9th Quarterly Progress Report

October 1, 2004 to December 31, 2004

Neural Prosthesis Program Contract N01-DC-02-1006

The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation

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This quarterly progress report presents our progress in the 9th quarter of this contract. In this quarter, we completed six experiments that continued and extended our investigations of the interaction between auditory information channels. Specifics of these experiments, as well as other work completed during the quarter, are summarized briefly in the following sections, which describe our experiments and other work undertaken during execution of this contract. A following section describes the software strategy we have implemented to removal electrical stimulation artifacts from our neuronal recordings. The final section preceding the appendix of this report outlines the experiments and other work we will plan for the next quarter. Finally, the bulk of this report, collected in an Appendix, describes the analysis techniques we have developed for studying channel interaction using pulse trains interleaved on two cochlear implant channels, and the results from our preliminary experiments.

(N.B. The work described in the Appendix comprises preliminary work that will be submitted for peer-reviewed publication in an archival journal within the next year. Authors of this work may include S.Bierer, B.Bonham, R.Snyder, and S.Rebscher. The working title for this manuscript is "Neurophysiological interactions observed in the inferior colliculus during simultaneous two-channel electrical stimulation of the cochlea." Notification will be made in a future quarterly progress report when this manuscript has been accepted for publication.)

Summary description of work over last quarter

- Completion of six neurophysiology experiments investigating channel interaction in the inferior colliculus (IC). These experiments include:
    - Continued investigation of the effects of changing the Remote Current Fraction (RCF) during electrical stimulation via a cochlear implant. The RCF (see QPR #8) describes the proportion of the current applied to the active electrode that is returned via a remote (usually extracochlear) electrode, rather than via nearby intracochlear electrodes. If the RCF is 1, all current is returned via the remote electrode (i.e., stimulation is monopolar), and if the RCF is 0, all current is returned on the intracochlear return electrodes (i.e., stimulation is tripolar). This work was conducted in collaboration with Advanced Cochlear Systems, who provided the liquid crystal polymer implant electrode used in some of the experiments.
    - Continued investigation of (acoustic) channel interactions between two simultaneously presented acoustic tones in normal-hearing animals. Along with results of our earlier studies using an acoustic forward masking paradigm, these studies indicate the degree to which the spatial separation (equivalent to the *spectral* separation in normal hearing) between two stimuli influences the effect of one stimulus on the response to the other during normal hearing. These experiments provide baseline data for comparison with multi-channel stimulation of electrically-stimulated deafened animals.
    - Investigation of channel interactions between electric and acoustic channels in normal-hearing animals implanted with cochlear prostheses. These experiments model effects of electrical stimulation in implant patients who retain some residual hearing. These experiments were conducted in collaboration with Maike Vollmer of UCSF and Jochen Tillein of MedEl.
    - Continued investigation of (electric) channel interactions between interleaved current pulse trains presented on one and two channels of an intracochlear prosthesis. Our analysis techniques and the results of preliminary experiments describing interactions between two low-rate current pulse trains presented on the same implant channel are described in the Appendix.
- Fabrication of one guinea pig cochlear implant electrode used in experiments at UCSF.
- Pamela Bhati and Jamille Hetke of the University of Michigan are developing a silicon cochlear implant array and have consulted with us on insertion strategies. After preliminary discussions, we have completed plans for silicone carrier "blanks" that will be used to implant the silicon cochlear electrode arrays into cat cochleas. We have also inserted one of their arrays into the cochlea of a cat cadaver. This insertion and the subsequent dissection suggested several modifications to their array.
- During this period, we analyzed data from the above experiments, and continued analysis of data collected during previous quarters.
- We developed and implemented software (described below) to reject electrical artifacts caused by electrical stimulation from analysis of neuronal activity recordings.
- We identified a candidate new-hire for a Development Technician position. The person hired in this position will assist Steve Rebscher in implant electrode fabrication. The increased effort provided for electrode fabrication will increase our ability to make implant electrodes for our own experiments, as well as our ability to

provide implant electrodes for researchers at other institutions.

- We prepared a podium presentation for the Neural Interfaces Workshop held in Bethesda, MD.

Presentations

R.L. Snyder, "The Neurophysiological Effects of Simulated Auditory Prosthesis." Neural Interfaces Workshop, Bethesda, MD (November, 2004).

Travel

Ben Bonham, Matt Schoenecker, and Russell Snyder attended the Neural Interfaces Workshop in Bethesda, MD.

Ben Bonham, Matt Schoenecker, and Russell Snyder visited the laboratory of Xiaoqin Wang at Johns Hopkins University to discuss techniques for chronic recording in awake experimental subjects.

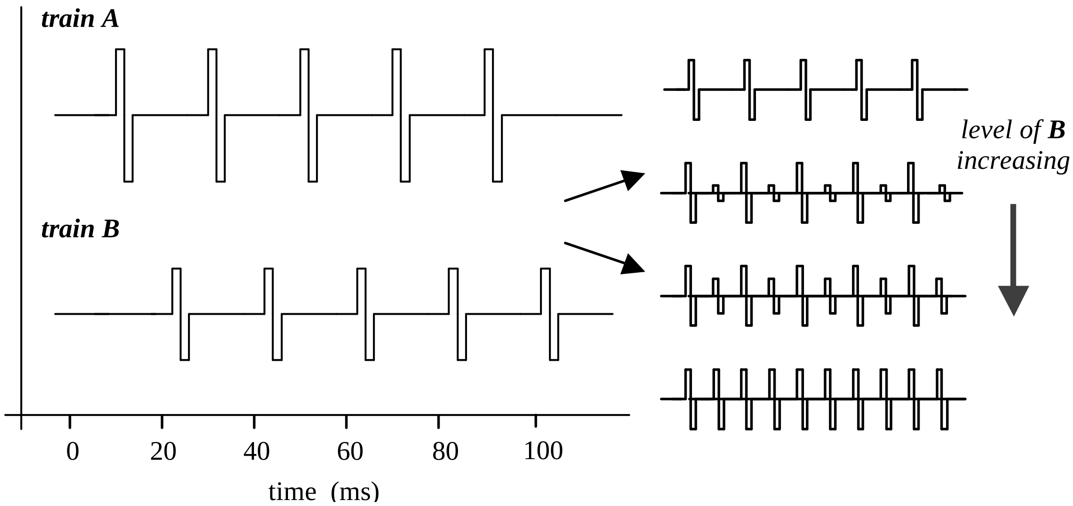

Figure 1. *Left*. Two symmetrically-interleaved, biphasic, 50 us/phase pulse trains presented at a rate of 50 pulses per second. Pulses of train B are delayed by 10 ms with respect to the pulses of train A. *Right*. The net stimulus waveform "seen" by spiral ganglion (SG) neurons at four locations relative to the two implant channels. For SG neurons that are (electrically) very far from one implant channel, the effective stimulus is the single pulse train presented on the nearer of the two channels (top). For SG neurons that lie exactly midway between the two stimulus channels, the effective stimulus is an unmodulated pulse train at twice the frequency of the individual pulse trains (bottom). But for the remaining majority of SG neurons, the effective stimulus is a modulated pulse train (center panels).

Artifact rejection and spike detection

Artifact Rejection Overview

Prior to analysis, recorded multi-channel neural activity was pre-processed off-line in two stages to remove artifacts caused by electrical current pulse stimulation and slow-wave evoked potentials. Stimulus artifacts appeared in the raw data streams as large amplitude transients. Evoked potentials appeared in the data as slower excursions of the waveform baseline. An example is shown in Figure A1. In this figure, the two transient artifacts of the top trace are similar in shape to the recorded neuronal action potentials. Without appropriate processing to remove these transient artifacts, they could be misclassified as neuronal spikes by spike detection software during the thresholding procedure described later in this section. Slow evoked potential artifacts, which begin 7-8 ms after the transient artifacts in this figure, could cause further classification errors by shifting the baseline of the recorded potential above or below the detection threshold. To avoid the influence of stimulus artifact and evoked potentials on spike detection, we developed off line tools to automatically identify and remove artifacts prior to the detection stage.

The general strategy for the rejection of transient artifacts was to pinpoint their times of occurrence on every sweep of recorded data. These transients were later deleted from the pool of candidate spikes identified during the subsequent threshold detection. In the example of Figure A1, the two identified transients are indicated by asterisks just below the middle trace.

Removal of slow-wave evoked potentials was accomplished by averaging the raw waveforms across stimulus repetitions, subtracting the average waveform from individual traces of the raw data, and high-pass filtering the resulting signal. The middle trace of Figure A1 shows the estimated slow-wave potential of that example. The signal remaining after subtraction of the evoked potentials and rejection of the transient artifacts is shown in the bottom trace.

A second example is given in Figure A2. The raw waveforms shown in the left panel were recorded at three IC depths in response to five pulses of a 50 pps pulse train. The waveform remaining after application of the artifact rejection process is shown in the right panel.

Procedure for artifact identification

All artifacts were detected separately for each stimulus condition *and* for each IC recording site. The procedure is outlined as follows:

a) A measure of the background noise was estimated for each recording site. This was calculated as the average root-mean-square amplitude of the first 10 ms of all raw data traces.

b) A threshold for the detection of transient artifacts was fixed at 3.0 times the background noise amplitude. This threshold level was low enough to detect small artifacts and most spikes. Threshold detection was performed on the absolute value of the raw waveforms.

c) Initial estimates of the slow-wave evoked potentials were made by averaging the raw recorded traces across all repetitions of a given stimulus. To prevent neuronal spikes from contributing to the estimate of the evoked potential, each individual trace was systematically examined for time points that exceeded the threshold for transient detection defined in part (b). Measured values at these time points were replaced by the average of the preceding four time points. The final estimate of the evoked potential was calculated from these spike-free traces. Most transient artifacts were eliminated from the slow-wave estimate by this procedure.

d) Transient artifacts were detected in four stages. First, the slow-wave artifacts, estimated in (c), were subtracted from every raw data trace. Second, traces were high-pass filtered, and points of each filtered trace above the threshold were designated as candidate events. Third, for each unique stimulus, a post-stimulus time histogram (50 us bins) was made of these candidate events, summed across stimulus repetitions and recording sites. A high count in any single histogram bin was interpreted as an indication that the supra-threshold events contributing to that count were artifacts, rather than neuronal spikes, since stimulus-related artifacts usually appeared on many recording channels and on all repetitions of a given stimulus. (Timing jitter of neuronal spikes and their localization to at most two recording sites prevents even repeatably occurring spikes from contributing significantly to any single 50 us bin of the histogram.) Fourth, all candidate events contributing to a high-count bin in the histogram were marked as transient artifacts. Transients typically spanned one or two bins when stimulus current pulses were 40 us/phase, and typically spanned six bins when current pulses were 200 us/phase.

e) The transient artifacts were initially identified separately for each unique stimulus and each recording channel. For some analyses, e.g., for comparison of neuronal responses between trials with different pulse rates, artifact times from all stimuli were grouped into a single pool and this common pool of times was applied in the artifact-rejection algorithm for every stimulus. This approach eliminated bias that could occur when a high number of artifact times accepted for one condition might have artificially reduced its spike counts compared to other conditions. By forcing all conditions to have the same artifact times, any analysis based on spike counts (or spike times) contains less subjective bias.

<u>Procedures for spike detection.</u>

a) Slow-wave evoked potentials were identified as described above and subtracted from recorded raw waveforms. The remaining signal was high-passed filtered to remove additional low frequency artifacts that were not synchronized to the stimulus (e.g. EMG, 60 Hz line noise). b) Candidate spike events were detected by identifying points at which the filtered waveform crossed a threshold of +/-3.2 times the background noise level. For every threshold crossing, the time of the highest peak (or valley for negative threshold crossings) of the waveform before it returned below threshold was marked as the event time. Any event that followed another event by a time less than the imposed minimum refractory time (0.33 ms) was rejected in order to avoid double-counting events with negative and positive phases or with multiple peaks. Spikes from two neurons that were recorded on the same electrode within the minimum refractory time would be counted using this method as a single spike.

b) Candidate spike event times were compared with the previously stored transient artifact times to eliminate artifacts from the candidate pool. The remaining candidate times were marked as “true” spike times and used in subsequent analyses.

An inherent risk of the artifact rejection method described above is the inadvertent rejection of neuronal spikes. The risk is greater when the stimulus artifacts overlap temporally with evoked neuronal spikes. Optimally rejecting stimulus artifacts relies upon determining an appropriate balance between detecting every spike and removing the influence of every artifact; over-estimating or under-estimating the number or the extent of the artifacts can create bias in the data analysis. Stimulus artifacts are generally different on each recording site and vary with the stimulus (e.g. with the current level or site of stimulation in the cochlea), so inappropriate application of artifact rejection can lead to artificially low spike counts for some stimulus conditions but not others. Prevention of this potential bias in data analysis guided our development of the artifact rejection procedure.

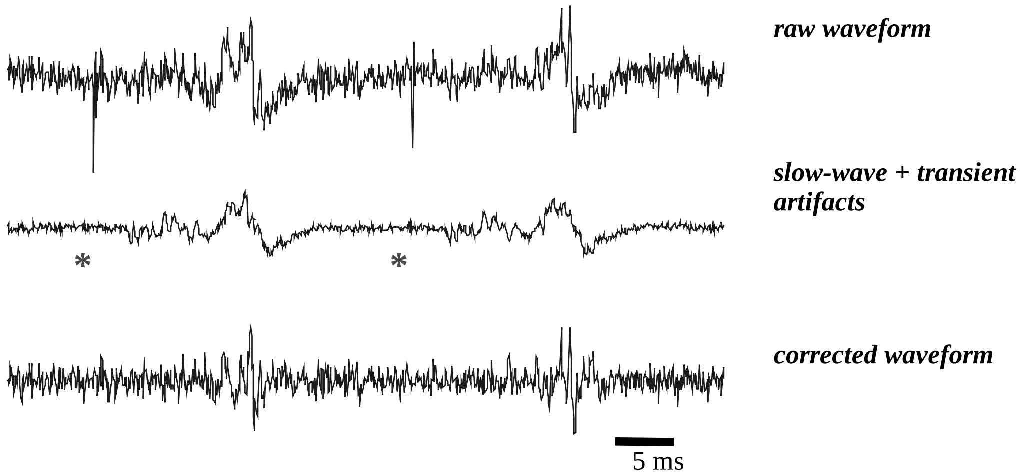

Figure A1. Illustration of the artifact rejection process. *Top panel*: A segment of the raw data from one recording channel. Two cycles of a 50 pps pulse train are shown. The timing of the pulses is easily seen as negative-going transients, which are followed by increases in spiking activity (the signal to be measured) and slow-wave evoked potentials. *Middle panel*: Identified artifacts. The trace is the slow-wave artifact, calculated as the average raw waveform over 20 repetitions of the electrical stimulus. The transient artifacts are indicated by the two asterisks. *Bottom panel*: Final corrected waveform with the artifacts removed. The slow-wave artifact is subtracted from the raw data and the difference is low-pass filtered to remove additional drift and low-frequency perturbations not related to the stimulus. The transient artifacts are rejected by setting their amplitude to zero. (In practice, transient artifacts are removed by deleting their occurrence times from the pool of detected candidate spikes.)

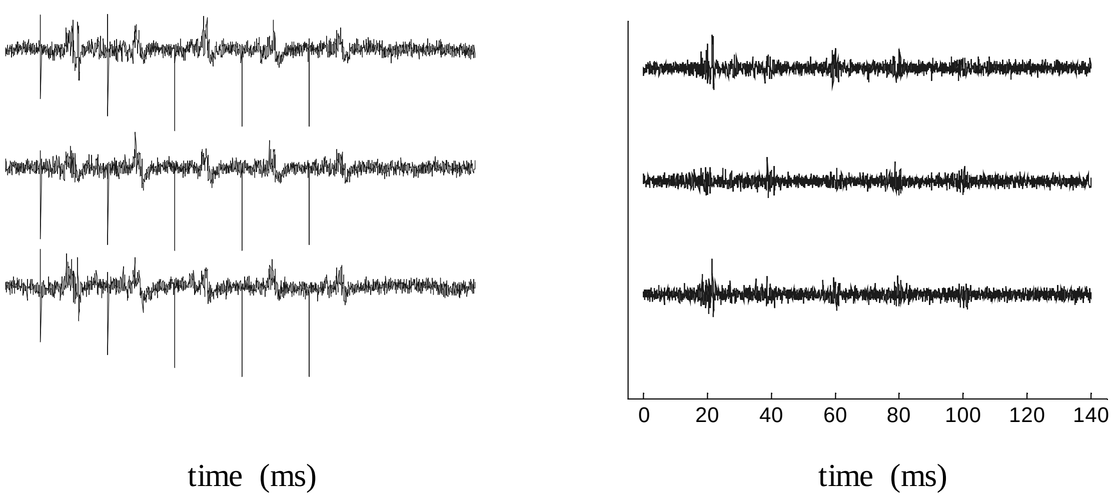

Figure A2. Artifact rejection applied to three repetitions of a 5-pulse stimulus train. *Left panel*: raw waveforms. *Right panel*: slow-wave and transient artifacts removed.

Work Planned for Next Quarter

During the next quarter:

- We will continue our investigations of electrical two-channel interaction using forward-masking (in collaboration with John Middlebrooks) and two-channel interaction using simultaneously-presented electrical pulse trains.
- We plan to assemble our new photolithographically-defined guinea pig electrode onto a space-filling silicone carrier and test it.
- We plan to continue our collaborative studies of interactions between acoustic and electrical auditory information channels (with Maike Vollmer and Jochen Tillein).
- With Leo Litvak of Advanced Bionics, we plan to begin studies of intracochlear measurements of the electrically-evoked cochlear action potential (ECAP) in guinea pigs. These measurements may provide a means to determine the spread of spiral ganglion activation during electrical stimulation. ECAP measurements will be compared with measurements made within the IC to determine the degree of agreement between the two measurement techniques, and the applicability of these measurements to human implant systems.
- Pamela Bhati and Jamille Hetke of the University of Michigan are developing a silicon cochlear implant array, and have consulted with us on insertion strategies. During the next quarter, we will provide them with silastic carriers, similar our cat electrodes, which can be used as carriers for the silicon arrays. Russell Snyder will travel to Ann Arbor to help them develop techniques for implanting these carriers with the silicon array attached.
- We will begin investigations of inter-electrode impedance measurement to determine if these measurements may be used to determine proximity of cochlear implant electrodes to tissue. If this preliminary study proves to be successful, we plan to use these measurements during electrode insertion in order to reduce incidence of trauma to cochlear structures during implantation.
- We will prepare two posters and one invited talk and present these at the annual meeting of the Association for Research in Otolaryngology (ARO).
- We have ordered a multi-channel D/A converter (RX-8) from Tucker Davis Technologies. We will install this new equipment and configure our experiment software to use it.