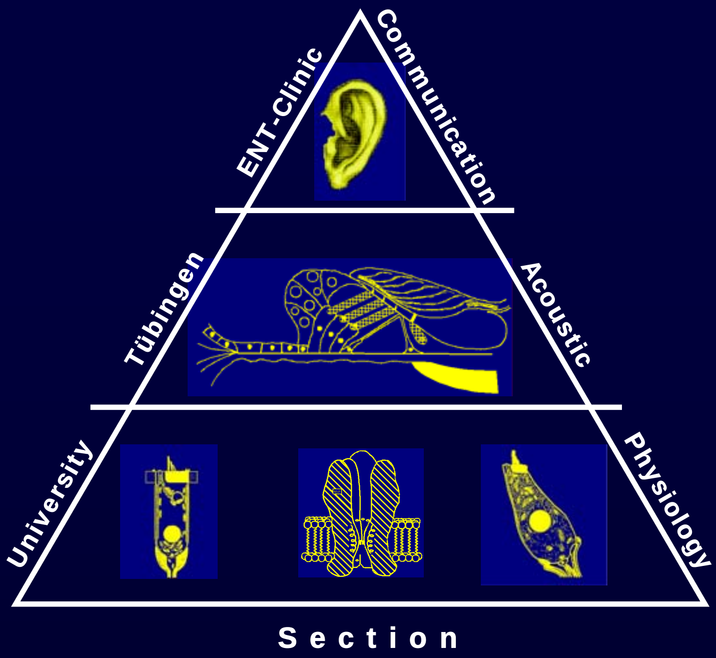
Sound Processing in the Cochlea

Anthony W. Gummer©



Sound Processing

Cochlea

A.W. Gummer

Tübingen Hearing Research Centre

Department Otolaryngology

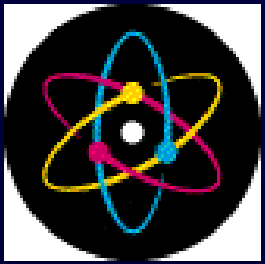
- *160 million people in Europe suffer from sensorineural hearing loss*
- *85% without causal therapy*

- *Understand cochlear function and dysfunction*
- *Develop new differential diagnostic techniques and causal therapies*

Responsible for sensorineural hearing loss

- *Malfunction of the cochlear amplifier*

Cochlear amplifier is responsible for

- ***Sensitivity***  **1Å at threshold**
- ***Frequency selectivity*** $\frac{\textbf{1 Hz}}{\textbf{1000 Hz}}$
- ***Dynamic range*** **x10^6 *re*. threshold**

decibel:

Cochlear amplifier is responsible for

- *Sensitivity* **1Å at threshold**
- *Frequency selectivity* $\frac{\textbf{1 Hz}}{\textbf{1000 Hz}}$
- *Dynamic range* **x10^6 *re*. threshold = 120 dB**

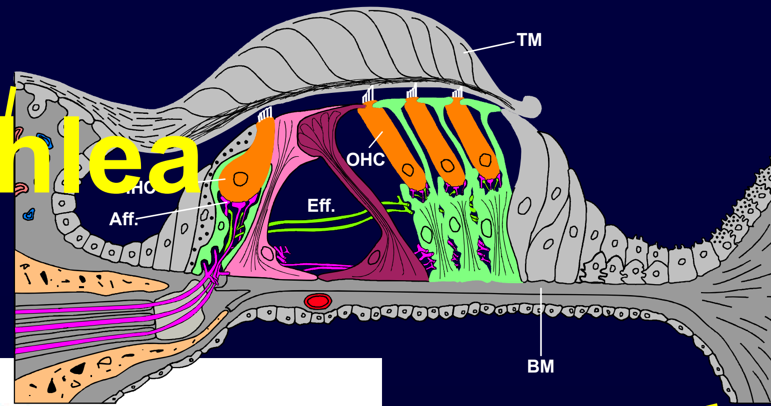
decibel: dB = 20 $\log_{10}$ (P / P_{ref})

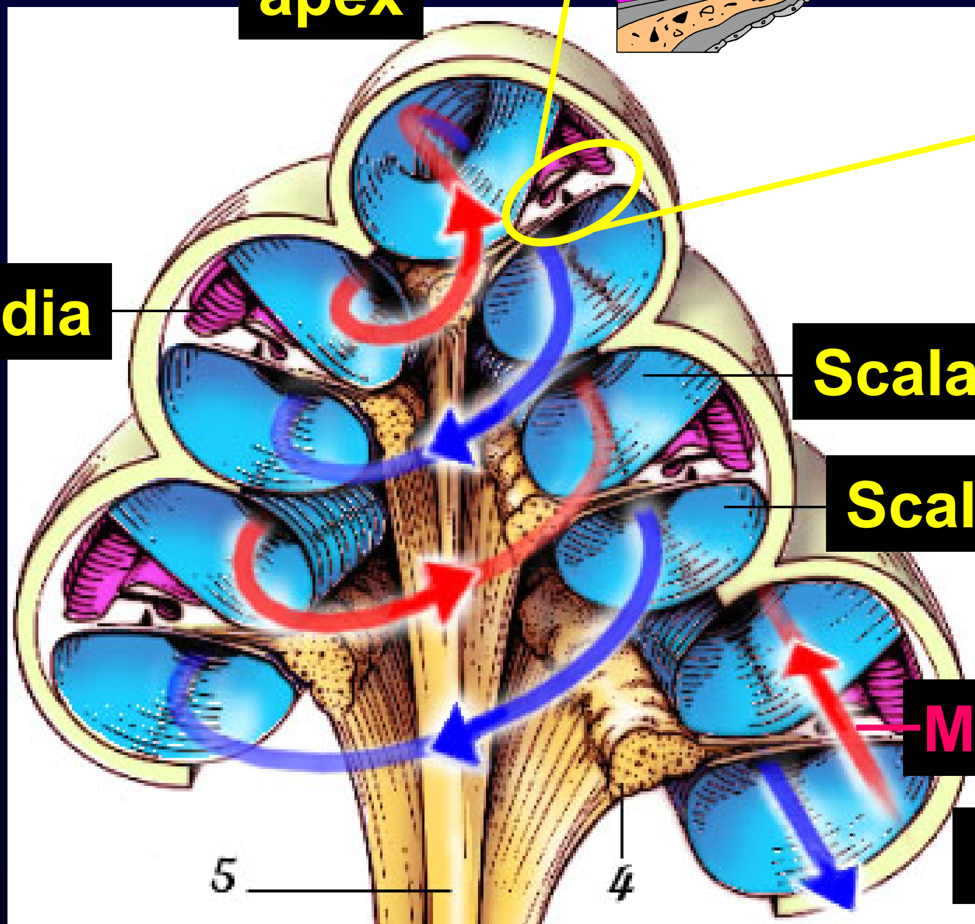
P_{ref} = 20 μPa ≈ Pressure at threshold

0 dB SPL

Amplifier required

The cochlea



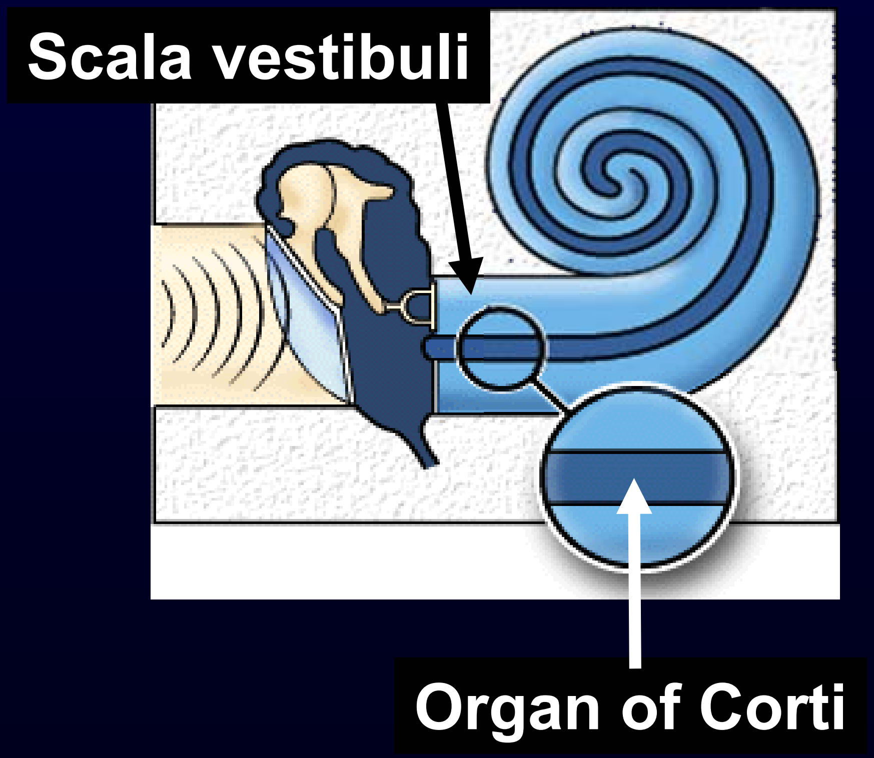


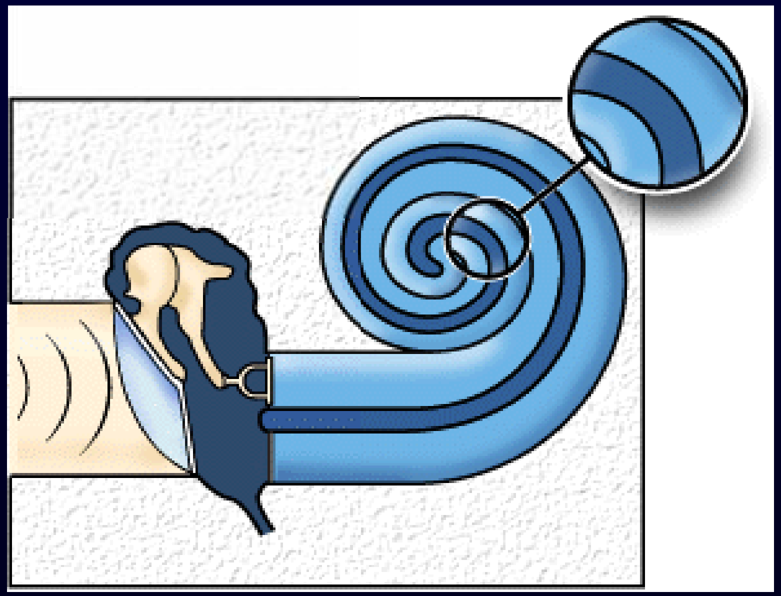
INSERM

Cochlea is tonotopically organized

High-frequency **base**

Low-frequency **apex**



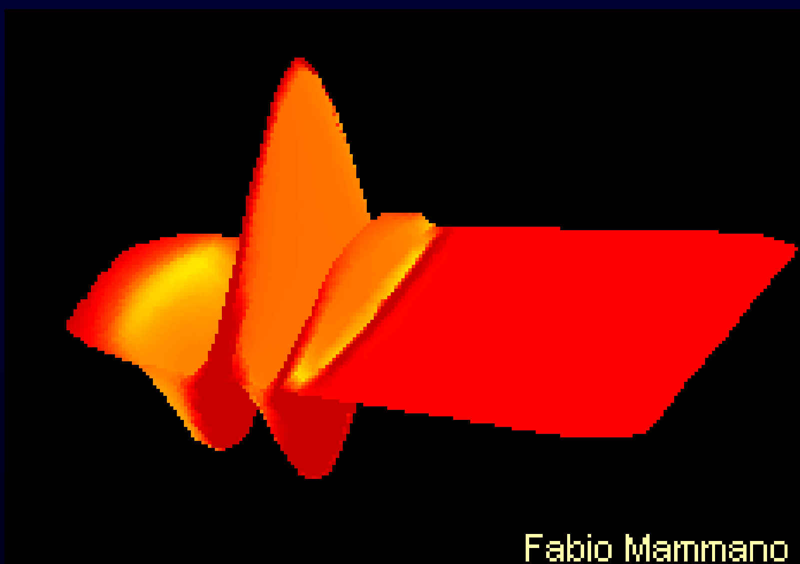


INSERM

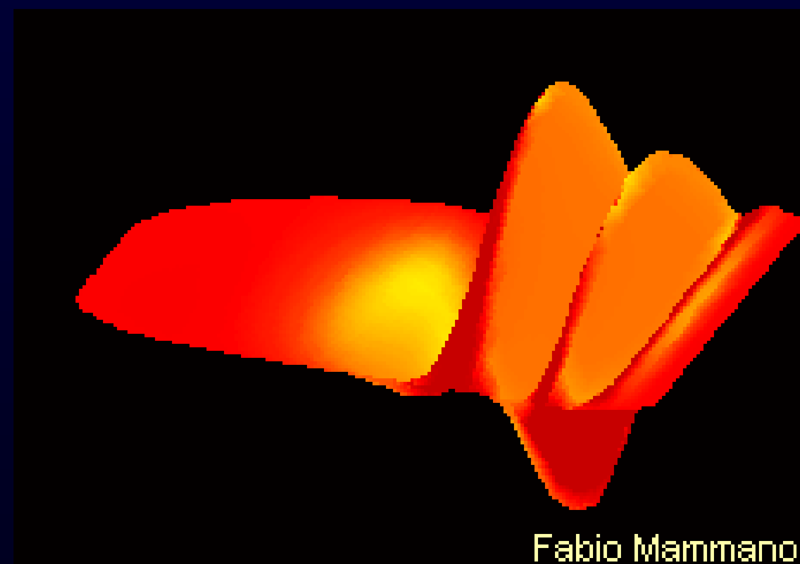
Travelling wave on basilar membrane

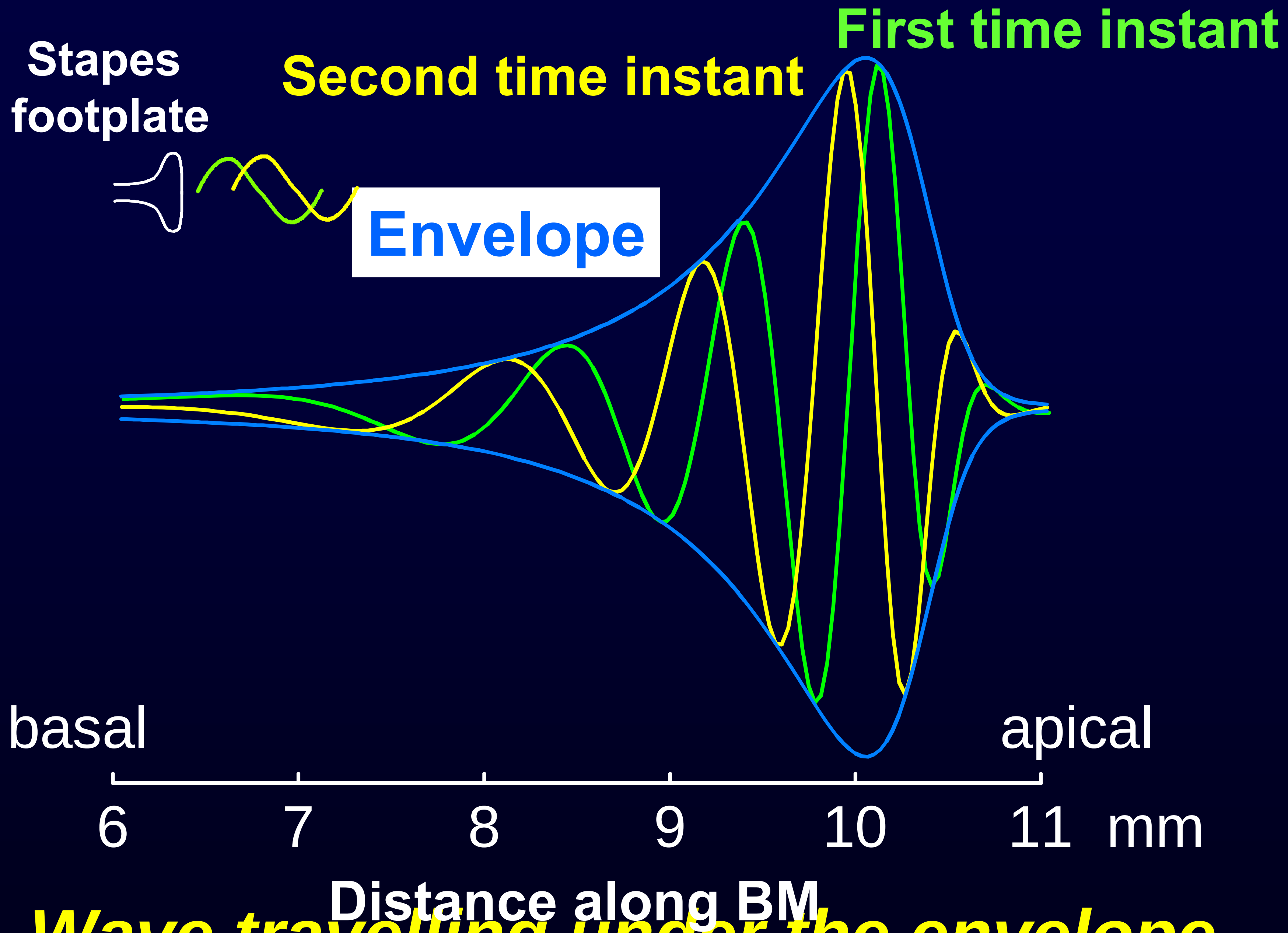
Tonotopy due to spatial change of stiffness
width

4000 Hz

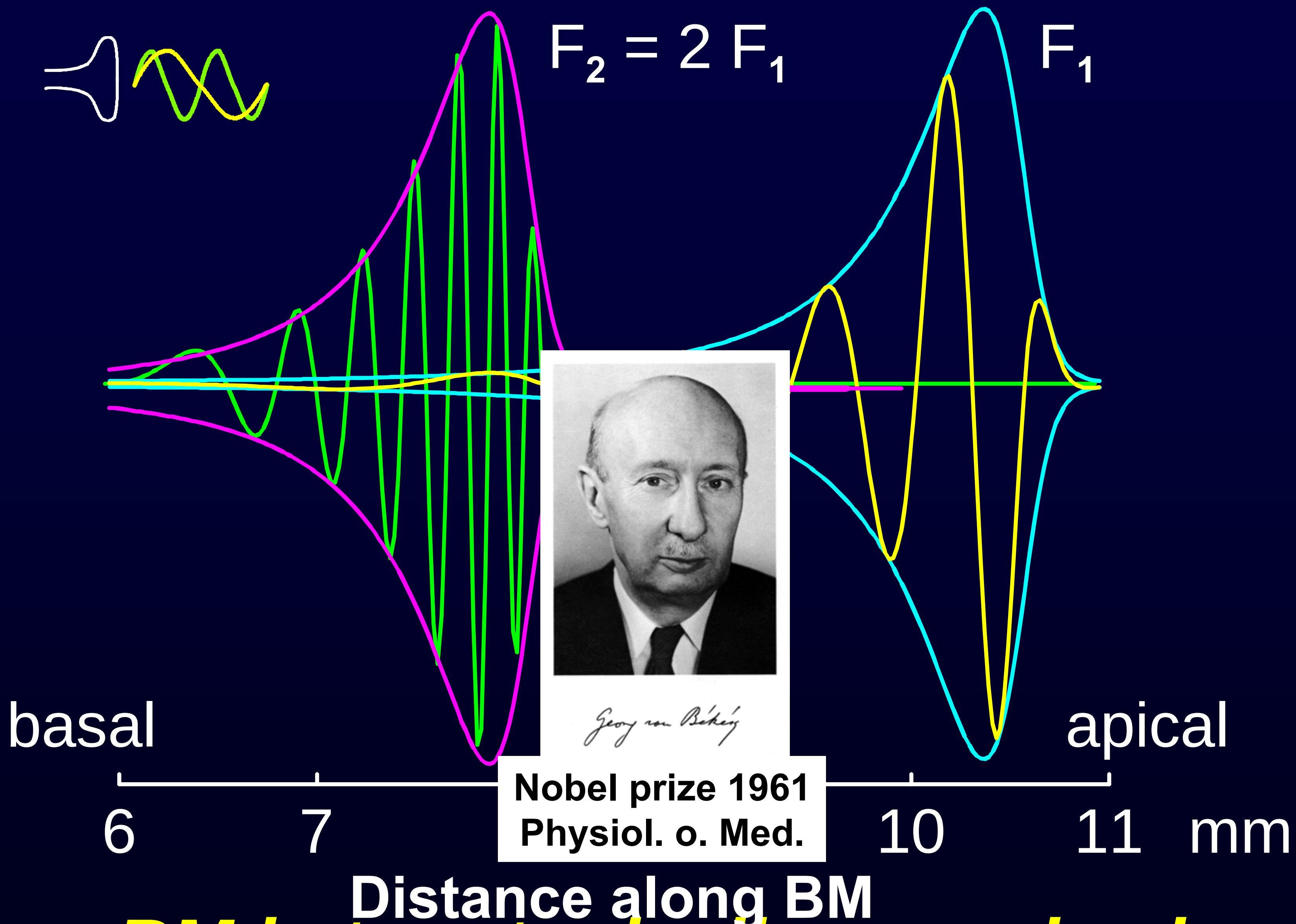


400 Hz



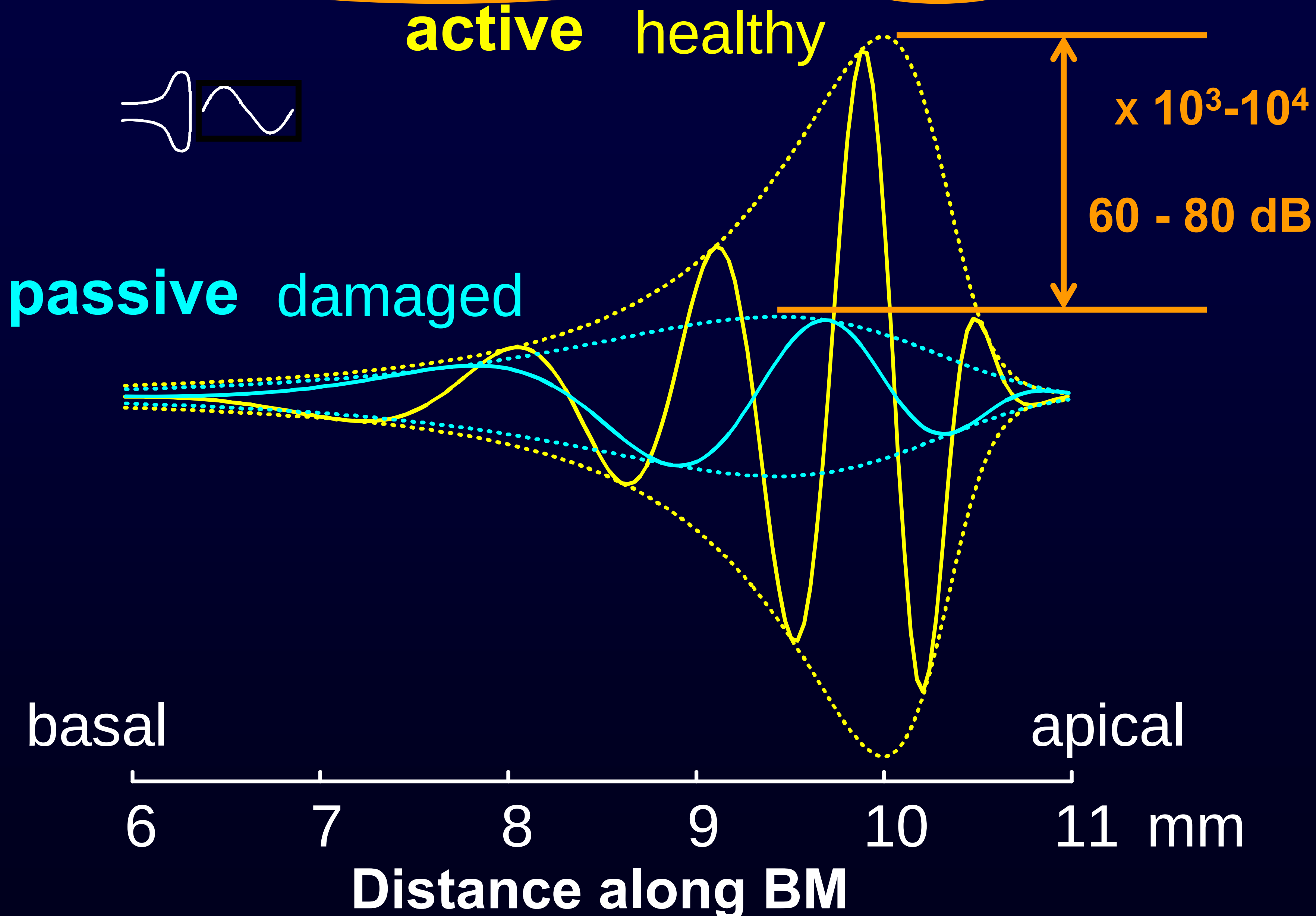


Wave travelling under the envelope

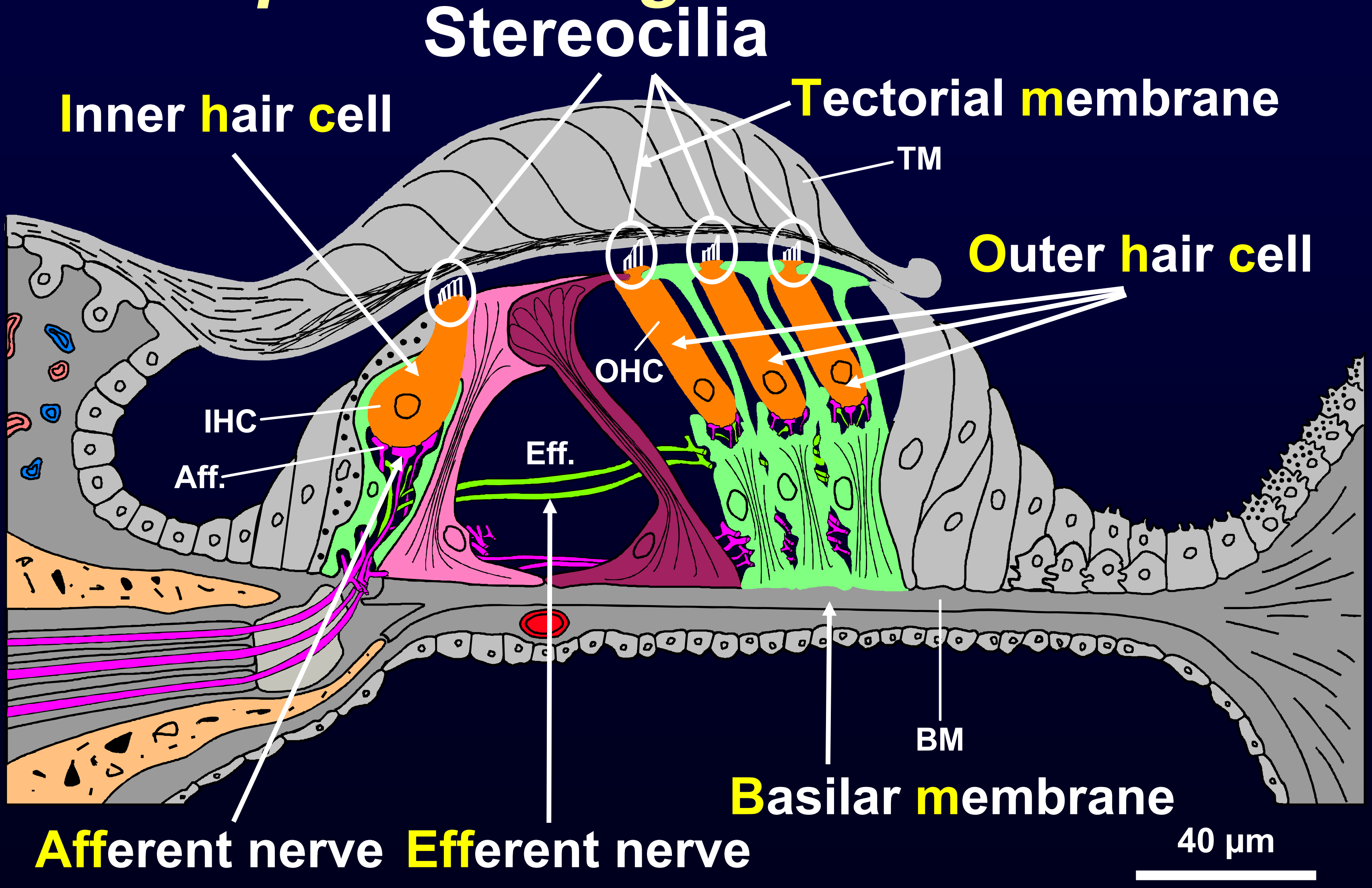


BM is tonotopically organized

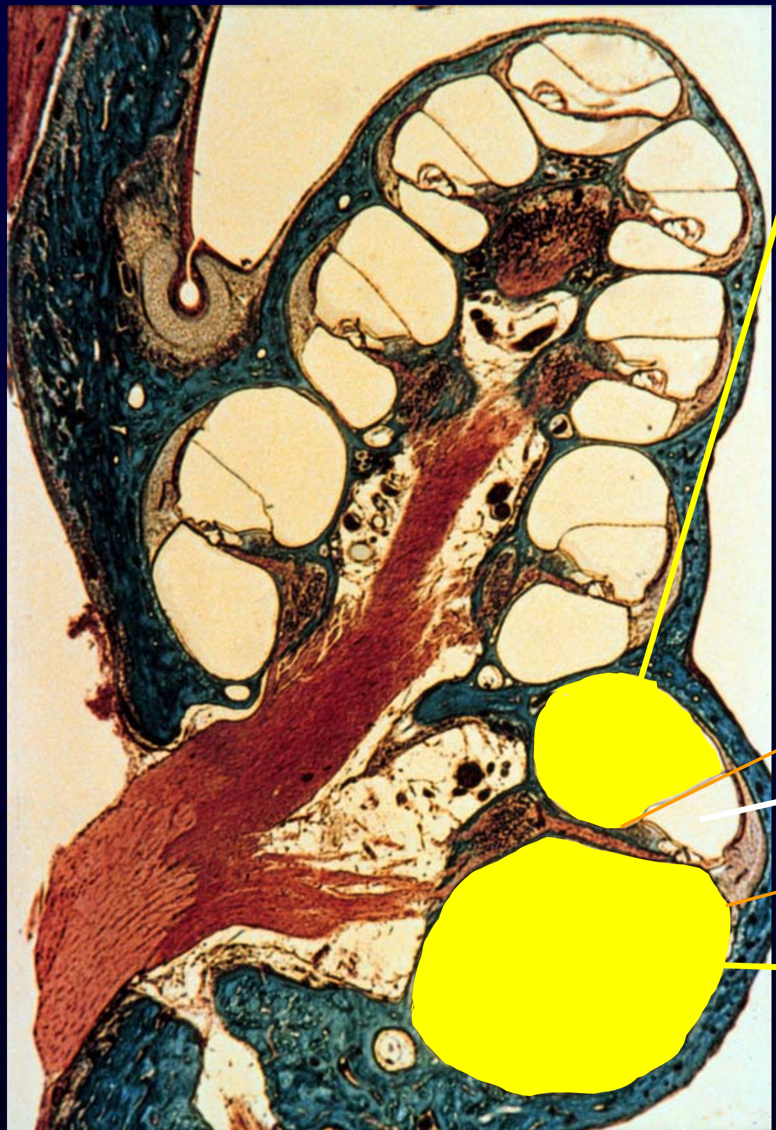
? *Amplification is active* ?

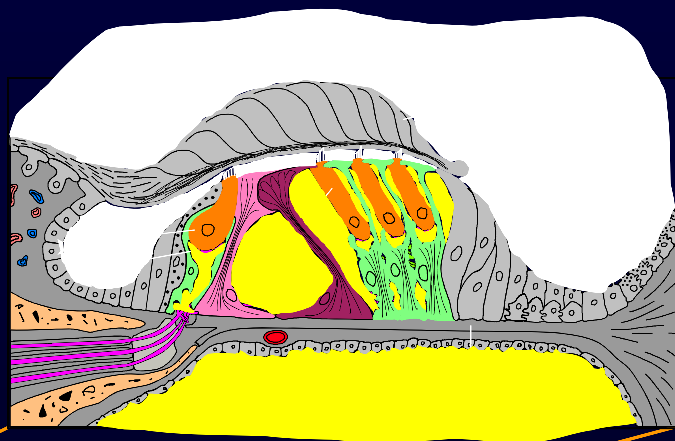


Organ of Corti
3200 repeats along the human cochlea



Hair cells have two extracellular ionic surroundings





Scala vestibuli perilymph

$[K^+]$ = 4 mM $[Na^+]$ = 140 mM

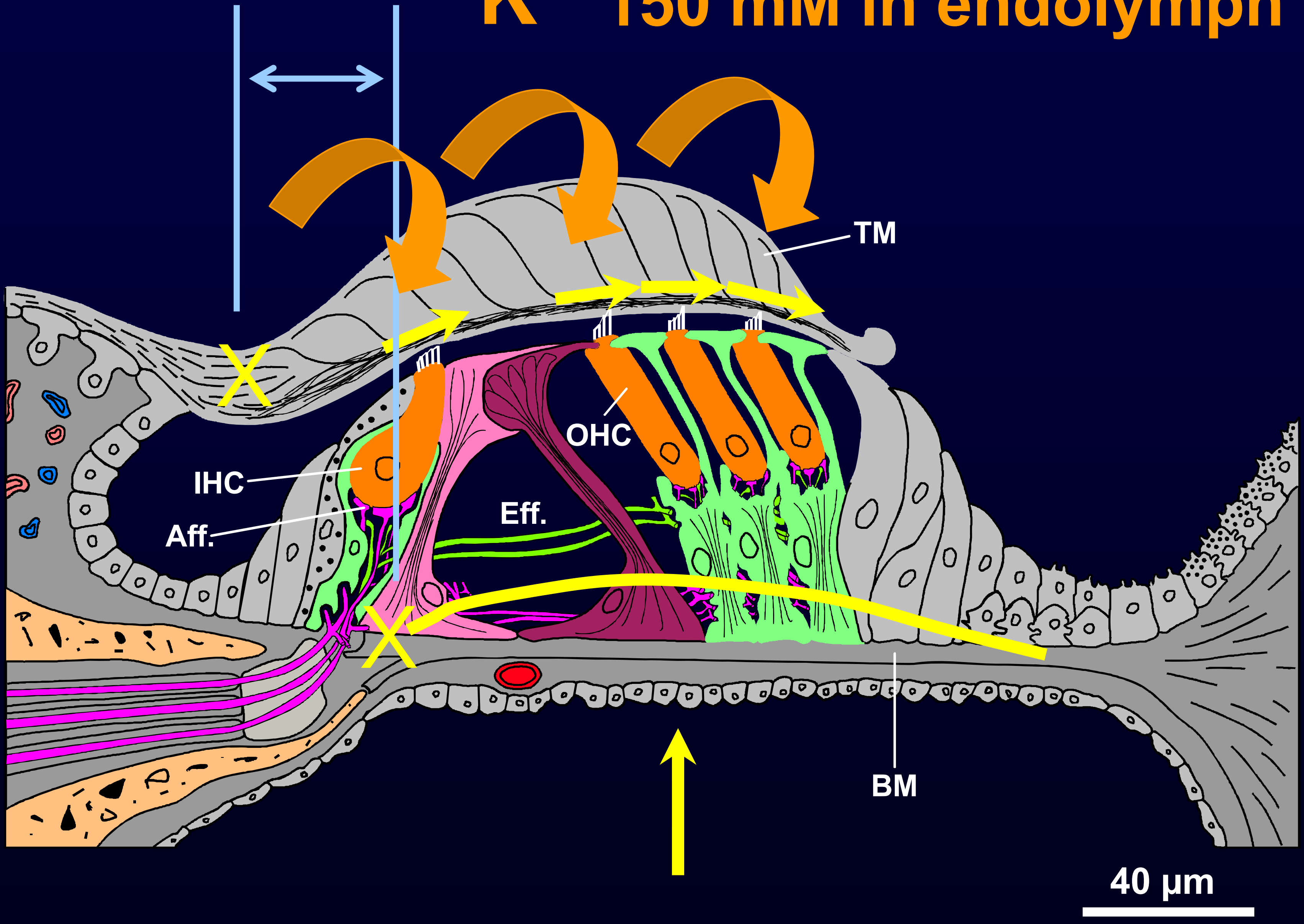
Scala media endolymph

$[K^+]$ = 150 mM $[Na^+]$ = 13 mM

Scala tympani perilymph

$[K^+]$ = 4 mM $[Na^+]$ = 140 mM

K^+ 150 mM in endolymph



Mechanoelectrical transduction

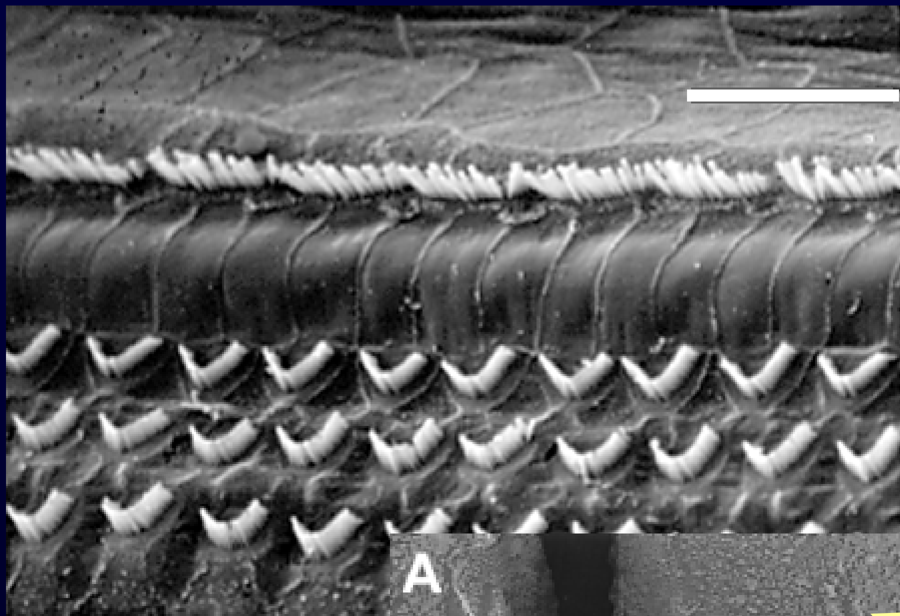
in the

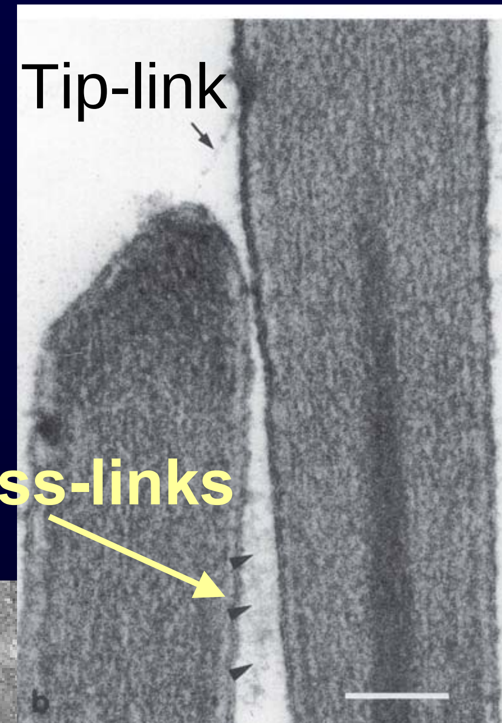
stereocilia

Stereocilia and tip-links

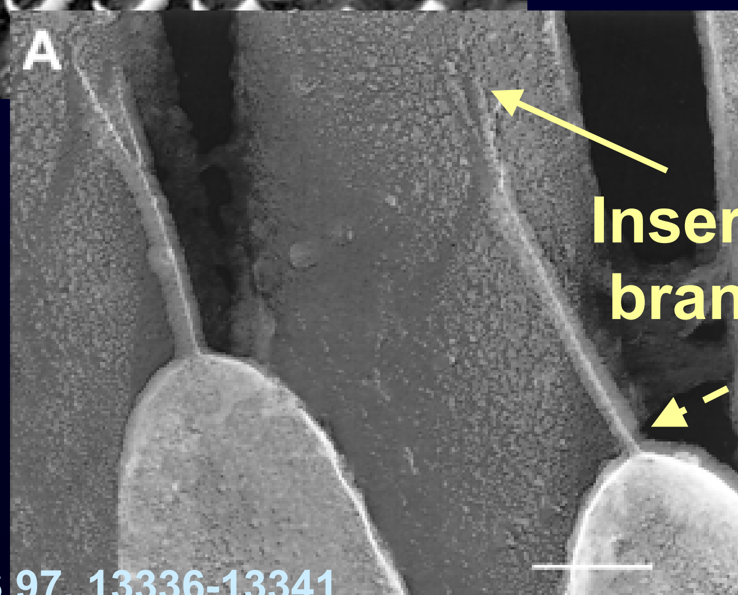
IHC

OHC





Cross-links



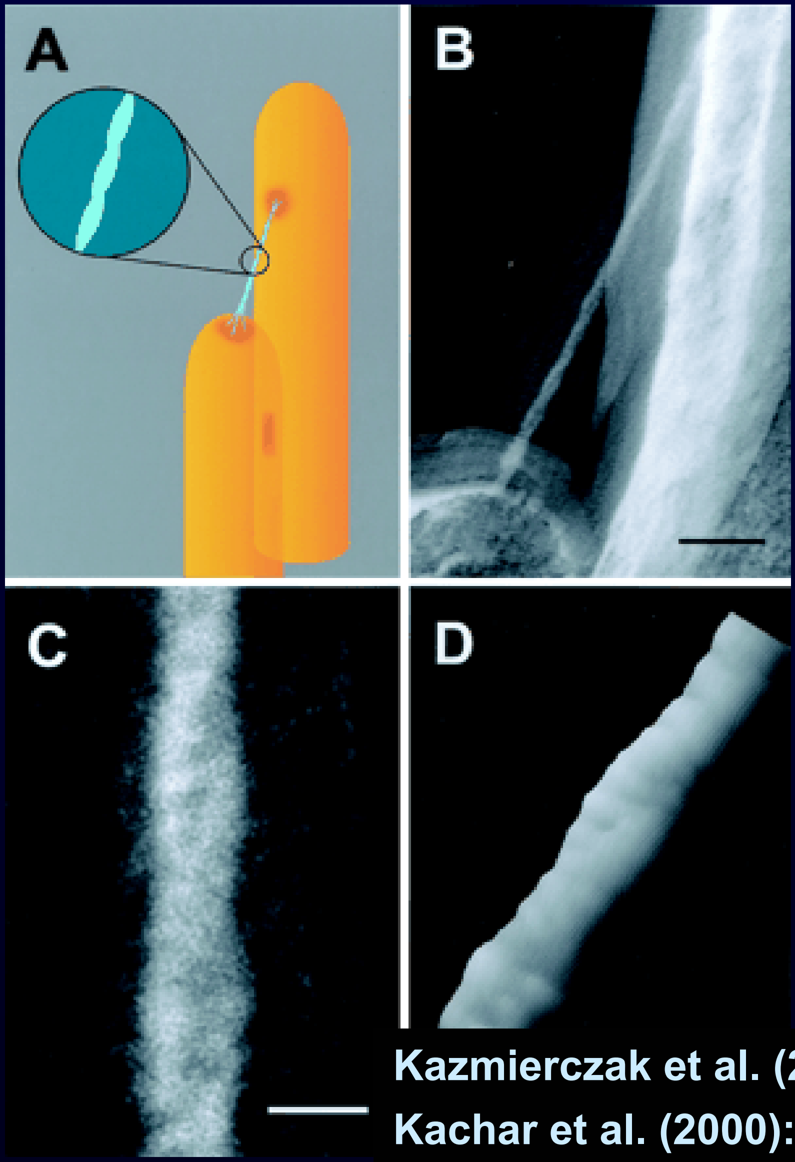
Insertion points
branched

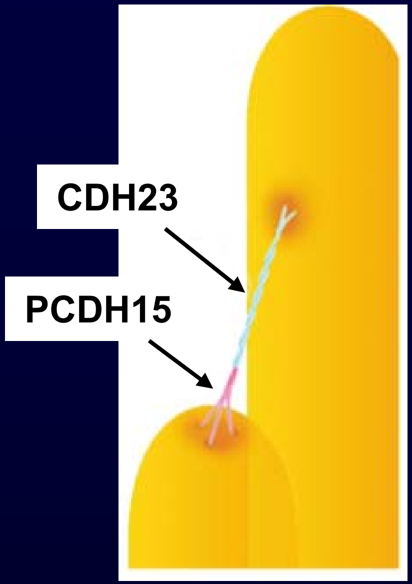
8 - 10 nm

elastic ?

Kachar et al. (2000): PNAS 97, 13336-13341

Cadherin 23 and protocadherin 15 form the tip link





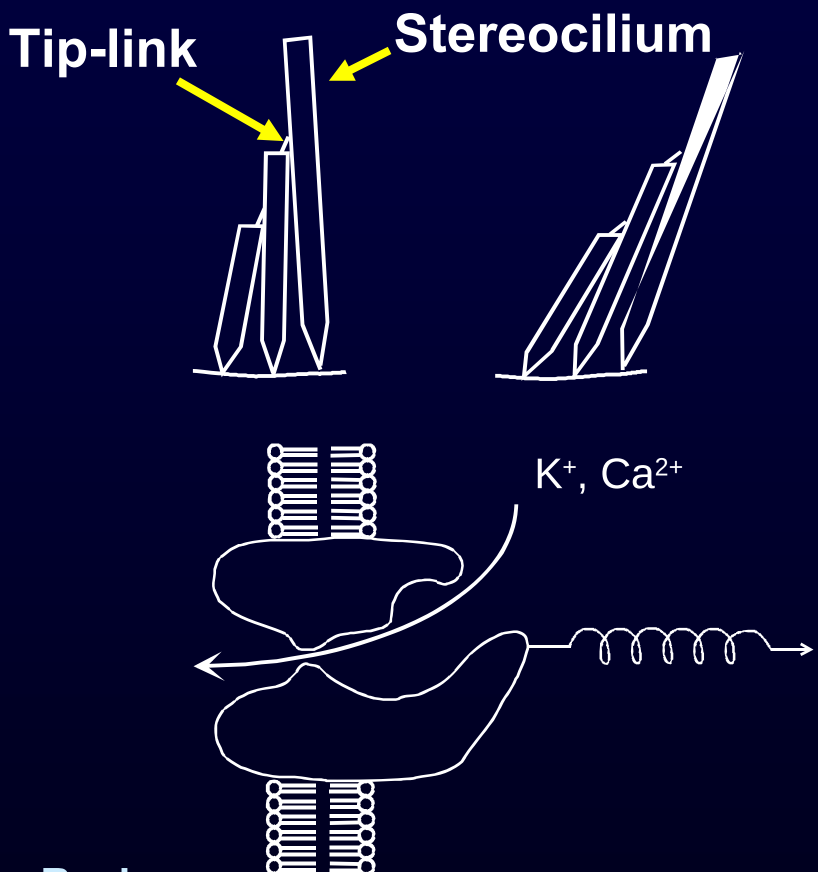
very stiff

~~elastic~~ ?

Kazmierczak et al. (2007): Nature 449, 87-92

Kachar et al. (2000): PNAS 97, 13336-13341

Mechanoelectrical transduction



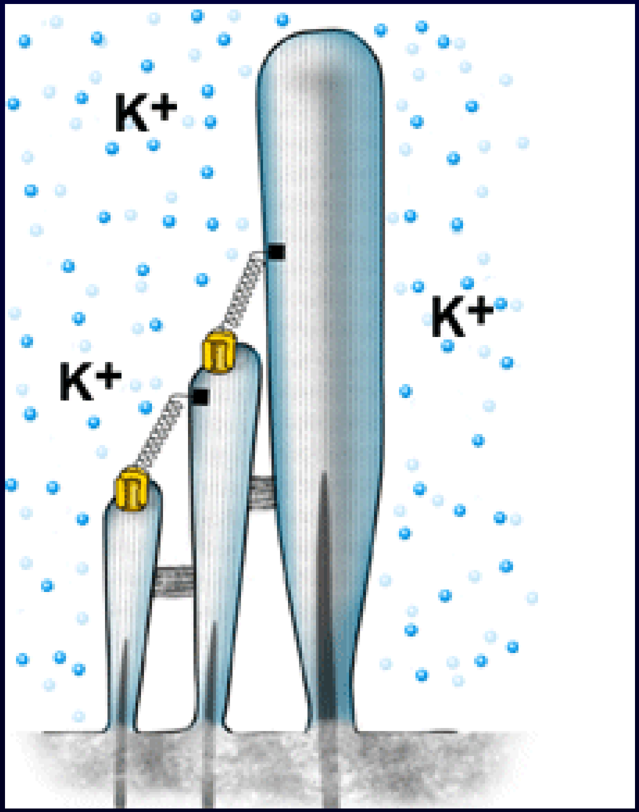
- "positive" deflection
- Tip-links stretched
  force application
- Direct mechanical opening of channel
- K^{+} and Ca^{2+} influx
- Depolarisation

Channel candidate: TRP

Corey (2006): J. Physiol. 576, 23-28

Reviews:
Hudspeth (1989): Nature 341, 397-404
Ricci (2003): J. Am. Acad. Audiol. 14, 325-338
LeMasurier, Gillespie (2005): Neuron 48, 403-415

Mechanoelectrical transduction



INSERM

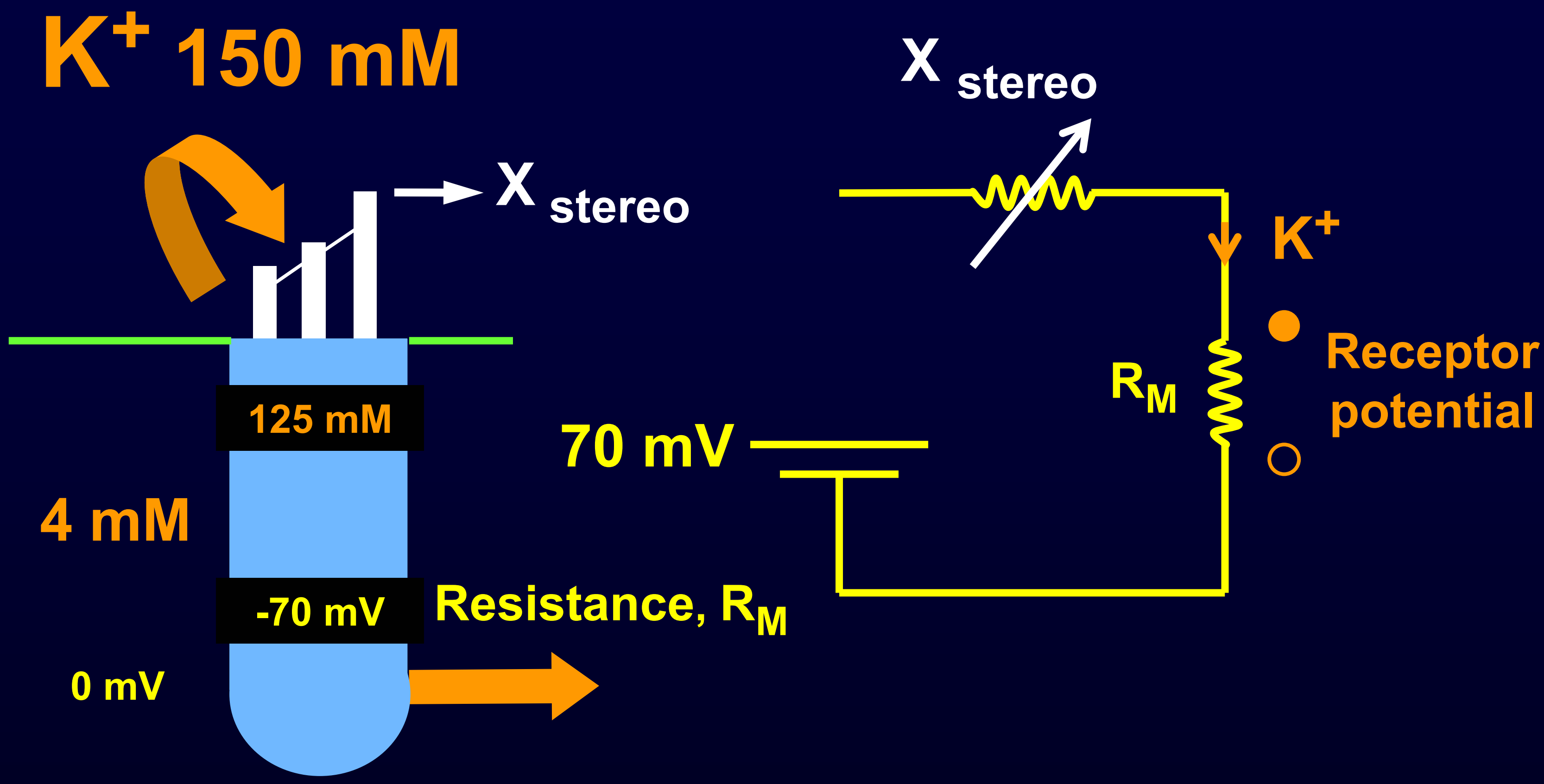
- "positive" deflection
- Tip-link force application
- Direct mechanical opening of channel
- K^+ and Ca^{2+} influx
- Depolarisation
- Ca^{2+} acts on channel and myosin motor
- Tip-links relaxed
- Channel closed
- Resting position

Reviews:
Hudspeth (1989): Nature 341, 397-404
Ricci (2003): J. Am. Acad. Audiol. 14, 325-338
LeMasurier, Gillespie (2005): Neuron 48, 403-415

Where is/are the energy source(s)

for

mechanoelectrical transduction ?

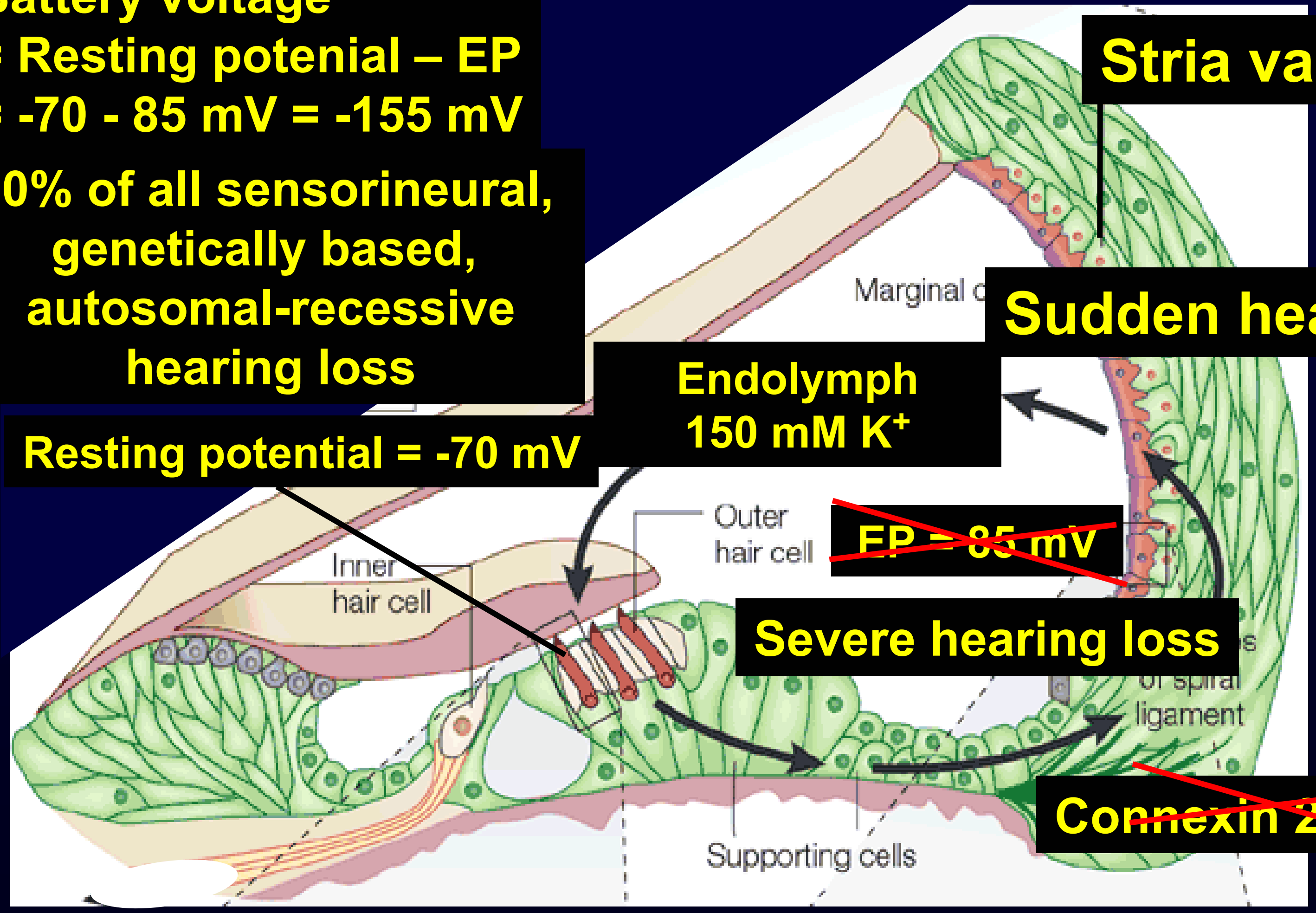


Resting membrane potential = -70 mV

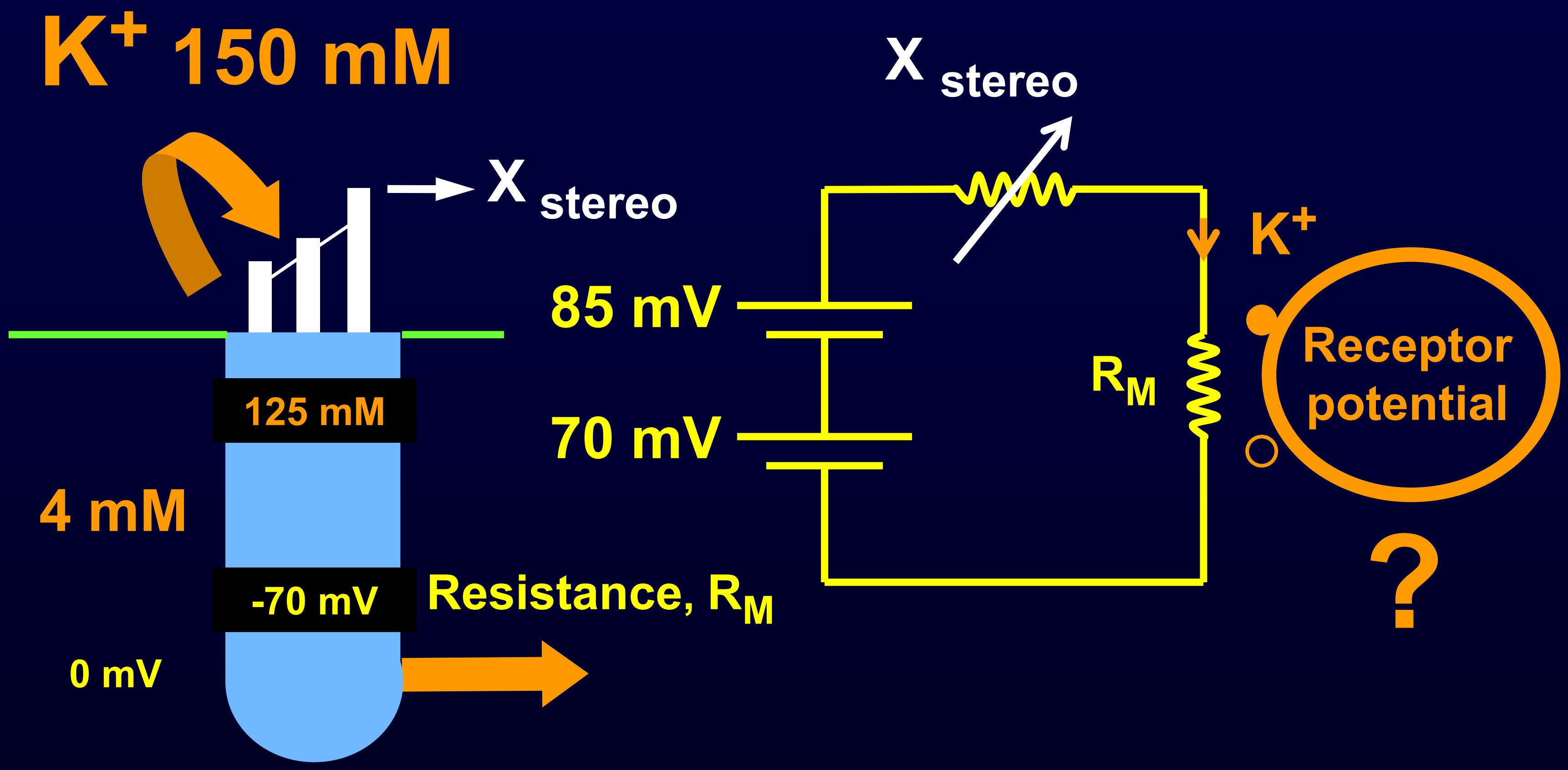
Stria vascularis:
Endolymph production, $[K^+] = 150$ mM
Endocochlear potential (EP) = 85 mV

Battery voltage
= Resting potenial – EP
= -70 - 85 mV = -155 mV

60% of all sensorineural, genetically based, autosomal-recessive hearing loss



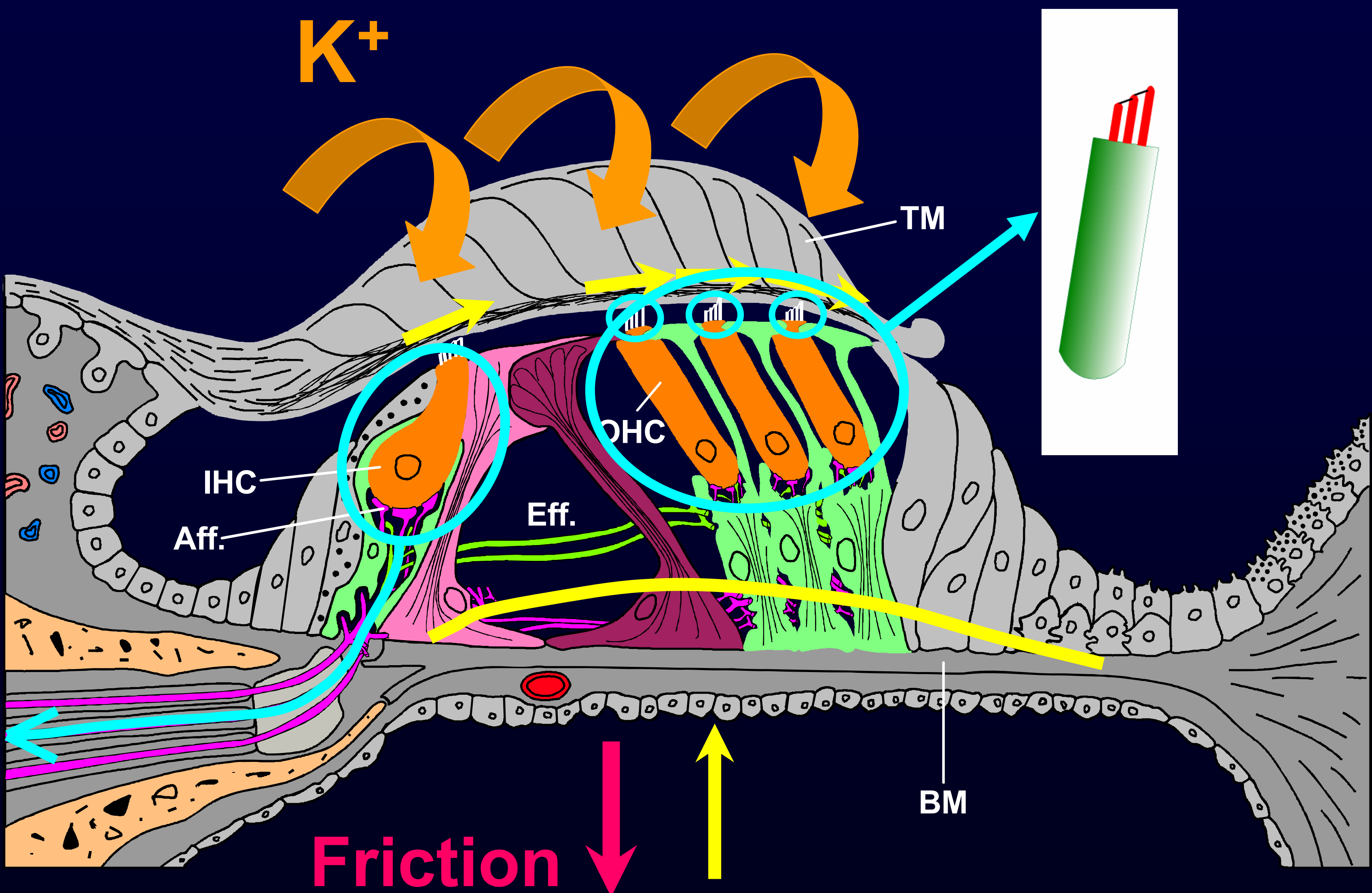
Two energy sources for transduction



Resting membrane potential = -70 mV

Endocochlear potential = 85 mV

Outer hair cells are electromotile
Inner hair cells are purely sensory



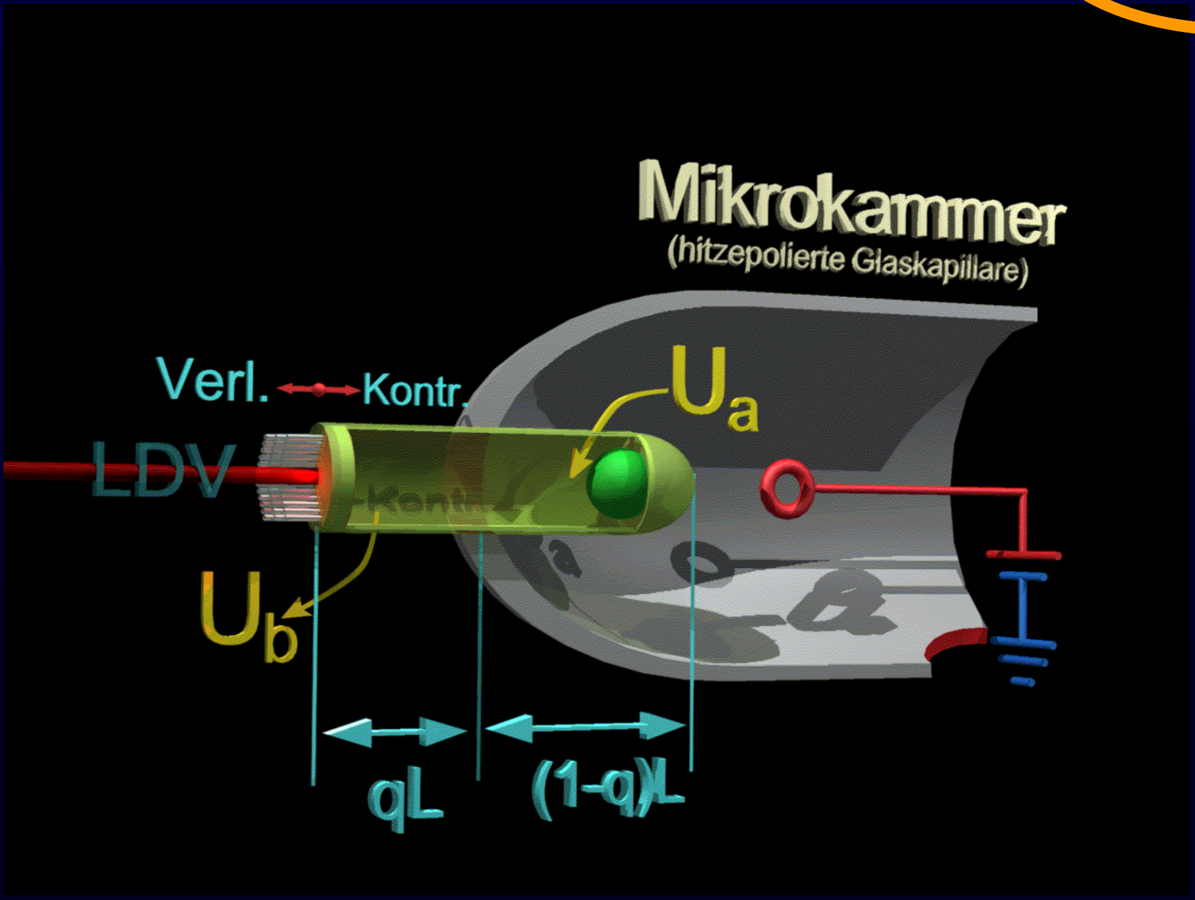
Amplification by electromechanical feedback

outer hair cell in whole-cell patch

from Serena Preyer

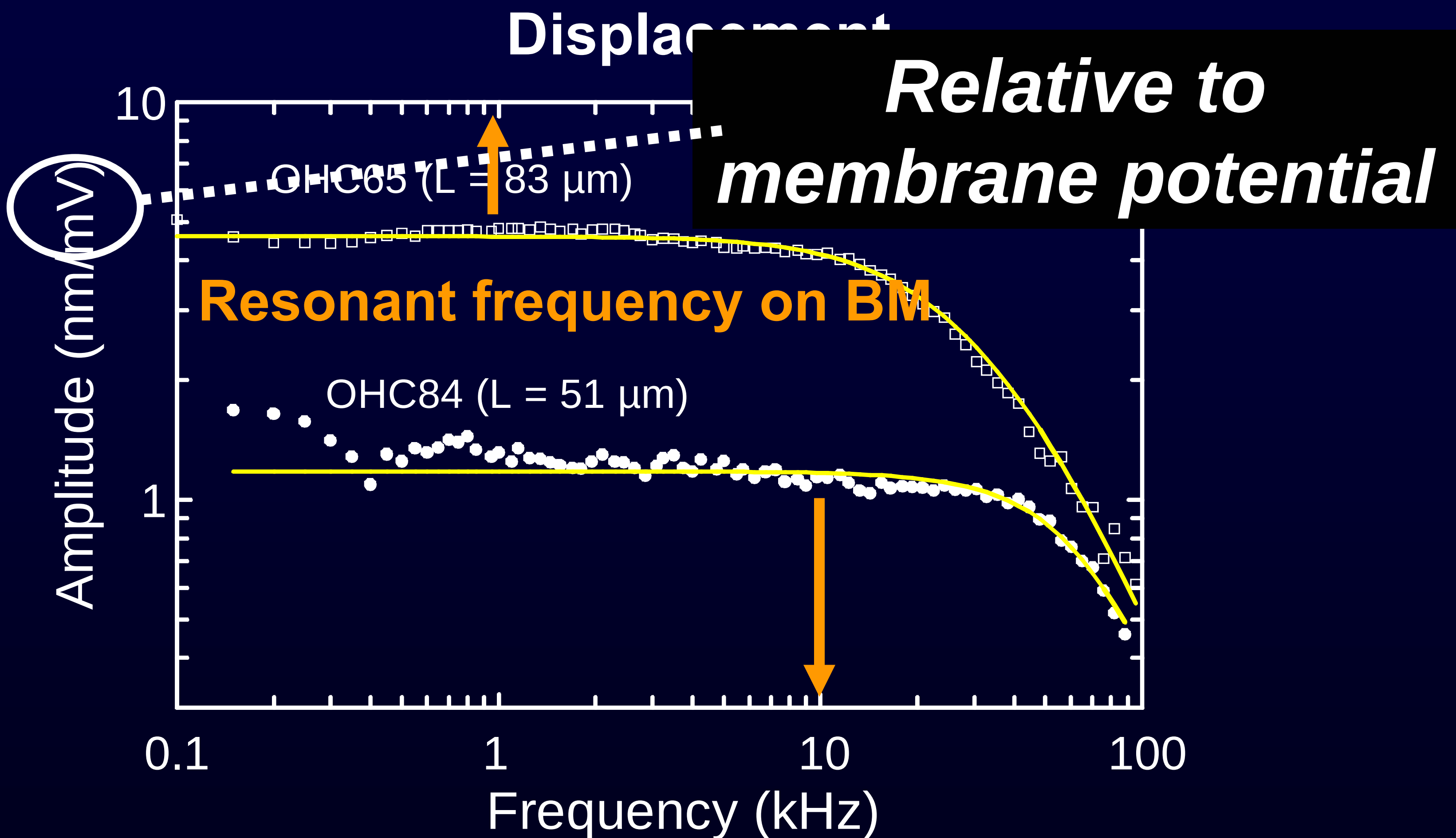
Experimental configuration

Transmembrane potential, U, is clamped

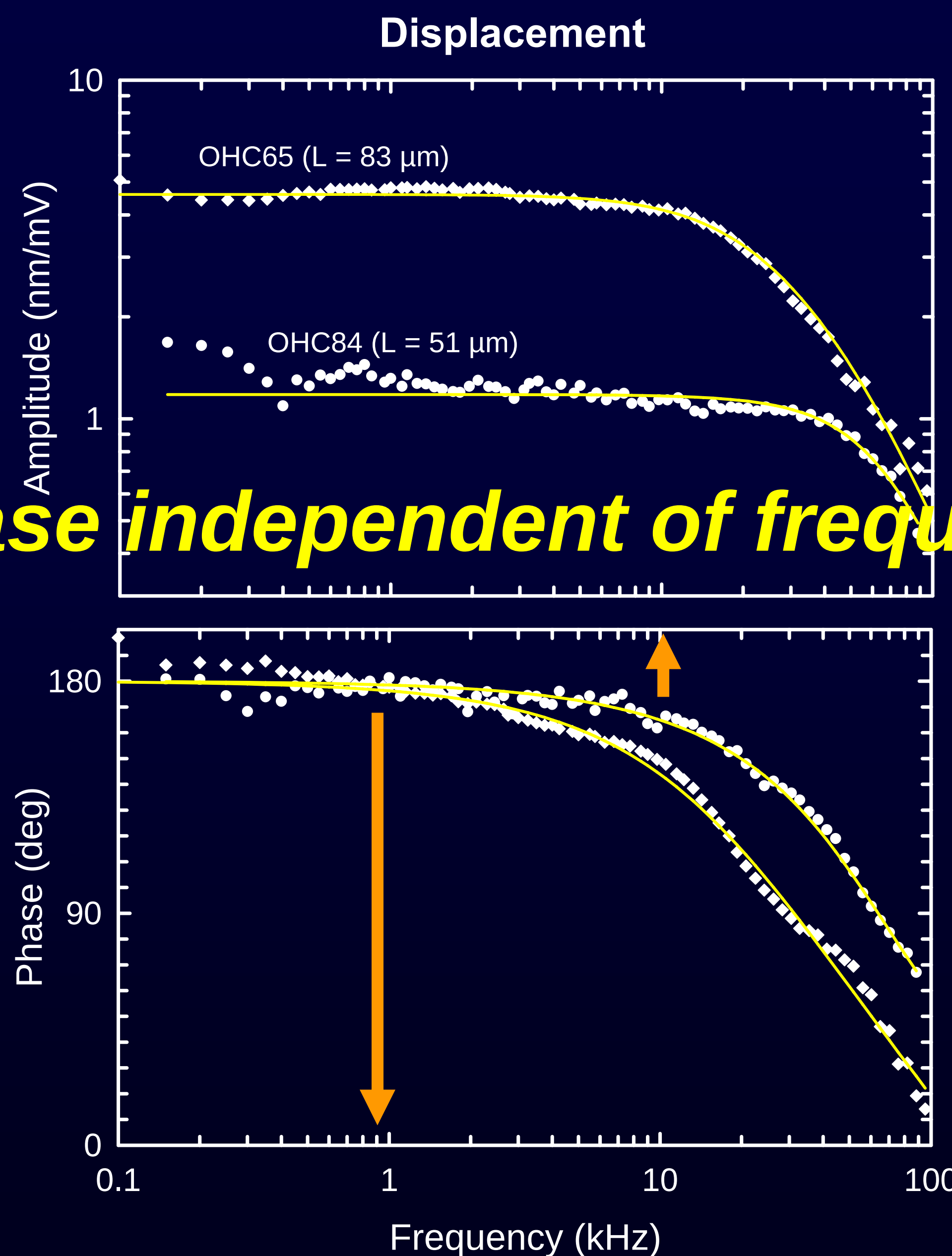


Dallos et al. (1993): J. Neurophysiol. 70, 299-323

Electromotility amplitude independent of frequency at its tonotopic place in the cochlea



Frank, Hemmert & Gummer (1999): PNAS 96, 4420-4425

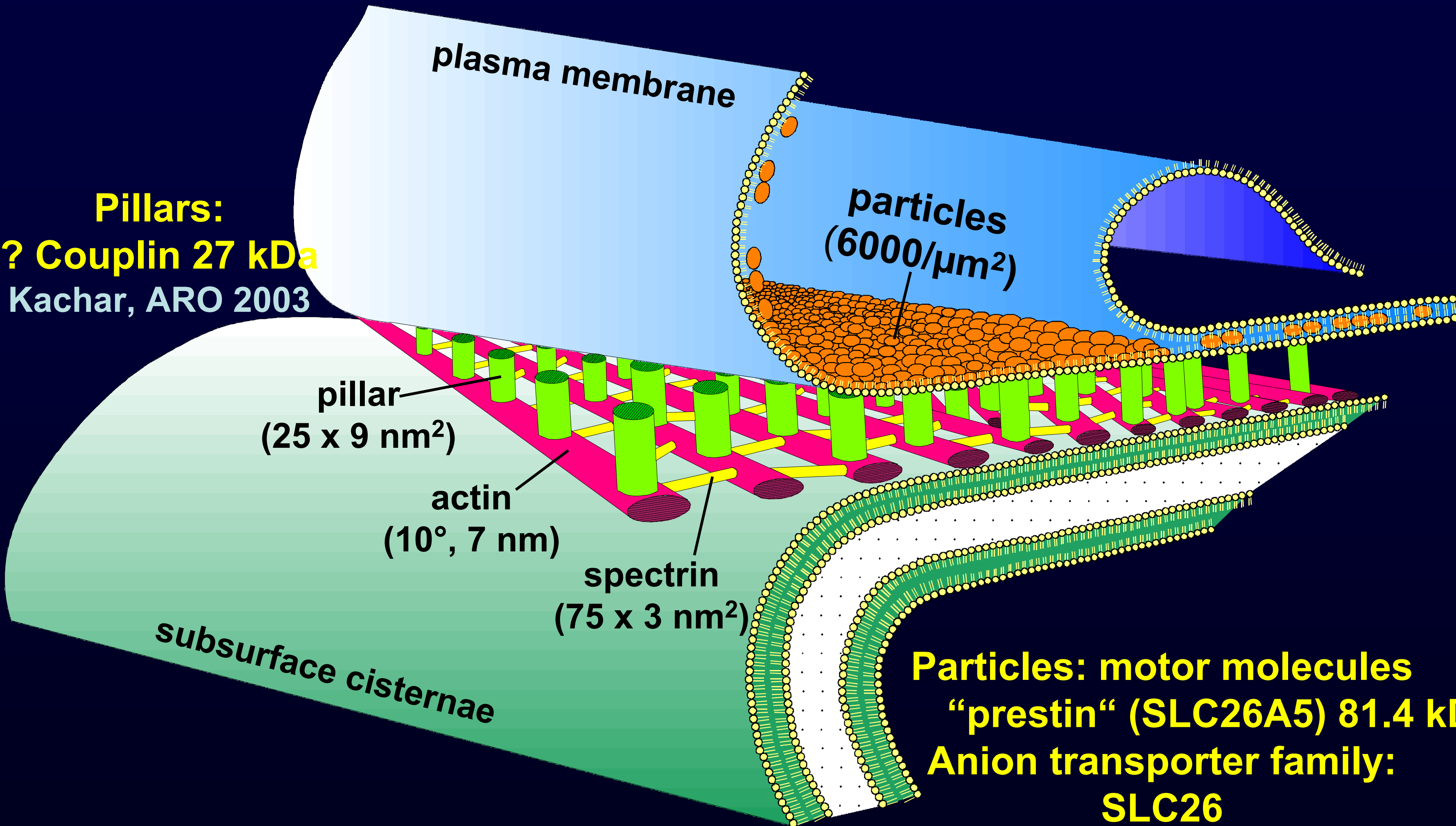


Phase independent of frequency

Frank, Hemmert & Gummer (1999): PNAS 96, 4420-4425

Basolateral membrane of the outer hair cell

Pillars:
? Couplin 27 kDa
Kachar, ARO 2003

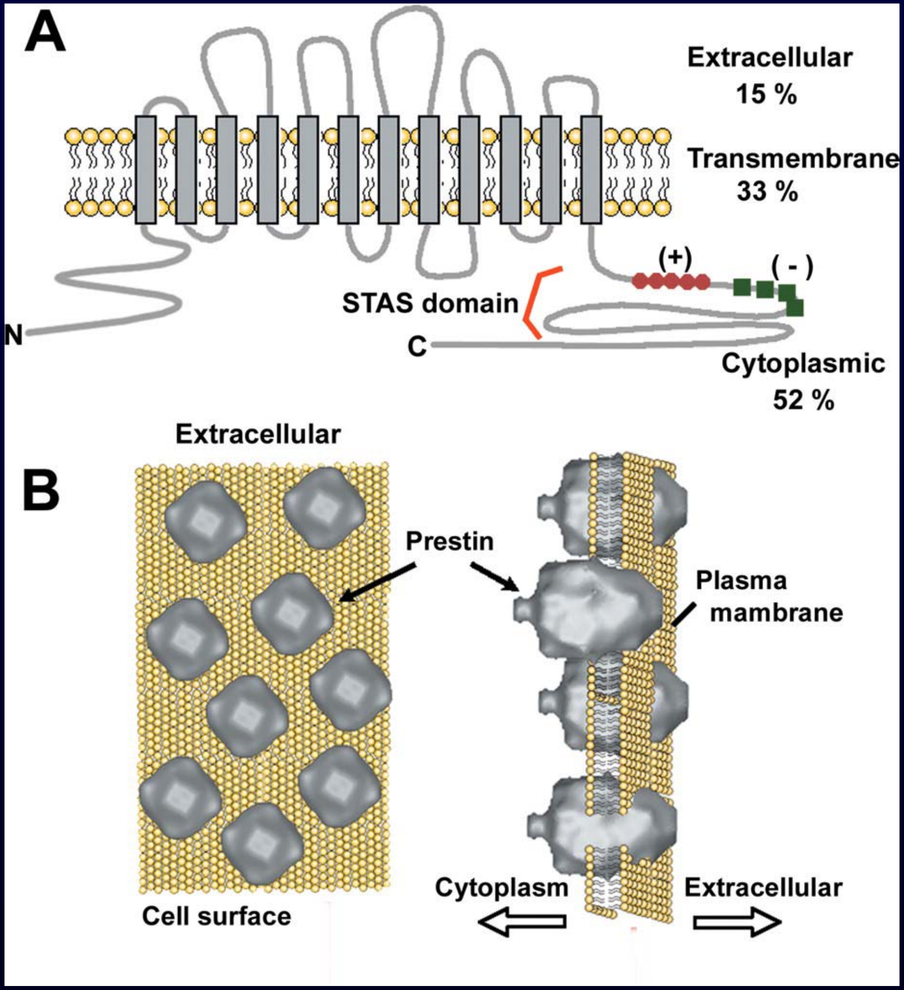


Particles: motor molecules "prestin" (SLC26A5) 81.4 kDa
Anion transporter family: SLC26

Dallos & Fakler (2002): Nat. Rev. Mol. Cell Biol. 3, 104-111

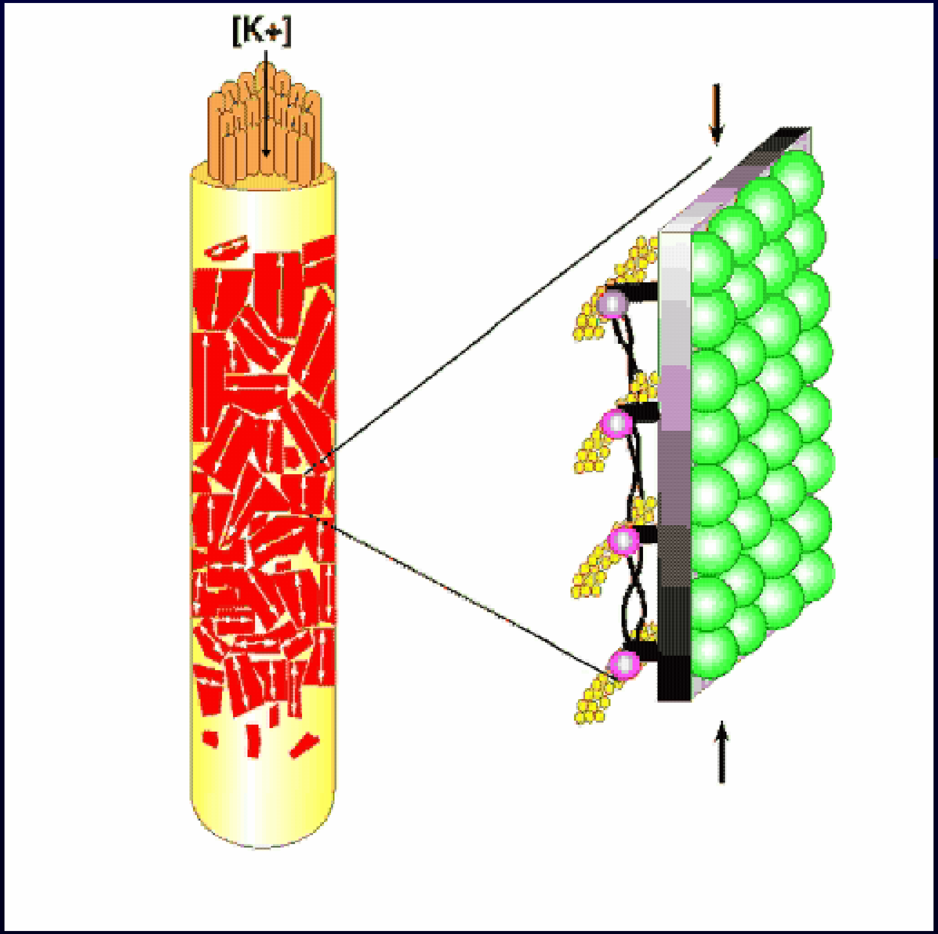
Adapted from:
Oghalai, Patel, Nakagawa, Brownell (1998): J. Neurosci. 18, 48-58

Prestin forming a tetramer as a bullet-shaped molecule with inner cavities



Mio et al. (2008): J. Biol. Chem. 283, 1137-1145

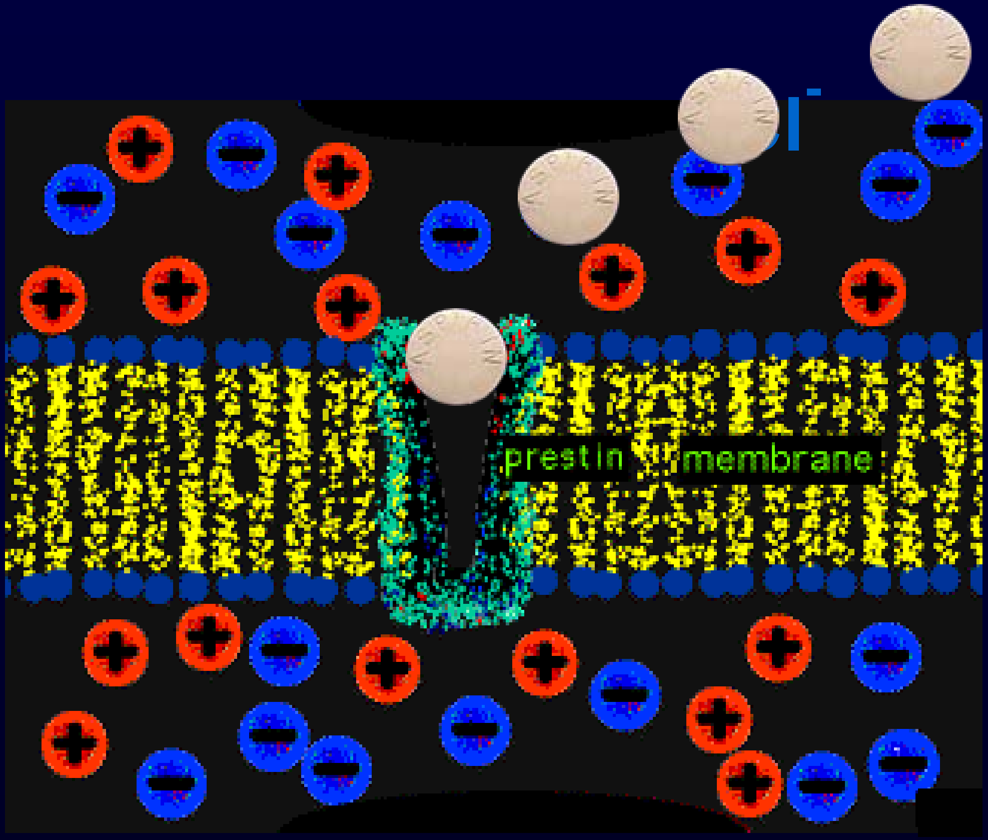
Electromotility of whole cell by synchronization of area changes of the motor molecules



Motor proteins

adapted from Frederico Kalinec

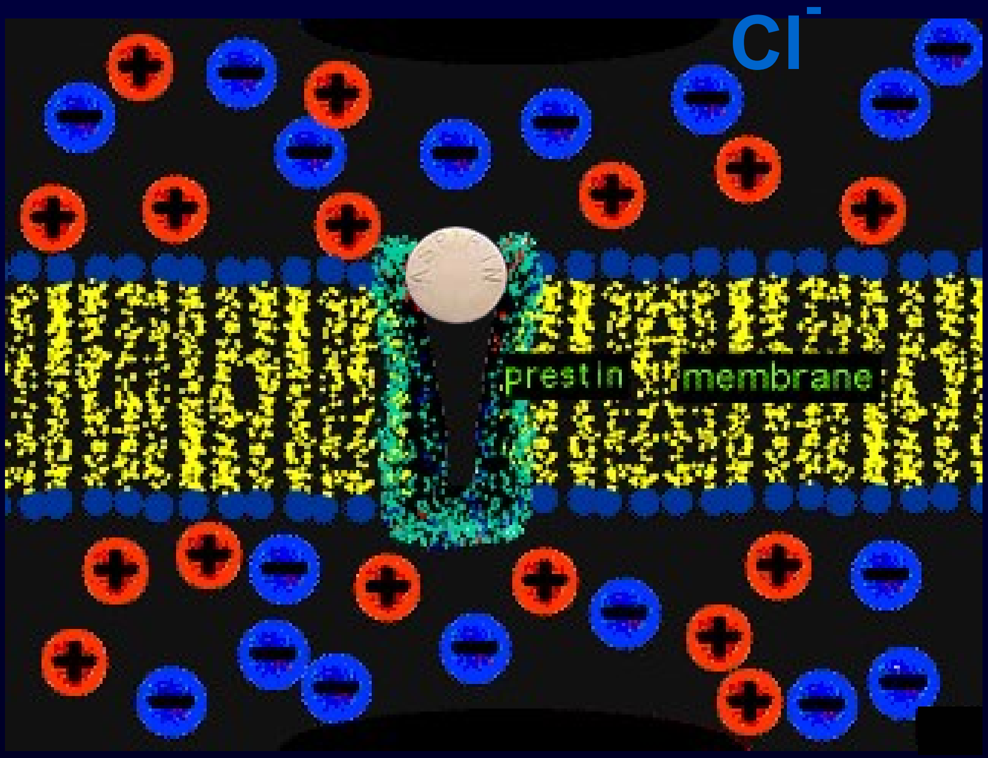
Intracellular chloride ions act as the voltage sensor for prestin



extracellular

Adapted from:
Oliver et al. (2001): Science 292, 2340-3

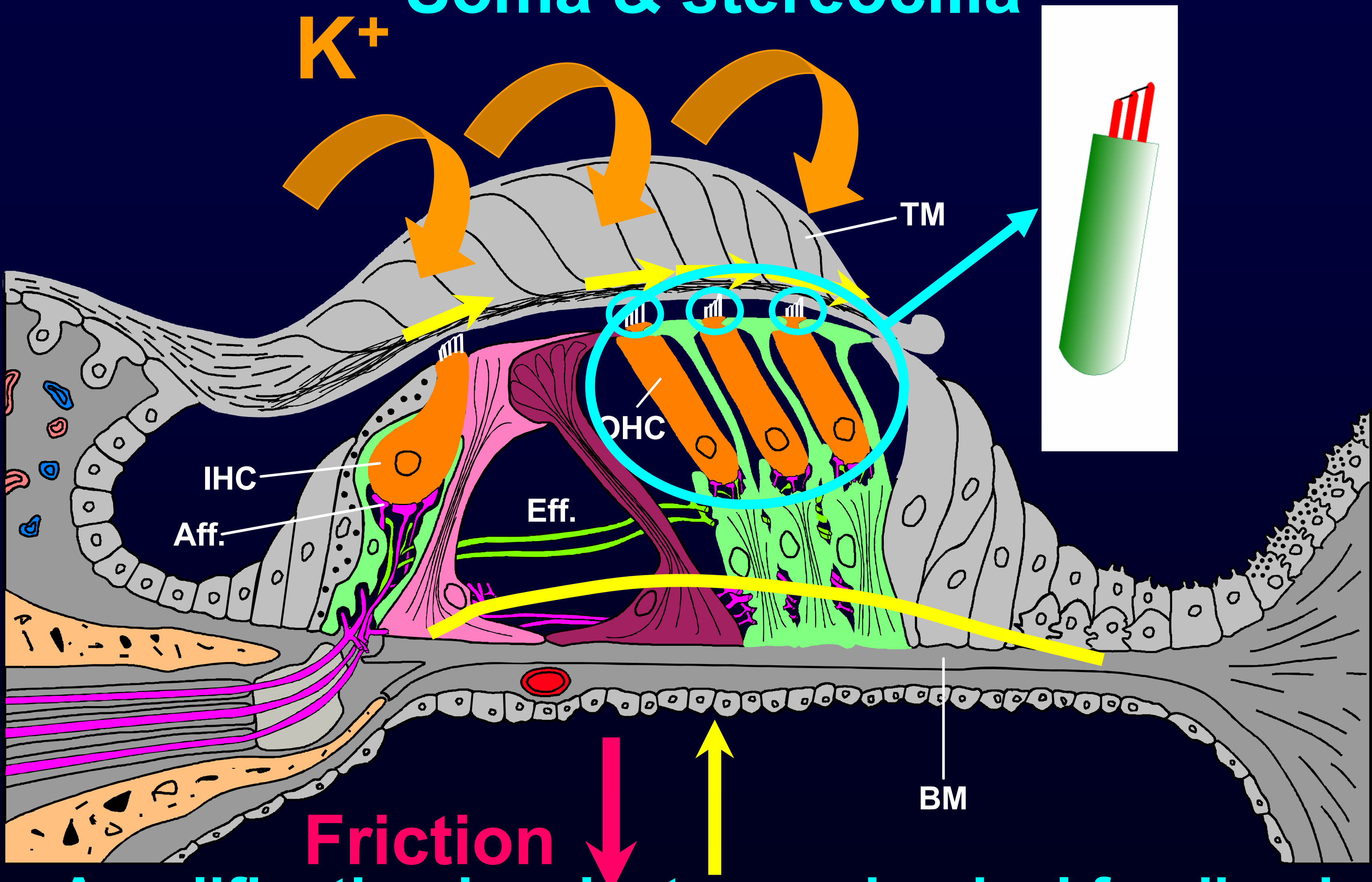
Competitive binding of salicylate to the anion-binding site(s) on prestin



extracellular

Adated from:
Oliver et al. (2001): Science 292, 2340-3

Outer hair cells are electromotile
- Soma & stereocilia

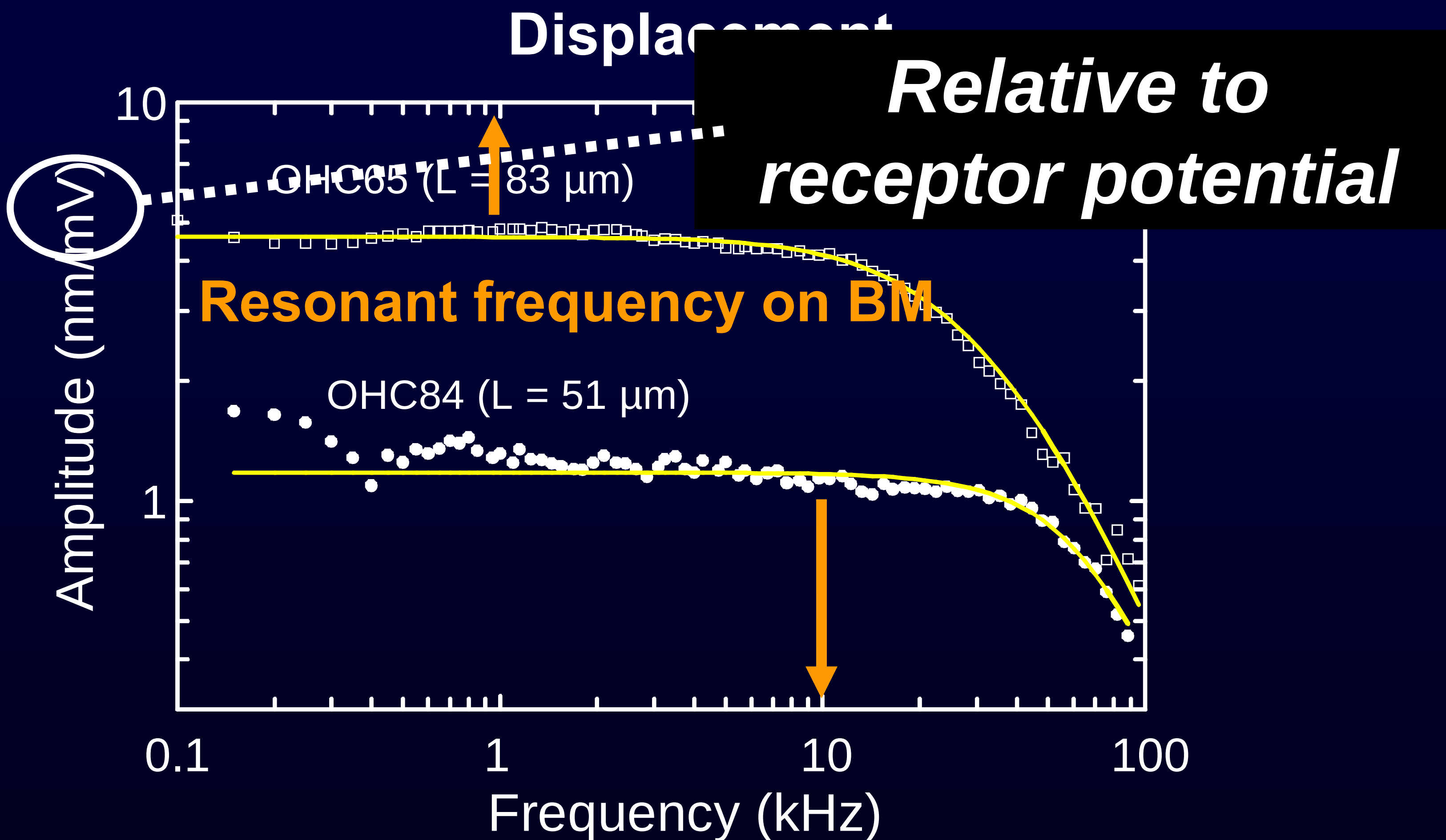


Amplification by electromechanical feedback

Amplifier required for

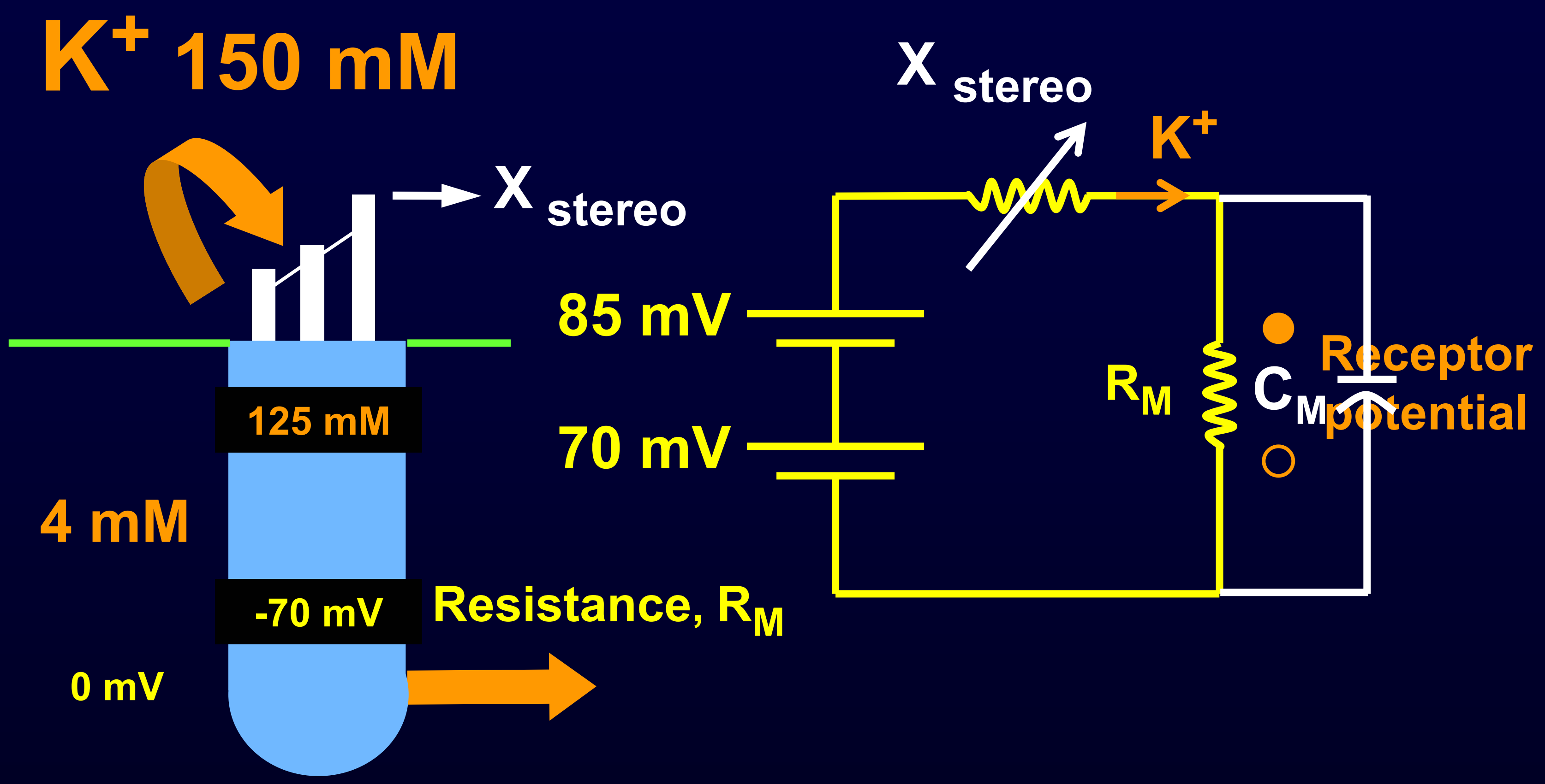
- √ *Sensitivity* — **1Å at threshold**
- √ *Frequency selectivity* — $\frac{\text{1 Hz}}{\text{1000 Hz}}$
- ? *Dynamic range* — **120 dB**

Electromotility independent of frequency at its tonotopic place in the cochlea



Frank, Hemmert & Gummer (1999): PNAS 96, 4420-4425

The cell membrane has capacitance



Resting membrane potential = -70 mV

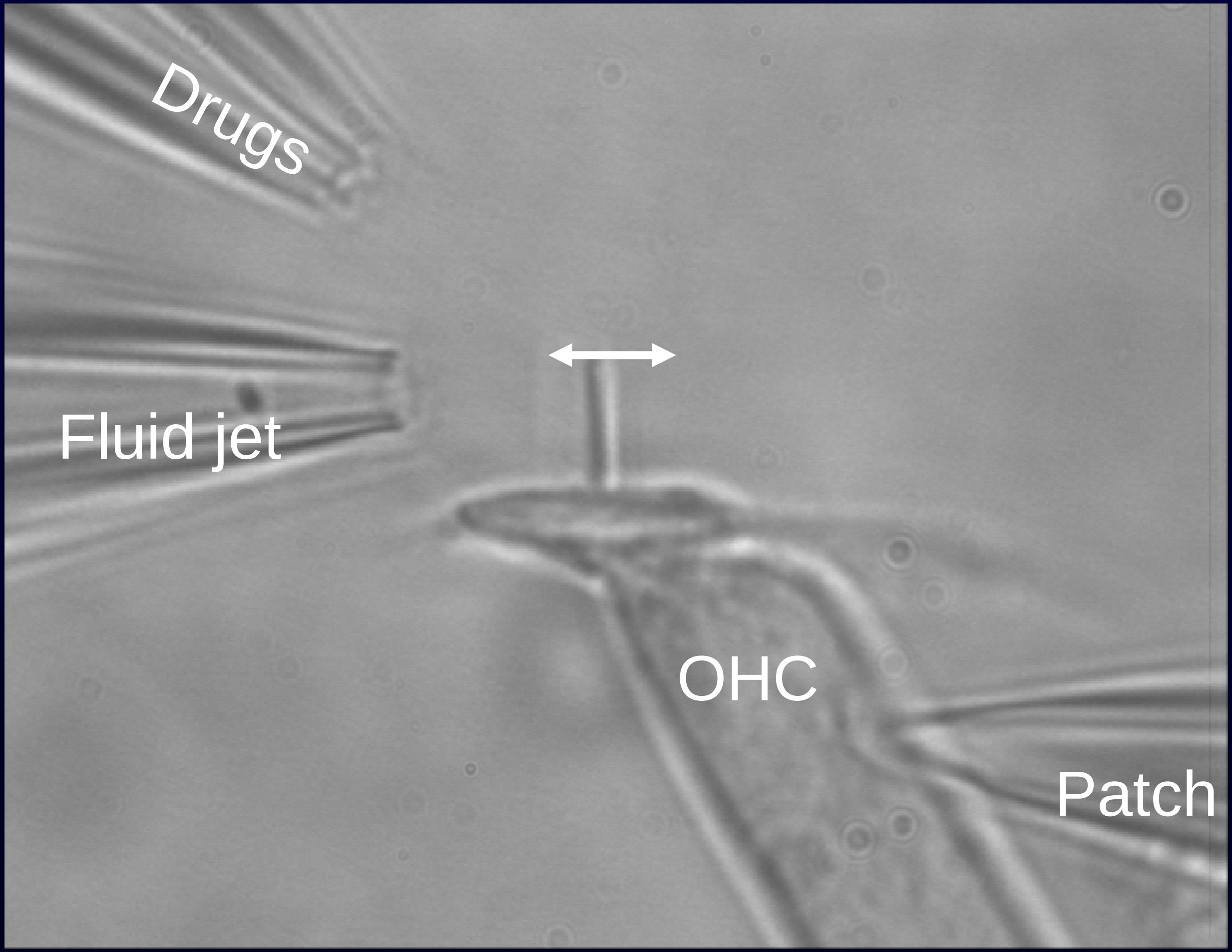
Endocochlear potential = 85 mV

The problem

of the

membrane time constant

Measurement of receptor potential or current

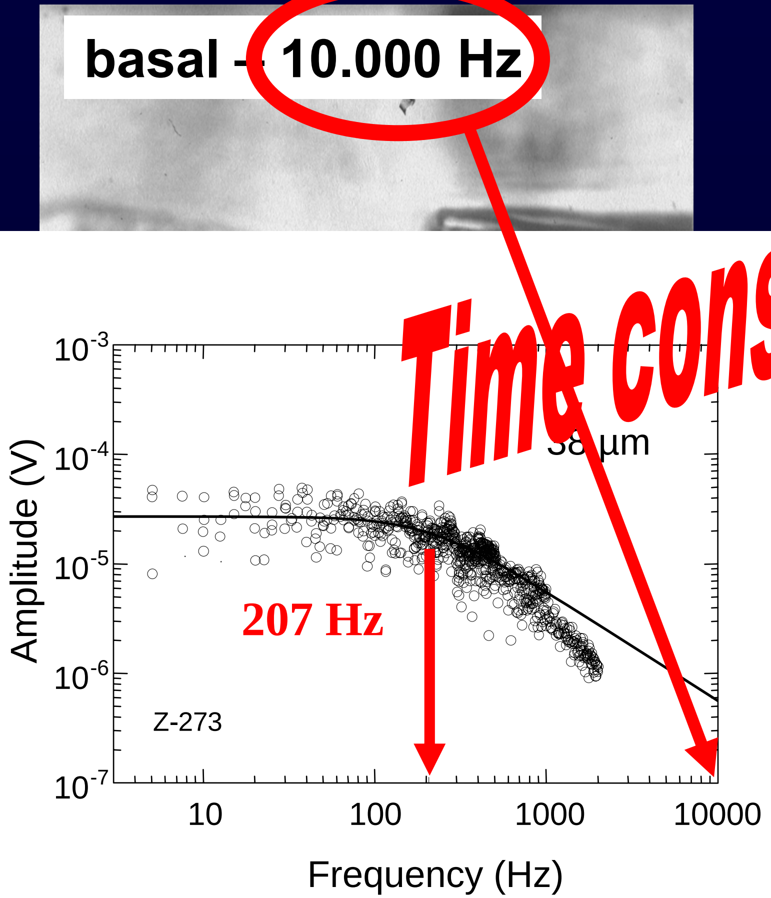


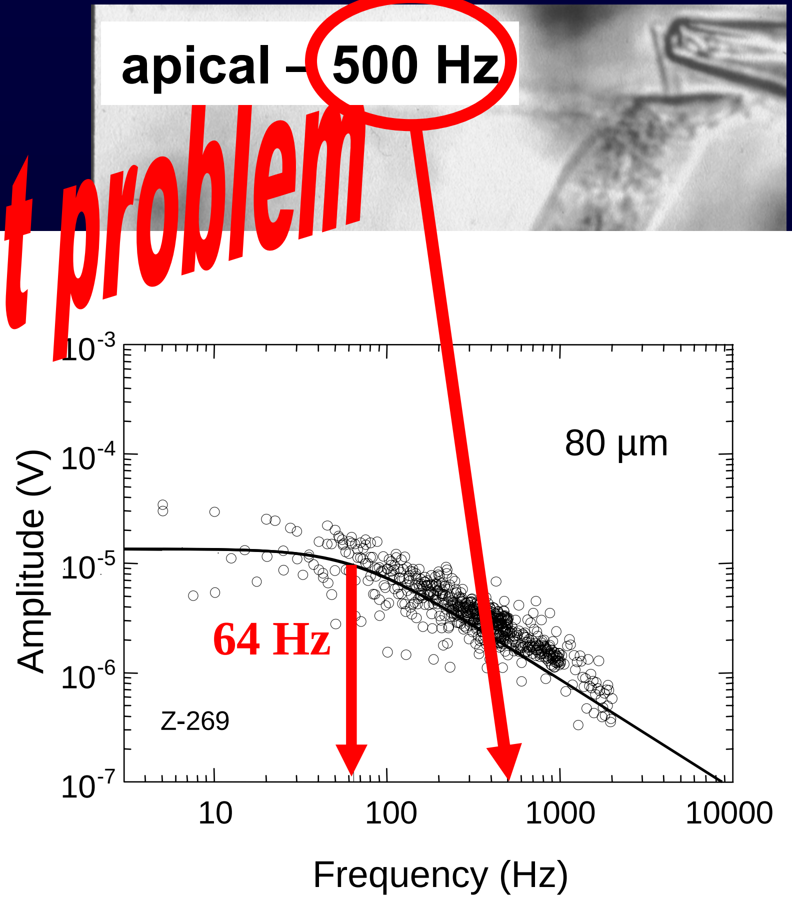
Serena Preyer

Attenuation of receptor potential at high frequencies

Resonant frequency on BM

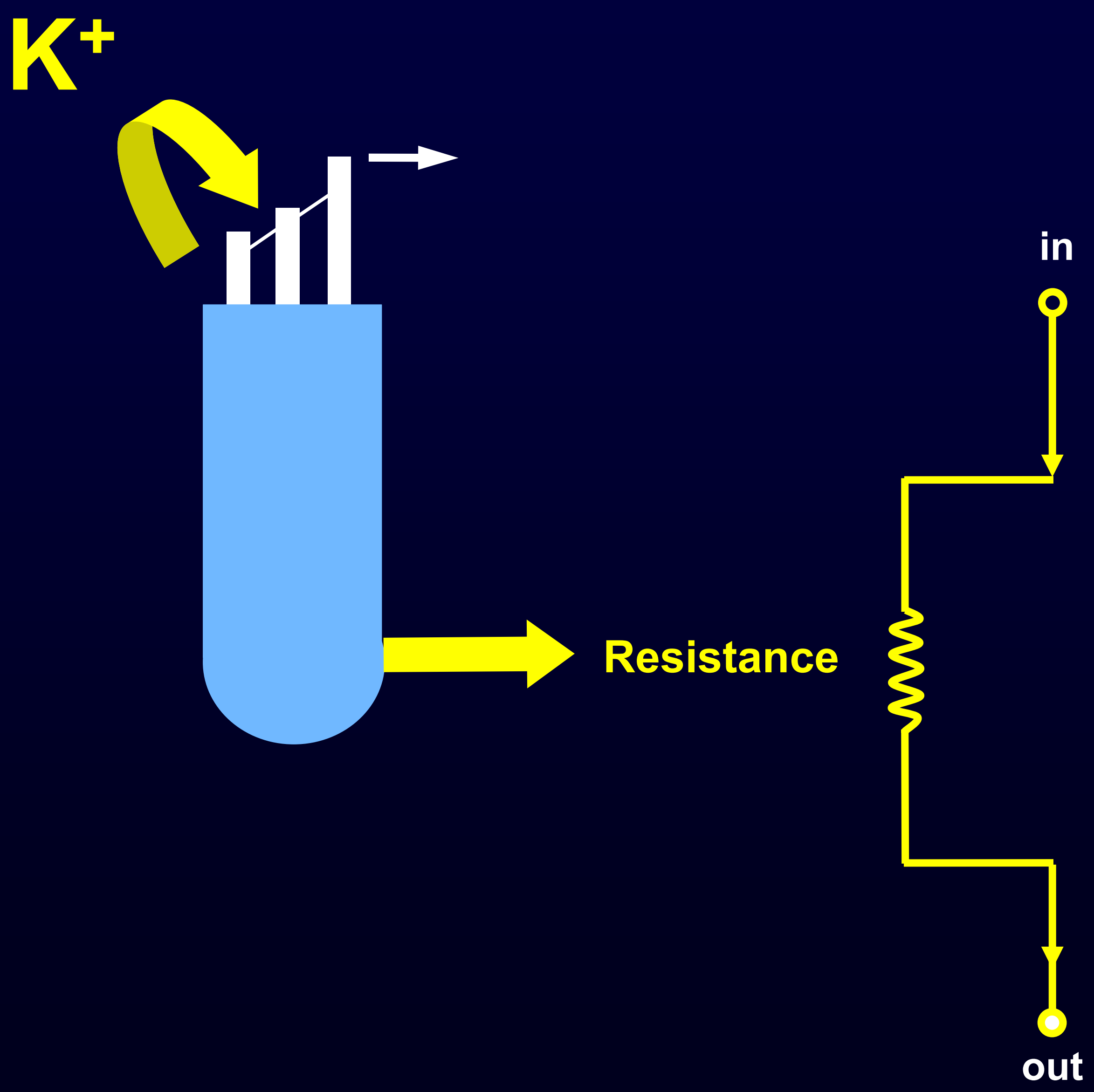
Time constant problem





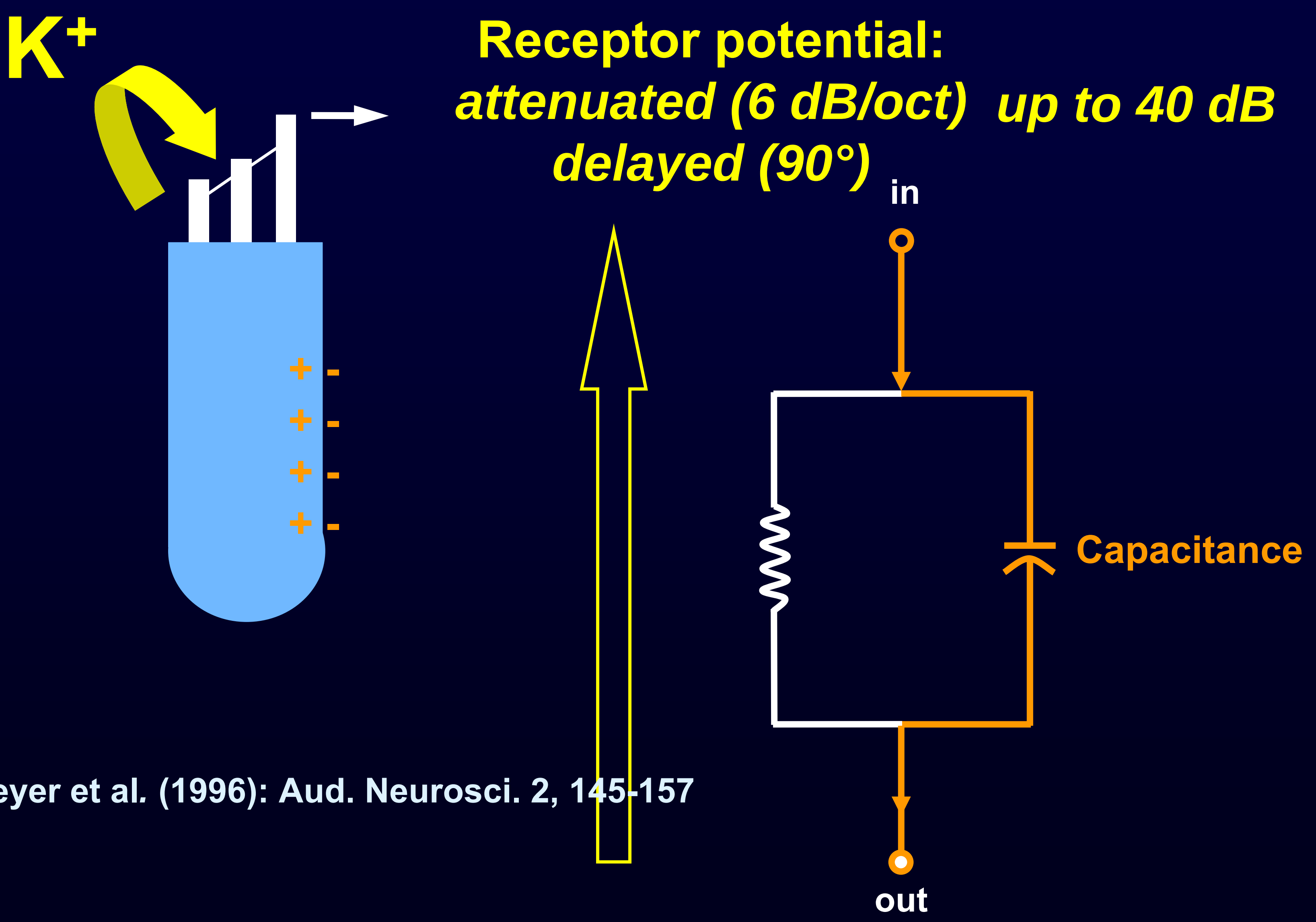
Preyer et al. (1996): Aud. Neurosci. 2, 145-157

Membrane current is resistive at low frequencies



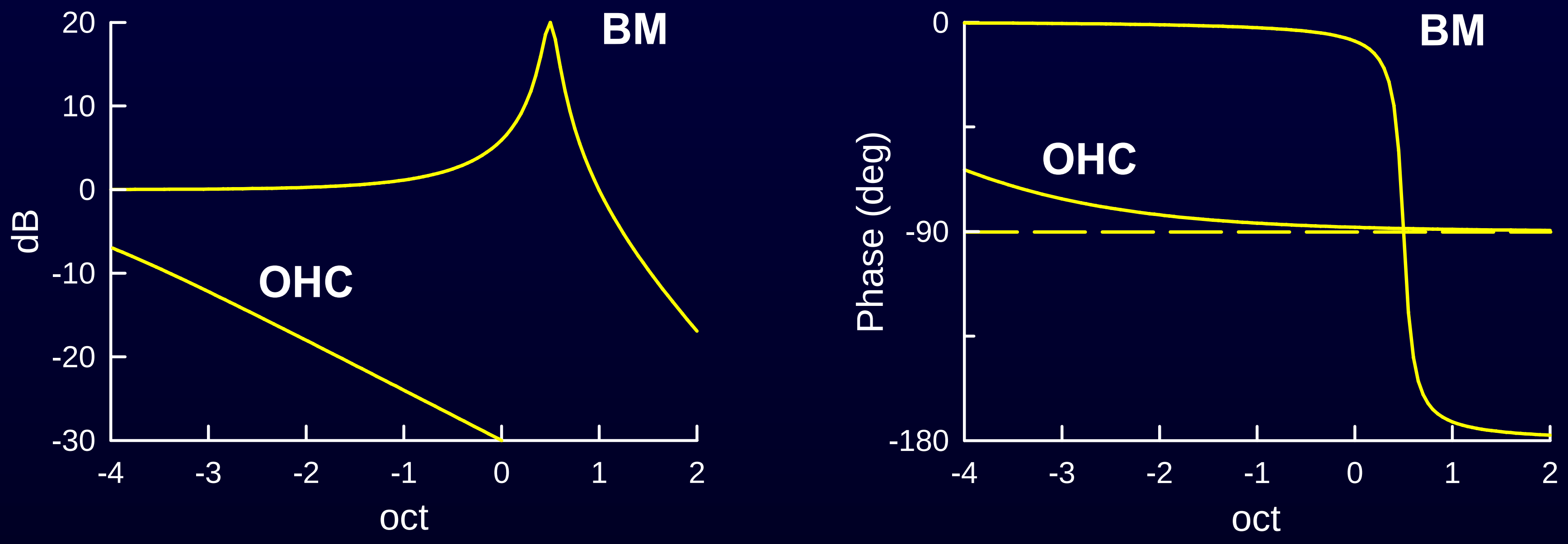
Membrane current is resistive at low frequencies

Membrane is capacitively charged at high frequencies



Preyer et al. (1996): Aud. Neurosci. 2, 145-157

Attenuation & 90° phase lag

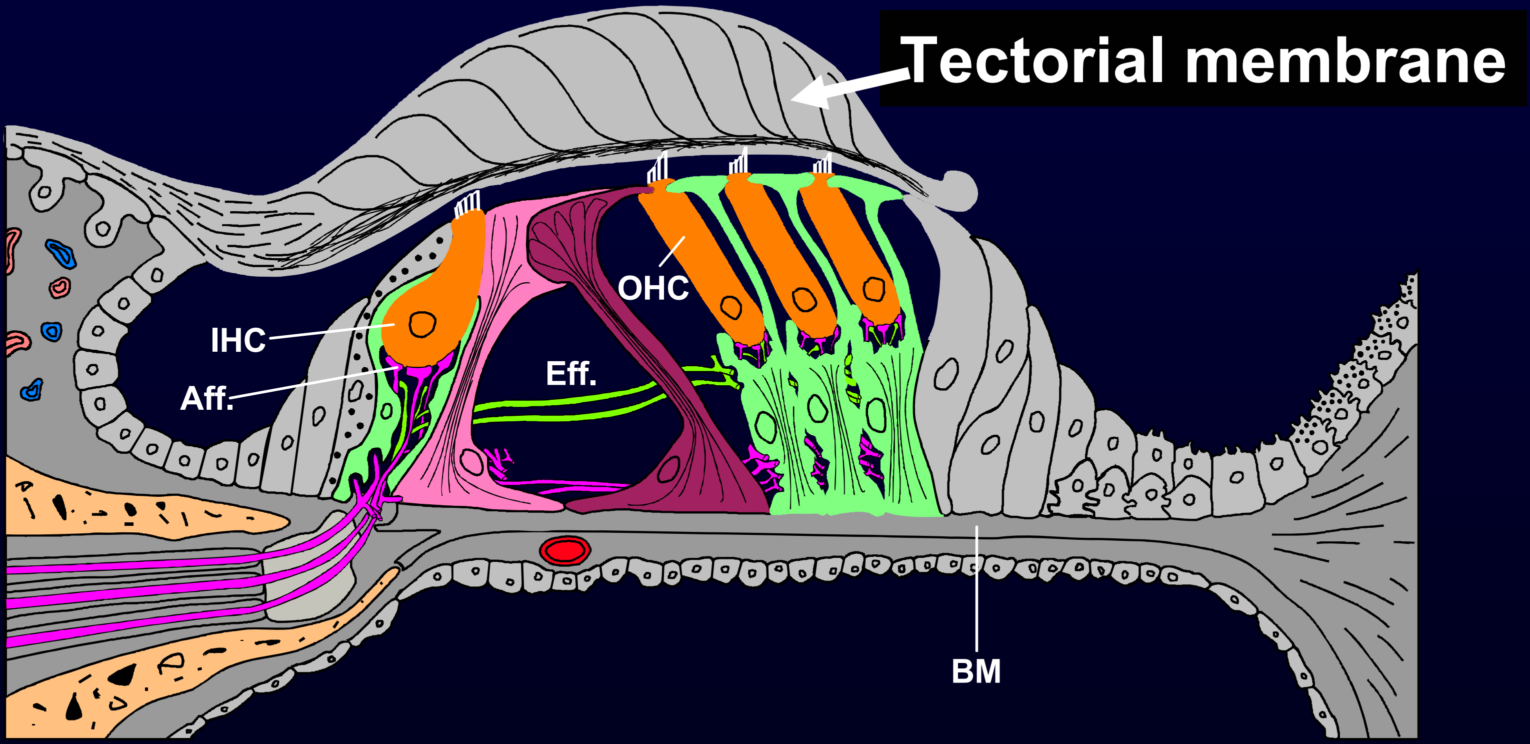


How is the OHC force

coupled into the cochlea ?

at the correct moment ?

The solution with the tectorial membrane

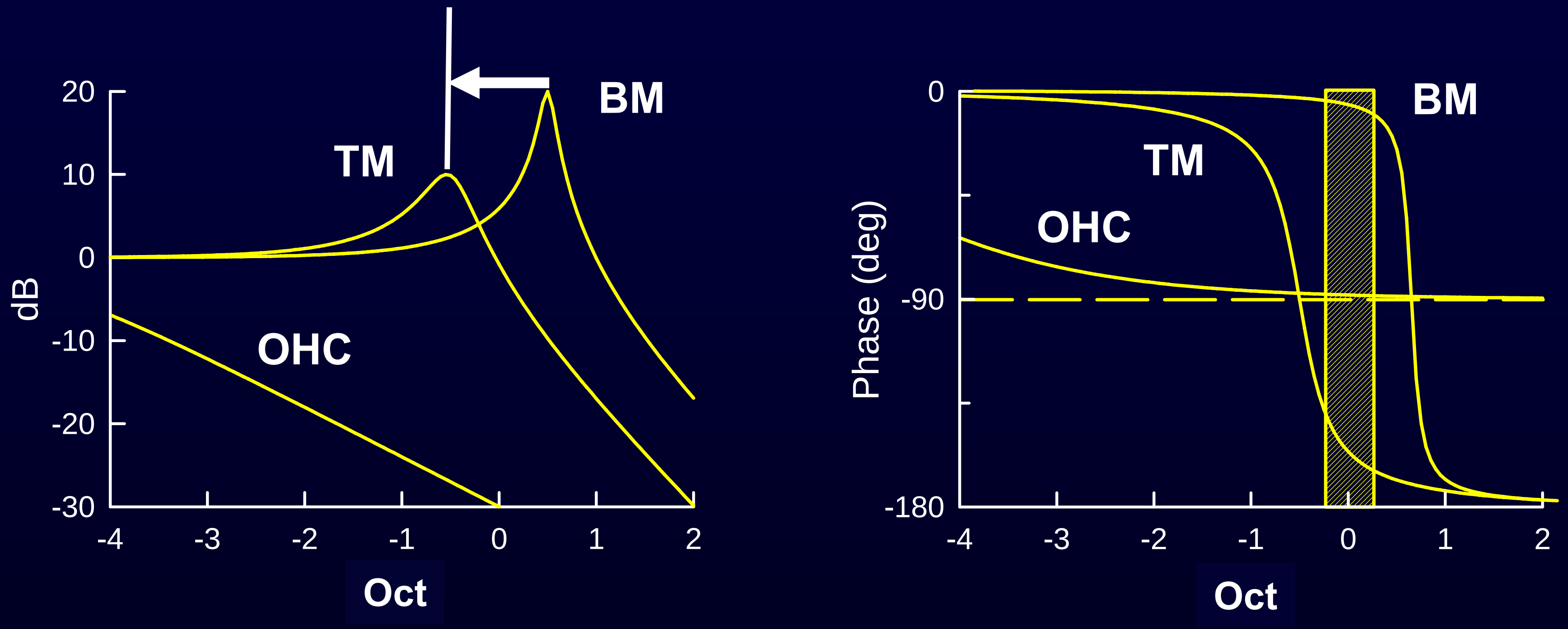


Zwislocki & Kletzky (1979): Science 204, 639-641
Allen (1980): J. Acoust. Soc. Am. 79, 1472-1480

OHC lags BM by 90°

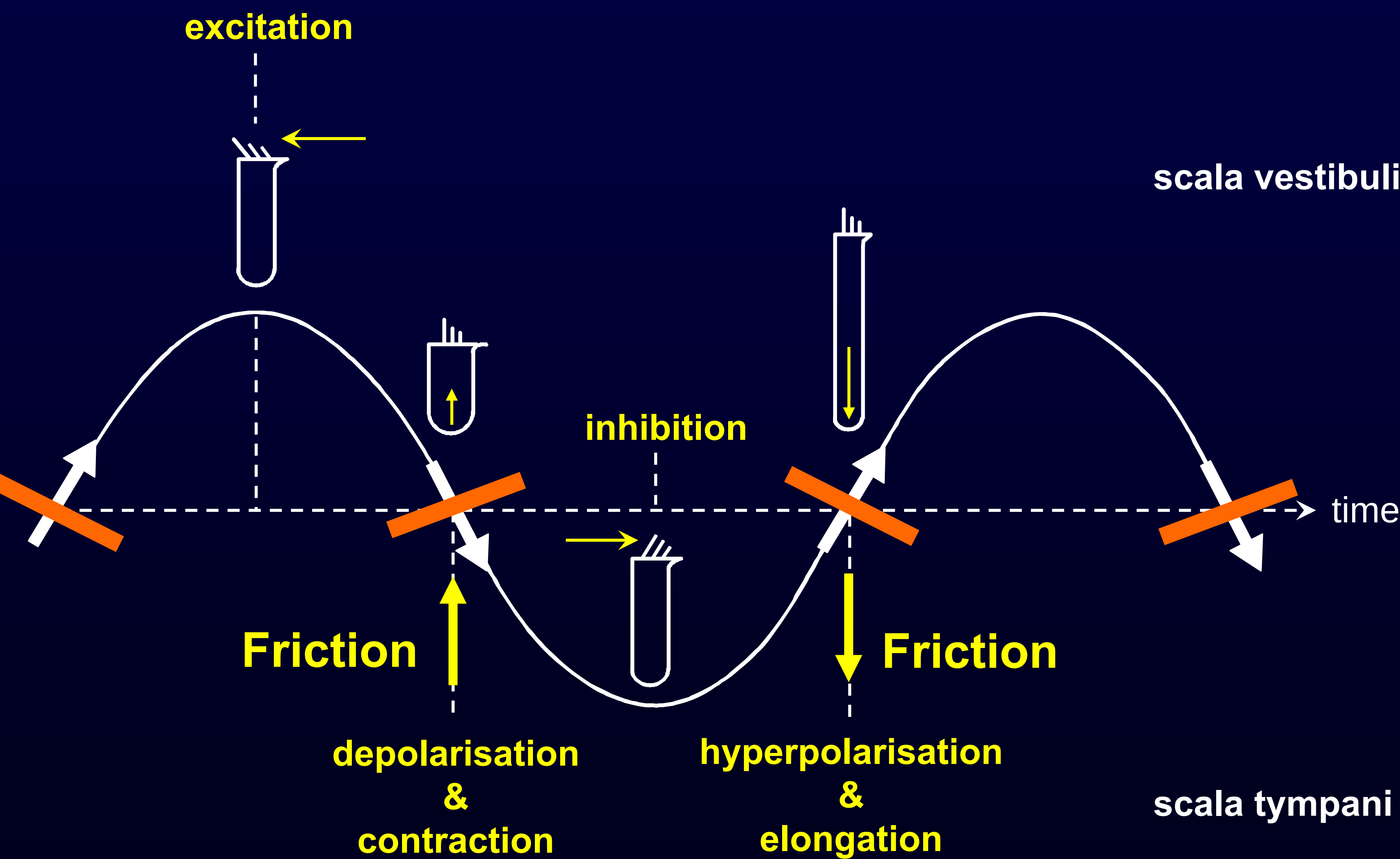
TM lags BM by 180°

TM-Resonance below BM-Resonance



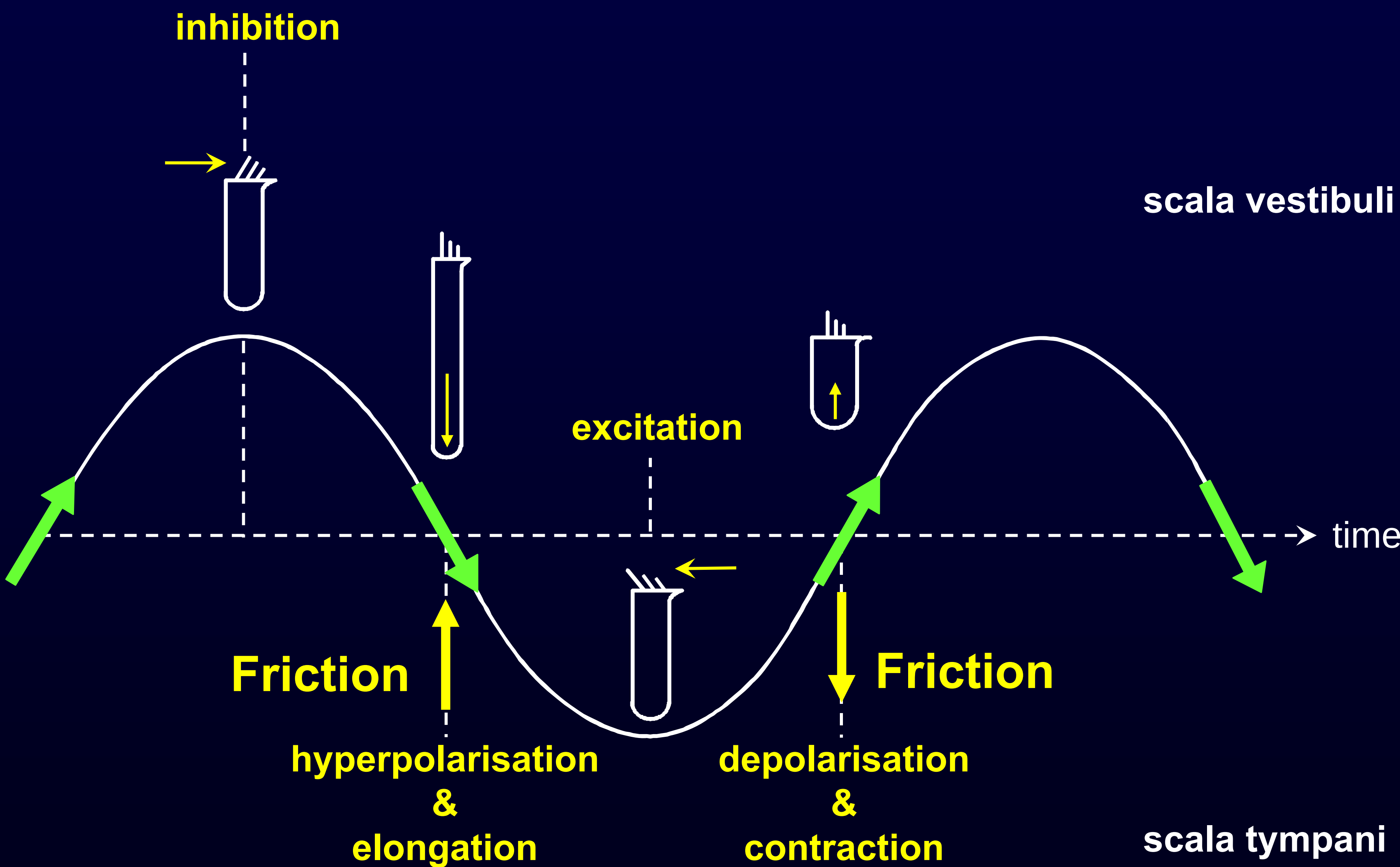
Gummer et al. (1996): PNAS 93, 8727-8732

Stiffness model → Active attenuation



Gummer et al. (1996): PNAS 93, 8727-8732

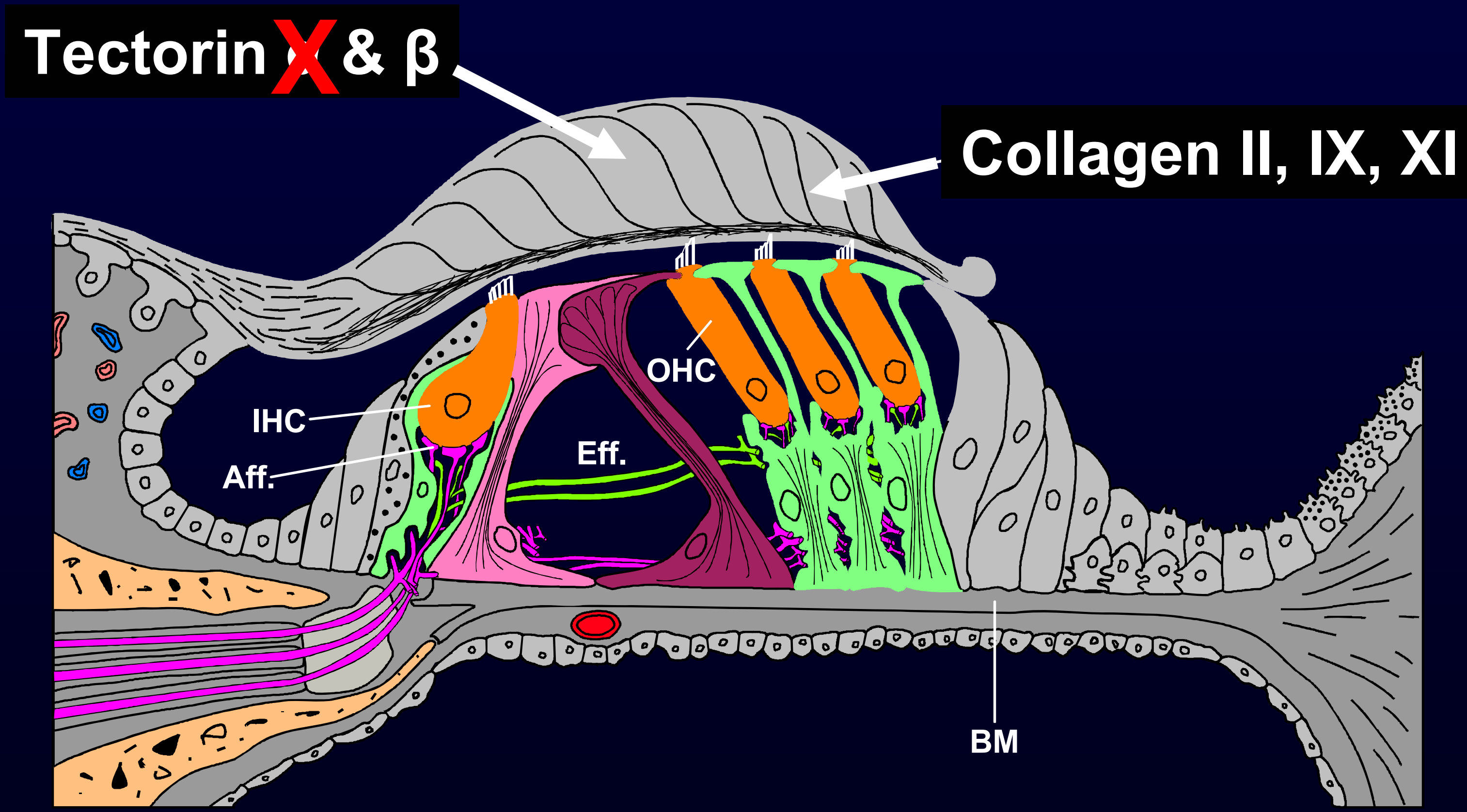
Stiffness-mass model → Active amplification



Gummer et al. (1996): PNAS 93, 8727-8732

Deletion of α-tectorin:
TM is required for amplification and timing

Legan et al. (2000): Neuron 28, 273-285



How is dynamic range achieved ?

The need for dynamic-range compression

1. Threshold: 1 Å → 120 dB SPL: 100 µm

BM thickness ~ 2 – 7 µm

Organ of Corti thickness ~ 50 – 150 µm

→ RUPTURE

The need for dynamic-range compression

1. Threshold: 1 Å ⟶ 120 dB SPL: 100 µm

   BM thickness ~ 2 – 7 µm

   Organ of Corti thickness ~ 50 – 150 µm

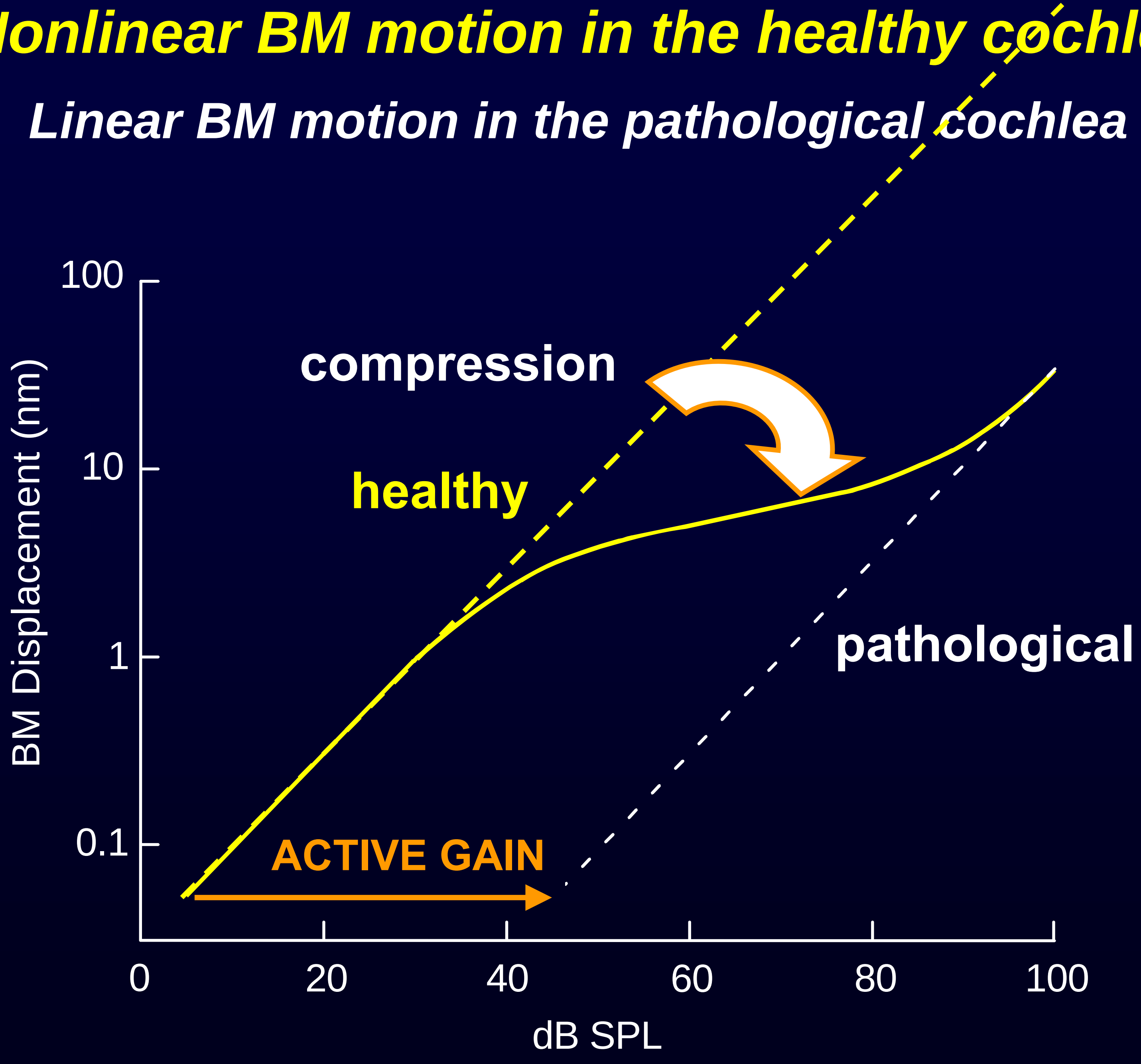
   ⟶ RUPTURE

2. Limited dynamic range of the detector,

   IHC – Afferent synapse of 20 – 30 dB SPL

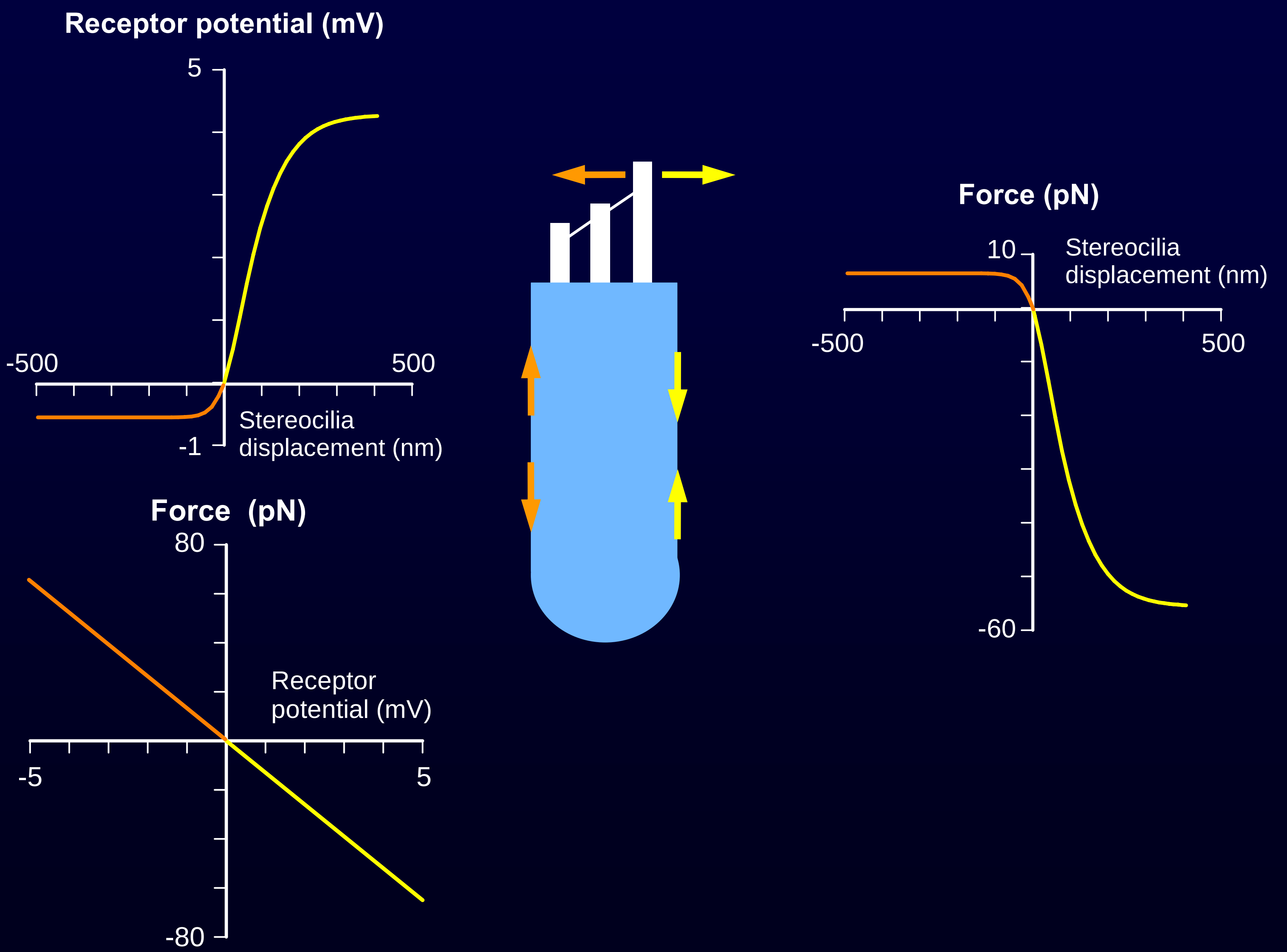
Nonlinear BM motion in the healthy cochlea

Linear BM motion in the pathological cochlea

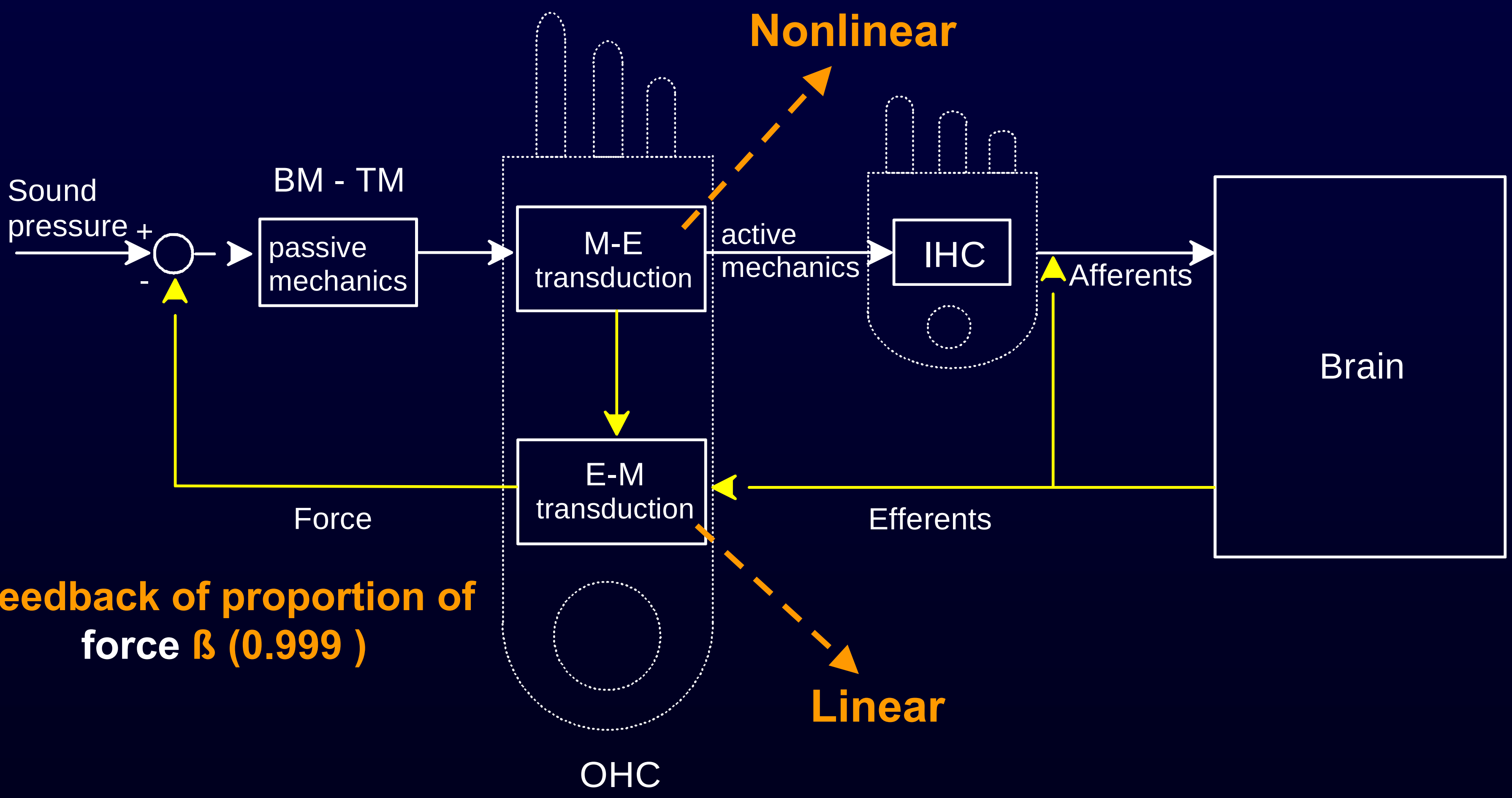


How is nonlinear BM motion achieved ?

Stereocilia responsible for generating nonlinear force

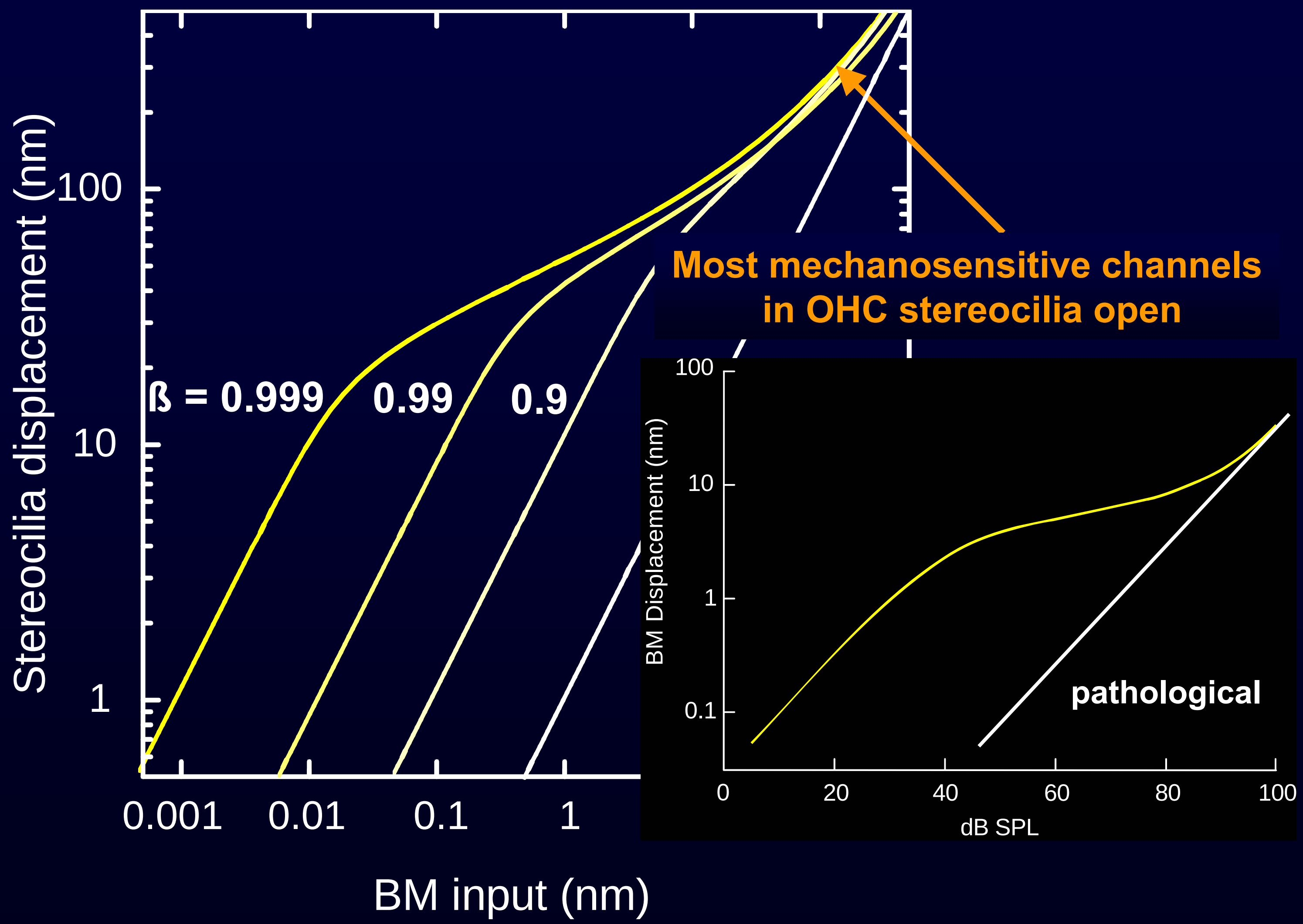


Hearing process with feedback



Feedback of proportion of force ß (0.999)

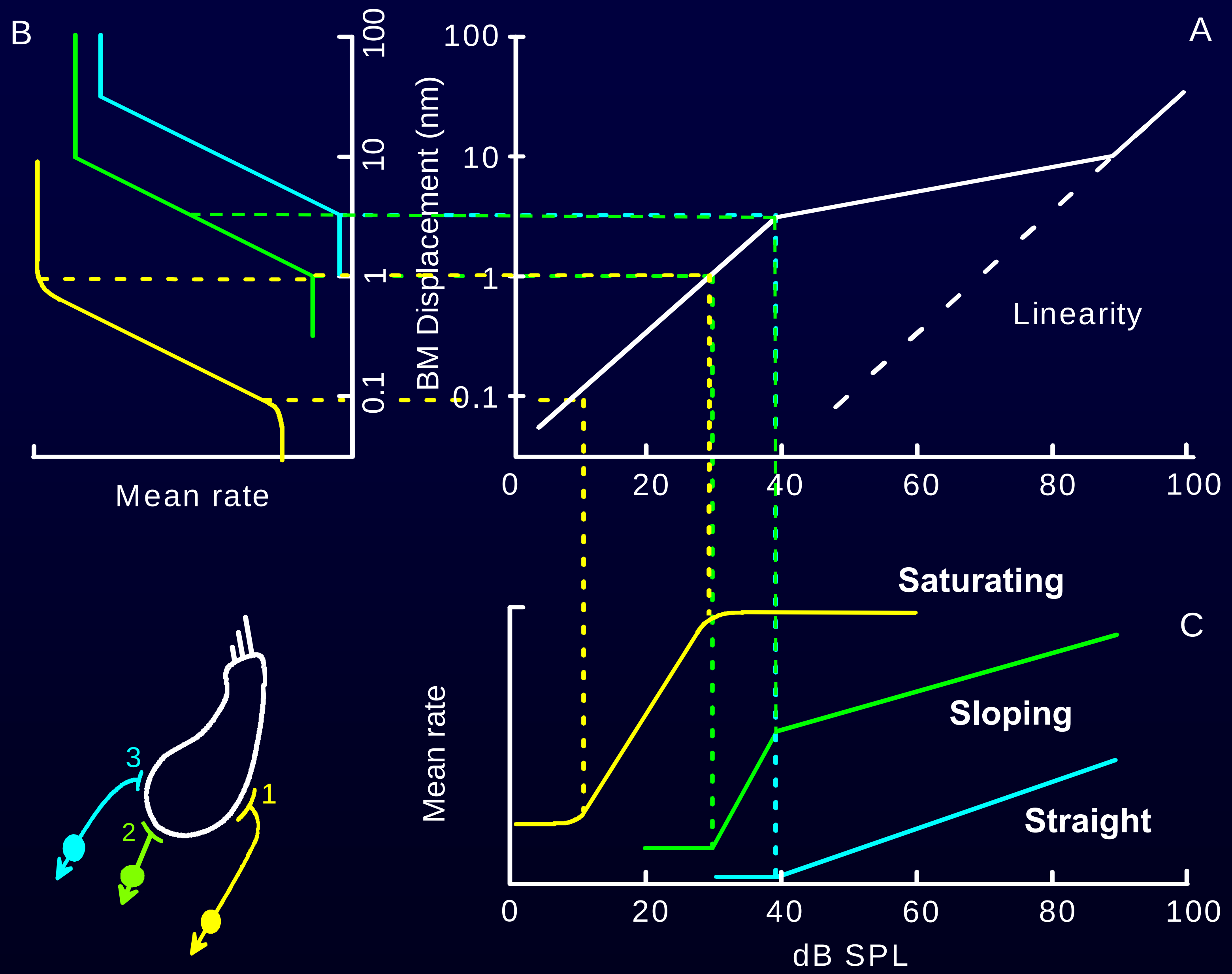
Nonlinear amplification by nonlinear mechanotransduction of OHC stereocilia in a positive feedback pathway



Preyer & Gummer (1996): Aud. Neurootol. 1, 3-11

Neural encoding with

IHCs of limited dynamic range ?


B
A
C
100
10
1
0.1
BM Displacement (nm)
Mean rate
Linearity
0
20
40
60
80
100
Saturating
Sloping
Straight
Mean rate
dB SPL
1
2
3

Solution

Synapses of different threshold
and
Nonlinear amplification of BM motion