

Thermodynamic Signatures of Sensing and Amplification by Periodically Driven Hair-Cell Bundles

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Hair cells actively drive oscillations of their mechanosensitive organelles—the hair bundles that enable hearing and balance sensing in vertebrates. Why and how some hair cells expend energy by sustaining this oscillatory motion in order to fulfill their function as sensors and amplifiers remains unknown. Here, we develop a stochastic thermodynamic theory to describe flows of *mechanical* energy in a periodically driven hair bundle. Our analysis of thermodynamic fluxes associated with hair-bundle motion and external sinusoidal stimulus reveals that these organelles function as thermodynamic work-to-work machines under different operational modes. One mode allows the cell to harvest energy of the external signal, whereas another channels the power supplied by the cell into the signal. These two regimes might represent thermodynamic signatures of signal sensing and amplification, respectively, which we further connect to the receptor currents through ion channels controlled by the hair bundles. In addition to energy harvesting and work transduction, our model also substantiates the capability of hair cells to operate as heaters and, at the expense of external driving, as active feedback refrigerators. We quantify the performance and robustness of the mechanical work-to-work conversion by hair bundles, whose thermodynamic efficiency in some conditions exceeds 80% of the applied power.

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I. INTRODUCTION

Our sense of hearing and balance is mediated by hair bundles—mechanosensory organelles on the apical side of the namesake receptor cells of the inner ear (Fig. 1). It is generally accepted that hearing relies on an active process, responsible for four cardinal features: amplification, frequency selectivity, compressive nonlinearity, and spontaneous otoacoustic emissions [1–5]. In mammals, two components most likely contribute to the active process on the cellular level: somatic motility and active hair-bundle oscillations. How these components precisely contribute to the four cardinal features of the ear is still debated. Here we use stochastic thermodynamics to identify distinct operational regimes of active hair-bundle oscillations that may be associated with signatures of different biological functions.

The nonlinear character of the hair-bundle's motion, as well as the nonequilibrium nature of its dynamics and

fluctuations, were previously analyzed using various stochastic models [3–22]. These studies were focused on principles, mechanisms, and properties of the observed dynamics. The hair bundle is thought to operate near a Hopf bifurcation, undergoing limit-cycle oscillations, but also shows traits of bistability [23]. Hair-bundle nonlinear mechanisms are associated with the cells' exquisite sensitivity and selectivity for transducing signals of particular frequencies and power. In bullfrogs—a paradigmatic model system in research on hair cells—the energy dissipated by the hair bundle per one oscillation cycle is estimated to be at least of the order of $100 k_B T$ at room temperature T , with Boltzmann constant k_B [5,21,24,25]. This amount of energy is comparable to the free energy released in the hydrolysis of approximately ten molecules of adenosine triphosphate (ATP) by myosin motors [25], which presumably drive the motion of the hair bundle [5]. However, it remains so far unknown how this energy consumption serves to implement the cells' functions and how efficiently the concomitant thermodynamic processes support amplification and information transmission.

The thermodynamic interpretation of earlier models encompasses interactions of the hair bundle with the environment as a heat reservoir, and with an active feedback force controlled by a hidden state variable, which is in contact with a second, active heat bath at an effective temperature. Herein, we simplify the theoretical description by neglecting

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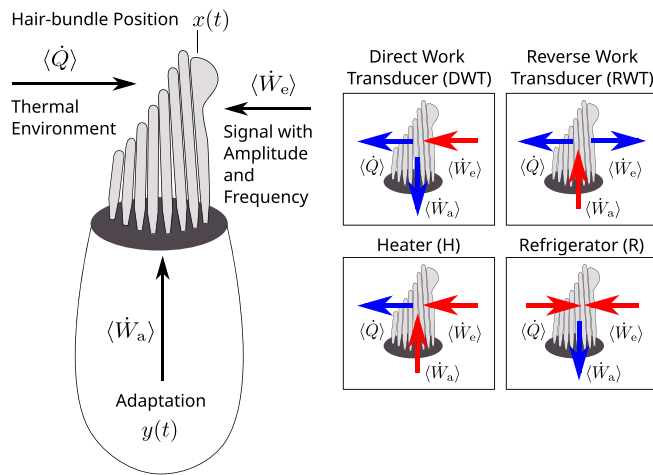


FIG. 1. Left: Schematic of a hair cell with its hair bundle on top. Energy is exchanged between the thermal environment, the hair bundle characterized by the position $x(t)$ of its tallest cilium—the kinocilium—and two agents: an internal active adaptation described by the hidden variable $y(t)$ and an external signal of a certain amplitude and frequency. The average rates of energy exchange between the hair bundle and these three agents represent flows in the system: heat $\langle \dot{Q} \rangle$ exchanged with the environment, active power $\langle \dot{W}_a \rangle$ applied by the internal adaptation, and external power $\langle \dot{W}_e \rangle$ supplied by the signal. Black arrows indicate the positive sense of individual energy flows. Insets on the right illustrate four thermodynamic regimes, in which the hair bundle operates, with blue and red arrows indicating the negative and positive sense of energy flows, respectively.

the second active heat bath, which represents spontaneous fluctuations associated with an internal adaptation mechanism [5,10,11,17], and by retaining only the deterministic features of the feedback dynamics. Notably, within such a minimalist approach, we are able to fit experimental data with high accuracy, substantiating our quantitative analysis. On the other side, we incorporate into our model an external signal in the form of a time-periodic force, unveiling four distinct thermodynamic regimes characterized by the net direction of various energy flows within the system, as we discuss below.

Thermodynamics offers a unique perspective on information processing in physical systems like hair bundles [26–41]. According to the dynamical Landauer’s principle, the transmission of information in a communication process is typically accompanied by an exchange of entropy manifested in the form of thermodynamic work, for example, between a signal and a sensor that interprets it, or as heat dissipated into the environment. Inspired by recent theoretical advances in stochastic and information thermodynamics of active processes, we investigate the energy flows that result from *mechanical* interactions of a hair bundle with the thermal environment and two active agents—a feedback force and an external sinusoidal stimulus (Fig. 1). We refer the readers to Refs. [42–45] for recent thermodynamics insights on periodically driven and feedback-controlled minimal models of active matter.

Adopting the thermodynamic sign convention with positive net flow of heat or work from the environment or agent into the system, and negative otherwise, three components of the

energy flows are considered. First, the power $\dot{Q}$ absorbed from the environment as heat. Second, the active power $\dot{W}_a$ supplied to the hair bundle by the hair cell. Third, the power $\dot{W}_e$ extracted from the signal. Our analysis shows that, depending on the parameters of the system, the hair bundle can operate as an isothermal work-to-work machine with a feedback force in two distinct regimes. The power can be either extracted from or injected into the external signal by the hair cell. In the former case, which we call direct work transduction (DWT), the average active power is negative ($\langle \dot{W}_a \rangle < 0$) and, whereas the average external power is positive ($\langle \dot{W}_e \rangle > 0$), correspond to a flow of *mechanical* energy through the hair bundle into the cell (Fig. 1). The second mode of operation is the reverse work transduction (RWT), characterized by the opposite sense of energy flow—from the cell to the external signal with positive active and negative external power. As we hypothesize, these two regimes might represent thermodynamic signatures of a hair cell’s main functions: signal detection and amplification.

Besides the work transduction between the two active agents, we also identify another nontrivial mode of operation, a *feedback* refrigeration [46], which consumes power of the external signal ($\langle \dot{W}_e \rangle > 0$) in order to absorb heat ($\langle \dot{Q} \rangle > 0$) into the hair cell ($\langle \dot{W}_a \rangle < 0$), thereby “cooling” the environment. This effect is thermodynamically viable due to the information flow exchanged between the active feedback force and the hair-bundle position [33,47–51]. If not operating as a work transducer or refrigerator, the hair bundle falls back to the heater regime ($\langle \dot{Q} \rangle < 0$, $\langle \dot{W}_a \rangle > 0$, $\langle \dot{W}_e \rangle \geq 0$), as when there is no external signal present.

Using experimental data of hair-bundle oscillations from the bullfrog sacculus [Figs. 2(a) and 2(b), Materials and Methods], we identify a specific range of the external signal’s frequencies and amplitudes that makes the hair bundle operate as a work-to-work machine. The DWT regime is viable when the signal amplitude exceeds a certain threshold and is most pronounced close to the natural frequency of the organelle’s oscillations. These conditions suggest the presence of a threshold-gated sensing mechanism, which might trigger neuronal activity in the cell depending on the intake of the energy from the external stimulus. The RWT regime occurs at low signal amplitudes, oscillating within a narrow range below the hair bundle’s natural frequency. Thus, a low-power stimulus could be amplified in a frequency-dependent manner by the internal adaptation process, which sustains oscillations of the organelle.

Our analysis of the experimental observations is based on a nonlinear parsimonious model [10,11,13,14,18] and assisted by a simulation-based inference (SBI [21,53,54]). By estimating model parameters of hair bundles oscillating in laboratory conditions at various frequencies [52, Table S6], we predict their *mechanical* response to external signals of a sinusoidal form. We inspect in detail how the thermodynamic interactions of the system and its active environment depend on the frequency and amplitude of the external stimulation and on other parameters of the model, which control the nonlinear regime of oscillations. Notably, we find that the self-sustained oscillations with the rectangular patterns [Figs. 2(a), S5(a), and S5(c)] display better performance in the RWT mode, whereas our examples of shark-fin-like time series [Figs. 2(b), S5(b), and S5(d)] ensure a robust DWT regime.

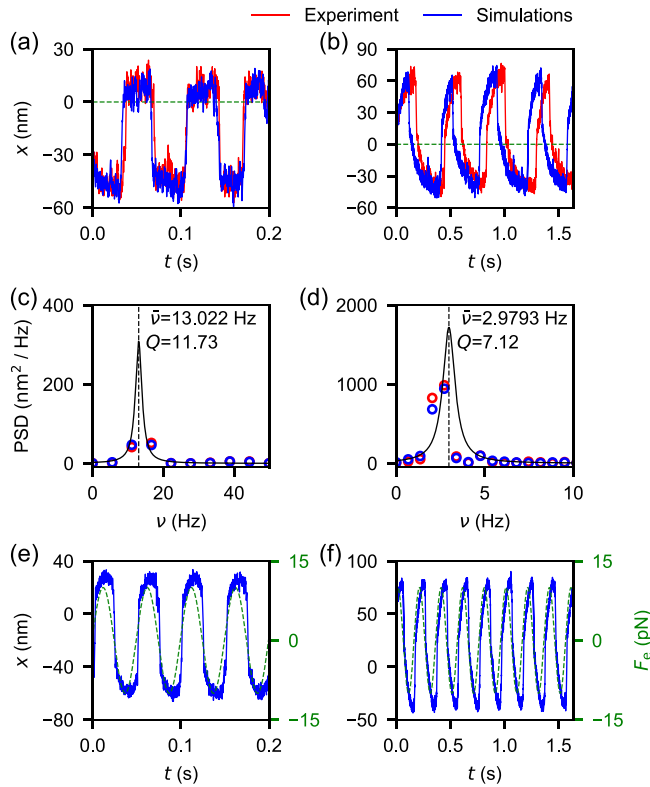


FIG. 2. Two examples of spontaneously oscillating hair bundles: Experimental time series of a hair bundle's tip position x (red) without an external stimulus in case 1 [panel (a), Fig. S5(a)], and case 2 [panel (b), Fig. S5(b)]. Both are compared to simulations (blue) of Eqs. (4)–(6) with the parameter sets found by the simulation-based inference. Note that the phase of oscillations varies stochastically in each simulation of the model. Therefore, we report representative simulated trajectories with $t = 0$ chosen so as to match the initial phase of experiments. Panels (c) and (d): Power-spectrum density (PSD) calculated from the same data (red and blue circles for the experiments and simulations, respectively). To determine the natural frequency of oscillations $\bar{\nu}$ (dashed vertical line), we fit the Lorentzian profile (solid black curve) to the spectra obtained from simulated time series extended over a longer duration of 500 s [52, Figs. S5(e)–S5(h)]. Panels (e) and (f): Simulations of Eqs. (4)–(6) with an external sinusoidal force F_e (dashed green line) of amplitude $A_e = 10$ pN and frequencies $\nu_e = 20$ Hz [panel (e), parameter set 1] and $\nu_e = 5$ Hz [panel (f), parameter set 2].

Because our model does not include the part of the sensing apparatus that triggers the neuronal activity, we are focusing on the mechanical interactions. In particular, generation of the neuronal signal requires explicit modeling of the conversion between mechanical and electrical forms of energy, for which multiple mechanisms are proposed (see Ref. [14, Supporting Information]). While still in debate, these details do not affect the conclusions drawn from the thermodynamic theory describing the mechanical interactions, which are prerequisite for the efficient information transmission, as the entire cascade of signal-transduction processes may include additional sources of energy dissipation.

Nonetheless, by employing a simple model of ion flow through channels regulated by hair bundles [5], we can

explore a possible influence of the external stimulus on the generation of electrical signals. In particular, we find that the driving force elicits significant ion-channel currents in cells that most robustly carry out DWT. This behavior supports our interpretation of such cells as sensory units. In contrast, cells that are more efficient in the RWT regime yield negligible currents, whose magnitudes remain below their standard errors.

II. NONLINEAR ACTIVE DYNAMICS OF A HAIR-BUNDLE OSCILLATION

In a laboratory, the spontaneous oscillations of a hair bundle's tip can be routinely observed by using a double-chamber preparation [24,55–58]. We recorded the time series of a hair bundle's position of cells from the bullfrog sacculus [Figs. 2(a) and 2(b), Materials and Methods] and selected four examples presenting regular oscillations at natural frequencies in the range 1–15 Hz for analysis.

To introduce a minimal set of equations that describe the time series $x(t)$ of the hair bundle's tip position *in the laboratory frame*, we start from an established biophysical model that is based on the gating spring mechanism and relates the internal active adaptation to the movements of molecular motors influenced by the opening of ion channels [10,11,13]. In this model, the dynamics of the hair-bundle position X (in its rest reference frame), coupled to the state of adaptation motors X_a , is governed by

$$\gamma \dot{X} = -K_{GS}(X - X_a - DP_o(X - X_a)) - K_{SP}X + F_e(t) + \sqrt{2k_B T \gamma} \zeta(t), \quad (1)$$

with the following constants: a friction coefficient γ , the gating spring K_{GS} , the gating swing displacement D , and the pivotal spring constant of the stereocilia K_{SP} . The nonlinear coupling P_o represents the open probability of the ion channels P_o and follows from a Boltzmann argument:

$$P_o = [1 + \exp(C_1 - C_2(X - X_a))]^{-1}, \quad (2)$$

in which

$$C_1 = \frac{2N\Delta G + K_{GS}D^2}{2Nk_B T}, \quad C_2 = \frac{K_{GS}D}{Nk_B T}$$

for N ion channels with a free-energy difference ΔG between their open and closed states [52, Sec. 1].

In addition, the tip of the hair bundle is subject to an external driving force $F_e(t)$, which represents the signal, and to thermal noise of amplitude $\sqrt{2k_B T \gamma}$. The stochastic term ζ is the standard Wiener noise of zero mean ($\langle \zeta(t) \rangle = 0$) that is δ delta correlated in time ($\langle \zeta(t)\zeta(s) \rangle = \delta(t - s)$).

Similarly, the dynamics of the adaptation motors is described by

$$\gamma_a \dot{X}_a = K_{GS}(X - X_a - DP_o) - K_a X_a - F_{\max}(1 - SP_o) + \sqrt{2k_B T_a \gamma_a} \zeta_a(t), \quad (3)$$

with friction coefficient γ_a , maximal active force $F_{\max}$, channel-coupling constant S , extent spring constant K_a [59], an effective temperature T_a , and another independent standard Wiener noise ζ_a . We simplify the above description by neglecting the noise $\sqrt{2k_B T_a / \gamma_a} \zeta_a(t)$ in the limit of large friction γ_a [52, Sec. 1].

To relate our model to experimental data, it is critical to note that an origin of the reference frame for any experimental measurement of the position $X(t)$ does not in general correspond to $X = 0$ in Eqs. (1) and (3). Therefore, the laboratory frame is shifted by a constant $X_{\text{off}} = x - X$, implying the observable hair bundle's tip position $x \equiv X + X_{\text{off}}$ and a shifted value $Y \equiv X_a + X_{\text{off}}$. We also reduce the nonlinearity of the model by expanding P_0 around the most sensitive operational point with half-open probability up to the fourth order and assume that $F_{\text{max}}S \approx K_{\text{GS}}D$ [52, Sec. 1]. Finally, we introduce a new variable $y \equiv Y + C_1/C_2$ and rewrite Eq. (1) into an overdamped Langevin equation of motion for the hair bundle's position as

$$\gamma \dot{x} = -\partial_x U(x, y) + F_e + \sqrt{2k_B T \gamma} \zeta, \quad (4)$$

in which a potential $U(x, y)$, generating the conservative force

$$\partial_x U(x, y) = -A(x - y) + B(x - y)^3 + K_{\text{SP}}x - C_x, \quad (5)$$

includes the following constants derived from Eqs. (1) and (2) [52, cf. Eq. (S22)]: coupling coefficients A and B , the pivotal stiffness K_{SP} , and a bias term C_x . We express the dynamics of $y(t)$ as

$$\dot{y} = -ey + bx + c_y, \quad (6)$$

with constants e , b , and c_y [52, cf. Eqs. (S19)–(S21)].

Equation (6) describes the internal active adaptation of the hair bundle to a new position. As follows from the detailed biophysical analysis, this adaptation arises due to the interplay between mechanical forces, molecular motors, and calcium feedback, leading to experimentally validated timescales on the order of a few milliseconds [9].

By using the SBI approach [53], we determined values of the model parameters in Eqs. (4)–(6) from four experimental time series [52, Table S6] of hair bundles oscillating at a natural frequency $\bar{\nu}$ in absence of the external driving [$F_e \equiv 0$, Figs. 2(a)–2(d)] [52, Fig. S5]. In the following, these four cases and the corresponding parameter sets are consistently numbered 1–4. Whereas results for all four cases are reported in Ref. [52], here we focus on no. 1 and no. 2, which display, respectively, rectangular and shark-fin-like patterns of oscillations. Cases 3 and 4 demonstrate that our results and conclusions are reproducible in other experiments not discussed here to avoid redundancy. With the values of the model parameters inferred from experiments, we can probe the response of these hair bundles to a hypothetical external periodic signal

$$F_e(t) = A_e \sin(2\pi \nu_e t) \quad (7)$$

of amplitude A_e and frequency ν_e by performing numerical stochastic simulations [Figs. 2(e) and 2(f)].

III. THERMODYNAMICS OF PERIODICALLY DRIVEN ACTIVE HAIR-CELL BUNDLES

The physical model, as introduced above, allows us to apply systematically concepts of stochastic thermodynamics [60–62]. In our setup the hair bundle's tip position x describes the state of the system that exchanges heat Q with an isothermal bath at temperature T (the extracellular medium). Furthermore, two external agents, the periodic external signal

and the cell's active adaptation process, exert the work W_e and W_a on the system, respectively (Fig. 1). Such a thermodynamic system is commonly known as an isothermal work-to-work machine with a feedback control [33,47–51,63], as it is capable of transducing mechanical energy between the two external agents.

Following the formalism of Sekimoto [64], the rate of heat absorption $\dot{Q}$ by the hair bundle from the heat bath in the time interval $[t, t + dt]$ is defined as

$$\dot{Q} \equiv (-\gamma \dot{x} + \sqrt{2k_B T \gamma} \zeta) \circ \dot{x} = [\partial_x U(x, y) - F_e] \circ \dot{x}, \quad (8)$$

in which we interpret $\circ$ as the Stratonovich-type product. The stochastic power $\dot{W}_a$ exerted by the internal active adaptation process on the hair bundle is then

$$\dot{W}_a \equiv \partial_y U(x, y) \circ \dot{y}, \quad (9)$$

whereas the power applied by the external signal on the hair bundle reads

$$\dot{W}_e \equiv F_e \circ \dot{x}. \quad (10)$$

The above definitions, Eqs. (8)–(10), ensure that the sum

$$\dot{Q} + \dot{W}_a + \dot{W}_e = \partial_x U(x, y) \circ \dot{x} + \partial_y U(x, y) \circ \dot{y} = \dot{U} \quad (11)$$

yields the total change of internal energy and thereby fulfills the first law of stochastic thermodynamics at the single-trajectory level on the time interval $[t, t + dt]$ [64].

The thermodynamic regime of the hair-bundle oscillatory state can thus be characterized by time averages of the heat flow $\langle \dot{Q} \rangle$ (dissipated energy), of the active power $\langle \dot{W}_a \rangle$, and of the power supplied by the external signal $\langle \dot{W}_e \rangle$, which all can be estimated numerically in simulations. In the presence of a sinusoidal oscillatory signal $F_e(t)$ of the form (7), these net energy-flow rates become functions of the amplitude A_e and the frequency ν_e of the external stimulus.

From our numerical results, we systematically identified four distinct thermodynamic regimes in the space of parameters A_e and ν_e associated with different sign combinations of $\langle \dot{Q} \rangle$, $\langle \dot{W}_a \rangle$, and $\langle \dot{W}_e \rangle$ (Fig. 3, [52, Fig. S6]). To categorize these regimes of our system for a specific set of parameters, we require that the three averaged energy flows, $\langle \dot{Q} \rangle$, $\langle \dot{W}_a \rangle$, and $\langle \dot{W}_e \rangle$, measured from 500-s time series of simulations, are greater than or equal to the standard error of their means. Close to the boundaries between the different regions, the energy flows fluctuate so much that a thermodynamic classification of such steady oscillatory states becomes impractical or would require very long simulations.

Heater regime. For the experimental conditions of spontaneous oscillations ($F_e \equiv 0$, $\langle \dot{W}_e \rangle \equiv 0$), we find $\langle \dot{W}_a \rangle > 0$ and $\langle \dot{Q} \rangle < 0$, which amount to active work done by the cell on the hair bundle and dissipated into the heat bath. When $F_e \neq 0$, the hair bundle is exposed to a harmonic signal, which typically carries a total energy proportional to $\nu_e^2 A_e^2$. The effect of this external driving on the energy flows in the system has a nontrivial dependency on the amplitude A_e and frequency ν_e (Fig. 4, [52, Fig. S7]).

For frequencies ν_e of the signal which exceed the natural frequency of the hair bundle $\bar{\nu}$, the rate of heat exchanged with the environment becomes progressively more negative as the total power carried by the signal grows with ν_e and A_e in all the four sets of parameter values [Figs. 4(a) and 4(d)]

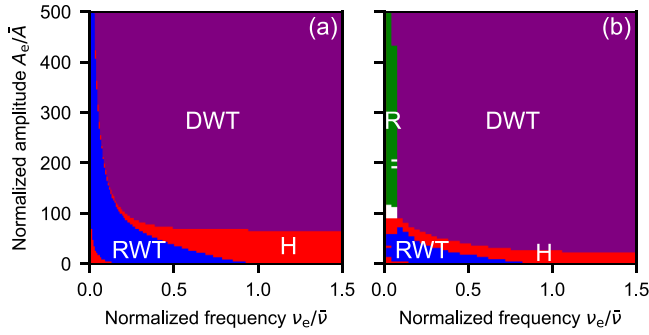


FIG. 3. Diagram of thermodynamic regimes for hair bundles described by the parameter sets 1 [panel (a)] and 2 [panel (b)]: direct (DWT, purple) and reverse (RWT, blue) work-to-work transduction, heater (H, red), and refrigerator (R, green). White-colored areas correspond to noisy regimes in which fluctuations of energy flows are too large to assign one of the listed regimes with confidence. The amplitudes of the external signals are normalized by $\bar{A} = \sqrt{2k_B T \gamma \bar{\nu}}$. The normalization constants take the value $\bar{A}_1 = 0.12 \pm 0.01$ pN and $\bar{A}_2 = 0.112 \pm 0.001$ pN with the natural frequencies $\bar{\nu}_1 = 13.022 \pm 0.002$ Hz and $\bar{\nu}_2 = 2.9793 \pm 0.0008$ Hz of the unperturbed oscillations described by the respective parameter sets.

[52, Fig. S8]. This trend reflects the increase of the dissipated power ($\dot{W}_a + \dot{W}_e$) because of the additional external source of work ($\dot{W}_e$) up to a 100-fold increase of the entropy production rate $\dot{S} = -\langle \dot{Q} \rangle / T$ in comparison with the unperturbed spontaneous oscillations of hair bundles [5]. Provided that the signal amplitude is small, in this regime of negative heat flow $\langle \dot{Q} \rangle < 0$, and positive applied powers ($\dot{W}_e > 0$, $\dot{W}_a > 0$) the system operates as a heater.

Refrigerator regime. Besides the above heater regime, the system may also act as a weak refrigerator with $\langle \dot{Q} \rangle > 0$, $\dot{W}_a < 0$, $\dot{W}_e > 0$ at very low frequencies ν_e but sufficiently large amplitudes A_e [Figs. 3(b) and 4(d)] [52, Fig. S6(d)]. We found this regime only for the examples of slow oscillations with parameter sets 2 and 4. In cases 1 and 3, we observed a weakly suppressed heat dissipation, which, however, remained on average always negative ($\langle \dot{Q} \rangle < 0$), in a similar region of A_e and ν_e .

The active force exerts feedback on the hair bundle by processing an information transfer between the tip position x and the active process y . Such feedback control enables a refrigerator regime compatible with generalized second laws of thermodynamics which take the form

$$\langle \dot{S} \rangle = -\frac{\langle \dot{Q} \rangle}{T} \geq -\langle \dot{I} \rangle. \quad (12)$$

Here, $\dot{I}$ is a continuous information flow rate between x and y , whose average may be positive or negative depending on the direction of the information flow [33, 39, 47–51, 65]. Due to the nonlinear structure of the equations of motion, analytical forms (and even reliable numerical estimates) of the time-averaged rate of information transfer $\langle \dot{I} \rangle$ are not available yet for our system. However, we can prove the viability of the refrigerator regime by using an equivalent formulation of our system with a second heat bath whose temperature tends to zero [52, Sec. 4].

Work-to-work transduction regimes. Two other regimes, which appear more relevant to the biological function of hair bundles, are characterized by negative heat $\langle \dot{Q} \rangle < 0$ and transduction of mechanical energy between the external signal and the cell. We call them the *direct* and *reverse* work-to-work machines (DWT and RWT, respectively). In the DWT mode the hair cell channels a fraction of the signal energy ($\dot{W}_e > 0$) as active power ($\dot{W}_a < 0$), whereas in the RWT mode a fraction of the active power $\dot{W}_a > 0$ is channeled into the signal ($\dot{W}_e < 0$) [Figs. 4(b), 4(c), 4(e), and 4(f)] [52, Figs. S9 and S10]. Next, we introduce appropriate efficiencies to quantitatively characterize these thermodynamic regimes.

Because the time-averaged internal energy $\langle U \rangle$ is constant, by virtue of the first law Eq. (11),

$$\langle \dot{U} \rangle = \langle \dot{Q} \rangle + \langle \dot{W}_a \rangle + \langle \dot{W}_e \rangle = 0.$$

From this equation together with the conditions of the direct work-to-work transduction, $\dot{W}_e > 0$, $\dot{W}_a < 0$, and $\dot{Q} < 0$, we find that the ratio of active power to the external power is always bounded by $-1 \leq \langle \dot{W}_a \rangle / \langle \dot{W}_e \rangle \leq 0$. In the reverse mode, the conditions are inverted, with $\dot{W}_e < 0$, $\dot{W}_a > 0$, and $\dot{Q} < 0$, leading to the bounds for the reciprocal ratio $-1 < \langle \dot{W}_e \rangle / \langle \dot{W}_a \rangle < 0$. Therefore, the efficiency of the mechanical work-to-work transduction may be quantified by the fraction of the total supplied power,

$$\eta_{\text{in}} = -\langle \dot{W}_a \rangle / \langle \dot{W}_e \rangle, \quad \eta_{\text{out}} = -\langle \dot{W}_e \rangle / \langle \dot{W}_a \rangle \quad (13)$$

for the direct and reverse modes, respectively. The upper bound of mechanical efficiency, with 100% of the applied power being transduced, e.g., when $\langle \dot{Q} \rangle$ vanishes as in equilibrium, is not observed in practice.

Note that Eq. (13) does not characterize the *optimality* of the thermodynamic scheme that the system implements because we do not include the entropic information costs of the feedback mechanism [33, 47–51], cf. Eq. (12). The efficiencies we defined above strictly quantify the fraction of work—treated as the information flow in the DWT regime—successfully transduced between the active force and the signal.

Our numerical results for the efficiencies associated with the DWT and RWT modes of the parameter sets 1 [Figs. 5(a) and 5(c)] and 2 [Figs. 5(b) and 5(d)] reveal a nonmonotonous behavior of both η_{in} and η_{out} as functions of the signal frequency. Within the explored parameter ranges, the peak efficiencies in general increase with the signal amplitude and may exceed 80% of the supplied power. The location of their maxima depends on both the frequency and amplitude of the external signal [Figs. 5(a)–5(d)]. At intermediate values of the amplitudes A_e , the peak of η_{in} matches closely the natural frequency of the hair-bundle oscillation, shifting to the lower or higher frequencies for smaller or larger values of A_e , respectively. The maximum of η_{out} occurs when the ratio $\nu_e / \bar{\nu} < 1$ also moves toward lower or higher frequencies as the amplitude A_e increases or decreases. These observations confirm that efficiency and heat dissipation do not correlate in active systems, as suggested recently in Ref. [66].

The parameter set no. 1 is notably less efficient than no. 2 in the DWT at small and moderate amplitudes $A_e \leq 10$ pN of the external signal [Figs. 5(a) and 5(b)]. Conversely, in the RWT regime the parameter set 1 performs better than

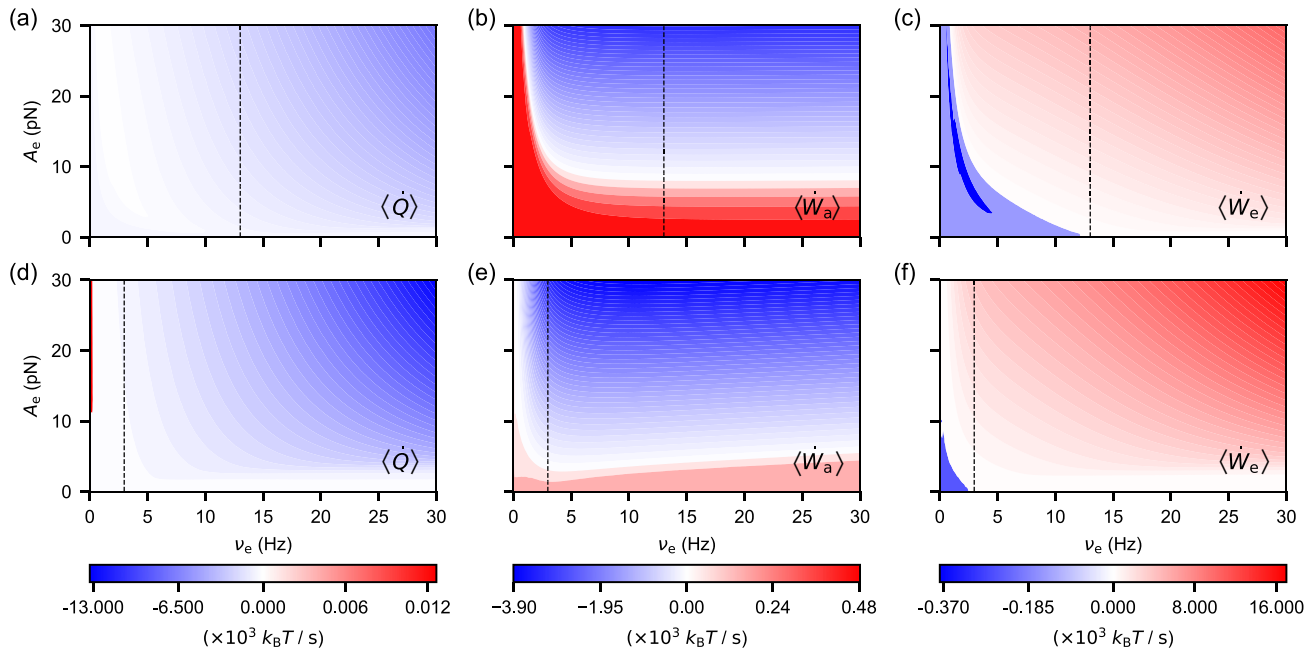


FIG. 4. Thermodynamic time-averaged energy flows of an externally stimulated hair bundle as functions of the stimulus' frequency ν_e and amplitude A_e , characterized by the parameter sets 1 [panels (a)–(c)] and 2 [panels (d)–(f)]: heat dissipation rate [panels (a), (d)], active power [panels (b), (e)], and external power [panels (c), (f)]. The vertical dashed line indicates the natural frequency of the unperturbed hair bundle $\bar{\nu}$. The respective energy flows are determined by integrating numerically Eqs. (8)–(10) with a simulation time step of 0.1 ms and averaging over 500 s.

set 2 [Figs. 5(c) and 5(d)]. Parameter sets 3 and 4 compare similarly by their efficiencies η_{in} and η_{out} [52, Figs. S11–S13]. As discussed in the next section, these differences can be attributed to distinct nonlinear regimes, in which the sets 1, 3, and 2, 4 operate.

The DWT requires that the signal amplitude exceeds a certain threshold depending on the model parameters and is most pronounced when the stimulus frequency matches the natural frequency of the hair bundle. This tendency is further emphasized if we consider the extracted work $\langle \dot{W}_a \rangle$ as the signal relayed to the cell and the standard deviation of the mean active power $\text{Std}[\dot{W}_a]$ as the uncertainty of the signal. We thus evaluate the signal-to-noise ratio as

$$\text{SNR} = -\langle \dot{W}_a \rangle / \text{Std}[\dot{W}_a], \quad (14)$$

which saturates close to the natural frequency of the hair bundle's oscillations [Figs. 5(e) and 5(f)].

The reverse regime of work transduction is limited to low frequencies $\nu_e < \bar{\nu}$ and amplitudes A_e [Figs. 5(c) and 5(d)]. Assuming that the power carried by the signal is an increasing function of the signal and frequency, typically $\propto \nu_e^2 A_e^2$ for a harmonic oscillator, this regime is triggered only by and enhances weak stimuli.

In summary, our systematic analysis of the system's thermodynamics suggests four different operating regimes of a hair bundle, depending on the energetic flows induced by external signals of different amplitudes and frequencies. In particular, the shape of the bundle oscillations appears related to its performance in the direct and reverse modes of work transduction. For a deeper understanding of the role of the dynamical regimes, we seek to characterize in the next section thermodynamics of the forced hair bundles near the Hopf

bifurcation points and refer the reader to recent publications highlighting the link between dissipation and the quality of stochastic oscillatory motion [67,68].

IV. THERMODYNAMIC SIGNATURES OF A HOPF BIFURCATION

Hair bundles are believed to fulfill their functions by operating in proximity of a Hopf bifurcation [7,69–71]. Our experimental time series fall into two kinds of nonlinear regimes out of the total four types available in our model [52, Sec. 2]. Namely, examples with rectangular oscillatory patterns 1 and 3 belong to a *uninodal* regime of relaxation oscillations, whose phase space contains a single unstable fixed point and a limit cycle. The models characterized by parameter sets 2 and 4, which exhibit a shark-fin-like profile of oscillations in their time series, fall into a particular kind of a *monostable* regime—with a single stable fixed point—because of the constant offset terms C_x and c_y in Eqs. (5) and (6). In the absence of these terms, the system would be bistable and contain one saddle and two stable nodes. Instead, the latter nodes become imaginary for sufficiently large values of C_x and c_y , but the remaining “phantoms” of these nodes distort the system's phase portrait. Although both the monostable and bistable regimes, by themselves, do not display self-sustained relaxation oscillations [72,73], when driven by noise they may resemble a limit-cycle behavior, as the system slows down near the stable nodes or their “phantoms.”

Below, we analyze how the thermodynamic flows change as the model's parameters approach a Hopf bifurcation. To this end, we consider an equivalent formulation of hair-bundle dynamics which eliminates the variable y by considering the

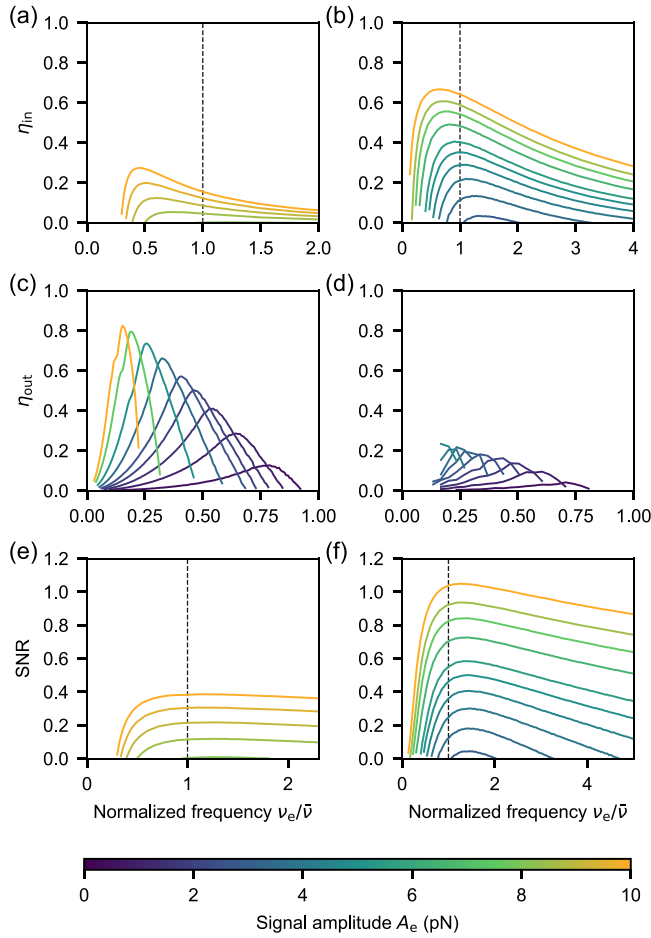


FIG. 5. Characterization of the hair bundles' mechanical work transduction by thermodynamic efficiencies [Eq. (13)] and by signal-to-noise ratio [SNR, Eq. (14)] for parameter sets 1 [panels (a), (c), (e)] and 2 [panels (b), (d), (f)]: the efficiency η_{in} of DWT [panels (a), (b)], the efficiency η_{out} of RWT [panels (c), (d)], and the SNR [panels (e), (f)]. While the hair bundle characterized by the parameter set 1 performs more efficiently in the RWT regime [panel (c)], the hair bundle characterized by parameter set 2 has a larger efficiency of DWT [panel (b)] and displays a larger SNR [panel (f)].

difference $z = x - y$ [52, Sec. 2]. This formulation reveals a hidden Van der Pol–Duffing oscillator $z(t)$ characterized by constants c_0, c_1, c_2, c_3 , and f_0 , and acting on the hair bundle's position $x(t)$:

$$\begin{aligned} \ddot{z} + c_0\dot{z} + c_1z + c_2z^2\dot{z} + c_3z^3 \\ = f_0 + \sqrt{\frac{2k_B T}{\gamma}} \dot{\zeta}(t) + \frac{\dot{F}_e(t)}{\gamma} \\ - (b - e) \left(\sqrt{\frac{2k_B T}{\gamma}} \zeta(t) + \frac{F_e(t)}{\gamma} \right), \end{aligned} \quad (15)$$

$$\begin{aligned} x = \frac{1}{\gamma} \int_0^t ds g_x(t-s) [Az(s) - Bz(s)^3 + C_x + F_e(s) \\ + \sqrt{2k_B T \gamma} \zeta(s)], \end{aligned} \quad (16)$$

in which $g_x(t) = \exp(-K_{Spt}/\gamma)$ is a Green function.

To approach the Hopf bifurcation, we fix the values of c_1, c_2, c_3, f_0 , and scale the frictionlike parameter $c_0 \rightarrow \lambda \hat{c}_0 - (1 - \lambda)c_2 Z_0$ with respect to its original value $\hat{c}_0$ and the fixed point $(z, \dot{z}) = (Z_0, 0)$ by the dimensionless factor $0 \leq \lambda \leq 1$, so that for $\lambda = 0$ the system is at the bifurcation point. To implement this scaling, we choose to adjust the values of the original model parameters A, b, c, e , and c_γ while keeping the rest fixed (Supplemental Material, SM, Tables S7 and S8).

In the uninodal regime characterized by parameter set 1, approaching the Hopf bifurcation as $\lambda \rightarrow 0$ has little effect on the active and external power exchange [Figs. 6(a) and 6(b)]. This minor effect, however, considerably enhances η_{in} and η_{out} in the DWT and RWT modes, respectively [Figs. 6(c) and 6(d)]. A minor increase of the power intake $|\langle \dot{W}_a \rangle|$ in the direct regime is accompanied by a subtle decrease of the energy $|\langle \dot{W}_e \rangle|$ extracted from the signal and leading to a drastic increase in the efficiency η_{in} . In the RWT regime, the increase of η_{out} is less striking, as both power intake $|\langle \dot{W}_a \rangle|$ and output $|\langle \dot{W}_e \rangle|$ are decreasing, but the latter decreases slower with $\lambda \rightarrow 0$.

Remarkably, with the no. 2 set of parameters, scaling by $\lambda \rightarrow 0$ enhances interactions with the active adaptation and external signal: both the active and external energy flows $\langle \dot{W}_a \rangle$ and $\langle \dot{W}_e \rangle$ change severalfold [Figs. 6(a) and 6(b)]. In the DWT regime, the increase of power intake $|\langle \dot{W}_a \rangle|$ is afforded thanks to even more intense extraction of energy $|\langle \dot{W}_e \rangle|$ from the external signal, resulting in a lower efficiency η_{in} [Fig. 6(c)]. The proximity of the Hopf bifurcation also extends the range of reverse work transduction to higher levels of signal amplitudes than in the original set of parameters 2 [Fig. 6(d)].

Comparing the two parameter sets 1 and 2, we notice that the SNR exceeds 100% only in the second case, sufficiently far ($\lambda \rightarrow 1$) from the Hopf bifurcation [Fig. 6(e)]. Overall, the scaling by λ seems to affect the direct work transduction much more strongly than the reverse. The reverse work transduction, which is triggered by oscillations of the external signal below the hair bundle's natural frequency, resembles an antiresonance phenomenon. To highlight this similarity, we apply another scaling procedure by a dimensionless factor h so that $c_0 = h\hat{c}_0$, $c_2 = h\hat{c}_2$, and $c_3 = h\hat{c}_3$ with respect to the original values $\hat{c}_{i=0,2,3}$ of parameter set 1. This scaling turns (15) into an undamped harmonic oscillator as $h \rightarrow 0$. To implement such a transformation, we again adjust parameters A, b, c, e , and c_γ , keeping all others fixed (SM Table S7).

While approaching the regime of a weakly damped harmonic oscillator with $h \rightarrow 0$ from the uninodal regime of the parameter set 1, the reverse work transduction of the hair bundle is enhanced by an order of magnitude [Fig. 6(f)]. In this limit, the system's linear response converges to that of an undamped harmonic oscillator with a fundamental frequency

$$\nu_0 = \sqrt{c_1}/(2\pi) \quad (17)$$

and amplitude $4\sqrt{c_2/c_0}$, which can be estimated by perturbative methods [52, Sec. 5]. Extraction of the power by $F_e(t)$ then corresponds to the phenomenon of antiresonance, when $\nu_e = \bar{\nu}_0/2$. Given a fixed amplitude A_e of the stimulus, with $h \rightarrow 0$ we indeed observe an emergent peak in $\langle \dot{W}_e \rangle$ near $\nu_e \approx \nu_0/2$ [Fig. 6(f)] [52, Fig. S14(f)].

By inspecting the thermodynamic behavior near a Hopf bifurcation [Figs. 6(a)–6(e), SM Figs. S14(a)–S14(e)], we thus

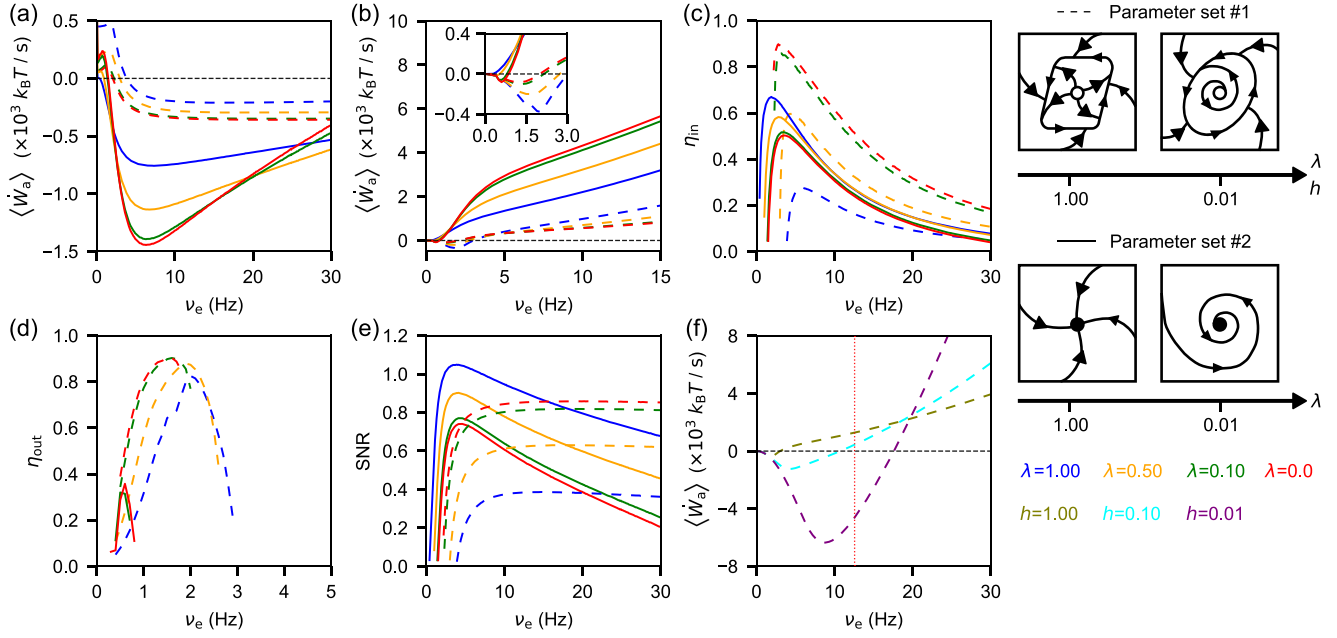


FIG. 6. Work transduction in different dynamical regimes: parameter sets 1 (dashed curves, unimodal relaxation oscillations, approaching the Hopf bifurcation as $\lambda \rightarrow 0$ and the undamped harmonic oscillator as $h \rightarrow 0$) and 2 (solid curves, monostable regime, approaching the Hopf bifurcation as $\lambda \rightarrow 0$) for the external signals of the same amplitude $A_e = 10$ pN and various frequencies ν_e . Panel (a): While approaching the Hopf bifurcation ($\lambda \rightarrow 0$), curves describing the active power shift down in both cases, 1 and 2, implying more power intake in the direct work transduction and less power expanded in the reverse regime. Panel (b): The curves of the external power become steeper in the proximity of the Hopf bifurcation of the parameter set 2, indicating that more energy is consumed, but also more is transduced by the reverse work-to-work machine. The opposite trend is observed in case 1—the curves flatten. Panel (c): Whereas the power intake of the monostable regime (2) increases closer to the Hopf bifurcation, the efficiency of mechanical work transduction decreases. The unimodal regime (1) transduces much less power but more efficiently in the proximity of the Hopf bifurcation. Panel (d): At a given amplitude of the external signal, the Hopf bifurcation enables reverse work transduction in parameter set 2 and improves its efficiency in set 1. Panel (e): The signal-to-noise ratio is maximal in the monostable regime, far from the Hopf bifurcation as $\lambda \rightarrow 1$. Panel (f): The low-friction and weak-nonlinearity limit of the Van der Pol–Duffing Eq. (15) ($h \rightarrow 0$, case 1) resembles an underdamped harmonic oscillator. In the limit of $h \rightarrow 0$, cf. $h = 0.01$, the reverse work transduction is enhanced with a local optimum moving closer to half of the resonance frequency $\nu_0/2$ [red dotted vertical line, cf. Eq. (17)]. The sketches on the right illustrate how the phase portraits of the system change when the scaling parameters λ or h change, with their values color-coded as shown in the legend.

found how the energy flowing between the periodically driven hair bundle, the active feedback mechanism, and the external signal contribute to the efficiency of work transduction in proximity of the bifurcation point. Interestingly, two dynamical regimes discovered in our experiments, that determine the pattern of the oscillatory time series, exhibit qualitative differences in the direct transduction mode. While in one regime the mechanical efficiency of DWT is enhanced close to the bifurcation, in the other it is compromised. However, the proximity to the bifurcation improves the RWT efficiency in both dynamical regimes.

V. ION-CHANNEL CURRENT

The electric response of sensory hair cells to external stimuli is most likely connected to the flow of charged ions (e.g., calcium) through transduction channels, which play a key role in hair-cell adaptation to external stimuli. Our parsimonious model, which does not explicitly describe the conversion of mechanical energy into an electrical signal, is nonetheless derived from a power-series expansion of the ion channels'

opening probability:

$$P_o(x - y) = \frac{1}{2} + C_2(x - y) + O((x - y)^2), \quad (18)$$

cf. Eq. (2) and Ref. [52, Eq. (S8)]. This approximation allows us to analyze the response of the ionic current through the open channels to the mechanical stimuli as described below.

Because we cannot obtain the coefficient C_2 in Eq. (18) from the inferred values of the model parameters, we approximate the flow of ions $I \propto P_o$ —assumed to be proportional to the number of open channels [5]—by a linear constitutive relation $I \approx I_{\text{base}} + L(x - y)$, where L is a generalized Onsager coefficient and I_{base} is a constant base current. Then from simulations we estimate the average *offset* of the receptor current:

$$\frac{1}{L} \langle \Delta I(F_e) \rangle = \langle x - y \rangle_{F_e} - \langle x - y \rangle_0. \quad (19)$$

Here we consider the offset current normalized to the unknown value of the Onsager coefficient L by averaging $\langle x - y \rangle_{F_e}$ in the presence of the stimulus F_e and $\langle x - y \rangle_0$ in the absence of the external force ($F_e \equiv 0$).

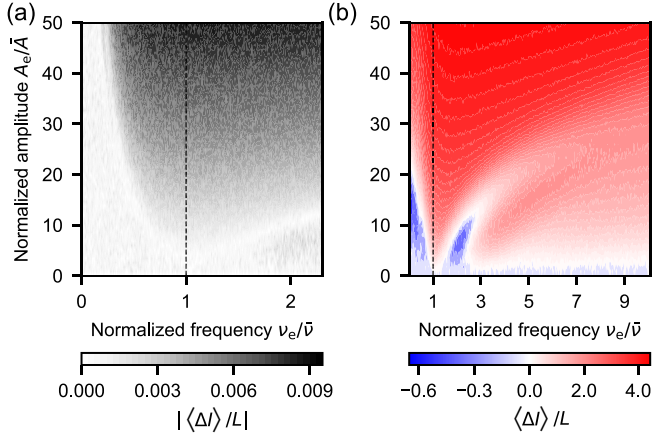


FIG. 7. Average offset of the ion-channel receptor current $\langle \Delta I \rangle$ [Eq. (19)] normalized by the generalized Onsager coefficient L [panels (a) and (b), Figs. S19(a) and S19(b)] as functions of the stimulus' frequency ν_e and amplitude A_e obtained from numerical simulations of parameter sets 1 [panel (a)] and 2 [panel (b)]. The absolute values of the current in (a) remain below one standard error and, therefore, are shown in grayscale tones. In (b) we plot only the data points where the magnitude of $\langle \Delta I \rangle / L$ exceeds one standard error. The horizontal and vertical axes are normalized by the natural frequency of the unperturbed hair bundle $\bar{\nu}$ (vertical dashed line) and $\bar{A} = \sqrt{2k_B T \gamma \bar{\nu}}$. The natural frequencies of the parameter sets 1 and 2 ($\bar{\nu}_1 = 13.022 \pm 0.002$ Hz and $\bar{\nu}_2 = 2.9703 \pm 0.0008$ Hz) respectively yield $\bar{A}_1 = 0.12 \pm 0.01$ pN [panel (a)] and $\bar{A}_2 = 0.112 \pm 0.001$ pN [panel (b)].

Interestingly, the parameter sets 1 and 3, which describe the uninodal oscillations, generate no significant current ΔI in response to the external stimulus: the magnitude of its average value always remains below its standard error $|\Delta I| < \text{SE}(I)$ and, thus, is dominated by fluctuations, cf. Fig. 7(a) [52, Figs. S19(a) and S19(c)]. In contrast, the external stimulus elicits large offsets of the ion-channel current, i.e., $|\Delta I| > \text{SE}(I)$ (above “one sigma”), in parameter sets 2 and 4, cf. Fig. 7(b) [52, Figs. S19(b) and S19(d)].

The above findings support our interpretation of DWT as a signature of the sensory function of hair cells. While low-amplitude signals generally tend to close ion channels, in these two cases large values of A_e sustain ion-channel currents whose mean offsets $\langle \Delta I \rangle$ appreciably exceed by magnitude the standard error of their fluctuations.

VI. MECHANICAL SENSITIVITY

The mechanical response to a periodic external stimulus is often characterized from experiments by the oscillator phase entrainment [74]. To this end we performed Fourier analysis of the power transmission and reconstructed average phase differences between the signal and the affected hair bundle [52, Sec. 7]. In particular, following Martin and Hudspeth [74], we estimated the phase-locking parameter [Figs. 8(a) and 8(b), Fig. S16]

$$R \equiv \frac{x_{\text{rms}, \omega_e}}{x_{\text{rms}}}, \quad (20)$$

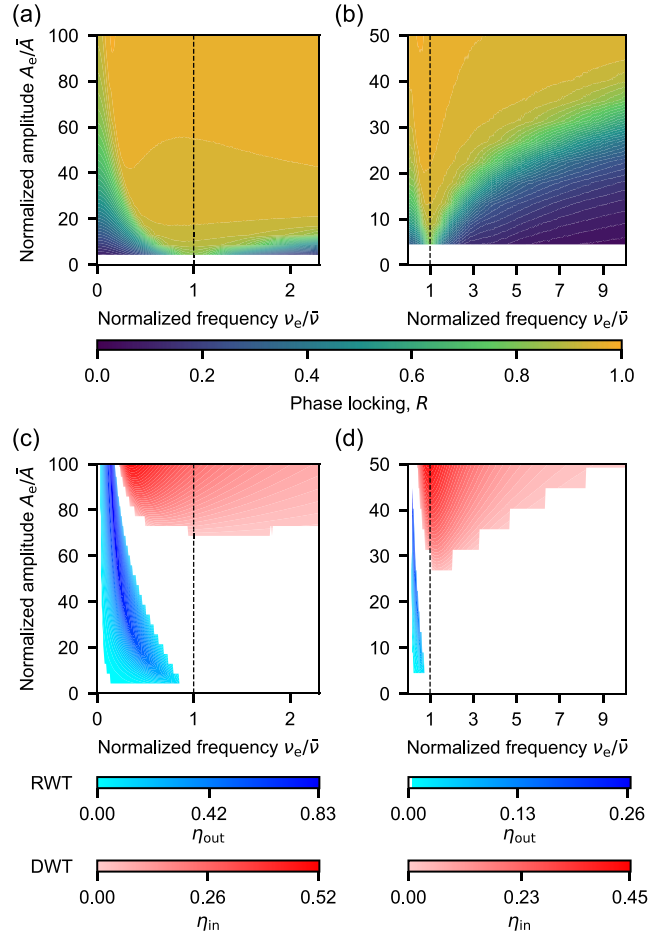


FIG. 8. The degree of entrainment of a hair bundle's movement [panels (a) and (b)] and the efficiency of direct (DWT, red) and reverse (RWT, blue) work-to-work transduction regimes [panels (c) and (d)] as functions of the stimulus frequency ν_e and amplitude A_e obtained from numerical simulations of parameter sets 1 [(a), (c)] and 2 [(b), (d)]. Heater and unresolved (when the average of any flow $\dot{Q}$, $\dot{W}_a$, or $\dot{W}_e$ is less than its standard error) regimes are white in (c) and (d). The horizontal and vertical axes are normalized by $\bar{\nu}$ (vertical dashed line) and $\bar{A} = \sqrt{2k_B T \gamma \bar{\nu}}$ with a minimal amplitude of $A_e = 0.5$ pN for both cases.

in which

$$x_{\text{rms}} = \sqrt{\frac{1}{2\pi} \int_0^{+\infty} \tilde{C}(\omega) d\omega}, \quad (21)$$

$$x_{\text{rms}, \omega_e} = \sqrt{\frac{1}{2\pi} \int_{\omega_e - \omega_b}^{\omega_e + \omega_b} \tilde{C}(\omega) d\omega}, \quad (22)$$

are the rms magnitudes of the hair bundle's spontaneous motion and in response to the stimulus angular frequency $\omega_e = 2\pi \nu_e$ within a bandwidth 0.1 Hz. $\tilde{C}(\omega)$ and $\tilde{C}(\omega|\omega_e)$ stand here for the power spectrum of the time series $x(t)$ in absence and presence of the external stimulation.

The phase locking $R \in [0, 1]$ measures the fraction of power transmitted through the hair bundle in a narrow range around the signal frequency ν_e . While generally saturating with the amplitude A_e of the driving force, this parameter of the response indicates a maximum sensitivity at the natural

frequency of the hair bundle $\nu_e \approx \bar{\nu}$ [Figs. 8(a) and 8(b)] [52, Fig. S15]. However, the power transmission *through* the hair bundle characterizes the ability of the system to absorb only transient mechanical energy from the stimulus. This energy may either be dissipated as heat—displaying low efficiency η_{in} or no DWT at all—or forwarded into the cell as $\dot{W}_a$.

Interestingly, we observe that high values of phase locking are prerequisite for DWT [Figs. 8(c) and 8(d)], whereas RWT occupies the region of low mechanical sensitivity below the natural frequency of oscillations. In particular, in the uninodal oscillations the parameter R increases with A_e on a broader spectrum of frequencies [Fig. 8(a)], [52, Figs. S15(a) and S15(c)] than in the monostable cases [Fig. 8(b)], [52, Figs. S15(b) and S15(d)]. Coherently, DWT of a uninodal hair bundle emerges over a broad range of frequencies and high magnitudes of the signal [Fig. 8(c)], [52, Figs. S20(a) and S20(c)], whereas the monostable hair bundle begins to extract power from the signal at almost twice as low amplitudes A_e and in a specific narrow range around $\bar{\nu} \approx \nu_e$ [Fig. 8(d)], [52, Figs. S20(b) and S20(d)].

VII. DISCUSSION

Our parsimonious stochastic model of hair-cell bundle oscillations reveals that interactions between an active feedback mechanism and external periodic driving encompass four possible thermodynamic regimes. These regimes are triggered by specific frequencies and amplitudes of the stimulus. They include a basic mode of operation as a heater, a nontrivial mode of feedback refrigerator, as well as the direct and reverse work transduction.

The flow of energy $\langle \dot{W}_e \rangle$ from the external force into the system turns negative in a narrow region of signals with low frequencies and amplitudes. That is, the intracellular active process can selectively power up, and thus amplify, such weak signals by exploiting the regime of reverse work transduction. This result, which is also supported by previous experimental observations that a hair bundle exerts work on an externally attached fiber oscillating at low frequencies and small amplitudes [24], relates to the phenomenon of antiresonance. In agreement with Ref. [24], the RWT appears viable only when the external driving oscillates below the natural frequency of the hair bundle—typically displaying phase lead in this operational mode [52, Sec. 7, Fig. S16]—in both uninodal and monostable regimes of our experimental time series. These results may generate promising avenues of research in the emerging field of energy harvesting from the efficient rectification of fluctuations in small (e.g., nanosize) systems [75–77].

Though an unperturbed active hair bundle continuously dissipates energy received from the internal adaptation force, when externally stimulated it is also capable of harvesting energy from signals of frequencies $\nu_e \gtrsim \bar{\nu}$ and amplitudes $A_e \gg \sqrt{2k_B T \gamma \bar{\nu}}$. This regime of direct work transduction, where the power intake is interpreted as information flow, is suggestive of a hypothetical mechanism that could trigger the neural activity to support the sensing function of a hair cell. The signal detection does not necessarily imply a large inflow of energy but might rely on a high quality of the signal relative

to its fluctuations, e.g., as characterized by the signal-to-noise ratio.

The intake efficiency $\eta_{\text{in}} = -\langle \dot{W}_a \rangle / \langle \dot{W}_e \rangle$ estimates the upper bound for the fraction of work—here interpreted as information flow—preserved by the mechanical transduction. How this work is converted into information and interpreted by the signal-processing cascade within the cell remains an open question for future research. In particular, the conversion of harvested mechanical energy into a neural signal should incur additional losses and thus further reduce the efficiency of information passage.

In our experimental data, we identified two dynamical regimes of a hair bundle’s oscillatory behavior: uninodal relaxation oscillations with a remarkable potential of signal amplification, and a monostable regime capable of harvesting energy with a high signal-to-noise ratio. In principle, hair cells might rely on the affinity of the two regimes to the RWT and DWT to fulfill their amplification and sensing functions, respectively. This interpretation is further supported by our estimates of the ion-channel currents. The external driving substantially offsets ion-channel currents in the regime, which we associate with the sensory function, but evokes no appreciable response of the ion channels in the regime attributed to the signal amplification.

Moreover, like in some other biological systems [78], the Hopf bifurcation associated with the above two dynamical regimes may affect the hair-cell function. While approaching the bifurcation point, the uninodal regime displays more efficient amplification capabilities, and the monostable regime loses its high signal-to-noise ratio of the direct work transduction. The parameters of the active oscillatory mechanism could also be controlled by additional active processes within hair cells or by the accessory structures present in the hearing and balance-sensing organs. These additional mechanisms are capable of fine-tuning the target levels of power transduction. In particular, hair cells must be able to sustain and assimilate relevant amounts of transduced energy to avoid mechanical damage, which could be caused by interactions with excessively powerful sources.

Active power outlet in the reverse work transduction thermodynamically may also trigger efferent information transmission toward the auditory nerve. Therefore the cells displaying the uninodal relaxation oscillations like cases 1 and 3 may at least detect the external stimulation. This observation concurs with the fact that outer hair cells, which are believed to specialize in signal amplification, are found to engage in neural signaling as well [79]. However, whereas RWT is capable of signal amplification, DWT is not, which strongly suggests that the affinity of uninodal and monostable oscillations to one of these two respective regimes is related to the cell function.

Our findings align well with the current understanding of the cochlear function. While progressing from the base toward the apex of the cochlea, a traveling wave passes by the bundles arranged in the tonotopic order according to their natural frequency. Hair bundles oscillating slower than the wave, traversed first, increase its power. At the characteristic place, where the hair bundles oscillate at the stimulus frequency, the wave’s energy reaches its maximum and decays afterward [80,81]. Basal to this characteristic place, hair cells

experiencing stimulation below their own natural frequency might operate in the RWT regime to power the signal. The hair cells at the location of maximum sensitivity detect the stimulus by DWT, while apical to this site, hair cells dissipate energy, thus attenuating the signal.

While our study examines hair-bundle dynamics under continuous stimulation, where the system reaches a steady oscillatory state, exploring their response to signal impulses or wave packets of finite duration suggests another promising direction for future research [82]. Such stimuli would probe properties of transient dynamics, the system's capacity for entrainment over finite timescales, and how its response depends on the internal phase of oscillations.

VIII. MATERIALS AND METHODS

Recording oscillations of a hair bundle's tip in a two-chamber preparation. A dissected mechanosensitive epithelium of a bullfrog's sacculus was mounted between two chambers, one filled with perilymph and the other with endolymph, to mimic the physiological condition of the inner ear. Under these conditions, the hair bundles of healthy cells display spontaneous, robust oscillations, as reported previously [24,55–58]. We observed oscillating hair bundles under an upright microscope with differential-interference-contrast optics. Because slowly oscillating bundles are easy to identify visually, we directly projected a high-contrast image of such a hair bundle onto a dual photodiode. After low-pass filtering at 4 kHz, the calibrated signal of the photodiode reported the bundle's position in time.

The experiments were conducted in accordance with the policies of The Rockefeller University's Institutional Animal Care and Use Committee (IACUC Protocol 16942).

Simulation-based inference. To identify parameter values of the model, which reproduce the experimentally recorded time series of the hair bundles' tips [52, Table S6], we applied a simulation-based inference method [53]. For each experimental case 1–4, we generated 5×10^6 trajectories of the corresponding duration with parameter values sampled from a uniform prior in order to train neural posterior estimators.

As the posterior density estimator, we chose a backend based on the normalizing flows. The parameter values [52, Table S6] were inferred by maximizing the *a posteriori* probability of the trained estimator given summary statistics of the time series. Further implementation details are discussed in Ref. [52, Sec. 3].

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DATA AVAILABILITY

The data that support the findings of this article are openly available [83].

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