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A Novel Stimulus Artifact Removal Technique for High-Rate Electrical Stimulation

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Abstract

Electrical stimulus artifact corrupting electrophysiological recordings often make the subsequent analysis of the underlying neural response difficult. This is particularly evident when investigating short-latency neural activity in response to high-rate electrical stimulation. We developed and evaluated an off-line technique for the removal of stimulus artifact from electrophysiological recordings. Pulsatile electrical stimulation was presented at rates of up to 5000 pulses/s during extracellular recordings of guinea pig auditory nerve fibers. Stimulus artifact was removed by replacing the sample points at each stimulus artifact event with values interpolated along a straight line, computed from neighbouring sample points. This technique required only that artifact events be identifiable and that the artifact duration remained less than both the inter-stimulus interval and the time course of the action potential. We have demonstrated that this computationally efficient sample-and-interpolate technique removes the stimulus artifact with minimal distortion of the action potential waveform. We suggest that this technique may have potential applications in a range of electrophysiological recording systems.

Keywords

Stimulus Artifact; Artifact Removal; Electrical Stimulation; Electrophysiology; Auditory Nerve

Introduction

Studies of neural responses to electrical stimulation are often complicated by the presence of stimulus-induced contaminants within the recorded signal. These contaminants, or stimulus artifacts, often obscure part or all of the neural signal under investigation; particularly when investigating short-latency neural responses such as the auditory nerve fiber response to electrical stimulation. Removal of the stimulus artifact is important for the reliable detection of electrically evoked neural signals. While stimulus artifact may be minimized through the careful consideration of stimulator and amplifier specifications (Grumet, 1999) and experimental techniques (McGill et al., 1982), additional tools are usually required to completely remove the remaining artifact from the recorded signal.

Signal filtering is perhaps the most common technique used to remove stimulus artifact and their harmonics from a neural signal. However, as the frequency spectra of the neural signal and stimulus artifact often overlap (Nagel, 1995), filtering the frequency components of the

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stimulus artifact can result in distortion of the neural signal. Alternatively, by attempting to conserve the frequency components of the neural signal, residual stimulus artifact often remains in the recorded waveform. Another commonly used hardware-based technique, often used in conjunction with signal filtering, is the sample-and-hold method (Freeman, 1971). This technique has been used in studies of auditory neurophysiology in our laboratory for over 20 years (Black et al., 1983). These circuits switch to “hold” mode immediately prior to stimulation to prevent the recording amplifier from detecting the stimulus artifact. At the end of the “hold” period, the circuit is switched back to “sample” mode and the neural signal again passed through to the recording amplifier. This technique is particularly useful when the artifact and signal are clearly separated in time, although significant distortion to the recorded signal can occur when the artifact and signal overlap temporally. Furthermore, if the “hold” duration is too long, the signal may be completely abolished from the recorded signal, while if too short, residual artifact will remain within the recorded signal. Consequently, the sample-and-hold method has largely been limited to studies using low-rate pulsatile electrical stimulation (<1000 pulses/s) and those investigating long latency responses.

The analogue to digital converter has become a pivotal part of the modern-day electrophysiological laboratory, diminishing the need for real-time, hardware based signal processing. Thus the focus for signal processing has shifted to highly flexible and adaptable software-based solutions. One of the primary advantages of these techniques is that multiple methods may be trialed and optimized for each experiment by modifying or adapting the software processing tools. While software-based implementations of signal filtering (Gnadt et al., 2003; Litvak et al., 2003; Zhang et al., 2007) and artifact blanking, a modified version of the sample-and-hold circuit (O’Keeffe et al., 2001), have been successfully developed for a number of experimental conditions, the fundamental issues of spectral and temporal overlap still apply (see Table I). Consequently, a number of techniques have been developed to remove the stimulus artifact from recorded neural signals whilst minimizing signal distortion. These techniques include, among others, artifact template subtraction (Miller et al., 1999; Wichmann, 2000; Litvak et al., 2001; Hashimoto et al., 2002), artifact blanking combined with artifact template subtraction (Montgomery et al., 2005) and even removal of stimulus artifact identified by local curve fitting algorithms (Wagenaar and Potter, 2002).

Artifact template subtraction involves the collection and subsequent removal of an averaged artifact “template” at the time of each stimulus presentation. This technique has been used with varying degrees of success in a wide range of experimental conditions and has been successfully used in studies investigating auditory nerve fibre responses to pulsatile electrical stimulation at stimulation rates of up to 1000 pulses/s (Miller et al., 1999; Miller et al., 2006; Zhang et al., 2007). However at stimulation rates of 5000 pulses/s, this method was unable to completely remove the stimulus artifact from recordings immediately following the onset of a stimulus pulse train (Litvak et al., 2001). Subsequent studies investigating auditory nerve fibre responses to stimulation rates above 1000 pulses/s have used digital filtering to remove these stimulus artifact events (Litvak et al., 2003; Zhang et al., 2007).

One of the primary difficulties associated with artifact template subtraction is matching the artifact template to individual artifact waveforms, as differences between these events can result in incomplete removal of the artifact waveform from the recorded signal. It is known that the stimulus artifact waveform can vary across multiple presentations of an identical stimulus pulse (Fig. 1a) and to an even greater extent as stimulus current is varied (Fig. 1b). The artifact waveform can also vary throughout the presentation of a train of stimulus pulses (Miller et al., 2006). Changes in artifact waveform across stimulus intensity levels may be partially overcome by scaling the amplitude of the artifact to match the stimulus intensity presented (Litvak et al., 2001; Miller et al., 2006). However, as the relationship between stimulus intensity and artifact waveform is complex (Fig. 2) and often unknown, this technique

can result in residual artifact remaining in the recorded signal (Litvak et al., 2001). Another technique used to overcome artifact waveform variations is to optimize the fit of an artifact template to each artifact event (Wichmann, 2000; Wagenaar and Potter, 2002). While these modifications improve the effectiveness of the artifact template subtraction technique, they also significantly increase the computational requirements. As computational efficiency is essential for the rapid processing of large numbers of stimulus artifact events, these modifications are not suitable for use within experiments investigating responses to high-rate electrical stimulation.

To overcome some of the limitations associated with current artifact removal techniques, we developed a simple, computationally efficient technique for the removal of stimulus artifact from recorded neural data. The stimulus artifact was removed by replacing the sample points at each stimulus artifact event with values interpolated along a straight line, computed from neighboring sample points. This sample-and-interpolate technique required only that the artifact events be identifiable and that the artifact duration remained less than both the inter-stimulus interval and the time course of the neural response. We demonstrate the efficacy of this method in removing stimulus artifact from recordings of guinea-pig auditory nerve fibers, with minimal distortion of the neural signal, during periods of electrical stimulation at rates from 200 to 5000 pulses/s.

Methods

Animal Preparation

Electrophysiology experiments were conducted in healthy, normal hearing, adult Duncan-Hartley tri-colored guinea-pigs. Many of the surgical protocols used in the current study have been described previously (Sly et al., 2007) and all experimental procedures were approved by the Royal Victorian Eye and Ear Hospital Animal Research and Ethics Committee. Briefly, animals were anesthetized via intramuscular injection of ketamine (60 mg/kg for induction, 40 mg/kg for maintenance) and xylazine (4 mg/kg). Core temperature was maintained at 37 degrees Celsius via a thermostatically controlled DC heating pad. Anaesthesia depth was monitored throughout the experiment by observing respiration rate and depth and testing of the pedal withdrawal reflex; additional anesthetic was administered as required. A stimulating cochlea electrode array (Xu et al., 1997) modified for the guinea-pig, consisting of three platinum band electrodes, was inserted through the round window of the cochlea and into the basal turn of the scala tympani. A craniotomy was made and the cerebellum aspirated to expose the cochlear nucleus. In some experiments, the cochlear nucleus was retracted medially to visualise the underlying auditory nerve.

Stimulus Presentation

Electric stimuli were generated using a custom made, optically isolated stimulator (RE Millard, Department of Otolaryngology, The University of Melbourne) controlled via a PC. Stimuli consisted of biphasic current pulses (25 μ s/phase, 8 μ s interphase-gap, cathodic phase first at intra-cochlear electrode) presented at rates of 200, 1000, 2000 and 5000 pulses/s. Each stimulus train had a duration of 100 ms and there was a 150 ms period between successive trains. Stimulus current was varied between 0.1 and 2 mA depending upon neural threshold. All stimuli were presented between the apical band of the intracochlear electrode and a stainless-steel needle located in the ipsilateral pinna.

Response Recording

Standard extracellular recording techniques were used to record auditory nerve fiber action potentials. A quartz microelectrode (1.0 mm O.D., 0.7 mm I.D.), filled with 3M KCl and an initial impedance of 30-80 M ohm (measured at 250 Hz), was advanced through the cochlear

nucleus and into the underlying auditory nerve in 1-2 μM steps using a remotely controlled micromanipulator (Narashige Scientific Instrument Laboratory, Tokyo, Japan). Electrode potentials were amplified ($\times 1$) and low-pass filtered (30 kHz, 3 dB/decade) using an Axon Instruments headstage and amplifier (HS-2A; Axoclamp-2B; Axon Instruments Inc., Union City, USA) and sampled at a rate of 100 kHz and stored for off-line analysis.

Stimulus Artifact Removal

Microelectrode recordings of auditory nerve fiber activity were contaminated by electrically evoked stimulus artifact. The stimulus artifact amplitude were one to two orders of magnitude greater than the recorded action potentials and, at stimulation rates above 1000 pulses/s, temporally overlapped the recorded action potentials. We have developed a simple and computationally efficient sample-and-interpolate technique to remove these stimulus artifact events while minimizing distortion of the underlying action potentials.

Prior to the removal of the stimulus artifact, DC offset was removed and a 5 Hz digital high-pass filter applied to correct for baseline drift. While signal filtering can distort the recorded action potential waveform, it was found that this level of filtering caused negligible changes in the recorded waveforms. Any environmental noise within the recorded signal (e.g. line noise) may be removed at this stage using appropriate noise-cancellation techniques (e.g. Woo et al., 2006).

The stimulus artifact amplitude and duration was examined for all neurons included in this study. Stimulus artifact duration was defined as the time between the recorded signal increasing above the signal noise level and the time at which it returned to below the same level. Across all neurons recorded and all stimulus rate and currents presented within this study, total artifact duration was always less than 170 μs . Thus to decrease the computational requirements of this technique, artifact duration was assumed to be 170 μs for all artifact events - although this assumption reduced the fidelity of the action potential waveform when compared to using a variable artifact duration (see discussion).

In the experiments described, stimulus artifact event times were identified in the recorded signal using an amplitude threshold level crossing. Alternatively, artifact event times may be identified by recording stimulus trigger pulses or determined by computer control of the stimulus. For each stimulus artifact event, the sample point immediately prior to the onset of the stimulus artifact was identified. The sample point occurring at the end of the stimulus artifact (i.e. 170 μs later in these experiments) was then identified and the original samples between these points (i.e. the stimulus artifact) were replaced with values calculated along a straight line between these points.

Technique Implementation

The procedure for performing the artifact removal is summarised below.

- I.** Initialize parameters
 - i.** Assign maximum artifact duration with a priori knowledge, or
 - ii.** Measure and assign maximum artifact duration from recorded data
- II.** Identify stimulus artifact events
 - i.** A priori knowledge, e.g. computer control of stimulation, or
 - ii.** Use signal threshold level crossing
- III.** Remove stimulus artifacts

For each stimulus artifact event

- i. Identify sample point prior to stimulus artifact onset
- ii. Identify sample point following end of stimulus artifact
- iii. Interpolate straight line between these two points
- iv. Replace original samples with interpolated values

IV. Artifact free data

Results

The sample-and-interpolate artifact removal technique was developed using recordings of auditory nerve fiber responses to high-rate monopolar electrical stimulation in the guinea-pig. It was further tested and refined during subsequent experiments.

During the development of the sample-and-interpolate artifact rejection technique, the stimulus artifact shape associated with all auditory nerve fibre recordings was recorded and measured. Examples are illustrated in Figures 1 and 2. The stimulus artifact consisted of two large phases (P1 and P2) followed by a third smaller phase (P3). All three phases of the artifact increased in amplitude with stimulus current; the amplitude growth for P1 and P2 was relatively steep while P3 exhibited a much shallower and more variable growth in amplitude. Total artifact duration also varied with stimulus current. While P1 duration remained relatively consistent across all stimulus current levels presented, P2 and P3 had a longer duration that increased with stimulus current. As noted previously, total stimulus artifact duration remained less than 170 μ s for all artifact events recorded. Complex relationships between stimulus current and stimulus artifact amplitude and duration were observed in all auditory nerve fibre recordings examined in this study. The precise nature of these relationships varied between experiments and depended upon, among other things, the recording electrode impedance and the interface between the recording electrode and the auditory nerve fibre.

To ensure that the stimulus artifact was removed with minimal distortion of the underlying neural response, the recorded waveform following artifact removal was visually compared to the original waveform. A typical waveform recorded in response to 5000 pulses/s stimulation is illustrated in Fig. 3a, before (upper trace) and after (lower trace) stimulus artifact removal. Viewing only the first 5 ms of this waveform (Fig. 3b), the recorded signal before (grey) and after (black) artifact removal are shown. These figures demonstrate that the artifact, an order of magnitude larger than the recorded action potentials, completely obscures the underlying neural action potentials. Additionally, it demonstrates that the sample-and-interpolate technique effectively removes stimulus artifact from the recorded waveform with minimal distortion of the underlying action potential shape. To further examine the output of the sample-and-interpolate technique, a single action potential (Fig. 3b; outlined section) was viewed (Fig. 3c). This figure illustrates the sample points unaffected by the stimulus artifact removal process (black dots), as well as the interpolated values used to replace the stimulus artifact (solid black line), overlaid against the raw recorded signal (grey line). This further demonstrates that the sample-and-interpolate technique removes the stimulus artifact while maintaining the action potential waveform.

To assess the efficacy of the sample-and-interpolate artifact rejection technique compared with other commonly used methods, we viewed the action potential waveform following artifact removal using four different techniques (Fig. 4). This figure shows two action potentials (black) following the removal of stimulus artifact associated with 5000 pulses/s pulsatile electrical stimulation overlaid against action potentials uncontaminated by stimulus artifact (grey), elicited by 200 pulses/s pulsatile electrical stimulation, recorded from the same neuron. As the

time between stimulus onset and action potential initiation in auditory nerve fibers is approximately 500-800 μ s, the stimulus artifact is temporally separate from the evoked action potential (at 200 pulses/s) and is not visible in this figure. The sample-and-interpolate technique (Fig. 4a) was able to effectively remove the stimulus artifact while causing minimal distortion to the action potential waveform. While signal filtering (Fig. 4b) and the digital sample-and-hold method (Fig. 4c) removed the stimulus artifact, filtering caused a decrease in the action potential waveform and both distorted the action potential shape. Template subtraction (Fig. 4d) resulted in an ~75% decrease in artifact amplitude, however the artifact amplitude remained more than double that of the action potential amplitude.

At the lower stimulation rates examined, where the overlap between stimulus artifact and neural response was significantly reduced or absent, the sample-and-interpolate technique was able to successfully remove the stimulus artifact while causing minimal or no distortion to the evoked action potential waveform.

Discussion

Stimulus artifacts often contaminate recorded neural signals, making the analysis of the neural response difficult. We have demonstrated that the newly described sample-and-interpolate technique can eliminate stimulus artifact from segments of recorded neural activity while minimizing distortion to the action potential waveform. Importantly, we have shown that this may be achieved during periods of significant overlap between the stimulus artifact and the neural response.

An advantage of the sample-and-interpolate technique over other currently available artifact rejection methods is the relative computational efficiency of this method. This is important as it allows for the rapid removal of stimulus artifacts and processing of neural responses; thereby enabling response-dependent variations in the stimulation protocols during an experiment. This is particularly valuable when considering the limited time an individual nerve fiber may be electrically stimulated and recorded. In the described experiments, the sample-and-interpolate technique was implemented immediately after the signal recording had been completed and required only the stimulus timing and stimulus artifact duration information. As the stimulus artifact duration was obtained from previous artifact recordings, only the stimulus timing information was calculated during an experiment. With the use of a digital signal processor and a recorded stimulus trigger pulse, this technique may even be implemented in near real-time, offering even greater flexibility throughout an experiment.

In contrast, the simple implementation of template subtraction required both stimulus timing information as well as artifact shape information. Despite the increased computational requirements demanded from the capture and storage of the stimulus artifact shape, this method resulted in only partial removal of the stimulus artifact. Improvements in this method may be achieved via a number of modifications (Wichmann, 2000; Wagenaar and Potter, 2002; Miller et al., 2006), although these all increase the computational requirements of this method. While signal filtering required no information regarding the stimulus artifact shape, timing, amplitude or duration, it resulted in distortion of the recorded signal waveform due to the spectral overlap between the stimulus artifact and the neural response. In addition, while signal filtering re-calculates the entire signal based upon the filter parameters, the sample-and-interpolate technique re-calculates the values only where stimulus artifact events are known to have occurred. Thus signal filtering is computationally more intensive and also results in significant distortion of the recorded signal waveform.

While the sample-and-interpolate artifact rejection technique is effective, there are some requirements for the successful implementation of this technique. One such requirement is the

analogue to digital sample rate at which the recorded signal is digitized. While lower sample rates are more computationally efficient, the sample rate must be at least sufficiently high to capture the shape of the neural response and the timing of the stimulus artifact events (if a threshold level crossing is used to determine artifact event times). And although higher sample rates generally improve the fidelity of the recorded signal waveform, it also increases the computational requirements of this technique. Another requirement for the effective implementation of the sample-and-interpolate technique is that the stimulus artifact duration always remains shorter than the latency of the neural response under investigation. If the artifact duration extends beyond this, part or all of the response of interest will be masked by the stimulus artifact.

In experiments where multiple stimulus pulses are presented, the effectiveness of this technique is determined by interactions between the sample rate, the stimulus artifact duration and the rate at which successive stimulus pulses are presented. If adjacent stimulus artifacts overlap, for example, any neural response present will be masked by the artifact. At rates of stimulation where each stimulus artifact and neural response are temporally separate, this requires only that the artifact duration is less than the response latency and that the sample rate is adequate (as discussed previously). However, at stimulation rates where the stimulus artifact temporally overlaps the neural response of interest, the artifact duration must be shorter than both the inter-stimulus interval and the neural response duration. Furthermore, where the shape of the neural response is of interest, the artifact duration must be quite short, and the sample rate sufficiently high, to ensure adequate uncontaminated sample points between adjacent stimuli. In the present study, 70-85% (140-170 μ s of each 200 μ s stimulus interval) of the recorded neural response was masked by stimulus artifact during stimulation at 5000 pulses/s. While the broad shape of the action potential was preserved using this artifact rejection technique, some fine detail was lost (see Fig. 4a). In this case, the fidelity of the recorded action potential waveform was determined primarily by the artifact duration and stimulation rate. Consequently, decreasing the stimulus artifact duration and/or the stimulation rate would provide significantly better improvements to the fidelity of the recorded action potential waveform than increasing the sample rate alone. In experiments where the aforementioned requirements are not met, other artifact rejection techniques such as signal filtering must continue to be used.

This study has demonstrated the effectiveness of the computationally efficient sample-and-interpolate method for removing electrical stimulus artifact from electrophysiological recordings at stimulation rates from 200 to 5000 pulses/s. While this technique will also work at stimulation rates below 200 pulses/s, any reduction in stimulus artifact duration may also allow it to operate at rates above 5000 pulses/s. This technique may also be adapted to studies investigating other electrically evoked potentials, and may be particularly useful where the stimulus artifact and neural response overlap temporally.

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Fig. 1.

a) Variation in the stimulus artifact waveforms across multiple repetitions of a single stimulus. The stimulus, delivered to bipolar intracochlear electrodes, was a biphasic, charge-balanced electrical stimulus current pulse (100 μ s/phase, 50 μ s interphase gap) delivered at 1.5 mA. Artifact waveforms, recorded from a cat auditory nerve fiber, were provided by A. Wise. b) Stimulus artifact waveforms, recorded from a guinea-pig auditory nerve fiber, following an electrical stimulus pulse delivered via a monopolar electrode pair. The biphasic, charge-balanced electrical stimulus pulses (25 μ s/phase, 8 μ s interphase gap) were presented at 0.8 mA, 1.0 mA and 1.2 mA. The artifact is comprised of two large phases, P1 and P2, and a third, smaller phase, P3. c) The amplitude of P3, while much smaller than P1 or P2, is comparable to that of the recorded action potentials.

Fig. 2. Stimulus artifact amplitude (a) and duration (b), measured for each of the three artifact phases identified (mean $\pm$ sem), in one neuron in response to a 5000 pulses/s stimulus pulse train across all stimulus currents. Large changes in artifact amplitude and duration were observed with increasing stimulus intensity. While the amplitude of P3 is relatively small compared to P1 and P2, it was as large as many action potentials (up to 20 mV) at the lowest stimulus current levels and much larger than most action potentials (up to 100 mV) at the highest stimulus current levels presented.

Fig. 3.

a) The upper trace shows the raw signal recorded for the duration of a stimulus train presented at 5000 pulses/s while the lower trace shows the same recorded signal following the removal of the stimulus artifact using the sample-and-interpolate technique (Note different scale bars). The stimulus artifact, which obscures the neural response entirely, is 20 times larger than the underlying action potential. The sample-and-interpolate technique can successfully remove the stimulus artifact from the underlying neural response, even at high rates of electrical stimulation. b) Shown is the raw signal (grey) overlaid with the output of the sample-and-interpolate artifact rejection method (black) for the first 5 ms of the signal in a. c) An enlarged section of the recording shown in b (indicated by the outlined box). The regions where the artifact have been replaced with values interpolated along a straight line (solid black line), as well as the remaining raw sample points (single points), are shown. This method effectively removes the stimulus artifact while causing minimal distortion to the neural signal.

Fig. 4.

Action potentials evoked by pulsatile electrical stimulation presented at 5000 pulses/s (black) overlaid against spikes uncontaminated with stimulus artifact (grey; spikes evoked by 200 pulses/s stimulation). Stimulus artifact was removed using one of four software-based methods; a) sample-and-interpolate, b) signal filtering (Low Pass: 2000 Hz, High Pass: 50 Hz), c) sample-and-hold and d) template subtraction. The sample-and-interpolate technique effectively removed the stimulus artifact from the recorded signal while causing minimal distortion to the underlying action potential. Signal filtering and sample-and-hold removed stimulus artifact, although these methods both distorted the underlying action potential. Template subtraction, without template matching optimization, significantly reduced, but did not completely remove, the stimulus artifact.

Commonly used artifact rejection techniques were assessed against four criterion and compared to the newly described sample-and-interpolate technique. A tick affirms that, for the artifact rejection technique assessed, the criterion statement is true; a cross indicates it is false and a question mark indicates that the criterion statement depends upon the technique implementation. While the hardware based techniques have no computational requirements, they are not suited to all experimental conditions; the software based implementations of these methods have the same fundamental limitations. Artifact template subtraction overcomes some of these limitations, although it requires a known or predictable artifact shape. Template optimization methods may be used to improve the fit between the artifact template and a variable artifact shape, although this also increases the computational requirements. The newly described sample and interpolate technique is computationally efficient and is able to overcome many of the limitations of previously available methods.

Table 1

Method	Signal and artifact can overlap in time	Signal and artifact can overlap in frequency	Artifact waveform can vary	Computationally efficient
Hardware Based	Filter Sample-and-Hold	✓ ✗	✓ ✓	- -
	Filter Template Subtraction Sample-and-Interpolate	✓ ✓ ✓	✓ ? ✓	? ? ✓