Eighth Quarterly Progress Report

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The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation

P.J. Abbas, C.A. Miller, J.T. Rubinstein,
B.K. Robinson, Ning Hu

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

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1 Introduction

The purpose of this contract work 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 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 eighth quarterly progress report (QPR), we focus on the first of these three aims reporting on experiments characterizing the properties of adaptation in response to electrical stimulation of auditory nerve fibers. In addition, while this contract funds animal research and modeling, there is a need to apply the results of our work to cochlear implants in humans. In the second part of this progress report, perceptual measures in humans, based on previous work done under this contract, are discussed.

2 Summary of activities in this quarter

In our eighth quarter (1 July - 30 September, 2001), the following activities related to this contract were completed:

1. We hosted a productive meeting with our consultant group consisting of Don Eddington, Blake Wilson, and Bob Shannon to review progress on the contract as well as to discuss future directions of the research.

2. We attended the 2001 Conference on Implantable Auditory Prostheses at Asilomar Conference Grounds in Pacific Grove, California. Charles Miller presented a summary of much of the work on this contract regarding the assessment of spatial selectivity in the auditory nerve. Chris Runge Samuelson also presented a poster on her measurements of responses to continuous stimulation in the presence of high-rate conditioners.

3 Adaptation in response to electrical stimulation in the deafened cochlea

3.1 Introduction

Research findings from our previous contracts have described significant effects of adaptation to repetitive electrical stimulation of the nerve. We have reported such effects at the single-fiber level (Miller et al., 1999a) and in gross-potential measures of auditory nerve activity (Matsuoka et al., 2000a). These adaptive effects are clearly relevant to prosthetic stimulation regimes, as most use trains of modulated pulses. At the least, adaptive effects produce threshold shifts that change the effectiveness of prosthetic stimulation over time. However, properties in addition to threshold (e.g., stochastic and temporal properties) will also arguably be altered under conditions of adaptation. For instance, Javel and Shepherd (2000) recently described changes in jitter of single fiber characteristics with high-rate pulse trains. Characterization of these effects is essential in order to design stimulus processing schemes that either minimize such effects or somehow compensate for them.

Experiments with two-pulse stimuli demonstrate refractory properties and temporal integration. Responses to more complex stimulus patterns (such as those produced by the cochlear implant speech processor) are likely not only affected by these properties, but also by others, such as stochastic effects and long-term adaptation. Responses to pulse trains in humans with cochlear implants generally demonstrate an alternating pattern of the electrically evoked compound action potential (ECAP) amplitude in response to a constant-amplitude pulse train (Wilson et al., 1997; Wilson, 1997; Abbas et al., 2000a). Measures in animal subjects with acute hearing loss have demonstrated a smaller alternation effect but also a decrease in amplitude that occurs across the duration of the electrical pulse train (Abbas et al., 1999; Matsuoka et al., 2001; Javel, 1990; Vischer et al., 1997; Haenggeli et al., 1998). Killian et al. (1994) have reported similar effects as well as recovery during the period after stimulation. These data are consistent with a hypothesis that the time course of adaptation and recovery is affected by a peripheral neural component lasting several hundred milliseconds. Data described in this QPR investigates effects of electrical stimulation on the responsiveness of the auditory nerve over several minutes to assess long-term adaptation.

3.2 Methods

Methods of animal preparation and recording are similar to those reported in previous progress reports. These experiments involve both measures of single nerve-fiber responses as well as recordings of ECAP measured from an electrode placed on the surface of the auditory nerve.

3.3 Results

In our studies of single-fiber response characteristics (Miller et al., 1999), we have observed adaptation in terms of reduced firing efficiency over the course of repeated measures. In some cases, this amounted to a discrete upward shift in the FE-vs-level function, where in a few other cases, the fiber simply became unresponsive at all stimulus levels under test. We have reported (in Miller et al., 1999) that upward threshold shifts were observed in about 10% of the sampled fibers over the course of data collection.

We also noted that the degree and incidence of adaptation was greater with responses evoked with anodic current pulses than with cathodic pulses. We explicitly examined this issue in a number of fibers from which repeated measures where obtained in order to quantify the degree of adaptation. Figure 1 displays the degree of threshold shift observed across repeated measures in 41 fibers of two cats. Inspection of that data shows that larger upward shifts were observed for anodic monophasic pulses. Paired-comparison t-tests across stimulus polarity also indicated that the greater adaptation with anodic stimuli was statistically significant ($p=0.007$).

The influence of pulse rate was explicitly examined in one fiber in which the stimulus presentation rate was varied between two rates (8.3 and 33.3 pulses/s). Figure 2 depicts the firing efficiency produced by a fiber that was excited by constant-level pulses presented at the two rates. Note that firing efficiency becomes progressively lower at the higher stimulation rate, while firing efficiency recovers when the fiber is stimulated at the lower pulse rate.

More recently, we have collected data investigating the changes in response to continuous pulsatile stimulation to more carefully evaluate the time course of such changes. Because we record ECAPs with an electrode positioned on the nerve, we can (in some cases) record ECAP waveforms in response to individual pulses, without the need for time-averaging techniques. Figure 3 (left panel) plots the ECAP amplitudes for each pulse of a

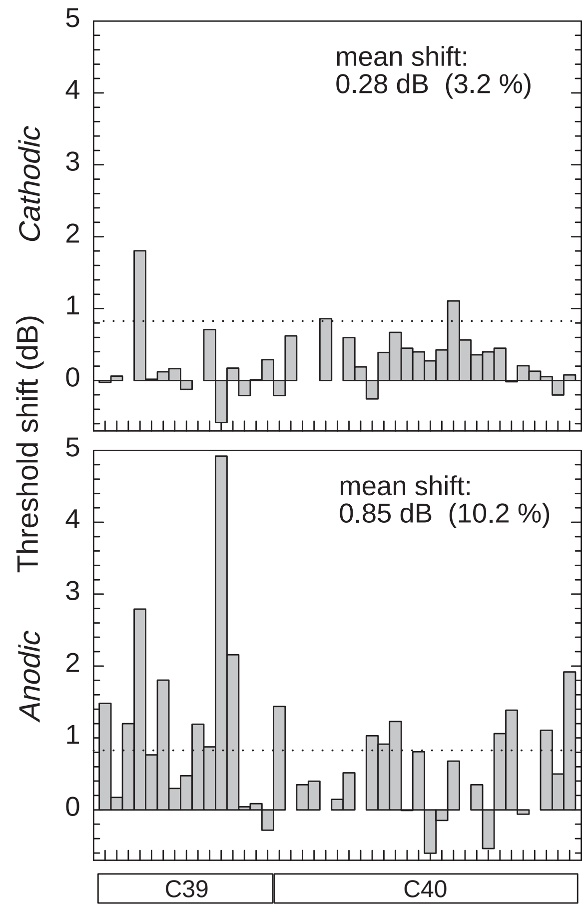

Figure 1: Threshold shifts in 41 fibers of two cats. In most cases the FE-vs level functions were obtained for both cathodic and anodic stimulus polarity. The mean shift across fibers is shown in each graph in decibel and percent units. The dotted horizontal line indicates a 10% shift in threshold.

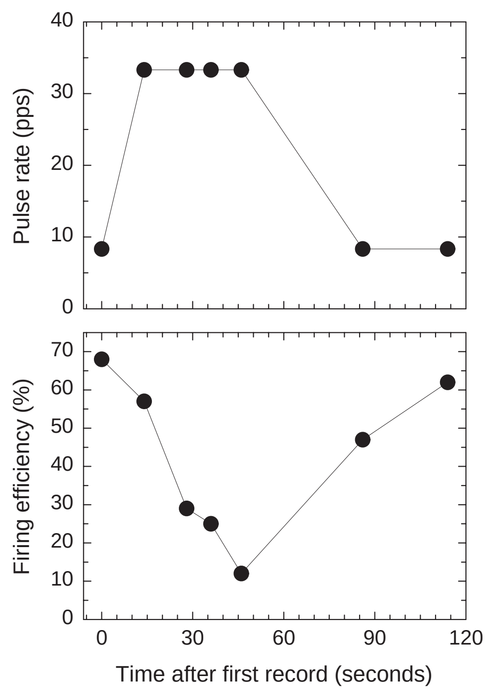

Figure 2: Demonstration of the effect of stimulus pulse rate on the responsiveness of a single auditory nerve fiber to repetitive electrical stimulation. The top panel displays the two stimulus pulse rates used to elicit responses from a single fiber. Stimulus level was kept constant across all conditions. The bottom panel plots the fiber's firing efficiency produced over the course of those stimuli, with each datum representing the firing efficiency computed over 100 sequential pulse presentations. Note how the fast pulse rate produces adaptation, whereas recovery occurs during resumption of stimulation at the slower rate.

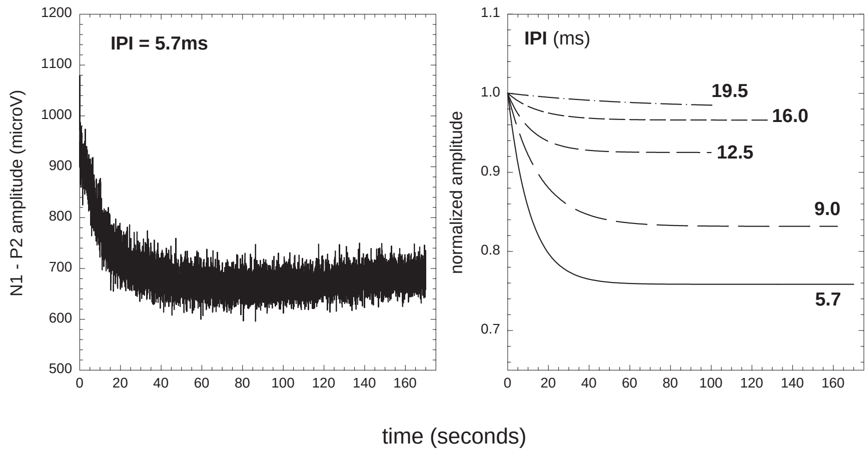

Figure 3: Assessment of adaptive effects produced by repetitive stimulation of the auditory nerve by a train of biphasic current pulses. Left graph shows ECAP response amplitude to each biphasic pulse presented in a train. Pulse amplitude was 2.08 mA at a duration of 40 μs/phase presented in train with IPI 5.7 ms. The response amplitudes are somewhat variable since the response is based on one sweep. Nevertheless there is a clearly decreasing trend. On the right graph, plots are fit with a decreasing exponential function to illustrated the differences in adaptation for different IPIs.

long-duration train of current pulses presented at an interpulse interval of 5.7 ms. The measured amplitudes are somewhat variable since the waveforms are recorded from a single presentation. Nevertheless, the trends over time are clear in that a large decrement in the ECAP amplitudes is observed over a period of about 50 seconds. Smaller, though significant, decrements were also observed at slower pulse rates. Shown in the right panel are fitted-curve solutions to ECAP amplitude trends obtained at several different interpulse intervals.

The effect of stimulation rate is illustrated in Figure 4. The asymptotic ECAP amplitude (calculated as the mean value of the amplitude in response to last 30 pulse presentations) is plotted as function of stimulation rate. The data suggest that rates as low as 50 pps are necessary to avoid significant adaptation in ECAP amplitude. These data are relevant to common implant programming procedures in that, although stimulation is not commonly a constant amplitude, stimulation rates are typically much greater and significant adaptation would be expected. In addition, these data are relevant to

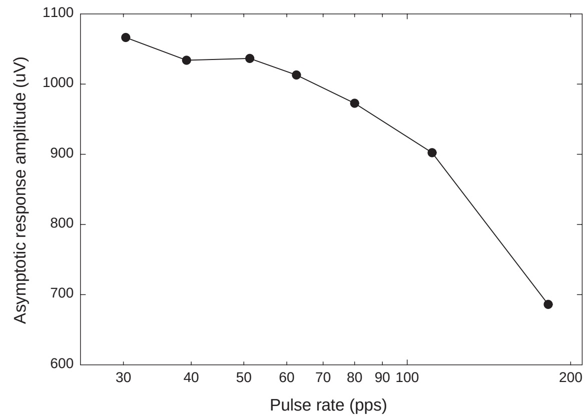

Figure 4: This re-plots the data represented in Figure 3. The average ECAP amplitude over the last 30 pulse presentations for each pulse rate represents the asymptotic response amplitude. The current level was held constant over pulse rate and the asymptotic amplitude is plotted as function of pulse rate to demonstrated changes in adaptation.

the implementation of measurements of responses from the auditory nerve in human subjects, such as with telemetry systems, since rates significantly above that value are commonly used.

We reported similar data on the effect of acoustic noise on the response to electrical stimulation in ears with surviving hair cells (Abbas et al., 2001b). The time course of such changes, both in the decrease in responsiveness during noise presentation and recovery after noise presentation, is similar to that observed in Figure 3. We also noted in that work that the latencies of the ECAP responses were 0.2 - 0.3 ms, clearly indicating that the responses were not electrophonic in origin, but rather a result of "direct" depolarization of the neuron membrane.

3.4 Summary

These data with electrical pulse trains demonstrate that cumulative effects of electrical stimulation may be evident for periods of 50-100 seconds. These changes are evident for interpulse intervals as high as 16 ms. Data in animals with acoustic sensitivity have demonstrated similar long-term effects of adaptation and recovery with acoustic noise adapters (Abbas et al., 2001b). Data with ECAP in human subjects have also demonstrated similar long-term decreases in response (Schmidt-Clay et al., 2002). While observations of single fiber measures of long-term adaptation are limited, effects on fiber threshold observed over the time course in which the fiber activity was isolated are consistent with ECAP measures (Miller et al., 1999).

4 Conditioning pulses in human subjects

4.1 Introduction

Based on results obtained in computer and animal models under this and the previous contract, we have proposed use of high-rate conditioning pulses to enhance dynamic range and temporal resolution of responses to analog or lower rate modulated pulse trains (8th QPR of first contract). Over the last two years we have been developing the capacity to test this hypothesis in human cochlear implant recipients. Using the Nucleus 24 device, we have been limited to speech testing under highly constrained experimental conditions but have demonstrated subjectively improved sound quality in two subjects with the use of conditioning pulses on two electrodes of a 6-channel CIS processor. With the advent of the Clarion C-II cochlear implant and the CRI-2 research interface, better controlled psychophysical experiments have become possible. We have developed psychophysical testing software that allows threshold, loudness and frequency discrimination measures using low frequency sinsoids both with and without a 5000 pps conditioner.

4.2 Methods

Twelve human subjects implanted with the C-II have been tested to date under an IRB-approved protocol. The CRI-2 research interface has been programmed to allow the initial introduction of an unmodulated conditioner at levels between 0 and 1024 μA (50 μs/phase). At somewhere between 200 and 500 μA, the subject will note the onset of the pulse train but the perception will rapidly adapt over a time course between ten seconds and ninety minutes depending on the subject and level of the conditioner. The higher the conditioner level above onset threshold, the longer adaptation may take. Once adaptation has occurred, the termination of the stimulus is perceived readily by the subject but a precise description of this percept is impossible for all subjects to date. We had previously considered such adaptation to be a central phenomenon but our animal studies make us strongly question that assumption.

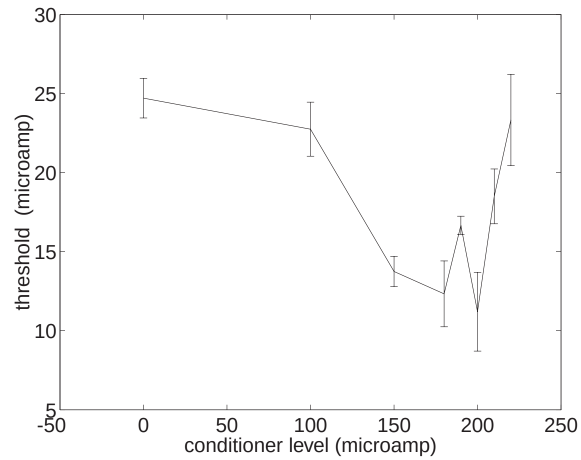

Figure 5: A 202 Hz sinusoid (500 ms bursts) is presented at conditioner levels over a range from zero to 230 μA. Theshold is assessed after adaptation to the conditioner. At least four threshold measures were obtained at each conditioner level.

After adaptation has occurred, threshold, loudness growth and maximum comfortable loudness can be assessed at that conditioner level. In most cases, these levels are stable over time regardless of the conditioner levels used but in two subjects, these levels appear nonstationary with increases in all measures seen with repeated testing. While statistical measures are difficult with these two subjects, standard deviations were fairly small with repeated testing in all others.

4.3 Results

4.3.1 Psychophysical demonstration of stochastic resonance

Three subjects have demonstrated evidence of stochastic resonance for threshold. Figure 5 illustrates the data from one of these. A 202 Hz sinusoid is presented at conditioner levels over a range from zero to 230 μA. At least four threshold measures were obtained at each conditioner level. There is clearly an optimal conditioner level (i.e. an optimal noise level) and it produces approximately a six dB decrease in the threshold. This is a fairly unambiguous demonstration of stochastic resonance in the human auditory nerve.

4.3.2 Enhancement of dynamic range

Ten of twelve subjects have demonstrated enhancement of dynamic range to a 202 Hz sinsuoid of between two and ten dB. In most subjects, at least six dB of enhancement is seen. In all cases, the enhancement is due to a decrease in threshold. One example of increased maximum comfort level has been seen.

4.4 Summary

Conditioner pulses have demonstrated clinically and statistically significant enhancement of dynamic range and clear evidence of stochastic resonance in human subjects. Studies are ongoing to assess the effects of conditioning pulses on frequency discrimination and sound quality assessment. A laboratory speech processor using condtioned analog stimuli is currently under development.

5 Plans for the next quarter

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

- Begin experiments investigating the effects responses of the auditory nerve in response to chopped analog stimulation.
- Continue experiments investigating the effects of stimulating electrode configuration.
- Complete experiments and write-up (Runge-Samuelson dissertation) on experiments investigating effects of high-rate conditioners on continuous analog stimulation.

6 Appendix: Presentations and publications

- Miller C.A., Abbas P.J., & Brown C.J. (2001). Physiological measurements of spatial excitation patterns produced by electrical stimulation (Abstr.). Conference on Implantable Auditory Prostheses, Pacific Grove, CA.

- Runge-Samuelson C.L., Rubinstein J.T., Abbas P.J., Miller C.A., Smith G.J., Robinson B.K., & Abkes B.A. (2001). Sinusoidal electrical stimulation of the auditory nerve with and without high-rate pulses. (Abstract) Conference on Implantable Auditory Prostheses, Pacific Grove, CA.

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