

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

J.T. Rubinstein, C.A. Miller, P.J. Abbas, H. Mino

Department of Otolaryngology - Head and Neck Surgery
Department of Speech Pathology and Audiology
Department of Biomedical Engineering
University of Iowa
Iowa City, IA 52242

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1 Introduction

In this contract, we are conducting physiological experiments and computational model simulations to assess the effects that functional hair cells have on the auditory nerve's response to electrical stimulation. This work is relevant to the widening pool of cochlear implant candidates as audiological criteria (e.g., aided speech discrimination scores) are becoming more relaxed and patients with more residual hearing are being implanted. Intact hair cells may interact with the electrically transduced signal in several ways. Acoustically evoked neural activity may interact or compete with electrically evoked activity. Also, the very presence of hair cells - without any exogenous acoustic stimuli-may also modify the electrically evoked neural response. It is possible that electrical stimuli may depolarize hair cells and initiate the release of neurotransmitter and nerve-fiber activation. It is also possible that quiescent release of neurotransmitter may modulate the response characteristics of nerve fibers, thereby changing their responsiveness to electrical stimuli. The experiments of this contract are designed to acquire evoked potential data from sets of experimental animals that have functional and nonfunctional hair cells. Comparisons will then be performed to assess the effect of functional hair cells on the neural coding of electrical stimuli delivered by intracochlear electrodes. Computational simulations are presented to complement the experimental data, assist in its interpretation, and help guide future experiments.

2 Summary of activities in this quarter

In our fifth quarter (1 October through 31 December, 2000), the following activities related to this contract were completed:

1. We attended the Neural Prosthesis Workshop and presented a summary of our progress to date. This included results of both simulations and experiments pertaining to the effects of intact hair cells on responsiveness to electrical stimulation.
2. We submitted three abstracts to the ARO meeting. One was on the computational efficiency of different stochastic simulation algorithms, one was on the effects of acoustic noise and sinusoids on ECAP responses to electrical stimulation in a hearing ear, and one was on model development for a vestibular prosthesis. The latter work, while

initially thought to represent a rather separate area of inquiry, now appears to have substantial relationship to this contract. Although there has been little effort in the past, experimental or theoretical, to develop a vestibular prosthesis, *vestibular investigators have long used electrical stimulation as a tool to study the vestibular nerve in the presence of normal hair cells*. Thus there is a rich collection of experimental data in multiple species demonstrating interactions between synaptic and externally applied potentials. There is also substantial theoretical development to draw upon. While vestibular neurons have many fundamental differences from auditory neurons, they do represent a hair-cell innervated bipolar neuron which possesses several important similarities to the auditory system. This area will be further explored in a subsequent Quarterly Progress Report.

3. We have prepared a manuscript detailing the contents of the fourth Quarterly Progress Report. This will be submitted next quarter.
4. We completed further experiments on effects of acoustic stimuli on response to electrical stimulation.

3 Aims and methods

In the third Quarterly Progress Report, we presented comparisons of ECAP responses obtained both before and after chemical deafening in the same preparations. Repeatable differences were seen in ECAP threshold, rate of growth, and response patterns to pulse train stimuli. These differences reinforced the hypothesis that intact hair cells modify the neural responses to electrical stimulation in ways consistent with the notion of enhancements due to stochastic (hair-cell mediated) activity. In the second Quarterly Progress Report, we began theoretical explorations of the synaptic mechanisms underlying these interactions. In this Quarterly Progress Report we will carry on that work to attempt to explain quantitatively the experimental results obtained.

The methods used are identical to those described in the second Quarterly Progress Report. A single-node, space-clamped model of the node of Ranvier was studied. In some cases it was stochastic (Rubinstein, 1995) and in others, deterministic but with identical membrane parameters to the stochastic model. Synaptic currents were simulated with a Poisson vesicle release process with a constant mean rate of 300 vesicles/s with each

vesicle producing a 1 ms rectangular current pulse. The synaptic current (i.e. vesicle size) was controlled as a parameter. Additional membrane current was provided by a 2 kHz sinusoid representing electrical stimulation. A population of from 50 to 200 of these nodes were simulated using both a uniform threshold and a Gaussian distribution of thresholds of varying standard deviation to match the range of thresholds we have seen experimentally (Miller et al., 1999a). When the stochastic membrane was used, the number of voltage-sensitive sodium channels were chosen ($N = 280$) to yield an RS of about 7%, near the mean of 6% established experimentally (Miller et al., 1999a).

4 Results

Figure 1 demonstrates the post stimulus time (PST) histogram of 100 uniform deterministic nodes of Ranvier to a constant 14 nA electrical sinusoid in the presence of a range of synaptic currents. If the synaptic current is absent (0 nA), the nodes all respond on every other cathodal phase and continue to do so throughout the stimulus. This situation is reminiscent of responses seen in human subjects (Wilson et al., 1995) but differs in the “all or none” nature of the responses. It represents an extreme case of “determinism” without membrane noise, synaptic noise, or a threshold distribution. As will be seen below, the addition of a threshold distribution makes the alternating pattern more closely resemble ECAP recordings from human subjects.

Adding a small amount of synaptic noise (1 nA) dramatically changes the response sequence so that the alternating pattern exists but decays over the course of the stimulus. With increasing synaptic noise, the alternation decays more rapidly. In the lower right panel (10 nA), the synaptic noise is sufficient to evoke 65 spikes/s of spontaneous activity visible in the first 5 ms of the response. This reduces the response to the first cathodal phase of the electrical stimulus. Both the more rapid decay and the decreased response amplitude in the presence of synaptic activity (before deafening) was demonstrated experimentally in the third Quarterly Progress Report.

Figure 2 demonstrates the PST histogram of 50 uniform deterministic nodes of Ranvier to a variety of sinusoidal currents when the synaptic current is held constant at 2 nA. The lower left panel of Figure 2 is the same stimulus condition as the lower left panel of Figure 1. This panel appears to

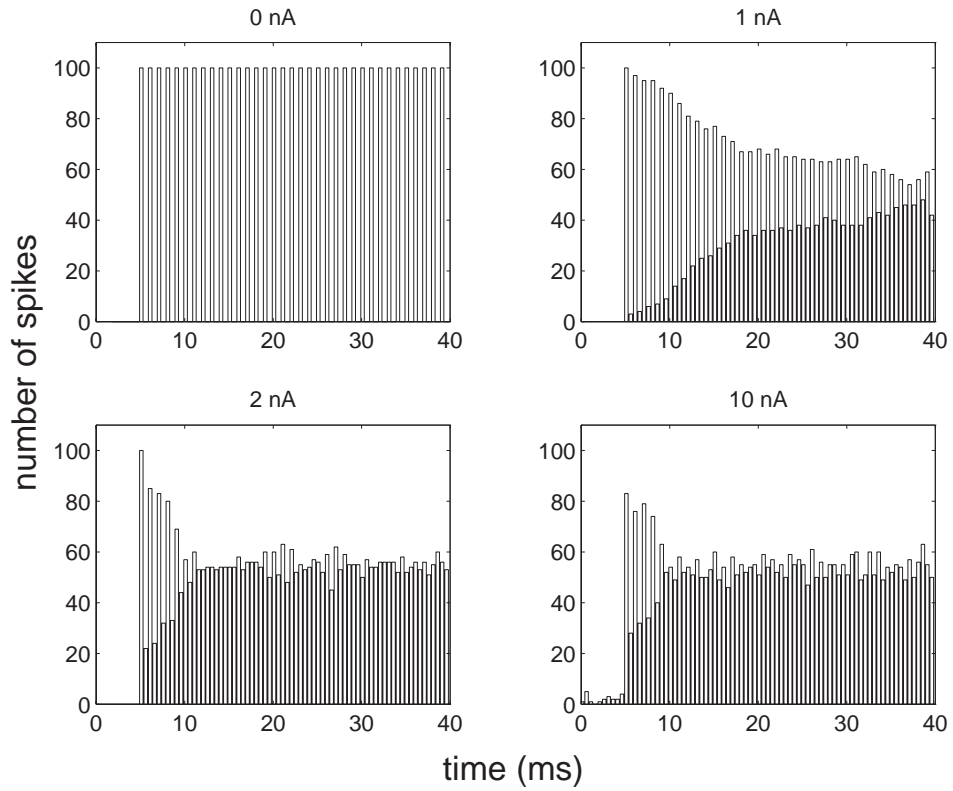


Figure 1: Post stimulus time histogram of 100 uniform deterministic nodes of Ranvier stimulated by a 14 nA electrical sinusoid. Parameter is level of synaptic current. Sinusoidal stimulus begins at $t = 5ms$.

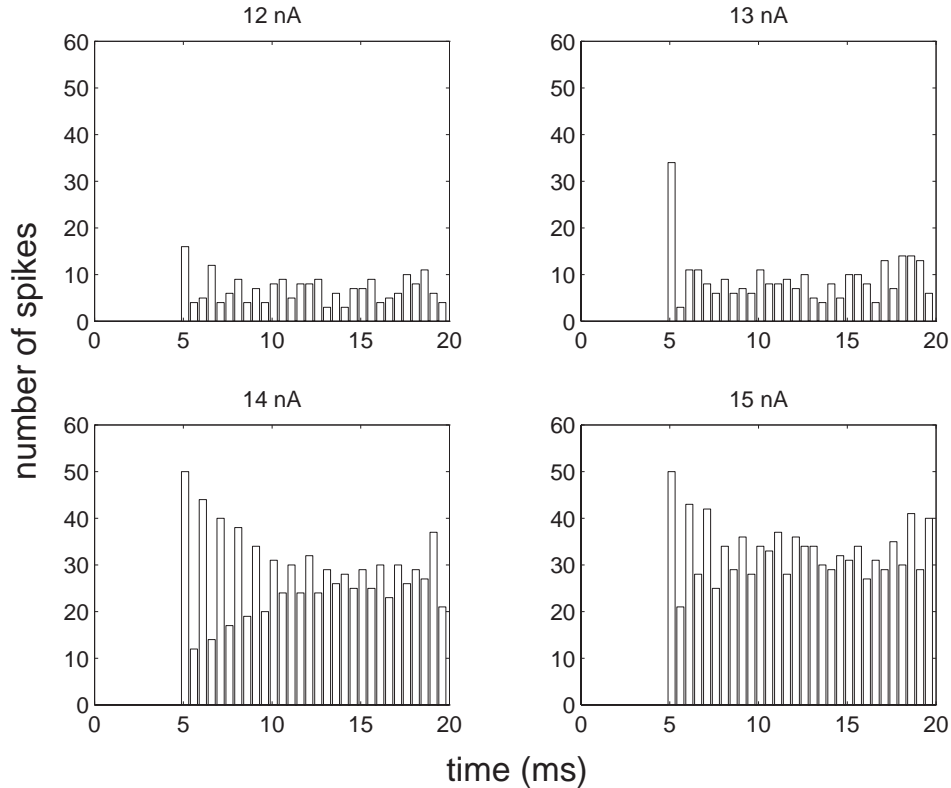


Figure 2: PST histogram of 50 uniform deterministic nodes of Ranvier with 2 nA of synaptic current. Parameter is the level of a 2 kHz sinusoidal electrical current. Sinusoidal stimulus begins at $t = 5ms$.

represent the optimal stimulus intensity (14 nA) at which alternation may be observed. It is clear that at higher or lower sinusoidal stimulus currents, orderly alternation gives way to a more chaotic and flatter response pattern. The extremely intensity sensitive nature of ECAP response alternation has been noted experimentally in two animal preparations (Matsuoka et al., 2000).

In our previous work (Miller et al., 1999b) we have demonstrated that fiber threshold distribution is of greater importance to ECAP growth than is intrinsic membrane noise (RS). One might expect that a threshold distribution would have a significant effect on the temporal pattern of ECAP responses. We have therefore explored a range of nodal thresholds using a

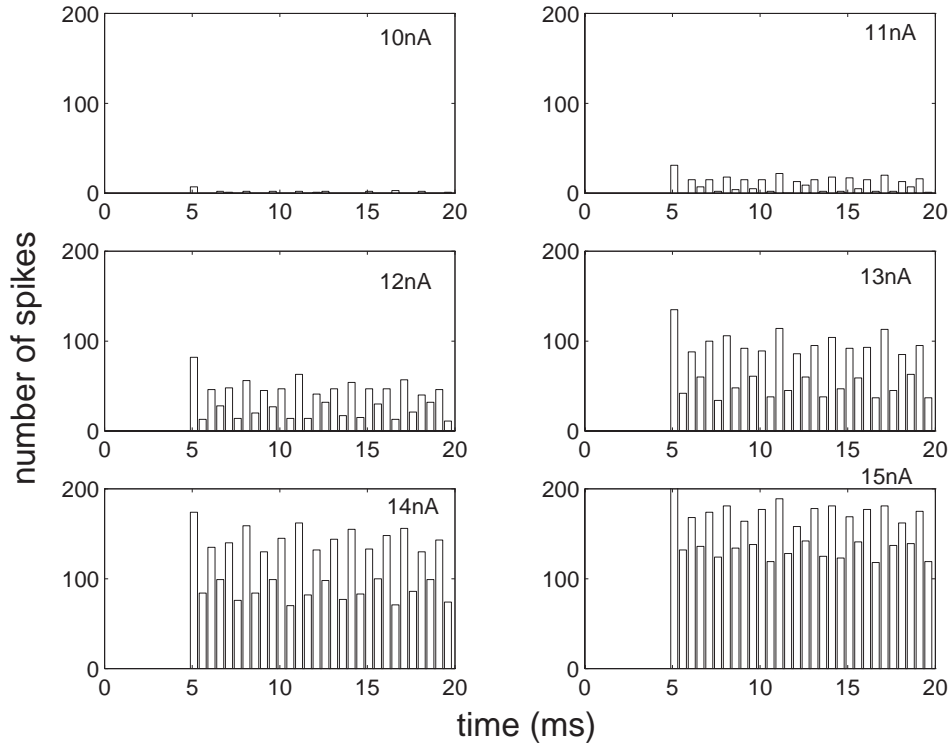


Figure 3: PST histogram of 200 deterministic nodes of Ranvier with no synaptic current (0 nA). Parameter is the level of a 2 kHz sinusoidal electrical current. Sinusoidal stimulus begins at $t = 5ms$. The nodes have a range of thresholds with $\sigma = 15\%$.

Gaussian distribution of thresholds of a variety of standard deviations (defined as percentage of mean). $\sigma = 0$ corresponds to the uniform threshold case, while $\sigma = 25\%$ is comparable to the single-fiber threshold distribution seen experimentally (Miller et al., 1999a). An intermediate example with $\sigma = 15\%$ is seen in Figure 3 which demonstrates the PST histogram of 200 deterministic nodes of Ranvier to a variety of sinusoidal currents when there is no synaptic current (0 nA).

Figure 3 demonstrates an ongoing alternating pattern that much more closely resembles human ECAP recordings (Wilson et al., 1995) than the first panel of Figure 1. In fact, Figure 3 is physiologically a fairly realistic simulation as human ECAP measures have been performed primarily

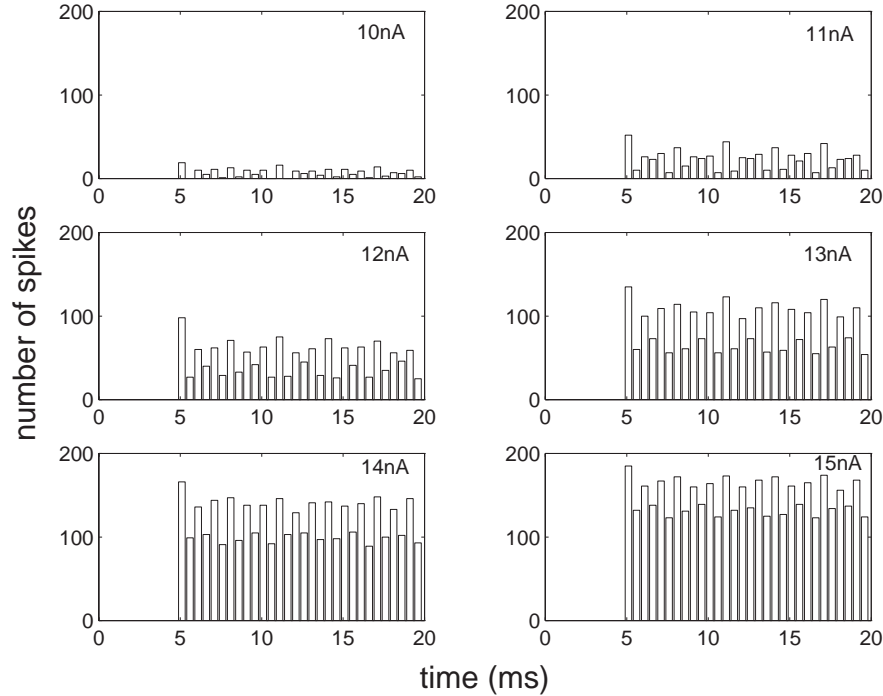


Figure 4: PST histogram of 200 deterministic nodes of Ranvier with no synaptic current (0 nA). Parameter is the level of a 2 kHz sinusoidal electrical current. Sinusoidal stimulus begins at $t = 5ms$. The nodes have a range of thresholds with $\sigma = 20\%$.

in subjects who have been profoundly deaf for many years and presumably have little or no synaptic activity present. While the threshold distribution ($\sigma = 15\%$) is smaller than that seen in acutely deafened cats, it could reasonably reflect survival patterns in humans with long-term deafness and spiral ganglion cell degeneration. The range of stimulus intensities explored in Figure 3 is a significant fraction of the dynamic range of the fiber population which at 3.5 dB is small compared with human psychophysical dynamic range but well within an order of magnitude.

The effects of a wider threshold distribution ($\sigma = 20\%$) are illustrated in Figure 4. The persisting alternating pattern seen earlier is still present but the typical large discrepancy between the amplitude of the ECAP response to the first and subsequent cathodal phases is diminished. The wider dynamic range relative to the simulations of Figure 3 is apparent.

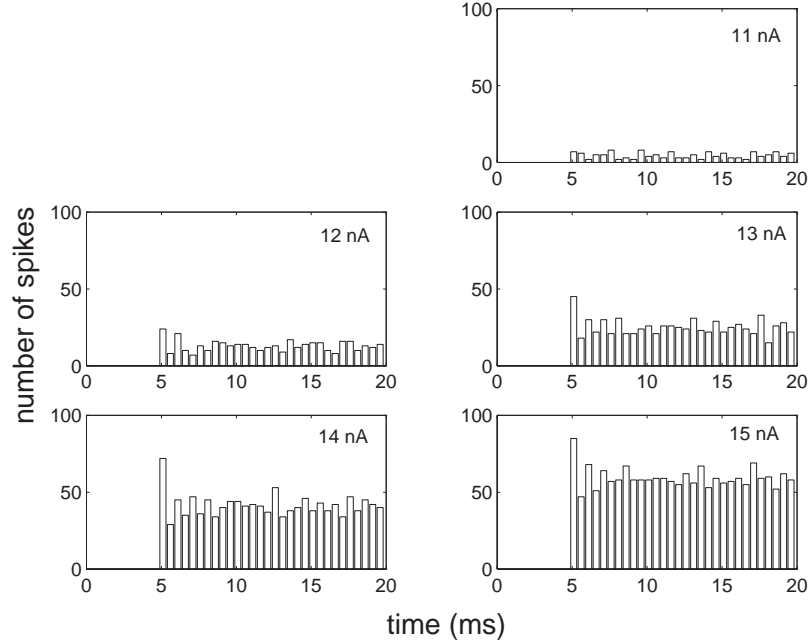


Figure 5: PST histogram of 100 stochastic nodes of Ranvier ($RS = 7\%$) with no synaptic current (0 nA). Parameter is the level of a 2 kHz sinusoidal electrical current. Sinusoidal stimulus begins at $t = 5ms$. The nodes have a range of thresholds with $\sigma = 15\%$.

Until this point all simulations have neglected intrinsic membrane noise by using a deterministic model ($RS = 0\%$). By using instead a stochastic membrane model, the effects of this additional noise source can be studied. Our previous work has established a value of $RS = 6\%$ as a reasonable mean for single auditory nerve fibers (Miller et al., 1999a). With 280 voltage-sensitive sodium channels our stochastic model has an RS of approximately 7%. In Figure 5 we study such a model in the absence of synaptic noise but in the presence of a threshold distribution ($\sigma = 15\%$). Figure 5 demonstrates that membrane noise has a substantial effect on the temporal pattern of ECAP responses even in the presence of a threshold distribution. It is clear that the robust, intensity-independent, ongoing alternating pattern of Figures 3 and 4 is replaced by a transient, decaying alternating pattern that is highly intensity-dependent. Synaptic noise has a similar effect in the presence of a threshold distribution without membrane noise (simulations not shown).

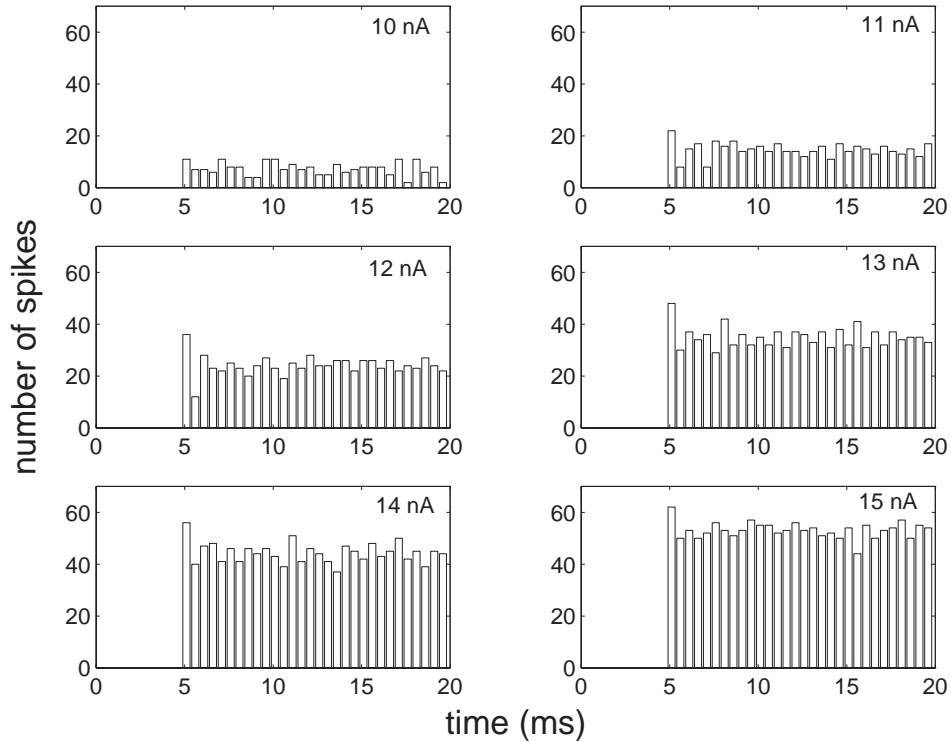


Figure 6: PST histogram of 100 stochastic nodes of Ranvier ($RS = 7\%$) with no synaptic current (0 nA). Parameter is the level of a 2 kHz sinusoidal electrical current. Sinusoidal stimulus begins at $t = 5ms$. The nodes have a range of thresholds with $\sigma = 25\%$.

The effects of a combining a wider threshold distribution ($\sigma = 25\%$) with intrinsic membrane noise ($RS = 7\%$) are illustrated in Figure 6. It is apparent that the combination of a physiologic threshold distribution with a physiologic quantity of membrane noise essentially eliminates any alternating pattern. This may help explain the difficulty of obtaining alternation in our animal experiments, relative to what has been seen in human subjects. It also suggests that the chronically deaf human spiral ganglion has less intrinsic membrane noise relative to an acutely deafened cat.

5 Discussion

We have simulated the effects of synaptic noise, threshold distribution and intrinsic membrane noise on ECAP responses. All three parameters can be reasonably viewed as different types of noise sources with somewhat different effects. The alternating ECAP pattern is produced by refractoriness, which by itself results in an “all or none” alternating pattern. Threshold distribution modifies this pattern to produce an ongoing alternating pattern similar to that seen in human subjects. Either synaptic noise or intrinsic membrane noise causes this ongoing pattern to become a decaying pattern similar to that seen in experimental animal subjects. The greater the synaptic or intrinsic noise, the more rapidly the decay process. Synaptic and intrinsic noise are additive in this property. Lastly, simulations verify that adequate synaptic noise causes a decrease in the ECAP amplitude to the onset of electrical stimulation via the mechanisms postulated in our third Quarterly Progress Report.

6 Plans for the next quarter

In the seventh quarter, we plan the following activities:

- Model simulations of the effects of modulated synaptic activity on ECAP responses to correspond with the experimental activities of the fifth Quarterly Progress Report.
- Dr. Hu Ning has joined our research group as a postdoctoral fellow. He has experience in auditory physiology and will play a key role in conducting physiological experiments.
- Planned experiments using furosemide as a deafening agent in order to assess response properties to electrical stimulation with and without functional hair cells will be conducted.

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