UiT THE ARCTIC UNIVERSITY OF NORWAY

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Associations of pulmonary parameters with accelerometer data

Focusing on Cystic Fibrosis and COPD

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Passo por esta Universidade como cão por vinha vindimada.
Nem eu reparo nela nem ela repara em mim.

— Miguel Torga

Dedicated to Helena

ABSTRACT

Most western countries are currently facing the reality of an ageing population that puts increasing pressure on social and health systems that are struggling to maintain high quality of care. In Europe it is estimated that the number of elderly people aged above 65 will have doubled by 2060. Many of these people will suffer from chronic conditions requiring permanent care. Of particular importance is the care of chronic patients, given the need for continued care over long periods of time. In several chronic pulmonary diseases, patients can suffer recurrent exacerbation episodes. These episodes, with many different causes, lead to severe breathing difficulties and can cause death.

In this thesis we focus on exploring the association of physical activity to lung health parameters. We focused our work on cystic fibrosis and chronic obstructive pulmonary disease patients and a group of the general population recruited in the scope of the KORA-Age study. The three main goals of the thesis were to assess the feasibility of classifying exacerbation episodes in cystic fibrosis and chronic obstructive pulmonary disease patients and to propose and implement new parameters of physical activity in the context of a cohort study such as KORA-Age.

We conducted four distinct studies with different subject groups involving in total over 250 subjects. In all studies we asked the subjects to wear a set of off-the-shelf accelerometers, including GT1M, GT3X and RT3 sensors, to record physical activity patterns for a total of up to 14 days during their daily life. The data recorded by the sensors was then processed with Matlab and several sets of features were extracted. Some of these features were used as inputs in three different classification algorithms in order to classify exacerbation episodes: logarithmic regression, neural networks and support vector machines. Other features, in the KORA-Age context, were tested and submitted to the central study database for future use by the researchers cooperating in the study.

We achieved an area under the curve of 67% with logarithmic regression, 83% with neural networks and 90% with support vector machines when classifying exacerbation episodes in chronic obstructive pulmonary disease. A neural network was able to achieve an accuracy of 85% distinguishing cystic fibrosis patients from healthy controls. We were not able to record enough data to tackle the problem of classification of exacerbations in cystic fibrosis. We proposed, discussed, extracted and tested a large set of physical activity parameters for use in the KORA-Age study

by the collaborating researchers. The feedback from the subjects in the early studies led us to identify several challenges in the acceptance of long-term monitoring with sensors, related to social pressure and usability of the sensors.

The work on classification of normal days and days of exacerbations in COPD patients is, to our knowledge, the first attempt to extract a set of features from accelerometer data. Overall SVM showed to be the most robust classifier for this task. The best results indicate an area under the curve of the classifier of 90%. Nevertheless the number of patients and episodes is too low to draw definitive conclusions. These results were achieved with a significant number of features, but within a limited scope of information extracted. We envisage that future approaches with larger feature sets and with a larger scope of information present in such features can improve the classification quality. Only then is it feasible to aim at the clinical use of accelerometers in the management of COPD patients.

Our approach achieved reasonable sensitivity and specificity in distinguishing cystic fibrosis patients from control subjects when conducting simple PA modeling with subsequent use of a neural network. Naturally, the clinically interesting application is not the distinction from healthy subjects but the individual characterization of patients, as well as the possibility to detect changes over time, possibly supported by an individually trained neuronal network implemented in the activity monitor itself. Correspondingly, the detection or prediction of exacerbations in CF patients remains an issue for further studies.

We identified several barriers to participation and retention of subjects in our studies: the social and comfort aspects of wearing sensors for long periods, limitations of the sensors regarding data reliability and battery limitations.

The next logical step in the effort to classify exacerbations in COPD patients is to design a larger study, aiming to obtain data for a statistically significant number of exacerbation episodes. This is the essential step towards assessing the feasibility of the proposed approach, and to gain better insight into the medical consequences.

We can only see a short distance ahead,
but we can see plenty there that needs to be done.

— Alan Turing

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Second to the colleagues at Technical University of Munich who where a significant part of this work was carried out. To Lukas Gorzelniak that braved the path of a PhD in new grounds at the same time as me. This lead us to a great team work with shared goals and ideas, but also problems. Chen Chen joined the team in Munich short after, bringing smiles and good mood together with essential discussion on our studies. We shared an office and each other's laughs and the problems for two years.

Many of the researchers at Tromsø Telemedicine Laboratory and the Medical Informatics and Telemedicine provided excellent ground for idea sharing and introduced me to many crucial concepts and ideas. I would like to thank Taxiarchis Botsis, Luis Luque, Stein-Olav Skrovseth and Gustav Bellika for the discussions along these years.

The research work in Munich was only possible with the exchange of ideas and cooperation with the teams at KORA-Age, Klinik Bad Reichenhall and Ludwig Maximilians University. A special word to Angela Döring for the continued support and sharing of ideas.

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NOMENCLATURE

AUC	Area Under the Curve
CF	Cystic Fibrosis
COPD	Chronic Obstructive Pulmonary Disease
DLW	Doubly Labeled Water
EE	Energy Expenditure
FFT	Fast Fourier Transformation
GSISH	Graduate School of Information Systems in Health
IMSE	Institute for Medical Statistics and Epidemiology
KORA	Kooperative Gesundheitsforschung in der Region Augsburg
LMU	Ludwig-Maximillians University of Munich
MEMS	Micro-Electro-Mechanical Systems
MET	Metabolic Equivalent of Task
NN	Neural Network
PA	Physical Activity
PAEE	Physical Activity Energy Expenditure
SVM	Support Vector Machines
TUM	Technische Universitat Muenchen
VMU	Vector Magnitude Unit

LIST OF PAPERS

No	Title	Publication
P1	Measuring Physical activity with Sensors: A Qualitative Study (Dias, Fisterer, Lamla, Kuhn, Hartvigsen, Horsch 2009)	Medical Informatics Europe 2009
P2	Assessing physical activity in the daily life of cystic fibrosis patients (Dias, Gorzelniak, Jörres, Fischer, Hartvigsen, Horsch 2012)	Pervasive and mobile computing Journal
P3	Comparison of Recording Positions of Physical Activity in Patients with Severe COPD Undergoing LTOT (Gorzelniak, Dias, Schultz, Wittman, Karrasch, Jörres, Horsch 2012)	Journal of COPD
P4	Classification of exacerbation episodes in Chronic Obstructive Pulmonary Disease patients (Dias, Gorzelniak, Schultz, Wittmann, Rudnik, Jörres, Horsch 2012)	Accepted in Methods of Information in Medicine
P5	Recommendations for Collecting and Processing Accelerometry Data in Older Healthy People (Ortlieb, Gorzelniak, Dias, Schulz, Horsch 2012)	Poster at Medinfo 2013

ADDITIONAL PAPERS

No	Title	Publication
A1	Extracting Gait Parameters from Raw Electronic Walkway Data (Dias, Gorzelniak, Döring, Hartvigsen, Horsch 2011)	Medical Informatics Europe 2011
A2	Using a Robotic Arm to Assess the Variability of Motion Sensors (Gorzelniak, Dias, Soyer, Knoll, Horsch)	Medical Informatics Europe 2011
A3	A Prototype of a Wireless Body Sensor Network for Healthcare Monitoring (Chen, Dias, Knoll and Horsch 2011)	Medical Informatics Europe 2011
A4	Does the Low Power Mode of the Actigraph GT3X+ Accelerometer influence the Device Output in Sleep Research? (Gorzelniak, Dias, Bakhirev, Knoll, Horsch)	Poster at Medinfo 2013
A5	Detecting Periodic Limb Movements with Off-the-shelf Accelerometers: A Feasibility Study (Dias, Gorzelniak, Rudnik, Stojanovic, Horsch)	Medinfo 2013
A6	Scale-Space Methods for Live Processing of Sensor Data (Skrøvseth, Dias, Gorzelniak, Godtliebsen and Horsch 2012)	Medical Informatics Europe 2012
A7	Multi-morbidity and successful aging: the population- based KORA-Age study (Peters et al. 2011)	Zeitschrift für Gerontologie und Geriatrie

Part I

SUMMARY OF STUDIES

1 INTRODUCTION

1.1 CHALLENGES OF AN AGEING POPULATION

Most western countries are currently facing the reality of an ageing population that puts increasing pressure on social and health systems that are struggling to maintain high quality of care. In Europe it is estimated that the number of elderly aged above 65 will be double by 2060. Many of these people will suffer from chronic conditions requiring permanent care. Future changes in employment patterns with increasing percentages of women working is expected to provoke a shortage of labor to care for this population.

Of particular importance is the care of chronic patients [1], given the need for continued care over long periods of time. To maintain the current levels of care, we need to develop new approaches and concepts of care. New technologies and solutions will result from extensive research and reach the mass market, supporting the daily life of elderly people and chronic patients [2]. Chronic diseases account for 75-85% of the total health care spend in overall health care costs. One path to mitigate some of the costs from chronic disease is to help the patients maintain stable health, stick to the medication regime, and quickly respond to changes in vital signs before they turn into a costly emergency. Through better monitoring, we can also provide a higher quality of life for the patient and their loved ones.

As the world population grows older, the number of individuals needing some sort of assisted living is continuing to increase. One of the possible approaches to reduce the burden and improve the overall quality of life is to provide elderly people with means to help them age gracefully in the comfort of their own home. By providing non-obtrusive monitoring and simple daily support from remote family, an elderly person may live in their home for a longer period of time thereby avoiding costs of assisted living.

In several chronic pulmonary diseases, patients can suffer recurrent exacerbation episodes. These episodes, with many different causes, lead to severe breathing difficulties and can cause death. The recurrence of such episodes in turn can lead the patients to enter a vicious circle of health status degradation. Given the complicatons of exacerbation, patients become afraid of such episodes and they tend to avoid exercise and activities that may start them, but by doing so they lower the physical activity which contribute to worsening of the underlying pulmonary disease.

The first proposals to assess human body movement using electronic devices capable of measuring acceleration, later known as accelerometers, happened in the 1950s. Obviously the devices proposed at that time were expensive, bulky and not reliable, making them unsuitable for applications outside a laboratory, namely in daily living [3, 4, 5]. But, as with most electronic systems, the past decades provided a significant increase of quality of such devices, with significant motivation from the air-bag industry. The recent generations of accelerometers provide low-cost off the shelf devices, with high-volume production, in miniature forms and reliable operation. The power consumption has also been dramatically reduced to the point of autonomy of measurement for several days on standard batteries.

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality and represents a substantial economic and social burden throughout the world [6] and it is the fifth leading cause of death worldwide and further increases in its prevalence and mortality are expected in the coming decades. The substantial morbidity associated with COPD is often underestimated by health-care providers and patients; likewise, COPD is frequently under-diagnosed and under-treated. COPD develops earlier in life than is usually believed. Tobacco smoking is by far the major risk for COPD and the prevalence of the disease in different countries is related to rates of smoking and time of introduction of cigarette smoking[7]. Contribution of occupational risk factors is quite small, but may vary depending on a country's level of economic development. Severe deficiency of alpha-1-antitrypsin is rare and the impact of other genetic factors on the prevalence of COPD has not been established [7]. COPD should be considered in any patient presenting with cough, sputum production, or dyspnoea, especially if an exposure to risk factors for the disease has been present. Clinical diagnosis needs to be confirmed by standardized spirometric tests in the presence of not-fully-reversible airflow limitation. COPD is generally a progressive disease and continued exposure to noxious agents promotes a more rapid decline in lung function and increases the risk of repeated exacerbations. Smoking cessation is the only intervention shown to slow the decline, even if the disease may still progress due to the decline in lung function that normally occurs with aging, and some persistence of the inflammatory response.

Cystic fibrosis (CF) is a hereditary disease that affects the whole body causing progressive dysfunction of several organs that ultimately leads to premature death. Approximately 1 in 25 individuals of European descent carry the CF allele as heterozygotes. In accordance with the allele frequency, disease incidence is about 1:2500 births [8]. There are many genetic variants of the CF disorder and significant effects of the genetic environment that are associated with differences in severity and phenotype of the disease. In CF patients, dysfunction of the CF Transmembrane Regulator protein creates disturbances in chloride transport through the epithelium, resulting in dehydration of the mucosal surfaces. The subsequent formation of dense mucus favors the development and persistence of bacterial infections. This in particular leads to a deterioration of pulmonary function. Pulmonary causes are responsible for more than two thirds of all CF-related deaths [8]. CF is diagnosed in males and females with the same frequency but for reasons that remain unclear males tend to have a longer life expectancy [9]. According to the CF Foundation the average life expectancy for infants born with CF, in the United States, in 2008 is 37.4 years[10].

Physical activity (PA) and associated fitness levels seem to be particularly important in CF, [11, 12] as patients with higher aerobic capacity have higher life expectancy [13], aerobic capacity correlates with quality-of-life [14], and in adults with CF professional achievements are related to physical fitness [15].

Given the clinical impact of CF [16, 17], objective measurement of PA appears to be an under explored research topic [18]. This is especially in view of the possibility that PA could play a role in the prediction of exacerbations in CF, similar to COPD [19, 20]. This would require patients to wear sensors for extended periods of time or even all time. Although the extension of monitoring is currently restricted by factors such as battery and memory capacities of the devices, this could be technically handled in future.

1.2 RESEARCH PROBLEMS AND QUESTIONS

Aiming at exploring the potential use of accelerometers as source of information for robust models of lung diseases we set to explore the following general question:

How can we model pulmonary health parameters from short and long term data recorded, in daily life settings, with accelerometers?

Previous research looking into the associations between physical activity and lung health have focused on quantifying exercise into parameters that were mostly based on questionnaires, such as total time of exercise. The use of sensors became, in this scope, a tool for more accurate data and while being easier to apply. Unfortunately this approach leads to under-usage of the data produced by accelerometers which is rich in details of the activities performed. Nevertheless, this first application provided the essential ground for testing and validation of such tools and that resulted in the technological development and acceptance by the medical community.

With better sensors, that are more reliable and have higher sampling rates, comes the opportunity to explore more dimensions of the recorded data. It raises the possibility to correlate this rich information with the medical and health outcomes associated with lung diseases.

This thesis will focus on three different groups of subjects, covering a wide spectrum of baseline characteristics. I explored a young group of patients, suffering from CF, that can be more prone to accept new technologies and support our study. I worked with COPD patients, with a higher average age and potentially less aptitude to technology and acceptance of new methods of care. I explored the utility of objective measurement of physical activity with sensors in the general elderly population, in the scope of epidemiology research.

Narrowing my general question to the groups of subjects included in structured studies I defined a set of four health focused questions:

- RQ1 - Is it feasible to study episodes of exacerbation in CF patients by analysing accelerometer data?
- RQ2 - Can we distinguish normal days from exacerbation in COPD patients looking at accelerometer data?
- RQ3 - Can we extract innovative parameters from accelerometer data that are useful for pulmonary research in the population?
- RQ4 - What are the essential barriers to long term monitoring of PAand Heart Rate of chronic patients and elderly people?

To achieve clear answers to these questions with medical focus it is essential to apply existing computational methods to process the accelerometer data and build classification tools. This need raises a technology focused question:

- RQ5 - What is the performance of different methods applied to the previous research questions?

The first research question RQ1 focuses on a young group of patients suffering from chronic lung disease that has very important impacts on their quality of life, to which physical activity can be a crucial aspect of management of the disease, namely in the event of exacerbation episodes. A very similar role of physical activity is also present in the management of COPD, the focus of the second research question, RQ2, but in this case an older group of patients.

Besides these two patient groups, I also set out to explore the measurement of physical activity in the elderly population within the scope of lung health research, the focus of RQ4. The role of PA is understood in the general quality of life, although not well understood in the context of lung health.

The research question RQ4, has a bigger scope and was addressed in most of the studies we conducted, aiming at providing general knowledge to all researchers using similar techniques in the future. It is an under reported question in most studies that focus on the technical aspects of the sensors and the medical findings, but might be a bottleneck in the wide adoption of sensors in daily living.

I focused the research on data acquired by accelerometers, mostly as a result of the reliability of these devices to accurately measure physical activity in different settings and better usability in medical scenarios. Technological development of both hardware and software and decreasing prices and complexity brought accelerometers into an increasing range of applications in health care. Current trends indicate that their use will see a steady growth in the future, with new promising applications contributing to a better care of many conditions and improving the daily life of people in need.

1.3 RESEARCH CONTEXT

This thesis culminates the research cooperation between several clinical and research institutions both in Norway and Germany. The thesis was developed in the scope of the Tromsø Telemedicine Laboratory research program on medical sensor technology. The project evolved into a close cooperation with the Institute of Medical Statistics and Epidemiology (IMSE) of the Technische Universitat München (TUM), where the field work took place, including close work with medical clinics on discussion of research goals and recruitment of subjects.

Stemming from the association to IMSE and the scope of a PhD project I was invited as associated member of the Graduate School of Information Systems in Medicine (GSISH) at TUM. This provided a dynamic and rich ground for discussion and interaction with other researchers with very close interests. GSISH also provided significant financial and logistical support for the research work in Munich.

Since before the start of the project leading to this thesis IMSE had established cooperation with the KORA collaboration, namely on the KORA-Age project, on objective measurement of physical activity by means of accelerometers. Naturally this turned to be an excellent working cooperation, providing us with high quality infrastructure of the research network and stimulating innovative approaches to the questions at hand.

Given the large scope of the KORA-Age project and the necessary preparatory work among all the partners, when combining the timeframe of our research project with the overall KORA-Age planning, we realized the opportunity for smaller scale studies, aiming to gather valuable knowledge for the larger KORA-Age cooperation and topics of this thesis.

This research was funded/supported by the Graduate School of Information Science in Health (GSISH) and the Technische Universität München Graduate School. André Dias is supported by the Portuguese Foundation for Science and Technology (FCT), by scholarship SFRH/BD/39867/2007 and Research Council of Norway Grant No. 174934.

1.3.1 *KORA cohort and KORA-Age study*

In the scope of this thesis we cooperated with the KORA-Age project contributing to the technology and methods aspects of PA assessment with sensors. KORA-Age is the current effort within the large cohort initiative KORA.

KORA stands for Cooperative Health Research in the Augsburg Region ("Kooperative Gesundheitsforschung in der Region Augsburg") [21]. It constitutes a research platform that is used by various national and international partners. The Infrastructure, organization and the administration of the KORA studies are supervised by scientists at the Helmholtz Zentrum München, more precisely by the Institute of Epidemiology and the Institute of Health Economics and Health Care Management. Tight collaboration with the Central Hospital Augsburg, the local general practitioners, the city of Augsburg and the local health office of the university is needed to run the KORA surveys. Several partners in Germany and abroad cooperate in the implementation and evaluation of the surveys.

KORA-Age focuses on the research of determinants and consequences of multi-morbidity and to look for means for successful aging. The KORA-Age Consortium is part of the research program „Health in Old Age" financed by the German Ministry of Education and Research.

The research consortium composed of clinicians, epidemiologists and social scientists has the objective to identify determinants and consequences of multi-morbidity in aged persons, based on the KORA cohort. The KORA-Age network is organized into several sub-projects, each with specific aims, but sharing common infrastructure and data.

We conducted cooperation within the scope of lung sub-project and aging sub-project 1 of KORA-Age. The former focuses on surveys of lung function in the general elder population, and the later explores the factors and conditions associated with frailty in elderly population. For both sub-projects the recruitment process was responsibility of the KORA study center and the cooperation hospital.

Three studies compose KORA-Age: Mortality follow-up of subjects of the KORA cohort age 65 to 94 years in 2008 and morbidity follow-up by means of a telephone interview of all living subjects[21]. Examinations in a random sample of the cohort, age 65 to 89 years assessing intermediate phenotypes of diseases and aging, functioning and disability, mental health and cognitive impairment, social support and attachment. An intervention study with myocardial infarction survivors aged 75 years and older. The details of the KORA-Age study can be found elsewhere [22].

1.3.2 *Klinik Bad Reichenhall*

The Clinic Bad Reichenhall is a traditional, nationally recognized, specialized clinic for patients with respiratory diseases and musculoskeletal problems. Bad Reichenhall is a privileged location with its mild climate and excellent air quality of a wide and flat valley surrounded by mountains. The clinic has permanent reserach activity setting standards for many treatments[23]. For this it cooperates with several research institutions across Germany.

We established a long term cooperation effort with this clinic, starting with a study on physical activity patterns of severe COPD patients. While working at the clinic we had opportunity to discuss and deepen our knowledge of COPD and impacts on patients life, through direct contact with care givers and the patients.

1.3.3 *Klinik Innenstadt of the Ludwig-Maximillians University*

In order to focus on a group of patients in younger age groups we established a working cooperation with the Medizinische Klinik Innenstadt of the Ludwig-Maximillians Universität (LMU). We cooperated with Privatdozent Dr. Rainald Fischer at the Pulmonary section. The clinic provides care to most patients with diagnosed Cystic Fibrosis in the city, more than one hundred in total. This provided a valuable recruitment pool for this rare disease. We agreed with the medical staff to conduct a short study with two-fold34bjectives: assess the usability of the PA sensors in long term monitoring and assess the feasibility of predicting exacerbation of such patients through changes in physical activity preceding it.

1.4 CLAIMED CONTRIBUTIONS

The goal of this thesis is to investigate the potential of accelerometer devices in the care and research of chronic lung diseases. Based on this objective and the answers provided to the research questions, I claim that the thesis has scientific contributions. The main contributions are:

- *Knowledge of the physical activity patterns of Cystic Fibrosis patients when compared to healthy subjects.* Papers appendidy sample, the physical activity patterns of CF patients differ from the patterns of healthy subjects. This gives us an indication that larger and better designed studies might be able to identify associations between physical activity and health status of CF patients.

- *Implementation of a classification system to distinguish normal days from exacerbation episodes in patients suffering from COPD.* I implemented and tested several features extracted from accelerometer data and used them for the classification of normal days and exacerbation days in patients suffering from COPD. This is a first and very simple attempt at the long term goal of predicting exacerbations in these patients and, if possible, contribute to the prevention of exacerbations by preventive care.

- *Exploration of the associations of Cystic Fibrosis and COPD health parameters to physical activity estimated by accelerometer data.* I extracted several innovative features from accelerometer data that can be used for classification tasks and potentially for exploration of other health related questions that can be influenced by patterns of physical activity.

- *Methodological contributions to the long term monitoring and analysis of physical activity data recorded with accelerometers.* In the scope of the KORA-Age study and generally applicable to all studies I developed several methodological and usability recommendations for successful long term monitoring of physical activity with accelerometers.

- *Exploration of usability and acceptance problems arising from long term monitoring.* The research identified usability concerns from a group of young patients towards the long term use of sensors, namely fashion and social pressure. I decided to drop the use of heart rate sensors in this thesis over the concerns of usability and reliability earlier in the process.

Moreover, five papers have been produced and included in this thesis. Table 1.1presents a synthesis of key findings and they presence in each of the papers.

Table 1.1: Detailed contribution of the thesis: key findings and research questions relation

Key finding	Addressed in paper(s)	Research question(s)
Accelerometer data may provide sufficient information to distinguish exacerbation episodes from normal days in COPD	P3, P4	RQ2, RQ3
Accelerometer data can be the source of important PA parameters for cohort studies	P5	RQ3
Our best classification results were achieved with Support Vector Machines, and second with neural networks	P4	RQ2, RQ3, RQ5
Heart rate monitoring poses challenges in long term monitoring studies	P1	RQ1
Long term usage of sensors poses significant acceptance and usability challenges	P1, P2	RQ4

1.5 INCLUDED PAPERS

This thesis includes five papers, as presented in table 1.2.

The relevance of each paper to the thesis and my contribution to each papers are presented below:

- P1: Measuring Physical activity with Sensors: A Qualitative Study (Dias, Fisterer, Lamla, Kuhn, Hartvigsen, Horsch 2009).
  Relevance to this thesis: The goal of this work was to gain experience on the acceptance and technical questions raised by long term monitoring with sensors. We recruited healthy volunteers and monitored the usage of a set of sensors, collecting information about the data quality and the concerns shown by the users.
  My contribution: Bernhard Fisterer was responsible for the recruitment and supervision of the study. I discussed the study, analyzed the data and wrote the draft paper.

- P2: Assessing physical activity in the daily life of cystic fibrosis patients (Dias, Gorzelniak, Jorres, Fischer, Hartvigsen, Horsch 2012).
  Relevance to this thesis: This study focused on a young population of chronically ill subjects. We established a cooperation with the Pneumonologie section of the University hospital of the Ludwig Maximilians University in Munich for the study. We recruited several Cystic Fibrosis patients in order to study the feasibility of using physical activity to classify exacerbation events. At the same time we recorded their concerns about the usability of the sensors.
  My contribution: I started, together with Alexander Horsch and Rudolf Jörres, the collaboration with the university hospital, discussing the study setup with Rainald Fischer. Later Lukas Gorzelniak and I conducted the recruitment of patients. I analyzed the data from the study and wrote the text.

- P3: Comparison of Recording Positions of Physical Activity in Patients with Severe COPD Undergoing LTOT (Gorzelniak, Dias, Schultz, Wittman, Karrasch, Jorres, Horsch 2012)
  Relevance to this thesis: In this study we explored the statistical association of PA to the COPD health outcomes. It provides us insights, as well, to the best body locations for measuring PA and knowledge on PA that was used on the setup of further studies.
  My contribution: I contributed to the study design with all the authors. Later Lukas Gorzelniak and me recruited the patients at Klink Bad Reichenhall, with local support from

Table 1.2: Papers included in the thesis and the research partners involved

Nº	Title (authors)	Partner	Research question(s)
P1	Measuring Physical activity with Sensors: A Qualitative Study (*Dias*, Fisterer, Lamla, Kuhn, Hartvigsen and Horsch 2009)	IMSE	RQ4
P2	Assessing physical activity in the daily life of cystic fibrosis patients (*Dias*, Gorzelniak, Jorres, Fischer, Hartvigsen and Horsch 2012).	Klinik LMU	RQ4, RQ1, RQ5
P3	Comparison of Recording Positions of Physical Activity in Patients with Severe COPD Undergoing LTOT (Gorzelniak, *Dias*, Schultz, Wittman, Karrasch, Jorres and Horsch 2012)	Klinik Bad Reichenhall	RQ2
P4	Classification of exacerbation episodes in Chronic Obstructive Pulmonary Disease patients (*Dias*, Gorzelniak, Schultz, Wittman, Rudnik, Jorres and Horsch 2012)	Klinik Bad Reichenhall	RQ2, RQ5
P5	Recommendations for Collecting and Processing Accelerometry Data in Older Healthy People (Ortlieb, Gorzelniak, *Dias*, Schulz, Horsch 2012)	KORA-Age	RQ4, RQ1

Konrad Schultz. I contributed the analysis of the data, with Lukas Gorzelniak, and the writing of the final text.

- P4: Classification of exacerbation episodes in Chronic Obstructive Pulmonary Disease patients (Dias, Gorzelniak, Schultz, Wittman, Rudnik, Jorres, Horsch 2012)
  Relevance to this thesis: In this study we explored the data set of PA in COPD in order to classify exacerbation episodes. We implemented several features and machine learning methods that provided insight to the capacity of classifying normal days and exacerbation days in COPD patients. The results indicate good potential for the approach, with reasonable classification accuracy, but still not medically relevant results.
  My contribution: This work was based on the same accelerometer data as paper P3. I discussed the study design with all the authors, and implemented and tested all the necessary code for the classification system. I analyzed the data and wrote the final text.

- P5: Recommendations for Collecting and Processing Accelerometry Data in Older Healthy People (Ortlieb, Gorzelniak, Dias, Schulz, Horsch 2012)
  Relevance to this thesis: This paper provides a summary of our experience in the measurement and processing of the accelerometer data recorded in the scope of the KORA-Age project. This constitutes a methodological contribution for large cohort studies.
  My contribution: In this study I participated in the discussion and planing of the PA measurement activities. I developed the subject deliverable information sheets and improved the handling protocol for the sensors. I developed the scripts for processing the recorded data and planed and executed the testing procedures for the code. I also work to the final text of the paper.

2 BACKGROUND

This chapter presents the importance of objective measurement of several health related parameters with the use of accelerometers, and introduces the essential concepts and technologies used in the development of accelerometer sensors. We give greater attention to the measurement of physical activity and energy expenditure, given that they are the main research topic of the community.

2.1 ACCELEROMETERS AND PHYSICAL ACTIVITY

Sensors allow the detection, analysis, and recording of physical phenomena that are hard to quantify directly by converting the underlying phenomenon into a convenient signal. Sensors convert physical measurements such as velocity, displacement, force, acceleration, pressure or flow into electrical signals. The value of the original physical parameter can then be calculated taking into account the appropriate characteristics of the electrical signal (amplitude, frequency, pulse-width, etc.).

An accelerometer is a transduction device, a sensor, that converts mechanical energy into an electrical signal. They are essentially force sensors that are capable of measuring linear acceleration along one or several directions [24, 25]. They are distinct from gyroscopes, another inertial sensor that measures angular acceleration. The basic building concept of accelerometers is of having a seismic mass attached to a mechanical suspension that has a reference to a fixed frame. Inertial forces, according to Newton's second Law, will move the seismic mass. This movement can be measured and converted to an electrical current or voltage.

Commercially available motion sensing devices are based on 3 distinct technologies: piezoelectric, piezoresistive, differential capacitor, all implementing the basic concept of a mass system.

Piezoelectric accelerometers are made of a piezoelectric element that is bent by a seismic mass when the device undergoes acceleration. This bend causes a charge to accumulate in one side of the element, producing an output voltage proportional to the applied acceleration. These sensors have high outputs for small strains and the potential of a large dynamic range [26]. Piezoelectric accelerometers do not respond to the constant component of movement.

Piezoresistive accelerometers are typically manufactured from a surface micro machined polysilicon structure, where springs arranged in Wheatstone configuration sit. When forces are applied the electrical resistance of the surface changes, producing an output voltage change proportional to the acceleration. These sensors, given their characteristics, are useful for detecting low frequency vibrations. The major drawbacks of piezoresistive sensing are the temperature-sensitive drift and the lower level of the output signals [26].

Differentiable capacitor accelerometers exploit the effect of proportional capacitance change due to applied acceleration. They are built around a differentiable capacitor with central plates attached to moving mass and fixed external plates. Acceleration changes the balance of the capacitor and produces an output voltage. The capacitive nature of the sensor provides a low power consumption, large output level, fast response and low noise levels. Currently this kind of accelerometer has widely been used in most applications [26].

2.2 IMPORTANCE AND MEASUREMENT OF PHYSICAL ACTIVITY

Human movement is the result of many contributing factors such as physiology, mechanics, psychology, etc. Analyzing, assessing and quantifying human movement is an important source of knowledge for care givers and clinicians to diagnose and treat a variety of conditions. Many conditions have been directly linked to the quantity and quality of human movement, for instance, obesity, osteoarthritis, stroke and COPD [20]. In COPD for instance, according to the global initiative on lung diseases, the dyspnea or shortness of breath prevent regular PA which leads to a decommissioning of the overall condition. For this condition the usual recovery program consists of programmed moments of low intensity exercise, such as walking, to improve lung function and overall quality of life [20].

Furthermore, there may be beneficial effects for many other diseases and causes of death which have so far been less studied. The physical activity and patterns of movement have been focused in the scope of other conditions, not directly related, in literature, to PA. For instance, Pan et al. [27] analyzed PA and social engagement in children with autism, concluding that such children that have frequent interactions displayed a higher level of PA.

It is assumed that PA is one of the factors, together with tobacco control and body weight control, yielding the most promising approach to alleviate the burden of disease in industrialized countries [28]. Nevertheless, PA is a complex phenomenon which is only partly understood, especially the interrelation of its components and how they contribute to the development of chronic conditions. PA is a multidimensional construction that can be regarded as type of activity, frequency, duration, intensity, and setting. It can be defined as body movements produced by the activation of skeletal muscle leading to an increase of energy expenditure above the basal level [28]. These body movements induce a machinery of metabolic effects on the cellular, organ, and whole body level which are responsible for the expected impact on disease.

Such findings indicate the importance of PA as a factor for general life quality and well being.

Several methods exist for the assessment of movement, including questionnaires or diaries, direct observation and technological (force plates, video recording and optical motion analysis). Many of these techniques have clear drawbacks for long term measurement, or pose a significant burden for the subjects.

The real importance of PA on health and quality of life is likely to be underestimated due to substantial measurement error in the existing PA assessments. Most epidemiological studies to date exclusively used questionnaires to assess PA, with most of them focusing on estimates of energy expenditure. However, there is wide agreement that PA questionnaires have limited validity to estimate energy expenditure and to quantify PA. Misclassification of PA would tend to bias studies towards finding no association. Therefore, it could be suspected that more precise measures would likely yield even stronger evidence for known associations or reveal still unknown associations with health outcomes [29][5].

2.3 ENERGY EXPENDITURE ESTIMATION

Energy expenditure (EE) can be estimated from measurements of physical activity. The most reliable methods in use, considered as gold standards for EE, are the doubly labeled water method (DLW) and indirect calometry, that consists of measuring oxygen consumption, carbon dioxide production and parameters from cardiac and pulmonary function. Nevertheless these are complex and expensive methods, posing a financial and skills barrier in large scale studies[30]. Despite the availability of such complex methods and techniques that assist in the determination of the energy expended by the human body, an accelerometer provides a simple tool that gives details of such measurements in order to make the relevant medical intervention on a patient. In the free living environment, the accelerometer can be used to determine the amount of energy used for activities such as running and walking. Such specific activities are identifiable their pattern movement when recorded at the anterior to posterior positions.

The acceleration values recorded during activities can be used as an input to several different models and equations that estimate the energy expenditure of the recorded activity[31]. Depending on several factors such as age, weight, height, gender, etc, these models estimate the Physical Activity Energy Expenditure (PAEE) that can be combined with Rest Energy expenditure, to achieve the Total Energy Expenditure. During the last years, intense research has been devoted to build and validate these models. Nevertheless, they don't achieve high accuracy rates when compared to gold standard methods such as DLW. Validation of such models is hard, not only because of the factors influencing accuracy, but also the dependence on the particular hardware used and the wide range of accelerometers available.

There are a number of other systems that are used in the determination of physical energy consumed for use in, for instance, in the evaluation of the progress of patient's recovery therapy. Magnitude of acceleration picked by various accelerometer target parameters is converted to represent the level of activity in the respective parameter, for instance walking [32].

Other environmental factors such as external vibrations and possible gravity related artifacts that can cause some extra acceleration detection can result in the wrong data interpretations[33]. An analysis of such data is therefore supposed to include the actual factors that are likely to affect the ideal real figure expected in the measurement of energy expended by the patient. Certain positions on the body are more representative of bodily motion than others for instance the amount of acceleration recorded at the lower back is not the same as that on the lumbar cavity and vertebrae regions. Specificity is important in analyzing the actual acceleration for the translations thereon to imply respective energy expenditure. Special analysis enhancement techniques such as pressure detection on the accelerometer were used to reveal the various changes in the vertical and horizontal motion positions.

The lack of satisfactory results on estimation of PAEE is due to the models not fitting to all modes of activity, wich varies in intensity, type or duration for instance. The equations were developed for certain movement patterns, and so can't cope with movements not picked up by the sensors or totally different patterns of movement. To overcome these limitations some researchers have proposed two different sensors (accelerometer and heart rate) [34, 35, 36], using branched equations or cross-sectional time series [31]as modeling technique. Nevertheless, usability poses a significant barrier for this approach.

Besides simple formulas for estimating PAEE, some authors have explored more robust modeling techniques such as neural networks [37][38], reporting a significant reduction of the confidence interval associated with the estimations.

For estimating EE in children[39], several equations have been proposed, such as Freedson et al. [40], Hendelman et al.[41], Swartz et al.[42], Ekelund et al.[43], Puyau et al. [44], Trost et al. [45, 46], Corder et al.[47], Sun et al[48]). Nilson et al. [49] used an MTI accelerometer model 7164 (Manufacturing Technology Inc., Fort Walton Beach, Florida, USA) to compare three of these equations (Ekelund et al., Puyau et al., Trost et al.) in data collected in a total of 1321 children in 4 countries during daily life activities. They concluded that the estimations vary substantially depending on the model used, with standard deviations of 290 kcal/day. They argue that such laboratory created models can not be used interchangeably and the comparison of results should be avoided. Trost et al. compared the equations by Trost et al, Freedson et al. and Puyau et al., and reached similar conclusions, that each equation as developed in laboratory setting could only correctly estimate PAEE for certain types of activities. Graauw et al. conducted a literature review on existing models for PAEE estimation, including several accelerometer models, and is an exhaustive tool for researchers looking for insights. They concluded that such models can explain up to 45% of daily living PAEE. They indicate that tri-axial accelerometers, that became the norm nowadays, seem to improve the accuracy.

As for adults, more equations have been proposed for estimating PAEE. Crouter et al. in 2006 [50]examined the validity of the equations proposed by several authors before: Brage et al. [51]; Brooks et al.[52] ; Freedson et al. [40]; Heil et al. [53]; Hendelman et al. [41]; Leenders et al. [54]; Nichols et al. [55]; Swartz et al. [42]; Yngve et al. [56] and Klippel et al. [57] for the Actigraph and Actical accelerometers, in group of preset activities. More recently, and taking into consideration new sensors and equations, Lyden et al. [58]revisited the same problem, this time using the most common accelerometers Actigraph, Actical and RT3, and compared 11 different equations including the RT3 proprietary equations and some of the ones taken into consideration by Crouter et al. In a similar approach Rothney et al.[59]asked subjects to wear 3 sensors at the same time and compared the output of each sensor regarding energy expenditure. They found very good results for vigorous activities of less than 2% differences between sensors.

The main point that comes from this extensive testing and comparison is that current techniques produce a single average over time of the accelerometer, thus not using the rich features of the signal. This means that very different activities produce similar outputs in terms of energy expenditure estimated by the accelerometer.

2.3.1 *Gait parameters estimation*

Gait parameters can be a source of information to assess balance control, functional ability but also risk of falls. Accelerometers have been proposed to simply identify the moment of heel strike [60] on leveled and inclined surface [61]walking, but also more complex parameters as gait cycle frequency, stride symmetry and regularity [62]. These spatio-temporal parameters can be measured over long periods of walking, providing a significant advantage over existing systems that are only feasible in a laboratory setting. Moe-Nilssen et al. [63, 64] estimated gait parameters using a tri-axial accelerometer attached to the lower back. They used standard signal filtering auto correlation analysis to estimate cadence, step length and gait regularity. They tested their approach in up to 9m walks for a small number of subjects.

Research has also been focusing on differences of gait features between group ages, for instance between young and elderly[65, 66], using root mean square values of acceleration[67]. The harmonic ratio has been proposed as an estimation of gait smoothness, as defined by the ratio between the sum of even-numbered harmonics and odd-numbered ones after finite Fourier Transform [68].

When using higher sampling rate accelerometers the Butterworth filter, in conjunction with simple threshold-based algorithms, have been used and tested in a few dozens subjects under very controlled conditions.

Nowadays, accelerometers are not widely used as gait parameter estimators. One reason for this is that proper methods to deal with variability in gravity components of the signal have not yet been developed. Methods exist to reduce the gravity component and assess acceleration during locomotion, but not yet to deal with the intrinsic variability of gravity.

2.3.2 *Circadian rhythm analysis*

The study of rest-wake periods has a long history in the medical community. The introduction of robust accelerometers provided an increase in the reliability of such studies. Prolonged measurements with accelerometers spanning several cycles of rest-wake (typically days), provides insight into chronological-biological patterns.

The most popular method for analyzing actigraphy data for sleep disturbance studies and circadian rhythms has been the cosinor analysis [69, 70, 71], in which a cosine curve with a period of 24 hours is fit to the data by the least square method. After the fitting process we can extract some interesting parameters such as: acrophase (time of peak activity), amplitude (peak-to-nadir difference), alpha (width of the rhythm), beta (steepness of the fitted curve, which can approximate a square wave if beta is high) and mesor (mean) of the fitted curve. Some authors extended this approach by calculating the autocorrelation index over a day cycle or the inter-day stability of the fitted curve. Some standard statistical features such as standard deviation of sleep time, average activity or intra-day variability have also provided evidence for several studies.

Sensors used for this purpose can detect circadian rest-activity cycles, changes in sleep length [72, 73] and annual phase changes. Nevertheless, given the nature of sleep, regardless of the algorithms used, accelerometers have significant limitations in assessing subjects with high mobility during sleep or motor disorders, and the lack of validation between different methods and sensors makes comparison or quality assurance very difficult [74].

2.3.3 *Seizure detection*

Godfrey et al. [75, 76] used features extracted using wavelets analysis to classify motion from patients with delirium - an umbrella term to denote acute generalized disturbances of cognitive function, that affects up to 50% of hospitalized elderly people - into three classes of hyperactive, hypoactive and mixed. They used continuous wavelet transformation as well classification trees, with good results. They first ran a study to define the best mother wavelet for further use, based on three typical patients whose classification was known. After applying the best wavelet, a high pass filter was applied to the coefficient in each level. Then, counting, minimum, maximum, average and standard deviation were calculated for each level and used as classification values. In the second study a classification tree was applied to the remaining patients. They achieved up to 96% accuracy of classification

Nijsen et al. [77] used wavelets and energy analysis with the goal of detecting seizures, in particular myoclonic seizures - a very subtle and difficult to detect symptom - in institutionalized patients suffering from epilepsy. The goal was to detect serious seizures for triggering alarms or the more subtle ones for diagnose purpose. They used continuous wavelet transform and short time fourier transform to typify 4 different situations: isolated seizures, seizures within certain intervals of other movements, slow non-seizure movement and sharp peaks in other movements. Based on 4 sets of features (all, range, normalized, and range of normalized powers or coefficients) they achieved in the best setup a sensitivity of 1 with 4 false positives (of 10 total seizures).

Fast Fourier Transformation (FFT) converts a time-based signal into its main frequency components and it is a standard tool for time-series analysis, specially for classification of activities. Given the high sampling rates and sensitivity of current accelerometers, several authors have explored fractal structures in data. Fractal values extracted from maximum-likelihood-estimate analyses and wavelets of acceleration at the trunk are good indicators of the stability of unperturbed walking patients suffering from Parkinson's [78, 79] or Stroke [80, 81, 82, 83, 84]. They found that the fractal dimensions were significantly capable of detecting differences in gait related to the disease, as for the patients with Parkinson's disease the fractal dimensions tended to be higher than those of healthy subjects.

2.3.4 *Fall detection and prediction*

Injuries caused by falls are a source of significant trauma and loss of quality of life in the general elderly population. A fall can be defined as a rapid postural change from upright to reclining to ground position, excluding the ones that arise from a violent blow, loss of consciousness, stroke or epileptic seizure. With current population dynamics the number of people living alone is on the rise, and so therefore is the risk of people to have recurrent falls, especially those in frail conditions. Gait parameters during normal walking or standing can be a source of information leading to early warning of risk situations. In addition accelerometers can be used to determine accidental motions caused by a fall [85].

Some fall detection applications report temporal gait parameters in order to determine the actual position of the body parts, thereby creating a detection system that can assist in clinical interventions. In the gait detection system, the analysis is dependent on the presumed pattern of body movement which is recorded for comparison with abnomarl values obtained during a fall. Gait cycle parameters are provided to the system in order to establish an correlation between the recorded and actual body movements [86, 87]. Ordinarily, fluctuations from the standard values are reported as possible causes of concern for the patient. The recorded values for the waves are compared with the peak magnitudes to demonstrate the correlativity of the values. A healthy person without motion issues has a regular pattern of motion waves.

The first proposal of an accelerometric system was published by Williams et al. [88, 89] incorporating along the accelerometer a mercury switch to identify the orientation of the apparatus. It was based on a two stage detection algorithm with first step detecting the sudden movement and impact (accelerometry) and the final resting orientation (mercury switch), in order to reduce the number of false positives. This approach became a commercial product. Others have taken similar approaches to solve the problem [90, 91].

Various values of body parameters are considered in the analysis some of which are step symmetry, cadence, step regularity and stride regularity. Deviations from these parameters are analyzed as possible causes of concern for the person who could have fallen and be in need of assistance. According to Budge et al. [92], it is possible to enhance the reporting of such fall reports in order to manage and monitor the motion of the patients in a remote setting. In the enhanced, real-time systems for monitoring such fall cases can be important in implementing prompt interventions in cases of emergencies where patients and older people are followed from a distance. Morbidity is reduced in such instances since remote deployment of assistance protocols is facilitated and can also be exploited in the management of care for the elderly.

According to the study conducted by Bourke et al. [93], algorithmic analysis of the data obtained from possible falls by patients is dependent on the velocity and impact sustained as well as the effective posture parameters recorded. Fall detection devices fitted with accelerometers therefore internalize the various posture settings as well as determining the impact pressure upon falling, thereby showing important fall parameters. The accuracy of such a device that analyzes the velocity of various movements is important in this application since such parameters are important in the determination of fall positions. In most devices, it is the analysis of more than one data type that contributes to the determination of reliable fall assessment. It is therefore expected that a combination of all these parameters in the analysis of the patient's movement as well as position can be used to determine the appropriate intervention without interpretation difficulties. Before the implementation of such algorithms in the system is conducted satisfactorily, certain tests are conducted on the patients' natural systems to ensure that their motion parameters are not confused with fallen position parameters that raise alerts and consequent intervention protocol. Such tests such as the Timed Up and Go (TUG) are important in establishing the data analysis procedure based on the inherent parameters posted by a naturally functioning system and one with motion difficulties.

Hsu and Yang [91] present a decision tree approach to identify the various human movement artificats or alterations. In the study, the authors found out thresholds for classification of motion that are important in the classification of input of an accelerometer. These can be applied in a hierarchical decision tree for analysis for the various motion data recorded by an accelerometer, identifying the actual position of the patient with respect to normal posture data.

Transormation of the data to constitute an alarm may also include a threshold for an emergency where the alarm is generated. In such an instance, the initial threshold of the acceleration is met but if the patient fell and does not stands-up again, it is sufficient to be considered an alert value. Fall accuracy algorithms that use better analysis threshold for instance include determination of three derived parameters in order to constitute an alarm. A sensitive axis must be defined in the detection system and a set of accelerometers are incorporated in the device and orthogonally worn on a strategic position on the body of the patients. Lindemann et al. [94] used such approach in their system, based on a ear mounted sensor. Nevertheless, given the size and weight of the proposed system, they concluded that the ergonomics and design of the system was a barrier.

Marschollek et al. [95] built an expert system, using classification trees and logistic regression, based on features extracted from accelerometry and physical activity scores. For this they extracted a set of features using spectral analysis [96]. They achieved a classification specificity of up to 80% on retrospective prediction of subjects at a risk of falling within one year.

To explore the stability of walking some authors have also explored nonlinear time series analysis, for example lyapunov exponents [97].

2.3.5 *Models of health outcomes in CF and COPD*

Some authors have explored the modeling of health outcomes in chronic obstructive pulmonary disease and cystic fibrosis, but from other variables not related to physical activity.

Troosters et al. [17] used the Sensewear device (Body media, Pittsburgh, USA) in 20 CF patients and 20 healthy control individuals over 5-7 days, to study skeletal muscle weakness and PA. Their results indicate a contribution of physical activity to exercise tolerance, which is a crucial aspect of rehabilitation programs. Hebestreit et al. [11] monitored 7 days of PA, using the MTI/CSA 7164 accelerometer (MTI Health Services, Fort Walton Beach, USA), and correlated the results with exercise capacity. They found that average daily accelerometer count, moderate and vigorous PA independently explained part of the variance in maximal oxygen uptake, contributing to understanding the importance of rehabilitation programs in CF. Fournier et al. [18] recruited 15 CF patients, in whom they measured PA for 7 days, and correlated the results with pulmonary function and exercise tolerance. To study energy expenditure in CF patients during Pseudomonas aeruginosa-related pulmonary exacerbation, Béghin et al. [16] assessed PA in 16 children, but only for 24 hours, including a normal day at school. In this group they found no significant decrease of PA in the time between two intravenous antibiotic therapy sessions. In contrast, Wells et al. [98] evaluated the output of the Actigraph accelerometer over two weeks in 14 patients and compared data with the habitual activity estimation scale and a diary, concluding that a questionnaire is a reliable instrument for estimation of PA levels in patients with CF.

There is little research into the use of machine learning and modeling of health outcomes or health parameters from accelerometer and PA data. One of the limiting factors for this is the need for high sampling rates and long periods of measurement in order to extract robust features from the data.

Several studies [99, 100, 101, 102, 103] have investigated the forecast of exacerbations in COPD, but with only partial success. Marin et al. [99] and Ong et al. [102] proposed using the BODE index, a composite marker of COPD disease, to predict the probability of exacerbation within a year period. Miniati et al. [100] also aimed to predict exacerbations over the period of one year but using the C-reactive protein as source of information. Jensen et al. [103] looked at the various physiological dimensions, such as blood pressure, as predictors for exacerbation on a scale of several months, using data that was collected by several medical sensors in a telemedicine project. Other authors have explored the predictive capacity of PA in COPD, but focussing on the mortality rate [104] or the overall health status of the patients [105]. Garcia-Rio et al. [104] found that the time until first admission to hospital due to exacerbation was linked to lower physical activity levels, which hints at a relation between PA and exacerbations.

2.3.6 *Summary*

The most common use of accelerometers in medical applications is still the estimation of PA in patients or healthy subjects. This is conceptually the simplest of the applications and comprises the conversion of the acceleration recorded into a measurement of total physical activity carried out. Increasing amount of research and effort is going into new fields of application. Sleep medicine can benefit from the type of monitoring provided by small and unobtrusive sensors.

More complex and robust applications have been developed as well, from estimation of gait parameters to the calculation of fall risks. In order to provide reliable results these aproaches probably need either increased accuracy of the hardware available, or extensive research into better methods of analyzing the data.

3 MATERIALS

This chapter presents the decision-making process, the materials and methods used in the research. We present off-the-shelf sensors and their essential characteristics and details. We also introduce the computational methods used for signal processing, model construction and analysis of the results.

At the start of our studies we defined crucial criteria for sensor selection: sensors had to be off-the-shelf, readily available and validated sensors. We couldn't develop or support the development of new sensors, even if they would provide technical advantages for the research. The timeframes of the research and goals would make it unfeasible. The commercial offer of such devices is robust nowadays, with several dozen manufacturers proposing different solutions, which creates a competitive environment with constant evolution. We have no expertise in designing of electronics and have no intention to validate sensors, an essential step if we had opted to develop our own hardware.

After detailed analysis of off-the-shelf sensors we decided on the use of a small set for feasibility studies in the first instance.

3.1 SENSORS

Modern devices are small, lightweight and can be attached at the body using elastic belts with minimal burden for the participant. The hip is the preferred place of attachment, as it is the centre of the body mass. Devices should be worn for at least seven days to cover intra-week variations between work days and weekend. Its size and water resistance allow the participants to wear the device for several days continuously without the need to take it off. This reduces problems with compliance and non-wearing periods.

Table 3.1 shows a comparison of key aspects of several off-the-shelf sensors. This is the result of our exploratory assessment of several sensors on the market. It provides an easily accessible tool for comparison and facilitates decision-making on which sensors to use on a given research project.

3.1.1 *GT1M and GT3X*

The GT1M (Actigraph, Pensacola Florida, USA) is a uni-axial acceleration sensor with micro-electromechanical technology. The GT3X (Actigraph LLC, Pensacola Florida, USA) is a tri-axial

Table 3.1: Main characteristics of readily available off-the-shelf sensors for physical activity and heart rate measurement (updated March 2010)

		Validated				Non-validated	
		ActiGraph GT3X	SenseWear	StayH RT3	Polar	Shimmer	Curvus
Accelerometry	Battery life	10 d	5-7d	21d	months	8 d	2d
	Tri-axial	yes	yes	yes		yes	no
	Raw data >32 Hz	yes (30-100 Hz)	no(32Hz)	no (2-10Hz)		yes (1-500Hz)	
	Storage	8 d at 80 Hz (250MB)		21d		80d	
	Integration interval	1s to 1m	1m	1s to 1m		programmable	
	Ability to disable filters	yes	no	no		yes	
ECG	HR + R-R				yes	yes	yes
	led				1	1+	1
	ECG/HR storage				99h	80d	2d
General	Size	very small (4.6cm x 3.3cm x 1.5cm)	large (55mm×62mm ×13mm)	medium	small	medium (53mm×32mm ×15mm)	small
	# of scientific studies	>100	>100	>100	>10	1	2
	Usability*	9 – small, easy straps	8 – arm, large	8 – belt, visible,AAA batteries	8 – skin irritation	7 – electrodes, skin irritation	6 – large parts, skin irritation

Figure 3.1: GT1M and GT3X. Both share the same casing design

acceleration sensor. Both use a Micro-Electro-Mechanical Systems (MEMS) technology and have a sampling rate of 30Hz. The firmware can be configured to record steps, activity counts, inclination. Although the sampling rate is 30Hz, configuration allows recording on samplings of 1 second to 1 minute or raw data, before or after filtering. The filter, implemented in the firmware is, according to the manufacturer, a bandpass between 0.25 to 2.5 Hz. The inclinometer measurement can be used for identification of moments when the sensors are not worn. The battery is built-in, with capacity of up to 30 days of recording, with safe duration of 21 days. They are small and lightweight (3,8 x 3,7 x 1,8 cm, 27g). The software provided by the manufacturer supports several processing algorithms, including the estimation of energy expenditure through several equations. Both sensors have been validated in medical applications for estimation of energy consumption [106, 52, 40, 56]. Vries et al[107] reported that the ActiGraph series was the most studied activity monitor, and many studies have validated its reliability and performance. Figure 3.1 shows the external appearance of both GT1M and GT3X sensors.

Figure 3.2: Stayhealthy RT3, a tri-axial and wide use sensor

3.1.2 *RT3*

The RT3 (Stayhealthy, Monrovia, CA) is designed as a complete activity recording and measurement system for clinical and research applications. It uses piezoelectric accelerometer technology and provides data as a three-dimensional vector and a vector magnitude. It is usually worn on the waist, as a holster is provided for the attachment. For the calculation of the calorie consumption estimation or the metabolic equivalent units, the weight of the subject is taken into consideration. The software provides an estimation of metabolic activity units taking into consideration the activity counts and age, gender, height and weight of the person. It is able to record three hours of acceleration data with a resolution of 1 second or 21 days at 1 minute resolution. It has been validated in medical applications for energy consumption estimation [48]. The RT3 sensor, shown in figure 3.2, also replaces the previous version TritracR3D, which has been widely used in a number of studies and research applications. It uses standard AAA batteries that need to be removed to be replaced or recharged. This causes total loss of memory contents and it is a potential source of data loss if the battery is removed by accident during measurement or before data is downloaded from the sensor. The interface of the RT3 to the computer is an outdated RS-232 port, with a docking station as direct interface to the sensor. The docking mechanism is highly unreliable, causing a high number of connection errors. Its dimensions are 7,1 x 5,6 x 2,8 cm and it weighs 65,2g.

3.1.3 *GAITRite*

The GAITRite walkway is a roll-up carpet containing many sensors for analyzing the gait of a person. Its active area, a 365 cm long and 61 cm wide measurement zone, is composed of 6 sensor pads, with each being 155 square cm. One sensor pad contains

Figure 3.3: Polar RS800CX heart rate sensor (not to scale)

2304 sensors arranged in a 48x48 grid and each of the sensors is placed on a 1.27 cm center. While a person walks over the walkway, those sensors collect information about the footprints, the step length, the rhythm, etc. The GAITRite program stores these data into a structured database.

3.1.4 *Polar RS800*

For heart rate we used the Polar RS800CX sensor. It consists of a strap-on chest unit and a wrist unit. The chest unit contains electrodes in a textile band and a wireless transmission unit.

Polar RS800, shown in figure 3.3, is a recent model and was not used, to our knowledge, in any scientific study to date. According to the manufacturer the RS800 model is functionally equivalent to the S810 model, which was independently validated.

3.2 SUBJECTS

Recruitment of subjects and patients for all the studies was conducted with different cooperation partners, namely the KORA-Age study run by HelmholtzZentrum in Munich, the pneumonology division at Ludwig Maximilians University hospital and Klinik Bad Reichenhall.

3.2.1 *Studies*

As presented earlier, we conducted a total of 4 studies with different goals and subjects. Table 3.2 presents an overview of the different studies, the goals, criteria and subjects for each one of the studies. These studies developed chronologically in the order presented, and also in terms of subjects involved.

Study	Goal	Subjects	Criteria	Recruitment
Feasibility	Study the feasibility of long term monitoring with accelerometers and heart rate sensors	7 healthy people	No known health issues that affect PA	Among social contacts of researchers
CF	Explore the possibility of PA and exacerbation association. Acceptance.	10 CF patients. 10 healthy individuals	CF patients, > 18 years. No known health issues that affect PA	Klinik Innenstadt, Munich
COPD	Explore classification of exacerbation episodes	58 COPD patients	Severe COPD undergoing therapy	Klink Bad Reichenhall
KORA-Age	Propose and implement new parameters for PA	200 subjects	Participants in the KORA cohort	Helmholtz zentrum, Munich

Table 3.2: Studies in this thesis, their goals, subjects and criteria

Table 3.3: Relevant characteristics of the 7 subjects in the feasibility study

Age	Gender	Activity level	Height (cm)	Weight (Kg)
22	F	5	178	59
25	M	3	181	70
56	F	4	162	70
62	M	4	178	77
78	F	4	151	78
85	M	1	160	65
86	M	2	163	76

3.2.2 *Feasibility study*

We asked 7 people to wear the sensors while performing their daily life activities and report their opinions on the sensors, namely the comfort, ease of use and problems if any. We did not request any information on their health status as it was considered irrelevant for the objectives of this study. Their essential characteristics are shown in table 3.3. In the table the activity level is a subjective assessment of their activity level in daily life in a scale of 1 to 5, with 1 being the lowest.

Our goal in the first feasibility study was not to use the measurements for a quantitative assessment, but rather to perform a qualitative evaluation of the sensors in order to assess their feasibility for bigger studies. In particular, we were interested in checking out limitations and identifying problems that arise when using the sensors over long measurement periods.

3.2.3 *Chronic Obstructive Pulmonary Disease - Klinik Bad Reichenhall*

We recruited, in Klinic Bad Reichenhall, 58 patients (35 males and 23 females) diagnosed with severe smoking related COPD, undergoing Long Term Oxygen Therapy, and admitted to a pulmonary rehabilitation program. All patients had a diagnosis of COPD related to smoking, in stage IV according to GOLD guidelines. See table 3.4 for detailed clinical indicators for the recruited patients. We asked them to wear a GT1M sensor at leg and arm and a RT3 sensor at the hip, from getting up to going to bed, for a period greater than a week. Patients with type 2 respiratory failure or with less than four days of accelerometry data for two of the locations were excluded from the study, leaving us with a total of 52 valid datasets for further processing. All procedures were approved by the relevant ethics commission.

Figure 3.4: Photo showing one of the COPD patients wearing the arm and hip sensor

The photo in figure 3.4 was taken during the study, and represents one of the subjects wearing the arm and hip sensor (leg sensor not visible).

3.2.4 *Cystic Fibrosis - Klinik Innenstadt*

We asked 15 CF out-patients to participate in the study whose details are shown in table 3.5. The interview took place during their routine consultation with their doctor at the clinic. Only patients aged >18 years and in a stable clinical condition were included. Participation was voluntary, with no compensation. A written informed consent was obtained from each participant, and the Ethics Committee approved the study protocol. Besides the CF patients we recruited 10 age-matched healthy subjects without known history of disease or condition influencing their PA, as control subjects. In order to provide useful feedback to the patients and to increase their motivation to participate in the study, the acquired data was offered to inform the patients about potential findings indicating a restless leg syndrome. An overview of the participating CF patients' health status is given in table 3.5. One of the patients has a clearly higher FEV1%pred. assessment than the average, most likely the result of her/his younger age, and thus her/his lung capacity hasn't been severely affected by the disease.

Table 3.4: Characteristics of the participating COPD patients

Variable	Average±SD
Age (y)	62.2±9.6
Gender (F/M)	22 / 30
BMI (Kg/m)	25.5±7.0
FEV1 %pred	38.0±11.8
FEV1 %VC	44.9±13.0
6MWD	265.4±93.7
BORG CR10	5.2±2.1
MMRC	3.0±1.0
BODE Score	6.2±1.9

To obtain information on different aspects of movement, we used the uniaxial accelerometer Actigraph GT1M, placed at the ankle, and the tri-axial accelerometer RT3 placed at the hip. The sensors were configured to record activity once a minute.

3.2.5 *KORA cohort and KORA-Age study*

Two hundred subjects from the KORA-Age study were screened for participation. The study center was responsible for recruitment of subjects in the context of the KORA-Age study. After agreeing to participate each subject was asked to visit the research laboratory at LMU. We provided the staff at LMU with individual sets of sensors as needed. Each set consisted of the sensors themselves, fully configures and with charged batteries, a postage paid envelope for returning the sensors to our laboratory and an information sheet, date of return and contact for questions. See appendix iv.

Participants are members of the KORA cohort, a subsample from the epidemiological cooperative health research in the region of Augsburg study [21], who were born in the year 1943 or before, and who were assigned to the lung function and physical activity examination sub-project, based on previously measured spirometry in the KORA study center Augsburg.

The inclusion criteria were: older than 65 years, without known pulmonary disease (COPD, asthma or bronchitis). Of these, 191 subjects agreed to participate and we recorded a total of 1696 valid days with a sensor wear time of $x>3$ hours. Of these, 179 subjects provided a full week of data, with 2 drop-outs who wore the sensors for less than a day. The subjects wore the sensors from 7 AM till 9 PM, 12 hours on average, including a mean of 9 short periods of non-wearing.

Table 3.5: Characteristics of the participating CF patients. Characteristics (FEV1 = forced expiratory volume in one second, PaO2 = arterial oxygen pressure, PaCO2 arterial pressure for carbon dioxide, %pred = values as percent of predicted normal values)

ID	Age	Height	Weight	FEV1	FEV1% pred.	PaO2	PaCO2
P1	40	175	66	1.49	39	72,2	38.1
P2	25	179	67	3.11	81	83.0	33.4
P3	26	166	50	1.95	51	94.0	41.0
P4	21	160	61	4.34	119	86.4	37.2
P5	26	184	74	1.91	41	75.0	40.3
P6	31	180	55	3.27	75	84.3	40.2
P7	30	157	49	2.13	75	77.0	33.3
P8	35	190	85	4.14	89	76.8	37.6
P9	36	169	62	1.69	46	50.2	40.3
P10	25	160	57	1.42	39	68.0	42.1
Avg	29.5	172	62.6	2.55	65.5	76.7	38.4

Table 3.6: Characteristics of the KORA-Age participating subjects. Values are average±standard deviation

	All	Male (n=92)	Female (n=98)
Age (y)	75.1±6.6	75.3±6.4	74.9±6.8
Weight (kg)	75.2±11.7	79.4±10.2	71.3±11.7
Height	164.1±9.0	170.3±6.6	158.3±6.8
BMI (Kg/m)	28.0±4.0	27.4±3.3	28.5±4.5

The KORA-Age study was approved by the Ethics Committee of the Bavarian Medical Association. Written informed consent has been obtained from the participants and all investigations have been conducted according to the principles expressed in the Declaration of Helsinki.

3.3 SUMMARY

We planned the recruitment of subjects following a logical pattern of starting with a small group of healthy subjects known socially to the research team and later recruiting larger groups of subjects. We started with young CF patients, expecting that due to their younger age they would be motivated to participate in the studies and then moved to older COPD patients. Later we cooperated with the KORA-Age study with a large group of subjects, which posed different challenges, due to size and recruitment strategy.

During these studies we established strong and long-lasting research relationships with the medical partners.

4 METHODS

In this chapter we present the operating procedures for the handling of the sensors and the software methods implemented to process the data collected. We present general aspects of the research setup, namely handling of the sensors and software tools used, and then the experimental methods for the core studies relating to the research questions. I did all the software analysis and development presented in this chapter, after discussion and feedback from the team and our partners.

4.1 SENSOR HANDLING

For all the studies in this thesis we adopted a very similar protocol for handling the sensors and delivery to the subjects. The main difference among studies was the method for collecting the sensors, either by post or in person.

The sensors were prepared at the laboratory, by charging the batteries, initializing the correct configuration and assigning tracking number to each one. After this preparation they were assembled into sets of sensors and information sheets to the subjects, see the information sheets in appendixiv. The sets were then delivered to the subjects in the interview process, when an explanation of the study and the sensors was also given. After this the measurement period started and the subjects took care of the handling of the sensors themselves. When the period finished, or in case of drop-out, the sensors were returned to the team. In the CF study and KORA-Age the return of the sensors was carried by post, in envelopes that were pre-paid and pre-addressed back to the laboratory. In the COPD study as the patients were in the clinic the whole period they returned the sensors to the medical or nursing staff, and they were later collected by a team member.

After the sensors with data were returned to the laboratory all data was downloaded to a central repository and stored according to a standard procedure. We investigated all suspected sensor failures, namely when data was missing or showing odd values. The probable cause of failure and the tracking number of the problematic sensor was recorded, so we could assess if a given sensor had a permanent or recurring failure in order to put them aside.

The CF study provided us very relevant feedback on the usability of the sensors, namely the locking mechanism of the straps. This made us replace the standard, manufacturer provided, clip mechanism with a velcro strap. This provided a significant improvement on the usability of the sensors for the remaining studies.

I formalized the operating procedures and information sheets for the patients, after discussing the needs with the team members and after initial feedback from previous studies.

4.2 MATLAB

We opted for implementing a toolbox of computational routines given the large datasets that our projects would generate. This was driven by the need to implement standard though highly computationally complex methods, and the need to repeat a set of tasks numerous times for each subject in the dataset. After checking and comparing the features, advantages and disadvantages of several commercially available tools, we decided to implement the toolbox in Matlab.

Matlab, which is developed by MathWorks inc (Natick, MA, USA), is a numerical computing environment and a programming language. It can be used for matrix manipulations, plotting functions and data, implementing algorithms, creating user interfaces and interacting with programs written in other languages such as for example C, C++, Java and Fortran. Having native array operations that work without explicit loops, gives these operations a good execution time. Vectorisation is therefore an effective way of optimising the runtime of a function or script; the speed can be improved by a factor of 10 or more. The speed of a function or script can be improved by 10 times or even better. We used Matlab version 7.0.4 (R14SP2) running on GNU Linux (Ubuntu 10.4 and 12.04) and MacOs X (10.6).

The simplicity of the code needed for most tasks and the significant speed over conventional programming tools were the main factors to choose Matlab as the platform for implementation of the algorithms for this thesis.

4.3 CYSTIC FIBROSIS PATIENTS PROFILES

From the accelerometer daily data from 6AM to 10PM we extracted 8 features from a scatter plot of the filtered values measured by each sensor. The scatter matrix used for the feature extraction consisted of consecutive values that were plotted against each other. For each two consecutive activity measurements Xi and Xi+1 , at minute i and i + 1, Xi is the coordinate on the x-axis and Xi+1 is the coordinate on the y-axis. The features were: coordinates of the centroid of all points (median coordinate along X and Y axis), proportion of points within 5% of the area around the centroid (percent relative to maximum area defined by the signal amplitude), density of points in each of the four quadrants (also defined by the maximum area of the signal amplitude) and average distance of points to the centroid. We choose these features after comparison of all the scatter plots and identifying visual distinctions between patients and controls. These features were used as input for a feed-forward neuronal network with 20 hidden neurons. The NN was trained to discriminate between patients and control subjects using the leave-one-out method which is a standard cross-validation scheme for small data sets. Algorithm 4.1 represents the pseudo-code for the feature extraction. The first step is the creation of the scatter matrix, as explained above, where two consecutive measurements are X and Y coordinates of each point in the matrix. From this matrix we check if each point is inside a square, comprising 5% of the total plot area, around the centroid of all points. Next we check which quadrant of the plot the point is. Last we calculate the distance from the origin to the point, to calculate the average distance of all points. The extracted features are normalized to a percentage of total points.

4.4 COPD EXACERBATION CLASSIFICATION

In this first approach to the overall prediction problem of exacerbations we focused on the task of classifying exacerbation days from control days. We explored several features, some of wich are commonly used in signal processing and others have been previously used in classification tasks of accelerometer data [62, 108-113].

For a given day n, we extracted features from the data set of day n-w, ... n-1 and n, except the day when the patient was diagnosed. With w as a feature window indicating how many days preceding the n day were used in the feature extraction. We considered that data from the day before diagnosis of the exacerbation could be already influenced by the onset and so cannot be safely considered a non-exacerbation. We extracted a total of 20 different features from the accelerometer data for classification. They include features that focus on the characteristics of the PA data from each individual sensor separately (set 1), frequency and time-scale features of each sensor that are commonly used in signal processing problems, and have been previously used in the classification of accelerometer data, specially in the scope of activity detection (set 2). The last set is composed of cross-information of data collected at different body parts (set 3). See table 4.1 for details of the extracted features.

For all the above features we calculated them twice with time window w of 3 and 2 days before the feature day. We explored the best time window by running tests with window values rang-

Algorithm 4.1 Pseudo-code for the feature extraction phase in the CF data

```
for i 1 to numberSubjects
 scatterMatrix = createScatter(subjectData)
 centroid(1) = sum(scatterMatrix(1)) / length
 centroid(2) = sum(scatterMatrix(2)) / length
 for j 1 to lengthMatrix(1)
  if scatterMatrix (j) is inside( square(0.05, centroid(1),
      centroid(2))
  count= count+1
  if scatterMatrix(j) inside (quadrant1)
   Q1 = Q1+1
  if scatterMatrix(j) inside (quadrant2)
   Q2 = Q2+1
  if scatterMatrix(j) inside (quadrant3)
   Q3 = Q3+1
  if scatterMatrix(j) inside (quadrant4)
   Q4 = Q4+1
  sumDistances = sumDistances + linearDistanceFromCntroid(
      centroid,scatterMatrix(j)
 endfor

 feature_squaredensity(i) = count/lenght
 feature_quadrant_1(i) = Q1/length
 feature_quadrant_2(i) = Q2/length
 feature_quadrant_3(i) = Q3/length
 feature_quadrant_4(i) = Q4/length
 feature_average_distance(i) = sumDistances / length
endfor

function createScatter(subjectData)
 i = 0
 while i < length(subjectData)
  scatterMatrix(i)(1) = subjectData(i*2)
  scatterMatrix(i)(2) = subjectData(i*2+1)
  i = i+2
 endwhile
endfunction
```

Algorithm 4.2 Pseudo-code for the feature extraction phase of COPD data

```
for i 1 to numberSubjects
 for w 2 to 3
  for d w to numberDays(subjectData)
   windowData = subjectData(d-w, d)
   feature_M(w) = average(windowData)
   feature_SD(w) = std(windowData)
   feature_SK(w) = skewness(windowData)
   feature_KT(w) = kurtoisis(windowData)
   feature_MAX(w) = max(windowData)
   feature_MIN(w) = min(windowData)
   feature_LC(w) = correlationCoeficient(windowData)
   feature_MC(w) = meanCrossRate(windowData)
   feature_AC24(w) = autocorrelation(24,windowData)
   feature_AC24_5(w) = autocorrelation(24,movingaverage(5,
       windowData))
   feature_MF(w) = averageFrequency(windowData)
   feature_DF(w) = dominantFrequency(windowData)
   feature_E(w) = energy(windowData)
   feature_LCF(w) = linearCorrelationCoeficient(windowData)
   feature_HLC(w) = correlation(windowData.leg, windowData.
       hip)
   feature_HAC(w) = correlation(windowData.leg, windowData.
       arm)
   feature_LAC(w) = correlation(windowData.arm, windowData.
       hip)
   feature_HLCC(w) = correlationCoeficient(windowData.leg,
       windowData.hip)
   feature_HACC(w) = correlationCoeficient(windowData.leg,
       windowData.arm)
   feature_LACC(w) = correlationCoeficient(windowData.arm,
       windowData.hip)
  endfor
 endfor
endfor
```

ing from 1 day to 5 days (half the recorded period). Given the time frames of the exacerbation episodes and the amount of data recorded before the onset event, we found that smaller windows would not carry significant information and larger values would reduce the number of possible features too much. We have for instance the features MAX2 and MAX3, respectively the maximum value calculated over the data series from two and three days prior to the focus day. Besides these three sets of features, we further merged all features into a large feature set and selected the most relevant ones by applying the sequential feature selection algorithm. Of the original 90 features, the algorithm selected 17 and we run the classification methods based on them.

Table 4.1: Features extracted for the classification of exacerbation episodes in COPD

Feature name	Description	Set
Mean (M)	We used Matlab implementations of these functions over the data of the corresponding days	1
Standard deviation (SD)		
Skewness (SK)		
Kurtosis (KT)		
Maximum (MAX)		
Minimum (MIN)		
Linear correlation coefficient (LC)		
Mean crossing rate (MC)	Provides an estimation of the movement pattern, specially for signals that are subject to noise	
Autocorrelation over 24 hours (AC24)	Indicates the similarity of the data over a period of 24 hours to the next period. It is an estimation of the changes of activity from day to day	
24 hours autocorrelation after 5 minutes moving average (AC245)	Similar feature as the previous one but after the original data as been smoothed with a moving average filter with 5 minutes window	
Mean frequency (MF)	Calculates the average frequency of the movement in the period	2
Dominant frequency (DF)	Calculates the most common frequency in the movements. It indicates the nature, fast of slow, of the movement.	
Energy (E)	Calculates the energy normalized over each sub-band of the spectrum of the data	
Linear correlation coefficient (LCF)	The frequency domain linear correlation coefficients reveal the presence of a strong correlation between similar movements	
Cross-correlation of the data from the pairs hip-leg (HLC), hip-arm (HAC) and leg-arm (LAC)	This feature indicates the extent of the offset, if any, between the two data series from different sensors	3

Correlation coefficient of hip-leg (HLCC), hip-arm (HACC), leg-arm (LACC)	An estimation of the similarity between the data from two different sensors, indicating the coordination of movements between different body parts	

After extracting all the features we implemented three different classification methods to apply to the datasets. They were logarithmic regression, support vector machines (SVM) and feed-forward neural network (NN) with 50 neurons in the hidden layer. We established the configuration for the neural network after running a test with 5, 10, 20, 50 and 100 neurons and finding the most robust one. We used a 10-fold cross validation method for assessing the robustness of the algorithms, given the low number of test and control cases in the dataset. For each algorithm and feature set we plotted the ROC curve, averaged over all of the 10 runs. These methods are standard machine learning methods and have been previously used in the classification of accelerometer data, for instance in [111, 90, 114, 115, 116, 117, 118].

4.5 Parameters of PA for Lung Research

As part of the cooperation with KORA-Age we implemented the necessary methods and extracted a set of basic features from the accelerometer data. This data was then submitted to a central database of the study and made available to all other cooperation partners. The definition of the set of features to be extracted was the result of a careful discussion with the medical partners and consisted of 42 features comprising different aspects of the physical activity. See table 4.2 for details.

After importing the data from .csv files into Matlab we applied an adjusted algorithm of Hecht et al. [119] on the cohort data based on the triaxial VMU representation to determine the wearing time. This algorithm was originally developed for the RT3 accelerometer, and so the authors chose a threshold Vector Magnitude Unit (VMU) value of five because it was the highest value recorded by the RT3 when resting on a stationary surface. We adapted the algorithm using a VMU value of zero, instead of five, because GT3X did not show any noise when resting, that is no values higher than zero.

To check if the algorithm is valid, we plotted the data of wearing time for visualization (leg and hip). Two researchers analyzed the plots independently to identify the days the package with sensors was in the postal system and thus still recording unusable data. The plot typically has a sparse and irregular spike pattern during the transport period (see figure 4.1). For each

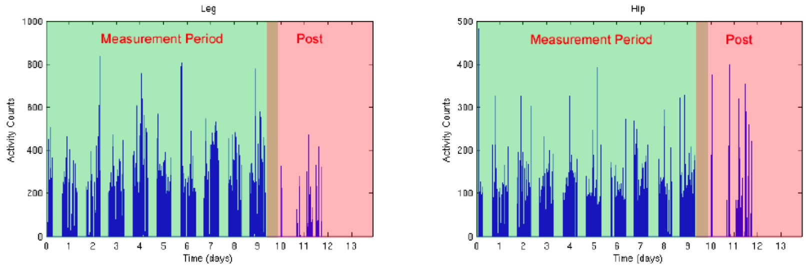

Figure 4.1: Plot showing the different pattern for accelerometer data during transport

subject both researchers noted the number of days to be considered for analysis. In case of disagreement consensus had to be reached, with the default rule to drop the day in case of doubt. In the next step the days considered as valid in the previous step were cut out and new plots were generated with the data before and after this cutting out.

Table 4.2: Features extracted from PA data for the KORA-Age study

Name	Description
totalHWearL	Total number of hours sensor was worn at the leg, including short time gaps of non wearing. Leg.
totalHWearH	Total number of hours sensor was worn at the hip, including short time gaps of non wearing. Hip.
startWearHL	Hour of day when sensor started to be worn. Leg.
startWearML	Minute of hour when sensor started to worn. Leg.
startWearHH	Hour of day when sensor started to be worn. Leg.
startWearMH	Minute of hour when sensor started to worn. Hip.
nonWearPerCntL	Number of periods during the day that the sensor was not worn. Leg.
nonWearPerCntH	Number of periods during the day that the sensor was not worn. Hip.
avgNonWearL	Average duration of non wearing periods. Leg
avgNonWearH	Average duration of non wearing periods. Hip

averageActL	Average of activity during the periods sensor was worn. Leg.
standardDevL	Standard deviation of activity during the periods sensor was worn. Leg.
averageActH	Average of activity during the periods sensor was worn. Hip.
standardDevH	Standard deviation of activity during the periods sensor was worn. Hip.
max1HMovAvgH	Maximum value of 1 hour moving average function over activity. Hip.
max1HMovAvgL	Maximum value of 1 hour moving average function over activity. Leg.
HMax1hMovAvgL	Approximate hour of day when 1hour moving average reached maximum. Leg.
MMax1hMovAvgL	Approximate minute when 1hour moving average reached maximum. Leg.
HMax1hMovAvgH	Approximate hour of day when 1hour moving average reached maximum. Hip.
MMax1hMovAvgH	Approximate minute when 1hour moving average reached maximum. Hip.
avgDailyMETL	Average of MET for periods when sensors where worn. Leg. Integer. Range: 0-...
avgDailyMETH	Average of MET for periods when sensors where worn. Hip.
sedentaryMETL	Percentage of time spent in sedentary levels, according to MET calculation. Leg.
lowMETL	Percentage of time spent in low levels, according to MET calculation. Leg.
mediumMETL	Percentage of time spent in medium levels, according to MET calculation. Leg.
highMETL	Percentage of time spent in high levels, according to MET calculation. Leg.
sedentaryMETH	Percentage of time spent in sedentary levels, according to MET calculation. Hip.
lowMETH	Percentage of time spent in low levels, according to MET calculation. Hip.
mediumMETH	Percentage of time spent in medium levels, according to MET calculation. Hip.
highMETH	Percentage of time spent in high levels, according to MET calculation. Hip.

sedQrtActL	Percentage of time spent in sedentary activity levels, from maximum activity quartiles. Leg.
lowQrtActL	Percentage of time spent in low activity levels, from maximum activity quartiles. Leg.
medQrtActL	Percentage of time spent in medium activity levels, from maximum activity quartiles. Leg.
highQrtActL	Percentage of time spent in high activity levels, from maximum activity quartiles. Leg.
sedQrtActH	Percentage of time spent in sedentary activity levels, from maximum activity quartiles. Hip.
lowQrtActH	Percentage of time spent in low activity levels, from maximum activity quartiles. Hip.
medQrtActH	Percentage of time spent in medium activity levels, from maximum activity quartiles. Hip.
highQrtActH	Percentage of time spent in high activity levels, from maximum activity quartiles. Hip.
longPrdSedL	30ngest period of time in sedentary (quartiles) activity. Leg.
longPrdSedH	Longest period of time in sedentary (quartiles) activity. Hip.

4.5.1 *Code validation*

All the features we implemented were defined after a discussion with the medical team in the study, and naturally there was the need to test the developed code. For this validation, we adopted a two-step strategy: first, we tested with simulated time series of a known pattern, and then we checked the results of a small set of subjects for plausibility of the output.

We generated five different artificial time series, each one day long, containing different patterns: Constant value of 10 (figure 4.2); pattern of 20 minutes zero and 10 minutes value 100 (figure 4.5); pattern of 30 minutes zero and 30 minutes value 100 (figure 4.6); sequence 1 to 100 repeated (figure 4.4); normally distributed random values of average 100 with standard deviation 50 (figure 4.3). Each of the time series aimed to check a particular

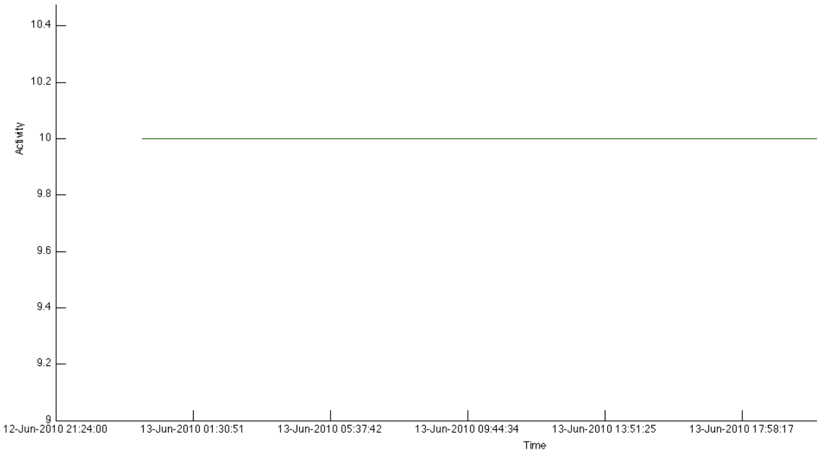

Figure 4.2: Artificial time series for test with constant value 10

critical aspect of the scripts, such as the correct implementation of the algorithms for wearing time by Hecht et al., the correct values for predictable outputs or the statistical coherence of the outputs for the random inputs. For the second step we selected 10 random subjects from the dataset, plotted the data at random days, and checked the output of the scripts for plausibility. This included, for example, checking the number of estimated hours of sensor wearing (less than 24 hours, coherent with the data plot), assessment of mean and standard deviation of values to the expected value from the plot, and cross-checking of dependent variables for accurate values, such as start time and end time of wearing to number of hours of wearing.

Figure 4.2 represents the constant value 10 which allows us to do the most basic test of the code, expecting that the wearing time must be at 100% and a constant value for physical activity quantification. Figure 4.5 depicts a pattern of 20 minutes with value zero followed by 20 minutes of value 100 allowing to test the wearing time estimation according to Hecht et al. The interval of 20 minutes was chosen because it is below the threshold in the algorithm. Figure 4.6 is very similar to the previous one, but rather uses a interval of 30 minutes, cross testing the wearing time implementation. Both of these tests also provide data for the remaining features, as their values are deterministic. The test in figure 4.4 is intended to test the algorithms across a larger range of values, from 0 to 100, but maintaining a deterministic output for easy analysis. The last test, seen in figure 4.3, comprises a large range of possible values, from 0 to 100, but generated randomly. This provides a more complex test where the expected output can't be pre-estimated, but rather only estimated values can be observed or not.

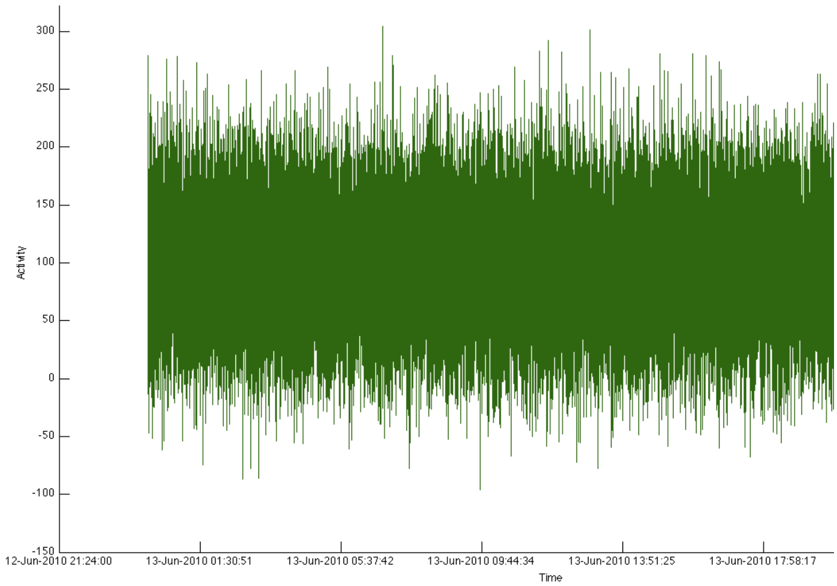

Figure 4.3: Test time series with normal random distribution, average 100 and standard deviation 50

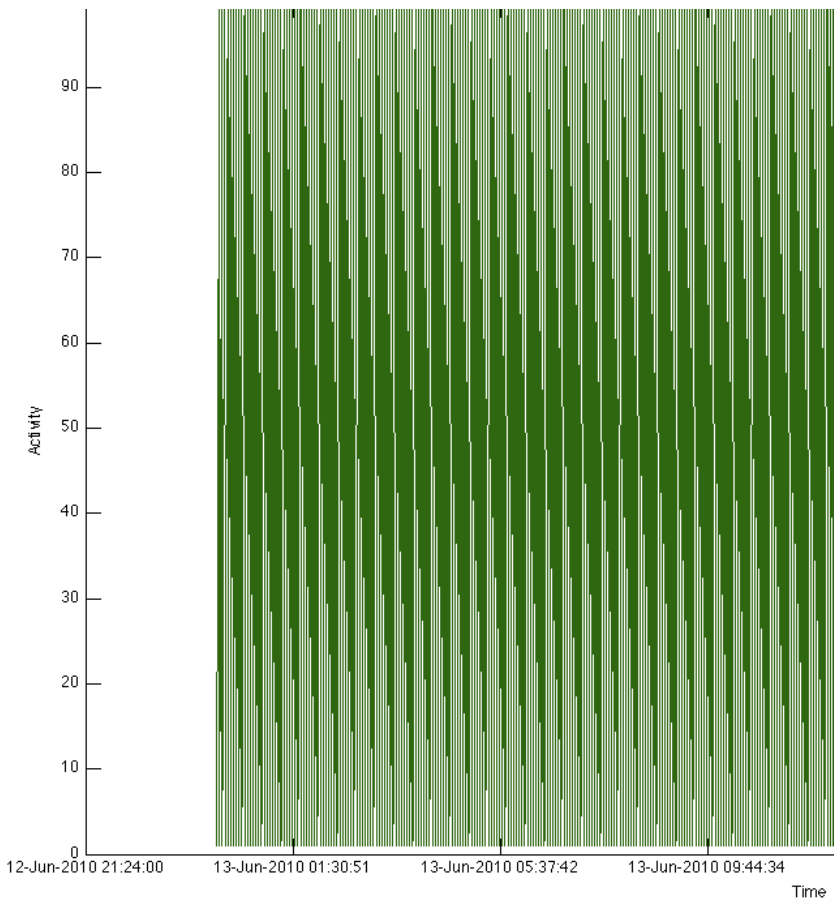

Figure 4.4: Artificial time series consisting of a sequence 1 to 100 repeated

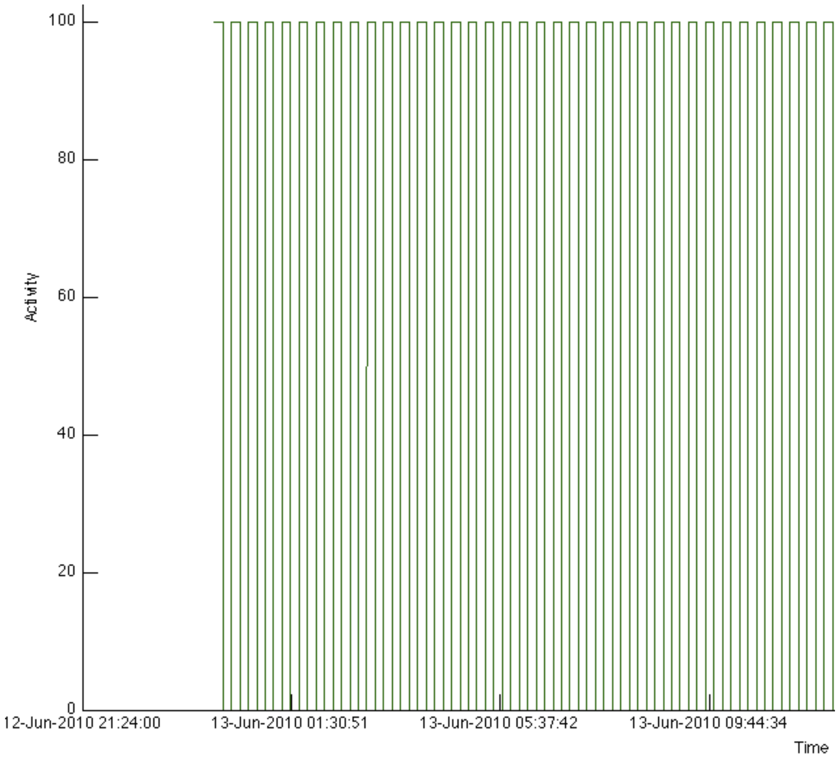

Figure 4.5: Time series with pattern of 20 minutes value 0, 20 minutes value 100

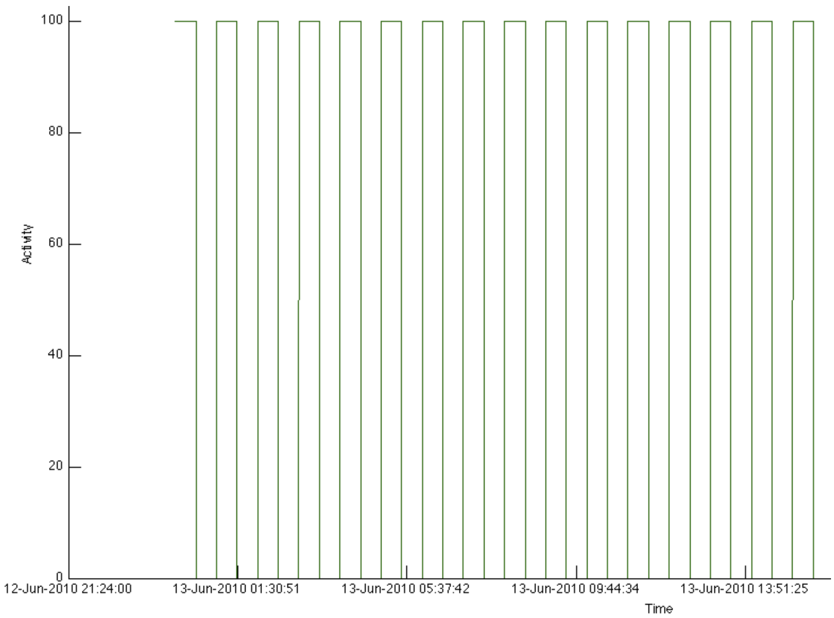

Figure 4.6: Time series with pattern of 30 minutes value 0, 30 minutes value 100

4.6 CRITIQUE OF THE METHODS

We used standard feature extraction and classification methods in the CF and COPD study. We are aware that better feature extraction process can result in improved quality of the final results. Nevertheless, as we are dealing with a first attempt at the classification of exacerbation days, no direct prior experience of research exists.

The features extracted for the KORA-Age study are very general and of a wide nature. Although they are inspired by previous research, it remains open if they are the most relevant for the future needs of the cohort partners. This poses a challenge, because future needs can change. For this reason we stored all accelerometer raw data, so that if future needs arise, more features can be extracted as requested. Still, because of the KORA-Age internal structure this may prove a very long process.

For the classification tasks we choose to use three standard algorithms (logarithmic regression, neural networks and support vector machines) based mostly on previous published research on classification of accelerometer data. These are either very simple, without configurable parameters, or widely used in similar tasks, making them reasonable choices. Nevertheless we can't state that other algorithms are able or not to achieve better results.

We didn't conduct formal and extensive research on the usability aspects of sensor use. The conclusions are related to the team experience and summarize the challenges we faced. We believe that other researchers can have significantly different results, depending on subjective factors and criteria.

4.7 SUMMARY

We opted on all the studies to use only off the shelf and validated sensors, choosing the RT3 and GT1M and GT3X family sensors as generic solution. The analysis of data comprised the extensive use of Matlab, as it is a robust and mature computational platform providing essential implementations of common tools. From the sensor data we extracted different sets of features, according to the needs of the study, that were later used. The classification of CF and COPD patients, was achieved with the use of standard machine learning techniques, such as neural networks and support vector machines. A large set of features was extracted, from the KORA-age study data, tested and submitted for later usage by all the cooperating partners in the study.

5 RESULTS

This chapter presents the results related to the main research questions of this thesis. The chapter presents results of the classification of patients with CF and controls, the classification of different days on COPD and the extraction of PA parameters for the KORA-Age project. In the scope of this work I used several machine learning methods for the classification of the data from CF and COPD studies, with data fed to them from a feature extraction step, using standard features. For the KORA-Age data I discussed with the partners and implemented a large set of features that were later submitted and made available to all the project partners. We also present results regarding the usability questions and acceptance of the sensors.

5.1 CF CLASSIFICATION

The results from our study with CF patients contribute to answering question RQ1, RQ4 and RQ5. This section presents the results relevant to RQ2 and RQ5, relating to the study of exacerbation episodes in cystic fibrosis and the best methods to classify data collected from accelerometers during long term monitoring.

Figure 5.1 shows the PA time series for one CF patient, the only one that experienced an exacerbation during the study period (exacerbation period marked), where the exacerbation period is marked. Unfortunately, PA had not been measured for a long enough time in the days preceding the exacerbation. Nevertheless there appeared to be a prolonged drop in the activity level during the exacerbation episode irrespective of the shorter drops seen afterwards. This renders it a sensible aim to further explore the potential of using PA as an early predictor of exacerbations.

We explored several techniques to model the individual patients' PA profiles. As an example, figure 5.2 shows an exploratory scatter plot of the distance between two consecutive measurements, from two CF patients and one control subject. The top images are the patients and the bottom one is the control subject. These plots show distinct physical activity profiles among subjects and even hint at a distinction between CF patients and controls. They show the patterns of physical activity change at 1-minute intervals. Higher density of points around a central point indicates a smooth pattern of movement with low amplitude changes along time. On the other hand, sparse plots in-

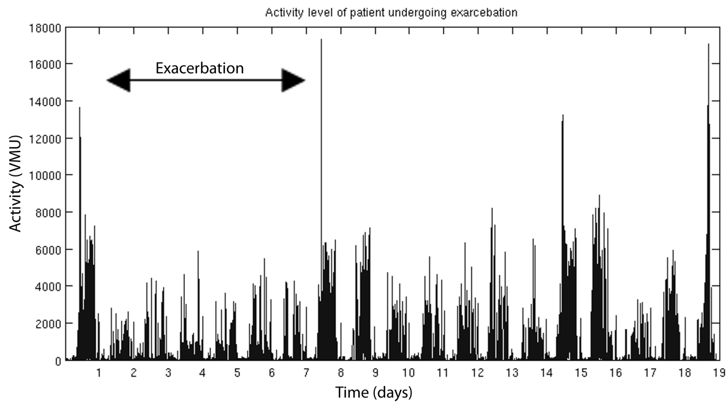

Figure 5.1: Plot of the recorded data for the only CF patient undergoing an exacerbation

Table 5.1: Confusion matrix for PA modeling of Cystic Fibrosis patients and controls using neural network and 8 features extracted from accelerometry data

	Patients	Controls	Sum
NN predicted patient	8	1	10
NN predicted control	2	9	10
Sum	10	10	20
		Accuracy	85%
		Sensitivity	80%
		Specificity	90%

dicate highly dynamic changes of activity. The location of the highest density cluster along the diagonal indicates the overall intensity of PA.

Based on the scatter plots above, we extracted several features, as introduced in the previous chapter, and used a NN to distinguish patients from control subjects. The NN could be successfully trained by the filtered leg sensor data, achieving an accuracy of 85%, with sensitivity of 80% and specificity of 90%. The F-score for this setup was 84% and the Area Under the Curve (AUC) 81%. By contrast the NN trained with data from the hip sensor achieved an accuracy of 63%, with sensitivity of 65% and specificity of 70%. The confusion matrix for the NN trained with leg data is shown in Table 5.1.

5.2 CLASSIFICATION OF DAYS IN COPD

The results from the study regarding the classification of exacerbation days in COPD contributes to answering questions RQ4

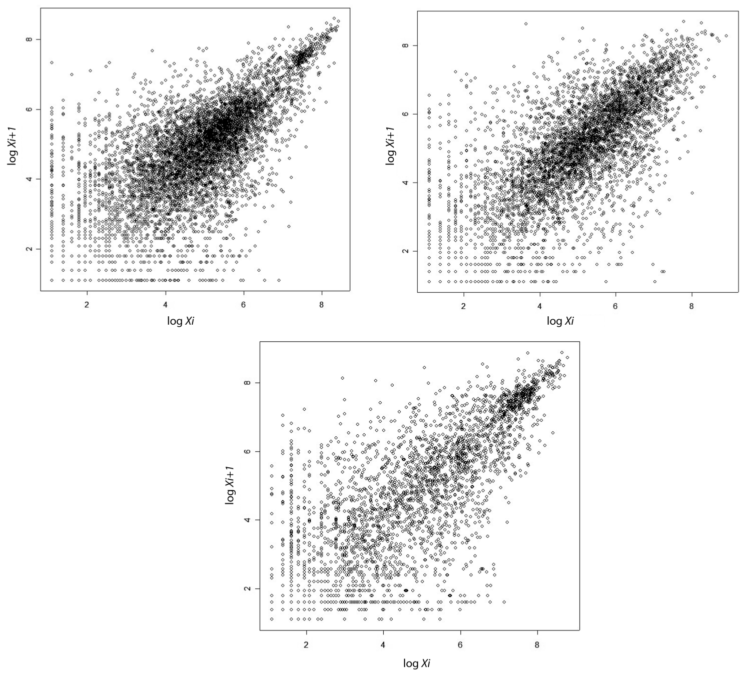

Figure 5.2: Scatter plot showing different activity profiles for patients and control subjects

and RQ5. Providing information to the viability of detecting and classify exacerbation days and non-exacerbation days based on the accelerometer data, exploring several classification methods.

In Figure 5.3 we can see the ROC for the three classification algorithms when using feature set 1, composed of common features used in data mining. We can observe that the support vector machine has the best performance with an AUC of 74%. The logarithmic regression algorithm has a very poor performance. Overall we can affirm that this set of features does not provide useful classification information.

Figure 5.4 shows the ROC of set 2 of features, as described in the methods chapter it is composed of features based on the frequency domain of the time series, where we can see an overall improvement of the classification power of the features and methods over set 1. SVM achieves the best results as well, with NN unable to improve the AUC with the new feature set.

In Figure 5.5 we present the performance of the three algorithms for set 3 of features, comprising features that focus on the relation of the data recorded at different body parts. The SVM classifier is the best classifier for this feature set. The logarithmic regression and NN achieve very similar AUC. These results indicate that the differences or similarities of movement between body parts hold useful information.

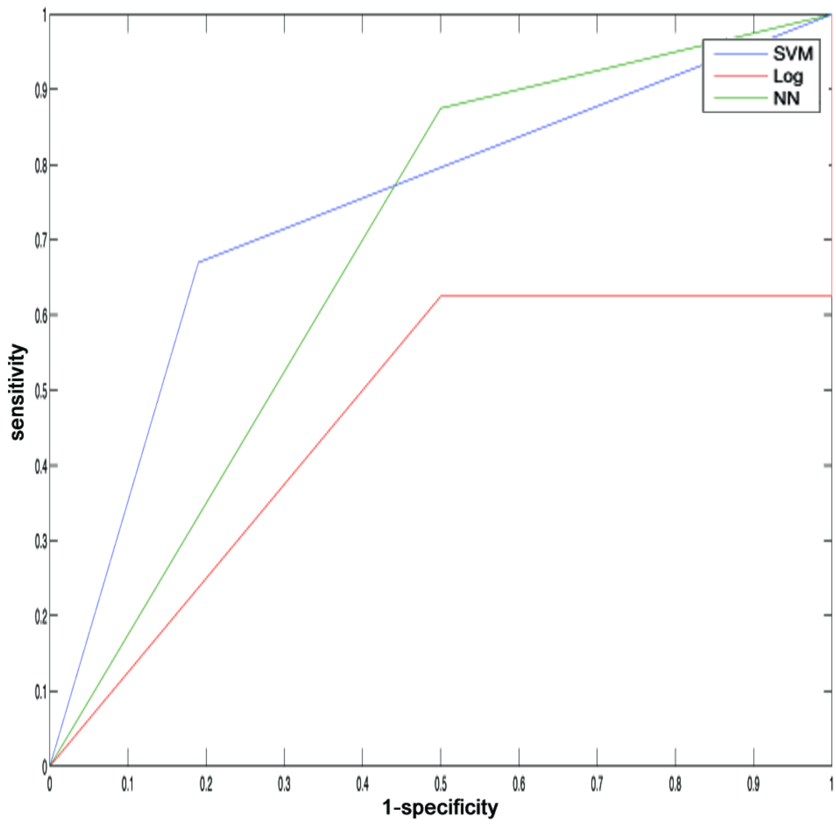

Figure 5.3: ROC curve for Feature Set 1

Table 5.2 shows the AUC for the 4 feature sets and the three classifiers for the COPD dataset. Overall SVM achieved the highest AUC while logarithmic regression showed the lowest performance. Overall the results indicate a fairly low classification capacity of the different algorithms. With the best classifier, SVM, using all the features, we can achieve 100% sensitivity, with a specificity level of 85%, see figure 5.6. That is, to have all exacerbation episodes correctly classified we will have 17 out of 20 of the non-exacerbations classified as exacerbation episodes - i.e. as false positives.

Table 5.2: Area under the curve for the several feature sets and classifiers for the classification normal days and exacerbation in COPD

Features	Log. regression	Neural Net	SVM
Set 1	45.0 (13.6)	68.7 (3.0)	74.0 (20.3)
Set 2	65.7 (14.0)	67.0 (17.6)	82.0 (21.4)
Set 3	58.9 (12.1)	59.5 (7.1)	75.0 (16.5)
All	66.5 (15.3)	82.5 (16.2)	90.0 (8.7)

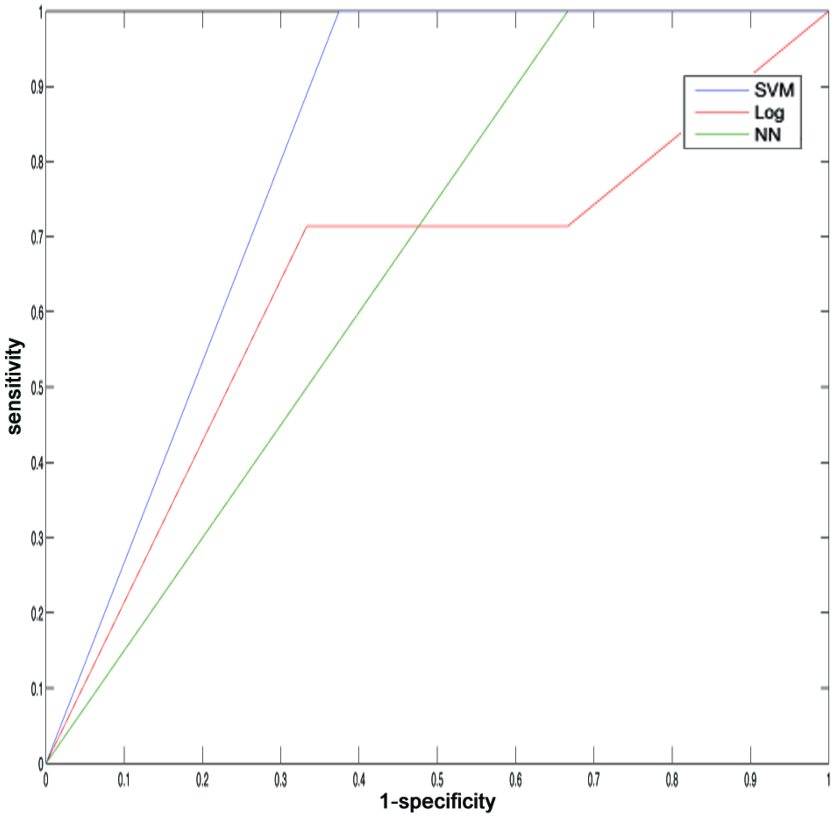

Figure 5.4: ROC curve for Feature Set 1

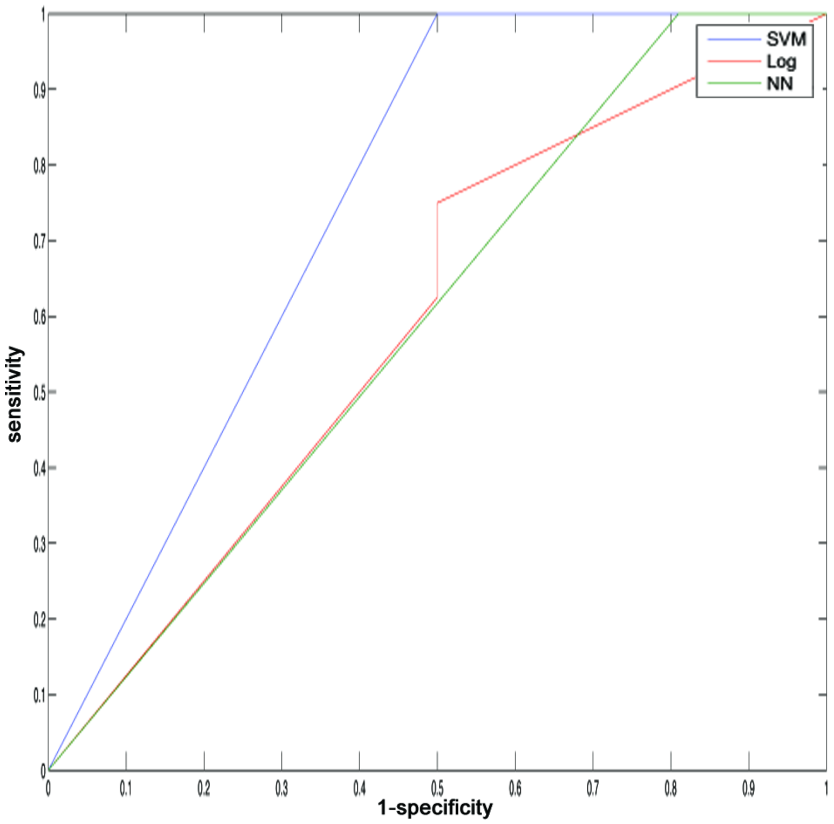

Figure 5.5: ROC curve for Feature Set 1

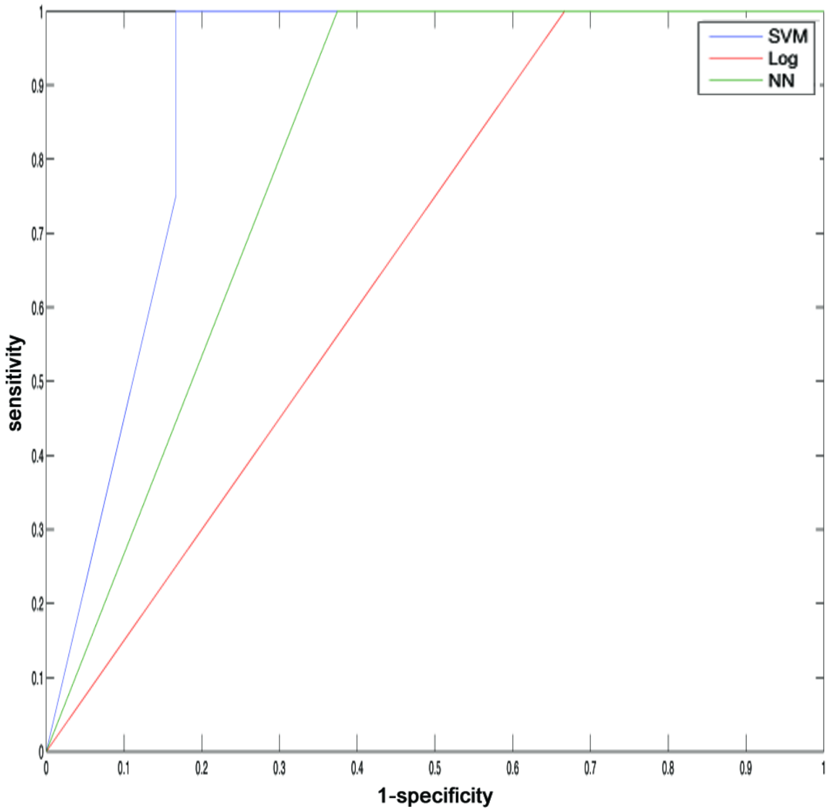

Figure 5.6: ROC curve for the feature set after selection

5.3 PARAMETERS OF PA IN KORA-AGE

The research in cooperation with the KORA-Age project and its results, presented in this section, contribute to the answer to research question RQ3 regarding the extraction of features from accelerometer data for research in pulmonary health.

Following the stated criteria, 162 subjects were eligible for analysis. In total 24 subjects were excluded due to insufficient days of recordings (ankle: n=3, hip: n=2, both: n=19). All outcome variables were checked by artificial time series as well as by PA data from randomly chosen subjects.

Analysis of the artificial time series in table 5.3: For all tests the start and stop times indicated that the sensors were worn all through the day with some gaps during the day. This is expected as all time series had the length of one day, although the 30minute test had wearing gaps during the day that aren't considered for the start and stop time. *Non-wear periods:* The tests const10 and 1to100 produced results that indicate that sensors are used all the time. The random test produced a plausible random output. The 20minutes test had an identified nonwearing period by the last minutes of the time series and was accurate within the expected results of the algorithm by Hecht. The

30minutes test produced several non-wearing periods as it has zero sequences longer than the threshold of 20 minutes. *Average time non-worn:* Tests const10 and 1to100 output a zero, because sensors were used all the time. The 20minutes test produced result zero because the Hecht threshold period is 20 minutes and overlapped with the time series. The 30minutes test showed the 10 minutes that separate the 30minute pattern to the threshold of Hecht et al. which is 20 minutes. *Activity levels in Metabolic Equivalent of Task* (MET): The values in test const10 are all in the low activity quartile. 1to100 is as expected. 20minutes and 30minutes return very close results as expected. *Activity levels in Quartiles:* const10 shows all results in the last quartile as it is constant. In the Random test, because of the moving average the upper quartile limit is close to 100% and the values in the test are averaged around 100, so most time shows on the fourth quartile. The test 1to100 is correct because of applying a moving average to a step function, quartiles are evenly distributed. The tests 20m and 30m are either on the first or fourth quartile.

Table 5.3: Output of the features for the artificial timeseries

Variable	Const10	Random	1to300	20min	30min
daysTotal	1.00	1.00	1.00	1.00	1.00
avgNonWearL	0.00	0.00	0.00	0.00	10.00
totalHWearL	24.00	23.99	24.00	23.83	15.81
totalHWearH	24.00	23.99	24.00	23.83	15.81
startWearHL	0.00	0.00	0.00	0.00	0.00
startWearML	0.00	0.00	0.00	0.00	0.00
startWearHH	23.00	23.00	23.00	23.00	23.00
startWearMH	59.00	59.00	59.00	49.00	29.00
nonWearPerCntL	0.00	10.00	0.00	1.00	46.00
nonWearPerCntH	0.00	10.00	0.00	1.00	46.00
avgNonWearH	0.00	0.00	0.00	0.00	10.00
averageActL	10.00	99.96	50.50	50.35	75.91
standardDevL	0.00	49.61	28.87	50.00	42.76
averageActH	10.00	99.96	50.50	50.35	75.91
standardDevH	0.00	49.61	28.87	50.00	42.76
max1HMovAvgH	10.00	102.62	50.50	50.00	50.00
max1HMovAvgL	10.00	102.62	50.50	50.00	50.00
HMax1hMovAvgL	0.00	20.00	0.00	0.00	0.00
MMax1hMovAvgL	44.00	4.00	46.00	34.00	14.00
HMax1hMovAvgH	0.00	20.00	0.00	0.00	0.00

daysTotal	1.00	1.00	1.00	1.00	1.00
avgNonWearL	0.00	0.00	0.00	0.00	10.00
MMax1hMovAvgH	44.00	4.00	46.00	34.00	14.00
avgDailyMETL	1.45	1.52	1.48	1.48	1.50
avgDailyMETH	1.45	1.52	1.48	1.48	1.50
sedentaryMETL	1.00	0.32	0.76	0.50	0.24
lowMETL	0.00	0.68	0.24	0.50	0.76
mediumMETL	0.00	0.00	0.00	0.00	0.00
highMETL	0.00	0.00	0.00	0.00	0.00
sedentaryMETH	1.00	0.32	0.76	0.50	0.24
lowMETH	0.00	0.68	0.24	0.50	0.76
mediumMETH	0.00	0.00	0.00	0.00	0.00
highMETH	0.00	0.00	0.00	0.00	0.00
sedQrtActL	0.00	0.08	0.14	0.50	0.24
lowQrtActL	0.00	0.12	0.13	0.00	0.00
medQrtActL	0.00	0.19	0.14	0.00	0.00
highQrtActL	1.00	0.61	0.56	0.50	0.76
sedQrtActH	0.00	0.08	0.14	0.50	0.24
lowQrtActH	0.00	0.12	0.13	0.00	0.00
medQrtActH	0.00	0.19	0.14	0.00	0.00
highQrtActH	1.00	0.61	0.56	0.50	0.76
longPrdSedL	0.00	1.00	2.00	7.00	7.00
longPrdSedH	0.00	1.00	2.00	7.00	7.00

Table 5.5 shows the output of the parameter extraction process for the randomly selected subjects. It shows the values produced by my code, for each of the proposed features. For instance the first table indicates the estimated number of days the sensors were worn, feature named daysTotal, and since the test was performed on a single day of data the result is always 1. All the values are within expected ranges for a normal subject. Subject K78 has a very distinct value for the features avgNonWearL and avgNonWearH, 10 and 117 respectively, unlike all other subjects. This most likely due to not wearing one of the sensors, for comfort, on the day under analysis. Several subjects show no counts at the high levels of activity, an indication of sedentary behavior, as indicated by the features highMETL and highMETH. During the test day subject K96 had a continuous activity profile with no long breaks - an unusual pattern in the overall study.

Table 5.5: Output of the features for the randomly selected subjects

Variable	K1	K9	K76	K78	K92	K96	K102	K114	K145	K186
standardDevH	30.77	41.64	28.98	23.9	35.65	111.43	37.36	39.98	27.74	41.62
MMax1hMovAvgH	33	55	16	8	4	1.47	7	28	16	21
highQrtActL	0.04	0.01	0.03	0.01	0.06	0.89	0.05	0.01	0.01	0.03
daysTotal	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
totalHWearL	10.13	13.55	12.82	5.67	14.43	9.45	12.56	15.23	14.08	11.92
totalHWearH	9.30	13.23	13.12	5.39	13.59	10	12.56	15.23	11.70	11.92
startWearHL	9	7	6	12	7	22	9	8	0	8
startWearML	5	42	52	1	19	23	3	14	0	34
startWearHH	22	22	20	19	22	59	23	23	23	20
startWearMH	11	17	44	21	11	20	53	28	58	29
nonWearPerCntL	16	10	13	10	3	23	22	0	33	0
nonWearPerCntH	20	12	10	1	9	1	26	1	19	0
avgNonWearL	11	6	5	10	9	11	6	0	18	0
avgNonWearH	11	7	5	117	9	33.89	5	0	39	0
averageActL	23.41	43.95	35.81	14.79	31.52	92.62	24.02	29.45	22.01	34.23
standardDevL	71.82	101.79	99.93	42.72	55.82	12.67	70.81	79.84	63.04	110.41
averageActH	12.64	19.95	10.16	7.28	23.35	36.26	14.82	16.13	10.78	18.55
max1HMovAvgH	112.48	242.3	83.2	24.12	59.94	27.09	78.04	120.45	53.00	128.88
max1HMovAvgL	42.84	96.15	21.4	15.62	37.33	12	39.76	61.16	21.95	45.92
HMax1hMovAvgL	10	14	15	17	10	46	11	11	1	10
MMax1hMovAvgL	30	55	12	22	7	14	2	28	16	30
HMax1hMovAvgH	10	14	11	17	10	50	11	11	11	15
avgDailyMETL	1.4	1.47	1.47	1.45	1.46	1.45	1.46	1.46	1.45	1.47
avgDailyMETH	1.4	1.45	1.45	1.44	1.46	0.86	1.45	1.45	1.44	1.45
sedentaryMETL	0.93	0.84	0.87	0.92	0.82	0.14	0.9	0.89	0.89	0.9
lowMETL	0.13	0.16	0.13	0.08	0.18	0	0.1	0.11	0.10	0.1
mediumMETL	0	0	0	0	0	0	0	0	0	0
highMETL	0	0	0	0	0	0.93	0	0	0	0
sedentaryMETH	0.91	0.88	0.95	0.98	0.91	0.07	0.9	0.92	0.95	0.91
lowMETH	0.14	0.12	0.05	0.02	0.09	0	0.1	0.08	0.04	0.09
mediumMETH	0	0	0	0	0	0	0	0	0	0
highMETH	0	0	0	0	0	0.94	0	0	0	0
sedQrtActL	0.92	0.87	0.89	0.92	0.76	0.04	0.9	0.94	0.91	0.94
lowQrtActL	0.03	0.04	0.04	0.05	0.09	0.02	0.03	0.04	0.05	0.02
medQrtActL	0.02	0.08	0.04	0.03	0.09	0	0.02	0.02	0.02	0.01
sedQrtActH	0.83	0.82	0.88	0.91	0.63	0.06	0.85	0.87	0.87	0.86
lowQrtActH	0.02	0.06	0.05	0.05	0.08	0.04	0.03	0.06	0.07	0.08

Variable	K1	K9	K76	K78	K92	K96	K102	K114	K145	K186
standardDevH	30.77	41.64	28.98	23.9	35.65	111.43	37.36	39.98	27.74	41.62
MMax1hMovAvgH	33	55	16	8	4	1.47	7	28	16	21
highQrtActL	0.04	0.01	0.03	0.01	0.06	0.89	0.05	0.01	0.01	0.03
medQrtActH	0.05	0.06	0.05	0.02	0.07	0.02	0.03	0.04	0.03	0.03
highQrtActH	0.05	0.06	0.02	0.02	0.21	566	0.09	0.04	0.01	0.03
longPrdSedL	506	265	128	340	97	239	192	419	173	306
longPrdSedH	90	263	139	306	56	0	99	216	131	256

5.4 ACCEPTANCE AND RELIABILITY

The results on usability and reliability of the different sensors from the pilot and CF studies contribute to answering research question RQ4, focusing on the feasibility of long term monitoring with off the shelf sensors.

We identified several technical limitations of the sensors. The most severe one is the short battery life on RT3 and the inability to recharge it while in use. Furthermore and even worse all the values stored on the sensor are lost if the battery runs empty. This leads to a limited time window for measuring, collecting the sensors and storing the acquired data in a permanent storage.

The data quality is very high, on average, for the GT1M, RT3 and Polar RS800 sensors, with stable measurements and few or no missing values. The only exception was the Polar RS800 after a few hours of use in some of the subjects. The electrodes need some moisture to provide a good electrical conductivity with the skin. With long uninterrupted use they tend to dry out severely and the signal quality is significantly degraded. The wrist unit on the sensor warns the user on this situation most of the times, and allows a solution by moistening the skin under the electrodes.

Figure 5.7 illustrates the data collected for one of the measurement period from an 86 years old subject. The data of the heart rate sensor (Polar) is missing from 12:50 until 16:00 due to poor electrode conductivity. Some spikes in the measured heart rate, around 16:40 and 17:10 are also likely due to poor contact as the activity level was very low and stable at these times.

In Table 5.7 we present the feedback from the cystic fibrosis patients we asked to participate in the study, regarding the reasons for not accepting to take part.

5.5 SUMMARY

We presented, in this chapter, the main results of our research. While applying classification algorithms to the data from ac-

Table 5.7: Feedback from the patients about participation in the study

Gender	Feedback
M	none
M	"I do not know what my girlfriend is going to think about me wearing the sensors"
F	"The sensors are too clumsy too wear at work."
F	"Cannot use red one beneath the tight trousers or the high shoes. The grey one is too visible to wear"
M	none
M	"3 weeks is too long. I will accept 1 week. Are the alarms in the shops going to start because of the sensor?"
F	"3 weeks is too long"
M	"Going for a golf tournament for 10 days. Cannot use them because of balance"
F	"Having other complications from asthma. Physical activity very low"
F	none
M	"I have bad sleep, so the night movement info is very important"
M	"21 days is very long" Extensive explanation of the questionnaire was needed
M	none
F	none
M	none

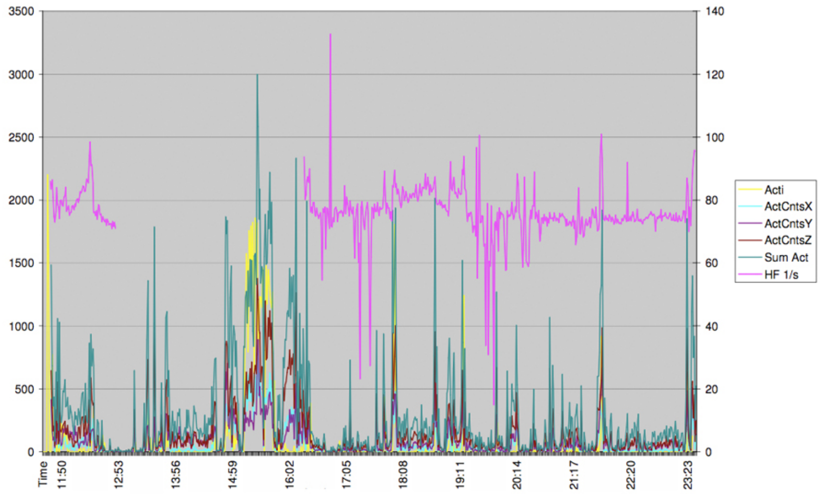

Figure 5.7: Example recording from the feasibility study with missing data from heart rate sensor

celerometers we achieved 85% accuracy in distinguishing CF patients from healthy subjects, based on a small set of features extracted from the data. With larger sets of features from the COPD study we were able to distinguish exacerbation days from normal days in patients, with the best algorithm support vector machines able to achieve an area under the curve of 90%. The features we extracted from the KORA-Age data indicate a low activity profile of the subjects. Our results indicate that the code we developed for the extraction of these features is formally correct.

We found that in terms of usability the long term use of sensors pose challenges. We had a group of young CF patients refusing to participate in the study mostly on usability concerns. We noted that the long term monitoring of heart rate is prone to errors and missing data, and is badly accepted by the subjects.

6 DISCUSSION

In this chapter we discuss the essential aspects of the research results. The first section discusses the usability concerns relating to research question RQ4. Section 2 deals with the results and shortcomings of the classification in CF patients, relating to research question RQ1 and giving insight to research question RQ5 on the methods used. The third section is focused on the classification of days in COPD, relating to research question RQ2 and providing more insight to research question RQ5. The last section is devoted to the discussion of the results of extracting features for the KORA-Age study, contributing for research question RQ3.

6.1 CLASSIFICATION OF CF PATIENTS AND CONTROLS

I achieved reasonable sensitivity and specificity in distinguishing Cystic Fibrosis patients from control subjects, when conducting simple PA modeling with subsequent use of a neural network. My results indicate that the data collected by the leg sensor is more robust for this task. I used a set of simple features as input for the NN, inspired by the scatter plot of the data. These results help us to answer the feasibility of studying classification tasks of Cystic Fibrosis patients (research question RQ1), aiming at studying the classification of exacerbation episodes and gives us information on the best methods for such tasks (research question RQ5). The results are not statistically significant due to study limitations and low acceptance of potential participants.

Many other types of features have been used and proposed for the analysis of accelerometer data, namely large sets of heterogeneous features [117] and other instances based on frequency domain [77] or time-scale analysis [81, 80]. According to the published results existing applications focus on short-term monitoring. To our knowledge this was the first use of a classification system for data from long-term monitoring with accelerometers. Our results with this small set of simple features indicate that further work on more robust features may increase the accuracy of classification.

Naturally, the clinically interesting application is not the distinction from healthy subjects but the individual characterization of patients as well as the possibility to detect changes over time, possibly supported by an individually trained neuronal network implemented in the activity monitor itself. Correspondingly, the detection or prediction of exacerbations in CF patients remains an issue for further studies. Future studies must consider longer periods of recording and a larger study group to be able to cover a significant number of exacerbations.

The small size of the study group in Cystic Fibrosis does not allow us to draw definitive conclusions.

I present the results of the whole study with CF patients and controls in paper P2.

6.2 CLASSIFICATION OF DAYS IN COPD

The work on classification normal days and days of exacerbations in COPD patients is, to my knowledge, the first attempt to extract a set of features from accelerometer data. Although we recruited 45 patients to the study, I was dealing with unpredictable exacerbation occurrences, making it hard to capture a significant number of episodes during a monitoring period. To increase the number of exacerbations I would need ask the patients to wear the sensors for very long periods, raising usability and acceptance issues.

I carried out the study in an in-clinic setting with patients under daily medical supervision, thus it is hard to generalize the results to a daily living setting. Overall the classifiers achieved reasonable performance but I think it is not enough for medical relevance, even if the current alternative is having no classification method at all. Even if the SVM had a 90% AUC for the best feature set, the other classifiers never exceeded 82%.

Overall SVM showed to be the most robust classifier for this task. As for features, none of the basic feature sets proved robust enough for this problem. Only the combination of all the extracted features (after a feature selection process) provided enough information for reasonable classification power.

The difference of classification power between the 3 feature sets I implemented hint that the relationship between the movement of different body parts holds useful information for this task. To some extent this information has previously been explored in the existing algorithms for activity identification, for instance in user interface research. The basic features, such as average and standard deviation, included in feature set 1 is of little use alone.

I think that future work on the classification of exacerbations will be needed including recruiting a larger study group, achieving higher number of exacerbation episodes, as well on exploring other sets of features focusing on different aspects of the accelerometer data.

I present the main results and conclusions of the data collection, analysis and classification of exacerbation episodes in paper P3 and P4

6.3 PA PARAMETERS FOR LUNG RESEARCH

The experience I acquired while collecting and processing accelerometer data in the scope of the KORA-Age study contributes to global knowdlege of the best practices in accelerometry studies.

After research by the team on methods to determine total time of wearing as well as the time spent in different PA levels, we decided to adapt and apply the algorithm by Hecht et al. for the estimation of wearing time and the algorithm by Freedson et al. for estimation of PA levels. The algorithm by Hecht et al. seemed to be most appropriate because of the use of a triaxial accelerometer and similar age of the study population (66.8 years vs 75.1years).

I developed customized Matlab scripts to calculate several PA outcome parameters from accelerometer data. These scripts were thoroughly tested in a two-step approach. The tests of the code proved the scripts to be producing reliable and reasonable outputs, ensuring high quality of data for the cohort colaborators.

The results indicate a very sedentary activity profile, from 10 random subjects, with little or no activity recorded at the medium and high quartiles. The extracted features provided a good overall picture of the activity profiles of the subjects, including total activity at leg and hip, profile of the resting/no activity periods as well absolute and individual specific measurements of the activity. This will give the opportunity to compare technical aspects of measurement, such as best location of the sensors, but also associations to the health outcomes.

Our experience, results and conclusions with KORA-Age cohort are detailed and discussed in paper P5.

6.4 RECRUITMENT AND ACCEPTANCE

I found few significant reports of the difficulties and methods used in one crucial step of all projects: the recruitment of participants for the studies. Most studies refer in one paragraph to monetary compensation of the participants, place where recruitment occurred, but provide no references to the recruitment method, lessons learned and feedback from it. I present the usability results and problems in papers P1, P2 and P3. Paper P1 is essential focused on the usability and reliability problems of long term sensor wearing. P2 and P3 present some insights and results on this question as complement to a main research question (RQ4).

Kahan et al.[120] and Coevering et al.[121] presented a significant report of recruitment strategies for physical activity studies in adults. Kahan et al. focused on Middle Eastern-American young adults, but only reports on non-clinical environment setups. They conclude that active recruitment techniques such as presentations at target communities were more effective than passive techniques such as flyers. Coevering et al.explored different strategies to recruit and increase compliance of American middle school students. They suggest that compensation or incentives are a good strategy for improving compliance, as well as frequent personal contact with participants. Trost et al .reviewed several methodological issues when conducting accelerometer based studies, including compliance of participants, which is closely related to acceptance and recruiting. Nevertheless they don't provide relevant information on the recruitment issue.

Other works present some discussion on recruitment, for instance Jancey et al.[122] research the motivational factors for exercise in elderly people and Duncan et al.[123] focus on participation of school children who need consent from their parents to participate. I believe that we can't relate their studies to mine because they focus on the motivation for exercise itself or consent from a third person.

Books [124] on recruitment for clinical trials discuss topics of patient acceptance and strategies for good patient recruitment and retention. Nevertheless, such literature focuses on drug trial studies where the perceived health benefit for participants is more immediate.

When I started to conduct studies in this topic, taking into consideration the existing literature and reports, I aimed at designing good study protocols and define clear scientific goals – which are obviously fundamental aspects – but assumed recruitment would not pose a major challenge.

From the first feasibility study with healthy volunteers it became clear that some technical aspects of the sensors can become a big drawback on the setup of a large study. Battery life and its implications on the storage of measured values is a critical one, not only limiting the duration of the trial but also putting the whole data set's collection in jeopardy. Correct preparation and handling of the sensors by the staff is also crucial, as proven by the high rate of unsuccessful measurement periods due to mishandling and preparation of the sensors. For this I produced an extensive set of work instructions, covering all aspects of data collection, reset and handling of the sensors. The skin irritation from prolonged use of heart rate sensors is also critical, as the data quality is affected and the user must be prompted to take an active role by moistening the electrodes. Although other kinds of electrodes do exist, they are inappropriate for a passive, non-interfering use of sensors.

Regarding the feedback from potential participants in the CF study I think that young subjects are more concerned about fashion and personal appearance. Therefore, strange-looking devices are not welcome in their daily life. I identified a gender dependence of the acceptability of such devices that has not been widely reported. The color and positioning of the devices were clearly a major drawback. Women showed less willingness to wear devices citing reasons of fashion or comfort. Men, on the other hand, used technical proficiency and social status arguments as reasons to accept the disturbance of wearing these fairly uncomfortable devices. These usability issues seem to be confirmed by the lower compliance rate for this group as compared to older patients. The RT3 sensor, possibly because of the old-fashioned design, had slightly shorter wearing time than the GT1M. Our observations point towards the need for inconspicuous devices if these should be implemented in the long-term monitoring of patients in future. They also suggest that devices placed at the ankle will always face acceptance problems.

Nevertheless, it took the team a significant amount of effort and time to achieve acceptable recruitment rates and I clearly improved the methods and techniques as experience increased.

7 CONCLUSIONS

RQ1 - Is it feasible to study episodes of exacerbation in Cystic Fibrosis patients by exploring accelerometer data?

I didn't achieve robust results regarding the study of exacerbation episodes in CF. The low number of exacerbation episodes in the study period made it statistically difficult. I explored the capacity of the accelerometer data to distinguish the movement patterns of patients and control subjects. Using a very simple set of features extracted from the data I obtained results that indicate good capacity of classification of a neural network.

Many other types of features have been used and proposed for the analysis of accelerometer data [81, 80, 77, 117], focused on short term monitoring. This is the first use of data from long-term monitoring and analysis for classification of chronic disease. However, the small sample size of this pilot study did not allow me draw further conclusions. Naturally, the clinically interesting application is not the distinction from healthy subjects but the individual characterization of patients as well as the possibility to detect changes over time, possibly supported by an individually trained neural network implemented into the activity monitor.

Future studies exploring the use of PA data in exacerbations in CF must be longer and with more subjects involved, in order to increase the number of exacerbations recorded. In this study I overestimated the likelihood of exacerbations during winter time. The data in one of the patients seemed promising, although I had missed the period prior to the exacerbation from recording. Future studies must consider longer periods of recording and a larger study group to be able to cover a significant number of exacerbations.

Other authors have explored similar concepts of predicting exacerbations in CF from other data sources not directly from PA, but no definitive results are known [15]. The question remains open to future research.

RQ2 - Can we distinguish normal days from exacerbation in COPD patients looking at accelerometer data?

To the best of my knowledge this thesis presented the first attempt to distinguish days with exacerbation episodes from normal days in COPD patients using accelerometer data. I achieved promising results with our approach, that indicate good potential for future improvement and clinical application. The best results indicate an area under the curve of the classifier of 90%. Nevertheless the number of patients and episodes is too low to draw definitive conclusions. These results were achieved with a significant number of features, but in a limited scope of information extracted. I envisage that future approaches with larger feature sets and with larger scope of information present in such features can improve the classification quality. Only then is it feasible to aim at clinical use of accelerometers in the management of COPD patients.

I would like to emphasize that the use of PA recording for the purpose of exacerbation prediction in patients with COPD seems a very reasonable approach for future research, given the unreliability of lung function recording at home and the non-objectivity of symptoms. From clinical studies and common experience it is well known that physical capacity and activity are associated with the clinical state, in particular exacerbations [17]. The results in this thesis indicate that not only there is such statistical association, but that we can directly distinguish events in the life of patients based on PA data. Data from accelerometers should be explored for not only linear changes of physical activity before and during exacerbation, but also exploring other dimensions of the time series, such as frequency or scale. The ease of use and large datasets generated make them good tools for that.

One of the limitations in our studies is the low sampling rate, a few samples per minute, of the sensors used, as I focused on off the shelf sensors. Currently, there is technology capable of sampling rates above the Mhz during long periods of time. When these sensors become available in a easy to use and validated product, a greater improvement in the results can be expected. I can also expect better results with a more robust approach to the data processing. Instead of a simple and straightforward approach as the one presented, we propose the use of activity identification from accelerometer data as input for the classification algorithms. The accelerometer data can be used to estimate the type and duration of the different activities performed (walk, running, standing....) and that information to be fed to the classification algorithms, together with other features, as input. This approach becomes feasible with sensors capable of high sampling rate.

RQ3 - Can we extract innovative features from accelerometer data that are useful for pulmonary research in general population?

Yes, I extracted a large set of parameters from the accelerometer data according to the needs and recommendations from the scientific staff of the KORA-Age study dealing with lung health studies. These features will be available to all study partners and can provide a working platform for future epidemiological studies. These features can be used in the study of the importance of PA to the pulmonary health at the population level. By making the results available to other researchers this study contributes to the knowledge of the PA in the general population. It is also an improvement on the common guidelines that focus only on activity levels and compare them to existing guidelines [125].

The testing procedures were focused on analyzing the data extracted for correctness and expected values. We found no abnormal values, neither did the cohort partners. The data is already available for lung research and any other research topic that the partners may find relevant.

The experience acquired in this thesis can contribute to future work in large cohorts and studies using accelerometers to assess PA in the population, by providing guidelines for best practices and avoiding common mistakes and pitfalls.

RQ4 - What are the essential barriers to long term monitoring of chronic patients and elderly people?

I identified several barriers to participation and retention of subjects in our studies: the social and comfort aspects of wearing sensors for long periods, and limitations of the sensors regarding data reliability and battery limitations.

During the recruitment of subjects for our studies I received different responses from the potential participants and significant feedback from the participants. I had to exclude the long term monitoring of heart rate because of the early feedback regarding the skin problems and low usability of the Polar heart rate sensor. I found that recruitment and acceptance of participation in studies that require the use of sensors for long periods measuring physical activity is under-reported. Kahan et al.[120]and Coevering et al.[121]discuss the recruitment strategies for physical activity studies in adults, but do not address the use of sensors as a source of refusal to participate.

The younger CF patients mentioned aesthetics and social reasons to refuse participation in the study. The color and size of the sensors were mentioned. The complexity of use was not raised as a barrier.

According to my results, manufacturers of accelerometer devices for medical applications should pay more attention to fashion related issues and aim to develop devices which appeal to a young population by choosing neutral or skin-like colors, trendy form factors or perhaps by integrating these sensors into commonly used devices such as mobile phones. The success of products, focused on the sports market, such as Nike + ipod (Nike corp. Beaverton, Oregon) and Fitbit (Fitbit, San Francisco, California), should be taken into consideration when designing sensors for medical applications. I suggest that this can raise the acceptance of usage in such groups to a reasonable percentage, with the consequence that long-term, quasi-continuous recording becomes feasible.

The older participants of the COPD study were generally more willing to participate, although I expected at the beginning that the age would increase the concerns with usability. A confusing factor is that in the COPD study we had direct medical support on the recruitment. This might have changed the perceived benefit and difficulty of participation.

In the KORA-Age study we achieved the best acceptance of the subjects. This is in line with the experience from the other KORA-Age researchers.

RQ5 - What is the performance of different methods applied to the previous research questions?

In this work it was found that Neural Networks and Support Vector machines provide the best results in classification tasks based on accelerometer data. For the classification of CF patients and healthy subjects I tested neural networks with a simple set of features and achieved an accuracy of 85%. In the classification of COPD exacerbations neural networks achieved an area under the curve of 82.5% and the support vector machines a area of 90%. These results indicate good classification capacity for both methods, nevertheless one must take into consideration the small sample size of both studies. I think that improvements in the feature extraction phase combined with larger studies can lead to clinical applications of the exacerbation classification in COPD patients.

Future work

The next logical step in the effort to classify exacerbations in COPD patients is to design a larger study, aiming to obtain data for a statistically significant number of exacerbation episodes. This is the essential step towards assessing the feasibility of the proposed approach, and to gain better insight into the medical consequences.

Obviously the question of medical interest is not to classify the exacerbations episodes after they occur or when they are occurring, but be able to alert the patients ahead of their onset. I think that the approach proposed in this thesis is also valid for this scenario: the same data can contain this information. A larger study looking at the classification of exacerbations after they were detected, can also provide information on the feasibility of the same data providing cues for the forecast of the same exacerbations. The data processing, namely the feature extraction step and classification, need to reflect the different task, but essentially the steps will be the same.

As I used a simple classification method, in future studies existing knowledge must be taken into account when exploring and implementing better features from the accelerometer data. This can provide an improvement of the classification results. Namely, I think that an approach based on identifying the type of activity, such as walking or standing, and its duration can provide better information. There are several known algorithms that can identify to a good degree the activities, so this shouldn't pose a major obstacle.

Naturally researchers in KORA-Age will continue to use the data collected, and explore the medical and epidemiological associations of PA. The continued research will provide future insights into new parameters of use that can be extracted from accelerometer data. It is important that such collaboration is kept and extended.

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Part II

INCLUDED PUBLICATIONS

PAPER 1

Dias, A. ; Fisterer, B.; Lamla, G.; Kuhn, K. A.; Hartvigsen, G.; Horsch, A.. Measuring Physical Activity with Sensors: A Qualitative Study. Studies in Health Technology and Informatics 2009 ;Volume 150. p. 475-479

PAPER 2

Dias, A.; Gorzelniak, L.; Jorres, R.; Fischer, R.; Hartvigsen, G.; Horsch,A.. Assessing Physical Activity in the daily life of cystic fibrosis patients. Journal of Pervasive Computing. Volume 8, Issue 6, December 2012, Pages 837–844

PAPER 3

Gorzelniak, L.; Dias, A.; Schultz,K.; Wittmann, M.; Karrasch, S.; Jorres, R.; Horsch,A.. Comparison of recording positions of physical activity in severe COPD. Journal Of Chronic Obstructive Pulmonary Disease; Volume 9, Issue 5. Dias, A.; Gorzelniak, L.; Doring, A.; Hartvigsen, G.; Horsch, A.. Extracting Gait Parameters from Raw Data Accelerometers. Studies in Health Technology and Informatics 2011; Volume 169.

PAPER 4

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PAPER 5

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Part III

ADDITIONAL PUBLICATIONS

ADDITIONAL PAPER 1

Dias, A.; Gorzelniak, L.; Doring, A.; Hartvigsen, G.; Horsch, A.. Extracting Gait Parameters from Raw Data Accelerometers. Studies in Health Technology and Informatics 2011; Volume 169. p. 445-449

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