Tenth Quarterly Progress Report

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The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation

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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 tenth quarterly progress report (QPR), we focus on the second of these three aims and expand upon human data reported in the tenth QPR. While this contract funds animal research and computational modeling, there is a need to apply the results of our work to cochlear implants in humans. While the goal is not to supplant human studies performed under the NPP speech processing contracts, proof of theory developed in our laboratories demands perceptual assessment in human subjects. Thus while we have not as yet completed a speech processor which implements conditioning stimuli, psychophysical testing of concepts developed under our contract seems appropriate. It should be noted that support for our testing of human subjects comes from our NIH program project DC00242 and from a Doris Duke Clinical Research Fellowship to R. Hong. Hardware and software for human testing was developed under this contract and with the support of Advanced Bionics and Texas Instruments.

2 Summary of activities in this quarter

In our tenth quarter (1 January - 30 March, 2002), the following activities related to this contract were completed:

1. We presented findings produced by our contract work at the 2002 Midwinter Meeting of the Association for Research in Otolaryngology.

2. Dr. Rubinstein was appointed to the outreach faculty of the University of Michigan Wireless Integrated Microsystems Engineering Research

Center and presented a seminar at their Cochlear Testbed Design Review.

3. We hosted a visit by Dr. Lianne Cartee of RTI to discuss single-fiber data collection techniques and data interpretation.

4. Dr. Miller visited with faculty of Kresge Hearing Research Institute and consulted with the University of Michigan CNCT investigators (Anderson and Hetke) regarding designs and applications for the thin-film electrode effort that is a part of this contract.

5. We performed additional electrophysiological studies of adaptation-like phenomena associated with electric pulse-train stimulation. Experiments focusing on these effects were performed on five acute guinea pig preparations.

6. We performed an additional experiment with an acute cat preparation for the evaluation of Michigan thin-film electrodes for use with intraneural recordings. In this experiment, PSU4 electrodes were inserted in different orientations (both parallel and orthogonal to the fibers) to assess spatial selectivity. Our initial analysis of electrophysiological responses suggest that, although some spatial selectivity is produced by our currently selected designs (i.e., the PSU4/5 family and our custom three-shank model), the surface areas of the electrodes are too large to produce the desired, highly selective, responses. After discussion with the Michigan CNCT group, we have selected another electrode design that features electrode pad areas that are approximately one-sixth the size of electrodes previously used. The Michigan group will supply us with samples of that design for evaluation in future acute experiments.

7. We performed an additional experimental study of patterns of neural excitation produced by monopolar and bipolar intracochlear stimulation. This study involved both gross-potential (ECAP) and single-fiber measures obtained from an acute cat preparation.

8. We have completed an extensive series of model simulations of refractory effects with two-pulse stimuli. This has generated some specific hypothesis regarding mechansisms underlying the shape of the PST histogram which will be addressed in a future QPR.

3 Conditioning pulses in human subjects

3.1 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 [**?**]. These findings have been verified by animal studies in our laboratories[**?**] and elsewhere[**?**]. 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 CII 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.

3.2 Methods

Thirty adults implanted with the Clarion CII (Advanced Bionics, Sylmar, CA, U.S.A.) device between January 2001 and February 2002 at the University of Iowa Hospitals and Clinics participated in this study. All electrodes were fully inserted. Subjects ranged in age from 25 to 79 years old. Dynamic range data was collected for 28 out of 29 patients; it was not collected for 1 patient because her initial thresholds (without conditioner) were at the noise floor of our measuring capabilities. Data presented here were collected between connection and up to 1 year post-stimulation. The study was approved by the University of Iowa Institutional Review Board. The cochlear implants of study participants were driven using the Clarion Research Interface for 2nd generation Clarion products (CRI-2). The software for the CRI-2 was designed using MATLAB and Texas Instruments Code Composer. All patients were presented electrical stimuli with electrodes in the bipolar configuration, corresponding to electrodes 1-2, 7-8 or 15-16. Stimuli consisted of sinusoid bursts (202 Hz, 515 Hz, or 1031 Hz) at duration of either 200 or 500 ms, with and without the prior application of a 5 kpps conditioning biphasic pulse train (50 μs/phase). During testing, subjects were presented first with a 5 kpps conditioner at levels ranging from 0 to

900 μA and asked to indicate if he/she could hear the conditioner. The sinusoid was added only after the subject could no longer hear it. Seven subjects, however, continued to perceive the conditioner alone at a level between threshold and "soft" after 5 minutes. For these subjects, sinusoid was added after the 5 minutes elapsed. Importantly, by the end of the testing session, all seven subjects could no longer hear the conditioner. Cochlear implant recipients were systematically tested for threshold and most comfortable loudness (MCL) of sinusoidal stimuli at increasing levels of 5 kpps conditioning pulse trains. The threshold was measured using a manually controlled up-down adaptive procedure to the 50% level[**?**]; the number of reversals within each adaptive procedure varied from four to sixteen, with more reversals used for thresholds demonstrating greater variability. The most comfortable loudness was measured with a manually controlled procedure in which subjects heard a pulsing sequence of sinusoidal stimuli (200 or 500 ms burst, followed by 1 second silence) that steadily increased at an approximate rate of 1, 2 or 5 μA per second. Subjects were instructed to indicate the exact moment when the sound became most comfortable. The dynamic range is taken as the difference between threshold and MCL. Values reported for threshold and MCL at the smallest and largest measured dynamic range per patient represent the average of at least 4 to 5 distinct trials of the procedures described above.

3.3 Results

Three distinct patterns of response of dynamic range to increasing levels of conditioner are observed. In the first pattern, dynamic range increases with addition of higher levels of conditioner up to an optimal point, whereby further increases in conditioner result in loss of dynamic range. Figure 1 illustrates this pattern as found in Subject AT. This may represent a form of stochastic resonance (15), in both the threshold and dynamic range. Dynamic range is initially 12.2 dB and increases to 25.2 dB at the optimum conditioner level of 300 μA, corresponding to a 13.0 dB increase in dynamic range. However, as the conditioner is increased further, dynamic range decreases, culminating in a dynamic range of 19.5 dB with 500 μA conditioner.

The second pattern is illustrated in Figure 2. In this pattern, dynamic range again increases with addition of higher levels of conditioner up to a certain point. However, increases in conditioner beyond this point, up to the maximum conditioner level tested do not result in further changes in dynamic range. As shown in Figure 2, for Subject VK, dynamic range is

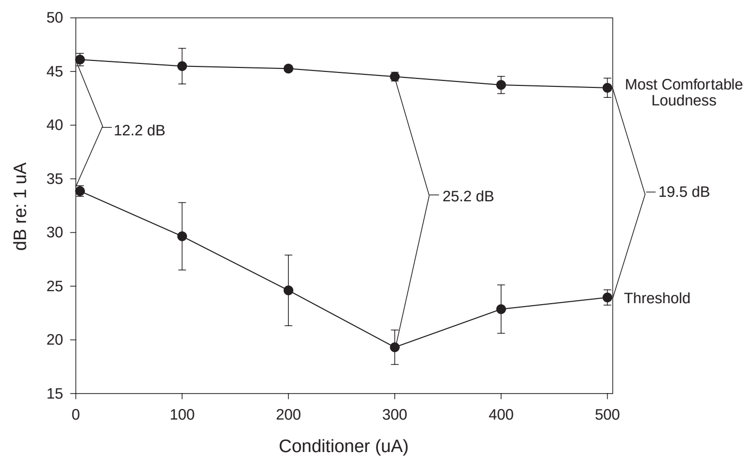

Figure 1: Dynamic range of Subject AT, electrodes 1-2 (bipolar mode), for a 515 Hz sinusoid (500 ms bursts) at different levels of 5 kpps conditioning pulse train. The figure shows the 95% confidence intervals for threshold and most comfortable loudness. Dynamic range increases from 12.2 dB without conditioner to 25.2 dB with 300 μA conditioner. Further increases of conditioner level result in loss of dynamic range. The increase in dynamic range with addition of optimal conditioner is 13.0 dB.

6.8 dB without conditioner and gradually increases to 17.2 dB with 500 μA conditioner. This largest increase in dynamic range (10.4 dB) is then maintained from 500 to 800 μA of conditioner.

In the third pattern, dynamic range continues to increase across the range of conditioner levels tested. Figure 3 illustrates this pattern in Subject LH. The dynamic range is initially 6.9 dB and continues to increase as conditioner level is raised, with the largest increase (11.9 dB) occurring at 900 μA conditioner.

This study reports each subjects largest observed increase in the psychophysical dynamic range for sinusoidal stimuli with the addition of a 5 kpps conditioning pulse train. Figure 4 depicts the initial dynamic range of each subject tested (n=28) and the corresponding increase in dynamic range that results from addition of an optimal level of conditioner, where optimal is defined as that level resulting in the largest observed increase in dynamic range. Across subjects, the dynamic range without conditioner ranges from 2.6 to 17.5 dB (mean = 8.6 dB). Dynamic range with optimal conditioner ranges from 5.0 to 26.9 dB (mean = 15.3 dB). Increase in dynamic range due to addition of optimal conditioner ranges from 2.3 to 16.8 dB, with an

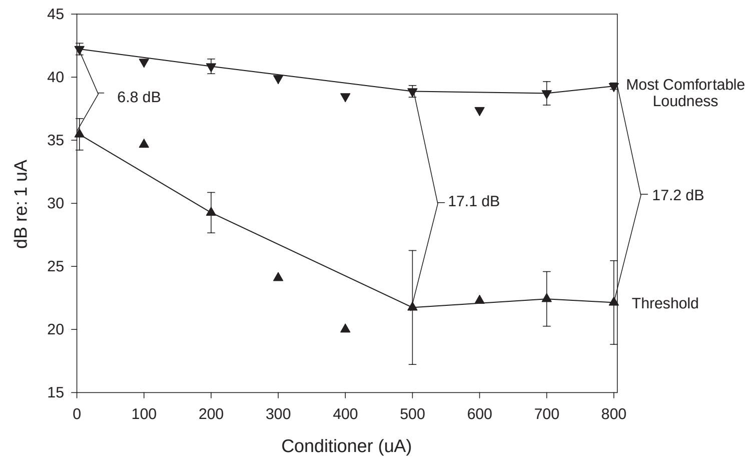

Figure 2: Dynamic range of Subject VK, electrodes 1-2 (bipolar mode), for a 1031 Hz sinusoid (500 ms bursts) at different levels of 5 kpps conditioning pulse train. The figure shows the 95% confidence intervals for threshold and most comfortable loudness. Dynamic range increases from 6.8 dB with no conditioner to 17.1 dB with 500 μA conditioner and stays approximately constant with further increases of conditioner level. The increase in dynamic range with addition of optimal conditioner is 10.4 dB.

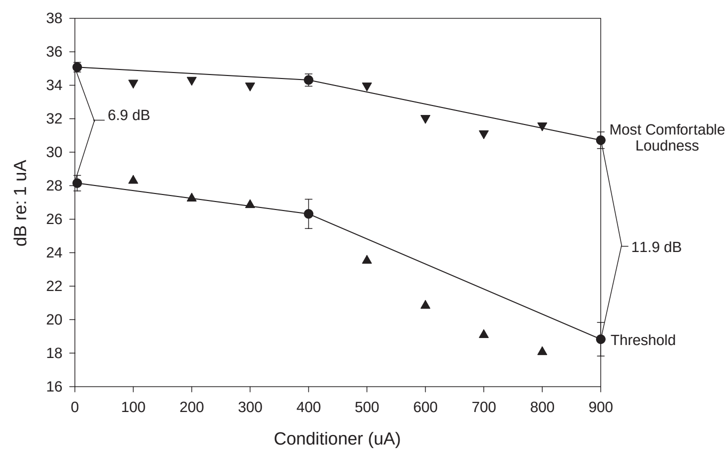

Figure 3: Dynamic range of Subject LH, electrodes 1-2 (bipolar mode), for a 202 Hz sinusoid (500 ms bursts) at different levels of 5 kpps conditioning pulse train. The figure shows the 95% confidence intervals for threshold and most comfortable loudness. Dynamic range increases from 6.9 dB without conditioner to 11.9 dB with 900 μA conditioner (upper limit of testing range of conditioner). The increase in dynamic range with addition of maximum conditioner is 5.0 dB.

average increase of 6.7 dB. The individual subject data grouped by dynamic range increase is shown in Figure 5.

3.4 Discussion

The results in this study suggest that increases in electrical dynamic range averaging 7 dB can be obtained in cochlear implant patients through the addition of an appropriate level of 5 kpps conditioning pulse train. Significantly, positive increases in dynamic range were found in every patient in this study. However, the extent to which this gain in dynamic range is maintained across different electrode pairs, frequency ranges, or time (months to years) is currently unclear.

The values of dynamic range presented in this study are a conservative estimate of the dynamic ranges of cochlear implant recipients both with and without the 5 kpps conditioner. This is because our methodology records the lower bound of most comfortable loudness as the upper bound of dynamic range. Nevertheless, the dynamic ranges of the subjects in this study without conditioner (from 3 to 18 dB) are relatively consistent with the values commonly reported elsewhere (from 6 to 30 dB) [**?**]. Furthermore, because our methodology for measuring most comfortable loudness is the same before and after addition of conditioner, our results for increases in dynamic range are valid.

The patterns described in this study of the response of dynamic range to increasing levels of conditioner are meant to be descriptive and not necessarily mutually exclusive. Due to the time-consuming demands of our protocol, our experiments with the conditioner were initially performed in increasing, 100 μA increments. Additional experiments with a finer amplitude resolution of conditioner were performed as needed if time permitted. The relatively large step size of 100 μA used in our experiments creates the possibility that we may not have detected the exact level of conditioner that results in the largest increase in dynamic range. In some cases, therefore, the pattern presented in Figure 2 may actually be that of Figure 1 if smaller step sizes had been used. Thus, our results likely underestimate the actual largest increases in dynamic range that may be realized with addition of the 5 kpps conditioning pulse train.

Additional underestimation of the largest increases in dynamic range is suggested by the pattern represented in Figure 3. In this case, we were

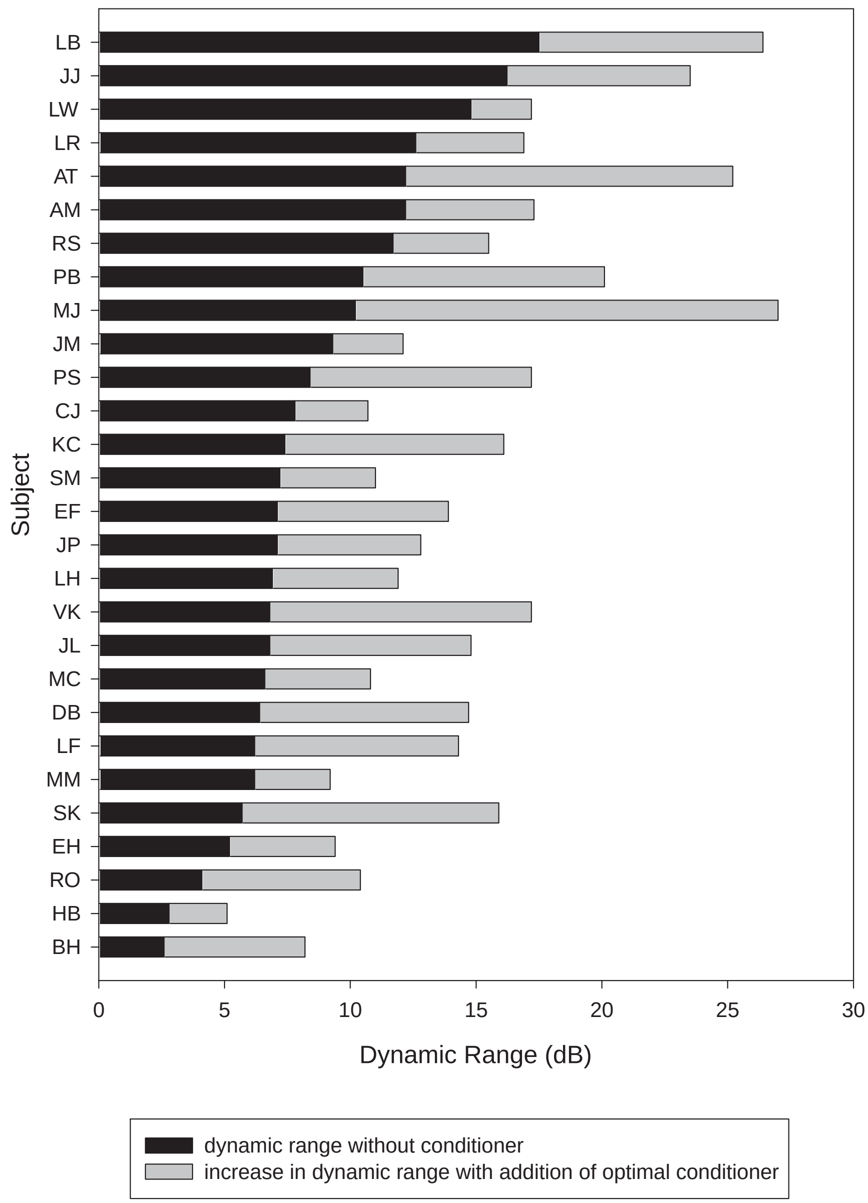

Figure 4: Dynamic range of cochlear implant patients prior to and upon addition of the optimal level of 5 kpps conditioning pulse train. Shown is the largest benefit found for each respective patient (n=28). The black represents the dynamic range of patients without conditioner. The gray represents the increase in dynamic range with addition of optimal conditioner.

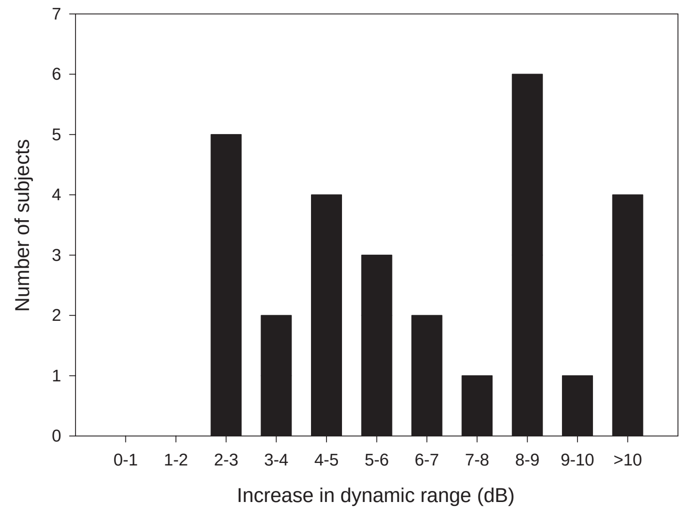

Figure 5: Increase in dynamic range in cochlear implant patients with addition of the optimal level of 5 kpps conditioning pulse train. Subjects (n=28) are grouped according to the largest increase found. The mean increase in dynamic range is 6.7 dB. The largest increase is 16.8 dB.

unable to increase the level of conditioner any further due to limitations in software and hardware. However, extrapolation of this pattern suggests that further increases in conditioner level would result in continued increases in dynamic range.

The implementation of a signal processing strategy with a continuous 5 kpps pulse train holds significant promise for cochlear implant patients. The resulting increases in dynamic range suggested by this study could lead to improvements in both speech recognition and sound quality. Furthermore, theory predicts that application of the 5 kpps unmodulated pulse train will result in a better resolution of temporal fine structure by implant patients[**?**]. Such improvements in the representation of fine structure may lead to improved sound localization in binaural implant patients and music perception [**?**]. All of these potential benefits highlight the importance of characterizing the effects of a conditioned signal processing strategy in cochlear implant recipients in the near future.

4 Plans for the next quarter

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

- We will complete our evaluation of adaptation-like phenomena produced by repetitive electric stimuli.
- We will complete single-fiber and ECAP studies of the influence of stimulus electrode configuration on neural excitation.
- We will begin evaluation of intraneural recordings with thin-film electrodes featuring smaller pad areas.
- We will submit a manuscript regarding effect of electrode-fiber separation on stochastic properties of the response.

5 Appendix: Presentations and publications

- Mino, Rubinstein, Abbas, Miller. Effects of electrode-to-fiber distance on temporal variation of neural spikes. ARO abstracts, 2002.
- Miller, Abbas, Robinson. Electrode configuration affects the ensemble response properties of the auditory nerve. ARO abstracts, 2002.
- Rubinstein, Hong, Wehner. Stochastic resonance in cochlear implant patients. ARO abstracts, 2002.

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