Sixth Quarterly Progress Report

November 1, 2007 to January 31, 2008
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Neurophysiological Studies of Electrical Stimulation for the Vestibular Nerve

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Implantation of vestibular prostheses:

At the end of Quarter 5, 2007, we implanted the first rhesus monkey with a nerve stimulation and recording chamber and began single unit recording mapping studies of the vestibular nerve as it passes under the flocculus. These studies have been ongoing in our laboratory during Quarter 6. The aim of these recording studies is to identify an ideal location for implantation of a prototype vestibular stimulating electrode in the vestibular nerve. While these studies will be a focus of our next Quarterly progress report, we focus here on the implantation and stimulation studies for our prototype vestibular prosthesis in the vestibular end organ.

In quarter 6, we implanted a second rhesus monkey with a prototype vestibular prosthesis in the vestibular end organ. This animal, a rhesus macaque, had already been behaviorally trained for vestibular research and had eye coils and an appropriate connector surgically placed under a separate general anesthesia from the vestibular implant surgery. Because our goal is to assess and minimize the impact of the implantation on native vestibular function, as well as determine the effects of electrical stimulation, only one of the three electrode arrays of our implant was placed into the labyrinth. This array was placed into the lateral semicircular canal as far from the ampulla as possible. "Soft-surgery" was performed, making a labyrinthotomy so as to preserve the membranous canal, borrowing techniques learned from Hybrid cochlear implant surgery in humans. The array was inserted within the bony semicircular canal attempting to avoid compression or injury to the membranous canal. The labyrinthotomy was sealed using temporalis fascia. The receiver/stimulator and ball ground electrode were placed underneath the temporalis muscle superior to the external auditory canal. The two other electrode arrays were placed within the mastoidectomy cavity where they could potentially be used during any revision surgery. Intraoperative testing of the device demonstrated similar electrode impedances of about 15-16 kOhms for the three intralabyrinthine electrodes and the six extralabyrinthine electrodes, with the exception of electrode 6 (18 kOhm), which was deepest into the lateral semicircular canal (Figure 1).

The time required for this first surgery was a little over four hours. With further experience, it is expected that all three canals could be implanted in a rhesus monkey or human subject in under two hours. The animal was eating again two hours postoperatively, and did not show signs of nausea or vomiting that would be expected after an ablative vestibular procedure. Indeed, by the next day there were no signs of any abnormalities and at one month the vestibulo-ocular reflex (VOR) was normal (see below). Electrode impedances were measured again one month postoperatively and had changed dramatically (Figure 2). The extralabyrinthine electrodes were all in the 13-20 kOhm range but the intralabyrinthine electrode impedances had climbed to 23-29 kOhm consistent with being sealed in a small bony semicircular canal. Such changes in electrode impedance are well described after cochlear implants but are particularly dramatic here due to the extremely small size of our vestibular implant's electrode contacts.

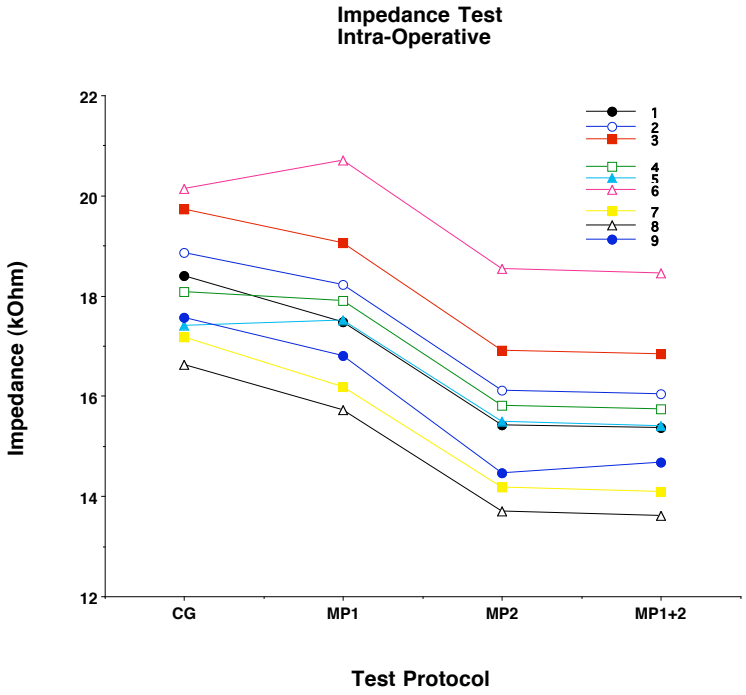

Figure 1: Intraoperative electrode impedance measurement. Electrodes 1,2,3,7,8,9 are in the mastoid cavity and Electrodes 4,5,6 are in the lateral semicircular canal. Impedance is measured relative to four different ground electrode montages. MP1+2 uses the case and ball ground together. These measurements are made with standard clinical cochlear implant software from Cochlear Corporation.

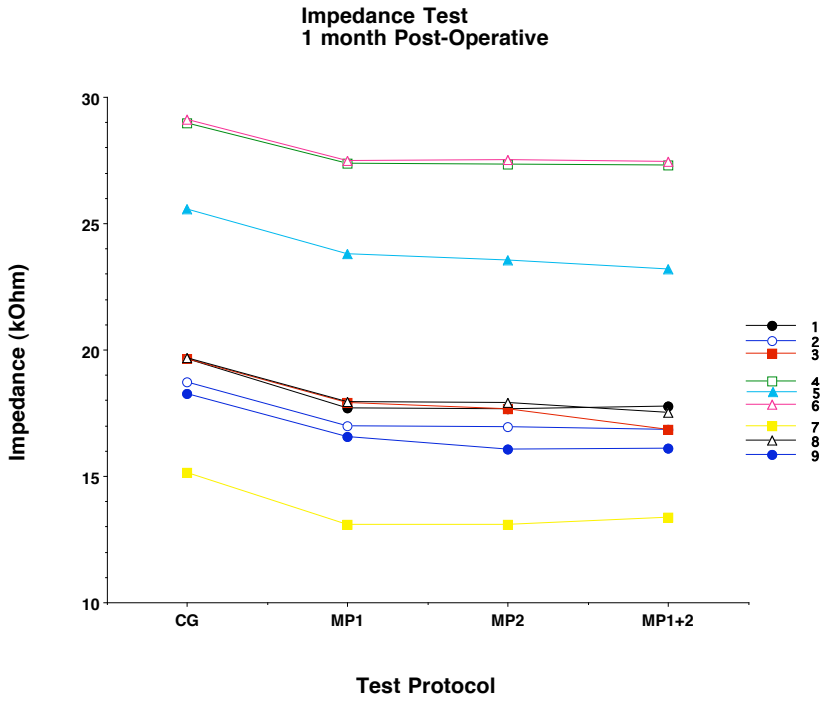

Figure 2: One month postoperative electrode impedance measurement. Impedances of most electrodes had increased, but particularly the intralabyrinthine ones (electrodes 4,5,6).

Current source compliance

The high impedances of our electrodes raised concerns about the feasibility of driving sufficient current to evoke physiologic responses. Given the 10 V supply voltage of the Cochlear device, in theory 400 µA can be driven into a 25 kOhm load. However these devices cannot always provide the predicted current. Due to the hardware compliance limitation, we were unsure whether the stimulation current source could still deliver the required current at this high electrode impedance. We measured the actual current output by connecting a 24.7 kOhm resistor between electrode 6 and the ground electrode in the implant-in-a-box. The pulse rate was set to 400 pulses/sec and the pulse width was at 100 µs. Figure 3 shows the relationship between the actual current measure and the ideal current output. A linear relationship was found from 20 µA up to 340 µA and then it became saturated after 360 µA. This measurement gives us useful information in choosing the appropriate current levels of electrical stimulation. 340 µA was therefore chosen as the upper current limit we demanded of the device during our initial stimulation experiments. Based on the surface area of our electrodes, such currents can be safely delivered chronically for the phase durations with which we are working. We could increase pulse width to overcome the hardware compliance limitation.

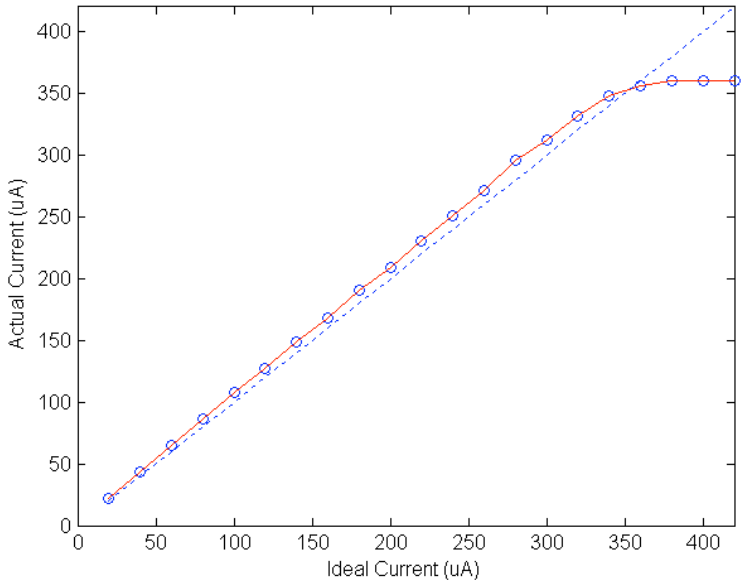

Figure 3 Actual current versus ideal current using our electrode impedances and the implant in a box.

Five weeks postoperatively we began studies of activating eye movement behavior with the device *in vivo*. This was done using an L34 research signal processor from Cochlear Corporation driven by custom software described in previous quarterly reports. The laboratory interface we created provides a wide variety of options for stimulating the vestibular periphery with an array of modulated biphasic pulse trains. Both frequency and amplitude modulation, with detailed control over pulse shape are available. Monopolar, bipolar or common-ground electrode montages are possible as well as control over pulse width, pulse rate and size of the interphase gap in the biphasic stimulus. This

stimulus interface is linked to our eye-movement recording system, as well as a single-unit and multi-unit electrophysiological recording system so that short latency brainstem single-unit, and eye-movement responses driven by the stimulus can be obtained.

Stimulation interface

To improve interfacing of the vestibular implant processor with the Spike2 data acquisition system, we revised the stimulation software, VIStream (described in Quarter 3), to work in either one of two triggering modes. The output trigger mode is intended for "free running" of the implant, such that the timing of the pulse trains is determined by the inter-stimulus interval set in the software. In this mode, one or more pulse trains are loaded onto the processor buffer via the research interface and stimulation begins as soon as the processor is ready. When the first pulse is generated, the research interface delivers a TTL pulse to the Spike2 system. This mode is useful for stimulation made when the animal is in the dark and its eye movement behavior is not important. The input trigger mode, on the other hand, is necessary for behaviorally controlled stimulation. In this case, the pulse train sequence is loaded onto the buffer but the stimulation does not occur until a TTL trigger is detected by the research interface. The TTL pulse is sent by the Spike2 software, usually in response to a behaviorally-relevant event, such as a saccade correctly made by the animal to a visual target. With this mode, the visual target can be turned off just prior to stimulation.

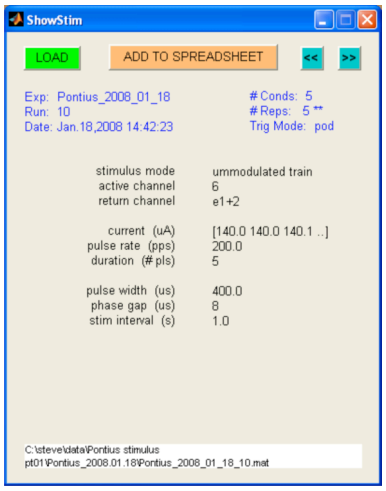

Figure 4. Graphical user interface for creation of a stimulation spreadsheet from Matlab data files.

Some changes have been made to accommodate data recording and analysis. We added a saving function to the VIstream control software. All stimulus parameters, as well as the real pulse sequence for each trial, were saved automatically to a Matlab data file. A time stamp is also saved in the file, allowing the stimulus information to be coordinated with the behavioral and neural data contained in separate Spike2 files. The stimulation parameters can also be exported to an Excel spreadsheet for rapid review of individual experiments. The graphic user interface for this function is displayed in figure 4.

Changes in electrode impedance during behavioral studies.

During our electrical stimulation studies we observed that there were significant reductions in the impedance of the stimulated electrode consequent to its repeated use. For example, during one experimental session we measured the electrode impedances before and after stimulation primarily through one of the electrodes (electrode 6) over the full recording session of one hour. Figure 5 displays a screen shot of the impedance test before (A) and after (B) the recording session. It shows that the impedance of electrode 6 dropped from 23.95 to 18.46 kOhm in the MP1+2 mode.

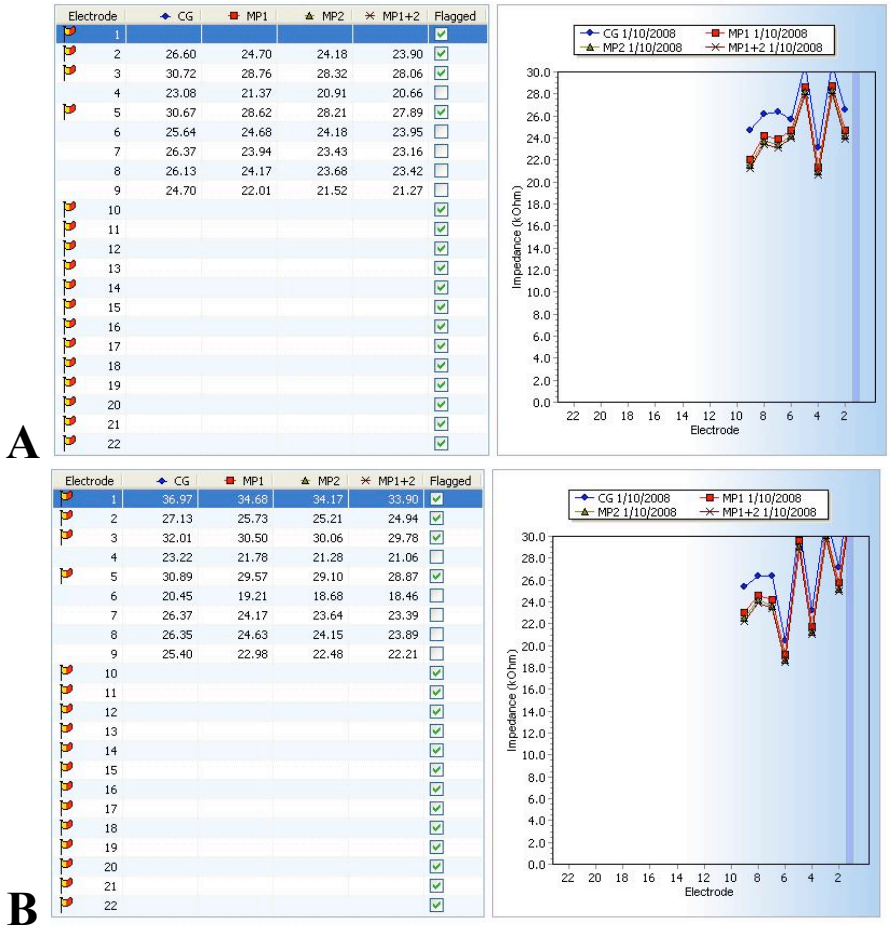

Figure 5. Screen shots of impedance testing of the vestibular prosthesis before (A) and after (B) a single recording session utilizing electrode 6.

Stimulation experiments to elicit eye movement behavior.

Our initial functional evaluation of the vestibular end organ prosthesis has utilized eye movement as the dependent measure for stimulation studies. Activation of the vestibular end organ should produce short latency activation of the extraocular muscles via the three neuron vestibular ocular reflex. This activation should produce eye movements that are time locked to the stimulation.

Data from our first stimulation experiments using the vestibular implant are shown in Figure 6. Activation of electrode 6, which was most deeply inserted in the lateral semicircular canal far from the ampulla, by a brief biphasic pulse-train burst consistently evokes eye-movements in both vertical and horizontal directions. This suggests that vertical and horizontal canal afferents are being activated due to current spread. Methods to control such spread of excitation will need to be developed for vestibular prostheses to successfully restore a functional vestibulo-ocular reflex. In the animal tested, the electrode was placed as far from the ampulla as possible so as to minimize potential loss of vestibular function. This distant placement likely increases spread of excitation, which could be minimized by placing the electrodes closer to the ampulla. The more focused excitation would come at the cost of greater risk to residual vestibular function, a problem that would not be a concern in treating a patient who already has profound vestibular loss.

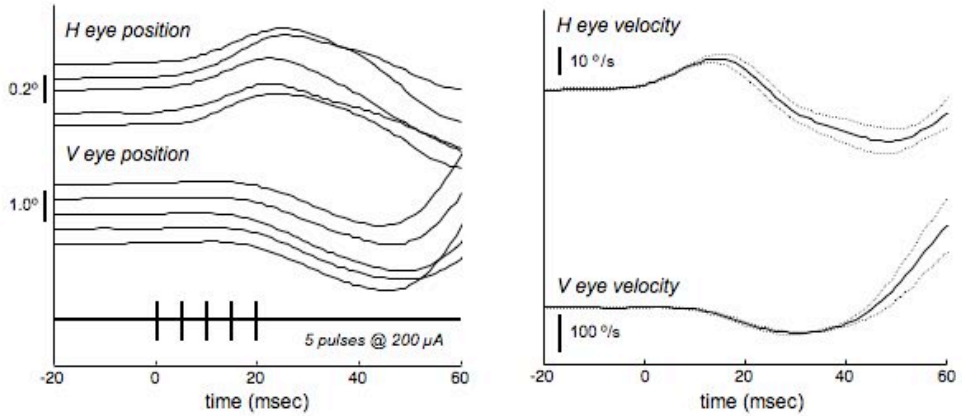

Figure 6: Short-latency eye movements in response to electrical stimulation of the lateral semicircular canal of a rhesus with the UW/Cochlear vestibular implant. Stimuli were five short pulse trains on electrode 6 with extralabyrinthine ground electrodes. The parameters were 200 µA, 5 pulses, 200 pps, 400 us/phase, and 8 us interphase gap. Each pulse train was triggered on the animal's behavior, such that a train occurred only if gaze was on target (a small spot of light) as the target moved from a 10 degree eccentric position to the center position (0 horizontal, 0 vertical). 200 ms prior to each pulse train the spot target was turned off. The current threshold for this channel was ~170 µA. The left panel displays horizontal and vertical eye positions for five consecutive trains that occurred 5-7 seconds apart. The traces are stacked top to bottom in temporal order. The lower trace is a schematic showing the timing of the stimulus. The right panel shows the average horizontal and vertical eye velocities (solid lines), bounded by +/- 1 standard deviation (dotted lines).

The stimulation parameters for eliciting eye movement were systematically explored in a series of experimental sessions. The stimuli used in these initial sessions ranged from single biphasic pulses, to short unmodulated pulse trains (<100 ms), to longer unmodulated and modulated trains (>1 s). The movements we elicited not only typically had a large vertical component, but also were often associated with a later eye blink or facial twitches at higher current intensities. This meant that the effective operational current range for the device was limited. At higher current intensities, the device probably stimulated the facial nerve.

Eye movements in response to pulse trains.

We initially stimulated with short trains of biphasic pulses, as exemplified above in figure 6. The standard stimulus consisted of 5 pulses spaced by 5 ms (i.e. at a rate of 200 pps). The pulses were 400 µs per phase, and the phases were separated by a short 8 µs gap to account for capacitive effects. Successive pulse trains were at least 5 seconds apart. Phase durations shorter than 400 us failed to produce observable eye movements, even at the maximum allowable current level (determined by the ~25 kOhm electrode impedance). Electrode 6 on the implant had the lowest threshold for activation of an eye movement response. Stimuli were typically applied to electrode 6 with both extracochlear sites (ECE1 and ECE2) acting as returns. Threshold for activation of eye movements was approximately 120 µA. We also measured channel 6 thresholds with current returning through the extracochlear returns separately (6 vs ECE1 or 6 vs ECE2). The thresholds were slightly higher, at 140 µA for both conditions. An example of the consistent eye movement responses to brief stimulus trains of increasing current intensity is shown in figure 7, which displays the result of stimulation of 5 pulses, 200 pps, 400 us/phase, and 8 us interphase gap. As the current intensity was increased, the amplitude of the movements also consistently increased.

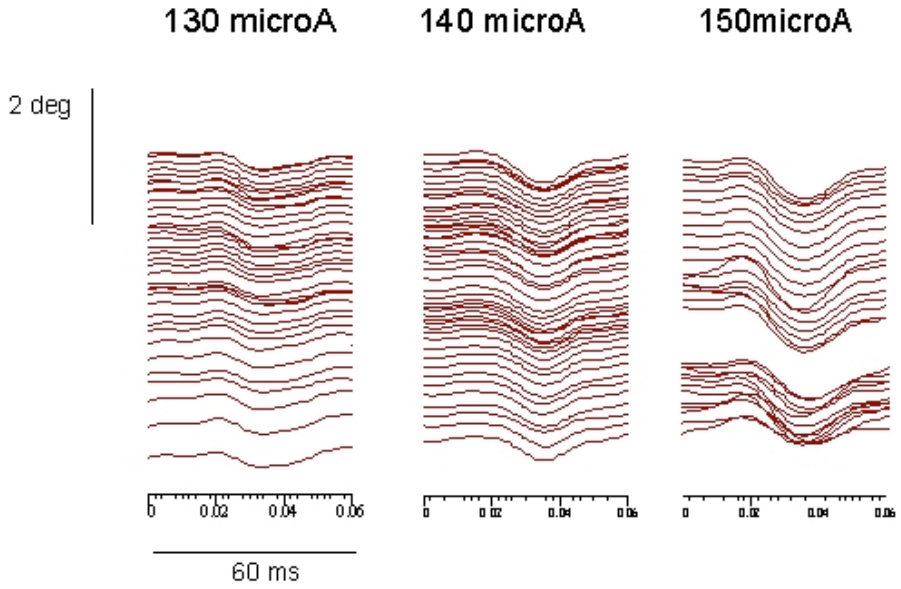

Figure 7. Vertical eye position rasters showing the result of stimulation with short pulse trains at different current intensities.

Longer stimulation trains in the dark at higher stimulus frequencies produced small eye movements that were time locked to the stimulus pulses superimposed on slow eye drift. Since the animal also displayed an intermittent slow drift in the dark, it was difficult to ascertain if the stimulation per se was producing the drift or merely evoking an underlying gaze instability. Figures 8 displays the result of stimulation of 500 pps, at 160uA for 5 seconds. Stimulus pulses were 400 us/phase with an 8 us gap. A nystagmus is present with superimposed twitches of very low amplitude.

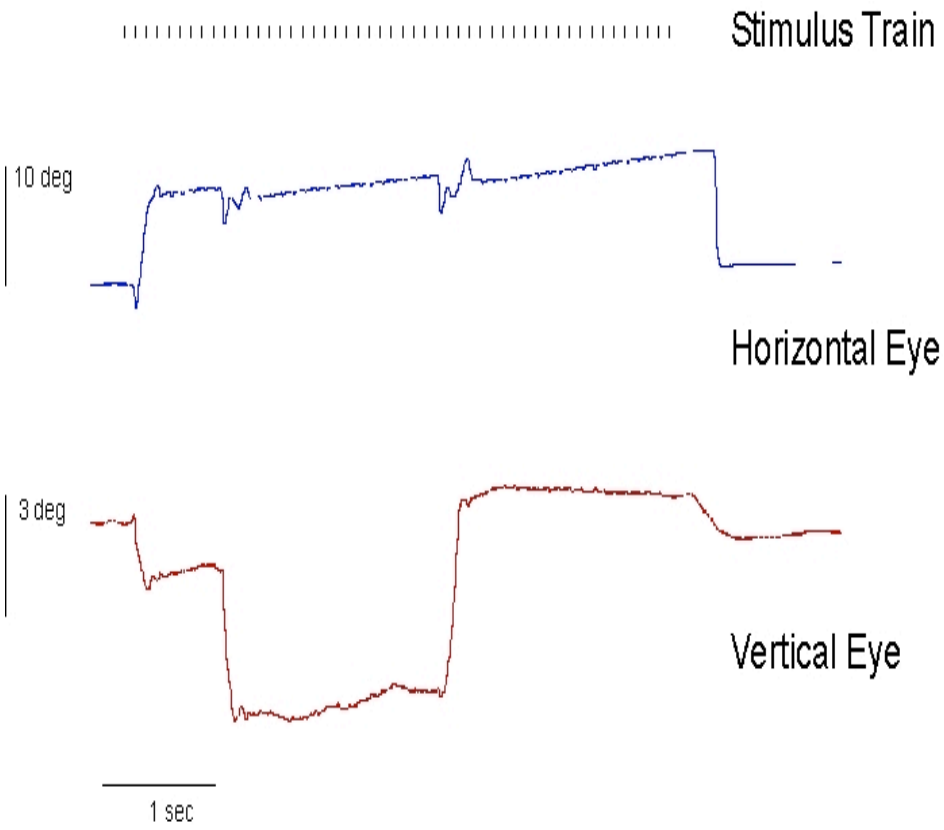

Figure 8. A stimulus train of 5 second duration elicits a horizontal nystagmus and small superimposed twitches (seen as an oscillation in the eye position trace during the stimulus train).

In addition, we also recorded eye movements in response to sinusoidal frequency modulated pulse trains. The results, shown in figure 9, demonstrate that sinusoidal stimulation can produce small amplitude, sinusoidally modulated, eye movements. For the trial shown, the stimulation used electrode 6 with ECE1+2 as return (both extra-cochlear electrodes). The stimulation rate was modulated between 10 and 80 pps at 1 Hz. The stimulus pulses were 180 μA and lasted 5 seconds; 400 us/phase and 8 us interphase gap. The visual target was turned off ~100 ms before the electrical pulses began, and turned on about 2 seconds after the pulses stopped. The stimulation produced small, primarily horizontal eye movements.

Facial movement in response to electrical stimulation.

Eye movement responses were obtained consistently on all days of testing, although the absolute threshold depended on the particular stimulus conditions employed. At higher current levels, stimulation also produced activation of the facial musculature. When this occurred, the stimulus current intensity was reduced. Facial movements were apparent on the video monitor as slight eye brow or jaw movements synchronized to the applied pulse trains. We continuously monitored the animal to make sure the stimulus presentations did not produce behavior that indicated distress. The facial movements did not distract the animal from tracking the visual target for a food reward. For the 200 pps 5-pulse trains on channel 6, facial movement thresholds

ranged between 170 and 200 μA across the multiple days of testing. Facial movements were not elicited with bipolar stimulation between channels 6 and 4 or channels 6 and 5, up to the maximum current tested (330 μA). This finding suggests that the electrical fields produced with bipolar stimulation are indeed restricted, but that monopolar stimulation produces current spread to the facial nerve at higher current levels.

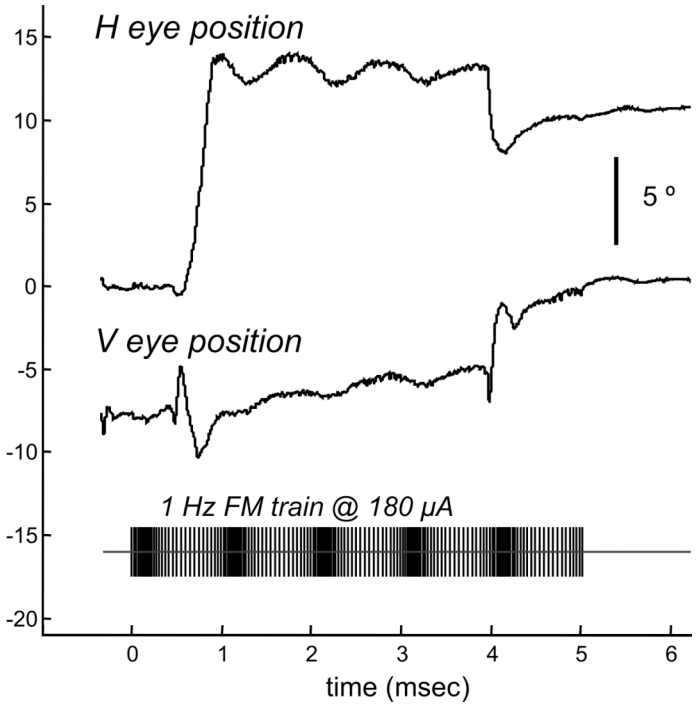

Figure 9. Sinusoidal eye movements elicited by sinusoidal frequency modulated stimulation at 180 μA.

Response to natural vestibular stimulation.

One of the objectives of the prosthesis design is to provide electrical stimulation of the vestibular end organ without impairing overall vestibular sensitivity to natural rotational stimuli. Since the animal had one unoperated ear, it was not possible to unambiguously define the rotational response of the implanted ear alone. However, we did study the overall vestibulo-ocular reflex (VOR) response of the animal to sinusoidal rotation across a range of stimulus frequencies and velocities. Figure 10 shows the response of the animal to this rotational stimulus more than 11 weeks following implantation of the vestibular prosthesis. In this animal, the VOR gain remained high across frequency, and the response showed a normal phase advance with decreasing frequency. When tested at chair velocities <5 deg/s, the gains remained above 0.6 at frequencies to 0.02 Hz.

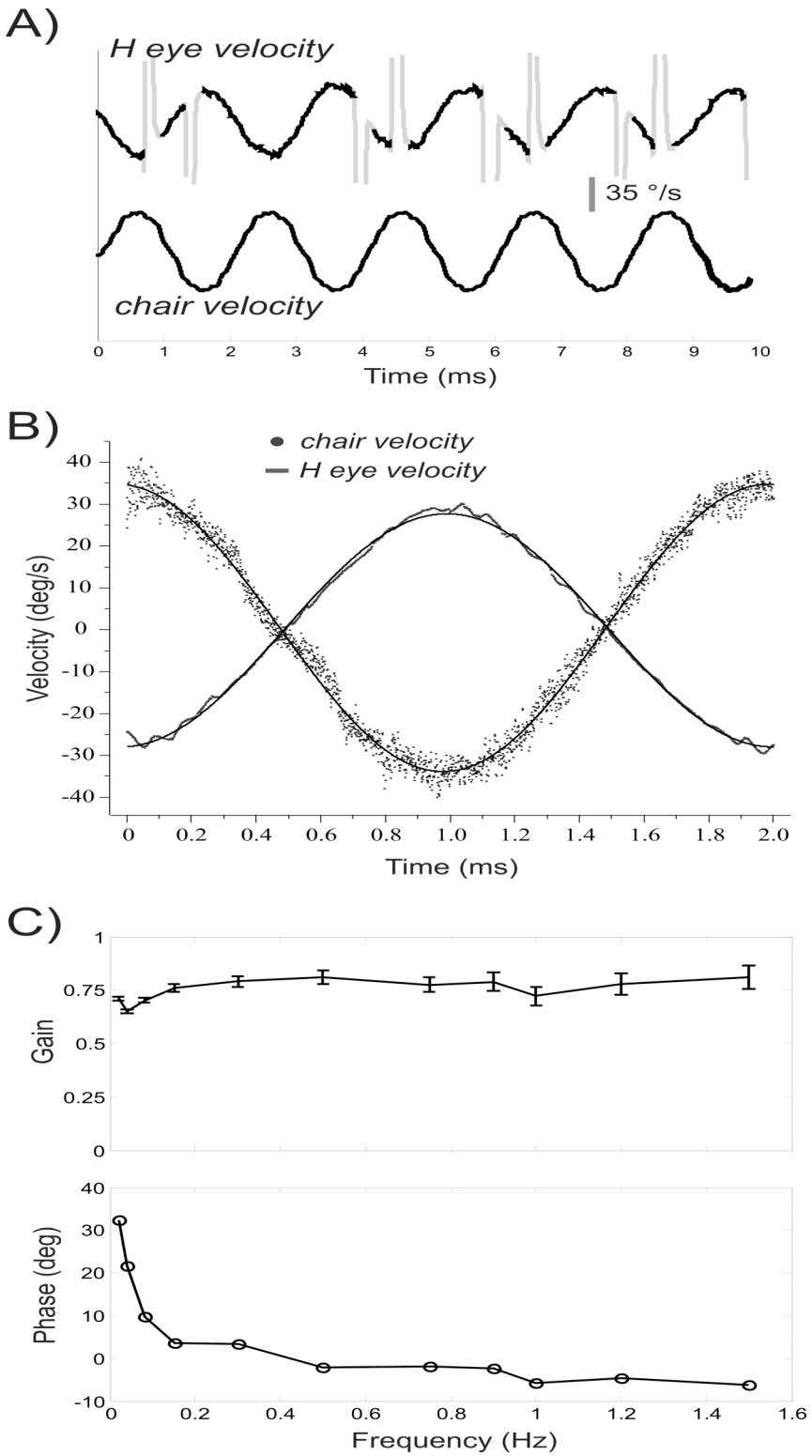

Figure 10. Vestibulo-ocular reflex (VOR) response to natural rotation in a rhesus monkey implanted with a vestibular prosthesis. (A) Several cycles of eye and chair velocity. (B) An expanded single cycle of eye and chair velocity. (C) Gain and phase of the VOR eye velocity versus the frequency of chair rotation.

Summary of progress in Quarter 6.

This quarter we have continued or initiated stimulation studies in two animals. We have successfully implanted a prototype vestibular prosthesis in the vestibular end organ. We have been able to elicit eye movements in response to stimulation using single stimuli, short trains (up to 5 pulses), longer stimulus trains, and frequency modulated stimulus trains. We have evaluated the current source compliance of the stimulation device. We have measured the impedance of the implanted electrodes at regular intervals, both before and after stimulation experiments. We have demonstrated that the VOR remains intact in an implanted animal. We have evaluated the stimulation parameters that produce an eye movement.

Challenges presented by our current results and our strategy for addressing them.

Our current results present two challenges that we will address in our continuing work.

First, our current thresholds for eliciting eye movement were too high with our first electrode placements. Moreover, there was only a very limited range of effective stimulation currents before current spread produced activation of the facial nerve. It also gives us a limited range of currents above threshold before we reached the calculated maximum current limit of the device. To address these issues we will perform a revision surgery in our current animal to reinsert the first electrode array closer to the ampulla of the lateral canal. In addition, we will implant an additional electrode array at a second, more distant, site in the lateral canal and an array in the inferior canal, close to the ampulla. We will also implant an additional animal with this electrode configuration during the next quarter, and we are training another animal for implantation later this year.

Second, the movements that we elicited were small and not in the plane of the lateral canal. Increasing the current did produce larger eye movements, but our ability to provide larger currents was limited by the issues described above. Also, increasing the stimulation current did not resolve the issue of the direction of the eye movements. To address these issues, we will attempt to insert the electrode array deeper into the bony labyrinth, so that practical bipolar stimulation may be possible. If we can limit current spread, and effectively stimulate an individual ampulla at lower currents, larger and more appropriately directed eye movements should result.