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How well do we understand the cochlea?

Renato Nobili, Fabio Mammano and Jonathan Ashmore

As sensory cells, hair cells within the mammalian inner ear convert sounds into receptor potentials when their projecting stereocilia are deflected. The organ of Corti of the cochlea contains two types of hair cell, inner and outer hair cells, which differ in function. It has been appreciated for over two decades that although inner hair cells act as the primary receptor cell for the auditory system, the outer hair cells can also act as motor cells. Outer hair cells respond to variation in potential, and change length at rates unequalled by other motile cells. The forces generated by outer hair cells are capable of altering the delicate mechanics of the cochlear partition, increasing hearing sensitivity and frequency selectivity. The discovery of such hair-cell motility has modified the view of the cochlea as a simple frequency analyser into one where it is an active non-linear filter that allows only the prominent features of acoustic signals to be transmitted to the acoustic nerve by the inner hair cells. In this view, such frequency selectivity arises through the suppression of adjacent frequencies, a mechanical effect equivalent to lateral inhibition in neural structures. These processes are explained by the interplay between the hydrodynamic interactions among different parts of the cochlear partition and the effective non-linear behaviour of the cell motor.

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COMPARED WITH THE visual system, advances in the understanding of the auditory system have been slower. One reason is that experimental access to the inner workings of the cochlea is difficult, and a review published only a few years ago[1] stressed the open questions still surrounding hearing. In this article we aim to show that, by integrating physical principles with novel information on sensory receptor function, a multidisciplinary research effort has substantially improved our view of cochlear mechanics, although many questions remain unresolved.

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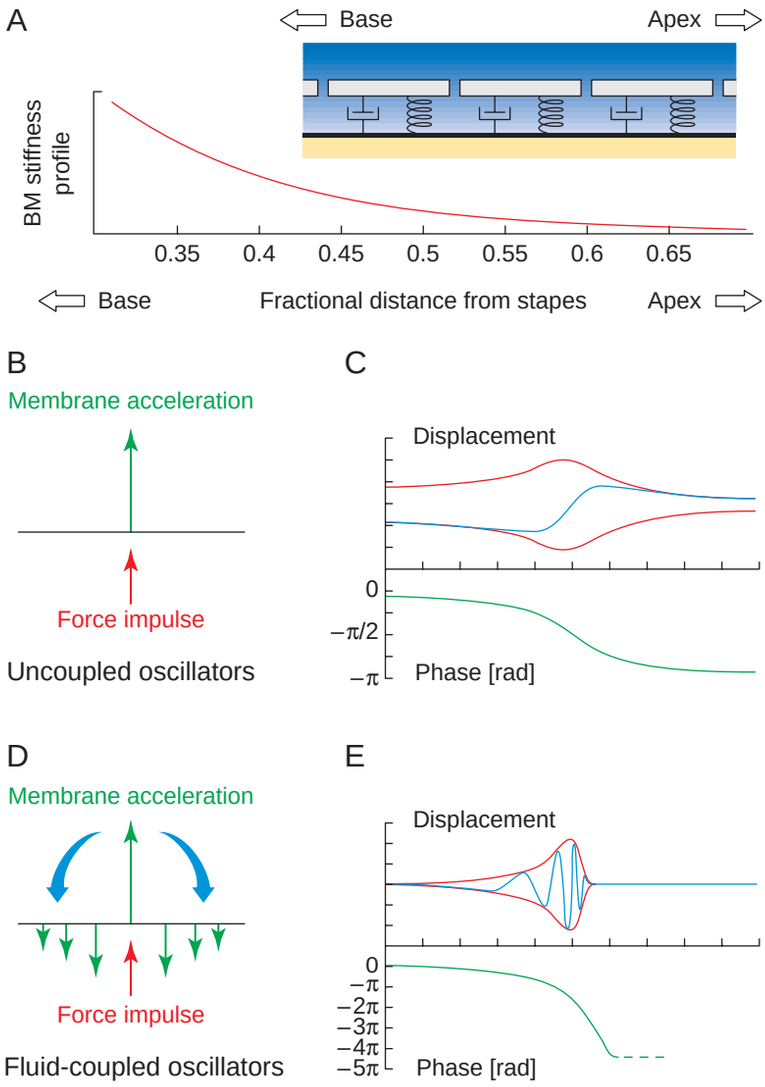
Box 1. Travelling wave generation



The basilar membrane of the mammalian cochlea is an elastic strip tensioned across the fluid-filled cochlear duct[a,b]. The membrane, whose different portions interact through the fluid[c,d], is the supporting medium for 'travelling waves' that form when sound is transmitted through the middle ear. For the sake of physical clarity, the basilar membrane can be conveniently pictured as a bank of spring-mounted micro-pistons (modules) immersed in an inviscid fluid (Fig. A, inset). Each piston's stiffness is an exponentially decreasing function of the distance from the stapes[e] (Fig. A).

To explain the formation of travelling waves, as described by von Békésy[f], how such an array of modular oscillators interact instantly with each other through the fluid must be analysed. The instantaneous character of the fluid-mediated coupling amongst the modules is a consequence of the negligible delay (about 10 μs) when the pressure field propagates within the cochlear duct compared with the basilar-membrane oscillation periods (typically ranging from 50 ms to 50 μs). As can be inferred from direct observation of basilar membrane motion[g,h], in normal acoustic conditions the minimum wave length of the travelling wave spans five to ten modules. For the mathematics it is therefore more satisfactory to treat the micro-piston system as a continuum.

In the absence of fluid coupling, a local-force impulse would produce an instantaneous membrane acceleration proportional to the force, with the proportionality factor being the inverse local mass (Fig. B). Correspondingly, under the action of a sinusoidal force synchronously acting over the whole membrane, the response would be a typical resonance profile (Fig. C), with 180° phase difference on opposite sides of the resonance point. This 'dry cochlea' model was originally proposed by Helmholtz[i] and influenced cochlear physiology for over a century.

Hydrodynamic coupling alters substantially this acceleration pattern. The instantaneous membrane acceleration elicited by a local-force impulse applied to the membrane at rest (as above) displays the profile in Fig. D. Fluid pressure spreads instantaneously from the force application site and pushes adjacent membrane segments in the direction opposite to the force impulse (curved blue arrows). Thus, in general, any local basilar membrane oscillation generates forces that tend to drive flanking modules to swing with opposite phases. However, due to the exponentially graded membrane stiffness, the effect is different at opposite sides, the response being smaller at the stiffer (more basal) side, so that the semi wavelength of the oscillation decreases from base to apex (Fig. E). Under the action of a sinusoidal input at the stapes, this dynamic effect results in a monotonically increasing phase delay of the local oscillations versus distance from stapes. This asymmetry bears important consequences on wave dynamics as the 'apparent mass' of the fluid locally involved in the oscillation decreases from base to apex far more rapidly than all other graded quantities, resulting in the characteristic shrinking of the travelling wavelength at a frequency-dependent critical point. The wave amplitude profile tends to elevate markedly in the proximity of this point, beyond which the membrane motion, as well as that of the fluid, undergoes a steep fall. The peak height of the travelling wave would increase without limit if the intrinsic viscosity fell to zero[d].

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Cochlear models

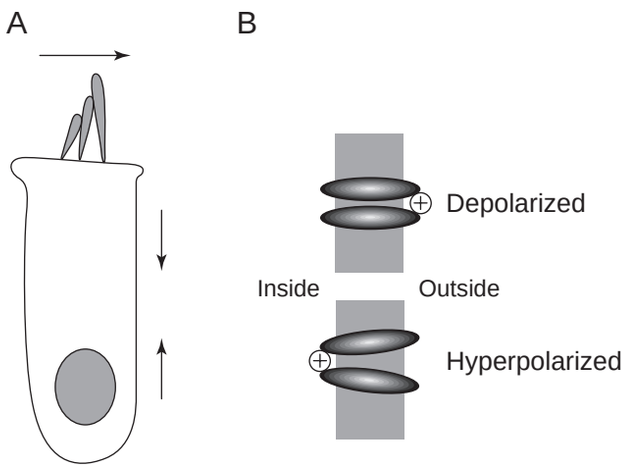
The mammalian auditory system can rapidly detect and track the time-varying features of sound sources, notably those of biological significance, over a wide range of frequencies and amplitudes[2]. Interfacing the world of mechanical vibrations with nerve signal transmission, the cochlea differs appreciably from a typical Fourier analyser, the cochlea model proposed by Helmholtz over one century ago[3]. Helmholtz proposed that the cochlea consisted of a set of uncoupled filters, ordered in frequency like the strings of a piano, each receiving the same input and connected to a nerve fibre. The filter was structured from the basilar membrane, which he represented as a dense set of elastic fibres tensioned across the fluid-filled cochlear duct with fibre stiffness decreasing exponentially along the coiled axis of the cochlea. With this arrangement, it was thought that the basilar membrane could

Box 2. Hair cells and molecular motors

Figure A shows the schematic outer hair cell (OHC). Displacement of the stereocilia towards the tallest produces a cell depolarization[a,b] as the current flows in through the mechanoelectric transducer channels[c]. In the cochlea, mechanical input to the stereocilia is provided by the overlying tectorial membrane[d] (not shown). The OHC responds by changing length (vertical arrows)[e–g]. The shortening is reversible[h].

OHCs exhibit a voltage-dependent capacitance[i–l] or equivalently a 'gating charge' movement that can be measured by rapidly changing the cell potential. The resulting transient current is closely related to the motor function of the cell[k] as pharmacological manipulations capable of blocking the current also suppress cell motility[j,m,n]. Both the amplitude and the kinetics of the transients depend upon the size of the voltage step. For a typical pipette access resistance of 10 MΩ, the transients peak in 0.7–0.5 ms and relax in 0.8–0.4 ms over the range of –50 to +30 mV, being approximately 1.5 times faster at the offset. Integration of the current yields a maximum charge transfer, Q_{max}, of about 2 pC or equivalently about 10^7 single motor molecules in a cell 50 μm long.

Ultrastructural analysis of OHC lateral plasma membrane indicates that electromotility might be based upon conformational changes of a dense array of integral membrane proteins[o]. The simplest models suggest that the transient is due to a single charge being displaced across the membrane associated with a conformational change of the motor molecule. Changes in membrane potential might act as the driving force for the re-arrangement of the proteins in the plane of the membrane, possibly involving the movement of a cation into a deep access pore[p] (in analogy to that found in Na^+/K^+ ATPases). Both the rate of change of the motor and the absence of ionic-current flow indicate that the motor is not an ion channel. Figure B shows a cartoon of the membrane protein structure and illustrates how charge and conformation are associated[q]. The molecular identity of the motor is not known.



The force exerted by the cell length change[r] is the derivative of the membrane free energy with respect to elongation from a charge neutral potential of V_o = –20 mV. In view of the above-mentioned reversibility[s], the energy variation associated with the largest length change (about 4% of the total cell length[h]) is approximately $\Delta E = Q_{max} V_o$ = 2pC × 20 mV = 0.04 pJ. Recent experiments show that the loading-releasing of the non-linear charge fraction starts to roll off at a cycling rate of around 25 kHz (Ref. p), so the maximum power delivered by a single OHC is a fraction of 1 nW, depending on the motor efficiency. Were the efficiency 1, taking 4×10^{-15} kg for the cell mass, the power output would be 250 kW/kg! This number should be compared with about 0.4 kW/Kg for a typical motorcar engine and about 0.25 kW/Kg for an electric engine.

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organize incoming sounds into a pattern of activity in the auditory nerve.

Fluid interactions were completely overlooked by Helmholtz. As demonstrated later by von Békésy[4], the basilar membrane supports 'travelling waves' that form under the action of the fluid-pressure field transmitted by the stapes in the middle ear to the high-frequency end of the cochlea. Von Békésy's discovery that the basilar membrane responded to pure tones by peaking at frequency-dependent locations established a mechanical map that associated a 'characteristic frequency' with each site along the cochlea. In more refined models aimed at explaining von Békésy's observations, each filter was coupled to its adjacent neighbours to form a sort of transmission line[5]. Thus, sound entering at the high-frequency end propagated along the filter-bank, and the neural response was thought to represent the oscillation pattern associated with frequency-dependent waves travelling on the basilar membrane.

It is now clear that the dynamics of the cochlea are yet more subtle. Cochlear models must include the finding that instantaneous hydrodynamic coupling among different basilar membrane portions has a long-range character that is only approximately represented by nearest-neighbour transmission-line interactions (Box 1). Models must also account for the observation that frequency selectivity depends on the extent to which the active processes of the cochlea influence basilar-membrane dynamics (Box 2) and is much broader for sounds of normal loudness than for low-level sounds[6–9].

The traditional view of the cochlea as a spectral analyser thus needs to be modified to include those non-linear properties that allow only the perceptually relevant features of sound to be transmitted. Once the frequency selection by the cochlea has been carried out, the information is encoded directly in the firing rates in the auditory nerve fibres and the intervals between peaks of neural activity[10] (Box 3).

Box 3. Step by step through the mathematics of cochlear modelling

The elementary differential equation governing the elongation x of a harmonic oscillator under the action of an external force $f(t)$ is:

$$m\frac{d^2x}{dt^2}+h\frac{dx}{dt}+kx=f(t),$$

where m is the oscillator mass, h its viscosity and k its stiffness. The filter bank equation is a simple generalization of the above equation to a set of N oscillators:

$$m_i\frac{d^2x_i}{dt^2}+h_i\frac{dx_i}{dt}+k_ix_i=f_i(t),$$

where $i = 1, \ldots, N$. All quantities depend on oscillator index i in such a way that the corresponding set of proper frequencies and frequency resolutions take suitable values. In Helmholtz's model, $f_i(t)$ is the force generated by the negative acceleration $a_s(t)$ of the stapes and transmitted by the cochlear fluid to oscillator i. These forces can be written as:

$$f_i(t) = -G_ia_s(t),$$

where G_i are suitable positive constants. This equation set represents the filter bank model of cochlea. It can only be an approximation because three important force terms have been neglected on the right hand side of this equation:

(1) The hydrodynamic term:

$$-\sum_{j=1}^{N}G_i^j\frac{d^2x_j}{dt^2},$$

representing the force caused by the negative acceleration of oscillator j and transmitted to oscillator i by the fluid pressure field. The fluid coupling is represented by positive coefficients G_i^j.

(2) The shear viscosity term:

$$s_i^+\left(\frac{dx_{i+1}}{dt}-\frac{dx_i}{dt}\right)+s_i^-\left(\frac{dx_{i-1}}{dt}-\frac{dx_i}{dt}\right)$$

representing the viscous forces acting on oscillator i caused by possible different velocities of its adjacent partners, s_i^+ and s_i^- are the viscosity coefficients at the two sides. Shear viscosity depresses wave amplitudes at the short wavelength portions of the collective oscillation pattern.

(3) The force term to oppose damping (i.e to produce 'undamping'):

$$-U_i(y_i),$$

representing the forces generated by the outer hair-cell motors when the stereocilia undergo displacements y_i. This force term vanishes at $y_i = 0$ and has a sigmoidal shape to account for the saturation properties of the cochlear amplifier.

Putting all the components together, and assuming $s_i^+ = s_i^- = s_i$ for simplicity, the motion equation of the cochlea can be written as:

$$\sum_{j=1}^{N}\left(G_i^j+m_i\delta_j^i\right)\frac{d^2x_i}{dt^2}+h_i\frac{dx_i}{dt}+U_i(y_i)+$$
$$s_i\left(2\frac{dx_i}{dt}-\frac{dx_{i-1}}{dt}-\frac{dx_{i+1}}{dt}\right)+k_ix=-G_ia_s(t)$$

where the Kronecker delta $\delta_j^i = 1$ for $I = j$ and $= 0$ otherwise.

The effect of the tectorial membrane can be modelled through the dynamical coupling of the set y_i of stereocilia displacements, to the acceleration of x_i. Although scarcely coupled, the tectorial membrane behaves approximately like a second array of damped oscillators resonating at frequencies close to the characteristic frequencies of the primary oscillators, whose degree of freedom is described by x_i.

The equations of motion of the second oscillator set have the form:

$$\bar{m}_i\frac{d^2y_i}{dt^2}+\bar{h}_i\frac{dy_i}{dt}+\bar{k}_iy_i=-C_i\frac{d^2x_i}{dt^2}$$

for $i = 1, \ldots, N$ where $\bar{m}_i$, $\bar{h}_i$, $\bar{k}_i$, C_i represent mass, damping, stiffness and coupling constants, respectively. Shear viscosity between adjacent oscillators can be neglected. At resonance, the first and third terms at the left hand side of the above equations cancel leaving after time integration:

$$y_i=-\frac{C_i}{\bar{h}_i}\frac{dx_i}{dt}.$$

Therefore, the outer hair-cell force terms $U_i(y_i)$, in the linear approximation, behave like negative viscosity terms and undamp cochlear motion.

Active mechanics

For each input frequency, the amplitude of the basilar membrane vibration at the characteristic frequency does not increase linearly with intensity (as would be expected for a simple passive system) but shows signs of saturating, even within the physiological input range of 30–90 dB sound pressure level (SPL)[1] (for comparison, the lowest threshold for hearing is 0 dB SPL and normal speech is typically at a level of 40–70 dB SPL). This phenomenon, referred to as 'compressive nonlinearity', arises because there are energy-dependent processes operating within the cochlea[11] that neutralize viscous damping over a limited range of input sound levels by positive mechanical feedback[12] (Fig. 1).

The cellular basis of such active processes is now thought to depend on the correct operation of outer hair cells of the organ of Corti. This structure is highly organized and rides on the basilar membrane. The organ of Corti also includes an acellular structure, the tectorial membrane[13], that lies above the reticular lamina (the top surface)[14]. The tectorial membrane is attached to the tallest stereocilia of the outer hair cells (Fig. 2A). The organ of Corti contains two types of sensory cells, inner hair cells and outer hair cells (OHCs) (about 15 000 cells in the human cochlea). Both types of hair cell convert the displacement of their stereocilia[15], caused by the relative motion of the reticular lamina and the tectorial membrane, into transducer current[16] that produces a modulation of the cell receptor potential[17]. There is considerable evidence that inner hair cells are the sensory cells of the cochlea because they synapse directly on to the auditory nerve. OHCs are motile and can convert membrane potential into a force.

The molecular basis for OHC motility is a fast motor[18,19], located within the cell plasma membrane, whose mechanism (Box 2) differs substantially from those operating in other motile cells: it is independent of ATP hydrolysis, extremely fast and able to generate forces at frequencies above 20 kHz under the direct control of the cell transmembrane potential[20,21]. Both the rate of change of the motor and the absence of ionic-current flow indicate that the motor is not an ion channel, but its molecular identity is not known.

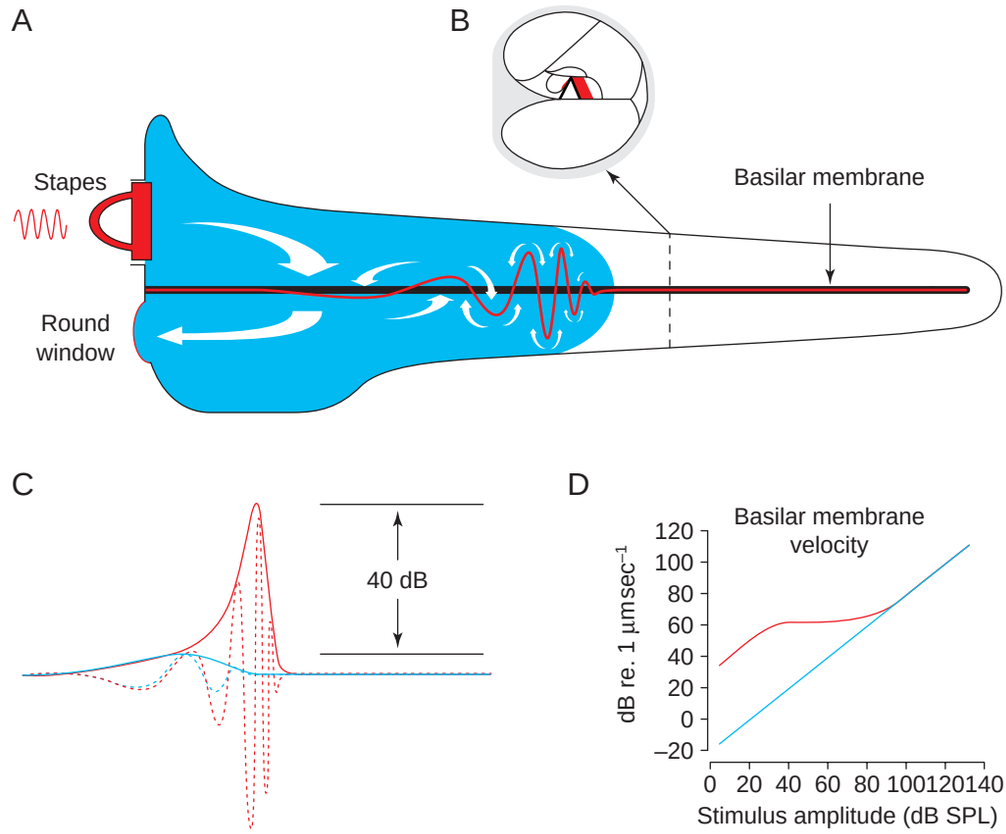

Fig. 1. ***Travelling waves on the basilar membrane of the cochlea.*** **(A)** *A longitudinal section of the uncoiled cochlea is represented with vertical dimension expanded by about three times. A travelling wave elicited by a 3 kHz tone is shown as a red line displacing the basilar membrane (unbroken black line) from its resting position (the wave amplitude has been magnified about 10^6 times for clarity). Arrows around wave peaks indicate the direction of local fluid flow. The fluid mass affects the dynamics of the basilar membrane, loading its different parts by amounts that depend upon the local wave length. Notice the progressive shortening of the wave length up to a critical point beyond which both the basilar membrane and the fluid remain at rest.* **(B)** *Cross-section of the cochlear duct, showing that the basilar membrane is laterally clamped across the duct and supports the organ of Corti that hosts two types of sensory hair cells: inner hair cells, that transmit signals to the acoustic nerve, and outer hair cells (OHC), that provide mechanical amplification to the basilar membrane motion.* **(C)** *Two travelling waves, produced by a low-level input, are shown for different amplification levels (broken lines). Solid lines are wave-amplitude envelopes.* **(D)** *Basilar membrane velocity (in dB relative to 1 μm sec^{-1}) versus input sound pressure level (in dB SPL) at fixed input characteristic frequency for the same two amplification levels as in* (C). *When the OHCs function properly (red line), the basilar membrane motion at low-input levels (below 20 dB SPL) is linear but greatly enhanced (40–60 dB) compared with the passive case (blue line). At higher input levels transducer currents saturate, limiting the undamping action provided by OHCs, and producing a compressive non-linearity in the basilar membrane response between 30 and 90 dB SPL. Above 90 dB SPL OHC forces are negligible compared with the intrinsic viscous forces and the response approaches the linear, passive case.*

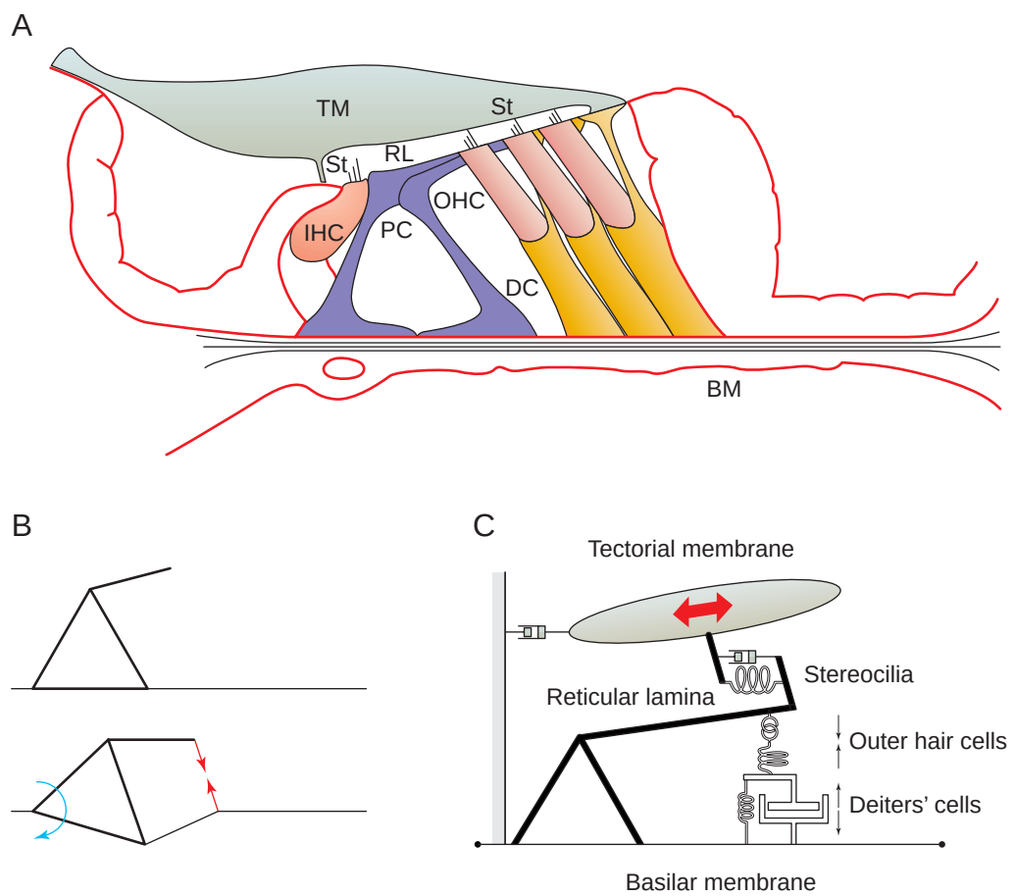

Fig. 2. ***Organ of Corti mechanics.*** **(A)** *The basilar membrane (BM) supports a rigid structure formed by the pillar cells (PC) and the reticular lamina (RL). One inner hair cell (IHC) sits at the left of the pillars with its stereocilia (St) close to, but not inserted in, the overlying tectorial membrane. A triplet of outer hair cells (OHCs), firmly anchored at their apex within the reticular lamina and cupped by Deiters' cells (DC), have their tallest stereocilia inserted in the tectorial membrane (TM). Deiters' cells provide visco-elastic coupling between the motile OHCs and the elastic basilar membrane.* **(B)** *The organ of Corti distorts under hair-cell contraction: the lever effect associated with cell-length change forces the arch structure formed by PCs to pivot around the inner attachment of the basilar membrane. The outermost basilar membrane segment keeps almost at rest.* **(C)** *Functional representation of the organ of Corti with the OHCs represented as a displacement generator and the visco-elastic components added as shown. The tectorial membrane is coupled visco-elastically to the reticular lamina through the cell stereocilia and the interposed fluid layer. Viscosity plays an important role in organ of Corti dynamics: the viscosity of the organ of Corti itself acts as a mechanical high-pass filter that compensates for the electrical low-pass filtering of the OHC receptor potential. An analogous compensation for the IHC capacitance might be provided by the high-pass filtering properties of the coupling between the stereocilia and the tectorial membrane.*

Changes in membrane potential might act as the driving force for the re-arrangement of molecular motors in the plane of the membrane. The axial stiffness of the cell (3×10^{-3} N m^{-1}) depends primarily on the structure of the plasma membrane, which contains a high density of membrane proteins and is much stiffer than, for instance, the membrane of red blood cells (1×10^{-5} N m^{-1})[22]. Cell deformation is funnelled along the longitudinal axis of the cell by the cortical cytoskeleton, a highly orthotropic structure that lines the inner surface of the plasma membrane[23]. Cell membrane stiffness must account for a considerable fraction of the total axial stiffness, otherwise most of the energy associated with the motor protein conformational change would be stored as plasma membrane internal energy and the cell would not undergo appreciable resting-length changes[22]. These mechanical properties make OHCs work like springs of variable resting length. The axial stiffness of the cell determines how much force they can deliver and how the forces are matched to the visco-elastic properties of the organ of Corti in which they are embedded.

Another class of cell within the organ of Corti appears to be important in estimating the contribution of OHC to cochlear mechanics. Deiters' cells surround the OHC at their basal ends and make contact with the basilar membrane while the apical end of the hair cell, the cuticular plate, appears to be held firmly within the reticular lamina (Fig. 2A). Cell motility, which produces forces along the OHC length, contributes to a tight, mechanical feedback loop capable of distorting the organ of Corti and altering basilar membrane dynamics[24]; however, the compliance of the Deiters' cells determines how OHC forces are distributed to the basilar membrane.

A contentious issue surrounding this proposed mechanism arises because the OHC transducer current is shunted by the cell membrane capacitance, producing, at high frequencies, a severe attenuation of the potential drive for the OHC motor[25]. This low-pass filtering of the receptor potential would be expected to produce a fall-off with frequency of the cell motile response, while at the same time it would be expected that the internal viscous forces would increase with frequency[1]. How, then, can OHCs be responsible for undamping a range of frequencies extending up to tens of kHz? Several attempts to solve this problem have been proposed and it currently seems likely that, despite electrical capacitative shunts, the potential across the basolateral membrane of the OHCs might be sufficient to drive motility in the intact cochlea[20,26–28]. The question can also be addressed on a purely mechanical basis by considering the functional aspects of the organ of Corti.

Cochlear micromechanics

Understanding how the organ of Corti reacts to cellular forces is central to cochlear micromechanics. One simple scheme is that, during OHC contraction, the organ of Corti would distort as shown in Fig. 2B (Ref. 29). This hypothesis is consistent with experiments[24,30] that also show that the coupling between the basilar membrane and the reticular lamina, provided by OHCs in series with Deiters' cells, is dominated by the viscosity of the Deiters' cells (Fig. 2C). Such viscous coupling makes the force applied to the basilar membrane by the OHCs increase with frequency, whereas the attenuation of the receptor potential with frequency operates to cancel this effect. Cancellation can ensure that any residual frequency dependence of the OHC force is determined by the stimulus applied to the stereocilia and suggests that the tectorial membrane might control the receptor potential generation in a crucial manner.

There is little experimental information about tectorial-membrane dynamics. However, some of its properties can be inferred semi-quantitatively if we assume that it has the properties of a collagen gel: for oscillatory motion, at the characteristic frequency, the coherence length (that is, the distance over which a transversal section of the membrane will appear to move as a single structure) is about 120 μm at the base and 1.2 mm at the apex of the cochlea. Both these figures are in excess of the corresponding tectorial membrane thickness, implying that it oscillates like a solid mass attached to the top of the OHC stereocilia bundles. These considerations support the suggestion made nearly 20 years ago[31–33] that the tectorial membrane resonates and contributes to the magnitude of the displacement applied to the tips of the stereocilia of both OHCs and inner hair cells.

Accordingly, let us assume that various portions of the tectorial membrane behave as a secondary system of oscillators affected by appreciable damping, with resonance frequencies close to the characteristic frequency all along the basilar membrane length. With this hypothesis, a straightforward computation shows that, at resonance (that is, near the characteristic frequency), tectorial-membrane radial displacement, and therefore stereocilia deflection, is proportional to basilar membrane velocity. Also, because viscous force, which affects the motion of the cochlear partition is proportional to velocity, but with opposite sign, it produces undamping[34], neutralizing viscous losses in the range of relatively small oscillations (up to about 10 nm)[12]. At larger amplitudes the transducer current saturates[35], undamping is overcome by viscous losses and the basilar-membrane response approaches that of a passive cochlea. The transition between the two different damping levels makes the basilar membrane input/output function highly non-linear[6] (Fig. 1D). It is noteworthy that, for speech sounds of normal intensity, the cochlea works across the transition reason between two different regimes.

Non-linearity

If the cochlea operated linearly, it would perform like a bank of linear filters which separated the Fourier components in a sound, and travelling waves would be equivalent to linear combinations of harmonic oscillation modes as in Helmholtz's model. Mechanical non-linearity breaks down this equivalence, producing effects that are important for acoustic-signal processing at normal loudness levels. Ironically, discovery of the active processes shifted researchers' attention towards the sharp profiles of threshold-tuning curves[7], which reflect the behaviour of the cochlea in the linear undamped regime, erroneously emphasizing the idea of the cochlea as a bank of narrow-band filters. If the responses to synthesized speech-like sounds in large populations of cat auditory fibres are analysed in the time domain, the patterning suggests that groups of fibres respond similarly, even though their characteristic frequencies might differ by

nearly an octave[10]. This segregation suggests that the effective bandwidths of cochlear filters are much wider than the narrow tuning curves found in mechanical and neural measures based upon iso-response increments at detection threshold. To account for the observed neural responses, basilar-membrane vibration must segment into a set of regions, each coherently oscillating at a prevailing frequency (although with a progressive phase lag of the oscillation towards a maximum of a few cycles towards the apex).

To filter the perceptually relevant features of sound, the cochlea exploits the saturation property of the OHC amplifier, which produces two main effects: equalization of the response and tone-on-tone suppression. Equalization makes the perception of sufficiently different sound frequency-components largely independent of their intensity. Suppression of one tone by an adjacent one produces an effect equivalent, at a mechanical level, to lateral inhibition typical of neuronal structures[36–41]. This effect is probably the main cause of the psycho-acoustic phenomenon of frequency masking. Thus, frequency selectivity is achieved, not only by a decomposition of the incoming sound by the pattern of travelling waves on the basilar membrane, but relies on further effects that apply especially to complex patterns of sound input. These results support the qualitative conclusion that cochlear filters are effectively wide-band, even if, almost paradoxically, each filter selects only one frequency in output. Such considerations bear significant consequences for improved designs of cochlear implants and hearing aids.

Otoacoustic emissions

Otoacoustic emissions are low-level sounds of cochlear origin that can be recorded from the external auditory canal either spontaneously or in response to sound stimuli[42]. Emissions can also be detected when electric current is applied to the cochlea[43,44]. The observation that otoacoustic emissions are band-pass filtered sounds with a centre frequency related to the place of generation within the cochlea[45] has strengthened the belief that they reflect the active processes taking place in the cochlear partition. However, there are still unanswered questions about the precise mode of generation.

Transmission-line models of elicited otoacoustic emissions explain the striking periodicity in their frequency spectra as originating through the reflection of forward-travelling waves by corresponding spatial irregularities in the mechanics of the cochlea[46]. More recently, other reflection mechanisms have been proposed, suggesting that evoked emissions originate from scattering in nonuniform, disordered media[47]. However, the product of forward and reverse gain of the middle ear has a pronounced maximum in the 1–2 kHz region, which is close to the frequency dependence of click-elicited and distortion-product otoacoustic emissions[48]. This suggests that the characteristics of the middle ear dominate the spectrum of ear-canal emission[49].

Feedback control

The mechanical feedback loop provided by the OHC must be finely regulated to guarantee optimal functioning of the cochlear amplifier and its maintenance at the threshold of spontaneous oscillations[29]. The problem of simultaneously regulating the response to both transient and tonic stimuli poses a serious challenge to the regulatory mechanisms. A minimum requirement is the control of the operating point and gain of the motor through a direct action of nerve efferents.

Outer hair cells of the cochlea are the target of a centrifugal efferent system that projects from the superior olivary complex[50,51]. Activation of this pathway suppresses afferent sound-elicited activity of the auditory nerve by the release of ACh (Ref. 52) on two time scales: a rapid action (tens of milliseconds) is responsible for modulating nerve responses to transient acoustic stimulation, whereas a slower action (tens of seconds) is thought to protect the ear from acoustic overstimulation[53]. Whole cell patch-clamp recordings from isolated OHCs of the mammalian cochlea provide functional evidence for a cholinergic efferent synapse[54–57]. The action of ACh is mediated by a novel ACh receptor[58,59], and *in vivo* ACh infusion through the cochlea can elevate thresholds for basilar membrane displacements[60]. There are also documented effects of ACh on cell axial stiffness[61] that indicate that the inhibitory influence of ACh on basilar membrane motion *in vivo* could be explained as OHC axial stiffness determining the amount of force that can be applied on the basilar membrane[62].

Forward transduction is a second sensitive target for control mechanisms[63]. OHCs possess ATP-gated ion channels[64] that have been found on the apical surface of the cells, within the endolymphatic fluid compartment of the cochlea, and possibly on stereocilia themselves[65,66]. ATP is present at a low nanomolar concentration in the endolymph, even under quiescent conditions[67]. Changes in ambient ATP levels might significantly alter receptor potentials (hence OHC motile responses), because ATP-gated channels are capable of shunting transducer current[68], which flows down the stereocilia when the mechanotransducer channels are activated[69]. Possible stores that could release ATP have been identified in the marginal cells of the stria vascularis[70], but the precise link between hair cell activity and ATP concentration in the endolymphatic compartment remains to be identified clearly. A final regulatory mechanism might involve Ca^{2+} in the endolymphatic compartment. Ca^{2+} plays an important role in regulating mechano-transduction[71] and it therefore seems highly likely that Ca^{2+} homeostasis in the fluid surrounding the transduction machinery in the stereocilia would regulate the sensitivity of mechanical transduction[72].

Cochlear evolution

Mammalian hearing has evolved to use frequencies above one kHz to improve detection and communication in noisy environments and to improve the ability to localize discrete sound sources. To do so it has exploited cellular mechanics rather than a purely electrical or neural mechanism to enhance the extraction of frequency information. There are, however, other designs for auditory organs that do not employ active mechanics using OHC analogues. Many lower vertebrates, for example, use hair cells where each behaves like a tuned filter so that the same mechanical stimulus is delivered to each hair cell, but the receptor cell itself extracts frequency information.

Box 4. Web sites

There are a rapidly increasing number of world wide web sites devoted to cochlear processing. Some of these are sites that provide graphics and further explanation of the topics covered in this article. Of note are

http://www.aro.org/
(Association for Research in Otolaryngology site)

http://www.bp.sissa.it/cochlea/
[Author's site, hosts downloadable Video for Windows (AVI) movies illustrating the motion of travelling waves and organ of Corti]

http://www.boystown.org/cel/cochmech.html
(Stephen Neely's original models for the cochlear partition)

http://kuni.nidcd.nih.gov/
(Kuni Iwasa's site, providing information on several aspects of outer hair cell function)

http://www.allhear.com/index.htm
(House Ear Clinic in Los Angeles, providing clinical information)

http://www.bme.jhu.edu/~tratnana/ears.html
(part of the Johns Hopkins Medical School site emphasizing biomedical engineering)

http://www.cochlea.com/
(a site devoted to clinical otology)

http://www.ears.com/quinn/auditory_physiology.html
(a check sheet for physicians with basic facts about the cochlea)

This design, particularly where the hair cell uses electrical tuning, has been described extensively in reptiles and in amphibia. In acoustic specialists such as bats and cetaceans, the demands of echolocation have evolved cochleas that can detect incoming sound in some species at frequencies above 100 kHz (Ref. 73). All present information suggests that such cochleas use modified design principles to measure sound frequencies over a limited range of frequencies in the high kilohertz range (Box 4). Indeed, mammalian cochlear designs such as our own, which balance a frequency range of between six and nine octaves coupled with an upper limit of approximately 20–40 kHz, appear to have evolved the system of mechano-electrical feedback to prefilter sounds that we describe here.

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Pro-epileptic changes in synaptic function can be accompanied by pro-epileptic changes in neuronal excitability

Howard V. Wheal, Christophe Bernard, John E. Chad and Robert C. Cannon

Repetitive sensory input, stroboscopic lights or repeated sounds can induce epileptic seizures in susceptible individuals. In order to understand the process we have to consider multiple factors. The output of a set of neurones is determined by the amount of excitatory synaptic input, the degree of positive feedback and their inherent electrical excitability, which can be modified by synaptic inhibition. Recent research has shown that it is possible to separate these phenomena, and that they do not always behave in unison.

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EPILEPTIC SEIZURES result from multiple, synchronous discharges from a population of neurones. Temporal lobe epilepsy accounts for ~40% of the total incidence of epilepsy, and is more a multi-factorial syndrome than a tightly defined disease process. The pattern of useful pharmacological interventions reveals some commonality within the syndrome: enhancement of GABAergic inhibition, reduction of glutamatergic excitation and reduction of neuronal excitability appear to be the common mechanisms of beneficial drug action. However, the underlying neuronal pathologies and compensations are not well understood and are the subject of a large body of research directed at improving treatments and the possibility of interventions. In temporal lobe epilepsy, the hippocampus has been shown to have the lowest threshold for induction of transient and sustained high-frequency discharge in the EEG.

For cellular and biophysical studies it is necessary to use experimental animal models of epilepsy[1]; hippocampal activity, similar to that observed in humans, has been shown to be mediated by populations of principal neurones together with their synaptic connections[2]. CA3 pyramidal cells intrinsically produce bursts of electrical activity ('bursting') and provide a synchronous synaptic drive for the downstream CA1 pyramidal cells. Although CA1 pyramidal cells themselves do not burst intrinsically, under certain conditions they have been shown to become hyperexcitable and even spontaneously active, generating prolonged bursts of action-potential (AP) discharges[3]. These neurones also form a major output of the hippocampus to the cortex. A stimulus-evoked synchronized burst of activity from a population of CA1 pyramidal neurones, referred to as an epileptiform burst, is illustrated in Fig. 1.

'Epileptiform' bursts of action potentials in the CA1 region of the hippocampus

Assuming that pathological changes to the function of the CA1 pyramidal neurones are a potential mechanism for epilepsy, it becomes important to understand the underlying mechanisms. In this article we will concentrate on the analysis of one of these animal models of epilepsy, the kainic acid (KA)-lesioned hippocampus of the rat, which has been studied in detail at the cellular and synaptic level. Unilateral intraventricular injection of kainate leads to a reproducible pattern of change that occurs over several weeks and involves loss of ipsilateral CA3 pyramidal neurones and synaptic reorganization. This results in 'epileptiform' bursts of CA1 pyramidal cell discharge in isolated hippocampal slices in response to stimuli[4].

In this model, three potential contributions to 'epileptiform' activity can be assessed: first, the intrinsic properties of the pyramidal cells could be modified such that the neurones themselves are hyper-responsive to excitatory inputs, or even spontaneously active; second, the synaptic inhibition could be dysfunctional, leading to a failure to terminate activity; and third, the excitatory input could be strengthened or modified to lead to sustained activity[5,6].

When recorded intracellularly from the KA-lesioned hippocampus of the rat, epileptiform bursts are observed as multiple APs superimposed on a depolarizing wave (Fig. 1). These action potentials involve both Na^+ and Ca^{2+} currents through voltage-gated channels. Control CA1 pyramidal cells do not show intrinsic bursting at the soma level[7] but bursts can be evoked in the dendrites[8,9].

Presumably there are inherent processes that prevent multiple AP discharge from the soma from passing down the axon. One possible mechanism is that

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