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Least-squares deconvolution of evoked potentials and sequence optimization for multiple stimuli under low-jitter conditions

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HIGHLIGHTS

- The proposed least-squares (LS) deconvolution is based on a combination of convolution theory and squared error minimization.
- The LS deconvolution can be applied to low-jittered sequences containing multiple stimuli.
- Optimization of the stimulus sequence allows a better recovery of response.

ABSTRACT

Objective: Rapid presentation of stimuli in an evoked response paradigm can lead to overlap of multiple responses and consequently difficulties interpreting waveform morphology. This paper presents a deconvolution method allowing overlapping multiple responses to be disentangled.
Methods: The deconvolution technique uses a least-squared error approach. A methodology is proposed to optimize the stimulus sequence associated with the deconvolution technique under low-jitter conditions. It controls the condition number of the matrices involved in recovering the responses. Simulations were performed using the proposed deconvolution technique.
Results: Multiple overlapping responses can be recovered perfectly in noiseless conditions. In the presence of noise, the amount of error introduced by the technique can be controlled a priori by the condition number of the matrix associated with the used stimulus sequence. The simulation results indicate the need for a minimum amount of jitter, as well as a sufficient number of overlap combinations to obtain optimum results. An aperiodic model is recommended to improve reconstruction.
Conclusions: We propose a deconvolution technique allowing multiple overlapping responses to be extracted and a method of choosing the stimulus sequence optimal for response recovery.
Significance: This technique may allow audiologists, psychologists, and electrophysiologists to optimize their experimental designs involving rapidly presented stimuli, and to recover evoked overlapping responses.

1. Introduction

During stimulation with a stimulus (sound, light, odour, touch, taste, motion), the electroencephalogram (EEG) undergoes typical changes that are related to alterations in that stimulus in a time-locked fashion. They occur at a more or less fixed interval and with a similar waveform after the onset, offset, or change in the stimulus. These electrophysiological responses are known as evoked potentials (EPs).

Because EPs are often many times smaller than the background electrophysiological noise that is simultaneously present, the EP is detected by applying the stimulus many times, and then averaging the response synchronously with the stimulus. To avoid the response caused by previous stimuli from overlapping with the response to the current stimulus, it is conventional to present the stimuli further apart in time than the duration of the EP.

There are, however, advantages from presenting stimuli at rates sufficiently fast that the duration of the EP is greater than the reciprocal of the rate of presentation. This causes successive responses

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to overlap in time. In particular, this will allow us to study stimuli in close proximity to each other which humans are constantly exposed to in their daily lives. Moreover, it has been suggested that pathologies can more sensitively be detected using faster presentation rates than with those being used in conventional methods (Tanaka et al., 1996).

There are four existing techniques for separating overlapping responses which all involve averaging to reduce the magnitude of electrophysiological background noise.

One technique, known as maximum length sequence (MLS) testing, applies stimuli with a timing specified by a set of mathematical rules. The averaging and separation processes are performed by applying a mathematical formula, which relies on the specific timing of the MLS, to the continuous overlapping response (Eysholdt and Schreiner, 1982). A disadvantage of the MLS technique is that the allowable stimulus onset asynchrony (SOA), measured from one stimulus onset to the next, has to be integer multiples of the shortest interval in the set. This means that there is a large range of SOAs. As the response to any presentation is affected by the recency of the preceding stimulus, successive stimuli elicit responses with different shapes and/or amplitudes. This variation in response waveform degrades the effectiveness of the averaging process.

A second technique, known as the ADJAcent Response (ADJAR) procedure, applies stimuli with a range of SOAs randomly chosen from within a specified range of durations (Woldorff, 1993). Simple averaging, synchronous with the onset of each stimulus, is applied to recover the averaged waveform. The effect of responses to previous or succeeding stimuli is minimized because these responses will not be averaged synchronously, and will thus have smaller magnitudes than the stimuli to which the averaging is synchronized. The first stage of the ADJAR processing involves convolving the averaged response with the distribution of SOAs to estimate the actual effect of the preceding and succeeding stimuli on the averaged response. This estimated disturbing effect of the non-synchronized stimuli is then subtracted from the simple average to provide an improved estimate of the response to a stimulus. In the second stage, the process can be repeated by convolving the current estimate of the average response with the distribution of SOAs and subtracting this from the current estimate to produce an improved estimate. However a major problem we have encountered with the ADJAR technique is that errors inevitably occur because of initial insufficient estimates due to too few averages and/or too much overlap in the first stage. In the first stage of the ADJAR technique, a wide SOA range is then necessary to have a good estimation of the original waveform. In the second stage, these errors can give rise to multiple solutions, and iteration can then produce a divergent incorrect solution rather than converging towards a unique, correct solution.

A third technique referred to as continuous loop averaging deconvolution (CLAD) uses jittered stimulus sequences with high stimulation rates (Delgado and Ozdamar 2004). In this case, the deconvolution relies on theoretical time domain matrix equations. The technique has been explored in the frequency domain as well (Jewett et al., 2004, Ozdamar and Bohorquez, 2006). Examples of implementation of this deconvolution technique were demonstrated on electrochochleograms (ECochGs), auditory brainstem responses (ABRs), middle latency responses (MLRs) and auditory steady-state responses (ASSRs), showing that deconvolution both in the time and frequency domain can disentangle EPs effectively (Bohórquez et al., 2009; Presacco et al., 2010). However, their theoretical framework limits these methods to the same acoustic stimulus in a sequence of high stimulation rates. The amplification of noise by certain stimuli sequences has also been a concern for the technique (Ozdamar and Bohorquez, 2006; Wang et al., 2008).

A fourth technique introduces the concept of least-squared error deconvolution, the mathematical derivation being similar to the one described in this manuscript, but is again limited to a single stimulus (Presacco et al., 2010).

To summarize, the techniques described above, with the exception of the ADJAR technique, have one significant limitation. They rely on the repetition of a single stimulus. Although the ADJAR technique allows more than one type of stimulus, recovery becomes rapidly more complex when increasing the number of stimulus types. In addition, the technique only works sufficiently well with a large amount of SOA jitter. As a result, it is necessary to have a technique that enables overlapping responses to be separated when the train of rapidly presented stimuli contains different stimuli, each of which may produce EPs with different (or absent) response waveforms. In addition, these waveforms should be generated using stimuli that have limited jitter between the SOAs to avoid changing response morphologies. The technique described in this manuscript addresses these limitations, and is based on the mathematical concepts of deconvolution and squared error minimization. The proposed deconvolution method makes it possible to disentangle overlapping EPs generated by multiple stimuli presented with time-jittered SOAs shorter than the length of the EP. Moreover, this temporal jitter can be kept small enough (i.e. by using a low-jitter condition) to avoid the physiological constraint of changing response morphologies with varying SOAs, a problem that is especially relevant when recording cortical responses due to their varying nature.

A further limitation of deconvolution techniques is the characteristics of the stimulus sequence from a mathematical point of view. These characteristics are of great importance for the numerical stability of the deconvolution and by consequence the quality of the recovery process (Ozdamar and Bohorquez, 2006; Wang et al., 2008). However, there is no procedure available yet to predict the ideal jittered sequence. We propose here a method to determine the optimal sequences for any experimental design using simulations. Optimization will lead to a non-singular system that improves the extraction of overlapping waveforms. The optimization technique employs a simulation model to predict the quality of the recovered response. It will include the ability to (1) choose the minimal range of SOAs and (2) the optimal length of the stimulus sequence for any number of stimuli. It will also be suggested through simulation that an *aperiodic* deconvolution model might improve the recovery process. Noise calculations on the recovered responses will also be considered.

Possible uses for this technique can be found both in research and clinical practice. First, the use of faster presentation rates possibly could reduce testing time in clinical assessment. Second, faster presentation rates could provide additional insight into the neurophysiological mechanisms of the brain. As real-world stimulation typically consists of trains of rapidly varying stimuli (e.g. the successive phonemes and words in speech), it is necessary to test with rapidly presented stimuli if we are to discover how neural processing operates with this type of stimuli. The variation of stimulus type is also known to increase the magnitude of some electrophysiological responses, so the use of stimuli that vary in some way from presentation to presentation may enable more efficient clinical testing.

This paper is written in such a way that psychologists, electrophysiologists, and audiologists who have a minimum knowledge of digital signal processing and programming, can still apply the proposed technique practically. In an accompanying paper (Bardy et al., 2014), an application of the deconvolution technique on a real EEG data set containing evoked potentials is presented.