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Overview: Cochlear Neurobiology

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1. Introduction

All environmental and biologically significant sounds change from frequency to frequency and from instant to instant. The hearing organ must be capable of analyzing time-varying frequency components and representing them in a spatiotemporal array of neural discharges in the fibers of the auditory nerve. When a signal is analyzed, its frequency spectrum and temporal characteristics are reciprocally related. The simplest signal in terms of its spectrum is an ongoing sine wave, corresponding to a pure tone in acoustics, and has only one spectral component, the frequency of the sound. This simple spectral line is achieved by having a signal that, at least in theory, lasts forever. In contrast, the simplest temporal signal, an impulse, or a click in acoustics, is infinitesimally short in duration but, in theory, contains all frequencies. Of course, natural sounds are in a continuum between these extremes; they have finite duration and finite spectral breadth. However, the reciprocal relation holds. The shorter the signal, the broader its frequency content and, conversely, the longer the signal, the narrower the band of frequencies that represents it. A device constructed to analyze signals is constrained in the same way. In order to ensure good frequency resolution of the signal, one must process in narrow-frequency bands and observe for long durations. In contrast, to resolve short temporal features in the signal, the analysis must be relatively broad band. These are conflicting requirements for which advanced ears must find a solution. Let us inquire about the severity of the requirements.

Under laboratory conditions, young adult humans can discriminate two sounds whose frequencies are only about 0.2% apart. To put this in an easily understood context, consider that two adjacent keys on the piano represent a tempered semitone and are approximately 6% apart in frequency, as the cartoon of Figure 1.1 depicts. The frequency resolution of the young ear then is 30 times greater than what is needed to discriminate a "musical unit." This indicates that the neural representations, prepared by the cochlea, of two sounds 0.2% apart are sufficiently different to enable
affords analysis of higher frequencies than does electrical resonance. In the
dinosaur lizard the best frequencies range between 900 and 4000 Hz (Weiss
et al. 1978). The cochlea in all amniotes is remarkable for its spatial
organization. Receptor cell and ciliary dimensions change along the length
of the papilla (Lim 1980; also Slepecky, Chapter 2), and such gradients are
thought to underlie physical alterations that control resonant frequency.

In mammals the hearing range is generally extended to higher frequencies
and the process of spectral analysis is greatly elaborated. The means of
reconciling the demands upon the mammalian cochlea appears to be a
profoundly nonlinear local feedback process. The feedback is most commonly
assumed to be manifested in a cycle-by-cycle boost in the vibratory
amplitude within the cochlea and thereby the amplification of the signal
(Gold 1948; Davis 1983; see Patuzzi, Chapter 4; de Boer, Chapter 5; Holley,
Chapter 7). The amplification preferentially operates at low signal levels
and, because of the saturating nonlinear nature of the process, becomes
inconsequential at about 40 dB (100-fold increase in signal amplitude)
above threshold (Zwicker 1979). The process confers high sensitivity and
permits operation over a wide dynamic range. It is advantageous in
effectively increasing signal-to-noise characteristics at the hair cell input
(Bialek 1987) and is essential in producing the necessary degree and
configuration of cochlear spectral filtering along with optimizing time-
analysis capabilities. Finally, one consequence of the nature of the cochlear
amplification process is the nonlinear processing of auditory signals over
much of their intensity range.

This book considers cochlear function in mammalian ears only. It does
not consider specializations such as those developed to subserve infra- or
ultrasonic hearing. Readers interested in those topics may wish to consult
Fay and Popper (1994) and Popper and Fay (1995). The emphasis of
chapters dealing with mechanisms of sound analysis by the ear tends to be
on spectral analysis, since this is a predominantly cochlear process. In
contrast, peripheral representation of temporal features cannot, by itself,
account for the time analysis capabilities of the mammalian auditory
system. Temporal processing apparently relies on the central auditory
nervous system's simultaneous analysis of signals presented in multiple
narrow bands by the two cochleae.

Our understanding of cochlear frequency analysis progressed through
three main epochs. The first was dominated by Helmholtz's suggestions that
lightly damped, spatially ordered, resonant elements in the cochlea per-
formed the spectral analysis (this early period was reviewed by Wever 1949;
also see Patuzzi, Chapter 4). The second epoch, lasting from the late 1940s
to the early 1970s, was dominated by von Békésy's description of the
traveling wave (von Békésy 1960) and its incorporation into a theoretical
schema of cochlear frequency analysis (Zwislocki 1953). The third period is
now (an overview of its evolution is given in Dallos 1988; also see Patuzzi,
Chapter 4; de Boer, Chapter 5) and it is an active period indeed during
which a new "party line" has emerged on the basis of a wide array of
experiments and theoretical considerations. According to this, von Békésy's
traveling wave is boosted by a local electromechanical amplification process
(Patuzzi, Chapter 4; de Boer, Chapter 5) in which outer hair cells function
as both sensors and feedback elements (Kros, Chapter 6; Holley, Chapter
7). The local amplification process is under the control of the central
nervous system (Guinan, Chapter 8), and information is conveyed to the
central nervous system by the mechano-electro-chemical operation of inner
hair cells and their afferent synapses (Kros, Chapter 6; Sewell, Chapter 9).

The entire system is maintained by an elaborate homeostatic apparatus
(Slepecky, Chapter 2; Wangemann and Schacht, Chapter 3). The resulting
performance, noted above, is a remarkably achievement of this complex
sensory system. This Overview visits the salient features of the cochlea's
structure and operation. The purpose is to anticipate the details provided
by the contributors of this volume, to offer a coherent overview, and to
mention some topics that did not conveniently fit into other chapters.1

2. Anatomy and Homeostasis

The key elements for the understanding of the neurobiology of the cochlea
are contained within the cochlear partition. This triangular-shaped duct
(shown in Figs. 2.1 and 2.2, Slepecky, Chapter 2) is the cochlear portion of

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1 Portions of this material were included in the author's paper, The active cochlea
the cortex to distinguish between them. Then, engaging a relatively simple model of frequency discrimination (Zwicker 1970), one can estimate that filters used to perform such analysis would have to possess bandwidths of approximately 1.2% of the center frequency of the filter. Theory tells us that a filter of this sharpness, when excited by a brief transient, would persist in its ringing oscillatory response for a significant time period, corresponding to a time-constant equivalent to 26 cycles. Such long persistence would preclude, for all practical purposes, useful analysis of brief sounds. Yet, timing differences of 6–10 μs between signals presented to the two ears can be detected by human observers. Furthermore, at threshold, the hearing organ responds to sound with internal movements that are subatomic in dimensions. From recent measurements one can estimate these displacements to be $10^{-10}$–$10^{-11}$ m (Sellick, Patuzzi and Johnstone 1982). To gauge such motions, consider the comparison presented in Figure 1.2. The proximal input structure of the ear's sensory receptor cells is their stereocilia (Slepecky, Chapter 2). If one scales the dimensions of a single stereocilium to that of the world's tallest building, Chicago's Sears Tower, then the motion of the tip of the cilium at auditory threshold corresponds to an approximately 5-cm displacement of the top of the tower.

Broad-band root mean square (RMS) thermal noise motion of the sensory cell's input structure, its ciliary bundle, is estimated to be at least $10^{-9}$ m (Bialek 1987). After prefitering by the cochlea's mechanical frequency analysis, the thermal noise reaching the cilia may be of the order of $10^{-10}$ m. We see that the cells detect signals that may be smaller than or of the same magnitude as the background noise.

The ear is also capable of processing sounds over a remarkably wide intensity range, encompassing at least a million-fold change in energy. To appreciate this range, in Figure 1.3 we represent a similar range of potential energies by contrasting the weight of a mouse with that of five elephants. Another requirement is the ability to respond over a wide frequency range. An ordinary mammal can process sounds that range over 10 octaves. Nonmammalian vertebrates generally respond to the much narrower bands of frequencies that encompass the bottom of the mammalian range. In fact, the extension of the frequency range may have been the primary pressure for developing mammalian specializations.

Among vertebrates the biological processes that subserve frequency analysis vary a great deal. In other words, there is no such thing as the cochlear mechanism. One well-understood and apparently widely utilized arrangement among lower vertebrates is spectral analysis by the sensory receptor cells themselves in a process of electrical resonance. An excellent review of this scheme is available (Fettiplace 1987). Electrical resonance relies on the interplay between inward ($Ca^{2+}$) and outward ($K^+$) membrane currents. It is a specialization that utilizes common cellular components and is ideally suited for regulation by changes in membrane potential. Setting of the cell's center frequency is determined by the activation rate of the $K^+$ current and by the number of $K^+$ channels. In the turtle cochlea electrical resonance frequencies are seen between 20 and 600 Hz, and the cells line up along a spatial axis of frequency in the auditory papilla (Crawford and Fettiplace 1980). Electrical resonance also determines frequency analysis in amphibian papilla (Pitchford and Ashmore 1978) and saccule (Lewis and Hudspeth 1983) and probably in some avian hair cells (Fuchs and Mann 1986). Mechanical resonance of the ciliary bundle itself may be the principal means of frequency analysis in some lizard cochleae (Weiss et al. 1978; Holton and Hudspeth 1983; Nielsen and Turner 1983). This mechanism
the membranous labyrinth that contains the sensory epithelia of the auditory and vestibular systems. The elaborate duct system roughly conforms to the shape of the bony labyrinth, a system of cavities in the temporal bone. The entire cavity is fluid-filled; between the bony and membranous labyrinths is a filtrate of cerebrospinal fluid or blood, the perilymph, while within the contiguous duct system the fluid is endolymph, about which more is said later (Slepecky, Chapter 2; Wangemann and Schacht, Chapter 3). The boundaries of the cochlear duct (or scala media) are the basilar membrane, which separates it from one of the perilymph-filled channels (the scala tympani); Reissner's membrane, which separates it from the other perilymphatic channel (the scala vestibuli); and the lateral wall of the cochlea. The auditory sensory epithelium, the spiral organ of Corti, is a cellular matrix situated on the scala media side of the basilar membrane. The endolymphatic space is separated from the surrounding structures by a luminal layer of cells sealed by tight junctions (Jahneke 1975). This arrangement affords the biochemical isolation of the endolymphatic space from its surround. Lining the lateral wall is an important structure, the stria vascularis. The stria is a three-cell-layer epithelium incorporating a vascular bed. Both it and the organ of Corti may be thought of as typical ion-transporting epithelia (Wangemann and Schacht, Chapter 3).

Reissner's membrane is only two cell layers thick. Its only function is to separate endolymph from perilymph. In other words, it is "acoustically transparent" and does not influence the cochlear's mechanical functions. From the vantage point of cochlear fluid mechanics, the scala vestibuli and the scala media may be thought of as a single compartment. In contrast, the basilar membrane is one of the salient hydromechanical elements in the workings of the cochlea. Its mechanical properties control the passive, von Békésy-type traveling wave that it sustains upon sound stimulation (Patuzzi, Chapter 4; de Boer, Chapter 5). If the basilar membrane were flattened and straightened out, it would be wedge-shaped with its width gradually increasing from the cochlea's "input" end (its base) toward the far end (its apex). The change in width, generally severalfold, results in a highly significant reduction of the membrane's stiffness of more than 100-fold from base to apex.

The primary structure of the organ of Corti (Figs. 2.2 and 2.4, in Slepecky, Chapter 2) and its principal mechanical properties are conferred by the arrangement and structure of two rows of pillar cells and three rows of Deiters' cells. These cells have their nuclei located inferiorly, near the basilar membrane, and they send actin-packed phalangeal processes toward the roof of the organ. At the roof, the so-called reticular lamina, these phalangeal processes flatten into an intermeshed network that is closed to the endolymphatic space above by tight junctions between adjacent cells. The apices of sensory cells are incorporated into the reticular lamina, again sealed by tight junctions (Smith 1978). The cell bodies of the Deiters' cells also serve to anchor the bottoms of one group of sensory cells, the outer hair cells (OHCs). The other sensory cell group, the inner hair cells (IHCs), are completely surrounded by support cells. The physiological function of the several supporting cell types of the organ of Corti, such as Hensen's, Deiters', border, and inner phalangeal cells, is obscure. It is possible, however, that some of these are involved in K+ and neurotransmitter buffering (Johnstone et al. 1989; Oesterle and Dallos 1989; 1990).

The remaining structure of great importance lying outside the organ of Corti, is the tectorial membrane. This structure is a collagenous acellular gel that floats above the reticular lamina. Its principal anchoring points are its intimate connection to the interdental cells of the spiral limbus and the firm attachment to the tips of the OHC cilia. A connection with the peripheral edge of the organ of Corti in the region of Hensen's cells via a thin marginal net is possible. The space between the tectorial membrane and the reticular lamina is open to endolymph. Consequently, the apical faces of the hair cells and the entire reticular lamina are bathed in endolymph. Relative motion between the tectorial membrane and the reticular lamina is the primary mechanical input to the hair cells of the organ of Corti (Patuzzi, Chapter 4; Kros, Chapter 6).

Afferent and efferent nerve fibers enter the cochlea from its center core, the modiolus, through a spiraling, hollow-cored, bony shelf, the osseous spiral lamina. This lamina is also the central anchor to the basilar membrane. The cell bodies of primary afferent neurons are collected at the junction of the osseous spiral lamina and the modiolus in Rosenthal's canal and form the spiral ganglion. The peripheral extensions of the bipolar spiral ganglion neurons enter the organ of Corti through small openings in the osseous spiral lamina, the habenulae perforata, and subsequently approach the IHCs and OHCs. Efferent neurons, after entering the modiolus, diverge from the afferent nerve trunk to travel with the vestibular portion of the 8th nerve to their cell bodies in the superior olivary complex (Slepecky, Chapter 2; Guinan, Chapter 8).

The cochlear endolymphatic space has two peculiarities. First, the medium filling it is similar to intracellular fluid in its major ion contents (reviewed by Bosher and Warren 1968; Anniko and Wróblewski 1986; Slepecky, Chapter 2; Wangemann and Schacht, Chapter 3). Second, within the cochlear duct, endolymph is polarized to a high positive potential, approximately +80 mV, with respect to indifferent tissue (von Békésy 1960). Formation of endolymph is the function of the cells of the stria vascularis in the cochlea and the dark cell epithelium around vestibular sensory structures. As the DC trace obtained by penetrating through the stria and dye-marked cell indicates (Fig. 1-4A,B), the resting polarization of marginal cells is about 10 mV more positive than that of endolymph and about 80–90 mV positive with respect to indifferent tissue (Offner, Dallos and Cheatham 1987).

An outstanding and detailed recent review of hair cell function is
available (Hudspeth 1989). Hair cells are the common receptors of the auditory and vestibular sensory organs. They are epithelial cells of somewhat variable morphology. IHCs are flask-shaped with a flat apical surface from which the stereocilia bundle, or sensory hairs, emerge. OHCs are cylindrical, with a ciliary bundle crowning their flattened apex. Ciliary bundles are strictly organized, both on a given cell and from cell to cell. Each bundle contains cilia in an array that has a distinct organization and an axis of symmetry. This axis is largely radial in the coiled cochlea. IHC cilia form a shallow "\[\]" and OHC cilia present a "\[\]" or "\[\]". The foot of the configuration invariably points toward the periphery of the cochlear spiral. Within a bundle, the cilia form three parallel rows of nested "\[\]"s or "\[\]"s that are graded in height. The most peripheral row is invariably the tallest; the most central row is the shortest. There is a general gradation of ciliary height along the length of the cochlea, with the shortest dimensions found in the base and the longest in the apex. For example, the tallest row of cilia on OHCs changes from <1 μm in the base to ~6 μm in the apex, with a corresponding variation of ~2 to ~5 μm for IHCs (Lim 1980). Paralleling ciliary bundle change is a significant variation in OHC length, amounting to a fourfold increase toward the apex, reaching ~100 μm. OHC diameter (8–10 μm) and IHC soma shape are largely invariant. In addition to a longitudinal gradation of OHC height, OHC length also changes radially. The outermost row is the tallest and the innermost the shortest. This gradation is highly pronounced in the apex and gives a strong tilt to the reticular lamina with respect to the basilar membrane. In the base, the gradation is very modest and results in an almost parallel appearance of reticular lamina and basilar membrane. It is then clear that OHC height alone is an insufficient indicator of its longitudinal position. Cilia are evaginations of the cell sheathed with the plasma membrane. When displaced at the tallest cilia, the entire bundle bends as a unit. Adjacent cilia in a bundle are connected to one another with filamentous material (Slepecky, Chapter 2). Whereas the apical aspect of the hair cell is dominated by the cilia, their basal, infranuclear end has the hallmarks of presynaptic regions (IHCs) and both pre- and postsynaptic regions (OHCs) (Slepecky, Chapter 2; Sewell, Chapter 9).

The IHCs are completely surrounded by supporting cells, allowing very narrow intercellular spaces. The OHCs are unique in that virtually their entire longitudinal extent is free of cellular neighbors and is bathed in perilymph that fills the spaces within the organ of Corti. The OHCs are only supported at their apices, where the cuticular plate is anchored to the reticular lamina by tight junctions, and at their bases, where the cell's bottom is cradled in the hollow of the Deiter's cells. The tips of the tallest row of cilia on OHCs are firmly embedded in the bottom layer of the tectorial membrane, whereas all their shorter cilia are free of attachment. In the adult mammal, it appears that IHC cilia are free-standing in the
surrounding endolymph or at most are loosely coupled to the tectorial membrane (Lindemann et al. 1971; Lim 1980).

What may well be one of the most profound contemporary observations about the mammalian auditory system is the finding that the vast majority of afferent neurons innervate IHCs. Heinrich Spoendlin's 1969 discovery of the disparity in innervation patterns between IHCs and OHCs clearly paved the way to our present concept of cochlear function in which IHCs take the role of the sensory receptor in the hearing organ and in which the search is ongoing for assigning a primary function to OHCs (Dallos 1985a; Kim 1986). The peripheral processes of IHC afferents arise from approximately 30,000 (in the human) type I spiral ganglion cells that comprise 90%-95% of the afferent pool. Afferents destined for OHCs arise from type II pseudomonopolar ganglion cells. They are unmyelinated thin axons approximately 0.5 µm in diameter. As they enter the organ of Corti, they turn basally to project to a group of OHCs located approximately 0.6 mm away from the fiber's entrance. These afferents branch profusely and may innervate about 10 OHCs in the cochlear base and as many as 50 in the apex. In the adult ear, no fiber innervates both IHCs and OHCs. Central axons of both type I and II ganglion cells synapse in the ipsilateral cochlear nucleus.

It is not only the afferent innervation pattern that differs between the two receptor cell types; their efferent connections differ as well. The final descending path emerges in the superior olivary complex. Unmyelinated fibers originating in small cells around the lateral superior olivary (LSO) nucleus descend, mostly ipsilaterally, toward IHCs. They terminate on the afferent dendrites coming from IHCs and rarely on the cell bodies themselves. Myelinated fibers stemming from larger cell bodies around the medial superior olivary (MSO) nucleus travel mostly contralaterally toward OHCs. These fibers terminate in large granulated endings on OHC cell bodies and dominate their neural surround. An overview of efferent innervation is found in Warr and Guinan (1979), Warr (1992), Slepecky, Chapter 2, and Guinan, Chapter 8. The dominant neurotransmitter substance of efferents is acetylcholine; however, enkephalins, dynorphins and γ-aminobutyric acid (GABA) are also present (reviewed in Fox and Altschuler 1986; Klinke 1986; Eybalin 1993; Sewell, Chapter 9).

A simple summary of the neural connections between the organ of Corti and the central nervous system is that IHCs are almost exclusively innervated by afferents, whereas the dominant innervation of OHCs is efferent.

3. Mechanics and Micromechanics

3.1 Input to the Cochlea

All jawed vertebrates have evolved means to collect environmental sounds and funnel them to their cochleae. The external and middle ears jointly fulfill this role and their characteristics largely determine the frequency response properties (audiogram) of a given species (Dallos 1973a; Rosowski 1991, 1994). This implies that the cochlea performs as a detector of acoustic power at threshold and that the relationship between the sound power delivered to it by the middle ear and the sound power collected by the external ear is the principal determinant of the frequency profile of audibility (Khanna and Tonndorf 1969).

The resonance and diffraction effects of the head, earlobe and ear canal confer frequency-dependent pressure transformations between the external diffuse sound field and sound available at the eardrum (tympanic membrane). These linear sound transformations are dependent on the position of the head vis-à-vis the sound source (Shaw 1974) and generally produce a midfrequency boost. Sound-induced vibrations of the tympanic membrane are transmitted into the oval window of the fluid-filled cochlea by the middle ear ossicles, numbering from one to three, depending on species. The eardrum-to-oval window transformation accounts for a significant boost in sound pressure, especially at midfrequencies (between 1000 and 3000 Hz). The amplification derives from the lever action of the ossicular chain in some species, and in all species from the acoustic transformer action due to the different effective surface areas of the eardrum and the "footplate" of the innermost bone of the chain, as well as from possible force amplification by the eardrum itself. Not all power available at the eardrum enters the middle ear and not all power entering it is delivered to the cochlea. This is the consequence of shunting power away by parallel acoustic elements and losses occurring in the middle ear (Rosowski 1991). Since the middle ear is linear, sound transmission through it is quantified by a transfer function (Guinan and Peake 1967), which has been measured for several species.

The critical variable, average power into the cochlea ($W_c$), may be computed as $W_c = |U_r|^2 Re[Z_c]/2$, where $U_r$ is the footplate volume velocity and $Z_c$ is the input impedance of the cochlea. The pressure delivered to the cochlear fluid at the oval window ($P_o$) is obtained as $P_o = U_r Z_c$. We note that in the midfrequency range, where the input impedance of the cochlea is resistive (Zwislocki 1953), both $W_c$ and $P_o$ are directly determined by the volume velocity of the footplate of the innermost ossicle in mammals, the stapes. Inasmuch as the cochlea is driven by the pressure at the oval window, the consequence is that the temporal characteristics of this drive are controlled by the derivative of stapes motion.

The contemporary view of the operation of the mammalian hearing organ is that a hydromechanical event, von Békésy's traveling wave, inherent to the physical structure of the cochlea, provides the basis of frequency analysis. This rather crude analysis is augmented by a local cochlear amplification process that relies on OHCs as the feedback elements. The amplification operates effectively at low signal levels and is gradually disabled as sound input increases. When OHCs are prevented
from fulfilling their feedback role, as in the case of loud sound input or injuries to the cochlea, the operation reverts to the analysis by the Békésy wave alone. Our task is to understand the physical genesis of this "passive" Békésy wave, to be followed by a discussion of the "active" feedback process that is thought to be mediated by OHCs (Patuzzi, Chapter 4; de Boer, Chapter 5; Kros, Chapter 6; Holley, Chapter 7).

3.2 Passive Mechanics

The following discussion is aided by the schematic diagram of Figure 1.5. Sound-induced, piston-like motion of the stapes in the oval window produces pressure changes in the immediate vicinity of the footplate. The resulting acoustic events can be thought of as two waves (Peterson and Bogert 1950). The first is a pressure wave in both perilymphatic channels, traveling with the very high speed of sound waves in a liquid within rigid confines. This wave produces no forces upon the cochlear partition because it is the same in both scalae. The other wave develops as a pressure gradient across the partition. This gradient is made possible by the effective "grounding" of the scala tympani at the base by the flexible round window membrane that is placed at resting, atmospheric, pressure by its fronting on the air-filled middle ear space. The pressure difference exerts a force on the cochlear partition, setting it in motion. At low frequencies, the partition displacement is controlled by its stiffness, according to Hooke's law. Consequently, the motion is in phase with the pressure difference, which is in phase with fluid velocity, which, in turn, is determined by stapes velocity.

One obvious result of this is that with a low-frequency tonal signal, the basilar membrane displacement leads in phase the stapes displacement, and thus the sound, by $\sim 90^\circ$. At the far apical end of the cochlea, the endolymphatic space ends blindly and there is communication between the two perilymphatic scalae through an opening called the helicotrema. This opening provides an acoustic shunt across the cochlear partition for infrasonic frequencies. Therefore, extremely slow variations in sound pressure are entirely ineffective in displacing the cochlear partition.

To understand wave propagation in the cochlea, it is useful to consider a simple situation that is somewhat analogous and quite illuminating. When waves propagate in an open, fluid-filled channel, their properties are somewhat akin to those observed in the cochlea. The open water surface is the analog of the basilar membrane, whereas the rigid channel walls represent the bony boundaries of the cochlear scalae. If the wavelength is long in comparison to the depth of the channel, then the propagation velocity is independent of wavelength. Conversely, when the wavelength is short in relation to the channel depth, the propagation velocity depends directly on the wavelength. In the first, so-called long-wave case, the propagation is nondispersive. This means that in a complex multifrequency signal, all components travel together and a wave packet maintains its original shape. In the latter, short-wave case, propagation is dispersive. This means that different frequencies that start together, as in a complex acoustic signal, do not travel at the same speed. How does this relate to the cochlea?

As we saw, a pressure gradient across the basilar membrane–organ of Corti structure produces a force upon it, setting it in motion and originating a wave that propagates away from the window region. The wave's speed of travel and properties are determined by the physical characteristics of the flexible boundary between the two scalae, the basilar membrane–organ of Corti complex (Lighthill 1981). Since the stiffness of the partition decreases away from the window region, the speed of travel of this gradient wave also decreases while its amplitude increases. At a given frequency, $f$, as the pressure wave's velocity decreases, its wavelength ($\lambda$) becomes shorter, since $\lambda = v/f$. As a result of this shortening is that the relation between the depth of the scalae and the wavelength is altered, which produces important consequences. The depth of penetration of pressure into the canal away from the partition is roughly the reciprocal of the wave number, or $\lambda/2\pi$. Consequently, as $\lambda$ decreases, the pressure across the scala becomes less and less uniform, with its increasing concentration near the partition. The less uniform the pressure, the more dispersive the wave. In other words, as a wave travels, it starts out as a nondispersive "long wave" in terms of the water-channel approximation and ends up as a dispersive "short wave." Moreover, the speed of propagation of acoustic energy (group velocity) decreases even more than that of the actual wavefronts (phase velocity). So, energy propagation progressively slows until the wave effectively halts, with
the energy “piling up” at a particular, “characteristic,” place (Lighthill 1991). As the energy is concentrated in a very narrow region, traveling at very low speed, any mechanical loss (damping) of the basilar membrane is sufficient to dissipate it, since this process of dissipation can take a long time. The location where this occurs depends on the frequency of the input.

Consider the local displacement of the basilar membrane at position \( x \) from the base to be \( y(x) \). The local stiffness of the membrane is \( k(x) \), while its local mass is \( m_s(x) \). The fluid that moves with the membrane contributes an effective mass \( m_f(x) \). Since the wave is concentrated more toward the basilar membrane as wavelength decreases, \( m_s(x) \rightarrow 0 \) as \( \lambda \rightarrow 0 \). Since at a given point the kinetic and potential energies associated with membrane motion are equal, we can write for the sinusoidal case (i.e., for \( y = Ae^{\pm \omega t} \)):

\[
\frac{1}{2}k(x)A^2 = \frac{1}{2}(m_s(x) + m_f(x))A^2(2\pi f)^2, \text{ or } (2\pi f)^2 = \frac{k(x)}{m_s(x) + m_f(x)}
\]

We note that as \( m_f(x) \rightarrow 0, f \) approaches the membrane’s own resonant frequency (\( f_r \)):

\[
f_r = \frac{1}{2\pi} \left( \frac{k(x)}{m_s(x)} \right)^{1/2}
\]

At this location, the membrane is purely dissipative and the wave is extinguished. Any location has a characteristic frequency, largely determined by the membrane’s local stiffness. These frequencies are arranged in a spatial map so that they progressively decrease from cochlear base to apex, just as stiffness decreases along the length. One may envision this situation by noting that any location, \( x \), has a resonant frequency that is the limiting frequency for waves propagating toward it. A wave whose frequency is the same as the resonance frequency will achieve zero wavelength at \( x \); that is, it becomes extinguished. Waves with lower frequency propagate through this point.

The considerations above indicate that a particular basilar membrane motion pattern may be expected on simple physical grounds. With sinusoidal stapes movement, a sinusoidal pressure gradient is established across the basilar membrane. As a result, a wave motion is initiated at the basal end of the membrane. As the wave progresses away from its origin, it gradually increases in amplitude and slows down while its wavelength decreases. At a characteristic frequency-specific place, the wave energy is absorbed in the membrane’s dissipation; consequently, the amplitude of vibrations rapidly diminishes. This “traveling wave” sustained on the basilar membrane was first measured by von Békésy (1960) in human cadaver ears. Some of his observed amplitude and phase patterns are reproduced in Figure 1.6. Note that as measured at the apical end of the cochlea for different low-frequency inputs, one sees at any frequency a gradual buildup of amplitude, a distinct maximum, and then a more rapid decline. Along with the amplitude changes, the phase accumulates. The lower the stimulus frequency, the closer to the apex are these features apparent. This hydrodynamic behavior of the cochlea is the fundamental basis of its frequency-analyzing capability. Von Békésy measured the actual spatial pattern of vibrations by observing, at a given frequency, the amplitude and phase of basilar membrane motion at several locations (“panoramic view”; see Patuzzi, Chapter 4). An alternative method, one used exclusively in contemporary data gathering, is to observe the motion at a given point while varying frequency. This generates a so-called tuning curve or frequency response function. Some examples of this representation are given in Figure 4.11 (Patuzzi, Chapter 4).

### 3.3 Active Mechanics and Micromechanics

Von Békésy’s traveling wave was linear; in others words, its shape was not dependent on stimulus level. It also showed shallow tuning. It is now known that von Békésy described the behavior of the “passive” or dead cochlea. In the living ear, the wave motion sustained by the basilar membrane is similar in its appearance to a traveling wave. It is, however, different both qualitatively and quantitatively from von Békésy’s traveling wave, particularly in being exceedingly nonlinear and much more sharply tuned (Rhode 1971; Sellick, Patuzzi and Johnstone 1982). An example is shown in Figure 1.7 that
Figure 1.7 Normalized basilar membrane (BM) amplitude (gain) at a basal turn location in the guinea pig. Measurements are made at various constant sound pressure levels (SPL) as indicated. Note that the gain is independent of level below 10 kHz and is strongly dependent on level around the best frequency of ~18 kHz. Also note that the frequency of peak response shifts toward lower values as sound level increases. (Fig. 4B from Johnstone, Patuzzi and Yates 1986.)

highlights the increased sharpness of tuning. This plot is expressed as a gain function, that is, the ratio of basilar membrane and ossicular displacement. The gain is conspicuously dependent on stimulus level. At a given location along the basilar membrane, if measured at a high sound level, the displacement is similar to that found by von Békésy. As the sound level decreases, however, the gain functions become increasingly sharper. Note that the gain increases in the vicinity of the characteristic frequency (CF) only, and that for frequencies less than an octave below the CF the gain is independent of sound level. One may state that the response reflects a band-limited nonlinearity that is particularly pronounced at and around the CF. This phenomenon was first observed by Rhode (1971). This nonlinearity, and indeed the sharpness of tuning itself, depends on the physiological condition of the cochlea (Rhode 1973). This is convincingly demonstrated in Figure 4.14B (Patuzzi, Chapter 4). With increasing level and with cochlear deterioration, the best frequency shifts to lower values. This shift is just shy of an octave.

Some theoretical work intimates that the frequency response patterns are so sharp that they cannot be reproduced by a model in which all basilar membrane vibratory energy is derived from the original sound input (de Boer 1983; Neely and Kim 1983; Diependahl, deBoer and Viergever 1987; Geisler 1991; Zweig 1991; de Boer, Chapter 5). Passive linear models are well suited to characterize the dead cochlea. Passive nonlinear models, particularly those that allow for more than one degree of freedom in describing basilar membrane–related movements, are successful in representing many features of contemporary data but are generally incapable of quantitatively describing both amplitude and phase patterns (Viergever 1986). Active models incorporate a local supply of energy that may be utilized to selectively boost basilar membrane motion. Energy needs to be supplied to the traveling wave in a region that is basal to the best frequency. This is usually done with the formalism of providing “negative damping,” meaning that there is some mechanism of counteracting the inherent damping (viscous friction) of the basilar membrane and cochlear fluids (Neely and Kim 1983). The basic idea is the following. If somehow a force is provided to the basilar membrane in opposite phase with the force produced by the passive damping, then the two forces cancel. Damping force is proportional to the velocity of motion. Augmentation requires a cycle-by-cycle force that lags displacement by 90°. We should note that expert opinion is not divided as to the necessity of an active cycle-by-cycle feedback process. For example, Allen and Fahey (1992) maintain that the cochlear amplifier, as generally construed, is not necessary to explain the extant data.

Theoretical considerations, requiring amplification in the form of feedback, yield several predictions about possible vibratory patterns and also impose certain requirements on the system. Among the predictions is the possibility of instability, that is, oscillations due to excessive feedback. Interestingly, these may be observed in some situations. Acoustic energy has been shown to be produced in some ears where spontaneous oscillations, apparently of cochlear origin, are retransmitted by the middle ear and are detectable as sound in the ear canal (Wilson 1980). These so-called spontaneous otoacoustic emissions are the strongest evidence available that there is a possibility for the production of vibrations in the cochlea. It was demonstrated, by examining the amplitude spectrum of such emissions, that
they are not merely noise filtered by a sharply tuned resonant element but the products of an active oscillatory source (Bialek and Wit 1984). One should note, however, that spontaneous otoacoustic emissions have been recorded from several nonmammalian vertebrates in which no evidence for cochlear amplification (active feedback process) exists (for review see Manley and Taschenberger 1993). Sound emissions from the ear that originate in the cochlea in response to acoustic inputs also support the validity of active processes providing amplification of the traveling wave (Kemp 1978). A requirement of any theoretical scheme of cochlear amplification is that energy is supplied locally and in a frequency-specific manner. This implies that the mechanism that provides the feedback needs to be tuned or at least possess some frequency-dependent characteristics. This requirement is considered after the identity and properties of the putative feedback element are discussed.

A great deal of evidence gathered in numerous laboratories during the 1970s (reviewed in Dallos 1988; Patuzzi, Chapter 4) indicated that OHCs were intimately associated with the sensitivity, frequency selectivity, and nonlinearity of the cochlea. Figure 1.8 summarizes the results of many investigators. It shows that damage to OHCs desensitizes, detunes, and linearizes the cochlear response. Fibers located near the lesion, while maintaining normal tuning curve shape, lose some two-tone suppression and have elevated $2f_1 - f_2$ thresholds (middle panel). Fibers originating from the region of absent OHCs have abnormal tuning curves, no two-tone suppression, and do not show responses at $2f_1 - f_2$. In many ways, without OHCs the cochlea behaves as in a dead animal. It is generally accepted today that OHCs function as the feedback elements in the cochlear amplification process. The key discovery was that OHCs isolated from the cochlea are capable of shape changes at audio frequency rates upon electrical stimulation (Brownell 1983; Brownell et al. 1985; Kachar et al. 1986; Zenner 1986; Ashmore 1987). These electromotile responses are primarily length changes of up to 3%-5% of the total length under maximal electrical stimulation. Depolarization of the cell results in contraction and hyperpolarization results in elongation (Ashmore 1987). Small diameter changes are also measurable. The controlling variable is transmembrane voltage change (Santos-Sacchi and Dilger 1988). The motile response is nonlinear and shows strong rectification in the contraction direction (Evans, Dallos and Hallworth 1989; Santos-Sacchi 1989). The sensitivity of the response is approximately 2-30 nm/mV at low frequencies. The correlated behavior under voltage clamp of motile response and nonlinear capacitive (“gating”) currents suggest that motility involves the movement of membrane-bound charged molecules (Ashmore 1990; Santos-Sacchi 1991). Other work also intimates that OHC electromotility is produced by the concerted direct action of a large number of independent molecular motors that are closely associated with the cell’s.

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**Figure 1.8** Schematic depicting the effects of OHC lesions on various characteristics of single auditory nerve fiber responses. **Bar graph** on the top depicts the presence (solid) or absence (open) of IHCs and OHCs along the length of the cochlea. Bottom three graphs are frequency response plots. **Dashed line** indicates neural threshold. At the boundary of the lesion the threshold becomes poorer by 40-50 dB (Ryan and Dallos 1975). For a fiber that originates far from the lesion (top panel), all responses are normal. Thus the tuning curve (FTC, solid lines) is sharply tuned with long tip segment. There is a prominent high-frequency two-tone suppression area (2TS) and the fiber responds to the $2f_1 - f_2$ distortion component when the primaries $f_1$ and $f_2$ are presented at very low levels, even if the fiber does not respond to the primaries themselves. As the fiber's location of origin approaches the lesion, the FTC remains normal while the nonlinear responses, 2TS and $2f_1 - f_2$, diminish. A fiber originating from the lesioned region (bottom panel) has a high threshold, a short or nonexistent tip, and does not produce nonlinear responses (Smoorenburg 1972; Dallos and Harris 1978; Harrison and Evans 1979; Dallos et al. 1980; Schmiedt, Zwischen & Hamernik 1980).
basolateral membrane (Holley and Ashmore 1988; Dallos, Evans and Hallworth 1991; Holley, Chapter 7). This response is clearly a biophysical process and not dependent on ATP or Ca\(^{2+}\) (Kachar et al. 1986; Holley and Ashmore 1988). It is of such speed as to rule out all hitherto described motile mechanisms (Dallos and Evans 1995a).

In vivo, the electromotile response may be driven by the receptor potential produced in OHCs in response to acoustic stimulation (see below). Length changes resulting from altering depolarization and hyperpolarization may feed back a cycle-by-cycle mechanical force upon the basilar membrane–tectorial membrane system. In addition, due to the rectifier properties of electromotility, a DC length change in the contraction direction would be produced as well. The AC force can act to counteract viscous damping, whereas the DC force may alter the basilar membrane–tectorial membrane relationship, thus setting the operating point of the micromechanical system (Dallos 1988). Aside from stimulus-evoked fast motile responses, a wide variety of agents are capable of stimulating slow contractions of OHCs (Brownell et al. 1985; Zenser, Zimmerman and Schmitt 1985; Flood, Flood and Ulfendahl 1986) or eliciting interactions with fast motility (Sziklai and Dallos 1993; Housley, Connor and Raybould 1995). Of particular interest is the modulatory effect elicited by focal application of acetylcholine, the transmitter substance for cochlear efferents (Sziklai and Dallos 1993). The possibility is thus open that the state of the organ of Corti may be mechanically modified by the central nervous system (see Guinan, Chapter 8) via alteration of motility gain mediated through efferent influence (Kim 1986; Zenser 1986) as well as stimulus-evoked DC contractions (Dallos 1988).

Energetic considerations intimate that the receptor potential is capable of supplying energy greatly in excess of that required to overcome the cell's own internal stiffness in producing extension–elongation cycles that are commensurate with basilar membrane movements in vivo. How this is affected by the mechanical load upon the cell in situ is unknown. The OHC motor itself, if driven by constant membrane voltage changes, is capable of AC displacements of undiminished amplitude up to at least 24 kHz (Dallos and Evans 1995a). However, an often-mentioned problem in associating OHC electromotile responses with a feedback role in vivo is the high-frequency attenuation of the receptor potential due to the cell's basolateral membrane capacitance. The high-frequency attenuation of the cell's receptor potential clearly reduces the cell's ability to produce sufficient motile feedback at the high end of the audio range. One can estimate that OHC electromotile displacement amplitude becomes less than basilar membrane motion at approximately 6 kHz. At higher frequencies, it is unlikely that electromotility, as commonly construed, would be capable of influencing cochlear mechanics. We have recently suggested as a partial remedy that the driving voltage for OHC motility at higher frequencies is an extracellular AC potential\(^2\) gradient between scala media and intra-organ of Corti fluid spaces (Dallos and Evans 1995a,b). It was shown that the voltage gradient across the basolateral membranes of weakly excited cells basal to the CF location is greater (for the 6- to 20-kHz region) than that for strongly excited CF cells (Dallos 1996). This would allow basally located cell groups to provide electromotile feedback at frequencies where CF cells could no longer do so. Of course, it is also possible that in mammals some other hitherto unobserved aspects of motility, such as ciliary movement or change in ciliary stiffness (Kros, Chapter 7) are the critical feedback variables. Such phenomena have been detected in nonmammalian hair cells (Crawford and Fettiplace 1985; Howard and Hudspeth 1988; Assad, Hacohen and Corey 1989). Finally, the door still needs to be left open to the possibility that the feedback action in vivo is not produced by outright OHC motility, but that when these cells are constrained by the organ of Corti framework, the significant variable is a change in their axial stiffness and the consequent modulation of the total basilar membrane–organ of Corti stiffness (Kolston et al. 1989).

A locally active cochlea (see de Boer, Chapter 5) requires the presence of two frequency-analyzing systems. The second is obvious; this is the preanalysis by the traveling wave, which is then boosted by cochlear amplification. The first system is related to the selection of the cochlear region, for a given frequency, from which energy is provided to the traveling wave. Consider for argument's sake that the traveling wave peaks at 5 mm from the stapes for a pure tone \(f_0\). Assume further that the active process operates about \(\frac{1}{2}\) octave basal from the traveling wave peak, or approximately at the 4.2 mm location in the guinea pig. In order for this location to be different from its neighbors and for it to "know" that it needs to provide feedback (OHC motility), it needs to be selective to \(f_0\). This implies a second cochlear map that is systematically detuned from the "main" map by about \(\frac{1}{2}\) octave. It is generally assumed that this second filter can be found in a resonance between tectorial membrane and OHC cilia (Zwislocki and Kletsky 1979) or by resonance of the tectorial membrane itself (Allen 1980). There is some preliminary experimental evidence that indicates that the tectorial membrane may possess such tuned characteristics (ITER 1989; Allen and Fahey 1993; Guummer et al. 1993).

3.4 Transmission of Forces to Cilia

Forces exerted on the ciliary bundle may derive directly from the relative displacement between the reticular lamina and the tectorial membrane to which some of the cilia are attached. Alternatively, the flow of endolymph in the narrow gap between the two moving surfaces may be a consequence

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\(^2\)Extracellular potentials and their origins are discussed below.
of the aforementioned relative motion and deliver viscous forces to the cilia (Billone and Raynor 1973; Freeman and Weiss 1990). The latter forces are more efficient in stimulating cilia that are not attached to the tectorial membrane. In OHCs only the tallest row of cilia are connected to the tectorium, and it appears that IHC cilia are either entirely free-standing or only tenuously connected to the tectorial membrane (Lim 1980). There are important functional consequences of these anatomical differences.

As a result of the viscoelastic coupling of forces to IHC cilia, their displacement is likely to be proportional to basilar membrane velocity at low frequencies (Billone and Raynor 1973; Freeman and Weiss 1990). There is experimental evidence to support this claim, both indirectly through cochlear microphonic data (Dallos et al. 1972; Dallos 1973b) and directly from intracellular recordings from IHCs (Nuttall et al. 1981; Russell and Sellick 1981; Dallos and Santos-Sacchi 1983). At higher frequencies, above 300–500 Hz, ciliary displacement becomes proportional to basilar membrane displacement. The low-frequency velocity dependence, aside from imposing a dynamic characteristic upon the IHC response, has a more profound consequence. Because of the coupling properties of IHC cilia, very-low-frequency (DC) signals are probably ineffective in stimulating IHCs. In other words, the DC displacements of basilar and/or tectorial membranes, if any, that may arise from asymmetrical nonlinear processes are not likely to produce an IHC response (Dallos and Cheatham 1989).

4. Transduction and Receptor Potentials

4.1 Transduction

The excitatory proximal stimulus to any hair cell is the bending of the ciliary tuft toward the kinocilium (Hudspeth and Corey 1977; Hudspeth and Jacobs 1979) or, in the case of mammalian hair cells, toward the tallest row of stereocilia (Russell and Richardson 1987). We have already considered how the forces that bend the bundle may arise. Extracellular current measurements indicate that the sink for transducer current is near the top of the ciliary bundle (Hudspeth 1982). An attractive and coherent hypothesis of hair cell transduction implicates mechanically gated channels located at or near the tips of stereocilia that are controlled by changing tension in attached elastic elements, termed gating springs (Hudspeth 1989). Slender filamentous tip links (Fig. 2.6D, Slepecky, Chapter 2) reach up from the tops of short cilia to the sides of adjacent tall cilia in a bundle, parallel to the mirror-symmetry axis (Pickles, Comis and Osborne 1984). The arrangement of tip links is consistent with the cell's directional sensitivity; stretching the links by displacing the bundle toward the tallest cilia is excitatory, movement in the opposite direction is inhibitory, while orthogonal displacement is ineffective (Shotwell, Jacobs and Hudspeth 1981). Approximately 50% of the hair bundle's total stiffness (~300 μN/m) may be attributed to its basal pivot, while the rest resides in the gating springs. The latter stiffness depends on bundle position. It is minimal at displacements about the resting position where transduction gain is highest, suggesting an association between gating stiffness and open or closed states of transducer channels (Howard and Hudspeth 1988).

Figure 6.6 (Kros, Chapter 6) represents a version of the mechanical gating process of channels via the tip link (gating spring) connection. The number of channels per cilium is estimated to be few (Howard and Hudspeth 1988) and the “swing” of the gate about 4 nm. Because of its direct activation by the mechanical stimulus, the opening and closing times of the gate are very short, certainly less than 50 μs. The times are likely to be much shorter in animals in need of very-high-frequency hearing, such as chiropterans (Hudspeth 1989). There is strong evidence that during maintained bending of the cilia, the attachment point of the tip link is actively modified and travels up and down the cilium to produce a resetting of its elasticity and, thereby, adaptation of the receptor current (Eatock, Corey and Hudspeth 1987; Corey and Assad 1991).

The transducer channels themselves are nonselective aqueous pores that permit the passage of both monovalent and divalent cations (Corey and Hudspeth 1979) and probably possess single-channel conductance of ~50–100 pS (Ohmori 1984; Crawford, Evans and Fettiplace 1991). In all inner ear systems, the cilia, and hence the transducer channels, are in contact with endolymph, making K⁺ the likely carrier of transducer current. The driving force for K⁺, instead of an electrochemical potential, is the electrical gradient across the ciliary membrane produced by the sum of the cell's resting potential and the positive endocochlear potential. In the absence of stimulation, about 5%–15% of the transducer channels are open (Hudspeth and Corey 1977; Crawford and Fettiplace 1981; Russell, Cody and Richardson 1986). As a consequence, there is a standing current producing a “biased epithelium,” in that the cell is normally somewhat depolarized to bring it closer to the range of activation of voltage-gated channels of the basolateral cell membrane. The resting potential of cochlear IHCs in vivo, measured with sharp microelectrodes, is between –40 and –50 mV (Russell and Sellick 1978; Dallos 1985b). A necessary caveat to these data is that the microelectrode almost certainly creates a significant leak conductance so that the cell appears more depolarized than it really is (see Kros, Chapter 6).

The transducer current in response to ciliary deflection has been measured for different hair cells. The relationship between current and ciliary rotation is sigmoidal and indicates great asymmetry for deflections in opposing directions. The gating process underlying transduction is probably describable as a three-state Boltzmann function (Corey and Hudspeth 1983;
Holton and Hudspeth 1986). Strong saturation is seen for bundle displacements in excess of 0.5 µm, which corresponds to a rotation of about 5°, and about 90% of the useful range is encompassed within ±1°. In the best hair cells, the transducer conductance is 2.5–5 nS and the sensitivity of the process is about 600 pA/µm (Crawford, Evans and Fettiplace 1989). This is similar to that found in frog saccular hair cells (Holton and Hudspeth 1986). Patch-clamp recordings reveal single-channel currents of ~9 pA and single-transducer-channel conductance of ~106 pS (Crawford, Evans and Fettiplace 1991). Assuming a hair cell input resistance in vivo of ~50 MΩ (Russell and Sellick 1978), the receptor potential produced may be around 0.1 mV at 1 nm ciliary displacement. This is of the same order as is seen experimentally around zero dB sound pressure level (Dallos 1985b).

It is noted that virtually all information about transducer channels and transducer gating comes from work on nonmammalian vertebrates. It is likely that the process of transduction is highly conserved for all hair cells and that the above information is applicable to the mammalian hearing organ and presumably to both IHCs and OHCs. In contrast, as noted below, the properties of the hair cell’s basolateral membrane are likely to show considerable divergence that will not permit easy generalizations.

4.2 Basolateral Membrane and Receptor Potentials

Acoustic simulation and its mechanical consequences are AC signals. In other words, these are the sums of sinusoidal variations about a resting value. Nonlinearities at any stage of processing may distort the frequency composition of the signal and add DC components due to rectification and asymmetries. It is customary when analyzing receptor potentials to distinguish between their frequency-following, or AC, and their unidirectional, or DC, components.

Voltage drops produced by the receptor current may be shaped and altered by voltage-dependent conductances found in the cell’s basolateral membrane. The measured receptor potential is the result of interaction among all active conductances. In some hair cells, turtle cochlear hair cells serving as a prime example, the basolateral conductances dominate the character of the cell’s voltage response (Crawford and Fettiplace 1981). In contrast, the dominant character of the receptor potential of mammalian IHCs is likely determined by the transducer conductance itself (Kros and Crawford 1990). One form of ubiquitous influence by the basolateral membrane is due to the inevitable low-pass filtering, owing to the parallel resistance-capacitance (RC) of this membrane segment. The filter shunts those frequencies that are above its corner frequency \( f_c = 1/2\pi RC \), and consequently limits the size of the AC receptor potential at high frequencies. It is widely assumed that limitations on neural phase-locking are largely a consequence of this presynaptic filtering action (Palmer and Russell 1986; Weiss and Rose 1988; Kidd and Weiss 1990). Inasmuch as \( R \) (incorporating time- and voltage-dependent conductances) is dependent on the basolateral membrane voltage (Dallos and Cheatham 1990; Russell and Kössl 1991), the corner frequency changes with receptor potential (stimulus) level (Kros and Crawford 1990). The larger the input and hence the receptor potential, the higher the frequencies that may be transmitted by the hair cell. Even if these conductances are fully activated, it is unlikely that the corner frequency would much exceed 1 kHz, setting a maximum lower limit for the deterioration of phase-locked transmitter release.

Voltage-gated \( \text{Ca}^{2+} \) channels and \( \text{Ca}^{2+} \)-gated \( K^+ \) channels have been identified in nonmammalian hair cells (Crawford and Fettiplace 1981; Lewis and Hudspeth 1983; Pitchford and Ashmore 1987; Fuchs and Evans 1988; Fuchs, Nagai and Evans 1988). In nonmammalian vertebrate hair cells, the rapidly activating \( \text{Ca}^{2+} \) inward current and delayed \( K^+(\text{Ca}^{2+}) \) outward current interact together and with the membrane capacitance to produce damped oscillations with high quality factor (Q). There is no direct evidence for resonant behavior in mammalian cochlear hair cells except for a very rapidly damped resonance in IHCs at driving current levels that are unlikely to be physiological (Kros and Crawford 1990; Kros, Chapter 6). In anuran hair cells, the \( \text{Ca}^{2+} \) channels and the \( K^+(\text{Ca}^{2+}) \) channels cluster together with preference to the synaptic region and probably correspond to presynaptic active zones (Roberts, Jacobs and Hudspeth 1990). In these same cells, the only conductances found in the cell’s ciliated apex are those associated with transducer channels. The uneven division of ion channels between the apical and basolateral surfaces is a common characteristic of secretory and sensory epithelia. A preliminary report on OHCs indicates the possibility of the presence of conductances other than those of the transducer in the apical membrane (Gitter, Zenner and Frömter 1986). We now know that purinergic channels are present in the apex (Housley, Greenwood and Ashmore 1992).

Basolateral membrane conductances in IHCs (Kros and Crawford 1990) are dominated by two different voltage-gated \( K^+ \) channels, which are active in the −60 to −20 mV membrane potential range that encompasses all values seen in vivo. The two outward \( K^+ \) currents shape the receptor potential, in that a very rapid initial decline is a consequence of the activation of the tetraethylammonium (TEA)-sensitive conductance and a gradual, adaptation-like decline is produced by the activation of the 4AP-sensitive conductance. Neither \( K^+ \) current appears to be dependent on \( \text{Ca}^{2+} \) influx into the cell. Isolated IHCs have a zero-current membrane potential of approximately −67 mV and a conductance of about 2 nS. The conductance increases to 300–500 nS when fully activated; it decreases to as low as 0.5 nS when the cell is hyperpolarized. Figure 6.15 (Kros, Chapter 6) depicts the various currents and channels that dominate IHC electrical phenomena.

OHC basolateral membranes are endowed with two types of \( \text{Ca}^{2+} \)-activated \( K^+ \) channels (Ashmore and Meech 1986). It is likely that the
basolateral membrane also possesses Ca$^{2+}$ channels, inasmuch as blocking the K$^{+}$ current by internal Cs reveals a voltage-dependent inward current (Santos-Sacchi and Dilger 1988). The zero-current membrane potential of isolated OHCs ranges from $-10$ to $-68$ mV (Santos-Sacchi and Dilger 1988), "up to" $-70$ mV (Gitter, Zenner and Frömter 1986), and from $-15$ to $-40$ mV (Ashmore and Meech 1986). Apparently a rapid loss of internal K$^{+}$ and Na$^{+}$-loading occurs upon isolation and is responsible for the variable and low membrane potentials. If the cytoplasm is loaded with K$^{+}$, the resting potentials stabilize around $-60$ mV (Ashmore and Meech 1986). The mean conductance around this resting potential is 9.2 nS (Santos-Sacchi and Dilger 1988).

The first successful intracellular recordings from in vivo mammalian IHCs were obtained by Russell and Sellick (1977) and from OHCs by Dallos, Santos-Sacchi and Flock (1982). The properties of these receptor potentials have been extensively characterized (Russell and Sellick 1978, 1983; Russell 1983; Dallos 1985b, 1986; Cody and Russell 1987; Dallos and Cheatham 1989, 1991; Zwisslocki 1989). Receptor potential measurements are also available from organotypic cultures of the mouse cochlea (Russell, Cody and Richardson 1986; Russell and Richardson 1987).

The schematic of Figure 1.9 depicts the two techniques employed for in vivo recordings from hair cells of the mammalian cochlea. In the original method of Russell and Sellick (1978), the organ of Corti is approached from the scala tympani. The method permits excellent control over the orientation and direction of electrodes, but for this probe it is applied to only that region of the cochlea having CFs between 16 and 20 kHz. With the technique developed by Dallos, Santos-Sacchi and Flock (1982), the electrode reaches the organ of Corti through an opening on the lateral bony wall of the cochlea. In theory, this approach is usable in all cochlear turns and has been applied to the fourth (CF = 200 Hz), third (CF = 1000 Hz), and second (CF = 4000 Hz) turns. A drawback of the technique is the limited ability to visualize the target organ of Corti.

Both recording techniques reveal similar membrane potentials, approximately $-40$ mV for IHCs and $-70$ mV for OHCs. Similarly, both techniques yield IHC receptor potentials that imply invariance in the behavior of these cells along the length of the cochlea. In response to tones, all IHCs produce stereotyped receptor potentials. These contain a fundamental response, a DC component, and a harmonic series. At low sound levels, the fundamental response increases in proportion to the signal level, whereas the DC response reflects square-law behavior. Harmonics also rise faster than the fundamental. All responses saturate at moderately high sound levels. As the time patterns in Figure 1.10 show, the harmonic content is clearly manifested in the waveforms. The harmonic content plus the DC make the response waveforms exceedingly asymmetrical about the resting potential. The positive and negative peaks of the

![Figure 1.9 Schematic showing the two approaches to intracellular recording from cochlear hair cells in vivo. In the lateral approach (Dallos, Santos-Sacchi and Flock 1982), the electrode passes through a fenestra in the cochlear bone and approaches the organ of Corti through the scala media. The method has been used to collect data from the three low-frequency turns of the guinea pig cochlea (three left arrows). In the scala tympani (ST) approach (Russell and Sellick 1978), the electrode passes into the organ of Corti through the basilar membrane from the opened scala tympani. This approach is suitable to the high-frequency region of the cochlea (right arrow) (Fig. 2 from Dallos and Cheatham 1992.)](image)

response plotted against sound pressure in the $\pm 1$ Pa range show the asymmetry of the receptor potential. Particularly severe saturation is always evident in the hyperpolarizing direction. The properties of the receptor potential versus sound pressure functions seem to be common among hair cell responses in various systems and may be quantified as rectangular hyperbolas or Boltzmann functions (Hudspeth and Corey 1977; Crawford and Fettiplace 1981; Russell and Sellick 1983; Dallos 1986).

The pattern is similar for a given IHC at all stimulus frequencies, but the quantitative properties of the response differ. In terms of sensitivity and many nonlinear response properties, the IHC reflects its mechanical input. Thus the tuning of its place along the cochlea is the prime determinant of the quantitative features of the IHC’s response. As Figure 1.11 depicts for AC, and Figure 6.9 for DC, both fundamental and DC response components are tuned and the sharpness of tuning decreases with stimulus level. The plots of Figure 1.11 are gain plots, i.e., amplitude plots normalized for
Figure 1.10 Intracellular recording from a fourth-turn OHC near the best frequency. *Left:* linear plot of peak receptor potential magnitude as a function of peak sound pressure at the eardrum. *Right:* waveforms of responses to sinusoidal tone burst stimuli at the indicated sound pressure levels. (Fig. 9 from Dallos 1986.)

Sound level. Response saturation is most evident at the CF and more linear responses are found far from CF. All such features reflect the properties of basilar membrane vibrations (e.g., Ruggero and Rich 1991).

The low-level, low-frequency steepening of the AC plots reflects the velocity-dependence of the IHCs' low-frequency response. Concomitant with the slope change, there is an associated phase-lead that reaches 90° at the lowest frequencies (not shown). Aside from shape changes with level, there are also phase changes that depend on the relation between stimulus frequency and CF. This behavior also reflects the preceding mechanical nonlinearity. We note that the magnitude function of the DC component is sharper and reflects a square-law relation with the fundamental. It is also noted that no matter what the stimulus conditions, the DC response of IHCs is always depolarizing. When tuning curves (iso-response functions) are compared for AC and DC components, they have the same shape both at low frequencies (Dallos 1985b) and at high frequencies, after correction for the filtering of the AC (Russell and Sellick 1978). Inasmuch as high-frequency receptor potentials are shunted by the IHCs' basolateral RC filter (Russell and Sellick 1978), they cannot be effective in stimulating synaptic transmitter release. It follows that stimulus-related discharge-rate changes in primary auditory afferents and changes in their precursor transmitter exocytosis must be governed by DC receptor potentials produced in the nonlinear response of the IHC itself. This DC is likely to arise in the rectifier properties of the IHC transduction process (Russell and Sellick 1983; Dallos 1986; Dallos and Cheatham 1989), but may be enhanced by nonlinear properties of the cell's basolateral membrane (Dallos and Cheatham 1990). IHC receptor potentials reflect all well-studied nonlinear features of cochlear function, such as intermodulation distortion, harmonic production, and two-tone suppression (Sellick and Russell 1979; Cheatham and Dallos 1990).

Aside from two primary differences to be considered below, the previous description of IHC behavior could be applied to OHCs as well. In other words, OHC and IHC receptor potentials are more similar than different (Fig. 1.11). The first generally observed difference is seen in recordings of AC and DC responses from low-frequency IHCs and OHCs. There is a ~6 dB/octave low-frequency slope difference coupled with a ~90° phase difference between frequency responses of OHCs and IHCs. Both features reflect the basilar membrane displacement-dependence of OHCs and the velocity-dependence of IHCs at low frequencies. Second, whereas IHCs produce only depolarizing DC responses, OHCs generally show a frequency- and level-dependent transition between hyperpolarizing and depolarizing asymmetries. The frequency response plots of Figure 1.11 show AC responses, while those of Figure 6.9 (Kros, Chapter 6) depict DC
responses at several levels, and the below-CF, low-level hyperpolarizing responses are amply evident. Such hyperpolarizing responses are more prominent in basal-turn OHCs below the CF (Cody and Russell 1987).

Certain features of OHC receptor potentials, however, are dependent on cochlear location, technique, or both. Recordings from OHCs in the high-frequency end of the cochlea via the scala tympani approach reveal a fundamental difference from that seen in lower-frequency regions. It is found that at the CF, and at low and moderate sound levels, the receptor potential versus sound pressure functions are symmetrical. In other words, little or no DC is produced. The comparison between the two types of recording is highlighted in Figure 1.12A. First, note that because of the basolateral membrane filters, the AC component is negligibly small in the basal turn recording for either IHCs or OHCs. The DC response does not appear in OHCs until the sound level reaches ~90 dB, whereas from an IHC located at the same place, the DC component is already very prominent at 10 dB sound pressure level. In contrast, at the 1-kHz location, both IHC and OHC DC responses are measurable at 30 dB. When measured in organotypic cultures of mouse cochleas (Russell, Cody, and Richardson 1986), both IHCs and OHCs exhibit the type of receptor potential versus input level functions as exemplified in Figure 1.12B. In other words, in the culture both cells show asymmetry.

All intracellular recordings in vivo suffer from a potential problem. We have already alluded to the artifact produced by imperfect sealing of the cell membrane around the recording microelectrode and the leakage conductance produced thereby. Aside from altering the cell's membrane potential, the leak conductance shunts out the effects of voltage-gated conductances of the cell's basolateral membrane (see Kros, Chapter 6). As a consequence, in vivo recordings of receptor potentials may not reflect the behavior of these potentials as they would appear in the absence of the recording electrode. What these recordings do reflect is the receptor current as it produces a voltage drop on the (largely ohmic and linear) basolateral leak resistance. The receptor current, in turn, renders ciliary deflection, as driven by macro- and micromechanical processes, through the nonlinearity of the transducer itself. At low signal levels, well below transducer saturation, the intracellular receptor potential is certainly a good representation of the preceding mechanical processes.

Some representations of the hair cell receptor currents can be measured extracellularly within various fluid compartments of the cochlea and even at more remote extracochlear locations. One can consider hair cells as sources of current that spreads through the complex electrical network surrounding them and that produces voltage drops, according to Ohm's law, on any electrical impedance across which the measurements are made. Aggregate receptor currents produced by groups of hair cells generate voltage drops on any external impedance in the current path. Consequently, these voltage drops (the extracellular receptor potentials) also reflect the transducer

![Figure 1.12](image-url)

**Figure 1.12** (A) DC response from IHCs in the base of the cochlea at best frequency (after Russell and Sellick 1978) and AC and DC responses from an IHC in the third turn at best frequency. (Dallos unpublished.) (B) DC response from an OHC in the base of the cochlea at best frequency (after Russell, Cody and Richardson 1986) and AC and DC responses from OHCs in the third turn (after Fig. 6 from Dallos 1985b). (C) Peak response magnitude versus ciliary bundle displacement recorded intracellularly from an IHC in a mouse organotypic cochlear culture. (D) As in C, but from an OHC. (From Fig. 5 of Russell, Cody and Richardson 1986.)
process. This reflection, however, is weighted and distorted by a spatial integration process over all active, current-producing hair cells (Whitfield and Ross 1965; Dallos 1973a). Connection between the intracellular and extracellular receptor potentials is made via a knowledge of cochlear "electroanatomy," the study of electrical impedance patterns in the cochlea (von Békésy 1960).

Indeed, the electrical activity of the cochlea was identified from such remote measurement of voltage drops, first of the AC component (cochlear microphonic, CM; Weyer and Bray 1930), then of the DC component (summatting potential, SP; Davis, Fernández and McAuliffe 1950). Aside from their limited clinical utility, contemporary interest in extracellular receptor potentials stems from some of their properties. The principal one is that the production of the extracellular AC potential is dominated by OHC receptor currents (Davis et al. 1958; Dallos and Cheatham 1976; Oesterle and Dallos 1989). The theoretical reason for this is examined below, but the utility of the relationship is noted here. In spite of its 14-year history (Dallos, Santos-Sacchi and Flock 1982), it is now apparent that intracellular recording from OHCs will never be routine. Consequently, there is a significant motivation to evaluate how well various extracellular responses can be used to assess OHC operation (Patuzzi, Yates and Johnstone 1989). Furthermore, we recently proposed that extracellular AC voltage gradients may have a direct function in stimulating OHC electromotility in vivo at high frequencies (Dallos and Evans 1995a,b). To evaluate this proposal, it is necessary to obtain detailed measurements of extracellular receptor potentials and electrical impedance patterns (electroanatomy) within the cochlea and, specifically, within the organ of Corti. Such information is as yet lacking.

Although there appears to be nearly universal agreement that OHCs dominate extracellular AC responses (Patuzzi, Yates and Johnstone 1989; Russell and Kössl 1991), the source of the extracellular DC is controversial. Recordings from high-frequency OHCs in vivo at their best frequency do not reveal a significant DC component except at very high sound levels. However, IHCs produce pronounced tonic response (Cody and Russell 1987; Kössl and Russell 1992). Consequently, it is quite commonly stated that the extracellular DC is of IHC origin (Geisler et al. 1990). In contrast, intracellular recordings from OHCs in the apical, low-frequency half of the cochlea show that they do produce large depolarizing DC responses at their best frequencies, and therefore do not differ substantially in their behavior from IHCs (Dallos and Cheatham 1990). Experiments with hair cell damage also point to OHCs as sources for extracellular DC responses, at least in the low-frequency region of the cochlea (Johnstone and Cheatham 1996). Measured in organ cultures, both IHCs and OHCs generate DC receptor potentials (Fig. 1.12B). It is only in vivo that the DC component is lacking (Russell and Richardson 1987). The proposed explanation of the different OHC behavior in vitro and in vivo is the lack of a tectorial membrane in the culture. This would produce "open loop" operation for the OHC, inasmuch as the presumed motile OHC could not feed energy back in the absence of the tectorial membrane and in the presence of direct ciliary stimulation. The suggestion is that the fundamental transducer asymmetry of OHCs and IHCs is similar and is expressed in the culture. However, in vivo the OHCs, via their cilia and the tectorial membrane, feed energy back and alter the response so as to minimize the DC component (Russell, Cody and Richardson 1986). In this view, low-frequency OHCs either do not participate in the feedback process (the cochlear amplifier) or, less charitably, the lateral approach produces a mechanical bias that results in an artificial DC component. The converse, noncharitable view of the lack of a DC in high-frequency OHCs is that the scala tympani approach produces a mechanical bias that eliminates the DC response. However, there are no direct proofs extant that would show the reality of either of the above. Undoubtedly, an electrode dwelling in the organ of Corti will introduce some mechanical bias, no matter which approach is used. It remains to be determined which method produces less deleterious conditions. If a longitudinal dichotomy in the cochlea between high- and low-frequency OHC behavior does exist, then the low-frequency pattern extends at least to the 4-kHz location. We note in passing that OHCs from any cochlear location show electromotility, the presumed feedback link in cochlear amplification. It is mentioned that the distortion of the organ of Corti that may arise from either recording method has a relatively minimal effect on the AC response. These distortions probably affect the operating point of the OHC transducer and, thereby, the response asymmetry, without significantly altering the phasic response.

Why would OHCs produce more of the extracellular response? On the basis of relatively simple analysis of the organ of Corti circuit (Dallos 1983), it was shown that the ratio (\( \rho \)) of extracellular potential due to OHCs versus IHCs can be approximated as

\[ \rho = k \frac{R_{i\text{OHC}}^{IHC}}{R_{i\text{OHC}}^{OHC} (1 + \beta)^3} \]

where \( k = 3.8 \) in the ratio of the numbers of OHCs and IHCs in a cochlear region, and the so-called shape factors are defined from the basolateral \( R_{ba} \) and apical \( R_a \) membrane resistances of OHCs and IHCs as

\[ \alpha = \frac{R_{ba}}{R_{a\text{OHC}}} ; \beta = \frac{R_{ba}}{R_{a\text{IHC}}} \]

while the cells' input resistance, \( R_i \), is obtained as

\[ R_{i\text{OHC}} = \frac{R_{ba} R_a^{IHC}}{R_{ba} R_a^{IHC} + R_{ba}^{OHC}} \]
The input resistance of an average OHC is estimated as 40 MΩ (Housley and Ashmore 1992) and that of an IHC as 16 MΩ (Russell and Kössl 1991). Assuming a transducer conductance per cilia of 100 pS (Crawford, Evans and Fettiplace 1991), 100 cilia per OHC and 40 per IHC yield α = 0.66 and β = 0.07. Combining all the numbers results in p ~ 4. Although the estimated numbers are quite uncertain (see Kros, Chapter 6), one may hazard the theoretical estimate of a 12-dB dominance of OHCs over IHCs in the production of extracellular potentials. This is in the direction of the experimental results (Dallos and Cheatham 1976).

5. Summary

Instead of providing a capsule summary of the above Summary, attention is called to a variety of unsolved problems, uncertain results, and opportunities for inquiry. The list is sketchy and is not in any particular order of significance. Most importantly, it is idiosyncratic, representing the questions that are of the greatest interest to this author.

The presence of spontaneous otoacoustic emissions obtained from different mammals has been construed as proof of an active cochlear process. One should note, however, that spontaneous otoacoustic emissions have been recorded from several nonmammalian vertebrates (Manley and Tashchenberger 1993) in which no evidence for cochlear amplification (active feedback process) exists. How these internal oscillations arise and what general cochlear property they might signify is somewhat of a mystery.

No matter how much is written about the cochlear amplifier and no matter how clever its modeling descriptions are becoming, there are still some fundamental uncertainties about this process. The most obvious need is to resolve the controversy concerning whether the cochlear amplifier actually exists (Allen and Neely 1992; de Boer 1995). Although the evidence in favor appears overwhelming, the issue is not yet closed. Assuming that the cochlea is indeed locally active, additional questions relate to the exact location of this activity vis-à-vis the peak of the traveling wave and, most importantly, to the means whereby this location is established. In other words, is a tuned tectorial membrane (Zwislocki and Kletsky 1979; Allen 1980), a tuned OHC (Brundin, Flock and Canlon 1989), or some other distributed resonance that establishes the second cochlear map? Can the local activity lie in the form of a reactance change (Kolston et al. 1989) or is negative damping imperative? A related question is whether it is OHC displacement or stiffening change that represents the feedback parameter of importance. Or, could it be that OHC somatic motility is an epiphenomenon, merely accompanying ciliary motility or stiffness change? Whatever it is, how does it work at high frequencies where the cell's self-generated receptor potential is drastically filtered? Could the extracellular potential field be of some help (Dallos and Evans 1995a,b)? What are the real properties of in vivo receptor potentials—without mechanical interference and electrical leak-conductance produced by the microelectrode? What are all the different classes of ion channels doing in IHCs if, seemingly, they are inactive around the cell's normal resting potential (Kros, Chapter 6)?

Whatever aspect of OHC motility-related phenomena will turn out to be relevant in cochlear amplification, the motor process proper is certainly novel and apparently unique in the animal kingdom. Identification of the putative motor protein is one of the most interesting current problems in molecular biology.

Probably the most productive research of the next decade will address the measurement of detailed micromechanical movements within the organ of Corti. It is obvious that micromechanics is one of the remaining frontiers of cochlear neurobiology. Thus far, due to the unavailability of suitable techniques, we have no substantive knowledge of how the many parts of the organ of Corti move during acoustic stimulation. We do have models, but they are pure fantasy: actual measurements are needed.

How do the medial efferents interact with the cochlear amplification process? Do they fine-tune the cochlea according to recent acoustic history or according to attentional and environmental needs? Do the type II afferents report on the mechanical state of OHCs and thereby participate in the feedback process?

Why are there so many well-established differences between the functioning of the apical and the basal cochlea? Why are there differences in efferent innervation pattern and neurotransmitters (Guinan, Chapter 8; Sewell, Chapter 9)? Does the cochlear amplifier even work in the apex? After all, tuning characteristics at low frequencies are not different between mammals and nonmammalian vertebrates. But then, why are apical OHCs motile? Are there real differences between DC receptor potentials in apical and basal OHCs?

The energy source of the organ of Corti, the stria vascularis, is the subject of a great deal of theoretical and experimental work (Wangemann and Schacht, Chapter 3). Yet it is still unclear how the three cell types in the stria interact, using what cell biological machinery, to pump K⁺ into and Na⁺ out of the scala media and produce the endocochlear potential. The explosion of cell and molecular biology has already had a salutory effect on cochlear research and promises to have an even greater effect in the future. What was the hunting ground for engineers and physicists is also rapidly becoming the legitimate province of biologists. The hallmark of contemporary neuroscience, the integration of disciplines and techniques brought to bear on a complex problem, is now exemplified in cochlear research. The chapters that follow clearly illustrate this.

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