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Generalized framework for stimulus artifact removal

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ABSTRACT

Stimulation is extensively used in neuroscience research in diverse fields ranging from cognitive to clinical. Studying the effect of electrical and magnetic stimulation on neuronal activity is complicated by large stimulation-derived artifacts on the recording electrodes, which mask the spiking activity. Multiple studies have suggested a variety of solutions for the removal of artifacts and were typically directed at specific stimulation setups. In this study we introduce a generalized framework for stimulus artifacts removal, the Stimulus Artifact Removal Graphical Environment (SARGE). The framework provides an encapsulated environment for a multi-stage removal process, starting from the stimulus pulse detection, through estimation of the artifacts and their removal, and finally to signal reconstruction and the assessment of removal quality. The framework provides the user with subjective graphical and objective quantitative tools for assessing the resulting signal, and the ability to adjust the process to optimize the results. This extendable publicly available framework supports different types of stimulation, stimulation patterns and shapes, and a variety of artifact estimation methods. We exemplify the removal of artifacts generated by electrical micro- and macro-stimulation and magnetic stimulation and different stimulation protocols. The use of different estimation methods, such as averaging and function fitting is demonstrated, and the differences between them are discussed. Finally, the quality of removal is assessed and validated using quantitative measures and combined experimental-simulation studies. The framework marks a shift from "algorithm" and "data" centric approach to a "workflow" centric approach, thus introducing an innovative concept to the artifact removal process.

1. Introduction

Stimulation in different areas of the central nervous system is widely used in neuroscience, for both exploring basic science, and for treating the symptoms of multiple pathological states (Benabid et al., 1994; Wichmann and DeLong, 2006). Stimulation is carried out in a large spectrum of experiments including in vitro (Wagenaar et al., 2005), in vivo, and even human studies, and may take different forms ranging from electrical micro-stimulation (Dostrovsky et al., 2000; Erez et al., 2009) to electrical macro-stimulation (Hashimoto et al., 2003; Carlson et al., 2010) and magnetic stimulation (Moliadze et al., 2003; Strafella et al., 2004). The study of neuronal activity during electrical or magnetic stimulation is a challenge because of the large artifacts generated by the stimulation pulses which mask the spiking activity and make standard methods of spike identification and sorting impractical. When a stimulus pulse is delivered, large electrical transients are evident in the signal recorded by the electrodes. These large, rapid electrical changes, which in most cases reach saturation in the acquisition systems, result in a period during which spikes cannot be extracted at all. Following this initial period, the stimulus effect, termed 'stimulus artifact', is still present for a time period of milliseconds or even tens or hundreds of milliseconds, distorting the recorded signal (Wagenaar and Potter, 2002). These changes are a result of the combination of several factors such as the capacitive properties of the acquisition device, the tissue properties, the electrode properties, and others. During this second period spikes are distorted but may be observed, although their identification in the raw recorded signal by automatic or even semi-automatic methods is impossible in most cases. These stimulation artifacts can be partially suppressed by online hardware and software solutions (Wagenaar and Potter, 2002; Brown et al., 2008). However when these are not applicable, or do not fully remove the artifacts, the use of offline artifact removal algorithms is a necessity.

The shape of a stimulus artifact is influenced by a complex non-linear combination of multiple parameters, such as the stimulation type (e.g., electrical, magnetic), properties of the stimulating and recording electrodes (e.g., impedance, shape of tip), the distance between the stimulation and recording sites, single stimulus pulse properties (mono- vs. biphasic, duration and amplitude), the stimulation protocol (such as frequency, temporal organization) and

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even properties of the amplification, filtering and acquisition system (Ranck, Jr., 1975; Merrill et al., 2005). Previous studies have demonstrated the utility of offline removal of stimulation artifacts using different methods, which can be divided into three main types. The first type includes methods in which the stimulus artifact is removed, including its decaying tail, and set to baseline values or replaced by a linear interpolation linking the two closest remaining sampled points before and after the pulse (O'Keeffe et al., 2001; Heffer and Fallon, 2008). This type of removal is efficient in terms of time, but inevitably leads to a loss of spiking activity within the whole tail of the artifact. The other two types try to cope with the tail of the artifact to preserve the spiking information that might exist there. The second type covers averaging-based methods. These methods assume that consecutive artifacts of stimulation pulses are similar in shape, and therefore can be removed using the average shape (Wichmann, 2000; Hashimoto et al., 2002; Montgomery, Jr. et al., 2005), while preserving the spiking activity which differs following different stimulation pulses. The third type includes function fitting methods, in which a specific function (or function family) is fitted for each stimulus artifact. After the subtraction of the function, which approximates the slow components of change in the signal, the spiking activity, which is characterized by rapid changes in the signal, can be extracted. Different functions may be used for this artifact removal, and are primarily based on their resemblance to the shape of the artifact. For example, in many cases the artifacts decay exponentially; thus, an exponential function, or the sum of two exponential functions, may be fitted to the artifact (Harding, 1991). Another family of functions that may be fitted to the artifacts is polynomials of varying degrees, where a single polynomial can be fitted for the whole artifact, or a different polynomial can be fitted for a predefined window around each sampled point (Wagenaar and Potter, 2002).

Previous solutions for the removal of artifacts focused on specific data sets of stimulation which were performed for special purposes. This required the *de novo* development of an artifact removal solution tailor-made for each stimulation configuration. In this paper we address this problem by introducing a general framework, the Stimulus Artifact Removal Graphical Environment (SARGE), aimed at the removal of artifacts from multiple types of stimulations (micro-stimulation, macro-stimulation, magnetic stimulation) and stimulation patterns (high frequency, low frequency, etc.). The SARGE has a graphical interface for a multi-stage process that considers multiple aspects of the stimulus and recorded signal to best remove the artifacts and reconstruct the signal, thus enabling the extraction of spiking activity. It combines semi-automatic calculations, but also makes it possible to adjust various parameters to different artifacts. The framework provides a convenient graphical user interface (GUI) and workspace in which large data sets can be relatively easily processed, as increasing amounts of data can be acquired as a result of the advanced technology. Additionally, quality assessment tools are provided within the framework to insure accurate results and successful extraction of spiking activity in later stages of analysis. In this study, we present the SARGE and the methods of analysis, and illustrate their application on simulated data and on experimental recordings from behaving animals.

2. Materials and methods

2.1. Animals and electrophysiological recordings

Neurophysiological recordings from three cynomolgus (*Macaca fascicularis*) male monkeys were used. The monkeys' water and food consumption and weight were checked daily and their health was monitored by a veterinarian. All procedures were in accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals* and *Bar Ilan University guidelines for the use and care of laboratory animals in research* and were approved and supervised by the *Institutional Animal Care and Use Committee (IACUC)*. Full details of the experimental protocol appear elsewhere (Erez et al., 2009). Briefly, data were acquired simultaneously via up to 12 glass-coated tungsten microelectrodes (impedance 0.2–0.7 MΩ at 1 kHz). The electrode signal was amplified (*1000) and band-pass filtered (2–8000 Hz four-pole Butterworth filter) (MCP-Plus 4.10, Alpha–Omega Engineering, Nazareth, Israel). The signal was continuously sampled at 40 kHz with 14-bit resolution (Alphamap 10.10, Alpha–Omega Engineering), yielding a ∼0.5 μV acquisition amplitude resolution.

2.2. Stimulation

Three basic types of stimulation were used to assess the performance of the artifact removal framework: electrical micro-stimulation, electrical macro-stimulation and magnetic stimulation. All recording protocols were comprised of a period of spontaneous baseline activity followed by the application of stimulation.

2.2.1. Electrical micro-stimulation

Monopolar micro-stimulation generated using an optically isolated stimulator (STG-2008, Multichannel Systems, Reutlingen, Germany) was delivered using one of the microelectrodes (impedance 0.2–0.35 MΩ at 1 kHz). The stimulation pulses were current stabilized and consisted of 40–80 μA biphasic (200 μs cathodal followed by 200 μs anodal phase) pulses. The distance between the stimulating and recording electrodes varied and ranged from ∼500 μm up to 5 mm.

Multiple patterns of stimulation were used for the assessment: (1) continuous stimulation, either at a high frequency (HF) (135 Hz) or low frequency (LF) (10 Hz), (2) bursts of stimulation—30 bursts of stimulation, separated by an interval of 500 ms; each burst was comprised of 40 pulses at 135 Hz, (3) continuous high frequency stimulation with variable intervals between pulses (5, 6, 7, 8, 9 ms, equally distributed, yielding an average frequency of 135 Hz).

2.2.2. Electrical macro-stimulation

Electrical macro-stimulation was used to simulate the pulses applied for therapeutic purposes during deep brain stimulation (DBS) in Parkinson's disease and other disorders. Monopolar macro-stimulation generated using an optically isolated stimulator (STG-2008, Multichannel Systems) was delivered through a Narylene coated 28 G tube (impedance 2 kΩ at 1 kHz). The stimulation pulses were voltage stabilized and consisted of 0.5–3 V monophasic (60 μs cathodal phase) or 2–6 V biphasic (200 μs cathodal followed by 200 μs anodal phase) pulses. These were applied at a continuous high frequency (125 Hz or 135 Hz) for 120 s. The distance between the stimulating and recording electrodes varied and ranged from ∼500 μm up to 4 mm.

2.2.3. Magnetic stimulation

Magnetic stimulation pulses were generated using a custom-made magnetic stimulator. The stimulation was applied using a custom-made 25 mm diameter circular coil. The stimulation pulses were comprised of a cosine shape, with a 200 μs cycle length. The generated fields were up to 1.5 T using voltages of 200–800 V. The stimulation pulses were applied using the coil located within the recording chamber. Each stimulation session consisted of 60–120 pulses at a frequency of 0.2–4 Hz.