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D I P L O M A R B E I T

Mathematical indices and models for the quantification of the diurnal profile and variability of pulse wave analysis parameters

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unter der Anleitung von

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Ort, Datum

Unterschrift

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Abstract

Cardiovascular diseases are one of the leading causes for morbidity and mortality. It is therefore of crucial importance to identify indicators for these diseases at an early stage to find proper treatment, prevent fatal outcome and launch preventive actions. There are many parameters describing the health condition of the cardiovascular system, the most popular being systolic and diastolic blood pressure (BP). Nevertheless, hypertension is only able to predict 40% of coronary heart diseases. Therefore, further indicators have to be found.
The Mobil-O-Graph (I.E.M., Stolberg, Germany) is an oscillometric brachial-cuff based sphygmomanometer which allows to perform 24 hour (24h) ambulatory blood pressure monitoring (ABPM) including pulse wave analysis (PWA). The recording involves the measurement of standard ABPM parameters as well as the estimation of central aortic pressures and other systemic cardiovascular parameters, such as augmentation index (AIx) and cardiac output (CO), at regular time intervals throughout the day. The resulting time series often show a diurnal profile. Therefore, the analysis of these profiles and their variability is of interest in the field of biomedical engineering and medical pathophysiology. The aim of this thesis is to identify suitable mathematical models and indices to quantify this profile and the variability of the time series. Furthermore, algorithms which are applicable to the data sets and provide these indices, need to be implemented. In this context, the analysis of diurnal BP profiles serves as a model. In this thesis, the methods used in literature to assess blood pressure variability (BPV) are researched and documented in detail. These methods, which have been used in clinical studies for 24h BP profiles for considerable time, are adopted for other parameters of the PWA in order to mathematically quantify the variability of a time series regardless of the parameter. Additionally, other indices, which have not yet been analysed at all in the context of BP and PWA parameter, but are rather general measures of variation within a time series, are presented. The considered methods include simple variability indices, such as the standard deviation (SD), average real variability (ARV), successive variation (SV) and the coefficient of variation (CV). Other methods aim to assess the diurnal profile of the parameter time series. In general, this is achieved by curve fitting methods. An ansatz function of a specific from is fitted to the data set by a least squared error criterion. One of the most popular models is the fourier fit. The sum of cosine waves with different period lengths builds the ansatz function. If only one cosine wave with a period of 24h is used, the method is called cosinor fit. Another model, the square-wave (SW) fit, assumes that the profile can be described by two constant plateaux. These and further models provide indices quantifying the profile. There are also simple indices which capture certain aspects of the profile. The nocturnal fall (NF), for instance, quantifies to what extent values at night differ from day measurements on average.
As a next step, the methods are implemented in MATLAB (The MathWorks Inc., Natick, Massachusetts, USA) to allow the application of the approaches on data sets recorded by the Mobil-O-Graph. Some of the methods impose conditions on the data sets to be computable, such as a minimum number of valid recordings in a given time period. Therefore, an algorithm is created to test data sets for the required quality.

The variability indices provided by the methods are calculated for a selection of the ABPM and PWA parameters of a healthy population as well as a patient group suspected to suffer from left ventricular hypertrophy (LVH) in order to test them for significant differences. Beforehand, data sets of insufficient quality are excluded with the help of the above mentioned quality algorithm. The demanded quality is thereby based on common settings in literature. The parameters analysed are heart frequency (Hf), peripheral systolic blood pressure (pSBP), central systolic blood pressure (cSBP), peripheral pulse pressure (pPP), central pulse pressure (cPP) andAIx.

The results show that pSBP, cSBP and AIx have significantly different 24h average values among the two cohorts. In contrast, Hf as well as the PP average values are not statistically different for the two groups. However, for Hf, several variability indices provide statistically different values, among them SD, ARV and SV. For each of the PP parameters only one index is significantly different - the NF for cPP and the CV at night for pPP. Even if pSBP, cSBP and AIx have 24h average values, which have a statistical difference, additional information might be obtained by the variability indices. The NF and the indices of the cosinor fit are significantly different for cSBP as well as pSBP. Indices of several methods, for instance, SD, ARV and NF are significantly different for the AIx.

The large amount of indices gives a wide-ranging number of aspects to be considered. Even if not all of the PWA parameters have been analysed in the frame of this work, the findings are of interest in the context of identifying indices with possible prognostic relevance. The mathematical models prove to be adequate to assess the diurnal profile and variability of 24h PWA parameters and the implemented algorithms are feasible to be applied to the data sets. This enables further investigation of clinical questions based on variability analysis.

Kurzfassung

Kardiovaskuläre Erkrankungen sind eine der häufigsten Ursachen für Morbidität und Todesfälle. Es ist daher von größter Wichtigkeit, Indikatoren zu identifizieren, welche diese Krankheiten in einem möglichst frühen Stadium diagnostizieren können, um geeignete Behandlungen einzuleiten, Todesfolgen zu vermeiden und präventive Maßnahmen zu setzen. Es gibt viele Parameter, die den Gesundheitszustand des Herz-Kreislaufsystems beschreiben. Unter diesen sind der systolische und der diastolische Blutdruck die Bekanntesten. Bluthochdruck kann jedoch nur etwa 40% der Koronarerkrankungen vorhersagen. Daher müssen weitere Indikatoren gefunden werden.
Der Mobil-O-Graph (I.E.M., Stolberg, Deutschland) ist ein oszillometrisches Blutdruckmessgerät mit Oberarmmanschette, welches ambulatorische Blutdruckmessung mit zusätzlicher Pulswellenanalyse über einen Zeitraum von 24 Stunden ermöglicht. Die Aufzeichnungen finden in regelmäßigen Zeitabständen statt und beinhalten sowohl die Messung der üblichen Werte der ambulatorischen Blutdruckmessung als auch die Berechnung zentraler Drücke und anderer systemischer kardiovaskulärer Parameter, wie Augmentationsindex und Herzminutenvolumen. Die resultierende Zeitreihe zeigt oft einen tageszyklischen Verlauf. Deshalb ist die Analyse dieses Profils beziehungsweise der Variabilität der Aufzeichnungen im Bereich der Biomedizinischen Technik und der medizinischen Pathophysiologie von großem Interesse. Ziel dieser Arbeit ist es, geeignete mathematische Modelle und Indizes zu bestimmen, um den Verlauf und die Variabilität zu quantifizieren. Des Weitern sollen Algorithmen entwickelt werden, die auf die Datensätze anwendbar sind und jene Indizes berechnen. In diesem Zusammenhang ist die Analyse von 24-Stunden-Profilen des Parameters Blutdruck vorbildgebend.
In dieser Arbeit werden die Methoden, die in der Literatur verwendet werden, um Blutdruckvariabilität zu quantifizieren, recherchiert und detailiert dokumentiert. Diese Methoden, die schon seit geraumer Zeit Gegenstand klinischer Studien zur Untersuchung des Tagesprofils von Blutdruck sind, werden für andere Pulswellenanalyseparameter adaptiert. Damit soll die Quantifizierung von Variabilität unabhängig vom Parameter ermöglicht werden. Zusätzlich werden noch weiter Methoden für die Variabilitätsanalyse von Zeitreihen aufgeführt, welche noch nicht im Zusammenhang mit Blutdruck- oder Pulswellenparametern untersucht wurden. Die in dieser Arbeit betrachteten Methoden beinhalten simple Variabilitätsindizes, wie die Standardabweichung, mittlere reale Variabilität, sukzessive Variation und den Variationskoeffizienten. Andere Herangehensweisen versuchen den tageszyklischen Verlauf der Parameterzeitreihe zu erfassen. Im Allgemeinen wird das mit der Lösung eines Ausgleichsproblems erreicht. Eine Ansatzfunktion mit einer speziellen Form wird mittels der Methode der kleinsten Fehlerquadrate an den Datensatz angepasst. Das bekannteste Model ist die Fourieranalyse. Dabei bildet die Summe von Kosinusfunktionen mit verschiedenen Periodenlängen die Ansatzfunktion. Wird nur eine einzelne Kosinusfunktion mit einer Periodenlänge von 24 Stunden verwendet, so spricht man von der Kosinusmethode. Ein anderes Modell, der Square-Wave-fit, geht davon aus, dass das Profil durch zwei konstante Plateaus beschrieben werden kann. Dieses und noch weitere Modelle liefern Indizes zur Quantifizierung des Profils. Des Weiteren gibt es auch simple Indizes, die gewisse Aspekte des Tagesverlaufs erfassen. Der nächtliche Rückgang beispielsweise sagt aus,

in welchem Ausmaß sich die in der Nacht gemessenen Werte von den tagsüber gemessenen im Mittel unterscheiden.
Anschließend werden die Methoden in MATLAB (The MathWorks Inc., Natick, Massachusetts, USA) implementiert, um deren Anwendung auf vom Mobil-O-Graphen erhobene Daten zu ermöglichen. Für die Berechenbarkeit einiger Indizes müssen die Datensätze gewisse Bedingungen erfüllen, beispielsweise eine minimale Anzahl von vorhandenen Messdaten in einem bestimmten Zeitintervall. Es wird daher ein Algorithmus enwickelt, welcher die Datensätze auf die geforderte Qualität testet.
Die von den Methoden abgeleiteten Variabilitätsindizes werden für eine Auswahl von Parametern der ambulatorischen Blutdruckmessung und der Pulswellenanalyse sowohl für eine Kohorte gesunder Probanden als auch für eine Gruppe von Patienten mit Verdacht auf linksventrikuläre Hypertrophie berechnet, um diese auf signifikante Unterschiede zu testen. Zuvor werden mit Hilfe des oben erwähnten Algorithmus Datensätze mit unzufriedenstellender Qualität ausgeschlossen. Die geforderte Qualität ist dabei gestützt auf übliche Anforderungen in der Literatur. Die analysierten Parameter sind Herzfrequenz, peripherer systolischer und diastolischer Blutdruck, peripherer und zentraler Pulsdruck und der Augmentationsindex.
Die Ergebnisse zeigen, dass für die beiden Kohorten das 24-Stunden-Mittel des peripheren und zentralen systolischen Blutdrucks sowie des Augmentationsindex signifikant unterschiedlich sind. Im Gegensatz dazu kann für die Herzfrequenz und den peripheren und zentralen Pulsdruck kein signifikanter Unterschied im 24-Stunden-Mittel festgestellt werden. Allerdings liefern für die Herzfrequenz einige der Variabilitätsindizes Werte, welche signifikant unterschiedlich für die beiden Gruppen sind. Dazu gehören beispielsweise die Standardabweichung, die mittlere reale Variabilität und sukzessive Variation. Für die Pulsdruckparameter ist jeweils nur ein Index signifikant unterschiedlich - der nächtliche Rückgang für den zentralen und der Variationskoeffizient in der Nacht für den peripheren Pulsdruck. Auch wenn mit dem 24-Stunden-Mittel bereits ein signifikanter Unterschied für zentralen und peripheren systolischen Bludruck und den Augmentationsindex festgestellt werden kann, wird mit Hilfe der Variabilitätsindizes zusätzliche Information gewonnen. Der nächtliche Rückgang sowie die Indizes der Kosinusmethode sind signifikant unterschiedlich für beide Blutdruckwerte. Für den Augmentationsindex liefern einige Methoden signifikant unterschiedliche Indizes, zum Beispiel die Standardabweichung, mittlere reale Variabilität und der nächtliche Rückgang.
Die Vielzahl an Indizes ermöglicht die Betrachtung breitgefächerter Aspekte. Auch wenn im Rahmen dieser Arbeit noch nicht alle Pulswellenanalyseparameter analysiert wurden, sind die Ergebnisse im Zusammenhang mit der Identifikation von Indikatoren mit möglicher Vorhersagekraft von kardiovaskulären Krankheiten von Interesse. Die mathematischen Modelle erweisen sich als geeignet, um den tageszyklischen Verlauf und die Variabilität von Pulswellenanalyseparametern zu quantifizieren und die implementierten Algorithmen sind auf die Datensätze anwendbar. Das ermöglicht die Untersuchung von weiterführenden klinischen Fragestellungen basierend auf einer Variabilitätsanalyse.

Danksagung

An dieser Stelle möchte ich mich bei all denjenigen bedanken, die mich auf dem Weg zur Entstehung dieser Arbeit begleitet und unterstützt haben.

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Ich widme diese Arbeit meinem Großvater Ernst, der leider in der finalen Phase der Entstehung dieser Arbeit von uns gegangen ist.

Contents

Chapter 1

Introduction

1.1 Motivation and Physiological Background

Cardiovascular diseases (CVDs) are one of the leading causes for morbidity and mortality. In 2015, approximately 31% of all global deaths occured due to CVDs [89]. It is therefore of crucial importance to identify indicators for these diseases at an early stage to find proper treatment, prevent fatal outcome and launch preventive actions.

There are many parameters describing the health condition of the cardiovascular system, the most popular being systolic and diastolic blood pressure (BP). The practice of 24 hour (24h) ambulatory blood pressure monitoring (ABPM) is the automated assessment of these peripheral BP values during a whole day. The measurements are made by a brachial-cuff based sphygmomanometer which can be programmed to initiate recordings at regular time intervals (for instance every 15 minutes). The possibility to assess the diurnal profile of BP is important, since it is a strongly varying value [21], [22], [31], [46]. The variations are partly explained by behavioural reasons (e.g., exercise and rest) but they occur to a large extent because of central cardiovascular control. The heart and the blood vessels are modulated by the central nervous system to act as an intrinsic regulatory mechanism [46] which causes different pressure values but also varying heart frequency (Hf). A detailed summary of physiological aspects concerning blood pressure variability (BPV) can be found in [31]. Due to these physiological fluctuations, the meaningfulness of a single measurement is limited and it has already been shown that the correlation of hypertensive end-organ damage is higher with ABPM readings than with clinical brachial BP readings [84]. Each recording is also influenced by inaccuracy of measurement, which adds to a variable signal.

Nevertheless, hypertension based on brachial measured BP values is only able to predict 40% of all coronary heart diseases [15]. Therefore, further indicators have to be found.

Many studies have been done to investigate the ability of other haemodynamic parameters, such as central (i.e., aortic) systolic and diastolic BP, pulse wave velocity (PWV) and pulse pressure (PP), to predict cardiovascular events [2], [5], [20], [35]. Considering systolic BP and PP, which is the difference of systolic and diastolic BP [88], it is reasonable to distinguish between central

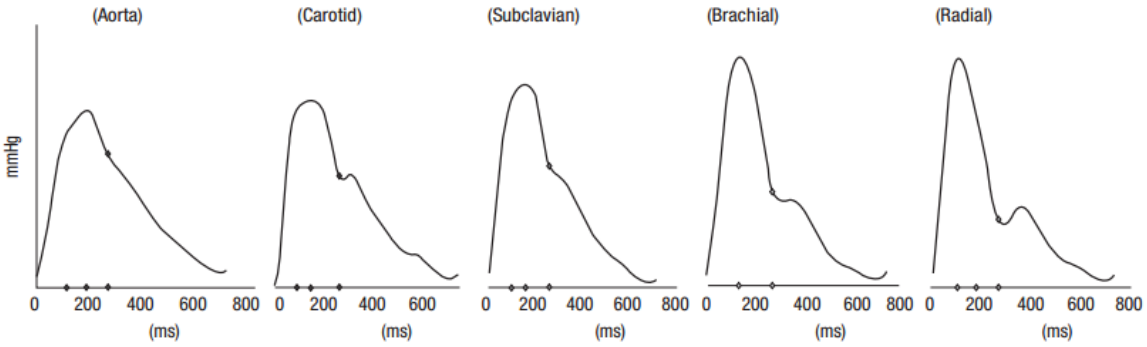


Figure 1.1: Change of the pressure wave when traveling from the aorta to the distal arteries ([40], p. 570): The systolic pressure increases. As a consequence PP values are higher as well.

and peripheral values. Brachial measured values are higher than the central pressures measured at the aorta (cf. figure 1.1). The amplification of pressure is physiologically explained by the diameter reduction and stiffness increase as one moves from the heart to the distal end of the arterial tree [84]. Furthermore, studies have confirmed the superiority of central values, when is comes to the predictability of cardiovascular diseases [52], [80]. However, these central values are difficult to assess. Either an invasive measurement is required, which is not feasible for practical usage, or non-invasive devices assessing these parameters require trained personnel [82], [84]. The Mobil-O-Graph (I.E.M., Stolberg, Germany) is an oscillometric brachial-cuff based sphygmomanometer which allows to perform 24h ABPM including pulse wave analysis (PWA). The recording involves the measurement of standard ABPM parameters, such as peripheral systolic and diastolic BP. Subsequently, for a duration of ten seconds, the pulse wave is recorded. With the ARCSolver method (tranfer-function like algorithm), developed by the Austrian Institute of Technology (AIT), central aortic pressures are estimated from these brachial recordings (cf. figure 1.2) [81], [84], [85]. The PWA includes the calculation of several other parameters, such

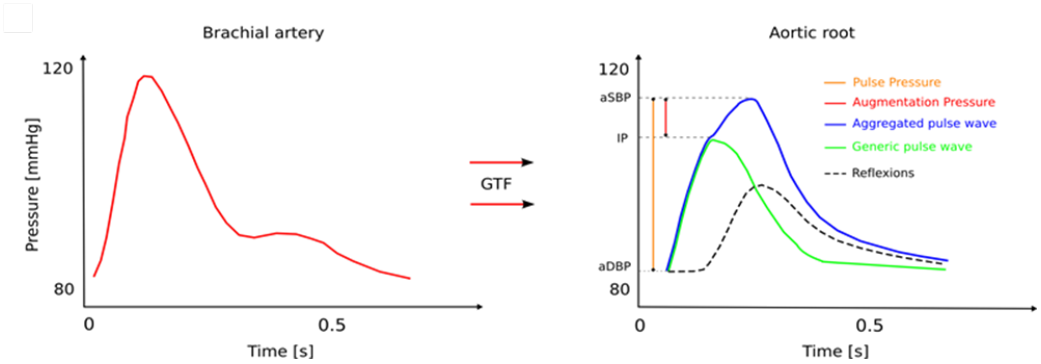


Figure 1.2: The validated ARCSolver algorithm uses a general transfer function to obtain a central pressure wave from the brachial measured curve [81].

as peripheral resistance (R_p), cardiac output (CO) and the PWV. The augmentation pressure (AP) is computed as well. It is the difference of systolic BP and inflection pressure [27], [82]. The latter one is determined as follows. When the heart contracts, it ejects blood into the

aorta. The pulse wave propagates through the arterial tree, but it is also reflected back to the proximal aorta. The inflection pressure is the pressure at the time point when the backward wave meets the forward wave [27], [81]. Another parameter, the augmentation index (AIx), is defined as the percentage ratio of augmentation pressure (AP) and PP. As mentioned before, PP is the difference of systolic and diastolic BP.
Some of these parameters have been found to be of prognostic value. The AIx and PWV, for instance, can be seen as surrogates for arterial wall stiffness. The consequences of this artery property on cardiovascular mortality are notable [27], [81].
However, the impacts of these parameters have not yet been analysed in a diurnal variability frame like BP. When considering their definitions (cf. PP and AIx), it becomes clear that they are varying as well. With the availability of non-invasive measurements of central haemodynamic parameters of the PWA in regular time distances throughout a whole day, a variability analysis is made possible for more than just peripheral BP data.

1.2 Aim of the Thesis

In order to analyse the diurnal profile of PWA parameters, methods established for ABPM data serve as a model. The aim of this work is to collect a wide range of these methods and prepare a detailed documentation of the derived variability indices. Furthermore, the models are implemented in MATLAB to be applicable to parameter time series which were previously collected by the Mobil-O-Graph and to study their feasibility. To assess the practicability of the indices, another aim is to identify advantages and disadvantages. The indices gathered are calculated for a selection of PWA parameters of a healthy population as well as a patient group suspected to suffer from left ventricular hypertrophy (LVH) in order to test them for significant differences. This may contribute to the task of determining pathologies by the use of haemodynamical parameters.

1.3 Thesis Outline

This thesis is structured in six chapters including this introduction as the first one. The motivation for this work is laid out and the aim is presented. Chapter 2 builds the core of this thesis as it contains the collection of a wide range of methods and models assessing the variability and the diurnal profile of PWA parameters. In addition to a detailed description and examples, advantages and disadvantages of each index are gathered. As the methods impose certain conditions on the data sets to be computable, the third chapter is dedicated to a quality assessment algorithm for the data sets. The indices collected in chapter 2 are applied on a selection of PWA parameter profiles for a control group of healthy individuals and for a patient group suspected to suffer from LVH. After these data under investigation are introduced in chapter 4, the indices are tested for statistical significance. In chapter 5 the results are presented. Finally, the findings are discussed in chapter 6 and an outlook for possible future work is given.

Chapter 2

Methods Assessing Variability

The present chapter deals with a range of different methods to calculate mathematical indices quantifying the variability of measurements assessed at more or less equidistant time points over a period of 24h. Many of the following indices have been developed to analyse the variability and the profile of 24h BP data and have already been examined in a wide range of studies concerning 24h BPV, in certain cases also 24h Hf variability. Other indices have not yet been analysed at all in the context of BP and PWA parameters, but are rather general measures of variation within a time series. The calculation itself as well as the advantages and disadvantages - if known - will be discussed. The aim is to optimize the algorithms calculating these indices by gathering their technical limits as well as the restriction they force onto the given data set, for instance the availability of a minimum number of data points. Eventually, the aim is to apply these algorithms to 24h PWA parameter data which are considered in this work.

2.1 Crude Standard Deviation cSD

2.1.1 Definition of cSD

One of the most widely used methods for the quantification of the variability of a data set is the calculation of the (crude) standard deviation (SD) [3], [13], [28], [46], [55], [90]. Interpreting the data set as a random sample allows the calculation of the SD as the square root of the second empirical moment (= random sample variance). It is a consistent estimator, but not unbiased [86].

Definition 2.1. The crude standard deviation (cSD) is calculated as

$$cSD := \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \overline{X})^2}, \tag{2.1}$$

where x_i and n indicate the measured value at time point t_i and the number of available

measurements, respectively. Furthermore $\overline{X}$ denotes the mean of measurements

$$\overline{X} = \frac{1}{n}\sum_{i=1}^{n} x_i. \tag{2.2}$$

2.1.2 Advantages of cSD

This parameter is very simple to implement. Furthermore, there are little to no restriction on the data set to make its calculation reasonable. The only requirement is, of course, the presence of at least one data point.
This index has been used in several (rat and human) studies to show the existence of an association between BPV and different kinds of heart diseases, target organ damage (TOD) and even mortality [21], [32], [58], [61].

2.1.3 Disadvantages of cSD

In some articles, it is pointed out that an unweighted SD such as cSD other than the later mentioned weighted standard deviation (wSD) (cf. 2.2) overestimates the variability [3], [14].
On one hand this overestimation is due to the ignorance of cSD of the so called nocturnal blood pressure fall (NBPF) (cf. section 2.12). Another aspect which needs to be taken into account is the following: if different measurement intervals are chosen (e.g., at night time every 30 minutes and at day time every 15 minutes), day time variations are proportionally more represented in cSD. To overcome both these issues one introduces a weighting. This is futher described in section 2.2 which deals with the index wSD.
Furthermore, it is mentioned that other parameters, such as wSD or average real variability (ARV) (cf. 2.3), have a better performance in predicting cardiovascular disease than cSD [36], [48], [49], [60]. In [14] and [83], it is stated that, since cSD as well as wSD only indicate to what extent the measurements spread from the mean, they both lack to differentiate random variation from physiological or systematic variation of BP. This is specially an issue, if BP follows a trend over time (for instance as a reaction to drug treatment), or if there is a high correlation between the variability of the signal and its mean, which usually is the case. However, the first mentioned issue is more relevant, if measurements are taken over a long-time period, such as weeks or months. In this case, cSD will provide large values due to the trend over time, but not necessarily due to variability [83]. Moreover, cSD has to be questioned as a reliable parameter, since some contradicting results have been found when using cSD as an experiment variable [36], [48]. Furthermore, since cSD is independent of the order in which measurements are given, it does not reflect the time series structure of the signal considered, which may erase important information [21], [36], [61], [92].
Another issue which has to be stressed, is the fact that SD correlates strongly with the mean value of the data set. Prognostic value of variability might therefore be due to the significance of mean. Either this correlation has to be taken into account in the statistical model evaluating the relevance of the index or the index has to be transformed appropriately to obtain the

independence of the mean (cf. section 2.6). In some studies, SD lost its predictive value after adjusting the model, while in others it did not [61].
Even if the number of measurements is not relevant to make the calculation of SD reasonable, many authors point out that this index is sensitive to a low frequency of measurements per day [21], [36], [49]. Thijs et al. [70], for instance, claim that an accurate determination of this index is only then obtained, if measurement are available every 30 minutes.

2.1.4 Implementation - Restrictions on the Data Set and Features of the Algorithm

The algorithm allows to calculate the standard deviations of the whole 24h and of the sub-periods day time and night time, which can be defined individually. It is also optional to obtain a plot of the data which includes vertical lines for the beginnings and endings of day and night time, respectively. The time axis (= abscissa) can be chosen to be presented as decimal numbers or as hours of the day (cf. figure 2.1).
Since this index is algebraic, the only restriction to make the calculation itself reasonable is the presence of ‚enough' data points in each of the periods. The code gives a warning, if the number of data points is below a user defined threshold number.
However, it has to be stressed that even if the simple calculation in fact only requires a single measurement, a certain larger number of measurements is needed to obtain a value for the SD which is reliable when used in statistical tests (cf. 2.1.3).

2.2 Weighted Standard Deviation wSD

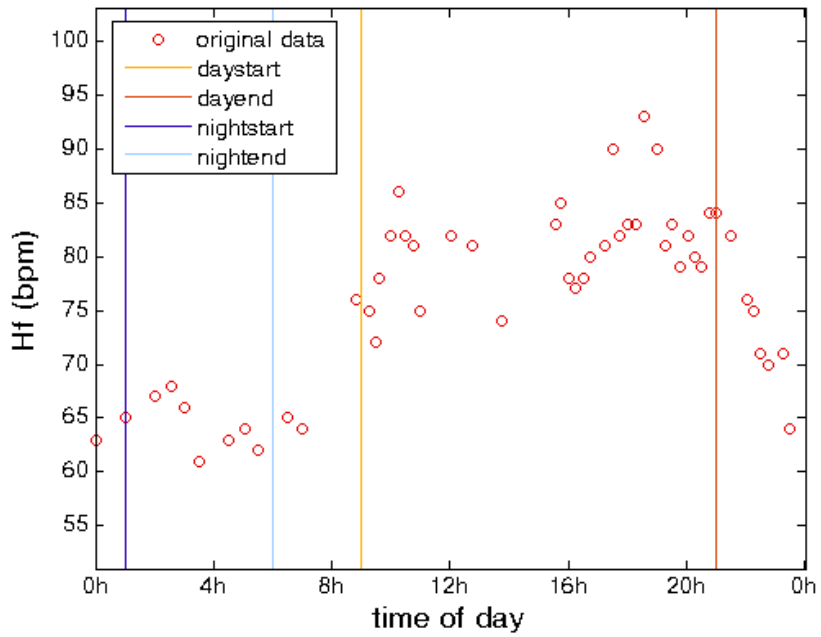
2.2.1 Definition of wSD

For a refinement of the cSD, one may include a weighing. Commonly this is done by a day-night distinction. In particular, this means that one calculates the cSDs for all measurements during day time and during night time separately and builds the arithmetic average afterwards [3], [4], [38], [46], [61]. ‚Day time' and ‚night time' are of course no fixed time intervals and have to be determined as two disjoint periods within the 24h. The corresponding formula reads as follows.

Definition 2.2. The weighted standard deviation (wSD) can be calculated as

$$wSD = \frac{(cSD_{day} \cdot k) + (cSD_{night} \cdot l)}{k + l}, \tag{2.3}$$

where cSD_{day} and cSD_{night} indicate the cSDs of measurements during day time and night time. Furthermore, k and l denote the number of measurements which were recorded during these periods.




```
 !!!WARNING!!! number of valid measurements during night time (= 10) is less than 12
*************
crude_standard_deviation:
cSD_day = 4.2828
cSD_night = 3.4705
cSD_24h = 8.5008
*************
```

Figure 2.1: Output of the function `calc_cSD.m` in MATLAB. (The threshold number of 12 measurements has been choosen arbitrarily to provoke the output of the warning message and should not be seen as a scientific value.) This figure nicely shows the approximate transition periods between the higher level day values and the lower level night values.

Comment 2.3. Note that, if the defined day and night intervals are a cover of $[0, 24)$, the formula reads as

$$wSD = \frac{(cSD_{day} \cdot k) + (cSD_{night} \cdot (n-k))}{n}, \tag{2.4}$$

where n is the number of all valid measurements. However, typically the hours of the transitional periods between day and night will be excluded. [3]. □

2.2.2 Advantages of wSD

This method is easy to implement and applicable to practically all possible data sets without any restrictions as long as there are measure points available. Additionally, the weighing leads to a more sophisticated estimation of the variability compared to the cSD [3]. This is due to the fact that the weighing takes into account a well known pattern in the BP behaviour. That is to say, BP tends to vary around a higher level during wakefulness than during night while being asleep in healthy patients [10], [31], [39], [59]. The key component for this behaviour is in fact a matter of being asleep or awake, since it has been shown that 24h BP profiles of shift workers being on duty at night and going to sleep in the morning show a reversed pattern [8], [31].

Taking this into account, wSD circumvents an overestimation of variability such as detected in the calculation of cSD [3], since differences of day- or night measurements to the corresponding means will be smaller than to the 24h mean. When considering BPV as a risk factor for cardiovascular events (CEs), but simultaneously being aware of the fact that dipping at night is a proven healthy behaviour [3], one needs to exclude this effect in the calculation of BPV [61]. The phenomena of the decrease of BP when going to sleep and also the rise of BP when waking up, have been given the names nocturnal blood pressure fall (NBPF) and early morning surge (EMS). These effects will be discussed in the following sections (cf. 2.12 and 2.13).
According to the studies in [3], [46], [61] and [60], wSD can be considered as a superior index to measure BPV compared to cSD, since it correlates better with TOD and is a better predictor of cardiovascular risk.
In general, it might give a more detailed insight in the study of BPV, when looking at day time and night time SDs separately [60]. This is for instance supported by studies, where it has been shown that only one of the indices cSD_{day} and cSD_{night} was affected by a certain drug treatment for hypertensive patients [21].

Comment 2.4. The weighting is a method primarily introduced to overcome the overestimation of variability with cSD due to the ignorance of the NBPF. There is also another effect responsible for this overestimation. Usually there will be a lower number of usable measurements during night time then during day time either because measurements during sleep are more difficult to asses (due to technical reasons [71]) or simple because a lower number of measurements is scheduled [43]. The weighting partly compensates this bias. Other possibilities to overcome this issue, are, of course, to schedule the same number of measurements during day time and night time or to weight the whole dataset by the time intervals between consecutive measurements. In [43], another approach is used. To obtain values for BP throughout 24h, each hour during day time and during night time is assigned with the mean value of the measurements within this hour. They compared this time-weighted approach to asses BP over 24h with other possible measurement schedules and concluded that overestimation was lowest with the time-weighted method and reliable analysis of the data set should include approximately the same number of measurements at each period of the day. If this is not possible, a weighting should be included. The weighting methods can of course not compensate for the physiological effect, that one is awake for a longer period than asleep [43].

2.2.3 Disadvantages of wSD

It has already been mentioned that cSD does only quantify to what extend the data points are spread from the mean and does not account for the order in which the measurements are taken [21], [92]. Therefore, the data sets of two individuals may exhibit the same SDs, even if the profiles show a completely different behaviour (cf. fig. 2.2) [1], [36].

Comment 2.5. In figure 2.2, it is said, that cSD is equal to 10 in both cases. This calculation included the normalization factor $\frac{1}{n}$ instead of $\frac{1}{n-1}$ which appears in formula 2.1 under the square root. Otherwise the cSDs in both cases would be approximately 10.54. □

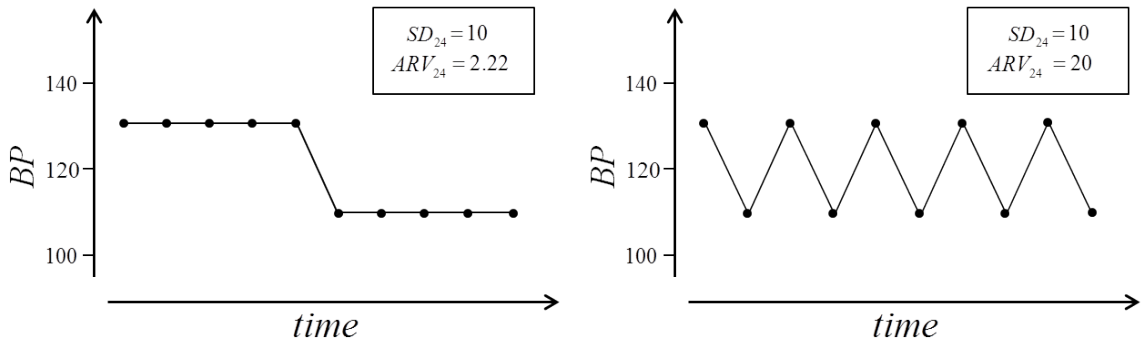


Figure 2.2: Illustration of ‚ARV vs. SD' in the context of the sequential structure of the data set (adapted from [16]).

Besides the studies in favour of the index wSD, there have also been studies such as the one by Bjelakovic et al. [4], which found that wSD was not a reliable index to predict the risk for left ventricular hypertrophy (LVH) in children.
The weighted SD does partly account for the factor ‚time' in the calculation as it differs between measurements taken during day and during night. Still it does not fully capture the time series structure of the given data. This may erase information about variability.
As mentioned previously, wSD lacks to distinguish between variation contributed by physiological processes and random variability in BP [14] (cf. 2.1.3). An improvement for this challenge will be presented in section 2.15 using another index called personalized SD, which aims to mathematically exclude physiological variation such that only random variation is measured [14].
A further inconvenience is the fact that wSD similar to cSD strongly depends on the overall level (mean) of the data, as it has been shown that variability measured with SD, whether crude or weighted, increases and decreases with the level of mean [32]. An improvement can be achieved, when using indices such as variation independent of mean (VIM) or the coefficient of variation (CV) [1], [32]. Both will be discussed in following sections (cf. sections 2.10 and 2.6).

2.2.4 Implementation - Restrictions on the Data Set and Features of the Algorithm

The features of the algorithm to calculate the wSD are similar to those of the algorithm calculating the cSD. The same data queries for quality are performed and warnings are given if a data set fails the requirements (cf figure 2.1). Day time and night time are input parameters of the program, but in order to exclude the physiological effects of NBPF and EMS, an initial square wave or fourier fit could be performed to properly define these periods [22] (cf. sections 2.14.1, 2.14.3 and 2.12.2).

2.3 Average Real Variability *ARV*

2.3.1 Definition of *ARV*

ARV is the sum of the absolute values of differences between consecutive readings, normalized by the number of measurement gaps. Thus, it is an estimator for the average change of values between readings and therefore can reflect beat-to-beat variability [90]. The background for this index is the mathematical concept of total variation commonly used in the analysis of functions [36], [83], [90].

Definition 2.6. Average real variability is defined as

$$ARV = \frac{1}{n-1} \sum_{i=1}^{n-1} |x_{i+1} - x_i|, \tag{2.5}$$

where x_i indicates the measurement at time point i and n is the number of valid measurements.

2.3.2 Advantages of *ARV*

ARV provides a lot of advantages especially compared to SD, while the calculation complexity stays equally simple.
It has been suggested in several studies, that BP variability indices, which are sensitive to the sequential structure of the given data show a better performance in predicting cardiovascular disease than those ignoring it. The main advance of ARV compared to previously mentioned indices is precisely that it takes the order of the given data into account [21], [36], [49], [61]. With this feature, ARV is a more elaborate index for variability as it excludes such issues as observed for the SD in section 2.2.3 figure 2.2. While SD fails to capture the differences in the two profiles, ARV does not. In general, several authors state that ARV is a superior index compared to SD to prove association between BP variability and the risk for CEs, TOD or other complications [16], [21], [36], [46], [48]. For instance, Schillaci et al. [60] were able to show an association between large-artery stiffness and BPV assessed with ARV independent of BP level, age and heart rate. Although the relationship was notable for wSD and SD as well, the association was strongest with the index ARV. Artery stiffness was measured by calculating the carotid-femoral pulse wave velocity (cfPWV). However, since the relation between BPV and the latter index might be bidirectional, the causality is not clarified. It might as well be the case that increased artery stiffness leads to an increased BPV, instead of high BPV predicting less artery distensibility and therefore TOD. There have been animal studies, identifying BPV as an independent marker for artery-stiffness, but such studies are not feasible with humans [60]. A similar study by Xiong et al. trying to relate BPV with carotid intima-media thickness - an indicator of atherosclerosis and therefore a predictor for CEs and stroke - also found ARV as the index with the best association of these two variables in consideration [90]. It should be stressed that in both studies systolic BPV was the significant index.

Another example is the study of Mena et al. [36], in which ARV, in contrast to SD, was found to be an independent risk factor for cardiovascular events compared to factors such as age, smoking status, cholesterol, systolic BP and others.
Furthermore, this index is also suggested to be a useful tool to represent variability of other time series parameters, such as heart rate.
Another improvement of ARV is that it is not as influenced as SD by a low frequency sampling number of ambulatory monitoring [21], [83]. This index is also used to assess visit-to-visit BP variability [41].

2.3.3 Disadvantages of *ARV*

Even if ARV was found to be a more reliable index than SD, it has been claimed that BP variability measured with ARV also has limitations as a predictor for cardiovascular risk. BP variability quantified with ARV does improve the ability to predict cardiovascular events compared to indices measuring the level of BP such as systolic BP mean values (sBP), but only by 0.1% [66]. Thus BPV assessed with ARV is considered a significant risk factor, but only in a statistical frame and not for clinical practice [1].
Another study, with the aim to predict the risk for children with hypertension to suffer from left ventricular hypertrophy, found both, wSD and ARV as unreliable indices [4].
Although ARV has been a considerable improvement in many aspects of the quantification of variability compared to SD, there is a certain limitation, when it comes to the prognostic value of ARV. It has been mentioned, that this index is less sensitive to a lower number of measurements. However, to avoid the loss of prognostic information, a minimum amount of data points is required. One of the observation of the study in [37] is, that ARV increases, when fewer readings are used in the calculation. This may veil the differences between subjects with high and low variability. The number of readings affects not only the predictive power, but also the reproducibility of BPV, when calculated with ARV. With the aim to determine a minimal quantity of readings necessary to guarantee the reliability of ARV as a variability index, they found 48 measure points over 24h to be an appropriate amount to calculate ARV without loosing any significant information. Despite this possible limitation the study supports the predictive relevance of ARV for cardiovascular and cardiac mortality, while concomitantly questioning its independence from other risk factors. Nevertheless, they recommend a minimum of 48 measure points when prospectively analysing BPV with ARV.
Another aspect, in which ARV does not improve compared to SD deviation is the fact, that it strongly depends on the mean level of BP as well [1].

Comment 2.7. In [66] and [37] a weighted form of ARV was used (cf. 2.4) . □

2.3.4 Implementation - Restrictions on the Data Set and Features of the Algorithm

The requirements on the data set stay essentially the same as for the before mentioned indices. The only difference is, that the number of desired measurements within 24h is set to 48 as sug-

gested by [37] as the minimum number, which is needed to prevent loss of statistical significance of this index.
The plot features are the same as for the previous indices.

2.4 Weighted Average Real Variability $wARV$

2.4.1 Definition of $wARV$

To compensate for the loss of data or generally a low number of measurements in the calculation of the index ARV itself, one may include a weighting with the time intervals between consecutive readings as the weighting factors [37], [66].

Definition 2.8. Weighted average real variability (wARV) is defined as

$$ARV_w = \frac{1}{\sum_{i=1}^{n-1}(t_{i+1} - t_i)} \sum_{i=1}^{n-1} |x_{i+1} - x_i| \cdot (t_{i+1} - t_i), \tag{2.6}$$

where x_i indicates the measurement at the time point t_i and n is the number of valid measurements.

2.4.2 Advantages and Disadvantages of $wARV$

The advantages and disadvantages of the index ARV have been discussed before in the sections 2.3.2 and 2.3.3. Specific focus on the weighted version of ARV was present in the publications of Stolarz-Skrzypek et al. [66] and Asayama et al. [1]. The findings of this studies have as well already been mentioned in these sections.

2.4.3 Implementation - Restrictions on the Data Set and Features of the Algorithm

Since the main problem in the calculation of ARV is the possible loss of significance due to a low number of measurements, the request of a minimum number of readings is reasonable. The weighting aims to compensate for this. Therefore the query of a minimum number is dropped. Nevertheless, a large gap between two consecutive readings is still undesirable. It may be of interest to state other quality requests for the data set such as, within one hour there should be at least two valid readings.

2.5 Successive Variation SV

2.5.1 Definition of SV

Another index measuring variability is the so called successive variation (SV). It is closely related to ARV as the calculation concept is very similar [83], [92].

Definition 2.9. Successive variation (SV) is calculated as

$$SV = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n-1}(x_{i+1} - x_i)^2}, \tag{2.7}$$

where x_i indicates the measurement at the time point t_i and n is the number of valid measurements.

SV is highly correlated with ARV, but it will usually be larger and is more sensitive to more prominent differences between consecutive readings [83].

2.5.2 Advantages and Disadvantages of SV

Similar to ARV, SV as well captures the time sequence of the measurements [92]. The authors of the study of Yong et al. [92] emphasize that this is an important aspect, when studying the profile of BP. They analysed 72h BP profiles of patients after they suffered from acute ischemic stroke. Among other profile indices they found decreased SV of dyastolic BP during the 72h after stroke as an independent predictor of a convenient outcome for the patient, i.e. no relevant symptoms affecting everyday life.

Comment 2.10. As the two indices correlate strongly disadvantages (as well as advantages) of ARV can be seen as equivalently valid for SV. □

Comment 2.11. SV was used as reference value for BPV in the validation analysis of CUSUM (cf. section 2.16) as an index for quantifying the circadian pattern of the BP profile [65]. The results and findings are of course only then favourable, if SV is seen as a suitable index to adequately quantify variation.
It was also used as the index measuring variability, when showing that an increased systolic BP variability independently predicts deep and infratentorial cerebral microbleed (CMB) progression and diastolic BP variability is associated with CMB development in deep regions [28]. It has to be mentioned, that visit-to-visit variability was examined.
Another study tried to find an association between albuminuria variability and progression in patients with type 2 diabetes and visit-to-visit variability. Among other indices SV was found to be an independent predictor. Interestingly, ARV, did not perform likewise despite their notable resemblance [41]. □

2.5.3 Implementation - Restrictions on the Data Set and Features of the Algorithm

The quality queries as well as the plot features are exactly the same as for ARV (cf. section 2.3.4).

2.6 Coefficient of Variation CV

2.6.1 Definition of CV

Previously mentioned indices were often dependent on the mean of the time series under consideration. This is an issue since higher variability measured with these indices might only appear due to a trend of mean, but not due to real variability. A range of indices already mentioned can be slightly transformed to overcome this trouble. The first one to be discussed is the coefficient of variation. A simple division of the SD by the mean value of the data yields to the sought for independence [46], [83], [90].

Definition 2.12. The coefficient of variation is a normalized form of the standard deviation. It is defined as

$$CV = \frac{SD}{\overline{X}} \cdot 100\%, \tag{2.8}$$

where SD is the standard deviation and $\overline{X}$ indicates the mean (cf. def. 2.1, equ. 2.2).

Comment 2.13. The multiplication by 100 is optional. It defines whether the CV is given as decimal number or as a percentage. The division by the mean is the essential operation to non dimensionalize. This is an often used technique in modelling with differential equations to identify dominant terms of the equation. □

2.6.2 Advantages of CV

The CV was found to indeed fulfil its purpose to correct for the correlation of SD and mean level of 24h ABPM data [1], [23], [55]. While the SD of the data grows proportional to the rise in their mean value, CV does not do so. This was observed even when the mean value increased solely in subperiods of the 24h measurement period [46]. For visit-to-visit variability analysis this is not valid as correlation (partly) remains. In this case other transformations of SD are required to obtain independence of mean (cf. section 2.10) [13], [55], [56], [83]. Similar to SD the CV is a widely used index and has been proven helpful to show associations between different cardiovascular diseases and BPV [7], [21], [61], [74], [90], [91]. In the study of Wenhong et al. [28], which was already mentioned in section 2.5.2, besides SV, CV of BP was also related to CMB progression. CV was used to assess variability. However, visit-to-visit variability was analysed. In two studies by Rothwell et al. [55], [56] as well visit-to-visit variability was analysed. On one hand, systolic BPV assessed with CV was shown to be an independent risk factor for stroke (independent of mean systolic BP) and on the other hand, the results suggest that BP lowering drugs as treatment to reduce stroke risk should not only avoid to increase (visit-to-visit) BPV, but ideally even lower it concomitantly. However, both studies classified CV as a minor index compared to VIM since correlation to mean BP partly remained.

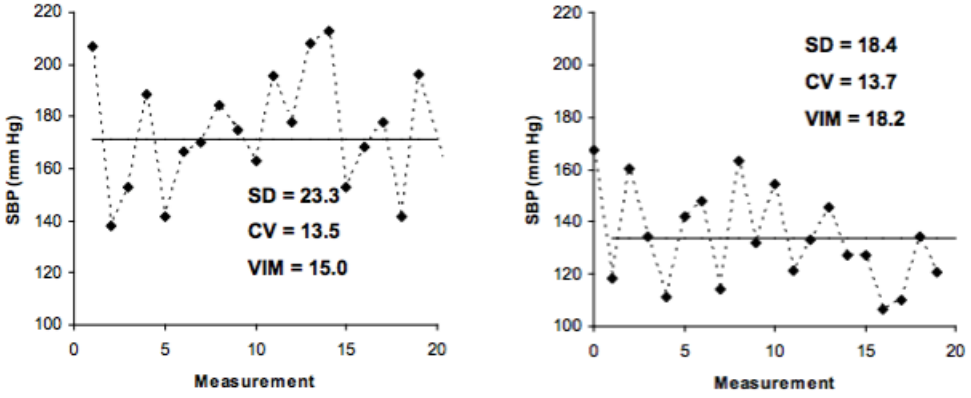


Figure 2.3: Illustration of ‚SD vs. CV' in the context of the dependence on the mean of the data set [36]. The data on the left show a higher mean value. While the cSD gets smaller as the mean level decreases, the CV is almost the same for both data sets. The index variation independent of mean (VIM) is discussed in section 2.10.

2.6.3 Disadvantages of CV

Some of the issues regarding the index SD remain for CV. Again this index ignores the sequential structure of the data [92]. Therefore, the problem discussed in section 2.1.3 illustrated by figure 2.2, that SD can be the same for observable different data profiles, remains [32]. Likewise the primary determination of SD by the NBPF and the resulting overestimation of variability is an issue unresolved by CV [23]. Also the sensitivity to the low frequency of measurements per day remains [21]. Since SD and CV are both influenced by changes that occur during a relatively long period (hours to one day), extreme values weight stronger [55]. Thus, instability in BP due to certain stress factors, contributes stronger to these values more likely resulting in overestimation. Although CV is an often used index to assess and analyse visit-to-visit variability and has lead to favourable results, there have also been studies, in which, in contrast to other measures for BPV such as SD or VIM (cf. section 2.10), CV was not a predictor of certain diseases which are believed to be associated with BPV [41].

2.7 Higher Empirical Moments HEM

2.7.1 Definition of HEM

Definition 2.14. For a random variable X the moment of order k with $k \in \mathbb{N}$ and the $k-$th central moment are defined as

$$m_k := \mathbb{E}(X^k) \quad \text{and} \quad M_k := \mathbb{E}((X-\mu)^k), \tag{2.9}$$

where $\mu = \mathbb{E}(X)$ is the expected value of the random variable. [86]

The interpretation of the data set in consideration $x_i, \ldots, x_n$ as a random sample of a random

variable suggests the calculation of the SD (cf. section 2.1), which is the square root of the second central empirical moment. However, the computation of higher empirical moments, which can be seen as estimators of the (unknown) moments of the random variable, is possible as well as they always exist for a random sample.

Definition 2.15. The k-th empirical moment is defined as

$$\hat{m}_k = \frac{1}{n}\sum_{i=1}^{n}(x_i)^k \quad \text{or in central form as} \quad \hat{M}_k = \frac{1}{n}\sum_{i=1}^{n}(x_i - \overline{X})^k, \tag{2.10}$$

where x_i indicates the i-th measure value and $\overline{X}$ is the (empirical) mean value.

Comment 2.16. These moments are sometimes given as *absolute empirical moments*. This means that x_i is replaced by $|x_i|$ and $(x_i - \overline{X})^k$ by $|x_i - \overline{X}|^k$, respectively.

The calculation of the first four empirical moments seems reasonable, since they can be interpreted as sample mean (1st), sample variance (2nd) (cf. section 2.1), skewness (3rd) and kurtosis (4th). To be precise, if X indicates a random variable, the latter two are defined as the central moments of order three and four respectively, normalized by the corresponding power of the SD [86]

$$S = \frac{\mathbb{E}(X - \overline{X})^3}{SD(X)^3}, \quad W = \frac{\mathbb{E}(X - \overline{X})^4}{SD(X)^4}, \tag{2.11}$$

where $\mathbb{E}$ is the expected value.
The empirical moments defined in definition 2.15 divided by the corresponding power of the SD estimator (cf. def. 2.1) are precisely estimators for S and W obtain from $x_1, \ldots, x_n$, when interpreting these measurement values as a random sample of a random variable.

Definition 2.17. For a random sample, empirical skewness and empirical kurtosis are defined as

$$\hat{S} := \frac{\frac{1}{n}\sum_{i=1}^{n}(x_i - \bar{X})^3}{\sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \overline{X})^2}^3} \quad \text{and} \quad \hat{W} := \frac{\frac{1}{n}\sum_{i=1}^{n}(x_i - \bar{X})^4}{\sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \overline{X})^2}^4}. \tag{2.12}$$

Note, that the used estimator for the SD is normalized by $(n-1)$. As mentioned in section 2.2, normalization by n is possible as well (cf. comment 2.5).

2.7.2 Advantages and Disadvantages of $HEMs$

These indices, except for the SD, which is basically the square root of the variance, have not yet been discussed in studies regarding the association of the variability of a PWA parameter and cardiovascular outcome.

2.7.3 Implementation - Restrictions on the Data Set and Features of the Algorithm

The algorithm calculates empirical skewness $\hat{S}$ and empirical kurtosis $\hat{W}$ for day time, night time and for 24h. The Matlab built in functions `skewness` and `kurtosis` are used. It has to be mentioned that these function use the normalization by n for the SD. If precisely the formula of definition 2.17 is desired the calculation has to be done ‚manually' (cf. function description of `calc_HEM.m`).

2.8 Functions of Order Statistics OSs

Definition 2.18. Let $x_1, ..., x_n$ be the recorded measurement values. Define

$$Y_1 := \min\{x_1, \ldots, x_n\} \tag{2.13}$$
$$Y_2 := \min\{\{x_1, \ldots, x_n\} \backslash \{Y_1\}\} \tag{2.14}$$
$$\vdots$$
$$Y_i := \min\{\{x_1, \ldots, x_n\} \backslash \{Y_1, \ldots, Y_{i-1}\}\} \tag{2.15}$$
$$\vdots$$
$$Y_n := \max\{x_1, \ldots, x_n\}. \tag{2.16}$$

Then there holds $Y_1 < Y_2 < \cdots < Y_n$ and Y_i is called the $i-$th order statistic . The sorted random sample values $Y_1, \ldots, Y_n$ are also called rank list [86].

It appears that certain functions of order statistics provide a proposition about the 24h profile of the data set $x_1, \ldots, x_n$ and its variability.

2.8.1 Maximum max and Minimum min

The simplest indices obtained from the order statistics are the maximal and the minimal value of the data set.

Definition 2.19. For the measurement values $\{x_1, \ldots, x_n\}$, the maximum (max) and the minimum (min) are defined as

$$\mathbf{max} = \max\{x_1, \ldots, x_n\} = \boldsymbol{Y_n}, \tag{2.17}$$
$$\mathbf{min} = \min\{x_1, \ldots, x_n\} = \boldsymbol{Y_1}. \tag{2.18}$$

Advantages and Disadvantages of max and min

Probably because of the simplicity of these indices, at least max is widely used and (despite the low complexity) favourable results have been achieved. For instance Matsui et al. showed

that the maximal value of home systolic BP is a strong predictor of TOD. The correlations of left ventricular mass index and carotid intima-media thickness (as measures for TOD) were significantly larger with the maximum than with mean systolic BP [33]. However, It has to be mentioned that maximum was defined in some sense differently than above. For 14 days, there were taken three BP measurements in the morning and in the evening, respectively. Each triple was averaged and the maximum among these mean values was defined as maximum. Similar studies by Rothwell et al. and Matsui et al. showed the predictive importance of maximal systolic BP in association with cardiovascular events and the development of brain hemorrhagic transformation [33], [56].
A major disadvantage of this index is that it is very sensitive to outliers. In the above mentioned studies this was alleviated by taking the mean of the triplicate assessed BP value. Another study found that maximum BP and maximum PP did not have any effect on cardiovascular mortality in hemodialysis patients, where BP and PP was assessed over three months at each dialysis treatment session [11], [21].
It has to be emphasised that in the above mentioned studies, the time series of which the maximum is taken of, extend over more prolonged time periods than 24h ranging from 72h to several months. So the definition of ‚maximum' can differ from the one given in 2.19.
Regardless of the advantages and disadvantages maximum as well as minimum are two parameters among several others often used to assess the 24h BP profile [92] as done in the study of Yong et al., when the profile of patients after an ischemic stroke was aimed to be assessed. The maximum value showed a significant difference between the groups of favourable and unfavourable outcome after 90 days after the stroke, in a group receiving drug treatment as well as in a placebo group.
Wenhong et al. [28] as well used the maximum value to assess BPV.

Comment 2.20. In [63] and [71] the time point of the appearance of the maximum systolic and diastolic BP is mentioned. This might therefore be an interesting index as well. □

2.8.2 Range

The range is the simplest measure of dispersion in statistics [57], [86]. Interpreting the discrete dataset as node points, the performance of a linear interpolation allows to identify the range with the oscillation of the resulting continuous function f.

Definition 2.21. The range can be calculated as

$$\boldsymbol{range} = osc(f) = \max_{y\in\Omega} f(y) - \min_{y\in\Omega} f(y) = \boldsymbol{Y_n - Y_1}, \tag{2.19}$$

where n is the number of measurements, Y_n is the maximal value x_{max}, i.e. the n-th order statistic, and Y_1 is the minimal value x_{min}, i.e. the first order statistic. The set Ω is the 24h interval.

Comment 2.22. If one is interested in the range of the values within another time interval

than 24h, Ω will be a subinterval of $[0, 24)$, for instance, the day time interval. To calculate the range, one has to determine the maximal and minimal value within this time period - typically these will not be Y_1 and Y_n - and compute the difference. □

Advantages and Disadvantages of *range*

On one hand, this index is very suitable for small random samples, hence it is not sensitive to a low frequency of sampling [57]. On the other hand, the range is not robust against outliers and looses its meaningfulness if the amount of data gets too big [86]. This index might therefore be more suitable for data sets with a notable loss of readings than others.
This index is somehow closely related to the NBPF, which will be discussed in section 2.12. This is loosely speaking the difference between the mean day time and the mean night time values. Since the largest value is typically expected to appear during wakefulness and the lowest typically during sleep at night, NBPF and range should be correlated. Such as wSD also other indices, for instance personalized standard deviation (cf. section 2.15), try to exclude this effect in the measurement, since it is a physiological phenomenon considered to be healthy [14], [32].

2.8.3 Interquartile Range IQR

As an alternative to the range the interquartile range can be chosen. It is a measure of the range of the medial 50% of the data points [86].

Definition 2.23. The interquartile range (IQR) is defined as

$$\begin{aligned} \boldsymbol{IQR} &= Q_3 - Q_1 = 75\%\text{-percentile} - 25\%\text{-percentile} \\ &\approx \boldsymbol{Y_k - Y_m} \end{aligned} \tag{2.20}$$

with the following labels:

i) Q_3 indicates the 3rd (or upper) sample quartile, which can be estimated by the $k-$th order statistic Y_k with $k = \lfloor 0.75 \cdot (n-1) \rfloor$.

ii) Q_1 stands for the 1st (or lower) sample quartile, which can be estimated by the $m-$th order statistic Y_m with $m = \lfloor 0.25 \cdot (n-1) \rfloor$.

iii) The number of measurements is indicated by n.

Advantages and Disadvantages of IQR

In contrast to the ordinary range, IQR is robust and therefore not as sensitive to outliers, since the upper as well as the lower 25% of the data points are not taken into account.

2.8.4 Midrange MR

Another possible measure is the midrange, which gives the mid point of the range and therefore measures central tendency [12].

Definition 2.24. The midrange (MR) is defined as

$$\boldsymbol{MR = \frac{Y_1 + Y_n}{2}} \tag{2.21}$$

with the following labels:

i) $Y_n = x_{max}$ is the maximal value of all measurements.

ii) $Y_1 = x_{min}$ is the minimal value of all measurements.

iii) The number of measurements is indicated by n.

Advantages and Disadvantages of MR

The calculative advantages and disadvantages can be seen as equivalent to those of the ordinary range (cf. section 2.8.2). It is highly sensitive to outliers, and therefore not robust as the change of one single data point can change its value randomly. It takes into account only two values, namely the minimum and the maximum. If either of these values are changes by x, the midrange changes by $\frac{x}{2}$. In comparison, the mean of a data set of length n would change only by $\frac{x}{n}$ [75].

2.8.5 Median

The median is a commonly used measure of central tendency.

Definition 2.25. The median is calculated as

$$\boldsymbol{median} = Q_2 = 50\% - \text{percentile} = \begin{cases} \frac{\boldsymbol{Y_{\frac{n}{2}} + Y_{\frac{n}{2}+1}}}{\boldsymbol{2}}, & \textbf{for } \boldsymbol{n} \textbf{ even,} \\ \boldsymbol{Y_{\frac{n+1}{2}}}, & \textbf{for } \boldsymbol{n} \textbf{ odd,} \end{cases} \tag{2.22}$$

where Y_i indicates the i-th order statistic [86].

Advantages and Disadvantages of $median$

Unlike the range, the median is robust against outliers [86]. The median is a common used tool in descriptive statistics to assess the profile of the time series [4]. Often it is just used to separate cohorts in 2 groups, for instance those with high BP ($>$ median) and those with low BP ($<$ median) [56], [86].

2.8.6 Peak and Trough

Peak can be defined as the difference between the maximal value and the mathematical mean value [41]. Trough measures the distance of the mean to the minimal value [56].

Definition 2.26. The formulas for peak and trough are

$$\boldsymbol{peak = Y_n - \overline{X}} \tag{2.23}$$

$$\boldsymbol{trough = \overline{X} - Y_1}, \tag{2.24}$$

where $Y_n = x_{max}$ is the maximal value, $Y_1 = x_{min}$ is the minimal value of all measurements and $\overline{X}$ indicates the mean value.

Advantages and Disadvantages of *peak* **and** *trough*

In the study of S. Noshad et al. [41] peak was one of the indices to assess the BP profile of type 2 diabetes patients. Visit-to-visit variability of BP was measured with different indices and it was shown that among them, peak was the one with the highest predictive value to show that systolic BPV contributes to the progression of microalbuminuria in diabetes patients.
The index trough was mentioned in an article by Rothwell et al. They investigated which indices perform better in predicting stroke in patients who had already suffered an ischaemic attack. Among many other results they found peak to be a better predictor than trough [56].
Peaks and troughs interpreted in the actual meaning of the words, namely simple sharp rises and drops in the time series profile, lead to a detailed description of the profile. White [87] dissected the BP profile and tried to identify periods of the day with the highest risk for a cardiovascular event.

2.9 Runs

2.9.1 Runs-test

Employing a runs test (Wald-Wolfowitz) enables the examination of the randomness of a sequence [6], [71]. Since the runs test in general analyses a sequence with only 2 attributes, the first step is to obtain such a sequence from the original data.

Definition 2.27. The procedure of a runs test according to [71] reads as follows

i) Calculate the weighted mean value $w\overline{X}$ (cf. 2.12.2) of the data set.

ii) Assign each data point with either the attribute 1 or 0 according to the instruction

$$\boldsymbol{a_k := a(x_k) := \begin{cases} 1, & x_k \geq w\overline{X} \\ 0, & x_k < w\overline{X}. \end{cases}} \tag{2.25}$$

iii) The test hypotheses are

$\boldsymbol{\mathcal{H}_0}$: The sequence (a_k) is random. vs. $\boldsymbol{\mathcal{H}_1}$ The sequence (a_k) is not random.

iv) Calculate the number of runs. These are subsequences of identical elements of the sequence (a_k). The runs counter is increased by 1 whenever the sequence changes from 0 to 1 or from 1 to 0, respectively.

$$\boldsymbol{r := |\{01 - \text{changes}\}| + |\{10 - \text{changes}\}|} \tag{2.26}$$

v) Let n_1 be the number of 1s and n_2 the number of 0s. The test statistic is given by

$$\boldsymbol{Z = \frac{r - \mu}{SD(r)}}, \tag{2.27}$$

with μ being the expected number of runs according to the null hypothesis

$$\mu = \frac{2n_1n_2}{n_1 + n_2} + 1 \tag{2.28}$$

and $SD(r)$ being the SD of r

$$SD(r) = \sqrt{\frac{2n_1n_2(2n_1n_2 - n_1 - n_2)}{(n_1 + n_2)^2(n_1 + n_2 - 1)}}. \tag{2.29}$$

vi) Finally the null hypothesis is rejected at a significance level of $\alpha = 0.05$, if

$$\boldsymbol{|Z| > z_{1-\frac{\alpha}{2}} = 1.96}, \tag{2.30}$$

where $z_{1-\frac{\alpha}{2}}$ is the $(1 - \frac{\alpha}{2})$-quantile of the standard normal distribution.

Comment 2.28.

- Provided, that the number of data points is sufficiently large (> 40), the Z-statistic is approximately normally distributed with an expected value of 0 and a variance of 1. Therefore the above rejection rule is used.
- According to [6], a continuity correction should be included, if the number of attributes is small ($n_1, n_2 < 30$) . This means that the test statistic is given by

$$\boldsymbol{Z = \frac{|r - \mu| - 0.5}{SD(r)}} \tag{2.31}$$

instead of the one given by formula 2.27.

- The version of the runs test in definition 2.27 is the so called non-sequential form. In [6] also a sequential form is described. Since this test works under the assumption that the alternatives 0 and 1 appear equally often, it is appropriate to use the median value

to separate all data points in two alternatives to guarantee this requirement without assuming normal distribution. Therefore also a median - dichotomization in formula 2.25 seems reasonable. □

Mathematical Background [69], [79]

The starting point of the runs test is the null hypothesis, in particular this is the assumption that the sequence was generated completely random. This means that the distributions for the elements with the first attribute has to be the same as for the ones with the second attribute. The test seeks to determine a number of runs for which this hypothesis is rejected. Therefore, the distribution R of the runs hat to be ascertained. Due to symmetry reasons, the probability for each 01-sequence has to be the same and there are

$$\binom{n_1+n_2}{n_1} = \binom{n_1+n_2}{n_2} = \frac{(n_1+n_2)!}{n_1!n_2!} \tag{2.32}$$

possibilities to create a sequence from the $n = n_1 + n_2$ elements. These are the possible cases. To determine the probability $P(R = r)$ one needs to calculate the number of sequences with precisely r runs. These favourable cases are obtained by

$$\begin{cases} 2\binom{n_1-1}{k-1}\binom{n_2-1}{k-1}, & \text{for } n = 2k \text{ even}, \\ \binom{n_1-1}{k-1}\binom{n_2-1}{k} + \binom{n_1-1}{k}\binom{n_2-1}{k-1}, & \text{for } n = 2k+1 \text{ odd}. \end{cases} \tag{2.33}$$

Division of 2.33 by 2.32 gives $P(R = r)$.

2.9.2 Sequence-Sign Iteration Test of Wallis and Moore

With the help of this statistical test one can check, whether variation of the signs of differences of consecutive readings is random ($\mathcal{H}_0$) or systematic ($\mathcal{H}_1$) [6]. In contrast to the runs-test this test does not assume that the two features (here positive and negative signs respectively) appear with constant probability at any time, since for instance the maximum value can only be followed by a smaller value. Hence the sign of difference has to be negative. This test gives the motivation to investigate the index *updownups* (cf. def. 2.29).

2.9.3 Definition of Runs

The number of runs itself might as well be a measure for variability since it counts how often the sequence switches between values above and beneath the median. This suggests the assumption that a higher number of runs indicates a more pronounced variability.
Another possible way to count runs is to identify changes in the trend of the data set. Therefore, one calculates the differences between consecutive readings and stores their signs. If zeros appear in the sequence of differences, they are erased since they do not indicate a real trend change. The counter for these runs is increased, whenever there is a change of sign. A graphical illustration is given in figure 2.4.

Definition 2.29. The two kinds of runs are defined as

$$\boldsymbol{runs := r := |\{01 - changes\}| + |\{10 - changes\}|} \tag{2.34}$$

$$\boldsymbol{updownups := |\{changes\ of\ sign\}|} \tag{2.35}$$

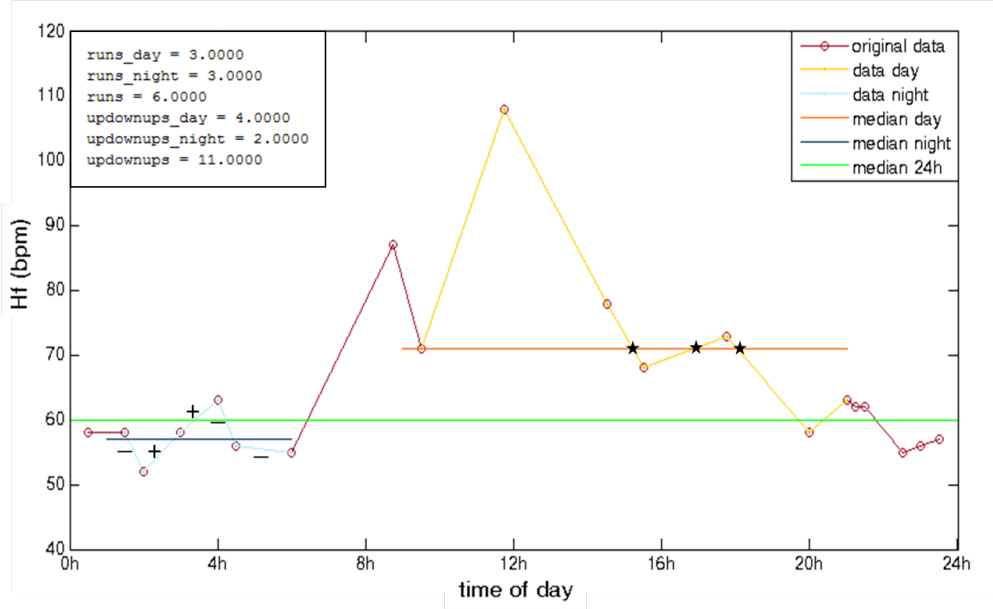


Figure 2.4: Illustration of the two kinds of runs. The legend in the top left corner is the output of the algorithm (`calc_runs.m`). In the night period (light blue data points) the calculation of *updownups* can be comprehended. The lines connecting two consecutive measurement values are assigned with + or - considering the sign of the difference of each measure point and the preceding one. Every sign change adds to the index *updownup* which results in 2 *updownups* during night time. To count *runs*, one has to count intersections between lines connecting data points (within the period in consideration) and the median value line of the according period. The 3 day time *runs* are marked with black star symbols ($\star$). Analogously, *runs* and *updownups* are calculated within all 3 periods.

2.9.4 Advantages and Disadvantages of Runs

The runs test was applied to 24h BP readings in healthy men to prove the presence of a diurnal pattern in the profile [71]. It is stated that the independence if the runs-test of the sleep time and wakefulness is an important advantage of this method. Additionally, in contrast to the periodogram test which is frequently used to test for a periodic rhythm, it can be applied to non - equidistant data.

2.9.5 Implementation - Restrictions on the Data Set and Features of the Algorithm

The reference value in the implementation is chosen as the median. The weighted mean or the mean value are also possible, but since the distribution of the data is not known beforehand and might not be a normal distribution, it seems reasonable to chose the median. The function

`calc_runs.m` allows an to chose, if for subperiod calculations the reference value is the 24h median (option = 1) or the subperiod median (option = 0, default, cf. figure 2.4).

2.10 Variation Independent of Mean VIM

2.10.1 Definition of VIM

As it has been mentioned before, many authors emphasize the issue that some mathematical indices such as SD or ARV quantifying variability, strongly depend on the mean value of the data set in consideration [1], [83]. One possible way to circumvent this problem, is to divide the index by the mean as it is done in section2.6, when SD was transformed to the CV. Another modification of the SD is the so called variation independent of mean (VIM) , which represents a refined transformation of SD compared to the CV [13], [83], for which it was observed that independence is only achieved on short term scale [83].

Definition 2.30. Variation independent of mean (VIM) is defined as

$$\boldsymbol{VIM = k \cdot \frac{SD}{\overline{X}^p}}, \tag{2.36}$$

where $\overline{X}$ is the mean value of the data set, k is a certain constant and p is a parameter to be determined.

It remains to specify, how to determine the variables k and p. VIM can only be obtained for an individual as part of a cohort. Therefore it is not feasible to measure variability with VIM in an individual independent of a group.
The calculation procedure is the following [1], [13], [83]:

i) The first step is to plot the mean value of each individual in the cohort (x-axis) against the SD of each individual (y-axis).

ii) A curve of the form $y = kx^p$ is considered.

iii) Finally a curve fitting of this curve is performed to obtain the parameter p.

iv) The constant k can (optionally) be chosen such that the scales for VIM and SD are on the same scale. If M is the mean value of the cohort, then $k = M^p$. Thus the curve $y = (Mx)^p$ has to be fitted.

v) VIM for each individual of the cohort is then calculated as $VIM = k\frac{SD}{\overline{X}^p}$.

2.10.2 Advantages and Disadvantages of VIM

The desired independence of the mean value is obtained, but another dependence, the one on the cohort, appears. To obtain the parameter p the data of a whole group have to be available. This index should be seen more as a statistical tool than a clinical measure [13]. Nevertheless,

it was used as an index for BPV in a study by Rothwell et al. [55] when investigating the effects of different drugs on variability and the risk of stroke.

Comment 2.31. In a similar fashion also ARV and SV can be made independent of the mean level to obtain the indices average real variability independent of mean (ARVIM)[41] and successive variation independent of mean (SVIM)[28]. □

2.11 Approximate Entropy *ApEn*

2.11.1 Definition of *ApEn*

Approximate entropy (ApEn) is a statistical technique to test a time series for irregularities or unpredictability of its fluctuation. Many previously mentioned parameters such as the mean or the SD would not capture the differences of the two series

$$(1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,2,\dots) \tag{2.37}$$

$$(1,1,2,2,2,2,1,1,2,1,2,2,1,2,1,1,1,2,1,2,1,1,\dots), \tag{2.38}$$

even if the first one is perfectly regular and the second one is random with a probability of $\frac{1}{2}$ for the appearance of 1 or 2, respectively [50]. The ApEn is supposed to measure irregularity in the data set. To be precise, $ApEn(m,r)$ indicates the logarithmic frequency, with which vectors of the length m, that are similar with a threshold r stay similar, when one further component is added to each of them [34], [51]. This method has already been used to measure irregularities in BP [44] and heart rate [34] sequences.

Definition 2.32. For a given data set $x_1,\dots,x_N$, and fixed values for $m \in \mathbb{N}$ and the threshold $r \in \mathbb{R}$ the following procedure gives the value for ApEn[34].

i) Separate the data set $x_1,\dots,x_N$ in overlapping sequences $\{X_1^m,\dots,X_{N-m+1}^m\}$ of length m with $X_i^m := \{x_i,\dots,x_{i+m-1}\}$.

ii) Define

$$C_i^m := |\{1 \le j \le N-m+1 : d(X_i^m, X_j^m) < r\}| \tag{2.39}$$

with

$$d(\vec{a},\vec{b}) := \max_i |a_i - b_i| \tag{2.40}$$

the Chebyshev-Norm, thus the maximal distance between elements of $\vec{a}$ und $\vec{b}$.

iii) Repeat everything for the fixed length $m+1$ to obtain C_i^{m+1}.

iv) Define

$$\phi^m := \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln\left(\frac{C_i^m}{N-m+1}\right) \tag{2.41}$$

$$\phi^{m+1} := \frac{1}{N-m} \sum_{i=1}^{N-m} \ln\left(\frac{C_i^{m+1}}{N-m}\right) \tag{2.42}$$

v) ApEn is then defined as

$$\boldsymbol{ApEn(m,r) := \lim_{N\to\infty} (\phi^m - \phi^{m+1})}, \tag{2.43}$$

which is estimated by

$$\boldsymbol{ApEn(N,m,r) := \phi^m - \phi^{m+1}}. \tag{2.44}$$

Typical choices for m and r are $(m,r) = (2, SD(X)\cdot 0.2)$ or $(m,r) = (3, SD(X)\cdot 0.2)$, when X is the data set of one single individual. The reason for r to be chosen as a percentage of the SD is that one wishes ApEn to be a regularity index uncorrelated to SD [34], [51]. In general a smaller value for ApEn indicates regularity, while larger values suggest, that the time series is more irregular [44].

2.11.2 Advantages and Disadvantages of $ApEn$

The non-linearity of the method enlarges the complexity and makes it more difficult to implement. On the other hand this might allow for deeper insights in the sequences profile.

2.12 Nocturnal Blood Pressure Fall $NBPF$

The phenomenon of BP to decrease after going to bed and falling asleep is well known. As previously mentioned (section 2.2.2) this is a fairly healthy mechanism which might influence other variability indices in an unfavourable fashion as variability is overestimated.

2.12.1 Definition of Nocturnal Fall NF

There are different terminologies used in different scientific articles to describe similar events concerning NBPF to be measured. The quantification of (BP) decline during sleep can be accomplished by a rather wide range of possible indices. Without raising claim to completeness the following definitions give an overview of them. Since the indices are aimed to be used for other parameters as well than only BP, the term nocturnal fall (NF) is used instead of nocturnal blood pressure fall (NBPF).

Definition 2.33. The night-to-day ratio (NDR) measures the rate of the night time mean

value $\overline{X}_{night}$ of the day time mean value $\overline{X}_{day}$ and is given by

$$\boldsymbol{NDR = \frac{\overline{X}_{night}}{\overline{X}_{day}}}, \tag{2.45}$$

which can be expressed as percentage as

$$\boldsymbol{NDR_p = NDR \cdot 100\%} \tag{2.46}$$

To express the actual fall, or to be precise, the percentage decline from day to night the definition

$$\boldsymbol{NF = 100 - NDR_p\%}. \tag{2.47}$$

is appropriate [62], [63].

Definition 2.34. The absolute day-night-difference (ADND) gives the absolute difference between the mean day value $\overline{X}_{day}$ and the mean night value $\overline{X}_{night}$

$$\boldsymbol{ADND = \overline{X}_{day} - \overline{X}_{night}}. \tag{2.48}$$

Additionally, the rate of this value of the mean day value is of interest

$$\boldsymbol{ADNDtoD_{ratio} = \frac{ADND}{\overline{X}_{day}}}. \tag{2.49}$$

Both values can be expressed as percentages as well [3], [38], [63], [70].

Comment 2.35. From the parameters in definition 2.34 one as well obtains the same value for the NF as in equation 2.47 by calculating [38]

$$\boldsymbol{NF = ADNDtoD_{ratio} \cdot 100\%}. \tag{2.50}$$

□

Comment 2.36. The indices NDR and ADND (NBPF, respectively) are often used to classify subjects as so called *‚extreme or strong dippers'*, *‚(intermediate) dippers'*, *‚non-dippers'* or *‚inverted dippers'* according to the degree of BP profile differences between day time and night time. The following excerpts serve as examples. In [63] subjects were classified as *strong dippers*, if their night-day ratio (NDR) was less than 0.78, as *non-dippers*, if the ratio was greater than 0.87 and as *intermediate dippers*, if their night-day ratio ranged between those two values.
In terms of NBPF in [3] subjects were rated as *‚extreme dippers'*, if their NBPF was $\geq 20\%$, as *‚dippers'*, if the percentage was $\geq 10\%$ but $< 20\%$ and as *‚non-dippers'*, if the fall was $< 10\%$.
The same classification was done in [38] with an additional category of *‚inverted dippers'* which

contained readings with a NBPF of less then 0%. These classification are done for systolic as well as for diastolic BP.
All values need to been seen as vague references, since they depend on the cohorts mean values of BP as well on the definitions of day time and night time periods. However, the above mentioned classification in terms of NBPF with a daytime period from 8a.m. to 10p.m and a night time from midnight to 6a.m. is more or less standard. To get an impression, in the study of Staessen et al. [63] the size of the nocturnal decline defined as ADND in a randomly chosen group of 399 subjects of a small town expressed in absolute numbers of mmHg (mean±SD) is about 16 ± 9 for systolic and 14 ± 7 for diastolic BP. In the study by Metoki et al. [38] baseline values for NF are $12.8 \pm 7.9/15.7 \pm 7.8\%$ for systolic and diastolic BP, respectively. Those were the mean values in a group of 1430 subjects. □

Comment 2.37. In some studies, the insight in the studys issue might be clearer, if the day time mean is subtracted from the night time mean. The proposition of the index does not change. Therefore, this can be seen more or less as a matter of taste.

> *‚Nocturnal BP fall was calculated by subtracting daytime from night time BP, such that a more negative difference indicated a larger BP fall at night. Night-day BP ratios were multiplied by 100, therefore expressing nighttime BP as a percentage of the daytime level. A ratio of 100% or higher signified the absence of a BP fall at night.'* [62]

□

2.12.2 Advantages and Disadvantages of NF

The motivation to investigate this index is present, because some studies have suggested, that there is a correlation between the fall of BP during sleep and the prognosis of cardiovascular events [42], [63]. However, the discussion, whether the decline of BP is associated with a higher risk of stroke is very controversial. According to study of Metoki et al. the total risk is not associated with the NBPF, but non-dippers and extreme dippers had a higher risk of cerebral infarction and intracerebral hemorrhage, respectively [38].
It has to be emphasized that the periods ‚day' and ‚night' are no given quantities, but have to be defined. This leads to several issues. If one wants to quantify the NBPF, this value strongly depends on the time, when a subject goes to sleep, since in general, this is the time point, when BP starts to decrease. It has to be guaranteed that the transition times ‚going to bed' an ‚arising' are excluded when calculating the day time and night time mean values. There are several methodological approaches in the studies to accomplish that. Patients may for instance keep a journal and consequently take notes when they go to sleep and get up [3], [38], [45]. Another possibility is, that patients are instructed to do so at fixed prespecified times. The latter approach may, however, interfere in their natural rhythm. If one wants to identify and afterwards exclude the transition times from the raw data without any feedback from the patient, the yet to be mentioned curve fitting methods (cf. section 2.14) might be a useful tool.

Nevertheless, there have been studies, which identified 0h to 6h as night time and 10h to 20h as day time to be the best choices to exclude the periods with the most rapid and considerable BP changes [3], [71] (cf. figure 2.1 and table 3.1). This index keeps of course being dependent on these defined intervals.
Another difficulty is again the possible disturbed estimation of the NBPF due to an imbalance of readings during sleep and during wakefulness. In general the amount of readings during day time is higher that during night. It is therefore advisable to calculate weighted mean values for the two periods when computing NDR and ADND to not distort these values because of an overestimation [43]. The weights are simply the time periods between consecutive readings.
Let $x_{d_1}, \ldots, x_{d_k}$ be the consecutive readings taken during the period ‚day'. Let t_{d_j} and t_{n_j} be the corresponding time points. Then the weighted mean of the day can be calculated as

$$\boldsymbol{w\overline{X}_{day}} = \frac{\mathbf{1}}{\boldsymbol{t_{d_k} - t_{d_1}}} \sum_{\boldsymbol{i=1}}^{\boldsymbol{d_k}} x_{d_i} \cdot (t_{d_{i+1}} - t_{d_i}). \tag{2.51}$$

Analogously, the mean over the night and over 24h values can be calculated.
Another positive aspect of this index is that there is no correlation to the BP mean level of the individual. However, there was found that NBPF is reduced by about 0.7 mmHg per ten years of life [63].
Even if the presence itself of a diurnal BP rhythm is an undoubted and reproducible observation (cf. section 2.9.4), the parameters describing the NBPF show a rather poor reproducibility. So the differences between day and night levels vary pretty much, which influences 24h average values [63]. In the publication of Thijs et al. [70] the objective of the study was to investigate precisely the number of measurements needed to assess parameters describing the diurnal BP profile without loss of information. One of those parameters was NBPF. They found that at least 2 readings per hour are needed to obtain a value for NBPF, which is reproducible with an relative repeatability coefficient $< 25\%$ (favourable value).
The NBPF is also strongly connected to standard deviation calculations. It almost solely determines the difference of SD and wSD as shown in [3]. This relationship between wSD and NBPF has already been discussed in section 2.2.2.

2.13 Early Morning Surge EMS

2.13.1 Definition of EMS

The terminology for this index is not uniform, similar as for NBPF. The EMS (sometimes just morning surge (MS)) or morning pressor surge (MPS) is an abrupt rise of BP (in the morning) after waking up. Although the significance of this index concerning its predictive power in the context of cardiovascular disease is not uniformly rated [38], [76], it is a frequently used value, especially in association with stroke [26], [38]. Nevertheless, on one hand, the risk of cardiovaskular events can be associated with an abrupt rise or a high level of BP in the morning, on the other hand it is to a certain degree healthy if BP rises in the morning as Staessen et al. [64]

found an increase of 1 mmHg per hour to decrease the risk of all cardiovascular events by 8%. However, one has to stress that, depending on the subtype of stroke and on the definition of MPS used, several ‚dipping to stroke' or ‚surge to stroke' associations could be proven and falsified, respectively [26], [38]. Characteristic values for the surge are 3 and 2 mmHg per hour in systolic and diastolic BP, respectively for $4-6$ hours after waking up [87]. The following terms can be found in literature: *sleep-through MPS*, *rising BP surge*, *morning-evening (ME) difference* and *pre-awaking MS*. The latter is sometimes also called *sleeping-to-waking MPS* [38]. In order to properly define those indices, a couple of help parameters defined as follows are required.

Definition 2.38. [25], [26], [76]

- **Morning BP** := mean of the first 4 measurements after awaking (2h mean of four 30-min measurements)
- **Lowest night time/nocturnal BP** := mean of the lowest value during night time, the preceding and the subsequent reading (1h mean of three 30-min measurements)
- **Pre-awake BP** := mean of the four measurements immediate before waking up (2h mean of four 30-min measurements)
- **Morning BP on rising** := first value after arising
- **BP on supine** := last value before getting up (in supine position, less than 30 min before rising)
- **Evening BP** := mean of the last 4 measurements before going to bed (2h mean of four 30-min measurements)

(cf. figure 2.5)

Comment 2.39. The parameters in definition 2.38 are often defined as an average value of a certain number of measurements preceding or following a specific event. It is important to notice that these definitions are only than equivalent to the temporal definitions (given in brackets in def. 2.38), if there is a valid measurement every 30 minutes. Because of the loss of readings, this is not very realistic and it might be more reasonable to work with fixed time intervals and calculate mean values, other than to use ‚the first 4 measurements after waking up' (in case of the parameter morning BP), since these readings might stretch over several hours. If so, they would not be related any more to the event of waking up. Furthermore, definitions of the help parameters by means of measurement numbers after a certain event may be problematic, if the measurements are scheduled in different time distances in different studies. To gain comparability, it would be better to take the mean value of all readings taken within a certain time window after the event. Nevertheless, in this case a minimum number of measurements in this time period should be demanded. □

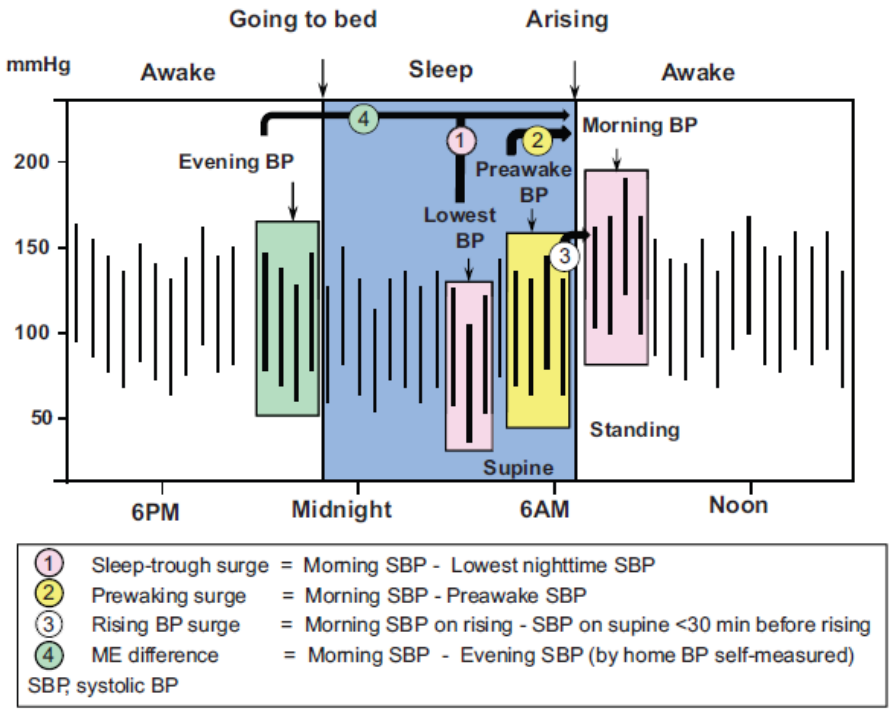


Figure 2.5: Illustration of the different definitions of surges with the help of the parameters defined in definition 2.38 [25]

With the help of these parameters, the above mentioned indices found in literature can be defined.

Definition 2.40. [1], [25], [38], [87]

- **Sleep-trough MPS := morning BP - lowest night time BP**
- **Pre-awaking MS := morning BP - pre-awake BP**
- **Rising BP surge := morning BP on rising - BP on supine**
- **ME difference := morning BP - evening BP**

Another definition of morning surge can be found in [56].

Definition 2.41. Morning surge with fixed time (ft) intervals is defined as the highest value between 09:00-11:00 minus the lowest value between 06:00-08:00 [56]

$$\boldsymbol{MS_{ft} := \max_{t_i \in [9,11]\text{a.m}} x_i - \min_{t_i \in [6,8]\text{a.m}} x_i}, \tag{2.52}$$

where x_i is the reading value at the time point t_i.

Comment 2.42. ‚Normal values' for MPS when defined as pre-awaking MS are 13.9±13.9/9.9± 8.4 mmHg for systolic and diastolic BP, respectively. Those were the mean values in a general

group of 1430 subjects without any history of symptomatic stroke in the follow-up study of Metoki et al.[38]. □

2.13.2 Advantages of EMS

Kario et al. [26] were able to show that sleep-through MPS in systolic BP is associated with risk of stroke, while the association with pre-awaking MS was not found.

2.13.3 Disadvantages of EMS

Likewise, as for NBPF, Metoki et al. [38] did not find an association between the total risk for stroke or the risk of cerebral infarction and the MPS. However, a MPS of more than 25 mmHg significantly increased the risk of cerebral haemorrhage.
This index cannot be understood completely independent of the NBPF. A higher BP in the morning - which is associated with the occurence of a cardiovascular events - might be due to a humble or even missing decline of BP during sleep, i.e. a small NBPF. In [38] they mention a significant correlation between the amplitude of the morning pressor surge (= preawaking surge) and the nocturnal blood pressure fall. They found a dual relationship between extreme dippers and subjects with a large MS. It is therefore important to report possible interactions between the two indices [38].
One faces similar problems in the calculation of MS as in the computation of NBPF as the more or less variable periods of day and night time influence the value. It has been discussed in section 2.12.2, how to deal with such issues.
Additionally, missing readings in rather short time periods (e.g. 2h after 'arising') required a high schedule frequency (cf. table 3.1).

2.13.4 Implementation - Restrictions on the Data Set and Features of the Algorithm

The calculation of surge values is highly sensitive to the time points of ‚going to bed' and ‚arising'. The resulting difficulties of such dependence has been discussed before (cf. section 2.12.2). To obtain a certain flexibility the code `calc_surge.m` allows to define the time point for these events. Additionally it is possible to adjust the interval length in the calculation of morning BP and pre-awake BP. The default value for this time duration is 2 hours.
The reasonability of the user defined input parameters is tested and warnings are given if possibly unwanted results appear such as if the time of going to bed is earlier in the day than waking up.

2.14 Curve Fitting Methods

Since the diurnal pattern, i.e. the change of the parameters over the day, is of interest, it seems reasonable to draw a (not yet specified) curve through the discrete dataset. This enables to appoint some sort of 24h profile. It has been frequently shown that especially the characteristics

of this profile highlight the presence of different kinds of cardiovascular diseases [22]. It is part of the following subsections to find out, how to obtain these curves and which indices can be derived from them. The different kinds of curves can be grouped into two methods with respect to the underlying ansatz.

- Interpolation:
  In this method new data points are added to the discrete data set. Stated simply, the given data points are connected with lines. How these lines behave precisely depends on the used method of interpolation. Some examples are
  - piecewise constant
  - linear
  - polynomial interpolation
  - spline interpolation
  - Gauß-interpolation
  - interpolation with rational or trigonometric functions
- Smoothing:
  In contrast to the interpolation method, the curve does in general not go through the given dataset. The ansatz function has a lower amount of degrees of freedom compared to the number of given values. The task is then to determine these degrees of freedom (= variables) in a way such that the discrepancy to the data set in consideration is minimal. Here as well numerous possibilities for the ansatz functions are used.
  - ‚Best-fit curve'
  - ‚Square-wave-fit'
  - ‚(Weighted) (Spectral) Fourier Analysis'
  - ‚Gauss-Newton Algorithm'
  - ‚Minnesota Cosinor Method'
  - ‚Double-logistic analysis'
  - A related topic is regression analysis.

The ansatz functions should be chosen in a manner, such that they *fit* the data. The methods discussed in the following section do so (with some restrictions). The mathematical formulation of this requirement will be part of the following subsections, in which several smoothing curve methods will be presented.

2.14.1 Square Wave Fit

A square-wave (SW) is a piecewise constant function attaining only two different values a and b on two disjoint complementary neighbouring segments of the considered domain. These segments are determined such that they fit the data, while the periods have to cover the interval (cf. figure 2.7). This is usually realised with a least squared error criterion [22].

Motivation

The presence of a diurnal BP profile with two levels, those basically being sleep time and time awake, has been discussed before (cf. section 2.2.2). Additionally the transitions from night-time to day-time levels and reverse seem to be rather abrupt, although high to low level descent is more gradual. Also the length of the two periods are in general different from subject to subject. A SW as depicted in figure 2.7 captures these features to a large extend while the degrees of freedom are essentially limited to two, the two time points, when the level changes [22].

Calculation of the SW according to [22]

Without loss of generality let $a > b$ from now on. The ansatz for the curve is a discrete function, which is only defined at points where measurement values are given. It attains the value a at all points within an interval and the value b at all time points of measurements within the complementary interval.

Definition 2.43. Let $\{t_1, \ldots, t_n\}$ be the time points within the 24h interval corresponding to the measurement points $\{x_1, \ldots, x_n\}$. The ansatz for the square-wave (SW) is then given by

$$SW(t) := \begin{cases} a, & \text{for } t \in \{t_i, t_{i+1}, \ldots, t_{i+k}\}, 1 \leq k < n \\ b, & \text{for } t \in \{t_1, \ldots, t_n\} \backslash \{t_i, \ldots, t_{i+k}\}, \end{cases} \tag{2.53}$$

where a and b are chosen constants and the parameters i and k remain to be determined.

Comment 2.44. The fact, that a and b can be chosen arbitrarily becomes clear in the next steps, when all possible SWs are standardised, such that they fit the plateaus levels. □

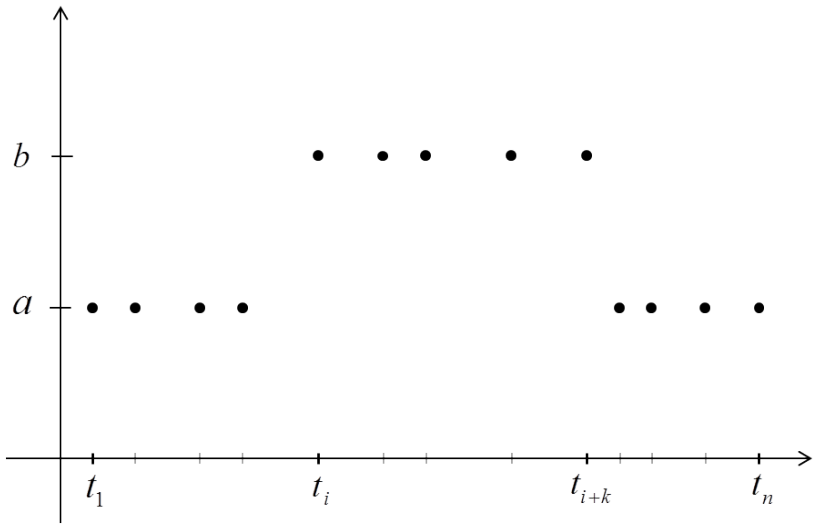


Figure 2.6: Ansatz for the square-wave.

In the procedure the next step is to calculate all possible SWs of the above form with fixed a and b, but all possible values for i and k.

Theorem 2.45. For a data set of n measurements there exist $n \cdot (n-1)$ SWs.

Proof. Given n data points, the 24h interval can be divided into n intervals from one corresponding time point to the adjacent, where the last to the first time point as well form an interval. In order to chose the segment, where the value a is attained, there are n possible choices to fix the left interval boundary. For the right boundary $n-1$ possible choices remain since interval lengths of 0 or n are forbidden. Otherwise one would not obtain 2 segments. Since the determination of the segment for a automatically fixes the segment for b, precisely $n \cdot (n-1)$ SWs are obtained. □

Subsequently, the SW of the $n \cdot (n-1)$ possible ones, which fits the data the best, is identified. In order to do so, the measurement values as well as the curves are standardized (or to be precise studentized, since the distribution of the data is not known). This is precisely the reason why a and b can be chosen arbitrarily (e.g. as the mean value of the data). The aim is to obtain a mean of zero and a standard deviation of 1 in order to receive outcomes for the cross correlation values ranging from -1.0 to 1.0.

The data are transformed

$$x_1, \ldots, x_n \longmapsto \tilde{x}_1, \ldots, \tilde{x}_n \tag{2.54}$$

with

$$\tilde{x_i} := \frac{x_i - \overline{X}}{cSD}. \tag{2.55}$$

The curve is transformed

$$SW(t) \longmapsto SW_{st}(t) \tag{2.56}$$

with

$$SW_{st}(t) := \begin{cases} \frac{a-\overline{SW}}{\sigma_{SW}}, & \text{for } t \in \{t_i, t_{i+1} \ldots, t_{i+k}\}, 1 \leq k < n \\ \frac{b-\overline{SW}}{\sigma_{SW}}, & \text{for } t \in \{t_1, \ldots, t_n\} \backslash \{t_i, \ldots, t_{i+k}\} \end{cases} \tag{2.57}$$

and with

$$\overline{SW} = \frac{k \cdot a + (n-k) \cdot b}{n} \tag{2.58}$$

$$\sigma_{SW}^2 = \frac{1}{n-1}\Big(k \cdot (a - \overline{SW})^2 + (n-k) \cdot (b - \overline{SW})^2\Big) \tag{2.59}$$

For each of the standardized SWs the cross-correlation coefficient is calculated as the average product of corresponding values of the curve and the original data, i.e.

$$cc_j = \frac{1}{n} \sum_{i=1}^{n} SW_{st_j}(t_i) \cdot \tilde{x}_i. \tag{2.60}$$

These $n \cdot (n-1)$ values are between -1.0 and 1.0, where a low value stands for a poor fit and 1.0 means that the curve is a perfect fit. Therefore the curve with the highest cross-correlation value is chosen to be the best fit curve. It is an optimal curve with respect to the residual sum

of squares (or squared error). Let cc_{max} denote the according correlation coefficient.

Definition 2.46. Let $\{t_1, \ldots, t_n\}$ be the time points within the 24h interval corresponding to the measurement points $\{x_1, \ldots, x_n\}$. Let $X(t)$ be the model function. Then the squared error or residual sum of squares (RSS) is defined as

$$RSS = \sum_{i=1}^{n} (x_i - X(t_i))^2. \tag{2.61}$$

The *mean* squared error is calculated in the same manner divided by the number of measure points.

Parameters characterizing the SW according to [22]

Basically the SW is characterized by 4 parameters, with the help of which profile indices can be calculated [22].

Definition 2.47.

- $\boldsymbol{PM_{high}} \ldots$ ‚period mean high'; mean value of the measurements in the segment, that was determined to be the higher level period (previously indicated as the a-period)
- $\boldsymbol{PM_{low}} \ldots$ ‚period mean low'; mean value of the measurements in the segment, that was determined to be the lower level period (previously indicated as the b-period)
- $\boldsymbol{t_{up}} \ldots$ time point of the transition from the PM_{low}-period to the PM_{high}-period
- $\boldsymbol{t_{down}} \ldots$ time point of the transition from the PM_{high}-period to the PM_{low}-period

From these parameters, further indices can be deduced [22], [70].

Definition 2.48.

- $\boldsymbol{TD_{high}} \ldots$ ‚time duration high'; time duration of the high level period

$$\boldsymbol{TD_{high} := t_{down} - t_{up}} \tag{2.62}$$

- $\boldsymbol{TD_{low}} \ldots$ ‚time duration low'; time duration of the low level period

$$\boldsymbol{TD_{low} := t_{up} - t_{down} = 24h - TD_{high}} \tag{2.63}$$

- $\boldsymbol{M} \ldots$ overall mean value of 24h measurements

$$\boldsymbol{M := \frac{PM_{high} \cdot TD_{high} + PM_{low} \cdot TD_{low}}{24}} \tag{2.64}$$

- $\boldsymbol{LD}$ ... ‚level difference'; difference between the levels of the high period and the low period

$$\boldsymbol{LD := PM_{high} - PM_{low}} \tag{2.65}$$

The three values LD, t_{up} and t_{down} are considered as the characterizing indices of the circadian variation around the overall mean level.

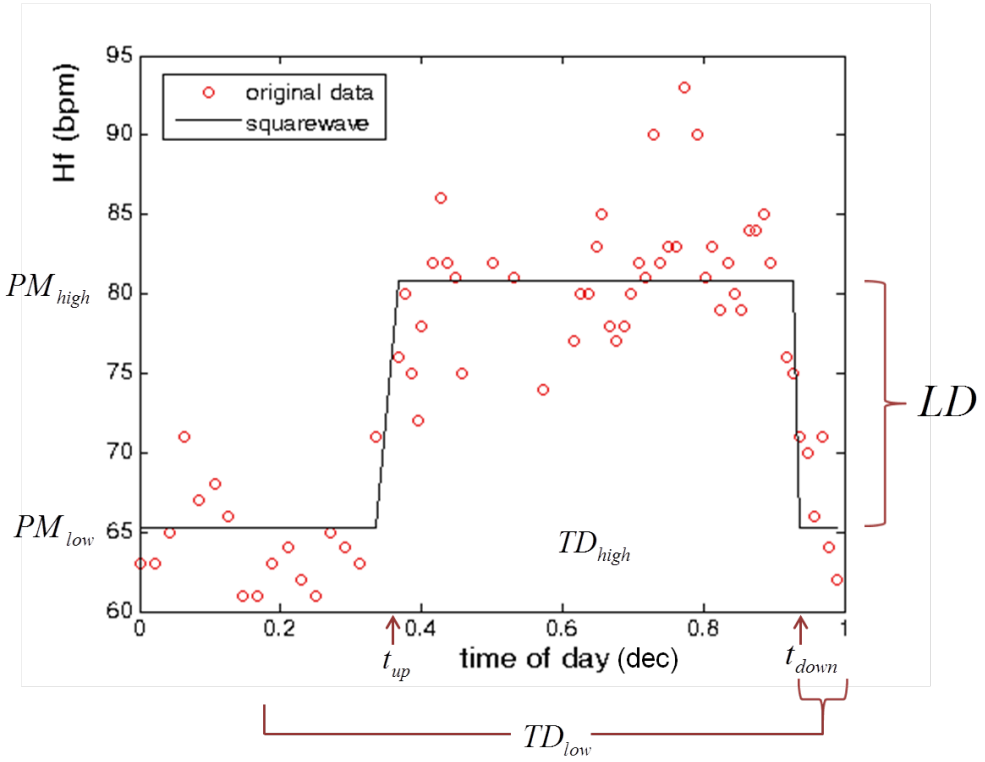


Figure 2.7: Parameters and indices of the square wave (cf. definitions 2.47 and 2.48) adapted from [70]. The time of day is given in decimal numbers.

Another index obtained from this method, is a measure for the variability of the signal. The value of cc^2_{max} expresses to what extend the model accounts for the total variation of the 24h profile. This leads to the following definition.

Definition 2.49. The percentage of the total 24h variability (PVA) captured by the square wave fit can be expressed as

$$\boldsymbol{PVA = 100 \cdot cc^2_{max}}. \tag{2.66}$$

Advantages and Disadvantages of the SW

This method of capturing the profile of the dataset is a refinement to the approach NBPF discussed in section 2.12. There, the averaging is done over *defined* day time and night time periods which includes a subjective component in the analysis. The SW is advanced in the sense of objectivity and correctness since is is a method based on a mathematical model and the periods are implicitly determined [22]. On the other hand this fact might affect comparability

of the data sets when day time and night time differ from individual to individual depending on the purpose of the study.
The SW method has been applied to invasive BP measuring with a catheter, but it has been pointed out that it is as well suitable for ABPM data [22]. In [45] it is further stated that the SW approach performs better in fitting the BP as well as the heart rate changes than the yet to be discussed Cosinor method (cf. 2.14.2).
One drawback of this approach is that the ansatz assumes that the transitions between night time and day time values are extremely abrupt. This does not reflect the fact that these transitions vary strongly from subject to subject [45].

Implementation - Restrictions on the Data Set and Features of the Algorithm

The algorithm offers the opportunity to fix a minimal period duration for the high level and the low level period. This seems reasonable since some data sets would lead to a square wave, where one of the periods is essentially one data point (cf. figure 2.8).

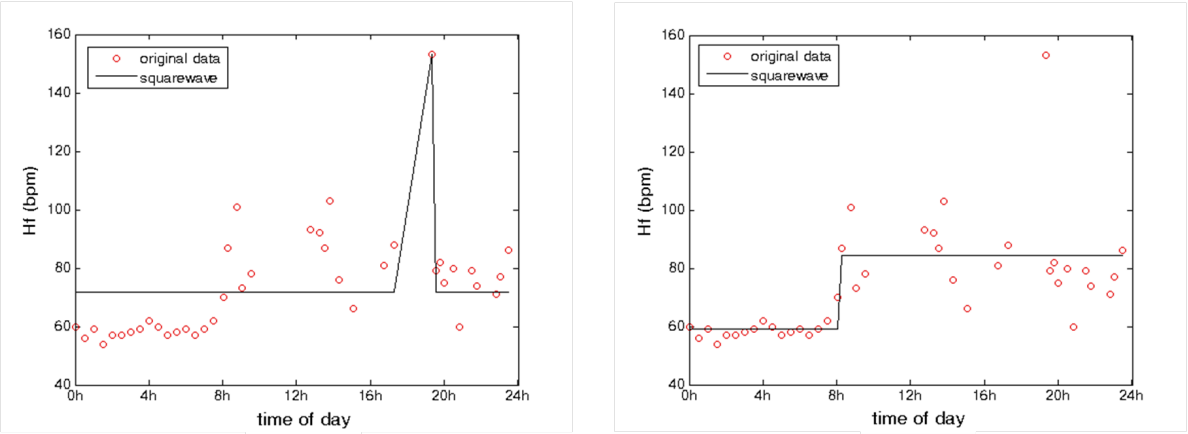


Figure 2.8: The figure on the left side was obtained by the MATLAB function `calc_squarewave2neu.m` without any restrictions on the period length. The figure on the right side was obtained with the same function including the restriction that each period should at least include 6 data points. (Considering a data set with ideal recording quality (i.e. no missing measurement) this is a time period of approximately 3 hours.) The correlation coefficient for the square wave on the left side is approximately 0.6707 while it is about 0.6608 for the one on the right side, which seems to be an acceptable decrease.

Due to methodological/algorithmic reasons this approach, to ask for a minimum number of measurements, is sensitive to the time gaps between consecutive readings. With a schedule of one reading every 30 minutes during 24h, the demand of 40 readings within a period for instance would mean a demand of 20 hours for each period, which is not possible. The code gives a warning if the input parameter `mindur` indicating this minimum number of measurements is greater than half the number of all readings.

2.14.2 Cosinor Method

Motivation

As the name of this method indicates, a single cosine curve or a linear combination of cosine waves with different amplitudes and acrophases but known period (24h in case one single cosine wave is used) are fitted to the data. The motivation for this ansatz is the fact that circadian signals can be seen as smooth rhythms with noise [53]. In this section, the *‚single component cosinor'* method will be discussed. The ansatz with multiple cosine waves (*‚multiple component analysis'*) is part of section 2.14.3.

Single Component Cosinor

In this case the ansatz is a single cosine function. It is fitted to the data set by a least squared error criterion. Since for circadian signals the period of the cosine function can be assumed to be known, namely one oscillation during 24h [9].

Calculation of the Cosine Wave

Definition 2.50. The ansatz for the cosinor method is given by a cosine function of the form[9], [53]

$$X(t) = M + A \cdot \cos\left(\frac{2\pi t}{P} + \varphi\right) \tag{2.67}$$

where M, A and ϕ are the unknown variables which are obtained by the fitting and P is the period which is assumed to be known.

The variables of this function can be interpreted as follows.

- $M \ldots$ MESOR (*'midline estimating statistic of rhythm mean'*); This value is an estimation for the average value of the variable under investigation. If the data are not equidistant and/or the number of cycles in the data is not an integer number, the value for the MESOR differs from that for the arithmetic mean value [53].

- $A \ldots$ amplitude of the oscillation; This is a measure for the predicted variation of the signal. It indicates half of the extend of the variation within a cycle [9]. Without loss of generality one can assume that $A \geq 0$, where $A > 0$ indicates the presence of a rhythm [72].

- $\varphi \ldots$ acrophase; This value is a measure of the time frame, when high level values will recur in each cycle, so it should predict the period of high level values [9]. It is the phase of the maximum in relation to a fixed reference time [53]. Typically the reference point of $0°$ is set as midnight [72]. Sometimes simply the time point, when the maximum occurs is called acrophase [63].

- $P \ldots$ period; This is the duration of a single cycle. This period is assumed to be (at least approximately) known. Since the data points appear in a time period of about 24h, the

period can be assumed to be equal to 24h [9]. The linear regression model for data points x_i and corresponding time points t_i can be written as

$$x_i = M + A \cdot \cos(\vartheta_i + \varphi) + e_i, \tag{2.68}$$

where e_i is an unknown error term and $\vartheta_i = \frac{2\pi t_i}{P}$ are the trigonometric angles [53]

- $\frac{2\pi}{P} = \omega \ldots$ angular frequency; Since P is assumed to be known, so is ω. Assuming $\omega = 1$ [72] means that the period length is 2π and thus the frequency is $\frac{1}{2\pi}$ i.e. one oscillation in an interval of 2π. This needs to be rescaled such that one oscillation within 24h is obtained [72]. This leads to

  -) rad: scale $t \longmapsto \frac{\pi}{12} t$

  -) deg: scale $t \longmapsto 15t$

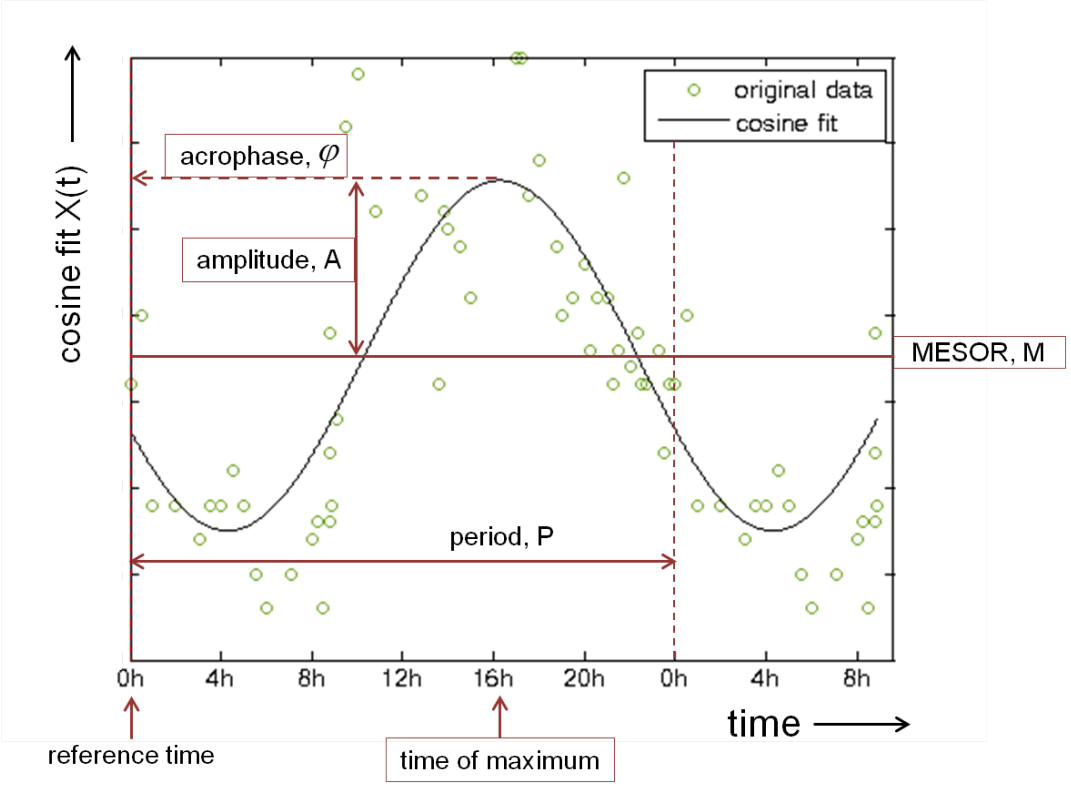


Figure 2.9: Parameters of the cosine function (adapted from [9]). The MESOR M is an approximation to the mean value of the data, adjusted for the rhythm of the signal. The amplitude A is a measure for half of the extend of the expected variation within one cycle. The acrophase φ measures when overall high values recur within a cycle and it is expressed in (negative) degrees as the relation to a reference time which is set to $0°$. The period P is the duration of a single cycle and it is equivalent to $360°$.

Definition 2.51. According to the previous remarks and definitions a legitimate ansatz for the curve is given by [9], [72]

$$X(t) = M + A \cdot \cos(\omega t - \varphi) \tag{2.69}$$

with

$$\omega = \begin{cases} \frac{\pi}{12}, & \text{for rad} \\ 15, & \text{for deg} \end{cases}, \tag{2.70}$$

with M, A and φ as the three degrees of freedom.

For convenience reasons the following analysis is done in the previous notation.

Comment 2.52. In the implementation calculations are done within the interval $[\frac{0}{24}, \frac{24}{24})$ thus $[0, 1)$ instead of $[0, 24)$. Accordingly the period length $P = 1$ and therefore the scaling for ω reads as

$$\omega = \begin{cases} 2\pi, & \text{for rad} \\ 360, & \text{for deg} \end{cases}. \tag{2.71}$$

□

With the help of the following identities

$$\beta = A\cos(\varphi), \quad \gamma = -A\sin(\varphi), \quad y = \cos\left(\frac{2\pi t}{P}\right), \quad z = \sin\left(\frac{2\pi t}{P}\right) \tag{2.72}$$

and the addition theorems, formula 2.67 can be transformed to

$$X(t) = M + \beta y + \gamma z. \tag{2.73}$$

The idea is now to minimize the RSS. This is the sum of the squared differences between each measure point x_i at the time point t_i and the estimated values given by the model at the same time point [9] (cf. definition 2.46). Adapted to the model under consideration the RSS reads as

$$RSS = \sum_{i=1}^{n} (x_i - \underbrace{(M + \beta y_i + \gamma z_i)}_{=X(t_i)})^2. \tag{2.74}$$

The task is now to determine the unknown variables M, β and γ in a way that the above value is minimal. This is achieved when its first derivatives with respect to the three variables vanish. Based on this observation one obtains the so called normal equations. Solving them leads to

the optimal combination of the variables M, β and γ with respect to the RSS.

$$\frac{\partial}{\partial M}RSS = \sum_{i=1}^{n} 2(x_i - (M + \beta y_i + \gamma z_i)) \cdot 1 \stackrel{!}{=} 0 \tag{2.75}$$

$$\frac{\partial}{\partial \beta}RSS = \sum_{i=1}^{n} 2(x_i - (M + \beta y_i + \gamma z_i)) \cdot y_i \stackrel{!}{=} 0 \tag{2.76}$$

$$\frac{\partial}{\partial \gamma}RSS = \sum_{i=1}^{n} 2(x_i - (M + \beta y_i + \gamma z_i)) \cdot z_i \stackrel{!}{=} 0 \tag{2.77}$$

Dividing the equations by 2 and rearranging some terms yields

$$\sum_{i=1}^{n} x_i = Mn + \beta \sum_{i=1}^{n} y_i + \gamma \sum_{i=1}^{n} z_i \tag{2.78}$$

$$\sum_{i=1}^{n} x_i y_i = M \sum_{i=1}^{n} y_i + \beta \sum_{i=1}^{n} y_i^2 + \gamma \sum_{i=1}^{n} z_i y_i \tag{2.79}$$

$$\sum_{i=1}^{n} x_i z_i = M \sum_{i=1}^{n} z_i + \beta \sum_{i=1}^{n} y_i z_i + \gamma \sum_{i=1}^{n} z_i^2. \tag{2.80}$$

This can be expressed in matrix - vector form as

$$\begin{pmatrix} \sum_{i=1}^{n} x_i \\ \sum_{i=1}^{n} x_i y_i \\ \sum_{i=1}^{n} x_i z_i \end{pmatrix} = \begin{pmatrix} n & \sum_{i=1}^{n} y_i & \sum_{i=1}^{n} z_i \\ \sum_{i=1}^{n} y_i & \sum_{i=1}^{n} y_i^2 & \sum_{i=1}^{n} y_i z_i \\ \sum_{i=1}^{n} z_i & \sum_{i=1}^{n} y_i z_i & \sum_{i=1}^{n} z_i^2 \end{pmatrix} \begin{pmatrix} M \\ \beta \\ \gamma \end{pmatrix} \tag{2.81}$$

which can be written in compact from as

$$\vec{b} = S \cdot \vec{l}. \tag{2.82}$$

Estimates for M, β and γ are then obtained by calculating

$$\hat{\vec{l}} = S^{-1}\vec{b}. \tag{2.83}$$

Finally, the solutions β and γ are used to estimate the amplitude A and the acrophase ϕ given by

$$A = \sqrt{\beta^2 + \gamma^2} \tag{2.84}$$

$$\varphi = \tan^{-1}\left(-\frac{\gamma}{\beta}\right) + K\pi, \tag{2.85}$$

where $K \in \mathbb{N}$ is determined by the signs of β and γ. For the exact calculation of K see equation 2.87 in the following comment.

Comment 2.53. [53] The calculation of the variables is simpler, if the data points are equidistant and the cycle number is an integer. In this case, the MESOR M is simply the arithmetic

mean of the data ($M = \overline{X}$), while A and φ are estimated by

$$A = \sqrt{\beta^2 + \gamma^2} \tag{2.86}$$

$$\varphi = \begin{cases} -\tan^{-1}|\frac{\gamma}{\beta}| & \gamma > 0 \wedge \beta \geq 0 \\ -\pi + \tan^{-1}|\frac{\gamma}{\beta}| & \gamma \geq 0 \wedge \beta < 0 \\ -\pi - \tan^{-1}|\frac{\gamma}{\beta}| & \gamma < 0 \wedge \beta \leq 0 \\ -2\pi + \tan^{-1}|\frac{\gamma}{\beta}| & \gamma \leq 0 \wedge \beta > 0 \end{cases}, \tag{2.87}$$

where in this case

$$\beta = \frac{2}{n}\sum_{i=1}^{n} \cos\left(\frac{2\pi t_i}{P}\right) x_i \tag{2.88}$$

$$\gamma = \frac{2}{n}\sum_{i=1}^{n} \sin\left(\frac{2\pi t_i}{P}\right) x_i. \tag{2.89}$$

□

Comment 2.54. At this point, statistical test can be performed to ‚rate' the obtained variables and therefore the signal profile. It is for instance interesting to decide, whether the amplitude is significantly different from 0 so a rhythm is present [53]. The significance of the model itself as well can be tested with an F-test [9]. □

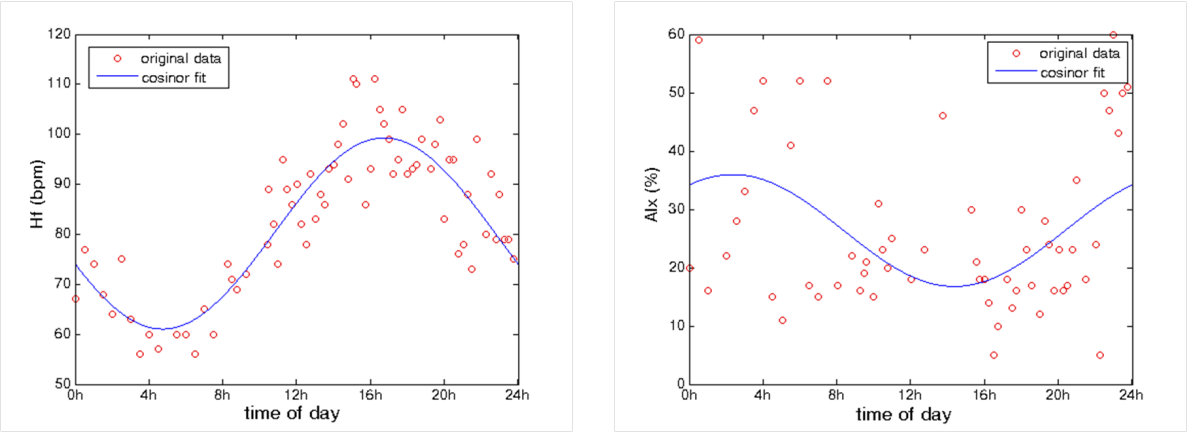


Figure 2.10: While in the plot on the left hand side displaying Hf data the cosine wave seems to fit the data well, the data in the figure on the right hand side showing AIx values create a profile not predestined for a cosinor fit. Both figures were obtained by the MATLAB function `calc_cosinorfit.m`.

Advantages and Disadvantages of the Cosinor fit

One advantage of this method is that, since it is conceived as a regression problem, it is suitable for non-equidistant data, what will usually be the case at hand [9]. Furthermore the appli-

cation is rather simple [45] and the meaning and interpretation of the parameter obtained is intuitive [67]. The method provides useful information about the amplitude of the oscillation and its phase [18].
The method operated under the assumption that $TD_{high} = TD_{low}$, so the duration of the period with higher values is as long as the duration of the period with lower values, which affects the correctness of the model. In general many assumption have to be made, which can not necessarily be justified. Besides the already mentioned assumption that day time and night time period are of equal length, it is additionally supposed that the transitions between the periods can be modelled smoothly and symmetrically. Both assumptions are often not too close to reality [45], [71].

2.14.3 Truncated Fourier Analysis

Motivation

The considered data set can simply be seen as a time series. In the field of time series analysis the Fourier analysis or spectral analysis is a pervasive tool. The idea is based on the following

> *‚Fourier analysis (also called "spectral analysis") is based on Fourier's revolutionary insight that any time series, regardless of its shape or regularity, can be described by a series of sine and cosine waves of various frequencies (Fourier 1822).'* [53]

Calculation of the Fourier Curve - Multiple Component Analysis

The general ansatz in a fourier analysis is given by a fourier series

$$F(t) = a_0 + \sum_{k=1}^{\infty} (a_k \cdot \cos(kt) + b_k \cdot \sin(kt)) \tag{2.90}$$

Definition 2.55. The model curve which is desired to describe the 24h data profile is given by [71]

$$f(t) = M + C_1 \cos\left(\frac{2\pi t}{24} - \phi_1\right) + \cdots + C_k \cos\left(\frac{2\pi kt}{24} - \phi_k\right), \tag{2.91}$$

where M is the mesor, $C_1, \ldots, C_k$ are constants representing the amplitudes of the cosine components ($= \frac{max-min}{2}$). The acrophases (given in rad) are indicated by $\phi_1, \ldots, \phi_k$. The model curve f is a function of the time t given in hours with decimal fractions as minutes. For detailed interpretation of the variables cf. section 2.14.2.

Comment 2.56. For $k = 1$ one obtains the single component cosinor method (2.14.2). □

As a first observation one sees that a finite number of ansatz functions instead of the infinite series is used (‚truncated'). Further it is sufficient to solely use cosine functions, since a sine function can always be replaced by a cosine function due to the relation $\sin(x) = \cos(x - \frac{\pi}{2})$. Furthermore, all constants $C_1, \ldots, C_k$ can be assumed to be greater or equal to zero, since the

sign of the cosine can be changes by a phase shift: $-\cos(x) = \cos(x - \pi)$. The period of the $i-$th harmonic is equal to $\frac{24}{i}$ hours. The reference time is here as for the single component cosinor method usually set to midnight.

Comment 2.57. Again it has to be noted, that for the implementation the time from midnight to midnight of the following day is converted to the interval $[0, 1)$. Accordingly, in the formula for the truncated fourier series (and also in the following formulas), 24 is substituted by 1. For convenience reasons the previous notation is retained in the following analysis. □

As a next step the ansatz from definition 2.55 is transformed and some terms are renamed. Using the addition theorem $\cos(A - B) = \cos(A)\cos(B) + \sin(A)\sin(B)$ yields

$$\begin{aligned} f(t) = M &+ C_1 \cos\left(\frac{2\pi t}{24}\right)\cos(\phi_1) + C_1 \sin\left(\frac{2\pi t}{24}\right)\sin(\phi_1) + \\ &+ C_2 \cos\left(\frac{2\pi 2t}{24}\right)\cos(\phi_2) + C_2 \sin\left(\frac{2\pi 2t}{24}\right)\sin(\phi_2) + \\ &+ \quad \cdots \quad + \\ &+ C_k \cos\left(\frac{2\pi kt}{24}\right)\cos(\phi_k) + C_k \sin\left(\frac{2\pi kt}{24}\right)\sin(\phi_k). \end{aligned} \tag{2.92}$$

The substitutions

$$X_i(t) = \cos\left(\frac{2\pi it}{24}\right), \quad a_i = C_i \cos(\phi_i) \tag{2.93}$$

$$Z_i(t) = \sin\left(\frac{2\pi it}{24}\right), \quad b_i = C_i \sin(\phi_i) \tag{2.94}$$

for $i = 1, \ldots, k$ then leads to the linear regression model

$$\begin{aligned} f(t) = M &+ a_1 X_1(t) + b_1 Z_1(t) + \\ &+ a_2 X_2(t) + b_2 Z_2(t) + \\ &+ \quad \cdots \quad + \\ &+ a_k X_k(t) + b_k Z_k(t) \end{aligned} \tag{2.95}$$

The independent variables are here X_i and Z_i, $i = 1, \ldots, k$. The variables M, a_i and b_i, $i = 1, \ldots, k$ have to be determined employing a (weighted) least square analysis. The (optional) weights are the lengths of the intervals between two consecutive measurements. The distance is seldom constant [70].

Finally, one obtains the sought for values for the amplitudes and the phases by calculating

$$C_i = \sqrt{a_i^2 + b_i^2}, \quad i = 1, \ldots, k \tag{2.96}$$

$$\phi_i = \begin{cases} \frac{24}{2\pi i} \arctan\left(\frac{b_i}{a_i}\right), & \text{for } a_i > 0 \\ \frac{24}{2\pi i} \arctan\left(\frac{b_i}{a_i} + \pi\right), & \text{for } a_i < 0 \end{cases}, \quad i = 1, \ldots, k \tag{2.97}$$

In the case, that $\phi_i < 0$, the value $\frac{24}{i}$ has to be added to ϕ_i to obtain a value between 0h and 24h.

Comment 2.58. This calculation for the acrophases is taken from the scientific article [71]. When implementing this method, it becomes apparent that it is not fully correct, since the curves do not fit the data. Appropriate curves are obtained when the calculation of the acrophases is done in the same manner as in formula 2.87, dependent on both signs. The calculation can only be done exactly as for the cosinor method if the ansatz is made with '$+\varphi_i$' and accordingly $\cos(A+B) = \cos(A)\cos(B) - \sin(A)\sin(B)$. Further the regression model in formula 2.95 holds, if b_i is defined as $-C_i \sin(\varphi_i)$. If the value of φ_i is needed one has to pay attention to that in the calculations.
Alternatively, as done in the implementation, a_i and b_i as obtained from the regression model can be used directly to set up the model function (cf. formula 2.95). □

Implementation - Least Square Method [68]

Similar as for the cosinor method the values for a_i, b_i und M have to be determined in a way, that the RSS is minimal. In the following, the case is studied, where the sum of squared errors is extended by a weight w_i for each data point x_i. Therefore the following expression has to be minimized

$$RSS = \sum_{i=1}^{n} w_i (x_i - f(t_i))^2 = \sum_{i=1}^{n} w_i \Big(x_i - \Big(M + \sum_{j=1}^{k} (a_j X_j(t_i) + b_j Z_j(t_i)) \Big) \Big)^2, \tag{2.98}$$

where x_i is the measurement value at the time point t_i and $f(t_i)$ is the value of the model curve at t_i as the approximation by the model of x_i. The variables w_i indicate (optional) weights. A mentioned before, in our case, these weights can be chosen as the time intervals between consecutive readings. If calculations should be done without any weighting, all w_i can be set to 1 in the whole scheme.
The above error estimate is minimal, if all the derivatives with respect to each parameter are equal to zero. Consider therefore

$$\frac{\partial}{\partial M} RSS = \sum_{i=1}^{n} 2 \cdot w_i \Big(x_i - \Big(M + \sum_{j=1}^{k} (a_j X_j(t_i) + b_j Z_j(t_i)) \Big) \Big) \cdot (-1) \tag{2.99}$$

By setting this expression equal to zero, dividing by (-2) and rearranging the terms leads to the first equation:

$$\sum_{i=1}^{n} w_i x_i = M \cdot \sum_{i=1}^{n} w_i + \sum_{i=1}^{n} w_i \Big(\sum_{j=1}^{k} a_j X_j(t_i) \Big) + \sum_{i=1}^{n} w_i \Big(\sum_{j=1}^{k} b_j Z_j(t_i) \Big) \tag{2.100}$$

The last two sums can be rearranged such that the variables of interest, namely a_j, b_j and M, are made ‚explicit'. This is required to properly set up the linear equation system.

$$\sum_{i=1}^{n} w_i x_i = M \cdot \sum_{i=1}^{n} w_i + \sum_{j=1}^{k} a_j \Big(\sum_{i=1}^{n} w_i X_j(t_i) \Big) + \sum_{j=1}^{k} b_j \Big(\sum_{i=1}^{n} w_i Z_j(t_i) \Big) \tag{2.101}$$

The derivative with respect to one of the $a_s, 1 \leq s \leq k$ yields

$$\frac{\partial}{\partial a_s} RSS = \sum_{i=1}^{n} 2 \cdot w_i \Big(x_i - \Big(M + \sum_{j=1}^{k} (a_j X_j(t_i) + b_j Z_j(t_i)) \Big) \Big) \cdot (-X_s(t_i)) \tag{2.102}$$

Again, zeroing the equation, dividing by (-2) and rearranging the terms leads to

$$\begin{aligned} \sum_{i=1}^{n} w_i x_i X_s(t_i) = M \cdot \sum_{i=1}^{n} w_i X_s(t_i) + \sum_{j=1}^{k} a_j \sum_{i=1}^{n} w_i X_j(t_i) X_s(t_i) + \\ + \sum_{j=1}^{k} b_j \sum_{i=1}^{n} w_i Z_j(t_i) X_s(t_i) \end{aligned} \tag{2.103}$$

Analogously, the derivatives with respect to the $b_s, 1 \leq s \leq k$ provides k equations

$$\begin{aligned} \sum_{i=1}^{n} w_i x_i Z_s(t_i) = M \cdot \sum_{i=1}^{n} w_i Z_s(t_i) + \sum_{j=1}^{k} a_j \sum_{i=1}^{n} w_i X_j(t_i) Z_s(t_i) + \\ + \sum_{j=1}^{k} b_j \sum_{i=1}^{n} w_i Z_j(t_i) Z_s(t_i). \end{aligned} \tag{2.104}$$

For the $2 \cdot k + 1$ unknown variables, the equally many equations can be written as a linear equation system in matrix form

$$S \cdot \vec{l} = \vec{b} \tag{2.105}$$

with

$$S = \begin{pmatrix} w_i & w_i X_1 & w_i X_2 & \cdots & w_i X_k & w_i Z_1 & \cdots & w_i Z_k \\ w_i X_1 & w_i X_1^2 & w_i X_2 X_1 & \cdots & w_i X_k X_1 & w_i Z_1 X_1 & \cdots & w_i Z_k X_1 \\ w_i X_2 & w_i X_1 X_2 & w_i X_2^2 & \cdots & w_i X_k X_2 & w_i Z_1 X_2 & \cdots & w_i Z_k X_2 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots \\ w_i X_k & w_i X_1 X_k & w_i X_2 X_k & \cdots & w_i X_k^2 & w_i Z_1 X_k & \cdots & w_i Z_k X_k \\ w_i Z_1 & w_i X_1 Z_1 & w_i X_2 Z_1 & \cdots & w_i X_k Z_1 & w_i Z_1^2 & \cdots & w_i Z_k Z_1 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ w_i Z_k & w_i X_1 Z_k & w_i X_2 Z_k & \cdots & w_i X_k Z_k & w_i Z_1 Z_k & \cdots & w_i Z_k^2 \end{pmatrix}, \tag{2.106}$$

where in front of each entry of the matrix stands a sum $\sum_{i=1}^{n}$, and each X and each Z has t_i

as argument. Further

$$\vec{b} = \begin{pmatrix} \sum_{i=1}^{n} w_i x_i \\ \sum_{i=1}^{n} w_i x_i X_1(t_i) \\ \sum_{i=1}^{n} w_i x_i X_2(t_i) \\ \vdots \\ \sum_{i=1}^{n} w_i x_i X_k(t_i) \\ \sum_{i=1}^{n} w_i x_i Z_1(t_i) \\ \vdots \\ \sum_{i=1}^{n} w_i x_i Z_k(t_i) \end{pmatrix} \quad \text{and} \quad \vec{l} = \begin{pmatrix} M \\ a_1 \\ \vdots \\ a_k \\ b_1 \\ \vdots \\ b_k \end{pmatrix}. \tag{2.107}$$

This linear equation system can be written as

$$(X^T \cdot W \cdot X)\vec{l} = (X^T \cdot W)\vec{x}, \tag{2.108}$$

where $W = diag(w_1, \ldots, w_n)$ is a diagonal matrix containing the weights, $\vec{x} = (x_1, \ldots, x_n)$ is the vector containing the given data and X is the matrix

$$X = \begin{pmatrix} 1 & X_1(t_1) & \cdots & X_k(t_1) & Z_1(t_1) & \cdots & Z_k(t_1) \\ 1 & X_1(t_2) & \cdots & X_k(t_2) & Z_1(t_2) & \cdots & Z_k(t_2) \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & X_1(t_n) & \cdots & X_k(t_n) & Z_1(t_n) & \cdots & Z_k(t_n) \end{pmatrix}. \tag{2.109}$$

This representation is simpler to implement. The solution is now given by

$$\vec{l} = (X^T \cdot W \cdot X)^{-1} \cdot (X^T \cdot W)\vec{x}. \tag{2.110}$$

Indices obtained from the Model

Basically the model provides two indices [70], which are defined in definition 2.59 and are graphically shown in figure 2.11.

Definition 2.59. (cf. figure 2.11)

- ***AMP*** ... 'overall amplitude'; half of the difference between the maximal and the minimal value of the model curve

$$\boldsymbol{AMP} := \frac{\max\limits_{x \in [0,24]} f(x) - \min\limits_{x \in [0,24]} f(x)}{2} \tag{2.111}$$

- ***AP*** ... 'overall acrophase'; time point, at which the first global maximum occurs

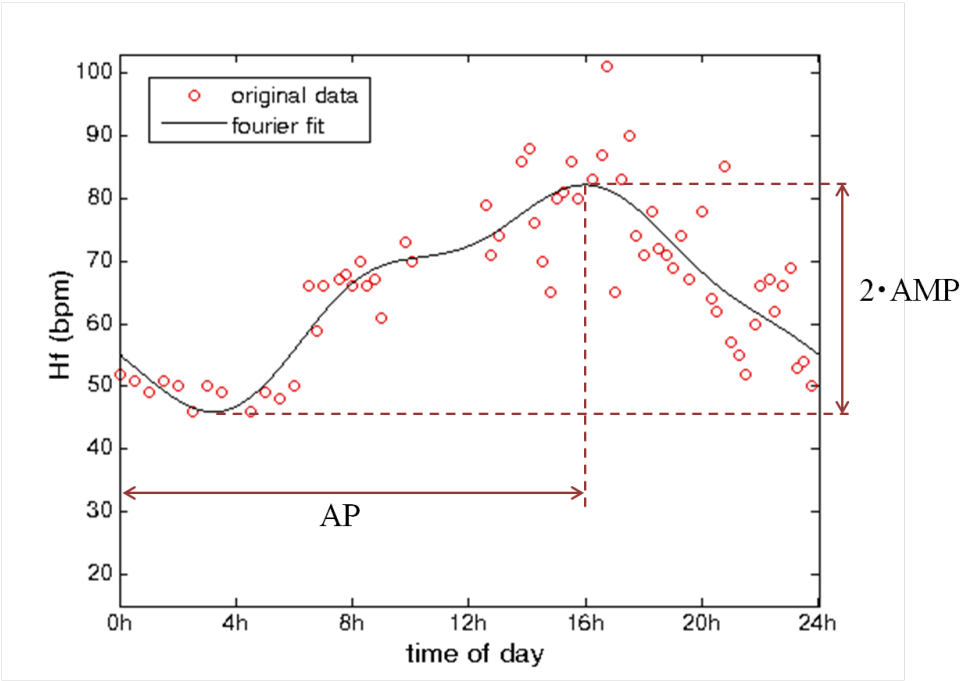


Figure 2.11: Indices of the 'truncated fourier analysis' (adopted from[70]); AMP =overall amplitude; AP =overall acrophase (cf. definition 2.59). The plot was obtained by the MATLAB function `calc_weightedfourier.m`, but the optional weighting was excluded. Three harmonics were used.

Comment 2.60.

- There is no distinct statement which number of harmonics is the best choice. It is conjectured that various numbers of harmonics are possible 'best choices' depending on the (temporal) distance between two measurements [22]. Other authors hold that the model is better the more harmonics are used [71]. However, their recommended number is 4 harmonics, since the method performed best for different data sets and the influence of added harmonics on the indices of the model were negligible.

- As well as the square wave also the fourier analysis can be used to segment the 24h interval in a lower level and a higher level period. However, using this model for segmentation is rather onerous. Idema et al. [22] found at least ten harmonics to be needed for adequate segmentation. In general the authors claim the square wave method to perform better considering segmentation. □

Advantages and Disadvantages of the Fourier Analysis

This method captures the complexity of the signal better than previously mentioned approaches of this section. Furthermore, up to 11 indices can be derived from the model. However, for some of them the biological interpretation is unclear. Also the smoothing effect might lead to an 'over-modelling' of the measurements. However, this is (only) an issue, if one is interested in short time fluctuations [45]. Another advantage of this method is that it is applicable to

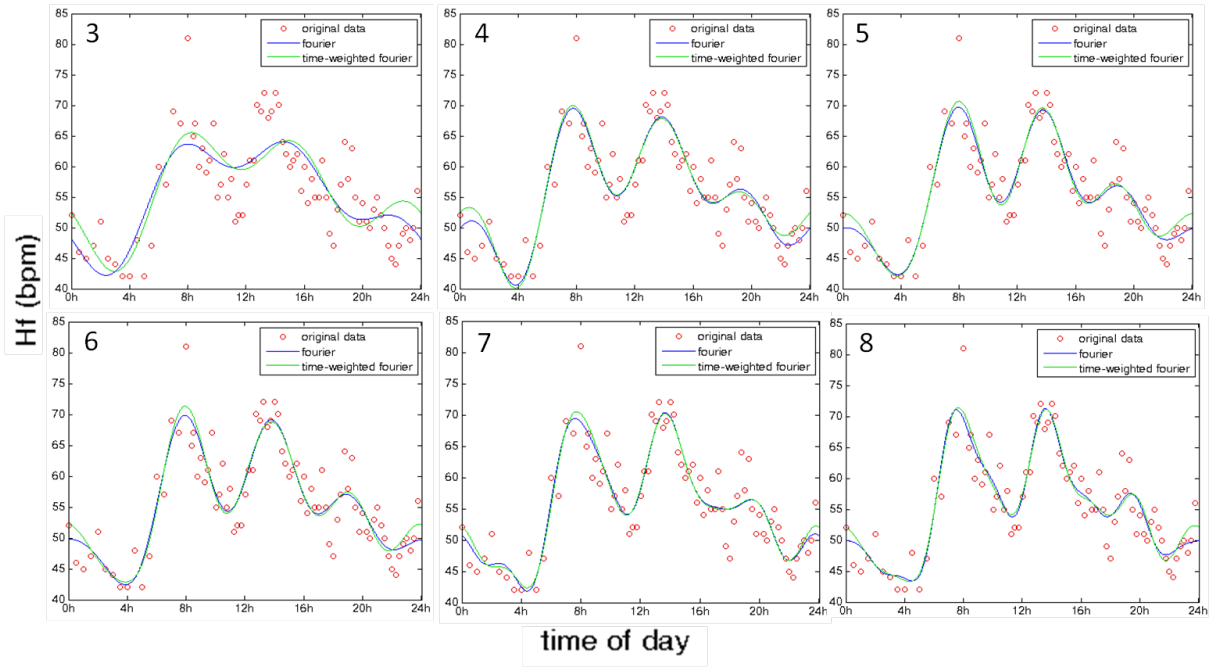


Figure 2.12: The above plots were produced with the MATLAB function `compare.m`. The number in the top left corner within each plot indicates the number of harmonics used for the fourier fit, where weighted (green) as well as unweighted (blue) regression analysis curves are depicted.

non-equidistant data sets same as the cosinor method. Additionally it overcomes the flaw of the latter mentioned assuming symmetrical period transitions and equal period durations [71]. Although some parameters might not be biologically interpretable, the amplitude and the acrophase are. Therefore these values might be of interest in statistical studies, where different groups are compared or one tries to predict cardiovascular diseases [71].

Implementation - Restrictions on the Data Set and Features of the Algorithm

The algorithm offers the opportunity to chose the number of used harmonics as well as whether weighting should be included. Figure 2.12 shows the influence of added harmonics as well as the differences between weighted and unweighted fourier fits. The time axis can be chosen as decimal numbers or as hours of the day.

2.14.4 Double Logistic Analysis

Motivation

Considering previously mentioned curve fitting methods, each of them, except the fourier model, works under at least one of two non legitimate assumptions.

i) The parameter profile is perfectly symmetric. The assumption is that the decline of the parameter (in the evening) shows exactly the same characteristics as its surge (in the morning) (cosinor method and SW fit).

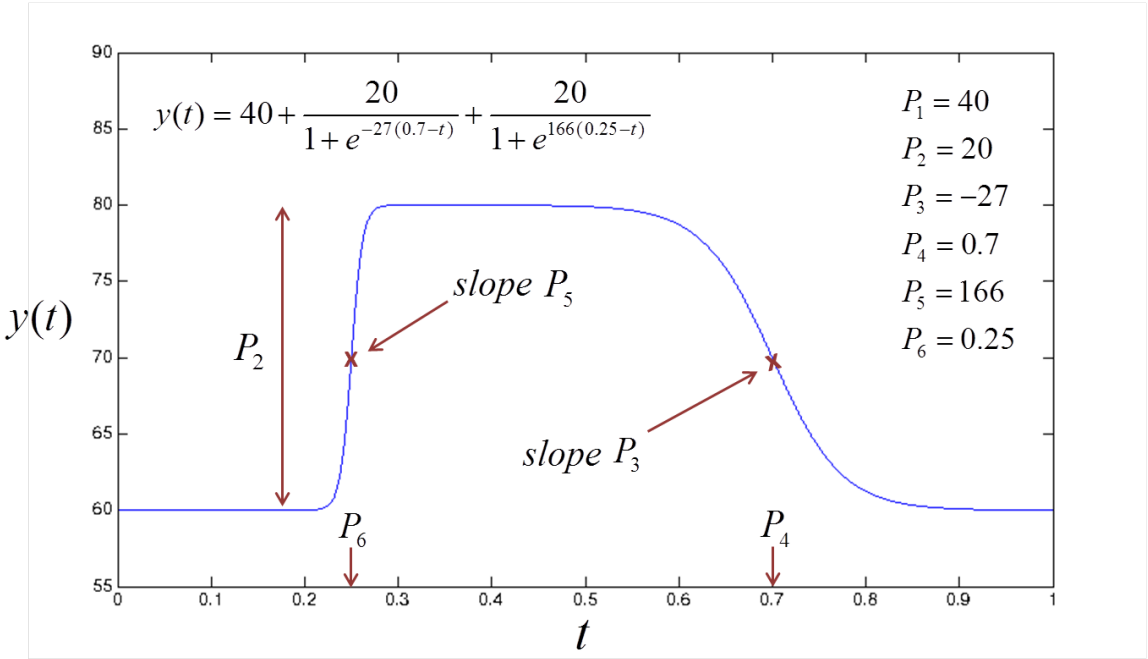


Figure 2.13: Example of a double logistic curve.

ii) The periods in which the considered parameter is higher respectively lower have the same length (cosinor method).

Both assumptions do not reflect reality - at least not for BP, for which the models were developed. The method of the double logistic analysis does not include any of these hypotheses. Therefore, this model excels with a better or at least equally good performance - also in comparison to the fourier fit - in different aspects of the analysis of the parameter profile [18], [45]. Head et al. developed this method for heart rate and BP data of rats [18]. In [19] they applied the method to heart data of humans.

> *‚We [...] developed a new analysis method which would be applicable to circadian changes of blood pressure and HR and which would not make a priori assumptions about the abruptness or symmetry of changes.'* [18]

Calculation of the Double Logistic Curve according to [18], [19]

Definition 2.61. The model curve which is desired to describe the 24h profile is given by

$$y(t) = P_1 + \frac{P_2}{1 + e^{P_3(P_4 - t)}} + \frac{P_2}{1 + e^{P_5(P_6 - t)}}, \tag{2.112}$$

where P_1 to P_6 have to be determined.

Such curves can, depending on the choice for P_1 to P_6, among others take a form like shown in figure 2.13. The parameters P_1 to P_6 represent the following qualities.

- $P_1 + P_2$ ... ‚baseline', ‚night - time - plateau'; This value is approximately the mean of the data measured during the lower level period.

- P_2 ... ‚amplitude'; This represents the range of the data, the difference between the lower level and the higher level period, respectively.

- Accordingly, P_1 is the lower level value minus the difference of the two plateaus. Therefore, to obtain the approximation of the mean value of the high level period, one has to add the difference of the plateaus P_2 to the lower level plateau $P_1 + P_2$, which equals $P_1 + 2P_2$.

- P_3 and P_5 serve the modelling of the transitions between the plateaus. They indicate the extend of steepness of the change between the levels. While P_3 is the slope from the higher to the lower plateau, P_5 gives the slope of the reverse transition.

- The values P_4 and P_6 are the time points at which 50% of the transition is reached. Therefore, they are the middle time points within the transition periods.

The curve is then fitted to the data with a least squared error criterion.

Implementation by Head et al. [18], [19]

The model descibed in [18], [19] proceeds more complex as the authors add 4 terms to the model curve in equation 2.112 to obtain a quasi periodic function. These additional terms are related to the preceding and the following day. Another term $P_2 \cdot q$ is added as a compensation parameter. The parameter q is equal to -2, if the data begin with the transition from high to low. Otherwise q is chosen as 2. The actual fitting curve therefore takes the form

$$\begin{aligned} y(t) = P_1 &+ \frac{P_2}{1 + e^{P_3(P_4 - t)}} + \frac{P_2}{1 + e^{P_5(P_6 - t)}} \\ &+ \frac{P_2}{1 + e^{P_3(P_4 - t - 24)}} + \frac{P_2}{1 + e^{P_5(P_6 - t - 24)}} \\ &+ \frac{P_2}{1 + e^{P_3(P_4 - t + 24)}} + \frac{P_2}{1 + e^{P_5(P_6 - t + 24)}} + P_2 \cdot q. \end{aligned} \tag{2.113}$$

This double logistic ansatz function is then fitted by a specially developed computer program written in Labview. It makes use of the Marquardt algorithm, which optimizes the parameters by the least squared error criterion. This requires adequate start values for the variables P_1 to P_6. By iteration the parameters are optimized by minimizing the squared error. To obtain first approximations for these values, another fitting method, namely the cosinor model, is used. For instance, a first approximation for P_2 is taken as two times the amplitude of the cosinor fit. Furthermore, for the parameters several constraints are made. The limits for P_1 and P_2 are determined from the SW fit. Mean values and standard deviations of the higher level period as well as of the lower level period, according to the SW, are calculated. Define y_{max} as the mean of the higher level values plus two times the according standard deviation and y_{min} as the mean of the lower level values minus two times the according standard deviation. The constraints for

P_1 and P_2 can then be chosen as

$$\begin{aligned} y_{min} \leq P_1 + P_2 < y_{max} \\ P_2 > 0 \\ y_{min} \leq P_1 + 2P_2 < y_{max}. \end{aligned} \tag{2.114}$$

Constraints for the curvature parameters were chosen in a way that transition phases lasted for at least 30 minutes. Plateaus should be at least 5 hours long. Details to the algorithm can be found in [18], [19].

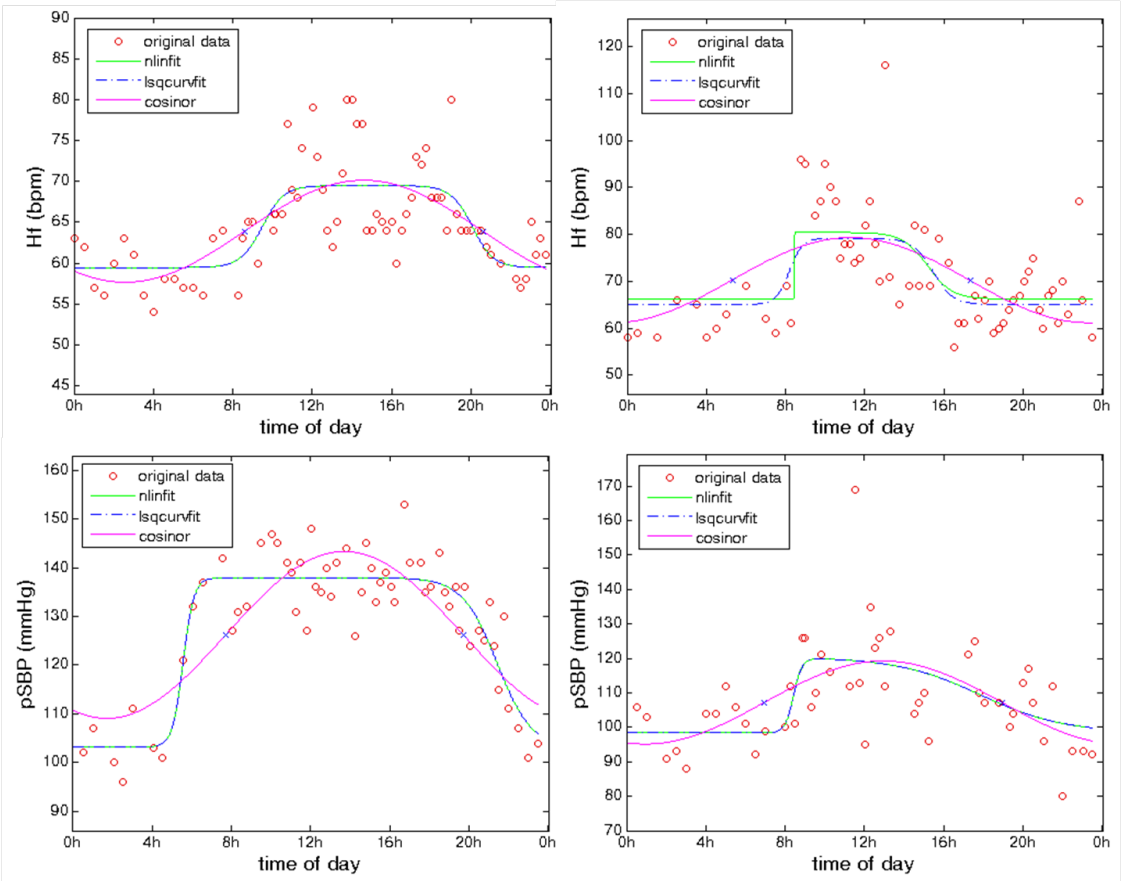


Figure 2.14: The plots were obtained by the MATLAB function `calc_doublelogisticfit.m`. As can be seen, the double logistic functions take reasonable forms. For the data in the top right corner, `nlinfit` and `lsqcurvefit` provide different curves. Nevertheless, both seem comprehensible.

Implementation - Restrictions on the Data Set and Features of the Algorithm

The approach to obtain a double logistic curve fit in this work is a simplified version of the one described above. It is done by the use of two different MATLAB built in functions, namely `nlinfit` and `lsqcurvefit`, which fit the function given in formula 2.112 to the data set by the least squared error criterion. These two functions as well require start values for the parameters

P_1 to P_6. These are obtained from the cosinor fit. The slopes at the two inflection points and their according time points are the initial values for P_3 to P_6. The level difference P_2 is chosen as the difference between the high level and the low level period as determined according to the cosinor method. P_1 is approximated by the difference of the low level mean and the approximation of P_2. This approach often yields favourable results for both of the functions as can be seen in figure 2.14 at pSBP as well as heart frequency (Hf) data. However several issues occur, when applying this algorithm. These will be discussed in the following.

One of the observations when applying the algorithm to different data sets is, that the curve does rise to the higher level but fails to fully return to the lower level plateau as can be seen in figure 2.15. To avoid this unfavourable effect, two approaches are made.

Since the start of the sleep time lies approximately within the interval (22h,2h), (BP) values begin to fall rather close to the end of the 24h monitoring period. This might hinder the curve to perceive another low level period. To obtain enough lower values, the data set may be extended by a certain number of measurements of the following day. In the absence of these measurements, simply the first couple of hours of the same day with the according measurements are added. The MATLAB function `calc_doublelogisticfit.m` provides an optional parameter `extension`, which is the number of hours the user wishes to add to the data set. Applying the MATLAB function `calc_doublelogisticfit.m` with an extension of 6 hours to the same data sets as in figure 2.15 leads to the desired return to the lower level plateau. This can be seen in figure 2.16

The second option is to shift the time point of the beginning of the measurements such that transition periods are most likely not close to the beginning or the end of the observation period. The MATLAB function `calc_doublelogisticfit2.m` includes the parameter `start` which is the time point when measurements should start. Applying this function again to the same data sets as in figure 2.15 and 2.16, respectively, with the start time set to 4 p.m. yields to the double logistic curves depicted in figure 2.17. However, the shape of the curve is rather sensitive to the starting time, since the fitted functions in 2.16 and 2.17 show - at least for the data set on the left - notably different characteristics.

Despite the presented favourable results, some further observations have to be mentioned. The implementation of this method by Head et al. is rather complex and the design of the curve in general seems to be only applicable to data sets with a specific shape. This can be seen in figure 2.18. The data sets do not show a typical diurnal BP tenor, which leads to a rather unfamiliar double logistic fit. The same could be said about the SW or the cosinor method and they do indeed not provide perfect fits for every data set, but the number of variables in these models is much smaller and therefore can be controlled easier. Head at al. include a lot of restrictions on the parameters of the model. This inclusion might improve the approach presented in this work.

Another observation made when applying the function `calc_doublelogisticfit.m` on the data sets is, that the resulting curve is rather sensitive to the initial values. The improvement of the calculation of adequate initial values presents another field of investigation to obtain a solid method. As the two MATLAB function often provide different results for the data sets, they require further analysis to find distinct quality criteria for the decision in favour of one of them.

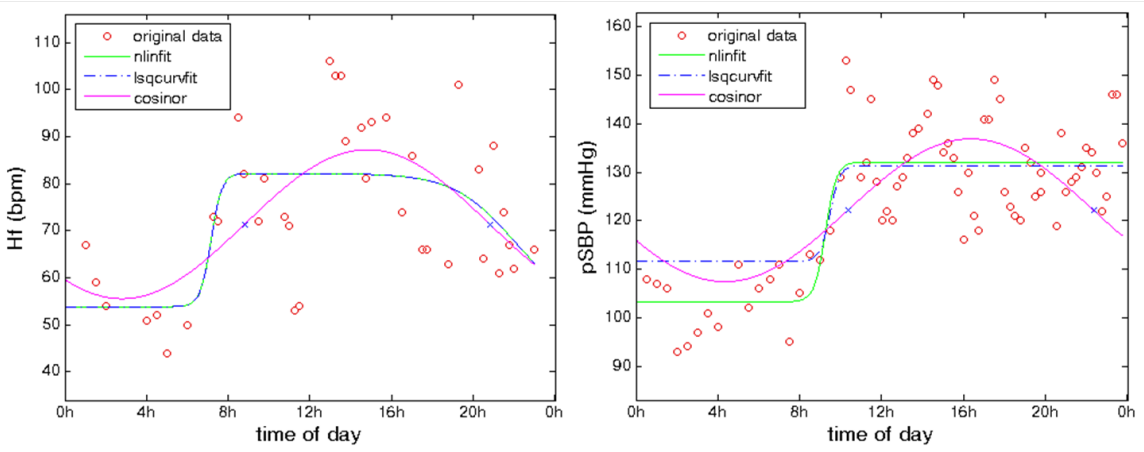


Figure 2.15: The plots were obtained by the MATLAB function `calc_doublelogisticfit.m`. They show the unfavourable effect, that the double logistic curve does not return to the lower level plateau.

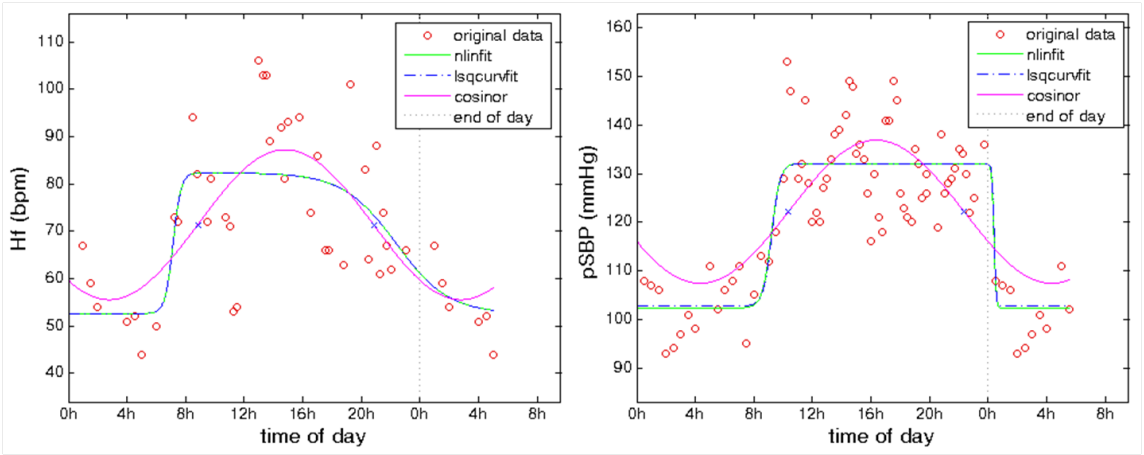


Figure 2.16: Applying the MATLAB function `calc_doublelogisticfit.m` with an extension of 6 hours to the same data sets as in figure 2.15 leads to the desired return to the lower level plateau.

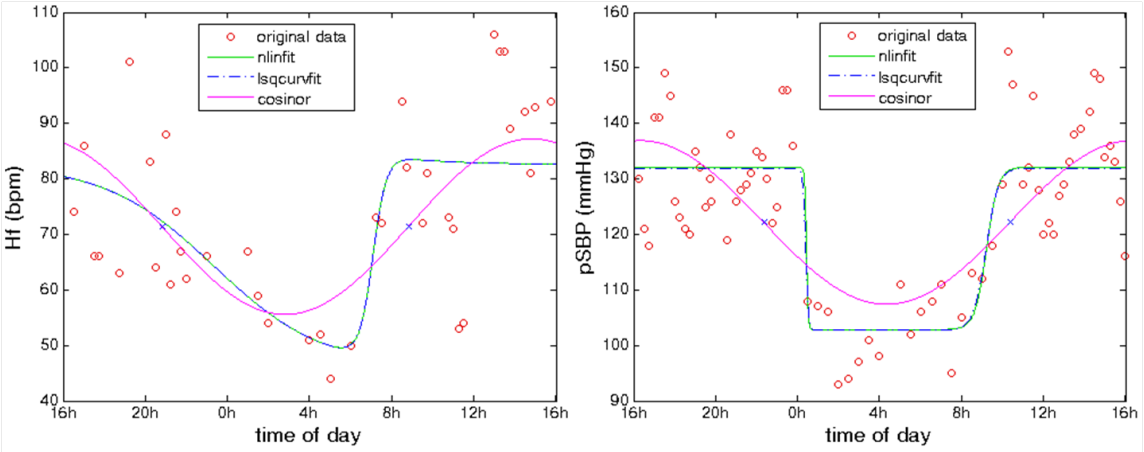


Figure 2.17: This double logistic curve was obtained by the MATLAB function `calc_doublelogisticfit2.m` with a shift of the starting time of the observations to 4 p.m.

Advantages and Disadvantages of the Double Logistic Analysis

The method is said to improve the modelling of the surge of BP in the morning, which is known to be a risk factor for stroke [18], [26]. The crucial innovation of this method is the possibility to consider BP decline when going to sleep and BP rise when getting up separately [19].

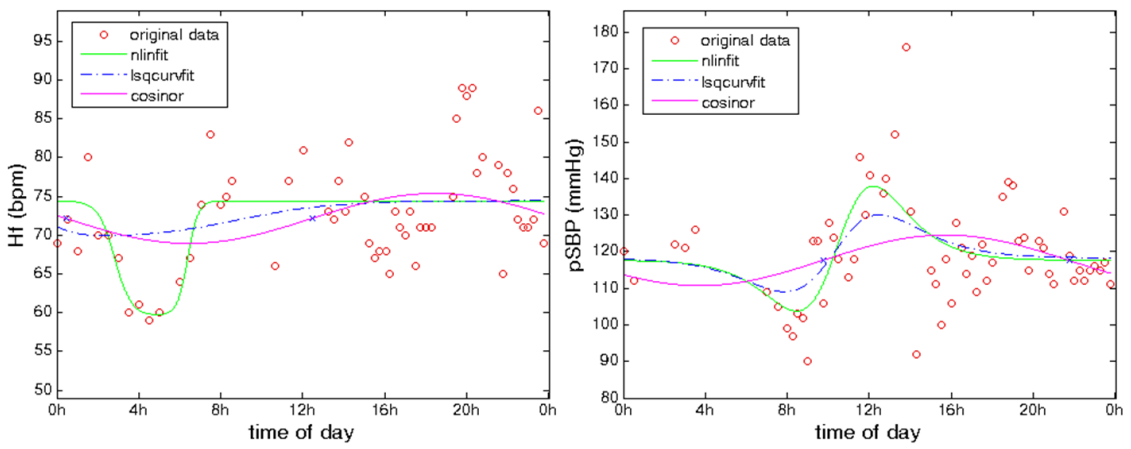


Figure 2.18: This double logistic curve was obtained by the MATLAB function `calc_doublelogisticfit2.m`. The shape seems unfamiliar.

2.15 Personalized Standard Deviation

In [14] another variant of the SD called personalized standard deviation (pSD) is described. In contrast to the cSD, which calculates the variance around the mean value, here the variance around the ‚expected' value is calculated. This ‚expected' value is obtained using the ‚smooth-curve method' (‚curve-fitting'). To the piecewise linear curve F (with $F_i = F(t_i) = x_i$), which results from linear interpolation of the measurements (a), a smooth curve f ($\hat{=} X$ in previous fitting models) is fitted (b). The calculation of the pSD is similar to the one for cSD, but normalization is done by the number of measurements and the expression $(F_i - \overline{X})$ is replaced by $(F_i - f_i)$ (with $f_i = f(t_i)$). This ‚difference curve' is shown in (c) (cf. figure 2.19).

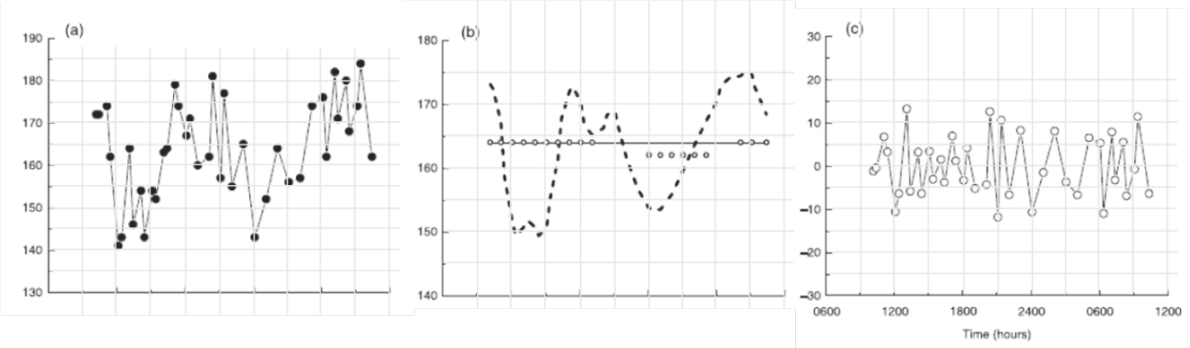


Figure 2.19: Curves for the calculation of pSD

Definition 2.62. The personalized standard deviation (pSD) is calculated using the formula

$$pSD = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(F_i - f_i)^2}, \tag{2.115}$$

where $F_i = x_i$ is the measured value at the time point t_i and $f_i = f(t_i)$ is the expected value at t_i given by the model function f.

Comment 2.63. In the paper [14] no specification is made which particular curve fitting method is used. However, according to the plots in the paper, it seems reasonable to use a fourier fit (cf. section 2.14.3). □

Comment 2.64. This index can be calculated for 24h, only day time or only night time data. The algorithm returns these 3 values. □

2.15.1 Advantages and Disadvantages of pSD

This index takes random variation and physiological variation into account. In contrast to other afore mentioned methods, such as cSD or wSD this method eliminates physiological variation mathematically and consequently extracts random variation [14]. (Although wSD at least partly takes physiological variation into account by excluding the NBPF (cf. section 2.12)) In their study, the authors were able to find an association between BPV measured by cSD, wSD as well as pSD and lacunar infarction (LACI), but the correlation was strongest when pSD was used to quantify BPV.

2.16 Cumulative Sum Analysis

2.16.1 Definition of Cusum

General Method

The method of cumulative sums is a statistical tool to analyse the changes in sequential data or time series. It is especially powerful when trying to detect abrupt changes [17]. Through the data an arbitrary but relevant [65] line is drawn. Successively the deviations from the data points to this line are calculated, summed (= cumulative sum) and plotted afterwards [65], [70]. If the values lie continuing above the reference line, positively leant curves are generated. Likewise the cusum plot shows a decreasing behaviour, if values keep lying below the reference line. The extend of the deviations is reflected by the more or less prominent slope of the curve. The changes in the trend of the data are much more revealed in the cusum plot than in the data [65].
As the name indicates, cumulative sums are calculated, which gives this technique a sequential structure [17]. The values from the measurements x_i are assigned with values ω_i - commonly ω

is a likelihood function - and summed according to the rule

$$S_0^+ := 0 \tag{2.116}$$

$$S_n^+ := \max(0, S_{n-1}^+ + x_n - \omega_n), \quad n \geq 1 \tag{2.117}$$

where S_n indicates the n-th cumulative sum.
If a given threshold value s^+ is exceeded by S_n, a change in the data is found. Considering the formula from above (cf. 2.116), changes are only recognized in the positive direction. For changes with negative sign, the maximum has to be replaced by a minimum. Changes are then present, if the sum drops below the given negative threshold value s^-. Sums are then indicated by S_n^+ and S_n^- respectively. In an overall cumulative sum indicated by S_n both trends are considered. This means that in every step the difference between the next data point and the reference value $(x_n - \omega_n)$ is added to the current sum [17]. The formulas read as follows.

$$S_0 = S_0^+ = S_0^- := 0 \tag{2.118}$$

$$S_n^+ := \max(0, S_{n-1}^+ + x_n - \omega_n) \tag{2.119}$$

$$S_n^- := -\min(0, -(S_{n-1}^- - x_n + \omega_n)), \quad n \geq 1 \tag{2.120}$$

$$S_n := S_{n-1} + (x_n - \omega_n) \tag{2.121}$$

Modified Method for the Data in Consideration

This general model of CUSUM can be applied to the time series under consideration in this work. Stanton et al. adopted this idea and proceeded as follows [65]. When analysing the variability of BP, heart rate and other parameters of interest, the above mentioned reference line can be chosen as the mean value of the parameter under consideration. This corresponds to ω_n from before, which is now constant for every n [65].

2.16.2 Construction of the CUSUM-Plot

The following (pseudo code) algorithm constructs the CUSUM-plot

Definition 2.65. Let $x_1, \ldots, x_n$ be the measurement values at the corresponding time points $t_1, \ldots, t_n$.

(1) Within each interval between two consecutive measurements the parameter value is assumed to be the constant mean value of the measurements at the left and right interval limit ($\overline{x}_i = \frac{x_{i+1}+x_i}{2}$).

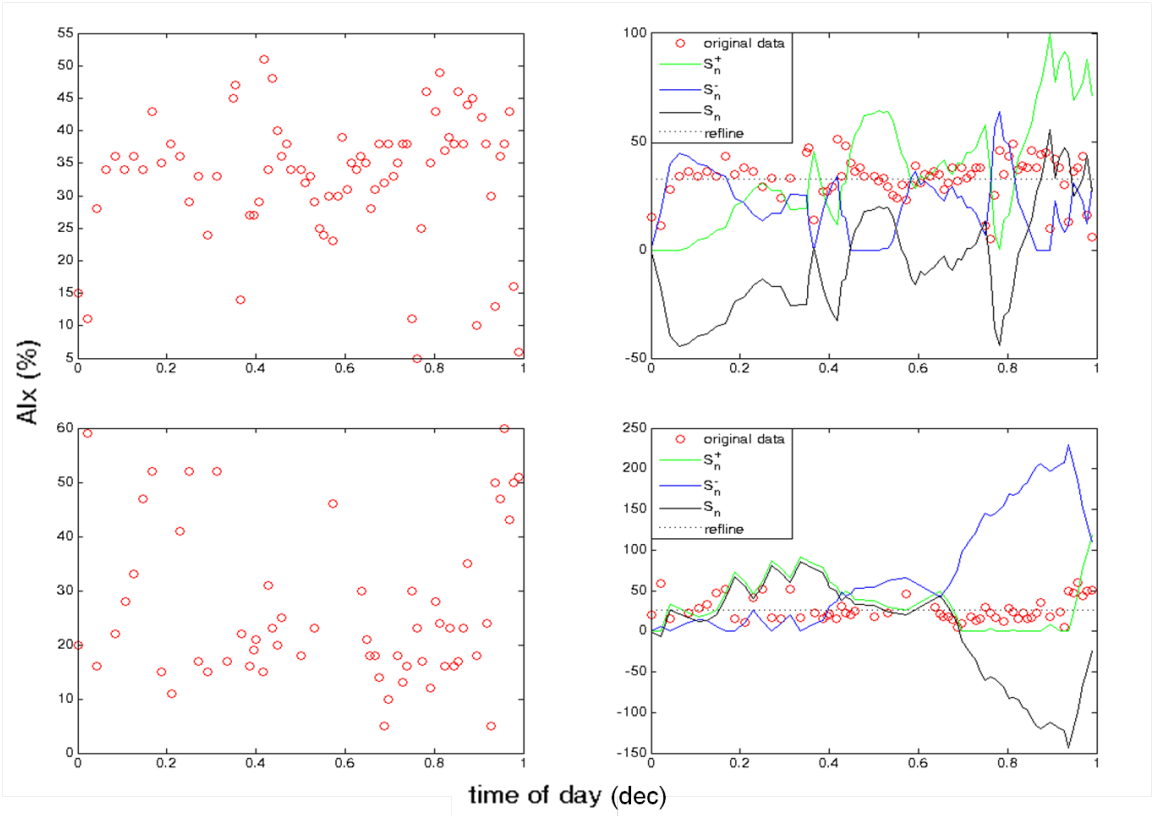


Figure 2.20: Data plot (left) and corresponding CUMSUM plots obtained by the MATLAB function `calc_cusum_classic.m` (right). While the data plots on the left side in both cases do not reveal any trend, the cusum plots differ a lot. The top right figure is rather confuse, while the right bottom figure shows a cusum plot of certain trend. The reference line is simply chosen as the mean value of the data. Adapted from [17]

(2) By use of these 'local mean values', the reference value

$$\overline{X}_w = \frac{1}{D}\sum_{i=1}^{n-1} \overline{x}_{i+1}(t_{i+1} - t_i), \tag{2.122}$$

the weighted 24h mean value, can be calculated, where $D = \sum_{i=1}^{n-1}(t_{i+1} - t_i)$ is the duration of the measurements (here approximately 24h) and $\overline{x}_i$ is the mean value of x_i and x_{i+1}.

(3) $i = 1$. Set $S_i = 0$.

(4) Subtract the reference value $\overline{X}_w$ from the interval mean $\overline{x}_i$

$$R_i := \overline{x}_i - \overline{X}_w. \tag{2.123}$$

(5) Multiply the resulting remainder R_i with the corresponding interval length $(t_{i+1} - t_i)$.

(6) Add this product to the current sum

$$S_{i+1} = S_i + R_i(t_{i+1} - t_i) \tag{2.124}$$

(7) Set $i := i + 1$.

(8) While $i \leq n$ repeat steps (4) – (7).

(9) The CUSUM-plot is finally obtained by plotting S_i against t_i.

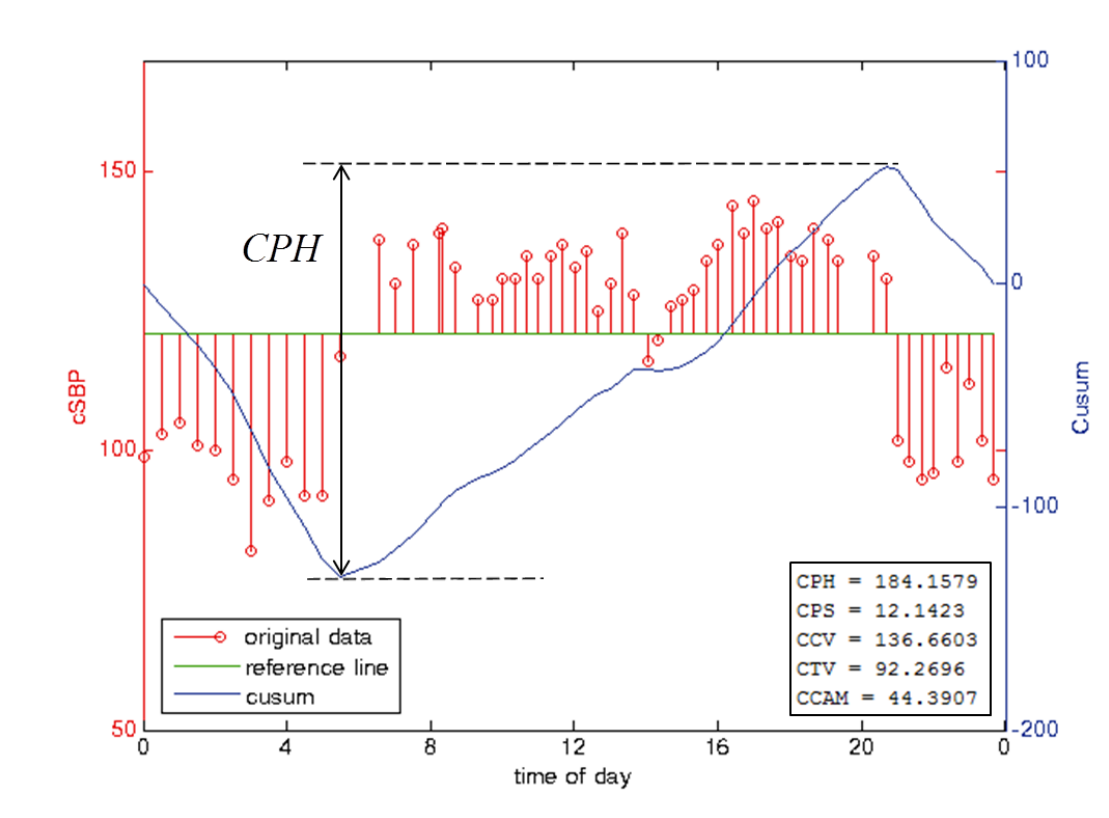


Figure 2.21: Cusumplot created with `calc_cusum_option.m` in MATLAB. The beginning of the plot is set to 0h and the weighted version is chosen (cf. section 2.16.5). Vertical lines leading from the circled data point The CPH as well as the output of the function `calc_cusum_option.m` are also shown in the figure.

2.16.3 Significant Indices obtained from the CUSUM Model

The following 5 indices can be obtained from the CUSUM model curve [30], [65], [70].

i) ‚CUSUM plot height (CPH)': This is defined as the difference between maximum and minimum of the plotted curve. One one hand it reflects the extend and on the other hand the duration of the NBPF .

ii) ‚CUSUM plot slope (CPS)': For a given time period this is defined as the change in the CUSUM within this period, divided by the time change of this period. (To make cal-

culations easier, an interval has to have integer numbers as left and right limit.) This corresponds to the temporally weighted mean of the data within this period and the 24h mean of the data.

iii) ‚CUSUM derived crest value (CCV)': This is defined as the largest temporally weighted mean value in a period of at least 6 hours. This value of 6 hours was determined empirically to quantify continuing and not random changes. It measures the highest continuing value in a 6 hour period.

iv) ‚CUSUM derived trough value (CTV)': This is defined as the smallest temporally weighted mean value in a period of at least 6 hours.

v) ‚CUSUM derived circadian alteration magnitude (CCAM)': The CCAM quantifies the extend of the circadian change and it is defined as the difference of the latter two indices.

Definition 2.66. Calculation of the parameters [65]:

- CUSUM plot height (CPH)

$$\boldsymbol{CPH} = \Big| \sum_{i=i_1}^{i_k} (\overline{x}_i - \overline{X}_w) d_i \Big| = \max_i S_i - \min_i S_i, \tag{2.125}$$

  with d_i being the length of the i-th interval $(t_i - t_{i-1})$. Further $i_1, \ldots, i_k$ denotes the indices of the intervals between the maximum and the minimum of the CUSUM (or between minimum and maximum, if the minimum occurs first).

- CUSUM plot slope (CPS)

$$\boldsymbol{CPS} = \frac{CS_E - CS_B}{d_p}, \tag{2.126}$$

  where CS_E and CS_B indicate the cumulative sums at the end, respectively the beginning of the period and d_p stands for its duration.

- CUSUM derived crest value (CCV)

$$\boldsymbol{CCV} = CPS_{crest} + \overline{X}_w \tag{2.127}$$

  Here, CPS_{crest} denotes the largest among all CPS-values obtained for all possible 6h-periods. The calculation in this manner is explained by the fact that the CPS value over a given time period is equal to the difference between the mean value for that period and the mean 24h value.

- CUSUM derived trough value (CTV)

$$\boldsymbol{CTV} = CPS_{trough} + \overline{X}_w \tag{2.128}$$

Here, CPS_{trough} denotes the smallest among all CPS-values obtained for all possible 6h-periods.

- CUSUM derived circadian alteration magnitude (CCAM)

$$\boldsymbol{CCAM} = CPS_{crest} - CPS_{trough} \tag{2.129}$$

Comment 2.67. The authors of [65] stress that it is crucial to plot the products of parameter deviations and corresponding time intervals instead of only using the CUSUM of the parameter differences to ensure that the mathematical relation is correctly interpreted. The multiplication overcomes missing readings as well as different interval durations. □

2.16.4 Advantages and Disadvantages of the CUSUM Method

Stanton et al. [65] state that the CUSUM method is one of the simplest statistical tools. Since normally for BP data higher values during day and lower values during night are measured, CUSUM-derived mean values, such as CCV and CTV, approximate day time and night time mean values. The authors claim that these CUSUM derived mean values are superior to those obtained by fixed day time and night time intervals, because awake time and sleep time differs from subject to subject. Therefore, the values are still interpreted correctly for instance if data from shift workers are analysed.
Parati et al. [45] claim that the CUSUM method circumvents some of the limitations of the square wave fit as it does not model transition periods as abruptly. Additionally, the derived parameters are not influenced by short-term oscillations. However, one limitation of the method is the fact that it ‚over-models' the actual parameter cycle. This smooths away all other indices (except the ones considered in the CUSUM).
The study by Thijs et al. [70] investigated the influence of measurement frequency on the parameters on several methods, amongst them the CUSUM method. By stepwise reducing measurement frequencies starting from every 7.5 minutes during day time (8 a.m. to 8 p.m.) and 15 minutes during night time (8 p.m. to 8 a.m.), they concluded that at least 2 measurements per hour are required to accurately determine CUSUM derived indices. (The same was concluded for the cSD, the NBPF and the amplitude of the fourier model.)

2.16.5 Implementation - Restrictions on the Data Set and Features of the Algorithm

The Matlab function `calc_cusum_option.m` calculates the CUSUM plot and the parameters mentioned in definition 2.66. The CPS is calculated over the period from the maximum to the minimum. The algorithm allows two options. First, the start time of the plot can be set to any full hour of the day. Second, it can be chosen if weighting should be included or excluded (cf. definition 2.65). Then the reference value is simply the mean value of the data and the

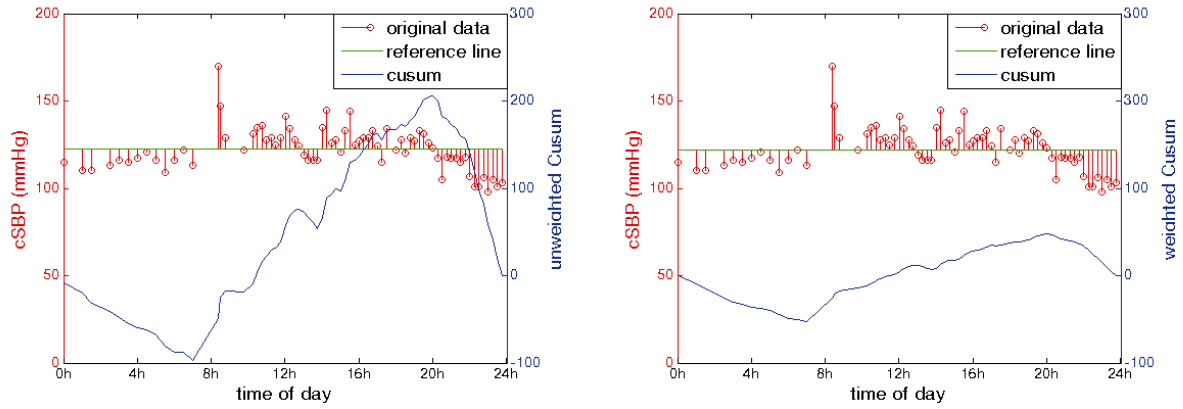


Figure 2.22: Both figures were produced by the Matlab function `calc_cusum_option.m` with the start time set to 0h. For the left figure no weighting was included, while the right figure shows the weighted CUSUM plot for the same data set. As can be seen, the weighting, which should overcome missing readings, does change the characteristic of the plot.

calculation is done in the fashion of section 2.16.1, where the general method is described. In figure 2.22 the difference between the weighted and the unweighted version can be seen.

Chapter 3

Quality Assessment

As mentioned in chapter 2, some of the indices impose certain conditions on the data set, such as a minimum total number of measurements or a minimum number of measurements within an hour. Some are due to technical reasons, some are required to guarantee the statistical reliability or reproducibility of the index. For a model to be of practical use, as few limitations as possible are desired.

3.1 Collection of Settings in Literature

In several publications, different quality requirements have been established including distinct intervals for day time and night time. It is important to distinguish between the definitions of day and night for recording purposes - this fixes the recording frequency during certain periods of the 24h - and the definitions of day and night for calculation reasons concerning the indices. While the day and night intervals for schedule purposes are always intervals covering the whole 24h period, the day and night periods for calculations purposes are possible (disjoint) subperiods of the 24h interval, since it is sometimes of interest to exclude transition phases (e.g., day 9 a.m. to 9 p.m., night 1 a.m. to 6 a.m.).

Table 3.1 gives an overview of different possible settings, but does not raise claim to completeness based on literature. The models variation independent of mean (VIM) and approximate entropy (ApEn) were not implemented. Therefore, they are missing in table 3.1. The indices higher empirical moments (HEM), runs (and updownups) have not been analysed in literature so far. Thus, they are not included in the table as well.

The publication by Mena et al. [37] gives a summery over the settings of several studies. In general, these studies scheduled readings at time points every 15 to 30 minutes during day time and every 30 to 60 minutes during night time. At least 70% of the readings throughout the 24h period had to be valid for a data set to be included in the studies. Other exclusion criteria were less than 32, 57 or 59 measurement points during 24h. In one of the studies, at

least 10 day time and at least 5 night time readings were stipulated. Additionally, data sets were excluded if readings were missing in a period of three consecutive hours [16]. The purpose of their own study was to determine the minimum number of measurements needed such that the index ARV does not loose its prognostic significance, which they concluded to be 48.
Parati et al. [47] published a scientific article, which aims to define practice guidelines for ambulatory blood pressure monitoring (ABPM). They claim that there is no distinct answer to the question how many measurements are required to obtain a satisfactory ABPM recording. However, if recordings are taken at least every 30 minutes throughout the whole 24h period and a minimum of 70% of the scheduled data should remain, at least 20 readings during day time and at least 7 readings during night time are acceptable. These day time and night time periods are best determined using the reported 'going to bed' and 'waking up' time points by the patients. If fixed periods have to be chosen without the subjects' journal, transition periods should be excluded (e.g., day time from 9 a.m. to 9 p.m. and night time from 1 a.m. to 6 a.m.). A repetition of the recording is recommended if either less than the above mentioned readings are available or if less than two valid readings per day time hour or less than one valid reading per night time hour are present.

When considering all these settings in literature, it has to be mentioned that they are all established for ABPM data and not for ABPM and PWA data. The latter data assessment procedure is more prone to error due to a longer-lasting recording and more complex calculations of the parameters (cf. section 4.1.2).

3.2 Algorithm for Quality Test

Based on the above listed (partly similar) settings in literature basically two features are desired:

I) a minimum number of readings in total and in the subperiods day and night.

II) regularly distributed readings, which means that gaps between consecutive readings should be limited.

The MATLAB function `quality.m` outputs whether a data set does or does not fulfil the user defined requirements.

```
1 function qualitycheck = quality(time,data,day,night,day_schedule,night_schedule,
2                                 schedule,percent,num_day,num_night,num_total,cons,missing)
```

INPUT arguments

- `time` ... vector containing the time points of valid readings
- `data` ... vector containing the measurement values corresponding to the time points
- `day` ... defined day period (e.g., $[\frac{9}{24}, \frac{21}{24}]$)

- `night` ... defined night period (e.g., $[\frac{1}{24}, \frac{6}{24}]$)
- `day_schedule` ... defined interval for day time schedule (e.g., $[\frac{8}{24}, \frac{23}{24}]$)
- `night_schedule` ... defined interval for day time schedule (e.g., $[\frac{23}{24}, \frac{8}{24}]$)
- `schedule` ... 1×2 vector, the first argument is the reading frequency during `day_schedule`, the second argument is the reading frequency during `night_schedule` expressed in minutes, (e.g., $[15, 30]$ means, measurements were recorded every 15 minutes during `day_schedule` and every 30 minutes during `night_schedule`')
- `percent` ...

  -) if `percent` > 0, this is the aimed percentage of valid readings in total (during 24h), during `day` and during `night` relative to the number of expected readings in these periods according to the reading schedule specified by `schedule` (e.g., `percent` $70 \hat{=} 70\%$)

  -) if `percent` $= 0$ the aimed number of measurements during `day`, `night` and 24h is given by `num_day`, `num_night` and `num_total` respectively

  - `num_day` (e.g., 20)
  - `num_night` (e.g., 6)
  - `num_total` (e.g., 50)
- `cons` ... number of allowed consecutive hours without any valid reading (e.g., 3)
- `missing` ... allowed total number of hours without any valid reading throughout the 24h period (e.g., 6)

OUTPUT arguments

The output is a 1×5 vector `qualitycheck = [dq, nq, tq, crq, mhq]` containing zeros and ones indicating whether the quality criterion is fulfilled ('1') or not fulfilled ('0'). These quality criteria precisely are

I) a minimum number of readings

- `dq` ... the number of readings during `day` is *sufficient*
- `ng` ... the number of readings during `night` is *sufficient*
- `tg` ... the number of readings during 24h is *sufficient*

II) regularly distributed readings

- `crq` ... the maximal number of consecutive hours without any readings is not greater than `cons`
- `mhq` ... the total number of hours without any readings is not greater than `missing`

The feature *sufficient* is either specified by the input argument `percent` or by the input arguments `num_day`, `num_night` and `num_total` (in this case `percent` has to be set to 0).

3.2.1 Percentage Quality vs. Absolute Number Quality

The use of the input parameters concerning the percentage quality test (`day_schedule`, `night_schedule`, `schedule` and `percent`> 0) is only reasonable, if the reading schedule of the device, which provided the data sets, is known, since only then the expected number of readings is calculated appropriately. The percentage criterion is rather a quality test for the reading device - the quality might be tested with the algorithm by setting `day` = `day_schedule`, `night` = `night_schedule` and `percent` as the aimed percentage rate. For the purposes of this work, absolute numbers of *present* readings are more relevant. Therefore, the requirement of sufficiently many readings will be tested by the absolute number criterion (`num_day`, `num_night` and `num_total`).

3.3 Setting

Based on section 3.1 the setting for the statistical analysis will be chosen. Nevertheless, certain observation as described as follows have to be taken into account.
Since the number of indices under investigation is rather large (≥ 50), it is difficult to choose a quality test which is perfectly attuned for each of them. Furthermore, it is also a quality feature of an index whether it works for a wide range of data sets. If the index can only be calculated under very strict constraints on the data set, it may not be relevant for practical use.
Additionally, since the reading schedule of the hereinafter used data sets is not known, the quality query is chosen to be made with absolute numbers instead of percentage values (cf. section 3.2.1). As a consequence the input parameters `day_schedule`, `night_schedule`, `schedule` do not have to be specified.
As mentioned before (cf. section 3.3), the settings in literature are made for BP data. Since the assessment of the data in consideration in this work, namely PWA data, is more prone to errors, in general milder constraints are chosen.
Furthermore, no reports are available when patients were awake and asleep. According to literature [47], day and night should be defined by excluding transition periods.
The general setting is finally given by

- `day` $= [\frac{9}{24}, \frac{21}{24}]$, `night` $= [\frac{0}{24}, \frac{6}{24}]$
- `num_day` $= 10$, `num_night` $= 5$, `num_total` $= 25$
- `cons` $= 6$, `missing` $= 10$

The only index highly sensitive to missing data points is EMS (cf. section 2.13). Further setting adjustments are possible, probably even necessary. If so, the specifications will be explained in the according statistical analysis parts.

method	scheduled day	schedule (d/n)[min]	day (d) period	night (n) period	exclusion criteria	literature
cSD	06:00 - 22:00	30/60	06:00 - 22:00	22:00 - 06:00	< 75% total	Duan et al. [14]
		30	09:00 - 21:00	01:00 - 06:00	-	Rothwell et al. [55]*[56]*
		15	07:00 - 24:00	00:00 - 07:00	-	Cay et al. [7]
	07:00 - 23:00	30/60	07:00 - 23:00	23:00 - 07:00	-	Xiong et al. [90]
	-	-	08:00 - 22:00	00:00 - 06:00	< 70% total < 2/dayhour < 1/nighthour	Bilo et al. [3]
		15	10:00 - 20:00	00:00 - 06:00	< 80% total cons. h w/o read. > 4 h w/o read.	Schillaci et al. [60]
wSD	06:00 - 22:00	30/60	08:00 - 22:00	00:00 - 06:00	< 75% total	Duan et al. [14]
	06:00 - 24:00	15/30	-	-	< 70% total	Bjelakovic et al. [4]
	-	-	08:00 - 22:00	00:00 - 06:00	< 70% total < 2/dayhour < 1/nighthour	Bilo et al. [3]
		15	10:00 - 20:00	00:00 - 06:00	< 80% total cons. h w/o read. > 4 h w/o read.	Schillaci et al. [60]
ARV	06:00 - 23:00	15/30	06:00 - 23:00	23:00 - 06:00	< 70% total	Mena et al. [36]
	06:00 - 24:00	15/30	-	-	< 70% total	Bjelakovic et al. [4]
	07:00 - 23:00	30/60	07:00 - 23:00	23:00 - 07:00	-	Xiong et al. [90]
		15	10:00 - 20:00	00:00 - 06:00	< 80% total cons. h w/o read. > 4 h w/o read.	Schillaci et al. [60]
CV		30	09:00 - 21:00	01:00 - 06:00	-	Rothwell et al. [55]*[56]*

		15	07:00 - 24:00	00:00 - 07:00	-	Cay et al. [7]
	07:00 - 23:00	30/60	07:00 - 23:00	23:00 - 07:00	-	Xiong et al. [90]
NBPF		15	diary	diary	-	Verdecchia et al. [76]
	08:00 - 22:00	20/45	10:00 - 20:00	00:00 - 06:00	-	Staessen et al. [63]
	08:00 - 20:00	7.5/15	10:00 - 20:00	00:00 - 06:00	$< 80\%$ total	Thijs et al. [70]
	06:00 - 24:00	20/30	08:00 - 22:00	00:00 - 06:00	< 15 during day < 5 during night	Lurbe et al. [30]
	-	-	08:00 - 22:00	00:00 - 06:00	$< 70\%$ total < 2/dayhour < 1/nighthour	Bilo et al. [3]
EMS		15	diary	diary	-	Verdecchia et al. [76]
		30	diary	diary	missing morning values	Metoki et al. [38]
		30	diary	diary	$< 80\%$ awake $< 80\%$ asleep	Kario et al. [26]
SW	08:00 - 20:00	7.5/15	10:00 - 20:00	00:00 - 06:00	$< 80\%$ total	Thijs et al. [70]
fourier	08:00 - 22:00	20/45	10:00 - 20:00	00:00 - 06:00	-	Thijs et al. [71]
	08:00 - 22:00	20/45	10:00 - 20:00	00:00 - 06:00	-	Staessen et al. [63]
logistic		30	07:00 - 22:00	22:00 - 07:00	-	Head et al. [19]
CUSUM	08:00 - 20:00	7.5/15	10:00 - 20:00	00:00 - 06:00	$< 80\%$ total	Thijs et al. [70]
		30	-	-	> 1 h w/o read.	Stanton et al. [65]

Table 3.1: Collection of settings in literature: Horizontal lines indicate missing information in the publication. The **scheduled day** period indicates the time period within which recordings were scheduled with a frequency as indicated in the first argument of the column **schedule**. The scheduled night period is always given by the remaining hours of the 24h period. The frequency is indicated by the second argument of the column **schedule**. A single value in the column **schedule** indicates that this is the recording frequency throughout the whole 24h. The publications marked with a * investigated visit to visit variability. Whenever one of the criteria in the column **exclusion** was fulfilled, the data set was excluded. Percentage specifications have to be interpreted as relative to the expected number of readings according to the reading schedule. Absolute numbers always indicate reading numbers (e.g., '< 2/dayhour' means 'data sets were excluded, if day hours with less than two readings were present'). The expression 'cons. h w/o read.' means that data sets were excluded whenever there were at least 2 consecutive hours without readings.

Chapter 4

Statistics and Data Description

The previously collected models, or to be precise the derived indices quantifying the diurnal profile and variability of PWA parameters, require further analyses to test their performance in predicting cardiovascular diseases. The aim is to identify those indices which provide significantly different values for a control group of healthy subjects compared to a group of patients suffering from a certain cardiovascular condition. The current chapter describes the data of two cohorts for which the variability indices are compared as well as the statistical tools used for the comparison.

4.1 Data

4.1.1 Study Design - Groups to be Compared

The data of the patient group (further termed **Wels**) consists of 63 subjects (47 male, 16 female) aged between 16 and 84 (median [IQR-limits]: 53 [45.25, 63]). These data were assessed through the Cardiology department at the Klinikum Wels-Grieskirchen in Wels (Austria) to be part of a multicenter study investigating the relationship between 24h central blood pressure and left ventricular mass [84]. For patients to be included, they had to fulfil certain criteria. Subjects in this group suffer from an enlargement of their left ventricle (left ventricular hypertrophy (LVH)) suspected due to hypertension, which must not be treated with antihypertensive medication. The detailed study design is described in [84].
The data of the control group (further termed **Lübeck**) were acquired in Lübeck (Germany). The cohort consists of 91 healthy subjects (36 male, 55 female) aged between 20 and 68 (median [IQR-limits]: 33 [24, 49.5]). Subjects in this group stated not to suffer from dyslipidemia, mental disorders, electrocardiography abnormalities, diabetes or hypertension. They were also free from drug intake.

4.1.2 Data Assessment

From each subject of both groups 24h ABPM including PWA was assessed with an oscillometric brachial-cuff based sphygmomanometer (Mobil-O-Graph NG, I.E.M., Stolberg, Germany; ARC-

Solver Version 172; diastolic/systolic calibration). The recordings involved the measurement of standard ABPM parameters such as peripheral systolic and diastolic BP at time points scheduled every 15 to 30 minutes during a period of 24h. Subsequently, for a duration of ten seconds, the pulse wave is recorded. With the ARCSolver method, developed by the AIT, central aortic pressures and other systemic cardiovascular parameters are estimated from these recordings. The recording device as well as the ARCSolver method have been validated successfully [81], [84], [85]. A total of 20 parameters are derived from the measurements, namely

peripheral systolic blood pressure (pSBP)
peripheral diastolic blood pressure (pDBP)
peripheral pulse pressure (pPP)
peripheral mean arterial pressure (pMAP)
central systolic blood pressure (cSBP)
central diastolic blood pressure (cDBP)
central pulse pressure (cPP)
heart frequency (Hf)
augmentation index (AIx)
augmentation index at 75 bpm (AIx@75)
augmentation pressure (AP)
cardiac output (CO)
reflexion magnitude (RM)
peripheral resistance (R_p)
heart index (HIx)
amp. of the early syst. peak pressure (P_1)
amp. of the late syst. peak pressure (P_2)
backward pressure wave amplitude (P_b)
forward pressure wave amplitude (P_f)
pulse wave velocity (PWV)

4.2 Statistical Tests

The statistical analysis is done with MATLAB R2014a (The MathWorks Inc., Natick, Massachusetts, USA). Since the data are derived from two different independent groups, unpaired statistical tests are used. Whenever NaNs (not a number values) occurred in the calculation of an index, they are treated as missing values.

For each group the index values are tested whether they are normally distributed. This is done with the help of the one-sample Kolmogorov-Smirnov test. If so, the two-sample F-test is employed to decide, whether both value sets come from a normal distribution with equal variances. The two-sample (Student's) t-test is then applied in the case of equal variances, but the Welch test is used if different variances are given.

If (at least) one of the index data sets is not normally distributed and both data sets include only values > 0 a logarithm transformation is applied to both sets. If still not both (transformed) sets are normally distributed the Mann-Whitney U test (also called two-sided Wilcoxon rank-sum test) is employed. If the data sets are normally distributed after the log-transformation, the transformed data are further processed in the same way as normally distributed data (cf. first paragraph).

For all statistical tests the significance level is chosen as $\alpha = 5\%$. If the p-value $p \leq 0.05$, the null hypothesis is rejected.

Data are presented as mean (SD), if they are normally distributed for both groups otherwise the median (IQR-limits) is given.

Chapter 5

Results

5.1 Exclusion of Data Sets

As a first step, measurements are only then included, if the recording quality, which is returned by the ARCSolver algorithm alongside the PWA parameters, is 1 or 2. Recorded values with quality 3 or unsuccessful measurements (NaN) are excluded. This guarantees a certain accuracy of the measured values which are taken into account for the calculations of the indices. Furthermore, this provides that, per subject, the number of data points for an ABPM parameter is equal to the number of data points for a PWA parameter. This is relevant when comparing the central with the peripheral parameters (e.g., cSBP vs. pSBP). Subsequently, for all indices the setting determined in section 3.3 is chosen. Essentially this equals the function call

```
1 qualitycheck = quality(time, data, [9/24,21/24], [0/24,6/24], day_schedule,
2 night_schedule, schedule, 0, 10, 5, 25, 6, 10);
```

Note, that here the input variables `day_schedule`, `night_schedule` and `schedule` do not have to be specified, since they will not be used in the algorithms' calculations (`percent` = 0). Applying this quality test to all data sets of both groups results in the remaining of 80 out of 91 (Lübeck) and 58 out of 63 (Wels) data sets. Table 5.1 shows some characteristics of the remaining data sets in the two groups, which are tested for significant differences.

	Lübeck	**Wels**	**p-value**	**test**
male/female	32 (40%)/48 (60%)	44 (75.9%)/14 (24.1%)	-	-
age (years)	31 [24,47.5]	52.5 [46,62]	< 0.001	3
weight (kg)	73 (12.9 SD)	82.8 (13.1 SD)	< 0.001	1
height (m)	1.74 (0.0852 SD)	1.76 (0.0855 SD)	0.12	1
BMI ($kg \cdot m^{-2}$)	24.1 (3.88 SD)	26.6 (3.49 SD)	< 0.001	1

Table 5.1: Absolute numbers and percentage ratios of male and female individuals within the groups are shown in the first row. BMI stands for 'Body Mass Index' and is the weight divided by the squared height. The numbers in the column **test** indicate the used test for the statistical analysis: 1 t-test, 3 Mann-Whitney U test (Wilcoxon ranksum test). Significant p-values are highlighted in green.

5.2 24h Averages

For each subject the 24h mean value of every parameter is calculated. These 24h average values are tested for significant differences between the two groups. Table 5.2 shows the results.

	Lübeck	**Wels**	**p-value**	**test**
pSBP	116 (8.51 SD)	123 (9.1 SD)	< 0.001	1
pDBP	73 (7.21 SD)	81.5 (9.17 SD)	< 0.001	2
pPP	43.3 (6.35 SD)	41.8 (6.9 SD)	0.17	1
pMAP	92.9 (7.15 SD)	101 (8.46 SD)	< 0.001	1
cSBP	106 (8.13 SD)	115 (8.79 SD)	< 0.001	1
cDBP	74.5 (7.27 SD)	82.9 (9.17 SD)	< 0.001	1
cPP	31.9 (4.6 SD)	31.9 (5.2 SD)	0.99	1
Hf	70.3 (7.91 SD)	68.7 (9.47 SD)	0.28	1
AIx	20.4 (6.51 SD)	23.8 (7.43 SD)	0.005	1
AIx@75	17.9 (8.16 SD)	20.2 (7.01 SD)	0.08	1
AP	7.01 (2.61 SD)	8.33 (3.42 SD)	0.02	2
CO	4.73 (0.382 SD)	4.66 (0.392 SD)	0.29	1
RM	60.8 (5.67 SD)	62.8 (5.16 SD)	0.04	1
R_p	1.21 (0.108 SD)	1.32 (0.107 SD)	< 0.001	1
HIx	2.54 (0.261 SD)	2.33 (0.242 SD)	< 0.001	1
P_1	99.4 (7.58 SD)	106 (9.03 SD)	< 0.001	1
P_2	106 (8.13 SD)	115 (8.79 SD)	< 0.001	1
P_b	12.9 (2.07 SD)	13.1 (2.4 SD)	0.64	1
P_f	20.9 (2.94 SD)	20.5 (3.16 SD)	0.42	1
PWV	5.32 $[4.9, 6.5]$	7.41 $[6.49, 8.68]$	< 0.001	3

Table 5.2: Significant differences of the 24h mean values of all parameters. The numbers in the column **test** indicate the used test for the statistical analysis: 1 t-test, 2 Welch test, 3 Mann - Whitney U test (Wilcoxon ranksum test). Significant p-values are highlighted in green.

5.3 Variability Indices

In the following subsections for six parameters are chosen from the list in table 5.2 (cf. also section 4.1.2). All variability indices are calculated for these parameters. The results include the mean values or median values for the two groups and the p-values. If additional settings for the calculation of the index had to be made (e.g. number of harmonics chosen for the fourier analysis), this is also stated. All values are rounded to three significant digits.
The choice of the parameters and the settings will be explained in the discussion chapter 6.

5.3.1 Heart Frequency (Hf)

Table 5.3 shows the results for the parameter Hf. All variability indices are calculated and tested for significant differences. In addition to the mean (or median) values, the p-values and the used tests are given. Possible additional settings are stated as well.

method	index	Lübeck	Wels	p-value	test	add. sett.
cSD	cSD_{day}	9.82 (3.49 SD)	8.53 (3.4 SD)	0.03	1a	-
	cSD_{night}	4.96 [3.52, 6.45]	4.17 [2.63, 5.85]	0.05	2b	-
	cSD_{24h}	11.5 (3.64 SD)	10.1 (3.09 SD)	0.02	1a	-
wSD	wSD	8.66 (2.82 SD)	7.57 (2.64 SD)	0.02	1a	-
ARV	ARV_{day}	7.89 (2.82 SD)	6.63 (2.92 SD)	0.01	1a	-
	ARV_{night}	4.68 [3.18, 5.75]	3.71 [2.44, 5]	0.04	2b	-
	ARV_{24h}	7.29 (2.11 SD)	6.08 (1.91 SD)	< 0.001	1a	-
wARV	$wARV$	8.41 (2.72 SD)	6.81 (2.34 SD)	< 0.001	1a	-
SV	SV_{day}	10.6 (4.12 SD)	8.98 (4.25 SD)	0.03	1a	-
	SV_{night}	5.7 [3.99, 7.56]	4.39 [2.93, 6.09]	0.03	2b	-
	SV_{24h}	10.2 (3.23 SD)	8.58 (3.13 SD)	0.003	1a	-
CV (%)	CV_{day}	13 (4.11 SD)	11.7 (4.34 SD)	0.07	1a	-
	CV_{night}	8.3 [5.86, 10.7]	6.96 [4.53, 9.63]	0.06	2b	-
	CV_{24h}	16.3 (4.56 SD)	14.6 (4.12 SD)	0.03	1a	-
HEM	$skew_{day}$	0.584 (0.744 SD)	0.546 (0.678 SD)	0.76	1a	-
	$kurt_{day}$	3.04 [2.44, 4.25]	2.72 [2.41, 3.59]	0.40	1b	-
	$skew_{night}$	0.468 (0.647 SD)	0.286 (0.683 SD)	0.11	1a	-
	$kurt_{night}$	2.17 [1.86, 2.94]	2.15 [1.78, 2.71]	0.49	1b	-

	$skew_{24h}$	0.674 (0.601 SD)	0.577 (0.576 SD)	0.34	1a	-
	$kurt_{24h}$	2.92 [2.27, 4.1]	2.78 [2.38, 3.44]	0.56	1b	-
OS	$range$	49.3 (16.6 SD)	43.1 (15.3 SD)	0.03	1a	-
	IQR	16.1 (6.64 SD)	13.7 (4.91 SD)	0.01	2a	-
	$midrange$	77.3 (10.2 SD)	74 (11.4 SD)	0.08	1a	-
	$median$	69.3 (8.3 SD)	67.4 (9.54 SD)	0.21	1a	-
	$peak$	31.6 (13.4 SD)	26.8 (12.6 SD)	0.04	1a	-
	$trough$	17.7 (5.3 SD)	16.3 (4.42 SD)	0.10	1a	-
	max	102 (17.4 SD)	95.5 (17.7 SD)	0.04	1a	-
	t_{max} (dec)	0.593 (0.198 SD)	0.597 (0.184 SD)	0.91	1a	-
	min	52.6 (6.61 SD)	52.4 (7.88 SD)	0.88	1a	-
	t_{min} (dec)	0.208 [0.167, 0.359]	0.188 [0.127, 0.271]	0.27	3	-
runs	$runs_{day}$	8.32 (3.78 SD)	7.9 (3.34 SD)	0.49	1a	subperiod median
	$runs_{night}$	3 [1, 4]	3 [1, 4]	0.89	3	(cf. sec. 2.9.5)
	$runs_{24h}$	10.4 (4.67 SD)	10.2 (4.54 SD)	0.79	1a	
	$UDUs_{day}$	13.9 (5.61 SD)	14.6 (5.38 SD)	0.46	1a	(UDUs not
	$UDUs_{night}$	4 [3, 6]	4 [3, 5]	0.13	3	affected)
	$UDUs_{24h}$	26.5 (8.34 SD)	26.1 (7.65 SD)	0.77	1a	
runs	$runs_{day}$	6.06 (3.61 SD)	5.93 (2.68 SD)	0.81	2a	24h median
	$runs_{night}$	1 [0, 2]	0 [0, 1]	0.07	3	(cf. sec. 2.9.5)
	$runs_{24h}$	10.4 (4.67 SD)	10.2 (4.54 SD)	0.79	1a	
NBPF	NDR	0.816 (0.0934 SD)	0.826 (0.101 SD)	0.53	1a	-
	NDR_p	81.6 (9.34 SD)	82.6 (10.1 SD)	0.53	1a	-

	$ADND$	14.1 (8.14 SD)	13.1 (7.72 SD)	0.46	1a	-
	$ADNDtoDR$	0.184 (0.0934 SD)	0.174 (0.101 SD)	0.53	1a	-
	NF	18.4 (9.34 SD)	17.4 (10.1 SD)	0.53	1a	-
	NDR	0.801 (0.0911 SD)	0.808 (0.11 SD)	0.67	1a	
weighted	NDR_p	80.1 (9.11 SD)	80.8 (11 SD)	0.67	1a	time
NBPF	$ADND$	15.3 (8.08 SD)	14.7 (8.82 SD)	0.65	1a	weighted
	$ADNDtoDR$	0.199 (0.0911 SD)	0.192 (0.11 SD)	0.67	1a	
	NF	19.9 (9.11 SD)	19.2 (11 SD)	0.67	1a	
	mesor	70.3 (8.19 SD)	68.2 (9.26 SD)	0.17	1a	-
cosinor	*amplitude*	10.3 (5.02 SD)	9.66 (4.09 SD)	0.46	1a	-
	acrophase	-3.99 (0.701 SD)	-3.77 (0.759 SD)	0.08	1a	-
	t_{max} (dec)	0.636 (0.112 SD)	0.6 (0.121 SD)	0.08	1a	-
fourier	*amplitude*	16.5 (5.76 SD)	14.9 (5.68 SD)	0.12	1a	4 harmonics
	t_{max}	0.587 (0.193 SD)	0.58 (0.171 SD)	0.82	1a	no weighting
weighted	*amplitude*	17.4 (6.18 SD)	15.3 (5.59 SD)	0.04	1a	4 harmonics
fourier	t_{max}	0.564 (0.191 SD)	0.6 (0.171 SD)	0.26	1a	time weighted
	LD	18 (7.75 SD)	15.9 (5.8 SD)	0.08	2a	
	TPP_{max}	0.375 [0.297, 0.45]	0.345 [0.292, 0.471]	0.44	1b	minimal
SW	TPP_{min}	0.845 [0.657, 0.922]	0.813 [0.667, 0.903]	0.31	3	number of
	PD_{high}	0.456 (0.207 SD)	0.451 (0.182 SD)	0.87	1a	read. per
	PD_{low}	0.544 (0.207 SD)	0.549 (0.182 SD)	0.87	1a	period = 5
	PVA	47.1 (14.3 SD)	49.6 (12.5 SD)	0.30	1a	
pSD	pSD_{day}	7.11 (3 SD)	6.19 (2.88 SD)	0.07	1a	fourier

	pSD_{night}	4.47 (1.75 SD)	3.91 (2.11 SD)	0.09	1a	4 harmonics
	pSD_{24h}	6.72 (2.35 SD)	5.78 (2.3 SD)	0.02	1a	no weights
	CPH	180 (97 SD)	163 (72.9 SD)	0.22	2a	
	CPS	12.6 [7.47, 19.9]	13.1 [9.42, 17.4]	0.78	3	no weights
CUSUM	CCV	81.7 (11.5 SD)	78.7 (11.6 SD)	0.13	1a	start of
	CTV	58.6 (7.37 SD)	57.6 (8.18 SD)	0.42	1a	plot = 0h
	$CCAM$	23 (9.12 SD)	21.1 (7.42 SD)	0.19	1a	
	CPH	89 (38.1 SD)	84 (32.8 SD)	0.42	1a	
weighted	CPS	6.54 [4.35, 10.4]	6.92 [5.12, 9.86]	0.67	3	time weighted
CUSUM	CCV	82.8 (11.8 SD)	79.3 (11.8 SD)	0.09	1a	start of
	CTV	57.8 (7.52 SD)	56.7 (8.03 SD)	0.41	1a	plot = 0h
	$CCAM$	25 (9.65 SD)	22.6 (8.35 SD)	0.13	1a	
	STS	16.3 (11.5 SD)	14.6 (9.17 SD)	0.35	1a	going to bed = 9 p.m.
	PS	1.94 (12 SD)	0.0461 (10.2 SD)	0.37	1a	arising = 9 a.m.
EMS	RS	0.45 (14.1 SD)	-1.33 (10.9 SD)	0.41	2a	duration = 2h
	MED	-0.742 (13.6 SD)	2.22 (11.1 SD)	0.20	1a	(MS_{ft} not
	MS_{ft}	22.7 (15.6 SD)	17.7 (15.2 SD)	0.08	1a	affected)

Table 5.3: Indices calculated for the parameter Hf. The column **Lübeck** contains the mean values of the indices for the control group, the column **Wels** contains the mean values for the patient group. If data are not normally distributed, median and IQR are denoted instead. Significant p-values are highlighted with a green background. If additional settings have to be chosen for the calculations of an index, these are mentioned in the 'additional settings' (**add.sett.**) column. Time points are given in decimal (dec) numbers. Multiplication by 24 yields hours. UDUs stands for 'updownups' (cf. section 2.9.3). The numbers in the column **test** indicate the used test for the statistical analysis: 1a t-test, 1b t-test applied on log - transformed data, 2a Welch test, 2b Welch test applied on log - transformed data, 3 Mann - Whitney U test (Wilcoxon ranksum test).

Exemplary Illustrations regarding the Results for Hf

As can be seen in figure 5.1, the data of a representative of the control group (Lübeck, left figure) spread in a wider range than in the plot for the representative of the patient group (Wels, right side plot). Therefore, it seems reasonable that the index *amplitude* of the weighted fourier fit is significantly larger for the control group. Consistently, also the index *range* is significantly different.

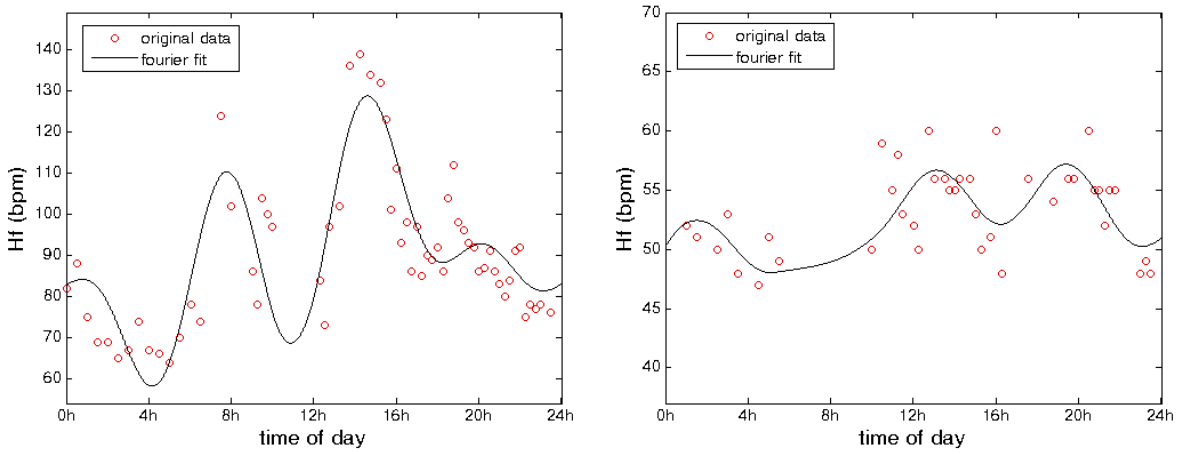


Figure 5.1: The left figure shows the *weighted fourier* fit for one subject from the Lübeck cohort. The plot on the right side depicts the *weighted fourier* fit for a representative of the Wels group.

The index wARV of the Hf is significantly lower for the patient group than for the control group. This can be seen in the boxplot shown in figure 5.2.

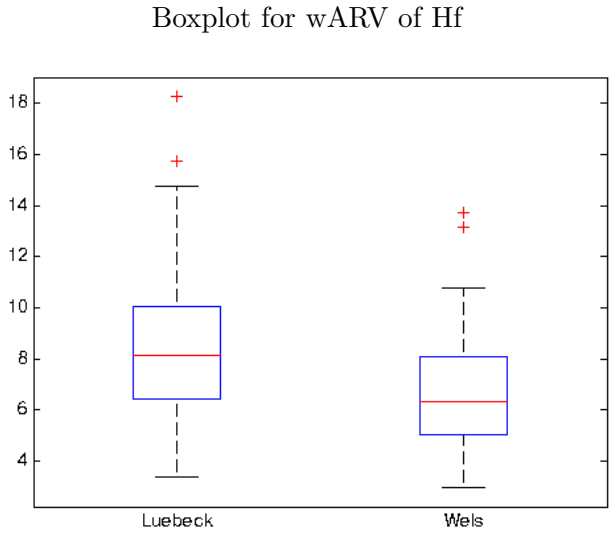


Figure 5.2: Boxplot for the index *wARV* of the Hf.

Remarks on Early Morning Surge (EMS)

The calculations for EMS have been done with the same settings for the data sets as for the other indices. Since time periods of up to six consecutive hours without any valid readings can appear, the calculation of some EMS indices is not possible in some of the data sets and NaN is stored instead. Nevertheless, since NaN values are ignored in the statistical analysis (cf. section 4.2) the evaluation is still possible. The only difference to the other indices is that not all 80 (Lübeck) and not all 58 (Wels) data sets may be taken into account. To be precise, the remaining numbers of data sets are shown in table 5.4. This is valid for all parameters due to the choice of the required recording quality (cf. section 5.1).

	Lübeck	Wels
STS	77	54
PS	74	46
RS	80	58
MED	75	52
MS_{ft}	75	49

Table 5.4: Remaining data sets for the calculation of the EMS indices.

5.3.2 Peripheral Systolic Blood Pressure (pSBP)

Table 5.5 shows the results for the parameter pSBP. All variability indices are calculated and tested for significant differences. In addition to the mean (or median) values, the p-values and the used tests are given. Possible additional settings are stated as well.

method	**index**	**Lübeck**	**Wels**	**p-value**	**test**	**add. sett.**
cSD	cSD_{day}	11.2 (3.46 SD)	11.7 (3.14 SD)	0.35	1a	-
	cSD_{night}	9.27 (3.64 SD)	9.81 (4.59 SD)	0.44	1a	-
	cSD_{24h}	13.3 (3 SD)	13.5 (2.86 SD)	0.61	1a	-
wSD	wSD	10.7 (2.99 SD)	11.3 (2.85 SD)	0.26	1a	-
ARV	ARV_{day}	10.5 (3.75 SD)	10.5 (3.66 SD)	0.99	1a	-
	ARV_{night}	8.65 [6.67,11.1]	9.01 [6.78,12.3]	0.42	1b	-
	ARV_{24h}	10.1 (2.65 SD)	10.4 (3 SD)	0.55	1a	-
wARV	$wARV$	11 (3.15 SD)	11.3 (3.8 SD)	0.62	1a	-
SV	SV_{day}	13.7 (4.91 SD)	13.8 (4.75 SD)	0.90	1a	-
	SV_{night}	10.5 [8.23,13.8]	11.1 [8.5,14.5]	0.51	1b	-
	SV_{24h}	13.4 (3.63 SD)	13.7 (4.04 SD)	0.62	1a	-
CV (%)	CV_{day}	9.17 (2.55 SD)	9.24 (2.45 SD)	0.88	1a	-
	CV_{night}	8.88 (3.25 SD)	8.66 (3.99 SD)	0.71	1a	-
	CV_{24h}	11.4 (2.27 SD)	11 (2.15 SD)	0.28	1a	-
HEM	$skew_{day}$	0.136 (0.745 SD)	0.045 (0.703 SD)	0.47	1a	-
	$kurt_{day}$	3.51 (1.6 SD)	3.34 (1.39 SD)	0.52	1a	-
	$skew_{night}$	0.094 (0.655 SD)	0.2 (0.575 SD)	0.32	1a	-
	$kurt_{night}$	2.58 (0.954 SD)	2.4 (0.731 SD)	0.22	2a	-

	$skew_{24h}$	-0.0594 (0.556 SD)	-0.0231 (0.582 SD)	0.71	1a	-
	$kurt_{24h}$	3.05 [2.56,3.73]	2.85 [2.53,3.5]	0.40	1b	-
OS	$range$	60.7 (15.5 SD)	60.1 (13.7 SD)	0.83	1a	-
	IQR	17.2 (5.28 SD)	17.8 (5.33 SD)	0.47	1a	-
	$midrange$	116 (11 SD)	124 (11.5 SD)	< 0.001	1a	-
	$median$	117 (8.29 SD)	124 (9.4 SD)	< 0.001	1a	-
	$peak$	30.4 (10.9 SD)	30.8 (9.87 SD)	0.81	1a	-
	$trough$	30.3 (8.49 SD)	29.3 (8.18 SD)	0.50	1a	-
	max	147 (16.2 SD)	154 (15.7 SD)	0.009	1a	-
	t_{max} (dec)	0.625 (0.192 SD)	0.562 (0.198 SD)	0.06	1a	-
	min	86.1 (10 SD)	94 (10.7 SD)	< 0.001	1a	-
	t_{min} (dec)	0.215 [0.121,0.422]	0.366 [0.104,0.694]	0.20	3	-
runs	$runs_{day}$	9.28 (3.82 SD)	9.79 (3.84 SD)	0.43	1a	subperiod median
	$runs_{night}$	3 [3,5]	3 [2,5]	0.31	3	(cf. sec. 2.9.5)
	$runs_{24h}$	13.6 (5.11 SD)	14.2 (4.6 SD)	0.50	1a	
	$UDUs_{day}$	14.9 (5.28 SD)	15 (5.43 SD)	0.90	1a	(UDUs not
	$UDUs_{night}$	4 [3,5.5]	4 [3,5]	0.72	1b	affected)
	$UDUs_{24h}$	27.6 (6.93 SD)	27.9 (7.56 SD)	0.75	1a	
runs	$runs_{day}$	8.39 (4.14 SD)	8.48 (3.45 SD)	0.89	1a	24h median
	$runs_{night}$	1 [0,2]	2 [0,3]	0.03	3	(cf. sec. 2.9.5)
	$runs_{24h}$	13.6 (5.11 SD)	14.2 (4.6 SD)	0.50	1a	
NBPF	NDR	0.862 (0.0629 SD)	0.893 (0.0832 SD)	0.02	2a	-
	NDR_p	86.2 (6.29 SD)	89.3 (8.32 SD)	0.02	2a	-

	$ADND$	17 (8.39 SD)	14 (11 SD)	0.09	2a	-
	$ADNDtoDR$	0.138 (0.0629 SD)	0.107 (0.0832 SD)	0.02	2a	-
	NF	13.8 (6.29 SD)	10.7 (8.32 SD)	0.02	2a	-
weighted NBPF	NDR	0.854 (0.063 SD)	0.891 (0.0905 SD)	0.009	2a	
	NDR_p	85.4 (6.3 SD)	89.1 (9.05 SD)	0.009	2a	time
	$ADND$	18 (8.58 SD)	14.4 (12 SD)	0.05	2a	weighted
	$ADNDtoDR$	0.146 (0.063 SD)	0.109 (0.0905 SD)	0.009	2a	
	NF	14.6 (6.3 SD)	10.9 (9.05 SD)	0.009	2a	
cosinor	$mesor$	116 (8.4 SD)	123 (8.92 SD)	< 0.001	1a	-
	$amplitude$	10.5 (4.55 SD)	10.2 (4.87 SD)	0.66	1a	-
	$acrophase$	-4.19 (0.543 SD)	-3.57 (1.02 SD)	< 0.001	2a	-
	t_{max} (dec)	0.668 (0.0864 SD)	0.568 (0.162 SD)	< 0.001	2a	-
fourier	$amplitude$	17.8 (5.24 SD)	18 (6.03 SD)	0.87	1a	4 harmonics
	t_{max}	0.633 (0.178 SD)	0.563 (0.218 SD)	0.04	1a	no weighting
weighted fourier	$amplitude$	19.5 (5.87 SD)	20 (6.78 SD)	0.64	1a	4 harmonics
	t_{max}	0.663 (0.184 SD)	0.538 (0.216 SD)	< 0.001	1a	time weighted
SW	LD	19.6 (5.89 SD)	20.5 (6.22 SD)	0.42	1a	
	TPP_{max}	0.359 [0.292,0.455]	0.334 [0.271,0.481]	0.63	2b	minimal
	TPP_{min}	0.891 [0.458,0.943]	0.839 [0.604,0.917]	0.62	3	number of
	PD_{high}	0.542 (0.212 SD)	0.535 (0.252 SD)	0.86	1a	read. per
	PD_{low}	0.458 (0.212 SD)	0.465 (0.252 SD)	0.86	1a	period = 5
	PVA	43.1 (14.6 SD)	40.4 (16.8 SD)	0.32	1a	
pSD	pSD_{day}	9.05 (2.99 SD)	9.21 (2.7 SD)	0.74	1a	fourier

	pSD_{night}	7.53 (2.8 SD)	8.09 (3.45 SD)	0.30	1a	4 harmonics
	pSD_{24h}	8.74 (2.16 SD)	9.07 (2.34 SD)	0.39	1a	no weights
	CPH	191 (82.6 SD)	192 (92.9 SD)	0.92	1a	
	CPS	13.3 [7.24,20.9]	12.7 [8.16,24.3]	0.58	3	no weights
cusum	CCV	127 (10.1 SD)	135 (10.6 SD)	< 0.001	1a	start of
	CTV	102 (8.57 SD)	109 (8.67 SD)	< 0.001	1a	plot = 0h
	$CCAM$	25 (7.91 SD)	25.6 (8.54 SD)	0.67	1a	
	CPH	93.8 (31.7 SD)	92.1 (38 SD)	0.77	1a	
weighted	CPS	6.58 [-4.55,8.47]	6.32 [1.75,10.2]	0.57	3	time weighted
cusum	CCV	127 (10.3 SD)	135 (11.2 SD)	< 0.001	1a	start of
	CTV	100 (9.59 SD)	105 (10 SD)	0.003	1a	plot = 0h
	$CCAM$	27.1 (9.55 SD)	30 (10.7 SD)	0.09	1a	
	STS	20.1 (12.6 SD)	22.5 (13.9 SD)	0.31	1a	going to bed = 9 p.m.
	PS	5.03 (13.5 SD)	3.89 (10.4 SD)	0.63	1a	arising = 9 a.m.
EMS	RS	2.55 (18.4 SD)	4.36 (13.2 SD)	0.50	2a	duration = 2h
	MED	-3.7 (13.5 SD)	5.56 (13.6 SD)	< 0.001	1a	(MS_{ft} not
	MS_{ft}	25.7 (16.2 SD)	24 (14.4 SD)	0.55	1a	affected)

Table 5.5: Indices calculated for the parameter pSBP. The column **Lübeck** contains the mean values of the indices for the control group, the column **Wels** contains the mean values for the patient group. If data are not normally distributed, median and IQR are denoted instead. Significant p-values are highlighted with a green background. If additional settings have to be chosen for the calculations of an index, these are mentioned in the 'additional settings' (**add.sett.**) column. Time points are given in decimal (dec) numbers. Multiplication by 24 yields hours. UDUs stands for 'updownups' (cf. section 2.9.3). The numbers in the column **test** indicate the used test for the statistical analysis: 1a t-test, 1b t-test applied on log - transformed data, 2a Welch test, 2b Welch test applied on log - transformed data, 3 Mann - Whitney U test (Wilcoxon ranksum test).

Exemplary Illustrations regarding the Results for pSBP

Figure 5.3 shows the *cosinor* fit for one subject from the Lübeck cohort (left side plot) and for one individual of the Wels group (right side plot). In the mean, the predicted maximum according to the model appears approximately 2.5 hours later for individuals of the control group than for subjects of the group Wels. Therefore, it seems reasonable that the index t_{max} of the *cosinor* fit is significantly larger for the control group.

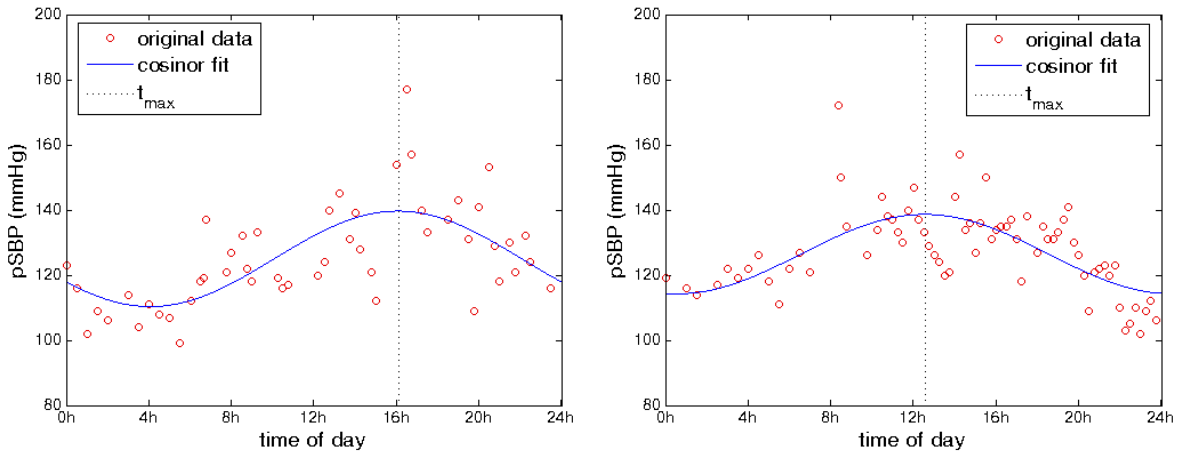


Figure 5.3: The left figure shows the *cosinor* fit for one subject from the Lübeck cohort. On the right side the cosinor fit of a patient of the Wels cohort is plotted. The time point of the predicted maximum t_{max} is marked as well.

Consistently, the time points of the predicted maximum derived from the weighted as well as the unweighted fourier fit are as well significantly later for the control group than for the patient group (cf. figure 5.4).

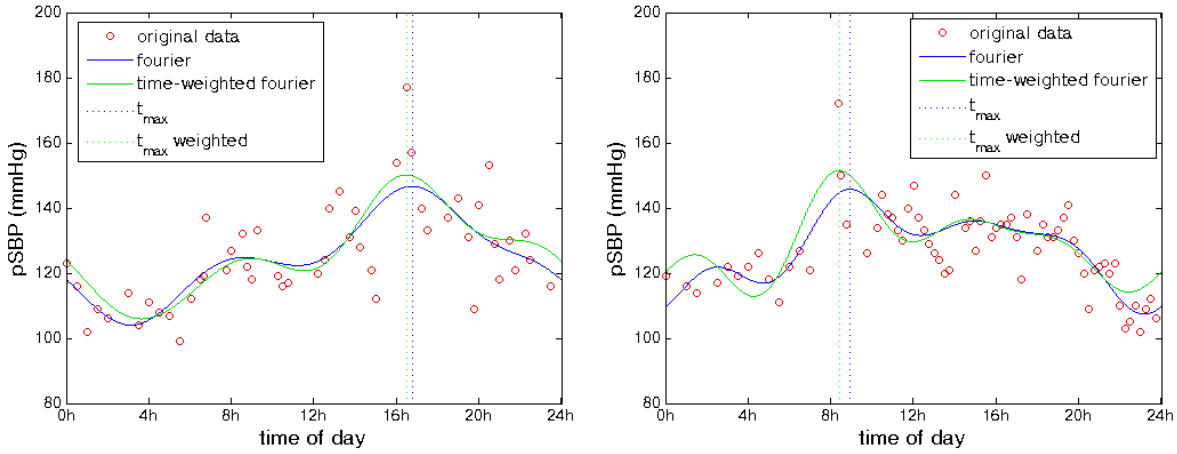


Figure 5.4: The plots show the weighted as well as the unweighted fourier fits for the same subjects as in figure 5.3. The time points of the predicted maxima t_{max} and t_{max} *weighted* are marked as well.

5.3.3 Central Systolic Blood Pressure (cSBP)

Table 5.6 shows the results for the parameter cSBP. All variability indices are calculated and tested for significant differences. In addition to the mean (or median) values, the p-values and the used tests are given. Possible additional settings are stated as well.

method	**index**	**Lübeck**	**Wels**	**p-value**	**test**	**add. sett.**
cSD	cSD_{day}	10 (2.85 SD)	10.8 (2.73 SD)	0.10	1a	-
	cSD_{night}	9.71 (3.42 SD)	10 (4.24 SD)	0.62	1a	-
	cSD_{24h}	12 (2.73 SD)	12.7 (2.71 SD)	0.10	1a	-
wSD	wSD	9.97 (2.48 SD)	10.6 (2.51 SD)	0.13	1.00a	-
ARV	ARV_{day}	9.53 (3.15 SD)	9.53 (2.78 SD)	1	1a	-
	ARV_{night}	10.2 (4.23 SD)	10.6 (4.21 SD)	0.56	1a	-
	ARV_{24h}	9.61 (2.29 SD)	9.78 (2.5 SD)	0.68	1a	-
wARV	$wARV$	10.4 (2.7 SD)	10.7 (3.1 SD)	0.47	1a	-
SV	SV_{day}	12.2 (4.01 SD)	12.5 (3.83 SD)	0.73	1a	-
	SV_{night}	12.3 (4.85 SD)	13.1 (5.5 SD)	0.35	1a	-
	SV_{24h}	12.6 (3.08 SD)	12.9 (3.49 SD)	0.60	1a	-
CV (%)	CV_{day}	9.05 (2.33 SD)	9.19 (2.39 SD)	0.73	1a	-
	CV_{night}	10.1 (3.5 SD)	9.5 (4.13 SD)	0.34	1a	-
	CV_{24h}	11.2 (2.34 SD)	11.1 (2.27 SD)	0.74	1a	-
HEM	$skew_{day}$	0.118 (0.681 SD)	-0.0214 (0.648 SD)	0.23	1a	-
	$kurt_{day}$	3.36 (1.25 SD)	3.28 (1.14 SD)	0.68	1a	-
	$skew_{night}$	0.038 (0.575 SD)	0.208 (0.612 SD)	0.10	1a	-
	$kurt_{night}$	2.42 (0.657 SD)	2.45 (0.664 SD)	0.74	1a	-

	$skew_{24h}$	-0.157 (0.475 SD)	-0.131 (0.528 SD)	0.76	1a	-
	$kurt_{24h}$	3.18 (0.941 SD)	3.1 (0.914 SD)	0.60	1a	-
OS	$range$	54.3 (12.9 SD)	56.8 (12.6 SD)	0.27	1a	-
	IQR	15.4 (4.49 SD)	16.8 (5.65 SD)	0.11	1a	-
	$midrange$	106 (9.66 SD)	114 (10 SD)	< 0.001	1a	-
	$median$	107 (8.11 SD)	115 (9.26 SD)	< 0.001	1a	-
	$peak$	26.4 (7.93 SD)	28 (7.7 SD)	0.23	1a	-
	$trough$	27.9 (7.8 SD)	28.8 (8.45 SD)	0.55	1a	-
	max	133 (13.6 SD)	143 (12.6 SD)	< 0.001	1a	-
	t_{max} (dec)	0.642 (0.206 SD)	0.585 (0.202 SD)	0.10	1a	-
	min	78.4 (9.28 SD)	86.1 (11 SD)	< 0.001	1a	-
	t_{min} (dec)	0.208 [0.104, 0.36]	0.418 [0.106, 0.719]	0.07	3	-
runs	$runs_{day}$	9.76 (4.11 SD)	9.55 (3.97 SD)	0.76	1a	subperiod median
	$runs_{night}$	3.5 [3, 5]	3 [2, 5]	0.33	3	(cf. sec. 2.9.5)
	$runs_{24h}$	14.9 (5.12 SD)	14 (4.85 SD)	0.29	1a	
	$UDUs_{day}$	15 (5.59 SD)	15.1 (5.63 SD)	0.91	1a	(UDUs not
	$UDUs_{night}$	4.55 (2.21 SD)	4.41 (1.62 SD)	0.68	2a	affected)
	$UDUs_{24h}$	27.7 (7.78 SD)	28.1 (8.02 SD)	0.74	1a	
runs	$runs_{day}$	8.81 (3.8 SD)	8.09 (3.32 SD)	0.25	1a	24h median
	$runs_{night}$	1.5 [0, 3]	2 [1, 3]	0.54	3	(cf. sec. 2.9.5)
	$runs_{24h}$	14.9 (5.12 SD)	14 (4.85 SD)	0.29	1a	
NBPF	NDR	0.877 (0.0685 SD)	0.901 (0.087 SD)	0.09	2a	-
	NDR_p	87.7 (6.85 SD)	90.1 (8.7 SD)	0.09	2a	-

	$ADND$	13.8 (8.2 SD)	12.2 (10.7 SD)	0.35	2a	-
	$ADNDtoDR$	0.123 (0.0685 SD)	0.0991 (0.087 SD)	0.09	2a	-
	NF	12.3 (6.85 SD)	9.91 (8.7 SD)	0.09	2a	-
weighted NBPF	NDR	0.871 (0.0701 SD)	0.901 (0.095 SD)	0.05	2a	
	NDR_p	87.1 (7.01 SD)	90.1 (9.5 SD)	0.05	2a	time
	$ADND$	14.5 (8.47 SD)	12.3 (11.7 SD)	0.23	2a	weighted
	$ADNDtoDR$	0.129 (0.0701 SD)	0.0992 (0.095 SD)	0.05	2a	
	NF	12.9 (7.01 SD)	9.92 (9.5 SD)	0.05	2a	
cosinor	$mesor$	106 (8.01 SD)	114 (8.64 SD)	< 0.001	1a	-
	$amplitude$	8.48 (4.34 SD)	9.24 (4.67 SD)	0.33	1a	-
	$acrophase$	-4.08 (0.894 SD)	-3.56 (1.15 SD)	0.005	2a	-
	t_{max} (dec)	0.65 (0.142 SD)	0.567 (0.183 SD)	0.005	2a	-
fourier	$amplitude$	15.8 (5.39 SD)	17.1 (5.89 SD)	0.21	1a	4 harmonics
	t_{max}	0.646 (0.211 SD)	0.58 (0.209 SD)	0.07	1a	no weighting
weighted fourier	$amplitude$	17.2 (5.6 SD)	19 (6.77 SD)	0.08	1a	4 harmonics
	t_{max}	0.661 (0.212 SD)	0.56 (0.233 SD)	0.009	1a	time weighted
SW	LD	17.2 (5.58 SD)	19 (5.96 SD)	0.08	1a	
	TPP_{max}	0.367 [0.271,0.536]	0.334 [0.25,0.53]	0.66	1b	minimal
	TPP_{min}	0.88 [0.292,0.938]	0.844 [0.583,0.917]	1.00	3	number of
	PD_{high}	0.532 (0.24 SD)	0.531 (0.247 SD)	0.99	1a	read. per
	PD_{low}	0.468 (0.24 SD)	0.469 (0.247 SD)	0.99	1a	period = 5
	PVA	38.4 (14.5 SD)	39.6 (16.2 SD)	0.63	1a	
pSD	pSD_{day}	8.1 (2.46 SD)	8.4 (2.18 SD)	0.47	1a	fourier

	pSD_{night}	7.86 (2.81 SD)	8.28 (3.31 SD)	0.42	1a	4 harmonics
	pSD_{24h}	8.21 (1.84 SD)	8.55 (2.08 SD)	0.32	1a	no weights
	CPH	159 (72.7 SD)	179 (87.4 SD)	0.14	1a	
	CPS	10.7 [-5.11,17.4]	13.2 [5.5,20.3]	0.26	3	no weights
cusum	CCV	115 (9.38 SD)	125 (10.2 SD)	< 0.001	1a	start of
	CTV	94 (8.65 SD)	102 (8.53 SD)	< 0.001	1a	plot = 0h
	$CCAM$	21.5 (8 SD)	23.5 (8.12 SD)	0.14	1a	
	CPH	77.6 (30.7 SD)	84.6 (36.3 SD)	0.22	1a	
weighted	CPS	5.73 [-5.53,7.22]	6.12 [1.48,8.97]	0.27	3	time weighted
cusum	CCV	116 (9.22 SD)	126 (10.7 SD)	< 0.001	1a	start of
	CTV	92.5 (9.01 SD)	98.1 (10.3 SD)	< 0.001	1a	plot = 0h
	$CCAM$	23.8 (8.94 SD)	27.7 (11.1 SD)	0.02	1a	
	STS	18 (11.4 SD)	19.5 (13.8 SD)	0.48	1a	going to bed = 9 p.m.
	PS	3.47 (11.9 SD)	2.59 (10.1 SD)	0.68	1a	arising = 9 a.m.
EMS	RS	2.48 (16.2 SD)	3.59 (12.2 SD)	0.65	2a	duration = 2h
	MED	-3.05 (11.9 SD)	4.82 (13.9 SD)	< 0.001	1a	(MS_{ft} not
	MS_{ft}	22.5 (15.2 SD)	21.7 (13.7 SD)	0.78	1a	affected)

Table 5.6: Indices calculated for the parameter cSBP. The column **Lübeck** contains the mean values of the indices for the control group, the column **Wels** contains the mean values for the patient group. If data are not normally distributed, median and IQR are denoted instead. Significant p-values are highlighted with a green background. If additional settings have to be chosen for the calculations of an index, these are mentioned in the 'additional settings' (**add.sett.**) column. Time points are given in decimal (dec) numbers. Multiplication by 24 yields hours. UDUs stands for 'updownups' (cf. section 2.9.3). The numbers in the column **test** indicate the used test for the statistical analysis: 1a t-test, 1b t-test applied on log - transformed data, 2a Welch test, 2b Welch test applied on log - transformed data, 3 Mann - Whitney U test (Wilcoxon ranksum test).

Exemplary Illustrations regarding the Results for cSBP

The plot on the left side of figure 5.5 shows the diurnal cSBP data of an individual from the Lübeck cohort. The dipping behaviour at night can clearly be observed. The representative of the Wels group on the right side has a different cSBP profile. The decline of the values at night is less prominent. Therefore, the NF is notable different among the two groups, although only the weighted form is significantly different. This distinction among the groups is even sharper for pSBP (cf. table 5.5).

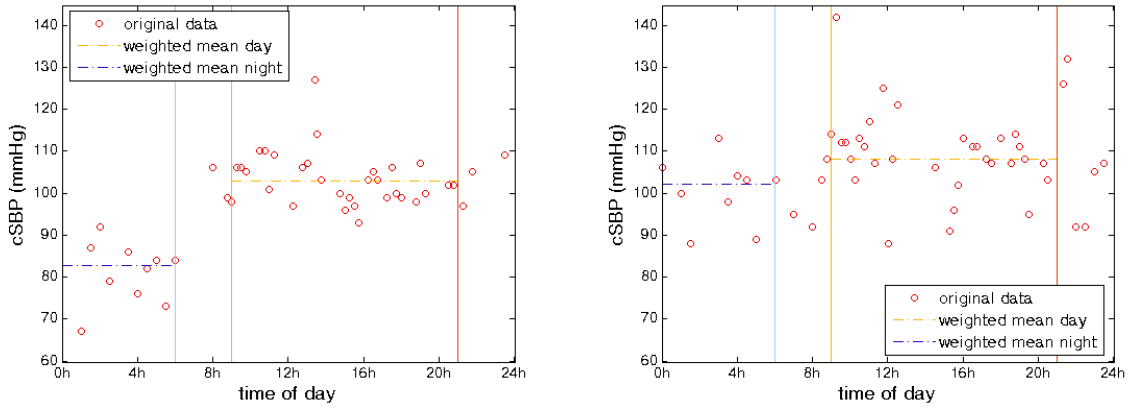


Figure 5.5: The plots show the diurnal cSBP data of an individual from the Lübeck cohort (left) and of a representative of the patient group (right). Vertical lines indicate the beginning and end of day (09:00 - 21:00) and night (00:00 - 06:00).

Considering the weighted NF method, 10 out of 58 individuals of the Wels group even show an inverted dipping behaviour. The data set of one of them can be seen in the right plot of figure 5.6. This phenomenon of a rise in BP at night does only appear in 3 out of 80 subjects of the control group. Nevertheless, the most steep nocturnal rise observed among those is only about 3.2% (left plot in figure 5.6), while the top value was about 15.6% for the Wels group (right plot in figure 5.6).

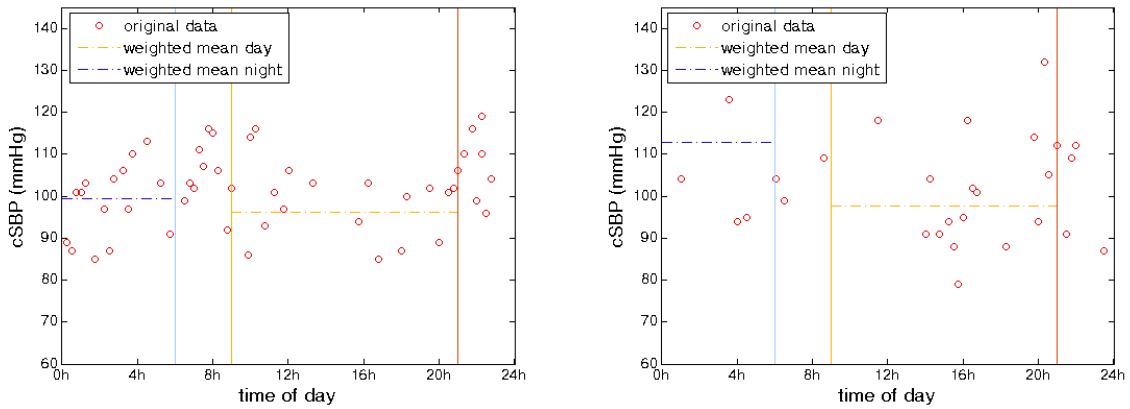


Figure 5.6: The plots show inverted dipping behaviours of an individual of the control group (left) and a subject of the patient group (right). Vertical lines indicate the beginning and end of day (09:00 - 21:00) and night (00:00 - 06:00).

5.3.4 Augmentation Index (AIx)

Table 5.7 shows the results for the parameter AIx. All variability indices are calculated and tested for significant differences. In addition to the mean (or median) values, the p-values and the used tests are given. Possible additional settings are stated as well.

method	index	Lübeck	Wels	p-value	test	add. sett.
cSD	cSD_{day}	8.31 (2.15 SD)	9.15 (2.43 SD)	0.04	1a	-
	cSD_{night}	10.8 (4.99 SD)	12.6 (5.21 SD)	0.04	1a	-
	cSD_{24h}	10.1 (2.46 SD)	11.2 (2.34 SD)	0.01	1a	-
wSD	wSD	9 (2.39 SD)	10.1 (2.36 SD)	0.007	1a	-
ARV	ARV_{day}	8.4 (2.19 SD)	9.21 (3.27 SD)	0.10	2a	-
	ARV_{night}	11.2 (6.18 SD)	13.3 (6.68 SD)	0.05	1a	-
	ARV_{24h}	9.33 (2.64 SD)	10.6 (2.69 SD)	0.007	1a	-
wARV	$wARV$	9.64 (2.78 SD)	11.2 (2.82 SD)	0.002	1a	-
SV	SV_{day}	10.8 (2.77 SD)	11.8 (4.01 SD)	0.12	2a	-
	SV_{night}	14.8 (7.54 SD)	17.1 (7.66 SD)	0.09	1a	-
	SV_{24h}	12.8 (3.34 SD)	14.2 (3.35 SD)	0.02	1a	-
CV (%)	CV_{day}	44.5 (14.6 SD)	44 (14 SD)	0.83	1a	-
	CV_{night}	57 (26.6 SD)	55.4 (25.3 SD)	0.73	1a	-
	CV_{24h}	52.3 (15.4 SD)	50.8 (15 SD)	0.57	1a	-
HEM	$skew_{day}$	0.403 (0.68 SD)	0.0792 (0.821 SD)	0.01	1a	-
	$kurt_{day}$	2.55 [2.16, 3.24]	2.7 [2.1, 3.58]	0.46	1b	-
	$skew_{night}$	0.669 (1.02 SD)	0.0909 (1.05 SD)	0.001	1a	-
	$kurt_{night}$	2.53 [1.7, 3.34]	1.94 [1.55, 2.99]	0.10	1b	-

	$skew_{24h}$	0.717 (0.821 SD)	0.226 (0.787 SD)	< 0.001	1a	-
	$kurt_{24h}$	2.67 [2.14, 4.3]	2.63 [2.11, 3.48]	0.10	2b	-
OS	$range$	38.9 (7.37 SD)	41.9 (5.56 SD)	0.007	2a	-
	IQR	14.2 (5.74 SD)	16 (5.65 SD)	0.08	1a	-
	$midrange$	26 [23.8, 28.3]	26.5 [25, 27.5]	0.35	3	-
	$median$	18.6 (8.46 SD)	23.1 (9.31 SD)	0.004	1a	-
	$peak$	24.3 (6.39 SD)	23.2 (6.22 SD)	0.30	1a	-
	$trough$	14.6 (5.96 SD)	18.8 (6.33 SD)	< 0.001	1a	-
	max	47 [43, 49]	49 [47, 50]	0.004	3	-
	t_{max} (dec)	0.313 [0.135, 0.678]	0.314 [0.125, 0.833]	0.58	3	-
	min	6 [3.5, 9]	5 [4, 7]	0.13	3	-
	t_{min} (dec)	0.495 (0.305 SD)	0.516 (0.294 SD)	0.69	1a	-
runs	$runs_{day}$	10.9 (4.56 SD)	10.9 (4.53 SD)	1.00	1a	subperiod median
	$runs_{night}$	4 [2, 5]	3 [3, 5]	0.96	3	(cf. sec. 2.9.5)
	$runs_{24h}$	18.2 (6.43 SD)	19.1 (5.49 SD)	0.36	1a	
	$UDUs_{day}$	14.8 (5.56 SD)	16.1 (6.38 SD)	0.21	1a	(UDUs not
	$UDUs_{night}$	4 [3, 6]	4 [3, 5]	0.03	3	affected)
	$UDUs_{24h}$	28.1 (7.51 SD)	28.8 (8.38 SD)	0.59	1a	
runs	$runs_{day}$	10.2 (4.42 SD)	10.5 (4.48 SD)	0.68	1a	24h median
	$runs_{night}$	3 [2, 4]	3 [2, 4]	0.40	3	(cf. sec. 2.9.5)
	$runs_{24h}$	18.2 (6.43 SD)	19.1 (5.49 SD)	0.36	1a	
NBPF	NDR	0.942 [0.769, 1.16]	1.1 [0.909, 1.34]	0.08	1b	-
	NDR_p	94.2 [76.9, 116]	110 [91, 134]	0.08	1b	-

	$ADND$	-0.448 (7.77 SD)	-3.48 (8.46 SD)	0.03	1a	-
	$ADNDtoDR$	0.0584 [-0.164,0.231]	-0.102 [-0.345, 0.0908]	0.01	3	-
	NF	5.84 [-16.4,23.1]	-10.2 [-34.5, 9.08]	0.01	3	-
weighted NBPF	NDR	0.981 [0.719, 1.35]	1.11 [0.838, 1.52]	0.25	1b	
	NDR_p	98.1 [71. 9,135]	111 [84, 152]	0.25	1b	time
	$ADND$	-1.35 (8.62 SD)	-3.77 (9.29 SD)	0.12	1a	weighted
	$ADNDtoDR$	0.0191 [-0.35, 0.281]	-0.107 [-0.519, 0.162]	0.07	3	
	NF	1.91 [-35, 28.1]	-10.7 [-51.9, 16.2]	0.07	3	
cosinor	$mesor$	20.6 (6.59 SD)	23.9 (7.34 SD)	0.006	1a	-
	$amplitude$	4.62 (3.09 SD)	5.29 (3.49 SD)	0.23	1a	-
	$acrophase$	-2.86 (1.69 SD)	-2.43 (2.01 SD)	0.17	1a	-
	t_{max} (dec)	0.456 (0.27 SD)	0.387 (0.32 SD)	0.17	1a	-
fourier	$amplitude$	11 (4.42 SD)	12.1 (4.6 SD)	0.16	1a	4 harmonics
	t_{max}	0.36 (0.263 SD)	0.377 (0.298 SD)	0.73	1a	no weighting
weighted fourier	$amplitude$	12.9 (5.13 SD)	14.7 (5.28 SD)	0.05	1a	4 harmonics
	t_{max}	0.327 [0.175, 0.582]	0.216 [0.0722, 0.58]	0.20	3	time weighted
SW	LD	12.8 (5.09 SD)	13.6 (4.25 SD)	0.30	1a	
	TPP_{max}	0.385 [0.22, 0.792]	0.75 [0.252, 0.861]	0.04	3	minimal
	TPP_{min}	0.493 (0.28 SD)	0.481 (0.301 SD)	0.81	1a	number of
	PD_{high}	0.378 (0.263 SD)	0.439 (0.277 SD)	0.19	1a	read. per
	PD_{low}	0.622 (0.263 SD)	0.561 (0.277 SD)	0.19	1a	period = 5
	PVA	22.3 [17.4, 27.9]	23.5 [15.2, 30.8]	0.80	1b	
pSD	pSD_{day}	7.11 (1.84 SD)	7.78 (2.21 SD)	0.06	1a	fourier

	pSD_{night}	9.13 (4.14 SD)	10.3 (4.69 SD)	0.11	1a	4 harmonics
	pSD_{24h}	8.18 (2.01 SD)	9.12 (2.06 SD)	0.008	1a	no weights
	CPH	86.9 [67.4, 121]	104 [81, 126]	0.05	1b	
	CPS	6.73 [-7.32, 11.9]	-6.09 [-13.5, 6.99]	0.003	3	no weights
cusum	CCV	27.7 (8.5 SD)	31.6 (8.75 SD)	0.009	1a	start of
	CTV	14.5 (6.11 SD)	16.8 (6.89 SD)	0.04	1a	plot = 0h
	$CCAM$	12.1 [9.1, 16]	14 [10, 17.8]	0.10	1b	
	CPH	50.8 (22.4 SD)	55.7 (24 SD)	0.22	1a	
weighted	CPS	2.03 (7.17 SD)	-2.77 (5.51 SD)	< 0.001	2a	time weighted
cusum	CCV	29.7 (9.5 SD)	34.1 (10.1 SD)	0.01	1a	start of
	CTV	12.6 (6.9 SD)	14 (8.09 SD)	0.28	1a	plot = 0h
	$CCAM$	17.1 (7.25 SD)	20.1 (8.26 SD)	0.03	1a	
	STS	2.33 (10.5 SD)	3.35 (11.2 SD)	0.59	1a	going to bed = 9 p.m.
	PS	-1.63 (8.91 SD)	-0.966 (9.68 SD)	0.70	1a	arising = 9 a.m.
EMS	RS	-1.91 (12.9 SD)	1.86 (13.5 SD)	0.10	1a	duration = 2h
	MED	0.652 (8.46 SD)	-0.121 (9.64 SD)	0.63	1a	(MS_{ft} not
	MS_{ft}	14.1 (11.3 SD)	15.4 (11.8 SD)	0.53	1a	affected)

Table 5.7: Indices calculated for the parameter AIx. The column **Lübeck** contains the mean values of the indices for the control group, the column **Wels** contains the mean values for the patient group. If data are not normally distributed, median and IQR are denoted instead. Significant p-values are highlighted with a green background. If additional settings have to be chosen for the calculations of an index, these are mentioned in the 'additional settings' (**add.sett.**) column. Time points are given in decimal (dec) numbers. Multiplication by 24 yields hours. UDUs stands for 'updownups' (cf. section 2.9.3). The numbers in the column **test** indicate the used test for the statistical analysis: 1a t-test, 1b t-test applied on log - transformed data, 2a Welch test, 2b Welch test applied on log - transformed data, 3 Mann - Whitney U test (Wilcoxon ranksum test).

Exemplary Illustrations regarding the Results for AIx

The figures below show boxplots for the index CUSUM plot slope (CPS) of the unweighted (cf. figure 5.7) and the weighted (cf. figure 5.8) CUSUM method. As can be seen, both indices are significantly larger for the Lübeck than for the Wels group.

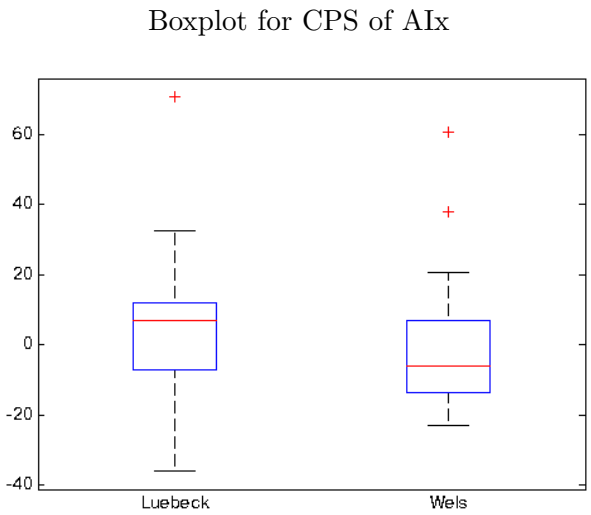


Figure 5.7: Boxplot for the index *CPS* of the CUSUM method.

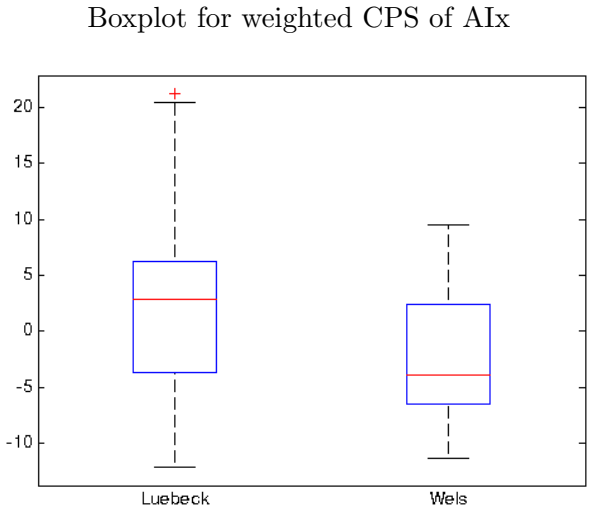


Figure 5.8: Boxplot for the index *CPS* of the weighted CUSUM method.

5.3.5 Peripheral Pulse Pressure (pPP) and Central Pulse Pressure (cPP)

For each of the parameters cPP and pPP only one of the methods provided significant indices - NF for cPP and CV for pPP. Therefore, the following tables (5.9 and 5.8) do not contain the results for the other methods.

Peripheral Pulse Pressure (pPP)

method	index	Lübeck	Wels	p-value
CV (%)	CV_{day}	25.1 (7.48 SD)	24.7 (6.93 SD)	0.76
	CV_{night}	16.5 (6.7 SD)	19 (7.86 SD)	0.05
	CV_{24h}	23 (4.95 SD)	23.5 (4.78 SD)	0.57
NBPF	NDR	1 (0.119 SD)	0.987 (0.13 SD)	0.50
	NDR_p	100 (11.9 SD)	98.7 (13 SD)	0.50
	$ADND$	0.354 (5.26 SD)	0.661 (5.39 SD)	0.74
	$ADNDtoDR$	-0.0017 (0.119 SD)	0.0126 (0.13 SD)	0.50
	NF	-0.17 (11.9 SD)	1.26 (13 SD)	0.50

Table 5.8: Indices calculated for the parameter pPP. The column **Lübeck** contains the mean values of the indices for the control group, the column **Wels** contains the mean values for the patient group. Significant p-values are highlighted with a green background. All data were normally distributed and analysed with the t-test.

Central Pulse Pressure (cPP)

method	index	Lübeck	Wels	p-value
CV (%)	CV_{day}	28.3 (7.42 SD)	27.3 (7.64 SD)	0.43
	CV_{night}	21 (8.32 SD)	23.3 (9.31 SD)	0.14
	CV_{24h}	27.2 (4.99 SD)	27.1 (5.35 SD)	0.84
NBPF	NDR	1.13 (0.191 SD)	1.07 (0.197 SD)	0.05
	NDR_p	113 (19.1 SD)	107 (19.7 SD)	0.05
	$ADND$	-3.49 (5.34 SD)	-1.67 (5.82 SD)	0.06
	$ADNDtoDR$	-0.133 (0.191 SD)	-0.0674 (0.197 SD)	0.05
	NF	-13.3 (19.1 SD)	-6.74 (19.7 SD)	0.05

Table 5.9: Indices calculated for the parameter cPP. The column **Lübeck** contains the mean values of the indices for the control group, the column **Wels** contains the mean values for the patient group. Significant p-values are highlighted with a green background. All data were normally distributed and analysed with the t-test.

Chapter 6

Discussion

In the following, the results and findings of chapter 5 will be discussed. Due to the large amount of data (20 different parameters and more than 50 indices) a detailed discussion of all parameters and all different settings for the indices would go beyond the scope of this work. Therefore, a selection of aspects will be considered. Attention will be paid to parameters which have already been mentioned in literature as important to be investigated in the context of cardiovascular prognostics (BP [3], [7], [14], [45], [71], Hf [31], [34], [45], [54], PP [78], [84], AIx [81], [82]) and on parameters which could not be determined as significantly different for the two groups by comparing their 24h averages (cf. section 5.2). The possible additional settings for the calculation of the indices are primarily chosen as the default values of the MATLAB algorithms. They are deduced from literature and are mentioned in detail in chapter 2. To obtain better comparability, the same setting was used for each of the parameters.

6.1 Sensitivity of the Indices to the Data Set Quality

The calculation of all indices was possible with the chosen setting of section 3.3. The setting is reasonable in consideration of literature related to similar studies as the one presented in this work. Even if data quality was chosen less restrictive than in other publications, still no problems occurred, when indices were calculated for different parameters. The only index for which not all preselected data sets were included was EMS (cf. section 5.3). The sensitivity of this index to the loss of readings has been discussed in section 2.13.3. In table 3.1, it can be seen that this index requires short time gaps between scheduled (and in the following successful) readings as well as very strict exclusion criteria. Nevertheless, on one hand, the sensitivity of the presented indices to the quality of recordings is satisfying (apart from EMS). On the other hand, it has to be mentioned that a fairly low schedule frequency and consequently a smaller number of valid measurements might influence the statistical meaningfulness of one or the other index. Thijs et al. [70], for instance, point out that an accurate determination of cSD is only obtained, if measurement are available every 30 minutes. They observed the same for the amplitude of the fourier model, the parameters of the CUSUM method and NF. Mena et al. [37] concluded

that ARV can only be assessed without loss of prognostic significance, if at least 48 readings are available. Both studies investigated 24h BP data. It seems likely that similar results could be observed for other parameters and indices.

6.2 Indices Considered for the Analysed Parameters

6.2.1 24h Averages

As can be seen in table 5.2, quite a few of the 24h averages of the ABPM and PWA parameters differ significantly in the mean among the control and the patient group. All BP values, central as well as peripheral systolic and diastolic values, are significantly different for the cohorts. This is to be expected, since various studies have shown that the level of BP is a strong indicator and predictor of cardiovascular or cerebrovascular conditions and even mortality [13], [24], [70], [78], [82]. It especially appears natural that the two cohorts analysed in this work have unlike BP average values, since patients of the group Wels are suspected to suffer from an enlargement of their left ventricle, which was found to be triggered by hypertension [4], [29], [84]. However, the relation between left ventricular mass and *central* BP values is not so well investigated at the present time, although some results have already been published. Protogerou at al. [52] found that LVH in hypertensive patients is better associated with 24h central pressure than with 24h peripheral pressure values.
Nevertheless, not all parameters attain significantly different 24h average values for the two groups including Hf (ABPM), central and peripheral PP and AIx**@**75 (PWA), which can be abstracted from table 5.2.

6.2.2 Variability Indices

Heart Frequency (Hf)

Hf is one of the parameters for which the 24h average was not significantly different among the two groups (cf. table 5.2). There are several variability indices, however, which show a statistical difference, such as unweighted and weighted SD, unweighted and weighted ARV and SV. Each of them is significantly different for all three time periods day, night and the whole 24h period and in every case the value for the Lübeck group is higher. Since ARV and SV are strongly correlated, it is consistent that both indices show the same behaviour considering the absence of presence of statistical significances. As expected, SV is larger in all three time periods (cf. section 2.5). The latter two observations can be made for all other parameters as well. The only exception is AIx, for which significance was different for the night period.
Interestingly, the difference between the groups can not be explained by the index CV. Only the 24h value is statistically significant. Since the above mentioned indices (SD, ARV and SV) depend on the average value (cf. chapter 2), which was not found to be significantly different, but CV is independent of the average value, one would expect CV to perform at least equally good.

The methods modelling the 24h profile do not provide indices which show a significant difference among the groups, the weighted fourier model being the single exception. These models (cosinor, fourier, SW and CUSUM) have been developed for BP and Hf profiles, which show a similar diurnal behaviour. Nevertheless, the indices obtained from them are not significantly different. On one hand, this might be due to the limitations of the models which have been summarized in chapter 2 (cf. also [45]). On the other hand, some indices are expected not to be significantly different, such as the mesor of the cosinor model as this is an approximation of the 24h average. In figure 5.1, the weighted fourier profiles of two subjects - one of each group - is depicted. The amplitude is significantly different. Consistently, also the index *range* is significantly different.

Peripheral Systolic Blood Pressure (pSBP) and Central Systolic Blood Pressure (cSBP)

These parameters attain significantly different 24h average values for the two groups. As has been mentioned before in section 6.2.1, this is not surprising. Other than for Hf the indices SD, ARV, SV and CV are not statistically significant. Controversial results have been found, when analysing BPV assessed with these indices (cf. chapter 2). In some studies associations with cardiovascular diseases have been found [21], [60], while in others their reliability has been questioned [3], [4].
Since mean values and median values were found to be normally distributed for pSBP as well as for cSBP, it seems reasonable that also the index median is significantly higher for the patient group. Likewise, the mesor of the cosinor method, which represents an approximation of the 24h mean value, shows statistical significance.
The significant difference of the indices obtained by the NBPF method are supported by findings in literature [65]. Verdecchia et al. [77] found an inverse relation between left ventricular mass and the decline of BP at night. Since individuals of the Wels group are believed to suffer from an enlargement of the left ventricle, it is in accordance with this observation that their NF in BP is significantly smaller. This is true for the peripheral as well as for the central systolic BP, but for cSBP only the weighted form was found to be significantly different. In the light of this reflections, it appears consistent that the ME difference is significantly different as well, not only for peripheral but also for central systolic BP, since this index is closely related to NBPF as has been discussed in section 2.13.3. Nevertheless, this index has to be treated with caution as additional data sets had to be excluded. Furthermore, the fixed time points 'arising' and 'going to bed' can not meet reality for each individual. The dependence of this index on the definition of these events has already been discussed (cf. section 2.13.3).

Augmentation Index (AIx)

It has been suggested to analyse this PWA parameter alongside BP itself to obtain an optimized hypertension drug treatment [82]. Furthermore, it has been shown that an increased AIx is an independent predictor of mortality for patients suffering from end-stage renal disease and coronary heart disease [81]. This supports its consideration in this work, especially since AIx

was found to be correlated with left ventricular mass in normotensive as well as hypertensive men [81]. However, in contrast to BP and Hf, the 24h variability of AIx or the diurnal profile has not yet been analysed in literature. AIx has a significantly different 24h average among the groups with a p-value of 0.005. One would expect this difference to be even stronger considering the highly significant BP values. The relatively large p-value might be explained by the different ratios of male and female individuals within the groups. AIx values have been found to be higher for women than for men [73]. Therefore, since the percentage of women in the control group is notable larger than in the patient group (cf. table 5.1), this might mask differences between the control and the patient group.
There is also a fair amount of variability indices which differ between the two cohorts (cf. table 5.7). Again, the median, and the mesor of the cosinor method are statistically significant which is consistent with the significantly different 24h average. The NF is again appropriate to observe differences among the two cohorts, although the weighted form is not significantly different. Another method, which seems to provide indices to distinguish the patient from the control group is the CUSUM method. This might be a better choice for modelling the diurnal profile, since the CUSUM plot - contrary to the cosinor method, the SW or the double logistic model - does not assume a certain diurnal profile. Such profiles with a lower plateau at night and a higher plateau during day time with differently steep transition periods have been determined to be present in BP and Hf data [45], but might not be suitable for AIx. This can be seen in figure 6.1. The top three plots and the bottom three plots each belong to the same subject denoted by **A** and **B**, respectively. For subject **B** the SW model seems appropriate for the AIx as well as the pSBP data. Considering subject **A**, the AIx data do not show a profile, such that the SW seems to fit, but the pSBP data approximately follow the typical pattern. The CUSUM method can be seen in the third column. A certain different behaviour of the CUSUM plot can be observed between the two individuals. Nevertheless, both plots show specific features.

Peripheral Pulse Pressure (pPP) and Central Pulse Pressure (cPP)

In several studies, PP was found to be an indicator for cardiovascular risk [78]. However, neither peripheral nor central PP is statistically different among the two groups considering 24h mean values (5.2). Even if cPP was found to have a stronger association with LVH than pPP in several studies [84], the mean differences between the groups Lübeck and Wels are larger for pPP. Nevertheless, for both parameters the 24h average values as well as a large number of variability indices are not significantly different (cf. tables 5.8 and 5.9). The NF again provides a significantly different index, but only for cPP. Peripheral PP only has a significantly higher CV at night for the patient group than for the control group. However, significance in both cases is borderline (p-value = 0.05).

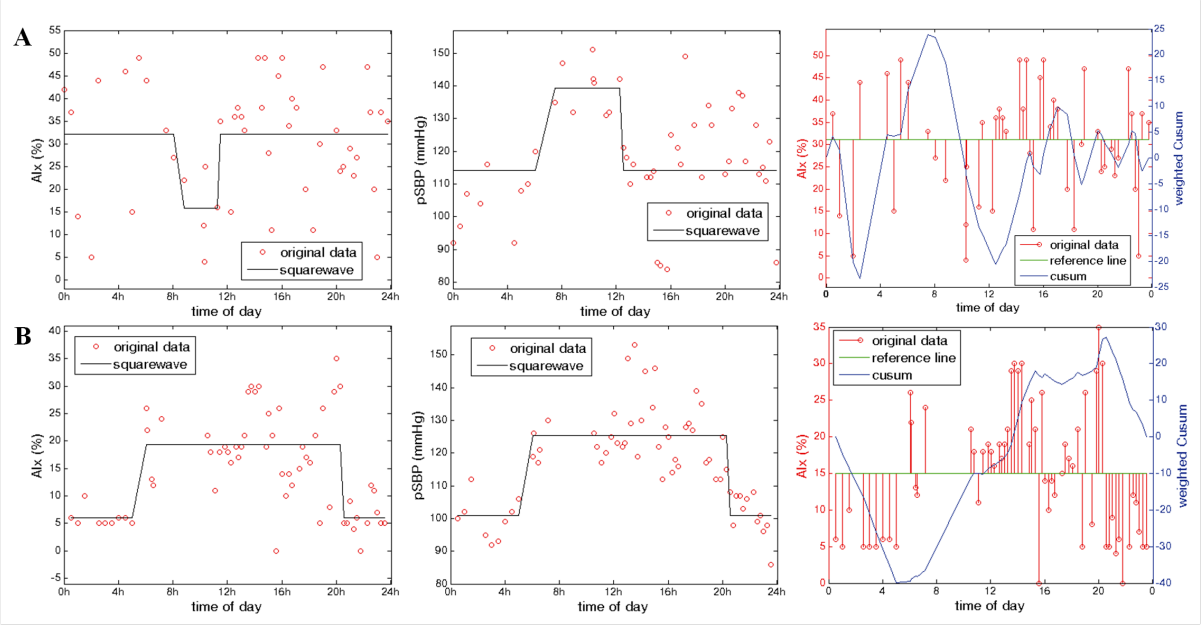


Figure 6.1: The above plots were produced with the MATLAB functions `calc_squarewavefit2neu.m` and `calc_cusumoption.m`. The top three plots and the bottom three figures each belong to the same subject denoted by **A** and **B**, respectively.

6.3 Weighted vs. Unweighted

For several indices there exists a weighted version, which basically means that not only measurement values alone are considered, but also the time gaps between consecutive readings are taken into account. This is achieved as each data point is weighted by the time period to the preceding measurement (wARV, weighted CUSUM, weighted fourier, weighted NF). This approach tries to overcome the loss of readings and, as a results, varying interval durations. Another possibility which aims to compensate the lower number of readings at night is to weight by the number of hours within day and night time periods (cSD).

Several publication are in favour of the weighted indices compared to the unweighted version. Bilo et al. [3] and Duan et al. [14], for instance, claim that wSD is superior to cSD as the latter one overestimates variability. Stanton et al. [65] stress the crucial importance to weight measurements by the time intervals between readings to correct for missing recordings and differences of the time periods between them. They analysed the CUSUM method. Octavio et al. [43] as well support the use of weighted mean values as they determined an overestimation of BP mean values due to a higher number of day time readings. This effect was largest in subjects with a pronounced NBPF. This motivates the calculation of wNBPF.

Considering the results in this work, for some parameters and indices the weighting had an influence on the significance. For the parameter Hf, for instance, the index *amplitude* of the fourier method is only significantly different among the groups, when the weighted form is calculated. For the CUSUM method the weighting does not make any difference. The indices of the NBPF method as well as of the fourier model have a smaller p-value, when weighting is

included - for pSBP and cSBP. The same is true for the CUSUM method, but only for cSBP. These results may be interpreted as supportive for the above mentioned publications in favour of the weighted methods. However, considering the parameter AIx, contradicting results are given. While the amplitude of the weighted fourier method has a smaller p-value than of the unweighted fourier model, the significant difference of the NBPF is lost when weighted indices are calculated. The results for the CUSUM method are as well indefinite as some parameters gain significance while for others it declines. For cPP the single significantly different index is NF, which is no longer statistically significant, if calculations are done with weighting.
It has to be mentioned that the comparison of p-values is only reasonable, if the same statistical test was used. This was the case for all above mentioned indices. Only CPH for Hf and CPS for AIx were analysed differently.

6.4 Central vs. Peripheral

Scientific studies have determined that peripheral systolic as well as peripheral pulse pressures are higher than the according central values. It has also been shown that central pressures have a stronger association with LVH than the peripheral values [84], [85]. Associations of indices with LVH were not considered in this work, but one might expect to find differences in the results for central and peripheral pressures. These expectations are not fulfilled. Considering systolic BP values, the indices show an almost identical significance pattern (cf. tables 5.2, 5.5 and 5.6). PP values are not significantly different among the patient and the control group, neither peripheral nor central values. The p-values for 24h averages are far above the significance level. For each PP parameter only one of the variability indices is significantly different among the two cohort. However, significance is weak in both cases (p-value = 0.05).

6.5 Conclusion

The indices gathered in this work require further analysis. Nevertheless, interesting observations have been made. It appears that for systolic BP values the 24h averages provide a significantly different index among patients suspected to suffer from LVH and healthy individuals. However, not all PWA parameters have a significantly different average value among the groups. For some of them variability indices might provide an improvement, others like cPP and pPP remain nearly indistinguishable by the indices provided.
The NF turned out to be the most 'stable' index for the parameters considered in this work as it is significantly different for all parameters, but Hf and pPP. Additionally, it is the only index with a p-value ≤ 0.05 for the parameter cPP, for which 24h average values are not significantly different and which was determined to be closely associated with LVH. The significance of NF concerning BP values might be due to the non dipping tendency of LVH patients. Since PWA parameters have an influence on each other this might explain the statistical significance in the other cases.
The large amount of indices gives a wide-ranging number of aspects to be considered. Even

if not all of the PWA parameters have been analysed in the frame of this work, the findings are of interest in the context of identifying indices with possible prognostic relevance. The mathematical models prove to be adequate to assess the diurnal profile and variability of 24h PWA parameters and the implemented algorithms are feasible to be applied to the data sets.

6.6 Outlook

The large amount of possible methods to assess variability leaves room for some more aspects to consider in future analysis.
Several methods allow different settings - the fourier analysis can be calculated with different numbers of harmonics, a different number of minimal period durations is possible for the SW and pSD might be analysed with different best fit curves to name a few.
The method EMS and the double logistic curve fit require deeper analysis. The challenges regarding these methods have been discussed before (cf. section 2.13.3 and 2.14.4). For the first mentioned, the time points of 'arising' and 'going to bed', for instance, might be identified with curve fitting methods such as the SW.
Another interesting aspect which was only tangentially treated is the comparison of different models which aim to calculate identical indices. The expected time point of the maximum, for example, is obtained by the models cosinor and weighted as well as unweighted fourier. Furthermore, they could be compared with the actual time point of the maximal value.
One of the methodological issues which occur when investigating BPV is reproducibility [1]. Thijs et al. [71] emphasize that indices of BPV can only be of clinical relevance, if they are reproducible when ABPM is repeated under standardized circumstances. For several indices considered in this work reproducibility was already analysed for example the cSD, the fourier model, the CUSUM method and the NBPF [70]. Reproducibility of these variability parameters was found to be more sensitive to the number of available readings than the 24h blood pressure mean. Lurbe et al. [30] investigated the same methods except cSD and concluded as well the relatively poor reproducibility compared to 24h average values. This aspect definitely leaves room for further investigations and improvements.
Finally, the algorithms which were implemented in the course of the formation of this thesis to assess the variability and the diurnal profile of PWA parameters might be used in studies investigating clinical questions based on variability analysis to determine risk factors predicting cardiovascular diseases.

Index

Acronyms

Symbols

P_1 amp. of the early syst. peak pressure. 74, 76

P_2 amp. of the late syst. peak pressure. 74, 76

P_b backward pressure wave amplitude. 74, 76

P_f forward pressure wave amplitude. 74, 76

R_p peripheral resistance. 2, 74, 76

A

ABPM ambulatory blood pressure monitoring. 1–3, 15, 40, 68, 73–75, 100, 105

ADND absolute day-night-difference. 29–31

AIT Austrian Institute of Technology. 2, 74

AIx augmentation index. 3, 45, 74, 76, 93, 96, 97, 99–102, 104

AIx@75 augmentation index at 75 bpm. 74, 76, 100

AP augmentation pressure. 2, 3, 74, 76

ApEn approximate entropy. 27, 28, 67

ARV average real variability. 6, 11–14, 26, 27, 68, 71, 77, 83, 88, 93, 100, 101

B

BP blood pressure. 1–3, 5, 6, 8–12, 14–16, 19, 21, 22, 25, 27–34, 36, 40, 53, 56, 58, 60, 64, 70, 74, 92, 99–104

BPV blood pressure variability. 1, 5, 6, 9, 11, 12, 14–16, 19, 22, 27, 59, 101, 105

C

CCAM CUSUM derived circadian alteration magnitude. 63, 64

CCV CUSUM derived crest value. 63, 64

cDBP central diastolic blood pressure. 74, 76

CEs cardiovascular events. 9, 11

CMB cerebral microbleed. 14, 15

CO cardiac output. 2, 74, 76

CPH CUSUM plot height. 62, 63, 104

cPP central pulse pressure. 74, 76, 98, 102, 104

CPS CUSUM plot slope. 62–64, 97, 104

cSBP central systolic blood pressure. 74–76, 88, 91, 92, 101, 104

cSD crude standard deviation. 5–10, 16, 58, 59, 64, 71, 77, 83, 88, 93, 99, 103, 105

CTV CUSUM derived trough value. 63, 64

CV coefficient of variation. 10, 15, 16, 26, 71, 77, 83, 88, 93, 98, 100–102

E

EMS early morning surge. 9, 10, 31, 70, 72, 80, 82, 86, 91, 96, 99, 105

H

HEM higher empirical moments. 67, 77, 83, 88, 93

Hf heart frequency. 1, 5, 45, 56, 74, 76, 77, 80, 81, 99–104

HIx heart index. 74, 76

I

IQR interquartile range. 20, 73, 80, 86, 91, 96

L

LACI lacunar infarction. 59

LVH left ventricular hypertrophy. 3, 10, 73, 100, 102, 104

M

max maximum. 18

ME morning-evening. 32, 33, 101

min minimum. 18

MPS morning pressor surge. 31–34

MR midrange. 21

MS morning surge. 31–34

N

NBPF nocturnal blood pressure fall. 6, 9, 10, 16, 20, 28–31, 34, 39, 59, 62, 64, 72, 78, 79, 84, 85, 89, 90, 94, 95, 98, 101, 103–105

NDR night-to-day ratio. 28, 29, 31

NF nocturnal fall. 28–30, 92, 98, 99, 101–104

O

OS order statistics. 78, 84, 89, 94

P

pDBP peripheral diastolic blood pressure. 74, 76

pMAP peripheral mean arterial pressure. 74, 76

PP pulse pressure. 1–3, 19, 99, 100, 102, 104

pPP peripheral pulse pressure. 74, 76, 98, 102, 104

pSBP peripheral systolic blood pressure. 56, 74–76, 83, 86, 87, 92, 101, 102, 104

pSD personalized standard deviation. 58, 59, 79, 85, 90, 95, 105

PVA percentage of the total 24h variability. 39

PWA pulse wave analysis. 2, 3, 5, 17, 68, 70, 73, 75, 100, 101, 104, 105

PWV pulse wave velocity. 1–3, 74, 76

R

RM reflexion magnitude. 74, 76

RSS residual sum of squares. 38, 43, 44, 48

S

SD standard deviation. 5–7, 9–12, 15–18, 23, 26–28, 30, 31, 58, 100, 101

SV successive variation. 13–15, 27, 77, 83, 88, 93, 100, 101

SW square-wave. 35–40, 52, 54, 56, 72, 79, 85, 90, 95, 101, 102, 105

T

TOD target organ damage. 6, 9, 11, 19

V

VIM variation independent of mean. 10, 15, 16, 26, 67

W

wARV weighted average real variability. 13, 77, 81, 83, 88, 93, 103

wSD weighted standard deviation. 6, 7, 9–12, 20, 31, 59, 71, 77, 83, 88, 93, 103

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