The collusion of flexoelectricity and Hopf bifurcation in the hearing mechanism

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How do the weak sound waves get amplified in a cochlea? This deceptively simple question has attracted a fair amount of attention and several creative mechanisms have been proposed that purport to understand how the inner ear’s hair cells actively collude to achieve the requisite amplification, sensitivity, frequency selectivity, and range. Some of the proposed mechanisms target the nature of the mechanical transduction mechanism while others adopt a more dynamical systems approach and focus on the fact that stereocilia of the hair cells operate on the verge of an instability phenomenon—the so-called Hopf bifurcation. In this work, we propose a physics-based model to understand how flexoelectricity, a universal electromechanical coupling that exists in all dielectric substances, facilitates the active motion of hair bundles. A key feature of our model is that we eschew a “black-box” approach, and all parameters are well-defined physical quantities such as membrane bending modulus, geometrical characteristics, and others. Furthermore, the model is derived from the well-accepted principles of thermodynamics and continuum mechanics. While the role of flexoelectricity in the hearing mechanism has been noted before, we show for the first time that flexoelectricity is an essential ingredient in inducing the Hopf bifurcation. We state that the biomembranes’ bending modulus and the intracellular charge concentration (which for instance could represent $K^+$ or $Ca^{2+}$) are the two key control parameters that significantly impact the stability of the cochlea and hence the hearing mechanism. Our work highlights the importance of flexoelectricity, confirms earlier assertions that the cochlea amplifies the acoustic stimuli through its exceptional electromechanical energy conversion property, and provides insights into how physical properties such as biomembranes’ bending modulus impact the performance of the hearing system.

The active processes and the features of the hearing mechanisms mentioned in the preceding paragraph are intimately related to the hair cells located in the cochlea.

Significance Statement

How do the weak sound waves get amplified in a cochlea? This deceptively simple question has attracted a fair amount of attention and several creative mechanisms have been proposed that purport to understand how the inner ear’s hair cells actively collude to achieve the requisite amplification, sensitivity, frequency selectivity, and range. In this work, we propose a physics-based model to understand how flexoelectricity, a universal electromechanical coupling that exists in all dielectric substances, facilitates the active motion of hair bundles and is an essential ingredient in inducing an instability state considered responsible for several highly nonlinear and idiosyncratic features of the hearing mechanism. Our work highlights the importance of flexoelectricity, confirms earlier assertions that the cochlea amplifies the acoustic stimuli through its exceptional electromechanical energy conversion property, and provides insights into how physical properties such as biomembranes’ bending modulus impact the performance of the hearing system.

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Despite decades of research and the concomitant progress in our understanding of the hearing mechanisms, there is still an active debate concerning several aspects of the active processes in the cochlea (15). For instance, it has been speculated that the somatic motility of outer hair cells (OHCs) or the motility of the OHC’s hair bundles or both may contribute to the active processes (1–3, 7–11, 16–18).

We briefly review below some of key literature and debate in the community to establish the context underpinning the central contribution of our work.

The somatic motility of OHCs was first observed by Brownell and his collaborators in 1985 (19). This electromechanical coupling is thought to be achieved through the protein called prestin embedded in the cell membranes of OHCs (1). Prestin is found to change its conformation in response to an applied electric field and this has been characterized “piezoelectricity” (20). Although the hair cell’s membrane time constant is around 1 ms, with the implication that the electromechanical response of the OHC should be the most significant around 1 kHz, experiments indicate that the somatic motility could be much faster. Indeed, OHC can respond to a vibration whose frequency is as high as several tens of kHz (25, 26). It has been experimentally observed that the OHC change their length nonlinearly with respect to the applied transmembrane electric field (27–29). The nonlinearity of the OHC’s response is thought to originate from two factors: (1) the electromechanical coupling between the applied electric field and the length change of the OHC is deformation dependent (30); (2) the induced polarization reaches a saturation value if the applied mechanical loading is large enough (28, 30). Eguiluz et al. believe that the nonlinearity is a key for the active process in hearing (12).

Moreover, spontaneous otoacoustic emissions sounds in the external ear canal that originate from the cochlea, were thought to be closely related to a nonlinear oscillation described by a van der Pol limit cycle oscillator model (31). However, so far, there are few pure somatic motility models proposed to explain the active processes in the cochlea.

Another nonlinear process, the hair bundle’s motility, has also been thought to be closely related to the active processes in the cochlea (9, 17, 18, 32–34). The hair bundle’s mobility can be both slow and fast adapted (1). The slow adaption is believed to be related to the molecular motor, Myo1c, a member of the myosin family (35). Experiments indicate that small clusters of Myo1c molecules are essential to keep tip-links under tension, which cause the reopening of the ions channel gates (36). The entry of cations provokes the slipping down of the upper insertional plaque of the tip-link attached to the longer stereocilia and causes the closure of the ions channel. Then the Myo1c reopens the channel by increasing the tension in the tip-links which causes the further deflection of the hair bundle in the direction of the stimulation. In this way, the energy is fed into the oscillation of the hair bundle. However, the fast adaption mechanism is still poorly understood (1).

Regardless of its unclear mechanism, the hair bundle’s motility is believed to play an important role in the active process of the cochlea, for both mammals with OHCs (18, 32, 33) and non-mammals which lack OHCs (7, 37–39). So far, there are two key open questions pertaining to hair bundle motility:

1. How does the hair bundle motility boost the active process in cochlea?

2. How does the hair-bundle achieve its electromotility?

Fig. 1. The key ideas pertaining to the active process and its importance to the amplification function of the hearing system are described by Fig. 1(a)-(d). Fig. 1a shows a cross-section of the organ of Corti which contains both outer and inner hair cells located on top of the basilar membrane. The acoustic wave propagating in the basilar membrane causes the vibration of the outer hair cells and the hair bundles. The hair bundle itself consists of “hair-like” objects called stereocilia. Each stereocilium is connected to its tallest neighbor by a fine molecular strand called tip link. It is believed that, located on each hair bundle and around the connection with the tip link, are several mechano-sensitive ions channels. When the hair bundle is deflected, the increase in tip-link tension causes the opening of the ion channel gates which allows the influx of ions (both K⁺ and Ca²⁺). The charge flow triggers the active motion of the hair bundle through a (somewhat debated) electromechanical coupling mechanism. As shown in Fig. 1c, since the charge flow changes the voltage of the hair bundle, it affects the shape and consequently the motion of each stereocilium. Evidently, nature has evolved to tune parameters like ion concentration, the membrane’s bending stiffness and even the length and spring constant of the tip links, in subtle ways, so that the system runs on the verge of the so-called Hopf-bifurcation (Fig. 2d). Being on the verge of instability is speculated to be the key mechanism that allows the amplification of weak sounds in a rather specific way and several other critical and idiosyncratic features.

So far, one of the most accepted explanations that purports to address the first question is based on the unstable nonlinear oscillation of the hair bundles. The schematic in Fig. 1(a)-(d) shows a cross-section of the organ of Corti. The organ of Corti contains both OHCs and inner hair cells (IHCs) located on top of the basilar membrane. As can be seen in the shape, the tip of each OHC hair bundle penetrates into the Tectorial Membrane (TM)—a membrane located right above the hair cells. As the acoustic wave propagates in the BM, it causes the vibration of the OHCs and the hair bundles. Normally, each hair bundle consists of dozens to hundreds of actin based microvilli called stereocilia. The stereocilia within the same hair bundle have differing nature and can be both slow and fast adapted (1). The slow adaption is believed to be related to the molecular motor, Myo1c, a member of the myosin family (35). Experiments indicate that small clusters of Myo1c molecules are essential to keep tip-links under tension, which cause the reopening of the ions channel gates (36). The entry of cations provokes the slipping down of the upper insertional plaque of the tip-link attached to the longer stereocilia and causes the closure of the ions channel. Then the Myo1c reopens the channel by increasing the tension in the tip-links which causes the further deflection of the hair bundle in the direction of the stimulation. In this way, the energy is fed into the oscillation of the hair bundle. However, the fast adaption mechanism is still poorly understood (1).

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2. How does the hair-bundle achieve its electromotility?
are shown. Each stereocilia is connected to its neighbor by a fine and elastic molecular strand called the tip link. It is believed that, located on each stereocilia and around the connection with the tip link, are several mechano-sensitive ions channels (8, 9, 17). When the hair bundle is deflected, the increase of tip-link tension causes the opening of the ions channel gates and allows the influx of ions (both K⁺ and Ca²⁺). The actual relationship between the tip link force and the channel gate is complex. Power and coworkers proposed a biophysical model to analyze how the force that arise in tip links influence the channel of the stereocilia (40, 41). Since the tip link force depends on the deflection of a stereocilia, the probability of the channel’s open-state is thought to be a nonlinear function of the stereocilia deflection. Fig. 1(c) shows that the vibration of a stereocilia is actively coupled with the charge flow through its channel gates (3, 7). This active motion of the stereocilia is able to amplify a vibration with small amplitude into another with much larger amplitude. The nonlinear electromechanical behavior of the stereocilia is thought to be the reason for the active motion and the amplification. As the charge flow changes the transmembrane electric field, due to the electromechanical coupling, the shape and consequently the motion of the stereocilia also changes accordingly. Nature appears to have well-tuned the parameters of the whole system, such as: the ions concentration, the membrane’s bending stiffness and even the length and spring constant of the tip links, so that it runs on the verge of the so-called Hopf-bifurcation. Fig. 1(d) shows the trajectory for the motion of a stereocilia in the phase space. As shown in the figure, if a perturbation slightly displaces the system away from its stationary point, then the system starts oscillating due to the lose of stability of the system. With the passage of time, the radius of the oscillation keeps increasing until the system eventually enters a limit cycle with a relatively larger radius.

The second question is related to the origin of the electromechanical coupling in stereocilia. Although the electromechanical coupling plays a critical role in the whole process, currently, the precise mechanism for the electromechanical coupling in stereocilia is still under debate. The electromechanical coupling is reminiscent of “piezoelectricity” observed in certain hard crystals, but there is no basis to believe that stereocilia are “piezoelectric” as they lack the atomistic structure to act that way. The myosin-based mechanism mentioned above is thought to be effective for low frequency (less than 1kHz) hair bundle motions (1). For high frequency motions, a mechanism based on the cation’s concentration-sensitive channel is proposed (3, 9). It has been argued that each channel is anchored to the stereocilia cytoskeleton by an adaptation spring whose stiffness decrease with the increase of the Ca²⁺ concentration. As the channel is open, Ca²⁺ ions flow in and release the tension in the adaptation spring. Then the reduction of the tension in adaptation spring causes the closure of the channel. Maaløeïd and Hudspeth have shown that, during these open-close cycles, energy is fed into the system in terms of the Ca²⁺ current flow. This process is much faster than the myosin-based process and could account for fast adaption (3). Lumpkin and Hudspeth believed that the free Ca²⁺ concentration in a stereocilia was critical to its adaption process and developed a model for stereociliary Ca²⁺ homeostasis (42). We remark here that flexoelectricity, like electrostriction, is a universal electromechanical coupling mechanism that is present in all dielectrics including of course biological membranes (43). There are strong indications in the work of Brownell, his colleagues and others that flexoelectricity is a key element of the hair bundle’s electromotility (30, 44–46).

While substantial research has been performed by several groups elucidating the myriad aspects of the hearing mechanism, we highlight a few that the current work is based on. Hudspeth’s group was probably the first to link the active process in cochlea with the dynamical instability—Hopf-bifurcation (2, 7, 9, 11, 32). In their model, the motility of hair bundles plays a critical role to link the charge flow to the active motion of the OHCs and the Hopf-bifurcation, the characteristic of the nonlinear system they construct plays an essential role in the amplification process. Brownell and his collaborators have advocated the viewpoint that membrane flexoelectricity is the source for the electromechanical coupling in hair bundles (30, 44, 45). Using a theoretical model, they have shown that flexoelectricity is a possible source for the hair bundle’s fast adaption (45). The flexoelectric effect, first observed in liquid crystals (47), is a universal two-way electromechanical coupling phenomenon in dielectric materials. Mathematically, flexoelectricity links the polarization to the gradient of deformation of materials via the material property parametrized by the so-called flexoelectric coefficient. Petrov (48–50) has argued that flexoelectricity of the nanometer thick biomembranes is the basic mechnoelectric effect for living matter. Within a lipid bilayer membrane, lipids are organized to form a liquid crystal membrane. This membrane exhibits a strong flexoelectric response due to its small thickness (~1nm) and low bending stiffness (~10⁻¹⁰ J). In a lipid bilayer membrane, the polarization caused by the direct flexoelectric effect is proportional to its mean curvature (48–50). A phenomenological expression for this relationship is given by:

\[ p_\text{s} = \mu H, \]

where \( p_\text{s} \) (in C/m) is the electric polarization per unit area, \( H \) (in 1/m) is the membrane’s mean curvature and \( \mu \) (in C) is the area flexoelectric coefficient. Note that \( p_\text{s} \) relates to the polarization volume density \( P \) by (51, 52)

\[ p_\text{s} = Ph. \]

with \( h \) denotes the thickness of the membrane. The direction of \( p_\text{s} \) is assumed to be normal to the middle plane during the deformation. Since the coupling between \( p_\text{s} \) and \( H \) is two-way, a change in \( p_\text{s} \) or transmembrane potential also results in the change of the membranes’ mean curvature (49) due to the converse flexoelectric effect. Experimentally, this converse flexoelectric effect has been observed using an atomic force microscope (AFM) to measure the deformation of a biomembrane in response to an applied voltage (53, 54).

In the present work, we attempt to construct a physical model that takes into account the nonlinear dynamics, mechanics and flexoelectricity of the hair bundle. The physical model is constructed based on the following three facts: (1) the rotation of the hair bundle changes the tension of the tip links; (2) the ions channel gates are mechano-sensitive 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 stereocila due to the flexoelectric effect.
Although there are numerous parameters that could affect the
performance of the hair bundle, such as: the length of the
stereocila, the spring constant for the tip link, the viscosity
of the surrounding fluid, and the channel gate parameters,
two parameters that make our model different from others
are the intracellular charge density (which may, potentially,
be linked with K\(^+\) and Ca\(^{2+}\) ions) and the biomembrane’s
bending stiffness; both of which also play a critical role in
several other biological contexts. Without fitting any artificial
parameters—and using merely the thermodynamically defined
properties of biomembranes determined by experiments—the
current model shows that the hair bundle indeed runs at the
edge of a Hopf-bifurcation for typical values of the intracellular
charge density and the membranes bending stiffness. The
model also indicates that, as the above two parameters deviate
from their normal value, Hopf bifurcation and the active
motion of the system is severely suppressed. In particular, we
find that flexoelectricity can be a possible cause for the fast
adaptation for hair bundle’s motility and serve as an essential
ingredient for the occurrence of Hopf bifurcation. Through
the proposed model, we can quantitatively relate the intracel-
lular cations concentration and the membrane’s mechanical
properties to the nonlinear dynamic behavior of the hair bundle.

Recently, Maoiléidigh and Hudspeth have proposed a
nonlinear model which combines the somatic motility of
OHCs and the hair bundle’s motility to show that the active
process in the cochlea is caused by the Hopf-bifurcation(3, 33).
The insights from their work emerge to be crucial to the
development of the present work. However, our proposed
differs from these aforementioned works in the following aspects:

(1) Maoiléidigh and Hudspeth proposed an adaption spring
type that attempts to account for the electromechanical
coupling in hair bundles(3, 33). They assume that the
adaption spring located right at the ions’ channel gate
is sensitive to cations(more precisely, Ca\(^{2+}\)). As cations
flow in the channel and bind to the adaption spring, the
spring constant decreases. However, this adaption spring
has not been identified by experiments yet. In our model,
the electromechanical coupling of hair bundles originates
from a well accepted behavior of lipid bilayer membranes,
flexoelectric effect, which has been identified both theoretically
and experimentally;

(2) Maoiléidigh and Hudspeth’s model combines the
motions of OHCs and hair bundles. The OHC is thought
to be piezoelectric. In their model, the Ca\(^{2+}\) concentration
is linked to the dynamics of the hair bundle through the
opening probability of ion channels(3, 7, 33). We have been
unaware to understand the possible mechanism could lead to
piezoelectricity in the outer hair cells—the symmetry rules
of condensed matter physics would appear to preclude this
phenomenon in OHC’s. In our model, the electromechanical
coupling is based on flexoelectricity. Through flexoelectricity,
the concentration of K\(^+\) or Ca\(^{2+}\) is qualitatively related to
the dynamics of the system;

(3) Maoiléidigh and Hudspeth’s model, as well as any other
existing models, are unable to connect the bending stiffness
of biomembranes to the active process in cochlea(3, 33).
In our model, which directly incorporates the elasticity of
membranes, we can see that the change in the biomembranes’
bending stiffness should cause the loss of the amplification
function. In particular, our model yields contour maps of
the combination of membrane bending modulus and intercellular
charge density that yields the Hopf bifurcation phenomenon.

Breneman, Brownell and Rabbitt (45) proposed that
flexoelectricity of stereocilia is critical to the hearing. Our
present work/model differs from their’s in the following
respects:

(1) Breneman, Brownell and Rabbitt’s model is linear in
terms of hair bundle dynamics (45). The linear nature of the
model ensures that Hopf-bifurcation is not predicted. Our
model simply utilizes the principles of thermodynamics and
mechanics to derive a set of nonlinear equations from which
Hopf-bifurcation emerges naturally for a range of physically
measurable parameters;

(2) Breneman, Brownell and Rabbitt’s model doesn’t
take into account the activity of mechano-sensitive ions
channels(45). The ion flow is treated as a known input to the
system. Our model takes into account the highly nonlinear
behavior of ion-channels. In our nonlinear model, the ions’
flow is no longer a given function, but depends on the motion
of the stereocilia;

(3) Breneman, Brownell and Rabbitt’s model is able to
explain the frequency selectivity of hair bundles. However, for
the amplification function and the compressive nonlinearity,
their model is not suitable since a nonlinear dynamical model
is required for that(45).

The outline of the paper is as follows: in Section 1, we
derive the central physical model for the hair bundle dynamics
based on thermodynamics and continuum mechanics. We
propose that the phenomenon of membrane flexoelectricity is
a key mechanism underpinning membrane electromotility. We
perform an analytical linearized stability analysis in Section
2 to understand the stability and the frequency selectivity
of the hearing system. To confirm our interpretation of the
link between Hopf-bifurcation and flexoelectricity, we perform
all-numerical simulations of the derived nonlinear model in
Section 3 and finally conclude that the hair bundles do run
close to a supercritical Hopf-bifurcation for a broad range of
physical parameters. The numerical simulations show that an
oscillation that initiates within the limit cycle can be amplified
to the limit cycle, while an oscillation that initiates outside
the limit cycle is pulled back into the limit cycle. This observation
is consistent with the experimental observation of nonlinear
compression of the active motion of hair bundles.

1. A physical model for the dynamics of hair bundles

Normally, a hair bundle is comprised of dozens to hundreds
of stereocilia. Each stereocilia is connected to its shorter
and longer neighbors by tip links. Without loss of generality,
only four stereocilia are shown in the schematic drawing (Fig. ??(a)) to describe the motion of a hair bundle due to the vibration of its base, the BM. The mass block $M_{TM}$ located on the top of the longest stereocilia represents the tectorial membrane (TM). Since the weight of the TM is much larger than that of the hair bundle, we simply ignore the weight of the hair bundle. When the vibration of the BM propagates to the hair bundle, it causes the rotation of the stereocilia. This rotation leads to the increase or decrease of the tip link forces which are proportional to the length changes of the tip links. Subsequently, the changes in tip link forces lead to the opening or closing of ion channels gates in stereocilia.

A schematic drawing for the relative motion of a hair bundle. (a) The vibration of a hair bundle in response to the vibration of the BM. Although a hair bundle usually contains dozens to hundreds stereocilia, here, without loss of generality, we only plot four of them to illustrate the central ideas. As the vibration of the BM causes the rotations of stereocilia, the tip links’ length will change accordingly. For each tip link, its length change usually leads to a tip link force. (b) An effective model describes the mechanics of a stereocilia. The tip link force $F_{TLK}$ is along the tip link.

We assume that the tip link force is linearly proportional to the tip displacement of the connected stereocilia. This assumption has been used in prior works as well (3, 7, 10, 45). In Fig. ??(b), we idealize the stereocilia and propose that while it can stretch and rigidly rotate (as shown), it does not “bend”. These simplifications, while approximations, are fairly well-grounded based on the phenomenology of the problem. We denote the relative displacement of the stereocilia tip to its base, the BM, by $x$ and the base displacement by $x_{BM}$. Assuming that the rotation angle $\theta$ is always very small, the motion of the stretchable bar is governed by the following equation:

$$M_{TM}(\ddot{x} + \dot{x}_{BM}) + c_{eff}(\dot{x} + \dot{x}_{BM}) + K_{eff}x = F_{tip}\cos \varphi. \quad [3]$$

where $c_{eff}$ is the effective damping coefficient and $K_{eff}$ is the effective spring constant which can be obtained from experiments. $F_{tip}$ is the tip link force applied from the tip link to the stereocilia. The tip link force is in the direction of the tip link and proportional to the length change of it. Without loss of generality, we assume that the length change of a tip link is proportional to the relative tip displacement $x$. Thus, the tip link force may be given by

$$F_{tip} = K_L(x \cos \varphi - \Delta l \sin \varphi), \quad [4]$$

where $K_L$ is the effective tip link spring constant which links the tip displacement to the tip link force, $\Delta l$ denotes the length change of the stereocilia.

Substituting Eq. (4) into Eq. (3) and after some manipulations, we arrive at the following equation for the motion of a stereocilia (in terms of the two unknowns $x$ and $\Delta l$):

$$M_{TM}\ddot{x} + c_{eff}\dot{x} + (K_{eff} - K_L \cos^2 \varphi)x = -K_L \sin \varphi \cos \varphi \Delta l + F_{stim}, \quad [5]$$

where

$$F_{stim} = -M_{TM}\dot{x}_{BM} - c_{eff}\dot{x}_{BM} \quad [6]$$

is the effective stimulation force due to the vibration of the BM. This stimulation force can (“be” is missing here) also regarded as an input to the system. This input comes from the sound heard by our ears. An additional equation is required to resolve both $x$ and $\Delta l$ which is tied to the electro-mechanical coupling exhibited by the system.

Other than the rotation motion mode, the stereocilia can also change its shape in response to the mechanical and electrical stimulations. There are several factors that may affect the shape change of the stereocilia significantly. Firstly, the pressure difference between the inner and the outer walls of the stereocilia can cause the shape change of the stereocilia. Secondly, the fluid inside the stereocilia makes it difficult for the total volume to change in a short time (several ms). Thus, in the analysis of high frequency vibration, it is reasonable to assume that the volume enclosed by the stereocilia is conserved which implies that the changes in the radius $R$ and the length $l$ are coupled (as stated by Eq.(S9)). So the length change $\Delta l$ can be expressed in term of the radius as

$$\Delta l = \left(\frac{R_0^2}{R^2} - 1\right)l_0, \quad [7]$$

where $l_0$ denotes the current length of the stereocilia and $l_0$, $R_0$ respectively denote its initial length and the radius. Thirdly, the shape of the stereocilia is also affected by its voltage difference between the inner and outer walls through flexoelectricity. In this work, we propose that this is the main reason for the active motion of the stereocilia since it can keep transferring ions flow into mechanical vibration and supply energy to compensate that has been dissipated by the surrounding fluid.

Considering the elasticity and flexoelectricity of the stereocilia, and using a variational procedure, we obtain the following governing equation (detailed derivation is given in Supplementary Information):

$$c_h \dot{R} = \left(\frac{1}{\sigma}k_0 - \frac{f^2 \epsilon_0}{\eta}\right)\dot{R} + \frac{f q^-(x)}{b \eta} R^2 + \Delta \varepsilon R^4, \quad [8]$$

where the expression for $q^-(x)$ is given by Eq.(S17).

Eq. (5) and Eq. (8) can be combined to solve for the two variables $x(t)$ and $R(t)$. With $R(t)$ determined, the variable $l(t)$ can be obtained using the constant volume equation (S9), the constant volume constraint. If $l(t)$ and $\Delta \phi(t)$ can be calculated based on $R(t)$ through Eq.(S20).
2. Sharp frequency selectivity of hair bundles due to flexoelectricity

In the previous section, we have introduced two different modes of motion for the hair-bundles: rotation and change of shape. These two modes are coupled to each other by the tip-link forces and the flexoelectric effect of the biomembrane. As the force in a tip-link is changed by a small vibration, that also causes a change of the state (open probability) of the surrounding ion channels. If the ion channel is open, more cations flow inside the stereocilia and subsequently alter its voltage. Due to the converse flexoelectric effect, the voltage change across the lipid bilayer membrane may lead to a change in its curvature. So the stereocilia experience a shape change in response to the opening of its ion channels. According to Eq. (4), the tip-link force also depends on the length change \( \Delta l \) of the stereocilia. Thus, the tip-link force and the length change \( \Delta l \) interact with each other during the vibration of the stereocilia.

One of the main objectives of this section is to study how the cations’ flow powers an active motion of the stereocilia through the flexoelectric effect. To begin with, we choose the parameters according to references (3, 45, 49, 50, 55). As an ideal model for the ions channel gate, we set \( \alpha = 1 \) which means that the channel can be completely open or closed according to the tip-link force. The parameters \( q_0 \) and \( \kappa_b \) are set to their normal values initially. In the later analysis, we will alter these values within a reasonable range to examine the sensitivity of the system’s dynamical behavior to these choices.

### Table 1. Parameters for the rotation physics pertaining to the hair bundle

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<tr>
<th>Symbol</th>
<th>Values</th>
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<tr>
<td>( M_{TM} ) (mg)</td>
<td>32(3)</td>
<td>( \kappa_b ) (J)</td>
</tr>
<tr>
<td>( c_{eff} ) (nN·s·m(^{-1}))</td>
<td>150(3)</td>
<td>( \epsilon_r )</td>
</tr>
<tr>
<td>( K_{eff} ) (nN·m(^{-1}))</td>
<td>4.5(3)</td>
<td>( \rho ) (kg/m(^3))</td>
</tr>
<tr>
<td>( K_L ) (nN·m(^{-1}))</td>
<td>4.5(3)</td>
<td>( c ) (N·m·s(^{-1}))</td>
</tr>
<tr>
<td>( R_0 ) (( \mu m ))</td>
<td>0.16 (45)</td>
<td>( h ) (nm)</td>
</tr>
<tr>
<td>( l_0 ) (( \mu m ))</td>
<td>0.45 (45)</td>
<td>( \Delta ) (nm)</td>
</tr>
<tr>
<td>( \phi )</td>
<td>( \pi/4 )</td>
<td>( \mu ) (C)</td>
</tr>
<tr>
<td>( q_0 ) (mC/m(^2))</td>
<td>0.2</td>
<td>( \alpha )</td>
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For the system governed by Eq. (5) and Eq. (8), we anticipate that the effect of \( \kappa_b \) is significant due to nonlinearities. Another parameter of interest is the initial charge density \( q_0 \) of a stereocilia’s inner surface which largely depends on the cations’ density of the surrounding electrolyte. Accordingly, we vary \( \kappa_b \) and \( q_0 \) separately and study how the dynamical behavior of the system changes as a result. The rationale for choosing these two parameters is that a variety of environmental causes may alter these in mammalian or human body e.g. diseases, medicines, or temperature. Using the proposed theoretical model, we aim to set the basis to link the human hearing ability to the above mentioned conditions.

Initially, before the application of external stimulations, the stereocilia is at its equilibrium state (stationary point) where the time derivatives of \( x \) and \( R \) are both zero. The stationary point \( (x^*, R^*) \) can be solved from Eq. (5) and Eq. (8) by setting \( \dot{x} = \ddot{x} = \dot{R} = 0 \). Fig. 2 shows that, for different combinations of \( \kappa_b \) and \( q_0 \), the stationary point remains at \( (x^* = 0, R^* = R_0) \). So we conclude that the position of the stationary point is independent of the choice of \( \kappa_b \) and \( q_0 \). This conclusion ensures that the subsequent studies need be performed using only a single stationary point.

Linearizing the system at the stationary point may provide us some general ideas of the dynamics of the system. Based on the stationary point found above, the linearized version of the system of equations Eq. (5) and Eq. (8) is:

\[
\begin{bmatrix}
\dot{x} \\
\dot{v} \\
\dot{R}
\end{bmatrix} =
\begin{bmatrix}
0 & 1 & 0 \\
K_1 & K_2 & K_3 \\
0 & K_4 & K_5
\end{bmatrix}
\begin{bmatrix}
x \\
v \\
R - R_0
\end{bmatrix}
\]

where \( v = \dot{x} \) is the hair bundle’s tip velocity, \( K_1 = -\frac{K_{eff}(K_{eff} - K_L)}{M_{TM}} \), \( K_2 = -\frac{\kappa_b}{M_{TM}} \), \( K_3 = \frac{K_{eff} R_0}{R_0 M_{TM}} \), \( K_4 = \frac{q_0 R_0^2}{4 \pi L \kappa_b} \), and \( K_5 = \frac{\kappa_b}{h} \frac{\tau}{r c} + \left(4 \Delta r_0 \Delta R_0 + \frac{f_0 R_0}{\kappa_b} \right) / (h c) \).

Suppose the external stimulation \( F_{stim} \) is harmonic, i.e. \( F_{stim} = F_0 e^{i \omega t} \) with \( \omega \) being the angular frequency, then for the linearized system Eq. (9), the responses \( x(t) \) and \( R(t) \) are both harmonic such that, \( x(t) = A e^{i \omega t} \) and \( R(t) = R_0 + B e^{i \omega t} \). Substituting the above expressions for \( F \), \( x \) and \( R \) into Eq. (9) and solving for the amplitude \( A \) for the variable \( x \), we have

\[
A(\omega) = \frac{-F_0}{M_{TM} (\omega^2 + K_1 + i K_2 + \frac{K_{eff} R_0}{R_0 M_{TM}})}
\]

Obviously, \( A(\omega) \) is a function of multiple parameters and the angular frequency \( \omega \) of the stimulation. To study the frequency dependence of \( A \), we use the parameters given in Table 1. To simulate a small acoustic stimulation, \( F_0 \) is chosen to be 1pN. Fig. 3 shows the comparison of the frequency dependence of \( A \) for the cases with and without flexoelectricity. As shown in Fig. 3, the resonance frequency of the linear system changes from 1276Hz to 3178Hz due to the consideration of flexoelectricity. This result indicates that flexoelectricity allows the system to resonant at higher frequencies. Fig. 3 also shows that, if we normalize \( A(\omega) \) by its value at low frequency where \( A(\omega) = A_0 \) is almost a
constant, the curve with flexoelectricity exhibits a much sharper peak around the resonance frequency than that for the case without flexoelectricity. This implies that the stereocilia may utilize flexoelectricity to enhance its frequency selection performance. In the plot of Fig. 3, we consider three cases to show how does flexoelectricity affect the frequency selectivity of the system. It is found that the case for $\kappa_b = 30 k_B T$ and $q_0 = 0.2 mC/m^2$ shows the best frequency selectivity among the others. Later, we will show that $\kappa_b = 30 k_B T$ and $q_0 = 0.2 mC/m^2$ correspond to a special situation at which the system runs at the verge of the Hopf-bifurcation. Thus, we may also conclude that the Hopf-bifurcation helps to enhance the frequency selectivity.

![Image](image.png)

Fig. 3. The frequency dependence of $A$ for the cases of with and without flexoelectricity. The blue line corresponds to the case of with flexoelectricity has sharper peak which indicates that flexoelectricity enhances the frequency selection.

We note that, in the discussed linearized case, the actual values for $A$ are very small (less than 1 nm). However, in reality, the response of a stereocilia is much larger due to a process of amplification. It is expected that the amplification probably stems from a Hopf-bifurcation related active motion of the stereocilia. Next, we explore this aspect—i.e. the response of a stereocilia to a small perturbation.

Firstly, we calculate the eigenvalues of the system to check its stability and predict how it behaves when losing stability. Normally, there are three eigenvalues for Eq. (9). With the parameters given by Table 1, it is found that two of the eigenvalues are a pair of complex conjugates whose real parts $(Re(\lambda))$ are positive. We also find that varying the values of $\kappa_b$ and $q_0$ alters the values of $Re(\lambda)$.

In Fig. 4, we plot the real part of the conjugate pair $Re(\lambda)$ as a function of the parameters $\kappa_b$ and $q_0$. The white line in the figure represents the condition under which $Re(\lambda)$ becomes zero. This white line corresponds to the supercritical Hopf-bifurcation points of the system. As shown in Fig. 4, on the right hand side of the white line, $Re(\lambda)$ is less than zero which implies that the vibration of the system is unstable. Since the imaginary part of $\mu$ are basically nonzero, when $Re(\lambda) > 0$, the system has a limit cycle whose radius may be determined by the parameters $\kappa_b$ and $q_0$. If the radius of this limit cycle is large enough, the system may act as an amplifier that transforms a small input stimulation vibration into a larger one.

Starting from the region $Re(\lambda) > 0$, keep increasing $\kappa_b$ or decreasing $q_0$ would eventually make $Re(\lambda)$ negative which means the loss of the ability of amplification. As has been addressed previously, the charge, $q_0$ depends on the intracellular cations’ density ($K^+$ and $Ca^{2+}$) when the ions channel is open. Thus, $q_0$ also depends on the cations’ density of the environment where the stereocilia located. Higher concentration of cations in the environment leads to larger absolute value of $q_0$ and vice versa. When the cations’ concentration of the environment is too small, the system would become stable and the active motion would disappear. The bending stiffness $\kappa_b$ of the biomembranes is another key factor that affect the stability of the system. Medicine, for instance, has been known to alter the bending stiffness $\kappa_b$ of the biomembranes. According to the results shown in Fig. 4, the hair bundle may in such a case, lose its ability of amplification. In other worlds, the hearing system may malfunction.

3. Nonlinear analysis of the dynamical behavior of hair bundles

Most prior studies have focused on studying a version of the linearized system in Eq. (9). To further confirm and investigate the mechanism of the amplification, we carry out a fully numerical study to solve the nonlinear system described by Eq. (5) and Eq. (8).

To investigate the importance of flexoelectricity to the function of amplification of the hair bundle, we compare the cases with and without the consideration of flexoelectricity. Fig. 5(a) shows the variation of the tip displacement with respect to time without the consideration of flexoelectricity. Fig. 5(b)
shows the result for the case of with flexoelectricity. It is seen from the figure that a slight perturbation is amplified to about 100nm vibration in about 3ms. Comparing Fig.5(a) and (b) we infer that in the absence of flexoelectricity, the system will loose its ability to amplify small perturbations of sound. This confirms our speculation that the amplification arises flexoelectric effect which converts the energy of ions flow into the deformation of stereocilia.

Regarding the flexoelectric effect, a practical question is how much energy of the flowing ions can be converted into the mechanical energy of stereocilia. In other words, is this energy sufficient to adapt an active motion of hair bundles? To answer this question is not easy. In what follows, we attempt to show how some parameters affect the energy conversion efficiency. From the results we obtained from the linear analysis, it is found that the parameters $q_0$ and $\kappa_b$ are critical to the performance of the dynamic system. So, here we also study the effects of these two parameters on the nonlinear behavior of the system. Fig.5(c) and (d) give the tip displacement vs time curves for $\kappa_b$ unchanged but $q_0$ equals to 0.15$mC/m^2$ and 0.08$mC/m^2$, respectively. Comparing these two figures with Fig.5(b), we can easily see that decreasing the absolute value of $q_0$ suppresses the amplification significantly. As shown in Fig.5(c), decrease of the absolute value of $q_0$ by about 25% can reduce the amplitude of the tip displacement by about 50% (around 50nm in magnitude) and increase the time for the amplification to 7ms. When $q_0$ is further reduced to 0.08$mC/m^2$, the system looses its function of amplification. This finding indicates that reducing the cations concentration of the environment could lead to the loss of hearing.

In Fig.6(a) and (b), the effect of bending modulus $\kappa_b$ on the dynamical behavior of the system is studied. As shown in Fig.6(a), if we increase $\kappa_b$ to 40$k_b T$, the amplitude for the tip displacement decrease to around 50nm and it takes more than 8ms for the vibration of the tip displacement to become stable. If we further increase $\kappa_b$ into 50$k_b T$, as shown in Fig.6(b), the system would lose its ability of amplification. Compare Fig.6(a) and (b) with Fig.5(b), we find that increase the membranes’ bending modulus $\kappa_b$ leads to the suppression of the amplification.

Fig.7(a) and (b) respectively show the 3D and 2D plot for the phase diagram for the vibration of the stereocilia with $q_0 = 0.2mC/m^2$ and $\kappa_b = 30k_b T$. From the figures, it is found that, starting from different points, the trajectories always converge to a fixed loop which is identified as a limit cycle. An important implication of this is that upon loss of stability, the vibration of the hair bundle will not increase to “infinity” but limits itself. The amplitude of the vibration is always kept to several hundred nanometers. The system therefore exhibits a supercritical Hopf-bifurcation for the chosen parameters. Imagine that a very weak sound wave perturbs the hair bundle by a small distance from its stationary point, the active process will amplify the perturbation towards the radius of the limit cycle. However, for a relatively strong sound wave that perturbs the hair bundle outside the limit cycle, the active process will attenuate the response and pull the vibration back to the limit cycle. In this way, the hair bundle is protected from extremely strong acoustic stimulations. Although not rigorous, the above mentioned supercritical Hopf-bifurcation is consistent with the reported nonlinear compressibility of the hearing system.

Similar to the finding of Murphy et al. (31), the limit cycle shown in Fig.7(a) and (b) may also partially provide the rationale for the origination of otoacoustic emissions. Mathematically, for a system whose dynamic behavior can be depicted by Fig.7(a) and (b), a infinite small oscillation about its steady point can be amplified into a detectable oscillation within few
The physical nature of our model allows us to assess
in a facile way the effect of external parameters on the performance of the hearing apparatus. For example, we are able to show that the ability of amplification of the stereocilia is due to the Hopf bifurcation related motion of the system. We find that an increase in the bending modulus, $\kappa_3$ or a decrease in the absolute value of $q_0$—both may happen due to illness or medicine, may stabilize the system and cause the malfunction of the hair bundle in its function of amplification of external stimulations. In the current model, $q_0$, the density of ions that binding to the inner surface of the stereocilia when the ionic channel is open, could be linked by future experiments to cations (K$^+$ and Ca$^{2+}$) concentration of the environment. This conclusion is consistent with the known fact that reducing the concentration of Ca$^{2+}$ would result in the loss of electromotility of stereocilia.

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