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Research paper

# Selective processing of auditory evoked responses with iterative-randomized stimulation and averaging: A strategy for evaluating the time-invariant assumption



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**Hearing Research** 

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## **ABSTRACT**

The recording of auditory evoked potentials (AEPs) at fast rates allows the study of neural adaptation, improves accuracy in estimating hearing threshold and may help diagnosing certain pathologies. Stimulation sequences used to record AEPs at fast rates require to be designed with a certain jitter, i.e., not periodical. Some authors believe that stimuli from wide-jittered sequences may evoke auditory responses of different morphology, and therefore, the time-invariant assumption would not be accomplished. This paper describes a methodology that can be used to analyze the time-invariant assumption in jittered stimulation sequences. The proposed method [Split-IRSA] is based on an extended version of the iterative randomized stimulation and averaging (IRSA) technique, including selective processing of sweeps according to a predefined criterion. The fundamentals, the mathematical basis and relevant implementation guidelines of this technique are presented in this paper. The results of this study show that Split-IRSA presents an adequate performance and that both fast and slow mechanisms of adaptation influence the evoked-response morphology, thus both mechanisms should be considered when timeinvariance is assumed. The significance of these findings is discussed.

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### 1. Introduction

The conventional auditory evoked potential (AEP) recording method consists in the periodical presentation of stimuli and the average of their associated auditory neural responses (sweeps) in order to increase the signal-to-noise ratio (SNR) [\(Thornton, 2007\)](#page--1-0). The conventional method presents the limitation that the period of stimulation (i.e., the inverse of the stimulation rate) must be greater than the averaging window, avoiding sweeps to be overlapped ([Wong and Bickford, 1980](#page--1-0)); otherwise it would not be mathemat-ically possible to recover the transient evoked response ([Kjaer,](#page--1-0) [1980](#page--1-0)). This rate limitation implies that auditory brainstem

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responses (ABR) and middle latency responses (MLR) cannot be recorded with the conventional technique at rates faster than 100 Hz and 10 Hz, respectively, considering standard averaging windows of 10 ms in ABR and 100 ms in MLR signals. However, the recording of these signals at higher rates present several advantages, such as the study of neural adaptation ([Burkard et al., 1990;](#page--1-0) [Lasky, 1997\)](#page--1-0), the diagnosis of certain pathologies [\(Jiang et al.,](#page--1-0) [2000; Yagi and Kaga, 1979](#page--1-0)) and better performance in hearing threshold estimation [\(Leung et al., 1998](#page--1-0)).

The maximum length sequence (MLS) technique was developed by [Eysholdt and Schreiner \(1982\)](#page--1-0) to overcome the rate limitation imposed by the conventional technique. This technique was extensively used not only to record AEPs at fast stimulation rates, when the responses are overlapped ([Burkard and Palmer, 1997;](#page--1-0) [Eggermont, 1993; Lasky et al., 1995\)](#page--1-0), but also to analyze the linear and non-linear interaction components of otoacoustic emissions ([de](#page--1-0) [Boer et al., 2007; Hine et al., 1997, 2001; Lineton et al., 2006\)](#page--1-0).



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Stimulus-onset asynchrony (SOA), i.e. the distribution of time intervals between adjacent stimuli, are multiples of a minimum pulse interval in MLS sequences, which leads to stimulation sequences of a large jitter [\(Burkard et al., 1990;](#page--1-0) Ö[zdamar et al., 2007](#page--1-0)). The jitter of a stimulation sequence determines dispersion of the SOA distribution.

Several techniques have emerged to deconvolve overlapped AEPs using narrow-jittered stimulation sequences. Some of the most relevant techniques are quasi-periodic sequence deconvolution (QSD) ([Jewett et al., 2004\)](#page--1-0), continuous loop averaging decon-volution (CLAD) [\(Delgado and](#page--1-0) Ö[zdamar, 2004;](#page--1-0) Ö[zdamar and](#page--1-0) [Boh](#page--1-0)ó[rquez, 2006](#page--1-0)), and least-squares deconvolution (LSD) ([Bardy](#page--1-0) [et al., 2014a\)](#page--1-0). These techniques have been successfully used in several research applications (Bardy et al., 2014b; Bohórquez and Özdamar, 2008; Özdamar et al., 2007). The major limitation of these techniques is that obtaining efficient, narrow-jittered stimulation sequences may require an extensive search, since they must accomplish frequency-domain restrictions to avoid noise amplifi-cation in the deconvolution process [\(Jewett et al., 2004;](#page--1-0) Özdamar and Bohórquez, 2006).

A recently published paper describes iterative randomized stimulation and averaging (IRSA), which allows AEPs to be recorded at fast rates using narrow-jittered sequences [\(Valderrama et al., 2014c\)](#page--1-0). This is achieved by the estimate and removal of the interference associated with overlapping responses through iterations in the timedomain, providing better estimates of the response in succeeding iterations. This technique assumes that the AEP morphology is timeinvariant, i.e., all stimuli evoke the same neural response, which may constrain the flexibility of this technique in certain applications.

Despite the great effort in developing different methodologies to record AEPs at fast rates using narrow-jittered sequences, it is still controversial whether or not stimulation sequences of a wide jitter are a problem. Some authors believe that stimuli in high-jittered sequences may evoke auditory responses of different morphology as a consequence of the effects of neural adaptation, contradicting therefore the time-invariant assumption [\(Jewett et al., 2004;](#page--1-0) Özdamar and Bohó[rquez, 2006; Valderrama et al., 2014b](#page--1-0)). However, to the best of our knowledge, we have not found any technique that allows evaluation of the time-invariant assumption.

This paper describes an extended version of IRSA [Split-IRSA] which allows selective averaging and processing when AEPs of different morphology are recorded. In this study, the performance of this technique is assessed with both artificially synthesized and real experiments. The Split-IRSA technique is applied to evaluate the time-invariant assumption on ABR and MLR signals recorded with 16 ms-jittered stimulation sequences. The results of this study show that (a) the Split-IRSA technique presents an adequate performance, (b) the time-invariant assumption in auditory responses recorded on jittered stimulation sequences can be evaluated following a methodology based on Split-IRSA, and (c) the morphology of individual sweeps in ABR and MLR signals is influenced by both fast and slow mechanisms of adaptation. The potential of this method and the significance of the findings obtained in this study are discussed.

#### 2. Methods

This section presents the basis and the mathematical formulation of the Split-IRSA technique, the protocols followed in the recording of real electroencephalograms (EEGs), and the objectives, hypotheses and procedures of the experiments.

### 2.1. Split-IRSA

The fundamentals for the Split-IRSA algorithm are very similar

to those of IRSA, described in detail in [Valderrama et al. \(2014c\).](#page--1-0) AEPs are estimated in Split-IRSA through an iterative process in the time domain. Each iteration includes estimation of the interference associated with overlapping responses, subtraction of this interference from the recorded EEG, and re-estimation of the AEPs. Better AEPs estimates can be obtained recursively since improved AEPs estimates lead to a better interference estimate, which leads to more accurate AEPs estimates. The precision of the AEPs estimates increases with the number of iterations. In contrast to IRSA, this updated formulation [Split-IRSA] allows selective processing of sweeps, and therefore, AEPs of different morphology can be separately estimated.

Stimulation sequences are generated in Split-IRSA as the combination of independent sub-sequences, each of them based on randomized stimulation, in which the SOA of the stimuli vary randomly according to a predefined probability distribution ([Valderrama et al., 2012](#page--1-0)). The Split-IRSA technique retrieves the time-invariant component of the AEPs belonging to each subsequence, i.e., it is assumed that all stimuli from the same subsequence evoke the same AEP.

The mathematical formulation for the Split-IRSA technique is outlined below. Let  $[s_1(n), s_2(n), ..., s_T(n)]$   $(n = 1,...,N)$  be T subsequences, each of them composed of  $[K_1, K_2, ..., K_T]$  stimuli that evoke, respectively, T AEPs of different morphology, represented by  $[x_1(j), x_2(j), ..., x_T(j)]$   $(j = 1,...,J)$ , where N and J represent, respectively, the length in samples of the EEG and the averaging window. The recorded EEG  $y(n)$ , can be modeled as the summation of the convolutions (\*) of each sub-sequence with their corresponding AEP plus noise:

$$
\mathbf{y}(n) = \mathbf{s}_1(n)^* \mathbf{x}_1 + \mathbf{s}_2(n)^* \mathbf{x}_2 + \dots + \mathbf{s}_T(n)^* \mathbf{x}_T + \text{noise.} \tag{1}
$$

The AEPs corresponding to each sub-sequence ( $\tau = 1, \ldots, T$ ) in the iteration *i*,  $\hat{\mathbf{x}}_{\tau,i}(j = 1, ..., J)$ , are estimated in Split-IRSA according to

$$
\widehat{\mathbf{x}}_{\tau,\mathbf{i}}(j) = \frac{1}{K_{\tau}} \cdot \sum_{k=1}^{K_{\tau}} \mathbf{y}_{\tau,\mathbf{k}}(j + \mathbf{m}_{\tau}(k)),
$$
\n(2)

where  $y_{\tau,k}$  represents the EEG in which the auditory responses adjacent to the stimulus k (from the sub-sequence  $\tau$ ) are suppressed; and  $m<sub>\tau</sub>$  is a trigger vector that includes the samples of the EEG in which the stimuli of the sub-sequence  $\tau$  occur ( $k = 1, \ldots, K_{\tau}$ ). The  $y_{\tau,k}$  signals can be obtained for each stimulus k at each subsequence  $\tau$  by suppressing from the recorded EEG the AEPs estimated on the preceding iteration  $(i-1)$  corresponding to all subsequences ( $t = 1, \ldots, T$ ) and by adding the AEP corresponding to the stimulus k of the sub-sequence  $\tau$ :

$$
\boldsymbol{y}_{\tau,\boldsymbol{k}}(n) = \boldsymbol{y}(n) - \sum_{t=1}^{T} \left[ \mathbf{s}_t(n)^* \widehat{\boldsymbol{x}}_{t,i-1} \right] + \mathbf{s}_{\tau,\boldsymbol{k}}(n)^* \widehat{\boldsymbol{x}}_{\tau,i-1},
$$
(3)

where  $s_{\tau,k}$  represents the stimulation sequence for the stimulus k of the sub-sequence  $\tau$ . Considering  $z_i(n)$  as the EEG on the iteration i with all AEPs estimated on the preceding iteration suppressed:  $z_i(n) = y(n) - \sum_{t=1}^T [s_t(n)^*\hat{\mathbf{x}}_{t,i-1}]$ , then equation (3) can be rewritten as

$$
\boldsymbol{y}_{\tau,\boldsymbol{k}}(n) = \boldsymbol{z}_{\boldsymbol{i}}(n) + \boldsymbol{s}_{\tau,\boldsymbol{k}}(n) \ast \widehat{\boldsymbol{x}}_{\tau,\boldsymbol{i}-1}.
$$
 (4)

Hence, the sections of  $y_{\tau,k}$  corresponding to the averaging window can be obtained as

$$
\mathbf{y}_{\tau,k}(j+\mathbf{m}_{\tau}(k)) = \mathbf{z}_i(j+\mathbf{m}_{\tau}(k)) + \mathbf{s}_{\tau,k}(j+\mathbf{m}_{\tau}(k))^* \widehat{\mathbf{x}}_{\tau,i-1}.
$$
 (5)

The  $s_{\tau,k}(n)$  signal can be expressed as  $\delta(n-m_{\tau}(k))$ , where  $\delta(n)$ 

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