On the physical limit of hair-bundle mechanosensitivity:

friction, noise, coupling.

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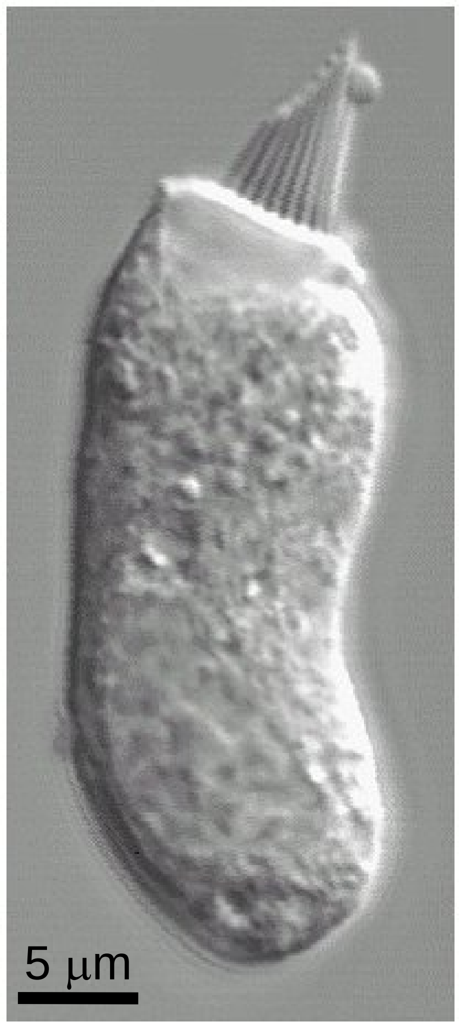
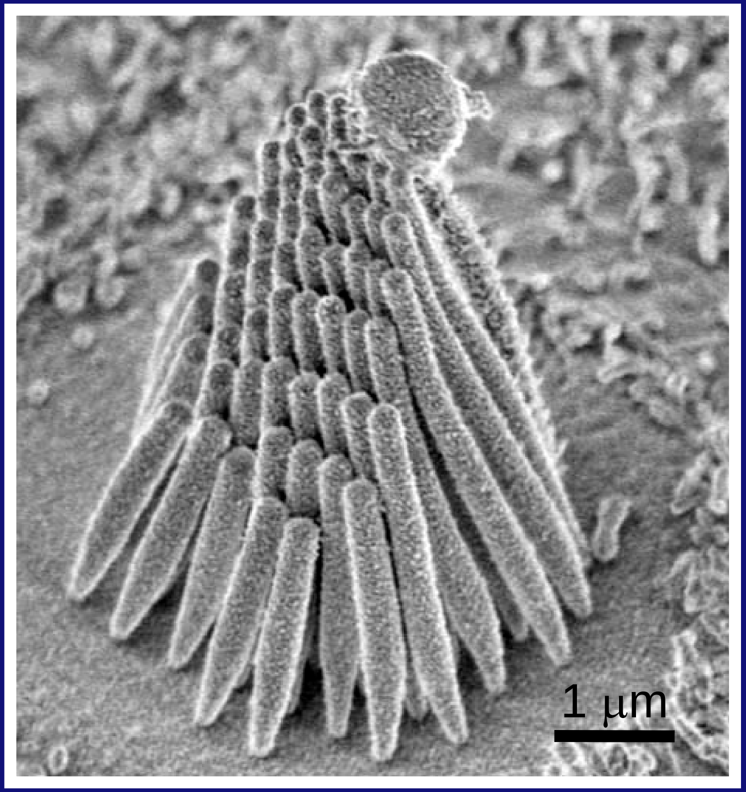
The hair cell

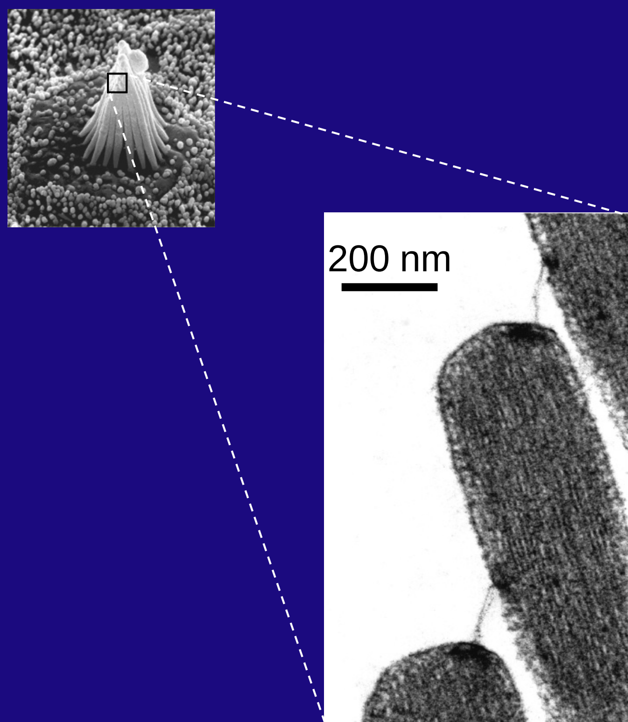


(A.J. Hudspeth)

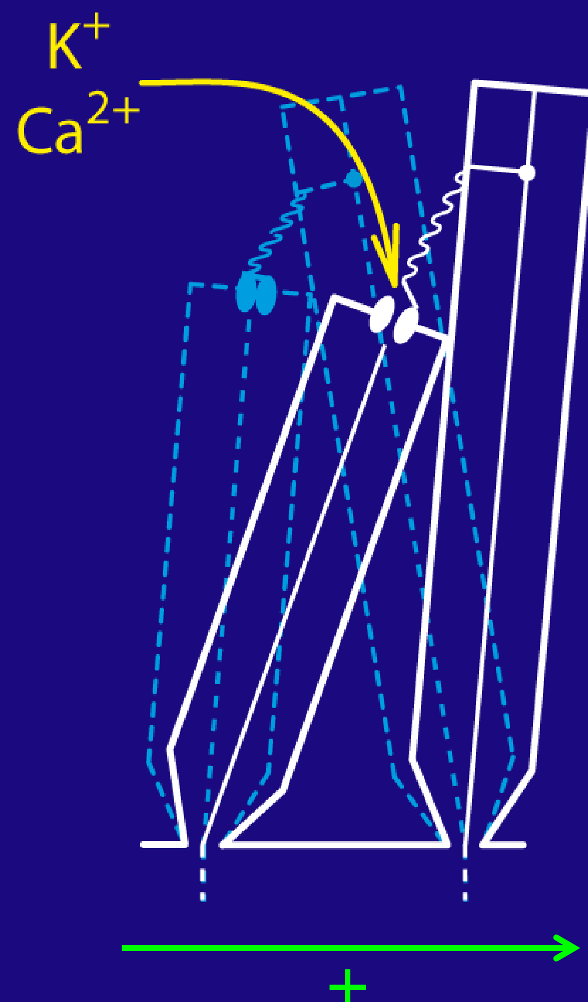


(P. Gillespie)

The hair-cell bundle: mechanical antenna



(A.J. Hudspeth)



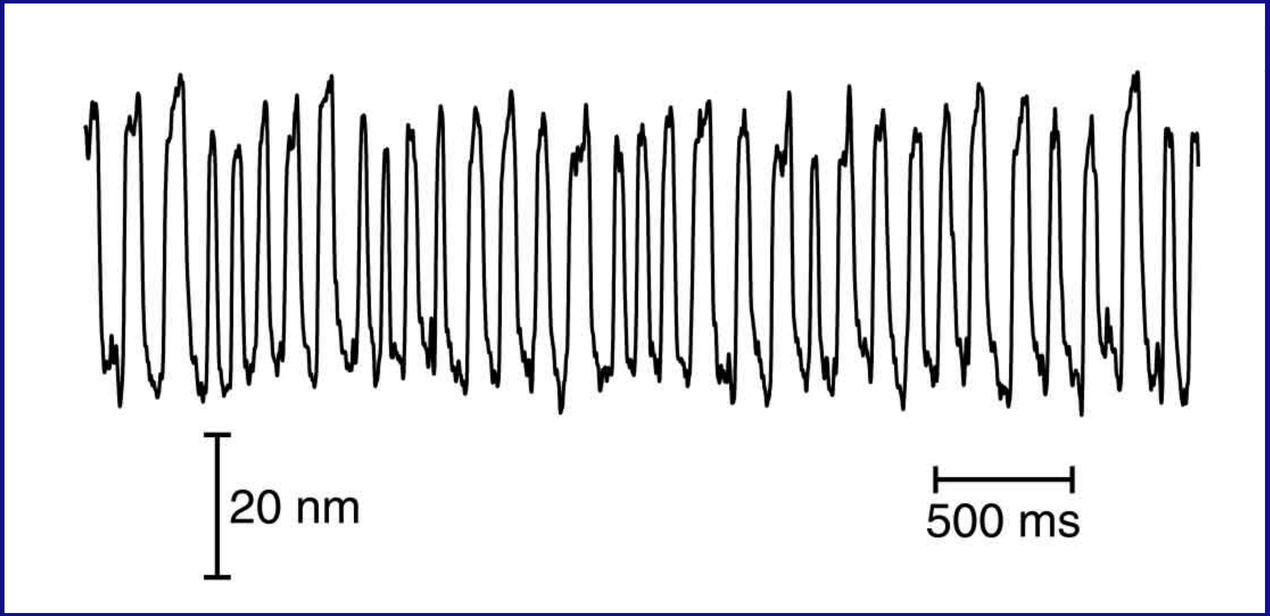
(bullfrog)

The hair-cell bundle

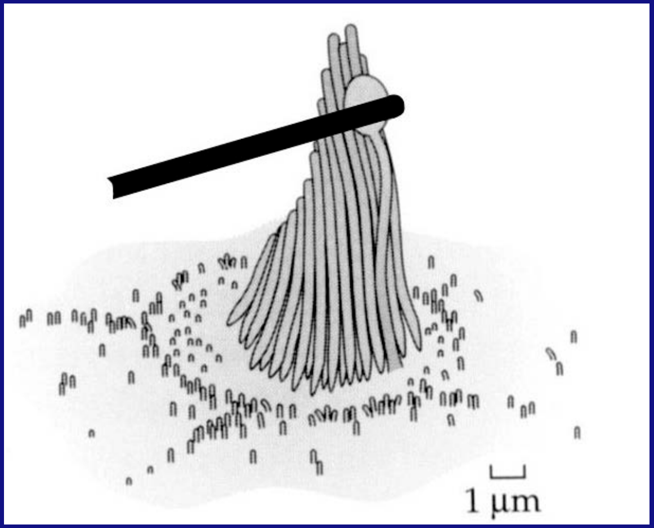
$\rightarrow$ sensory and motile

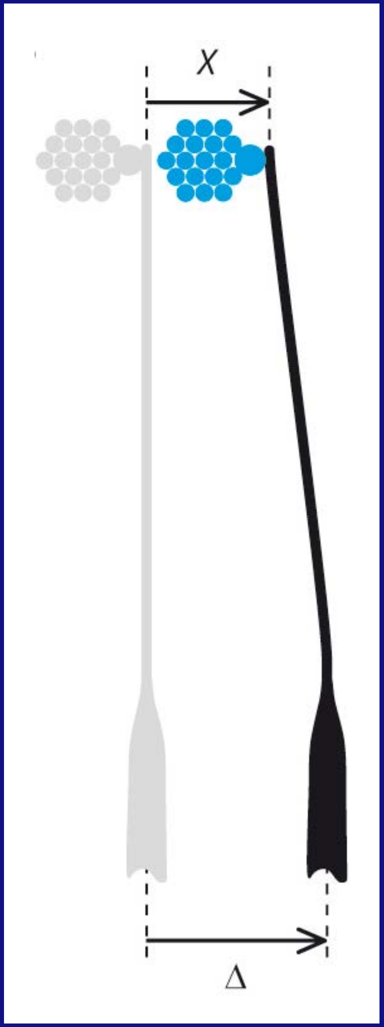
1 μm

SPONTANEOUS OSCILLATIONS



(Martin and Hudspeth, PNAS (1999))

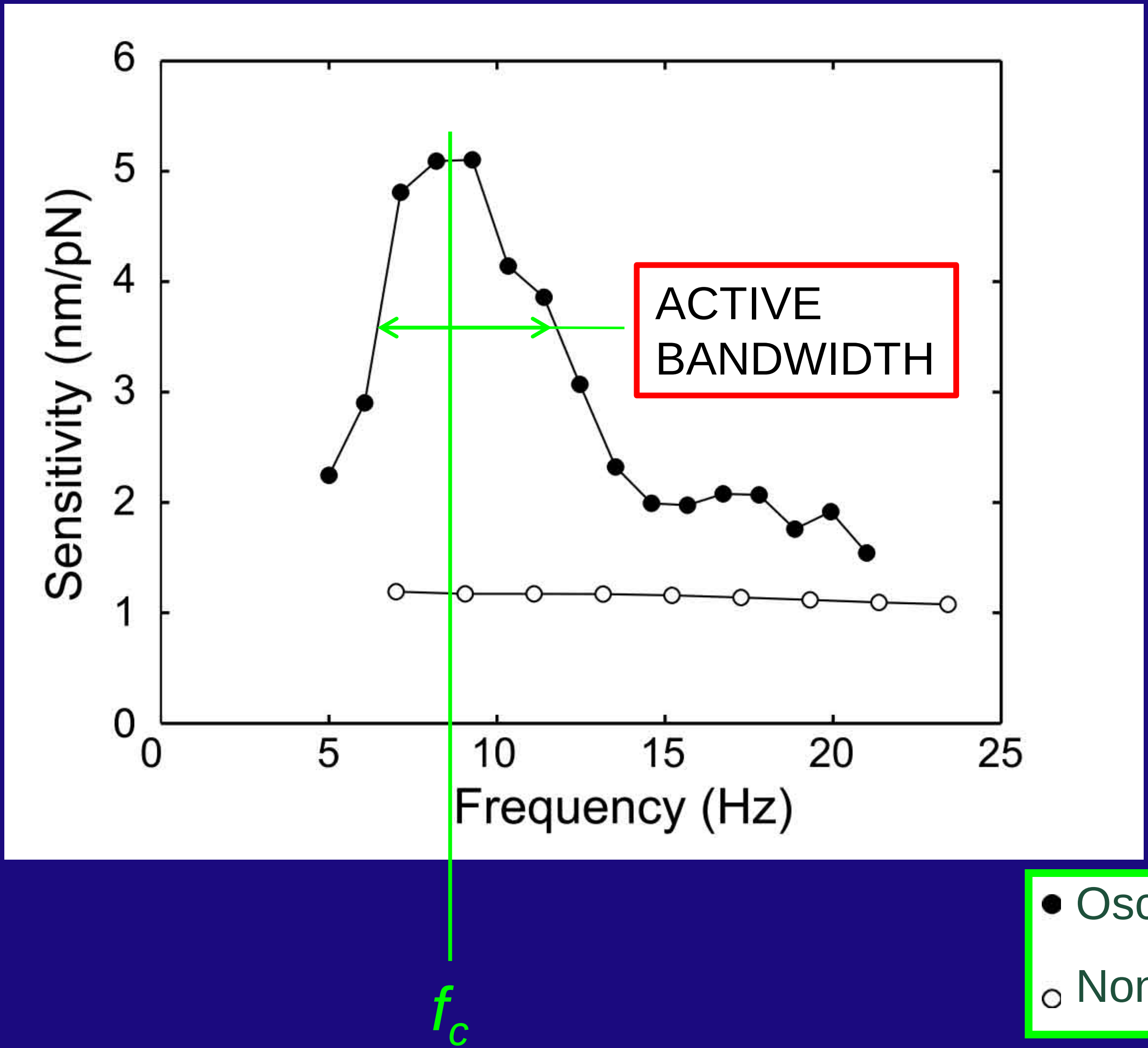

1 µm


X
Δ

Active resonance

($F_1 \cong 5$ pN)

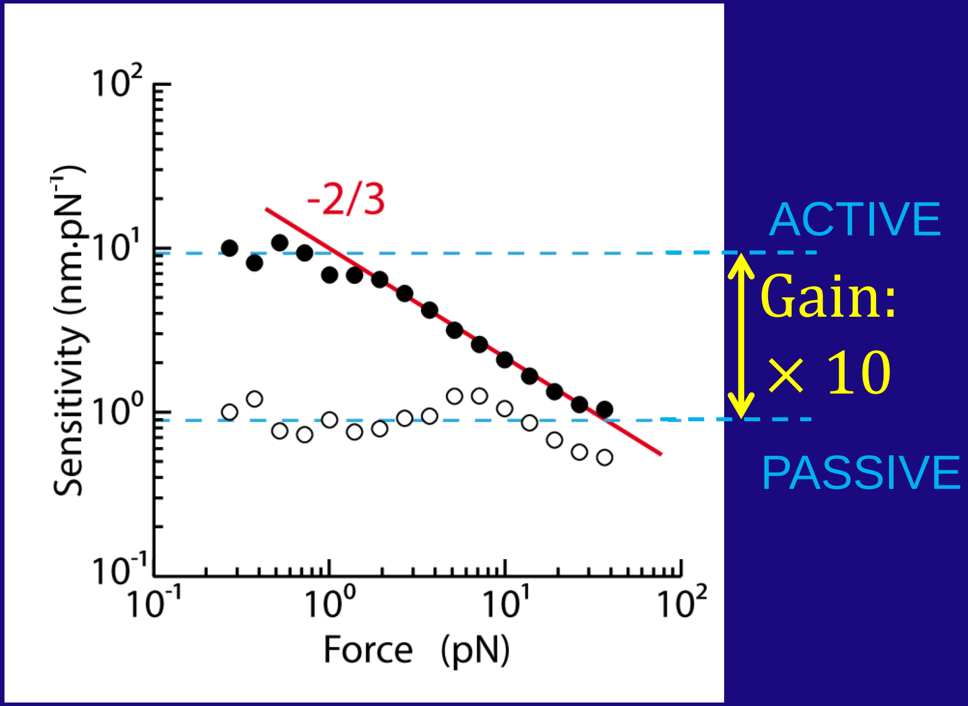
STIMULUS: $F(t) = F_1 \sin(2\pi f_1 t)$



- Oscillatory (~ 8 Hz)
- Non oscillatory

Nonlinear amplification

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



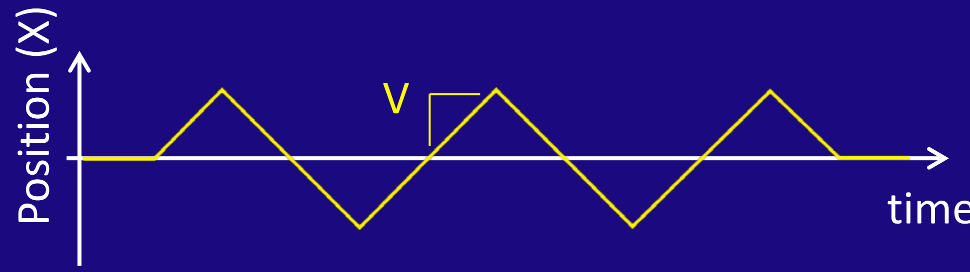
● at resonance (f_1 = 9 Hz)
○ off resonance (f_1 = 180 Hz)

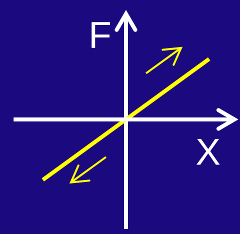
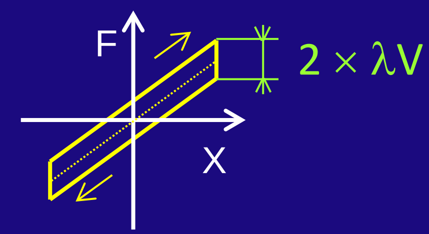
(Martin and Hudspeth, PNAS (2001))

What limits the sensitivity to weak stimuli?

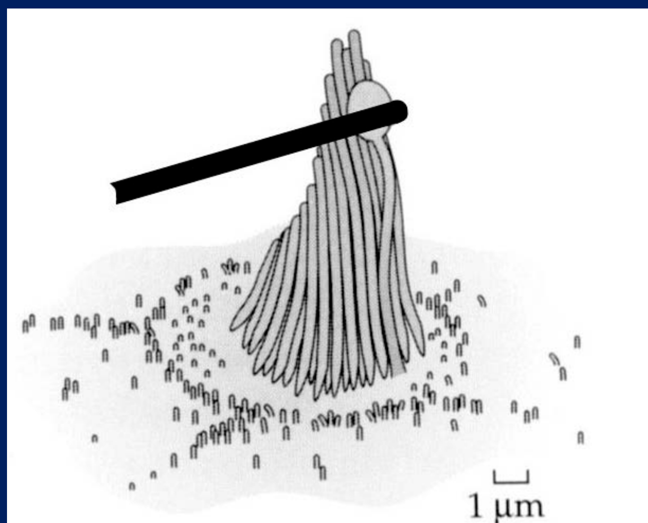
Friction

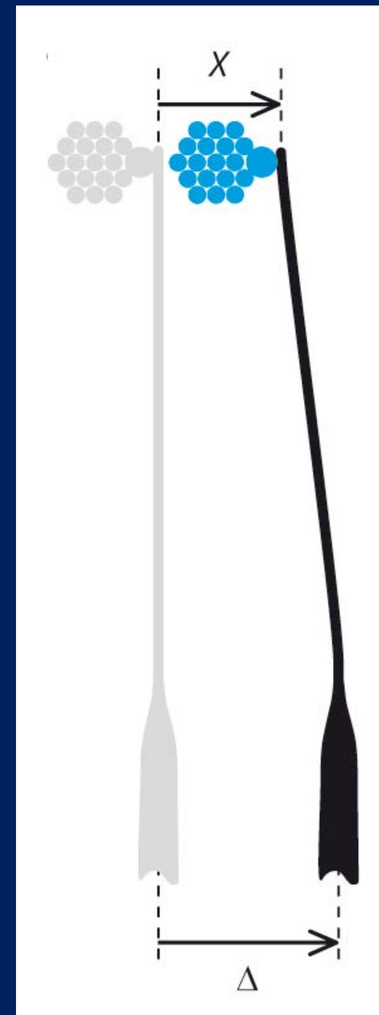
How to probe friction?



	Elastic	Elastic + friction
		
Force-displacement		
External force	$F = k\,X$	$F^{+} = k\,X + \lambda\,V$ $F^{-} = k\,X - \lambda\,V$

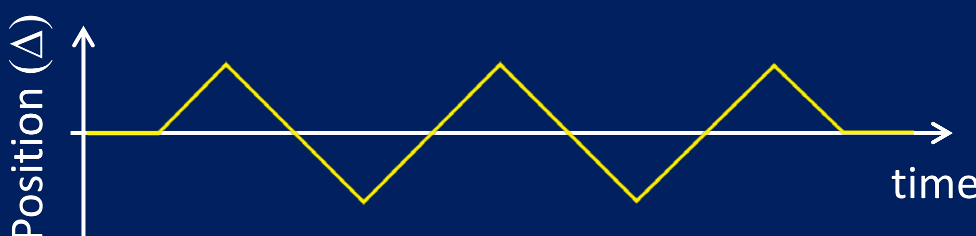
Friction force: $$\Phi(X) = \frac{F^{+}(X) - F^{-}(X)}{2}$$ $= \lambda V$





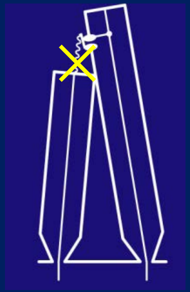
$X = \pm 80$ nm
$\dot{X} = 0.2 - 90$ µm/s

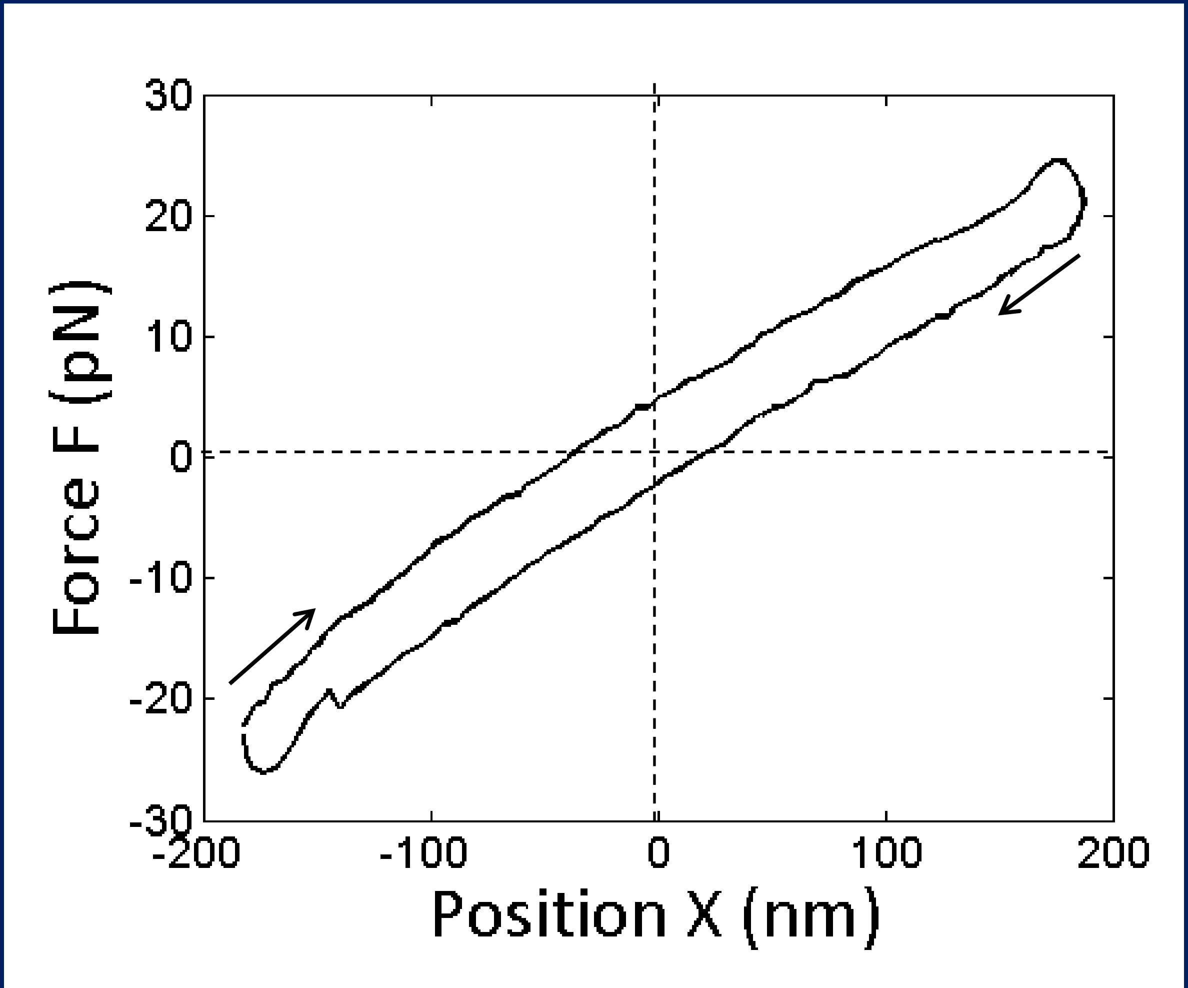
$\Delta = \pm 300$ nm
$\dot{\Delta} = 1 - 300$ µm/s



Hysteretic cycle

→ tip-links broken (with BAPTA)

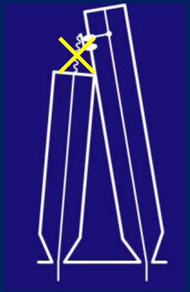




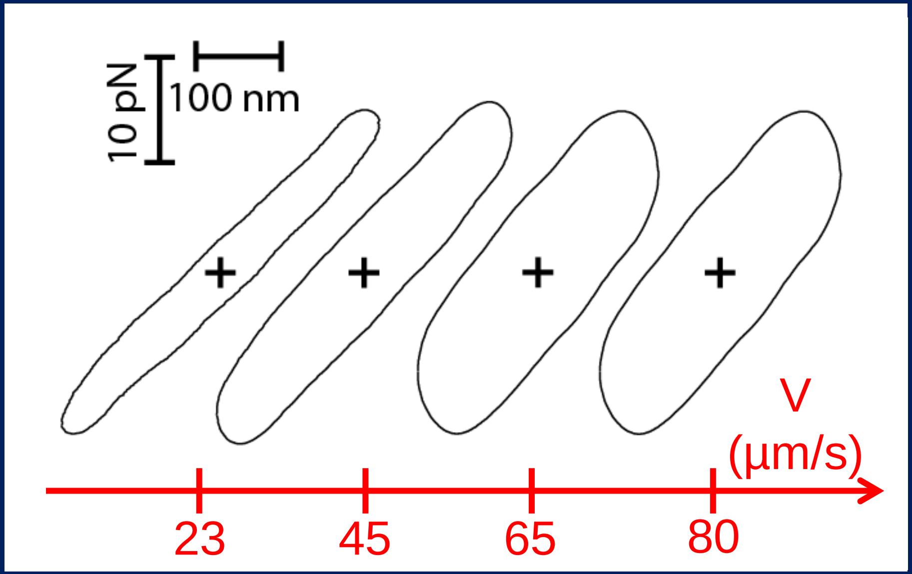
(V = 23 µm/s)

Hysteretic cycle

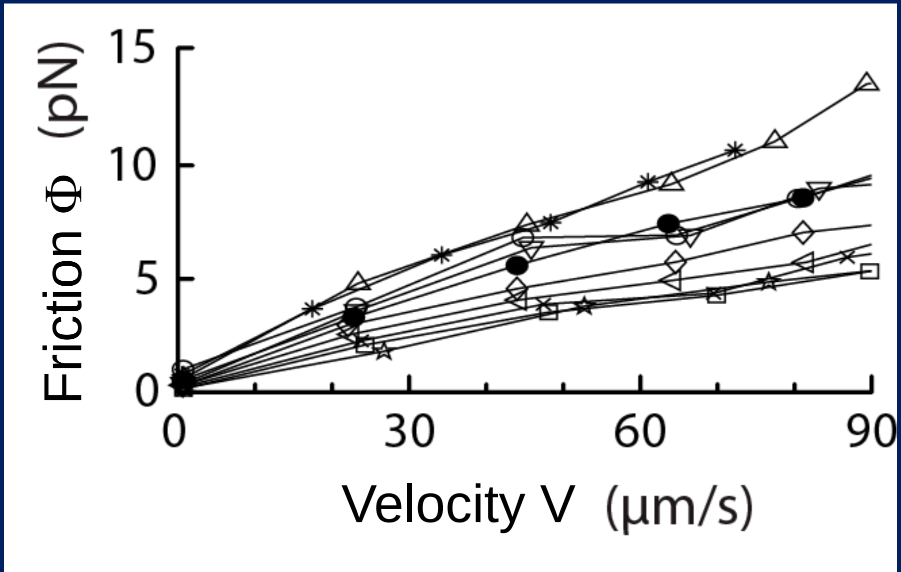
→ tip-links broken



Force-displacement cycles



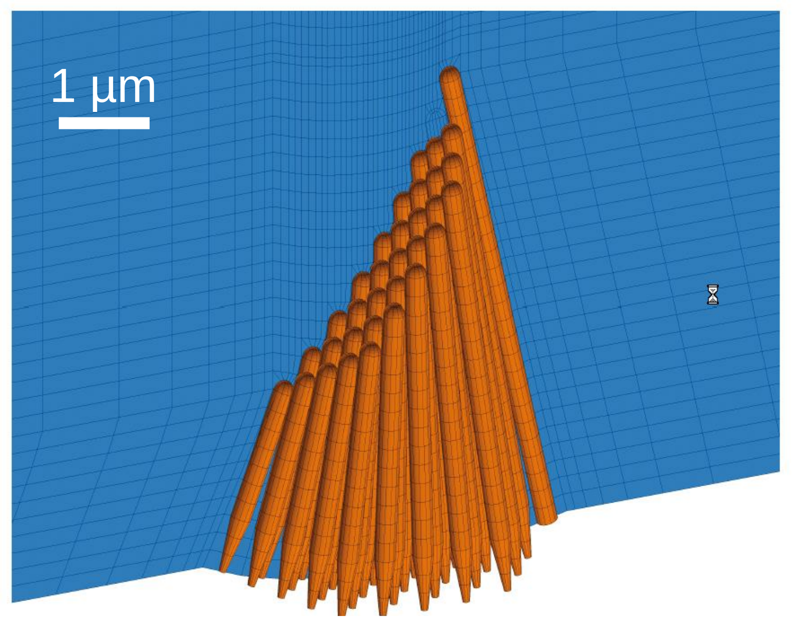
Friction force vs. velocity



Friction coefficient: $\lambda_H = 86 \pm 29$ nN·s/m (n =10)

Viscous drag

(calculation from finite-element analysis)

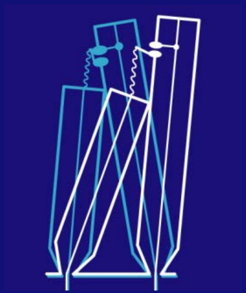


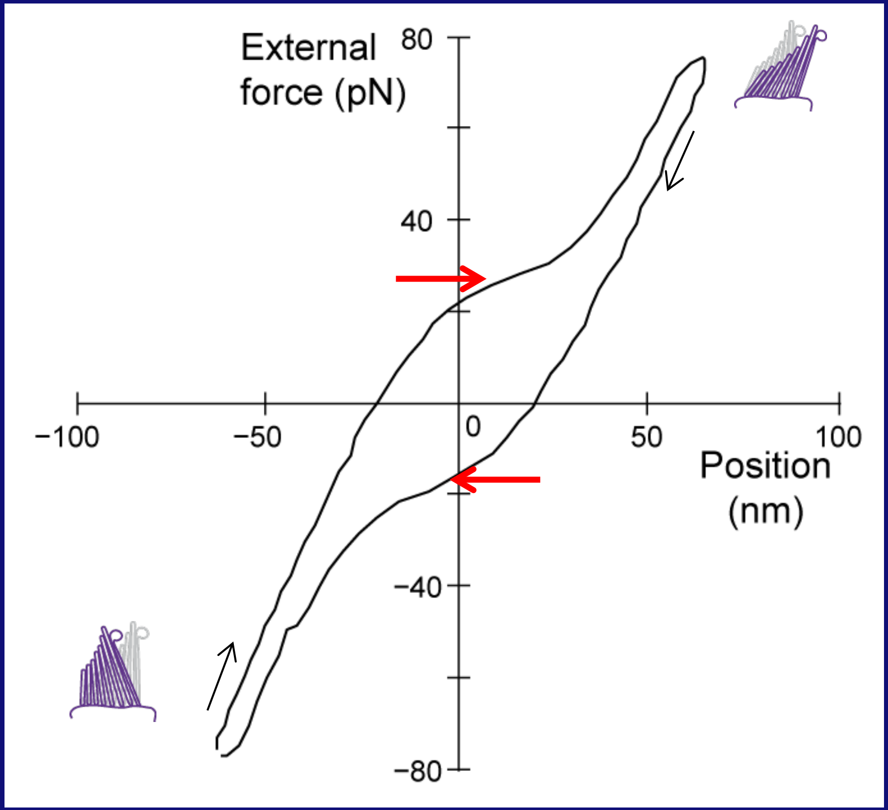
Friction coefficient:
≅ 100 nN·s/m

Velocity of 10 µm/s ⟹ Friction force of 1 pN

(Kozlov, Baumgart et al, Nature (2011))

Hysteretic cycle
→ functional hair bundle

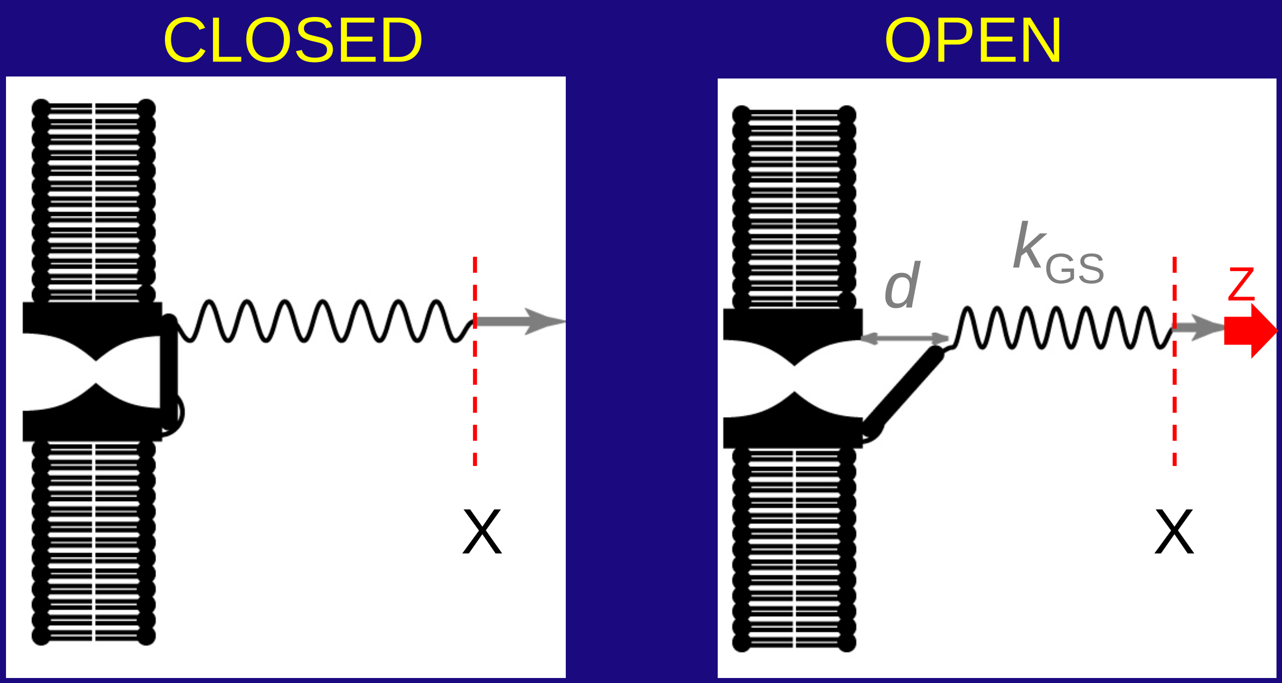




Bundle velocity:
25 µm/s

Gating compliance

(Howard and Hudspeth, 1988)



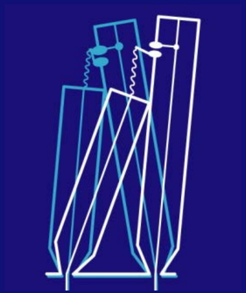
"gating force": $Z = k_{GS}\, d$

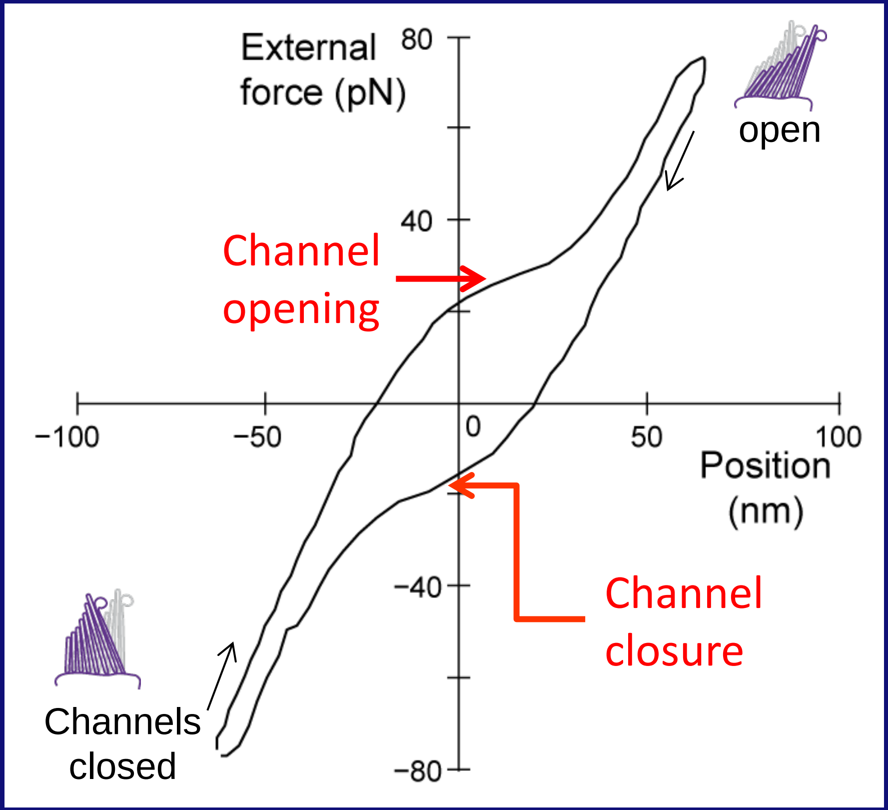
$$\langle F_{EXT} \rangle (X) = k_{GS}\, X - P_o(X)\, Z + F_0$$

Open probability

Hysteretic cycle

→ functional hair bundle

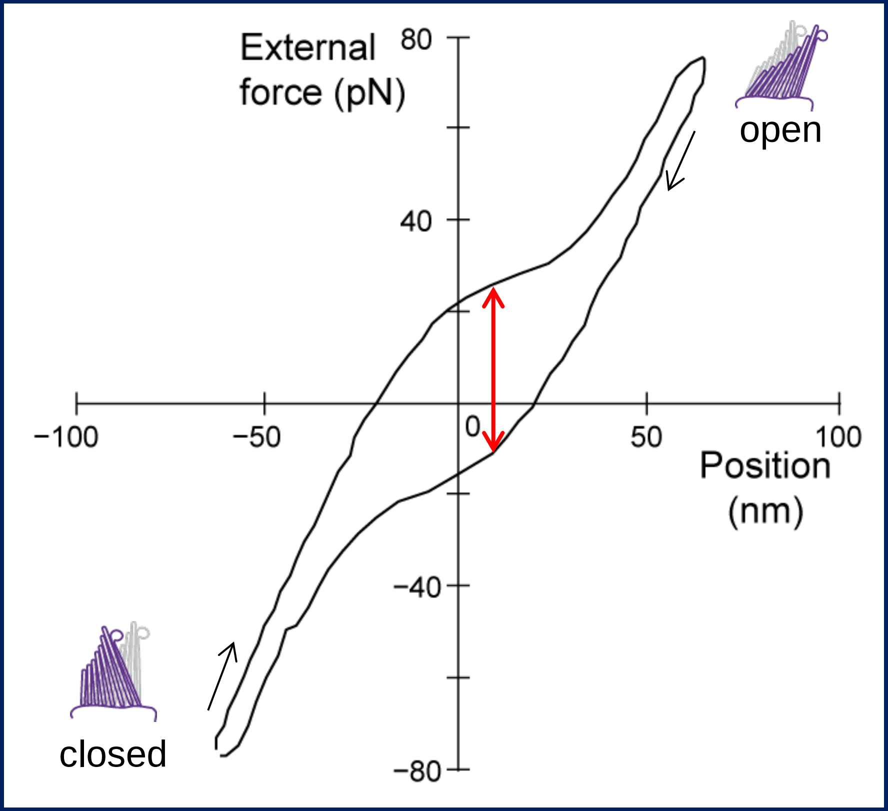




Bundle velocity:
25 µm/s

Hysteretic cycle

→ higher friction in the region of gating compliance

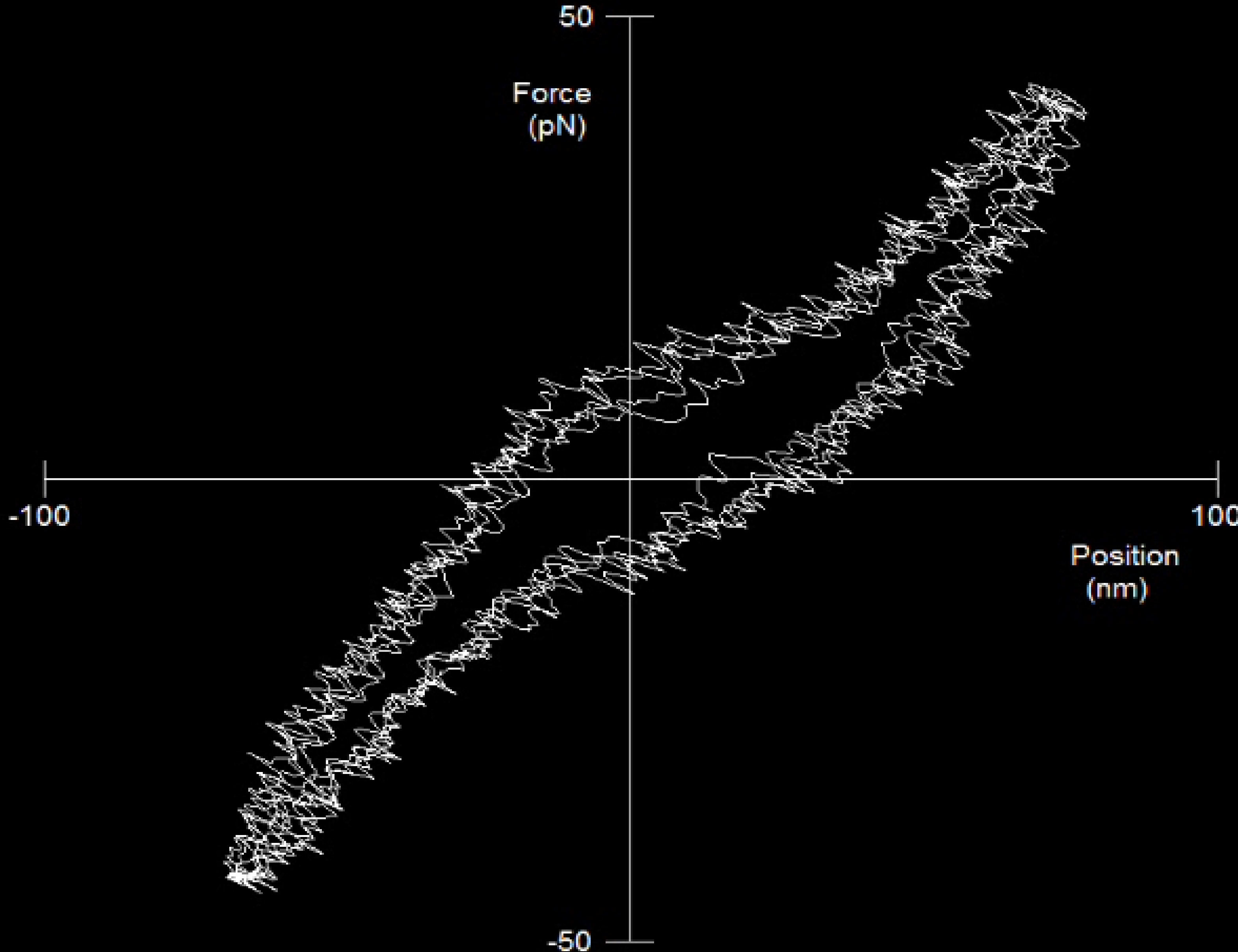


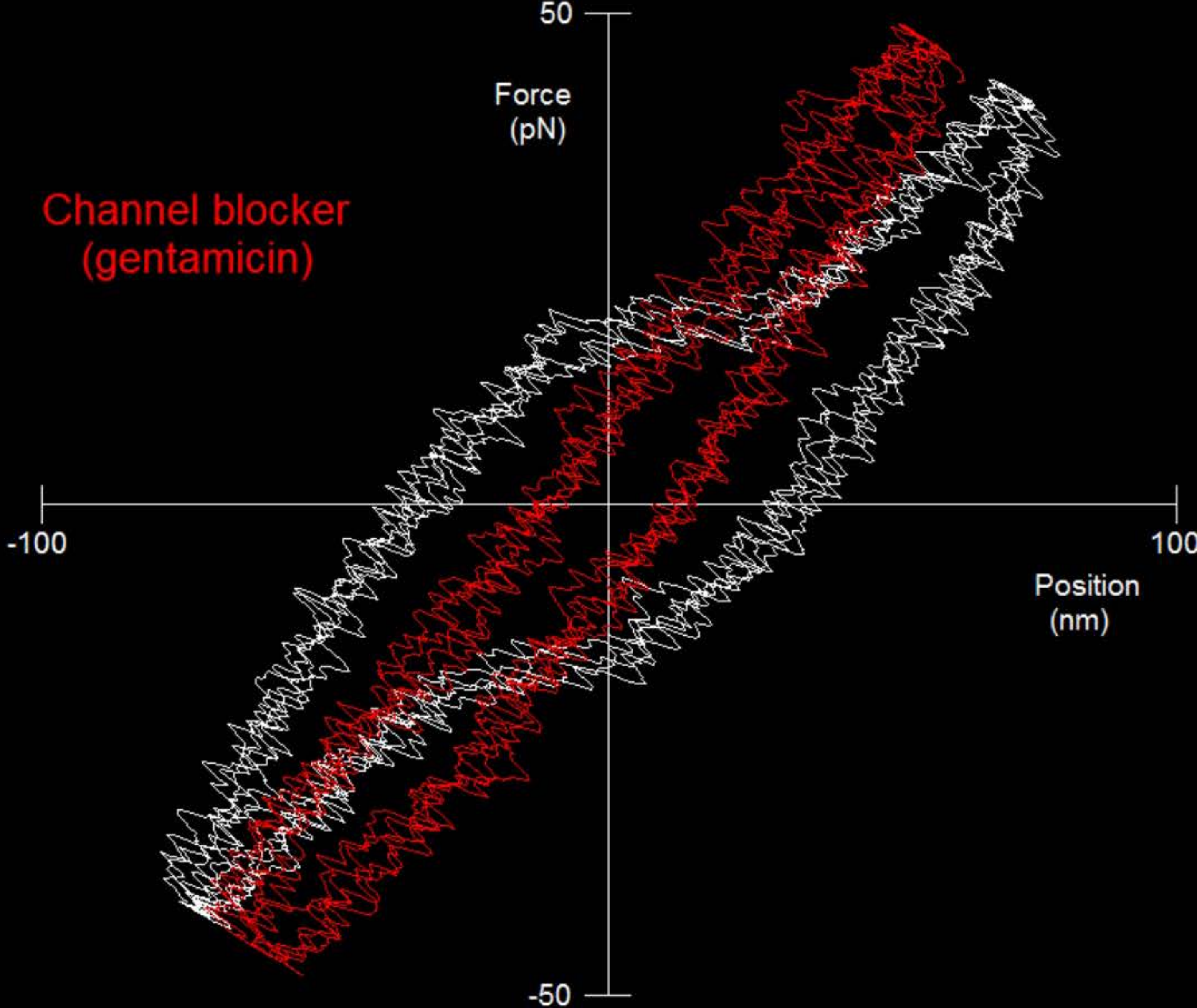
Bundle velocity:
25 µm/s

Friction force (20 pN) >> Expected hydrodynamic friction (2.5 pN only!!)

Are the transduction channels contributing to hair-bundle friction?

→ use a channel blocker (gentamicin)

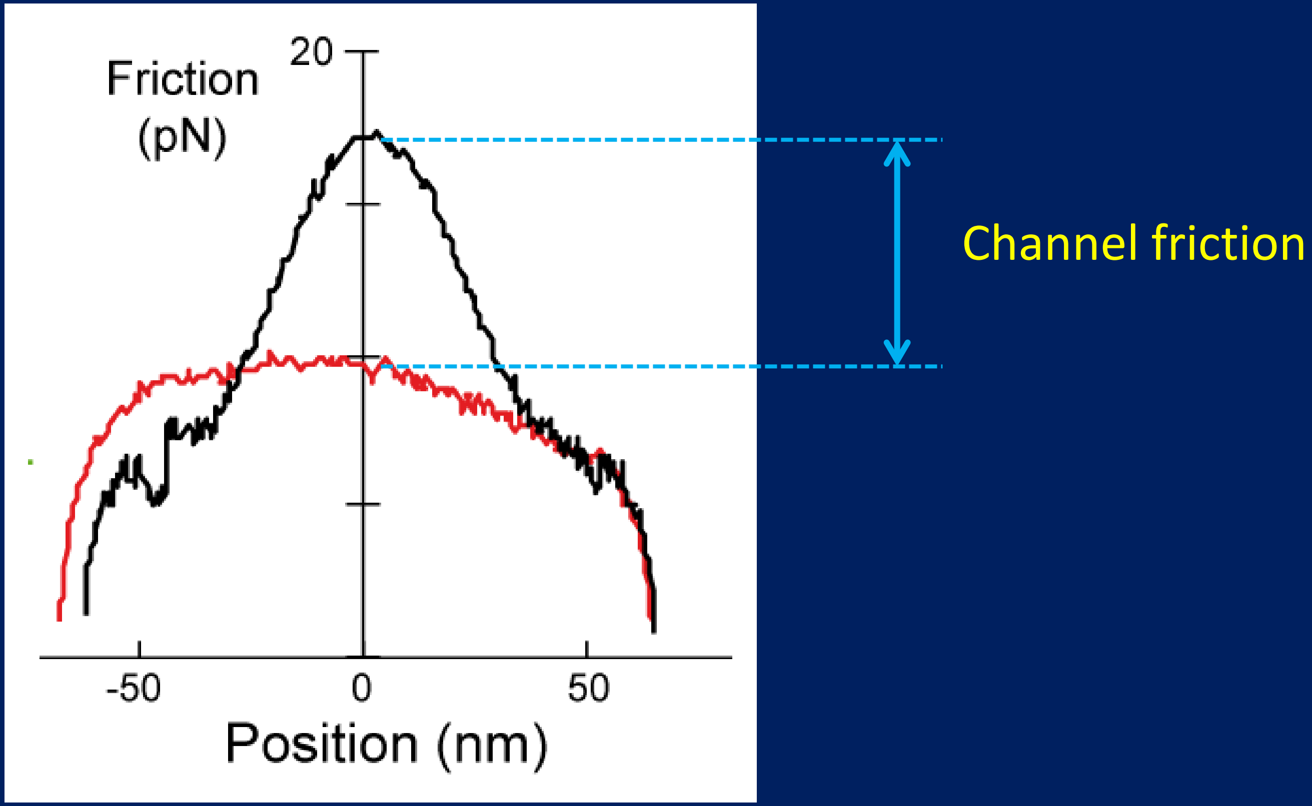

50
Force
(pN)
-100
100
Position
(nm)
-50



50
Force
(pN)
Channel blocker
(gentamicin)
-100
100
Position
(nm)
-50

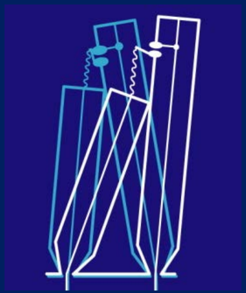
Friction from channel gating

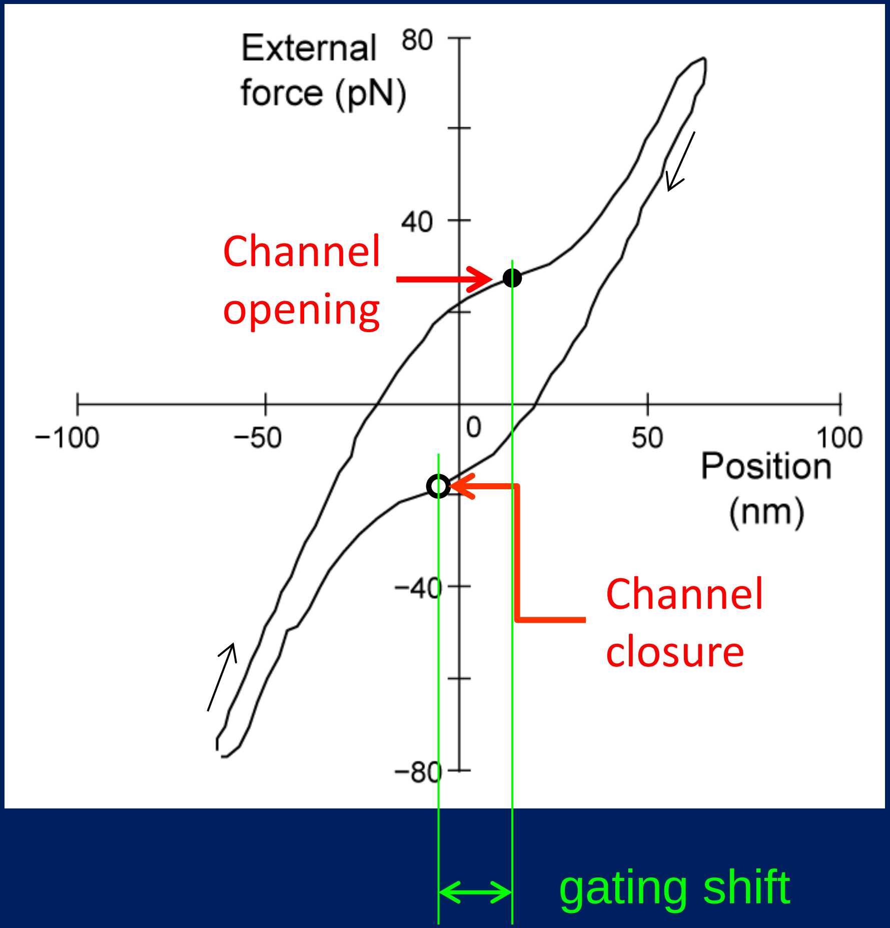
Bundle velocity:
25 µm/s



: control conditions
: channels blocked (Gentamicin)

Hysteretic cycle
→ functional hair bundle

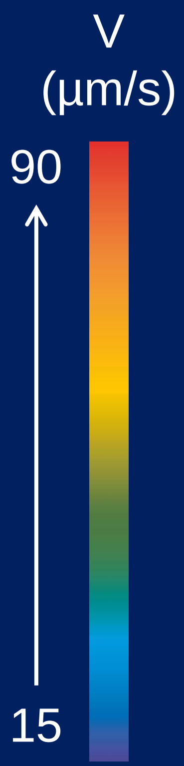


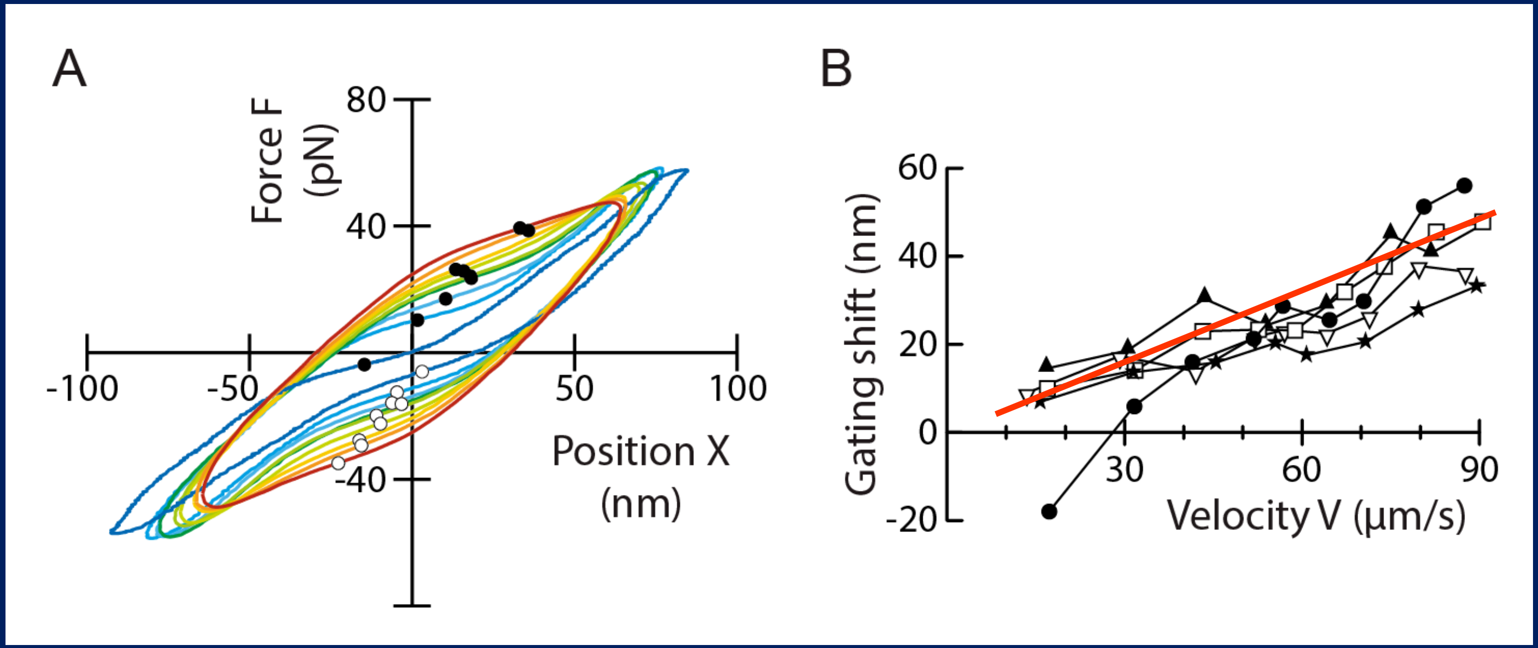


Bundle velocity:
25 µm/s

Gating shift

→ it takes time to open a channel!



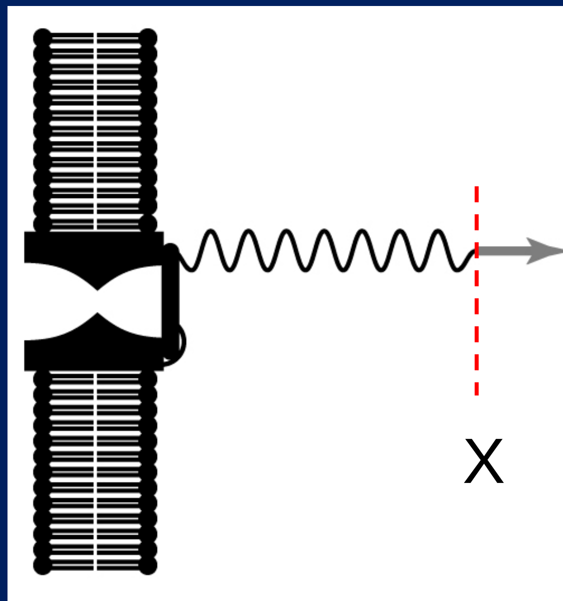


Characteristic activation time: $\tau_{exp} = 230 \pm 40\ \mu s$ (n = 5)

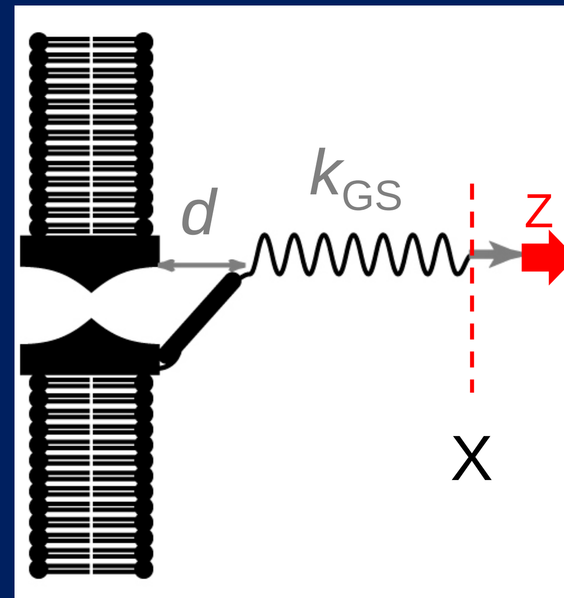
Gating-spring model

(Corey and Hudspeth, 1983)

CLOSED



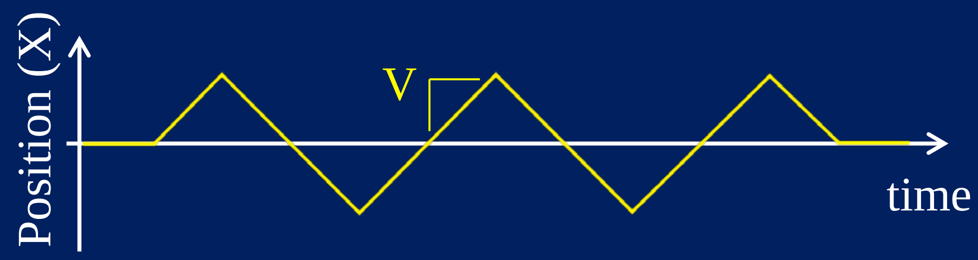
OPEN



"gating force": $Z = k_{GS}\, d$

activation time : τ

Physical description



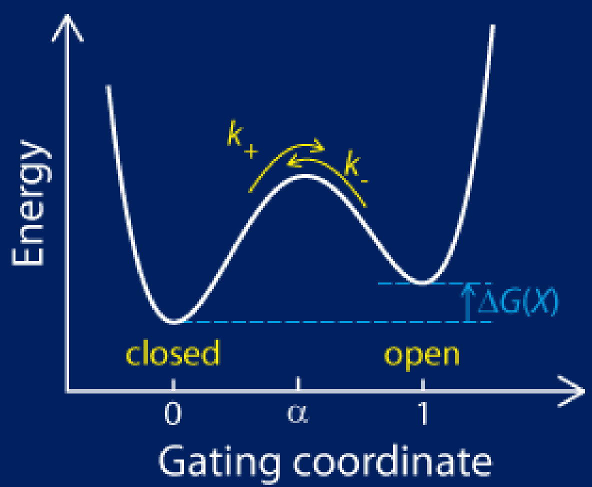
Force
-displacement:

$$F_{EXT}(X) = K_{HB}X - NP_o(X)\,Z + F_0$$

gating
compliance

Channel kinetics:

$$\tau \frac{dP_o}{dt} = P_\infty - P_o$$



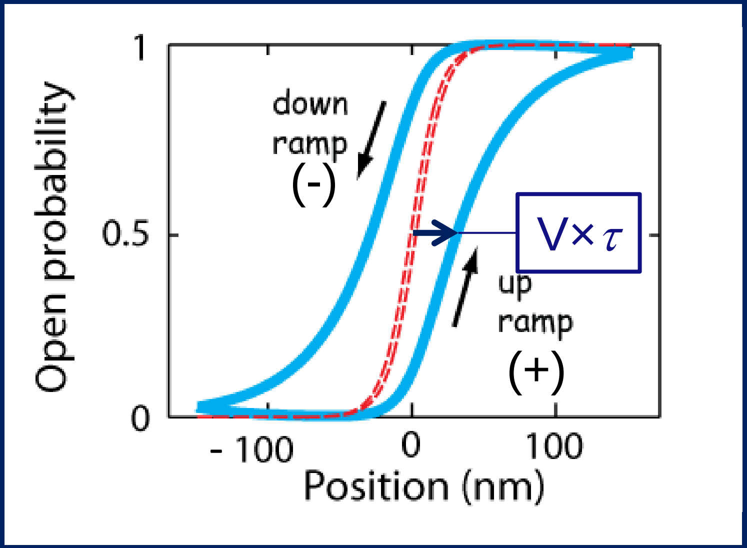
with

$$\tau = 1/(k_+ + k_-)$$

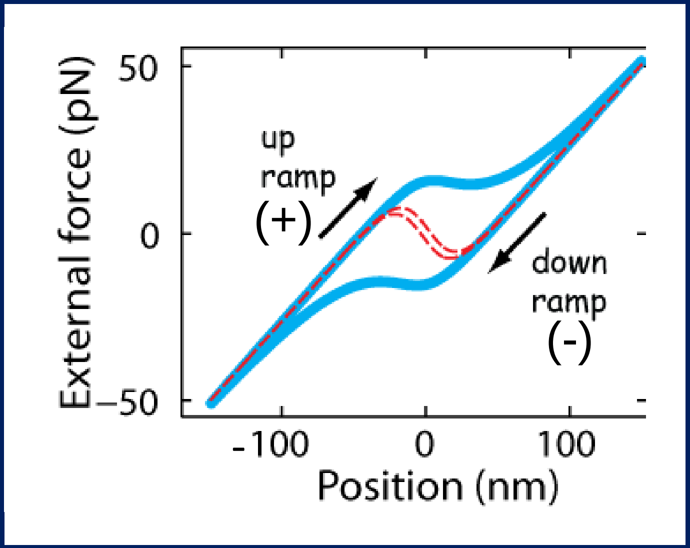
$$P_\infty = \frac{1}{1 + \exp\left(-\frac{Z \times X}{k_B T}\right)}$$

Dissipation from slow channel kinetics
→ simulations

Delayed channel gating



Dissipation



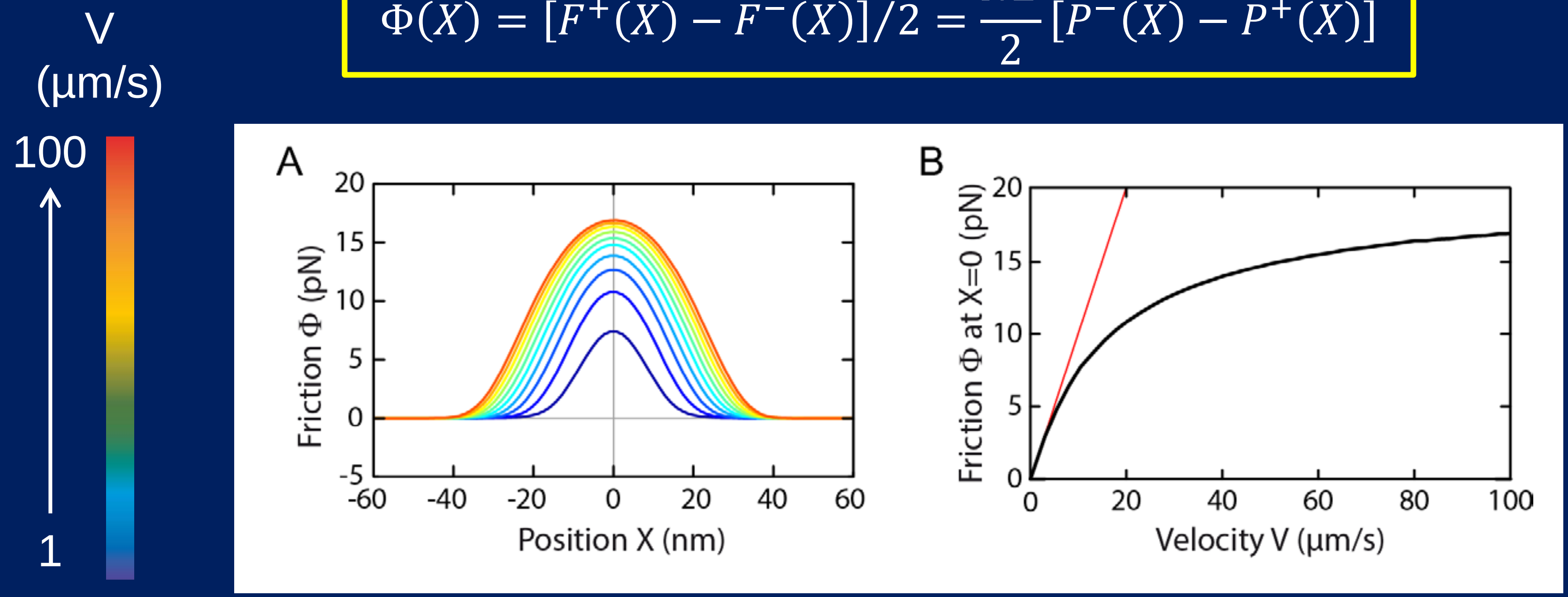
$$F^{\pm}(X) = K_{HB}X - NZ\, P_o^{\pm}(X) + F_0$$

- - - : low velocity
—— : high velocity

Channel friction
→ simulations

τ = 0.5 ms
Z = 0.8 pN
N = 50

$$\Phi(X) = [F^{+}(X) - F^{-}(X)]/2 = \frac{NZ}{2}[P^{-}(X) - P^{+}(X)]$$



$$\Phi(X=0) \leq \Phi_{MAX} = NZ/2 = 20 \text{ pN}$$

Friction force:

$$\Phi\,(X=0) \cong \left(\frac{NZ^2}{4k_BT}\,\tau\right) \times \mathrm{V}$$ at low velocities

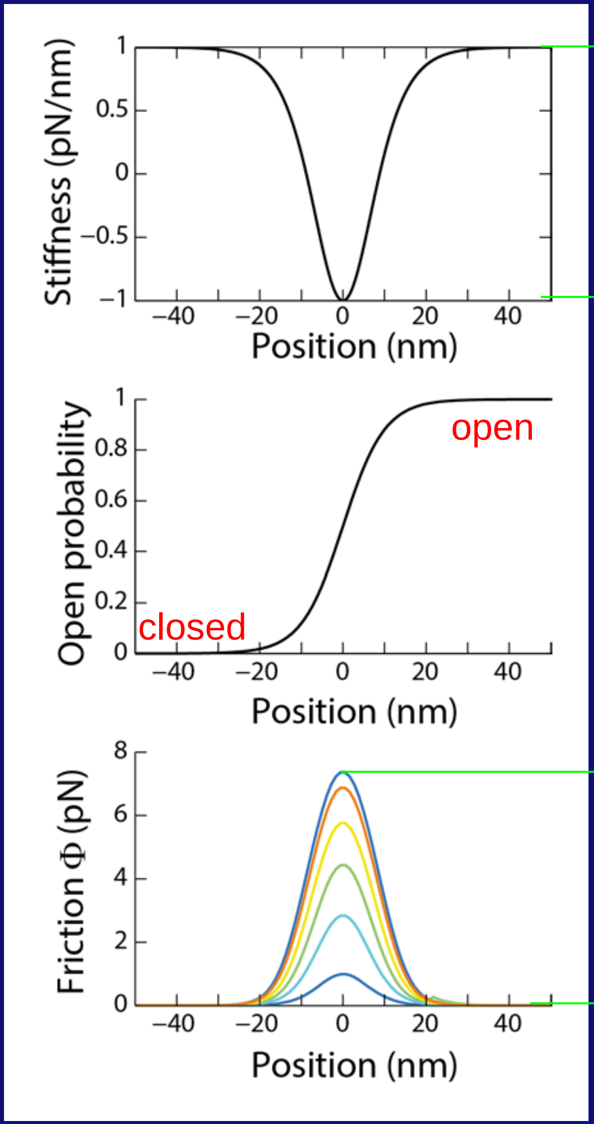
1 µN·s/m
(= 10 × λ_{Hydro})

Channel friction

- Gating of the transduction channels provides a major contribution to hair-bundle friction (up to $\times$10 hydro)
- Channel friction result from large gating forces and finite activation kinetics

(Bormuth, Barral, Joanny, Jülicher and Martin, PNAS (2014))

Dual role of gating forces (Z)



$$\Delta K = \frac{NZ^2}{4\,k_B T}$$

$$\Phi = \lambda_C\, V$$

Gating compliance

At low velocity:

$$\lambda_C = \Delta K \times \tau$$

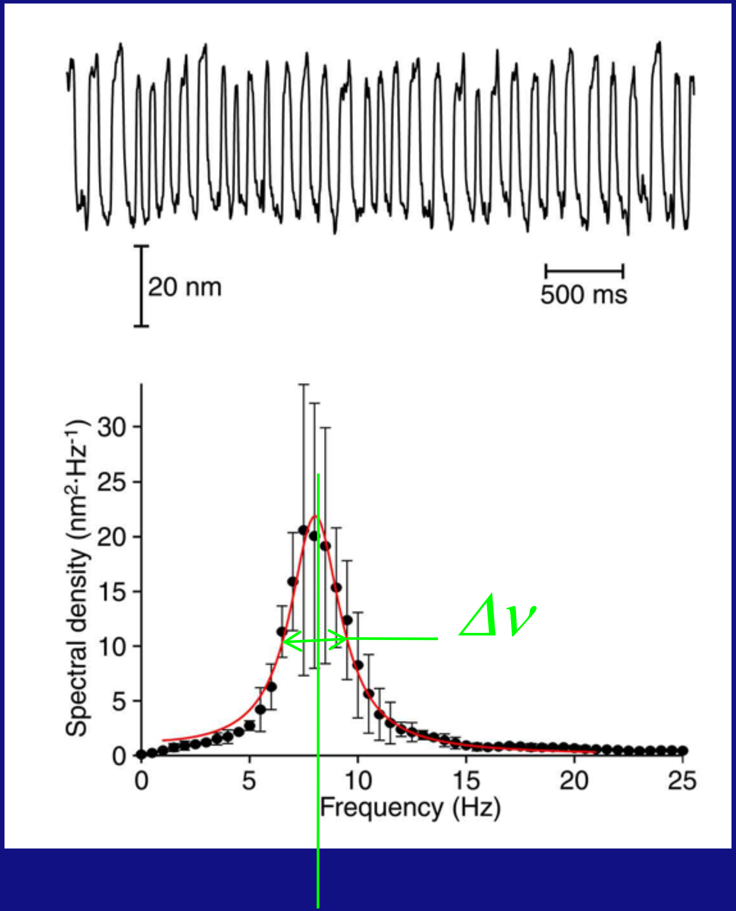
Gating friction

Noise

Characteristic frequency

Hair-bunde position

Spectral density



Noisy!

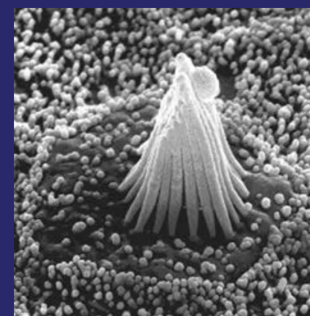
Low quality factor
(Q = $\nu_C/\Delta\nu \cong 2$)

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

(Martin and Hudspeth, PNAS (1999))

Noise sources

• Hydrodynamic:



Noise force η:

$$\langle \eta_H \rangle = 0$$

$$\langle \eta_H(t)\eta_H(0) \rangle = 2k_B T \,\lambda_H \,\delta(t)$$

friction

• Channel clatter:

$$\langle \eta_C \rangle = 0$$

$$\langle \eta_C(t)\eta_C(0) \rangle \cong 2k_B T \,\lambda_C \,\delta(t)$$

(Nadrowski, Martin and Jülicher, PNAS (2004))

Active dynamical system

$$\begin{cases} \text{Hair bundle:} \quad \lambda \frac{dX}{dt} = -K_{GS}(X - X_a - DP_o) - K_{SP}X + F_{EXT} \\ \text{Motors:} \quad \lambda_a \frac{dX_a}{dt} = K_{GS}(X - X_a - DP_o) - F_a \end{cases}$$

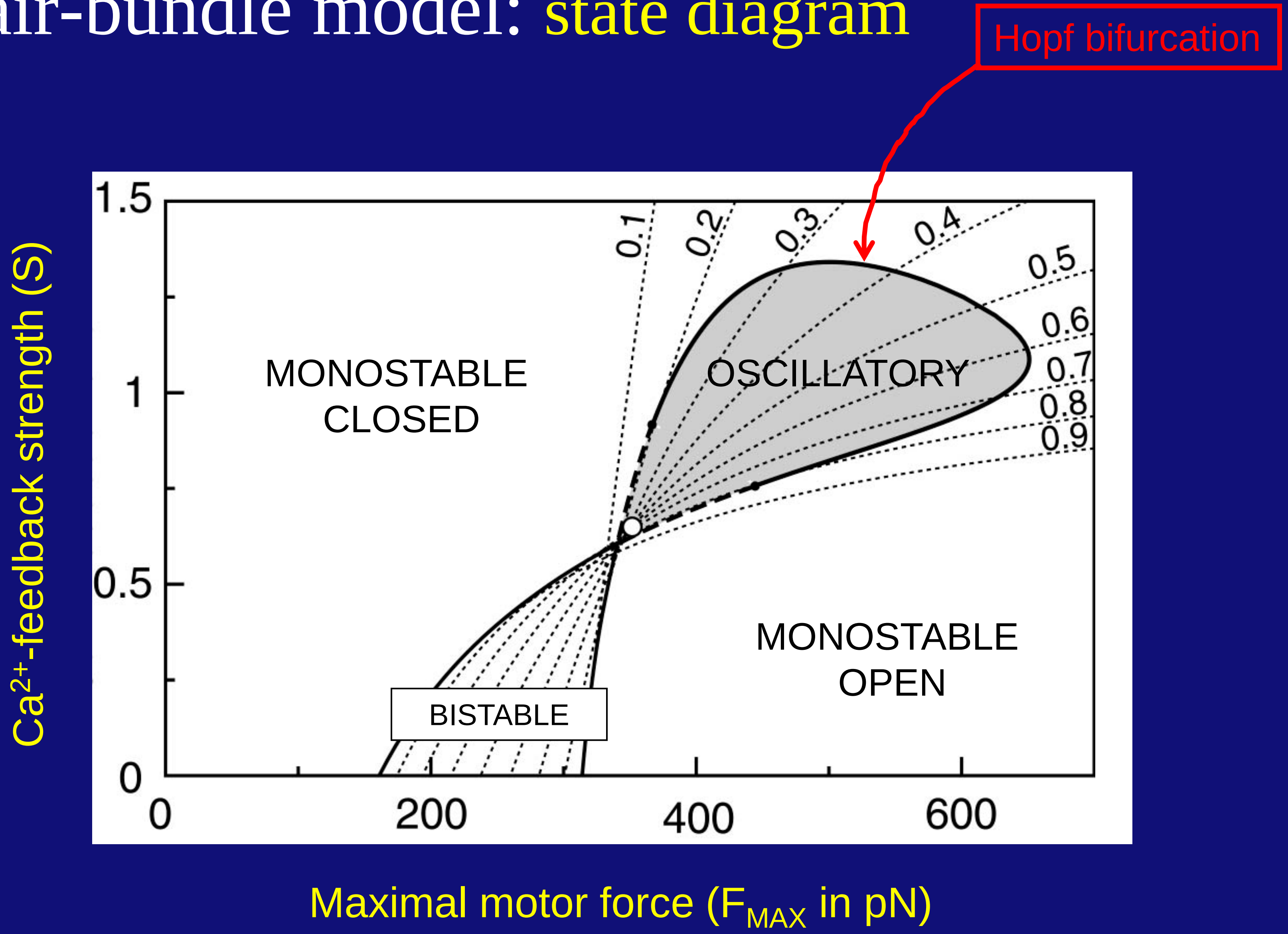
Tip-link tension

Motor force: $F_a = F_{MAX}(1 - SP_o)$

Open probability: $P_o = 1/[1 + A\exp(-Z(X - X_a)/(k_B T))]$

(Nadrowski, Martin and Jülicher, PNAS (2004))

Hair-bundle model: state diagram



(Nadrowski, Martin and Jülicher, PNAS (2004))

Active dynamical system WITH NOISE

Hair bundle: $\lambda \frac{dX}{dt} = -K_{GS}(X - X_a - DP_o) - K_{SP}X + F_{EXT} + \xi_X$

Motors: $\lambda_a \frac{dX_a}{dt} = K_{GS}(X - X_a - DP_o) - F_{MAX}(1 - SP_o) + \xi_a$

Tip-link tension

$$\langle \xi_X \rangle = 0;\ \langle \xi_X(t)\, \xi_X(0) \rangle = 2k_B T\, \lambda\, \delta(t)$$

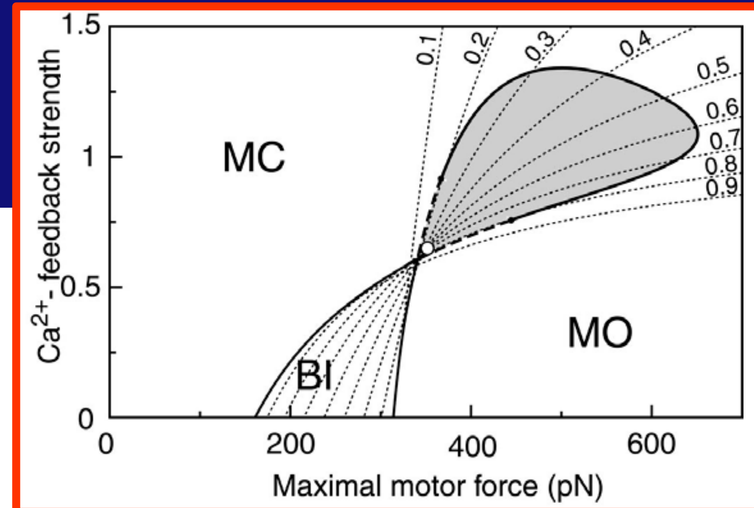
$$\langle \xi_a \rangle = 0;\ \langle \xi_a(t)\, \xi_a(0) \rangle = 2k_B T_a\, \lambda_a\, \delta(t); T_a = 1.5\, T$$

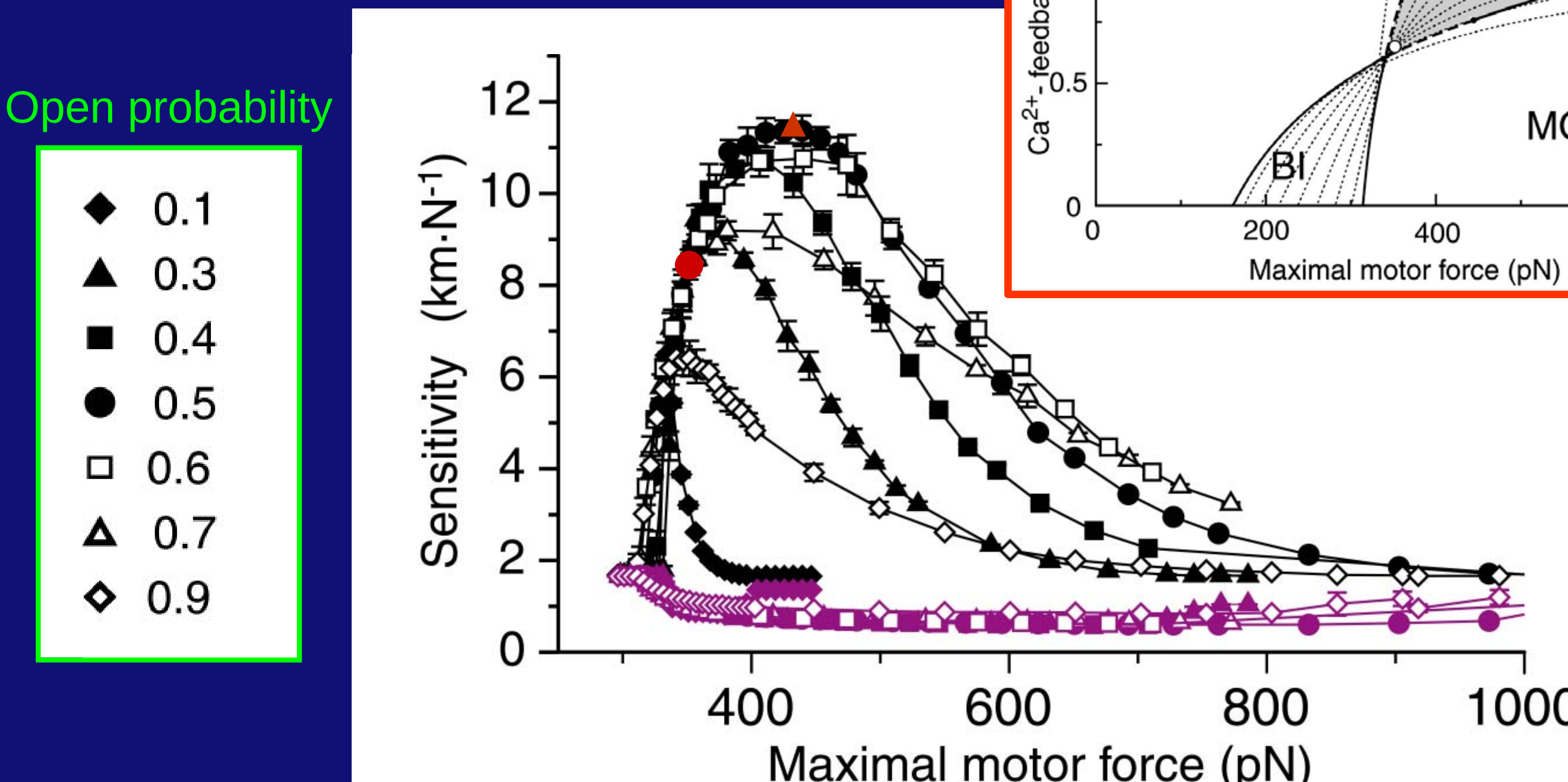
Open probability: $P_o = 1/[1 + A \exp(-Z(X - X_a)/(k_B T))]$

(Nadrowski, Martin and Jülicher, PNAS (2004))

Optimum of mechanosensitivity

→ limited by noise !

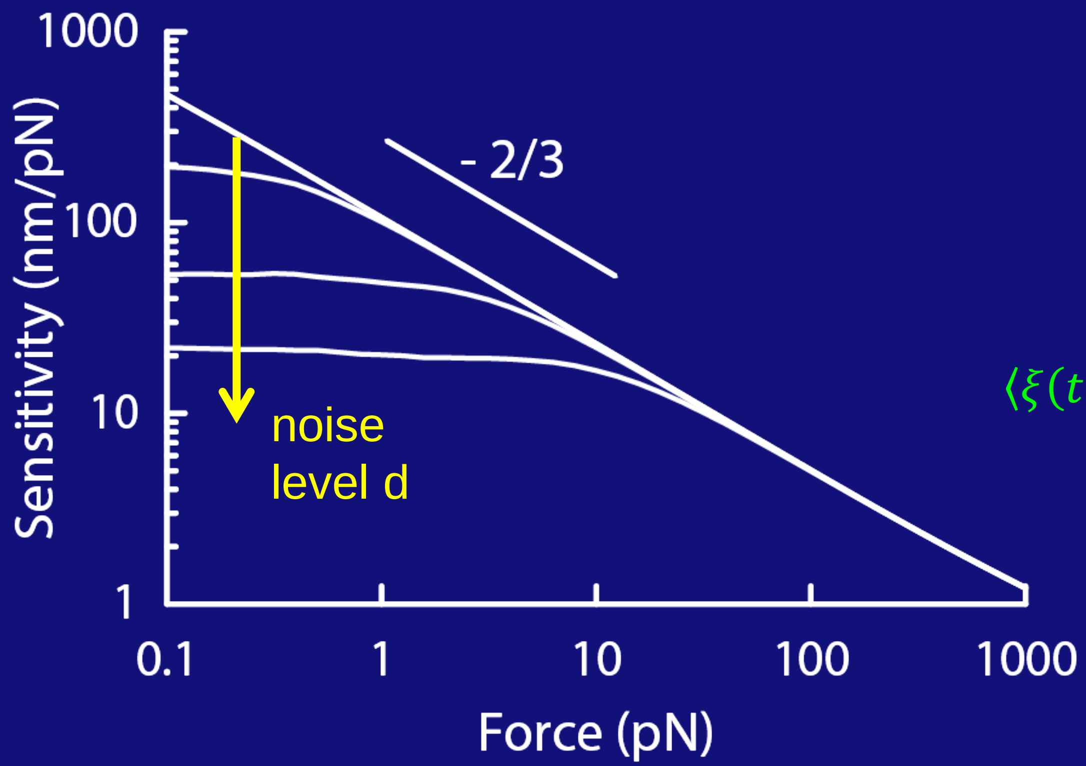




Hopf bifurcation

→ « critical oscillator » with noise

$$\frac{dZ}{dt} \cong -(\Omega_c - \Omega - \mathrm{i}\,\omega_0)\,\mathrm{Z} - \mathrm{B}|Z|^2 Z + \frac{F+\xi}{\Lambda}$$



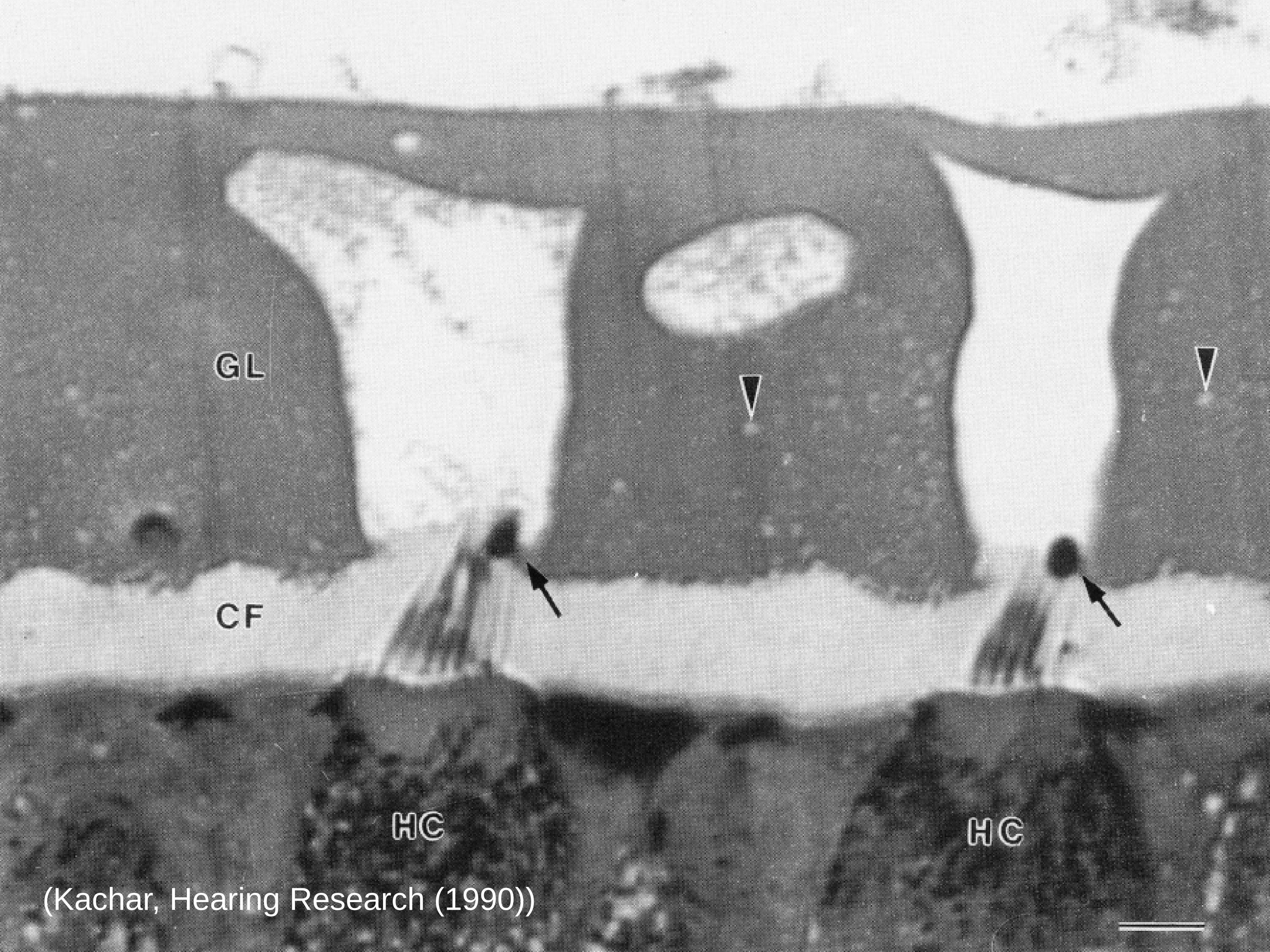
$$\Omega = \Omega_C$$

$$F(t) = F_0 \sin(\omega_0 t)$$

Noise force:

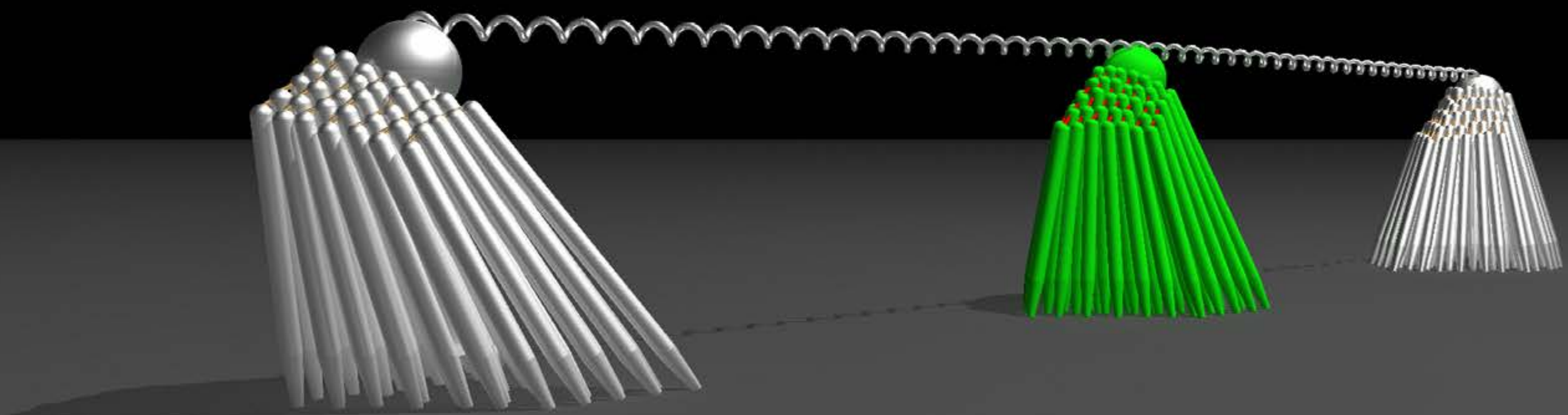
$$\langle \xi(t) \rangle = 0$$

$$\langle \xi(t)\xi(0) \rangle = 2d\,\delta(t)$$



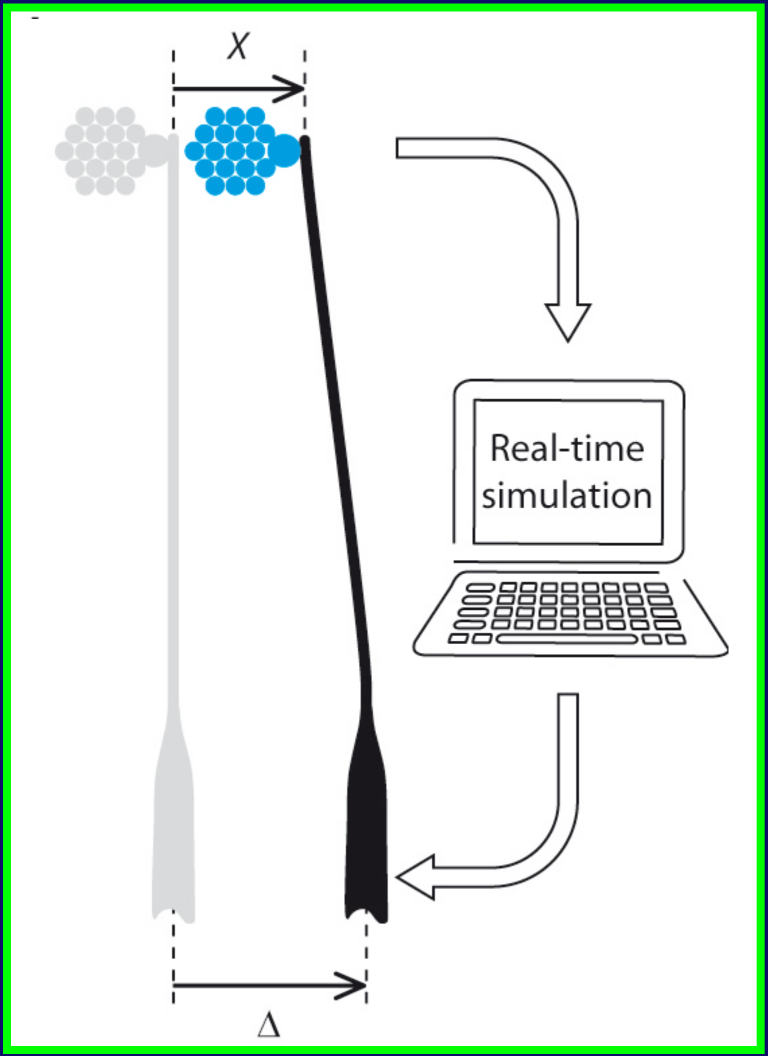
(Kachar, Hearing Research (1990))

Coupling



(Kai Dierkes)

Coupling to « cyber clones »



« virtual reality »

Cyber clone?

Stochastic simulation that mimics quantitatively:

1. Spontaneous hair-bundle oscillations
(frequency, magnitude and quality factor)

2. Hair-bundle responsiveness
(sensitivity and gain)

Active dynamical system WITH NOISE

Hair bundle: $\lambda \frac{dX}{dt} = -K_{GS}(X - X_a - DP_o) - K_{SP}X + F_{EXT} + \xi_X$

Motors: $\lambda_a \frac{dX_a}{dt} = K_{GS}(X - X_a - DP_o) - F_{MAX}(1 - SP_o) + \xi_a$

Tip-link tension

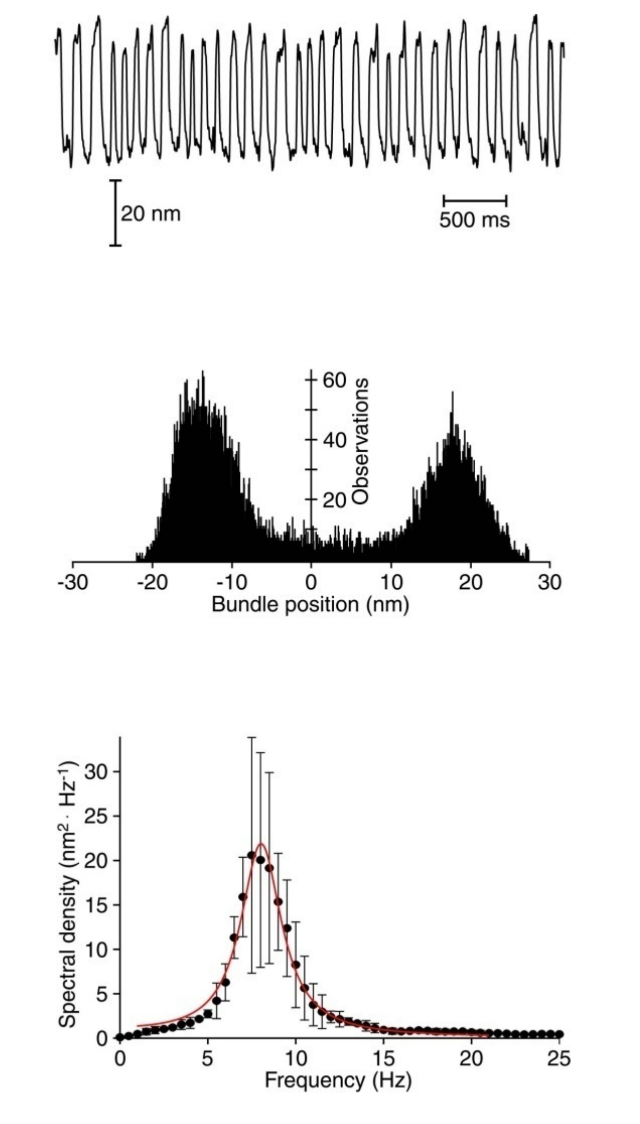
$$\langle \xi_X \rangle = 0;\ \langle \xi_X(t)\, \xi_X(0) \rangle = 2k_B T\, \lambda\, \delta(t)$$

$$\langle \xi_a \rangle = 0;\ \langle \xi_a(t)\, \xi_a(0) \rangle = 2k_B T_a\, \lambda_a\, \delta(t); T_a = 1.5\, T$$

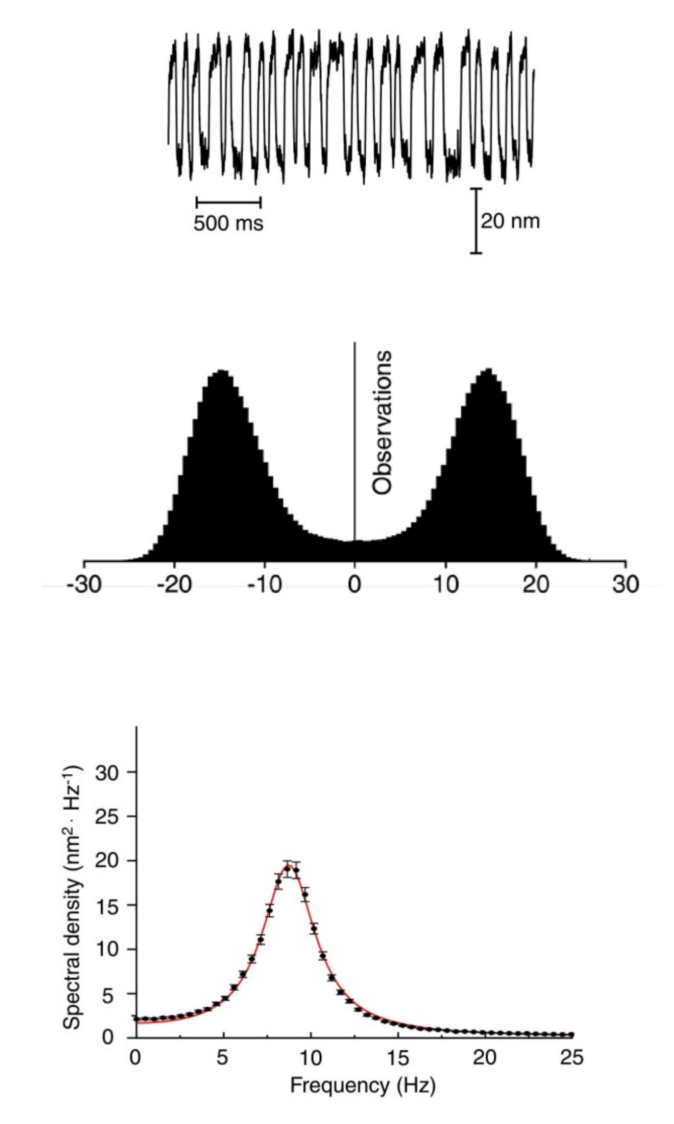
Open probability: $P_o = 1/[1 + A \exp(-Z(X - X_a)/(k_B T))]$

(Nadrowski, Martin and Jülicher, PNAS (2004))

Experiment

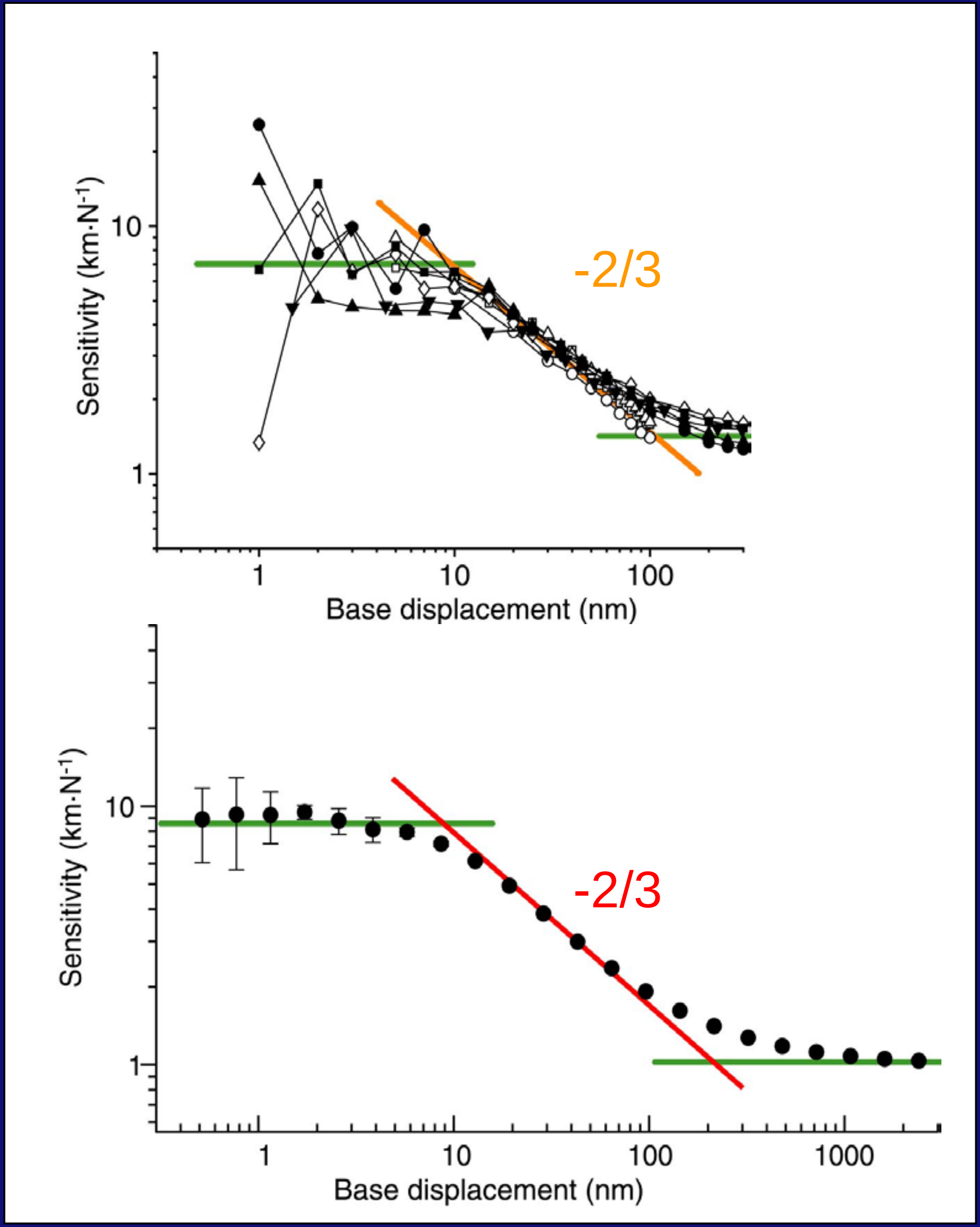


"Cyber clone"

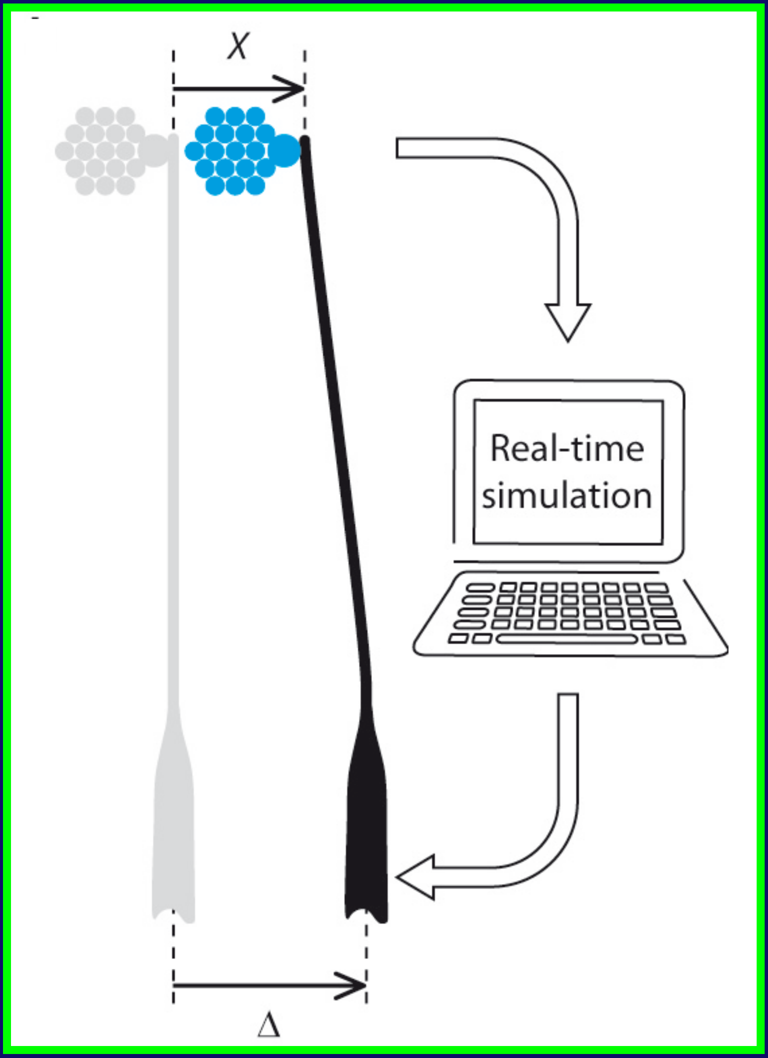


Experiment

Simulation



Dynamic force clamp

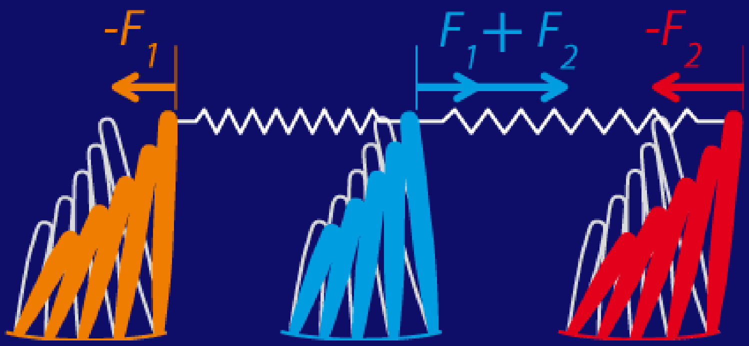


(Time: t = n dt ;
sampling rate: 2.5 kHz)

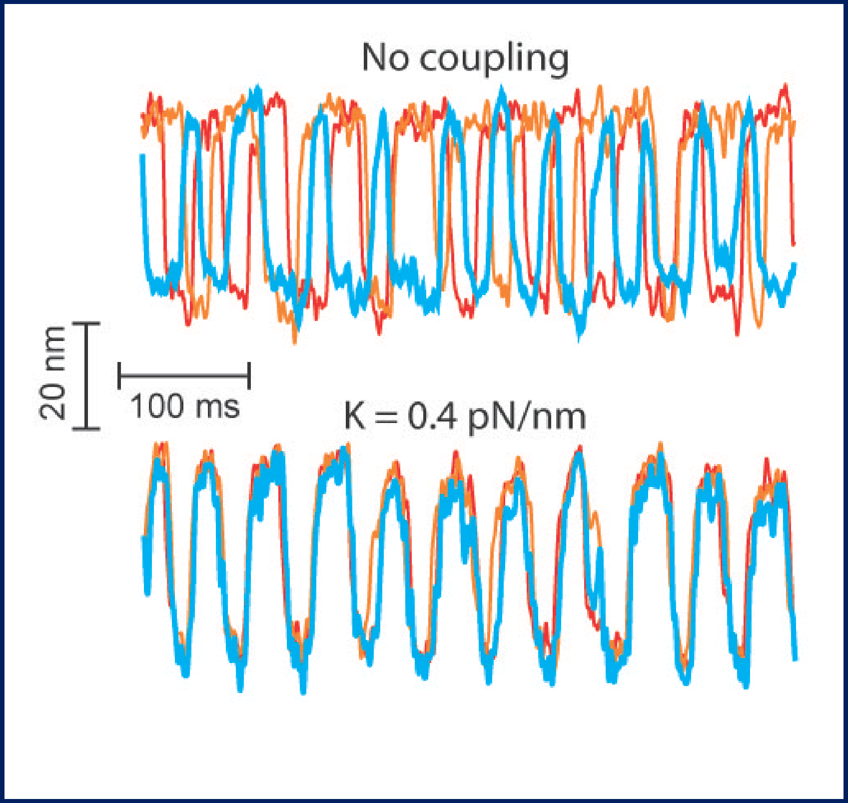
1. Measure X(n)
(X_1(n) and X_2(n) known from step n-1)

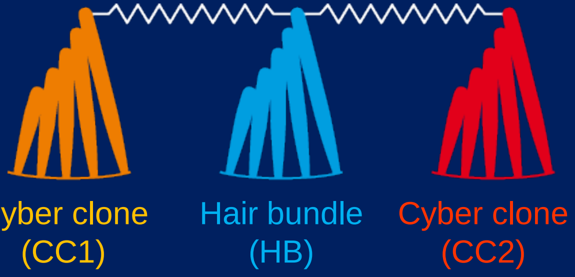
2. (i) Calculate F_1(n) and F_2(n)
   (ii) Integrate stochastic differential equations with $-F_1$(n) and $-F_2$(n) to get X_1(n+1) and X_2(n+1)

3. Move the fiber to $\Delta(n)=X(n)+F(n)/K_F$ with $F(n)=F_1(n)+F_2(n)+F_{EXT}$

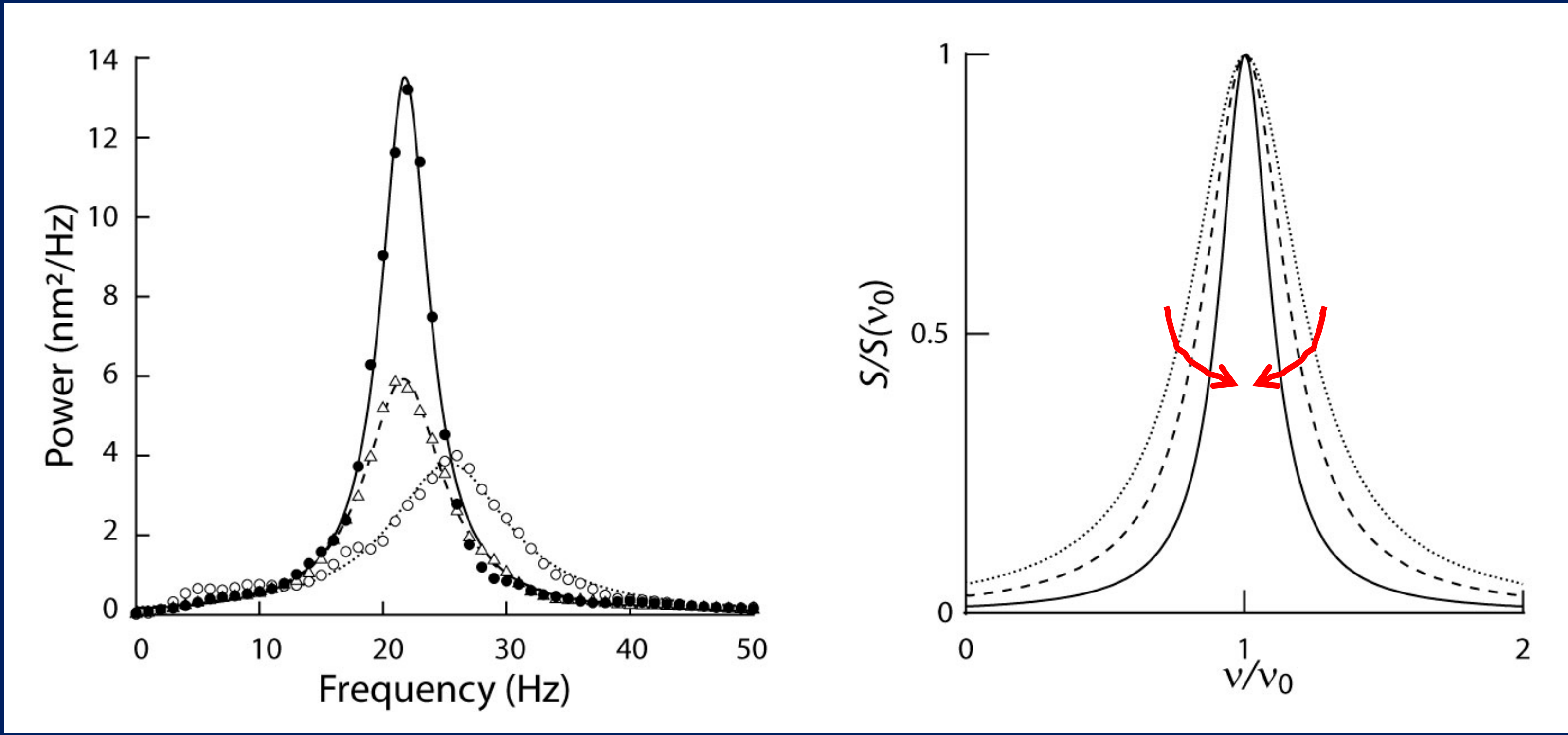


Synchronization





More regular oscillations!



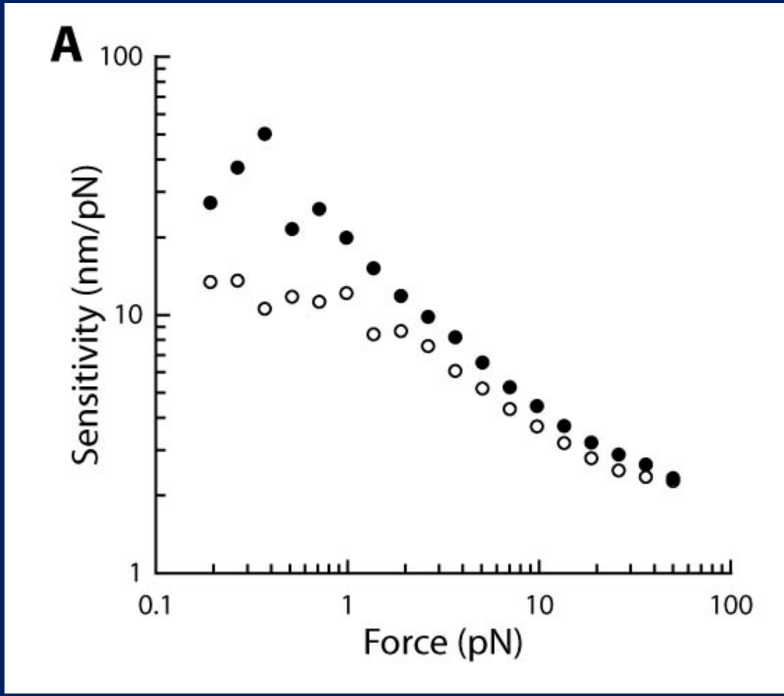
: no coupling

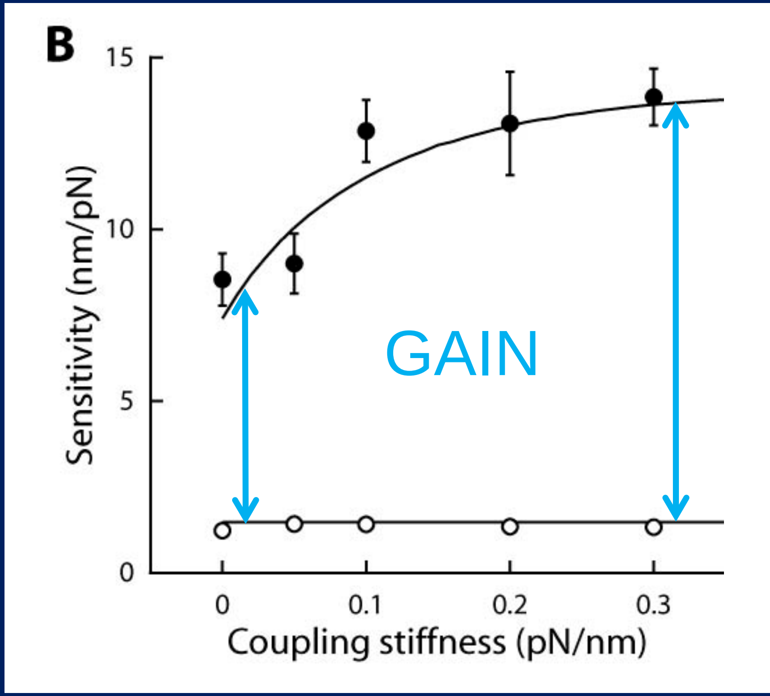
: *K* = 0.2 pN/nm

: *K* = 0.4 pN/nm

Sensitivity to external stimuli

$F_{EXT} = F_0 \sin(2\pi\, \nu_0\, t)$

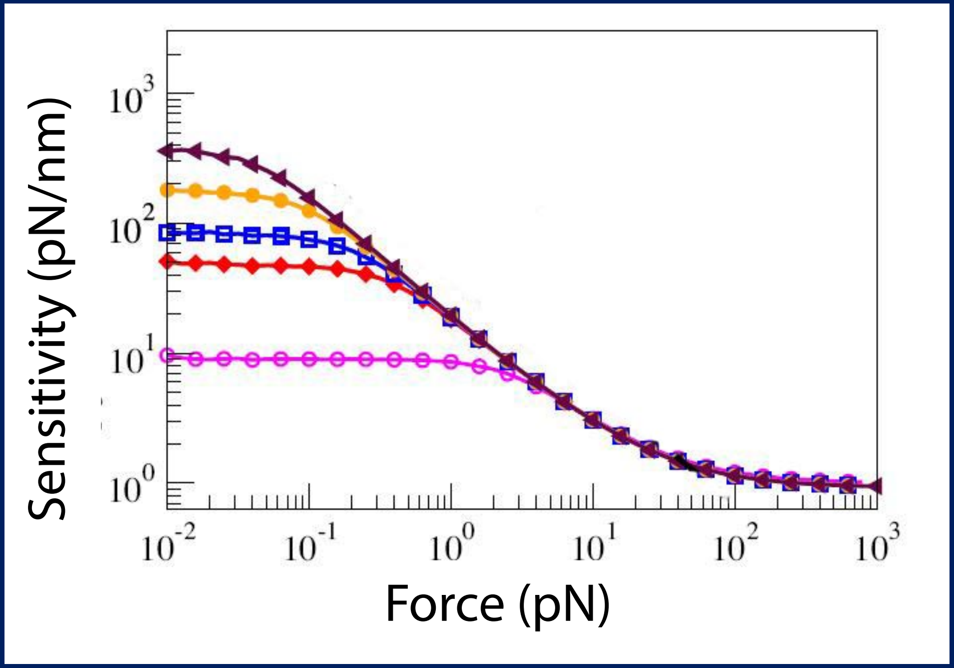




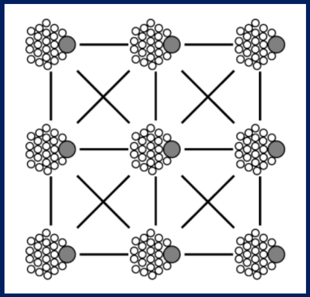
●: K= 0.2 pN/nm
○: no coupling

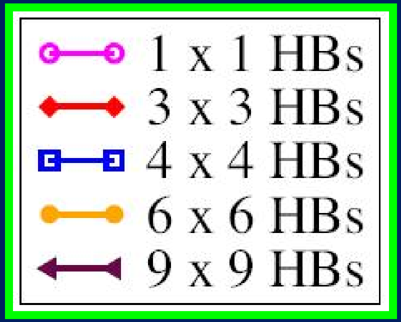
●: F_{EXT} = 0.5 pN
○: F_{EXT} = 50 pN

Groups of coupled hair bundles
(simulations)



Oscillatory module:

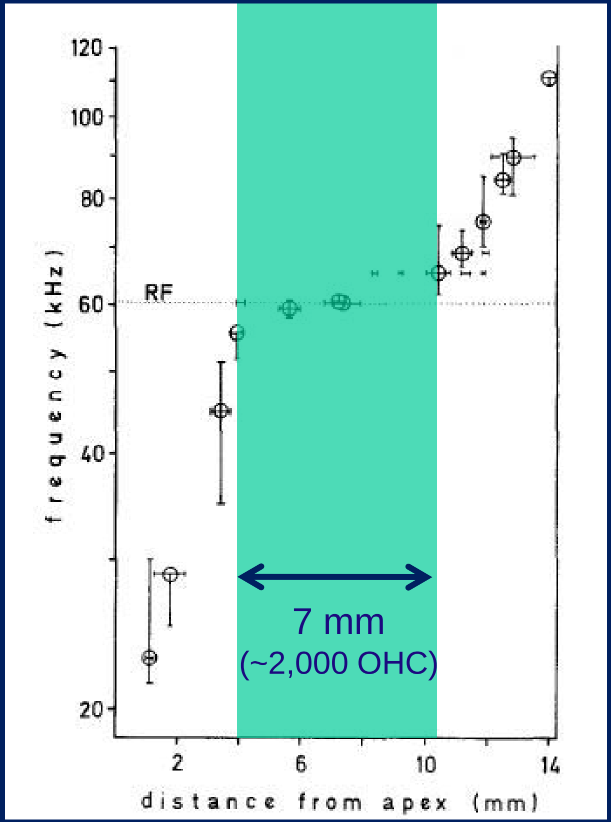




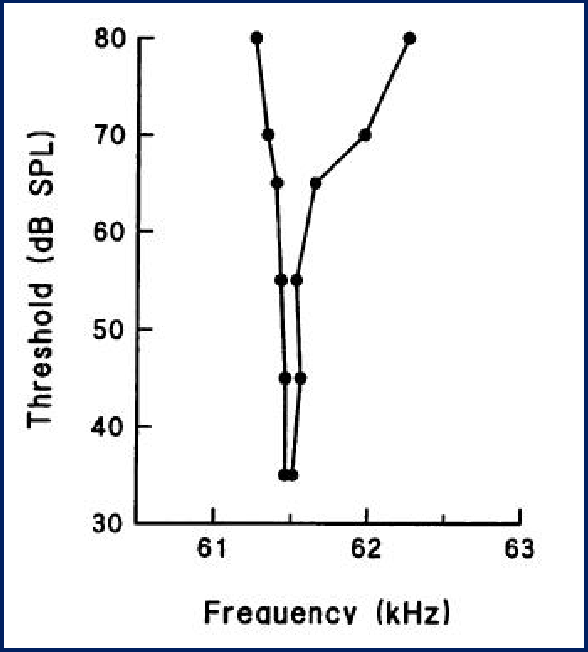
(Dierkes et al., PNAS (2008))

Tuning in the cochlea of the mustache bat *(Pteronotus)*

Tonotopic map



Iso-response tuning curve



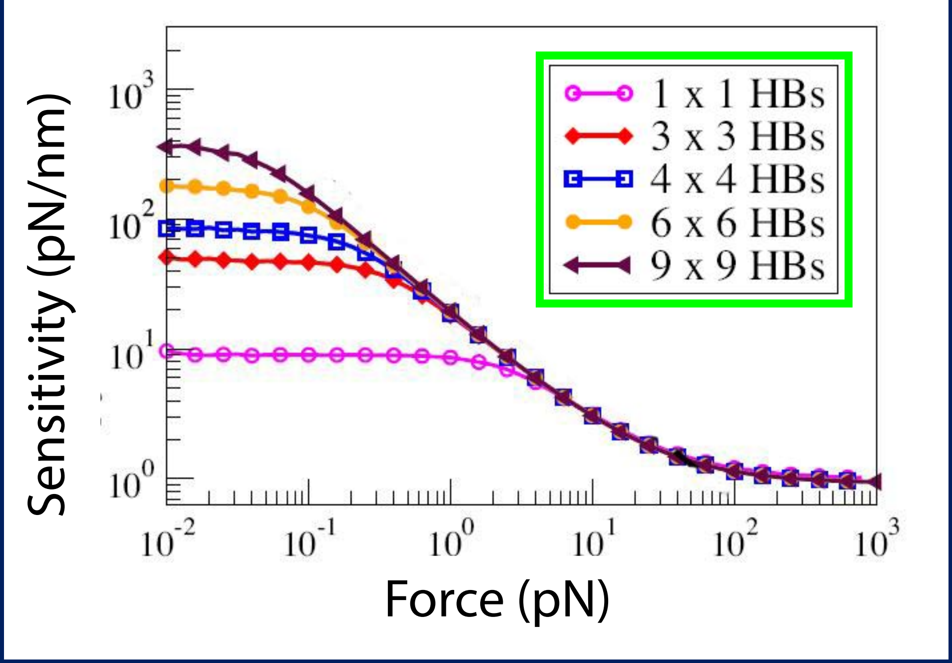
Q > 1000!

(Kössl and Russel, PNAS (1995))

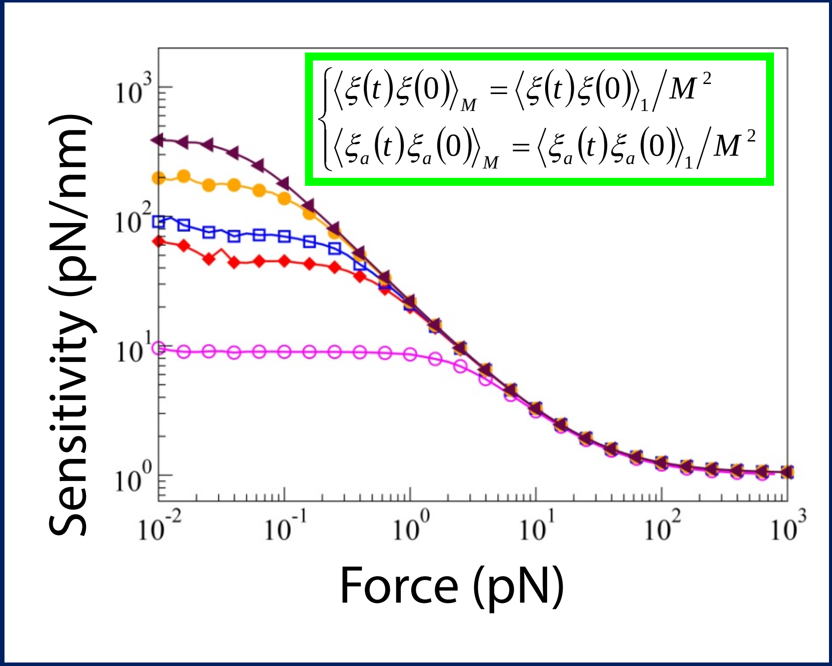
Coupling ⟶ noise reduction

(simulations)

M × M cyber bundles



1 cyber bundle - reduced noise



(Dierkes et al., PNAS (2008))

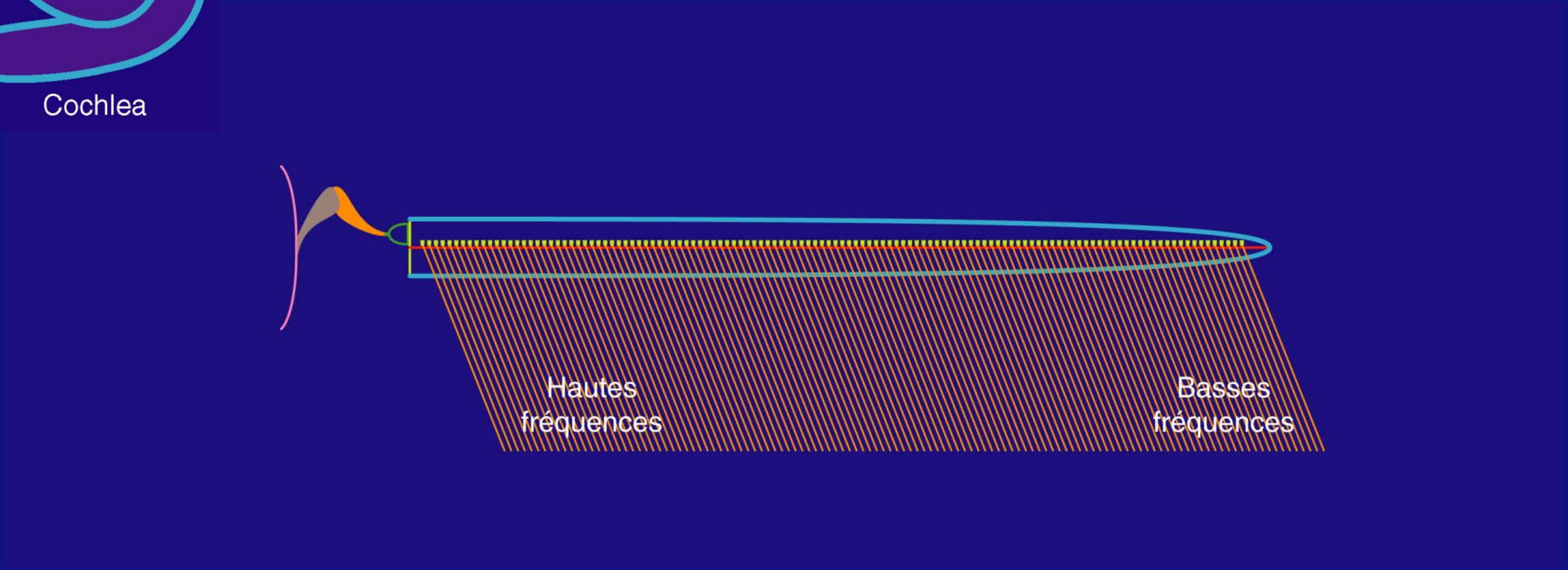
Self-sustained oscillators:

nonlinear amplifiers for hearing

1. Amplified movements for small stimuli
2. Extended dynamic range of responsiveness
3. Increased frequency selectivity
4. « Essential » compressive nonlinearity: prominent cubic distortions within the active bandwidth.
5. Channel friction / noise limits amplification by a single cell
6. Coupling between cells reduces noise and enhances amplification

Outlook:

tonotopic organisation of critical oscillator modules



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