Active contractility of adherent cells

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Cell biophysics

Why cells are called cells

MICROGRAPHIA:

OR SOME

Physiological Descriptions

OF

MINUTE BODIES

MADE BY

MAGNIFYING GLASSES

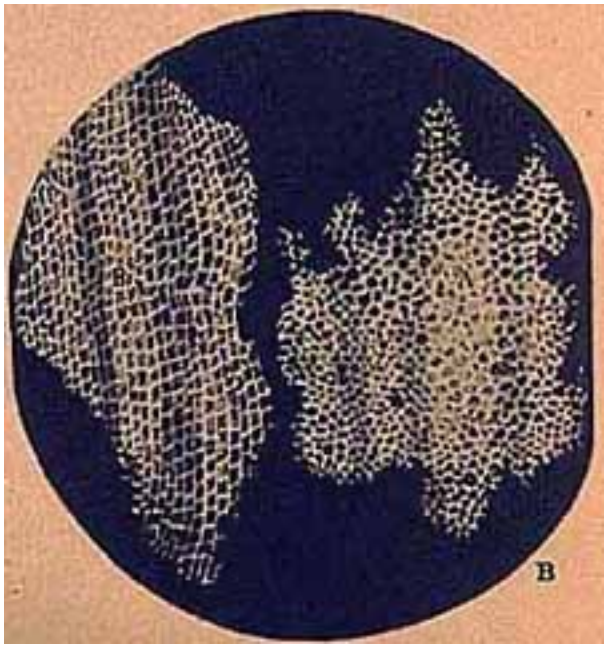
WITH

OBSERVATIONS and INQUIRIES thereupon.

By *R. HOOKE*, Fellow of the ROYAL SOCIETY.

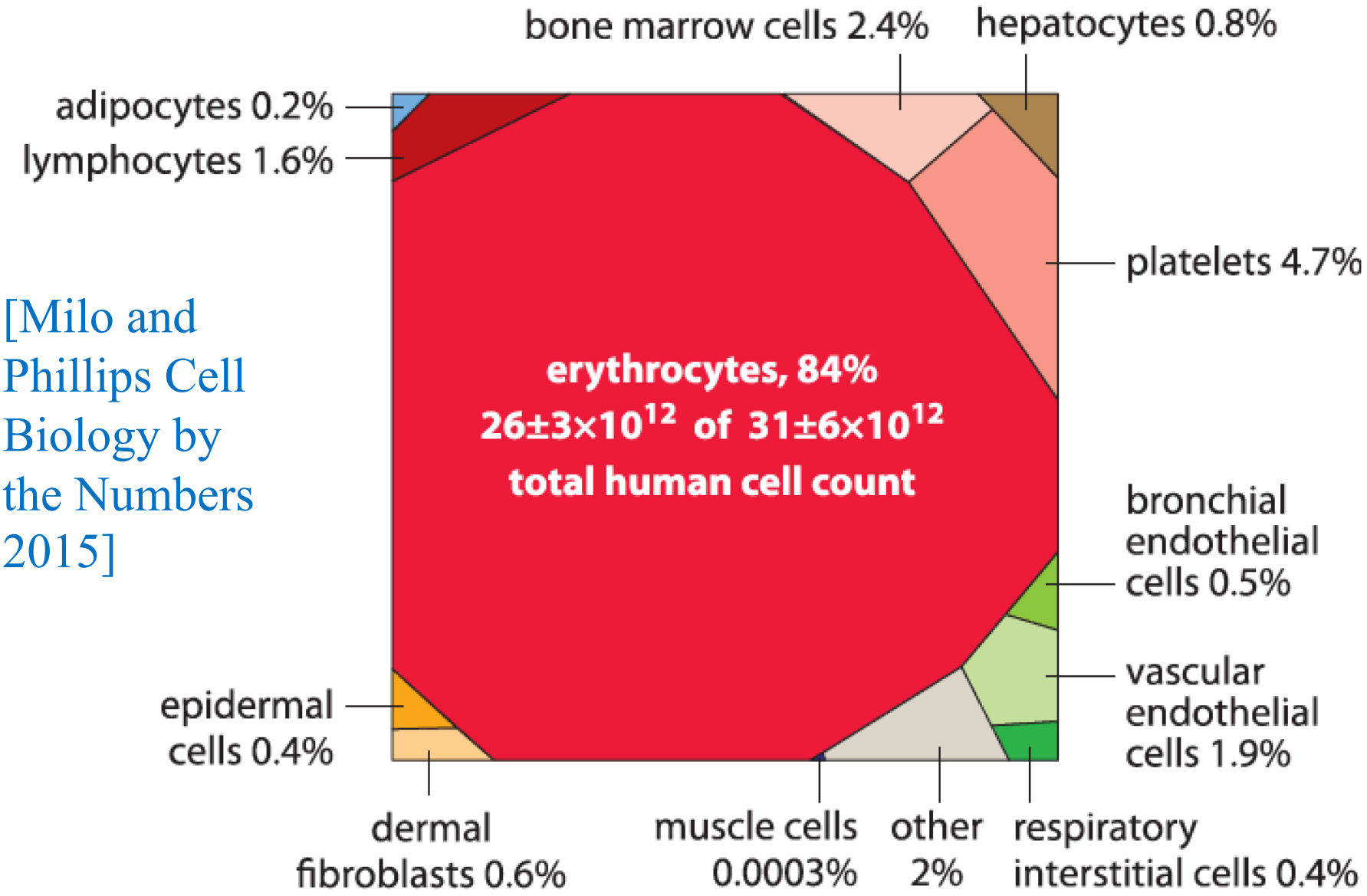
Nampossis oculo quantum contendere Lynceus,
Non tamen idcirco contemnas Lippus inungi. Horat. Ep. lib. 1.

LONDON, Printed by *Jo. Martyn*, and *Ja. Allestry*, Printers to the ROYAL SOCIETY, and are to be sold at their Shop at the *Bell* in S. *Paul's* Church-yard. M DC LX V.



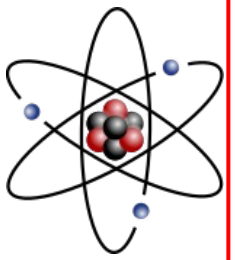
In 1665, the box-like compartments in cork reminded Robert Hooke of cells in a monastry

Breakdown of cell types in humans

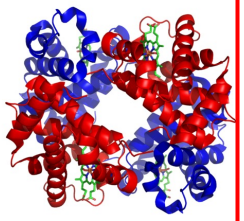


[Milo and Phillips Cell Biology by the Numbers 2015]

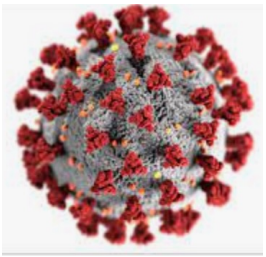
Biological systems are multiscale



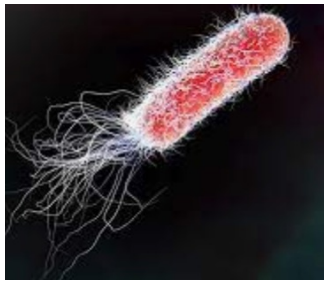
atom
1 A



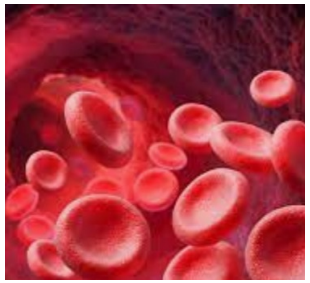
molecule
1 nm



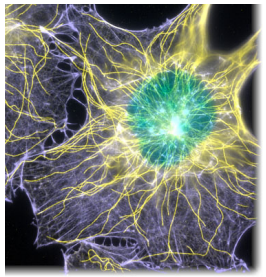
virus
100 nm



bacterium
5 um



RBC
8 um



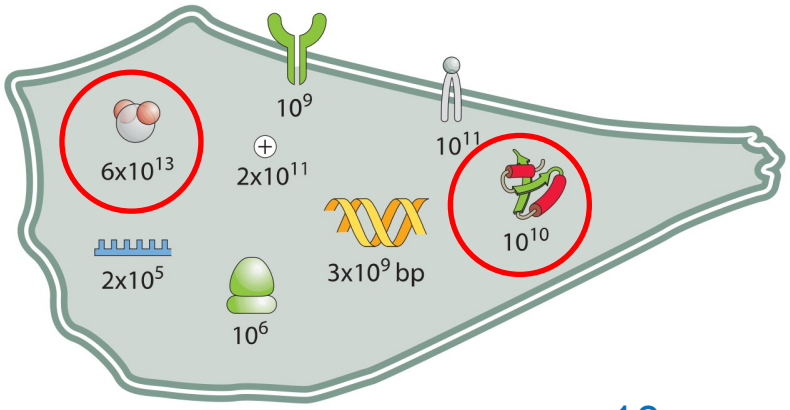
skin cell
50 um

cryo-EM, superresolution microscopy

electron microscopy

diffraction limit

Inventary of a human cell



[Ron Milo and Rob Phillips, Cell Biology by the Numbers 2015]

- 70% water
- Different kinds of biomolecules (dry mass): proteins (60%), lipids (13%), RNA (4%), DNA (1%)
- 10^{10} proteins per cell, concentration $10^7/\mu m^3$ = mM, distance 10 nm
- Each protein is surrounded by a water layer. The distance of 10 nm leaves lots of space for movement.
- Two equations determine the movement of the biomolecules:
  - Equipartition theorem

$$\frac{1}{2}mv^2 = \frac{k_B T}{2} \Rightarrow v = 10\frac{m}{s}$$

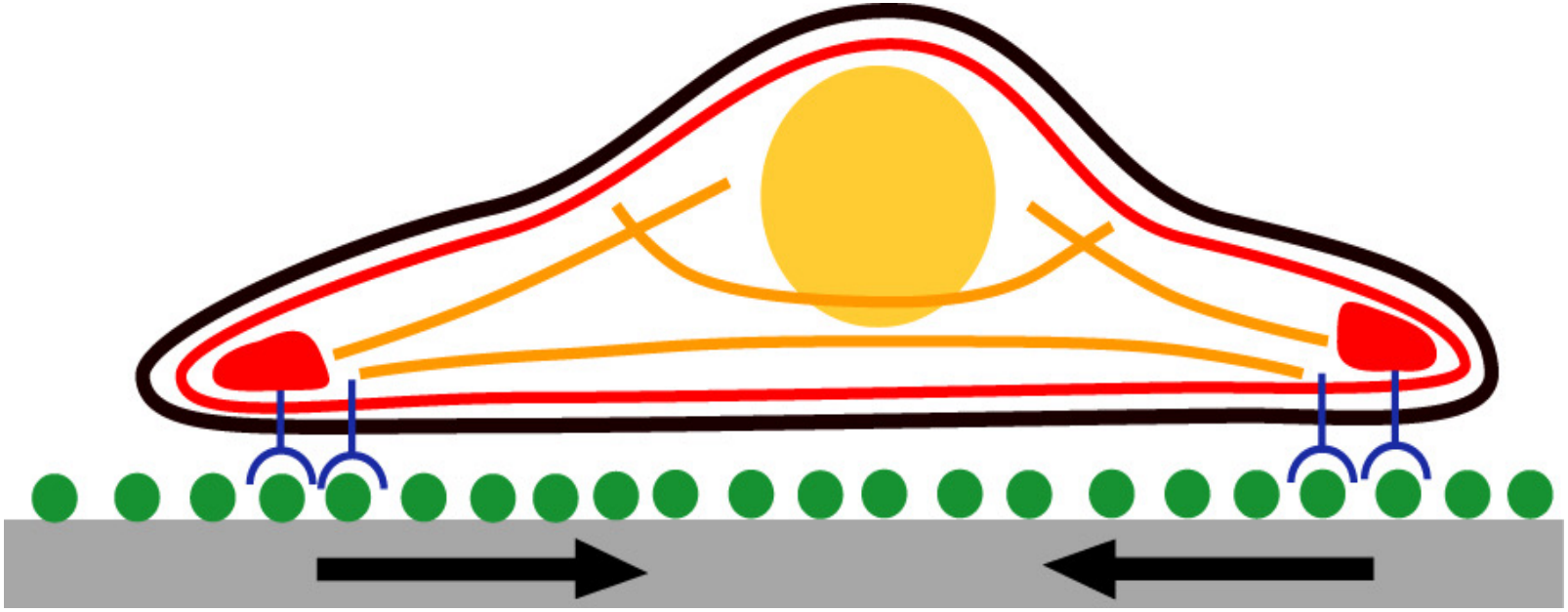
  - Stokes-Einstein relation

$$D = \frac{k_B T}{6\pi\eta R} \Rightarrow D = \frac{(10\mu m)^2}{s}$$

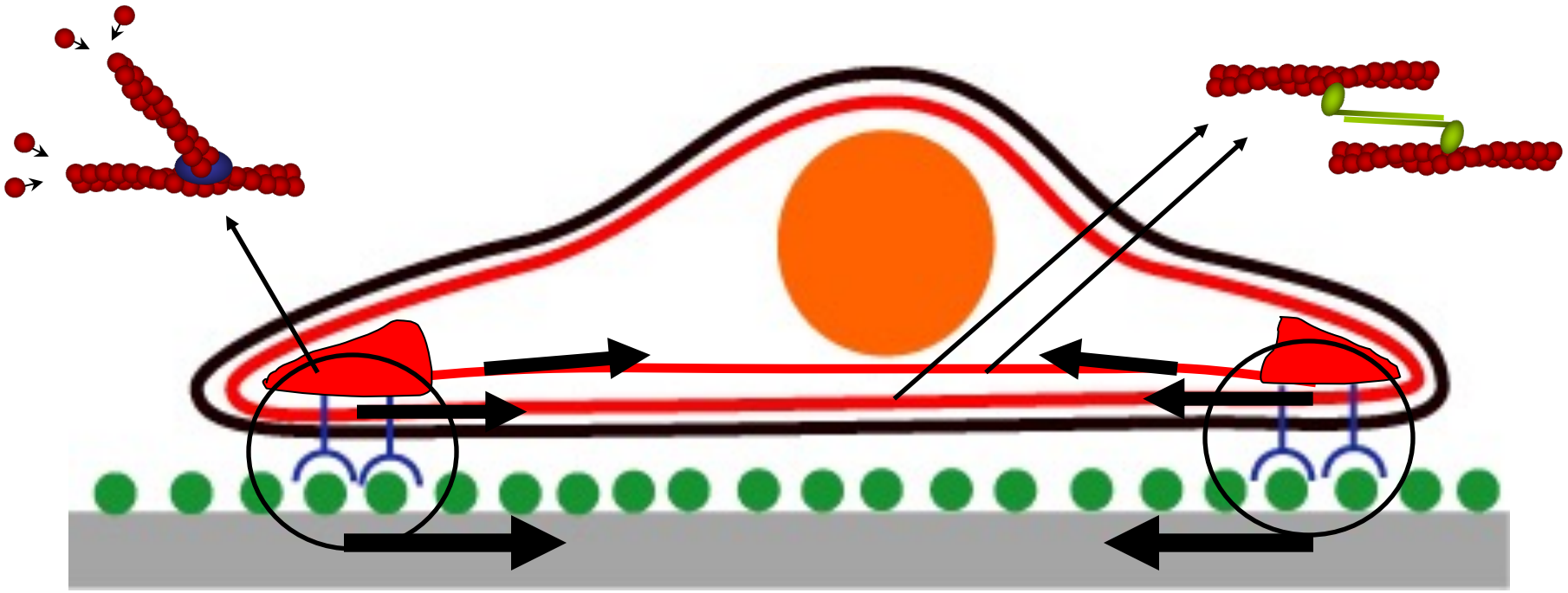
Cell adhesion and contractility

Signature image Schwarz group

https://www.thphys.uni-heidelberg.de/~biophys/

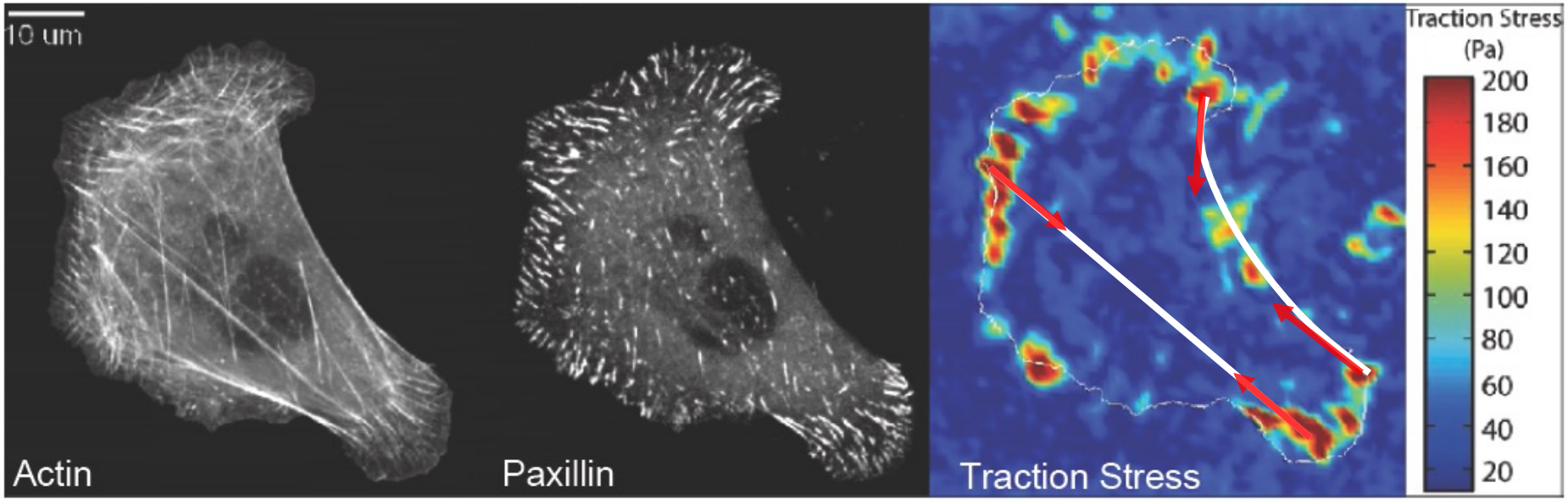


Active forces from tissue cells



- actin polymerization pushes out **lamellipodia**, actin flows backward
- contractile forces generated in **stress fibers**, **actin cortex** and **lamellum**
- force is transmitted to substrate through **focal adhesions**

Traction forces reflect cell shape and internal cell organzation



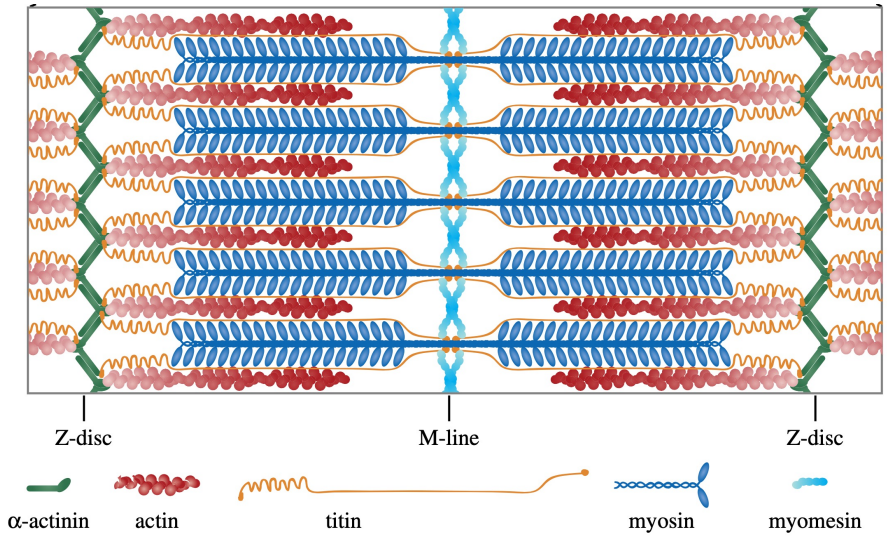
Cell forces are often related to actomyosin stress fibers ending in integrin-based focal adhesions. Typical forces at focal adhesions are nN (kPa-stresses).

[Schwarz and Gardel JCS 2012]

Force generation by

muscle

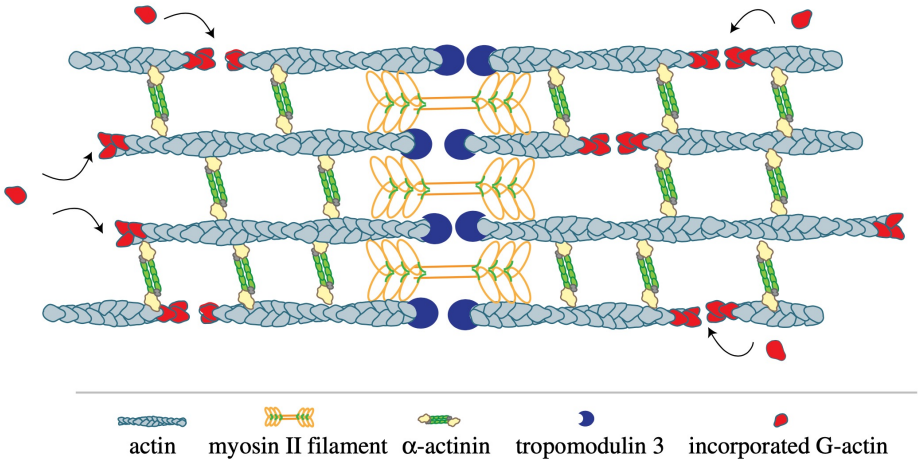
thick filament with 150 monomers in half-sarcomere, length 1600 nm



striated muscle sarcomere

non-muscle

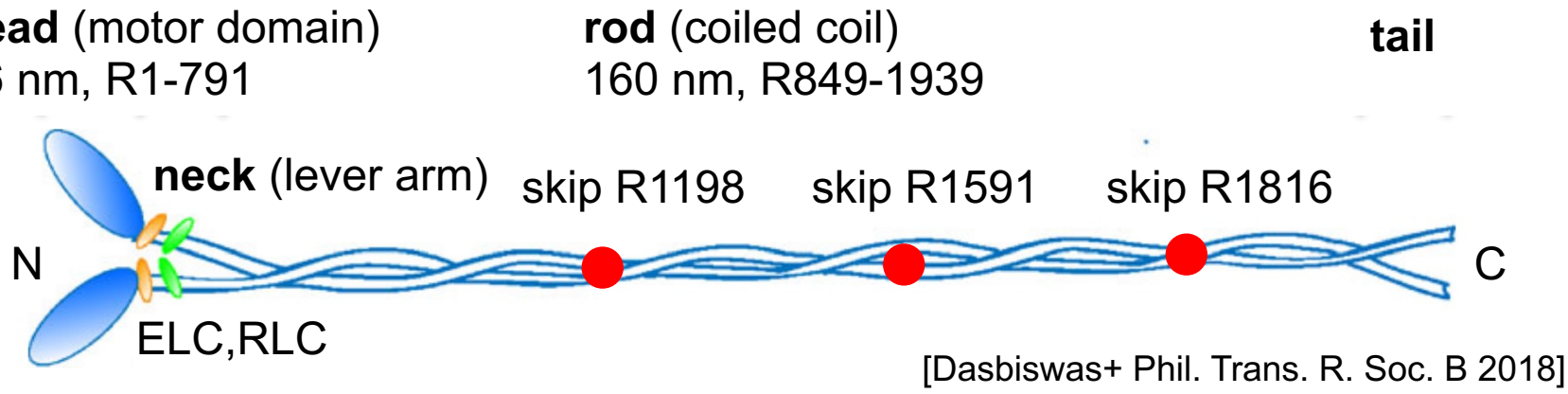
minifilament with 15 monomers per half, length 300 nm



MF in stress fiber

[Dasbiswas+ Phil. Trans. R. Soc. B 2018]

Non-muscle myosin II (NM2)

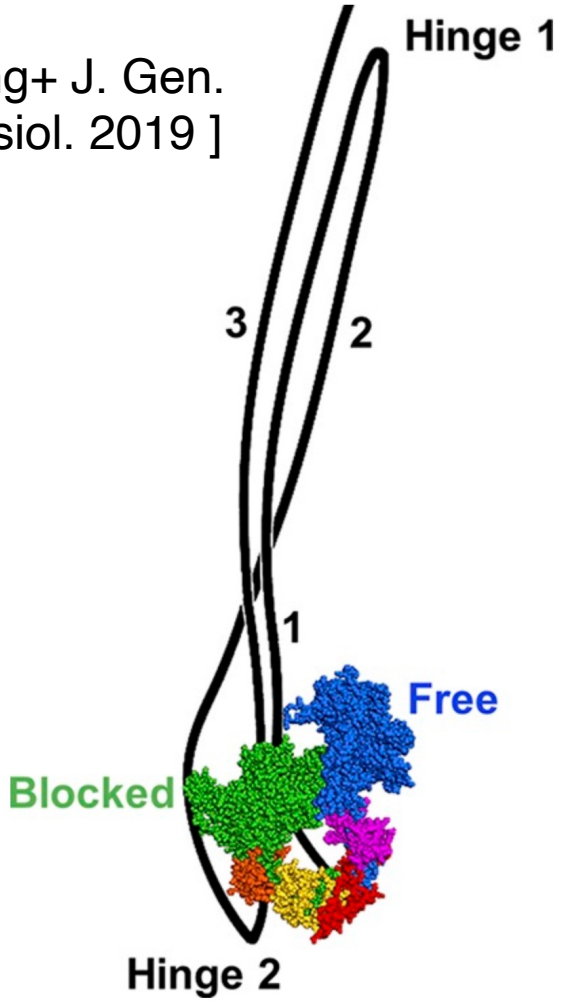


[Dasbiswas+ Phil. Trans. R. Soc. B 2018]

- Three skip residues along coiled coil
- Phosphorlyation sites in neck (RLC) and tail
- In humans three isoforms A, B and C with similar head domains and shared ELCs and RLCs
- „Monomer“, „dimer“ or „hexamer“ depending on context

Inactive form of myosin II (10S)

[Yang+ J. Gen. Physiol. 2019]

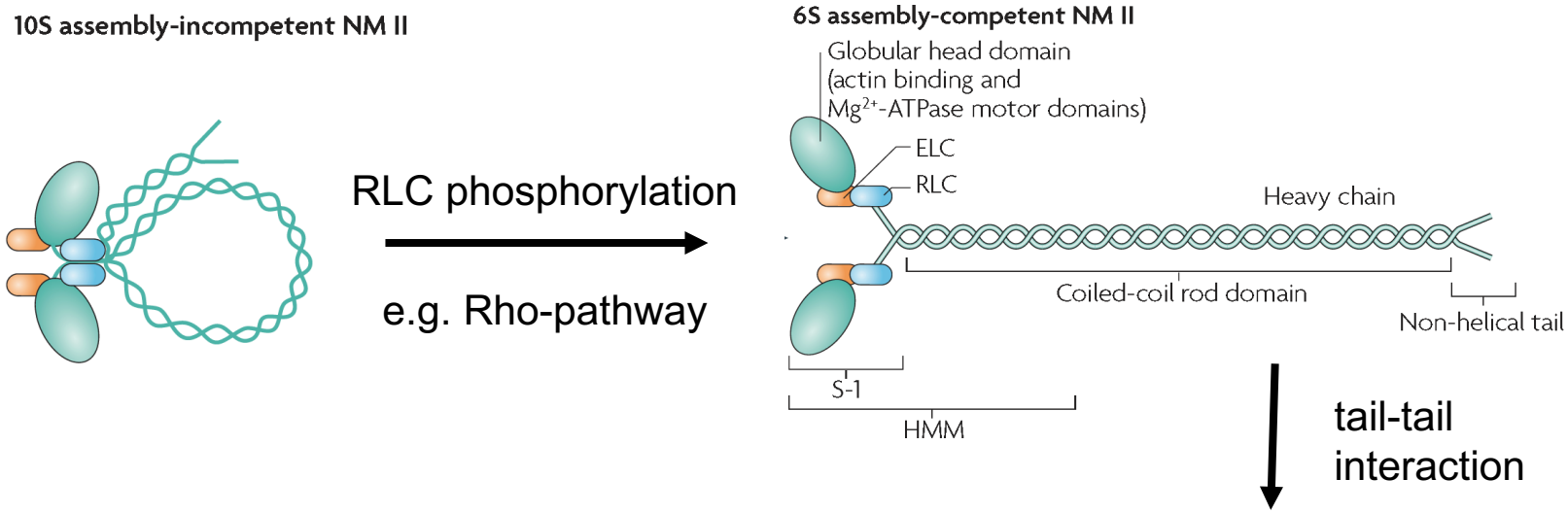


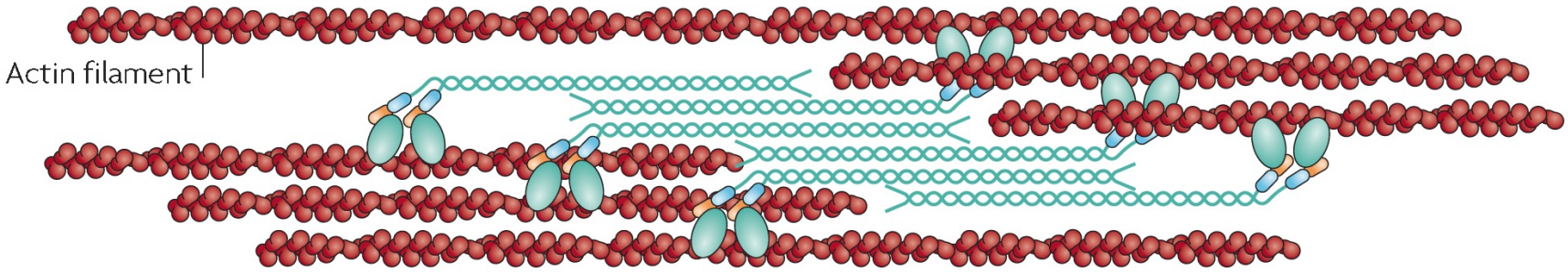
Tail folding blocks the essential features of the active form (6S):

- Actin binding
- ATPase activity
- Assembly into filaments

It leads to dispersion through diffusion and saves energy (similar to super-relaxed state in striated muscle)

The active form assembles into minifilaments





[Vicente-Manzanares+ NRMCB 2009]

30 non-muscle myosin II molecules build up one bipolar minifilament

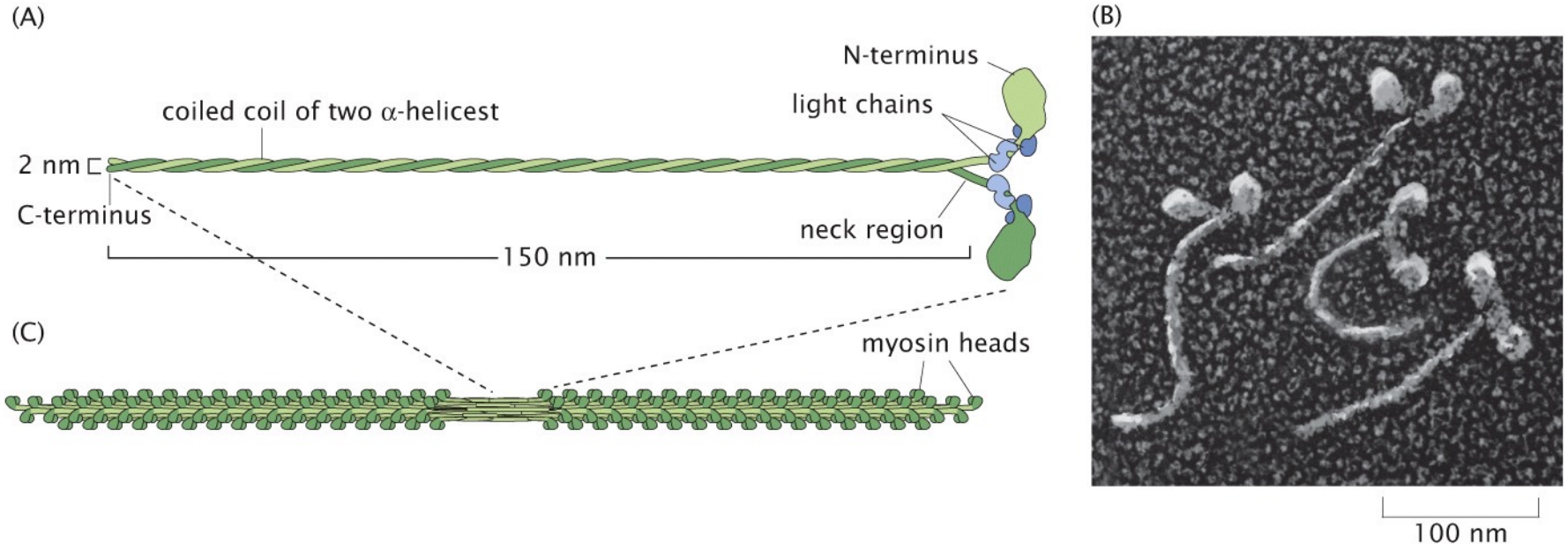
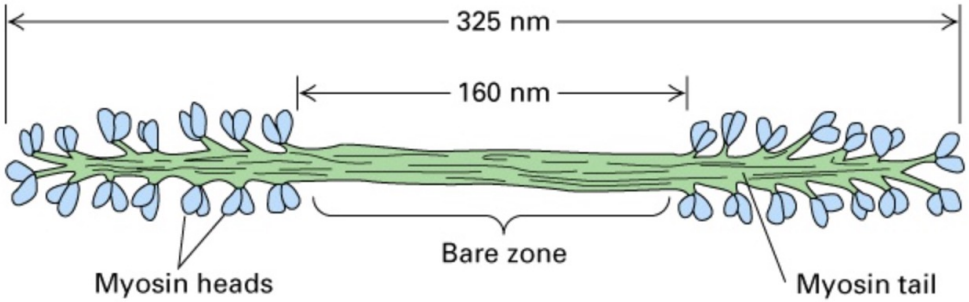


Figure 16.6 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

NM2 minifilaments

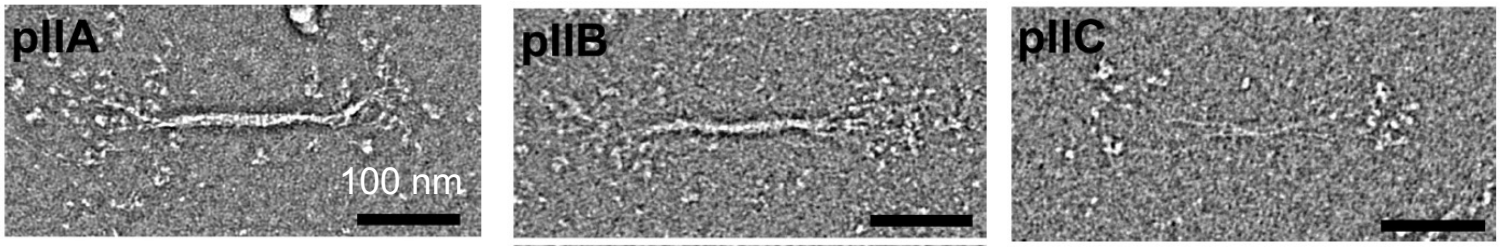
Cartoon:



[Lodish 4th ed.]

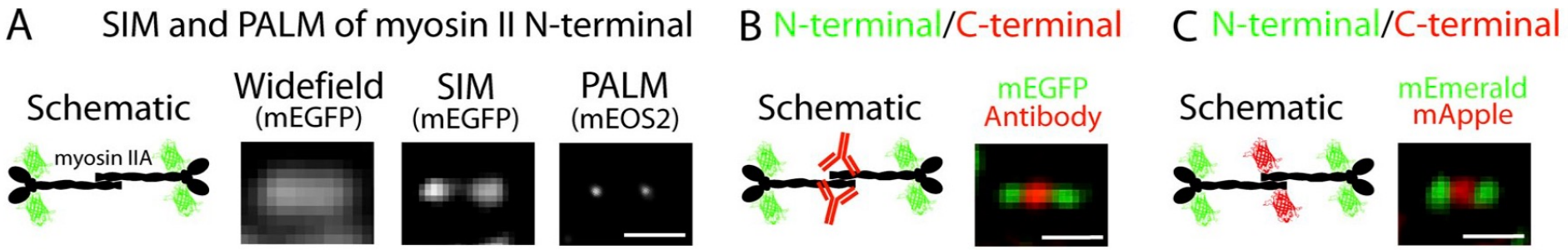
Electron microscopy:

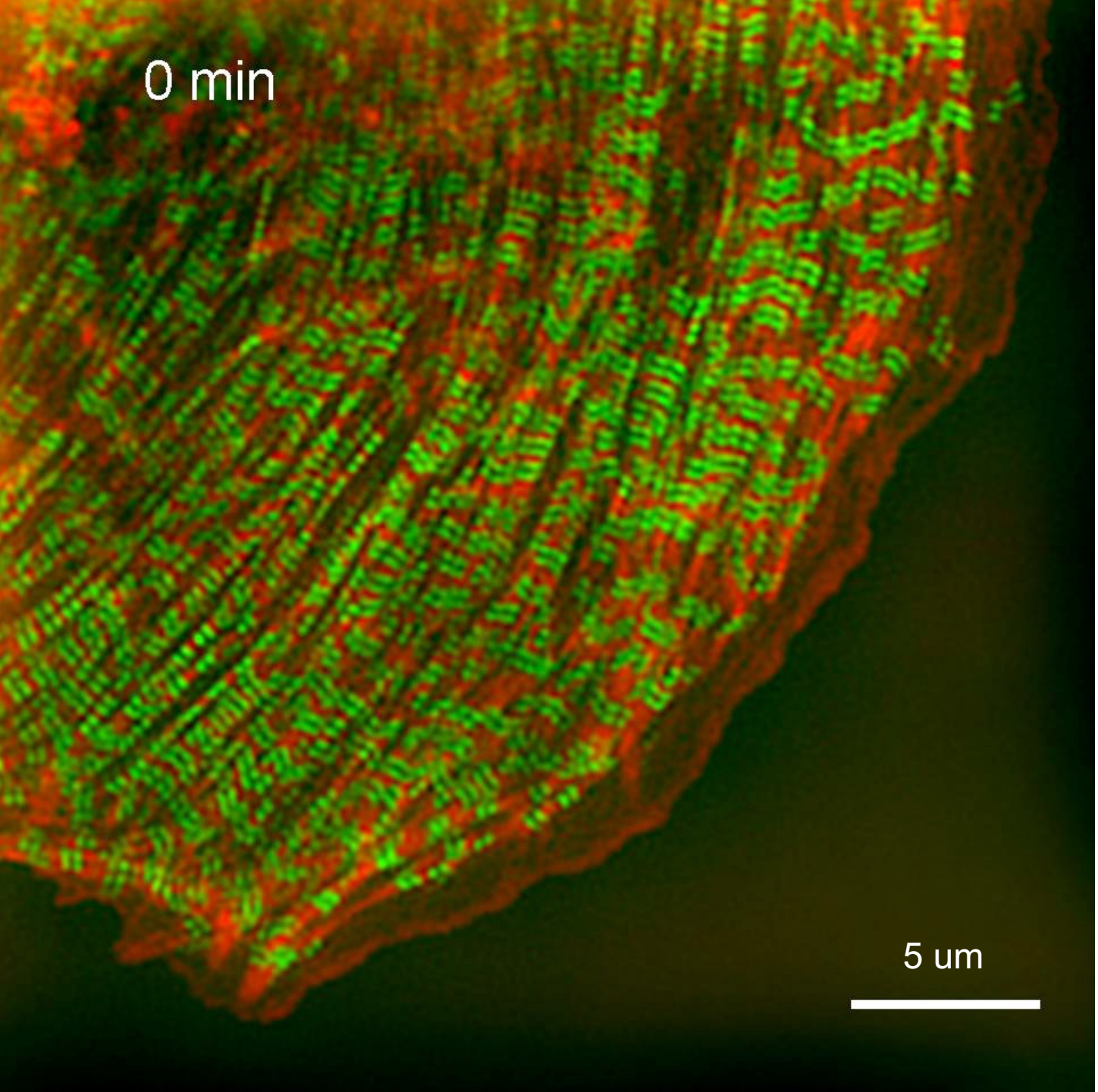
[Billington+ J Biol Chem 2013]



Super-resolution microscopy:

[Burnette+ J Cell Biol 2014]

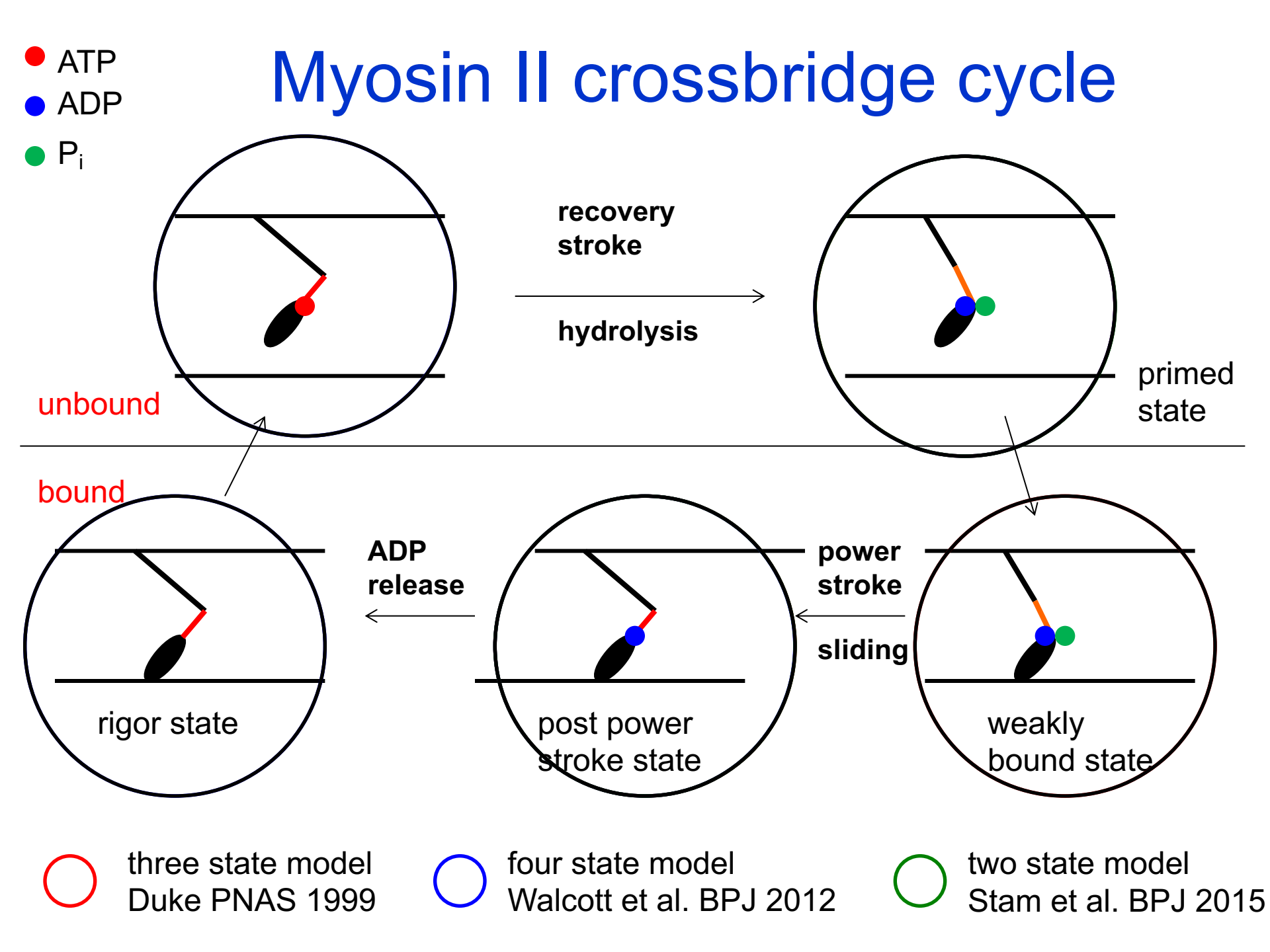


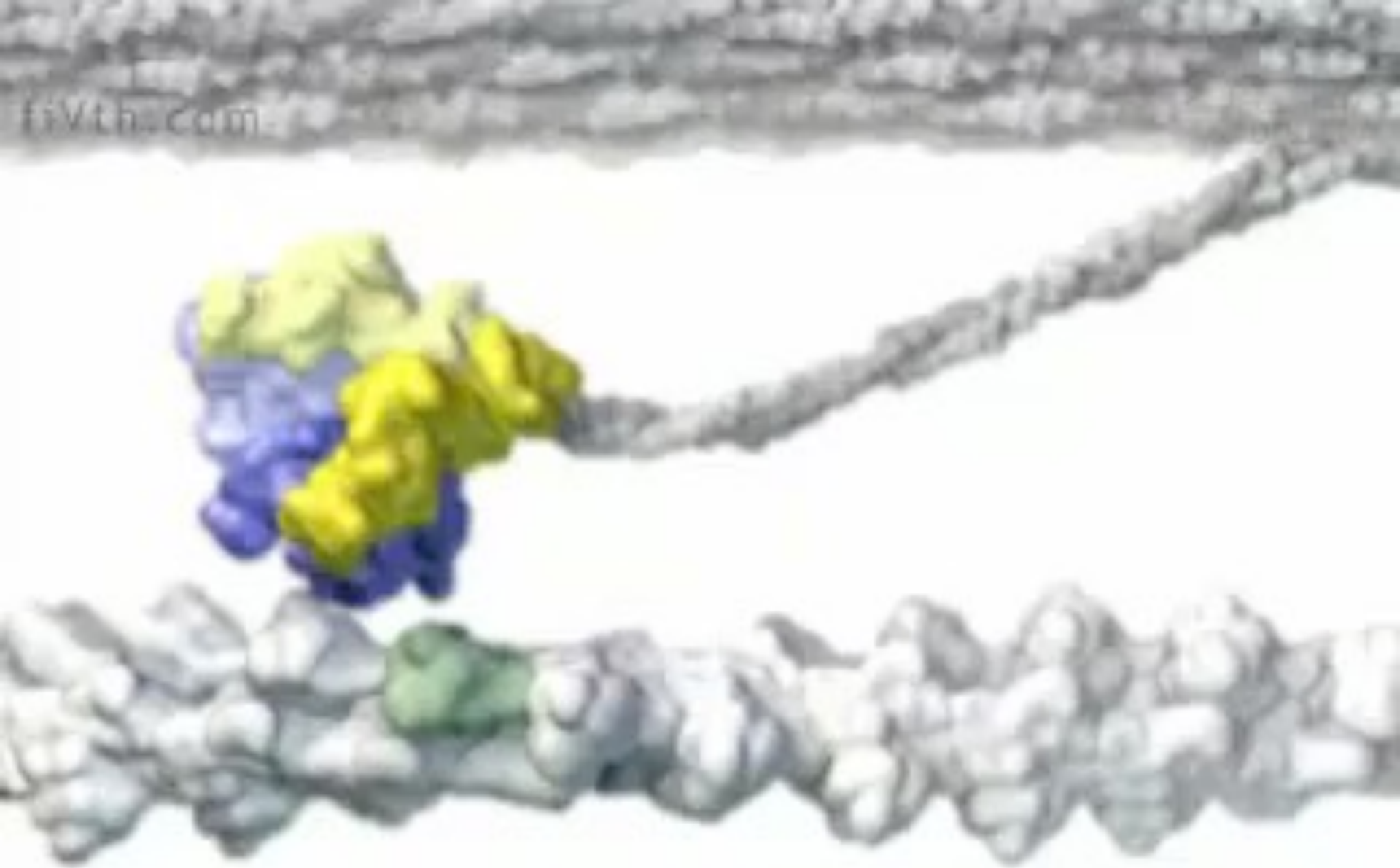


3D-SIM live

REF52 cells
green: NM2 RLC
red: alpha actinin

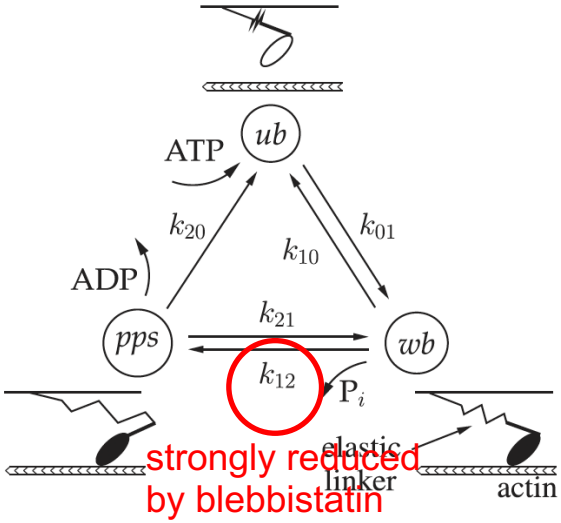
[Hu et al. NCB 2017]

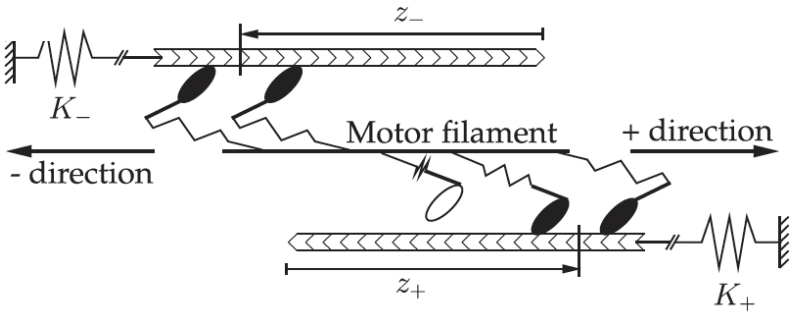

ATP
ADP
P_i
Myosin II crossbridge cycle
recovery stroke
hydrolysis
unbound
primed state
bound
ADP release
power stroke
sliding
rigor state
post power stroke state
weakly bound state
three state model
Duke PNAS 1999
four state model
Walcott et al. BPJ 2012
two state model
Stam et al. BPJ 2015



Myosin II walking on actin

Modelling the crossbridge cycle with master equations





Three main mechanochemical states of myosin II; NM2A detaches faster than NM2B

The different motors in a MF are mechanically coupled through the backbone

[Erdmann and Schwarz PRL 2012, Erdmann et al. JCP 2013, Albert et al. NJP 2014, Bartelheimer et al. PRE 2016, Grewe and Schwarz PRE 2020 and arXiv 2020]

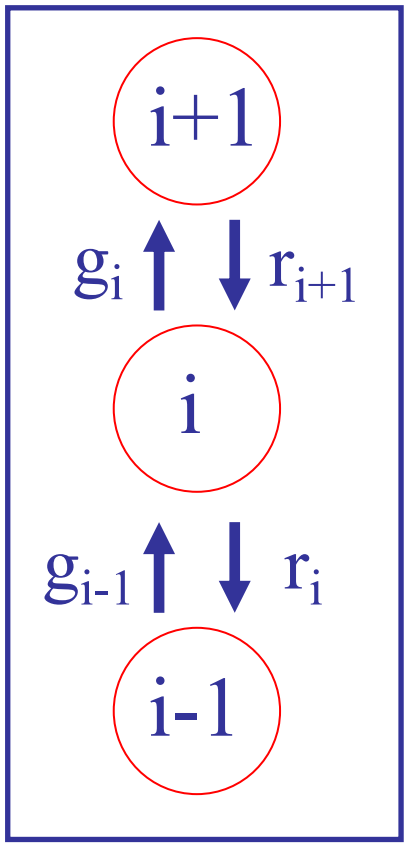
One-step master equation for adhesion clusters

• $p_i(t)$ probability that at time t exactly i bonds are closed $(0 \le i \le N_t)$

$$\frac{dp_i}{dt} = -[r_i + g_i]p_i + r_{i+1}p_{i+1} + g_{i-1}p_{i-1}$$

• rupture rate r_i from Kramers theory with load sharing, rebinding rate g_i force-independent

$$r_i = ie^{f/i}, \qquad g_i = \gamma(N_t - i)$$



Dimensionless quantities: $f=F_b/F_0$ $\gamma=k_{on}/k_0$ $\tau=k_0t$

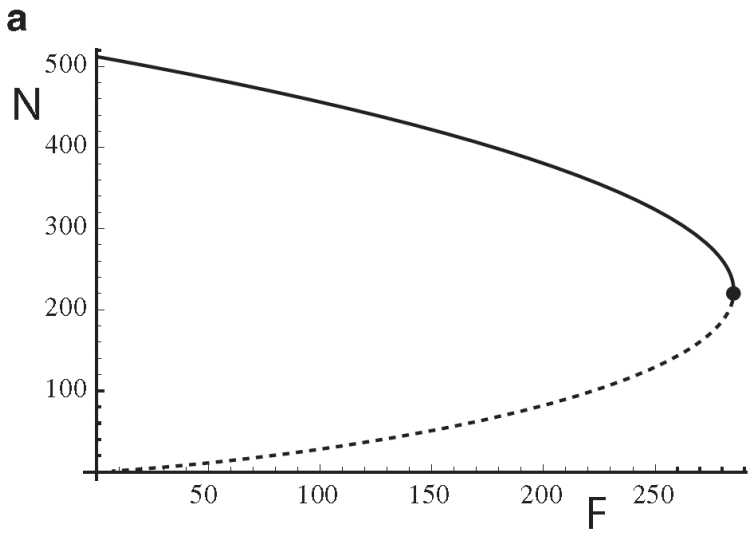
[Erdmann and Schwarz PRL 2004, JCP 2004]

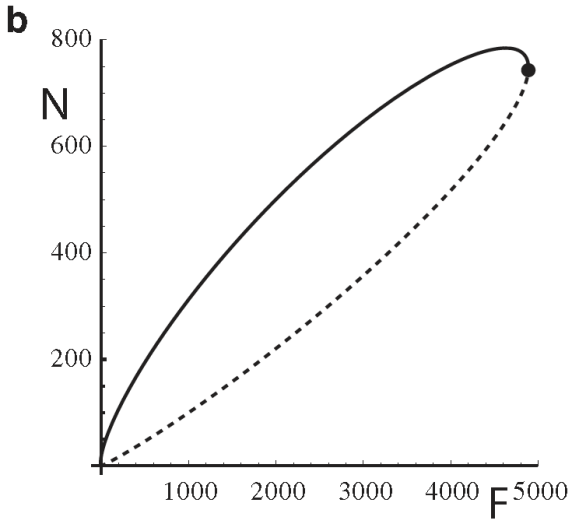
Mean field or first moment equation

$$\frac{dN}{d\tau} = -r(\langle i \rangle) + g(\langle i \rangle) = -Ne^{f/N} + \gamma(N_t - N)$$

Saddle-node bifurcation at $f_c = N_t \, \mathrm{plog}(\gamma/e)$.

Rebinding generates stability threshold under force.





Slip bond, [G. Bell Science 1978]

[Erdmann and Schwarz PRL 2004, JCP 2004]

Catch-slip bond,
[Novikova and Storm BPJ 2013]

Plan for lecture and exercises

We will introduce step-by-step the basics needed to understand the active gel model for cell migration from Drozdowski et al. PRE 2021. Important elements are th Maxwell model, active stress and the partial differential equations of continuum mechanics, which can be solved with finite differences or finite volumes. A similar model also allows us to understand the essentials of the traction of adherent cells (cells as contractile bars on an elastic foundation).

PHYSICAL REVIEW E **104**, 024406 (2021)

Optogenetic control of intracellular flows and cell migration: A comprehensive mathematical analysis with a minimal active gel model

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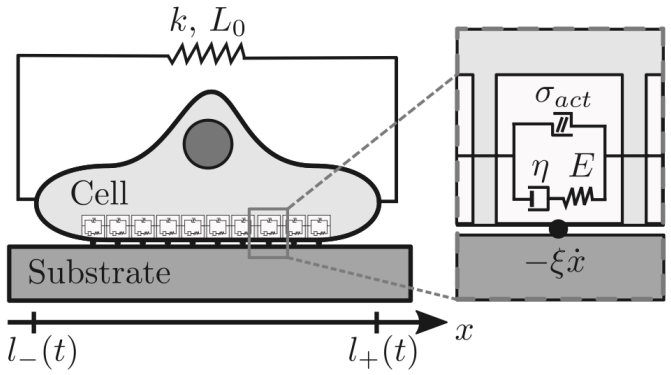
(Received 29 April 2021; revised 6 July 2021; accepted 14 July 2021; published 4 August 2021)

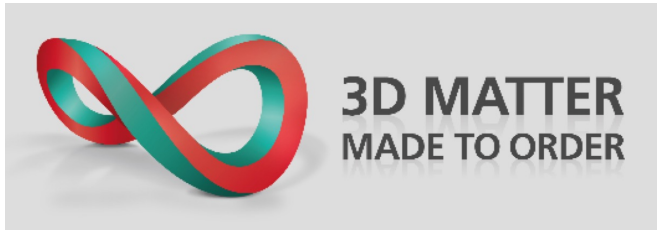
The actin cytoskeleton of cells is in continuous motion due to both polymerization of new filaments and their contraction by myosin II molecular motors. Through adhesion to the substrate, such intracellular flow can be converted into cell migration. Recently, optogenetics has emerged as a new powerful experimental method to control both actin polymerization and myosin II contraction. While optogenetic control of polymerization can initiate cell migration by generating protrusion, it is less clear if and how optogenetic control of contraction can also affect cell migration. Here we analyze the latter situation using a minimal variant of active gel theory into which we include optogenetic activation as a spatiotemporally constrained perturbation. The model can describe the symmetrical flow of the actomyosin system observed in optogenetic experiments, but not the long-lasting polarization required for cell migration. Motile solutions become possible if cytoskeletal polymerization is included through the boundary conditions. Optogenetic activation of contraction can then initiate locomotion in a symmetrically spreading cell and strengthen motility in an asymmetrically polymerizing one. If designed appropriately, it can also arrest motility even for protrusive boundaries.

DOI: 10.1103/PhysRevE.104.024406

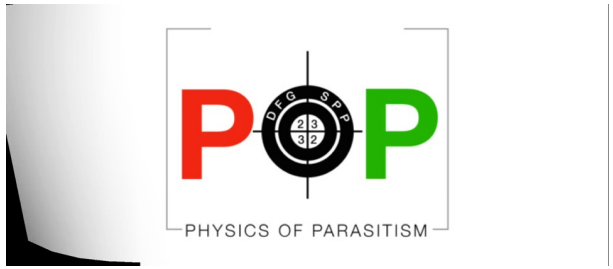


Acknowledgements

STRUCTURES
CLUSTER OF
EXCELLENCE



DFG



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