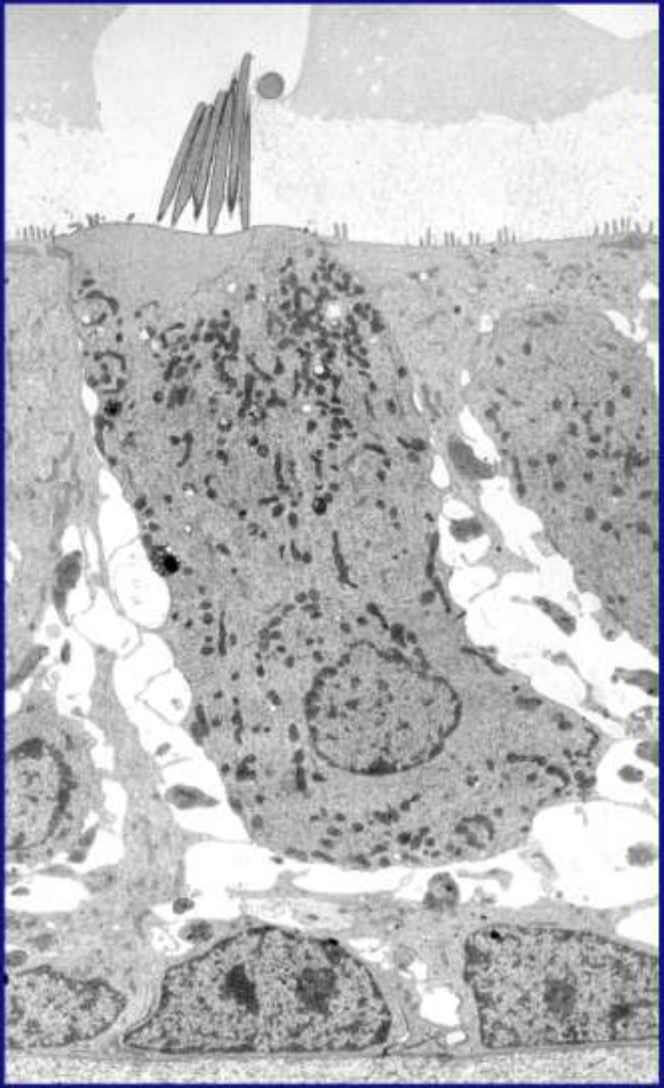
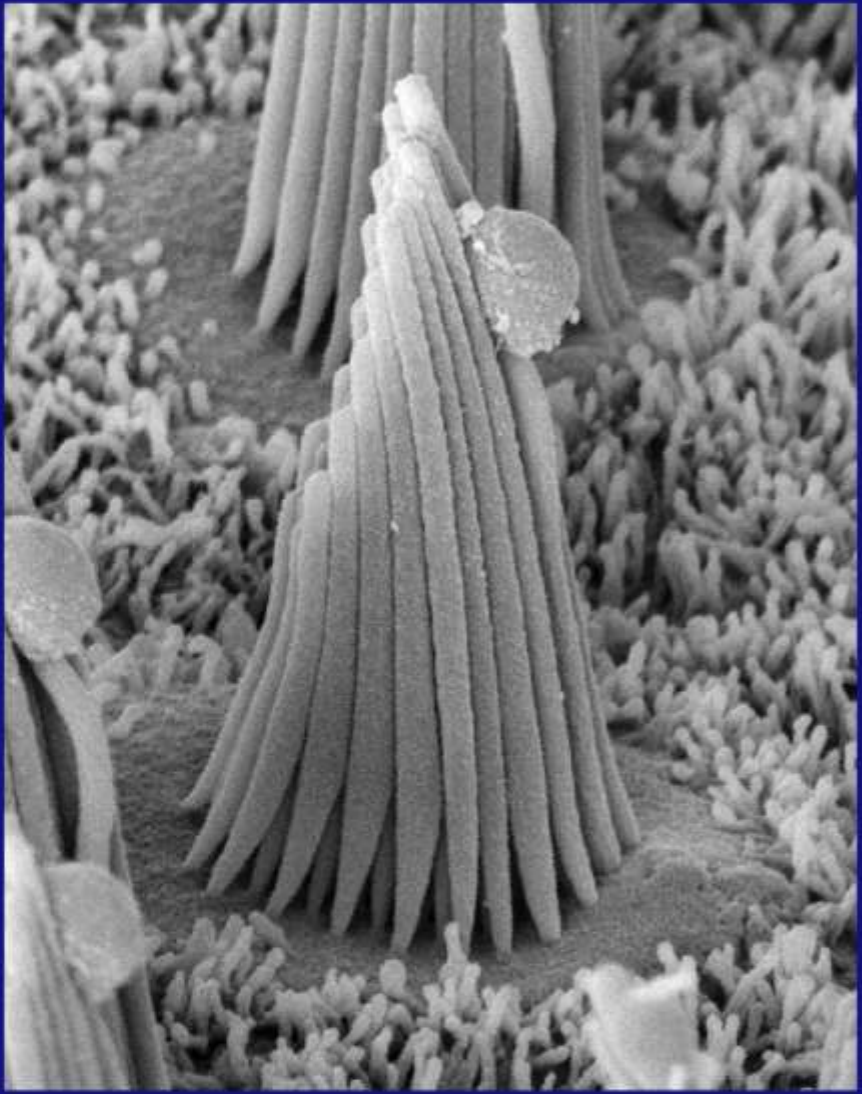
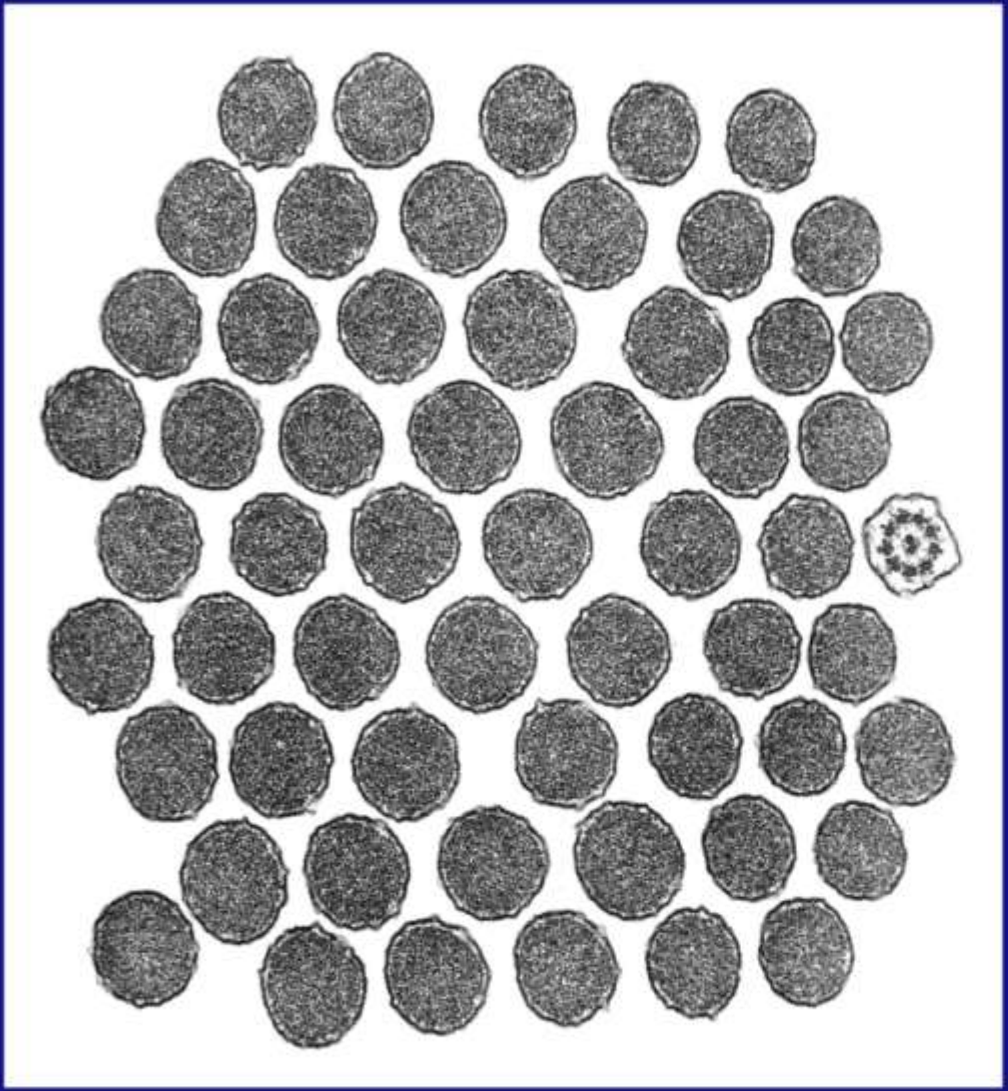
SENSORY TRANSDUCTION

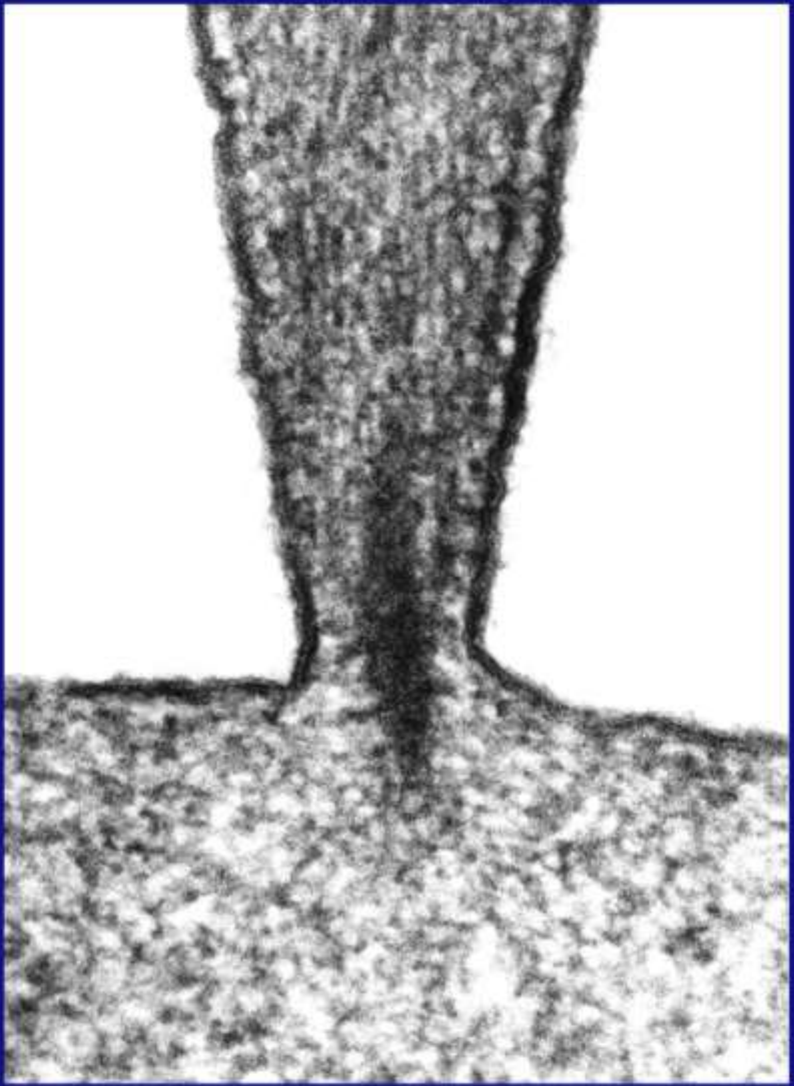
Principal pathway

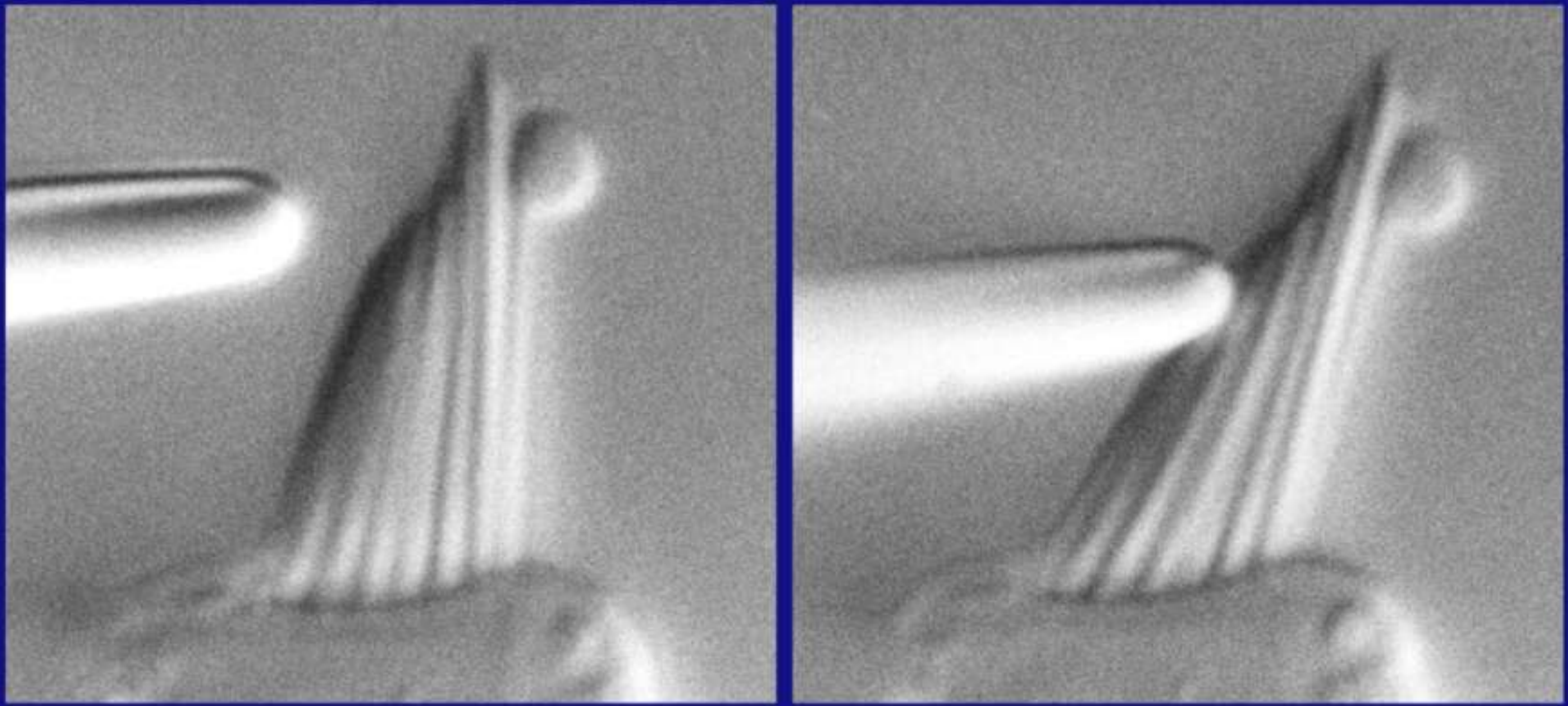
Input → Energy capture → Transduction → Amplification → Encoding → Output

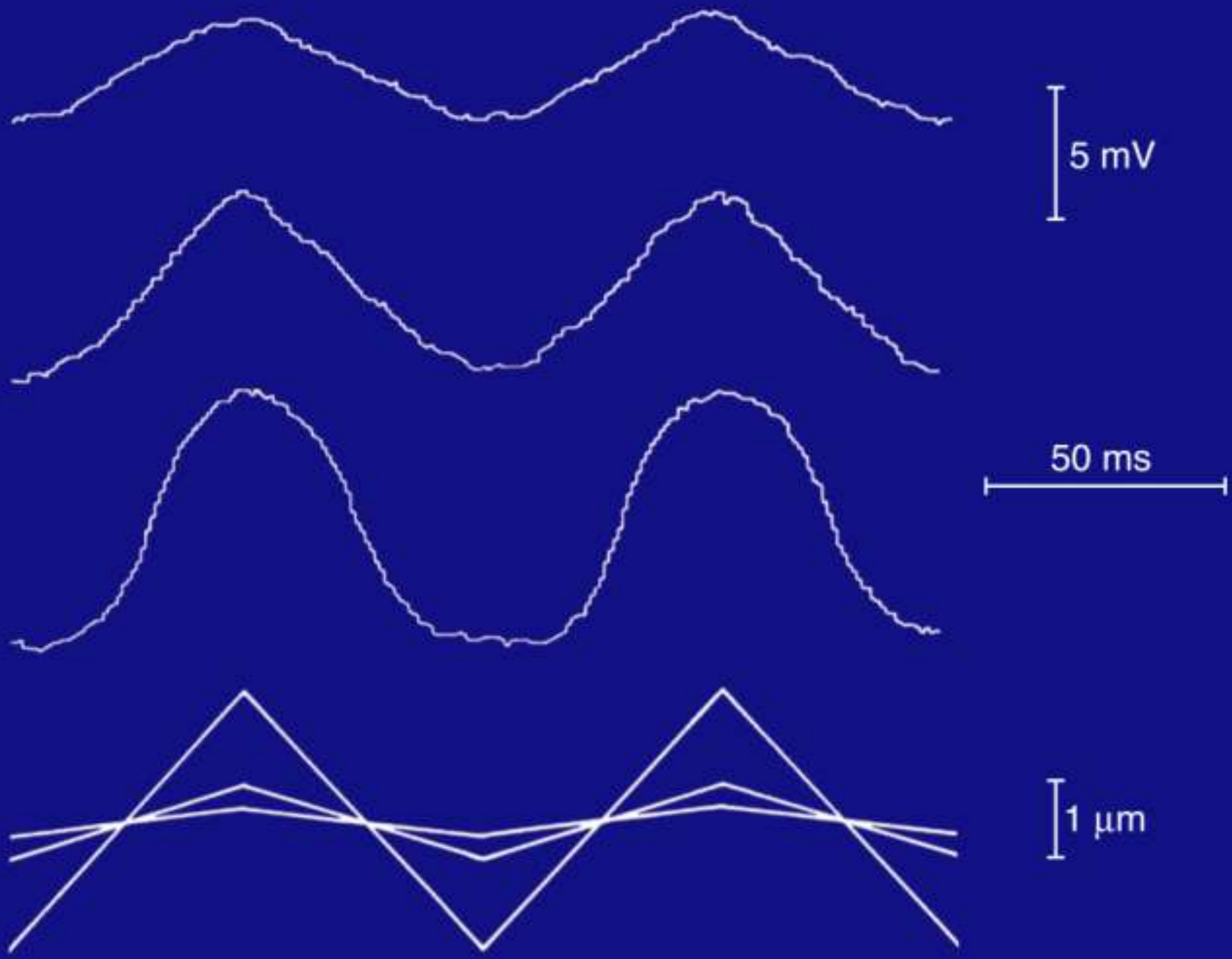


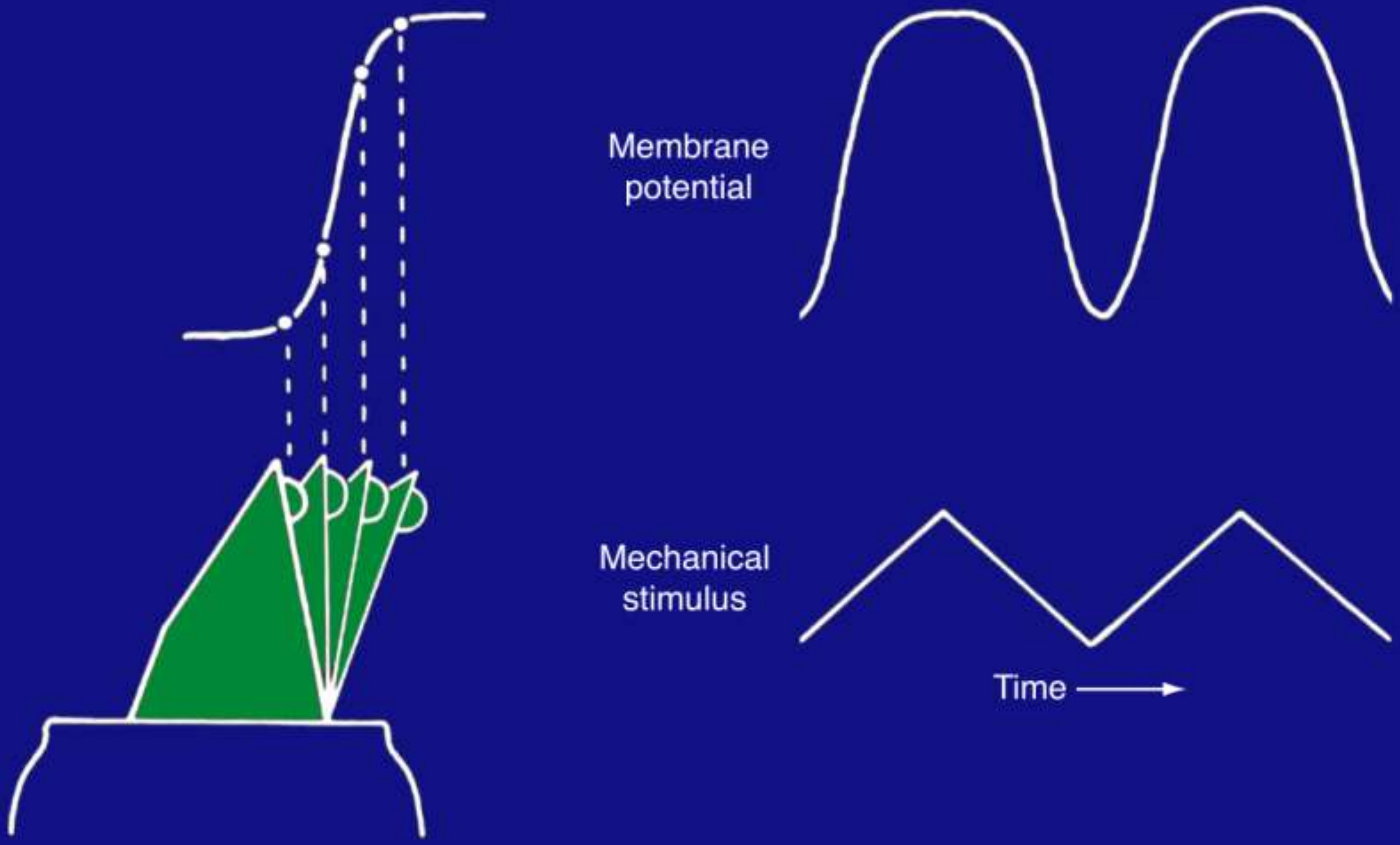




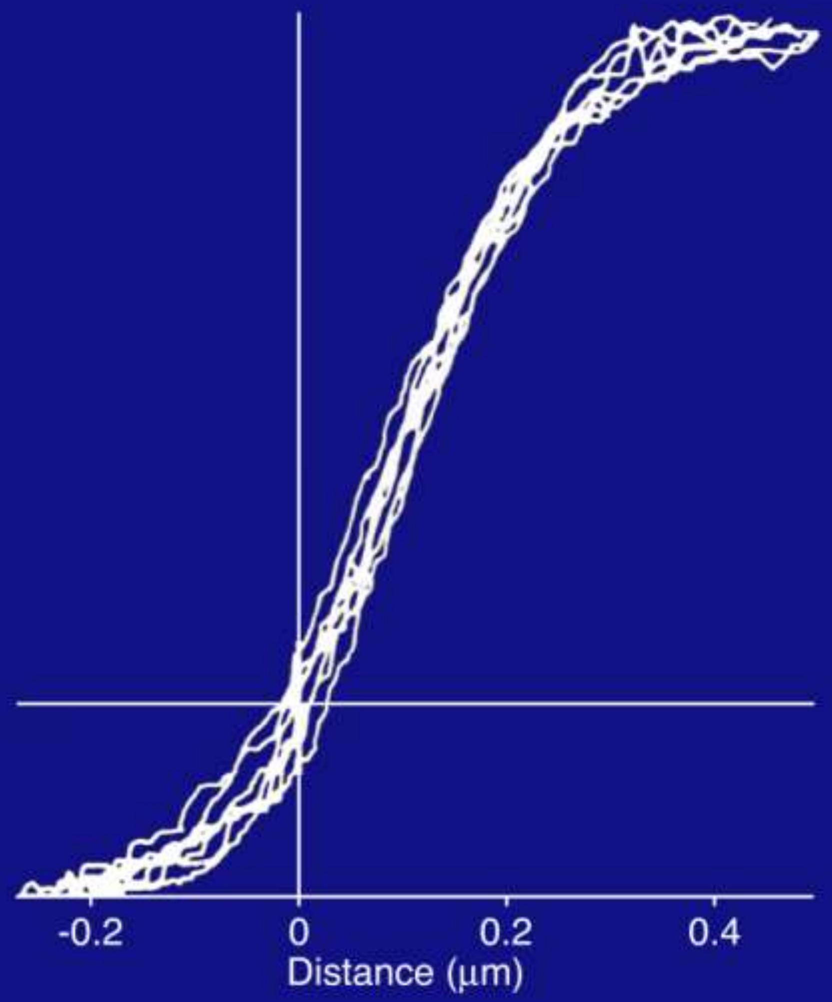


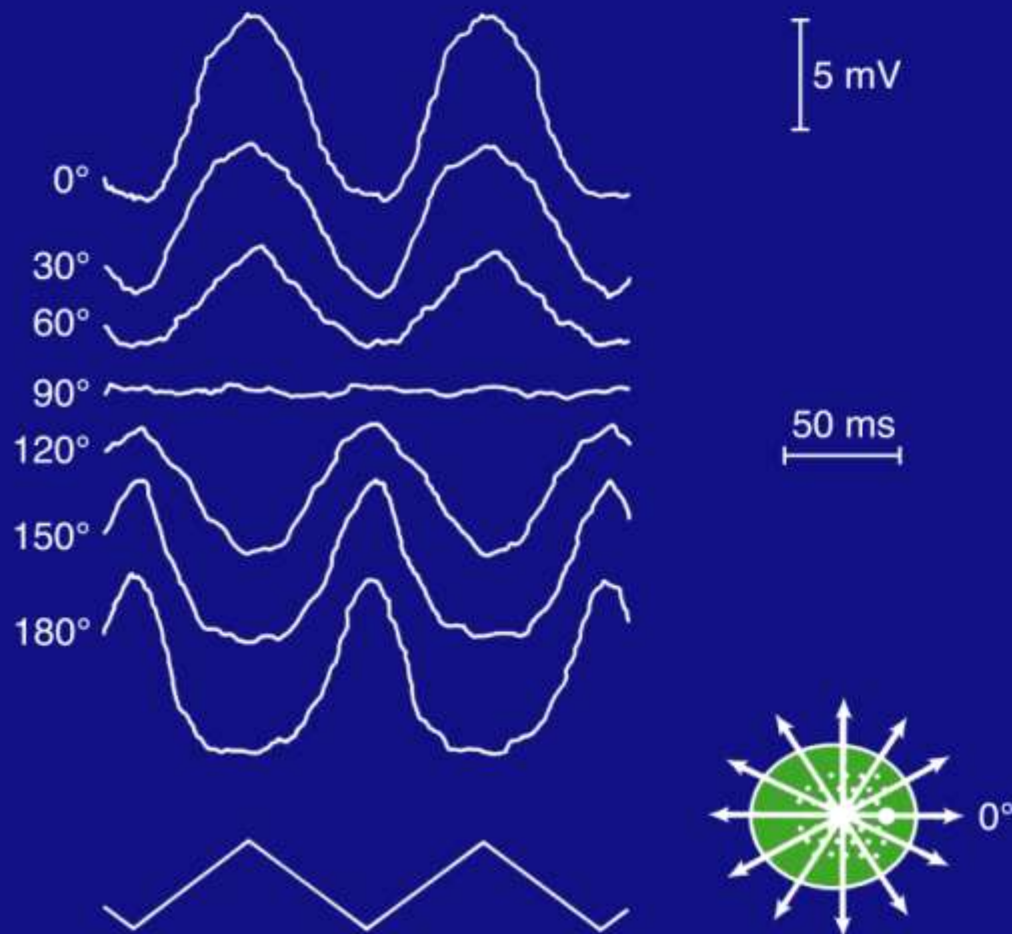


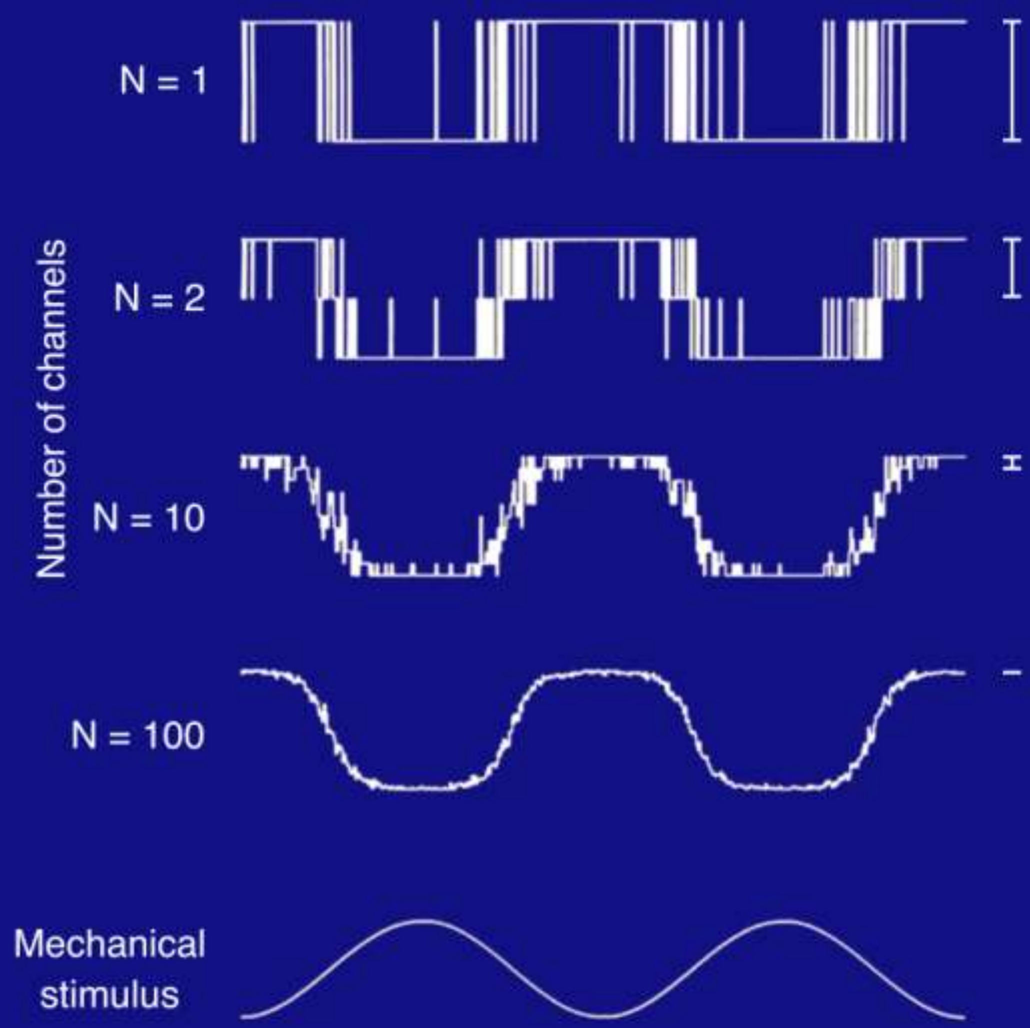

5 mV
50 ms
1 µm



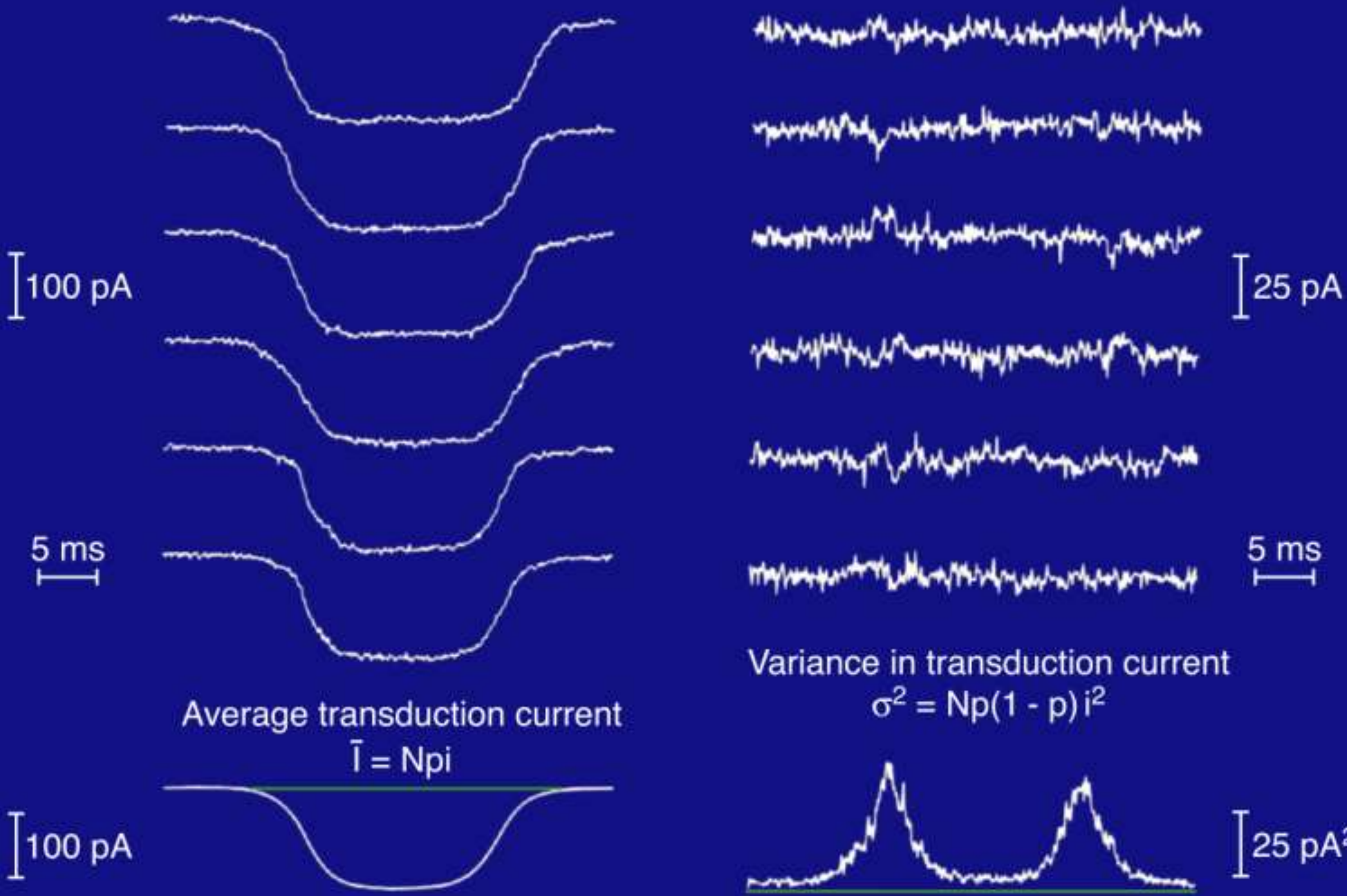
Membrane
potential
Mechanical
stimulus
Time

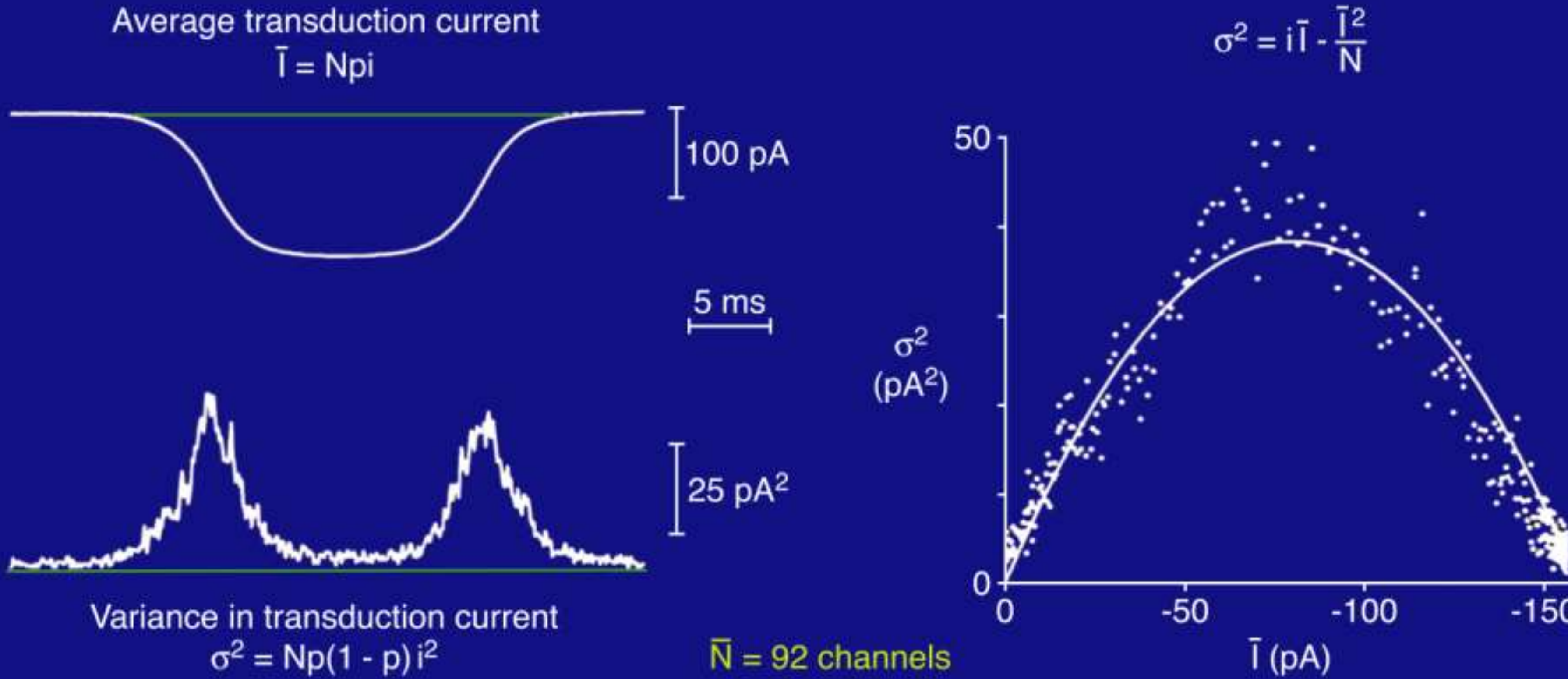

-0.2
0
0.2
0.4
Distance (µm)


5 mV
0°
30°
60°
90°
120°
150°
180°
50 ms
0°

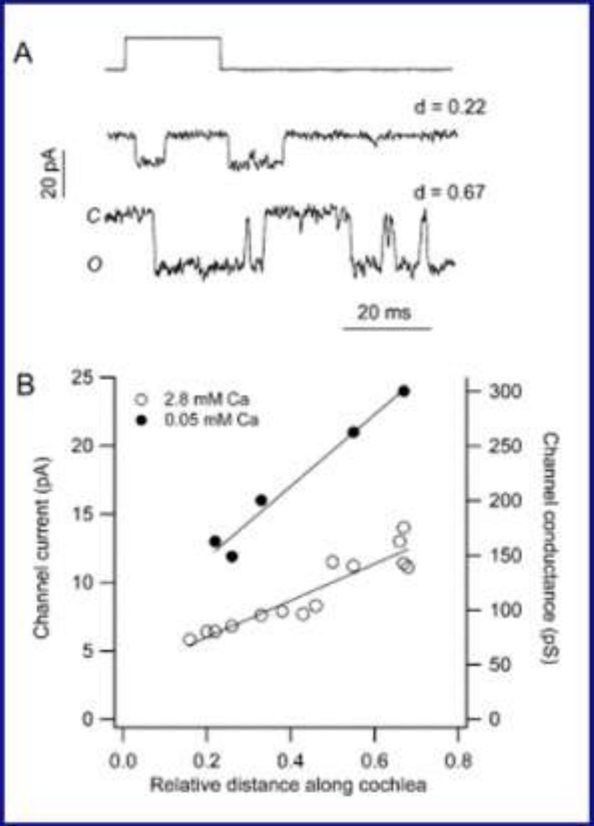


N = 1
N = 2
N = 10
N = 100
Number of channels
Mechanical stimulus


100 pA
5 ms
Average transduction current
Ī = Npi
100 pA
25 pA
5 ms
Variance in transduction current
σ² = Np(1 - p) i²
25 pA²

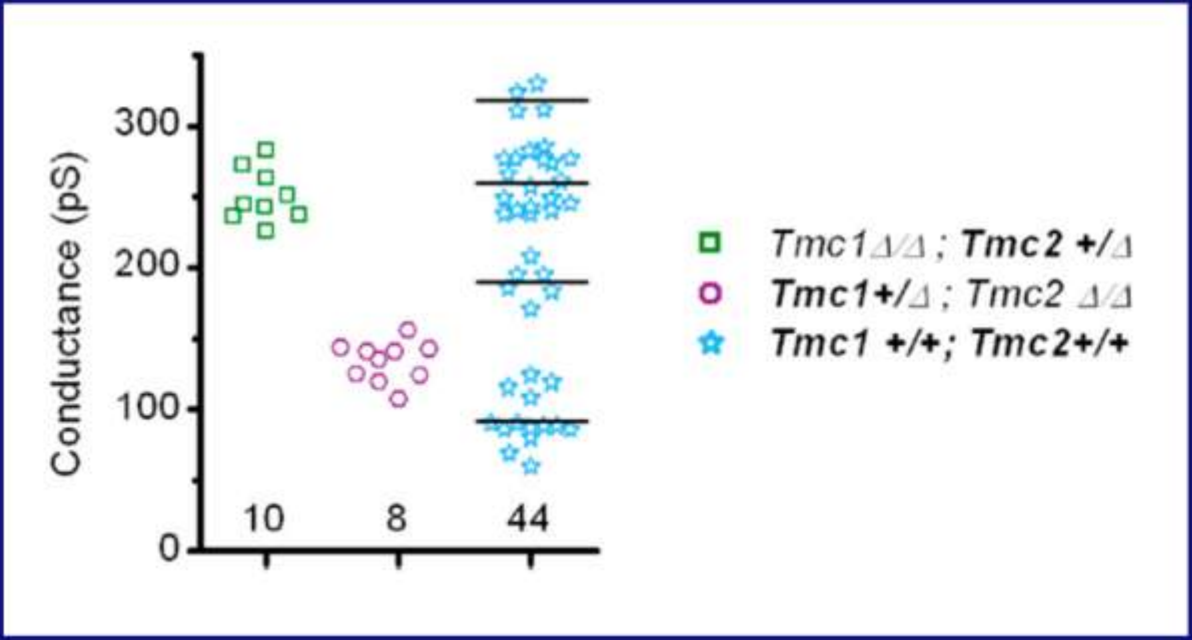

Average transduction current
$\bar{I} = Npi$
100 pA
5 ms
25 pA^2
Variance in transduction current
$\sigma^2 = Np(1 - p)\, i^2$
$\bar{N}$ = 92 channels
$\sigma^2 = i\bar{I} - \frac{\bar{I}^2}{N}$
50
0
σ^2 (pA^2)
0
-50
-100
-150
$\bar{I}$ (pA)

TONOTOPIC VARIATION IN SINGLE – CHANNEL CONDUCTANCE OF MECHANOELECTRICAL – TRANSDUCTION CHANNELS



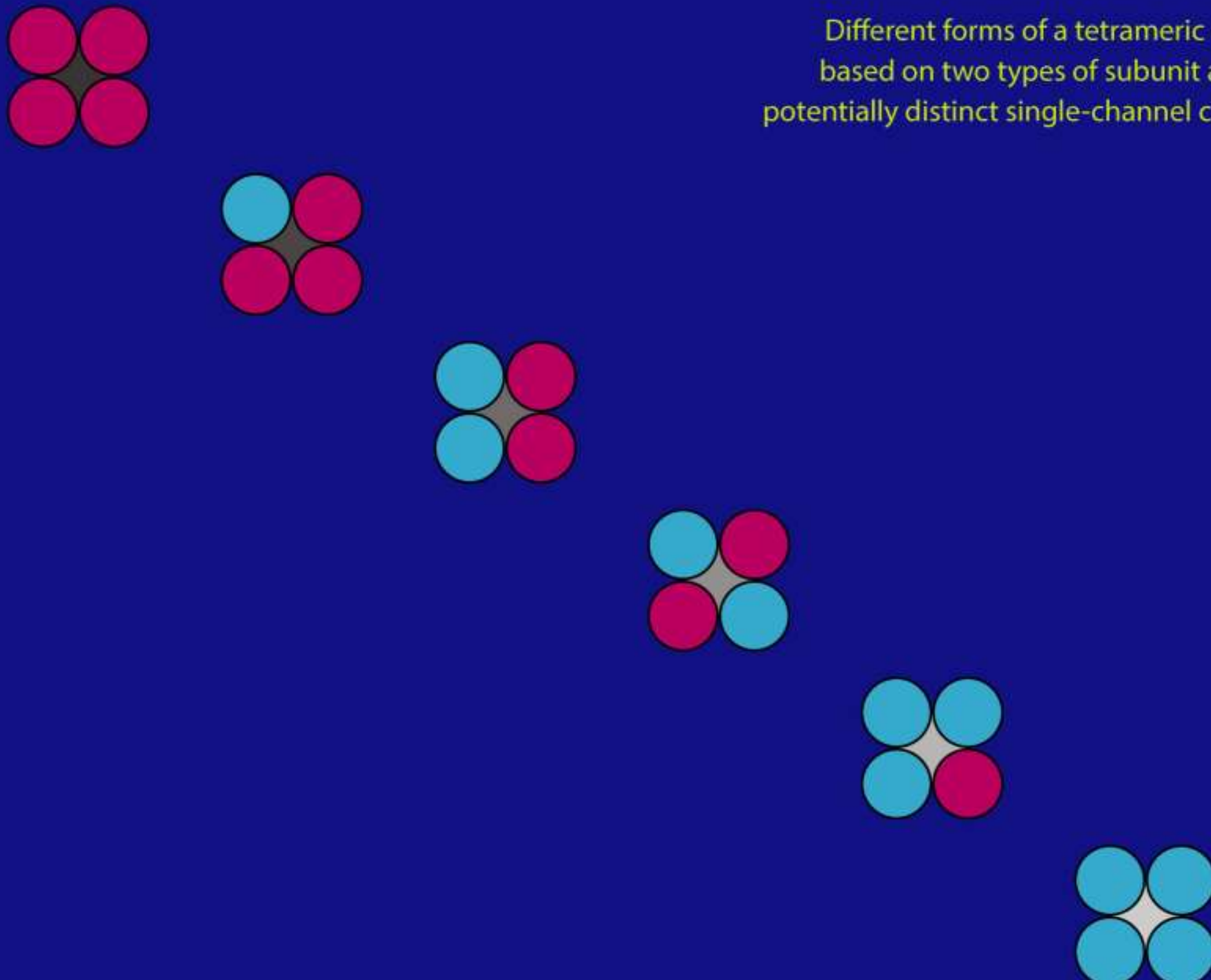
After Ricci *et al.*, 2003

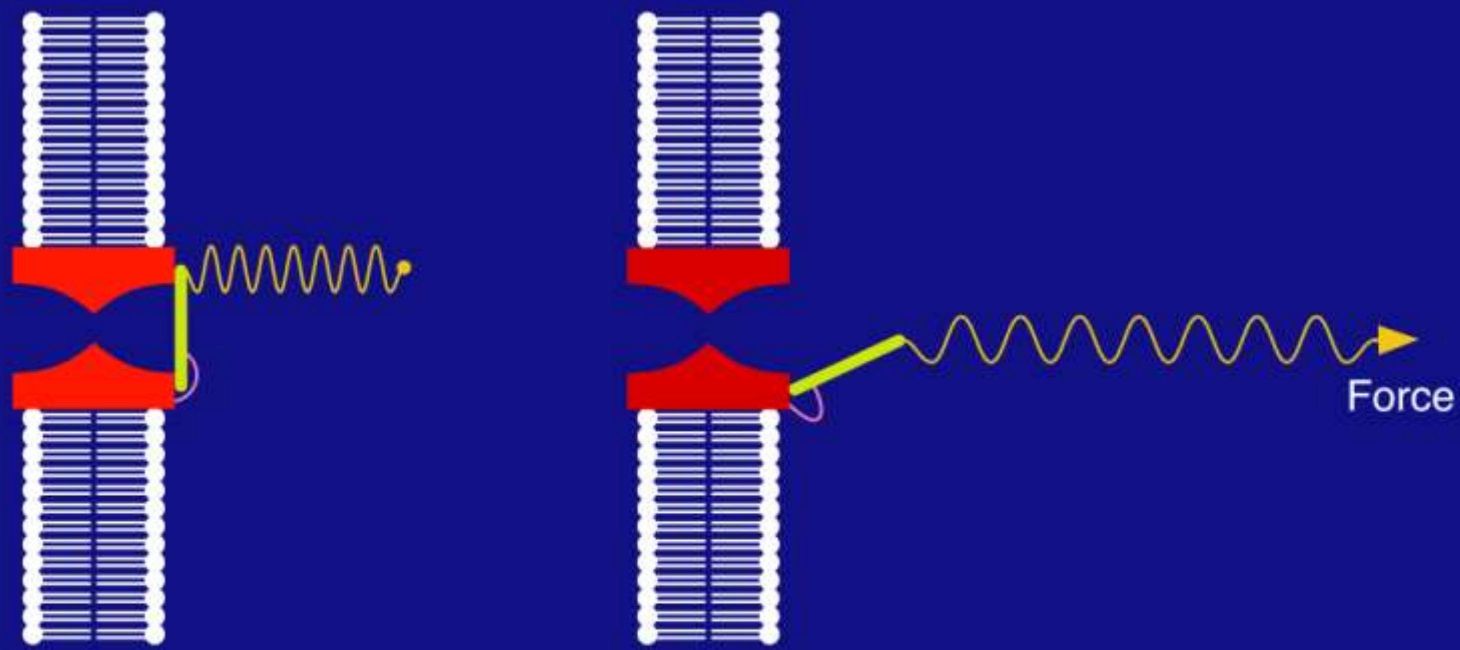
Range of single-channel conductances
in immature mutant and wild-type murine inner hair cells

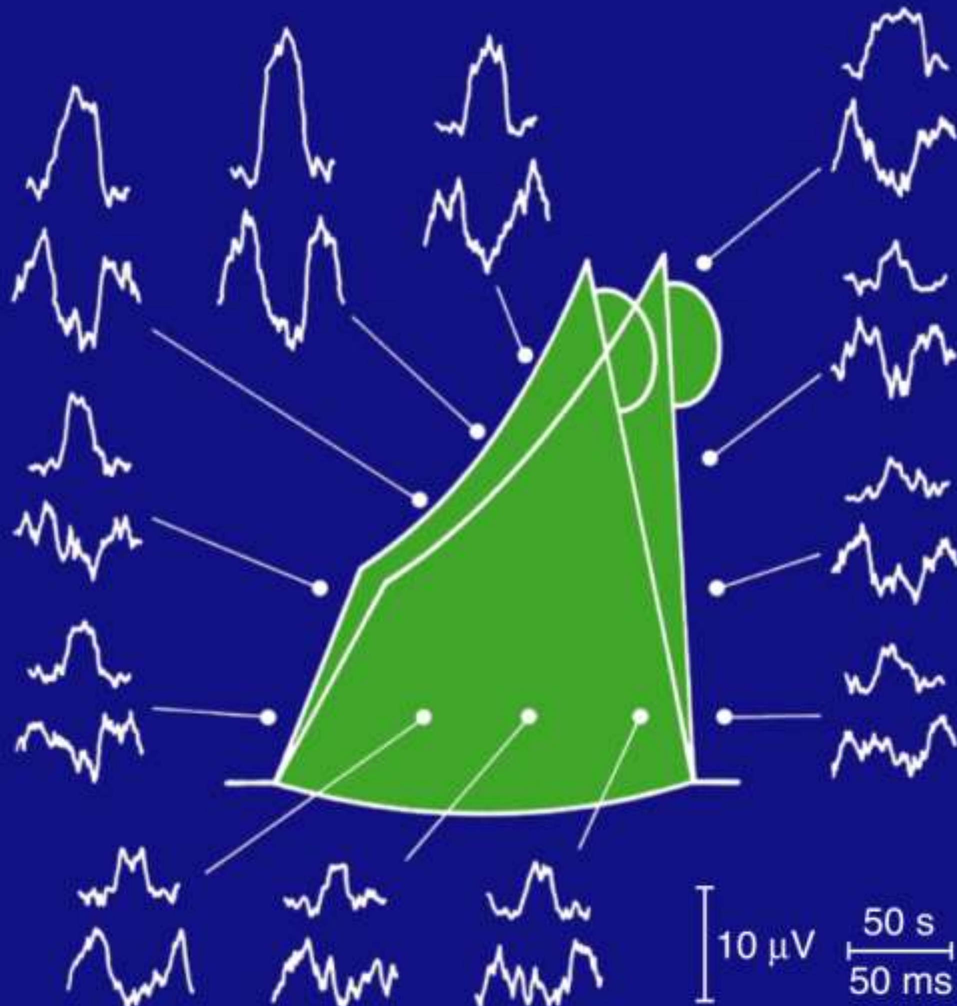


After Pan *et al*., 2013

Different forms of a tetrameric channel
based on two types of subunit and with
potentially distinct single-channel conductances

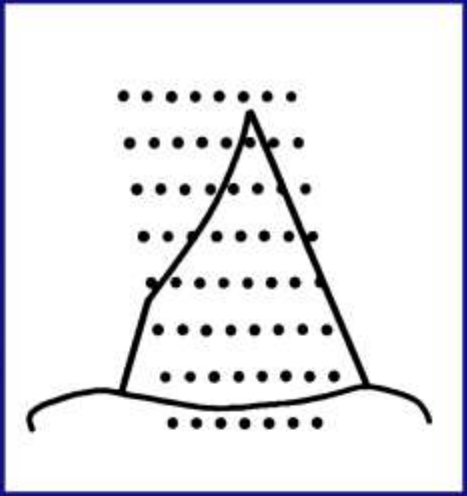



Force

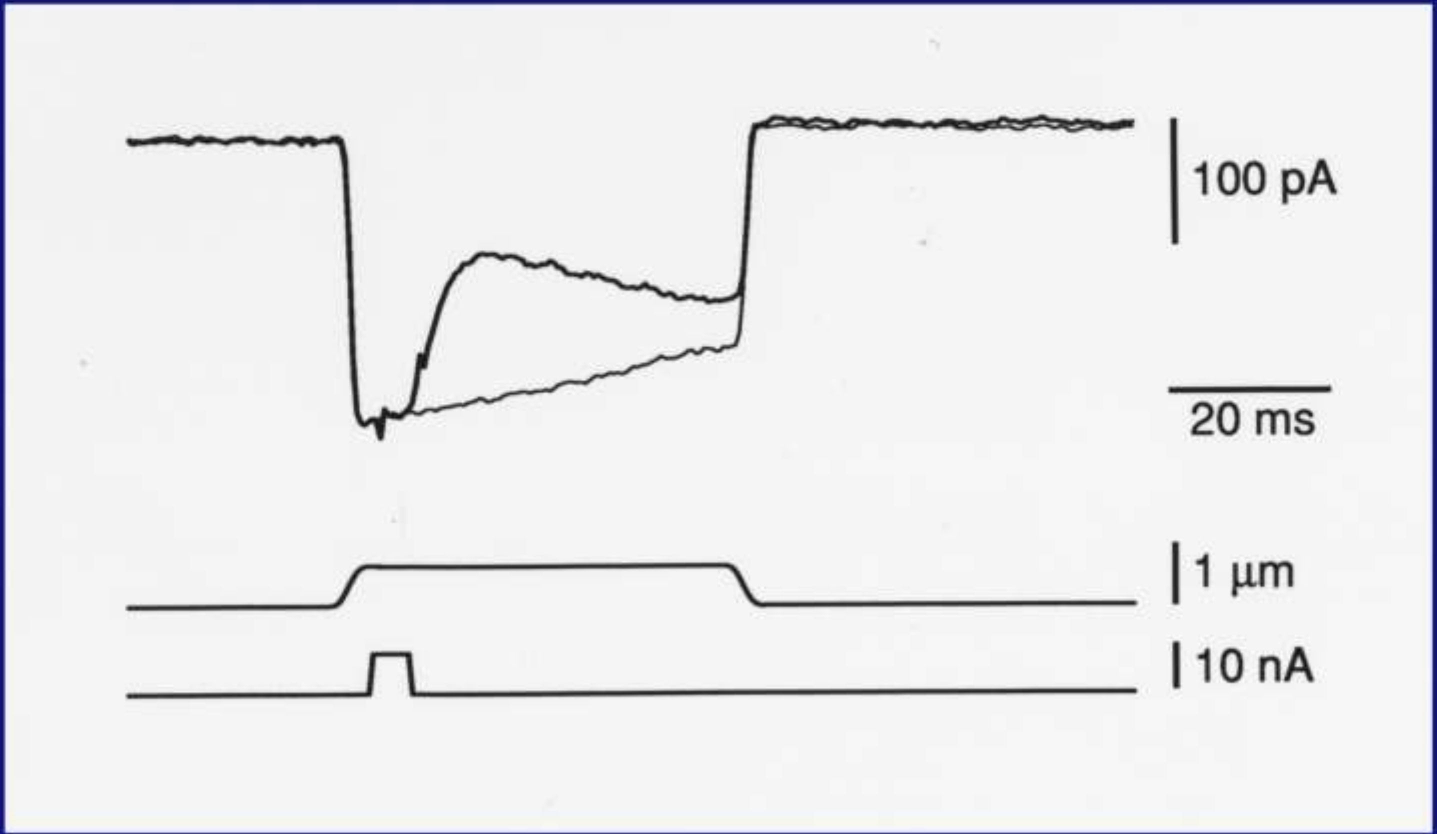

10 µV
50 s
50 ms

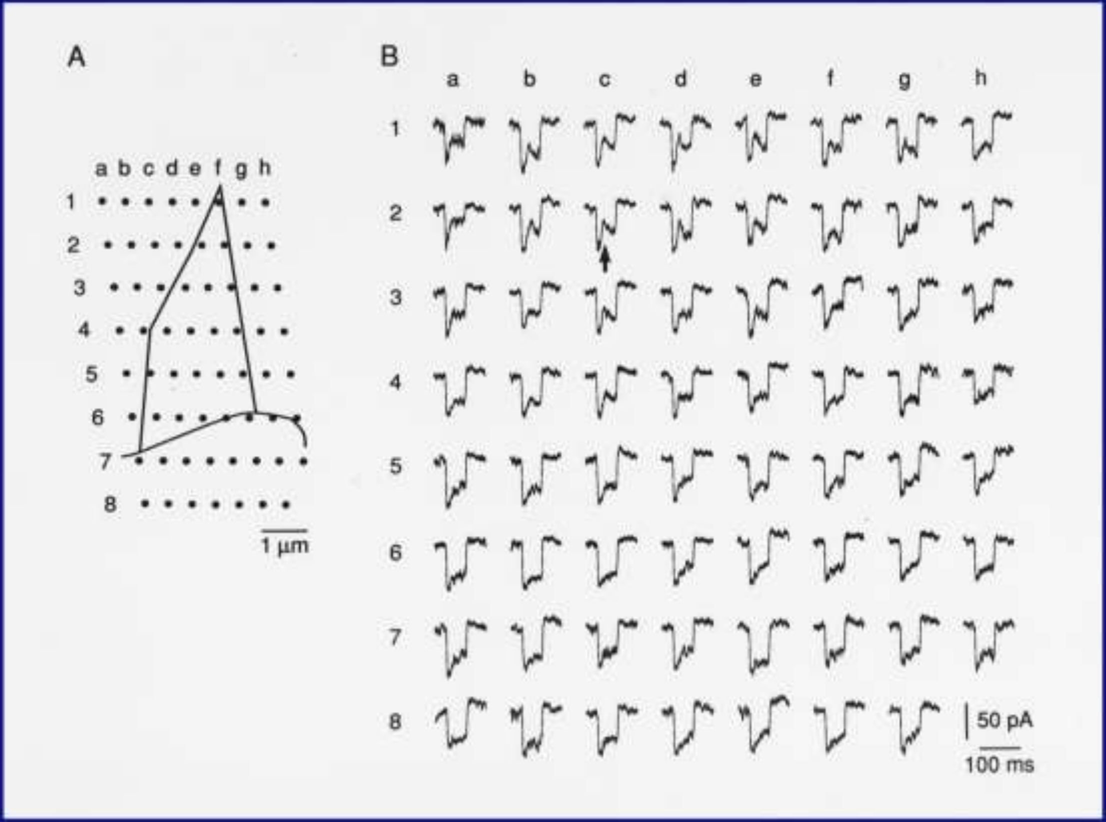
Hair bundle and
stimulus probe

Iontophoretic
pipette

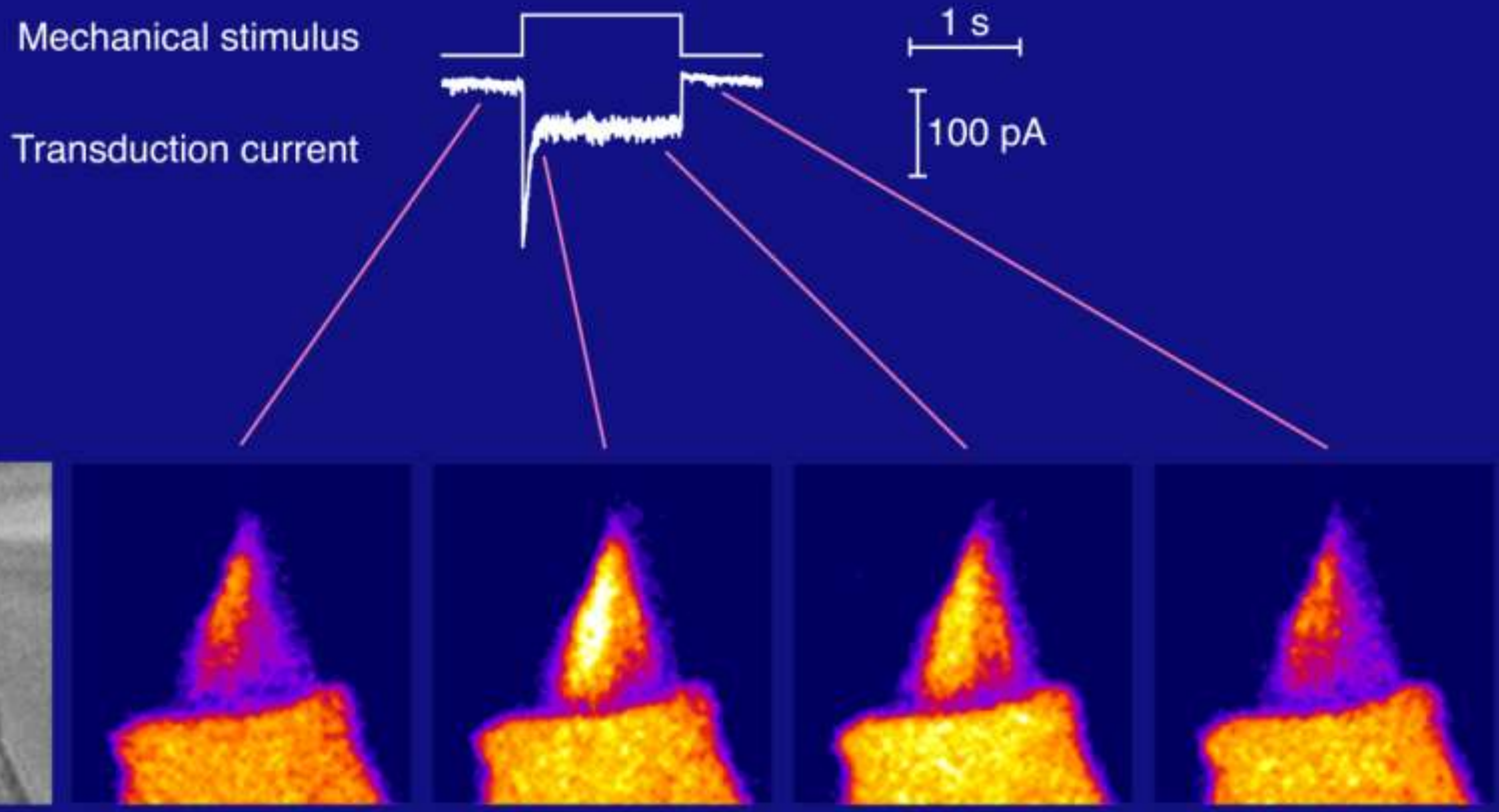


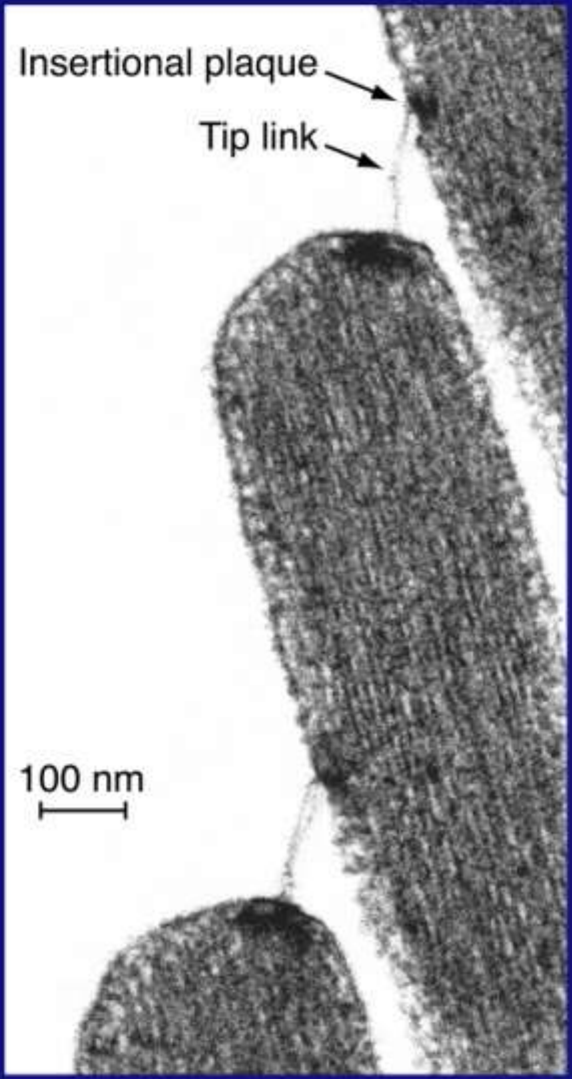
63 sites of
iontophoresis


100 pA
20 ms
1 µm
10 nA

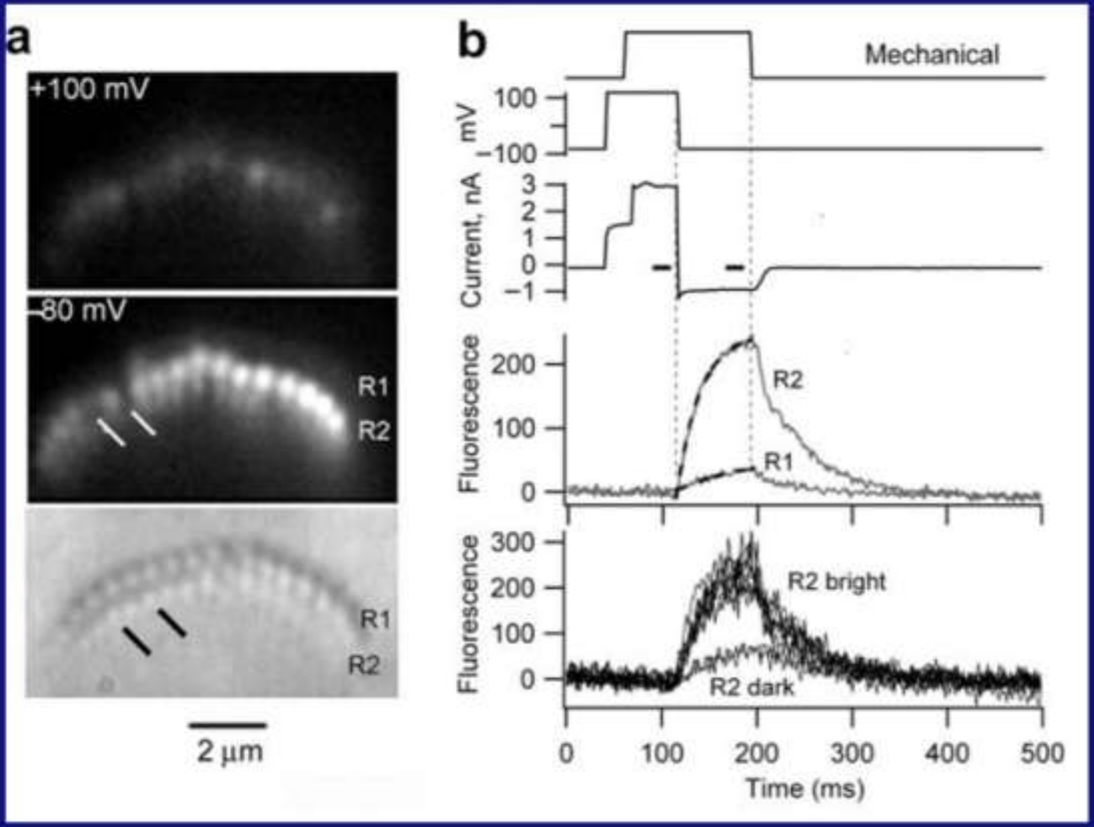


A
B
a b c d e f g h
1 2 3 4 5 6 7 8
1 µm
50 pA
100 ms

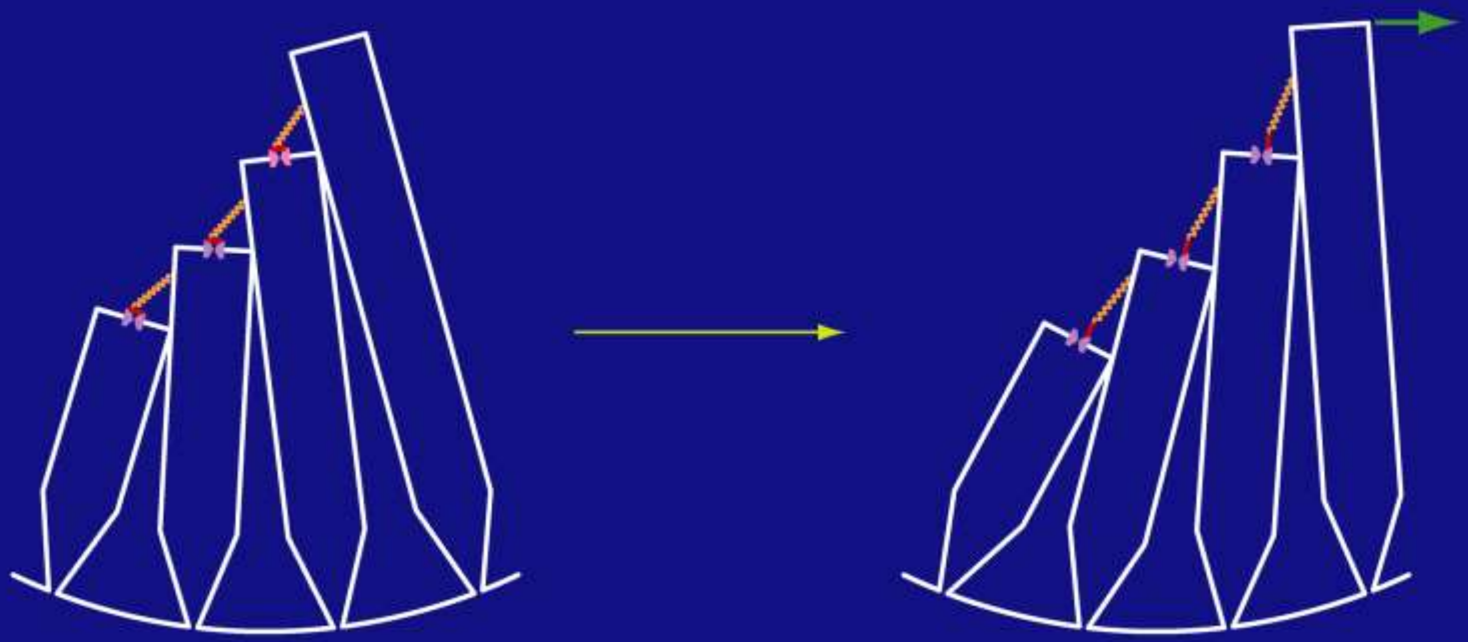

Mechanical stimulus
Transduction current
1 s
100 pA

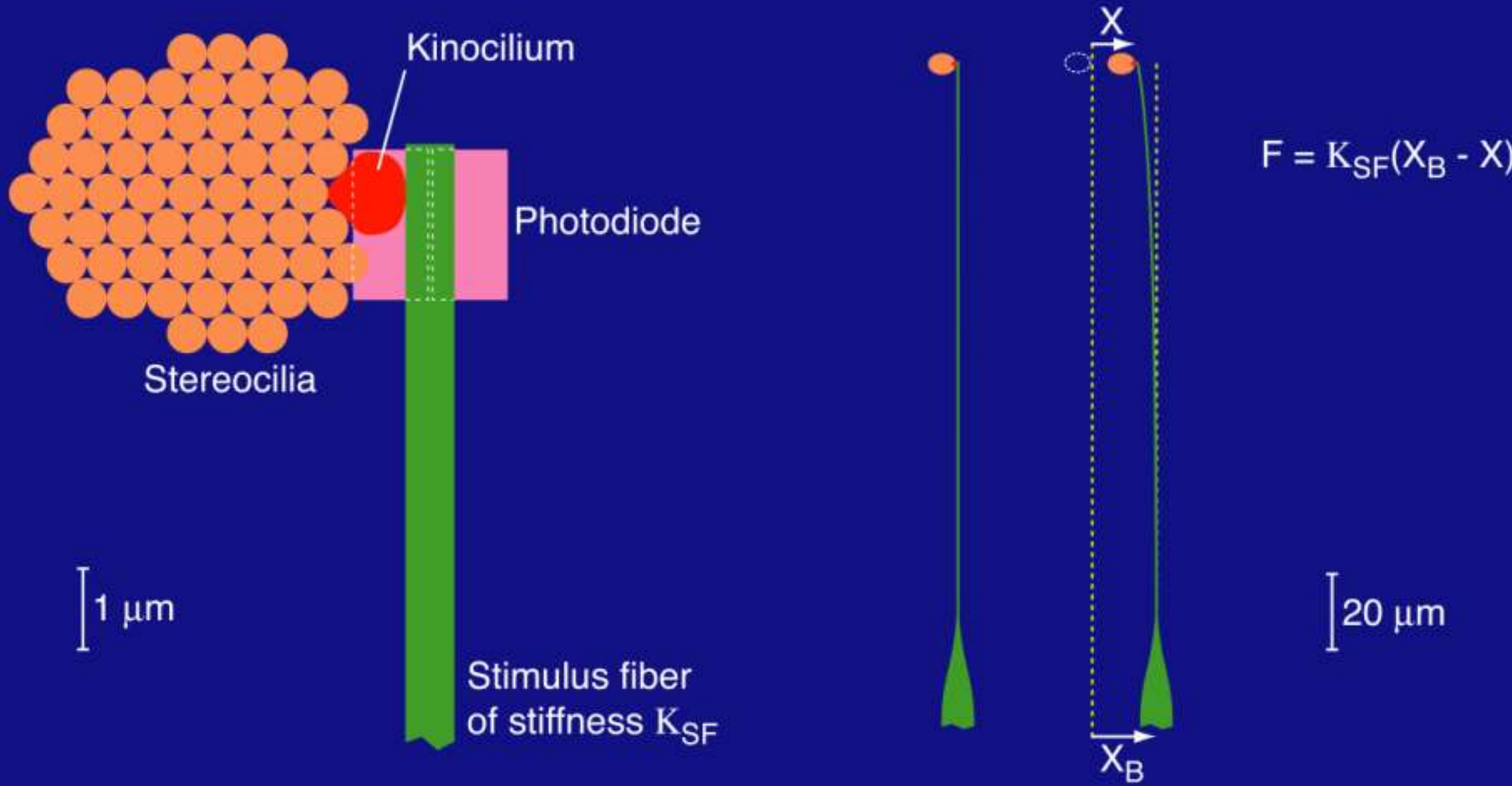

Insertional plaque
Tip link
100 nm

Transduction-channel localization in rat inner hair cells with Fluo-4FF

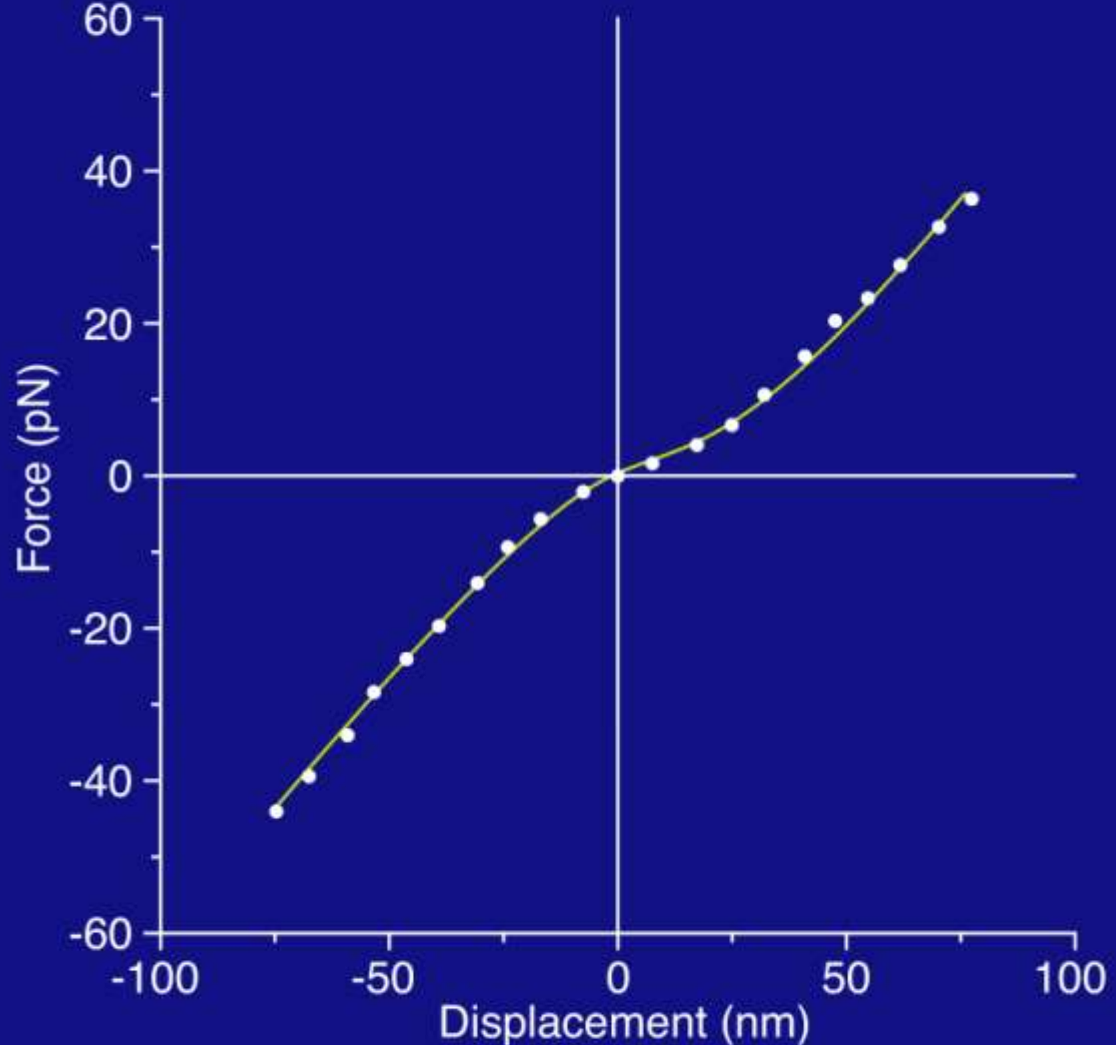


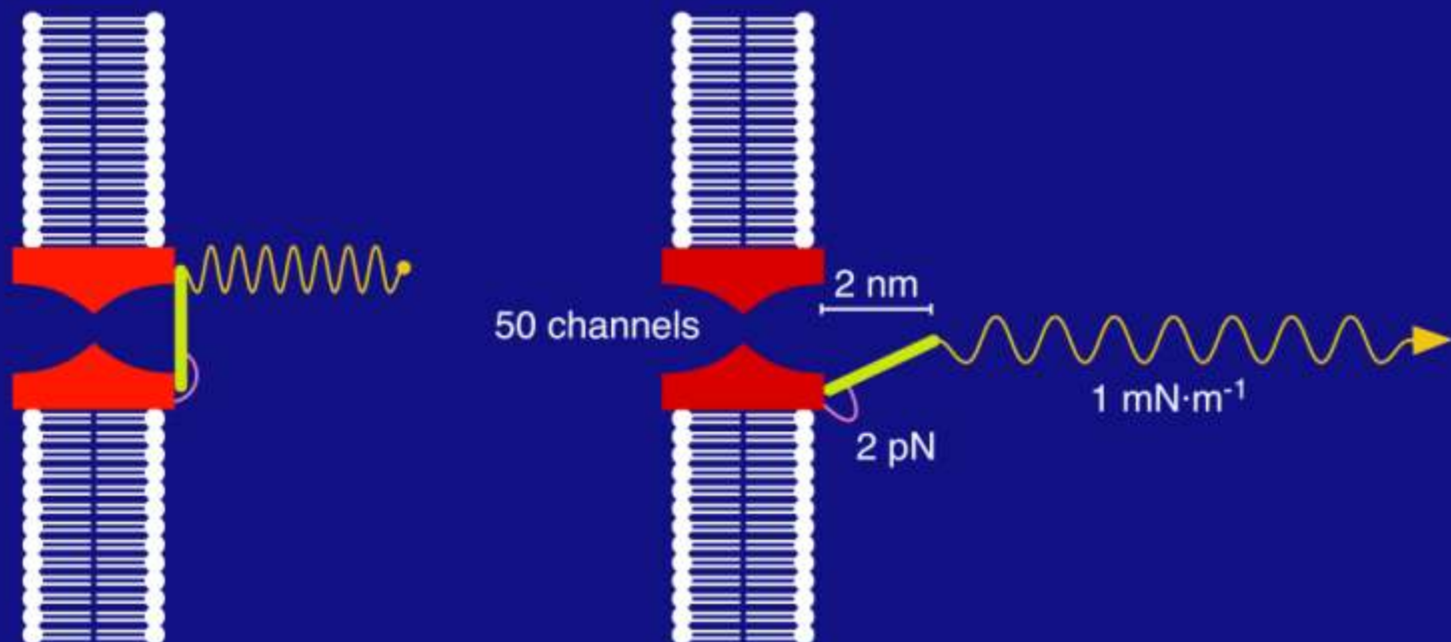
After Beurg *et al*., 2009





Kinocilium
Photodiode
Stereocilia
1 μm
Stimulus fiber
of stiffness K_{SF}
X
$F = K_{SF}(X_B - X)$
20 μm
X_B


60
40
20
0
-20
-40
-60
Force (pN)
-100
-50
0
50
100
Displacement (nm)



50 channels
2 nm
1 mN·m-1
2 pN

Giuseppe Tartini (1714)

phantom tones, distortion products, difference tones, combination tones

De'Principj dell'Armonia Musicale (Padua, 1767)

Actual stimulus:

higher frequency	f_2
lower frequency	f_1

Perceived sound:

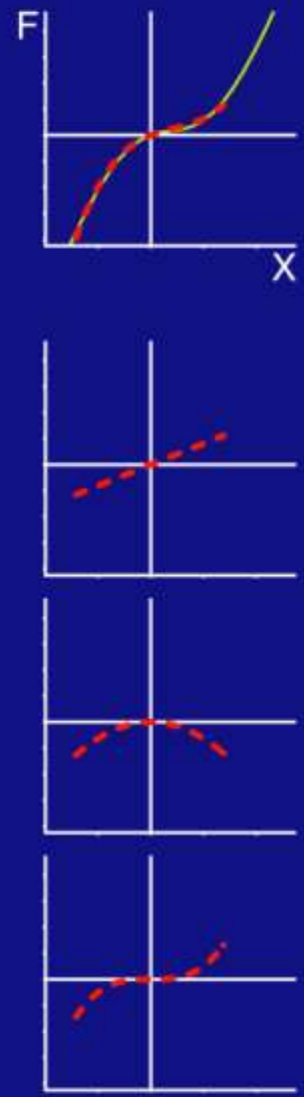
original frequencies	f_2, f_1
quadratic distortion products	$f_2 \pm f_1$
cubic distortion products	$2 \cdot f_2 \pm f_1,\ 2 \cdot f_1 \pm f_2$

Original relation
(polynomial fit)

Linear term
(A = 0.92)

Quadratic term
(B = 0.07)

Cubic term
(C = 0.01)



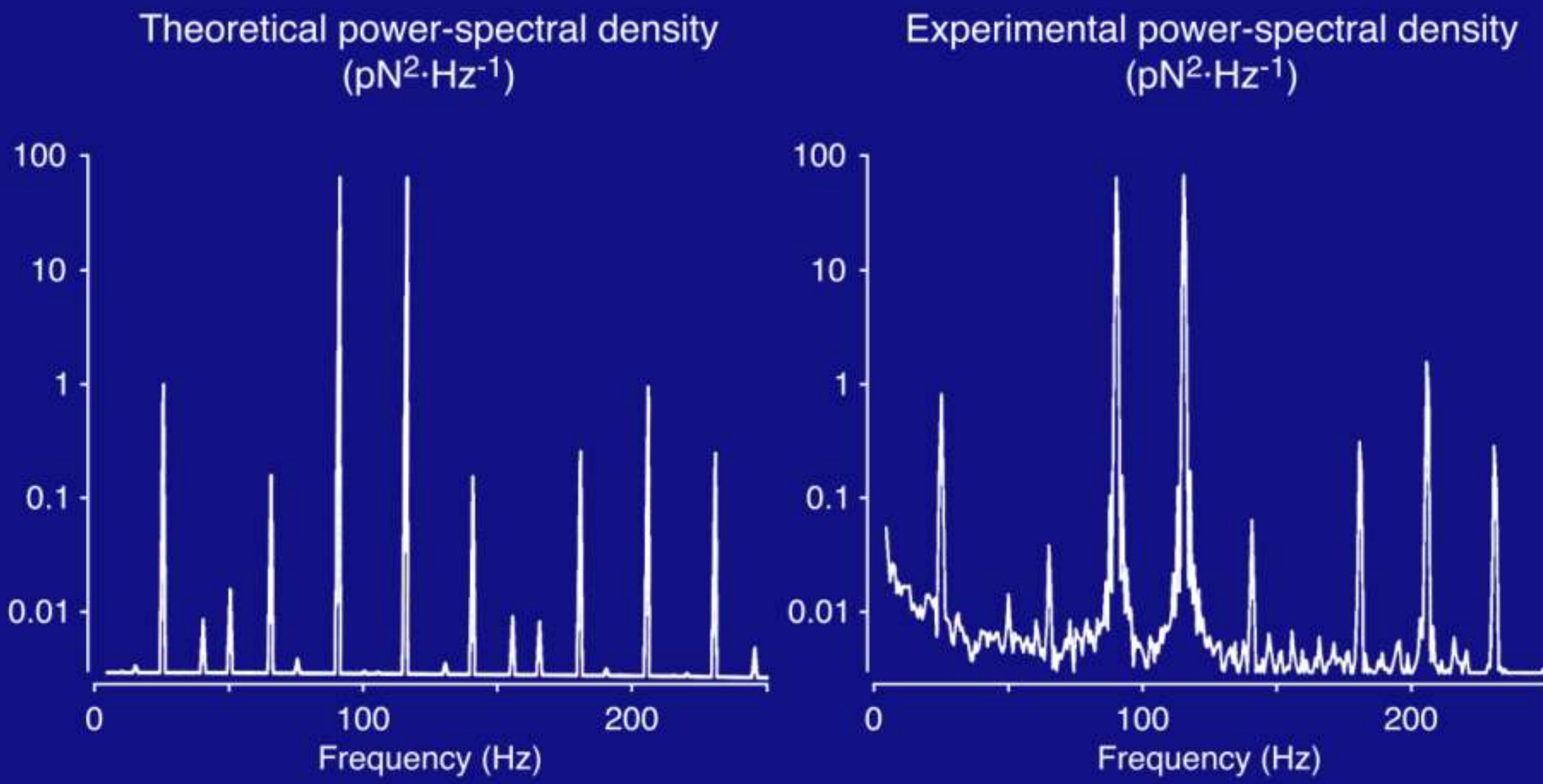
$$F = A\cdot X + B\cdot X^2 + C\cdot X^3 + \ldots$$
$$X = \sin(2\pi f_1 t) + \sin(2\pi f_2 t)$$

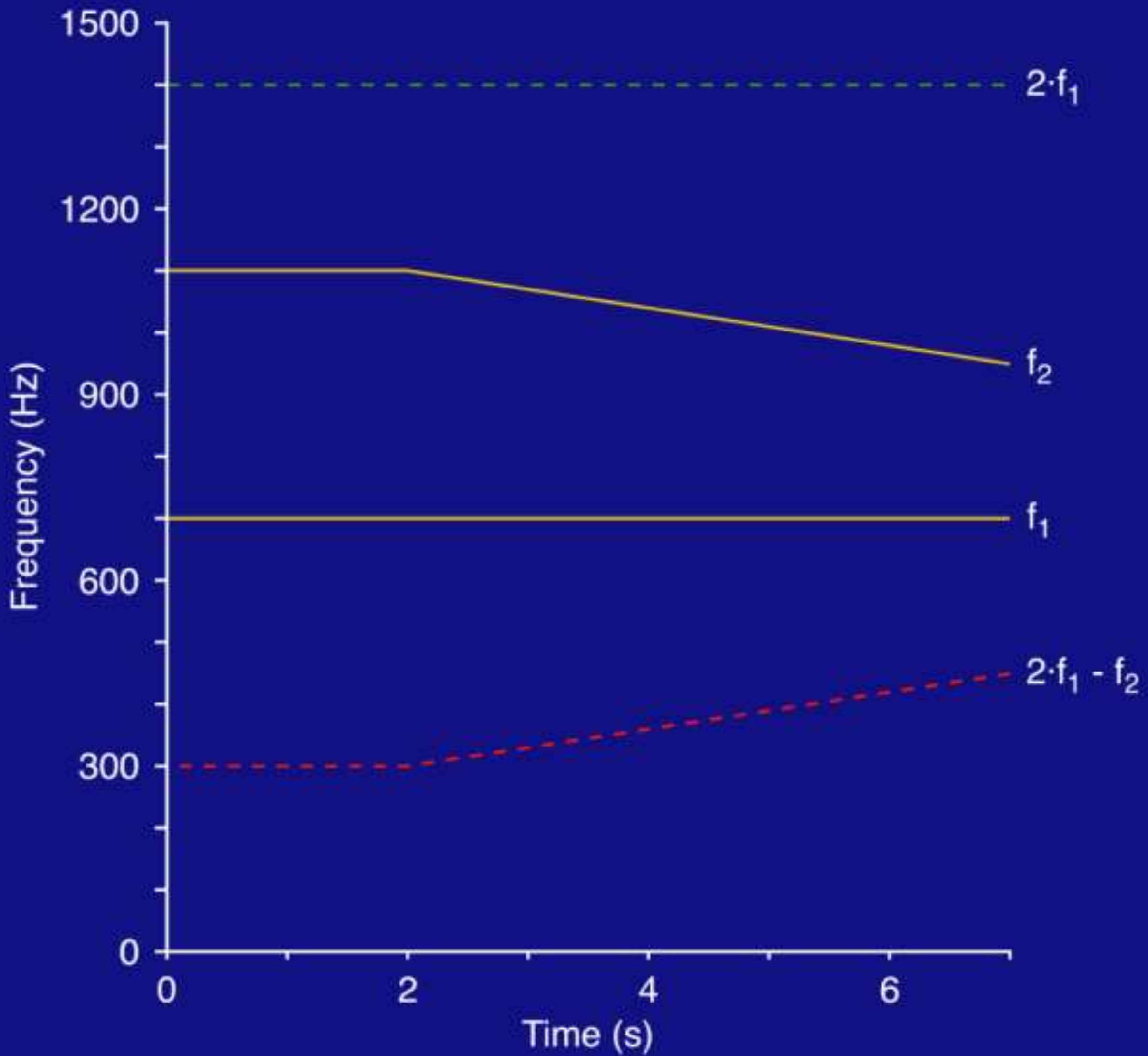
Frequencies produced:

Linear term → f_2, f_1

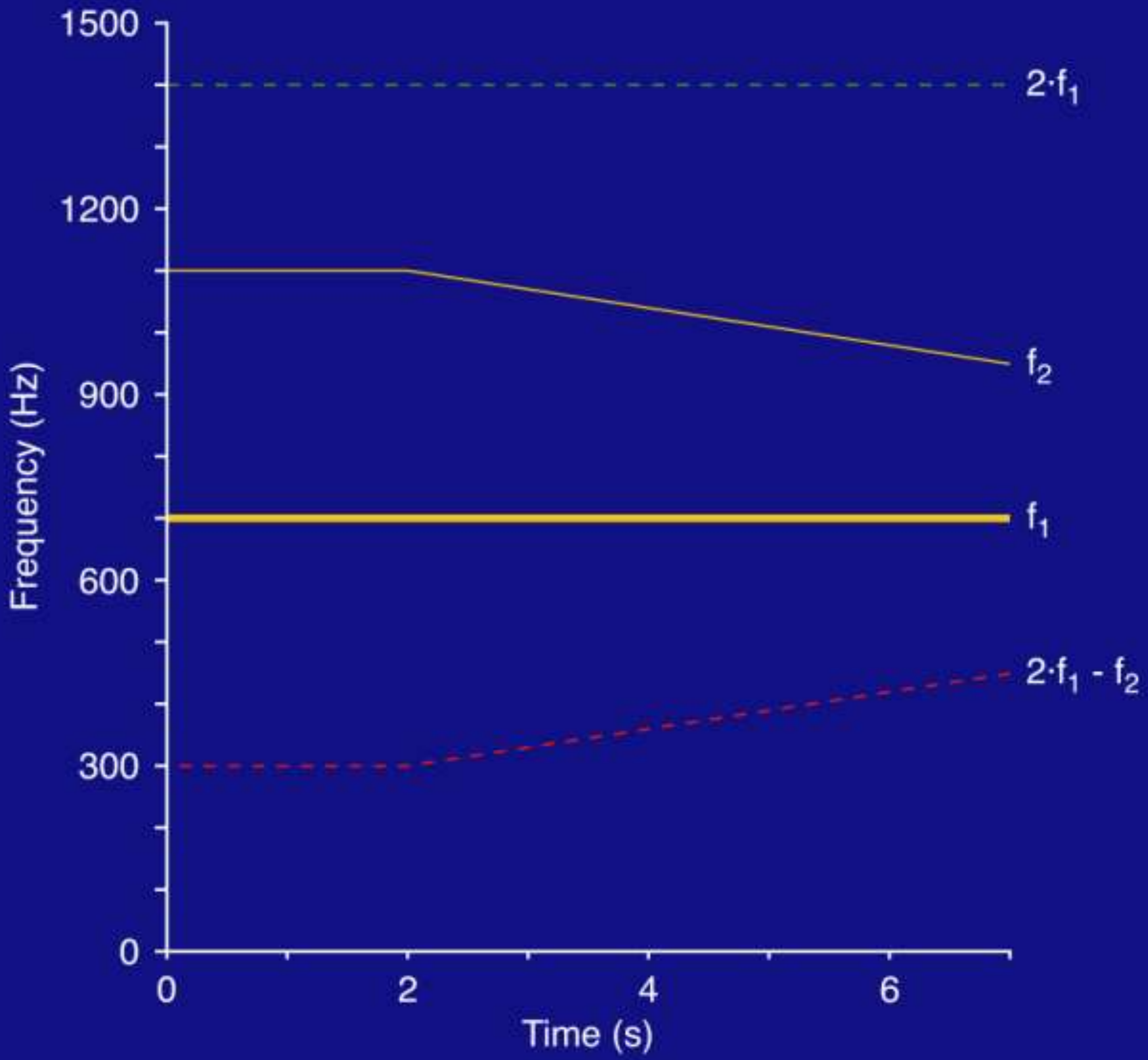
Quadratic term →
Steady offset
$2\cdot f_2$, $2\cdot f_1$
$f_2 + f_1$, $f_2 - f_1$

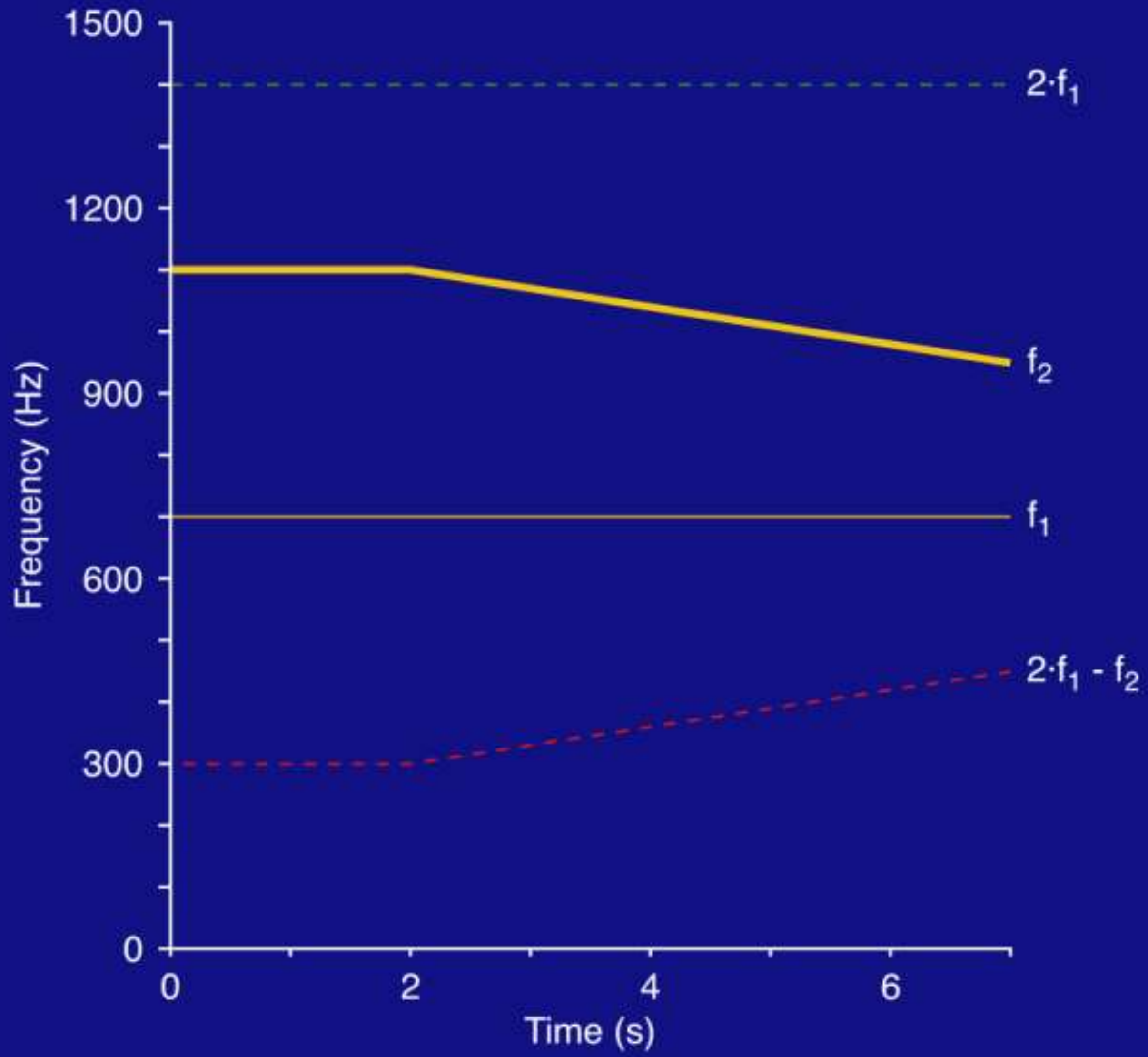
Cubic term →
f_2, f_1
$3\cdot f_2$, $3\cdot f_1$
$2\cdot f_2 + f_1$, $2\cdot f_2 - f_1$,
$2\cdot f_1 + f_2$, $2\cdot f_1 - f_2$


Theoretical power-spectral density
(pN2·Hz-1)
100
10
1
0.1
0.01
0
100
200
Frequency (Hz)
Experimental power-spectral density
(pN2·Hz-1)
100
10
1
0.1
0.01
0
100
200
Frequency (Hz)

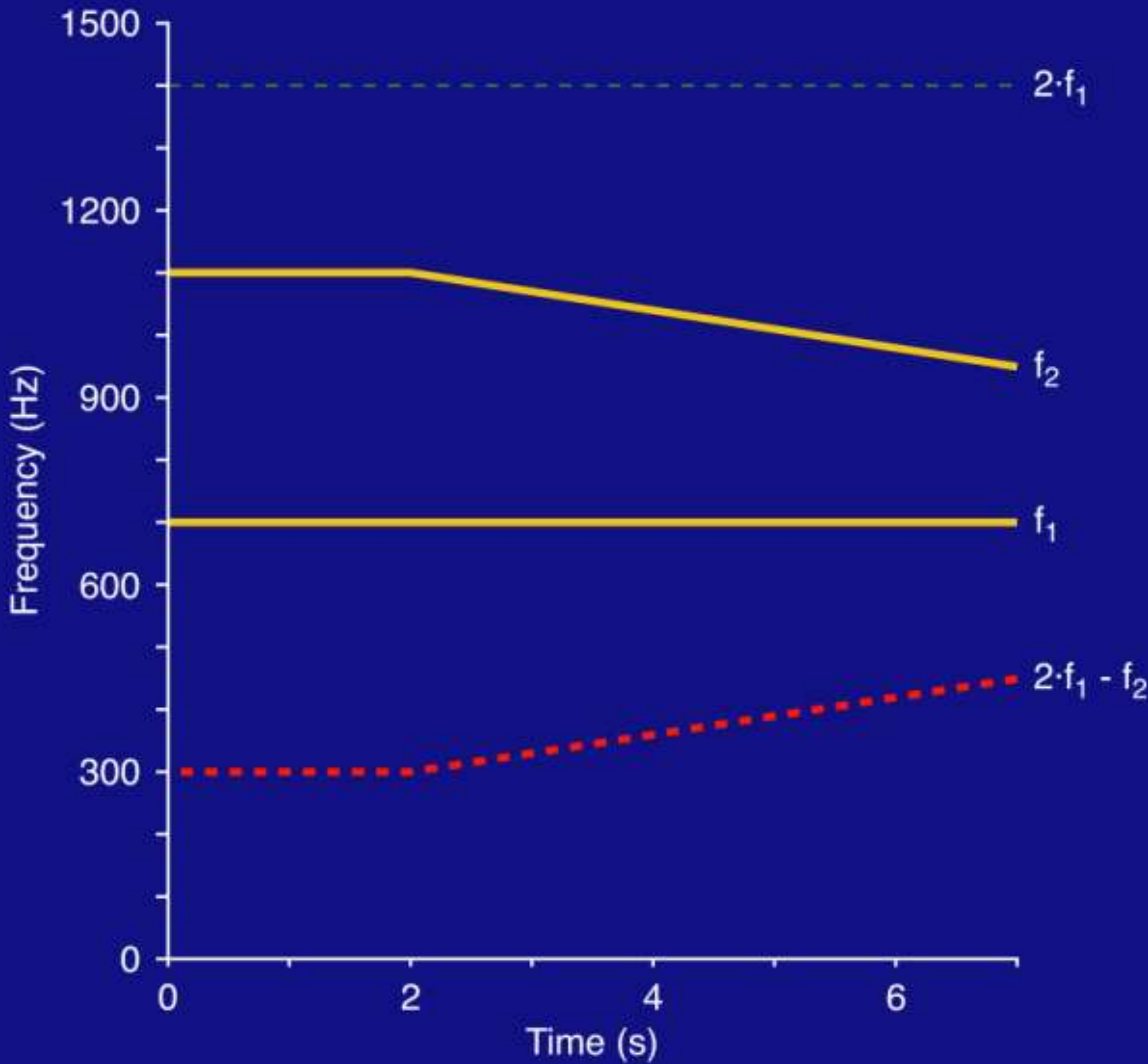


1500
1200
900
600
300
0
Frequency (Hz)
0
2
4
6
Time (s)
2·f1
f2
f1
2·f1 - f2

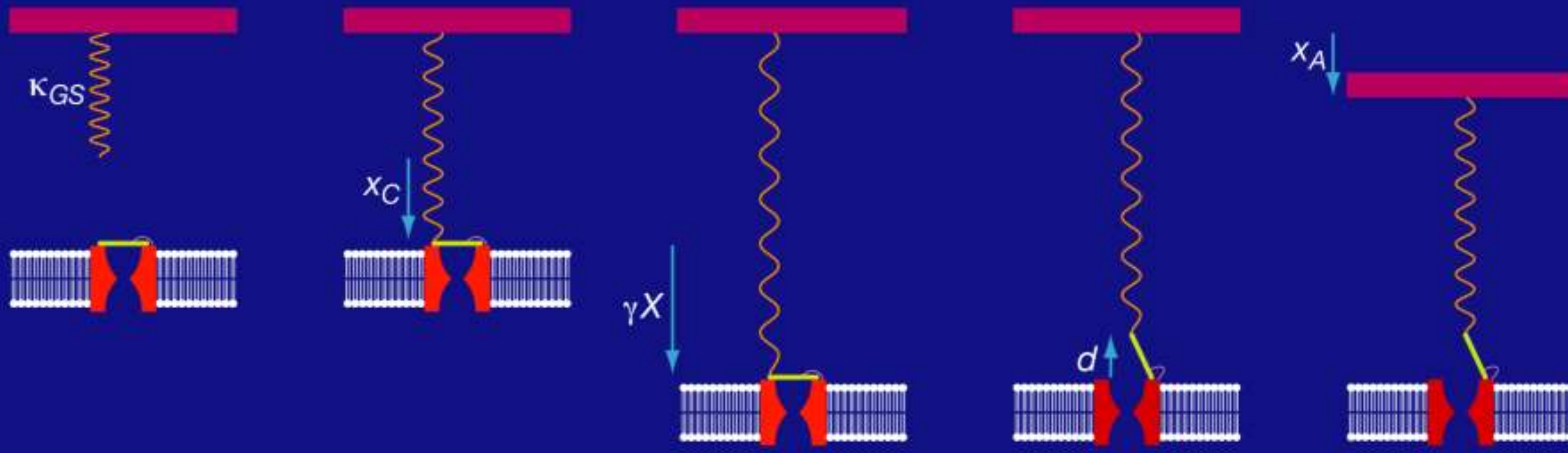

1500
1200
900
600
300
0
Frequency (Hz)
0
2
4
6
Time (s)
2·f1
f2
f1
2·f1 - f2



1500
1200
900
600
300
0
Frequency (Hz)
0
2
4
6
Time (s)
2·f1
f2
f1
2·f1 - f2


1500
1200
900
600
300
0
Frequency (Hz)
2·f1
f2
f1
2·f1 - f2
0
2
4
6
Time (s)

GATING – SPRING MODEL



Force produced by a single gating spring: $f = \kappa_{GS}(\gamma X + x_C - x_A)$
(as measured locally; channel closed)

Force produced by a single gating spring: $f = \kappa_{GS}(\gamma X + x_C - x_A - d)$
(as measured locally; channel open)

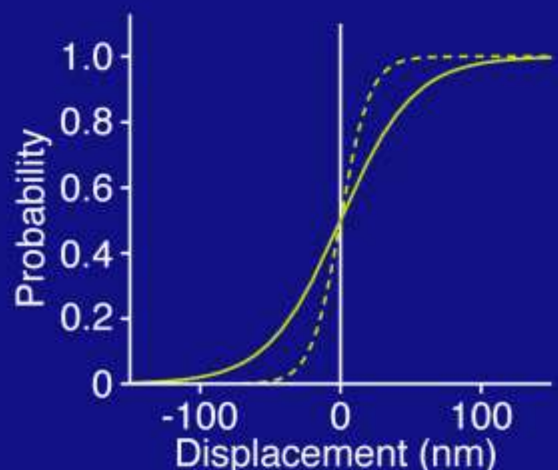
Force produced by *N* gating springs in parallel: $F = N\gamma\kappa_{GS}(\gamma X + x_C - x_A - P_O d)$
(as measured at hair bundle's top)

Force produced by an entire hair bundle: $F_{HB} = N\gamma\kappa_{GS}(\gamma X + x_C - x_A - P_O d) + K_{SP}(X - X_{SP})$
(as measured at hair bundle's top)

GATING – SPRING MODEL

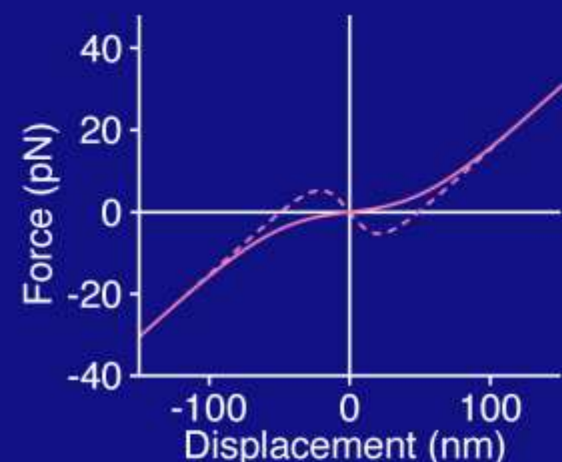
Channel open probability

$$P_O = \frac{1}{1+e^{-Z(X-X_0)/kT}}$$



Hair-bundle force

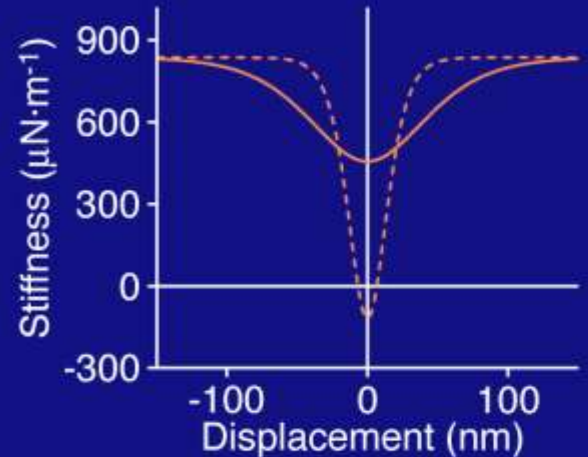
$$F_{HB} = N\gamma\kappa_{GS}(\gamma X + x_C - x_A - P_O d) + K_{SP}(X - X_{SP})$$

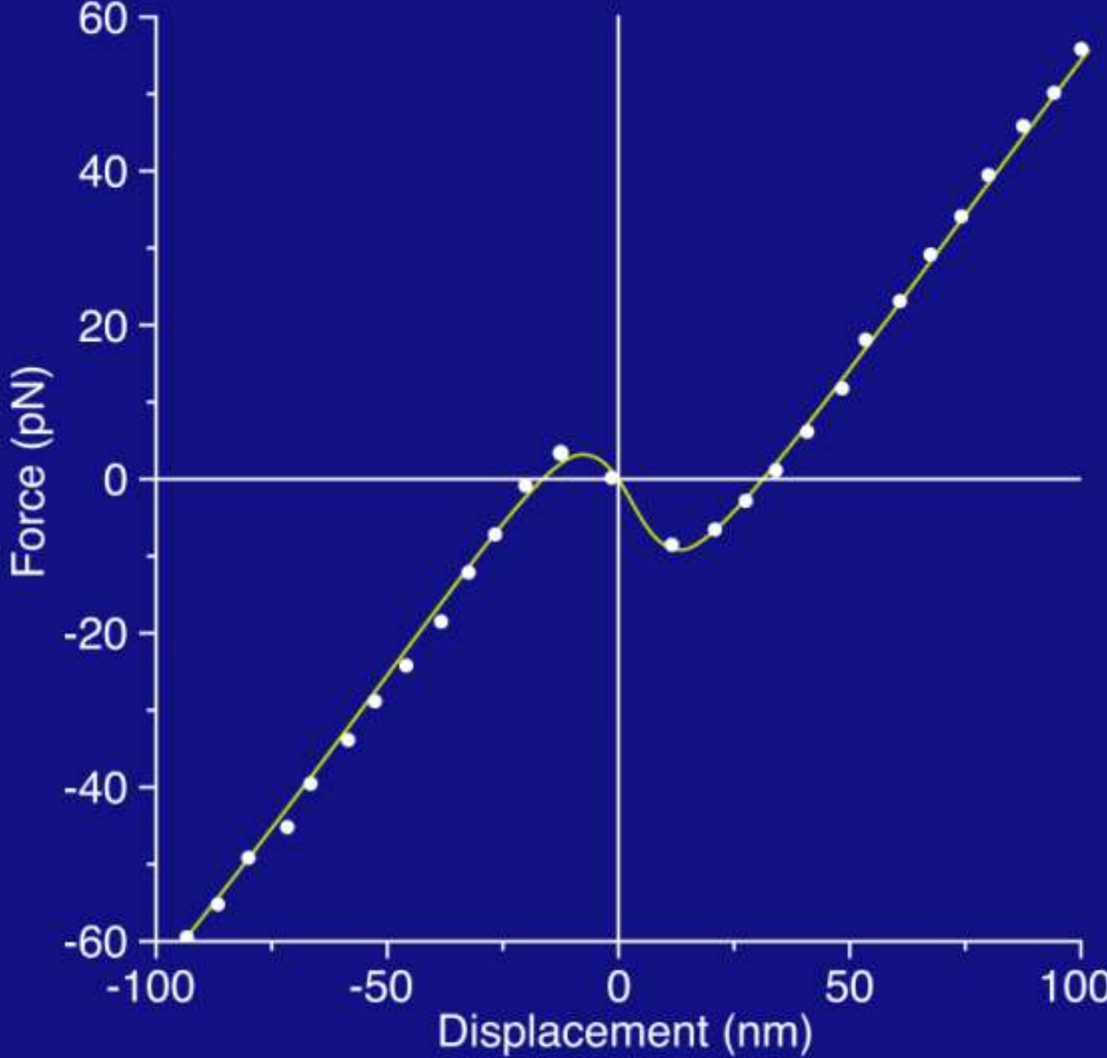


GATING – SPRING MODEL
(Gating compliance)

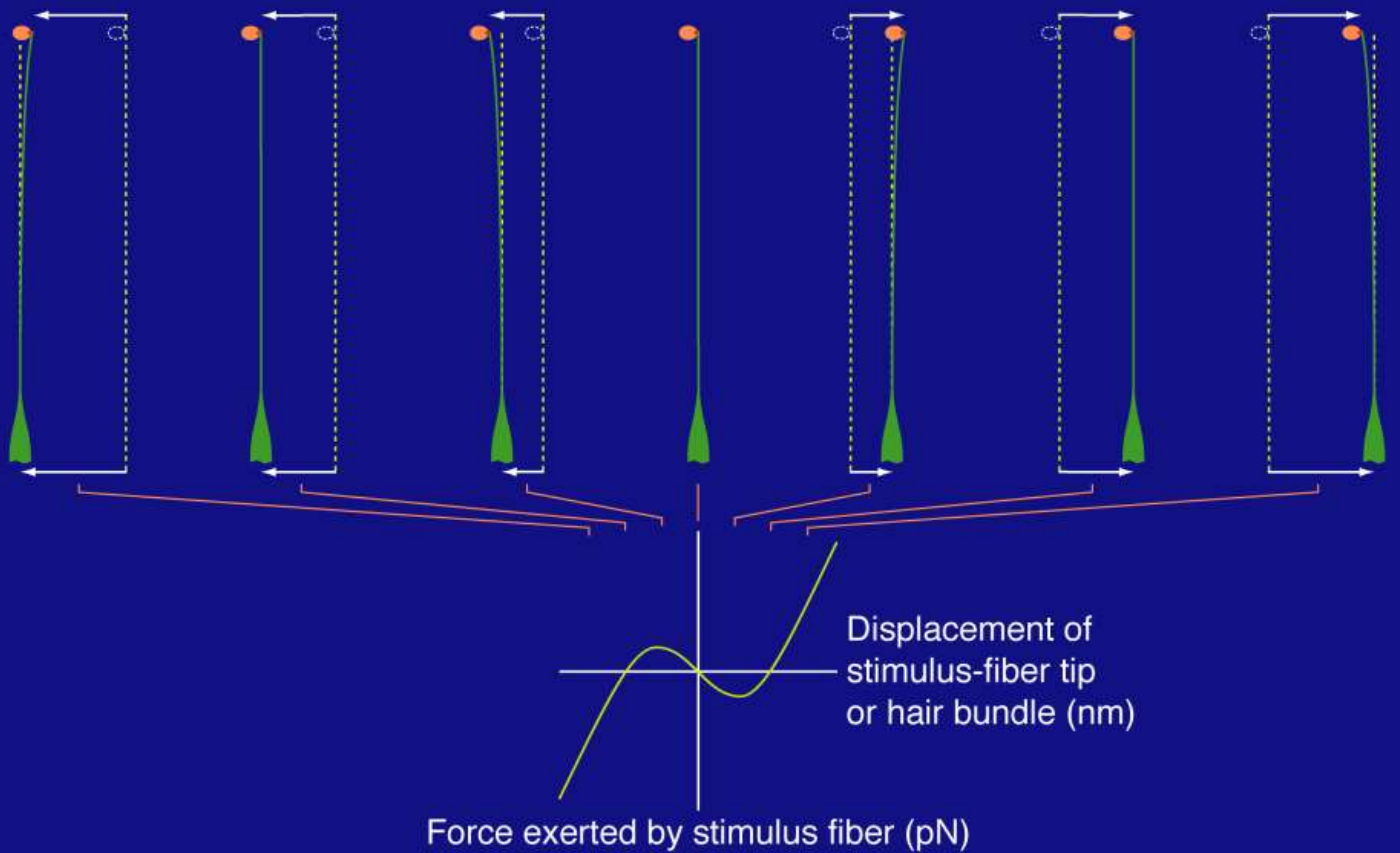
Hair-bundle stiffness

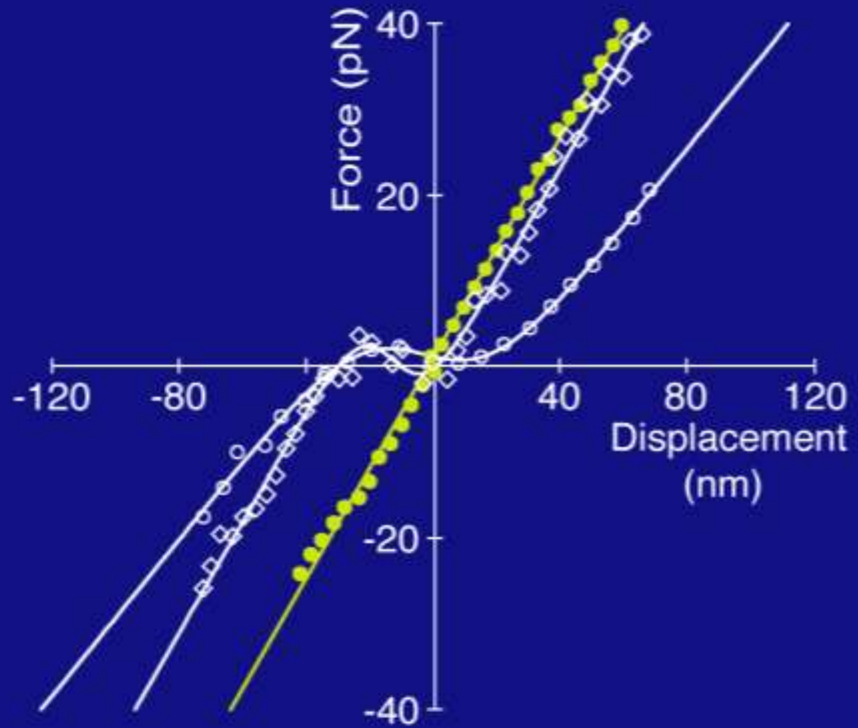
$$K_{HB} = N\gamma^2\kappa_{GS} + K_{SP} - \left(\frac{NZ^2}{kT}\right)P_O(1-P_O) = K_\infty - \left(\frac{NZ^2}{kT}\right)P_O(1-P_O)$$

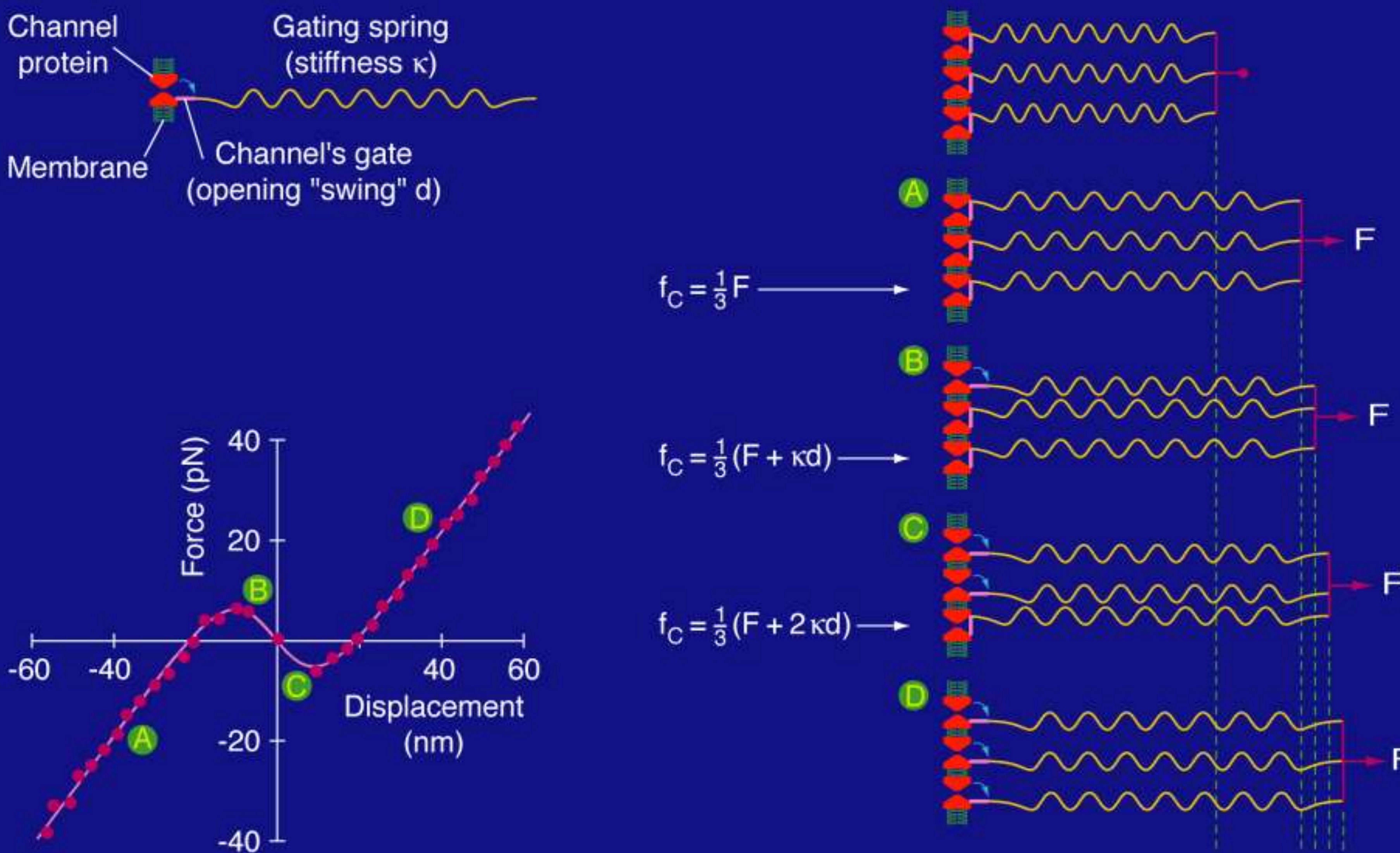




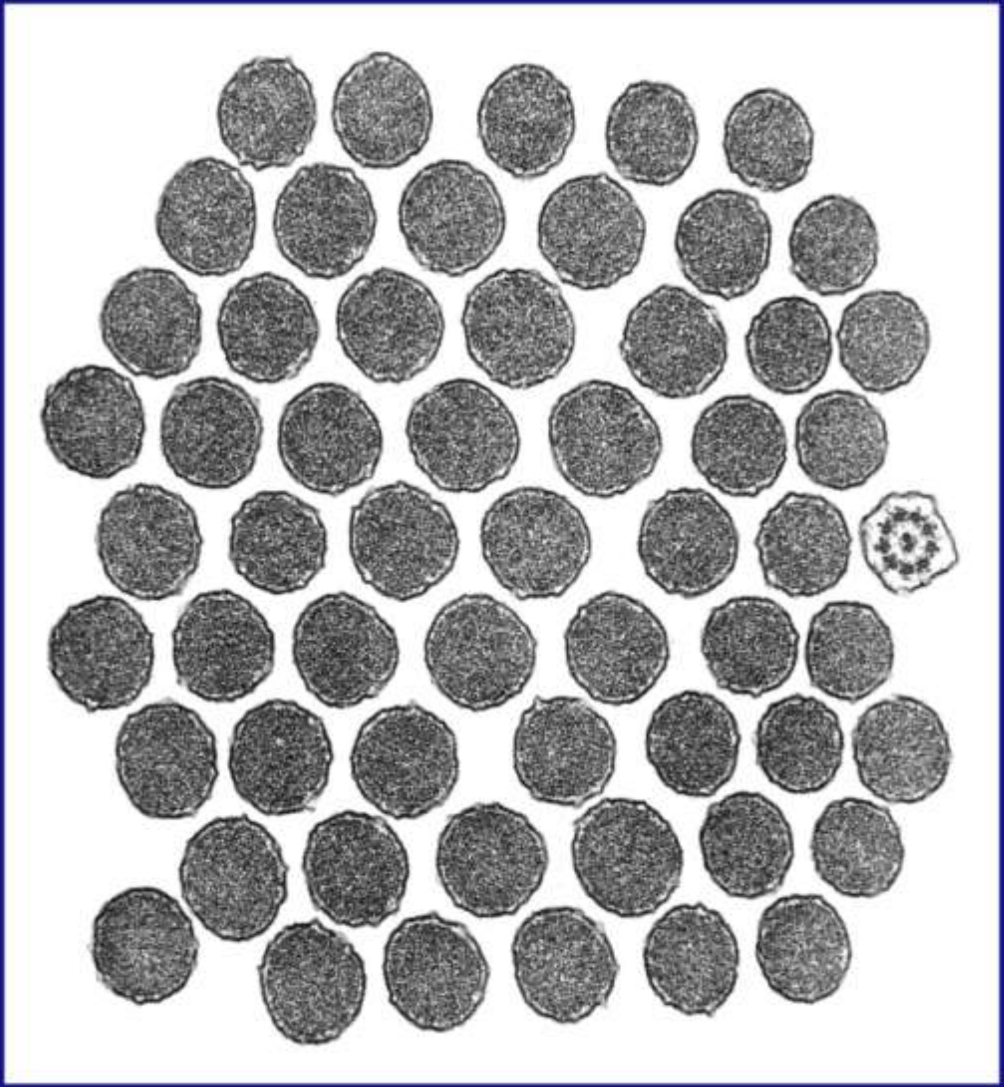
60
40
20
0
-20
-40
-60
Force (pN)
-100
-50
0
50
100
Displacement (nm)

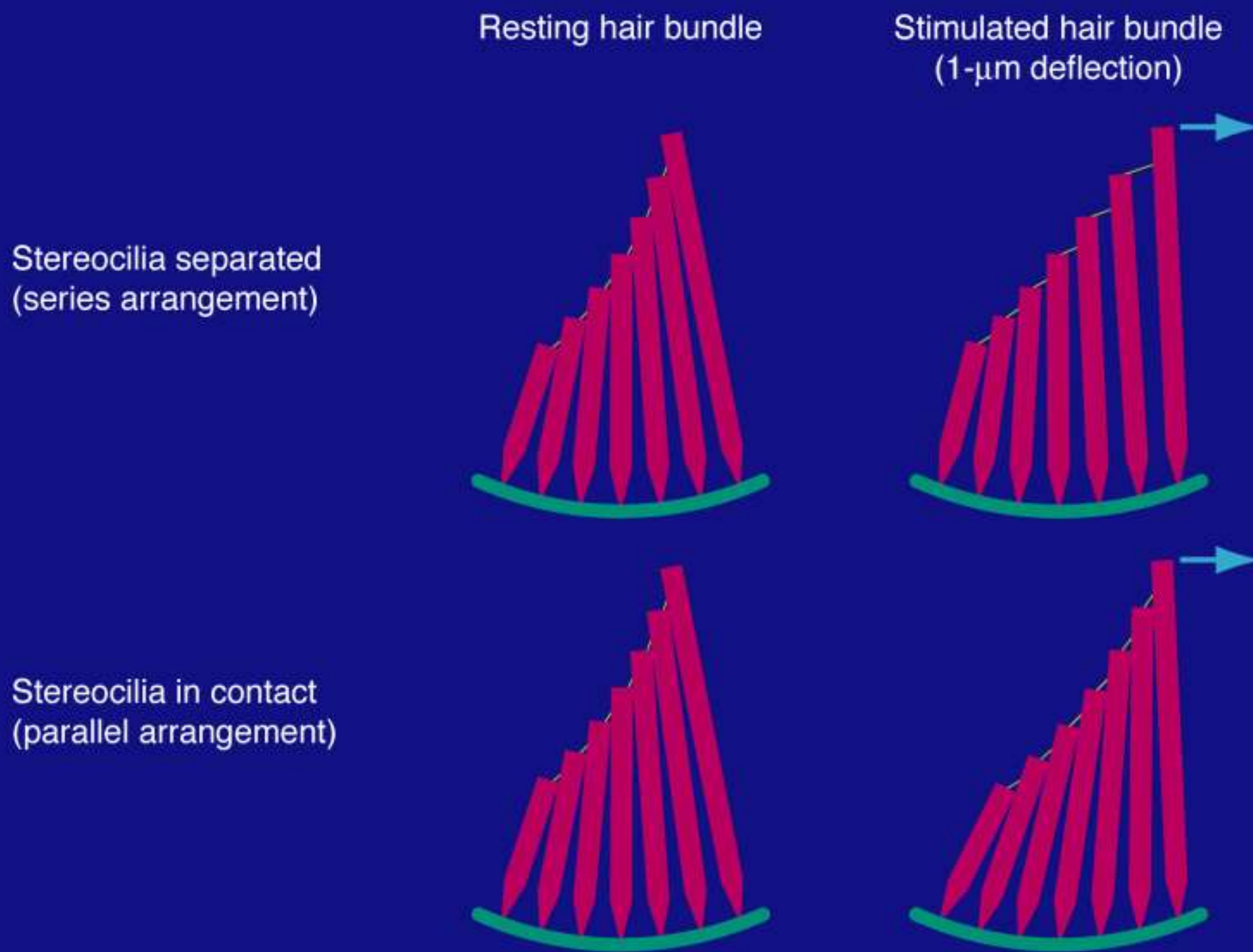

Displacement of
stimulus-fiber tip
or hair bundle (nm)
Force exerted by stimulus fiber (pN)

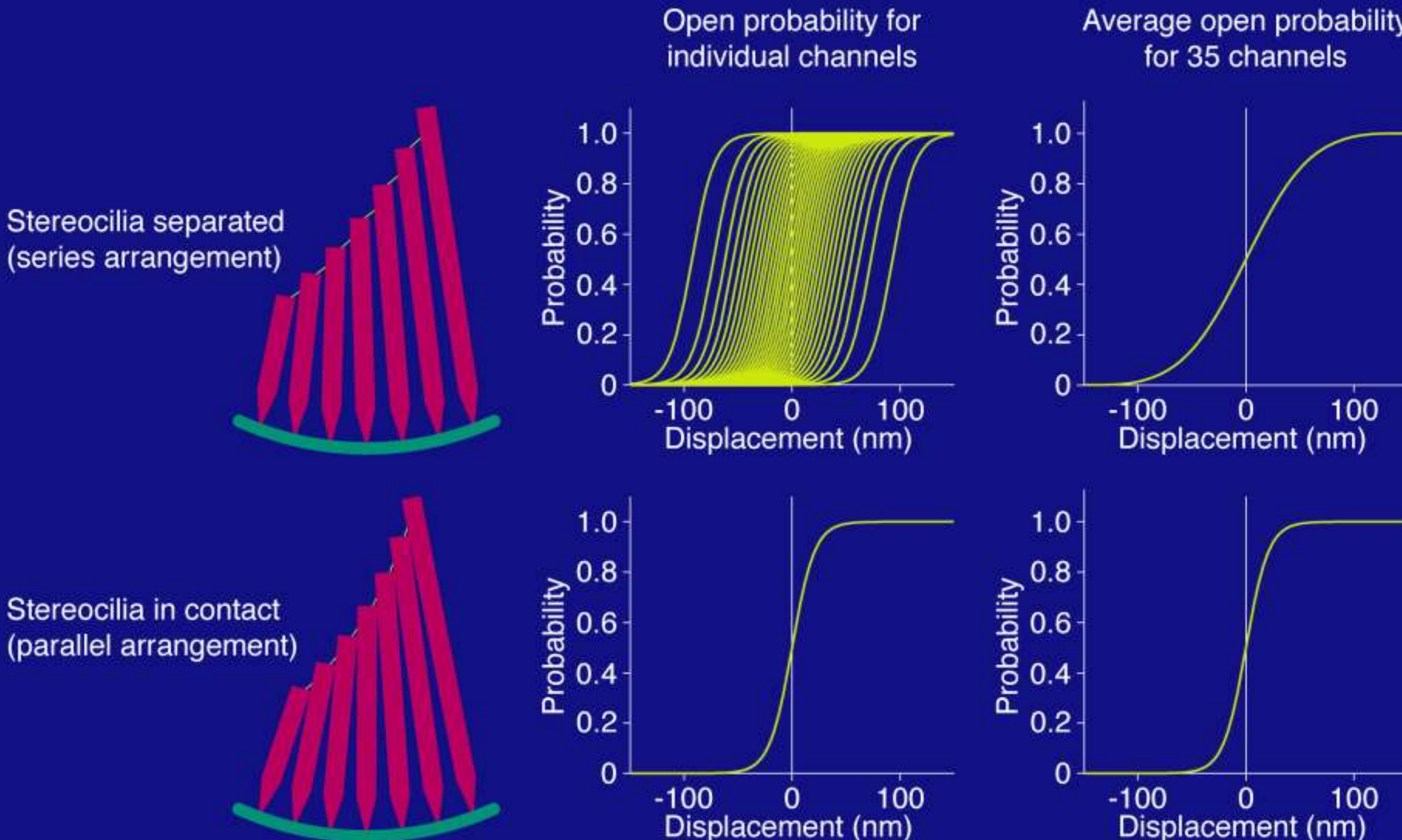

Force (pN)
40
20
-20
-40
-120
-80
40
80
120
Displacement
(nm)



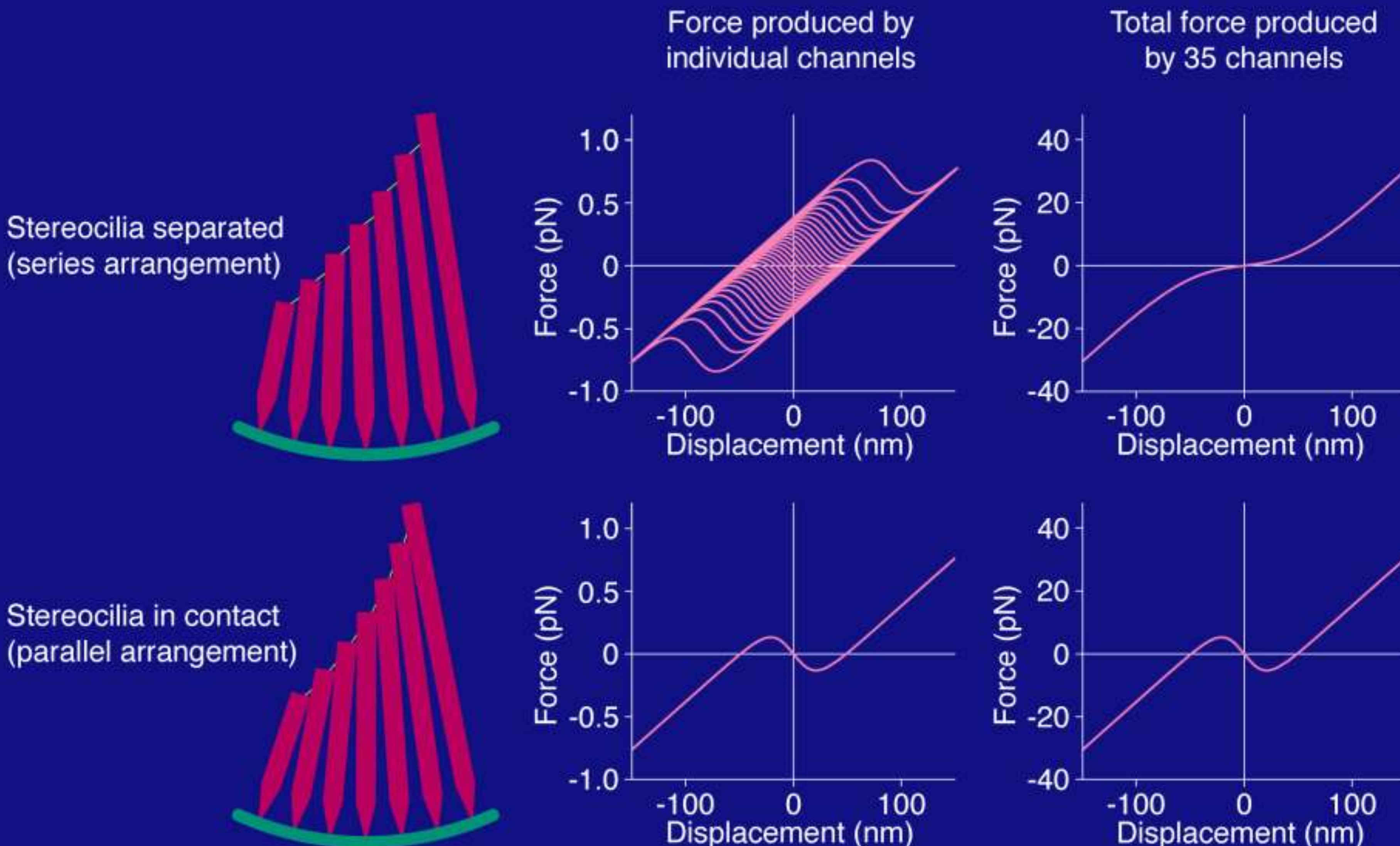
Channel protein
Gating spring (stiffness κ)
Membrane
Channel's gate (opening "swing" d)
Force (pN)
40
20
-20
-40
-60
-40
40
60
Displacement (nm)
A
B
C
D
$f_C = \frac{1}{3}F$
$f_C = \frac{1}{3}(F + \kappa d)$
$f_C = \frac{1}{3}(F + 2\kappa d)$
F
F
F
F




Resting hair bundle
Stimulated hair bundle
(1-μm deflection)
Stereocilia separated
(series arrangement)
Stereocilia in contact
(parallel arrangement)



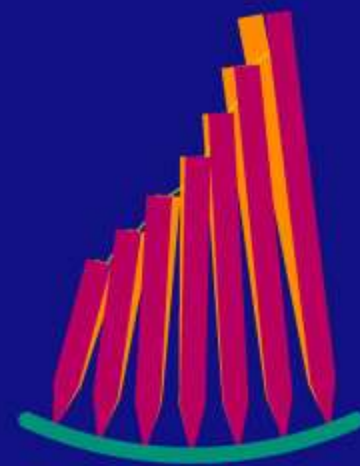
Open probability for individual channels
Average open probability for 35 channels
Stereocilia separated (series arrangement)
Stereocilia in contact (parallel arrangement)
Probability
1.0
0.8
0.6
0.4
0.2
0
-100
0
100
Displacement (nm)



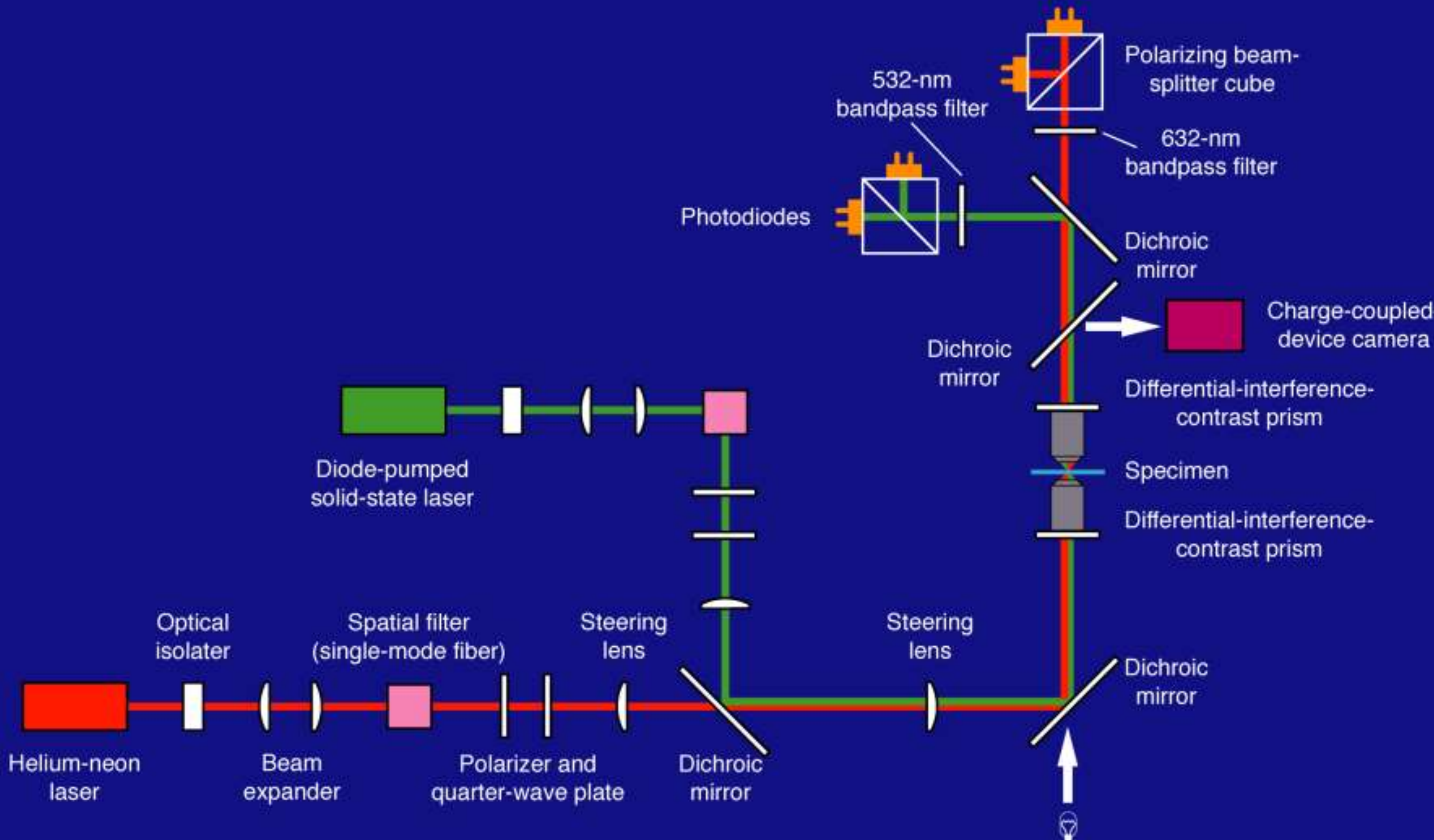
Force produced by individual channels
Total force produced by 35 channels
Stereocilia separated (series arrangement)
Stereocilia in contact (parallel arrangement)
Force (pN)
1.0
0.5
0
-0.5
-1.0
40
20
0
-20
-40
-100
0
100
Displacement (nm)

Thermal (brownian) motion of resting hair bundle

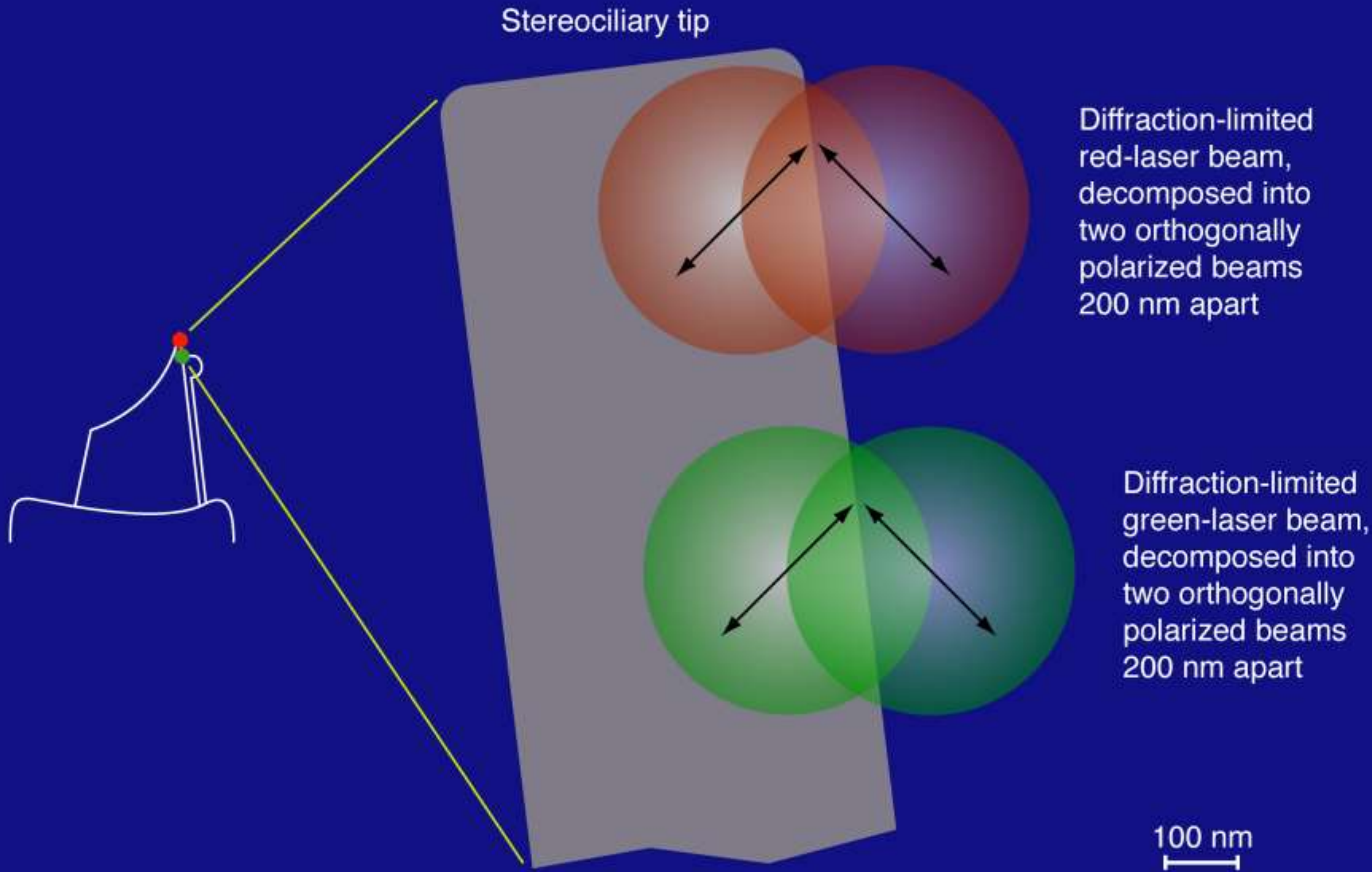
Stereocilia separated (series arrangement)

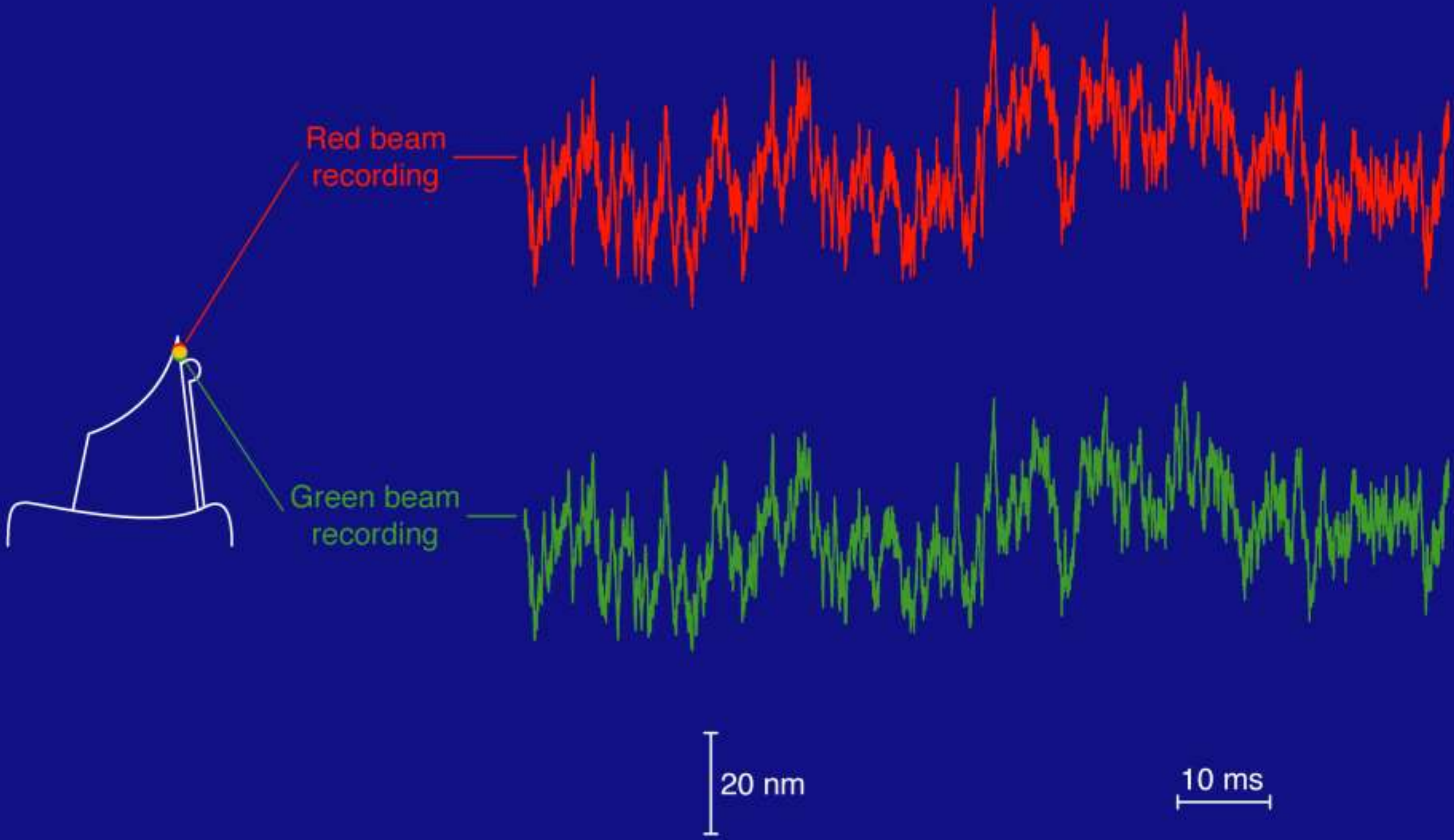


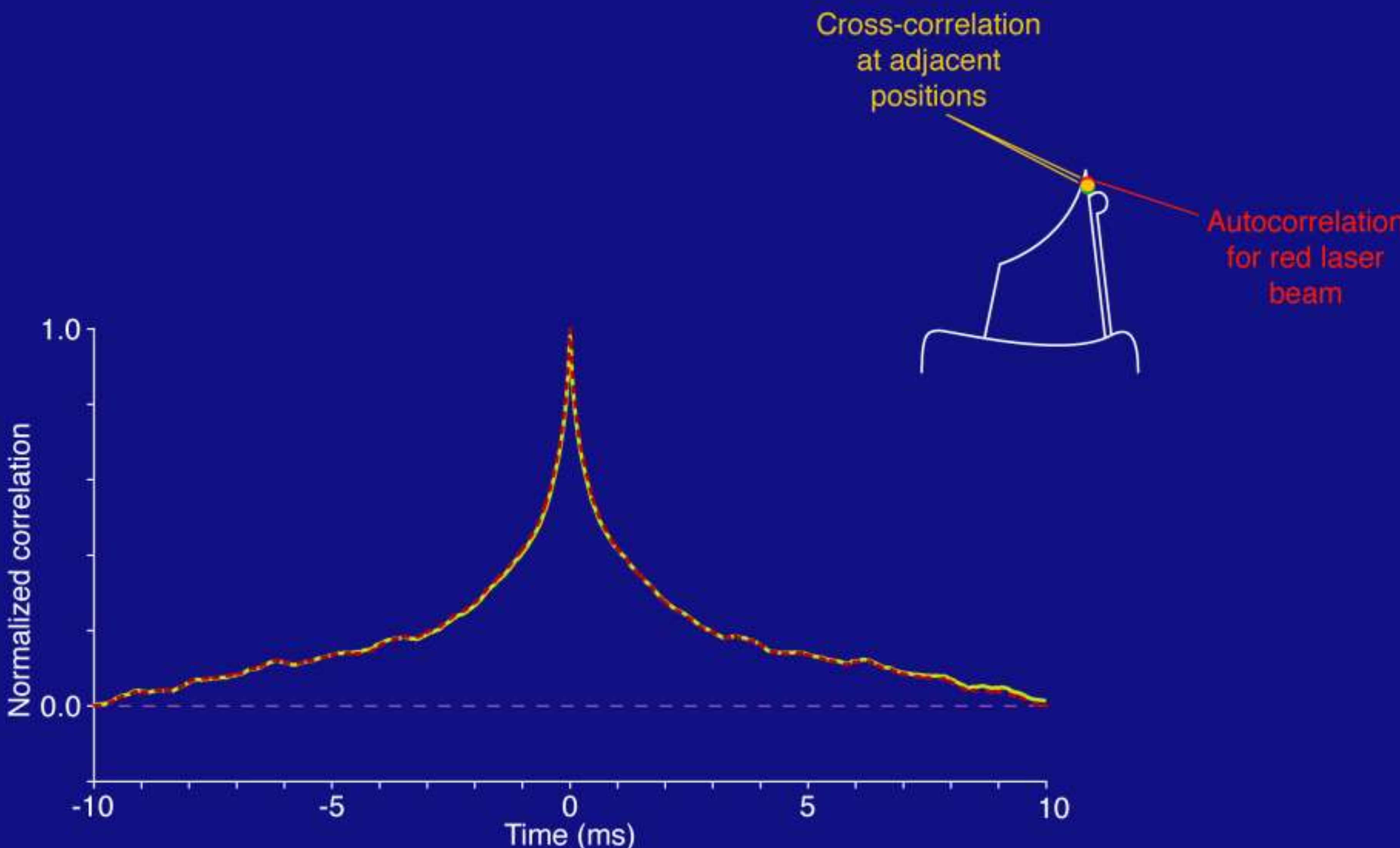
Stereocilia in contact (parallel arrangement)

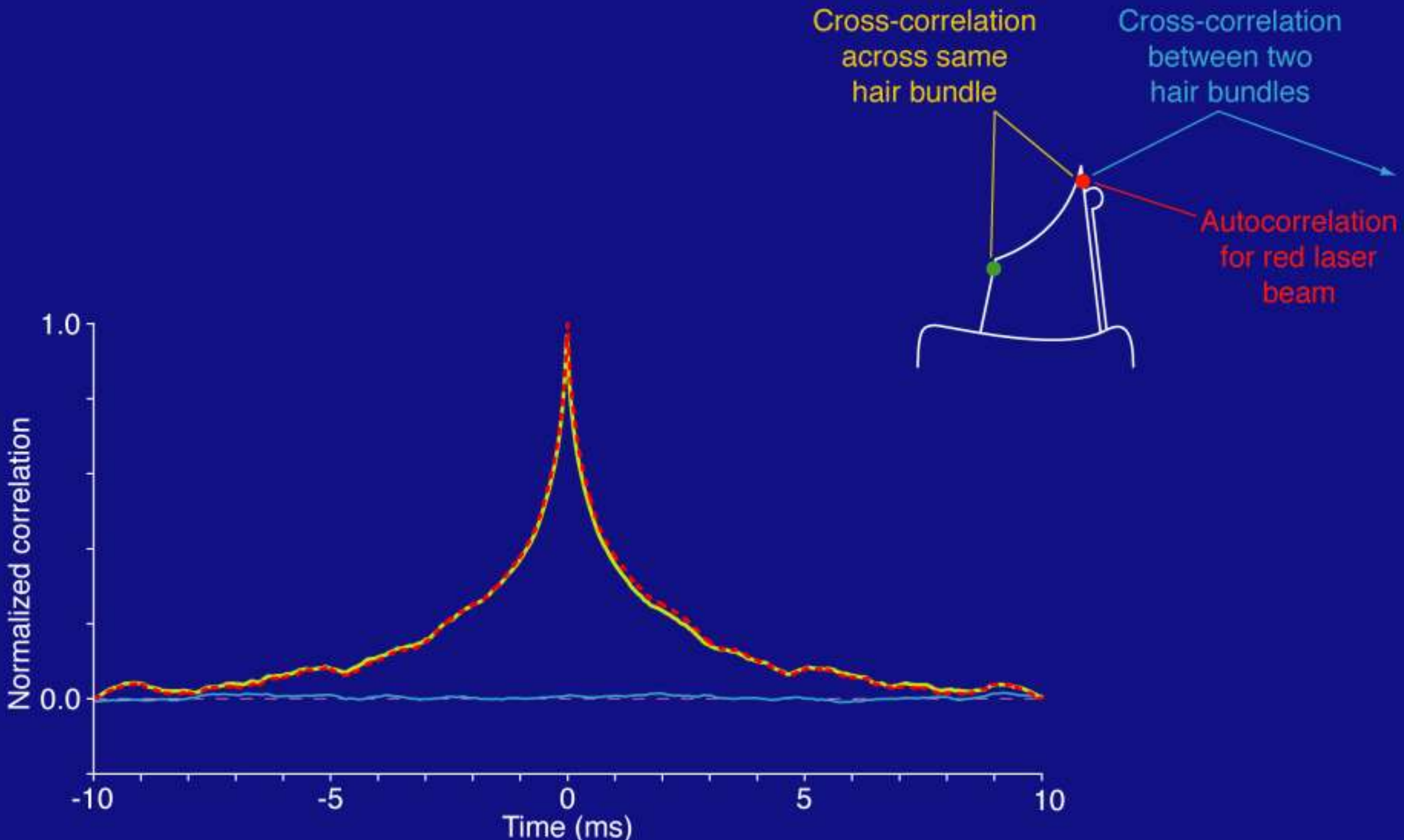


Polarizing beam-splitter cube
532-nm bandpass filter
632-nm bandpass filter
Photodiodes
Dichroic mirror
Charge-coupled-device camera
Dichroic mirror
Differential-interference-contrast prism
Diode-pumped solid-state laser
Specimen
Differential-interference-contrast prism
Optical isolater
Spatial filter (single-mode fiber)
Steering lens
Steering lens
Dichroic mirror
Helium-neon laser
Beam expander
Polarizer and quarter-wave plate
Dichroic mirror

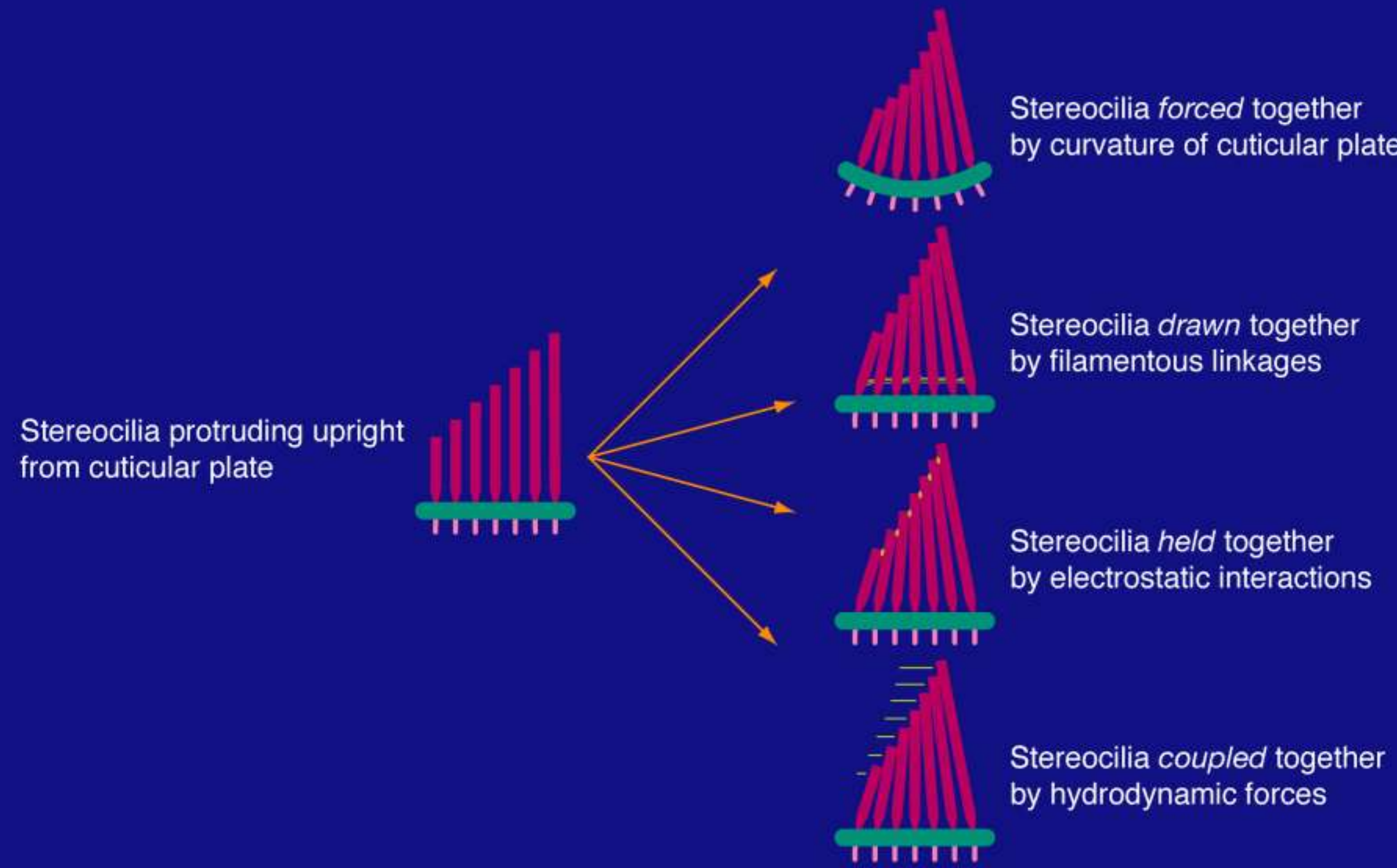

Stereociliary tip
Diffraction-limited red-laser beam, decomposed into two orthogonally polarized beams 200 nm apart
Diffraction-limited green-laser beam, decomposed into two orthogonally polarized beams 200 nm apart
100 nm

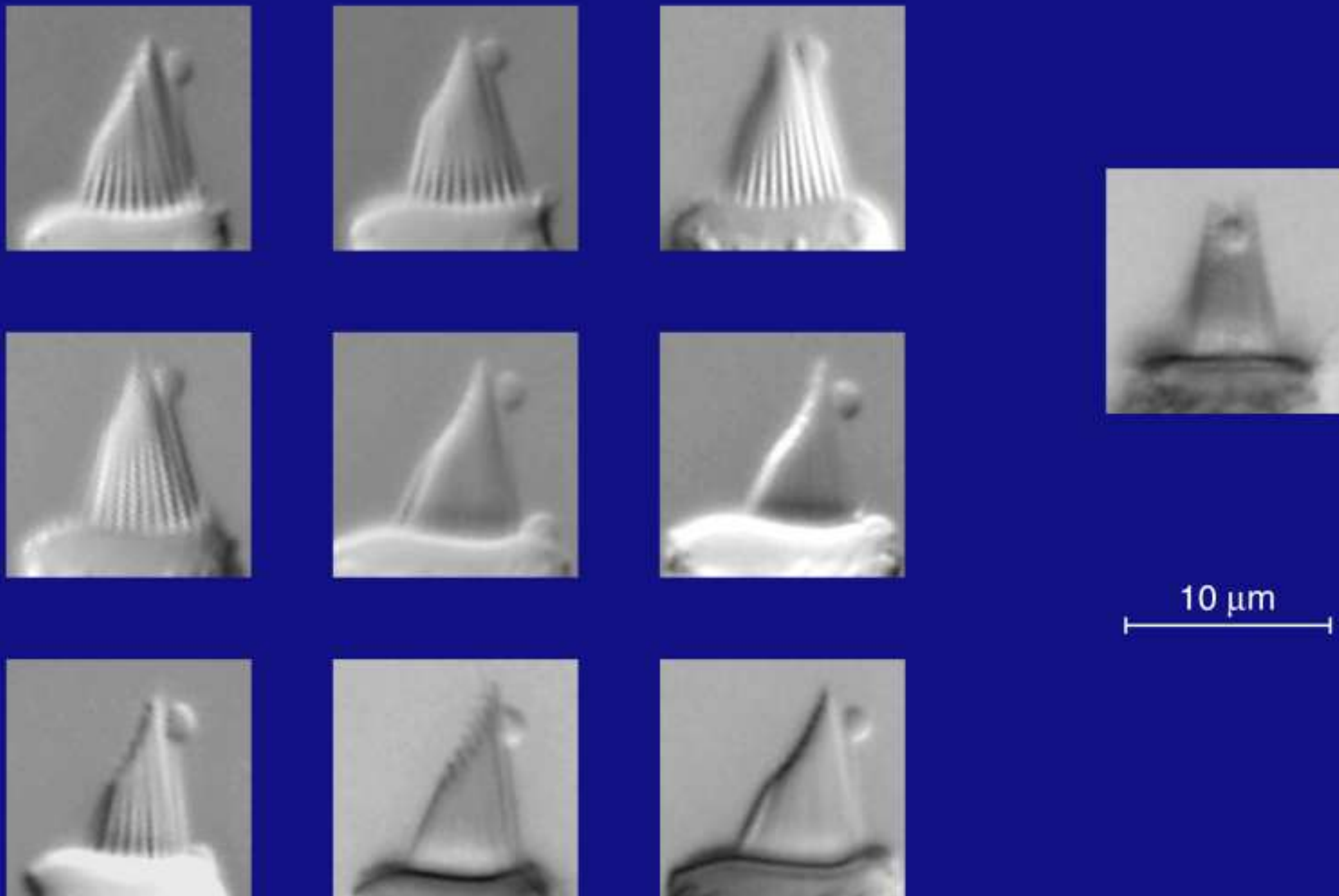

Red beam
recording
Green beam
recording
20 nm
10 ms


Cross-correlation at adjacent positions
Autocorrelation for red laser beam
1.0
0.0
Normalized correlation
-10
-5
0
5
10
Time (ms)



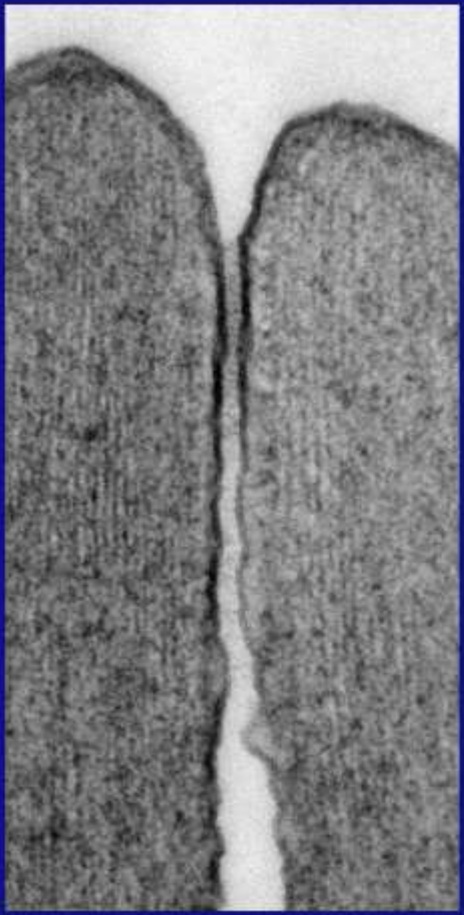
Cross-correlation across same hair bundle
Cross-correlation between two hair bundles
Autocorrelation for red laser beam
1.0
0.0
Normalized correlation
-10
-5
0
5
10
Time (ms)


Stereocilia protruding upright
from cuticular plate
Stereocilia *forced* together
by curvature of cuticular plate
Stereocilia *drawn* together
by filamentous linkages
Stereocilia *held* together
by electrostatic interactions
Stereocilia *coupled* together
by hydrodynamic forces

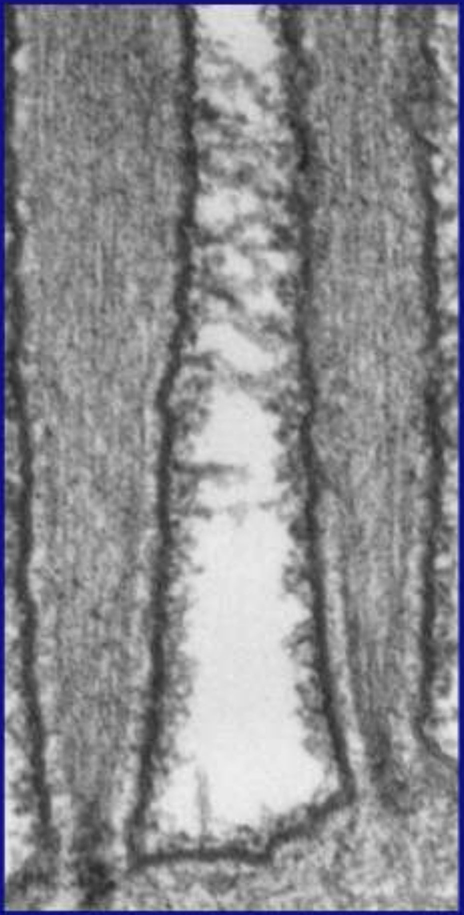

10 μm

Filamentous linkages between adjacent stereocilia

Tip links



Horizontal top connectors



Basal links

Finite-element modeling of hydrodynamic coupling between stereocilia

Detailed, quantitative representation of the bullfrog's saccular hair bundle and surrounding liquid

60 stereocilia and a kinocilium in a realistic array

Optional tip links, basal links, and horizontal top connectors

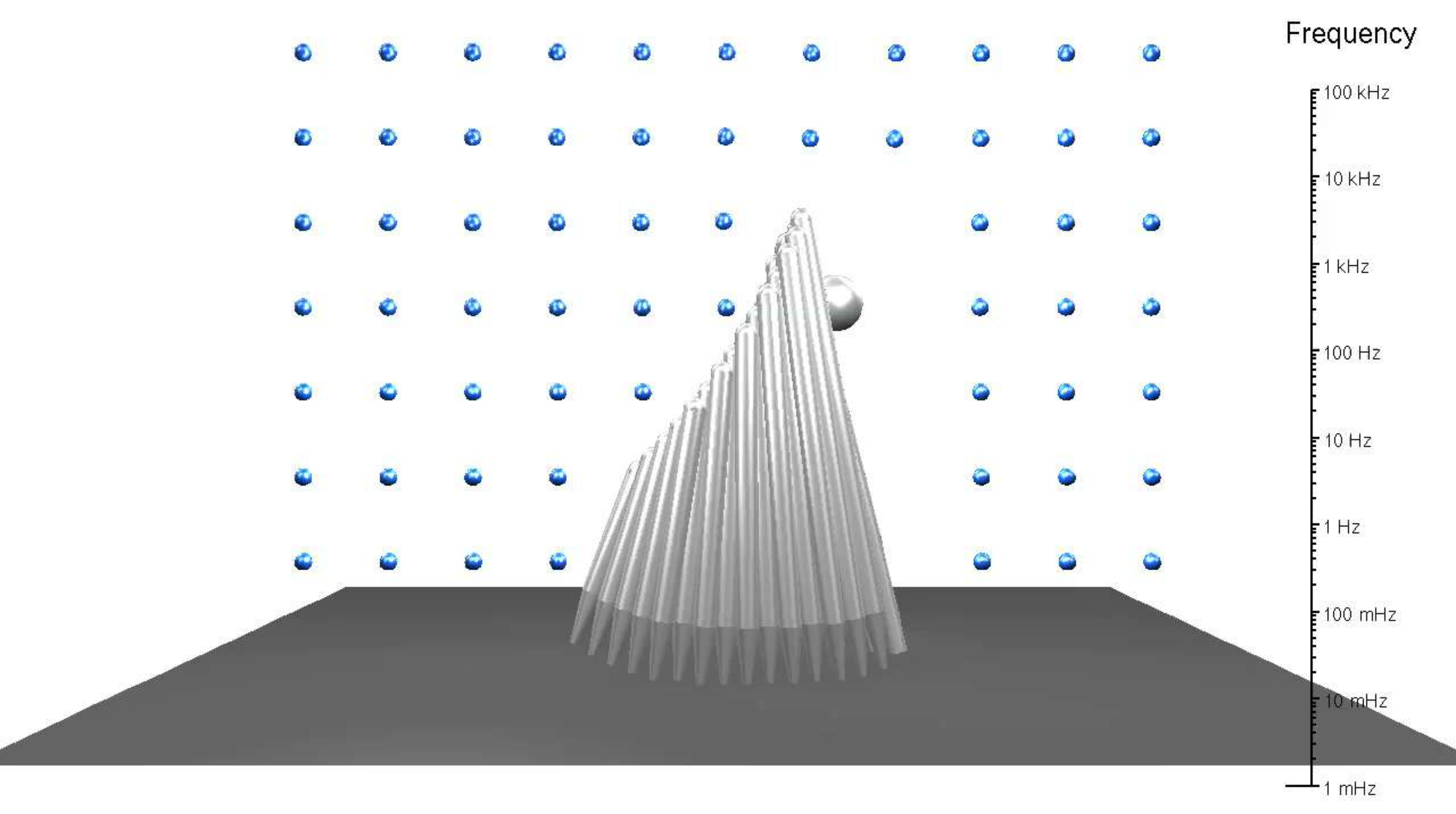
50,000 volume elements (voxels) of sizes adapted to local hydrodynamic conditions

200,000 nodes and 800,000 degrees of freedom

Used in solution of the Navier-Stokes equation for an incompressible liquid:

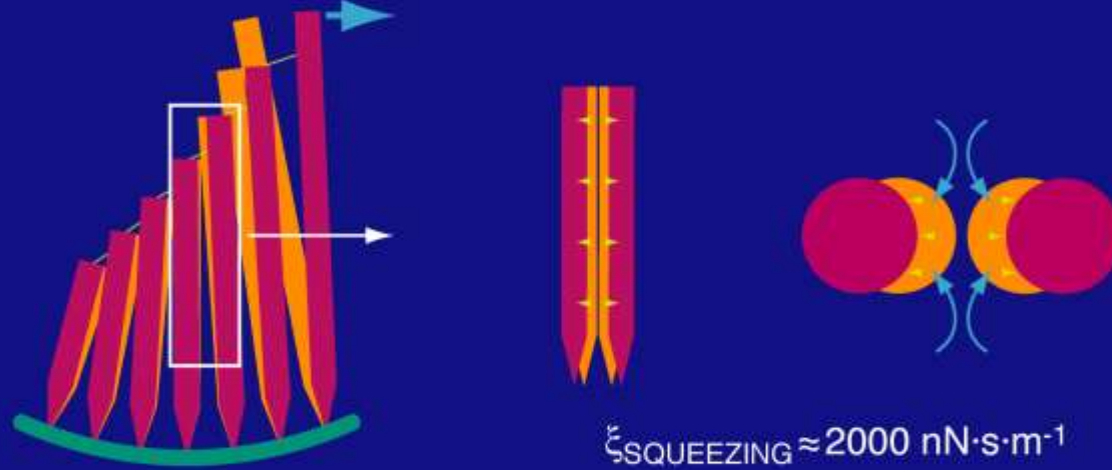
$$\rho\left(\frac{\partial \mathbf{v}}{\partial t} + \mathbf{v}\cdot\nabla\mathbf{v}\right) = -\nabla p + \mu\nabla^2\mathbf{v}$$

for flow velocity $\boldsymbol{v}$, density ρ, pressure p, and dynamic viscosity μ

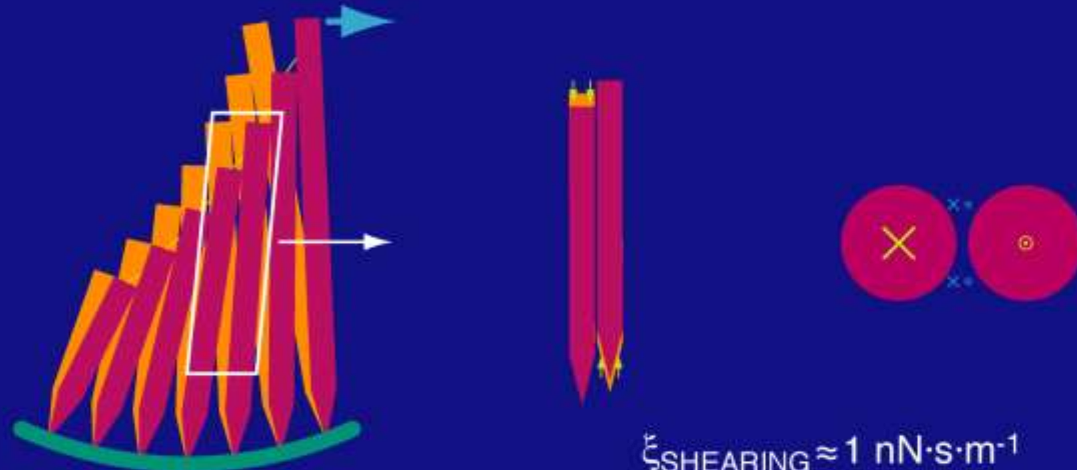


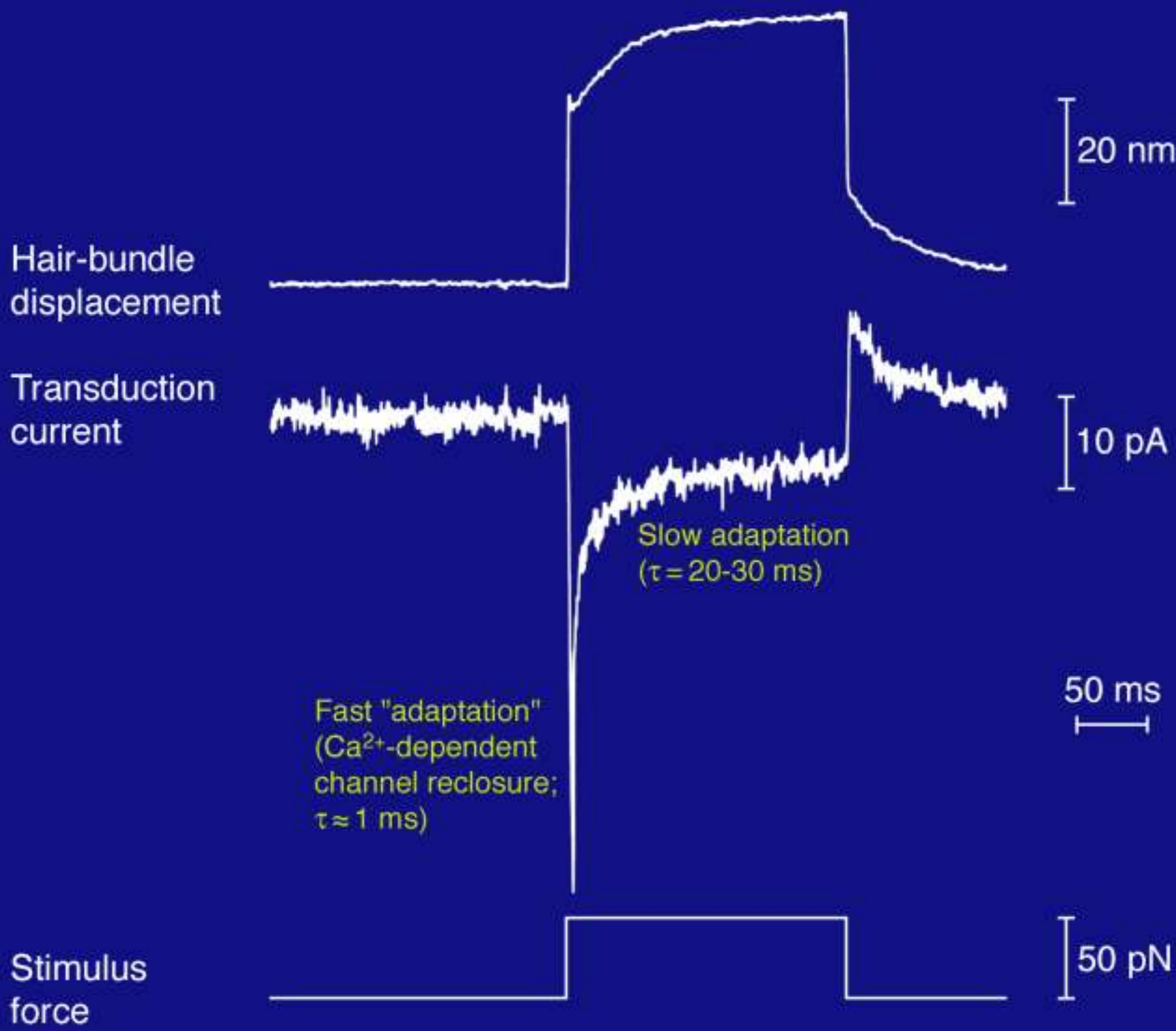
Frequency
100 kHz
10 kHz
1 kHz
100 Hz
10 Hz
1 Hz
100 mHz
10 mHz
1 mHz

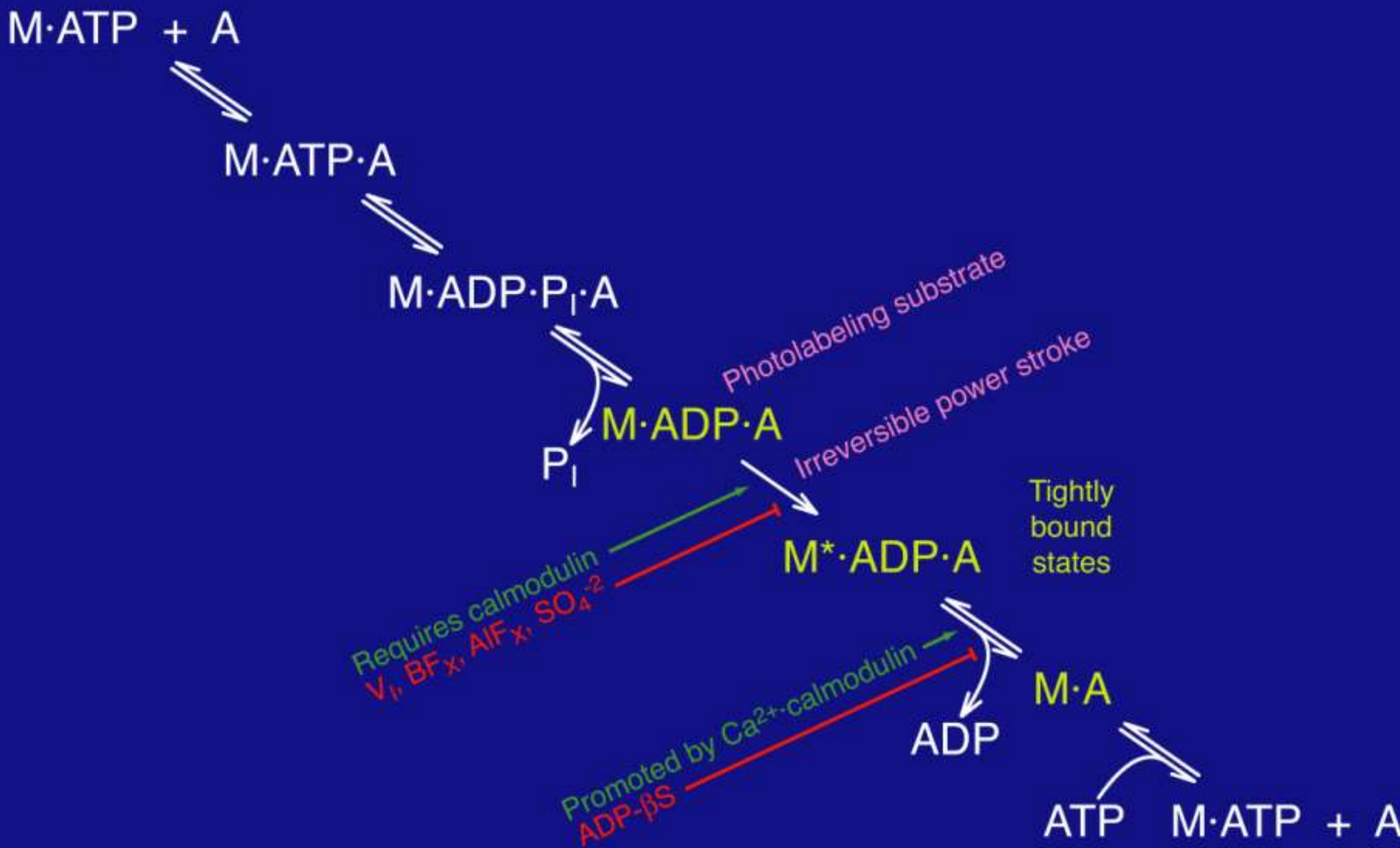
Squeezing mode of stereociliary motion



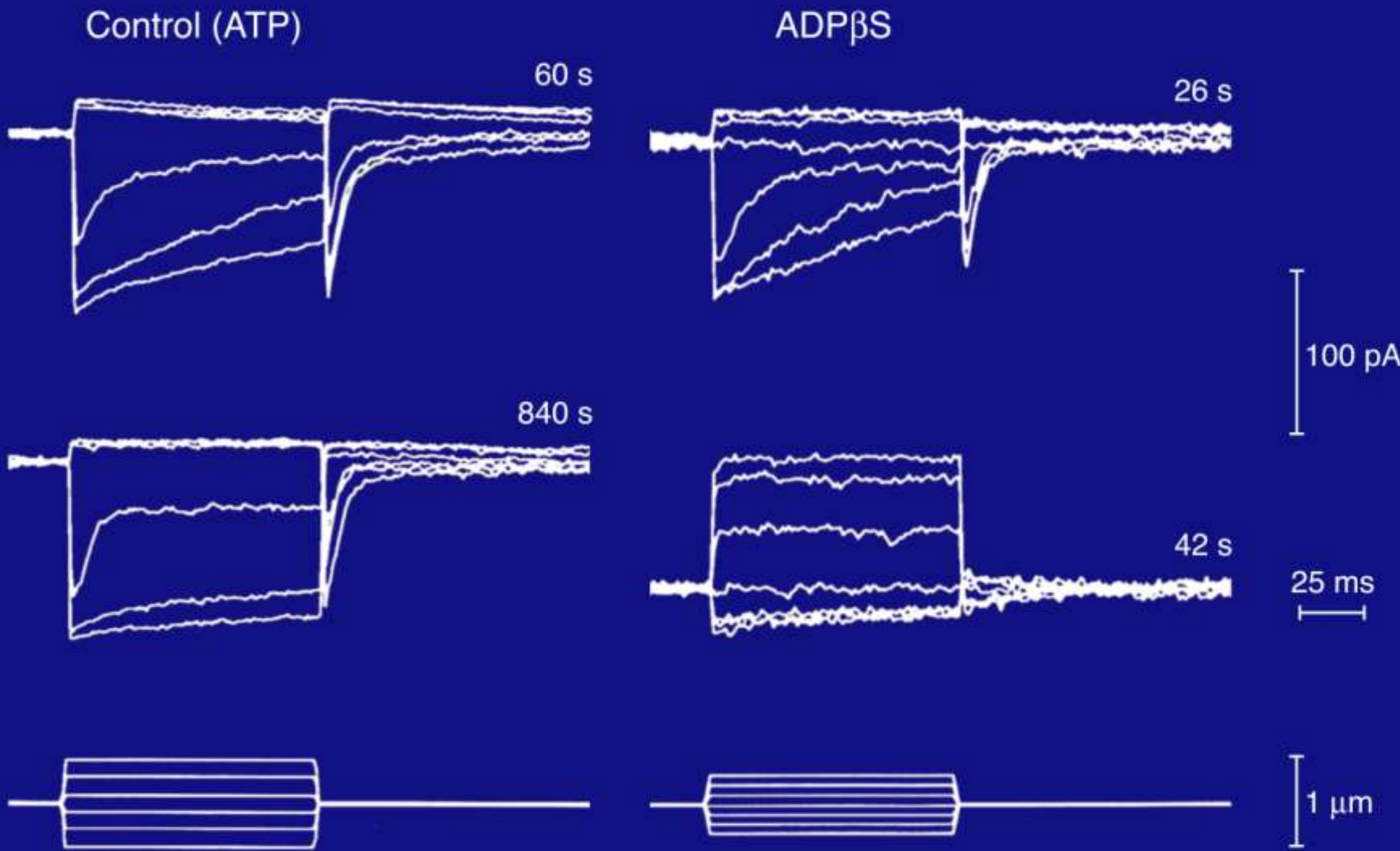
Shearing mode of stereociliary motion

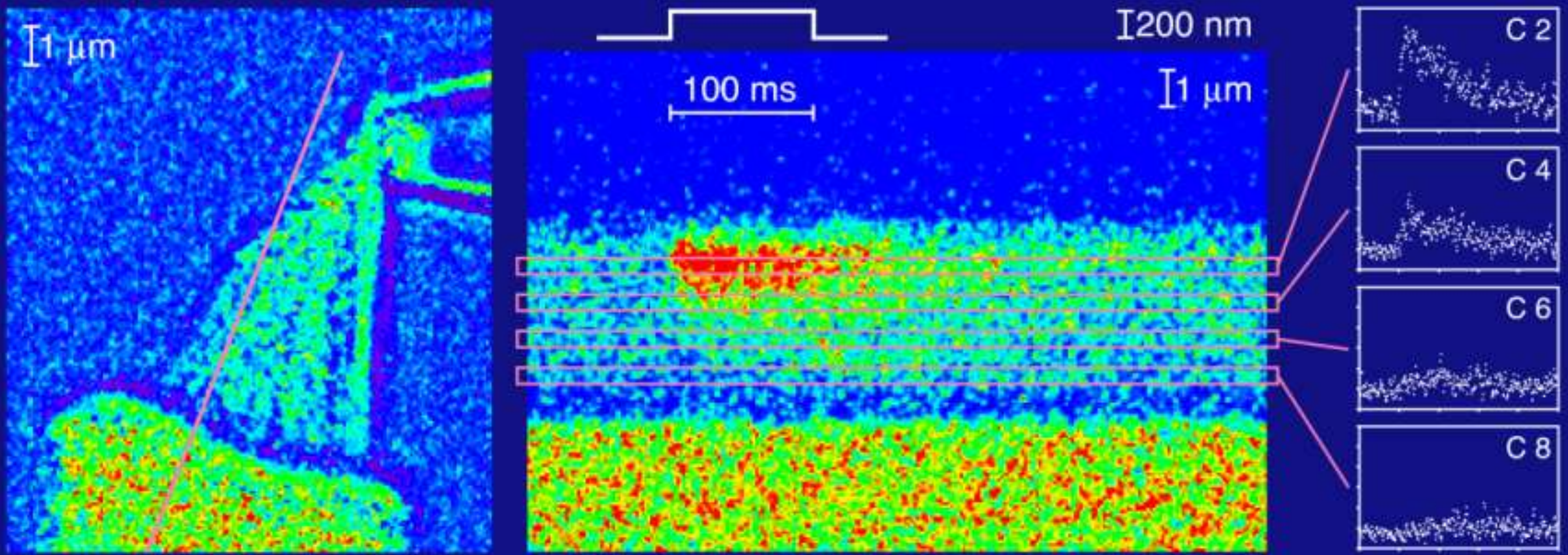



Hair-bundle displacement
Transduction current
Stimulus force
20 nm
10 pA
50 ms
50 pN
Slow adaptation
(τ = 20-30 ms)
Fast "adaptation"
(Ca2+-dependent
channel reclosure;
τ ≈ 1 ms)



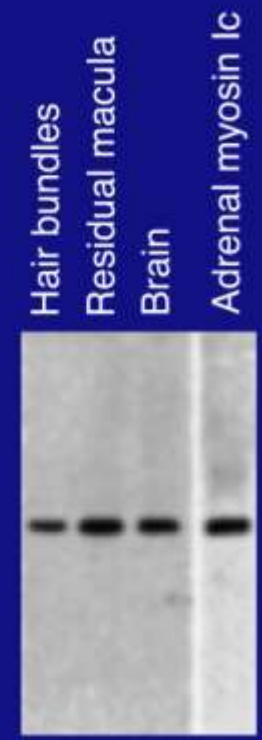
M·ATP + A
M·ATP·A
M·ADP·P_I·A
Photolabeling substrate
Irreversible power stroke
M·ADP·A
P_I
Tightly bound states
M*·ADP·A
Requires calmodulin
V_I, BF_X, AlF_X, SO₄⁻²
Promoted by Ca²⁺-calmodulin
ADP-βS
M·A
ADP
ATP
M·ATP + A

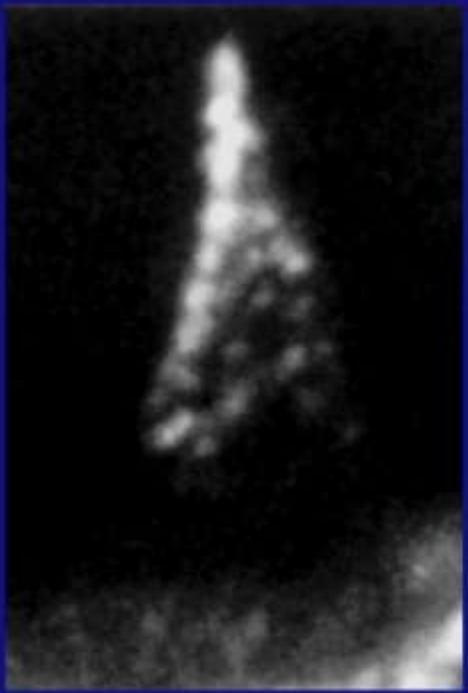

Control (ATP)
ADPβS
60 s
26 s
100 pA
840 s
42 s
25 ms
1 µm


1 µm
200 nm
100 ms
1 µm
C 2
C 4
C 6
C 8

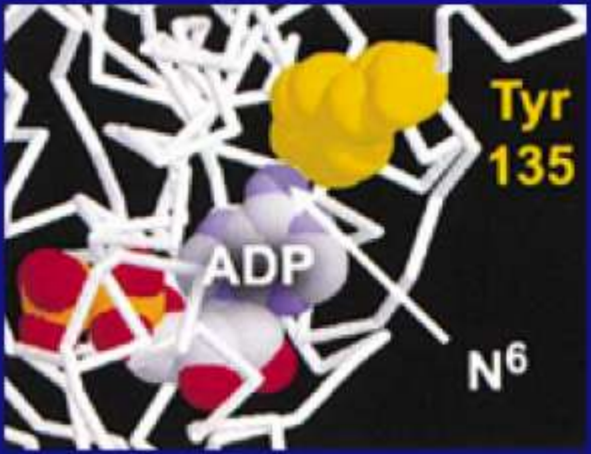
Myosin labeling
with[α-^{32}P]UTP
by vanadate trapping
and photo-crosslinking

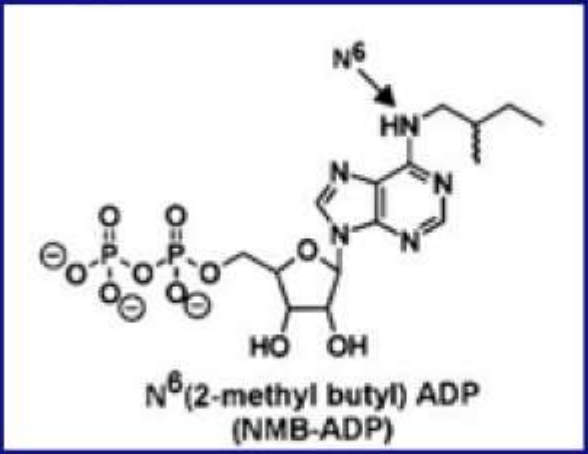
Immunoblotting
with anti-mammalian
adrenal myosin Ic

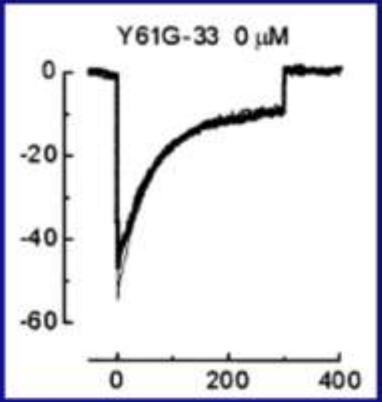


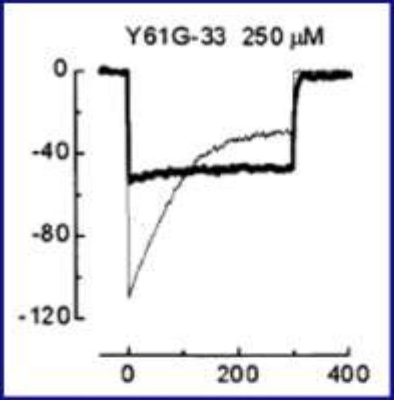
Site-directed mutagenesis of transgenic myosin-1c to permit binding of a blocker





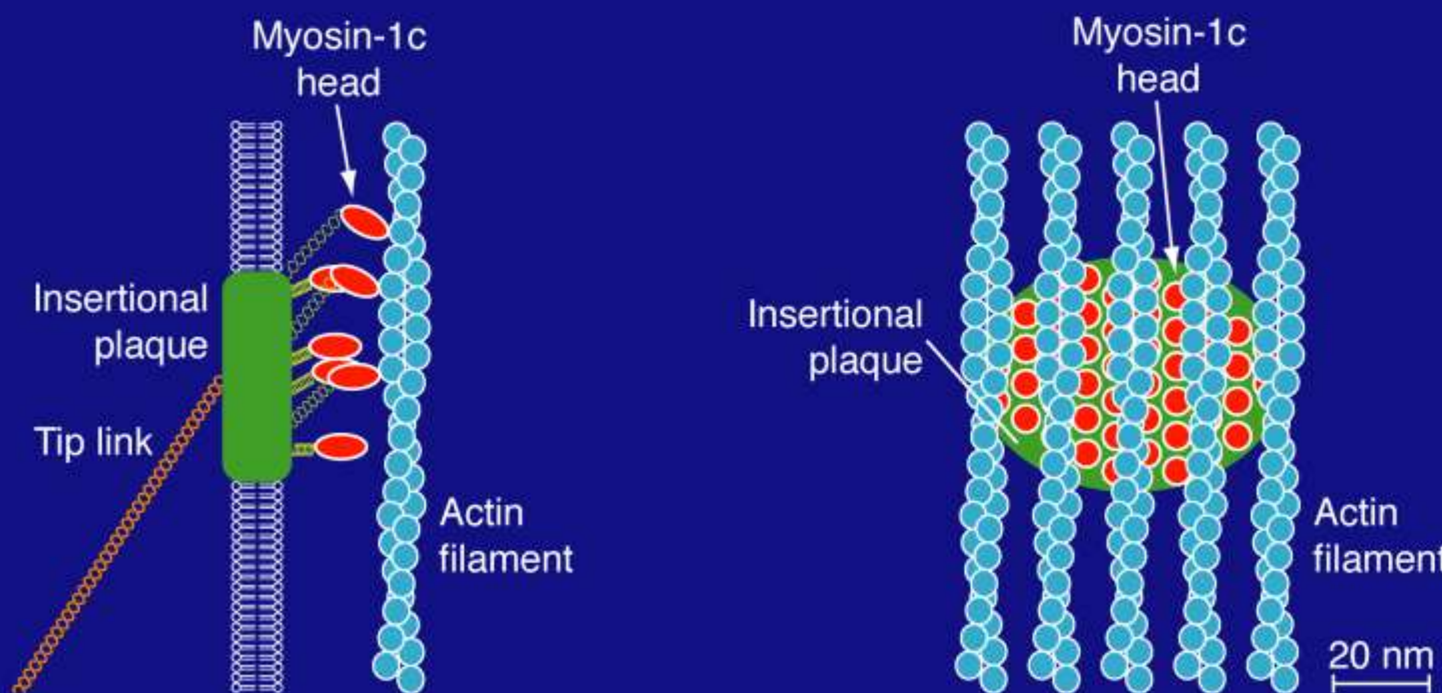


Mutant myosin-1c
with ordinary ATP

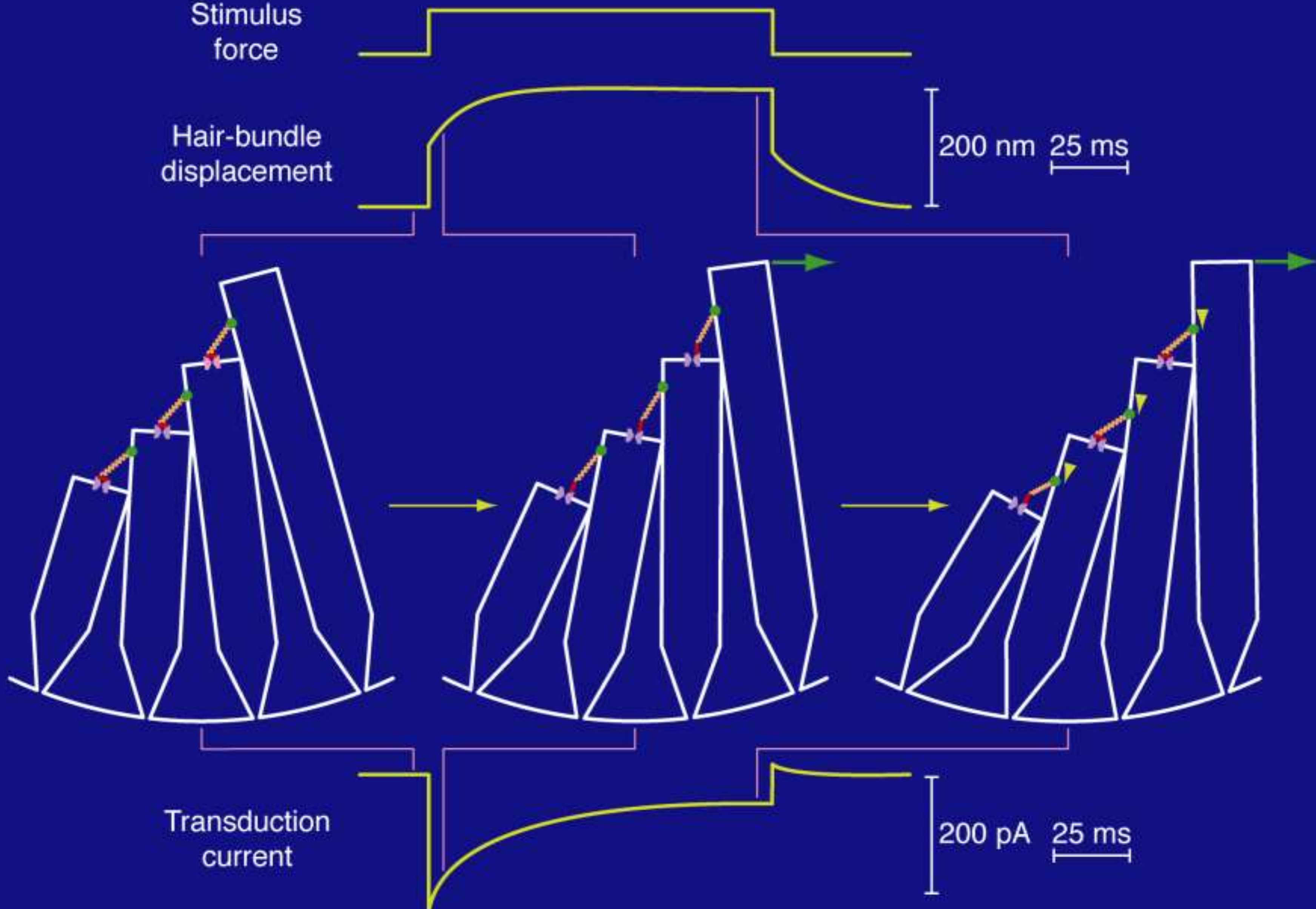


Mutant myosin-1c
with ADP analog

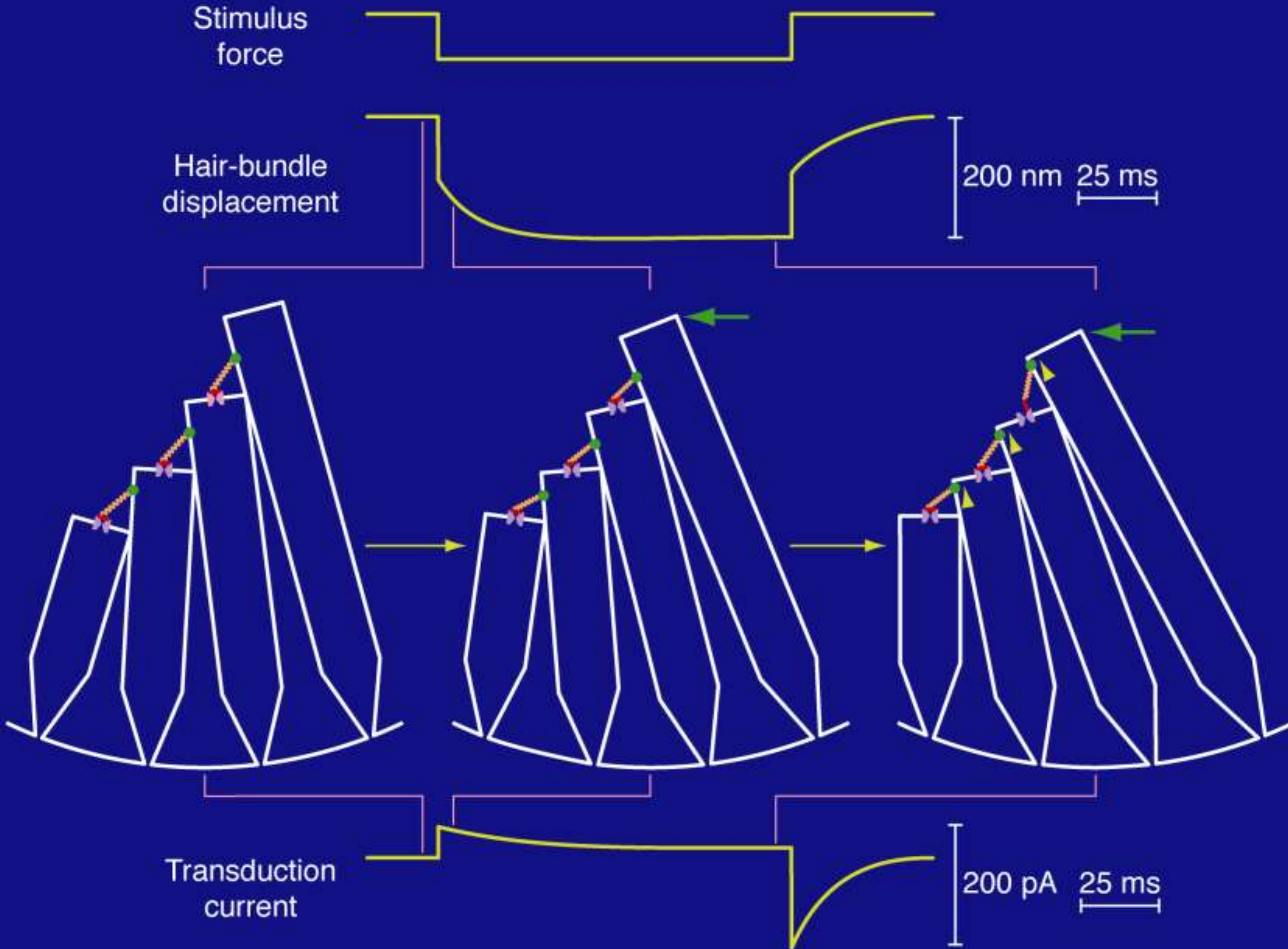
After Holt *et al.*, 2002

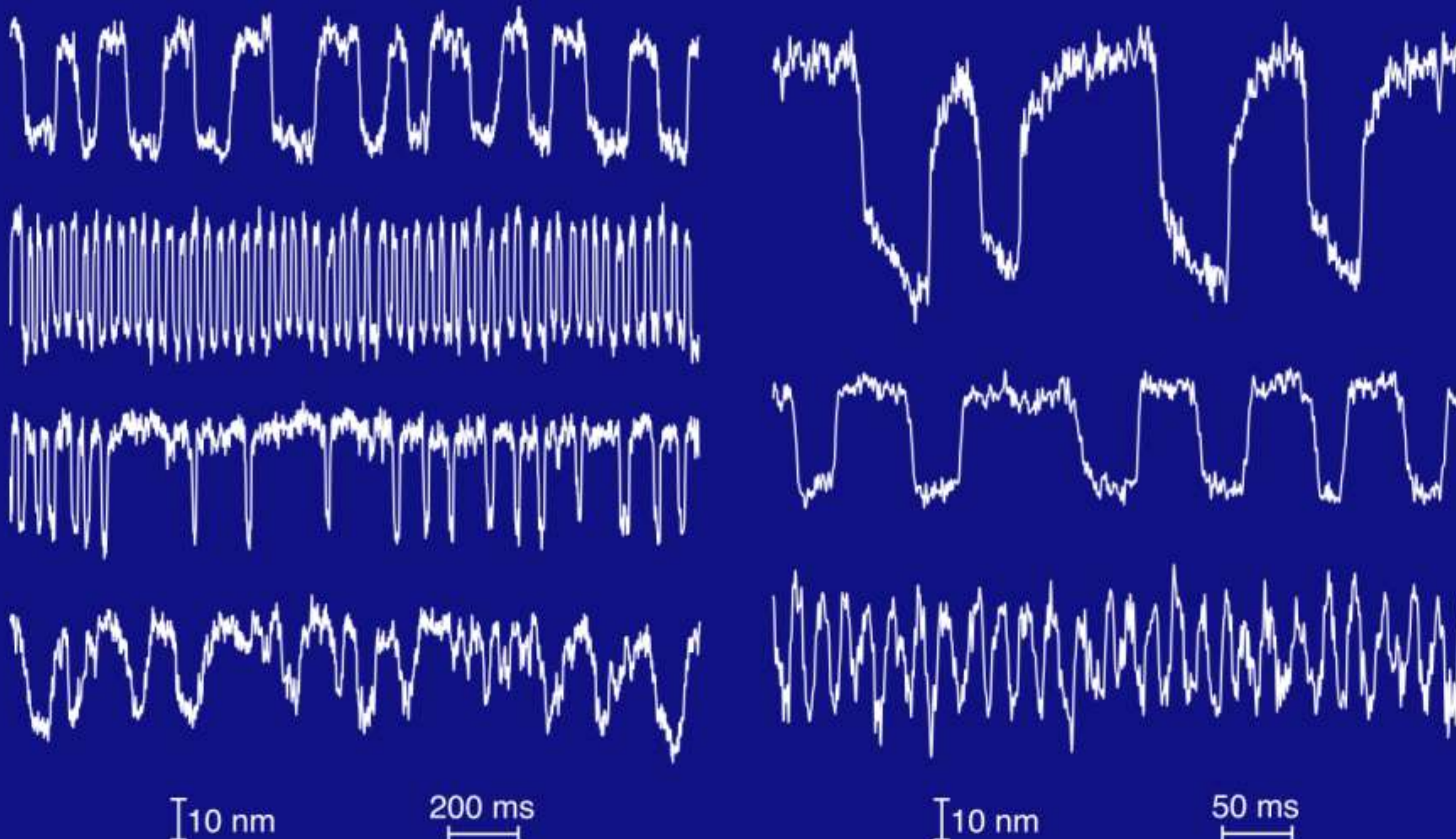


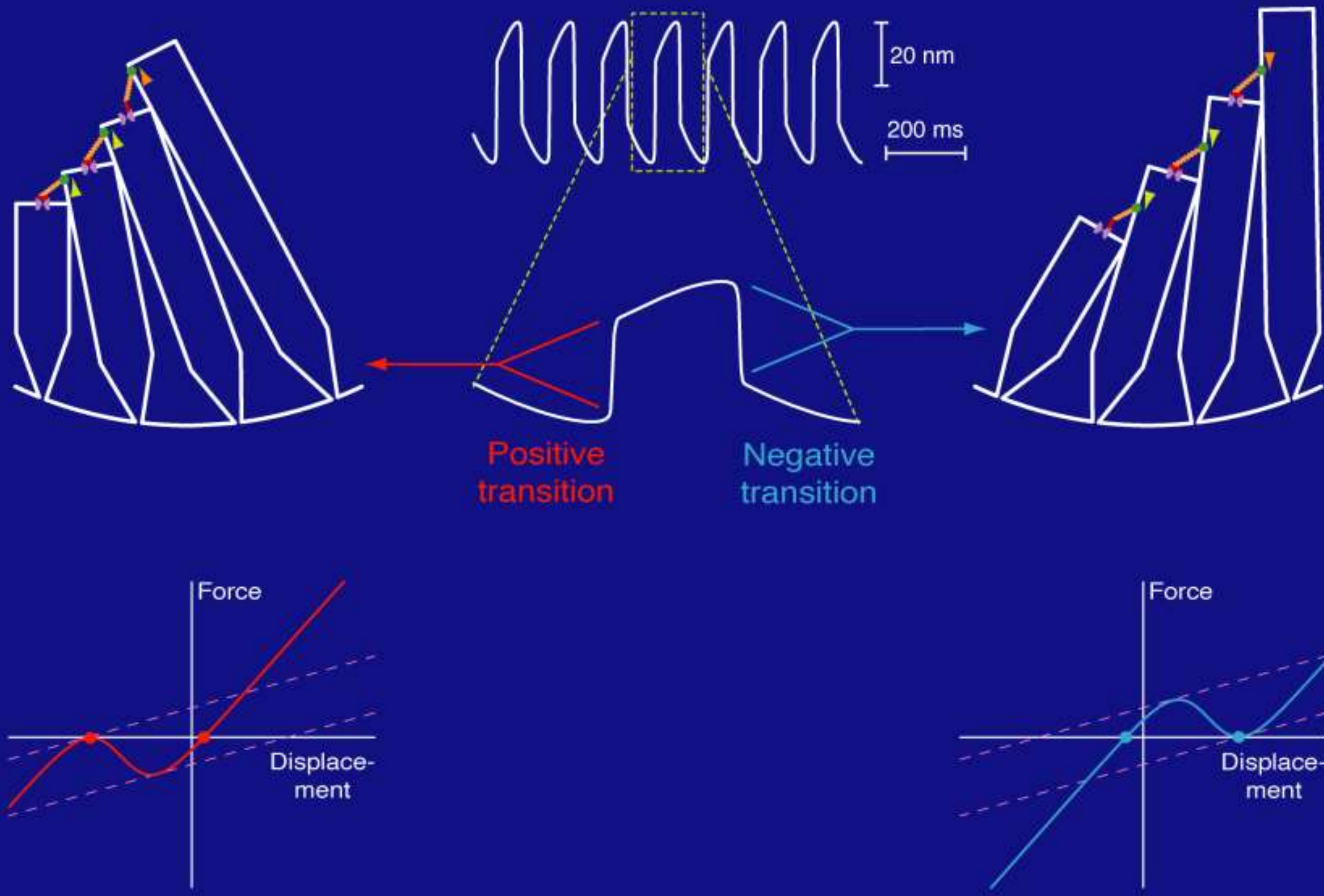
Myosin-1c head
Insertional plaque
Tip link
Actin filament
Myosin-1c head
Insertional plaque
Actin filament
20 nm



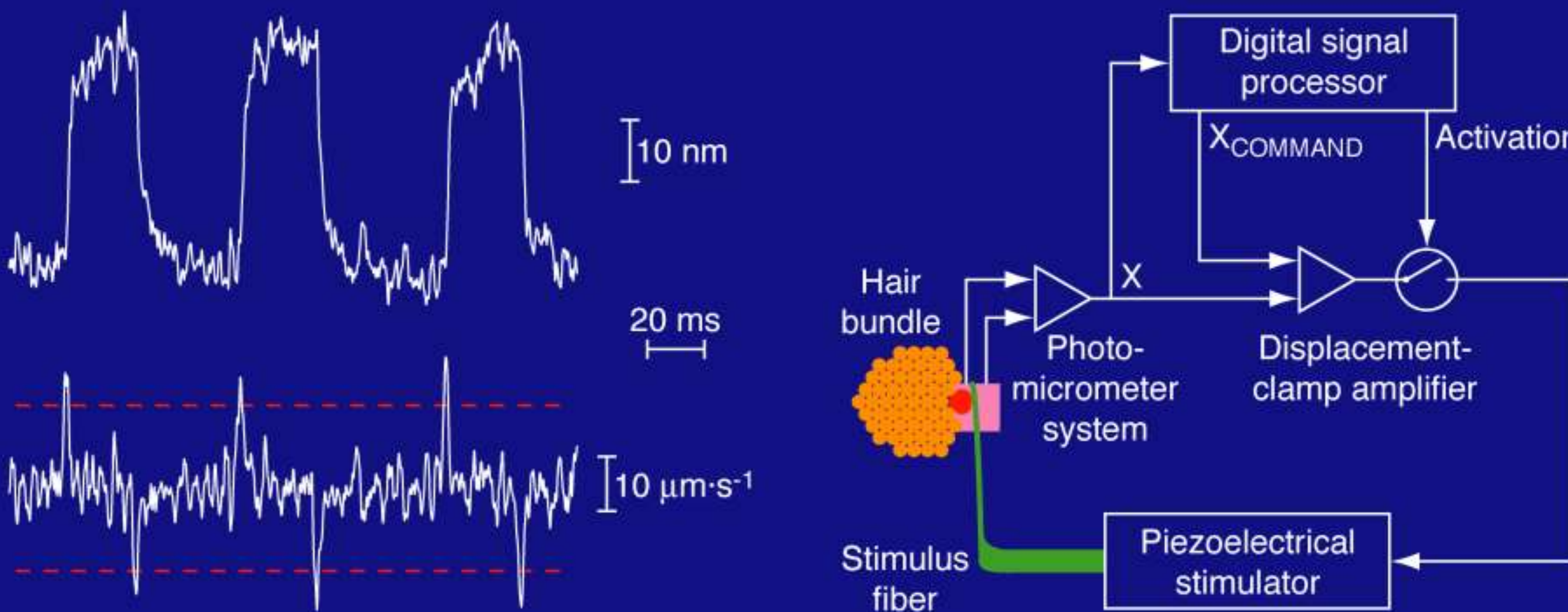
Stimulus
force
Hair-bundle
displacement
200 nm
25 ms
Transduction
current
200 pA
25 ms

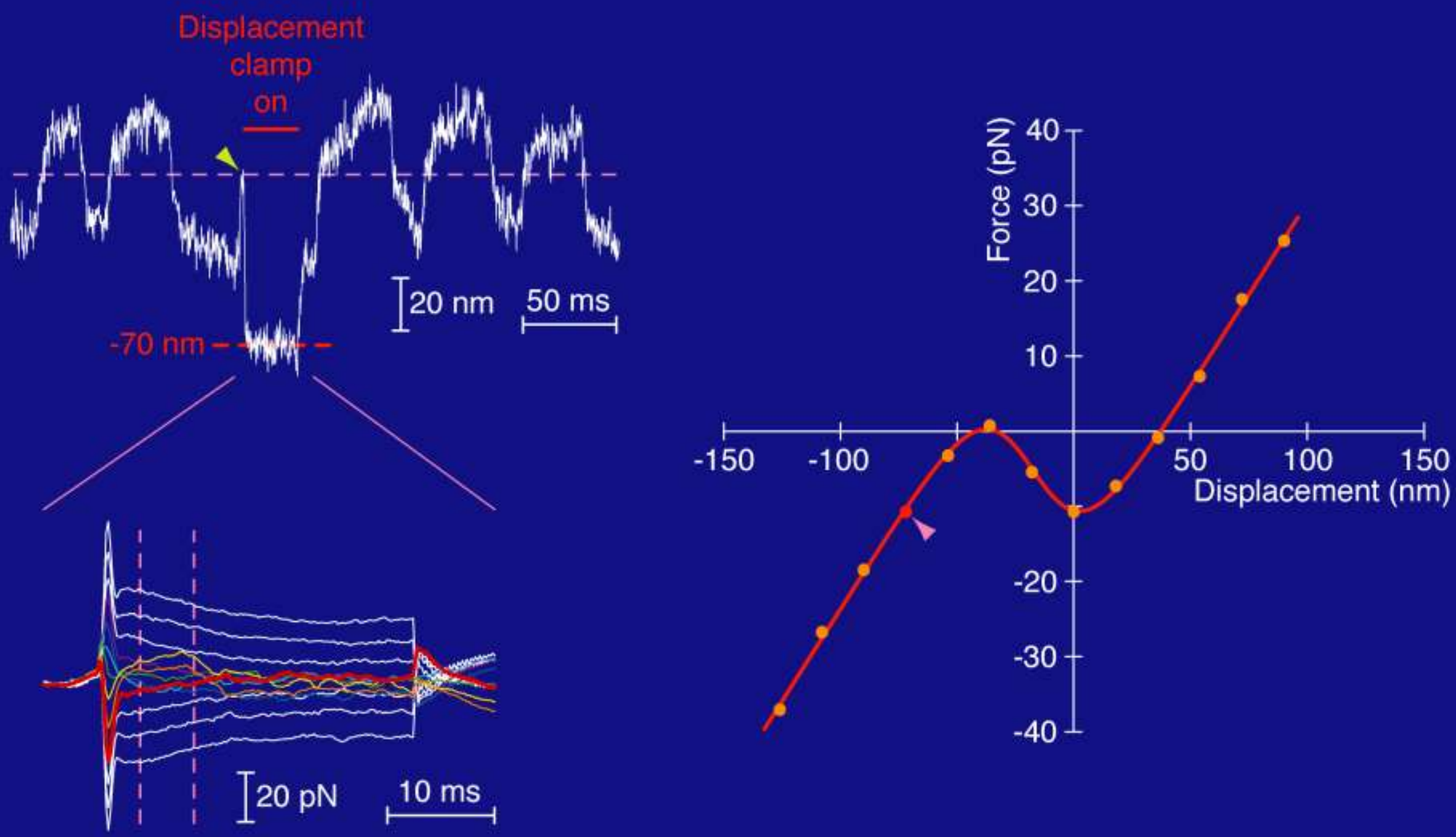

Stimulus
force
Hair-bundle
displacement
200 nm
25 ms
Transduction
current
200 pA
25 ms


10 nm
200 ms
10 nm
50 ms

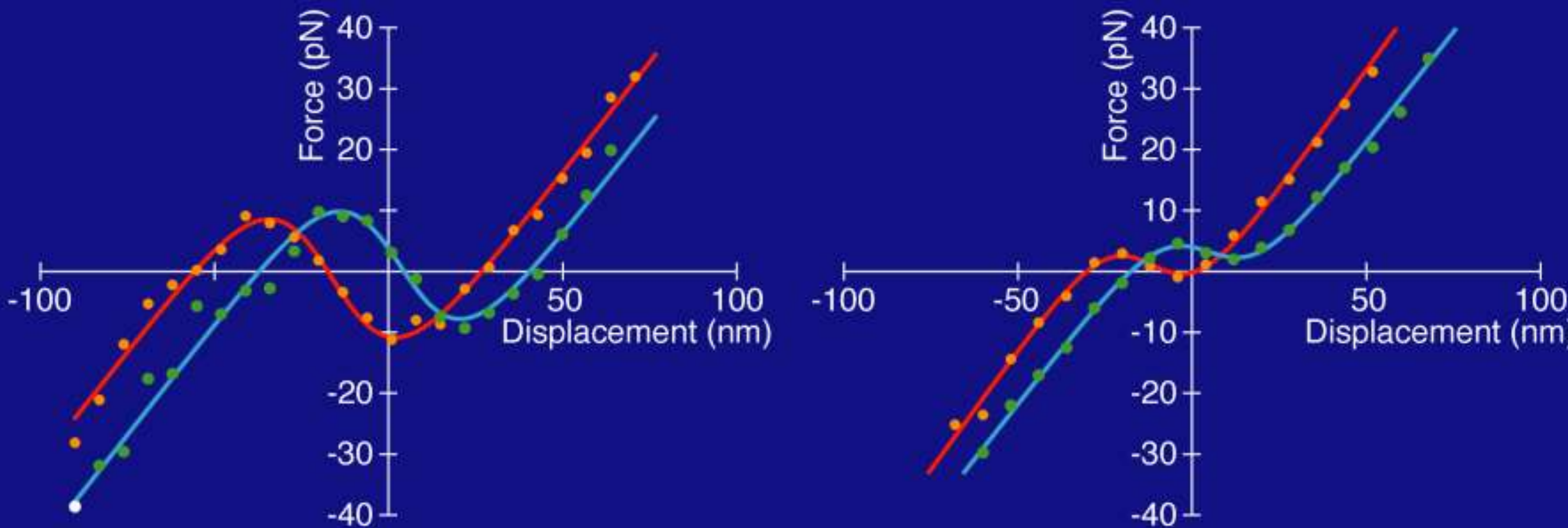


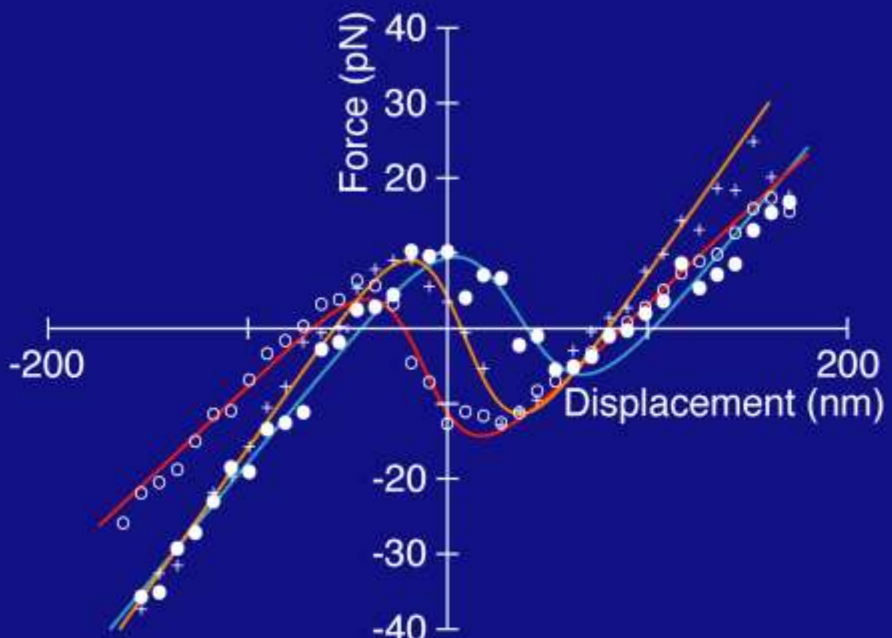
20 nm
200 ms
Positive transition
Negative transition
Force
Displace-ment
Force
Displace-ment


10 nm
20 ms
10 µm·s-1
Digital signal processor
XCOMMAND
Activation
Hair bundle
X
Photo-micrometer system
Displacement-clamp amplifier
Stimulus fiber
Piezoelectrical stimulator

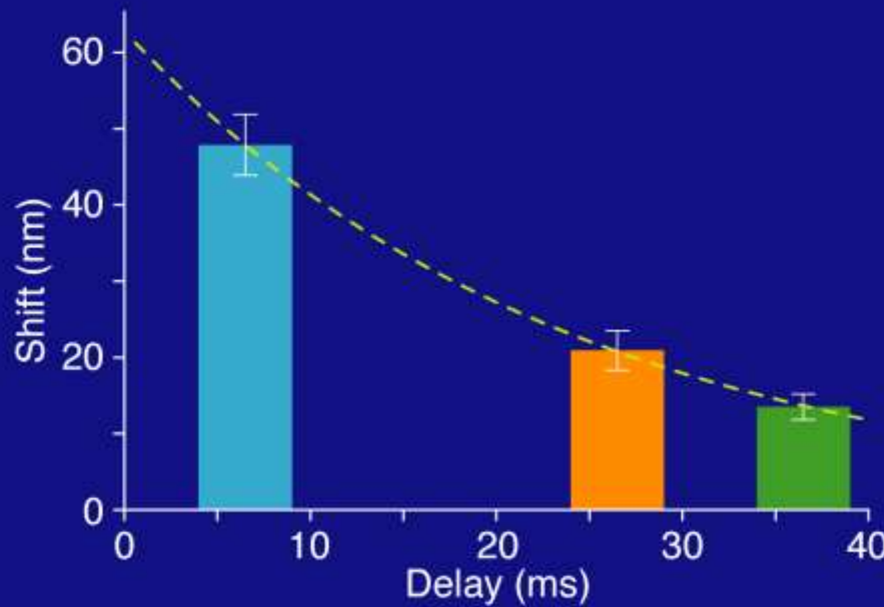


Displacement clamp on
20 nm
50 ms
-70 nm
20 pN
10 ms
Force (pN)
40
30
20
10
-20
-30
-40
-150
-100
50
100
150
Displacement (nm)

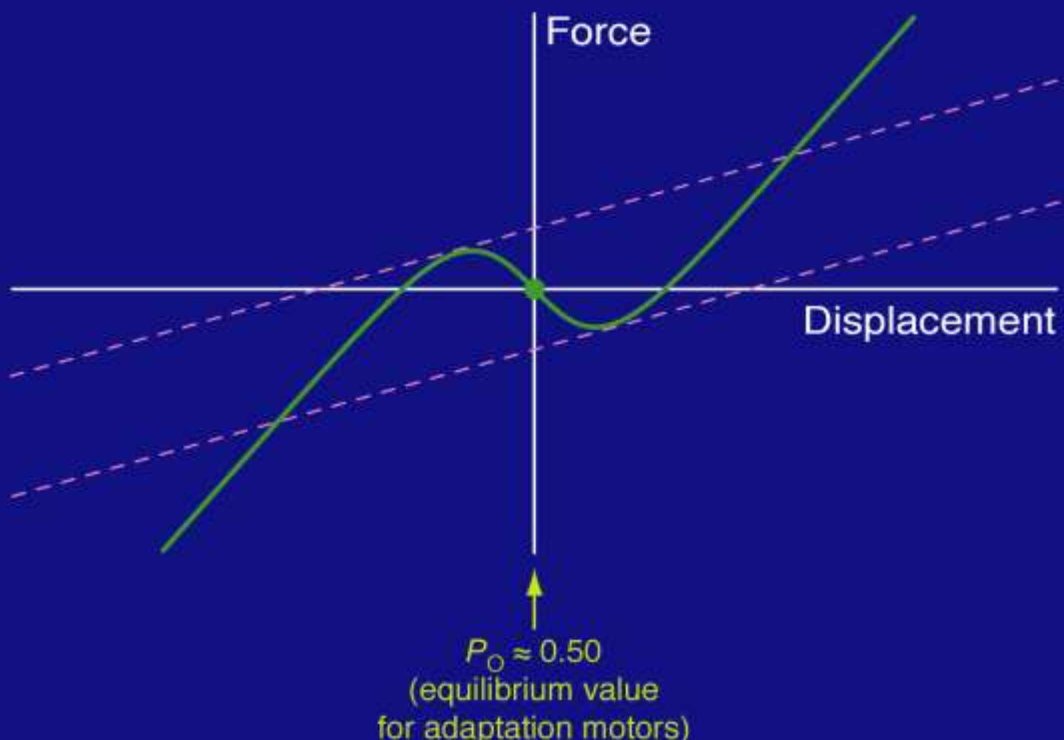

Force (pN)
40
30
20
-20
-30
-40
-100
50
100
Displacement (nm)
Force (pN)
40
30
20
10
-10
-20
-30
-40
-100
-50
50
100
Displacement (nm)

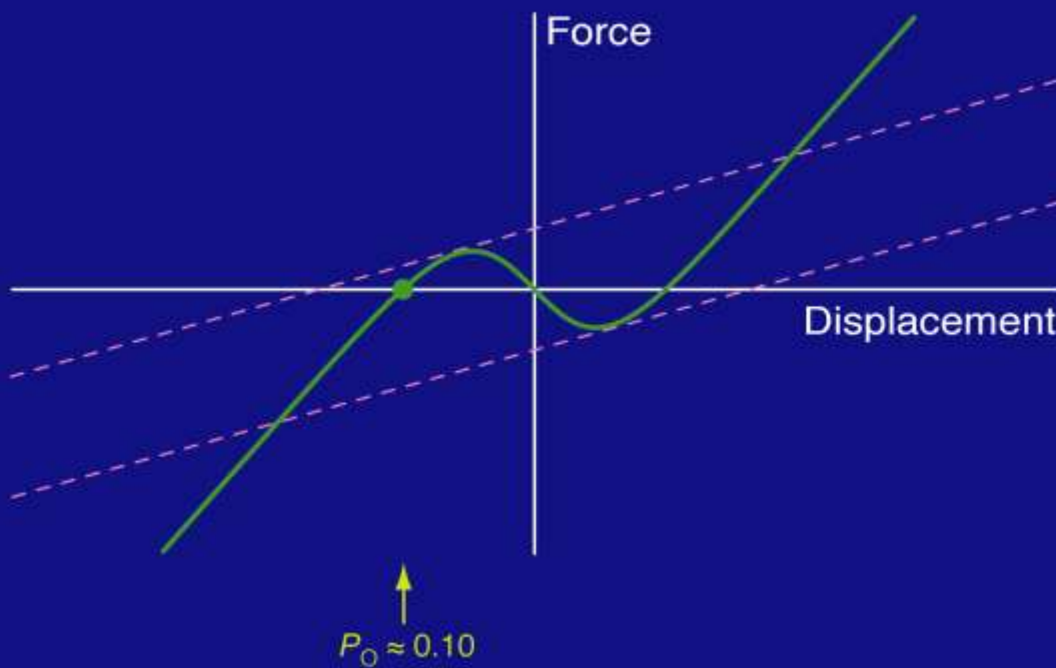


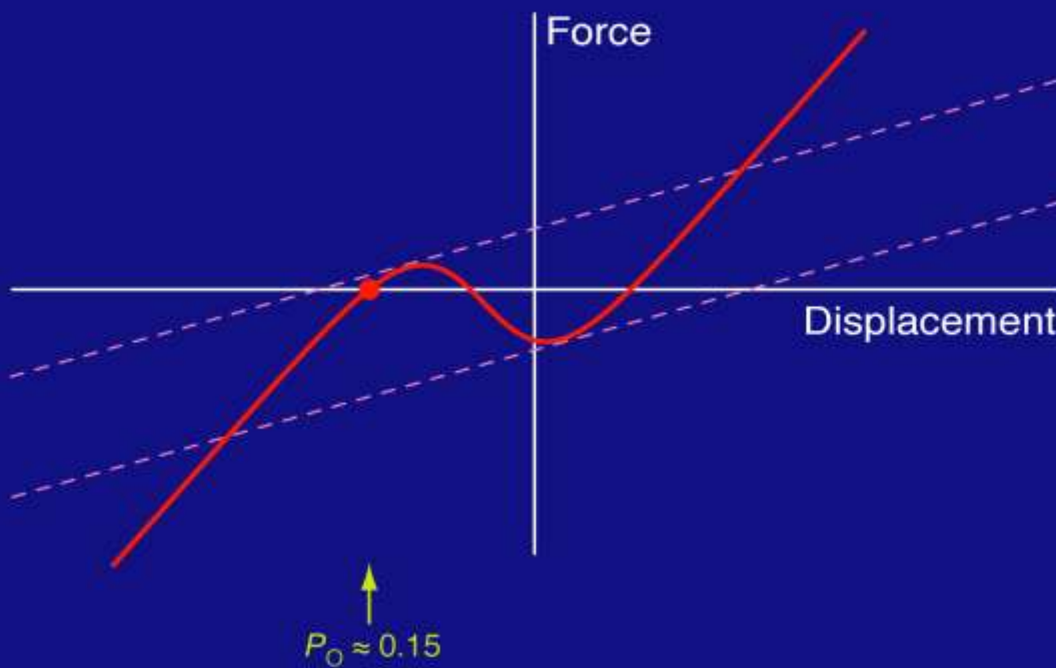
Force (pN)
40
30
20
-20
-30
-40
-200
200
Displacement (nm)

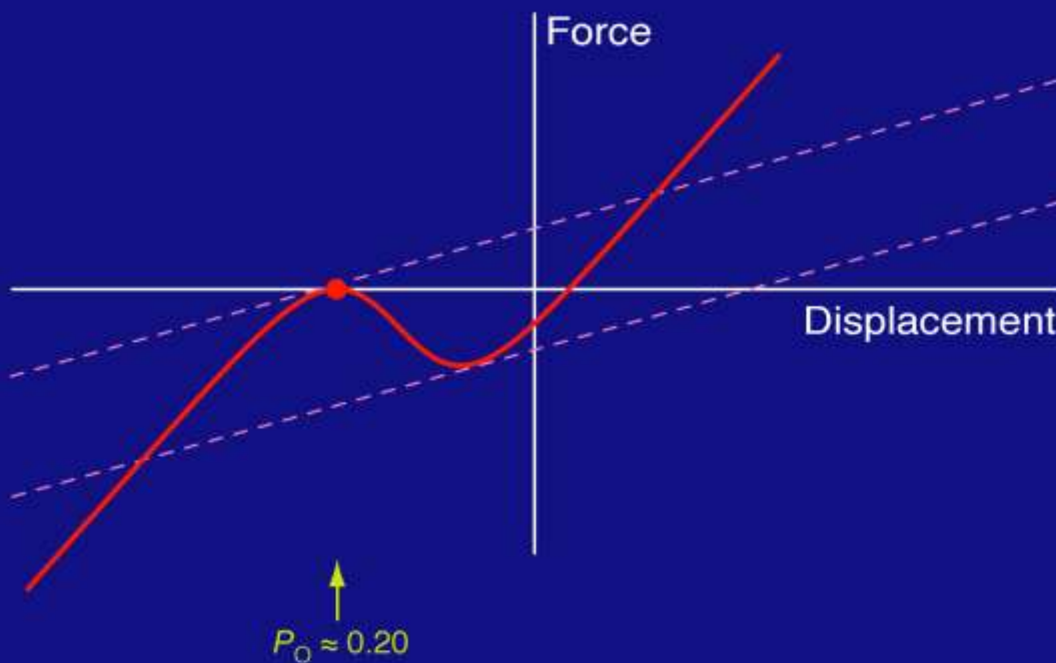


Shift (nm)
60
40
20
0
0
10
20
30
40
Delay (ms)

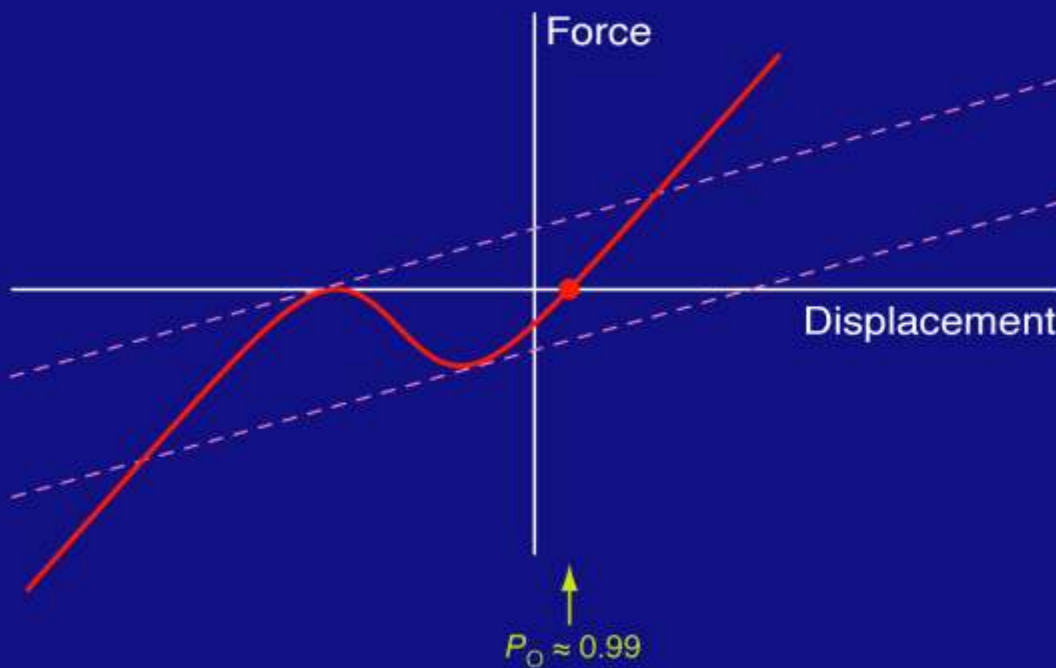

Force
Displacement
$P_O \approx 0.50$
(equilibrium value
for adaptation motors)

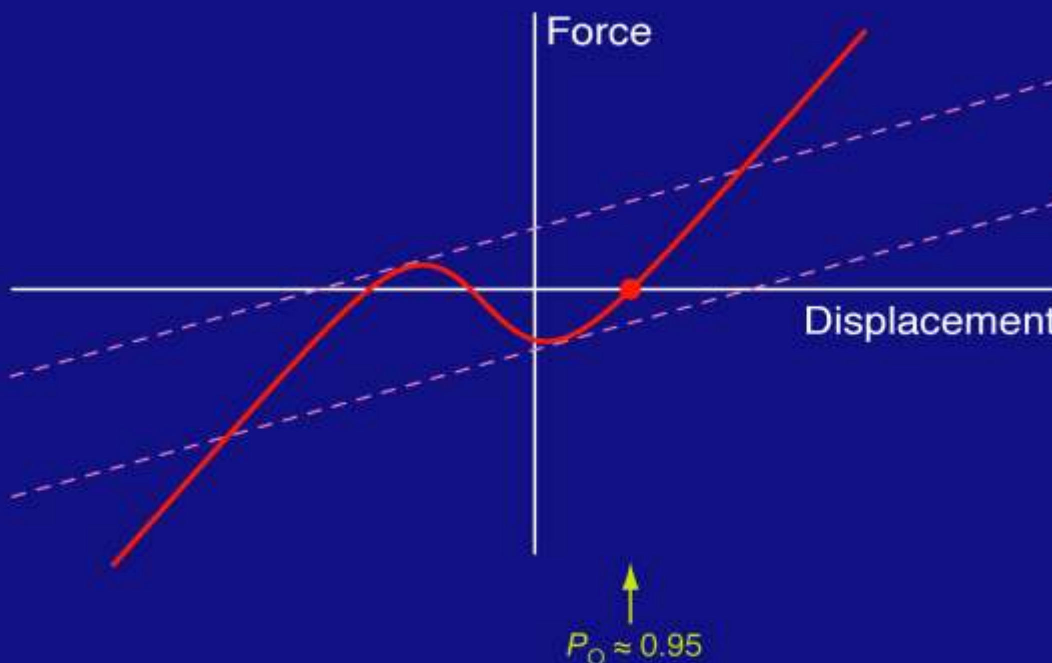

Force
Displacement
$P_O \approx 0.10$

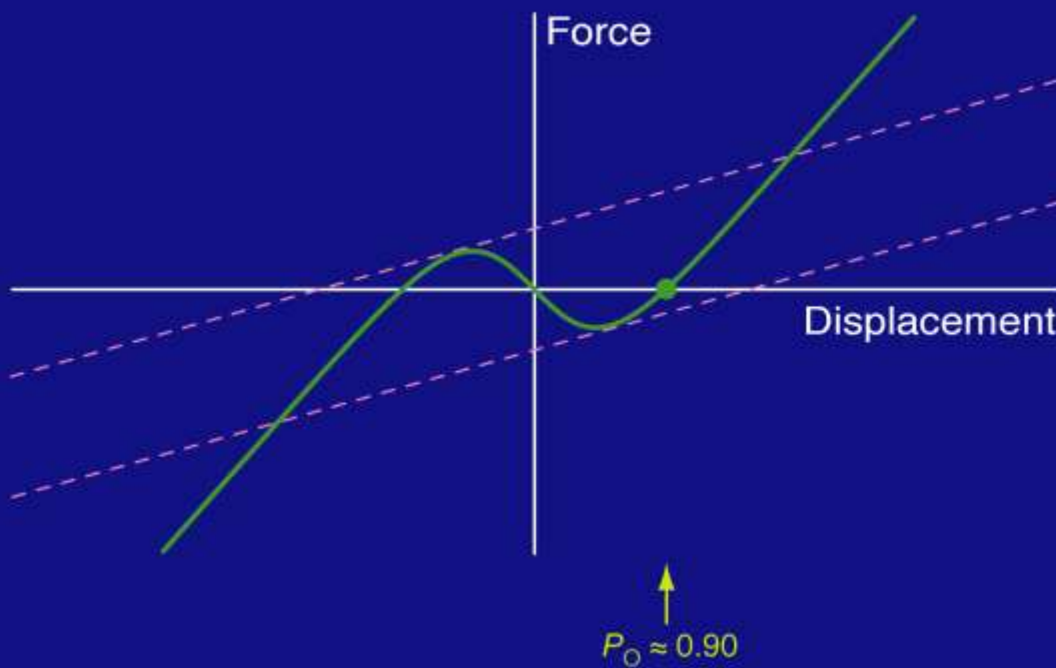

Force
Displacement
$P_O \approx 0.15$

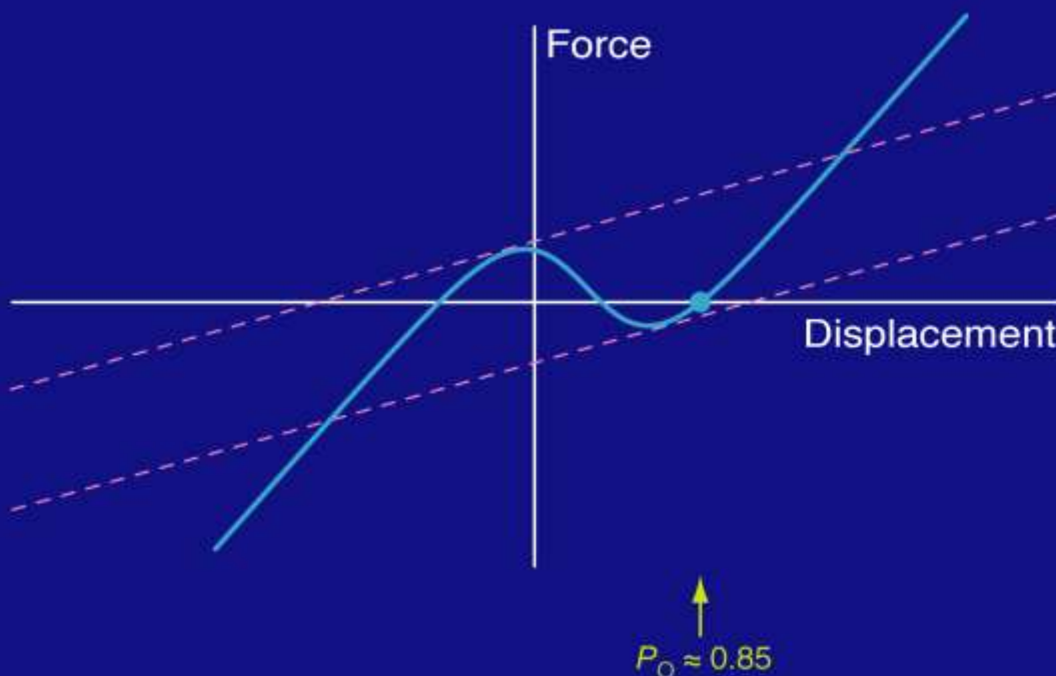


Force
Displacement
$P_O \approx 0.20$

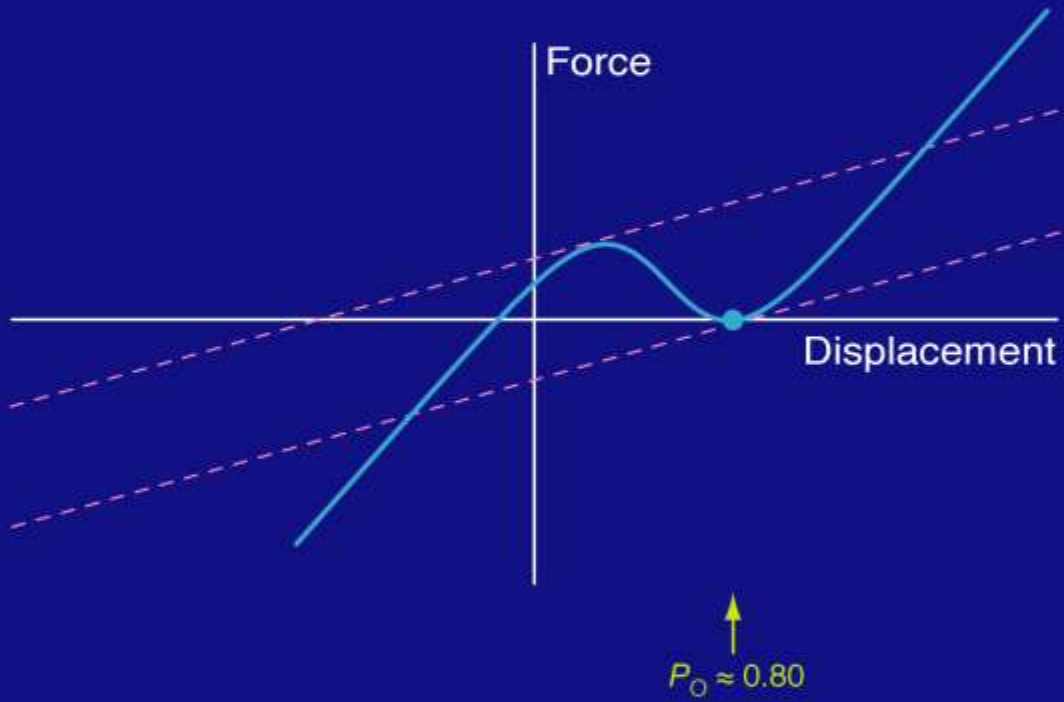

Force
Displacement
$P_O \approx 0.99$

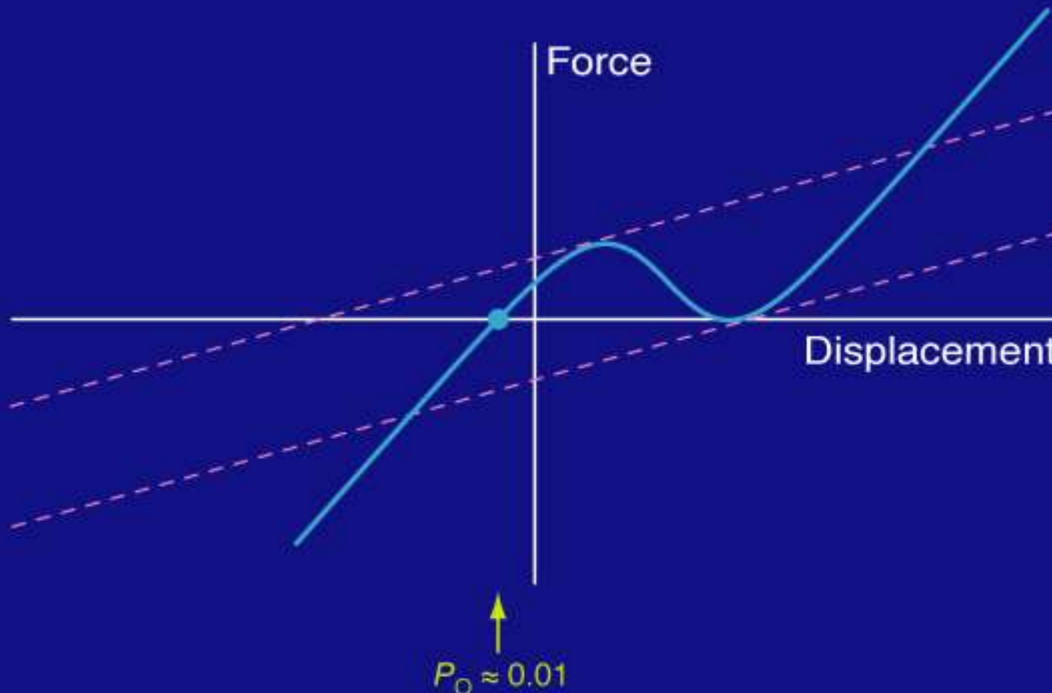

Force
Displacement
$P_O \approx 0.95$


Force
Displacement
$P_O \approx 0.90$

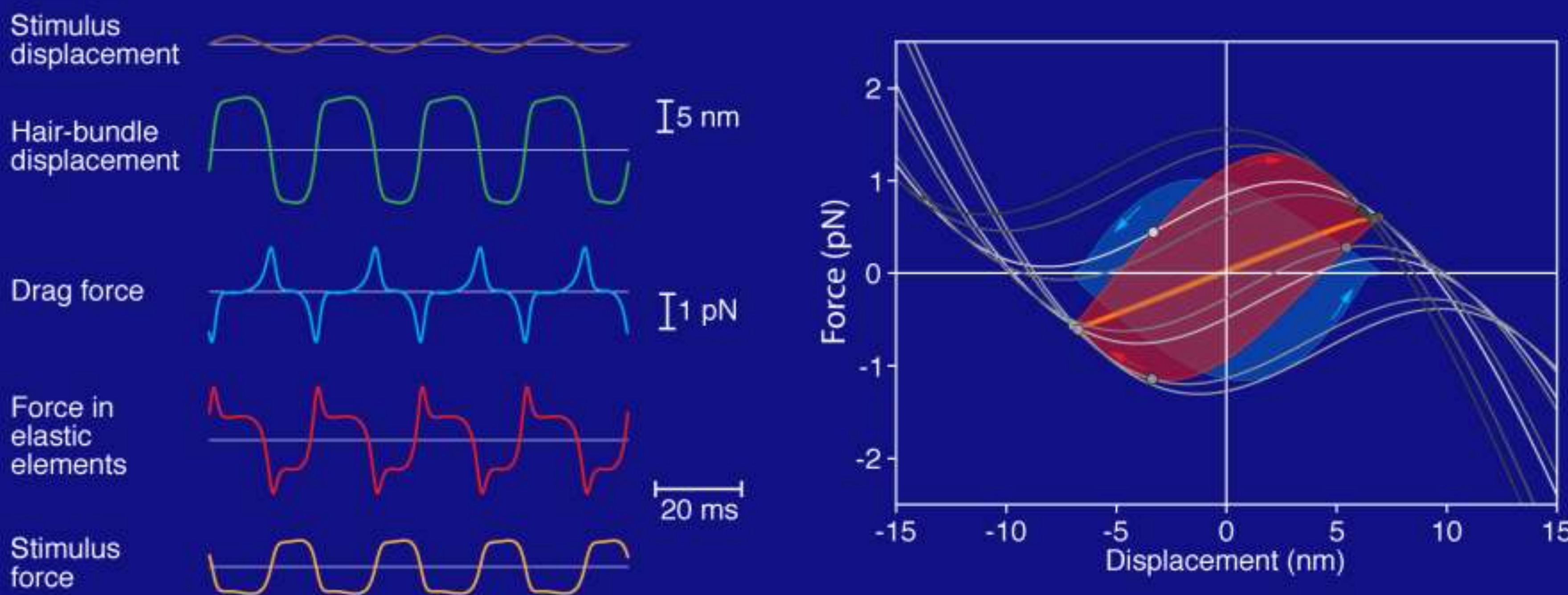


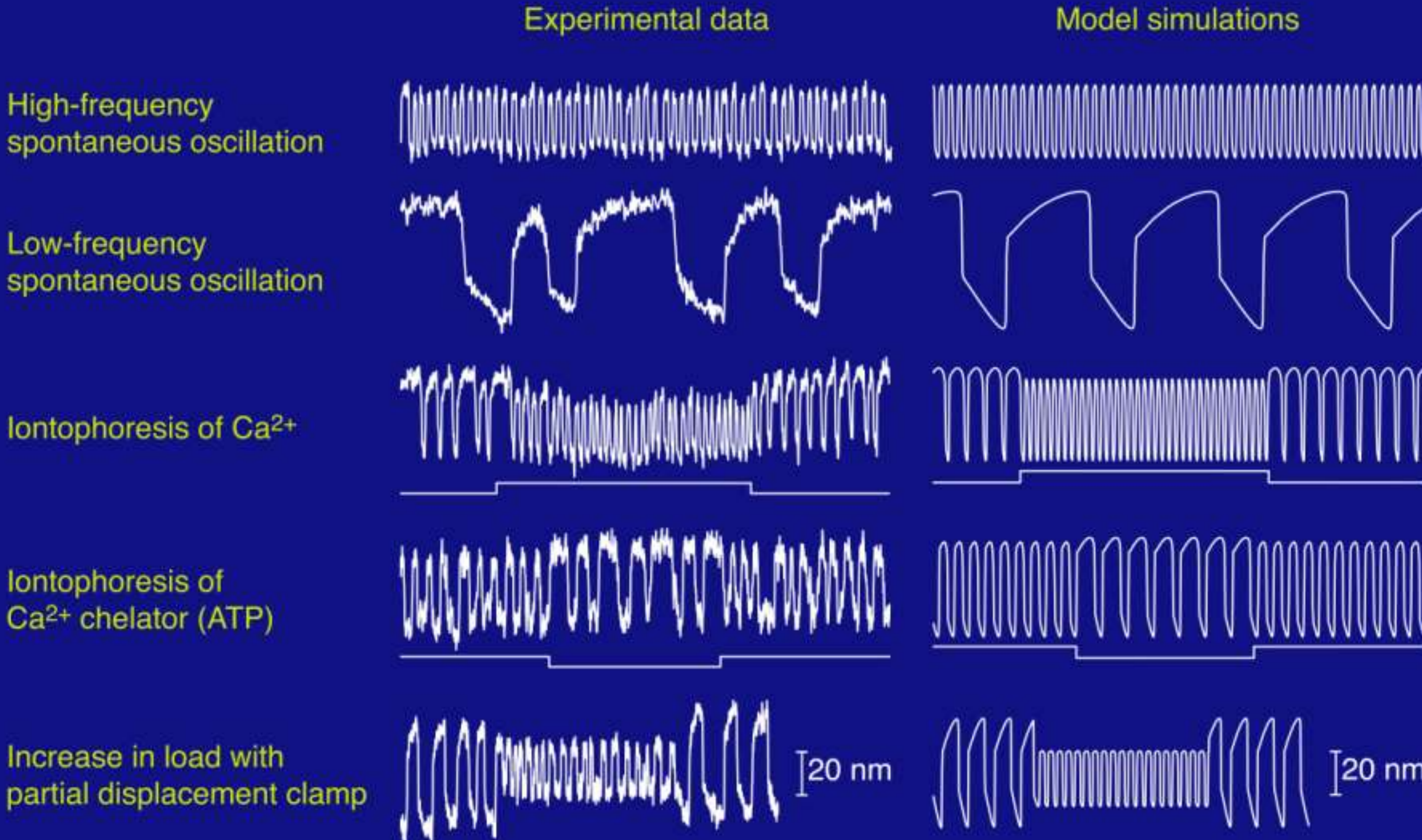
Force
Displacement
$P_O \approx 0.85$


Force
Displacement
$P_O \approx 0.80$

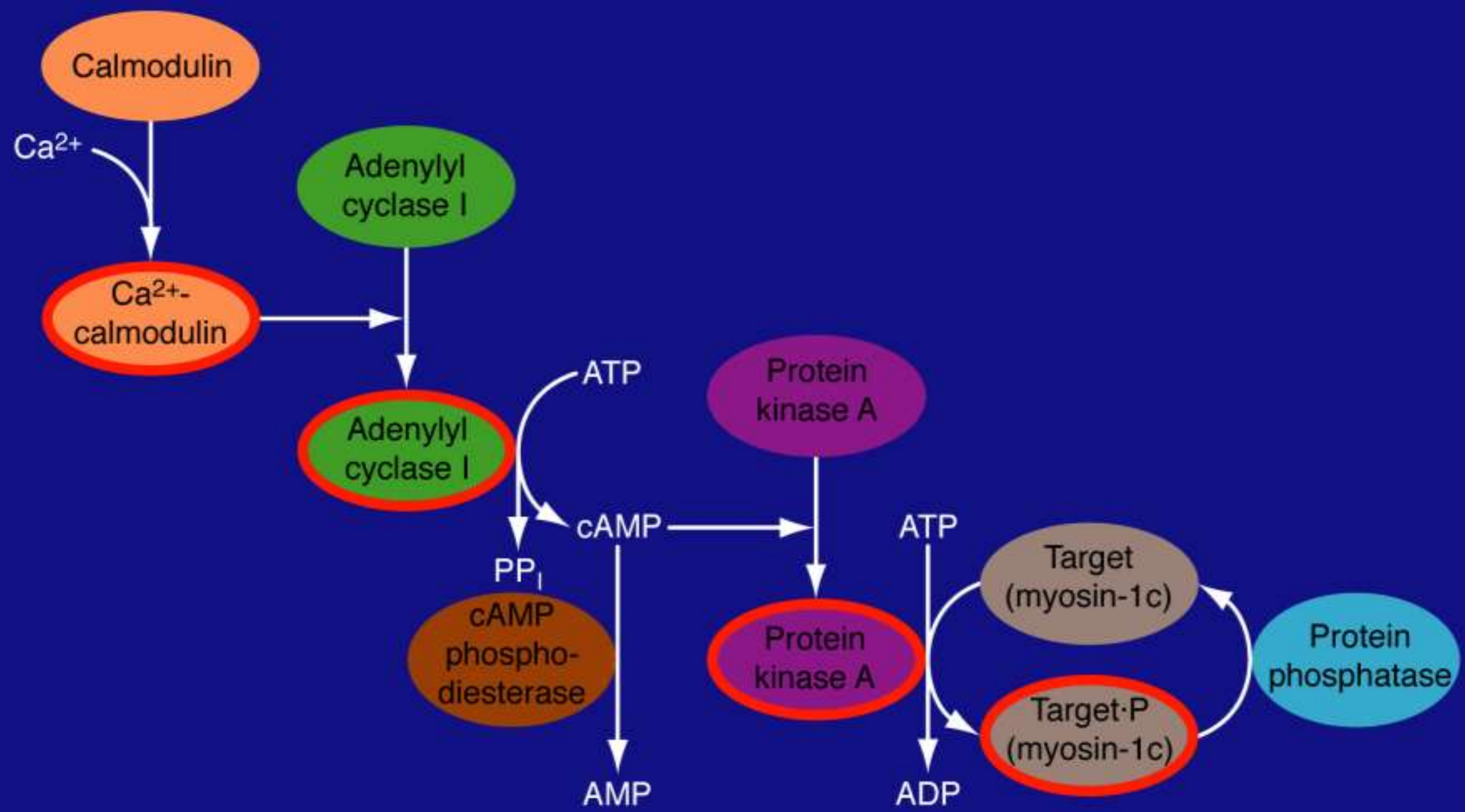


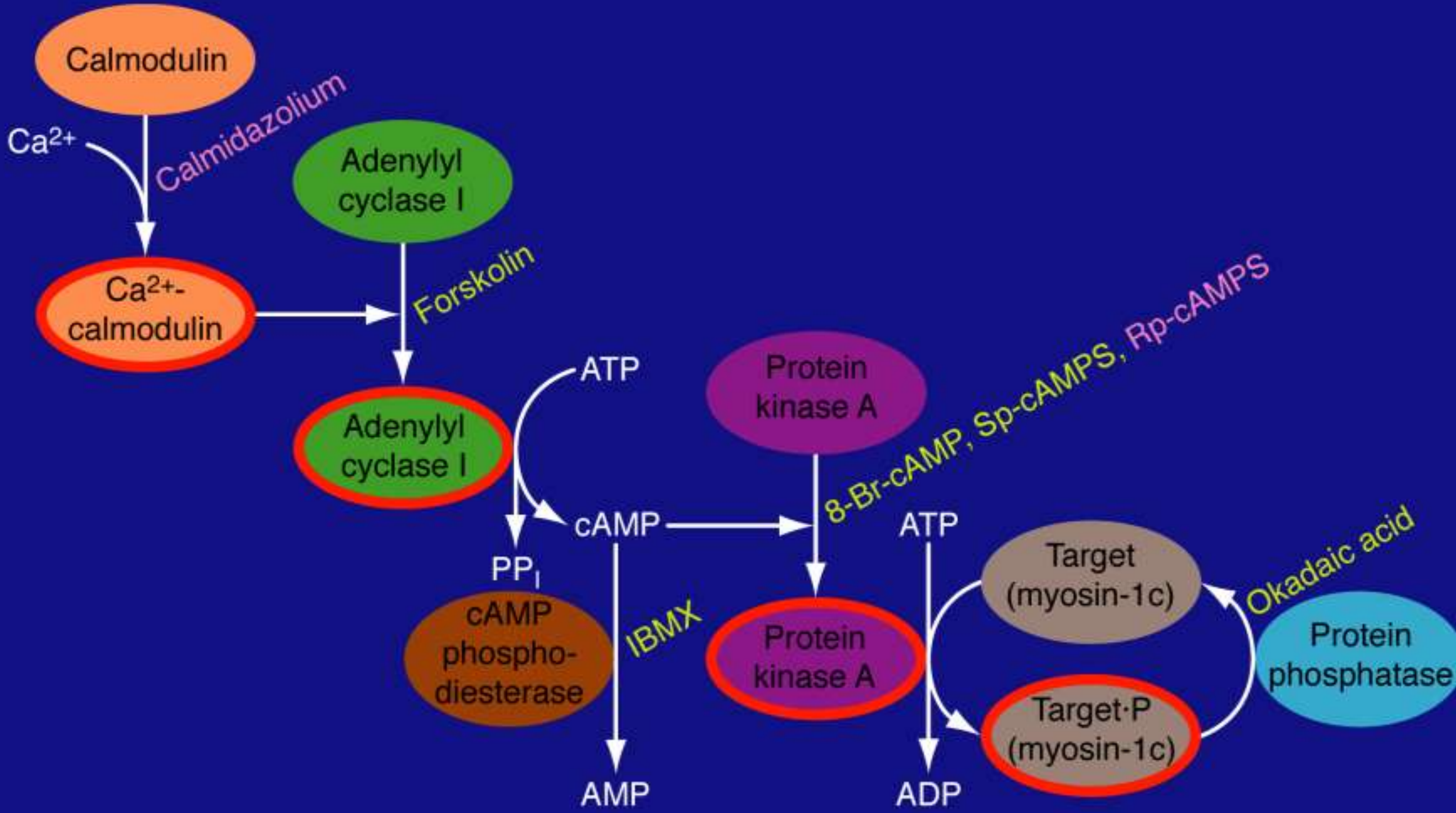
Force
Displacement
$P_O \approx 0.01$


Stimulus displacement
Hair-bundle displacement
5 nm
Drag force
1 pN
Force in elastic elements
20 ms
Stimulus force
Force (pN)
2
1
0
-1
-2
-15
-10
-5
0
5
10
15
Displacement (nm)

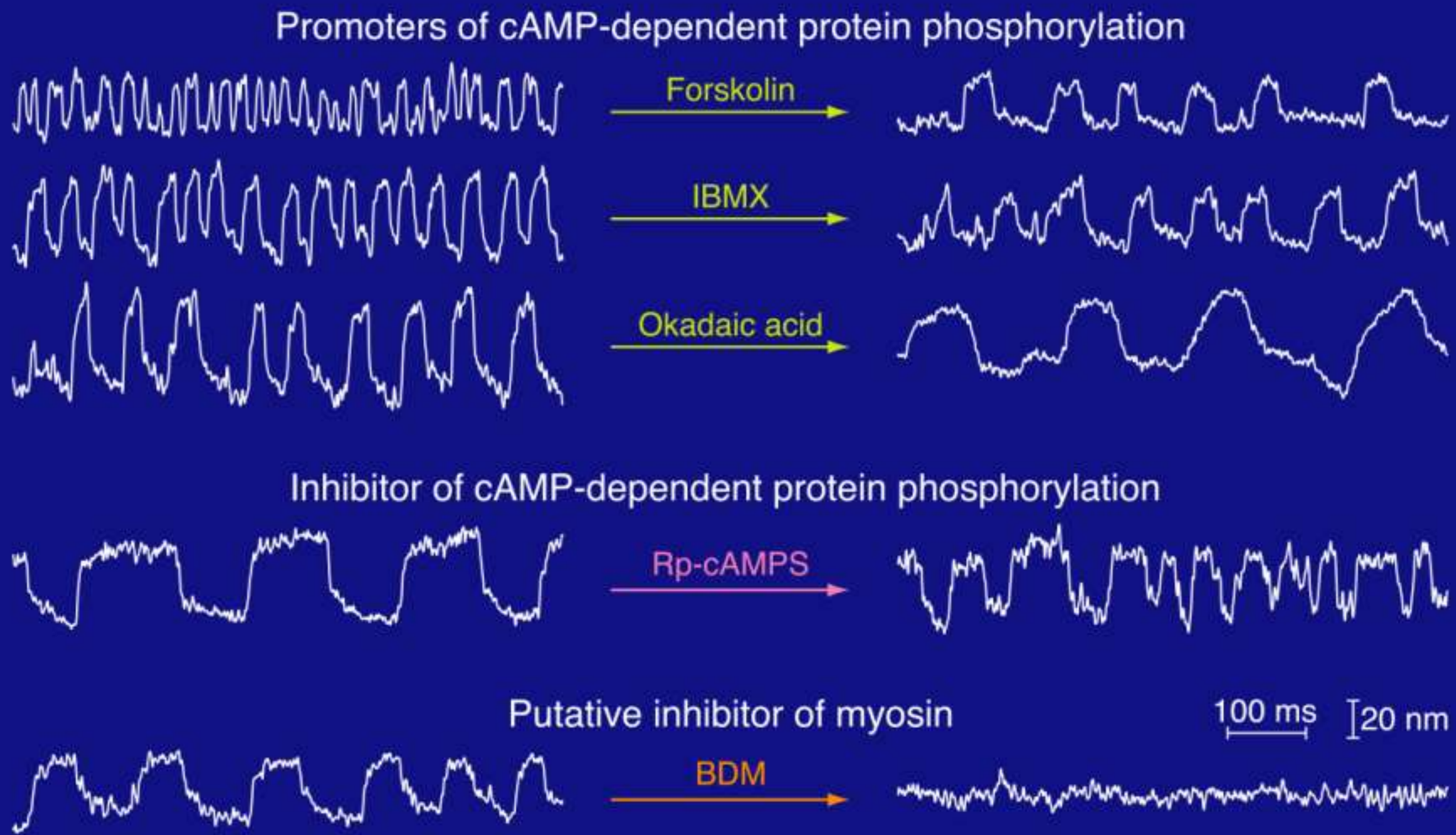


Experimental data
Model simulations
High-frequency spontaneous oscillation
Low-frequency spontaneous oscillation
Iontophoresis of Ca2+
Iontophoresis of Ca2+ chelator (ATP)
Increase in load with partial displacement clamp
20 nm
20 nm


Calmodulin
Ca2+
Ca2+-calmodulin
Adenylyl cyclase I
Adenylyl cyclase I
ATP
PPi
cAMP
cAMP phosphodiesterase
AMP
Protein kinase A
Protein kinase A
ATP
ADP
Target (myosin-1c)
Target·P (myosin-1c)
Protein phosphatase



Calmodulin
Ca2+
Calmidazolium
Adenylyl cyclase I
Ca2+-calmodulin
Forskolin
ATP
Protein kinase A
8-Br-cAMP, Sp-cAMPS, Rp-cAMPS
Adenylyl cyclase I
cAMP
PPi
ATP
Target (myosin-1c)
Okadaic acid
cAMP phospho-diesterase
IBMX
Protein kinase A
Protein phosphatase
Target·P (myosin-1c)
AMP
ADP


Promoters of cAMP-dependent protein phosphorylation
Forskolin
IBMX
Okadaic acid
Inhibitor of cAMP-dependent protein phosphorylation
Rp-cAMPS
Putative inhibitor of myosin
100 ms
20 nm
BDM