Tool for bio-signal analysis - Application to multichannel single trial estimation of evoked potentials

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In this thesis the term bio-signal is used for time varying quantities measured from the human body. The various bio-signals are one of the main tools for examining of human physiology and health. For instance, heart-rate variability is a widely used quantitative marker of autonomic nervous system activity.

Event-related potentials (ERPs) are one of the bio-signals. ERPs are used for studying brain activity associated with higher mental functions. They are short transient type waveforms caused by the electrical activity of the central nervous system as a response to a cognitively meaningful stimulation of the sensory system. It has been shown that ERPs depend on internal factors related to the cognitive state of the studied person. This kind of internal factors are, e.g., level of motivation, tiredness, or habituation.

Some of the most commonly used bio-signals and their analysis are described in this work. Especially event-related potentials and their single trial analysis has been in the focus. A software package for bio-signal analysis is also introduced.

Two subspace regularization based methods for single trial estimation ERPs are described and their performance is compared using both simulated and real data. The first method is based on the single-channel data. The second method is an extension of the first one to take spatial correlation of multiple measurement channels into account in the estimation. The comparison shows that both estimation methods give meaningful estimates. Peak amplitude and latency estimates are comparable to the results of traditional averaging of the time locked responses. The main difference between the methods is in the ability to estimate amplitude differences between different measurement channels. The multichannel data based method gives much better estimates.

A Matlab-based software for single trial analysis of ERPs developed in this work is part of the larger software package for bio-signal analysis developed at the Department of Applied Physics at University of Kuopio. Matlab is a mathematical programming language which allows easy implementation of the described methods using matrix notation, and easy creation of graphical user interfaces. Both single-channel and multichannel method were implemented in the software together with the traditional averaging of the time locked ERPs. In addition to the estimation algorithms, the software for ERP analysis consists tools for reading NeuroScan data files, an application for splitting continuous EEG data to stimulus locked epochs, and an application for inspecting the results of the estimation process.
Acknowledgments

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Introduction

Electrical activity of the human body and the brain opens a window for observing the human health. These electrical signals, so-called bio-signals, originate mainly from the activity of the muscles and various nervous systems. Typical examples of the bio-signals are the electrical activity of the heart (electrocardiogram; ECG) and the electrical activity of the brain (electroencephalography; EEG). Both have an important role in research and medical treatment.

Brain electrical activity caused by physical stimulation of sensory system is referred as an evoked potential (EP) or an event related potential (ERP) [33]. The term ERP is used to emphasize the event related nature of the potential since evoked potentials are sometimes emitted also without any clear physical stimulus. ERPs originate from the psychological reaction to the stimulus, and they are not related with the physical properties of the stimulus. The term event related potential (ERP) is used commonly in this work, even if sometimes the evoked potential might have been more accurate.

Classical example of ERP measurement is the P300 paradigm. In this test the subject hears two tones. One of the tones can be neglected but when person hears the more rarely presented “target” tone, a button must be pressed. This target tone evokes a brain response called as P300 peak. The actual origin of the P300 is still unclear. It is suggested to be related to the end of the cognitive processing, to memory updating after information evaluation or to information transfer to consciousness [42]. Thus this response is not due to actual hearing of the sound, nor is the response related to moving a finger when person presses the button. The P300 response can be recorded also with visual or somatosensory stimulation. The real data used in this work is from the P300 experiment. However, the presented methods are not in any sense restricted to this specific brain potential; instead they can be easily applied for analysis of other ERPs as well. As an example the used simulated data does not exactly imitate the properties of the P300 peak.

The basic problem in the ERP analysis is to separate actual response from background EEG caused by other on-going brain activity. Signal-to-noise ratio (SNR) is very low for many of the ERPs. Traditional approach to compensate low SNR is to repeat stimuli many times and average the time-locked responses. This is the most efficient way to increase SNR. The problem with averaging is that all information about the possible changes in the responses during the test is lost. One way to study these changes in the responses is to repeat the whole measurement for a group of people. Then responses in different phases of the test can be averaged over this group. However, as the person to person variations in the responses are typically large and the properties of the responses might be related to person’s age, sex, handedness etc. [45] the results are hard to interpret. Nevertheless, with group studies it has been shown that for example P300 response may change during the test and that these changes can give information about the mental state of the test person, for example, the habituation of the response or the level of attention [27].

This work includes two parts: The first part describes the subspace regularization based analysis method and its extension from single channel to multi-channel data. The second part of the work presents the development Matlab\textsuperscript{TM} based software for analysis of different bio-signals.
The first part of the work studies the subspace regularization based analysis method described in [26]. The method is extended to take into account the additional information included in multi-channel measurements in form of spatial correlation of the channels. The extension is based on the principle presented in [24]. These two approaches are then compared using both simulated data and real measurement data from P300 experiment. Both methods are capable to estimate latency and amplitude of the P300 peaks on single-channel data reliably. However, multichannel method appears to give amplitude estimates which are more comparable between different measurement channels. Thus in case when amplitude ratios between channels are in focus the multichannel method is preferable.

The second part of the work was the development of Matlab-based software for the analysis of bio-signals. Especially the tools for the single trial analysis of ERPs are discussed. The Matlab is a programming language well suited for mathematical programming. It offers very powerful syntax for matrix algebra and is thus an efficient environment for rapid testing and implementing of different algorithms. In addition, Matlab can be used to build graphical user interfaces. Main limitations of Matlab are limited performance in some situations and inefficient memory handling in some cases.
The bio-signals, covered by the developed Matlab\textsuperscript{TM} based software package, and their commonly used analysis methods are described in this chapter.

2.1 Galvanic skin response (GSR)

The galvanic skin response (GSR) can be used for capturing the autonomic nerve response. Due to relative simplicity of measurement, and a quite good repeatability GSR can be considered to be useful and simple method for examining autonomic nervous system function, specifically the peripheral sympathetic system [18].

Physically GSR is a change in the electrical properties of the skin in response to different kinds of stimuli. In GSR measurements changes in the voltage measured from the surface of the skin are recorded. The main origin of the signal has suggested to be the activation of the sweat glands [18]. Any stimulus capable of an arousing effect can evoke the GSR. The amplitude of the response is more dependent on the surprise effect of the stimulus than on the physical stimulus strength. The most commonly used stimuli to elicit GSR are an electrical shock delivered to a peripheral nerve or auditory stimuli.

GSR is also known as, or closely related to, the sympathetic skin response (SSR) and skin conductance response (SCR). In clinical neurophysiological literature, the response is known also as the peripheral autonomic surface potential (PASP). Most of the GSR studies in last decades are concerned with the normal values of response amplitude and latency, for example [2, 58, 11, 10, 1, 23, 57, 7]. In [11] an auditory stimulus was delivered to both ears and a mean amplitude of $(2.8 \pm 1.2)$ mV measured from the palm was observed. Observed latency measured from the palm to auditory stimulus was $(1.50 \pm 0.09)$ seconds in [11] and $(1.49 \pm 0.17)$ seconds in [58]. Also the habituation of response amplitudes during repeated stimulations has been studied in [11, 1, 57]. Response amplitudes vary substantially, depending on the experimental conditions.

Typical GSR waveshapes have been studied e.g. in [1, 57]. Fig. 2.1 shows a set of typical GSR responses for a healthy person and for a person suffering from psychosis. Normal wave shape is usually biphasic or triphasic and lasts several seconds. Because GSRs are such long lasting waveforms inter-stimulus interval (ISI) should be sufficiently long. When using short ISIs response overlapping should be considered by decomposing the overlapped responses. Such a decomposition for SCRs is presented in [30].

Within-subject GSRs amplitudes habituate, latencies may increase slightly but waveshapes remain fairly unaltered in repetitions, as can be seen in Fig. 2.1. The decrease in amplitudes and increase in latencies is affected by the weakening of the surprise effect of stimulation and by the weakening of alertness of the subject during the experiment [57].

In recordings a low pass filter can be used to avoid high frequency noise. As the signal-to-noise ratio (SNR) of the GSR signal is high, individual responses are usually studied without any signal
processing. In some studies, several responses are averaged but this can lead false interpretation due to variability of the response. Thus, it is generally suggested that averaging should not be used [2, 11].

<table>
<thead>
<tr>
<th>Classification</th>
<th>$\Omega_1$</th>
<th>$\Omega_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (+)</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Patients (o)</td>
<td>0</td>
<td>13</td>
</tr>
</tbody>
</table>

Figure 2.2: Clustering of healthy controls (+) and psychotic patients (o). The x-axis is the sum of the two largest eigenvalues ($\lambda_1 + \lambda_2$) of data correlation matrix, the y-axis is the sum of the eigenvalues $\lambda_4$, $\lambda_5$ and $\lambda_6$. The figure is presented in [54].

2.1.1 Principal component analysis for GSR

An advanced method for analyzing the patterning of successive galvanic skin responses is presented in [54]. The method is based on principal component analysis (PCA) in which the stochastic sample is presented as a weighted sum of orthogonal basis vectors. The method was then tested using measurements from 20 healthy controls and 13 psychotic patients. As seen in Fig. 2.1 responses between healthy and psychotic persons differ remarkably. For most of the healthy controls there
is a clear pattern in reproduced GSRs, whereas within psychotic patients the lack of time-locking of GSRs seemed to be characteristic. In [54] the two groups of test persons could be separated by clustering algorithm based on the largest eigenvalues of the data correlation matrix, Fig. 2.2.

Promisingly all patients could be ranked correctly, giving the described method sensitivity of 100%. It is possible that in future this kind of GSR based methods may offer a new and potential tool for screening risk groups and populations in evaluating drug effects by revealing also the early and subtle alternations [59]. However, some normal subjects were found to have “psychotic” GSRs as well (Fig. 2.2).

2.2 Heart Rate Variability (HRV)

The oscillation in the interval between consecutive heart-beats (RR intervals) as well as between the consecutive instantaneous heart rates is called heart rate variability (HRV) [55]. This phenomenon is a result of continuous alternation of the autonomic neural regulation of the heart i.e. the variation of the balance between sympathetic and parasympathetic neural activity. The increase of sympathetic tone or decrease of parasympathetic activity will increase heart rate. Thus HRV can be used as quantitative marker of autonomic nervous system activity. However it should be noted that although the autonomic nervous system may play a major role in neural regulation of cardiovascular system, also other endocrine and behavioral responses arising from central nervous system contribute to the regulation.

HRV is used in wide range of clinical applications. Various cardiac diseases affect heart rate variation and it is generally accepted that HRV is a strong and independent predictor of mortality after an acute myocardial infarction [55, 56].

2.2.1 Analysis methods for HRV

The base of the HRV analysis is the electrocardiography (ECG) from which the QRS complexes are determined, see Fig. 2.3. The time elapsing between consecutive heart-beats is defined as the time between two P waves. However usually the QRS complex is detected at the R wave and the RR time series is used in the HRV analysis. Because the R wave has a better signal-to-noise ratio than the P wave, it can be more easily and reliably detected. As the time interval between P and R deflections is constant, the R waves can be used reliably for recognition of QRS complexes. Sometimes the term normal-to-normal (NN) is used instead of RR to emphasize that the intervals are between adjacent QRS complexes resulting from normal sinus node depolarization and not e.g. from some malfunction in the conduction system of the heart.

Both time and frequency domain methods are used in HRV analysis. The usual time domain variables are the mean RR interval, the standard deviation of the RR intervals, the mean heart rate, and the difference between the longest and shortest RR interval [55, 3]. As the standard deviation correlates to the measurement length, the standard deviation of the average RR intervals calculated over a given time period (SDANN) can be used. Time period for calculating standard deviation is usually 5 minutes.
The other commonly used statistical variables are the square root of the mean squared differences of successive RR intervals (RMSSD), the number of interval differences of successive RR intervals greater than 50 ms (NN50), and the percentage value of NN50 over all RR intervals (pNN50). These three variables estimate the short term components i.e. high frequency variations in heart rate and are highly correlated. From these variables the RMSSD is recommended to be used [55] due to its better statistical properties.

In addition to statistical measures, some geometric variables are sometimes analyzed. These are based on the analysis of the properties of the RR distribution histogram. The length of the histogram bins is usually approximately 8 ms. The HRV triangular index is defined as proportion of the integral of the density distribution to the maximum of the density distribution. In practice this is calculated by dividing the total number of RR intervals with the number of RR intervals in the distribution modal bin. The triangular interpolation of RR interval histogram (TINN) is the baseline width of the distribution measured as a base of a triangle approximating the RR interval distribution. The triangle is fitted to the distribution in the sense of minimum square difference. Details of the practical calculation of the TINN are presented in [55]. The advantage of the geometrical variables is their relative insensitivity to the analytical quality of the series of RR intervals. However major disadvantage is that for the reliable construction of the geometric pattern duration of the ECG recording must be at least 20 minutes but 24 hours is more preferably. This makes the geometric methods unsuitable for short recordings.

The frequency domain analysis methods are based on the estimation of the power spectrum density (PSD) of the RR signal. The PSD estimation methods used can be divided to the parametric, e.g. autoregressive (AR)-model, and nonparametric, e.g. Welch periodogram, methods. The nonparametric methods are in generally faster to compute but on the other hand the parametric methods will produce smoother spectral components and allow accurate PSD estimation with smaller number of samples. Power spectrum estimates for a short RR series calculated with Welch periodogram and AR-model of order 12 are shown in Fig. 2.4.

The estimated PSD is divided spectral components, whose power is then compared. The division depends on the duration of the measurement. For the short measurements from 2 to 5 minutes the usual division is: very low frequency (VLF) ≤ 0.04 Hz, low frequency (LF) 0.04-0.15 Hz and high frequency (HF) 0.15-0.4 Hz, [56]. However the physiological background of VLF component in short measurements is not defined and it is probably usually caused by the baseline distortions in the measurements [55]. In the longer measurements the VLF component is caused by thermoregulation. The LF component is mainly due to the systems regulating blood pressure and reflects the sympathetic tone in heart regulation. The HF component reflects the parasympathetic tone and is also related to the frequency of respiration. The ratio LF/HF describes the balance between sympathetic and parasympathetic neural activity. For long measurements, 24-hour period, ultra low frequency (ULF) component, ≤ 0.003 Hz, is sometimes derived from VLF.

Usually the QRS detection algorithm produces irregular sampled RR series i.e. the gap between individual samples is $R_i$. For the frequency domain analysis of HRV this discrete event series has to be re-sampled to form an evenly spaced time series. This is especially important for nonparametric methods to avoid distortion and spurious harmonics in the spectrum. The regularly sampled interpolation of RR series is suitable also for the parametric methods and thus the re-sampling can be suggested to be standard procedure [55].

The implicit requirement in both time and frequency domain methods is that the signal is at least weakly stationary. However HRV signal is usually nonstationary, containing slow linear or more complex trends. The origins of these phenomenon are discussed e.g. on [3]. To avoid distortion in analysis, spurious low frequency components or biased time domain variables, the slow nonstationary trends must be removed from the HRV signal before analysis. Smoothness priors based trend removal algorithm for HRV signal is proposed in [54].
2.3 Quantitative EEG (qEEG)

Properties of EEG are traditionally analyzed visually. In quantitative EEG some measures are used to describe the EEG. Thus the term qEEG covers wide range of different methods. Most commonly the measures are based on spectral properties of the measured signal. In these thesis and in developed software we are focused to the frequency domain measures of EEG.

The qEEG has sometimes been used in analysis of slow evoked potentials, but usually the analysis is applied to spontaneous EEG in resting conditions. Other commonly used measurement is difference between two tasks e.g. resting vs. summing of numbers or eyes open vs. eyes closed. For example when the eyes are closed the power in the 10Hz range increases in occipital brain areas compared with eyes open situation, (Figure 2.5).

The frequency range analyzed in the quantitative EEG is usually 0-30 Hz [43]. Classically frequency spectrum has been divided to following bands: 0-4 Hz (delta), 5-7 Hz (theta), 8-13 Hz (alpha) and ≥ 14 Hz (beta) [38]. However these divisions are not always followed in quantitative EEG techniques. Theta band is commonly concerned to be 4-8 Hz activity. It is also common to consider that beta activity begins at 12 Hz instead of 14 Hz. These changes allow adjacent bands of 4 Hz intervals (e.g. 0-4 Hz, 4-8 Hz, 8-12 Hz, etc.). Moreover beta band is often broken into subcomponents, beta-I 12-16 Hz and beta-II from 16 Hz up to 30 or 20 Hz. Band 20-30 Hz is also called beta-III. Other frequency bands are also sometimes broken to their subcomponents for example alpha-I (8-10 Hz) and alpha-II (10-12 Hz) [38]. Anyhow there is no definite division of the human EEG frequency range and used frequency boundaries vary in the literature.
Figure 2.5: Quantitative EEG analysis. On the top are two data samples for eyes open and for eyes closed situations. Total four data samples for each case has been in calculations of results, shown below the data. Power spectrums are divided to following frequency bands: $0.5-4$, $4-7$, $7-13$, $13-20$ and $20-30$. From power spectrums it can be seen how power of the frequency band increases when eyes are closed.

The common approach in frequency based analysis is to select artifact free samples of length 4-8 seconds, calculate PSD estimates for each sample and then average the PSD estimates. The EEG can be assumed to be at least weakly stationary in such short samples though some baseline correction may be needed. Other methods have to be used for the continuous analysis, e.g. for the sleep staging [20, 47].

The absolute amplitude and power values in the different frequency bands vary between subjects. Relative power, the amount of EEG activity in a frequency band divided by the amount in all bands [43] can be used to overcome this problem. However, absolute power measures are needed for interpretation of variations in a frequency band. The mean frequency based either amplitude or power spectrum, and maximum frequency i.e. the frequency of the largest power peak can also be calculated. In resting condition, more than 50% of the total power should be alpha, both theta and delta band should be less than 15% and the mean frequency should be over 8 Hz [41]. Difference of two or more properties indicates brain dysfunction.

The clinical aspects of quantitative EEG are reviewed in great detail in [39].
2.4 Event Related Potentials (ERPs)

Originally evoked potentials (EP) were defined to be potentials caused by the electrical activity of central nervous system after a simulation of the sensory system. It was believed that the potentials reflected the brain activity that was strictly ‘evoked’ by the representation of the stimulus. However, some potentials reflect more than just evoked activity, thus the more neutral term event-related potentials (ERP) is used [6].

Event related potentials (ERPs) have been widely used for studying brain activity associated with higher mental functions. At the current stage, despite long research, ERPs are still mostly used for research purposes.

ERPs and especially positive and negative peaks in the responses are named according to their electrical sign, N for negative potentials and P for positive, and the time of appearance. For example N100 indicates a negative peak around 100 ms after stimulus. Furthermore, some potentials are bound with some specific test settings. As number of electrodes with which the potentials are measured is increasing it has been proposed that also scalp distribution of the evoked response should be taken into account when specific names are given to potentials [52].

One of the most investigated potential is the P300, which is a positive potential with its maximum at midline parietal or midline central sites of the head at a latency of about 300 milliseconds from the stimulus. The P300 is elicited by randomly presented informative task-related targets among frequent standard stimuli (the so called odd-ball paradigm). The distribution of the potential is relatively unaffected by physical stimulus properties, such as modality or intensity, if they do not provide task-relevant information. The amplitude of P300 is inversely proportional to the probability of occurrence of stimuli that have different meanings in the context of the task [16, 42]. Typical P300 response is shown in Figure 2.6.

The P300 has been correlated with many psychophysiological variables in [45]. The possibilities to use of the P300 as clinical assay has been reviewed in [42, 44]. Since the cerebral origin and the exact role of the P300 in cognitive processing are uncertain the clinical usefulness of the P300 is limited. The amplitude of the P300 peak might be useful in tracking of mental work load [27]. Abnormally delayed P300 wave may indicate cognitive dysfunction [42].

2.4.1 Traditional analysis of ERPs

The ERPs are usually measured from the scalp. The measured potential is superposition of all electrical activity that is strong enough to be observed on the measuring electrode. Thus one of the fundamental problems in the analysis of event related potentials is to extract information about the potential from measurements that contain also on-going background EEG.

The most common method of analysis of the parameters of ERPs is take an average over time-locked single trial measurements. The implicit assumption made in the averaging is that the event-related brain signal occur at the same time after the stimulus on each trial, while the background EEG has random or no relation to the stimulus. However, it has been evident for few decades that in many cases this assumption of constant timing is not valid [21]. The assumption of the same shape and same degree of present of potentials on every trial is inaccurate as well [14]. Instead, it has become evident that the variation of the parameters of the ERPs represents the changes in the human cognitive state [15].

2.4.2 Single trial analysis of ERPs

The interest to the variation of the responses during the measurement session has been growing. Sometimes the goal in the analysis of the ERPs is in the estimation of the single trial potentials (single trial estimation).

A classical approach to denoise single trial ERPs is to form a filter which will filter out the unwanted contribution of the on-going background activity of the brain as well as possible. However,
the problem is often the very low signal-to-noise ratio.

Filtering can be thought to be an estimation problem in which the measurement is used as data in estimation of the underlying signal. Estimation can be improved if we have some additional information about the underlying signal and a way to apply this information to the estimation process. In event related potentials this additional information can be the assumed smoothness of the evoked potentials or some limits for the possible locations of the peaks in the potentials. [63] introduces a time-varying filter which includes this kind of assumptions. The implementation of the filter, however, necessitates information about the covariance of the event related potentials. This is, in fact, another estimation problem that has no easy solution.

Another, more interesting way to add temporal information to the estimation is to use the so-called regularized least squares method. As the other regularization methods it has its origin in the theory of ill-posed inverse problems [17]. The method has been introduced in [26], where it was used in the case of single-channel measurements. In [48] same method is extended for the case of multichannel measurements. In the next chapters these two methods are described in detail and compared. The main benefit of the subspace regularization method is its easy implementation for different kinds of data.

Also many other methods for estimation of single trial ERPs have been proposed in the literature. Many of these methods and their properties are described in [25]. The most popular methods are wavelet based approaches, for example [9, 13, 8, 49, 46], and independent component analysis (ICA), for example [31, 32, 22]. However, the applicability of wavelets to the analysis of single trial ERPs can be questioned [25]. They deal with temporal spectrum of the signal and that is only meaningful if the signal can be assumed to nearly stationary within the time window. Some limitations of the ICA are discussed in [22].

2.4.3 Multichannel measurements

In practice potentials measured in the recording electrodes are superposition of signals from many sources in the brain. This is due the fact that electric currents generated by sources in the brain are volume conducted through brain, cerebrospinal fluid, skull and scalp. Thus the potentials from a localized source are spread over a considerable scalp area. This is true especially for signals, such as P300, which are generated by large populations of perhaps $10^7$ to $10^9$ neurons [16, 37].

The ERP measurements are usually performed with several electrodes. This means that also
spatial information is gathered in the measurements. Obviously we should not neglect this information in the estimation of the single trial ERPs. One possible solution is to interpret the spatial correlation of the multichannel measurements in the form of additional information. This type of multichannel time varying Wiener filter is introduced in [61]. The proposed filter is optimal in the mean square sense in the class of unbiased estimators. However, the implementation of the method is quite complicated and as filter introduced in [63] it necessitates basically information that is not available prior to the estimation. Another approach to take the additional information of the spatial correlation of the channels into account is to use the regularization approach. The approach is briefly introduced in [24] and in more details in [48].

In this thesis these subspace regularization based methods are reviewed and a systematic method for single trial analysis of multi channel event-related potential measurements is described. These methods are used in developed Matlab$^\text{TM}$ toolbox. The methods are based on the regularized least squares scheme. The multichannel method uses both spatial and temporal information in the estimation.
This section describes the subspace regularization based method for estimation of single trial ERPs and derivation of relevant formulas.

The main idea in the regularization-based estimation approach is to add additional a priori information about the estimated potentials to the estimation process.

In practice this can be done by modeling the evoked potentials with some generic model. These preliminary estimates are then regularized, i.e., modified to be more optimal in the sense of the a priori information. Generic model means here a model which is capable to model different kinds of data equally and thus do not contain any specific information about the data. It however might contain some implicit assumptions about the data. For example the model we use here favours smooth responses. Common properties of the measurements are used as a priori information. A priori information is then combined with the generic model by using subspace regularization. The described method is capable to estimate different kinds of measurements.

3.1 Estimation with linear observation model

We use here linear additive noise model for the ERP measurements. This model means that the observations are thought to be of the form

\[ z_i = s_i + e_i \]  \hspace{1cm} (3.1)

We denote here the sampled potential measurement after i’th stimulus with a column vector \( z_i \). The evoked potential \( s_i \) corresponds to the part of the activity that is correlated with the stimulus. It is usually a transient waveform that consists of activity peaks of some duration. The other part of activity, the background EEG \( e_i \), is usually thought to be independent of the stimulus and the evoked potential \( s_i \). Thus the electrical activity of the brain is the source for both \( s_i \) and \( e_i \).

The evoked potential \( s_i \) can be further modeled as a linear combination of some pre-selected basis vectors \( \psi_j \). The vectors \( s_i \) can then be written in the form

\[ s_i = H \theta_i \]  \hspace{1cm} (3.2)

Where \( H \) is a matrix that contain the basis vectors \( \psi_1, \ldots, \psi_k \) in its columns and \( \theta_i \) is a length \( k \) vector of parameters. Thus the observation model is now

\[ z_i = H \theta_i + e_i \]  \hspace{1cm} (3.3)

In the modeling of the evoked potentials we then have to estimate parameters \( \theta_i \) based on the measured data \( z_i \) using some estimation criterion. One solution is to minimize the square norm of the error term \( e_i \), i.e.

\[ \hat{\theta}_i = \arg \min_{\theta_i} \left\{ \|e_i\|^2 \right\} = \arg \min_{\theta_i} \left\{ \|(z_i - H\theta_i)\|^2 \right\} \]  \hspace{1cm} (3.4)
This will lead to least squares (LS) solution. The desired norm will have its minimum value when vector \( e_i \) belongs to the orthogonal complement of \( H \), that is \( z_i - H \theta_i \in \mathcal{R}(H)^\perp \). Or more loosely speaking, when \( e_i \) is perpendicular to subspace spanned by the columns of matrix \( H \). Graphical presentation of the situation is shown in the Fig. 3.1.

![Figure 3.1: Schematic presentation of the LS solution.](image)

The condition \( z_i - H \theta_i \in \mathcal{R}(H)^\perp \) equals to

\[
H^T(z_i - H \theta_i) = 0
\]  

which is same as

\[
H^T z_i = H^T H \theta_i
\]  

Now we can write

\[
\hat{\theta}_i = (H^T H)^{-1} H^T z_i
\]  

This kind of derivation of LS solution (3.7) is, of course, only formal. We have assumed here that the null spaces of the observation matrix \( H \) and \( H^T \) are trivial, i.e. \( \mathcal{N}(H) = \mathcal{N}(H^T) = 0 \). This means that we have over-deterministic situation, i.e. we have more measurements than parameters to estimate. In practice this limits the number of columns of matrix \( H \) i.e. number basis functions to be used.

The estimated evoked potentials \( \hat{s}_i \) can then be obtained using the estimated parameters \( \hat{\theta}_i \) with equation

\[
\hat{s}_i = H \hat{\theta}_i
\]

### 3.2 Selection of the basis

With linear observation model the choice of the observation matrix \( H \) has a significant role. In the case of the ERPs, the best choice would be the true physical model which could model both temporal and spatial information in the measurements. However, that would necessitate the modeling of the sources as physical current generators as well as proper modeling the electrical properties of the head. Obviously this would not be a trivial task. In this work we use a simpler phenomenological model.

First we assume that the evoked potentials consist of positive and negative deflections. Sampled Gaussian or sigmoid functions can then be a good choice for the basis. We call this kind of basis, that do not depend on the data, a generic basis. A typical observation matrix constructed from this kind of generic basis functions is show in Fig. 3.2.

Other choices for basis functions could be e.g. Fourier basis or several possibilities of wavelet bases. It is also possible to use the \( p \) first eigenvectors of the correlation matrix of the measurements as a basis. The least squares solution with this basis is then equivalent to the so-called principal component regression approach \([5]\). However it should be noted that when e.g. wavelet bases is used some implicit assumptions of the potentials are made. It is remarkable that these assumptions are not always evidently or easily controllable. In the case of the wavelet bases this is due the
fact that the wavelet families are usually optimal for certain kind of data [4, 49]. Thus they may emphasize certain properties of the data. Problem is that these properties are more related to the selected wavelet family than actual ERP response. In the case of principal component regression selection of the number of the eigenvectors is crucial and hard task to automatize.

Both the use of generic basis vectors and the principal component regression approach have their own benefits. On one hand the generic vectors are usually robust and easy to generate. They also commonly model different intervals of the measurement vector in a homogeneous way. On the other hand the eigenvector basis is optimal for a set of measurements, although this is strictly true only for jointly Gaussian measurements. These two approaches can be combined together, as will be shown in the following sections.

3.3 Regularized least squares

As we are using linear observation model the task now is to estimate the parameters $\theta_i$ in (3.8) based on the measurements $z_i$. A common approach to solve the problem is to use least squares method. However, to be able to combine the prior information to the estimation we will use more general approach. We state the so-called generalized least squares solution for the parameters $\hat{\theta}_i$

$$\hat{\theta}_i = \arg\min_{\theta_i} \left\{ \| (z_i - H\theta_i) \| ^2 + \alpha^2 \| L\theta_i \| ^2 \right\}.$$ (3.9)

The solution of (3.9) is called the generalized Tikhonov regularized solution [19] and it is clearly a modification of the ordinary least squares solution (3.4) to the direction in which the semi norm $\| L\theta_i \|$, the so-called side constraint, gets smaller. The parameter $\alpha$ controls the weight of the side-constraint in the solution.

The so-called regularization matrix $L$ in the side constraint could be e.g. the second derivative approximation [12]. Minimization of the second derivative obviously smooths sharp spikes in the estimated vector when compared to the ordinary least squares solution. The second derivative constraint can also be used to fit a trend or base line to the signal. A trend removing method for the HRV signal based on this idea is described in [54].

The solution of (3.9) can be written in matrix form, similarly to (3.7).

$$\hat{\theta}_i = \left( H^T H + \alpha^2 L^T L \right)^{-1} H^T z_i$$ (3.10)

Figure 3.2: Example of the observation matrix $H$ in the case of the single-channel measurements. Measurement length $T$ is 125 and number of Gaussian shaped basis vectors is 20. The values of vectors range from zero to one. For the sake of the visualization in the figure is actually $H^T$ i.e the vectors shown horizontally are the columns of the matrix $H$. 

The solution of (3.9) can be written in matrix form, similarly to (3.7).
Derivation of this matrix formulation can be found, for example, in [53]. The derivation for the more general form of the equation (3.9) is also presented in Section 3.7, where it is described how to take the properties of the background EEG into account in the estimation of ERPs.

In this form the solution is easy to calculate in any computer program which use matrix notation, such as Matlab™.

**3.4 Subspace regularization method**

The eigenvectors of data correlation matrix carry information about specific properties of the data set. With the regularized least squares method this information can be combined with the use of generic basis vectors.

The idea is to use a generic shifted Gaussian basis vectors of the form

$$\psi_j = e^{-(t_j - t_j)^2/(2w^2)}, \quad j = 1, \ldots, N \tag{3.11}$$

in the columns of the observation matrix $H$. In (3.11) $w$ is relative to the width of the Gaussian hump, typical values used in this study for $w$ are 7 and 10. The latency term $t_j$ has chosen so that basis functions have their maximum values equally located in the interval $[1, T]$, where $T$ is length of ERP response $z_i$. Observation matrix is visualized in Figure 3.2.

Next we calculate the eigenvectors of the correlation matrix $R_z$ of the measurements and use first eigenvectors corresponding to the largest eigenvalues as the columns of the matrix $H_S$. The matrix $H_S$ will now contain an orthonormal basis of the subspace $S$. We want that the estimated evoked potential is close to this subspace. This can be achieved by using subspace regularization. All we have to do is to formulate appropriate side constraint.

The projection of estimate $s_i = H\theta_i$ onto subspace $S$ is $(H_S H_S^T) H \theta_i$. The distance of $s_i$ from the subspace $\mathcal{S}$ can be written in the form $\|(I - H_S H_S^T) H \theta_i\|$. Our goal is to construct such a matrix $L$ that the side constraint $\|L \theta_i\|$ in (3.9) is small for all expectable $\theta_i$. Thus we select matrix $L$ to be $(I - H_S H_S^T) H$. The term $L^T L$ in (3.10) will then be $H^T (I - H_S H_S^T) H$, since the term $(I - H_S H_S^T)$ is symmetric and idempotent [25]. A graphical interpretation of the situation is shown in Fig. 3.3.

By using this selection of $L$ the desired solution for the parameters $\theta_i$ can now be written in the form

$$\hat{\theta}_i = (H^T H + \alpha^2 H^T (I - H_S H_S^T) H)^{-1} H^T z_i \tag{3.12}$$

The estimate for the evoked potential is then

$$\hat{s}_i = H \hat{\theta}_i \tag{3.13}$$
This is called the subspace regularized solution [26]. The Bayesian aspects of the subspace regularization method are discussed in [25].

3.5 The multichannel measurements

Although the evoked potential and the background EEG are independent by definition both the activities $s_i$ and $e_i$ are highly correlated between different channels $j = 1, \ldots, M$. This spatial correlation could be taken into account in the formulation of the observation matrix $H$. However, to be accurate this task would necessitate the true physical modeling of the head as a volume conductor. The subspace regularization based method can provide us much more simpler approach.

For the multichannel measurements we use the following notation. Let $z_i^{(j)}$ denote the evoked potential for the $i$’th stimulus measured using the $j$’th channel. We concatenate the measurements in the following way.

$$z_i = \begin{pmatrix} z_i^{(1)} \\ \vdots \\ z_i^{(M)} \end{pmatrix} = \begin{pmatrix} s_i^{(1)} \\ \vdots \\ s_i^{(M)} \end{pmatrix} + \begin{pmatrix} e_i^{(1)} \\ \vdots \\ e_i^{(M)} \end{pmatrix}$$ (3.14)

The vector $z_i$ is thus a vector of length $MT$, where $M$ is the number of channels.

As in the single-channel case we use a generic Gaussian basis for each channel separately. The columns of the observation matrix $H^{(j)}$ are thus Gaussian shaped vectors. Modeling the channels separately means that the matrix $H$ is a block diagonal matrix

$$s_i = \begin{pmatrix} H^{(1)} & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & H^{(M)} \end{pmatrix} \begin{pmatrix} \theta_i^{(1)} \\ \vdots \\ \theta_i^{(M)} \end{pmatrix}$$ (3.15)

where the matrices $H^{(j)}$ are identical. Thus this model itself does not contain any dependence between the channels and does not force the potentials to be continuous on channel boundaries.
Next we form the eigen decomposition of the data correlation matrix

\[ R_z = \begin{pmatrix} R_z^{(1,1)} & \cdots & R_z^{(1,M)} \\ \vdots & \ddots & \vdots \\ R_z^{(M,1)} & \cdots & R_z^{(M,M)} \end{pmatrix} \]  

(3.16)

and use a few eigenvectors corresponding to the largest eigenvalues to form the regularization matrix \( H_S \). Typical correlation matrix of real measurement data of three channels (FZ, CZ, PZ) is shown in Fig. 3.4. In Fig. 3.5 are shown the eigenvectors of the correlation matrix corresponding the four largest eigenvalues.

Because the correlation is calculated using the concatenated measurements \( z_i \), the eigenvectors model also the correlation between the separate channels. As in the single-channel case the estimates for the evoked potentials can be obtained with the equations (3.12) and (3.8).

The subspace regularization method provides an efficient and simple approach to take the spatial correlation of the measurement channels into account in the estimation of the ERPs.

### 3.6 Choice of the regularization parameter

A common problem with all regularization based methods is that the choice of optimal value of the regularization parameter \( \alpha \) can be complicated. Several methods have been developed for the estimation of the optimal value of that parameter. The so-called GCV (Generalized Cross Validation) method [60] is one of the possibilities. The use of GCV in the selection of the regularization parameter in the single-channel approach is discussed in [26].

The estimation methods for single trial evoked potentials proposed here are quite robust to small changes of \( \alpha \). Thus we have based the selection of the regularization parameter on the experience. Typical values of \( \alpha \) range from 0.05 to 20. If the value of \( \alpha \) is too small the estimated evoked potential will be non-smooth and follow spurious peaks, caused by the background EEG, in the data closely. Too large value will force the estimation be near zero. This behavior is demonstrated in Figure 3.6 where estimates obtained with three different values of \( \alpha \) are shown together with measured data. The effect of the selection of the regularization parameter to the estimates is studied in more details with simulated data in the next chapter.
Figure 3.5: The eigenvectors corresponding the four largest eigenvalues $\lambda$ of the correlation matrix of the real measurement data in the multichannel case. The vertical lines show the channel borders.
3.7 Taking background EEG into account

If the covariance of the background EEG can be estimated, both the single-channel and multichannel approaches can then be expanded to take the background EEG into account in the estimation. The solution for parameters $\hat{\theta}$ (3.9) can be written in a more general form

$$\hat{\theta}_i = \arg \min_{\theta_i} \left\{ \| L_1 (z_i - H \theta_i) \|^2 + \alpha^2 \| L \theta_i \|^2 \right\}$$

(3.17)

which is a modification of the ordinary weighted least squares solution

$$\hat{\theta}_{LS} = \arg \min_{\theta_i} \left\{ \| L_1 (z_i - H \theta_i) \|^2 \right\}.$$  

(3.18)

First step to derive matrix form of solution of the equation (3.17) is to note that the equation can be written in form

$$\hat{\theta}_i = \arg \min_{\theta_i} \left\{ \left\| \begin{pmatrix} L_1H \\ \alpha L \end{pmatrix} \theta_i - \begin{pmatrix} L_1z_i \\ 0 \end{pmatrix} \right\|^2 \right\}$$

(3.19)

Now, if we make following notations

$$H' = \begin{pmatrix} H \\ I \end{pmatrix}$$

(3.20)

$$z' = \begin{pmatrix} z_i \\ 0 \end{pmatrix}$$

(3.21)

$$L' = \begin{pmatrix} L_1 \\ 0 \\ \alpha L \end{pmatrix}$$

(3.22)

the solution will be of the form

$$\hat{\theta}_i = \arg \min_{\theta_i} \left\{ \| L' H' \theta_i - L' z' \|^2 \right\}$$

(3.23)

the formal solution is thus

$$\hat{\theta}_i = \left( H'^T L'^T L' H' \right)^{-1} H'^T L'^T L' z'$$

$$= \left( H^T L_1^T L_1 H + \alpha^2 \alpha L^T L \right)^{-1} H^T L_1^T L_1 z_i$$

(3.24)

(3.25)

With selection $L_1 \equiv I$ equation (3.25) reduces to the form of equation (3.10).

Now, to take background EEG into account we can select $L_1^T L_1 = C_v^{-1}$, where $C_v$ is the estimate for the covariance of the background EEG. The estimates for the evoked potentials can
again be calculated with equation (3.8). The detailed derivation of the optimality of the selection
\[ L_T^T L_1 = C_v^{-1} \] is presented in [25]. It can also be seen that with \( \alpha = 0 \) this selection reduces to the
ordinary Gauss-Markov (minimum variance) estimate [51].

Taking background EEG into account in estimation of ERPs is necessary if the properties
of the background EEG change significantly trial to trial. However, this will make the method
more sensitive for small changes of regularization parameter \( \alpha \) and thus the choice of \( \alpha \) will be
more crucial. Also the range of common values will change to the level of 0.001 – 0.01, the
suitable value however depends heavily on the data. In all case studies with simulated and real
data presented later in this thesis, we have not used any information of the background EEG i.e.
we have chosen \( C_v \equiv I \) to avoid the disturbances of the possible non optimal selection of the
regularization parameter \( \alpha \).
Evaluation of the proposed single trial estimation methods with simulated and real data

An efficient way to compare the described estimation methods and evaluate their performance is to use simulated data. The idea is that the properties of the simulated peaks and potentials can be controlled and the estimated potentials can then be compared to the 'real' simulated potentials. In this section the proposed methods are compared using simulated data.

Simulations can, however, only imitate real measurements. Thus to get idea about the real usability of the methods some example studies are carried out with real measured data of three test persons.

4.1 Simulation of multichannel measurements

Various methods to simulate single-channel ERP measurements have been proposed in the literature. However, because we are interested in the estimation of the multichannel ERP measurements we need a method for the reasonably realistic simulation of multichannel data. The challenge in the simulation of the multichannel measurements is to simulate the inter-channel correlation of the potentials and the background EEG realistically.

A common way is to base simulations to the additive noise model, (see equation 3.1). Thus the observations are described as a superposition of the event related part and the part of the signal which is independent of the stimulus. In the case of ERPs this second part represents background EEG. The simulation process can thus be divided to the simulation of evoked response and to simulation of background EEG.

One possibility to simulate spatially correlated evoked responses is to use some real measured data set as a starting point. Then a few eigen vectors of correlation matrix of the data can be used as basis functions to generate simulated responses. This kind of simulation method is, however, very close to the described estimation methods. Thus this method would lead to 'inverse crime' situation i.e. we would use almost the same method for generating simulations and for the estimation. That would cause unreliable and probably unrealistic results. This kind of simulation method does not solve the problem of simulating spatially correlated background EEG.

Another way to simulate multichannel ERP measurements is to use a model for the electrical properties of the head and calculate potential distributions on the scalp caused by some dipoles inside the head. This is known as forward problem in the context of source localization of EEG. This kind of simulation method has been discussed, e.g., in [62, 28]. The real sources of ERP peaks are simultaneous activation of number of brain structures [36] and can not be totally described by some small set of dipoles. Nevertheless, this method is a good way to produce simulated measurements. It allows full control of the properties of the simulated measurements and the simulations are reasonably realistic especially in the sense of spatial correlation of the channels.
4.2 Modeling of evoked responses

To model electrical properties of the human head realistically we used 3D finite element head model based on segmentation of a MRI image. Two dipoles were placed inside the head model to simulate evoked response, see Fig. 4.1. Time variation of the dipoles, in fixed locations, was generated by multiplying magnitude of the dipoles by Gaussian shaped functions, shown in lower right corner of Fig. 4.1. The potential distribution in the scalp was then calculated by using the Finite Element Method in each time instant. Thus the simulation of one ERP measurement required the solution of the scalp potential distribution 125 times, when the simulated sampling rate was 250 Hz and the length of the ERP was 500 ms. Thus simulating a full set of measurements, say e.g. 90 stimuli, would require quite a lot computer power and is time consuming.

The simulated potentials do not imitate any real ERPs. Thus to avoid any confusion the peaks in the simulated potentials are called early negative and late positive peak.

The latency and the amplitude of the Gaussian humps was varied between stimuli to simulate variation in the peaks of the ERPs. Variation was uniformly distributed and the amplitude and the latency of the late positive peak were allowed to vary in larger scale than in those of the early negative peak. Simulated responses for three channels are shown in Fig. 4.2. From the figure it can be seen that the simulated late positive peak had its maximum at CZ channel and the amplitude of the PZ channel was larger than FZ channel.

4.3 Adding background EEG to simulation

The background EEG could also be modeled as random activity of several random dipoles. However, generating reasonably realistic background EEG would require a large number of random dipoles to be placed in the head model. Most probably the optimal distribution of the position and magnitude of the random dipoles is not easy to specify. Thus imitating the statistical properties of the real human EEG with this method would be a hard and a computationally burdensome process. Some other method is therefore needed for background EEG.

For the single-channel measurements the background EEG can reasonably well be simulated by using a auto regressive (AR) model. However, this kind of methods cannot easily be extended to the
Figure 4.2: Simulated ERPs. In top axes is shown a one sample of simulated response, the ERP with the background EEG is shown in the second row of axes. The third row shows all simulated ERP responses. The fourth row contains the simulated ERPs with added background EEG i.e. the simulated ERP measurements. The form of the simulated potentials can be recognized also from the noisy simulations. The bottom row of axes shows the average of simulated ERP responses (thin line) and the average of the noisy simulated measurements (thick line).
realistic simulation of the multichannel measurements. Hence, instead of simulating background EEG we choose to use real EEG recordings as background noise in the simulations.

The EEG recordings were from the test in which the P300 responses were recorded using the odd-ball paradigm and auditory stimuli. The -600 – 0 ms prestimulus period was separated from the recordings of responses to standard stimuli and used as background EEG: the periods with strong alpha rhythm or other disturbances were excluded. The selected background EEG and the simulated responses were summed together. The total number of simulated ERP responses was 59. The simulated ERPs are shown in the fourth row of axis in Fig. 4.2.

As it can be seen from Fig. 4.2 the shape of the response can still be recognized from the simulated signals. Calculating signal-to-noise ratio (SNR) for the simulated signals is not a straightforward task. The individual background EEG samples can be considered to be zero mean stochastic stationary signals. But the evoked response is transient, deterministic and non-stationary signal. Thus the SNR of the simulated ERP signal is a function of time. An estimate for the SNR of the late positive peak of the simulated response can be calculated with \[ SNR = 20 \log_{10} \frac{u_p}{\sigma_{\text{EEG}}} \] (4.1)

where \( u_p \) is the peak amplitude and \( \sigma_{\text{EEG}} \) is the standard deviation of the background EEG. The mean of the SNR estimates for the late positive peak in simulated ERP measurements were: 6.5 dB for channel FZ, 9.4 dB for channel CZ and 7.7 dB for channel PZ. Due to previously mentioned reasons the SNR is not optimal measure for the noise contamination of the ERPs.

### 4.4 Comparison of single-channel and multichannel estimates with simulated data

Single trial estimates were calculated for the simulated data using single-channel and multichannel methods. Similar observation matrix \( H \) was used in both methods. The observation matrix consisted of 30 Gaussian shaped humps for each channel in the single channel method. In the multichannel method we combined the estimation of the channels FZ, CZ and PZ. With the used simulated data combining more than three channels in the estimation changed the estimates slightly but not remarkably. However, further studies are needed to evaluate behavior of the multichannel method as a function of number of channels. Increasing number of channels will significantly enlarge the amount of computer memory needed to perform calculations.

To be able to select optimal value for the regularization parameter \( \alpha \) we plotted the estimated latencies and the amplitudes of estimated late positive peak as functions of the parameter \( \alpha \). These plots are shown in Fig. 4.3. To keep figure readable the results for the channel PZ are not included in the figure, they were similar than the results of channels CZ and FZ. The estimation of the peak locations was based on the fitting of the second-order polynomial to the estimate in the vicinity of the peak. The method is introduced in [34]. From the figure it can be seen that the methods behave identically as the parameter \( \alpha \) increases. Our selection was to use value \( \alpha = 10 \) in the following studies with both methods.

Estimates for four randomly selected simulations calculated with both methods are shown in Fig. 4.4. It can be seen that both methods give estimates of good quality for each separate channel. When the influence the background EEG to the simulated signal is small, as in case of 6th stimulus, estimates are quite close to the simulated potential. In the case of the 21st stimulus the disturbance of the background EEG is larger. Both methods are still able to produce good estimates. Neither of the estimates follows the spurious positive peak around 300 ms in channels FZ and CZ. The estimates calculated with the multichannel method are closer to simulated responses, especially in channel FZ. When the simulated ERP response is strongly disturbed by the background EEG in all channels, as in the case of 39th simulated response, both methods seem to fail.

One situation when the multichannel method gives estimates that are closer to the true simulated potential is the case when the data has e.g. baseline disturbances. The single-channel
Figure 4.3: The effect of the regularization parameter $\alpha$ to latency (top row) and amplitude (bottom row) of late positive peak estimates. The results for channel PZ were similar than the results shown in the figure. It shows up that the regularization parameter mainly affects to the amplitude of the peak and not that much to the latency of the peak. Both single and multi channel method perform almost equally well in all cases.

estimates tend to follow the biased data more closely. This can be seen in the vicinity of the early negative peak in channel PZ in estimates for stimuli 6, 21, and 33, and in the vicinity of the late positive peak in channel FZ in estimates for stimulus 21. It is obvious that e.g. in the case when there exist baseline drifts in the data of one measurement channel the multichannel method is less sensitive to these disturbances. Thus the amplitude estimates obtained with the multi channel method can be more reliably compared between the channels.

The mean and the standard deviation of the peak estimates are shown in Table 4.1 with the corresponding values calculated by applying the same peak picking algorithm to the simulated noiseless potentials. The latencies and the amplitudes estimated from the traditional averages of noisy simulations are also shown in the table. It can be seen that both methods can estimate the latency equally well and also the amplitude estimates seem to be equivalent. The averages of the latency estimates of both methods are quite close to the average of the simulated latencies. The traditional average gives good results for the peak latency as the variation in the simulated latencies was uniformly distributed.

The main difference of the methods seems to be in the ability to preserve the amplitude differences between different channels. This can be seen from Table 4.2 where the mean and the standard deviation of the amplitude differences between the channels CZ and FZ and between the channels CZ and PZ are shown. The percentage of the potentials for which the difference between the amplitudes of the peaks on different channels is greater than zero are also shown in the table. The multichannel method clearly performs better. This can also be seen from the histograms shown in Figure 4.5. The amplitude difference histograms corresponding to the multichannel method are much closer to the histograms of the noiseless simulations than the histograms corresponding to
the single-channel method.

From the Table 4.2 it can be seen that the means in the multichannel method are slightly more biased. The bias generally depends on the source configuration and it also depends on the value of the regularization parameter $\alpha$ for both of the methods. There is no general rule to solve this bias. However, the most important result in Table 4.2 is that the estimated amplitude differences in the multichannel method are much closer to the true variation of the simulated differences than in the single-channel method. This can also be seen from the histograms shown in the Fig. 4.5. This behavior makes it possible to use the multichannel method in the estimation of the variation in the amplitude differences between the channels.

To ensure that the result of better amplitude difference estimation of the multi channel method
Table 4.1: Mean ($\mu \pm \sigma$) and Standard deviation (S.D.) for the latency and the amplitude of both simulated (Sim.) and estimated (sc, mc, Avg.) late positive peaks for three channels. sc refers to the single-channel method and mc to the multichannel method and Avg. to the traditional average.

<table>
<thead>
<tr>
<th>Ch.</th>
<th>Latency [ms]</th>
<th>Amplitude [$\mu$V]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\mu$</td>
<td>$\sigma$</td>
</tr>
<tr>
<td>Sim.</td>
<td>342.8</td>
<td>5.8</td>
</tr>
<tr>
<td>FZ</td>
<td>328.1</td>
<td>5.9</td>
</tr>
<tr>
<td>mc</td>
<td>330.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Avg.</td>
<td>344.0</td>
<td>-</td>
</tr>
<tr>
<td>Sim.</td>
<td>342.8</td>
<td>5.8</td>
</tr>
<tr>
<td>CZ</td>
<td>327.4</td>
<td>6.1</td>
</tr>
<tr>
<td>sc</td>
<td>329.1</td>
<td>6.3</td>
</tr>
<tr>
<td>mc</td>
<td>344.0</td>
<td>-</td>
</tr>
<tr>
<td>Avg.</td>
<td>344.0</td>
<td>-</td>
</tr>
<tr>
<td>Sim.</td>
<td>342.8</td>
<td>5.8</td>
</tr>
<tr>
<td>PZ</td>
<td>324.5</td>
<td>7.3</td>
</tr>
<tr>
<td>sc</td>
<td>324.8</td>
<td>6.7</td>
</tr>
<tr>
<td>mc</td>
<td>336.0</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4.2: Mean ($\mu \pm \sigma$) and Standard deviation (S.D.) of the amplitude differences [$\mu$V] of late positive peak in the simulated data. Sim. refers to simulated responses, sc to the estimated potentials obtained with the single-channel approach and mc to estimates obtained with the multichannel approach. Column $>0$ show the percentage of the differences which are greater than zero.

<table>
<thead>
<tr>
<th></th>
<th>$\mu$</th>
<th>$\sigma$</th>
<th>S.D.</th>
<th>$&gt;0$ [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sim.</td>
<td>5.1</td>
<td>0.1</td>
<td>0.7</td>
<td>100</td>
</tr>
<tr>
<td>CZ-FZ</td>
<td>sc</td>
<td>4.1</td>
<td>0.5</td>
<td>3.9</td>
</tr>
<tr>
<td>mc</td>
<td>3.2</td>
<td>0.2</td>
<td>1.5</td>
<td>98.3</td>
</tr>
<tr>
<td>Sim.</td>
<td>1.9</td>
<td>0.0</td>
<td>0.3</td>
<td>100</td>
</tr>
<tr>
<td>CZ-PZ</td>
<td>sc</td>
<td>1.9</td>
<td>0.5</td>
<td>3.9</td>
</tr>
<tr>
<td>mc</td>
<td>1.9</td>
<td>0.3</td>
<td>2.2</td>
<td>84.5</td>
</tr>
</tbody>
</table>

Figure 4.5: Simulated and estimated amplitude differences between different channels. Numbers in the corners of histogram axes show the percentage of positive differences.
is not achieved by a fortunate selection of the regularization parameter $\alpha$ we calculated the data of Table 4.2 with different values of $\alpha$. The results of these calculations are shown in the Fig. 4.6. The figure shows that the better ability of the multichannel method to estimate amplitude differences is not generally dependent on the choice of the regularization parameter $\alpha$. The figure also shows that the multichannel method may have larger bias in the mean of the amplitude differences. However, the standard deviation of the amplitude differences is always smaller with the multichannel method. In the single trial analysis this is more important than the small bias in the mean.

An interesting question is also the ability of the methods to estimate trends in the amplitude differences between the channels. Individual estimated amplitude differences between the channels are shown in Fig. 4.7 as function of sorted simulated differences. Sorting of the simulated differences serves here as a model for the trend in the amplitude differences. The change in the spatial distribution of the ERP responses could also be modeled by changing the direction of the dipole moment from trial to trial during simulation. This approach would, however, make the simulations more complicated and increase number of parameters which have to be taken into account in the analysis of the results.

Two things can be seen from Figure 4.7. It seems that both methods are able to follow the trend in the amplitude difference between channels CZ and FZ. The trend in the amplitude differences between CZ and FZ seems to be more correct with the multichannel estimates. In the case of the channels CZ and PZ it is seen that the multichannel method is more biased than the single-channel method. However, as the reliability lines around the fitted trend line show, the variation of the single-channel estimates is high. Further studies with simulated data having different SNR showed that the much smaller variation of the amplitude difference estimates of the multichannel data is really a property of the multichannel method. This is probably the most important property of the multichannel method. However, some further studies with more complicated trend model might
be necessary to be able to have a clear picture of the differences between the methods in trend estimation case.

4.5 Real P300 measurements

Data of three test persons (A, B and C) was used to analyze the performance of the described methods with real data. The data was recorded using a classical oddball paradigm. In the recording about 600 auditory stimuli were presented with an inter-stimulus interval of 1 second, 85% of the stimuli at 800 Hz and randomly presented 15% deviant tones at 560 Hz. Subjects were sitting in a chair and were asked to press a button every time they heard the deviant target tones.

Responses were measured using sampling rate of 500 Hz. In the beginning of the analysis, the data was downsampled to 250 Hz. Continuous EEG data was then split to stimulus locked epochs. Length of each epoch was 500 ms i.e. 125 points. To avoid disturbances caused by eye movements epochs containing amplitude values over \( \pm 70 \) \( \mu \)V were rejected from further analysis. About 60 individual epochs remaining for analysis in each subject.

4.6 Comparison of the methods with real data

To be able to do a realistic comparison between the methods we first studied the effect of the regularization parameter to the estimates. Results for the test person B are shown in Figures 4.8 and 4.9. Results for test the persons A and C were similar.

The figures are similar to the ones calculated with the simulated data. Because we are now dealing with the real data the correct values are not known. Since the behavior of the methods

Figure 4.7: Estimated amplitude differences, crosses, as function of sorted simulated amplitude differences. The blue dots mark the trend generated by sorting of the amplitude differences. The line is fitted to the estimates to show the estimated trend. The reliability bounds of the fitted trend line are shown as dotted curves. Estimates for which the peak picking method failed are not shown in the figure.
with the real data is similar to the situation with the simulated data it seems that the results are reasonable. Our selection for the value of the regularization parameter to be used was mainly based on Figure 4.9. The value of $\alpha$ was fixed to 10 for all subjects. As in the simulation studies, eigen vectors corresponding the four largest eigen values were used to in the regularization matrix, i.e., value of parameter $p = 4$.

![Figure 4.8: Effect of the regularization parameter $\alpha$ to latency and amplitude estimates of P300 peak in data of test person B.](image)

Single trial estimates were then calculated with both methods for all three subjects and the peaks were estimated with the same method than with the simulated data. The statistics of the P300 peak estimates are shown in Table 4.3. It can be seen that the mean of individual estimates obtained with both of the methods are similar to the results based on averaging. Largest differences are in the data of the test person C. Especially the mean latencies of the P300 peaks on the channel PZ differ from the value based on the average of the epochs. This difference does not, however, mean that the single trial estimates are poor, since actually the peak picked from the average response does not have to be the same as the average of the peaks picked from the individual responses. Thus strict comparison between the peaks in the average response and the mean values of the peaks of single trial estimates is not meaningful.

The Figures 4.8 and 4.9 show that the main difference between the methods seems to be, also with real data, in the ability to estimate amplitude differences between the channels. The amplitude differences between channels CZ vs. FZ and CZ vs. PZ for all test persons are shown in Table 4.4. Results are again similar to the simulated ones. The histograms of the amplitude differences are not shown here. Using the values of the standard deviation shown in the table it can be concluded that they would look similar to those shown for the simulated data.

With the single trial estimates it is possible to examine the trends in the peak latencies and the amplitudes during the test. Some possible trend examination criteria are shown in the Figure 4.10 where the estimates of the P300 peaks in the data of the test person C are sorted with different rules. On the top left axis of the figure the amplitudes of the P300 peak are shown as the function of stimulus time. On the top right axes amplitudes are sorted according to the number of standard
Table 4.3: The mean ($\bar{x} \pm \sigma_x$) and the standard deviation (S.D.) for the latency and the amplitude of the P300 peaks of estimated potentials for the test persons A-C. The latency and the amplitude estimates calculated from the average (Avg.). sc refers to the single-channel method and mc to the multichannel method.

<table>
<thead>
<tr>
<th>Ch.</th>
<th>Latency [ms]</th>
<th>Amplitude [μV]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\bar{x}$</td>
<td>$\sigma_x$</td>
</tr>
<tr>
<td>Test Person A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sc 326.1</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>FZ mc 328.7</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Avg. 324.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>sc 338.8</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>CZ mc 338.3</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Avg. 332.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>sc 355.1</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>PZ mc 352.2</td>
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</tr>
<tr>
<td></td>
<td>Avg. 352.0</td>
<td>-</td>
</tr>
<tr>
<td>Test Person B</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sc 315.1</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>FZ mc 315.4</td>
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</tr>
<tr>
<td></td>
<td>Avg. 308</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>sc 319.7</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>CZ mc 317.0</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>Avg. 308</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>sc 332.8</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>PZ mc 325.3</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>Avg. 316.0</td>
<td>-</td>
</tr>
<tr>
<td>Test Person C</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>sc 312.8</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>FZ mc 315.9</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Avg. 308.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>sc 318.7</td>
<td>3.8</td>
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<tr>
<td></td>
<td>CZ mc 318.7</td>
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<tr>
<td></td>
<td>Avg. 308.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>sc 332.4</td>
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<td></td>
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<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Avg. 320.0</td>
<td>-</td>
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Table 4.4: Mean ($\bar{x} \pm \sigma_x$) and Standard deviation (S.D.) of amplitude differences of P300 peak for test persons A-C. sc refers to single-channel method and mc to multichannel method.

<table>
<thead>
<tr>
<th></th>
<th>$\bar{x}$</th>
<th>$\sigma_x$</th>
<th>S.D.</th>
<th>&gt; 0 [%]</th>
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<td></td>
</tr>
<tr>
<td>A</td>
<td>CZ-FZ sc 7.2</td>
<td>0.7</td>
<td>6.3</td>
<td>87.7</td>
</tr>
<tr>
<td></td>
<td>mc 7.0</td>
<td>0.4</td>
<td>4.7</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>CZ-PZ sc -2.6</td>
<td>0.6</td>
<td>5.6</td>
<td>35.8</td>
</tr>
<tr>
<td></td>
<td>mc -2.9</td>
<td>0.3</td>
<td>2.3</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>CZ-FZ sc 3.9</td>
<td>0.7</td>
<td>5.3</td>
<td>78.2</td>
</tr>
<tr>
<td></td>
<td>mc 3.9</td>
<td>0.3</td>
<td>2.2</td>
<td>98.2</td>
</tr>
<tr>
<td></td>
<td>CZ-PZ sc 2.1</td>
<td>0.8</td>
<td>5.9</td>
<td>63.6</td>
</tr>
<tr>
<td></td>
<td>mc 2.9</td>
<td>0.3</td>
<td>2.6</td>
<td>87.3</td>
</tr>
<tr>
<td></td>
<td>CZ-FZ sc 3.6</td>
<td>0.8</td>
<td>6.1</td>
<td>76.4</td>
</tr>
<tr>
<td></td>
<td>mc 3.5</td>
<td>0.3</td>
<td>2.5</td>
<td>94.5</td>
</tr>
<tr>
<td></td>
<td>CZ-PZ sc 5.5</td>
<td>1.0</td>
<td>7.2</td>
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<tr>
<td></td>
<td>mc 5.1</td>
<td>0.5</td>
<td>3.8</td>
<td>89.1</td>
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</table>

31
Figure 4.9: Effect of the regularization parameter $\alpha$ to the amplitude difference in data of test person B.

stimuli preceding the target tone. If two or more targets have the same number of preceding standards they are shown in the order of the stimulus time. Thus the x-coordinates of the points are not the same as the number of the preceding stimuli. From the lines fitted to the peak estimates it can be seen that the amplitudes tend to decrease as function of the time and on the other hand the amplitudes are higher for the target tones that have many preceding standard tones.

On the lower left axes of Figure 4.10 latency estimates of P300 peaks are divided to six groups according to stimulus order. The x-axis shows the limits of each group. On the bottom right axes latency estimates are divided to the groups according to the number of preceding standard stimuli. Again limits of each group are shown in x-axis. The mean values of peaks in each group are marked to the axes, box around mean value shows the standard deviation. The lines are fitted to the mean values of the groups. It can be seen that latency tends to increase as a function of stimulus order and decrease when the number of preceding standard tones increases. However, as these remarks are based only to the data of one test person they can not be generalized. In any case this figure shows some of the new possibilities that the single trial estimation gives to the ERP analysis.

The Figure 4.10 is based on the screen capture of the developed software package. The software package and Results Navigator, from which the pictures are, are described in the next chapter.
Figure 4.10: Different kind of trends in the responses of the test person C. a) On the left axis are amplitude estimates of P300 peak plotted as function of stimulus time from the start of the recording. On the right axis amplitudes are plotted as a function of sorted stimulus history. b) Latency estimates of P300 peak grouped according to stimulus time (on left side) and according to the stimulus history (on right side). Estimates were calculated with the multichannel method.
Chapter V

Matlab toolbox for bio-signal analysis

This chapter describes the developed Matlab™ toolbox for bio-signal analysis. The presentation is, however, mainly limited to ERP analysis part of the software.

5.1 Overview

The need for a toolbox which would combine the analysis of different bio-signals become apparent as we wanted to research applicability of the bio-signals as quantitative markers of mental workload. Another target was to enable correlation of the bio-signals with the actual work performance.

It is clear from existing literature that no bio-signal by itself can be used as complete marker of workload. Instead we hope that by correlating analysis results of different bio-signals and the actual work performance we can get new measures for mental load. Thus a common frame for the analysis programs is required. This objective of the combination of the analysis of different bio-signals is illustrated in the Fig. 5.1.

No toolbox suitable for this kind of application existed. Thus we decided to develop our own software package. Another reason for this decision was that we wanted to observe performance of the different existing analysis methods and develop new methods without any limitations posed by existing software. Matlab™ was chosen to be the programming language of the project as it enables quick development of software and is thus very practical for testing new methods and algorithms.

One of the design goals of this software package was to implement practical user interfaces for different analysis methods. This allows easy handling of various tunable parameters of different methods. It also enables easy switching between different tools and methods. Other usability related goal was to implement efficient way to handle results. Basically the analysis result can be exported in ASCII format from every analysis part. This enables post processing of the results with, for example, statistical tools. The results can also be printed out or attached to other programs as report sheets. Target has been to make those report sheets as comprehensive as possible without losing readability and clearness.

5.1.1 Data formats

As the developed software package is designed for the analysis of the bio-signals not for recording of the signals, support for different existing file formats is crucial.

As our initial data were measured with NeuroScan™ by Compumedics Ltd., support for the file format of Neuroscan Continuous data files (so-called cnt-files) was essential. This file format had also some influence for the internal structures of the software. Due to this and large amount of existing NeuroScan data we have had, the support for cnt-file format is the most complete.

1http://www.neuro.com
This data format is also very practical for storing response related information and some other triggering information in strict time-sync with the signals.

Later we have developed support also for the file formats of Biopac™ by Biopac Systems Inc.\(^2\) and for the Embla™ by Flagahf\(^3\). The HRV tool supports also plain text format for the RR-time series data, this enables support for e.g. some Polar heart rate monitors.

Due to design of the software package adding support for a new input file format is a quite straightforward process. In the future support for the European Data Format\(^4\) (EDF) might be necessary.

### 5.2 Bio-Signal browser

A signal browser interface combines the data and analysis results from different analysis tools. It also works as a launch pad for the analysis tools. A screen capture of the signal browser is shown in the Figure 5.2.

#### 5.2.1 Reading measured data

When the signal browser is started the first thing to do is to read the data. User interface for reading data is shown in Figure 5.3. All measured channels are shown in the head map. From this map it is possible to select up to ten channels to be used in the analysis. This limitation of number of channels does not, however, affect to the ERP analysis since the channels used in the ERP analysis will be selected separately, as we will see later. These analysis channels specified

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\(^2\)http://www.biopac.com  
\(^3\)http://www.flagahf.is  
\(^4\)http://www.hsr.nl/edf/
5.2.2 Browsing signals

The signal browser application enables viewing of the signals in synchrony (Figure 5.2). It is easy to look through the whole data for any measurement artifacts. If necessary, parts of the recording can be omitted from the further analysis.

At the top left corner of the program window is some generic information about the recording. The controls in the bottom of the figure enable selection of the time window of the signal view. There are also buttons for automatic scrolling, i.e., “playing” of the recorded signals. By pressing the button labeled with channel's name individual channels can be unselected and left out from further analysis. This will not remove any data, and by clicking the same button again the channel can be reactivated.

Some or all of the stimuli can be selected from the ‘View’ menu to be shown in the topmost

Figure 5.2: Signal browser. Selected data channels are shown in time-sync with stimuli. On the left panel of the user interface are buttons for launching different analysis programs.
axes of the browser. Activation on the GSR channel is seen in Figure 5.2. The stimulus view at the top of the signal window shows that the activation occurs after type 3 stimulus (the green number on the StimType row). If information about patient responses, for example button presses, are included in the continuous data file, latencies of the responses can also be inspected with the browser. Settings for this are also in the 'View' menu.

Buttons for launching different analysis tools are in the left panel of the user interface. When launched analysis program ends the signal browser gets activated again. All analyse results are returned to the browser. Thus it is possible to print different analysis reports from menus of the signal browser at once after all wanted analysis are ready. In the future when the correlation tool is available, the system fully follows the idea presented in Figure 5.1.

5.3 Tools for single trial analysis of ERPs

In the next sections we will go through the user interfaces of the single trial ERP analysis tool of the software. This tool implements both single-channel and multichannel methods, for single trial analysis of ERPs. In addition to the single trial analysis the tool also calculates the traditional average of the responses.
5.3.1 Selecting channels

When the single trial ERP analysis tool is launched from the Bio-signal browser the first appearing window will be the channel selection user interface (Figure 5.4). By default, all active channels in the signal browser are selected. There is no automatic recognition or omitting for example ECG channel from ERP analysis. Thus the user has to unselect irrelevant channels from further analysis. Automatic recognition of these channels would be hard to implement as there are no standardized names for the channels in general. The software only recognizes most commonly used names for the EEG channels and places buttons for them to the head map. All other channels are listed aside from the head map.

In addition to removing irrelevant channels from the analysis it is possible to select additional channels as all recorded channels are shown in the head map. This way, the limitation of the number of channels set by the signal browser does not affect to the ERP analysis. The only side effect of adding channels, not selected by default and thus not shown in signal browser, is the need for rereading the data file. This is, however, done automatically whenever it is necessary.

Other important function of the channel selection tool is the selection of the decimation rate. The decimation rate controls the re-sampling of the data. It can be necessary to perform actual measurements with a quite high sampling rate, for example HRV analysis requires at least 500 Hz sampling rate to be used. However for ERP analysis lower sampling rate is more practical. Our rule of thumb has been to down-sample measurements to 250 Hz. Taking into account that the ERPs are relatively slow potentials, generally without any sharp spikes it can be concluded that no information about the actual signal is lost in this down sampling. However, it makes data matrices smaller, calculations faster and numerically more stable.

Controls for changing part of the recording to be analyzed are also in the left panel of the user
interface. However, setting of the analyzed part of the recording should be made in the signal browser because changes made here will not be transferred back to the signal browser. Thus analysis results from different analysis tools are not necessary comparable if the analyzed part of the signal is modified here.

5.3.2 Splitting continuous data to epochs

Next step in the ERP analysis is to split continuous recording to the stimulus locked epochs. Screen capture of the splitting tool is shown in the Figure 5.5. This tool also allows rejection of the epochs with, for example, eye movement artifacts from further analysis.

![Figure 5.5: User interface for splitting continuous recording to the stimulus related epochs.](image)

Settings for epoch time window and stimulus identification of the stimuli to be analyzed are under the general recording information in the left panel. Epoch times will be rounded to nearest sample point so that epoch covers at least the input time. In the future it might be possible to select responses to multiple stimulus types for analysis. But currently this is not supported.

Controls for epoch rejection enable selection of the rejection channels, amplitude limits for the rejection and the time window in which signal is inspected. The modify button next to the list of rejection channels opens a new window with a head map, from which the rejection channels can be selected. Information about the number of accepted epochs and total number of epochs is shown under the list of rejection channels. Choices for rejection time window are the pre-stimulus time, after stimulus time or both.
Controls for epoch view are over the signal axes. Number of channels and type of epochs; rejected, accepted or both, can be selected. In addition there is a list-box for stimulus numbers of the epochs. From the list-box it can be seen which epochs are accepted and which ones are rejected. Individual epoch can be selected with the list-box control. Selected epoch is highlighted in the data axes. At maximum three data axes can be shown at the same time.

Each of the data axes shows data of one channel. The shown channel can be selected from the pop-up menu in the up left corner of each axes. Rejected epochs are drawn on red and accepted on gray. When accepted epoch is highlighted it is drawn on green. Edit boxes on the left side of the data axes control the limits of the y-axes. The 'Equal' button forces upper and lower limit to be the same.

A small menu pops up when the signal curve is clicked with the right mouse button. The menu can be seen also in Figure 5.5. The menu shows some information about the epoch. The epoch can also be accepted or rejected from this menu. However, if amplitude based rejection limits are changed afterwards all these hand made rejections or acceptances are lost. The blue dashed lines in the data axes show the amplitude based rejection limits. The limits can be set by dragging these lines with the mouse. The number of rejected epochs in the left panel and the list-box of the epochs in the top panel will be updated when mouse button is released.

From the raw data shown in the Figure 5.5 some form of the P300 response can be recognized, especially on the topmost channel where the data of channel FZ is presented. Next step after pressing 'OK' button of epoch splitting and rejection user interface is to tune parameters of the single trial estimation methods.

5.3.3 Calculating estimates

The user interface for selecting single-channel or multichannel method for analysis and for setting the tunable parameters of the selected method is shown in the Figure 5.6. The user interface allows also final selection of the analyzed channels and contains settings for the peak picking method.

Either single-channel or multichannel method can be selected from the pop-up labeled as ‘Analysis type’ under the section ‘ERP analysis’ on the left panel. The ‘Analysis method’ setting basically allows changing of the analysis method. However, currently the only meaningful choice for that is ‘Linear TV’ which means the subspace regularization based method described in section 3.4. ‘Error calc.’ is another experimental setting. With this setting the generalized cross-validation is used to find an optimal value for the regularization parameter. This is still experimental and thus it is a good choice to leave the pop-up menu to its default value ‘No’.

By selecting EEG covariance to be something else than ‘Eye’ the background EEG can be taken in to account in the analysis as described in section 3.7. The term EEG means here the pre-stimulus part of the epochs. Available choices for calculating covariance matrix of the EEG are ‘Cov.’, ‘AR-model’, ‘Eye’ and ‘Block’. ‘Cov.’ means normal covariance calculated with Matlab command cov. If the ‘AR-model’ is selected the covariance is estimated from the AR-model fitted to the EEG data. ‘Block’ is only meaningful in the case of the multichannel method. It means that cross-covariance parts of the data covariance matrix are not calculated. The covariance matrix thus consist only nonzero blocks on its diagonal corresponding to auto-covariance matrices of each channel. cov command is used for calculating autocorrelation matrices. The default choice here is ‘Eye’ which means that pre-stimulus part of the epochs is ignored when the estimates for the ERPs are calculated.

The pre-stimulus data correlation matrix need to be inverted in the equation (3.25). The method used to calculate inversion can be selected with ‘EEG cov. inversion’ pop-up. Choices are ‘Inv’, ‘Eye’ and ‘Pseudo inv.’. ‘Inv’ means normal matrix inversion. That can be, however, numerically instable and it is usually better to use ‘Pseudo inv.’ which means that the matrix inversion is approximated with the truncated SVD. In the case of the multichannel method and ‘Block’ type covariance matrix only auto-covariance blocks are inverted. Default choice is ‘Eye’ which means that the inversion is not calculated and the background EEG is not taken into account.
in the estimation of the ERPs.

'ERP correlation' pop-up menu allows selection of the method used for calculation of the correlation matrix of ERP part of the epochs, i.e., the part after the stimulus. Choices are ‘$x \times x^T$’, ‘AR-model’ and ‘Eye’. ‘$x \times x^T$’ means the outer product of the data matrix. With the ‘AR-model’ the covariance is estimated from the autoregressive model fitted to data. ‘Eye’ is not meaningful choice here since the methods described in Section 3.4 are based on the properties of the data correlation matrix.

Figure 5.6: User interface for setting various parameters of the single trial ERP analysis.

The value of the regularization parameter can be set with the edit box labeled as ‘gamma’. Number of eigenvectors used in the subspace regularization can be set with 'Nbr. of base vec.' edit box. The magnifying class button next to the edit box opens small window in which the eigenvectors are shown (Figure 5.7). In the window six eigenvectors corresponding to six largest eigenvalues are shown, each one in its own axis. In the lower left corner of the each axis are the number of the eigenvector and the corresponding eigenvalue. From this little window it is possible to select the eigenvectors used in the calculations one by one by clicking appropriate axis. White axis background means that vector is selected and gray background is used to mark unselected vectors. In the 'Settings' menu of this window are options for the smoothing used to get rid of the small ripple of the eigenvectors. Smoothness priors method is used for the smoothing. Both smoothed and non-smoothed eigenvectors are actually shown in the axes. A report sheet about the eigenvectors and values can be printed from the 'Print' menu of the window.

The last setting of the 'ERP analysis' panel is the length of the amplitude baseline. This value
is width of the time window used to calculate baseline for the amplitude values. Window is set to have its end at the stimulus time. Maximum value for the baseline length is the length of the pre-stimulus part of the epoch.

The channels for which the ERP estimates are calculated are selected with the head map at the center of the user interface. In the case of the multichannel method all the selected channels are used to build up common correlation matrix. Mean of the epoch data with ±2 SD curves is shown in the channel axes. Channels can be selected and deselected by clicking the axis. Axes with white background are the selected ones. This final selection allows to use some channels, for example eye movement channels, only in the rejection of the epochs and then they can be excluded from the actual ERP estimation.

On the right side of the user interface are settings for the observation matrix and for the peak picking method. Settings for peak picking parameters are in the bottom panel. The first setting under the title 'Analysis model' is for the type of the basis functions used in the observation matrix. The choices are 'Gaussian', 'Natural' and 'Sigm'. 'Natural' means eye matrix. 'Sigm' is shortening for sigmoid functions. Shape of the sigmoid and Gaussian functions can be controlled with the 'Shape of basis' edit box.

'Peak picking' section consist of settings for number of peaks, peak picking method used and for visualization of the peak picking process. Available peak picking methods are simple min/max value of selected time window or fitting of parabola to the vicinity of the min/max value of the time window. In the later case the peak is at the vertex of the parabola.

Label for each peak can be set in the topmost row of the edit box table in the bottom panel of the user interface. If the label is beginning with 'n' the peak is interpret to be negative. If the first letter is 'p' the peak is assumed to be positive. 'Peak window' row is used to set the window in which the parabola is fitted. This setting has no meaning if 'MinMax' method is used for peak picking. Two bottom rows of the table specify the time windows from which each peak is going to be searched. 'Min' is for the starting time and 'length' means width of the window. So for example in Figure 5.6 the window of the P3 peak is set to be 240 - 400 ms. The place of each window can also be set with the mouse by dragging the correspondingly colored patch shown in the axis at
right side of the table. All values are rounded towards the closest sampled data point. The peak picking in progress is shown in Figure 5.8.

5.3.4 Inspecting results

Tool for analyzing the results of the single trial estimation is named as Results Navigator. This tool enables viewing of the estimates and automatic peak latency based rejection of poor estimates. Individual estimates can also be accepted or rejected by the user. It is also possible to sort the estimates according to the number of preceding standard stimuli or, if response information is available, sorting can be made according to the response latency. Trends can be fitted to amplitude or latency data of any of the peaks with different sorting methods. It is also possible to divide estimates to small number of groups according to the stimulus order, the number of preceding standard stimuli or to the response latency. Means and standard deviations of each group are then calculated automatically and a line is fitted to the means to show trend between the groups. User interface of the Results Navigator is shown in Figure 5.9.

The user interface is divided to three parts: upper panel contains information about recording and analysis parameters together with information about the peaks of the currently shown estimate. Data axes are in the middle and controls for different settings are in the bottom panel.

The top left corner of the user interface contains general information about the recording and analysis. On the right side of the top panel there is a table for latencies and amplitudes of different peaks of the currently shown estimate. The active estimate can be changed with a list-box control on the bottom left panel. The list-box also shows the number of currently shown estimate. The amplitude limits, under the list-box, control the y-axes of estimate view. These limits, however, have no effect to axes showing amplitude or latency data of specified peak.

Number of data axes shown in the user interface can be selected with the pop-up menu on the top of the 'View' panel. The maximum number of data axes is three, it is also the default number of axes. Under the number control there is a pop-up menu for selecting active peak. Data of the active peak are shown in the data axes. There is also an experimental choice in the pop-up menu to show all the peaks at the same time. However, this does not work very well yet.

Data shown together with the estimated ERP signal can be selected with the check-boxes under the peak selection. Available are: raw measured data, average of the estimates, average of the measurements, average of the peak estimates, peak picked from the average of the measurements and amplitude baseline. Most of the choices are quite self descriptive. When amplitude baseline is selected the time axis is expanded to cover also the time specified for the calculation of the amplitude baseline. The actual amplitude baseline will then be shown as a grey line in the estimate view. Amplitude baseline correction can be used to compensate possible different baselines set by the background EEG between the estimates. When the correction is used amplitude values of the
peaks describe change to the baseline rather than absolute amplitude value relative to reference point used in the measurements. Amplitude correction is used by default, it can be deactivated from the 'Settings' menu.

Figure 5.9: User interface for inspecting the single trial estimation results.

Data shown in each of the data axis can be selected with pop-up menus over the axis. The pop-up in the upper left corner of the axis is used to select the measurement channel. In the Figure 5.9 all axes are set to view the data or results of channel FZ. Because the channel shown in each axis can be selected independently it is easy to compare estimates of different channels or, as shown in the figure, it is possible to view latency and peak trends aside with the estimates. Pop-up menu on the right side of the channel selection pop-up controls which kind of data is shown in the axes. Possible choices are estimate corresponding the currently selected stimulus or either latency or amplitude values of all the estimates of the selected peak. Value corresponding to the selected stimulus is encircled in latency and amplitude views (see middle axes in Figure 5.9).

When either latency or amplitude estimates are shown the third pop-up menu over the axis becomes visible. The data on the x-axis can be selected with this pop-up menu. Choices are: 'number', 'time', 'target group', 'sorted history', 'history length' and 'history group'. If the information about the responses is available also 'response latency' or 'response group' can be selected. From the choices 'number' and 'time' are self descriptive. In the case of 'sorted history' estimates are sorted according to the number of preceding non-target stimuli. If the estimates have same number of preceding stimuli second sorting criteria is order of the presence. When 'history length' is selected second sorting criteria is not applied and estimates with the same number of preceding non-target stimuli share the same x value. In the trend calculations this corresponds to taking
average of the values. However, the number of the estimates sharing the same \( x \)-values are usually different and thus reliability of the trend may not be optimal. Different grouping choices have the same kind of behavior. Members of each group share the same \( x \)-axis value. Mean of the group values is drawn as a line and the standard deviation of the values is a drawn as dark yellow box around the mean value. See the rightmost axis in Figure 5.9. A trend line is fitted to the mean values and the equation of the line is shown in the top of the axes.

\[ \text{Figure 5.10: Small user interfaces for a) setting division of the estimates to stimulus history based groups and b) for selecting items shown in the report sheet.} \]

Division of the estimates to different groups can be controlled from the Settings menu. In Figure 5.10a is shown a control window for the stimulus history based grouping. Number of groups can be set with the edit box on the top of the window. Dashed lines show the group boundaries. Boundaries can be changed by dragging dashed lines with mouse. Text in the each group shows the number of accepted versus the total number of estimates belonging to the group.

In the rejection menu estimates can be rejected according to the latency limits of one of the peaks specified. The selected estimate can also be rejected or accepted from the menu. Rejection can also be done by clicking the estimate or the latency/amplitude point corresponding to the estimate with the right mouse button. From the appearing small pop-up menu estimate can be rejected or accepted. Rejected estimates are not taken into account when latency and amplitude trends are calculated.

Properties of the data axes can be controlled from the pop-up menu accessible by clicking the axes by the right mouse button. From the pop-up menu it is possible to add grid to the current axes, change limits of y-axis and make rejected estimates invisible. Coordinates of the mouse pointer relative to the axes can be made visible by selecting 'Show coordinates' form the pop-up menu. However, this currently works only with the estimate view. In the latency and amplitude views the same functionality can be achieved by selecting appropriate estimate with the right mouse button. Then the coordinates i.e amplitude and latency value are shown in the table upper right corner of the user interface.

Latencies and amplitudes of the peaks, different trends, histograms and other analysis results can be exported to ASCII-file from the Reports-menu or printed out as customizable report sheets. Report sheet customization dialog is shown in Figure 5.10b). An example report sheet corresponding to the dialog settings shown in Figure 5.10b) is shown in Figure 5.11.

The Result navigator can be closed from the 'File' menu. When the program is closed the results of the analysis will be transferred to the Bio-signal browser. In the 'File' menu there is also a 'Recalc' option which allows to go back to the previous user interface and alter the analysis.
parameters. This same functionality is also in the parameter setting and epoch splitting user interfaces, so it is possible to go all the way back to the channel selection dialog. However, it is not recommended to switch between the programs endlessly since each switch backwards will leave small amount of memory which is not correctly set free.

5.4 Other parts of the software package

In addition to the single trial analysis of ERPs the software contains tools for the analysis of heart rate variability, galvanic skin reaction and quantitative EEG. Tools for time-frequency analysis of EEG and analysis of eye blinks and spontaneous GSR i.e. continuous GSR signal are currently under development. In the following subsections these other programs of the software package are briefly described.

5.4.1 HRV analysis

The tool for the analysis of heart rate variation is one of the most complete programs in the software package. A screen capture of the user interface of the program is shown in the Figure 5.12. In addition to the input data formats mentioned in the beginning of this chapter the HRV analysis tool supports ASCII files for importing RR time series directly. In the case of continuous ECG data, program first detect QRS complexes from the data and builds RR time series to be used in the HRV analysis.

With the program it is possible to calculate commonly used parameters for HRV [55]. The analysis results can be printed or saved to ASCII file for further analysis. It is also possible to export the printable report sheet to some other file format e.g. portable document format (PDF) or JPEG. This feature is common to all report sheets of the software package. An example printout of the HRV report sheet is shown in Figure 5.12.

5.4.2 GSR analysis

The tool for GSR analysis allows inspection of stimulus locked GSR responses. The responses can be visualized many different ways. Thus it is easy to visually inspect the habituation of the responses. With the tool it is possible to do principal component analysis for the GSR responses. This analysis program was used to calculate results for the article [54]. However this analysis program does not contain clusterization methods used in the article.

In addition to the examination of the GSR data in stimulus locked epochs it might be useful to analyze the data as continuous signal. This so called spontaneous GSR (sGSR) is related to alertness of the subject. Tool for analysis of sGSR is currently under development. Analysis methods applicable for the sGSR are similar to those used in the time-frequency analysis of EEG.

5.4.3 EEG analysis

The EEG analysis is divided to two programs in the software package. The first one of these programs is for traditional quantitative EEG analysis. It allows selection of disturbance free sections of raw EEG data. Classical frequency domain parameters can then be calculated for these sections. Final results are then averaged results of each section.

The second program is for time-frequency analysis of EEG. Instead of traditional spectrum estimation with FFT the program uses more advanced time varying methods. It is thus possible to study frequency spectrum of the EEG during, for example, event-related EEG synchronization (ERS) and desynchronization (ERD) process. An example of this kind of process is eyes open versus eyes closed situation. When at awake the eyes are closed the power in the alpha frequency band increases in occipital brain areas compared with eyes open situation.

Visual layout of both of these programs is based on the bio-signal browser. Thus they allow easy viewing of raw EEG data. Both programs produce report sheets of the analysis results. The
### Data

File name: 4177p  
Read part of meas. [s]: 0→end  
Analysis type: Multi Chan. (3 Ch)  
Date: 10/30/97 – 12:59:17  
Accepted/Measured: 60 / 84  
Regul. param. [α]: 25

### Peak Statistics

<table>
<thead>
<tr>
<th>Latency [ms]</th>
<th>Mean</th>
<th>Std.</th>
<th>Average</th>
<th>Mean</th>
<th>Std.</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base line cor.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CZ</td>
<td>318.0 ± 3.5</td>
<td>26.8</td>
<td>408.0</td>
<td>24.7 ± 1.4</td>
<td>10.4</td>
<td>27.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FZ</td>
<td>313.0 ± 2.8</td>
<td>21.2</td>
<td>408.0</td>
<td>21.1 ± 1.2</td>
<td>9.0</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PZ</td>
<td>333.6 ± 3.9</td>
<td>29.9</td>
<td>420.0</td>
<td>20.0 ± 1.1</td>
<td>8.5</td>
<td>21.9</td>
</tr>
</tbody>
</table>

### Latency histograms

![Latency histograms](image1)

### Amplitude histograms

![Amplitude histograms](image2)

### Latency vs. Stimulus number

![Latency vs. Stimulus number](image3)

### Latency vs. Sorted stimulus history

![Latency vs. Sorted stimulus history](image4)

**Figure 5.11**: Example report sheet of the ERP analysis program.
tools for the classical qEEG analysis is quite complete but the other tool is still under development, although it is already usable.

5.4.4 Blink analysis

The tool for the eye blink analysis is the latest addition to the software package. The tool detects the blinks from the electro-oculography (EOG) channels or from the frontal EEG channels. It calculates the latencies, amplitudes and durations of each blink. Eye blinks are related to the visual workload. Increasing visual workload will decrease the amount of blinks and their duration. The analysis tool allows also task related analysis of eye blinks. In the future the tool is further developed to allow removing of the blinks from the EEG data.

Figure 5.12: Screen capture from the HRV analysis tool of the software package and an example report sheet of the tool.
Discussion and conclusions

This work describes some of the most commonly used bio-signals together with their analysis methods. Especially event related potentials and their single trial analysis has been in the focus. Together with the signals, a software package for bio-signal analysis is introduced. The description of the software package is focused to the ERP analysis tools developed by the author.

The work has been focused to comparison of two subspace regularization based method. An extensive review of other single trial methods is presented in [25]. The first of the single trial methods described in this work was introduced in [26, 25]. The other method is an extension of the first method which take the spatial correlation of the measurement channels in case of multi channel measurements into account in single trial estimation. Idea of this extension is introduced in [24].

Comparison of the methods was based on simulated and real measurement data. The simulation method was based on dipole model of evoked potentials. In this method the scalp potential caused by a few time-varying dipoles inside a head model is calculated. Spherical head model has been usually used due to its easy formulation. However, in this study a realistic head model was used. The model was based on MRI images of human head. Scalp potentials caused by two time-varying dipoles were then calculated with the finite element method. The background EEG was not simulated. Instead, real measured EEG was used. This way the spatial correlation of measurement channels was tried to be taken into account as realistically as possible. As the spatial correlation is in an important role in the multichannel single trial estimation method accurate modeling of the correlation was essential for meaningful comparison of the estimation methods.

The comparison showed that both estimation methods give meaningful estimates. Peak amplitude and latency estimates are comparable to the results of traditional averaging of the time locked responses. The regularization approach used in both of the methods makes the selection of number of the eigenvectors used in the estimation less crucial. In practice it has become evident that the number of eigenvectors can be fixed to some small number for most of the cases. This is a considerable benefit compared with traditional principal component regression.

The main difference between the methods was shown to be in the ability to estimate amplitude differences between the different measurement channels. The multichannel method gave much better estimates. Overall it seems with the simulated data that when the data has e.g. baseline disturbances the multichannel method gives estimates which are much closer to the simulated potentials. The single-channel estimates tend to follow the biased data more closely. It seems that the amplitude estimates obtained with the multichannel method are more comparable between the channels.

This opens new possibilities in studying spatial distribution of evoked potentials. However, there is still a place for further development since the results in this work were calculated using only data of three adjacent channels. It has been planned to do some experiments with the method using all the measuring channels. In the practice this can mean combination of the data of, up
to, 64 channels in the estimation. Since both methods require a set of measurements for reliable calculation of the correlation matrix the minimum number of responses needed for the estimation is probably around 20. It would be worth of examination if this number could be decreased without loss of quality of the estimates by adding more channels to the estimation.

There is also need for more complex simulations. The used two dipole model for the ERP responses is very simplified. The used dipole locations and dipole moments weren't based on any physiological model. They were selected simply by trial and error in the purpose to produce realistic looking potential distribution on the used three electrode locations. The presented simulation results were based the background EEG of one person. It would be interesting to examine the performance of the estimation methods with same simulated ERP responses but different background EEG and with different signal-to-noise ratios. It would be also interesting to examine behavior of the methods when spatial or temporal distribution of the evoked potential changes during the measurement. A Kalman filtering based approach for single channel case when there is a substantial trend in the responses is proposed in [25]. This approach could probably also be extended to the multichannel case. This could improve estimates in the case of large spatial transitions in the responses.

The most promising application of the single trial estimation methods is the ability to study e.g. habituation of the potentials during long tests. Usually habituation affects especially the amplitude of the potentials. Rating of the psychological importance of the stimulus will also necessitate exact amplitude information about the potentials. Hence the methods described in this work can have many applications in the future. The better preservation of the amplitudes in the multichannel method is also important if one aims to use the single trial estimates in the source localization or cortical imaging applications [50]. The use of single trials in topographic estimates is suggested also in [29].

In this work a Matlab based software for the single trial analysis of ERPs was developed. The software is part of the larger software package for bio-signal analysis developed at Department of Applied Physics at University of Kuopio in collaboration with Brain@Work Laboratory of Finnish Institute Occupational Health. In the future the software will be used in Brain@Work laboratory for the analysis of mental workload in the control room environment. The Matlab is a mathematical programming language with which the described methods were easy to implement using matrix notation. The language also allows easy creation of graphical user interfaces.

Both single-channel and multichannel method were implemented in the software. In addition to estimation algorithms the software for ERP analysis consists tools for reading NeuroScan data files, an application for splitting continuous EEG data to stimulus locked epochs and an application for inspecting the results of the estimation process. There are no big missing issues in the ERP analysis software, although there are still some smaller improvements under development. However, these modifications are more related to the usability and flexibility of the software to suite for different kinds of test settings. There is also still some bugs to be found to ensure stability of the program.

When considering the whole software package for bio-signal analysis, the biggest missing link in the analysis is the correlation tool which will bind the different analysis programs together. Development of this tool has not yet been started. We have focused our efforts to implement state of the art analysis methods for different bio-signals. The tools for ERP, HRV, GSR and qEEG analysis are quite finished at the moment. The main development is with the time-frequency analysis of EEG, blink analysis and in the analysis of spontaneous GSR.

The HRV analysis tool has gathered some international interest. At present a stand-alone i.e. Matlab independent version of the software has been published [35]. The stand-alone -version is limited in sense of supported input data formats. Only ASCII file with RR data is supported. This tool is available in the Internet for free of charge 1.

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1http://it.uku.fi/biosignal/winhrv.shtml


