

# Enhancement of sensitivity gain and frequency tuning by coupling of active hair bundles

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**The vertebrate inner ear possesses an active process that provides nonlinear amplification of mechanical stimuli. A candidate for this process is active hair bundle mechanics observed, for instance, for hair cells of the bullfrog's sacculus. Hair bundles in various inner ear organs are coupled by overlying membranes. Using a stochastic description of active hair bundle dynamics, we study the consequences of an elastic coupling on the properties of amplification. We report that collective effects in arrays of hair bundles can enhance the amplification gain and the sharpness of frequency tuning as compared with the performance of an isolated hair bundle. We also discuss the transient response elicited by the sudden onset of a periodic stimulus and its relation to temporal integration curves. Simulations of systems with a gradient of intrinsic frequencies show an enhanced amplification gain while preserving a frequency gradient, provided the coupling strength is similar to the hair bundle stiffness. We relate our findings to the situation in the bullfrog's sacculus and the mammalian cochlea.**

auditory amplifier | hair cells | nonlinear oscillators | stochastic processes

The extraordinary ability of the vertebrate ear to detect sound stimuli over many orders of magnitude in sound amplitude relies on active processes. The key features of the auditory amplifier are (i) the amplification of weak stimuli, (ii) a compressive nonlinearity for stronger stimuli, (iii) frequency selectivity, and (iv) the generation of spontaneous emissions (1–3). All these properties could be understood as the consequence of nonlinear dynamic oscillators that operate in the ear (4–7). There is clear evidence for nonlinear amplification to occur in all vertebrates (3) and even some insects (8). However, the specific molecular and cellular mechanisms underlying the amplifiers in different species are still under debate.

Mechano-sensitive hair cells play a key role in the amplification. Two mechanisms have been suggested. First, outer hair cell electromotility, which involves cell body contractions (9), could be an important element of the amplifier in the mammalian cochlea (10–12). Second, the hair bundle, which is the mechano-sensitive organelle at the apical surface of the hair cell, could generate forces and movements that contribute to amplification (13–15).

Electromotility is absent in nonmammalian vertebrates, which nevertheless display exquisite signal detection with all signatures of the auditory amplifier (3). It has been shown in turtles and frogs that hair bundles are able to generate noisy spontaneous oscillations (13, 16–19). Furthermore, mechanical stimulation of individual hair bundles of the frog revealed a frequency selective response (13), a compressive nonlinearity (20), and a high sensitivity at weak stimuli (20). This suggests that the hair bundles themselves are an essential part of the nonlinear amplifier (21). However, the properties of an individual hair bundle are not sufficient to account quantitatively for the properties of the auditory amplifier. For example, an important characteristic of the amplifier is the amplification gain, defined as the ratio of sensitivity for weak and strong stimulation. The amplification gain measured in the mammalian cochlea is  $\approx 1,000$  (22), whereas for a single hair bundle of the bullfrog a value of only  $\approx 10$  was observed (20). The amplification gain of a hair bundle

is largely limited by random influences, such as thermal fluctuations, channel clatter, and stochastic variations occurring at the scale of the hair bundle (23).

This raises the question what mechanisms underlie the discrepancy between single hair bundle properties and those of the auditory amplifier. In mammals, outer hair cell electromotility could enhance amplification by hair bundles. Another mechanism to increase signal amplification is the cooperative response of groups of coupled hair bundles. In most hearing organs, hair bundles are mechanically coupled via an overlying membranous structure as sketched in Fig. 1A. For example, the outer hair cells of the mammalian cochlea are directly linked via their hair bundles to the tectorial membrane, which is an elastic polymer network (24). Otolithic membranes can also provide an elastic coupling of hair bundles as for instance in the bullfrog's sacculus (25).

Here, we study the consequences of elastic coupling of hair bundles for their amplification properties. Although our model does not describe an entire hearing organ it characterizes groups of hair bundles as active subunits that are key elements of the auditory amplifier. Specifically, we investigate the properties of groups of hair bundles that are coupled mechanically by elastic springs, excluding from our description inertial elements, such as cochlear fluids or otolithic masses. We discuss properties of spontaneous oscillations and of the nonlinear amplification in response to mechanical stimulation of coupled hair bundles as a function of the coupling strength. Individual hair bundles in the group are described by a simple stochastic model (23, 26) that takes into account random fluctuations and can capture the noise-limited amplification gain of a single hair bundle. Because this example is best studied, we choose parameters that correspond to hair bundles observed in the sacculus of the bullfrog. The same model, however with different parameters, could also be used to describe hair bundles in the cochlea (26).

**Physical Description of Coupled Hair Bundles.** We discuss a regular arrangement of hair bundles that are mechanically coupled by elastic elements to their neighbors. In our model, hair bundles are arranged on a square lattice with spacing  $d$  (see Fig. 1B). They are labeled  $(i, j)$  according to their position on the lattice where  $i = 1, \dots, N$  and  $j = 1, \dots, M$ . Each hair bundle is described by two variables  $X^{i,j}$  and  $X_a^{i,j}$ , characterizing the stereociliary deflection and the state of adaptation motors, respectively. We consider hair bundles that are all oriented with their excitatory direction in the positive  $X$  direction and  $X^{i,j}$  are the deflections along this direction. In the following, we ignore deflections in the

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27 coupled hair bundles. For sufficiently strong coupling, we recover the amplification gain of homogeneous systems of the same number of hair bundles. In this case, the frequency gradient is drastically reduced because of synchronization effects. Our analysis shows that there is characteristic range of coupling strengths  $K$  approximately  $K \approx K_{SP}$  where amplification is significantly enhanced while at the same time frequency variability is preserved. For smaller  $K$  values, synchronization is lost, whereas, for larger  $K$  values, frequency variability is lost.

In our work, we have studied the effect of coupling on hair bundle dynamics as a function of coupling strength  $K$ . Values of  $K$  in different hearing organs can be estimated from the elastic properties of otolithic or tectorial membranes. In the otolithic membrane of the bullfrog, direct mechanical measurements show that the membrane constitutes an elastic medium and local stresses lead to displacements that decay exponentially with a characteristic length  $\ell$ , which depends on direction in the sacculus (31). Such a decay with  $\ell \approx d(K/K_{SP})^{1/2}$ , where  $d$  is the spacing between hair cells, also occurs in our model (data not shown). Using  $d \approx 50 \mu\text{m}$ ,  $\ell \approx 150 \mu\text{m}$  (31), and  $K_{SP} = 1 \text{ mN}\cdot\text{m}^{-1}$  (including contributions from subotolithic filaments; see ref. 31) results in  $K \approx 9 \text{ mN}\cdot\text{m}^{-1}$ . Alternatively, we can estimate the coupling strength based on the Young's modulus  $E$  of the membrane overlying the hair bundles as  $K \approx Ed$ . For the otolithic membrane of the bullfrog's sacculus  $E \approx 6.6 \text{ kPa}$  has been suggested (31, 32), leading with  $d = 50 \mu\text{m}$  to an estimate of  $K \approx 330 \text{ mN}\cdot\text{m}^{-1}$ . Both estimates of  $K$  correspond to the strong coupling regime and lead to complete synchronization and reduction of frequency heterogeneities in our simulations. Note that these estimates do not take into account the 3 dimensional

shape of the otolithic membrane that exhibits large cavities inside which hair bundle tips are attached (25). This specific geometry and a potentially soft coupling of the hair bundle to the otolithic membrane could reduce  $K$ , thus permitting different frequencies to coexist. Furthermore, inertial effects introduced by otolithic masses that we have neglected in our simulations might also influence synchronization in the system.

In the mammalian cochlea the Young's modulus of the tectorial membrane has been estimated and exhibits a gradient of tectorial stiffness (33–37). Values reported range from  $E = 0.3 \text{ kPa}$  at the apex to  $3 \text{ kPa}$  at the base in gerbil (37) and from  $E = 24 \text{ kPa}$  at the apex to  $224 \text{ kPa}$  at the base in mouse (36). With  $d = 10 \mu\text{m}$  the values observed in gerbil correspond to a range  $K = 3\text{--}30 \text{ mN}\cdot\text{m}^{-1}$ . As discussed above, to benefit from hair bundle coupling, while retaining a frequency profile, the coupling strength provided by the tectorial membrane should be within an order of magnitude of the hair bundle stiffness. Hair bundle stiffness does indeed vary along the cochlea. In guinea pig values of  $K_{SP}$  of outer hair cells ranging from  $\approx 0.5 \text{ mN}\cdot\text{m}^{-1}$  at the apex to  $\approx 40 \text{ mN}\cdot\text{m}^{-1}$  at the base, have been reported (38). This suggests that the tectorial membrane stiffness is tuned to the local hair bundle stiffness following a similar gradient (37), ensuring that the local coupling strength  $K$  is adjusted to the local hair bundle stiffness  $K_{SP}$ . Our work shows that such an adjustment of coupling permits a significant enhancement of amplification via coupling while preserving at the same time gradual frequency changes.

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- Dallos P (1992) The active cochlea. *J Neurosci* 12:4575–4585.
- Hudspeth AJ (1997) Mechanical amplification of stimuli by hair cells. *Curr Opin Neurobiol* 7:480–486.
- Manley GA (2001) Evidence for an active process and a cochlear amplifier in nonmammals. *J Neurophysiol* 86:541–549.
- Choe Y, Magnasco MO, Hudspeth AJ (1998) A model for amplification of hair-bundle motion by cyclical binding of  $\text{Ca}^{2+}$  to mechano-electrical-transduction channels. *Proc Natl Acad Sci USA* 95:15321–15326.
- Camalet S, Duke T, Jülicher F, Prost J (2000) Auditory sensitivity provided by self-tuned critical oscillations of hair cells. *Proc Natl Acad Sci USA* 97:3183–3188.
- Eguiluz VM, Ospeck M, Choe Y, Hudspeth AJ, Magnasco MO (2000) Essential nonlinearities in hearing. *Phys Rev Lett* 84:5232–5235.
- Martin P, Hudspeth AJ, Jülicher F (2001) Comparison of a hair bundle's spontaneous oscillations with its response to mechanical stimulation reveals the underlying active process. *Proc Natl Acad Sci USA* 98:14380–14385.
- Göpfert MC, Humphris ADL, Albert JT, Robert D, Hendrich O (2005) Power gain exhibited by motile mechanosensory neurons in *Drosophila* ears. *Proc Natl Acad Sci USA* 102:325–330.
- Brownell WE, Bader CR, Bertrand D, Derbauptierre Y (1985) Evoked mechanical responses of isolated cochlear outer hair cells. *Science* 227:194–196.
- Ashmore JF, Geleoc GSG, Harbott L (2000) Molecular mechanisms of sound amplification in the mammalian cochlea. *Proc Natl Acad Sci USA* 97:11759–11764.
- Santos-Sacchi J (2003) New tunes from Corti's organ: The outer hair cell boogie rules. *Curr Opin Neurobiol* 13:459–468.
- Dallos P, et al. (2008) Prestin-based outer hair cell motility is necessary for mammalian cochlear amplification. *Neuron*, 58:333–339.
- Martin P, Hudspeth AJ (1999) Active hair-bundle movements can amplify a hair cell's response to oscillatory mechanical stimuli. *Proc Natl Acad Sci USA* 96:14306–14311.
- Kennedy HJ, Crawford AC, Fettiplace R (2005) Force generation by mammalian hair bundles supports a role in cochlear amplification. *Nature* 433:880–883.
- Fettiplace R, Hackney CM (2006) The sensory and motor roles of auditory hair cells. *Nat Rev Neurosci* 7:19–29.
- Martin P, Bozovic D, Choe Y, Hudspeth AJ (2003) Spontaneous oscillation by hair bundles of the bullfrog's sacculus. *J Neurosci* 23:4533–4548.
- Crawford AC, Fettiplace R (1985) The mechanical properties of ciliary bundles of turtle cochlear hair-cells. *J Physiol* 364:359–379.
- J. Howard, Hudspeth AJ (1987) Mechanical relaxation of the hair bundle mediates adaptation in mechano-electrical transduction by the bullfrog's saccular hair cell. *Proc Natl Acad Sci USA* 84:3064–3068.
- Denk W, Webb WW (1992) Forward and reverse transduction at the limit of sensitivity studied by correlating electrical and mechanical fluctuations in frog saccular hair-cells. *Hear Res* 60:89–102.
- Martin P, Hudspeth AJ (2001) Compressive nonlinearity in the hair bundle's active response to mechanical stimulation. *Proc Natl Acad Sci USA* 98:14386–14391.
- Manley GA, Kirk DL, Koppl C, Yates GK (2001) In vivo evidence for a cochlear amplifier in the hair-cell bundle of lizards. *Proc Natl Acad Sci USA* 98:2826–2831.
- Robles L, Ruggero MA (2001) Mechanics of the mammalian cochlea. *Physiol Rev* 81:1305–1352.
- Nadrowski B, Martin P, and Jülicher F (2004) Active hair-bundle motility harnesses noise to operate near an optimum of mechanosensitivity. *Proc Natl Acad Sci USA* 101:12195–12200.
- Freeman DM, Masaki K, McAllister AR, Wei JL, Weiss TF (2003) Static material properties of the tectorial membrane: A summary. *Hear Res* 180:11–27.
- Kachar B, Parakkal M, and Fex J (1990) Structural basis for mechanical transduction in the frog vestibular sensory apparatus. 1. The otolithic membrane. *Hear Res* 45:179–190.
- Tinevez JY, Jülicher F, Martin P (2007) Unifying the various incarnations of active hair-bundle motility by the vertebrate hair cell. *Biophys J* 93:4053–4067.
- Eddins DA, Green DM (1995) Temporal integration and temporal resolution. *Hearing*, ed Moore BCJ (Academic, San Diego), pp 207–242.
- Florentine M, Fastl H, Buus S (1988) Temporal integration in normal hearing, cochlear impairment, and impairment simulated by masking. *J Acoust Soc Am* 81:195–203.
- Pollak G, Novick A, Henson OW (1972) Cochlear microphonic audiograms in the "pure tone" bat *Chilonycteris parnellii*. *Science* 176:66–68.
- Russell IJ, Kössl M (1999) Micromechanical responses to tones in the auditory fovea of the greater mustached bat's cochlea. *J Neurophysiol* 82:676–686.
- Benser ME, Issa NP, Hudspeth AJ (1993) Hair-bundle stiffness dominates the elastic reactance to otolithic-membrane shear. *Hear Res* 68:243–252.
- Kondrachuk AV (2000) Computer simulation of the mechanical stimulation of the saccular membrane of bullfrog. *Hear Res* 143:130–138.
- Zwislocki JJ, Cefaratti LK (1989) Tectorial membrane II: Stiffness measurements in vivo. *Hear Res* 42:211–228.
- Abnet CC, Freeman DM (2000) Deformations of the isolated mouse tectorial membrane produced by oscillatory forces. *Hear Res* 144:29–46.
- Shoelson B, Dimitriadis EK, Cai HX, Kachar B, Chadwick RS (2004) Evidence and implications of inhomogeneity in tectorial membrane elasticity. *Biophys J* 87:2768–2777.
- Gueta R, Barlam D, Shneck RZ, Rouso I (2006) Measurement of the mechanical properties of isolated tectorial membrane using atomic force microscopy. *Proc Natl Acad Sci USA* 103:14790–14795.
- Richter CP, Emadi G, Getnick G, Quesnel A, Dallos P (2007) Tectorial membrane stiffness gradients. *Biophys J* 93:2265–2276.
- Strelhoff D, Flock A (1984) Stiffness of sensory-cell hair bundles in the isolated guinea pig cochlea. *Hear Res* 15:19–28.