1st Quarterly Progress Report

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Neural Prosthesis Program Contract N01-DC-02-1006

The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation

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Abstract

This Quarterly Progress Report presents our progress in the first three months of this contract. It summarizes our progress in two areas: 1) design and fabrication of a multichannel intracochlear electrode for the guinea pig and 2) results of preliminary studies designed to model interactions among intracochlear channels as indicated by the responses of interior colliculus (IC) neurons to two-tone stimuli.

An important specification of this contract's RFP states "Using neurophysiological recording techniques in the chosen animal model(s), study the activation of target and, if appropriate, more central auditory system neurons by patterns of electrical stimulation, elicited with suitable configurations of stimulating electrodes, that mimic those used or being considered for use in human auditory prostheses." In our response, we have proposed to fabricate a guinea pig multichannel electrode that could be inserted into the guinea pig scala tympani (ST) and that closely models those used in humans. Since this electrode is the *sine qua non* of many of our neurophysiological experiments, its development represents our first priority. However, the design and fabrication of such an electrode presents a significant challenge. The guinea pig cochlea is smaller than the human cochlea. Its cross-sectional dimensions are smaller and its radii of curvature are much greater. Thus, its tolerances for design and fabrication are much narrower. In order to meet this challenge, we had first to make precise measurements of the three-dimensional structure of the guinea pig ST. We accomplished this by making high-resolution casts of it and the taking measurements of the critical dimensions from these casts. We next located a precision machinist who could convert those measurements into a CAD/CAM drawing of our electrode and could convert that drawing into a precision mold. Finally, the mold had to be assembled and initial fillings of the mold produced. Once these filling were completed, the resultant blanks were inserted into clear plastic models of the guinea pig ST, which we had fabricated in the meantime, to confirm the fit of the electrode and to determine the final contact placements. All these steps have been completed and are describe in this report. All that remains is that the contact placements must be finalized by milling small, precisely placed dimples in the floor and sides of mold, one dimple for each contact. This final step will be completed within the next couple of weeks.

In addition to fabricating an electrode mold, we have been developing an acoustic model of intracochlear channel interaction. Since very little information is available regarding channel (two-tone) interactions in normal hearing subjects, we believe that such a model will be useful as a basis of comparison with electrical channel interaction. This report summarized some of our preliminary results using this model.

A. Development of a guinea pig multichannel intracochlear stimulating electrode

The guinea pig offers several advantages over other small animal species for studying the neurophysiologic effects of electrical stimulation in the inferior colliculus (IC). These advantages include a large resource of data from previous studies, good surgical access to both the cochlea and the IC and an IC is well matched in dimensions to the readily available multichannel recording probes. These probes are produced at the University of Michigan. They allow measurement of neural responses across a broad range of frequencies distributed across the tonotopic organization of the IC.

However, multichannel intracochlear stimulation in guinea pigs requires the development of a new intracochlear-stimulating electrode. In previous guinea pig experiments, intracochlear-stimulating electrodes consisted of either flamed PtIr balls on insulated wires or multichannel arrays designed to fit the cochlear dimensions of other species. These multichannel arrays were produced at UCSF are designed for cats, whereas those produced by Cochlear Corporation, Australia are designed for humans. The electrodes consist of 4 to 6 stimulating contacts in a silicone rubber carrier and in each case, the larger dimensions and mechanical characteristics of these electrodes often results in significant trauma to intracochlear structures. It also prevents full insertion into the scala tympani, which limits the cochlear frequency representations that can be activated by the electrodes. Therefore, it was clear that an electrode array specifically designed to fit the guinea pig cochlea and that could position contacts more appropriately and with greater density would facilitate the experiments specifically designated in this contract.

Given these considerations, we have designed and begun fabrication of a new multichannel electrode array, which is specifically designed for use in guinea pigs. Our goals in the development of this array include:

1) Appropriate dimensions for the guinea pig cochlea
2) Minimization of intracochlear trauma
3) Reliable placement of contacts within the scala tympani
4) Increased contact density to enable stimulation with multipolar contact configurations and NRI (intracochlear neural response measurement)

Implementation

In order to produce a guinea pig electrode, it was first necessary to accurately measure the guinea pig scala tympani (ST). We made these measurements by making a metal replicate cast of the SF using fixed cadaver temporal bones (for details see Rebscher, 1996). Briefly, temporal bones were removed and fixed in a solution of 2% formaldehyde and 2% glutaraldehyde in phosphate buffer (0.1M). Each cochlea was isolated from the surrounding temporal bone and the round window (RW) and stapes were removed. A small fenestration was made at the apex of the cochleas to allow excess metal to overflow and standard Leur type syringe fitting was attached to the round window using histoacryl cement and dental acrylic. In a hot water bath at 70° C, low-melting-point metal (LMA 117, Small Parts, Inc.) was melted, drawn into a 1.0 cc syringe and gently injected through the RW port and into the scala tympani until excess metal was extruded from the apex and/or oval window. The cochlea was removed from the hot water bath and allowed to cool at room temperature. Finally, overlying bone was removed from the metal cast by decalcification in an acid solution accompanied by gentle dissection of remaining tissue. An example of the resulting scala tympani (ST) cast is shown in Figure 1. These casts were digitally imaged and analyzed to create a database for the

electrode mold design. LMA casts were also embedded in epoxy resin, then removed by melting, to create clear models of the guinea pig scala tympani. We have made three clear plastic models in additions to several casts of the guinea pig ST. These models and casts will be used to assess the variability in the dimensions of the ST. Our goal is to produce an electrode array that fits into the ST of most guinea pigs, but which leaves as little excess space as possible

Figure 1. Low-melting-point metal (LMA117) casts were made from cadaver guinea pig cochleae. Casts were used for dimensional analysis and to make clear plastic models of the guinea pig ST as described in Rebscher (1996). The plastic models are used to aid in evaluation of the newly developed electrodes.

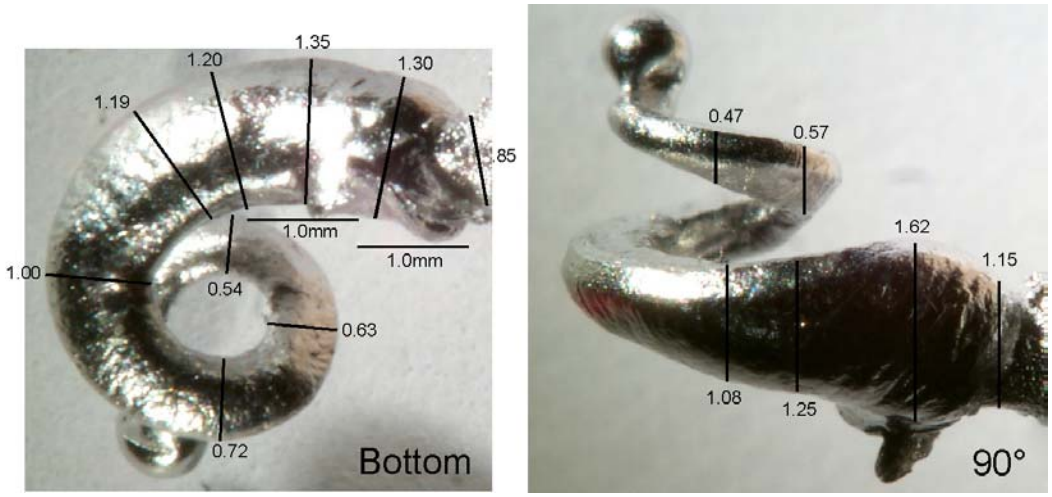

Figure 2. LMA casts were imaged and measured from five perspective angles to derive a database of dimensions for design of the guinea pig electrode mold.

Metal casts were digitally imaged and measured using Photoshop (Adobe, Inc.) and Canvas (Denaba Software, Inc.) applications. Each cochlea was imaged and measured from five perspectives to permit measurement of all relevant features. Typical examples of these images are shown in Figure 2. Height, width and radius of curvature (at 90° intervals) were included in these measurements. Round and oval cross-sections and a basic tool path were drafted based on these measurements. These templates, as well as mold features such as fill and exit channels and lead wire channels, were integrated in a full 2-D drafted layout of the upper and lower mold surfaces. These detailed specifications were transmitted to Wright Engineered Plastics (WEP, Santa Rosa, California) for fabrication of a mold. WEP is a precision plastics molding vendor with extensive experience in CAD/CAM design and mold manufacturing. At WEP, draft CAD drawings were completed, rendered in 3-D (see Figure 3, left column), reviewed at UCSF and modified based on our feedback.

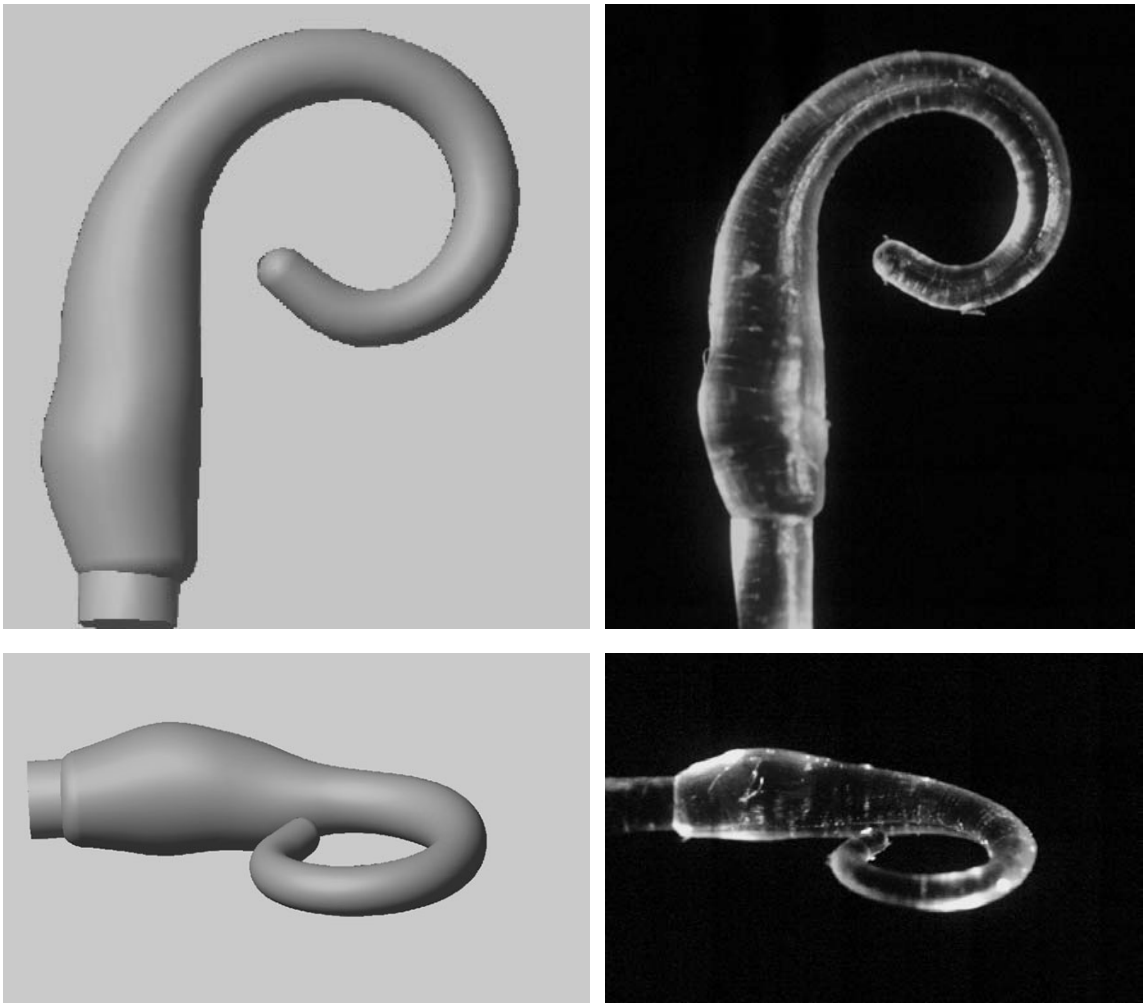

Figure 3. Rendered CAD images (left) and silicone molded parts (right).

The actual cochlear spiral portion of the mold was machined in a small, removable insert to minimize the cost and time required to make iterative design changes in the future. The first mold was produced using a CAD driven CNC milling machine followed by hand polishing. Basic dimensions were confirmed at this stage and the mold was cleaned and prepared for test filling. The resulting silicone (NuSil MED 4011) part is shown in Figure 3 (right column). When the mold was filled, both surface defects and edge flash were found to be well within acceptable limits. The final step in mold fabrication will be placement of the contact locating holes in the mold cavities. This step will be completed during the next quarter followed by fabrication of functional electrodes.

The mold base is shown in Figure 4 below. The series of dimples along the inner edge of the mold cavity (0.25 mm c-c spacing) will be used to orient the mold for machining to precisely locate positioning holes for the stimulating contacts.

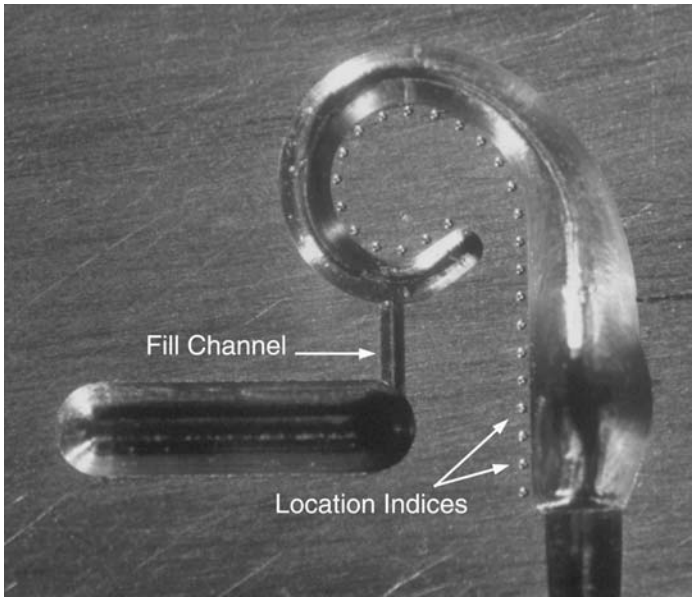

Figure 4. The lower half of the mold cavity is shown at the left. The cochlear portion of the mold was machined in a removable insert. This will allow more efficient modification of the future mold shapes and features.

B. Development of acoustic models of multichannel electrical stimulation.

Introduction

The ideal of multi-channel cochlear prosthesis design would transmit multiple independent channels of information in parallel through multiple cochlear sites. If multiple channels stimulate

identical or severely overlapping neuron populations the signal will be distorted and the result may not be better than those obtained with a single-channel implant. If the stimulation of one channel influences the perception of stimuli presented on other channels, then channel interaction is said to occur (e.g., see McDermott and McKay, 1994; McKay and McDermott, 1996).

Human psychophysical studies have sought to quantify channel interactions by comparing the perception of single-channel with two-channel stimuli using loudness estimation/ summation (Shannon 1983; Tong and Clark, 1986; McKay and McDermott 1998; 2001) and pitch perception (Townshend et al., 1987; Wilson et al., 1994; McDermott and McKay, 1994). However, these measures are difficult to test physiologically in an animal model.

Another psychophysical measure of channel interaction is forward masking and that measure has a clear physiological correlate, a change in threshold or suprathreshold response rate. Forward masking occurs when the first stimulus, the masker, reduces the detectability (threshold or loudness) of the second stimulus, the probe. The degree of spatial overlap in the excitation of the auditory nerve fibers is likely to be related directly to the degree of forward masking that occurs. Psychophysical forward masking experiments have been performed in cochlear implant users and have been compared to acoustic forward masking and to physiological data (see Shannon 1983; Chatterjee and Shannon 1998).

To study channel interactions physiologically, one should compare the spatial spread neuronal responses to each of two stimuli and then the responses evoked by the stimuli together. We plan to examine auditory interactions using both a simultaneous and a forward masking paradigm for both acoustic and electrical stimuli. In developing an animal model of channel interaction in the auditory system, we have begun by examining the physiological responses to simultaneous and forward masked acoustical stimuli. These acoustic experiments will provide a basis for direct comparison of channel interactions between normal hearing subjects and cochlear implant listeners.

Methods

Two-tone stimuli were generated by Tucker-Davis Technologies RP2.1 signal generators running at 100 kHz. The levels of these signals are controlled by TDT PA-5 digital attenuators, amplified by Samson model 220 audio amplifiers, and presented in the free-field through a Radio Shack super tweeter (model 40-1310). The sound system was calibrated using a B&K 4182 microphone and custom software. After calibration, the speaker transfer function was flat within +/- 2 dB SPL from 2000 - 41500 Hz (see appendix 1). Both masking and probe tone stimuli were 50 ms long, and had 2 ms raised-cosine onset/offset ramps. The interval between onsets of the first (masker) and the second (probe) tones was fixed for a given stimulus series; but may be different in different series. A series consisted of a masker tone that was varied in frequency and level. The masker tone frequency range was 3.8 octaves, from 3084 through 41500 Hz, and its intensity range was 65 dB, from15 through 80 dB SPL. This is a standard range of stimuli used to determine frequency response areas (FRAs) for auditory neurons. The second or probe tone was fixed in frequency and intensity. Its parameters were chosen so that it was clearly within the excitatory area of at least one of the sixteen recording sites (see next paragraph). (Figures show 15 kHz at 35 dB SPL constant tone beginning 20 ms after start of varying tone.) Neuron responses were recorded from the central nucleus of the inferior colliculus (ICc) using 16-channel silicon recording probes (16Chan and 16ChanR, single 5 mm shank probes, see appendix II) obtained from the Center for Neural Communication Technology at the University of Michigan. Probes were inserted along a

standard trajectory into the IC to a depth where responses to broadband noise bursts were observed on all 16 channels. Coarse tuning curves were recorded to determine approximate FRAs at each the 16 recording sites. These low resolution FRAs were used to adjust the probe depth. If response areas on superficial or deep electrodes indicated that advancing or retracting the probe would increase the number of sites with CFs within the desired range, then the probe was advanced or retracted slighty. After adjusting the depth, a low resolution FRAs was again recorded. When the probe depth was determined to be adequate, the probe was stabilized by filling the cranial deficit with 2% agarose and the agarose and exposed calvarium covered with dental acrylic. Each probe electrode site recorded spike activity from several neurons. In many instances, however, activity of single neurons could be sorted from the multi-unit activity by using custom software to determine single-unit responses. Stimulus presentation and recording of neural responses were controlled by custom software written in LabView and Matlab.

Acoustical forward masking used for the present experiment included two tones of equal durations with varying stimulus onset. Figure 5 is a schematic representing the stimulus envelopes for the subsequent examples.

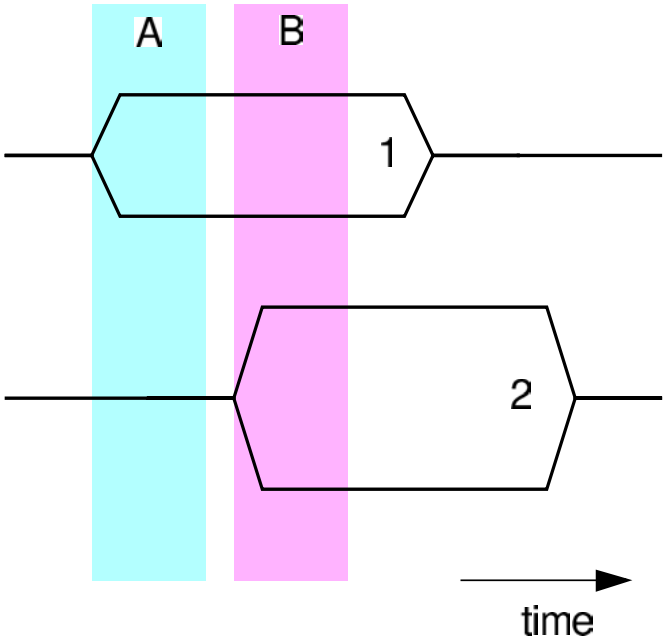

Figure 5. Diagram of Two-Tone stimulus envelops. First or masker tone (1) is of variable frequency and intensity (3.08-41.5 kHz; 15-80 dB SPL). Second or probe tone (2) is fixed in frequency and intensity at 15 kHz; 35 dB SPL. Onset of second tone is delayed 20 ms from onset of the first tone. Responses illustrated in **Figures 6** was recorded during interval "A" when the two tones do **not** overlap. **Figure 8** was recorded during interval "B"when they do overlap.

The first tone – masker (tone 1) – was varying in tone frequency between 3.08 and 41.5 kHz in steps of one-eighth octave and in sound pressure level between in 15 and 80 dB in steps of 5

dB while the second tone – probe (tone 2) – was presented at a fixed frequency and level, 15 kHz at 45 dB.

Results

Frequency response areas were obtained across 16 locations in the ICC simultaneously (Figure 6). To obtain frequency response areas, responses to masker tones were recorded during interval A (see Figure 5). Each panel of Figure 6 represents the response area obtained

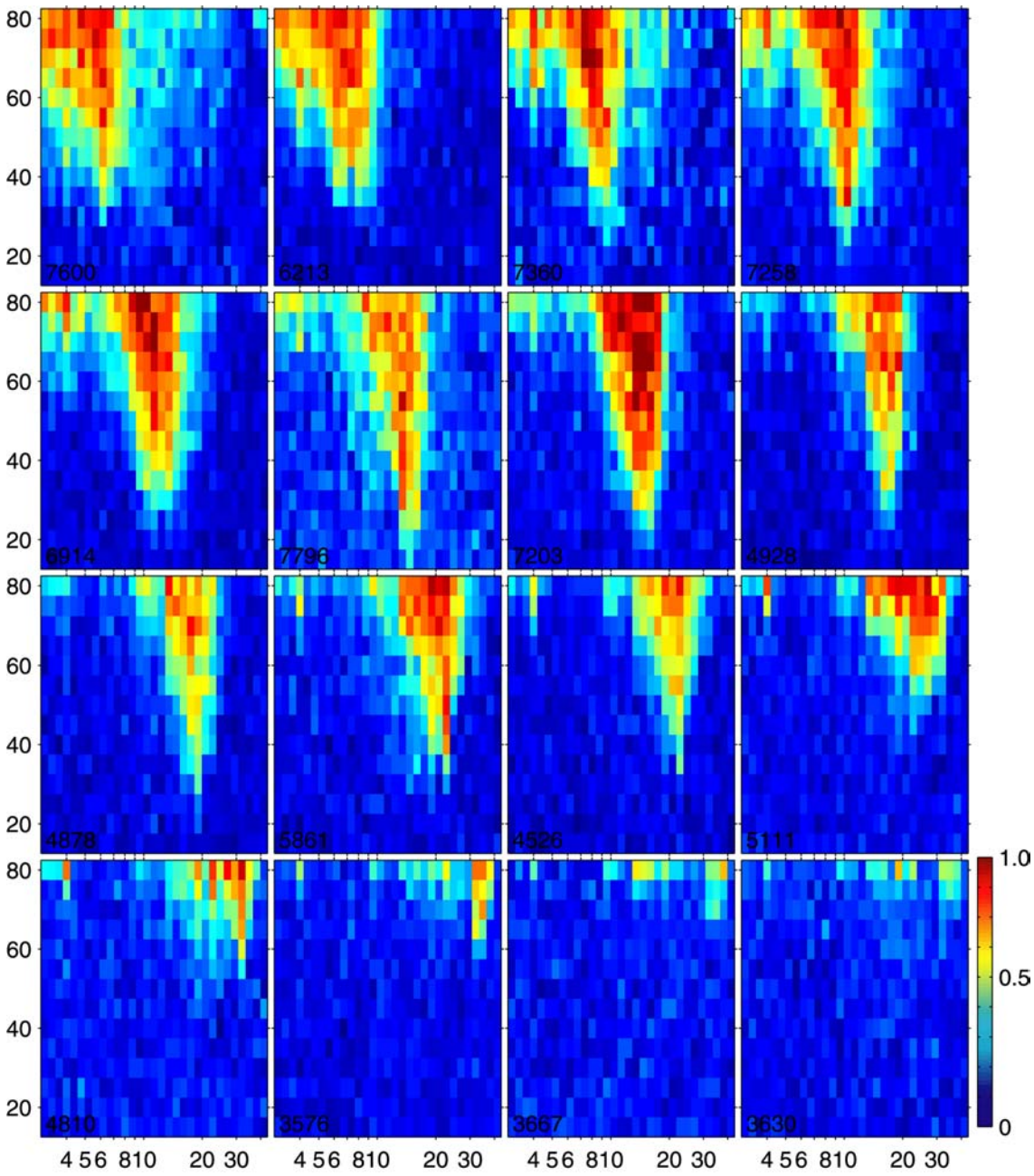

Figure 6. Frequency response areas (FRAs) evoked by the masker tone and recorded during interval "A" (see Figure 5). Each panel represents the

responses recorded at each of 16 probe sites in guinea pig 24. Scale on the right indicates the response rate scaled between zero spikes and the maximum rate recorded at any of the 16 sites.

at each sequential recording site along the recording probe (from left to right, top to bottom). The abscissa and ordinate in each panel represent tone one frequency and level, respectively. The normalized spike rate is represented by color with increasing activity represented from blue (lowest) to red (highest). In these panels there is a progression of characteristic frequency (CF) – the frequency at which the spike activity is greatest at the lowest stimulus level – from low to high frequencies as the recording site depth increases. CFs ranging from 7 to 38 kHz for the 1.5 mm of ICC represented in the present example. Most excitatory regions of the frequency response areas have the typical "V" shapes of auditory tuning curves.

Figure 7 represents the post-stimulus-time responses at each recording site for both tones, i.e., the entire unmasked and forward-masked stimulus. In this figure, the ordinate and abscissa are frequency and post-stimulus time at a fixed stimulus level for the variable tone, respectively with the variable tones level fixed at 65 dB. In each panel, there is an onset response to the variable frequency masker tone at 65 dB SPL at a latency of approximately 20 ms. At some frequencies there is also a sustained response that follows the onset response. The frequency range across which these responses are observed depends upon the site. Sites, which are most sensitive to lower frequencies (the upper row of panels), show responses that begin at 20 ms for low frequency masker tones; those sensitive to higher frequency tones (lower two panels) show responses beginning at 20 ms for higher frequency tones. Those sites that respond to both the variable frequency masker tones and the fixed probe tone (15 kHz, 25 dB SPL) there are onset response beginning at 20 ms (the masker response) and responses beginning at approximately 40 ms (the probe response).. For these sites, the probe response is masked (diminished in amplitude) by the masker tone when the masker evokes a response. However, the magnitude of the masking does not correspond directly to the amplitude of the masker response. For example, at site #5 (1st panel, 2nd row) masker frequencies between 16 and 20 kHz evoke a weak onset response, but they completely suppress the probe response. However, masker frequencies between 8 and 10 kHz evoke a strong response and have little effect on the probe response. This is a common observation that regardless of the site's CF masker tones that are above the probe frequency are maskers that are more effective.

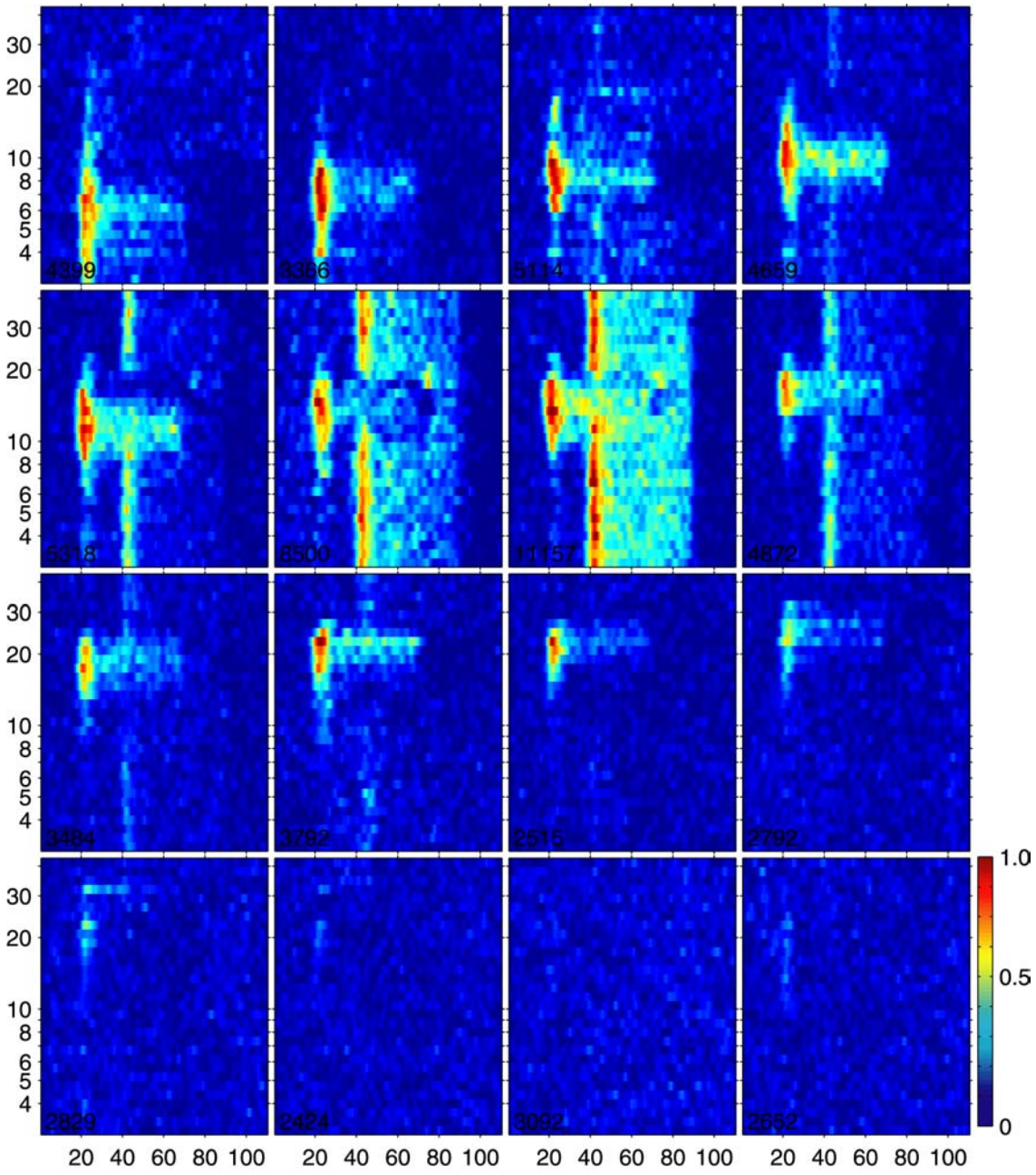

Figure 7. Post-Stimulus time histograms with in guinea pig 24. Each panel represents the responses recorded at each of 16 probe sites in guinea pig 24.

The effects masking described in temporal response in the previous figure can be observed as a function of masker frequency and intensity in FRAs in Figure 8. These FRAs were constructed from responses during the time interval of 35 to 55 ms, when both signals are being presented to the animal. By comparing the FTCs in this figure with those in Figure 6 some of the effects of channel interaction (using two tones) can be appreciated. In these masked FRAs, masking is seen primarily at sites that respond strongly to the probe. In these areas masking is indicated by areas that have no response or are nearer the blue end of the response scale as compared to the background activity. The recording site that responded most

strongly to the probe tone, panel 7 is mostly excitatory with an inhibitory region near 15 to 20 kHz. Panel 6 shows a "V-shaped" region of inhibition where the masker alone elicited an excitatory pattern. Panel 5 shows a "V-shaped" excitatory pattern with the upper-bound having a region of inhibition bordering the excitation. These regions of excitation and inhibition vary dramatically not only with variations in the frequency and intensity of the probe but also with the temporal relationship between the probe and the masker. Although some of these effects are comparable to those observed in the auditory periphery, many are dramatically different and appear to be intrinsic to neurons in the IC.

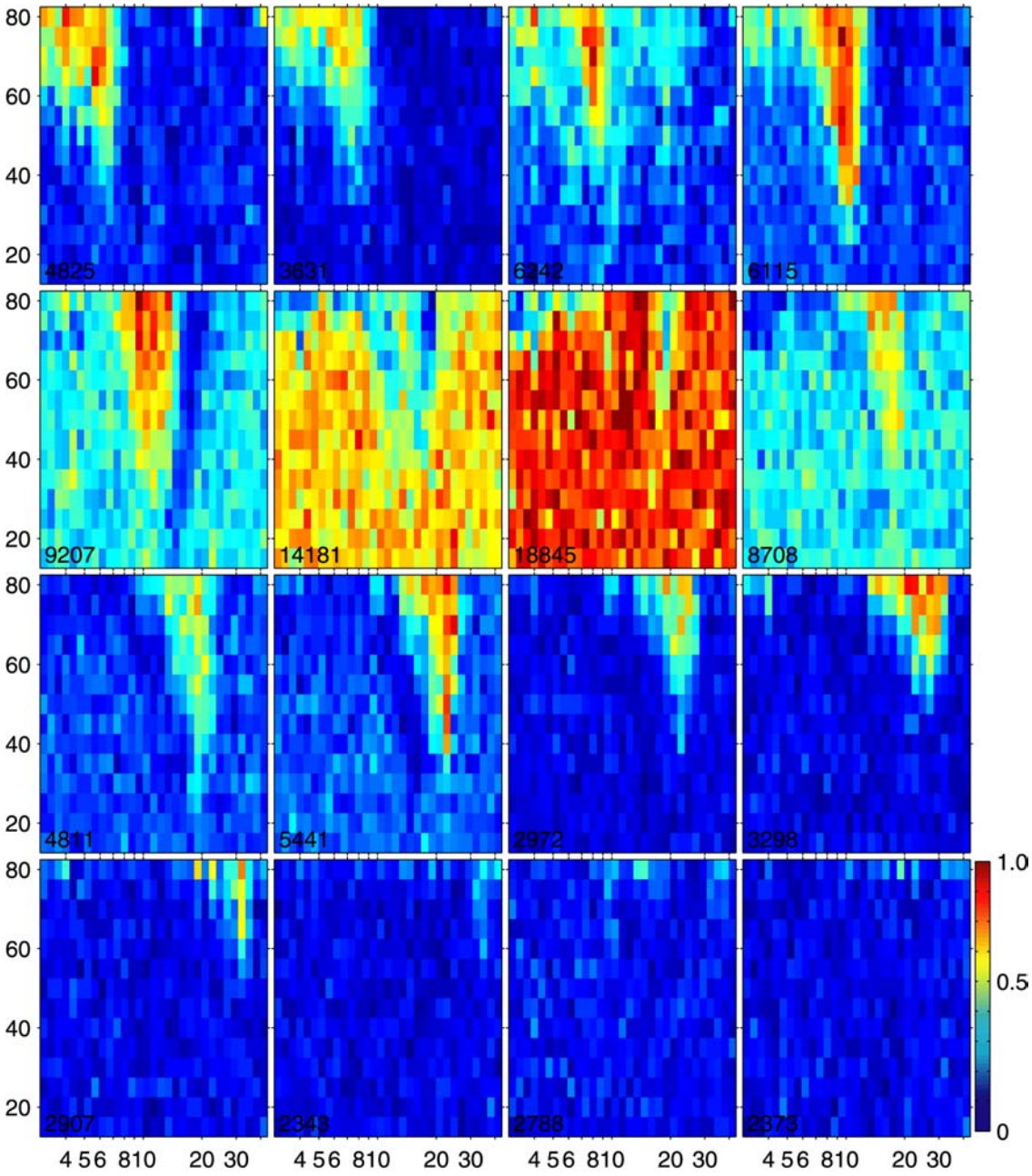

Figure 8. FRAs) evoked by masker and probe tones recorded during interval "B", 35 to 55 ms after the recording interval began (see Figure 5). in guinea pig 24.

Discussion

These preliminary findings suggest that the spatial extent of the effective masker is about half an octave; masking was elicited in neurons that respond to 12 to 20 kHz for a 15 kHz probe tone. Further investigation of acoustical stimuli to model electrical stimuli will be performed. Similar experiments with electrical stimulation using the guinea-pig specific cochlear implants discussed earlier could reveal some of the physiological mechanisms underlying perceptual channel interaction observed in cochlear implant patients.

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Work Planned for the Next Quarter

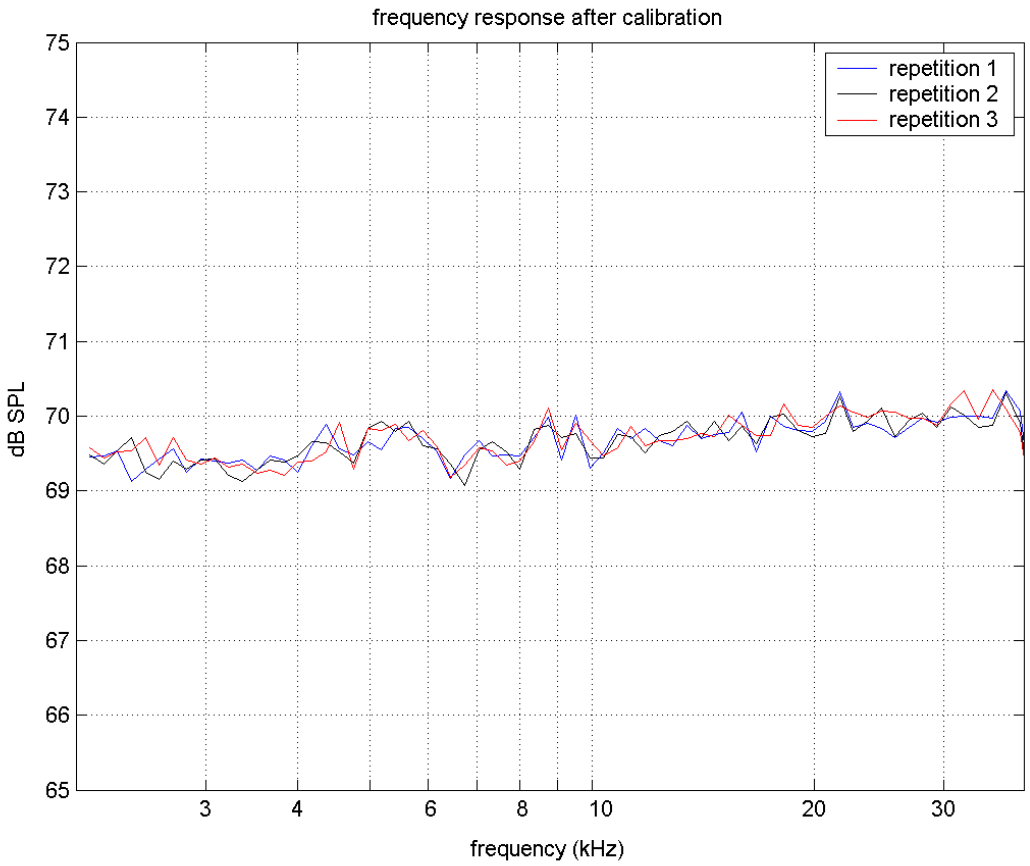
1) The dimples specifying the locations of the contact balls will be made in the mold and finished intracochlear electrodes for the guinea pig will be manufactured.

2) Experiments employing these electrodes will be initiated.

3) Work will continue on the acoustic model of channel interaction and we will begin experiments looking channel interaction using electrical stimulation.

4) Experiments will be initiated to look at the effects of electrode configuration on single channel and multichannel stimulation.

Appendix I. Acoustic Calibration Transfer Functions



Appendix Figure. This figure illustrates three successive calibration run of our closed system, an ear bar sealed in the external ear canal with a Radioshack supertweeter attached. The sound pressure level was measured with a B&K 4182 probe microphone.

Appendix II. 16 Channel Silicon Probes