Effects of Remaining Hair Cells on Cochlear Implant Function

14th Quarterly Progress Report

Neural Prosthesis Program
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1. Summary of Activities in This Quarter

During this reporting period (1 October – 31 December, 2005) we accomplished the following:

1. Conducted single fiber experiments focused on adaptation and recovery from electric masker. Off-line analysis of data from five animals (D49, 50, 51, 52, and 56) were conducted and the preliminary results of that analysis is the topic of this progress report.

2. Three experiments were conducted on guinea pigs recording the electrically evoked compound action potential to address the effects of furosemide treatment on the refractory and adaptation properties. Also, further development of ECAP model based on single fiber responses was accomplished.

3. We completed preparation of a manuscript, entitled "Electrical excitation of the acoustically sensitive auditory nerve: Effects of acoustic stimulation" and have submitted it for peer review. Among other things, this manuscript describes the "hybrid" (i.e., acoustically and electrically sensitive) animal model and compares the electrically evoked single-fiber responses from cats with near-normal acoustic sensitivity and single-fiber responses from deaf ears.

4. We completed analyses of single-fiber data pertaining to combined acoustic and electric stimulation of the cat cochlea. We also began preparation of another manuscript (again, for peer-reviewed publication) that details the results obtained in those studies.

5. We began preparation of a manuscript on binaural interaction measures to be submitted within early 2006.

6. We made final revisions to a reviewed manuscript dealing with improved noise reduction for single fiber recordings. This paper, entitled "Improved Noise Reduction in Single Fiber Auditory Neural Responses using Template Subtraction" describes a cross-correlation technique and will be published in the Journal of Neuroscience Methods.

7. We submitted three abstracts for presentations at the 2006 Midwinter Meeting of the Association for Research in Otolaryngology.

8. Charles Miller was invited to present research results at the KHRI (Ann Arbor, Michigan) seminar series. While there, he conducted evoked potential measures in chronically implanted "hybrid" guinea pigs (of the laboratory of Dr. Bryan Pfingst) to assess the possibility of recording acoustic-electric interactions in such implanted animals. The feasibility was demonstrated: electrophonic responses were recorded from one animal and were masked by acoustic stimuli. This early results suggest some intriguing possibilities for new animal models of "hybrid" hearing in chronically implanted subjects.

2. Focus topic: Single-fiber measures of electric forward masking

2.1 Introduction

A primary focus of work being conducted on this contract has been the characterization of the interaction of acoustic and electric stimulation at the level of the auditory nerve. The basic paradigm that we have used has involved measures of responses to electric pulses and comparison of those responses to those evoked during simultaneous presentation of wide-band acoustic noise. We have used two basic measures of peripheral response, the electrically evoked compound action potential (ECAP) and single-fiber responses of the auditory nerve using standard micropipette recording techniques.

Previous progress reports have outlined significant interactions both during the presentation of an acoustic stimulation as well as residual effects after the offset of the acoustic stimulus (Nourski et al., 2005a; Miller et al., 2005). ECAP recordings have demonstrated significant decreases in response amplitude during acoustic noise presentation. There were also significant residual effects observed after offset of the acoustic stimulus. The ECAP amplitude recovery could, in many cases, be characterized by a nonmonotonic function, suggesting both adaptation (reduced responsiveness) as well as increased synchrony in the response to electrical stimulation. Our measures of single-fiber responses have been generally consistent with the ECAP measures. Single-fiber responses to electric stimulation during the presentation of an acoustic noise exhibited significantly reduced synchrony. Single-fiber responses to electrical stimulation after noise offset demonstrated decreased jitter in many cases, along with reduced firing probability. These two effects could demonstrate different time courses, and thus account for the non-monotonic ECAP recovery functions that we have reported. Thus, our working hypothesis has been that adaptation recovery and recovery of suppression of spontaneous activity determine the time course of ECAP recovery.

More recently, we have conducted a series of experiments to evaluate the degree to which the aforementioned response properties are unique to acoustic/electric interactions at the level of the auditory nerve. To that end, we adopted a paradigm that replaced the acoustic stimulus with a high-rate (5000 pulse/s) electric pulse train. This would enable us to determine the extent to which the nature of the “masker” stimulus was critical to, say, non-monotonic ECAP recovery, or simply based upon the degree of neural activity that was evoked. Preliminary studies of the electric-electric stimulus paradigm for evoking ECAPs were recently reported (Nourski et al., 2005b). We have more recently made analogous measures with single-fiber recordings. Those measures are the topic of this report.

As in the case of the previous ECAP measures, single-fiber measures were obtained from animal preparations implanted with the same minimally invasive intracochlear stimulating electrode. Measures were obtained from adult cats used as acute preparations. The stimulus paradigm, illustrated in Figure 1, consists of a “masker” stimulus (a 5000 pps electric pulse train, 200 ms duration) followed by a “probe”

stimulus (a 250 pps electric pulse train, 300 ms in duration). Each stimulus was followed by a silent period of 1200 ms to avoid cumulative effects. The 5000 pulse/s rate of the "high-rate" masker stimulus was used to simulate, to some degree, the stochastic response pattern that is typical of responses to acoustic noise (Litvak et al., 2003). The low-rate pulse train is consistent with that used in our previous work. We have shown that only moderate amounts of adaptation our caused by this stimulus, making it a useful probe to assess the time course of recovery pattern from previous stimulation. As with our acoustic/electric stimulation paradigm, we interleaved presentations of masker alone, probe alone, and the combined masker-plus-probe stimulus in order to assess differences in responsiveness with and without the masker stimulus. To assess auditory nerve firing properties, we typically used 25-40 repeated presentations of each of the three types of stimuli.

Details of the methods and stimulus protocols have been described in previous reports and are unchanged from those reports unless specifically noted otherwise. One difference in spike analysis is that during the masker response we have used a method of filtering introduced by Litvak et al. (2003) to eliminate stimulus artifact. During the probe presentation we use our usual template subtraction method described in earlier reports.

We have completed measurements of single-fiber responses using this paradigm in five animals to date. In some cases, the measurements were collected from acoustically sensitive animals (D50, D52). We also wished to assess the possible effects of hair cell loss on the response properties. Consequently, in other cases, the animals were deafened with intracochlear neomycin injections (D51, D56). In another animal, hearing sensitivity was lost after introduction of the electrode array into the cochlea without chemical intervention. The general characteristics of the responses will be described in this progress report; more detailed comparisons to acoustic stimulation effects and possible effects of hearing status will be presented in future reports.

2.2 Adaptation and recovery in response to electric stimulation

Figure 2 shows a typical example of the responses of a single fiber to the electric pulse train stimuli described above. The upper graph is a PST histogram of the response to a 200 ms long high-rate (5000 pulse/s) masker. The response rate is initially high and adapts to an approximate steady state by approximately 100 ms, similar to the general response pattern reported with acoustic stimulation. The temporal pattern of the high-rate response undergoes a significant transition within the first 50 ms of high-rate presentation. Within the first 20 ms, an oscillating pattern is observed that is presumably driven by the refractory properties of the fiber. After that initial period, no clear peaks are observed in the histogram, suggesting a less deterministic, more stochastic, pattern of the underlying response. The second plot of Figure 2 is a PST histogram of the response to the probe (i.e., a 250 pps train starting at 200 ms with a duration of 300 ms). The responses show clear phase-locking to the stimulus period. The third plot is a histogram of the responses to the combined stimulus, the high-rate masker followed by the low-rate

probe. As expected, the response to the high-rate masker is similar to that shown in the top plot. The response to the probe pulse train still shows clear phase-locking to the 250 pps stimulus but the rate is significantly decreased due to the effects of the masker. The decrease in responsiveness and the time course of subsequent recovery over the duration of the 300 ms probe pulse train are of primary interest in this study.

To quantify these interaction effects, we have analyzed the data for six different 20-ms windows across the stimulus presentation. These intervals are centered at 10, 110, 210, 260, 310 and 490 ms after onset of the high-rate train, as shown at the bottom of Figure 2. They were chosen to sample activity during the masker as well at various points along the probe pulse train, so that both high-rate effects and the recovery time course could be evaluated. Note that the three stimuli are defined as shown in Figure 2. Thus, "Stimulus 2" of Figure 2 describes a stimulus that consists of an initial silent period of 200 ms duration, followed by the low-rate electric train.

Results of such analyses are shown in Figure 3. Each of the six graphs of the figure presents responses from a different fiber and they show the generally consistent pattern of activity that is evident in our data. The open circles in each plot represent the discharge rates over each 20 ms analysis window to the high-rate masker stimulus alone. The filled circles indicate responses to the low-rate probe, and the filled triangles show the responses to the combined stimuli. The effect of the masker on the probe pulses can be appreciated by comparing the triangles to filled circles at each analysis interval. The masker effect is greatest at probe onset (200 ms) and decreases over the probe interval. In general we see clear effects of the masker over the first 100 ms but in most cases the effects are diminished by end of the probe pulse train (300 ms after masker offset, corresponding to the 500 ms point of Figure 3).

In most cases, we adjusted the level of the high-rate masker such that it would evoke a high rate of response during the first analysis interval. This was done on the presumption that interaction effects would be maximal for conditions in which the high-rate masker evoked a significant neural response. In five of the six cases shown in Figure 3, that is the case, as can be seen by examining the functions plotted with open circles. However, we noted that significant "masker" effects were elicited at masker levels that were minimally effective (if at all) in eliciting a response. Notably, in the remaining case (fiber D51-1-2) there is no significant response to the masker, but the response to the probe is still decreased. While this was not observed in many cases, it was not an isolated instance, as will be seen in subsequent plots (such as those shown in Figures 8 and 9, below).

Fibers that were held for substantial time periods provided us with the ability to explore the effects of stimulus level. Figure 4 illustrates results from one fiber for which the probe level was held constant while the masker level was systematically varied. The format of the plots of Figure 4 is the same as those shown in Figure 3. Each of the five graphs shows the responses obtained for a different masker level, as indicated in the each case. The upper panels, with relatively low masker levels, show little effect of the high rate masker stimulus on the probe response. This is again seen by comparing the filled

triangles to the filled circles. The lower panels, with higher masker levels, show significant decreases in the probe response rate during the first 100 ms after probe onset.

To more clearly illustrate the effects of stimulus level, we examined the ratios of the response rates obtained with and without the masker for the first three analysis windows that occur *after* the probe onset (i.e., intervals 3, 4, and 5, corresponding to the analysis time epochs centered at 210, 260 and 310 ms). Figure 5 plots these rate ratios as a function of the high-rate masker level for 6 fibers from which data were obtained at three to five different masker levels. The trends are generally consistent across all the fibers. Interval 3, immediately after masker offset, tends to have the smallest ratio (i.e., the greatest decrement) and the Interval 5 ratios tends to show smaller effects. Thus, as masker level is increased, the ratio for all intervals tends to decrease, showing greater adaptation.

Additionally, we have collected data from several fibers in which the masker level was fixed and the probe level was varied. Figure 6 illustrates data from 4 fibers which generally show consistent across-fiber trends. While interval 3 is still characterized by smaller ratios (i.e., greater decrements), the spike ratios demonstrate clear increases with increases in probe level.

We have also obtained measures from fibers in which the masker and probe levels were co-varied. The analysis of data from two fibers from which such data were obtained is shown in Figure 7. In both cases, we observed an increase in the spike ratio (smaller decrement) with increasing overall current level. While more data is clearly needed to adequately describe this trend, this initial analysis suggests that the effect of probe level tends to dominate the response when masker level and probe level are co-varied.

As we have seen, the effects of the electric masker tended to be greatest at relatively higher current levels, that is, at conditions in which the response to the masker was greatest. However, we also noted that, in some cases, the high-rate masker could exert effects on the low-rate probe even at levels at which the high-rate stimulus elicited little or no response. One case was noted in Figure 3 (D51-1-2). Detailed histograms, constructed using finer (100 μs) bin widths, are shown for this fiber for two masker levels in Figure 8. These plots show the response to the probe alone in (shown in the colored bars) superimposed on the response to the "masker+probe" condition (black bars) for easy comparison. In these cases, the masker levels are relatively low and there is no detectable response during the masker interval (0-200 ms). Nevertheless, there is significant decrease in the response to the probe at the lower level and a greater decrement when the masker level is increased.

A more detailed examination of another fiber with "sub-threshold" masker effects is shown in Figure 9. In this case, we recorded responses for a wider range of masker levels. Only the highest-level masker (bottom plot, Figure 9) elicited a significant response to the masker. However, even at that level, the response to the masker is characterized by relatively fast adaptation so that activity is limited to within the first 50 ms after onset of the masker pulse train. For each masker level, we observed significant

decreases in the response to the probe. That effect tended to be greater with increasing masker level despite the lack of response to the masker. Such data suggest that the effect of the masker may be due, at least in part, to sub-threshold effects of electrical stimulation on the neuronal membranes unrelated to action potential generation.

Finally, although the primary effect of the masker on the probe response that we have observed is that of a decreased response rate, in some cases, we have observed responses to the probe that were enhanced by the presentation of the "masker". Figure 10 illustrates histograms in response to two levels of masker. In both cases, the response to the probe, particularly near probe onset, is greater than that without the masker. The mechanism of such an effect is not clear. Nevertheless, we stress that the stimulus paradigm is such that the presentations of the stimuli with or without the masker are interleaved so that differences in the responses shown in Figure 10 are not likely due to a cumulative effect or change in the state of the fiber over time.

2.7 Discussion

This report demonstrates effects of high-rate electric stimulation on the response to low-rate probe qualitatively similar to those that we have reported earlier with acoustic noise stimulation. Further analyses will attempt more specific quantitative comparisons between response adaptation patterns after acoustic and electric stimulation.

The responses to the high-rate pulse train show a similar pattern of adaptation to that of acoustic noise bursts in that the pattern is dominated by a fast component that demonstrates a relatively large degree of adaptation. Preliminary analyses of the time course of adaptation to the masker pulse train have shown that a "two exponential" fit — similar to that reported by Westerman and Smith (1984) — adequately describes the adaptation time course. Analyses of the low-rate probe pulse train generally show a slower time course and can typically be fit with a single, decreasing exponential function. More detailed analyses will be reported in a future progress report.

In earlier QPR's, we noted decreases in single-fiber responsiveness to electrical pulse trains after (acoustic) noise presentation. That decrease in responsiveness was sometimes accompanied by decreases in spike jitter. We have suggested that non-monotonic ECAP recovery after noise offset may be due to differences in the recovery time course of these two properties. The data presented here with electric maskers shows clear adaptation and recovery of responsiveness (spike rate) after electric masker offset. Preliminary analyses of these data with electric maskers have not, however, shown evidence of decreased jitter in many fibers. In earlier acoustic masking data, the degree of jitter reduction was found to be dependent upon the fiber's spontaneous rate. In these data several of the subjects were deafened and spontaneous activity was not evident and consequently one may expect less effect on jitter in those cases. Further analyses of deafened vs. hearing ears and effects of spontaneous activity will be conducted to evaluate the effects on jitter with electric maskers. Such comparisons will provide additional insight regarding the mechanisms involved in both "hybrid" ears and deaf ears that are stimulated electrically.

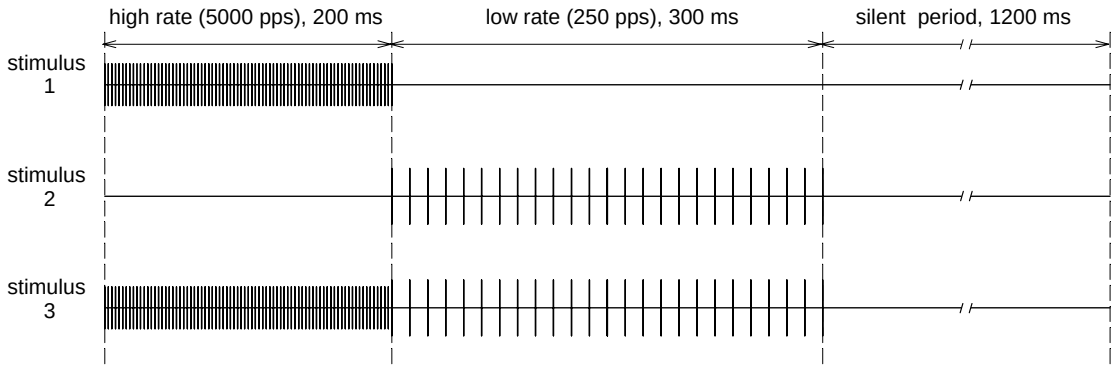

Figure 1. Schematic of the stimuli used in data collection for this report. The three stimuli were interleaved during data collection to prevent any cumulative effects from biasing the results of one type of stimulus presentation.

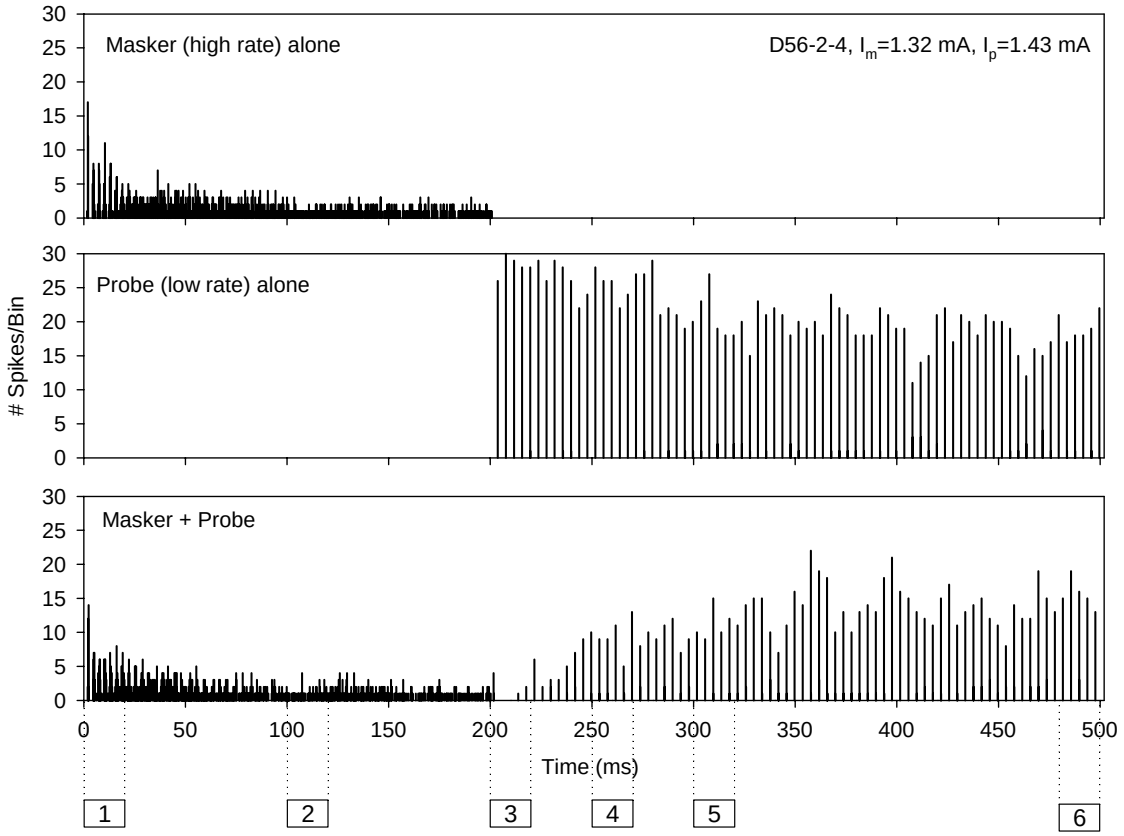

Figure 2. PST histograms in response to each of the three stimuli shown in Figure 1us (see Figure 1) are shown as indicated on each panel. Number of spikes in each 100 us bin are indicated as a function of time after stimulus onset. Twenty-ms intervals for further analysis (Figures 3-7), labeled 1 through 6, are indicated below the plot.

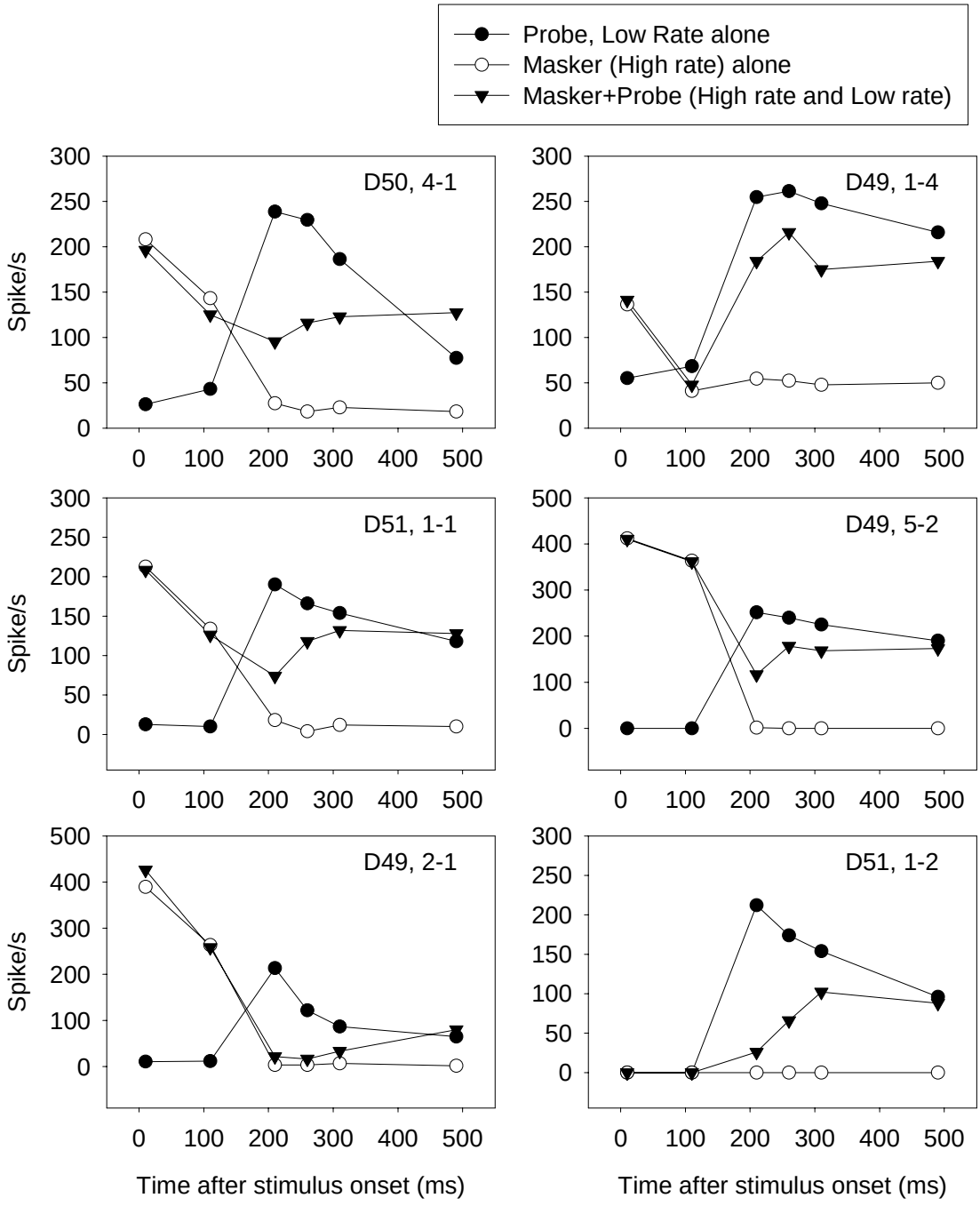

Figure 3. Spike rate is plotted for each of six 20 ms analysis windows (as indicated in Figure 2). Each panel presents data from a different fiber (animal number and fiber number are indicated). In each plot, the response to the probe alone, masker alone and combined stimuli are plotted separately (See legend at the top of the figure).

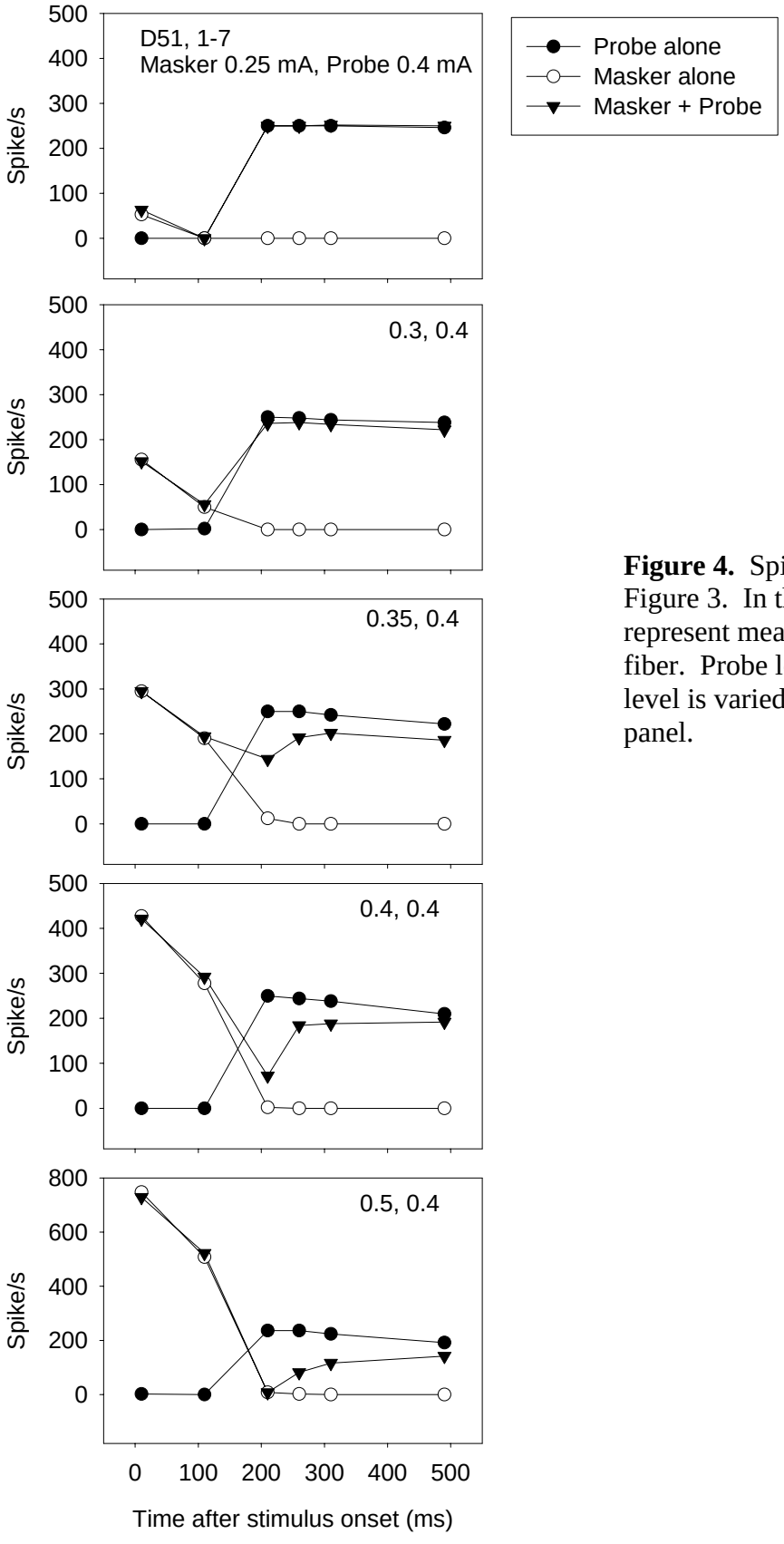

Figure 4. Spike rate is plotted as in Figure 3. In this figure all panels represent measurements from the same fiber. Probe level is fixed and masker level is varied as indicated in each panel.

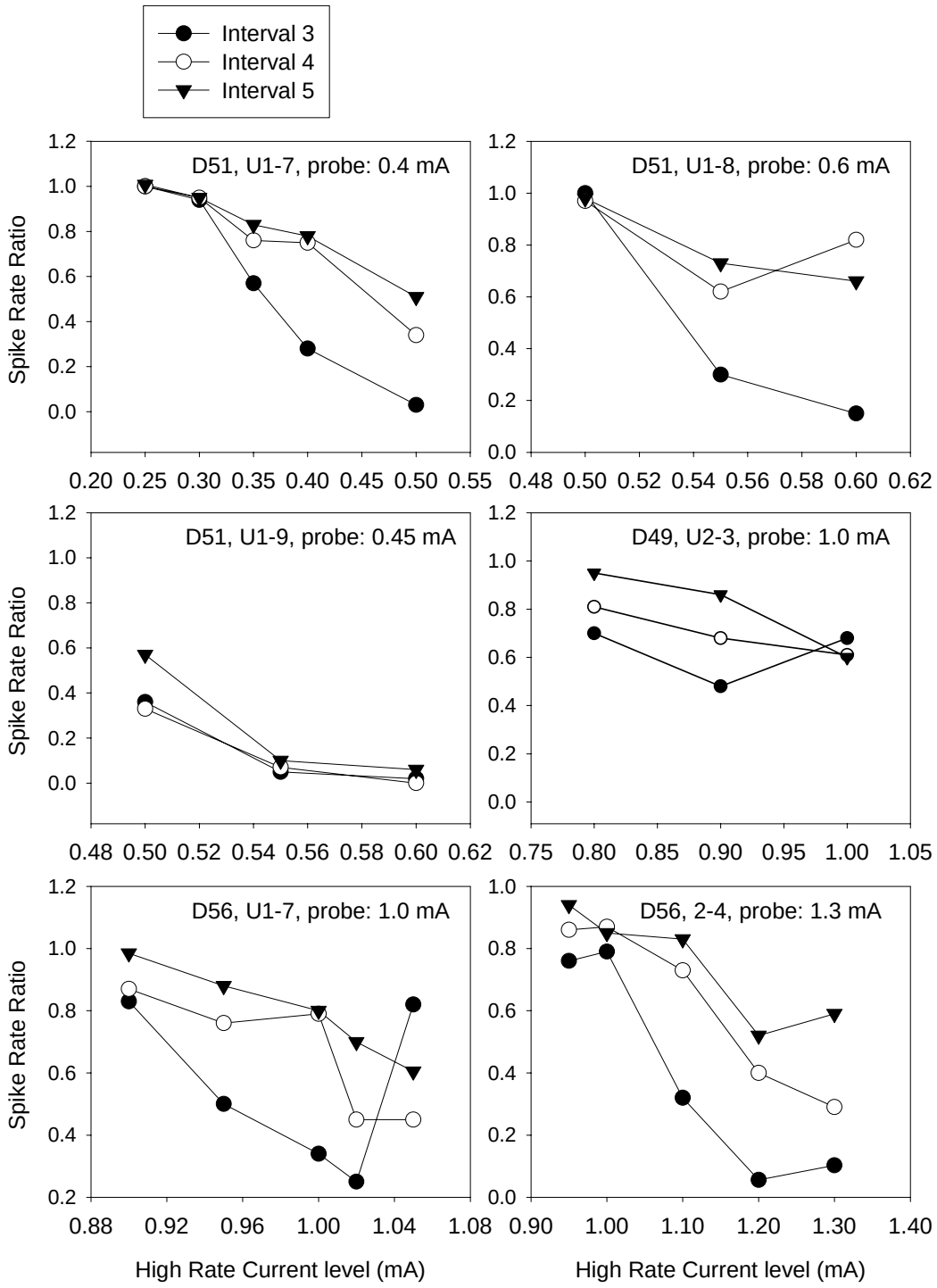

Figure 5. Spike rate ratio (with masker/without masker) in the three intervals following probe onset are plotted as a function of masker level (210, 260, 310 ms). Each panel represents data from a different fiber. In each case probe level is constant and is indicated on the panel.

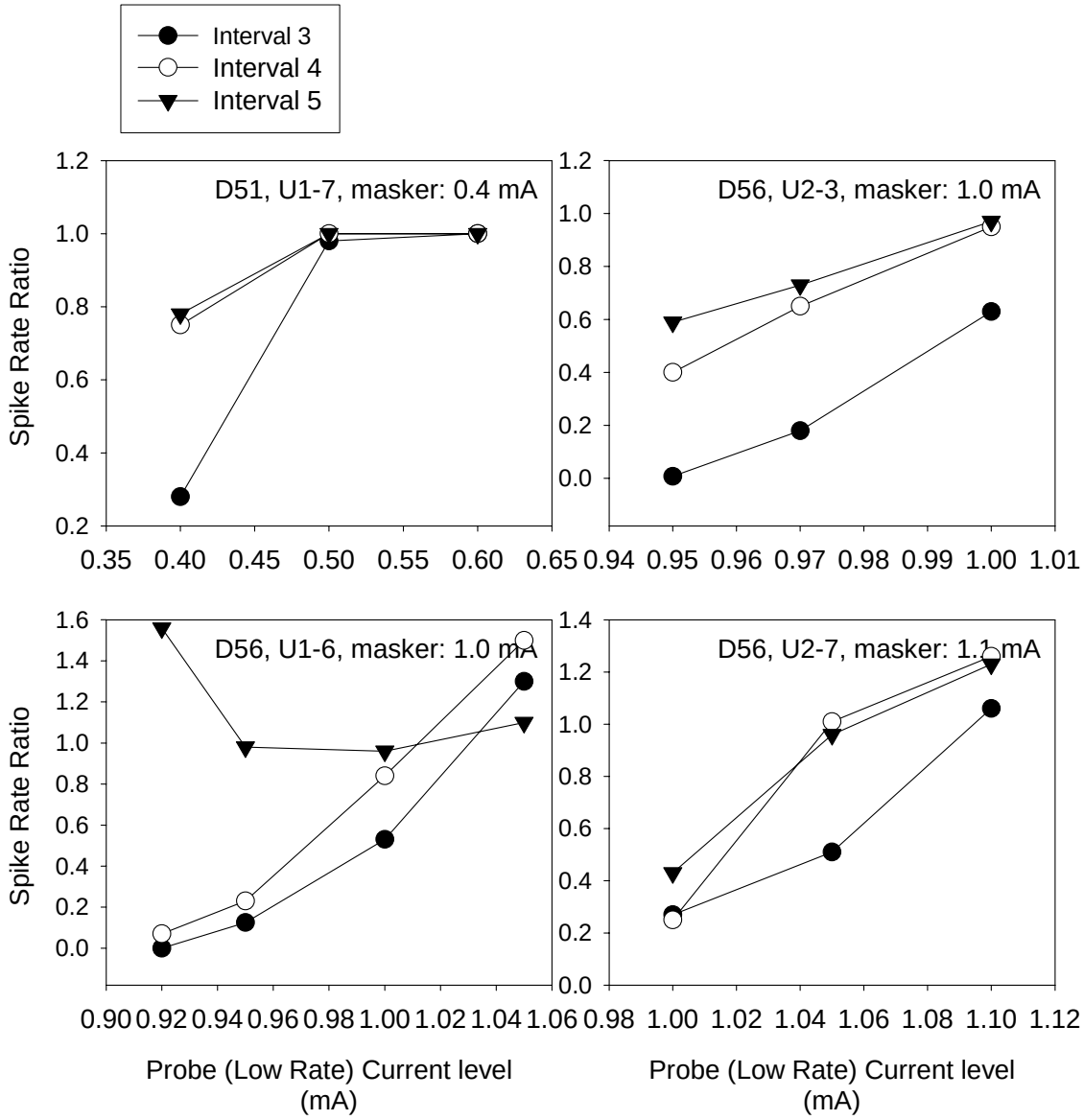

Figure 6. Same as Figure 5 except that masker level is fixed, as indicated on each panel, and probe level is varied.

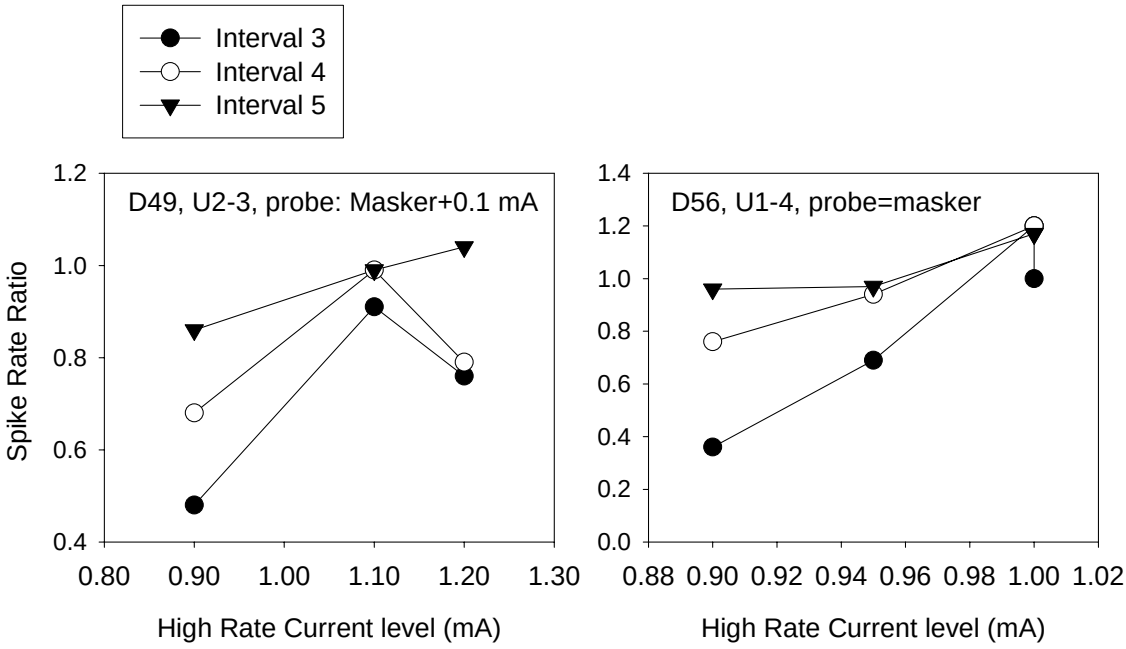

Figure 7. Same as Figure 5, except that masker and probe are fixed relative to each other and overall level is varied. In each panel, the probe level relative to masker level is indicated.

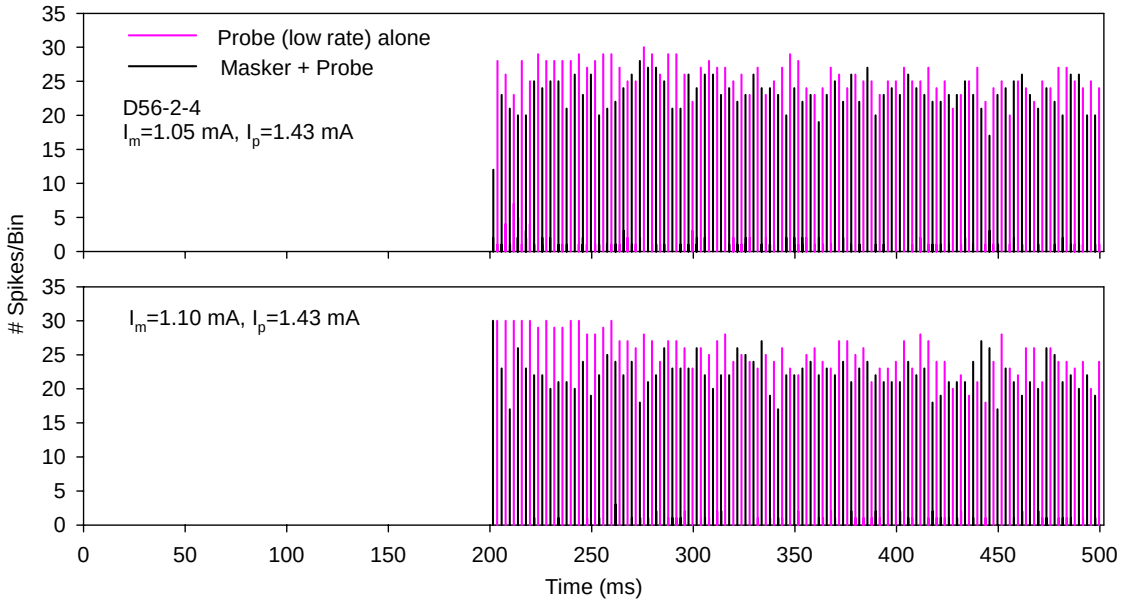

Figure 8 PST histograms are plotted for two stimulus conditions: probe alone (pink) and masker+probe (black). This fiber illustrates a case where there is significant decrease in the response to the probe where there is no significant response to the masker.

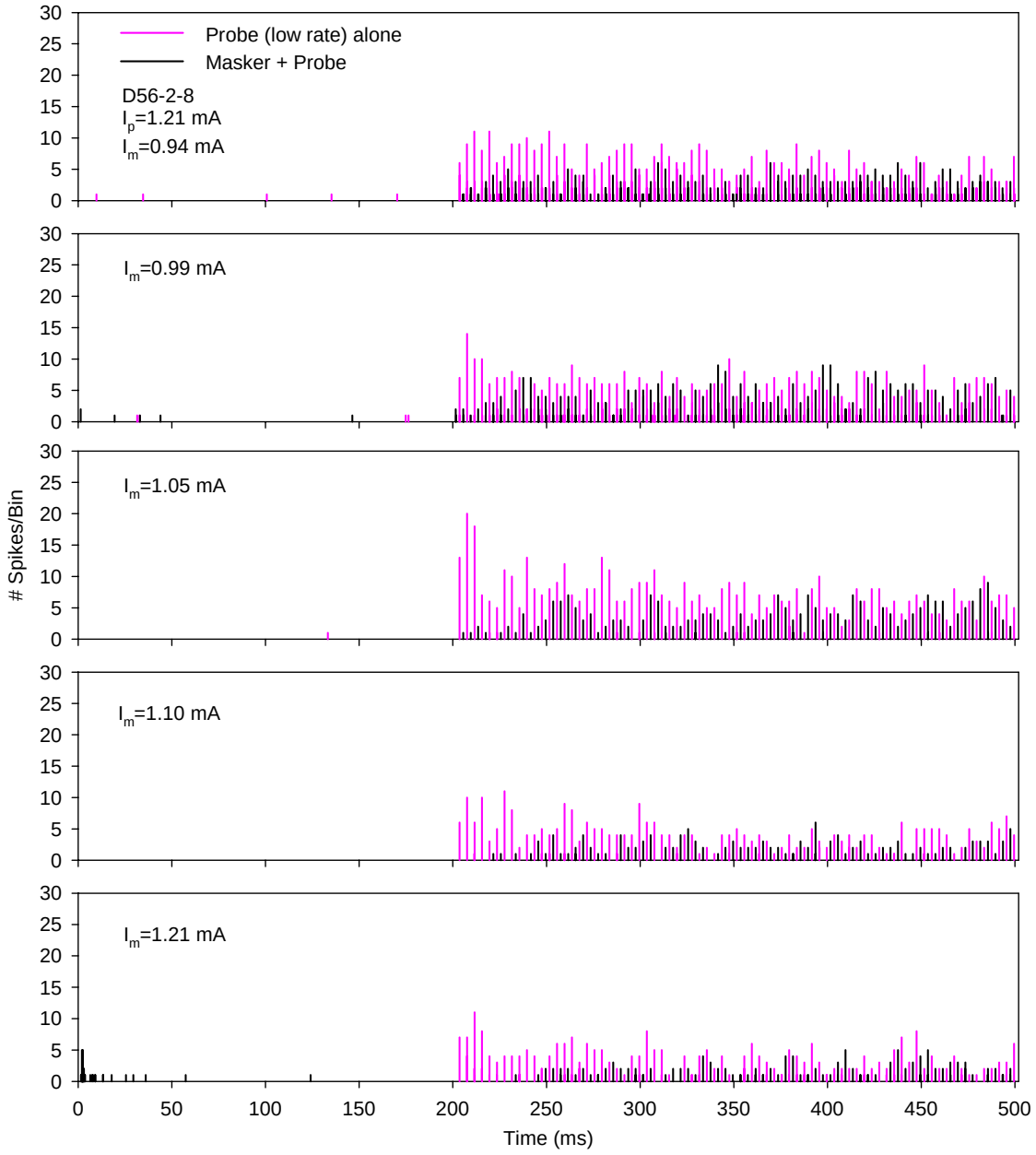

Figure 9 PST histograms are plotted for two stimulus conditions: probe alone (pink) and masker+probe (black). Each panel represents data for a different masker level as indicated; probe level is fixed at 1.21 mA.

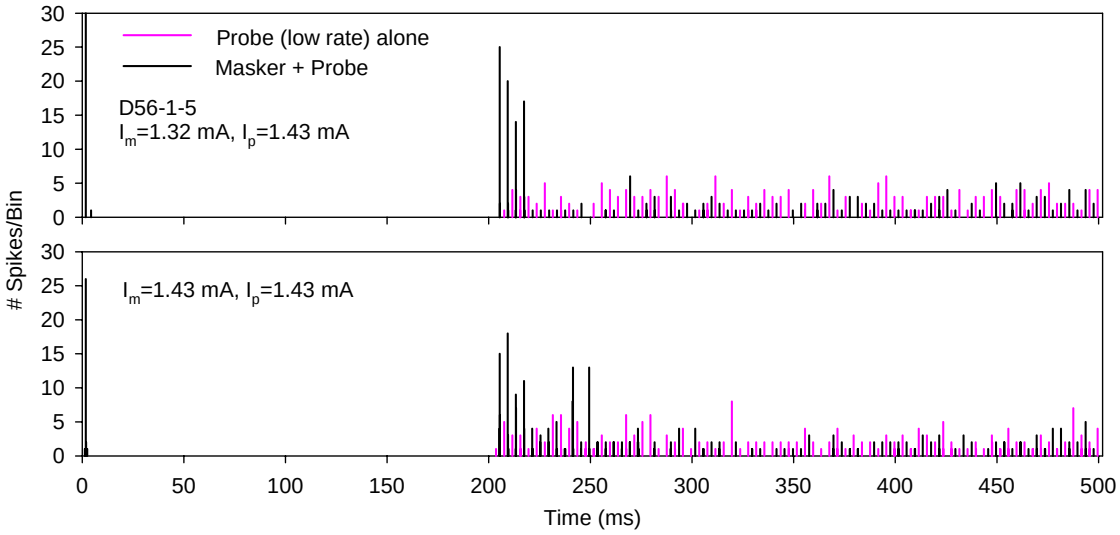

Figure 10 PST histograms are plotted for two stimulus conditions: probe alone (pink) and masker+probe (black). This fiber illustrates a case where there is an enhanced response to the probe after masker offset.

2.8 References

1. **Litvak, L.M., Smith, Z.M., Delgutte, B., Eddington, D.K. (2003).** Desynchronization of electrically evoked auditory-nerve activity by high-frequency pulse trains of long duration. *J. Acoust. Soc. Am.* 114(4):2066-78.

2. **Miller, C.A., Robinson, B.K., Abbas, P.J., Nourski, K.V., Jeng, F.C. (2005).** Effects of remaining hair cells on cochlear implant function, 12th Quarterly Progress Report, *Neural Prosthesis Program contract N01-DC-2-1005 NIH*.

3. **Nourski, K.V., Abbas, P.J., Miller, C.A., Robinson, B.K., Jeng, F.C. (2005a).** Effects of acoustic noise on the auditory nerve compound action potentials evoked by electric pulse trains. *Hear. Res.* 202:141-153.

4. **Nourski, K.V., Abbas, P.J., Miller, C.A., Robinson, B.K., Jeng, F.C. (2005b).** Effects of remaining hair cells on cochlear implant function, 13th Quarterly Progress Report, *Neural Prosthesis Program contract N01-DC-2-1005 NIH*.

5. **Westerman, L.A., Smith, R.L. (1984).** Rapid and short-term adaptation in auditory nerve responses. Hear. Res. 15(1-2):249-260.

4. Plans for the next quarter

Activities to be conducted in the 15th quarter include:

1. Continuation of both off-line analysis and further data collection of single-unit responses for experiments involving electric adaptation and recovery.

2. Conduct additional single-fiber experiments to obtain more information on possible relationships among single fiber properties (best frequency, spontaneous rate, etc.) and the nature of acoustic-electric interactions. Specifically, we wish to collect sufficient best-frequency information to address the question of whether or not the nature of the acoustic-electric interactions varies systematically with fiber-to-electrode distance. One such interaction of interest is the observed enhanced electric responses reported in this QPR.

3. Preparation of a second manuscript on the single-fiber responses to acoustic noise and electric pulse trains. This manuscript will specifically examine interactions with an emphasis on interpreting the ECAP in terms of observed single-fiber properties.

4. Present material related to this contract at the 2006 ARO Midwinter meeting in Baltimore, MD.

5. Present material related to this contract by invitation to a symposium sponsored by Cochlear Corporation (March 17-19).

6. Further development of the computational model examining the relationship between ECAP and single-unit measures.