Unified cochlear model for low- and high-frequency mammalian hearing

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The spatial variations of the intricate cytoarchitecture, fluid scalae, and mechano-electric transduction in the mammalian cochlea have long been postulated to provide the organ with the ability to perform a real-time, time-frequency processing of sound. However, the precise manner by which this tripartite coupling enables the exquisite cochlear filtering has yet to be articulated in a base-to-apex mathematical model. Moreover, while sound-evoked tuning curves derived from mechanical gains are excellent surrogates for auditory nerve fiber thresholds at the base of the cochlea, this correlation fails at the apex. The key factors influencing the divergence of both mechanical and neural tuning at the apex, as well as the spatial variation of mechanical tuning, are incompletely understood. We develop a model that shows that the mechanical effects arising from the combination of the taper of the cochlear scalae and the spatial variation of the cytoarchitecture of the cochlea provide robust mechanisms that modulate the outer hair cell-mediated active response and provide the basis for the transition of the mechanical gain spectra along the cochlear spiral. Further, the model predicts that the neural tuning at the base is primarily governed by the mechanical filtering of the cochlear partition. At the apex, microscale fluid dynamics and nanoscale channel dynamics must also be invoked to describe the threshold neural tuning for low frequencies. Overall, the model delineates a physiological basis for the difference between basal and apical gain seen in experiments and provides a coherent description of high- and low-frequency cochlear tuning.

Author contributions: A.S. and K.G. designed research, performed research, analyzed data, and wrote the paper.

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Significance

Developing a mathematical model that predicts the response of the cochlea over the entirety of the cochlear spiral has been an outstanding challenge in the field. Without such a model, an accurate representation of interactions occurring inside the cochlea in response to complex signals like speech sounds or tone combinations that evoke clinically relevant otoacoustic emissions is impossible. We show that incorporation of the taper of the cochlear ducts and macro- and microscale fluid viscosity along with the subtle change of the intricate cochlear cytoarchitecture into a mechano-electric-acoustic model provides the key ingredients to represent the mechanical and neural tuning from the base to the apex of the cochlea.

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The model calculation of the magnitude of the RL gain for the 3.9-mm location is shown in Fig. 2D and the computed phase is shown in Fig. 2D, where the RL gain is the ratio of the RL motion to the stapes motion. The solid red line shows the RL gain spectrum for the active model and the corresponding passive model prediction is shown with the red dashed line. The active and passive BM gains from Fig. 2A and B are replotted in Fig. 2C and D for reference. In the passive model, the RL gain is similar to that of the BM, and the RL moves in phase with the BM at all frequencies. However, in the active model, the RL gain is 13 dB more than the passive RL gain at 0.5 CF, in stark contrast with the BM gain spectrum (Fig. 2D) where the active and passive BM response spectra overlap for frequencies at or below 0.5 CF, consistent with experimental observations (28, 29). In addition, the RL moves out of phase with the BM at frequencies lower than the CF, transitioning to in-phase motion at frequencies close to the CF (Fig. 2D, Insets), in agreement with the phase difference between the RL and the BM gains at frequencies less than the CF, as well as the phase difference between the RL and the BM seen in experiments at low SPL in guinea pigs (30), gerbils (28), and mice (29). Hence, the model successfully recreates the dramatic difference between the RL and the BM gains at low and high stimulus levels. Comparison of our model results with data from an independent experiment is shown in SI Appendix, Fig. S5.

The comparison between model and experimental results for the RL gain at more apical locations, 75%, 80%, 92%, and
95% of the length of the cochlear partition from the stapes, is shown in Fig. 3. We analyzed the RL gain at these locations because of the availability of in vivo experimental data near the RL, probably between the third row of outer cells and the medial edge of the Hensen cells (3). Fig. 3 A–D shows the magnitude of the RL gain in the active model with solid red lines and the magnitude of the RL gain in the passive model with dashed red lines. The symbols show the experimentally measured RL gain spectra in response to 20- and 76-dB SPL stimuli (corresponding to the active and passive models), respectively. The gains are normalized to their corresponding maximum passive RL gain. The computed RL gain spectrum transitions from a response resembling a low-quality factor band-pass filter at the 75% location to an even lower-quality factor filter at the 95% place, reflecting the transition seen in experiments. Further, the peak active RL displacement gain spectrum is ~15–20 dB higher than the peak passive response for both experiment and theory at these locations. The phase accumulation from the model is around 1 cycle at CF and 3 cycles at the high-frequency plateau, similar to that seen in experiments (3, 6). The experimental results for the low-frequency phase (ref. 3, as shown in Fig. 3 E–H with symbols) showed no significant phase difference between the active and passive RL gain spectra, while our model predicts a half-cycle difference between the active and passive RL phase spectra for frequencies below the CF. As discussed in SI Appendix, section 7, we attribute the difference between experiments and model predictions to 2 factors. First, the optical axis of the measurement is described as roughly normal to the BM (3) while in our model predictions are made normal to the RL (as shown in Fig. 1C) or roughly 30° different. Second, as mentioned above, the tissue measured in the experiment likely includes the medial edge of the Hensen cells, which is a region whose response is not directly predicted by the model.

Prediction of Response to Electrical Stimulation. We compared the model predictions of the RL and BM response to electrical stimuli with experimental results from Warren et al. (2). The model parameters were not changed from those used in Figs. 2 and 3. Fig. 4 shows the displacement of the RL and the BM at 11 mm from the stapes window due to a unipolar linear current ramp from −5 μA to 5 μA in the scala media. The experimental data from in vivo electrical stimulation in the guinea pig cochlea (2) have been overlaid for comparison. Both the model and experimental data have been normalized by the corresponding RL displacement at 5 μA. The BM displacement predicted by the model was negligible compared with the RL displacement, in line with the observations from ref. 2. Further, the BM displacement was out of phase with the RL displacement, similar to what has been observed in an isolated cochlear preparation (32). We found that the asymmetry of the RL response to positive and negative currents was due to transients during the onset of the ramped current stimulus and can be systematically varied by changing the onset time. Other effects such as saturation and adaptation may also play a role during negative current stimulation, but the inclusion of these effects was not necessary for accurate simulation.

Base-to-Apex Transition of Neural Tuning Curves. We have developed a simple model (described in SI Appendix) of the stimulus to the ANF from TM shear motion that includes the high-pass filtering due to 2 effects, the fluid dynamical entrainment of the inner hair cell (IHC) HB to the TM (33, 34) and the adaptation of the mechano-electric transducer (MET) channels in

![Fig. 3](image-url)

Panoramic view of the tuning of the RL in the guinea pig apex. (A–D) The magnitude of the RL gain at 75%, 80%, 92%, and 95% of the length of the cochlear partition from the stapes. The solid red lines show the model prediction of the RL gain in the active model and the dashed red lines show the RL gain in the passive model. The symbols show the gain seen in vivo (3) from a feature close to the RL at 20 dB SPL (diamonds) and 76 dB SPL (circles). All gains have been normalized to the corresponding maximum passive RL gain. The model matches the experimental gain magnitude well, with some discrepancies seen at frequencies higher than the CF at 92% and 95% from the stapes. The model and experiment display a monotonic decrease of the CF from base to apex, except for the experimental CF at 75% that is less than the CF at 80%. (E–H) The corresponding phase spectra. The phase of the passive model matches well with that of the passive RL from the experiment. Our model predicts a half-cycle shift between the active and the passive RL at frequencies less than the CF, which was not observed in the experiment, likely because the anatomical feature measured and direction of motion in the theory and experiment differed (main text). Other than the location analyzed, the models used here and in Fig. 2 are identical.
To test the response of the RL and the BM to unipolar electrical stimulation in the scala media. The stimulus was chosen to be a \(-5-\mu A\) to \(+5-\mu A\) current ramp, with onset and offset time of 5 ms. The solid blue line shows the model prediction of the BM displacement and the solid red line shows the model prediction of the RL displacement in response to the current sweep. The symbols show the data from Warren et al. (2). The displacements have been normalized to the peak RL displacement. The current-evoked RL motion is much higher than the BM motion due to the lower RL stiffness as well as the OoC geometry favoring RL over BM excitation by the OHCs. Further, the RL and BM displacements are antiphasic to each other because the force from the somatic electro-motility acts in opposite directions on the RL and the BM (32). The RL displacement at 5 \(\mu A\) predicted by the model is 150 nm, 3.75 times larger than the 40-nm RL displacement observed in the experiment.

The IHC HB (35–38). The computed ANF stimulus is inverted and normalized to its value at CF to estimate the normalized threshold frequency tuning curves (FTCs) shown in Fig. 5. The solid black lines in Fig. 5 A–C show the model prediction of the normalized threshold FTCs at 9 locations, 3 at each of the basal (Fig. 5A), middle (Fig. 5B), and apical (Fig. 5C) turns of the guinea pig cochlea. The red circles are normalized threshold FTCs from measured single ANF data obtained from the guinea pig cochlea. The computed ANF stimulus is inverted and normalized to its value at CF to estimate the normalized threshold frequency tuning curves (FTCs) shown in Fig. 5. All curves display a low-frequency filtering below 80 Hz due to the shunting of the fluid pressure across the helicotrema. Both the NT-NV and T-NV models exhibit underdamped system resonances associated with apical reflections and the global motion of the entire organ of Corti (23). These nonphysiological modes of vibration are damped out in the T-V model. Further, the reduced duct height in the T-V and T-NV models led to increased fluid mass loading on the cochlear partition, reducing the CF of the location (39). Although both the T-V and the T-NV models predict a downward shift of the CF compared with the NT-NV model due to increased mass loading, only the T-V model displays a reduced CF as well as realistic low-frequency tuning.

Discussion

The Effect of Macroscopic Fluid Viscosity on Cochlear Tuning. Oscillating flow of viscous endolymph and perilymph in the scala media results in the formation of boundary layers (BLs) at the walls of the duct as well as in the sub-tectorial space (STS). Previous studies (33, 34, 40) have analyzed the dissipation due to the BLs in the STS, while others (41) have studied the effect of viscosity on the bulk or macroscopic fluid flow in the scala ducts. In the present study, we concentrated on macroscopic viscous dissipation in the scala because the accurate modeling of this effect in our model is one of the key factors that led to the transition from basal to apical dynamics (STS damping is used in all simulations). The combined thickness of the BL on the BM and the bony wall is given by \(d_{BL} = 2\sqrt{\nu/(\pi f)}\) (23, 42), where \(\nu\) is the kinematic viscosity of the fluid. In the basal turn of the guinea pig cochlea, \(d_{BL}\) is much smaller than the duct height at CF. Consequently, macroscopic fluid viscosity plays a minor role in the mechanical tuning at the base. However, at the apex, the height taperers significantly (Fig. 4A and SI Appendix, Fig. S2), resulting in \(d_{BL}\) being comparable to the duct height for frequencies at and below CF. The increased effect of macroscopic viscosity leads to overdamped motion of the BM and the RL (Fig. 6, T-V), resulting in a low-quality factor gain and the reduction of reflections from
In addition to macroscopic fluid viscosity, the cytoarchitecture of the organ of Corti (OOC) influences the effectiveness of somatic electromechanical forces in modulating the vibrations of the BM and the RL. While orientation of the cytoarchitecture in the longitudinal direction (i.e., base-to-apex direction; Fig. 1B) is included in our model and has been studied extensively by others (43), our study primarily focuses on the cellular geometry is further exemplified by the mouse cochlea where the axes of OHCs are oriented nearly perpendicular to the BM over the entire length of the cochlea (44). Experimental observations show that, unlike in guinea pigs, the compressive nonlinearity in the BM gain spectrum in mice is greater than 20 dB throughout the cochlea (26, 45). This lends credence to our conclusion that the transition of the geometry of the organ of Corti plays a major role in reducing the effect of nonlinear compression of the BM motion at the apex of the guinea pig cochlea.

Species-Specific CFs are Shaped by the BM Gain.

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**Different Factors Shape Threshold Neural Response at Base and Apex.**

Comparison of Figs. 2C and 5A shows that the shape of the mechanical tuning (roughly the inverse of the gain function at low levels) is similar to that of the threshold neural tuning at the base of the guinea pig cochlea. This is because the high-pass filtering associated with the fluid coupling between the basal turns of the cochlea and the TM and the IHC HB (33, 34, 40), as well as the high-pass filter associated with the MET channel adaptation (35–37), has corner frequencies much lower than the CF in the basal turn. Consequently, the baseline threshold FTCs are primarily shaped by the mechanical dynamics of the organ of Corti (1, 46). However, in the apical turn, the model predicts that each of the high-pass filters associated with the STS fluid–HB coupling and the MET channel adaptation filter contributes a slope of 6 dB per octave for the low-frequency limb of the threshold ANF FTC (Fig. 5C) as discussed in refs. 21 and 47. An additional 6 dB per octave roll-off in the ANF filter is present for frequencies below the cut-in of the high-pass filter associated with the shunting of the acoustic pressure at the helicotrema (at around 80 Hz in our model, as seen in Fig. 6). The helicotrema cut-in frequency shifts to a higher frequency when the cochlear walls are fenestrated at the apex for measurement (as in refs. 3 and 48) or in species with larger helicotrema (21).

**Improvements and Suggested Future Modeling Work.**

We have presented results from a physiologically based model of the cochlea that replicates the mechanical responses to acoustic and electrical stimuli over the entire length of the spiral and predicts ANF thresholds. Like most models that use a simplified geometry, the helicotrema was modeled as an opening in the cochlear wall at the apical end. However, the model predicts that including the helicotrema is complex and warrants more detailed 3D finite-element modeling, especially to model the response below 100 Hz. In addition, instead of incorporating the cochlear compression through a fully nonlinear formulation, we have used the quasi-linear approach to connect our active and passive linearized models of the cochlea to the response of the in vivo cochlea to low and high SPLs, respectively, as in other models such as refs. 13 and 17. This is related to the EQ-NL theorem (49) and has been shown to be true for pure tone stimuli (50). Finally, only the Couette flow was included in the STS, and other modes of fluid structure interaction (51) were not modeled due to the additional complexity. However, these modes might play an important role in predicting the nontip response in the threshold ANF FTCs (52).
Materials and Methods
  
We have used a 2.5D hybrid finite-element model of the guinea pig cochlea (e.g., ref. 13) that incorporates physiological parameters based on measurements in the guinea pig or similar mammals. The scalae have been modeled as tapered prismatic ducts, as shown in Fig. 1, to accommodate the change in area observed in anatomical measurements of the guinea pig cochlea (9). The BM has been modeled as an orthotropic plate (13, 53), and the TM has been modeled as a longitudinally coupled viscoelastic beam (13). The kinematics and dynamics are derived from a Langrangian formulation as discussed in ref. 12. The macroscopic fluid viscosity has been incorporated in the scalae through viscous corrections to the compressible Helmholtz equation as in Cheng et al. (54). A description of the model and the list of parameters are included in SI Appendix.

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