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Protective Effects of Patterned Electrical Stimulation on the Deafened Auditory System

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ABSTRACT

One goal of this contract is to determine the functional consequences of chronic electrical stimulation by a cochlear implant in the deafened, developing auditory system. One important measure of the functional capacity of central auditory neurons is the ability of these neurons to follow stimulus pulses presented in rapid sequence. We have reported previously that chronic electrical stimulation has a significant effect on the maximum frequency following ability of single units in the inferior colliculus. In order to evaluate the effects of stimuli delivered by current clinical devices, it is first necessary to define how more complex electrical signals are represented in the temporal response properties of the central auditory system. In this progress report we present single unit data describing responses of IC neurons to amplitude modulated (AM) signals which are similar to those used by many clinically applied cochlear prostheses to encode speech. In this later group of animals unit responses to both unmodulated pulse trains and amplitude modulated trains were recorded and compared. Several parameters of modulated stimuli were varied systematically including carrier rate, modulation frequency and modulation depth.

In summary, the phase-locked frequency following capacity of IC neurons was greater for unmodulated signals than for modulated signals. The mean maximum following frequency (Fmax) for unmodulated trains was 104 pulses per second (pps). The mean maximum modulation frequency (modFmax) was 42 Hz for sinusoidally amplitude modulated pulse trains. The correlation value for these two stimuli in the same unit was positive but low (r2= .101, n=129). Most IC units (74%) were relatively insensitive to differences in carrier frequency up to at least 600pps. Most of the IC units measured (70%) were low-pass modulation filters, 30% of these neurons were band-pass in character.

In addition, we observed aliasing based distortions in unit responses to amplitude modulated signals when the ratio of modulation frequency was greater than ¼ – $^{1}/_{6}$ the carrier rate. This distortion resulted in frequency representations which were sub-multiples of the intended modulation frequency. Most currently applied cochlear implant speech processing strategies permit modulation frequencies which are significantly greater than ¼ -$^{1}/_{6}$ carrier rate indicating that severe distortion and signal degradation may occur frequently in these devices.

Introduction:

Cochlear prostheses have been implanted in post-lingually deaf adults for more than 25 years. These implanted devices have proven so successful that direct electrical activation of the auditory nerve (AN) is now widely accepted as a safe and effective treatment for profound sensorineural hearing loss (Gates et al., 1995). Even using devices and coding strategies that were developed more than a decade ago, most adult cochlear implant users benefit substantially in terms of improved speech perception as well as speech production, especially when visual cues (lip-reading) are available. Moreover, there have been significant improvements in both device design and speech processing strategies in the last several years. Given these improvements, many cochlear implant (CI) users implanted with contemporary devices are able to correctly identify greater than 80% of high context sentences without visual cues (Wilson et al., 1991,1994), allowing these otherwise profoundly deaf individuals to verbally communicate using the telephone.

Much of the recent improvement in speech reception and speech production of cochlear implant users can be attributed to advances in sound processing strategies. One particular advance involves the use of amplitude modulated pulse trains to transmit the auditory information from the intracochlear electrode to AN fibers. Speech information is encoded by amplitude modulation of a pulsatile carrier using the envelope of the speech signal within selected frequency bands as modulators. Although in some systems there can be as many as 22 channels, usually, there are four to eight such channels. Thus contemporary speech processing in cochlear implants consists of breaking the speech signal into 4 to 8 frequency bands, extracting the envelope of each band, using the fluctuating envelope to amplitude modulate (AM) a constant pulse-rate carrier and distributing each AM signal to a different intracochlear electrode contact (or pair of contacts). Each contact or pair of contacts 1) is located in different region of the cochlea; 2) activates a different frequency region of the tonotopically organized AN array; and 3) constitutes a different channel for the transmission of information. In addition to processing the speech signal into frequency bands whose envelope modulates a pulsatile carrier, attempts are made to route these AM signals to electrode contacts thought to be appropriate for the selected speech frequency band. For example, the envelope of a highest frequency speech band is delivered to an electrode located at the most basal region of the cochlea, whereas the envelopes of lower frequency bands are delivered to electrodes located at more apical regions.

Since these amplitude modulation strategies have proven useful to CI users, attention has been focused on the ability of CI subjects to detect differences in AM signals, and comparisons have been made to normal listeners detecting AM sounds. Psychophysical studies of AM sounds in normal hearing humans (Viemeister, 1979; Bacon and Viemeister, 1985; Yost et al., 1989; Houtgast, 1989) macaque monkeys (Moody, 1994) and chinchillas (Salvi et al., 1982) have measured the ability of hearing subjects to detect a difference between amplitude modulated and unmodulated sounds as a function of modulation frequency. These studies determine the minimum modulation depth necessary to allow differentiation of a *modulated* from an *unmodulated* sound and permits a plot of minimum modulation depth as a function of modulation frequency, a temporal modulation transfer function (TMTFs). These TMTFs are then used estimate temporal resolution in a given subject and to compare the temporal resolution across subjects and across species. The results of these studies of normal hearing subjects demonstrate that TMTFs are similar in all these mammals, in that they are 1) low-pass or broad band-pass functions with a high-frequency slope of 3-4 dB per octave, 2) that they have maximum sensitivities of approximately 20-80 Hz; and 3) that

they have a high frequency cutoff of between 55 and 160 Hz. The similarity of these acoustic TMTFs suggests that temporal resolution is not dramatically different among these various mammalian species with normal hearing.

Psychophysical studies among CI subjects have demonstrated that modulation detection among implant patients share many of the same general characteristics with that of normal hearing subjects (Eddington et al., 1978; Pfingst, 1988; Shannon, 1983; 1985; 1992; Townsend et al., 1987), and that temporal resolution is important for the perception of temporal pitch, prosody, and speech. For example, these studies have shown that CI users have TMTFs that are low pass functions with a cutoff frequency of 140 Hz and the highest sensitivity to modulations of 80 - 100 Hz (Shannon, 1992). Both the cutoff frequency and frequency of highest sensitivity of TMTF in CI subjects responding to direct electrical activation of the AN approximates that of normal hearing subjects responding to acoustic activation of cochlear hair cells.

The similarity of the results from psychophysical studies of temporal resolution in normal listeners and CI users suggest that the processes limiting temporal resolution in the auditory system are located in the central nervous system and not in the periphery. This suggestion is supported by physiological studies of the responses of single neurons using both acoustic and electrical activation of the AN.

In physiological studies of single neurons using acoustic signals temporal resolution has been estimated by measuring the ability of neurons to encode fluctuations in the envelope of amplitude modulated tones or bands of noise. The magnitude of the neuron's synchronized response as a function of the modulation frequency is used to construct neuronal TMTF's. Typically cutoff frequencies for these neuronal TMTFs in the AN and cochlear nucleus are higher than those reported in the psychophysical studies cited above. In AN fibers TMTF cutoff frequencies range between 500 and 1500 Hz for fibers with characteristic frequencies greater than 10 kHz where modulations are not limited by tuning curve bandwidth (e.g., see Joris and Yin, 1992; Palmer, 1982). Likewise, cutoff frequencies for cochlear nucleus (CN) neurons range between 50 and 1300 Hz (Møller, 1974; Frizina et al., 1990; Kim et al., 1990) and are higher than those reported in psychophysical studies.

In contrast to the discrepancy between single AN and CN neuron responses and psychophysical responses, cutoff frequencies for TMTFs of inferior colliculus (IC) neurons more closely approximate those observed in psychophysical studies. IC single and multi-neuron TMTFs have been measured in several species, including rats (Rees and Møller, 1983;1987), guinea pigs (Rees and Palmer, 1989), cats (Langner and Schreiner, 1988; Schreiner and Langner, 1988), and rabbits (Batra et al., 1989). In all these studies the average TMTF cutoff frequency is approximately 100 Hz and individual cutoff frequencies range from 10 Hz to 1000 Hz. The similarity in the temporal resolution of single IC neurons responding to acoustic signals and that estimated in psychophysical studies of normal hearing and CI users raises the possibility that the IC neurons may play an important role in defining the limits of temporal sensitivity.

In previous studies we began an examination of the spatial and temporal response properties of IC neurons to intracochlear electrical stimulation (Snyder et al., 1990, 1991). In these studies we described the basic temporal response patterns observed in poststimulus time histograms (PSTHs) of responses of IC neurons after stimulation with both pulsatile and sinusoidal signal. These responses were compared to response patterns seen after acoustic stimulation and found to be similar. In a subsequent study (Snyder et al., 1995) we estimated, as a first step, the temporal resolution of IC neurons by examining the ability of these neurons to follow trains of unmodulated biphasic electrical pulses that were delivered via chronically implanted intracochlear electrodes. The results showed that the response of all IC neurons could be characterized as low-pass functions, i.e., IC neurons

would respond to each supra-threshold pulse when it was delivered at a low frequency (20 pps or less). However, at higher frequencies, the amplitude of their response (measured in spikes per pulse) decreased progressively as the frequency of the pulse train increased, until at some frequency (the maximum cutoff frequency) the response consisted of a brief onset response followed by silence. The average high frequency cutoff of all IC neuron's in that study was approximately 100 pps.

The present study extends the examination of temporal resolution of IC neurons to intracochlear electrical stimulation (ICES) using sinusoidal amplitude modulation (SAM) of biphasic pulse trains. We have focused on these stimuli because they resemble the amplitude modulated pulsatile carriers used in the processed stimuli of CI subjects and are more similar to the stimuli used in previous acoustic and physiological studies of temporal resolution. The carrier frequencies in this study were varied between 100 and 1000 pps and the modulation frequencies were varied between 10 and 400 Hz. These parameters were chosen in order to mimic the stimuli used in CI speech processors. The major objectives of the study are: 1) to determine the temporal resolution of IC neurons to ICES using SAM pulse trains; 2) to relate that temporal resolution to the measures of temporal resolution in responses evoked by unmodulated pulses; and 3) to compare these measures to psychophysical measures of temporal resolution observed in CI users and in IC responses to SAM acoustic stimulation.

Methods:

Deafening, implantation and chronic stimulation:

Experiments were conducted in 6 prior normal adult cats that were acutely deafened two weeks prior to the physiological experiment and in 7 adult cats deafened as neonates. The left cochleas of six neonatally deafened cats were implanted and chronically stimulated, beginning at 7.5-10.5 weeks of age and continuing for at least 14 weeks prior to the terminal acute physiological experiment. The three remaining neonatally deafened cats were implanted as adults, about 2 weeks prior to the acute experiment. The implantation and stimulation histories of the chronically stimulated animals are summarized in Table I.

TABLE I

CAT #	Age at Deafening wks	Age at Implantation wks	Duration of Stimulation wks	Duration of Deafness wks	Type of Chronic Stimulation mod. freq./carrier
K101	0-2	7	28	37	33/300
K102	0-2	7	36	46	30/300
K104	0-2	9	34	42	20/800
K105	0-2	8	28	37	20/800
K106	0-2	8	32	42	20/800
K109	0-2	6	24	31	30/300
K117	0-2	6	22	30	SP*
CH158	adult	adult	22	24	30/300
CH087	adult	adult	32	33	30/300
CH497	adult	adult	30	32	30/300
CH611	adult	adult	28	188	SP* & 30/300
CH645	adult	adult	none	2	none
CH122	adult	adult	none	2	none

* SP = modified human analogue speech processor

Details of the procedures for neonatal deafening, surgery, implantation, chronic stimulation, and acute physiological preparations and recordings have been reported previously (Snyder et al. 1990b, 1991, 1994). In brief, kittens were deafened by daily intramuscular injections of neomycin sulfate (50 mg/Kg/day) beginning 24 hrs after birth and continuing for the next 16 days. During this developmental period hearing thresholds are known to be elevated by more than 90 dB SPL in normal kittens and do not reach normal adult thresholds until after 21 days postnatal (Brugge and O'Connor., 1984; Walsh and McGee, 1986). The ototoxic effect on hearing thresholds was monitored by recording click-evoked auditory brainstem responses (ABRs) and 500 Hz tone-evoked frequency following responses (FFRs). ABR and FFR thresholds were measured during the third post-natal week and at approximately 6 weeks of age. Normal adult cats were deafened 2-3 weeks prior to implantation by a single subcutaneous injection of neomycin sulfate (400 mg/kg) followed by an subcutaneous injection of amino oxyacetic acid (25 mg/kg). ABR and FFR

thresholds were tracked in these animals until they were greater than 110 dB SPL -- approximately 2-3 hr. (Leake et al., 1987). All animals included in this study had ABR and FFR thresholds above 110 dB SPL.

Prior to all surgical procedures, animals were sedated with an intramuscular injection of ketamine (22 mg/kg). While sedated, an intravenous catheter was inserted into the cephalic vein. Sterile mammalian Ringer's solution was continuously infused through the catheter. A surgical level of anesthesia was induced and maintained by infusion of sodium pentobarbital (60 mg/ml) via the intravenous catheter,. The animal's scalp was shaved, and the head mounted in a Kopf mouth-bar head holder..

Intracochlear implants were inserted into the scala tympani through the round window and consisted of four wire electrodes which have been described in detail elsewhere (see Rebscher, 1985, Rebscher et al., 1988).. However, in brief, the electrodes consist of four Teflon coated and Paralene-C insulated, platinum-iridium (90%:10%) wires, embedded in a Silastic carrier. Each wire ended as a 250-300 μm ball contact. The contacts were arranged as off-set radial pairs, an apical pair (labeled 1,2) typically located approximately 10 mm from the cochlear base and a basal pair (labeled 3,4) typically located about 6 mm from the base. Each contact of a pair was separated from the other by 1 mm, and the centers of the two pairs were separated by a distance of 3 mm.

In most animals stimuli for chronic electrical stimulation were capacitively-coupled, charge-balanced signals consisting of biphasic square-wave pulses (0.2 msec/phase), alternating in polarity and delivered continuously at 30 or 80 pulses per second (pps). In one animal the chronic electrical stimuli were electrical analogues of the ambient acoustic environment. This animal was maintained in a open wire cage in the laboratory. The spectral content of the ambient acoustic environment was difficult to characterize and highly variable. The environment consisted primarily of noises generated by this very active animal, speech from the workers in the laboratory, and occasionally music and speech from a nearby radio. The analogue wave forms were band-pass filtered between 0.1 and 3 kHz and subjected to logarithmic amplitude compression. The maximum output of the device was set to 6 dB above the ABR threshold. For all animals the stimulating signals were delivered using constant current stimulators (Vureck et al., 1981). Chronic stimuli were delivered to one intracochlear electrode pair at a maximum intensity 2-6 dB above electrically evoked auditory brainstem response (EABR) threshold and presented 4 hr/day, 5 days/week, for periods of 36 – 22 weeks (see Table 1). The currents specified in all cases are peak currents set relative to EABR threshold. EABR thresholds were measured approximately twice monthly.

Acute electrophysiological experiments:

In acute physiological experiments animals were anesthetized as described above and a canula inserted into the trachea via a tracheostomy. A urinary canula was also inserted into the bladder via the urethra. After the scalp over the right side of the scull was reflected and the temporalis muscle removed, a craniotomy was performed through the right parietal bone just anterior to the tentorium to give access to the middle cranial fossa. The dura was excised and the right occipital cortex aspirated to expose the tentorium. Using a diamond burr, an opening was made in the tentorium that was adequate to expose the entire dorsal and dorsolateral surface of the IC. Tungsten microelectrodes were inserted in the coronal plane at an angle 45° off the parasagittal plane. Neural activity was amplified (10,000-20,000 times) with a band-pass of 300 Hz to 3 kHz

using a battery powered preamplifier (WPI DAM50) along with a second stage amplifier (Tektronix 5A22N) and monitored on a Tektronix 5110 oscilloscope. Action potentials from single neurons were isolated from both background activity and electrical artifacts using a spike discriminator (BAK DIS-1). The time of occurrence of each discriminated spike was recorded and stored using a PC microcomputer with an accuracy of 10 μsec.

Search stimuli consisted of biphasic pulses (0.2 μsec/phase) delivered at 3/sec. Once a neuron had been isolated, its threshold was determined to the search stimulus. Then the intensity was set to 6 dB above threshold, and the neuron responses to 40 presentations of a 10 pulse per second (pps) pulse train were recorded and displayed as poststimulus time histograms [PSTHs). The pulse train was 320 msec in duration with a 1 sec interval between pulse trains. After the responses at this frequency were recorded, the pulse frequency was increased by 10 pps and the process repeated until the neuron no longer responded in a time-locked manner, i.e., responded with only an onset burst. The amplitude of the time-locked response was estimated the following formula:

$$R_{t\text{-}l}=(R_t-R_o)*VS/N_{pls}$$

where $R_{t\text{-}l}$ is the time-locked rate, R_t is the total number of spikes, R_o is the number of spikes in the onset discharge, VS is the vector strength and N_{pls} is the number of electrical pulses in the train -1 (the spike that produced the onset burst). Vector strength was computed after constructing a period histogram in which an onset delay was introduced such that the onset burst was excluded from the analysis. From the responses to a series of pules trains at increasing pulse frequencies at a single intensity (called a frequency series), a frequency transfer function was constructed and the spike rate (usually express as the number of time locked spikes/pulse) was plotted as a function of pulse rate (a frequency transfer function or FTF). Frequency series were usually recorded at three intensities: 2, 4 and 6 dB above threshold.

Since electrical artifact can have an amplitude that is comparable to, or larger than a neuron's recorded action potential, single neuron recordings can be contaminate by artifacts of the electrical pulses, especially when high stimulus rates and/or carrier rates are used. Therefore, great care was taken to record the responses of neurons whose spikes could be clearly discriminated from the electrical artifacts. In every case, the PSTHs of responses at all three intensities were examined for evidence of inclusion of electrical artifacts in the recorded responses both at the time of the recording and during later analysis. If no acceptance pulses were recorded from the window discriminator with a latency of less than 1 msec in the PSTH and if there were no highly synchronized peaks at or near zero phase in the period histograms of the frequency series, then the data were included in this study. Moreover, although frequencies series were recorded at low (2 dB above), intermediate (4 dB above) and high (6 dB above threshold) intensities, all modulation responses were recorded at the intermediate intensity. This intermediate intensity was chosen, since stimulus intensity has only a small or negligible effect on temporal resolution and since it was reasoned that if there was no evidence of artifact at the higher (6 dB) intensity where the artifact should be larger and more difficult to discriminate from the response, then at the intermediate intensity there was a minimal probability of artifact contaminating the modulation responses.

Responses to 100 % sinusoidal amplitude modulation (SAM) of 500 msec pulse trains separated by an interstimulus interval of 2 sec were initially recorded using carrier frequencies which increased from 100 to 1000 pps in 100 pps steps. In subsequent experiments in order to save time carrier were incremented in 200 pps steps or the carrier frequencies were incremented to only 500 pps

when the response was constant using a range of carriers from 100 to 500 pps. Modulation series using modulation frequencies ranging from 8 Hz to as high as 400 Hz were tested. Each modulation series consisted of a fixed modulation frequency and fixed modulation level, while the carrier frequency was increased. The stimulus intensity was chosen by adjusting the maximum pulse current to be equal to be 4-5 dB above threshold, i.e., equal to the intermediate intensity used in the frequency series as described above. Modulation frequencies were selected in pseudo random order beginning with 30 Hz, followed by 8 Hz, 16 Hz, 24 Hz, 40 Hz, 60 Hz and then increasing in 20 Hz steps. The maximum modulation frequency for each neuron was determined when that neuron ceased to respond in a time locked manner at that modulation frequency using any carrier between 100 and 1000 pps. The amplitude of the time-locked modulation response was estimated by the following formula:

$$R_{t\text{-}l}=(R_t-R_o)*VS/N_c$$

where $R_{t\text{-}l}$ is the time-locked rate, R_t is the total number of spikes, R_o is the number of spikes in the onset discharge, VS is the vector strength and N_c is the number of modulation cycles in the train -1 (the cycle that produced the onset burst).

Stimulus levels were controlled using an Hewlett-Packard attenuator (model 350D). and were delivered to the intracochlear electrodes by a constant current stimulator. Responses were recorded differentially using two impedance-matched paralene-coated tungsten microelectrodes with an impedance of approximately 1 MΩ at 1 kHz. One "reference" microelectrode was positioned at the surface of the IC, while the other, "active" electrode was mounted on an hydraulic microdrive mounted in a micromanipulator. Using micromanipulators the electrodes were positioned at the surface of the IC. Then the active electrode was advanced through the nucleus using the microdrive. A standardized trajectory was employed for all electrode penetrations. The trajectory was in the coronal plane tilted off the parasagittal plane by 45° so that the penetrating electrode entered the IC at its dorsolateral margin and advanced toward its ventromedial edge.

Results:

As described previously (Snyder et al., 1995), neurons in the IC of respond vigorously to intracochlear electrical pulses. Each electrical pulse produces a time locked spike or burst of spikes when the pulse frequency is low (20 pps or less), but as pulse frequency increases the number of spikes per pulse diminishes monotonically (e.g., see Fig. 1A, 3A, 5A). Thus the temporal responses of IC neurons to unmodulated electrical pulses can be described by low pass functions when response rate in spikes/pulse is plotted against pulse frequency. As can be seen in Figure 1A, the decrease in the response of IC neurons occurs as a result of adaptation. At low pulse rates each pulse evokes a spike and the number of spikes evoked by each pulse in the train is roughly equivalent. At moderate pulse rates, the number of spikes evoked by pulses occurring near the end of the train are fewer than those evoked by pulses at the beginning. At some moderate pulse rate or frequency (F6dB), the average number of spikes/pulse decreases to half that of the maximum response amplitude. At still higher pulse frequencies, only the first few pulses evoke a response. Finally, at some still higher frequency (maximum following frequency or Fmax), IC neurons respond to sustained trains of intracochlear current pulses with only a brief on-set burst evoked by the first pulse of the train followed by no spikes or randomly timed spikes at a very low rate (see Fig. 1A, 160 pps).

FIGURE 1

Effects of stimulus intensity:

Even the earliest studies of responses of peripheral and central neurons to intracochlear electrical stimulation have commented upon their relatively narrow dynamic range when activated with intracochlear electrical pulses (e.g. see Kiang and Moxon, 1972, Merzenich, 1974). In a previous study, Snyder et al. (1995) determined that the dynamic range of large sample of IC neurons was between 8 - 12 dB when activated by unmodulated electrical pulses, and that, once stimulus intensity reached 2-3 dB above threshold the frequency following capacity (temporal resolution) of most IC neurons was not significantly affected by stimulus intensity. Nevertheless, in order to control for intensity effects, responses of most neurons in this study were recorded at three stimulus intensities, 2-3 dB, 4-5 dB and 6-7 dB above threshold. Examples of a typical neuron's responses at these three intensities are illustrated in Figure 1. In Figure 1A the PSTHs to pulse trains at increasing pulse frequencies are illustrated at 2 dB (158 μAmps), 4 dB (200 μAmps) and 6 dB (251 μAmps) above threshold. At all three intensities, the responses display little or no adaptation at pulse rates below 80 pps. The number of spikes evoked by each pulse is vigorous and relatively uniform. The number of spikes evoked by the first pulses is the same or nearly the same as that elicited by the last pulse. At rates of 80 pps and the greater, there is clear adaptation across the duration of the stimulus and the rate of adaptation increases progressively, until at approximately 150 pps, the neuron responds with an onset burst followed by no discharges. Thus an examination of the PSTHs indicates that increasing pulse rate has a similar monotonic effect on this neuron's responses regardless of stimulus intensity and that Fmax is the same (approximately 150 pps) at all three intensities.

If the spike rate is plotted in spikes per second as a function of pulse frequency (Fig. 1B upper), the shape of the frequency transfer function varies with intensity. At low intensity (2 dB above threshold or 158 μAmps) the neuron's response is a relatively sharply tuned band-pass function with the maximum response at 80 pps. When the intensity is raised to 6 dB above threshold or 251 μAmps, the neuron's response becomes relatively broad with the maximum response at a

slightly lower frequency (approximately 70 pps). The band-pass shape of these functions suggests that this neuron responds 'best' to frequencies between 70-80 pps and more or less equally poorly to frequencies above and below this rate. However, an examination of the PSTHs indicates that despite the similarity in the overall spike rates for pulse frequencies of, for example, 10 and 110 pps, this neuron responds much more strongly to individual pulses at pulse frequencies below the 'best' frequency than it does to pulse frequencies above that frequency.

If the spike rate is plotted in spikes per pulse as a function of pulse frequency (Fig. 1B lower), the shape of the frequency transfer functions are consistently low-pass and it is clear that the responses to pulses delivered at low rates is much stronger than the responses to high pulse rates. Thus, despite the common practice of reporting spike rates in spikes per second, we have chosen to analyze and report our results in neurons of spikes per pulse (spk/p) for frequency transfer functions (FTFs) and numbers of spikes per modulation cycle (spk/c) for the temporal modulation transfer functions (TMTFs). Moreover, we have chosen to examine the TMTFs at intensities (4-5 dB above threshold) where pulse amplitude has little effect on the temporal resolution.

Effects of modulation and carrier frequency:

The effects of modulation frequency and carrier frequency on the responses of IC neurons to SAM pulse trains are complex. And one might predict that these effects would interact strongly with the temporal resolution of that neuron (as indicated by its maximum following frequency to unmodulated pulse trains). For example, it might be expected that a given neuron might respond solely to *modulation* frequencies at or below its maximum following frequency regardless of the carrier frequency. Or, alternatively, one might predict that a neuron would respond poorly to all modulations of *carriers* frequencies that are above its maximum following frequency. In this section we will describe the influence of these three factors (modulation frequency, carrier frequency and maximum following frequency (Fmax) on the responses of IC neurons.

FIGURE 2

We estimated Fmax at a moderate stimulus intensity (4-6 dB above threshold) in **207** IC neurons (Figure 2). The average Fmax for all these neurons was **104** pps, and the modal Fmax was **60** pps. Indicating that on average IC neurons produced no time-locked responses to unmodulated pulse trains at frequencies above approximately 60-100 pps. We have arbitrarily divided these neurons into three groups: low, medium and high temporal resolution groups. Low resolution neurons were neurons with an Fmax below 60 pps. Medium resolution neurons were neurons with an Fmax between 60 and 120 pps. High resolution neurons were those with an Fmax above 120 pps. In the next several figures the responses of low, medium and high resolution neurons will be illustrated to both unmodulated and SAM pulse trains. Representative responses are illustrated across a range of modulation and carrier frequencies to demonstrate the influence of these two parameters on modulation. Although responses were recorded at three intensities (usually 2, 4 & 6 dB above threshold), all these figures will illustrate responses evoked by the intermediate intensity (assuming Fmax was the same at the intermediate and higher intensity).

FIGURE 3

Figure 3 illustrates the responses of one low resolution neuron to both unmodulated pulse trains (Fig 3A) and SAM pulse trains (Fig. 3B). This neuron has a Fmax of approximately 30 pps . It responded strongly to unmodulated pulses delivered at 10 pps, moderately to 20 pps, weakly to 30 pps and with only an on-set burst at 40 pps. Given this low Fmax, one might make either of two predictions. One might predict that this neuron would respond only to modulation frequencies of 30 Hz or below. Or, alternatively, one might predict that this neuron would respond poorly to all modulation frequencies when stimulated with SAM carrier frequencies above 40 pps. The second hypothesis proves to be correct in this case (Fig. 3B). This low resolution neuron responded with a strong onset response to the first modulation cycle of all carrier frequencies, but this onset response was followed by either weak or no responses to subsequent modulation cycles. This poor modulation response was observed regardless of the frequency of the carrier. At the lowest carrier frequency of 96 pps (top row in Fig. 3B) there was a weak modulated response, but at higher carrier frequencies (e.g., 417 pps; Fig. 3B, bottom row) there was not modulated response. The average time locked response (total response minus the onset response for all carrier frequencies) is low (approximately 3 spk/c) at the lowest modulation frequency (8 Hz) and decreases at higher modulation frequencies to less than 1 spk/c (Fig. 3C). Thus Fmax, a measure of temporal resolution using unmodulated pulse trains, is a poor predictor of this neuron's sensitivity to modulation frequency. However, Fmax is a reasonable predictor of this neuron's sensitivity to changes in carrier frequency in the sense that it correctly predicts that it doe not respond to high frequency pulses (modulated or not). However, this extreme sensitivity to carrier frequency such that no modulation response could be recorded was observed in only 7 (3%) of IC neurons: 5 were low resolution neurons, 1 medium resolution and 1 high resolution neuron.

FIGURE 4

The responses of most IC neurons were the relatively insensitive to carrier frequency. In these neurons Fmax was a relatively good predictor of the neuron's sensitivity to modulation frequency and a poor predictor of its sensitivity to carrier rate. Figure 4 illustrates the responses of a second low resolution neuron whose modulated response was insensitive to carrier frequency and in which Fmax underestimates the response to modulated signals. At 4 dB above threshold (501 μA), this neuron responded strongly to 10 and 20 pps unmodulated trains, moderately to 30 pps trains and very weakly to 40 pps trains (Fig. 4A). Thus its Fmax is estimated to be 40 pps (only slightly higher than that of the previous neuron). However, at an identical peak intensity, it responded strongly to all SAM carriers from 96 to 345 pps (the highest carrier frequencies tested) and to modulation frequencies up to 40 Hz (the highest modulation frequency recorded). Carrier frequency had little influence on this neuron's modulation response. The amplitude of the modulation response in spk/c is similar for all carrier frequencies up to 345 pps (responses along vertical columns, Fig. 4B). Moreover, in Figure 4C the average spk/c over all SAM carriers (solid diamonds) is greater than amplitude of the unmodulated time-locked response (open triangles) at all repetition frequencies. Thus Fmax is a poor predictor of this neurons response to SAM of high frequency carriers, but a good predictor of its response too modulation frequencies. It responded to these carriers when they are modulated, but not when they are unmodulated.

In addition to responding to relatively high frequency carriers, this neuron responded to modulation frequencies which are above its Fmax. A comparison of the response to 40 pps pulses (last response, Fig. 4A) with the 40/345 response, i.e., 40 Hz modulation of a 345 pps carrier (last response in far right column, Fig. 4B) illustrates this stronger modulation response. Excluding the

onset burst, this neuron responded at a rate of less than 1 spk/p to 40 pps unmodulated pulse train (Fig. 4C), whereas its average response rate to 40 Hz modulation is 7 spk/c. It might be argued that at this intensity there are many more pulses above threshold in a 40/345 pps stimulus than there are in a 40 pps pulse train of comparable duration and, therefore, one might expect that the modulated response would be larger than the unmodulated response. However, the carrier frequency has little influence on either the amplitude or temporal dispersion of the modulated response. There are four times as many pulses in each modulation cycle of a 345 pps carrier than in a 96 pps carrier. Yet, at all modulation frequencies the responses at both carrier frequencies are similar. Moreover, it is clear that this neuron does not resolve the individual pulses in these carriers. The temporal dispersion (vector strength) of responses evoked by modulated pulses at all carrier frequencies is comparable to that observed in the responses to unmodulated pulses. Thus it is not the case that this neuron is responding to each supra-threshold pulse in the 40 Hz modulated carrier and, therefore, has a stronger response to 40 Hz modulation of a carrier than to pulses presented at 40 pps. Rather, modulation of relatively high frequency carriers activated this neuron more strongly and produced a time-locked response at higher modulation frequencies than at comparable unmodulated pulse frequencies.

FIGURES 5, 6, 7

To summarize this neuron's response properties: It is a low frequency neuron (i.e., a neuron with relatively low temporal resolution to unmodulated pulse trains) which responds to relatively high *modulation* frequencies, i.e., it responds to Fm's that are above its Fmax. Both its frequency transfer function and modulation transfer function are low pass. The responses to different carrier frequencies appear to be all pass (or the cut off is higher than any carrier frequency tested) and the response to SAM pulse trains is relatively insensitive to carrier frequency, i.e., it responds vigorously to modulations of carrier frequencies that are more than 10 times its Fmax. These characteristics are typical of most IC neurons. In 138 (74%) of the 185 neurons in which it could be measured, modulation responses were relatively insensitive to carrier frequency, i.e., carrier filter function was low pass with an upper cutoff frequency greater than 600 pps (Fig.). However, like most IC neurons, this neuron is very sensitive to modulation frequency. It did not response to any carriers modulated at frequencies above 40 Hz. Typically, the modulation response was a low pass function; 70% are low pass, whereas 30% are band pass (Fig. 6) and the average maximum modulation frequency (maxFm) was 42.2 Hz with a range of 8 to 220 Hz (Fig. 7). Thus the responses of the neuron illustrated in Figure 4 are typical of IC neurons, although one unusual aspect of its response is that its maxFm is higher than its Fmax. It responds to higher modulation frequencies than it can respond to as unmodulated pulses.

FIGURES 8

Figure 8 illustrates the response of a medium resolution neuron with a modulation response that is similar the low resolution neuron illustrated in Figure 4. Its modulation response is not sensitive to carrier frequency. The frequency series (Fig. 8A) demonstrates that this neuron has an Fmax of approximately 70 pps. At frequencies of 80 pps and above, it responds to a sustained series of pulses with only an onset burst and a small number of randomly timed spikes. Yet, when it is stimulated with all SAM carriers varying from 96 to 417 pps (Fig. 8B), it responds strongly at modulation frequencies from 8 to 24 Hz. At a modulation frequency of 30 Hz, the modulation

response is clearly diminished at lower carrier frequencies (30/96 and 30/185), whereas at higher carrier frequencies the response is still quite strong. At a modulation frequency of 40 Hz, the modulation response is diminished even further and the nature of the responses it dependent upon the carrier frequency. The response to 40/96 (40 Hz modulation of 96 pps carrier) consists of spikes time locked to alternating modulation cycles, so that the primary component of the response corresponds to 20 Hz. At higher carrier frequencies (40/185 and 40/268) the overall response and its 20 Hz component decrease progressively. At the highest carrier frequencies (40/345 and 40/417) the overall response recovers somewhat and the primary component corresponds to 40 Hz. In Figure 8C the neuron's responses in terms of spikes/pulse and spikes/cycle (respectively) are illustrated. Both the time locked (spikes/cycle) modulated and unmodulated responses are low pass functions with comparable cut off frequencies. Thus Fmax in this neuron is a good predictor of the maxFm, although it is a poor predictor of the effect of carrier frequency. The modulation responses are relatively insensitive to carrier frequency, but are highly sensitive to modulation frequency.

FIGURE 9

The responses of the previous two neurons are typical of 74% of IC neurons in that their modulation responses were insensitive to carrier frequency and were a low pass function of modulation frequency. Figure 9 illustrates the response of a second medium resolution neuron which is sensitive to both carrier and modulation frequency. The frequency series (Fig. 9A) demonstrates that this neuron responds strongly when stimulated with unmodulated pulses at repetition rates up to 40 pps. Above that frequency the time locked response diminishes progressively, but it is still measurable up to 100 pps. Thus the Fmax of this neuron is approximately 100 pps. When stimulated with a SAM 100 pps carrier (top row in the modulation series) this neurons responds to modulations from 8 to 40 Hz. However, at carrier frequencies above 100 pps its response is progressively attenuated and this attenuation is modulation frequency dependent. For example, modulation of a 185 pps carrier (Fig. 9B, 2nd row), produces a very weak response at 8 Hz modulation (8/185), but a strong response at all other modulation frequencies, whereas modulation of a 268 pps carrier produces weak modulation response at all modulation frequencies. Thus the response of this neuron is sensitive to both carrier and modulation frequencies. The carrier filter is a low pass function with a cutoff frequency of approximately 185 pps and the modulation filter is also low pass with a cutoff of just above 40 Hz. Moreover, the relationship between Fmax and maxFm is the reverse of that seen in the previous neuron. Ignoring for the moment the 40/96 (which will be discussed below), the responses to 40/185 - 417 are much weaker than the response to 40 pps unmodulated pulses (Fig. 9A) indicating that this neuron can follow higher repetition rates when the pulses are unmodulated than when they are modulated. Sensitivity to both modulation and carrier frequencies was observed in 26% (44 of 185) of IC neurons.

FIGURE 10

Figure 10 illustrates the responses of a high resolution neuron. This neurons responds strongly to unmodulated pulses delivered at rates up to 90 pps, responds moderately to pulses at rates of 100 to 150 pps and responds weakly to pulses above 150 pps (Fig. 10A). At a pulse rate of approximately 350 pps, it no longer responds in a time locked fashion, its Fmax is approximately 350 pps. When stimulated with SAM pulse trains (Fig. 10B), this neuron has a strong phase-locked response to modulation frequencies from 8 to 30 Hz. It has a modest response to 40 Hz modulation

and weak but significant responses to modulations from 60 to 100 Hz, especially at carrier frequencies above 345 pps. Thus this high resolution neuron can follow higher modulation frequencies than any of the previous lower resolution neurons. Figure 10C demonstrates that the modulation transfer function (filled diamonds) parallels the frequency transfer function (open triangles) although it rolls off at a much lower repetition frequency. This suggests that there is a tendency for neurons which display high resolution to unmodulated pulses to display higher resolution to modulated carriers. However, this is just a tendency as is illustrated in Figure 11 in which maxFm is plotted as a function of Fmax for 129 neurons for which both values could be determined. Most of the data points fall below the equal frequency contour (dashed line) indicating, as suggested previously, that most of these neurons have a maxFm which is less than Fmax. Linear regression analysis (solid line) indicates that on average maxFm is approximately half Fmax. The positive slope of the regression line confirms that there is a tendency for maxFm to increase as Fmax increases, but the low r^2 value (0.101) indicates this relationship is relatively weak.

FIGURE 11

An examination of the modulated responses of the high resolution neuron in Figure 10 illustrates two additional important aspects of modulated responses characteristic of many IC neurons responding to SAM electrical pulse trains. First, at low modulation frequencies, these high resolution neurons resolve individual pulses in the carrier. For example, in response to an 8/96 stimulus (upper left response, Fig. 10B) this neuron produces a series of four spike clusters, each cluster corresponding to a maximum in the 8 Hz envelope of the stimulus. Within each cluster there are a series of peaks, each time locked to the 96 pps carrier. Thus each supra-threshold pulse in the carrier evokes a spike and the probability of a spike is modulated by the envelope. In this way both the modulation frequency and carrier rates are represented in these low-modulation-frequency / low-carrier-rate signals. Second, in response to low carrier rates modulated at high modulation frequencies (low Fc to Fm ratios), there are distortions in the response, i.e., peaks in the response at unexpected intervals. These unexpected distortion intervals arise as a result of under-sampling of the modulation frequency by the carrier frequency. For example, when stimulated by a 96 pps carrier modulated at 40 Hz the response has peaks that are separated by intervals that are multiples of the modulation interval. Similar response interval doubling can be seen in responses described previously (see 30/96 in Fig. 4B; 40/96 & 40/185 in Figs. 4B, 8B, 9B). In other cases these distortions take the form of a low frequency modulation of the modulated response. For example, when stimulated by 30/96 pps modulated at 30 Hz or 185 pps carrier modulated at 60 Hz, the neuron illustrated in Figure 10B responds with spikes clustered at peaks corresponding to 60 Hz modulation, but these peaks are themselves modulated at a frequency of just over 6 Hz. The 6 Hz distortion produces three modulations of the 60 Hz response over the 500 msec recording. Similar, but higher, 'aliasing' modulations can be seen in this unit's responses, when it is stimulated with 80/185 to 80/417 modulation/carrier combinations (top four responses in the 80 Hz column). When stimulated at higher carrier frequencies (80/606 and 80/714), the overall amplitude of the neuron's response is diminished, but its response is time-locked to the 80 Hz modulation frequency. Thus when an IC neuron responds to modulation frequencies that are greater than 1/3 to 1/6 the carrier frequency, the major response intervals are distorted and unpredictable.

FIGURE 12

Band-pass modulation responses:

In all the examples examined so far, and in the modulation responses of most IC neurons, the responses to SAM pulse trains are low pass, i.e., they are equally strong to modulation frequencies below some 6dB cutoff frequency (modF6dB). Above this cutoff frequency the responses diminish, until at some maximum frequency it consists of only an onset burst. However, 30% of IC neurons (Figure 6) have band pass modulation responses. They respond poorly to low and high modulation frequencies and produce only an onset burst, but at intermediate modulation frequencies they produce a strong modulation response. One such neuron is illustrated in Figure 12. Figure 12A illustrates that this neuron is a low resolution neuron with an Fmax of approximately 60 pps. When presented with SAM pulses modulated at 8 Hz (Fig. 12B) this neuron responds with a only an onset burst at all carrier frequencies tested (96 and 606 pps). However, as the modulation frequency increases to 16 and 20 Hz, the neuron's modulation response increases such that there is a strong response at all carrier frequencies. At still higher modulation frequencies (>30 Hz), the modulation response gradually decreases, until at 40 Hz modulation the response again consists primarily of an onset response at carriers above 268 pps. As illustrated in Figure 12C, the frequency transfer function (in spk/pls, triangles) is low-pass, whereas the TMTF (in spks/c, diamonds) is band-pass. The modulation responses of this neuron are typical of the IC neurons (30%) with band-pass modulation response (|Fig. 6). The average maxFm of band-pass neurons was 34.2 Hz (Fig. 13) and the average maximum response occurred at 17.5 Hz.

FIGURE 13

Effects of modulation depth:

Given the differences between responses to modulated and unmodulated pulses trains, it is clear that modulation depth is an important factor determining the response of an IC neuron. Most of these neurons do not respond to an unmodulated (0% modulation) pulse train at 200 pps, whereas most respond vigorously to that same pulse train when it is 100% amplitude modulated at some appropriate modulation frequency (e.g., 30 Hz). Figure 14 illustrates the response of a typical IC neuron to unmodulated and modulated signals at various modulation frequencies and depths. In response to unmodulated pulses, this neurons has an Fmax of 50 pps (Fig. 14A). It has a vigorous time-locked response to unmodulated pulses at frequencies from 10 - 40 pps, a weak time-locked response at 50 pps and only an onset response at 60 pps and higher pulse rates. Thus this neuron's time-locked response to unmodulated signals decreases dramatically between 40 and 60 pps.

FIGURE 14

The modulation response of this neuron also decreases dramatically at modulation frequencies between 30 and 60 Hz (Fig. 14B). It responds vigorously to modulation frequencies of up to 30 Hz and to all carrier frequencies up to 417 pps (and to carriers up to 900 pps -- not shown). At a modulation frequency of 60 Hz, this neuron's modulation response decreases dramatically at all carrier frequencies. There is only a weak 60 Hz modulation response using carriers of 185 pps and

268 pps and no significant modulation response (i.e., only an onset response) at carriers above 345 pps.

Using carrier frequencies higher than this neuron's Fmax, its modulation response varies dramatically with modulation depth. When this neuron is stimulated with 30 Hz AM of a 96 pps carrier at depths from 0% to 90% (Fig. 12C), its response varies from no time-locked response to a strong time-locked response. As expected from the responses illustrated in the frequency series, 0% modulation of the 96 pps carrier produces only an onset burst. At modulation depths from 5 - 20 % the response consists primarily of an onset burst with a small number of time-locked spikes. As the modulation depth increases from 20% to 90% modulation, a sustained time-locked response increases progressively. At modulation depths of 30% to 50%, this neuron produces spikes at intervals corresponding to 3 times the modulation interval (or a frequency of 10 Hz) with some spikes at intervals corresponding to 30 Hz. At depths of 60% and 70%, the dominant response intervals correspond to 2 times the modulation interval; at 80% and higher modulation depths the dominant response interval corresponds to 30 Hz. When the carrier frequency is increased from 96 pps to 268 pps (Fig. 12D), this neuron responds only at intervals corresponding to the modulation frequency. These changes in dominant response intervals as a function of modulation depth are due to under-sampling (aliasing) of the modulation frequency by the carrier frequency as can be seen by increasing the carrier frequency or decreasing the modulation frequency. When the carrier frequency is increased from 96 pps to 368 pps, this neuron's 30 Hz responses make a smooth transition from the expected onset only response at 0% modulation to a 30 Hz time-locked modulation response at 100% modulation. Thus the dominant frequency represented in the modulation response of this neuron (and most IC neurons) can be a function of both modulation frequency and modulation depth when the carrier frequency is less than 4-6 times the modulation frequency.

Discussion:

In this investigation all experiments were conducted in adult cats deafened more than two weeks prior to the experiment. This protocol was adopted in order to avoid electrophonic effects, i.e., the indirect activation of AN fibers by depolarization of cochlear hair cells either by electromechanical movements of the basilar membrane or direct electrical depolarization. The activation of AN fibers solely by direct electrical stimulation makes interpretation of these results simpler and more closely models electrical stimulation in chronically deaf cochlear implant users.

In present studies we have examined the responses of IC neurons when trains of unmodulated and amplitude modulated current pulses are applied to the AN and we have estimated the temporal resolution of these neurons by measuring the amplitude of their time-locked responses as a function of the pulse (carrier) and modulation frequencies. We have found that the all frequency transfer functions and most modulation transfer functions are low-pass with an average maximum cutoff frequency for unmodulated pulses of 104 pps and an average maximum modulation frequency of 42.2 Hz for SAM pulses. These frequency maxima for synchronized responses are far below those seen following electrical stimulation of AN fibers which have been demonstrated to synchronize to electrical stimuli with repetition rates above 1 kHz (Hartmann and Klinke, 1989; van den Honert and Stypulkowski, 1984; Parkins, 1989; Dynes, 1996). Thus the relatively low Fmax of IC neurons does not reflect the temporal resolution of peripheral nerve fibers.

This differential between the temporal resolution of AN fibers on the one hand and IC neurons on the other is not specific to electrical stimulation. The discharges AN fibers (phase-lock) to acoustic pure tones at frequencies above 3 kHz (Johnson, 1980) and synchronize to the modulations of amplitude modulated tones to comparable frequencies (Kim et al., 1990; Joris and Yin, 1992; Greenwood and Joris, 1996). Whereas, the discharges of the average IC neuron can only synchronize to tones amplitude modulated at rates of approximately 100 Hz. The temporal resolution of IC neurons responding to amplitude modulation of intracochlear electrical pulses in deaf cats is slightly lower than of that estimated for IC neurons responding to acoustic stimulation using amplitude modulation of CF tones in normal hearing mammals. Langner and Schreiner (1988) estimated the best modulation frequency or BMF, i.e., the one which produced the highest spike rate in a large number of IC neurons responding to modulation of CF tones. Although these authors did not report an average BMF, 98% had BMFs below 300 Hz, 23% had BMFs below 30 Hz., Langner (1992) suggested that the average would be between 30 and 100Hz. Batra et al. (1989) reported an average BMF of 87 Hz for single neurons and multi-neuron clusters to amplitude modulated tones in rabbits. Rees and Møller (1987) found the modal modulation frequency of 100-120 Hz IC neurons in rats. These results using acoustic stimuli and examining the temporal resolution of IC neurons in normal hearing mammals are all somewhat higher than those reported here using AM pulse trains in deaf cats.

The similarity of the results suggests that the temporal resolution of IC neurons responding to repetitive electrical (artificial) stimulation is not dramatically different from that seen following acoustic (natural) stimulation in cats, rabbits, and rats despite the fundamentally different nature of the stimuli.

Much of the recent improvement in speech reception and speech production of cochlear implant users can be attributed to advances in sound processing strategies. One particular advance involves the use of amplitude modulated pulse trains to transmit the auditory information from the

intracochlear electrode to AN fibers. Typically, this strategy uses amplitude modulation of a fixed pulse frequency carrier. A different modulation frequency is delivered to each of a selected number of contacts in a multi-channel intracochlear electrode. Depending upon the speech processing system, the pulse frequency of the carrier can be as low as 250 pps (McDermott et al., 1992) to greater than 800 pps (Wilson et al., 1997). the speech signal is divided into several frequency bands by a bank of band-pass filters-- one filter with a different center frequency for each stimulation channel. The speech information is encoded by amplitude modulation of the pulsatile carriers using the envelope of the speech signal as the modulator. Although in some systems there can be as many as 22 channels, usually, there are four to eight such channels. The output of each band-pass filter is then put through a low-pass filter (200 - 400 Hz) to extract the envelope of the frequency band. This envelope is then used to modulate the amplitude of the carrier. Thus contemporary speech processing in cochlear implants consists of breaking the speech signal into frequency bands, extracting the envelope of the band, using the fluctuating envelope to amplitude modulate (AM) a constant pulse-rate carrier and distributing each AM signal to a different electrode contact (or pair of contacts). Each contact or pair of contacts 1) is located in different region of the cochlea; 2) activates a different frequency region of the tonotopically organized AN array; and 3) constitutes a different channel for the transmission of information. In addition to processing the speech signal into frequency bands whose envelope modulates a pulsatile carrier, attempts are made to route these AM signals to electrode contacts thought to be appropriate for the selected speech frequency band. For example, the envelope of a highest frequency speech band is delivered to an electrode located at the most basal region of the cochlea, whereas the envelopes of lower frequency bands are delivered to electrodes located at more apical regions.

FIGURE 15

ALIASING OF CARRIER BY THE MODULATION FREQUENCY

When IC neurons are stimulated with pulsatile carriers modulated at modulation to carrier ratios of less greater than 1:4, unpredictable distortions in the temporal patters of response occur. What is the cause of these unpredictable distortions? An examination of the stimuli indicate that they arise as a consequence of carrier frequencies which 'under-sample' the modulation frequency. This under-sampling can occurs when the peak stimulus current is near the neuron's threshold, as it often will be, given the narrow dynamic range of intracochlear electrical stimulation. When a threshold mechanism is applied to a modulated pulse train and the carrier and modulation frequencies are time locked relative to each other, the stimulus crosses threshold and evokes a spike at intervals that depends upon several factors including: the threshold and temporal resolution of the neuron, the ratio between the carrier and modulation frequencies, and the depth of modulation. This interaction is illustrated in Figure 15 which illustrates 15 cycles (500 msec) of a 96 pps carrier modulated at 30 Hz. The modulation envelope is illustrated by the solid line in the lower half of the figure. A hypothetical neural threshold at 4 dB below peak current is indicated by the horizontal dashed line in the upper half of the figure. By focusing on the peak pulses, three (6 Hz) modulations of the carrier can be clearly seen. The amplitude and timing of these 'supra-threshold' pulses closely match the discharges produced in the 30/96 response illustrated in Figure 10B. Thus, under certain conditions, under-sampling occurs which can lead not only to modulation of the modulation response but also to variations in the timing of neuronal discharges such that they occur over a range of intervals that are integral multiples of the carrier interval and to skipping of whole modulation cycles altogether (see for example the 40/96 response in Figure 8 and the 40/185 response in Figure

9). These distortions can occur despite the fact that the carrier frequency is more than 2.5 times the modulation frequency, i.e., the modulation frequency is well below the Nyquist frequency for the carrier. The responses of IC neurons indicate the pulsatile carrier frequencies must be between 4 and 6 times the modulation frequency in order to avoid the production of these unpredictable and undesirable distortions.

In these applications acoustic signals are encoded by filtering the ambient acoustic signals (including speech) into frequency bands. The amplitude fluctuations in the envelope of each band are extracted by rectification and low-pass filtering. An these envelope frequencies are used to amplitude modulate a pulsatile carrier which is used as the input for one (usually) channel of a multi-channel intracochlear electrode. Thus within any given implant, the pulsatile carrier frequency is fixed; only the amplitude, phase and frequency of the modulations varies across channels. The modulation frequencies contained in each channel is obviously determined by the fluctuations in the amplitude of the ambient signal, but the maximum modulation frequency is set by the cutoff frequency of the low pass filter. Our results indicated the cutoff frequency of this filter should not be higher than 1/4 -1/6 the carrier frequency.

IC NEURON AND PSYCHOPHYSICAL MEASURES OF TEMPORAL RESOLUTION:

The measures of temporal resolution in IC neurons reported here for ICES can be compared to psychophysical measures of temporal resolution or rate pitch in human subjects. Several studies have examined rate pitch discrimination in cochlear implant patients with multi-channel devices (Eddington et al., 1978; Shannon, 1983, 1992; Townshend et al., 1987). Eddington et al. (1978) reported that rate or periodicity pitch increased with pulse frequency and saturated at 800 pps, but that discriminations of 25 Hz could be made only up to a maximum frequency of 400 pps. Shannon (1983) reported pitch saturation at approximately 300 Hz. In contrast, Townshend et al. (1987) reported difference limens of 150 pps using pulse frequencies above 1000 pps. These pitch discrimination tasks are difficult to interpret since changing the frequency of electrical stimuli also changes other perceptual cues, especially loudness (Pfingst, 1988). Shannon (1992) tried to address this question by measuring the ability of cochlear implant patients to detect the AM and beat frequencies of high frequency carriers, whose percept changes little over the modulation frequency range used. He studied implant patients with three different multi-channel devices using both pulses and sinusoids at several stimulus levels. He found that the temporal modulation transfer functions (TMTFs) of most of these implant patients were low pass with an average 3 dB cutoff frequency of 148.8 Hz and a maximum discrimination frequency of 300-500 Hz. Moreover, he found that the shape of these functions and their cutoff frequencies were independent of stimulus level once the level was greater than 4-5 dB SL.

In normal-hearing subjects comparable temporal resolution studies have used AM noise to examine non-spectral (periodicity) pitch discrimination. Harris (1963) estimated the maximum modulation frequency at which AM noise produced a pitch percept and estimated that maximum modulation frequency at between 750 and 2000 Hz. Likewise Burns and Viemeister (1976) found that 1 kHz was the maximum modulation frequency at which a change in frequency produced a change in pitch. Veimeister (1979) and Bacon and Viemeister (1989) determined sensitivity to modulation depth rather than the detection of pitch changes for normal-hearing subjects. They reported that these TMTFs were low pass with a 3 dB cutoff frequency of 50 Hz and saturation at 1000 Hz. Thus the function describing temporal resolution in normal-hearing subjects appears to a

be a low pass function with a 3 dB cutoff frequency of 50-70 Hz and a maximum cutoff frequency of 500-1000 Hz. Shannon (1992) has made comparable measurements and constructed the analogous TMTFs in cochlear implant patients. He found that these TMTFs were also low pass functions with a slightly higher 3 dB cutoff frequency (100-200 Hz), but a slightly lower maximum cutoff frequency (300-500 Hz) . However, he suggests that these differences in cutoff frequency between acoustic and electrical TMTFs may be more apparent than real given the differences in the dynamic ranges of these two sets of stimuli. In either case, the maximum cutoff frequency (300-700 pps) reported here for IC neurons following electrical stimulation is within the range of estimates of maximum resolution seen for normal-hearing subjects and cochlear implant patients.

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Figure Legends:

FIGURE 1. Responses of a high resolution inferior colliculus (IC) neuron activated by intracochlear electrical stimulation (ICES) at three intensities: 2, 4, and 6 dB above threshold (i.e., 158, 200 and 251 μAmps, respectively). The stimuli are unmodulated pulse trains of increasing pulse frequency from 10 to 160 pulses per second (pps). A. Each column of poststimulus time histograms (PSTHs) represents a frequency series of responses evoked by unmodulated pulse trains delivered at the intensity indicated above it. The maximum number of spikes/bin in this an all subsequent figures is 26. B. Frequency transfer functions (FTFs). Plots of total spikes and time-locked spike rates expressed in spikes/sec at each intensity as a function of stimulus frequency. C. FTFs of time-locked spike rates expressed in spikes/pulse at each intensity.

FIGURE 2. Histogram of the maximum following frequencies (Fmax) for 207 neurons. The average Fmax is 104 pps. N=207.

FIGURE 3. Responses of a low resolution IC neuron responding to ICES using modulated and unmodulated pulse trains at 6 dB above threshold or 125 μA peak current. A. A frequency series of PSTHs evoked by unmodulated pulse trains delivered at pulse rates from 10 to 40 pps (indicated to the left of each PSTH). The total number of spikes and an estimate of the time locked response (total spikes minus onset spikes) are indicated in the upper right of each PSTH. B. PSTHs of Responses evoked by stimulation with sinusoidally amplitude modulated (SAM) pulse trains. Each column represents this neuron's response at one modulation frequency (indicated at the top of each column) presented using five carrier frequencies (indicated to the left of each row). C. Plots of time-locked spike rates to unmodulated pulse trains in spikes/sec (open triangles) and spikes per pulse (open circles) and average time locked response to SAM pulse trains in spike/cycle averaged across all five carrier frequencies (closed diamonds) as function of fundamental repetition rate (pulse or modulation frequency).

FIGURE 4. Responses of a second low resolution IC neuron responding to ICES using modulated and unmodulated pulse trains at an intensity 4 dB above threshold or 501 μA. A. Frequency series of four PSTHs evoked by unmodulated pulse trains of increasing frequency from 10 to 40 pps. Pulse rate is indicated in the upper left of each PSTH. The total number of spikes and an estimate of the time locked response (total spikes minus onset spikes) is indicated in the upper right of each PSTH. B. Four modulation series consisting of PSTHs of responses evoked by SAM pulse trains at four carrier frequencies. Each column represents this neuron's responses to one modulation frequency (indicated at the top of each column) using four carrier frequencies (indicated to the left of each row). C. Plots of time locked spike rates to unmodulated pulse trains (open symbols) and the average time locked rate to SAM pulse trains (closed symbols) for all four carrier frequencies as a function of fundamental repetition rate (pulse or modulation .

FIGURE 5. Histogram of the maximum carrier frequency to which the recorded IC neurons were able to respond.. Most (74%) IC neurons were insensitive to carrier frequency with a cut off frequency greater than the maximum frequency tested (usually >600 pps). A small number of neurons displayed low pass (LP) carrier filters with cut off frequencies below 600 pps and a very small number (3%) of neurons displayed band pass (BP) carrier filters with modulation responses only with carriers between 200 and 500 pps.

FIGURE 6. Histogram illustrating the percentage of neurons with low pass (LP) and band pass (BP) modulation filters.

FIGURE 7. Histogram illustrating the maximum modulation frequency (maxFm) to which neurons with low pass modulation filters would respond. The average maxFm is 42.2 Hz. The bin marked >40 indicates neurons that were lost before their maxFm could be determined.

FIGURE 8. Responses of a medium resolution IC neuron responding to ICES using modulated and unmodulated pulse trains at an intensity 4 dB above threshold or 562 μA. A. Frequency series consisting of ten PSTHs evoked by unmodulated pulse trains of increasing frequency from 10 to 100 pps indicated in the upper left of each response. The total number of spikes and an estimate of the total time-locked response (total spikes minus onset spikes) is indicated in the upper right of each PSTH. B. Five modulation series consisting of responses to SAM pulse trains. Each column represents this neuron's response to one modulation frequency (indicated at the top of each column) presented at five carrier frequencies (indicated to the left of each row). C. Plots of total time-locked spike rates to unmodulated pulse trains (open symbols) and the average time-locked SAM pulse trains (closed symbols) for all five carrier frequencies as function of fundamental repetition rate (pulse or modulation frequency).

FIGURE 9. Responses of a medium resolution IC neuron responding to ICES using modulated and unmodulated pulse trains at an intensity 4 dB above threshold or 708 μA. A. Frequency series consisting of ten PSTHs evoked by unmodulated pulse trains of increasing frequency from 10 to 100 pps indicated in the upper left of each response. The total number of spikes and an estimate of the total time-locked response (total spikes minus onset spikes) is indicated in the upper right of each PSTH. B. Five modulation series consisting of responses to SAM pulse trains. Each column represents this neuron's response to one modulation frequency (indicated at the top of each column) presented at five carrier frequencies (indicated to the left of each row). C. Plots of total time-locked spike rates to unmodulated pulse trains (open symbols) and the average time-locked SAM pulse trains (closed symbols) for all five carrier frequencies as function of fundamental repetition rate (pulse or modulation frequency).

FIGURE 10. Responses of a high resolution IC neuron responding to ICES using modulated and unmodulated pulse trains at an intensity 5 dB above threshold or 1.25 mA. A. Frequency series consisting of PSTHs evoked by unmodulated pulse trains of increasing frequency from 10 to 390 pps indicated to the right of each PSTH. The total number of spikes and an estimate of the time locked response (total spikes minus onset spikes) is indicated in the upper right of each PSTH. B. Eight modulation series consisting of responses to SAM pulse trains. Each column represents this neuron's response to one modulation frequency (indicated at the top of each column) presented at seven carrier frequencies (indicated to the left of each row). The responses to 60/96, 80/96, 100/96, 100/185 stimuli were not recorded since the modulation frequencies exceed the Nyquist frequency for these carriers. C. Plots of total time-locked spike rates to unmodulated pulse trains (open symbols) and the average time-locked SAM pulse trains (closed symbols) for all seven carrier frequencies as function of fundamental repetition rate (pulse or modulation frequency).

FIGURE 11. Maximum unmodulated pulse frequency (Fmax) to which each neuron could respond plotted against the maximum modulation frequency (maxFm) to which it could respond. The diagonal dashed line is the equal frequency contour. The solid diagonal line represents a linear regression analysis of the data with the r^2 value indicated at the right.

FIGURE 12. Responses of a low resolution IC neurons with a band pass TMTF responding to modulated and unmoduated pulse trains. A. Frequency series of seven PSTHs evoked by unmodulated pulse trains of increasing frequency from 10 to 70 pps indicated to the right of each PSTH. The total number of spikes and an estimate of the time locked response (total spikes minus onset spikes) is indicated in the upper right of each PSTH. B. Five modulation series consisting of responses to SAM pulse trains. Each column represents this neuron's response to a modulation frequency from 8 to 40 Hz (indicated at the top of each column) presented at six carrier frequencies (indicated to the left of each row). C. Plots of total time-locked spike rates to unmodulated pulse trains (open symbols) and the average time-locked SAM pulse trains (closed symbols) for all seven carrier frequencies as function of fundamental repetition rate (pulse or modulation frequency).

FIGURE 13. Histogram illustrating the maximum modulation frequency (maxFm) to which neurons with band pass modulation filters would respond. The average maxFm is 34.2 Hz. The bins marked >30 and >60 indicates neurons that were able to respond to those modulation frequencies but were lost before their maxFm could be determined.

FIGURE 14. Responses a low resolution IC neuron responding to ICES at an intensity 4 dB above threshold or 708 μA. A. Frequency series consisting of seven PSTHs evoked by unmodulated pulse trains of increasing frequency from 10 to 70 pps indicated to the right of each PSTH. The total number of spikes and an estimate of the time locked response (total spikes minus onset spikes) is indicated in the upper right of each PSTH. B. Four modulation series consisting of responses to SAM pulse trains. Each column represents this neuron's response to a modulation frequency from 8 to 60 Hz (indicated at the top of each column) presented at five carrier frequencies (indicated to the left of each row). The response to 60 Hz modulation of a 96 pps carrier was not recorded, since 60 Hz modulation is above the Nyquist frequency for a 96 pps carrier. C. Modulation depth series consisting of responses to PSTHs of responses evoked by 30 Hz SAM of a 96 pps carrier using increasing modulation depth as indicated to the left of each response. D. Modulation depth series consisting of PSTHs evoked by 30 Hz SAM of a 268 pps carrier as indicated to the left of each response.

FIGURE 15 Diagram of 15 cycles (500 msec) of an AM pulse train consisting of a 96 pps carrier 100% modulated at 30 Hz. In the lower half, the solid line traces the modulation envelope of the pulse train. In the upper half of the signal, the dashed line indicates a hypothetical 'threshold' 4 dB below the peak current. Three modulations (6 Hz) of the highest peaks can clearly be seen above this 'threshold'. These peaks correspond closely to the 6 Hz distortions seen in the 30/96 response illustrated in Figure 10B.

Work Planned for the Next Quarter

1. Chronic stimulation periods (32 weeks) will be completed in the final two cats in a series of adult deafened animals, and both will be studied in terminal acute electrophysiology experiments. This series of animals parallels the previous temporally challenging stimulation group of neonatally deafened cats, implanted as juveniles (6-7 weeks of age) and chronically stimulated using 300 pps carriers, amplitude modulated at 30 Hz. The analysis of these results and comparison with results from the neonatally deafened group, will address the issue of what role developmental critical periods play in the alterations induced by chronic electrical stimulation with a cochlear implant.

2. Three additional neonatally deafened juvenile cats which have received exogenous administration of GM1 ganglioside (30 mg/Kg, SQ, SID) during the period between deafening (P1 - P16) and implantation (six weeks of age). Preliminary results in two animals indicate that ganglioside maintains increased survival of spiral ganglion neurons in these animals. Study of additional animals is necessary to provide a sufficient n that will allow us to make statistical comparisons of ganglioside-treated animals with stimulation-only animals that are matched for age and duration of stimulation.

3. Analysis of results from two-channel chronic stimulation experiments in neonatally deafened cats will continue, examining the effects of multiple site stimulation on the spatial selectivity, neural survival and temporal resolution of neurons in the inferior colliculus, and comparing results to those obtained in single channel stimulation experiments.

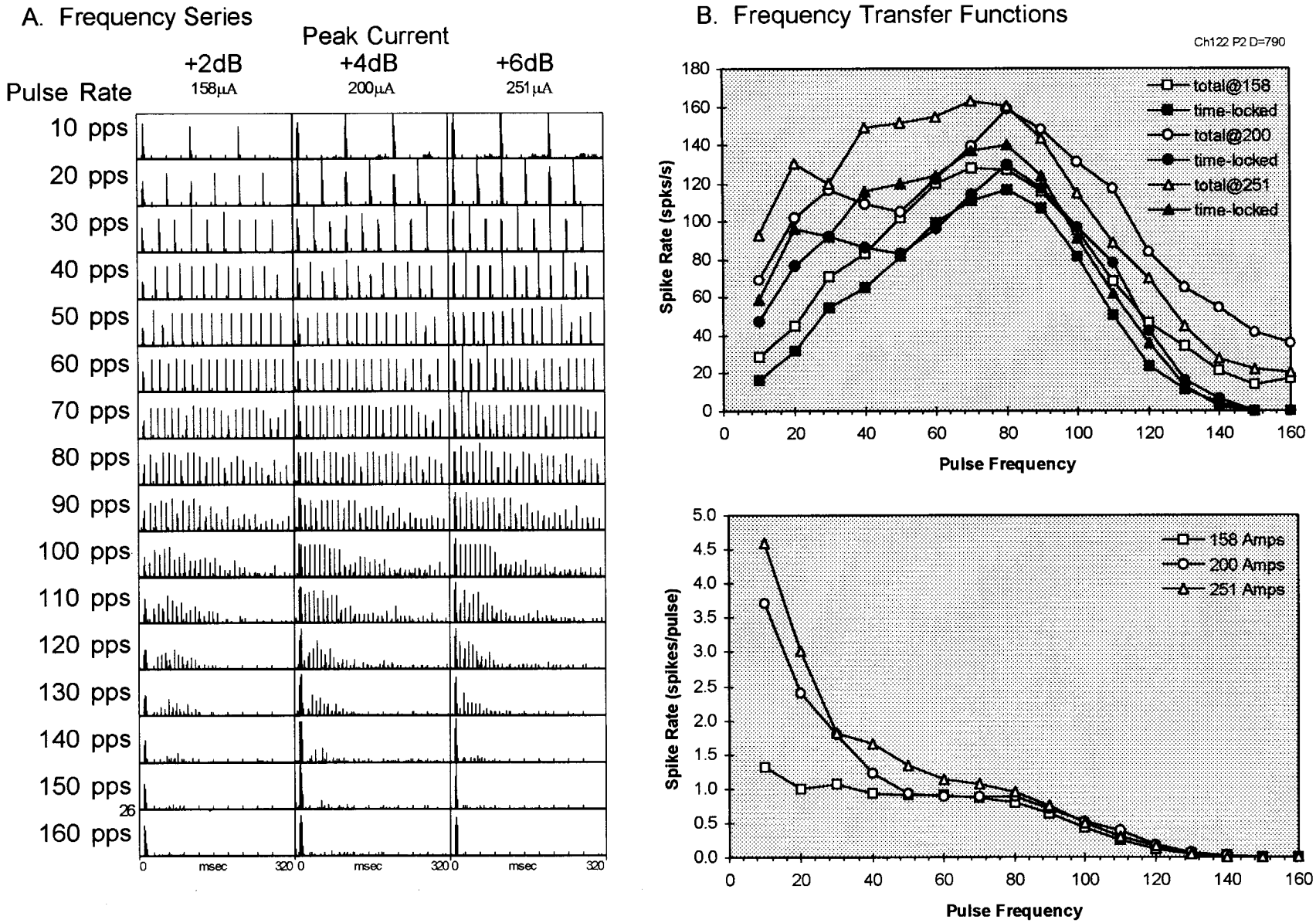
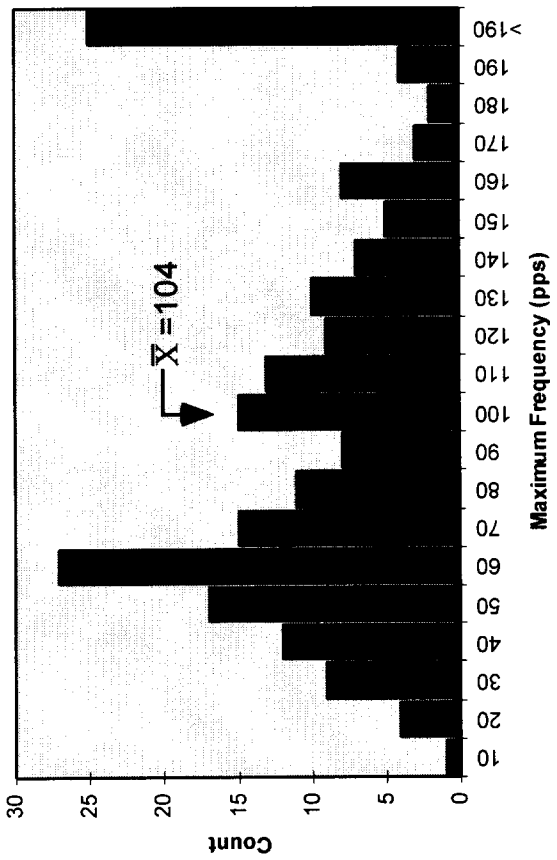
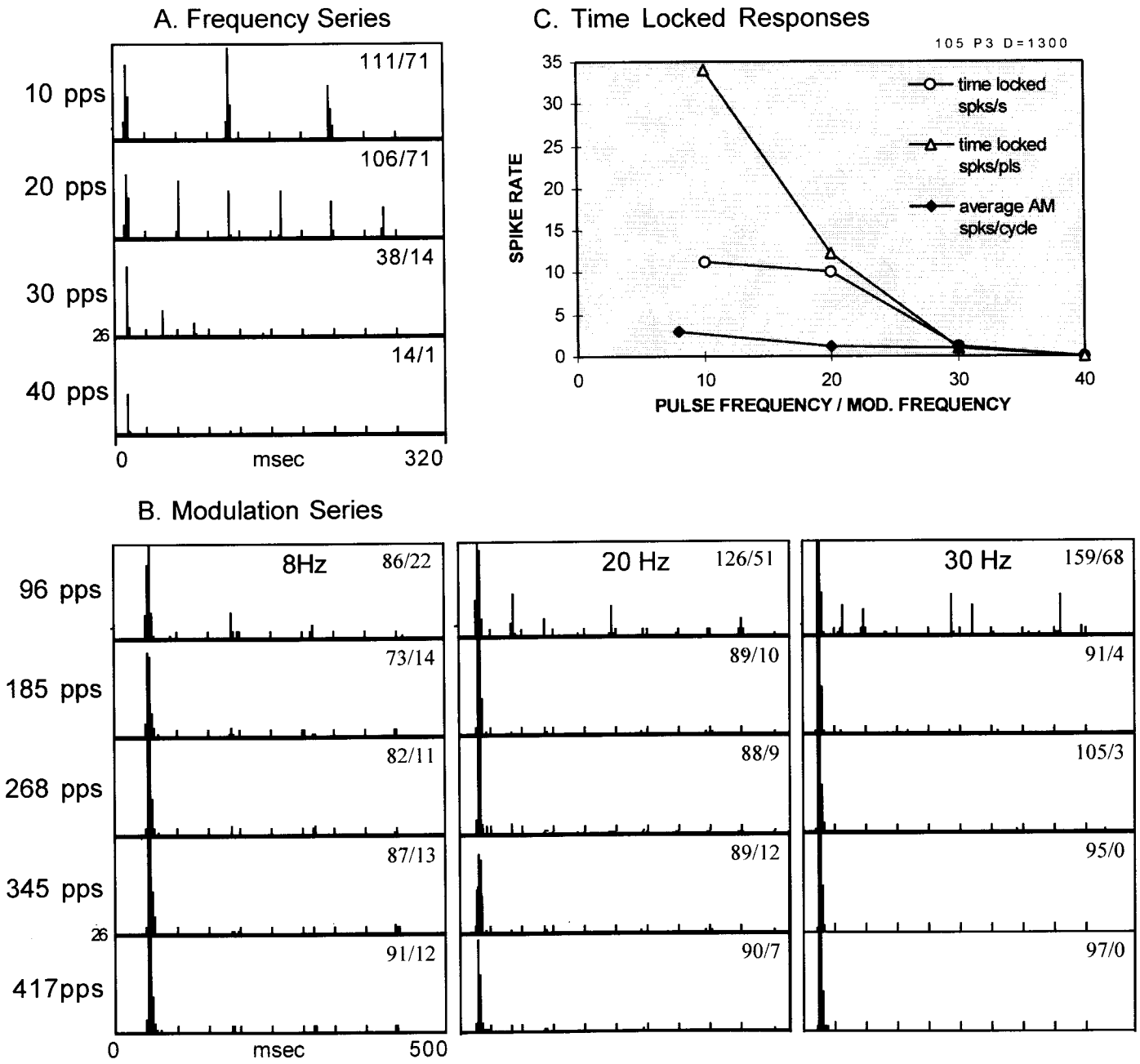
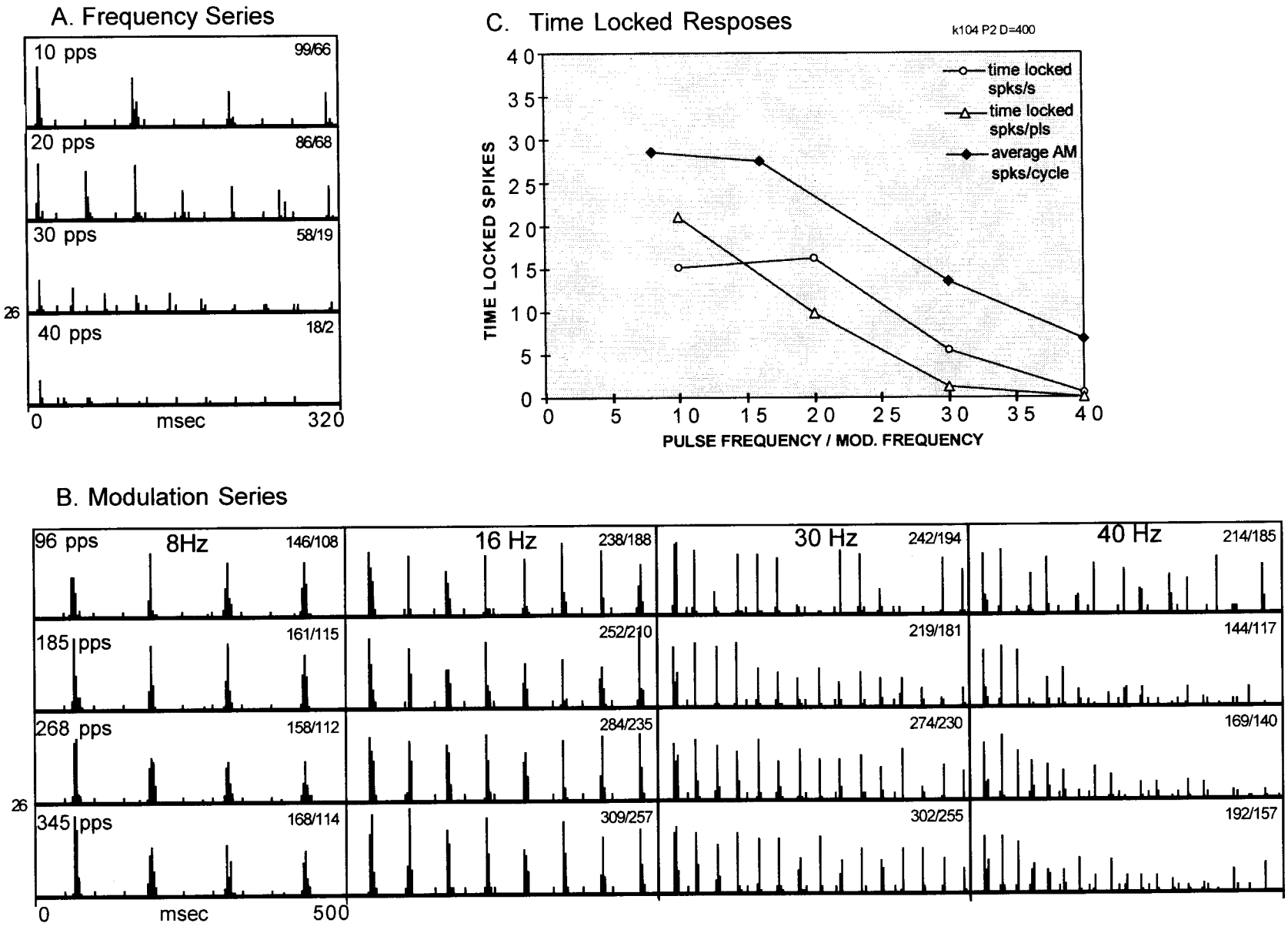

A. Frequency Series
Peak Current
+2dB
158μA
+4dB
200μA
+6dB
251μA
Pulse Rate
10 pps
20 pps
30 pps
40 pps
50 pps
60 pps
70 pps
80 pps
90 pps
100 pps
110 pps
120 pps
130 pps
140 pps
150 pps
160 pps
0
msec
320
B. Frequency Transfer Functions
Ch122 P2 D=790
Spike Rate (spks/s)
Pulse Frequency
total@158
time-locked
total@200
time-locked
total@251
time-locked
Spike Rate (spikes/pulse)
158 Amps
200 Amps
251 Amps

FIGURE 2


Count
0
5
10
15
20
25
30
X =104
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
>190
Maximum Frequency (pps)


A. Frequency Series
10 pps
111/71
20 pps
106/71
30 pps
38/14
26
40 pps
14/1
0
msec
320
C. Time Locked Responses
105 P3 D=1300
time locked spks/s
time locked spks/pls
average AM spks/cycle
SPIKE RATE
35
30
25
20
15
10
5
0
0
10
20
30
40
PULSE FREQUENCY / MOD. FREQUENCY
B. Modulation Series
96 pps
8Hz
86/22
20 Hz
126/51
30 Hz
159/68
185 pps
73/14
89/10
91/4
268 pps
82/11
88/9
105/3
345 pps
87/13
89/12
95/0
26
417pps
91/12
90/7
97/0
0
msec
500


A. Frequency Series
10 pps
99/66
20 pps
86/68
30 pps
58/19
26
40 pps
18/2
0
msec
320
C. Time Locked Resposes
k104 P2 D=400
time locked spks/s
time locked spks/pls
average AM spks/cycle
TIME LOCKED SPIKES
0
5
10
15
20
25
30
35
40
PULSE FREQUENCY / MOD. FREQUENCY
B. Modulation Series
96 pps
8Hz
146/108
16 Hz
238/188
30 Hz
242/194
40 Hz
214/185
185 pps
161/115
252/210
219/181
144/117
268 pps
158/112
284/235
274/230
169/140
26
345 pps
168/114
309/257
302/255
192/157
0
msec
500

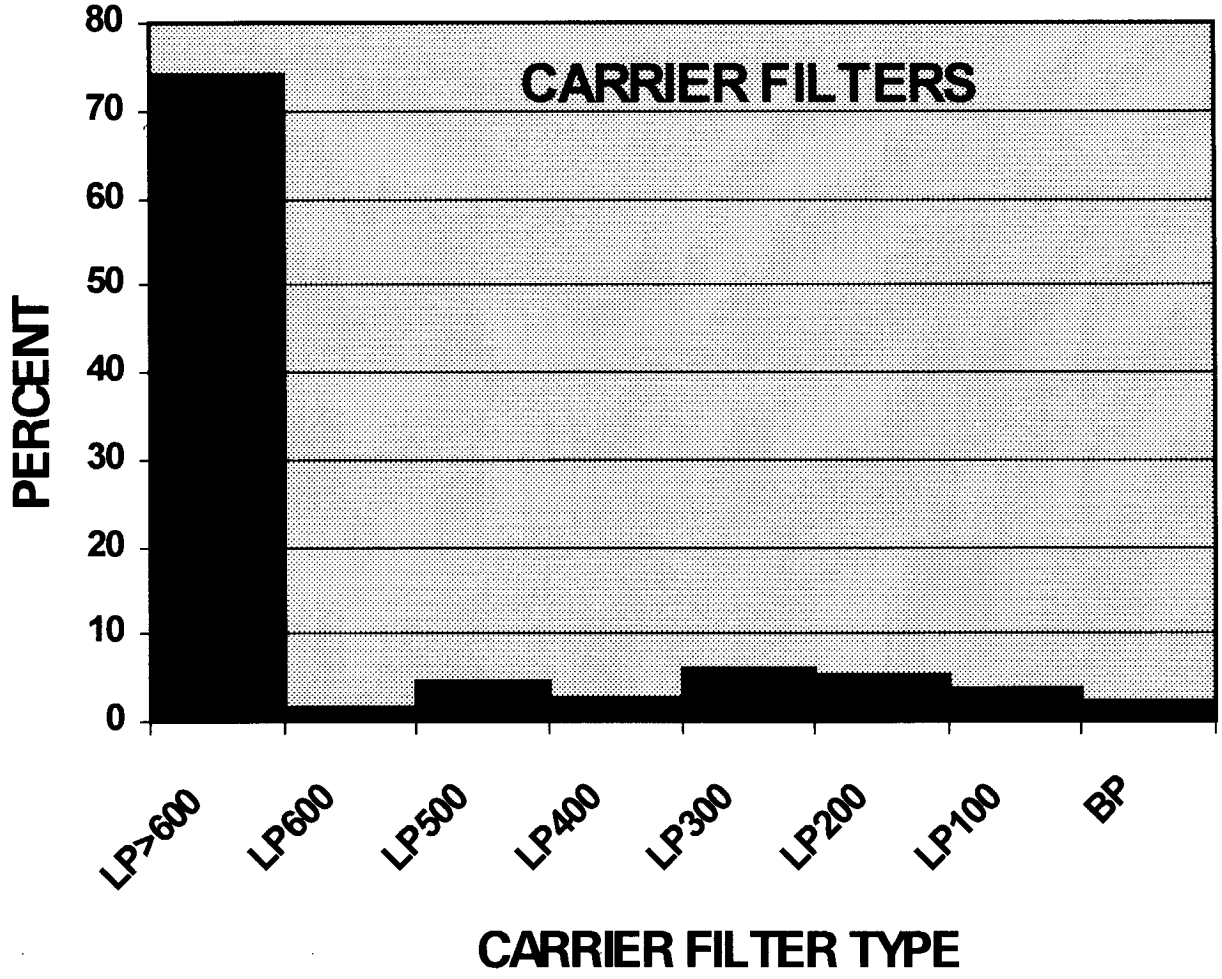

CARRIER FILTERS
PERCENT
80
70
60
50
40
30
20
10
0
LP>600
LP600
LP500
LP400
LP300
LP200
LP100
BP
CARRIER FILTER TYPE

FIGURE 6

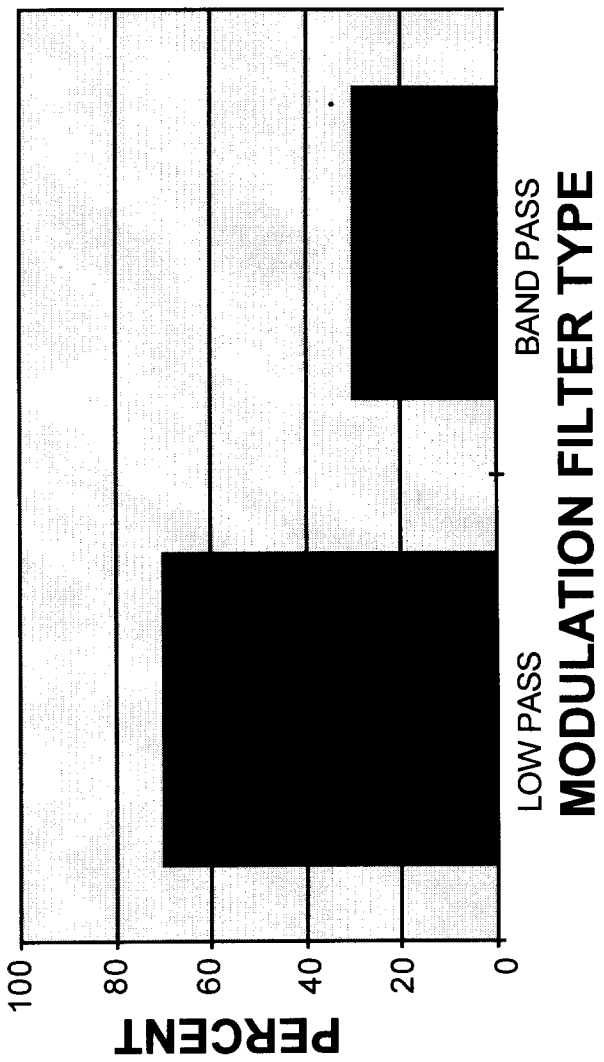
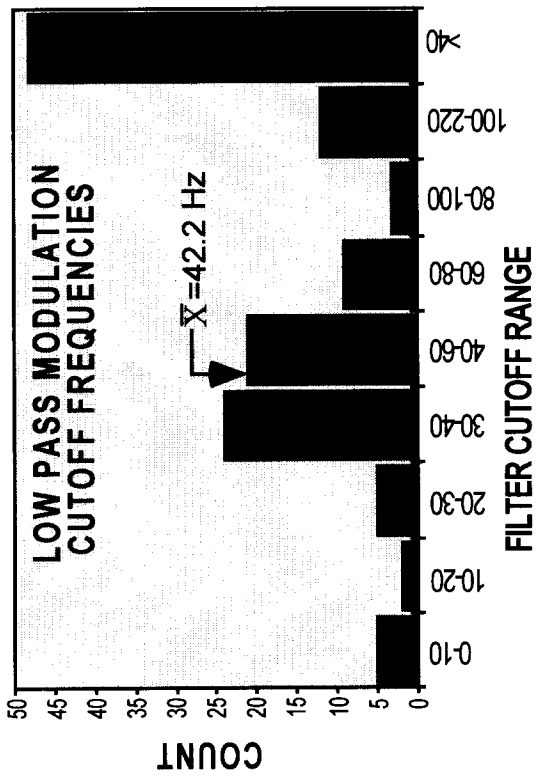
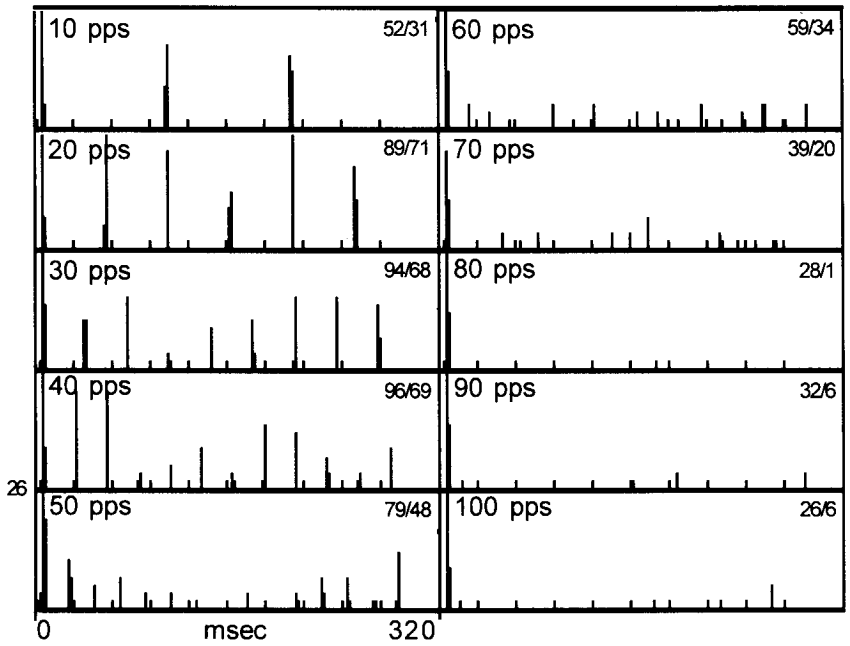

100
80
60
40
20
0
PERCENT
LOW PASS
BAND PASS
MODULATION FILTER TYPE

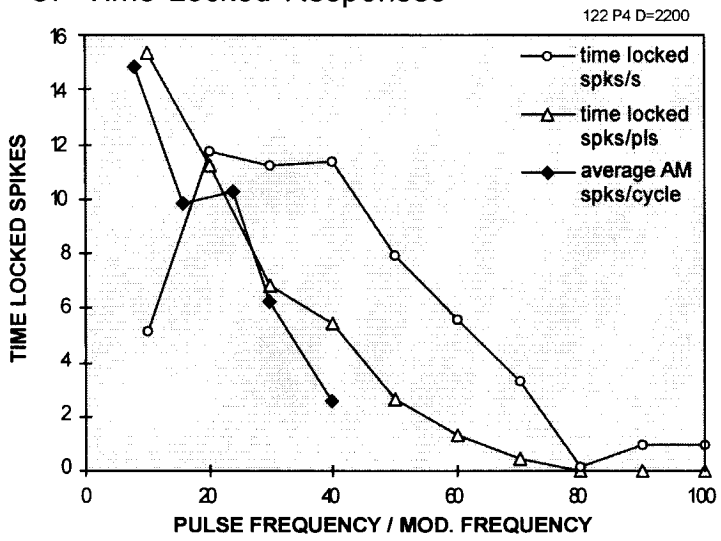
FIGURE 7


LOW PASS MODULATION
CUTOFF FREQUENCIES
X=42.2 Hz
COUNT
0
5
10
15
20
25
30
35
40
45
50
0-10
10-20
20-30
30-40
40-60
60-80
80-100
100-220
>40
FILTER CUTOFF RANGE

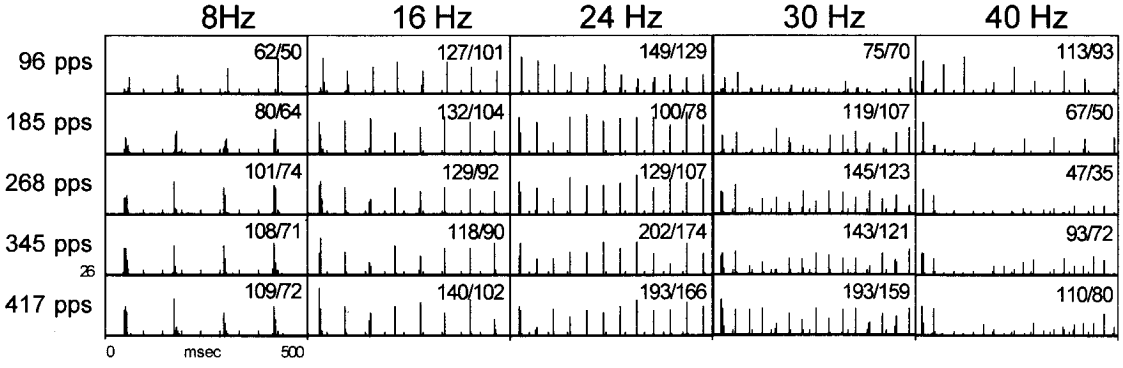
A. Frequency Series



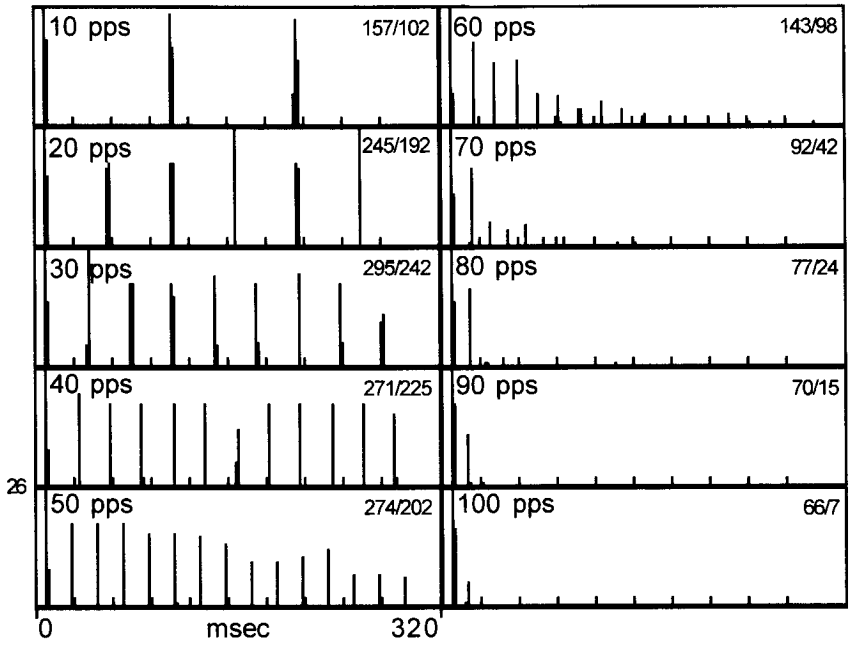
C. Time Locked Responses



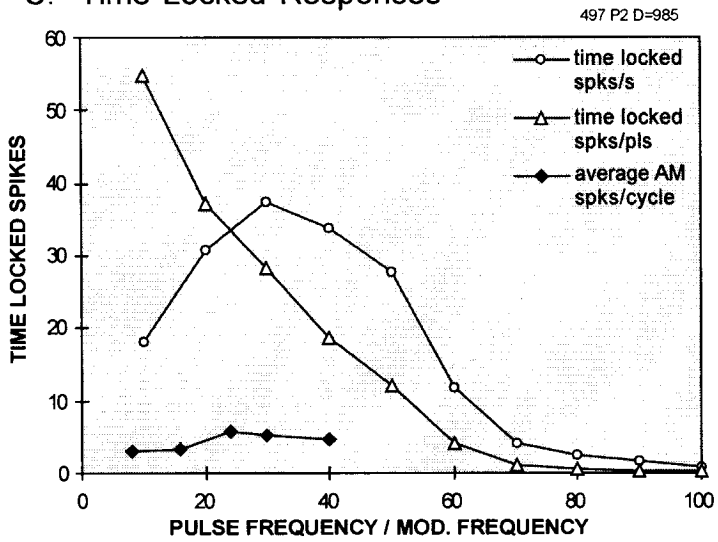
B. Modulation Series



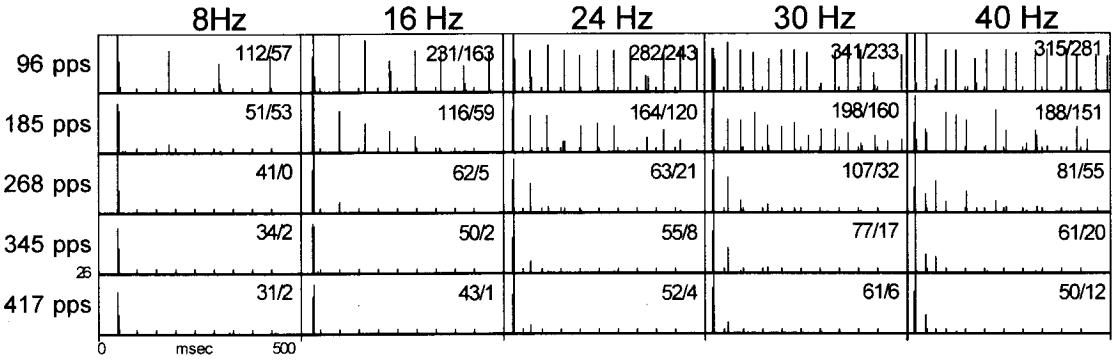
A. Frequency Series



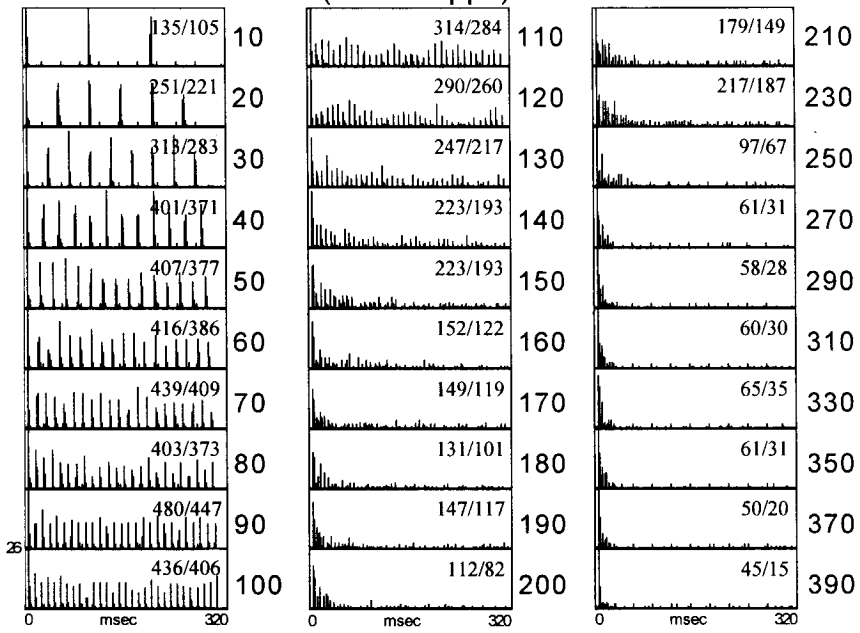
C. Time Locked Responses



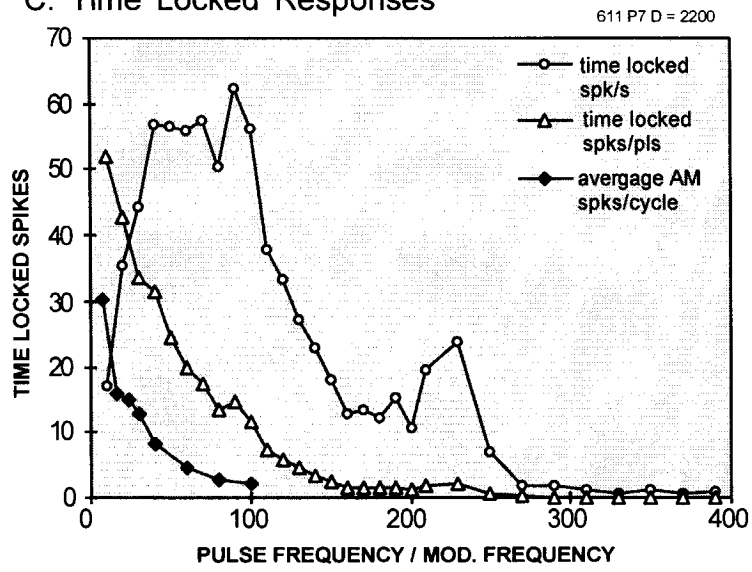
B. Modulation Series



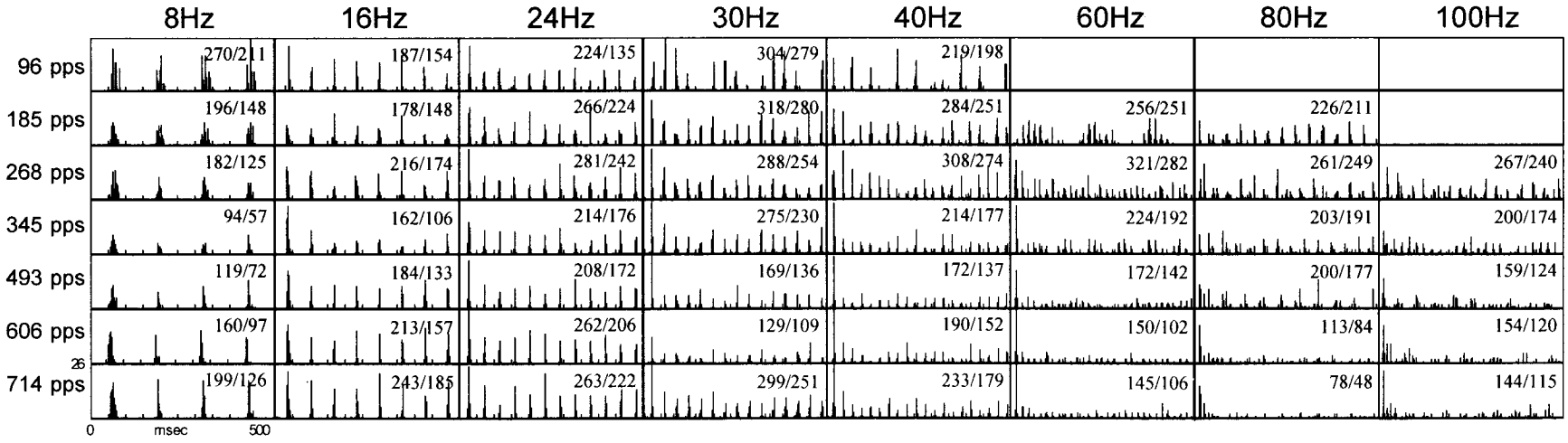
A. FREQUENCY SERIES (10 -390 pps)

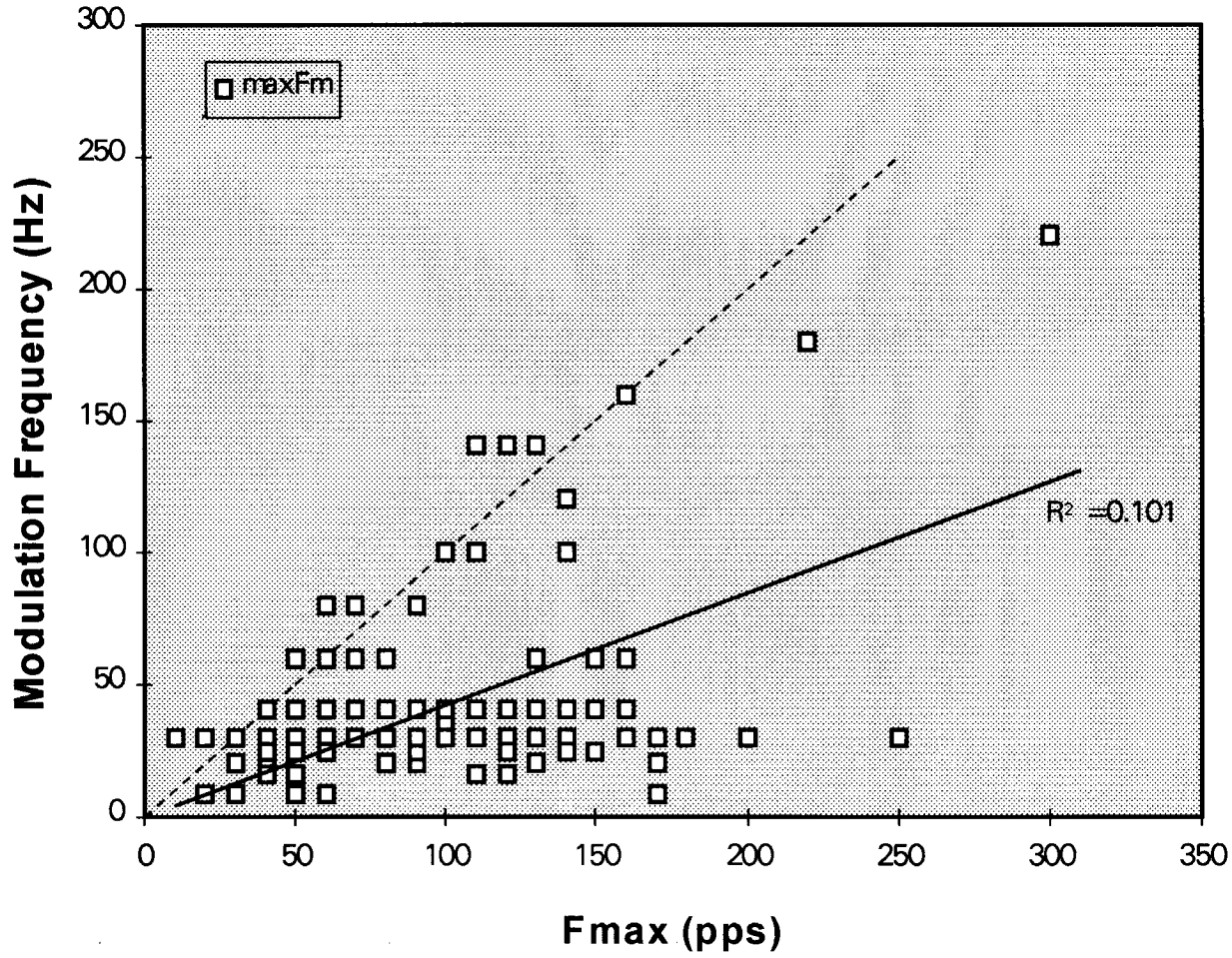


C. Time Locked Responses



B. MODULATION SERIES (8-80 Hz)




maxFm
Modulation Frequency (Hz)
Fmax (pps)
R² =0.101
0
50
100
150
200
250
300
350

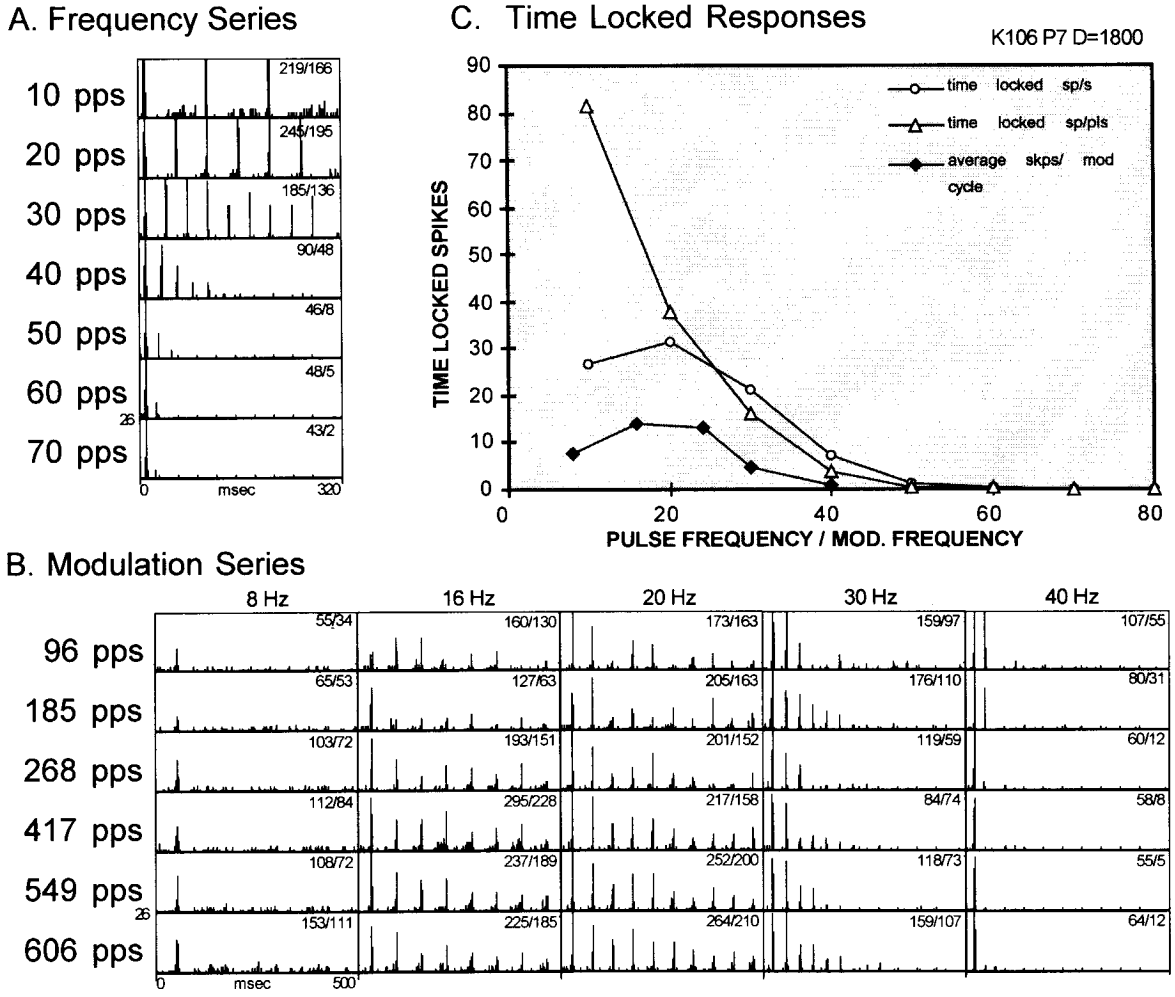
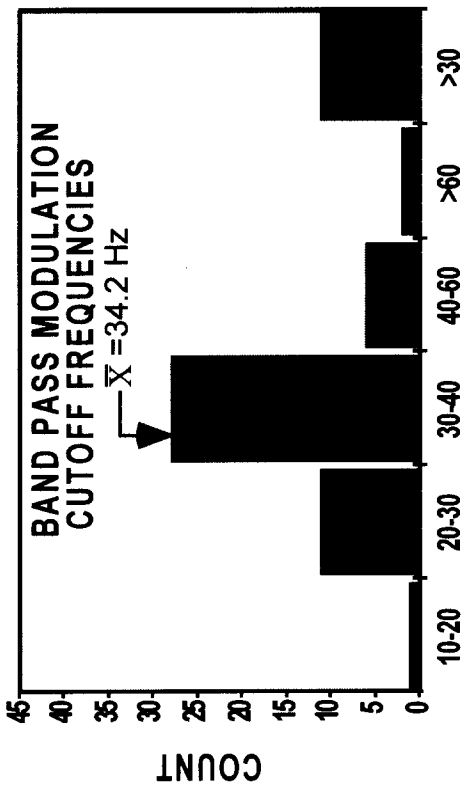

A. Frequency Series
10 pps
20 pps
30 pps
40 pps
50 pps
60 pps
70 pps
219/166
245/195
185/136
90/48
46/8
48/5
43/2
26
0
msec
320
C. Time Locked Responses
K106 P7 D=1800
time locked sp/s
time locked sp/pls
average skps/ mod cycle
TIME LOCKED SPIKES
PULSE FREQUENCY / MOD. FREQUENCY
0
10
20
30
40
50
60
70
80
90
0
20
40
60
80
B. Modulation Series
8 Hz
16 Hz
20 Hz
30 Hz
40 Hz
96 pps
185 pps
268 pps
417 pps
549 pps
606 pps
55/34
160/130
173/163
159/97
107/55
65/53
127/63
205/163
176/110
80/31
103/72
193/151
201/152
119/59
60/12
112/84
295/228
217/158
84/74
58/8
108/72
237/189
252/200
118/73
55/5
153/111
225/185
264/210
159/107
64/12
26
0
msec
500

FIGURE 13


BAND PASS MODULATION
CUTOFF FREQUENCIES
X̄ =34.2 Hz
COUNT
0
5
10
15
20
25
30
35
40
45
10-20
20-30
30-40
40-60
>60
>30

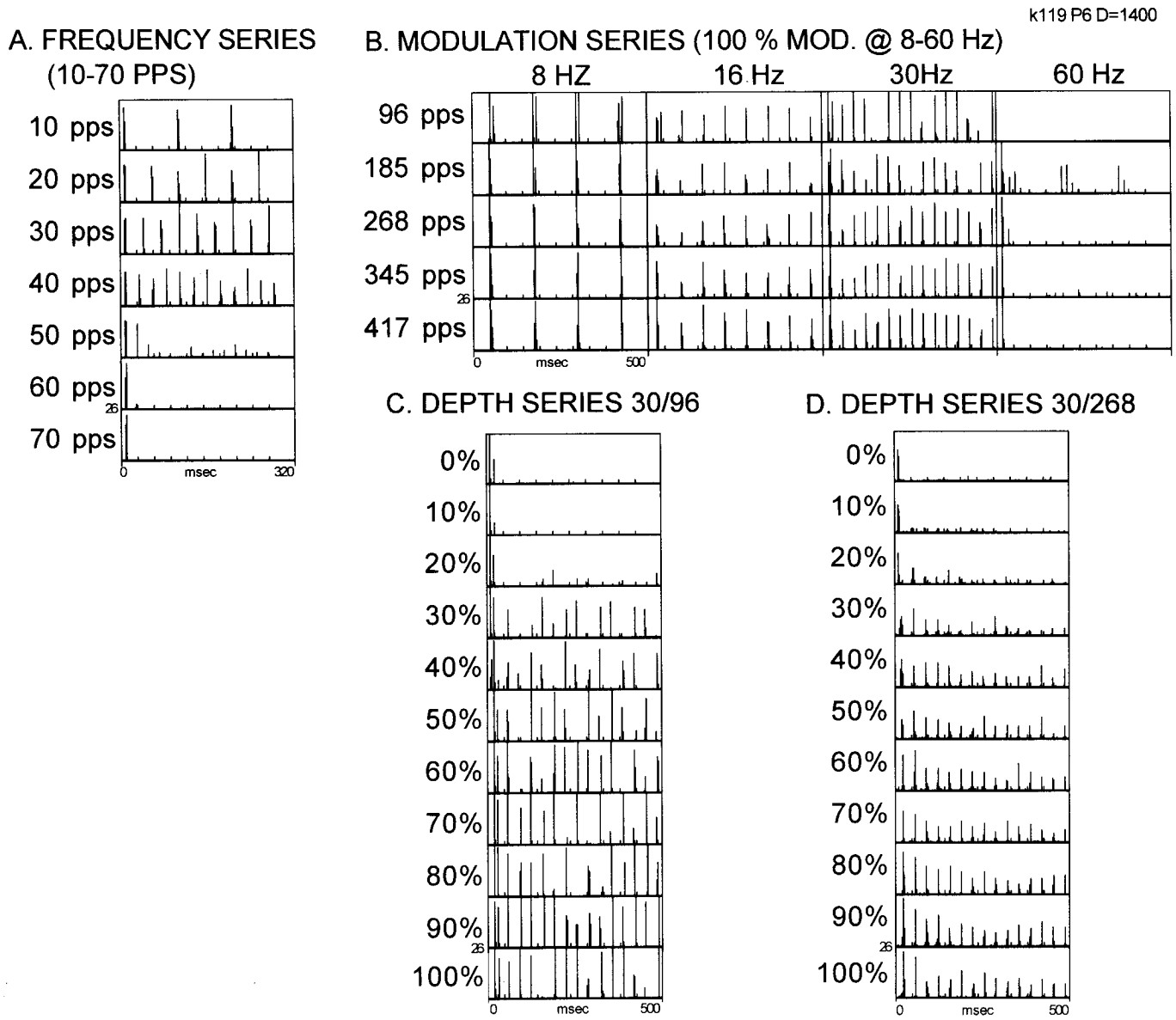
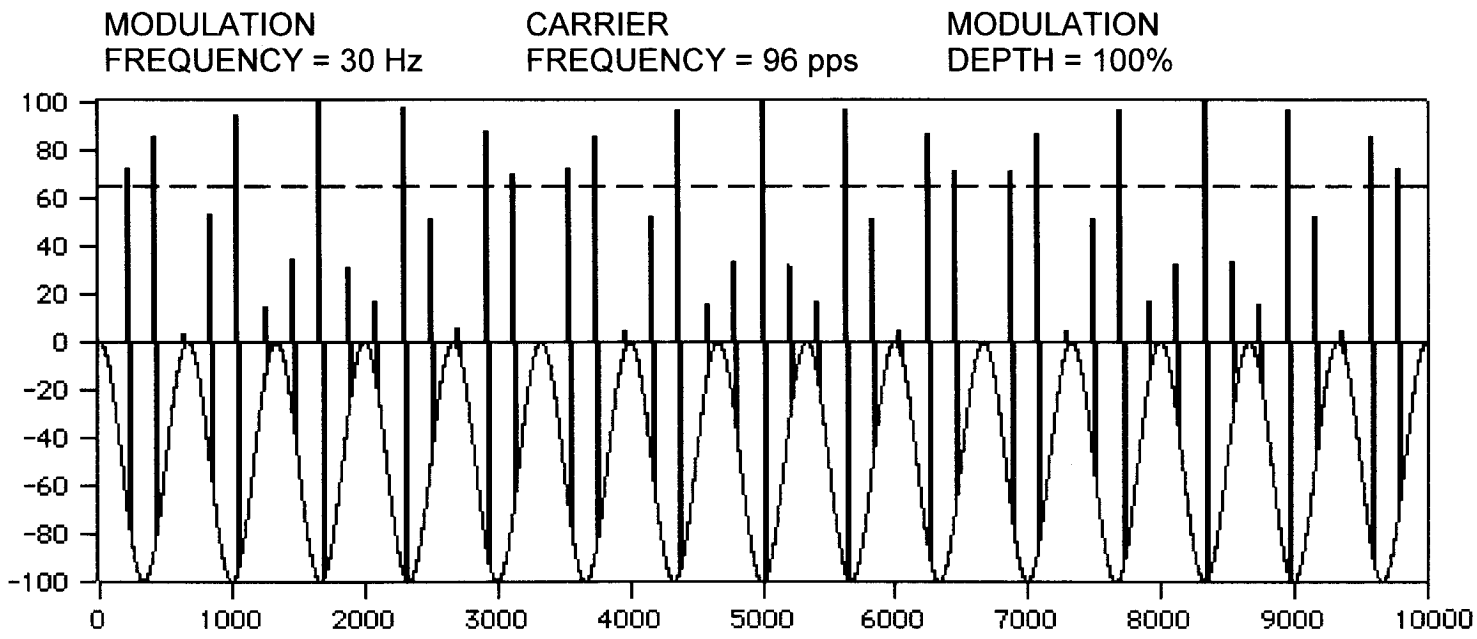

k119 P6 D=1400
A. FREQUENCY SERIES
(10-70 PPS)
10 pps
20 pps
30 pps
40 pps
50 pps
60 pps
70 pps
0
msec
320
B. MODULATION SERIES (100 % MOD. @ 8-60 Hz)
8 HZ
16 Hz
30Hz
60 Hz
96 pps
185 pps
268 pps
345 pps
417 pps
0
msec
500
C. DEPTH SERIES 30/96
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
0
msec
500
D. DEPTH SERIES 30/268
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
0
msec
500

FIGURE 15


MODULATION
FREQUENCY = 30 Hz
CARRIER
FREQUENCY = 96 pps
MODULATION
DEPTH = 100%
100
80
60
40
20
0
-20
-40
-60
-80
-100
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000