Fourth Quarterly Progress Report

N01-DC-9-2107

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.

2 Summary of activities in this quarter

In our second quarter (1 July - 30 September, 2000), the following activities related to this contract were completed:

1. A protocol for an improved means of collecting 8th nerve evoked-potential data from human implant patients has been published in the journal Ear & Hearing (see Appendix). This method can be readily modified for use with the Nucleus Neural Response Telemetry system to reduce distortion in the electrically evoked compound action potential (ECAP) responses recorded with the nerve in a state of partial refractoriness. This work was a direct result of our studies of the refractory auditory nerve conducted in cat preparations.

2. A manuscript detailing auditory nerve responses to monophasic, biphasic, and pseudomonophasic electrical stimulus pulses has been accepted for publication in the journal Hearing Research (see Appendix). This manuscript is an elaboration of the preliminary findings outlined in the 2nd quarterly progress report.

3. Two manuscripts characterizing auditory nerve responses to constant-amplitude pulse trains have been published in the journal Hearing Research (see Appendix). One describes EAP recordings to the pulse train stimuli, and the other details the effects of additive Gaussian noise on the EAP responses to the pulse train stimuli.

4. Jay Rubinstein presented the talk, "Application of stochastic resonance in auditory electrical stimulation" at the World Congress on Medical Physics and Biomedical Engineering meeting in Chicago, IL, July, 2000.

5. Our new data collection software (using Labview code) has been customized and is now being used for neural recording in our laboratory. This new system allows for stimulating and recording capabilities that our previous system did not offer, including simultaneous output of independent waveforms on multiple channels, and collection of up to 8 channels of data (using time-division multiplexing) for use with our planned multichannel neural recordings.

3 Examination of EAP responses to sinusoidal electrical stimulation with and without high-rate pulses

3.1 Introduction

Electrical stimulation of the auditory nerve results in highly synchronized, deterministic neural response patterns, particularly in the absence of functional hair cells, which are responsible for normal spontaneous synaptic activity (Hartmann, et al., 1984). The consequences of this highly synchronous behavior may be a narrow dynamic range of hearing and relatively poor representation of the temporal details of the stimulus. Several modeling and physiologic investigations have been undertaken in our lab to address these issues, particularly with the objective of simulating the spontaneous activity of the IHC/SGN synapse by adding high-rate pulsatile stimulation, producing what we refer to as 'pseudospontanoeous' activity (Rubinstein et al. 1999b). This pseudospontaneous activity is thought to have a desynchronizing effect on auditory nerve fibers.

In the Eighth QPR for contract N01-DC-6-2111 (1998), we reported on simulation of single-unit recordings to stimuli consisting of a 1 kHz sinusoid in association with a 5 kHz monophasic pulse train. The pulse train was referred to as the "conditioning" stimulus, as it was conditioning the nerve fiber to produce pseudospontaneous activity. Without the conditioning stimulus, the fiber responded in a highly synchronous manner, primarily to the peak of the sinusoid. The presence of the conditioning stimulus was found to improve the dynamic range of rate-level functions, and to improve the temporal resolution of the fiber's response to the sinusoid by allowing the fiber to respond to most of the waveform changes over time. The addition of the conditioning stimulus resulted in simulated responses that resemble neural responses to acoustic stimuli.

In the modeling experiments of the Second QPR of contract N01-DC-9-2106 (2000), we used stimuli of 2 kHz, both alone and in the presence of simulated spontaneous synaptic activity. Stimulation of 2 kHz was chosen over 1 kHz because of the short refractory time of individual nodes of Ranvier. The response of the simulated deterministic node of Ranvier to the sinusoid revealed responses to every other positive phase, while response times in the presence of spontaneous synaptic activity displayed a more random response behavior. Period histograms for these two conditions were shown. The responses of the deterministic condition were perfectly synchronized to the peak of every other positive phase of the sinusoid. In the presence of the synaptic currents, the synchrony of the responses was decreased so that responses were more randomly timed, and they better represented the temporal pattern of the stimulus. This release from deterministic alternating response patterns with high-rate pulses has also been observed with pulsatile stimuli in both modeling and EAP investigations (Rubinstein , 1999a; Wilson et al., 1997).

Ideally, the speech processor of an auditory prosthesis would preserve as much detail of the original acoustic signal as possible, therefore investigation of continuous analog stimulation holds significant clinical relevance. Advanced Bionics Corporation has implemented the simultaneous analog stimulation (SAS) speech processing strategy that allows for analog stimulation to occur simultaneously across channels, while minimizing the distorting channel interaction effects which had made analog stimulation problematic in the past (Osberger and Fisher, 1999) by using bipolar electrodes. For the preservation of the original signal to be effective for a cochlear implant user, the neural encoding of the signal also needs to be as accurate as possible. We hypothesize that the addition of high-rate pulsatile stimulation will be beneficial to the neural encoding of analog stimuli.

Up to the present time, our investigations of the effects of adding a high-rate conditioner have included modeling single-unit responses to sinusoidal and low-rate pulse train stimuli, and measuring EAP responses to low-rate pulse trains. In the past, EAP responses to sinusoidal stimuli had not been examined due to the difficulty of artifact rejection of the continuous stimulus. We have recently developed a method of stimulus artifact rejection for sinusoidal stimuli which makes it possible for us to extract the EAP responses. In this QPR, we describe our method of recording responses to analog stimulation as well as preliminary results from our studies of EAP responses to sinusoidal stimuli with and without high-rate pulses.

3.2 Experimental methods

The methods used in these experiments are similar to those described in Miller et al. (1998), except that the round window membrane was not removed. Rather, a small cochleostomy was made below the round window using a 30 gauge needle, and a Pt wire monopolar stimulating electrode was placed in the defect. The deafening protocal using a combination of kanamycin and ethacrynic acid was described in detail in the Third QPR for contract N01-DC-9-2106 (2000). Data reported here are from two guinea pigs and one cat that were acutely deafened. The electrical stimuli consist of 100 Hz sinusoidal stimuli, with the first 5 ms as the cathodic phase and the last 5 ms as the anodic phase, and 5000 Hz biphasic conditioning pulses.

3.3 Analysis of responses

An important part of this study is the minimization of noise and the elimination of stimulus artifact to extract the EAP response. Stimulus artifact rejection with continuous sinusoidal stimulation is difficult, particularly because the stimulus is ongoing and has the EAP response embedded in it, changing the amplitude of the stimulation signal at those points. These characteristics make it imprudent to use established methods of artifact rejection for discrete stimuli such as the alternating polarity method, the subtraction method (Brown and Abbas, 1990), or with template subtraction (Miller et al, 1998). Post-mortem measures were considered for artifact rejection, however, as one goal of this research is to develop applications to human cochlear implant users, we developed an alternate method of artifact rejection.

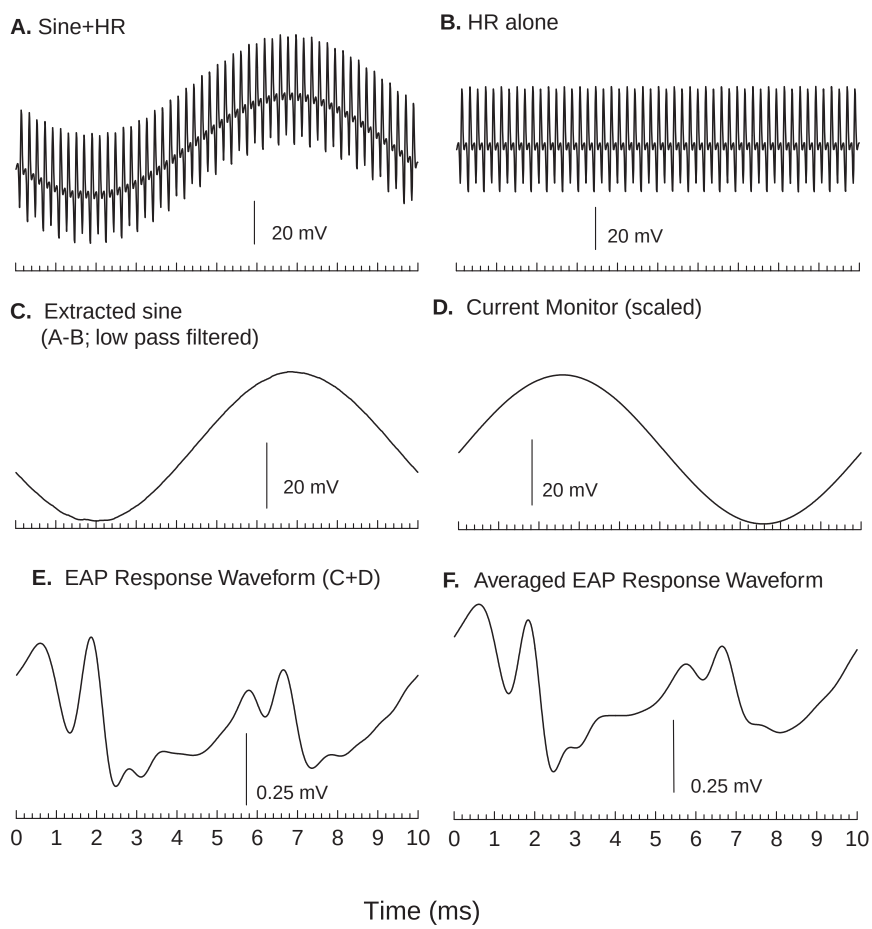

Figure 1: Example of artifact rejection. Shown are 10 ms of the 100 ms sine+HR (A) and the HR alone (B) stimuli. The HR alone is subtracted from the sine+HR to extract the sinusoidal stimulus (C). The scaled, phase shifted current monitor recording (D) is added to C resulting in the EAP response waveform (E). The last nine 10 ms intervals are averaged to result in one average 10 ms EAP waveform (F).

The data collection and analysis techniques applied in this study for noise reduction and artifact rejection are shown in Figure 1. Data analysis is performed using Matlab version 5.2 (Math Works, Inc., 1998). The recordings used in the program are obtained from the subject in response to the 100 Hz sine-alone (sine-alone), 100 Hz sine and 5000 Hz conditioner (sine+HR), 5000 Hz conditioner alone (HR). Recordings of the sinusoidal stimulus are also obtained directly from the current source monitor. Noise reduction is accomplished during data collection by averaging the response to multiple stimulus presentations. The number of measurement sweeps is dependent on the signal-to-noise ratio, with more sweeps taken at lower stimulus levels and fewer sweeps at higher stimulus levels. To further reduce noise, during the analysis the HR is subtracted from the sine+HR, and both the sine-alone and sine+HR recordings are low pass filtered.

To extract the EAP, the digitally windowed waveforms are used to calculate a FFT. The amplitude of the current monitor FFT at the stimulus frequency is then scaled to match the amplitude at the stimulus frequency of the sine-alone and sine+HR FFTs. These scale values are applied to the current monitor time waveform to match the amplitudes of the sine-alone and sine+HR time waveforms. The data analysis program determines the phase angles of the recordings and corrects the phase of the scaled current monitor waveform to be exactly 180 degrees out of phase from the subject waveforms. The EAP responses are then isolated by adding the amplitude scaled and phase shifted current monitor recording, which has no EAP response, to the sine-alone or sine+HR recordings, thus the sinusoidal component of the applied current as well as any distortion inherent in the current source is subtracted from the recorded waveform. After the EAP responses are extracted from the stimulus artifact, one response waveform is derived from an average of the responses over nine stimulus cycles to further reduce the noise. The response to the first cycle is subject to stimulus onset effects, and is not included in the averaging.

3.4 Results

An example of the averaged EAP response waveforms to the sine-alone and sine+HR are shown in Figure 2 for cat C57. The sine level was 0.08 mA, and nine levels of HR were added to the sine for the sine+HR condition. The sine-alone waveform (thin line) is plotted by itself, and is replotted with

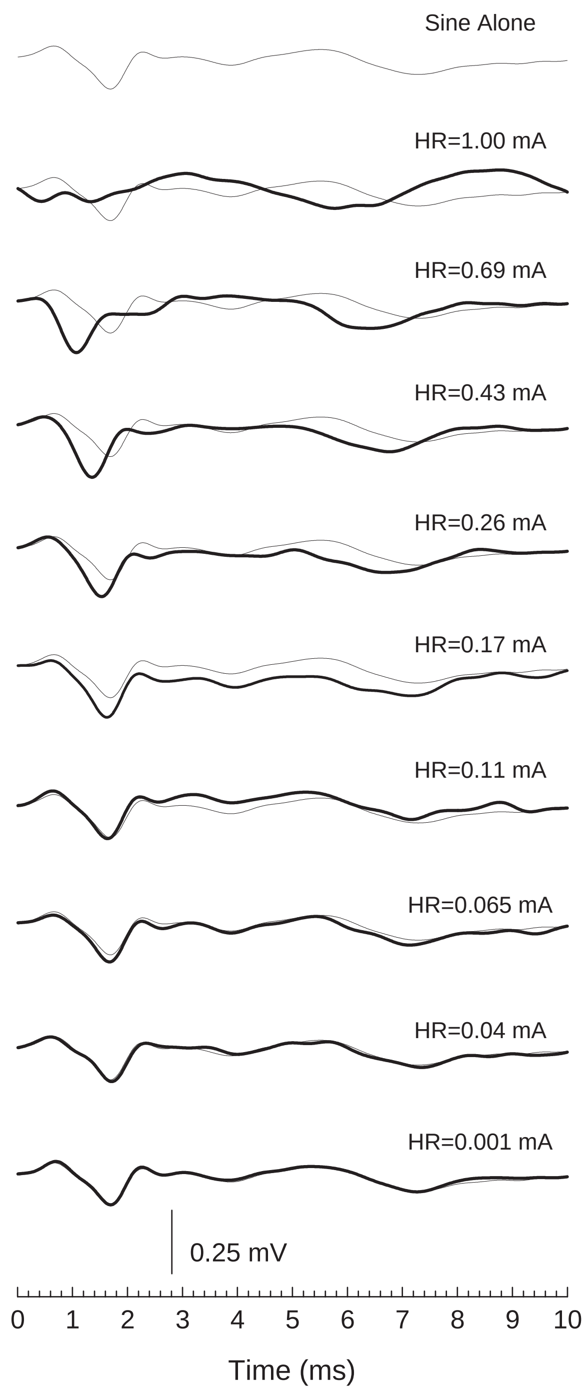

Figure 2: Averaged EAP response waveforms to sine alone (thin line) and sine+HR stimuli (thick line) for cat subject C57, sine level=0.08 mA. The sine alone waveform is replotted with each sine+HR waveform for comparison.

each sine+HR waveform (thick line) for direct comparison of the responses to the two stimulus conditions. At this level of sine, the addition of the HR resulted in changes in waveform morphology, magnitude of response, and peak latency. These changes are quantified in further analyses.

With increases in sine level, additional peaks appeared in the EAPs, resulting in more complex wave morphologies which made it difficult to determine what peaks would best reflect the response waveform characteristics. For this reason, simple measurements of peak amplitude and latency did not seem appropriate. Instead, cross-correlations between the sine-alone and sine+HR responses were performed to evaluate the morphology and latency differences between the conditions' response peaks. The magnitude of the EAP was characterized by the RMS measurement of the entire waveform. In Figure 3 panel A, the growth of response amplitude with sine level is shown for the sine-alone and the sine+HR conditions. The boxed areas emphasize the response amplitudes to the sine-alone and sine+HR conditions for a moderate level (0.26mA) and a low level (0.08mA) of sine. These sine levels were chosen to demonstrate the occurrence of larger response amplitudes in the presence of HR stimulation at low levels of sine, and smaller response amplitudes with HR at moderate to higher sine levels. The waveforms that correspond to these levels are shown in panels B and C, and are plotted in the same manner as in Figure 2. The response amplitudes to the sine-alone and the sine+HR are shown next to the corresponding waveforms. The sine-alone waveforms for the two stimulus levels also demonstrate the level-dependent response characteristics to different phases of the stimulus. For the cat subject, the higher sine level results in responses to both the cathodic and anodic phases, while the lower level sine stimulus elicits a response primarily to the cathodic phase.

Data obtained from a guinea pig are shown in Figure 4. The family of RMS growth functions (panel A) shows a trend similar to those seen with the cat subject in Figure 3, with larger RMS amplitudes at low sine levels in the presence of HR stimuli, and smaller RMS amplitudes for the sine+HR at higher levels of sine. This trend is particularly apparent at the highest level of HR. Like the cat, the response waveforms to the low and moderate sine levels also show level-dependent responses to the phases, and have EAP responses to both phases at the higher sine level. Unlike the cat, however, the lower level of sine evokes a response from the anodic phase with very little, if any, response from the cathodic phase. This species difference

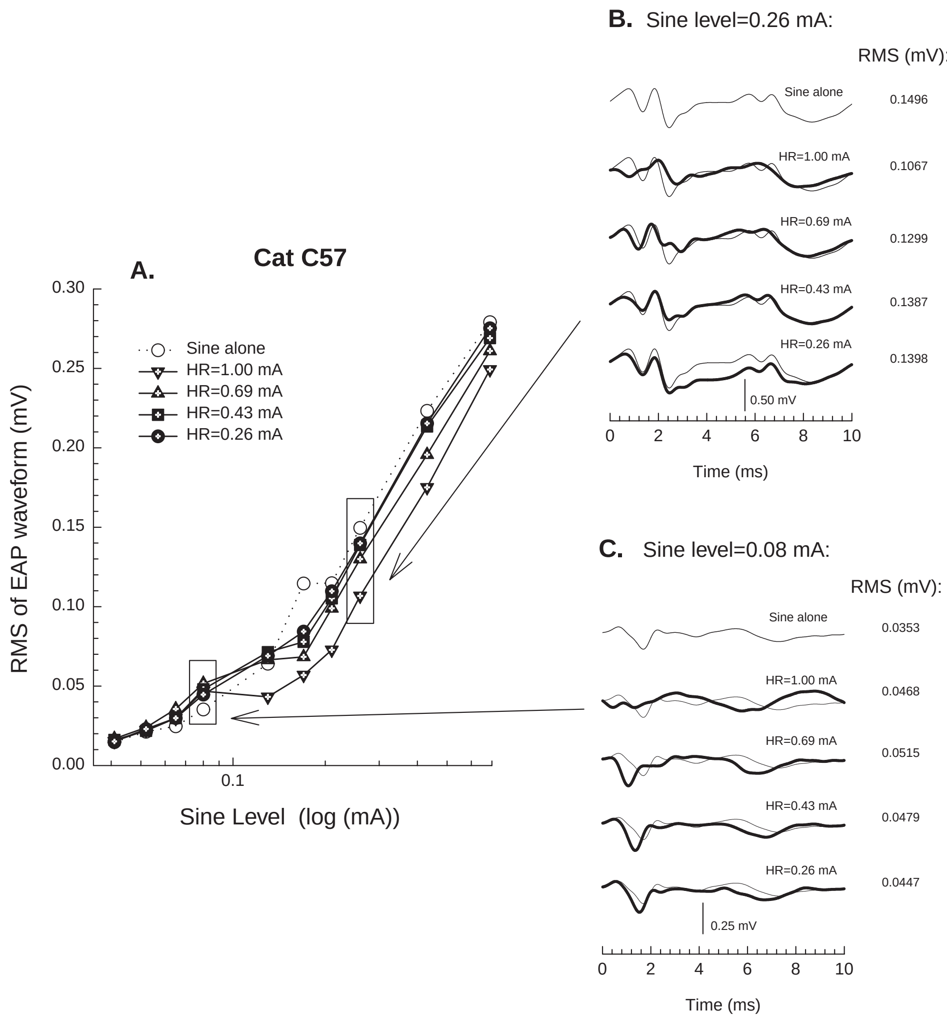

Figure 3: Response amplitudes, derived from the RMS of the response waveforms, for cat C57. The abscissa is plotted in log (mA) to better view the low level growth properties. Panel A shows the growth of response amplitude with level for both sine alone and sine+HR conditions. The boxed areas emphasize the response amplitudes for a moderate (0.26 mA) and a low (0.08 mA) sine level. The corresponding waveforms are shown in panels B and C, respectively.

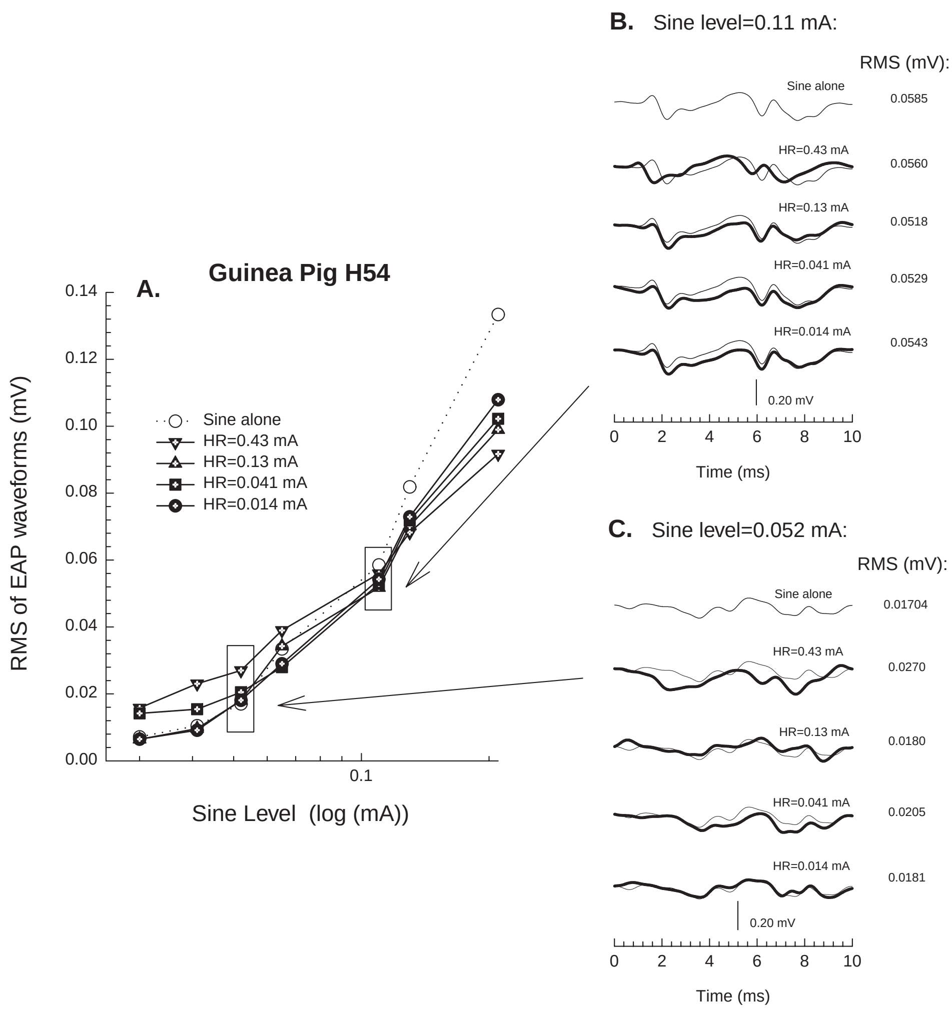

Figure 4: Response amplitude growth functions and waveforms from guinea pig H54, plotted the same as in Figure 3.

with respect to phase sensitivity has been seen previously in our lab with monophasic pulsatile stimuli (Miller et al., 1998).

Effects of sine level and high-rate level on response amplitude are shown in Figure 5. The response amplitudes of the sine+HR conditions are normalized to the response amplitudes of the corresponding sine-alone conditions. Values above 1.0 indicate greater response amplitudes of the sine+HR condition relative to the sine-alone condition, and values below 1.0 indicate smaller response amplitudes of the sine+HR condition. The level effects of sine and high-rate are most clearly demonstrated by the cat data, although the trends are consistent for all subjects. Muscle artifact at higher levels of sine and high-rate pulses prevented the measurement of these levels in the guinea pig. The addition of high-rate pulses to sinusoidal stimuli have the greatest effect on response amplitude for the lower levels of sine, and result in an increase of response amplitude. These effects tend to increase with high-rate level, until between 0.69 and 1.0 mA where the response amplitude shows some decrease.

To examine the effects of high-rate level on the response amplitudes at lower sine levels, an amplitude response criterion for each species was arbitrarily determined, and the sine level required to induce this response amplitude was extrapolated from the RMS growth functions. The response criterion for the cat was 0.04 mV RMS, and for the guinea pig 0.025 mV RMS. The sine levels required to reach the response criteria for each level of high-rate are shown in Figure 6. In general, the data for all subjects indicate that with an increase in the level of high-rate there is a decrease in the level of sine required to reach the response criterion. The effect of high-rate stimulation for the cat data shows a gradual reduction in required sine level that began with the very low levels of high-rate, while the data for both guinea pig subjects show a more precipitous effect of high-rate pulse level.

As mentioned previously, the latency of the EAP responses were characterized by taking the cross-correlation of the response waveforms. Figure 7 shows the cross-correlations for the sine-alone and sine+HR waveforms in Figure 2. The responses to the cathodic and anodic phases were analyzed separately to avoid measuring correlations between responses to the different phases. The correlations are larger and narrower for the cathodic phase than the anodic phase, consistent with the more peaked cathodic responses. A cross-correlation peak occurring at a time of 0 ms indicates that the EAP

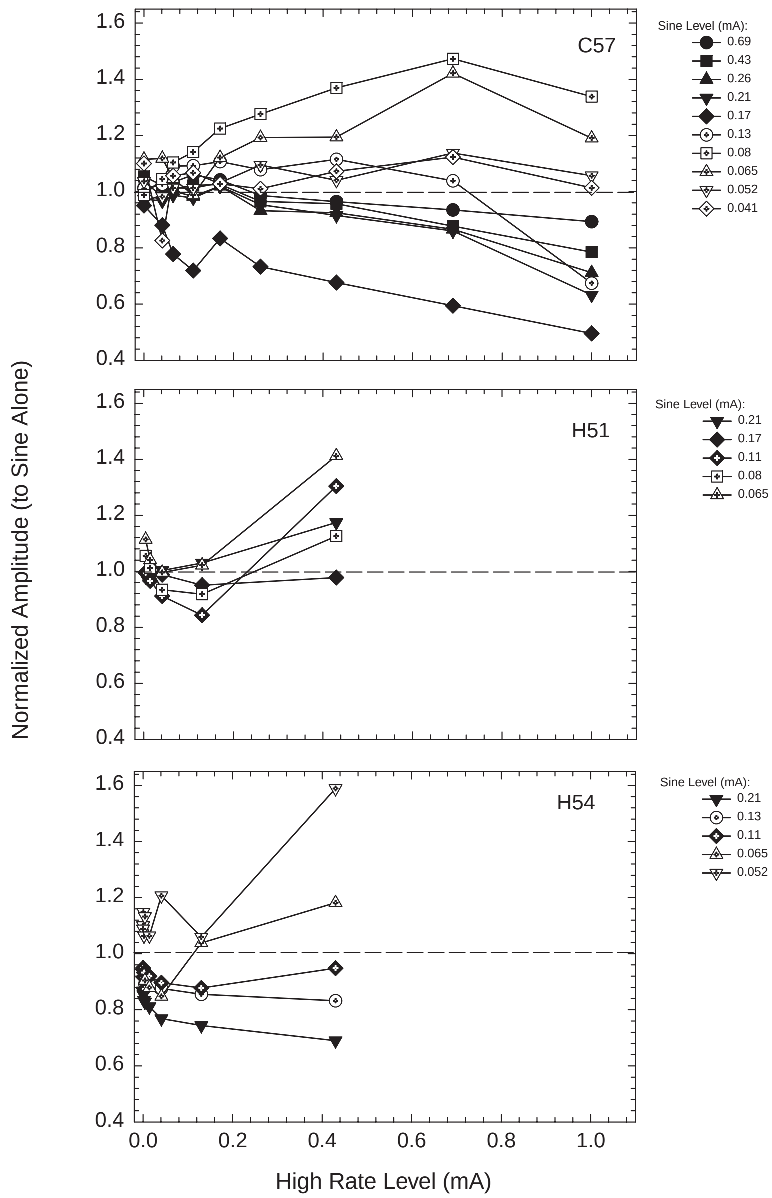

Figure 5: Normalized response amplitudes as a function of high-rate conditioner level for all subjects. Sine level is the parameter. To normalize, each response amplitude to the sine+HR condition was divided by the response amplitude at the corresponding sine level.

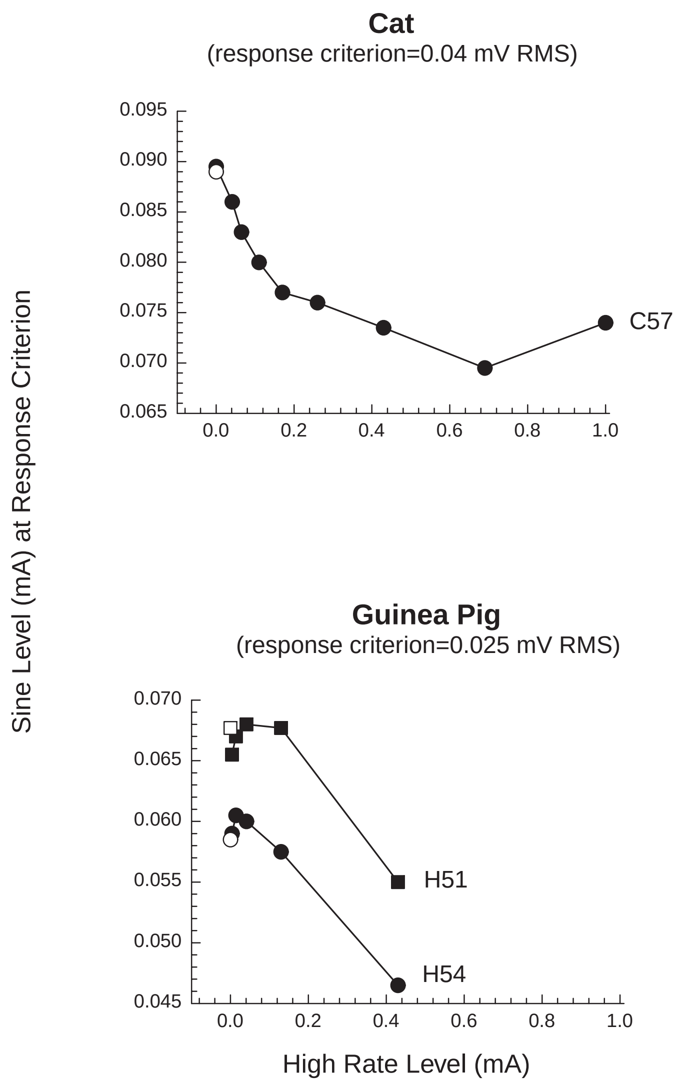

Figure 6: Sine level required to elicit the response amplitude criterion (0.04 mV RMS for the cat and 0.025 mV RMS for the guinea pig) as a function of high-rate conditioner level. Open symbols represent the sine-alone condition, while filled symbols represent the sine+HR condition.

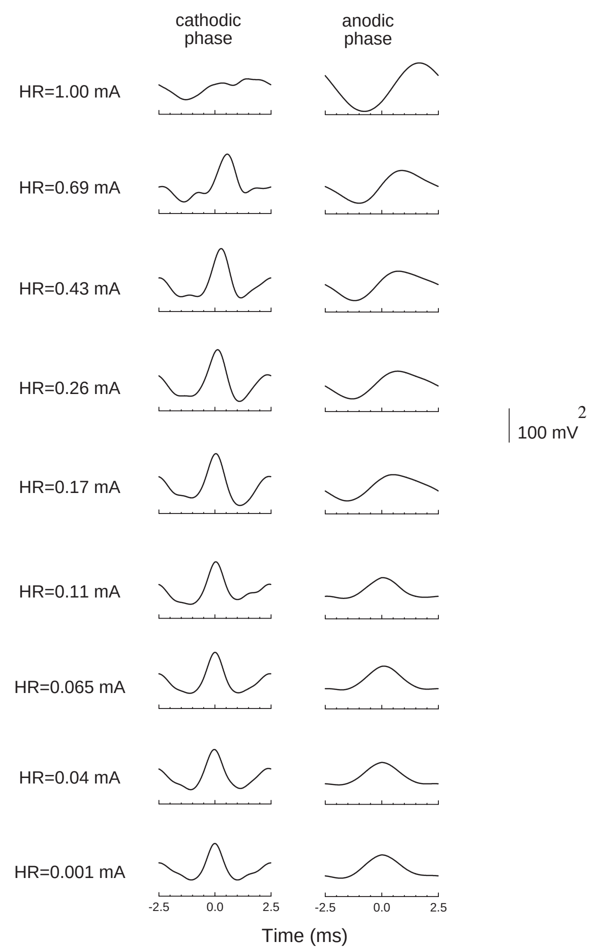

Figure 7: Cross-correlations for the sine alone and sine+HR waveforms in Figure 2, as the comparison of EAP response latency. The cathodic and anodic phases are analyzed separately. The cross-correlations are calculated by convolving the response waveforms of the two conditions: At time=0 ms the waveforms are multiplied without any time adjustment, giving a correlation amplitude value in mV^2 at t=0 ms. The sine+HR waveform is then multiplied by the sine-alone waveform while being adjusted in time by +2.5 ms and -2.5 ms from the zero point, for a total cross-correlation over 5 ms (the time period of one phase). The peak of the cross-correlation waveform reflects the time difference, if any, between the responses that is required for them to be most highly correlated. Cross-correlation peak latency time>0 ms indicates a shorter latency of the sine+HR EAP peak relative to the sine-alone EAP peak, and correlation peak latency time<0 ms indicates a longer latency. When the correlation peak latency time=0 ms there is no difference between the EAP response peak latencies.

peaks for the two waveforms have the same latency, and a peak that is positive in time reflects a shortening of the latency of the sine+HR EAP peak relative to the sine-alone peak.

Latency differences between the sine-alone and sine+HR EAP peaks are shown in Figure 8 for all subjects, for cathodic and anodic phases, derived from the cross-correlation waveforms. A peak latency of zero indicates equal EAP peak latencies between the two conditions, and a positive peak latency indicates a shorter latency of the sine+HR EAP peak relative to the sine-alone EAP peak. Any cross-correlation measure that did not reveal a single, clear peak indicated a poor correlation between the waveforms and was not included in this figure. The effects of high-rate stimulation on latency for all subjects are dependent on the levels of both the sine and high-rate. In general, the data show that for higher levels of sine stimuli, the addition of high-rate pulses have little or no effect on latency across high-rate level. For lower levels of sine, there is a tendency for the latency for the EAP peaks of the sine+HR condition to become shorter, and this effect becomes greater with increasing high-rate levels. As in Figure 5, these trends are more apparent in the cat data for which several levels of sine and high-rate were able to be measured.

4 Conclusions

The addition of high-rate pulsatile stimulation to produce pseudospontaneous activity may have a desynchronizing effect on auditory nerve fibers, which in turn may result in an increased dynamic range of hearing. The findings of this study support the notion of the desynchronizing effects of pseudospontaneous activity when presented with 100 Hz analog stimuli. The normalized response amplitudes shown in Figure 5 may demonstrate desynchronization of the nerve fibers with high-rate stimulation. A possible result of the reduced neural synchrony may be enhancement of the response at low sine levels, and a slight decrease in amplitude for the high sine levels. Therefore, at low levels, the addition of background noise may result in an increase in dynamic range. At high sine levels, the addition of neural noise may result in smaller response amplitudes from the increase in neural activity. This increase in activity leaves fewer nerve fibers available to respond to the stimulus, and these fibers may have smaller action potentials due to refractory effects (Miller et al. 2000).

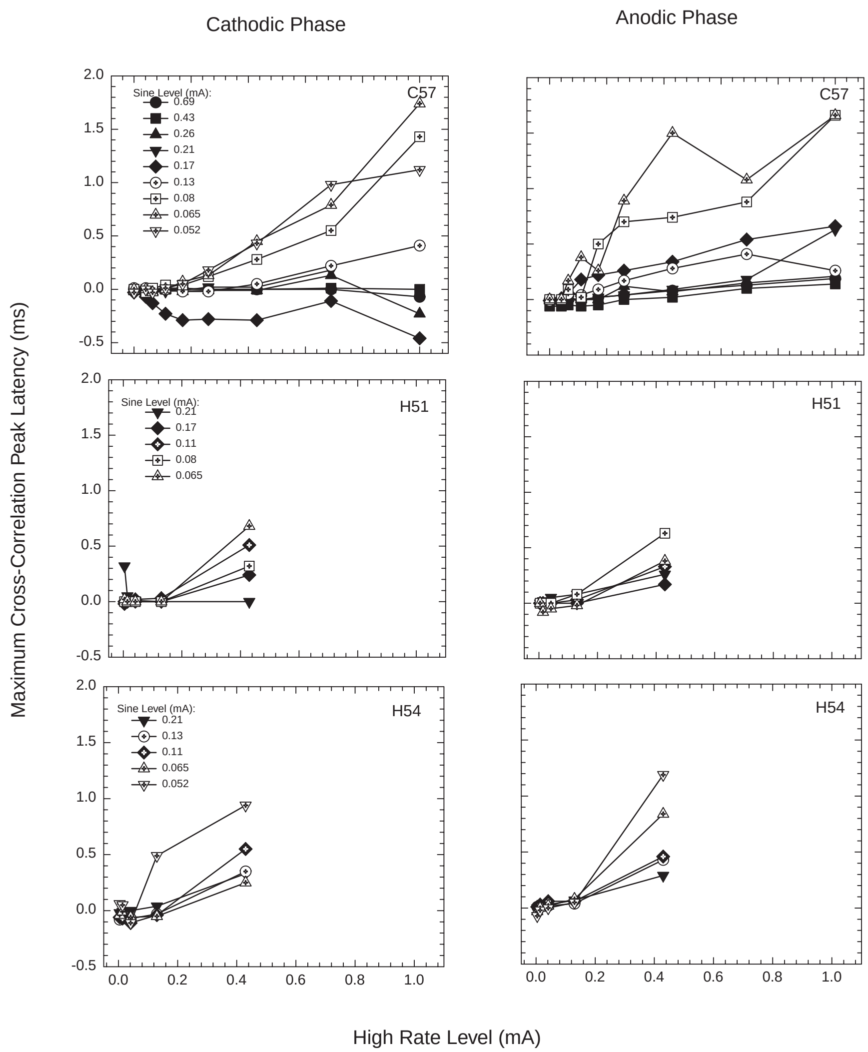

Figure 8: Cross-correlation peak latencies for both cathodic and anodic phases as a function of high-rate conditioner level for all subjects. Sine level is the parameter.

In addition to the changes in dynamic range with high-rate pulses, we also observed a change in latency of the EAP at high levels of high-rate pulses. As seen in Figure 8, the peak latencies for low level sine stimuli were shorter in the presence of moderate to high levels of high-rate pulses, while there was little or no effect in latency for higher levels of sine. This is consistent with a lower threshold in the presence of the conditioning stimulus.

The relationship between measures of EAP and underlying single fiber responses is relatively complex. For instance, single pulse data show that growth of the EAP is affected maximally by the distribution of single-fiber thresholds (Miller et al., 1999), and the EAP growth is affected secondarily by the relative spread (RS) of individual fibers (Rubinstein et al., 1997; Miller et al. 1999). Thus, despite the relatively small effect observed in EAP growth, if the effects that we have observed are truly the result of underlying changes in single-fiber RS, those changes are likely very large. In addition, changes in EAP growth with sinusoidal stimulation are made more complex by the wider distribution of action potentials across time. Consequently, the relationship between changes observed in the EAP growth and the underlying single-fiber response properties must be interpreted cautiously.

5 Plans for the next quarter

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

- Continue development of methods to assess spatial response to multichannel electrode stimulation using thin electrodes from the University of Michigan.
- Development of detailed properties of the biophysical model to match neural properties measured in our single-fiber experiments.

6 Appendix: Presentations and publications

The following publication appears in the August 2000 edition of Ear & Hearing:

- Miller, C.A., Abbas, P.J., Brown, C.J. (2000). An improved method of reducing stimulus artifact in the electrically evoked whole nerve potential. Ear & Hear. 21, 280-290.

The following publications appear in the September 2000 edition of Hearing Research:

- Matsuoka, A.J., Abbas, P.J., Rubinstein, J.T., & Miller, C.A. (2000). The neuronal response to electrical constant-amplitude pulse train stimulation: evoked compound action potential recordings. Hear. Res. 149, 115-128.
- Matsuoka, A.J., Abbas, P.J., Rubinstein, J.T., & Miller, C.A. (2000). The neuronal response to electrical constant-amplitude pulse train stimulation: additive Gaussian noise. Hear. Res. 149, 129-137.

The following manuscripts have been accepted for publication in Hearing Research and IEEE Transactions on Biomedical Engineering:

- Miller, C.A., Robinson, B.K., Rubinstein, J.T., Abbas, P.J., Runge Samuelson, C. (in press). Auditory nerve responses to monophasic and biphasic electric stimuli. Hear. Res.
- Matsuoka, A.J., Rubinstein, J.T., Abbas, P.J., & Miller, C.A. (in press). The effects of interpulse interval on stochastic properties of electrical stimulation: models and measurements. IEEE Trans. on Biomed. Eng.

The following manuscript was submitted to IEEE Transactions on Biomedical Engineering:

- Rubinstein, J.T., Miller, C.A., Mino H. & Abbas, P.J. Analysis of Monophasic and Biphasic Electrical Stimulation. IEEE Trans. on Biomed. Eng.

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