Fourth Quarterly Progress Report
NO1-DC-6-2111

The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation

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October 30, 1997

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1 Introduction

In this contract, we are using experimental and computer models to investigate issues relevant to electrical stimulation the auditory nerve. In addition to studying basic response properties of the nerve, we are also examining possible means of enhancing the transfer of information from implanted electrodes to auditory nerve fibers.

We have used several measures of the electrically evoked compound action potential (EAP) to characterize important properties in auditory nerve fiber response that may be most relevant to stimulus coding in prosthetic devices. Basic threshold and amplitude-level (i.e., growth) characteristics are important in relation to changes in stimulus intensity. Two-pulse (masker-probe) stimulus paradigms provide a means of characterizing temporal interactions that occur when the nerve is placed in a refractory state by a prior stimulus. More complex stimuli, such as pulse trains and modulated pulse trains, are used to examine both short-term and long-term adaptation effects. Such pulse trains provide stimulus conditions more representative of the regimens used in current designs of auditory prostheses. Finally, we measure channel interaction effects to assess the independence of information transmitted on different electrodes of a multi-electrode array. We view the close coupling of computer model simulations and physiologic recordings as a key feature of this project. These parallel approaches are used to both measure and simulate the EAP of the auditory nerve as well as responses of single auditory nerve fibers.

The EAP in response to monophasic pulsatile stimuli was the subject of our first quarterly progress report. We have recently submitted a paper (Miller et al.) for publication, outlining the features of EAP in response to monophasic stimuli delivered to a monopolar, intracochlear electrode. That paper outlined several important features of the EAP including waveform morphology, latency, response threshold, strength-duration characteristic, growth of amplitude with level, and saturation amplitude. Measures were obtained using both anodic and cathodic stimulus pulses in both the guinea pig and the cat. The response characteristics were found to be sensitive to stimulus polarity in several respects. Although there were a few notable interspecies differences, the data from both cat and guinea pig were similar in most respects. An underlying goal of this work is the application to human patients who are candidates or users of cochlear implant. The fact that we observed similar response properties in guinea pig and cat – two species with considerable differences in cochlear anatomy – suggests that

some response characteristics may be conserved across species and apply also to the human. Response properties of the EAP that differed between the two species may point to issues that we need to consider more carefully in terms of modeling responses in humans.

The EAP in response to monophasic pulses was also generally consistent with the single fiber data collected thus far from the cat (summarized in the third quarterly progress report) and with simulations generated by the computer model of the stochastic auditory nerve fiber.

In summary, our measures of basic EAP properties revealed several differences in the response to anodic and cathodic pulses presented through monopolar electrodes:

- EAP waveforms tend to be polarity dependent. Cathodic stimuli typically evoke a triphasic waveform (P1-N1-P2), but in some cases can be biphasic; anodic stimuli evoke a biphasic response waveform (N1-P2).

- The latency of the anodic response is consistently less than that of the cathodic response across all stimulus levels.

- In the cat, EAP threshold is higher for anodic pulses than for cathodic pulses. EAP data from the guinea pig show the opposite trend, suggesting that anatomical differences may play a role in the relative thresholds of anodic and cathodic stimulation.

- The amplitude of the EAP generally increases for both anodic and cathodic stimulation. The slope of the amplitude-level (growth) function is greater for cathodic stimulation. This is generally true for cats and is also true in the guinea pig when slope is normalized to threshold.

- The maximum (i.e., saturation) amplitude of the EAP at high levels tends to be larger for the cat than the guinea pig, as one might predict based upon the relative sizes of the two nerves. In most cases, both stimulus polarities evoke an EAP that saturates at the same response amplitude at high stimulus levels. Although there were two notable exceptions in our data from the cat, the fact that most animals show the same saturation amplitude for both polarities suggests that a saturated EAP amplitude may reflect the contribution of the full complement of responsive neurons of the auditory nerve.

This fourth progress report focuses on temporal response properties. First, we will summarize data collected with two-pulse stimuli in which

we investigate facilitation and refractory behavior. Second, we discuss the responses to constant amplitude pulse trains, stimuli which integrate both refractory, facilitory, and more long-term temporal effects. Finally, we report some of our initial results in response to amplitude-modulated pulse trains. Such stimuli are of particular interest, since they simulate to a greater extent the normal pattern of stimulation that may be encountered with cochlear implants.

2 Activities of the Fourth Quarter

- We contributed two invited presentations and two posters at the 1997 Conference on Implantable Auditory Prostheses, held in Pacific Grove, California. These primarily covered work conducted on the contract. (Abbas et al., 1997; Rubinstein et al., 1997; Miller et al., 1997; Matsuoka et al. 1997).

- A consulting visit was hosted for Blake Wilson and Don Eddington in September 1997. They reviewed the progress to date and discussed plans for further experiments.

- We hosted a visit by Jerry Loeb in which we conducted initial measurements of intracochlear electrode impedances and EAP responses in an animal implanted with an experimental compartmental electrode.

- As discussed above, a paper describing basic EAP response properties was submitted to Hearing Research for publication (Miller et al., submitted).

- We continued EAP and single unit recordings for both monophasic and biphasic stimuli in acutely deafened animals.

- We conducted initial testing with both impedance and EAP measurements using multi-electrode arrays.

- Potassium current sources were added to the stochastic model to simulate the after hyperpolarization that has been observed in single unit studies.

- We conducted simulations of responses to high rate pulse trains, demonstrating activity with temporal properties similar to spontaneous activity in single auditory nerve fibers.

3 Methods

In this progress report, data describing the EAP represent measurements obtained from both cats and guinea pigs. Methods for acute experiments were described in detail in the first quarterly progress report. In all the data reported here, animals were acutely deafened with an intracochlear infusion of neomycin sulfate solution. The EAP was recorded by an electrode placed on the auditory nerve at the point at which it emerges from the internal auditory meatus. In all cases, stimuli were presented through a monopolar intracochlear electrode placed in the basal turn through the round window. Experiments are planned under the contract to measure and compare responses to both biphasic and monophasic stimuli. In this report, stimuli in the two-pulse experiments are limited to monophasic pulses, 20 or 40 μs in duration, capacitively coupled to effect a charge-balanced stimulus delivery. Stimuli in experiments using constant amplitude pulse trains were either "pseudomonophasic" or biphasic pulses. Pseudomonophasic pulses accomplished charge-balancing by delivering an equal amount of opposite phase charge during the period between successive pulses in the train. These stimuli were used with pulse trains instead of capacitive coupling to avoid charge buildup during the pulse train. To date, stimuli for experiments using amplitude modulation have been limited to biphasic pulse trains as a carrier. The amplitude of the EAP responses were always computed and are reported here as the difference between negative peak (N1) to the following positive peak (P2).

4 Results

4.1 Two-pulse stimuli - temporal interactions

In the two-pulse experiments, we refer to the first pulse in the sequence as the masker and the second pulse as the probe. We have investigated temporal interaction and refractory effects in two ways. In the first, we constructed what we term "refractory growth functions", where the growth functions to the probe are measured at different IPIs, with masker level fixed at a constant value. Results from those experiments were reported in our second quarterly progress report. IPI affects both threshold and slope of the growth function, as well as its saturation amplitude. In more recent experiments, we have focused on the refractory recovery process, examining functions of response amplitude versus IPI. In later reporting periods, we

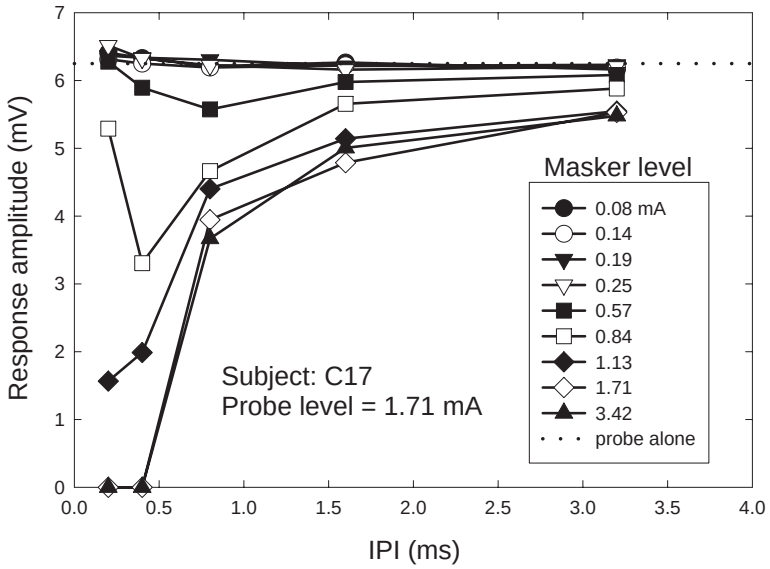

Figure 1: EAP response amplitude to a forward masked pulse is plotted as a function of interpulse interval (IPI) for the two-pulse stimuli. The level of the first pulse (masker) is the parameter. The level of the second pulse (probe) is fixed at 1.71 mA.

will use such measures to characterize refraction properties across animals with various degrees of neural degeneration. Such measures could then find application to (human) cochlear implant patients, potentially as a means of assessing physiological status.

Figure 1 illustrates some features of two-pulse interactions evident in the EAP. Amplitude of response to the probe pulse is plotted as a function of masker-probe interpulse interval (IPI). With this paradigm, we observed temporal interactions resulting in both facilitation and refraction. In each graph, the level of the probe is fixed at a constant value, while the level of the masker pulse is varied parametrically. At low masker levels and short IPIs, there is evidence of facilitation or integration (masker levels = 0.08-0.25 mA). At higher masker levels and short IPIs, there is a decrease in amplitude indicative of refractory behavior (masker level = 0.57-1.71 mA). Amplitudes at longer IPIs display recovery from refraction. Across data sets where masker level is greater than the probe, the time course of recovery is generally constant (masker level = 1.71 and 3.42 mA).

Since the effective range of stimulus levels may vary significantly across

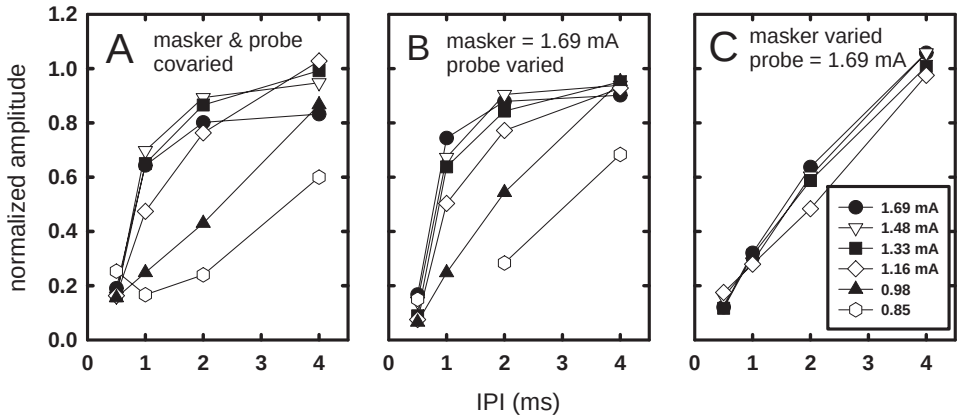

Figure 2: EAP amplitude in response to a forward masked probe normalized relative to unmasked response is plotted as a function of IPI. In (A) the masker and the probe is the parameter. In (B) the masker is fixed at 1.69 mA and the level of the probe is the parameter. In (C), the level of the probe is fixed at 0.98 mA and the level of the masker is the parameter.

subjects, particularly those with partially depleted neural systems, we are interested in the effects of stimulus and response level on the recovery characteristics. Figure 2 shows recovery functions normalized to the unmasked response as masker and probe levels are varied in different combinations. Figure 2A shows recovery functions where the level of the masker and probe pulses are held at the same level and IPI is varied. The parameter is level of both masker and probe. Figure 2B shows normalized functions in which masker level is fixed and only probe level is varied. Figure 2C shows the same functions for the condition where probe level is fixed and masker level is varied. For conditions where the masker and probe level are varied together and where the masker level is fixed and probe level varies, we observe similar recovery behavior: there are clear level effects, with slower recovery at low current levels. When masker level is varied with a fixed probe, rate of recovery is unaffected, suggesting that recovery characteristics are primarily determined under these stimulus conditions by probe level as long as probe level is less than the masker level.

It is important to comment on what may be interpreted as different trends in Figures 1 and 2. In Figure 1, recovery functions are clearly different for low level maskers, but for the two levels of masker equal to and above the level of the probe, the recovery functions superimpose. Data from other

animals such as those in Figure 2, in which we have used more masker levels above that of the probe, reinforce this observation. One interpretation of this observation is that when the masker is greater than the probe, most fibers that are responsive to the probe also respond with high probability to the masker pulse. As masker level is increased above that value, more fibers are adapted, but those fibers do not respond to the probe pulse and therefore have little effect on the response. Thus, for masker levels greater than the probe, similar recoveries are evident.

The effect of probe level observed in the EAP is also evident in computer simulations using the stochastic model. Figure 3 illustrates recovery functions calculated on the basis of simulated responses of 100 neurons, all with the same threshold and membrane characteristics. Percent of fibers responding is plotted as a function of IPI, analogous to the plots of Figure 2. Plots are shown for four different probe levels; in all cases, below that of the masker. The range of IPI shown here is much smaller than of the recorded data (Figure 2); nevertheless, the trend of increasing recovery time with decreasing probe level is evident in both. The model results suggest that this effect is at least partially the result of fibers overcoming a relative refractory state more quickly by using a higher level of stimulation.

Recordings of the EAP have been made from humans implanted with the Ineraid device, a prosthesis with a percutaneous plug that allows direct electrical access to the implanted, intracochlear electrodes (Brown et al., 1990, Wilson et al., 1997). Intracochlear recordings can also now be made using a reverse telemetry system incorporated into the Nucleus CI24M implant (Abbas et al., 1997; Brown et al., in press). Due to large-amplitude stimulus artifacts recorded with this device, a forward-masking subtraction technique (Brown et al., 1990) is needed to extract the EAP. Using this protocol, we measure the response to the probe stimulus with and without a preceding masker pulse. Since the probe response is reduced by the presence of the masker yet the stimulus artifact is unaffected, subtracting the two response traces largely eliminates the stimulus artifact while leaving the neural response intact. The upper graphs in Figure 4 were calculated using this subtraction method.

We believe it important to compare the EAP data obtained using the subtraction with that obtained using the traditional (direct) approach, particularly in light of clinical application of the subtraction technique. Figure 4 illustrates recovery data measures using two different methods (upper vs lower graphs) and in response to both cathodic and anodic stimuli (right vs left graphs). The recovery curves obtained with the subtraction method

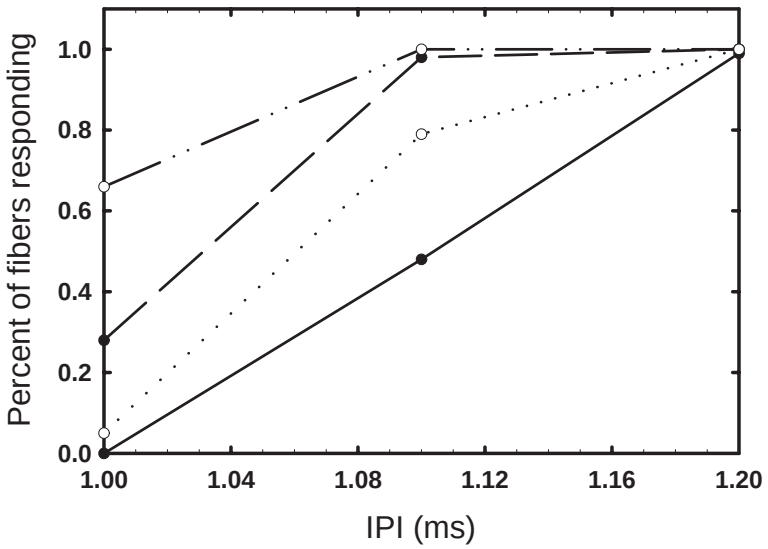

Figure 3: Model EAP simulation of percent of fibers responding as a function of IPI. Masker level is held constant in the model at 430 μA. Level of the probe is the parameter.

(upper graphs) are opposite in direction compared to those obtained with the direct method (lower graphs). This is direct consequence of the subtraction technique: at short IPIs, the amplitude is large since the response to the probe is reduced and the subtracted difference is great. At longer IPIs, the response to the probe is more similar to that obtained with no masker, so that the subtracted response is small. As has been our custom in previous research, we normalize the subtraction recovery functions to the amplitude obtained at an IPI of 500 μs.

We wish to make two observations relative to the data of Figure 4. First, the recovery functions measured using the two methods (direct and subtraction), while inverted, show similar characteristics as a function of level and stimulus polarity. Such comparisons suggest that the subtraction method may be assessing the same properties of neural function surveyed with the direct method. Second, in several animals, we have observed recovery characteristics that differ with stimulus polarity. Although it is important to note that this is not a consistent finding across all animals, the animal data shown in Figure 4 demonstrated recovery functions in response to cathodic stimulation which show a consistently slower recovery than those in response to anodic stimulation. This observation is consistent with hypotheses involving

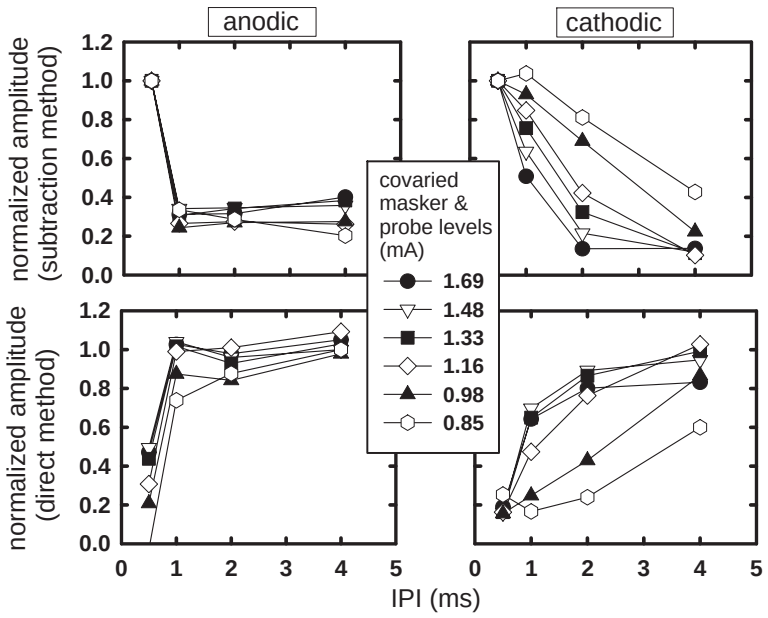

Figure 4: Normalized EAP recovery functions are plotted for monophasic anodic stimuli (on left) and cathodic stimuli (on right). Two methods are used to assess recovery (see text). Results from the subtraction method are plotted in the two upper graphs; results from the direct recording method are plotted in the lower graphs.

polarity dependent sites of action potential initiation which may also have different refractory recovery characteristics.

As part of another project (Iowa Cochlear Implant Project III, NIDCD, DC00242), we have been making measurements of the human EAP using the aforementioned reverse telemetry system of the Nucleus CI24M device. Recovery functions measured in implant users show characteristics similar to those observed in cats reported here. An example from those data is illustrated in Figure 5, where the same manipulations of masker and probe level, shown in Figure 2, were performed. While the subtraction method recovery functions are in opposite direction to those reported in the cat (due, again, to the methodology), the effects of varying masker and probe are similar. Such data suggest that level of probe may be an important factor in comparing recovery data across subjects and across electrodes within a subject. Finley et al. (1997) have also reported significant effects of level on EAP refractory recovery functions measured in human implant users. Nevertheless, in limited data collected using the telemetry system with Nucleus CI24M implant users, we have compared recovery functions across different electrodes showing that if stimulus level (relative to threshold) is accounted for, then comparisons across electrodes within a subject are consistent.

4.2 Constant-amplitude pulse train data

Responses to trains of current pulses, typically 100 ms in duration, were measured while systematically varying current level and interpulse interval. We have recorded responses to "pseudomonophasic" pulses as well as responses to biphasic pulses. Phase duration is 40 μs for the data presented in this report. We have made recordings in both cats and guinea pigs, both showing qualitatively the same basic response characteristics.

Figures 6 shows a sequence of EAP responses to a constant amplitude pulse train recorded from the auditory nerve of a cat. Typical of data obtained with pulse trains, the data from this animal demonstrates refractory effects, as seen in the large diminution of response to the second pulse compared to that of the first. In addition, the responses to successive pulses show an alternating pattern as well as an overall decrease in response amplitude, likely the result of refractory recovery as well as long-term, cumulative effects of stimulation. With pulse train stimulation, the stochastic axonal model produces EAP variations that are quantitatively different but qualitatively similar to those seen in the animal preparations, as shown in Figure 7. The waveforms were calculated by evaluating 240 spatial segments over

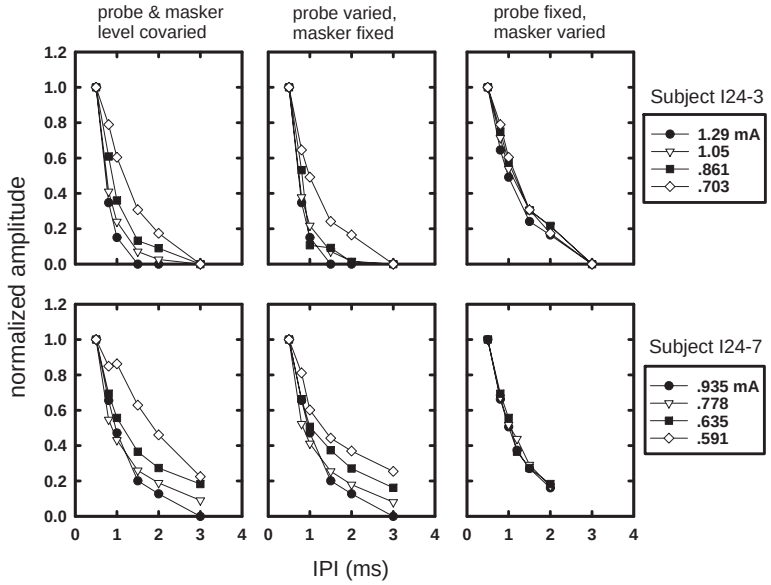

Figure 5: EAP recovery functions from two human subjects are plotted for data collected using the telemetry system of the Nucleus CI24M implant. Data were collected using the subtraction method. The same three conditions are plotted as in Figure 2 (masker and probe equal, fix masker - vary probe, and fix probe - vary masker). Data from subject I24-3 are plotted in the upper graphs; data from subject I24-7 are plotted in the lower graphs. Levels were specified by the implant's programming system. Values reported in the legend correspond to calibrated values from a typical implant, not the specific device in that subject.

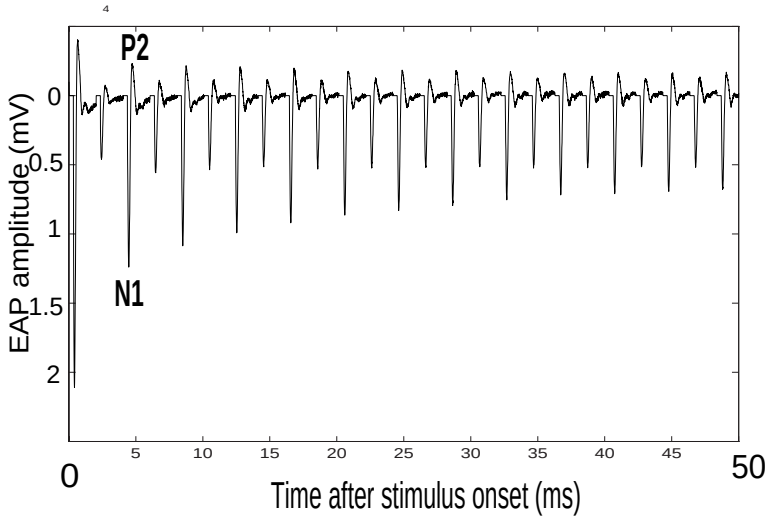

Figure 6: EAP waveforms in response to a train of pseudomonophasic (see text) pulses are plotted as a function of time after stimulus onset.

30,000-50,000 us time intervals with 24 nodes of Ranvier and 4149 voltage-sensitive sodium channels. The EAP was simulated as a summation of 100 fiber responses, with each fiber having the same threshold.

Examples of EAP amplitude (measured for each EAP response from each pulse in the train) as a function of time after stimulus onset are shown in Figures 8 and 9. In all cases, the amplitude of response is plotted normalized to the amplitude of the first pulse in the train. The general trends seen in this figure are typical of those we have observed. At the longest IPIs (e.g., 4 and 8 ms), the response shows little change across the set of pulses in the train. At IPI=2 ms, one observes a significant decrease in the response amplitude after the first pulse; response amplitude then decreases further across the duration of the stimulus. At shorter IPIs, the decrease in response becomes increasingly more severe and at certain IPIs, an alternating pattern appears in the response. The amount of adaptation and the degree and time course of the alternating response varies with stimulus level, stimulus type (monophasic vs biphasic), and subject.

We have observed some trends across animals in the EAP responses to pulse trains and have attempted to quantify some these properties. For instance, the "steady state" response to the pulse train (that is, the asymptotic response amplitude, estimated by averaging responses across the last

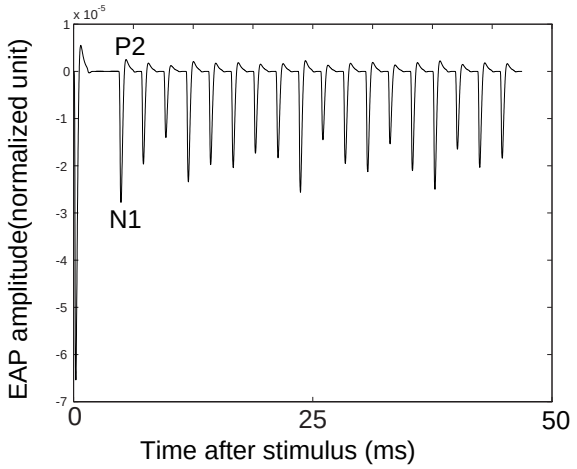

Figure 7: EAP waveforms calculated by the stochastic axonal model in response to a monophasic pulse train.

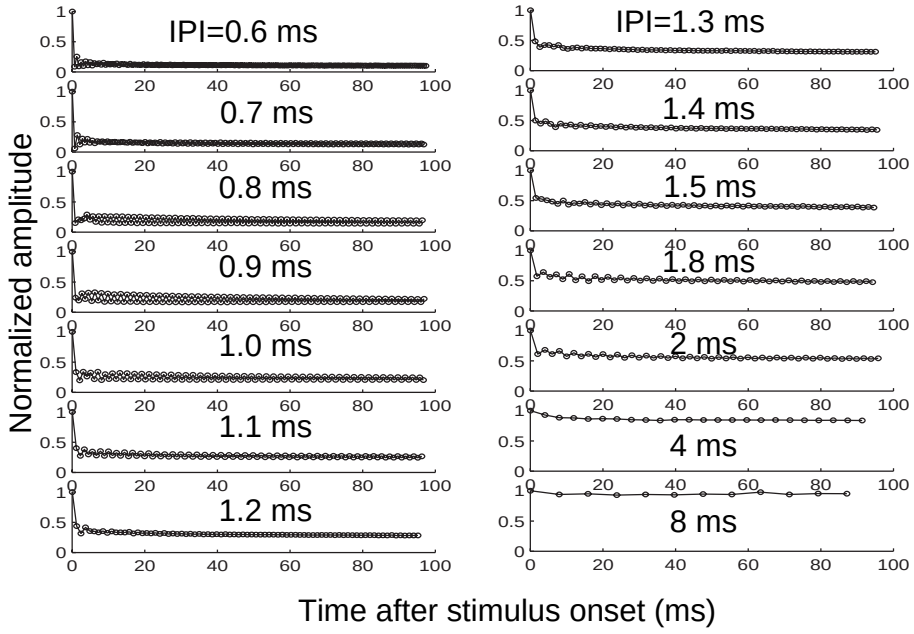

Figure 8: Amplitude of EAP response to successive pulses in a pulse train, normalized to the amplitude in response to the first pulse of the train. Train duration was 100 ms. Stimulus was a pseudomonophasic pulse, 40 μs in duration. IPI for each pulse train is indicated.

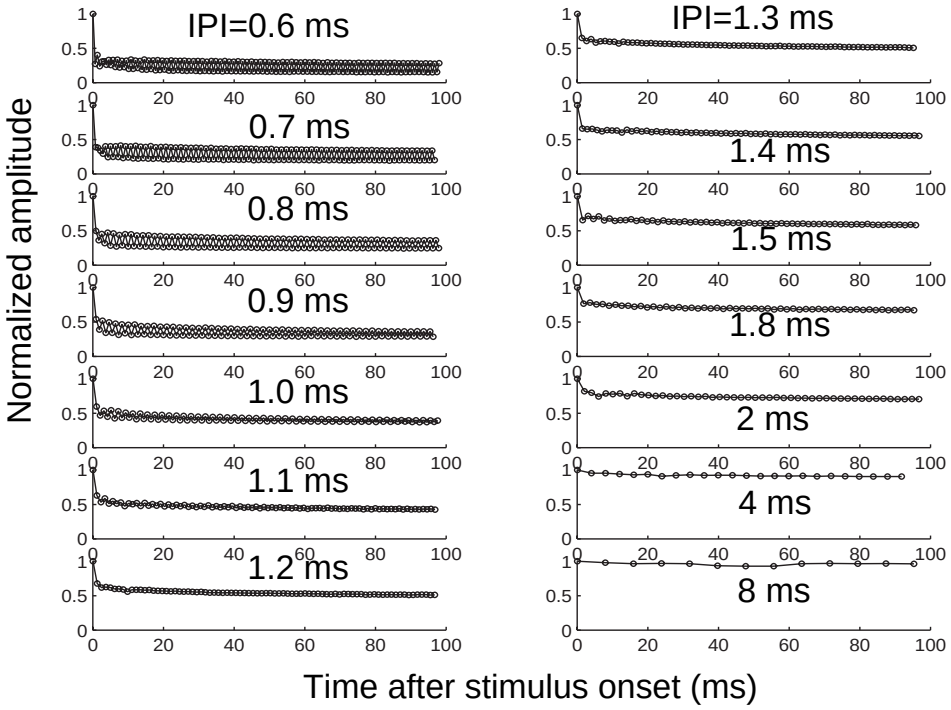

Figure 9: Amplitude of EAP response to successive pulses in a pulse train, normalized to the amplitude in response to the first pulse of the train. Train duration was 100 ms. Stimulus was a biphasic pulse, 40 $\mu s/phase$. IPI for each pulse train is indicated.

50 ms of the pulse train) tends to adapt to an amplitude lower than that in response to the second pulse. Figure 10 illustrates measures designed to parametrically describe this pattern in two cat preparations obtained at two stimulus levels. The response to the second pulse in the train (normalized to the response amplitude to the first pulse) is plotted as a function of IPI – essentially the same as the refractory recovery functions of Figure 2. Also plotted on the same axes are the steady state amplitudes, averaged across the last 50 ms of the pulse train, as a function of IPI. Within the range of IPIs of 0.8 to 4 ms, the amplitude of the steady state amplitude is less than or nearly equal to that for the second pulse. In other words, there is a cumulative effect of pulse train stimulation that, in general, is greater than that in response to the initial pulse. At small IPIs, we have sometimes observed a cross-over of these functions, indicating that the second pulse response was the smallest observed for the train. Furthermore, as indicated in Figure 10, we have observed variations in the recovery with both subject and level. For example, cat C25 at a high stimulus level shows very different recovery (both amplitude and time course) for the 2nd pulse response relative to the steady state amplitude. For cat C26 at the low levels, the recovery functions are very similar.

The response patterns observed with these animals are qualitatively similar to those observed by Wilson et al. (1995,1997) in human implant users. In general, however, we have seen a smaller variation in amplitude, that is, the alternation pattern in the response amplitude is less pronounced. Also, the pattern of alternation appears to decay at a faster rate; in some animals, alternations may be evident for less than 50 ms. Finally, although our analysis is incomplete, the decay of stimulation as evidenced in Figure 10 appears to be somewhat different in our animal preparations. These differences between our animal work and that in human implant users may be at least partly due to stochastic properties of the stimulated neurons. For example, higher noise levels in the neural membranes of may exist in recently deafened animals, resulting in a more stochastic response pattern. The expected result would be a smaller-amplitude alternation, a shorter persistence of the alternating pattern and less refraction after the initial pulse.

4.3 Amplitude modulation of pulse trains

Responses to amplitude-modulated pulse trains take one further step toward a realistic simulation of neural excitation likely occurring with prostheses using continuous interleaved sampling (CIS) strategies. In this investigation,

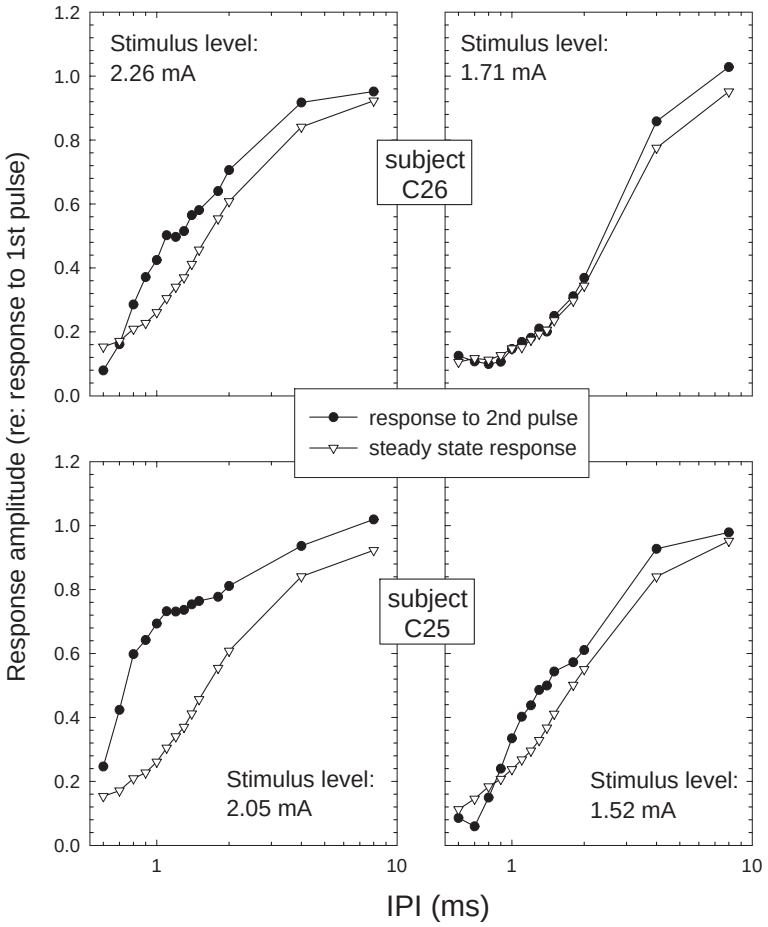

Figure 10: Normalized amplitude of response is plotted as a function of IPI for pseudomonophasic, cathodic, pulse train stimuli, 100 ms in duration. On each graph, the response to the second pulse is plotted in addition to the averaged response to the pulses presented during the last 50 ms of the pulse train. Data from two cats (C25 and C26) are plotted as well as data at a low level (near the middle of the subject's dynamic range and at a high level (in the upper part of the subject's range).

data were collected in the same way as that for constant amplitude pulse trains. To date, we have data only for biphasic pulse train responses obtained from guinea pigs. We have varied the IPI (250-1000 Hz), modulation frequency (25-400 Hz) and modulation depth (0-50%). The plots in Figure 11 show amplitude of EAP measured across a 200-ms interval of a pulse train. This plot begin 50 ms after onset of the modulated pulse train so that we avoid initial refractory effects and an approximate steady state response has been reached. Note that in the case of 0% modulation (constant amplitude pulse train), the response is constant (i.e., any alternating pattern as evident in Figures 8 and 9 has decayed after the first 50 ms of the pulse train). As modulation depth is increased, an approximately sinusoidal modulation of response amplitude emerges. At the higher modulation depths, the response pattern shows larger variations, but becomes a more distorted version of the input modulation. We can quantify these observations using spectral analysis of the response amplitudes as shown in Figure 12. In all cases, there is the expected increase in the component of the response at the modulation frequency (in this case, 50 Hz) as modulation depth increases. At the highest modulation depths (10% and 50%), there is considerable harmonic distortion. Results are at least qualitatively similar to those measured in human implant users (Wilson et al progress report (1995), i.e., the modulated response amplitudes indicate a distorted version of the modulated stimulus. The range of frequencies and modulation depths over which a sinusoidal response is evident may be indicative of limitations in the ability to transmit information over the electrically stimulated auditory nerve. By modeling the differences between responses in acutely deafened animals and the human system that may be relatively compromised due to neural degeneration, we may provide some insight into the mechanisms responsible for these effects.

Figure 13 plots the amplitude of the response for a fixed modulation depth at several modulation frequencies (25 Hz - 400 Hz). In all cases the IPI of the carrier pulses is 1 ms. Figure 11 showed an increasing variation in amplitude with increasing modulation depth. In Figure 13 modulation depth is fixed, but there is an increasing variation in response amplitude with modulation frequency. We attribute this effect to refractory properties of the stimulated neurons. At low frequencies, the amplitude of the pulses changes relatively slowly, so that refractory effects decrease the response to succeeding pulses in the train. At higher frequencies, the pulse amplitude increases very quickly resulting in a higher amplitude response. Wilson et al. (1995) have observed similar behavior in an Ineraid implant

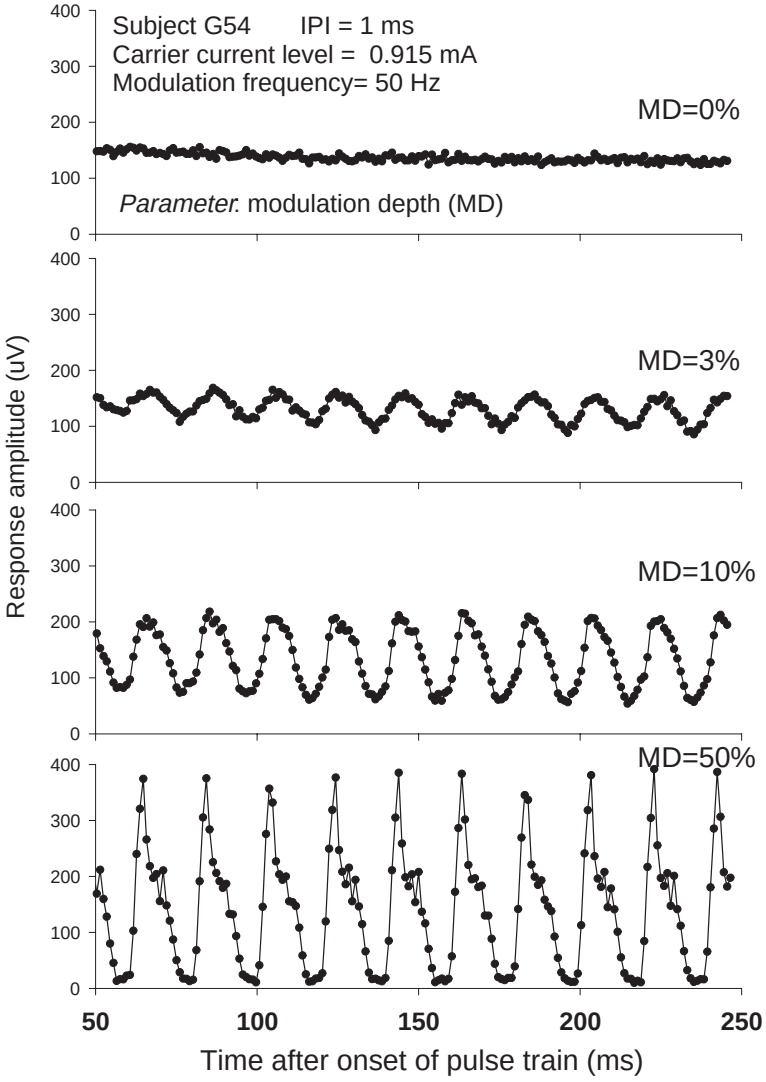

Figure 11: Amplitude of EAP response to successive pulses in an amplitude modulated pulse train. Duration of the pulse train was 250 ms. Response are plotted after the first 50 ms of the train. Parameters of the stimulus are indicated on the figure. Effects of changing modulation depth are illustrated.

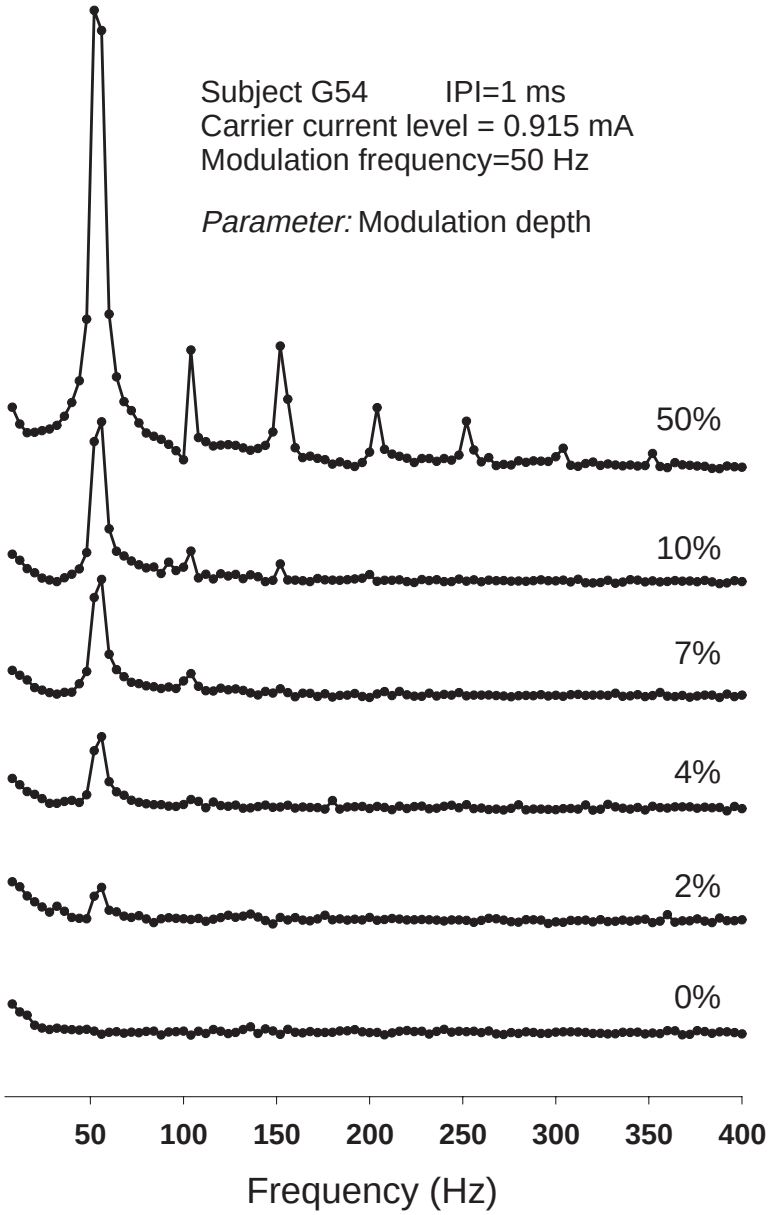

Figure 12: Fourier transform of the response amplitude vs time function (such as Figure 11) for response to amplitude modulated pulse trains. Modulation depth is the parameter.

user. Psychophysical data investigating the detection of such signals generally has shown the opposite effect, i.e., percent modulation for detection threshold increases with modulation frequency (Shannon, 1992). The contrasting trend in the physiological and psychophysical data are in agreement with a hypothesis that psychophysical responses may be in fact limited by central neural mechanisms rather than the peripheral response properties.

5 Plans for the fifth quarter of this project

The following activities are planned for the fifth quarter (October - December, 1997) of this research project:

- Continue and extend studies of cat single-fiber responses.
- Expand the study of EAP measured with multiple electrode intracochlear arrays.
- Begin studies investigating the addition of noise and high rate pulse trains to increase stochastic properties of the responses to trains of pulses.
- Conduct model simulations in response to amplitude modulated pulse trains.
- Conduct further impedance and EAP measurements with an animals implanted with the experimental electrode array fabricated by Advanced Bionics.
- Begin experiments using triphasic waveforms.

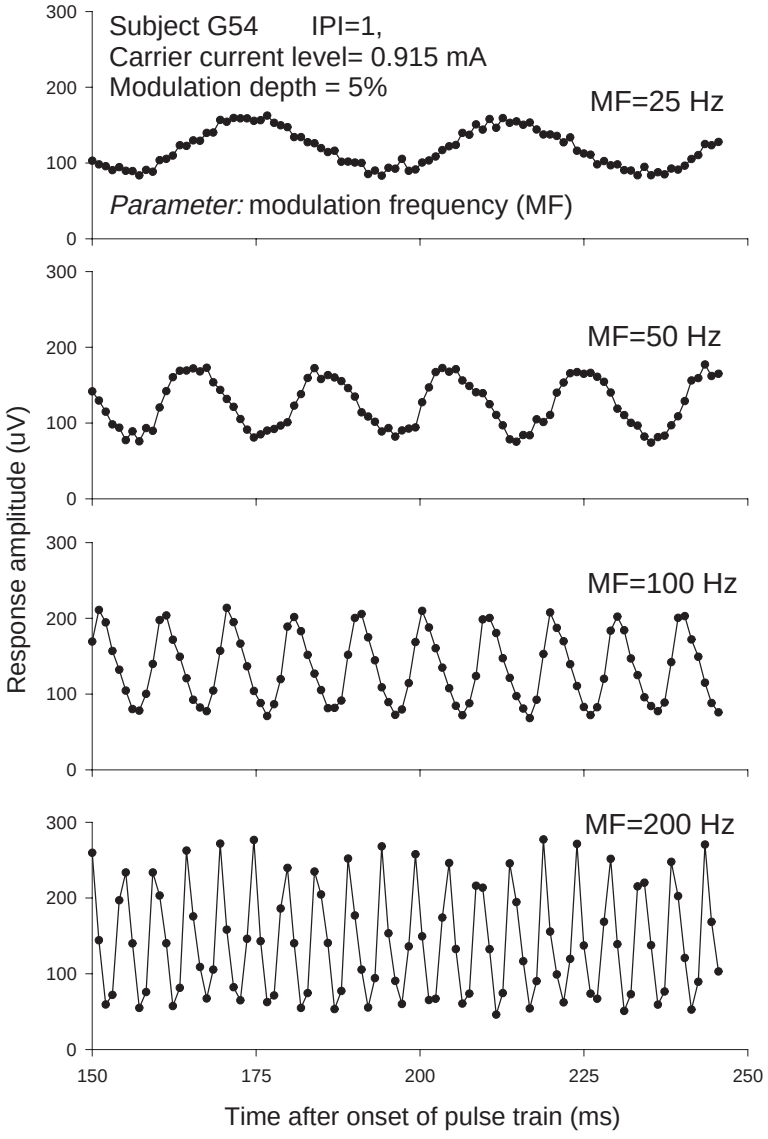

Figure 13: Amplitude of EAP response to successive pulses in an amplitude modulated pulse train. Duration of the pulse train was 250 ms. Response are plotted after the first 150 ms. Parameters of the stimulus are indicated on the figure. Effects of changing modulation frequency are illustrated.

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