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Evolving critical oscillators for hearing

A. J. Hudspeth & Pascal Martin

Vertebrate hearing uses mechanosensory cells operating near an oscillatory instability. Physics reveals how this mechanism might have evolved from "chance and necessity".

Biological sensory receptors are specialized to achieve two objectives: to capture the energy in appropriate stimuli with high sensitivity and low noise, and to encode those inputs into neural signals. In the inner ears of vertebrates, so-called hair cells are key to achieving these goals. The 'hairs' of each cell are clustered in a hair bundle that serves as the cell's mechanoreceptive antenna (FIG. 1a). Hair cells transduce mechanical vibrations that impinge on their hair bundles. They can respond over a broad frequency range and can encode more than six orders of magnitude of sound-pressure levels with sharp frequency selectivity. Experimentation on single hair cells *ex vivo* and on intact auditory organs *in vivo* has led to the proposal that these properties stem from a general principle: the hair cells operate near an oscillatory instability, namely a Hopf bifurcation^{1,2}. Within this framework, the different frequencies of sound are detected by a set of 'critical oscillators,' each tuned to a distinct frequency.

It is remarkable that evolution has found essentially the identical solution—critical oscillators—in arthropods, such as fruit flies and mosquitoes, but uses entirely different proteins^{3,4}. General principles are rare in biology, for the characteristics of living things are shaped by the vicissitudes of evolution. How might something as generic and seemingly sophisticated as a critical oscillator arise through a series of accidents subject to the reinforcement of natural selection? In fact, only two major steps, both mandated by physical constraints on the auditory apparatus, would be needed to bring about the process.

What hair cells need to accomplish

The first of these requirements of the auditory apparatus is a fast response. Most sounds of biological relevance, such as those produced by the vocal apparatus of some mammals and birds, occur in the range of hundreds to hundreds of thousands of hertz. To decode such frequencies, the auditory apparatus must operate on a timescale of a few microseconds to a few thousand microseconds, faster than transduction can proceed by biochemical reactions. The necessary solution for auditory responsiveness is direct mechano-electrical transduction, that is, a physical connection—a 'gating spring'—between the apparatus that delivers force derived from sound to the ion channels that open and close to produce an electrical response (FIG. 1b). Such a direct connection implies reciprocity: the stimulus force modulates channel opening by modulating gating-spring tension, but channel opening also feeds back on gating-spring tension to influence the mechanical input.

Direct mechanical transduction imposes a second constraint: if an oscillatory input is associated with a sufficiently large static bias, the receptor's response may saturate and cease to be useful. The range of hair-bundle vibrations that elicits a response is actually very narrow, spanning only a few tens of nanometers. Some form of mechanical adaptation is therefore necessary to adjust the range of stimuli over which the system is responsive, to ensure that the hair cell is sensitive to small vibrations. Adaptation results from an interplay between two mechanisms. Fueled by adenosine triphosphate (ATP), myosin molecular motors adjust the gating-spring tension to which the transduction channels

are exposed at rest. In addition, calcium ions flowing through open channels bind at or near the channels to promote channel re-closure, which also affects gating-spring tension. By implementing force feedback on the gating springs, adaptation not only sets an optimal operating point but also performs mechanical work: the receptor is active.

Bringing hair cells to criticality

Under the pressure of natural selection, the combination of direct mechano-transduction and adaptation leads to a useful active dynamical process⁵. The sensitivity of transduction depends on both cooperative gating of the transduction channels and the change in elastic energy stored in the gating spring upon channel gating. As transduction becomes more sensitive through the evolutionary enhancement of these two physical features, the system reaches a point at which it becomes thermodynamically bistable, corresponding to negative stiffness of the transduction apparatus⁶ (FIG. 1c). If the system operates just beyond the onset of bistability, however, the adaptation process actively drives the system back-and-forth about an unstable operating point: the receptor oscillates near a Hopf bifurcation. Moreover, the receptor oscillates at a characteristic frequency that can be tuned both by the system's mechanical properties and by biochemical characteristics such as the rate of myosin's reaction cycle or the binding rate of calcium ions to the channel³. Most importantly, the generic properties of a critical oscillator ensure that the tuned receptor amplifies weak stimuli, and thus expands the dynamical range of responsiveness for a narrow range of frequencies near the characteristic frequency—precisely what is needed for auditory sensitivity.

Operating near a Hopf bifurcation has three other consequences. First, the inherent nonlinearity associated with criticality yields pronounced distortions of the input. In humans, distorted vibrations in the cochlea result in audible 'phantom tones' with properties that accord with the generic dynamic nonlinearity of critical oscillators: distortions are produced at very low stimulus levels when input frequencies are near the characteristic frequency of the oscillator, and their magnitude grows in proportion to that of the responses at the stimulus frequencies⁷. Nonlinear suppression by a pure tone of fluctuations at nearby frequencies also enhances the signal over background noise, a requirement for the intelligibility of speech in a noisy environment.

Second, because the gain-bandwidth product of a critical oscillator is constant, sensitivity to weak stimuli implies large rise times of the response. Remarkably, however, the mammalian cochlea violates this rule: sensitivity is high but responses grow relatively quickly. In the cochlea, mechanical traveling waves deliver the energy at each specific frequency of sound to the place where hair cells are endowed with the appropriate characteristic frequency. As well as coupling hair cells of different characteristic frequencies, traveling waves result in poorly understood nonlocal effects—now important topics of research—that might resolve the conundrum of rapid responsiveness.

Third, by definition, a critical oscillator operates at the onset of an oscillatory instability. A small change of its operating point can thus result in spontaneous oscillations. Remarkably, the ears of many vertebrate species, including humans, emit sounds—spontaneous oto-acoustic emissions—even in the absence of external stimulation. Spontaneous mechanical oscillations of individual hair bundles provide a cellular substrate for these emissions. However, the detailed mechanism that determines whether and at what frequencies active cellular vibrations collectively produce sound is still debated.

Limits to hair-cell function

The Hopf bifurcation is a concept that applies to deterministic dynamical systems. The hair cell, however, experiences noise: immersed in a viscous liquid, hair bundles are subject to the thermal bombardment of the surrounding fluid. In addition, the bundles experience intrinsic fluctuations such as the thermal clatter of transduction channels and the stochastic activity of adaptation motors⁹. Noise conceals the Hopf bifurcation, limiting a receptor's sensitivity to weak stimuli, but the signatures of critical oscillation can persist provided that the noise intensity is not too large. Moreover, in a mammalian cochlea, sound of a given frequency mobilizes not just a single hair cell, but about one hundred similarly tuned cells. By teaming up, coupled hair cells of nearby characteristic frequencies effectively reduce the amount of noise to which each is subjected, increasing the sensitivity to weak stimuli⁹.

However, the total pool of available hair cells is limited: for instance, 16,000 in the human cochlea. There is accordingly a tradeoff between sensitivity at a given frequency, which is enhanced by devoting many hair cells to its detection, and detection over a broad frequency range, which calls for hair cells with distributed characteristic frequencies. The acoustic fovea of some echolocating bats provides an example in which a large fraction of the hair cells is specialized to detect frequencies near that of the echolocation call, at the expense of other frequencies. Conversely, in the human cochlea, a similar number of hair cells are positioned according to an exponential frequency map, in which the characteristic frequency changes continuously along the organ to cope with the large frequency range of human perception.

Violation of the fluctuation–dissipation theorem has demonstrated that noisy hair-bundle oscillations must result from an active process. How much energy must the hair cell dissipate to power active movements of its mechanosensory hair bundle and in turn mediate frequency-selective amplification of its inputs? Developments in stochastic thermodynamics provide tools to tackle this fundamental question, specifically by quantifying time irreversibility in the spontaneous hair-bundle oscillations or using thermodynamic uncertainty relations to estimate lower bounds on entropy production¹⁰.

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Competing interests

The authors declare no competing interests.

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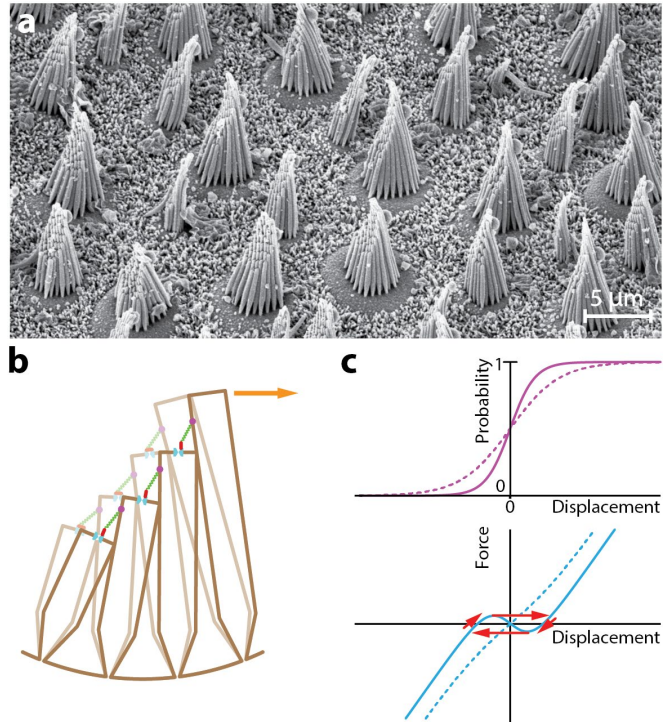


Fig. 1 | Hair-cell structure and operation. **a** | Electron micrograph of hair bundles protruding from the smooth, rounded surface of hair cells from the frog's ear. **b** | Mechanism of mechano-electrical transduction. Ion channels are physically linked to filamentous tip links. When the bundle is moved toward its tall edge, tip-link tension increases, the channels open, and there is an influx of ions into the hair cell. **c** | Electrical and mechanical responses to hair-bundle displacement. Upper: Sigmoidal relationship of channel open probability to displacement (dashed curve). An active adaptation process imposes an operating point at rest within the steep region of the curve. As the sigmoid becomes steeper, sensitivity to displacement increases (smooth curve). Lower: The force-displacement relationship displays a shallow nonlinearity when sensitivity is low (dashed curve). Higher sensitivity can result in negative stiffness (smooth curve). As a result, the operating point becomes unstable and the active adaptation process drives spontaneous oscillations around that point (red arrows).