

Sixth Quarterly Progress Report
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**The Neurophysiological Effects of
Simulated Auditory Prosthesis
Stimulation**

C.A. Miller, P.J. Abbas, J.T. Rubinstein

Department of Otolaryngology - Head and Neck Surgery
Department of Speech Pathology and Audiology
Department of Physiology and Biophysics
University of Iowa
Iowa City, IA 52242

J.F. Hetke
Center for Neural Communication Technology
Department of Electrical Engineering and Computer Science
University of Michigan
Ann Arbor, MI 48109

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1 Introduction

The purpose of this contract is to explore issues involving the transfer of information from implantable auditory prostheses to the central nervous system. Our investigation includes the use of animal experiments and computer model simulations to:

1. Characterize the fundamental spatial and temporal properties of intracochlear stimulation of the auditory nerve.
2. Evaluate the use of novel stimuli and electrode arrays.
3. Evaluate proposed enhancements in animal models of partial degeneration of the auditory nerve.

In this sixth quarterly progress report (QPR), we report on preliminary efforts in applying thin-film electrode arrays for the recording of field potentials within the auditory nerve. The small electrode contact dimensions and invasive nature of these recordings present a promising new means of assessing spatial excitation patterns within the auditory nerve and estimating neuronal conduction velocity. This work represents a collaborative effort between the University of Iowa group and the Center for Neural Communications Technology at the University of Michigan.

2 Summary of activities in this quarter

In the sixth quarter (1 January - 31 March, 2001), the following activities related to this contract were completed:

1. We attended and presented at the Midwinter Meeting of the Association for Research in Otolaryngology in St. Petersburg Beach Florida. See the Appendix for a list of the abstracts.
2. A manuscript comparing four computational algorithms for simulating action potentials was submitted for publication (See Appendix).
3. A manuscript detailing the refractory properties of the electrically stimulated auditory nerve was accepted for publication in the Journal of the Association for Research in Otolaryngology. Some of the highlights of this manuscript were presented in the last (fifth) QPR of this contract.

4. We welcomed a new member to our research team. This quarter, Dr. Ning Hu, from the People's Republic of China, joined us as a postdoctoral associate and is now participating in research related to our NPP contracts.

3 Focus topic: Preliminary results of experiments with University of Michigan thin-film recording electrodes.

3.1 Introduction

The University of Michigan's Center for Neural Communication Technology (CNCT) has contributed its novel, thin-film electrode technology to a number of research initiatives involving neural stimulation and evoked-potential recording (see <http://www.engin.umich.edu/facility/cnct/>). We have identified promising uses of these electrode designs for the recording of neural potentials within the auditory nerve. Because this electrode technology requires direct (line-of-site) access to the neural tissue, we have chosen the cat as the experimental species since it provides adequate surgical exposure of the auditory nerve.

The CNCT electrodes are built using thin-film technology common to the micro-electronics industry and provides for the fabrication of a relatively dense array of electrode contacts suitable for recording from multiple electrode sites within either cortical tissue or peripheral nerves. As such, these electrodes offer the assessment of spatial patterns of excitation within neural tissue. The probes are constructed of a micro-machined silicon substrate upon which thin-film conductors are deposited. These conductive pathways form both the two-dimensional electrode surfaces and the leads from each electrode. Details of the fabrication process can be found at the CNCT website. The CNCT electrodes are typically constructed as one or more parallel probe shanks that occupy a single two-dimensional plane. Due to its mechanical properties, these electrode shanks are inserted into tissue along a path parallel to the axis of the probe shanks (in a manner similar to the insertion of glass micropipettes).

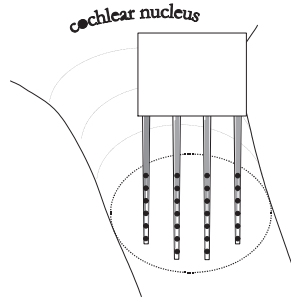


Figure 1: Sketch of our approach to using penetrating, thin-film electrode arrays to record neural potentials within the auditory nerve. A hypothetical, four-shanked array is shown inserted into a plane orthogonal to the axis of the nerve. Each shank has several electrode sites by which local potential fields can be recorded. Much of our effort to date has been to determine the feasibility of inserting such electrodes into the surgically exposed trunk of the feline auditory nerve.

3.2 Application to auditory-nerve studies

Although thin-film electrodes could be used for the stimulation of neural tissue, our efforts focus on their use as recording electrodes. The cross-sectional dimensions of each CNCT electrode shank are sufficiently small that they allow for their insertion deep into the auditory nerve trunk. This makes possible the recording of evoked potentials from a cross-section of auditory nerve fibers, as suggested by the sketch of Figure 1, which attempts to depict the insertion of a hypothetical 4-shank electrode array into a transverse cross-sectional plane of the nerve trunk. With such an insertion, it can be seen how such an electrode array could provide information relevant to a survey of fiber activation across place. One of our proposed applications of the CNCT electrodes is to assess patterns of neural excitation with various types and locations of intracochlear recording electrodes. Such information could provide insight into the degree of place-specificity provided by various stimulus electrode configurations.

In his study of lesions to restricted regions of the cochlea, Sando (1965) demonstrated that auditory nerve fibers are arranged within the nerve trunk in a tonotopic fashion. However, this organization is not straightforward, but transformed by the spiraling course of the fibers within the nerve trunk. There is no simple low-to-high arrangement of fiber characteristic frequency (CF); furthermore, the distribution of CF over each nerve cross section varies along the length of the nerve trunk (Sando, 1965). To overcome this com-

plication, we propose the following two-step process.

1. First, we determine the contours of the tonotopic map as "seen" by the two-dimensional array of recording electrodes by using acoustic pure-tone stimuli. By systematically varying stimulus frequency, we can determine the frequency specificity of each recording electrode. Such a survey will provide a map that links each recording electrode site to a "best frequency" region and, hence, the corresponding region of the cochlea along the apical-basal dimension.

Step 1 requires a normal-hearing preparation. After this acoustic assessment, the intracochlear stimulation electrode array is inserted through the round window (or cochleostomy).

2. In the second step, we again use the intraneural recording array to assess the patterns of neural excitation produced by each electrode of an intracochlear array. By using the best-frequency map provided by the work of the first step, we can estimate the pattern of fibers that are excited by each stimulating electrode.

3.3 Approach

For successful application of this technique to intraneural recordings from the auditory nerve, the CNCT electrodes must meet some important design criteria. These requirements are listed below.

1. Each intraneural electrode will be capable of providing place-specific information by demonstrating greater sensitivity to fibers that make relatively close passage to the electrode. At this stage, we do not know the degree of place-specificity that is possible with these electrodes. Part of our proposed work with the CNCT electrode will be to evaluate their selectivity using acoustic probe stimuli that will be systematically varied by both intensity and frequency.
2. The inserted electrode array will produce an acceptably small degree of trauma to the nerve population. Low insertion force will be desirable, requiring a small cross-sectional area of each electrode shank. In one respect, the construction of the multi-shanked CNCT electrodes is less-than-ideal for the cross-sectional nerve assessment suggested by Figure 1. Due to the planar fabrication of the CNCT electrodes and the resultant cross-sectional dimensions of each shank, insertion force

will be relatively high for insertions within a plane orthogonal to course of the axons.

3. The electrode array will have a high level of mechanical integrity to resist breakage during insertion or deformation of the nerve.
4. A sufficient number of electrode sites will be needed to provide an adequate sampling of different regions of the auditory nerve. At this point, we do not have a good appreciation of a minimum number of electrode sites. To some degree, that will be determined by the degree of place-specificity provided by each electrode site. Furthermore, the ideal electrode array would provide a two-dimensional array of electrode sites with equal vertical and horizontal spacing. However, the required insertion force will increase proportionally with the number of electrode shanks. Given this limitation, it is likely that the horizontal spacing of electrode sites will exceed the vertical spacing.

It is clear from these design goals that any electrode design will be, at best, a compromise. For example, greater rigidity will likely require larger cross-sectional area and, hence, result in greater tissue trauma. The number of electrode shanks will be limited for similar reasons. Our approach to an appropriate electrode design has been to first evaluate existing CNCT electrode designs with our acute cat preparation. After some trials, we found that an existing design, the single-shanked PSU5 electrode, could be successfully inserted into the nerve and provide multiple-site recordings. The physiological recordings presented in this QPR were obtained using this electrode. We have recently designed and fabricated a three-shank array with shank and electrode dimensions deemed appropriate for auditory nerve recordings. We also report some results of our preliminary work with that electrode.

The CNCT electrode arrays are typically bonded onto a circuit board that provides pins for convenient termination onto a standard dual-inline socket provided by the end user. In our case, this socket is mounted onto a small circuit board comprising surface-mount components for sixteen channels of unity-gain amplifiers. This headstage, shown schematically in Figure 2, is then secured to a micromanipulator for controlled insertion into the auditory nerve.

Electrophysiological potentials were amplified (by 40 dB) and then low-pass filtered using four-pole Bessel filters with half-power cut-off frequencies

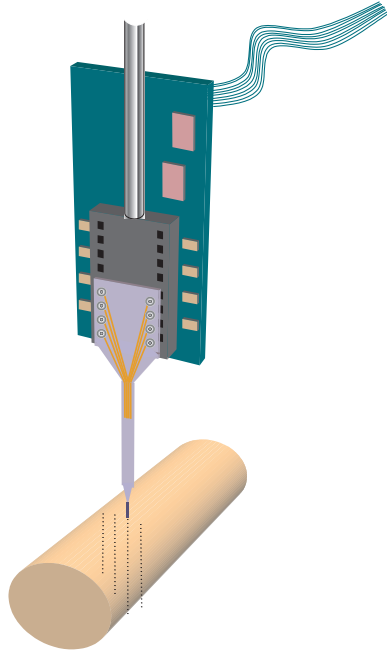


Figure 2: Sketch of a single-shank CNCT electrode array inserted into a custom-built headstage that is, in turn, mounted onto a micromanipulator to facilitate insertion into the auditory nerve. The headstage contains 16 unity-gain followers built onto the headstage circuit board. The vertical dotted line segments suggest the location of four electrode insertion tracks.

of 5 kHz. Each filtered signal was then sampled at 50,000 sample/s.

3.4 Recordings using the single-shank PSU5 electrode array: acoustic stimulation

The PSU5 electrode was fabricated by CNCT for Andy Hoffer of Simon Fraser University for use in recording from cat sciatic nerve. As with other CNCT designs, the thin-film electrode array is bonded onto a phenolic carrier and socket to facilitate convenient connection to a standard DIP package. Included in Figure 2 is a schematic depiction of this single-shank electrode as it is mounted to our headstage. A diagram of the PSU5 electrode itself, illustrating its eight electrode sites, conductive pathways, and dimensions, is provided in Figure 3. The shape of the tip was designed to ease insertion into the nerve. The probe has eight electrode sites spaced on 125

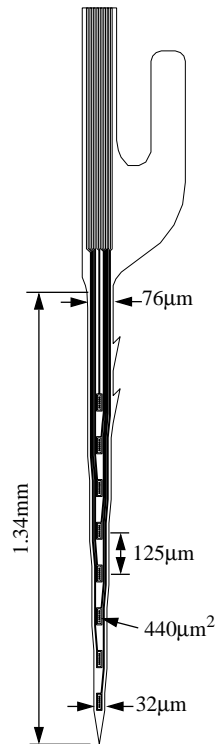


Figure 3: Schematic diagram of the planar surface of the PSU5 electrode used for the intraneural recordings presented in this QPR. Shown are the eight electrode pads positioned on 125 micron centers.

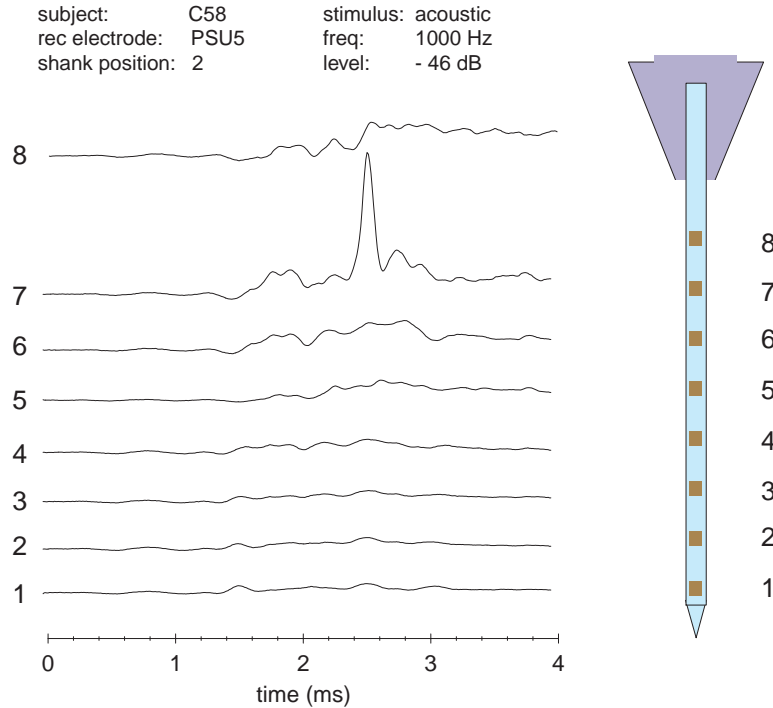


Figure 4: Responses recorded by a PSU5 electrode array in response to 1000 Hz tone bursts. The electrode diagram shown at the right margin indicates the relative position of the eight electrodes.

micron centers. The dimensions of each site is 10 x 44 microns and electrode impedances in saline are on the order of 1 MOhm when measured at 1 kHz. This electrode was inserted into the exposed auditory nerve to a total depth of about 1 mm such that one of the side notches was visible outside the nerve.

An example of response waveforms obtained with this electrode is shown in Figure 4. In this case, the acoustic stimulus was a 1000 Hz sinusoidal burst (1 ms cosine-squared ramps, 3 ms plateau, 5 ms total duration) delivered by a Beyer DT-48 earphone. The starting phase of each acoustic stimulus was presented in alternating fashion and the averaged recordings were comprised of responses to both stimulus polarities to minimize stimulus artifacts and the cochlear microphonic.

Each of the responses was recorded using a monopolar recording con-

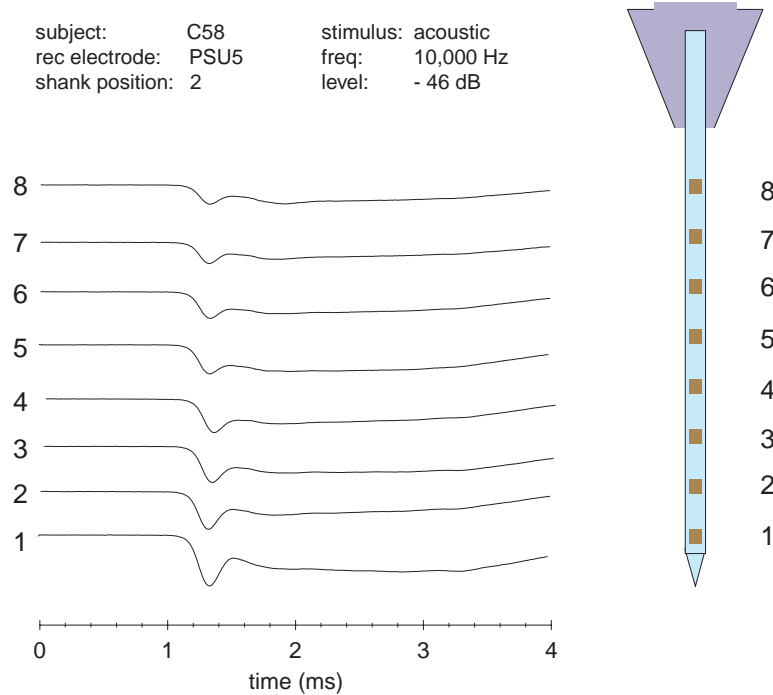


Figure 5: Responses recorded by a PSU5 electrode array in response to 10 kHz tone bursts.

figuration; that is, the return electrode (for differential amplification) was a needle electrode positioned within muscle at the margin of the cranial defect. Due to synaptic and acoustic delays, the first neural responses occur at about 1.5 ms into the traces. In this example, there is generally only a modest change in the magnitude of the responses across the eight sites, with response magnitude decreasing with increasing electrode depth. It is notable, however, that electrode 7 yielded a large-amplitude, spike-like response not observed at the other sites. The amplitude gradient across electrodes, and in particular, the unique response waveform from electrode 7, suggests that these electrode sites are capable of recording localized neural responses within the auditory nerve.

A different response pattern was observed when a higher stimulus frequency, 10,000 kHz, was used (Figure 5). In contrast to the 1000 Hz data, a gradient of increasing response magnitude is observed with increasing electrode depth. Also, the responses have a somewhat shorter latency and more

well-defined onset response. Such features would be expected for this relatively high-frequency stimulus. The contrasting response amplitude gradients for the two stimulus frequencies again suggests that this electrode array is capable of providing place-specific response information.

We have used the PSU5 electrode to make multiple penetrations and recordings within the nerve along a rostral-caudal axis. We have been able to make as many as four penetrations at different sites in one preparation. Shown in Figure 6 are the acoustically-evoked response contours obtained over a range of stimulus frequencies for two different shank penetrations. These response contours indicate electrode-specific responses that vary with electrode number, shank position, and stimulus frequency. In the future, we plan to collect similar data sets, only with finer frequency steps, in order to construct frequency tuning curves for each recording electrode site. By doing so, we hope to assess the degree of place specificity that is possible with these electrodes.

3.5 Recordings using the single-shank PSU5 electrode array: electric stimulation

A key to the success with the CNCT electrodes is to be able to record both acoustically and electrically evoked potentials. We therefore assessed the feasibility of recording electrically evoked potentials using the same (PSU5) electrode array. Figure 7 illustrates electrically evoked waveforms recorded by the array in response to a 40 microsecond/phase biphasic stimulus pulse. These waveforms are unprocessed and were not subjected to any stimulus artifact reduction scheme. The response waveforms are similar in morphology to our recordings of the gross, compound action potential obtained with a surface electrode (e.g. Miller et al., 1998). The response amplitudes vary slightly, with a larger response amplitude for the deeper electrode sites. Note that the response latencies vary somewhat from one site to the next (dashed line segments), indicating that the responses are not merely amplitude-scaled versions of each other.

3.6 Preliminary results with a three-shanked depth probe

The above results obtained with the single-shank PSU5 demonstrate the feasibility of recording acoustically-evoked and electrically-evoked potentials from within the nerve trunk. We have now begun preliminary experiments

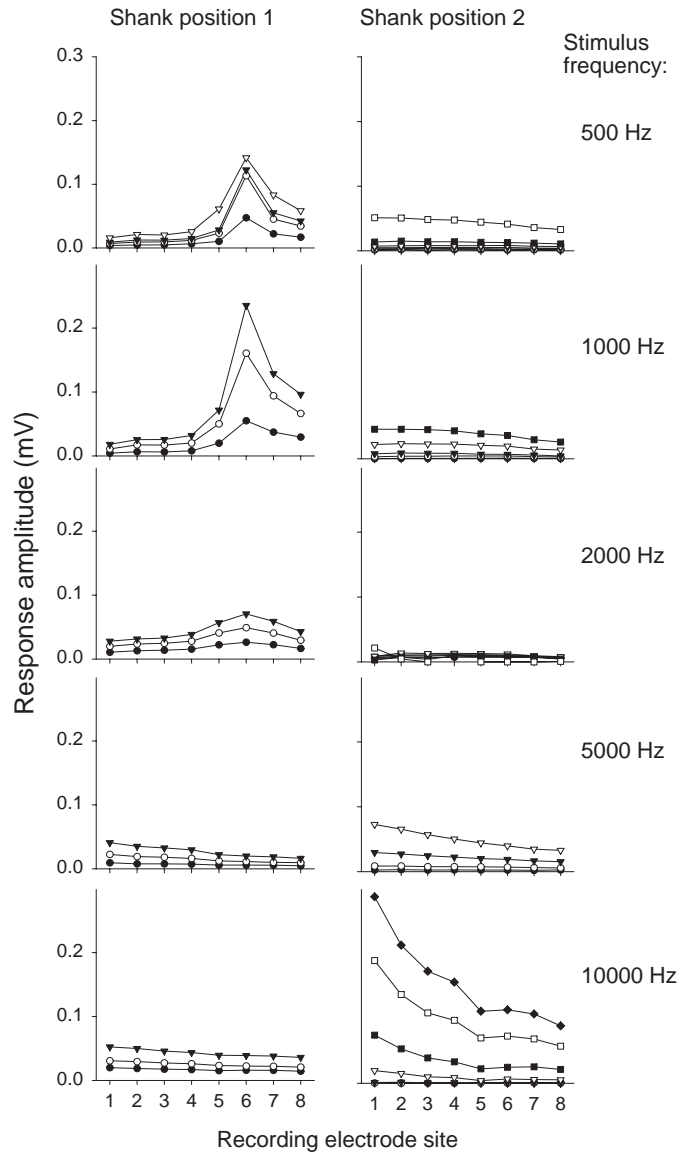


Figure 6: Plots of acoustically evoked response amplitudes recorded from PSU5 electrodes positioned along two different vertical tracks through the auditory nerve. Response data from each of the two tracks are arranged in the two columns of this figure. Five different stimulus frequencies (listed along the right margin) were used. Each of the ten graphs depicts response amplitude plotted as a function of the electrode position along the PSU5 shank. The individual plots of each graph were collected at sound pressure levels chosen at 10 dB increments.

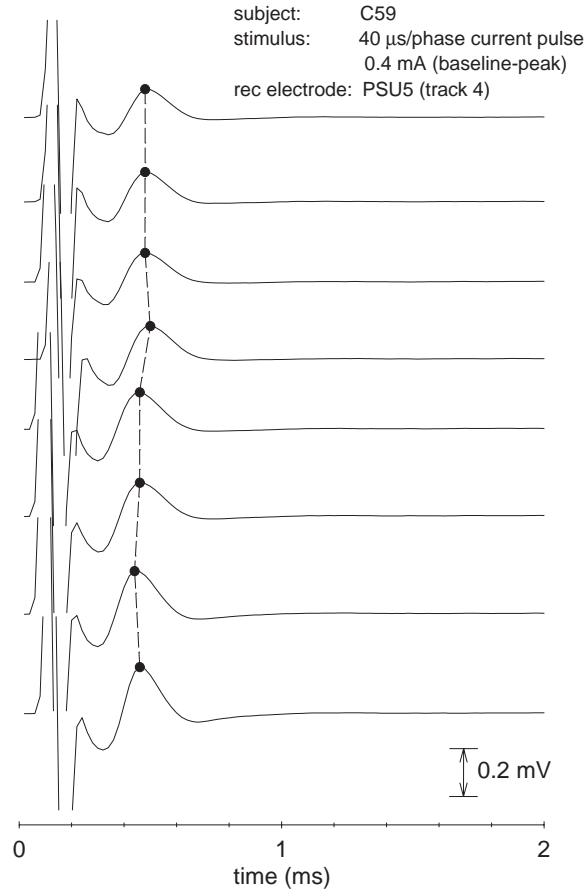


Figure 7: Electrically evoked responses recorded with the PSU5 single-shank electrode array. Dots and dashed line segments connect the positive peaks of each adjacent response.

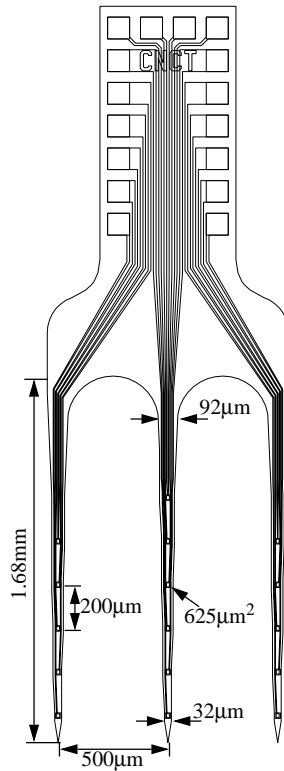


Figure 8: Diagram of the three-shank electrode array designed specifically for the recording of neural potentials within the feline auditory nerve. A total of 16 electrode sites are distributed across the three shanks.

with a new design that was configured specifically for use within the feline auditory nerve trunk. A schematic of this CNCT design is shown in Figure 8. A total of 16 recording sites are distributed across three shanks, thus affording two-dimensional spatial assessments. The inter-shank spacing was chosen such that we can fully insert all three shanks into the nerve such that simultaneous recordings can be made.

Preliminary tests with this design have been conducted in two cat preparations with some success. The photograph of Figure 9 provides a view of the three-shank electrode as seen through the operating microscope prior to insertion into the nerve. We have obtained acoustically-evoked response patterns similar to those reported with the PSU5 array. We have also encountered some difficulties during our initial trials. Some problems have been readily addressed with slight changes to the manufacturing process. The most significant difficulty concerned breakage of the shanks over the course of the experiments. This breakage may be due to vibration problems or stresses placed on the shanks during insertion or electrode removal. Future work will directly address this concern.

3.7 Discussion

The efforts reported here represent our preliminary efforts with thin-film electrodes for intraneural recordings. We have had good success using the single-shank PSU5 design to record both acoustically-evoked and electrically-evoked potentials and have begun experiments using a three-shank design more amenable to our research goals. Additional experiments will be conducted in the seventh quarter.

Our initial work has pointed the way for future efforts along multiple directions. We will first attempt to strengthen the three-shank design by coating the back planar surfaces of each shank with an epoxy. Another possible solution to the breakage problem would be to use flexible leads from the electrode to the headstage. This, of course, would entail the development of a new means of inserting (and retracting) the electrode array.

Another issue requiring attention concerns the proper interpretation of the evoked potentials. An assumption is made that the potentials recorded by each electrode primarily represent a local field potential, with the fibers closest to each electrode contributing the largest response. This requires the assumption that the nerve trunk acts as a uniform conducting medium,

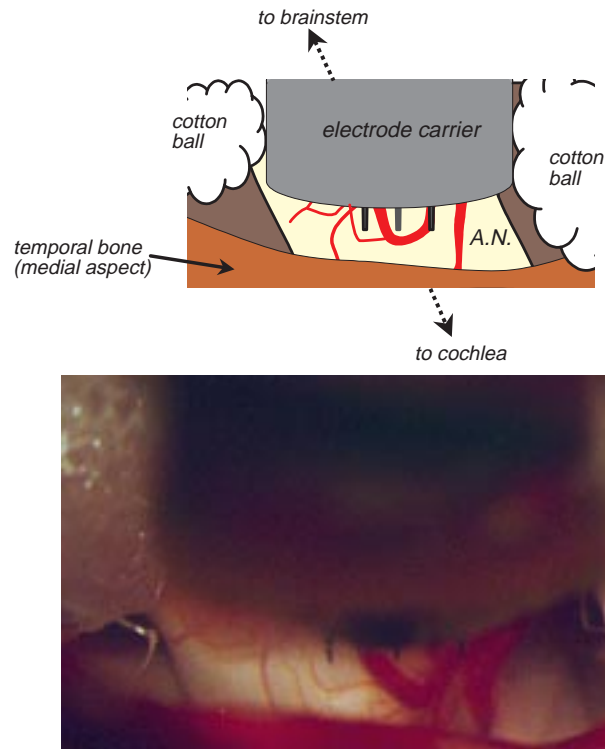


Figure 9: Diagram (top) and photograph (bottom) of the three-shank electrode array positioned above the surgically exposed auditory nerve. In the photograph (taken through the surgical microscope), the body of the phenolic electrode carrier obscures a large portion of the photographic field. However, the lightly-colored surface of nerve can be seen, along with the tips of the three electrode shanks. In this photograph, the electrode has not yet been inserted into the nerve.

which may not be warranted. Furthermore, we do not have a good understanding of the "receptive fields" of these electrode surfaces. The spike-like response seen in Figure 4 is intriguing in that it suggests the possibility that single-fiber responses may be obtainable with these electrodes. We have observed similar potential waveforms (not shown here) from another cat preparation. Such observations, however, are relatively infrequent. We intend to assess the spatial selectivity of each electrode in a systematic way by obtaining detailed frequency tuning curves for each electrode site. We suggest that the degree of frequency tuning will reflect the degree to which each electrode can assess a small, restricted population of fibers with similar tuning properties.

Furthermore, we have only presented monopolar recordings in this QPR, using a relatively distant second electrode site for the negative input to the differential amplifiers. It is possible that each monopolar electrode site may record an evoked response from a relatively distant generator. For example, the summing potential originating from the cochlea may contribute to the response waveforms obtained with acoustic stimulation. Differential spatial potentials can be computed from monopolar recordings by subtracting the response waveform from one electrode from that of another (presumably nearest-neighbor) electrode. By doing so, we can increase the spatial selectivity of the electrode array. In future work, we plan on analyzing responses from each recorded monopolar electrode configuration by deriving various difference waveforms. By doing so, we will be able to assess whether or not recorded potentials have local sites of origin.

It may also be possible to use our three-shank array design to make neural measures at different sites along the length of the nerve bundle by inserting it in a plane parallel to its axis. Such an orientation would be useful for making estimates of conduction velocity. The thin-film CNCT electrodes may be well-suited for such measures.

Finally, we also plan to evaluate electrically evoked responses using an intrascalar, multiple-electrode stimulating array to determine whether or not different sites of stimulation produce different response contours. Such recordings represent a long-term goal of these experiments - to assess spatial excitation patterns produced by intracochlear electrical excitation.

4 Plans for the next quarter

In the seventh quarter, we plan to do the following:

- Conduct additional experiments with the Michigan CNCT thin-film electrodes. This will involve evaluating modified electrode designs, making some refinements to our experimental procedures, and making additional measures as described in the above discussion.
- Conduct additional experimental data using high-rate conditioning stimuli to determine their effect on the electrically evoked compound-action potential.
- Perform systematic analyses of computational model parameters to obtain model fiber temporal properties in closer agreement with experimental results. This ongoing work will be reported in a future QPR

5 Appendix: Presentations and publications

The following presentations of work conducted under this contract were made at the 2001 Midwinter Meeting of the Association for Research in Otolaryngology (February 4-8, St. Petersburg Beach, FL):

- Paul J. Abbas, Charles A. Miller, Carolyn J. Brown (2001) Assessment of spatial spread of electrical stimulation in the cochlea. Assoc. Res. Otolaryngol. Abs. (abstr. 1048).
- Hiroyuki Mino , Jay T. Rubinstein , Charles A. Miller , Paul J. Abbas (2001) Comparison of four computational algorithms to simulate stochastic neural responses to electrical stimulation. Assoc. Res. Otolaryngol. Abs. (abstr. 912).
- Christina Lee Runge-Samuelson, Jay T. Rubinstein, Paul J. Abbas , Charles A. Miller, Gregory J. Smith , Barbara K. Robinson , Bruce A. Abkes (2001) Sinusoidal electrical stimulation of the auditory nerve with and without high-rate pulses. Assoc. Res. Otolaryngol. Abs. (abstr. 916).

The following paper, describing work with our biophysical computational model efforts, was recently submitted for publication:

- Mino, H., Rubinstein, J.T., White, J.A. (2001) Comparison of algorithms for the simulation of action potentials with stochastic sodium channels.

The following manuscript was accepted for publication in the Journal of the Association for Research in Otolaryngology:

- Miller, C., Abbas, P., Robinson, B. (2000) "Responses Properties of the Refractory Auditory Nerve Fiber" JARO, Volume 2

References

- [1] Miller, C. A., Abbas, P. J., Robinson, B. K., Rubinstein, J. T., Matsuoka, A. J. (1999). Electrically evoked single-fiber action potentials from cat: responses to monopolar, monophasic stimulation. *Hear. Res.* 130, 197-218.
- [2] Sando, I. (1965) The anatomical interrelationships of the cochlear nerve fibers. *Acta Oto-laryng.* 59, 417-436.