

Signal Transmission in the Auditory System

RLE Groups

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1. Middle and External

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The external and middle ears are important to auditory function as they are the gateway through which sound energy reaches the inner ear. Also, middle-ear disease is the most common cause of hearing loss, and while a wide range of treatments have been developed, many lead to unsatisfactory hearing results. We use measurements of middle-ear structure and function in animals, live human patients and cadaver ears in order to investigate the effects of natural and pathological variations of middle-ear structure on ear performance.

1.1 Comparative Structure and Function in Middle Ears

Correlations between ear structure, skull structure and habitat have been found in the 36 species of the cat family. These correlations suggest an inter-relationship between specializations for hearing and other behaviors (e.g. olfaction) in cat species adapted for arid environments.

1.2 Measures of Middle-Ear Function in Diseased Middle Ears: Human Studies

We have used a human cadaver temporal-bone preparation to investigate the pathological effects of middle-ear fluid and various degrees of ossicular fixation on middle-ear function.

The fluid studies demonstrate two interrelated effects of middle-ear fluid on function: (1) Fluid on the tympanic membrane adds to the mass of the middle-ear system and limits high-frequency function. (2) Fluid also acts to reduce middle-ear volume, essentially decreasing the compliance of the middle-ear air spaces and reducing low-frequency function.

The studies of the effects of pathological stiffening of the ossicular joints point out a role of the non-rigid ossicular joints in uncoupling the effects of local ossicular fixations from other ossicles. For example, the application of cyanoacrylic glue to the stapes footplate caused dramatic reductions in the sound-induced motion of the stapes footplate, but caused only a small reduction in the motion of the malleus. This uncoupling is being used clinically to help differentiate different forms of ossicular pathology before corrective surgery.

1.3 Measures of the Effect of a Vestibular Dehiscence on Auditory Function

A newly described clinical entity, produced by a hole (a dehiscence) in the superior semicircular canal wall, has been investigated by our group. One hallmark of this pathology is a super-sensitivity of the ear to vibratory stimuli and a decreased sensitivity to sound stimuli. A series of animal experiments was performed to investigate the mechanism associated with these hearing pathologies. These measurements demonstrated that the dehiscent semicircular canal acts as a "Third cochlear window" which alters the inner ear's response to vibration and shunts sound energy that enters the inner ear away from the hearing organ.

Journal Articles Published

J.J. Rosowski, J.E. Songer, H.H. Nakajima, K.M. Brinsko, and S.N. Merchant, "Investigations of the Effect of Superior Semicircular Canal Dehiscence on Hearing Mechanisms," *Otol Neurotol*, 25:323-332 (2004).

M.E. Ravicz, J.J. Rosowski, and S.N. Merchant, "Mechanisms of Hearing Loss Resulting from Middle-ear Fluid," *Hear Res*, 195:105-130 (2004).

H.H. Nakajima, M.E. Ravicz, J.J. Rosowski, W.T. Peake, and S.N. Merchant, "Experimental and Clinical Studies of Malleus Fixation," *Laryngoscope*, 115: 147-154 (2005).

Journal Articles Accepted for Publication

H.H. Nakajima, M.E. Ravicz, S.N. Merchant, W.T. Peake, and J.J. Rosowski, "Experimental Ossicular Fixations and the Middle-ear's Response to Sound: Evidence for a Flexible Ossicular Chain," *Hear. Res.* forthcoming.

S.N. Merchant, J.J. Rosowski, and M.J. McKenna, "Vertical Canal Dehiscence Mimicking Otosclerotic Hearing Loss," *Adv ORL* forthcoming.

Meeting Papers Published

W.T. Peake and H.C. Peake, "Interspecies Variation in Cat-family Middle Ears," in *Proceedings of the Third Symposium on Middle-ear Mechanics in Research and Oto-surgery*, (eds) K. Gyo, H. Wada, N. Hato, T. Koike, (World Scientific, Singapore) pp. 11-18 (2004).

H.H. Nakajima, M.E. Ravicz, J.J. Rosowski, W.T. Peake, and S.N. Merchant, "The Effects of Ossicular Fixation on Human Temporal Bones," in *Proceedings of the Third Symposium on Middle-ear Mechanics in Research and Oto-surgery*, (eds) K. Gyo, H. Wada, N. Hato, T. Koike, (World Scientific, Singapore) pp. 189-198 (2004).

H.H. Nakajima, J.J. Rosowski, W.T. Peake, and S.N. Merchant, "Effects of Stiffening the Anterior-malleal Ligament," in: K Gyo, H Wada, N Hato, T Koike (eds) in *Proceedings of the Third Symposium on Middle-ear Mechanics in Research and Oto-surgery*, (eds) K. Gyo, H. Wada, N. Hato, T. Koike, (World Scientific, Singapore) pp. 197-202 (2004).

M.E. Ravicz, W.T. Peake, H.H. Nakajima, S.N. Merchant, and J.J. Rosowski, "Modeling Flexibility in the Human Ossicular Chain: Comparison to Ossicular Fixation Data," in *Proceedings of the Third Symposium on*

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J.J. Rosowski, S.N. Merchant, and H.H. Nakajima, "The Use of Laser-Doppler Vibrometry in Human Middle-ear Research: The Effects of Alterations in Middle-ear Load," in *Proceedings of the Third Symposium on Middle-ear Mechanics in Research and Oto-surgery*, (eds) K. Gyo, H. Wada, N. Hato, T. Koike, (World Scientific, Singapore) pp. 27-36 (2004).

J.E. Songer, K.M. Brinsko, and J.J. Rosowski, "Superior Semicircular Canal Dehiscence and Bone Conduction in Chinchilla," in *Proceedings of the Third Symposium on Middle-ear Mechanics in Research in Oto-surgery*, (eds) K. Gyo, H. Wada, N. Hato, T. Koike, (World Scientific, Singapore) pp. 234-241 (2004).

2. Cochlear Mechanics

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Project Staff

Professor Dennis M. Freeman, Professor Thomas F. Weiss, Dr. Alexander J. Aranyosi, Gary Chan, Roozbeh Ghaffari, Kinuko Masaki

2.1. Material Properties of the Tectorial Membrane

Introduction

The tectorial membrane (TM) is a gelatinous structure that lies on top of the mechanically sensitive hair bundles of sensory cells in the inner ear. From its position alone, we know that the TM must play a key role in transforming sounds into the deflections of hair bundles. But the mechanisms are not clear, largely because the TM has proved to be a difficult target of study. It is 97% water, and is therefore fragile. It is small: the whole TM would roll up and fit into little more than an inch of one human hair. Finally, it is transparent.

We have developed methods to isolate the TM so that its properties can be studied. Results using this technique (reported in previous RLE Progress Reports) show that the TM behaves as a gel. The material properties of a gel are a direct consequence of its molecular architecture. Charge groups on gel macromolecules attract mobile counterions from the surrounding fluid. Thus gels concentrate ions, and thereby increase osmotic pressure. The increase in osmotic pressure induces water to move into the gel and cause it to swell. The swelling stretches the macromolecules and increases the stiffness of the gel. The important consequence is that gels have mechanical, electrical, osmotic, and chemical behaviors that are all linked by their common molecular basis.

Bulk modulus

Measurements of point impedance allow us to characterize the viscoelasticity of the TM and compare TM impedance to that of other structures, but the measured value depends on the size and shape of the probe. In contrast, bulk material properties such as the bulk modulus depend only on the material itself, and can be used to infer impedance, even for irregularly shaped objects. For this reason, measurements of bulk material properties of the TM are critical for understanding the interaction of the TM, cochlear fluids, and hair bundles of the cochlea. Using a novel technique, we have characterized the bulk modulus of the TM.

Bulk modulus is typically measured by applying a mechanical stress, but such techniques are not easily adapted to the small, irregularly shaped TM. Instead, we used osmotic pressure to induce a change in TM volume. The osmotic pressure is exerted using polyethylene glycol (PEG), a polymer that is available in a wide range of molecular weights (MWs). PEG molecules that are sufficiently large are excluded from the TM, creating an osmotic pressure gradient across the TM boundary. Although the osmotic pressure exerted by PEG is a nonlinear function of concentration and MW¹, calibration experiments confirm that we can exert a known osmotic pressure using PEG. By exerting such pressure and measuring the resulting change in TM volume, we can determine bulk material properties of the TM.

¹ H. Hasse, H.P. Kany, R. Tintinger, and G. Maurer, "Osmotic Virial Coefficients of Aqueous Poly(ethylene Glycol) from Laser-light Scattering and Isopiestic Measurements," *Macromolecules*, 28:3540-3552 (1995).

One important bulk material property of the TM is the pore size, which determines the balance between viscous and elastic material properties. Molecules smaller than the pore size can pass into the TM and thus exert no osmotic pressure. By measuring the volume change that results from bathing the TM in PEG of differing MWs, we have determined that the pore size of the TM is about 16 nm — large enough to allow small solutes to diffuse freely, but small enough to exclude many proteins. This large pore size allows water to flow easily through the TM, causing the shear impedance of the TM to have both viscous and elastic components over the frequency range of hearing.

The bulk modulus, another key material property, was determined by varying the osmotic pressure applied by PEG and measuring the resulting volume change. Volume changes were primarily in the transverse direction. At each location on the TM, the thickness change of the TM was proportional to the original thickness (Figure 1). The slope of this proportionality as a function of applied osmotic pressure describes the bulk modulus. This volume change was a nonlinear function of osmotic pressure: at the lowest osmotic pressures the bulk modulus was about 1.1 kPa, while at higher pressures the bulk modulus increased to about 37 kPa. These bulk moduli are among the smallest measured for any connective tissue; for example, they are two orders of magnitude smaller than that of cornea², and nearly four orders of magnitude smaller than that of cartilage^{3,4}. Thus the TM is an extremely compliant tissue.

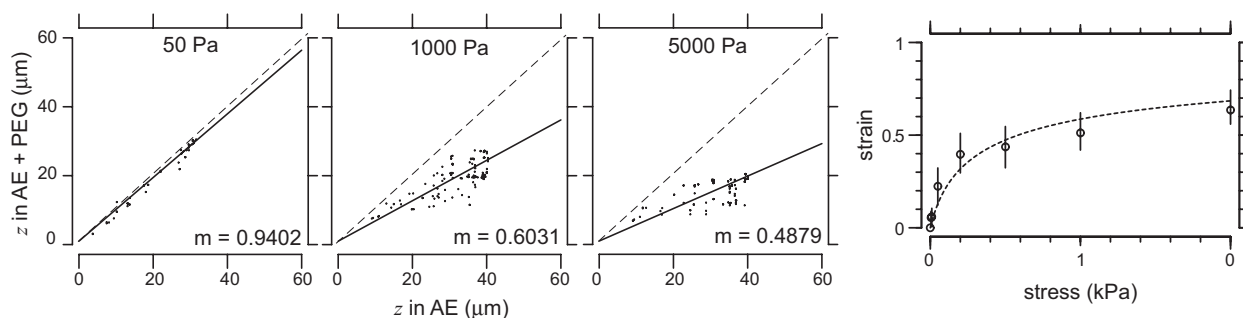


Figure 1. Measurements of the bulk modulus of the TM. The left three plots show measurements of TM volume change at three different osmotic stresses. For each set of measurements, a regression line was fit to the data. The strain was determined from the slopes of these lines. The right plot shows the strain of the TM as a function of osmotic stress; the circles show the best-fit slope, the vertical lines show the range of slopes for which the error in the fit was less than twice the minimum error. The bulk modulus, which is the slope of the stress-strain relation, is a nonlinear function of osmotic stress. The dotted line shows the best fit of a gel model of the TM to the measurements.

The results in Figure 1 cannot be described by a single bulk modulus, which would predict a linear relation between stress and strain. A closer fit can be made using an isotropic polyelectrolyte gel model of the TM we have previously developed, as shown in the figure. In this model, the bulk modulus arises from both the stiffness of the matrix and the presence of fixed charge. If the mechanical stiffness of the TM matrix is ignored so the resistance to compression is entirely due to the presence of fixed charge, the fixed charge concentration that best fits the measurements is 20.5 mmol/L of negative charge. These results suggest that the compressional stiffness of the TM is due primarily to the presence of fixed charge. However, the isotropic polyelectrolyte gel model overestimates the bulk modulus for small stresses. A power law relationship provides a better fit to the measurements, suggesting that either the mechanical stiffness or the amount of fixed charge may be a function of applied stress.

² D.A. Hoeltzel, P. Altman, K. Buzard, and K. Choe, "Strip Extensimetry for Comparison of the Mechanical Response of Bovine, Rabbit, and Human Corneas," *J. Biomech. Eng.*, 114:202-215 (1992).

³ V.M. Gharapuray, "Fibrocarrilage," in *Handbook of Biomaterial Properties*, J. Black and G. Hastings, eds., pp. 48-58, Chapman & Hall, London (1998).

⁴ J.R. Parsons, "Cartilage," in *Handbook of Biomaterial Properties*, J. Black and G. Hastings, eds., pp. 40-47, Chapman & Hall, London (1998).

Fixed charge concentration

Since the fixed charge of the TM clearly interacts with the mechanical matrix, quantifying this charge is important for understanding TM mechanics. The electrical potential difference across the boundary of the TM is a function of bath ion concentration and fixed charge. Since the TM lacks a cell membrane, it has been difficult to measure this potential using microelectrode or patch electrode techniques. Using “soft lithography” techniques, we have microfabricated a chamber that allows us to quantify the fixed charge within the TM (Figure 2). The chamber, based on a planar patch clamp technique⁵, positions the TM at the interface between two baths. A junction potential between the TM and each bath develops; if the two baths have different ion concentrations, the two junction potentials do not cancel. The resulting potential difference between the baths depends on the concentration of fixed charge within the TM.

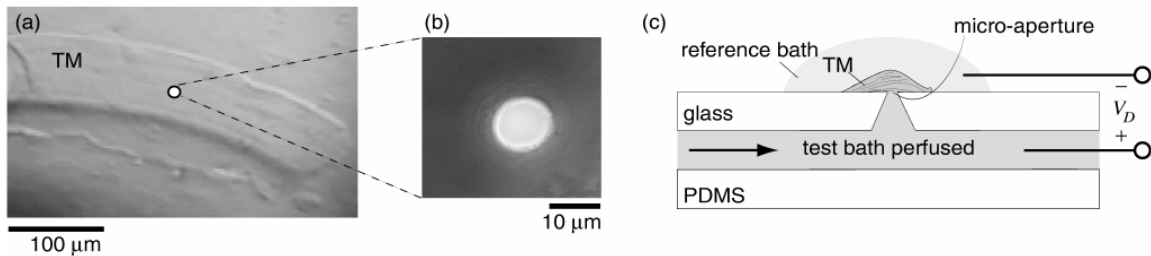


Figure 2. A microfluidic chamber for measuring TM fixed charge. (a) Top view of a section of TM placed in the chamber over a micro-aperture, drawn as a white circle for visibility. (b) Closer view of the micro-aperture with the TM removed. (c) The test bath in the underlying fluidics channel was perfused with solutions of differing ionic strength during voltage recordings.

Measurements show that as the ion concentration of one bath is reduced, the potential between the baths becomes more negative (Figure 3). These measurements were well fit by a gel model of the TM, which assigns -26 mmol/L of fixed charge to the TM. This value is comparable to that predicted from measurements of the bulk modulus of the TM. The fixed charge concentration is high enough to contribute up to 1.8 kPa to the TM bulk modulus, indicating that a significant fraction of the material stiffness of the TM comes from charge repulsion.

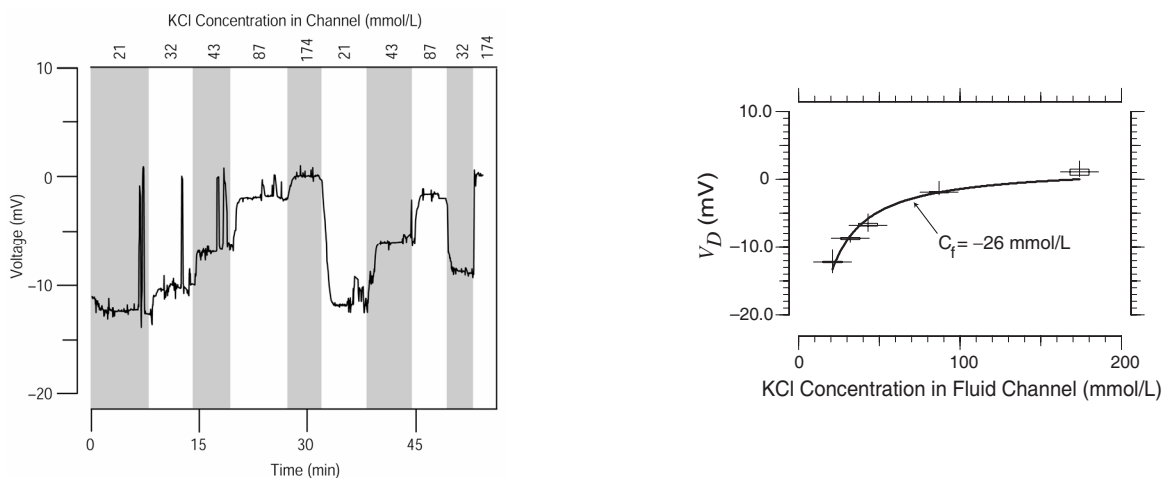


Figure 3. (Left) Voltage measurements with various test solutions. Voltages were found to be stable and repeatable over several minutes up to hours during perfusion and TM voltage recordings. The shaded regions indicate times

⁵ N. Fertig, R.H. Blick, and J.C. Behrends, “Whole Cell Patch Clamp Recording Performed on a Planar Glass Chip,” *Biophys. J.*, 82:3056-3062 (2002).

with different perfusates. The large transient voltage spikes result from intentionally shorting the two baths to check for drift in the measurement system. (Right) The potential between the two fluid baths as a function of KCl concentration in one bath. The KCl concentration in the second bath was 174 mmol/L. As the KCl concentration of the first bath was decreased, the potential became more negative. The best fit of a gel model to these measurements assigns the TM–26 mmol/L of fixed charge (solid line).

2.2. Mechanical Properties of the Cochlea

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Project Staff

Professor Dennis M. Freeman, Professor Thomas F. Weiss, Dr. Alexander J. Aranyosi, Dr. Stanley Hong, Jianwen Wendy Gu, Joseph R. Kovac

Introduction

The cochlea is responsible for turning the mechanical vibrations of sound into neural signals that are sent to the brain. The mechanical processes underlying this transformation are highly nonlinear and poorly understood. We have recently presented measurements showing that, in lower vertebrates, a mechanical tuning of the sensory hair bundles of receptor cells plays a key role in determining how the cells respond to sound. However, it has become increasingly clear in recent years that the cochlea also contains a nonlinear mechanism that increases the sensitivity and frequency selectivity of the ear at low sound levels⁶. To explore how such a mechanism might work, we have incorporated nonlinear force generators into simple models of cochlear function. The results show that when such force generators are used to counteract damping, a small number of simple resonators is sufficient to account for many properties of the level-dependent response of the cochlea to sound. These results have important implications not only for understanding how the cochlea works, but for designing more effective hearing aids, cochlear implants, and similar treatments for hearing loss.

Modeling an active element in hair bundles

Our measurements of the motion of free-standing hair bundles show that these bundles are broadly tuned at high sound levels⁷. This broad tuning matches the measured tuning of hair cell receptor potentials at similar sound levels, indicating that frequency tuning in this cochlea arises primarily from mechanical processes at the level of the hair bundle. A hydrodynamic model⁸ shows that the sharpness of this tuning is limited by fluid viscosity, suggesting that some active mechanism is necessary to sharpen tuning at lower sound levels. Recent studies in other vertebrates have shown that hair bundles can generate force, suggesting that the bundles themselves may constitute the active mechanism in these species.

To test whether active hair bundles could sharpen tuning in the alligator lizard cochlea, we extended the hydrodynamic model by adding an active force at the level of the hair bundle, and compared the frequency response at various sound levels to that of hair cell receptor potentials⁹. Three types of active mechanism were considered: a negative stiffness, a negative damping, and an added torque, each acting over a limited range of hair bundle deflections. The mechanism most consistent with measured tuning curves was a negative damping, which counteracted about 90% of the fluid-generated damping and operated over a range of deflections of about 10-20 nm (Figure 4). This negative damping generates a peak force at low sound levels equivalent to about 2 pN, roughly consistent with the force exerted by hair

⁶ P. Dallos, "The Active Cochlea," *J. Neurosci.*, 12:4575-4585 (1992).

⁷ A.J. Aranyosi and D.M. Freeman, "Sound-induced Motions of Individual Cochlear Hair Bundles", *Biophys. J.*, 87:3536-3546 (2004).

⁸ D.M. Freeman and T.F. Weiss, "Hydrodynamic Analysis of a Two-dimensional Model for Micromechanical Resonance of Free-standing Hair Bundles," *Hear. Res.*, 48: 37-68 (1990).

⁹ A.J. Aranyosi and D.M. Freeman, "Negative Damping by Hair Bundles can Sharpen Tuning in the Alligator Lizard Cochlea," *Abstr. Assoc. Res. Otolaryngol.*, 28:791 (2005).

bundles in a frog saccule preparation¹⁰. In contrast, the negative stiffness reduced the sharpness of tuning at lower sound levels, and the added torque caused little change in tuning. Thus an active hair bundle that operates as a negative damping provides a plausible explanation for the level-dependent sharpening of tuning in this cochlea.

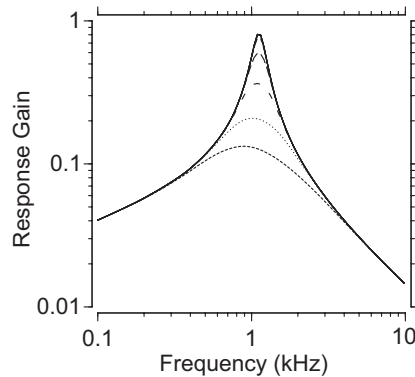


Figure 4. The gain of cochlear tuning at a variety of sound levels, simulated with a hydrodynamic model of the alligator lizard cochlea containing an active negative damping. The lowest curve, corresponding to the shallowest tuning, is comparable to the measured mechanical tuning at high sound levels. As the sound level is decreased, the negative damping counteracts more of the fluid damping, causing the sharpness of tuning to increase.

A coupled-resonator model of mammalian cochlear amplification

In the mammalian cochlea, outer hair cell (OHC) somatic motility mediated by Prestin plays a critical role in establishing the frequency selectivity and sensitivity of the cochlea^{11,12,13}. However, evidence from lower vertebrates, and recently from mammals, shows that hair bundles can also generate active forces which may increase cochlear sensitivity^{14,15,16,17}. We have used this idea to develop a new paradigm for modeling cochlear amplification. Many cochlear models include two resonant systems: one at the level of the basilar membrane, and another at the hair bundle – TM complex. We have built a simple model in which two resonant systems each contain a nonlinear force generator to counteract damping, and these two systems are coupled together through passive interactions.

Each active element exerts a force over a limited range of displacements to counteract damping. The first resonator exerts a force proportional to velocity on the second, which exerts a force proportional to a linear combination of displacement and acceleration back on the first. Incoming sound exerts a force on

¹⁰ P. Martin, A.D. Mehta, and A.J. Hudspeth, "Negative Hair-bundle Stiffness Betrays a Mechanism for Mechanical Amplification by the Hair Cell," *Proc. Nat. Acad. Sci. USA*, 97:12026-12031 (2000).

¹¹ W.E. Brownell, C.R. Bader, D. Bertrand., and Y. de Ribaupierre, "Evoked Mechanical Responses of Isolated Cochlear Outer Hair Cells," *Science*, 227:194-196 (1985).

¹² J. Zheng, W. Shen, D.Z. He, K.B. Long, L.D. Madison, and P. Dallos, "Prestin is the Motor Protein of Cochlear Outer Hair Cells," *Nature*, 405:149-155 (2000).

¹³ M.C. Liberman, J. Gao, D.Z. He, X. Wu, S. Jia, and J. Zuo, "Prestin is Required for Electromotility of the Outer Hair Cell and for the Cochlear Amplifier," *Nature*, 419: 300-304 (2002).

¹⁴ A.C. Crawford and R. Fettiplace, "The Mechanical Properties of Ciliary Bundles of Turtle Cochlear Hair Cells," *J. Physiol.*, 364:359-379 (1985).

¹⁵ M.E. Benser, R.E. Marquis, and A.J. Hudspeth, "Rapid, Active Hair Bundle Movements in Hair Cells from the Bullfrog's Sacculus," *J. Neurosci.*, 16:5629-5643 (1996).

¹⁶ H.J. Kennedy, A.C. Crawford, and R. Fettiplace, "Force Generation by Mammalian Hair Bundles Supports a Role in Cochlear Amplification," *Nature*, 433:880-883 (2005).

¹⁷ D.K. Chan and A.J. Hudspeth, "Ca²⁺ Current-driven Nonlinear Amplification by the Mammalian Cochlea *In Vitro*", *Nature Neurosci.*, 8:149-155 (2005).

the first resonator; the position of the second resonator corresponds to the motion of the basilar membrane.

Despite its simplicity, this model does a remarkable job of predicting basilar membrane click responses, compressive nonlinearity, and the sharpness of tuning at a variety of sound levels (Figure 5). The response to low-intensity tones is sharply frequency selective with a rounded peak, similar to the tuning curves measured from auditory nerve fibers and at the basilar membrane. The peak becomes broader as the stimulus level is increased, with a nonlinear compression that extends over more than 60 dB. This peak is symmetric with frequency, suggesting that asymmetry is introduced by the cochlear traveling wave. The response to clicks is multi-lobed, with the response phase switching by 180 degrees between each lobe. This click response also has a level-dependent nonlinearity; the response magnitude grows slower than linearly, and the peak of the response shifts earlier in time as the sound level is increased.

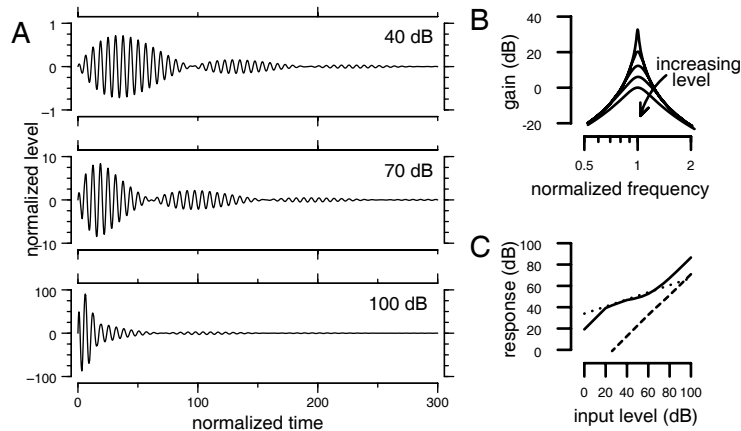


Figure 5. Predictions of a simple coupled-resonator model of cochlear amplification. (A) The model response to clicks at three levels. The top plot corresponds to the lowest click level; the click level increases by 30 dB for each subsequent plot. Multiple lobes are present, and the response peak shifts earlier in time at higher click levels. (B) The model gain in response to tones as a function of frequency and tone level. The response is sharper for lower tone levels. This plot is symmetric in frequency because it does not include the effect of the cochlear traveling wave. (C) Nonlinear growth at the best frequency. The solid curve shows the response amplitude as a function of input level for a tone at the best frequency. The growth with level is compressive, having a slope of about 1/3 (as shown by the dotted line) over about a 60 dB range of input levels. Away from the best frequency, the growth with level is linear (dashed line).

In this model, the cochlea is compressively nonlinear over a wide range of sound levels because each resonator keeps the other in its nonlinear regime. Tuning curves are rounded at the peak partly due to the fourth-order nature of the impedance, and partly because in the nonlinear regime, a decrease in the effective gain of one amplifier is offset somewhat by an increase in gain of the other. Click responses rise gradually over time as energy is transferred from the first resonator to the second. The multiple lobes of click responses result from energy transfer between the resonators. Thus despite the simplicity of this model, it not only predicts cochlear responses over a wide range of sound levels, it provides a conceptual framework to explain some of the most remarkable mechanical properties of the cochlea.

Meeting Papers Published

A.J. Aranyosi and D.M. Freeman, "Negative Damping by Hair Bundles can Sharpen Tuning in the Alligator Lizard Cochlea," *Abstr. Assoc. Res. Otolaryngol.*, 28:791 (2005).

R. Ghaffari, and D.M. Freeman, "Electrical Properties of the Isolated Tectorial Membrane Measured with a Microfabricated Planar Clamp Technique," *Abstr. Assoc. Res. Otolaryngol.*, 28:341 (2005).

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K. Masaki, T.F. Weiss, and D.M. Freeman, "Measuring the Equilibrium Bulk Modulus of the Tectorial Membrane with Osmotic Stress: Caveats of Using Polyethylene Glycol," *Abstr. Assoc. Res. Otolaryngol.*, 28:342 (2005).

K. Masaki, G. Chan, R.J.H. Smith, and D.M. Freeman, "Hearing Loss Measured by DPOAEs Correlates with an Increase in Equilibrium Bulk Modulus of Tectorial Membranes from Col11a2 ^{-/-} Mouse Mutants," *Abstr. Assoc. Res. Otolaryngol.*, 28:343 (2005).

K. Masaki, G. Richardson, and D.M. Freeman, "TectaY1870C Missense Mutation Increases the Equilibrium Bulk Modulus of the Tectorial Membrane," *Abstr. Assoc. Res. Otolaryngol.*, 28:344 (2005).

Papers Published

A.J. Aranyosi and D.M. Freeman, "Sound-induced Motions of Individual Cochlear Hair Bundles," *Biophys J.* 87, pp 3536-3546 (2004).

A.J. Aranyosi and D.M. Freeman, "Two Modes of Motion of the Alligator Lizard Cochlea: Measurements and Model Predictions," *J Acoust Soc Am*, in press.

Advanced Undergraduate Projects

J.R. Kovak, *High Resolution Laser Doppler Vibrometer for Measuring Sound Induced Motions in the Inner Ear*, Department of Electrical Engineering and Computer Science, MIT, June 2005.

Masters Theses

J.W. Gu, *Measuring Mechanical Properties of the Tectorial Membrane with a Microfabricated Probe*, Division of Biological Engineering., MIT, June 2004.

Doctoral Theses

S. Hong, *Scanning Standing-wave Illumination Microscopy: A Path to Nanometer Resolution in X-ray Microscopy*, Department of Electrical Engineering and Computer Science, MIT, November 2004.

3. Neural Mechanisms for Auditory Perception

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Project Staff

B. Delgutte, A. Oxenham, L. Cedolin, C.V. Seshagiri, A. Dreyer, E. Larsen

The long-term goal of our research is to understand the neural mechanisms that mediate the ability of normal-hearing people to process speech and other sounds of interest in the presence of competing sounds, and how these mechanisms are degraded in the hearing-impaired. Studies in the past year focused on the neural representation of the pitch of harmonic complex tones and on the neural mechanisms for binaural hearing at high frequencies.

3.1 Spatio-temporal Representation of the Pitch of Harmonic Complex Tones in the Auditory Nerve

Previous studies of the coding of the pitch of complex tones in the auditory nerve suggest that neither a rate-place representation, nor a temporal representation based on interspike interval distributions fully account for psychophysical data. Here we explore an alternative spatio-temporal representation based on rapid changes in the phase of the cochlear traveling wave at the place of each resolved spectral component.

We recorded from auditory-nerve fibers in anesthetized cats in response to equal-amplitude harmonic complex tones with a missing fundamental frequency (F_0). For a given fiber, the F_0 range was chosen so that the “harmonic number” CF/F_0 varied from 1.5 to 4.5 in order to capture low-order harmonics likely to be resolved. We computed the derivative of the period histogram with respect to harmonic number in order to approximate a lateral inhibitory process operating on the spatio-temporal response pattern of the entire auditory nerve.

For F_0 s below about 1 kHz, the spatial derivative shows local maxima when a fiber's CF coincides with one of the first 2-4 harmonics of F_0 , thereby giving information about the frequencies of resolved harmonics. Resolved harmonics remain apparent in the spatial derivative even at stimulus levels where the average discharge rate is saturated. For F_0 s above 1 kHz, the spatiotemporal representation degrades due to poorer phase locking, while the rate-place representation improves as harmonics are better resolved. The spatio-temporal representation is thus consistent with the psychophysical upper F_0 limit near 1 kHz to the pitch of missing-fundamental stimuli.

These results suggest that the spatio-temporal representation of pitch may be both more stable with respect to stimulus level and more consistent with psychophysical data than the rate-place representation. Future studies will investigate whether these spatio-temporal pitch cues can be extracted by neurons in the cochlear nucleus.

3.2 Neural Coding of Pitch in the Auditory Nerve: Two Simultaneous Complex Tones

Often, we listen to sounds consisting of harmonic complex tones in the presence of other harmonic complex tones, for example in symphonic music or in cocktail party situations. Perceptually, listeners can match the pitches of two instruments playing different notes, and a pitch difference aids in segregating

sound sources. Physiologically, little is known about the neural basis for this ability. Thus, we investigated the representation of simultaneous pitches in the auditory nerve of anesthetized cats.

We measured the responses of single neurons to two simultaneous complex tones (missing fundamental, equal-amplitude harmonics) with a wide range of fundamental frequencies. The fundamental frequencies of the two tones differed by either 7% or 22%. Each harmonic was about 15 dB above the threshold at CF, corresponding to 20-50 dB SPL. Pitch estimates were obtained from both rate-place (average discharge rate against CF) and temporal (interspike interval distribution) representations of the stimulus.

Highly accurate (rms errors about 1%) estimates of both pitches of the two complex tones were obtained over nearly the entire range of fundamental frequencies that was investigated using either of the two neural representations. For fundamental frequencies below about 1 kHz, best pitch estimates were obtained from the temporal representation. Also, the lower tone tended to be more prominently represented than the higher tone in interspike interval distributions, an effect reflecting the asymmetry of cochlear filtering. For fundamental frequencies above about 1.5 kHz, best pitch estimates were obtained with the rate-place representation. This limit may be lower in human, if cochlear tuning is sharper than in cat.

In conclusion, the auditory nerve faithfully transmits pitch information for simultaneous complex tones to higher auditory centers. Future studies will examine whether the spatio-temporal representation described above is also effective when there are two simultaneous pitches.

3.3 Predicting Lateralization Performance at High Frequencies from Auditory-nerve Spike Timing

While human listeners can lateralize sounds based on interaural time differences (ITD) in either the waveforms of low-frequency pure tones or the envelopes of high-frequency sinusoidally amplitude modulated (SAM) tones, performance is generally poorer for SAM tones than for pure tones. ITD sensitivity at high frequencies might be improved using “transposed stimuli”, which seek to produce the same temporal discharge patterns in high-frequency neurons as in low-frequency neurons for pure tones. Here, we study ITD sensitivity for pure tones, SAM tones and transposed stimuli using neurophysiology, psychoacoustics and computational models.

Phase locking of auditory-nerve fibers in anesthetized cats was characterized using both the synchronization index and autocorrelograms. With both measures, phase locking is stronger for pure tones than for transposed stimuli, and for transposed stimuli than for SAM tones. Phase locking to SAM tones and transposed stimuli degrades with increasing stimulus level, while remaining more stable for pure tones.

ITD discrimination was measured in humans for stimuli presented either in quiet or with band-reject noise intended to restrict listening to a narrow frequency band. Performance improved slightly with increasing stimulus level for all three stimuli both with and without noise. ITD sensitivity to transposed stimuli was comparable to pure-tone performance only in the absence of noise.

To relate psychophysical performance to auditory-nerve activity, we used an optimal binaural processor model with delay lines and coincidence detectors. In the no-noise condition, model performance is stable with stimulus level, consistent with psychophysics, because there are always unsaturated fibers with good phase locking on the edges of the excitation pattern. However, in the band-reject noise condition, model performance for transposed stimuli degrades with increasing level, contrary to psychophysics. The model also predicts worse-than-observed performance for transposed stimuli relative to pure tones.

These results have implications for the relative roles of peripheral patterns of activity and the binaural processor in accounting for ITD sensitivity at low versus high frequencies. They point to a dynamic range problem in the coding of envelope ITDs at high frequencies similar to the classic dynamic range problem in intensity discrimination and loudness perception.

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4. Bilateral Cochlear Implants: Physiological and Psychophysical Studies

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The long-term goal of our research is to identify the best stimulus configurations for effectively delivering binaural information with bilateral cochlear implants using closely-integrated neurophysiological, psychophysical and theoretical studies. Studies in the past year have focused on measuring sensitivity to interaural time differences (ITD) of bilaterally implanted human subjects and neurons in the auditory midbrain of implanted cats.

4.1 Psychophysics

We continued the exploration of ITD sensitivity in bilaterally-implanted human listeners as a function of stimulation parameters. For unmodulated pulse trains delivered to a single interaural electrode pair, just-noticeable differences (JND) in ITD increase from 140 μ s to 535 μ s as the repetition rate increases from 50 pps to 200 pps. For sinusoidally amplitude-modulated (SAM) pulse trains, JNDs for 50 Hz modulation decrease as the carrier rate increases from 200 pps (JND > 1 ms) to 5000 pps (JND \approx 125 μ s).

Preliminary measures using unmodulated pulse trains indicate that the ITD JND increases significantly when the onset cue is degraded by increasing the rise time. For instance, the ITD JND for a pulse train at 1450 pps (the carrier rate for the Clarion CIS processing strategy), almost doubles when the rise/fall time increases from 0 ms to 20 ms. With a CIS strategy, a 540-Hz tone burst at the center frequency of an analysis channel produces an electric stimulus that approximates an unmodulated pulse train at 1450 pps. Even when the tone-burst has an abrupt onset, the ITD JND measured through the sound processor does not reach the sensitivity available by directly controlling the implanted receiver/stimulator, probably because the envelope's rise time is limited by the filtering associated with the analysis channel. When a 5-ms rise/fall time is applied to the tone, the JND becomes greater than 2 ms, larger than the naturally occurring range of ITDs.

We also initiated a series of experiments aimed at assessing subjects' ability of make use of specific binaural cues when localizing sounds through their processors. In one subject, a set of head related transfer functions (HRTFs) was computed for each of 7 speaker positions evenly distributed from -90° to $+90^\circ$ in the horizontal plane using recording from the subject's right and left microphones. This set of HRTFs were processed to produce an additional three sets of HRTFs in which some of the binaural cues were degraded: (1) The ILD measured at 0° azimuth is imposed on the HRTFs of all other azimuths with ITDs left intact; (2) The ITD recorded at 0° azimuth is imposed for all azimuths with ILD cues left intact; and (3) The envelopes are left intact but uncorrelated noise replaces the fine-structure for all speaker positions. With ILD fixed at 0° , the r.m.s. error in localization increased significantly over that with normal HRTFs, suggesting that ILD is used by this subject to localize sound sources. Localization error also increased significantly for both manipulations of the ITD cue (fixed at the 0° value and randomized). Thus, ITD cues seem to provide substantial binaural information that is used in the localization task event though this subject has poorer ITD sensitivity than normal.

Our results suggest that, even though ITD sensitivity for electric stimulation decreases with increasing modulation frequency, implant subjects are able to use this degraded sensitivity in every-day tasks. This means, that to the extent we are able to improve ITD sensitivity using new stimulation strategies, the binaural benefits patients receive from their implants are also likely to improve.

4.2 Neurophysiology

The neural processing of binaural cues in normal-hearing listeners is essential for accurate sound localization and speech reception in noise. Bilateral implantation seeks to restore the advantages of binaural hearing to cochlear implant users. While psychophysical tests show good sensitivity to interaural level differences with bilateral implants, sensitivity to interaural timing differences (ITD) is generally poor. To better understand the neural processing of ITD with electric stimulation, we recorded from single-units in the inferior colliculus (IC) of acutely deafened, anesthetized cats implanted bilaterally with intracochlear electrode arrays. Stimuli were electric pulse trains with and without sinusoidal amplitude modulation (SAM).

The discharge rates of the majority of cells in the central nucleus of the IC were sensitive to ITD for low-rate (40 pulses per sec - pps) pulse trains. Best ITDs and tuning widths were similar to those seen for acoustic stimulation with clicks. For many neurons, however, well defined ITD sensitivity existed only over a small range (2-3 dB) of stimulus levels near threshold. As pulse rate was increased, responses became largely limited to the onset and ITD tuning degraded. When high-rate (1000 pps) pulse trains were amplitude modulated (40 Hz), sustained responses were again observed and good ITD sensitivity sometimes reappeared. When ITD was independently controlled in the modulation and carrier of SAM stimuli, about twice as many cells showed sensitivity to ITD in the modulation than in the carrier. However, modulation ITD functions were broad with little or no change in discharge rate within the physiological range of ITD, at least for this low modulation frequency.

Our physiological results show that ITD sensitivity in the IC can be as good as normal with electric stimulation. However, the limited dynamic range over which most units show good sensitivity may be problematic. Our finding that ITD sensitivity to the fine-structure of modulated pulse trains dominates sensitivity to the envelope is relevant to clinical devices that only deliver ITD information via envelope modulations. New stimulation strategies may have to precisely control the interaural timing of carrier pulses in order to achieve good ITD sensitivity.

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