



# The Energetic Ear

*A. J. Hudspeth*

*Abstract: As the gateway to human communication, the sense of hearing is of enormous importance in our lives. Research on hearing has recently been revolutionized by the demonstration that the ear is not simply a passive receiver for sound, but also an amplifier that augments, filters, and compresses its inputs. Hair cells, the ear's sensory receptors, use two distinct methods to implement an active process that endows our hearing with these remarkable properties. First, the vibration-sensitive structures of the ear, called hair bundles, display a mechanical instability that allows them to oscillate in response to stimulation. And second, the membranes of hair cells are replete with proteins that contract in response to electrical stimuli, thus enabling the cells to act like tiny muscles. The activity of these two motile processes can be so exuberant as to cause normal ears to emit sounds.*

Most of us use hearing aids. Electronic devices amplify sound for the benefit of those with compromised hearing, whereas the ears of people with normal hearing contain biological structures that serve an identical function. This so-called active process can amplify sounds by more than a hundred-fold. The ear's intrinsic amplifier additionally tunes our responsiveness to specific frequencies of sound, thus facilitating the recognition of sound sources and the discrimination of speech. The active process also allows us to analyze acoustic signals over a million-fold range of magnitudes, compressing responses so that we can appreciate both soloist and orchestra. Most remarkably, the ear's native hearing aid can, like an electronic device, become unstable, leading to the emission of sounds from the ear. Hearing is a highly adaptive sensory modality, for it provides an early warning of potential adversaries or predators and a foretaste of possible prey while they are still distant. In these endeavors, there is a clear advantage in having the most sensitive and discriminating auditory apparatus. Evolution has accordingly fostered an active process whose performance approaches the limits set by the physics of sound.

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Because hearing is the key sense in human communication, its importance is most apparent in persons whose hearing is deficient. Hearing is ordinarily the means by which children acquire language and thus their avenue to other forms of symbolic communication. One child in a thousand is born deaf, however, and a comparable percentage will become deaf before maturity, largely a result of the several hundred forms of genetic hearing loss.<sup>1</sup> Before the advent of a simple and effective test to identify these children within days of birth, many suffered years of retarded development owing to their unrecognized condition.

Verbal exchanges not only facilitate the transmission of information but also situate us in our social milieux, yet forty million Americans – an eighth of the populace – have hearing loss severe enough to mar their daily lives, for example by impeding conversation on the telephone or in a noisy environment. Age-related hearing loss, or presbycusis, affects 25 percent of our population at age sixty-five and 50 percent by age eighty, distancing many individuals from friends and family and greatly diminishing their quality of life. Finally, abrupt hearing loss – whether from overloud sounds, infections, or certain medications – may afflict individuals of any age. Deafness can be psychologically devastating, leading to depression and even suicide as a result of the isolation that it imposes. As Helen Keller remarked in a letter:

I am just as deaf as I am blind. The problems of deafness are deeper and more complex, if not more important, than those of blindness. Deafness is a much worse misfortune. For it means the loss of the most vital stimulus – the sound of the voice that brings language, sets thoughts astir and keeps us in the intellectual company of man.<sup>2</sup>

The basic outline of the hearing process is familiar to us from high school biology.<sup>3</sup> Sound waves – the alternate compressions and rarefactions of the air associated with a sound – are captured by the external ear, traverse the ear canal, and strike the thin, elastic eardrum. The ensuing vibrations propagate through the three miniscule bones of the middle ear – the hammer, anvil, and stirrup – to the cochlea. Named for its resemblance to a spiraled snail shell (*κόχλος* in Greek), the cochlea encompasses three helical turns in an organ the size of a chickpea. Abutting the cochlea within the temporal bone of the skull are the five receptor organs of the vestibular labyrinth, our source of information about rotatory movements and linear accelerations including gravity.

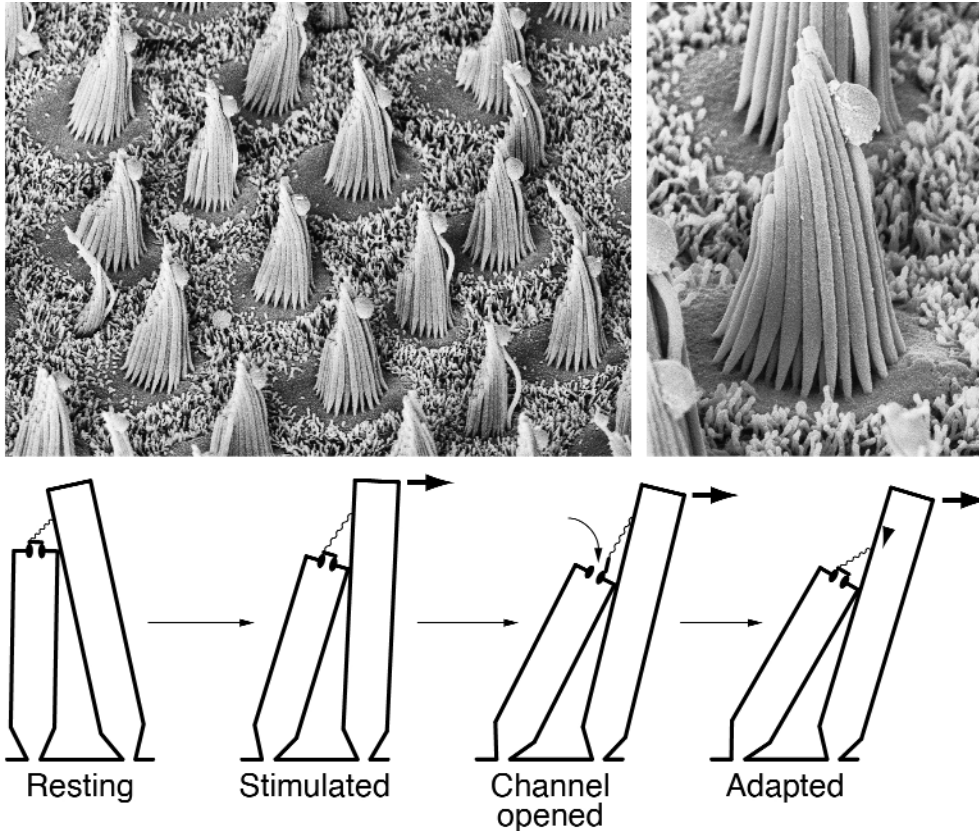
The cochlea comprises three tiny, liquid-filled tubes that spiral in parallel from the organ's base to its apex. Vibration of the stirrup bone applies an alternating pressure to the contents of one chamber, setting in motion the elastic boundaries between the tubes. One of these boundaries, the basilar membrane, supports the mechanically sensitive structure of the ear, the organ of Corti. Here the vibration occasioned by the incoming sound is interpreted as an electrical signal, the common currency of signaling throughout the nervous system. This process, the analog of detecting light in the eye or an odorant in the nose, constitutes auditory transduction.

The receptors responsible for transduction are termed hair cells, for each bears on its top surface a mechanically sensitive organelle called the hair bundle, which comprises between ten and three hundred regularly spaced, erect, cylindrical protrusions called stereocilia (Figure 1). This name, which means “stiff hairs,” characterizes an important feature: each stereocilium contains a rigid fascicle of cross-linked filaments of the protein actin. When a mechanical force is applied at the top of the



Figure 1  
The Mechanotransduction Process of Hair Cells

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The scanning electron micrograph at the upper left shows the surface of the sacculus, a sensory organ in the inner ear of a frog. Conical hair bundles extend about three ten-thousandths of an inch, from the smooth tops of the mechanically sensitive hair cells. The hair cells are separated by supporting cells marked by a stubble of fine protrusions called microvilli. The enlargement at the upper right portrays a single hair bundle comprising about sixty stereocilia and a lone kinocilium with a bulbous tip at the tall edge of the bundle. Note the progressive increase in stereociliary length from left to right; deflecting the bundle in the same direction excites the cell.

The diagram of two adjacent stereocilia schematizes the mechanism of transduction. When the hair bundle stands at rest, the filamentous tip link interconnecting the stereocilia bears little tension and the channel at its lower end is usually closed. An excitatory stimulus (thick arrow) deflects the bundle toward its tall edge, causing a sliding motion between the stereocilia and consequently increasing the tension in the link. This tension opens the channel, allowing positively charged ions to carry electrical current into the cell (curved arrow). If the stimulus persists for more than a few hundredths of a second, the hair cell adapts: the upper insertion of the tip link slides down the longer stereocilium (arrowhead), relaxing the tip link and allowing the channel to reclose. Note that the relative proportions in the diagram have been exaggerated in the interest of clarity. In reality, the loudest tolerable stimulus would deflect the hair bundle by only one-quarter of a stereociliary diameter and the channel would be smaller than the line thickness. Source: Figure prepared by the author.



*The Energetic Ear* hair bundle, each constituent stereocilium pivots at its tapered base, with minimal flexing along its shaft. This movement entails a sliding motion between adjacent stereocilia that is central to the transduction process.

The stereocilia in a hair bundle are not of uniform length. A poorly understood developmental process causes one row of these stereocilia to grow longest, while also rendering each successive row progressively shorter. Every hair bundle is accordingly beveled like the tip of a hypodermic needle. This characteristic is of importance in transduction, for the bundle is most sensitive to deflection along the direction of its bevel. Displacement of the hair bundle's top toward its tall edge excites the hair cell, whereas motion in the opposite direction has an inhibitory effect. Movement at a right angle, perpendicular to the bundle's plane of mirror symmetry, elicits no response. The hair bundle can thus be considered a biological strain gauge that is excited or inhibited by appropriately oriented mechanical stimuli.

Like other excitable cells, the hair cell produces electrical signals across its surface membrane through the action of ion channels, which are proteins that traverse the membrane and offer tiny pores through which electrically charged ions can flow. Most channels are equipped with some form of molecular gate that can open or close to regulate the flux of ions. The channels responsible for signaling in the nervous system, for example, include those responsive to membrane voltage, which underlie the propagating signals called action potentials, and those sensitive to neurotransmitter chemicals, which mediate the synaptic interactions between neurons. The ion channels of the hair bundle instead have mechanically sensitive gates that open and close in response to bundle displacements.

Stimuli are conveyed to the mechano-electrical-transduction channels by tip links, which are molecular threads consisting of four molecules of extracellular proteins called cadherins that run obliquely from the tip of each stereocilium to the flank of the longest adjacent stereocilium (Figure 1). Each of these tip links is likely connected to two ion channels at its lower end. When the top of a hair bundle is pushed toward its tall edge, the sliding between adjacent stereocilia increases the tension in the obliquely mounted link, which pulls the channels open. Movement in the opposite direction allows a small fraction of the channels that are open at rest to close. Because the tip links are oriented parallel to a bundle's bevel, they do not sense perpendicular stimuli.

The direct linkage of channel opening to hair-bundle movement has three important consequences for our hearing. First, because there are no chemical intermediates in the transduction process, hearing is rapid. We are able to detect sounds at frequencies as great as twenty thousand oscillations per second, and bats and whales can respond to stimulation at frequencies five times that great. By comparison, we process visual stimuli at only one-thousandth of that speed: in motion pictures and television, images presented twenty or thirty times per second are construed as continuous because they exceed the eye's rate of transduction.

The direct opening of channels next explains why hearing is so sensitive. The faintest sounds that we can perceive vibrate hair bundles by ten billionths of an inch, which is an atomic dimension. This movement is analogous to the apex of the Washington Monument budging by less than an inch. The sensitivity of hearing is limited by noise produced by the water molecules of the inner ear's fluids that, excited by heat, continually buffet hair bundles.



The third and most important consequence of the direct mechanical gating of transduction channels is the mechanical instability of the hair bundle. Applying a small force to a hair bundle tenses the tip links, which may in turn activate several transduction channels. Because opening the channels' molecular gates relaxes the attached tip links, the links associated with the remaining channels must bear more of the stimulus force. If these channels then open as a consequence, an avalanche ensues: the activation of a few channels triggers the opening of the rest. Similar behavior occurs when more than a certain number of channels have been shut by stimulation in the opposite direction; now the remaining channels close in concert. The consequence is that a hair bundle becomes bistable, adopting either a configuration with open channels upon stimulation toward its tall edge or a state with closed channels in response to force in the opposite direction. The bundle cannot, however, remain stably in a position between the two extremes. This behavior resembles that of a child's click toy, a metal strip that snaps between two shapes with an audible pop. As we shall see, the instability of the hair bundle has been harnessed by evolution to implement the active process.

Sounds can be captured effectively through the phenomenon of resonance, in which each cycle of a stimulus tone adds a tiny increment of energy to a vibrating structure. This is how an opera singer's voice can shatter a champagne glass: prolonged vocalization of the note to which the glass is tuned causes an oscillation that grows in amplitude until the material fails. Hearing would be most sensitive if the ear's structures were free to accumulate sound energy through resonance; each individual hair bundle would vibrate at a specific frequency determined by its di-

mensions and material properties. Doing this would present a challenge, however, because a hair bundle, like other cellular components, requires a liquid environment. Movement through the extracellular fluid causes a sound wave to dissipate, losing power due to viscosity, which reflects the friction between a hair bundle and the surrounding water molecules. The active process represents evolution's reconciliation of these issues. By continually supplying energy to the vibrating hair bundles, the active process counters the energy-dissipating effects of hydrodynamic friction and allows our hearing to exploit resonance.

As its name suggests, the *active* process must work to overcome viscosity and amplify a hair bundle's mechanical inputs.<sup>4</sup> The law of conservation of energy implies that a hair cell must draw on some source of biochemical energy to power its active process. At least in the ears of land-dwelling, non-mammalian vertebrates, a form of myosin – the type of protein that animates our muscles – does the work that underlies the active process. Rather like the participants in a tug o' war, myosin molecules consume cellular energy to pull against intracellular strands of the protein actin. Through such exertions, a cluster of myosin molecules at the upper end of each tip link continually tightens the link and thus ensures that some transduction channels remain open. If movement of the hair bundle toward its tall edge further tenses the link and activates more channels, then the myosin molecules work less and allow the link to relax and some channels to reclose. Conversely, when a negative hair-bundle movement slackens the link and closes the channels, the myosin molecules ascend, restoring tension and thereby reopening the channels. This process is called adaptation: whenever a protracted displacement is applied to the bundle, transduction channels transiently

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*The Energetic Ear* open or close, after which the myosin movements restore the *status quo ante* within a few hundredths of a second. The adaptation process ensures that the machinery of transduction is always poised where it is most effective: on the brink of channel opening.

Imagine that a hair bundle is somehow deflected toward its tall edge, perhaps by collision with an energetic water molecule, such that most of the channels snap open. The myosin molecules react by lowering the tip-link tension in an effort to restore the probability of channel opening to an equilibrium value of one-half. Before that point is reached, however, the closure of some channels triggers an avalanche in the opposite direction and most of the remaining channels snap shut as well. In response, the myosin molecules begin to ascend in a renewed effort to achieve equilibrium. But again they are thwarted, for as the rising tip-link tension opens some channels, the remainders stampede in the same direction. As the system jumps back and forth in a futile attempt to achieve equilibrium, the hair bundle oscillates from side to side. Mechanical recordings from hair bundles have demonstrated these spontaneous movements *in vitro*.<sup>5</sup>

A mechanical stimulus applied to an oscillatory hair bundle harnesses this activity. If the frequency of stimulation is significantly greater or less than that at which the hair bundle oscillates spontaneously, then the ensuing response is small. If the stimulus accords with the bundle's natural frequency of oscillation, however, the adaptation process can pump an increment of energy into each cycle of movement. Just as the motion of a child's swing gradually increases with each parental push, the response grows over a few cycles to a peak amplitude at least a hundred times larger than that of a passive system. In the extensively studied ear of the frog, active hair-bundle motility accounts quan-

titatively for the active process. Bundle motility contributes to the active process in mammals as well, but, as discussed below, in these animals it is supplemented by an additional mechanism.

Among the most striking and useful features of hearing is our ability to distinguish tones of different frequencies. Although a semitone, the narrowest interval on a piano, represents a frequency difference of about 6 percent, a trained listener can readily detect an interval of only 0.2 percent – in musical parlance, three cents, or hundredths of a semitone. Frequency discrimination is of obvious importance in the performance and appreciation of music. However, this faculty is also used continually in daily life in our recognition of sound sources and our interpretation of speech. The distinctions between various phonemes, or speech sounds, rest upon the frequencies present in each (Figure 2). To identify a speaker and, more particularly, to determine what she has said, the cochlea must somehow parse complex sounds into their constituent frequencies.

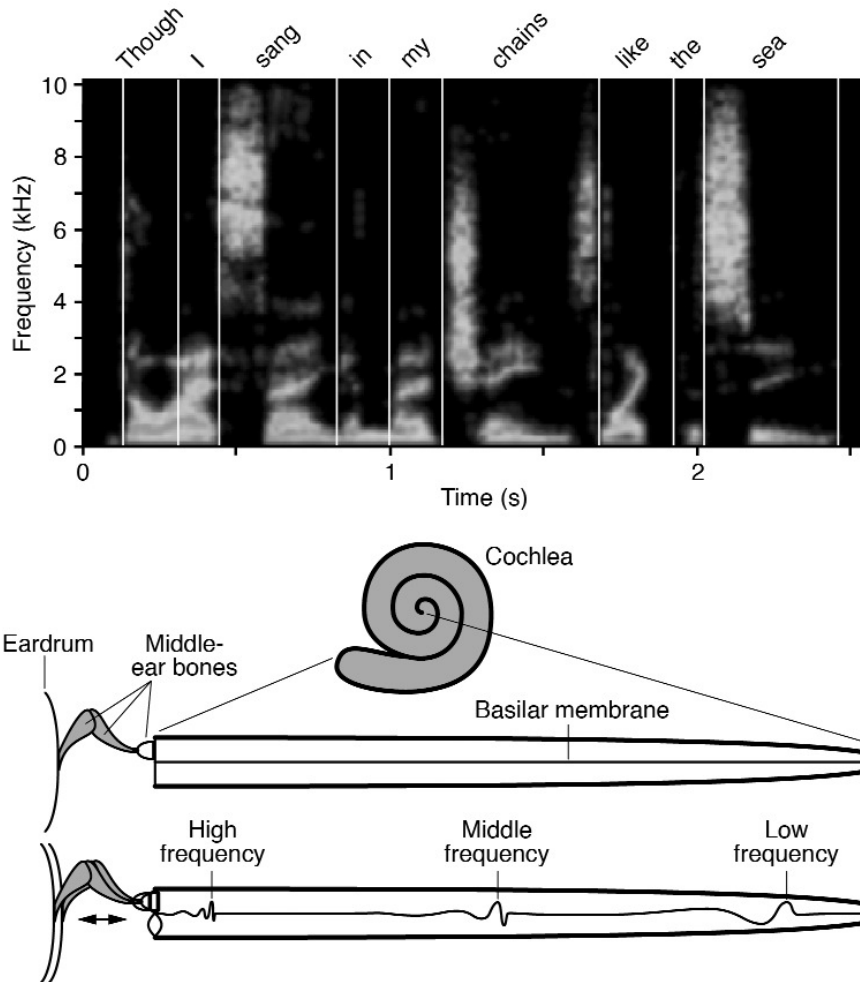
In 1863, German physician and physicist Hermann von Helmholtz first appreciated that the cochlea works like an inverse piano. A piano blends the sounds from several independent resonators – the oscillating strings – into a harmonious whole. The cochlea undoes this effort, separating from a complex sound the various pure tonal constituents. Every component is then analyzed independently so that the brain receives a description of each successive phoneme in terms of its constituent frequencies. From this information, the central nervous system can calculate what word was spoken while also abstracting such nuances as accent and emotional inflection.

How are the different components of a complex sound separated? This operation



Figure 2  
The Operation of the Mammalian Cochlea

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The sonogram in the upper panel analyzes my voice declaiming the final line of Dylan Thomas's poem "Fern Hill."<sup>6</sup> Time (in seconds) is represented on the horizontal axis and frequency (in thousands of cycles per second) on the vertical; loudness is signified by brightness. The prominent vowels in "though," "sang," "my," "chains," and "sea" involve multiple low frequencies – the formants – whereas the consonants are represented by high frequencies. When responding to speech such as this, the cochlea rapidly and continuously deconstructs phonemes into their constituent frequencies; the brain then uses the resultant information to infer what has been heard.

The schematic drawings in the lower panel show how the snail-shaped cochlea would look if unrolled: a long, bone-enclosed tube bisected by the elastic basilar membrane. Sound striking the eardrum sets it and the three tiny bones of the middle ear into oscillation, which is communicated to the liquid contents of the cochlea. Each frequency component of the sound elicits a traveling wave that propagates along the basilar membrane and peaks at a specific position corresponding to that frequency. By this means, the cochlea separates complex sounds into vibrations that stimulate certain of the sixteen thousand hair cells arrayed along the basilar membrane. Note that the vertical motion of the membrane has been exaggerated three hundred thousand-fold with respect to the cochlea's length. Source: Figure prepared by the author.



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is performed by the basilar membrane, one of the elastic boundaries of the cochlear chambers that are deflected by sound pressure. The basilar membrane extends about one and one-third inches along the cochlear spiral and varies continuously in its physical attributes. At the base of the cochlea the membrane is narrow, light, and taut; like the thinnest string on a violin, it oscillates at a high frequency. The basilar membrane at the cochlear apex, which like the coarsest string on a contrabass is broad, massive, and floppy, instead resonates upon stimulation at a low frequency. Each intermediate position is most responsive to stimulation at a specific frequency that grows incrementally from the apex, which responds to twenty vibrations per second, to the base, which is sensitive to twenty *thousand* cycles a second.

When a particular tone is sounded, the basilar membrane begins to vibrate at the same frequency. The membrane does not move as a unit, though; instead, the oscillation propagates from the base toward the apex as a traveling wave (Figure 2). The motion is small at the membrane's base but grows progressively larger as the wave approaches the place that responds to that specific frequency. There the wave achieves its peak amplitude before rapidly dissipating like a comber breaking upon a beach.

A complex sound engenders overlapping but largely independent traveling waves for each of its components. The position at which each wave peaks specifies its frequency; the magnitude of each peak indicates the wave's loudness. Arrayed in single file along the basilar membrane, four thousand receptors called inner hair cells detect these vibrations and produce electrical responses that are then conveyed to the brain by thirty thousand nerve fibers. The cochlea thus acts as a frequency analyzer, providing the central nervous system with a nearly instantaneous report of the tones present in any acoustic stimulus.

Because the basilar membrane oscillates within the liquids that fill the cochlear chambers, it too loses energy to viscosity. Research conducted during the past two decades has demonstrated how the active process counters this problem. In the mammalian cochlea, the active process is facilitated by twelve thousand outer hair cells that spiral along the basilar membrane in three parallel rows adjacent to the single row of inner hair cells. The outer hair cells transmit a negligible amount of information to the brain; instead, they serve as dedicated amplifiers that enhance the mechanical stimuli delivered to the inner hair cells. When sound displaces the basilar membrane, side-to-side movements of the tectorial membrane tweak the underlying hair bundles, exciting active hair-bundle motility like that of other hair cells. In addition, transduction of the mechanical input elicits in outer hair cells an electrical response that drives a unique phenomenon called *somatic motility*. When the cell's voltage becomes more negative, the millions of prestin molecules studding the membrane of each outer hair cell expand; a more positive voltage causes contraction. The entire cell consequently changes in length, respectively elongating or shortening like a tiny muscle. And like a muscular contraction, somatic motility delivers energy, accentuating the basilar membrane's vibrations. This activity constitutes an example of positive feedback in which sound-induced vibrations beget still larger oscillations. And in the active process, as in a public-address system, positive feedback can lead to instability.

For decades after the first proposal that the ear employs an active process, there was little evidence to support the hypothesis. This changed when careful measurements showed that, in a very quiet sound chamber, the ears of at least 70 percent of normal humans emit one or more tones. In other





words, the ear not only takes sound in, but also puts sound out! These spontaneous otoacoustic emissions are not pathological, but on the contrary are a hallmark of healthy ears whose hair cells are capable of exuberant activity.

As discussed above, the active process is an example of positive feedback. Moreover, like many man-made feedback systems, the active process exhibits gain control: it can be turned up or down as circumstances dictate. When amplification is unnecessary in a loud environment, the feedback largely vanishes and the ear is essentially passive. Under the conditions that prevail through most of daily life, corresponding to sound-pressure levels of approximately sixty decibels, amplification makes only a modest contribution to the ear's responsiveness. Near the threshold of hearing around zero decibels, however, we feel that we can hear a pin drop: indeed, our acoustic sensitivity is enhanced more than a hundredfold by the active process operating at its highest gain. An individual who lacks the active process as a consequence of hair-cell damage loses this amplification and therefore becomes hard of hearing.

What happens if the strength of feedback increases still further? The result is called a bifurcation: an abrupt, qualitative change in the behavior of the auditory apparatus. Just as slowly turning up a public-address system suddenly elicits a howling noise, the ear can reach the point at which some hair cells begin to oscillate spontaneously. The vibrations are transmitted back out of the cochlea, resulting in spontaneous otoacoustic emissions that can be measured in the ear canal. In rare cases, these sounds can be heard by nearby people, even at a distance of several inches. There can be no doubt in such instances that the cochlear amplifier is active, for the ear radiates energy into the surrounding air.

Spontaneous otoacoustic emissions are not the only unexpected emanations of a normal human ear. The instability in hair-cell transduction also generates combination tones, sounds that are heard and even emitted from ears though they are absent from acoustic stimuli. Suppose one listens to simultaneous, moderately loud sounds of two distinct but nearby pitches: a higher frequency  $f_2$  and a lower one  $f_1$ . In addition to these two tones, a normal listener then hears the prominent combination tone  $2f_1 - f_2$ , twice the lower frequency minus the higher. This tone is somewhat fainter than the two that are actually sounded, but is nevertheless loud enough to be perceived clearly. In fact, composers have created music in which no instrument actually plays the audible melody. Two streams of tones are played instead, and the listener's ear synthesizes the melody from the successive tone pairs. Composers György Ligeti and Karlheinz Stockhausen are among those who have experimented with this effect, which was first discovered in the eighteenth century by violinist and composer Giuseppe Tartini.<sup>7</sup>

Because combination tones originate from the instability of normally functioning hair bundles, they provide a useful assay for normal hearing. Most newborn children in the United States are now subjected to a simple test in which two tones are played into each ear while a sensitive microphone records the sounds in the ear canal. If the measured intensity of the combination tone exceeds a certain threshold, hearing in that ear is almost certainly normal. If the response is diminished, however, other tests can confirm whether a hearing defect is present and how it might be remedied.

**H**earing loss is a growing problem in a society characterized by increases in both lifespan and noise pollution. Although cell

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division continually replenishes most cells in the human body, a few critical types of cell – including hair cells in the ear as well as nerve cells in the brain and muscle cells in the heart – are unfortunately not replaced by this means. As we lose hair cells, we also forfeit the advantages afforded by the cochlea's active process. The ear's sensitivity thereby declines, rendering us hard of hearing. A diminished capacity to distinguish frequencies impairs our ability to recognize the subtle nuances of speech. And loss of the cochlea's compressive quality means that weak sounds become inaudibly soft and strong sounds offensively loud. It is for this reason that a hearing aid is so often unsatisfactory: the device intensifies the sounds reaching the ear but cannot restore the normal sharpness and dynamic range of hearing.

American Sign Language (ASL) provides one successful means of communication for the hearing-impaired. Used by half a million people in the United States and Canada, this form of signing represents a highly evolved language quite distinct from spoken English. Regional derivatives of ASL and other distinctive sign languages are used throughout the world. During the last few decades, the deaf have also benefitted from the introduction and evolution of the cochlear prosthesis. Surgically implanted into a damaged ear, this array of electrodes restores a degree of hearing by directly stimulating the nerve fibers that run from the cochlea into the brain. A receiver worn outside the head replaces the lost hair cells by deconstructing sounds into their component frequencies and sending electrical signals to the corresponding electrodes. As the most successful neural prosthesis to date, with nearly three hundred thousand users worldwide, the cochlear implant has raised hopes for progress with future electrode systems that might be used to restore vision or overcome spinal injuries.

The most enticing avenue for a long-term solution to deafness is through the regeneration of hair cells. Although fishes, amphibians, and reptiles (including birds) can readily replace these receptors, mammals for unknown reasons cannot. Numerous researchers are now attacking this problem, trying to understand how regeneration naturally occurs and why it is deficient in mammals. Although the pace of research is painfully slow for those with impaired hearing, recent results are encouraging. Various treatments have created mammalian hair cells *in vitro* and even in the damaged ears of animals, and investigators have begun to identify the molecular signals that underlie the decision of precursor cells in the ear to multiply and assume the role of hair cells.

The active process provides a striking example of the opportunistic nature of evolution. The direct mechanical gating of transduction channels – the simplest mechanism that might be envisioned – inevitably inflicts the distortion responsible for combination tones. This mode of action additionally imposes mechanical instability on the hair bundle. Despite these flaws, direct channel gating has apparently persisted by virtue of its great speed. The necessity of maintaining the transduction machinery within its narrow working range likely supported the evolution of adaptation. This process too has been implemented in a simple manner, through the activity of a common form of myosin, the workhorse of force production in cells. Yet most remarkably, combining the phenomena of direct transduction and adaptation has yielded the fundamental features of the active process: a tuned amplifier with a broad dynamic range, the foundation of our extraordinary hearing.





## ENDNOTES

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