Bachelor Project

Czech Technical University in Prague

F3

Faculty of Electrical Engineering
Department of Cybernetics

Actigraphic Data Processing of Patients with Bipolar Disorder

Miroslav Březík

Supervisor: Ing. Jakub Schneider
Field of study: Open informatics
Subfield: Computer and Information Science
May 2020

Acknowledgements

I am particularly thankful to my supervisor, Ing. Jakub Schneider, and to doc. Ing. Daniel Novák, Ph.D. for their guidance and constant support throughout the preparation for this bachelor thesis. I would like to express my gratitude to the Czech Technical University in Prague for providing me with the invaluable knowledge without which I would not be able to write this thesis.

Declaration

I declare that the presented work was developed independently and that I have listed all sources of information used within it in accordance with the methodical instructions for observing the ethical principles in the preparation of university theses.

Prague, date:

Signature:

Abstract

In this thesis exploratory analysis was performed on actigraphic signal from patients diagnosed with bipolar disorder. Physical manifestations were compiled as reported in a number of medical studies. The acquisition process and characteristics of actigraphy were described and subsequently related to psychological questionnaires. Two major analytical methods widely applied to physiological data were utilized: cosinor analysis and permutation entropy. In both cases the aim was to find configurations that best separate the three main episodes symptomatic of bipolar disorder: depression, mania and remission. Finally, support vector machine classifier was trained to classify an actigraphic signal based on computed indicators.

Keywords: actigraphy, bipolar disorder, permutation entropy, cosinor analysis

Supervisor: Ing. Jakub Schneider

Abstrakt

Náplní této bakářské práce byla explorační analýza aktigrafických dat pacientů s diagnostikovanou bipolární poruchou. Studiem odborné literatury byly shromážděny především fyzické příznaky bipolární poruchy. Dále byly popsány základní charakteristiky použitých aktigrafických signálů, psychologických dotazníků a vztahy mezi nimi. Byly použity dvě široce aplikované analytické metody: kosinorová analýza a permutační entropie. V obou případech bylo cílem nalézt konfigurace těchto metod tak, aby bylo možné provést separaci tří základních symptomatických epizod bipolání poruchy: deprese, mánie a remise. Nakonec byl natrénován klasifikátor pomocí metody podpůrných vektorů (support vector machine), který na základě vypočítaných indikátorů korektně identifikuje danou symptomatickou epizodu.

Klíčová slova: aktigrafie, bipolární porucha, permutační entropie, kosinorová analýza

Překlad názvu: Zpracování aktigrafických dat pacientů s bipolární poruchou

Contents

Figures

Tables

Chapter 1

Bipolar disorder

1.1 Introduction

Bipolar disorder is a mental illness that falls into a specific category of affective disorders. There are two main symptomatic behavior-shifting episodes that occur in patients with this diagnosis. One of them is *mania* which causes a person to have periods of unnaturally elevated mood. The other is *depression* which has opposite effects such as numbness, hopelessness, and negative thinking. These highs and lows are what often makes it hard or even impossible for patients to function well in society. The severity of bipolar disorder as a health issue was emphasized by The World Health Organization when it was included in the 2004 update of The Global Burden of Disease [O+08]. It rated among the top 10 diseases causing the highest *YLD* (years lost due to impairment).

Although a great amount of progress has been made to clarify the origins and manifestations of this debilitating disease, a number of major discoveries are still ahead of us. Due to the relatively high complexity of bipolar disorder combined with overlapping characteristics with schizophrenia and unipolar depression, decisive diagnostic methods are still yet to come. Broadening the scope of medical analytical tools might shed some light on the more ambiguous aspects of bipolar disorder. Actigraphy could prove to be a helpful addition to this toolset, as has been already explored elsewhere [JHE05] [KGHM+14]. One of the main motivators in choosing actigraphy as an analytical, or even a diagnostic tool, is that affective disorders are generally sensitive to disruptions of circadian rhythms [Gru15]. And actigraphy has been enjoying great success, especially in circadian rhythms monitoring as well as in many other areas (see chapter 2.2).

1.2 Phenotypes

There has been a long discussion on the subject of bipolar disorder categorization. A case in point is the chapter on bipolar disorder in two of the major medical diagnostic manuals: Diagnostic and Statistical Manual of Mental Disorders (*DSM*) [A+13] and International Statistical Classification

of Diseases and Related Health Problems (*ICD*) [Org04]. *DSM* states 4 main phenotypes: *bipolar I disorder*, *bipolar II disorder*, *cyclothymic disorder* and *bipolar disorder not otherwise specified*. For bipolar I disorder, it is required for the patients to have experienced depressive episodes and at least one manic episode. Bipolar II disorder differs from type I in patients experiencing milder manic episodes referred to as *hypomanias*. Cyclothymic disorder is very similar to type II except that depressive-like episodes often cannot be in these cases classified as full-blown depression because of their less severe nature. The final phenotype distinguished by *DSM* is bipolar disorder not otherwise specified with episodes of depression and hypomanic-like symptoms. *ICD*, in contrast to *DSM*, does not discriminate between bipolar I disorder and bipolar II disorder. However, it is stricter in a sense that it requires two episodes of mania or hypomania for the diagnosis of bipolar disorder.

Despite wide recognition of the four main phenotypes, a call for a dimensional spectrum approach has been prevalent in the scientific community [Gru15]. The similarities with unipolar depression and schizophrenia often lead to misdiagnosis and/or prescription of inappropriate medication (e.g. antidepressants triggering mania). The cause of this is usually attributed to, amongst other things, the lower frequency of manic episodes, their milder manifestation, and under-reported figures from patients.

1.3 Symptomatic episodes

In the subsequent chapters I will only concern myself with depressive and manic episodes and/or episodes of remission. This simplification is justified by two major features of the data used, described in detail in chapter 2. The first reason is that the cohort of bipolar patients may contain any proportion of the four main phenotypes. So focusing exclusively on the polar opposites, depression and mania, should lead to meaningful results regardless. Also the questions in questionnaires given to patients (see section 2.3) were constructed to indicate depression and mania on a scale. Restricting oneself to the extreme cases produces more easily interpretable results.

Depressive episodes are characterized by the following symptoms: loss of pleasure, reduced energy, psychomotor retardation, loss of appetite, disrupted sleep, etc. Mania, on the other hand, comprises elated mood, irritable mood, increased energy, reduced need for sleep, high-risk behavior, hyperactivity, etc. [Gru15] [PK13] Apart from these reported symptoms, depression generally differs from mania in both the frequency and length, depression having a higher recurrence and lasting for longer periods of time. Besides the discussed episodes patients also experience relatively asymptomatic periods referred to as *remission* or *euthymia*. Another evidence suggesting bipolar disorder phenotypes reside on a spectrum rather than being distinct categories is that of *mixed episodes*. Mixed episodes feature both depression and mania often with rapid alternation and thus are harder to identify. Therefore the widespread belief that depression and mania are two isolated phenomenons with no overlap is simply not accurate.

The apparent difficulties presented by the symptomatic episodes are not the only life impairment suffered by patients with bipolar disorder. Unfortunately, a number of studies concluded that mania, and to a lesser extent depression, have long-term negative impacts on memory, attention, and fine motor skills that have been observed even in subsequent remissions [LJLVG+10] [TMAdMB+12].

1.4 Cause

Bipolar disorder occurrence across cultures has been found to be close to uniform [WBC+96]. A large-scale study on the Swedish population implicated high heritability of bipolar disorder, especially from the maternal side [LYB+09]. Later generations show signs of a more severe character of bipolar disorder. This complex inheritance mechanism demands further inspections, as it is currently not entirely explained [Gru15]. What has been indicated is that the genes suspected in the heritability of bipolar disorder have considerable overlap with schizophrenia.

The higher variability in various aspects of bipolar disorder cannot be however explained solely by heritability. Epigenetics is also a major contributor when it comes to how bipolar disorder manifests. Although major breakthroughs are yet to come, we already have pieces of knowledge helping us in preventing or at least suppressing some symptoms, for example by early intervention [BBD+11].

Chapter 2

Data

2.1 Introduction

In this chapter I will introduce various types of data analyzed throughout the thesis, their acquisition process, and their relations. I will also outline some of the preprocessing techniques used in the following chapters, namely 3, 4, and 5. Firstly, I must preface this chapter by acknowledging that all of the data was kindly provided by MindPax Ltd., so they have my gratitude. Also, some aspects of the data cannot be disclosed in detail here as the nature of it is rather sensitive, and I am bound by a non-disclosure agreement. However, I will endeavor not to let this fact interfere with the interpretability of the results in any way.

2.2 Actigraphy

Actigraph is essentially a time series, meaning we have a fixed *sample rate*, and for each sample we have one measurement. In our case, the units of measurements are acceleration averaged over the three axes in space which are sampled every 30 seconds. In the following text I will refer to the actigraphic measurements as *actigraphic signal values*, *actigraphic signal* or simply *values* as the units and scale are of little importance to analytical methods discussed in chapters 3, 4 and 5. If the need arises to somehow transform the original signal, I will clarify the relevant proceedings further. The acquired signal has also gone through the process of quantization so that the minimum distance between values is approximately 8, making the final signal discrete in its nature. This aspect of the actigraphic data will later prove essential for choosing the most suitable *permutation entropy* modification (see chapter 4).

Below in figure 2.1 is the histogram of actigraphic values computed from a several-day signal of multiple patients. We can see that the histogram resembles normal distribution except the peak in the lower values. It is caused possibly by parts of the night signal with relatively low activity.

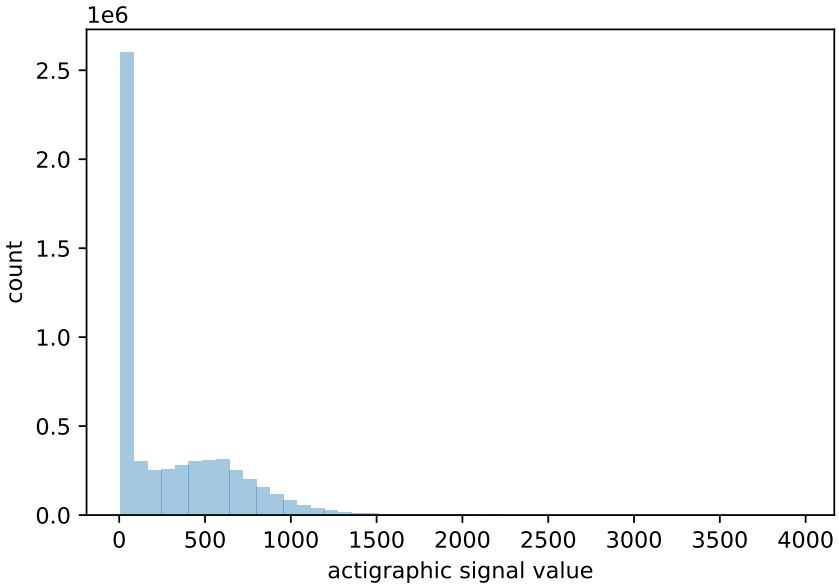

Figure 2.1: The signal from 78 patients during remission was used. The histogram was computed from the total of 1×10^7 data points. Parts of the signal containing missing values were left out.

Formal definition of a time series:

$$\boldsymbol{t} = (t_1, \ \dots \ , \ t_n) \tag{2.1}$$
$$\boldsymbol{s}_i = (t_i, \ \dots \ , \ t_{(i-1)+o}) \tag{2.2}$$
$$S = \{\boldsymbol{s}_1, \ \dots \ , \ \boldsymbol{s}_{(n+1)-o}\} \tag{2.3}$$
$$\tag{2.4}$$

where:

$\boldsymbol{t}$ ... time series of length n
$\boldsymbol{s}_i$ ... ith sub-string of time series $\boldsymbol{t}$
S ... all o-length sub-strings of time series $\boldsymbol{t}$

The leading measurement acquisition method is having patients wear a monitoring wristband. At the time of writing many models are used in the real world for research or diagnostic purposes, the current standard being MotionWatch manufactured by CamNtech. The model used for measuring activity here is called MindG. Both models were the subjects of a validation study conducted by MindPax Ltd. [AVN].

As discussed in chapter 1, psychiatric diagnosis relies heavily on subjective assessments. In recent years there has been a rise in utilizing other so-called objective methods. However arguments have been made that the extent to which the traditional methods are objective is on par with other medical fields [Pie07]. Distancing oneself from this argument there are

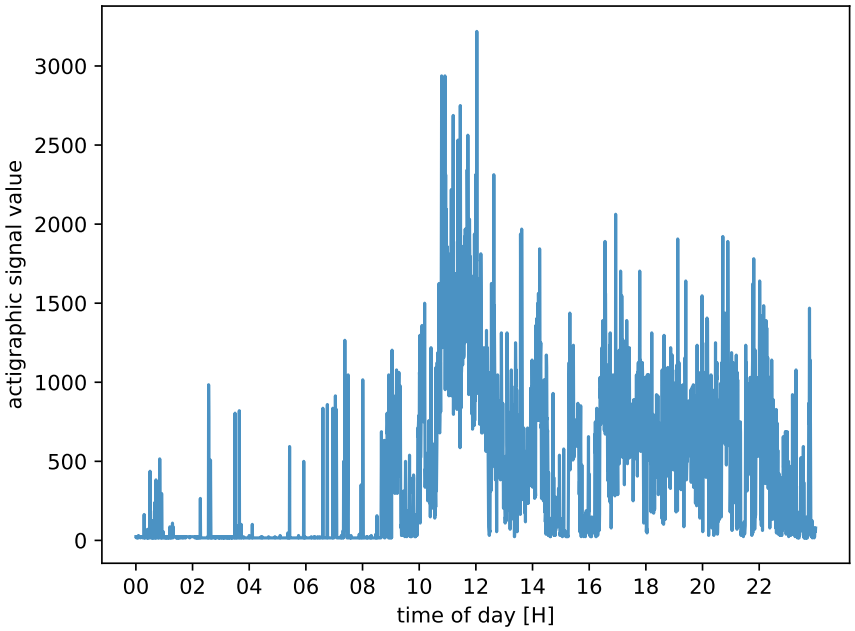

Figure 2.2: Actigraph of patient n. 350 from June 28th 2017. The signal uses original 30-second sampling period and contains no segments with missing values.

still other more immediate advantages to moving to objective assessment methods especially those facilitated by affordable modern technology such as actigraphy. Healthcare access is not universal and for many cannot be currently attained, be it on a geographical, financial, or social basis. This exact issue was addressed in The Bulletin of the World Health Organization [EHB13]. Actigraphy could alleviate at least some of the difficulties.

Actigraphy analysis methods have been applied in medical diagnosis with a great success. It is now an integral tool in analyzing sleep patterns [SA02] which alone makes it invaluable, as sleep disruptions accompany many mental disorders [BNR+16]. Plethora of mental disorders has been specifically studied with respect to actigraphy: bipolar disorder [KGHM+14], attention deficit hyperactivity disorder [CTM+01], depression [BMT+13] or schizophrenia [BHO+10].

There are two main groups of actigraphy data used throughout this thesis. Firstly, there are records from 40 healthy patients and, secondly, records from 358 patients diagnosed with bipolar disorder with basic statistics given in table 2.2 and 2.1 respectively. Some segments of bipolar patient's actigraphs were annotated by a medical professional with labels classifying them as episodes of remission, depression, or mania. General information about these annotations is displayed in table 2.3.

An important remark must be made here regarding data aggregation and filtering, used specifically in statistical tests in chapters 3 and 4. Due

patients	avg. days/patient	first date	last date	avg. value
358	463.36	2017-04-30	2020-03-14	235.95

Table 2.1: Bipolar patients' cohort information

patients	avg. days/patient	first date	last date	avg. value
40	140.35	2019-05-08	2020-03-16	269.51

Table 2.2: Healthy patients' cohort information

episode	patients	days	avg. days/patient	avg. days/record
depression	48	3645	75.94	41.42
mania	22	961	43.68	25.29
remission	85	19789	232.81	100.96

Table 2.3: Episode annotations information

to the underlying assumptions of independent sampling, precautions have been made to avoid violating them. As mentioned above, there are long periods of signal for each patient in both of the available actigraph datasets. When comparing population means that contain periods of depression, mania, remission (see sections 3.4 and 4.4) or periods containing weekend days, not containing weekend days (see section 3.3) the data is transformed in the following manner. Firstly, only one of the populations is picked for each patient. Secondly, each patient's multiple records are substituted by their average value. For example, patient n. 144 has a total of 17 days labeled as depression and 165 days labeled as remission. This patient is randomly assigned one of the possible population groups, say depression. Then average of measurement (i.e. permutation entropy in chapter 4 or cosinor parameters in chapter 3) that are of interest to us are computed from the 17 samples. So, only one sample for each patient in total is used in the tests. Although this transformation radically reduces the dataset size it can allow us to utilize the tests and thus obtain meaningful performance measures.

2.3 Questionnaire

Apart from the categorical labels described in the previous section, we have other means to validate our findings. In this thesis bipolar patients are sent structured questionnaires that they fill out in accordance with their mood in the previous one to two week period. The questionnaire consists of a series of depression and mania related statements. The patient is asked to choose a

number between 0 and 4, signifying the degree to which they agree with said statement. The exact contents of these questions cannot be disclosed because of the reasons mentioned in section 2.1. Questions that are of the most interest to us are q_0 to q_3 and q_4 to q_7 which correspond to depressive and manic moods respectively. sum_quest_dep and sum_quest_man are just the sum aggregates of these question groups. They function as a kind of a smoothing filter. Each patient is sensitive to different questions in various degrees and the aggregates should mitigate this phenomenon. Examples of filled questionnaires can be seen in table 2.5.

The questionnaires, of course, introduce more subjectivity as opposed to labels assigned by a professional. However, they can still, to some extent, serve as something to relate our results to.

records	patients	avg. records per patient
18218	349	52.20

Table 2.4: Questionnaires information

q_0	...	q_4	...	q_8	q_9	sum_quest_dep	sum_quest_man
1		0		3	1	7	1
4		0		0	2	13	0
1		0		2	1	4	0
0		0		1	0	1	0
0		2		3	1	3	8

Table 2.5: In the table we can see 5 instances of filled out questionnaires by bipolar patients. Each questionnaire instance is identified by an anonymized patient number and a timestamp. Each question's answer (q_0 to q_9) is on integer scale from 0 to 4 (4 signifying the highest intensity). sum_quest_dep and sum_quest_man are sum aggregates of questions q_0 to q_3 and q_4 to q_7 respectively. There is also other information bound to each questionnaire instance, such as filling out time or mixed state flag, that were omitted.

Chapter 3

Cosinor analysis

3.1 Introduction

One of the prominent phenomenons in the human body is that of *circadian rhythmicity* [Cir]. This biological process controls the cycle of sleep and wakefulness. It also permeates plethora of other bodily functions (e.g. body temperature [RM92], immune regulation [BLH+97], insulin secretion [BRUC96]). Disturbances in circadian rhythms have been linked to various physical and mental illnesses. Depression [GK08], schizophrenia [WDM+12], neurodegenerative diseases [WGWF10], as well as bipolar disorder [GMA+10] all manifest in changes to patient's circadian rhythms. Some treatments, such as light therapy, have been developed to directly effect circadian rhythms. More specifically, it exploits the mechanism adjusting the internal clock by natural light. It is because of these findings that conducting further analysis in this field is of great importance.

In general, when we refer to a circadian rhythm, we mean any biological process that has a period of approximately 24 hours. *Cosinor analysis* [Cor14] is one of the methods that can provide us with the means to extract information about these rhythms. By fitting the cosine curve of known periodicity to a relevant signal, we can study its properties and then try to relate them to the studied data. Cosinor analysis has been a highly regarded method with applications in biomedicine and other areas. It does not require equidistant samples in the underlying time series. This fact was greatly exploited in the past as physiological data collection suffers from a number of difficulties, one of which is the equidistant samples assumption. However, modern advances in technology have mostly eliminated these obstacles. Actigraphy is one such example.

3.2 Definition

Throughout this chapter we will focus on single-component cosinor and population-mean cosinor exclusively. Meaning, we will fit one cosine curve with assumed 24-hour period to each signal in the population. Afterwards, we compute the population mean with confidence intervals, as derived in

[BAG+82]. There are also extensions to this method, such as multi-component cosinor, extended linear-nonlinear cosinor, and amplitude-modulated cosinor model [BAG+82], which we will not delve into.

In single-component cosinor analysis we fit cosine curve to one-dimensional signal using the well known least squares regression method. This task can be transformed into the linear case using the cosine addition identity. We must, of course, still assume a certain period, which is demonstrated below.

$$Y(x) = M + Acos\left(\frac{2\pi x}{\tau} + \phi\right) + e(x) \tag{3.1}$$

$$cos(\alpha + \beta) = cos(\alpha)cos(\beta) - sin(\alpha)sin(\beta) \tag{3.2}$$

$$cos\overbrace{\left(\frac{2\pi x}{\tau} + \phi\right)}^{\alpha+\beta} = cos\left(\frac{2\pi x}{\tau}\right)cos(\phi) - sin\left(\frac{2\pi x}{\tau}\right)sin(\phi) \tag{3.3}$$

$$Y(x) = M + a_1 b_1(x) + a_2 b_2(x) + e(x) \tag{3.4}$$

$$\boldsymbol{t} = (t_1, \ \dots \ , t_n) \tag{3.5}$$

$$RMSE(\boldsymbol{t}) = \sqrt{\frac{\sum_{x=1}^{n}(Y(x) - t_x)^2}{n}} \tag{3.6}$$

where:

$M,\ A,\ \phi$	... mesor, amplitude, acrophase
$Y(x)$	... regression model with x - the time of day - as the input
$cos(\alpha + \beta)$	... cosine addition identity
a_1	$= Acos(\phi)$
a_2	$= -Asin(\phi)$
$b_1(x)$	$= cos\left(\frac{2\pi x}{\tau}\right)$
$b_2(x)$	$= sin\left(\frac{2\pi x}{\tau}\right)$
$\boldsymbol{t}$	... time series of length n
$RMSE(\boldsymbol{t})$	... root mean square error representing model fit

Three parameters that describe the cosine curve will be of interest to us. Mesor (midline statistic of rhythm) is the rhythm-adjusted mean or, in other words, the shift in the y axis. Intuitively, mesor represents the standard level of activity throughout the day. Amplitude is half the height of the cosine wave. Higher values of amplitude mean that the overall activity throughout the day varied significantly. Both mesor and amplitude have the same unit of measurement as the underlying time series (acceleration averaged over the axes). On the other hand, acrophase is usually expressed in degrees or in time units. Specifically, acrophase is the point on the x axis at which the highest activity occurs. Below, in figures 3.1 and 3.2 is an example of cosine fitted to one-day and one-week signal respectively.

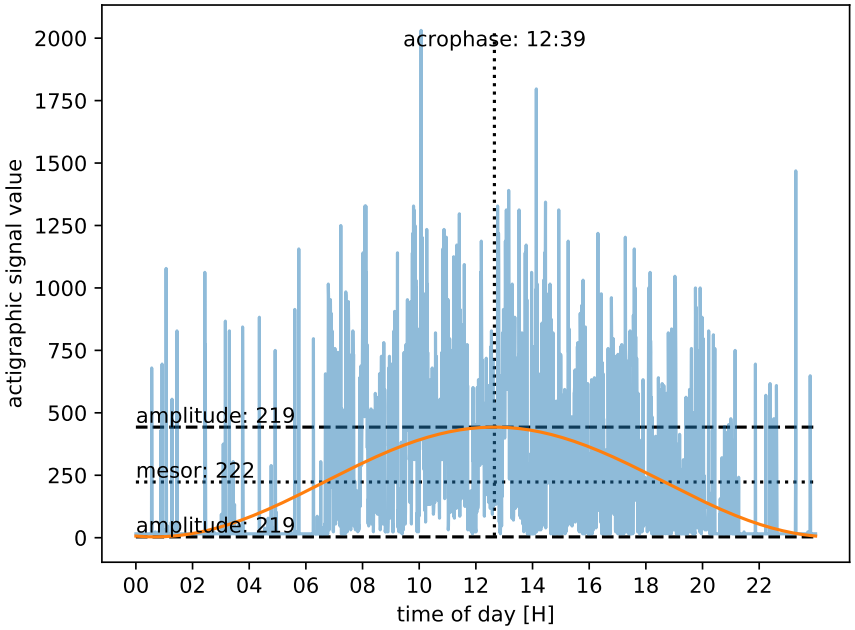

Figure 3.1: Cosine fitted to the actigraph of patient n. 350 from August 8th 2018. The signal uses original 30-second sampling period and contains no segments with missing values.

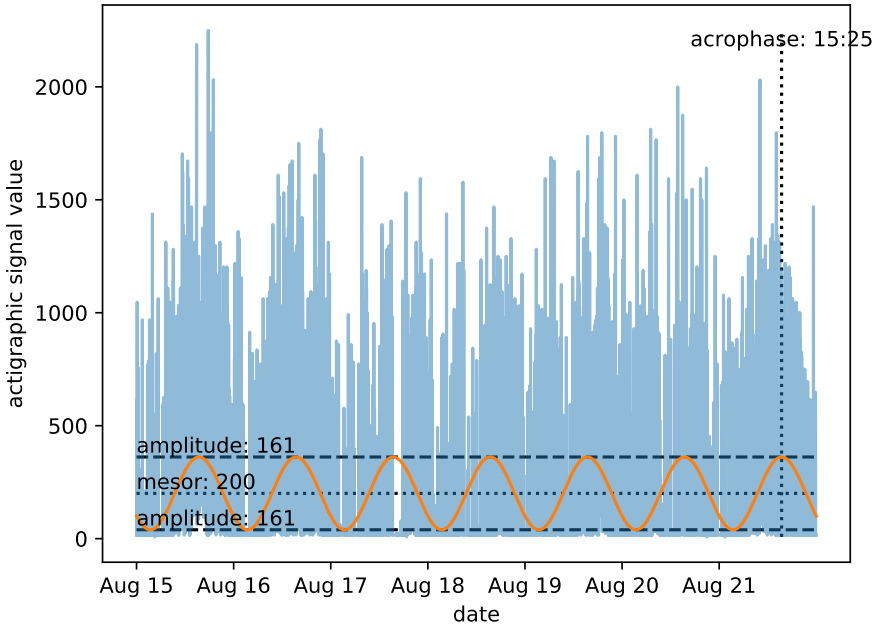

Figure 3.2: Cosine fitted to the actigraph of patient n. 350 from period from August 1st to August 8th 2018. The signal uses original 30-second sampling period and contains no segments with missing values.

3.3 Weekends

Before we analyze bipolar patient's actigraphic data, we will look at another use case of cosinor analysis. During this section only actigraphic data of 40 healthy individuals will be included, the reason being that patients with bipolar disorder diagnosis could potentially skew the results. In particular, we will study the effects of weekend days on the three cosinor parameters: mesor, amplitude, and acrophase. Below are the plots for each parameter separately.

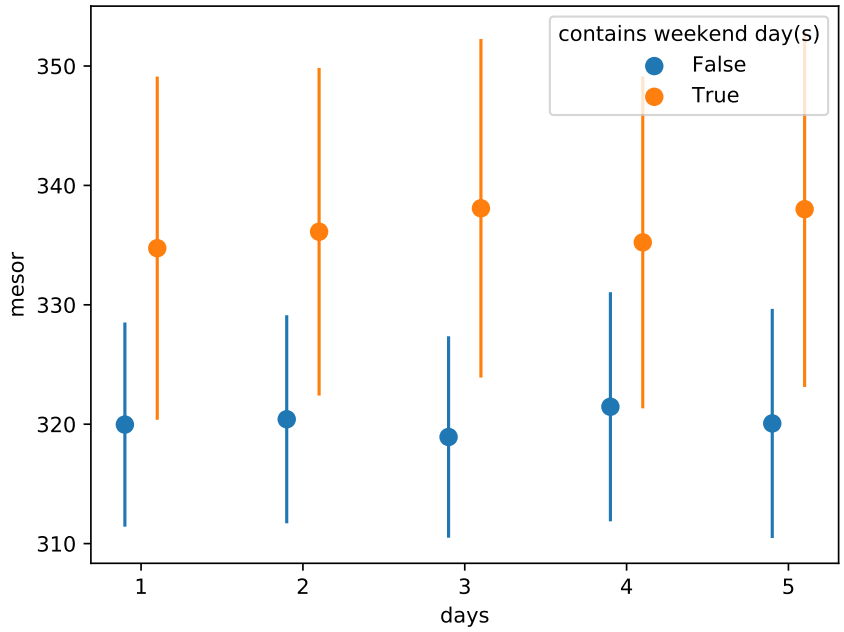

Figure 3.3: Mean mesor value is plotted alongisde 0.80 confidence interval, as derived in [BAG+82]. Populations of signals containing at least one weekend day have generally higher values of mesor, meaning mean level of activity is higher during weekends than on weekdays.

We can observe that both mesor and amplitude have higher values when weekend days(s) are included. This apparent distinction could be the result of dataset subjects' sedentary professions. On the other hand, this lifestyle may be balanced by engaging in sports or other higher energy activities on weekends (see figures 3.6 and 3.4). The increase in acrophase might be caused by waking up later on weekend days relative to Monday to Friday schedule (see figure 3.5). There is also the phenomenon of converging means noticeable both in amplitude and acrophase. It is because in 5 days the proportion of weekdays to weekend days can be much higher than say in 2 days and thus the influence of weekdays outweighs the influence of weekend days on the cosine fit. The generally wider confidence intervals in the weekend cases can

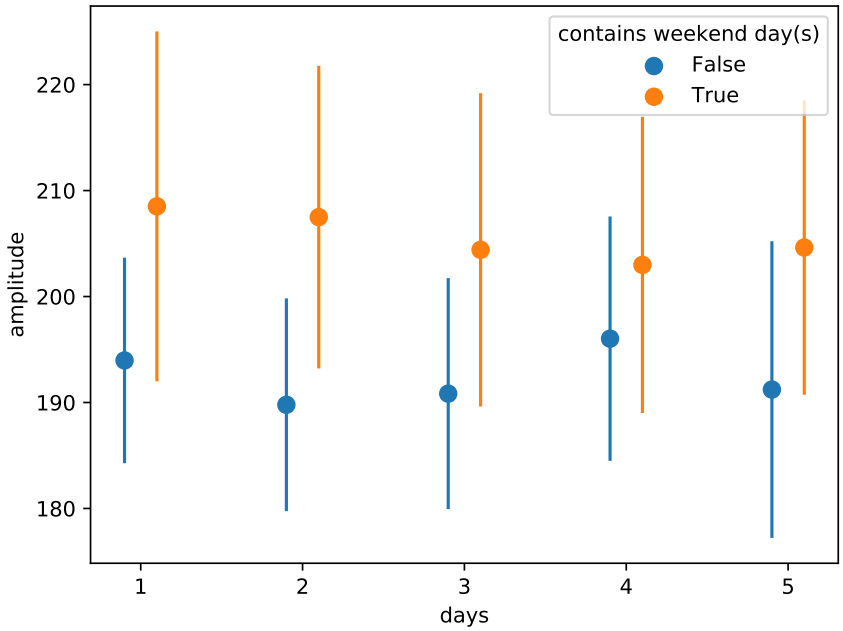

Figure 3.4: Mean amplitude value is plotted alongside 0.80 confidence interval, as derived in [BAG+82]. Populations of signals containing at least one weekend day have generally higher values of amplitude, meaning variance in level of activity is higher during weekends than on weekdays.

also be explained. People might be spending their weekends by doing plethora of activities varying across personality types, whereas the weekday routine might be more unified among the population in our dataset. In tables 3.1 and 3.2 are the relevant statistical tests for cosinor parameters when comparing between multiple populations.

days	F-value	0.50	0.75	0.90	0.95	0.99
1	2.17	0.46	1.36	2.84	4.08	7.31
2	1.30	0.46	1.36	2.84	4.08	7.31
3	1.61	0.46	1.36	2.84	4.08	7.31
4	0.85	0.46	1.36	2.84	4.08	7.31
5	2.06	0.46	1.37	2.85	4.11	7.37

Table 3.1: The tested hypothesis: Mesor means across both populations (i.e. with and without weekend day(s)) are equal [BAG+82]. In the table are $F-$ *values* for different confidence levels.

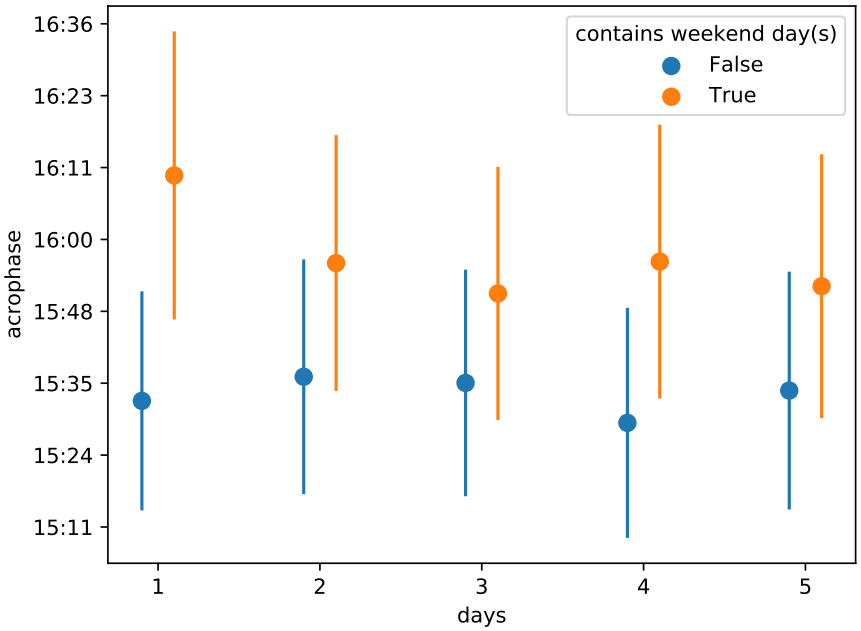

Figure 3.5: Mean acrophase value is plotted alongside 0.80 confidence interval, as derived in [BAG+82]. Populations of signals containing at least one weekend day have generally higher values of amplitude, meaning the peak activity is reached later in the day during weekends than on weekdays.

days	F-value	0.50	0.75	0.90	0.95	0.99
1	2.01	0.71	1.44	2.45	3.25	5.23
2	0.99	0.71	1.44	2.45	3.25	5.23
3	0.31	0.71	1.44	2.45	3.25	5.23
4	0.26	0.71	1.44	2.45	3.25	5.23
5	1.15	0.71	1.44	2.47	3.28	5.29

Table 3.2: The tested hypothesis: Amplitude means and acrophase means across both populations (i.e. with and without weekend day(s)) are equal [BAG+82]. In the table are $F - values$ for different confidence levels. Only approximate tests for separate comparison of amplitude and acrophase means are known and are not included here.

3.4 Episode separation

The same framework used in section 3.3 will be applied to annotated data of bipolar patients. This time we will try to distinguish between the three symptomatic episodes: depression, remission, and mania.

After inspecting figures 3.6, 3.7 and 3.8 we can conclude that the results

correspond to general characteristics of bipolar disease. Patients' level of activity during depressive episodes is lower than in normal state (see figure 3.6), whereas mania causes higher level of activity. These changes manifest more profoundly when comparing depression with remission than when comparing mania with remission. Quite an interesting finding is that the variance of daily activity is higher during remission than during depression or mania (see figure 3.7). Significant variation in acrophase amongst the three episodes is perceivable as well (see figure 3.8). The shift forward in peak daily activity in depressive patients is in accordance with reported symptoms, namely later wake-up time and insomnia [GK08].

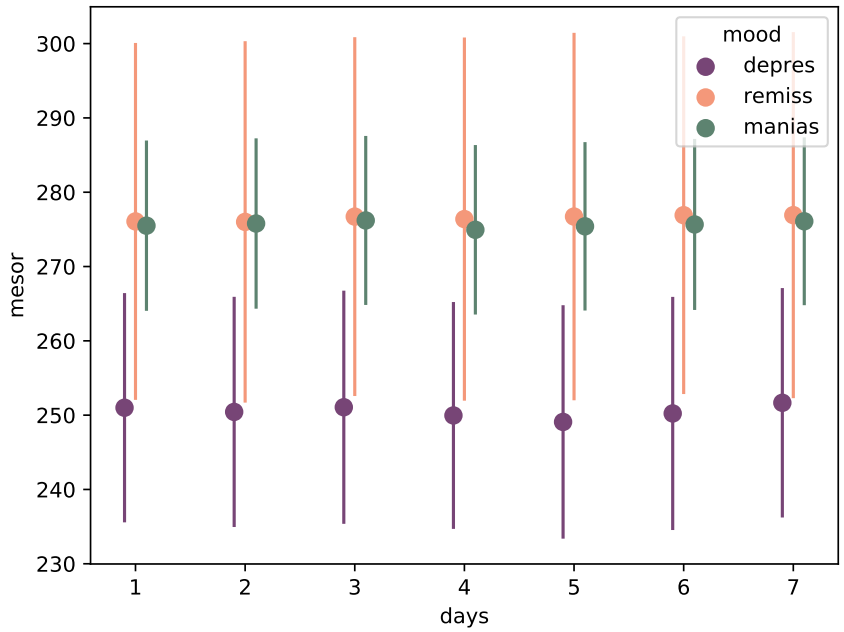

Figure 3.6: Mean mesor value is plotted alongisde 0.80 confidence interval, as derived in [BAG+82]. Population of signals from depressive patients have considerably lower values of mesor. Mania and remission is has a large overlap between them. However mania has the higher mean value.

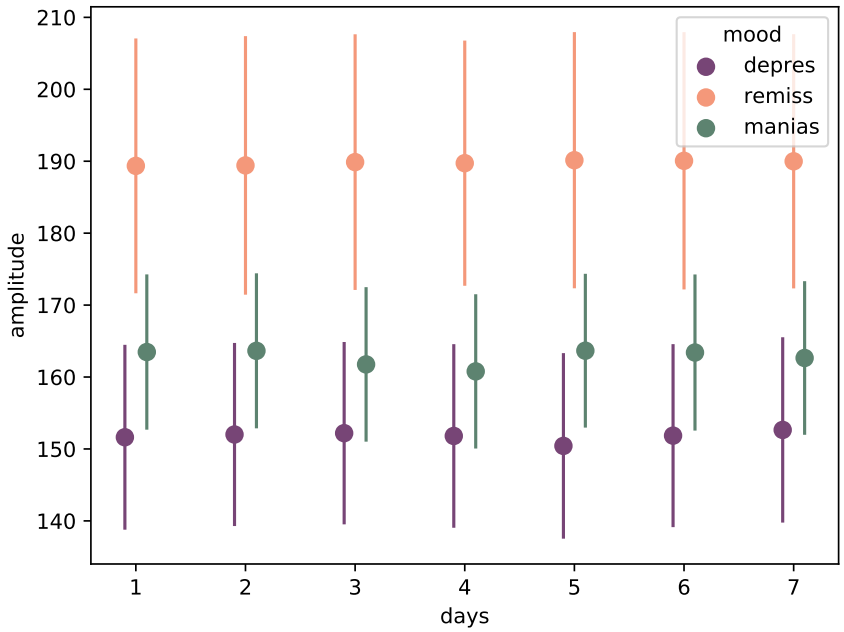

Figure 3.7: Mean amplitude value is plotted alongside 0.80 confidence interval, as derived in [BAG+82]. Population of signals from depressive as well as manic patients have lower values of amplitude then during remission.

days	F-value	0.50	0.75	0.90	0.95	0.99
1	1.45	0.70	1.41	2.37	3.11	4.87
2	1.51	0.70	1.41	2.37	3.11	4.87
3	1.47	0.70	1.41	2.37	3.11	4.87
4	1.61	0.70	1.41	2.37	3.11	4.87
5	1.67	0.70	1.41	2.37	3.11	4.87
6	1.56	0.70	1.41	2.37	3.11	4.87
7	1.45	0.70	1.41	2.37	3.11	4.87

Table 3.3: The tested hypothesis: Mesor means across all populations (i.e. depression, mania, and remission) are equal [BAG+82]. In the table are $F-$ *values* for different confidence levels.

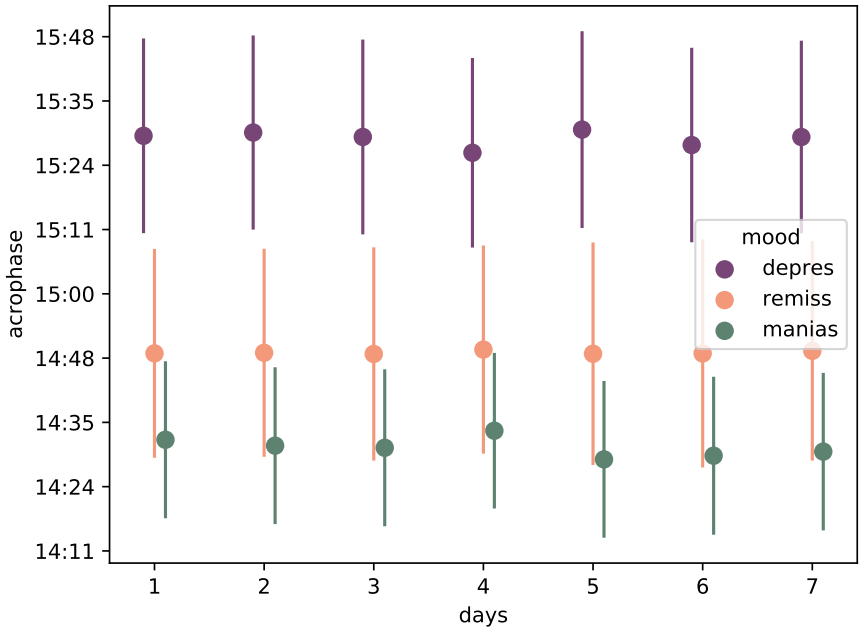

Figure 3.8: Mean acrophase value is plotted alongside 0.80 confidence interval, as derived in [BAG+82]. Population of signals from depressive patients have the highest value values of acrophase, meaning the peak activity is reached later in the day relative to mania and remission.

days	F-value	0.50	0.75	0.90	0.95	0.99
1	3.90	0.84	1.36	1.98	2.43	3.44
2	4.02	0.84	1.36	1.98	2.43	3.44
3	4.08	0.84	1.36	1.98	2.43	3.44
4	3.80	0.84	1.36	1.98	2.43	3.44
5	4.38	0.84	1.36	1.98	2.43	3.44
6	4.01	0.84	1.36	1.98	2.43	3.44
7	4.04	0.84	1.36	1.98	2.43	3.44

Table 3.4: The tested hypothesis: Amplitude means and acrophase means across all populations (i.e. depression, mania, and remission) are equal [BAG+82]. In the table are $F - values$ for different confidence levels. Only approximate tests for separate comparison of amplitude and acrophase means are known and are not included here.

Chapter 4

Permutation entropy

4.1 Introduction

When we are to capture complex systems, as is the human body, we need measures that provide high dimension reduction while still allowing for such complexities. There is a long history of applying various non-linear analytical measures when working with physiological data. Apart from *entropy*, both *fractal dimension* and *Lyapunov exponent* were successfully used in past [Kan98]. When it comes to entropy, a variety of types have been introduced: *approximation entropy*, *sample entropy*, *fuzzy entropy* [CZYW09]. As with many other similar measures, each has its own advantages and drawbacks. In this chapter we will focus specifically on *permutation entropy* (*PE*) and its modifications. Then we will observe how it relates to the actigraphic data.

4.2 Definition

PE is a complexity measure proposed in [BP02]. Its main advantages are conceptual simplicity, fast computation, robustness, and invariance to certain types of noise. Let us define it then:

$$\boldsymbol{t} = (t_1, \ \dots \ , \ t_n) \tag{4.1}$$

$$\boldsymbol{s}_i = (t_i, \ \dots \ , \ t_{(i-1)+o}) \tag{4.2}$$

$$S = \{\boldsymbol{s}_1, \ \dots \ , \ \boldsymbol{s}_{(n+1)-o}\} \tag{4.3}$$

$$p(\boldsymbol{s}_i) = (x_1, \ \dots \ , \ x_o) = \boldsymbol{x}; \ t_{x_1} \leq \ \dots \ \leq t_{x_o} \tag{4.4}$$

$$f_{PE_S}(\boldsymbol{x}) = \frac{|\{p(\boldsymbol{s}_i) = \boldsymbol{x} \mid \boldsymbol{s}_i \in S\}|}{|S|} \tag{4.5}$$

$$PE_S(\boldsymbol{t}) = -\sum_{\boldsymbol{x}} f_S(\boldsymbol{x}) log(f_S(\boldsymbol{x})) \tag{4.6}$$

$$NPE_S(\boldsymbol{t}) = \frac{PE_S(\boldsymbol{t})}{log(o!)} \tag{4.7}$$

where:

$\boldsymbol{t}$	... time series of length n
$\boldsymbol{s}_i$	... ith sub-string of time series $\boldsymbol{t}$
S	... all o-length sub-strings of time series $\boldsymbol{t}$
$p(\boldsymbol{s}_i)$	... permutation of $\boldsymbol{s}_i$ of samples in non-decreasing order
$f_{PE_S}(\boldsymbol{x})$	... frequency of permutation occurrence in S
$PE_S(\boldsymbol{t})$	... PE
$NPE_S(\boldsymbol{t})$	... normalized PE

Firstly, there is the order o in the definition that we must choose beforehand. Typical values for this parameter range from 3 to 7. The optimal value, of course, depends heavily on the application. However, there is one restriction that must be always addressed. Because there are $o!$ possible distinct permutations we should choose $n \approx o!$ at least, so that there is a chance that each permutation occurs.

4.3 Modifications

From the definition above, we can see that PE is only interested in the order of values in each sub-string, not in the absolute values. So both (1.0, 0.98, 0.99) and (1.0, 0.0, 0.5) sub-strings will map to the same permutation $p((1.0,\ 0.98,\ 0.99)) = p((1.0,\ 0.0,\ 0.5)) = (1,\ 0,\ 2)$. The inability to convey scale can result in a serious under-performance in some applications. All three above-mentioned entropies (*approximation entropy*, *sample entropy*, and *fuzzy entropy*) are sensitive to these nuances. Another option when base PE does not suffice in this regard is *fine-grained permutation entropy* (*fPE*) [XFY09]. In this modification we attach to the permutation term q which is computed in the following way:

$$q(\boldsymbol{s}_i) = \left\lfloor \frac{max(D(\boldsymbol{s}_i))}{SD(\boldsymbol{s}_i)}\ \alpha \right\rfloor \tag{4.8}$$

$$p_{fine-grained}(\boldsymbol{s}_i) = (x_1,\ \ldots\ ,\ x_o,\ q(\boldsymbol{s}_i)) = \boldsymbol{x};\ t_{x_1} \leq\ \ldots\ \leq t_{x_o} \tag{4.9}$$

where:

$D(\boldsymbol{s}_i)$	... all neighbouring differences in $\boldsymbol{s}_i$
$SD(\boldsymbol{s}_i)$	... the standard deviation of these differences
α	... the regulation factor
$p_{fine-grained}(\boldsymbol{s}_i)$	... permutation of $\boldsymbol{s}_i$ used in *fPE*

In our case, absolute values might be of little interest. Firstly, one of the main reported characteristics of the opposite symptomatic episodes is the change in physical activity. Manic episodes cause patients to behave impulsively and unusually. Depressed patients feel lethargic and are less active overall. Not considering absolute differences but only relative differences might prove crucial to overcoming the complexities of discriminating between the

episodes. Secondly, our actigraphic data's resolution is somewhat limited (see 2.2). In this instance, this means that the addition of the term q in *fPE* will not vary much. This whole statement is not to suggest that absolute values do not matter when separating the episodes (see chapter 3). Rather the goal here is to discover other characteristics that do not directly concern absolute differences between values.

The original *PE* was proposed on the assumption that time series' values are continuous. The same values in sub-strings are dealt with by merely sorting them in the order of their occurrence. If the underlying probability distribution the values in $\boldsymbol{t}$ are drawn from is indeed continuous or the resolution of the values is reasonably high, same values in sub-strings should be rare. Bandt and Pompe [BP02] considered breaking ties by introducing uniform noise into the original time series with amplitude lower than the smallest difference between values in the whole time series. In our case repeating values are not as much of a coincidence. Rather they signify the same level of activity. By following the advice above, we would lose some information about the patient and artificially increase total entropy. Another option is to compute *PE* without disturbing the original time series and consequently equating $p((1.0,\ 2.0,\ 3.0))$ to $p((1.0,\ 1.0,\ 1.0))$.

Modified permutation entropy (*mPE*) is a modification to *PE* proposed in [BQMS12] which does not neglect equal values. Instead, when there are multiple occurrences of a given value in a sub-string, the lowest index amongst them is repeated for each of them. Formally:

$$p(\boldsymbol{s}_i) = (x_1,\ \ldots\ ,\ x_o) \tag{4.10}$$

$$p_{mPE}(\boldsymbol{s}_i) = (x_1^*,\ \ldots\ ,\ x_o^*) = \boldsymbol{x}* \tag{4.11}$$

$$EQ_{\boldsymbol{s}_i}(x_m) = \{x_n \mid t_{x_n} \in \boldsymbol{s}_i \wedge t_{x_m} = t_{x_n}\} \tag{4.12}$$

$$x_m^* = \begin{cases} x_m & |EQ_{\boldsymbol{s}_i}(x_m)| = 1 \\ min(EQ_{\boldsymbol{s}_i}(x_m)) & else \end{cases} \tag{4.13}$$

$$f_{mPE_S}(\boldsymbol{x}^*) = \frac{|\{p_{mPE}(\boldsymbol{s}_i) = \boldsymbol{x}^* \mid \boldsymbol{s}_i \in S\}|}{|S|} \tag{4.14}$$

$$mPE_S(\boldsymbol{t}) = -\sum_{\boldsymbol{x}^*} f_{mPE_S}(\boldsymbol{x}^*)\ log(f_{mPE_S}(\boldsymbol{x}^*)) \tag{4.15}$$

$$NmPE_S(\boldsymbol{t}) = \frac{mPE_S(\boldsymbol{t})}{total\_permutations_o} \tag{4.16}$$

$$\tag{4.17}$$

where:

$p(\boldsymbol{s}_i)$	... base *PE* permutation is created
$p_{mPE}(\boldsymbol{s}_i)$	... x_m^* is substituted for x_m to create *mPE* permutation
$EQ_{\boldsymbol{s}_i}(x_m)$	... equivalence group inside $\boldsymbol{s}_i$
$total\_permutations_o$	... computed recursively for each o

o	2	3	4	5	6	7
PE permutations ($o!$)	2	6	24	120	720	5 040
mPE permutations	3	13	73	501	4 051	37 633
o^o	4	27	256	3 125	46 656	823 543

Table 4.1: The total possible permutations in PE and mPE are computed in a different manner. PE has the total number of possible permutation equal to $o!$ for a given order o. On the other hand, for the computation of the exact number mPE requires a recursive procedure [BQMS12]. However, the value always falls between the lower bound given by the original PE and the upper bound given by o^o. This upper bound holds because it expresses the total number of permutations with repetition and mPE includes only a subset of these.

4.4 Parameters

As the optimal parameters are specific to a given task, we need to choose the right ones here as well. Apart from the order o, we will also vary the number of days and resampling period of the actigraphic signal. For this task we will use the annotated data. We will search the parameter space using basic grid search method with the goal being to separate manic episodes, depressive episodes, and periods of remission. Our criterion will be the one-way analysis of variance ($ANOVA$). The stated hypothesis goes as follows: the groups in the test have all the same population mean. We will try to maximize $F - value$ computed from the test.

Amongst the three versions, PE, PE with tie-breaking by the addition of uniform noise, and mPE, the last has the highest $F - value$ and thus can be ruled as the best at separating the episodes. Or rather, at least one of the episodes has entropy values further apart from the others.

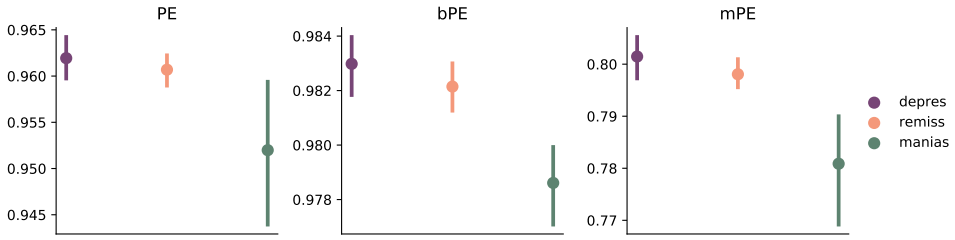

Figure 4.1: Here is a comparison of entropy values amongst the three modifications of permutation entropy. Mean entropy value is plotted alongside its 0.95 confidence interval computed using the bootstrap method. The three modifications' plots are ordered by the highest $F - value$ for their respective best parameter configurations (PE ranking lowest).

The top configurations for mPE can be seen in table 4.2. Probability density function estimation for the three episodes can be seen in figure 4.2.

Now, we can observe how mPE behaves when we vary one of the parameters

days	resample mode	o	F	p
2	00:05:00	5	13.79	6.52×10^{-6}
7	00:05:00	5	13.64	7.27×10^{-6}
1	00:05:00	4	13.33	9.20×10^{-6}
5	00:05:00	5	13.22	9.99×10^{-6}
3	00:05:00	5	13.12	1.08×10^{-5}
1	00:05:00	5	13.07	1.12×10^{-5}
14	00:05:00	5	11.55	3.64×10^{-5}
2	00:05:00	4	11.46	3.92×10^{-5}
7	00:05:00	4	10.57	7.94×10^{-5}
3	00:05:00	4	10.11	1.15×10^{-4}

Table 4.2: One-way ANOVA (analysis of variance) is here used to analyze entropy values across the three populations of signals: episodes of depression, mania and remission.

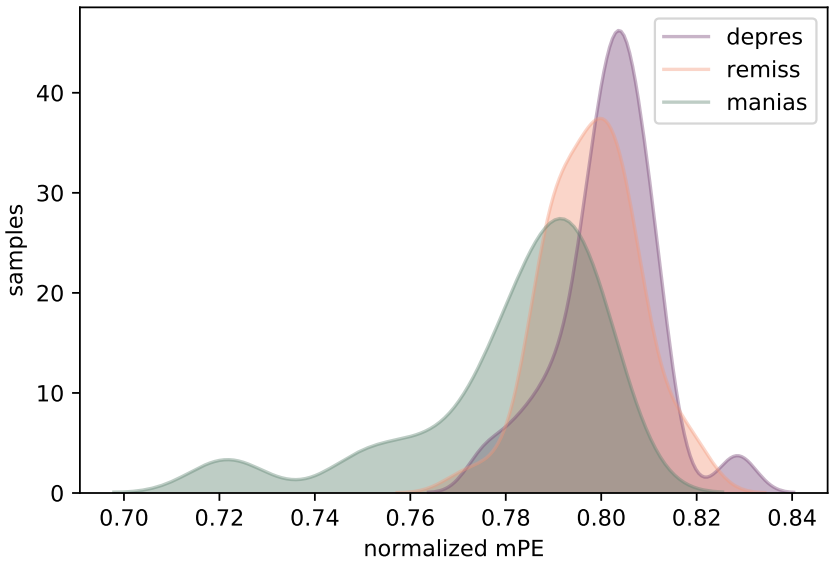

Figure 4.2: Here is an estimated density function for the best configuration according to one-way ANOVA $F - value$.

while fixing the other two and gather some knowledge about the data in the process. Increasing the number of days of the actigraphic signal increases entropy since there are simply more values in the window. So the probability of occurrence of each permutation is higher.

As in studies conducted in the past [ZZRP12], choosing the right entropy order can provide the capability to discriminate between episodes, whereas undershooting the target can make each group be perceived identical. Figure 4.4 demonstrates this exact behavior. For lower orders we get overlapping

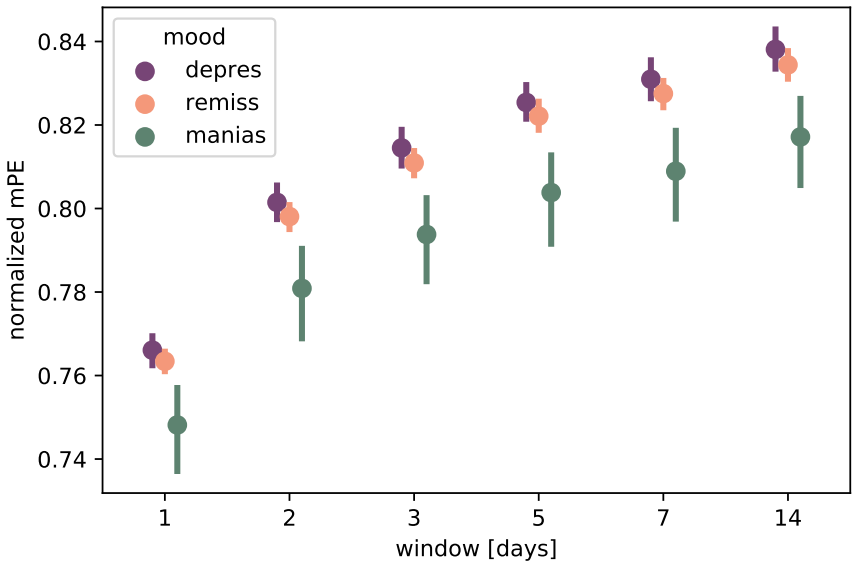

Figure 4.3: Varying the number of days in *mPE* computation

values for different episodes more often. Orders from 6 up could capture changes at a larger scale. However, we must still mind the restriction given by the total number of possible permutations which for $o = 6$ requires time series of length $n \approx 4051$ (see table 4.1). To demonstrate this, two days of actigraphic signal resampled to 5 minutes have only a length of 576.

The most striking evolution can be seen when varying the resampling period. The original signal with a sampling period of 30 seconds shows the most chaotic (i.e. highest entropy) behavior in patients during manic episodes. Yet increasing resampling period above this level causes manic episodes to appear less and less chaotic relative to depression and remission. How it relates to bipolar disorder directly is for medical researches to decide. One aspect that might explain this phenomenon is that of different scales. Mania might display a higher level of chaos in minute-to-minute activity but may look more regular on a larger scale.

As a validation step, *mPE* was computed using the best configuration (i.e. 2-day window, 5-minute resampling period, entropy order 5) for actigraphs accompanied by questionnaires this time. However, this data differs significantly from the annotated actigraphs in its nature. The annotated actigraphs were assigned categorical labels (i.e. episodes) by a medical professional. Questionnaires, as stated in section 2.3, contain questions with patient-filled numerical answers on an integer scale. Due to this discrepancy, we will observe whether answers to depression and mania related questions are positively/negatively correlated to *mPE* as our previous revelations would suggest. Also, we must address the manner in which questionnaires correspond to preceding periods in the actigraph. When filling out the questionnaire, patients are to reflect on the preceding two weeks. So to better reflect this, we will use the parameter

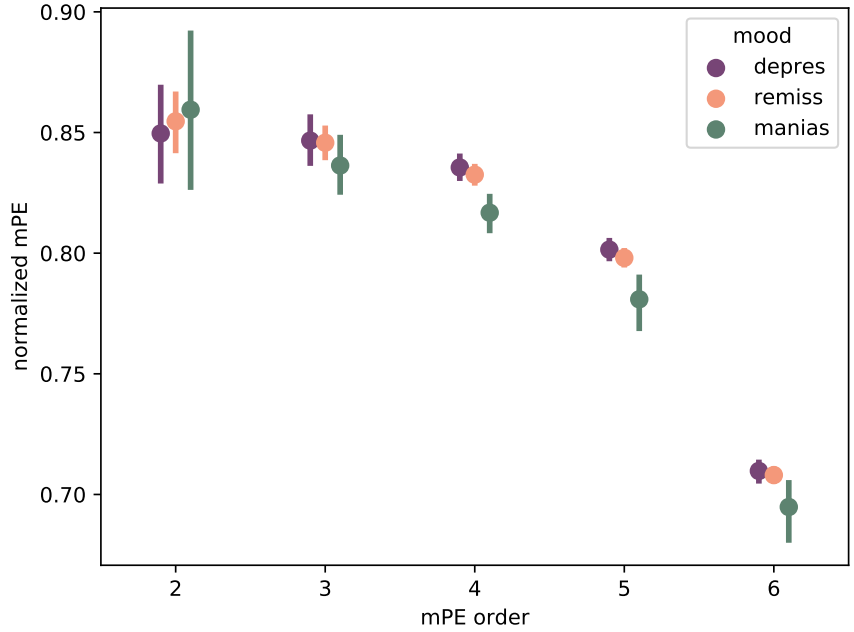

Figure 4.4: Varying the entropy order in *mPE* computation

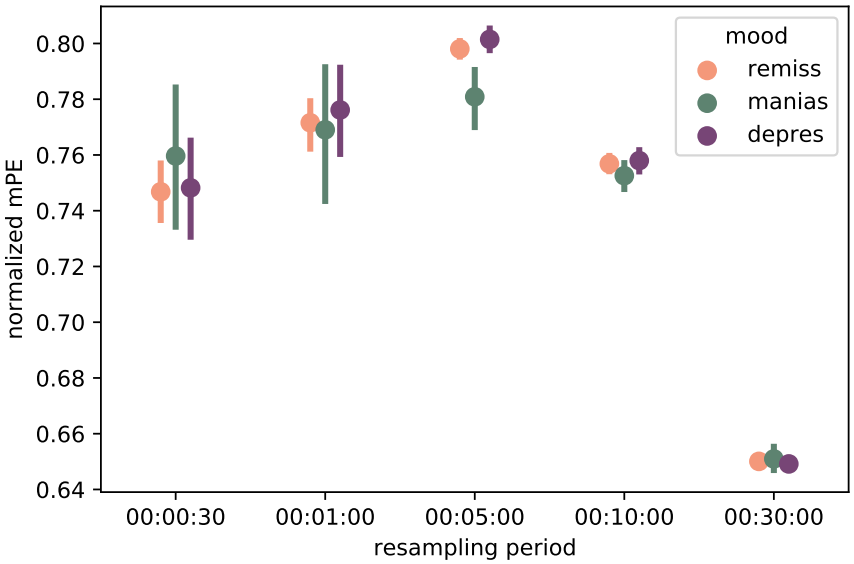

Figure 4.5: Varying the resampling period in *mPE* computation

configuration of 7-day window, 5 minute resampling period, and entropy order 5 instead of the one with the highest $F - value$. This is more akin to the kind of time scale that the questionnaires allow for while still being among

the top 10 configurations (see table 4.2).

Figures 4.6 and 4.7 show that the majority of patient's questionnaires are correlated as we expected.

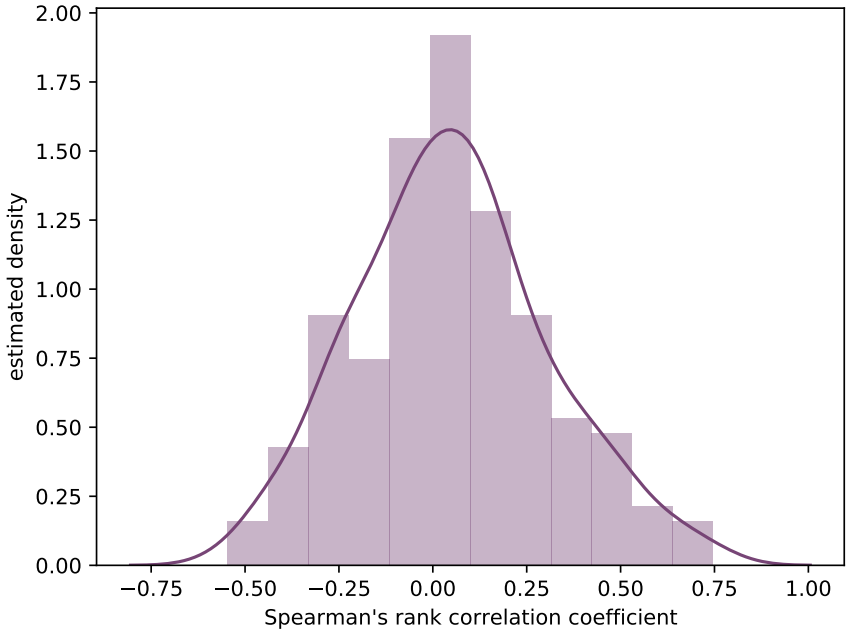

Figure 4.6: Histogram of correlation coefficients for sum_quest_dep values (see section 2.3) with normalized mPE

Figures 4.8, 4.9 and 4.10 depict correlation matrices for some of the patients with relatively high Spearman's rank correlation coefficients.

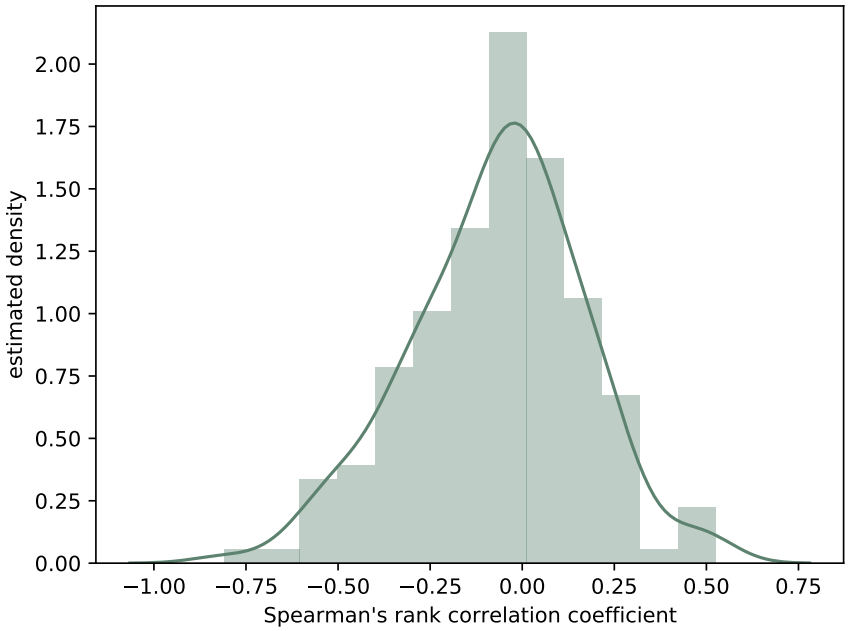

Figure 4.7: Histogram of correlation coefficients for sum_quest_man values (see section 2.3) with normalized *mPE*

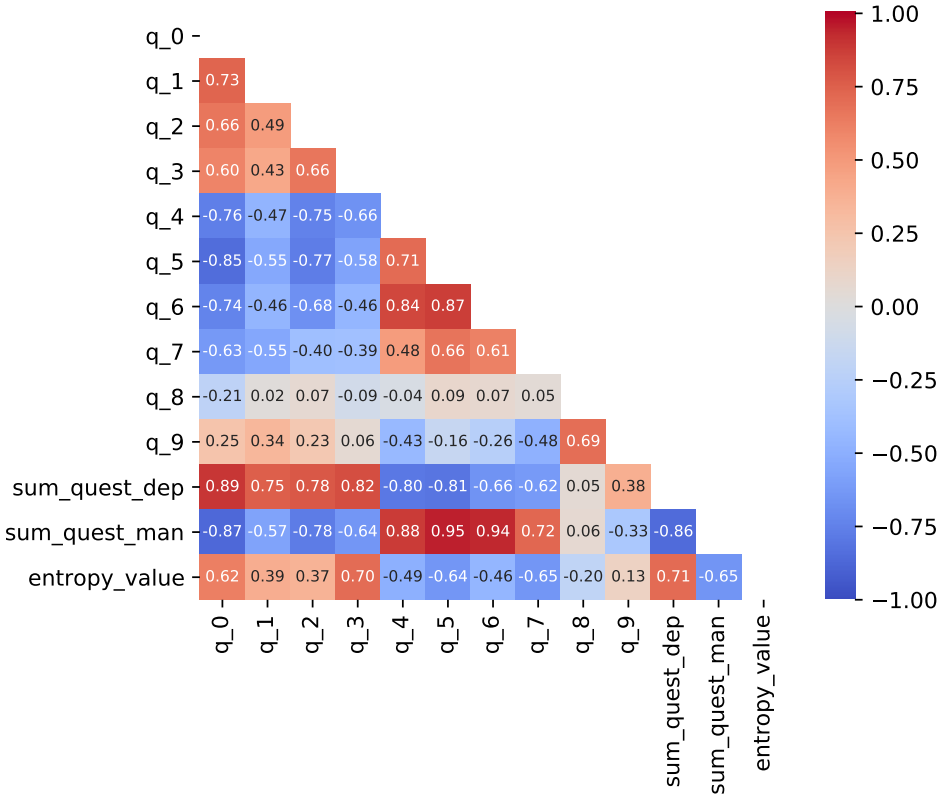

Figure 4.8: Correlation matrix for patient n. 961

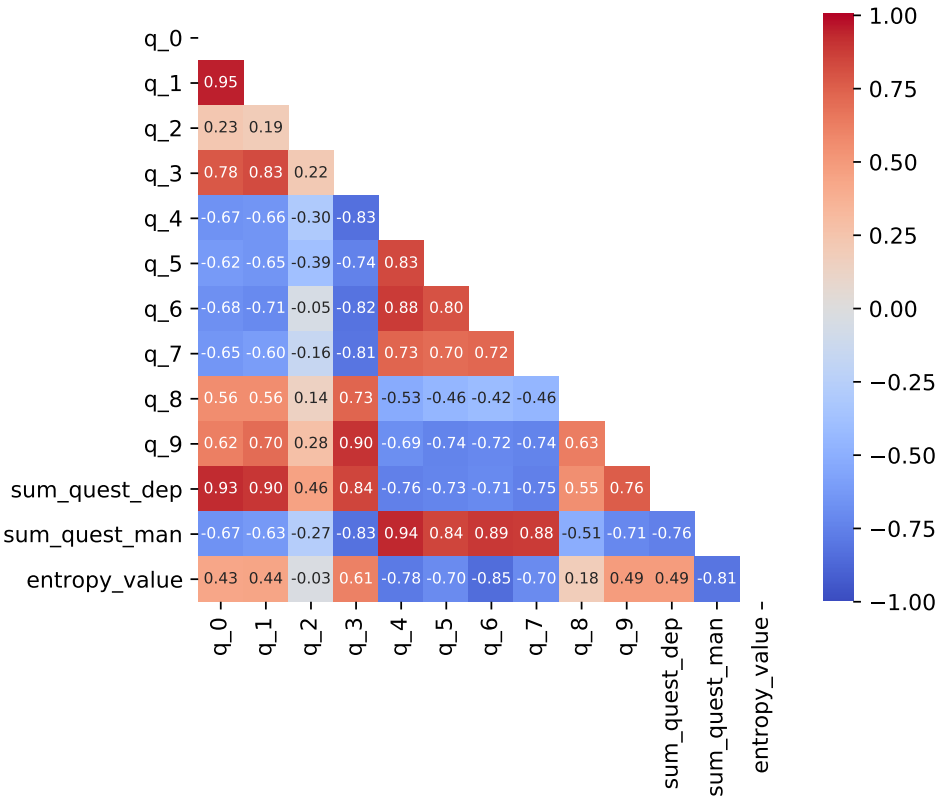

Figure 4.9: Correlation matrix for patient n. 1024

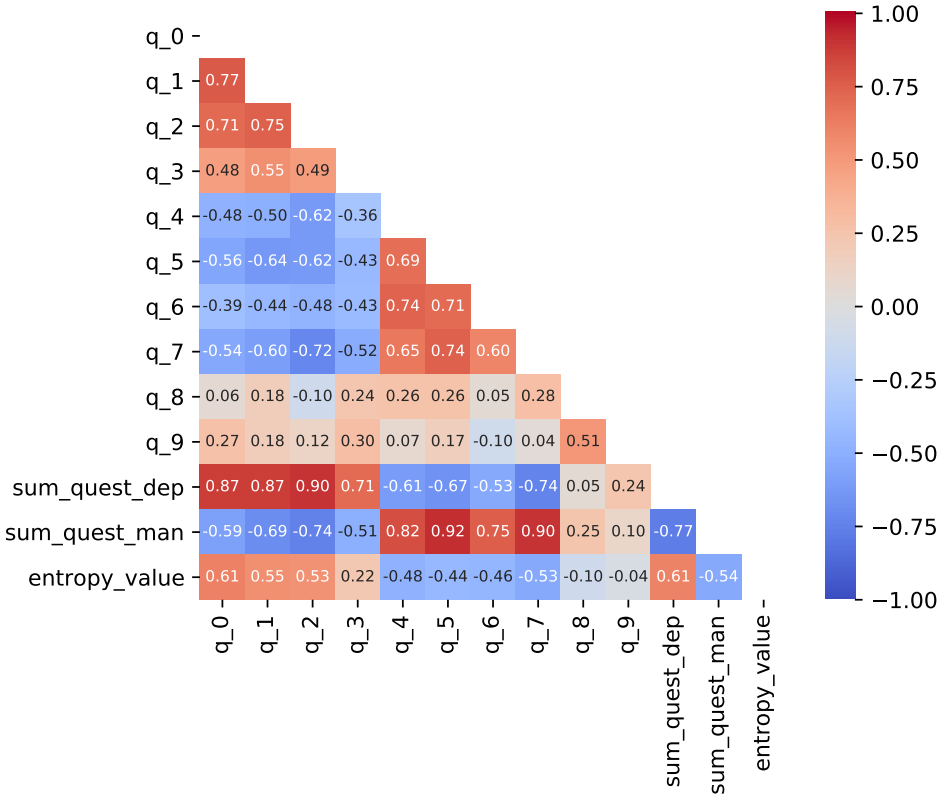

Figure 4.10: Correlation matrix for patient n. 1252

4.5 Missing data

In the final section on permutation entropy we will observe the influence of missing data. In figure 4.11 are depicted the two most used techniques when dealing with missing data imputation. The first one is linear interpolation which proves to be rather inadequate. As the share of missing data points increases the value of *mPE* decreases in an approximately linear fashion. This effect could be counter-balanced by introducing a scaling factor. The more suitable solution that was ultimately used throughout this chapter is to simply skip the areas with missing data. The curve is still monotonically decreasing but at a much slower rate than when interpolating.

Below, in figures 4.12 and 4.13 are the cumulative histograms of missing values share per day and week respectively. Shares higher than 0.4 are generally unlikely, meaning the decrease in *mPE* is small and thus scaling can be safely ignored.

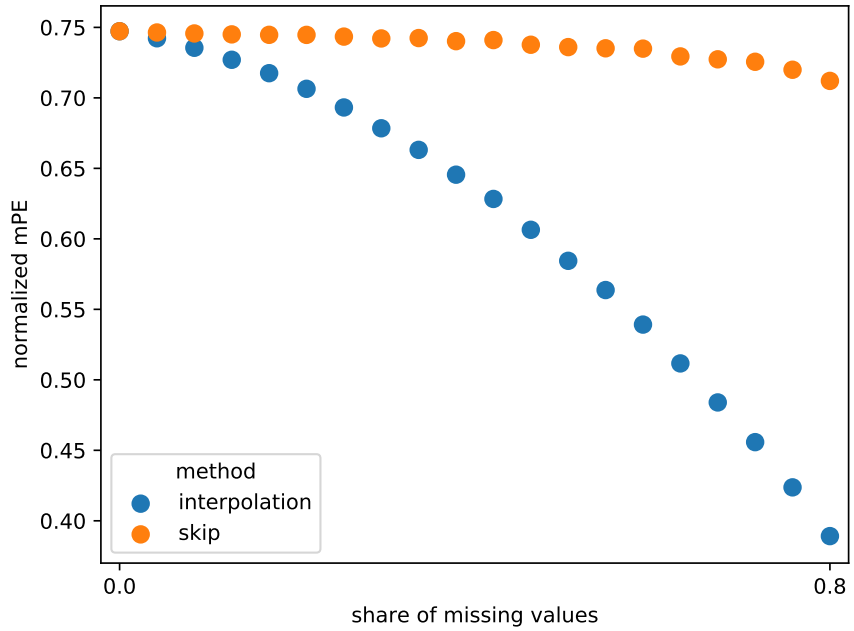

Figure 4.11: Here is a depiction of the influence of missing data on normalized *mPE*. One-day (January 1st 2019) actigraphic signal from patient n. 335 was arbitrarily chosen for this experiment. For each method and share of missing values, there were 100 trials conducted. In each trial the samples to be left-out were randomly picked. The 0.95 confidence interval was estimated by the bootstrap method. However, its amplitude is lower than can be observed in a picture of this size, so it can be neglected for the purposes here.

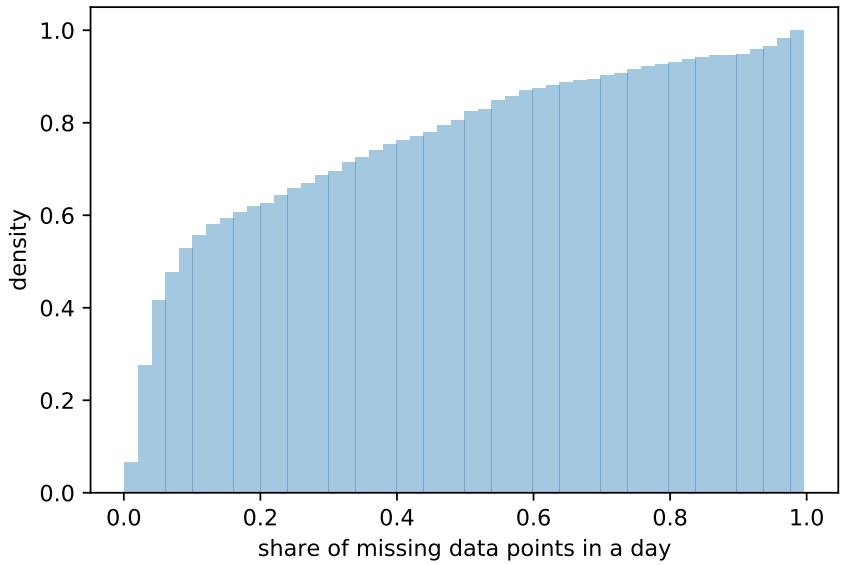

Figure 4.12: Here is a cumulative histogram of shares of missing data in a day. It was computed from a subset of 15 patients. Each one of them was observed for more than a year. 8048 days in total were used to compute this histogram.

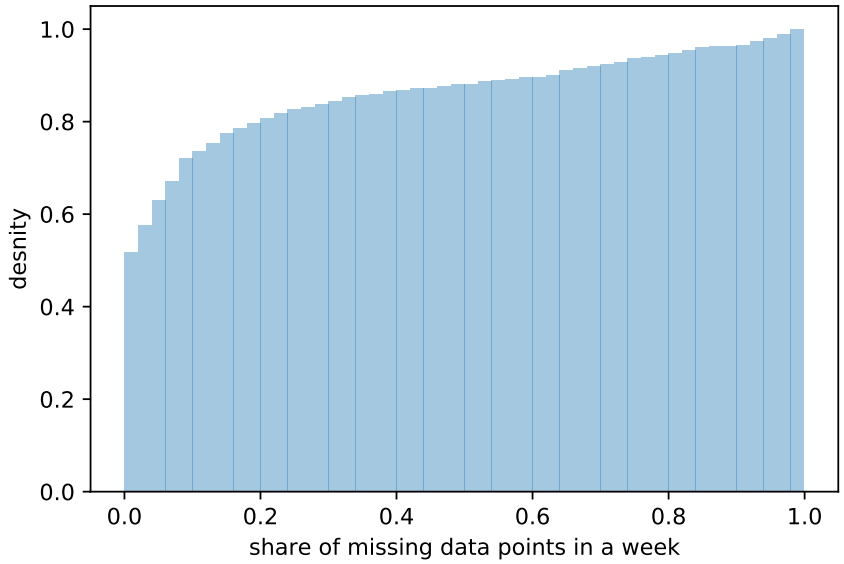

Figure 4.13: Here is a cumulative histogram of shares of missing data in a week. It was computed from a subset of 15 patients. Each one of them was observed for more than a year. 1192 weeks in total were used to compute this histogram.

Chapter 5
Classifier

5.1 Introduction

The task of classifying physiological signals using machine learning techniques is of great importance. It would aid medical professionals in monitoring patients without analyzing the indicators in person. Even classifiers achieving relatively low accuracies could improve the diagnostic routine immensely. The role of machine learning still may not supersede medical professionals' expertise entirely. However, automating even parts of the diagnostic process might improve the overall state of healthcare systems [WS18]. The exclusion of cases with a high probability of testing negative or prioritizing cases with a high probability of testing positive could both prove to be a helpful contribution of machine learning applications.

Support-vector machine (*SVM*) is a widely used model with a long history of successful applications. Its main advantages are effectiveness in high dimensional spaces, the option in the choice of a suitable kernel, the flexibility in the degree of regularization, the dependence on a relatively small subset of data points.

5.2 Data preprocessing

Only the annotated data was used for the purposes of this chapter. The goal here is to learn a model that will, when presenting it with an actigraphic signal, recognize which of the three symptomatic episodes was the patient experiencing. For each patient the annotated segments were split into single days. Subsequently, *mPE*, mesor, amplitude, and acrophase were computed for each day. The third-best parameter configuration (see section 4.4) was used in the case of *mPE*, the reason being two-fold. Firstly, *SVMs* require large quantities of data for the training process. By dividing the signals into single days, we acquire the largest total number of samples. And secondly, results achieved in chapters 3 and 4 suggest that one-day long signals are usually enough to discriminate between the episodes. To train the *SVM* faster and, at the same time, prevent numerical errors or even underflow/overflow, the computed values were scaled to zero mean and unit variance.

The dataset was split into training and test dataset in 9 to 1 ratio so that no overlap in patients between both datasets exists. Before proceeding to the training phase one major issue must be addressed. As discussed in chapters 2 and 1, the frequency of remission periods is considerably higher than the frequency of depressive episodes. Also, depressions have a generally higher occurrence and last longer than manic episodes. This is true for our data as well. The proportion of remission, depression, and mania is approximately 80 to 15 to 5 in this order. When an *SVM* is trained, while neglecting this fact, we often overfit the most frequent category. Many methods of tackling an imbalanced dataset have been developed. Some of those were applied in this task as well. There are two main categories: oversampling and undersampling. Oversampling is a group of techniques where we create new or duplicate existing samples from the less frequent categories. Undersampling, on the other hand, means that a fraction of the more frequent category is ignored. Both oversampling and undersampling have many modifications (e.g. *SMOTE* [CBHK02], *ADASYN* [HBGL08], clustering [ZZW10]). In this case a simple random undersampling method was used for the training dataset. The testing dataset was not manipulated to preserve the original probability distribution of the episodes and thus reflect more accurately the real world.

5.3 Support vector machine

SVM was trained with grid search combined with 5-fold cross-validation procedure. Linear, polynomial, and radial basis function kernels and the relevant parameters were tried as a part of grid search. The best configuration with the highest cross-validation score was radial basis function with $C = 100.0$ and $\gamma = 0.1$. Below, in table 5.1, is the classification report.

	precision	recall	f1-score
depression	0.18	0.63	0.28
mania	0.08	0.62	0.14
remission	0.92	0.45	0.60
accuracy			0.47
macro average	0.39	0.56	0.34
weighted average	0.82	0.47	0.5

Table 5.1: *SVM* classification report.

The overall accuracy of 0.47 can be deemed a mild success. This result is better than a random label assignment. Especially useful is the relatively high recall in the depression and mania cases. These episodes often require medical attention, so a fast warning about the possibility of their occurrence is particularly useful.

5.4 Discussion

There is a plethora of ways the *SVM* classifier might be improved. More data could be collected in the future. Other, more sophisticated balancing methods could be explored, as mentioned in section 5.2. The feature vector for each sample could be extended by computing additional indicators. There is also the possibility to train a completely different kind of classifier such as *decision tree*, *random forest*, *AdaBoost*, *neural network*, etc. *Convolutional neural networks* were used in the past to extract features from the actigraphic signal automatically [ACCdlHAL+20]. This approach might increase the overall accuracy in this case as well.

Chapter 6

Conclusion

In this thesis two major analytical methods were used to analyze actigraphic signals of bipolar patients. The motivations for this were explored in detail in chapter 1. The characteristics and relations between the used data were described in 2.

Cosinor analysis results were in accordance with generally reported characteristics of bipolar disorder (see chapter 3). Mesor values suggest that the mean level of activity during depressive episodes is lower than during periods of remission or mania. The variance in activity was found to be lower during mania and depression as opposed to remission. Finally, depressive patients achieve daily peak activity at a later hour on average. This is in accordance with common comorbidities of depression such as insomnia.

Three modifications of permutation entropy were compared in chapter 4. Modified permutation entropy was identified as the most suitable. The possible reason is that it does not neglect repeated values. Sine those appear to be carrying important information content in this case. Grid search was performed to locate the best permutation parameters (see chapter 4). Entropy orders 4 and 5 were similarly successful at separating the three main symptomatic episodes, whereas lower entropy orders caused that periods of depression, mania, and remission to have entropy values in the same range more often. Permutation entropy performed best for resampling period of 5 minutes.

The trained support vector machine model in chapter 5 had a test accuracy of 0.47. Although this is not as useful as a standalone classification method, it can still serve as an aid in attention prioritization. It has a high 0.92 remission precision score and a reasonably high 0.63 depression recall score (and 0.62 mania recall score). These characteristics mean that we can rely on the model when it comes to precisely classifying remission and thus not concern ourselves with periods that are most likely less severe. On the other hand, the higher recall scores for depression and mania mean that the classifier can emphasize most periods where depression or mania occurs. Of course, further improvements on this classifier could be made as it is not very powerful in its current state. Additional indicators could be computed to better discriminate between the episodes. Or entirely different approach could be tried, such as training various other models discussed in section 5.4.

Bibliography

[A+13] American Psychiatric Association et al., *Diagnostic and statistical manual of mental disorders (dsm-5®)*, American Psychiatric Pub, 2013.

[ACCdlHAL+20] Patricia Amado-Caballero, Pablo Casaseca-de-la Higuera, Susana Alberola-Lopez, Jesus Maria Andres-de Llano, Jose Antonio Lopez-Villalobos, Jose Ramon Garmendia-Leiza, and Carlos Alberola-Lopez, *Objective adhd diagnosis using convolutional neural networks over daily-life activity records*, IEEE Journal of Biomedical and Health Informatics (2020).

[AVN] Jiri Anyz, Pavel Vostatek, and Daniel Novak, *Comparison of the mindg wristband with the motionwatch wristband for monitoring of physical activity and sleep*, mindpax.me.

[BAG+82] Christopher Bingham, Bernard Arbogast, G Cornélissen Guillaume, Jung Keun Lee, and Franz Halberg, *Inferential statistical methods for estimating and comparing cosinor parameters.*, Chronobiologia (1982).

[BBD+11] Michael Berk, Alan Brnabic, Seetal Dodd, Katarina Kelin, Mauricio Tohen, Gin S Malhi, Lesley Berk, Philippe Conus, and Patrick D McGorry, *Does stage of illness impact treatment response in bipolar disorder? empirical treatment data and their implication for the staging model and early intervention*, Bipolar disorders **13** (2011), no. 1, 87–98.

[BHO+10] Jan O Berle, Erik R Hauge, Ketil J Oedegaard, Fred Holsten, and Ole B Fasmer, *Actigraphic registration of motor activity reveals a more structured behavioural pattern in schizophrenia than in major depression*, BMC research notes **3** (2010), no. 1, 149.

[BLH+97] Jan Born, Tanja Lange, Kirsten Hansen, M Mölle, and Horst-Lorenz Fehm, *Effects of sleep and circadian rhythm*

on human circulating immune cells., The Journal of Immunology **158** (1997), no. 9, 4454–4464.

[BMT+13] Christopher Burton, Brian McKinstry, Aurora Szentagotai Tătar, Antoni Serrano-Blanco, Claudia Pagliari, and Maria Wolters, *Activity monitoring in patients with depression: a systematic review*, Journal of affective disorders **145** (2013), no. 1, 21–28.

[BNR+16] Chiara Baglioni, Svetoslava Nanovska, Wolfram Regen, Kai Spiegelhalder, Bernd Feige, Christoph Nissen, Charles F Reynolds III, and Dieter Riemann, *Sleep and mental disorders: A meta-analysis of polysomnographic research.*, Psychological bulletin **142** (2016), no. 9, 969.

[BP02] Christoph Bandt and Bernd Pompe, *Permutation entropy: A natural complexity measure for time series*, Physical Review Letters **88** (2002), no. 17.

[BQMS12] Chunhua Bian, Chang Qin, Qianli D. Y. Ma, and Qinghong Shen, *Modified permutation-entropy analysis of heartbeat dynamics*, Phys. Rev. E **85** (2012), 021906.

[BRUC96] GUENTHER Boden, JOSE Ruiz, JL Urbain, and XINHUA Chen, *Evidence for a circadian rhythm of insulin secretion*, American Journal of Physiology-Endocrinology And Metabolism **271** (1996), no. 2, E246–E252.

[CBHK02] Nitesh V Chawla, Kevin W Bowyer, Lawrence O Hall, and W Philip Kegelmeyer, *Smote: synthetic minority oversampling technique*, Journal of artificial intelligence research **16** (2002), 321–357.

[Cir] *Circadian rhythms*, `https://www.nigms.nih.gov/education/fact-sheets/Pages/circadian-rhythms.aspx`, Accessed: 2020-05-14.

[Cor14] Germaine Cornelissen, *Cosinor-based rhythmometry*, Theoretical Biology and Medical Modelling **11** (2014), no. 1, 16.

[CTM+01] Penny Corkum, Rosemary Tannock, Harvey Moldofsky, Sheilah Hogg-Johnson, and Tom Humphries, *Actigraphy and parental ratings of sleep in children with attention-deficit/hyperactivity disorder (adhd)*, Sleep **24** (2001), no. 3, 303–312.

[CZYW09] Weiting Chen, Jun Zhuang, Wangxin Yu, and Zhizhong Wang, *Measuring complexity using fuzzyen, apen, and sampen*, Medical Engineering Physics **31** (2009), no. 1, 61–68.

[EHB13] David B Evans, Justine Hsu, and Ties Boerma, *Universal health coverage and universal access*, 2013.

[GK08] Anne Germain and David J Kupfer, *Circadian rhythm disturbances in depression*, Human Psychopharmacology: Clinical and Experimental **23** (2008), no. 7, 571–585.

[GMA+10] Larriany Maria Falsin Giglio, Pedro VS Magalhães, Mônica Levy Andersen, Julio Cesar Walz, Lourenço Jakobson, and Flávio Kapczinski, *Circadian preference in bipolar disorder*, Sleep and Breathing **14** (2010), no. 2, 153–155.

[Gru15] Heinz Grunze, *Bipolar disorder*, Neurobiology of brain disorders, Elsevier, 2015, pp. 655–673.

[HBGL08] Haibo He, Yang Bai, Edwardo A Garcia, and Shutao Li, *Adasyn: Adaptive synthetic sampling approach for imbalanced learning*, 2008 IEEE international joint conference on neural networks (IEEE world congress on computational intelligence), IEEE, 2008, pp. 1322–1328.

[JHE05] Steven Huntley Jones, Dougal Julian Hare, and Kate Evershed, *Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder*, Bipolar disorders **7** (2005), no. 2, 176–186.

[Kan98] Holger Kantz, *Nonlinear analysis of physiological data*, Springer, 1998.

[KGHM+14] Karoline Krane-Gartiser, Tone Elise Gjotterud Henriksen, Gunnar Morken, Arne Vaaler, and Ole Bernt Fasmer, *Actigraphic assessment of motor activity in acutely admitted inpatients with bipolar disorder*, PloS one **9** (2014), no. 2.

[LJLVG+10] Carlos López-Jaramillo, Juan Lopera-Vásquez, Aurora Gallo, Jorge Ospina-Duque, Vaughan Bell, Carla Torrent, Anabel Martínez-Arán, and Eduard Vieta, *Effects of recurrence on the cognitive performance of patients with bipolar i disorder: implications for relapse prevention and treatment adherence*, Bipolar disorders **12** (2010), no. 5, 557–567.

[LYB+09] Paul Lichtenstein, Benjamin H Yip, Camilla Björk, Yudi Pawitan, Tyrone D Cannon, Patrick F Sullivan, and Christina M Hultman, *Common genetic determinants of schizophrenia and bipolar disorder in swedish families: a population-based study*, The Lancet **373** (2009), no. 9659, 234–239.

[O+08] World Health Organization et al., *The global burden of disease: 2004 update*, World Health Organization, 2008.

[Org04] World Health Organization, *International statistical classification of diseases and related health problems*, vol. 1, World Health Organization, 2004.

[Pie07] Ronald Pies, *How "objective" are psychiatric diagnoses?:(guess again)*, Psychiatry (Edgmont) **4** (2007), no. 10, 18.

[PK13] Mary L Phillips and David J Kupfer, *Bipolar disorder diagnosis: challenges and future directions*, The Lancet **381** (2013), no. 9878, 1663–1671.

[RM92] Roberto Refinetti and Michael Menaker, *The circadian rhythm of body temperature*, Physiology & behavior **51** (1992), no. 3, 613–637.

[SA02] Avi Sadeh and Christine Acebo, *The role of actigraphy in sleep medicine*, Sleep medicine reviews **6** (2002), no. 2, 113–124.

[TMAdMB+12] Carla Torrent, Anabel Martinez-Arán, Caterina del Mar Bonnin, Maria Reinares, Claire Daban, Brisa Solé, Adriane R Rosa, Rafael Tabarés-Seisdedos, Dina Popovic, Manel Salamero, et al., *Long-term outcome of cognitive impairment in bipolar disorder.*, The Journal of clinical psychiatry (2012).

[WBC+96] Myrna M Weissman, Roger C Bland, Glorisa J Canino, Carlo Faravelli, Steven Greenwald, Hai-Gwo Hwu, Peter R Joyce, Eile G Karam, Chung-Kyoon Lee, Joseph Lellouch, et al., *Cross-national epidemiology of major depression and bipolar disorder*, Jama **276** (1996), no. 4, 293–299.

[WDM+12] Katharina Wulff, Derk-Jan Dijk, Benita Middleton, Russell G Foster, and Eileen M Joyce, *Sleep and circadian rhythm disruption in schizophrenia*, The British Journal of Psychiatry **200** (2012), no. 4, 308–316.

[WGWF10] Katharina Wulff, Silvia Gatti, Joseph G Wettstein, and Russell G Foster, *Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease*, Nature Reviews Neuroscience **11** (2010), no. 8, 589–599.

[WS18] Jenna Wiens and Erica S Shenoy, *Machine learning for healthcare: on the verge of a major shift in healthcare epidemiology*, Clinical Infectious Diseases **66** (2018), no. 1, 149–153.

[XFY09] Liu Xiao-Feng and Wang Yue, *Fine-grained permutation entropy as a measure of natural complexity for time series*, Chinese Physics B **18** (2009), no. 7, 2690–2695.

[ZZRP12] Massimiliano Zanin, Luciano Zunino, Osvaldo A. Rosso, and David Papo, *Permutation entropy and its main biomedical and econophysics applications: A review*, Entropy **14** (2012), 1553–1577.

[ZZW10] Yan-Ping Zhang, Li-Na Zhang, and Yong-Cheng Wang, *Cluster-based majority under-sampling approaches for class imbalance learning*, 2010 2nd IEEE International Conference on Information and Financial Engineering, IEEE, 2010, pp. 400–404.

BACHELOR'S THESIS ASSIGNMENT

I. Personal and study details

Student's name: **Březík Miroslav** Personal ID number: **474726**

Faculty / Institute: **Faculty of Electrical Engineering**

Department / Institute: **Department of Cybernetics**

Study program: **Open Informatics**

Branch of study: **Computer and Information Science**

II. Bachelor's thesis details

Bachelor's thesis title in English:

Actigraphic Data Processing of Patients with Bipolar Disorder

Bachelor's thesis title in Czech:

Zpracování aktigrafických dat pacientů s bipolární poruchou

Guidelines:

The goal of this thesis is to get acquainted with various methods of actigraphic data processing. The student has to detect different states of patients with bipolar disorder using the chosen features.
1) Familiarise yourself with symptoms of bipolar disorder especially those related to physical activity.
2) Study and implement cosine analysis and use it for the actigraphic data.
3) Implement method of actigraphic data analysis by using permutation entropy.
4) Test the influence of missing data on the accuracy of feature estimation.
5) Build a classifier to differentiate between patient's states and compare parameters using statistical analysis in both relapse and remission periods.
6) Validate acquired results on provided patient data.

Bibliography / sources:

[1] S. H. Jones, D. J. Hare, and K. Evershed, "Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder," Bipolar Disord., vol. 7, no. 2, pp. 176–186, 2005.
[2] G. Cornelissen, "Cosinor-based rhythmometry," Theor. Biol. Med. Model., vol. 11, no. 1, p. 16, Dec. 2014.
[3] K. Krane-Gartiser, T. E. G. Henriksen, G. Morken, A. Vaaler, and O. B. Fasmer, "Actigraphic assessment of motor activity in acutely admitted inpatients with bipolar disorder," PLoS One, vol. 9, no. 2, 2014.
[4] T. Hastie, R. Tibshirani, and J. Friedman, The Elements of Statistical Learning The Elements of Statistical Learning. 2017.

Name and workplace of bachelor's thesis supervisor:

Ing. Jakub Schneider, Analysis and Interpretation of Biomedical Data, FEE

Name and workplace of second bachelor's thesis supervisor or consultant:

Date of bachelor's thesis assignment: **07.01.2020** Deadline for bachelor thesis submission: **22.05.2020**

Assignment valid until: **30.09.2021**

Ing. Jakub Schneider	doc. Ing. Tomáš Svoboda, Ph.D.	prof. Mgr. Petr Páta, Ph.D.
Supervisor's signature	Head of department's signature	Dean's signature

III. Assignment receipt

The student acknowledges that the bachelor's thesis is an individual work. The student must produce his thesis without the assistance of others, with the exception of provided consultations. Within the bachelor's thesis, the author must state the names of consultants and include a list of references.

. _____
Date of assignment receipt

_____
Student's signature