

Channel Interactions During Synchronous Microstimulation with High Density Microelectrode Arrays

Hokanson JA¹, Ayers CA¹, Gaunt RA², Weber DJ^{1,2,3}

¹Dept. of Bioengineering, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

²Dept. of Physical Medicine and Rehabilitation, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

³Dept. of Veterans Affairs, Pittsburgh, Pennsylvania, USA

Abstract

Our lab is actively involved in trying to create a neural interface that provides somatosensory feedback using arrays of electrodes implanted in dorsal root ganglia (DRG). Experimental evidence suggests strong interaction effects on evoked cortical activity due to synchronously occurring stimulation pulses on nearby electrode channels (400 μm) at low stimulation amplitudes (5 μA). Justification for a neural model that can quantify the extent of interaction effects of the electric fields generated by each electrode at the site of neuron recruitment is presented. Issues with current neuron models are discussed in light of the transition to scales where previous model assumptions may no longer be valid.

Keywords: primary afferent microstimulation, neuron modeling, synchronous stimulation

Introduction

Somatosensory feedback is desired in motor prosthetics to improve motor control ^[1]. Currently we are trying to understand how to best provide feedback through artificial electrical activation of neurons. To do this our lab is examining primary afferent microstimulation (PAMS) through electrode arrays inserted into dorsal root ganglion (DRG) tissue in cats. We are working to develop a model in which we record the evoked responses in sensory cortex ^[1,2] to microstimulation in the DRG to experimentally understand the functional consequences of PAMS and compare between different stimulation patterns. The goal of this work is to identify in the vast array of possible spatiotemporal stimulation patterns a subset of stimulation parameters that are most effective in delivering information to the brain.

Within the context of our experimental work, intermediate structures between the electrodes and sensory cortex are treated as a black box. In these studies, the primary concern is the input/output relationship between stimuli and evoked cortical activity. We have also begun experiments and computational modeling studies aimed at understanding the direct effects of stimulation on the recruitment of DRG neurons ^[3-4]. Knowing the stimulation threshold and rate of recruitment for different fiber types in the DRG allows us to design protocols that are specified in terms of

primary afferent activation instead of just stimulus parameters.

One particularly unexpected experimental result was the observation of responses in S1 cortex that were tightly time locked to the occurrence of synchronous stimulation pulses applied 15 ms earlier. Fig. 2 shows an example in which 5 μA stimulation pulses occurring synchronously on a pair of neighboring electrodes evoked a very consistent response in cortex. Initially, we did not expect channel interactions to occur at such low intensities of stimulation. The importance of a neuron model in helping to understand this phenomenon is discussed.

Synchronous Stimulation

The increase in number of stimulus channels raises new questions as to how to best handle the potential increase in complexity from spatiotemporal patterning of multiple channels. The use of multiple “independent” feedback channels, whether consisting of single channels or groups of channels leads to an exponential increase in the likelihood of synchronous stimulation. Synchronous events between feedback channels could lead to changes in higher-order neuron activation and stimulus perception as compared the feedback provided by each channel in isolation.

Changes in higher-order activation from simultaneous stimulation can occur in one of two

ways, from synaptic convergence at downstream targets or from changes in primary afferent recruitment from electric field interactions. It is also possible to have some combination of both.

In general it is difficult to distinguish between these two interactions effects when only observing downstream neurons, as is done in our experiments. For example, it is possible for a cortical neuron to respond only when two neighboring channels are stimulated simultaneously. Field interactions caused by this synchronous stimulation could recruit additional primary afferent neurons having strong projections to the monitored cortical neuron. Alternatively, both stimulus channels could recruit neurons that project onto a common pool of intermediate neurons.. The synchronously timed stimulation pulses may give rise to improved spatial summation at post-synaptic cells receiving input from both stimulation sites. Since in general it is difficult to observe the recruited primary afferents directly, a neural model that could determine the extent to which field interactions occur at different stimulus amplitudes and relative stimulus timings is desirable.

Methods

Methods are described by Weber et. al. ^[1] in the context of “replay stimulation” and are summarized briefly here. An array of 48 channels was placed in sensory cortex, and two other arrays were placed in the L6 and L7 DRG. Cortical responses to a series of successive passive ramp and hold movements using a robot were recorded. Recordings in the ganglia during 1 passive movement set served as the basis for stimulation patterns, which attempted to evoke similar activity in sensory cortex. In the stimulation trial each previously recorded action potential is replaced with a stimulus pulse such that the spatio-temporal profile of activity across the array is maintained. This approach simplifies stimulus design and variants of this approach allow further probing into feedback processing by the neural system. Stimulus waveforms consisted of an initial cathodic phase of 200 μ s followed by an anodic phase at half amplitude and 400 μ s duration. All recordings shown, including those that were used as stimuli, are from unsorted multi-unit responses.

Experimental Results

The importance of synchronous stimulation using high-density microelectrode arrays was first considered based on experimental evidence. The following experimental results highlight one of the

possible cortical changes observed during synchronous stimulation.

Fig. 1A shows an example movement pattern. Fig. 1B shows the response recorded on one of the two DRG arrays during part of a set, and serves as the basis for the stimulus. In this example, stimulation occurred on 28 channels in L6 at 5 μ A. The cortical response on a single channel to 10 repetitions of the movement is shown in Fig. 1C while Fig. 1D shows the cortical response to 7 presentations of the electrical stimulus. This cortical channel clearly responds near/during movement. This channel’s response to stimulation is different, perhaps most noticeably in the striping observed in repeated trials of the same stimulus. It is this structure that we were interested in examining further.

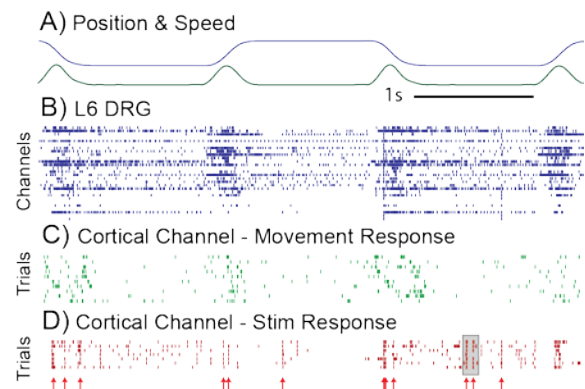


Fig. 1: Comparison of evoked multi-unit activity on a single cortical channel in response to passive movement and electrical stimulation. (A) Hip to toe distance (range 175 – 225 mm) and speed (max 24 cm/s). (B) Response in the L6 ganglia during one movement presentation. Additionally this is the spatiotemporal timing of the stimulus presented in (D). (C) Cortical response on a single channel to multiple presentations of the movement stimulus. (D) Response on the same cortical channel to multiple presentations of the electrical stimulus. Arrows indicate 1 ms windows in which at least 5 of the 7 stimulus presentations evoked a cortical response. The gray box in is shown in more detail in the next figure.

Fig. 2 examines the cortical response to DRG stimulation that occurred during a small time window of the response shown in Fig. 1. Fig. 2A shows that the cortical response is reliable and time-locked tightly to the occurrence of a synchronous stimulation event occurring on 2 adjacent DRG channels (3 and 5) 15 ms prior (Fig. 2B). For purposes of this analysis synchronous stimulation refers to stimuli on two or more channels that occurred within 1 ms of each other. It is important to note that considerable differences in electric field interactions may occur depending on the degree of synchronicity, but that complication has been ignored for this analysis. Fig. 2C shows the spatial layout of the array, from which it can be seen that stimulus channels 3 and 5 are neighbors, suggesting possible interaction effects between the

stimulation channels at the site of recruitment due to their proximity (400 μm).

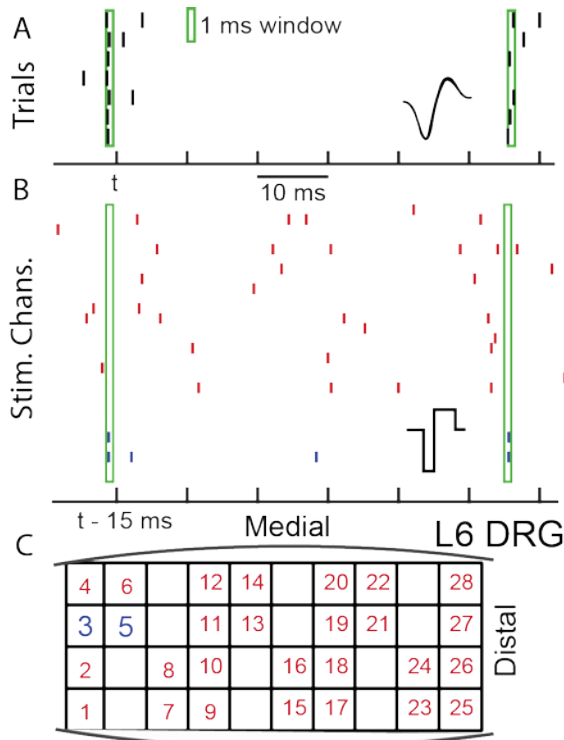


Fig. 2: Synchronous stimulation. (A) Reliable, time locked, cortical response to multiple repetitions of the same stimulus pair. (B) Timing of stimuli on all stimulus channels in the L6 DRG, each row is a stimulus channel. Channels 3 and 5 are shown in blue for visualization. Time is offset by 15 ms to account for conduction delays. (C) Spatial layout of the stimulus channels. Each channel is separated by 400 microns. As illustrated, the implant covers the majority of the ganglion.

All cases in which at least five of the seven stimulus repetitions evoked a response on this cortical channel within a 1 ms window were considered a consistent cortical response. This consistent cortical response occurred 42 times during a 15 second stimulation window, 31 of which occurred 14 – 15 ms after a synchronous stimulation event. Fig. 3A shows the number of times each stimulus was involved in a synchronous stimulation event that led to a consistent cortical response, with clear peaks for stimulus channels 3 and 5. Fig. 3B shows the total stimulus count for each channel to show that these peaks are not just due to high stimulus rates.

Discussion

The increase in number of stimulation channels available to provide somatosensory feedback leads to an increase in the likelihood of stimulus channels being active synchronously. As is shown in our results, this can lead to changes in downstream activation of neurons.

The implications of the observed stimulus interactions are currently unknown. It is proposed that a computational model to simulate PAMS

recruitment would clarify to what extent downstream effects are explainable by recruitment changes at the primary afferent level, as opposed to changes in synaptic integration at higher order neurons.

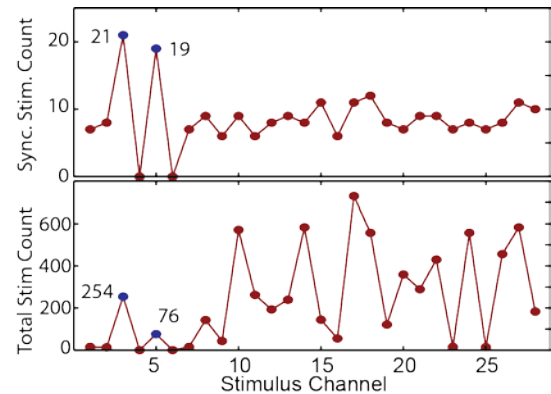


Fig. 3: Summary of stimuli. (A) Number of times stimuli were involved in synchronous stimulation that evoked a consistent cortical response. (B) Number of times each stimulus was delivered during the trial.

In our experiments any interaction between stimulus channels at the primary afferent level was unintentional, although it is possible that it could be manipulated to provide improved feedback through what is known as current steering or focusing [5]. The topic of inadvertent field interactions has been discussed considerably with cochlear implants. In 1991 Wilson presented a new cochlear implant stimulation processing strategy known as continuous interleaved sampling (CIS). By not having synchronous stimuli, speech recognition from cochlear implant use was greatly improved [6]. This concept has also expanded to retinal implants, where simultaneous stimulation is thought to reduce spatial contrast [7]. Although both fields suggest stimulation overlap is an important consideration, both contexts differ drastically from that of PAMS.

The development of a computational model to simulate primary afferent recruitment from multiple electrodes will require careful evaluation of previous models assumptions and sources of numeric parameters. As an example consider extracellular resistivity. The extracellular voltage applied to a cell is directly proportional to the extracellular resistivity. This has important implications for what is known as the current-distance relationship, or the amount of current needed to activate a neuron at a given distance. A wide range of extracellular resistivity values can be found in use in peripheral nerve models, from 55 $\Omega\text{-cm}$ [8] to 1211 $\Omega\text{-cm}$ [9] to The 55 $\Omega\text{-cm}$ value does not have a clear source. The 1211 $\Omega\text{-cm}$ is specifically for transverse resistivity in an anisotropic medium. Interestingly, the source of

this value ^[10] suggests a longitudinal resistivity of 138 to 212 Ω -cm, instead of the 300 Ω -cm used in Peterson et. al.^[9].

The values cited above give a glimpse into the variability of one of many parameters that are necessary for model specification. Resistivity in particular could have a large impact on spatial interaction of electrodes. Additional assumptions like point source modeling may be inaccurate at this scale ^[11]. Microstimulation involves distances (maximum of 200 - 300 microns) and currents (maximum of roughly 20 μ A) that have not been well examined before. Accurate modeling at this scale likely warrants a thorough review of previous models, paying specific attention to assumptions and sources of model parameters that may no longer be valid.

Conclusions

Work is ongoing to design stimulation paradigms that offer improved somatosensory feedback. One challenge with many stimulus channels is how best to use the multi-channel nature of the prosthesis. Design of a computational model that explains afferent recruitment from a number of channels should aid in this multi-channel design. A detailed understanding of synchronous stimulation effects at the level of recruitment can help to clarify downstream effects that are the result of electric field interactions versus synaptic integration at higher order neurons.

References

- [1] D. J. Weber et al., "Limb-state information encoded by peripheral and central somatosensory neurons: implications for an afferent interface.," *IEEE transactions on neural systems and rehabilitation engineering*, vol. 19, no. 5, pp. 501-13, Oct. 2011.
- [2] J. A. Hokanson et al., "Effects of spatial and temporal parameters of primary afferent microstimulation on neural responses evoked in primary somatosensory cortex of an anesthetized cat.," *Conference proceedings: IEEE Engineering in Medicine and Biology Society. Conference*, vol. 2011, pp. 7533-6, Aug. 2011.
- [3] R. A. Gaunt, J. A. Hokanson, and D. J. Weber, "Microstimulation of primary afferent neurons in the L7 dorsal root ganglia using multielectrode arrays in anesthetized cats: thresholds and recruitment properties.," *Journal of neural engineering*, vol. 6, no. 5, p. 55009, Oct. 2009.
- [4] D. J. Bourbeau et al., "A computational model for estimating recruitment of primary afferent fibers by intraneural stimulation in the dorsal root ganglia.," *Journal of neural engineering*, vol. 8, no. 5, p. 056009, Oct. 2011.
- [5] [B. H. Bonham and L. M. Litvak, "Current focusing and steering: modeling, physiology, and psychophysics," *Hearing research*, vol. 242, no. 1-2, pp. 141-53, Aug. 2008.
- [6] B. S. Wilson et al., "Better speech recognition with cochlear implants.," *Nature*, vol. 352, no. 6332, pp. 236-8, Jul. 1991.
- [7] R. G. H. Wilke et al., "Electric crosstalk impairs spatial resolution of multi-electrode arrays in retinal implants.," *Journal of neural engineering*, vol. 8, no. 4, p. 046016, Jun. 2011.
- [8] W. M. Grill and J. T. Mortimer, "The effect of stimulus pulse duration on selectivity of neural stimulation," *IEEE Transactions on Bio-Medical Engineering*, vol. 43, no. 2, pp. 161-166, 1996.
- [9] E. J. Peterson, O. Izad, and D. J. Tyler, "Predicting myelinated axon activation using spatial characteristics of the extracellular field.," *Journal of neural engineering*, vol. 8, no. 4, p. 046030, Jul. 2011.
- [10] J. B. Ranck and S. L. Bement, "the Specific Impedance of the Dorsal Columns of Cat: an Inisotropic Medium.," *Experimental neurology*, vol. 11, pp. 451-63, Apr. 1965.
- [11] C. C. McIntyre and W. M. Grill, "Finite element analysis of the current-density and electric field generated by metal microelectrodes.," *Annals of biomedical engineering*, vol. 29, no. 3, pp. 227-35, Mar. 2001.

Acknowledgements

The authors thank members of the Rehabilitation Neural Engineering Lab for their assistance during the animal experiments and with data analysis. Funding for this work was provided by the National Institutes of Health (NIBIB 1R01-EB007748, NINDS 1R21-NS-056136, NINDS 1F32-NS074565) and TATRC (W81XWH-07-1-0716).

Author's Address

James A. Hokanson
Graduate Student Researcher
jah104@pitt.edu