1. Spiegel MF & Watson CS (1984) Performance on Frequency-Discrimination Tasks by Musicians and Nonmusicians. *J Acoust Soc Am* 76(6):1690-1695.

* 300 ms sinusoidal tones to musicians and nonmusicians
* df/f = 0.001-0.0045 for musicians; df/f = 0.017 (though half of nonmusicians as low as musicians)

1. Knudsen VO (1923) The sensibility of the ear to small differences of intensity and frequency. *Phys Rev* 21(1):84-102.

* Review describing hearing – Painful stimuli around 120 dB

1. Green DM, Huanping Dai (1991) Is human hearing limited by Brownian motion? *J Acoust Soc Am* 89(4B):1889.

* Absolute threshold at 1 kHz is 9 dB SPL – About 10-16 W-s/cm2
* Ratio of signal energy to noise power density about 5000
* Limitation – Thermal fluctuations of molecules in the air

1. Manley GA (2001) Evidence for an active process and a cochlear amplifier in nonmammals. *Journal of neurophysiology* 86(2):541-549.

* Review – Evidence for active process in nonmammals – signal detection near level of noise; overcome fluid viscosity
* Shows frequency tuning, otoacoustic emission in different species (including humans)
* Bundle-based mechanisms evolved first and persists in nonmammals; Prestin motor then evolved in mammals

1. Hudspeth AJ, Julicher F, & Martin P (2010) A Critique of the Critical Cochlea: Hopf-a Bifurcation-Is Better Than None. *Journal of neurophysiology* 104(3):1219-1229.

* Review – Lays out four components of active process – uses Hopf bifurcation to explain them all

1. Zurek PM (1981) Spontaneous Narrowband Acoustic-Signals Emitted by Human Ears. *J Acoust Soc Am* 69(2):514-523.

* 32 humans with normal hearing – measured SOAEs in 22 ears of 16 people --- evidence of active biomechanical processes
* Suppression of OAEs by external tone – dependent upon frequency and stimulus amplitude

1. Daniel E (2007) Noise and Hearing Loss: A Review. *Journal of School Health* 77(5):225-231.

* 28 million americans with hearing impairment – about half are due to acute or chronic exposure to loud noise (NIHL)
* NIHL due to damage to hair cells in organ of Corti – 30-50% must be damaged for appreciable impairment of sensation

1. Shim K (2006) The auditory sensory epithelium: The instrument of sound perception. *The International Journal of Biochemistry and Cell Biology* 38(11):1827-1833.

* Hearing impairment due either to failure during embryogenesis or due to damage by noise or drugs

1. Gold T (1948) Hearting. II. The physical basis of the action of the cochlea. *Proceedings of the Royal Society of London Series B, Biological Sciences* 135(881):1-8.

* Lays out basics of the critical oscillator – Describes the “regenerative hypothesis” where the ear is compared to a radio
* Negative resistance overcomes viscous damping in the ear
* Describes potential for critical oscillators acting on the verge of an instability – too much gain will cause it to self-oscillate

1. Martin P, Bozovic D, Choe Y, & Hudspeth AJ (2003) Spontaneous oscillation by hair bundles of the bullfrog's sacculus. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 23(11):4533-4548.

* Increasing Ca2+ concentration rendered oscillations faster/smaller until suppressed
* Increasing gain on the clamp to increase effective stiffness reduced oscillation amplitude and increased their frequency
* Oscillations continued after detachment of kinocilium

1. Tinevez JY, Julicher F, & Martin P (2007) Unifying the various incarnations of active hair-bundle motility by the vertebrate hair cell. *Biophysical journal* 93(11):4053-4067.

* Twitch times much faster with increased calcium iontophoresis
* Ramp of calcium iontophoresis – Quiescent to oscillations of ~4 Hz to ~11 Hz with increased Ca2+ - no change in amplitude
* Increased calcium iontophoresis shifted force-displacement curve in the positive direction

1. Strogatz S (1994) *Nonlinear Dynamics and Chaos* (Addison-Wesley, Reading, MA).

* Basics of dynamical systems / bifurcations

1. Eguíluz VM, Ospeck M, Choe Y, Hudspeth AJ, & Magnasco MO (2000) Essential nonlinearities in hearing. *Physical review letters* 84(22):5232-5235.

* Nonlinearities in hearing appear near the Hopf bifurcation
* Shown to be *more* marked with smaller forcing – no audible sound small enough not to evoke them

1. Hudspeth AJ, Julicher F, & Martin P (2010) A critique of the critical cochlea: Hopf--a bifurcation--is better than none. *Journal of neurophysiology* 104(3):1219-1229.

- Review – Lays out four components of active process – uses Hopf bifurcation to explain them all

1. Gelfand M, Piro O, Magnasco MO, & Hudspeth AJ (2010) Interactions between Hair Cells Shape Spontaneous Otoacoustic Emissions in a Model of the Tokay Gecko's Cochlea. *PloS one* 5(6).

* SOAEs measured in tokay gecko
* Modeled as coupled van der Pol oscillators in a tonotopic array

1. Manley GA, Sienknecht U, & Koppl C (2004) Ca2+ modulates the frequency and amplitude of spontaneous otoacoustic emissions in the bobtail skink. *Journal of neurophysiology* 92(5):2685-2693.

* Increased calcium concentration increased SOAE peak frequency but reduced their amplitude – consistent with HB motion

1. Ó Maoiléidigh D, Nicola EM, & Hudspeth AJ (2012) The diverse effects of mechanical loading on active hair bundles. *Proceedings of the National Academy of Sciences of the United States of America* 109(6):1943-1948.

* Model for state space of hair bundle used in this paper

1. Simmons DD, Meenderink, S. & Vassilakis, P. N. (2006) Anatomy, Physiology, and Function of Auditory End-Organs in the Frog Inner Ear. *Auditory End-Organs*).

* Describes auditory end-organs in detail, focusing on AP/BP

1. Pickles JO, Comis SD, & Osborne MP (1984) Cross-Links between Stereocilia in the Guinea-Pig Organ of Corti, and Their Possible Relation to Sensory Transduction. *Hearing research* 15(2):103-112.

* Cross links between stereocilia in guinea pig cochlea seen on SEM

1. Kazmierczak P*, et al.* (2007) Cadherin 23 and protocadherin 15 interact to form tip-link filaments in sensory hair cells. *Nature* 449(7158):87-U59.

* Cadherin 23 on upper 2/3 of tip link, protocadherin 15 on lower 1/3 of tip link
* Cadherin 23 ~130 nm, Protocadherin 15 ~52 nm

1. Sul B & Iwasa KH (2010) Gating of Two Mechanoelectrical Transducer Channels Associated with a Single Tip Link. *Biophysical journal* 99(4):1027-1033.

* Two MET channels in parallel showed same results as single-channel models
* If they are in series, there are two minima for stiffness (as opposed to one), so that would not work

1. Vollrath MA, Kwan KY, & Corey DP (2007) The micromachinery of mechanotransduction in hair cells. *Annu Rev Neurosci* 30:339-365.

* Positive deflection <1 um elicit inward currents ~ 1 nA – activation curve has a width of 0.5 um or less
* Channel opening – time constant ~1000 us – too fast for second messengers
* MET channels permeable to ions up to ~1.2 nm in diameter
* Tip link – 8-11 nm in diameter, 150 nm in length
* Myosin-1c – tail binds to PIP2 – 100-500 per stereocilium; 100-200 in series with adaptation motor (5-24 with motor at a time) – binds 2-3 molecules of calmodulin with low Ca2+; Component of both slow and fast adaptation
* Calcium buffers – calbindin, calretinin, parvalbumin
* PMCA - ~2000 molecules/um2 – Ca2+/H exchanger dependent on ATP – blocked by *vanadate*
* TRP channels – candidates for MET channels – nompC/TRPN1 (frogs), TRPA1 (mammals)
* Ankle links – VLGR1; Shaft connectors – PTPRQ

1. Hudspeth AJ (1982) Extracellular Current Flow and the Site of Transduction by Vertebrate Hair-Cells. *Journal of Neuroscience* 2(1):1-10.

* Extracellular receptor potentials measured around hair bundle given numerous stimuli – greatest currents at stereociliary tips

1. Jaramillo F & Hudspeth AJ (1993) Displacement-Clamp Measurement of the Forces Exerted by Gating Springs in the Hair Bundle. *Proceedings of the National Academy of Sciences of the United States of America* 90(4):1330-1334.

* Gating spring exerts ~8 pN of force at rest with additional 4-13 pN possible
* ~100 fN necessary to open single transduction channel

1. Walker RG & Hudspeth AJ (1996) Calmodulin controls adaptation of mechanoelectrical transduction by hair cells of the bullfrog's sacculus. *Proceedings of the National Academy of Sciences of the United States of America* 93(5):2203-2207.

* Used calmodulin antagonists – these antagonists abolished adaptation in hair bundles
* Open probability of hair bundles 0.15

1. Howard J & Hudspeth AJ (1987) Mechanical Relaxation of the Hair Bundle Mediates Adaptation in Mechanoelectrical Transduction by the Bullfrogs Saccular Hair Cell. *Proceedings of the National Academy of Sciences of the United States of America* 84(9):3064-3068.

* Showed rapid twitch followed by slow relaxation in hair bundles, which was linked to receptor current
* Showed reduction in stiffness upon deflection with a time constant of 33 ms (slow adaptation)

1. Alharazneh A*, et al.* (2011) Functional Hair Cell Mechanotransducer Channels Are Required for Aminoglycoside Ototoxicity. *PloS one* 6(7).

* Aminoglycoside toxicity – MET channels or endocytosis? – used gentamicin in low calcium and showed its effect on MET channels
* Curare, quinine, amiloride – blockers of MET channels – reduced gentamicin uptake
* Concanavalin A – endocytosis inhibitor – did not reduce gentamicin uptake

1. Gillespie PG & Hudspeth AJ (1993) Adenine Nucleoside Diphosphates Block Adaptation of Mechanoelectrical Transduction in Hair-Cells. *Proceedings of the National Academy of Sciences of the United States of America* 90(7):2710-2714.

* Replacement of ATP by ADP abolished adaptation – due to myosin motor dependence on ATP – these are required for adaptation

1. Iwasa KH & Ehrenstein G (2002) Cooperative interaction as the physical basis of the negative stiffness in hair cell stereocilia. *J Acoust Soc Am* 111(5):2208-2212.

* Model of bundle describing negative stiffness – either a special microscopic structure within the channel controlling bending or the bundle, OR due to cooperativity in channel gating

1. Martin P, Mehta AD, & Hudspeth AJ (2000) Negative hair-bundle stiffness betrays a mechanism for mechanical amplification by the hair cell. *Proceedings of the National Academy of Sciences of the United States of America* 97(22):12026-12031.

* Interplay between negative hair bundle stiffness and adaptation results in spontaneous oscillations
* Nonlinearity within 20 nm of resting position – reversibly linearized by gentamicin blockade
* Negative stiffness averaged -360 uN/m, with linear stiffnesses 680 uN/m
* Shifted force-displacement curve by moving bundle outside negative stiffness regime (40 nm) for 70-100 ms (slow adaptation)
* Shift along line of 460 uN/m – stiffness of stereociliary pivots

1. Martin P, Bozovic D, Choe Y, & Hudspeth AJ (2003) Spontaneous oscillation by hair bundles of the bullfrog's sacculus. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 23(11):4533-4548.

* Increasing Ca2+ concentration rendered oscillations faster/smaller until suppressed
* Increasing gain on the clamp to increase effective stiffness reduced oscillation amplitude and increased their frequency
* Oscillations continued after detachment of kinocilium

1. Le Goff L, Bozovic D, & Hudspeth AJ (2005) Adaptive shift in the domain of negative stiffness during spontaneous oscillation by hair bundles from the internal ear. *Proceedings of the National Academy of Sciences of the United States of America* 102(47):16996-17001.

* Monitored spontaneous oscillations – triggered measurements at particular phases in movement cycle
* Shift in negative-stiffness region at extremes of oscillation
* Slope of 200-300 uN/m for stiffness of stereociliary pivots

1. Hudspeth AJ (2008) Making an effort to listen: mechanical amplification in the ear. *Neuron* 59(4):530-545.

* Review – discussion of four components of active process and Hopf bifurcation
* Ca2+ induced channel reclosure – direct binding to channel, relaxation of ankyrin repeats in channel (TRP channel) causing it to slip downward, reduction in myosin-1c’s binding probability (slip down), favor backward step by myosin, binding to calmodulin on IQ domains relaxing neck regions (move downward)

1. Izhikevich EM (2007) *Dynamical Systems in Neuroscience* (The MIT Press, Cambridge, Massachusetts).

* Basics of dynamical systems / bifurcations

1. Martin P & Hudspeth AJ (2001) Compressive nonlinearity in the hair bundle's active response to mechanical stimulation. *Proceedings of the National Academy of Sciences of the United States of America* 98(25):14386-14391.

* Sinusoidal stimulation of fiber’s base to 0.3 pN – phase-locking with response following one-third power of stimulus amplitude
* Sensitivity follows -2/3 power law with stimulus amplitude … indicative of supercritical Hopf bifurcation

1. Plomp RRR (1999) The Perception of Musical Tones. *The Psychology of Music,* Academic Press Series in Cognition and Perception, ed Deutsch D (Elsevier), 2nd Ed.

* Describes Tartini tones – Giuseppi Tartini

1. Campbell M GC (2002) *The Musician’s Guide to Acoustics.* (: Oxford Univ. Press,, Oxford, UK).

* Tartini tones in musical composition

1. Barral J & Martin P (2012) Phantom tones and suppressive masking by active nonlinear oscillation of the hair-cell bundle. *Proceedings of the National Academy of Sciences of the United States of America* 109(21):E1344-1351.

* Two-tone stimulation of hair bundles – showed that cubic components dominated in active bundle, quadratic in passive
* Two tone suppression of hair-bundle response – held one frequency constant near characteristic frequency and passed the second over a series of other frequencies – when the two were near one another, the one suppressed the major’s reponse
* Most significant for low amplitude stimuli

1. Martin P & Hudspeth AJ (1999) Active hair-bundle movements can amplify a hair cell's response to oscillatory mechanical stimuli. *Proceedings of the National Academy of Sciences of the United States of America* 96(25):14306-14311.

* Mechanical stimuli as small as 5 nm entrained a hair-bundle’s spontaneous oscillations
* “Negative damping” counters energy losses of viscous drag; amplification greatest with low sound levels
* Area enclosed by force-displacement curve in one cycle is the work of the fiber or bundle. -40 zJ was the work of the fiber, thus active

1. Fredrickson-Hemsing L, Strimbu CE, Roongthumskul Y, & Bozovic D (2012) Dynamics of Freely Oscillating and Coupled Hair Cell Bundles under Mechanical Deflection. *Biophysical journal* 102(8):1785-1792.

* 100 uN/m fiber and gave ramps – 5-50 nm/sec “slow ramps” – saw hysteresis presumably due to adaptation
* However, the group did not wait for steady-state response

1. Strimbu CE, Fredrickson-Hemsing L, & Bozovic D (2012) Coupling and elastic loading affect the active response by the inner ear hair cell bundles. *PloS one* 7(3):e33862.

* Attached fibers with stiffnesses ranging from 100-7000 uN/m and saw suppression of oscillations – less power on PSD
* Discrete frequency sweep over 5-50 Hz (1 Hz increments) at 0-18 pN (or less/greater) to recreate Arnold tongues with different stiffness probes on *different* hair bundles – loss of Arnold tongue around 400 uN/m
* Hypothesized mechanical control parameters – modulation of compliance by myosin motor activity, calcium-dependent relaxation, gating spring variable stiffness, or a voltage-sensitive element – also coupling by the otolithic membrane
* Coupling between nonlinear oscillators of different characteristic frequencies suppresses spontaneous oscillations
* Decrease in frequency tuning with coupling (Q < 1) – note that up to hundreds of hair cells innervated by a single nerve fiber
* Hair cell active process enough to evoke movement of the otolithic membrane

1. Camalet S, Duke T, Jülicher F, & Prost J (2000) Auditory sensitivity provided by self-tuned critical oscillations of hair cells. *Proceedings of the National Academy of Sciences of the United States of America* 97(7):3183-3188.

* Introduced concept of self-tuned criticality – dynein and myosin motors in hair bundle can generate oscillations
* Control of calcium flux modulates these motors, poising the bundle near an oscillatory instability
* Frequency of oscillations is reduced with an increased number of motors (referring here to dynein)

1. Gillespie PG & Cyr JL (2004) Myosin-1c, the hair cell's adaptation motor. *Annual review of physiology* 66:521-545.

* Activation of PKA, which inhibits myosin-1c, shift displacement-response curve to the right, *lowering the open probability* (response on y-axis is Popen, and x-axis is displacement)
* Slipping rate constant – 44 s-1; Climbing rate en masse – 6 um/sec; Working stroke of a motor – 4 nm;
* Gating spring extension – 5-7 nm; Resting tension – 5-10 pN (higher with less calcium); Max force – 1-2 pN
* Ca2+ reduces ton of myosin-1c – thus low Ca2+ (or depolarized conditions preventing Ca2+ entry) increases the tension from myo1c – reduces slipping and promotes climbing

1. Eatock RA, Corey DP, & Hudspeth AJ (1987) Adaptation of mechanoelectrical transduction in hair cells of the bullfrog's sacculus. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 7(9):2821-2836.

* Characterization of adaptation – reset hair bundle’s operating point – tens to hundreds of milliseconds – varied between cells

1. Chabbert CH (1997) Heterogeneity of hair cells in the bullfrog sacculus. *Pflugers Archiv : European journal of physiology* 435(1):82-90.

* Characterized two of the three classes of hair cells based upon morphology – central cylindrical and central flask-shaped
* Higher amplitude Ca2+ currents for cylindrical (-900 pA) over flask-shaped (-160 pA) cells
* Flask-shaped cells unique in having a Cs-resistant, apamin-sensitive, calcium-sensitive potassium current
* Apamin – blocks SK channels – Ca-activated K channel