

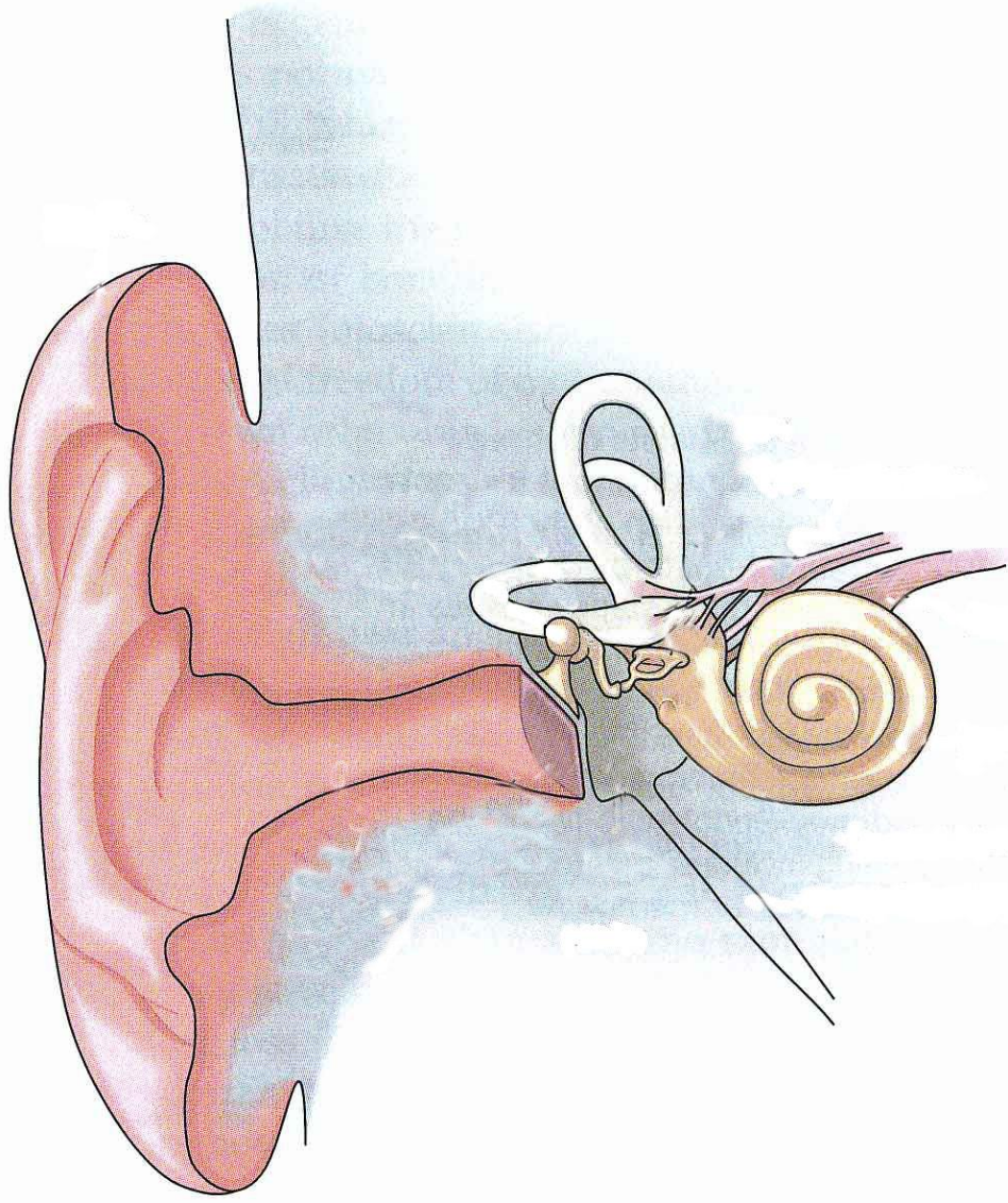
Modelling hair cells as sensory receptors and mechanical amplifiers for hearing

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Technical specifications of hearing

- fast periodic stimuli over a broad frequency range (20 Hz-20 kHz; up to 100 kHz in whales)
- sharp frequency selectivity ($\Delta f \simeq 3,5$ Hz pour un son à 1 kHz; $\Delta f / f \sim 0.35\%$)
- high sensitivity (limited by thermal noise; vibrations of atomic dimensions)
- enormous dynamical range (sound-pressure level: 20 μ Pa – 20 Pa)

$\times 1,000,000 !$

Sound-pressure level: **décibels (dB)**

→ a logarithmic scale

Level
(dB)

$$I_{dB} = 20 \log(p/p_{\text{ref}})$$

Air pressure

$$P(x, t) = P_{\text{atm}} + p(x, t)$$

$$P_{\text{atm}} = 100 \text{ kPa}$$

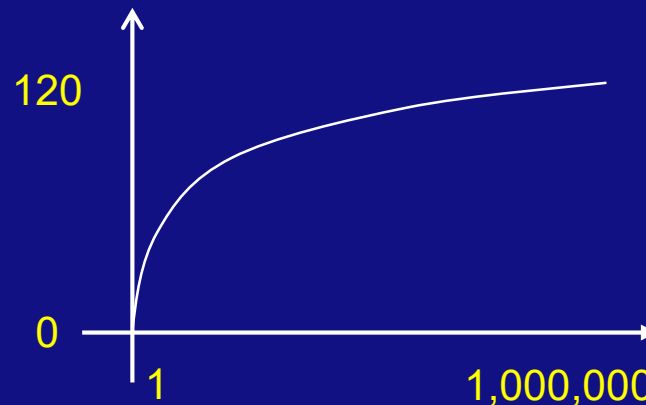
$$p_{\text{ref}} = 20 \text{ } \mu\text{Pa (hearing threshold)}$$

Intensity discrimination

$$1 \text{ dB or } \Delta p/p \cong 10\%$$

(Weber-Fechner law)

Level in dB



Sound
pressure (p/p_{ref})

Not a high-fidelity sound receiver!

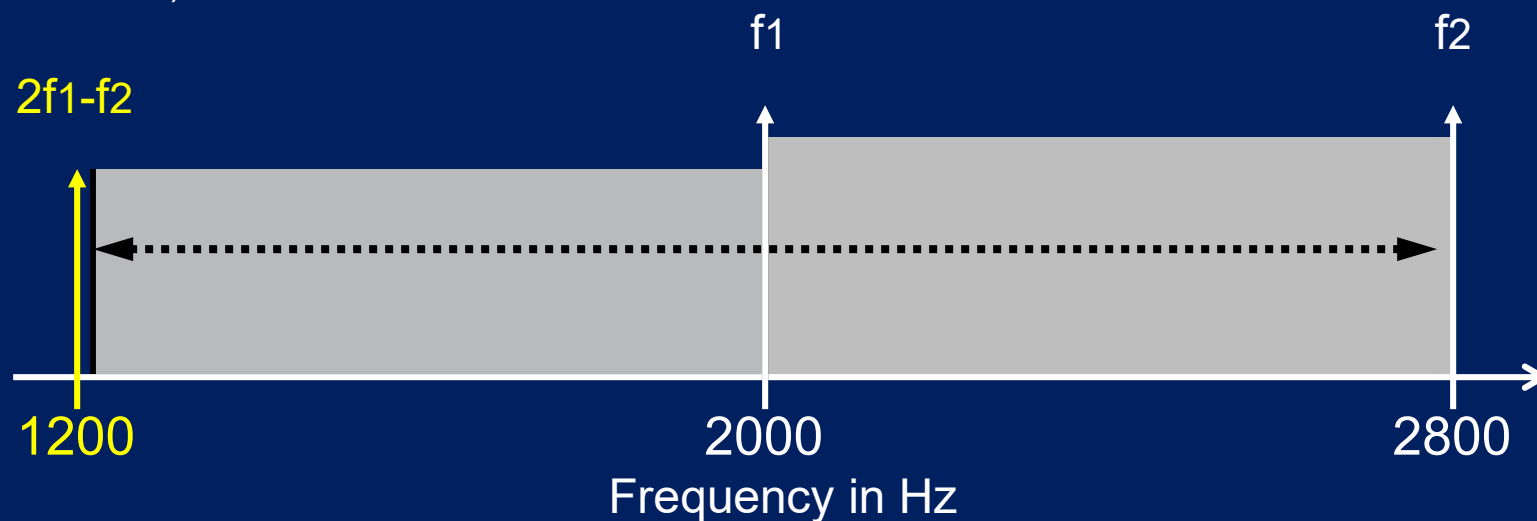


Tartini
(1692-1770)

« Phantom tones »

→ two-tone stimulus:

$$F(t) = \bar{F} \sin(2\pi f_1 t) + \bar{F} \sin(2\pi f_2 t) \quad (f_1 < f_2)$$



primary tone f_1



primary chirp f_2



f_1 and f_2



(Source: Daniel Presnitzer, ENS, Paris)

« Phantom tones »

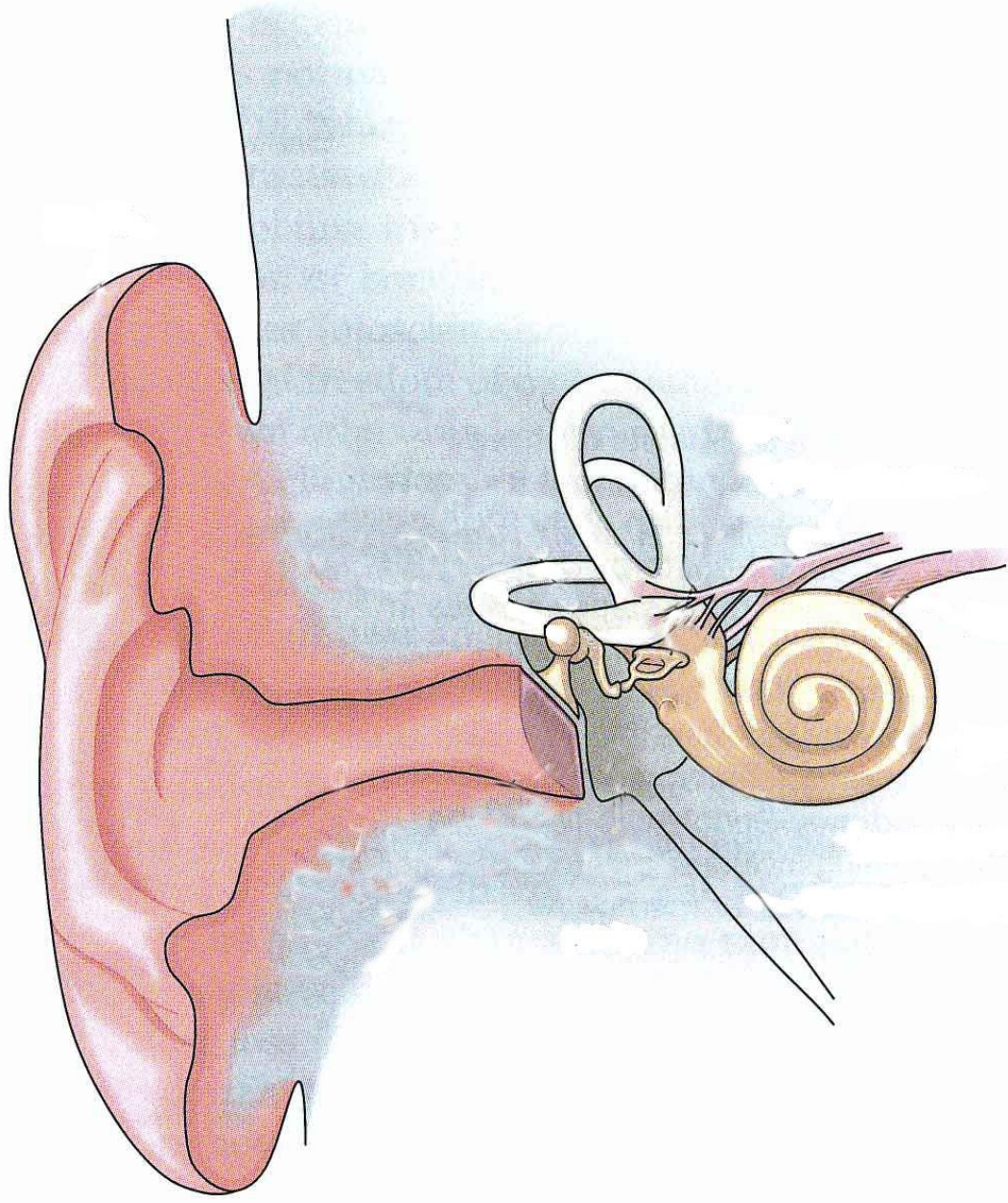
$$F(t) = \bar{F} \sin(2\pi f_1 t) + \bar{F} \sin(2\pi f_2 t) \quad (f_1 < f_2)$$

- $f_2 - f_1$ must be small ($f_2/f_1 = 1.1-1.3$)
- perceived even at low levels (threshold $\cong 20$ dB)
- distortion at $2f_1 - f_2$ dominates
- relative level at $2f_1 - f_2$ nearly independent of stimulus level (15-20%)

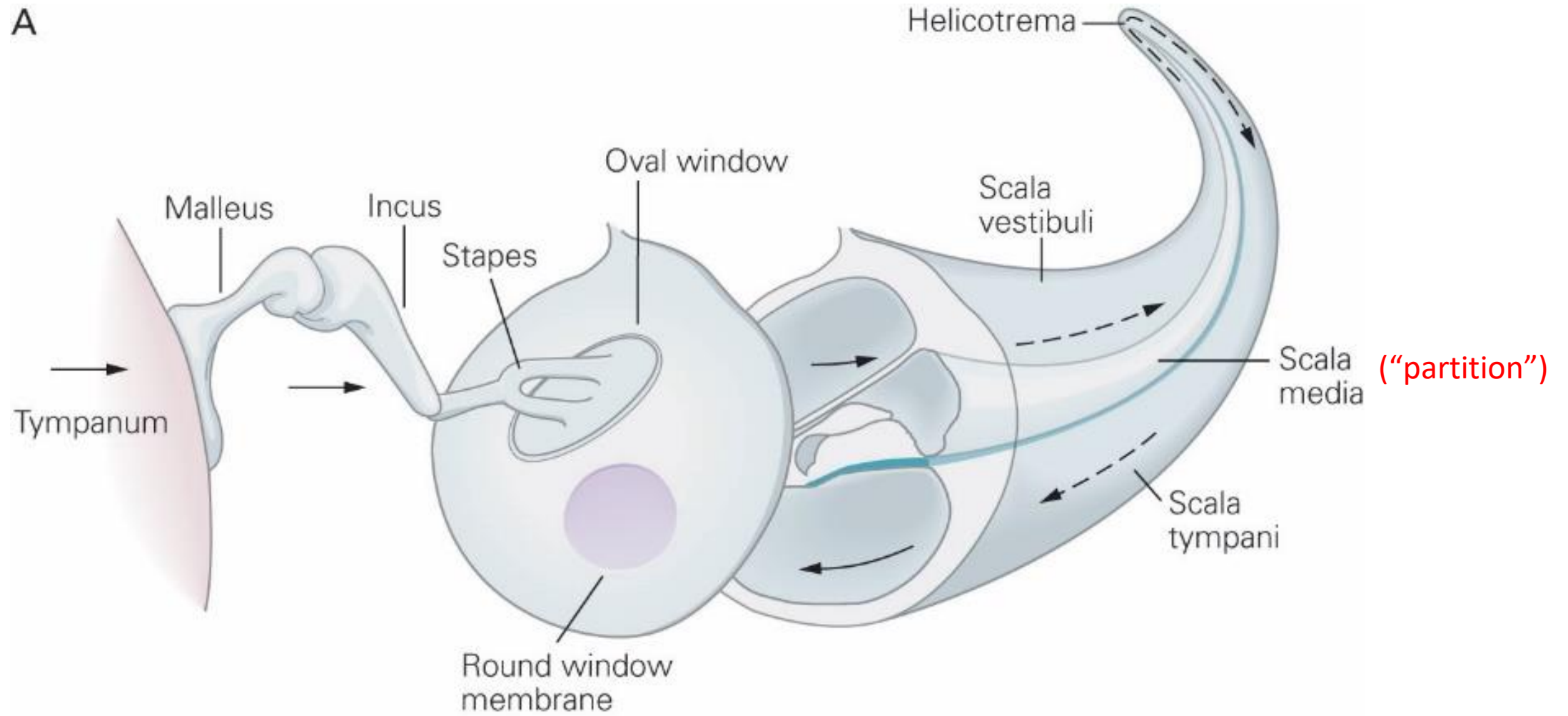
 Auditory nonlinearity

(J.L. Goldstein, JASA (1967))

A brief introduction to cochlear mechanics

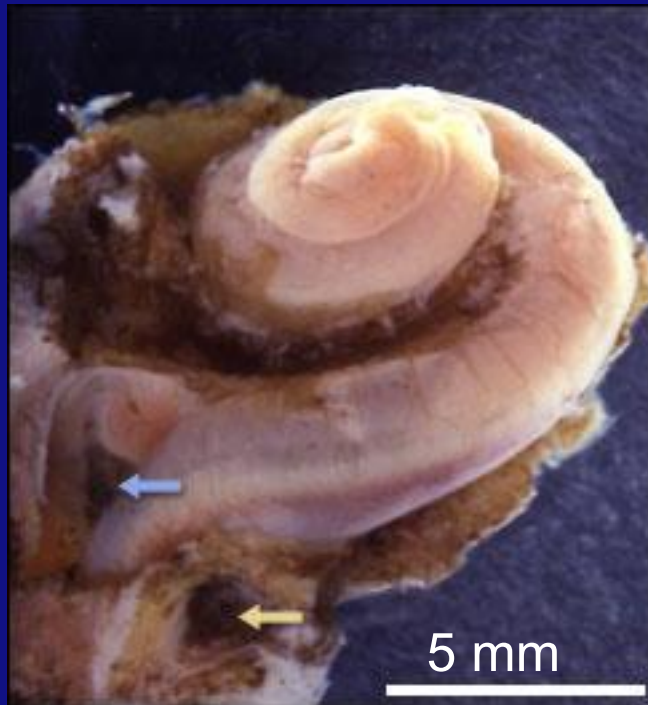


A

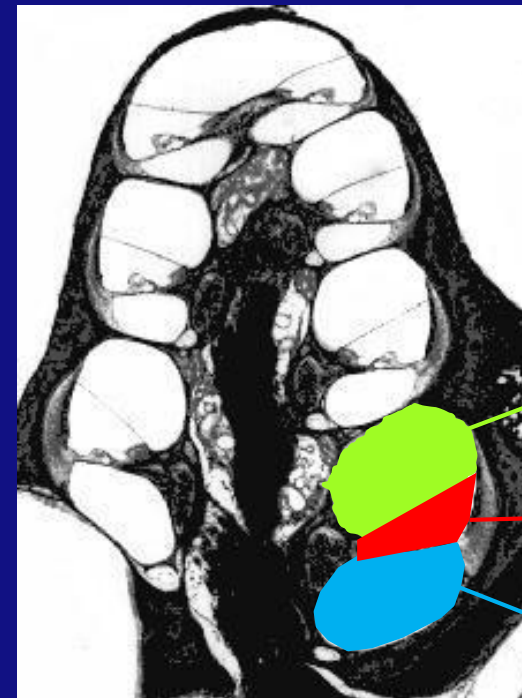


The cochlea: hearing organ

Human cochlea



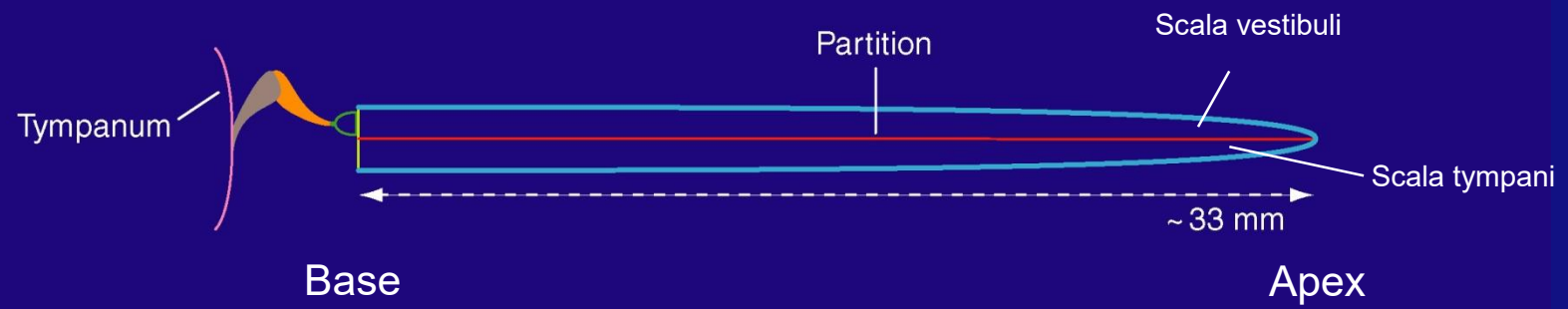
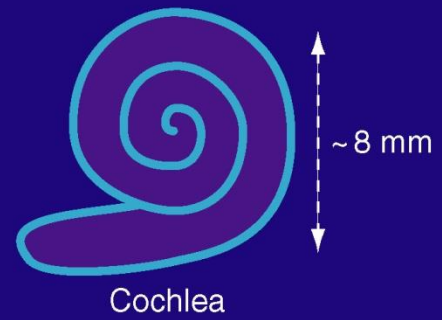
Guinea pig
(cross-section)

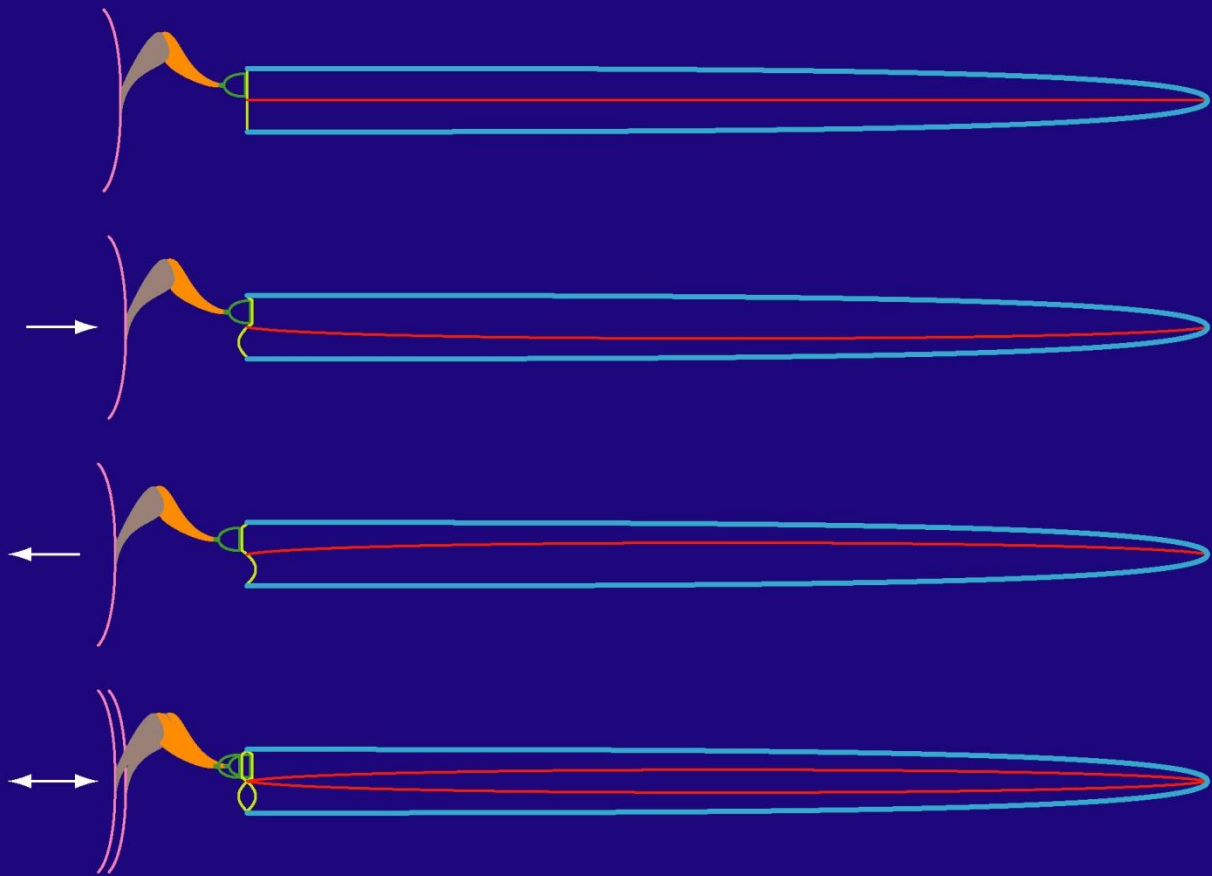


scala
vestibuli

Partition
(sensory cells)

scala
tympani

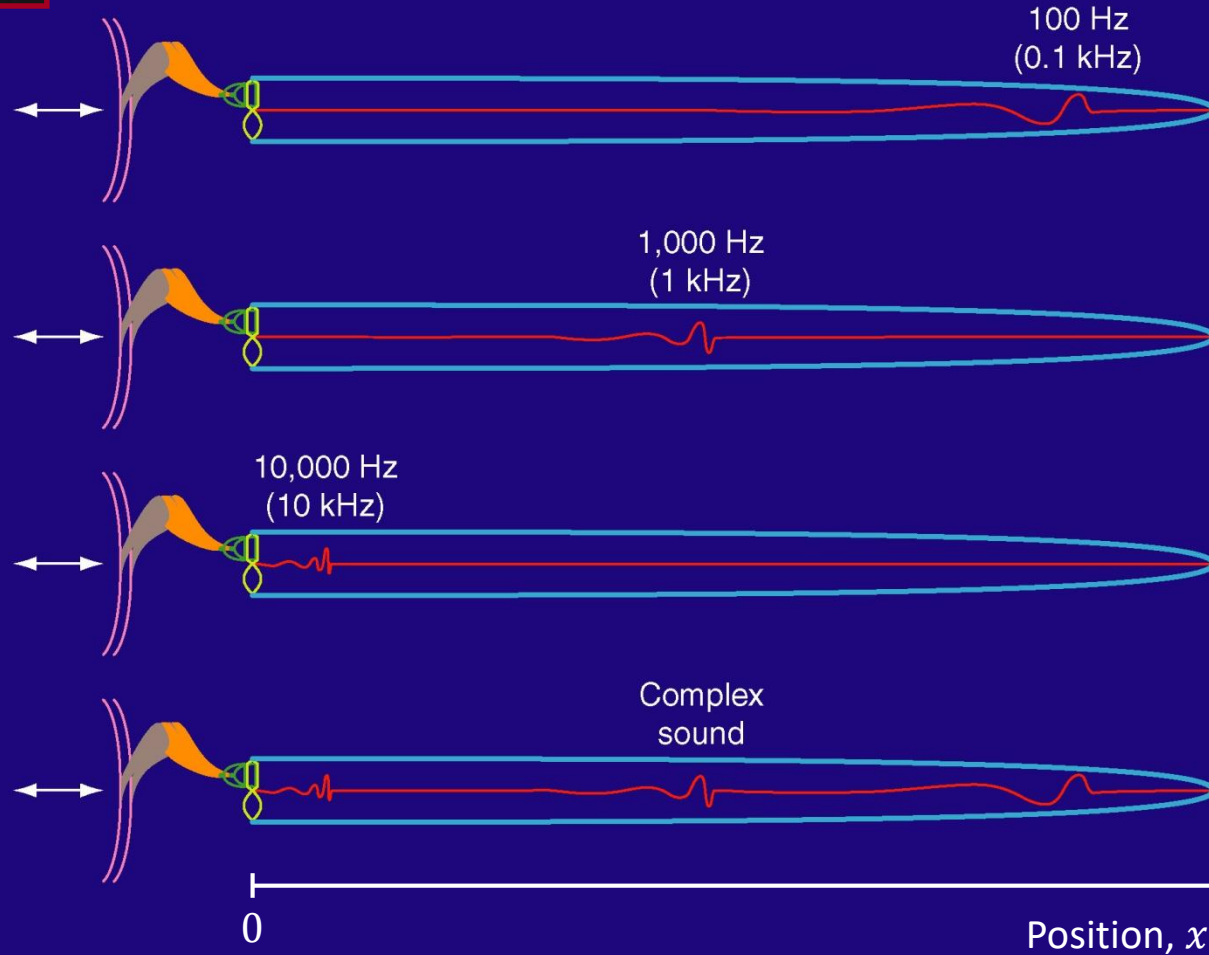






Frequency analysis

Georg von Békésy (1899-1972)



FREQUENCY MAP

$$f \approx f_0 \exp(-x/d)$$

In humans: $f_0 = 20 \text{ kHz}$
 $d = 7.5 \text{ mm}$

The cochlea as an “acoustic prism”

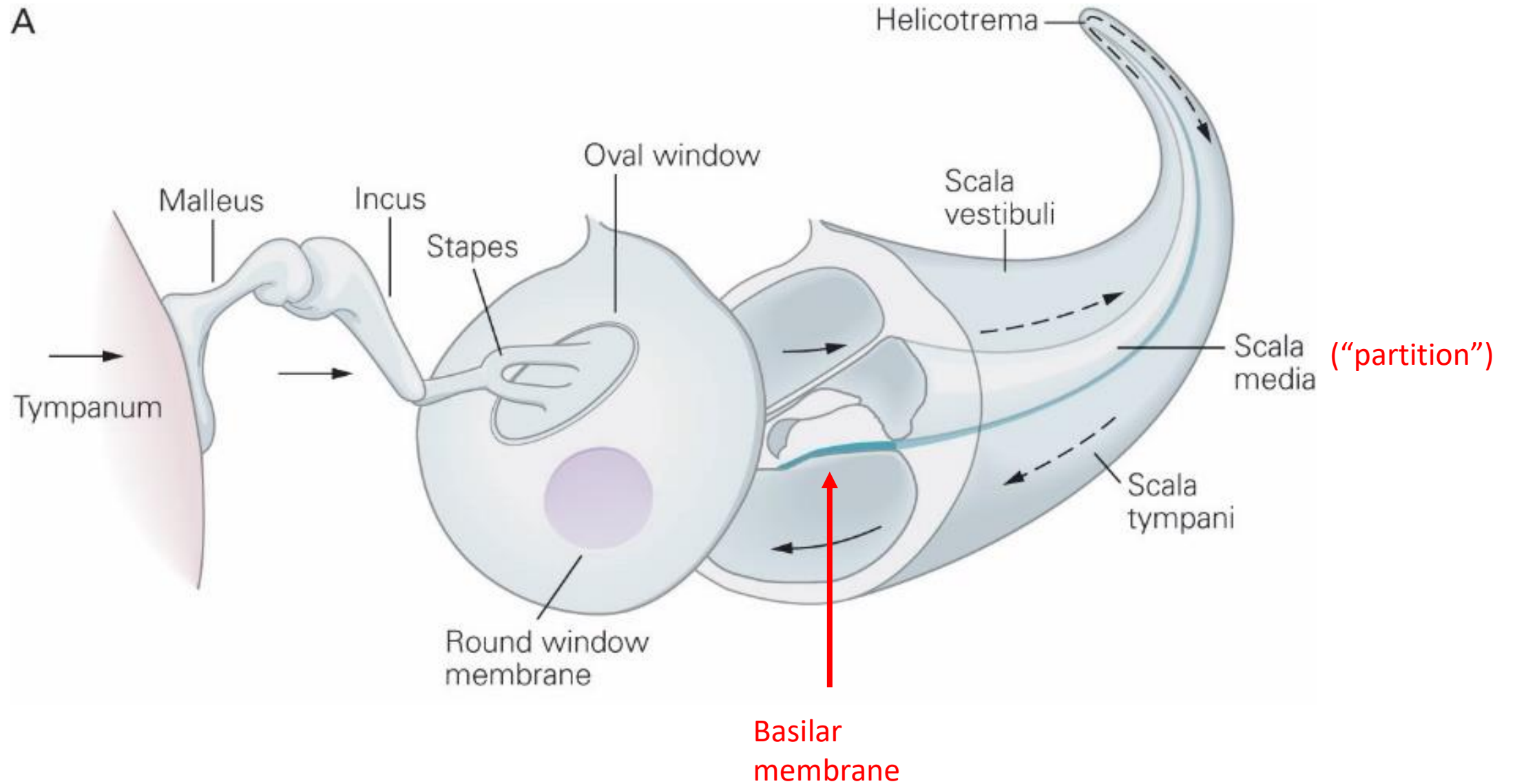
→ a dispersive medium

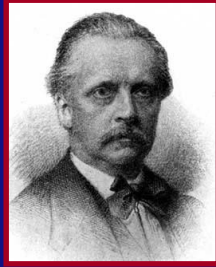




(source: Jim Hudspeth; Rockefeller University, New York)

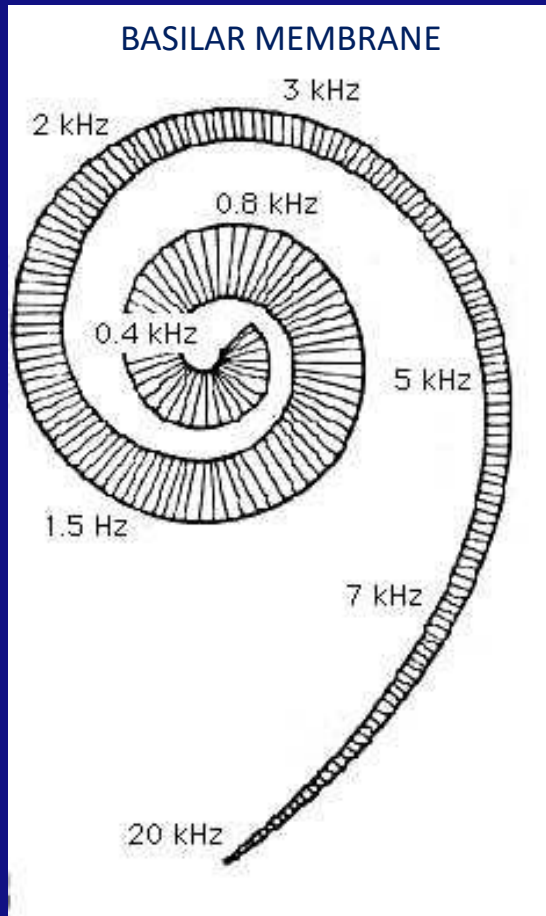
A





« Sympathetic vibration »

Hermann von Helmholtz (1821-1894)



« (...) the radial fibers of the basilar membrane may be approximately regarded as forming **a system of stretched strings** (...). In that case the laws of their motion would be the same as if **every individual string moved independently from the others**, and obeyed the influence of the periodically alternating pressure of the fluid (...). Consequently any exciting tone would set that part of the membrane into **sympathetic vibration** (...). »

(from “On the sensation of tones”, 1877)

Place of Section	Breadth of Membrane or Length of Transverse Fibres	
	Millimetres	Inches
0.2625 mm. [= 0.010335 in.] from root . . .	0.04125	.00162
0.8626 mm. [= 0.033961 in.] from root . . .	0.0825	.00325
Middle of the first spire	0.169	.00665
End of first spire	0.3	.01181
Middle of second spire	0.4125	.01624
End of second spire	0.45	.01772
At the hamulus	0.495	.01949

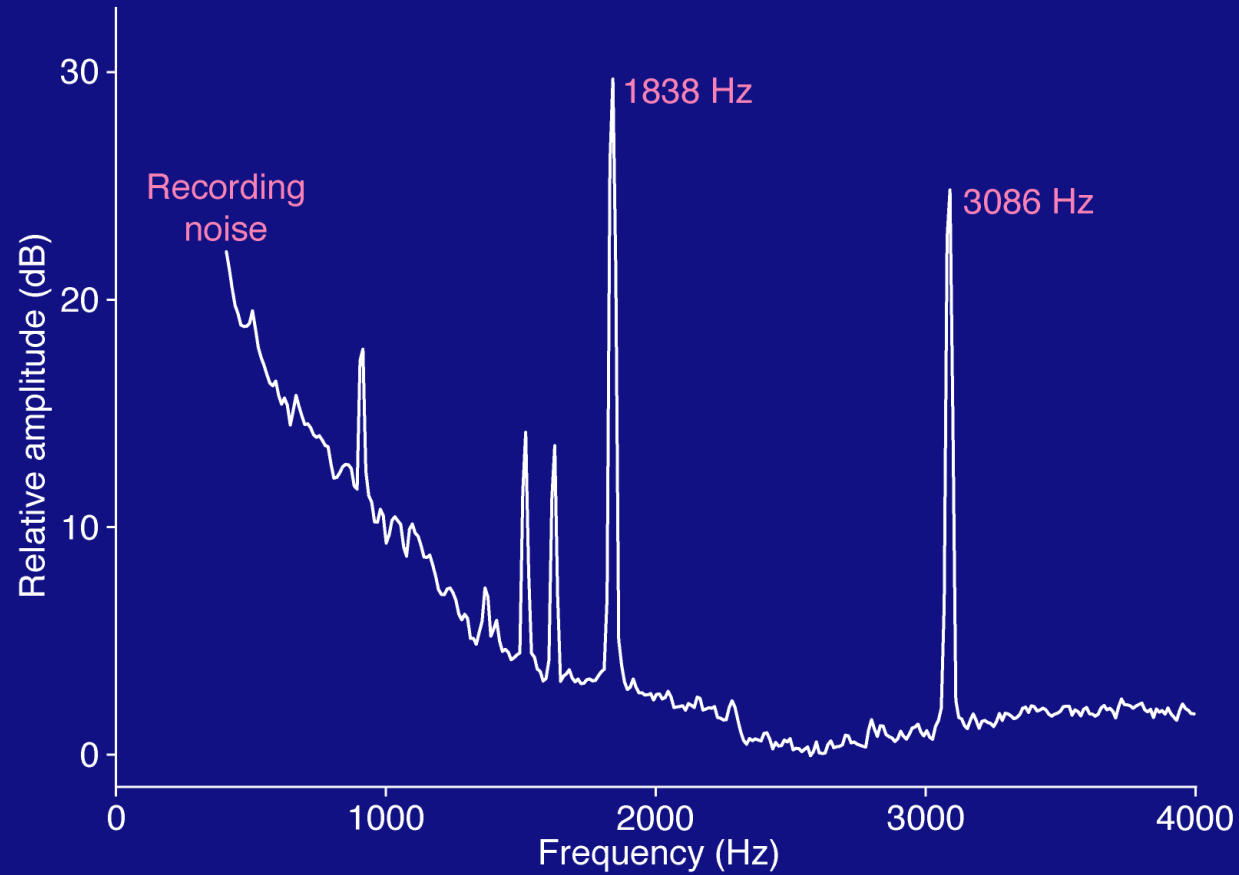
The breadth therefore increases more than twelvefold from the beginning to the end.



But the vibrating « strings » are immersed in a viscous fluid...

The ear can sing!

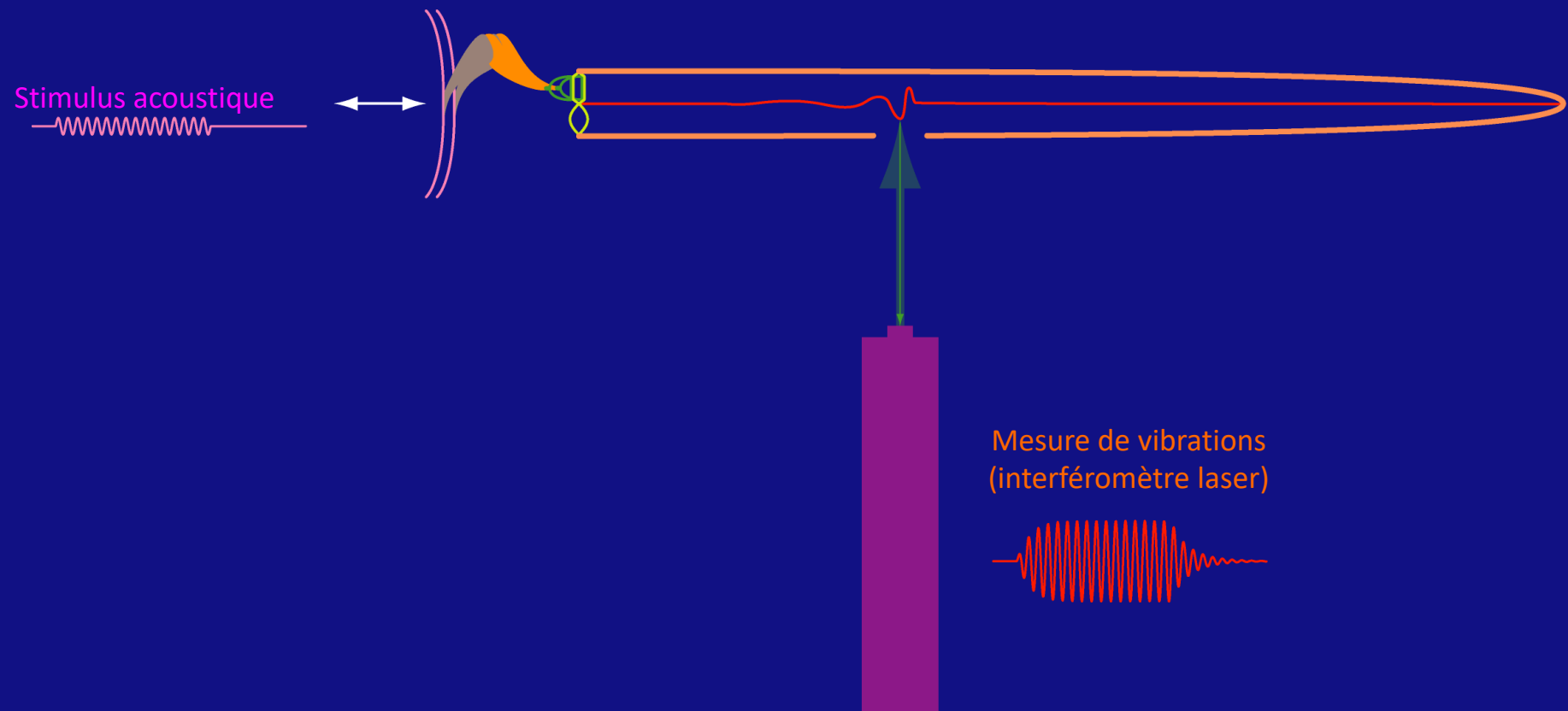
→ Spontaneous oto-acoustic emissions

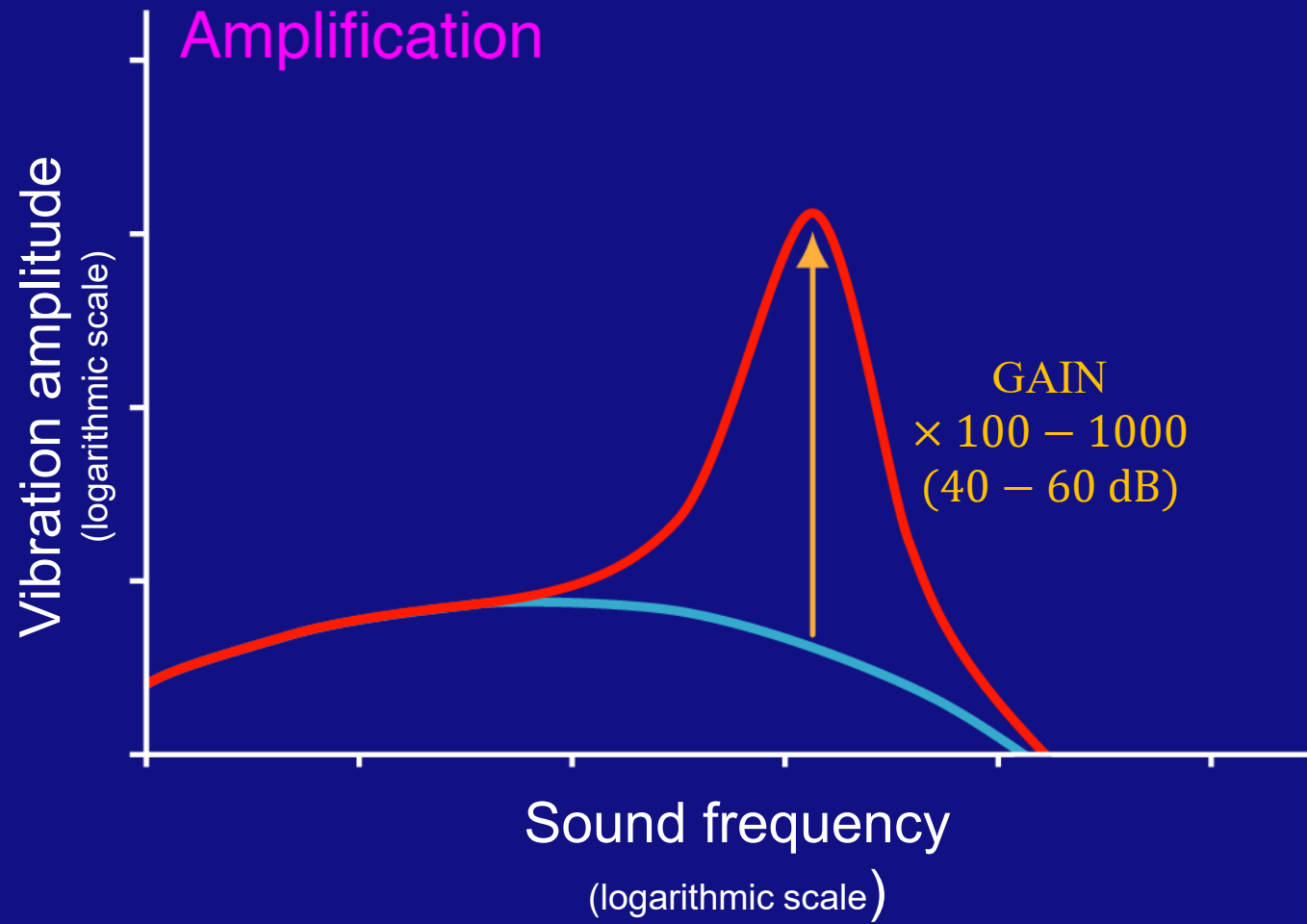


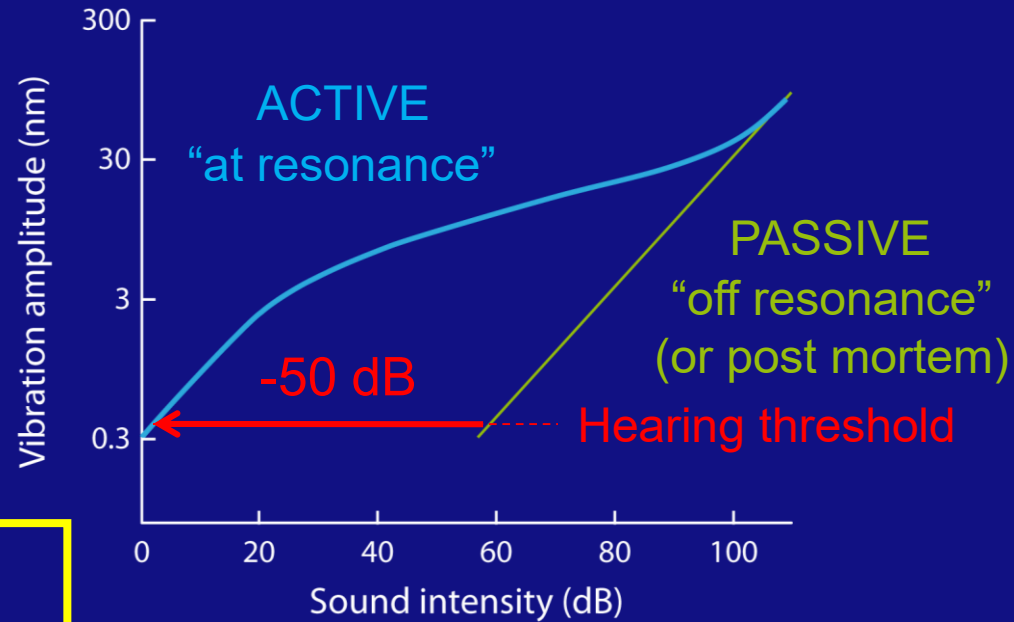
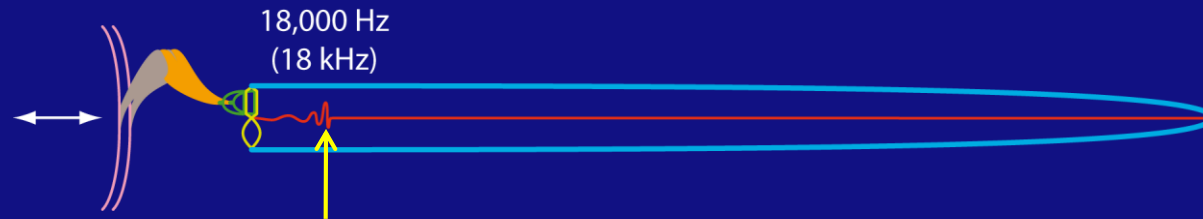
➡ ACTIVE
MECHANICS

Data from P. van Dijk









(adapted from: Ruggero et al., JASA (1997))

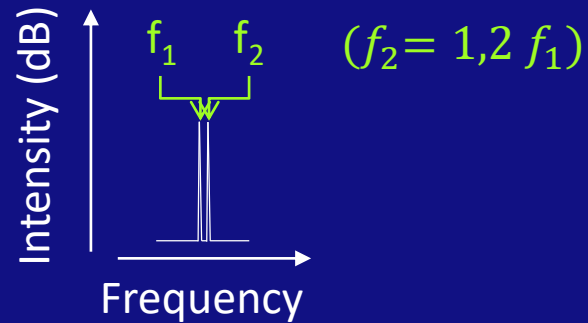
Amplification
of weak sounds
at a characteristic frequency

Distortion products

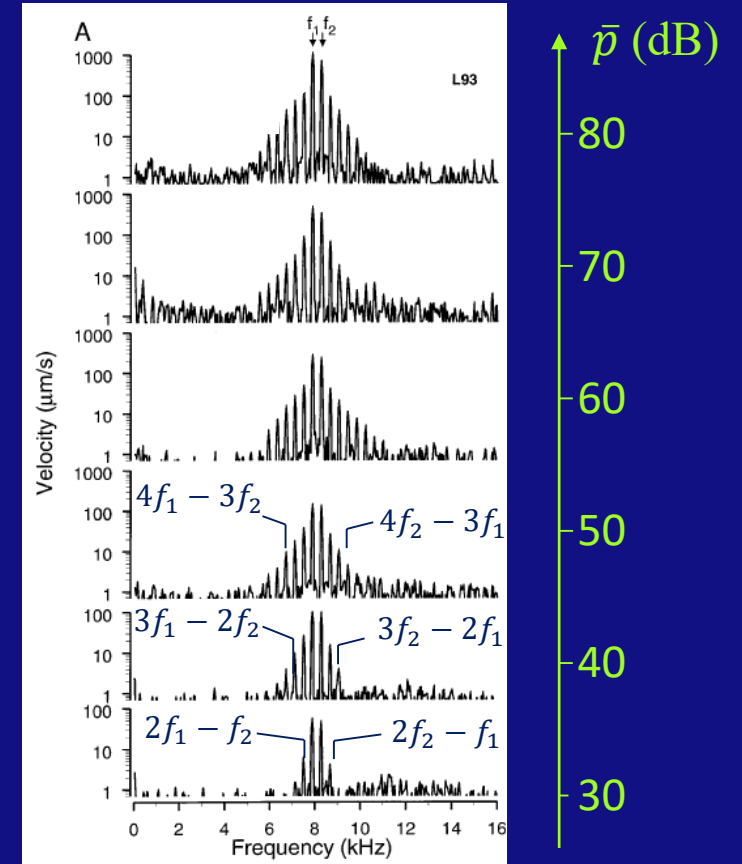
→ linear combinations $mf_1 + nf_2$ (m et n integers)

SOUND STIMULUS

$$p(t) = \bar{p} \sin(2\pi f_1 t) + \bar{p} \sin(2\pi f_2 t)$$



VIBRATION OF THE BASILAR MEMBRANE

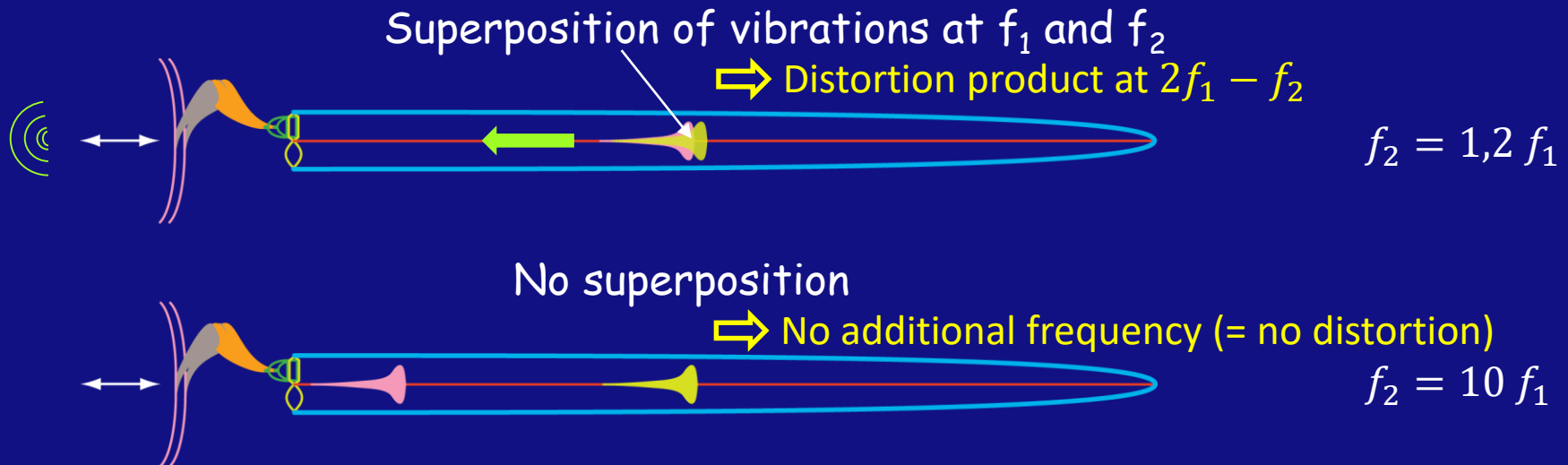


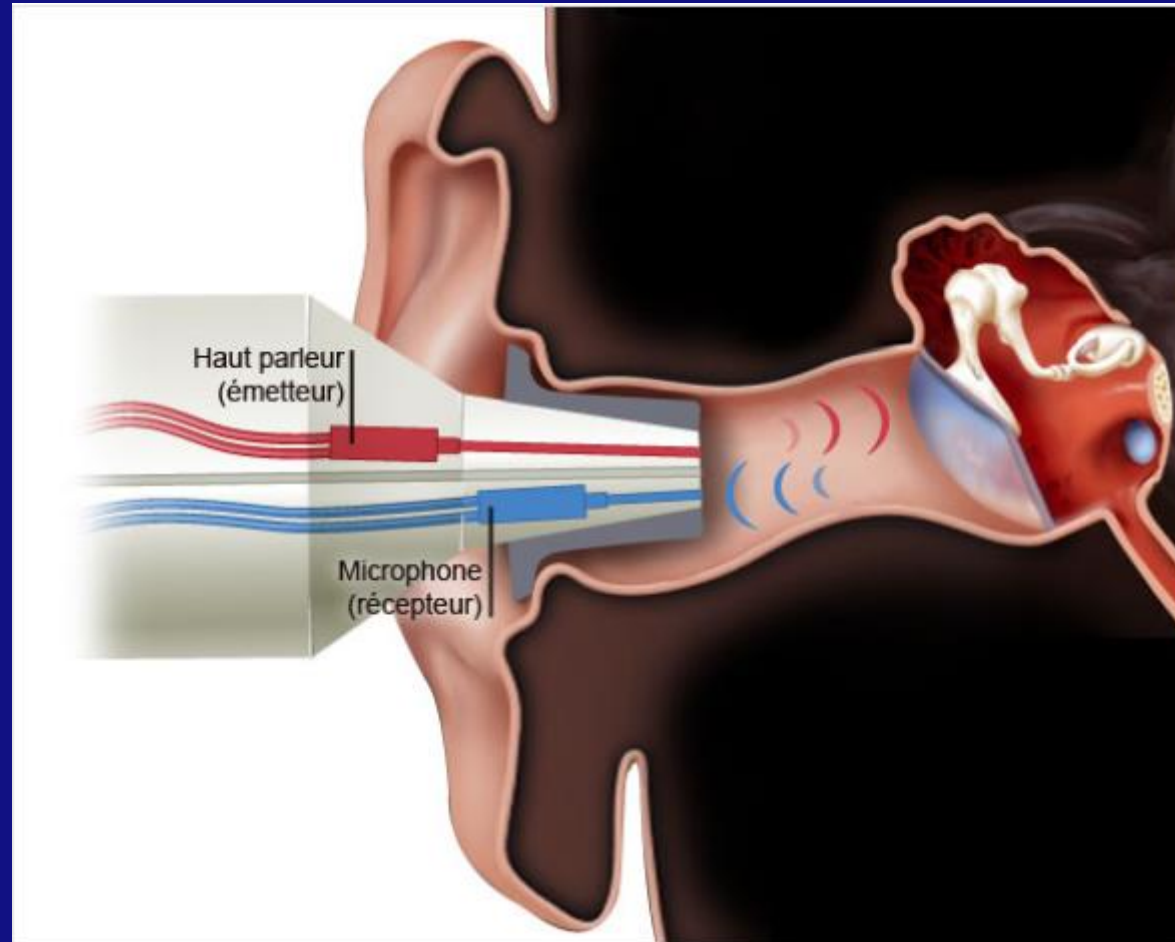
(Robbles, Ruggero, Rich (1997) *J Neurophysiol*)

Cochlear vibrations

→ evoked oto-acoustic emissions

STIMULUS: $F(t) = \bar{F} \sin(2\pi f_1 t) + \bar{F} \sin(2\pi f_2 t)$





Neonatal deafness screening

(since 2012 in France)

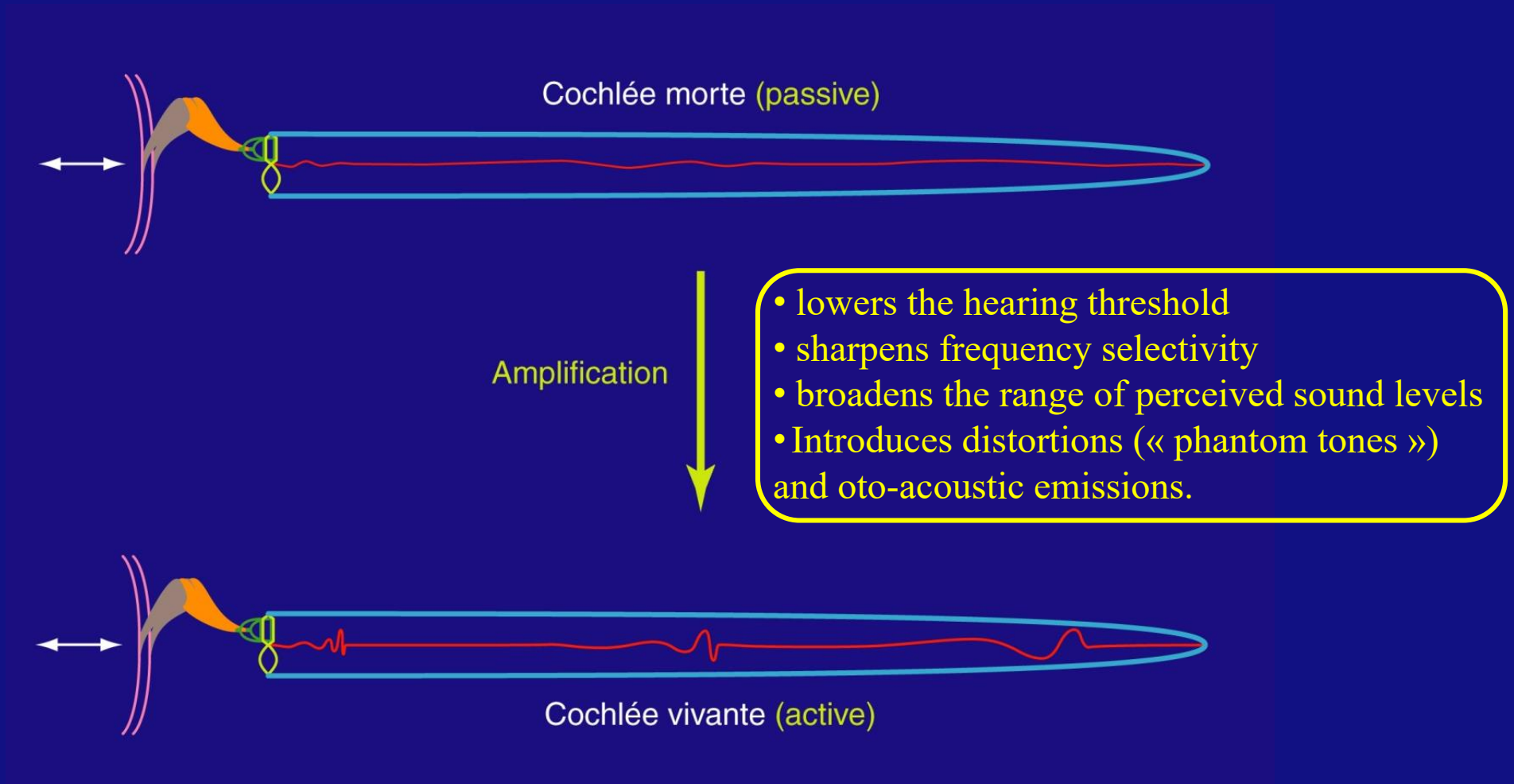
- Deafness: 1 birth in 700 to 1000 (> 800 / year in France)
- 50% : no a-priori pre-disposition
- Cochlear origin in > 97% cases
- Without early testing (P2 –P4), diagnostic 16 months to 3 years after birth (→ language problems)

CARNET DE SANTÉ

 Dépistage d'une déficience auditive			
	non ☐	oui ☐	
Méthode			
Résultat	normal	à surveiller	
OD	☐	☐	
OG	☐	☐	
Signature et cachet			



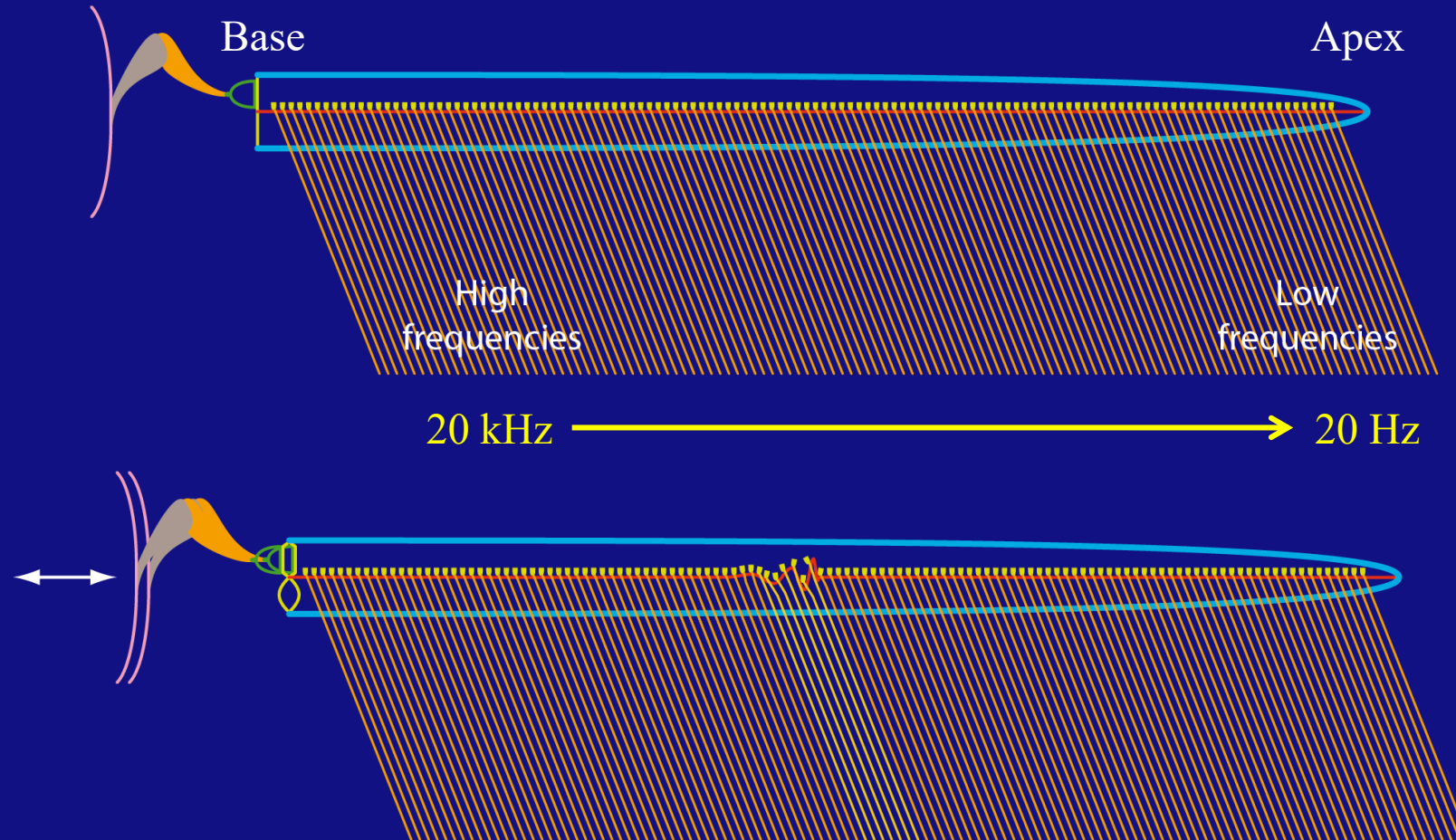
The cochlear amplifier





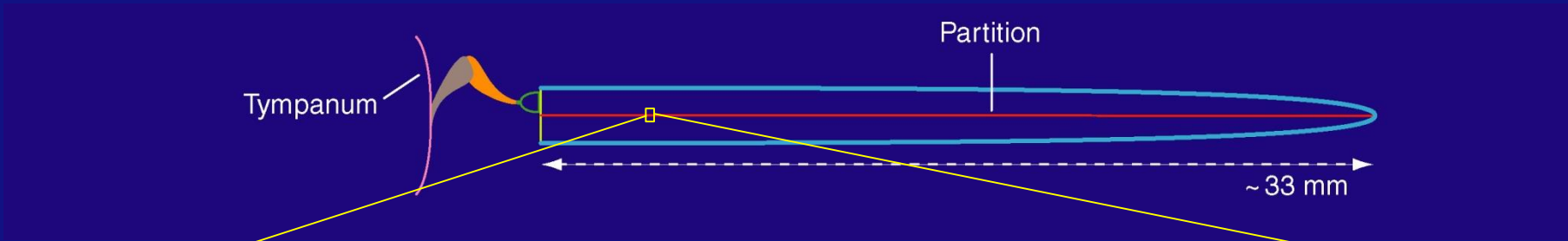
The cochlea

→ tonotopic map

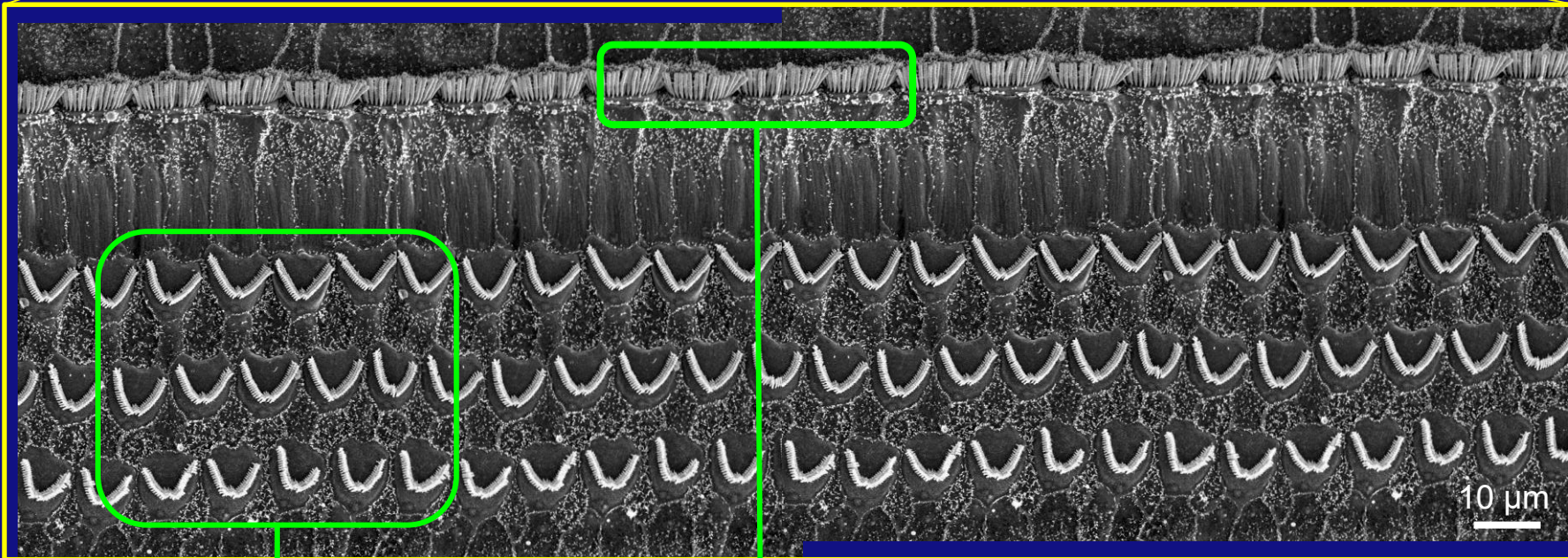


Hair cells

→ the sensory receptors of the inner ear

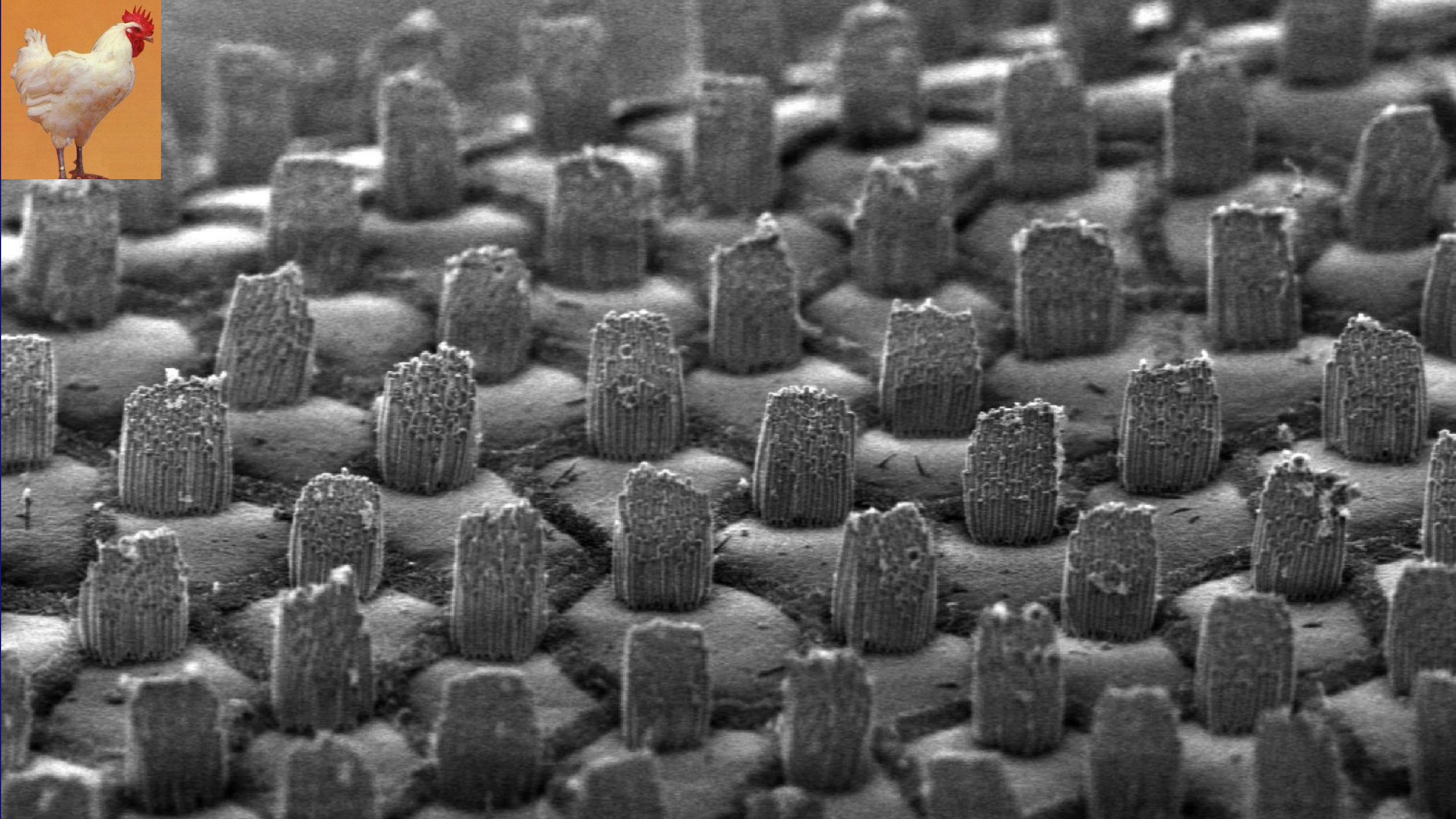
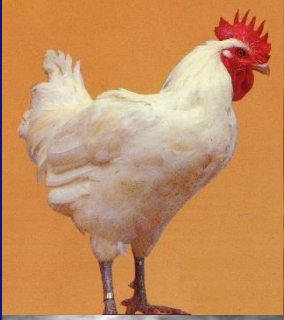


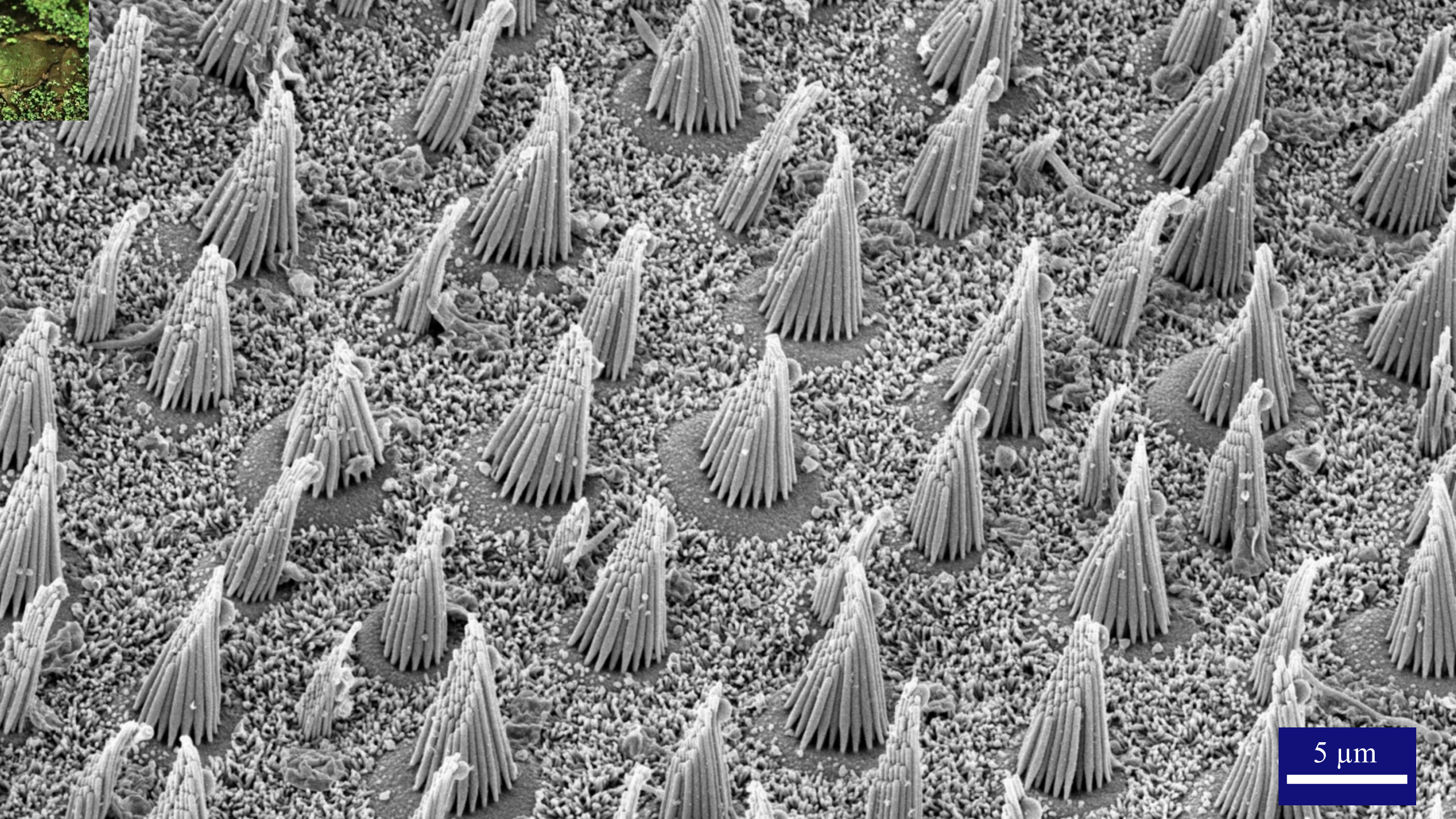
Seen from the top of the partition



Outer hair cells

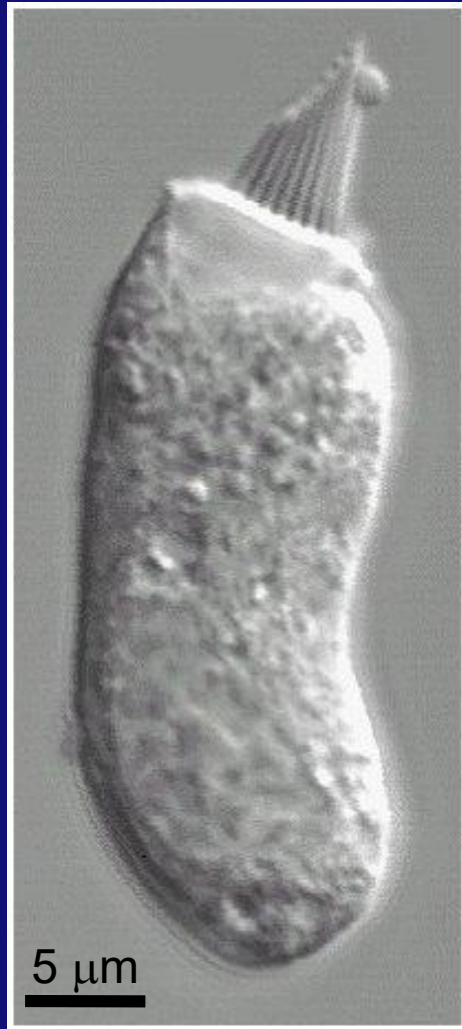
Inner hair cells



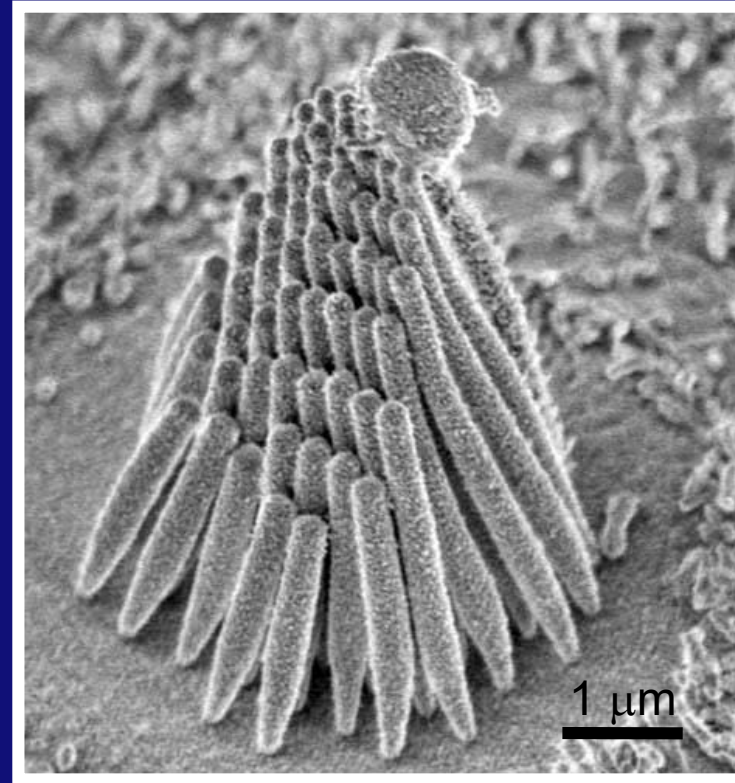


5 μm

The hair cell

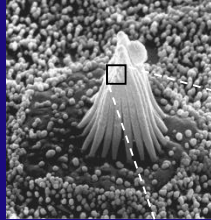


(A.J. Hudspeth)

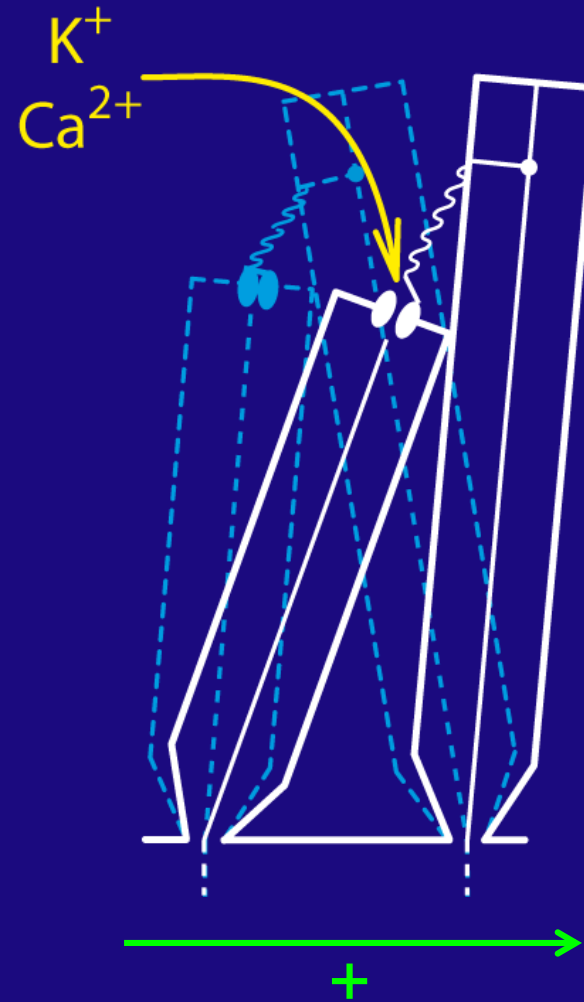


(P. Gillespie)

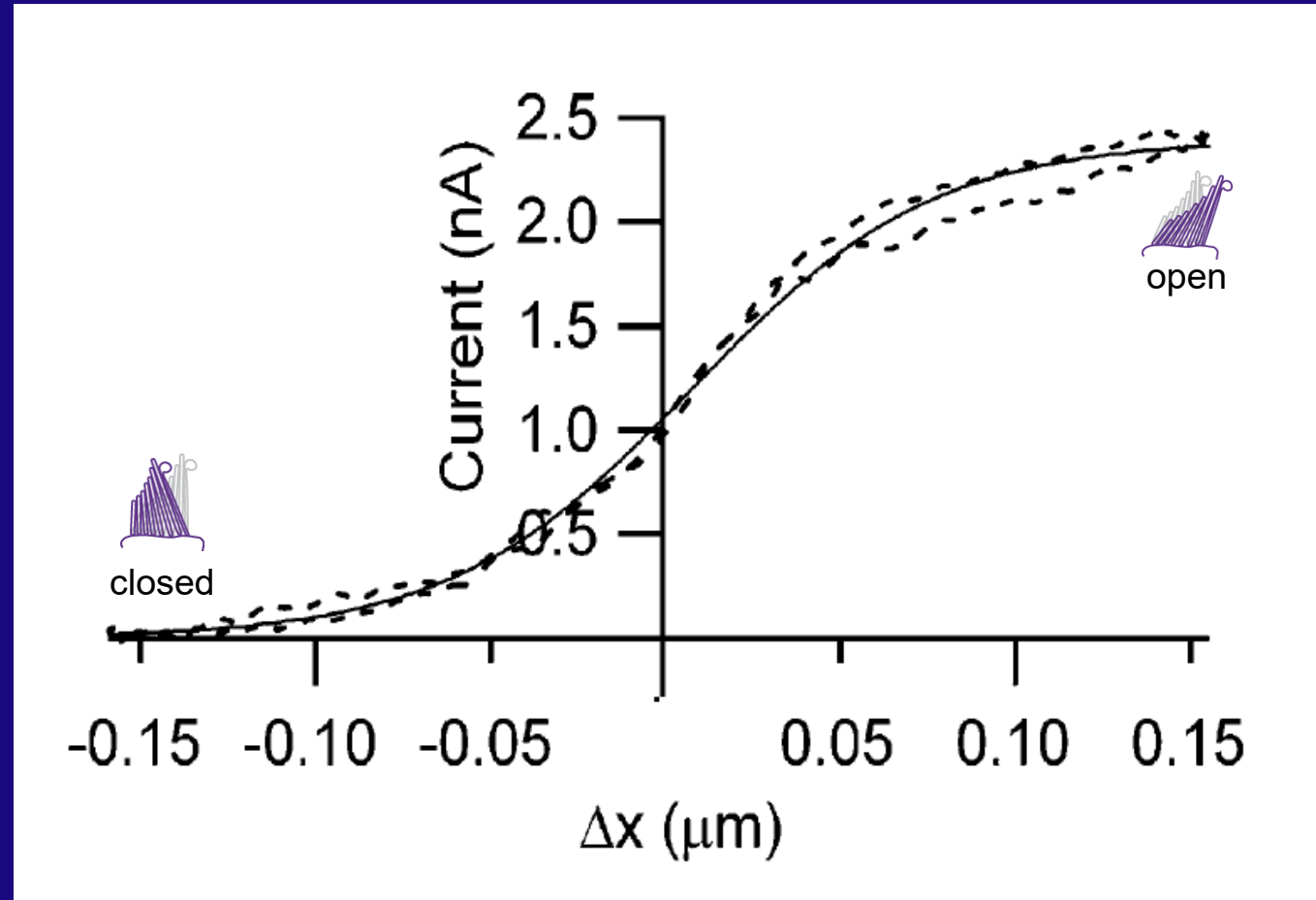
The hair bundle: mechanical antenna



(A.J. Hudspeth)



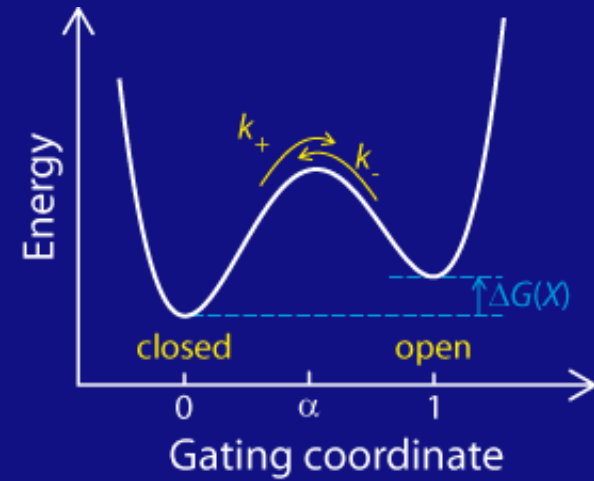
Transduction current



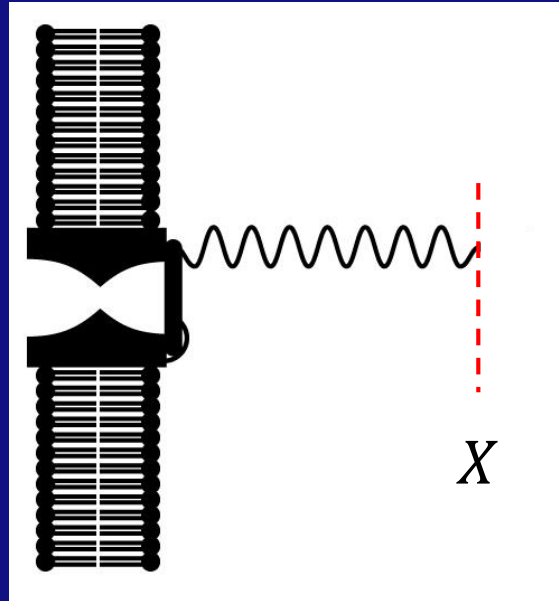
(Johnson et al, Neuron (2011))

Gating-spring model

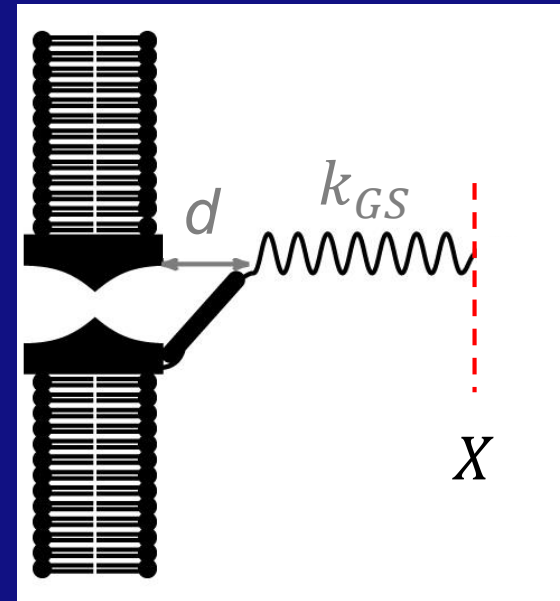
(Corey and Hudspeth, 1983)



Channel closed



Channel open



GATING FORCE

$$Z = k_{GS} d$$

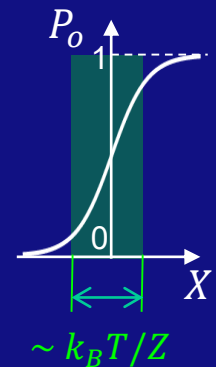
gating-spring
stiffness

gating
swing

OPEN PROBABILITY

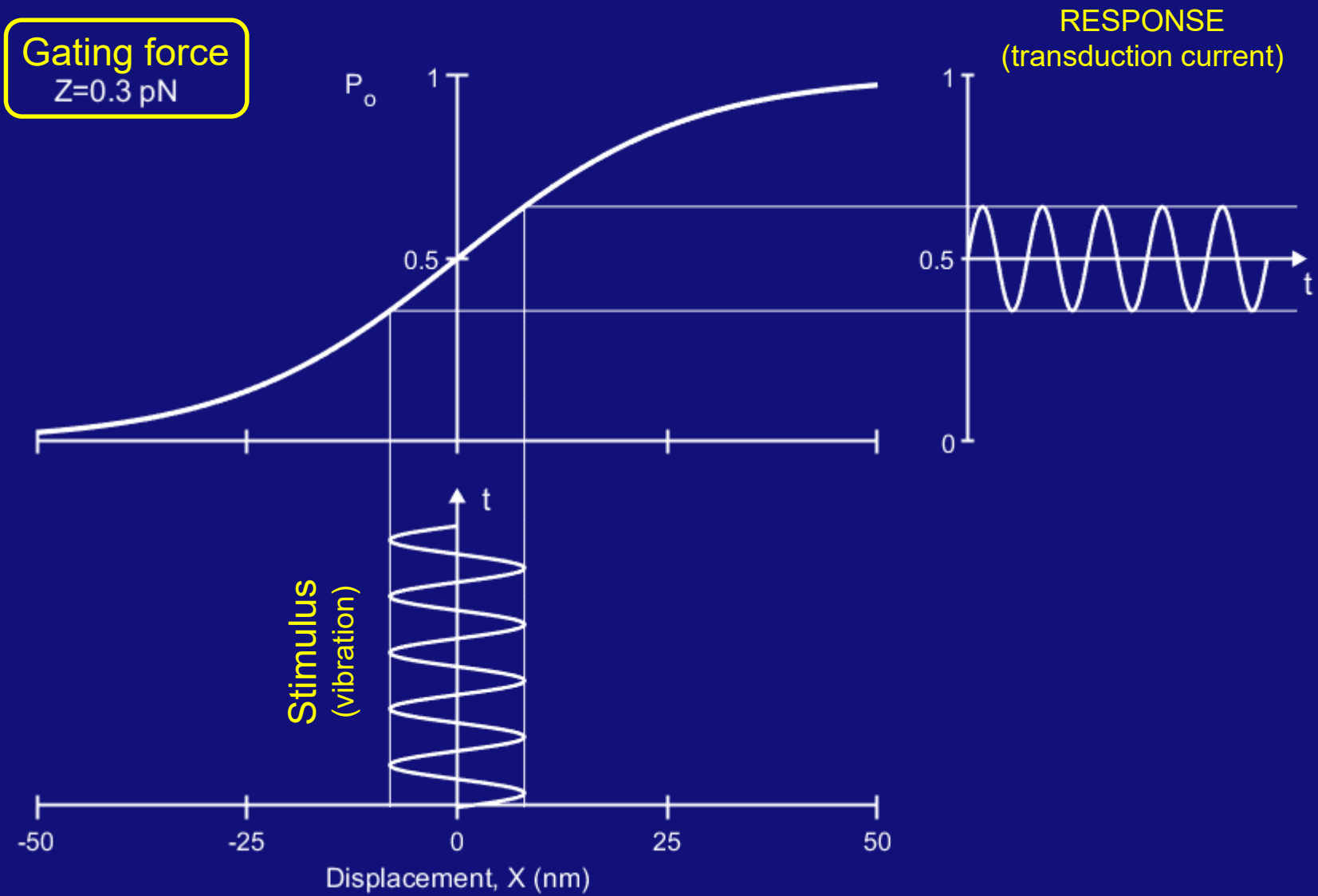
$$P_o = \frac{1}{1 + \exp\left(-\frac{Z(X - X_0)}{k_B T}\right)}$$

Energy difference $\Delta G(X)$

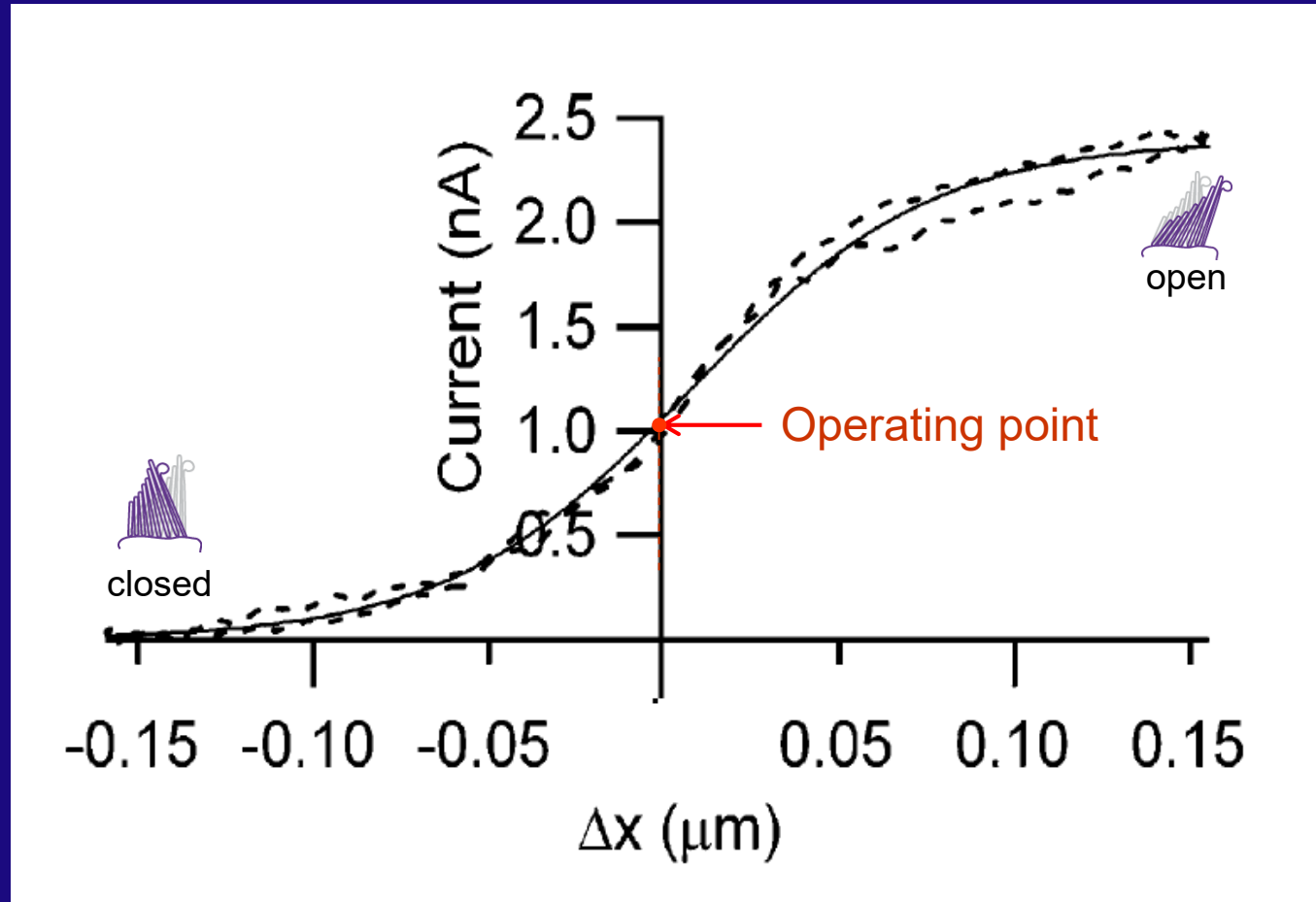


Gating force

$Z=0.3 \text{ pN}$

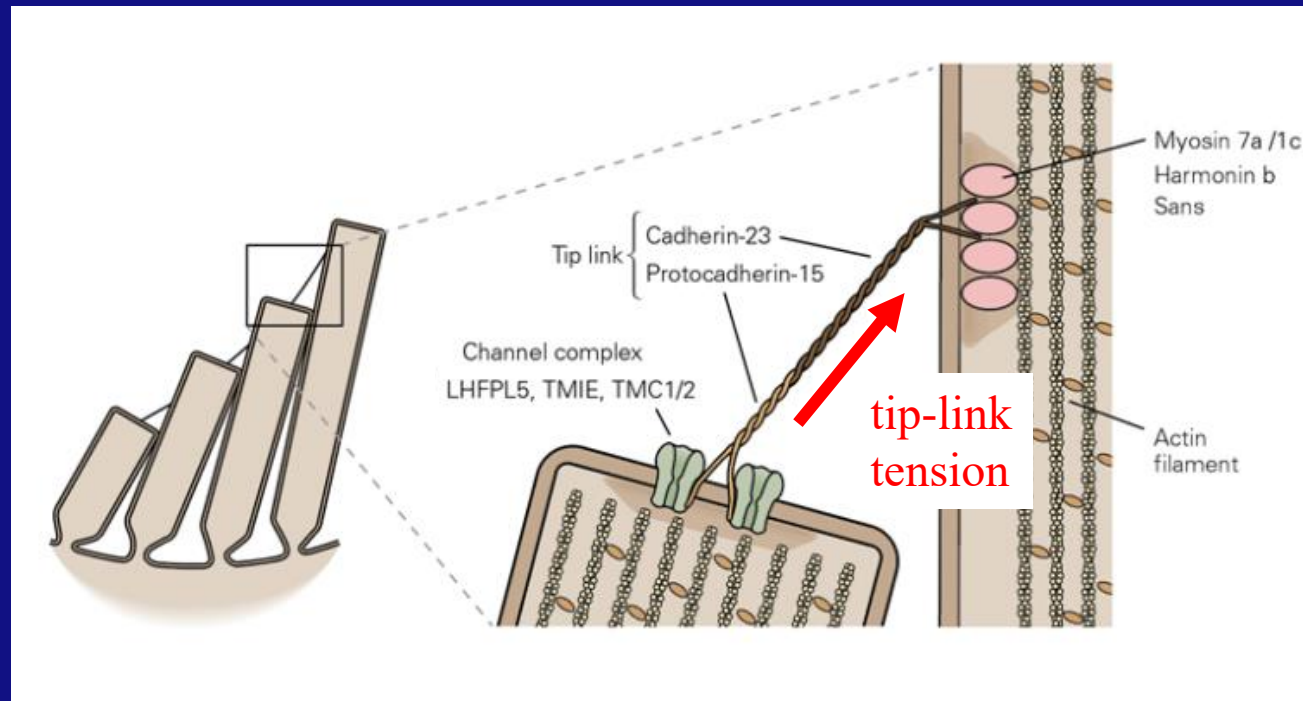


Transduction current

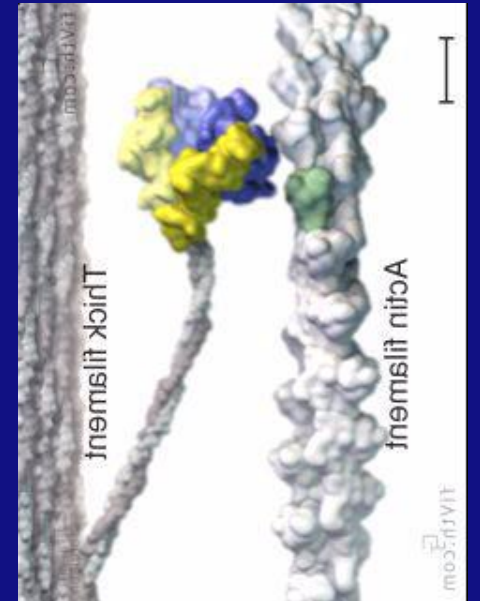


(Johnson et al, Neuron (2011))

The « tip-link complex »



Molecular motor

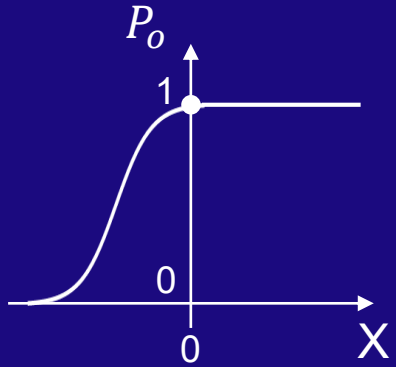


(Ron Vale)

The « tip-link complex »

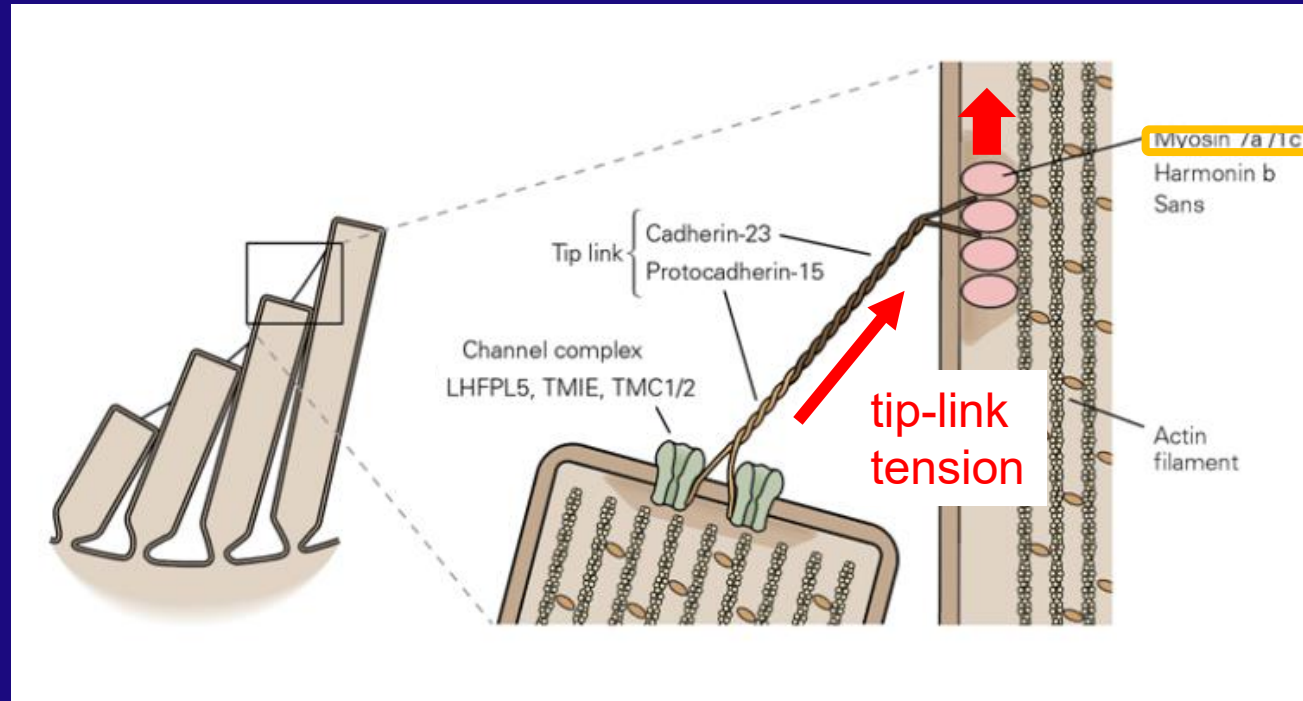
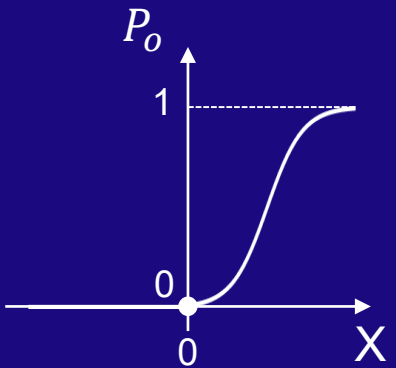
STRONG MOTORS

(open channels at rest)



WEAK MOTORS

(closed channels at rest)

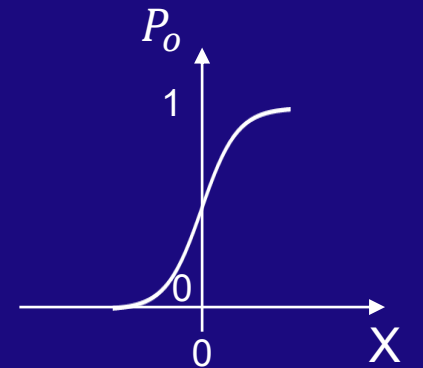


(Zheng and Holt, *Ann Rev Biophys* (2020))

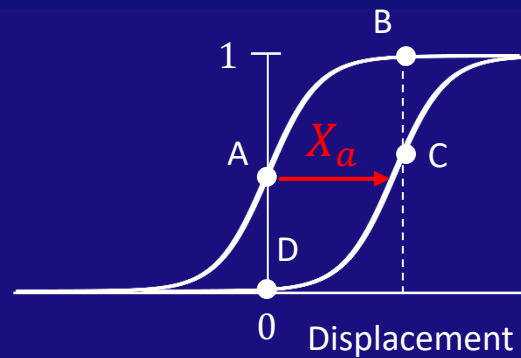
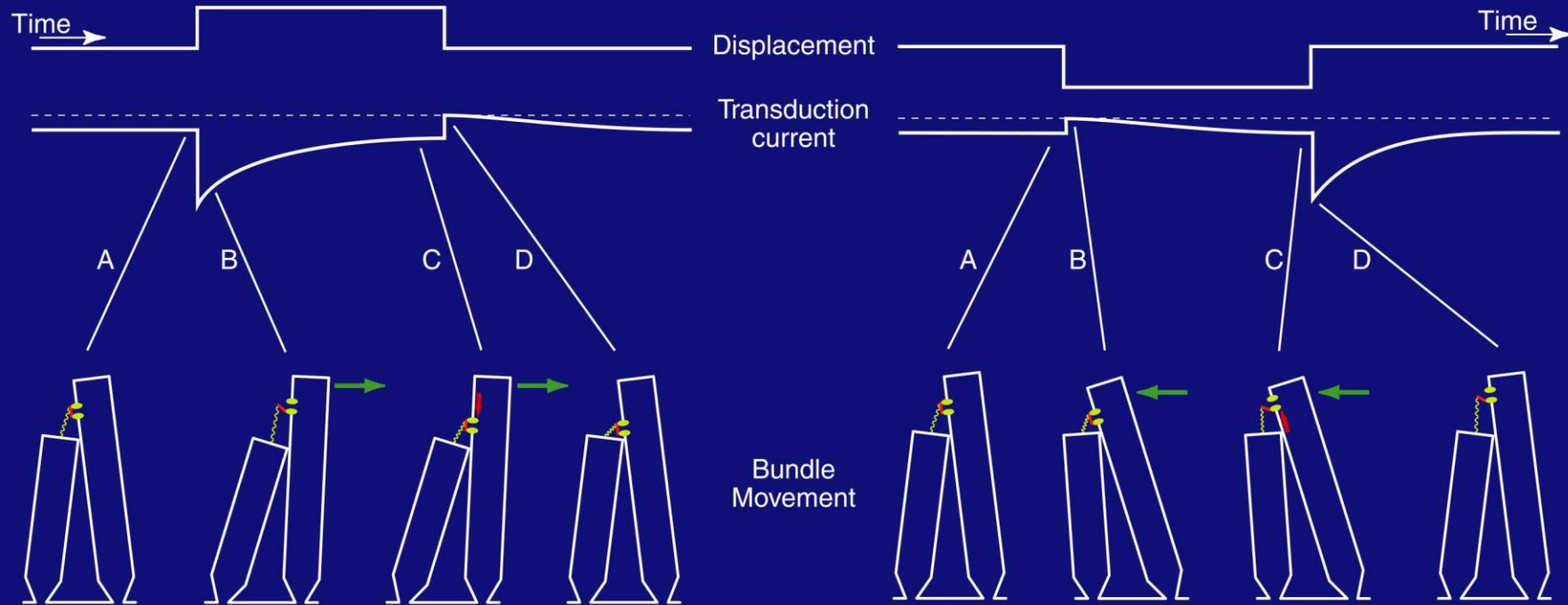
Molecular (myosin) motors

« ADAPTED » MOTORS

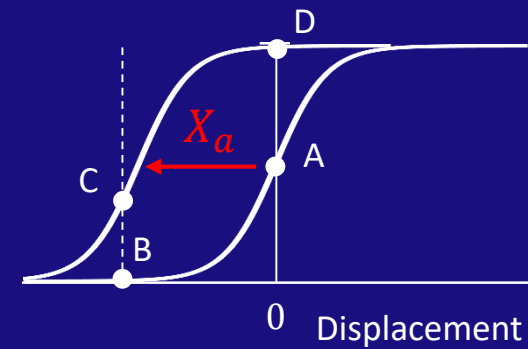
($P_o \sim 0.5$)



Motor-driven adaptation



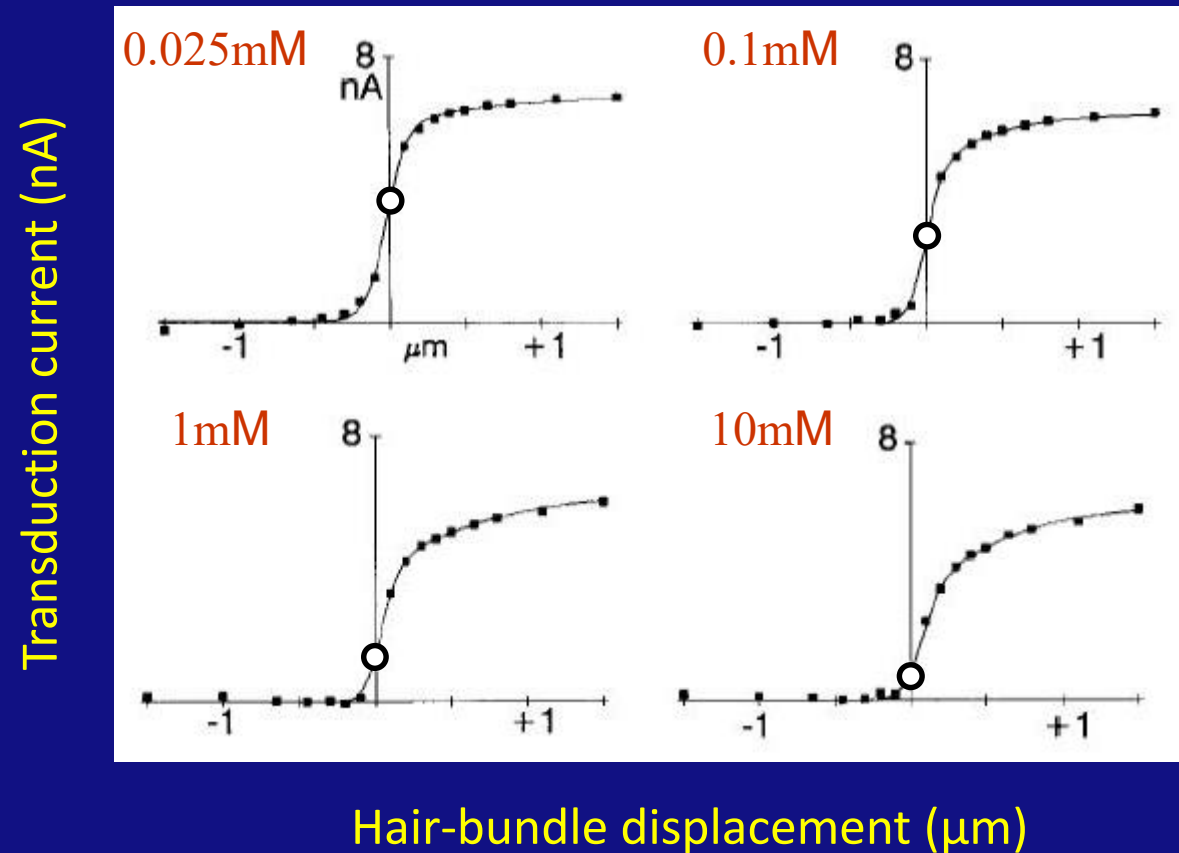
Open probability
vs. displacement



negative feedback
to maintain sensitivity

Ca^{2+} controls the operating point

→ channels close at higher $[\text{Ca}^{2+}]$



(Hacohen et al, *J Neurosci* (1989))

Two models to explain why channels close at higher Ca^{2+} :

- Adaptation motors are weaker ?
- The closed state of the transduction channels is more stable ?

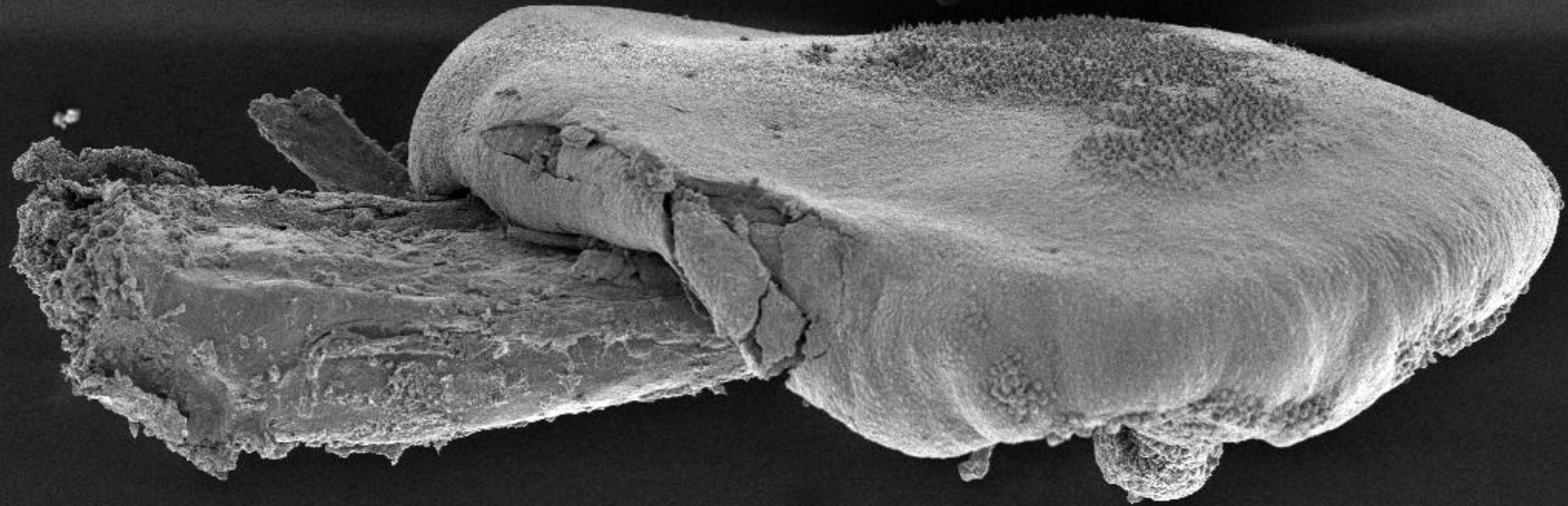
 active mechanics

Active hair-bundle motility

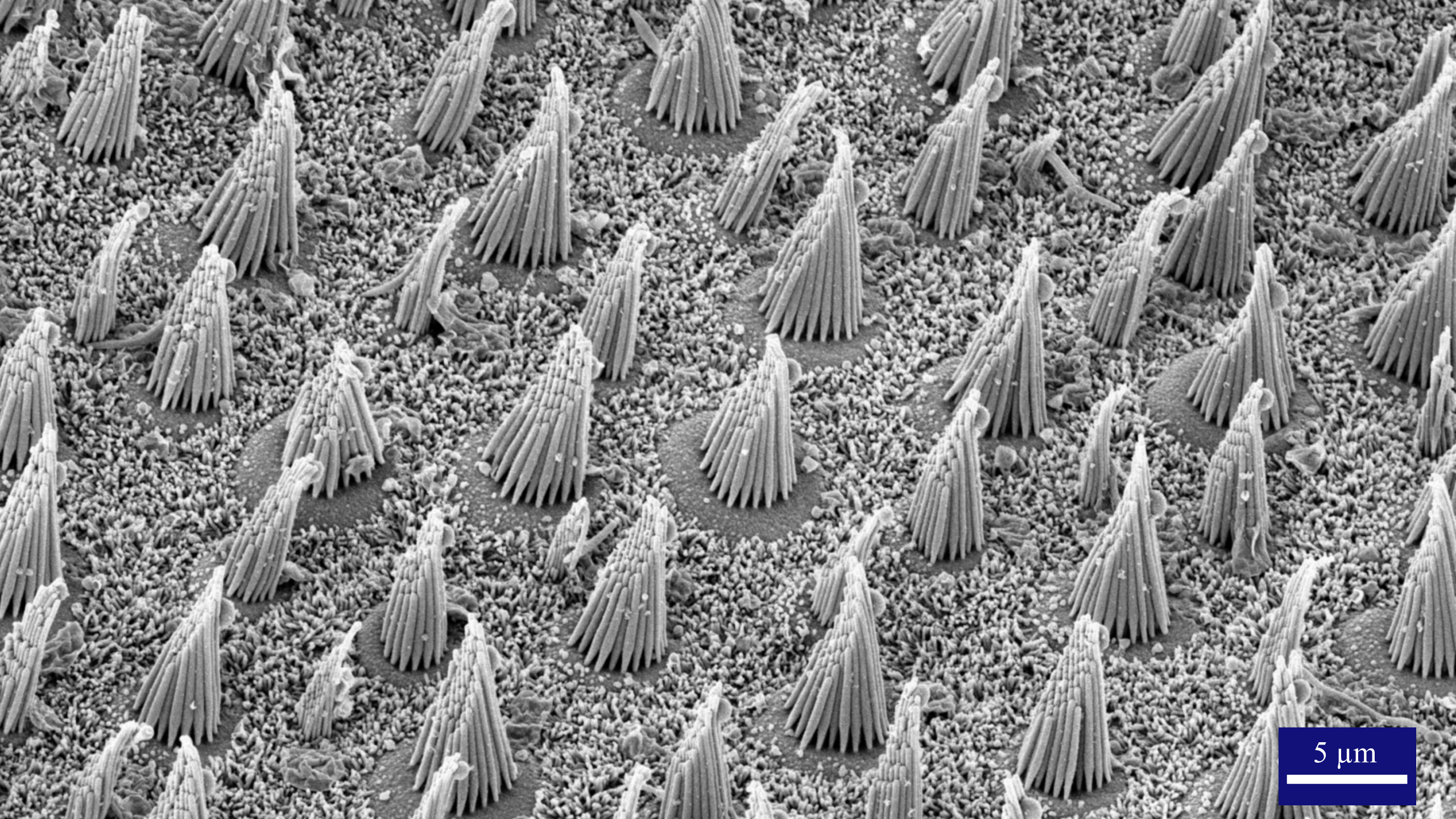


(bullfrog, *Rana catesbeiana*)

The frog's sacculus

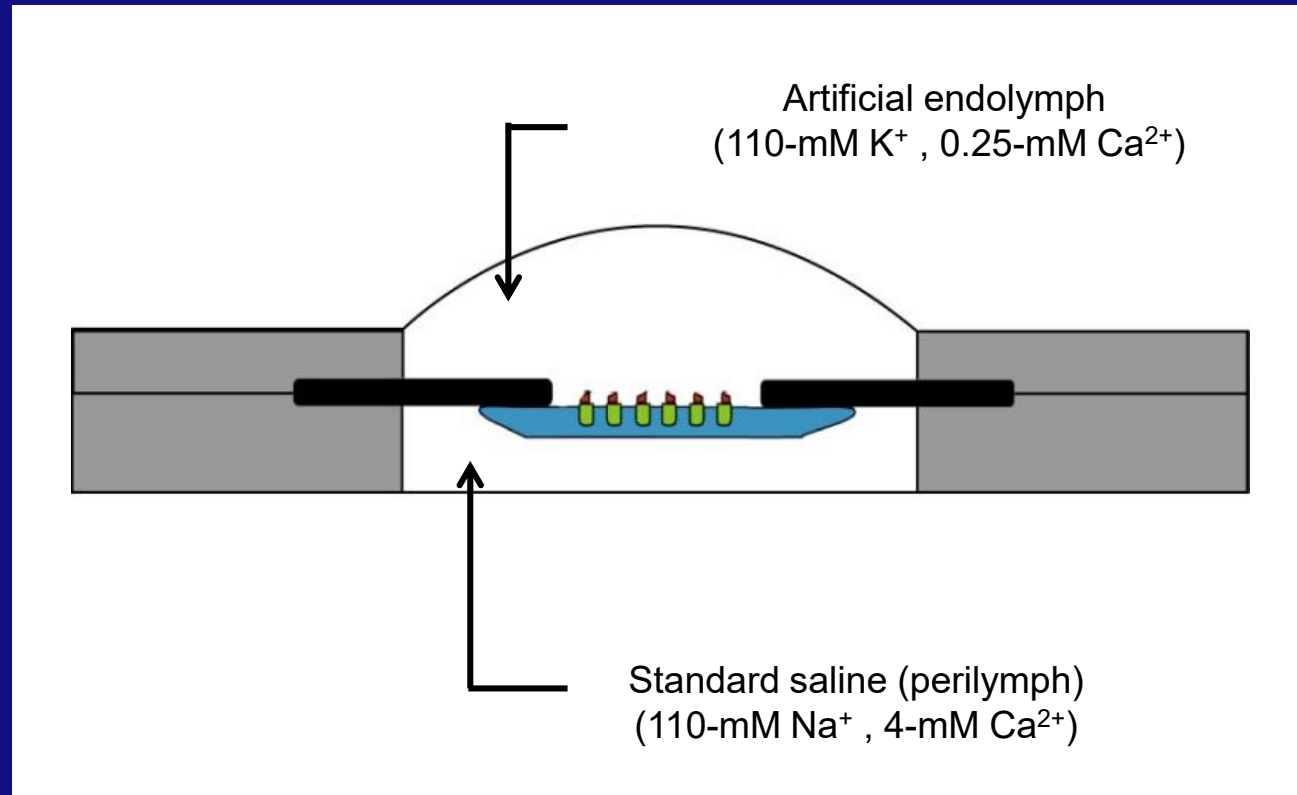


100 μm

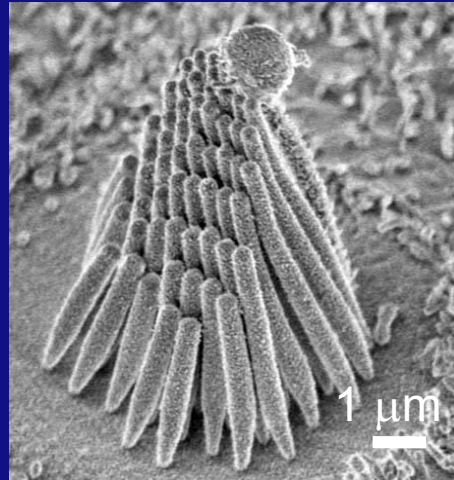
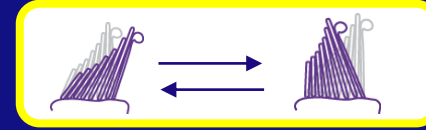


5 μm

Two ionic compartments (endolymph / perilymph)



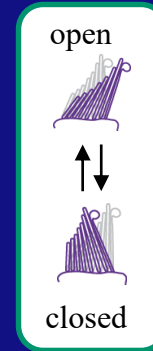
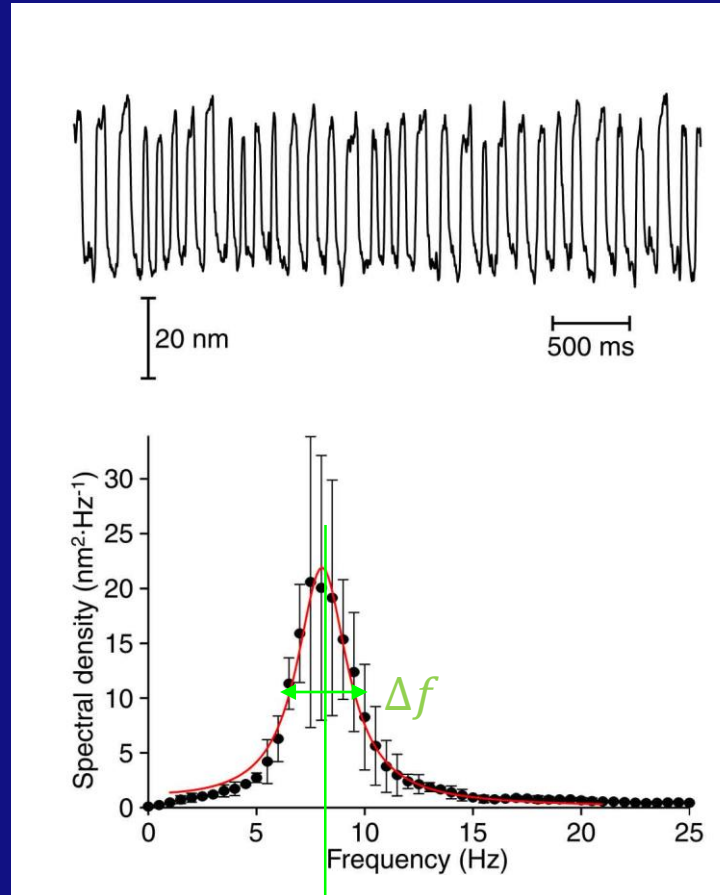
The hair bundle: **sensory and motile**



1 μm

Spontaneous oscillations

Hair-bundle
position, $X(t)$



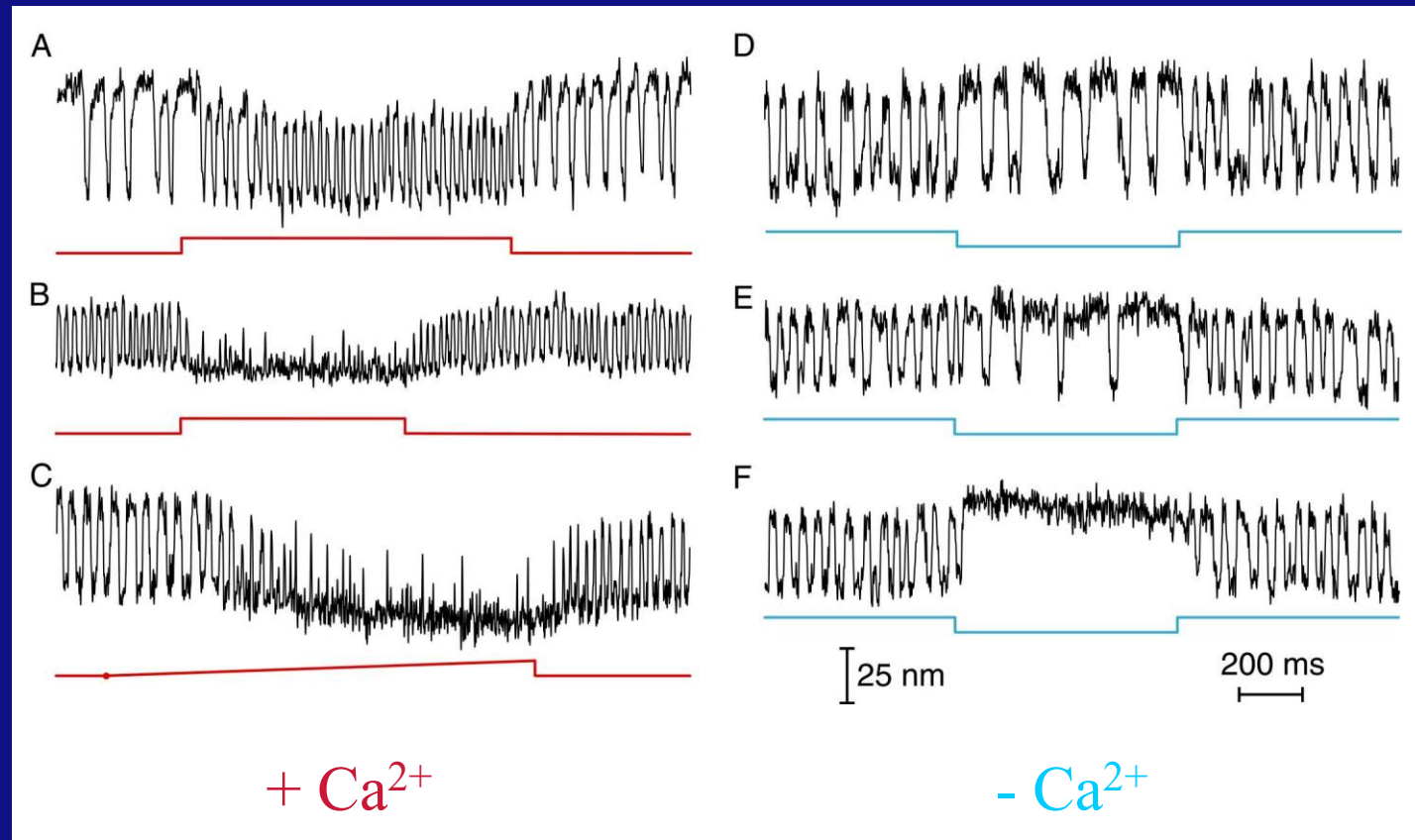
Spectral
density, $\tilde{C}(\omega)$

Noisy!

$$Q = \frac{f_c}{\Delta f} \simeq 1.6$$

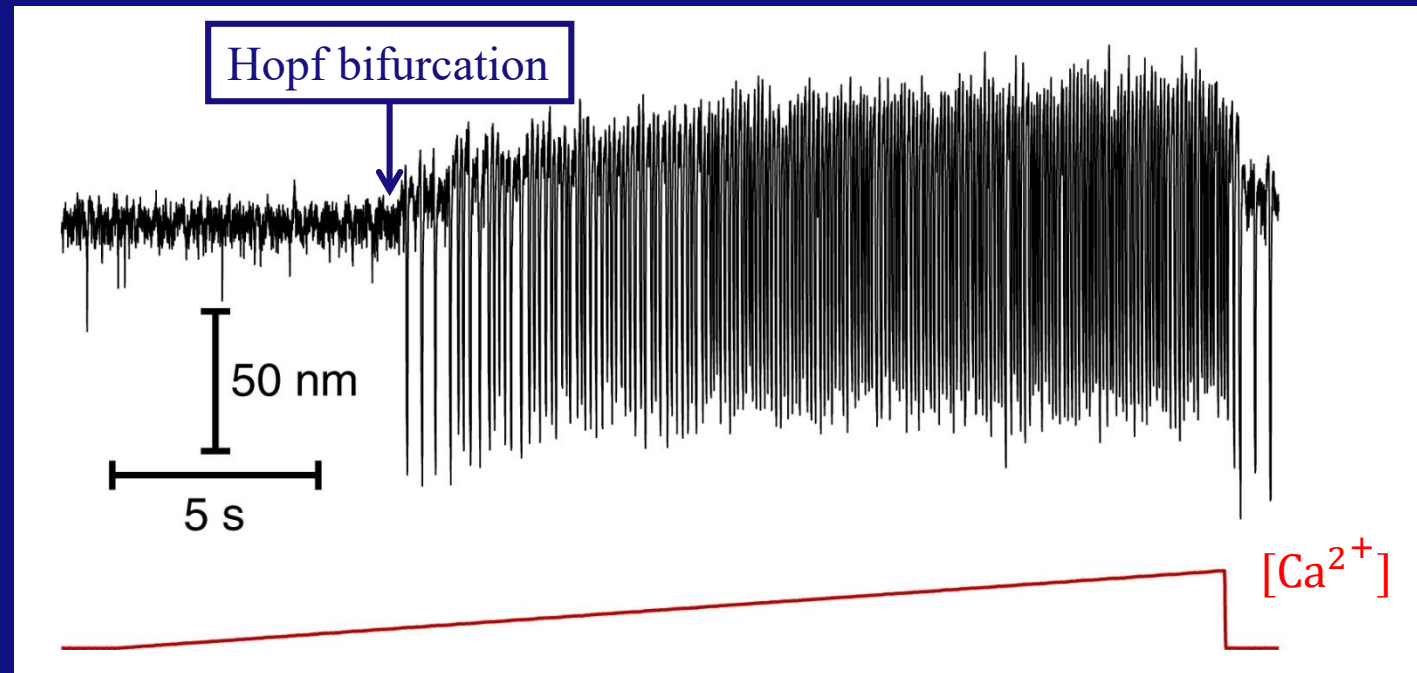
characteristic frequency: f_c (range: 5-50 Hz)

Ca^{2+} as a control parameter



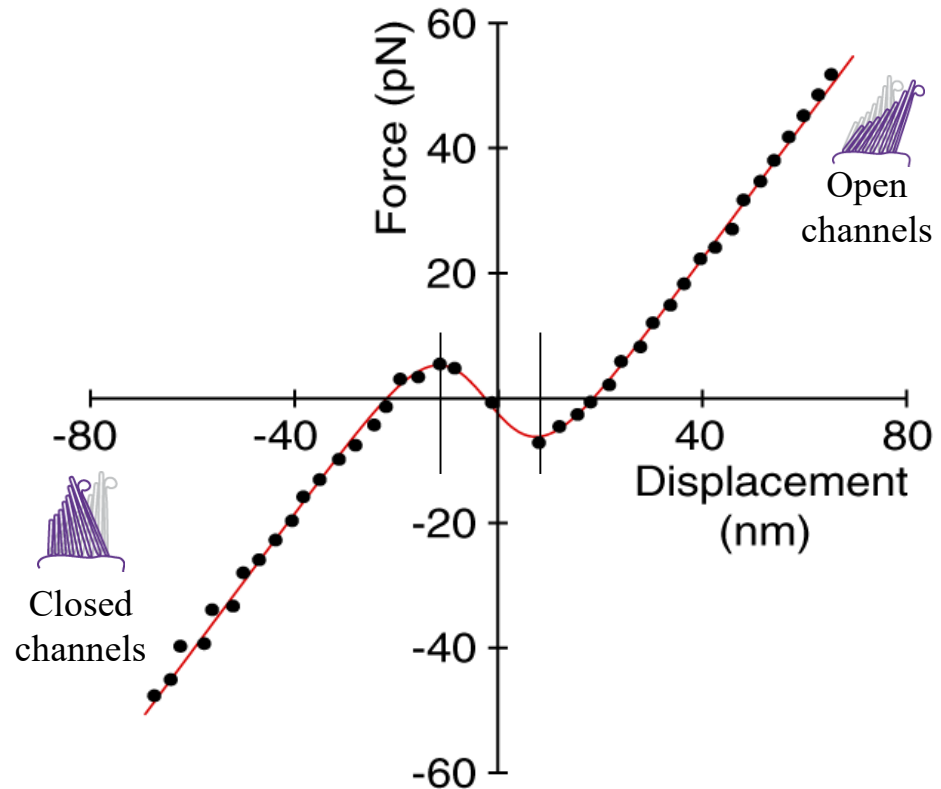
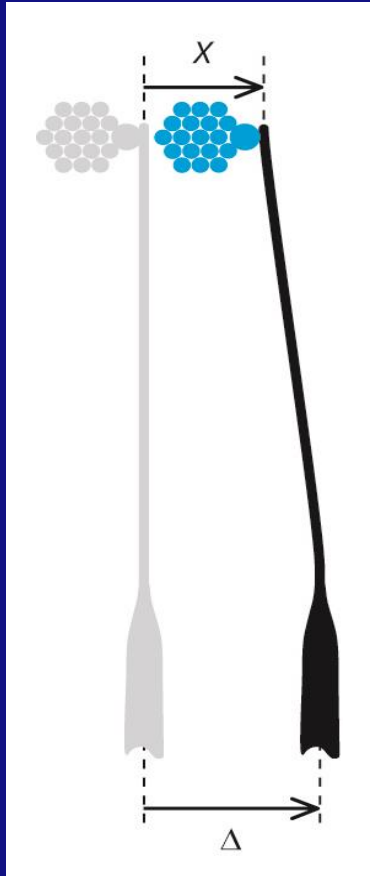
Ca^{2+} as a control parameter

→ oscillatory instability (« Hopf bifurcation »)



Oscillation mechanism?

Negative stiffness



Gating compliance

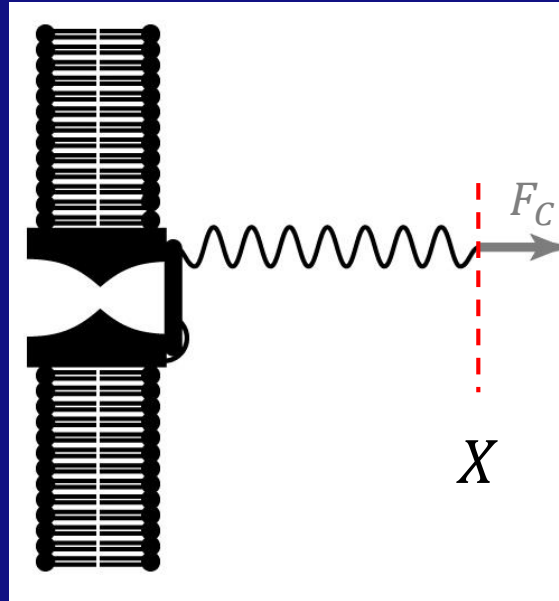
(Howard and Hudspeth, 1988)

GATING-SPRING TENSION

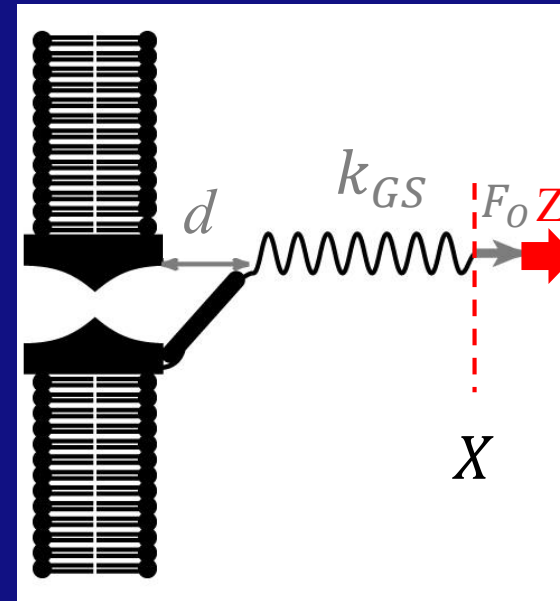
$$F_C = k_{GS} X$$

$$F_O = k_{GS} X - Z$$

Channel closed



Channel open



GATING FORCE

$$Z = k_{GS} d$$

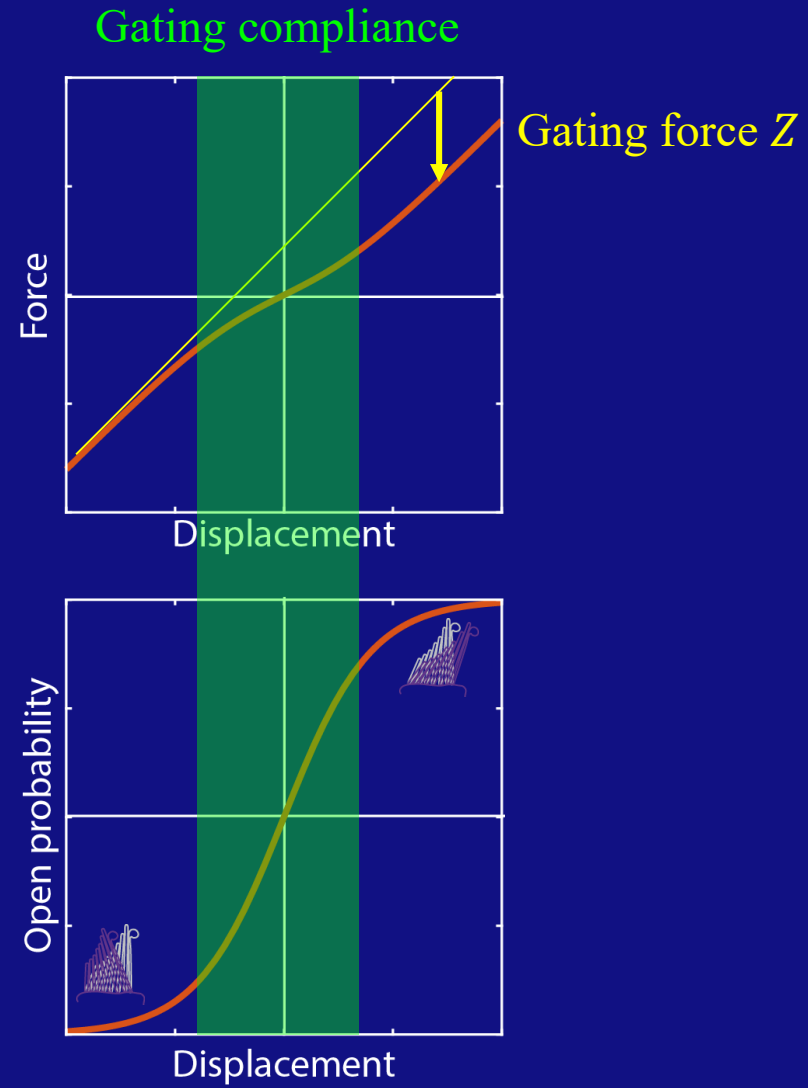
gating-spring
stiffness

gating
swing

FORCE-DISPLACEMENT RELATION

$$\langle F(X) \rangle = F_O P_o + F_C (1 - P_o) = k_{GS} X - Z P_o(X)$$

Channel's
open probability



FORCE-DISPLACEMENT

$$\langle F_{EXT} \rangle(X) = k_{GS} X - P_o(X) Z + F_0$$

OPEN PROBABILITY-DISPLACEMENT

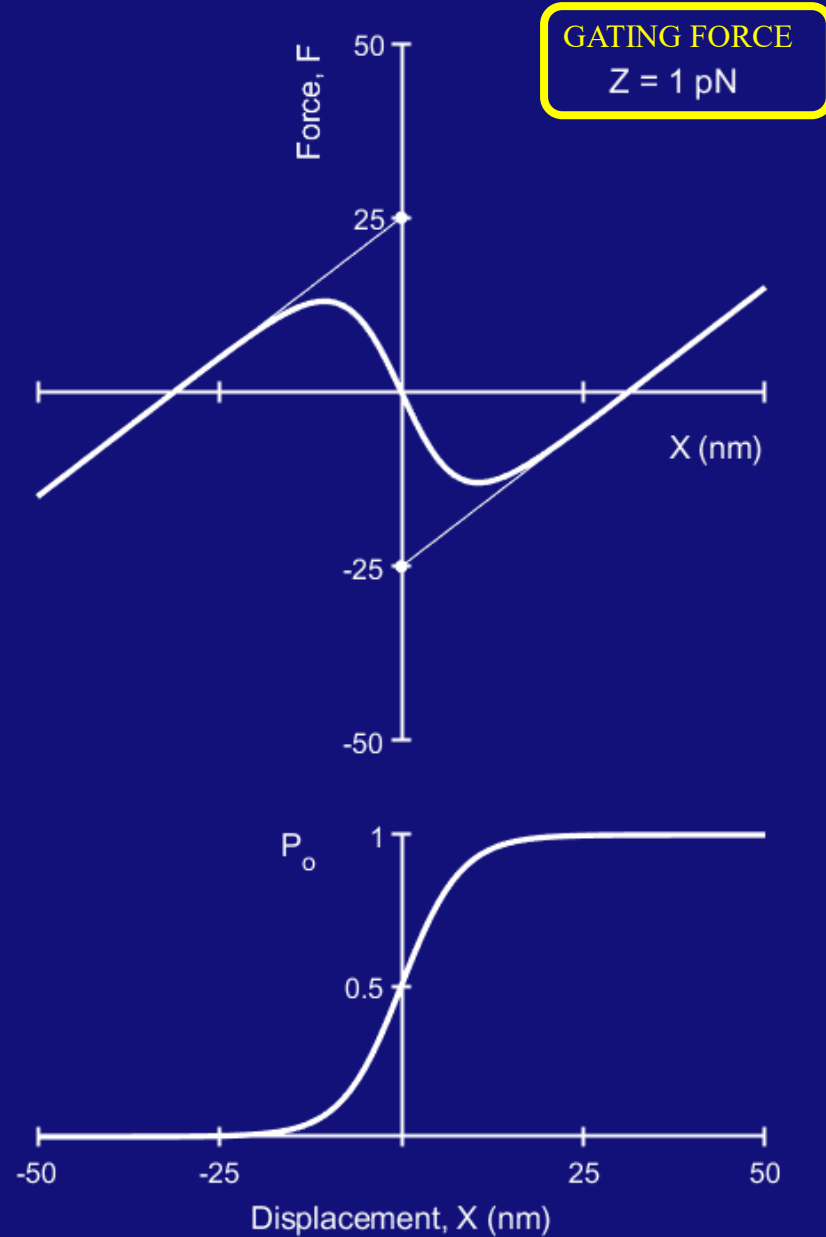
$$P_o = \frac{1}{1 + \exp\left(-\frac{ZX}{k_B T}\right)}$$

Force-displacement relation

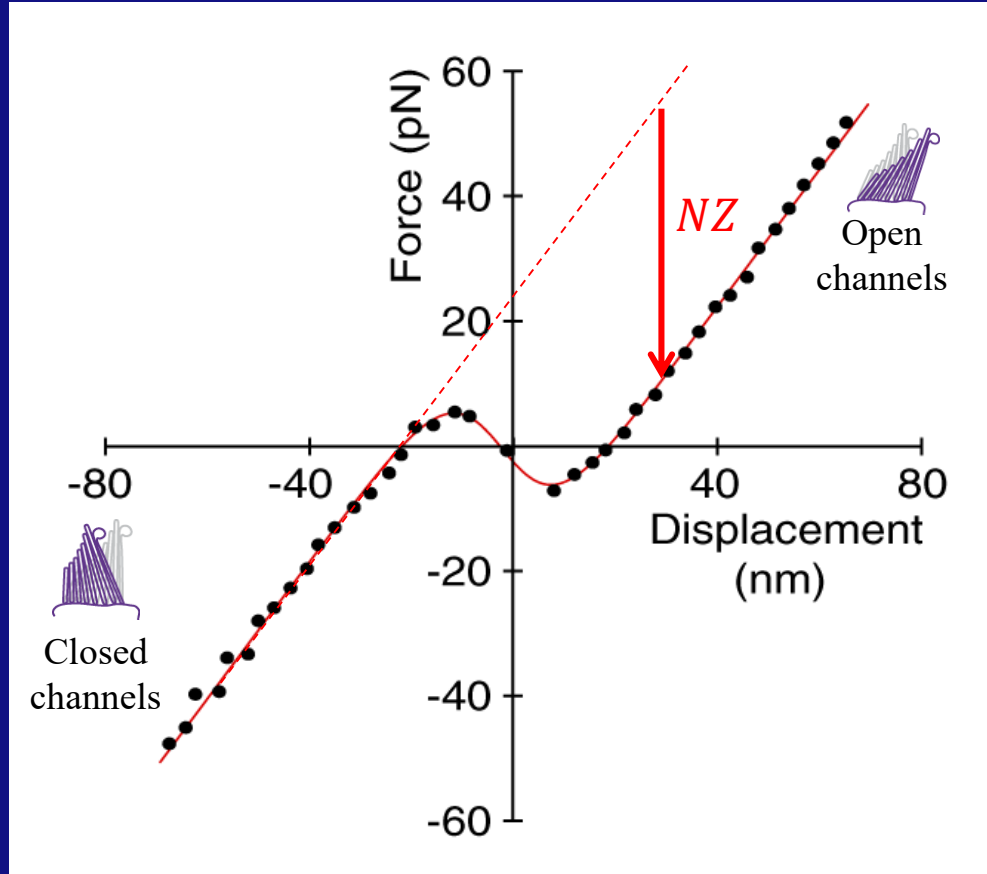
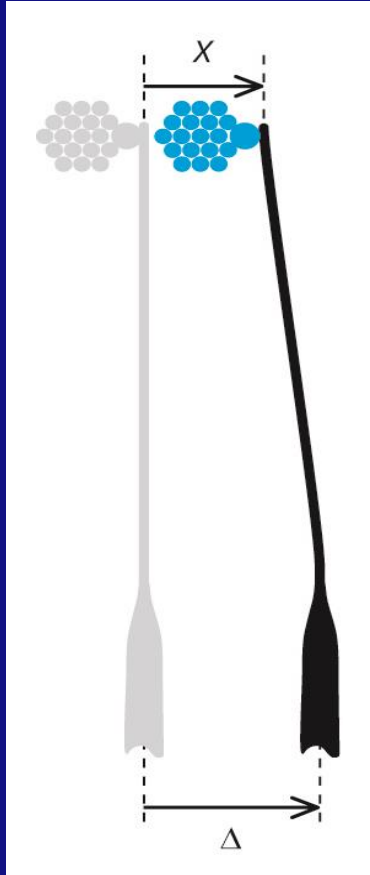
$$F = K_{HB} X - NZ (P_o(X) - 0.5)$$

Open probability-displacement relation

$$P_o = \frac{1}{1 + \exp\left(-\frac{ZX}{k_B T}\right)}$$



Negative stiffness



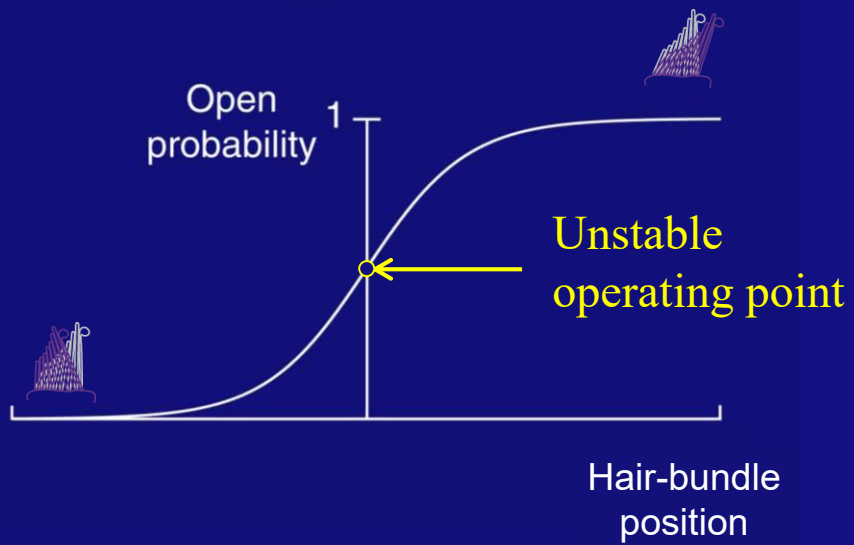
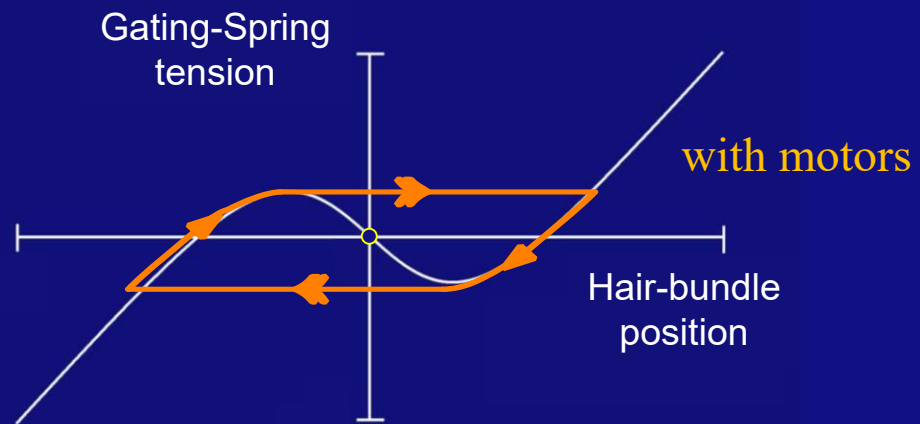
EXPERIMENTALLY

$$K_{HB} \simeq 0.7 \text{ pN/nm}$$

$$Z \simeq 0.8 \text{ pN}$$

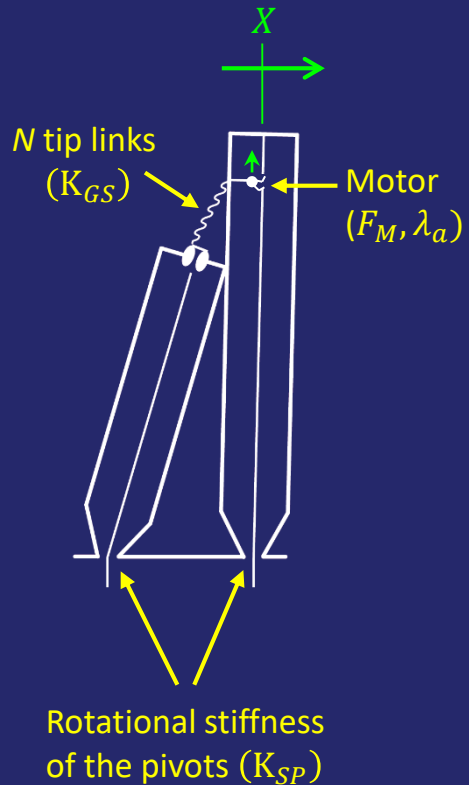
(40 pN for $N = 50$ channels)

$$F = K_{HB} X - NZ (P_o(X) - 0.5)$$



Motor-model of active hair-bundle motility

→ an active dynamical system



Hair-bundle position, X :

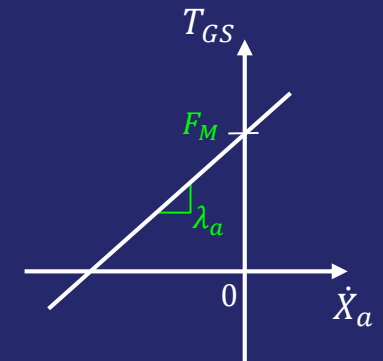
$$\lambda \frac{dX}{dt} = -K_{GS}(X - X_a - DP_o) - K_{SP}X$$

Motor position, X_a :

$$\lambda_a \frac{dX_a}{dt} = +K_{GS}(X - X_a - DP_o) - F_M$$

Tip-link tension, T_{GS}

Motors' force-velocity



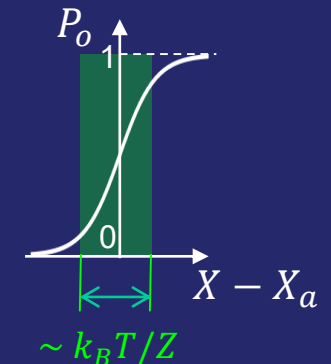
Motor force:

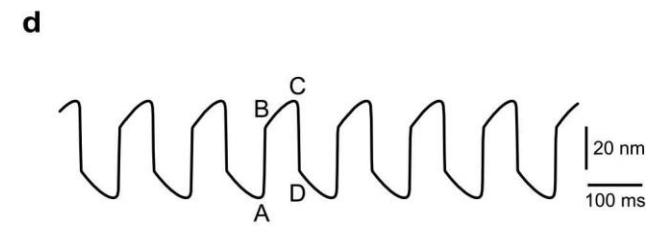
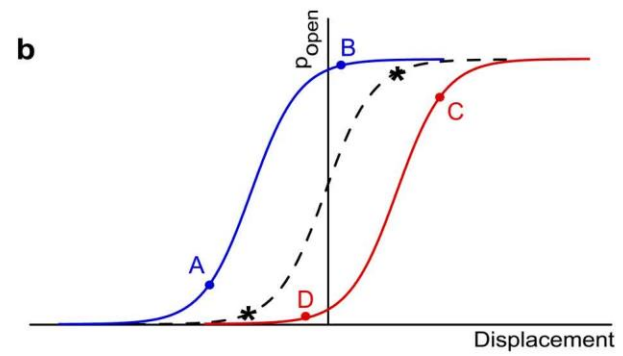
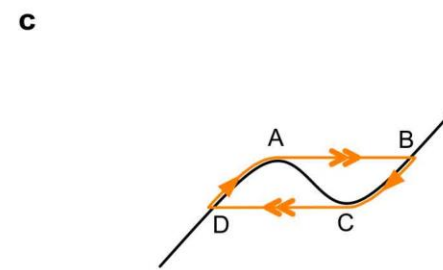
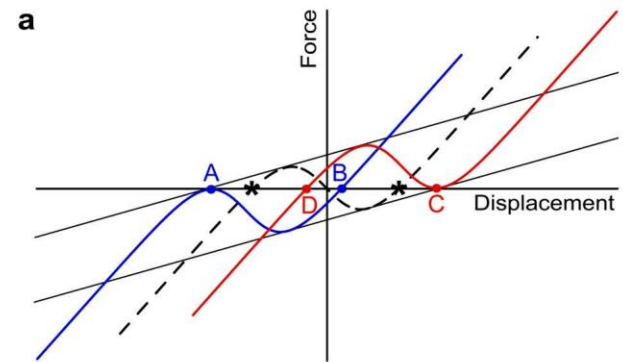
$$F_M = F_{MAX} (1 - S P_o)$$

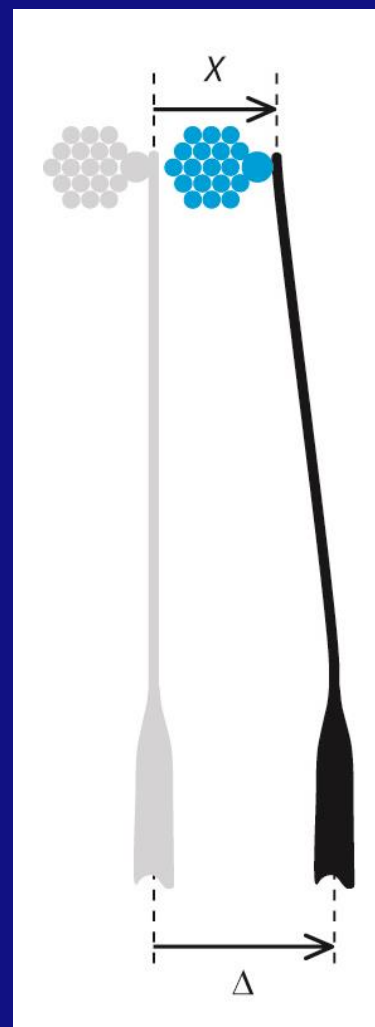
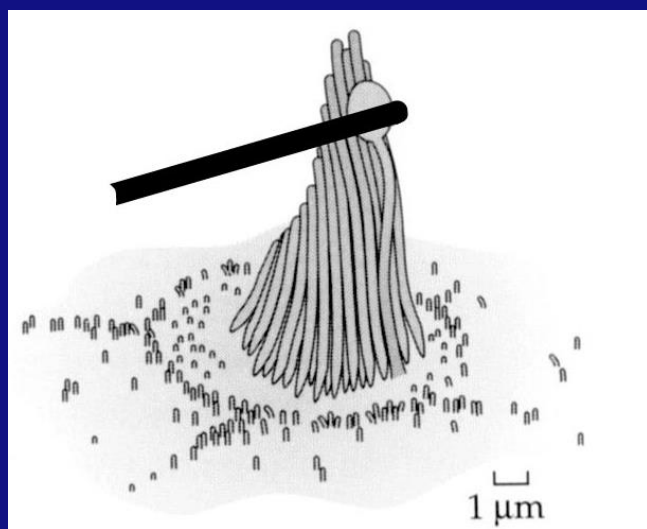
Ca^{2+} -feedback strength

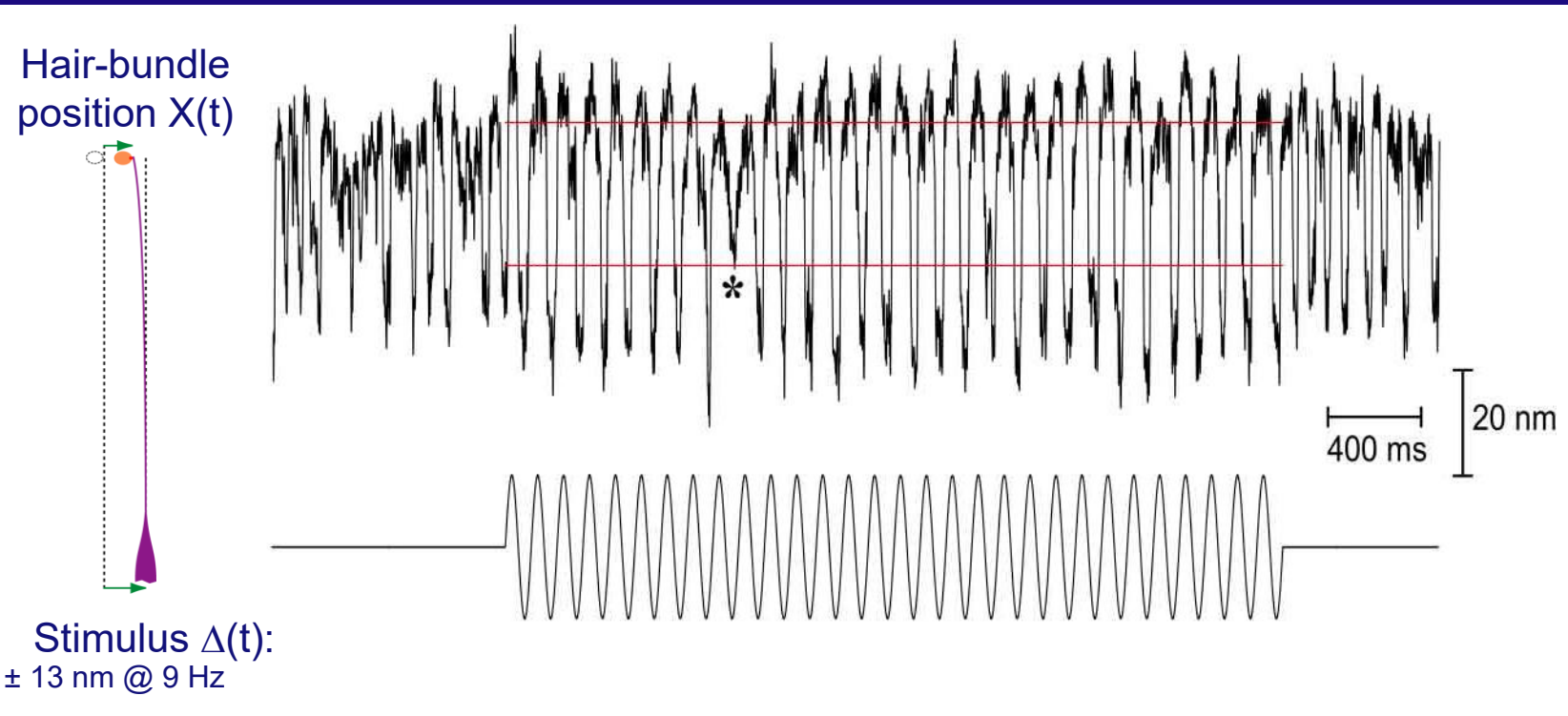
Open probability:

$$P_o = 1 / (1 + A \exp(-Z (X - X_a) / \delta))$$



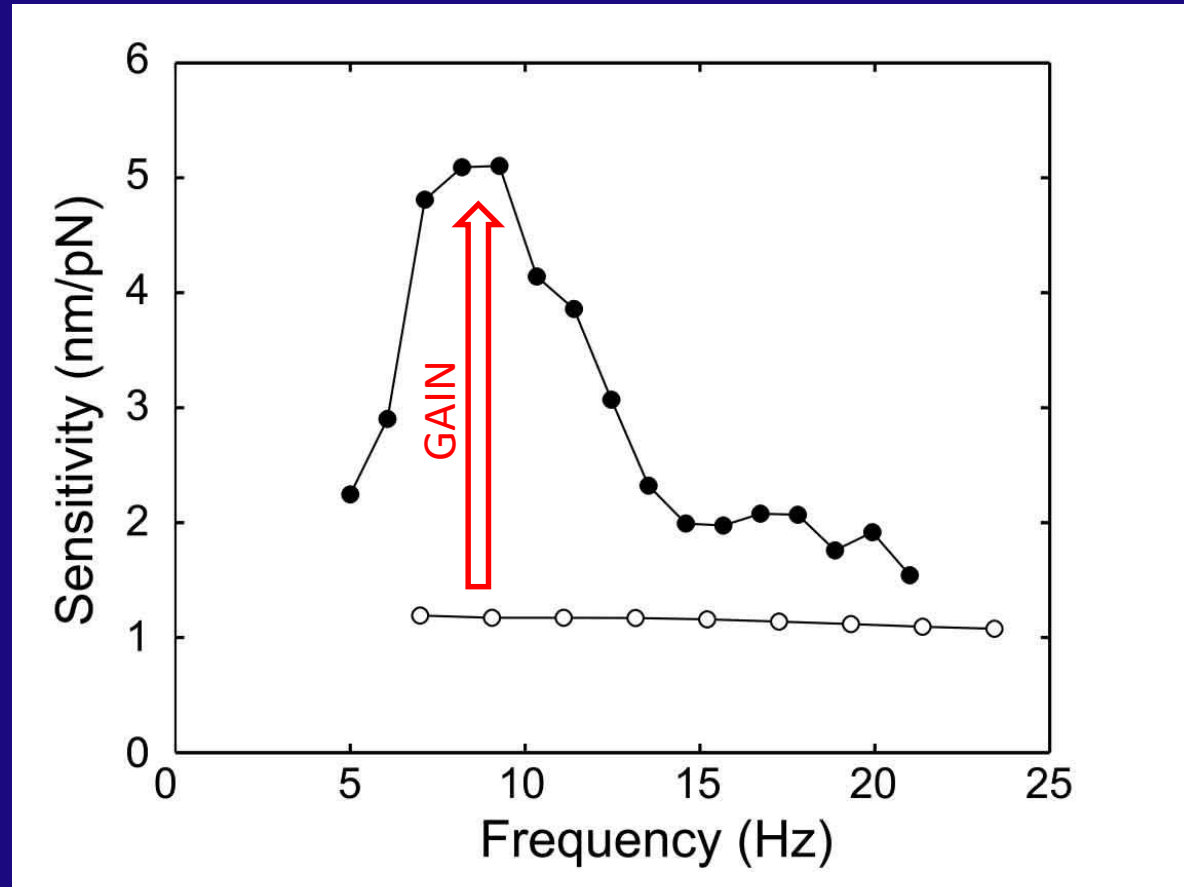






Enhanced sensitivity

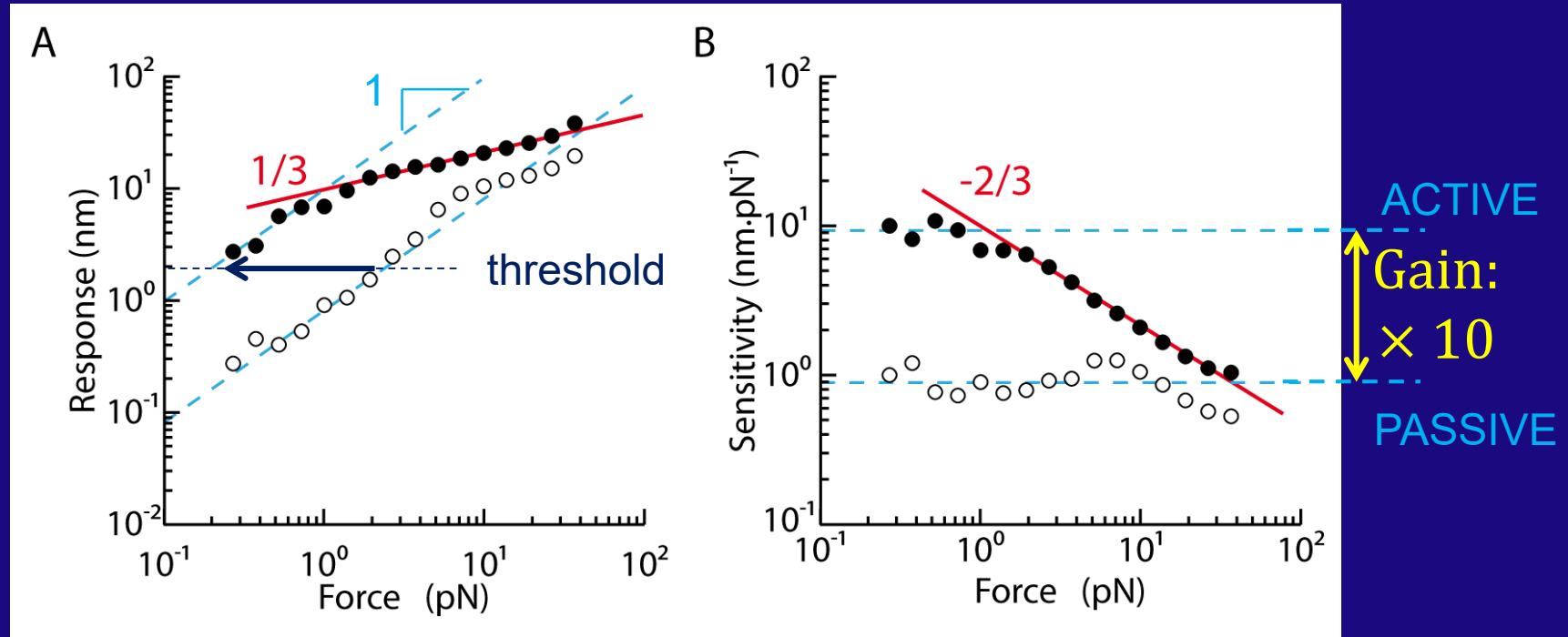
($F_{\text{EXT}} \cong 5 \text{ pN}$)



- Oscillatory (~ 8 Hz)
- Non oscillatory

Compressive non-linearity

STIMULUS: $F(t) = F_1 \sin(2\pi f_1 t)$



- at resonance ($f_1 = 9$ Hz)
- off resonance ($f_1 = 180$ Hz)

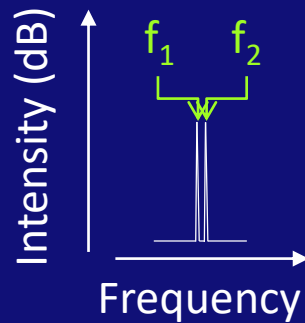


Two-tone distortions

→ “colored” response

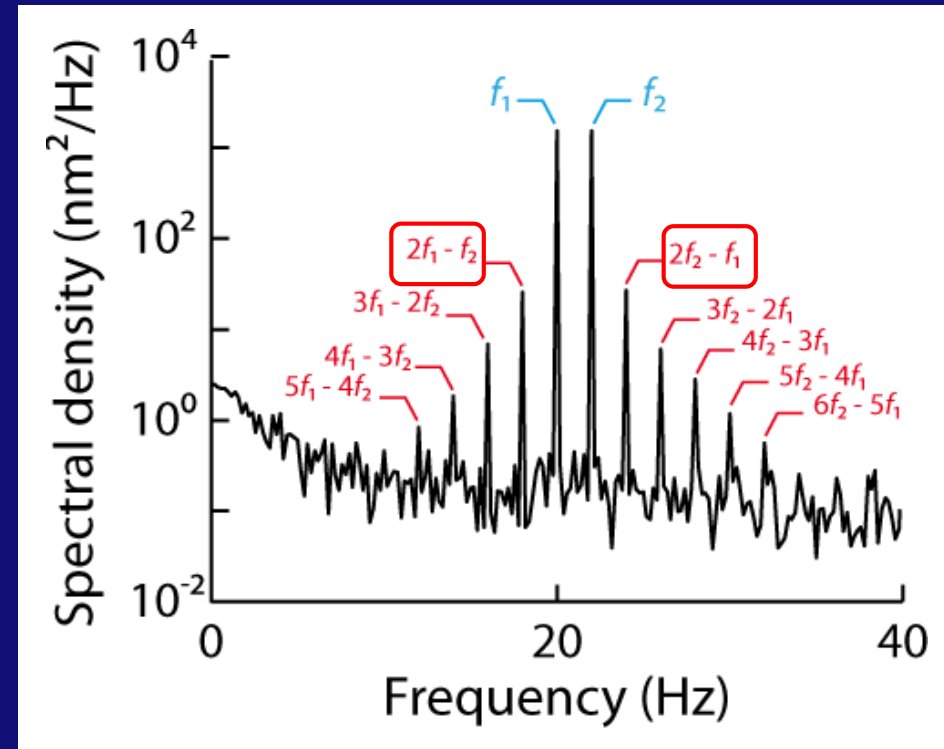
TWO-TONE FORCE STIMULUS

$$F(t) = \bar{F} \sin(2\pi f_1 t) + \bar{F} \sin(2\pi f_2 t)$$



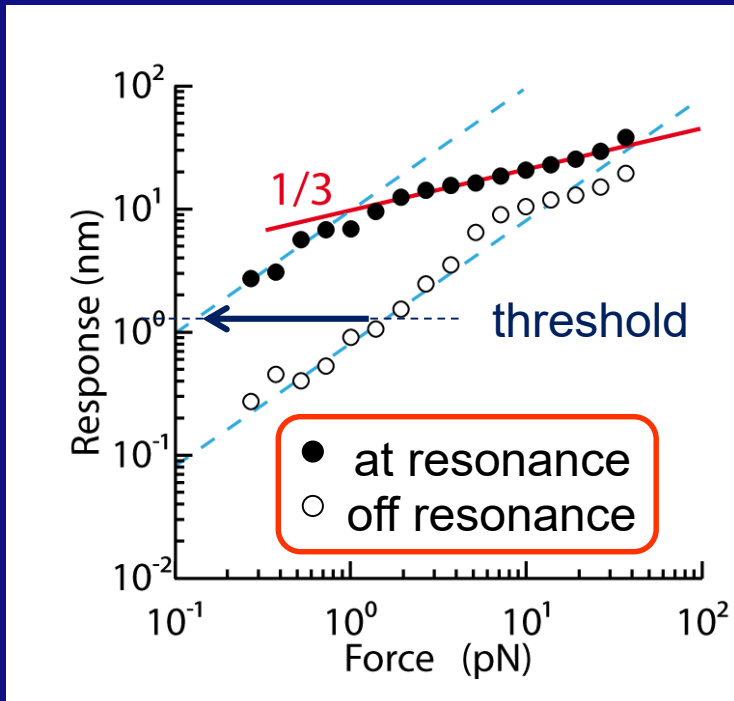
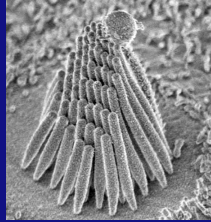
$$(f_2 = 1.2 f_1; \bar{F} = 10.8 \text{ pN})$$

HAIR-BUNDLE RESPONSE

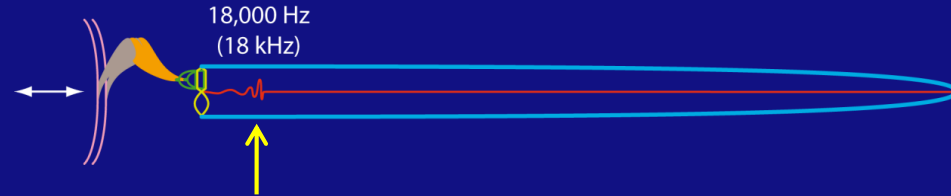


(PhD of Jérémie Barral)

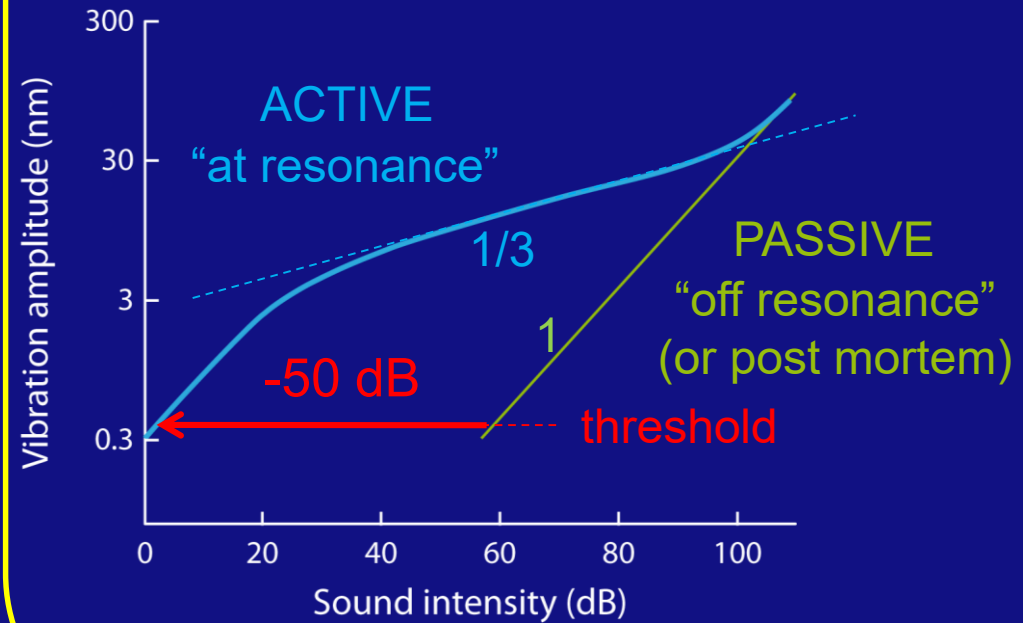
SINGLE HAIR-BUNDLE



COCHLEA IN VIVO



⇒ Same physics!



(inspired by: Ruggero et al., JASA (1997))

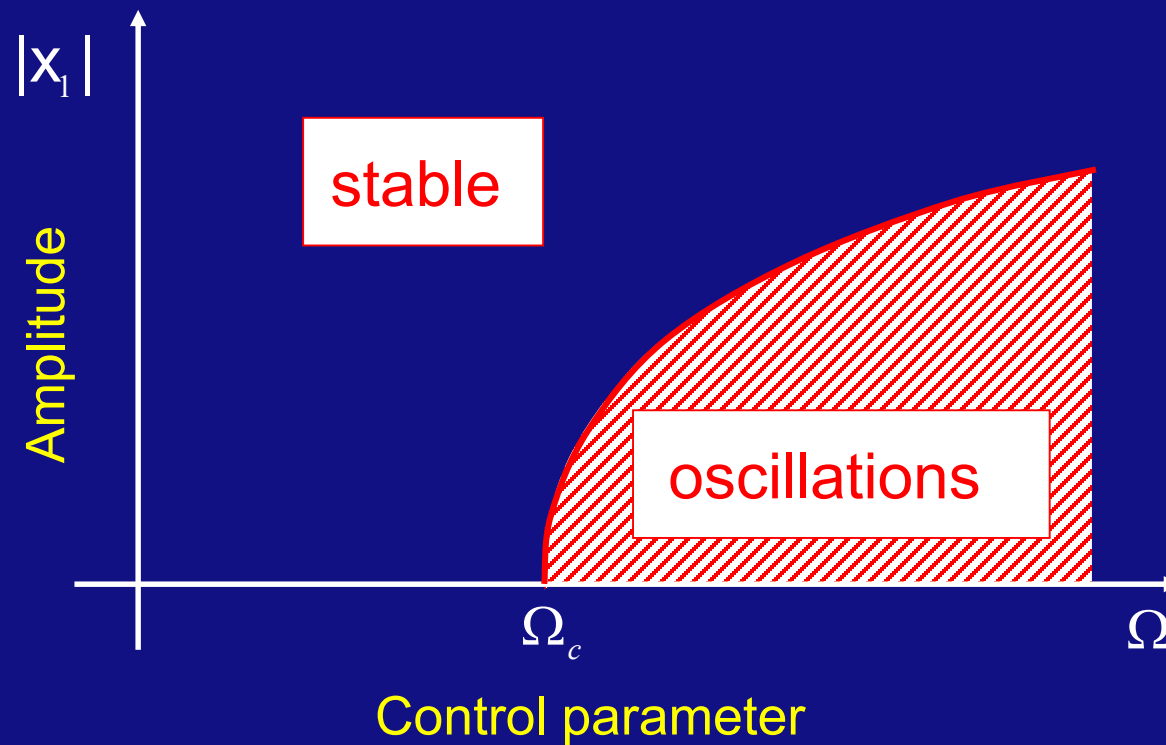
Generic properties of « critical » oscillators

Hopf bifurcation

→ « Normal form »

$$\frac{dZ}{dt} \cong -(\Omega_c - \Omega + i 2\pi f_c) Z - B|Z|^2 Z + \frac{F}{\Lambda}$$

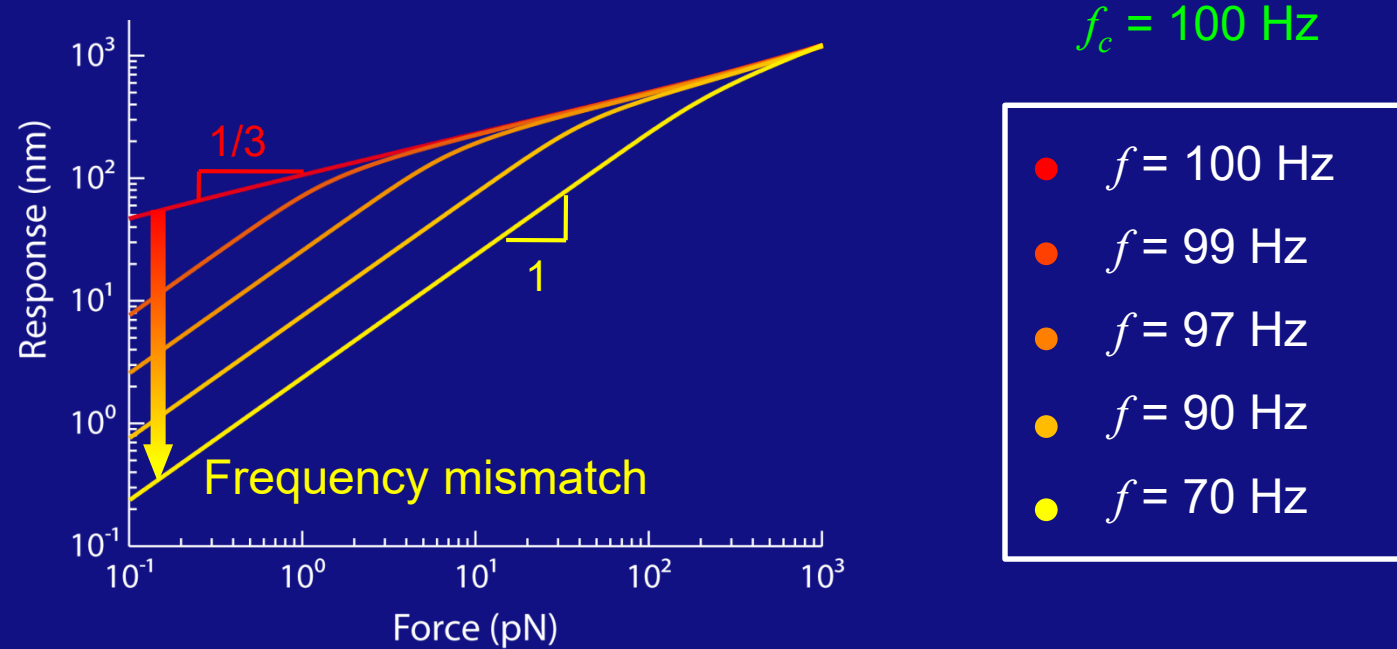
with $X = \text{Re}(Z)$



Critical point: $\Omega = \Omega_c$

« Critical » oscillator: generic properties

$$F(t) = F_1 \sin(2\pi f_1 t) \rightarrow X(t) = \sum_n X_n e^{i n \omega t}$$



$$F_1 \cong A(f) X_1 + \bar{B} |X_1|^2 X_1 \quad \text{with: } A(f = f_c) = 0 !$$

(Choe, Magnasco, Hudspeth, PNAS (1998); Camalet, Duke, Jülicher, Prost, PNAS (2000)
Eguíluz, Ospeck, Choe, Hudspeth, Magnasco, Phys. Rev. Lett. (2000))

Two-tone distortions

(simulations)

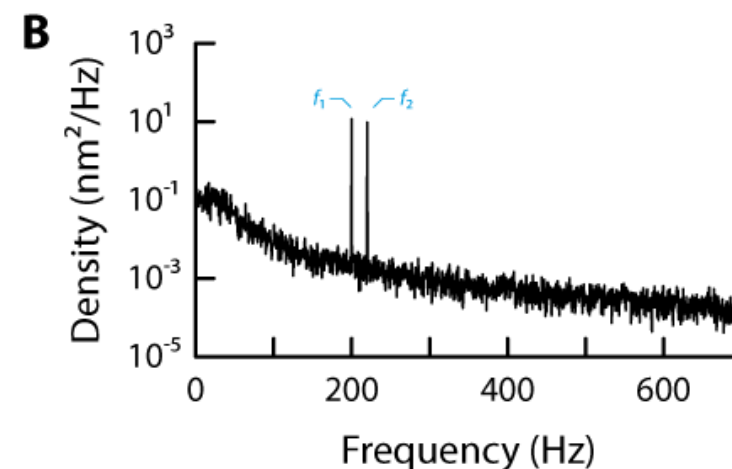
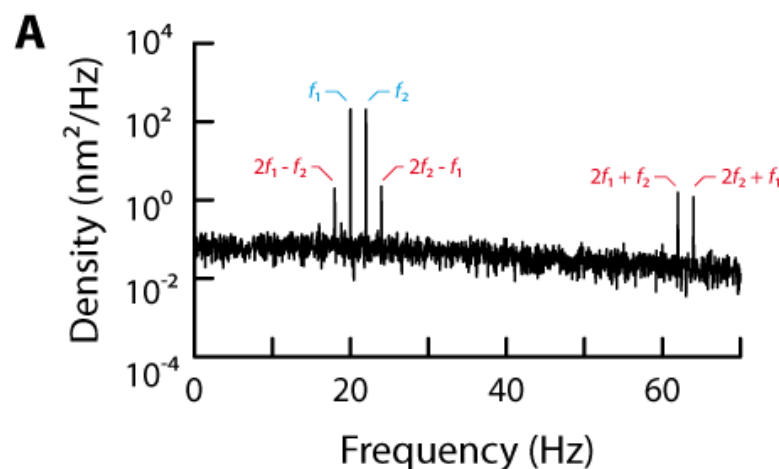
At resonance

$$(f_1, f_2 \approx f_c)$$

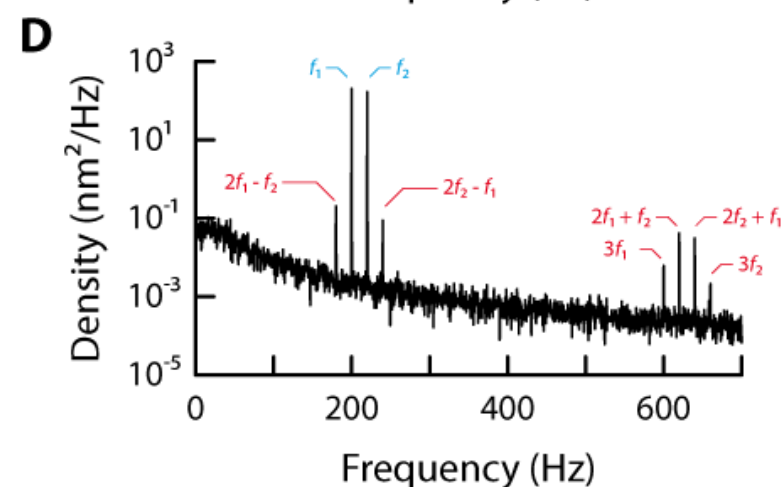
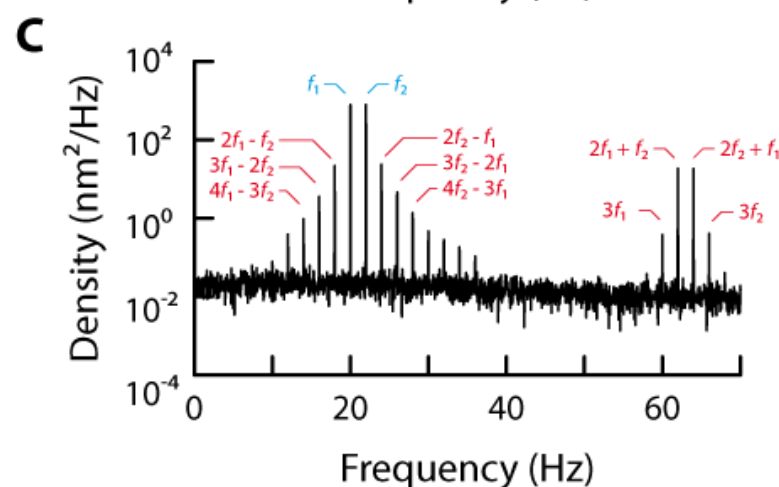
Off resonance

$$(f_1, f_2 \gg f_c)$$

0.9 pN



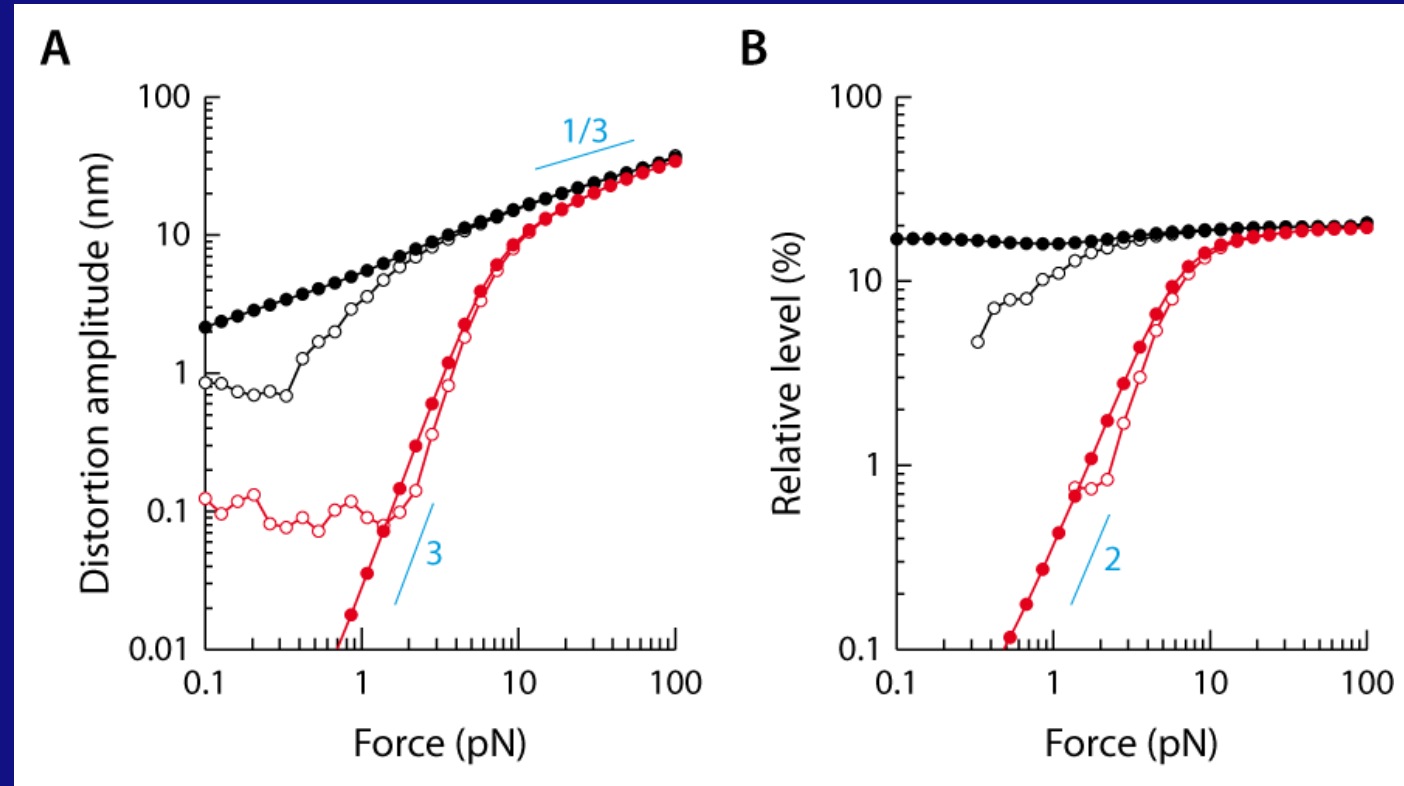
3.6 pN



Distortion $2f_1-f_2$: level functions

$$F(t) = \bar{F} \sin(2\pi f_1 t) + \bar{F} \sin(2\pi f_2 t)$$

(simulations)



No noise

With noise

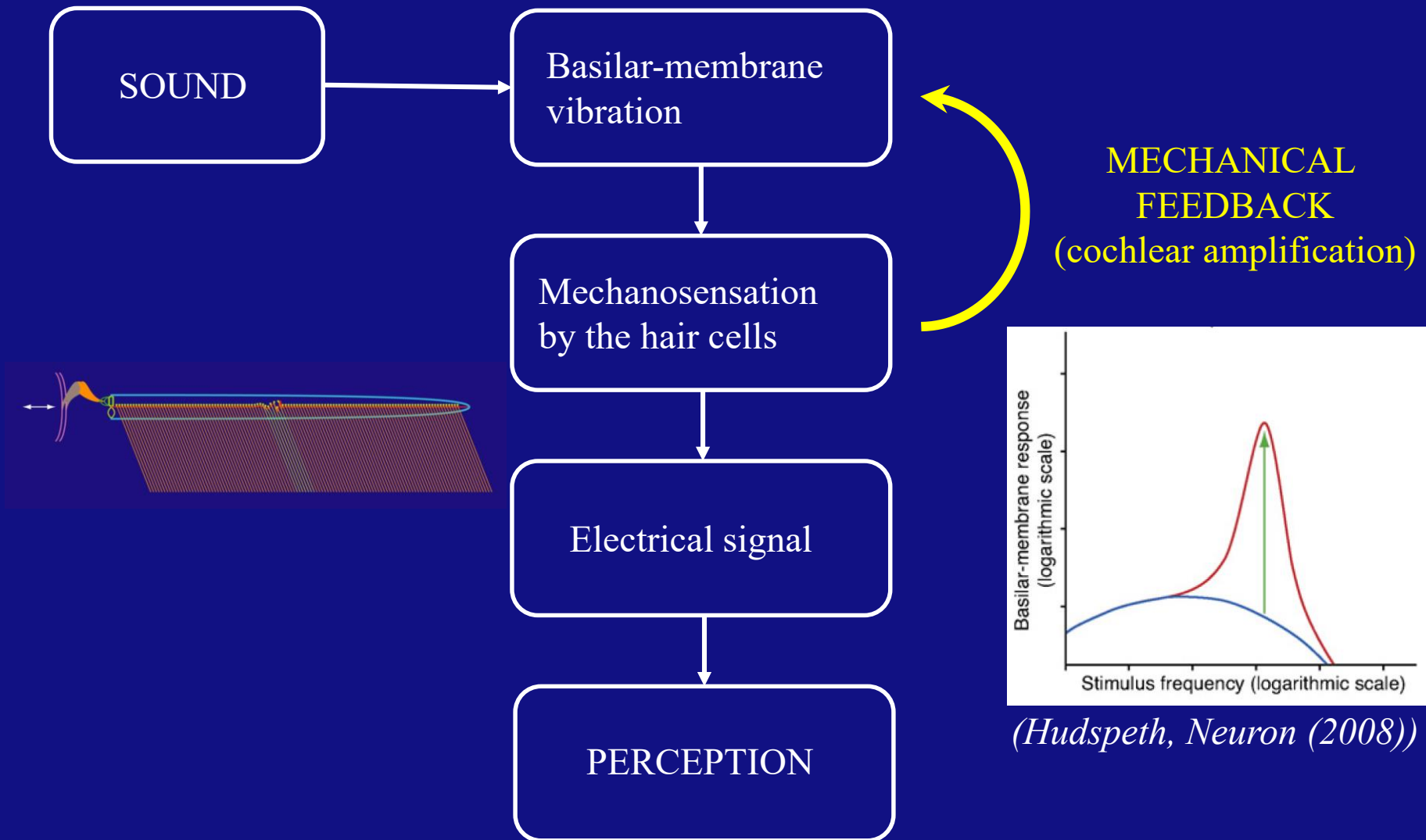
● : at resonance
● : off resonance

○ : at resonance
○ : off resonance

Critical oscillators:

→ nonlinear amplifiers for hearing

1. Amplified movements for small stimuli
2. Extended dynamic range of responsiveness
3. Increased frequency selectivity
4. « Essential » compressive nonlinearity: distortion of the input and evoked oto-acoustic emissions (non-invasive test for deafness).



Outlook:

TONOTOPIC ORGANIZATION OF CRITICAL OSCILLATORS

