4aPPa5. Active processes and sensing in the cochlea

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One key question in the biophysics of the mammalian cochlea is determining the relative contribution to cochlear amplification by the two active processes present in the outer hair cell, namely prestin-based somatic motility and hair bundle (HB) motility. In the biological cochlea, these two effects are intimately coupled as HB force generation is linked to fast adaptation of the transduction current via a calcium-dependent process and somatic force generation is driven by the depolarization caused by the same transduction current. To separately study these effects, we construct a global mechanical-electrical-acoustical mathematical model of the cochlea. The global cochlear model is coupled to linearizations of nonlinear somatic motility and HB motility. We find that the active HB force alone is not sufficient to power high frequency cochlear amplification while somatic motility can perform this task. However, there are limitations to this mathematical approach. We discuss these limitations along with existing seminal experiments and proposed experiments (both in the cochlea and in the auditory nerve) to map future directions for uncovering the micromechanical contributions to the system level response of the cochlea.

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INTRODUCTION

Normal hearing requires an active mechanism that amplifies the vibrations of the cochlea in response to low intensity sounds, allowing the cochlea to have a high sensitivity, a sharp tuning and a broad dynamic range. One key question in the biophysics of the mammalian cochlea [1] is determining the relative contribution to cochlear amplification by the two active processes present in the outer hair cell (OHC), namely prestin-based somatic electromotility and hair bundle (HB) motility. In the biological cochlea, these two effects are intimately coupled as HB force generation is linked to fast adaptation of the transduction current via a calcium-dependent process and somatic force generation is driven by the depolarization caused by the same transduction current. To separately study these effects, we construct a global mechanical-electrical-acoustical mathematical model of the cochlea. The global cochlear model is coupled to linearizations of nonlinear somatic motility and HB motility.

METHODS

A global computational model of the cochlea is used to investigate the role of the two active processes in hearing. The model couples the mechanical, electrical and acoustical domains of the cochlea [2]. At each cross-section, the structural model includes three degrees of freedom: one for the basilar membrane (BM), a tectorial membrane (BM) shearing mode and a TM bending mode. Structural longitudinal coupling is included, since we previously demonstrated that structural longitudinal coupling plays an important role in the tradeoff between frequency selectivity and transient capture [3]. Four electrical degrees of freedom, connected by longitudinal cables, represent the alternating part of the potentials in the scala vestibuli, scala media, scala tympani and the intracellular outer hair cell (OHC) potential. OHC electromotility couples the OHC force \( F_{ohc} \), displacement, \( u_{ohc}^{comp} \), transmembrane potential \( \Delta \phi_{ohc} \) and current, \( I_{ohc} \):

\[
F_{ohc} = K_{ohc} u_{ohc}^{comp} + \epsilon_3 \Delta \phi_{ohc} \\
I_{ohc} = \frac{\Delta \phi_{ohc}}{Z_m} + i \omega \epsilon_3 u_{ohc}^{comp}
\]

The mechano-electrical transduction (MET) channel conductance is assumed to be proportional to the open probability of the transduction channel, \( P_0 \). To model an active HB, the MET channel is modeled as a 6 state channel [4]. Calcium binding affects the open probability of the transduction channel, allowing the HB to convert chemical energy into mechanical energy. The nonlinear equations governing the HB dynamics are linearized for small harmonic perturbations around the operating point. As described in [5], the following equations are obtained between the HB force, \( \delta F_{hb} \), HB deflection \( \delta u_{hb} \) and transduction current \( \delta i_0 \):

\[
\delta F_{hb} = \left[ K_{pass} - K_{act}(\omega) \right] u_{hb} \\
\delta i_0 = G_{a}^{max} J(\omega)V_s u_{hb}
\]

where \( K_{pass} \) is the passive HB stiffness, \( K_{act}(\omega) \) is a frequency dependent term due to channel gating, \( G_{a}^{max} \) is the saturating conductance of the HB, \( J(\omega) \) is a frequency dependent term and \( V_s \) is the resting HB transmembrane potential. \( K_{act}(\omega) \) and \( J(\omega) \) are both proportional to a nondimensional bandpass frequency filter, \( TF(\omega) \). We also consider the case of a passive HB, modeled as a two state channel. In this case, Eq. 2 is still valid, but \( TF(\omega) \) becomes a lowpass filter.
Simulations of the response of the BM to acoustic stimulation with four different models are shown in Fig. 1. A passive model exhibits a poorly tuned response. The fully active model (with HB activity and OHC somatic electromotility) exhibit a sharply tuned response at the characteristic frequency (CF). The model with an active HB but without somatic motility has almost the same response as the passive model. The model with a passive HB and somatic motility has a lower peak frequency and a more sensitive response than the fully active model.

The results that somatic motility can power cochlear amplification. HB activity has two effects. One is the capacity of the HB to deliver mechanical energy, which tends to amplify the BM vibrations. The 2nd one is a reduction of the sensitivity of the MET channel to small harmonic stimuli due to current adaptation. The 2nd effect dominates in the model simulations, reducing the active response (as in Fig. 1), keeping all the parameters the same.

**NEEDED EXPERIMENTS AND FUTURE RESEARCH DIRECTIONS**

Model simulations suggest that somatic motility is the the main source of power for cochlear amplification. This result is consistent with measurements in the cochlea of prestin knock-in mice [6] or in cochleae perfused with salicylate [7, 8], which affect both force production by the OHC soma and cochlear amplification. The HB is unable to deliver as much power as the OHC soma at high frequencies. However, affecting the HB dynamics significantly alters cochlear amplification.

**RESULTS**
due to the dependence of somatic motility on the transduction channel sensitivity. Nin et al. [8] found that pharmacological perturbations of the HB reduces the compressive nonlinearity of the cochlea. Hence, using pharmacological agents that effect the HB make it difficult to parse the contributions of the two sources (HB and OHC somatic motility) conclusively in an experiment because of the dependence of somatic motility on the MET sensitivity.

A fundamental difficulty in developing a physiologically realistic model of the cochlea is the uncertainty in the measurements of the mechanical and electrical properties of the cochlea. Progress in measurements techniques, such as the development of faster recording techniques for HB dynamics [9], might allow to observe the active processes at acoustic frequencies. More complete characterization of the response of the cochlear cross section, such as those pioneered by Nuttall's group [10] using in vivo optical coherence tomographic methods will also test the models and provide for a more complete characterization. In addition, measurements of other nonlinear characteristics of the nonlinear response of the cochlea to acoustical (such as two tone suppression or distortion products) or electrical stimulation help to refine model parameters and to gain confidence in model predictions. Genetic mutation with a modified organ of Corti or tectorial membrane [11, 12] also provide critical information to test a theory (as discussed in [3]). Most recently, compounds that can be optically triggered to either activate or inhibit the action of prestin [13] provide another innovative way to reversibly alter the response of the in vivo preparation. Such a localized disruption can be modeling using in a mathematical model of the cochlea.

While a comparison to in vivo data will remain the gold standard of comparison, the development of models which match the more limited but more controlled in vitro testing environment may provide insights that are not possible in the in vivo situation, mainly due to the inaccessibility of the response over the entire cochlear geometry and to key features of the response - such as the deflection of the IHC hair bundle. Fridberger et al. [14, 15] measured the response of the in situ but in vitro apical motion of OHC and IHC HBs in response to acoustic stimulation with high level sounds in a passive preparation. Two in vitro preparations, that of Chan and Hudspeth [16] and that of Nowotny and Gummer [17], are notable for their controlled mechanical conditions as well as ensuring that the apical portions of the IHC and OHC are bathed in endolymph. Both groups demonstrate that the METchannels are kept at least partially operational and measure the IHC deflection due to pressure and/or electrical stimulation. These preparations hold the potential for uncovering not only the different effects of activity but also giving information regarding the excitation pattern of the IHC HB. Surprisingly, there have been no efforts aimed at modeling these experiments of which we are aware. We attribute this to the fact that until recently, no cochlear model was able to incorporate both OHC somatic and HB motility, something we have recently been able to achieve (see [5]). Hence, these experiments should be another target of modelers seeking to test there approach.

The ultimate goal of the amplificatory apparatus is hypothesized to be the stimulation of the HB of the inner hair cells (IHC), which are responsible for sensing. Describing the relation between the microfluidic flow stimulating the IHC HB and the active processes in the cochlea is a key future research direction. Coupling the cochlear model to a microfluidics model of the subtectorial space will allow to determine the IHC response to acoustic stimulus, which will allow to compare model simulations to IHC and auditory nerve data. Developing a micromechanically based model, will enable not only a more complete understanding of the fundamental operation of the cochlea, but also enable us to estimate the forces acting on the various cellular components and potential failure of these components.
REFERENCES


