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A minimal physics-based model for musical perception

Kosar Mozaffari[a], Fatemeh Ahmadpoor[b], Qian Deng[c], and Pradeep Sharma[a,d,1]

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Some people, entirely untrained in music, can listen to a song and replicate it on a piano with unnerving accuracy. What enables some to "hear" music so much better than others? Long-standing research confirms that part of the answer is undoubtedly neurological and can be improved with training. However, are there structural, physical, or engineering attributes of the human hearing mechanism apparatus (i.e., the hair cells of the internal ear) that render one human innately superior to another in terms of propensity to listen to music? In this work, we investigate a physics-based model of the electromechanics of the hair cells in the inner ear to understand why a person might be physiologically better poised to distinguish musical sounds. A key feature of the model is that we avoid a "black-box" systems-type approach. All parameters are well-defined physical quantities, including membrane thickness, bending modulus, electromechanical properties, and geometrical features, among others. Using the two-tone interference problem as a proxy for musical perception, our model allows us to establish the basis for exploring the effect of external factors such as medicine or environment. As an example of the insights we obtain, we conclude that the reduction in bending modulus of the cell membranes (which for instance may be caused by the usage of a certain class of analgesic drugs) or an increase in the flexoelectricity of the hair cell membrane can interfere with the perception of two-tone excitation.

mechanics | soft matter | flexoelectricity | music

A trained musician can discern one-thirtieth of the frequency difference between two successive piano keys which are a semitone apart (1). Many, without formal music training, are able to replicate melodies on an instrument like the piano. What makes some people able to "hear" music so much better than others? Almost certainly, as well documented, there are neurological aspects as well as training history that inform this question (2, 3). Our present work focuses on the physical and engineering aspects of the hearing apparatus that may provide a partial answer to distinguish our ability to perceive music (Fig. 1).

We cannot talk about processing complex sounds like music and speech without first discussing the mammalian hearing mechanism itself. Humans have an auditory range that spans three orders of magnitude (20 Hz to 20 kHz) and can handle sound waves with a million-fold variation in amplitude (1, 2, 4–6). We avoid a detailed description in the interest of brevity. Still, the key action involves how the ear hair cells actively conspire to achieve the requisite amplification, sensitivity, frequency selectivity, and range (3, 4, 7). Over the past few decades, it has come to be widely accepted that the ear system is not a passive sensor but actively assists in the audition and that hair bundle motility is an essential feature of the active process (5, 7–13). Specifically, cellular electromotility—which some have attributed to the flexoelectric effect—has been hypothesized to play a central role (14–17).

The key ideas regarding the hearing process are as follows: the acoustic wave propagates toward the ear and in the basilar membrane. This causes the vibration of the hair cells and the hair bundles, which consist of smaller hairlike objects named stereocilia*. Each stereocilia is connected to its neighbors by elastic molecular strands called tip links. On the stereocilia and around the tip link is an ion channel that activates by a mechanical movement of stereocilia and can allow passage of both K+ and Ca+ ions (9, 12). Therefore, each time the stereocilia is deflected, the influx of ions passing through the ion channel is altered (19, 20). Consequently, the voltage of the hair bundle changes. This change will influence the shape and, consequently, the motion of the stereocilia. All these physical parameters, including ion concentration, thickness and bending modulus of the membrane, etc., are well balanced naturally in subtle ways that the hearing system works on the verge of instability known as Hopf bifurcation.

*The hearing apparatus of a human contains 16,000 hair cells, each containing dozens to hundreds of stereocilia. Therefore, more than a million of these receptive organelles exist in the human ear (18).

Significance

Why do some people hear music better than others? This incredibly complex question requires an integration of multiple disciplines ranging from sociology, neurology to physics. We attempt to provide a partial answer based on the sole mechanism underpinning the physical characteristics of the cellular response complicit in our hearing mechanism. We use an entirely physics-based model to understand how our inner ear perceives multiple tones and, therefore, our ability to clearly distinguish between two pitches. Our model is mechanistic; thus, real structural biological information or physical properties (such as mechanical properties of the hair cells) are clearly identifiable. This allows for a facile investigation into how external factors such as environment or medicine (e.g., NSAIDs) may impact our musical perception.

Author affiliations: [a]Department of Mechanical Engineering, University of Houston, Houston, TX 77204; [b]Department of Mechanical and Industrial Engineering, New Jersey Institute of Technology, Newark, NJ 07102; [c]State Key Laboratory for Strength and Vibration of Mechanical Structures, School of Aerospace, Xi'an Jiaotong University, Xi'an 710049, China; and [d]Department of Physics, University of Houston, Houston, TX 77204

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[1]To whom correspondence may be addressed. Email: psharma@uh.edu.

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Fig. 1. Are there structural aspects of the hearing apparatus that render one human better poised than another to perceive music? Do external factors such as NSAID drugs play an important role in music perception and noise sensitivity?

We remark that the Hopf bifurcation is an oscillatory instability that occurs in nonlinear systems where the pertinent control parameter reaches its critical value. In supercritical Hopf bifurcation, which is the case for the hearing mechanism, the system tends to reach a limit cycle, regardless of its starting point. For deeper discussions, we refer the interested readers to ref. 10. This mechanism is the key factor in the amplification of weak sounds while allowing tolerance of excessively loud stimuli (4, 11, 12, 21–24).

Although electromechanical coupling is crucial in the hearing system, the mechanism behind this coupling is still not clear. The most well-known electromechanical coupling is "piezoelectricity," which exists in rare hard and brittle ceramic materials with specific noncentrosymmetric atomic structures (25). However, there is no evidence of piezoelectric material inside the ear; therefore, there must be another mechanism for this electromechanical coupling. It is hypothesized that flexoelectricity is the primary mechanism behind this electromechanical coupling (15–17). Flexoelectricity is a form of coupling between the strain gradient and the polarization, and it exists in all materials (26–30) and specifically in biological membranes (31–37). In the context of biological membranes, flexoelectricity is simply interpreted as the coupling between the polarization and changes in the curvature of the membrane (31–33).

Some exceptionally insightful work already exists in the literature on the hearing mechanism (9, 12, 13). The novelty of our proposition and its relevance for musical hearing is entirely based on the basic principles of physics as opposed to, for instance, a "black-box" model. We hasten to add that this is not a criticism of existing works. The past pioneering papers have considerably added to our understanding of the hearing mechanism. We aim to move beyond those and link the developed physics-based model to explain musical hearing. For example, the typical models that purport to describe the hearing mechanism adopt a dynamical systems approach, where hair bundles operate as nonlinear tuned amplifiers of weak sound waves. The hair bundles are considered as mathematical nonlinear oscillators, subjected to periodic forces. The displacement of the oscillator x_f is related to the amplitude of the force, F_f, and its frequency through a cubic equation (11): $F_f = Ax_f + Bx_f|x_f|^2$, where A and B depend on the frequency of the sound as well as a control parameter r. The Hopf bifurcation—the instability—happens at specific frequency values f and control parameter r when the corresponding value of $A(f, r) = 0$. What do these parameters mean? Are they related to the hair cells' density, size, or other properties? Such nuances are not captured in the existing models. All the parameters that appear in our work are real measurable constructs, e.g., the bending modulus of the outer hair cell membrane modulus, size-shape, etc. For example, certain types of medicine (NSAIDS) cause a change in the bending modulus of cell membranes (38). Our model may very well then explain how these medications may be tied to changes in our hearing mechanism and, in particular, sensitivity changes toward music and external noises. We remark that the impairment in hearing due to the consumption of NSAIDS (e.g., Ibuprofen) has attracted significant attention in recent years (39–43) and it has been conjectured that the consumption of macrolide antibiotics (e.g., Azithromycin) and salicylates (e.g., Aspirin) have a similar effect on the hearing mechanism as well (44–47).

In a preliminary work (48), we have made substantial progress toward creating at least the rudiments of a physics-based model of the hearing mechanism, which is based on flexoelectricity being the main culprit underpinning membrane electromotility and, additionally, links with the dynamics of hair cells to explain other features which are summarized in *Theoretical Formulation of the Hearing Mechanism*. As elaborated before, all parameters in the model are real measurable physical parameters. In this work, with the help of a physics-based model of the electromechanics of the hair cells in the inner ear, we investigate why some humans are physiologically poised to distinguish musical sounds better than others. A key feature of the model to be developed in this research is that the parameters of the model are known physical quantities such as membrane thickness and bending modulus, flexoelectric properties, and geometrical features, among others. The derived model is based on the well-accepted principles of thermodynamics and continuum mechanics.

Understanding music perception is a rather complex endeavor—to put it mildly. We do not wish to overstate what we set out to do so in this article. Our narrow objective is to isolate the structural or physical aspects that may play a role in the so-called two-tone problem. The response of the ear to two-tone excitation and understanding of the inference is at least a partial proxy for musical perception. The canonical problem that we address may be understood as follows. The frequency response curve of two tones is complicated due to physical nonlinearities and is consequently not simply the superposition of response to two single tones. Perception of two tones—as the simplest example of musical perception—acutely depends on their frequency ratio, i.e., f_2/f_1, with f_1 being the higher frequency (49). If the two tones are about an octave apart, i.e., $f_2/f_1 = 1/2$, the frequency response curves do not have much overlap (1)—as shown in Fig. 2. As the intervals between the two tones decrease, the response curves overlap significantly and make it much more difficult for the ear to distinguish them from each other.

The outline of the paper is as follows. In *Theoretical Formulation of the Hearing Mechanism* we briefly present the key element of the theoretical model we use to capture the key aspects of the hearing mechanism and adapt it for the two-tone problem. In *Results*, we probe the answer to the questions we have raised in the preceding paragraphs. The first problem we study is the compressive nonlinearity of the hair cells. This is predicated on the Hopf bifurcation and endows the hearing system with the ability to perceive a wide range of frequencies by amplifying the faint sounds while deamplifying the louder sounds. We investigate the effect of flexoelectricity on the two-tone inference problem. As concluded from our previous work (48), we observe that flexoelectricity has a crucial role in compensating for the damped energy inside the ear by injecting energy into the system. More germane to the present work, we also find that flexoelectricity plays a rather interesting role in the two-tone interference problem. The effect of physical

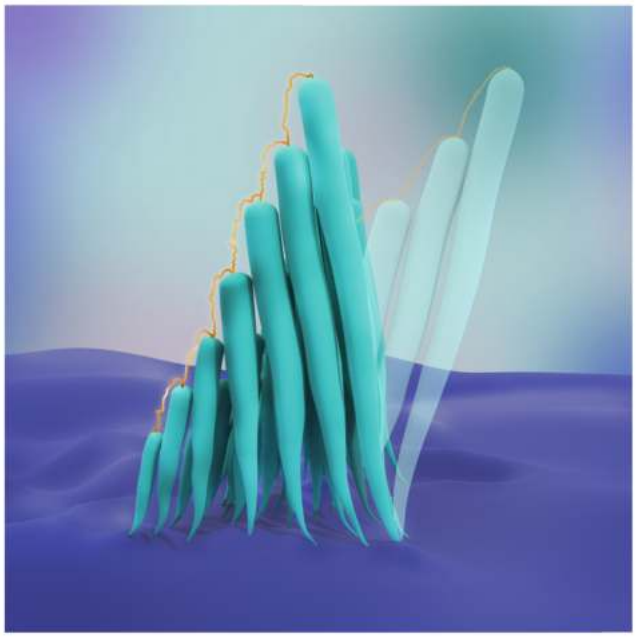

Fig. 2. Depicted is a schematic of a hair bundle with representative stereocilia. The active motion of stereocilia on the hair cells contributes to the sound amplification and several other compelling aspects of the human hearing mechanism.

characteristics, including the membrane thickness and bending modulus of the stereocilia, is discussed in detail. The latter becomes vital in medicine due to the effects of the NSAID type drugs on the cell-bending modulus. It is observed that the consumption of NSAID causes a decrease in the bending modulus (38), and we have shown that this can eventually disrupt the inference of the second tone. The last Section is devoted to the concluding remarks and future directions for the existing research.

1. Theoretical Formulation of the Hearing Mechanism

In this section, we closely follow the theoretical formulation discussed in our previous work (48) with some relevant modifications. Our physics-based model is based on the nonlinear dynamics, mechanics, and flexoelectricity of the hair bundle and is predicated on three key points: 1) The rotation of the hair bundle changes the tension of the tip links; 2) the ion-channel gates are mechanosensitive, and the change of tip link force, therefore, impacts the opening state of the gates; 3) the ions flowing through the channel gate can significantly change the voltage of the hair bundle and then alter the shape of the stereocilia due to the flexoelectric effect. Our model fully replicates the widespread belief that our hearing apparatus runs on the verge of Hopf bifurcation, which is responsible for several important aspects of our hearing mechanism, such as compressive nonlinearity. We remark that other works have pointed out the importance of Hopf bifurcation. The advantage of our model is that it is physically based, and indeed, flexoelectricity is critical to the occurrence of Hopf bifurcation.

Consider a hair bundle as shown in Fig. 3 which consists of several tens to hundreds of stereocilia. The stereocilia are connected to their neighbors by thread-like tip links. For brevity, we depict only one stereocilia in Fig. 4. The hair bundle undergoes motion due to the impingement of the acoustic wave on the basilar membrane. This leads to the rotation of the stereocilia, which in turn alters the length of the tip links, thus generating forces. These tip link forces may open or close ion-gate channels that regulate the flow of ions. Flexoelectricity then provides a mechanism to couple mechanical motion to electrical fields, thus leading to a highly coupled and nonlinear confluence of electromechanics on the time-dependent changes in the stereocilia's radius and length alter. We focus on two types of stereocilia motion: the rotation around the pivot and the shape change.

Since the stereocilia is a hollow tube filled with fluid, the total volume ($V(t)$) is considered to be conserved, i.e.,

$$V(t) = \pi R(t)^2 l(t) = V_0 = \pi R_0^2 l_0, \qquad [1]$$

where (V, l_0, R_0) and (V_0, l, R), respectively, stand for the enclosed volume by the stereocilia, length, and outer radius of the stereocilia in the initial and current states. Since the stereocilia are connected to the neighboring ones through tip links, as the base membrane vibrates, the stereocilia will vibrate, and therefore, the tip link length (and force) will change. Accordingly, the length of the stereocilia (l) will be modified. Consequently, any change in the length of the stereocilia Δl can be obtained as

$$\Delta l = l - l_0 = \left(\frac{R_0^2}{R^2} - 1\right) l_0. \qquad [2]$$

The change in the longitudinal direction can be written as linear expansion/contraction along its length and therefore is defined as

$$u(y, t) = \left(\frac{l(t)}{l_0} - 1\right) y = \left(\frac{\Delta l}{l_0}\right) y, \qquad [3]$$

where we have assumed that the origin of the coordinate y is at the bottom of the stereocilia as shown in Fig. 4.

Furthermore, by defining the thickness of the stereocilia as a constant (h), we can formulate the change in the radius of stereocilia as

$$w(t) = R(t) - R_0. \qquad [4]$$

To consider stereocilia rotation, we neglect the mass of the stereocilia and only consider the mass of the accessory structure, including the tectorial membrane (TM), which is on the longest stereocilia and is shown by M_{AS}. Let the horizontal deformation of the accessory structure be defined by x. The governing equation for the movement of stereocilia can be formulated as

$$\begin{aligned} K_{rsp}\theta &= K_{rsp}\frac{x}{l_0} \\ &= \left[F_{tip}\cos\varphi - M_{AS}\left(\ddot{x} + \ddot{x}_{BM}\right) - c_{eff}\left(\dot{x} + \dot{x}_{BM}\right)\right] l_0, \end{aligned} \qquad [5]$$

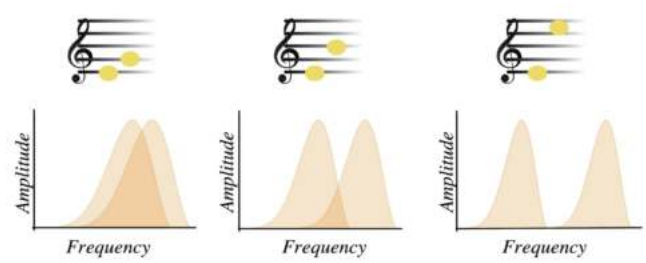

Fig. 3. Frequency response curve of two tones with different frequencies. When the two tones are well separated, the response curves do not have much overlap and the two tones are perfectly distinguishable. Adapted from ref. 1.

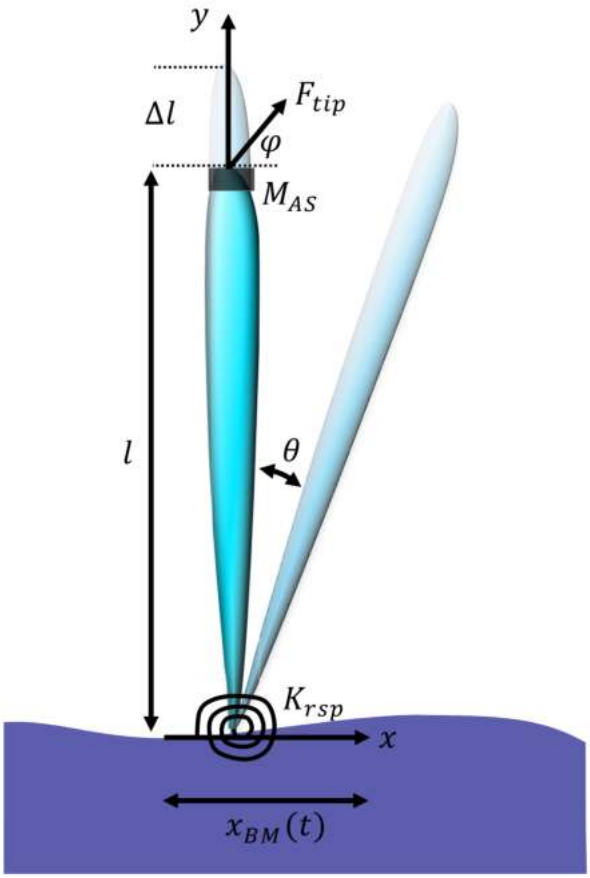

Fig. 4. Schematic of stereocilia capturing its rotational motion and shape change.

where, F_{tip}, c_{eff}, and K_{rsp} are the tip link force, effective damping coefficient, and effective rotational spring constant. The tip link force is in the direction of the link and, stipulating (to first order) a linear spring-like behavior, is linearly proportional to both change in stereocilia's length (vertical change) and its movement (horizontal change) with K_L being the constant of proportionality as follows (7, 9, 12, 16):

$$F_{tip} = K_L\left(x\cos\varphi - \Delta l\sin\varphi\right). \quad \textbf{[6]}$$

Defining $K_{eff} = K_{rsp}/(l_0^2)$, and rearranging Eq. **5**, we find

$$\begin{aligned} M_{AS}\ddot{x} + c_{eff}\dot{x} + \left(K_{eff} - K_L\cos^2\varphi\right)x \\ = -K_L\sin\varphi\cos\varphi\Delta l + F_{stim}, \end{aligned} \quad \textbf{[7]}$$

where $F_{stim} = -M_{AS}\ddot{x}_{BM} - c_{eff}\dot{x}_{BM}$ is the effective external stimulation force which includes the terms related to the base vibration of the structure.

We now take recourse in the Hamilton's principle to account for the longitudinal movement of the stereocilia, mainly due to the flexoelectric effect. With the kinematics as described in the preceding section, we may express the stereocilia's electromechanical behavior as ref. 48:

$$\begin{aligned} &\delta\int_{t_0}^{t_1} dt\left\{\int_{\omega}\left[\frac{h}{2}\rho\left(\dot{u}^2+\dot{w}^2\right)-\mathcal{H}\right]da - \lambda(V-V_0)\right\} + \\ &\int_{t_0}^{t_1} dt\left\{\int_{\omega^\pm} t^e\delta w da - \int_{\omega^\pm}\bar{q}\delta\phi da - h\int_{\omega}\mathcal{M}\delta H da\right\} = 0, \end{aligned} \quad \textbf{[8]}$$

where ω and $\omega^\pm$ denote the middle layer and outer and inner surfaces of the stereocilia membrane in the deformed state. Also, $\delta(*)$ stands for the variation of a functional, and ρ is the mass density. Furthermore, λ is the Lagrangian multiplier which ensures that the total enclosed volume of the stereocilia will not change during the deformation. The external pressure applied normal to the surfaces $\omega^\pm$ by the surrounding fluid is denoted by t^e. The density of the net charges attached to the surfaces $\omega^\pm$ is $\bar{q}$ and ϕ is the electric potential. The last term in Eq. **8** corresponds to the energy dissipation due to viscous damping and can be simply written as $\mathcal{M}\delta H$ where $\mathcal{M} = c\dot{H}$ is the effective moment, and c is the effective viscosity that links the mean curvature H to $\mathcal{M}$ (50).

The internal energy for the system can be defined as

$$\mathcal{H} = \frac{1}{2}\kappa_b H^2 + \frac{1}{2}ap_s^2 + f^f Hp_s - e\cdot\left(p_s + p^e\right) - \frac{h\epsilon_0}{2}e^2, \quad \textbf{[9]}$$

where κ_b, H, e, and ϵ_0 denote the bending modulus, mean curvature of the membrane, electric field, and permittivity of the vacuum. Besides, $a = 1/((\epsilon_r - 1)\epsilon_0 h)$ is the constant of proportionality between the polarization to the internal energy density. $p_s = -Hf^f/a$ is the polarization per unit area caused in the membrane due to the flexoelectricity where f is the flexoelectric coefficient, and p^e is the external or preexisting polarization due to the presence of (say) polarized proteins. For the sake of simplicity, we assume that p^e is constant throughout the deformation, although this assumption is easily relaxed if needed.

For convenience, we convert the integration of membrane surfaces in the current state to the undeformed states as Ω, $\Omega^\pm$, which, respectively, notate middle and outer/inner surfaces in the undeformed configuration. Moreover, in order to make the state variable p^s independent of the deformation, we define the polarization with respect to the mass as follows

$$\Pi = \frac{p_s}{h\rho}. \quad \textbf{[10]}$$

The membrane is thin enough that it is reasonable to assume a constant electric field across its thickness. Thus, the electric field can be simply expressed as

$$e = -\frac{\Delta\phi}{h}.$$

where $\Delta\phi$ is the potential difference across the membrane thickness. The variational calculation for each term in the Hamilton's principle is summarized below. Further details may be found in our previous work (48).

1) Variation of the kinetic energy:

$$\begin{aligned} &\delta\int_{t_0}^{t_1} dt\left[\int_{\omega}\frac{h}{2}\rho\left(\dot{u}^2+\dot{w}^2\right)da\right] \\ &= \int_{t_0}^{t_1} dt\left[\int_{\Omega} -\rho_0 h\left(\ddot{u}\delta u + \ddot{w}\delta w\right)dA\right]. \end{aligned} \quad \textbf{[11]}$$

2) Variation of the internal energy:

$$\begin{aligned} \delta\int_{t_0}^{t_1} dt\int_{\omega}\mathcal{H}\left(H,\Pi\right)da &= \int_{t_0}^{t_1} dt\int_{\Omega}\left(\delta\mathcal{H}J + \mathcal{H}\delta J\right)da \\ &= \int_{t_0}^{t_1} dt\int_{\Omega}\left[\left(\mathcal{H}_H\delta H + \mathcal{H}_\Pi\delta\Pi\right)J + \mathcal{H}\delta J\right]dA, \end{aligned} \quad \textbf{[12]}$$

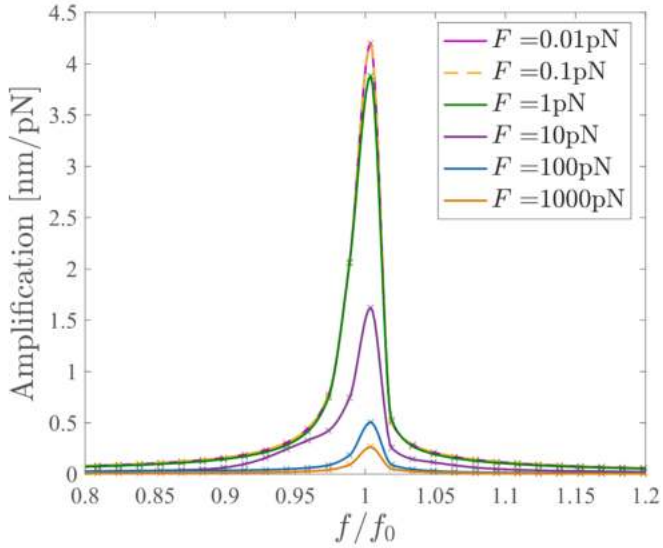

Fig. 5. The nonlinear compressibility aspect of the hearing mechanism. The ear amplifies faint sounds much more than the loud ones; therefore, the ear can perceive both high and low pitch to some extent without damaging its structure. The curves are interpolated based on the data points of the Fourier transform of the response. The amplification is calculated by dividing the response to the stimulation force, and the frequency response is normalized to the natural frequency of the system.

where $\mathcal{H}_H$ and $\mathcal{H}_\Pi$ denote the derivatives of the internal energy density function $\mathcal{H}$ with respect to the mean curvature H and the polarization per unit mass Π, respectively. Note that, the variation of J is given by $\delta J = \frac{R}{R_0 l_0}\delta l + \frac{l}{R_0 l_0}\delta R$.

3) Variation of the energy associated with the external pressure:

$$\int_{\omega^\pm} t^e \delta w d\mathrm{a} = \int_{\omega} \Delta t^e \delta w d\mathrm{a} = \int_{\Omega} \Delta t^e \delta w J dA, \qquad [13]$$

where $\Delta t^e = t^{e+} - t^{e-}$ stands for the pressure difference between outer and inner surfaces. We remark that since the membrane is very thin, the variation of the w is negligible across its thickness.

4) Variation of the virtual work done by the dissipative moment:

$$\int_{\omega} \mathcal{M}\delta H d\mathrm{a} = \int_{\omega} c\dot{H}\delta H d\mathrm{a} = \int_{\Omega} \frac{c}{R^4}\dot{R}\delta R J dA, \qquad [14]$$

by keeping in mind that $H = 1/R$.

5) Variation of the virtual work done by the surface charges attached to $\omega^\pm$:

We decompose the charges that are due to the ions in the electrolyte surrounding the membrane of stereocilia to an inner (q^-) part and the remainder on its outer side (q^+).Thus, we have

$$\begin{aligned}\int_{\omega^\pm} \bar{q}\delta\phi d\mathrm{a} &= \int_{\omega} \left(q^+\delta\phi^+ + q^-\delta\phi^-\right) d\mathrm{a} \\ &= \int_{\Omega} \left(q^+\delta\phi^+ + q^-\delta\phi^-\right) J dA.\end{aligned} \qquad [15]$$

Since the charge density outside the stereocilia is stable and does not vary much, we can safely assume that the variation of charge and electric potential on the outer side of the stereocilia is negligible. Therefore, $q^+\delta\phi^+ \approx 0$.

On the other hand, the charges inside the stereocilia are affected by the ion channels and play a role in the passage of K^+ and Ca^+ ions. It has been proposed that the channel opening is related to the deflection of the stereocilia (19, 20, 51) and thus, the probability of the channel opening (P_o) can be formulated as ref. 48

$$P_o = 1/\{1 + \exp[(x_0 - x)/\Delta]\}, \qquad [16]$$

where x_0 is the location of the mass above the stereocilia to half activate the ion channel. Here, for simplicity and without loss of generality, we proceed with assuming $x_0 = 0$. Furthermore, Δ stands for the range of the deformation that the channel goes from 10 to 90% opening. Assuming the case when the channel is fully open, the charge density will be $q^- = q_0$. Thus, considering the probability of opening of channel discussed in Eq. **16**, we can approximate the charge density q^- in a general form as

$$q^- \approx P_o q_0. \qquad [17]$$

Performing the variational calculation and simplifying the equations further, we obtain (48):

$$\begin{aligned}&\rho_0 h\left(\frac{R^5}{R_0} + \frac{4}{3}\frac{R_0^3 l_0^2}{R}\right)\ddot{R}m - 4\frac{\rho_0 h R_0^3 l_0^2}{R^2}\left(\dot{R}\right)^2 + ch\dot{R} \\ &-\left[\frac{3}{2}\kappa_b - \frac{\left(f^f\right)^2\epsilon_0}{\eta}\left(\frac{3}{2} + \frac{1}{\eta h}\right)\right]R - 2\frac{f^f q_{eff}^-(x)}{h\eta^2}R^2 \\ &+\frac{a\left(a\epsilon_0 h - 1\right)}{2\eta^2}\left(q_{eff}^-(x)\right)^2 R^3 = \Delta t^e R^4,\end{aligned} \qquad [18]$$

where $\Delta\phi = \phi^+ - \phi^-$ stands for the potential difference between outer and inner layer and $q_{eff}^- = q^- - \frac{p^e}{h}$ and $\eta = a\epsilon_0 + \frac{1}{h}$. In what follows, we ignore external polarization since its contribution can be equivalently introduced by appropriately adjusting the charge density q^- (52, 53).

Δt^e may be estimated in a simple way. Since the total volume of the stereocilia is constant, the dominant shape change is due to flexoelectricity and not from the pressure difference. Therefore,

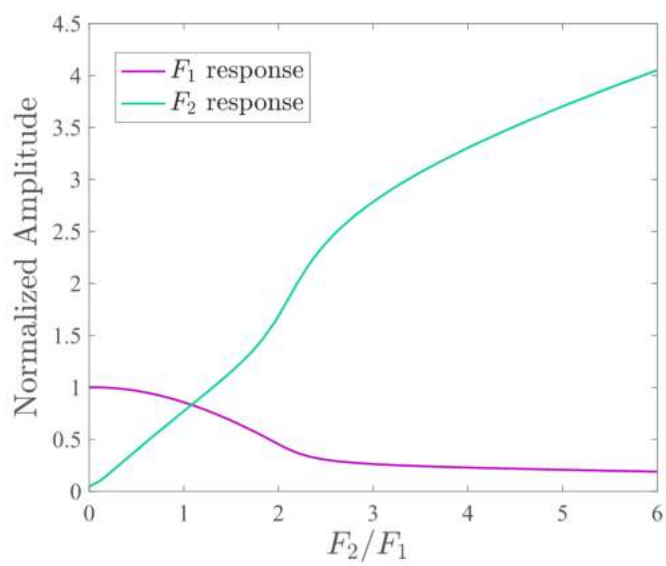

Fig. 6. Suppression of the first tone by addition of the second tone where F_1 and F_2 stand for the amplitudes of the stimulus forces of the first and second tone. Note that the first tone is tuned to the natural frequency of the stereocilia (i.e., $f_1 = f_0$), and the frequency of the second tone is related to the natural frequency of the stereocilia by $f_2 = 0.9f_1$.

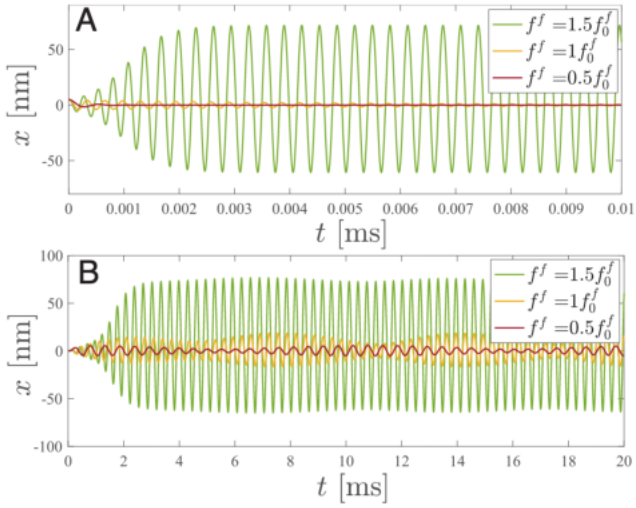

Fig. 7. Sensitivity of the stereocilia to the flexoelectric constant. Response of the system to (*A*) the free oscillation, (*B*) forced oscillation involving two-tone excitation, where $F_1 = 10$ pm, $F_2 = 0.5F_1$, $f_1 = f_0$, and $f_2 = 0.95f_1$. Flexoelectricity is responsible for compensating for the damping due to the viscous fluid, and lack(addition) of it results in a faster (much slower or never-ending!) damping of the stimuli inside the ear.

we can estimate the pressure difference Δt^e from the reference state. Thus, by assuming $R = R_0$, $\dot{R} = 0$, and $x = 0$, the pressure difference may be found as

$$\Delta t^e \approx -\left[\frac{3\kappa_b}{2} - \frac{\left(f^f\right)^2 \epsilon_0}{\eta}\left(\frac{3}{2} + \frac{1}{\eta h}\right)\right]\frac{1}{R_0^3} - \frac{\alpha f^f q_0}{\eta^2 h R_0^2} - \frac{a\left(1 - a\epsilon_0 h\right)\alpha^2 q_0^2}{8\eta^2 R_0}. \quad [19]$$

The final governing equations can be obtained from Eqs. **7** and **18**. In the next section, we attempt to gain some insights into the hearing apparatus and two-tone inference.

2. Results

The nonlinear differential equations describing the motion of the stereocilia are

$$\begin{cases} M_{AS}\ddot{x} + c_{eff}\dot{x} + \left(K_{eff} - K_L\cos^2\varphi\right)x \\ \qquad = -K_L\sin\varphi\cos\varphi\,\Delta l + F_{stim}, \\ \rho_0 h\left(\frac{R^5}{R_0} + \frac{4}{3}\frac{R_0^3 l_0^2}{R}\right)\ddot{R}m - 4\frac{\rho_0 h R_0^3 l_0^2}{R^2}\left(\dot{R}\right)^2 + ch\dot{R} \\ -\left[\frac{3}{2}\kappa_b - \frac{\left(f^f\right)^2\epsilon_0}{\eta}\left(\frac{3}{2} + \frac{1}{\eta h}\right)\right]R - 2\frac{f^f q_{eff}^-(x)}{h\eta^2}R^2 \\ +\frac{a(a\epsilon_0 h - 1)}{2\eta^2}\left(q_{eff}^-(x)\right)^2 R^3 = \Delta t^e R^4, \end{cases} \quad [20]$$

In what follows, we investigate the nonlinear amplification, the role of flexoelectricity, two-tone interference and distinction, and the attributes affecting the latter.

A. Nonlinear Amplification. Compressive nonlinearity is an essential aspect of our hearing mechanism and is considered to arise due to Hopf bifurcation (4, 11, 12, 21–24). This has been discussed by many authors c.f. ref. 11 and 2. We briefly first present results on this topic before tackling the two-tone problem.

We numerically solve the coupled equations on Eq. **20**. We have assumed that $F_{stim} = F\,\mathrm{Sin}(2\pi f_0 t)$, where f_0 is the natural frequency of the stereocilia. Fig. 5 shows the frequency amplitude and normalized frequency for specific stereocilia with natural frequency f_0. As depicted, the amplification is higher for smaller stimulation forces while it is negligible for extremely large stimulations. It is worthwhile to mention that there is a limit to this amplification. For instance, there is no difference in amplification for $F = 0.01$ pN compared to $F = 0.1$ pN, which demonstrates the existence of the upper limit for the amplification factor.

B. Two-Tone Interference. As discussed in the preceding sections, the ear has a very rich structure, and stimulating it with the second tone may impact the response to the first tone, and it is not simply the superposition of the responses. From prior work by Jülicher et al. (49, 54), we expect that the addition of the second tone ought to suppress the response of the first tone and vice versa (55–57). This phenomenon is known as "masking" (58) and has been investigated experimentally in ref. 56. We now use our physics-based model to interrogate this. We solve again Eq. **20** and assume that a stereocilia is excited by two tones where the stimulation forces are $F_{stim} = F_1\mathrm{Sin}(2\pi f_1 t) + F_2\mathrm{Sin}(2\pi f_2 t)$, where $f_1 = f_0$ and $f_2 = 0.9f_1$. In Fig. 6, the normalized amplitudes of the response in the frequency domain are plotted against the stimulus amplitudes of the two tones. The normalized amplitudes are the amplitude of the response divided by the case where the system is excited with solely the first tone. Evidently, the addition of the second tone, with a frequency that is "close" to the first tone, can suppress the response to the first tone by as 50%. This disruption is more observable when the amplitude of the second stimulus is comparable to that of the first stimulus.

C. Role of Flexoelectricity. In our view, flexoelectricity is the key electromechanical mechanism. Based on prior work (48),

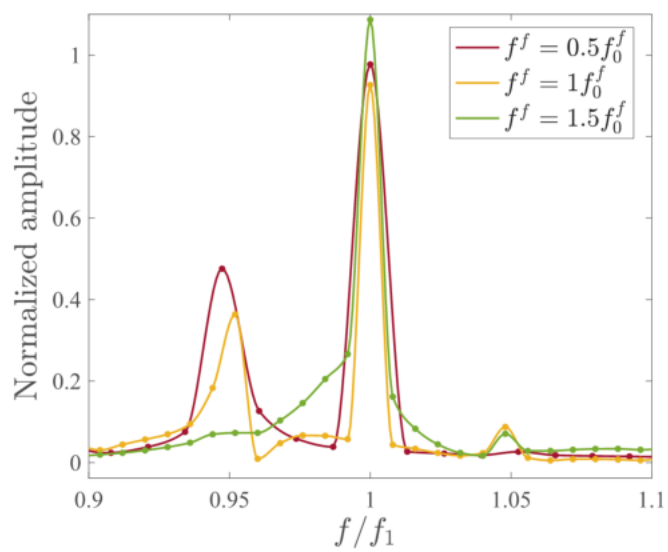

Fig. 8. Demonstration of the importance of the balance of flexoelectricity on inferring the second tone. The balance of flexoelectricity plays a crucial role in the perception of the two-tone excitation while dissipating for the lost energy due to friction. The system is excited with two tones where the first tone is fixed to the natural frequency of the system while the second tone frequency is $f_2 = 0.95f_1$.

flexoelectricity plays a crucial role in supplying energy to amplify the wave sounds in the ear. Consequently, it is one of the deciding factors in controlling the damping of the system. As an example, a slight decrease in flexoelectricity can cause the faster damping of the stimuli. Fig. 7 shows the sensitivity of the dynamic system response to the flexoelectric property. Modifying this parameter by 50% can dramatically impact the damping. The flexoelectric constant can be altered by the change of charges in the vicinity of the cell membrane (53, 59, 60).

Since we are interested in the effect of flexoelectricity on the second tone inference, we attempt to obtain its sensitivity to flexoelectricity. Fig. 8 elaborates this effect rather clearly. The system is excited with two tones where $f_1 = f_0$ and $f_2 = 0.95f_1$ (f_0 is the natural frequency of the system). As the flexoelectricity of the system increases, the second tone inference will vanish to the point that there is no sign of the second tone. This indicates that the balance of flexoelectricity is a critical factor in inferring the second tone.

In conclusion, flexoelectricity is responsible for reverse-damping and injects energy to preserve the system's vibration. Lack of it can cause a high damping effect, while its excessive amount can result in not inferring the second tone due to the addition of a considerable amount of energy to the system. Thus, any external factor that may alter the charges around cell membranes (e.g., changes in hydration, electrolyte imbalance) could potentially cause impairment of two-tone perception.

D. Second Tone Inference and Affecting Factors. For fixed characteristics of the hearing system, two tones should be distinguishable if they are reasonably apart. The human ear consists of over a million stereocilia that each are tuned to a specific frequency interval. If two tones are separated apart in a way that they are perceived by two different stereocilia, they are distinguishable to the human ear. However, in case both tones are closer in frequency and are "meant" to be perceived by a single stereocilia, what will be their influence on each other? There must be a certain frequency difference threshold that defines the distinguishability of the two tones. Fig. 9 demonstrates the two-tone distinction threshold by varying the second frequency (f_2) from $0.9f_1$ to $0.99f_1$, where $f_1 = f_0$. As discussed in Section B, the addition of the second tone will weaken the response to the first tone through interference. With this knowledge, and by inspecting Fig. 9, we conclude that there is a threshold on distinguishing between two tones, and in case the two tones are close enough (here 99%), the system infers them as a single tone. This is concluded from the fact that the response to the two-tone in this case is larger than the response of the system to the solely one-tone excitation and demonstrates that the system infers them as one tone.

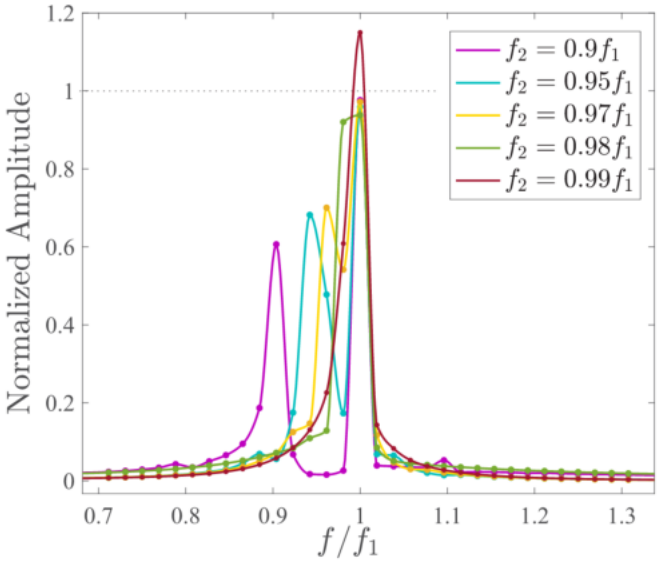

Fig. 9. The inference of the second tone is in the presence of the first tone for various frequencies of the second tone while the first tone is fixed at the natural frequency of the system. It can be inferred that there exists a threshold for the proximity of the two-tone frequencies where the hearing system can no longer distinguish between the two tones (here $f_2 = 0.99f_1$). The numerical values are $F_2 = 0.5F_1$.

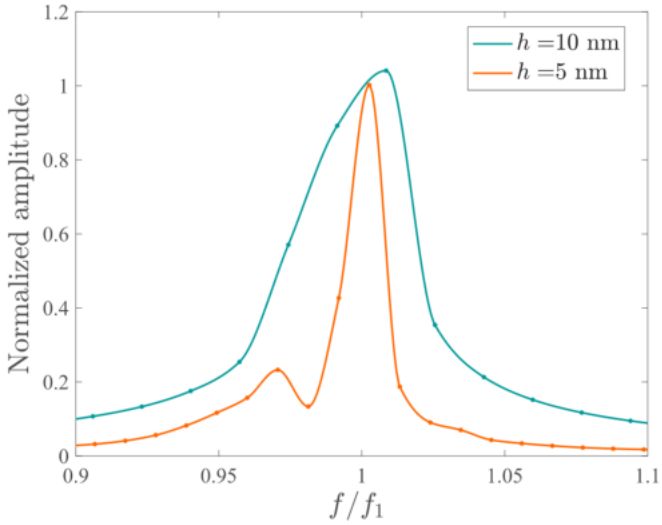

Fig. 10. The effect of the thickness of the stereocilia membrane on the two-tone interference and its influence on the amplitude of the first tone. The amplitudes of the response are normalized to the case where the second tone is absent. The 50% reduction in the membrane thickness can result in better distinguishment of two tones and less inference (this can also be concluded from the distance of normalized amplitude from 1). Also, it is assumed that $f_2 = 0.98f_1$. The numerical value for the membrane thickness is adopted from ref. 33.

We now ask the following question: What characteristics will affect distinguishing the second tone from the first tone when the frequencies of the tones are fairly close? Fig. 10 shows the sensitivity of the second tone distinction to the membrane thickness of the stereocilia (h). The amplitude responses are normalized to the case where the system is excited by only the first tone with a frequency identical to the system's natural frequency. We conclude that, in the case of $h = 10$ nm, the first and second tones are not distinguishable and are perceived as one tone with a larger amplitude (compare the peak with 1). In contrast, for the case where the thickness is 50% smaller (i.e., $h = 5$ nm), the two tones are perceived perfectly with minimal influence on the first tone inference.

An easy application of our work is that we may, somewhat easily, make a prediction of what effect (some) external medicine might have on the ability to resolve two tones. The impairment in the hearing due to the consumption of NSAID (e.g., Ibuprofen) has attracted huge attention in recent years (39). Research shows that upon NSAID drug consumption, the membranes' bending modulus will decrease up to 50% (38)[†]. Fig. 11 depicts the effect of the decrease in the bending modulus (as a consequence of NSAID consumption) on the inference of the second tone. While there is no significant effect on the inference of the first

[†] It has been established that the consumption of macrolide antibiotics (e.g., Azithromycin) and salicylates (e.g., Aspirin) has the decreasing effect on the bending modulus of membranes as well (61, 62).

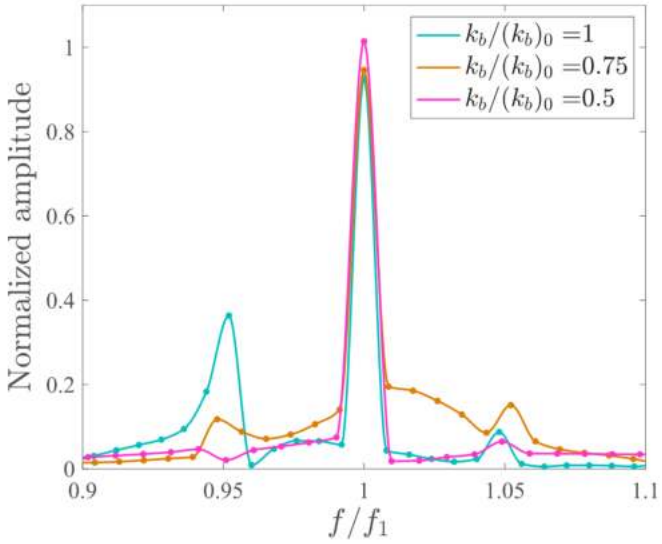

Fig. 11. The effect of NSAID drugs (e.g., ibuprofen) on the second tone inference. The maximum amplitude in the natural frequency of the system is normalized to the amplitude of the system on the one-tone stimulation. As it is shown, the decrease in the bending modulus by 50% which can be the result of consumption of NSAID drugs can disrupt the inference of the second tone where $f_2 = 0.95 f_1$. Also, it is assumed that $F_2 = 0.5 F_1$.

tone (which is matched to the natural frequency of the system), the second tone inference gradually vanishes as the bending modulus of the stereocilia decreases by the consumption of the NSAID to the point that no second tone is inferred in the extreme case of 50% decrease in the bending modulus.

3. Concluding Remarks

When it comes to a topic as complex as musical perception, we have barely scratched the surface. However, based on the mechanics of hair cells, we provide some important insights into the quantification of what physical parameters may impact the perception of two tones. The problem of two-tone perception is a useful (although hardly complete) proxy for musical perception. Since our model is based on physics rather than the systems-level approach, all parameters of our model are physically measurable such as flexoelectricity of the cell membrane, bending modulus, and geometry among others. This allows us, as example, to relate how the external environment may impact our hearing as long as the effect of the external stimuli on the physical parameter is known. NSAID drugs are well-known to alter the cell bending modulus hence we can conjecture that there could be an impact on two-tone interference and thus a disruption in musical perception. Future work may reveal how a person's physiological state may impact cell membrane flexoelectricity and thus provide yet more insights into the various factors impacting musical perception.

From a technical standpoint, several extensions are possible such as taking cognizance of nonlinear effects in viscous damping c.f., ref. 63, all-numerical simulations of multiple stereocilia and micromechanistic details of the ion-channel dynamics. We believe that atomistic simulations of the protein (Prestin) could play an important role in providing a connection between our continuum model and measurable (or discernible) microscopic details of the protein–membrane interaction (64). We remark that our model is capable of addressing the interaction of more than two tones, but the interpretation of the results would be, understandably, more complex and may be an interesting avenue for future study.

Data, Materials, and Software Availability. All study data are included in the article.

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