SLOVAK UNIVERSITY OF TECHNOLOGY IN BRATISLAVA
FACULTY OF ELECTRICAL ENGINEERING AND INFORMATION TECHNOLOGY

Mgr. Zuzana Rošťáková

Dissertation thesis abstract

PROBABILISTIC MODELLING AND FUNCTIONAL DATA ANALYSIS OF SLEEP STRUCTURE

Submitted to obtain the academic title of **Philosophiae Doctor, PhD.**

in the doctorate degree study programme:
Measurement Technology

in the field of study:
5.2.54 Measurement Technique

form of study**:**
full-time study

Bratislava, August 2018

SLOVAK UNIVERSITY OF TECHNOLOGY IN BRATISLAVA
FACULTY OF ELECTRICAL ENGINEERING AND INFORMATION TECHNOLOGY

Mgr. Zuzana Rošťáková

Dissertation thesis abstract

PROBABILISTIC MODELLING AND FUNCTIONAL DATA ANALYSIS OF SLEEP STRUCTURE

Submitted to obtain the academic title of **Philosophiae Doctor, PhD.**

in the doctorate degree study programme:
Measurement Technology

Bratislava, August 2018

Dissertation thesis has been prepared at Institute of Measurement Science
Slovak Academy of Sciences
Dúbravská cesta 9, 841 01 Bratislava

Author: **Mgr. Zuzana Rošťáková**
Institute of Measurement Science
Slovak Academy of Sciences
Dúbravská cesta 9, 841 01 Bratislava

Supervisor: **Ing. Mgr. Roman Rosipal, PhD.**
Institute of Measurement Science
Slovak Academy of Sciences
Dúbravská cesta 9, 841 01 Bratislava

Reviewers: **prof. Ing. Igor Farkaš, Dr.**
Department of Applied Informatics
Faculty of Mathematics, Physics and Informatics
Comenius University in Bratislava
Mlynská dolina, 842 48 Bratislava
Slovak Republic

doc. RNDr. Daniel Hlubinka, PhD.
Department of Probability and Mathematical Statistics
Faculty of Mathematics and Physics
Charles University in Prague
Sokolovská 83, 186 75 Prague 8
Czech Republic

Dissertation thesis abstract was sent on: May 31, 2018

Dissertation Thesis Defence will be held on **.....** at .....**h** (am/pm)

at Institute of Measurement Science (courtroom)
Slovak Academy of Sciences
Dúbravská cesta 9, 841 01 Bratislava

doc. Ing. Milan Tyšler, Csc.
Director of IMS SAS

Prof. Dr. Ing. Miloš Oravec
Dean of FEI STU

Abstrakt

Spánok je spojitý heterogénny proces, ktorý počas noci prechádza konečným počtom spánkových stavov. Jeho kvalita a štruktúra vo výraznej miere ovplyvňujú naše každodenné správanie. Spánkový elektroencefalogram (EEG) zachytávajúci aktivitu mozgu počas spánku tvorí základný kameň tejto práce. Nameraný EEG signál je následne spracovaný pomocou pravdepodobnostného spánkového modelu a reprezentovaný konečnou množinou spánkových pravdepodobnostných kriviek. Prvá časť práce je zameraná na detekciu spánkových profilov, ktoré významne súvisia s dennými mierami (subjektívne hodnotenie kvality spánku, fyziologický stav organizmu, kognitívne testovanie) pomocou metód funkcionálnej dátovej analýzy, konkrétne zhlukovej analýzy spánkových kriviek. Ak spánkové krivky nie sú synchronizované v čase, zhluková analýza môže viesť k zaradeniu kriviek s podobným profilom do rôznych zhlukov. Existujúce metódy simultánne kombinujúce zhlukovanie a synchronizáciu kriviek pri aplikácii na spánkové dáta nevedú k uspokojivým výsledkom. Z tohto dôvodu sme navrhli vlastnú metódu, ktorá iteračne kombinuje zhlukovú analýzu kriviek a časovú synchronizáciu. Jej benefity oproti existujúcim prístupom sú demonštrované na dvoch množinách spánkových dát. Vzniknuté zhluky obsahujú dva typy variability – medzi zhlukmi a v rámci zhlukov. Na detekciu a analýzu oboch druhov variability sme si zvolili viacstupňovú funkcionálnu verziu metódy hlavných komponentov. Táto metóda bola pôvodne určená len pre dáta s rovnakým počtom pozorovaní v rámci zhlukov. V tejto práci uvádzame aj jej verziu rozšírenú na prípad, keď sa počet pozorovaní medzi zhlukmi líši.

Contents

Introduction

Sleep is a dynamical process which plays important role in our lives. Its structure, quality and length influences humans daily behaviour, affectivity, mood and also health.

The Probabilistic sleep model (PSM) [17] provides a continuous representation of the sleep process. The PSM operates on three–second long time segments of the EEG and EMG signal for each of which probability values of their relationship to one of sleep states – called microstates – is computed. Considering the probability values of a sleep microstate as a function of time we obtain a sleep probabilistic curve.

Current studies dealing with relationship between sleep structure and humans' physiological state or well-being measures are based on the extraction of one–dimensional sleep characteristics and their correlation with variables representing daily life behaviour. We hypothesise, that this may result into the loss of an important information about the sleep dynamics. Fortunately, character of sleep probabilistic curves offers a way for inspection of the sleep structure through functional data analysis.

This thesis provides an overview of chosen techniques of the functional data analysis which may be useful in the sleep structure analysis and its relationships with daily measures representing subjective feelings in the morning, physiological state of an organism and performance of subjects in neuropsychological tests. We focus on functional cluster analysis as a method for detecting subgroups of patients with similar sleep profiles. Methods developed for the time synchronisation of curves are considered to prevent misclassification of curves due to the curves misalignment. In the thesis we carefully analyse and compare existing approaches where i) curves alignment precede the clustering step, and ii) curves alignment and cluster analysis are performed simultaneously with our own proposed method. Moreover, we pay a careful attention to the analysis of benefits of the curves alignment for each sleep microstate separately.

A major problem in the sleep structure research is individual pattern present in each subject's sleep profile. Despite the Multilevel functional principal component analysis [6] is a technique a priori developed for as a dimensionality reduction in functional datasets with repeated measurements, it can be used also for extraction of the subject–specific profiles. We adapt the methodology for the case when the number of observations differs among objects and applied it to a dataset of healthy sleepers.

1 Goals of the dissertation thesis

1. Analysis of sleep structure provided by the Probabilistic sleep model and methods of functional data analysis in i) dataset of healthy subjects without serious sleep problems and ii) patients following an ischemic stroke.

2. Detection of relationships between sleep structure and daily measures (questionnaires about sleep and awakening quality, mood or drowsiness; neurocognitive tests for short–term memory, fine motor activity; pulse rate, blood pressure) by methods of functional cluster analysis.

3. Adaptation of existing methods or proposition of a new method for simultaneous alignment and cluster analysis of sleep probabilistic curves.

4. Analysis of advantages and disadvantages of the curves alignment for each sleep stage and each sleep microstate separately.

5. Analysis of relationships between differences in sleep structure of two nights of subjects and corresponding difference in daily measures by the Multilevel functional principal component analysis (MFPCA).

6. Adaptation of the MFPCA method to datasets with repeated observations, where i) the order of observations within subjects is exchangeable, and ii) number of observations varies with subjects.

7. Application of the modified MFPCA method to the sleep dataset with the aim to extract the subject–specific profiles and consequently to remove the individual pattern from subjects sleep probabilistic curves.

2 Sleep datasets

In this section two sleep datasets used in the thesis are described in details – the database of subjects without serious sleep problems and the database of patients after ischemic stroke.

2.1 SIESTA database

The European sleep database SIESTA [15] is a systematic polysomnographic (PSG) database with sleep recordings of 300 subjects. In the thesis we used a subset of the SIESTA database including PSG recordings of 146 subjects without serious sleep problems spending two consecutive nights in the sleep lab. The database consists of 85 men and 61 women (average age of 53 years).

The PSG measurement started right after going to bed and switching the lights off, the recording stopped after a subject awoke spontaneously. The EEG signal was measured by three pairs of electrodes (Figure 1) – frontal (Fp1–M2, Fp2–M1), central (C3–M2, C4–M1) and occipital (O1–M2, O2–M1). The reference electrodes M1 and M2 were placed on the *mastoid*. Two electrodes for monitoring the muscle activity were placed above the chin of a subject, the reference electrode was applied below the chin.

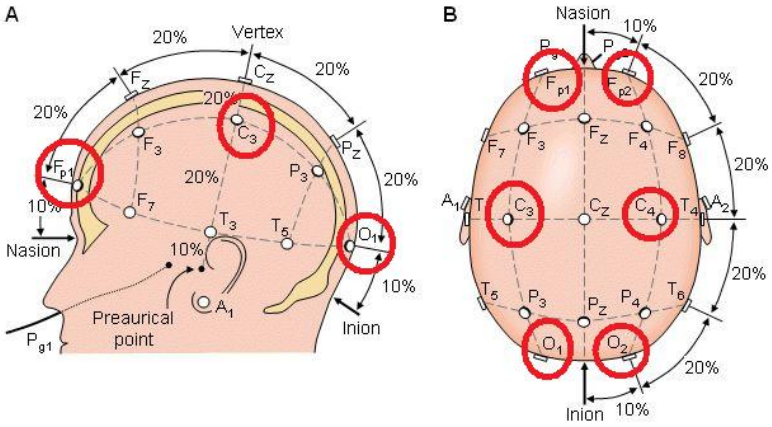


Figure 1: The scalp placement of three pairs of electrodes used for the EEG signal recording. The original image can be found in [21].

After awakening subjects filled out several questionnaires scoring their sleep and awakening quality [34], well–being [39] and the level of mood or drowsiness in the morning [1]. The subjects performed several neuropsychologic tests for the assessment of attention, attention variability, concentration, short–term memory and fine motor activity [11; 29]. Finally, the evening blood pressure and pulse values were recorded before bedtime and in the morning after sleep. The list

of all daily measures can be found in Table 1.

Daily measure
Self–rating questionnaire for sleep and awakening quality and somatic complaints [34]
Visual analogue scale test for drive, mood, affectivity and drowsiness [1]
Well–being self assessment scale [39]; morning/evening
pulse rate; morning/evening
systolic blood pressure; morning/evening
diastolic blood pressure; morning/evening
Numerical memory test [11]
Alphabetical cross–out test [11]; total score, attention variability, % of errors
Fine motor activity test [11]; right/left hand

Table 1: The list of daily measures of the healthy sleepers from the SIESTA database.

2.2 Patients following ischemic stroke

In the thesis the database of PSG recordings of 24 patients after ischemic stroke hospitalised at the 1^{st} Department of the Neurology, Comenius University in Bratislava was used. The standard overnight PSG recording took place one to 10 days after a stroke occurred.

The EEG signal of patients after stroke was measured only by two pairs of electrodes – central (C3–A2, C4–A1) and occipital (O1–A2, O2–A1). The reference electrodes A1 and A2 were placed on ear lobes. The EMG signal was measured in the same way as in the case of the SIESTA database.

The patients also took part in a battery of cognitive tests for the assessment of fine motor activity, attention (LANT [10]), reaction time and working memory [13] performed in the morning after the PSG recording. The T–MENSTAT questionnaire [25] was filled by subjects before and after performing the neurocognitive tests. The list of all daily measures can be found in Table 2.

Daily measure
Fine motor activity test - number of correctly retraced pixels in a pattern $n = 1, 2, 3, 4, 5, 6$ - number of successes in pattern n
Reaction time test - average reaction time in a trial $n = 1, 2, 3, 4$ - the minimal reaction time - the mean reaction time across trials
Working memory test [13]; forward/backward
Lateralised attention network test [10] - alerting - conflict - orienting facilitatory/ inhibitory
T–MENSTAT questionnaire [25]; performed before/after neurocognitive tests

Table 2: The list of daily measures for the patients after stroke.

3 Probabilistic sleep model

The Probabilistic sleep model (PSM) [17] characterises sleep with probability values of a finite number of sleep states called sleep microstates. Lewandowski et al. [17] empirically set the number of microstates to 20. In this thesis we focus on the modified version of PSM described in [31].

The EEG signal from all available pairs of electrodes and the EMG signal are partitioned into non–overlapping time intervals of the length of three seconds. Then, for each time window and each electrode separately, coefficients of an autoregressive model of order m are estimated with the Burg method ($m = 5$ for the EEG signal and $m = 2$ for the EMG signal) and presence of artefacts is properly detected by the Somnolyzer 24x7 [2] or BrainVision Analyser 2 [3] softwares. Finally, the autoregressive coefficients of the EEG signal from three EEG electrodes and the EMG signal are merged into one vector of the length 17 in the following order [Fpx, Cx, Ox, EMG], where x represents either left or artefacts free EEG electrode at the frontal (Fp), central (C) or the occipital (O) spatial site. In the case of patients after stroke the vector has the form [Cx, Ox] due to the absence of the EEG signal from the frontal pair of electrodes and presence of artefacts in the EMG signal.

Let a denotes the vector of autoregressive coefficients and $p(z)$ is an unknown probability, that we are in a microstate $z \in \{1, \ldots, 20\}$ in a given time window. A Gaussian mixture model is then

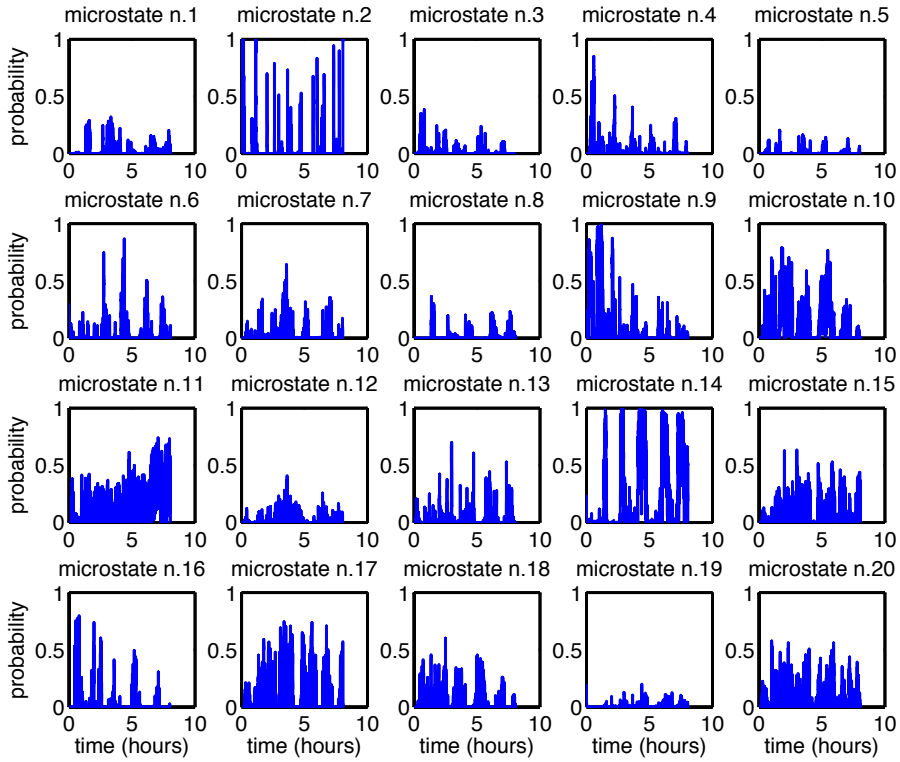


Figure 2: An example of the sleep probabilistic curves for 20 microstates of a 42–year–old healthy man.

estimated in the space of autoregressive coefficients

$$p(a) = \sum_{z=1}^{20} p(z)p(a|z) = \sum_{z=1}^{20} \pi_z \mathcal{N}\left(a|\mu_z, \Sigma_z\right). \tag{1}$$

Here, $\mathcal{N}\left(a|\mu, \Sigma\right)$ denotes the probability distribution function of a normal distribution with mean μ and covariance matrix Σ evaluated at the vector a.

Lewandovski et al. [17] estimated the unknown probabilities in (1) by the Expectation–Maximisation algorithm. Moreover, to improve physiological interpretation of sleep microstates the PSM also estimates the probability weights for each microstate to the standard sleep stages *Wake, S1, S2, slow wave sleep* (*SWS*) and *REM* [28]. For example, Microstate 2 is similar to the *Wake* stage with probability 73% and to the *S1* stage with probability 21%. The sum of probabilities of similarity to the sleep stages *S2, SWS* and *REM* is then 6%.

Considering the probability values for a given microstate z as a function of time we obtain a sleep probabilistic curve. An example of the sleep probabilistic curves for a 42–year–old healthy man is depicted in Figure 2.

4 Cluster analysis of sleep probabilistic curves

The focused objective of our thesis is to identify specific sleep profiles (sleep biomarkers) associated with selected physiological aspects of sleep. An important property of such sleep biomarkers would be their relationship with different physiological, demographic or daily life measures. This may include physiological factors as blood pressure, pulse rate or others, results of questionnaires about subjective sleep quality, mood, drowsiness or results of neurophysiological tests focused on attention, fine motor activity or short–term memory [29].

In the literature a common practise is to use one–dimensional characteristics and to compute their correlation with daily measures. However, these one–dimensional variables may miss some information about the over–night sleep dynamics. Therefore we prefer to use the whole sleep probabilistic curve information when detecting relationships between the sleep structure and daily life behaviour.

One possible approach in the sleep probabilistic curves analysis is cluster analysis – the set of all sleep probabilistic curves is divided into subgroups according to the similarity in their shape. Then the Kruskal–Wallis test can be applied with the aim to detect whether the formed clusters significantly differ in values of daily measures.

However, the cluster analysis of the sleep probabilistic curves faces problems when curves misalignment is present. We say, that two curves are similar, but misaligned in time, if they have a common overall shape, but their important features like local maxima, minima or zero crossings occur at different time points (Figure 3a). Therefore, the distance measures for curves may reach high values and consequently the clustering techniques will consider these curves as dissimilar and assign them into different clusters.

Ramsay and Silverman [27] recommend to align the curves in time before performing further analysis. In the next section we formulate the curves alignment problem in a mathematical way. A brief overview of the existing curves alignment methods is given as well.

4.1 Time alignment of curves

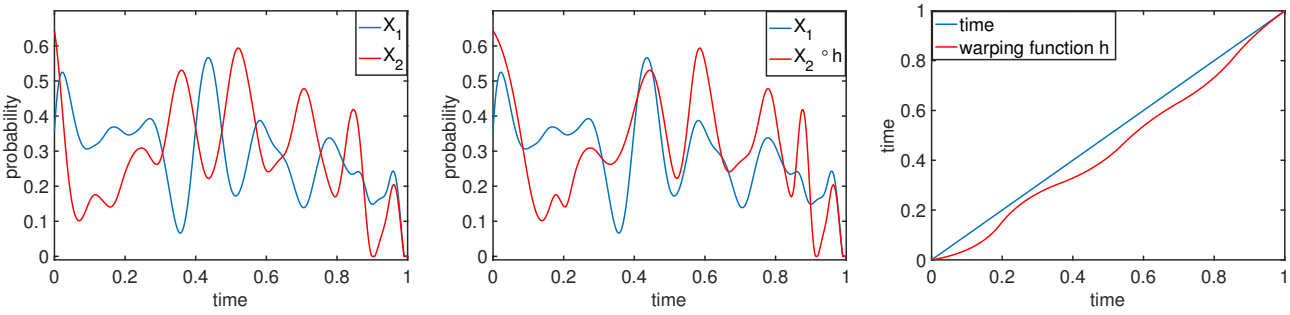
Let consider a pair of curves X_1, X_2 which are defined over a closed time interval T. Without loss of generality we assume $T = [0, 1]$. To register or temporally align a pair of curves X_1, X_2 means to find a continuous function $h^\star : T \to T$ from the set $\mathcal{H}$ of all strictly increasing transformations of the time interval T such that

$$h^\star \in \operatorname{argmin}_{h \in \mathcal{H}} S\left(X_1, X_2 \circ h\right), \tag{2}$$

under the condition of the common start and end point $h^\star(0) = 0$, $h^\star(1) = 1$. S in (2) denotes a distance between curves X_1, X_2; for example the L_n distance

$$L_n(X_1, X_2) = \left(\int_T \left(X_1(t) - X_2(t) \right)^n dt \right)^{\frac{1}{n}}. \tag{3}$$

The time transformation $h^\star$ is called the warping function. An example of two in time misaligned smoothed sleep probabilistic curves, their aligned version by using the criterion (3) and the corresponding warping function is depicted in Figure 3.



(a) original curves (b) aligned curves (c) warping function

Figure 3: An example of two smoothed sleep probabilistic curves varying in time (left), their aligned versions by using the criterion (3) with $n = 2$ (middle) and the corresponding warping function (right). The original time was transformed into the interval [0,1].

Many curves alignment methods [24; 37; 38] consider a restriction to the distance between the real time and the warping function to avoid close to ideal alignment of possibly dissimilar curves caused by the warping function running too far from the real time. For example, a penalty term

$$\lambda \int_T \left(h^{'}(t) - 1 \right)^2 dt,$$

is added into the cost function (2). More examples can be found in [36, Chapter 8].

4.2 Methods for time alignment and cluster analysis of curves

The most natural approach for solving the problem of clustering misaligned curves is to align the whole set of curves before the clustering step. The choice of the curves alignment method depends on the character of the given data. Following our practical experience with the time alignment of the sleep probabilistic curves in this thesis we focus on the Self–modelling time warping (SMTW) [9], the Pairwise curves synchronisation (PCS) [24] and the Elastic time warping (ETW) [38].

We observed, that the original algorithm of the SMTW method often results into nondecreasing instead of increasing estimated warping function when applied to the dataset of healthy sleepers. Therefore we proposed to add a penalty term to the algorithm to avoid warping functions with close to zero slope over subintervals of T.

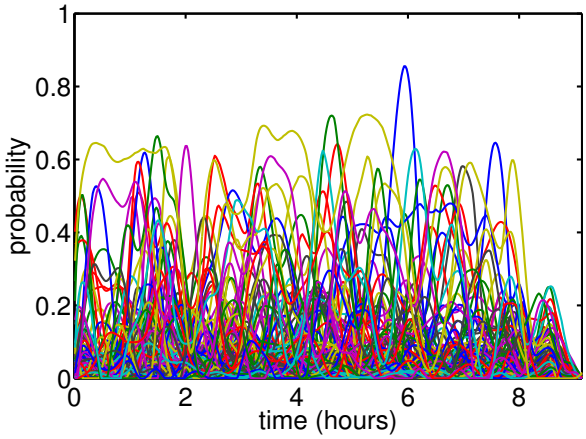
The direct alignment of the whole dataset of the sleep probabilistic curves doesn't yield to reasonable results. More specifically, because of many different sleep profiles present in our sleep curves dataset the PCS method and the both original and modified version of the SMTW algorithm were not able to align the curves properly (Figures 4b, 4c, 4d). Consequently, the results of the following cluster analysis were the same as in the case of clustering of original, in time misaligned curves. The ETW method produced close to ideal alignment of the dataset (Figure 4e), but at the cost of rapid distortions of the sleep probabilistic curves which consequently led to physiological misinterpretation of the results. A penalty to the distance between the real and the warping time in the ETW method led to visually better alignment than by PCS or SMTW, but the typical sleep profiles were difficult to detect (Figure 4f).

We hypothesised that it wold be reasonable to first divide the curves with similar shapes and features into homogeneous subgroups and then to register curves in each subgroup separately. In other words, to apply cluster analysis before the alignment process. But our initial goal was to align data before the clustering step. This is due to the fact that considering original misaligned curves may lead to improper assignment into clusters. It looks like we are facing "the chicken and the egg" problem.

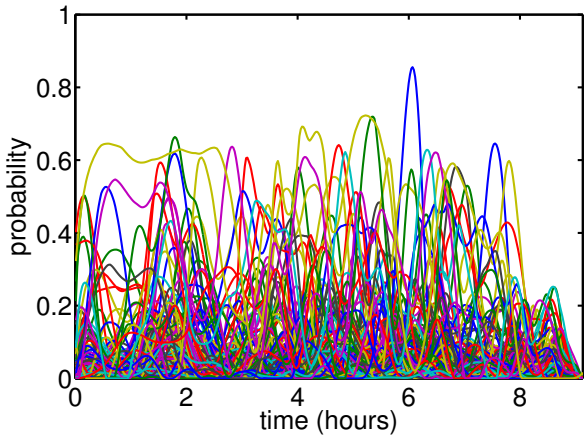
Fortunately, there are also methods which perform curves alignment and clustering simultaneously. The k–mean alignment for curve clustering (KMACC) [35] aligns each curve to a set of K template curves (cluster representatives) and assigns curves into clusters according to their similarity with the template curves. The Joint probabilistic curve clustering and alignment (JPCCA) [8] is based on a regression model with random effects with the cluster membership represented by a latent random variable. However, the both methods operate with a linear transformation of time

$$h(t) = at + b, \quad a > 0, \ b \in \mathbb{R}, \ t \in T$$

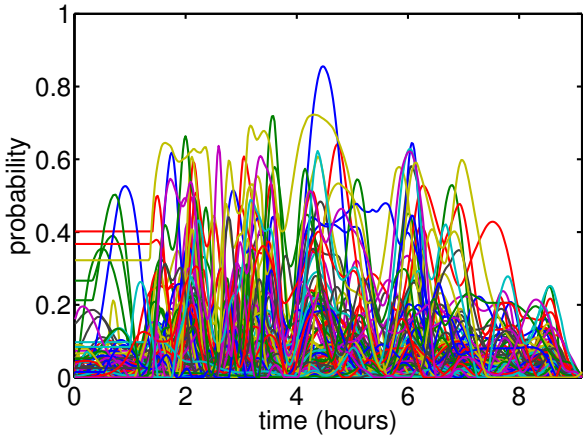
when solving the curves misalignment problem. This limits the flexibility of the methods to deal with situations where a nonlinear transformation of time is needed. In addition, we consider the same time interval for all sleep curves and therefore the only possible choices for the a and b constants are $a = 1$ and $b = 0$, effectively producing no alignment. Other values of a or b would annul the property of the common time interval.



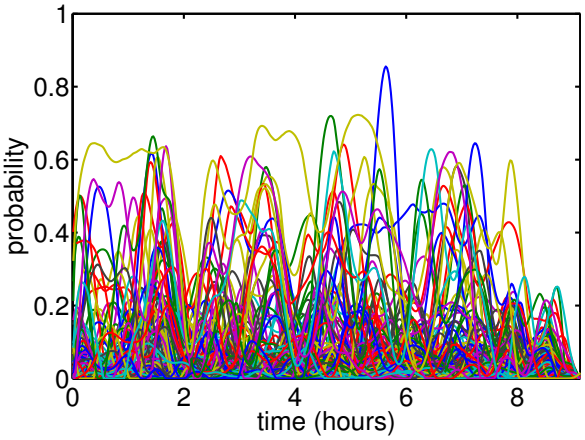
(a) Original data



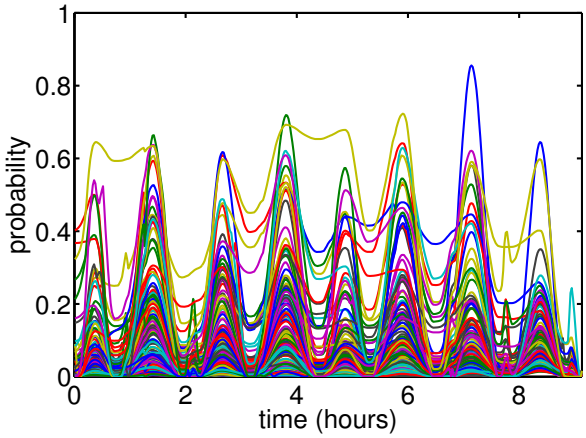
(b) Pairwise curve synchronisation (PCS)



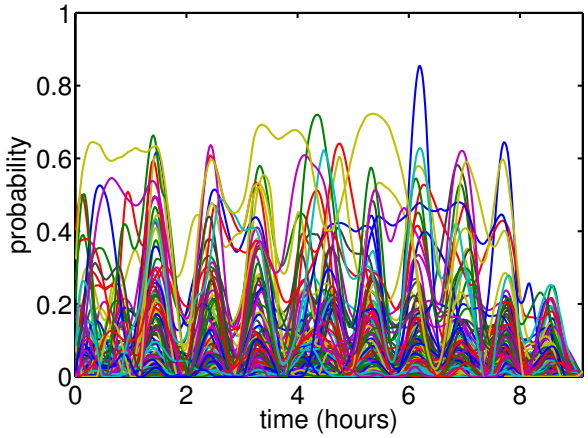
(c) Self–modelling time warping (SMTW)



(d) Modified SMTW with $\lambda = 0.1$



(e) Elastic time warping (ETW)



(f) Penalised ETW with $\lambda = 0.1$

Figure 4: Registration (time alignment) of 146 sleep probabilistic curves representing sleep Microstate 1 (85% *S2*). The curves were aligned by three different methods operating on the whole dataset. In the case of the Self–modelling time warping (SMTW) and Elastic time warping (ETW) both penalised and non–penalised versions of the algorithms were considered.

The only algorithm combining the curves alignment and clustering which seems to be appropriate for our sleep data is the truncated version of the PCS algorithm (tPCS). In contrast to PCS, where each pair of curves is aligned separately, the tPCS algorithm aligns a curve only with a set of the most similar curves. Therefore it can be viewed as an algorithm which takes into account similarity between curves within the alignment process. However, as we will show later, the results produced by tPCS were usually not satisfactory.

4.3 2–step approach

To address the problems of the existing methods for combined clustering and registration and also to introduce an algorithm with a higher flexibility of algorithmic choices in the registration step, we propose a new 2–step approach. This represents one of the important new contributions of this PhD thesis.

Let suppose that a set of N curves $X_1, \ldots, X_N$ is observed over a time interval $T = [0, 1]$ and should be divided into K clusters. First, we would like to introduce a clustering method based on the Dynamic time warping algorithm (DTW) [40].

The DTW algorithm is a method which was a priori developed and used for aligning curves with different lengths [26]. Let suppose that two curves $X_i, X_j,\ i \neq j$ are observed at a finite number of time-points

$$x_i = \{X_i(t_1), \ldots, X_i(t_{n_i}), 0 = t_1 < \cdots < t_{n_i} = 1\},$$
$$x_j = \{X_j(s_1), \ldots, X_j(s_{n_j}), 0 = s_1 < \cdots < s_{n_j} = 1\}.$$

It is not required that the sets of time-points $\{t_l\}_{l=1}^{n_i} \subset T$ and $\{s_k\}_{k=1}^{n_j} \subset T$ are equal.

Similarly to [23] we used the DTW algorithm for constructing a "distance" measure between a pair of curves

$$dtw(X_i, X_j) = \min_{w} \sum_{(k_m, l_m) \in w} |X_i(t_{k_m}) - X_j(s_{l_m})|, \tag{4}$$

where $w = \{(k_m, l_m), k_m \in \{1, \ldots, n_i\}, l_m \in \{1, \ldots, n_j\}, m = 1, \ldots, W_L\}$ is *warping path* and W_L is the length of w. We use the term "distance" despite the formula (4) does not show the symmetry property and therefore it is not a real distance. The minimisation is taken under similar constraints as in the case of the *warping function*, namely the condition of a common start and end point, monotonicity, continuity and restriction to the distance between the real time and warping path w. This optimisation problem can be solved by using the dynamic programming [40].

Then we can construct the DTW based distance matrix $M_{dtw} \in \mathbb{R}^{N \times N}$

$$(M_{dtw})_{ij} = dtw(X_i, X_j), \quad i, j = 1, \ldots, N.$$

The general idea of the 2–step approach is based on a direct combination of the clustering and registration steps into an iterative process, more specifically

i) In the first step, an initial clustering is done. Because at this first step the curves are misaligned, the standard k–means [19] or k–medoids algorithms [14] does not lead to reasonable results. Therefore, in this initial clustering step, we propose to apply the DTW method with the aim to obtain the distance matrix M_{dtw} and then to apply the k–medoids clustering algorithm operating on M_{dtw}.

ii) In the second step, we align curves separately in each cluster. In practise, one of the above mentioned three algorithms (SMTW, PCS or ETW) or their penalised versions can be used. The quality of alignment and clustering is measured by the L–criterion

$$L = \frac{1}{N} \sum_{i=1}^{K} \sum_{j:X_j^\star \in C_i} \int_T \left(X_j^\star(t) - \mu_i(t)\right)^2 dt, \tag{5}$$

$$\mu_i(t) = \frac{1}{|C_i|} \sum_{j:X_j^\star \in C_i} X_j^\star(t), \quad i = 1, \ldots, K,$$

where C_i represents the i^{th} cluster $i = 1, \ldots, K$, μ_i is its centroid and $|C_i|$ represents its cardinality. The aligned curves $X_j \circ h_j^\star, j = 1 \ldots, N$ are denoted by $X_j^\star, j = 1, \ldots, N$.

iii) The third step consists of re–clustering of the aligned curves using the same clustering approach as in the step i).

Steps ii) and iii) are the core steps of the 2–step approach for iterative clustering and alignment and are repeated until one of the following stopping criteria is met

- the number of iterations exceeds a given threshold (in this thesis set to 100),
- the L–criterion is lower than a given small constant,
- clusters in the $i^{th}, (i-1)^{th}$ and $(i-2)^{th}$ steps are not changed.

The chosen stopping criteria mimic those used in the standard clustering techniques, for example [19; 14]. Finally, the cluster membership and registered curves belonging to the iteration step with the smallest L–criterion are used as the final result.

From a mathematical point of view the 2–step approach represents an heuristic and not a fully rigorous mathematical method. However, our long–term analysis of the sleep data showed, that the sleep probabilistic curves are too difficult data for many existing methods with a more complex mathematical background. These existing methods were outperformed by the proposed approach.

4.4 Application to the sleep datasets

We applied the proposed 2–step approach to the set of sleep probabilistic curves of healthy sleepers (second night only) and patients after ischemic stroke and compared its performance with the tPCS method. Regarding to the 2–step approach we considered its version with the modified SMTW method (2DTW–SMTW), PCS (2DTW–PCS) and penalised version of the ETW algorithm (2DTW–ETW) used in the registration step. The k–means clustering of the raw sleep curves is also considered in this thesis and serves as a reference allowing us to compare the obtained results with the clustering operating on in time misaligned curves.

The quality of clustering and alignment was evaluated visually, by the L–criterion (5) and average *silhouette* (AS) [30]. *Silhouette* (*sil*) represents tightness and separation of each cluster. It reaches values from the interval $[-1, 1]$ and shows whether a curve is well–clustered ($sil \approx 1$), lies in between clusters ($sil \approx 0$) or is assigned into incorrect cluster ($sil \approx -1$).

Moreover, we aimed to find answer to the question for which sleep microstates the curves alignment is beneficiary when detecting relationships with daily measures and for which it is on contrary counter–productive.

4.4.1 Cluster analysis of sleep structure of healthy sleepers

Table 3 shows the L–criterion (5) and the AS values for five chosen sleep microstates clustered by the k–means algorithm, the tPCS method followed by the k–means algorithm and three versions of the 2–step approach. The highest AS and the lowest L–criterion values were observed in all microstates for the 2DTW–SMTW or the 2DTW–ETW algorithm. These results were confirmed also by the visual inspection of the formed clusters (Figures 5 and 6). From this point of view, the 2–step approach was able to form more compact and well–separated clusters in comparison to tPCS or the k–means clustering of original, misaligned curves.

Moreover, we were also interested, whether the 2–step approach helps to improve detection of relationships between sleep structure and daily measures.

- The relationship between the structure of Microstate 16 (96% *SWS*) and age or the physiological factor (representing morning and evening systolic and diastolic blood pressure) was visible for both in time misaligned and aligned curves and for an arbitrary number of clusters varying between 2 and 20. The clusters with increased probability for the microstate included mainly younger people with lower values of the physiological factor. On the other hand, the significant difference in the level of drowsiness between clusters was observed only when considering the 2DTW–PCS or 2DTW–ETW approach. In this case, increased probability for the sleep microstate was connected with increased drowsiness.

Average silhouette	number of clusters	k–means	tPCS	2DTW– –SMTW	2DTW– –PCS	2DTW– –ETW
Microstate 16	8	0.56	0.57	0.64	0.61	0.47
Microstate 8	9	0.33	0.34	0.48	0.44	0.46
Microstate 14	3	0.53	0.54	0.60	0.10	0.60
Microstate 1	2	0.77	0.79	0.79	0.64	0.80
Microstate 6	3	0.62	0.63	0.73	0.71	0.53
L-criterion	number of clusters	k–means	tPCS	2DTW– –SMTW	2DTW– –PCS	2DTW– –ETW
Microstate 16	8	0.40	0.39	0.26	0.33	0.19
Microstate 8	9	0.79	0.77	0.54	0.59	0.34
Microstate 14	3	4.55	4.51	2.71	5.01	1.77
Microstate 1	2	4.07	4.05	3.37	4.34	2.84
Microstate 6	3	1.02	1.01	0.78	0.85	0.73

Table 3: The average *silhouette* and the L–criterion eq. (5) values for methods used to validate the alignment and clustering performance on 146 probabilistic sleep curves of several microstates. The optimal number of clusters for each microstate is depicted in the second column.

- After the k–means clustering of sleep probabilistic curves for sleep Microstates 8 (73% *REM*) and 14 (72% *REM*) we detected relationship between increased probability for each of the microstates and increased diastolic blood pressure. After the curves alignment (2DTW–SMTW), we also observed that subjects with higher probability values for one of the microstates felt in the morning less drowsy and they subjectively scored their level of mood, drive or affectivity better. Moreover, they also showed fewer somatic complaints.

- The clusters of the sleep probabilistic curves for Microstate 1 (85%$S2$) significantly differed in the attention variability scored by the Alphabetical cross–out test [11], whether we considered misaligned curves or the tPCS method. After applying the 2DTW–SMTW algorithm, this difference remained significant but we detected also significant difference in the percentage of errors of the test between formed clusters. Higher variability in attention and increased percentage of errors was related with increased probability for Microstate 1.

  The Kruskal–Wallis test detected significant difference in the morning level of affectivity among clusters of misaligned curves. The 2DTW–SMTW approach formed clusters which

significantly differed also in the level of mood. We observed that increased probability for Microstate 1 results into impairment of mood and affectivity in the morning.

- Increased probability of sleep microstates related to wakefulness was observed to be typical for elderly people (above 60 years of age) whether we considered misaligned or in time aligned sleep probabilistic curves. Expected relationship between increased wakefulness and worst subjectively scored sleep quality or level of mood and drive was visible for the microstates only after the curves alignment.

- Microstate 6 (85% *Wake*) forms a special part of the sleep structure. In this case the relationship between increased wakefulness and worst subjective feelings after awakening diminished after the curves alignment. Therefore we hypothesise that in this case the exact occurrence of periods of increased wakefulness is important when detecting relationships with daily measures. The same phenomenon was observed also in the case of the *Wake* stage.

- When considering the sleep probabilistic curves for the standard sleep stages *Wake, S1, S2* and *SWS*, the relationship with age was observed for both misaligned and aligned curves. However, decreased number of periods of the *REM* stage with increased age was visible only in the case of the 2DTW–SMTW approach.

4.4.2 Patients after ischemic stroke

In the second step we applied the 2–step approach to the dataset of patients after stroke. Because of a smaller number of subjects (24) we considered two to four clusters.

- We observed that increased probability of sleep microstates similar to light sleep helped to improve performance in the Fine motor activity test. Similar result was observed when considering the curves representing the *S1* stage. On the other hand, increased probability for the microstate representing the "border" between stages *S1* and *S2*, led to the opposite results.

- Considering light sleep we also observed that subjects with higher probability values performed better in the LANT test [10], namely in the alerting component (LANT_A). When considering the standard sleep stages the only relationship with the LANT_A component was observed for the *S2* stage.

- Increased probability for microstates laying at the border between the *S2* and *SWS* stages led to the improvement in reaction times while the structure of microstates related only to *SWS* influenced the reaction speed in a negative way.

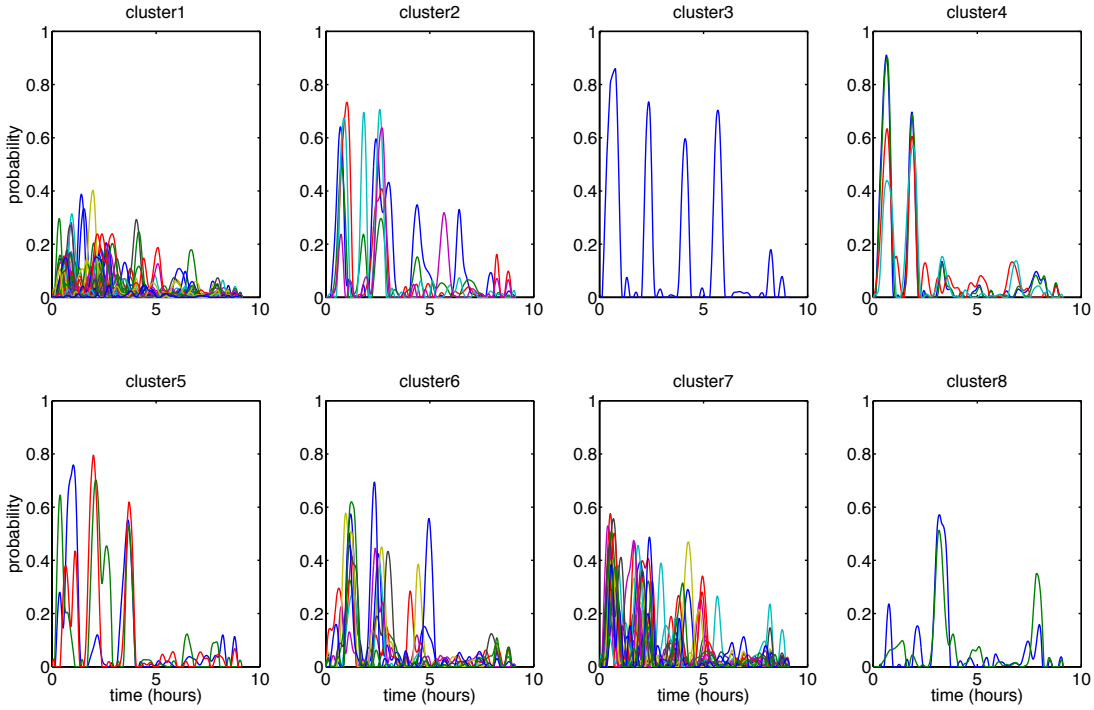
- The subjects with increased *SWS* during the whole night felt subjectively less drowsy, exhausted or irritated after performing the whole battery of neurocognitive tests. Moreover, they were able to remember in average more digits in the backward order in the Working memory test [13].

- Finally we observed that higher probability values for Microstate 19 (86% *SWS*) are typical for subjects following more severe stroke according to the National Institutes of Health Stroke Scale [4].

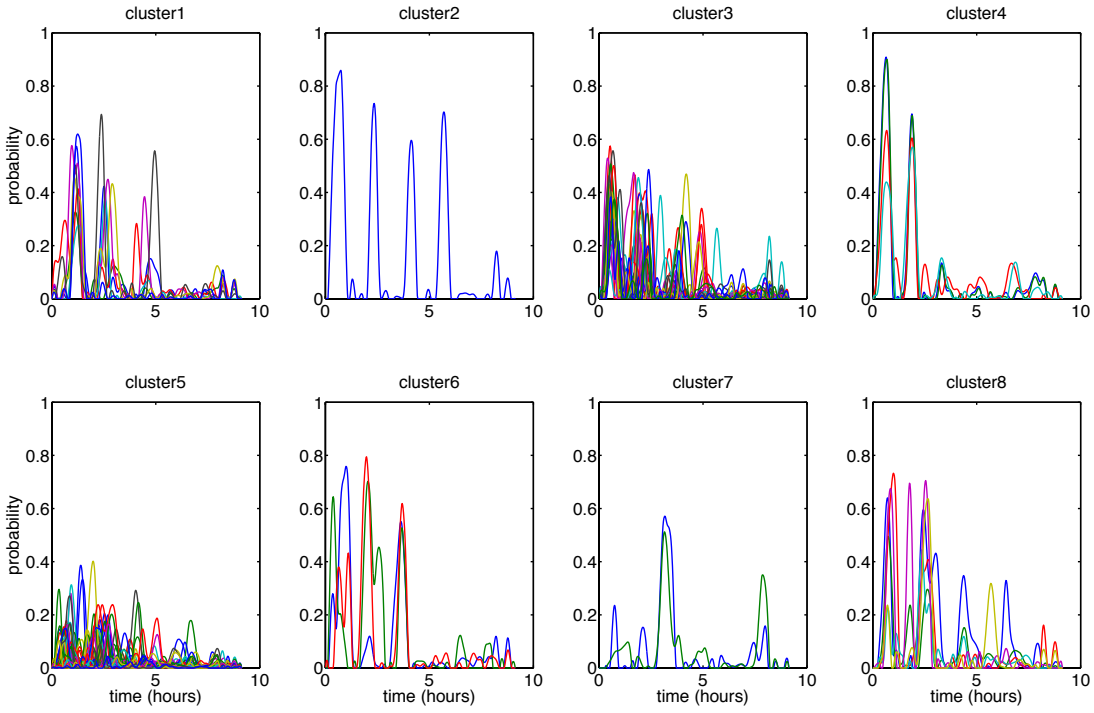
However, the benefit of the 2–step approach in comparison to the k–means clustering of in time misaligned curves was not so evident. This may be due to a small number of subjects and clusters. Considering the *S2* or *SWS* sleep stages and with them associated sleep microstates, the k–means clustering of misaligned curves produced the same results as the 2DTW–SMTW approach.

In the case of the *S1* stage we observed that similarly as in the case of the *Wake* stage or Microstate 6 of healthy sleepers, the time alignment seems to be counter–productive. In other words, the exact occurrence of the periods of light sleep is important when detecting relationships with the studied daily features. However, we observed the opposite phenomenon in the case of sleep microstates related to light sleep, where the time alignment helped to detect otherwise hidden relationships. On the other hand these analysed microstates also show not negligible weights for the *S2* stage.

Overall, we need to stress that due to a small number of patients these observations and conclusions can be viewed only as preliminary.

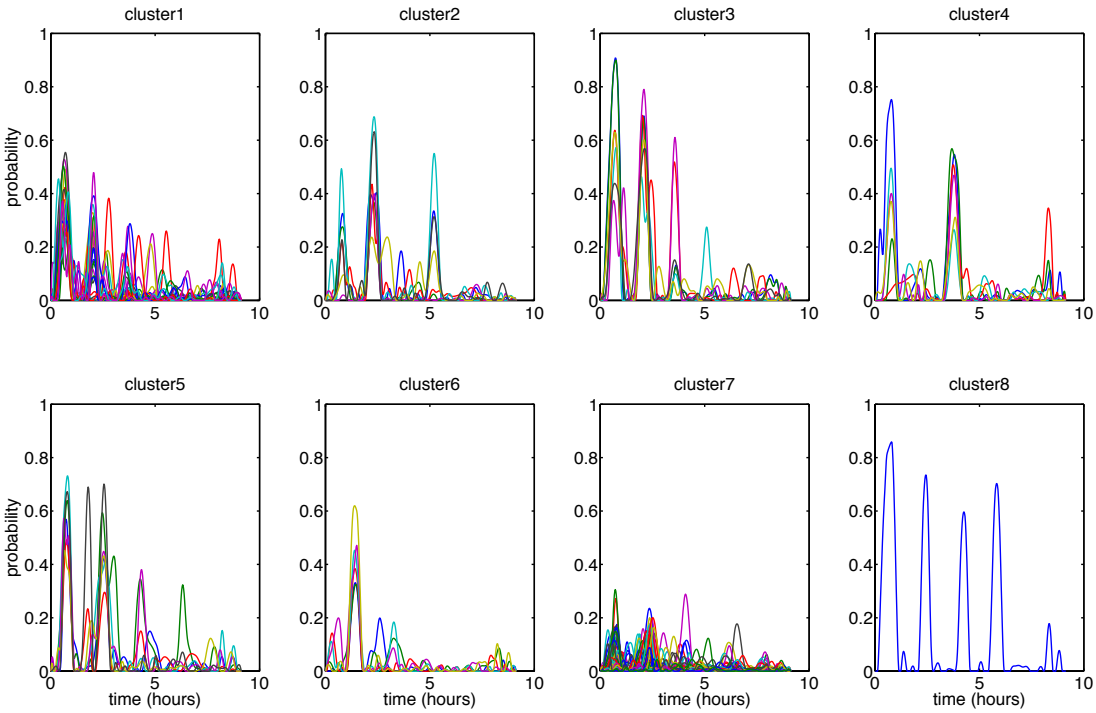


(a) The k–means clustering of misaligned sleep probabilistic curves

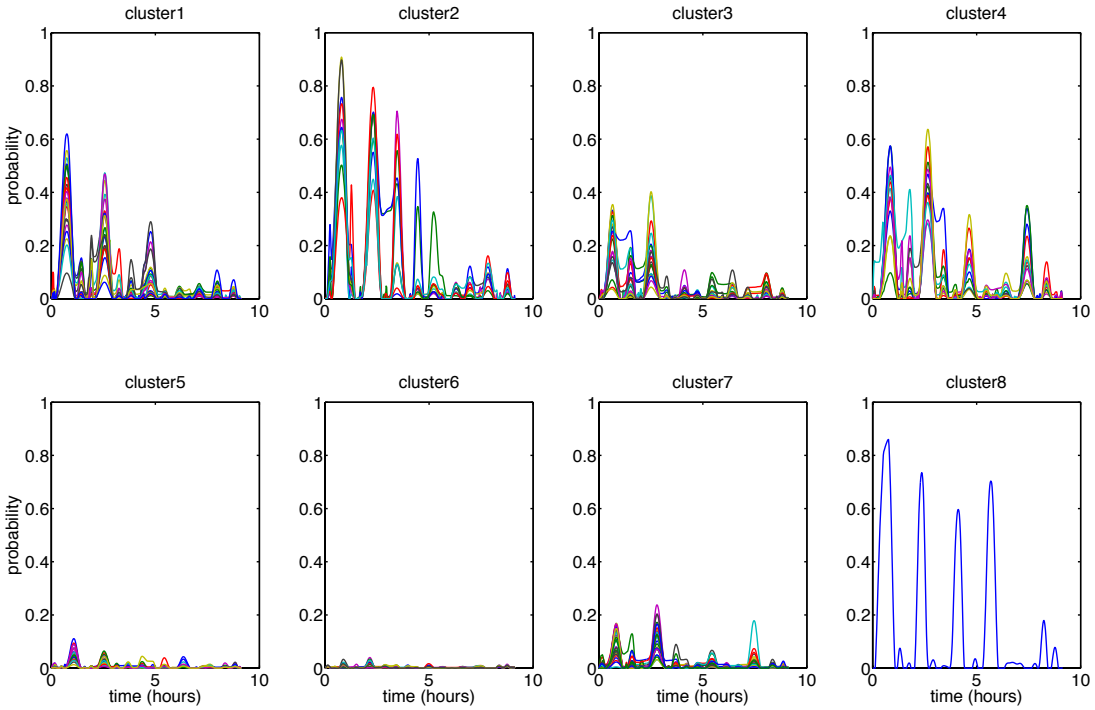


(b) tPCS followed by the k–means clustering

Figure 5: Microstate 16. Clustering of 146 probabilistic sleep curves into 8 clusters by using a) the k–means algorithm applied to misaligned curves and b) the truncated version of the Pairwise curve synchronisation algorithm (tPCS) followed by the k–means clustering.



(a) The 2–step approach with the modified SMTW algorithm (2DTW–SMTW)



(b) The 2–step approach with the ETW algorithm (2DTW–ETW)

Figure 6: Microstate 16. Clustering of 146 probabilistic sleep curves into 8 clusters by using the 2–step approach with the modified SMTW or ETW algorithm used in the registration step and k–medoids in the clustering step (2DTW–SMTW, 2DTW–ETW).

5 Multilevel functional principal component analysis

Multilevel functional principal component analysis (MFPCA) [6] is a dimensionality reduction technique developed for functional data (curves) with repeated observations for subjects. This method distinguishes two types of variability – the variability between and within subjects.

Let X_{ij} denotes the $j^{th}, j = 1, \dots, J$ observation for the $i^{th}, i = 1, \dots, I$ subject defined over the time interval $T = [0, 1]$. Di et al. [6] assume that each X_{ij} can be decomposed in the following way

$$X_{ij}(t) = \mu(t) + \eta_j(t) + Z_i(t) + W_{ij}(t), \;\; i = 1, \dots, I, \;\; j = 1, \dots, J. \tag{6}$$

Here, μ is the overall mean function and $\eta_j, j = 1, \dots, J$ is the observation–specific deviation from the overall mean satisfying $\sum_{j=1}^{J} \eta_j(t) = 0, \;\forall\; t \in T$ for identifiability. These functions are considered as fixed effects and their estimators by the method of moments can be found in [6].

Random effects $Z_i, i = 1, \dots I$ represent the subject–specific deviation from the observation–specific mean and W_{ij} is the residual deviation from the subject– and observation–specific profile. Z_i and W_{ij} are considered to be zero–mean stochastic processes defined over a common probability space $(\Omega, \mathcal{S}, \mathcal{P})$ with adequately smooth covariance functions $R_Z : T \times T \to \mathbb{R}$ and $R_W : T \times T \to \mathbb{R}$. Moreover, Z_i and W_{ij} are uncorrelated for each $i = 1, \dots, I$ and $j = 1, \dots, J$.

Using the Karhunen–Loewe expansion [12; 20] the random effects can be expressed as

$$Z_i(t) = \sum_{k=1}^{\infty} \alpha_{ik} \phi_k^{(1)}(t) \quad \text{and} \quad W_{ij}(t) = \sum_{k=1}^{\infty} \beta_{ijk} \phi_k^{(2)}(t), \qquad i = 1, \dots, I; \;\; j = 1, \dots, J.$$

Here, $\{\phi_k^{(1)}\}_{k=1}^{\infty}$ and $\{\phi_k^{(2)}\}_{k=1}^{\infty}$ are the eigenfunctions of R_Z and R_W respectively and they are called the level 1 and level 2 eigenfunctions or functional principal components. Coefficients $\{\alpha_{ik}\}_{k=1}^{\infty}$ and $\{\beta_{ijk}\}_{k=1}^{\infty}$ are random variables with zero mean and

$$\mathrm{E}(\alpha_{ik}\alpha_{il}) = \begin{cases} 0, & \text{if } k \neq l, \\ \lambda_k^{(1)}, & \text{if } k = l. \end{cases} \qquad \mathrm{E}(\beta_{ijk}\beta_{ijl}) = \begin{cases} 0, & \text{if } k \neq l, \\ \lambda_k^{(2)}, & \text{if } k = l. \end{cases}$$

We call them the level 1 and level 2 principal component scores. Moreover, $\{\alpha_{ik}, k = 1, 2, \dots\}$ are assumed to be uncorrelated with $\{\beta_{ijl}, l = 1, 2, \dots\}$ to mirror uncorrelation between Z_i and W_{ij}.

The functional principal components on both levels are estimated as eigenfunctions of the

covariance function estimators $\widehat{R}_Z$ and $\widehat{R}_W$

$$\widehat{R}_T(s,t) = \frac{1}{IJ}\sum_{i=1}^{I}\sum_{j=1}^{J}\left(X_{ij}(s) - \widehat{\mu}(s) - \widehat{\eta}_j(s)\right)\left(X_{ij}(t) - \widehat{\mu}(t) - \widehat{\eta}_j(t)\right), \tag{7}$$

$$\widehat{R}_Z(s,t) = \frac{1}{IJ(J-1)}\sum_{i=1}^{I}\sum_{j=1}^{J}\sum_{l\neq j}^{J}\left(X_{ij}(s) - \widehat{\mu}(s) - \widehat{\eta}_j(s)\right)\left(X_{il}(t) - \widehat{\mu}(t) - \widehat{\eta}_l(t)\right), \tag{8}$$

$$\widehat{R}_W(s,t) = \widehat{R}_T(s,t) - \widehat{R}_Z(s,t). \tag{9}$$

The proposed estimators are asymptotically unbiased estimators of the covariance functions R_Z and R_W for $I \to \infty$.

The method for choosing the optimal numbers P_1, P_2 of functional principal components on the both levels and estimation of principal component scores is in details described in [6] and therefore is omitted in the thesis.

5.1 Application to the sleep dataset

In this section we applied the MFPCA algorithm to sleep probabilistic curves representing two nights of 146 subjects from the SIESTA database [15] in order to detect the effect of night on the sleep profiles. The second goal was to analyse influence of changes in sleep profiles of subjects between two nights on changes in daily measures.

First, the night–specific profiles $\delta_j(t) = \mu(t) + \eta_j(t), j = 1, 2$ were estimated for each sleep microstate or standard sleep stage separately. We observed only negligible difference between the first and second night–specific profiles within the majority of the sleep microstates. Considering Microstates 13 (45% *Wake*, 41% *S1*) and 19 (88% *Wake*), for the first night a slightly higher probability was typical. On the contrary, higher probability values of Microstate 14 (72% *REM*) were typical for the second night.

More visible differences between the night–specific profiles were detected for the sleep stages. When a subject sleeps for the first time in a new environment, his or her sleep is lighter and problems with falling asleep occur ("the first–night effect"). The probability values for the *Wake* stage are higher for the first night in comparison to the second night. On the contrary, for the second night the sleep probabilistic curves of stages *S2, SWS* and *REM* lie higher (Figure 7).

In the second step we computed the coefficient of multiple correlation between difference in a daily measure and a vector of differences in the level 2 principal component scores representing changes in the pattern of a given sleep microstate between two nights. The coefficient of multiple correlations characterises how a single variable can be predicted by a linear combination of other variables [16].

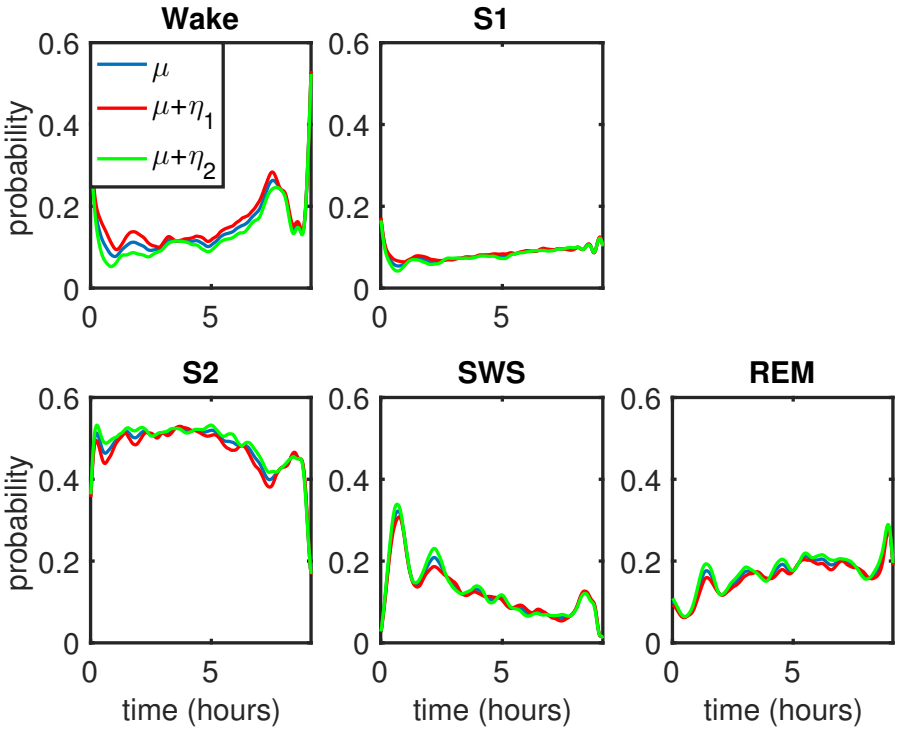


Figure 7: Night profiles of sleep stages mimicking the standard R&K staging and estimated by the MFPCA method. Before applying the MFPCA method the curves were aligned with the modified Self–modelling time warping method [9] for each subject separately. The overall mean function μ for each microstate is depicted in blue, red curve represents the first night effect $\mu + \eta_1$ and green curve represents the second night effect $\mu + \eta_2$.

However, the highest obtained correlations between changes in sleep structure and subjective feelings in the morning (the level of mood, drive, affectivity or drowsiness in the morning, sleep quality or somatic complaints) were at most 0.26. This indicates only moderate prediction power of changes in daily measure by changes in sleep structure. This resembles our preliminary studies [32; 29], where we also observed that the prediction of daily measure values with the one–dimensional characteristics of the sleep structure is a difficult task.

First reason, why we are not able to successfully predict the results of a daily measure by the characteristics of the sleep structure, is the lack of a deeper information and monitoring of the other subject's daily activities or feelings, which can affect the sleep pattern, but have only a slight influence on the monitored outcomes of the questionnaires or neuropsychological tests.

Second reason can be a presence of a high inter–subject variability or in the other words subject–based differences in sleep structure [18; 5], which is not adequately taken into account. For

example, existing sleep structure variation among two or more healthy sleepers may not strongly influence some of the daily measure results. On contrary, it is a strong variation of the subject's sleep pattern from his typical sleep profile which can be manifested by a strong change in his daily measure outcomes.

We hypothesise that an improvement in correlations between sleep structure and daily measures can be obtained by modelling a subject's specific profile present in its sleep probabilistic curves. The MFPCA method is a candidate for the subject specific profiles extraction. However, a longer, several nights sleep monitoring would be probably needed to better capture this subject specific sleep pattern variability.

Large datasets with multiple observations per subject would reflect a common feature – a few observations for several subjects may be missing either due to the presence of noise or simply due to the absence of a visit of the subject. We speak about datasets where the number of observations varies between subjects (unbalanced design) or the order of observations within subjects is exchangeable (unordered visits). Therefore, we need to ask if it is possible to apply the same MFPCA algorithm also in these cases?

The answer, in general, is no. We observed, that when the assumptions of the balanced design and ordered visits in MFPCA are violated, the covariance function estimators (8) and (9) proposed in [6] are biased and therefore the estimated eigenfunctions are bad representatives for the level 1 and 2 functional principal components.

5.2 MFPCA: case of balanced design and unordered visits

In the case of balanced design and exchangeable order of observations within subjects we observed, that unbiased covariance function estimators can be obtained by the method of moments and interchanging the order of estimators; in other words

$$\widehat{R}_{T_2}(s,t) = \frac{1}{IJ}\sum_{i=1}^{I}\sum_{j=1}^{J}\left(X_{ij}(s)-\widehat{\mu}(s)\right)\left(X_{ij}(t)-\widehat{\mu}(t)\right),$$

$$\widehat{R}_{W_2}(s,t) = \frac{1}{2}\frac{1}{IJ(J-1)}\sum_{i=1}^{I}\sum_{j=1}^{J}\sum_{l\neq j}^{J}\left(X_{ij}(s)-X_{il}(s)\right)\left(X_{ij}(t)-X_{il}(t)\right),$$

$$\widehat{R}_{Z_2}(s,t) = \frac{I}{I-1}\left(\widehat{R}_T(s,t)-\frac{IJ-1}{IJ}\widehat{R}_{W_2}(s,t)\right).$$

5.3 MFPCA: case of unbalanced design and unordered visits

More general case occurs when the design is unbalanced and the observations within subjects are unordered. Let consider I subjects with $J_i \geq 1,\ i = 1, \ldots, I$ visits. In this case we estimated the overall mean function μ as an unweighted mean $\widehat{\mu}_{uw}(t) = \frac{1}{I}\sum_{i=1}^{I}\frac{1}{J_i}\sum_{j=1}^{J_i} X_{ij}(t) = \frac{1}{I}\sum_{i=1}^{I}\overline{X}_{i\cdot}(t)$, because in contrast to the overall mean it puts equal weights to all subjects regardless of their sample sizes.

In the second step we constructed the estimator $\widehat{R}_W$ so as it minimises

$$\mathrm{E}\left(\|\widehat{R}_W - R_W\|^2\right) = \mathrm{E}\left(\int_T\int_T \left(\widehat{R}_W(s,t) - R_W(s,t)\right)^2 ds\, dt\right)$$

and has the form

$$\widehat{R}_W = \frac{1}{2}\sum_{i=1}^{I}\sum_{j=1}^{J_i}\sum_{l\neq j}^{J_i} w_i \left(X_{ij}(s) - X_{il}(s)\right)\left(X_{ij}(t) - X_{il}(t)\right), \qquad w_i \geq 0,\ \ i = 1, \ldots, I$$

where $\sum_{i=1}^{I} w_i J_i(J_i - 1) = 1$ guarantees the unbiasedness of the estimator.

Under the additional assumption, that W_{ij} is Gaussian process for all $i = 1, \ldots, I; j = 1, \ldots, J_i$ it can be proved that

$$\widehat{R}_{W_{opt}} = \frac{1}{2}\sum_{i=1}^{I}\sum_{j=1}^{J_i}\sum_{l\neq j}^{J_i} \frac{1}{(N_1 - I)J_i}\left(X_{ij}(s) - X_{il}(s)\right)\left(X_{ij}(t) - X_{il}(t)\right), \qquad N_1 = \sum_{i=1}^{I} J_i, \tag{10}$$

fulfils all above mentioned conditions. Then

$$\begin{aligned}
\widehat{R}_T(s,t) &= \frac{1}{N_1}\sum_{i=1}^{I}\sum_{j=1}^{J_i}\left(X_{ij}(s) - \widehat{\mu}_{uw}(s)\right)\left(X_{ij}(t) - \widehat{\mu}_{uw}(t)\right), \\
\widehat{R}_B(s,t) &= \frac{I}{I-1}\left(\widehat{R}_T(s,t) - \left(1 - \frac{2}{N_1} + \frac{1}{I^2}\sum_{i=1}^{I}\frac{1}{J_i} - \frac{L}{N_1}\frac{I-2}{I}\right)\widehat{R}_{W_{opt}}(s,t)\right)
\end{aligned} \tag{11}$$

is unbiased estimator for R_B. In (11) L denotes the number of subjects with only one observation.

5.3.1 Application to the sleep dataset

In the thesis we aimed to demonstrated extraction of the subject–specific profiles by the modified MFPCA algorithm. However, we don't posses an appropriate sleep database where the number of subjects' visits would be greater than two.

The functionality of our modified MFPCA for unbalanced data can be demonstrated on the results of the cluster analysis produced by the 2–step approach. Now, each cluster represents a "subject" and curves assigned into a cluster represent repeated observation for the "subject".

The sleep probabilistic curves for Microstates 16 (96% *SWS*) clustered by the 2DTW–SMTW approach and corresponding cluster–specific profiles estimated by the modified MFPCA method with the covariance function estimators (11) and (10) are depicted in Figure 8. We would like to highlight, that the outlier profile of Microstate 16 (cluster 8 in Figure 8) was estimated by the MFPCA method only with a negligible error.

The cluster–specific profiles estimated by the modified MFPCA method provide an alternative way for extracting cluster representatives. In comparison to the point–wise mean estimates, they can by expressed in both, the functional $\widehat{Z}_i(t) = \widehat{\mu}(t) + \sum_{k=1}^{P_1} \widehat{\alpha}_{ik}\widehat{\phi}_k^{(1)}(t)$ and vector $\widehat{\alpha}_i = (\widehat{\alpha}_{i1}, \ldots, \widehat{\alpha}_{iP_1})^T$ forms. However, the curves in a cluster are not represented with a common one–dimensional characteristics, therefore in the light of the previously used sleep to daily measures relationship investigation, we are not able to fully validate the benefit of the cluster–specific profiles extracted by the MFPCA method in comparison to the point–wise mean.

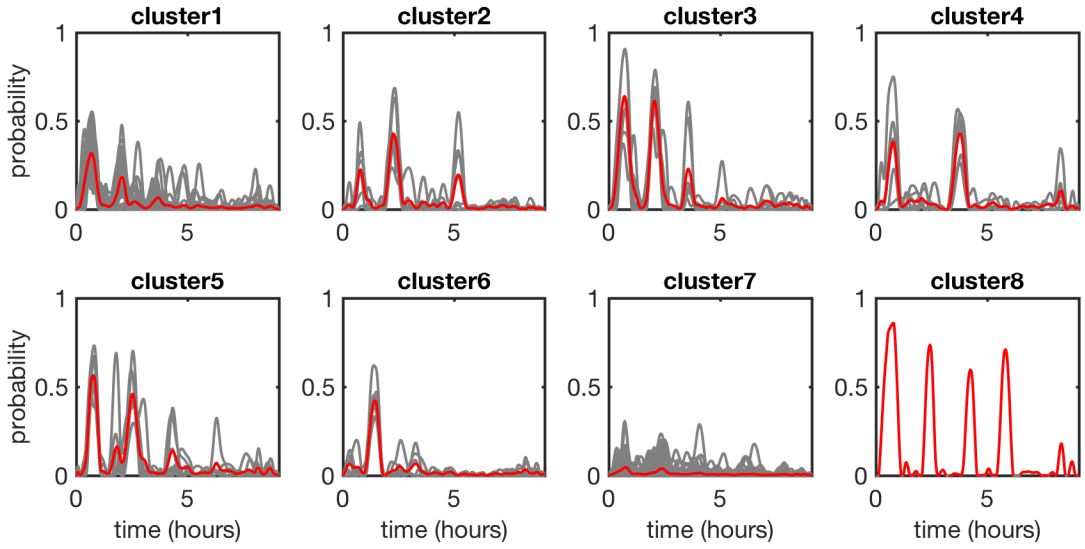


Figure 8: Microstate 16. Cluster analysis of 146 sleep probabilistic curves (grey) assigned into 8 clusters by the 2–step approach with the modified SMTW algorithm in the registration step and k–medoids in the clustering step (2DTW–SMTW). The cluster–specific profiles were estimated by the modified MFPCA algorithm (red curves).

6 Conclusion and Contributions of the thesis

Sleep as a dynamical process enters a finite number of states during night. Understanding its structure and impact on our daily life behaviour is important not only for medical practice. In this thesis we offered an alternative view on sleep structure analysis by using the methods of functional data analysis and probabilistic sleep modelling [17]. We would like to highlight that the analysis of the sleep structure in the functional data sense is a new approach in the area of sleep research and we are not aware of any other scientific teams which would consider this approach.

One of the major objectives of the thesis was to identify specific sleep profiles (sleep biomarkers) which significantly correlate with different physiological, demographic or daily life measures. Our previous studies [29; 31] showed several promising results. However, the first study did not take into account the whole dynamic of the sleep process or in [31] we did not consider the problem of misalignment of the sleep probabilistic curves. Therefore we hypothesised, that important relationships between the sleep structure and daily measures remained hidden.

In this thesis, for a given sleep microstate, we focused on finding subgroups or clusters of subjects with similar sleep probabilistic curve profiles and we tested whether there is a significant difference between results of daily measures among formed clusters. In contrast to [31] we also analysed the impact of the curves misalignment problem on results and we considered several methods to solve it.

The second approach is based on the Multilevel functional principal component analysis [6] and relationship between changes in the sleep structure and changes in daily measures between two nights of a subject.

The main results and contributions of the thesis are

- We proposed our own approach for iterative combination of the curves alignment and clustering which outperforms i) approaches where the curves alignment applied to the whole dataset precede the clustering step, and ii) approaches for simultaneous curves alignment and clustering. The benefit of our 2–step approach is also a higher flexibility of algorithmic choices in the registration step.

- The algorithm of the Self–modelling time warping method [9] does not guarantee, that the estimated warping function is strictly increasing which is in conflict with the basic assumption of the curves alignment. Therefore we considered a penalty term in the method which avoids an estimate of a non–decreasing warping function and also restricts the distance between real time and warping function.

- We showed, that the curves alignment plays important role in the analysis of the sleep structure. This is especially true for the *S2, SWS, REM* sleep stages and related sleep microstates. On the other hand, in the case of the *Wake* stage and several related sleep microstates, the exact occurrence of the periods of wakefulness during the night is important when detecting relationships with daily measures.

- Using the 2–step approach we detected new relationships between sleep structure and daily measures which were not observed in the case of in time misaligned sleep probabilistic curves.

- The Multilevel functional principal component analysis (MFPCA) [6] is a method a priori developed for the detection of variability in functional data with repeated measurements. After applying the MFPCA method to the dataset of healthy sleepers we detected the "first–night sleep effect" considering several sleep microstates and all standard sleep stages.

- Similarly as in [7; 32; 33] we observed that the prediction of daily measures by using characteristics of the sleep structure is a difficult task. We investigated a prediction power of the linear regression model with independent variables being the differences in the level 2 principal component scores and dependent variables being the differences in a daily measure. Then, the coefficient of multiple correlation validates the performance of the model. However, the observed correlations were at most 0.26 indicating only a moderate relationship between the changes in the sleep structure and changes in the values of a daily measure. We hypothesise that these weak correlations are mainly influenced by the individuality in the subjects' sleep profiles.

- We adapted the MFPCA algorithm for the case when the order of observations within subjects is exchangeable or when the number of observations varies within subjects (unbalanced design). We took into account also a special case of the unbalanced design when for several subjects only one observation is available. We wrote a user–friendly MATLAB [22] script for the implementation of the modified MFPCA algorithm.

- We assume that the original or the modified version of the MFPCA algorithm can be successfully used for the detection of subject–specific profiles in sleep dataset with repeated measurements.

Finally, we can conclude, that functional data analysis is a promising tool for sleep structure analysis. One of its major benefits stands from the possibility to take into account the whole overnight sleep dynamics, which can be partially lost when considering one–dimensional sleep characteristics; being the common practice in the other existing sleep studies. To overcome and

solve the discussed important problem associated with individuality of the sleep profiles, a larger database consisting of several nights sleep recordings for each subject is needed.

List of author's publications

Publications:

- **Z. Rošťáková** and R. Rosipal. Time alignment as a necessary step in the analysis of sleep probabilistic curves. *Measurement Science Review*, 18(1), p. 1-6, 2018.

Publications in conference proceedings:

- **Z. Rošťáková**, G. Dorffner, Ö Aydemir and R. Rosipal. Estimation of sleep quality by using microstructure profiles. In *Lecture Notes in Computer Science: 16th Conference on Artificial Intelligence in Medicine, AIME 2017*, vol. 10259 LNAI, p. 105-115, 2017. ISSN 0302-9743.

- **Z. Rošťáková** and R. Rosipal. Importance of the time alignment of the sleep probabilistic curves. In *MEASUREMENT 2017 : Proceedings of the 11th International Conference on Measurement.* Editors: J. Maňka, M. Tyšler, V. Witkovský, I. Frollo. - Bratislava, Slovakia : Institute of Measurement Science, Slovak Academy of Sciences, p. 27-30, 2017. ISBN 978-80-972629-0-7.

- **Z. Rošťáková** and R. Rosipal. Multilevel functional principal component analysis for unbalanced data. In *20th European Young Statisticians Meeting. - Uppsala, Sweden: Uppsala University*, p. 51-57, 2017.

Abstracts from scientific conferences

- B. Cimrová, **Z. Rošťáková**, M. Varga Doležalová, J. Rybár, I. Farkaš and R. Rosipal. Keď cievy zradia mozog: kvalita spánku a kognitívny výkon pacientov po náhlej cievnej mozgovej príhode. In *Srdce, mozog, cievy: od normálnej k patologickej fyziológii: zborník abstraktov, Smolenice, 4.-6. apríl 2017. - Bratislava: Ústav normálnej a patologickej fyziológie SAV*, p. 23, 2017. ISBN 978-80-971699- 7-8

- **Z. Rošťáková** and R. Rosipal. Multilevel functional principal components analysis in the case of unbalanced design and small number of subjects. In *Olomoucian Days of Applied Mathematics (ODAM 2017) : Book of Abstracts. - Olomouc, Czech Republic: Palacký University in Olomouc*, p. 52, 2017.

- **Z. Rošťáková** and R. Rosipal. A novel two-step iterative approach for clustering functional data. In *22nd International Conference on Computational Statistics (COMPSTAT 2016) and the CRoNoS Summer Course and Satellite Workshop on Functional Data Analysis (CRoNoS FDA 2016): Book of Abstracts*, p. 61, 2016.

- B. Cimrová, **Z. Rošťáková**, M. Varga Doležalová, J. Rybár, I. Farkaš and R. Rosipal. Linking the quality of sleep and cognitive performance in stroke patients. In *Journal of Sleep Research, 2016*, vol. 25, suppl. 1, p. 253-254, 2016. ISSN 0962-1105

- **Z. Rošťáková**, R. Rosipal and G. Dorffner. Continuous sleep profiles clustering with a novel two-step functional data approach. In *Journal of Sleep Research*, vol. 25, suppl. 1, p. 251, 2016. ISSN 0962-1105.

- **Z. Rošťáková** and R. Rosipal. Differences in sleep microstate curves among healthy sleepers and patients after stroke. In *Clinical Neurophysiology*, 127(3), p. 126, 2016. ISSN 1388-2457.

- **Z. Rošťáková** and R. Rosipal. Differences in sleep microstate curves among patients after stroke and healthy sleepers. In *PROBASTAT 2015 : The Seventh International Conference on Mathematical Statistics. Abstracts. - Bratislava : Institute of Measurement Science, SAS*, p. 44, 2015.

Participation in congresses and conferences:

- ELITECH 2018: the 20th Conference of Doctoral Students, May 23 2018, Bratislava, Slovakia,

- EYSM 2017: the 20th European Young Statisticians Meeting, August 14–18 2017, Uppsala, Sweden,

- AIME 2017: the 16th Conference on Artificial Intelligence in Medicine, June 21–24 2017, Vienna, Austria,

- ODAM 2017: Olomoucian Days of Applied Mathematics, May 31 – June 2 2017, Olomouc, Czech Republic,

- MEASUREMENT 2017: the 11th International Conference on Measurement, May 29–31, Smolenice Castle, Slovakia,

- ESRS 2016: the 23rd Congress of the European Sleep Research Society, September 13–16 2016, Bologna, Italy,

- CRoNoS FDA 2016: the CRoNoS Summer Course and Satellite Workshop on Functional Data Analysis, August 26–28 2016, Oviedo, Spain,
- COMPSTAT 2016: the 22nd International Conference on Computational Statistics, August 23–26 2016, Oviedo, Spain,
- ECCN 2015: the 15th European Congress on Clinical Neurophysiology, September 30 – October 3 2015, Brno, Czech Republic,
- PROBASTAT 2015: the 7th International Conference on Mathematical Statistics, June 29 – July 3 2015, Smolenice Castle, Slovakia.

References

[1] R. C. B. Aitken. Measurement of feelings using visual analogue scales. *Proceedings of the Royal Society of Medicine*, 62(10):989–993, 1969.

[2] G. Anderer, S. Gruber, M. Parapatics, T. Woertz, G. Miazhynskaia, B. Klösch, J. Saletu, M. Zeitlhofer, H. Barbanoj, S. Danker-Hopfe, B. Himanen, T. Kemp, M. Penzel, D. Grőzinger, P. Kunz, A. Rappelsberger, G. Schlögl, and G. Dorffner. An e-health solution for automatic sleep classification according to rechtschaffen and kales: validation study of the somnolyzer 24x7 utilizing the SIESTA database. *Neuropsychobiology*, 51(3):115–133, 2005.

[3] Brain Products, GmbH. Brainvision analyser 2, 2013.

[4] T. Brott, H. P. Adams, C. P. Olinger, J. R. Marler, W. G. Barsan, J. Biller, J. Spilker, R. Holleran, R. Eberle, and V. Hertzberg. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*, 20(7):864–870, 1989.

[5] L. De Gennaro, M. Ferrara, F. Vecchio, G. Curcio, and M. Bertini. An electroencephalographic fingerprint of human sleep. *NeuroImage*, 26(1):114 – 122, 2005.

[6] Chong-Zhi Di, C. M. Crainiceanu, B. S. Caffo, and N. M. Punjabi. Multilevel functional principal component analysis. *The Annals of Applied Statistics*, 3(1):458–488, 2009.

[7] J. Edinger, M. K. Means, C. E. Carney, and A. D. Krystal. Psychomotor performance deficits and their relation to prior nights' sleep among individuals with primary insomnia. *Sleep*, 31:599–607, 06 2008.

[8] S. J. Gaffney and P. Smyth. Joint probabilistic curve clustering and alignment. In L. K. Saul, Y. Weiss, and L. Bottou, editors, *Advances in Neural Information Processing Systems 17*, pages 473–480. MIT Press, 2005.

[9] D. Gervini and T. Gasser. Self-modeling warping functions. *Journal of the Royal Statistical Society. Series B*, 66(4):959–971, 2004.

[10] D. J. Greene, A. Barnea, K. Herzberg, A. Rassis, M. Neta, A. Raz, and E. Zaidel. Measuring attention in the hemispheres: The lateralized attention network test (lant). *Brain and Cognition*, 66(1):21–31, 2008.

[11] J. Grünberger. *Psychodiagnostik des Alkoholkranken. Methodischer Beitrag zur Bestimmung der Organizität in der Psychiatrie, für Ärzte, Juristen und Sozialhelfer.* Maudrich, Wien, 1977.

[12] K. Karhunen. *Über lineare Methoden in der Wahrscheinlichkeitsrechnung.* Suomalainen Tiedeakatemia, Helsinki, 1947.

[13] A. S. Kaufman and E. O. Lichtenberger. *Assessing adolescent and adult intelligence.* John Wiley & Sons, 2005.

[14] L. Kaufman and P. J. Rousseeuw. *Finding Groups in Data: An Introduction to Cluster Analysis.* Wiley, New York, 1990.

[15] G. Klösch, B. Kemp, T. Penzel, A. Schlögl, P. Rappelsberger, E. Trenker, G. Gruber, J. Zeitlhofer, B. Saletu, W.M. Herrmann, S.L. Himanen, D. Kunz, M.J. Barbanoj, J. Röschke, A. Varri, and G. Dorffner. The SIESTA project polygraphic and clinical database. *Medicine and Biology Magazine*, 20(3):51–57, 2001.

[16] F. Lamoš and R. Potocký. *Pravdepodobnosť a matematická štatistika. Štatistické analýzy.* Univerzita Komenského Bratislava, 1998.

[17] A. Lewandowski, R. Rosipal, and G. Dorffner. Extracting more information from EEG recordings for a better description of sleep. *Computer methods and programs in biomedicine*, 108(3):961–972, 2012.

[18] A. Lewandowski, R. Rosipal, and G. Dorffner. On the individuality of sleep eeg spectra. *Journal of Psychophysiology*, 27(3):105–112, 2013.

[19] Stuart P. Lloyd. Least squares quantization in pcm. *IEEE Transactions on Information Theory*, 28:129–137, 1982.

[20] M. Loeve. *Fonctions aléatoires de second ordre*. Compte Rend. Acad. Sci., 1945.

[21] J. Malmivuo and R. Plonsey. *Bioelectromagnetism - Principles and Applications of Bioelectric and Biomagnetic Fields*. Oxford University Press, New York, 1995.

[22] MATLAB. *version 8.3.0 (R2014a)*. The MathWorks Inc., Natick, Massachusetts, 2014.

[23] P. Montero and J. A. Vilar. TSclust: An R package for time series clustering. *Journal of Statistical Software*, 62(1):1–43, 2014.

[24] H. G. Müller and R. Tang. Pairwise curve synchronisation for functional data. *Biometrika*, 95(4):875–889, 2008.

[25] Pacific Development and Technology, LCC. T–menstat - sample form and scoring key, 2012.

[26] T. W. Parsons. *Voice and speech processing*. MCGRAW HILL SERIES IN ELECTRICAL AND COMPUTER ENGINEERING. McGraw-Hill, 1987.

[27] J. O. Ramsay and B. W. Silverman. *Functional data analysis*. Springer Series in Statistics, New York, second edition, 2005.

[28] A. Rechtschaffen and A. Kales. *A Manual of Standardized Terminology Techniques and Scoring System for Sleep Stages of Human Subjects*. Bethesda, MD, U.S. Dept. of Healthy, Education and Welfare, 1968.

[29] R. Rosipal, A. Lewandowski, and G. Dorffner. In search of objective components for sleep quality indexing in normal sleep. *Biological Psychology*, 94(1):210–220, 2013.

[30] P. J. Rousseeuw. Silhouettes: A graphical aid to the interpretation and validation of cluster analysis. *Journal of Computational and Applied Mathematics*, 20(1):53 – 65, 1987.

[31] Z. Rošťáková. Pravdepodobnostné modelovanie štruktúry spánku u pacientov s ložiskovou ischémiou mozgu. diploma thesis, Univerzita Komenského v Bratislave, Fakulta matematiky, fyziky a informatiky, 2015.

[32] Z. Rošťáková, G. Dorffner, Ö. Aydemir, and R. Rosipal. Estimation of sleep quality by using microstructure profiles. In Annette ten Teije, Christian Popow, John H. Holmes, and Lucia Sacchi, editors, *Artificial Intelligence in Medicine*, pages 105–115. Springer International Publishing, 2017.

[33] Z. Rošťáková and R. Rosipal. Time alignment as a necessary step in the analysis of sleep probabilistic curves. *Measurement Science Review*, 18(1):1–6, 2018.

[34] B. Saletu, G. Kindshofer, P. Anderer, and J. Grünberger. Short-term sleep laboratory studies with cinolazepam in situational insomnia induced by traffic noise. *International Journal of Clinical Pharmacology Research*, 7(5):407–418, 1987.

[35] L. M. Sangalli, P. Secchi, S. Vantini, and V. Vitelli. k–mean alignment for curve clustering. *Computational Statistics and Data Analysis*, 54:1219 – 1233, 2010.

[36] A. Srivastava and E. P. Klassen. *Functional and Shape Data Analysis*. Springer–Verlag New York, 2016.

[37] R. Tang and H. G. Müller. Time-synchronized clustering of gene expression trajectories. *Biostatistics*, 10(1):32–45, 2009.

[38] J. Derek Tucker, W. Wu, and A. Srivastava. Generative models for functional data using phase and amplitude separation. *Computational Statistics and Data Analysis*, 61:50–66, 2013.

[39] D. von Zerssen, D. Köller, and E. Rey. Die befindlichkeitsskala (b–s): Ein einfaches instrument zur objektivierung von befindlichkeitsstoerungen, inbesondere im rahmen von laengsschnittuntersuchungen. *Arzneimittelforschung (Drug Research)*, 20:915–918, 1970.

[40] K. Wang and T. Gasser. Alignment of curves by dynamic time warping. *The Annals of Statistics*, 25(3):1251–1276, 1997.