Artefactual origin of biphasic cortical spike-LFP correlation

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Abstract

Electrophysiological data acquisition systems introduce various distortions into the signals they record. While such distortions were discussed previously, their effects are often not appreciated. Here I show that the biphasic shape of cortical spike-triggered LFP average (stLFP), reported in multiple studies, is likely an artefact introduced by high-pass filter of the neural data acquisition system when the actual stLFP has a single trough around the zero lag.

Introduction

Local field potential (LFP) is a readily measurable signal that provides a wealth of information on neuronal activity in the vicinity of the recording electrode. In particular, the relationship between LFP and the firing of nearby neurons can lead to important insights into the cortical function, e.g., [1–8], and can be utilized in the design of brain-machine interfaces (BMIs) [9,10]. The simplest quantitative measure of the relationship between spiking activity and LFP is the spike-LFP cross-correlation, also known as spike-triggered LFP average (stLFP). stLFP can be computed for spike trains of individual neurons as well as for multi-unit spiking activity (MUA). In the former case, the shape and magnitude of stLFP are inherited from the cross-correlation between the membrane potential of the neuron (Vm) and the LFP [11].

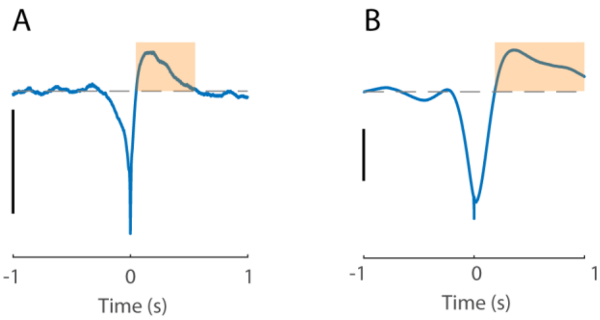

Figure 1. Examples of biphasic stLFP. (A) Recording performed with OpenEphys system (1 Hz cutoff setting) and Intan amplifier head-stages. **(B)** Recording performed with Cerebus system. The positive peak which follows the central trough and produces the characteristic biphasic shape of stLFP is highlighted. Scale bars: 50 µV. In both examples the spike train was comprised of all the spikes detected on a silicon probe used in the recording. The recordings were performed in the mouse primary visual cortex.[1]

In multiple previous studies, including our own, the stLFP often had a characteristic biphasic shape, whereby a trough around the 0 time lag is followed by a slower positivity, with a peak having an offset of several hundred milliseconds (Fig. 1 and [2,3,11–14,7]). This positive peak of stLFP is generally thought to have a biophysical origin, and several possible explanations were proposed [13,15]. Here,

[1] All experimental procedures were conducted according to the UK Animals (Scientific Procedures) Act 1986 (Amendment Regulations 2012). Experiments were performed at University College London under personal and project licenses released by the Home Office following institutional ethics review.

I show that in our data the positive peak of stLFP is a by-product of high-pass filtering of the actual LFP by the neural data acquisition system. Since passing the acquired signal through a high-pass filter with a cutoff frequency of ~0.1 – 1 Hz is a standard feature of extracellular recording systems, it would only be natural to presume that the same explanation applies to other similar reports in the literature. Such interpretation also explains why in some studies, most notably when LFP was measured with an intracellular amplifier (i.e. recording LFP in DC mode, which lets through all frequencies), a biphasic correlation between the LFP and the Vm of nearby neurons was not observed, e.g., [16,17].

Results

The way low frequency signals are processed by the neural data acquisition system is central to the understanding of the stLFP waveform. To measure the transfer function of an acquisition system, I connected a function generator (TG310, Thurlby Thandar Instruments, UK) to the head-stage of the amplifier, and delivered sine waves of equal amplitude (~5 mV) spanning frequencies between 30 Hz and 0.03 Hz. The signal generator also emitted a TTL signal, which marked the extrema of the input sine wave (Fig. 2A,C). Comparing the TTL signal to the output of the amplifier allowed estimating the phase shift introduced by its filters, while comparing the amplitude of the output across frequencies provided an estimate of the gain (Fig. 2B,D). In this manner I obtained the transfer function for Cerebus (Blackrock Microsystems, Salt Lake City, UT) and OpenEphys [18] systems. The Cerebus system was tested in the basic setting, where no digital filtering followed the initial analog high-pass filtering with a 0.3 Hz cutoff in the amplifier. OpenEphys recordings were performed with RHD2132 Intan amplifier head-stage (Intan Technologies, Los Angeles, CA). The OpenEphys system was tested with 1 Hz cutoff frequency of the high-pass filter, which is the default of its data acquisition software, and with 0.1 Hz cutoff, which is the lowest possible value in this system. The results of these measurements are presented in Fig. 2E,F.

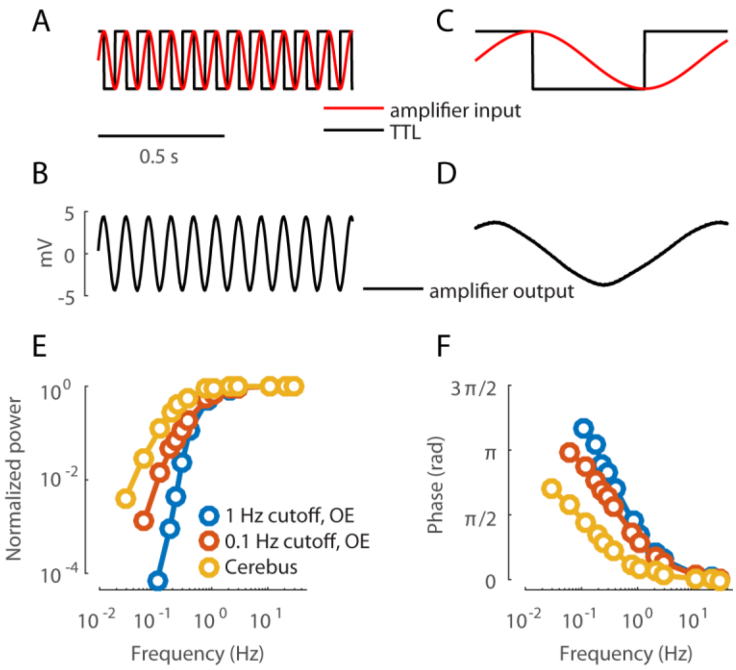

Figure 2. Measurement of the amplifier transfer function. (A) Output of the function generator: the sine wave (red) was fed into the head-stage of the amplifier, and the TTL signal (black) was stored for offline analysis. **(B)** The output of the amplifier, which was also stored for offline analysis. **(C,D)** As in A,B for a sine wave of lower frequency. A clear phase shift between the input (C, red) and output (D) sine waves is seen, with the output leading the input. A small reduction in amplitude (cf. B, D) is also apparent. **(E,F)** The gain and the phase shift introduced

by the amplifier, measured as demonstrated in A-D, for OpenEphys (OE) system with 0.1 Hz and 1 Hz cutoffs, and for the Cerebus system.

To understand the effect such high-pass filtering has on the LFP and its correlation with spikes or Vm of nearby neurons, consider two synthetic signals[2] with a symmetric correlation on the same timescale as empirical stLFPs (Fig. 3A). After the second signal was modified by the transfer functions of the amplifiers (this was done in the frequency domain), its correlation with the first signal became biphasic, similar to the observed cortical stLFP (cf. Figs. 1, 3B).

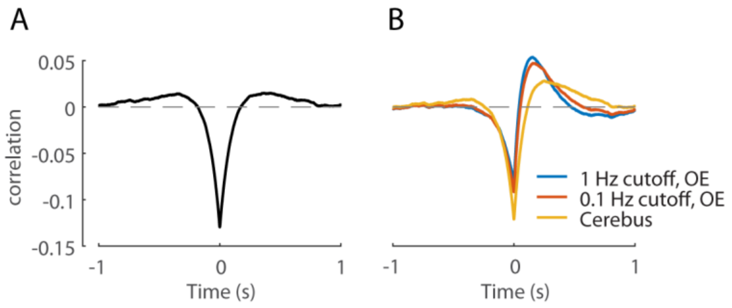

Figure 3. The effect of high-pass filtering on cross-correlation. (A) Symmetric cross-correlation between a pair of synthetic signals $x(t)$ and $y(t)$. **(B)** The cross-correlation of $x(t)$ with $y(t)$ after the latter was filtered with the transfer functions shown in Fig. 2E,F.

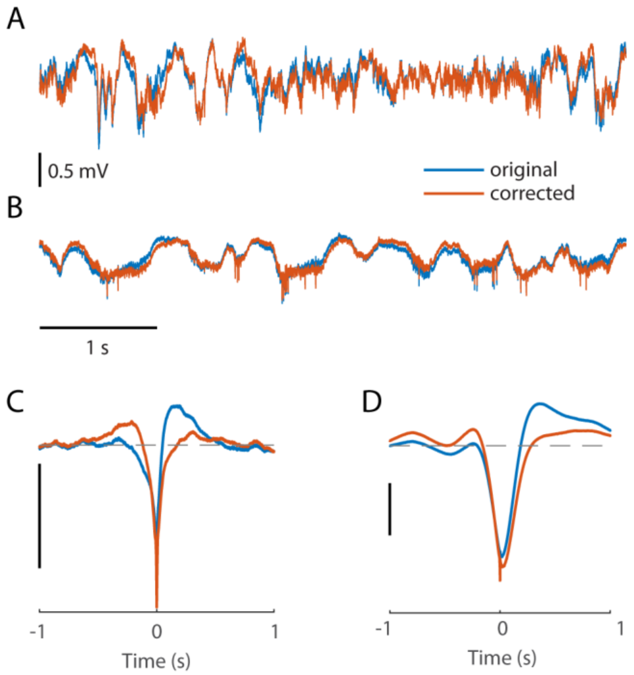

Figure 4. Offline correction of phase distortion. (A) Example of LFP in mouse primary visual cortex, recorded with the OpenEphys system with 1 Hz cutoff, before and after the phase correction. **(B)** As in A, for LFP exhibiting a rather different dynamics, recording performed with the Cerebus system. **(C,D)** stLFP for recordings shown in A-B, computed using LFP signal as it was recorded by the data acquisition system and after its phase was corrected. Scale bars: 50 µV.

The knowledge of the transfer function of the amplifier allows to reverse, via offline processing, the phase distortion the amplifier introduces into the LFP recording. Such offline processing involves shifting the phase of each frequency back by the same amount it was shifted by the amplifier's high-pass filter. In addition, for frequencies near the filter's cutoff that have a sufficiently high SNR, it is

[2] The two signals were generated in the frequency domain, with the same power spectrum peaking at 1 Hz and monotonically decreasing coherence.

possible to correct their amplitude. Examples of LFP traces before and after the phase correction (but no amplitude correction) are shown in Fig. 4A,B. As expected, the difference between the recorded and the corrected signals primarily involves lower frequencies, and at first glance might appear rather small. However, after the phase correction, the correlation with the spiking activity was no longer biphasic (Fig. 4C,D).

Discussion

A comprehensive overview of the distortions caused by recording electrodes and amplifier filtering was provided by Nelson et al. in [19]. Here I did not consider distortions introduced by the silicon probe because according to their measurements such a distortion is relatively small (< 20 degrees) for amplifiers with input impedance > 1 GΩ (which, according to the specifications, is the case for both Cerebus and Intan amplifier head-stages).

The methodological approach to measuring and correcting the distortion used here is virtually identical to the approach proposed in [19]. However, Nelson et al. do not provide any concrete examples, beyond a passing mention of numerous publications where LFP distortion might not have been accounted for. Therefore, to the best of my knowledge, the present note is the first to provide a concrete example of a well-documented feature of spike-LFP dynamics that appears to be produced by amplifier filtering rather than genuine biophysical mechanisms. The fact that low frequencies are distorted by the vast majority of neural data acquisition systems in use today has important potential implications for LFP studies, and I hope that the present example concerning stLFP will help illuminating this general point.

The distortion of the low frequencies of the LFP can be corrected offline. This requires measuring the transfer function of the amplifier system and reversing its effect, as demonstrated here and in [19]. An example Matlab code to perform this correction is provided in supplementary material of [19], and some vendors might already have a special utility for their neural data acquisition systems (e.g., FPAlign of Plexon Inc, Dallas, TX).

Acknowledgements

I would like to thank Sylvia Schroeder and Nicholas Steinmetz for commenting on the manuscript and Kenneth Harris and Matteo Carandini for supporting this work (via Wellcome Trust grants 95668 and 95669).

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