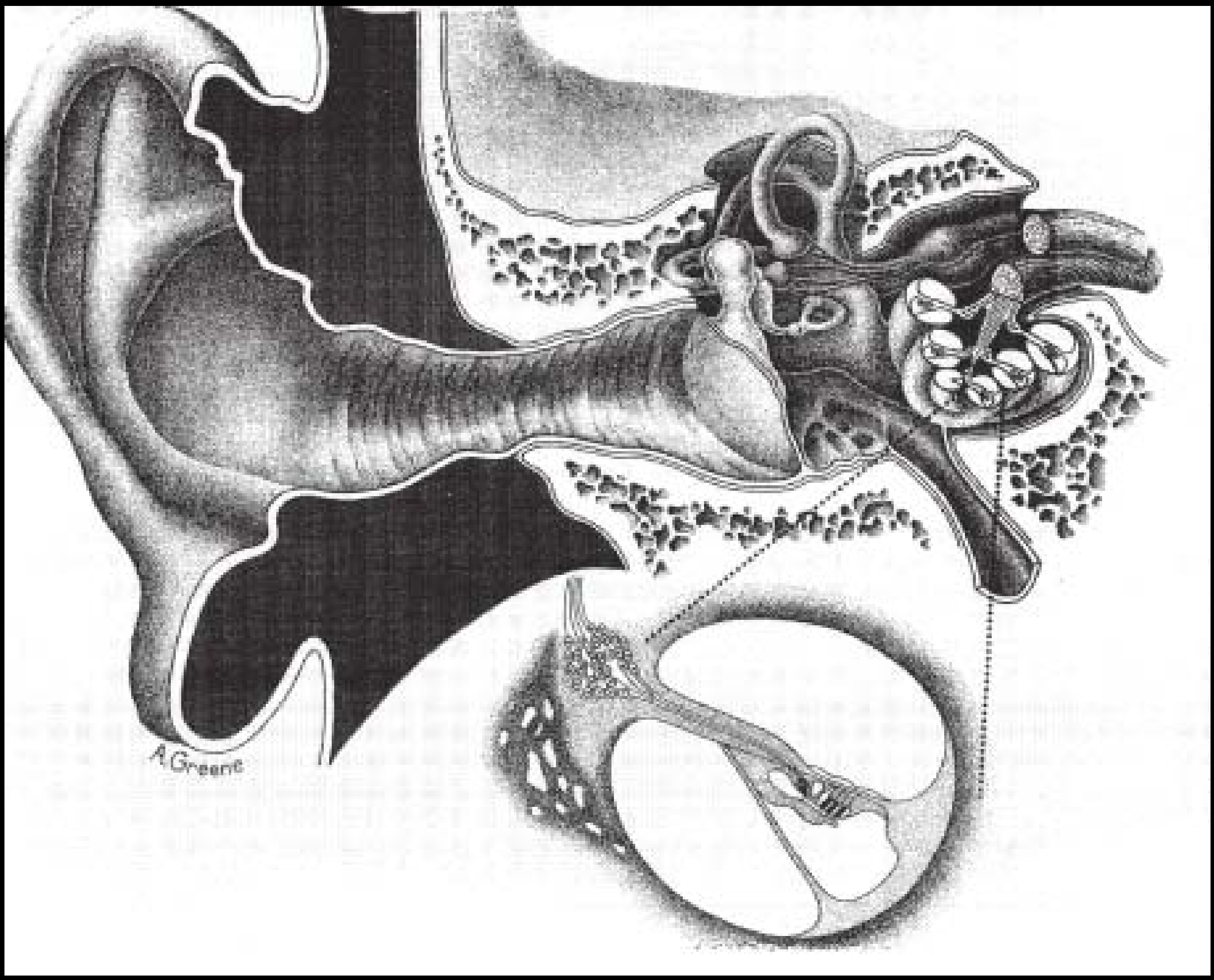
HST 721 Lecture 4:
Mechanics, electromotility and the cochlear amplifier



Cochlear Mechanics: Measures of Basilar Membrane Motion

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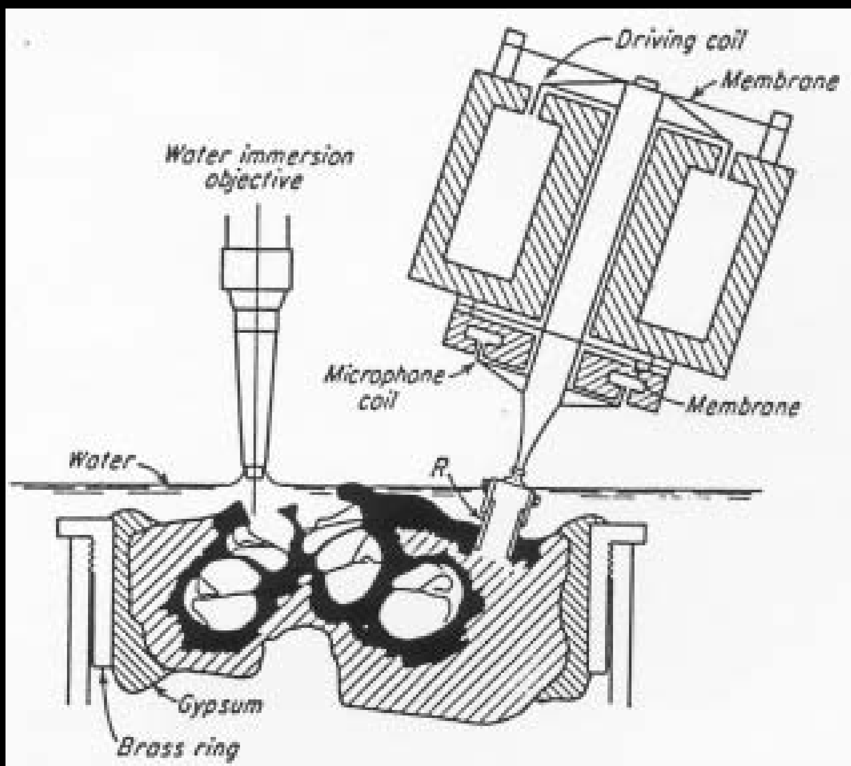
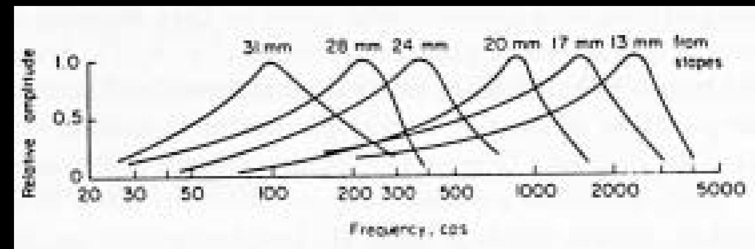
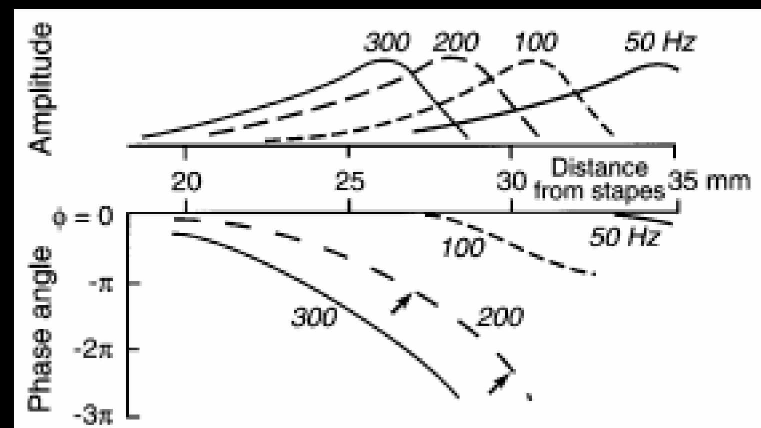
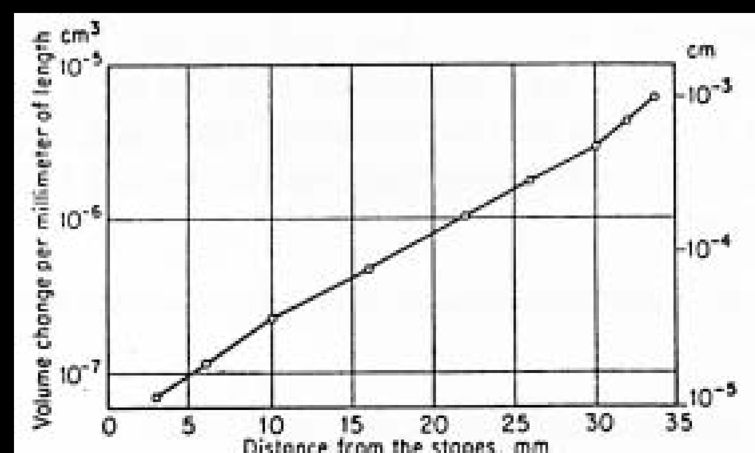
Bekesy's experiments on cadaveric ears 1924-1946



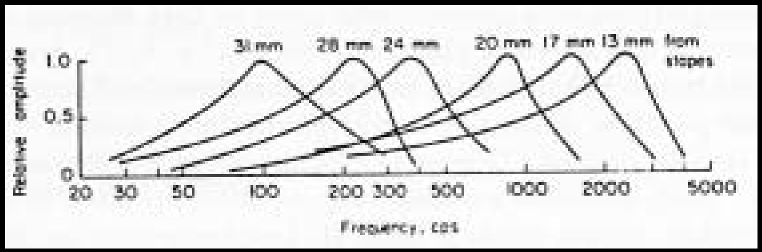


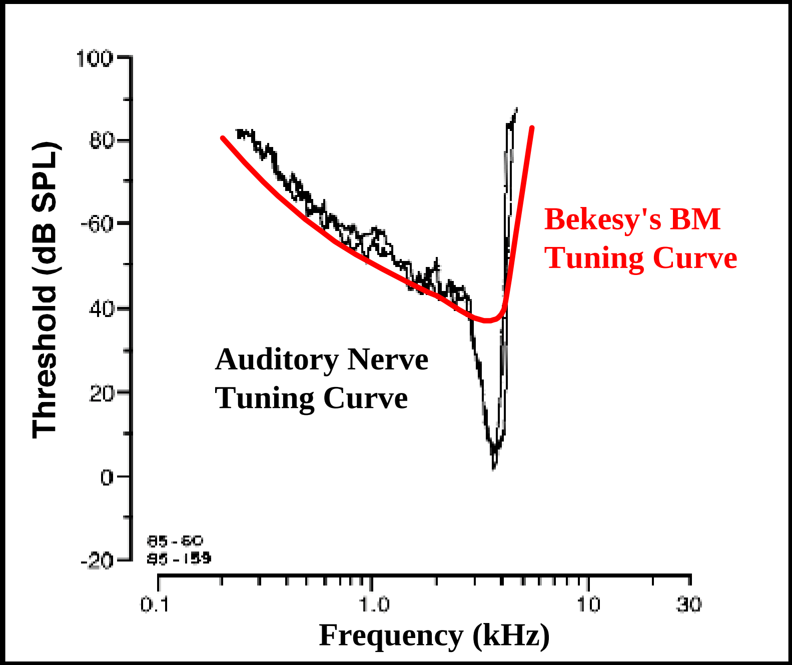




Cochlear Mechanics: Measures of Basilar Membrane Motion

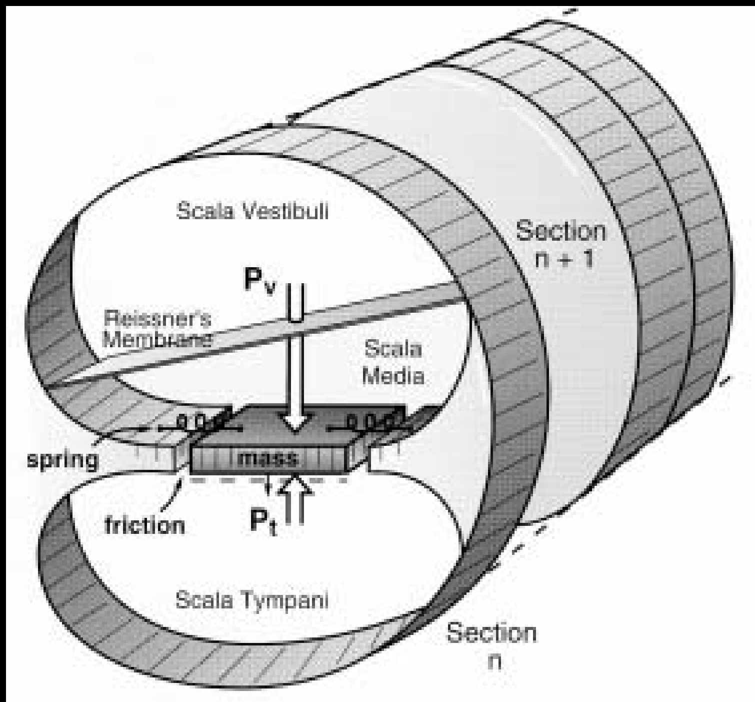
Bekesy's experiments on cadaveric ears 1924-1946





Is there a "second filter" ?:
Wilson and Johnstone, 1975

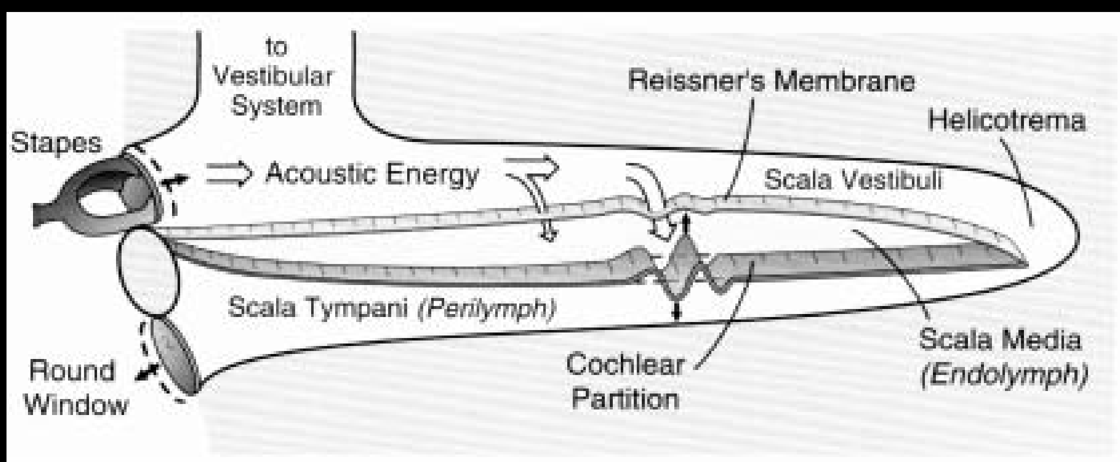
Cochlear Mechanics: Measures of Basilar Membrane Motion



Passive cochlear Models

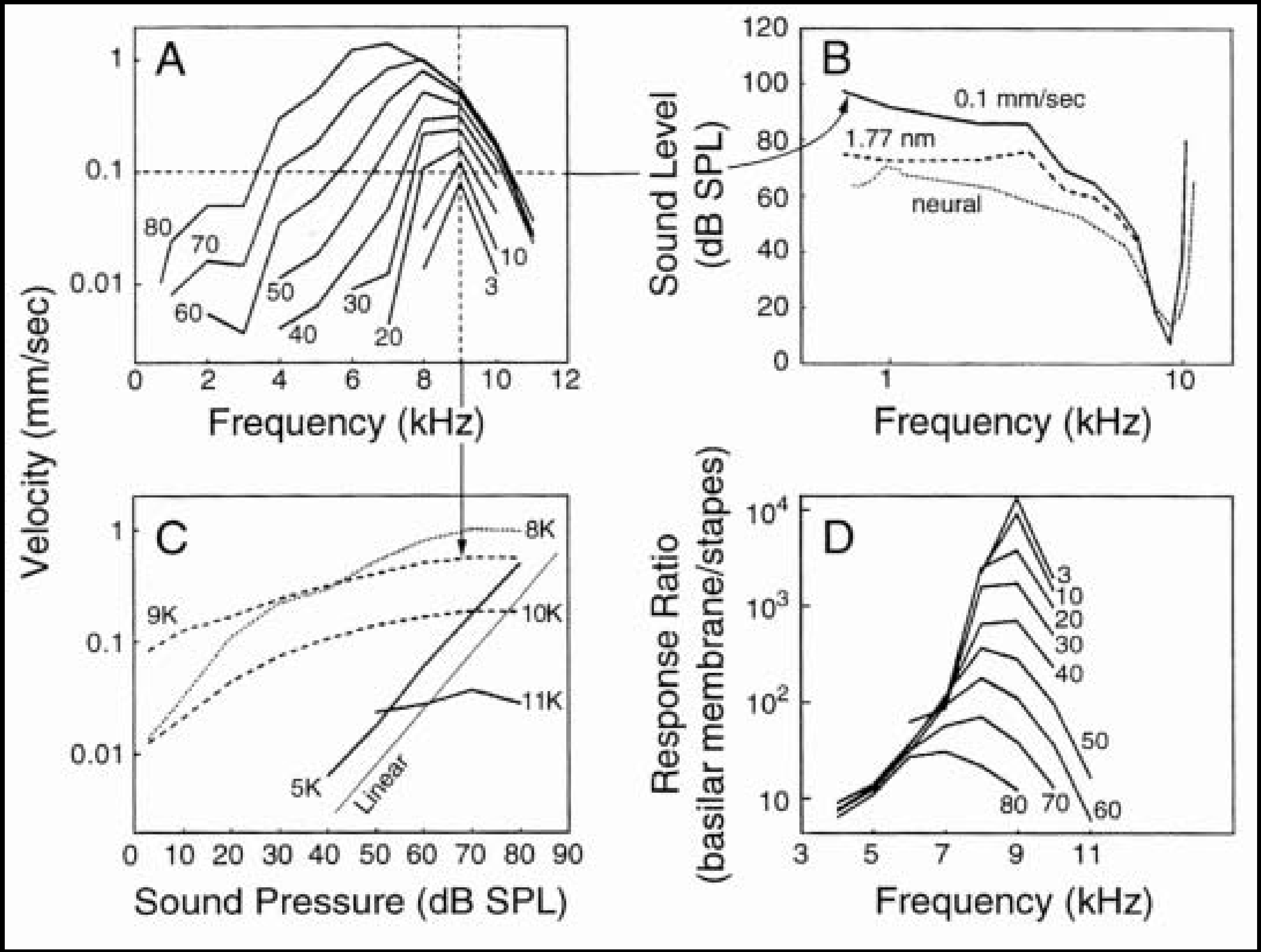
Vary mass and spring stiffness systematically from base to apex

Model will generate traveling waves, with resonant peaks like those observed by Bekesy in the dead ear.



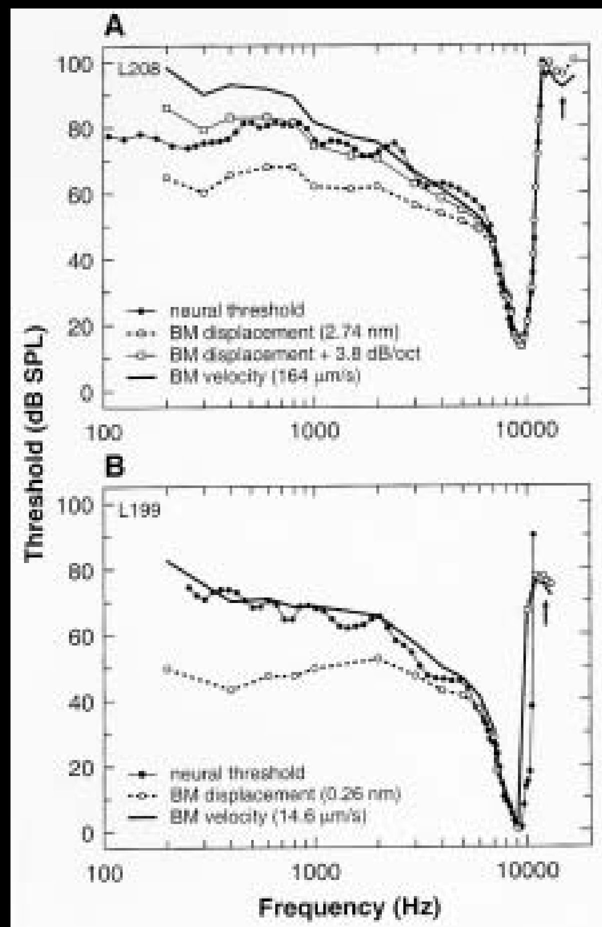
Cochlear Mechanics: Measures of Basilar Membrane Motion

BM has a vulnerable, compressive nonlinearity - 1971



Cochlear Mechanics: Measures of Basilar Membrane Motion

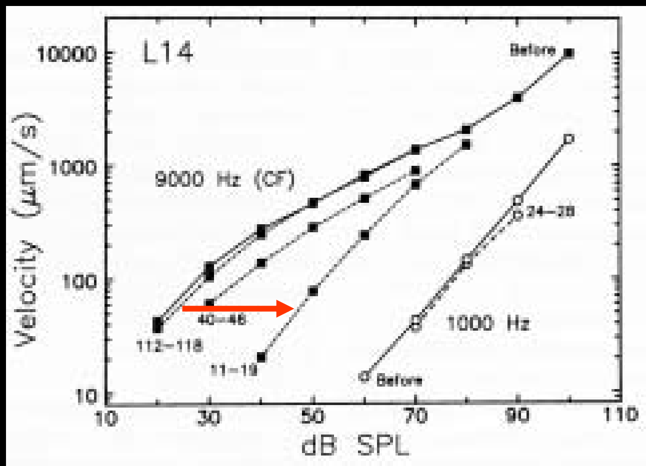
BM tuning is as sharp as AN tuning - 1982



Cochlear Mechanics: Measures of Basilar Membrane Motion

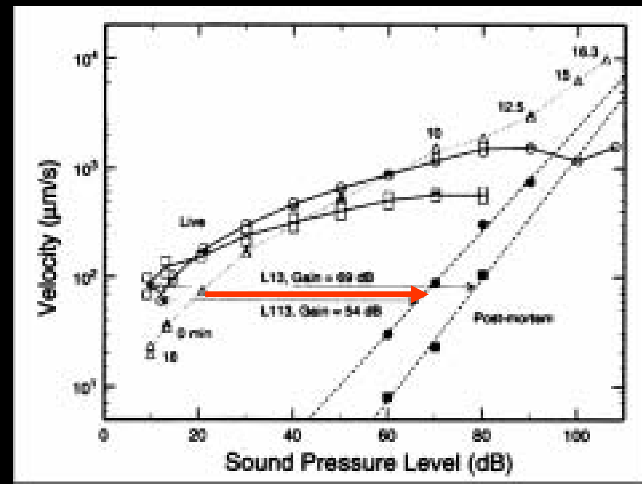
Effects of Furosemide:

BM

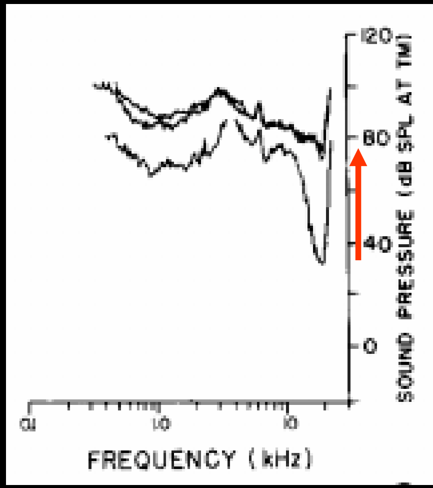


Ruggero and Rich, 1991

Effects of Death:



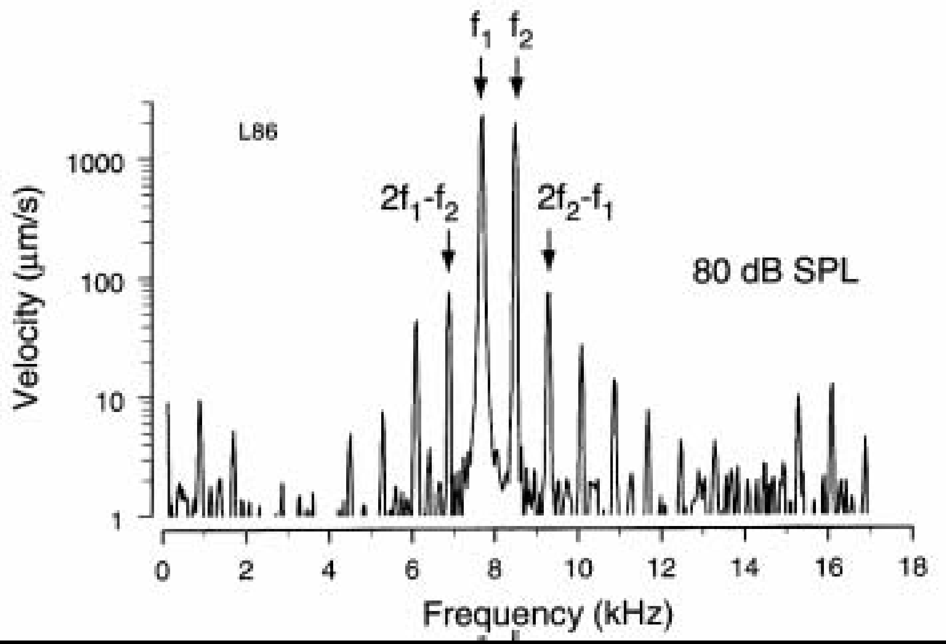
ANF



Most manipulations that raise AN thresholds (including death) are reflected in decreased and linearized BM vibration

Cochlear Mechanics: Measures of Basilar Membrane Motion

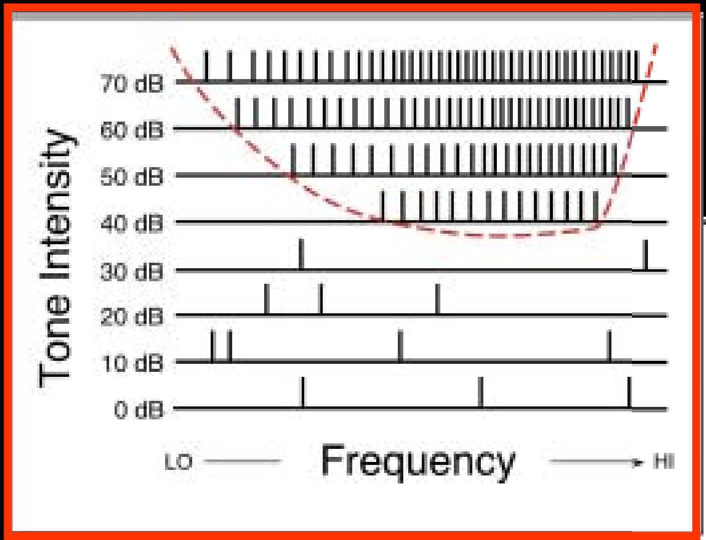
Major nonlinearities in AN response
are seen in BM vibration: e.g.
Distortion Products

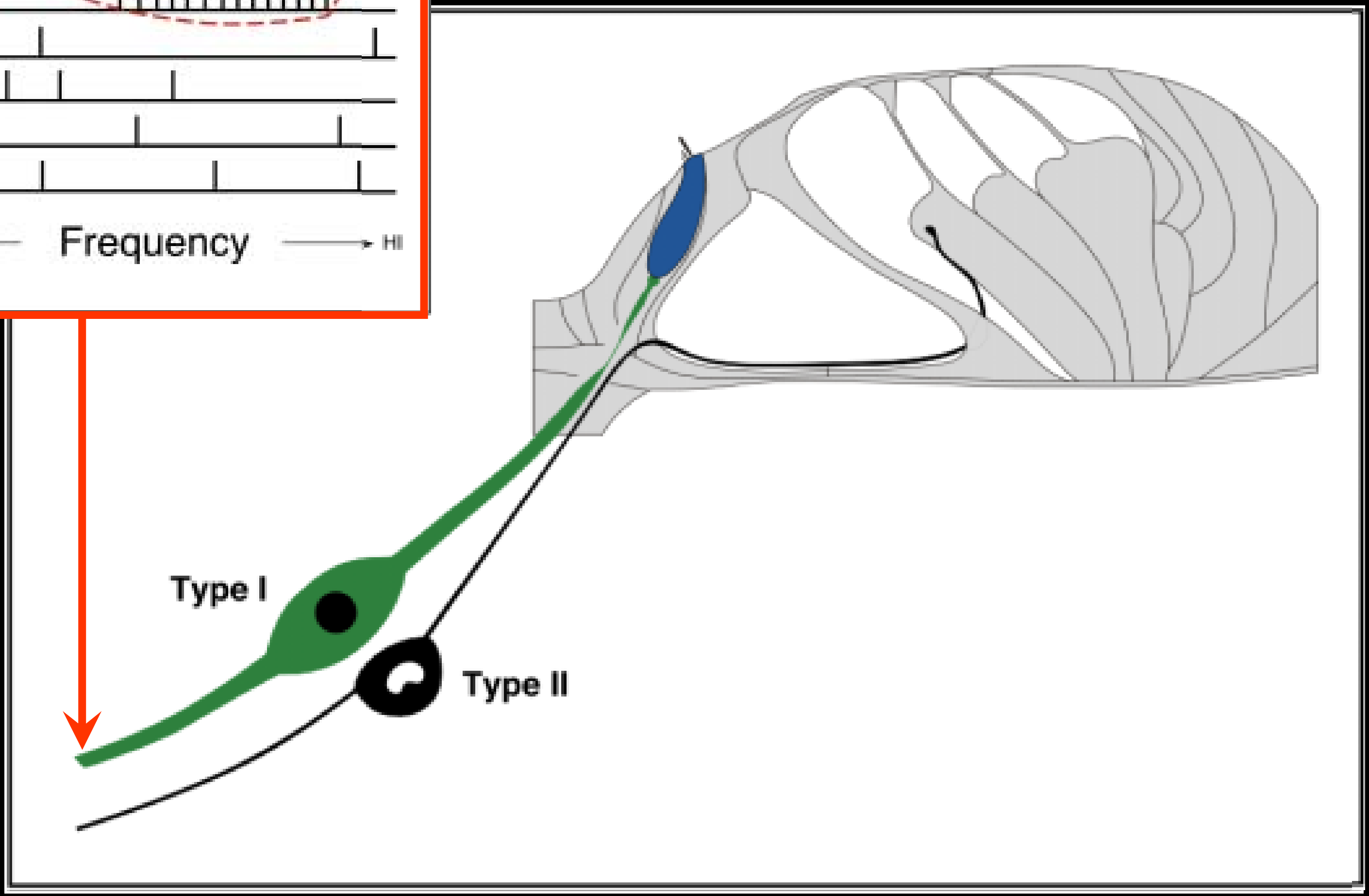


Cochlear Mechanics: What is the cochlear amplifier ?

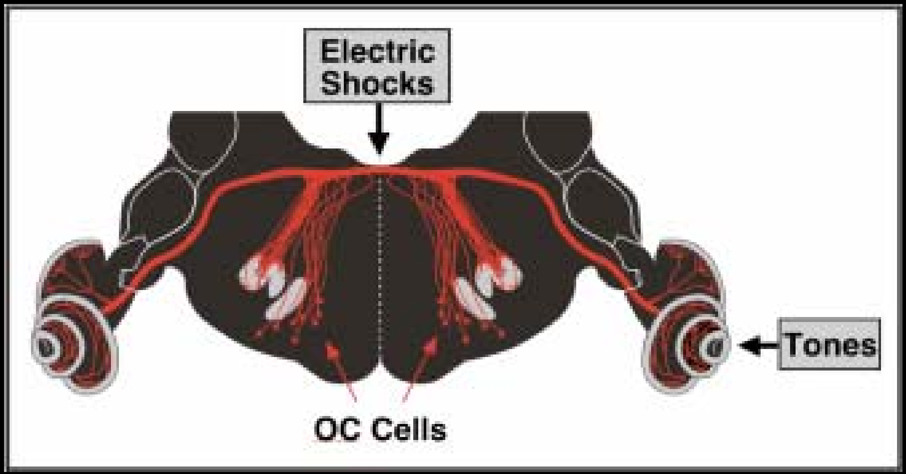
Cochlear Mechanics: What is the cochlear amplifier ?

Loss of OHCs elevates threshold at CF - 1970

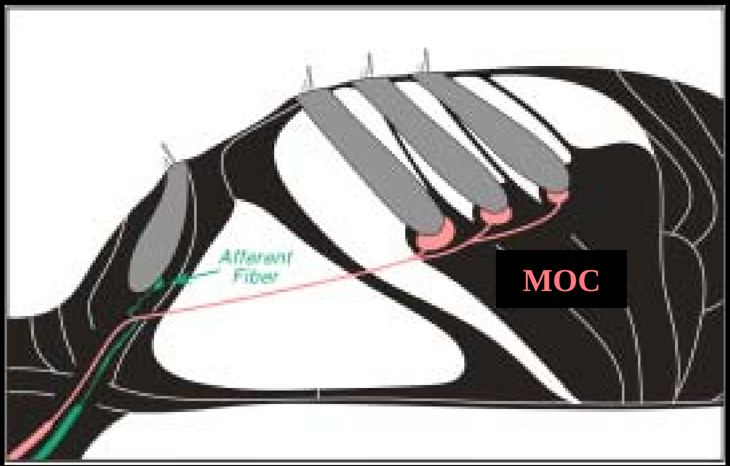


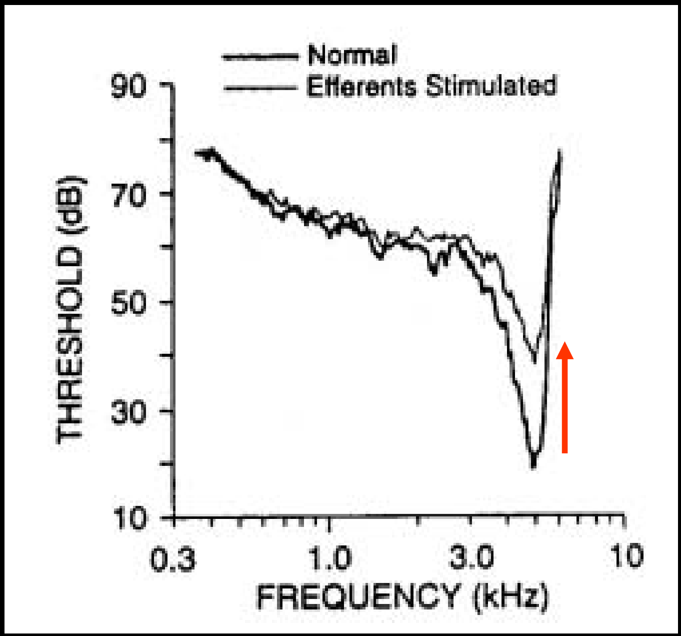


Cochlear Mechanics: What is the cochlear amplifier ?



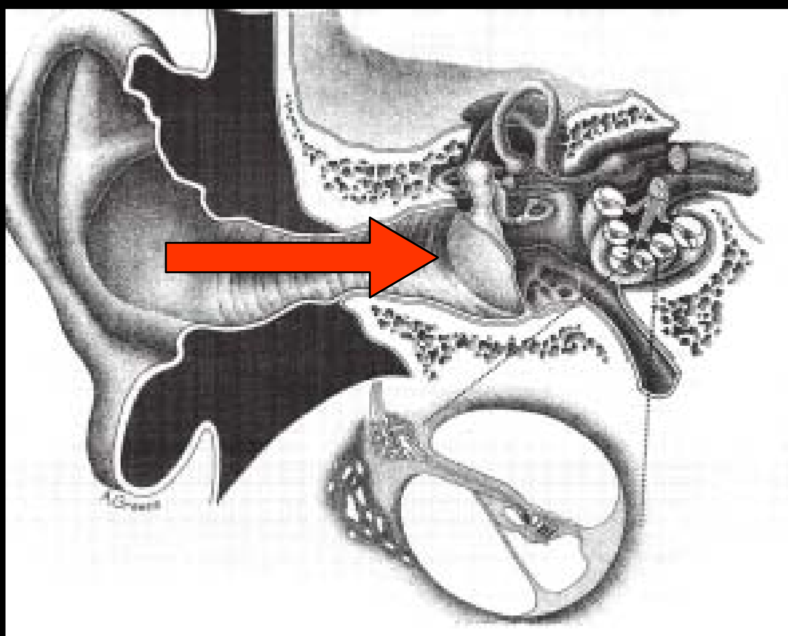
Stimulation of efferents to OHCs raises threshold at CF - 1970

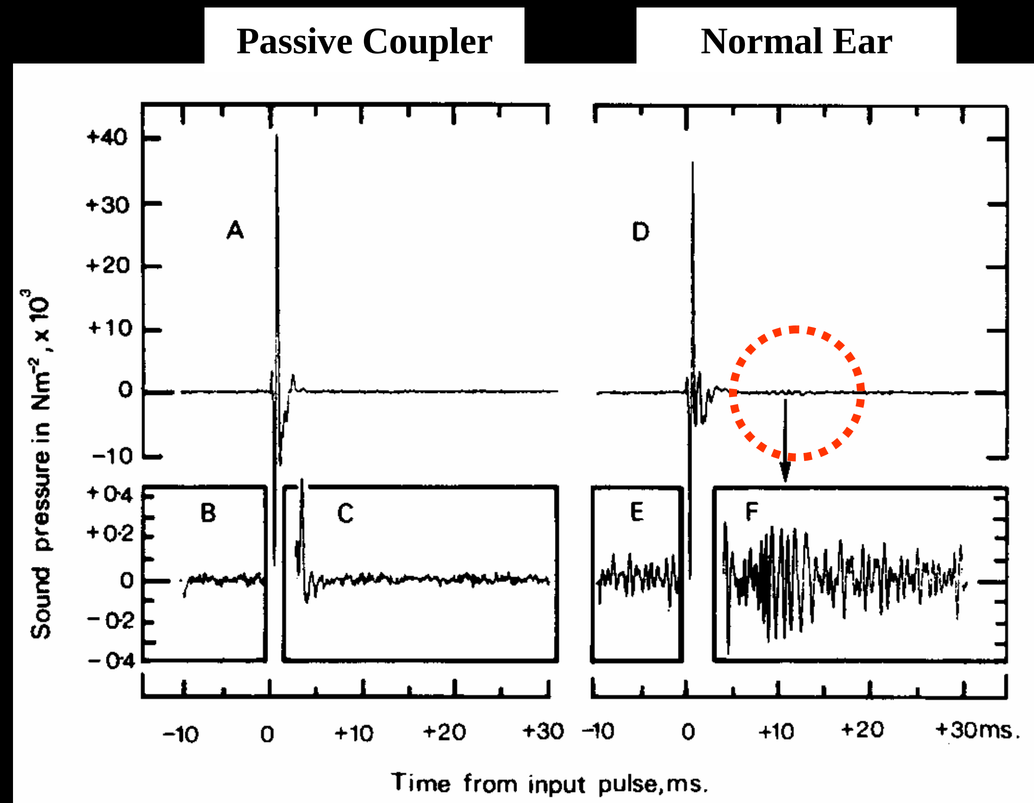




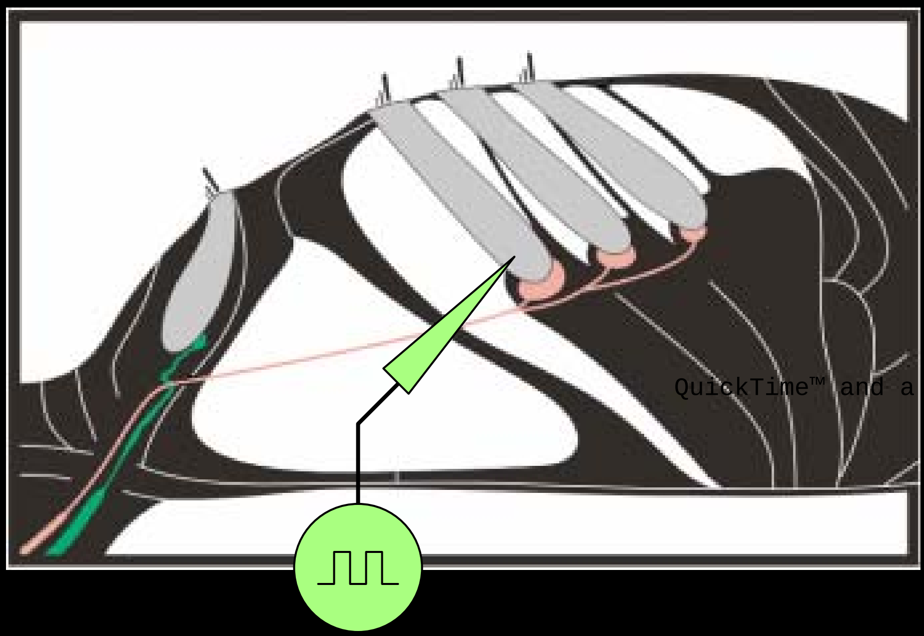
Cochlear Mechanics: What is the cochlear amplifier ?

Cochlear echoes: forward and reverse transduction - 1978





Cochlear Mechanics: What is the cochlear amplifier ?



Outer Hair Cells show electromotility in vitro - 1985

Cochlear Mechanics: What is the cochlear amplifier ?

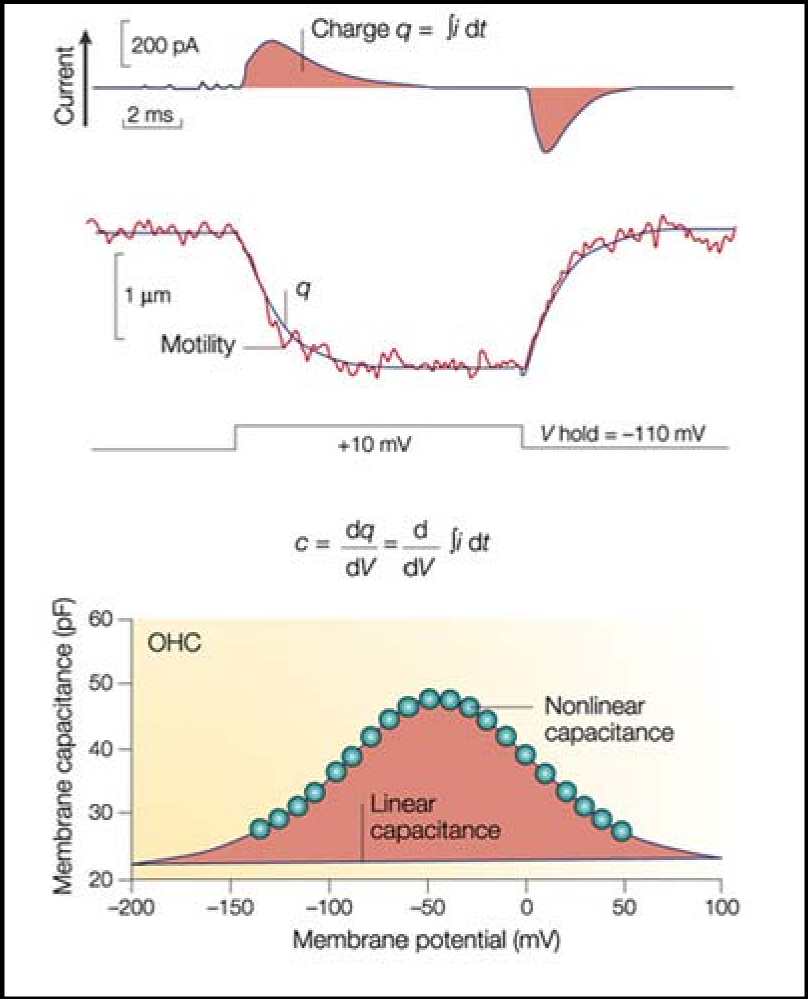
Electromotility Key Observations:

1. Seen in OHCs only

2. Survives total replacement of cell cytoplasm: Holley and Ashmore 1988

3. Motors present all along OHC supranuclear wall: Hallworth et al. 1993

Cochlear Mechanics: What is the cochlear amplifier ?

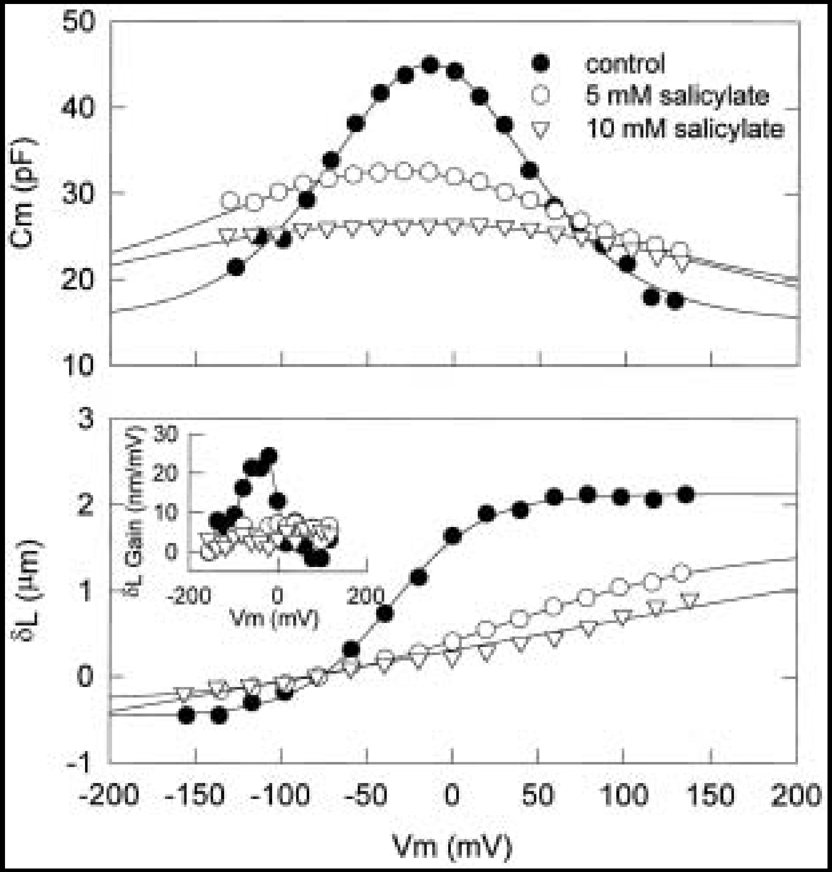


<u>More Key Observations:</u>

4. Charge flow during OHC movement suggests gating current (1990)

5. Charge flow (dq) from voltage step (dV) depends on starting voltage: i.e. nonlinear capacitance

Cochlear Mechanics: What is the cochlear amplifier ?

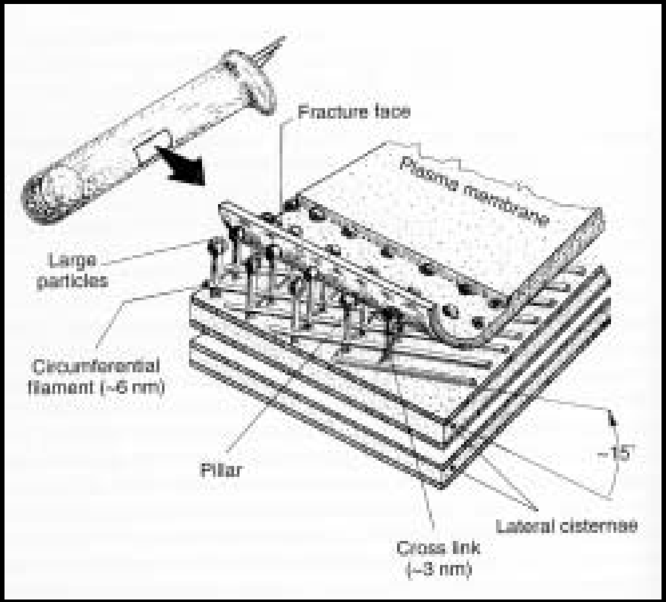


<u>More Key Observations:</u>

6. Manipulations that decrease nonlinear capacitance decrease motility (1996)

Cochlear Mechanics: What is the cochlear amplifier ?

Identifying the motor protein: Anatomical Observations



Cochlear Mechanics: What is the cochlear amplifier ?

The molecular biology approach:
Zheng et al. 2000

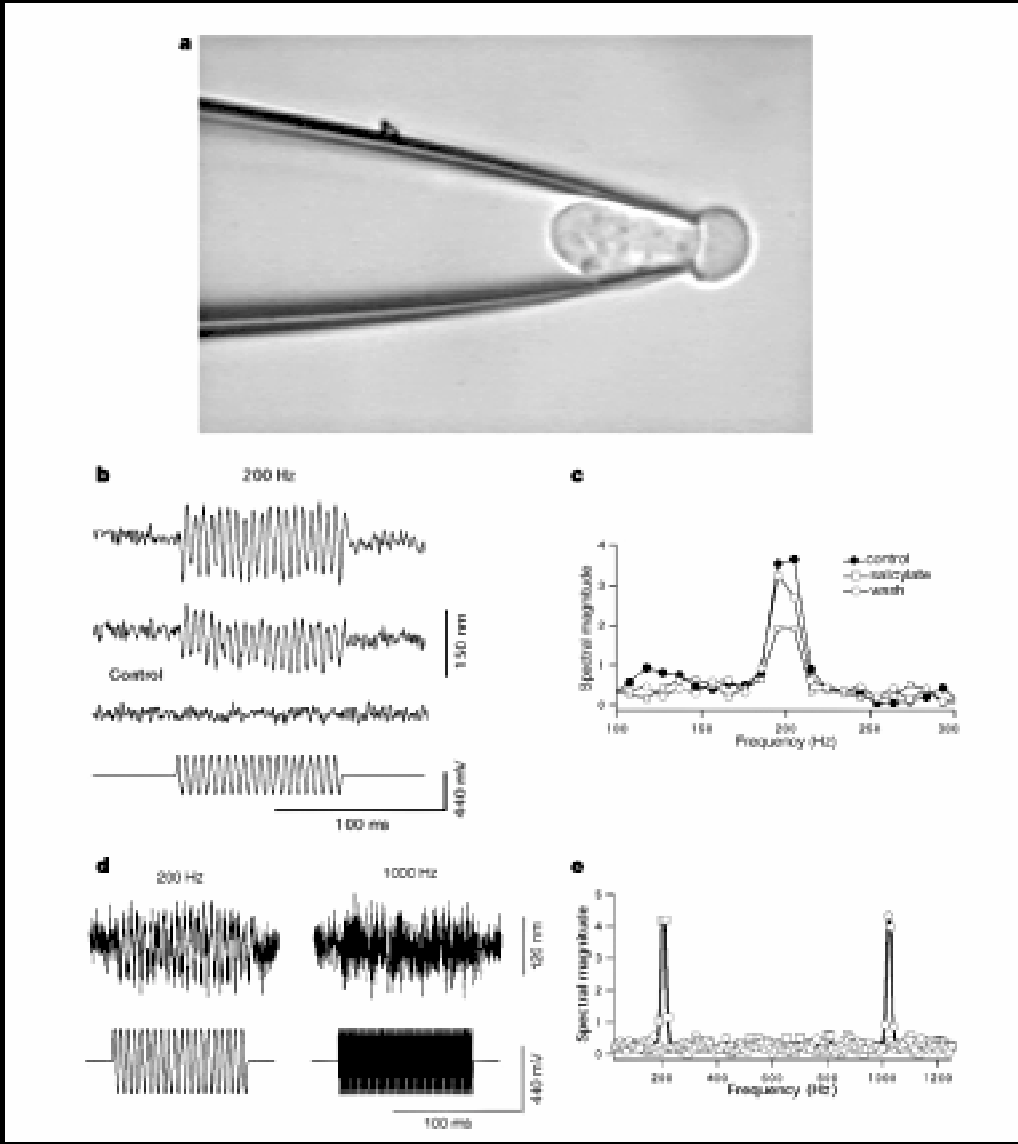
•isolate IHCs and OHCs

•purify RNA from each and make cDNA

•enrich for OHC-specific products by subtractive hybridization

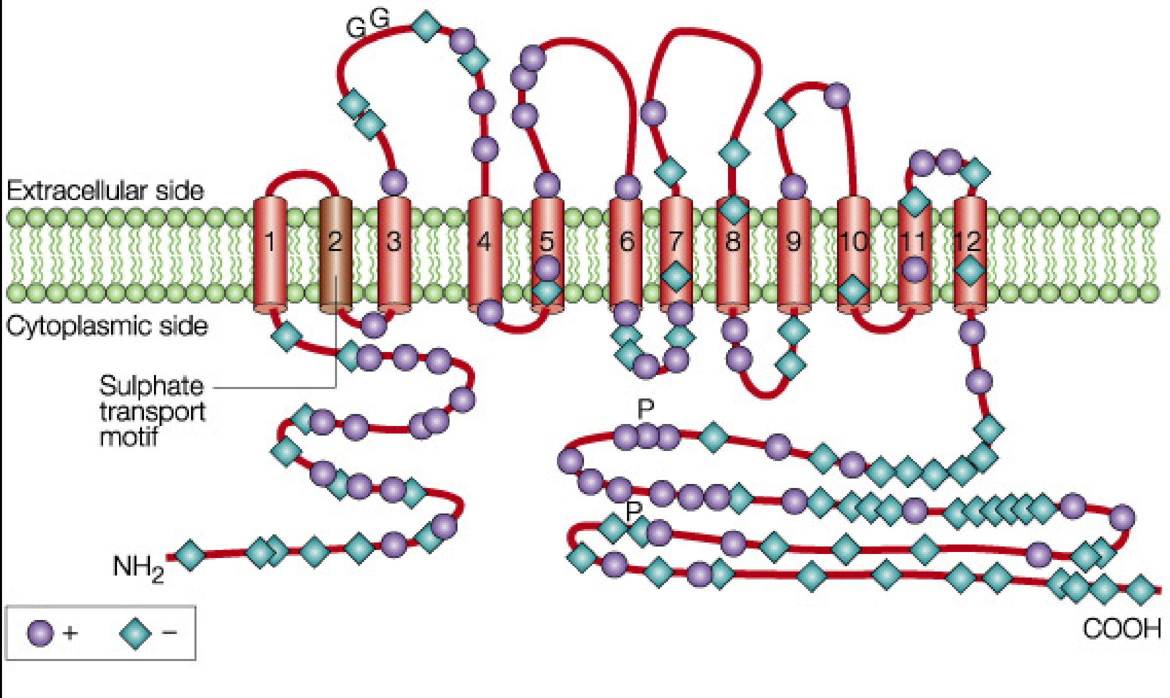
•sequence and choose candidates

•express genes in cell system and assess electromotility

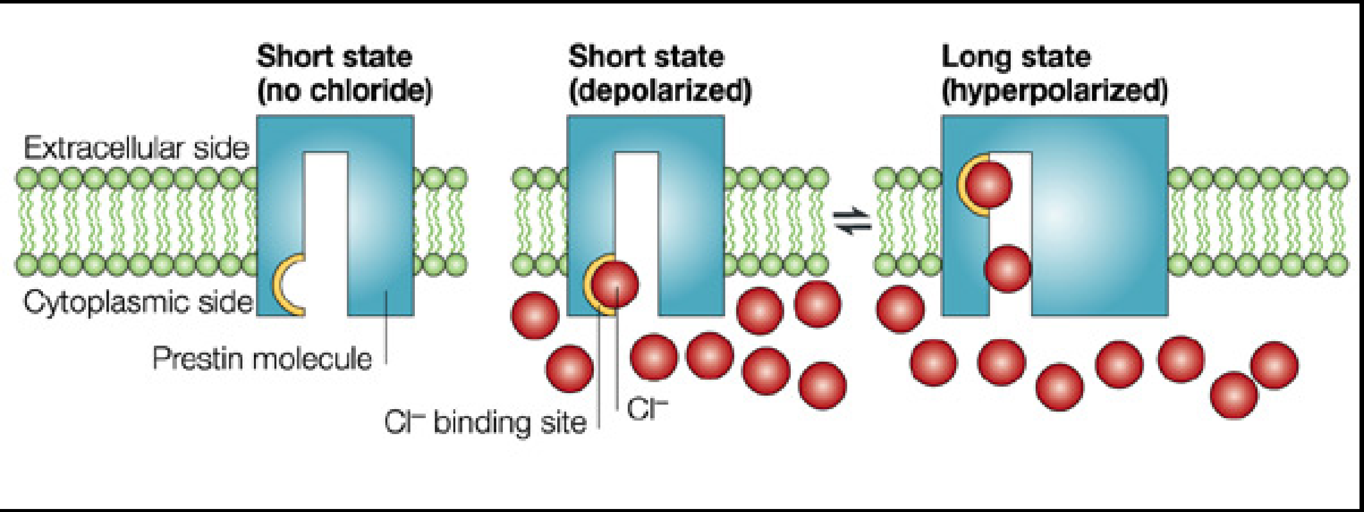


Cochlear Mechanics: What is the cochlear amplifier ?

The structure of Prestin

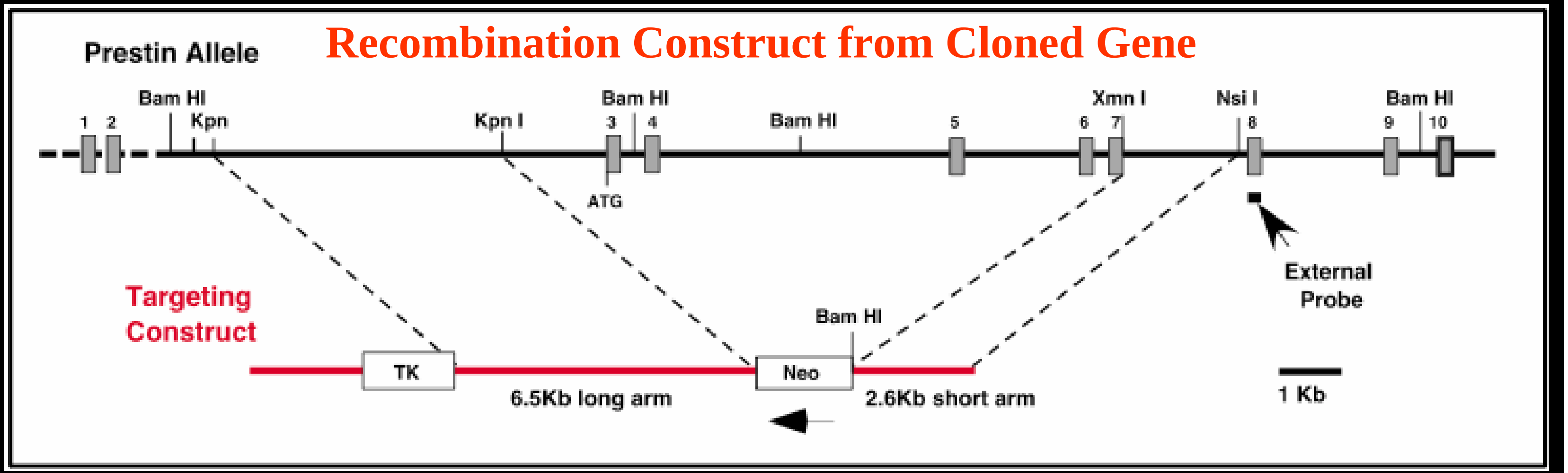


The model

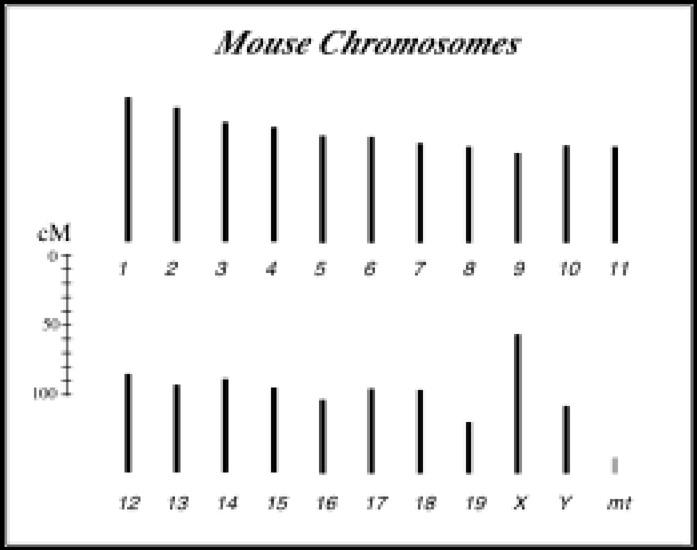


Cochlear Mechanics: What is the cochlear amplifier ?

Targeted Deletion: making a "knockout" mouse



1 cM = 1 Mb



Cochlear Mechanics: What is the cochlear amplifier ?

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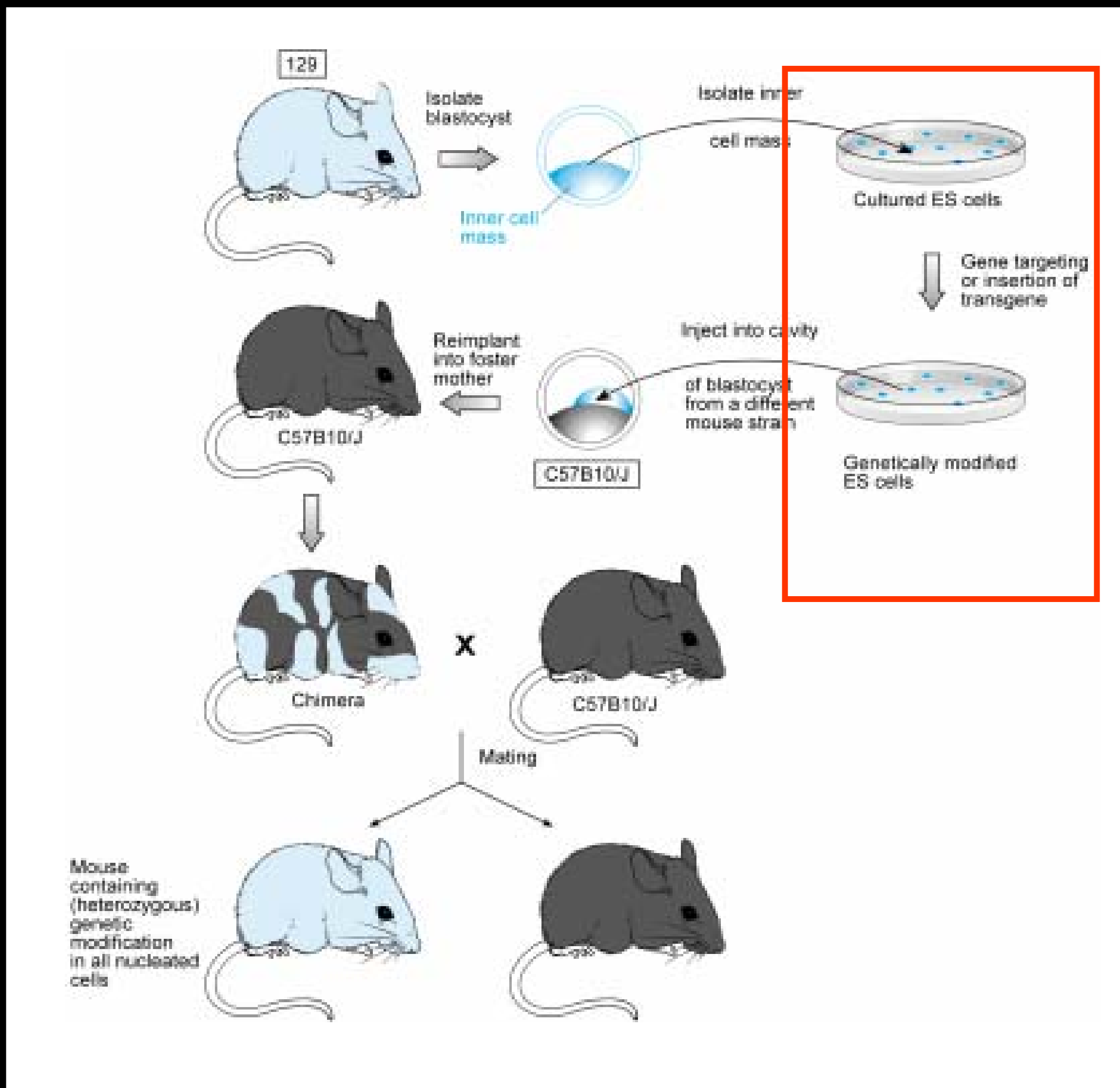
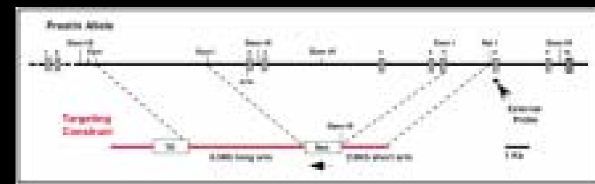
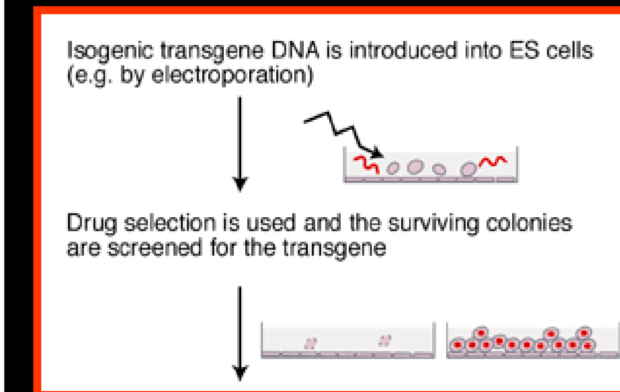






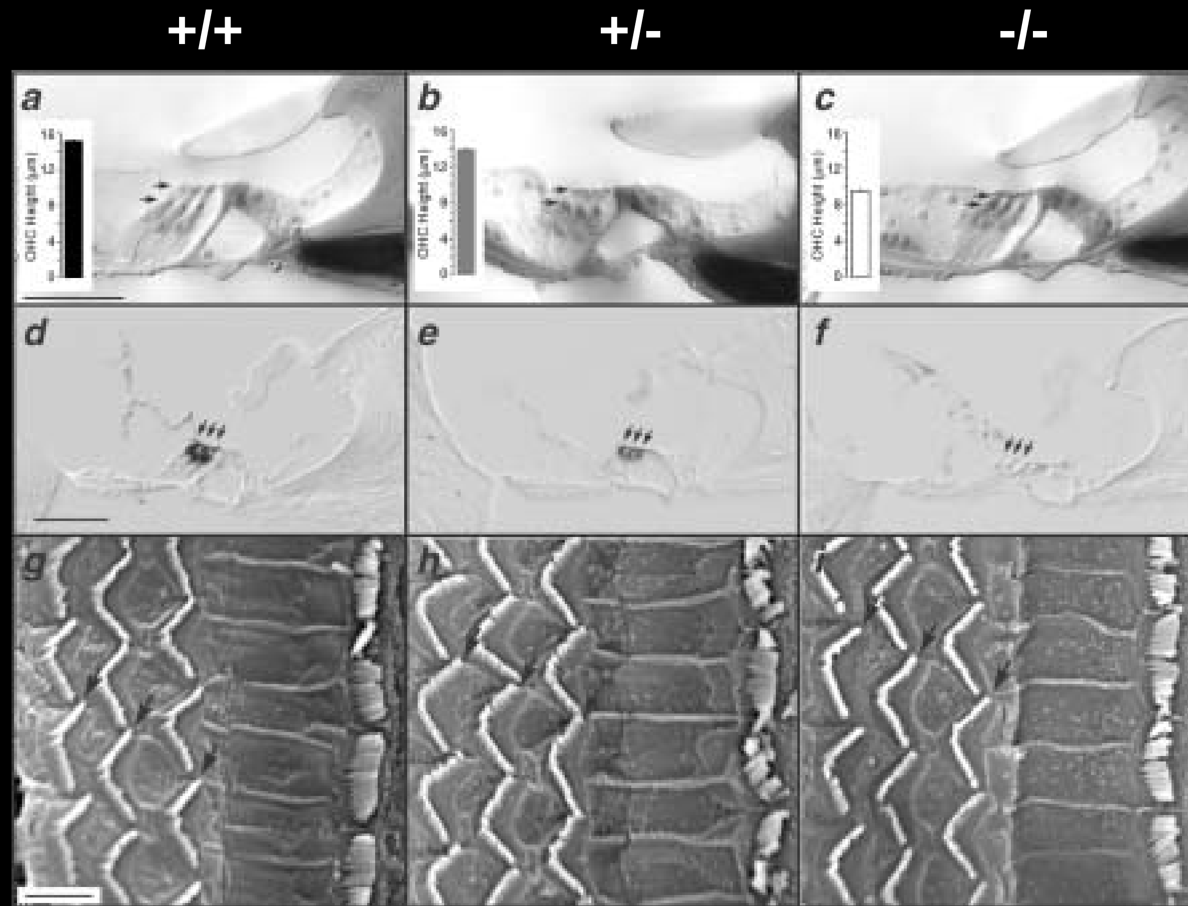
Knockout Mouse F1 is a hybrid strain:

C57Bl/6 + 129/SvJ

Cochlear Mechanics: What is the cochlear amplifier ?

The prestin knockout

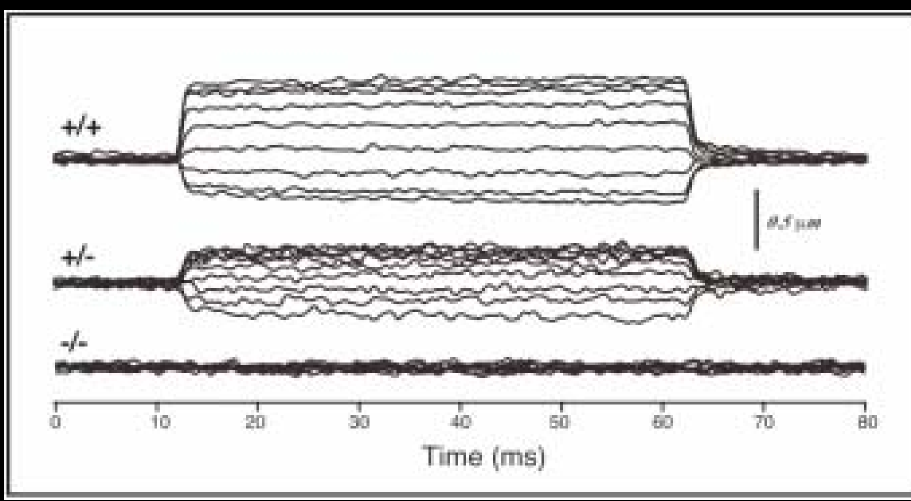
Assess function in vitro and in vivo



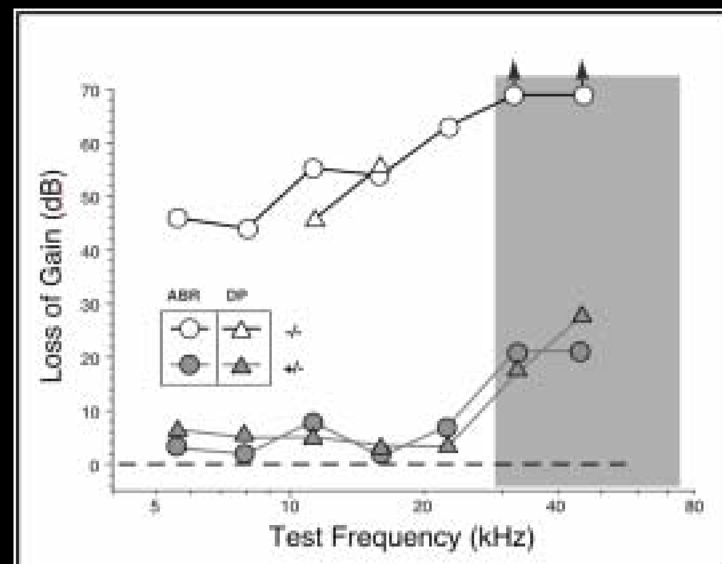
Cochlear Mechanics: What is the cochlear amplifier ?

The prestin knockout:

In vitro, OHCs from “knockout” mouse have no electromotility

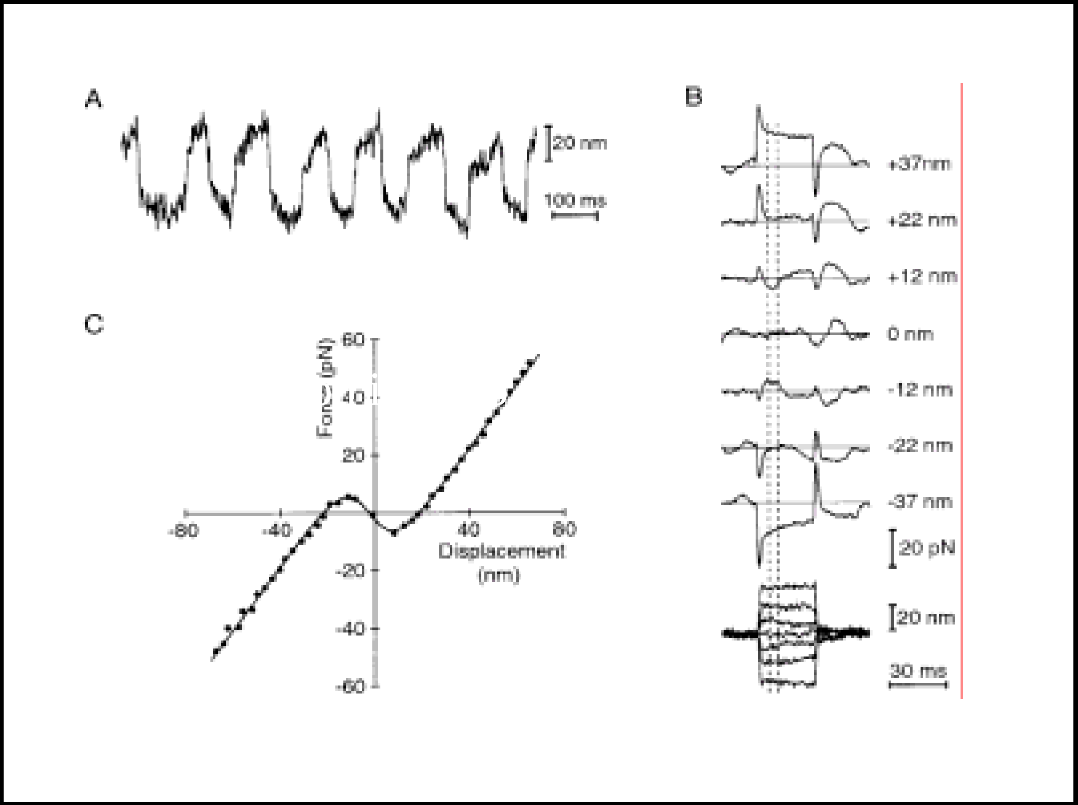


In vivo, “knockout” mouse shows 40 - 60 dB threshold elevation by ABR



Cochlear Mechanics: What is the cochlear amplifier ?

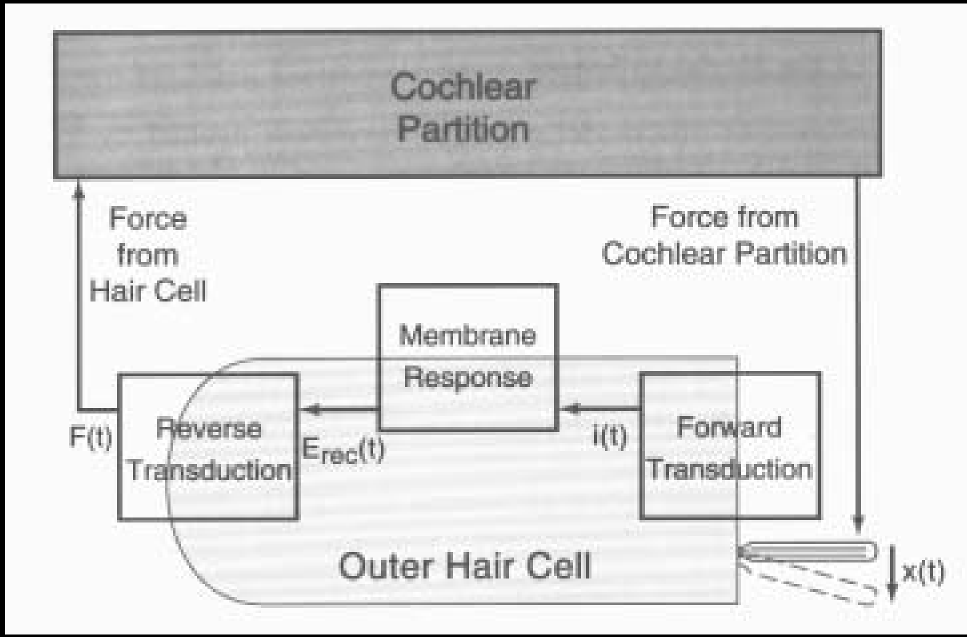
Is stereocilia motility important?



Other candidates for cochlear amplifiers include the motor which drives the spontaneous oscillations in hair bundles from non mammalian vertebrates

Martin, Mehta and Hudspeth, 2000.

Cochlear Mechanics: What is the cochlear amplifier ?



The prestin-mediated electromotility must form part of a feedback loop enhancing BM vibrations. Neely, 1993

Most details of cochlear micromechanics are still unclear

Cochlear Micro-mechanics: from BM motion to HC excitation

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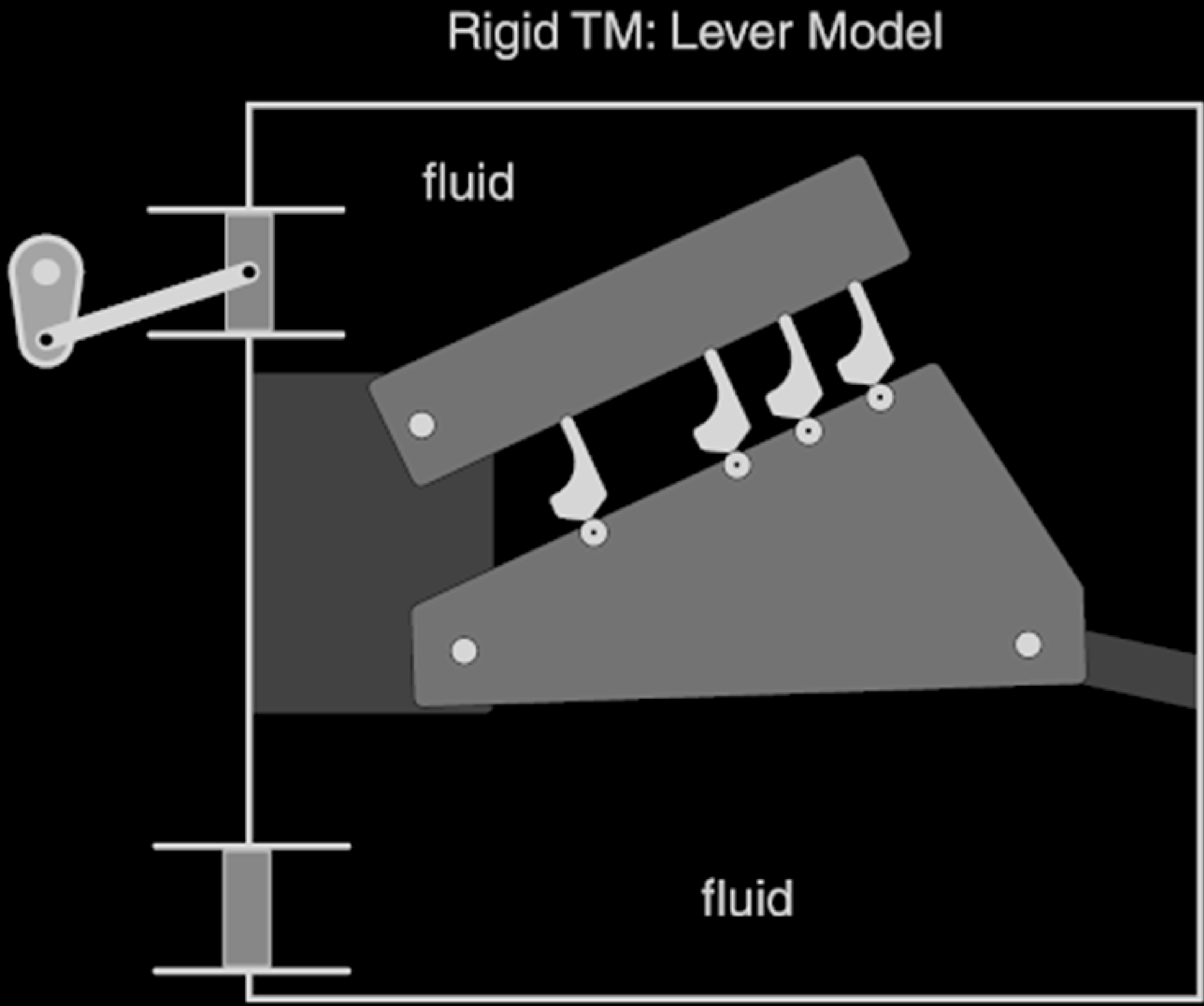
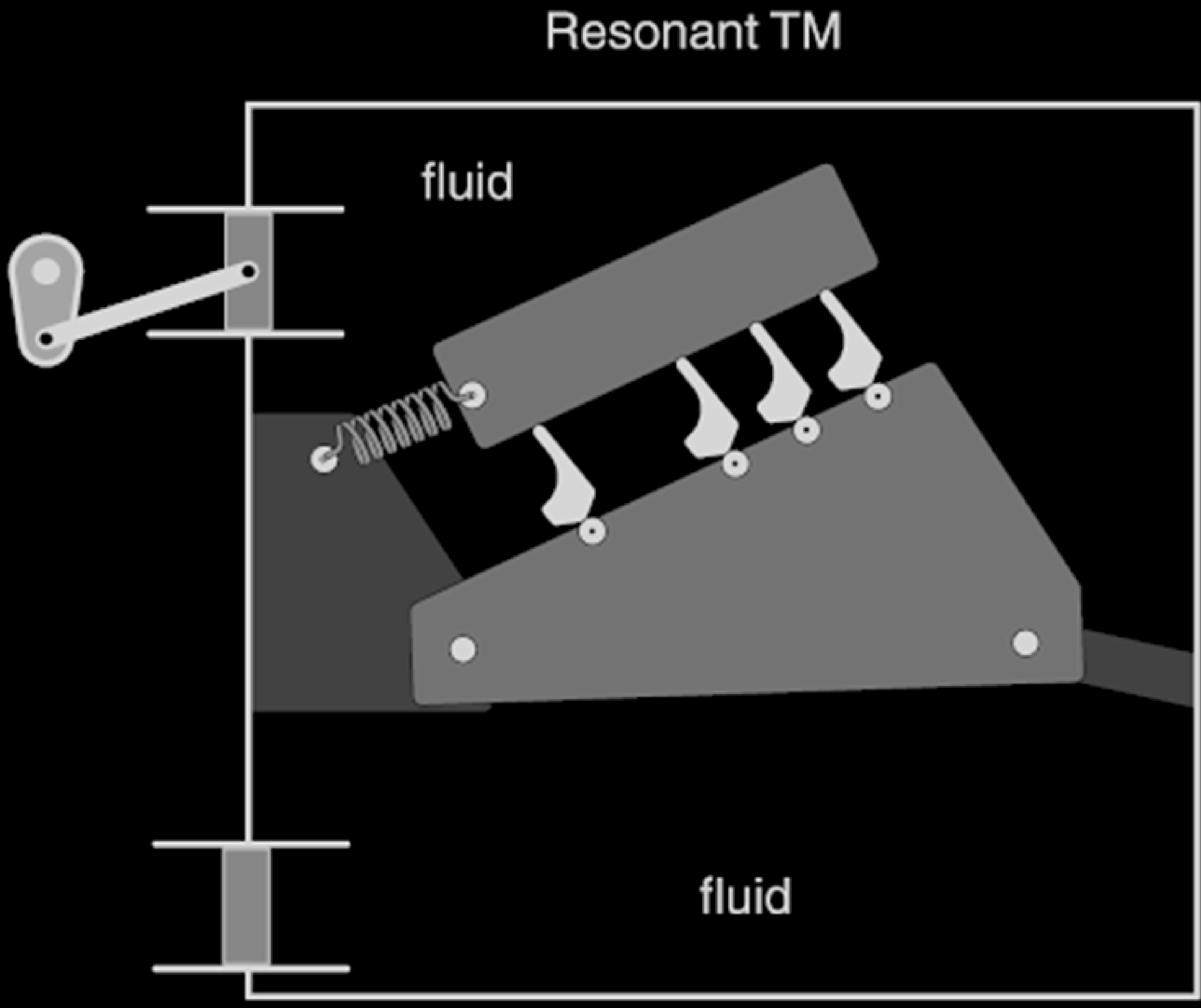
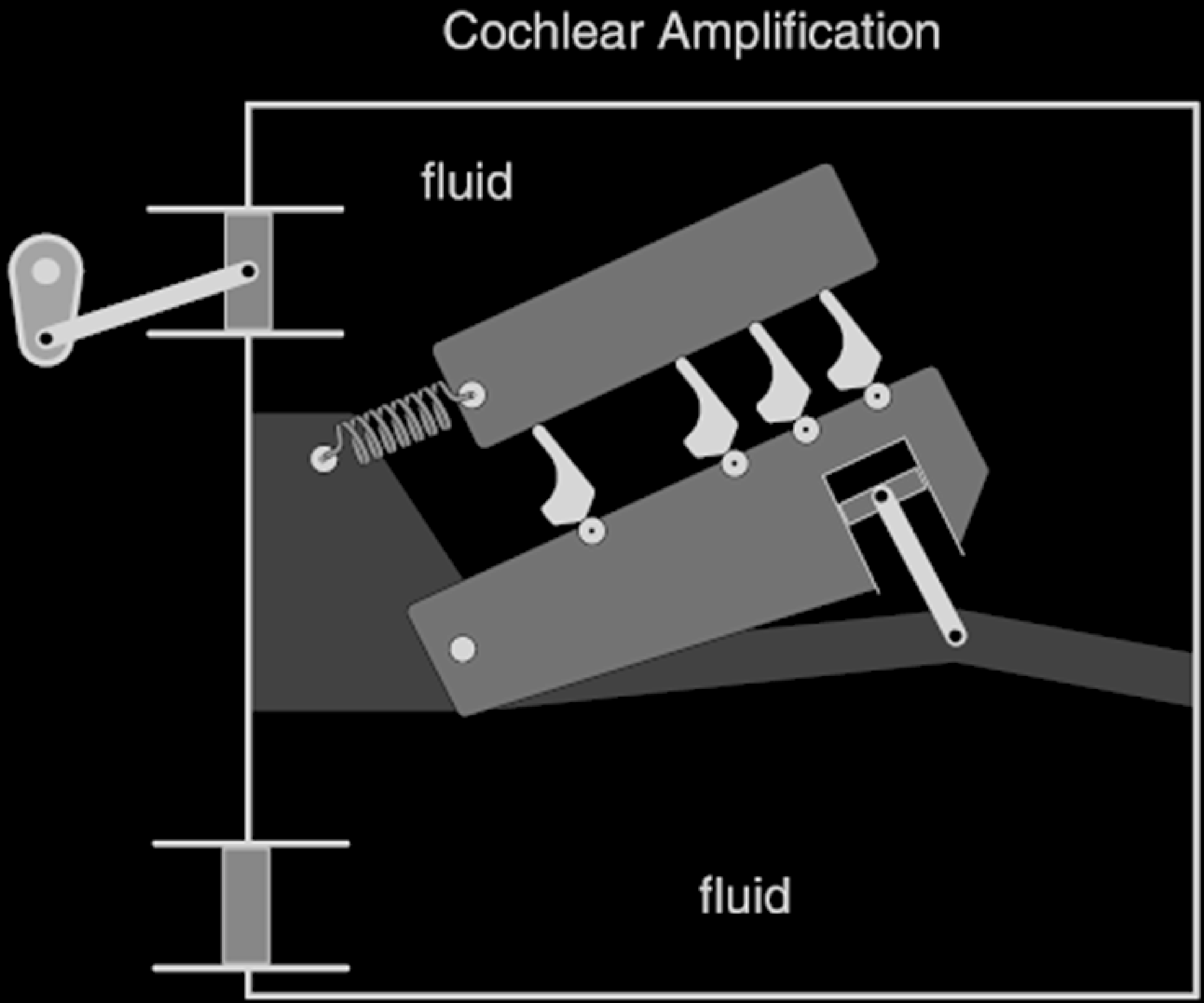


Cochlear Micro-mechanics: from BM motion to HC excitation



Cochlear Micro-mechanics: from BM motion to HC excitation

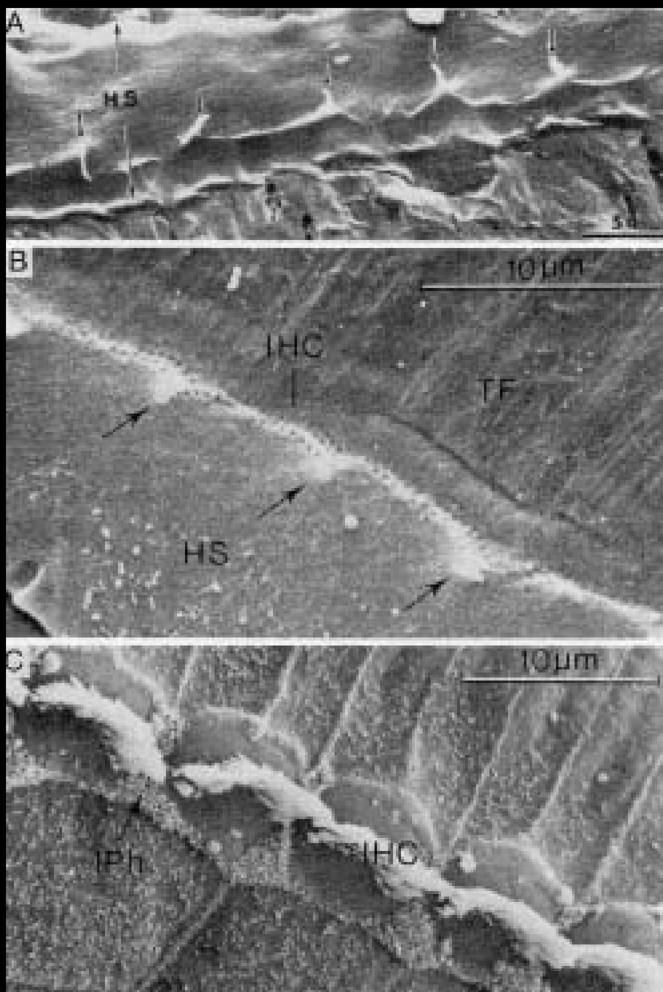


Cochlear Micro-mechanics: from BM motion to HC excitation

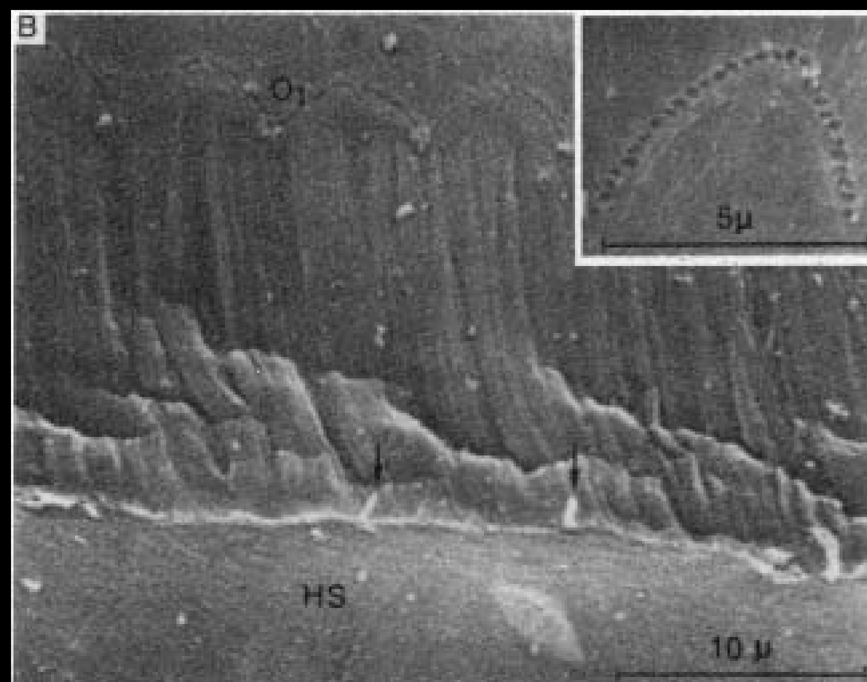
Tallest row of OHC stereocilia appear firmly embedded in TM in all mammals and all cochlear regions.

IHC stereocilia appear more loosely attached, especially in apical turns.

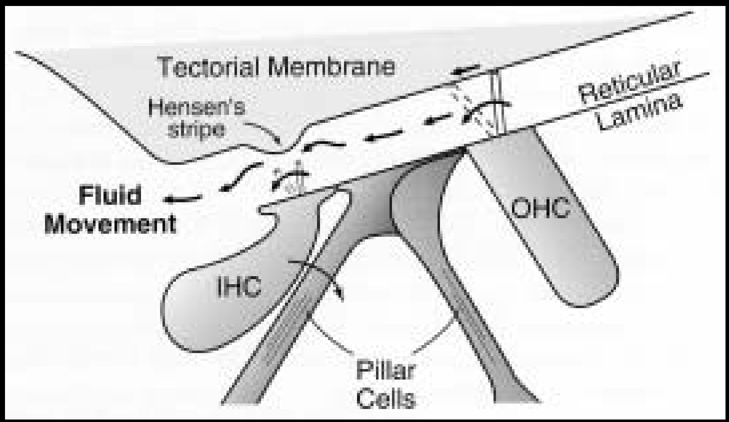
IHCs



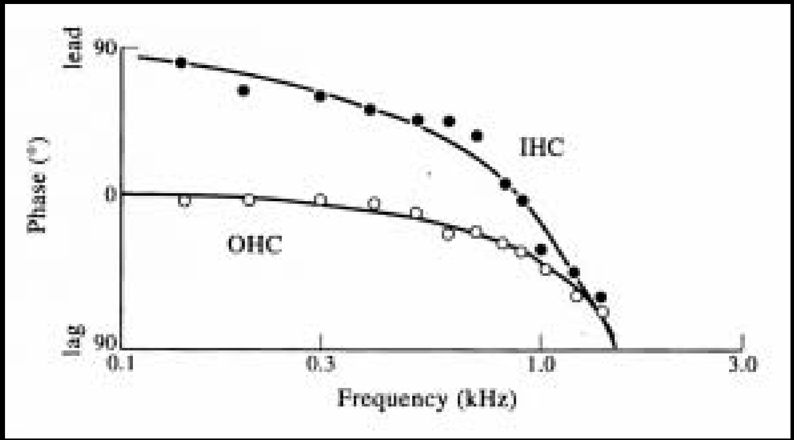
OHCs



Cochlear Micro-mechanics: from BM motion to HC excitation

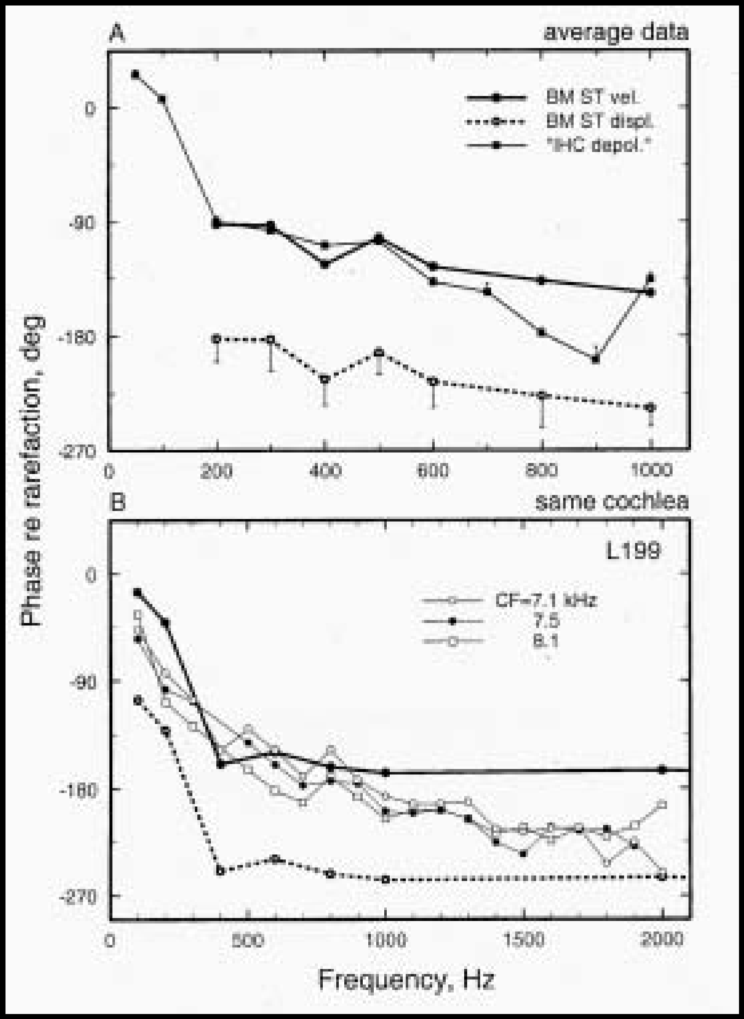


These differences in TM attachment inspired the view that displacement might be key to excitation in OHCs, whereas velocity might be key in IHCs.



At some frequencies and in some cochlear regions, the phase of response of IHCs is 90 degrees ahead of OHCs - consistent with displacement vs. velocity as the key to excitation

Cochlear Micro-mechanics: from BM motion to HC excitation



Data from AN fibers suggests a very complicated relation between phases of BM displacement/velocity and AN excitation