Regulation of cochlear outer hair cells

Insights from mathematical modelling

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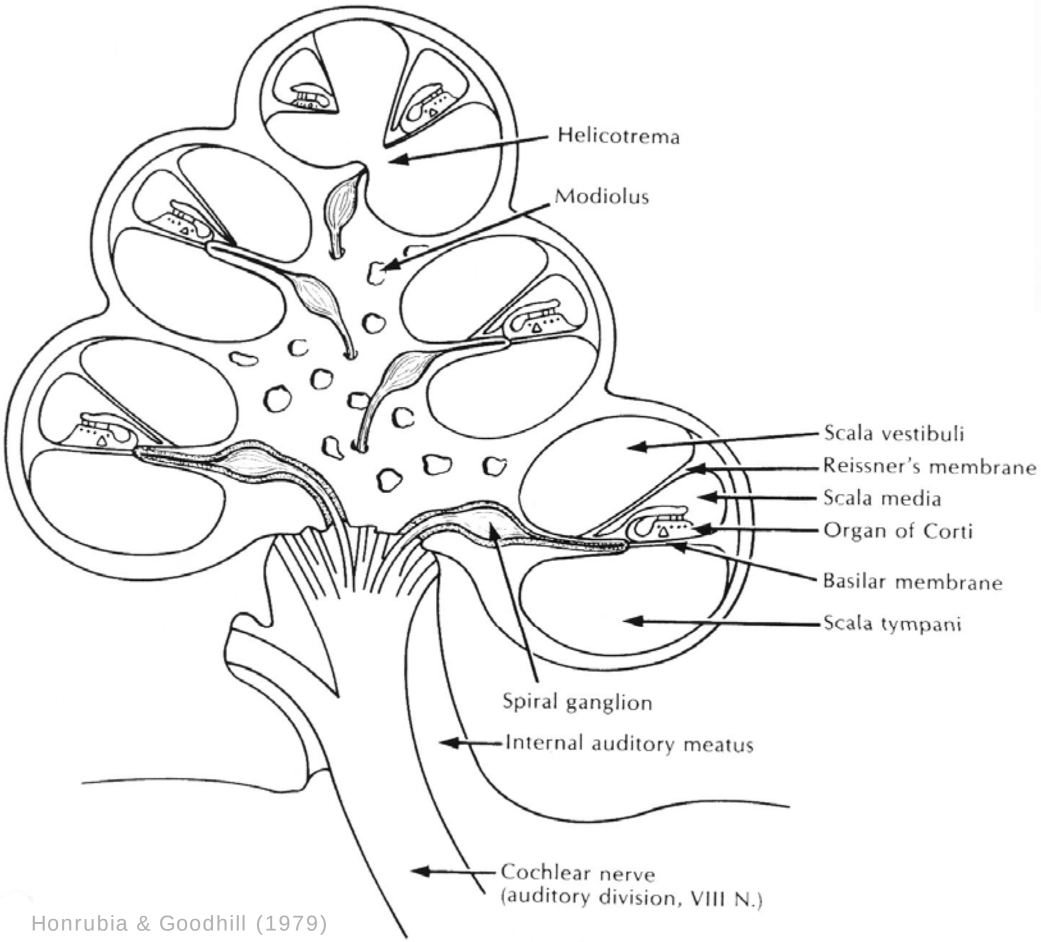
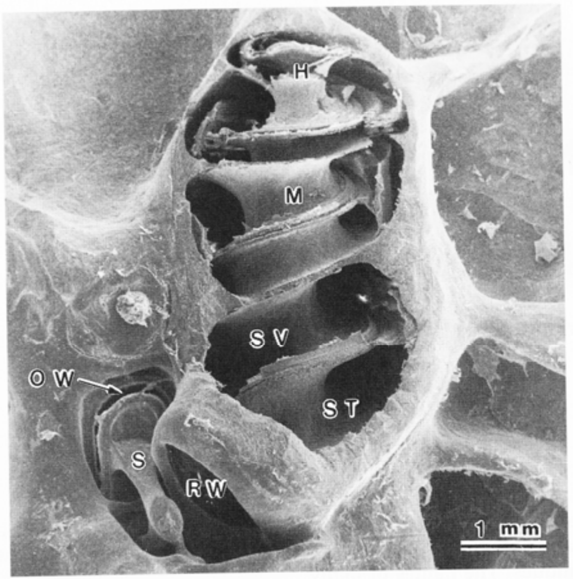
Mid-modiolar cross-section of the cochlea

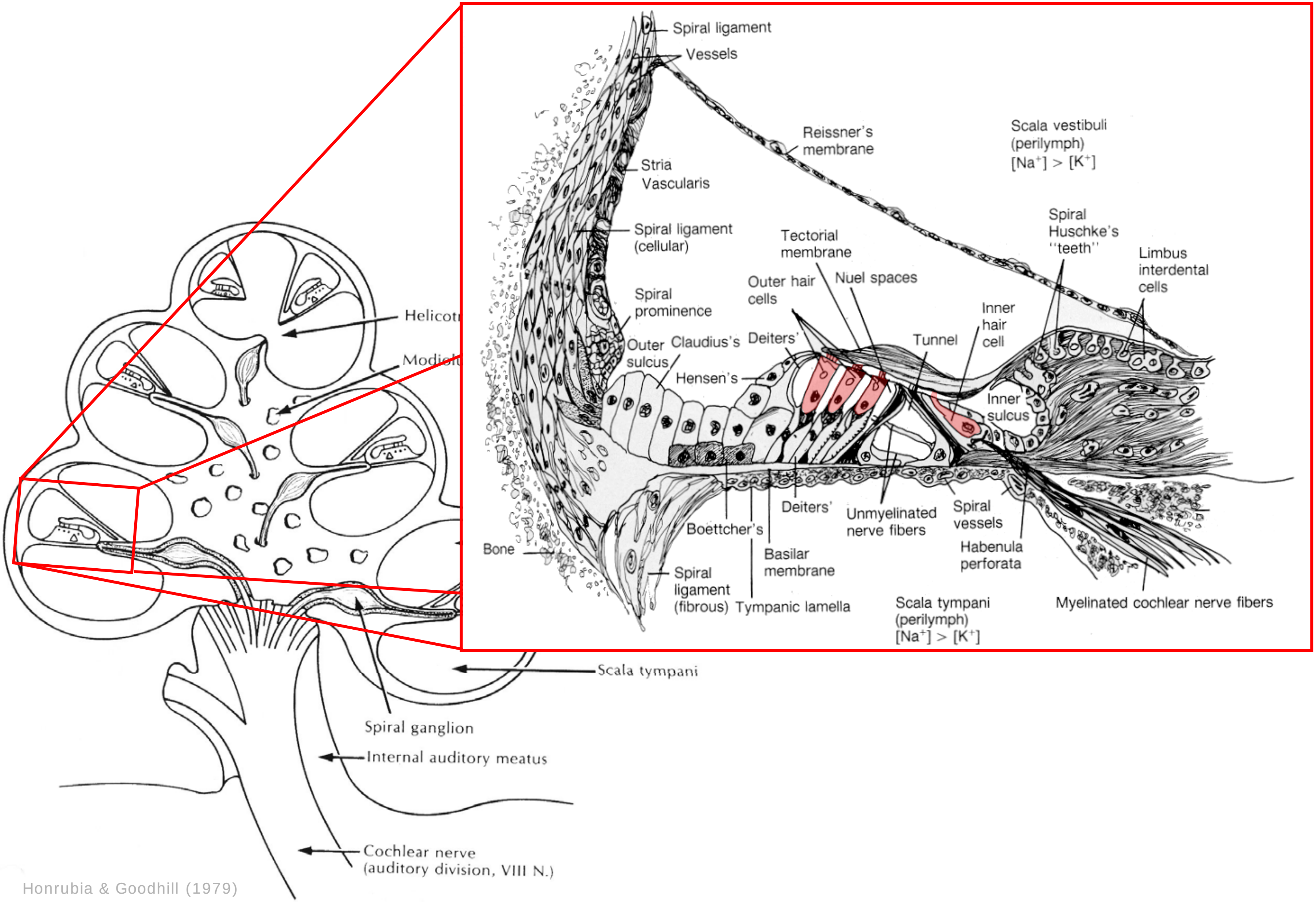


Honrubia & Goodhill (1979)



View of the cochlea after removal of the otic capsule

Mid-modiolar cross-section of the cochlea



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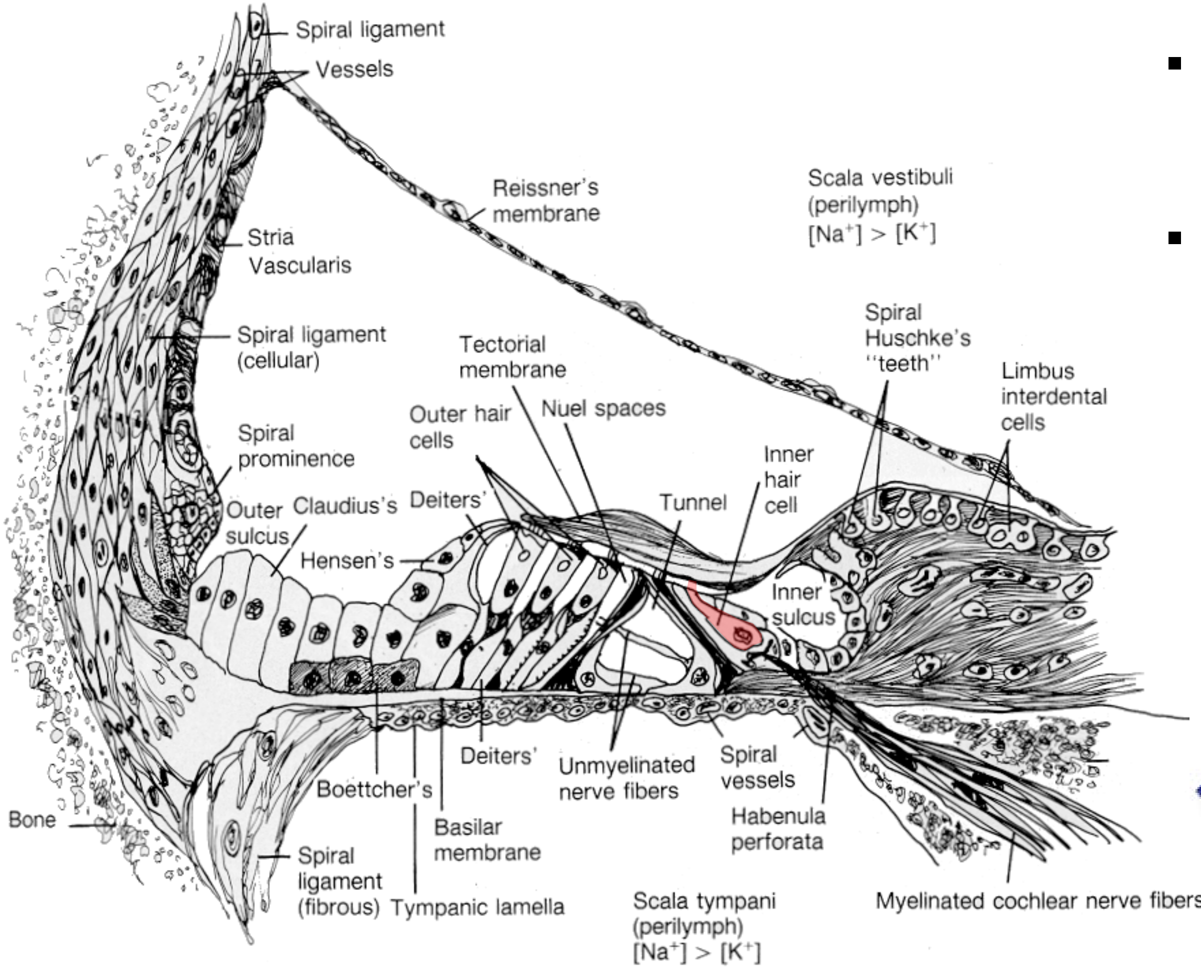
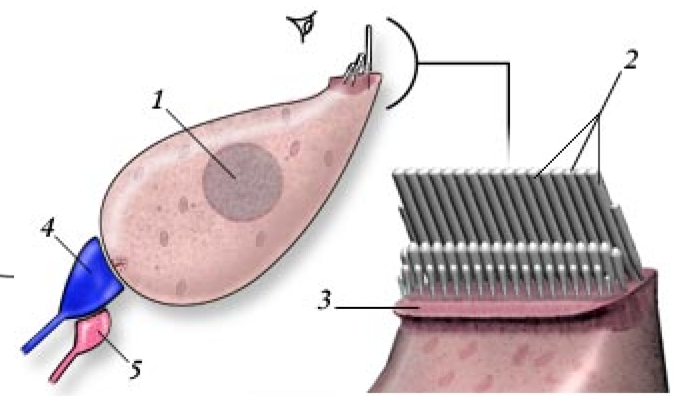
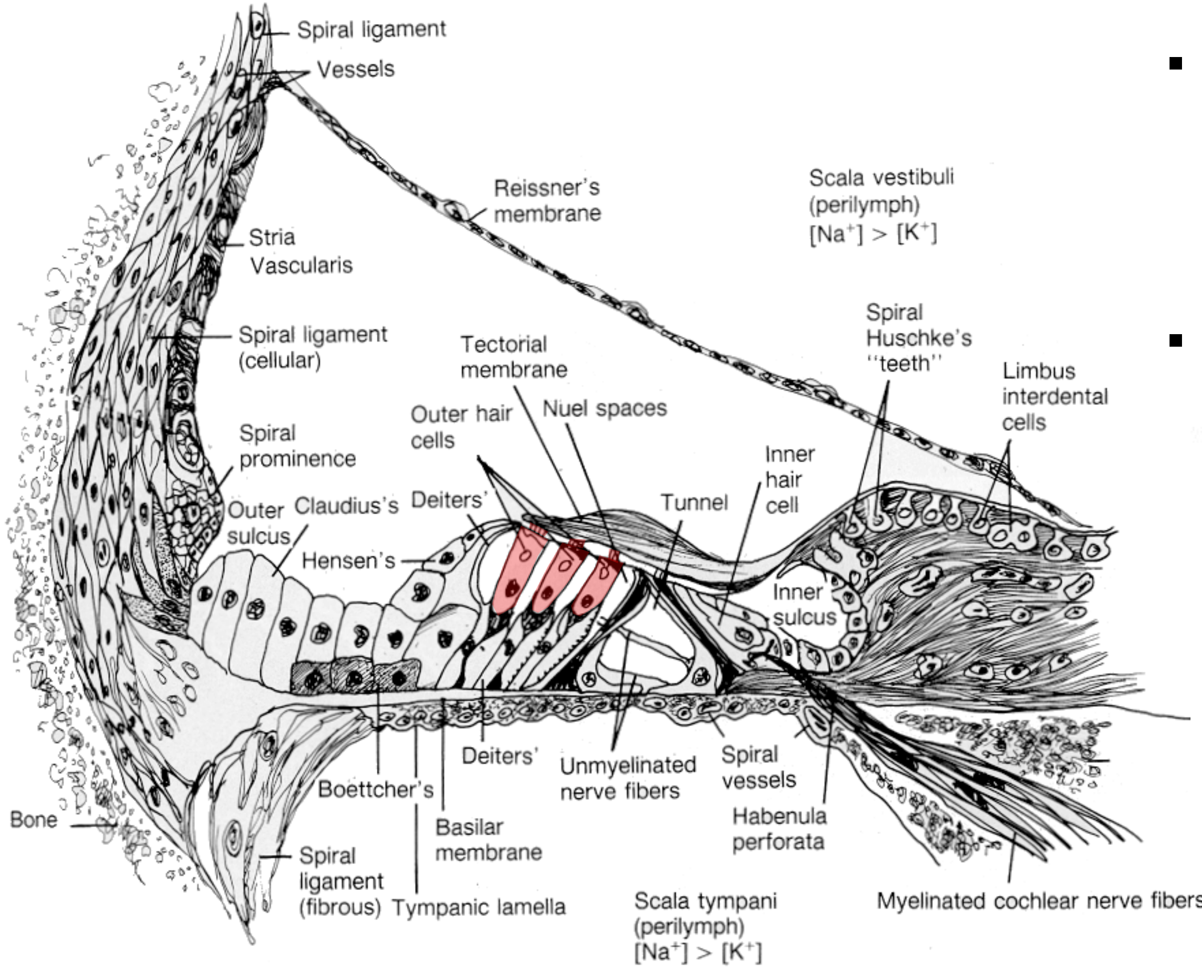
Inner hair cells



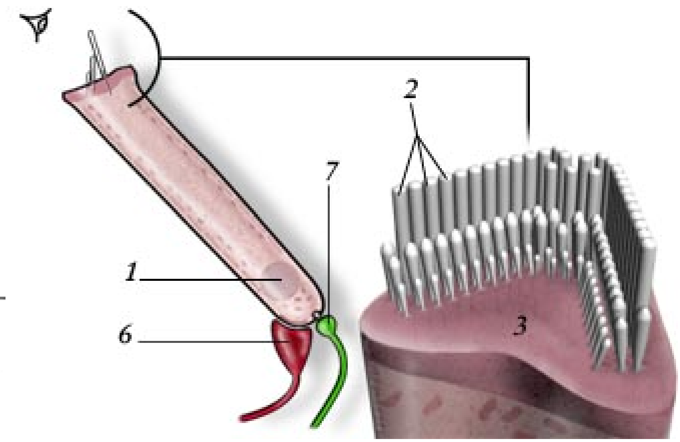
- Inner hair cells (IHCs) carry out **mechanoelectrical transduction** (or MET)
- Stereociliary deflection results in depolarisation and release of neurotransmitter



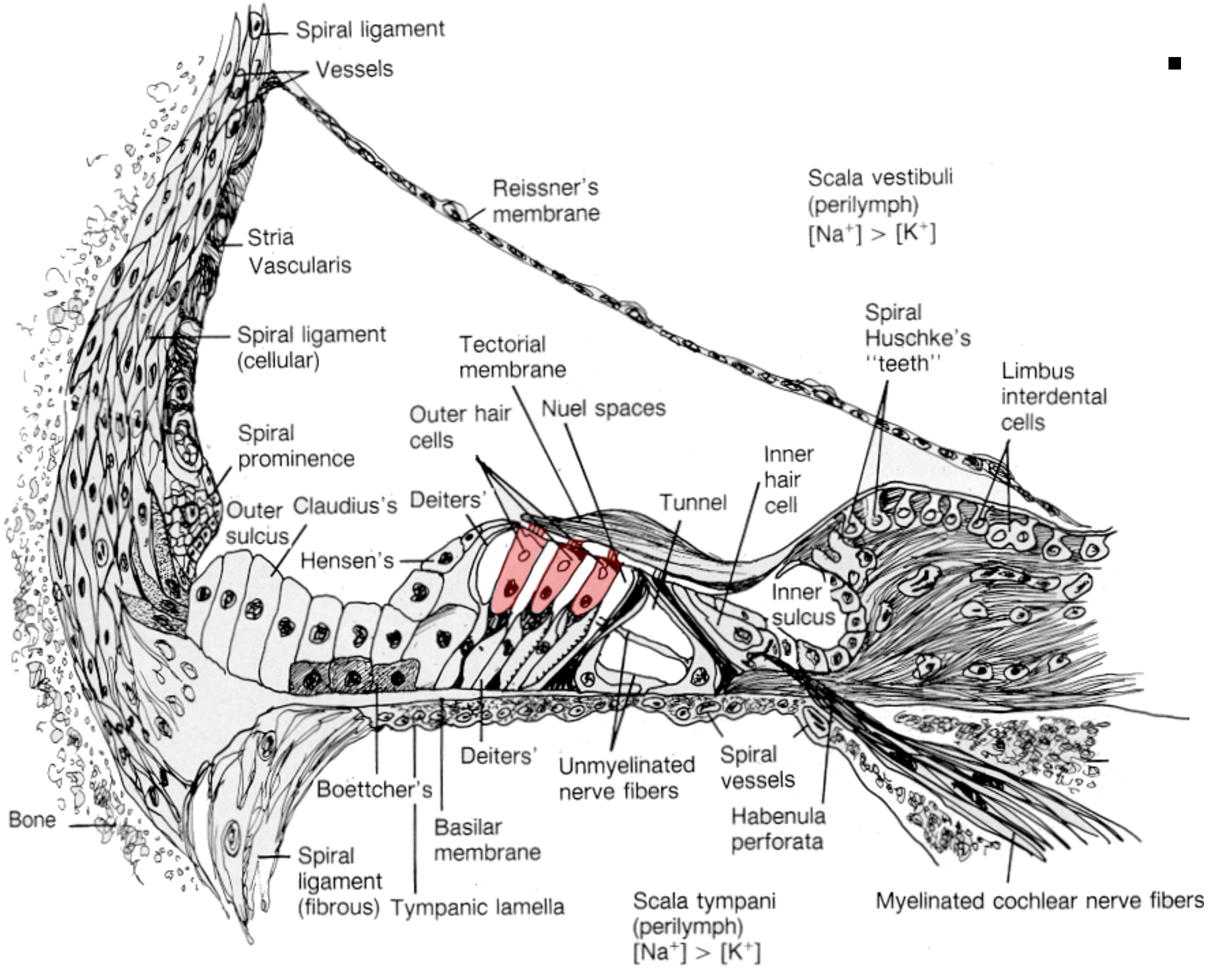
Outer hair cells



- Outer hair cells (OHCs) perform mechanoelectrical transduction, but also carry out **electromechanical transduction** (EMT)
- That is, they are **motile**.



Outer hair cells



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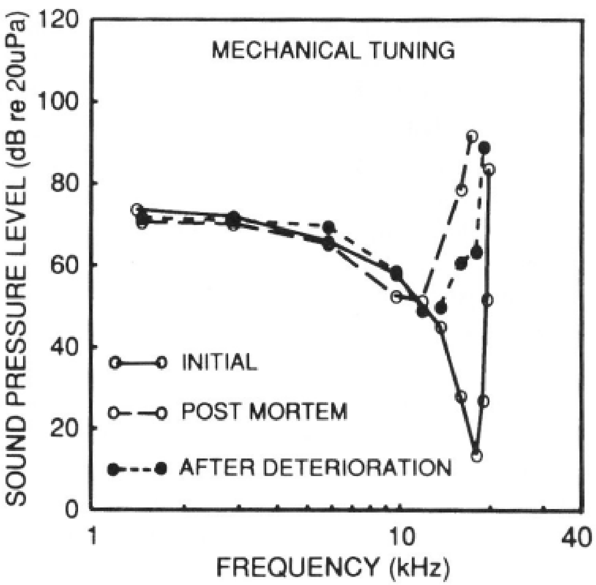
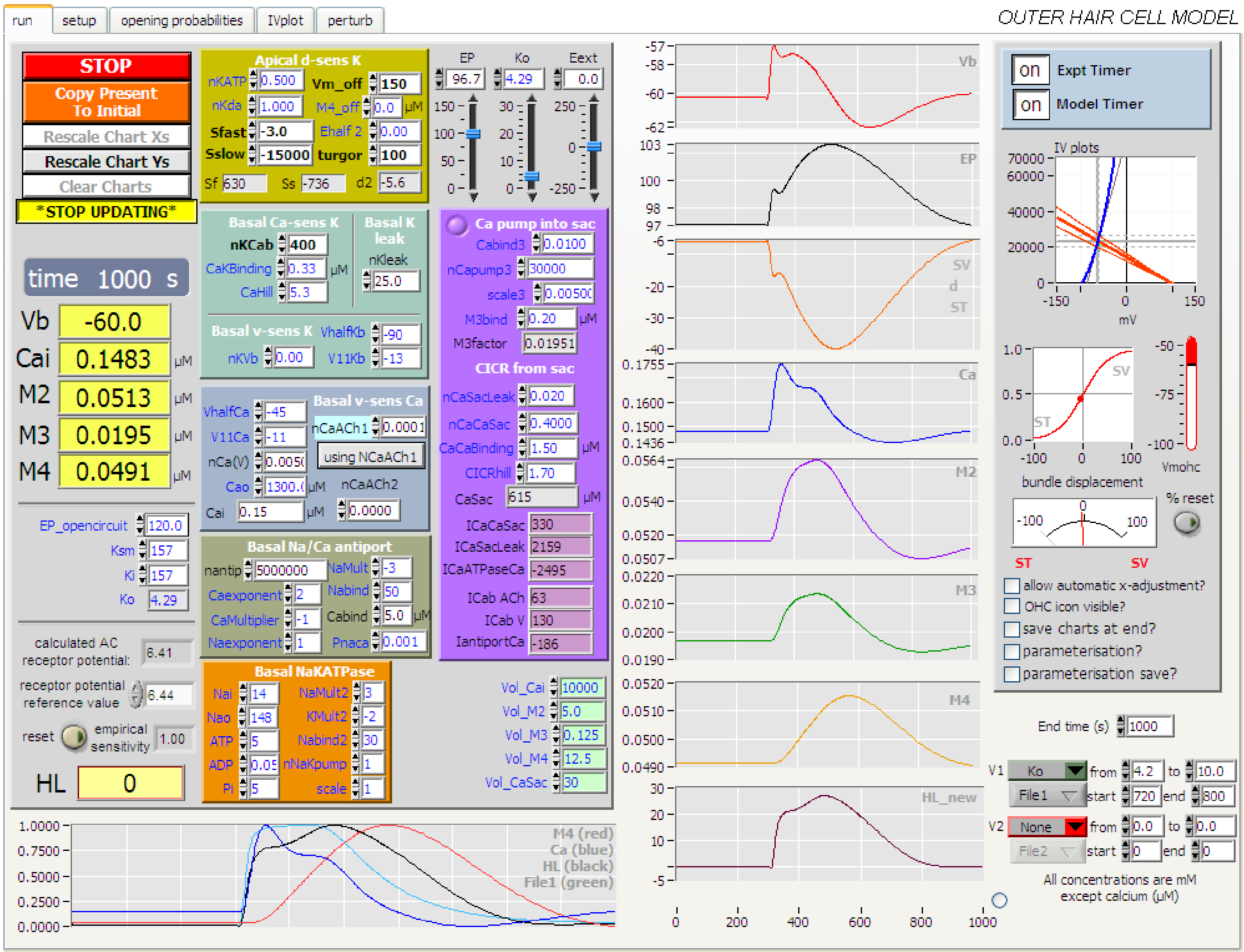


Patuzzi, 1992

- The "active process" increases basilar membrane vibration x1000 (or 60 dB)
- Allow sharp mechanical tuning and frequency resolution
- Compressive nonlinearity allows a million-fold range of sound pressures

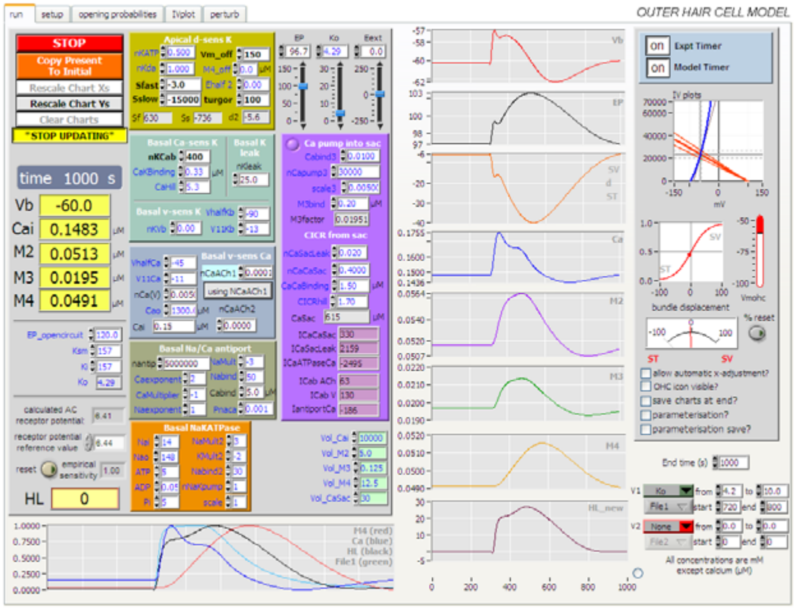
Outer hair cell mathematical model

O'Beirne, G.A. and Patuzzi, R.B. (2007). Mathematical model of outer hair cell regulation including ion transport and cell motility. Hearing Research 234:29-51.



Outer hair cell mathematical model

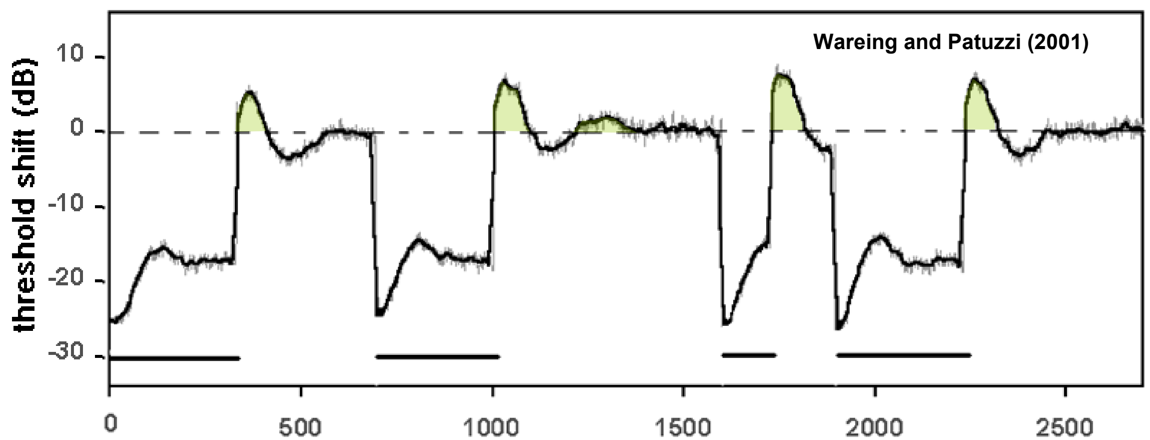
- incorporates known OHC electrophysiology
- includes effect of hair cell motility on the conductance of the apical membrane
- simulates perturbations by systematic and timed variation of model parameters

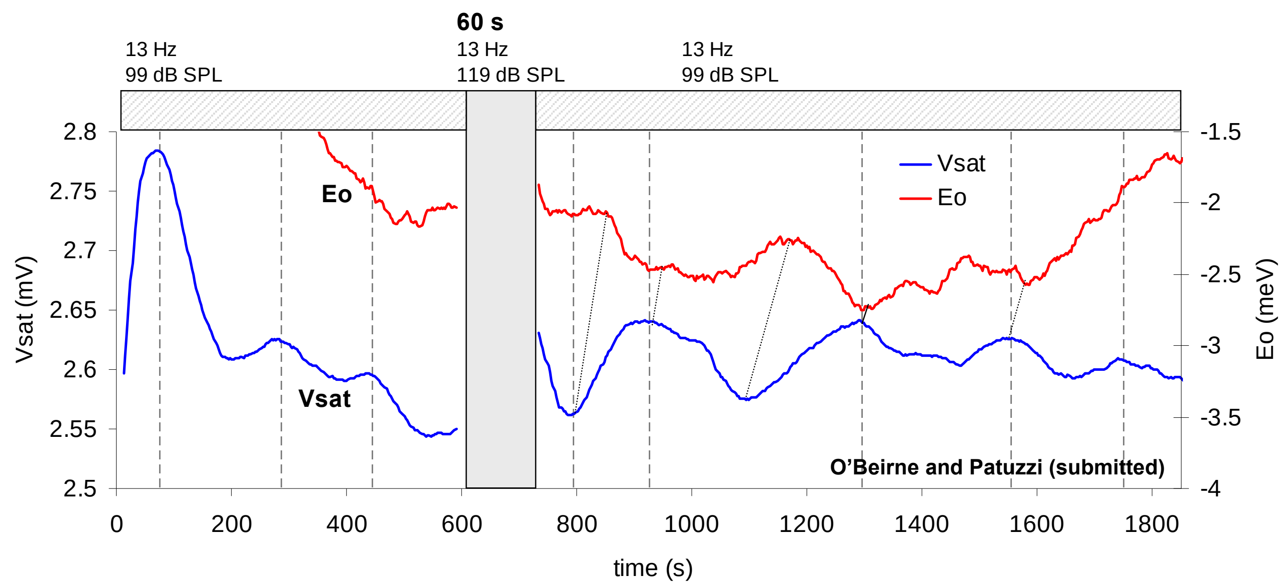


- predicts changes in active gain due to OHCs, and therefore hearing loss
- provides a plausible and consistent explanation for slow oscillatory behaviour observed in the cochlea

The low-frequency "bounce phenomenon"

- Oscillation of psychophysical thresholds in human subjects (Hirsch and Ward, 1952; Zwicker and Hesse, 1984; Wareing and Patuzzi, 2001)
- Mechanical in origin (Kemp, 1982, 1986; Kirk and Patuzzi, 1997; Kirk et al., 1997)
- Oscillations in measures of hair cell function (OAEs, LF CM) (Kirk and Patuzzi, 1997; Kirk et al., 1997; O'Beirne and Patuzzi, submitted.)



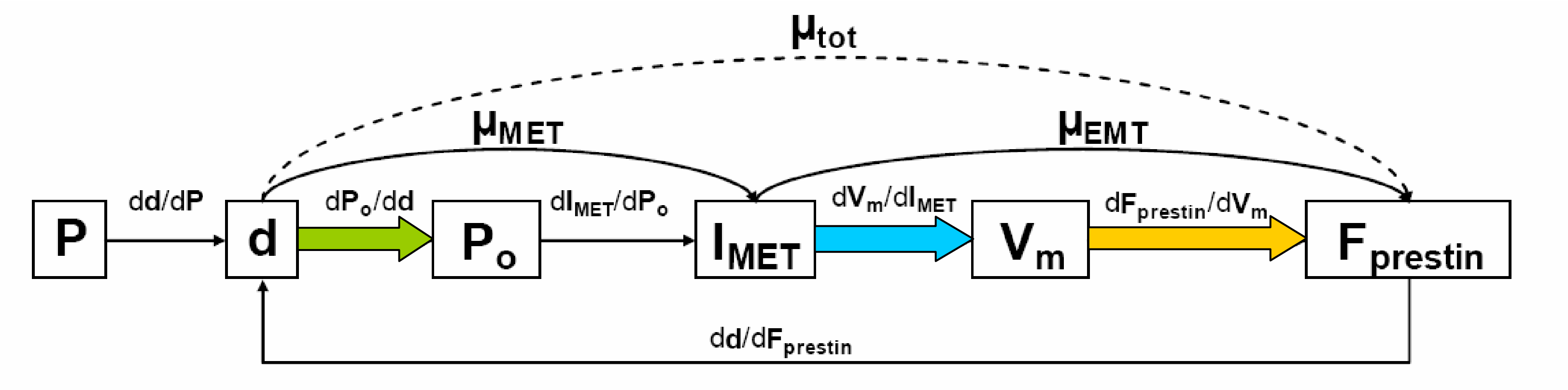


How? Why? What?

- How does the presentation of a low-frequency tone cause oscillations in hair cell performance?
- How do the hair cells perform *better than normal*?
- Why aren't they that good all the time?
- What is the underlying mechanism for the bounce?

What do OHCs need for maximum amplification?

- The OHC active process depends on the efficiency of each step from sound-induced movement to hair-cell produced movement.



O'Beirne (2005)

- In terms of normal regulation, the most critical factors are:

i. that the hair bundles are in their most sensitive position
(i.e. maximal receptor current for a given displacement)

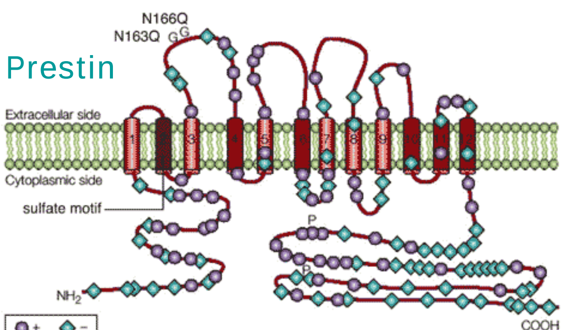
ii. that the resistance of the OHC basolateral wall is high
(i.e. maximal receptor potential for a given receptor current)

iii. that Vm is in the most sensitive region for motor proteins
(i.e. maximal force production for given receptor potential)

How does the OHC maintain hair bundle angle?

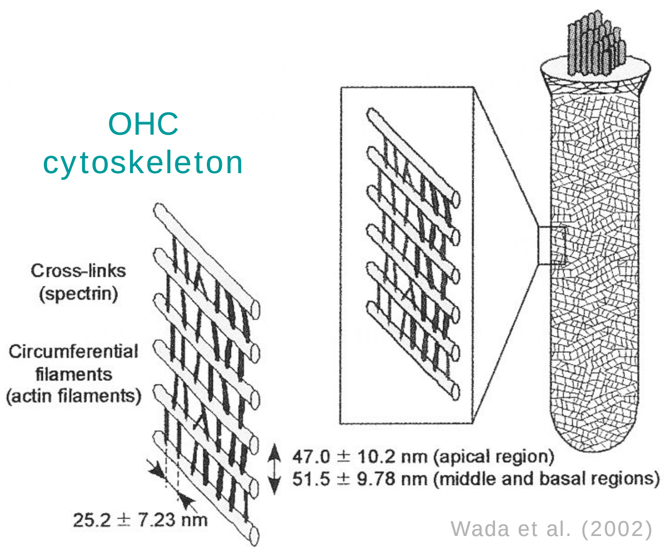
- Motility
  - Contractions or elongations of the hair cell alter the resting hair bundle angle (operating point)
  - Two types of motility:
    - – slow (calcium-based)
    - - fast (electromotility)

Prestin

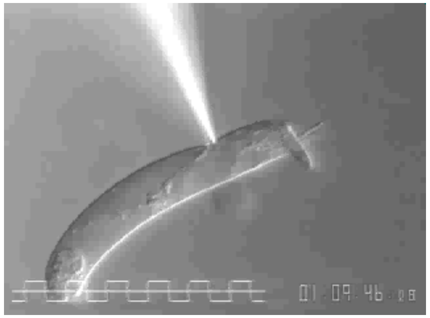


Zheng et al.

OHC cytoskeleton



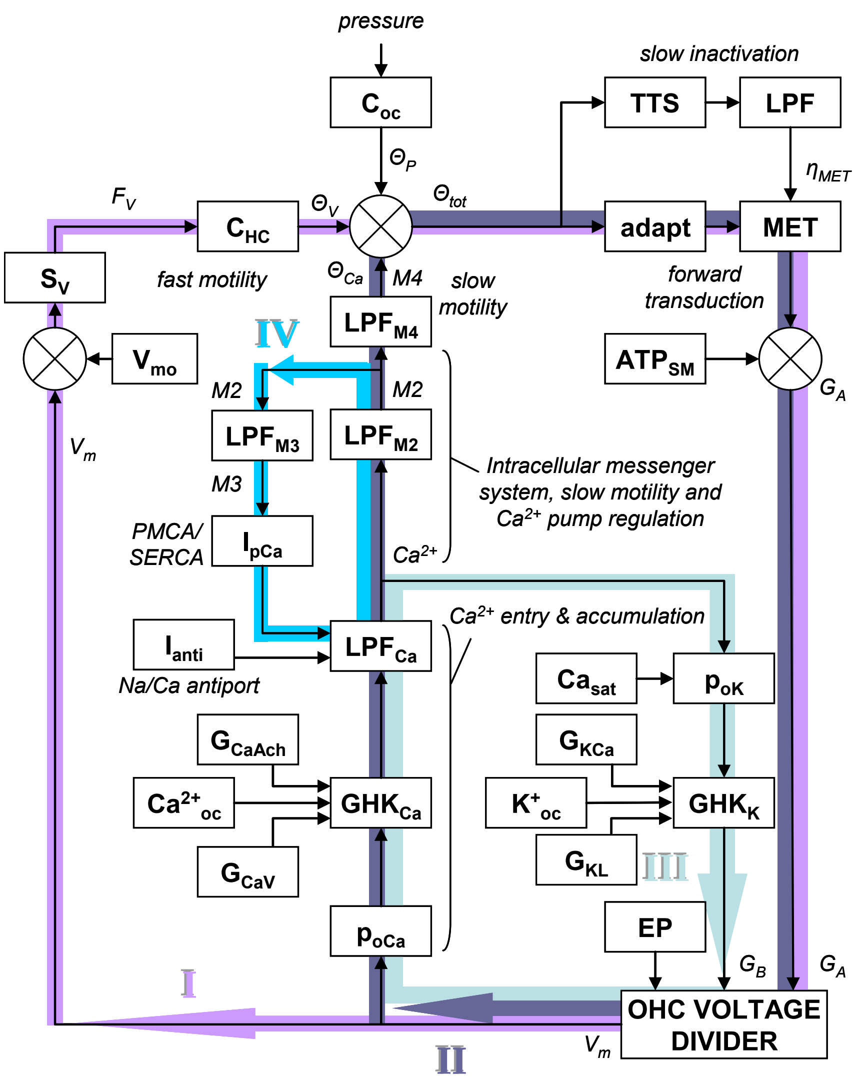
Wada et al. (2002)



Frolenkov et al. (1998)

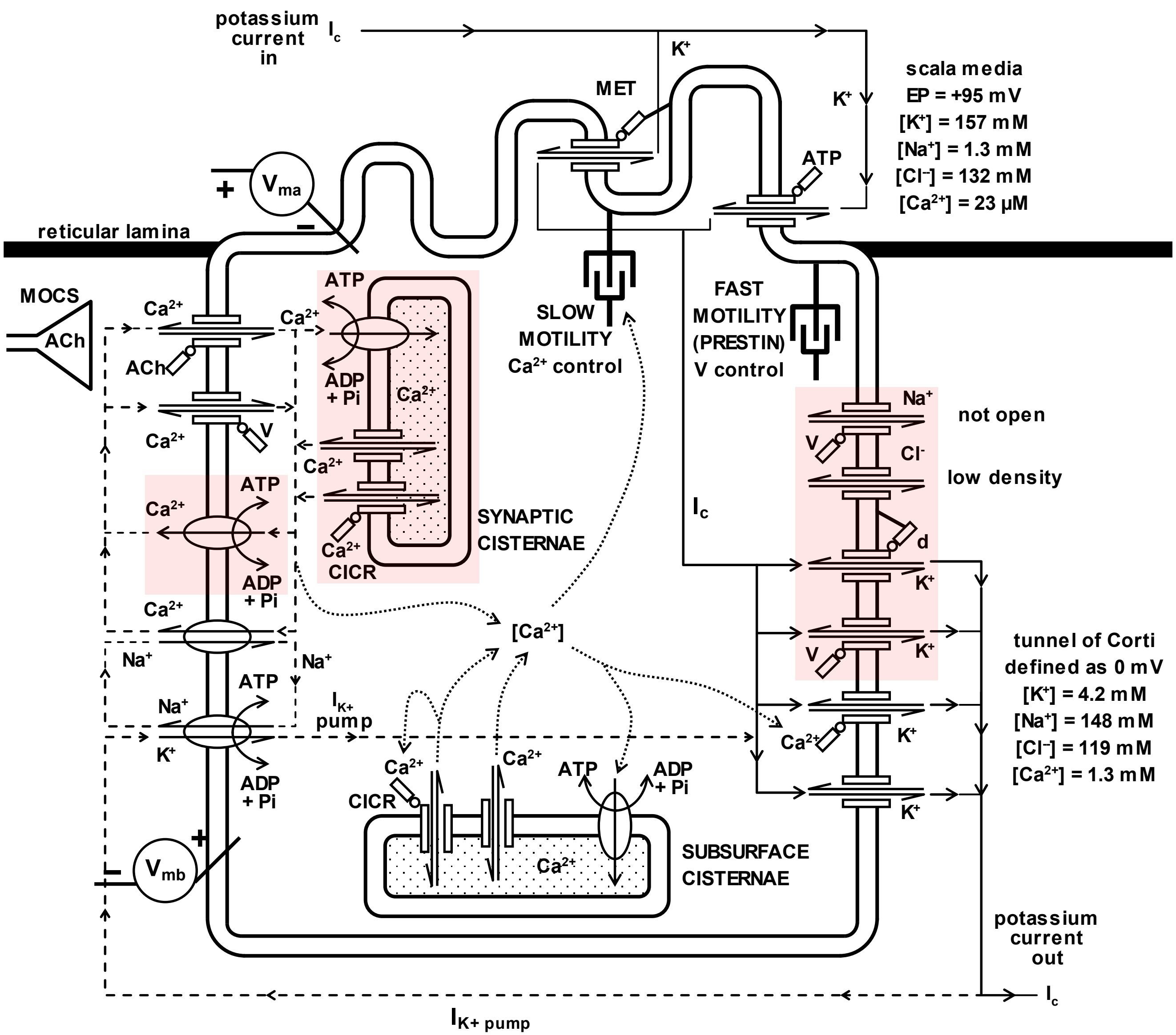
Homeostatic regulation of the OHCs - interlocking feedback loops

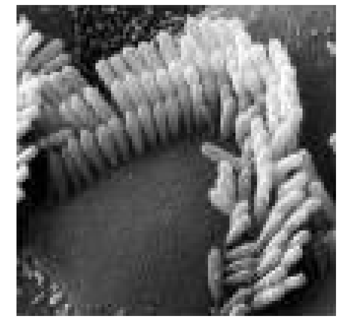
- Interlocking **negative feedback loops** within the OHCs
  i) control **operating point** via slow motility and fast electromotility,
  ii) control **basolateral permeability** via the effect of intracellular calcium on Ca^{2+}-gated K^{+} channels,
  iii) control **membrane potential** via the OHC voltage divider (apical and basolateral conductances).
- Every loop acts to reduce *(but not eliminate entirely)* the effect of any perturbation.
- Must be **slow**.
- Regulatory feedback loops prone to **oscillation in response to transient stimuli**.



O'Beirne & Patuzzi (2007). Hear Res 234:29-51.

Schematic diagram of OHC cellular components



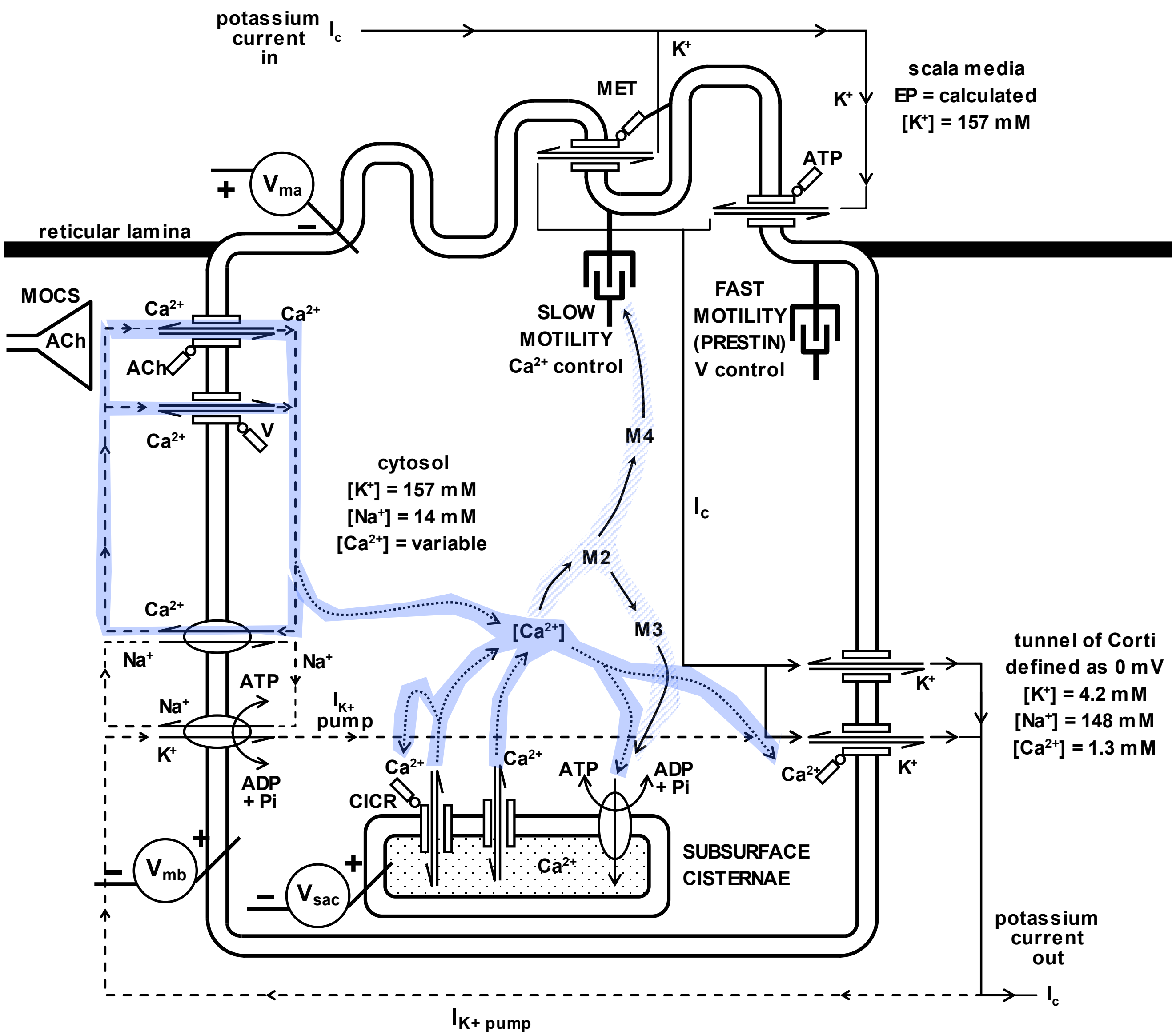


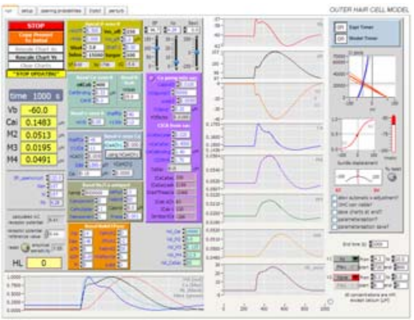
Apex
- d-sensitive K^+ channel
- ATP-sensitive cation channels

Base
- K^+ leakage channel
- Ca^{2+}-sensitive K^+ channel
- Na^+/K^+/ATPase
- Ca^{2+}/Na^+ antiport
- v-sensitive Ca^{2+} channel
- ACh-sensitive Ca^{2+} channel

Subsurface/Synaptic Cisternae
- Ca^{2+} induced Ca^{2+} release
- Ca^{2+} leakage
- Ca^{2+}ATPase

Simplifications/alterations required for modelling





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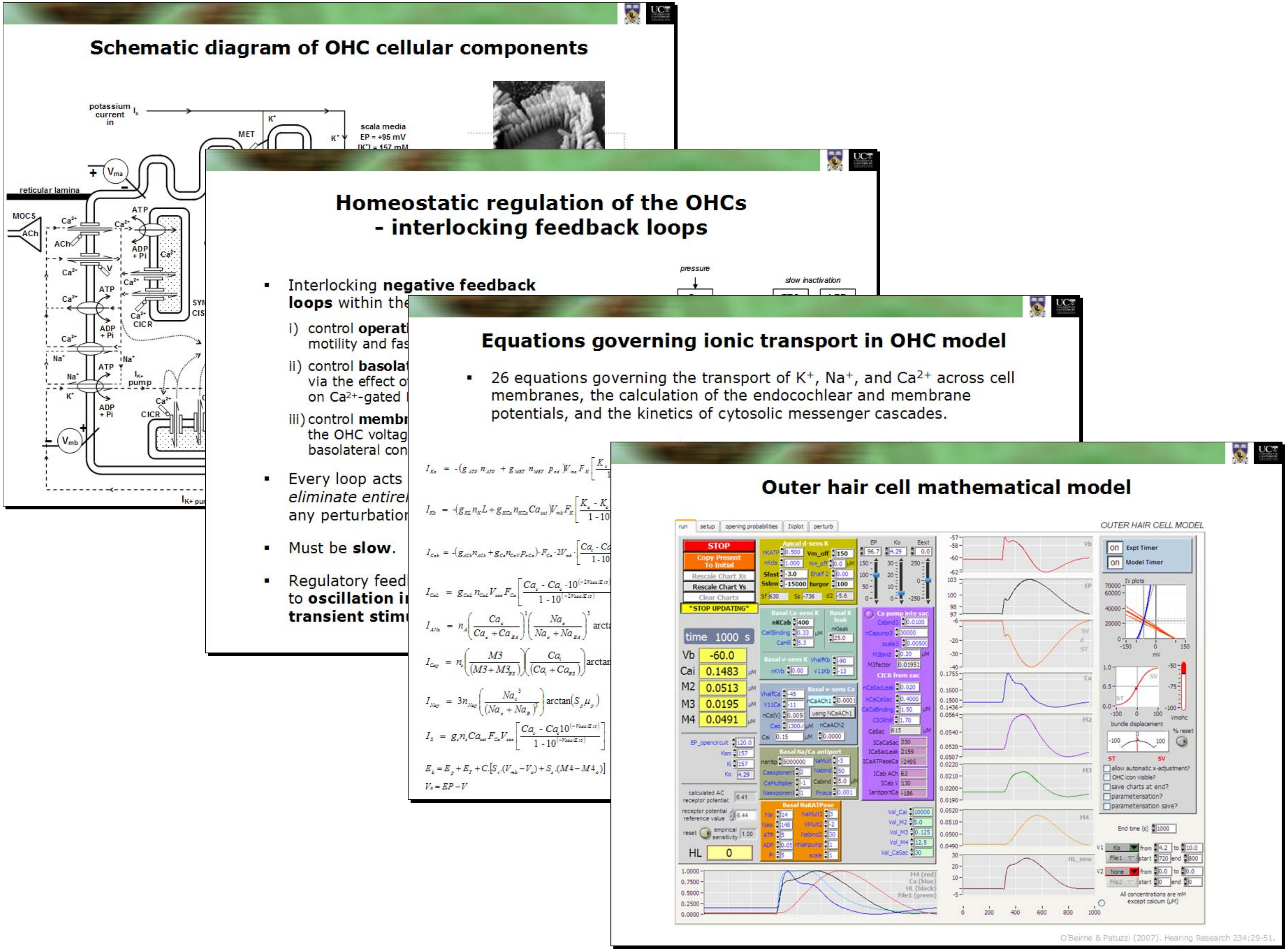


Schematic diagram of OHC cellular components
potassium current in
scala media
EP = +95 mV
MET
reticular lamina
MOCS
ACh
ATP
ADP + Pi
CICR
pump
Homeostatic regulation of the OHCs - interlocking feedback loops
Interlocking negative feedback loops within the
i) control operati
motility and fas
ii) control basola
via the effect o
on Ca2+-gated
iii) control membr
the OHC voltag
basolateral con
Every loop acts
eliminate entire
any perturbation
Must be slow.
Regulatory feed
to oscillation i
transient stim
pressure
slow inactivation
Equations governing ionic transport in OHC model
26 equations governing the transport of K+, Na+, and Ca2+ across cell membranes, the calculation of the endocochlear and membrane potentials, and the kinetics of cytosolic messenger cascades.
Outer hair cell mathematical model
OUTER HAIR CELL MODEL
STOP
time 1000 s
Vb -60.0
Cai 0.1483
M2 0.0513
M3 0.0195
M4 0.0491
HL 0
O'Beirne & Patuzzi (2007). Hearing Research 234:29-51.

Selection of model parameters based on experimental data

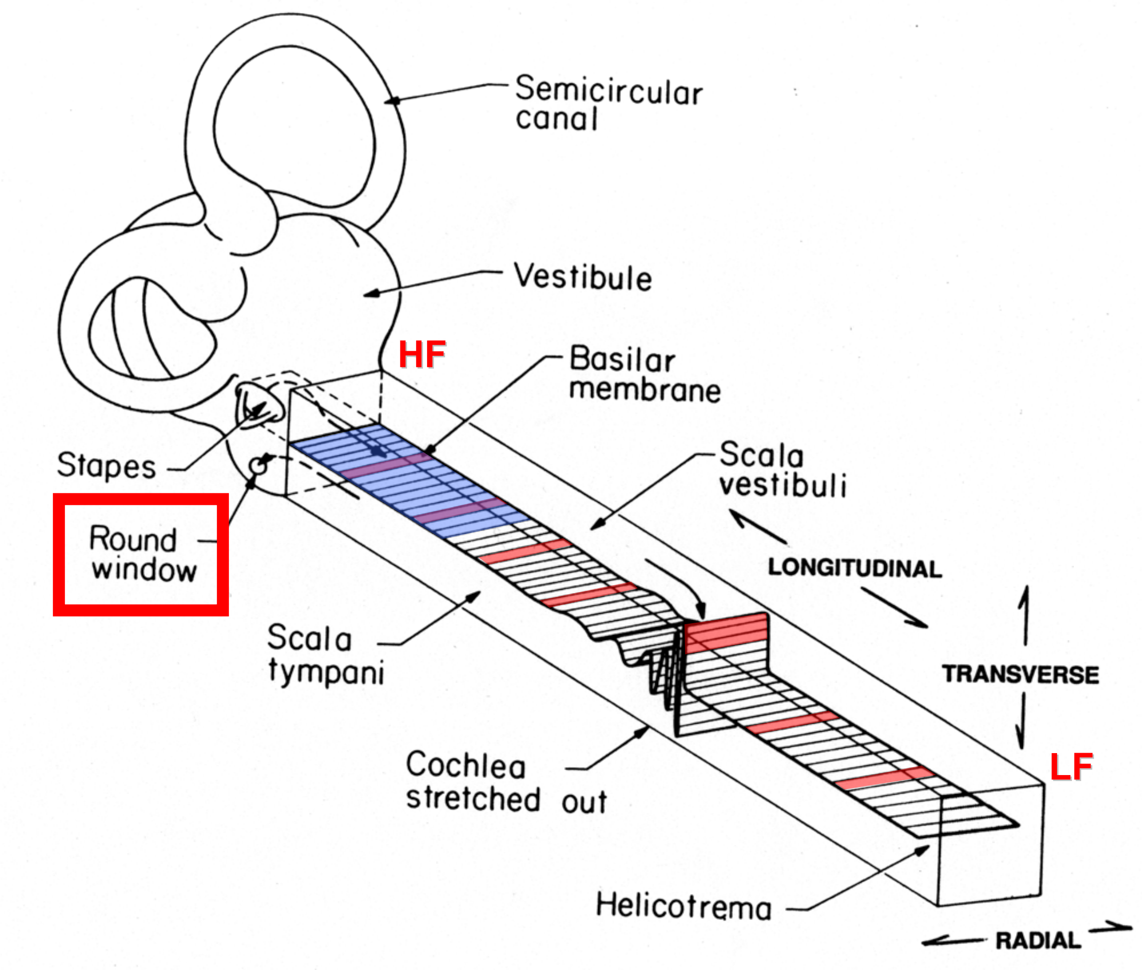
1. Electrophysiological experiments in guinea pigs
   - perturb the cochlea in some way
     (e.g. low-frequency tones, perfusions of artificial perilymph, current injection, mechanical bias)
   - measure just about everything simultaneously
   - analyse interactions between measured cochlear parameters

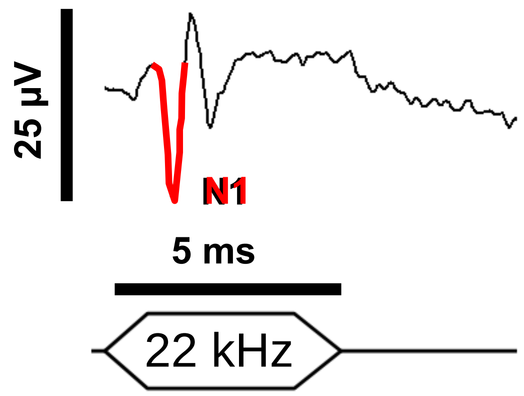
2. Simulate the experiment in the mathematical model and fine-tune parameters to match the experimental data

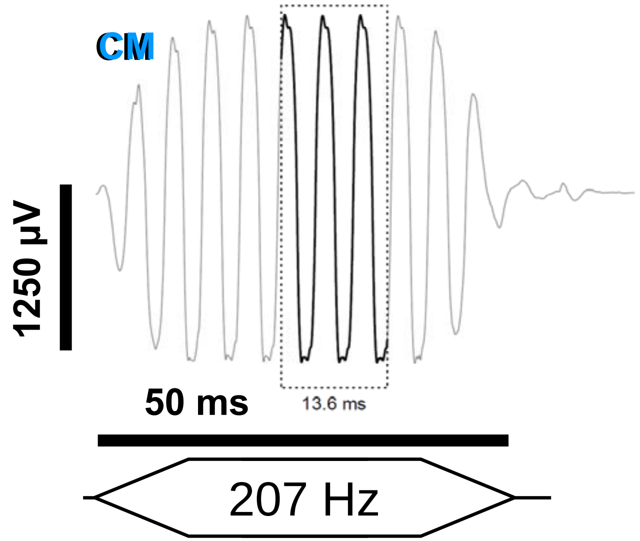
3. Repeat.

Electrophysiological monitoring of cochlear function

- Round-window electrocochleography

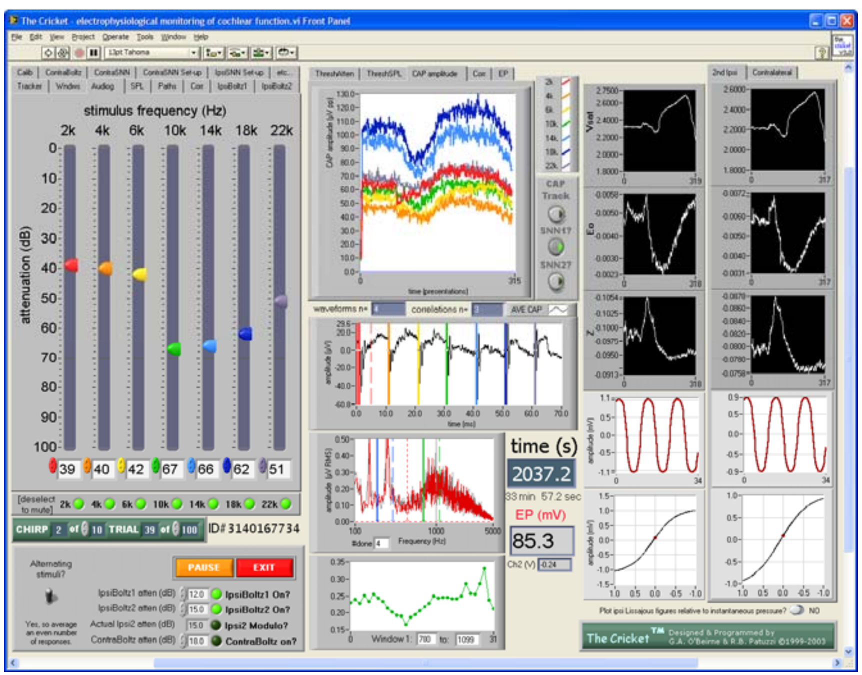


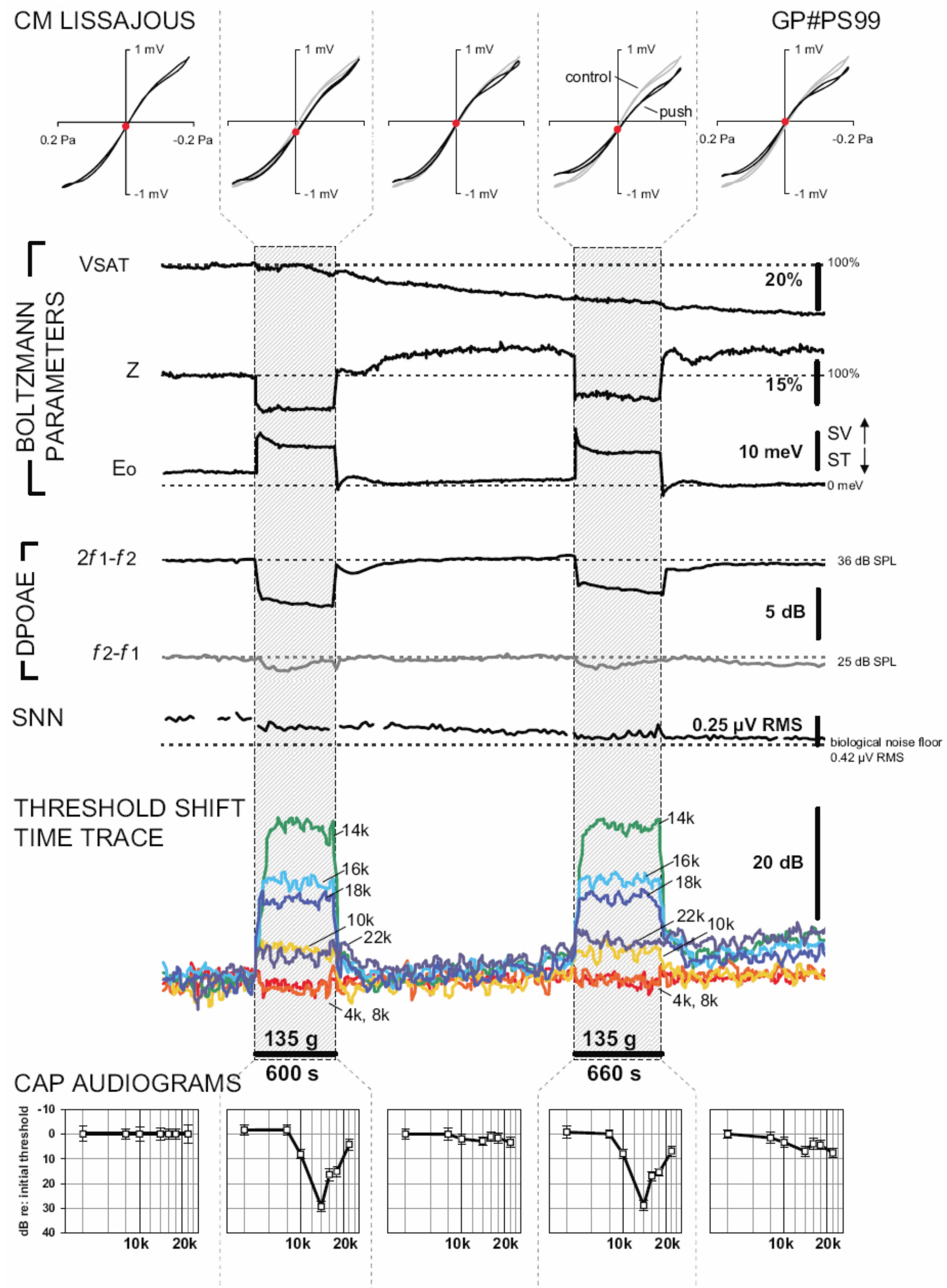




Electrophysiological monitoring of cochlear function

- Custom-written software allowed near-simultaneous measurement of:
  - CAP thresholds and waveforms at seven different frequencies
  - Boltzmann analysis of 200 Hz CM
  - Distortion-product OAEs
  - Endocochlear potential (EP)
  - Spectrum of neural noise (SNN)



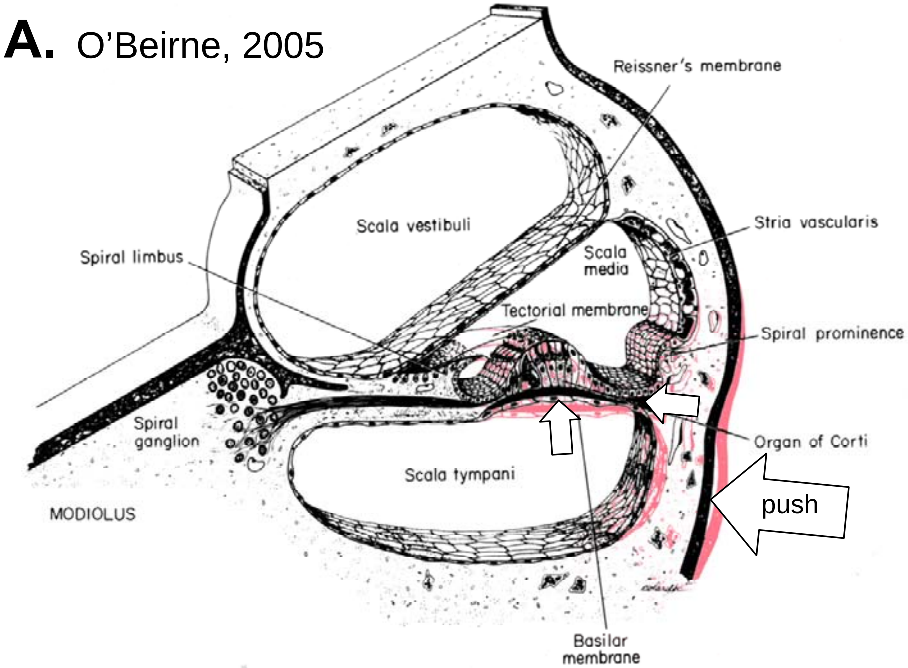


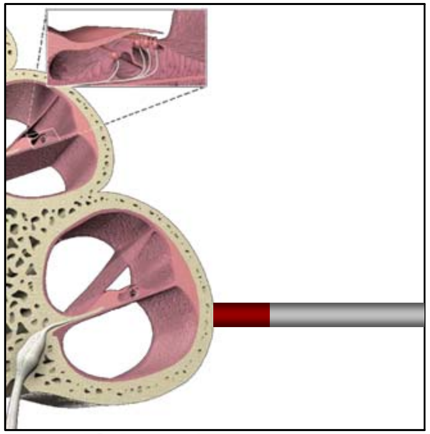
Examples of experimental perturbations and model results

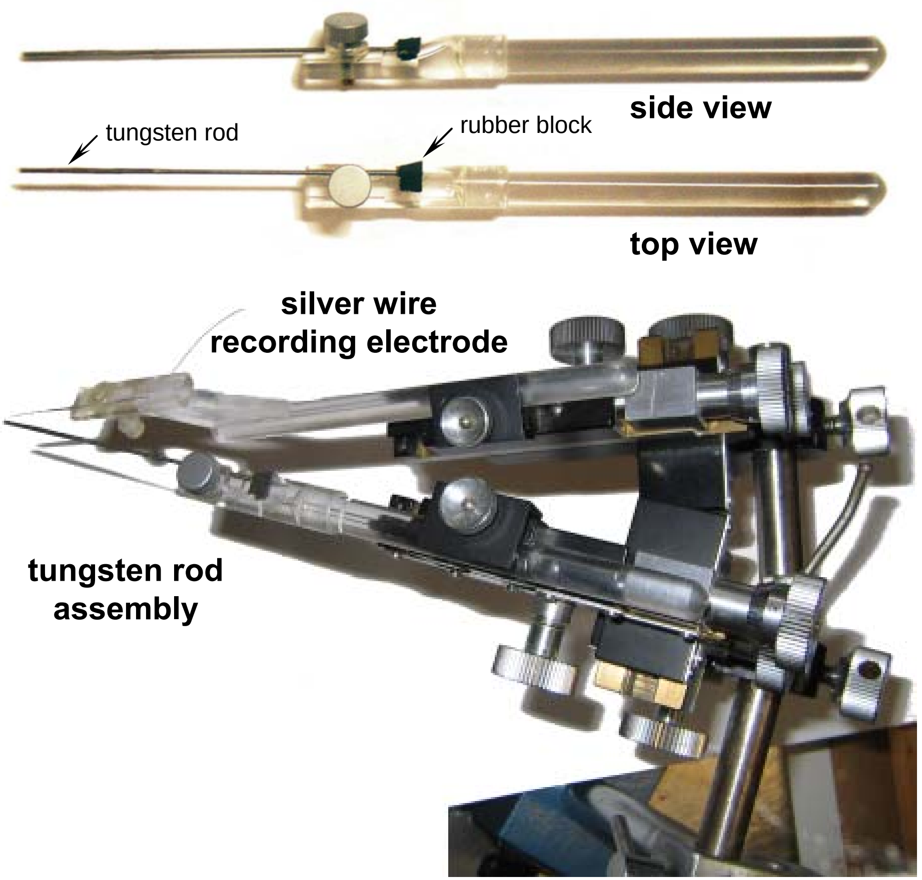
- Model tested and refined using data from experiments conducted in the guinea pig
- **Examples:**
  - Cochlear perfusions
    - Systematic variation of model parameters
  - Application of force to the cochlear wall
    - Generation of hair cell regulation curves
  - The bounce
    - Accumulation and removal of intracellular calcium
    - Effect on basolateral permeability

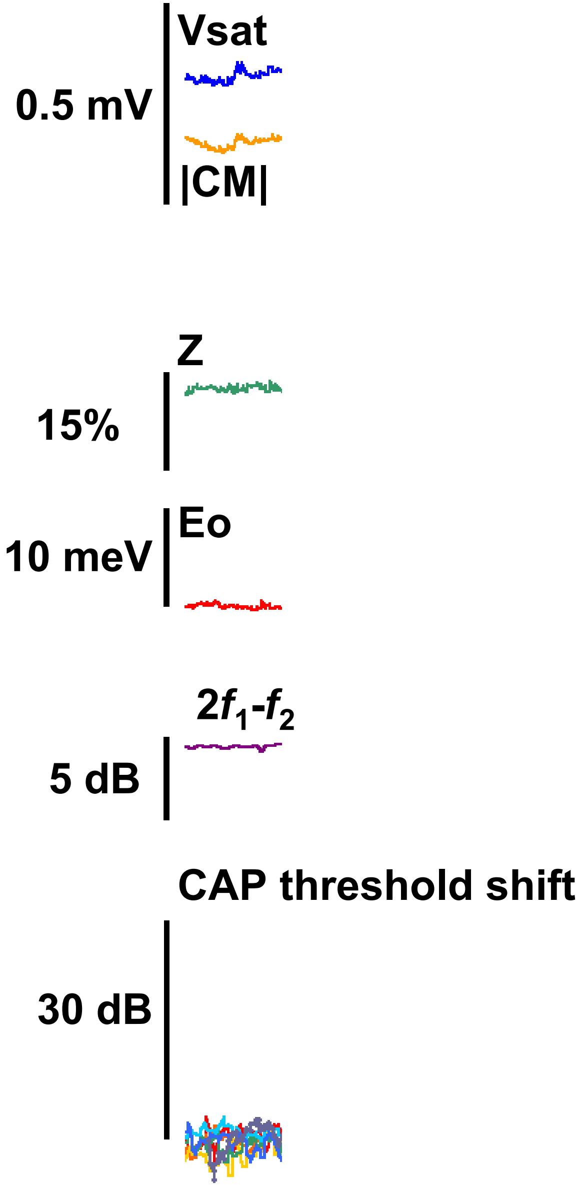
Application of force to the cochlear wall

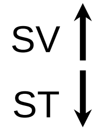
- Force applied to the cochlear wall using a 1 mm diameter insulated thoriated-tungsten rod.
- Static displacement of basilar membrane.



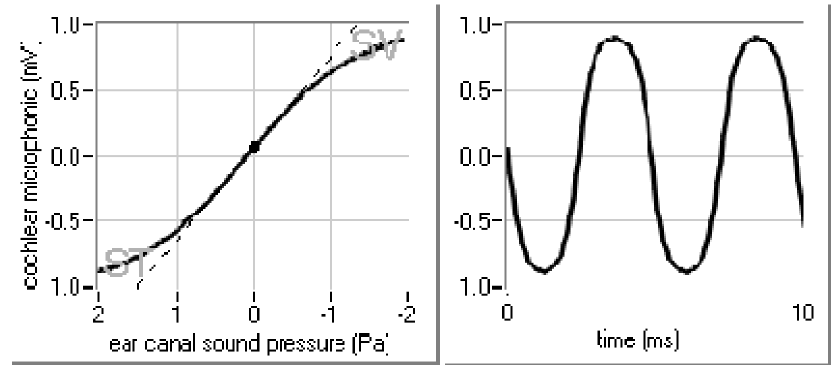


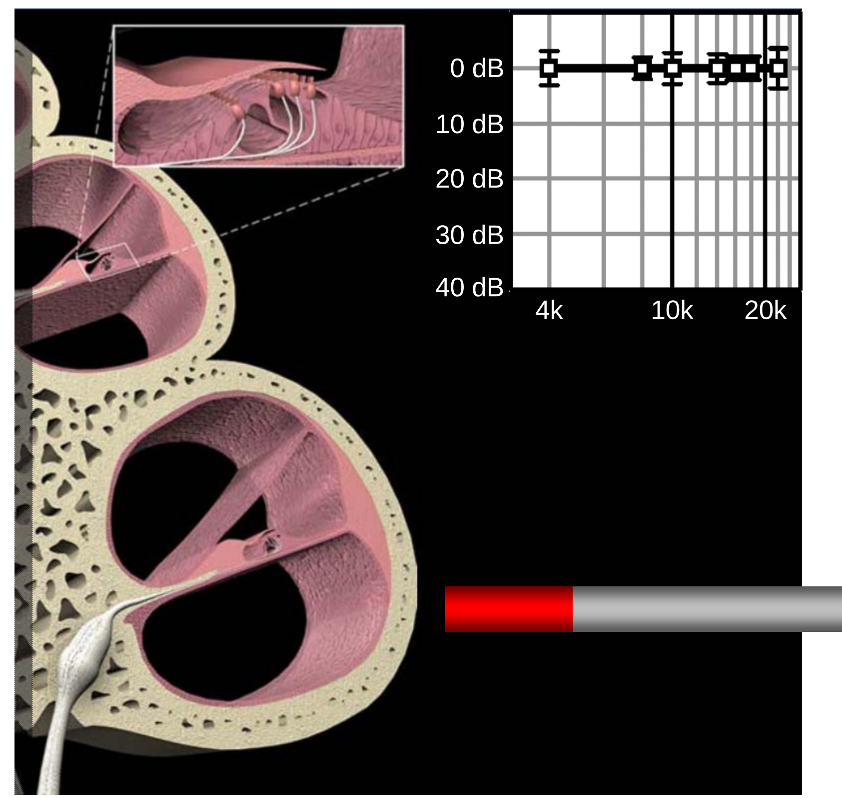






application of force to the cochlear wall





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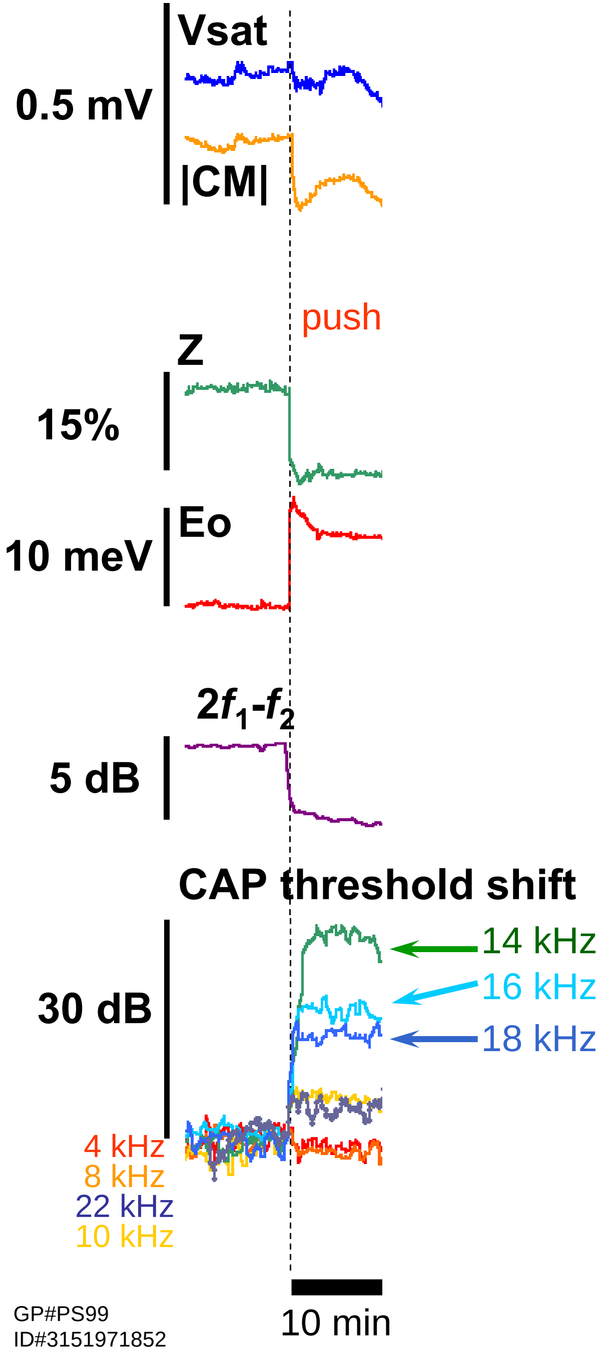
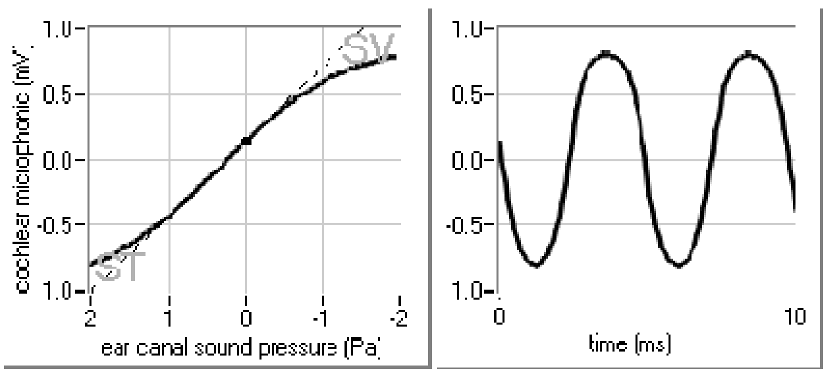
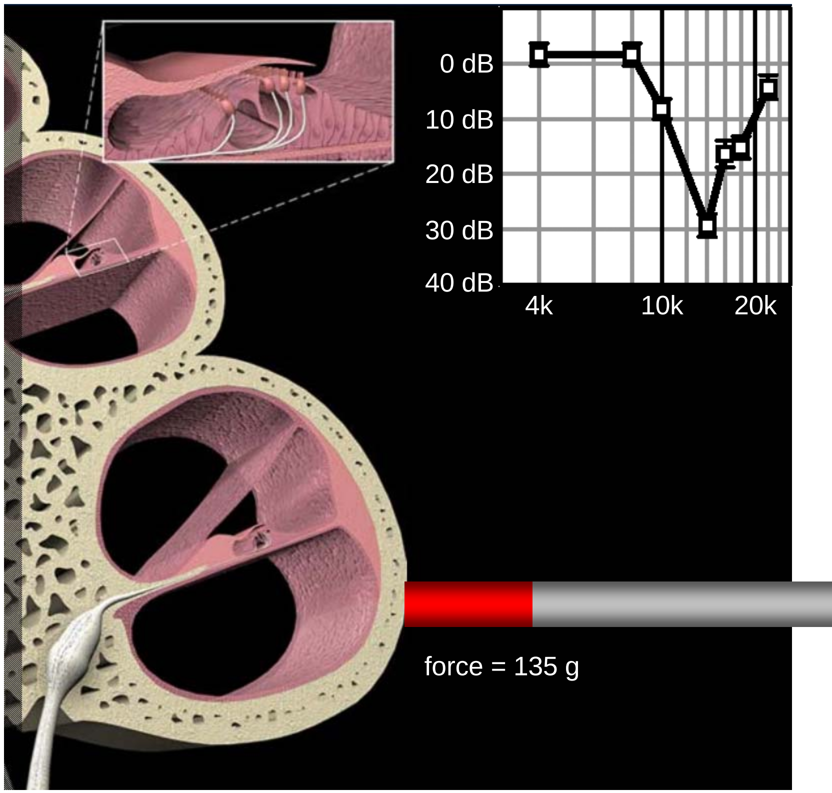
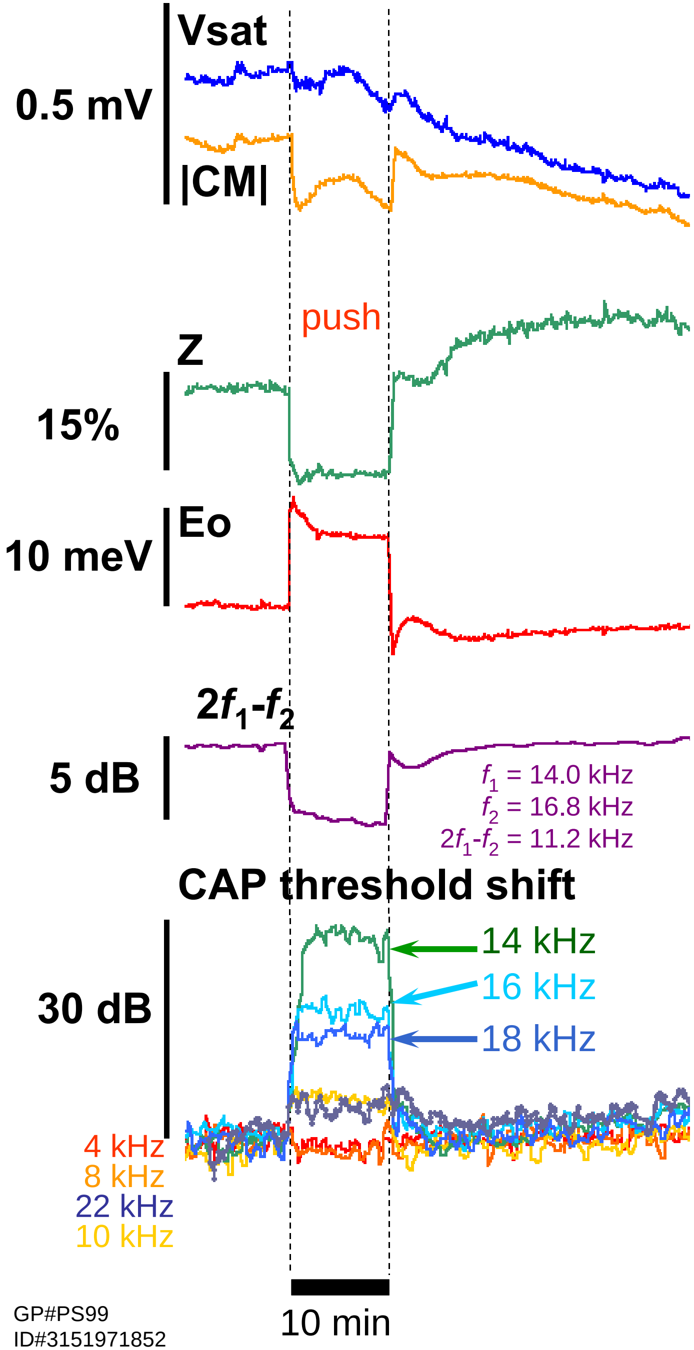
application of force to the cochlear wall









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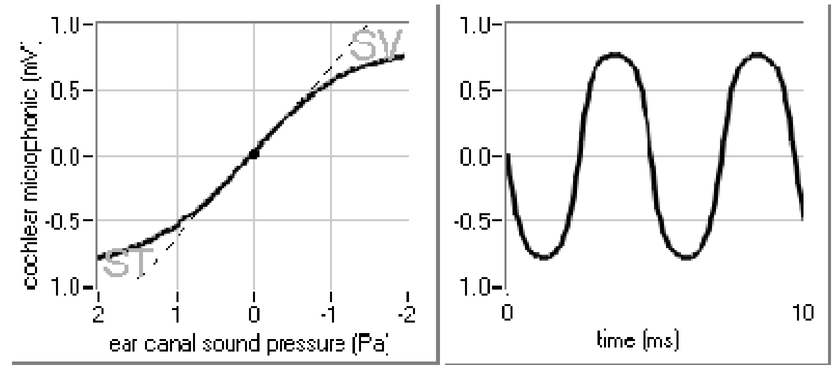
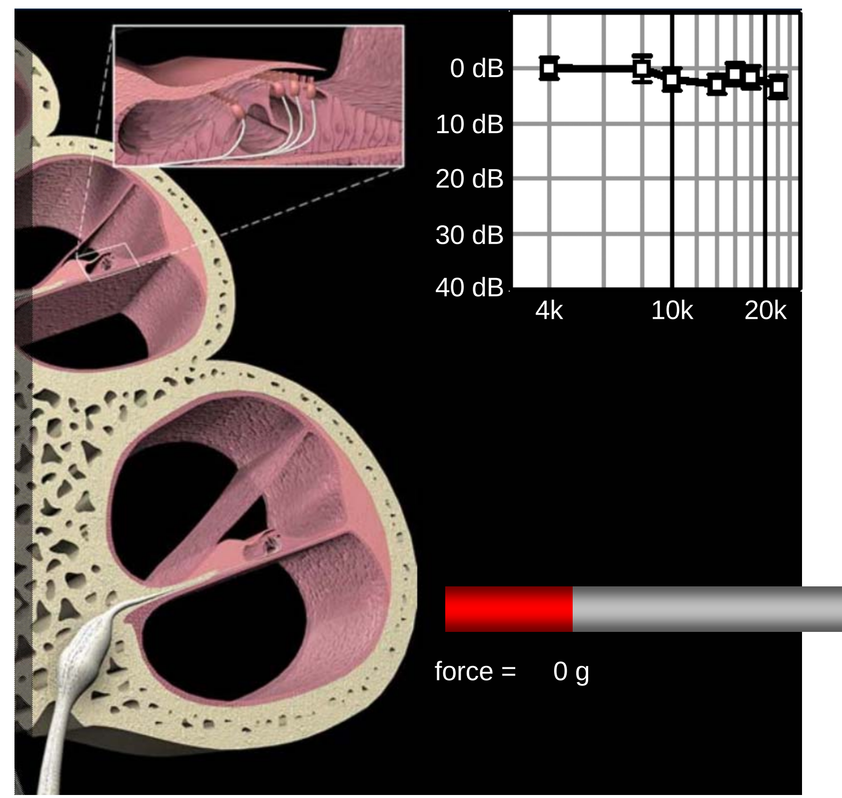
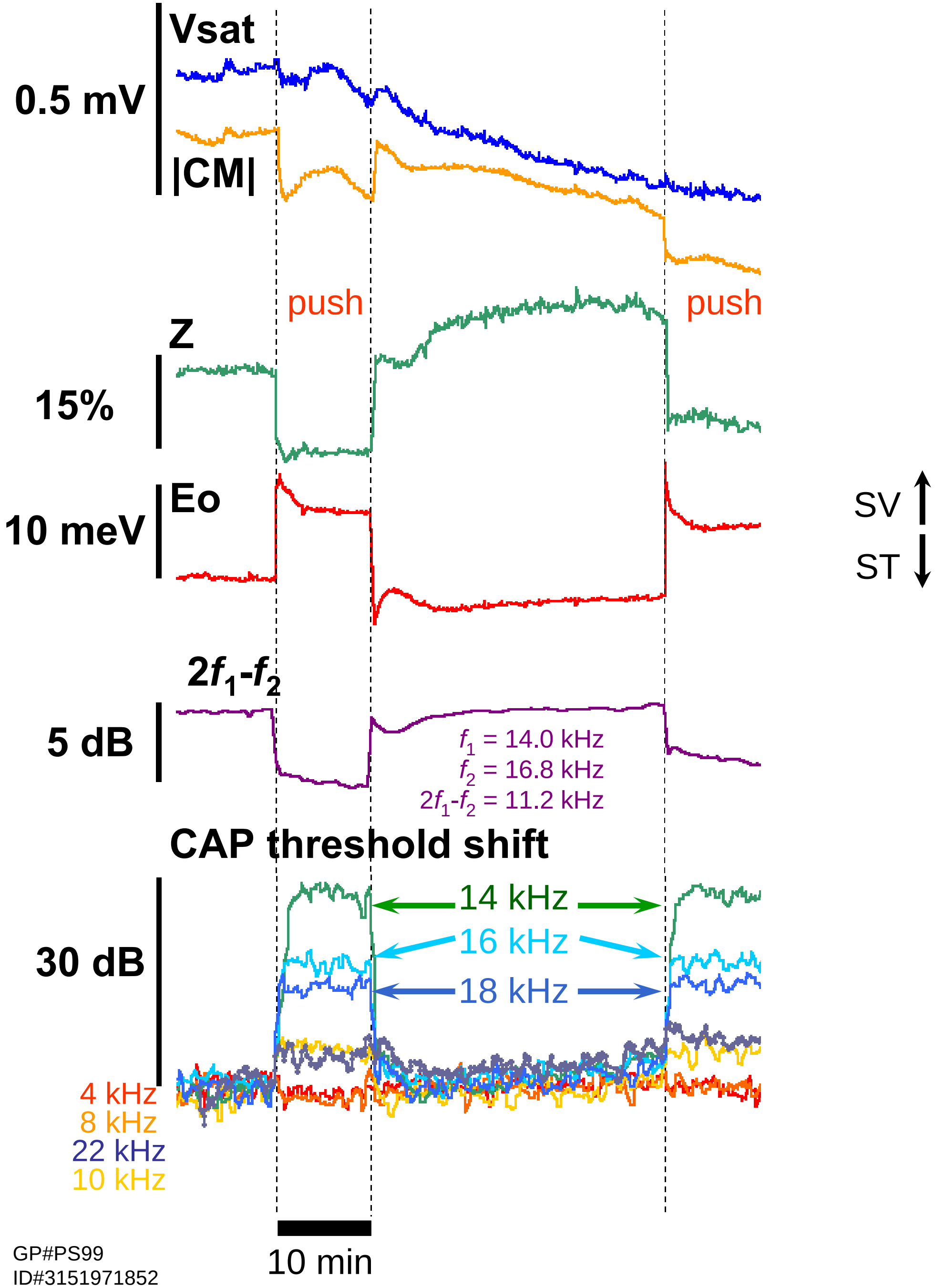


SV ↑

ST ↓





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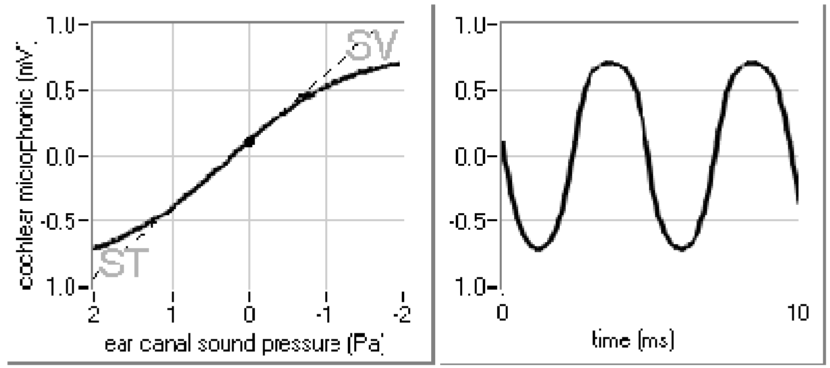

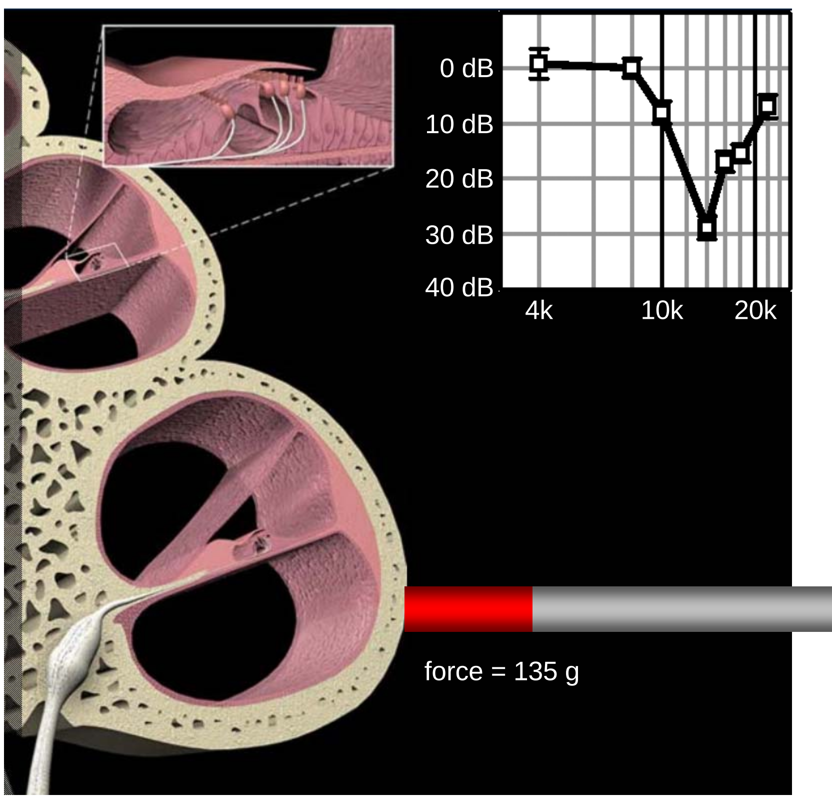

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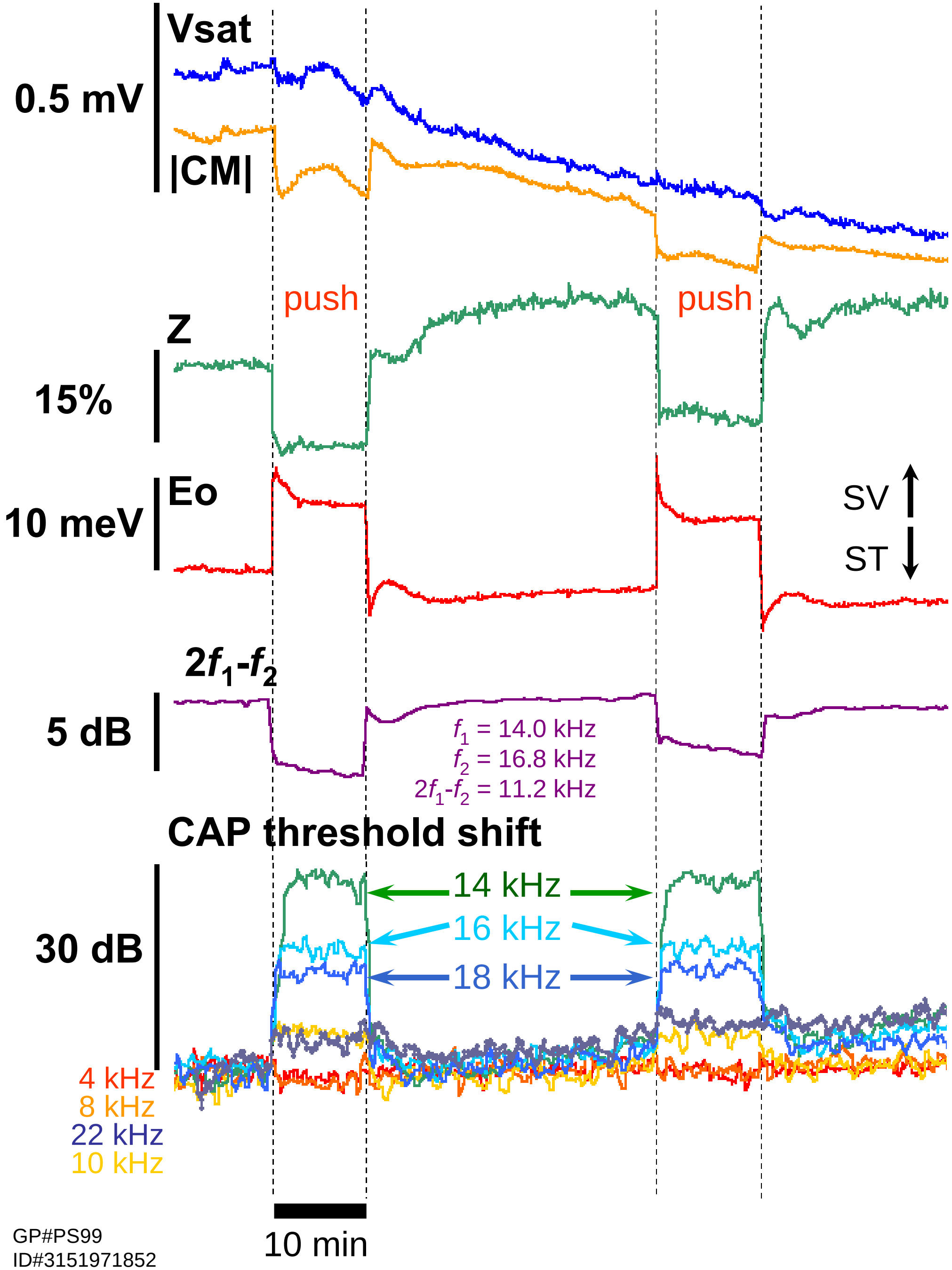

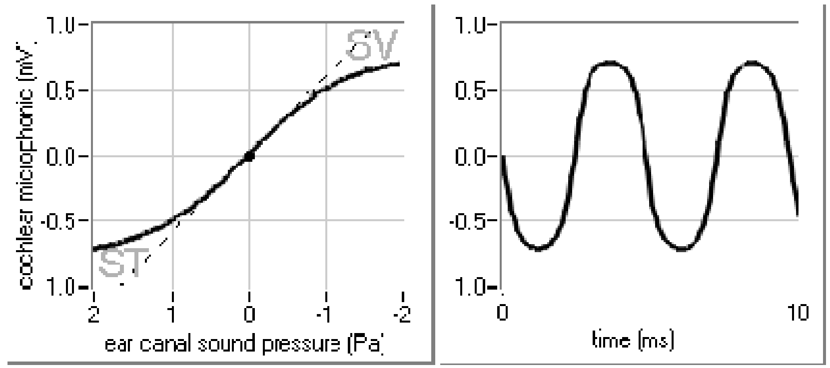

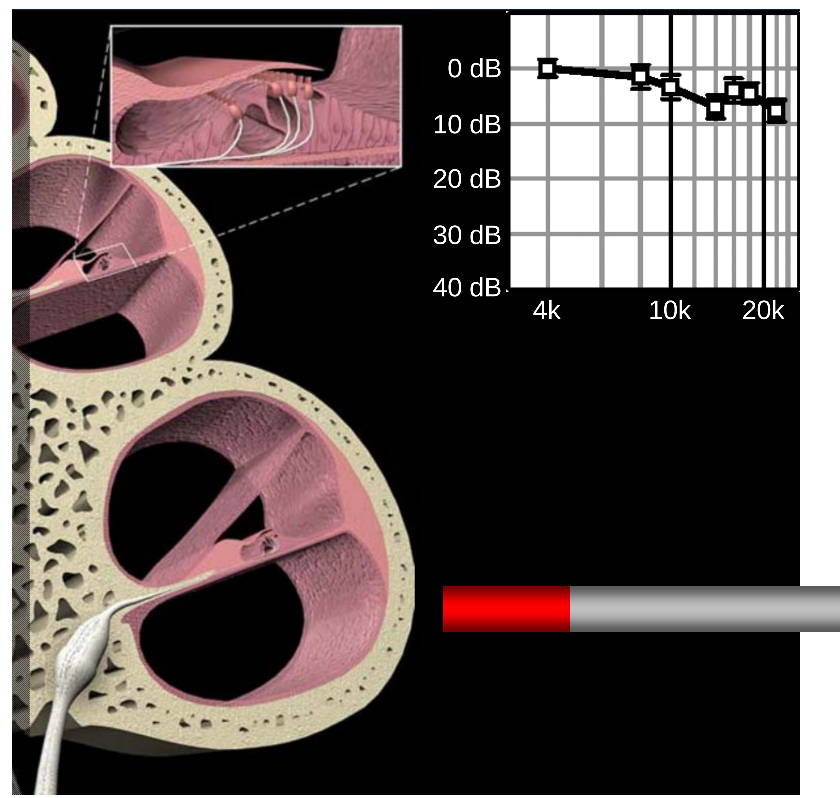

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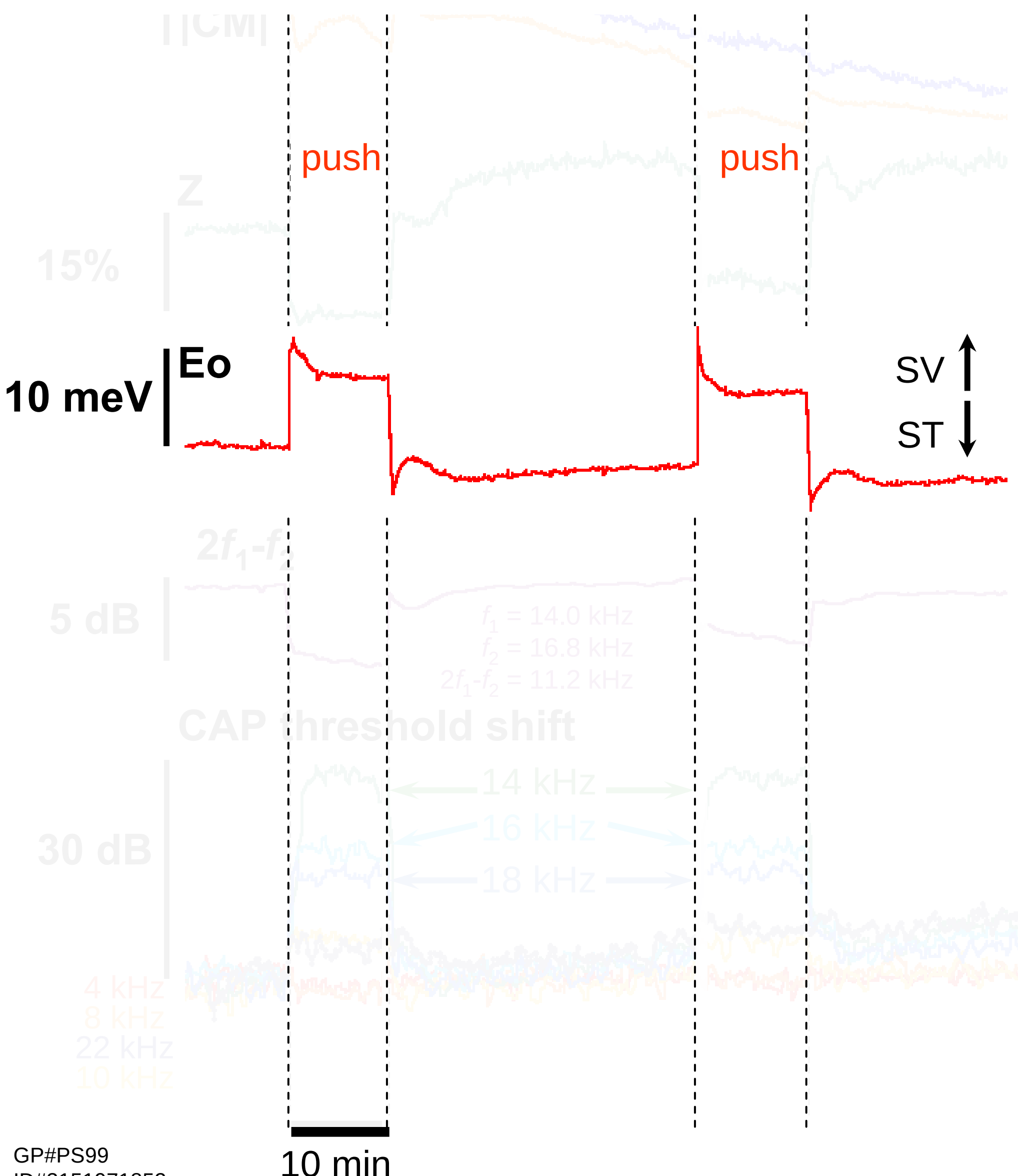

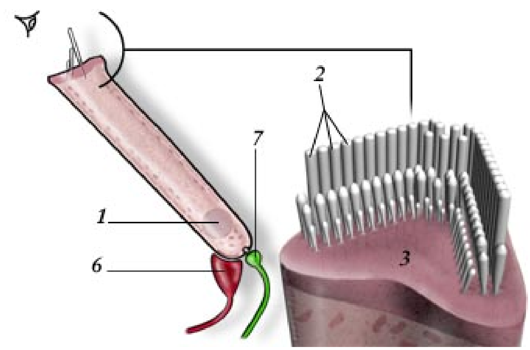

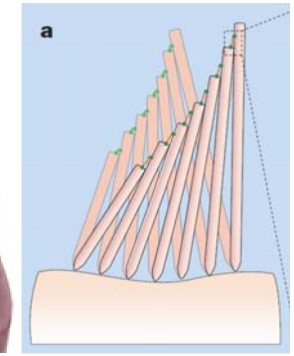

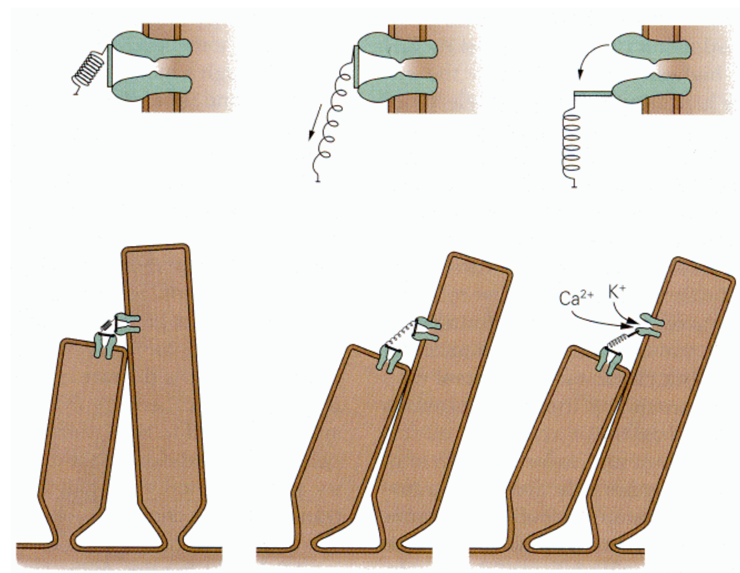

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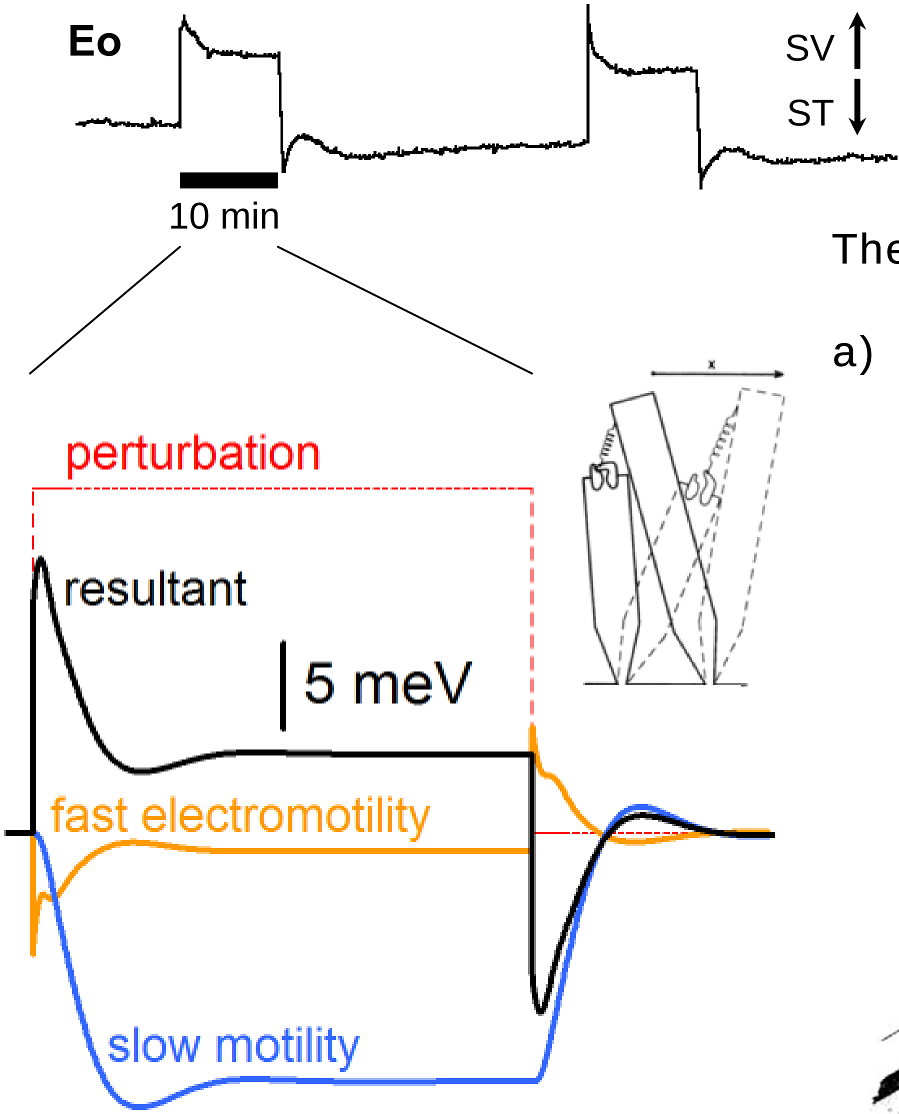
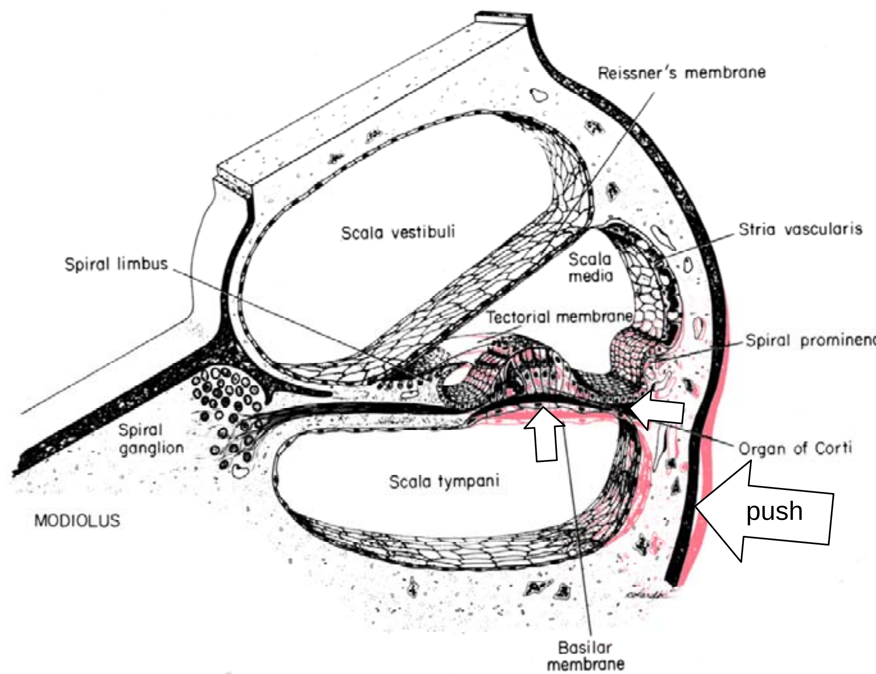
application of force to the cochlear wall

- Results from model -



The resultant operating point is sum of:

a) Perturbation (SV direction)
   i) Movement of the basilar membrane towards SV
   ii) Deflection of stereocilia
   iii) Opening of MET channels



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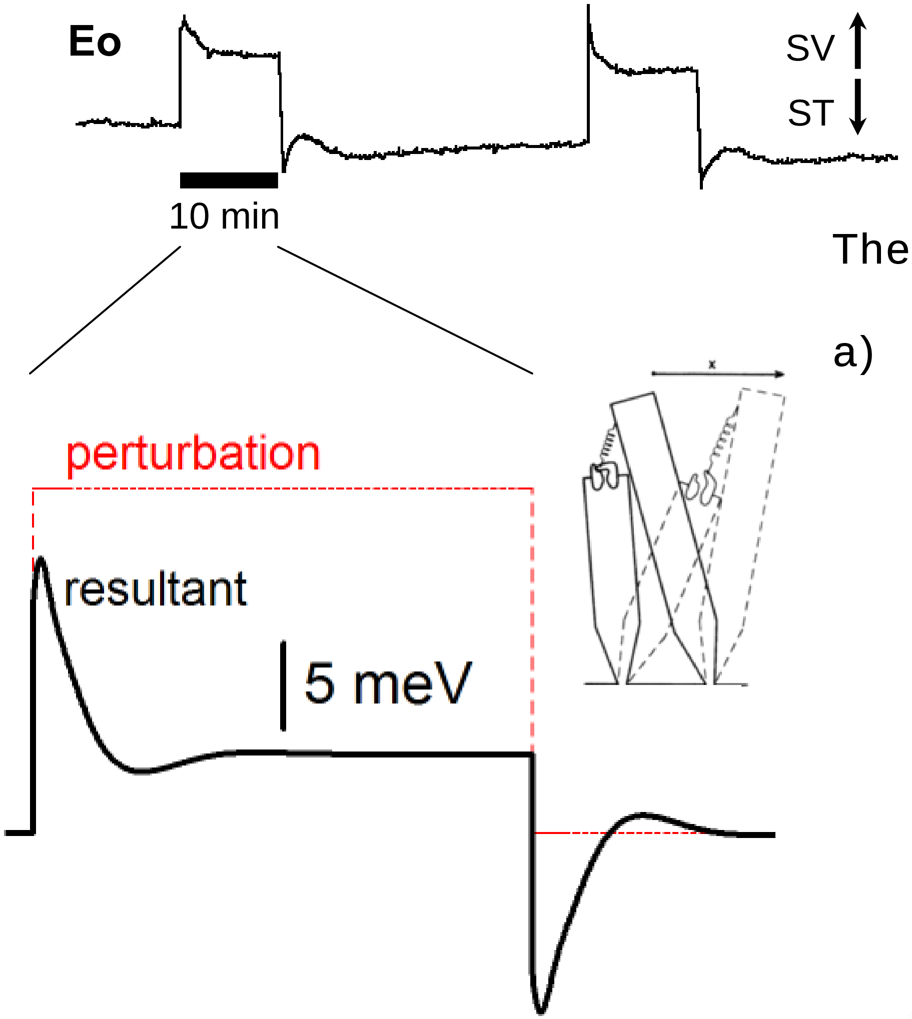
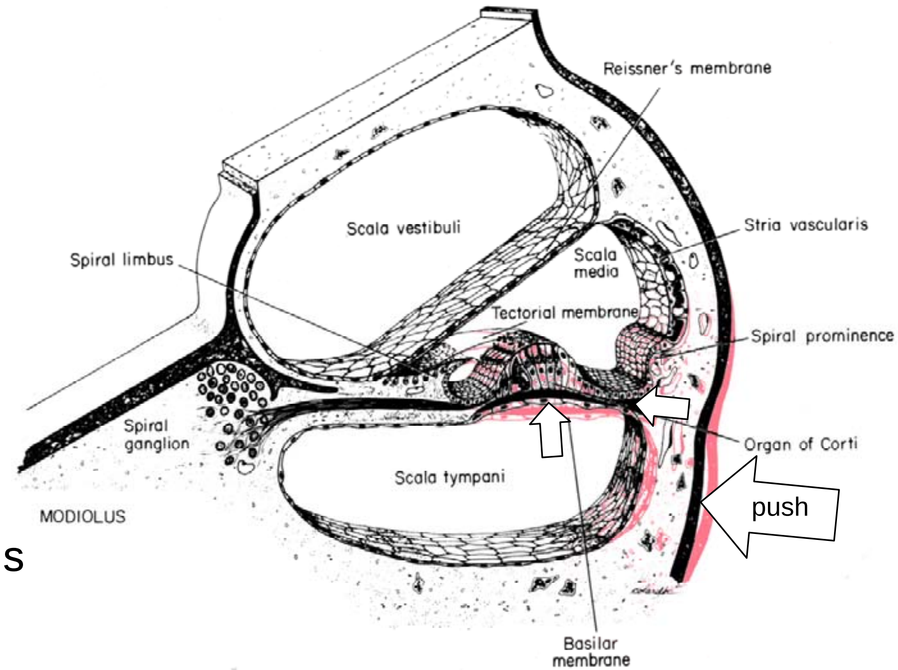




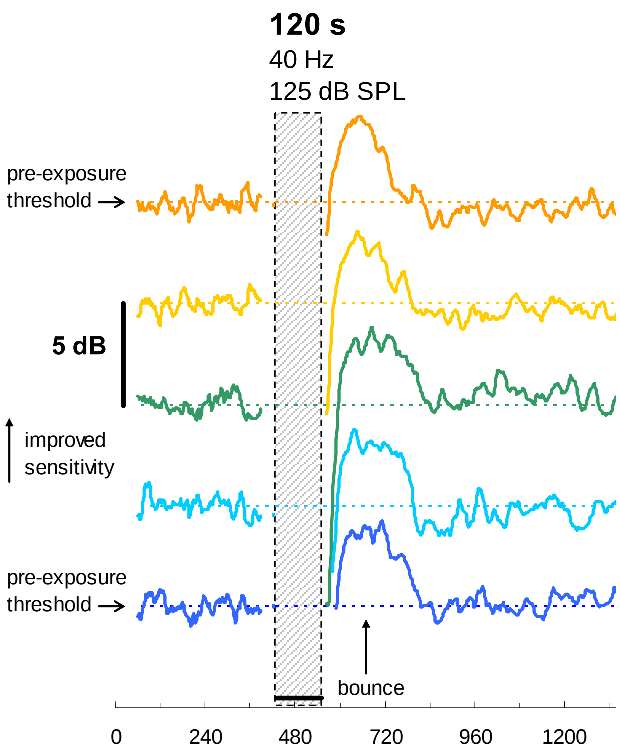
- Calcium mechanism dominates.
- OHC homeostatic regulation mechanisms are able to compensate for much of the perturbation, but not all of it.

Finally...

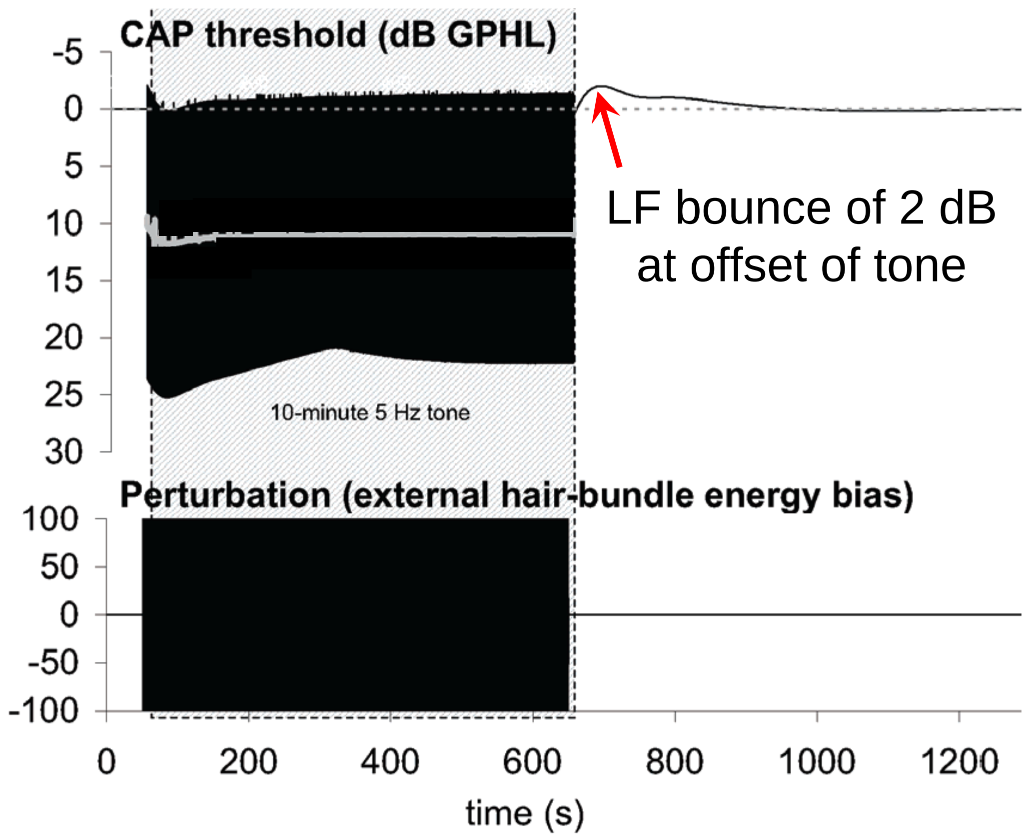
- What is the underlying mechanism for the bounce?

Experimental data:

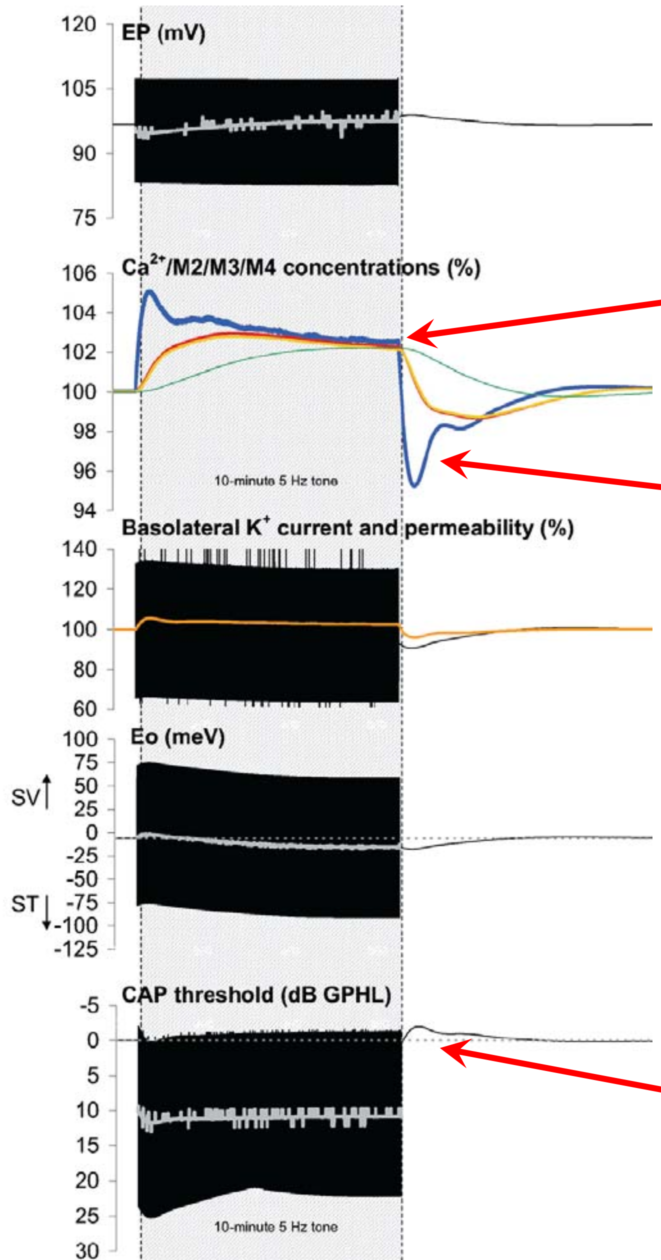
(O'Beirne & Patuzzi, submitted)



Model data:



Modelling of exposure to LF tones (the bounce)



Presence of LF tone causes cytosolic Ca^{2+} to rise, which causes a slow increase in messengers which accelerate Ca^{2+} removal

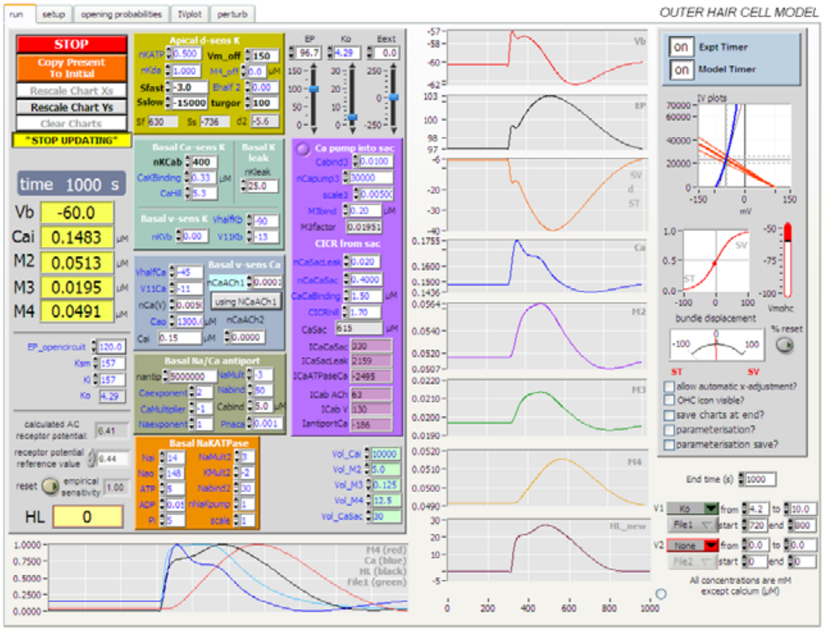
Ca^{2+} entry stops but its removal continues, causing Ca^{2+} levels to fall to 4.5% below control levels

The reduced levels of calcium causes Ca^{2+}-sensitive channels (SK type) in the OHC membrane to close, increasing basolateral resistance, and increasing the receptor potential that drives the active process (V=IR)

Increased sensitivity at offset of tone as Ca^{2+} falls below resting levels

Factors affecting oscillation amplitude

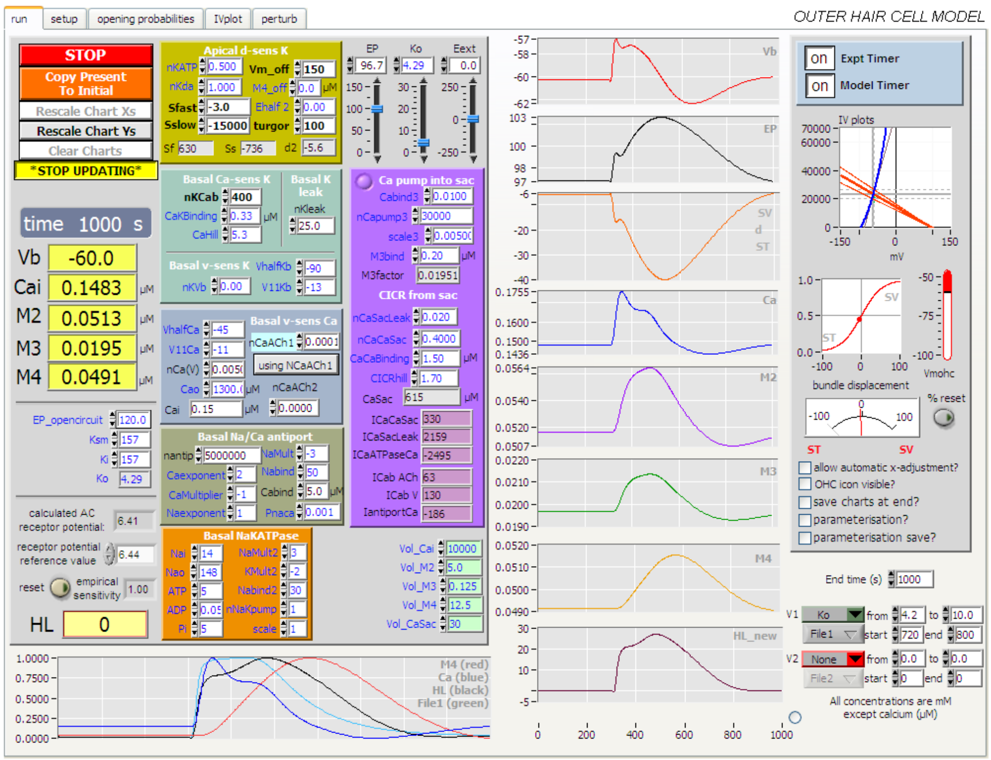
- Degree of damping of slow oscillations dependent on relative Ca^{2+} fluxes through voltage- and ACh-sensitive Ca^{2+} channels.
  - Ca^{2+} influx through ACh-sensitive channels on hyperpolarization phase reinforces membrane potential oscillations
  - Ca^{2+} influx through L-type v-sensitive channels on depolarization phase *quenches* membrane potential oscillations



Summary

- Known outer hair cell mechanisms are capable of regulating both membrane potential and MET operating point with great accuracy.
- First model to incorporate both the ion transport and mechanical properties of OHCs into a single framework
- Valuable step in understanding how perturbations of the ionic and electrical environment of the cochlea produce hearing loss and tinnitus.
- “Standard set” of model parameters capable of reproducing a number of key features of experimental data, but several key results the model cannot replicate.
- Modelling continuing using two functional pools of cytosolic Ca^{2+}, which decouples hair bundle angle and basolateral permeability, providing a better fit to these data.

Acknowledgements



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