c_n, m_{TR} \rangle \tag{6.21}$$

In the same way, the left thigh parameters could be calculated:

$$\langle a_1, a_2, \dots, a_n, m_{SR}, b_1, b_2, \dots, b_n, m_{SL} \rangle \times X_L = \langle d_1, d_2, \dots, d_n, m_{TL} \rangle \tag{6.22}$$

The prediction matrixes X_R and X_L were calculated using recorded signals of seven normal control subjects and seven PD patients form the *controlled study*. As a reminder, in this study each subject had several walking trials with normal and fast speeds and PD patients did the test twice, once with STN-DBS turned ON and once with STN-DBS turned OFF; thus providing a large variety of the stride lengths and stride velocities.

To calculate X_R and X_L matrixes, for each of the m gait cycles of the training data, $<a_k, m_{SR}>$ and $<b_k, m_{SL}>$ parameters describing the shank curves and $<c_k, m_{TR}>$ and $<d_k, m_{TL}>$ describing the real thigh curves were calculated. X_R and X_L were the least squares solution (Anderson, Bai *et al.* 1999) to these over-determined linear systems of equations:

$$\begin{pmatrix} a_{11} & \cdots & a_{1n} & m_{SR1} & b_{11} & \cdots & b_{1n} & m_{SL1} \\ \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ a_{1m} & \cdots & a_{mn} & m_{SRm} & b_{1n} & \cdots & b_{mn} & m_{SLm} \end{pmatrix} \times X_R = \begin{pmatrix} c_{11} & \cdots & c_{1n} & m_{TR1} \\ \vdots & \ddots & \vdots & \vdots \\ c_{m1} & \cdots & c_{mn} & m_{TRm} \end{pmatrix} \quad (6.23)$$

$$\begin{pmatrix} a_{11} & \cdots & a_{1n} & m_{SR1} & b_{11} & \cdots & b_{1n} & m_{SL1} \\ \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ a_{1m} & \cdots & a_{mn} & m_{SRm} & b_{1n} & \cdots & b_{mn} & m_{SLm} \end{pmatrix} \times X_L = \begin{pmatrix} d_{11} & \cdots & d_{1n} & m_{TL1} \\ \vdots & \ddots & \vdots & \vdots \\ d_{m1} & \cdots & d_{mn} & m_{TLm} \end{pmatrix} \quad (6.24)$$

X_R and X_L matrixes were calculated only once using the mentioned training data.

The curves of thigh angles could be reconstructed using the respective parameters of the right and left thigh, for each gait cycle of the length of N samples:

$$\theta_{TR}[m] = \sum_{k=0}^{n-1} c_k e^{jk\omega_0 m} + m_{TR}.m, \quad m = 1...N \quad (6.25)$$

$$\theta_{TL}[m] = \sum_{k=0}^{n-1} d_k e^{jk\omega_0 m} + m_{TL}.m, \quad m = 1...N \quad (6.26)$$

To find the suitable number of the Fourier series coefficients, different values of n between 2 to 12 were used, X_R and X_L matrixes were calculated using the training data and the error in prediction of the thigh angles based on the shank angles were evaluated using the data of the remaining three normal and three PD patients. For each case, the mean and standard deviation of the error in estimation of the *relative thigh angle* (θ_{thigh}), the *range of the rotation of thigh* during the gait cycle (ROR_{GC}), *range of rotation of thigh during the stance phase* (ROR_{ST}), *range of the rotation of the thigh during the swing phase* (ROR_{SW}), stride length and stride Velocity were calculated.

To evaluate the outcomes, the gait parameters estimated using this method have been compared to the outcomes of the previous system based on four gyroscopes. For the evaluations, we used the recorded data of the remaining three controls and three PD patients that were not used for training (i.e. calculating X_R and X_L matrixes).

7.2.5 Comparison to the reference, camera based system (Elite)

The value of four spatio-temproal parameters of gait provided by the Elite system for 229 gait cycles has been compared to the results estimated using the new algorithm. The error in estimating range of the rotation of the thigh (ROR_{thigh}), range of the rotation of the knee (ROR_{knee}), stride length and Stride velocity in comparison to the reference system has been calculated.

Using the same dataset, the errors of three other methods were also calculated:

- Our previous method based on four gyroscopes on the lower limbs (see chapter 6).

- A method based on two gyroscopes on the shanks and one gyroscope one the right thigh with an assumption of equal ranges of thigh movements (Aminian, Najafi *et al.* 2002).
- An alternative method using only two gyroscopes on the shanks with a simpler, one segment gait model.

The third method used a compass-like gait model. In this model the lower limbs were considered as a rigid segment connected at the hip joint. By finding the range of the rotation of the shank during the swing phase of the gait (θ_{shank}), the stride length could be estimated:

$$d = l\sqrt{2 - 2\cos\theta_{shank}} \tag{6.27}$$

Where l stands for the length of the segment (from hip to ankle) and d stands for the stride length. This model and our proposed model addressed the same problem, missing thigh angles, with two different approaches: in our proposed method we tried to estimate the missing parameters based on other available data while the alternative method tried to drop the missing parameters by simplifying the gait model.

7.2.6 Statistical analysis

Correlation between gait and posture sub-scores of UPDRS motor section (including sub-scores 27, 28, 29 and 30) and the estimated gait parameters were calculated using Spearman's rank correlation. For each walking period, the mean values of the parameters were considered. Each PD patient had several walking periods, hence the simple rank correlation between gait parameters and the UPDRS sub-score (ρ_{xy}) included both the effect of the parameter and the effect of repeated measurements. To solve this problem, for each subject the mean value of each gait parameter for the whole measurement period was also calculated. The patients were ranked between one to 12 (number of patients) for each gait parameter and the correlation between the rank of the patient and the UPDRS sub-score (ρ_{yz}) and also correlation between rank of the patient and value of the parameters (ρ_{xz}) were calculated to finally let us remove the effect of multiple walking periods from the correlation between gait parameters and UPDRS sub-score (ρ) using Spearman's partial rank correlation (Blalock 1961):

$$\rho = \frac{\rho_{xy} - \rho_{xz} \cdot \rho_{yz}}{\sqrt{(1-\rho_{xz})^2 + (1-\rho_{yz})^2}} \tag{6.28}$$

The average value of the spatio-temporal parameters of gait and ranges of the angles of thigh and shank of the PD patients during the period of Stim ON and Stim OFF were calculated. Wilcoxon's non-parametric paired test, the sign-rank test, was used to test if

the differences between the estimated parameters in the two groups were statistically significant. To calculate the accuracy of the gait detection algorithm, the periods of walking recorded by the observer in the time-tagged logs were compared to the periods of the walking detected by the algorithm. *Sensitivity*, *specificity*, *positive predictive value* (PPV) and the *negative predictive value* (NPV) were the calculated statistics to assess the accuracy.

7.3 Results

7.3.1 Estimating thigh angles from shank angles

Figure 7-5 shows a typical outcome of the algorithm. For three values of n (2, 4 and 6) the prediction matrixes X_R and X_L were calculated using the training data, and have been used to reconstruct thigh angle of in gait cycle of a subject out of the training data. The graph shows that as the number of Fourier harmonics increased, the similarity of the reconstructed thigh to the reference data increased.

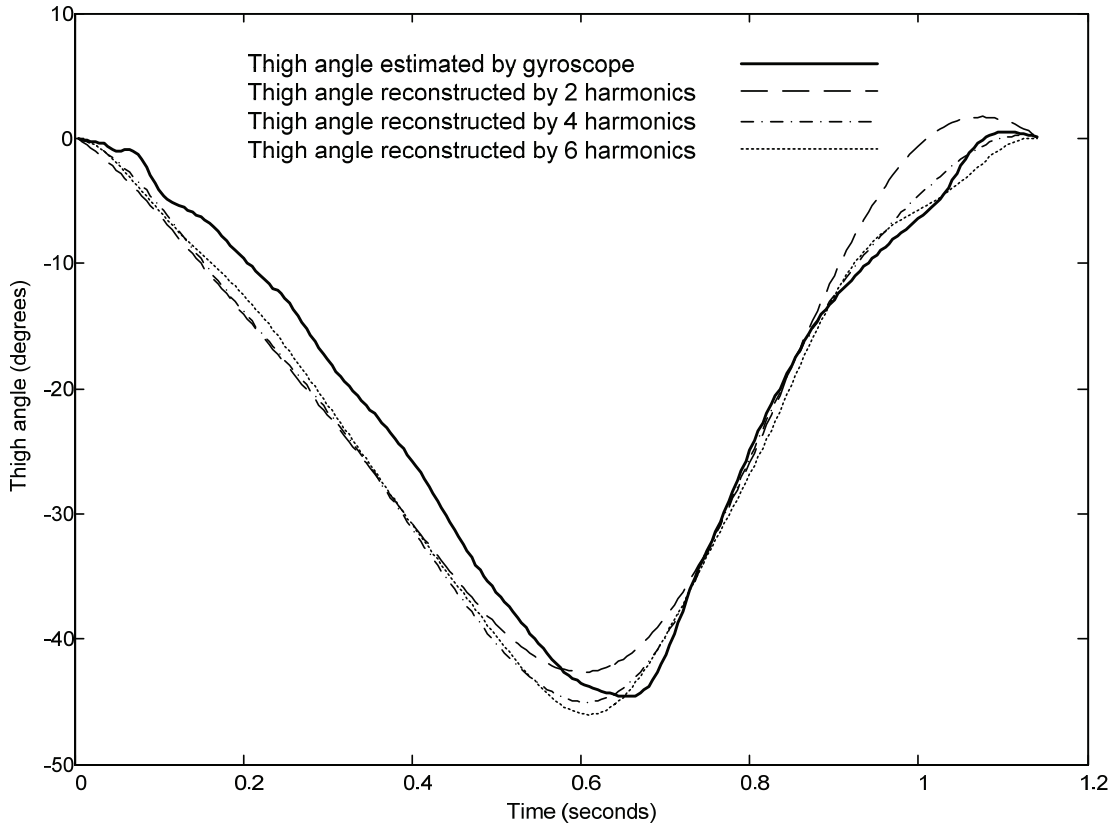


Figure 7-5. Results of estimating thigh angle from shank angles for a typical case not included in the training set.

7.3.2 Results of the controlled study

In total, 1666 gait cycles (including 615 gait cycles of the seven controls, 545 gait cycles of seven PD patients in the OFF and 506 gait cycles of the same seven PD patients in the ON state) were used to calculate the prediction matrixes X_R and X_L. To evaluate the effect on selection of different values of n, number of Fourier harmonics, 887 remaining gait cycles (including 295 gait cycles of three controls, 267 gait cycles of three PD patients in OFF and 325 gait cycles of the same three PD patients in ON state) were used to evaluate the error in prediction of spatial gait parameters and thigh angles.

n	θ_{thigh} (degrees)	RoR_{GC} (degrees)	RoR_{ST} (degrees)	RoR_{SW} (degrees)	Stride-Length (cm)	Stride Velocity (cm/s)
2	1.1 ± 6.6	-3.4 ± 4.3	0.8 ± 7.6	-0.9 ± 7.8	2.7 ± 8.1	3.6 ± 6.4
3	0.2 ± 6.2	-2.2 ± 3.9	0.4 ± 7.0	-0.8 ± 7.7	3.0 ± 7.4	3.6 ± 6.3
4	0.0 ± 6.2	-2.2 ± 4.0	0.0 ± 7.1	-0.4 ± 7.9	3.0 ± 7.2	3.6 ± 6.2
5	-0.6 ± 6.2	-1.3 ± 4.0	-0.5 ± 7.0	0.0 ± 7.7	3.3 ± 7.4	3.8 ± 6.3
6	-0.7 ± 5.7	-1.3 ± 3.7	-0.2 ± 6.6	-0.2 ± 7.5	2.7 ± 6.9	3.2 ± 6.1
7	-0.7 ± 5.9	-1.5 ± 4.2	-0.1 ± 6.6	-0.3 ± 7.4	2.1 ± 7.0	2.6 ± 6.2
8	-0.6 ± 5.9	-1.7 ± 4.3	0.2 ± 6.5	-0.7 ± 7.5	1.6 ± 7.3	2.2 ± 6.5
9	-0.9 ± 5.9	-1.5 ± 4.2	-0.0 ± 6.5	-0.5 ± 7.5	2.0 ± 7.5	2.6 ± 6.8
10	-0.7 ± 6.0	-1.4 ± 4.2	-0.1 ± 6.6	-0.4 ± 7.8	2.1 ± 7.7	2.7 ± 6.9
11	-0.8 ± 6.0	-1.2 ± 4.2	-0.3 ± 6.6	-0.2 ± 7.7	2.1 ± 7.7	2.7 ± 6.8
12	-0.8 ± 5.9	-1.4 ± 4.4	-0.0 ± 6.6	-0.5 ± 7.7	1.7 ± 7.6	2.3 ± 6.8

Table 7-1. Error of estimation of thigh angles and spatial parameters (values in Mean in ± S.D. format) in the two sensors system in comparison to the four sensors system for different values of the number of Fourier harmonics (n).

Table 7-1 shows the mean and standard deviation of the error (difference between the two systems) for different values of n. The results were rather close. The value of $n = 6$ had one of the lowest error figures for all parameters. For the rest of the study, we have used the prediction matrixes X_R and X_L calculated for the case $n = 6$.

Figure 7-6 shows a comparison of the estimated stride length of our previous method based on four gyroscopes and the new algorithm based on two gyroscopes. Six Fourier coefficients were used in this case to predict thigh angles. The results show a very good agreement between the results of the two methods over a wide range of stride lengths.

The estimated error in predicting the thigh angle (θ_{thigh}) for the three control subjects not included in the training set was -2.0 ± 5.0 degrees (mean ± S.D.) and for the three PD patients not included in the training set during ON and OFF state were -0.9 ± 5.1 and 0.5 ± 6.3, respectively. Table 7-2 shows the error (estimation – reference) and the value of the reference for the estimated ranges of thigh angles and spatial parameters for the case $n = 6$, for each of the groups of controls, PD patients with Stim ON and OFF.

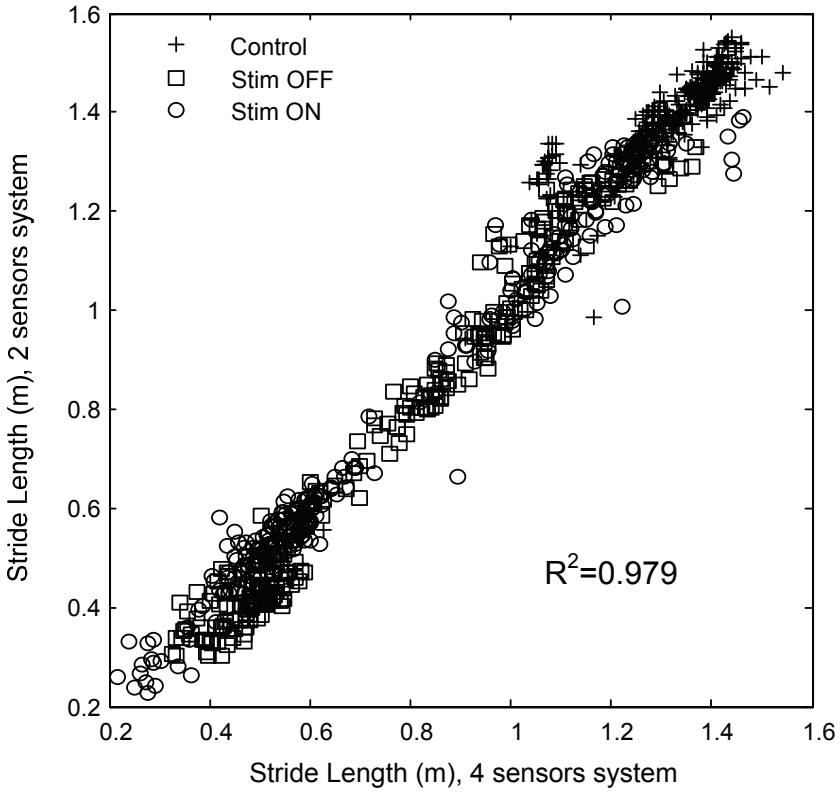


Figure 7-6. Comparison between the Stride-Length estimated using the four sensors system vs. the system with two sensors and thigh prediction method. Six Fourier harmonics (n = 6) was used to predict the thigh angles from shank angles.

Group		RoR_{GC} (degrees)	RoR_{ST} (degrees)	RoR_{SW} (degrees)	Stride-Length (cm)	Stride Velocity (cm/s)
Control	Error	-1.7 ± 3.6	-1.3 ± 4.9	1.4 ± 6.3	7.6 ± 5.6	7.9 ± 5.7
	Reference	46.7 ± 5.3	-38.4 ± 4.8	38.2 ± 5.3	132.4 ± 11.6	135.2 ± 22.5
Stim-ON	Error	-1.1 ± 3.3	0.1 ± 6.5	-0.7 ± 7.1	1.6 ± 5.4	1.6 ± 4.8
	Reference	30.5 ± 8.0	-21.6 ± 6.6	21.5 ± 6.9	78.6 ± 33.7	70.2 ± 40.1
Stim-OFF	Error	-1.1 ± 4.2	0.6 ± 8.1	-1.3 ± 8.9	-1.3 ± 6.8	-0.0 ± 4.6
	Reference	27.3 ± 7.2	-19.3 ± 5.8	19.2 ± 5.7	75.8 ± 28.3	59.8 ± 38.2

Table 7-2. The error in estimation of thigh angles and spatial parameters for the three groups of controls, PD patients with Stim ON and OFF. The four sensors system was used as the reference. (values in Mean in ± S.D. format)

7.3.3 Comparison to the reference, camera based system (Elite)

The error of the four gait analysis methods in calculating four different gait parameters comparing to the Elite system are presented in Table 7-3. The new algorithm's errors are slightly higher than the method based on four sensors and slightly better than the method based on three sensors. The results also shows that the method of using two sensors and a simplified gait model (one segments for the lower limbs) highly under-estimated the stride-length and stride velocity and was very different in comparison to all other methods.

Parameter	Four sensor method	Three sensors method	New algorithm	Two sensors method with single segment gait model
RoR_{thigh} (degrees)	-3.1 ± 4.4	-3.4 ± 6.2	-2.1 ± 5.3	N.A.
RoR_{knee} (degrees)	3.8 ± 9.6	N.A.	-5.5 ± 11.2	N.A.
Stride length (cm)	-3.4 ± 8.5	-2.8 ± 10.3	2.4 ± 9.3	-27.5 ± 8.6
Stride velocity (cm/s)	-2.6 ± 7.6	-2.1 ± 9.1	2.7 ± 8.3	-23.9 ± 7.9

Table 7-3. Error of four different algorithms compared to the reference system (values in Mean in ± S.D. format). Where an algorithm could not provide a parameters, the value was marked as Not Available (N.A.).

7.3.4 Gait analysis of free moving patients

The walking periods of the PD patients were automatically detected using the algorithm presented in section 6.3.3 and were analyzed using the new algorithm. Table 7-4 shows the results of the assessment of the accuracy of the gait detection algorithm for free moving PD patients.

Parameter	Algorithm vs. Observer	Observer vs. Observer
Sensitivity	95.3%	93.9%
Specificity	99.8%	99.8%
Positive Predictive Value (PPV)	95.9%	95.7%
Negative Predictive Value (NPV)	99.4%	99.7%
Prevalence	5.6%	5.6%

Table 7-4. Accuracy of the gait detection algorithm for the case of free moving PD patients in comparison to visual observation.

As the patients were free to move on will, the number of walking periods, the walking distance and their speeds varied. Some of the walking periods were short and inside the room and some were not in a straight line. For each detected walking period, the first and the last gait cycles were discarded and the average and stand deviation of the gait parameters for the remaining gait cycles were calculated.

Figure 7-7 shows a typical outcome of the algorithm. The average stride length of each walking period of a PD patient measured during more than four hours of the recordings is presented. The gait and posture sub-score of the UPDRS is also displayed.

Table 7-5 shows the summary of the results obtained in gait analysis of free moving PD patients. The results show that for some of the parameters estimated by the system, significant differences between Stim ON and Stim OFF could be found. During periods of walking, PD patients with Stim ON had significantly higher *peak shank angular velocity* (238.4 vs. 198.4 degrees/s), higher *stride velocity* (77.1 vs. 58.1 cm/s), shorter *stance* periods (62.4% vs. 67.5%) and shorter *double support* (24.9% vs. 34.9%) which are in agreement with the findings of gait analysis in controlled conditions in our previous study (chapter 6) and those of the other groups (Ferrarin, Lopiano *et al.* 2002; Krystko-

wiak, Defebure *et al.* 2000; Melnick, Radtka *et al.* 2000; Morris, McGinley *et al.* 1999; Zijlmans, Poels *et al.* 1996). Two other parameters i.e. *limp* and *gait cycle time* were not significantly different between Stim ON and OFF conditions (similar to our previous findings in chapter 6). However, although the remaining parameters i.e. *range of rotation of thigh and shank*, *range of flexion-extension of knee* and *stride length* showed differences between Stim ON and OFF in the same direction as previous findings, the differences were not statistically significant.

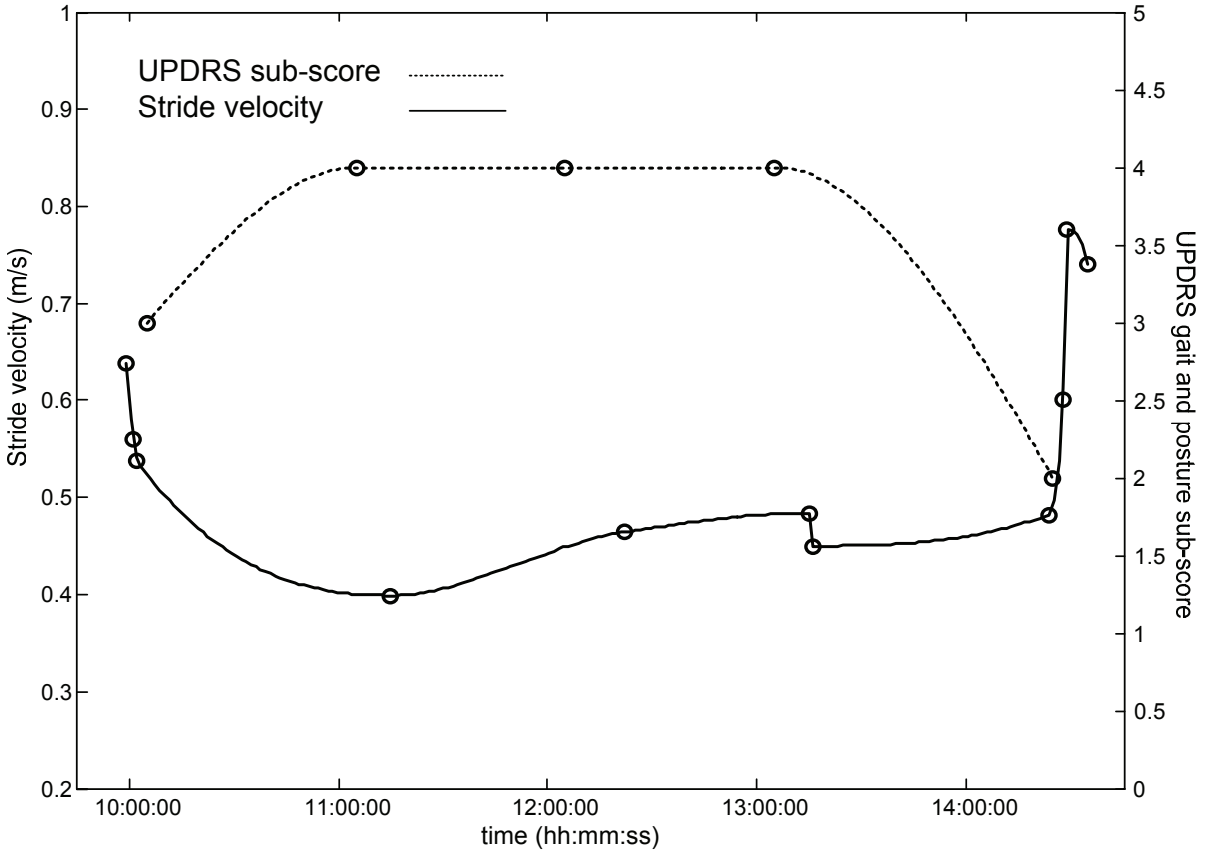


Figure 7-7. Stride velocity of a PD patient and his UPDRS sub-score of gait and posture. The circles on the graphs show when subject was walking and when UPDRS tests were performed.

The results of the study of the correlation between different gait parameters and the UPDRS gait and posture sub-score are presented in Table 7-5. All of spatial parameters and the angles showed significant correlation to the UPDRS gait and posture sub-score, after eliminating the effect of the repeated measurements. The temporal parameters however, unlike previous study in the controlled conditions did not show significant correlation to the UPDRS sub-score.

The stride-to-stride variability of all of the parameters were also calculated but in every case, it was neither significantly different between Stim ON and OFF conditions nor had a significant correlation to the UPDRS sub-score.

	Stim ON	Stim OFF	Sign-rank	Rank Correlation	
			p-value	ρ	p-value
Peak shank angular velocity (º/s)	238.4 ± 53.9	198.4 ± 61.6	0.04	-0.46	< 0.001
Stride length (cm)	87.2 ± 24.7	77.0 ± 36.1	0.65 (N.S.)	-0.34	0.003
Stride velocity (cm/s)	77.1 ± 23.9	58.1 ± 28.9	0.02	-0.46	< 0.001
Range of rotation of shank (°)	49.4 ± 11.3	43.1 ± 18.2	0.30 (N.S.)	-0.31	0.009
Range of rotation of thigh (°)	30.3 ± 6.2	26.5 ± 9.0	0.13 (N.S.)	-0.35	0.002
Range of flexion-extension of knee (°)	40.0 ± 4.9	35.8 ± 9.7	0.20 (N.S.)	-0.34	0.003
Stance (%)	62.4 ± 4.1	67.5 ± 7.0	0.004	-0.17	0.15 (N.S.)
Double Support (%)	24.9 ± 8.1	34.9 ± 14.1	0.004	0.17	0.15 (N.S.)
Limp (%)	3.3 ± 1.4	7.3 ± 7.9	0.16 (N.S.)	0.16	0.16 (N.S.)
Gait cycle time (s)	1.16 ± 0.18	1.38 ± 0.32	0.06 (N.S.)	0.03	0.80 (N.S.)

Table 7-5. Summary of the results gait analysis of free moving PD patients. The values for the parameters are shown in Mean in ± S.D. format. Where the p-value was more than 0.05, it was marked as N.S.

7.4 Discussion and conclusion

7.4.1 Estimation of thigh angles from shank angles

The results presented in Table 7-1 show that using only a few Fourier harmonics, thigh angle can be estimated using shank angles with acceptable accuracy. As the number of the harmonics increases from two to six, the accuracy also increases. However, by increasing the number of harmonics more and more, the accuracy remains constant or even starts to decrease. This could be explained by the fact that each of the X_R and X_L matrixes for n harmonics, included $2\times 2n+2$ rows and $2\times n+1$ columns. Moreover, the harmonics are complex numbers so each element of the matrixes corresponded to *two* real valued coefficients. So in total, for *each* prediction matrix the number of needed coefficients $N(n)$ was:

$$N(n) = (2\times 2n+2)\times(2\times n+1) = 8n^2 + 8n + 2 \qquad (6.29)$$

For example, for each of the X_R and X_L matrixes for the cases $n = 2, 6$ and 12 the number of real valued coefficients would be 50, 338 and 1250, respectively. The number of gait cycles used to calculate X_R and X_L matrixes were constant and relatively small (1666 gait cycles). By increasing the number of harmonics, the accuracy in estimation of the X_R and X_L elements would eventually reduce (because of lack of enough training data) and at a certain value of n, would out weight any benefits of using a model with higher number of harmonics.

7.4.2 Comparison to the reference, camera based system (Elite)

The results of evaluation of accuracy of four different approaches to calculate spatial parameters of gait have been presented in Table 7-3. The system with four sensors on the lower limbs had the best accuracy in comparison to the reference system. The system based on three sensors reduced one sensor (the left thigh's sensors) by assuming that the difference between the movement of the right and left thigh during the gait is small. The disadvantage of this approach was that the system could no longer estimate the knee angle of the left side and the error of the system in estimation of the *stride-length* and *stride-velocity* was slightly increased. The simplified model using compass-like gait model with two gyroscopes on shanks had the disadvantage of losing two gait parameters, range of rotation of thighs and flexion-extension of the knees and also showing the highest average value of the error in estimation of the stride length (see the rightmost column of the Table 7-3).

Our new algorithm was based on the two gyroscopes and predicting thigh angles. Looking at the Table 7-3 shows that estimation of thigh angles based on the shank angles could produce more accurate results than the system with three sensors. It means that assumption of small differences between the left and right thigh angles during the gait and taking them equal was weaker than the assumption of the predictability of thigh angles based on the shank angles. By better estimating the thigh angles, the error in estimation of stride-length and stride-velocity were also decreased in our method.

Moreover, the results show that estimated value for the stride-length and stride-velocity by the reference system lies almost in the middle of the estimated values using the new algorithm and the four sensors algorithm (similar standard deviation of the errors; systematic errors with similar magnitude but different signs). It means that while one method under-estimates the stride length, the other system over estimates it by almost the same magnitude, practically making them of the same value for clinical practice.

Finally, by comparing the new method to the four sensors method in Figure 7-6, we can see that over a very large range of stride-lengths (from 20cm to 160cm, i.e. eight times difference between minimum and maximum) there was a highly linear relationship between the outcomes of the two methods.

7.4.3 Gait analysis of free moving PD patients

The new system could be used to record movements of the lower limbs in PD patients for several hours. Periods of gait could be detected automatically. The results presented in Table 7-4 show that comparing to the visual observation, the sensitivity of gait detection

was high (95.0%) and specificity was very good (99.8%). In the previous chapter and in the controlled study, we had reported that the sensitivity of the system to detect the gait was 99.3% during Stim ON and 96.4% during Stime OFF comparing to video (see section 6.4.2).

For the case of the free moving PD patients, by comparing the logs recorded by two independent observers following the patients at the same time and taking one of them as the reference, results listed in Table 7-4 show that visual observation itself could not have a much higher accuracy. The problem could be mostly in deciding between very short periods of walking and active standing periods where subject may take a few steps while subjectively, observers would not consider that as walking.

Our previous study in the controlled situation showed that almost all of the gait parameters had a significant correlation to the UPDRS gait and posture sub-score (see section 6.5.3). The present study shows that the correlation between many gait parameters and UPDRS gait and posture sub-score was present though it was weaker than the controlled situation. Although the system could not differentiate between possible types of walking during long-term monitoring of free moving subjects (walking straight, walking indoor or outdoor, performing cognitive tasks while walking, etc.), yet gait parameters estimated in these unfavorable conditions showed significant correlation to the clinical score. Moreover, several parameters (Peak shank angular velocity, stride-length, periods of stance and double support) showed significant difference between Stim ON and Stim OFF conditions. These findings strongly suggest that our ambulatory monitoring system can provide clinically relevant objective evaluation of gait in PD patients even without any set protocol of activities and in conditions similar to the daily life.

7.4.4 Conclusions

Our ambulatory method to detect and analyze gait in PD patients has been evolved to a much simpler system, with half of the sensors sites of the previous method without significant increase of the error in estimation of the gait parameters. The results can be summarized as follows:

- With only one uni-axial gyroscope on each shank, it was possible to estimate all of the spatio-temporal parameters of gait in normal and PD patients that were previously obtained with a system with four sensors.
- The proposed method has good accuracy in estimation of the gait parameters comparing to the previous method or to a camera based reference system.

- By training the prediction coefficients used by the algorithm on a certain population and evaluating the system on different populations, we suggest that the method is robust enough to be used without any per-subject calibrations or training.
- The accuracy of automatic detection of gait in free moving PD patients reached almost to accuracy of the subjective visual observations.
- Gait analysis of free moving PD patients without restricting the type of the activities and without any set protocol of known tasks, can provide results that show significant correlation to a widely used clinical score.

Chapter 8 Detection of the periods of ON and OFF

Abstract

Background—Currently, no objective ambulatory method exists to classify ON and OFF states of the PD patients with good accuracy. While detection of ON and OFF by itself is of high clinical interest, reporting objective parameters associated with different symptoms of PD along side the ON/OFF state of the patient, can help us to put the reported parameters *in to context* and provides a more elaborated view of the state of PD patient in long term monitoring.

Objectives—Design and evaluation of a statistical classifier to detect periods of ON and OFF states based on the kinematic parameters provided by previous algorithms.

Method—15 different estimated parameters with addition of UPDRS motor score during ON period of the 13 PD patients monitored for several hours were used to train and evaluate a statistical classifier. All possible combinations of the input parameters were evaluated using a method based on k-fold cross validation approach to select the best group of the parameters to have a good accuracy in the classifier.

Results—Many combinations of the input parameters (more than 70 cases) could result in a good classification (i.e. good sensitivity and specificity) of ON and OFF states. The classifiers also could show the rapid changes in the performance of the patients occurring immediately after switching the state of the STN-DBS stimulator. The results show that it was possible to detect ON and OFF periods with a resolution of 10 minutes in ambulatory conditions. Moreover, a good detection and accuracy was possible using a relatively simple statistical classification method.

Main contributions—An objective approach has been proposed to classify ON and OFF states of the PD patients during long-term recordings using kinematic sensors.

8.1 Introduction

Fluctuations in the motor performance of the PD patients are a common and adverse problem of chronic levodopa therapy (Nutt, Carter *et al.* 1995). With progression of time, the therapeutic duration of each levodopa dose shortens resulting in reappearance of PD signs after a few hours (OFF state). Many patients, when levodopa is active (ON periods)

experience periods of involuntary abnormal movements, known as dyskinesia or levodopa induced dyskinesia (LID) (Nutt 1990). The diurnal pattern of changing between ON and OFF states has to be known in order to adjust the time and the dose of each levodopa intake during the day (Marsden, Parkes *et al.* 1981; Petit, Allain *et al.* 1994). Automatic detection of periods of ON and OFF during normal daily activities of the PD patients can provide an objective and potentially more reliable way of finding these patterns than relying on the diaries kept by the patients themselves.

In the previous chapters we have presented different methods to quantify several important aspects of motor functions in PD patients. We have shown that both in the tests inside the laboratory and also for the case of the free moving patients, many of the estimated parameters related to the motor function, such as tremor, gait, bradykinesia and body posture, show significant differences between the ON an OFF states.

However, finding significant differences in the objective parameters between ON and OFF state does not automatically translate into the possibility of finding ON and OFF periods *accurately*. A classification method is needed to be designed, applied and tested on the long-term recorded data from the free moving PD patients.

Recently, using accelerometry (Hoff, Van Der Meer *et al.* 2004) have used the outcomes of several methods to assess bradykinesia, hyperkinesias, tremor, dyskinesia and body posture (Dunnewold, Hoff *et al.* 1998; Dunnewold, Jacobi *et al.* 1997; Hoff, vander Plas *et al.* 2001; Hoff, Wagemans *et al.* 2001) to detect ON and OFF periods of the patients at home. However, they reported that the methods used in their study, yet are not able to perform the detection of these periods with high accuracy. To our knowledge, no other system exists that can successfully detect ON and OFF periods in the PD patients in ambulatory conditions.

In this chapter, based on a combination of the parameters obtained using the algorithms presented so far, we propose a statistical method to classify ON and OFF periods with a resolution down to 10 minutes, in a group of free moving PD patients.

8.2 Methods

8.2.1 Measurement system and experiment setup

13 PD patients participated in this study. They consisted of a group of seven males and six females. Each measurement took three to six hours (in total more than 59 hours for all patients) during ambulatory conditions where patients were free to move and perform activities they liked. An UPDRS test was performed at the beginning of the measurement

and then at least after every one hour. More details about patients and experiment protocol can be found in section 2.5, the *long-term* study.

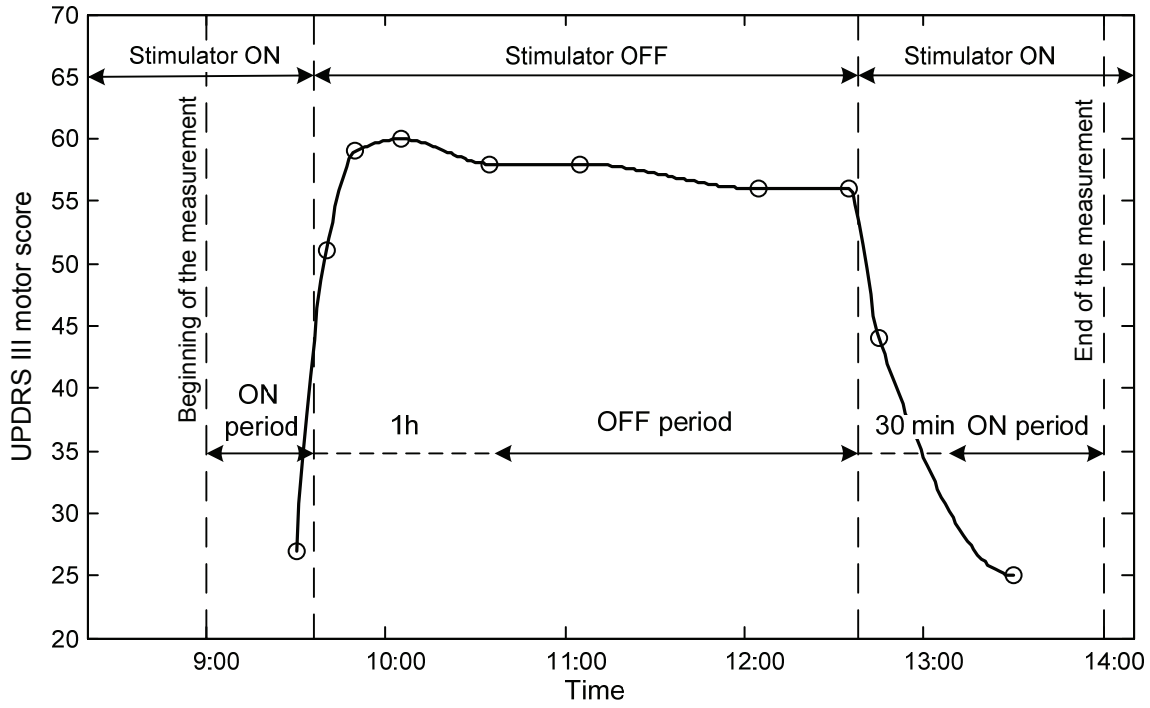


Figure 8-1. An example of the measurement protocol. Measurement started and 9:00am and ended at 14:00. The curve shows the UPDRS motor score of the subjects and circles shows when each UPDRS test has been performed. Periods of ON and OFF has been marked.

Figure 8-1 shows the details of the measurement protocol. Patients started the measurement while the stimulator was on. After a while (usually less than one hour) the stimulator was turned off. Until this time, patients were in the *ON* state. For a period of three hours the stimulator remained off, before it was turned on again. The period of time between one hour after turning off the stimulator until the time it was turned on again was considered as the *OFF* period (Vingerhoets, Villemure *et al.* 2002). Measurement continued for at least one more hour while the stimulator was on. Patients were considered to be in the ON state from 30 minutes after turning the stimulator on till the end of the measurement (Vingerhoets, Villemure *et al.* 2002).

The measurement system included five ASUR units (see Figure 8-2). One unit was attached on the trunk, two on the forearms and two on the shanks. In total, seven gyroscopes and two accelerometers were used in this configuration. The data was recorded with a sampling rate of 200Hz. More details about the measurement system is presented in the sections 3.4 and 3.5.

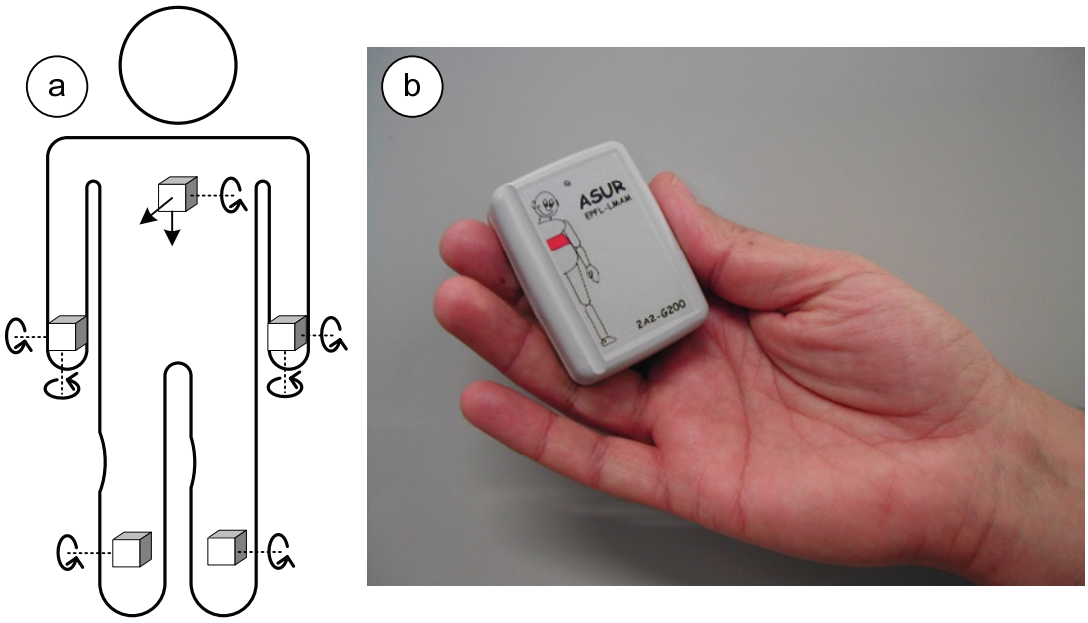


Figure 8-2. a) The attachment of the ASUR units on the body. The sensitive axes of the sensors are shown. b) An ASUR unit. All units have the same physical size and a logo on top of them designates the attachment site.

8.2.2 Ambulatory monitoring of motor function

In the previous chapters, we have presented different algorithms to detect and/or analyze tremor (chapter 4), bradykinesia (chapter 4), posture transitions (chapter 5), body posture (chapter 5) and gait (chapters 6 and 7). Each method provided several parameters. Most of them were significantly different between periods of ON and OFF states and moreover, many of them had significant correlation to the UPDRS clinical score (see respective chapters for more details).

Number	Parameter name	Description	Related symptoms
1	M_h	Movement of the hands	Bradykinesia
2	R_h	Range of the rotation of the hands	Bradykinesia
3	A_h	Activity of the hands	Bradykinesia, Akinesia
4	$\omega_{tr\text{-}h}$	Amplitude of the tremor of the hands	Tremor
5	$\omega_{tr\text{-}l}$	Amplitude of the tremor of the legs	Tremor
6	Max$\{\omega_{shank}\}$	Peak angular velocity of the shanks during swing	Gait
7	Stance	Period of the stance phase	Gait
8	Stride	Stride length	Gait
9	Speed	Stride velocity	Gait
10	RoR$\{\theta_{shank}\}$	Range of the rotation of the shanks	Gait
11	RFX$\{\theta_{knee}\}$	Range of the flexion-extension of the knees	Gait
12	DS	Period of double support	Gait
13	Posture	Body posture	Posture
14	TD	Transition time	Posture
15	Min$\{\hat{a}_{trunk}\}$	Minimum acceleration of the trunk during transitions	Posture
16	UPDRS-ON	The UPDRS motor score during ON state	The clinical score

Table 8-1. List of the parameters used in this study.

Table 8-1 shows the list of parameters used in this study, derived from our previous methods. The methods of estimation of parameters 1 to 15 have been already discussed in their respective chapters. We also used a 16th parameter, the UPDRS motor score during ON period: a patient with an advanced PD during ON may perform much worse than another patient in early stages of PD even during OFF state. Including the *UPDRS-ON* parameter may help performing a better classification of ON and OFF periods, both for the early and advanced PD patients.

Among the motor related parameters listed in Table 8-1, the only new parameter is number 13, *Posture*: the output of the posture analysis algorithm is series of time period designating each of the four basic body postures, i.e. *Sitting*, *Standing*, *Walking* and *Lying*. The *Posture(t)* parameter is simply a signal that combines the output of the posture analysis program in a time series:

$$Posutre(t) = \begin{cases} 1 & if \quad Subject\ is\ \text{Walking}\ at\ time\ t \\ 0.5 & if \quad Subject\ is\ \text{Standing}\ at\ time\ t \\ -0.5 & if \quad Subject\ is\ \text{Sitting}\ at\ time\ t \\ -1 & if \quad Subject\ is\ \text{Lying}\ at\ time\ t \end{cases} \tag{8.1}$$

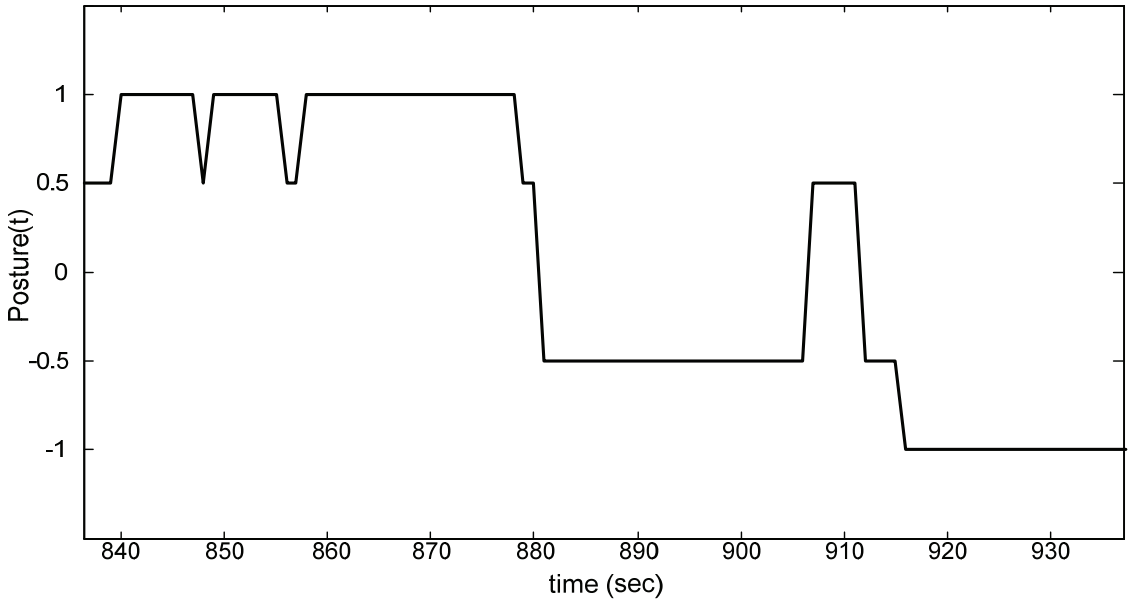


Figure 8-3. Part of the estimated *Posture(t)* signal for a patient.

Figure 8-3 shows a segment of the *Posture(t)* signal estimated for a PD patient. In this segment, he started from standing position, walked for round 40 seconds with some short stops in between, and round time $t = 880$ sit on a chair. After nearly 25 seconds he walked toward a bed and laid down on it.

The differences in anatomy of the patients, we normally expect a taller person to have a longer stride length than a shorter person. To compare two of the gait parameters, *stride length* and *stride velocity*, we normalized these two parameters based on each subject's leg length (Hof 1996; Hof and Zijlstra 1997).

8.2.3 Detecting ON and OFF states

The general idea of ON/OFF detection algorithm was to use a statistical classifier to estimate a probability p_{OFF} for each period of fixed sized time windows, using the average value of the estimated parameters from different analysis algorithms during that window (see Figure 8-4).

The method to estimate the parameters related to bradykinesia (M_h, R_h and A_h) was already based on fixed size time windows. The tremor detection algorithm could provide outcomes with a resolution of three seconds. The average value of the outcomes of this algorithm ($\omega_{tr\text{-}h}$ and $\omega_{tr\text{-}l}$) during each time windows was used. The algorithms to detect gait and to classify body postures, however, only provided their outcomes (gait parameters, parameters related to the posture transitions and *Posture(t)* signal) only when the respective activities were detected. Therefore, it was necessary to interpolate the values of these parameters before the averaging step.

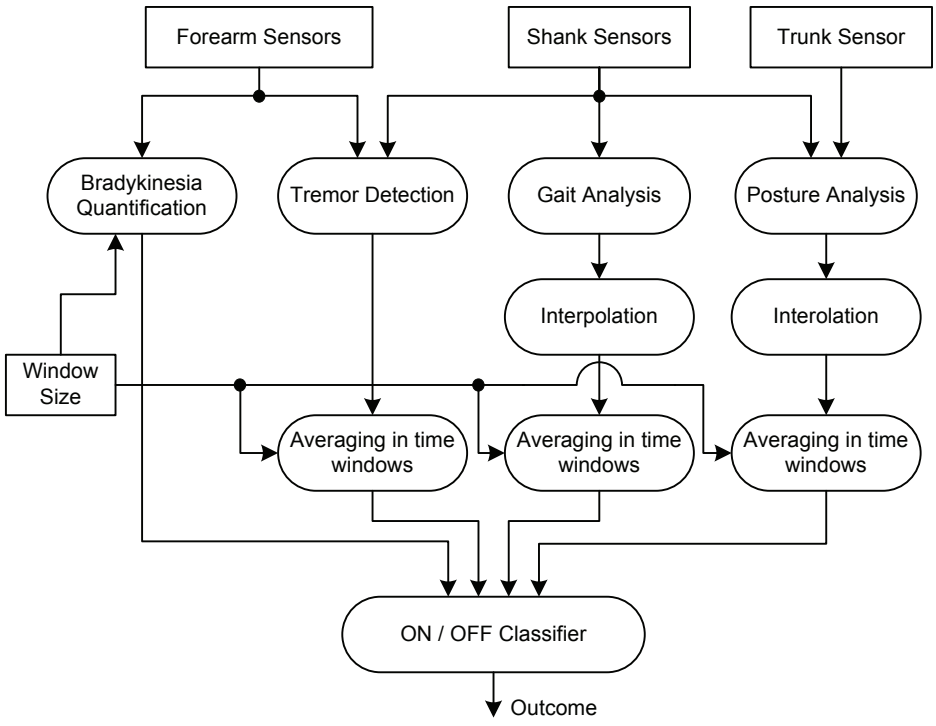


Figure 8-4. Flowchart of ON/OFF detection algorithm.

We used a window size of 10 minutes for this algorithm. Based on the study presented in the chapter 4, a window size of the 10 minutes was the smallest size that the bradykinesia and tremor related parameters could show a significant correlation to the UPDRS scores of the patients.

We used logistic regression (Hosmer and Lemeshow 1989) to classify each time window based on a subset S of the parameters presented in Table 8-1. (For a brief description of the logistic regression method see section 4.2.3.3). The regression function took the parameters estimated for a time window as the input and calculated a p_{OFF} probability showing how probable it was for that window to belong to an OFF period. In the output we marked the windows with a p_{OFF} of more than 0.5 as OFF and those with a value less of than 0.5 as ON.

As the number of the parameters was relatively small, we used a *brute-force* approach to evaluate all possible combinations of the parameters to find the best model for the classifier. UPDRS-ON (parameter number 16), however, was included in all models. With the remaining 15 parameters, the number of possible subsets S_i were 32767 (i.e. 2^{15} -1).

To compare classifiers based on different possible subsets S_i of the input parameters, we selected geometric mean of the sensitivity and specificity as the goal function to maximize the both statistics at the same time:

$$G(S) = \sqrt{Sensitivity \times Specificity} \tag{1.2}$$

To train and evaluate the classifier for each model, *k-fold cross-validation* method (Hastie, Tibshirani *et al.* 2001; Wasserman 2004) was used: We used $k = 13$ (i.e. number of the patients). For each model S_i, we used the data of the $k-1$ patients to fit the model using logistic regression, then estimated $G(S_i)$ using the remaining PD patient's data. This process was repeated for each of the k PD patients and the average of the $G(S_i)$ was calculated. This average indicated the quality of the selected model.

8.2.4 Statistical analysis

The average values of each of the input parameters (see Table 8-1) for each patient during the selected *ON* and *OFF* periods were calculated. Wilcoxon's non-parametric paired test (sign-rank test) was used to test if the median for the parameters were equal during the two states or not.

8.3 Results

8.3.1 Comparing ON and OFF states

The average value of all of the 15 parameters in the 13 PD patients participated in this study during ON and OFF states is presented in Table 8-2.

Number	Parameter name	ON state	OFF state	p-value
1	M_h (°/s)	51.1 ± 47.7	44.93 ± 37.98	0.233
2	R_h (°)	4.1 ± 0.9	3.29 ± 0.87	0.009
3	A_h (%)	33.4 ± 24.4	22.8 ± 12.9	0.110
4	$\omega_{tr\text{-}h}$ (°/s)	2.26 ± 4.56	16.15 ± 23.91	< 0.001
5	$\omega_{tr\text{-}l}$ (°/s)	0.00 ± 0.00	0.78 ± 1.64	< 0.001
6	Max{ω_{shank}} (°/s)	205.2 ± 57.5	178.81 ± 61.53	0.083
7	Stance (%)	64.6 ± 4.5	67.85 ± 5.62	0.005
8	Stride (m)	0.79 ± 0.29	0.66 ± 0.34	0.151
9	Speed (m/s)	0.65 ± 0.25	0.52 ± 0.27	0.019
10	RoR{θ_{shank}} (°)	44.6 ± 15.3	37.11 ± 17.89	0.064
11	RFX{θ_{knee}} (°)	36.9 ± 8.7	32.30 ± 8.91	0.067
12	DS (%)	29.2 ± 9.0	35.71 ± 11.23	0.005
13	Posture	0.56 ± 0.36	0.46 ± 0.24	0.092
14	TD (s)	4.30 ± 0.95	4.48 ± 0.88	0.910
15	Min{$\hat{a}_{trunk}$} (m/s^2)	-0.04 ± 0.06	-0.05 ± 0.05	0.677

Table 8-2. The mean and standard deviation of the estimated parameters for the periods of ON and OFF. The p-value is the results of the Wicoxon's non-parametric paired test. p-values greater than 0.05 can be considered as non-significant.

The UPDRS motor score of the patients was 23.7 ± 10.7 during the ON state and 54.0 ± 14.2 during the OFF state ($p < 0.001$). Among the measured parameters, range of rotation of the hands (R_h), the amplitude of the tremor in hands and legs ($\omega_{tr\text{-}h}$ and $\omega_{tr\text{-}l}$), periods of stance and double support and stride velocity showed significant difference between ON and OFF states. Some of the other parameters including activity of the hands (A_h), peak shank angular velocity ($Max\{\omega_{shank}\}$), range of the rotation of the shanks and the range of the flexion-extension of the knees ($RoR\{\theta_{shank}\}$ and RFX$\{\theta_{knee}\}$) and body posture ($Posture(t)$) showed a marked difference between the two states (p-value near 0.1).

8.3.2 Model Selection and Classification results

Using 10 minutes windows, in total 127 windows for the OFF period and 81 windows for the ON periods were selected. With this data set, all possible combinations for the 15 parameters used in this study were used with a k-fold cross validation method ($k = 13$, the number of PD patients) to train and evaluate the statistical classifier. Figure 8-5 shows the histogram of the goal function for all possible combinations of the input parameters.

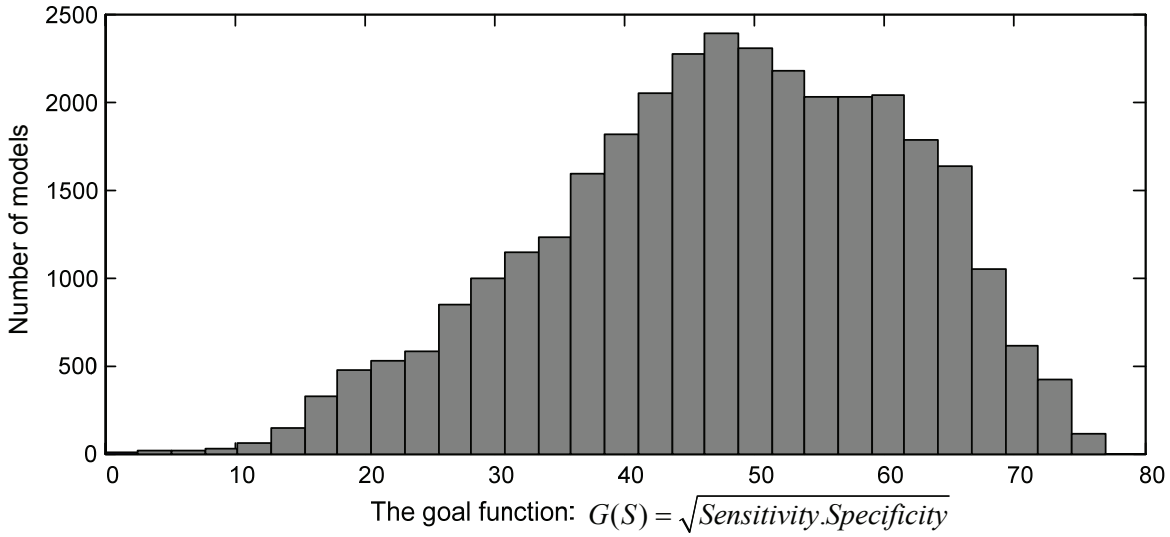


Figure 8-5. The histogram of the value of the goal function for all possible models.

Table 8-3 shows the results for some of the possible models. All models including only a single parameter had poor sensitivity and specificity ($G(S) < 42.4$). The best model had $G(S)$ of 77.0 and more than 70 different models had a $G(S)$ better than 75. The full model, i.e. the model including all parameters also didn't perform very well.

Rank	Parameters in the model	$G(S)$	Sensitivity	Specificity
1	1, 2, 3, 4, 10, 11, 13, 15, 16	77.0	90.1%	76.3%
2	1, 2, 3, 4, 6, 10, 11, 15, 16	76.9	89.6%	75.8%
3	1, 2, 3, 4, 10, 11, 15, 16	76.9	89.5%	76.3%
4	1, 2, 3, 4, 8, 9, 11, 15, 16	76.9	91.6%	74.4%
5	1, 2, 3, 4, 8, 9, 11, 13, 15, 16	76.9	91.6%	73.9%
6	1, 2, 3, 4, 9, 11, 15, 16	76.9	90.9%	73.5%
5147	full model (all parameters 1 to 15)	62.2	85.5%	56.6%

Table 8-3. Some of the evaluated models used to detect OFF state. Ranks of the models in comparison to all other possible models, the scores of the models and their sensitivity and specificity in detection of OFF state are presented.

Using the best model a typical outcome of the algorithm in estimating p_{OFF} is presented in the Figure 8-6.

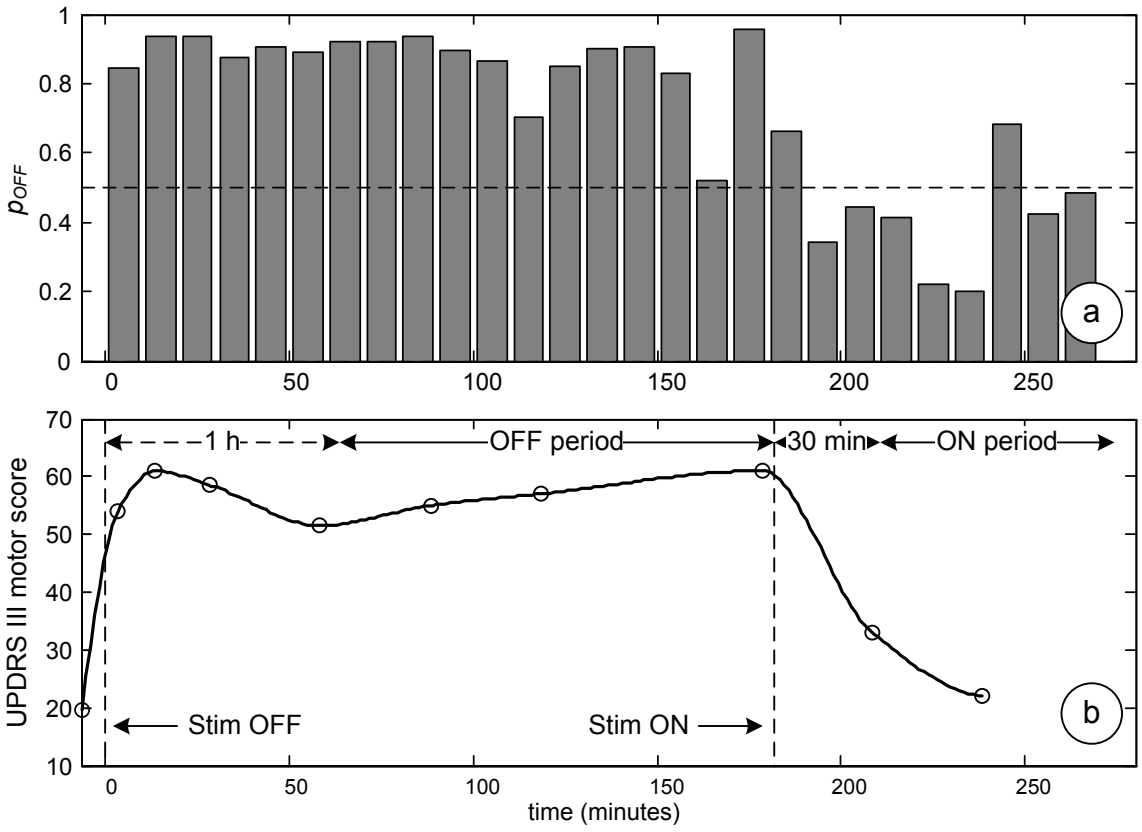


Figure 8-6. A typical output of the program. a) Estimated p_{OFF} b) The UDPDR score of the subject. The periods of ON and OFF are marked on the figure.

8.4 Discussion and conclusion

8.4.1 Selection of the classifier's input parameter

The histogram in Figure 8-5 shows that in this study, model selection was not really a very critical issue. Many of the possible models could separate ON and OFF states with similar accuracy. This encourages us to turn our attention also to the other considerations in model selection, rather than only focusing on the power of the classifier.

For example one can select models that included relatively simpler to calculate parameters or parameters that we can estimate with higher accuracy that characterized different aspect of PD abnormalities. This way, the model ranked two in Table 8-3 could be preferred to the model ranked one, as it uses $Max\{\omega_{shank}\}$ (Parameter number 6, the peak shank angular velocity during gait) which is an accurate and relatively easy to estimate (as gyroscopes directly measure angular velocity) instead of *Posture(t)* parameter (parameter number 13) which is much more complex and less accurate to estimate parameter.

We observed a significant improvement of the accuracy of the outcomes, by including UPDRS motor score during ON state as a parameter in all models. For example in the

case of the best model in Table 8-3, by removing parameter number 16 (UPDRS-ON score) the specificity of OFF detection would fall from 76.3% to 56.5%. This could be explained by the fact that the PD patients in the advanced staged of the disease, even during ON state could yet show some parkinsonian signs (for example, high bradykinesia) while the patients in the earlier stages of the disease would only show similar signs only during the OFF state. UPDRS-ON parameter in our models acted as a case-dependant, bias value to reduce the effect of inclusion PD patients in different stages of the disease in our input data.

As stated in the method section, we didn't use the periods of the first hour after turning the stimulator off and 30 minutes after turning it on in neither the training nor the evaluation of the classifier. It is interesting to see how the classifier performs during these periods.

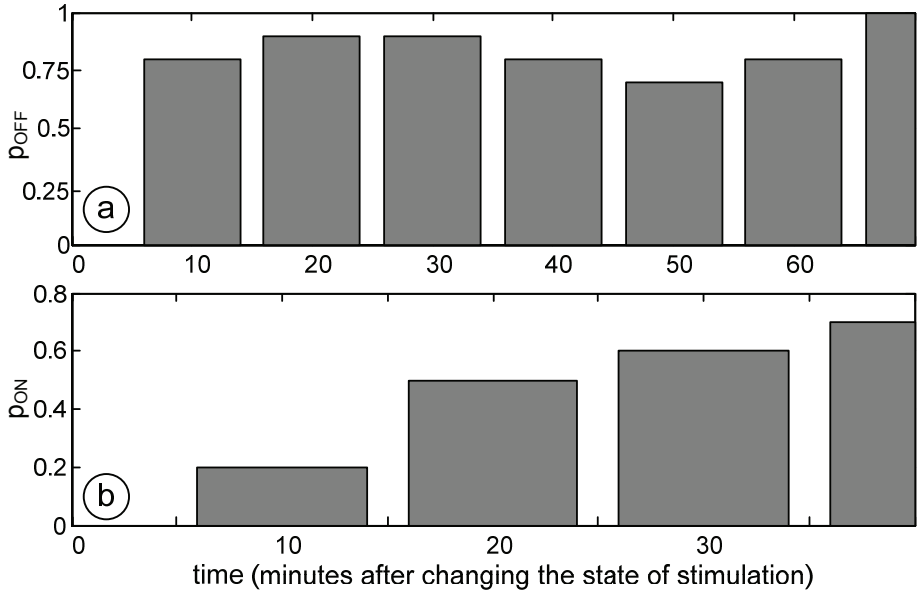


Figure 8-7. a) The average estimated valued of p_{OFF} during the first hour after turning STN-DBS off. b) The average estimated valued of p_{ON} during the first half an hour after turning STN-DBS on.

Figure 8-7 show the average value of the p_{OFF} and p_{ON} among our 13 PD patients during these periods. The very quick effect of changing the state of the stimulation (Temperli, Ghika *et al.* 2003) is visible in these graphs. By turning the stimulator OFF, in the first 10 minutes time window p_{OFF} was on average more than 0.75. The average value of p_{ON} 10 minutes after turning the stimulator ON, however, was less than 0.5 and only in second time window which is 20 minutes after turning the stimulator ON, reached 0.5. Most of the patients had tremor during the OFF state and no tremor during the ON state (see Table 2-5 and Table 2-6). The classifier was trained using these periods of ON and OFF

and detection of tremor played an important role in separating these periods. Changing the state of the stimulation very quickly affects tremor (Temperli, Ghika *et al.* 2003). When patients were during ON state with no tremor, by turning off the stimulator within a few minutes tremor re-emerged and was picked up by the classifier as an important sign of OFF state. At the end of the period of OFF where possibly the patients had tremor, however, by turning the stimulator on, tremor rapidly diminished however the sensitive tremor detection algorithm yet could pick up low amplitude tremor for a few more minutes before it was finally completely stopped.

To train and evaluate the statistical classifier, we used k-fold cross validation by separating the data from each patient from the others during the training and test of the classifier so that the same data would never be used for the both purposes at the same time.

An alternative approach would be to first randomly shuffle all the data and then to use k-fold cross validation with k groups of randomly selected, equally sized of data groups. At the beginning we considered this alternative and using a value of $k = 8$, we observed that some models have a $G(S)$ score better than 85 which is significantly higher than the best models in the Table 8-3. However, in this approach part of the data of the *same patient* would be used for training while another part would be used for the evaluation. This could leave a memory effect in the classifier that would limit the power of the method to predict the p_{OFF} for new patients not included in this study.

The measurement protocol for this study, however, was not optimal as finally we had a much shorter total periods of ON than the OFF periods with a prevalence of less than 39% (810 minutes vs. 1270 minutes). This unbalanced training and evaluation data showed its effect in obtaining higher sensitivity (i.e. p_{OFF}) than specificity (i.e. p_{ON}). A more balanced approach could include more recordings during ON period to cover a wider range of the movement patterns during this period and potentially improve the specificity.

Another limitation was the fact that the number of the patients and hence the range of the different activities they did during the monitoring period was relatively small. Moreover, some patients spent some of the ON periods in an examination by a logopedist (speech therapist). This examination took round 20 minutes and patients were all the time in an inactive sitting position as they were only supposed to talk and listen. This situation, i.e. long periods of inactive sitting position had similarities to some OFF periods where patients would get *blocked*, i.e. because of high rigidity and increased akinesia they spent a period of time with a very low level of activity, mostly in sitting or lying positions.

As our sensors could only detect movements on five body sites (trunk, hands and legs), periods of inactive sitting in the logopedist's examinations had a high similarity to the recorded signals of those OFF periods. As an example, Figure 8-6 shows a false positive period (an ON window detected as OFF) which has happened during the logopedist's examination.

There was a difference between the reported p-values in this study and those presented in the previous chapters for the long-term study, when comparing the parameters related to the ON and OFF states. In Table 8-2, the estimated average value of parameters during Stim OFF periods were taken from one hour after turning off the stimulator to the 3rd hour while in the previous chapters we only considered 3rd hour after turning off the stimulator. In the same way, the ON periods in this study were considered from 30 minutes after turning the stimulation on while in the previous chapter, only period of more than one hour after Stim ON were considered.

8.4.2 Comparing to other studies

Recently Hoff et al (Hoff, Van Der Meer *et al.* 2004) have published the results of a study with 15 PD patients about detection of ON and OFF periods using accelerometry. Their method was based on comparison of the self-assessment of PD patients (time tagged logs) and the objective parameters provided by their algorithm. They used 30 minutes windows and measured each patient for 24 hours. They reported a poor sensitivity (0.60-0.71) and specificity (0.66-0.76) in detection of ON an OFF sates and concluded that "multi-channel accelerometry currently can not detect ON and OFF in individual PD patients".

There are several important differences between our approach and theirs: We have used much smaller windows for evaluation (10 minutes vs. 30 minutes), the period of measurement was shorter in our case (5 hours vs. 24 hours), we used a larger number of parameters (15 parameters vs. 4 parameters), our group of PD patient didn't have any dyskinesia during the measurements and finally Hoff et al used per subject calibrations while we only used the UPDRS score during ON state. However, we believe that considering the significantly better sensitivity and specificity of our method, automatic detection of ON and OFF periods is possible and within reach. However, a larger number of patients and a more balanced measurement protocol maybe needed to obtain the optimal results.

8.4.3 Conclusions

Using five body fixed sensors recording kinematic signals and several analysis algorithms to detect and quantify tremor, bradykinesia, gait and physical activity in free moving PD

patients, we have proposed a statistical method to detect periods of ON and OFF during several hours of continues recording.

Although dyskinesia is not a symptom of PD per se and is a side effect of the therapeutic interventions, it is an aspect of the motor complexities of the PD patients that has not been addressed in our study. By adding a robust algorithm to accurately detect periods of dyskinesia to our method, we believe that ambulatory monitoring systems using kinematic sensors can effectively follow the ON/OFF fluctuations of PD patients during their daily activities.

While until now other groups have reached low accuracy in automatic classification of ON and OFF periods, we have found a relatively acceptable sensitivity and specificity using our method for time windows of 10 minutes. The classification maybe is not yet accurate enough for direct practice in clinic, but we believe by further studies and based on the foundations laid by our efforts so far, comprehensive and objective assessment of major PD motor abnormalities during daily life of PD patients is possible.

Chapter 9 Conclusions

9.1 Summary and contributions

The primary objective of this thesis was to design, validate and use a new portable movement analysis system (MAS) in clinical conditions. The goal was to use this device for long-term monitoring and quantitative assessment of motor abnormalities of PD patients during their daily activities. The major results and contributions of this thesis were:

1. The ASUR units.

Step by step, we have designed, tested and refined our new movement analysis system. The final system consisted of five lightweight (< 50g), independent autonomous sensing units that could be attached on five sites on the body (trunk, forearms and shanks). Depending on the body site, each unit included a specific combination of accelerometers and gyroscopes with specific sensitivity ranges. Designed based on the concept of integration of data-logger and sensors, each unit included the battery, sensors, memory and the necessary electronic circuits. Each unit could continuously record up to 14 hours.

2. Clinical protocols and a database of movement patterns.

At the same time that our MAS was evolving from a prototype to the final version, several clinical studies both in controlled and ambulatory conditions were performed using available version of the MAS at each stage. As a result, a rich 118 hours database of different movement patterns of 41 PD patients and 10 controls was created.

We performed a *pilot study* using available components to determine the basic structure of the MAS. In a *controlled study*, with a very specific protocol of daily activity, a group of PD patients and healthy control subjects used the first prototype of MAS for short recording sessions under an hour. The recorded data in this study was used several times in the design of movement detection and analysis algorithms. A *long-term study* was subsequently performed with the first prototype of the ASUR system on a group of free moving PD patients. The data was used to evaluate the designed algorithms in real clinical conditions. Finally, the final version of the MAS is being used for a new series of studies (see section 9.2, perspectives and further clinical studies).

The most challenging part of the thesis, however, was to devise several new methods and algorithms to detect and quantify various motor abnormalities of PD while the patients were performing their daily activity. Although the proposed methods used advanced signal processing and complex analysis techniques, a common goal and consideration in the design of all them was to make them as simple to use as possible for the users. For example, we tried to avoid using any per-subject calibrations, pre-test statistics, and designed all of the algorithms to be completely automatic in a *push-button* style interface. This way, the final system could be used in the clinic with minimal training and the least dependence on the skills of the operator.

3. Tremor detection and quantification.

Using gyroscopes attached on the forearms, an accurate algorithm (sensitivity 99.5%, specificity 94.2%) based on spectral estimation has been proposed to detect and quantify tremor with a resolution down to three seconds. We found that the amplitude of the tremor measured by our method shows a very good correlation to the UPDRS tremor sub-score of the patients (e.g. $r = 0.87, p < 0.001$ for the roll axis). As expected, the measured amplitude of the tremor was significantly different during ON and OFF states.

4. Quantification of bradykinesia.

We have proposed a new algorithm to quantify the bradykinesia in PD patients and tested it in both controlled and free conditions. We found that the outcomes of this algorithm also show significant and good correlation to the UPDRS bradykinesia sub-score ($r = -0.74, p < 0.01$) in the free moving PD patients. The outcomes also could separate controls, PD patients in ON and OFF states. The results of this study, together with the results of he tremor detection and quantification, has been submitted to be published in an IEEE journal (Salarian, Russmann *et al.* Submitted-b) and has been presented in several conferences (Russmann, Salarian *et al.* 2003a; Russmann, Salarian *et al.* 2002; Salarian, Russmann *et al.* 2003b).

5. Gait detection and analysis.

An algorithm to detect and analyze gait in PD patients was designed and tested. The algorithm could detect gait with a high accuracy (specificity of 99.6% for controls and 99.3% for PD patients during Stim ON and 96.4% during Stim OFF) and could provide spatio-temporal parameters of gait with good accuracy. We found that many of these estimated parameters separate controls, PD patients in ON and OFF states. We also found a high correlation between the gait parameters and UPDRS gait sub-score (e.g. for stride length $r = 0.90, p < 0.001$). The results of this study have been published in a journal

article (Salarian, Russmann *et al.* 2004b) and has been presented in two conferences (Russmann, Salarian *et al.* 2003b; Salarian, Russmann *et al.* 2003a).

We have further improved our algorithm and reduced the number of sensor sites on the body from four to two while keeping the same accuracy in estimation of the spatio-temporal parameters of gait. The method was based on predictions of thigh movements from the shank movements during the gait. For the free moving PD patients, comparing the visual observation, our system had a sensitivity of 95.0% and a specificity of 99.8% in detection of gait which were close to the limit of the accuracy of the visual observation itself. Again we found that many of these estimated parameters separate controls, PD patients in ON and OFF states. The results of this study have been presented in several conferences (Russmann, Salarian *et al.* 2004a; Russmann, Salarian *et al.* 2004b; Salarian, Russmann *et al.* 2005b; Salarian, Russmann *et al.* 2004a).

6. Body posture allocations and posture transitions.

Although several methods based on body fixed sensors have been proposed in the past to detect and classify main body postures in normal subjects, elderly and some pathologic cases, the presence of tremor and bradykinesia in PD patients made the application of these methods to this particular group of patients very difficult. By combining a statistical classifier to detect transitions between postures and a fuzzy classifier to detect the basic body posture, we have proposed a new algorithm that showed significantly better results than the previous methods both in PD patients and aged matched controls. Our algorithm had a sensitivity and specificity of 86.3% and 98.0% in detection of Sitting, 83.6% and 96.5% for Standing, 98.5% and 97.8% for Walking and 91.8% and 99.8% for Lying.

We also o found that many parameters related to the movement pattern of the transitions between sitting and standing were significantly different between ON and OFF states and some of them showed significant correlation to the UPDRS gait and posture sub-score. While some other researchers had used timed *UP & GO* tests with PD patients (Morris, Morris *et al.* 2001), the ambulatory detection and characterizing posture transitions during daily activity in PD patients and quantifying their differences between ON and OFF was not reported before. Base on the results of this study an article has been submitted to an IEEE journal (Salarian, Russmann *et al.* Submitted-a) and also the method and results has been presented in two conferences (Salarian, Russmann *et al.* 2005a; Salarian, Russmann *et al.* 2005b).

7. ON/OFF classification.

By combining the outcomes of the above algorithms using a statistical method, we proposed a new method to detect periods of ON and OFF with a resolution of 10 minutes in free moving PD patients. While currently no other objective ambulatory method exists to accurately detect ON and OFF states in PD patients, we found that it is possible to reach a sensitivity more than 90% and a specificity of more than 76% in detection of OFF periods.

9.2 Perspectives and further studies

9.2.1 Assessment of dyskinesia

Dyskinesia or more levodopa induced dyskinesia (LID), which is a side-effect of the chronic levodopa therapy (Nutt, Carter *et al.* 1995) is an important motor abnormality associated with ON state. While not a symptom of the PD per se, because of its highly disabling manifestation, a *comprehensive* ambulatory monitoring system for PD patients in general, should include its objective assessment. While some other researchers have reported ambulatory methods for assessment of dyskinesia (Burkhard, Shale *et al.* 1999; Hoff, vander Plas *et al.* 2001; Keijsers, Horstink *et al.* 2003b), the available methods are yet young and only been used in small groups of PD patients. Moreover some of the proposed systems require sensors sites that are not very useful in analysis of other PD symptoms (like sites on the shoulders in Keijsers's system) and in general are not compatible with our approach which is based on minimal number of sensors on the body.

At the first step, a new study based on the current MAS and sensor configuration is required to design and validate an algorithm to detect and quantify dyskinesia in free moving PD patient while they are performing their daily activities. In collaboration with CHUV and HUG, we have already started a few measurements using the final prototype of MAS, however, yet the number of recorded cases with dyskinesia is yet too small to develop a reliable algorithm.

9.2.2 Clinical validation of our new MAS for whole day measurements

We have now developed a measurement tool capable of recording the main motor features of PD, with the exception of rigidity (not accessible to measurement with this technique) and dyskinesia. The next logical step is to perform a clinical validation of the method for long-term (or whole day) recordings. Accurate detection of ON and OFF periods will be of great clinical relevance, which could be based on our proposed method (see chapter 8). This will allow a precise understanding of the functional impact of PD for each patient in everyday life, based on reliable and continuous data on motor state evolution.

9.2.3 Detection of Freezing of Gait (FOG) and Festinating Gait (FSG)

Freezing of the gait and festinating gait are common symptoms in PD patients during OFF state. Festination is a tendency to speed up the walking by taking very short steps in parallel with a loss of normal amplitude of the movements. Freezing of the gait occurs at the start or end of walking (start hesitation), during festinating gait or suddenly when patient turns or goes through a narrow doorway. While FSG and FOG are related together (Giladi, Shabtai *et al.* 2001), some recent studies suggest that FOG is not correlated with other parkinsonian features in OFF like bradykinesia, rigidity or postural instability and is apparently an independent motor symptom (Bartels, Balash *et al.* 2003).

We can already detect gait in PD using our method with high accuracy. Therefore, we expect that by recognizing very short gait cycle times, the festinating gait can be detected. Also by analyzing the movements of the shanks exactly before and after each detected walking period, detection of freezing of gait may be possible.

9.2.4 Comparing MAS measurements to metabolic data in PD patients, using FD-PET

Another interesting direction is to use the objective parameters estimated by our method in diagnosis of the Parkinson's disease, its evolution and treatment monitoring.

Based on this idea, we have started a new study to compare the objective outcomes of our system to the quantitative nigrostriatal deficit detected by 18F-6-Fluorodopa (FD) PET (Positron Emission Tomography) analysis in early Parkinson's disease. FD-PET has been validated against clinical scales in PD, and provides quantitative metabolic data on levodopa intake by the striatum, which is reduced in a characteristic manner in PD patients (Vingerhoets, Snow *et al.* 1994). Comparison between FD-PET data and MAS measurements is an important step in the clinical validation of our system. Some of our preliminary results have been presented in the 16th International congress on Parkinson's disease and related disorders (Cereda, Salarian et al. 2005).

9.2.5 Relationship between blood levels of levodopa and the parameters provided by MAS

Forty years after the discovery of its antiparkinsonian properties, levodopa remains the single best treatment for alleviating motor symptoms in PD. There is a correlation between blood levels of levodopa and motor parkinsonian features. Comparison of our MAS measurements with another quantitative parameter is then a further logical step in its clinical validation. Furthermore, this simple tool may well replace the cumbersome method of levodopa blood levels determination.

9.2.6 Other hyperkinetic disorders

Another direction could be developing new methods to identify postural tremor (or essential tremor, ET), chorea, tics and dyskinesia, which can be refined, improved and then validated against clinical scales. Whenever possible, efforts can be directed to adapt existing algorithms developed for PD, rather than designing entirely methods.

For ET, our PD tremor algorithm will need to be adapted for higher frequencies, since this type of tremor usually is in the range of 6 to 10 Hz. Also, ET is a postural and action tremor, a feature that will be of help to distinguish it from other types of tremor like the rest tremor of PD. Dystonia and chorea share some similarities with levodopa-induced dyskinesia of PD.

By designing these algorithms, our MAS can be used in long-term, ambulatory motor assessment of other neurological disorders like Huntington's disease and Tardive syndromes.

Bibliography

Albani, G., Sandrini, G., Kunig, G., Martin-Soelch, C., Mauro, A., Pignatti, R., Pacchetti, C., Dietz, V. and Leenders, K. L. (2003). "Differences in the EMG pattern of lea muscle activation during locomotion in Parkinson's disease." Functional Neurology **18**(3): 165-170.

Aminian, K., Najafi, B., Bula, C., Leyvraz, P.-F. and Robert, P. (2002). "Spatio-temporal parameters of gait measured by an ambulatory system using miniature gyroscopes." Journal of Biomechanics **35**(5): 689-699.

Aminian, K., Rezakhanlou, K., De Andres, E., Fritsch, C., Leyvraz, P. F. and Robert, P. (1999). "Temporal feature estimation during walking using miniature accelerometers: an analysis of gait improvement after hip arthroplasty." Medical & Biological Engineering & Computing **37**(6): 686-691.

Aminian, K., Robert, P., Buchser, E. E., Rutschmann, B., Hayoz, D. and Depairon, M. (1999). "Physical activity monitoring based on accelerometry: validation and comparison with video observation." Medical & Biological Engineering & Computing **37**(3): 304-308.

Aminian, K., Trevisan, C., Najafi, B., Dejnabadi, H., Frigo, C., Pavan, E., Telonio, A., Cerati, F., Marinoni, E. C., Robert, P. and Leyvraz, P. F. (2004). "Evaluation of an ambulatory system for gait analysis in hip osteoarthritis and after total hip replacement." Gait & Posture **20**(1): 102.

Anderson, E., Bai, Z., Bischof, C., Blackford, S., Demmel, J., Dongarra, J., Corz, J. D., Greenbaum, A., Hammarling, S., McKenney, A. and Sorensen, D. (1999). LAPACK User's Guide. Philadelphia, SIAM.

Andreeva, Y. A., Ivanova-Smoielnskaya, I. A., Kandel, E. I. and Khutorskaya, O. Y. (1985). "Envelope EMG spectral analysis in the studies of physiological and pathological tremor." Electroencephalography and Clinical Neurophysiology **25**: 273-293.

Bacher, M., Scholz, E. and Diener, H. C. (1989). "24 hour continuous tremor quantification based on EMG recording." Electroencephalography and Clinical Neurophysiology **72**: 176-183.

Badler, N. I., Phillips, C. B. and Webber, B. L. (1993). Simulating Humans: Computer Graphics, Animation, and Control, Oxford University Press.

Bartels, A. L., Balash, Y., Gurevich, T., Schaafsma, J. D., Hausdorff, J. M. and Giladi, N. (2003). "Relationship between freezing of gait (FOG) and other features of Parkinson's: FOG is not correlated with bradykinesia." Journal of Clinical Neuroscience **10**(5): 584-588.

Benabid, A. L., Benazzouz, A., Hoffmann, D., Limousin, P., Krack, P. and Pollak, P. (1998). "Long-term electrical inhibition of deep brain targets in movement disorders." Movement Disorders: Official Journal Of The Movement Disorder Society **13**(3): 119-125.

Blalock, H. (1961). Causal inference in nonexperimental research. Chapel Hill, UNC Press.

Boose, A., Spieker, S., Jentgens, C. and Dichgans, J. (1996). "Wrist tremor: investigation of agonist-antagonist interaction by means of long-term EMG recording and cross-spectral analysis."

Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control **101**(4): 355-363.

Boraud, T., Tison, F. and Gross, C. (1997). "Quantification of Motor Slowness in Parkinson's Disease: Correlations Between the Tapping Test and Single Joint Ballistic Movement Parameters." Parkinsonism & Related Disorders **3**(1): 47-50.

Brown, R. G., Maccarthy, B., Jahanshahi, M. and Marsden, C. D. (1989). "Accuracy Of Self-Reported Disability In Patients With Parkinsonism." Archives Of Neurology **46**(9): 955-959.

Burg, J. P. (1975). Maximum Entropy Spectral Analysis. Department of Geophysics, Stanford university.

Burkhard, P. R., Langston, J. W. and Tetrud, J. W. (2002). "Voluntarily simulated tremor in normal subjects." Neurophysiologie Clinique/Clinical Neurophysiology **32**(2): 119-126.

Burkhard, P. R., Shale, H., Langston, J. W. and Tetrud, J. W. (1999). "Quantification of dyskinesia in Parkinson's disease: validation of a novel instrumental method." Movement Disorders: Official Journal of the Movement Disorder Society **14**(5): 754-763.

Bussmann, H. B. J., Reuvekamp, P. J., Veltink, P. H., Martens, W. L. J. and Stam, H. J. (1998). "Validity and reliability of measurements obtained with an "activity monitor" in people with and without a transtibial amputation." Physical Therapy **78**(9): 989-998.

Bussmann, J. B. J., Martens, W. L. J., Tulen, J. H. M., Schasfoort, F. C., van den Berg-Emons, H. J. G. and Stam, H. J. (2001). "Measuring daily behavior using ambulatory accelerometry: The activity monitor." Behavior Research Methods Instruments & Computers **33**(3): 349-356.

Cereda, C. W., Salarian, A., Allaoua, M., Aminian, K., Burkhard, P. R. and Vingerhoets, F. J. G. (2005). Long Term Ambulatory Gait Analysis in Parkinson's Disease Correlates with Nigrostriatal Dopaminergic Deficit Observed on Fluorodopa Positron Emission Tomography (PET). . Presented in 16th International Congress on Parkinson´s Disease and Related Disorders, Berlin.

Cioni, M., Richards, C. L., Malouin, F., Bedard, P. J. and Lemieux, R. (1997). "Characteristics of the electromyographic patterns of lower limb muscles during gait in patients with Parkinson's disease when OFF and ON L-Dopa treatment." Italian Journal of Neurological Sciences **18**(4): 195-208.

Delwaide, P. J. and Gonce, M. (1998). Pathology of Parkinson's Signs. Parkinson's Disease and Movement Disorders. J. Jankovic and E. Tolosa, Williams & Wilkins**:** 159-176.

Desrosiers, J., Hebert, R., Bravo, G. and Dutil, E. (1995). "The Purdue Pegboard Test - Normative Data for People Aged 60 and Over." Disability and Rehabilitation **17**(5): 217-224.

Deuschl, G., Bain, P. and Brin, M. (1998). "Consensus statement of the Movement Disorder Society on tremor." Movement Disorders **13**: 2-23.

Dietz, V. and Colombo, G. (1998). "Influence of body load on the gait pattern in Parkinson's disease." Movement Disorders **13**(2): 255-261.

Dunnewold, R. J., Hoff, J. I., van Pelt, H. C., Fredrikze, P. Q., Wagemans, E. A. and van Hilten, B. J. (1998). "Ambulatory quantitative assessment of body position, bradykinesia, and hypokinesia in Parkinson's disease." Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society **15**(3): 235-242.

Dunnewold, R. J. W., Jacobi, C. E. and van Hilten, J. J. (1997). "Quantitative assessment of bradykinesia in patients with parkinson's disease." Journal of Neuroscience Methods **74**(1): 107-112.

Eberhart, R. C. (1999). Tremor quantification using digital actigraphy. Presented in BMES/EMBS Conference, 1999. Proceedings of the First Joint, Purdue Sch. of Eng. & Technol., Indianpolis, IN, USA, Experimental.

Efron, B. and Tibshirani, R. J. (1993). An introduction to the bootstrap. New York, Chapman & Hall.

Fahn, S., Elton, R. L. and Members of the UPDRS Development Committee (1987). Unified Parkinson's Disease Rating Scale. Recent developments in Parkinson's Disease. S. Fahn, C. D. Marsden, D. Calne and M. Goldstein. Florhan Park, New Jersay, Mc Millan Health Care Information. **II:** 153-163.

Ferrarin, M., Lopiano, L., Rizzone, M., Lanotte, M., Bergamasco, B., Recalcati, M. and Pedotti, A. (2002). "Quantitative analysis of gait in Parkinson's disease: a pilot study on the effects of bilateral sub-thalamic stimulation." Gait & Posture **16**(2): 135-148.

Foerster, F. and Smeja, M. (1999). "Joint amplitude and frequency analysis of tremor activity." Electromyography and Clinical Neurophysiology **39**(1): 11-19.

Frost, J. D., Jr (1978). "Triaxial vector accelerometry: a method for quantifying tremor and ataxia." IEEE Transactions on Biomedical Engineering **25**(1): 17-27.

Fujikane, M., Yokota, N., Hirata, K. and Katayama, S. (1995). "Quantitative evaluation of Akinesia in Parkinson disease using actigraph." Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control **97**(4): S147.

Ghika, J., Wiegner, A. W., Fang, J. J., Davies, L., Young, R. R. and Growdon, J. H. (1993). "Portable system for quantifying motor abnormalities in Parkinson's disease." IEEE Transactions on Biomedical Engineering **40**(3): 276-283.

Giannini, S., Catani, F., Benedetti, M. G. and Leardini, L. (1994). Gait analysis: methodologies and clinical applications, IOS press.

Gibb, W. R. and Lees, A. J. (1988). "The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease." J Neurol Neurosurg Psychiatry **51**(6): 745-752.

Giladi, N., Shabtai, H., Rozenberg, E. and Shabtai, E. (2001). "Gait festination in Parkinson's disease." Parkinsonism & Related Disorders **7**(2): 135-138.

Giovannoni, G., van Schalkwyk, J., Fritz, V. U. and Lees, A. J. (1999). "Bradykinesia akinesia incoordination test (BRAIN TEST): an objective computerised assessment of upper limb motor function." Journal of Neurology, Neurosurgery, and Psychiatry **67**(5): 624-629.

Hallett, M. (1998). "Overview of human tremor physiology." Movement Disorders **13**: 43-48.

Hastie, T., Tibshirani, R. and Friedman, J. H. (2001). The elements of statistical learning: data mining, inference and prediction, Springer-Verlag.

Hoehn, M. M. and Yahr, M. D. (1967). "Parkinsonism - Onset Progression and Mortality." Neurology **17**(5): 427-&.

Hof, A. L. (1996). "Scaling gait data to body size." Gait & Posture **4**(3): 222-223.

Hof, A. L. and Zijlstra, W. (1997). "Comment on "normalization of temporal-distance parameters in pediatric gait"." Journal of Biomechanics **30**(3): 299-299.

Hoff, J. I., Van Der Meer, V. and Van Hilten, J. J. (2004). "Accuracy of Objective Ambulatory Accelerometry in Detecting Motor Complications in Patients with Parkinson Disease." Clinical Neuropharmacology **27**(2): 53.

Hoff, J. I., vander Plas, A. A., Wagemans, E. A. H. and van Hilten, J. J. (2001). "Accelerometric assessment of levodopa-induced dyskinesias in Parkinson's disease." Movement Disorders **16**(1): 58-61.

Hoff, J. I., Wagemans, E. A. and van Hilten, B. J. (2001). "Ambulatory objective assessment of tremor in Parkinson's disease." Clinical Neuropharmacology **24**(5): 280-283.

Hosmer, D. W. and Lemeshow, S. (1989). Applied Logistic Regression. New York, John Wiley & Sons.

Hughes, A. J., Daniel, S. E., Kilford, L. and Lees, A. J. (1992). "Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases." Journal Of Neurology, Neurosurgery, And Psychiatry **55**(3): 181-184.

Inman, V. T., H.J., R. and F., T. (1981). Human walking. Baltimore, Williams and Wilkins.

Jerri, A. J. (1998). The Gibbs Phenomenon in Fourier Analysis, Splines and Wavelet Approximations. Dordrecht, Netherlands, Kluwer.

Judge, G. G., Hill, R. C., Griffiths, W. E., Lütkepohl, H. and Lee, T.-C. (1988). Introduction to the Theory and Practice of Economics. New York, Wiley.

Katayama, S. (2001). "Actigraph analysis of diurnal motor fluctuations during dopamine agonist therapy." European Neurology **46**: 11-17.

Keijsers, N. L. W., Horstink, M. and Gielen, S. (2003a). "Automatic assessment of levodopa-induced dyskinesias in daily life by neural networks." Movement Disorders **18**(1): 70-80.

Keijsers, N. L. W., Horstink, M. and Gielen, S. (2003b). "Movement parameters that distinguish between voluntary movements and levodopa-induced dyskinesia in Parkinson's disease." Human Movement Science **22**(1): 67-89.

Keijsers, N. L. W., Horstink, M. and Gielen, S. (2003c). "Online monitoring of dyskinesia in patients with Parkinson's disease." IEEE Engineering in Medicine and Biology Magazine **22**(3): 96-103.

Kiani, K., Snijders, C. J. and Gelsema, E. S. (1997). "Computerized analysis of daily life motor activity for ambulatory monitoring." Technol. Health Care **5**(4): 307-318.

Krystkowiak, P., Defebure, L. J. P., Blatt, J. L., Bourriez, J. L., Blond, S., Guieu, J. D. and Destee, A. (2000). "Influence of subthalamic nucleus stimulation on gait in Parkinson's disease: A study using the optoelectronic VICON system." Neurology **54**(7): A446-A446.

Lackovic, I., Bilas, V., Santic, A. and Nikolic, V. (2000). "Measurement of gait parameters from free moving subjects." Measurement **27**(2): 121-131.

Lang, A. E. and Fahn, S. (1989). Assessment of Parkinson's disease. Quantification of Neurologic Deficit. T. Munsat. Stoneham, Butterworth-Heinemann**:** 285-301.

Lang, A. E. and Lozano, A. M. (1998a). "Parkinson's disease. First of two parts." The New England Journal Of Medicine **339**(15): 1044-1053.

Lang, A. E. and Lozano, A. M. (1998b). "Parkinson's disease. Second of two parts." The New England Journal Of Medicine **339**(16): 1130-1143.

Larsen, T. A., LeWitt, P. A. and Calne, D. B. (1983). Theoretical and practical issues in assessment of deficits and therapy in parkinsonism. Lisuride and other dopamine agonists. D. B. Calne, R. J. McDonald, R. Horowski and W. Wuttke. New York, Raven Press**:** 363-373.

Mamdani, E. H. (1977). "Applications of fuzzy logic to approximate reasoning using linguistic synthesis." IEEE Transactions on Computers **26**(12): 1182-1191.

Manson, A. J., Brown, P., O'Sullivan, J. D., Asselman, P., Buckwell, D. and Lees, A. J. (2000). "An ambulatory dyskinesia monitor." Journal of Neurology, Neurosurgery, and Psychiatry **68**(2): 196-201.

Marsden, C., Parkes, J. and Quinn, N. (1981). Fluctuations of disability in Parkinson's disease: clinical aspects. Movement Disorders. C. Marsden and S. Fahn. London, Butterworth Scientific**:** 96-122.

Martinez-Martin, P. (1993). Rating scales in Parkinson's disease. Parkinson's disease and movement disorders. J. Jankovic and E. Tolosa. Baltimore, Williams & Wilkins**:** 281-292.

Melnick, M. E., Radtka, S. A., Sierra, N., Marks, W. J. and Starr, P. A. (2000). "Effects of deep brain stimulation on gait parameters using 3- dimensional gait analysis." Neurology **54**(7): A457-A457.

Mitoma, H., Hayashi, R., Yanagisawa, N. and Tsukagoshi, H. (2000). "Characteristics of parkinsonian and ataxic gaits: a study using surface electromyograms, angular displacements and floor reaction forces." Journal of the Neurological Sciences **174**(1): 22-39.

Mochio, S., Oka, H., Sato, H., Katayama, K., Kurita, A. and Inoue, K. (1997). "Quantitative evaluation of motor activity in Parkinson's disease using actigraphy." Journal of the Neurological Sciences **150**(1): S299.

Moe-Nilssen, R. and Helbostad, J. L. (2004). "Estimation of gait cycle characteristics by trunk accelerometry." Journal of Biomechanics **37**(1): 121-126.

Morris, M. E., McGinley, J., Huxham, F., Collier, J. and Iansek, R. (1999). "Constraints on the kinetic, kinematic and spatiotemporal parameters of gait in Parkinson's disease." Human Movement Science **18**(2-3): 461-483.

Morris, S., Morris, M. E. and Iansek, R. (2001). "Reliability of measurements obtained with the Timed "Up & Go" Test in people with Parkinson disease." Physical Therapy **81**(2): 810-818.

Najafi, B., Aminian, K., Loew, F., Blanc, Y. and Robert, P. A. (2002). "Measurement of stand-sit and sit-stand transitions using a miniature gyroscope and its application in fall risk evaluation in the elderly." IEEE Transactions on Bio-Medical Engineering **49**(8): 843-851.

Najafi, B., Aminian, K., Paraschiv-Ionescu, A., Loew, F., Bula, C. J. and Robert, P. (2003). "Ambulatory system for human motion analysis using a kinematic sensor: monitoring of daily physical activity in the elderly." IEEE Transactions on Biomedical Engineering **50**(6): 711-723.

Ng, J., Sahakian, A. V. and Swiryn, S. (2000). Sensing and documentation of body position during ambulatory ECG monitoring. Presented in Computers in Cardiology, Cambridge, MA.

Norman, K. E., Edwards, R. and Beuter, A. (1999). "The measurement of tremor using a velocity transducer: comparison to simultaneous recordings using transducers of displacement, acceleration and muscle activity." Journal of Neuroscience Methods **92**(1-2): 41-54.

Nutt, J. G. (1990). "Levodopa-induced dyskinesia: review, observations, and speculations." Neurology **40**(2): 340-345.

Nutt, J. G., Carter, R. N. and Woodward, W. R. (1995). "Long-duration resopnse to levadopa." Neurology **45**: 1613-1616.

O'Sullivan, J. D., Said, C. M., Dillon, L. C., Hoffman, M. and Hughes, A. J. (1998). "Gait analysis in patients with Parkinson's disease and motor fluctuations: Influence of levodopa and comparison with other measures of motor function." Movement Disorders **13**(6): 900-906.

Oppenheim, A. V. and Shafer, R. W. (1998). Discrete-Time Signal Processing, Prentice-Hall.

Õunpuu, S. (1994). Terminology for clinical gait analysis (Draft #2), Gait and Clinical Movement Analysis Society.

Paraschiv-Ionescu, A., Buchser, E. E., Rutschmann, B., Najafi, B. and Aminian, K. (2004). "Ambulatory system for the quantitative and qualitative analysis of gait and posture in chronic pain patients treated with spinal cord stimulation." Gait & Posture **20**(2): 113-125.

Parkinson, J. (1817). An essay on the shaking palsy. London: Sherwood, Neely and Jones.

Pataky, Z., Faravel, L., Da Silva, J. and Assal, J.-P. (2000). "A new ambulatory foot pressure device for patients with sensory impairment. A system for continuous measurement of plantar pressure and a feed-back alarm." Journal of Biomechanics **33**(9): 1135-1138.

Patrick, S. K., Denington, A. A., A.Gauthier, M. J., Gillard, D. M. and Prochazka, A. (2001). "Quantification of the UPDRS rigidity scale." IEEE Transactions on Neural Systems and Rehabilitation Engineering **9**(1): 31-41.

Perry, J. (1992). Gait analysis: Normal and Pathological function. Thorofare, NJ, Slack Inc.

Petit, H., Allain, H. and Vermersch, P. (1994). La Maladie de Parkinson. Clinique et Thérapeutique. Paris, Masson.

Reddon, J. R., Gill, D. M., Gauk, S. E. and Maerz, M. D. (1988). "Purdue Pegboard - Test-Retest Estimates." Perceptual and Motor Skills **66**(2): 503-506.

Russmann, H., Salarian, A., Aminian, K., Villemure, J., Burkhard, P. R. and Vingerhoets, F. J. (2004a). "Longtem ambulatory gait monitoring in Parkinson's disease: Validation of a new wireless measurement system." Movement Disorders **19**: S247-S247.

Russmann, H., Salarian, A., Aminian, K., Wider, C., Villemure, J.-G., Burkhard, P. R. and Vingerhoets, F. J. G. (2004b). Free Ambulatory Gait Monitoring in Patients with Parkinson's Disease. Presented in AAN 2004, San Franscisco, US.

Russmann, H., Salarian, A., Burkhard, P. R., Aminian, K., Villemure, J.-G., Blanc, Y., Dehollain, C. and Vingerhoets, F. J. G. (2003a). A Portable System for Objective Ambulatory Quantification of the Effect of STN-DBS on Bradykinesia and Tremor. Presented in XV International Congress on Parkinson's Disease, Beijing, China, 2003.

Russmann, H., Salarian, A., Burkhard, P. R., Blanc, Y., Aminian, K. and Vingerhoets, F. J. G. (2002). Objective quantification of bradykinesia in Parkinson's Disease. Presented in Congrès de la Société Suisse de Neurologie, Swiss Archives of Neurology and Psychiatry, Lausanne, Switzerland.

Russmann, H., Salarian, A., Vingerhoets, F. J. G., Aminian, K., Villemure, J.-G., Blanc, Y., Dehollain, C. and Burkhard, P. R. (2003b). Ambulatory measurement of gait parameters in Park-

inson's disease with and without STN DBS compared to normal control subjects. Presented in XV International Congress on Parkinson's Disease, Beijing, China.

Sabatini, A. M., Martelloni, C., Scapellato, S. and Cavallo, F. (2005). "Assessment of walking features from foot inertial sensing." IEEE Transactions on Biomedical Engineering **52**(3): 486.

Salarian, A., Russmann, H., Vingerhoets, F. J. G., Burkhard, P. R. and Aminian, K. (2005a). Ambulatory analysis of physical activities in Parkinson's disease using kinematics sensors. Presented in 3rd annual meeting of Swiss Scoiety for Biomedical Engineering, SSBE 2005, Lausanne, Switzerland.

Salarian, A., Russmann, H., Vingerhoets, F. J. G., Burkhard, P. R. and Aminian, K. (Submitted-a). "Ambulatory monitoring of the physical activities in patients with Parkinson's disease." Sumbitted to IEEE Transactions on Bio-Medical Engineering.

Salarian, A., Russmann, H., Vingerhoets, F. J. G., Burkhard, P. R. and Amininan, K. (2005b). Ambulatory analysis of gait and posture in Parkinson's disease: a novel method based on kinematics sensors. Presented in XVIIth conference on Posture and Gait Research (ISPGR), Mareseille, France.

Salarian, A., Russmann, H., Vingerhoets, F. J. G., Burkhard, P. R., Blanc, Y., Dehollain, C. and Aminian, K. (2003a). Ambulatory measurement of gait parameters in Parkinson's disease: Effects of subthalamic stimulation. Presented in International Society for Postural and Gait Research (ISPGR), Sydney, Autralia.

Salarian, A., Russmann, H., Vingerhoets, F. J. G., Burkhard, P. R., Blanc, Y., Dehollain, C. and Amininan, K. (2003b). An ambulatory system to quantify bradykinesia and tremor in Parkinson's disease. Presented in 4th International IEEE EBMS Special Topic Conference on Information Technology Applications in Biomedicine, Birmingham, UK, IEEE.

Salarian, A., Russmann, H., Vingerhoets, F. J. G., Burkhard, P. R., Dehollain, C. and Aminian, K. (2004a). Ambulatory gait analysis in Parkinson's Disease: Application of a novel method based on kinematics sensors. Presented in 13th Annual meeting of ESCMAC, Warsaw, Poland, ESMAC.

Salarian, A., Russmann, H., Vingerhoets, F. J. G., Dehollain, C., Blanc, Y., Burkhard, P. R. and Aminian, K. (2004b). "Gait Assessment in Parkinson's Disease: Toward an Ambulatory System for Long-Term Monitoring." IEEE Transactions on Biomedical Engineering **51**(8): 1434-1443.

Salarian, A., Russmann, H., Wider, C., Burkhard, P. R., Vingerhoets, F. J. G. and Aminian, K. (Submitted-b). "Quantification of tremor and bradykinesia in Parkinson's disease using a novel ambulatory monitoring system." Sumbitted to IEEE Transactions on Bio-Medical Engineering.

Scholz, E. and Bacher, M. (1995). Problems in measurement of parkinsonian tremor. Handbook of tremor disorders. L. Findley and W. Koller. New York, Marcel Dekker**:** 293-311.

Scholz, E., Bacher, M., Diener, H. C. and Dichgans, J. (1988). "Twenty-four-hour tremor recordings in the evaluation of the treatment of Parkinson's disease." Journal of Neurology **235**(8): 475-484.

Schrag, A., Jahanshahi, M. and Quinn, N. (2000). "How does Parkinson's disease affect quality of life? A comparison with quality of life in the general population." Movement Disorders **15**(6): 1112-1118.

Sekine, M., Tamura, T., Akay, M., Fujimoto, T., Togawa, T. and Fukui, Y. (2002). "Discrimination of walking patterns using wavelet-based fractal analysis." Neural Systems and Rehabilitation

Engineering, IEEE Transactions on [see also IEEE Trans. on Rehabilitation Engineering] **10**(3): 188-196.

Selles, R. W., Formanoy, M. A. G., Bussmann, J. B. J., Janssens, P. J. and Stam, H. J. (2005). "Automated estimation of initial and terminal contact timing using accelerometers; development and validation in transtibial amputees and controls." Neural Systems and Rehabilitation Engineering, IEEE Transactions on [see also IEEE Trans. on Rehabilitation Engineering] **13**(1): 81.

Smeja, M., Foerster, F., Fuchs, G., Emmans, D., Hornig, A. and Fahrenberg, J. (1999). "24-h assessment of tremor activity and posture in Parkinson's disease by multi-channel accelerometry." Journal of Psychophysiology **13**(4): 245-256.

Spieker, S., Boose, A., Breit, S. and Dichgans, J. (1998). "Long-term measurement of tremor." Movement Disorders: Official Journal of the Movement Disorder Society **13**(3): 81-84.

Stern, M. B. and Koller, W. C. (1993). Parkinson's disease. Parkinsonian syndromes. M. B. Stern and W. C. Koller. New York, Marcel Dekker Inc.

Temperli, P., Ghika, J., Villemure, J. G., Burkhard, P. R., Bogousslavsky, J. and Vingerhoets, F. J. G. (2003). "How do parkinsonian signs return after discontinuation of subthalamic DBS?" Neurology **60**(1): 78-81.

Tong, K. Y. and Granat, M. H. (1999). "A practical gait analysis system using gyroscopes." Medical Engineering & Physics **21**(2): 87-94.

Van Someren, E. J. (1997). "Actigraphic monitoring of movement and rest-activity rhythms in aging, Alzheimer's disease, and Parkinson's disease." IEEE Transactions on Rehabilitation Engineering: a Publication of the IEEE Engineering in Medicine and Biology Society **5**(4): 394-398.

Van Someren, E. J. W., Vangool, W. A., Vonk, B. F. M., Mirmiran, M., Speelman, J. D., Bosch, D. A. and Swaab, D. F. (1993). "Ambulatory Monitoring of Tremor and Other Movements before and after Thalamotomy - a New Quantitative Technique." Journal of the Neurological Sciences **117**(1-2): 16-23.

Van Someren, E. J. W., Vonk, B. F. M., Thijssen, W. A., Speelman, J. D., Schuurman, P. R., Mirmiran, M. and Swaab, D. F. (1998). "A new actigraph for long-term registration of the duration and intensity of tremor and movement." IEEE Transactions on Biomedical Engineering **45**(3): 386-395.

Veltink, P. H., Bussmann, H. B., de Vries, W., Martens, W. L. and Van Lummel, R. C. (1996a). "Detection of static and dynamic activities using uniaxial accelerometers." IEEE Transactions On Rehabilitation Engineering: a Publication Of The IEEE Engineering In Medicine And Biology Society **4**(4): 375.

Veltink, P. H., Bussmann, H. J., de Vries, W., Martens, W. J. and Van Lummel, R. C. (1996b). "Detection of static and dynamic activities using uniaxial accelerometers." Rehabilitation Engineering, IEEE Transactions on [see also IEEE Trans. on Neural Systems and Rehabilitation] **4**(4): 375-385.

Vingerhoets, F. J. G., Snow, B. J., Lee, C. S., Schulzer, M., Mak, E. and Calne, D. B. (1994). "Longitudinal fluorodopa positron emission tomographic studies of the evolution of idiopathic parkinsonism." Annals of Neurology **36**(5): 759-761.

Vingerhoets, F. J. G., Villemure, J.-G., Temperli, P., Pollo, C., Pralong, E. and Ghika, J. (2002). "Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up." Neurology **58**(3): 396-401.

Von Campenhausen, S., Bornschein, B., Dodel, R., Wick, R., Oertel, W., Berger, K., Sampaio, C., Poewe, W., Bötzel, K. and Siebert, U. (2005). "Prevalence and incidence of Parkinson's disease in Europe." European Neuropsychopharmacology **15**(4): 473-490.

Wasserman, L. (2004). All of statistics: a concise course in statistical inference. New York, Springer.

Watts, R. L. and Mandir, A. S. (1992). Quantitative methods of evaluating Parkinson's disease. The Scientific basis for the treatment of Parkinson's disease. C. W. Olanow and A. N. Lieberman. Park Ridge, Parthenon Publishing Group**:** 13-32.

Wilcoxon, F. (1945). "Individual Comparisons by Ranking Methods." Biometrics **1**: 80-83.

Willemsen, A. T. M., Bloemhof, F. and Boom, H. B. K. (1990). "Automatic stance-swing phase detection from accelerometer data for peroneal nerve stimulation." IEEE Transactions on Biomedical Engineering **37**(12): 1201-1208.

Zappia, M., Montesanti, R., Colao, R. and Quattrone, A. (1994). "Usefulness Of Movement Time In The Assessment Of Parkinsons-Disease." Journal Of Neurology **241**(9): 543-550.

Zijlmans, J. C. M., Poels, P. J. E., Duysens, J., vanderStraaten, J., Thien, T., vantHof, M. A., Thijssen, H. O. M. and Horstink, M. (1996). "Quantitative gait analysis in patients with vascular parkinsonism." Movement Disorders **11**(5): 501-508.

Zijlstra, W. and Hof, A. L. (2003). "Assessment of spatio-temporal gait parameters from trunk accelerations during human walking." Gait & Posture **18**(2): 1-10.

Curriculum Vitae

Personal Information

Name: Arash Salarian

Date of birth: 22 February 1972

Place of birth: Isfahan, Iran

Marital Status: Married

Email: arash.salarian@ieee.org

Education

2001-2005: EPFL, Lausanne, Switzerland

Research Assistant and PhD student at the Laboratory of Movement Analysis and Measurement.

1994-1997: Sharif University of Technology, Tehran, Iran

Masters of Science in Computer Architecture.

Thesis: Design and implementation of a hardware accelerator for logic simulation.

1990-1994: Isfahan University of Technology, Isfahan, Iran

Bachelor of Science in Computer engineering.

Thesis: Design and implementation of a real-time graphics library.

Thesis: Surveying data compression algorithms.

Working Experiences

1999-2001: Design Engineer in Basaamad Azma Co., Tehran, Iran

Designing DSP applications in FPGAs.

1997-1999: Design Engineer in Fara Pradaz Co., Tehran, Iran

Designing various IP cores for telephony applications.

1995-1997: Teacher Assistant in Sharif University of Technology, Tehran, Iran.

TA in Electronics and Digital Electronics Lab.

1993-1994: Teacher Assistant in Isfahan University of Technology, Isfahan, Iran.

TA in Peripheral Systems Lab.

Professional Affiliations

IEEE Institute of Electrical and Electronics Engineers. Member of Engineering in Medicine and Biology Society (EMBS) and the Computer society.

SSBE Swiss Society for Biomedical Engineering.

Publications

Gait assessment in Parkinson's disease: Toward an ambulatory system for long-term monitoring, A. Salarian, H. Russmann, F.J.G. Vingerhoets , C. Dehollain, Y. Blanc, P. R. Burkhard, K. Aminian, IEEE Transactions on Biomedical Engineering, Vol. 51, No. 8, pp. 1434-1443 Aug. 2004

Longterm ambulatory gait monitoring in Parkinson's disease: Validation of a new wireless measurement system, H. Russmann, A. Salarian, K. Aminian, J. Villemure, P.R. Burkhard, F.J.G. Vingerhoets, Movement Disorders, 2004, **19**: p. S247-S247

Quantification of tremor and bradykinesia in Parkinson's disease using a novel ambulatory monitoring system, A. Salarian, H. Russmann, C. Wider, P. R. Burkhard, F.J.G. Vingerhoets, K. Aminian, submitted to IEEE Transactions on Biomedical Engineering.

Ambulatory monitoring of the physical activities in patients with Parkinson's disease, A. Salarian, H. Russmann, F.J.G. Vingerhoets, P. R. Burkhard, K. Aminian, submitted to IEEE Transactions on Biomedical Engineering

Conferences

Ambulatory analysis of gait and postures in Parkinson's Disease: a novel method based on kinematics sensors, A. Salarian, H. Russmann, F.J.G. Vingerhoets, P. R. Burkhard, K. Aminian, XVIIth conference on Posture and Gait Research (ISPGR), Marseille, France, 2005 also published in Gait and Posture, vol 21, S1, pp. S98, 2005

Ambulatory gait analysis in Parkinson's disease: Application of a novel method based on kinematics sensors, A. Salarian, H. Russmann, F.J.G. Vingerhoets, P.R. Burkhard, C. Dehollain, K. Aminian, 13th Annual Meeting of European Society for Movement Analysis of Adults and Children (ESMAC), pp. 102, Warsaw, Poland, Sep. 2004 also published in Gait and Posture 20S, S61, 2004

Ambulatory measurement of gait parameters in Parkinson's disease: Effects of subthalamic stimulation, A. Salarian, H. Russmann, F.J.G. Vingerhoets, P. R. Burkhard, Y. Blanc, C. Dehollain, K. Aminian, International Society for Postural and Gait Research (ISPGR), March 2003

An ambulatory system to quantify bradykinesia and tremor in Parkinson's disease, A. Salarian, H. Russmann, F. J. G. Vingerhoets, P. R. Burkhard, Y. Blanc, C. Dehollain, and K. Amininan, 4th International IEEE EMBS Special Topic Conference on Information Technology Applications in Biomedicine, Birmingham, pp. 35-38, UK, 2003.

Other publications

Ambulatory analysis of physical activities in Parkinson's disease using kinematics sensors, A. Salarian, H. Russmann, F.J.G. Vingerhoets, P.R. Burkhard, K. Aminian, presented in the 3rd annual meeting of Swiss Scoiety for Biomedical Engineering, SSBE 2005, Lausanne, Septermber 2005

Long Term Ambulatory Gait Analysis in Parkinson's Disease Correlates with Nigrostriatal Dopaminergic Deficit Observed on Fluorodopa Positron Emission Tomography (PET), C.W. Cereda, A. Salarian, M. Allaoua, K. Aminian, P.R. Burkhard and F.J.G. Vingerhoets, presented at 16th International Congress on Parkinson´s Disease and Related Disorders, Berlin, 2005

Stratégie de marche et optimisation des performances chez les randonneurs, M. Casado Hernández, A. Salarian, O. Deriaz, M. Praz, K. Aminian, symposium de Questions de Sport, Institut des Sciences du Sport et de l'Éducation Physique (SSEP), Geneve, Nov. 2004

Free Ambulatory Gait Monitoring in Patients with Parkinsons Disease, H. Russmann, A. Salarian, K. Aminian, J.G. Villemure, P.R. Burkhard, F.J.G. Vingerhoets, 56th Annual Meeting of the American Academy of Neurology (AAN), April 24 - May 1, 2004

A Portable System for Objective Ambulatory Quantification of the Effect of STN-DBS on Bradykinesia and Tremor, H. Russmann, A. Salarian, P. R. Burkhard, K. Aminian, JG Villemure, Y. Blanc, C. Dehollain, F. J. G. Vingerhoets, XV International Congress on Parkinson's Disease, Beijing, China, 2003

Ambulatory measurement of gait parameters in Parkinson's disease with and without STN DBS compared to normal control subjects, H. Russmann, A. Salarian, F. J. G. Vingerhoets, K. Aminian, JG Villemure, Y. Blanc, C. Dehollain, P. R. Burkhard, XV International Congress on Parkinson's Disease, Beijing, China, 2003

Objective effects of STN-DBS on gait parameters in Parkinson's disease, H. Russmann, A. Salarian, F. J. G. Vingerhoets, Y. Blanc, K. Aminian, P. R. Burkhard, Congrès de la Société Suisse de Neurologie, Swiss Archives of Neurology and Psychiatry, 18.-22. November 2002

Objective quantification of bradykinesia in Parkinson's Disease, H. Russmann, A. Salarian, P. R. Burkhard, Y. Blanc, K. Aminian, F. J. G. Vingerhoets, Congrès de la Société Suisse de Neurologie, Swiss Archives of Neurology and Psychiatry, 18.-22. November 2002