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Subspace regularization method for the single trial estimation of evoked potentials

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Abstract A method for single trial estimation of evoked potentials is proposed. The method is based on the subspace regularization approach in which the second order statistics of the set of measurements is used to form the prior information model for evoked potentials. The method was originally developed for the regularization of ill-posed inverse problems and it is especially tolerant to small misspecifications in the assumptions. It is shown in this paper that the approach is well suited to the estimation of evoked potentials. The method has close relationship to Bayesian estimation. The performance of the proposed method is evaluated using realistic simulations and the method is then applied to real measurements of evoked potentials.

1 Introduction

In the analysis of evoked potentials the fundamental problem is to extract information about the potential from measurements that contain also on-going background EEG. The most widely used tool for the analysis of the evoked potentials has been the averaging of the measurements over a set of trials. This is the optimal way to improve the signal-to-noise ratio when the underlying model for observations is that the evoked potential is a deterministic signal in independent additive background noise.

However, for over three decades it has been evident that the nature of the evoked potentials are more or less stochastic. In particular, the latencies and the amplitudes of the peaks in the potentials can have stochastic variation between the repetitions of the stimuli [1]. The information on these kinds of variations in evoked potentials is lost when the signal is averaged. The resulting estimate for the evoked potential does not then possibly correspond to any physical or neuroanatomical situation.

In statistical terms, the averaged evoked potential, the vectorial sample mean, is an example of the use of the first order statistics, in which only the first moment of the joint distribution of the measurements is used. The evident improvement is to use second order statistics, that is, covariance analysis. Typical examples of the second order statistical methods are e.g. the principal component analysis [2] and the factor analysis of the evoked potentials [3]. With these methods measures for the variation of the potentials can be also obtained. However, also with these methods the information that is carried by single measurements is lost. Especially, all possible trend-like evolutions that occur during the repetition of the test are lost.

Currently the goal in the analysis of the evoked potentials is to obtain best possible estimates for single potentials. We call this task the single trial estimation. The most common approach to single trial estimation is to form an estimator (filter) with which the unwanted contribution of the on-going background activity of the brain can be filtered out from the observations as well as possible. A major difficulty in this task is the often very low signal-to-noise ratio.

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In all filtering or estimation methods several either explicit or implicit assumptions on the underlying signals are employed. The performance of the estimator depends then on the matching of these assumptions with reality. The most common assumptions are about the second order statistics of the evoked potential and the on-going background EEG. In addition to this we sometimes have prior information e.g. on the morphology of the evoked potentials. The information can be concerned with the assumed smoothness of the evoked potentials or be in the form of limits for the possible locations of the peaks in the potentials.

In order to obtain the best possible estimator, all prior information should be taken into account. A major problem in the implementation of prior information into the estimation algorithm is how to express it in feasible mathematical form. One possibility to employ prior information is to use so-called regularization methods that have their origin in the theory of ill-posed inverse problems [4]. The so-called subspace regularization method is a recent approach that is especially suitable to situations, when we have a set of measurements available [5, 6].

The regularization approach has a direct connection to Bayesian estimation [7]. The regularized solutions can usually also be interpreted as Bayesian point estimates with some probability density assumptions for both the measurement noise and the parameters. The latter density is usually referred to as the prior density. The Bayesian framework is especially important in the evaluation of the estimates. Most of the implicit assumptions whose effect to the estimates can not be evaluated, can be converted to evaluable explicit assumptions through the Bayesian formulation.

In this paper we propose a systematic method for the single trial estimation of evoked potentials. The method is based on the subspace regularization method. In this method second order statistical information that is extracted from a set of measured evoked potentials can be used to form the prior information for estimation. It is shown in this paper that the approach is well suited to the estimation of evoked potentials. The performance of the proposed approach is evaluated using realistic simulations and then applied to real measurements of evoked potentials.

The rest of the paper is organized as follows. Some existing single trial estimation methods are reviewed and their properties are discussed in Section 2. In Section 3 the estimation theoretical background of mean square estimation is reviewed briefly and the new approach is derived. The method is shown to be a generalization of two common approaches that are limiting cases of the proposed method. A systematic method for single trial estimation is then proposed in Section 4. In Section 5 the method is evaluated using realistic simulated evoked potentials. The method is applied to real measurements in Section 6. The applicability of the method is then discussed in Section 7.

2 Single trial estimation of evoked potentials

The term evoked potential is used here for the time-varying potential s in some location of the scalp caused by stimulation of the somatosensory system. We assume that the measurements z of these potentials contain also noise v. The source of v is the spontaneous brain activity and it is called the background EEG. The EEG is thought to be independent of the stimulation and additive to the evoked potential. This is also called the additive noise model for observations

$$z = s + v \tag{1}$$

where z is the vector of sampled measurement, s is the evoked potential and v is the vector of sampled background EEG.

In single trial estimation the goal is to form an estimator that gives an estimate for every single evoked potential s based on data z. It thus filters out the unwanted contribution of the background EEG v. We review here the most common approaches to single trial estimation.

2.1 Time-invariant digital filtering

The most evident single trial estimation method is the application of some time-invariant digital filter. The simplest filters are generic moving average transversal filters [8] while some slightly more complicated ones are specifically designed to estimate some specific peak such as P300 [9]. Time-invariant Wiener filtering has been used for single measurements in [10], [11]. In all cases the

filter has been designed to have a symmetric impulse response in order to avoid phase distortion. The main problem in linear time-invariant filtering is the fact that usually the spectrum of the evoked potential and the background noise overlap significantly. This has been discussed at least in [12] and [13]. This is not surprising since the evoked potential is a transient-like smooth waveform with no periodicity. The spectra of such waveforms is not defined properly and the effect of time-invariant filtering of such waveforms is therefore varying. The effect of digital filtering of single waveforms has been studied e.g. in [8], [14], [15], [16] and [17].

2.2 Adaptive filtering

The use of adaptive filtering in the analysis of evoked potentials has been studied intensively during the last ten years. Most attention has been paid for the use of the LMS algorithm (least mean square, stochastic gradient algorithm) in the filtering of single evoked responses. In the LMS algorithm the measurement z is selected as the so-called primary input. Several choices are proposed for the reference input. This approach is formally adaptive regression, in which the sample $z(t)$ of the measurement z is modeled as linear combination of the samples of the reference input. The recursion corresponds to stochastic steepest descent minimization. In the LMS algorithm the parameters are updated to the direction of the reference input. If the reference input is fixed, the iterative method can serve at most as a regularization method if the mean squared error diminishes in the direction that is determined by the reference input vector. In some cases, e.g. when the reference input changes during the iteration true adaptation can also be achieved.

In many papers it is emphasized that this approach does not necessitate prior information about the evoked potentials, see e.g. [18]. In fact, the reference signal and the model structure are the prior information used in LMS. Also the use of steepest descent method corresponds to the assumption that the covariance of the parameters are of the specific form [19]. The use of LMS in evoked potential analysis is discussed e.g. in [20, 21, 22, 23, 24]

2.3 Time-varying Wiener filtering

One evident approach is to use time-varying filtering approaches. We call the time-varying Wiener filter the equation

$$\hat{s} = R_{sz} R_z^{-1} z \tag{2}$$

where R_{sz} is the non-centered cross-correlation matrix of the measurements z and the evoked potential s and R_z is the non-centered auto-correlation matrix of the measurements. The estimate (2) can be shown to minimize the mean square error $E\{\|s - \hat{s}\|^2\}$. If the matrix $K = R_{sz} R_z^{-1}$ is a Toeplitz matrix, the estimator corresponds the time-invariant case. This is not the case in general.

The fundamental problem in this method is to obtain a good model for the cross-covariance R_{sz}. In general this task necessitates a model for the observations and some analytical model for the evoked potential s. This model can then be estimated using the observations. In [25] such an approach to the filter construction is proposed. This filter was called the *time-varying minimum mean square error filter*. First it was noted that when the signal and the noise are uncorrelated $R_{sz} = R_{ss}$. The signal is then modeled as the superposition of the components with random locations and amplitudes. The parametric form of the covariance of the signal can then be calculated. The presented form necessitates the probability densities of the peak locations as well as the means and the variances of the peak amplitudes. However, generally this information is not available prior to estimation. The approach is extended in [26] to the multichannel case.

2.4 Model based estimation

One possibility for the single trial estimation is to start with a linear observation model. The additive noise model for evoked potential s can be written in form

$$z = s + v = H\theta + v \tag{3}$$

The evoked potentials are thus modeled as a linear combination of some basis vectors, namely the columns of the matrix H. With this approach the linear estimators similar to (2) can be obtained. However, with the model based approach it is easier to take into account the model for the evoked

potential and the background EEG in the measurements. This approach is discussed in detail in Section 3.

3 Estimation with linear observation model

In this section we discuss the estimation of the single evoked potentials using the model based approach. The discussion is limited to linear observation models.

The ordinary Gauss–Markov (minimum variance) estimate is emphasized as a special limiting case of a more general estimation scheme. The so-called principal component regression is also derived as a special case of the Gauss–Markov estimate. The subspace regularization method is then introduced. The connection of the method with the Gauss–Markov estimation and principal component regression is shown.

The equation

$$z = H\theta + v \tag{4}$$

is called the linear observation model. It connects the vector $z \in \mathbb{R}^M$ of sampled measurements with the parameters $\theta \in \mathbb{R}^p$ and measurement errors $v \in \mathbb{R}^M$. H is a $M \times p$-matrix that does not contain parameters to be estimated. In the case of evoked potential estimation z is the vector of measurements after the stimulation of the sensory system. A new vector z is obtained after each stimulation. The vector v describes the background EEG and can not be accessed directly. The evoked potential s is modeled with linear model $s = H\theta$. The evoked potentials are then modeled as linear combination of some basis vectors ψ_i that are the columns of the matrix $H = (\psi_1, \ldots, \psi_p)$.

3.1 Regularized least squares and Bayesian estimation

First we state a generalized least squares solution

$$\hat{\theta}_\alpha = \arg\min_\theta \left\{ \|L_1(z - H\theta)\|^2 + \alpha^2 \|L_2(\theta - \theta^*)\|^2 \right\} \tag{5}$$

with positive definite $L_1^T L_1 = W_1$ and $L_2^T L_2 = W_2$. Here arg means the argument of the expression. This is called the generalized Tikhonov regularized solution [27]. This solution modifies the ordinary least squares solution to a direction in which the norm $\|L_2(\theta - \theta^*)\|$, the so-called *side constraint*, gets smaller. This direction coincides with the null-space of the matrix (operator) L_2.

For example, if the solution is assumed to be a smooth function, L_2 is often selected to be the second difference matrix

$$D_2 = \begin{pmatrix} 1 & -2 & 1 & 0 & \cdots & 0 \\ 0 & \ddots & \ddots & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & 1 & -2 & 1 \end{pmatrix} . \tag{6}$$

The exact meaning of *smoothness* is now concretized by the null space of L_2. It is easy to show (see Appendix A) that the regularized solution can be written in form

$$\hat{\theta}_\alpha = (H^T W_1 H + \alpha^2 W_2)^{-1} (H^T W_1 z + \alpha^2 W_2 \theta^*) \tag{7}$$

When L_2 is a (higher) difference matrix, we call the solution (7) the smoothness priors solution [28].

This kind of solutions arise from the theory of ill-posed inverse problems [4]. The modification of the ordinary generalized least squares solution with the side constraint is then called regularization. The idea in regularization is to use prior information about the solution in addition to the data in solution of the problem. In this sense regularization has a close relationship with the Bayesian approach. In fact it can be shown that if the errors v are jointly Gaussian with zero expectation and covariance C_v and the parameters θ are random variables with expectation η_θ and covariance C_θ, the solution

$$\hat{\theta}_{\mathrm{MS}} = (H^T C_v^{-1} H + C_\theta^{-1})^{-1} (H^T C_v^{-1} z + C_\theta^{-1} \eta_\theta) \tag{8}$$

minimizes the mean square estimation criterion $E\{\|\theta - \hat{\theta}\|\}$. Solution (8) clearly coincides with the regularized solution (7) with $W_1 = C_v^{-1}$, $W_2 = \alpha^{-2} C_\theta^{-1}$ and $\theta^* = \eta_\theta$.

The ordinary Gauss–Markov (minimum variance) estimate

$$\hat{\theta}_{\mathrm{GM}} = (H^T C_v^{-1} H)^{-1} H^T C_v^{-1} z \tag{9}$$

can be obtained by setting $C_\theta^{-1} = 0$. This selection for the covariance corresponds to "infinite" variance of the parameters, that is, nothing is assumed on the properties of the parameters. In addition, if we set $C_v = \sigma_v^2 I$, which corresponds to independent errors, we obtain the ordinary linear least squares solution

$$\hat{\theta}_{\mathrm{LS}} = (H^T H)^{-1} H^T z \tag{10}$$

This is the Bayesian interpretation of the equation (7) [29].

3.2 Selection of the basis

A key point in use of the model based approach is the selection of the observation matrix H, that is, the selection of the basis vectors ψ_i. The basis functions span a subspace that determines the model for the evoked potentials. However, an infinite number of different sets of basis functions span the same subspace. An obvious scheme is to use some generic basis selection. For example if we assume, that the measured evoked potential is composed of Gaussian shaped component potentials with preselected shape, we can use these as columns of matrix H. In this scheme it is also easy to add the basis functions $\varphi_0 = 1$ and $\varphi_1 = t$ that can model the first order trend in measurements. The most trivial selection is obviously $H = I$.

A special case is obtained when the basis vectors ψ_i are mutually orthonormal. This means that $H^T H = I$ and we have

$$\hat{\theta} = (H^T H)^{-1} H^T z = H^T z \tag{11}$$

The estimate for the observations z in this basis is then of the form

$$\hat{z} = H\hat{\theta} = H H^T z = \sum_{i=1}^{p} \psi_i c_i \ , \tag{12}$$

where $c_i = \psi_i^T z$, that is, the inner product of the data with the basis vector. If the measurements z are random, the coefficients c_i are also random parameters. Now we may require that the basis is such that we can express the evoked potentials with a minimum number of basis functions. For that we require that the coefficients c_i are uncorrelated so that we can write

$$\begin{aligned} E\left\{cc^T\right\} &= E\left\{H^T z z^T H\right\} && (13)\\ &= H^T R_z H = \mathrm{diag}\,(\sigma_1^2, \ldots, \sigma_p^2) && (14) \end{aligned}$$

This is of the form of an eigensystem. The desired basis vectors are then obtained as the eigenvectors of the data correlation matrix R_z. The sum (12) is called the discrete Karhunen-Loeve, or principal component transform (decomposition) [30]. It can be shown that this selection of the basis gives the minimum mean square error in $\hat{z}$ compared to any other set of same number of basis vectors. Using this basis the observation model can be written in form

$$z = K_{\mathcal{S}}\theta + v \tag{15}$$

where $K_{\mathcal{S}}$ contain the p first eigenvectors of the matrix R_z and $\mathcal{S}$ is the subspace that is spanned by these vectors. This method can be shown to be equivalent to the so-called principal component regression approach [31]. In principal component regression approach the evoked potentials are modeled as $s = K_{\mathcal{S}}\theta$.

3.3 Subspace regularization

As discussed above, in Gauss–Markov estimation and principal component regression the evoked potentials are modeled as linear combinations of some basis vectors. These are the columns of the matrices H and $K_{\mathcal{S}}$, respectively. In the linear algebraic framework we say that the evoked potentials are forced to lie in the subspace spanned by the columns of the observation matrix. If this subspace is approximative, we do not want to be so restrictive.

However, we can assume, that the subspace is qualitatively correct. We can thus assume that the solutions are only *close* to this subspace $\mathcal{S}$. It turns out that with this approach it is possible to obtain a smaller mean squre error than with the Gauss–Markov estimate (no assumptions on the solution) or the principal component regression (strict assumption on the correctness of the subspace). This is shown with an example in Section 5. This means that with the subspace regularization method we need only a qualitatively correct model for the evoked potentials.

We continue to assume that the columns of the matrix $K_{\mathcal{S}}$ contain an orthonormal basis of the subspace $\mathcal{S}$. This is automatically fulfilled if we use the Karhunen–Loeve decomposition. The projection of $s = H\theta$ onto $\mathcal{S}$ is then $(K_{\mathcal{S}}K_{\mathcal{S}}^T)H\theta$ and the distance of s from $\mathcal{S}$ is $\left\|(I - K_{\mathcal{S}}K_{\mathcal{S}}^T)H\theta\right\|$. Remembering that we should construct such a matrix L_2 that the side constraint $\|L_2\theta\|$ is small for all expectable θ, we thus select $L_2 = (I - K_{\mathcal{S}}K_{\mathcal{S}}^T)H$. Since $L_2^T L_2 = H^T(I - K_{\mathcal{S}}K_{\mathcal{S}}^T)^T(I - K_{\mathcal{S}}K_{\mathcal{S}}^T)H = H^T(I - K_{\mathcal{S}}K_{\mathcal{S}}^T)H$, the desired solution for the parameters θ can be written in form

$$\hat{\theta}_{\mathcal{S}} = (H^T L_1^T L_1 H + \alpha^2 H^T(I - K_{\mathcal{S}}K_{\mathcal{S}}^T)H)^{-1}H^T z \tag{16}$$

where $L_1^T L_1 = C_v^{-1}$. The estimate for the evoked potential is then

$$\hat{s}_{\mathcal{S}} = H\hat{\theta}_{\mathcal{S}} \tag{17}$$

This is called the subspace regularized solution [32]. This method has also been proposed in [6] for estimation of visual evoked potentials.

If we select $\alpha = 0$ the solution $\hat{\theta}_{\mathcal{S}}$ is clearly equivalent to the Gauss–Markov solution. In [33] it is shown that if α goes to infinity, the method equals the principal component regression.

Due limited amount of data on which the determination of the basis vectors is based, we know that any sharp spikes that occur in the basis functions and thus also in the estimates more likely have their origin in the noise than in true the evoked potentials. The estimated potentials can then be smoothed using smoothness priors approach. The model for the *estimated* evoked potentials $\hat{s}_{\mathcal{S}}$ can be written in form

$$\hat{s}_{\mathcal{S}} = \hat{s} + v_2 \tag{18}$$

with $C_{v_2} = \sigma_{v_2}^2 I$. That is, we assume that the estimated evoked potentials still have some additive noise. The smoothness priors solution for $\hat{s}$ is then

$$\hat{s} = (I + \alpha_2^2 D_d^T D_d)^{-1}\hat{s}_{\mathcal{S}} \tag{19}$$

4 A systematic method for single trial estimation

In this section we describe a systematic method for the single trial estimation of evoked potentials. The method is based on the subspace regularization with a generic choice of observation model. The final smoothing of the estimates is based on the smoothness priors approach. The proposed method is described stepwise as follows.

1. Measure set of noisy evoked potentials $z = (z_1, \ldots, z_{N_z})$ and background EEG $v = (v_1, \ldots, v_{N_v})$ where z_i and v_i are column vectors. Background measurements v_i are typically measured before the stimulus. The time between the repetitions should be long enough and random to avoid the late potentials to corrupt the background estimate and locking of the background to the stimulus.
2. Calculate $C_v \approx N_v^{-1}\sum v_i v_i^T$. This is an estimate for the background covariance. Other methods are also applicable for estimation of the covariance. The background can be modeled e.g. as an AR model and the covariance can then be calculated using the spectrum of the model.

3. Form the matrix H with some generic way. A set of Gaussian shaped vectors with different delays and pre-selected shape is a suitable choice. If the measurements have trend, it is possible to include the constant and the first order polynomial basis vectors as additions to the columns of H.
4. Calculate $R_z \approx N_z^{-1} \sum z_i z_i^T$. This is an estimate for the correlation matrix of the measurements. Note that when the correlation matrix is used here, an approximation for the mean of the evoked potentials is modeled automatically as first eigenvector of the correlation matrix. Also the use of the covariance matrix is possible, but the mean of the measurements has then to be included in the equations of the estimates explicitly.
5. Solve the ordinary eigendecomposition $R_z U = U\Lambda$ of the correlation matrix. The solution of only the principal eigenspace is also possible.
6. Form $K_{\mathcal{S}} = (u_1, \ldots, u_r)$ where u_i are eigenvectors of R_z. The natural choice is to use the r eigenvectors that are associated with the r largest eigenvalues.
7. Form the matrix D_d. Usually the second or third order difference matrices are used.
8. Fix α and α_2. The selection can be based on e.g. the generalized cross-validation method that is explained in Appendix B. Another possibility is to select the parameters experimentally. For example, a suitable value for the parameter α_2 can often be selected by visual inspection of the smoothed eigenvectors. A further possibility is to carry out realistic simulations and inspect the estimation error as function of the regularization parameters.
9. Calculate the estimate $\hat{s}$ for the evoked potentials with the equation

$$\begin{aligned} \hat{s} &= (I + \alpha_2^2 D_d^T D_d)^{-1} \\ &\quad H(H^T C_v^{-1} H + \alpha^2 H^T (I - K_{\mathcal{S}} K_{\mathcal{S}}^T) H)^{-1} H^T C_v^{-1} z \end{aligned} \tag{20}$$

The selection of the basis vectors in H can be different, but the idea is that the basis is quite general, that is, several different types of possible measurements can be modeled with the selected basis. In subspace regularization s is regularized towards the null space of the regularization matrix $K_{\mathcal{S}}$. Our approach is to use all the available prior information in the construction of the matrix $K_{\mathcal{S}}$. There are several other possibilities to select the matrix $K_{\mathcal{S}}$. The selection of the subspace in $K_{\mathcal{S}}$ is here based purely on the observations, that is, the dependent variable. It could also be based on the independent variables. This kind of an approach is used in [34], in which a set of expectable parameters were first simulated and $K_{\mathcal{S}}$ was formed as the principal eigenspace of the covariance of this set. The selection could also be based on both independent and dependent variables as in the partial least squares method [35].

In the form (20) the background EEG is assumed to be Gaussian, but no stationarity is assumed. In the stationary case the matrix C_v will be a Toeplitz matrix. One possibility to take into account the nonstationarity of the background EEG is to model the background before and after the stimulation as AR model. If the model parameters differ it is possible to model the background as a time-varying AR process with smooth transition of the parameters from a state to another. A method for the generation of smooth transition models for background EEG is proposed in [36].

The subspace dimension r and the number p of the basis vectors in H can also be interpreted as regularization parameters as emphasized in [37]. An extreme possibility is to formulate the whole problem as a fully empirical Bayesian problem in which all regularization parameters are treated as hyperparameters with suitable prior distributions [38]. The selection of the hyperparameters can then be based on the likelihood of the data given the hyperparameters.

5 Simulation study

Although the proposed method is widely applicable to different types of the evoked potentials, we concentrate here only on the specific application to the P300 potentials. The P300 is one of the most studied responses of the human brain. The P300 test is performed using the so-called oddball-paradigm. Two kinds of stimuli, the standard and the target, are used in the stimulation.

The subject is asked to perform some task when the target stimuli occurs. For definitions and significance of the P300 potential we refer to [39, 40].

We simulate the evoked potentials by generating peaks with random amplitudes and locations. The shapes of the peaks are extracted from the average waveform of a set of real EP data. A detailed description of the simulation method can be found in [31]. We use vectors of length 128 points in simulations.

The observation model is selected to be a generic Gaussian peak model

$$H = (\psi_1, \ldots, \psi_p) \tag{21}$$

where

$$\psi_i = \exp\left(-\frac{1}{2d^2}(t - \tau_i)^2\right) \tag{22}$$

The width parameter is $d = 10$ and the number of $p = 20$ basis functions is used.

The simulated evoked potentials are then estimated using the systematic estimation method that was introduced in Section 4. The results were calculated with various values for the regularization parameter α and the dimension r of the regularizing subspace. The norms of the estimation errors between the true (simulated) and measured evoked potential were then calculated. The dependence of the estimation error norm on these two parameters is shown in Fig. 1.

In the limit $\alpha \to \infty$ the method coincides the principal component regression as discussed in Section 3. On the other hand, in the limit $\alpha \to 0$ we obtain the Gauss–Markov estimate. The error norm has a minimum with respect to both the number of basis functions and the regularization parameter. The increase of the regularization parameter from $\alpha = 10$ (as shown in Fig. 1) to infinity does not change the estimation errors considerably. This means that the proposed subspace regularization method yields a smaller error norm than either of the limiting cases. Thus the proper selection of both parameters is important. The choosing of a too large p is called overfitting. If the number of the basis vectors is too high, the model usually tends to model also the observation noise. The same is also true for the subspace dimension r. The mean square error is seen to obtain the minimum with $r = 2$ or $r = 3$ and with α between 10^{-2} and 10^{-1}. The value $r = 3$ is selected for the dimension of the regularizing subspace. The regularization parameter $\alpha = 0.01$ and the smoothing parameter $\alpha_2 = 10$ were then fixed.

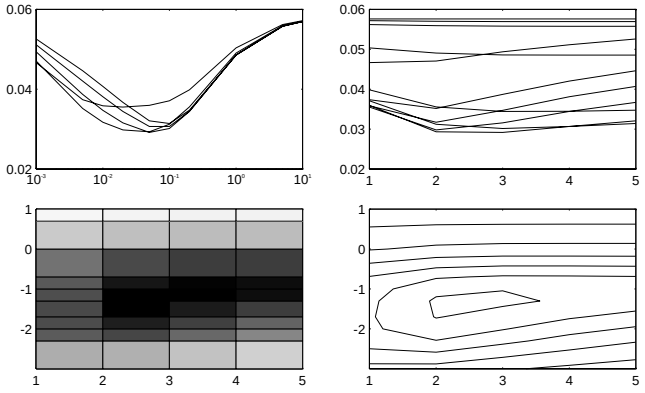

Figure 1: The estimation error norm in the case study 1 as a function of the regularization parameters α (top left) and r (top right). The same index as a gray scale image and as a contour plot (bottom left and bottom right, respectively) as function of α (vertical, logarithmic) and r (horizontal, linear).

The columns of the matrix $K_{\mathcal{S}}$ are plotted in this case in Fig. 2. The basis vectors are able to model the variations in the positive peak and the mean of the potentials. This can be seen easily by considering different linear combinations of the basis vectors. In the simulations the location of

the positive (P300) peak was independent of the location of other peaks by construction. This fact is reflected in the fact that the features that are related to the peaks occur in different eigenvectors.

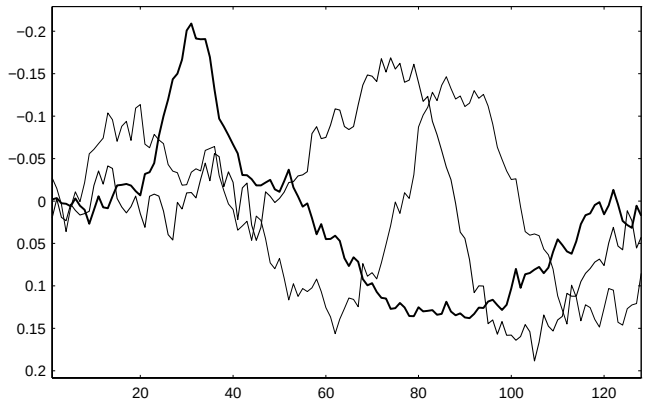

Figure 2: The columns of the matrix $K_{\mathcal{S}}$ with $r = 3$. The first, second and third eigenvectors (bold, medium and thin lines, respectively).

In Section 6 the latencies of the P300 are estimated. In order to be able to evaluate the accuracy of the latency estimates in Section 6, the latency estimation procedure is evaluated here with simulations. The latencies of the positive peak were extracted using the method that was introduced in [41]. The latency estimation is based on the fitting of the second order polynomial to the data in the vicinity of the absolute maximum of the estimate. The width of the fitting window was 40 points. The latency estimation was carried out for the estimated evoked potentials as well as for the noise-free simulations.

The estimated latency as a function of the true latency is shown in Fig. 3. The error in latency estimation is clearly homogenous through the simulations. In Fig. 4 eight single trial estimates are shown with the noiseless and noisy simulations. The effect of the regularization is clearly visible especially in estimates the 2 and 3 (counted from left to right, top to bottom). The estimates tend to follow the true potentials in the vicinity of the second negative peak although there are great variations in the data in this interval. The opposite effect is seen in the estimate 7 in which the estimate follows the data.

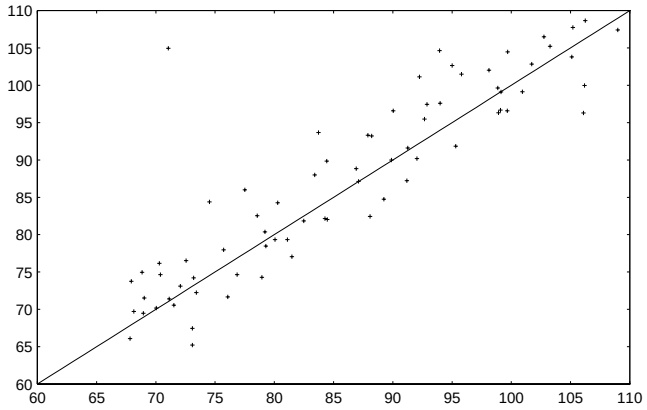

Figure 3: The latency of the estimated evoked potentials as a function of the latency of the noiseless simulations (+) in the case study 1. The straight line is the line with slope 1 that goes through the origin (the ideal case).

In Fig. 5 the mean and the standard deviations of the latencies are shown together with the histograms of the estimated latencies. Both histograms show that the estimated latencies are distributed uniformly over the interval in which the peak latencies are by construction.

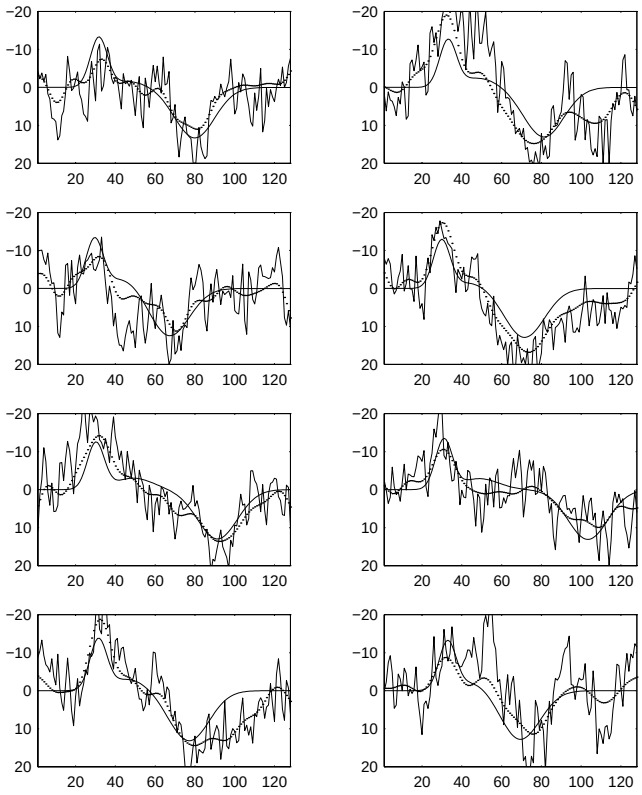

Figure 4: Eight randomly selected single estimates (dotted) with noisy simulations (solid rough) and noiseless simulations (solid smooth). Vertical axis is in micro volts and horizontal axis in points.

6 Real measurements

The estimation procedure was applied to three sets of real P300 measurements. The potentials were measured with sampling rate of 256 Hz. The vector length 128 thus corresponds to 0.5 s.We label the measurements as sets #1, #2 and #3. In this case the selection of the regularization parameters cannot be based on the difference between true and estimated potentials. The parameter selection is based here on the so-called generalized cross-validation criterion [42]. The definition and the specific application of the criterion is explained in Appendix B. The selection procedure was applied to the measurements #1 and the values $r = 5$ and $\alpha = 0.05$ are selected as regularization parameters. These parameters are also used for the other two measurement sets. The latency of the positive peak is then estimated as in Section 5. The results are shown in Figs. 6–8.

In all these cases the estimated latency of the third peak (P300) has more or less nonsymmetric histogram. This is natural since it is expectable that the latency of this component correlates with the latencies of the other components. It is even probable that the components have a causal relationship. An interesting finding is that the distribution of the latency is not time-independent in all data sets. In the case of measurements #2 and #1 the variance of the latency of P300 peak grows during the test. Most notably this means that the average is not a good estimator for any true potential of this kind. Thus we stress that in this kind of the test the single trial

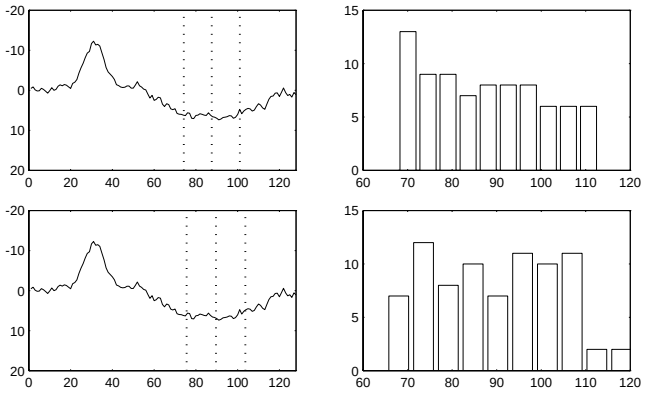

Figure 5: Left hand: the averaged simulations with the mean and standard deviation intervals of the estimated latencies. Right hand: histograms of the estimatd latencies. Top: estimates from the noiseless simulations. Below: estimates from the noisy simulations.

estimation should always be carried out prior to any inference on the data. Also in the case of the measurement #3 there seems to be variation in latency although no clear trend is visible.

In Fig. 9 estimates are shown together with the measurements for the measurement set #1. It is again seen that the estimate rejects sharp irregular spikes that can be interpreted as disturbances.

7 Discussion

We have proposed a new method for the single trial estimation of evoked potentials. The method is based on the subspace regularization method that can be seen as special form of a Bayesian estimation method. The method is shown to be well suited to the estimation of both realistic simulations and real evoked potentials. As a specific application the method was applied to the estimation of the P300 peak latency. It was shown that the method is able to extract the latencies with such accuracy that it enables e.g. reliable inference on the time evolution of the latencies.

The proposed method is easily modified to include even nonstationary background processes. Also different kinds of observation model selection schemes and prior assumptions are directly applicable to this observation model based approach. The extension of the method for multichannel measurements is straightforward. However, in the multichannel estimation methods the model for observations has to contain the dependence of the measurements in different electrode locations from each other. The proper modeling of this dependence necessitates the model for the head as a volume conductor. The complete estimation problem can then be formulated as a source estimation problem.

A Proof of the equation (7)

We show here that the solution

$$\hat{\theta}_\alpha = \arg\min_\theta \left\{ \|L_1(z - H\theta)\|^2 + \alpha^2 \|L_2(\theta - \theta^*)\|^2 \right\} \tag{23}$$

is given by equation

$$\hat{\theta}_\alpha = (H^T W_1 H + \alpha^2 W_2)^{-1}(H^T W_1 z + \alpha^2 W_2 \theta^*) \tag{24}$$

First we note that (23) can be written in form

$$\hat{\theta}_\alpha = \arg\min_\theta \left\{ \left\| \begin{pmatrix} L_1 H \\ \alpha L_2 \end{pmatrix} \theta - \begin{pmatrix} L_1 z \\ \alpha L_2 \theta^* \end{pmatrix} \right\|^2 \right\} \tag{25}$$

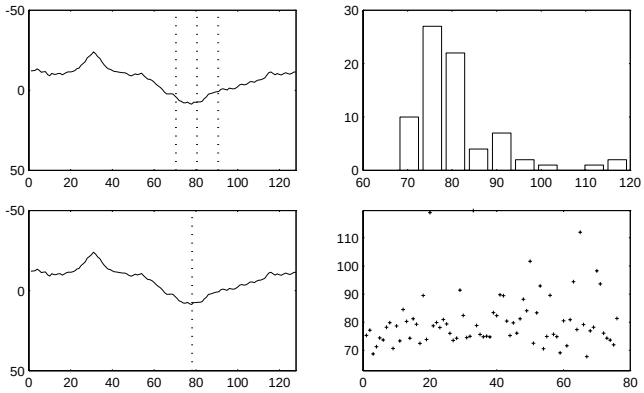

Figure 6: Top left: the mean and the standard deviations (vertical lines) of the latencies of the positive peak of the estimated potentials with the averaged measurements. Top right: the histogram of the latencies for the measurement set #1. Bottom left: the median of the latencies (vertical line) with the averaged measurements. Bottom right: the estimated latencies as a function of the number of the simulation.

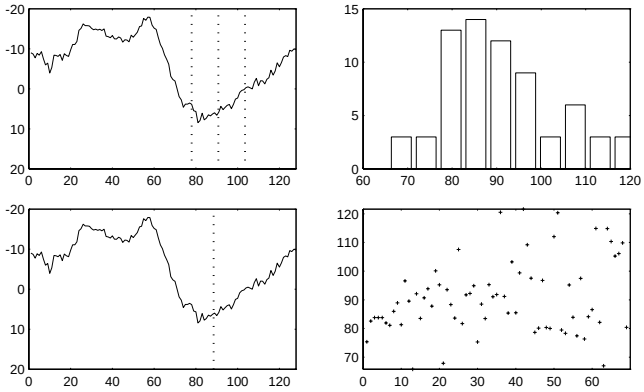

Figure 7: As in Fig. 6 but for the measurement #2.

and making notations

$$H' = \begin{pmatrix} H \\ I \end{pmatrix} \tag{26}$$

$$z' = \begin{pmatrix} z \\ \theta^* \end{pmatrix} \tag{27}$$

$$L' = \begin{pmatrix} L_1 & 0 \\ 0 & \alpha L_2 \end{pmatrix} \tag{28}$$

the solution is of the form

$$\hat{\theta}_\alpha = \arg\min_\theta \{\|L'H'\theta - L'z'\|^2\} \tag{29}$$

from which it is easy to see that the formal solution is

$$\hat{\theta}_\alpha = (H'^T L'^T L' H')^{-1} H'^T L'^T L' z' \tag{30}$$

$$= (H^T W_1 H + \alpha^2 W_2)^{-1} (H^T W_1 z + \alpha^2 W_2 \theta^*) \tag{31}$$

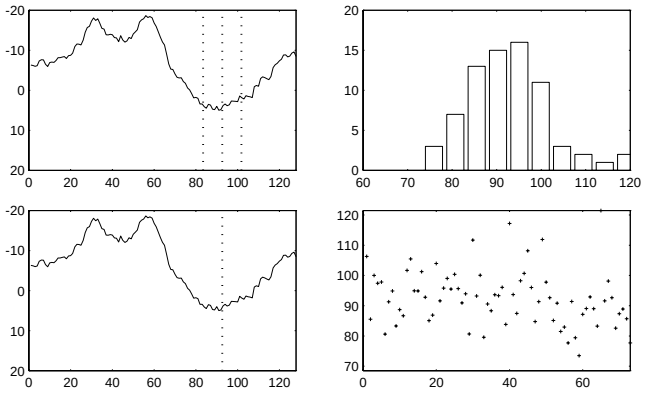

Figure 8: As in Fig. 6 but for the measurement #3.

B Selection of the regularization parameters

Selection of the regularization parameters is a fundamental problem in regularization. The methods for the selection of the regularization parameters are classically divided into two classes depending on whether or not the norm $\|v\|$ of the noise term in the observation model is known. In the so-called posterior methods all the necessary information for selection of the regularization parameters are extracted from the data. The so-called generalized cross-validation (GCV) belong to this class of the methods. It is based on the "leave-one-out" type procedure [42, 37]. The solution can be written as minimizer of the functional

$$f_{\mathrm{GCV}}(\alpha) = \frac{\left\| H\hat{\theta}_\alpha - z \right\|^2}{\left(\mathrm{trace}\,(I - HK) \right)^2} \tag{32}$$

where K is the matrix for which $\hat{\theta}_\alpha = Kz$ [43]. The criterion is calculated for measurements #1 as a function of both α and p and the result is shown in Fig. 10. The generalized cross-validation criterion is calculated for the whole data set. Thus the residual norm in numerator of (32) is then replaced with the stacked residual of the whole data set. The criterion is shown in Fig. 10. It is seen that the criterion does not have a clear minimum as a function of the parameters p and α. This is not surprising in view of the analysis that is carried out in [37]. There it is emphasized that the theory of GCV is asymptotic and the criterion may not have minimum for small data sets. However, it is seen that the criterion has a corner, a point of maximal positive curvature as function of both of the parameters. By our experience [31], this corner can be used in selection of the optimal parameters. The parameter values $p = 5$ and $\alpha = 0.05$ can then be selected.

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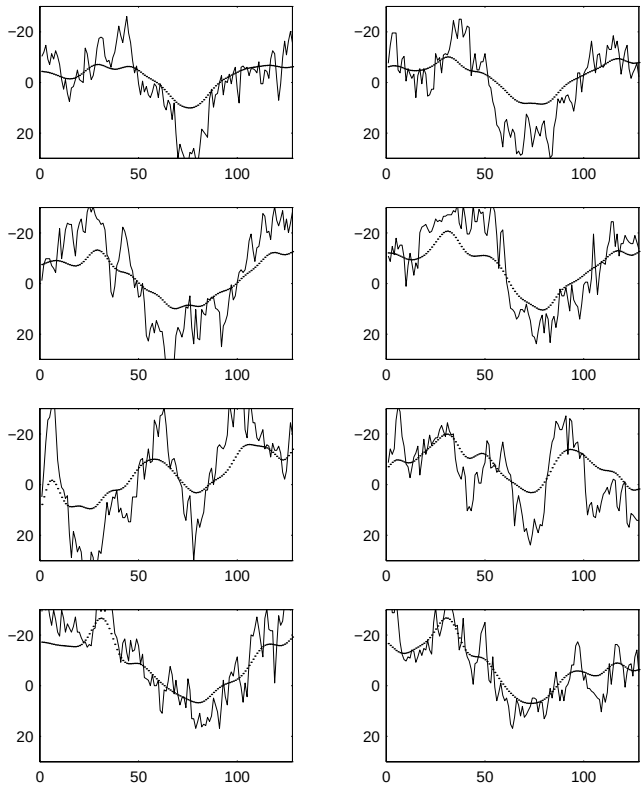

Figure 9: Eight randomly selected single estimates (dotted) with measured evoked potentials (solid) for measurement #1. Vertical axis is in micro volts and horizontal axis in points.

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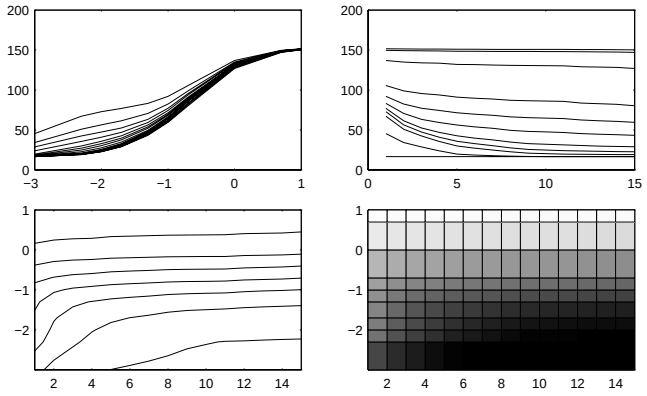

Figure 10: The generalized cross-validation criterion for measurements #1 as function of the logarithm of the regularization parameter α (top left) and p (top right). The same error as gray scale image and contour plot (bottom right and bottom left respectively) as function of α (vertical, logarithmic) and p (horizontal).

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