

Bachelor's thesis



**Czech
Technical
University
in Prague**

F3

**Faculty of Electrical Engineering
Department of Circuit Theory**

Analyses of heart rate variability in animal models of epilepsy

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Bachelor's thesis title in Czech:

Analýzy variability srde ní frekvence u animálních model epilepsie

Guidelines:

This bachelor thesis deals with the analysis of parameters predicting the risk of sudden death in epileptics (SUDEP) [1] in an animal model.

1. Perform a review of methods related to the analysis of heart rate variability (HRV) in the electrocardiogram.
2. Implement a robust algorithm for R peak detection and automatic segmentation of stationary segments in ECG signals of animal models.
3. Compare different methods of HRV analysis (temporal, frequency, nonlinear).
4. Evaluate the possibilities of predicting the risk of cardiac arrhythmia and SUDEP based on HRV analysis.

Bibliography / sources:

- [1] Tthijs, R. D., Rylvlin, P., Surges, R. 'Autonomic manifestations of epilepsy: emerging pathways to sudden death?'. Nature Reviews Neurology, 2021, 17.12: 774-788.
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[3] Kim, H. G., et al. 'Stress and heart rate variability: a meta-analysis and review of the literature'. Psychiatry investigation, 2018, 15.3: 235.
[4] Vollmer, M. 'HRVTool – an Open-Source Matlab Toolbox for Analyzing Heart Rate Variability,' 2019 Computing in Cardiology (CinC), 2019, pp. 1-4.

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III. Assignment receipt

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Declaration

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

In Prague, 16. May 2022

Abstract

This thesis focuses on determination of heart rate variability parameters with relation to the effect of epilepsy on heart rhythm. Research of commonly used heart rate variability parameters in time, frequency and non-linear domain was performed and parameters possibly tied to epilepsy were selected based on analysed studies. Additionally, algorithm finding time intervals between R peaks of ECG was implemented and these lengths were converted to heart rate. Only stationary segments were then selected from heart rate signal with use of Bayesian change-point detection and parameters were calculated from these segments. Based on various combinations of these parameters, classifications of 16 signals were made. Descriptors from non-linear domain - Poincaré plot descriptors, parameters from frequency domain of very low frequencies and time parameter pRR10 were concluded as the most likely related parameters to epilepsy. Certain combination of these parameters achieved over 80% success rate in classification.

Keywords: ECG, HRV, time domain analysis, frequency analysis, Poincaré plot, Epilepsy, SUDEP

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Abstrakt

Tato práce se zaměřuje na určení parametrů variability srdeční frekvence spojených s vlivem epilepsie na srdeční rytmus. Byla provedena rešerše standardně používaných parametrů srdeční variability v časové, frekvenční a nelineární oblasti a na základě předchozích studií byly vybrány parametry s možným vztahem k epilepsii. Dále byl vytvořen algoritmus hledající délky intervalů mezi R špičkami v EKG, které byly převedeny na srdeční rytmus. Ze signálu srdečního rytmu byly poté za využití algoritmu Bayesovského detektoru změn vybrány pouze stacionární úseky, z nichž byly spočítány parametry variability srdeční frekvence. Na základě různých kombinací těchto parametrů byly provedeny klasifikace 16 signálů. Jako parametry nejpravděpodobněji spojené s epilepsi se ukázaly deskriptory z nelineární oblasti - Poincaré plot deskriptory, parametry z frekvenční analýzy o velmi nízkých frekvencích a časový parametr pRR10. Jedna z kombinací těchto parametrů dosáhla úspěšnosti klasifikace přes 80%.

Klíčová slova: EKG, HRV, časová analýza, frekvenční analýza, Poincaré plot, epilepsie, SUDEP

Překlad názvu: Analýzy variability srdeční frekvence u animálních modelů epilepsie

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Abbreviations

ECG	Electrocardiogram	PSD	Power spectral density
HR	Heart rate	ULF	Ultra low frequencies
HRV	Heart rate variability	VLF	Very low frequencies
RR	R to R peak interval lengths	LF	Low frequencies
ANS	Autonomic nervous system	HF	High frequencies
bpm	Beats per minute	PP	Poincaré plot
std	Standard deviation	SUDEP	Sudden unexpected death in epilepsy patients
SDRR	Standard deviation of RR intervals	SMR	Standard mortality ratio
SDSD	Standard deviation of successive differences	BACD	Bayesian autoregressive changepoint detection
RMSSD	Root mean square of successive differences	MA	Moving average
HTI	HRV triangular index	CC	Control centroid
TIRR	Triangular interpolation of RR intervals	IC	Interictal centroid
FT	Fourier transform	CORR	Correlation coefficient
DFT	Discrete Fourier transform		
FFT	Fast Fourier transform		



Part I

HRV analysis



Chapter 1

HRV analysis

HRV can be described as analysis of changes in time intervals between consecutive heart beats [17]. Although HRV analysis can be also done on plethysmogram, the most common and precise way is using it with electrocardiography [18]. In this thesis, HRV analysis is performed on provided electrocardiography signals - electrocardiograms.



1.1 ECG

The electrocardiogram (ECG) is signal of voltage against time produced by electrocardiography and representing heart activity, mainly depolarisation and repolarisation of myocardial fibers [8]. ECG consists of several waves, each representing specific activity of heart's electrical system. The whole set of waves, named alphabetically, is referred to as PQRST complex and each PQRST complex is separated by isoline - part with no ECG electrical activity.

P-wave is the first positive deflection corresponding to depolarisation of atria [8]. Three adjacent waves - Q, R and S - create the QRS complex representing mainly ventricular depolarisation. Atrial repolarisation happens at the same time as ventricular depolarisation but its electrical response in ECG is covered in QRS complex [8]. T-wave symbolises repolarisation of ventricles [8]. In three quarters of population T-wave is the last part of PQRST complex, in the remaining quarter additionally U-wave occurs, its cause are probably after-potentials of electrical-mechanical feedback [8].

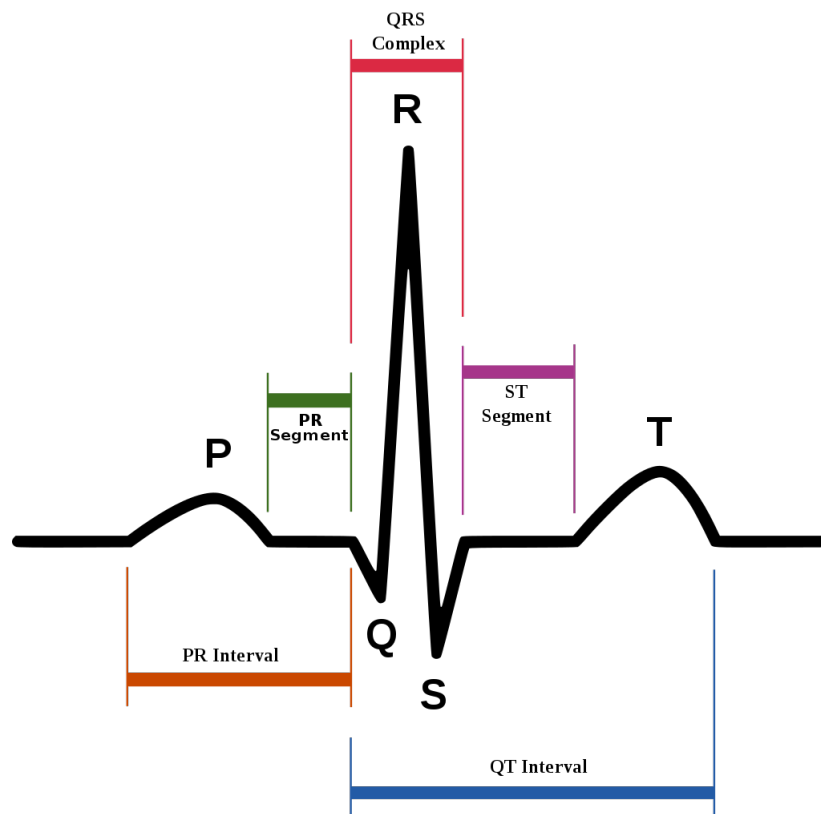


Figure 1.1: PQRST complex [1]

1.2 HRV

As stated above, R-wave lies in QRS complex and its highest point called R peak is in non pathological states the highest peak of ECG recording. Time intervals between R peaks, referred to as RR intervals, are essential for heart rate variability (HRV) analysis. In some articles terms RR intervals and NN intervals are distinguished, although, in this study, it is supposed that RR intervals used have artifacts already removed, thus only term RR interval is used further in this thesis [11][17][23]. RR interval lengths are measured in seconds.

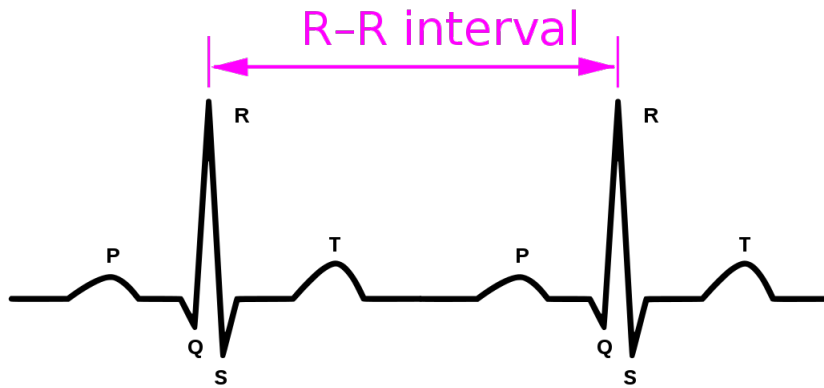


Figure 1.2: R to R peak interval [2]

In healthy state, heart rate (HR) is controlled by electrical conduction system of heart and stays regular. Additionally, HR is under the influence of autonomic nervous system (ANS). The signal depicting HR time course can be achieved with inverse of RR intervals multiplied with 60 to convert into beats per minute (bpm). Basic example of how to calculate HR:

$$\text{HR} = \frac{60}{\text{RR}} \text{ [bpm]}. \quad (1.1)$$

With this procedure, discrete signal representing HR is produced and it can be interpolated to form continuous signal showing heart rate. During physical activities RR interval lengths vary, HRV analyses these changes and extracts parameters which could provide quantitative measure of heart rate function.

■ 1.3 Overview of domains

HRV is usually measured with two domains - first called time analysis and second called spectral analysis, also referred to as frequency analysis [9]. While time analysis focuses mostly on statistical parameters providing the overview of the signal as a whole, applying spectral analysis leads to decomposition of signal into specific frequencies and amplitudes which are investigated. Additionally, non linear analysis which focuses on dynamic (time evolving) systems, was also proposed for ECG analysis [13].



Chapter 2

Time domain

Time domain analysis consists of statistical and geometrical measurement applied to set of RR intervals. The statistical measurement has no graphical interpretation and is divided into two sections, first being general formulas and second specific HRV statistical values. General formulas are included because they create solid basis for specific HRV statistical values. Compared to that, geometrical measures directly connect to graphical interpretation of physiological state.



2.1 General statistical parameters

The first three parameters are frequently used values in statistics, representing characteristics of mathematical set. Mean value and mode do not provide any pathological indication in most cases, since they up to a certain point link to physical activity of individual. Additionally, when applied on set with artifacts, changed misleading values could arise. The last parameter, standard deviation, has wide use in HRV analysis.

2.1.1 Mean value

Mean value or direct current component of signal, denoted as $\text{mean}(x)$ or μ is the sum of all sampled values divided by number of them. In signal analysis this value proves to be problematic because in most of the times noise is present and thus μ brings affected values. The mean of RR intervals can be calculated and average heart rate approximated as follows:

$$\begin{aligned}\mu(\text{RR}) &= \text{mean}(\text{RR}) = \frac{1}{N} \sum_{k=1}^N \text{RR}_n \quad [\text{s}], \\ \text{mean}(\text{HR}) &= \frac{60}{\text{mean}(\text{RR})} \quad [\text{bpm}],\end{aligned}\tag{2.1}$$

where N is number of RR intervals.

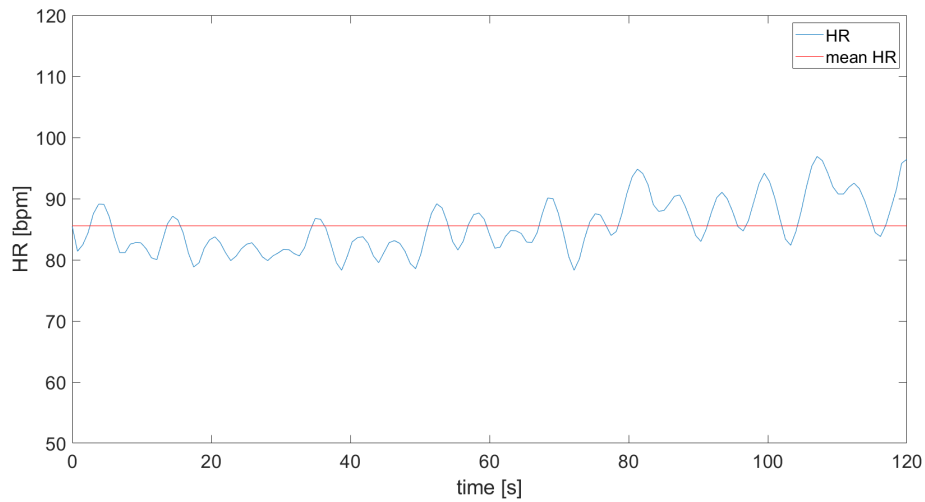


Figure 2.1: Human heart rate and its mean value

2.1.2 Mode

Mode is the item with most frequent occurrence in the given set, compared to μ it brings information without influence of noise, unless the noise is vast part of signal. The mode of given data set D is referred to as $\text{mode}(D)$.

2.1.3 Standard deviation

Standard deviation (std, σ) informs about dispersion of series of values and indicates pathological behaviour or large noise contamination of this signal. As mentioned above, σ is essential component of specific HRV parameters, values like standard deviation of successive differences or standard deviation of RR intervals (all described in next section) come directly from σ .

2.2 HRV statistical parameters

While previous section explained common statistical values which could be calculated from any finite data set, the remaining methods are used strictly for HRV analysis focusing on beat-to-beat RR interval set. Focus of those measures is aimed at comparing lengths and differences of lengths of RR intervals.

2.2.1 Standard deviation of RR intervals (SDRR)

Standard deviation of RR intervals reflects both short term and long term variability of RR series. Sometimes this can be summarized as total variability [14]. Formula for SDRR is [5]:

$$\text{SDRR} = \text{std}(\text{RR}) \text{ [s]}. \quad (2.2)$$

2.2.2 Standard deviation of successive differences (SDSD)

Standard deviation of successive differences of adjacent intervals shows deviation of beat to beat (short term) change [17]. The way to extract this parameter is to compute differences between RR interval times and then compute σ from this series [5].

$$\text{SDSD} = \text{std}(\text{diff}(\text{RR})) \text{ [s]}. \quad (2.3)$$

The function $\text{diff}(s)$ represents function returning differences between adjacent samples of series s .

■ 2.2.3 Number of differing intervals (RRi, pRRi)

This parameter, referred to as RRi, provides information about number of pairs of adjacent RR intervals differing more than i (in milliseconds). The pRRi value, computed from RRi by dividing with the number of all intervals, represents the fraction (or percentage) of successive differences longer than given time [11].

This parameter is frequently analysed in human ECG analysis with the use of $i = 20, 50$ (RR20, RR50) [5]. In contrary, in animal models this parameter seems problematic due to different heart rates of analysed animal species.

$$\begin{aligned} \text{RRi} &= \text{length}(\text{diff}(\text{RR}) > i) \quad [-], \\ \text{pRRi} &= \frac{\text{RRi}}{\text{length}(\text{RR})} (\cdot 100\%) \quad [-], \end{aligned} \quad (2.4)$$

where $\text{length}(s)$ corresponds to number of samples of series s [5].

■ 2.2.4 Root mean square of successive differences (RMSSD)

This widely used metric of HRV analysis shows averaged value of all RR interval differences.

$$\text{RMSSD} = \sqrt{\frac{1}{N-1} \sum_{k=1}^{N-1} (\text{RR}_{k+1} - \text{RR}_k)^2} \quad [\text{s}]. \quad (2.5)$$

■ 2.3 Geometrical parameters

Last two parameters are called geometric, since values are taken directly from graphical representation of RR series - histogram. Parameters are extracted with mathematical operations, mainly integration (sum) and triangular interpolation.

■ 2.3.1 HRV triangular index (HTI)

HRV triangular index can be calculated by integrating the density of RR histogram divided by its height [11]. Together with RMSSD, HTI can provide information of heart rate being arrhythmic [23].

$$\text{HTI} = \frac{1}{N} \sum_{k=1}^M h[k] \quad [-], \quad (2.6)$$

where M is chosen such that histogram edges are 50ms windows (in human HRV analysis) and N is number of RR intervals.

■ 2.3.2 Triangular interpolation (TIRR)

Triangular interpolation of RR intervals is equal to the baseline width of RR interval histogram. It can be achieved with triangular interpolation - approximation of distribution of histogram with triangle [23].



Chapter 3

Frequency analysis

This method focuses on decomposing the HR signal into periodic heart rate oscillations at specific frequencies. Fourier transform or autoregressive model can be used to compute the periodical parts of signal - the power spectrum.



3.1 Fourier transform

Fourier transform decomposes function into periodic frequency parts. It was defined for both continuous (FT) and discrete signals (DFT) using formulas with integral and sum, respectively.



3.1.1 DFT and FFT

In digital signal processing, due to all analysed signals being discrete, only DFT is used for frequency decomposition. Because of performance of software and hardware in the past, algorithm simplifying the calculation of DFT was invented. This algorithm, called fast Fourier transform, is in-built in most signal analysing software and is essential in any frequency domain signal analysis.

■ 3.2 PSD and frequency bands

Power spectral density (PSD), also known as power spectrum (referring to spectral energy distribution per unit of time) provides the information about energy distribution in several areas, depending on subject analysed. In human signals, the PSD analysis comprises of 4 areas - ultra-low, very-low, low and high frequencies (ULF, VLF, LF, HF) [17]. In animal models and mainly rats, the frequency areas used vary within studies and within specific rat species, but generally they consist of three areas - VLF, LF and HF [15].

■ 3.3 Analysed parameters

The above presented components of frequency domain are analysed mathematically, the main parameters of frequency analysis are areas (VLFa, LFa, HFa) of specific power bands, their peaks (VLFp, LFP, HFp) and ratio of LF to HF power (LF/HF).

LF part is associated with combination of sympathetic and parasympathetic response. It points to thermoregulation and vasomotor activity [23].

HF area is affected by only parasympathetic activity and could point to increased heart rate arrhythmia during respiration [23].

There is also proven correlation between HF and LF, so parameter including their ratio should be taken into consideration, hence the LF/HF parameter is derived [23]. Its increase shows low vagal activation [23].

3.4 Overview of human and animal model

Table A.1 shows comparison between human and rat frequency areas, specifically for Wistar rat. Wistar rat is shown because signals used in this thesis come from this species. All data in table are in Hz.

Frequency area	Human [23]	Wistar rat [24]
ULF	under 0.0033	n/a
VLF	0.0033 - 0.04	0.02 - 0.2
LF	0.04 - 0.15	0.2 - 0.75
HF	0.16 - 0.4	0.75 - 2.5

Table 3.1: Frequencies in spectral analysis, data in Hz



Chapter 4

Non-linear analysis

Non-linear means non-direct relationship in between variables. Some non-linear parameters correlate with time and frequency domain parameters, although, due to their nature, some pathological conditions can change their values, but this altered value does not have to implicate pathological state [17]. This chapter provides information about three types of analysis - Poincaré plot, correlation dimension and detrended fluctuation. From these parameters only Poincaré plot is discussed in-depth and only brief explanation of what is analysed in remaining analyses is described.



4.1 Poincaré plot

Poincaré plot (PP) is technique which has both visual representation in form of plotted points and quantitative representation in form of descriptors [14]. The idea of PP is to display and calculate beat to beat changes in form of pairs of adjacent RR intervals and then analyse deviations of this set from expected shape and values. Descriptors derived from data set of RR intervals are standard deviation in short term (SD1), standard deviation in both short and long term (SD2), ellipse area (S) and standard deviation of RR intervals (SDRR), or to be specific, its PP approximation [14].

4.1.1 Construction of Poincaré plot

In construction of Poincaré plot the vectors x^+ and x^- are defined as [14]:

$$\begin{aligned} x^+ &= (RR_1, RR_2, \dots, RR_{N-1}), \\ x^- &= (RR_2, RR_3, \dots, RR_N). \end{aligned} \quad (4.1)$$

Then PP representation can be depicted as ordered pairs of x_i^+ and x_i^- : (x_i^+, x_i^-) . The plot of those pairs in healthy person should look like ellipse shape with longer axis on first quadrant axis $y = x$ or rather $x_i^- = x_i^+$ as can be seen in figure 4.1.

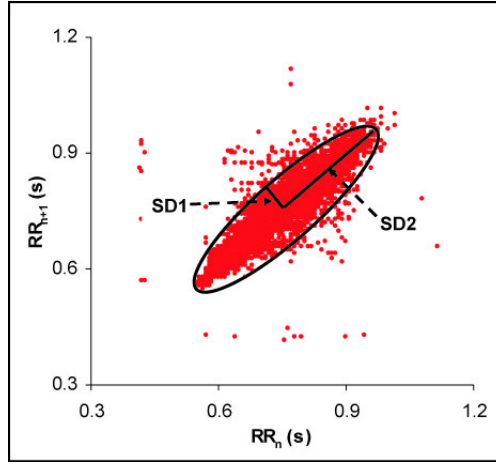


Figure 4.1: Poincaré plot with descriptors - SD1 and SD2 [19]

4.1.2 SD1 and SD2

SD1 is defined as the standard deviation of projection of the PP on the $y = -x$, alternatively $x_i^- = -x_i^+$, and SD2 as standard deviation of projection of the PP on $y = x$, alternatively $x_i^- = x_i^+$ [14].

$$\begin{aligned} \text{SD1} &= \sigma(x_1) \text{ [s]}, \\ \text{SD2} &= \sigma(x_2) \text{ [s]}, \\ \text{where} \\ x_1 &= \frac{x^+ - x^-}{\sqrt{2}}, \\ x_2 &= \frac{x^+ + x^-}{\sqrt{2}}. \end{aligned} \quad (4.2)$$

■ 4.1.3 SDRR

SDRR is deviation of all RR intervals and in PP procedure its approximate can be derived as [14]

$$\text{SDRR} = \frac{1}{\sqrt{2}} \sqrt{\text{SD1}^2 + \text{SD2}^2}, \quad [\text{s}]. \quad (4.3)$$

■ 4.1.4 Ellipse area

Area of the ellipse could also be taken into consideration as parameter and generally as an area is labeled with S. In Filtering Poincaré plots [14], it is argued that S is better descriptor of total variability than SDRR. Healthy Poincaré plot points should lie in the area of ellipse with longer principal axis lying in $x_i^+ = x_i^-$ and with $a = \text{SD2}$ and $b = \text{SD1}$.

$$S = \pi \cdot \text{SD1} \cdot \text{SD2} \quad [\text{s}^2]. \quad (4.4)$$

Although, the π can be omitted since it is only constant correcting the multiplication of SD1 and SD2 into area of ellipse.

■ 4.1.5 Filtering Poincaré plot

As well as time domain analysis, non linear analysis is affected by noise and filtration of data is needed. There are three types of filter used in Poincaré plot [14]. Annotation filter is very specific and usable only on particular type of data - with labels of beat type - and due to that, only square and quotient filters will be shown here.

Square filter removes points lying outside of square area and only points accepted by given condition remain:

$$\begin{aligned} x_-^+ &> \min \\ x_-^+ &< \max \end{aligned} \quad (4.5)$$

Quotient filter is more aggressive filter, meaning it removes more points, but it also tends to leave out unfiltered incorrect beats [14]. Points withstanding conditions shown in this formula are removed [14]:

$$\begin{aligned} \frac{x_i^\pm}{x_{i+1}^\pm} \geq 1.2 \quad \text{or} \quad \frac{x_i^\pm}{x_{i+1}^\pm} \leq 0.8 \\ \frac{x_{i+1}^\pm}{x_i^\pm} \geq 1.2 \quad \text{or} \quad \frac{x_{i+1}^\pm}{x_i^\pm} \leq 0.8 \end{aligned} \tag{4.6}$$

■ 4.2 Correlation dimension

Correlation dimension looks for fractal dimension (any noninteger dimension possessed by the set of points) and finds information about complexity of non-linear system [13]. As dimension increases, also complexity rises. The idea of this measurement is to determine the minimum number of dynamical variables describing the way of system to its final state [13].

■ 4.3 Detrended fluctuation

Detrended fluctuation looks for long range correlation and due to that needs to recognize trends caused by extrenal influences [13]. The time bounded series is unbounded and split to portions, least square fitting is applied and long time fluctuation is found for every part [13]. Last part of this analysis is to plot log-log graph describing self-similarity [13].

Part II

Epilepsy, SUDEP and proposed prediction parameters



Chapter 5

Epilepsy and SUDEP

One of the focal points of this thesis is development of algorithm analysing animal ECG model with ability to classify signals based on epilepsy severity. Epilepsy severity and classification based on it could also be tied to potential risk of sudden unexpected death in epilepsy (SUDEP). In this chapter, brief introduction to epilepsy and SUDEP is provided.



5.1 Epilepsy

Epilepsy is one of the most common disorders of brain [22] affecting about 65 million people worldwide [12]. Epilepsy is characterised by reoccurring unpredictable interruptions of brain function called epileptic seizures [6]. According to WHO up to 10% of people worldwide have one seizure during their lifetime thus at least two or more unprovoked seizures are needed to determine epilepsy [21]. While epileptic seizures are the defining factor of epilepsy, the patients also suffer from exclusion, restriction and isolation due to fear and misunderstanding surrounding epilepsy [6] [21]. Epileptic seizures vary in severity from small lapses of attention to long convulsions and also in frequency from less than one per year to more than few per day [21].

Mortality of epilepsy patients in developed countries had standard mortality ratio (SMR) ranging from 1.6 to 4.1 and while every study concluded used different standardisation, the overall mortality was generally far higher in epilepsy patients [7]. Additionally, information about SMR of 2-3 in epilepsy patients was also presented in Atlas [22].

To study the mechanism of epilepsy origin significant part of research in this field is done on animal models. In this thesis, rat model of temporal lobe epilepsy induced by local administration of tetanotoxin into hippocampus was used [10].

■ 5.2 SUDEP

As its name suggests, the definition of SUDEP is sudden and unexpected death, not caused by drowning, injury, intoxication or other factor [20]. As proposed in MORTality in Epilepsy Monitoring Unit Study (MORTEMUS) [16], SUDEP mechanism starts with severe alteration of respiratory and cardiac function. This mechanism might lead to immediate death in severe cases and to cardiorespiratory arrest in lesser cases [16]. In MORTEMUS, term near SUDEP is used when patient survived for more than one hour of resuscitation, terms fatal SUDEP and non-fatal SUDEP are also distinguished [16]. In all non-fatal near SUDEP cases, resuscitation started within 3 minutes, which shows that patients with near SUDEP occurrence can survive in case of fast resuscitation [16].

The incidence of sudden unexpected death in epilepsy may vary due to nature of its definition, in Atlas [22] information about its incidence of 2-18% is stated. In contrary, Autonomic manifestations of epilepsy [20] provides incidence rates of SUDEP in person-years, specifically 1.11-1.45 per 1000 person-years in children and 1.20 per 1000 person-years in adults.

It is desirable to find the indicators of SUDEP, but no trial or evidence is yet available to find effective way of preventing it [20]. If indicators are found, patients with possibility of SUDEP mechanism could be monitored and their death could possibly be prevented with caridopulmonary resuscitation. However, SUDEP phenomenon did not occur in any of the rats from which ECG signals came thus talking about SUDEP prediction in this thesis is rather hypothetical. Instead we focus on way to quantify severity of epilepsy with HRV parameters.



Chapter 6

Parameter extraction and idea of classification

In this chapter, we introduce the basic idea of how to classify signal along with parameters supposedly yielding information linked to this classification.



6.1 Supposed epilepsy severity measuring markers

As stated in Autonomic manifestations of epilepsy [20], there is currently no way to test an actual SUDEP prediction so we decided to quantify the severity of epilepsy effect on heart rate based on certain HRV analysis parameters. Aim of this thesis is on deciding whether there exist HRV parameters which could comprise classifier.

6.2 Overview of proposed parameters

We supposed these parameters would yield information about epilepsy severity based on analysed literature. These parameters are described in detail in part one so only brief overview with commentary of why this parameter was chosen will be provided here.

Domain	Parameter	Commentary
Time	RMSSD	Linked to SUDEP [4]
Time	pRRi	Correlates with RMSSD and HF [17], proposed $i = 10$
Frequency	VLFa	Associated with thermal and hormonal control [23]
Frequency	VLFp	Additional to VLF
Frequency	LFa	Associated with ANS [23]
Frequency	LFp	Additional to LF
Frequency	HFa	Associated with parasympathetic activity [23]
Frequency	HFp	Additional to HF
Frequency	LF/HF	Reflects sympathovagal balance [17]
Non-linear	SD1	Short term variability [14]
Non-linear	SD2	Short and long term variability [14]
Non-linear	SDRR	Total variability [14]
Non-linear	S	Total variability [14]

Table 6.1: Overview of classification parameters

Both non-filtered and quotient filtered 4.1.5 parameters of non-linear Poincaré plot markers were used, we will distinguish unfiltered parameters from filtered with use of lower index q with filtered parameters.



Part III

Implemented algorithms



Chapter 7

R peak finding algorithm

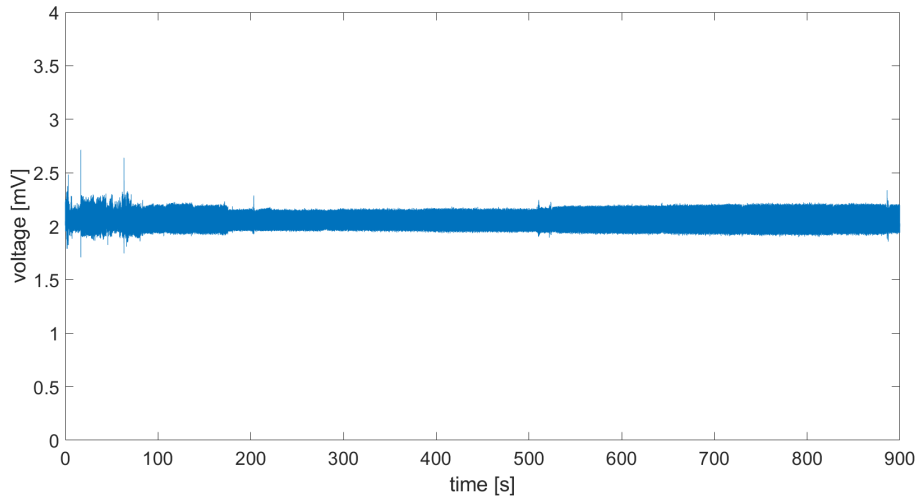
This chapter focuses on describing the implementation of R peak finding algorithm, its pros and cons and problems it faces. Information about provided data set is included in first section along with justification of using the algorithm. Second section contains description of implementation with adjustments solving problems tied to data set. Explanation of algorithm functions is included in appendix A.



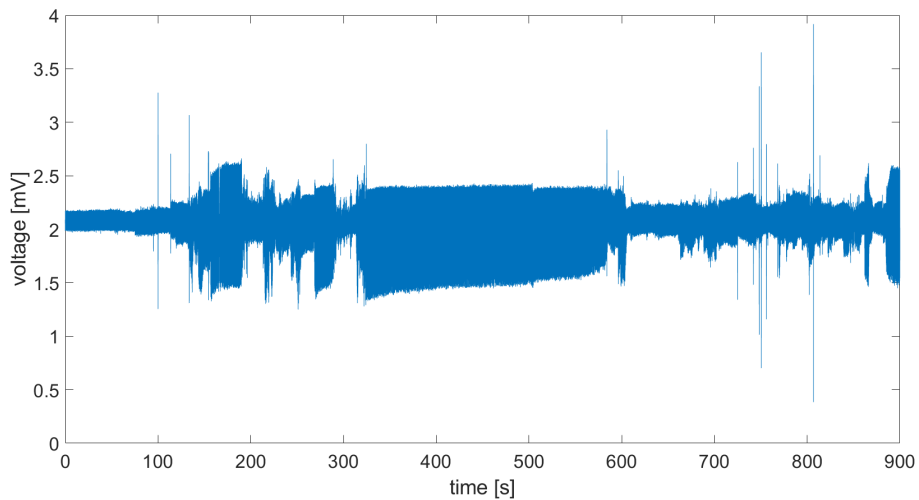
7.1 Introduction

HRV analysis can be done on provided R peak interval lengths. When R peaks are not denoted, we need to manually label them or use R peak finding algorithm to classify them. In this study, we chose to implement basic algorithm which finds peaks based on level of energetic change. As with almost every algorithm, the simplicity of this detection system caused a few errors which were needed to be solved and a certain amount of adjustments was made. We also encountered problems in provided signals. All those errors, problems and adjustments are discussed in this section.

Firstly, some signals have changing amplitude of R peaks. This is problematic in thresholding (described in 7.2), since the changes in amplitude also mean change in energy levels, thus affecting the choice of threshold. To compensate this problem, we segmented the ECG into shorter parts.



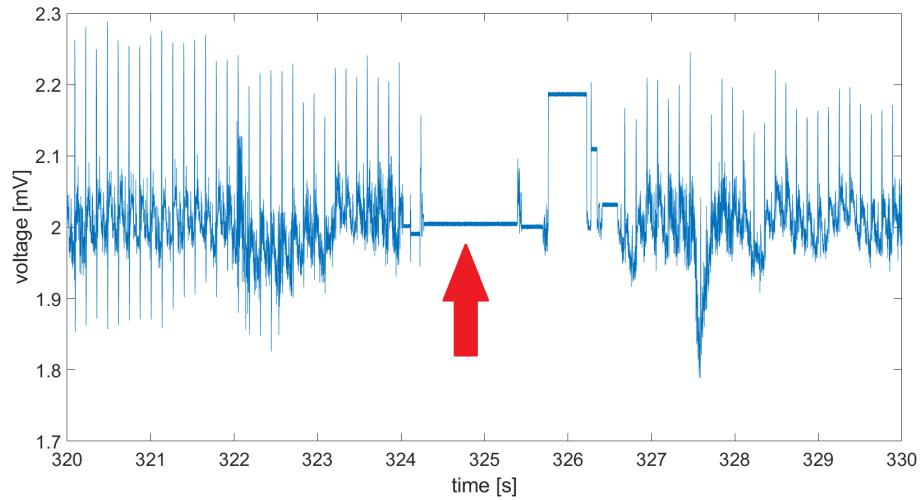
(a) Constant amplitude



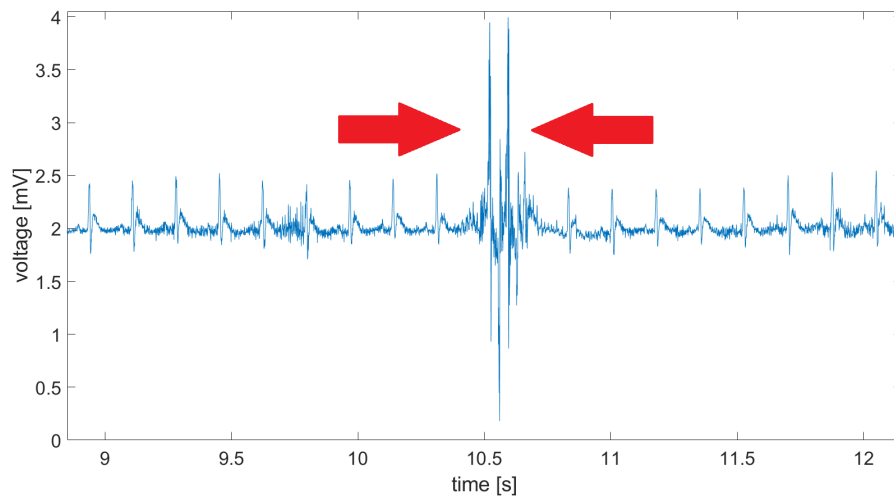
(b) Changing amplitude

Figure 7.1: Comparison of static and changing amplitude

Secondly, some parts of signals have omitted data or contain noise of enormous energy. In parts with omitted data, no R peaks are labeled. On the other hand, in parts with high energy, R peaks are labeled randomly. This problem was in most cases probably caused by the method of measuring or movement of subject.



(a) Data omission



(b) Unfilterable noise of high energy

Figure 7.2: Examples of measuring problems

These segments are not so simple to cut out from the original signal hence algorithm decomposing already extracted HR signal into stationary parts was used. Description of this algorithm is provided in chapter 8.

7.2 Implementation

The R peak finding algorithm was implemented in Matlab scripting language. The algorithm has three parts: prefiltration, segmentation and actual R peak labeling. All functions used are described in words and corresponding functions are provided as Matlab files. Figures showing how one specific signal behaves with applying these functions subsequently are also provided.

7.2.1 Prefiltration

To remove unwanted frequency parts of signal, we implemented the Lowpass (LP) and Highpass (HP) use of Butterworth filter. Butterworth filter has the most flat frequency response in passing band which makes it the most suitable filter due to its data preservation. Lowpass function filters out all frequencies of signal higher than given f_z while Highpass function subtracts all frequencies lower than given f_0 . Filtered signal has all components between these given cutoff frequencies.

7. R peak finding algorithm

Cutoff frequencies were set to $f_0 = 1$ Hz and $f_z = 200$ Hz, which already differs from human ECG filtering where usually f_0 under 1 Hz and f_z about 45 to 50 Hz are used.

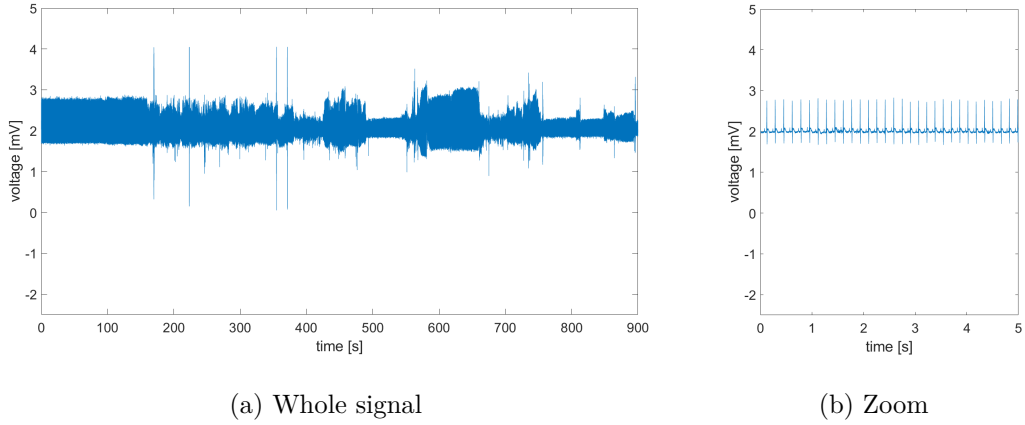


Figure 7.3: Unfiltered signal

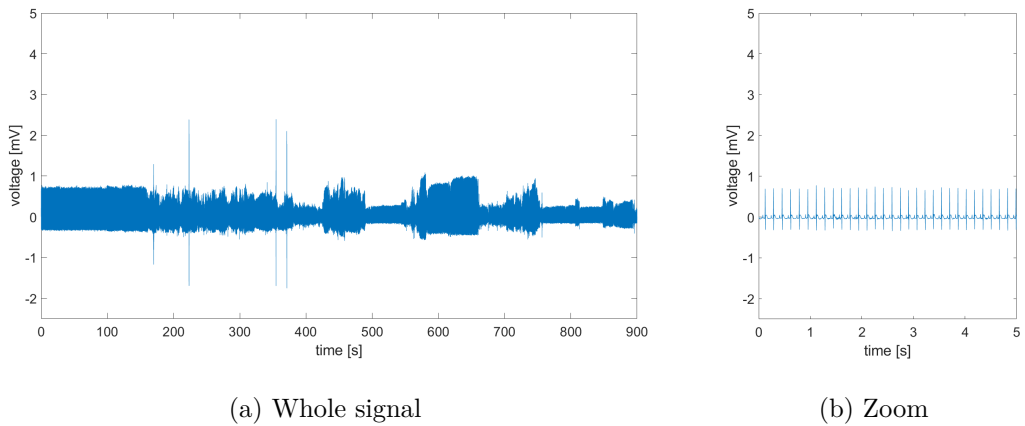


Figure 7.4: Filtered signal

7.2.2 Segmentation

High range changing amplitude with example in figure 7.2 caused problems in choosing threshold for R peak labeling which forced us to use segmentation of signal. Decomposition into second-long segments was used. Average rat heart rate is 400 bpm which means every second-long segment consists of approximately 6 to 7 beats including same number of R peaks which makes this length justifiable.

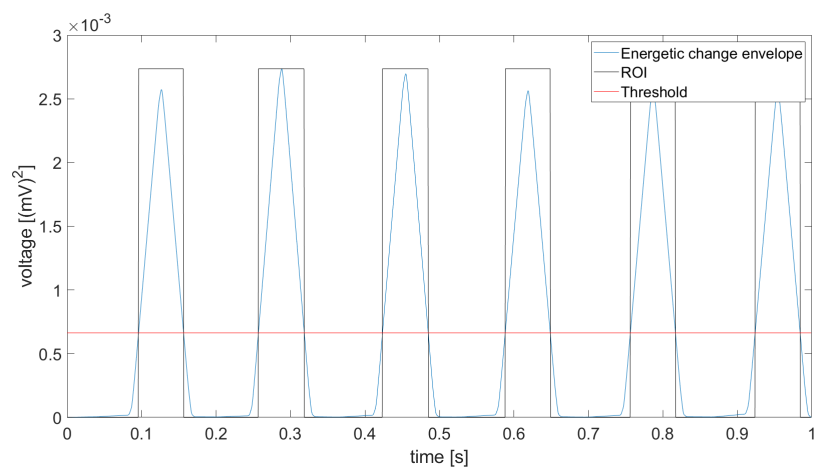
7.2.3 Labeling R peaks

After prefiltration and segmentation, the algorithm cycles through all of segments and looks for peaks with highest change in energetic level. Thus the change of energy level needs to be found, regions of interest selected and peaks labeled.

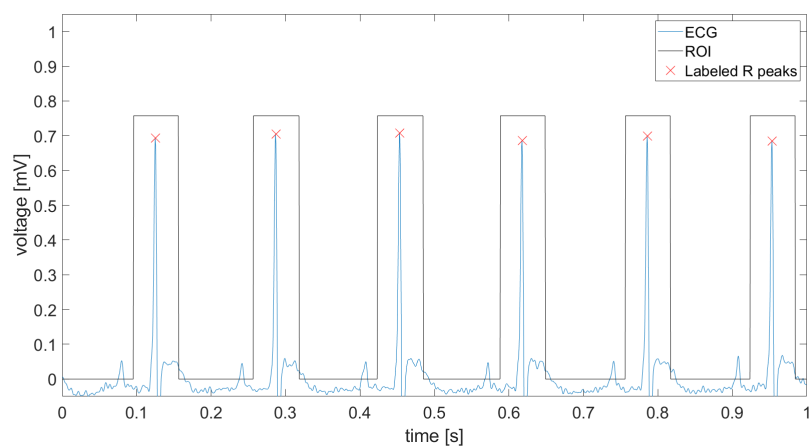
To find energetic change of signal, EMA (Energetic change, Moving Average filter) function is used. This function takes differences between adjacent samples of the signal to the power of two and filters them with moving average (MA) filter.

Last part of finding R peaks is setting the threshold and deriving timestamps of peaks. This is achieved by setting threshold to mean of energetic change and labeling one peak in each region of interest (where energetic envelope $>$ threshold, ROI). ROI in figure 7.5 is scaled down for clarity. We tried various thresholds ranging from 0.6 to 1.2 times and came to conclusion that simple mean without any coefficient should be used.

7. R peak finding algorithm



(a) Energetic change segment



(b) ECG segment

Figure 7.5: R peak labeling

After extracting timestamps of R peaks (RT), simple conversion to RR intervals can be done as follows

$$RR = \text{diff}(RT), \quad (7.1)$$

where function $\text{diff}(RT)$ returns differences between adjacent values of RT .

7.2.4 Interpolation

With RR interval set completed, the last thing remaining is to create continuous HRV signal with interpolation of the R peak lengths. We used cubic interpolation with built-in interpolation function `interp1` in Matlab. Interpolation can also be done using spline function but it tends to overfit and create large jumps in amplitude. We also decimated the signal with coefficient of 200 to get to the most important frequencies (0 - 5 Hz) in spectral analysis.

Final products of R peak labeling algorithm are RR intervals, RT peak timestamp for manual correction and lastly interpolated and decimated HR signal from which spectral parameters are extracted.

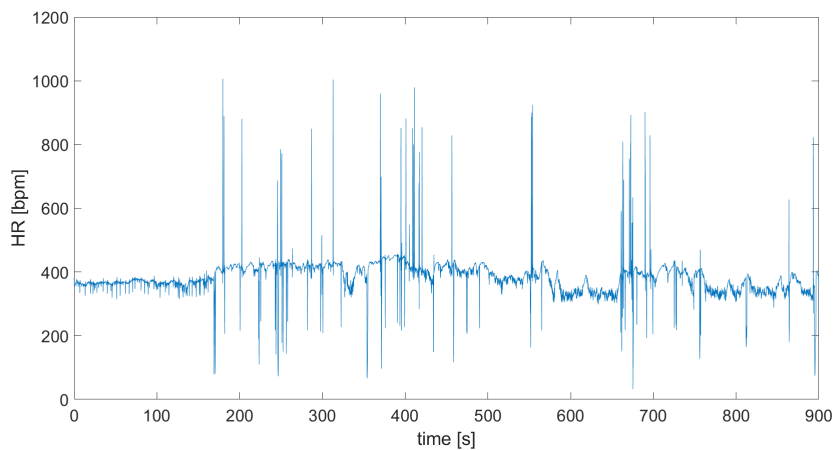


Figure 7.6: Cubic interpolated HR decimated with coefficient 200

Chapter 8

Stationary decomposing algorithm

In previous chapter, we described how to extract continuous decimated HR signal. This HR signal shows heart behaviour in time and along with RR intervals comprises the set for all analyses. While previous chapter described how to remove noise and how to counter changing amplitude of signal with filtering and segmenting, in this chapter we describe usage of Bayesian autoregressive changepoint detection (BACD) [3]. This technique was used due to changing mean HR and occurrence of outliers in HR signal.

8.1 Overview of encountered problems

While normal HR changes in sinusoidal rhythm, its mean value stays approximately the same when physical activity of individual has equal intensity. In measuring short term human ECG, the subjects undergo minimal physical activity and usually they just sit in calm. It is not the same case with animal models because the subjects change the intensity of physical activity frequently. Due to that, the HR signal does not have constant time course and changepoint detection to distinguish stationary segments needs to be used. This is crucial mainly for frequency analysis, because extracting frequency parameters showed very bad results with extraction from whole HR signals.

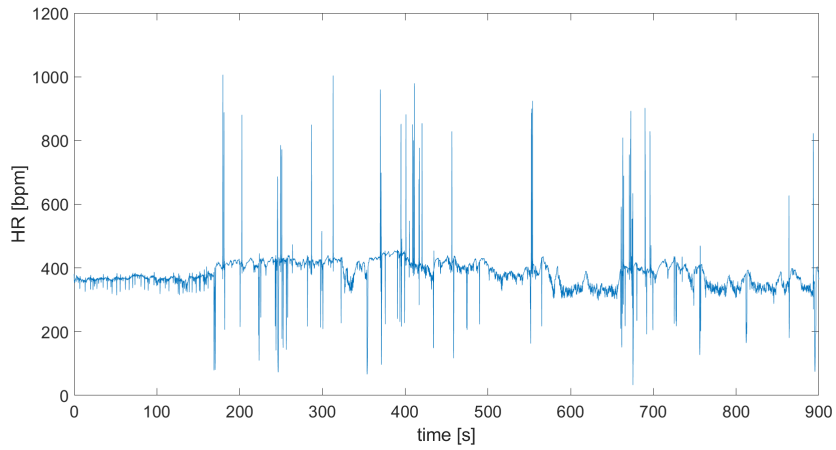
The last two complications faced can be summarized in one term and we refer to them with term outliers. These outliers come in form of spikes and drops of HR signal. Most of the HR signals have mean HR in interval from 300 to 500 bpm, but spikes ranged to more than 1000 bpm while drops came close to 0 bpm. Spikes were probably caused by unfiltered high energy noise and drops originated from data omission. We needed to remove HR segments with large amount of outliers and divide the signal into stationary segments.

8.2 Parameter estimation

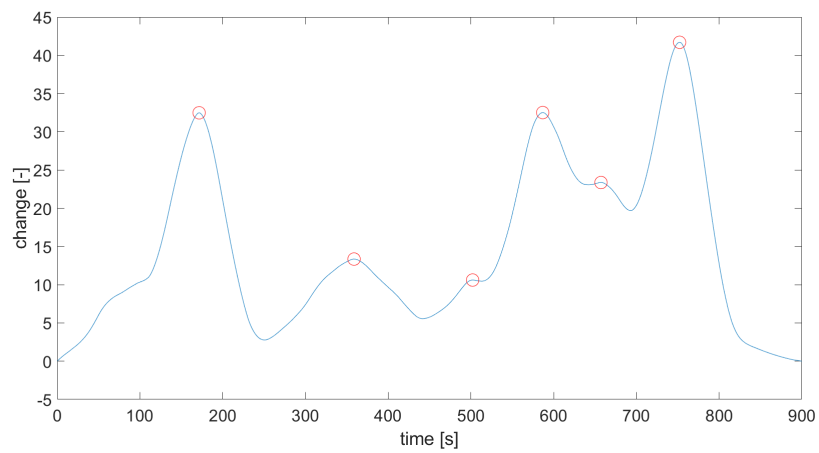
Used BACD assumes a priori probability that all parameters are equally likely thus it is possible to find a posteriori probability without the knowledge about noise [3]. BACD takes signal and sliding window length as inputs and outputs change curve, which has peaks in areas of substantial changes in signal. We can then take these peaks and decompose signal into parts separated in peak indexes.

8.3 Implementation

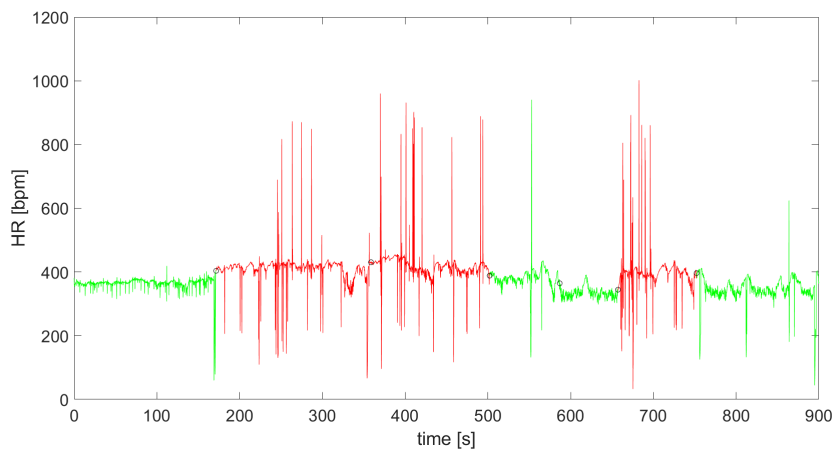
We looked for at least one minute long windows to be sure we achieve HR with very low frequencies A.1. This was supposed due to analysis of short human HR signals needing at least 2 minutes to distinguish VLF, LF and HF [9]. BACD sliding window length was set to 100 seconds to look for long term change and its output was filtered with MA filter of 60 seconds long window to simulate the desired segment length. We generalized outliers as samples differentiating by more than 250 bpm from mean HR of segment. After that, the segments were found, those with outlier number larger than 10 (less than 2% with decimated sampling frequency of 10) or $\frac{\sigma(\text{HR})}{\text{mean}(\text{HR})}$ higher than 0.15 were cut out. The remaining segments withstanding these conditions were used for extraction of HRV parameters.



(a) HR



(b) BACD estimated and MA filtered change function with peaks



(c) Chosen HR segments (green) and denied HR segments (red)

Figure 8.1: Stationary decomposing algorithm



Part IV

Measures

Chapter 9

Measures and classification

This chapter contains description of how classification of whether given signal is control (non-epileptic, healthy) or interictal (between seizures) is made. Additionally, results achieving highest succes rates with this classification method are presented.

9.1 Methods

We were provided with 8 control signals, 8 interictal signals and 16 blind signals with no label. The task was to find HRV parameters which could compose classifier. Parameters presented in table 6.1 were extracted from stationary parts produced by BACD 8.3. Frequency parameters were extracted from stationary HR and other parameters with corresponding RR intervals. We implemented the extraction of parameters based on research in first part of this thesis.

9.1.1 Classification

The most suiting and simplest method for this task was classification based on euclidean distance with parameters used as dimensions. We defined control centroid (CC) and interictal centroid (IC) as mean value along the axis of parameters.

$$\begin{aligned} \text{CC} &= \text{mean}(\text{control_signals}, 1), \\ \text{IC} &= \text{mean}(\text{interictal_signals}, 1), \end{aligned} \tag{9.1}$$

where *control_signals* and *interictal_signals* are sets of size $M \times N$. M is number of signals of given set and N is number of parameters used in one specific classification.

From now onward, the term classification will mean assigning control labels to blind signal with euclidean distance from CC lower than from IC, while assigning interictal labels otherwise. When classifying based on more parameters, they all need to be scaled to range from 0 to 1 individually. If parameters are not scaled and they are of different order, euclidean distance classification favours that of higher order.

■ 9.1.2 Correlation of parameters

Parameters from all signals were derived individually and correlation coefficient (CORR) for each pair of them was found.

$$\text{CORR} = \text{corrcoef}(\text{param}_i, \text{param}_j), \tag{9.2}$$

where $\text{CORR} \in \langle -1; 1 \rangle$ and `corrcoef` is Matlab function.

■ 9.1.3 Combining parameters

To get to the best classifier, we wanted to use as much parameters as possible, along with keeping their mutual correlation very low. We have done classification on all pairs of parameters withstanding the condition

$$|\text{CORR}| < 0.1 \tag{9.3}$$

to achieve outcome that is most independent on single parameter.

We wanted to construct classification with maximum amount of parameters, but with their increase we were forced to relax the correlation threshold due to lack of three parameters with correlation this low. The maximum value of correlation allowed was 0.4 for triplets of parameters.

9.2 Most successful measures

In this section, we present achieved success rates of classification. Only classifications with more than 65% correctly classified are shown.

In table 9.1, individual parameters with number of correctly classified signals and percentage of successful classifications are presented.

Parameter	Correctly classified	Percentage [%]
VLF peak	13	81,25
VLF area	12	75
pRR10	11	68,75

Table 9.1: Best individually performing parameters

With combination of two parameters, we achieved the same maximum result as with individual classification, but with higher frequency among parameter combinations. Also with combined parameter classification, the certainty of robustness gets higher. Pairs of parameters are shown in table 9.2.

Parameter 1	Parameter 2	Correctly classified	Percentage [%]
S_q	VLFa	13	81.25
pRR10	VLFa	12	75
SD1	VLFa	11	68.75
SD2	VLFa	11	68.75
SDRR	VLFa	11	68.75
S	VLFa	11	68.75

Table 9.2: Best performing doubles of parameters

Last part of classification was constructing triplets of parameters. There was significantly lesser number of mutually non-correlating parameters to do so. In this part we did not relax the correlation condition further and left it on 0.4 to ensure the parameters provide more objective take. Combinations of triplets and their success rate is displayed in table 9.3.

Parameter 1	Parameter 2	Parameter 3	Correctly classified	Percentage [%]
S	VLFp	pRR10	13	81.25
S	VLFa	pRR10	11	68.75

Table 9.3: Best performing doubles of parameters

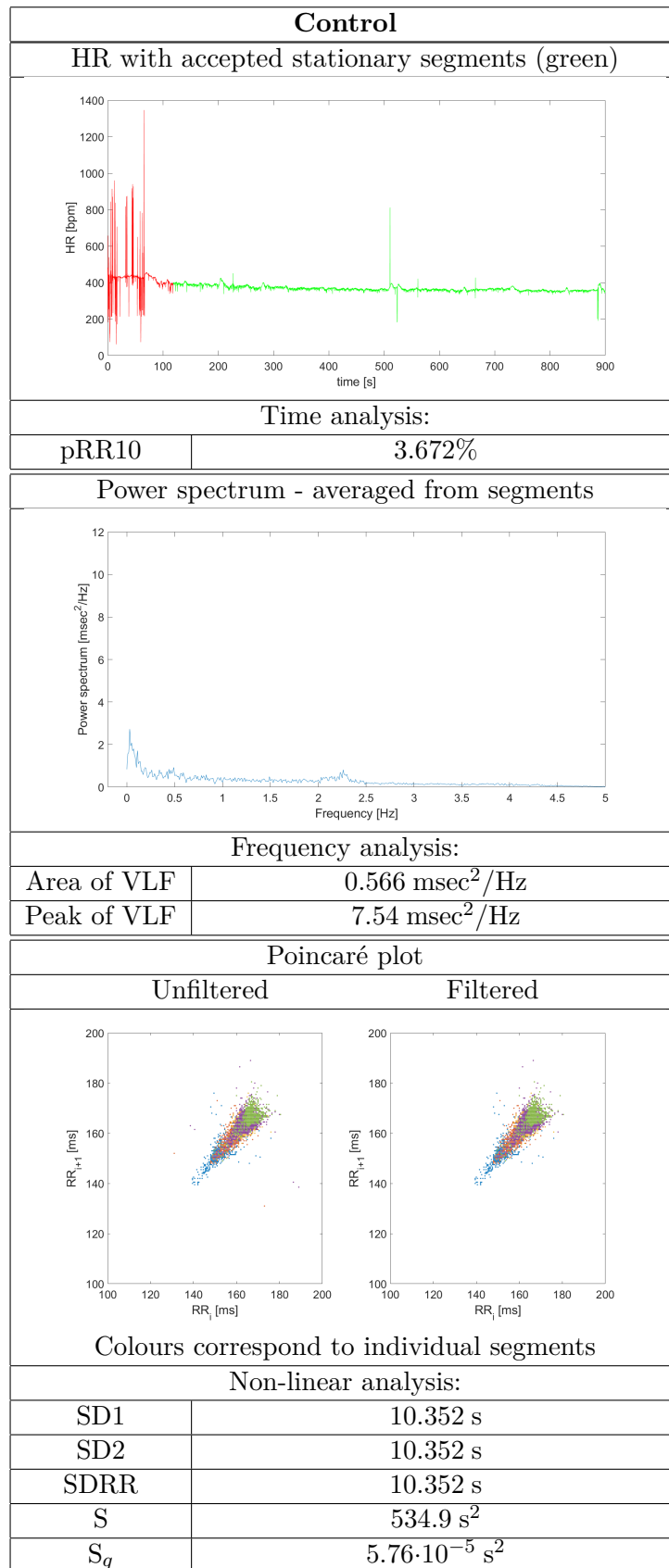


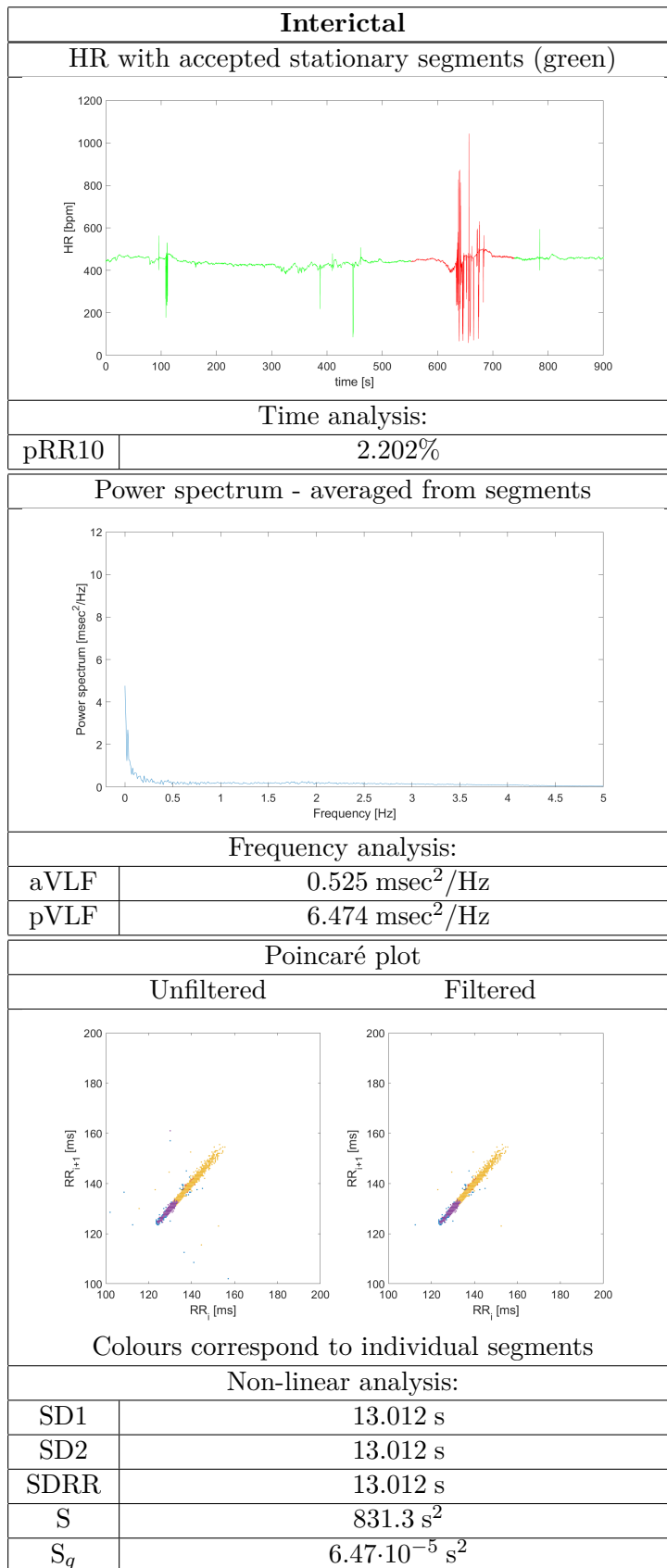
Chapter 10

HRV analyses and parameter values

In this chapter, we present two sided table with mean values of control signals and interictal signals. Additionally, pictures with HR, frequency power spectrum and Poincaré plot (both unfiltered and filtered) of one randomly chosen control signal and one interictal signal are provided for better understanding of those analyses.

These values were derived from provided data set and each number shown corresponds to averaged value of parameter extracted from 8 signals. If values presented in the protocol are extracted from larger data sets, they could prove as great indicator values for future HRV analyses.







Part V

Discussion and conclusion



Chapter 11

Discussion

The proposed HRV parameters were supposed to form classifier using as much of them as possible while maintaining their correlation at lowest. The parameters were evaluated individually at first and correlation was calculated. Then classifiers of individual parameters, pairs and triplets of them were formed and signal classification was performed.

Nine of thirteen proposed parameters showed good results in classifying. VLF parameters appeared as substantial markers from which meaningful classifications could be derived individually. Parameters from Poincaré plot (SD1, SD2, S, SDRR, S_q) and pRR10 in combination with VLF area of power spectrum proved as successful classifiers. As most noteworthy combination of two parameters seemed pair of S_q and VLF area, achieving above 80% classification success rate. From triplets only the combination of S, VLF peak and pRR10 achieved success rate above 80%.

As the most notable parameters seemed both VLF parameters and pRR10. VLF parameters were present in all classifiers achieving notable success rate. The second parameter, pRR10 also showed good performance in classification, but most interestingly, its value was defined only with suspicion that rat HR is approximately 5 times faster than human HR so its performance is rather surprising. Additionally, with optimization of pRRi parameter, far better results could probably be reached.

It is debatable why the 81.25% success rate of classification (13 out of 16 signals classified correctly) did not increase with increasing the number of combined parameters, but the most probable reason is usage of small data set for training or errors in algorithm.

One of these errors could be segmentation of signals in R peak labeling. In segments where amplitude changes, algorithm can still omit labeling of few R peaks due to higher threshold. This error could probably be fixed with overlapping segments and extracting only unique RT. Another problem which could bring in systematic error can be suboptimal chose of window length of used BACD signal. BACD and MA filter window lengths were chosen based on desired length of extracted stationary segments but this does not necessarily need to be the best solution. These problems possibly carrying systematic error into classifying show that the classification itself does not have to be entirely correct.

On the other hand, the systematic errors do not change the importance of derived parameters of HRV pointing to epilepsy severity. Parameters presented in protocol in fourth part of thesis show clear difference between control and interictal signal markers, or rather their mean values. Those presented mean values can be adjusted and optimized with larger data sets of signals with less measuring errors or with use of manual labeling. This would lead to standardizing and further analysis of this set of parameters.

The fact that parameters which are able to quantify signals exist, proves that HRV analyses are valuable in signal processing related with epilepsy. This holds true basically for any type of analysis, whether in time, frequency or non-linear domain. Another thing that increases the effectiveness of quantification of epilepsy severity is combining the analyses from different domains.



Chapter 12

Conclusion

The focal point of this thesis were analyses of animal models of epilepsy from ECG. The analyses focused specifically on HRV parameters. The goal was to decide whether there exist parameters which could point to pathology related with epilepsy.

First part of thesis presents overview of HRV parameters with their relation to some pathological states of heart. All three domains - time, frequency and non-linear - have their parameters discussed. Features of signals from used data set and difference between human and animal model in frequency area is also pointed out in this part.

Second part gives brief introduction into problematics of epilepsy and SUDEP. In this part, there is also discussed which parameters could point to quantification of epilepsy severity and basic idea of how to evaluate the quantification.

In the third part, description of the used algorithms is provided. First implemented algorithm is R peak finding algorithm with adjustments made due to signal measurement errors, it takes in ECG signal as input and outputs HR. The second algorithm used is BACD, decomposing HR signals into stationary parts without outliers.

Fourth part describes classification in detail and presents achieved success rates of classifiers with parameters of low correlation and success rates exceeding 65%. Most successful classifiers achieved success rate over 80%.



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Appendices

Appendix A

Code of classifier

All functions are contained in attached file functions.zip.

A.1 Full script

Function FULL_SCRIPT.m performs classification of 32 given signals on provided settings.

Setting	Function
f0	Highpass cutoff frequency
fz	Lowpass cutoff frequency
seg_length	Length of segments in segmentation
q1, q2	Quotient filter parameters
xx	Length of RRi parameter
dec	Decimation coefficient
type	Type of interpolation
MA_coef	MA filter window length
WD_length	BACD window length
VLF, LF, HF	Frequency bands

Table A.1: Settings of classifier

A.2 Description of attached functions

Functions described in table A.2 were implemented. They are run by FULL_SCRIPT.m to perform filtration, R peak labeling, HR interpolation, segmentation and data extraction. Functions shown in table A.3 were not implemented but only used in classifier.

Function	Use
func_load_signal	Load of signal from .mat file or .smrx file
func_highpass_filt	Butterworth highpass filtering
func_lowpass_filt	Butterworth lowpass filtering
func_rpeaks_algo	Adjusted R peak finding algorithm
func_rpeaks	Actual R peak labeling
func_ema_filt	Finding of MA filtered energetic change
func_MA_filt	MA filter
func_hrv	Interpolating RR intervals into HR
func_stationary	Finding stationary segments with use of BACD
func_stationary_analysis	Extracting parameters from stationary segments
func_static_params	Analysing time domain
func_poincare	Analysing non-linear domain
func_classify_uncovered	Classifying blind signals based on euclidean distance

Table A.2: Implemented functions, format .m

Function	Use
bscd	Bayesian changepoint detection
blcd	MAP changepoint detection
vzdal	Euclidean distance function
loadSmrxV3	Load of .smrx format signal

Table A.3: Not implemented used functions, format .m

Appendix B

Signals

All signal files are contained in files `signals_part1.rar`, `signals_part2.rar`, `signals_part3.rar` and `signals_part4.rar`.

Table B.1 gives information about signals used in this thesis. Labels of signals from `table_all_files_together.mat` are provided in B.2, labels: control - c, interictal - i, blind - ?.

File name	Signal type
<code>control.smr</code>	1 control
<code>interictal.mat</code>	1 interictal
<code>table_all_files_together.mat</code>	6 control, 6 interictal, 16 blind

Table B.1: Description of signals

Signal no.	Type	Signal no.	Type
1	?	16	?
2	i	17	?
3	i	18	?
4	i	19	?
5	?	20	i
6	c	21	?
7	?	22	i
8	c	23	?
9	c	24	c
10	?	25	?
11	?	26	?
12	?	27	?
13	i	28	i
14	c	29	c
15	?	30	c

Table B.2: Labels of table_all_files_together.mat



Appendix C

Measured values of all parameters

Provided tables show all measured parameters of signals. Signal id corresponds to their order in file `table_all_files_together.mat` (number) or whether they are from `control.mat` (c) or `interictal.mat` (i).

Signal id	RMSSD	pRR10
c	0,01097	0,054691
6	0,00707	0,010126
8	0,005838	0,005262
9	0,022011	0,090404
14	0,005819	0,010367
24	0,010907	0,03691
29	0,013259	0,049807
30	0,027297	0,036199

Table C.1: Time parameters of control signals

Signal id	aVLF	aLF	aHF	pVLF	pLF	pHF	aLF/aHF
c	0,394605	0,745694	1,673046	5,579513	2,791911	2,7011	0,44588
6	0,256452	0,519338	1,483054	3,907372	1,753514	1,559091	0,429222
8	0,193864	0,308099	0,743329	3,007916	1,050112	1,008689	0,380732
9	0,992617	1,676729	4,19981	13,47697	6,515142	5,858272	0,410877
14	0,242273	0,296764	0,594008	2,998545	1,242912	1,365525	0,497063
24	0,487919	0,530646	1,439018	7,506627	2,391873	1,907466	0,451424
29	0,613025	1,116552	2,141383	8,743319	4,212381	3,021125	0,580349
30	1,343659	2,309284	6,103718	15,102	8,041194	9,546166	0,37834

Table C.2: Frequency parameters of control signals

Signal id	SD1	SD2	SDRR	S	SD1 _q	SD2 _q	SDRR _q	S _q
c	9,572182	9,57291	9,5726	603,9848	0,002959	0,006453	0,00505	6,13E-05
6	11,67515	11,67552	11,67537	590,8127	0,000979	0,00402	0,002947	1,23E-05
8	7,33688	7,336956	7,336919	286,1278	0,000732	0,003126	0,002287	7,49E-06
9	6,775024	6,776753	6,775996	345,2187	0,002954	0,010599	0,0078	0,000118
14	8,462801	8,46269	8,462746	294,4389	0,002401	0,004647	0,003709	3,51E-05
24	8,249777	8,249532	8,249655	285,2402	0,002909	0,01079	0,007912	9,88E-05
29	9,518458	9,521108	9,519955	457,8987	0,002933	0,010147	0,007531	8,81E-05
30	21,2249	21,22396	21,22443	1415,214	0,001407	0,009048	0,006475	4E-05

Table C.3: Non-linear parameters of control signals

Signal id	RMSSD	pRR10
i	0,046975	0,074181
2	0,019965	0,020368
3	0,010062	0,021181
4	0,046451	0,030218
13	0,011745	0,030886
20	0,007973	0,005195
22	0,003229	0,007143
28	0,029731	0,101836

Table C.4: Time parameters of interictal signals

Signal id	aVLF	aLF	aHF	pVLF	pLF	pHF	aLF/aHF
i	1,192137	2,892459	2,613914	12,4923	9,837978	5,80546	1,074366
2	0,397896	0,7196	1,167765	6,532328	2,485255	1,944516	0,732354
3	0,32829	0,879152	2,275139	3,930213	3,018811	2,997956	0,41621
4	0,995165	1,903374	2,617756	10,67321	7,425744	3,915898	0,801989
13	0,251082	0,508618	1,254768	3,574518	2,153402	1,363739	0,444405
20	0,138635	0,123582	0,328681	3,073849	0,623829	0,424052	0,409352
22	0,201419	0,139915	0,226168	3,140478	0,839238	0,453206	0,618635
28	0,694359	1,365267	1,711896	8,372787	4,557996	2,809914	0,685599

Table C.5: Frequency parameters of interictal signals

Signal id	SD1	SD2	SDRR	S	SD1 _q	SD2 _q	SDRR _q	S _q
i	14,98576	14,98883	14,98755	1410,193	0,003255	0,008371	0,006383	8,47E-05
2	8,347821	8,348759	8,348391	306,9202	0,00248	0,00781	0,005829	6,09E-05
3	20,9887	20,98899	20,98885	2028,823	0,001859	0,004698	0,003607	2,82E-05
4	9,174155	9,175955	9,175215	380,7626	0,002343	0,010061	0,007308	7,9E-05
13	12,78616	12,78619	12,78618	519,2727	0,003099	0,004802	0,004045	4,75E-05
20	6,357014	6,357245	6,357132	216,8391	0,000603	0,004046	0,002899	8,67E-06
22	17,87937	17,87929	17,87933	1004,274	0,002286	0,008583	0,00628	6,16E-05
28	13,57431	13,57378	13,57405	783,3496	0,004084	0,011495	0,008693	0,000147

Table C.6: Non-linear parameters of interictal signals

Signal id	RMSSD	pRR10
1	0,006921	0,01494
5	0,013874	0,01937
7	0,004761	0,007419
10	0,02482	0,079404
11	0,013683	0,068763
12	0,012397	0,122063
15	0,015506	0,368272
16	0,010908	0,01158
17	0,008854	0,016179
18	0,035259	0,824376
19	0,007879	0,007385
21	0,002375	0,001406
23	0,03138	0,047127
25	0,015325	0,059619
26	0,004005	0,00956
27	0,012939	0,035081

Table C.7: Time parameters of blind signals

Signal id	aVLF	aLF	aHF	pVLF	pLF	pHF	aLF/aHF
1	0,274991	0,615775	1,0482	4,215382	2,553819	1,461652	0,672967
5	0,420557	0,849115	1,558163	9,759481	2,551733	1,928399	0,550608
7	0,411553	0,437207	1,155529	7,919935	1,552482	1,184848	0,464943
10	0,597353	1,009731	2,410245	10,57087	4,183616	3,740855	0,423528
11	0,855809	1,952554	5,918767	9,052054	8,858804	7,912805	0,330827
12	0,48212	0,685826	1,625566	7,905182	2,512949	2,194177	0,435201
15	0,32984	0,609315	2,833936	3,890022	2,131566	6,855084	0,282135
16	0,282607	0,518489	0,507613	3,167926	1,900136	1,088424	0,858113
17	0,283292	0,58458	0,705892	4,400344	1,896589	1,253486	0,729793
18	0,373641	0,94529	2,788423	3,492393	3,30657	6,282046	0,340044
19	0,54327	0,763095	1,669284	8,972371	2,877865	1,874508	0,500496
21	0,260174	0,151811	0,236485	5,112545	0,809783	0,386212	0,641948
23	0,576092	1,074375	3,039393	7,390163	4,749911	4,382708	0,34961
25	0,544319	0,709164	1,177181	8,241821	3,027214	1,694126	0,591686
26	0,089938	0,172061	0,385659	1,712497	0,734979	1,013994	0,434692
27	0,563373	0,887803	1,213191	7,838249	3,024014	1,478141	0,686563

Table C.8: Frequency parameters of blind signals

Signal id	SD1	SD2	SDRR	S	SD1 _q	SD2 _q	SDRR _q	S _q
1	15,79986	15,79969	15,79977	970,1821	0,002335	0,005992	0,004566	4,39E-05
5	6,953283	6,954917	6,95424	278,63	0,001061	0,005598	0,004087	1,63E-05
7	10,6473	10,64739	10,64735	566,7597	0,000914	0,005692	0,00409	2,02E-05
10	11,416	11,41585	11,41592	511,6946	0,003103	0,009337	0,006979	9,58E-05
11	14,10878	14,10893	14,10886	688,7127	0,002885	0,005642	0,004486	5,92E-05
12	12,46321	12,46457	12,46392	737,668	0,004088	0,009194	0,007144	0,000146
15	27,24818	27,24975	27,249	4664,024	0,008723	0,007956	0,008667	0,000241
16	10,48424	10,48593	10,48518	481,0453	0,002261	0,006037	0,00456	4,33E-05
17	16,11997	16,11973	16,11985	974,5464	0,00275	0,008918	0,006645	7,67E-05
18	16,36451	16,36388	16,36419	887,6001	0,016023	0,00956	0,013251	0,000476
19	9,763154	9,763921	9,763559	552,2727	0,000871	0,005363	0,003853	1,63E-05
21	20,28582	20,28558	20,2857	1292,796	0,001681	0,007536	0,00546	3,98E-05
23	7,823128	7,82323	7,823179	369,6792	0,001907	0,007304	0,005372	4,37E-05
25	7,74304	7,743331	7,743212	319,0743	0,003452	0,009391	0,007105	0,000105
26	11,54202	11,54187	11,54195	473,109	0,002596	0,004742	0,00383	3,9E-05
27	4,556794	4,559542	4,558503	91,58598	0,002681	0,009562	0,00707	8,05E-05

Table C.9: Non-linear parameters of blind signals