TUNING IN THE BULLFROG EAR

EDWIN R. LEWIS
Electronics Research Laboratory and Joint University of California-Berkeley/University of California-San Francisco Graduate Group in Bioengineering, University of California, Berkeley, California 94720

ABSTRACT When electrical resonances were observed in acoustic sensory cells of lower vertebrates, the hearing research community was presented with the exciting possibility that tuning in the ears of those animals might be explained directly in terms of familiar molecular devices. It is reported here that in the frog sacculus, where electrical resonances have been observed in isolated hair cells, the effects of those resonances are completely obscured in the tuning properties of the sacculus in the intact ear. This observation has important implications not only for students of the ear, but for reductionist biologists in general. All of the dynamic properties of a system of connected, bidirectional processes are consequences of all of those processes at once; in such a system, the properties of an experimentally isolated subsystem may be totally obscured in the operation of the system as a whole.

INTRODUCTION

Electrical resonances in acoustic receptor cells (hair cells) were observed first in the basilar papilla of the turtle (*Pseudemys scripta elegans*) (Crawford and Fettiplace, 1981). Then they were found in hair cells of amphibian papillae (auditory sensors) and sacculi (seismic sensors) in ranid frogs (Lewis and Hudspeth, 1983; Hudspeth, 1985; Ashmore and Pitchford, 1985). In each case, the resonant frequencies were within or very close to the known range of acoustical sensitivities of the sensor in question. In the turtle basilar papilla and the sacculus of the bullfrog (*Rana catesbeiana*), the resonances have been shown to result from an interplay between voltage-sensitive calcium channels and calcium-sensitive potassium channels in the hair cell membrane (Lewis and Hudspeth, 1983; Art et al., 1986). Thus the hearing research community has been presented with the exciting possibility that tuning in the ears of lower vertebrates might be explained directly in terms of familiar molecular devices.

When electrical resonances have been observed in the hair cells of the bullfrog sacculus (Lewis and Hudspeth, 1983), the experimental procedure has included either excision of the saccular sensor from the inner ear and removal of the gelatinous structure (otoconial membrane) that mechanically links one hair bundle to another (Hillman, 1969), or complete isolation of individual saccular hair cells (Lewis, 1985; Lewis and Hudspeth, 1983). The small-signal (linear) transient responses of the observed resonances consistently were simple exponentially decaying sinusoids, of the form $\exp(-bt)\cos(wt)$; and the quality factors (Qs) of the resonances ranged from <1 to >10 (Lewis, 1985). The resonance frequencies ranged approximately from 90 to 250 Hz. Serving as a spectral filter or tuning device, such a resonance could pass (or reject) signal and noise components with frequencies in a band (centered at the resonant frequency) whose width is approximately equal to the resonance frequency divided by Q.

In my laboratory, we have observed the linear response properties not of individual hair cells, but of afferent axons from the intact sacculus, each of which typically innervates from 2 to 30 hair cells (Lewis et al., 1982). In this short note, I report that among more than 100 such axons we have studied, only one exhibited the tuning behavior expected of a resonance. All of the others exhibited broad pass bands (Q typically <2) bordered on one or both edges by remarkably steep, sustained skirts. Furthermore, none of the axons exhibited the large, abrupt changes in phase shift (at the peaks or edges of the pass bands) that normally accompany the steep skirts of tuning curves derived from linear processes.[1] Instead, throughout their pass bands, the axons exhibited phase-shift vs. frequency relationships that are very close to the ideal (phase directly proportional to frequency) for optimum preservation of temporal waveforms. Thus evolution has sculpted spectral filters with precisely the properties that a master electrical engineer would specify in such a filter to achieve high resolution in both frequency and temporal analyses (Jones and Hale, 1982; Lewis, 1987). Engineers normally obtain near ideal phase properties by adding linear phase-compensating networks to their linear spectral filters (Guillemin, 1957).

The purpose of this note is to present these remarkable filters from the bullfrog sacculus as illustrations of a very general problem: the dynamic properties of experimentally isolated parts of a system often will be obscured in the operation of the intact system as a whole; every aspect of

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[1] Strictly speaking, phase is not well defined for transfer functions of nonlinear processes.

the dynamic behavior of a system of connected, bidirectional processes will be determined by all of those processes.

MATERIALS AND METHODS

The bullfrog preparation was adapted from that of Capranica and his colleagues (Capranica and Moffat, 1975). Animals were anesthetized with ~50 μg sodium pentobarbital per gram body weight. Through a small hole in the roof of the mouth, the VIIIth cranial nerve was exposed on its way from the intact otic capsule (with intact circulation) to the brain. Each animal was mounted upside down on a rigid platform, with its head held firmly against the platform surface. Individual axons in the anterior branch of the VIIIth nerve were penetrated with glass microelectrodes filled either with a KCl solution or with a solution of the ionic dye Lucifer Yellow (Stewart, 1978).

Attenuation of ambient microseismic noise was achieved by carrying out the experiments on a lab-built vibration isolation table comprising four second-order filter stages, each slightly underdamped and with corner frequencies in the neighborhood of 1 Hz, topped by a fifth second-order stage in the form of a commercial optical platform, also with corner frequencies in the neighborhood of 1 Hz. The entire structure was contained within the outer walls (reinforced concrete, 14-cm thick, with gasket-sealed double doors) of an acoustic isolation chamber; the last two stages were contained within the inner walls (plywood, 1.9 cm thick, with gasket-sealed doors) of the chamber. Thus, vibrations induced in the table by air-borne sound were greatly reduced. With this system, lineal vibrations in the frequency range of interest (10–300 Hz) were reduced to levels below the noise floor of our measuring system (~0.0002 cm/s^2 per $\text{Hz}^{1/2}$).

Dorsoventral sinusoidal vibrations were generated by a 4810 exciter (Bruel & Kjaer Instruments, Inc., Marlborough, MA) connected to the underside of the platform on which the frog was mounted. The stimuli were monitored with a calibrated Bruel & Kjaer 4370 accelerometer also mounted on the platform. The loaded platform was calibrated with respect to spatial variation of vibration amplitude and phase and found to be uniform to within 1 dB and 0.1 rad over the frequency range of interest (10–300 Hz). The sound pressure levels induced by the vibrations were measured with a calibrated Bruel & Kjaer 4186 microphone at the level of the frog's tympanum. By linear extrapolation, they were found to be <10 dB SPL for all frequencies and stimulus levels employed in the experiments. That is at least 10 dB below the lowest auditory thresholds reported for the bullfrog. The data presented in this paper were generated with single-frequency stimuli (Figs. 1 *B* and 2) and with continuous (logarithmic) frequency sweeps at 2–8 octaves per minute (Figs. 3–5).

Saccular axons were identified as such by two methods. In our earlier experiments, after each axon was characterized physiologically, it was filled with the fluorescent dye Lucifer Yellow and subsequently traced precisely to its source in the ear (Lewis et al., 1982). After executing this procedure on more than 60 axons from the anterior branch of the VIIIth nerve (which innervates the sacculus, utriculus, and two semicircular canals), we concluded that all seismic-sensitive axons in that branch originate at the sacculus. Subsequently, KCl electrodes were used in most experiments and most putative saccular axons were identified as such by their presence in the anterior branch and their seismic sensitivity. Occasionally, Lucifer Yellow was used to verify the identification.

TUNING IN THE BULLFROG SACCULUS

The bullfrog sacculus is extraordinarily responsive to substrate vibration (seismic stimuli) (Koyama et al., 1982). In the absence of such stimuli, its afferent axons typically exhibit random spontaneous spike activity at mean rates between 10 and 40 spikes/s. Crawford and Fettiplace (1980) found that afferent axons from the turtle basilar papilla exhibited spike-interval histograms with conspicuous periodicities. These took the form of multiple modes, with successive modes separated by intervals equal approximately to the reciprocal of the frequency at the center of the axon's tuning band. This is the sort of response one would expect from a spike initiator being excited by a generator potential arising from broad-band noise that has passed through a narrow-band filter (e.g., see Bishop et al., 1964; Lewis, 1965). The spike-interval data in Fig. 1 *A* are representative of all spontaneously active saccular axons we have observed and show no sign of such periodicity.

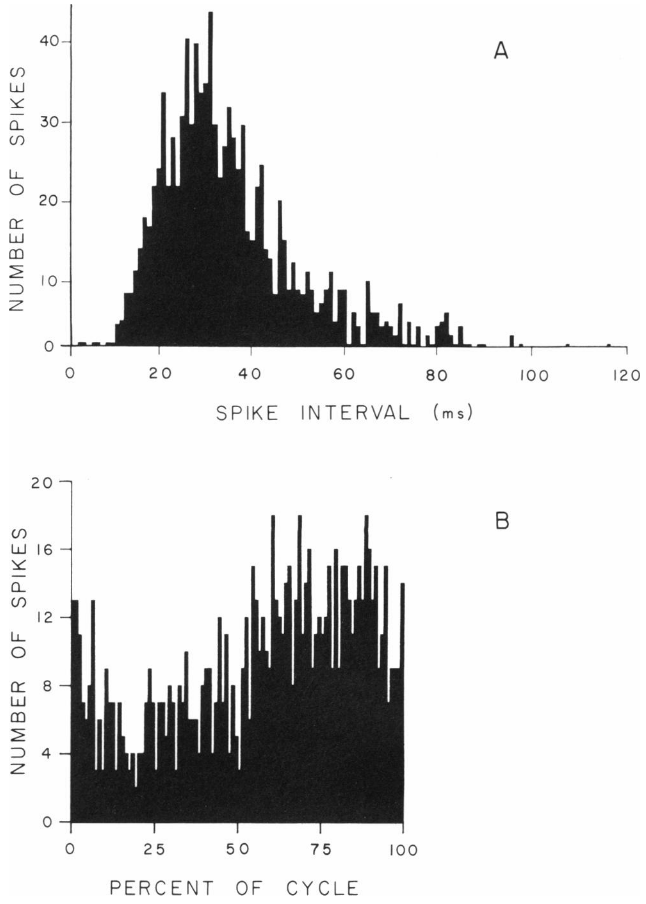

FIGURE 1 (*A*) Representative histogram of spike intervals for spontaneous activity in a saccular axon over a 30-s sampling time. (*B*) Representative histogram showing spike occurrence as a function of stimulus phase in a saccular axon responding to a sinusoidal stimulus (0.013 cm/s^2 peak acceleration, 30 Hz) over a 75-s sampling time.

Typically, in response to an applied sinusoidal seismic stimulus with peak accelerations up to 0.01 cm/s^2 or more, the instantaneous probability of spike occurrence is directly proportional to the instantaneous (phase by phase) amplitude of the stimulus sinusoid (with some phase shift), while the mean spike rate remains fixed at its spontaneous value (Fig. 1 *B*). Analysis with fast Fourier transform algorithms has shown that this instantaneous proportionality of response is robust over wide ranges of stimulus amplitudes and that the constant of proportionality is

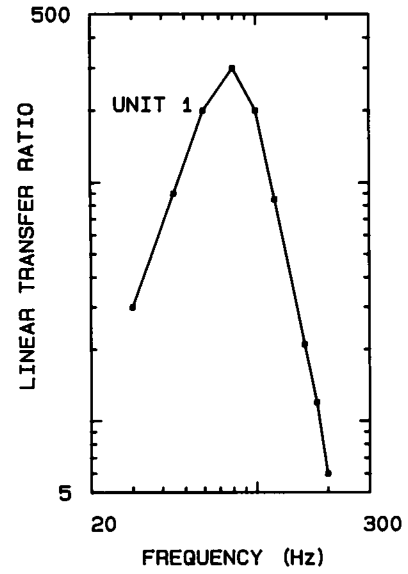

FIGURE 2 Transfer ratio (spikes/s per cm/s^2) obtained with fixed-amplitude, fixed-frequency stimuli, each applied for a 30-s sampling period. In each case, the stimulus amplitude had been adjusted to yield ~50% sinusoidal modulation of the background spike rate (~24 spikes/s). If this tuning curve were the consequence of a second-order resonance, the value of Q (~2) implied by the relative bandwidth would equal that (>50) implied by the observed extent of the steep skirt at the upper band edge. The fact that this is not so implies the presence of higher-order dynamics.

stationary over long periods of time and independent of the peak amplitude of the sinusoid (Lewis, 1986). At each stimulus frequency, one thus may obtain a linear transfer ratio (e.g., ratio of peak modulation of spike probability density to the peak amplitude of stimulus sinusoid) and a phase value (phase shift of the response sinusoid relative to the stimulus sinusoid). Figs. 2 and 3 show log-log plots of linear transfer ratio versus frequency for two saccular afferent axons. Fig. 4 shows linear plots of phase shift versus frequency for the same axons. In terms of frequency range and shape of the tuning curve, these data are representative of those from ~80% of the more than 100 bullfrog saccular axons that we have studied; all but one of the remaining axons displayed deep, sharp notches in otherwise broad pass bands, covering the same range of frequencies as that in Fig. 3 (~20–100 Hz); and that one remaining axon displayed a single, very high-Q (>50) pass band centered at 85 Hz.

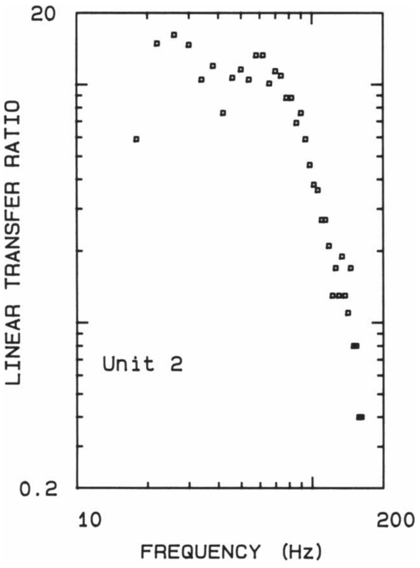

FIGURE 3 Transfer ratio (spikes/stimulus-cycle per cm/s^2) vs. frequency obtained with three frequency sweeps at 8 oct/min and fixed stimulus amplitude (peak acceleration). A transfer ratio was computed for each 4-Hz segment of the sweep.

NETWORK THEORY INTERPRETATION

Owing principally to the need for high-performance analogue filters, electrical engineers over the past several decades developed an extensive body of knowledge under the heading of network analysis and synthesis. This body of knowledge provides the beginnings of an epistemology for identification of systems or subsystems comprising several or many interacting nonequilibrium thermodynamic processes (e.g., the systems and subsystems of living organisms). Presently it is especially powerful with respect to interpretation of linear operation and especially weak with respect to interpretation of nonlinear operation. Applied to the linear transfer ratio and phase curves in Figs. 2–4, it tells us that in a direct path between the place at which signal energy enters the spectral filter or tuning structure and the point at which it emerges, there are several discrete locales or structures (which for simplicity I will call "bins") in which that energy can be stored independently and in sequence.[2] Independent storage implies that, at any instant, the amount stored in each bin is independent of that stored in the others. Sequential storage implies that signal energy stored in each bin either can be transferred directly to the next bin in the sequence or can gate a flow of

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[2] In network theory, each discrete reactive element is an energy storage bin (e.g., inertial or inductive reactances store kinetic energy, elastic or capacitive reactances store potential energy). We can carry these notions into general nonequilibrium thermodynamics as follows (see Oster et al., 1973): Select a conserved entity (e.g., a population of particles) that flows from place to place in state space; let U_0 be a point in state space defined to be the ground state, and let F_i be the free energy change per unit measure of flowing entity transferred from point U_0 to point U_i. Our limited ability to measure energy precisely inevitably would lead to the same observed value of F_i for all of the points in a finite neighborhood about U_i. That neighborhood will behave as a discrete capacitive reactance, with the ability to accumulate flowing entity and, concomitantly, to accumulate free energy. Examples of such neighborhoods include discrete chemical states and discrete physical locations. Define two neighborhoods to be adjacent if particles can flow from one to the other without passing through a third neighborhood. When particles flow with collective momentum, rather than independently, then kinetic energy can accumulate in the flow between adjacent neighborhoods; and the connections between those neighborhoods become discrete inertial reactances.

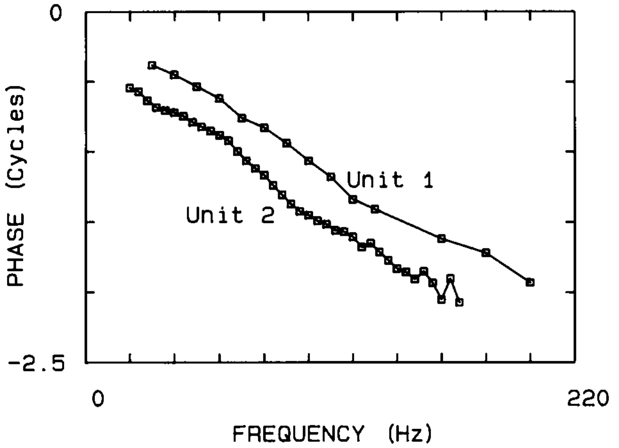

FIGURE 4 Phase shift vs. frequency, obtained over 10-Hz and 4-Hz segments, respectively, of logarithmic frequency sweeps for the axons of Figs. 2 and 3. The points at 160, 180, and 200 Hz for Unit 1 were taken with fixed-frequency samples.

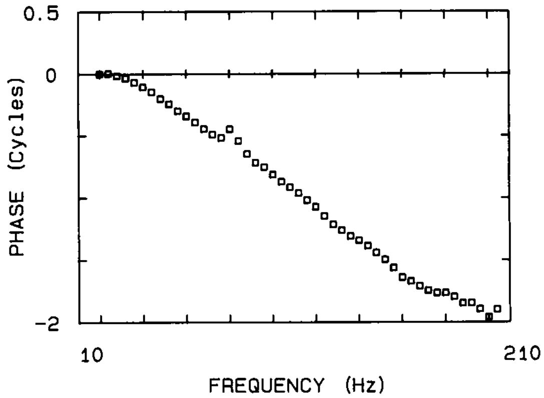

FIGURE 5 Phase shift vs. frequency obtained over 4-Hz segments of a logarithmic frequency sweep for a saccular axon with a pass band extending approximately from 40 to 150 Hz, with a sharp notch at ~80 Hz (note phase jump). At the low-frequency end, note the apparent approach to a nearly horizontal asymptote, which would imply the presence of very small acoustic and axonal time delays in the system.

energy into that bin from a non-signal source. Furthermore, the theory tells us that some of the energy-storage modes must be complementary to the others.[3]

We can estimate a lower bound to the number of independent, sequential energy storage bins by dividing the range of the observed phase shift by $1/4$ cycle (e.g., see Pinter, 1966; Chua et al., 1987). Thus the phase curves in Fig. 4 imply lower bounds of at least six bins. If the skirts at the high- and low-frequency edges of the pass band extend indefinitely without inflection (of which one cannot be certain), then a lower bound to the number of bins can be estimated from the apparent asymptotic slopes of those skirts in the log-log plots of linear transfer ratio vs.. frequency (see Levinson and Harmon, 1961; Pinter, 1966). In that case, the lower bound would be the magnitude of the slope of the low-frequency skirt (rounded up to the nearest integer value) plus the magnitude of the slope of the high-frequency skirt (also rounded up to the nearest integer). The data presented in Figs. 2 and 3 imply lower bounds of 10 and 11, respectively. The presence of complementary energy storage modes is implied by the sharpness of the peak in Fig. 2 and the sharpness of the corners of the curve in Fig. 3. Filters constructed from energy storage elements of one type only (e.g., entirely from point masses or entirely from elastic elements) inevitably exhibit linear-transfer ratio curves with conspicuously rounded peaks and corners (Guillemin, 1957; Jones and Hale, 1982).

The presence of nearly linear phase vs. frequency throughout the pass band suggests a traveling-wave process (the quintessential time-delay mechanism),[4] which in keeping with the tradition of Rayleigh and his contemporaries is conventionally modeled as having an infinite number of energy-storage bins, occurring in complementary pairs. However, analogue filter designers know that for a finite frequency range, these ideal filter properties can be approximated very well with finite numbers of elements (Guillemin, 1957). Indeed, the systematic deviations from linear phase that one consistently finds in the saccular data (e.g., view Figs. 4 and 5 on edge) are just what one would expect from such finite-element approximations. Taken over the entire pass band, the mean slope of saccular phase vs. frequency data consistently falls between 0.01 and 0.02 cycle/Hz, which would correspond to a time delay ranging from 10 to 20 ms.

An important question that arises is how much of that phase vs. frequency slope can we attribute to time delays already known to be present in the system: the extra-aural acoustic delay and the spike propagation delay from the inner-ear sensor to the electrode recording site. Among bullfrog auditory axons, the smallest phase slopes are found in those from the basilar papilla, and range from 0.001 to 0.002 cycle/Hz, implying that acoustic and axonal time delays in the signal paths must be <2 ms. In amphibian papillar axons, mean phase slopes range from 0.002 to 0.010 cycle/Hz. The acoustic transmission distances are essentially the same for all amphibian papillar

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[3] Two reactive processes are complementary if all of the energy from one can, in principle, be transferred directly to the other. Capacitive reactances are complementary to inertial reactances but not to each other, and vice versa. Coupled to an active process, or to a passive two-port device known as a gyrator, a capacitive or inertial reactance can become complementary to its own kind.

[4] A true, linear time delay operator is a functional that maps the continuous function $f(t)$ into the continuous function $f(t - T)$, where T is a positive, real constant (independent of the amplitude of $f(t)$). Since any physical process producing a true linear time delay must store an entire segment of the function $f(t)$ (i.e., an infinite number of values), the order of such a process must be infinite (i.e., it must have an infinite number of energy storage bins). Thus, for example, the conventional "synaptic delay" does not qualify as a true linear time delay.

axons, as are the spike propagation distances. Furthermore, the variation in mean slope is not correlated with axon diameter. Therefore, it must be attributed to mechanisms in the tuning structure itself. This conclusion is supported by two observations. First, the amphibian papillar phase slope is strongly correlated with tuning properties, consistently being higher in axons whose tuning pass bands are centered at lower frequencies (Lewis, 1984*a*; Hillery and Narins, 1984). Second, occasionally we find an amphibian papillar axon with a low-frequency pass band, but in which the steep phase slope within the pass band gives way to a sustained, shallow-sloped asymptote at higher frequencies (Lewis, 1984*a*). The asymptotic slopes are in the neighborhood of 0.001 cycle/Hz, implying that the irreducible time delays (including the axonal and extra-aural acoustic delays) are of the order of 1 ms or less, comparable to those implied by the data for basilar-papilla axons. The saccular axons from which we record appear to be essentially identical to those of the amphibian and basilar papillae, exhibiting the same range of diameters, typically 2–4 μm, and same thickness of myelin; and our saccular axon recording sites normally are closer to the inner-ear sensor (within 3 mm) than are our papillar recording sites. Therefore, we expect the phase contributions from spike propagation times in saccular axons to be comparable to those for papillar axons. Furthermore, there is no reason to expect significantly greater extra-aural acoustic delay for seismic stimuli (the accelerometer from which we derive our reference phase measures directly the vibratory motion of the frog's head) than we find for auditory stimuli (where the stimulus monitor measures the sound pressure within ~1 cm of the frog's tympanum). Therefore, we conclude that the combined extra-aural acoustic delay and spike propagation delay for the sacculus is also in the neighborhood of 1 ms. This estimate is corroborated by occasional saccular axons in which the phase slope approaches a very low apparently asymptotic value at stimulus frequencies below 30 Hz (Fig. 5). In such cases, the asymptotic phase slope always appears to be <0.001 cycle/Hz, corresponding to an irreducible time delay of <1 ms. Even if this estimate were off by several hundred percent, most of the apparent time delay implied by the saccular phase data still would have to reside in the dynamics of the sensor itself, rather than in spike propagation and extra-aural acoustic delays.

Applied to the linear responses of the electrical resonances in isolated hair cells (as observed by Lewis and Hudspeth), network theory tells us that each resonance comprises two (complementary) energy storage bins that are controllable and observable with respect to total membrane current and membrane voltage. This follows from the fact that the transient response of the electrical resonance consistently exhibits a single pair of (conjugate, complex) natural frequencies, corresponding to a single exponentially decaying sinusoid (Lewis, 1985). Thus, if any additional energy storage bins are present, they currently are invisible to investigators viewing the overall neuro-electric properties of the hair cell.

If we hypothesize that the filter properties observed in individual saccular axons somehow are derived from the electrical resonances observed in individual hair cells, then we should treat those resonances as they are observed, i.e., as second-order (two-energy-bin) systems with resonant frequencies in the 90–250 Hz range. The properties of second-order resonances (such as the classic underdamped harmonic oscillator) serving as spectral filters are well known (see Lewis, 1984*b* for a detailed quantitative review, Lewis, 1987, for a general qualitative review, and Fettiplace, 1987, for an example appropriately plotted [on log-log coordinates] for a single hair cell resonance). It is absolutely clear from those properties that the transfer relationships shown in Figs. 2–5 cannot be the consequences of such a resonance acting alone. Since individual saccular axons typically innervate from two to thirty hair cells, one must ask whether the transfer-ratio and phase curves of Figs. 2–5 might be derived from convergence (summation) of responses from several second-order resonance filters, each with a different resonant frequency and each resonating independently in response to the same stimulus. One flaw in this hypothesis is the fact that the resonance frequencies observed in isolated saccular hair cells do not span the frequency pass bands observed in the axons from the intact sacculus; instead, they consistently fall near the tops of those bands or beyond them. Even if this were not the case, the answer to the question still would be no. Independent resonance implies that the resonators do not exchange energy with each other, in which case signal energy could not be passed in sequence from one of them to another; and they would not provide the relatively large numbers of sequential energy storage bins implied by the data to be in the signal path. If we combined several independent resonances in that way, for example, the resulting filter would have a spectral zero falling between each pair of adjacent spectral poles, and therefore would yield a net phase range of only one-half cycle (i.e., each resonance would contribute one-half cycle of phase shift, but those contributions would not be cumulative). Therefore, the phase data from bullfrog saccular axons definitively exclude the possibility that saccular tuning is derived from summation of the outputs from many independent, second-order resonance filters.

If the filter properties of bullfrog saccular axons are derived in some way from the electrical resonances of the hair cells, then to yield the transfer-ratio and phase curves of Figs. 2–5, those resonances must be connected to each other in such a manner that energy can be transferred from one resonance to another. Once such energy-transferring connections are in place, a system of many second-order resonances becomes a high-order system, potentially capable of the observed saccular filter properties. In fact, if those resonances were driven at frequencies below their resonant frequencies, as the data imply, and if the mechanical elements coupling them behaved predominantly as masses (inertial reactances), then we could have multi-element networks analogous to the mammalian cochlea as it is modeled by Lighthill (1981) and others. The role of Lighthill's "critical-layer resonance" in these lower-vertebrate analogues would be played by the hair-cell electrical resonance rather than the basilar-membrane resonance.

EVIDENCE FOR ENERGY-TRANSFERRING CONNECTIONS

Several investigators have provided compelling evidence that energy-transferring connections do exist in the hair cells of lower vertebrates, and that the path for energy transfer includes the hair bundles of neighboring hair cells and the otoconial membrane that links those hair bundles to one another (recall that this linkage was removed in the experiments in which the resonances were observed in the bullfrog sacculus). It has been clear for a long time that signal energy can be transferred from the micromechanical elements to the neuroelectric elements of the hair cell. During the past decade, Hudspeth and his colleagues have shown that this transfer is accomplished by strain-sensitive, relatively nonselective ion channels in the cell membrane of the hair bundles (Corey and Hudspeth, 1983). For the required transfer of energy from hair cell to hair cell, however, there must be coupling in the other direction as well. We now know that this occurs. In hair cells of the turtle basilar papilla, the stereocilia bundle moves in direct response to excitation of the electrical resonance (Crawford and Fettiplace, 1985). The strongest evidence for the same phenomenon in the frog ear currently is the observation of spontaneous acoustic emissions from that organ (Palmer and Wilson, 1982). This observation implies that acoustic energy is derived ultimately from metabolic sources, is subsequently transferred into the micromechanical elements of the ear, and then is passed to the periphery. Recently, Howard and Hudspeth (1987) reported evidence that this energy is transferred through the hair bundle, as in the turtle. Thus, it appears that hair-cell transduction, in general, goes in both directions: with signal energy being passed back and forth between micromechanical elements and neuroelectric elements. Since this evidently is accomplished by gated channels and contractile elements, the way is open for the signal energy, in its travels, to be augmented from nonsignal sources (metabolic energy reservoirs). The possibility and the advantages of bidirectional transduction and this sort of energy augmentation were pointed out long ago by Gold (1948). More recently, they have been discussed by Bialek and Schweitzer (1980) and Weiss (1982). Evidence for bidirectional transduction in the mammalian cochlea now also is abundant (Kemp, 1978; Kim et al., 1980; Brownell et al., 1985).

CONCLUSIONS

Network theory has told us that each spectral filter in the intact bullfrog sacculus comprises a relatively large number of energy-storage elements, operating in complementary modes and connected in cascade fashion, so that signal energy can be transferred from one to another in sequence as it passes through the filter. The available biophysical and morphological evidence now suggests that this arrangement may be accomplished by a remarkable "neural network," one in which cells are coupled not synaptically, but through extracellular micromechanical elements (micromasses, micro-elastic elements, micro-viscous elements). The salient "neuronal network" within each cell evidently comprises populations of strain-sensitive ion channels, voltage-sensitive calcium channels, calcium-sensitive potassium channels, and contractile elements. The structural basis of the contractile element presently is unknown and is the focus of research in many auditory biophysics laboratories.

If the coupling between channel population dynamics and micromechanical dynamics indeed operates in both directions, then the fact that the channel populations resonate when the coupling is broken does not imply that they will do so when the coupling is intact. It tells us merely that they behave as a pair of complementary energy storage elements. In fact, what evolution evidently has sculpted with these elements is a high-order spectral filter with properties far superior to those of a simple resonance (Lewis, 1987).

There is a message here for those who would attempt to understand the operation of a complex mechanism in terms of its elements. If those elements involve bidirectional processes, such that every action of each process evokes a reaction that depends on the physical context of the process and directly affects the process itself (e.g., as acceleration of a point mass may evoke elastic or viscous forces that alter the rate of acceleration; or as accumulation of a chemical product affects the net rate at which product is formed), then every aspect of the dynamic behavior of the system as a whole is determined by all of the elements of the whole system. In other words, such systems are inherently irreducible entities in the sense that no measured property of the intact system is entirely attributable to any of its individual elements (see Lewis, 1970, and the "epilogue" section in Lewis, 1983).

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