Second Quarterly Progress Report
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The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation

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Contents

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 is being pursued along multiple tracks and include 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 second quarterly progress report (QPR), we focus on the second of these three aims. Recent animal experiments have been directed toward understanding the differences in auditory nerve responses to monophasic and biphasic stimulus waveforms. For safety considerations, the latter waveform is used extensively in existing auditory prostheses. However, monophasic stimuli may offer greater efficiency and specificity of neuronal excitation. To that end, we have studied the threshold and growth characteristics of the electrically evoked compound action potential (EAP) produced by both types of stimuli. Furthermore, we have examined EAP characteristics using a systematic range of pseudomonophasic stimuli. The results of these studies comprise the bulk of this QPR. They indicate that monophasic and biphasic stimuli excite and recruit nerve fibers in unique ways and illustrate the potential utility of pseudomonophasic stimulus pulses.

2 Summary of activities in this quarter

In our second quarter (1 January - 31 March, 2000), 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 reviewing the stochastic properties of neurons in both animal preparations and computational models, as well as their clinical implications, was published (see the Appendix).

3. A manuscript detailing an improved means of obtaining refractory data in human implant patients was revised and accepted for publication (see the Appendix).

4. We collected whole-nerve evoked response data from four guinea pigs and four cats. In the guinea pig preparations, we concentrated on examining responses to constant-amplitude pulse-trains, modulated pulse-trains, and pseudomonophasic stimulus pulses. In the cats, we examined both whole-nerve and single-fiber responses. In two of the cat preparations, we made preliminary measurements of intra-nerve field-potentials using University of Michigan thin-film electrode arrays. We also collected data on the forward-masked response properties of single fibers from one of these cats, using a two-pulse (masker-probe) stimulus paradigm.

5. We purchased and received Labview software from National Instruments for use in a new data acquisition system to be developed for this contract. We also received our new isolated current source, as well as a new capnometer to replace our old, failing unit.

6. We designed a head stage circuit and second-stage amplifiers for use with the University of Michigan thin-film microelectrodes. During preliminary experiments with the UM electrodes, we identified the need for improved, custom headstage circuits for use with the high-impedance (greater than 1 MegOhm) electrodes. Our new headstage will feature 8 to 16 low-noise instrumentation amplifiers packaged as surface-mount chips and mounted directly on the microelectrode holder to minimize induced noise currents. Output of these unity-gain impedance transformers will be fed to a newly designed 8-channel amplifier (with gain). These improvements will enable us to record from any chosen single electrode of the UM array (i.e. monopolar, single-ended, non-differential mode) so that we will be able to derive measures of differential evoked potentials from combinations of electrodes off-line.

7. As part of the relocation of the Otolaryngology department that occurred this quarter, we have moved our staff offices to a new location within the hospital complex. This move has relieved the overcrowded conditions within our lab space and facilitates the arrival of additional

research staff to support efforts related to our Neural Prosthesis Program contracts.

8. Dr. Hiroyuki Mino has arrived at Iowa and has joined our group. He has begun an investigation of algorithms to increase the efficiency of our computational modeling techniques.

3 Examination of responses to monophasic, biphasic, and pseudomonophasic stimulus pulses

3.1 Introduction

It is well known that, compared with biphasic current pulses, monophasic pulses elicit neural responses at relatively low stimulus levels. However, due to the noxious effects of direct-current stimulation on living tissue, cochlear prostheses have employed charge-balanced, biphasic stimuli to chronically excite nerve fibers. However, biphasic pulses (with phases of equal duration) are less efficient than monophasic pulses. Furthermore, since both cathodic and anodic phases can be excitatory, biphasic pulses may result in relatively complex excitation patterns across intracochlear nerve fibers. The greater spatial selectivity of monophasic stimulation has been demonstrated by research conducted with a spatial model of the cochlea developed by Frijns et al. (1996). As part of this contract, we have suggested the possible utility of a pseudomonophasic stimulus pulse, i.e. charge-balanced, biphasic, pulse with a second phase of relatively long duration so as to approximate a monophasic pulse. Such a stimulus may offer greater efficiency and control of neural recruitment patterns while maintaining the safety of charged-balanced stimuli.

To this end we have performed comparisons of monophasic and biphasic excitation in both guinea pig and cat preparations to systematically evaluate both stimuli. We have obtained gross-potential (the electrically evoked compound action potential, or EAP) measures in both species. The feline subjects also afforded us the ability to measure single-fiber response properties, something not feasible in our guinea pig preparations. By measuring both gross-potential and single-fiber measures, we can better elucidate mechanisms of excitation. We assume that response properties apparent at the single-fiber level will be reflected, to some degree, in gross-potential

responses, while properties present in the EAP and largely absent in single-fiber responses reflect across-fiber characteristics, such as fiber orientation and fiber threshold distribution.

3.2 Experimental paradigms

Our procedures for collecting the electrically evoked compound action potential and single-fiber responses are similar to those described in earlier QPRs and publications (e.g., Miller et al., 1998 and Miller et al., 1999, respectively). For EAP recordings, a recording electrode was positioned directly on the surgically exposed auditory nerve while stimulation was provided by a monopolar intracochlear electrode. In all cases, the animals were chemically deafened using systemic injections of kanamycin followed by ethacrynic acid. For single-fiber recordings, standard micropipette techniques were employed, using a posterior-fossa surgical approach. Single-fiber measures of threshold, mean spike latency, and jitter (standard deviation of spike latencies) were determined for a firing efficiency of 50%. For any stimulus condition, each fiber was stimulated with 100 repeated stimuli (interpulse interval of 60 ms) in order to compute these statistics. Relative spread (Verveen, 1961), a measure inversely proportional to the slope of the fibers firing-efficiency vs. level function, was computed by fitting an integrated gaussian curve to the input-output curve.

Electrical stimuli were delivered by an optically isolated current source that was capacitively coupled. The stimuli used were rectangular pulses of either one (i.e. monophasic) or two (biphasic and pseudomonophasic) phases. The monophasic stimulus consisted of a 40 μs pulse. While our biphasic and pseudomonophasic pulses were both composed of a biphasic waveform, we reserve the term biphasic to refer to a pulse with both phases of 40 microsecond duration. In the case of pseudomonophasic stimuli, the initial phase duration was fixed at 40 μs, while the second (charge recovery) phase was systematically varied from 100 to 4000 μs. The amplitude of the second phase was set to provide charge balance with the first phase (i.e., zero net charge delivered). For all stimuli, the polarity of the first phase was cathodic. Example stimulus waveforms are shown in Figure 1.

We collected EAP data from 10 guinea pigs and 12 cats in which both monophasic and biphasic stimuli were used to obtain responses over a range of stimulus levels. Most of the data presented here examine the differences obtained between these two stimulus types. In several animals, we also col-

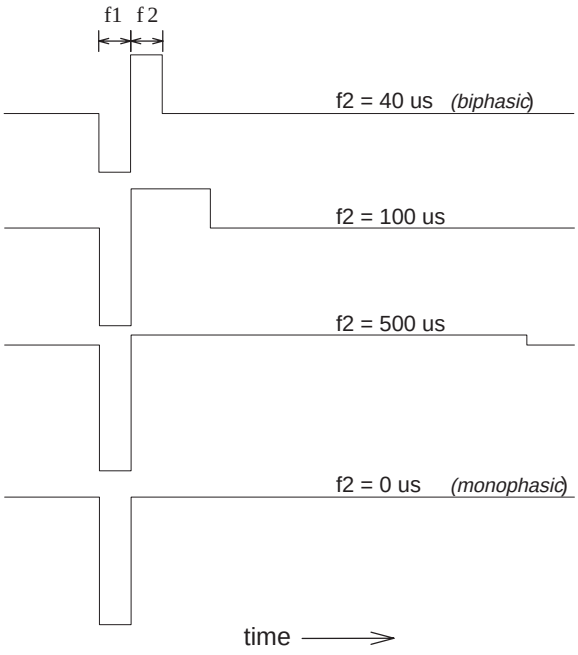

Figure 1: Examples of the biphasic, pseudomonophasic, and monophasic stimulus waveforms used in this study. In all cases, the first phase was a cathodic, 40 μs rectangular pulse. With pseudomonophasic stimuli, the first phase was immediately followed by a second, recovery phase to provide no net transfer of charge. The duration of the second phase was systematically varied and the amplitude of that phase adjusted to provide no net charge transfer.

lected additional EAP data using pseudomonophasic stimuli with a range of second-phase durations. The use of such pseudomonophasic stimuli allows us to further examine differences between monophasic and biphasic stimuli, since the pseudomonophasic pulses represent stimuli that are, in effect, intermediate conditions between the monophasic and biphasic extremes.

Shown in Figure 2 (panel A) is a series of EAP amplitude-level functions collected from a guinea pig. As shown in the legend, each data set plotted varies by the duration of the second phase of the stimulus. A difficulty with collecting this large amount of data is that it requires 1 to 2 hours of time. Some drift in recording conditions can occur over that time, presumably due to swelling of brain tissue. We account for this drift by obtaining repeated measures at selected stimulus pulse durations. By measuring the EAP amplitude at a fixed stimulus level over each of the 12 data sets plotted in Figure 2-A, we can quantify this drift. This drift is shown in Figure 2-B, where the squares and circles denote replications of the biphasic and monophasic conditions, respectively. We used the amount of drift across the two biphasic conditions to adjust the EAP amplitudes of all the data in plotted in panel A. The amplitude-level functions in panel C have been adjusted for this drift so that we can be quantify changes due to the effects of the duration of the second phase. Phase-duration effects are more clearly seen in the adjusted data of panels C and D. Note that the changes over time primarily involve response amplitude, not changes in neural sensitivity.

To examine across-animal trends, we defined three characteristics of the amplitude-level function. Threshold was defined as the level evoking an amplitude that is 10% of the maximum recorded EAP amplitude. Maximum slope was defined as the greatest slope value of each amplitude-level function, determined across all segments of each function. Maximum amplitude was defined to characterize the saturation amplitude of each function. In some cases this was problematic, as functions sometimes failed to demonstrate a clear saturation amplitude. We attribute the problem in these cases as contamination due to unfavorably large stimulus artifact that cannot be effectively cancelled by our techniques (Miller et al., 1998). In those cases, we have conservatively chosen to omit the data from group analyses to avoid biasing those data sets.

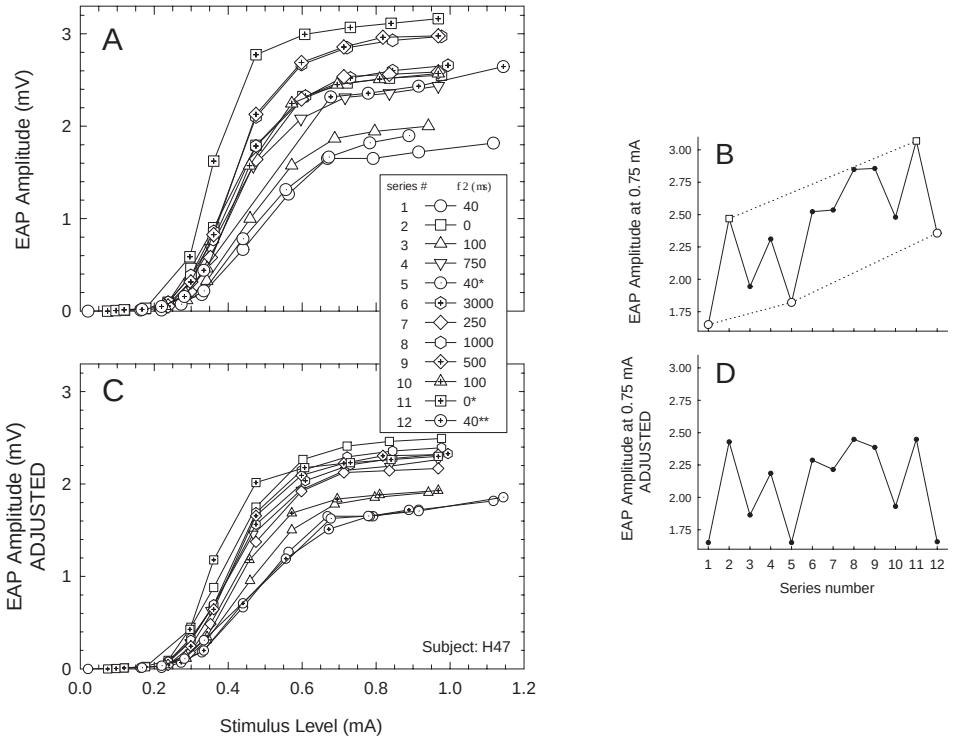

Figure 2: An example of EAP amplitude-level data obtained from a guinea pig across 12 different sets of data. All stimulus pulses had a first-phase duration of 40 μs. The stimuli differed by the duration of the second (recovery) phase, as indictated by the inset legend. Raw input-output functions are shown in panel A. Drift in recording conditions over time resulted in changes in amplitude, as indicated by panel B, which plots EAP amplitude at a fixed stimulus level for each of the 12 series of different stimuli. The original functions were corrected by the magnitude of these drifts to obtained the adjusted functions shown in panel C. Panel D also illustrates the effect of this adjustment.

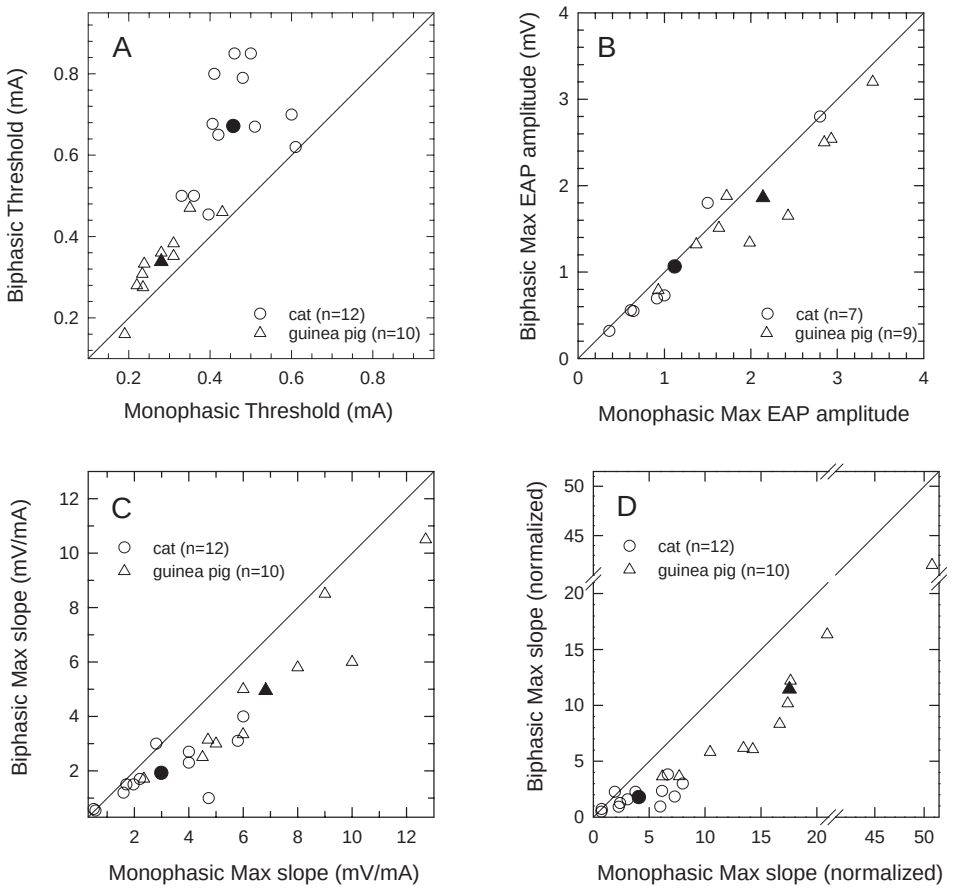

Figure 3: Summary of EAP measures obtained from 12 cats and 10 guinea pigs using both monophasic and biphasic stimulus pulses. Threshold (panel A) was defined as the stimulus level producing an amplitude 10% of the maximum amplitude. As explained in the text, the maximum slope of each subject's amplitude-level function was computed in two different ways. Maximum slope (panel C) was computed as the maximum rate-of-increase over all the segments of each amplitude-level function. As explained in the text, these slope values were normalized (panel D) to account for differences in thresholds occurring between monophasic and biphasic stimuli.

3.3 EAP measures obtained with biphasic and monophasic stimuli

3.3.1 Amplitude and threshold measures

Figure 3 provides an across-animal comparison of EAP measures obtained with both 40 microsecond monophasic and 40 microsecond/phase biphasic stimuli. Individual animal data are shown in the open symbols for both guinea pigs and cats; mean values for each species are shown by corresponding filled symbols. Panel A shows a clear bias toward lower monophasic thresholds. For both species, this trend is statistically significant at a probability of 5% using paired t-tests. A comparison of the mean difference between monophasic and biphasic thresholds indicates a larger effect in cats than in guinea pigs. In cats, the mean monophasic threshold is 3.4 dB lower than the mean biphasic threshold, while in guinea pigs, the mean monophasic threshold is 1.6 dB lower.

Strong trends are also evident in the maximum slope of the EAP amplitude-level functions (panel C), with statistically significantly greater slopes with monophasic stimuli for both species. Because both threshold and maximum slope varied with the stimulus type, there may be a question regarding the interpretation of the slope measure. Specifically, would the monophasic stimulus persist in producing a greater slope if its amplitude-level function was not shifted along the abscissa relative to the biphasic function? To address this, we normalized the maximum slope values by dividing each by the stimulus level at which maximum slope occurred. These normalized slopes, plotted in panel D, demonstrate the same statistically significant trends evident in the non-normalized plots. With regard to maximum (saturation) EAP amplitude (panel B), the trends with stimulus type are less pronounced. The guinea pig data demonstrate a small, but significant bias toward greater amplitudes, but the cat data do not.

3.3.2 Latency measures

We also observed differences in the latency of the EAP waveform in response to monophasic and biphasic stimuli. To quantify these differences, we focused on the latency of the positive peak that follows the large negative-going peak (N1) of the EAP. We have designated this peak as P2, since a positive peak preceding N1 can sometimes be observed. We chose to focus on P2 since it is the longest-latency component of the EAP and therefore the least

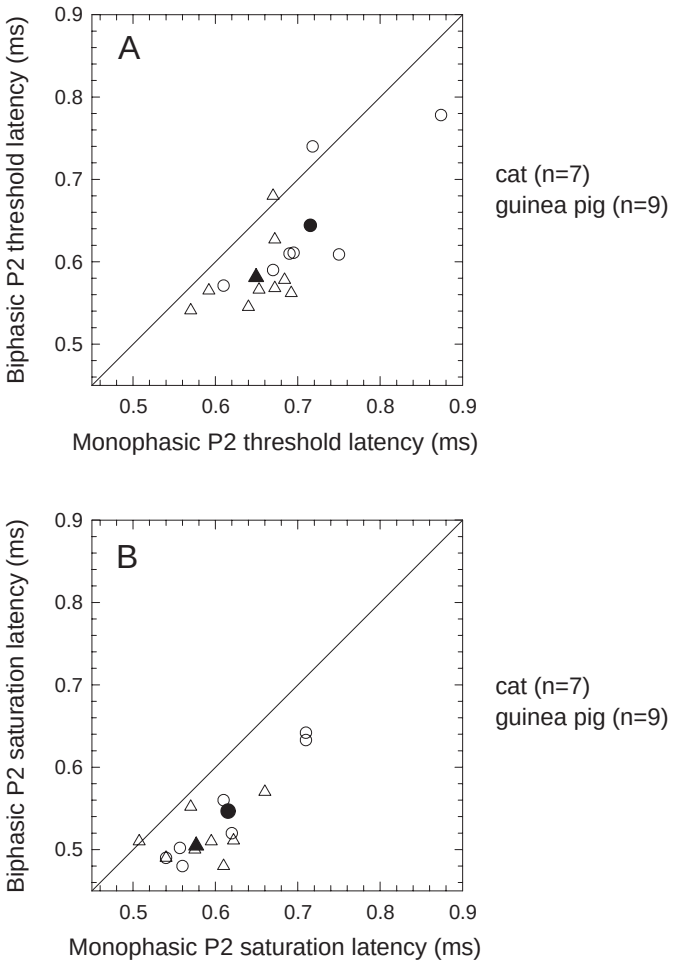

Figure 4: Summary of EAP latency measures obtained from 7 cat and 9 guinea pig preparations. The latency of the P2 peak (the positive peak occurring after the prominent negative peak) was measured from the onset of the stimulus pulse. Panel A plots P2 latencies measured at threshold, i.e., at a response amplitude 10% of the maximum EAP amplitude. Panel B plots P2 latencies measured at the stimulus level at which EAP amplitude was maximal.

prone to stimulus artifact influences. Figure 4 provides an across-animal comparison of monophasic/biphasic effects observed in P2 latency for both species. P2 latency was assessed at both threshold stimulus level (panel A) and at a level corresponding to that required for a saturated response (panel B). In both instances and in both species, statistically significant effects are observed, with longer P2 latencies measured for monophasic stimuli. In the case of cats, the mean P2 latency obtained with monophasic stimuli was 71 μs greater than that obtained with biphasic stimuli.

3.4 EAP measures obtained with a range of pseudomonophasic stimuli

Given the observed dependency of the EAP on stimulus waveform, we sought to determine the degree to which the second phase of biphasic pulses influenced the evoked gross potential. We therefore used pseudomonophasic stimuli to examine how EAP thresholds varied over a range of second-phase durations. Such data were obtained for 3 guinea pigs and 2 cats. The plots of threshold vs. phase duration shown in Figure 5 demonstrate heterogeneous trends. The data of guinea pig H48 and cat C56 show a limited, asymptotic, threshold advantage with increasing phase duration. However, the data of the five animals taken together do not suggest a single duration of the second phase at which EAP threshold achieves an asymptotic value. We note that these trends may be somewhat compromised by experimental error; data from additional subjects may help clarify the group trends.

3.5 Single fiber measures obtained with monophasic, biphasic, and pseudomonophasic stimuli

Single-fiber data collected under similar stimulus conditions can shed light on the mechanisms underlying the trends observed in the EAP measures and improve our understanding of effective stimulation of auditory nerve fibers. We have collected monophasic and biphasic input-output functions from 16 fibers of 3 cats, along with a smaller set of pseudomonophasic data. Figure 6 summarizes how the four fundamental properties of threshold, mean latency, jitter, and relative spread differ for monophasic (40 microsecond) and biphasic (40 microsecond/phase) stimuli. Individual single-fiber data are depicted by open circles and mean values are shown by the filled symbols. Figure 6-A indicates that monophasic thresholds are lower than biphasic thresholds. On average, monophasic thresholds are 4.1 dB lower than biphasic thresholds.

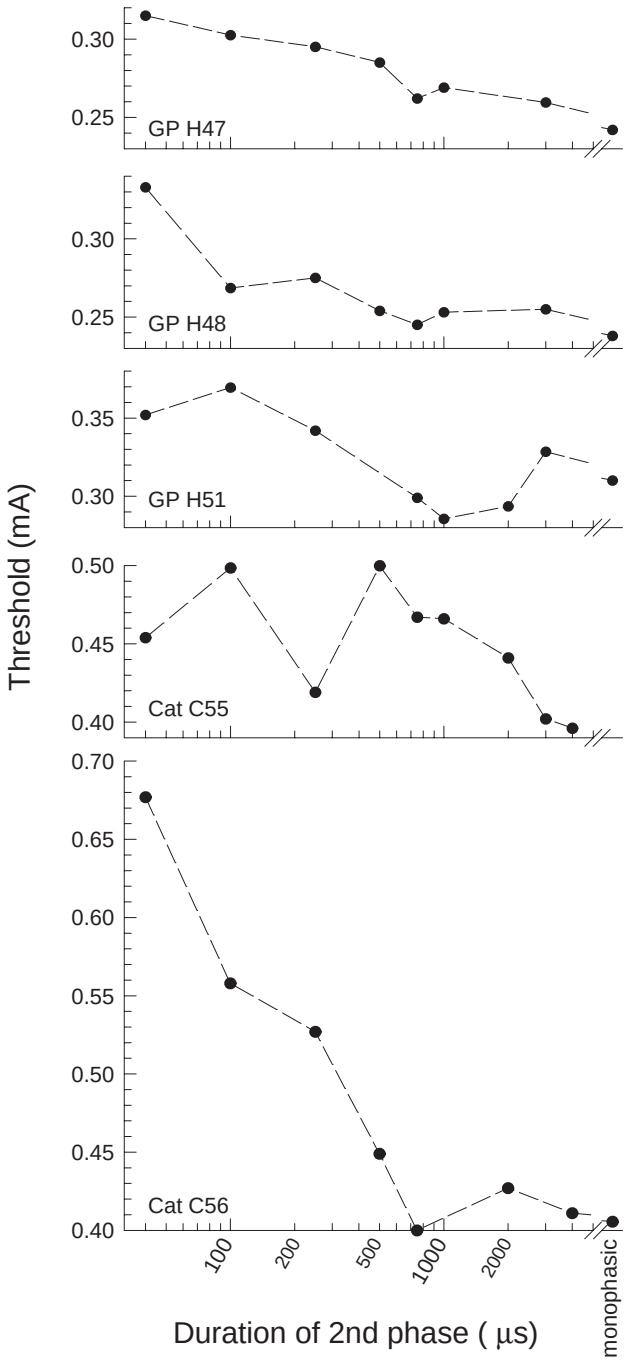

Figure 5: The effect of the duration of the second stimulus phase on EAP threshold level. Data are shown from all five subjects from whom such data were collected.

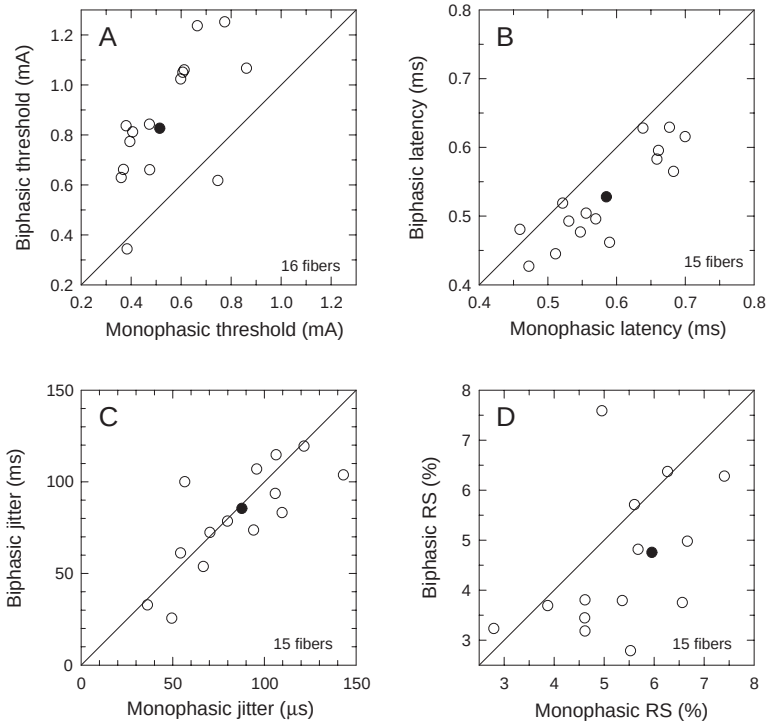

Figure 6: Summary of single-fiber measures obtained using both biphasic and monophasic stimuli. Individual data from 16 fibers of 3 cats are shown by open symbols; mean values are shown by the solid symbols. Threshold, latency, and jitter were all defined for the condition of a firing efficiency of 50%.

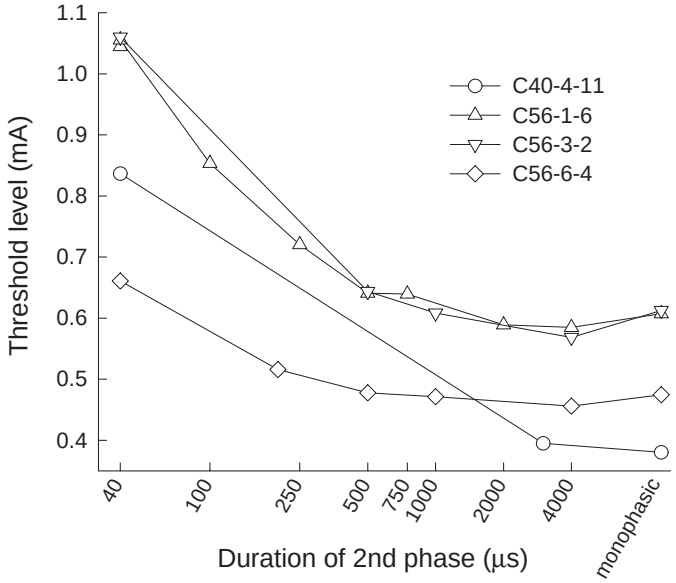

Figure 7: The effect of systematic variation of the second phase duration on single-fiber threshold. Shown are data from four single fibers.

Across the 16 fibers, a paired t-test indicates that this difference is statistically significant (t=6.59, p=0.00001, d.f.=15). A statistically significant trend was also observed in the analysis of mean spike latency (measured at 50% firing efficiency). These data are shown in Figure 6-B. On average, monophasic mean latency was about 60 μs longer. In our sample of fibers, spike jitter (the standard deviations of spike latencies measured at 50% firing efficiency) was not influenced by the change in stimulus waveform (Figure 6-C). Finally, relative spread was found to be statistically greater (t=2.24, p=0.041, d.f.=14) for monophasic stimuli than for biphasic stimuli. With monophasic stimuli, the mean RS of 15 fibers was 5.96%; with biphasic stimuli, mean RS was 4.76% (Figure 6-D).

As in the case of the gross-potential measures, we were also interested in determining how single-fiber threshold was influenced while systematically altering the duration of the second phase of pseudomonophasic stimuli. Since we routinely collect input-output curves for each stimulus pulse condition, this requires holding a fiber for several minutes; we report data from 4 fibers. Threshold as a function of 2nd phase duration is plotted for these fibers in Figure 6. Note that the greatest decrements in threshold occur over phase

durations less than 500 μs. From this small data set, it appears that there is an upper limit on the effect of increasing the duration of the second phase. This is similar to the asymptotic effect of 2nd phase duration observed in two of the five EAP data sets shown in Figure 4.

4 Discussion

The data presented here provide information on the effectiveness of monophasic stimulus pulses relative to comparable biphasic stimuli. Statistically significant reductions in EAP threshold were obtained with monophasic stimuli for both guinea pig and cat models (1.6 and 3.4 dB, respectively). Also, relative to biphasic stimuli, monophasic stimuli produced significant increases in the slope of the EAP amplitude-level functions for both species. This increase in the rate of fiber recruitment was independent of the threshold effect, as demonstrated by the measures of normalized slope. Finally, we somewhat unexpectedly observed changes in EAP response latency, with monophasic stimuli producing longer EAP latencies than did biphasic stimuli.

Additionally, consideration of both the feline single-fiber and gross-potential measures provide us with some insight into the neural mechanisms underlying the observed effects of different stimulus pulses. Comparison of the single-fiber and EAP trends indicate that similar threshold improvements (4.1 and 3.4 dB, respectively) are realized with monophasic stimuli vis-a-vis biphasic stimuli. In addition, comparably greater response latencies were observed with monophasic stimuli in the EAP and single-fiber mean measures (71 and 60 μs, respectively). These findings suggest that these particular monophasic/biphasic differences observed in the gross neural potential reflect underlying excitation mechanisms intrinsic to single-fibers.

A primary goal of these experiments was to ascertain the extent to which the duration of the second phase of a biphasic pulse influenced the response evoked by the initial phase. We therefore systematically extended the second phase duration to determine the effect on response threshold. The single-fiber results of Figure 7 suggest the greatest threshold reductions occur as the second phase is increased to a duration of about 500 μs; beyond that value, the duration-threshold functions begin to reach an asymptotic value. However, the gross-potential data of Figure 5 presented more equivocal results. While the threshold-duration curves of subjects H48 and C56 also

reached asymptotic values, other subjects produced functions that did not reach a clear minimum. It is unclear why the EAP threshold-duration functions fail to reliably reach asymptotic values; we will continue to explore this issue in further experimentation.

Our available single-fiber and gross-potential findings also differ in another important way. From Figure 6-D, it is clear that single-fiber relative spread values are greater for monophasic stimuli than for biphasic stimuli. That is, the rate of increased firing efficiency is lower for monophasic pulses than for biphasic pulses, since the slope of the firing efficiency vs. level function is inversely related to relative spread. However, our gross-potential data clearly demonstrate the opposite trend: a steeper growth of EAP amplitude with monophasic stimuli (Figures 3-C and 3-D). From our previous modeling work under this contract, it is not surprising that the relative spread properties of single-fiber effects do not strongly influence the rate of EAP growth (Miller et al., 1999). Given that the stimulus effects on the input-output functions of single fibers and the gross potential are in opposite directions, we must look beyond single-fiber physiology for an explanation. One possible cause for the effects of pulse type on EAP amplitude-level slope may be the interaction of the electrical stimulus field and the complex spatial arrangement of the recruited auditory nerve fibers. Given that fibers of the spiral ganglion are oriented in a helix, it is likely that any stimulus delivered by a monopolar electrode will produce many different patterns of membrane depolarization (i.e. activating functions). Computational modeling work by Rubinstein (1993) has shown that the fiber orientation relative to the stimulating electrode can greatly influence the pattern of membrane depolarization along the length of the axon. Frijns et al. (1996) has also demonstrated spatial-dependent excitation effects with his rotational model of the guinea pig cochlea.

In addition to our observation of an interaction between stimulus pulse type and the rate of neural recruitment, we also observed, in some preparations, a bias toward smaller saturation (maximum) EAP amplitudes with biphasic stimuli. This trend is seen both in the exemplar data of Figure 2 and the group-data scatter plot of Figure 3 (panel B). Both of the observations of reduced slopes and reduced saturation amplitudes may be manifestations of the same excitation phenomema, that of activating functions that are dependent not only on fiber orientation, but stimulus waveshape. We will examine these possibilities with additional computational modeling.

5 Plans for the next quarter

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

- Complete construction of the multi-channel headstages and amplifiers for use with the Michigan electrode arrays. We will also select and purchase new high-performance filters for use with the above electrode arrays. Our plan to use multiple-channel signal processing will enable us to perform simultaneous, multiple-channel recordings once our data acquisition software upgrades are complete.
- Perform additional EAP experiments with pseudomonophasic pulses to clarify or confirm some of the weaker trends presented in this report.
- Upon completion of the new headstages and amplifiers, perform more experiments with the UM thin-film electrodes.
- Work in concert with UM engineers to develop new electrode arrays that are eighth-nerve friendly; that is, have the appropriate overall dimensions, pad spacing, and shank dimensions to more efficiently perform evoked potential recordings with the exposed auditory nerve.
- Complete construction of the "appleseed", a Macintosh G4-based parallel supercomputer. This system will reside within our facilities to enhance the execution of our supercomputer-based simulations.

6 Appendix: Presentations and publications

The following two presentations were made at the 2000 Midwinter Meeting of the Association for Research in Otolaryngology (February 20-24, St. Petersburg Beach, FL):

- Miller, C., Abbas, P., Robinson, B. (2000) Assessing refractory properties of the electrically stimulated auditory nerve. Assoc. Res. Otolarygol. Abs. (abstr. 805).
- Rubinstein, J., Tyler, R., Brown, C. (2000) Perception of high rate electrical pulse trains and their effects on perception of tinnitus: preliminary results with round window stimulation. Assoc. Res. Otolarygol. Abs. (abstr. 744).

The following manuscript has been published in the journal Trends in Neurosciences:

- White, J.A., Rubinstein, J.T., Kay, A.R. (2000) Channel noise in neurons. Trends Neurosci. 23, 131-137.

The following manuscript has been accepted for publication in the journal Ear and Hearing:

- Miller, C.A., Abbas, P.J., Brown, C.J. (in press) An improved method of reducing stimulus artifact in the electrically evoked whole nerve potential. Ear Hear.

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