

Second Quarterly Progress Report
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**Effects of Remaining Hair Cells on
Cochlear Implant Function**

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1 Introduction

With relaxed audiological selection criteria for cochlear implants, many patients implanted today have significant hearing prior to implantation. If patients with significant hair cell function are implanted, an important issue is the extent to which the presence of hair cells impedes or assists with electrical hearing. Physiological studies of implanted animals have shown that viable hair cells respond to electrical stimulation. Furthermore, this response causes a pattern of nerve fiber activation different from that created by direct depolarization of auditory nerve fibers by electrical stimulation. Thus, in electrically stimulated cochleae with intact hair cells, the neural representation of the stimulus would consist of components arising from both hair-cell mediated and direct-nerve excitation. The major goal of this research is to characterize the nature and interactions of these two responses, particularly as they may occur with patterned stimulation used by implanted cochlear prostheses.

There are several general hypotheses concerning hair-cell mediated and direct-nerve excitation via electrical stimuli as well as potentially beneficial interactions between acoustic and electrical signals. To address these issues, we propose a sequence of experiments designed to first characterize the response patterns and interactions and then to explore techniques to best exploit them. These experiments employ both physiological measures and modeling of the effects of hair cells on the response to electrical stimulation. We have completed preliminary modeling studies that begin to assess possible effects of inner hair-cell activity on the response to direct electrical stimulation of auditory nerve fibers (ANF).

Models of the inner hair-cell (IHC) synapse have been a subject of substantial inquiry in auditory physiology. These models typically consist of a Poisson vesicle release process linked to a deterministic neural model of the post-synaptic membrane. This situation has been described as a self-exciting point process model (Schmich & Miller, 1997). An implicit assumption of these models is that the IHC synaptic noise is of sufficiently greater magnitude than the membrane noise of the ANF that the latter can be ignored. Our stochastic biophysical model of the ANF and node of Ranvier provides an opportunity to test this hypothesis.

We and others have recently demonstrated how the intrinsic membrane noise of the ANF might be amplified through the use of high-rate desynchronizing pulse trains (DPT). The DPT may produce activity similar to spontaneous activity (ie. pseudospontaneous activity) normally evoked at

rest by the IHC synapse (Rubinstein et al, 1999). It is of interest to compare the putatively beneficial effects of DPT conditioning stimuli with the desynchronization that might be provided by an intact IHC synapse.

2 Progress during the last quarter

- We have put great effort into recruiting the necessary personnel to ramp up our experimental & theoretical efforts. We have recruited Hiroyuki Mino, PhD from the Laboratory of Neural Control at Case-Western Reserve University to an Associate Research Scientist position. Dr. Mino was an Assistant Professor of Electrical Engineering at Toho University in Japan prior to pursuing post-doctoral training with D Snyder at Washington University in St Louis. There he developed extensive models of synaptic transmission at the neuromuscular junction. His theoretical expertise in this area is of obvious benefit to our program. He will work part-time on this project as well as on the Tinnitus Research Consortium grant (see below). He is a Japanese citizen and we expect to have his visa completed to begin work on 3/1/00. We are still actively recruiting another research scientist to help with the experimental protocols.
- Experimental EAP data were collected from a total of 7 guinea pig acute preparations. Of those, pre- and post-deafening measures were obtained from 4 guinea pigs using kanamycin / ethacrynic acid technique during data collection. Premature guinea pig deaths in two pilot preparations led us to adopt Ringers i.v. drip to better preserve electrolyte balance. Data sets included responses to single-pulses (growth functions), two-pulse refractory (forward-masking) paradigms, and pulse trains.
- We have been awarded a \$300,000, three year research grant from the Tinnitus Research Consortium to test the hypothesis (developed under NPP contracts) that high-rate pulse train stimuli can suppress tinnitus in cochlear implant patients and patients with mild high-frequency sensorineural hearing loss.
- We have implemented a conditioned speech processor on the CI-24 and have sent one subject for a field-trial with this strategy. Acutely, his already excellent speech perception is not improved (88% HINT in

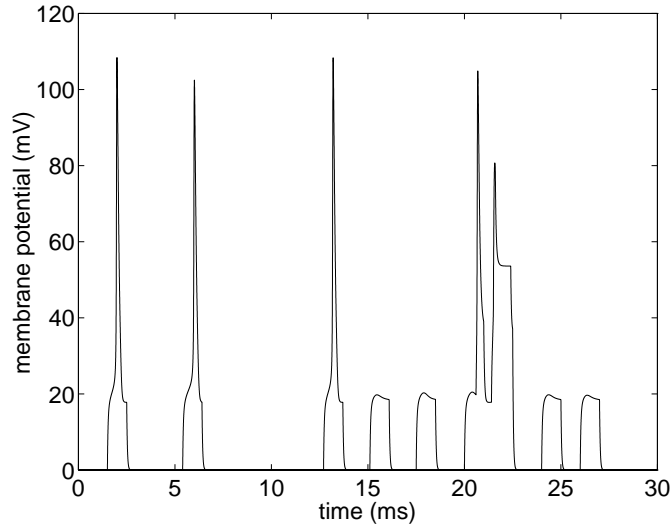


Figure 1: Spikes evoked by simulated spontaneous vesicle release in a deterministic node model. Mean vesicle release rate is 300/s and EPSC duration is 1 ms (Miller & Wang, 1992). EPSC amplitude adjusted to achieve spontaneous rate of 140 spikes/s.

quiet) but he has statistically significant improvement in music perception scores and prefers the sound quality with the conditioner.

3 Methods

Following the methods of Miller and Wang (1992) a Poisson vesicle release process has been simulated with excitatory post-synaptic currents (EPSC) of 1 ms duration. These have been applied to both a deterministic and a stochastic model of the node of Ranvier. The mean rate of vesicle release is 300/s (Miller & Wang, 1992) and the current level is adjusted to obtain a simulated spontaneous rate (SR) of 140 spikes/s. Figure 1 demonstrates a 30 ms simulation of the membrane potential.

It has previously been suggested that since synaptic noise is substantially larger magnitude than intrinsic membrane noise, models of spontaneous activity do not require stochastic neural models. Given recent work on the importance of intrinsic noise for normal neuronal behavior, this assumption deserves proof (White, Rubinstein & Kay, 2000). Figure 2 demonstrates the

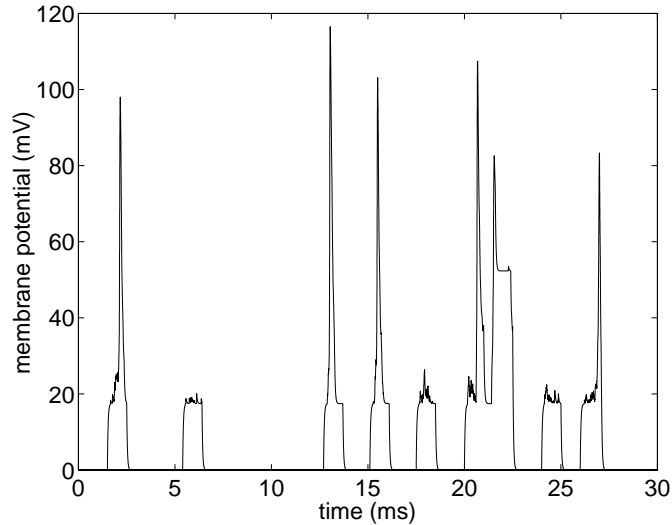


Figure 2: Spikes evoked by simulated spontaneous vesicle release. Stochastic node model. Membrane noise is apparent during the subthreshold EPSPs. Same synaptic parameters as in Figure 1.

simulated membrane potential for 30 ms when the Poisson EPSC is applied to a stochastic node model (Rubinstein, 1995).

A comparison between these two cases is provided in Figure 3 which illustrates interspike interval (ISI) histograms. The two histograms are quite similar suggesting minimal loss of detail when the deterministic neural model is used. Hazard functions are also similar but the comparison is limited by the small number of spikes, a computational limitation which can be bypassed with some effort if necessary.

Because the responses with deterministic and stochastic models are so similar when significant synaptic noise is present, our subsequent efforts to simulate responses to electrical stimulation in the presence of intact inner hair cells may not require the use of our stochastic neural model. This represents a two-order of magnitude savings in computation which is exploited in the next section.

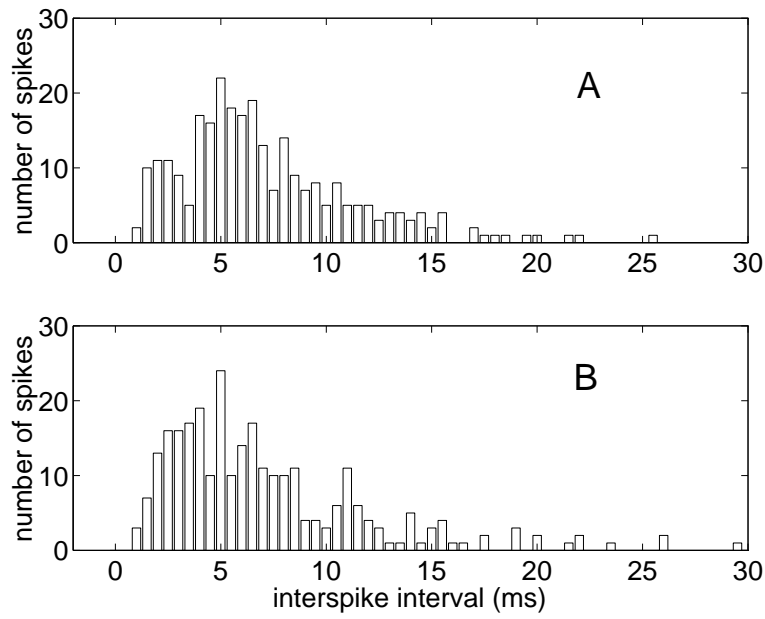


Figure 3: ISI histograms for simulated synaptic activity. Panel A shows results for a deterministic neural model and panel B for a stochastic neural model. The similarity of the histograms suggests that it is safe to assume that a deterministic neural model is adequate for simulating neural noise when synaptic noise is substantially greater than intrinsic membrane noise.

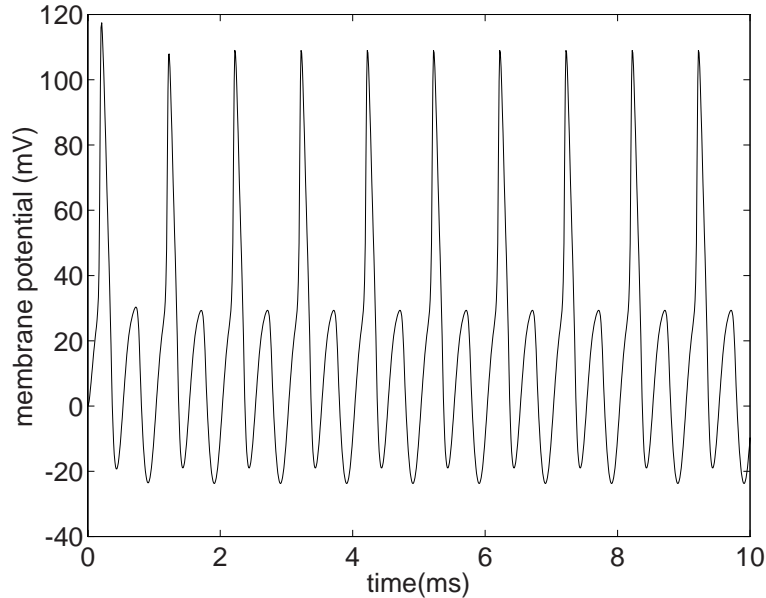


Figure 4: Response of deterministic node of Ranvier model to a 2 kHz sinusoid in the absence of spontaneous synaptic activity. Spikes occur on every other positive phase.

4 Results

In the first QPR for this contract we presented data from a single animal suggesting that the alternating pattern of EAP responses to 1 kHz pulse trains was attenuated in animals with functioning hair cells. We interpreted this as further evidence that the presence of neural noise is associated with relatively flat pulse-train responses, while an alternating pattern suggests the relative absence of noise. We can now demonstrate this in a computational model.

Figure 4 illustrates the simulated response of a deterministic node of Ranvier to a 2 kHz sinusoid. We choose 2 kHz rather than 1 kHz due to the short refractory period of the isolated node relative to that of a distributed axon. It is clear that the model responds to every other positive phase with an action potential. This behavior, known as “chopping” (Shepherd & Javel, 1997), represents the single-unit equivalent of the alternating pattern seen in the EAP of deafened animals and cochlear implant patients.

Figure 5 demonstrates the simulated response of a deterministic node of

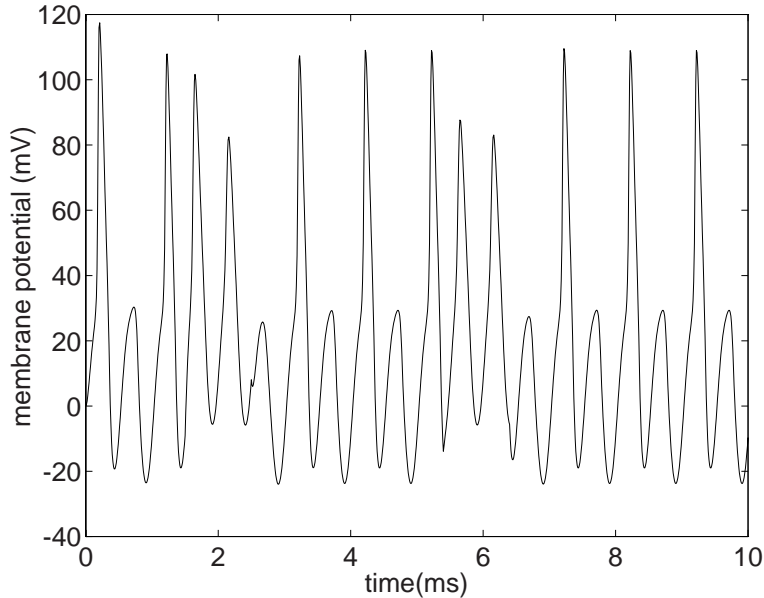


Figure 5: Response of deterministic node of Ranvier model to a 2 kHz sinusoid in the presence of spontaneous synaptic activity. Spikes no longer occur on every other positive phase.

Ranvier to the combination of a 2 kHz sinusoid and the spontaneous EPSCs described in the previous section. It is apparent that the model no longer responds on every other positive phase. The exact spike timing now appears to be a random process.

Figure 6 demonstrates the period histogram for the previous two cases demonstrating responses perfectly synchronized ($SI=1.0$) to every other positive phase in the absence of spontaneous EPSCs (panel A). When spontaneous EPSCs are present, the synchrony decreases significantly such that responses are present on every positive phase and better temporal representation is apparent as well. The double-peak characteristic seen in panel B is quite similar to that seen at high sinusoidal stimulus levels in the presence of pseudospontaneous activity (Rubinstein et al, 1998). We will carefully examine the intensity dependence of these behaviors in a future QPR.

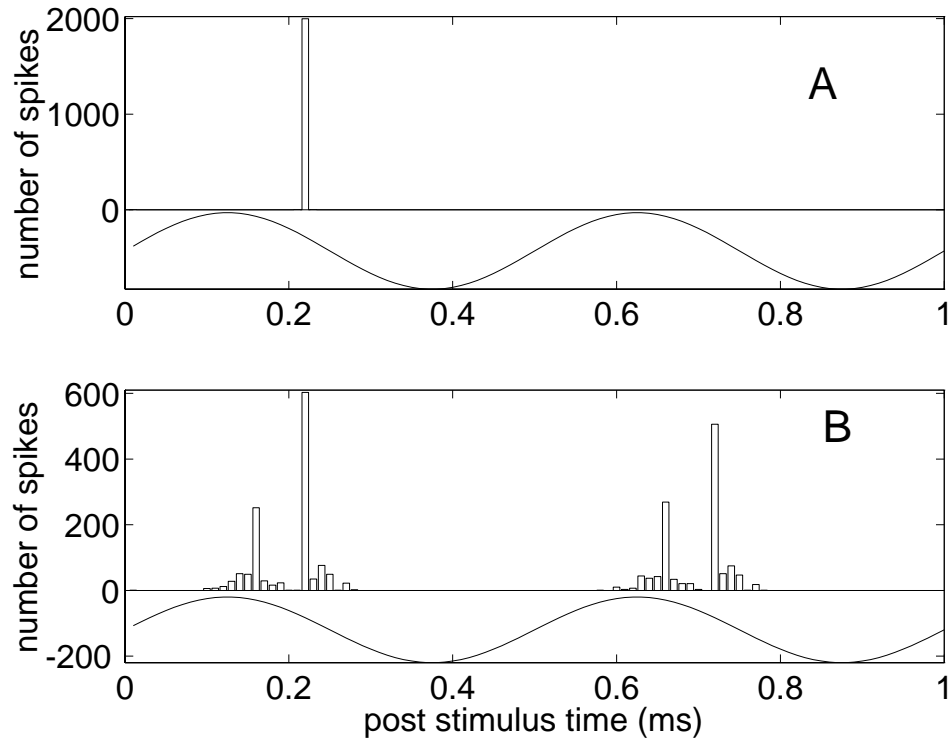


Figure 6: Period histograms of response to 2 kHz sinusoid in the absence (panel A) and in the presence (panel B) of spontaneous EPSCs.

5 Plans for the next quarter

- Data analysis for the four guinea pigs studied this quarter will be completed.
- Intensity dependence of the effects of simulated synaptic activity on responses to electrical sinusoids will be completed.

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