Eleventh Quarterly Progress Report

NO1-DC-6-2111

The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation

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July 31, 1999

1 Introduction

In this contract, we are using experimental animal and computational models to investigate issues relevant to electrical stimulation of 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.

The primary focus of this work has been enhancing basic understanding of electrical stimulation. We are also charged with "porting" this knowledge to clinical implant devices so that human testing of the results is possible. During the last quarter we have made great progress in making our technologic developments available for testing in human implant users and these efforts will be described below in addition to our most recent modeling work.

2 Activities of the Eleventh Quarter

- Perfected the use of the kanamycin/ethacrynic acid technique of chemical deafening and applied the method on 8 guinea pigs as part of the ongoing study of electrically evoked responses from neurally degenerate animals.

- Performed acute experiments on four chronically deafened guinea pigs, collecting gross potential measures and preparing the cochlear tissues for later histological analysis.

- Conducted single-unit and gross potential measures on three acute cat preparations. This included obtaining two-pulse refractory recovery data, to be reported in a future QPR as well as at the 1999 Conference on Implantable Auditory Prostheses.

- A manuscript detailing a phenomenological model of the cat gross potential (EAP) was accepted by *Hearing Research* and will appear in the September issue.

- An invited manuscript entitled "How do cochlear prostheses work" was submitted to and accepted by *Current Opinion in Neurobiology.*

- Three manuscripts detailing EAP responses to pulse trains were submitted to *IEEE Transactions on Biomedical Engineering.*

- The Clarion Research Interface was installed and tested. This will allow implementation of speech coding strategies in human Clarion users to complement the efforts at RTI and MEEI.
- The Cochlear Corporation Arbitrary Frame Generator software was installed and tested. This will allow psychophysical testing of new processing strategies in human CI-24 users to complement the efforts at RTI and MEEI.
- IRB approval was obtained for testing novel speech processing strategies in patients with the CI-24.
- Methods to implement a speech processsing strategy in the Nucleus CI-24 that attempts to exploit "pseudospontaneous activity" were developed and tested in two human subjects.
- Methods to implement a tinnitus suppression strategy that attempts to exploit "pseudospontaneous activity" were developed and tested in one human subject.

3 Pseudospontaneous activity: further analysis

In the fifth and eighth quarterly progress reports we described how 5 kHz pulse trains could evoke spontaneous-like, "pseudospontaneous" activity in simulated auditory nerve fibers. This activity is statistically similar to normal spontaneous activity and is independent across the stimulated fiber population. Its existence has been verified by direct single-unit measures (Litvak et al., 1999) When these pulse trains were added to electrical sinusoids, period histograms closely resembling those seen with acoustic stimulation of the normal auditory system were obtained. Many cochlear implant processors use nonsimultaneous pulsatile stimulation rather than analog stimulation to avoid the deleterious effects of channel interaction. Therefore we are motivated to study the effects of pseudospontaneous activity on responses to amplitude modulated pulse trains such as might be presented by a CIS, SPEAK, or n of m processor.

We have used animal models to verify the human electrophysiologic results reported by the RTI group in multiple Quarterly Progress Reports as well as in Rubinstein et al. (1999). With high-rate ($>$ 3 kHz) pulse trains, the typical alternating pattern of EAP response seen at 1 kHz is replaced by a relatively flat pattern that likely represents pseudospontaneous activity

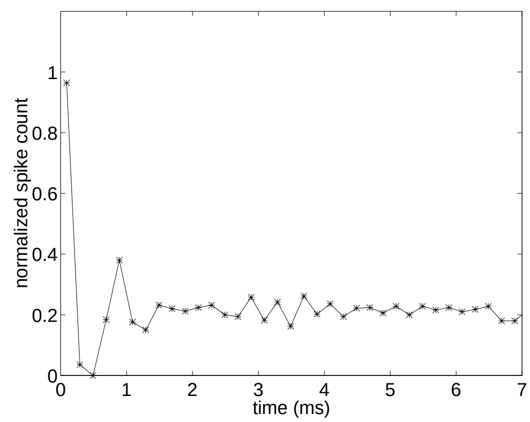

Figure 1: Compound PST histogram of 500 simulated nodes of Ranvier responding to a 5 kHz pulse train. There is an initial burst of spikes at the stimulus onset, followed by a "dead time", a recovery, and a subsequent uniform pattern of activity.

measured at the whole-nerve level. A simulated compound post-stimulus time histogram of 500 nodes of Ranvier responding to a 5 kHz pulse train is illustrated in Figure 1.

Based on our model of the single-unit dependence of the EAP (Miller et al, 1999), we would expect the EAP to have a qualitatively similar, relatively flat response to a 5 kHz pulse train after initial refractory effects are over in the first millisecond or so. The guinea pig EAP response to 1.25 kHz and 5 kHz pulse trains is seen in Figure 2. The 5 kHz response is obtained with the sequential subtraction technique developed by the RTI group (see Rubinstein et al., 1999 for details). The 1.25 kHz response is directly recorded.

The available data indicate that the alternating pattern apparent at 1.25 kHz is replaced by a pattern similar to that seen in Figure 1. We have suggested that the normal inner hair cell synapse may be emulated by applying a 5 kHz unmodulated pulse train so as to "condition" the nerve with spontaneous-like activity prior to the onset of a speech signal. This conditioning by the unmodulated high-rate pulse train may improve fidelity of neural coding of the modulator (Eighth QPR).

The simplest example of this strategy would be adding a high rate unmodulated pulse train (the conditioning stimulus) to a slower unmodulated pulse train (the data stimulus). Ideally, from a pure signal coding viewpoint, the neural output would approximate the modulator (a constant).

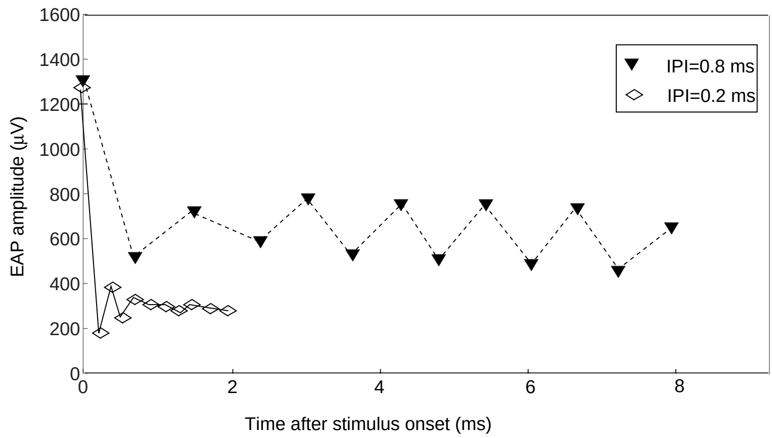

Figure 2: Guinea pig EAP responses to 1.25 kHz and 5 kHz biphasic pulse trains. Monopolar stimulating electrode in basal scala tympani. Recording electrode adjacent to the porus of the internal auditory canal. 5 Kz response obtained by sequential subtraction technique. The alternating pattern at 1.25 kHz is replaced by a uniform pattern at 5 kHz after the first 0.6 ms.

Using our computational model, we have simulated this scenario. Figure 3 demonstrates a compound PST histogram for 500 simulated nodes of Ranvier. They are "conditioned" for 19.8 ms with a 5 kHz biphasic pulse train at which time a constant 1.67 kHz biphasic pulse train is added. Without a conditioner, the response amplitude alternates while at conditioner levels above 240 μA there is a fairly constant response (i.e. the response is more like the modulator, a constant).

A guinea pig cochlea was stimulated with the same paradigm and the direct nerve EAP recordings are shown in Figure 4. The model prediction that addition of a conditioner flattens the alternating response to a constant pulse train has been verified in this animal.

The effects with a more complex modulator are shown in Figure 5. The left panel demonstrates the simulated compound PST histogram to a sinusoidally amplitude modulated (SAM) pulse train. The modulator is a 100 Hz sinusoid and the carrier is a 1 kHz biphasic pulse train. It is clear that significant distortions of the modulator are present in the response. At low levels, "floor" effects are seen and the valleys of the modulator are not represented in the response. At high levels, refractory distortions are seen as a "ceiling" effect on the peaks.

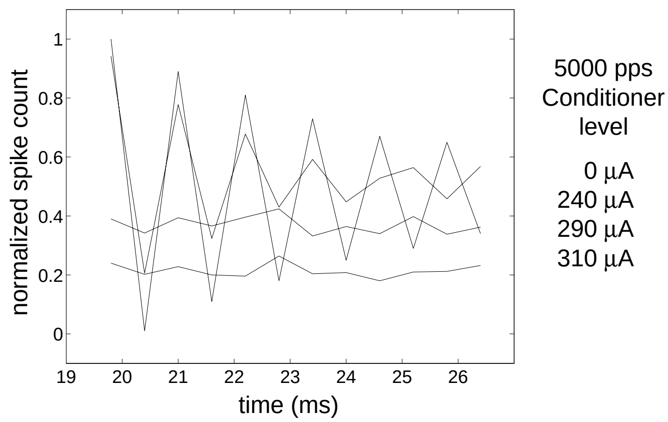

Figure 3: Simulated compound PST histogram of 500 nodes of Ranvier. A "conditioning" stimulus is presented at 5 kHz for 19.8 ms prior to and after the addition of a 1.67 kHz pulse train stimulus.

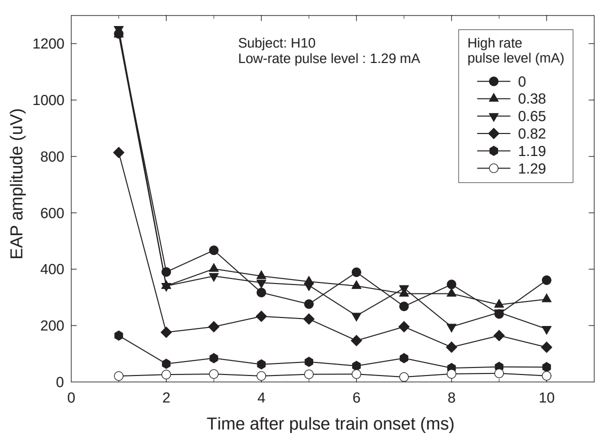

Figure 4: Effects of 5 kHz conditioner on EAP response to 1 kHz pulse train. Same stimulus and recording conditions as in Figure 2. Conditioning stimulus ("high rate pulse level") begins 28 ms prior to onset of low rate pulse train.

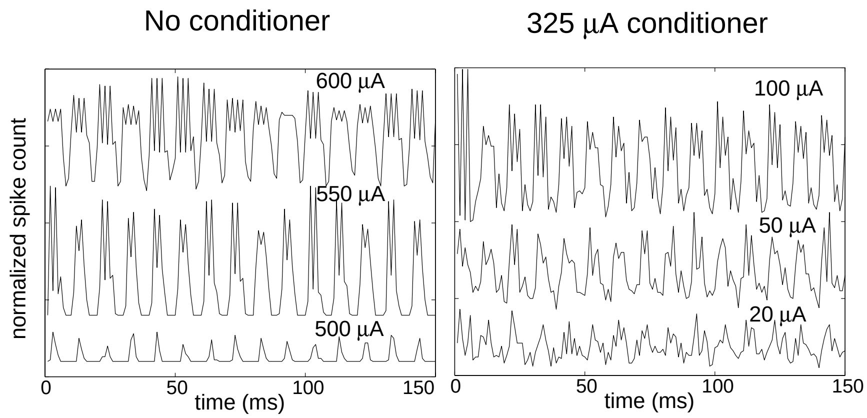

Figure 5: Compound PST histogram in response to a SAM pulse train of 500 simulated nodes of Ranvier. Modulation frequency is 100 Hz. Carrier is a 1 kHz biphasic pulse train. Representation of the modulator and dynamic range are both improved by addition of the conditioner. Modulation depth is 100% of the carrier amplitude.

The right panel of Figure 5 demonstrates the response to the same signal but in the presence of a 5 kHz biphasic pulse train conditioning signal. While similar distortions are seen, they are qualitatively much improved from the prior figure, particularly the "floor" effect. It is also apparent that dynamic range has been broadened and threshold has been reduced by the addition of the conditioner. The conditioner level of 325 μA by itself produces a pseudospontaneous rate of 116 spikes/s.

A quantitative analysis of these responses is shown in Figure 6. The percentage total distortion is calculated by dividing the summed energy of all frequency components not at the modulation frequency by the total energy in the signal. This measure is equivalent to $1 - vs$ where vs is the vector strength, or similarly the synchronization index. It is apparent from this figure that the conditioner substantially increases the stimulus range over which fidelity of the modulator is maintained in the simulated neural response.

As examples of the total distortion measure employed here, a 100 Hz sinusoid sampled at 1 kHz would itself result in a total distortion of 20%. A half-wave rectified 100 Hz sinusoid sampled at 1 kHz produces a total distortion of 50%. Thus, both the unconditioned and conditioned stimuli can produce a high fidelity coding of the modulator (as compared with an

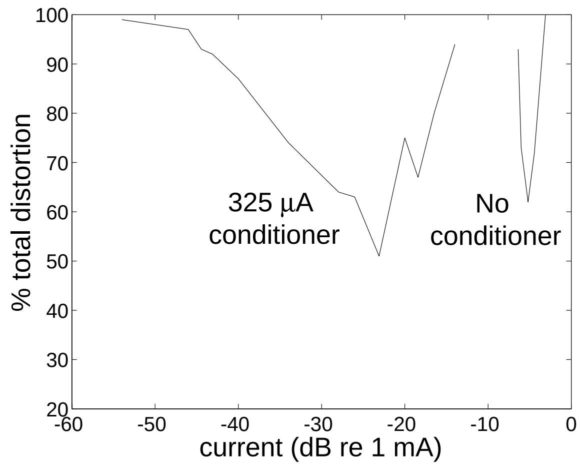

Figure 6: Percent total distortion in the compound PST histogram in response to a SAM pulse train. Representation of the modulator is improved by addition of the conditioner. A sampled sinusoid would produce a total distortion of 20%. A sampled half-wave rectified sinusoid produces a total distortion of 50%.

idealized inner hair cell) at one specific intensity. The conditioned response is a bit better at its peak, but more importantly, relatively less distortion is produced over a wider range of stimulus intensity than in the unconditioned response.

4 Clinical applications

4.1 Hardware/software modifications

In the last quarter we have made substantial progress in modifying clinical implant devices to allow presentation of high-rate pulse trains. While the laboratory systems at MEEI and RTI readily permit 5 kHz pulse trains to be added with other signals, no FDA approved commercial processor allows such rates in any standard configuration. The Med-El processor also allows these rates, but that limits our research to Ineraid subjects as we have no patients implanted with the Med-El.

Two of us (JTR and PJA) attended a workshop sponsored by Advanced Bionics Corporation on the programming of the Clarion Research Interface. We have installed and successfully tested this interface in Iowa. We are preparing to perform the necessary DSP programming to study the effects of high-rate conditioning pulses on psychophysics and speech perception with analog stimulation in Clarion subjects. This will allow laboratory testing but not field trials of promising strategies.

We have installed and successfully tested the Arbitrary Frame Generator software from Cochlear Corporation. This allows us to implement any pulsatile sequence allowed by the CI-24 implant hardware. It does not permit live speech testing and sequences are limited to the size of the non-volatile memory of the Sprint (about 3 seconds at 5000 pps). This is adequate for psychophysical studies but will not allow speech testing.

To bypass the limitations of the Arbitrary Frame Generator, we have exploited an anomaly in the clinical programming software WinDPS. While pulse rates are limited to 2500 frames/s, it is possible to route the output of multiple channels to a single electrode. This has allowed us to implement a 6 channel version of a conditioned CIS processor. In this implementation, 2 channels carry conditioned speech data, and 4 channels carry speech alone. By placing the conditioned channels amid the unconditioned ones, we hope to exploit current spread to apply some conditioning to the unconditioned channels as well. Unfortunately, WinDPS requires each channel to have an associated bandpass filter, so some portion of the input spectrum is lost in unmodulated conditioning pulses. We are currently testing a variety of schemes to minimize the impact of this loss of spectral information (see below). If these programs are successful, they can be placed in the processor's memory and be field tested.

4.2 Preliminary speech results

We have tested two CI-24 implanted subjects with different versions of our experimental 6-channel "conditioned CIS processor". In one subject, the loss of spectral information was so severe that both conditioned and unconditioned stimuli failed to produce measurable speech reception scores. In another subject, unconditioned scores on CUNY sentences were 14%. Conditioned scores were 40% (both measures were average of three lists). This is a significant gain, but was not useful to the subject as his baseline SPEAK score is 80% CUNY. The substantial decline of the unconditioned score is due to the spectral information loss caused by the software limitations of WinDPS. We hope to diminish the effects of this limitation in subsequent subjects. In both subjects, a remarkable degree of loudness adaptation was seen with the 4800 Hz pulse trains used as conditioners. In one subject, a stimulus which at onset was nearing an uncomfortably loud level, adapted to inaudible after about 100 seconds. Termination of this stimulus after adaptation produced a brief but fairly dramatic percept that the subject was unable to describe.

4.3 Tinnitus suppression

There are sound physiologic reasons to believe that restoration of spontaneous-like activity to the deafferented cochlea may ameliorate the perception of tinnitus (Kiang et al., 1970). We intended to study this hypothesis using the Med-El CIS-link processor to generate 5 kHz pulse trains. Due to the IDE status of the Med-El, our IRB determined that an IDE would be necessary to use this device for tinnitus suppression research. We subsequently determined that the WinDPS could be altered as described in the previous section to apply 5 kHz pulse trains to an implant, or a transtympanic round window electrode. Our IRB subsequently approved this approach. We have studied one subject, a music professor, with disturbing tinnitus associated with high-frequency sensorineural hearing loss. At high levels of stimulation, his tinnitus was reduced by over 50% in loudness, but an uncomfortable onset transient, probably somatosensory was produced. He could not hear the stimulus after the transient was over (several seconds). We could not study higher levels due to this transient, but we have reproduced it by applying similar stimuli to the tongue of one of us (JTR) and the transient is eliminated by slowly ramping up the stimulus level. We have constructed a shunt circuit to allow slow increases in stimulus level and we expect to study our next subject in the coming week. We have applied for funding of this study from the Tinnitus Research Consortium. We hope to study both implant patients with tinnitus and subjects with mild-moderate high-frequency hearing loss and tinnitus.

5 Plans for the twelfth quarter

The following activities are planned for the twelfth quarter (July - September, 1999) of this research project:

- Continue EAP data collection on chronically deafened guinea pigs.
- Continue histologic analysis of chronically deafened guinea pigs.
- Continue analysis of two-pulse refractory data on cat single-units.

- Give two podium presentations at the Asilomar meeting.
- Host a consulting visit by Blake Wilson and Don Eddington.
- Present a poster at the Whitaker Foundation meeting.

References

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