

XXII. COMMUNICATIONS BIOPHYSICS*

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RESEARCH OBJECTIVES AND SUMMARY OF RESEARCH

The principal scientific research objective of the Communications Biophysics Group is to obtain a better understanding of sensorineural processes. Our approach combines both electrophysiological and behavioral experimental techniques with machine data

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processing and analytical methods of communication theory. In addition to our scientific objectives we are interested in applications of our research results, methods, and new technological developments to clinical medicine.

Members of our group have ties with several hospitals and with the Harvard Medical School. In particular, we have a close working relationship, including sharing of facilities and joint staff appointments, with the Eaton-Peabody Laboratory of Auditory Physiology, which is operated jointly by the Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, and M. I. T. Another joint Harvard-M. I. T. endeavor is the Bioengineering Laboratory at the Thorndike Memorial Laboratory of Boston City Hospital.

Our research program can be divided into five major areas: Auditory Physiology, Auditory Psychophysics, Neuroelectric Correlates of Behavior, Other Physiological Research, and Biomedical Engineering. The programs for each will be discussed individually.

A. Auditory Physiology (Eaton-Peabody Laboratory)

The facilities of the Eaton-Peabody Laboratory, which were moved in 1970 from the Massachusetts Eye and Ear Infirmary in Boston to Cambridge, were in full operation throughout 1971. Our work continues to focus on signal transmission and coding in the auditory system. Experimental work in the past has been carried out mainly on cats. We have recently pursued certain questions pertaining to the signal-transmission processes in the inner ear with experiments in the alligator lizard, Gerrhonotus multicarinatus.

1. Mechanical Signals in the Middle and Inner Ear

a. Velocity measurements using the Mössbauer effect

A computer system now in operation produces oscilloscope displays of calibrated velocity waveforms.¹ We are now working on techniques to use this system to measure the velocity of the basilar membrane in the inner ear of the alligator lizard.

W. T. Peake

b. Middle ear of the alligator lizard

Observations of the middle ear under stroboscopic illumination have indicated that the motion of the columella is along its long axis.² We shall now measure the velocity using the Mössbauer system. Knowledge of the transfer function of the middle ear is necessary to determine the input signal to the inner ear.

W. T. Peake

c. Measurements of sound pressure in the inner-ear fluids

Previously, we developed techniques to calibrate a small fluid-filled pressure probe both in an air-filled cavity and in a water-filled tank. Recently, we have developed a new, superior technique with which we use a small fluid-filled vial rigidly mounted on a vibrator that generates a measured acceleration. The probe is inserted into the vial to a measured depth, d , from the surface of the fluid. The sound pressure, p , in the fluid can be calculated from the relation $p = \rho_0 a d$, where ρ_0 is the density of the fluid, and a is the measured acceleration. Calibrations performed with this new technique are in substantial agreement with those performed by other methods. The new

technique is superior, in that its calibrations are (i) relatively independent of the length of time the probe is left in the calibration apparatus, (ii) less subject to artifacts, and (iii) can be performed rapidly and conveniently in the course of a physiological experiment.

With the calibrated pressure probes, we have measured sound pressure in the basal turn (perilymphatic scalae) of approximately 25 cat cochleas. Measurements of the magnitude and phase of the fundamental component of the response to tones indicate that sound pressure in scala tympani and vestibuli is linearly related to sound pressure at the tympanic membrane over the frequency range from 30 Hz to at least 5 kHz and up to ~100 dB SPL at the eardrum. The sound pressure in scala vestibuli increases with frequency in the range from 30 Hz to approximately 1 kHz, and reaches a maximum value as high as 40 dB larger than the sound pressure at the tympanic membrane. Over this frequency range (30 Hz-1 kHz) the sound pressure in scala tympani is relatively constant (approximately 100 dB SPL \pm 5 dB for 105 dB SPL at the eardrum). Measurements have been made for frequencies as high as 10-20 kHz; these data show more scatter than the low-frequency data. We are extending these measurements to higher sound-pressure levels and investigating the waveforms of the responses to acoustic clicks, as well as to tones.

V. Nedzelnitsky, T. F. Weiss

d. Responses of the inner ear to electric stimulation

A doctoral thesis has been completed.³ This work is now being prepared for publication.

E. C. Moxon

2. Transduction Mechanisms in Hair-Cell Systems

a. Electric potentials in the inner ear of the cat

Results of measurements of electric potentials in the basal turn of the cat cochlea have been published recently.⁴⁻⁶

T. F. Weiss, W. T. Peake

b. Intracellular potentials in the inner ear of lizards

In collaboration with Dr. M. J. Mulroy we have recorded intracellular potentials from hair cells, supporting cells, and epithelial cells in the basilar papilla of the alligator lizard with the ear stimulated by sound. By using intracellular dye-marking techniques, we have attempted to determine the site of recording. We are preparing a manuscript for publication.

T. F. Weiss, D. W. Altmann, W. T. Peake

3. Stimulus Coding in Auditory-Nerve Fibers

a. Auditory-nerve fiber responses in cat

A book that will present our accumulated unpublished experimental results of the last eight years is in preparation. It will display within a unified conceptual framework our major empirical findings on auditory-nerve responses.

b. Theoretical treatment of auditory-nerve latencies, group delays, and tuning curves

Some theoretical restraints on plausible linear models for cochlear frequency

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analysis have been derived from auditory-nerve data. We found that the adequacy of linear models depends crucially upon assumptions of the underlying causes of the empirical group delays. A brief report of this study will be published.⁷

J. L. Goldstein, T. Baer, N. Y. S. Kiang

c. Spontaneous activity of VIIIth-nerve units

Spontaneous discharge patterns in the vestibular branch of the VIIIth nerve can be roughly classified into irregular and regular types. With B. T. Walsh, of Harvard Medical School, we have used certain parameters of the interspike interval histogram to classify units on an objective basis. By also determining the location within the nerve of the two types of discharge pattern, we can test hypotheses concerning the relation of spontaneous activity to fiber diameter. These results also should give indications concerning the source of spontaneous activity in auditory-nerve fibers. A manuscript is in preparation for publication.

N. Y. S. Kiang

d. Recordings from auditory-nerve fibers in the alligator lizard

Within the last year, in collaboration with Dr. M. J. Mulroy, we have begun to study the responses of single VIIIth-nerve fibers to acoustic stimuli in the alligator lizard. Initial results have shown that VIIIth-nerve fibers show frequency-selective responses to tones with the best frequencies of response lying in the range 100 Hz-4 kHz. Response characteristics show some similarities to those found in mammalian auditory-nerve fibers, and some interesting differences. Our present objective is to determine whether the morphological differences in hair cells in different regions of the basilar papilla are reflected in different response characteristics of auditory-nerve fibers. Preliminary findings suggest that this is the case.

R. G. Turner, Jr., T. F. Weiss

4. Single-Cell Responses in the Cochlear Nucleus

A doctoral dissertation⁸ recently completed in the laboratory correlates the response patterns of single units in the cochlear nucleus with particular cell groups in the cochlear nucleus of cat. Three papers are being prepared for publication.

N. Y. S. Kiang

5. Signal Transformations in Brainstem Nuclei

Manuscripts for three papers on the organization and properties of single units in the superior olivary complex are near completion. In the coming year we intend to investigate certain properties of neurons in the medial nucleus of the trapezoid body. In particular, we shall investigate the effects of the synapses on the dendrites of cells that receive large presynaptic endings (called Calyces of Held) on their cell bodies. This project is being carried out in association with Dr. D. K. Morest, of the Department of Anatomy, Harvard Medical School, who is studying the ultrastructure of these neurons and their synaptic connections.

J. J. Guinan, Jr.

6. Instrumentation

A substantial effort, in collaboration with M. Silverstein, E. Kohn, and A. Riedel of the Eaton-Peabody Laboratory, has been made to extend our system for automatic

measurements of frequency responses.⁹ The new system is designed to handle two signals simultaneously, for example, the voltage output of a pressure or acceleration transducer and voltage recorded by an intracochlear electrode. Thus it will be possible, for instance, to sweep the frequency of a tonal stimulus (holding the sound-pressure level constant) and to measure the magnitude and phase of the fundamental component of two response variables simultaneously. It will also be possible to measure distortion components in the signals as a function of frequency. The new system is designed to incorporate the calibration of new transducers in a flexible manner. We have also written programs to allow users of the system to perform a variety of transformations on frequency response characteristics measured by the automated system.¹⁰ In the coming year we plan to develop programs to incorporate automatic measurements of velocity (using the Mössbauer technique) into the computer system. We shall also plan to add digital hardware in order to place such computations as average responses of analog waveforms and histograms of spike activity under computer control.

D. W. Altmann, T. F. Weiss, R. M. Brown

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B. Auditory Psychophysics

The general goal of this research is to determine the performance of the auditory system, and to apply this understanding to problems in the perception of speech and music, the transmission of information by means of artificial auditory displays, and the diagnosis and treatment of hearing disorders. In some studies we can explain performance in terms of the physiology of the peripheral auditory system, and there is considerable interaction between our psychophysical and physiological research. In other studies the observed performance appears to depend strongly on parts of the nervous system about which knowledge is still relatively limited, and we cannot yet relate our models to the underlying physiology.

During the past year work has continued in the areas of intensity perception, pitch perception, binaural interaction, and aural combination tones. We have also worked to improve laboratory facilities. New projects have been initiated on middle-ear sound transmission, monaural localization, and (as background research for the development of improved hearing aids) limitations on the intelligibility of transformed speech. Research on pitch perception has been enhanced by the work of Professor F. A. Bilson, who has been with us as a visitor, on "dichotic repetition pitch." On the other hand, our attempts to develop a program relevant to hearing defects have been slowed by Professor L. D. Braida's assumption of additional administrative responsibilities in the Department of Electrical Engineering at M. I. T.

During the coming year we expect to continue the above-mentioned projects. We also expect to accelerate interaction between our research on pitch perception and our research on binaural hearing. This interaction is evident in our studies of binaural pitch phenomena. We anticipate formulating a new set of projects directed toward gaining a unified understanding of central processing. Comments on each of these research projects follow.

1. Intensity Perception

In recent work on the development of a unified theory of intensity perception we have analyzed more thoroughly our data from previous one-interval experiments, prepared the results of previous research for publication, and designed and performed new experiments.

The data analysis has been directed toward determining the accuracy of our method for estimating resolution, and has involved an examination of the extent to which the confusion matrices obtained in our one-interval experiments are consistent with our assumption of a Gaussian equal-variance decision model, and the extent to which estimates of resolution are affected by a lack of precision in the assumed form of the decision-model probability densities. Our results indicate that our method of estimating resolution is reasonably accurate and that, in general, estimates of resolution are remarkably insensitive to the form of the decision densities assumed in the construction of the estimates. Some of these results are presented in an appendix to the second paper in our series of papers on intensity perception.¹⁻⁴ The third and fourth papers in this series present further results on small-range identification and preliminary results on roving-level discrimination.

New experiments are directed toward improving our knowledge of many problems: (A) The dependence of resolution and bias on intensity range, intersignal duration, and feedback in roving-level intensity discrimination; (B) The dependence of intensity-ratio discrimination on the overall size of the ratios that are to be discriminated; (C) The effect of presenting a fixed standard on each trial in identification; (D) The precise form of the ROC in identification; and (E) The extent to which the cumulative sensitivity function in identification is invariant to changes in bias induced by changes in the payoff matrix.

The purpose of Experiment (A) is to dissect the memory process further and determine more fully the properties and interrelations of the two memory modes (context-coding and sensory-trace) postulated in our internal-noise model. This experiment differs from our preliminary experiments on roving-level intensity discrimination in the amount of data being obtained, the inclusion of stimulus duration and feedback as experimental parameters, and the consideration of bias as well as resolution. Experiments (B) and (C) are part of an effort to improve the model for context-coding to account for the effects of perceptual anchors. In particular, we wish to account for the phenomenon referred to as the "edge effect" (i. e., the tendency for resolution in identification and roving-level discrimination to improve as the intensity moves away from the center of the intensity range toward either of the two extreme intensities). We now think that the edge effect is caused by the observer's use of the edges of the context as anchors, and by a decrease in the accuracy of the coding with respect to an anchor with an increase in the distance between the anchor and the intensity that is to be coded. To the extent that the model we are developing for the dependence of coding accuracy on distance is correct, we should not only be able to predict the properties of the edge effect, but also the dependence of ratio-discrimination performance on the overall size of the ratios, the effect of presenting a standard in identification, and (to the extent that the presentation of feedback is equivalent to the presentation of a randomly varying standard) the effect of feedback in identification. Experiments (D) and (E) should yield further information on the decision process and decision densities in identification. If our present thoughts about the causes of the edge effect are correct, the variance of the densities should be slightly smaller at the extremes of the range than in the middle, and, consequently, the slopes of the ROC's obtained in Experiment (D) should be slightly less than unity at one extreme and slightly greater at the other. The preliminary results of Experiment (E) indicate that the cumulative sensitivity function in identification is strongly invariant to changes in bias induced by changes in payoffs.

During the coming year we hope to complete the new experiments and the revision of the context-coding model, and extend our theory of roving-level discrimination to account for the dependence of bias, as well as resolution, on the intensity level.

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2. Pitch Perception

a. Pitch of complex tones.

Investigations continue on perception of musical pitch with periodic sounds devoid of fundamental energy. Further support for the findings reported by Bilsen¹ has been obtained, and reports of these experiments have been prepared for publication.²⁻⁴ In new experiments we investigated some features of the previously postulated central pitch mechanism, which operates hierarchically on neural signals derived from stimulus

tones that are tonotopically resolved.

Interval identification experiments with complexes having up to six successive harmonics yielded results that are basically similar to those with two dichotic partials; thus, the basic properties of the central mechanism can be studied under stimulus conditions that are free from the confounding and irrelevant effects of cochlear nonlinear interactions among partials. Comparison of phase effects for monotic and dichotic tone complexes indicates that the central processor is insensitive to the relative phases of its inputs and that monaural phase effects must be caused by more peripheral mechanisms. Interval matching and interval identification experiments using inharmonic two-tone stimuli revealed for both monotic and dichotic presentations a systematic relationship between the stimulus partials and the musical note associated with the stimulus ("first effect"⁵); small deviations from this relationship ("second effect") which have been reported for monotic stimuli must originate more peripherally and are attributable to combination tones.⁶

Work has begun on a detailed investigation of the confusions subjects make when asked to identify a number of musical intervals represented by two partials of relatively high harmonic number. Confusion matrices obtained for one average fundamental frequency and different harmonic numbers suggest that a simple Gaussian decision model^{3, 7} is inadequate; the confusion structure reveals distinct ambiguities which may bear a relation to ambiguities predicted by the "first effect"⁵ or may reflect confusions between the sensation of the missing fundamental or "musical pitch" and the sensation of a single partial.

During the coming year we plan to continue our study of the confusions made in interval identification experiments with complex tones, and to extend our studies to musical-pitch perception with other types of stimuli.⁸

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b. Pitch of noise added to its delay

It is well known that if a wideband noise is presented to one ear and the same noise delayed to the other ear, and the delay is less than roughly 1-2 ms, a single noise image is perceived whose position depends on the delay. It is also well known that as the delay τ increases beyond this bound, the noise image remains at one side of the head, but becomes more diffuse. Recently, we have observed that, in addition to this increase in diffuseness, a faint but distinct pitch image corresponding to $1/\tau$ appears in the middle of the head. In view of the close analogy between this pitch phenomenon and monotic repetition pitch (MRP), produced by noise added to its delayed version in the same ear (Bilsen¹), we shall for convenience refer to the former as dichotic repetition pitch (DRP). Although DRP is fainter than MRP, both have equal subjective pitch and timbre qualities. There is, however, a significant difference in the existence region; MRP has been reported for $1 < \tau < 10$ ms, whereas DRP exists for roughly $\tau > 3$ ms.

Pitch-matching experiments by 5 subjects, using wideband, as well as narrow-band, white noise as basic stimuli, were initiated in the last half year to explore the characteristics of DRP in more detail. There is an essential difference between the pitch heard (DRP₋) when the delayed noise is also phase-inverted and the pitch heard (DRP₊) without inversion. The DRP₋ values deviate significantly from $1/\tau$; in general, two pitches can be perceived, one a little higher, the other a little lower than $1/\tau$ (i. e., ambiguity exists). With good approximation the results of the pitch matchings can be represented by the following empirical formulas:

$$\text{wideband noise: } \text{DRP}_+ \approx 1/\tau, \quad \text{DRP}_- \approx 1/(\tau \pm 0.8) \quad (1)$$

$$\text{narrow-band noise: } \text{DRP}_+ \approx 1/\tau, \quad \text{DRP}_- \approx 1/\left(\tau \pm \frac{1}{2f_0}\right), \quad (2)$$

where f_0 (the center frequency of the noise band) and DRP are in kHz, and τ is delay in ms.

The wideband DRP₋ values may be related to the narrow-band DRP₋ values by assuming the existence of a dominant spectral region for pitch. This dominant region (cf. Bilsen¹ for MRP) is found by setting Eq. 1 equal to Eq. 2; thus, f_0 (dominant) $\approx 1/(2 \times 0.8) \approx 625$ kHz. It is noteworthy that this is approximately the frequency region for optimal binaural beats (Licklider, et al.²).

Additional experiments with multiple-source dichotic stimuli show that the DRP phenomena are subjectively similar and probably involve the same binaural mechanisms as those studied by Fourcin.³ The principal new finding is that the pitch can be evoked by a single dichotically presented source.

Dichotic repetition pitch provides important information on auditory mechanisms for mediating pitch perception. Since the dichotic stimulus supplies the two cochleas with stimuli that differ only in time and contain no spectral cues, given the essential independence of the two cochleas, it is necessary that timing information in the cochlear outputs be processed. Central mechanisms that effectively add the cochlear outputs separately for each characteristic frequency have been postulated by Durlach⁴ and Colburn⁵ in their models for binaural signal detection. The outputs of this mechanism would provide short-term spectra for the monotic and dichotic repetition-pitch stimuli that are similar, except that the latter would be somewhat degenerated.

Consideration of how the central spectrum is further processed for pitch perception leads to the same questions of time or place-pattern processing that arise in monaural pitch (deBoer,⁶ Schouten,⁷ Ritsma,⁸ Whitfield,⁹ Bilsen¹). Houtsma and Goldstein¹⁰ have supplied evidence that musical pitch of complex tones is mediated by a central processor operating on neural signals derived from those effective stimulus partials that are tonotopically resolved. Thus, within the framework of the binaural mechanisms postulated by Durlach and Colburn, parsimony would require that we eliminate at least one commonly proposed pitch mechanism, namely, pitch mediation via single places in the spectral display by measurement of the autocorrelation function (Schouten, et al.,¹¹ Licklider,¹² Fourcin³).

We plan further experimental work on mechanisms in the perception of pitch, seeking an integrated view of pitch and binaural detection.

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3. Binaural Hearing

Work continues on a general theory of binaural hearing based on auditory-nerve data.¹ The theory comprises a mathematical description of the peripheral transduction from

pressure waves to nerve impulses on the auditory nerve and a central processor that is restricted in its capability to the use of counts from coincidence windows operating on interaural pairs of fibers with corresponding best frequencies.

We have been using a Poisson-process model for our description of the auditory-nerve patterns, together with a coincidence window that is relatively small (tens of microseconds). The Poisson process is inaccurate to the extent that it does not include the refractory properties observed in the data. A study of the effects of refractoriness, using both analytic and simulation techniques, has shown that the variance of the number of coincidences is essentially unaffected by refractoriness with the small coincidence window, but that this variance is strongly affected by refractoriness with a large window (e. g. , 1 ms).² A mathematically tractable auditory-nerve model with refractoriness is thus a prerequisite for serious analysis of the large-window case.

An experiment designed to test the ability of the binaural system to compare fine time structure on auditory-nerve fibers with different best frequencies has been completed.³ The results give no evidence that such comparisons are possible, and thus are consistent with the predictions of the theory.

Also, further work was done to determine the extent to which the binaural system is capable of discriminating between interaural time delays and interaural amplitude differences. As previously pointed out elsewhere,⁴ a careful evaluation of this capability requires extremely fine control of signal-generation equipment and earphone placement, and a failure to meet these requirements will result in overestimation of this capability. A binaural probe-tube system has been developed to monitor the signals in the ear canal, and we hope to obtain reliable estimates of this capability soon.

A series of papers describing the general theory, as well as a paper on previously completed research on the discrimination of interaural time off the midline,⁵ are being prepared.

During the coming year we hope to complete these papers, as well as to write two new chapters on binaural hearing for a forthcoming book.⁶ We also hope to extend the theory to include contralateral cuing and binaural pitch phenomena.

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4. Monaural Localization

It is well known that the direction of a sound source can be localized by sensing the differences in the signals arriving at the two ears. Some investigators have claimed that a considerable amount of localization information can be obtained even when only one ear is used and the head is held motionless. Theoretically, such localization information depends strongly on the observer's a priori knowledge of the characteristics of the transmitted signal. Despite this, in none of the previous experiments on monaural localization has a serious attempt been made to control (and systematically vary) this variable. As a consequence, it is extremely difficult to interpret the empirical results. In a new project, we intend to examine monaural localization performance and explore the roles played by the observer's a priori information concerning the transmitted signal, his knowledge of his ear's gain function, and his ability to identify signals at his eardrum.

5. Aural Combination Tones

Work continues on our comparative physiological and psychophysical study of aural combination tones. A psychophysical study performed on binaural lateralization with aural combination tones showed that the lateralization behavior is closely predicted by the results of cancellation experiments and by the simple interpretation that the aural combination tone is equivalent to a tone added to the stimulus.^{1, 2} We plan further study of the equivalence between combination tones and simple tones in binaural lateralization.

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6. Middle-Ear Sound Transmission

During the past year a program was initiated to study some middle-ear mechanisms in man. Using a new psychophysical technique based on aural combination tones,¹ we have measured changes in transmission through the middle-ear system resulting from static differential pressure applied across the eardrum, and the acoustically elicited middle-ear reflex. Preliminary results indicate sharp reductions in low-frequency middle-ear transmission for external ear canal pressures either positive or negative relative to the middle ear. A representative maximal transmission reduction at 500 Hz is 20 dB for differential pressures of ± 300 mm H₂O. Our measurements are in good agreement with studies on anesthetized cats in which cochlear microphonics were used as an indication of cochlear input (Møller²). Preliminary measurements of the attenuation produced by the acoustic reflex suggest a maximum of 10 dB at 500 Hz, and that the effectiveness of the acoustic reflex gradually diminishes with increasing signal frequency. Our results are qualitatively similar to those obtained by Møller² in the cat.

We plan to continue these measurements and also to measure the acoustic input impedance at the eardrum under the same experimental conditions. We shall study the theoretical and empirical relationships between transmission and input impedance changes, and compare our results with those available from other studies.

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7. Hearing Impairments, Hearing Aids, and Limitations
on the Intelligibility of Transformed Speech

The effort devoted to this project during the past year was less than anticipated because of unexpected competition for research time from other projects and because one of the principal investigators (L. D. Braida) was unexpectedly called upon to perform new administrative duties. Moreover, this effort has been confined almost exclusively to the continued planning of an appropriate research program. Some of the results of this planning can be summarized briefly as follows. First, the major long-term goal of this project will be the development of improved hearing aids. Second, as a means to this end, it will be necessary to develop a computer-controlled "master hearing aid" that is capable of providing and testing a wide variety of signal transformations (including frequency reduction and nonlinear elements) and that can be used as a research tool to study the intelligibility of transformed speech. Third, since the main difficulty in evaluating these transformations will probably arise from problems connected with training, it will be necessary to study seriously various training procedures and to develop criteria for distinguishing between ineffective transformations and ineffective training. Fourth, as a first step in this program, it will be extremely useful to improve our understanding of the limitations on the intelligibility of transformed speech for listeners (e. g., ourselves) whose hearing is normal.

During the coming year we intend to explore a variety of frequency-reduction schemes (achieved by computer processing, by a speaker inhaling a very dense gas, and so forth) with a view to improving the intelligibility of speech presented to a normal ear preceded by a lowpass filter. If we can identify such schemes, we shall then explore their use with listeners suffering from high-tone losses caused by sensorineural defects. Although transformations that are beneficial for a normal ear preceded by a lowpass filter may not be beneficial for an audiogram-equivalent impaired ear (and vice versa), we believe that such transformations constitute useful starting points and will provide us with valuable experience. If we cannot find such schemes, we shall attempt to understand our failure; in particular, we shall attempt to determine the extent to which the failure results from inadequate resolution at the lower frequencies, and the extent to which it results from inability to learn the new code. In general, we hope that studying the limitations on the intelligibility of transformed speech in normal listeners will contribute both to the design of the master hearing aid and to a better understanding of the fundamentals of speech perception.

8. Laboratory Facilities and Instrumentation

The development of facilities and design of instrumentation for auditory psychophysics continues to be keyed to the support of a wide range of psychoacoustic research. Although work on the completion of our computer-controlled laboratory facility continues, extensive experience has already been gained by initial users. We also are involved in the development of special-purpose instruments for signal processing and transduction.

During the past year we completed the development of timing, synchronizing, analog-to-digital conversion, and input-output circuitry for the PDP-8L and acquired an

additional 4000 words of core memory for it so that we now have three computers (PDP-4, 8, 12) with extensive capabilities for on-line experiments. Interface circuitry developed previously has been modified so that our programmable signal generating and processing equipment can be flexibly assigned among the computers. Two independent experiments can now be performed simultaneously under computer control while the third computer is used for data processing or programming. Work with interpretive computer languages has led to the development of two powerful, yet easily learned, programming systems, PSYCBL and CALCBL, which provide for on-line control and analysis of experiments, data processing, and model simulation. To compensate for some of the limitations which interpretation speed imposes upon the rate at which external events can be controlled, features equivalent to on-line compilation were incorporated into PSYCBL. Thus, for example, events such as the specification of an oscillator frequency can be timed with millisecond resolution and 0.01 ms accuracy even though interpretation speed is limited to 10-100 operations per second. Both PSYCBL and CALCBL also provide access to an easily controlled CRT display for alphanumeric information such as feedback and performance data. The high level of satisfaction experienced by users of these interpretive languages has led us to attempt to make them available on the PDP-4 installation. Initial work suggests that careful implementation can overcome many of the speed limitations associated with the longer cycle time of the older machine. With such an implementation, users of the computer facility would be assured of the availability of a machine-independent programming system for experiment control and data analysis.

Ongoing and future work will be focused on the completion of interpreter development, the investigation of a compatible compiler system, and the design of improved signal-control equipment. We intend to apply overlay techniques originally developed to provide PSYCBL and CALCBL with alphanumeric display capabilities to the problem of providing waveform handling capabilities. With these techniques we will be able to use the interpretive system in experiments in which a computer is used as a real-time signal processor (such as a generator of time delays of large duration-bandwidth product, or of nonlinear distortions) or generator of signals stored in bulk memory (such as complex signals or speech waveforms stored on a disk). Full exploitation of these waveform handling capabilities will require an increase in the size of available disk memory capacity. We are also exploring the development of a compatible compiler to supplement the interpretive systems and to provide additional control speed. Work on signal-control equipment is focused on completing a set of dual electronic switches with coherent gating and improved transient suppression, the development of high-quality controlled attenuators and programmable delay lines using FET switches, and the design of an improved wideband phase shifter for audio-frequency signals. Substantial instrumentation development continues for projects on stimulus specification, bone-conduction and impedance measurements, and acoustic transducers.

J. E. Berliner, F. A. Bilsen, L. D. Braida, D. J. Callahan, H. S. Colburn,
R. H. Domnitz, N. I. Durlach, J. L. Goldstein, P. W. Herman,
B. L. Hicks, A. J. M. Houtsma, W. F. Kelley, R. P. Lippman,
S. L. Moshier, W. M. Rabinowitz, J. B. Roberts, W. M. Siebert

C. Neuroelectric Correlates of Behavior

Studies of eyelid responses in the albino rat continue in both behavioral and physiological experiments. Control of eyelid movements through operant conditioning procedures has met with as little success during the past year as it had previously. An attempt was made in the more recent work to use procedures or "tasks" that seemed more "natural" or appropriate. So, for example, a Sidman avoidance procedure was employed in which the animal could avoid strong puffs of air directed periodically at the cornea by closing its eye sometime during the interstimulus interval. We were no

more successful here than we were in training the animal to close its eye to obtain a pellet of food.

The difficulty in achieving control of eyelid operants in the rat has led us to inquire how difficult it is for human subjects to learn to close their eyes under conditions resembling those under which the rat is trained. We hoped that in this way we might gain some insight into the problem with rats. Although this study is still in progress, we can say at least that the problem is not trivial for humans. Through additional experiments we are attempting to find out why this is so. One contributing factor, almost certainly, is that there is very little feedback from the response.

The unconditioned eyelid response of the rat to puffs of air directed at the cornea (the unconditional stimulus in our Pavlovian conditioning experiments) has often been seen to have two components: a brief early one with latencies of 5-15 ms and a larger, longer, later one that typically follows the early one after a silent period of 20-30 ms. Selective denervation of the eyelids or removal of the globe along with manipulations of the stimulus have shown that the early component is related to stimulation of the eyelids, especially the eyelashes, and the later component is related to stimulation of the cornea. The role of each in the conditioning experiments is still unknown, but it must be determined. We now raise the question whether similar complications may also be present in eyelid-conditioning experiments with rabbits and human subjects. Part of our work on the dual nature of the eyelid response was described in an undergraduate thesis by D. M. Bocard.

Our study of the organization of motor cortex in the rat has been completed. Representation of the eyelids has been found in a strip, approximately 3 mm long in the anterior-posterior dimension and 0.5 mm wide, lying near the midline of the dorsal cortex. This area appears to be coextensive with the area from which eye movements can be evoked. Our previous difficulties in finding the eyelid representation stemmed mainly from the fact that the eyelid response to "microstimulation" in the depths of the cortex is never an obvious closure of the lids. Quite the contrary, the response is nearly always a slight widening of the palpebral fissure, either through the movement of one or both eyelids, even with stimulus currents considerably above threshold. The movements are difficult to see without a microscope.

Our report a year ago that electrical stimulation through "semi-microelectrodes" below the cortical surface revealed a motor area which occupied much less cortex than the motor area described by Woolsey must now be qualified. Our first survey employed 25-ms bursts of 1-kHz sinusoidal current; a second mapping used stimuli of lower frequency, 300 Hz, and longer duration, 250 ms. Responses were evoked over an appreciably larger area by the 300-Hz stimulus. The area was substantially the same as that described by the earlier workers who employed 60-Hz sinusoidal currents at the cortical surface. The movements evoked by the 300-Hz stimulus, however, retained the very discrete character seen with the brief 1-kHz stimulus; very small movements of quite restricted parts of the face or body could be consistently evoked with suprathreshold currents that were frequently less than 50 μ A.

A survey of the potentials evoked in cerebral cortex by stimulation of the medullary pyramids has been described in an undergraduate thesis by R. L. Roth. In general the distribution of the antidromic responses is in agreement with published data from less extensive surveys and conforms to sensorimotor cortical areas in the rat as determined in this and other laboratories.

Several new projects have been initiated during the past year. A major effort has been directed toward delineating the activity in the trigeminal nuclei that is associated with eyelid responses to air puffs like those used in our Pavlovian conditioning experiments. We are examining the activity of single units and the gross potentials evoked by air puffs. This work is still in a preliminary stage. Like others before us we have had difficulty in finding units that respond to corneal stimulation, although there seem to be numerous cells with receptive fields that include the eyelids. Gross potentials appear to be rather widely distributed, related in complex ways to the site of stimulation,

and further complicated by feedback from motor responses evoked by the stimulus. The analysis of the activity in the trigeminal nuclei will be long and arduous.

Until recently our physiological experiments have been largely concerned with the activity and innervation of orbicularis oculi, the muscle responsible for closing the eyelids. We are now engaged in a search in the oculomotor nucleus for the motoneurons of levator palpebrae superioris, the muscle which raises the upper eyelid. We hope to describe their response characteristics under conditions like those used to study motoneurons of orbicularis oculi. The eyelid EMG as we have recorded it has confounded the activity from the two muscles, and we must attempt to determine the contributions of each. These responses are further confounded by activity in retractor bulbi, another problem requiring attention in the future.

We are still interested in motoneurons of orbicularis oculi; indeed, we have barely begun to study them. At present, we are working at putting microelectrodes into the appropriate region of the facial nucleus by a dorsal approach through the cerebellum. This approach involves very little surgical trauma and should permit permanent implantation of the electrodes or recording from curarized preparations under local anesthesia. Both procedures are potentially very useful in conditioning studies, as well as in other investigations. We also seek a meaningful measure of the motoneuron activity under such conditions, one that might be easier to obtain than records of single-unit activity in the behaving rat, and one that might provide a better estimate of the activity in the population of such motoneurons.

R. D. Hall, E. P. Lindholm

D. Other Physiological Research

1. Electric Properties of Nerve Membrane

The experiments on the dependence of ion conductances on concentration of external potassium ions in the lobster axon have been completed. The results have a bearing on such issues as the instantaneous linearity of the potassium conductance, and the independence of flow of potassium ions through the membrane. Although the work has been concentrated on measuring potassium current through the lobster axon membrane, sufficient data have been obtained on the sodium current to enable us to obtain a Hodgkin-Huxley-like description of membrane currents in the lobster axon.

P. Demko, Jr., T. F. Weiss

2. Properties of Primary Spindle Receptors

A study of muscle spindles in the cat's soleus muscle is being carried out in collaboration with Dr. James C. Houk of the Department of Physiology at Harvard Medical School. For small sinusoidal stretches of the muscle (e. g. , 30- μ m peak amplitude), the neural output of the receptor, as indicated by its instantaneous firing rate, is approximately linearly related to the stretch and shows a phase lead with respect to the muscle stretch down to a frequency of 0.001 Hz. The responses to slow ramp stretches (e. g. , 10 μ m/s), as well as to moderately fast ones, show nonlinearities. We are attempting to determine if a stictionlike element (which we presume represents a portion of the mechanics of the bag-type intrafusal fibers) can account for our results.

Z. Hasan

3. Cochlear Models

A new short-wave analytical model of the cochlea has been developed that leads to descriptions of cochlear behavior in virtually closed form which are extremely simple and transparent. The model appears to be particularly helpful in understanding

why the pattern of motion of the cochlear partition is substantially independent of the mode of stimulation, e. g., normal air conduction, bone conduction, artificial stimulation at the apex, and so forth. A paper describing the model is being prepared.

W. M. Siebert

4. Medullary Projections of Branches of the VIIIth Nerve of the Bullfrog

Central projections of portions of the VIIIth nerve of the bullfrog have been mapped by making lesions in the VIIIth-nerve ganglion and by determining the locus of subsequent degeneration in the medulla. Projections of the langenan and saccular branches of the nerve have been studied in this way.¹

L. S. Frishkopf

5. Transduction in Lateral-Line Organs

The objective of this research is to understand the processes by which lateral-line neuromasts transduce mechanical motion of the overlying cupula into neural activity. It has been established in Necturus that changes of the hair cell membrane potential (receptor potentials) occur as a result of cupular displacement.² During most of the past year our attention has been focused on the problem of describing cupular structure and motion in order to define adequately the input to the system. The results of this work can be summarized as follows (see also Sections XXII-A through XXII-D).

a. Structure

The cupula has been found to consist of a flat central ribbon surrounded by a gelatinous sheath. These two components are distinct in their mechanical, morphological, and staining characteristics. They appear to overlie the hair cell and supporting cell regions, respectively.

b. Mechanical response

A stroboscopic technique has been developed by which it is possible to observe directly amplitude and phase of cupular motion to sinusoidal stimulation. Preliminary measurements of phase vs frequency characteristics of cupulae have been made.³

c. Modeling

A second-order dynamic model of cupular motion has been developed. Parameters of stiffness, inertia, and damping of the cupula have been estimated, and the predictions of the model compared with preliminary data on cupular motion.

We are now developing techniques for reliably recording the neural response from the lateral-line organs of Necturus, and we plan to study these responses under a variety of stimulus and environmental conditions.

L. S. Frishkopf, C. M. Oman, H. J. Liff

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E. Biomedical Engineering

In broadest terms, our objective is to apply engineering technology to practical problems in patient care, health delivery systems, and clinical research. Our activities are not restricted to particular organ systems, although we have a strong interest in the cardiovascular system. Our research interest goes beyond the level of bioinstrumentation development into the clinical applications and medical research problems themselves. A well-equipped bioengineering laboratory has been established as a joint Harvard-M. I. T. endeavor at the Thorndike Memorial Laboratory of Boston City Hospital. This facility serves as a base of operations for engineering activities within the medical community. Graduate students often pursue thesis projects at the hospital — frequently in cooperative projects with physicians. Furthermore, the laboratory serves as a point of contact for members of the medical community who desire engineering consultation. The laboratory facility at the Research Laboratory of Electronics and the hospital facility complement each other. Complex instrumentation and/or computer software are pursued most intensively at M. I. T. and are later transferred to the hospital laboratory for clinical application. Studies involving clinical data, animal experimentation, and so forth, as well as a moderate amount of bioinstrumentation development are centered at the hospital. We have developed a small, portable, but rather powerful, computer system. This system features most of the peripherals necessary for on-line control and data processing, as well as an integrated software package with an interpretive compiler similar to the BASIC programming language. A duplicate of the system is now being installed in the hospital and will be applied to clinical problems occurring in the catheterization laboratory and the pacemaker clinic, as well as to research situations.

We have proposed, and expect to have funded, a hospital-based system for providing medical care at nursing homes. This is a pilot project to demonstrate the value of a system which provides follow-up medical care to patients discharged from the hospital to nursing homes. Specially trained nurse practitioners will act as the "front end" of the system. They will regularly follow up the patients in the nursing home and will be capable of taking histories, performing physical examinations, and doing simple laboratory work. A narrow-band communication system will permit consultation with, and supervision by, a hospital-based physician. A control group of nursing-home patients will be identified and both experimental and control groups will be studied to compare costs and effectiveness of care.

Several on-going research projects follow.

1. Ectopic Beat Detection

We continue our interest in the problem of reliably detecting and categorizing ectopic cardiac activity from EKG recordings. Detection based on a simple pulse-duration criterion is not adequate for all situations, particularly for the patient with conduction defects. We have therefore broadened our examination to include inter-beat interval and a more detailed examination of morphology. Work is progressing toward the development of a detection scheme using vectorcardiograms. This work offers considerable promise of successful detection in the presence of noise. In a completely different approach, a rather simple arrhythmia monitor has been built which records R-R intervals on a stripchart recorder running at a very slow speed. Twenty-four hours of

data can be compressed into 10 ft of chart length. The display clearly shows PVC's changes in heart rate, and artifacts.

2. Patient Monitoring

We have developed a computer-based system for monitoring multiple patients in a coronary-care unit. The system is interfaced to a commercially available patient monitor and uses its internal analog-to-digital conversion and digital storage for data acquisition. It performs a complete beat-by-beat analysis of EKG's from at least 12 patients and includes rather sophisticated interactive features permitting rather detailed attention to a specific patient, as well as considerable flexibility in the summarization of data.

3. Blood-Pressure Measurement

We have developed a portable blood-pressure recording instrument for epidemiological work. The first prototype has undergone successful clinical evaluation and we are now constructing two additional units. We continue our effort at developing an instrument to monitor blood pressure by measuring pulse wave velocity in the arterial system. We have accumulated encouraging verification of an approximately linear relationship between diastolic blood pressure and the velocity of pulse wave propagation in the major elastic arteries. Ultrasonic techniques seem to offer the most promise of detecting pulse wave arrivals, so we are developing and evaluating transducers.

4. Instrumentation for Muscle Physiology

We have developed a signal-processing device for use in muscle physiology experiments. It measures selected parameters of the length-tension curves and automatically prints out the result. This project is being done for the Tufts Cardiology Group at Boston City Hospital.

5. Remote Evaluation of Pacemakers

In connection with the Pacemaker Evaluation Clinic, we are developing instrumentation to permit us to obtain EKG and pacemaker rate from patients at home by telephone.

6. Vectorcardiograms

We have developed programs and peripheral hardware which allow us to record and manipulate vectorcardiograms and to display the recorded image in three-dimensional stereo, as well as to compute important quantitative parameters, such as areas and angles. We are examining the merit of computing the more common 12-lead scalar from the vectorcardiographic data. This study includes amassing considerable data from normal patients as well as those with diagnosed electrocardiographic pathologies.

7. Signal-Processing Instrumentation

We have developed a programmable digital matched filter that operates by correlating a transient (the template) stored in one 256-word recirculating memory with record of the most recent history of the input data stored in a second 256-word memory which both recirculates and processes. We are encouraged by the results of applying this to EKG records that have large amounts of noise.

8. Cardiovascular Instrumentation

We have developed an instrument for cardiac catheterization which provides a high degree of electrical isolation for the patient and computes functions of the pressure and

its first derivative which are quite useful in estimating cardiac work.

9. Electrocardiographic Data Displays

Clinical evaluation of our three-dimensional oscilloscope suggests that it would be quite useful in examining data recorded from ambulatory patients because isolated waveforms of abnormal morphology are clearly visible when displayed on the instrument. We are considering the addition of digital storage which would make it useful when scanning tapes on which the data are reproduced (typically) 64 times faster than originally recorded.

10. Tape Recording System

A data recording-reproduction system capable of multiplexing three low-frequency data channels on a single voice-bandwidth magnetic tape channel has been designed and constructed. Since the basic algorithm involves recording data on an exactly periodic frame, correction for variation in tape speed can be incorporated. Amplitude correction is provided by interpreting the pulse-duration modulated signal in terms of duty-cycle rather than absolute durations. Temporal variations are taken up in an 8-word first-in, first-out digital buffer memory. A second data magnetic tape system has been developed for recording minute-by-minute summaries of a patient's heart rate, blood pressure, and number of ectopic heart beats. In this system, the data are recorded once each minute in a digital code rather than continuously. Nearly 40 hours of data can be recorded on this system with a single tape and set of batteries.

R. G. Mark, S. K. Burns

A. STRUCTURE AND MOTION OF CUPULAE OF LATERAL-LINE ORGANS IN NECTURUS MACULOSUS: I. INTRODUCTION

The lateral-line system of fish and aquatic amphibians is an array of sensory organs distributed over the body surface. This system provides these animals with information regarding motion of their water environment. In amphibians, only relatively primitive freestanding organs are found, that is, organs that are in direct contact with the surrounding water, whereas in fish many of the lateral-line organs are contained within superficial canals.

Lateral-line organs are closely related embryologically to vestibular and auditory sense organs. The receptor cells of all of these systems are morphologically similar, comprising modified epithelial cells with ciliary processes projecting from their apical ends. These hair cells and the associated supporting cells are surmounted by a gelatinous structure (called a cupula, tectorial membrane, or otolithic membrane, depending on the system). The motion of this structure results in bending the cilia, thereby stimulating the hair cells and causing the nerve fibers that synapse upon them to fire. The detailed mechanism of the hair-cell transduction process is unknown, either at the apical hair-bearing end or in the basal synaptic region.

Although any disturbance that displaces the structure overlying the hair cells results in stimulation of the organ, each organ is constructed to respond to specific stimuli.

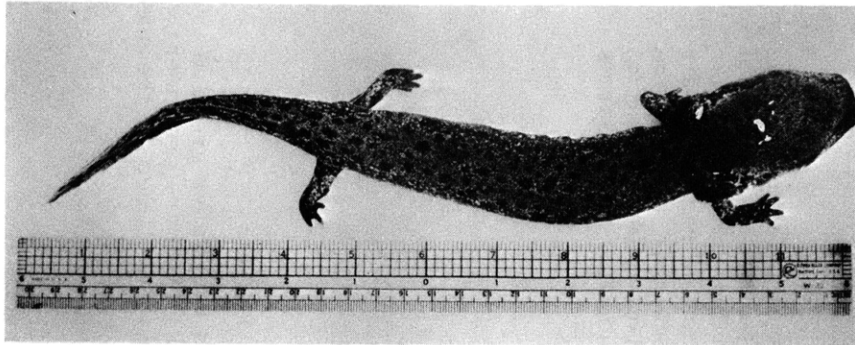


Fig. XXII-1.
Necturus maculosus in water.

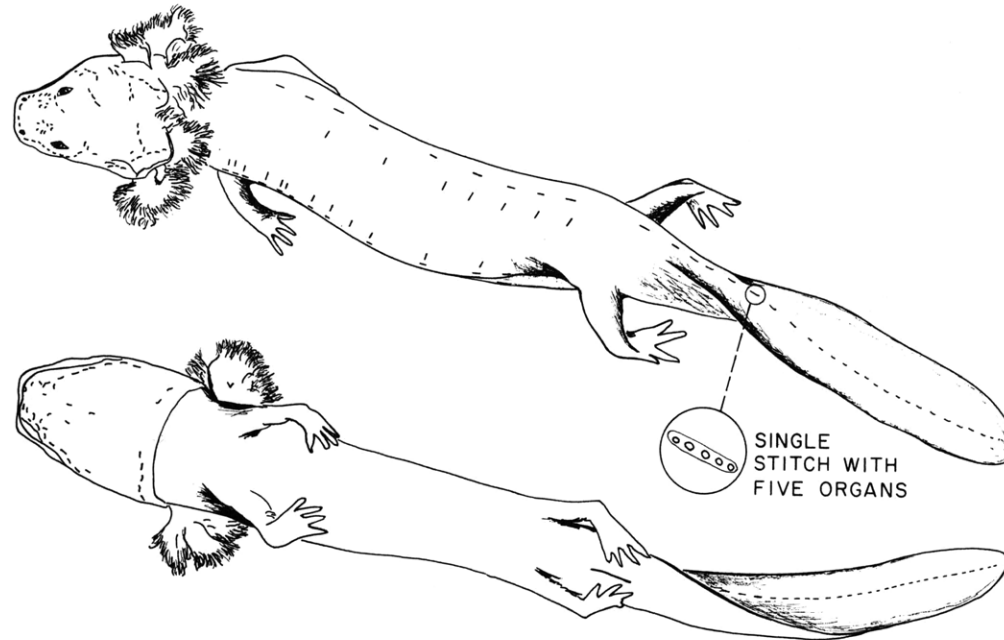


Fig. XXII-2. Dorsal and ventral sketch of Necturus showing distribution of lateral-line stitches.

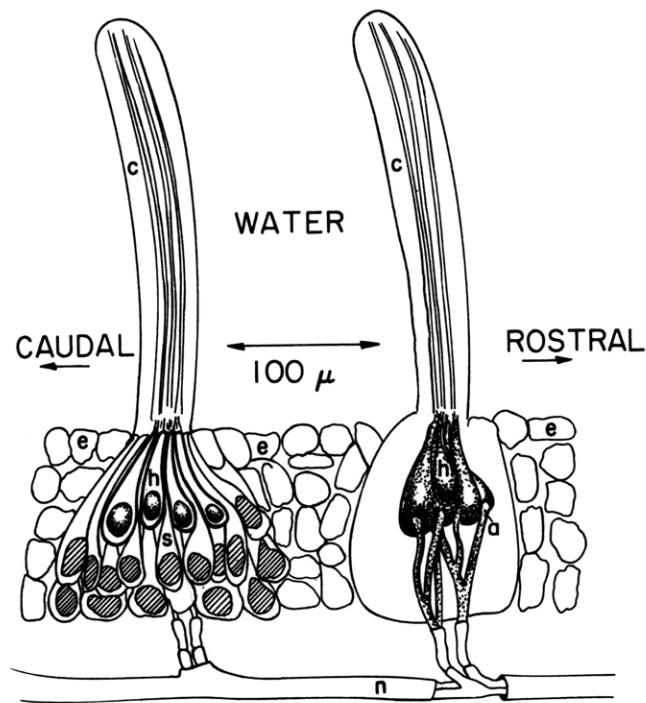


Fig. XXII-3. Two organs of a stitch in the lateral line of *Necturus*. The hair cells (h) are surrounded and separated by a nest of supporting cells (s) that is embedded in the epithelial layer of the skin (e). A cupula (c) extends from the region of hair cells upward into the water. The hair cells of a stitch are innervated by two afferent nerve fibers (n) which synapse (a) on the basal ends of the hair cells. (Modified from Harris et al.; ref. 1 in XXII-B.)



100 μ

Fig. XXII-4.

Detached cupula stained with Janus green B. The filaments of the central ribbon are prominent. At the base of the cupula the outlines of the sheath are faintly visible.

Thus cupulae of the semicircular canals are so situated as to respond to angular acceleration; the tectorial membrane to vibration of the tympanic membrane; the otoliths to linear acceleration; and the lateral-line cupulae to motion of the water surrounding the animal. Despite these differences, the common embryological origin and morphological similarities of these receptor organs suggest that the mechanisms of hair-cell transduction in all three classes of sensory organs may be much alike.

The mudpuppy (Necturus maculosus) is a large aquatic salamander found in lakes and streams of central and northeastern United States (Fig. XXII-1). Typically, they reach an overall length of 30 cm after several years growth. Although the animal has rudimentary lungs, it never undergoes metamorphosis, lives its entire life in water, and depends on an extensive system of external gills.

The lateral-line system of Necturus has a large number -- perhaps as many as 1000 -- freestanding organs distributed over the animal's dorsal and lateral surfaces. These are arranged in linear groups, called stitches, comprising approximately 1-8 organs (Fig. XXII-2). Each stitch is innervated by 2 afferent nerve fibers; efferent innervation has also been reported.^{1, 2}

The sensory epithelium (neuromast) of each organ contains 8-10 hair cells separated and surrounded by a large number of supporting cells; together they form a bulbous structure within the skin, roughly 200 μm in diameter. Figure XXII-3 is a diagram of the structure; Fig. XXII-4 is a photograph of the detached cupula. The cells of Necturus are generally large and the hair cells are no exception. A typical mammalian hair cell may be 40 μm long and 5 μm in diameter. Those of Necturus are approximately 80 μm long and 15 μm in diameter at the base, narrowing at the apical end to ~ 2 μm . In Necturus, the hair cells of an organ are arranged roughly in two rows of 4 or 5 hair cells each. At their apical ends the hair cells occupy a region perhaps 5 μm wide and 15 μm long, and are recessed somewhat from the surrounding epithelium. Surmounting the central portion of each neuromast and projecting into the surrounding water is a gelatinous cupula which serves to couple the motion of the water to the underlying hair cells. The research reported in Sections XXII-B through XXII-D has been directed toward clarifying the structure and dynamic behavior of the cupula.

L. S. Frishkopf, H. J. Liff, C. M. Oman

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B. STRUCTURE AND MOTION OF CUPULAE OF LATERAL-LINE
ORGANS IN NECTURUS MACULOSUS: II. OBSERVATIONS
OF CUPULAR STRUCTURE

The cupula of Necturus is normally colorless, transparent, and almost invisible. When either methylene blue or Janus green B (0.1%) is released locally in the water above a neuromast the entire cupula initially stains to reveal a slender cylindrical body $\sim 40 \mu\text{m}$ in diameter and 200-800 μm long. Subsequently the dye fades rapidly leaving visible 10-15 central filaments or tubules, each approximately 1 micron in diameter which together form a flat ribbon, some 15 μm wide and perhaps 2 μm thick, running the entire length of the cupula (see Fig. XXII-4, in Section XXII-A). The nature and origin of these filaments is uncertain. They may be tubular spaces over the hair cells left by the secretion of cupular material by the surrounding supporting cells. Methylene blue is taken up rapidly by these filaments but subsequently over an interval of a few minutes disappears entirely. It is significant that Harris et al.¹ have shown that methylene blue abolishes the receptor potentials of the hair cells, as well as the nerve response of the organ at the moment when the filaments become visible. The effect is reversible; the receptor potential returns first. Janus green B is also rapidly taken up by the filaments but does not completely disappear even after an hour or more. We have recently found that the nerve response of the organ is irreversibly abolished over such a time span by Janus green B.

The effect of both dyes on the response of an organ is extremely rapid and closely coincident in time with the staining of the cupular filaments. Both dyes are positive ions and known metabolic inhibitors. We may conjecture that these ions pass freely into the cupula, are taken up in the filaments, through the filaments rapidly reach the subcupular space and the ciliary processes of the hair cells, and poison these cells.

We have observed the outline of the cupula by depositing fine particles on its surface. For this purpose, we have used a white china ink in fine suspension. The outer boundary of the cupula is then apparent and its dimensions may be measured. The particles tend to line up on the surface parallel to the axis of the cylinder, suggesting a columnar structure for the outer portion of the cupula. This makes sense if we hypothesize that the supporting cells secrete the outer cupula as well as the central core, that each cell secretes a column of gel, and together these form the cupula. There is a difficulty, however, with the notion that the central filaments represent simply "holes" or tubes within this gel, for the central ribbon appears to have a structural integrity far surpassing that of the outer sheath. This becomes apparent when cupulae are removed from the animal, stained, and observed under the microscope during manipulation. The outer portion is fragile and often breaks up, but the ribbon remains intact despite considerable handling. In some cases we have seen the sheath separate from the ribbon. We conclude

that two separate structures are present. We have observed a corresponding dual structure in cupulae of the lateral-line organs of the tiger salamander (Ambystoma tigrinum) but because the number of hair cells per organ is larger in this animal than in Necturus, the central core occupies nearly all of the cupula, and the outer sheath can be seen with difficulty.

The occurrence of vertical striations in the cupulae of lateral-line organs has been reported previously^{2,3}; a canicular architecture has also been demonstrated in cupulae of semicircular canal organs.⁴ Inner and outer cupular structures have been previously described in the lateral line,^{2,5} but with characteristics very different from those reported here.

Water moving against the outer surface of the cupula causes it to displace and bend. The central ribbon is probably most rigid along its major cross-sectional axis. It would therefore best tend to transmit shear to the cilia of the hair cells in that direction. In the organs of the tail the major axis of the ribbon lies in a rostro-caudal direction; this observation is consistent with the reported rostro-caudal sensitivity of these organs.¹

We have been able to observe the growth of cupulae. After outlining with particles, a space gradually appears at the base as the cupula "lifts" off the organ. By measuring this space as it increases with time, we have determined the growth rate, at room temperature, as 15-30 μm per hour. Animals kept in the cold generally have much longer cupulae than animals maintained at room temperature. This may result from their relative inactivity in the cold. Apparently the lengths of cupulae are normally limited by continual wearing and breaking of the terminal portion.⁶

L. S. Frishkopf, C. M. Oman

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C. STRUCTURE AND MOTION OF CUPULAE OF LATERAL-LINE
ORGANS IN NECTURUS MACULOSUS: III. A TECHNIQUE
FOR MEASURING THE MOTION OF FREESTANDING
LATERAL-LINE CUPULAE

The sensory hair cells in lateral-line, vestibular, and auditory organs transduce mechanical stimuli into neural impulses. Although the details of the transduction process are unclear, it is generally believed that mechanical stimulation of the hair cells by an overlying cupula or tectorial membrane causes the release of a chemical transmitter that initiates spike discharges in the innervating sensory fibers. This process is accompanied by electrical changes across the hair-cell membrane. The accessibility of the mudpuppy's lateral-line organs, and the relatively large size of their hair cells, make these organs an attractive preparation for electrophysiological studies of hair-cell function. Harris et al.¹ have already succeeded in recording changes in the transmembrane potential of hair cells and the nerve spike activity from a single organ during stimulation of the overlying cupula.

We have been interested in continuing electrophysiological studies on the mudpuppy's lateral-line organs. We have developed a technique to measure the motions of free-standing cupulae in response to a sinusoidally moving source in the water. This technique will enable us to make a direct interpretation of hair-cell and neural responses recorded from an organ in terms of the motions of the cupula covering that organ. Observations with this technique have already contributed to a theoretical investigation into cupular dynamics (see Section XXII-D). In this report we describe the technique and briefly discuss certain aspects of cupular motion that we have observed.

1. Methods

We used mudpuppies (Necturus maculosus) 9-11 in. long, anesthetized by immersion in a 1:10,000 solution of MS-222 (Aldrich). Lateral-line organs were viewed through a binocular water-immersion microscope with a magnification of approximately 200X. The organs were illuminated by a trans-illumination system which focused the light from an incandescent source on a small spot. Because of this scheme, we were restricted to viewing organs only in the thin caudal portion of the tail.

Water motions were produced by a small glass ball (1-2 mm in diameter) placed in the water a few millimeters from the cupula that was observed. The ball was attached to a stimulator by a connecting rod and driven sinusoidally (Fig. XXII-5a). Velocity feedback from the stimulator was used to maintain either constant maximum displacement or constant velocity over a 5-200 Hz frequency range.

The normally transparent cupulae were visualized by depositing a solution of ink particles (Higgins white china ink) over the tail region. These particles were a few

microns in diameter and would adhere to the gelatinous cupular material. We could outline an entire cupula with particles by using very concentrated solutions; however, the loading would eventually cause the cupula to droop. We therefore preferred dilute solutions so that only a few particles adhered to each cupula. A 1:10 dilution of the ink was usually adequate. If we wished to outline a cupula to which only a few particles adhered, we could subsequently use stain, as reported in Section XXII-B. The ink particles were easily seen under stroboscopic illumination (General Radio 1531-A strobotac). The light was concentrated on the cupula of interest by using the trans-illumination system or by incident illumination through one of the ocular tubes of the water-immersion microscope.

Stroboscopic flashes were triggered externally as shown in Fig. XXII-5b. The velocity signal from the stimulator was amplified and hard-limited to produce a square wave whose transitions occurred at the velocity zero crossings. This square wave drove two one-shot multivibrators to generate pulses at both the positive- and negative-going

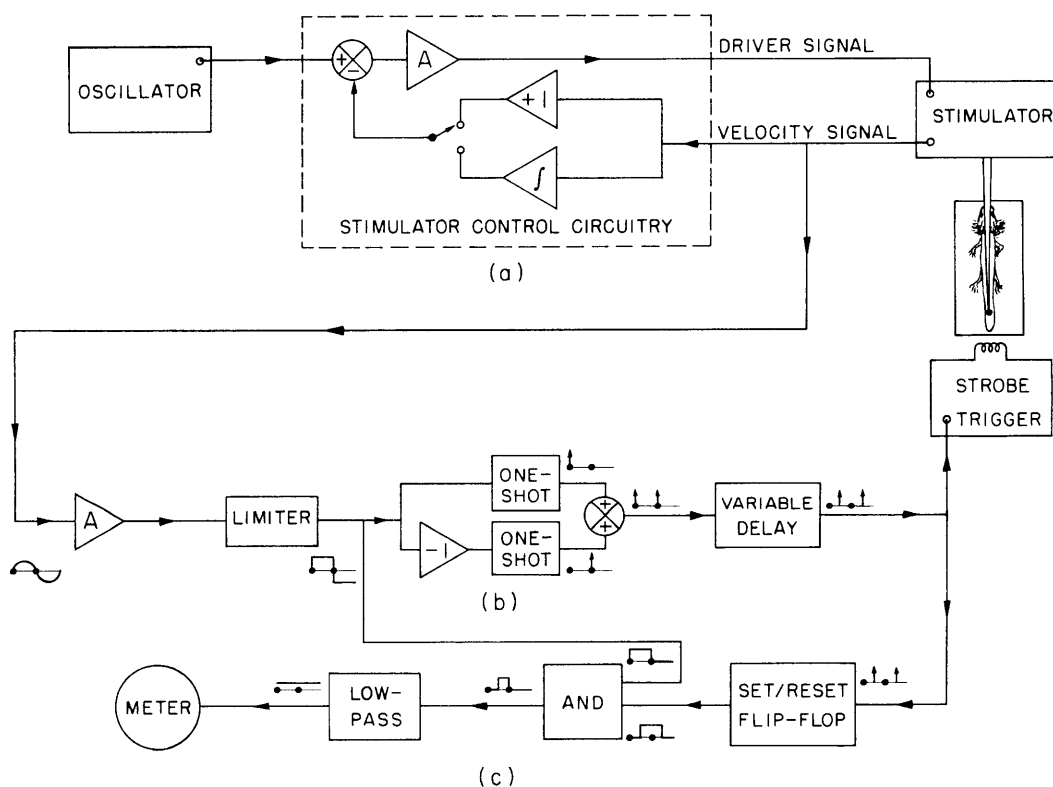


Fig. XXII-5. The experimental arrangement. Circuitry: (a) for driving stimulator; (b) for generating strobe trigger pulses; (c) for measuring the phase between strobe flashes and stimulator velocity. Signals at representative points in the pulse-generating and phase-measuring circuits are also shown in (b) and (c).

transitions. These pulses could be delayed and then used to trigger the stroboscope. Two flashes separated by 180° occurred during each cycle of the stimulator. The phase of each flash with respect to the velocity zero crossing varied between zero and 180° .

This scheme allowed us to measure the amplitude of cupular displacement and its phase with respect to the stimulator velocity. Since a particle on a cupula was illuminated twice in each cycle, it was generally seen as two spots whose separation depended upon the phase relationship between the flashes and cupular displacement. By adjusting the phase of the flashes until the spots were maximally separated, the maximum amplitude of cupular displacement could be measured by a calibrated microscope eyepiece. In the particular case wherein the flashes occurred at the zeros of cupular displacement the particle was illuminated at the same position twice in the cycle and therefore was seen as a single sharp spot. In this way, the phase angle ϕ between cupular displacement and stimulator velocity could be measured.

The circuitry for measuring ϕ is illustrated in Fig. XXII-5c. The trigger pulses drove a Set/Reset flip-flop switch generating a square wave whose transitions marked the times of flashing. This square wave and the square wave generated from the stimulator velocity signal were the inputs to an AND gate. The output was a periodic rectangular pulse whose width depended linearly upon the phase difference between the input square waves. By lowpass filtering and proper calibration, we obtained a dc voltage that directly indicated the phase angle between the flashes and the stimulator velocity.

2. Discussion

Our experimental results have demonstrated the feasibility of this technique for measuring the amplitude and phase parameters of sinusoidally moving cupulae. We have concentrated primarily on measuring ϕ , the phase angle between cupular displacement and stimulator velocity. Over the frequency range 5-200 Hz we measured ϕ with a repeatability of $\sim\pm 5$ deg for maximum cupular displacements of only a few microns. With larger maximum displacements ϕ could be measured within even smaller bounds. The limitation of the technique below ~ 5 Hz is attributable to flicker effects and poor illumination associated with infrequent flashing. The present high-frequency limitation results from stimulator characteristics. While we have not yet made systematic amplitude measurements, we believe that cupular displacements as small as a few microns can be reliably measured.

In Fig. XXII-6 we have plotted the phase angle ϕ as a function of frequency for a point near the top of a cupula 400 μm long. At 50 Hz, $\phi = -90^\circ$ so that cupular displacement at this point was in phase with stimulator displacement. Below 50 Hz this point on the cupula led the stimulator, while above 50 Hz it lagged the stimulator. Oman (see Section XXII-D) has proposed a simple model of cupular dynamics in terms of a

second-order transfer function between the local water velocity and cupular displacement. The data in Fig. XXII-6 are reasonably consistent with his model provided we

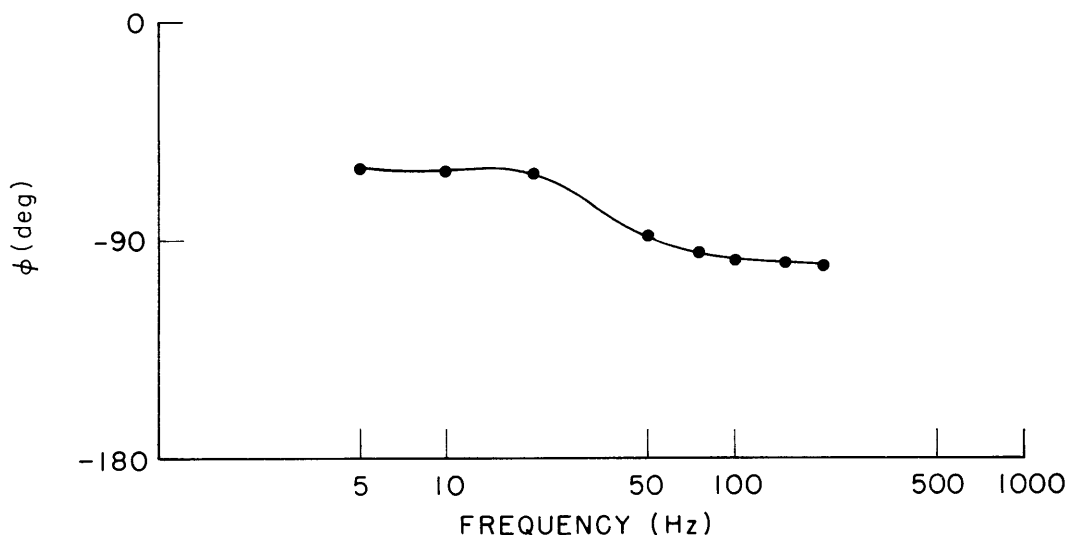


Fig. XXII-6. Plot of ϕ , the phase angle between cupular displacement and stimulator velocity as a function of the frequency of the sinusoidally driven stimulator. A point near the top of a cupula 400 μm long was observed.

assume that the cupula moves as a rigid body and neglect any phase shift between stimulator velocity and local water velocity. Although these assumptions may not be strictly valid, phase data from several cupulae show that at least to a first approximation cupulae respond to water motions in the same way as overdamped systems with undamped natural frequencies between ~ 10 Hz and 100 Hz.

Simultaneous phase measurements on two points of a cupula have shown that the phase of cupular displacement varies along the length of a cupula. In one example a cupula, 500 μm long, driven at 20 Hz showed a 20° phase shift between displacement of the top and displacement of a point 300 μm above the base. These observations appear to be inconsistent with a simple lumped model of cupular mechanics, but Oman (Section XXII-D) has suggested that the distributed character of the response may be the result of boundary-layer effects produced by the animal's body surface. Further experimental studies of this theory require extension of our present technique to measure local water motions around each cupula. This we believe can be accomplished by observing free ink particles dropped in the vicinity of a cupula.

The technique described here is capable of measuring the amplitude and phase

parameters of sinusoidally moving cupulae over frequency and amplitude ranges of physiological interest. We intend this technique to be used to aid in interpreting electrophysiological data from lateral-line organs and in further investigations of cupular mechanics.

H. J. Liff, S. Shamres

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D. STRUCTURE AND MOTION OF CUPULAE OF LATERAL-LINE ORGANS IN NECTURUS MACULOSUS: IV. PRELIMINARY MODEL FOR THE DYNAMIC RESPONSE OF THE FREESTANDING LATERAL-LINE CUPULA BASED ON MEASUREMENTS OF CUPULA STIFFNESS

The Communications Biophysics Group has been attempting to obtain phase measurements of the motion of the freestanding cupula of Necturus in an effort to determine the dynamic response of the organ. A preliminary mathematical model for the response of the cupula to local water flow has been prepared to aid in the planning of experiments, interpretation of the results, and in an attempt to clarify the concept of "adequate stimulus" for this dynamic system.

Microscopic examination of the lateral-line organs after deposition of china ink particles or staining (with methylene blue or Janus green B), shows that the cupula is a gradually tapering, gelatinous, cylindrical column, of diameter 30-50 μm . The lengths of cupulae in animals kept in 60° F water vary greatly, but are typically 200-500 μm . Cupula growth rates when the animal is placed in an anesthesia solution (1:10,000 MS222, Aldrich) appear to be of the order of 15-30 μm per hour, a range similar to that for human facial hair. Animals refrigerated for several days prior to examination generally show cupulae in the 400-800 μm range. We infer from this that in the natural situation cupulae are probably shed, wiped off, or broken off, and are constantly in the process of regeneration, with length primarily related to the activity level of the animal (see Section XXII-B).

The cupula itself is not a homogeneous structure in Necturus. When the cupula is stained with methylene blue, a central structure appears that has the appearance of a ribbon, ~ 15 μm wide and 2 μm deep. It appears to be composed of approximately 10 fibrils or tubes, running the length of the cupula (Section XXII-B).

Examination of the cupula in an oscillating flow suggests that primarily the cupula

deflects as a whole and appears to follow water displacement, except near zero frequency, where a constant bending angle results from sustained flow. At higher frequencies, of the order of 20 Hz, the phase of cupula motion may change somewhat along its length (see Section XXII-C). The exact nature of these higher bending modes is still uncertain. It should be noted, however, that linearized solutions of the Navier-Stokes equations for oscillating fluid flow near a plate show that substantial phase lags can develop between flow at any point within the boundary layer and flow in the free stream if the frequency is high enough. A preliminary analysis suggests that for the frequency range of interest the organs are well within the boundary layer. Consequently, phase measurements ought most properly to be referred to the local flow field at the height of the cupula, and not necessarily to flow at the oscillating driver. Furthermore, the analysis suggests that near the high end of the frequency range under consideration (>10 Hz) there could be phase differences between flow at various heights along the cupula. Unfortunately, however, rigorous extension of this theory to the exact problem considered here is not easy, and would be of dubious value because the exact morphology of the local epithelial surface would render such a solution highly individualistic. Hence, a less exact approach has been taken in an attempt to develop a linearized mathematical model which would be particularly applicable at low frequencies. This model would suggest the basic type of dynamics involved in a uniform flow field and assess the influence of fundamental parameters such as cupula length.

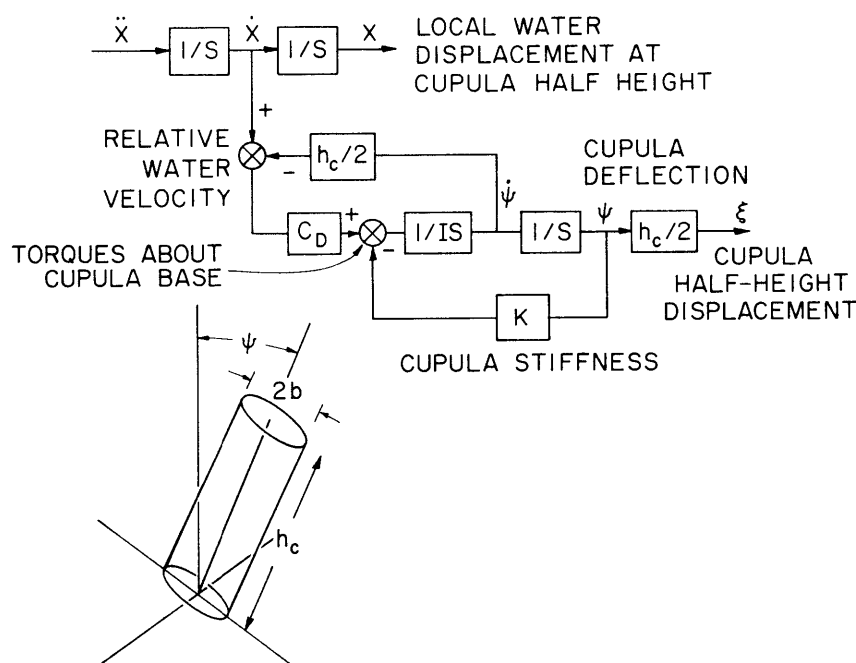


Fig. XXII-7. Dynamic model of a freestanding lateral-line cupula.

(XXII. COMMUNICATIONS BIOPHYSICS)

The model which resulted is shown in Fig. XXII-7. The cupula is represented as a cylindrical structure of radius $b = 20 \mu\text{m}$, and height h_c . Deflection is assumed to be linear with water drag torque, and to occur about its base. The stimulus to the organ is taken from the states of the local water flow at the half-height of the cupula. At the low Reynolds number associated with this case ($\text{Re} = 0.1$), it is expected that the viscous terms in the solution to the Navier-Stokes flow would usually far exceed the inertia terms, provided cupula stiffness is as expected, so that the difference between cupula velocity and local water velocity provides the effective stimulus. Hence, we define

X = local water displacement at cupula half height

C_D = drag torque about base of cupula per unit relative water velocity at cupula half height

K = stiffness torque per unit angular deflection

ψ = cupula deflection (rad)

ζ = cupula half-height displacement

I = moment of inertia of cupula about its base

b = radius of cylindrical cupula

h_c = height of cupula

μ = viscosity of water, 0.006 poise

Balancing torques about the base of the cupula, we have

$$I\ddot{\psi} = C_D \left(\dot{X} - \frac{h_c}{2} \dot{\psi} \right) - K\psi. \quad (1)$$

The moment of inertia about the base of cupulae of various lengths was estimated from the average dimensions and a density of unity, since the cupula appears to be neutrally buoyant. The drag torque coefficient, C_D , has been estimated, and the stiffness torque coefficient, K , measured by methods which will be described. Hence, the freestanding lateral-line organ should exhibit dynamics with a transfer function of approximately

$$\frac{\psi}{\dot{X}} = \frac{C_D/I}{s^2 + \left(\frac{h_c}{2} \frac{C_D}{I} \right) s + \frac{K}{I}}. \quad (2)$$

A technique has been developed for directly measuring the approximate stiffness of the freestanding organ by constructing a calibrated microspring, and observing the deflection of cupulae of several different lengths on an anesthetized animal in water. The microsprings were made by mounting a fiberglass fiber, $10 \mu\text{m}$ wide, 1.6 cm long, on the tip of a glass microelectrode. Fibers of this type can be obtained by dissection of the weft of glass matting used in regular fiberglass construction. The pipette was mounted in an electrode holder, with a second electrode mounted parallel to the first

to serve as a reference for fiber deflection. Calibration of the microspring fibers was accomplished directly by the use of different microweights prepared from very small lengths of copper wire, 53 μm in diameter. The weight of each bit of wire could be estimated from its size, since the weight per unit length of the wire had been determined by weighing a relatively large length of wire on an analytical balance. By using an assortment of weights in the 1-10 μm range, linearity in fiber deflection was established. Data were taken from several cupulae, 180 μm and 250 μm long, by bringing the fiber up to the tip of a cupula horizontally, and observing deflections of cupula and microspring under the operation microscope reticule. Although it was difficult to control the contact point precisely, the measurements appeared reasonably repeatable, and the deflections approximately linear. Large deflections could not be measured because of artifacts introduced by adhesion of the fiber to the cupula material. It was found that 10^{-3} dyn (10^{-6} gm) deflected a 180- μm cupula ~ 120 μm . A 250- μm cupula showed a deflection of 180 μm for a 0.3×10^{-3} dyn force. This reduction in stiffness was consistent with basic concepts of cantilever beam flexure. Therefore the stiffness coefficient, equal to torque at cupula half-height per radian of deflection, was calculated from these data with allowance for the difference between a point and a distributed load and for differences in cupula length, by fitting a theoretical relationship¹ through the available data points, as shown in Fig. XXII-8. Theoretical extrapolation to the longer lengths was necessary, as it was difficult to make measurements on cupulae of length greater than 300 μm because the

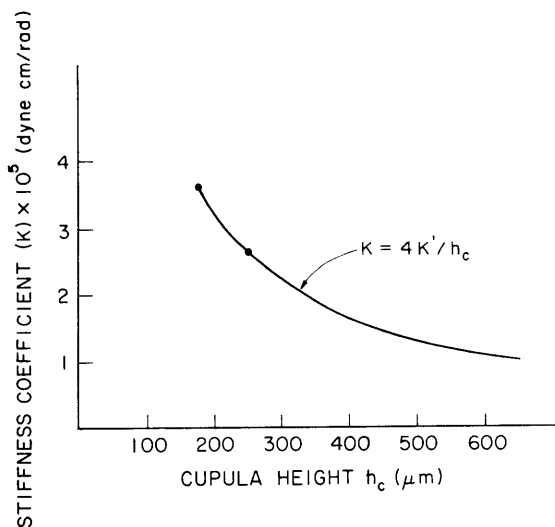


Fig. XXII-8.

Cupula stiffness coefficient as a function of cupula height. Theoretical curve is indicated by solid line and data by filled circles. K' is the cupular section constant (Young's modulus \times section moment of inertia).

longer organs drooped under the weight of the particles deposited, and because the fiber too often slipped off to give repeatable measurements. It is interesting to note that if we consider the cupula as a deflecting cantilever beam, the values of stiffness imply a

value for Young's modulus of the cupula material, taken as a whole of $\sim 10^3$. This can be compared with values of 10^6 for rubber, and unity for mucus found by Philipoff² and 10^3 to 850×10^3 for gelatin found by Pouradier.³ The values are consistent with values calculated by ten Kate⁴ for the cupula of the semicircular canal of the pike on the basis of dynamic data, and with a similar calculation for the same organ in humans by Oman and Young.⁵ The value is somewhat less than would be calculated on the basis of a stiffness measurement on the cupula of the enclosed organ of Acerina ceruna by Jielof, Spoor, and de Vries.⁶

Viscous flow drag is difficult to approximate because of the nonsteady aspect and the nature of flow detail around the cupula and over the epithelial surface. For the preliminary model, the drag was approximated by analogy with the steady-flow case of Stokes flow around a sphere. Cupula drag was assumed to act at the half-height of the cupula with a magnitude equal to the Stokes flow drag on a sphere of equal surface area. On this basis, we obtain the approximate expression

$$C_D = \mu\pi \frac{h_c}{2} \sqrt{18bh_c} \quad (3)$$

which yields values as shown in Fig. XXII-9. This approximation is probably accurate only with respect to the order of magnitude of the effect, but it does reflect the expected increase in drag coefficient as the cupula grows.

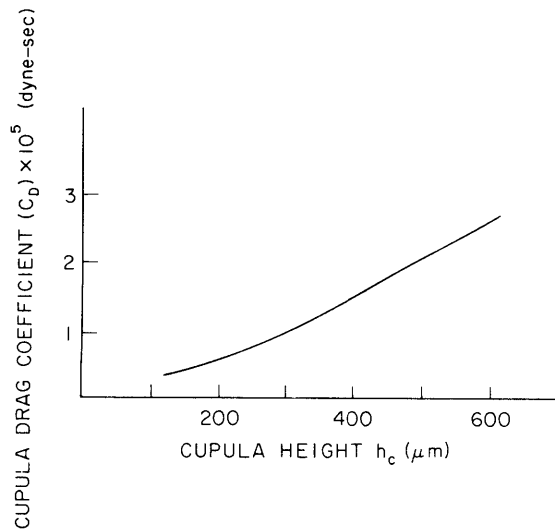


Fig. XXII-9.

Cupula drag coefficient as a function of cupula height, based on Stokes flow approximation.

These calculations were used as first estimates in order to predict the dynamics of the cupula-water interaction and to show how the parameters of these dynamics may shift as a function of increasing cupula length. The response plots which resulted from

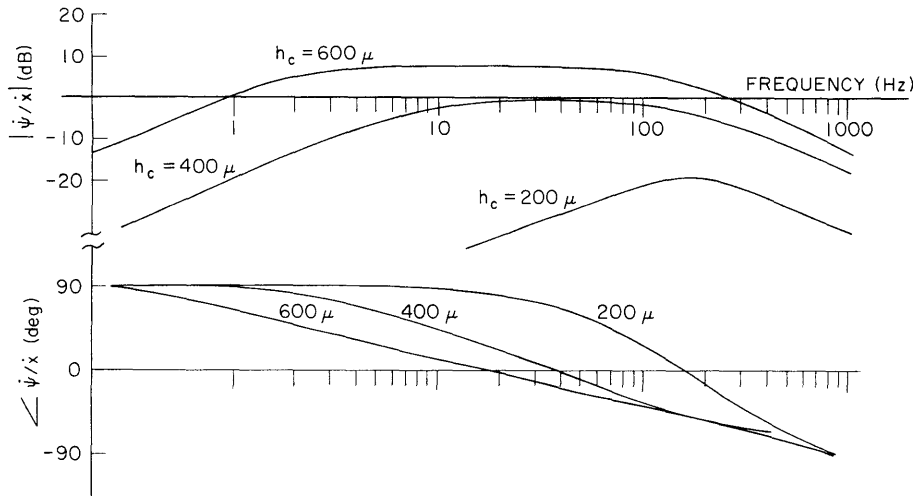


Fig. XXII-10. Frequency response of dynamic model of freestanding lateral-line cupula. Relative amplitude and phase of cupula velocity and water velocity are plotted as a function of frequency.

this preliminary analysis are shown in Fig. XXII-10 for representative cupula lengths of 200, 400, and 600 μm .

The analysis suggests that the cupula should exhibit second-order dynamic response to water velocity, so that near the natural frequency of the system cupula and water displacement should be overdamped, at least for cupula lengths greater than 200-300 μm . Increasing the cupula length decreases the natural frequency of the system, increases the damping ratio, and improves coupling to the water flow substantially.

At very low frequencies, cupula deflection is in phase with water velocity, as expected. For cupulae of 400-600 μm length, the velocity gain of the system between 10 and 100 Hz is given by $C_D h_c / 2K$. Evaluation of this ratio suggests that water displacement amplitude should be of the order of ten times greater than cupula displacement. This factor becomes smaller as cupula length increases.

A step input in water displacement, as shown in Fig. XXII-11 results in an almost immediate deflection of the cupula, and a relatively slow return, because of cupula stiffness.

Results of experimental attempts to validate the model by directly measuring cupula response to sinusoidal stimulation are only preliminary. Liff and Shamres (Section XXII-C) found that over the range 5-200 Hz, cupula displacement was nearly in phase with driver-ball displacement. A fit of the second-order model to their phase data for a single cupula, shown in Fig. XXII-12, indicates corner frequencies of 6 Hz and 400 Hz. The vertical height of the cupula was estimated at 400 μm , although the actual length of the organ was probably somewhat greater than this because the cupula was

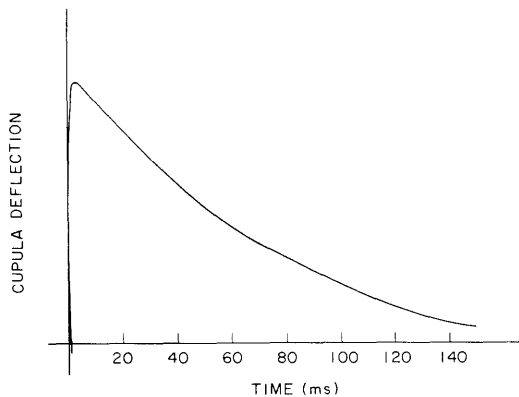


Fig. XXII-11.

Theoretical response of a cupula, 600 μm long, to a step in water displacement (velocity impulse).

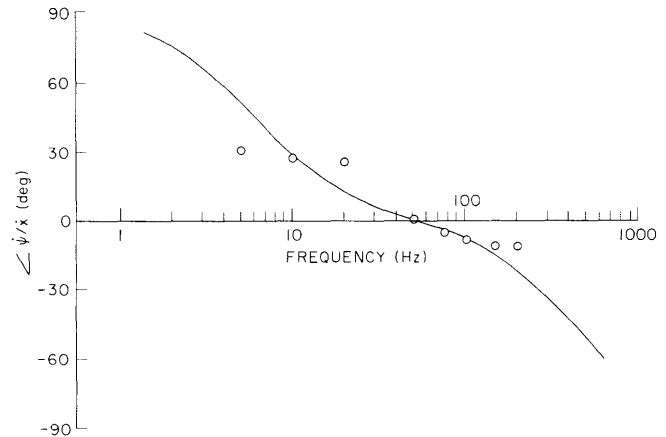


Fig. XXII-12.

Model fit of Liff and Shamres' data for a cupula 400 μm high.

bent under the weight of the deposited china ink particles. In terms of the fundamental model parameters, a fit of the data indicates that if the cupula had a stiffness of 1.62×10^{-5} dyn cm/rad (the value estimated for a cupula 400 μm long), cupula inertia would be 1.68×10^{-10} gm cm², and the drag coefficient would be 2.18×10^{-5} dyn-sec. Considering the sources of error involved in the experiment, and the deformed nature of the cupula observed, these values seem reasonably close to the theoretical estimates.⁷

Current experimental work is directed toward making more precise phase measurements on cupulae of known height in an attempt to determine phase shift with frequency, and to determine the magnitude of the water/cupula displacement slip ratio, so that the value of C_D/K can be more directly assessed.

C. M. Oman

Footnotes and References

1. For the same net load, a cantilever beam under uniform load deflects only 3/8 as much as the same beam with a point load at its end. Hence a uniform load of 10^{-3} dyn should deflect a 180- μm cupula 45 μm or 0.25 rad. Therefore the stiffness of this cupula is considered to be 3.6×10^{-5} dyn cm/rad.

In general, for a deflecting uniformly loaded beam, deflection = $h_c \psi = Fh_c^3/8K'$, where F is the load force, and $K' = EI'$, with E the section Young's modulus, and I' the section moment of inertia. Hence

$$K = \frac{Fh_c/2}{\psi} = \frac{4K'}{h_c}.$$

Since K' is a constant as the cupula grows, this relationship is used to extrapolate theoretically to other cupula lengths.

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7. A theoretical expression for cupula inertia based on the moment of inertia of a rigid cylindrical beam of density ρ , radius b , and length h_c about its base is

$$I = \frac{\pi}{12} \rho b^2 h_c (3b^2 + 4h_c^2).$$

For $\rho = 1$, $b = 2 \times 10^{-3}$ cm, $h_c = 4 \times 10^{-2}$ cm we obtain $I = 2.68 \times 10^{-10}$ gm cm².

The drag coefficient for a cupula of these dimensions in water is estimated from Eq. 3 to be $C_D = 1.43 \times 10^{-5}$ dyn-cm.

