Sensor-based knowledge- and data-driven methods

A case of Parkinson’s disease motor symptoms quantification

SOMAYEH AGHANAVESI
Abstract

The overall aim of this thesis was to develop and evaluate new knowledge- and data-driven methods for supporting treatment and providing information for better assessment of Parkinson’s disease (PD).

PD is complex and progressive. There is a large amount of inter- and intravariability in motor symptoms of patients with PD (PwPD). The current evaluation of motor symptoms that are done at clinics by using clinical rating scales is limited and provides only part of the health status of PwPD. An accurate and clinically approved assessment of PD is required using frequent evaluation of symptoms.

To investigate the problem areas, the thesis adopted the microdata analysis approach including the stages of data collection, data processing, data analysis, and data interpretation. Sensor systems including smartphone and tri-axial motion sensors were used to collect data from advanced PwPD experimenting with repeated tests during a day. The experiments were rated by clinical experts. The data from sensors and the clinical evaluations were processed and used in subsequent analysis.

The first three papers in this thesis report the results from the investigation, verification, and development of knowledge- and data-driven methods for quantifying the dexterity in PD. The smartphone-based data collected from spiral drawing and alternate tapping tests were used for the analysis. The results from the development of a smartphone-based data-driven method can be used for measuring treatment-related changes in PwPD. Results from investigation and verification of an approximate entropy-based method showed good responsiveness and test-retest reliability indicating that this method is useful in measuring upper limb temporal irregularity.

The next two papers, report the results from the investigation and development of motion sensor-based knowledge- and data-driven methods for quantification of the motor states in PD. The motion data were collected from experiments such as leg agility, walking, and rapid alternating movements of hands. High convergence validity resulted from using motion sensors during leg agility tests. The results of the fusion of sensor data gathered during multiple motor tests were promising and led to valid, reliable and responsive objective measures of PD motor symptoms.

Results in the last paper investigating the feasibility of using the Dynamic Time-Warping method for assessment of PD motor states showed it is feasible to use this method for extracting features to be used in automatic scoring of PD motor states.

The findings from the knowledge- and data-driven methodology in this thesis can be used in the development of systems for follow up of the effects of treatment and individualized treatments in PD.

Keywords: Parkinson’s disease, motion sensors, motor symptoms, smartphone, microdata, multivariate analysis, data-driven, knowledge-driven, support vector machine stepwise regression, predictive models
The presented research in this thesis was carried out in the Faculty of Data and Information Management, School of Technology and Business Studies, Dalarna University, Sweden during the years 2015-2019. Collection of data was done in a hospital in Uppsala, Sweden.

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Somayeh Aghanavesi
List of Papers

This thesis is based on the following papers. They are referred to in the text by their Roman numerals.


Reprints were made with permission from the respective publishers.
My contributions to the included papers were:

**Paper I** – Data processing, methodology development, data analysis, results interpretation, writing the first version of the manuscript and revising the manuscript.

**Paper II** – Partly involved in method development and data analysis, writing parts of the manuscript and reviewing the rest.

**Paper III** – Data processing, methodology development, data analysis, results interpretation, writing the first version of the manuscript and revising the manuscript.

**Paper IV** – Data processing, methodology development, data analysis, results interpretation, writing the first version of the manuscript and revising the manuscript.

**Paper V** – Data processing, methodology development, data analysis, results interpretation, writing the first version of the manuscript and revising the manuscript.

**Paper VI** – Data processing, methodology development, data analysis, results interpretation, writing the first version of the manuscript and revising the manuscript.
Papers not included in this thesis:


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# Abbreviations

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<td>Analysis of variance</td>
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<td>ApEn</td>
<td>Approximate Entropy</td>
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<td>DDS</td>
<td>DTW-based distance score</td>
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<td>DT</td>
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<td>Dys</td>
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<td>FDA</td>
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<td>MLP</td>
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<td>Principal Component</td>
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<td>PD</td>
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<td>SumUPDRS</td>
<td>Summation of UPDRS Scale items</td>
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<td>SVM</td>
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<td>TIS</td>
<td>Temporal Irregularity Score</td>
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<td>TRIMS</td>
<td>Treatment Response Index from Multiple Sensors</td>
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<td>TRS</td>
<td>Treatment Response Scale</td>
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<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
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<td>WSTS</td>
<td>Wavelet Spiral Test Score</td>
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Introduction

This is a doctoral thesis in the microdata analysis field, a multidisciplinary field that mainly involves research in complex processes, together with the creation and adaptation of tools for analysis of such processes. Microdata analysis is about gathering, modeling, summarizing, and interpreting data and the underlying algorithms, methods, and techniques. The thesis involves measurement techniques, data modeling, and visualization. A complex application domain that microdata analysis is applicable to is Parkinson’s disease (PD). The complexity is related to the variability present in the manifestation of symptoms between patients, within patients and at multiple body segments. This thesis uses a microdata analysis approach to fill the gap between data, information, and knowledge. With this view, the data refers to what was collected by sensors, the information refers to the extracted features, and the knowledge refers to the expertise and insights from the neurologists formed in the rating scores. Therefore, the aim of the thesis from the microdata point of view was developing methods that derive meaningful quantitative measures from raw sensor data, and relating them to neurological expertise. The thesis offers solutions for extracting information about motor symptoms, disease progression, and treatment-related changes using instrumented upper- and lower-limb data from patients with PD. First, the thesis focuses on assessment of fine motor tests and single sensor-based tests. Then, it provides solutions to assess the PD motor symptoms using multiple sensors data collected from upper- and lower-limbs of PD patients.

Parkinson’s disease

Parkinson’s disease is a chronic degenerative disorder of the central nervous system and progresses slowly. The slowly progressing neurodegenerative condition of the disease affects 1% of the population over the age of 60 [3]. Since general life expectancy is increasing, the burden of neurodegenerative disorders like PD will increase [4].

PD is characterized by a large number of motor symptoms that can impact on the motor function to a variable degree. The four cardinal symptoms of PD are tremor, rigidity, bradykinesia and postural instability [5] [6]. Diagnosis of PD is done by clinically evaluating the presence of cardinal symptoms and based on the response to medication. Treatment of PD consists of Levodopa-
Carbidopa oral tablets [7], continuous infusion pumps [8] and deep brain stimulation (DBS) [9]. Levodopa is a dopamine precursor considered as a gold standard oral treatment for PD [10].

Evaluation of the severity of PD symptoms is done by neurologists using the rating scales at clinics. They observe and examine PD symptoms by using rating scales at clinics. There are UPDRS [11], Treatment Response Scale (TRS) [8], dyskinesia scales, and Hoehn & Yahr scale (HY) [12]. UPDRS is the most widely used multidimensional clinical scale for assessing PD motor impairment and disability [13]. The UPDRS items that are used in this thesis are finger taps (#23), rapid alternating movements of hands (#25), leg agility (#26), arising from chair (#27), gait(#29), and body bradykinesia and hypokinesia (#31) each of which scored on a five-point scale ranging from 0 (normal function) to 4 (severe dysfunction). In addition, “SumUPDRS” score is a combined sum of some UPDRS items that were used for the presentation of total impairment. TRS is on a scale of -3 to +3 and ranges from -3 (very “Off”, severe Parkinsonism) to 0 (On, normal mobility) to 3 (Severe dyskinesia, severe choreatic dyskinesia). Dyskinesia scale was used to score the presence of dyskinesia on a scale ranging from 0 to 4 [13]. HY scale [12] is one common scale which is used to describe symptom progression of PD on a scale of 1 to 5. TRS was used by neurological experts to score the physical examination of patients with PD (PwPD) over the course of tests.

Using clinical ratings at clinics needs trained experts and requires PwPD to visit the clinics. PD symptoms change from time to time and require frequent assessment. But it is not feasible to perform a frequent evaluation of symptoms by clinicians since it is time-consuming and costly [14]. Therefore the assessment provides only limited and only part of the health status of the PwPD. Plus, there is inter- and intra-observer variability when using the scales [15]. These limitations affect the healthcare providers to manage the symptoms, improve the clinical outcomes, and offer treatment at an individualized level. These are the reasons for the necessity of repeated, unbiased, and observer-independent measurements to accurately measure a more complete extent of motor symptoms in PD [16].

Sensor-based assessment of PD symptoms

With the previously mentioned problems with PD and the limitations with clinical assessments, it is necessary to develop sensor-based PD motor symptoms assessment methods. The characteristics of responsiveness, accuracy, portability, and objectivity [17] are needed in technology-based objective assessments. The technology-based objective assessments can be seen as the results of instrumented clinical tests, conducted at clinics, and involve a variety of periodic or continuously gathered measures of motor functions to objectively measure specific behaviors in order to detect impairments of PD [18]. In order to improve the accuracy of PD diagnosis, several objective measures
have been proposed such as measures for detecting early PD, quantifying symptom severity, the progression of PD and the treatment responses. It is important that the objective measure can separate the controlled and uncontrolled movements, characterize the severity of symptoms and can discriminate between bradykinesia and dyskinesia. In the coming paragraphs, some potential sources for doing further research for the assessment of PD motor symptoms using sensor data are presented.

Dexterity problems manifest as a result of disruptions in normal motor control processes that are affected by PD [19]. The ability to perform small movements requiring hands, wrists, fingers and eye contact is defined as fine motor skills. PD affects the control of movement variables such as finger position and speed. In previous studies, the assessment of dexterity in PD was done by analyzing upper limb tests data collected by means of touch screen devices [20], [21], [22]. Physical, spatial and temporal properties of movements produced by pen tip recorded by touch screens were previously used for assessing fine motor dysfunctions such as tremor [22], dyskinesia [21], and drawing impairment [23], [24]. Quantitative measures during alternating tapping tests and digital spiral analysis have been previously used as measures of bradykinesia and severity of PD symptoms [20], [25]. However, the development of a smartphone-based system consisting of a combined tapping and spiral drawing tests related to objective measures such as various clinical ratings and actual treatment is required.

One of the disabilities associated with PD is the impaired ability to accurately time movements. Basal ganglia control the speed of a hypothetical “internal clock” which is related to the brain dopaminergic levels [26]. On the other hand, the deterioration of dopaminergic neurons among PwPD is associated with motor symptoms. Studies have shown an increase in timing variability among PwPD when compared to healthy subjects, suggesting the BG has a role in internal timing. For instance, in one study it was shown that treated PwPD had poorer timing control than untreated patients when modulating gait timing during externally-cued conditions [27]. Therefore, relating objective measures obtained by fine motor tests to pathological basal ganglia fluctuations might be beneficial. It can facilitate the assessment of high-frequency motor irregularities that could be difficult to be assessed visually. For this, Approximate Entropy (ApEn) is a technique to quantify the regularity, unpredictability, uncertainty of fluctuations in time-series. This method needs to be investigated by employing it to measure the upper limb temporal irregularity of patients in different stages of PD and healthy elderly subjects during spiral drawing tasks. It would also be of interest to compare the results of this method with the results from other spiral scoring methods.

Further investigation of the ApEn method would be to particularly investigate its clinimetric properties for PD where subjects performed spiral tests during a one-day single-dose levodopa study [28], [29].

Sensor technology includes connected and sensing components embedded in a smartphone and wearables providing means for repeated, long term,
remote, convenient and cost-effective motor symptom assessments which enhance the quality of life of PwPD [18], [30]. According to a review study by Rovini et al. [31], it was reported that there is a small number of studies that used sensor data from lower extremities. From the clinical point of view the leg agility test is seen as the least useful test for measuring PD motor symptoms. However, objective measures calculated from leg agility tests provided good predictors of PD severity [32], [33], [34]. This indicates that leg agility performance provides more information about the motor symptoms of the PwPD than what can be captured during clinical observations by movement disorder experts. In severely disabled patients, e.g. at Hoehn and Yahr stages 4 and 5, where there is a higher risk of falling, the leg agility test could be a better alternative than other examination tests. Therefore, developing methods that can quantify the PD motor states using data from leg agility tests, related to clinical rating scales and responsive to treatment are needed.

A complexity in PD is that the level and time of the day for manifestation of motor impairment fluctuate considerably within and between PwPD. To detect the motor state changes and identify individual PD-related symptom details and to derive individualized treatment plans, frequent and multiple sensor-based measurement of UPDRS-based tests may provide useful information [18]. Some works have quantified wearable sensor data collected from multiple limbs of PwPD and shown good results [35], [36], [37]. Despite the proposal and development of various methods, from the clinical point of view, their specificity and sensitivity are not sufficient [38]. For this, multiple and repeated motion sensor data from upper and lower extremities of PwPD need to be collected and quantification methods based on the fusion of motion sensor data should be developed.

When PwPD are at Off, On, or dyskinetic states, they may experience the similar tasks but at different amplitudes and frequencies. Therefore, the recorded signals of a repeated task experienced at different motor states can be dissimilar and they can vary in length and frequency. Measuring the dissimilarities/distances between these signals can be informative about the motor states of the PwPD. Investigation of a method that is capable of measuring these distances would be useful for understanding whether using such method can provide information about the motor states in PD. This information can be used in the development of methods for automatic motor scoring of PD.

Given the above mentioned needs, the thesis aimed at developing and evaluating new knowledge- and data-driven methods for supporting treatment and providing information for better assessment of PD, using the micro data analysis approach. The thesis work fits into the intersection of the three fields of sensors, neurology and machine learning. Sensor technology was used in this thesis to collect PD motor symptoms during a single-dose levodopa study. Neurological experts clinical ratings were used for setting the targets when modelling the data and machine learning were used to map the sensor data to targets. This process provided a path for development of methods for objective assessment of PD motor symptoms.
The coming sections present the research questions, research approach, contributions and a summary of the work done in the six papers. Subsequently, discussion and conclusion are presented.

Research questions

The overall research question of the thesis is: using the stages from microdata analysis approach, how to develop new knowledge- and data-driven methods using sensor data of PwPD to improve the PD motor symptom assessment and to support the PD treatment?

Besides, the following research questions are formulated to address the identified issues in the previous section:

1. How to develop new knowledge- and data-driven method to quantify the dexterity in PD using spiral and tapping tests in smartphones?
2. How to develop a method for measuring PD-related temporal irregularities and evaluate its clinimetric properties?
3. What are the clinimetric properties of an entropy based method measuring the upper limb temporal irregularities in PD using spiral drawing tests data collected during single-dose levodopa study?
4. How to develop knowledge- and data-driven methods for quantification of the PD motor states using motion sensor data from leg agility tests?
5. Can development of methods using fusion of motion sensor data collected from upper and lower extremities lead to a better clinimetric outcomes? How are the results compared to single sensor-based methods?
6. To what extent the Dynamic Time Warping method can assess the motor states in PD?

The first two questions were formulated in parallel. The third question was formulated after having insights from the second question to perform further investigation with new dataset. Likewise, after constructing a base in the fourth question, the fifth question was formulated. Finally, question 6 was developed towards enhancement of the answers provided to questions 4 and 5. The thesis attempts to answer the above stated questions through paper 1 - 6, respectively.

Research approach

To meet the research objectives and based on the concept of microdata analysis in this thesis, the data was collected, stored, and processed. The methods were developed and the performance of the methods were evaluated. In order
to achieve acceptable results at the end, the stages were recursively imple-mented. This means in case of not meeting the criteria in one stage the previ-ous stage was enhanced and the process was repeated. The overall process of the thesis architecture is depicted in Figure 1.

The sensor data included the data that was gathered from upper- and lower-limbs using smartphone touch screen and motion sensor triaxial accelerometer and gyroscope. Data was collected quantitatively from repetitive experiments of the PwPD and healthy controls. The tests were spiral drawing, alternate tapping, leg agility, alternate hand rotation and walking. The main dataset included data from recruited 19 PwPD and 22 healthy controls in a single center, open label, single dose observational clinical study. The clinical trial performed in a hospital Uppsala, Sweden, and written consent was given [39]. The study was approved by the regional ethical review board in Uppsala, Sweden (reference number: 2015/100). Another dataset was based on data from two clinical studies, both of which were approved by the relevant agencies and informed consent was given. 98 PwPD at different stages of PD and 10 healthy subjects were recruited for data collection. Out of 98 PwPD, 68 of them were advanced PwPD who were recruited in an open longitudinal 36-month study at nine clinics in Sweden [40]. On inclusion, 35 of these patients were treated with levodopa-carbidopa intestinal gel infusion (LCIG) and 30 patients were candidates for switching from conventional oral PD treatment to LCIG. In the latter group, the patients were LCIG treatment-naïve at study start. In the second study, 38 patients with a clinical diagnosis of idiopathic PD in Milan, Italy participated [41]. The Italian patients were divided into two groups: intermediate stage patients experiencing motor fluctuations (n = 16) and clinically stable, early PD patients (n = 17).

The processed data, features, and automated scores are the outcomes of the contributions described in the next section.
Contributions

The thesis scientifically contributes by offering solutions to improve the assessment of PD motor states. This contribution was developed over the course of the papers providing answers to the research questions. First, the thesis proposed solutions to extract the symptom related information and treatment related changes using the instrumented fine motor tests. It offered solutions to be included in the long term diagnostic tools with measuring the temporal irregularity presented in spiral drawings of PwPD. These findings relate to research questions 1, 2, and 3.

Then, towards improving the assessments of the lower limb motor symptoms, the thesis offered solutions for quantification of the leg agility tests. With those results, the thesis provided a base for developing motion sensor-based systems for follow up of the effects of treatment. Including fusion of sensor data from upper- and lower-limbs, the thesis offered a solution to measure the PD motor symptoms accurately, to be examined in individualization of the treatments in PD. It offered a comparison of the single sensor-based assessments collected from upper- and lower-limbs of PwPD. These findings relate to research questions 4 and 5. Finally, the thesis offers a data-driven solution for assessing the motor states in PD by measuring the similarity of the signals recorded from repeated tests of PwPD where the findings relate to research question 6.

In connection with the research approach, data preparation and processing was done to ensure that data to be used in the analysis are errorless and consistent. For the smartphone, this process included data transfer from the smartphone touch screen data to a computer, reformatting the data type from JavaScript Object Notation to string format, identifying the series of data for respective tests together with matching them with the videos of the performances, and handling missing/duplicate entries. For motion sensors, it included data transfer from motion sensors to a computer, identifying and matching the data segments with the videos of the performances, and segmenting the signals of performances for each test.

After data processing, depending on the research question, extraction of the features were done. A large extent of the contributions in this thesis was calculating features related to each experiment. The purpose of extracting features was to derive informative and non-redundant values that facilitate the subsequent learning processes in the next stage, which was the data modeling or machine learning. Calculating the features was done by knowledge-driven, data-driven, and multidisciplinary approaches. The knowledge-driven approach was used to extract the features by incorporating the knowledge, skills, and information of the neurologists about the symptoms, or by observing the videos of the tests performances. E.g., calculating the slowness of the speed or movement as a feature since during bradykinesia the speed of the movements slows down. The data-driven approach was used to extract information by mathematical and/or statistical approaches without including the intuitions
or emotional assumptions. For this, multivariate data analysis methods such as time-domain, wavelet-domain, and frequency-domain analysis methods were used. Besides, statistical moments, time series trends, irregularity components, and similarity measures were used.

Prior to the development of machine learning methods, to avoid overfitting and improve the performance of the methods, some feature selection and dimension reduction approaches were employed. For feature selection, Stepwise regression [42] was used. For dimension reduction, the principal component analysis (PCA) method was employed. Machine learning methods used the selected features or principal component scores to map the relationship between a set of independent quantitative measures to the dependent variable that was obtained from the clinical ratings. Regression and classification of dependent (response variable e.g. clinical ratings; healthy or patient) and independent variables (calculated features) were done. Regression (numeric prediction) was applied to numeric outcomes and classification was applied to nominal or ordinal outcomes.

The evaluation of the metrics from quantitative methods was done by assessing their validity, reliability, and responsiveness. Validity refers to whether the findings from the developed method represent the phenomenon related to the problem. The type of validity evaluated in this thesis is the convergent validity, where the correlation of the scores from methods to the scores of the clinical ratings was examined. Reliability refers to the consistency of method outcomes across items (test-retest reliability) and the consistency of the scores between clinical raters (inter-rater reliability). Responsiveness refers to the ability of the methods in detecting changes in motor symptoms at different medication levels over time. After the development of the methods in this thesis, the responsiveness of the produced scores was examined against the treatment interventions over time. Part of the thesis evaluated the ability of a quantification method in differentiating the PwPD at different stages of the disease with respect to the healthy controls (paper III) using the health-related history of the PwPD. Part of the thesis examined the correlation between the scores that were generated by various methods (paper II).
Summary of the papers

This section presents a summary of all included papers to provide an answer to the formulated research questions. It briefly describes the aim, method, and conclusion of each paper.

Paper I

In this paper, the aim was to quantify dexterity in PD using smartphone data collected from spiral drawing and tapping tests. Another aim of this paper was to investigate if a combination of spiral drawing and alternate tapping tests provide better results in terms of validity and responsiveness compared to previous studies.

The raw dexterity data were processed with time series analysis methods to calculate 37 spatiotemporal features, which represent the severity of symptoms. Different kinematic quantities, including time, distance, speed, and velocity were used as the primary signals to be processed and analyzed using time- and wavelet-domain methods.

The application of the principal component (PC) methods on the extracted spatiotemporal features yielded to seven PC scores. Multilayer Perceptron (MLP), Regression trees (RT), Support vector machines (SVM), linear regression (LR) machine learning methods were built while principal components of the features were used as predictors. Mean ratings of the specialists were used as the target.

The performance of the machine learning methods was assessed. Agreements between the three specialists' ratings and test-retest reliability of mean specialist and smartphone-based scores between the first two baseline measurements were evaluated. The degree of the relevance of the tapping and spiral features to clinical ratings was identified. The differences in mean PC scores between the groups of PwPD and healthy controls were examined using linear mixed effect modeling. The relative ability to detect the change from baseline (no medication) to follow up time points when PwPD were on medication was assessed by effect magnitudes.

Using SVM yielded higher correlations with clinical ratings compared to other methods. There were weak to moderate correlations between smartphone-based scores and mean ratings of UPDRS item #23 (finger tapping), UPDRS #25 (rapid alternating movements of hands), UPDRS #31
(body bradykinesia and hypokinesia), sum of the three UPDRS items, dyskinesia, and TRS. The correlations indicate that tapping and spiral drawing tests capture relevant symptom information corresponding to the clinical rating scales. The moderate agreements between SVM and mean clinician ratings can be because of the method of observation of the movement disorder specialists. They observed the PwPD while performing standardized motor tasks as defined in the UPDRS scale where the highest weight was given to the symptoms that were prominent during gross motor test e.g., walking ability. This contrasts with the tapping and spiral drawing tasks; only fine motor movements could be recorded by the smartphone touch screen.

In general, the clinical scores had better test-retest reliability than the smartphone-based scores. The smartphone-based predicted scores showed good repeatability only for TRS and dyskinesia scales. Smartphone-based scores differed significantly between PwPD and healthy controls.

In estimating the effect sizes to evaluate the responsiveness of the smartphone-based scores, clinician-based scores had higher effect sizes indicating better responsiveness in detecting changes in relation to treatment interventions. However, the first PC of the 37 features was able to capture changes throughout the levodopa cycle and had trends similar to the clinical TRS and dyskinesia scales.

The results show that combining spatiotemporal features extracted from tapping and spiral drawing data can be used to detect treatment-related changes in advanced PD.

In conclusion, the results presented in this paper indicate that tapping and spiral drawing tests of the smartphone contain relevant symptom information for detecting and assessing PD dexterity. The results suggest that the tests can be useful in detecting changes in motor symptoms related to treatment.

**Paper II**

This paper focused on developing and evaluating the clinimetric properties of a method for measuring PD-related temporal irregularity using data from the spiral drawing. At the time of this study the main data set including the clinical ratings were not available. In this paper, the data from the second dataset as described in the research approach section was used.

The amount of temporal irregularity during spiral drawing tasks was quantified using an Approximate Entropy (ApEn)-based method. The ApEn is a statistical method for measuring the repeatability of patterns within a signal. A signal containing a single frequency component is associated with a relatively small ApEn value whereas more complex signals containing multiple frequency components are associated with high ApEn values, indicating a high level of irregularity. ApEn reflects the similarity between a chosen window of a given duration and the next set of windows of the same duration.
A temporal irregularity score (TIS) was generated. Mean TIS between PwPD and healthy elderly subjects was investigated. The responsiveness of the ApEn based score was compared to the results of two methods. The first method was based on the standard deviation of the spiral drawing speed (SD-DV) and the second method was based on the spiral drawing radial velocity (WSTS). Test-retest reliability of the three methods was assessed. Long term trend of the methods was investigated for possible involvement of BG in temporal control during spiral drawing tasks.

The mean TIS score was significantly different between healthy subjects and advanced PwPD. In contrast to the TIS and WSTS scores, mean SD-DV scores were not significantly different across the groups. There were moderate correlations between WSTS and SD-DV scores. TIS was correlated to neither WSTS nor SD-DV scores. The calculated effect sizes for TIS were higher than WSTS and SD-DV which indicated greater responsiveness than the two other scores. In addition, TIS had higher test-retest reliability compared to the other two scores.

The ApEn-based method could be used for differentiating between PwPD in different stages of PD and healthy subjects. The responsiveness and test-retest reliability were good for the ApEn-based method. In conclusion, results from developing the ApEn method showed it is useful for measuring upper limb temporal irregularity.

Paper III

In paper II (ST1), the correlations between temporal irregularity score (TIS) and clinical ratings, the sensitivity of TIS to a single dose of levodopa over a course of test trials, and the reproducibility of the previously reported TIS properties have not been studied. Therefore, towards the development of a method that can provide better results in quantifying the PD motor symptoms, the investigation of this method was done using the main dataset and the methodology from paper II.

In this paper, the aim was to verify and further investigate the clinimetric properties of an entropy-based method for measuring PD-related upper limb temporal irregularities during spiral drawing tasks. More specifically, the properties of a TIS for PwPD at different stages of PD, and medication time points were investigated. The investigation was conducted using a new dataset, new patient groups, as well as another screen resolution, and during shorter-term measurements.

PwPD performed the tests before a single levodopa dose and at specific time intervals after the dose was given. Three movement disorder specialists rated videos of the PwPD based on the unified PD rating scale (UPDRS) and the Dyskinesia scale (Dys).
Initially, drawing speed was calculated as a rate of spatial change with respect to time. The ApEn technique was then applied to drawing speed (DS) signals to generate the TIS.

When assessing the differences of TIS between tests performed by PwPD at different PD stages and healthy controls, the values were found to be significantly different between healthy subjects and advanced PwPD, similar to the results in paper II. They were not significantly different between the healthy subjects and the whole patient group. There was a significant difference in age between the healthy controls and the whole patient group. There was no significant difference in gender distribution between healthy controls and PwPD. The test-retest reliability of TIS was similar to the results in ST1 indicating the consistency of TIS between the three spirals.

When assessing the sensitivity of TIS to the treatment response for PwPD, the results indicated that the patients’ scores can capture some effects of the medication from off to on and wearing off effects. For healthy subjects, the effect sizes were smaller than the effect sizes of patients. The correlations between TIS and mean clinical rating scores (UPDRS, Dys) were weak.

The results of this study suggest applying the current methodology to a larger dataset including more subjects at various stages of medication and subjects at various years of treatment. The age distribution was different, as healthy controls were younger than PwPD. The sensitivity results in this study were much higher for clinical rating scores than for TIS. The responsiveness to treatment in paper II was strong, while sensitivity to single-dose levodopa was weak. This indicates that TIS might be more useful in long-term diagnostic tools rather than in detecting the single-dose levodopa response. TIS was weakly correlated to clinical symptom ratings and may contribute together with other measures in combined scores.

Paper IV

In contrast to the smartphone data used in paper I, II, III and towards developing a method providing better validity and responsiveness, in this paper the motion sensor data was examined.

The paper aimed to develop data-driven methods and test their clinimetric properties to detect and quantify PD motor states using motion sensor data from leg agility tests. PwPD performed leg agility tasks while wearing motion sensors on their lower extremities. Clinical evaluation of video recordings was performed by three movement disorder specialists who used four items from the motor section of the UPDRS, TRS and a dyskinesia score.

Data-driven methods were developed and their clinimetric properties were examined for detection and quantification of PD motor states using motion sensors data of leg agility tests. Time series analysis techniques were used to
extract meaningful motor state information in the form of spatiotemporal features from motion sensors data during leg agility tests. 24 features were extracted. The relevance of the features to the clinical ratings was investigated using PCA and stepwise regression. Supervised machine learning methods including support vector machines (SVM), decision trees (DT) and linear regression (LR) with 10-fold cross-validation were employed to map the selected features to the mean clinical ratings on the four scales of TRS, UPDRS #31 (bradykinesia), SUMUPDRS (defined as the sum of UPDRS #26 (leg agility), UPDRS #27 (arising from chair), and UPDRS #29 (gait)), and dyskinesia. For each of the scales, there were individual models fitted and evaluated for their predictive performance.

Convergence validity of the machine learning methods was assessed. Agreements between the scores obtained by the machine learning methods and scores obtained by the three raters were analyzed. Test-retest reliability of the machine learning-based scores and inter-rater agreements were assessed. The responsiveness of the scores from the machine-learning algorithm to treatment effects was assessed. The differences in motor test results between right and left legs in PwPD who were asymmetric were assessed.

After employing machine learning methods (SVM, LR, and DT) on the selected features, the absolute correlation coefficients between the scores produced by machine learning methods and the mean clinical ratings ranged from 0.29 to 0.83. The best combination (feature selection plus machine learning method) was stepwise regression and SVM. SVM showed the best convergent validity with good correlation coefficients to TRS, UPDRS #31 (body bradykinesia and hypokinesia), SUMUPDRS (the sum of the UPDRS items: #26-leg agility, #27-arising from a chair and #29-gait), and dyskinesia. Additionally, the SVM-based scores had similar test-retest reliability in relation to clinical ratings. The SVM-based scores were less responsive to treatment effects than the clinical scores, particularly with regards to dyskinesia.

In conclusion, this study demonstrates good clinimetric properties of a data-driven methodology that quantifies the motor states in PD using motion sensors data during leg agility tests. The proposed methodology could form the basis for developing systems for follow up of the effects of treatment and individualizing treatments in PD. For this, developing methods using motion sensor data collected from multiple tests may provide better results.

Paper V

This paper aimed to construct a Treatment Response Index from Multiple Sensors (TRIMS) for quantification of motor state in PwPD during a single levodopa dose. Another aim was to compare TRIMS to sensor indexes derived from individual motor tasks.

PwPD performed three motor tests including leg agility (LA), pronation-supination movement of hands (PSM), and walking in a clinic while wearing
inertial measurement unit sensors on their wrists and ankles. They performed
the tests repeatedly before and after taking 150% of their individual oral levo-
dopa-carbidopa equivalent morning dose.

Three neurologists blinded to treatment status, viewed videos of PwPD and
rated their motor symptoms, dyskinesia, overall motor state based on selected
items of Unified PD Rating Scale (UPDRS) part III, Dyskinesia scale, and
Treatment Response Scale (TRS).

To build TRIMS, 178 features were initially extracted from upper- and
lower-limb data. Both knowledge- and data-driven methods were applied to
extract spatiotemporal features to represent motor dynamics during motor
tests. Twenty four features were extracted from the LA test and 88 from the
PSM test. For the walking test, thirty-seven features were extracted from the
lower limb data (LLM-W), and 29 from the upper limbs data (ULM-W).

In total, 39 features were selected by the stepwise regression method and
were used as input to SVM models to be mapped to mean reference TRS
scores using a 10-fold cross-validation method. Three different SVM models
were built using the selected features from ULM-W only, LLM-W, and from
the fusion of the four feature sets. For each model, the Pearson correlation
coefficients and root mean squared error (RMSE) between estimated scores
by SVM and reference TRS were calculated. These two metrics were used to
evaluate the models and identify the best model. Test-retest reliability, respon-
siveness to medication, and correlation to TRS as well as other UPDRS items
were evaluated for TRIMS.

There was a high correlation between TRIMS and TRS (r=0.93). TRIMS
had good test-retest reliability. The responsiveness of the TRIMS to medica-
tion was good compared to TRS indicating its power in capturing the treatment
effects. TRIMS was highly correlated to dyskinesia, bradykinesia, and gait
UPDRS items. In addition, there was a high correlation between the sensor
index from the upper-limb and TRS.

This study concludes that the constructed TRIMS based on the developed
multiple sensor fusion methods provides an accurate estimation of PD motor
states and was responsive to treatment, with relation to TRS clinical rating.
Quantification of sensor data collected from upper limbs during walking pro-
vides an attractive alternative to TRIMS involving only wrist sensors.

Paper VI

Since experiment of the tests were repeated by PwPD at different motor states,
the recorded signals of the experiments were dissimilar due to the differences
existing in their length and frequency. A novel approach is to measure the
distances between the signals and investigate whether the resulting scores re-
fect information about motor states of PwPD. Paper VI aimed to investigate
the feasibility and the extent of using the Dynamic Time Warping (DTW)
method to assess the motor states in PD. The feasibility of using the DTW
method for assessment of the motor states can provide information to be used in the development of methods for automatic motor scoring of PD.

3D acceleration and gyroscope signals were collected during leg agility tests and were segmented. The DTW method was used to find the best alignment between the signals of every consecutive test and calculate the distance between them.

Single-axis acceleration and gyroscope data together with the magnitude of the 3D signals were used by DTW to calculate nineteen features. The most important features in relation to clinical TRS ratings were found using the stepwise regression method. After the application of PCA on the set of the selected features, the first PC was remained for further analysis and denoted as DTW-based distance score (DDS). To investigate the trend of DDS for PwPD vs the trend of their mean TRS over the course of the test occasions, the differences between the mean DDS and mean TRS at each test occasion were calculated using ANOVA analysis. In addition, the trend of the DDS for healthy controls was included. Besides, the power of the DDS score for separating the different motor states as scores by TRS was investigated. For this, the mean DDS between the groups of PwPD at different motor states were assessed. To identify whether the normal mobility of the PwPD match with the healthy controls, the mean DDS of healthy controls were included. The power of DDS in detecting the changes between the motor states as scored by TRS was investigated using support vector machines and decision trees. Lastly, to investigate if there are individual features which match well for individual PwPD first, some PwPD who showed better response according to their TRS score were selected. Then their individual DTW-based feature which fitted best was investigated.

Investigating the trend of mean DDS vs mean TRS over the course of the test occasions, DDS shows a similar trend to TRS. There was a larger mean DDS score for PwPD with larger clinical TRS scores. The mean DDS for healthy controls matched well with the mean DDS of the PwPD at the TRS score of 0. The results from this analysis indicated that DDS can separate the PwPD at “Off” state from the ones at the “On” state. DDS was able to classify the motor state changes as scored by clinical TRS with good accuracy. For some PwPD there was an individual DTW-based feature that matched well with their TRS scores.

In conclusion, the results from this study showed that it is feasible to use the DTW method for extracting information about PD motor states. The information provided by using this method can be included in the development of the methods for automatic scoring of advanced PD motor states.
Discussion

This thesis describes the development and evaluation of sensor-based knowledge- and data-driven methods towards the improvement of assessment of PD. A focus of the thesis was to investigate using which motion sensor data collected from a body point during a test the PD motor symptoms could be detected best with relevance to the clinical rating scales.

The criteria for finding an answer to the research questions was to develop methods that provide acceptable clinimetric properties (validity, reliability, and responsiveness). This is to support PD treatment and provide information for better assessment of PD that was the overall goal of the thesis.

The development of the methods was enhanced over time and the course of papers. The development of the methods was recursively done after providing the results to clinicians and receiving their comments about the studies. During the development of the next paper we integrated their comments and improved the work by including more sources of data. Over time, it was learnt to select the most important features by employing a selection method (step-wise) and machine learning method (SVM) that leads to better clinimetric properties. Our research showed that the clinimetric properties of the methods in paper IV and V with motion sensors were better than the results in previous papers (papers I and III) where the spiral and tapping tests were analyzed. The fusion of sensor data collected from multiple upper- and lower-limbs provided enough information for an accurate quantification of the PD motor symptoms. This was because the PD motor symptoms manifest differently at body segments of PwPD when they are also different from one patient to another. The data collected from hands while walking contain more information about motor state than other tests. The developed methods using single sensor data e.g. data from motion sensors mounted on ankles during leg agility test, could be considered for special occasions e.g. when PwPD cannot walk.

The main part of the data in the thesis was collected during a one-day levodopa challenge which reflected the full cycle for possible PD motor states including Off, On/dyskinetic, Off. This full-cycle allowed sensor measurements to collect all relevant information needed for quantification and the individualization of levodopa doses which was another main goal of the study design [44]. The individualization of doses in PD requires adequate symptom information scores to be provided to the dosing algorithms. In many PwPD, the generic prescription might not be efficient since the response to levodopa varies and one dose does not fit all [45]. In a study by Thomas et al. [44] the
scores from quantification of sensor-data of hand rotation was used in individual dosing algorithm for oral administration of levodopa. In that study the correlation coefficient to clinical ratings was 0.82. Given that in paper V, using fusion of sensor data the accuracy was improved (r=0.95) it is of interest to use those scores for individualization of the levodopa dose. With this in mind, this thesis impacts on PD management by developing methods for accurate assessment of PD motor symptoms. Using the results from the development of the methods in the individualization of the doses, it enhances the quality of life of PwPD where they can take the right dose based on their state quantified accurately.

Clinical rating scales are the gold standards and were set as target in this thesis. However, they are non-linear and subjective and lack ability to reveal accurately the condition changes during the course of the disease. The thesis attempted to map the sensors data to clinical rating scores to introduce a way to develop methods that can relate the data collected from sensors to clinical scores. The opinions from experts in the form of ratings are the only sources that we can rely on. Then if results from using sensors provide interesting aspects that do not match the ratings, it needs to be discussed with the experts for making decisions. This is when the data and knowledge meet each other. With this in mind, it was observed that methods provided scores for cases that might be invisible to clinical observations. An instance was measuring temporal irregularity of the PwPD in paper II. TIS was worsening with increased disease severity whereas it showed improvement over a period of months after switching from levodopa to LCIG. We assumed that TIS reflect the BG oscillations which was in line to WSTS method where the drawing impairment seem to increase over time. Another instance was individual DTW-based scores calculated in paper VI. For some patients it was observed that the method detected a higher response that the mean clinical rating score which could reflect about the possible effect that was not visible in clinical observations.

Challenges in this thesis included data quality during the quantification of the smartphone-based data, efficient collection of data, choosing the right analysis methods and finding suitable algorithms. For extraction of the features the data required to be segmented, and to be synchronized with the videos of the subjects. This part of the work was time-consuming but the segmented data was reliable since labeling the segments helped to relate them to the subjects, and to the order of the tests. The criteria for extracting the features were to include the information using the knowledge of the experts when ratings the symptoms, what was highlighted in related articles, and the identified trends in data. After the extraction of the features, the relevance of the features was then examined using feature selection methods. The criteria were to get acceptable convergent validity (correlation to clinical assessment) when the features were used in machine learning methods. Therefore for the selection of the features, different methods were examined. The stepwise selection
method provided higher validity among the methods. This in line with another study where they investigated the effects of feature selection methods on the performance of machine learning methods for quantifying motor symptoms of Parkinson’s disease [46]. However, in that study after employing the stepwise for selection of the features, the responsiveness to treatment was calculated for up to 150 minutes. For the purpose of reducing the dimensionality of the features PCA was used. PCA mathematically rearranges the variables into components on the basis of their variance. PCA was used to have few scores containing the most amount of information from the feature set to be used in the machine learning methods.

For quantification of the motor symptoms and mapping them to clinical ratings, different machine learning methods including SVM, DT, LR, RF, MLP, etc. were employed. SVM provided promising results compared to other learning methods. This method was fast in implementation and able to separate the nonlinearly related data of motor symptoms and clinical ratings. Although we observed overfitting in modeling the data where the model picked the noise or random fluctuations in training data and learned as concepts but could not apply them on the new data. It negatively impacted the generalization ability of the methods and overestimated the cases at the lower end of the scales and underestimated cases at the higher end of the scales (e.g. results in paper IV and VI). Implementation of the deep learning method was not included. One reason was the lack of having a large enough dataset. Another reason was the transparency of the process that was required for each step including the data preparation, feature extraction, identifying the important features, and automating the motor states. Among the identified important features, some features were related but not evident in clinical observations. Identification of such features could help understand the PD. e.g. tracking back the origin of the features, the accelerometers contained more symptom related information compared to gyroscopes when evaluating the upper limb data, and vice versa. By contrast, when using deep learning there would not be resulting understandable features.

The take-home message from this thesis to clinicians are: i) Rotational data are associated with lower-limbs and acceleration data are associated with upper-limbs when evaluating the symptoms. ii) Hand movement while walking provide PD symptom related information. iii) Measuring micro movements not visible to experts observations can yield information about motor symptoms and disease progression. iii) Evaluating upper- and lower-body segments when assessing the symptoms provides more accurate results.

The take-home message for a micro data analyst are: i) Towards quantifying a target, including data with higher quality and from multiple sources may lead to better results compared to when using single source of data. ii) With the same goal, incorporating the knowledge of the experts by translating what they observe to what can be measured can add to the efficiency of the develop-
oped methods. iii) Filling the gap between information and knowledge in micro data complex systems, various methods shall be examined and the results need to be evaluated systematically.

The presented work is part of the projects “Flexible Levodopa Optimizing Assistive Technology” (FLOAT) and “Multimodal motor symptoms quantification platform for individualized Parkinson’s disease treatment” (MUSYQ) that were performed during 2015-2018. This work was also financed by the project “Remote monitoring of Parkinson's disease - Empowerment of patients and improved treatment using ICT-based tools” (EMPARK). The overall aim of the project was to develop a system to improve treatment for PwPD who consume Levodopa in microtablets [47]. The project mainly focused on measuring the symptoms accurately and objectively and simulating models of pharmacodynamics to predict the effect of a given dosage, both in terms of blood concentration levels and also resultant symptoms. The contribution of this thesis concerning the ultimate goal was to develop a new type of sensor technology platform that can accurately, objectively and quantitatively evaluate PD motor symptoms.

Limitations

The data in this thesis exhibited a considerable amount of inter-rater variability in rating scores of the clinical ratings. This is the case in studies including subjective ratings and cannot be avoided. This problem might be solved by training the raters for scoring the symptoms or to include more experts for ratings.

Another problem was that the scales like TRS contained few scores for extreme cases (e.g. score -3 and +3) which caused the methods to have not enough extreme observations to learn about those situations and perform better when quantifying such cases. With this limitation, the methods in paper IV and V tended to underestimate the scores and to concentrate their predictions around the means of the population. This made it difficult for the machine learning methods to predict cases outside of this range.

As in many other studies, a limitation in this thesis was the adopted small dataset which limits the generalizability of the results. In most of the papers, it was suggested to employ a larger dataset for the examination of the methods in the future. This would be made easier if PD researchers around the world could agree on a standard minimum set of sensors and a common protocol for collecting data.
Conclusion

Below the conclusion reached from papers providing the answer to the research question is presented.

Using data from dexterity tests experimented on a smartphone, the results of paper I showed that it is feasible to quantify PD motor symptoms via instrumented dexterity tests experimented on a smartphone. It was concluded that the system is useful for measuring treatment-related changes in PwPD.

Paper II described how to develop a method to capture the upper limb temporal irregularity related to timing variability in PwPD. Results from this development indicated that the temporal irregularity score that was calculated for the drawing speed during spiral tests was useful for the long term diagnostics. The results from further investigation of the method in Paper III showed that the method can reasonably discriminate well between spiral drawings performed by PwPD in different stages of PD and healthy subjects. As compared to the previous measures (see section paper II), this method quantifies a different aspect of upper limb motor severity. This method was able to capture some effects of levodopa medication that were presented in the performances of PwPD.

In paper IV, data-driven methods for quantification of PD motor states using motion sensor data of leg agility tests were developed. The results demonstrated good clinimetric properties and it was concluded that the proposed methodology could form the basis for developing systems for follow up of the effects of treatment and individualizing treatments in PD.

The results from the development of a multisensor fusion platform in paper V indicated that using a machine learning method that fused information from standardized motor tasks leads to a valid, reliable and sensitive objective measurement of PD motor symptoms. Besides, comparing the single sensor-based methods, it was concluded that the data from upper limbs (wrists) while walking were highly related to PD motor symptoms.

Paper VI described the extent that Dynamic Time Warping can measure the motor states in PD. The results showed that it is feasible to use the DTW method for the extraction of information about motor states. The method found to be useful in extracting features for the development of the methods for automatic scoring of advanced PD motor states.

In this thesis, the sensor-based knowledge- and data-driven methods were developed using the steps from the microdata analysis approach to contribute to improving the PD motor symptom assessment. The findings in this thesis
from the development and evaluation of methodologies can be used in the improvement of systems for follow up of the effects of treatment and individualized treatments in PD.
Future work

A goal of future work of this thesis is to develop a continuous or real-time objective monitoring of PD to be included in individualizing of the doses for PwPD. For this, the methods need to be evaluated in different and large datasets. For the results to be applicable in clinics the longitudinal and large-sized validations are needed [48]. A potential data-driven specific method is deep learning to process the records of PwPD and perform the non-linear transformation of input features.

With the promising results presented in paper V, the future study design may include motion sensor data from both upper and lower-limbs tests. Although employing wearable sensor data, sustainability and acceptance of the body-worn sensors in the life of PwPD need to be considered.

Analysis of the data from arms swings while walking in a larger scale would be of interest, since it provided interesting information about the motor symptoms. For this, smartwatches or wrist motion sensors can be employed for collecting the data. They are available in the market and performing the test with them is easy. Plus smartwatches are accepted accessories in the daily life of many patients [49].

The long term collection of data allows monitoring the progression of the disease. Besides, PwPD must receive feedback regarding the response they provide in questionnaires and the objective motor tests that they perform.

There are only a few systems that have the standards. Only two of them have regulatory FDA approval. Kinesia and Global kinetics [49], [50]. Practical guidance on objective measurement and the optimum use of devices is lacking [51]. Future work should incorporate the developed objective measures into clinical guidelines. Optimization of objective measures needs to be done by cutoff values that separate the controlled from uncontrolled symptoms. The cutoffs can be subsequently tested and redefined by consensus.

To expand the microdata analysis approaches presented in this thesis to areas other than PD, e.g. stroke, pain, rehabilitation, multiple sclerosis, etc. depending on what the research question requires, there needs to be set clear measurement priorities. This is like “what to measure” and “how to measure” depending on the specific symptoms manifested due to the impairment and how they are clinically evaluated. E.g. to measure symptoms in stroke, we may focus on how to measure visual changes, weakness, numbness, speech problems, and trouble thinking. The next step is to collect the data and do preprocessing. The preprocessing can include the segmentation or preparation.
of the data for making it ready for the analysis. Then the data analysis using mathematical/statistical methods related to the field to extract information from data and/or map the information to the knowledge of experts. Then, interpretation/visualization of the results with regards to the questions and evaluating the performances of the methods are necessary.
References

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