

UNIVERSITEIT UTRECHT

MASTER THESIS

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**Sit-to-stand Transition as a Novel Marker  
of Physical Activity in Patients with  
Amyotrophic Lateral Sclerosis**

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*A thesis submitted in fulfillment of the requirements  
for the degree of Master of Science*

*in the*

Applied Data Science  
Universiteit Utrecht

July 1, 2022



## Declaration of Authorship

I, Bc. Michal KUBINA, declare that this thesis titled, "Sit-to-stand Transition as a Novel Marker of Physical Acitivity in Patients with Amyotrophic Lateral Sclerosis" and the work presented in it are my own. I confirm that:

- This work was done wholly while pursuing a graduate degree at this University.
- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
- I have acknowledged all main sources of help.

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UNIVERSITEIT UTRECHT

## *Abstract*

Graduate School of Natural Sciences  
Universiteit Utrecht

Master of Science

### **Sit-to-stand Transition as a Novel Marker of Physical Activity in Patients with Amyotrophic Lateral Sclerosis**

by Bc. Michal KUBINA

The main goal of this master thesis is to examine amyotrophic lateral sclerosis and provide an analysis of this phenomenon to evaluate the importance of actigraphy for future medical use and simultaneously find novel markers describing a patient's physical activity based on raw actigraphy data. The topic is relatively new and there is not a significant amount of academic work done. The importance of a combination of actigraphy and amyotrophic lateral sclerosis lies in the monitoring of patients in a home-like environment.

In the thesis, I try to create new physical markers from the sit-to-stand transitions of a patient, and the data are compared against the ASLFRS-R questionnaire which provides a quantification of the disease's progression. This method is used in Parkinson's disease and was never used to describe amyotrophic lateral sclerosis.

My main finding is that the method is very promising and can in a way describe a patient's state. However, there are currently better methods available that describe the patient's state in a more meaningful way based on the actigraphy data. Nevertheless, the results could be of higher relevance if the algorithms used were validated and hyper tuned on an actigraph that was used to collect the data used in this thesis.



## *Acknowledgements*

I would like to express my particular gratitude to my supervisors, for their guidance and constant support during the preparation for this master thesis. Lastly, I would like to thank my family, which allowed me to attend university and which shows me constant support.





# Contents

<b>Declaration of Authorship</b>	<b>iii</b>
<b>Abstract</b>	<b>v</b>
<b>Acknowledgements</b>	<b>vii</b>
<b>1 Introduction</b>	<b>1</b>
1.1 Amyotrophic Lateral Sclerosis . . . . .	1
1.2 Actigraphy . . . . .	1
1.3 State of the Art . . . . .	2
1.4 Current Activity Measures . . . . .	2
1.5 Research Question . . . . .	2
<b>2 Raw Data</b>	<b>5</b>
2.1 Description . . . . .	5
2.2 Data Preparation . . . . .	5
2.3 Ethical and Legal Considerations of the Data . . . . .	5
<b>3 Methodology</b>	<b>7</b>
3.1 Description . . . . .	7
3.2 Wear Time Algorithm . . . . .	7
3.2.1 Description . . . . .	7
3.2.2 Hees Algorithm . . . . .	8
3.3 Sit-to-Stand Algorithm . . . . .	8
3.3.1 Description . . . . .	8
3.3.2 Displacement Algorithm . . . . .	9
3.4 Final Dataset . . . . .	9
3.4.1 Physical Activity Features . . . . .	9
3.4.2 ALSFRS-R Scale Features . . . . .	10
3.4.3 Description . . . . .	10
3.5 Linear Mixed Model . . . . .	11
<b>4 Results</b>	<b>13</b>
<b>5 Discussion and Conclusion</b>	<b>17</b>
5.1 Discussion . . . . .	17
5.2 Conclusion . . . . .	18
<b>A Explanation of the Data Processing Pipeline</b>	<b>21</b>
<b>B Sit-to-stand Detection Code</b>	<b>23</b>
<b>C Features Computation Code</b>	<b>25</b>

<b>D Correlations Computation Code</b>	<b>29</b>
<b>E Visualization Code</b>	<b>31</b>
<b>Bibliography</b>	<b>33</b>

# List of Tables

3.1	ALSFRS-R Questionnaire . . . . .	7
3.2	Features of the Displacement Algorithm's Transitions . . . . .	9
3.3	Computed Features from One Epoch (One Measurement of a Patient) . . . . .	10
3.4	ALSFRS-R Based Features . . . . .	11



## Chapter 1

# Introduction

### 1.1 Amyotrophic Lateral Sclerosis

*Amyotrophic lateral sclerosis (ALS)* is a disease with a devastating effect on a person's life. This condition is known as a motor neuron disease as it is a neurodegenerative illness that hugely affects the motor system of a patient. Specifically, in a patient's body occurs a loss of neurons. Consequently, the body is not capable of moving as it was before, and therefore swallowing, talking and other usual activities in daily life are getting worse and worse with upcoming time. Moreover, 50% of patients die within 3 years of disease onset and 18 months after the diagnosis. (Mitchell and Borasio, 2007)

The incidence is 1.89 people per 100 000/year on average in Europe and North America, and it seems that ALS affects more men than women. However, recent findings suggest that the ratio is in equilibrium. The symptoms of the disease are treated to improve the patient's life. However, currently, there is no systematic cure available and thus ALS patients are battling an impossible matter where the only way out is certain death. (Wijesekera and Leigh, 2009)

### 1.2 Actigraphy

*Actigraphy* as a phenomenon, in general, refers to a method using devices to monitor and collect data generated by a person's movement (Sadeh and Acebo, 2002). The actigraphy data are essentially a time series with a fixed sample rate where each sample corresponds to a particular value.

Actigraphy can be considered as a profound method that is relatively old. Moreover, actigraphy is used vastly across the professional community, determining patterns in mental or physical health disorders. As proof, actigraphy can be used with great success in assessing the sleep or circadian rhythms of people (Sadeh and Acebo, 2002). These features might help assess bipolar patients outside of acute manic or depressive episodes (Jones, Hare, and Evershed, 2005). Moreover, actigraphy can detect behavioural patterns in schizophrenia (Berle et al., 2010). Nevertheless, actigraphy plays a vital role as a good source of information about people with depression (Burton et al., 2013). (Kubina, 2021)

Actigraphy is vital in assessing physical-oriented diseases since it can monitor patients' movements and their changes during long-term supervision. For example, monitoring patients in the intensive care unit helps to assess a person's physical state and saves time for doctors (Schwab et al., 2020).

There is also utilization of this profound method in terms of monitoring general symptoms or sleep in Parkinson's disease (Pan et al., 2013). Another neurodegenerative disease where actigraphy is a vital research tool is Alzheimer's disease

where sleep measurements are used to describe the illness (Camargos, Louzada, and Nóbrega, 2013)

### 1.3 State of the Art

Actigraphy measurement is becoming more popular in terms of amyotrophic lateral sclerosis since actigraphy was rather used in other diseases mentioned in the previous section. The purpose of actigraphic data is to quantify ALS progression from a long-term perspective as some patients can live with the disease for a long time and others cannot. Moreover, remote monitoring maximizes the collection of information outside of clinical visits. However, disease's influence on physical activity should not be the only thing to measure. Clinical trials should focus on combining actigraphy and measurements of cognitive states such as speech capability or ability to complete motor tasks. (Eijk et al., 2019)

Usually, in the studies, the activity is computed based on the actigraphic data and then compared with the ALS Function Rating Scale-Revised (ALSFRS-R) which is a gold-standard measure of functional decline of movements to measure disease progression and treatment effects. (Kelly et al., 2020)

Another explanation, of why actigraphy and thus activity quantification might be a reasonable direction to explore, is that ALS patients suffer from fatigue due to the poor quality of sleep and excessive daytime somnolence. Moreover, these patients frequently report nocturia, muscle cramps, and restless legs syndrome. Thus, an actigraphy device that would be worn indefinitely might be a key component in the quantification of this disease even greater deal than just using an actigraphic device during a specific time of day. (Lo Coco and La Bella, 2012)

### 1.4 Current Activity Measures

Describing a person's activity based on raw data is a complex and arduous task. Usually, an activity measure is defined by the measuring device and comes together with the raw data as a feature in data output. However, this type of summary is not usually transparent and clinically validated. Thus, in recent years a few measurements were created that summarize raw actigraphy data and allow us to describe a patient's physical activity.

One of the most basic measurements which is used is already mentioned Euclidean Norm Minus One (*ENMO*). Other developed metrics are for example Activity Index *AI*, Activity Count *AC*. Based on the comparison of these three metrics it seems that *ENMO* underperformed in distinguishing light and sedentary activities and *AI* was more robust in terms of describing all ranges of activities. (Bai et al., 2016)

To conclude, all currently available metrics explain different degrees of movement of people but do not outperform each other in a meaningful way (Hees et al., 2013).

### 1.5 Research Question

As actigraphy is rarely used in terms of ALS disease, the activity measures which describe actigraphy raw data are rather focused on different diseases with different physical characteristics. Thus, it is essential to find a new physical activity marker

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that would describe the activity of patients who do not wear the accelerometer regularly and are rather in sedentary and very non-active lifestyle which keeps worsening. The aim of this thesis, therefore, is to explore and find new innovative metrics on how to summarize raw actigraphy data which would essentially describe a person's physical activity in a novel and meaningful way.





## Chapter 2

# Raw Data

### 2.1 Description

The data were gathered using hip worn accelerometer *ActiGraph gt3x* on patients' bodies (Santos-Lozano et al., 2013). The data collection frequency was set to 30 Hz. Raw files included timestamp, patient id, and value of acceleration on the x, y, and z-axis (*gravitational units*) and were stored in *gt3x* files. Specifically, the x-axis describes the upward movement, the y-axis is dedicated to sideward moves and the z-axis describes the backward movement of a patient's body.

The data were gathered over a long period with regular pauses. The earliest timestamp comes from 28.9.2016 and the most current timestamp is from 1.11.2018 across 43 patients. To sum up, there specifically 848 752 440 of data rows. Thus, it is a huge chunk of data that needs to be processed, minimized, and handled accordingly as a very powerful machine is needed to comprehend this amount of data points.

### 2.2 Data Preparation

Firstly, data were not prepared in any significant way as future methods will work with raw data, thus it was needed to keep the data as they are and edit them specifically based on selected methods in the upcoming chapter. However, for each row euclidean norm minus one of the x, y, and z vectors was computed to get a better insight into the data and to be able to visualize in terms of longer and shorter time intervals (Bakrania et al., 2016). The euclidean norm minus one equation can be seen below.

$$ENMO = \sqrt{x^2 + y^2 + z^2} - 1$$

Though, the raw data were processed to account for non-movement periods in the data, where the measured vector magnitude should be ideally the gravitational acceleration which is 1 g. However, sometimes, especially low-cost acceleration sensors tend to experience a calibration error. The reason behind this calibration error might be temperature. There is no proof, however, that the calibration error can affect acceleration metrics used for physical activity assessment. Despite this fact, I used an algorithm that tries to account for this calibration error and minimize it. (Hees et al., 2014)

### 2.3 Ethical and Legal Considerations of the Data

This thesis uses data from a study that was approved by the Medical Ethics Committee of the UMCU (16/606). All study participants gave written informed consent

to be approached digitally for research purposes and consented to participate in this study. (Eijk et al., 2019)

## Chapter 3

# Methodology

### 3.1 Description

To derive new metrics, we used a total number of sit-to-stand-ups in one measurement epoch/clinical visit of a patient divided by the total wear time in seconds. My reasoning comes from a belief that if a patient with ALS gets worse, then the number of sit-to-stand-ups will also decrease. Thus, in upcoming sections, I will describe the wear time algorithm and consequently sit-to-stand algorithm. The evaluation of this new measurement was based on a final correlation against items or a combination of items from the self-reported amyotrophic lateral sclerosis functional rating scale (*ALSFRS-R*) that can be seen in Table 3.1. (Cedarbaum et al., 1999).

TABLE 3.1: ALSFRS-R Questionnaire

Number	Category	Scale
1	SPEECH	0 (Worst function) - 4 (Normal function)
2	SALIVATION	0 (Worst function) - 4 (Normal function)
3	SWALLOWING	0 (Worst function) - 4 (Normal function)
4	HANDWRITING	0 (Worst function) - 4 (Normal function)
5A	CUTTING FOOD	0 (Worst function) - 4 (Normal function)
5B	HANDLING PEG	0 (Worst function) - 4 (Normal function)
6	DRESSING AND HYGIENE	0 (Worst function) - 4 (Normal function)
7	TURNING IN BED	0 (Worst function) - 4 (Normal function)
8	WALKING	0 (Worst function) - 4 (Normal function)
9	CLIMBING STAIRS	0 (Worst function) - 4 (Normal function)
10	DYSPNEA	0 (Worst function) - 4 (Normal function)
11	ORTHOPNEA	0 (Worst function) - 4 (Normal function)
12	RESPIRATORY INSUFFICIENCY	0 (Worst function) - 4 (Normal function)

### 3.2 Wear Time Algorithm

#### 3.2.1 Description

To detect wear and non-wear times from actigraphy data there are three epoch-based methods as a current state of the art. Specifically, there exists Hecht Algorithm (Hecht et al., 2009), Troiano Algorithm (Troiano et al., 2008) and Choi Algorithm (Choi et al., 2011). These algorithms work on already summarized data. However, this is different from Hees Algorithm (Hees et al., 2011). This algorithm works with raw data and thus, cannot be described as epoch-based. During a comparison of

these four different metrics, Hees Algorithm worked the best and scored the highest accuracy in detecting non-wear times (Syed et al., 2020). Thus, for detection wear and non-wear times, I will be using Hees Algorithm.

### 3.2.2 Hees Algorithm

The Hees Algorithm was developed in a study focused on deriving a summary measure based on raw triaxial accelerometer data in PA-related energy expenditure in pregnant and non-pregnant women. The algorithm estimates non-wear times based on the standard deviation and the value range of each axis of the accelerometer in 60-minute intervals. The specific formula can be seen below. (Hees et al., 2011)

$$NW_{acc} = \sum_{i=\{x,y,z\}} [(a_{(sd,i)} < S) \& (a_{(range,i)} < R)]$$

$$NW = NW_{acc} \geq 2$$

- $a_{(sd,i)}$  is the is the acceleration standard deviation of a window
- $window$  is a 60-minute interval
- $a_{(range,i)}$  is the range of acceleration of a window
- $S$  is an acceleration standard deviation threshold for determining non-wear with a value of 0.013.
- $R$  is an acceleration window range threshold for determining non-wear with a values set to 0.067.

Where all the parameters and specific values were assessed and tuned in studies (Hees et al., 2011) and (Hees et al., 2013).

## 3.3 Sit-to-Stand Algorithm

### 3.3.1 Description

A sit-to-stand detection algorithm for assessing a disease is a new and novel way how to describe one's disease even without a gyroscope. Sit-to-stand methodology was mainly used to evaluate patients with Parkinson's disease where the data were gathered by a force platform that measures the displacement of a body and velocity of the action (Fernandes et al., 2015).

However, recently, researchers started using actigraphy devices to monitor patients with Parkinson's disease. These devices allow monitoring of patients in a home environment without the necessity to use a force platform. Moreover, the accuracy of the actigraphy method compared to the force platform is very high, and thus very convenient way how to map the progress of Parkinson's disease. (Zijlstra et al., 2012)

This new method is getting more and more popular as in a recent study, an algorithm was developed to detect postural transitions across patients with Parkinson's disease using an accelerometer and gyroscope and validated against videotape from a home-like environment with a total accuracy of 0.99 (Pham et al., 2018).

Recent efforts in detecting sit-to-stand transitions in a home-like environment suggest that the data can capture differences in terms of age or fall risk (Iluz et al., 2015). Moreover, the disease severity of Parkinson’s disease can be described using sit-to-stand transitions too (Bernad-Elazari et al., 2016). However, sit-to-stand detection using actigraphy data was never used in terms of describing ALS or even suggesting monitoring the progression of this disease using this method.

### 3.3.2 Displacement Algorithm

To be able to detect sit-to-stand transitions usually the gyroscope is needed as a complement to an actigraph to measure orientation and angular velocity. Nevertheless, this requires a bigger device with a sufficient battery capacity which is not convenient for clinical assessment in a home environment. Thus, for my analysis, I used a new algorithm that can detect sit-to-stands together with other features that can be found in Table 3.2. The proposed method is orientation independent and was validated against video measurements and against other algorithms available with a precision of 0.990 and sensitivity of 0.947 in a healthy group and with a precision of 0.988 and sensitivity of 0.853 in a group with people suffering from Parkinson’s disease. (Adamowicz et al., 2020)

TABLE 3.2: Features of the Displacement Algorithm’s Transitions

Feature	Unit	Description
Duration	[s]	Duration of the transition
Max. Acceleration	[g]	Max. acceleration of the transition
Min. Acceleration	[g]	Min. acceleration of the transition
Vertical Displacement	[m]	Vertical displacement of the transition
SPARC	[-]	Signal smoothness (Balasubramanian et al., 2015)

The algorithm relies on tri-axis raw data from an accelerometer without the need to bear in mind orientation. The first part of the method tries to filter acceleration together with sit-to-stand identification. The second step of the algorithm is confirmatory and evaluates if all the sit-to-stand transitions are plausible. Two versions of the algorithm currently exist. One where the algorithm assumes that sit-to-stand transfers will be preceded by a period of stillness. This version is suggested for a home-like environment. The second does not have a constraint on a period of stillness. Thus, it is recommended to use in clinical settings with a doctor. In this thesis, I am using both versions of the algorithm. (Adamowicz et al., 2020)

## 3.4 Final Dataset

### 3.4.1 Physical Activity Features

In order to compare results against the ALSFRS-R scale, we need to compute features in each patient’s measurement. In other words, each patient’s measurement can represent one epoch. In each epoch, we have several sit-to-stand transitions and from that, I computed features that can be seen in Table 3.3. The idea behind this is to explore and find which physical activity markers correspond to which features based on the ALSFRS-R scale. Specifically, I used the output of sit-to-stand transitions and extracted the *mean*, *median*, *minimum*, *maximum*, and *standard deviation* of

the *duration*, *vertical displacement*, *minimal and maximal acceleration*, and *SPARC*. Moreover, I added a ratio of the number of sit-to-stand transitions and total wear time in seconds that was produced by the Hees Algorithm.

TABLE 3.3: Computed Features from One Epoch (One Measurement of a Patient)

Number	Feature
1	Mean of Duration
2	Maximum of Duration
3	Minimum of Duration
4	Median of Duration
5	Standard deviation of Duration
6	Mean of Min. Acceleration
7	Maximum of Min. Acceleration
8	Minimum of Min. Acceleration
9	Median of Min. Acceleration
10	Standard deviation of Min. Acceleration
11	Mean of Max. Acceleration
12	Maximum of Max. Acceleration
13	Minimum of Max. Acceleration
14	Median of Max. Acceleration
15	Standard deviation of Max. Acceleration
16	Mean of SPARC
17	Maximum of SPARC
18	Minimum of SPARC
19	Median of SPARC
20	Standard deviation of SPARC
21	Mean of Vertical Displacement
22	Maximum of Vertical Displacement
23	Minimum of Vertical Displacement
24	Median of Vertical Displacement
25	Standard deviation of Vertical Displacement
26	$\frac{\text{Number of Sit to Stand Transitions}}{\text{Total Wear Time in Seconds}}$

### 3.4.2 ALSFRS-R Scale Features

Features that I used to describe the state of the patient with ALS can be seen in Table 3.4. Specifically, I used individual questions of the scale as singular features together with the summarization of all of them. Moreover, features such as *motor*, *X7 – 9*, and *X8 – 9* are summarized questions of the questionnaire to create a new and novel way to describe a patient’s state.

### 3.4.3 Description

The preliminary dataset consists of 200 epochs across 41 patients. Every single epoch is represented by one data frame that consists of all sit-to-stand transitions during that epoch. One data frame includes all features mentioned in Table 3.2 together with the exact start and end of the transition. Each data frame is then aggregated

TABLE 3.4: ALSFRS-R Based Features

<b>Marker</b>	<b>Range</b>
<i>ALL</i>	I1 – I12
<i>MOTOR</i>	I4 – I8
<i>X7 – 9</i>	I7 – I9
<i>X8 – 9</i>	I8 – I9
<i>I1</i>	–
<i>I2</i>	–
<i>I3</i>	–
<i>I4</i>	–
<i>I5</i>	<i>I5A + I5B</i>
<i>I6</i>	–
<i>I7</i>	–
<i>I8</i>	–
<i>I9</i>	–
<i>I10</i>	–
<i>I11</i>	–
<i>I12</i>	–

in a way to compute features mentioned in Table 3.3. Simultaneously, features from Table 3.4 are extracted. Thus, the final dataset includes 200 rows where one row corresponds to one epoch and columns with features from the ALSFRS-R questionnaire and features describing the physical activity.

### 3.5 Linear Mixed Model

To calculate Pearson correlation in clustered data, or in other words repeated observations within individuals, it is needed to account for their dependencies. The linear mixed model is one of the ways how to solve this issue. This model can take into account a nonlinear process of the time trend in the continuous response variable based on the estimated regression coefficients. Therefore, the data are permitted to exhibit correlated and nonconstant variability. (Cnaan, Laird, and Slasor, 1997)





## Chapter 4

# Results

Across 41 patients there were 200 valid measurements where each measurement lasted from 1 to 13 days with an average of 2.7 days. On average, the real wear time during one measurement was 17.9 hours with a standard deviation of 18.6 hours. The number of sit-to-stand transitions on average was 60.6 with a standard deviation of 52.2 during one epoch.

Physical activity features are presented in Table 3.3 and ALS progression markers created from the ALSFRS-R questionnaire can be seen in Table 3.4. The Pearson correlations computed between these two domains are available in Figure 4.1. As can be seen in this figure, each cell represents the Pearson correlation between features on the y and x-axis.

Looking at the heatmap, there are no very high correlations present. To remind, my goal is to find physical activity markers that would describe ALS progression and the state of a patient. Thus, features of my interest should be 17, 18, 19, and their combination. These features have the highest correlations compared to other features. Specifically, the median duration of the sit-to-stand transition seems to have negative correlations around 0.3 with features that represent turning in bed, walking, and climbing stairs. This can be described in a way that the worse patient's state is, the longer it takes for him to stand up. This result supports my hypothesis, however, the correlations are not of great significance.

Interestingly, the small correlations found with question items 17, 18, and 19 do not describe the total ALSFRS-R score and other items of the questionnaire. This supports other research papers that suggest that ALSFRS-R has a problem with multidimensionality and subjective evaluation of the questions by patients. Thus, it is problematic to compare two patients with the same total score. Consequently, the questionnaire should be divided into subsections. (Rooney et al., 2016)

As can be seen in figure Figure 4.2, the median duration of sit-to-stand transitions is plotted against item 7,8,9 of the ALSFRS-R scale. The question that can be presented the most by the duration of the sit-to-stand transition, is walking. In other words, the answers of ALSFRS-R are getting higher with the lower median duration of the sit-to-stand transition. Approximately, each decrease of item 18 of the ALSFRS-R questionnaire slows the duration of the sit-to-stand transition by -0.8 seconds.

Another interesting result that can be seen in the heatmap is the correlation between the standard deviation of minimal acceleration and combinations of questions 8 and 9 of the ALSFRS-R scale. The correlation is -0.36. This can be interpreted in a way that the worse patient is the higher the differences in terms of minimal acceleration in the sit-to-stand transition.

To summarize, it seems that the duration of the sit-to-stand transition and standard deviation of minimal and maximal acceleration during this transition can describe ALSFRS-R motor-related questions. However, the correlations between these

items are not very high. Moreover, all standard deviations of computed physical markers seem to be more important than the mean and other aggregations. Thus, this suggests that the better the patient's state is, the more stable are his movements, and does not have differences in features such as acceleration during the sit-to-stand transition or duration of the transition.

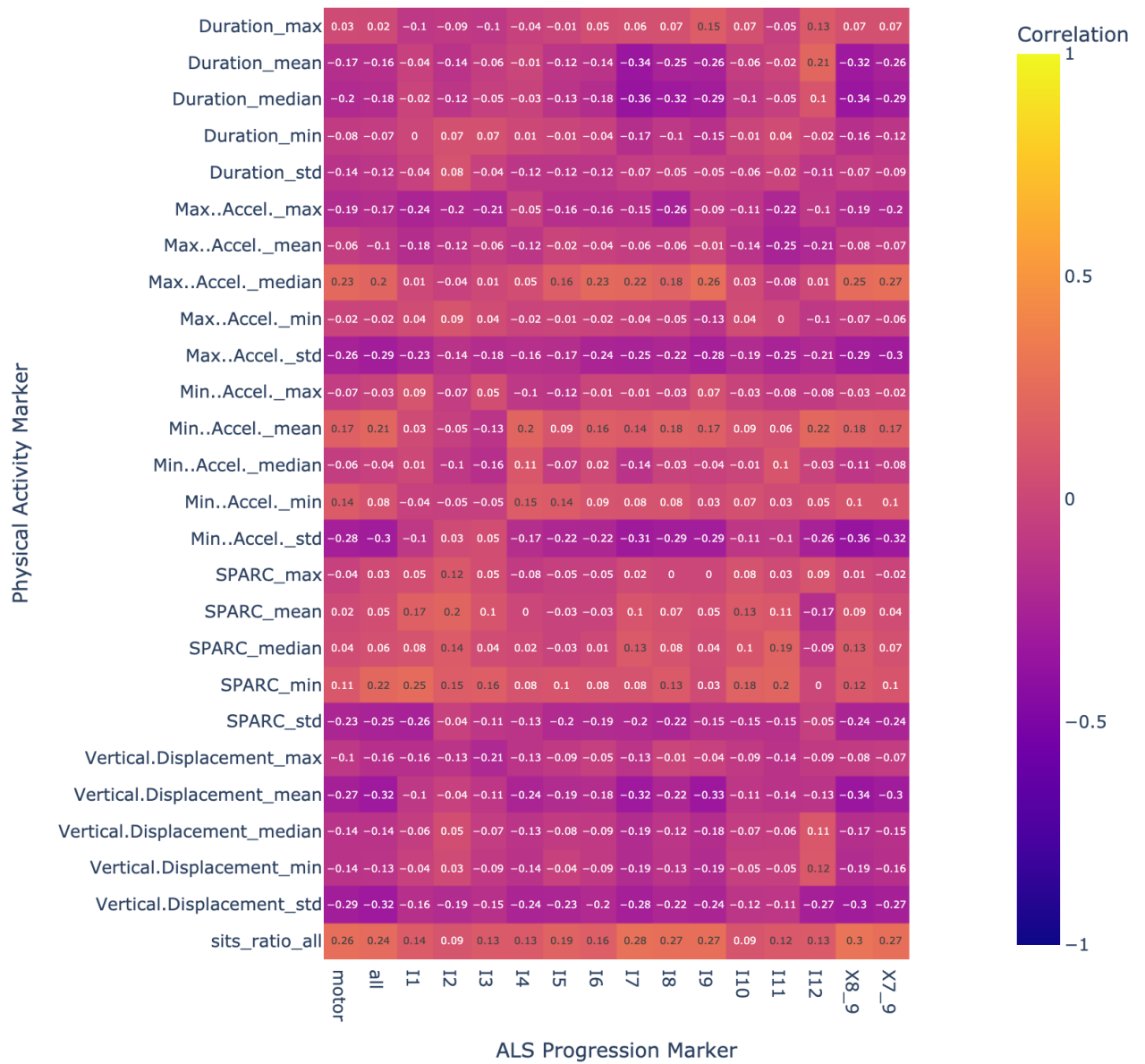


FIGURE 4.1: Results

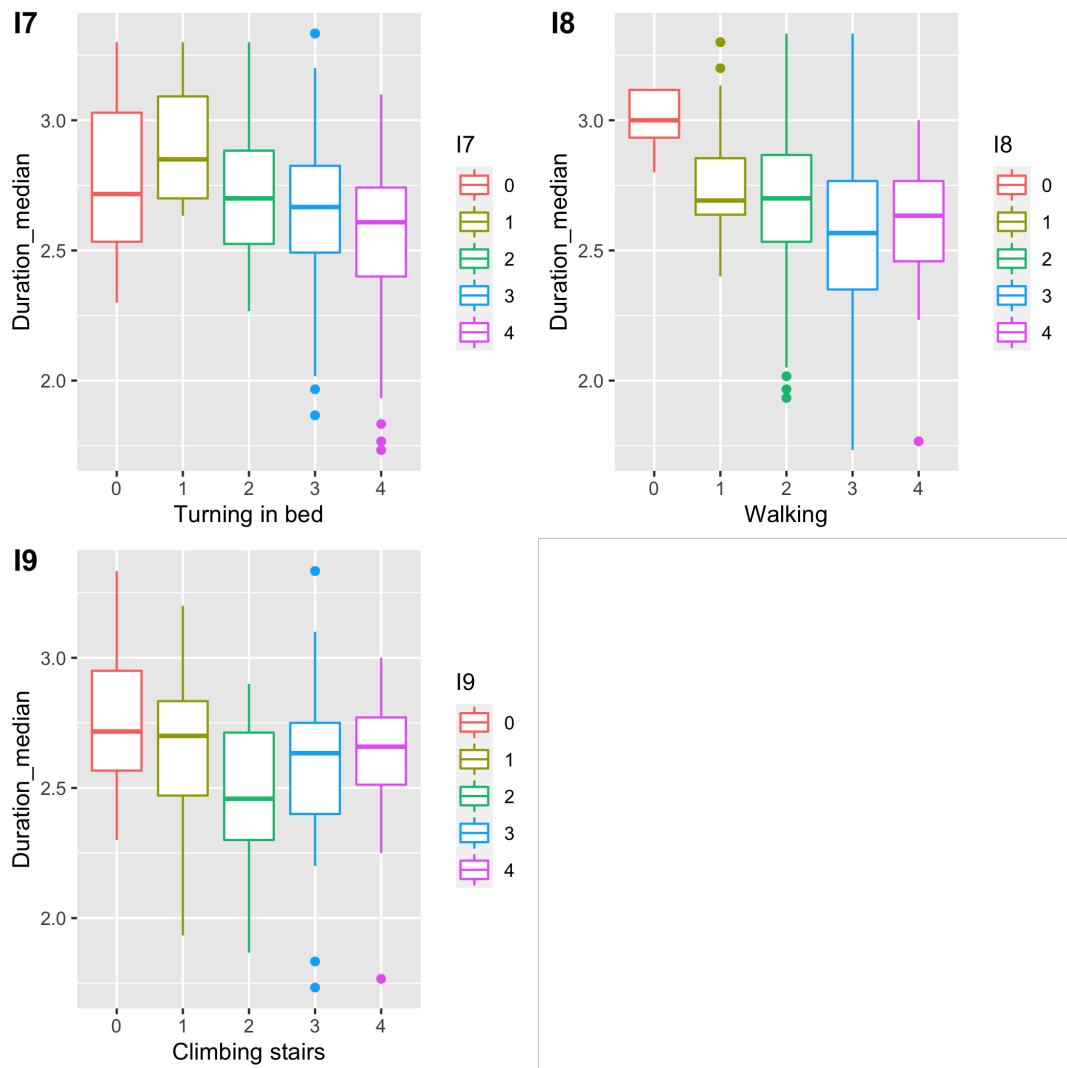


FIGURE 4.2: Items 7,8,9 of ALSFRS-R scale plotted against median duration of one transition

## Chapter 5

# Discussion and Conclusion

### 5.1 Discussion

In my thesis, I tried a new and novel way how to describe ALS disease progression using sit-to-stand transitions. As mentioned in Section 3.3, the sit-to-stand detection is used in patients with Parkinson's disease to detect postural control stability where variables such as the center of posture displacement and transition velocity are used (Fernandes et al., 2015). Nevertheless, I did not find any significant or high correlations between the ALSFRS-R questionnaire and my computed sit-to-stand transitions features.

ALS is different from Parkinson's disease. Parkinson's disease is one of the most common neurodegenerative disorders. It affects neurons in the brain which causes unintended and uncontrollable movements. The specific movements can be stiffness, shaking, or difficulties with balance and coordination. Moreover, Parkinson's can cause a loss of reflexes needed to maintain an upright posture which causes instability while standing upright. (Davie, 2008)

On the other hand, ALS affects neurons in localized areas such as hands or legs. Then the disease destroys neurons and spreads elsewhere in the body (Boill e, Vande Velde, and Cleveland, 2006). In other words, there is a big variability of symptoms in ALS disease compared to Parkinson's disease and thus it might be not possible to produce good quantification of this disease by just these sit-to-stand transitions.

Taking a different point of view, ALSFRS-R is a well-established metric that is used to detect ALS progress. However, a lot of information might be lost when using the total score, and is preferable to use subscores to lose this problem of multidimensionality (Rooney et al., 2016). Thus, we should take into account that direct comparison is not ideal since patients with the same total scores vary in terms of their prognosis and diagnosis (Eijk et al., 2021). Moreover, in a recent study, it was found that the values of item 9 (*climbing stairs*) are not in line with the clinical observation in terms of different environmental and external factors. (Franchignoni et al., 2013).

ALSFRS-R is reproducible and easily administered in clinical trials. However, it is highly subjective and affected by symptomatic treatment (Andres et al., 2017). Thus, the problem of finding no high correlations might be in the questionnaire itself.

To tackle this issue, I propose to include a new question in the ALSFRS-R questionnaire which would assess the difficulty of this sit-to-stand transition on a scale (0 - 4) and then compute connections against the total ALSFRS-R score and other items.

Moreover, in future home-like clinical studies, I propose to include a new rule that the patient has to complete, if possible: five sit-to-stand transitions in a specific period during the morning to be able to detect the disease's progression better.

Based on the results of this thesis, it would be beneficial to validate the values of hyperparameters of the Hees Algorithm based on the actigraph that was used to collect our data. The reason behind this is that hyperparameters tuned in studies (Hees et al., 2011) and (Hees et al., 2013) were validated on a different type of actigraphy device. Thus, it would be beneficial to gather wear times reported from patients and validate them with the results of the Hees Algorithm and simultaneously tune the hyperparameters.

Moreover, in future work, the Displacement Algorithm should be looked at from a similar point of view. The parameters and the algorithm itself were validated on a different type of actigraphy device than the device used to collect our data. Moreover, the device had a different sampling frequency. Though the algorithm is built in a way that the frequency and different devices should not matter, I would suggest validating against the human taken notes about sit-to-stand transitions or even against video with sit-to-stand transitions of patients with ALS. Another reason that supports my statement is the fact that there is no other study that used or validated this new method. It was tested only on patients with Parkinson's disease in a clinical setting.

From the ethical point of view, I believe that there are no ethical implications that need to be considered as the data were prepared and handled in a very conservative and privacy non-disturbing way.

## 5.2 Conclusion

In my thesis, I tried to find novel markers that would describe ALS disease progression based on the raw actigraphy data. Firstly, I used Hees Algorithm to detect wear time and then the Displacement algorithm to extract sit-to-stand transitions. After the computation of features in each epoch (*one measurement*) of the patient from the output of the Displacement algorithm, I extracted features from the ALSFRS-R scale. After that, I computed correlations between these two domains using a linear mixed model.

Description of ALS progression using actigraphy device is a novel way and does not have currently a very significant contribution in the academic sphere. Thus, it is very important to explore these possibilities to be able to help patients with ALS disease. Moreover, the usage of actigraphy devices helps us to monitor patients in a home-like environment.

The motor-related items of the ALSFRS-R questionnaire (7,8,9) correlated against the median duration of the sit-to-stand transition and standard deviation of minimal acceleration. However, the correlations were smaller than already published results with different methods on a similar dataset (Eijk et al., 2019). Even though the results were not of great success, the reason behind this might be the absence of a good fitting question in the ALSFRS-R scale. Thus, I proposed a new question that should be included in a scale and a new rule that the patients should do each morning of their measurement to provide better measurements of sit-to-stand transitions.

To summarize, the results of this thesis are not better than the current state of the art. However, it is still a promising area that should be explored, especially, in terms of creating a new question, including it in the ALSFRS-R scale, and looking at the results within the context of other items of the scale. It was not possible, in history, to explore the disease in terms of acceleration and duration of the transition. Thus, there was no need for this type of question. Nevertheless, currently, with

the advance in technology, this could give us a new view on the problem of ALS progression.





## Appendix A

# Explanation of the Data Processing Pipeline

The main part is run in Python 3. The statistical analysis is run in R. The scripts should be run in the following order as the input always relies on the previous output.

1. Sit-to-stand Detection (*Python*)
2. Features Computation (*Python*)
3. Linear Mixed Model - Correlation Computation (*R*)
4. Visualization (*Python*)





```
pipeline.add(skdh.preprocessing.DetectWear()) #detect wear time

pipeline.add(skdh.sit2stand.Sit2Stand(power_std_height=True,
                                     stillness_constraint = True
                                     ), save_file = to_save_name
            ) #sit2stand dection

try:
    pipeline.run(file=filepath) #run the pipeline
except:
    continue
df = pd.read_csv(to_save_name, skiprows = 5)
if len(df) == 0:
    continue
df.loc[:, "min_date"] = min_date
df.loc[:, "max_date"] = max_date
df.loc[:, "year"] = mean_date.year
df.loc[:, "month"] = mean_date.month
df.loc[:, "day"] = mean_date.day
df.to_csv("data_batches_new/" + to_save_name[22:], index =
        False)

if len(main_df) == 0:
    main_df = df
else:
    main_df = pd.concat([main_df, df], ignore_index=True)

#main_df.to_csv("sit2stand.csv", index = False)
```

## Appendix C

# Features Computation Code

Jupyter notebook which computes features from sit-to-stand detection.

```
import glob
import pandas as pd
import plotly.graph_objs as go
import plotly.express as px
from datetime import timedelta
import numpy as np
from sklearn.linear_model import LinearRegression
import skdh
import plotly
```

```
patients = []
for filepath in sorted(glob.iglob('data_batches/*.csv')):
    p = "I" + filepath.split("/") [1].split() [0]
    if p not in patients:
        patients.append(p)
patients
```

```
excel = pd.read_excel("als_stats.xlsx", sheet_name = "WEARTIME")
results = {}
results["motor"] = []
results["all"] = []
results["sits_ratio_all"] = []
results["sits_ratio_small"] = []
results["id"] = []

paras = ["min", "max", "mean", "median", "std"]
features = ["Vertical Displacement", "Max. Accel.", "Min. Accel.", "SPARC", "Duration"]

for feature in features:
    for par in paras:
        results[feature + "_" + par] = []
        results[feature + "_" + par + "_s"] = []

for col in excel.columns[9:22]:
    results[col] = []
for pat in patients:
    print(pat)
    for filepath in sorted(glob.iglob('data_batches_new/*.csv')):
        print(filepath)
        splitted = filepath.split("/") [1].split()
        print()
        pat_file = splitted[0]
        print(pat_file)
        if pat_file != pat:
            continue
```

```

pat_excel = pat_file
if "Baseline" in splitted[1]:
    id_excel = "0"
else:
    id_excel = splitted[2].split(".")[0]

temp = excel.loc[(excel.ID == pat_excel) & (excel.VISIT == int(
    id_excel)), :]

print(temp)
try:
    start = pd.Timestamp(str(temp["START"].item()) + " " + str(
        temp["tSTART"].item()))
except:
    continue
try:
    end = pd.Timestamp(str(temp["STOP"].item()) + " " + str(
        temp["tSTOP"].item()))
except:
    continue

sum_motor = 0
sum_all = 0
for col in temp.columns[9:22]:
    res = temp[col].item()
    if np.isnan(res):
        results[col].append(np.nan)
        continue
    else:
        results[col].append(int(res))
        sum_all += int(res)

for col in temp.columns[12:18]:
    res = temp[col].item()
    if np.isnan(res):
        continue
    else:
        sum_motor += int(res)

results["all"].append(sum_all)
results["motor"].append(sum_motor)
results["id"].append(pat)

ins = skdh.io.ReadGT3X()

new_file = "data/" + filepath.split("/")[-1].split(".")[0] + ".
    gt3x"

print(new_file)
tr = ins.predict(new_file)
inst = skdh.preprocessing.CalibrateAccelerometer()
tr = inst.predict(time = tr["time"], accel = tr["accel"])
ins2 = skdh.preprocessing.DetectWear()
tr = ins2.predict(time = tr["time"], accel = tr["accel"])

sum_time = 0
sum_time_small = 0

df = pd.read_csv(filepath)
temp_df = df.copy()

```

```

temp_df["st"] = pd.to_datetime(temp_df["STS Start"], unit='s')
temp_df["en"] = pd.to_datetime(temp_df["STS End"], unit='s')
print(start)
#print(end)
#print(temp_df)
temp_df = temp_df.loc[(temp_df.st >= start) & (temp_df.en <=
                        end)]

#print(temp_df)
#number_sits_ratio = len(temp_df)#/(start - end).seconds

for i in range (0, len(tr["wear"])):
    first = tr["wear"][i][0]
    second = tr["wear"][i][1]
    resh = pd.to_datetime(tr["time"], unit = "s")
    time_first = resh[first]
    time_second = resh[second]
    sum_time += (time_second - time_first).seconds

    if time_first >= start and time_second <= end:
        sum_time_small += (time_second - time_first).seconds

if sum_time == 0:
    results["sits_ratio_all"].append(np.nan)
else:
    results["sits_ratio_all"].append(len(df)/sum_time)
if sum_time_small == 0:
    results["sits_ratio_small"].append(np.nan)
else:
    results["sits_ratio_small"].append(len(temp_df)/
                                        sum_time_small)

for feature in features:
    for par in paras:
        if par == "min":
            res = df[feature].min()
            res_s = temp_df[feature].min()
        if par == "max":
            res = df[feature].max()
            res_s = temp_df[feature].max()
        if par == "mean":
            res = df[feature].mean()
            res_s = temp_df[feature].mean()
        if par == "median":
            res = df[feature].median()
            res_s = temp_df[feature].median()
        if par == "std":
            res = df[feature].std()
            res_s = temp_df[feature].std()

        results[feature + "_" + par].append(res)
        results[feature + "_" + par + "_s"].append(res_s)

#df_main["STS Start"] = pd.to_datetime(df_main["STS Start"], unit='
s')
#df_main["STS End"] = pd.to_datetime(df_main["STS End"], unit='s')
#visualize_sits(df_main)
#visualize_sits_count(df_main)
result["6_8"] = result["I6"].values + result["I7"].values + result["I8"
].values
result["7_8"] = result["I7"].values + result["I8"].values
result.to_csv("data_after_diff.csv", index = False)

```





## Appendix D

# Correlations Computation Code

```

library(lme4)
data <- read.csv("/Users/michalkubina/thesis_uu/data_after.csv")
names(data)[names(data) == 'X6_8'] <- 'X7_9'
names(data)[names(data) == 'X7_8'] <- 'X8_9'
correlation <- c()
confl <- c()
confu <- c()
feature <- c()
marker <- c()
y <- c()
markers <- c("motor", "all", "I1", "I2", "I3", "I4", "I5", "I6", "I7", "I8", "I9", "I10")

new_list <- c()
counter <- 1
for (c in data$I5B){
  if (is.na(c)){
    print(c)
    new_val <- data$I5A[counter]
    new_list <- append(new_list, new_val)
  } else {
    new_list <- append(new_list, c)
  }
  counter <- counter + 1
}
data$I5 <- new_list
drops <- c("I5A", "I5B")
data <- data[, !(names(data) %in% drops)]
summary(data)
for (main in markers){
  for (i in colnames(data)){
    print(i)
    if (i == "id"){
      next
    }
    if (i %in% markers){
      next
    }
  }
}

```

```
if (i == "sits_ratio_small"){
  next
}
if (main == "id"){
  next
}
m <- lmer(scale(get(i)) ~ scale(get(main)) + (scale(get(main))|id), da
correlation <- append(correlation, as.numeric(fixef(m)[2]))
#confl <- append(confl, as.numeric (confint (profile (m, which = 6)))[1])
#confu <- append(confu, as.numeric (confint (profile (m, which = 6)))[2])
y <- append(y, i)
marker <- append(marker, main)

}
}
res <- data.frame(marker, y, correlation)
res_sorted <- res[order(-correlation),]
write.csv(res, "results_normalalg_update_new.csv")
```

## Appendix E

# Visualization Code

```
import plotly.express as px
computed = pd.read_csv("results_normalalg_update.csv")
computed = computed.drop(columns = ["Unnamed: 0"])
computed = computed[~computed['y'].str.endswith('_s')]
#computed = computed[~computed['y'].str.endswith('_s')]
print(computed.head())

df3 = pd.DataFrame(columns=computed.marker.unique(), index = computed.y
                    .unique())

print(df3.columns)
for index in df3.index:
    print(index)
    for col in df3.columns:
        temp = computed.loc[computed.y == index]
        temp_res = temp.loc[temp.marker == col, "correlation"].item()
        df3.loc[index, col] = round(temp_res, 2)

array = []
for i in df3.columns:
    array.append(i)
array
```

```
fig = px.imshow(df3,
                labels=dict(x="ALS Progression Marker", y="Physical
                            Activity Marker",
                            color="Correlation"
                            ),
                x=array,
                y=df3.index, zmin=-1, zmax=1, text_auto = True)
#fig.update_xaxes(side="top")
fig.update_layout(height=800,width=800)
fig.show()
fig.write_image("fig1.png", scale = 2)
```



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