The Feasibility of an Intraneural Auditory Prosthesis Stimulating Electrode Array

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Abstract

The principle activities of the team during this reporting period were focused on 1) acute feline experiments to characterize the electrically evoked auditory brainstem response (eABR) evoked by currents injected directly into the cat auditory nerve, 2) acute experiments quantifying the extent of overlap of fibers excited by current injections through pairs of UEA electrodes implanted in auditory nerve, 3) metalizing the tips of the Utah Electrode Array (UEA) with iridium for chronic implantation and stimulation in cat auditory nerve, 4) implantation of iridium tipped UEAs and chronic stimulation of auditory cortex via portable 'back pack' stimulators in a chronically implanted cat.

1. INTRODUCTION

1.1. PROJECT GOALS

The goals of this contract have not changed, and are repeated here for continuity and completeness. This contract has three specific aims: 1) develop an array of microelectrodes that is suitable for implantation into the auditory nerve, 2) determine the functional potential for this technology to provide a useful sense of hearing, 3) evaluate the risks and benefits of this technology prior to human experimentation. Activities in the first year of this contract concentrate on validating our proposed technique for accessing the auditory nerve, estimating the dimensions of the arrays that can be implanted, and determining the spatial independence of the implanted electrodes. The second year will concentrate on other measures of the functional independence of the electrodes as well as the long-term biocompatibility of the array. The final year of the contract will finish the functional independence studies and center around the chronic electrical stimulation experiments.

1.2. PROGRESS REVIEW TO DATE

The review of progress to date is a cumulative log of results and findings from the beginning of the contract up to but not including this quarterly report.

Surgical Access: We have demonstrated a viable surgical access that allows placement of the Utah Electrode Array (UEA) into the feline auditory nerve. This allows us to use cats in our acute and chronic experimentation. We have also demonstrated a viable surgical access that allows insertion of the UEA into auditory nerve in cadaveric human temporal bones. These accesses should permit insertion of 20 electrodes in a 1.8mm x 2.2 mm array configuration (for 400 micron spaced electrodes), or 80 electrodes in a 200 micron spaced array.

eABR Electrophysiological Experiments: We have demonstrated that high velocity implantation of the UEA into the auditory nerve can be accomplished without significant injury to the nerve. This was demonstrated by recording electrically evoked auditory brainstem responses (eABR's) that were evoked by currents injected via a UEA that had been implanted into auditory nerve. Stimulation current thresholds for evoked eABR's

have been found to lie in 10μA-50μA range. We were able to record stable eABR's for up to 52 hours in one acutely implanted cat before the experiment was terminated.

Cortical Mapping Experiments: We have demonstrated that we are able to implant UEA's into cat auditory cortex, and that we are able to record single- and multi-unit responses to acoustic stimulation. In our six most recent experiments, we recorded acoustically evoked single- and multi-unit responses from an average of 69 of the 100 electrodes of the implanted array.

Measurements of auditory nerve dimensions in human cadaveric heads: We have measured the diameter of the auditory nerve using MRI measurements and compared these estimates with physical measurements of the same nerves. MRI estimates typically underestimate auditory nerve diameter by 32%.

Stimulation overlap: We have developed a technique by which we can estimate the extent of stimulation overlap in pairs of electrodes in arrays implanted into the auditory nerve. The technique uses paired sequential stimulation via two electrodes and monitoring of the eABR recorded with needle electrodes placed in the scalp. With short interstimulus intervals (the second stimulus is delivered within the refractory period of the nerve fibers excited by the first stimulus), stimulus overlap is reflected in the amplitude of the second eABR. We have seen some electrode pairs with virtually no stimulated fiber overlap, and others with considerable overlap.

Consequences of Chronic Stimulation: We have developed small, portable backpack stimulators that provide 'quasi' constant current stimulation of up to 16 electrodes. The stimulators are worn on a fabric backpack that the cats well tolerate. The stimulators are battery powered, lightweight, and provide 16 channels of stimulation per day. Interconnections (cables and connectors) between the stimulators and the animal, however, have proved to be problematic.

2. WORK PERFORMED DURING THIS REPORTING PERIOD

2.1. ANIMAL EXPERIMENTS

2.1.1 ACUTE EXPERIMENTATION

2.1.1.1 Characterization of eABR's evoked by stimulation via UEA's

Introductory Observations

Because of the initial successes we have enjoyed using eABR's to estimate the functional overlap of auditory nerve fibers accessed by the electrodes in implanted UEA's, we have expended additional effort at better characterizing the nature of the eABR's we are recording. Specifically, as the eABR is an evoked field potential recorded from the scalp with needle electrodes, we wished to document, as best possible, the nature of the components of the eABR responses we have recorded that were evoked by current injections via the UEA. This is particularly important as the kinetics and magnitudes of these potentials are affected by recording electrode placement, the degree of shunting by

the fluids surrounding the current injection sites and the eABR recording sites, the anesthetic status of the animals, and the filtering settings of our recording amplifiers.

Methods

The surgical details have been described elsewhere (Badi, Hillman et al. 2002), but are summarized as follows.

Animal preparation: Six cats were implanted with the UEA in the stimulation overlap experiments described herein. Principles of animal care were followed as outlined in the National Institutes of Health publication No. 86-23, revised 1985. Anesthesia was induced with Telazol®. The cats were intubated and placed under general anesthesia with 2%. Halothane. Animal status was observed by monitoring ECG, rectal temperatures, end-tidal CO_2, pulse oximetry, and non-invasive blood pressure. Body temperature was maintained with a water-filled thermostated blanket.

The cochlear nerve was exposed using a transbulla/transcochlear approach. The cat's bulla was exposed through a preauricular incision. The bulla was opened with a cutting burr and the promontory was exposed. A diamond drill was used to open the bone surrounding the round window and bony modiolus and the bone around the medial internal auditory canal was removed using an otologic pick.

The UEA was then prepared. Each electrode on the 3 x 4 array (12 electrodes) to be implanted was visually inspected and the impedance of each electrode was measured prior to insertion. The array was implanted using high-velocity pneumatic insertion (Rousche and Normann 1992). A preset travel distance of 1.0mm was selected to avoid implantation too deep into the nerve.

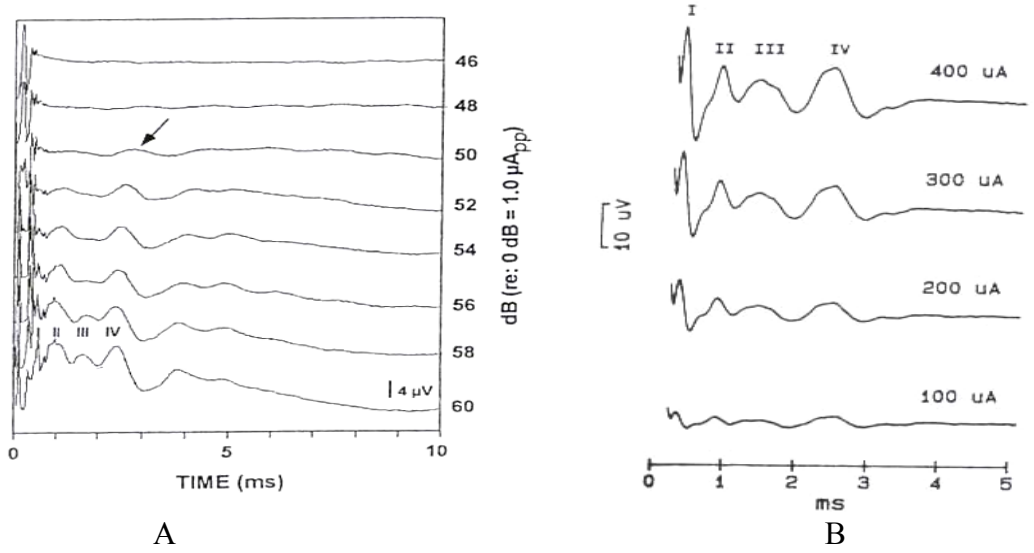
Recording: eABR's were amplified (band pass set between 300 to 10,000 Hz, gain 50,000) and averaged with a custom Labview based instrument. Typically 400 samples were averaged for each recording for noise suppression.

Stimulation: eABR's were evoked using a custom made, computer controlled stimulator. Biphasic, constant current stimuli of 100 microseconds per phase were delivered to electrodes in the implanted UEA. Thresholds were roughly determined using 5 to 7 logarithmically spaced current levels, typically spanning the range of 20 to 150 microamps. Thresholds were determined as the first detectable and repeatable waveform outside the stimulus artifact within 5ms from the original stimulus as determined by two separate observers.

Results

The kinetics of the eABR

In order to perform this analysis, we have compared our eABR recordings with those described in the literature (van den Honert and Stypulkowski 1986; Beitel, Snyder et al. 2000; Beitel, Vollmer et al. 2000). Figure 1 reproduces these published responses and shows the dependence of the kinetics of the eABR upon the magnitude of the current that evoked the responses.



A B

Figure 1 – The dependence of cat eABR responses upon the amplitude of the currents that evoked the responses. A) responses evoked by currents injected via bipolar electrodes inserted in the scala tympani(Beitel, Snyder et al. 2000; Beitel, Vollmer et al. 2000). B) eABR's evoked by currents injected via a concentric electrodes into the auditory branch of the VIIIth nerve at the level of the internal auditory meatus (van den Honert and Stypulkowski 1986).

The components of these oscillating responses, labeled waves I through IV, have been shown to reflect evoked neural activity of successively higher auditory centers (Achor and Starr 1980; Achor and Starr 1980). It has been suggested that wave I reflects mainly the compound action potential of the excited fibers in the auditory nerve. The amplitude of this component, therefore, reflects the fraction of auditory nerve fibers excited by the brief injection of electrical current into the nerve or the cochlea. The differences in the amplitudes of the responses seen in Figures 1A and B likely reflect differences in the fraction of auditory nerve fibers excited by these differing current injection loci. Of course, the varying amplitudes also reflect differing degrees of shunting of the responses by extracellular fluids around both the stimulating and recording electrodes.

Latencies of the eABR

There are also subtle differences in the kinetics of the responses in Figures 1A and B. Small differences in the kinetics of the eABR due to stimulating or recording variations will have little consequence in the analysis of the extent of the functional overlap between stimulated auditory nerve fibers in the experiments we have conducted and are continuing to conduct. Specifically, we have observed in our previous overlap experiments that the different components of the eABR are similarly affected by the masking stimulus: in experiments conducted in non-overlapping fibers, all eABR components are unaffected by the masking stimulus, and in experiments conducted in

overlapping fibers, the amplitudes of all components appear to be equally reduced by the masking stimulus. This finding is expected as the neural activity in the auditory centers that are responsible for the components of the eABR responses are all dependent upon the activity in the auditory nerve.

Because the site of the current injection in both these cases is relatively close to the brainstem, the latency of wave I is very short, and the kinetics of wave I are often difficult to extract due to the presence of the electrical artifact associated with the current injection. This is the case in Figure 1A, where the short latency of wave I, coupled with the duration of the 400 μsec long biphasic stimuli that evoked the eABR make wave I difficult to observe. In Figure 1B, however, the stimuli were 100 msec long, which allowed wave I to be more easily observed.

The amplitude of the eABR reflects (not necessarily linearly) the number of auditory nerve fibers that have been activated by the current injection. Further, the latency between the stimulus pulse and the activation of an action potential in each active fiber should be relatively independent of the magnitude of the current injection. Thus, one would expect that there would be little dependence of stimulus current on the latencies of the various waves in the eABR. This is the case as is illustrated in Figure 2 where we have plotted latency vs current amplitude curves for the waves I-IV from the data of Figure 1A and B.

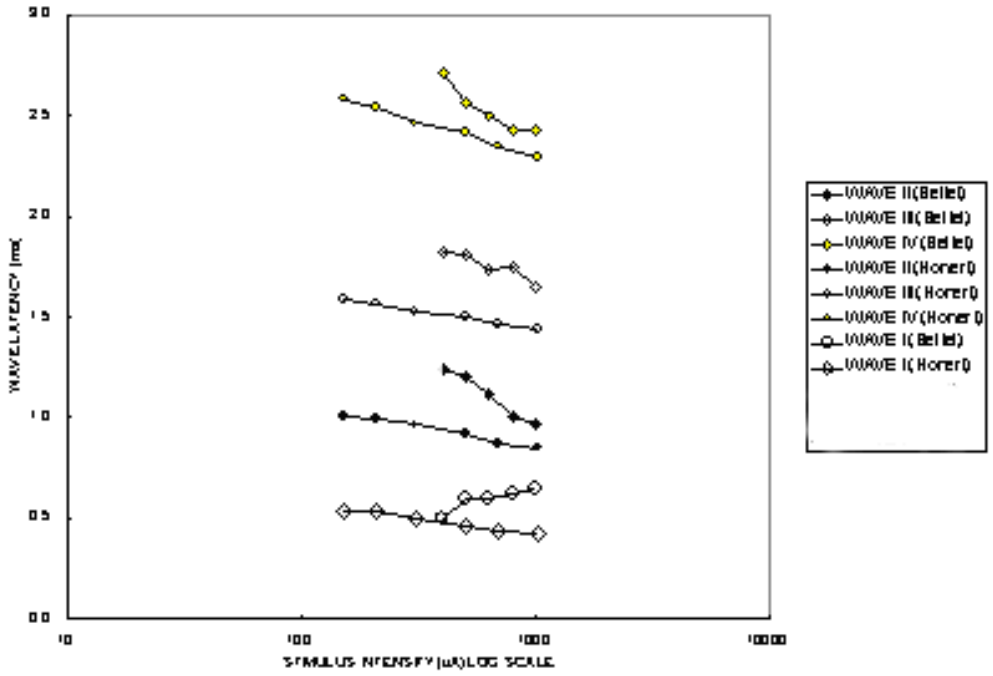


Figure 2– Dependence of latency of waves I-IV on current intensity (from data of Figure 1A and B).

This relative independence of latency upon stimulus strength makes comparison of eABR's recorded by different laboratories a relatively straightforward exercise. Thus, while there is a small decrease in latency of the peaks of the eABR waves with stimulus intensity for both Beitel's and van den Honert's data, there is also a relative agreement in

the latency of these four components of the eABR. Interestingly, the latencies of each of Bietel's components is a little longer than the latencies of each of van den Honert's components. This may reflect the fact that van den Honert was evoking eABR's with electrodes placed closer to the brainstem than was Bietel (van den Honert also used shorter stimuli than did Beitel which could also contribute to van den Honert's shorter latencies). We have summarized this latency data by averaging the latencies for all stimulus intensities for both studies in Table 1.

	Wave I		Wave II		Wave III		Wave IV	
	Beitel	VDH	Beitel	VDH	Beitel	VDH	Beitel	VDH
Latency	.59ms	.48	1.11	0.93	1.75	1.51	2.52	2.44

Table I – Latency of waves I – IV from data of Bietel and van den Honert.

Analysis of eABR's evoked by the UEA

The background of work done on eABR's evoked by electrical stimulation of the cochlea and the auditory nerve provides a framework in which to place our work. Strong support that the eABR's we have recorded were reflecting the same pathways that were excited in previous studies is provided by the kinetics of the eABR's we have recorded with the UEA. A set of eABR's recorded as a function of stimulus current intensity is presented in Figure 3.

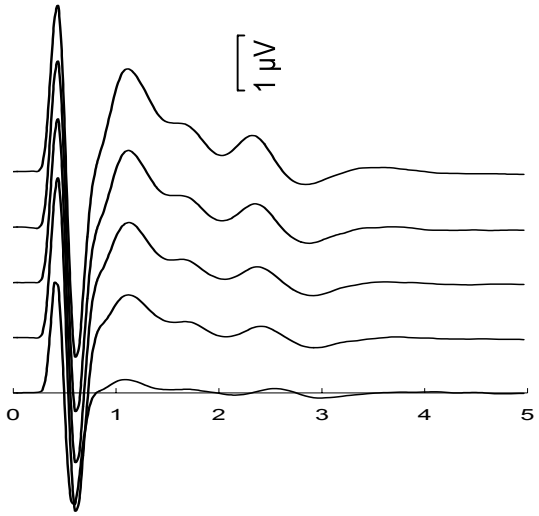


Figure 3 – eABR's evoked by currents injected into cat auditory nerve via a UEA implanted directly into the nerve. Biphasic currents used were 100 usec/phase and consisted of 80, 150, 199, 264, and 350 uamps.

These responses manifest three upward deflecting components which have latencies similar to those in Table 1 and which would appear to correspond to waves II-IV. We have replotted in Figure 4 the data of Figure 2, but have included the latency data from this figure in the plot.

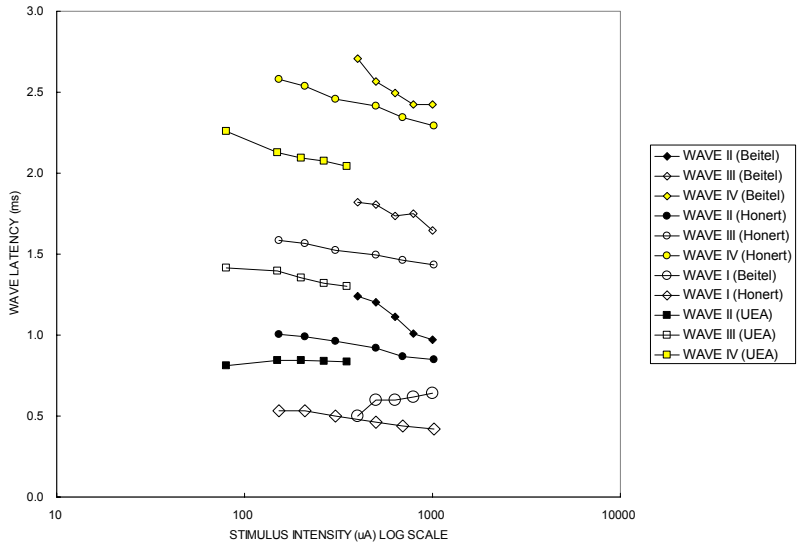


Figure 4 – Latencies of eABRs recorded by Beitel and van den Honert and those evoked by UEA's implanted in the auditory nerve (squares).

It is seen in this figure that the latencies of the components of the eABR's evoked with the UEA generally show a decrease as a function of stimulus strength, and that the average latency for each component is shorter than those of components in Beitel's and van den Honert's data. This could reflect the locus of the UEA in the nerve (closer to the brainstem than either other study), and the fact that the biphasic stimulus used in UEA experiments had a total duration of 160 usec (shorter than Beitel's. We have compared the average wave latencies of these three data sets in the table below.

	WI			WII			WIII			WIV		
	B	VDH	UEA	B	vdH	UEA	B	vdH	UEA	B	vdH	UEA
msec	0.59	0.48	n.a	1.11	.93	0.84	1.75	1.51	1.36	2.52	2.44	2.12

Auditory Nerve Fiber Recruitment

The growth of eABR's with the amplitude of the stimulating currents reflects the recruitment of successively larger numbers of fibers. This presumably is the reason why van den Honert's responses are larger than those of Beitel: van den Honert's bipolar electrode excitation at the auditory nerve recruited a larger number of fibers than the scalar electrodes of Beitel. As the UEA is intended to produce more focal stimulation of the fibers of the auditory nerve, we expect that the number of fibers recruited with stimulus currents will be smaller than obtained by Beitel and van den Honert. This is indeed the case as seen in the recruitment data shown in Figure 5 where we have compared the recruitment of fibers stimulated with the UEA with the data of Beitel and van den Honert.

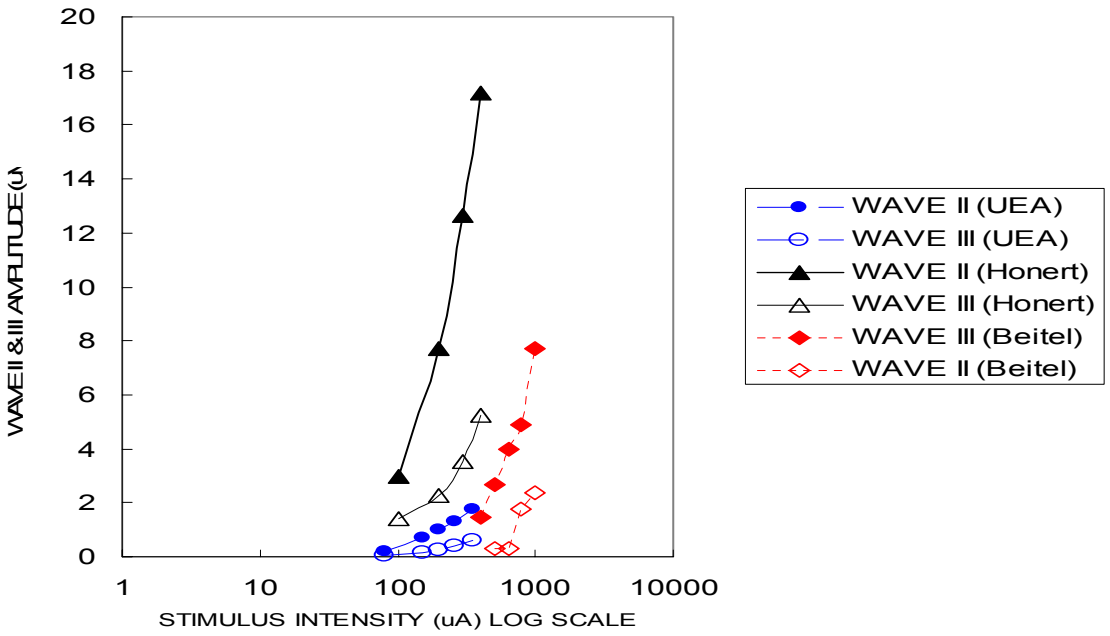


Figure 5 – Auditory nerve fiber recruitment versus stimulus intensity for recruitment with the UEA compared with recruitment reported in the literature (Beitel and van den Honert).

The UEA data shown in Figure 5 shows recruitment curves obtained with one of the electrodes in an implanted UEA. The threshold in this particular experiment was higher than typical, but the eABR's were somewhat larger than typical. As shown, the electrodes appeared to recruit smaller numbers of fibers than either other stimulation site. This finding is consistent with the more localized stimulation that is achieved with the UEA.

Summary

The kinetics of the eABR, the small dependence of eABR latency upon stimulus strength, the latencies of waves II-IV, and the comparison of these parameters with published data strongly supports the conclusion that current injection via the UEA evokes eABR's similar to those evoked by scalar injections. Because the short latency of the wave I response causes this component to appear very close to or within the relaxation from the stimulus artifact, it is difficult to reliably monitor its amplitude. However, because the amplitudes of waves II through IV basically reflect the amplitude of wave I, we have chosen to use the large amplitude wave II as our index of auditory nerve activation in our overlap experiments.

2.1.1.2 Acute experiments quantifying the extent of overlap of fibers excited by current injections through pairs of UEA electrodes implanted in auditory nerve

We have hypothesized that penetrating electrodes, inserted into the auditory nerve can achieve much more focal stimulation of the auditory nerve than can electrodes on arrays

inserted into the cochlea. We further postulated that focal stimulation should result in much more selective activation of a broader range of discrete frequency percepts than has been achieved with cochlear electrodes. In Progress Report #4, we described a set of preliminary experiments we conducted that we feel provides powerful insights into the issue of selectivity of auditory nerve fiber stimulation.

The experiments are based upon the premise that the amplitude of the eABR is proportional to the number of auditory nerve fibers that are activated simultaneously. Delivering two stimuli through a pair of electrodes that recruit completely independent populations of auditory nerve fibers should evoke an eABR that is the sum of the eABR's evoked by each electrode when stimulated by itself. Similarly, if these two stimuli are delivered sequentially but with a very short interstimulus interval (an interval equal to or less than the refractory period of the fibers excited by the first stimulus), each stimulus will evoke an identical eABR.

This will not be the case if the two stimuli excite the identical population of auditory nerve fibers. If these two stimuli are delivered sequentially but with this short interstimulus interval, the second stimulus will not evoke an eABR (the fibers will be incapable of excitation as they are still in a refractory state). Thus, we suggest that an index of the independence of auditory nerve fibers can be obtained by observing the amplitude of the eABR evoked by this second of a pair of stimuli. A number of these hypotheses have been tested in varying degrees in experiments by Miller (Miller, Abbas et al. 2001).

In our progress report #4, we provided preliminary results of experiments designed to quantify the extent of independence of the auditory nerve fibers excited via an implanted UEA. Over this past quarter, we have extended these experiments to more completely document the independence of the fibers excited by the UEA.

Shown in Figure 6 are two figures reproduced from Progress Report #4. Figure 1 (left) illustrates eABR's evoked by paired stimuli that excited independent populations of nerve fibers. Figure 6 (right) illustrates eABR's evoked by overlapping nerve fibers.

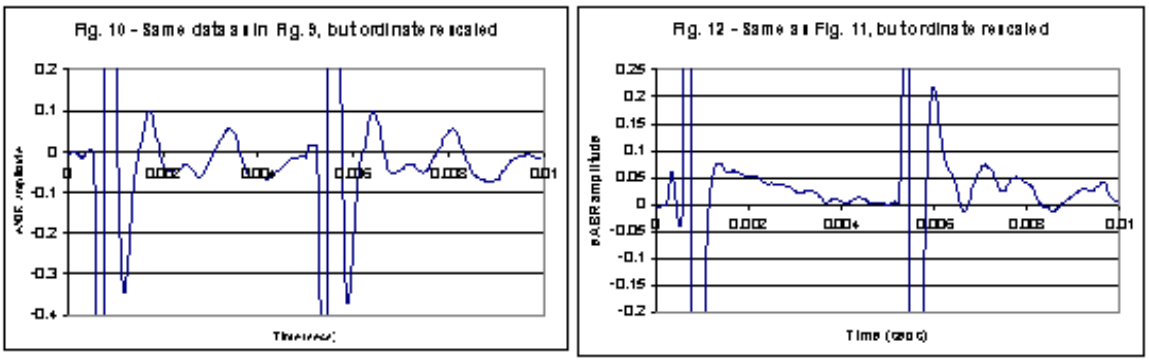


Figure 6 – Differential plots of paired stimulation via two electrodes implanted into cat auditory nerve. Stimuli were delivered at t = 0 via a masking electrode and at either t = 0.35 or t = 5 msec via a probe electrode. Left figure illustrates that mask and probe electrodes excite

independent sets of auditory nerve fibers. Right figure illustrates strong overlap in populations of excited fibers (from progress report #4).

Each of these two figures is a differential plot. The traces are the difference between two pairs of responses delivered via two of the electrodes in an implanted UEA. The first pair of responses was delivered at t = 0 through one electrode (the 'masking' electrode) and at t = 350 usec through the second electrode (the 'probe' electrode). The second pair of responses was delivered at t = 0 (the masking electrode) and at t = 5000 usec (the probe electrode). When these pairs of responses are subtracted, the responses evoked by the masking electrode at t = 0 cancel (almost perfectly), revealing the responses evoked by the probe electrode at t = 350 usec (in spite of the large contamination of this response by the artifact from the stimulus at t = 0) and the response at t = 5000 usec. In Figure 6 (left), the eABRs at t = 350 and t = 5000 usec are very similar in terms of amplitudes and kinetics, indicating the independence of the fibers excited by each electrode. This is not the case for the pairs of responses in Figure 6 (right) where the response at t = 350 usec is almost eliminated by the response at t = 0.

We can quantify the degree of functional independence between populations of fibers excited by the mask and probe electrodes using the following relation:

$$I = 100*(A_5 - A_{.35})/A_5$$

Where I is the quantified independence of the sets of fibers excited by the masking and the probe electrodes and is expected to vary from 0 for totally overlapping fibers to 100 for independent fibers, A_5 is the amplitude of one of the eABR wave components at 5 msec, and $A_{.35}$ is the amplitude of the selected eABR wave component at 0.35 msec. Measured values of I can be greater than 1 due to the fact that some nerve fibers are still in a relative refractory period even at 5 msec after a preceding stimulus, and there is usually a 100 msec interval between the stimulus delivered at 5 msec and the subsequent stimulus delivered at 0.35 msec. Thus, in cases where there is no apparent fiber overlap, the response at 0.35 msec can be larger than that at 0.5 msec.

In this relation, we have not specified any particular wave component, as all are reduced similarly by the overlap. Also, as the kinetics and amplitude of wave I is often contaminated by the stimulus artifact, we have chosen to use the amplitude of wave II in our analysis (it is not contaminated by the stimulus artifact and has a relatively large amplitude). As wave II is often superposed upon a changing baseline, we have had to adopt an *ad hoc* approach to measuring its amplitude. We have identified the peak of wave II from its latency (peaking between 0.7 and 1.2 msec) and taken the difference of this value from the average of the trough potentials immediately before and after this peak. If the trough preceding the peak of wave II could not be determined, we only used the trough following the peak of wave II in our determination. In the instances where we could not detect (using subjective observation) a peak discriminable from the noise in the recording in this range (as in Figure 6 right), we denote the amplitude of wave II as zero. We acknowledge that this quantification scheme is subject to error of estimation, but the goal of these experiments is to provide a broad overview of the extent of overlap between electrodes. Errors in the estimation of the amplitudes of wave II on the order of 20-30% will not substantially alter the conclusions of this study. Based upon these measurement

criteria, the fiber independence in Figure 6 (left) is 105 (no overlap), while that in Figure 6 (right) was 11 (almost complete overlap).

Extent of overlap versus probe stimulus intensity

The extent of functional independence between fibers excited by currents injected through masking and probe electrodes will be a function of the total number of fibers recruited by the injections via each electrode, and the spacing between electrodes. If each electrode recruits only a small number of fibers, the electrodes could be very closely spaced before any functional overlap was obtained. However, if the electrodes recruit a large number of fibers, then the electrodes must be widely spaced to eliminate functional overlap. As the extent of fiber recruitment is a function of stimulus current amplitude, the extent of functional overlap is expected to be a function of stimulus amplitude. This dependency of overlap on stimulus intensity is illustrated in Figure 7.

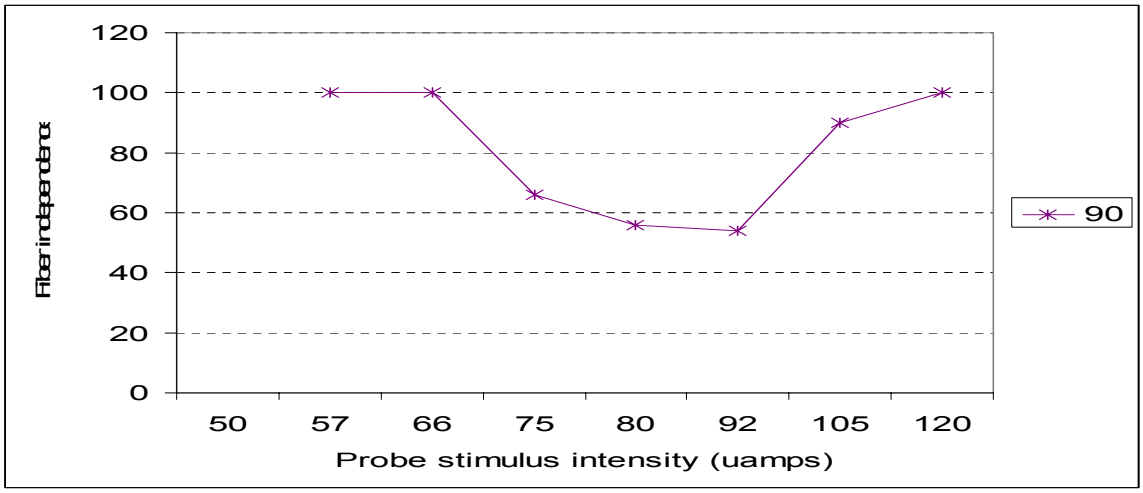


Figure 7 – Dependence of functional fiber overlap as a function of probe stimulus intensity (masking current is constant 90 uamps).

In this figure, we have plotted fiber independence (0 to 100) as a function of the amplitude of the probe stimulus, for a fixed 90 uamp masking stimulus amplitude. When the probe stimulus was of a small, but superthreshold amplitude, only a small population of fibers were excited by the probe stimulus, and this population was independent from the population of fibers excited by the masking stimulus. As the probe stimulus amplitude was increased, the number of fibers recruited by this stimulus increased, and this population of fibers began to overlap the fibers recruited by the masking stimulus, and the fiber independence decreased. However, as the amplitude of the probe stimulus was increased further, the number of fibers recruited by the probe stimulus became much larger, the amplitude of the eABR evoked by the probe became much larger than the population of fibers recruited by the masking electrode, and the fiber independence appeared to increase back towards unity. Rather than reflecting independence of the two sets of fibers, this increase reflects the fact that removing the set of fibers excited by the masking stimulus had only a small effect on the total number of fibers recruited by the probe stimulus, and, therefore, only a small effect on the eABR evoked at 350 usec.

Extent of overlap versus masking stimulus intensity

Increasing the intensity of the masking stimulus recruited a larger number of masking fibers to the point that the masking fibers now encroached upon the fibers excited by the probe stimulus, and greater fiber overlap was observed. The effects of masking stimulus intensity is shown in the plots of Figure 8 where we have plotted a family of curves that have stimulus intensity as the independent variable for each curve.

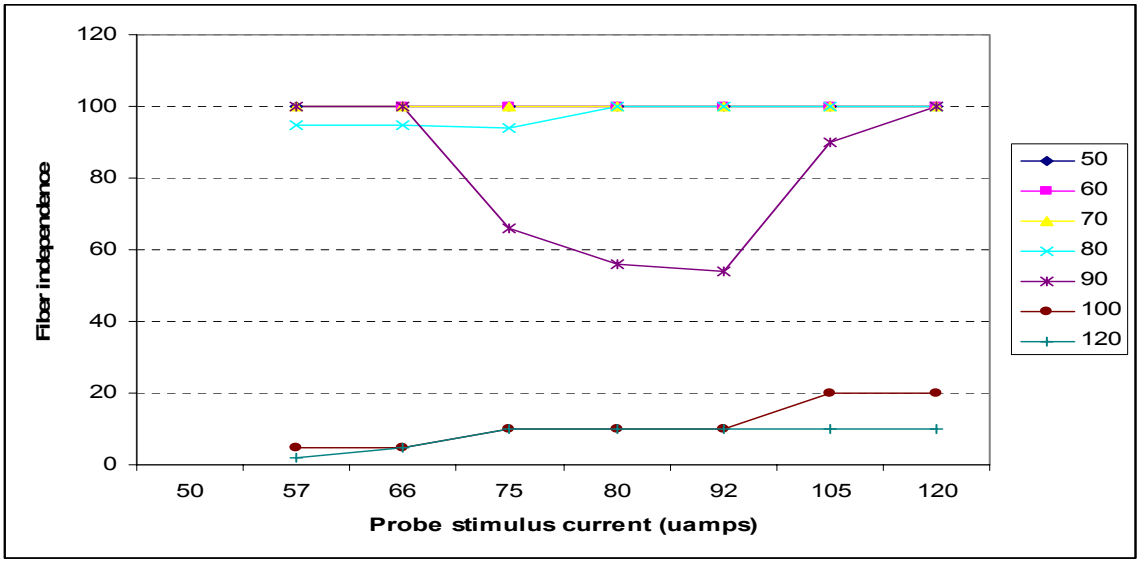


Figure 8 –Plot of fiber independence as a function of Probe current with masking stimulus intensity as the independent parameter (in legend).

These curves reflect the increasing encroachment of the masking fibers upon the population of fibers recruited by the probe electrode. The curves show that at low masking current, the pair of electrodes recruited independent sets of fibers. However, when the masking current reached 90 microamps, there was considerable overlap in the two sets of fibers. When the masking current reached 100 microamps, the masking stimulus recruited the set of fibers also recruited by the probe stimulus and virtually complete overlap resulted.

Spatial distribution of independence between pairs of electrodes

The analysis we have described above has been limited to a single pair of masking and probe electrodes. However, we have extended the analysis to all pairs of functional UEA electrodes implanted in the cat auditory nerve. Our most complete data set was obtained in one experiment in which a 3 x 4 array of electrodes was implanted. This array was connected to our data acquisition instrumentation via a 12 pin Microtech connector, one pin of which was used to connect to a 1 mil diameter reference wire placed beneath the stimulation site. Thus, only 11 of the 12 electrodes were connected to our

instrumentation. Of these 11 electrodes, only six electrodes had eABR stimulus thresholds consistent with intranerual implantation (the remaining five electrodes were presumably extraneural). We used each of these six electrodes as a masking electrode for the remaining five electrodes (each of these was treated as a probe electrode for this particular masking electrode). Each overlap experiment consisted of paired stimulation with one of six masking current levels, and six probe current levels for each masking level. Thus, each pair of electrodes resulted in 36 records (each record the result of averaging 400 times). These experiments were conducted in 20 pairs of the six electrodes. The plots of this data are reproduced in the appendices and very similar to that shown in Figure 8. The data illustrate that 18 of the 20 electrode pairs manifest little functional overlap for low amplitude stimulation.

2.3 INSTRUMENTATION

2.3.1 Iridium metallization of the tips of the UEA

This research contract requires the histological assessment of the effects of chronic electrical stimulation of auditory nerve for a two week period. We have constructed backpack stimulators that will be worn by the animals and that will deliver constant current stimuli to the UEA implanted chronically in the cat's auditory nerve. Much of the work we have performed to date has used UEA's with electrode tips that are metalized with platinum. While this is a reasonable electrode material for acute experiments, the polarizable nature of the metal is not ideal for long-term stimulation. As iridium oxide has been shown to have superior charge injection qualities over platinum (Brummer, Robblee et al. 1983; Agnew and McCreery 1990), we have refined our UEA manufacturing processes to allow us to metalize the electrode tips with iridium. The technique is similar to that described by Anderson et al (Anderson, Najafi et al. 1989). The overall 3-D architecture of the UEA is achieved as has been described elsewhere (Jones, Campbell et al. 1992), using dicing with a computer controlled dicing saw (K and S model), and a two step wet etching process. The tips of the electrodes are then pushed through an aluminum foil mask, and the array transferred to an RF sputtering chamber where first a platinum silicide, then titanium glue layer, and then a 1000 angstrom iridium layer are deposited. The foil mask is removed and the electrodes are then completely insulated with silicon nitride. The electrodes are once again pushed through an aluminum mask so that just the last 20-40 microns of the tips project beyond the mask, and the array is transferred to a LPCVD etcher where the silicon nitride is etched off the tips of the electrodes. Eleven lead wires are then soldered to eleven preselected platinum bond pads on the rear surface of the arrays, and the rear surface is cleaned and insulated with silicone elastomer. The lead wires are then soldered to eleven of the twelve pins of a 12-pin Microtek connector, and the base of the connector is potted with silicone elastomer.

The tips of the UEA are next activated using cyclic voltammetry in a three-electrode system diagrammed in Figure 9.

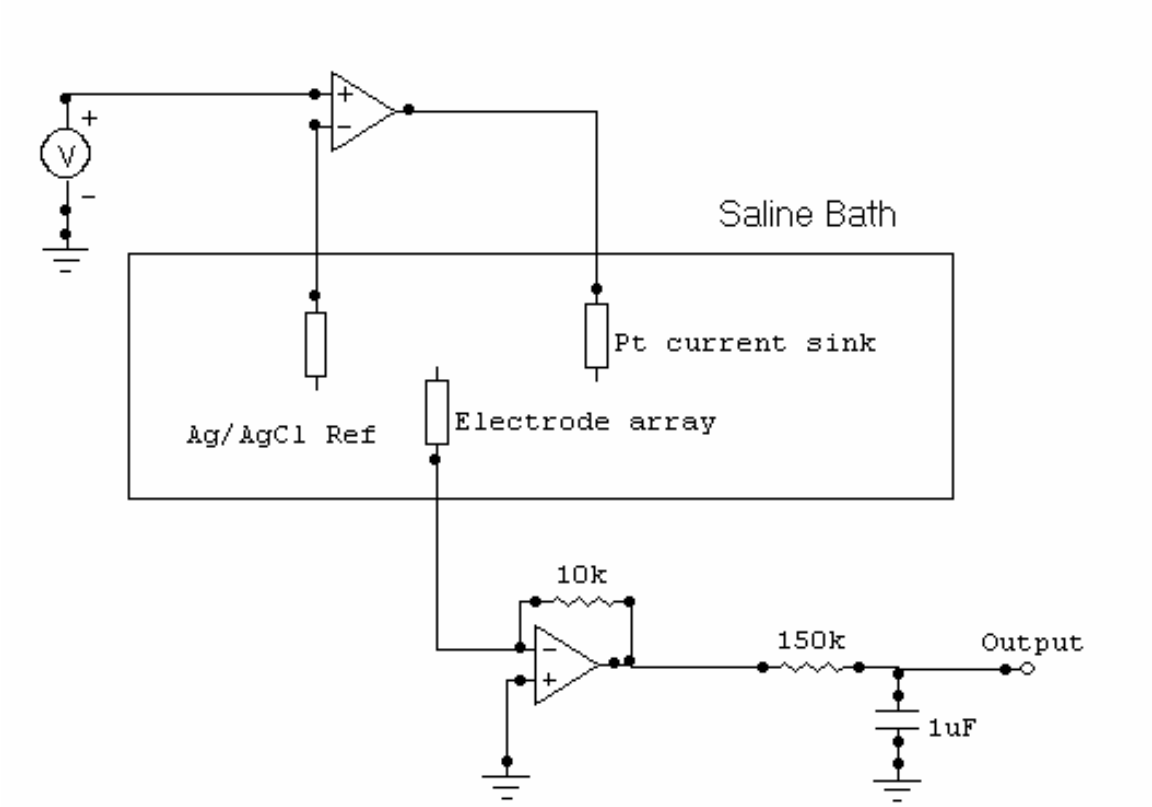


Figure 9 – Cyclic voltammetry circuitry used to characterize and activate the UEA electrode tips.

The activation of the iridium tips is achieved by a slow cycling of the voltage across the electrodes. A 0.5 Hz triangle wave is applied at a magnitude just within the water window of gas evolution for each electrode, typically between –1.1 and 1.2 Volts. This activation cycling is continued for just over an hour to achieve a total charge injection per area in excess of 30 mC/cm^2 (Beebe and Rose 1988). The cyclic voltammogram recorded during a typical activation of one of the tips is shown in Figure 10 and results in an increase in the current injection capability of the electrode from 5 millicoulombs/cm^2 prior to activation to 35 millicoulombs/cm^2 after activation using cyclic voltammetry to estimate potential charge injection capability. The current injection capability of our conventional platinum electrodes is typically 1-3 millicoulombs/cm^2 with a cyclic voltammetry curve estimate of potential charge injection.

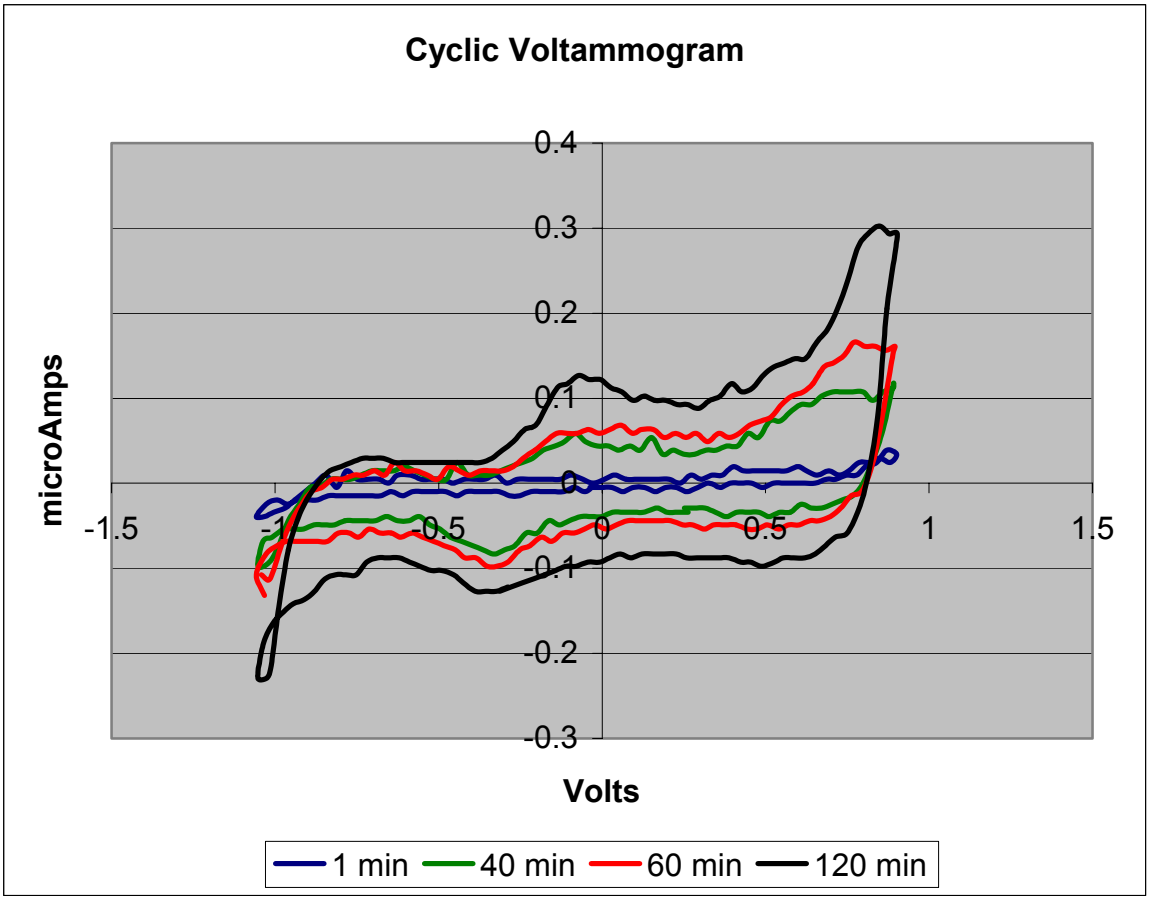


Figure 10 – Cyclic voltammograms recorded during the iridium activation procedure.

UEA electrodes that are intended to be used in our chronic stimulation experiments all are activated using this above procedure. However, the impedance of all electrodes is not constant but depends upon the amount of tip exposed during the deinsulation procedure (a somewhat variable quantity due to the 'hand-made' nature of the processes used in the UEA fabrication). For the inactive state, typical impedances range from 100 to 400 kohms when measured with 1 kHz, 100 nA constant current sine wave currents. Activation of the iridium tips results on average in an impedance drop to half the value of the inactive state.

2.3.2 Validation of chronic stimulation system.

Before we perform a set of chronic stimulation experiments in cat auditory nerve, we are proposing to evaluate the entire stimulation system in a set of experiments where we will be stimulating the cat auditory cortex. This will allow us to 'debug' the backpack, the backpack stimulator, the head mounted Microtek connector, the cabling between the stimulator and the connector, and the elements of the UEA that are implanted (lead wires, lead and potting leakage, mechanical robustness, etc.). Based upon previous experiments we have conducted with percutaneous lead systems, we have found this to be a critical

step in the development of a chronic stimulation system. Specifically, we have found that our initial attempts at developing a chronic stimulation system have failed within a few days of implantation due to breakage of the percutaneous leads. We have tried two different designs, without success. However, we have enjoyed considerable success with a head mounted Microtek connector system for recording. Cats have been chronically implanted and auditory responses recorded for a six month period without problems. We have returned to this system, with some modifications for chronic stimulation experiments.

Improvements to the backpack circuitry are also being investigated. By implementing an improved Howland current pump circuit for each electrode, we hope to make our stimulator a truly constant current system, more robust to electrode-tissue impedance variability. Presently we have tested a bench top model of this system and are in the process of completing a prototype stimulator using the improved circuitry. This model will be completed in time for the next quarterly review.

3. PLANS FOR NEXT REPORTING PERIOD

3.1. ACUTE EXPERIMENTS

3.1.1 Auditory nerve stimulation selectivity

We intend to continue the stimulation overlap studies we have described in 2.1.1.2, but using the Utah Slanted Electrode Array rather than the UEA's we have used to date. We are pleased that the degree of functional overlap in these experiments is so modest, but we expect that the USEA should provide even better functional independence of the stimulated fiber populations.

3.1.2 Acute AI mapping.

Our acute mapping experiments will continue. We expect to be able to acutely implant a 12 electrode UEA in the auditory nerve, and by electrical stimulation of the fibers, evoke single unit responses in AI which will be recorded with a 10 x 10 UEA implanted in AI. We will compare ipsilateral acoustically stimulated maps with contralateral electrical stimulation via the UEA implanted in the auditory nerve in order to identify the characteristic acoustic frequency representation of response fields that are activated by stimulation of the auditory nerve via UEAs implanted there. To do this, we must first determine if the characteristic frequency maps evoked by ipsilateral acoustic stimulation are similar to those evoked by contralateral acoustic stimulation. Work which we have begun to study these ipsilateral and contralateral acoustic maps will be continued over the next quarter.

3.2. CHRONIC IMPLANTS

3.2.1. Active implants.

The successful recent chronic implantation/chronic stimulation experiment we have performed has encouraged us to conduct the series of chronic stimulation experiments detailed in our contract. We plan to implant these cats in a sequential fashion, making sure that interconnection system we have developed continues to work effectively before we implant the next cat. Stimulation will be conducted for a 16 hour per day basis, for a

period of at least two weeks. Impedances will be monitored every 2-3 days. At the end of the 2 – 3 week stimulation period, the animals will be sacrificed for histological analysis of the auditory nerve in the region of the implanted UEA.

4. PUBLICATIONS AND PRESENTATIONS

The following publications/presentations have been made over this quarter.

Publications -

"Development of a Novel Eighth-Nerve Intraneural Auditory Neuroprosthesis", A. N. Badi, T. R. Kertesz, R. K. Gurgel, C. Shelton, R.A. Normann. Accepted for publication in Laryngoscope.

"Evaluation Of The Accuracy Of T2 Fast Spin Echo Magnetic Resonance Imaging Of The Cochlear Nerve", A. O. Owa, A.N. Badi M.D., J. Gull, R.Wiggins, T. Hillman, C. Shelton.- Accepted for Publication in Otology Neurotology.

Presentations - None

5. DISCUSSION

The contract focused on validation of the advantages of intraneural over cochlear stimulation as a potential means of restoring lost auditory function. We had originally proposed to use recordings of spatially localized neuronal activation in auditory cortex as our index of independence of activation by each electrode. At our last site visit, the site visitors suggested that a better approach might be to use the compound action potential, recorded at the auditory nerve, as an index of stimulation overlap. The overlap experiments described in this report strongly support the success of this approach, and indicate that the electrodes of the implanted UEA excite independent populations of auditory nerve fibers, even for moderately intense levels of stimulation. This suggests that higher density penetrating electrodes arrays (electrodes more closely spaced) could be used profitably in such an auditory prosthesis. This is especially the case for stimulation around thresholds.

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Apendices

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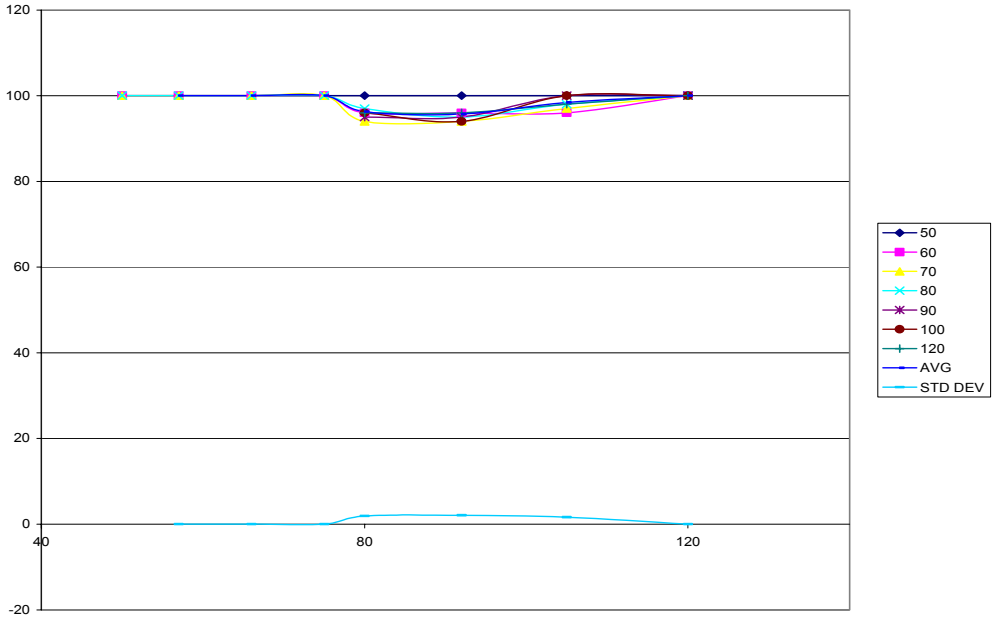

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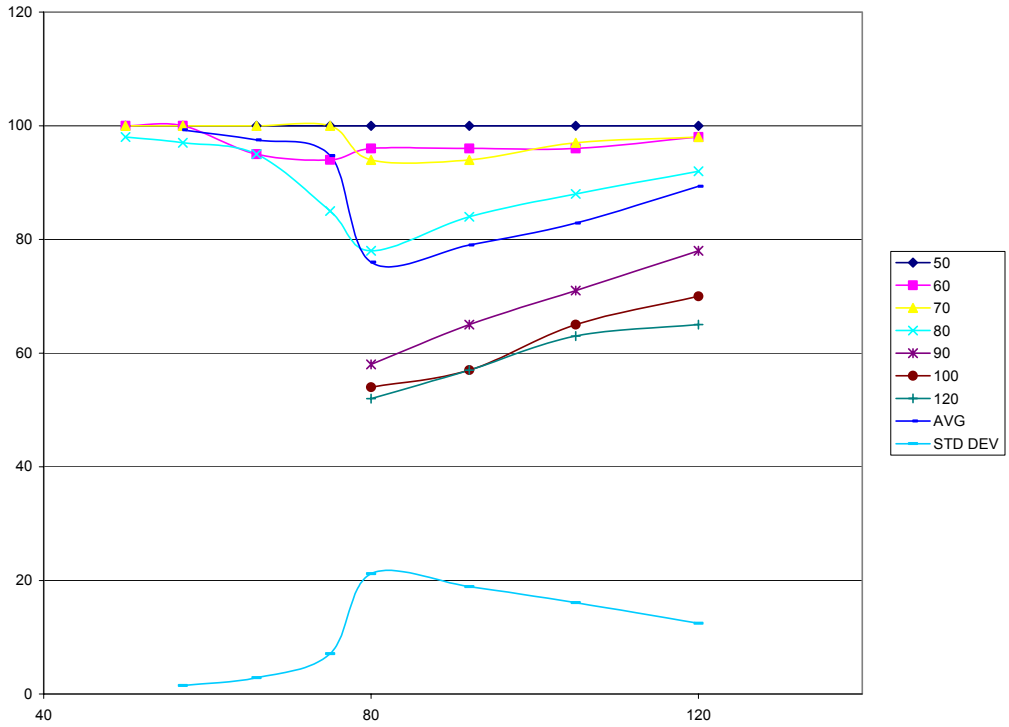

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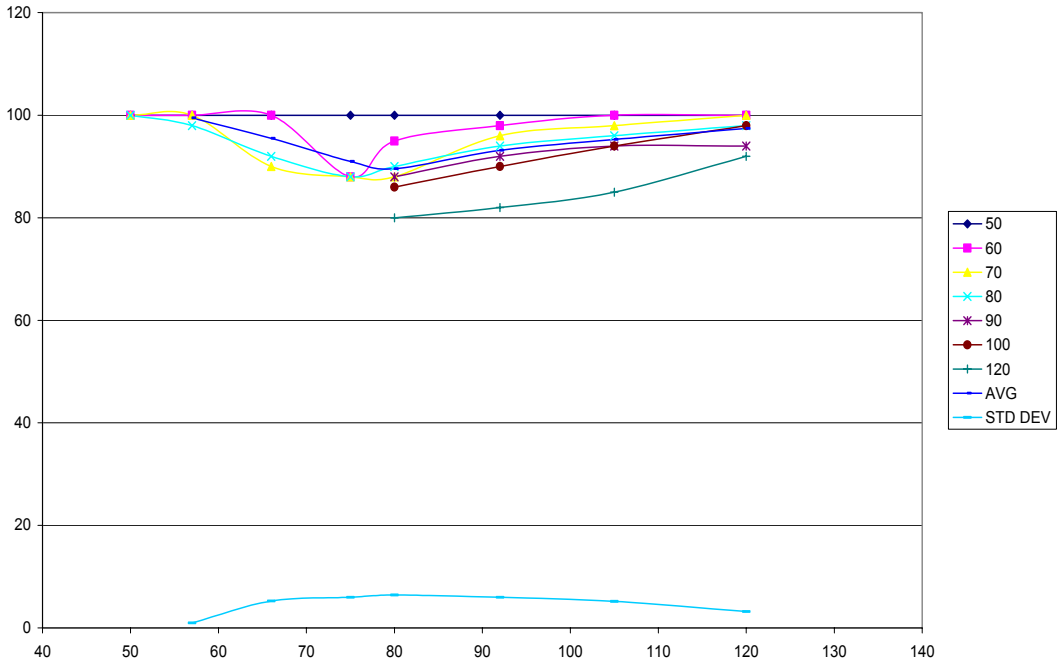
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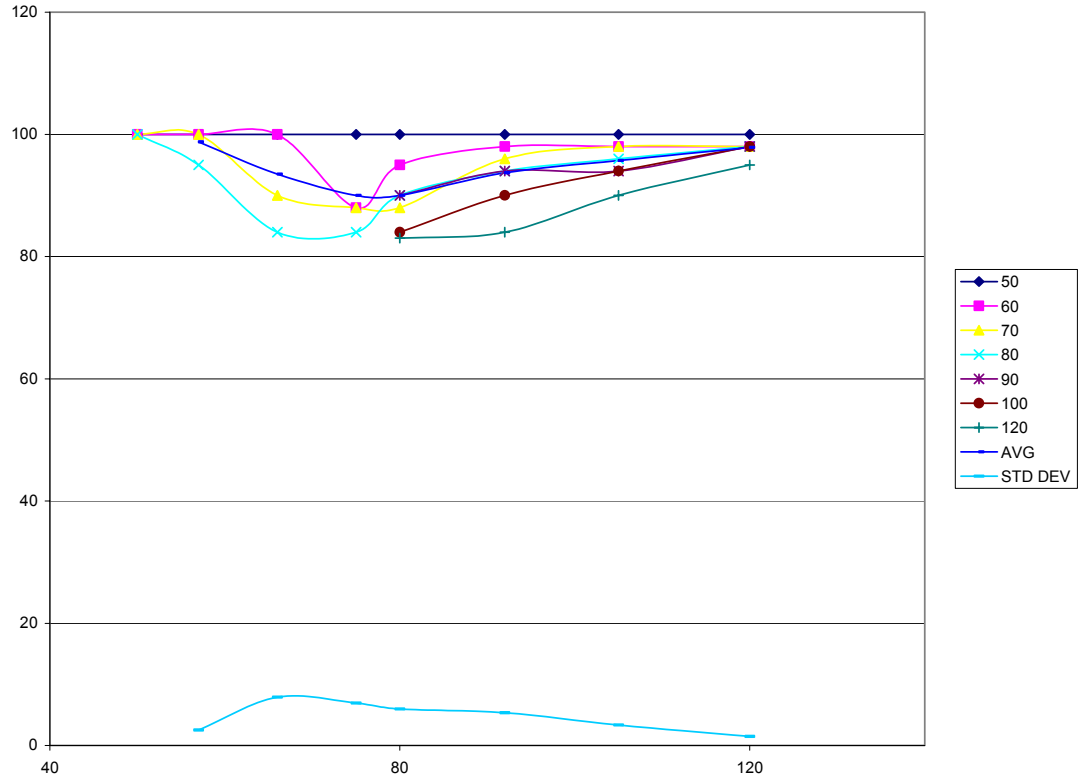
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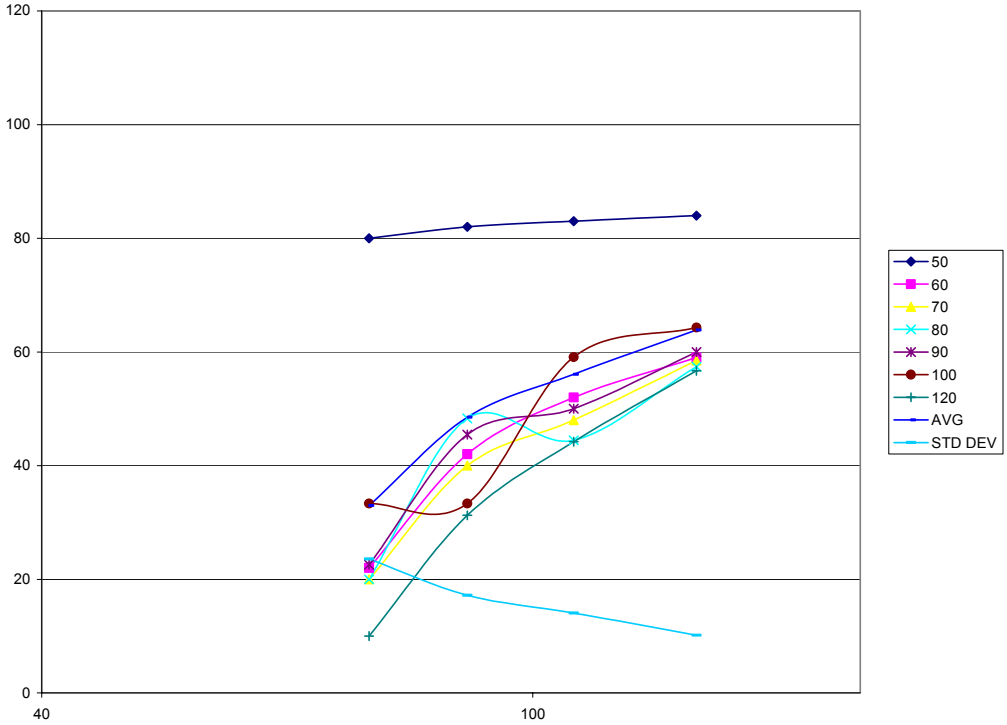
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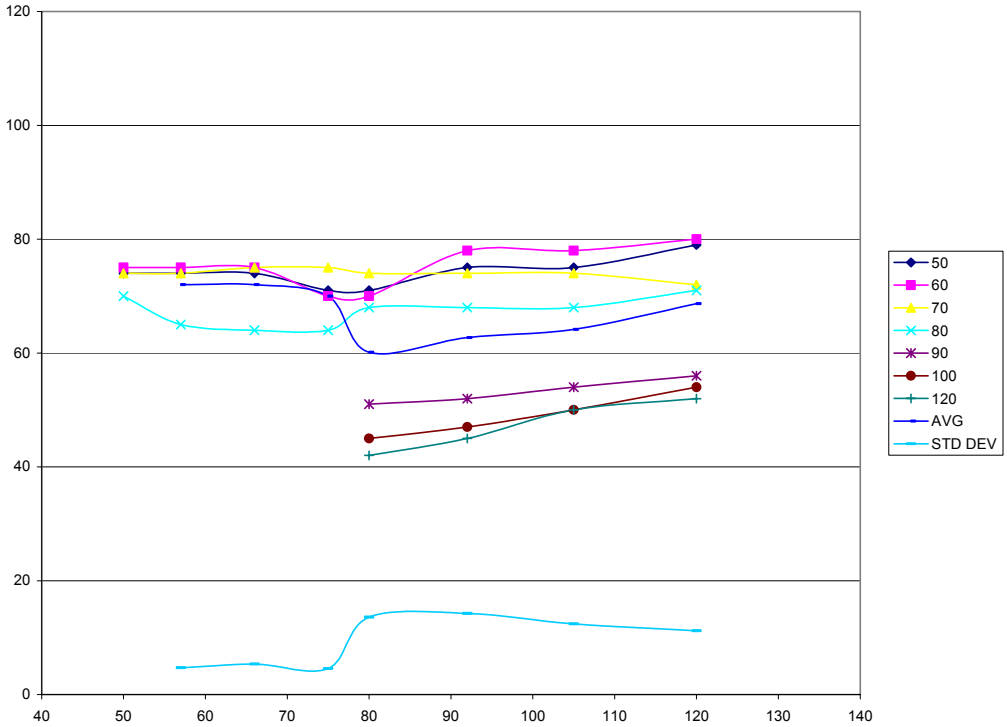
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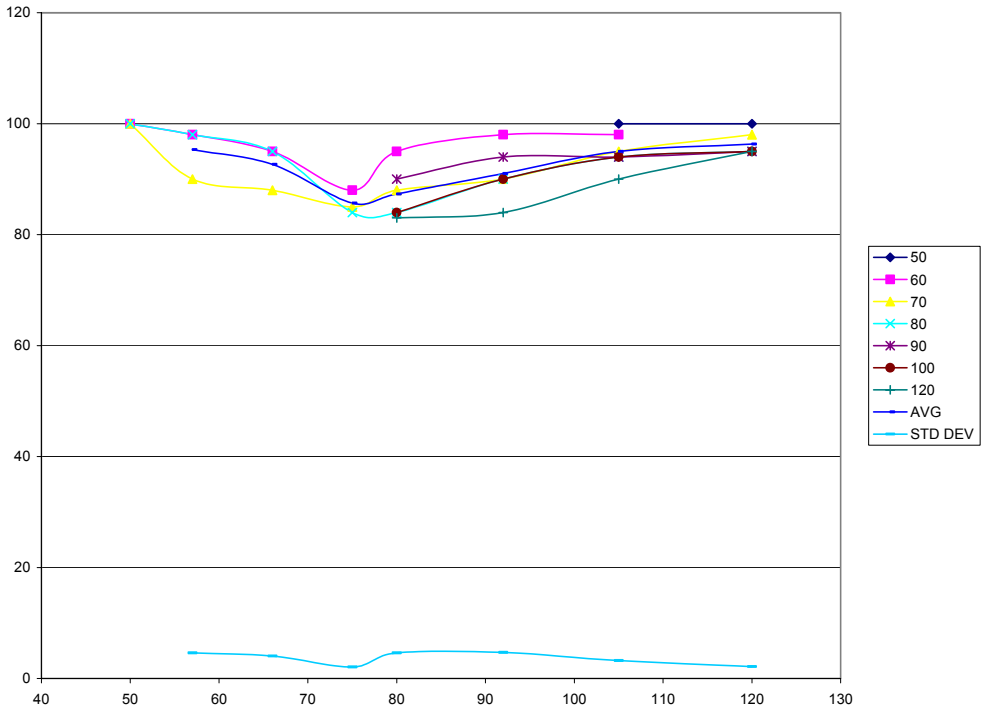
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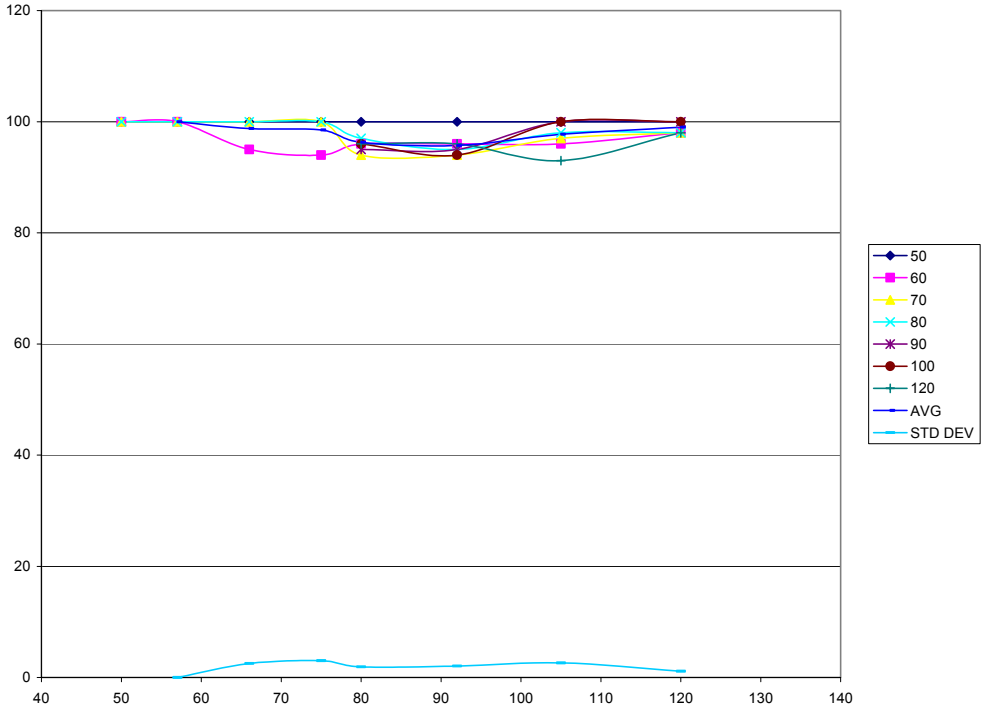
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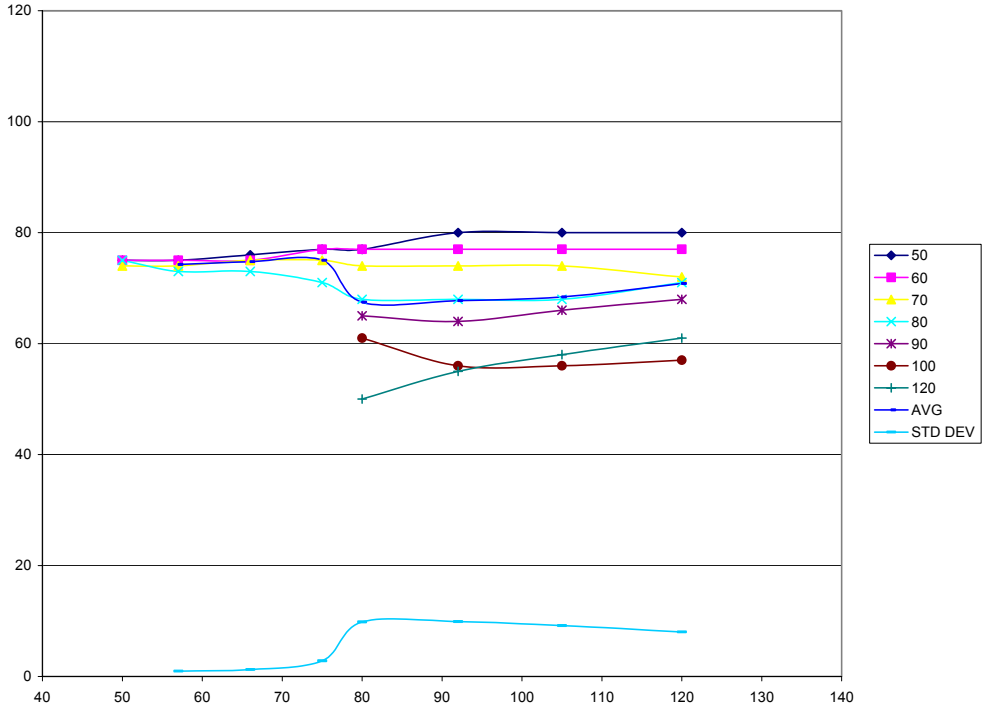
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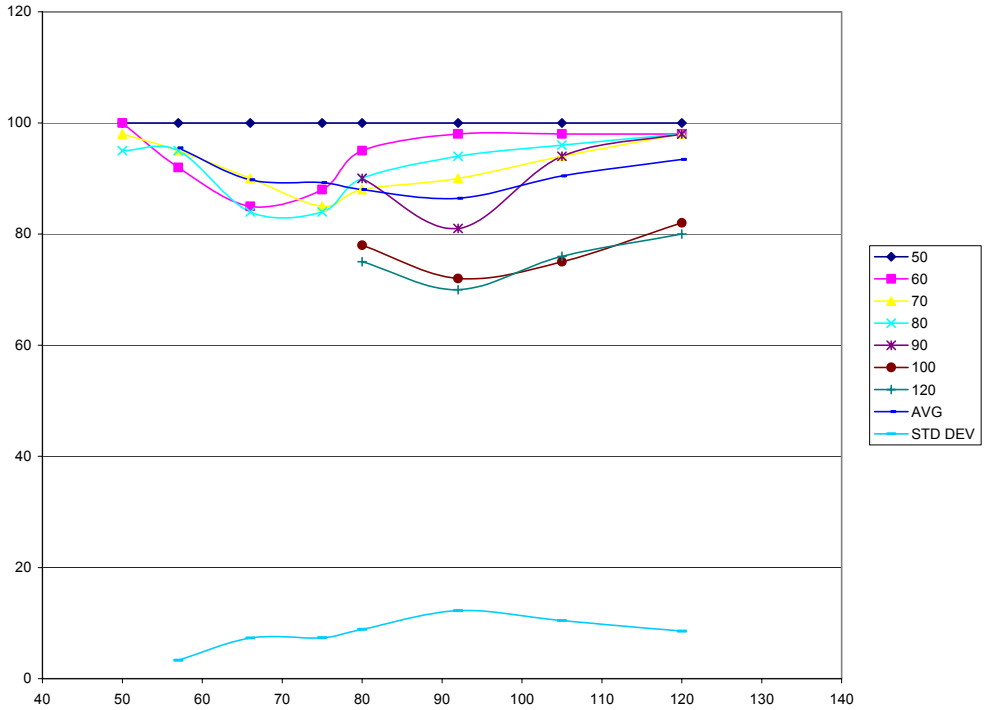
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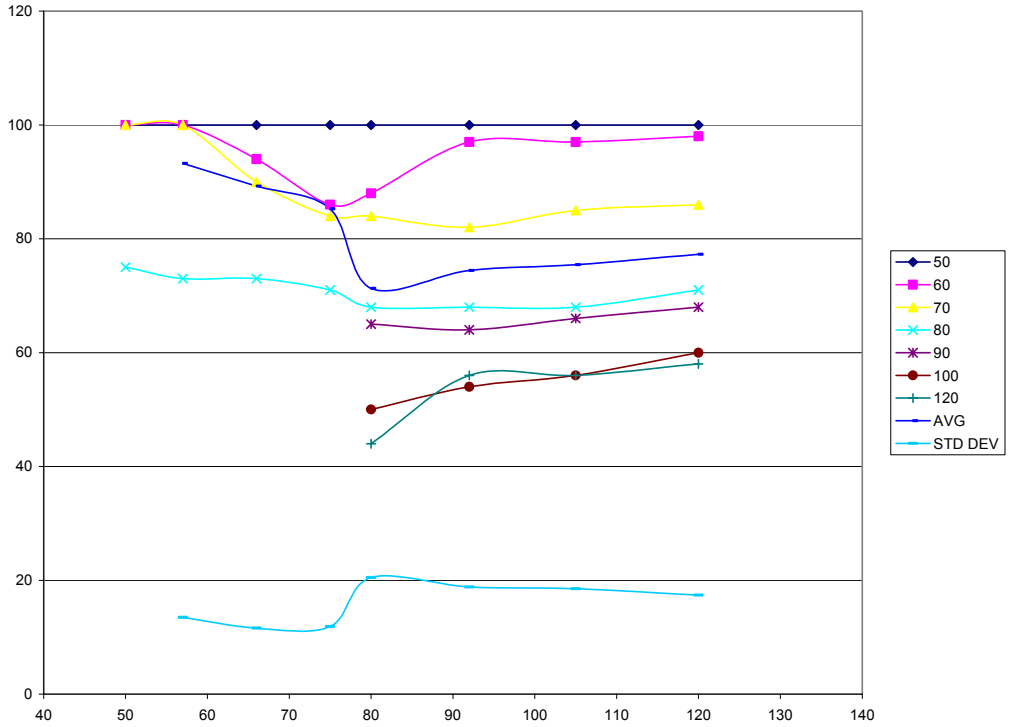
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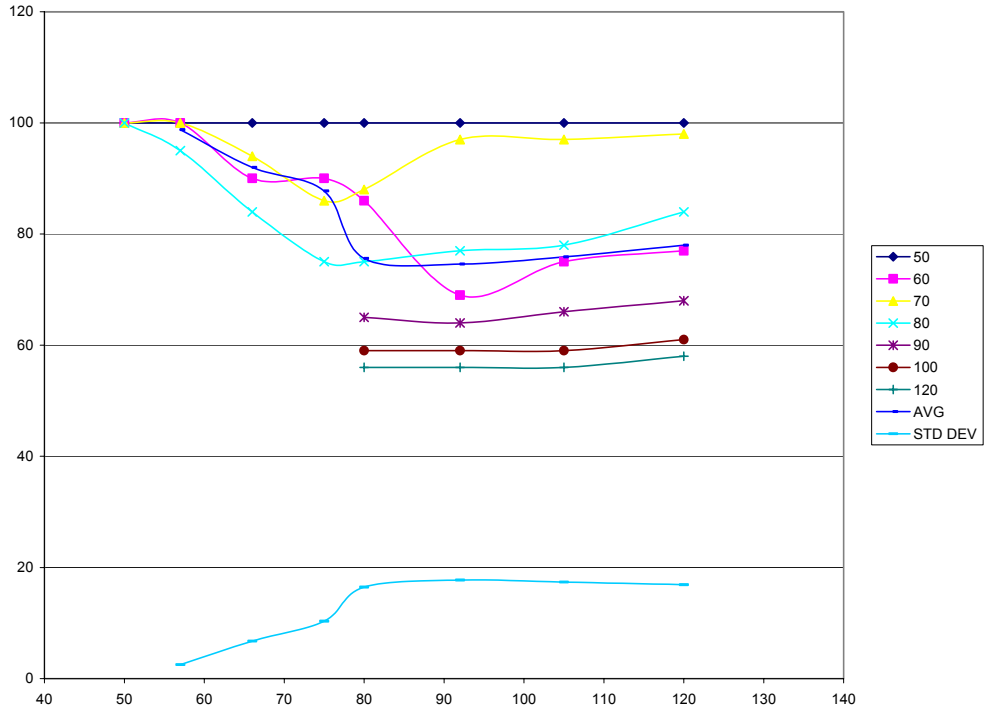
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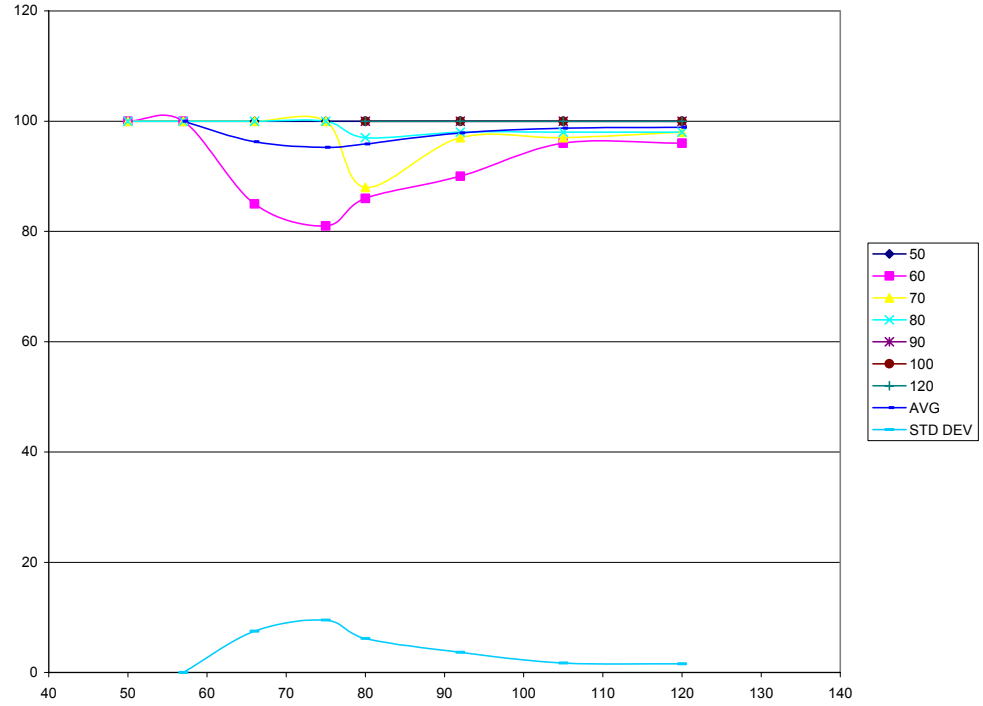
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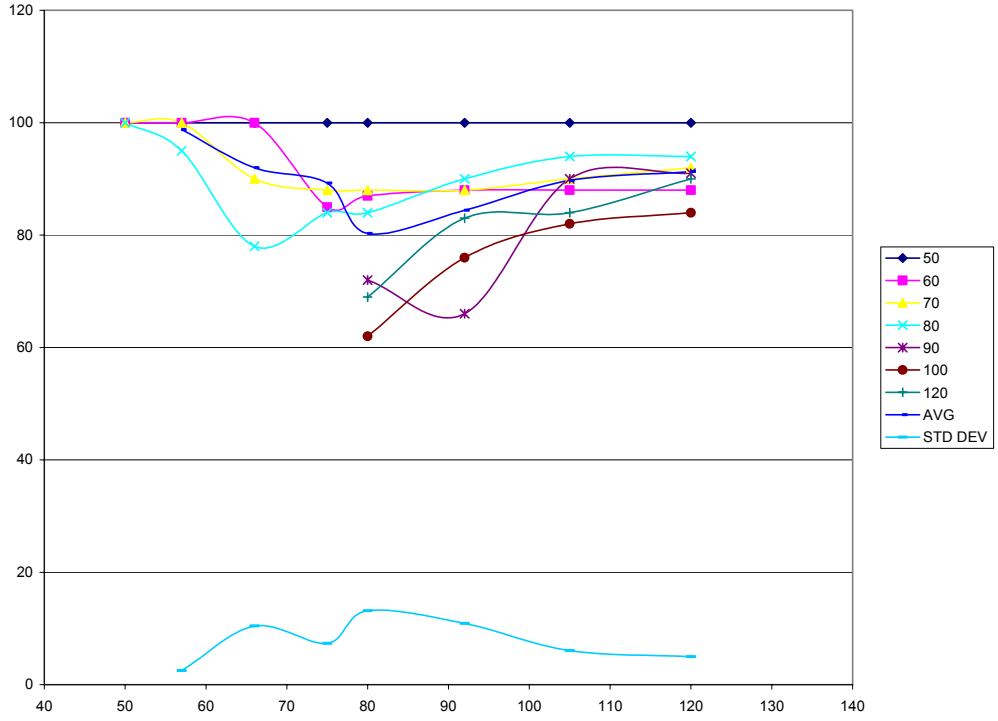
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