Motor proteins and mechano-chemistry

Martin Lindén

I. A mini-zoo of some motors, their biological functions, and some important experiments.

II. Qualitative (toy) models, and ingredients in quantitative models.

III. First passage time calculations

(Bias: single motors and single molecule experiments)

Part I: a small zoo of motor proteins.

- Motors in intracellular transport.
- The flagella rotary motor.
- Translocation through a pore, and the ratchet effect.

Motors in intracellullar transport

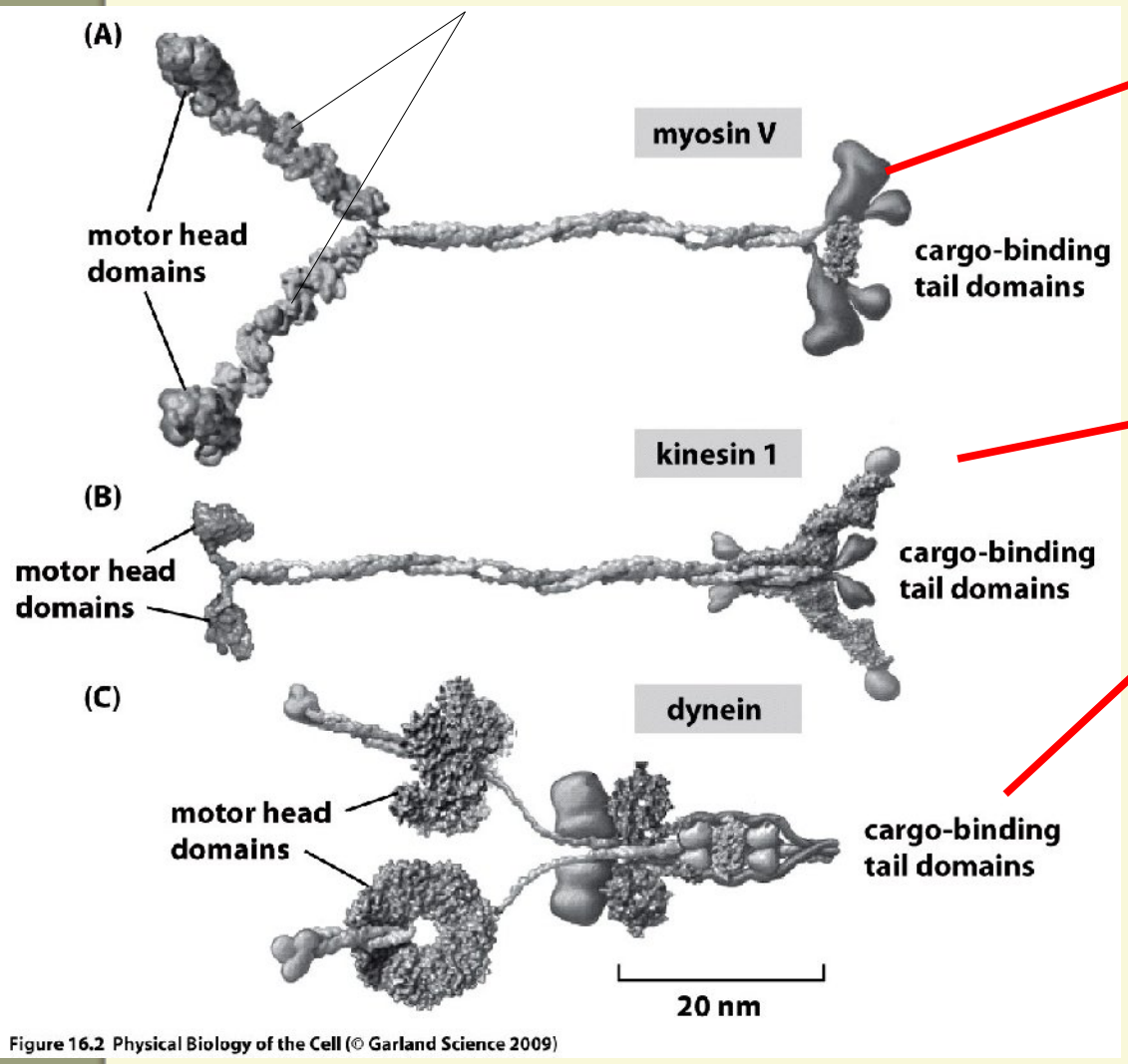
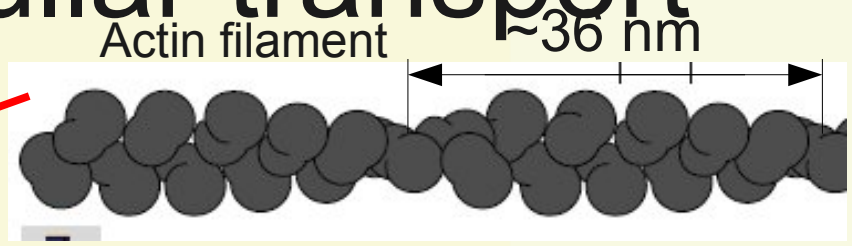
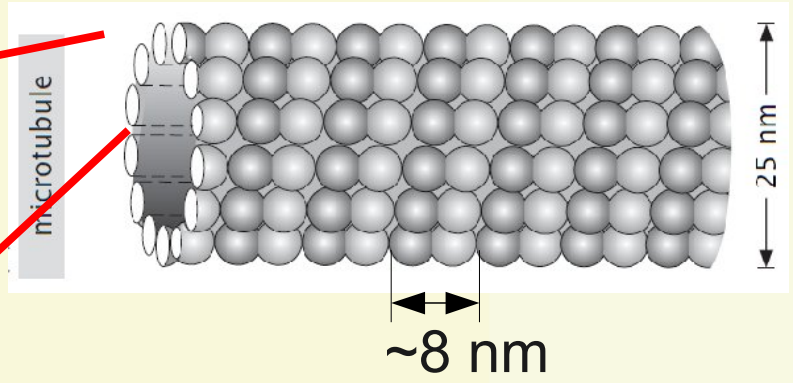
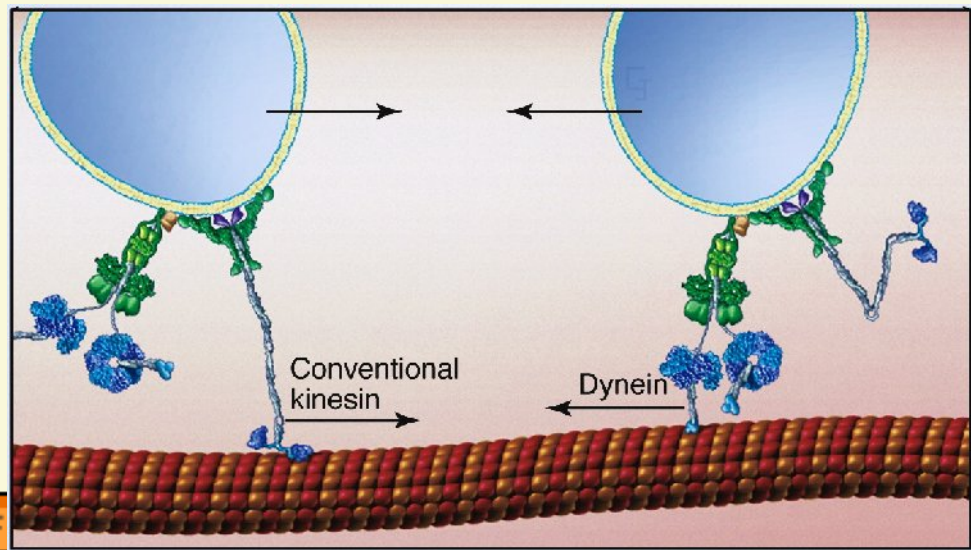


Figure 16.2 Physical Biology of the Cell (© Garland Science 2009)







Motors in intracellullar transport

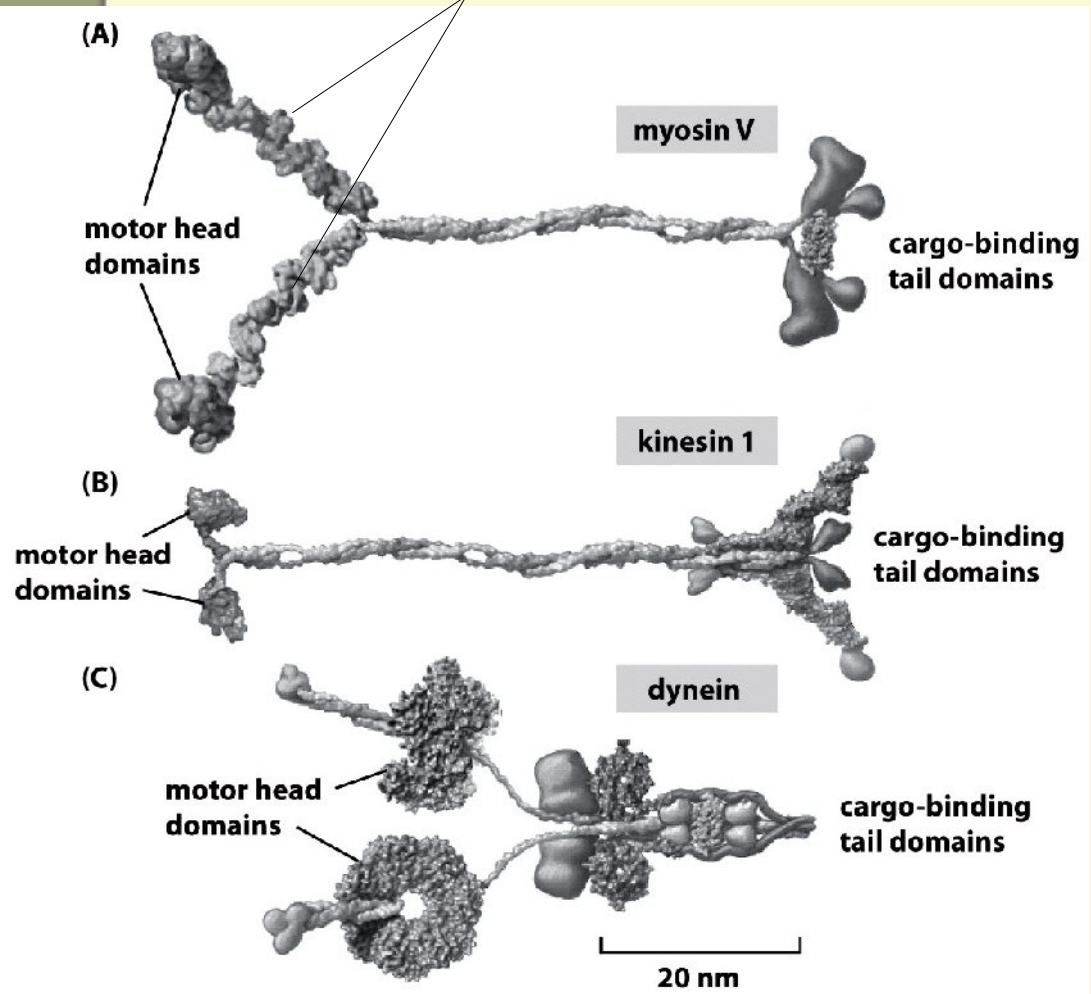
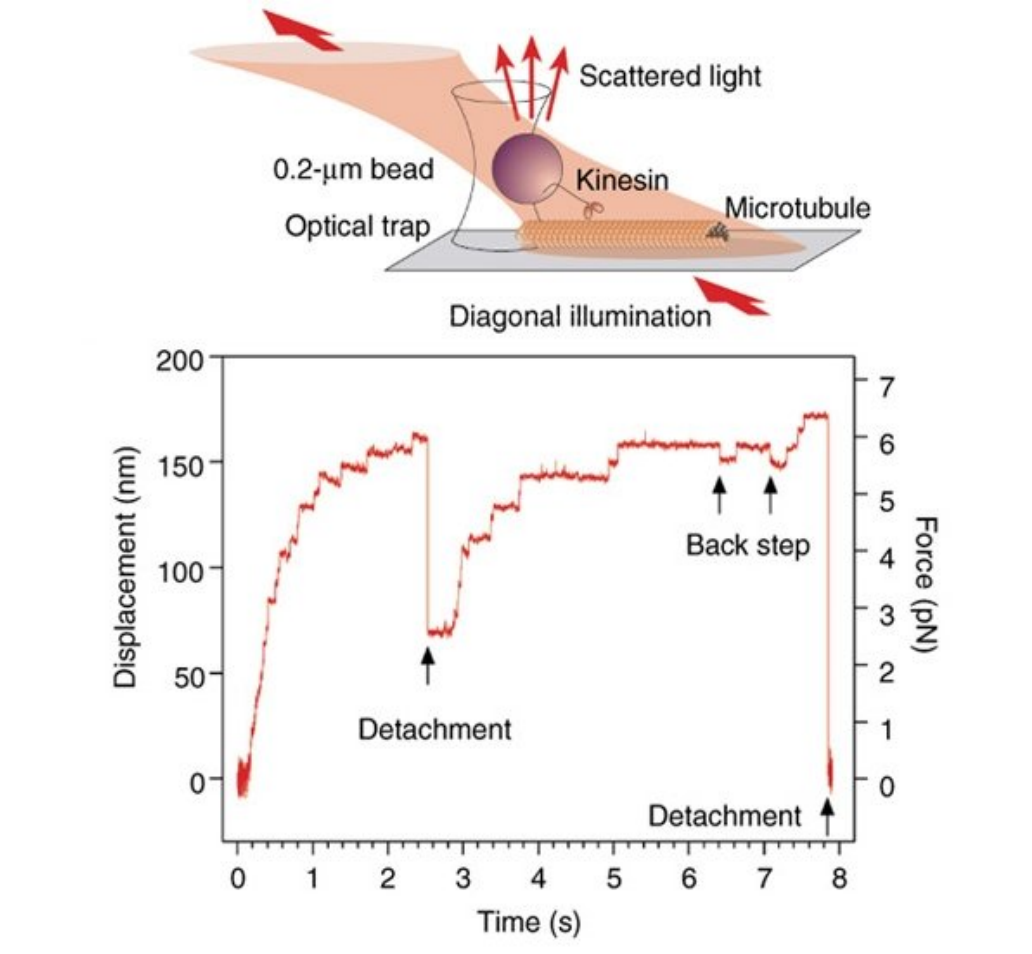


Figure 16.2 Physical Biology of the Cell (© Garland Science 2009)

- Driven by ATP
- Specific molecular track and direction
- Processive (in vitro)

  kinesin: ~100 steps/run
  myosin V: ~ 10 steps/run
- Works in small groups in vivo

Watching single motors in vitro



Nishiyama, Higuchi & Yanagida
Nature Cell Biol 4:790 (2002)

How does it walk?

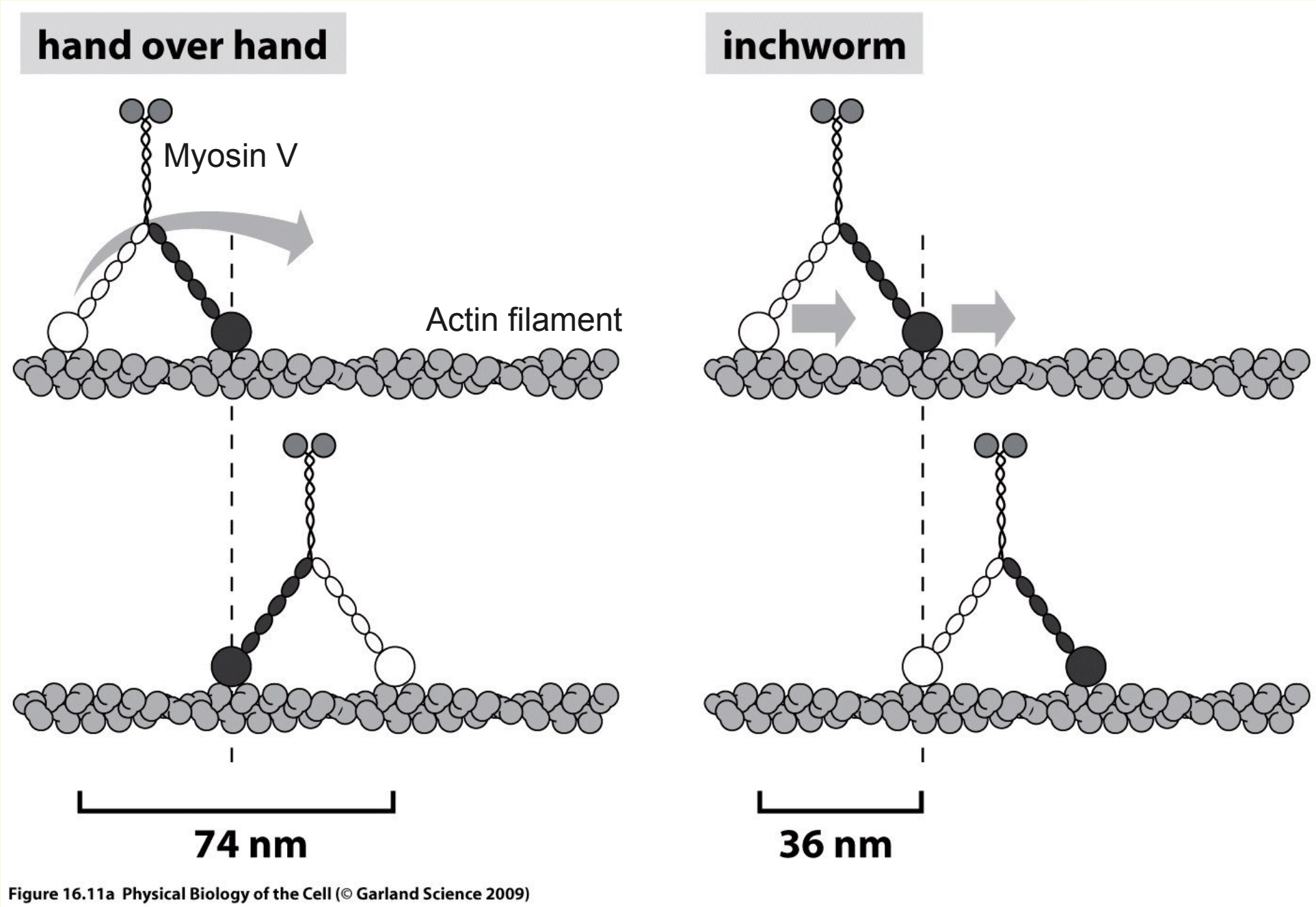
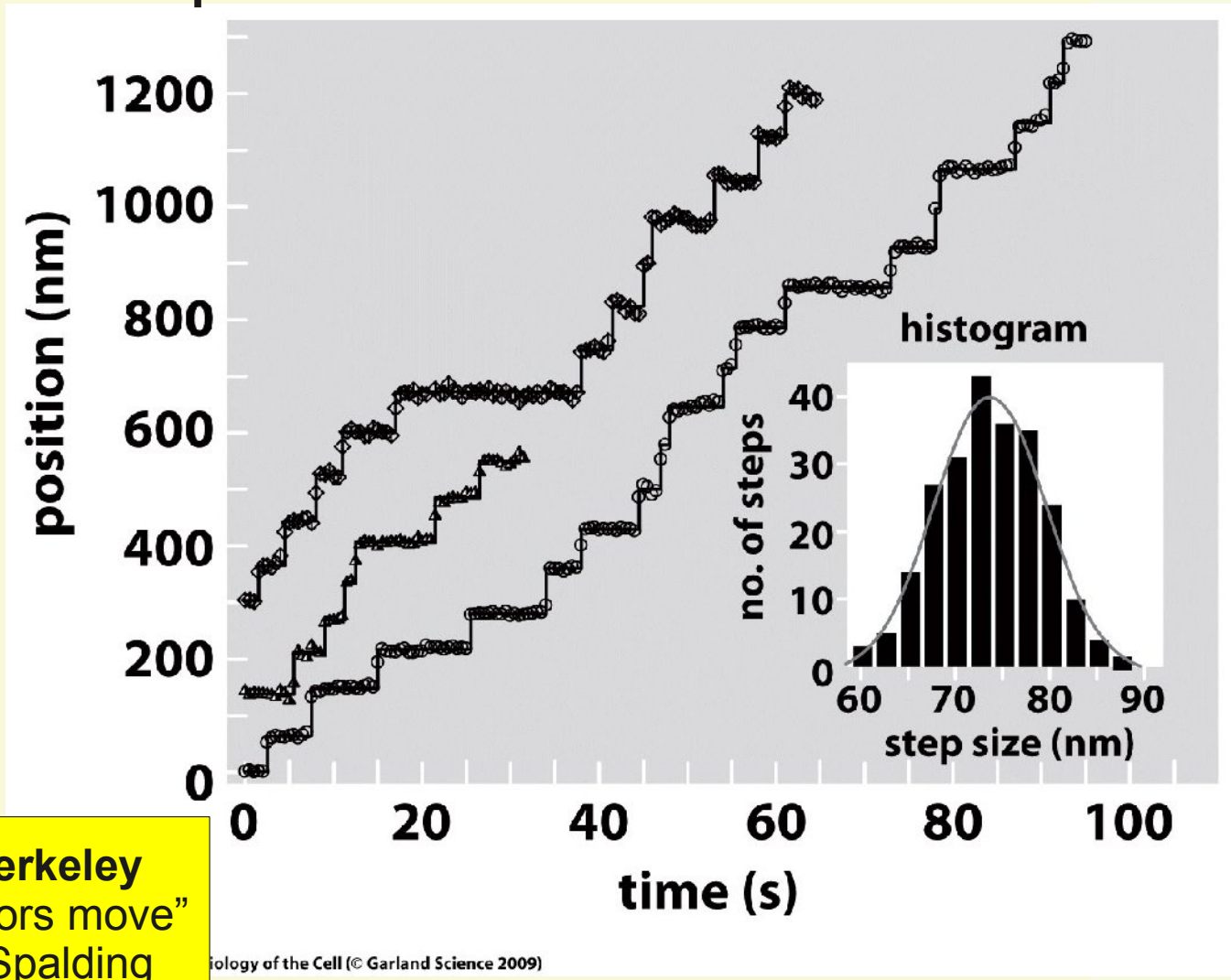


Figure 16.11a Physical Biology of the Cell (© Garland Science 2009)

Hand over hand motion

- Flourophore attached to one of the heads of Myosin V: step size indicates hand-over-hand motion.

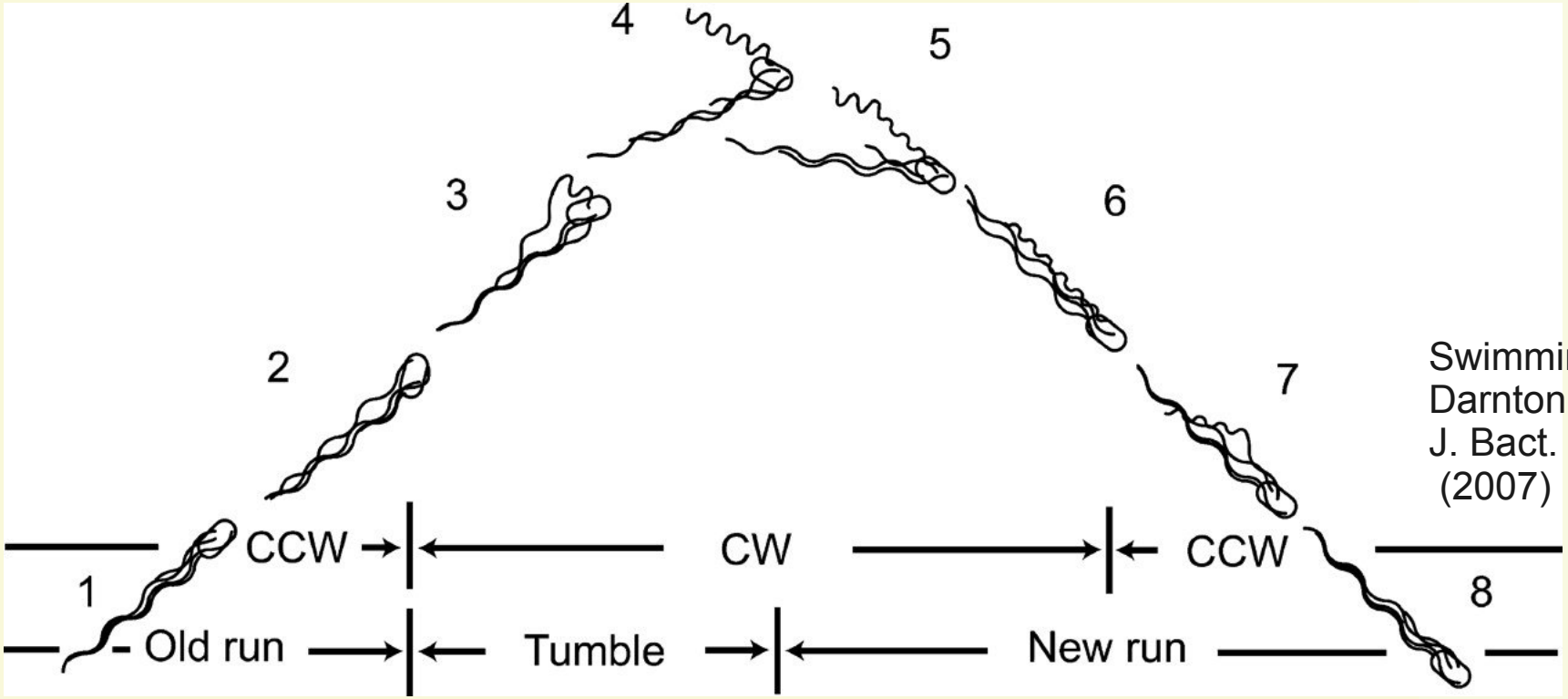


ology of the Cell (© Garland Science 2009)

Ahmet Yildiz, UC Berkeley
"How Microtubular motors move"
March 9, 4 PM, 106 Spalding

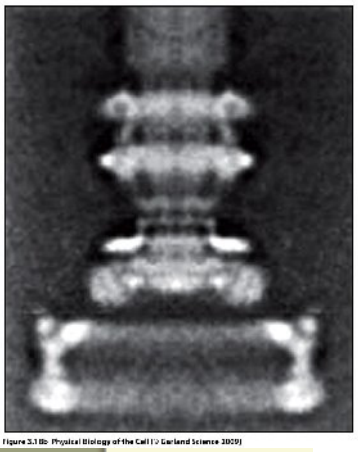
E coli swimming is driven by a rotary motor

- Rotating filaments (flagella) form screw-like bundles
- up to ~300 Hz rotation rate, v ~ few tens of μm/s
- switch between runs (CCW) and tumbles(CW): biased random walk in search of good conditions



Swimming E. coli
Darnton et al
J. Bact. 189:1756
(2007)

Swimming E coli



(H C Berg)

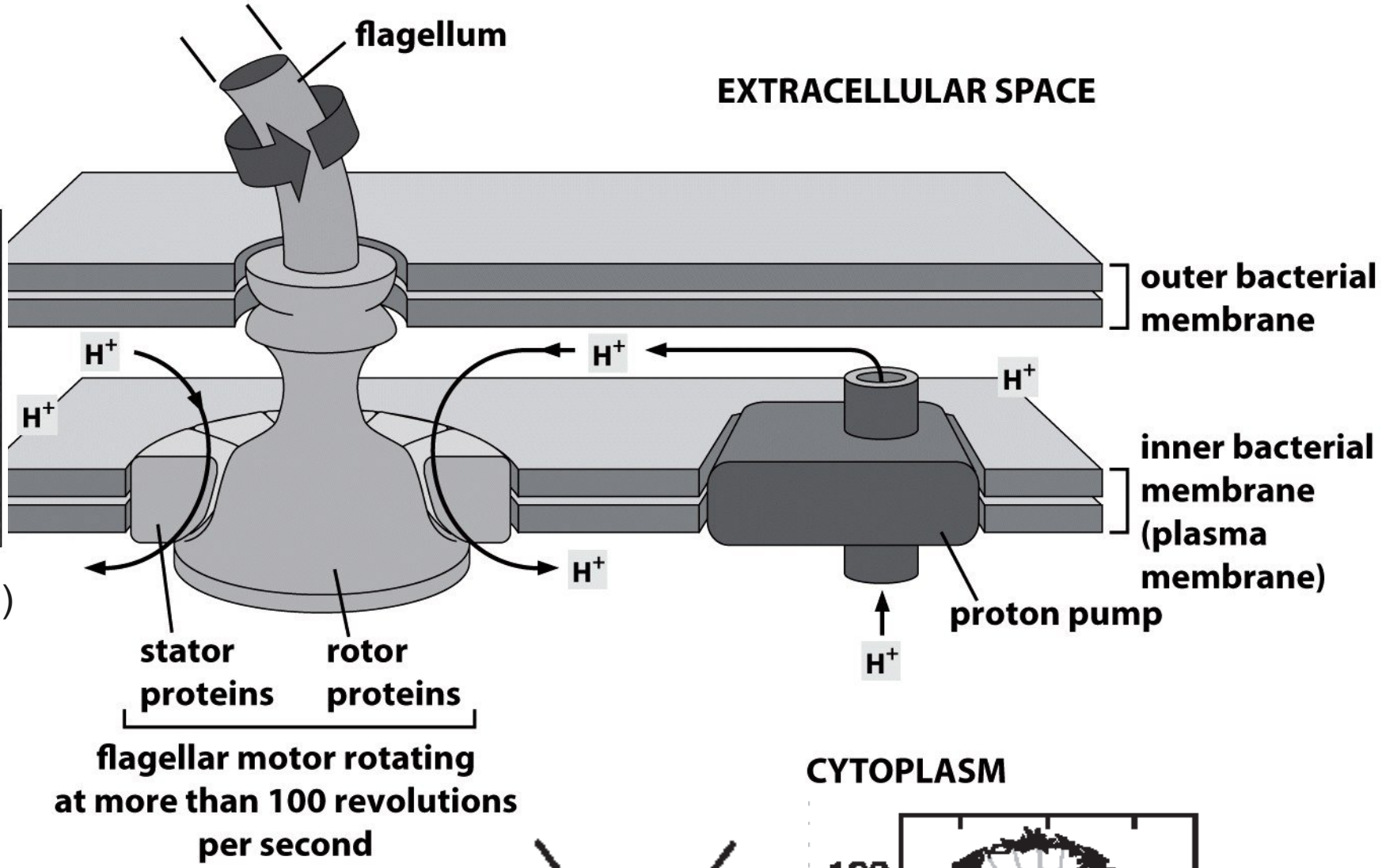
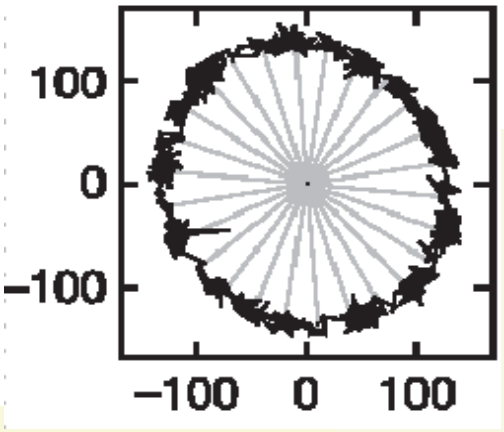


Figure 16.13a Physical Biology of the Cell (© Garland Scie



Steps in the flagellar motor (slow mutant version):
Sowa et al, Nature 437:916(2005)

Translocation: the ratchet effect

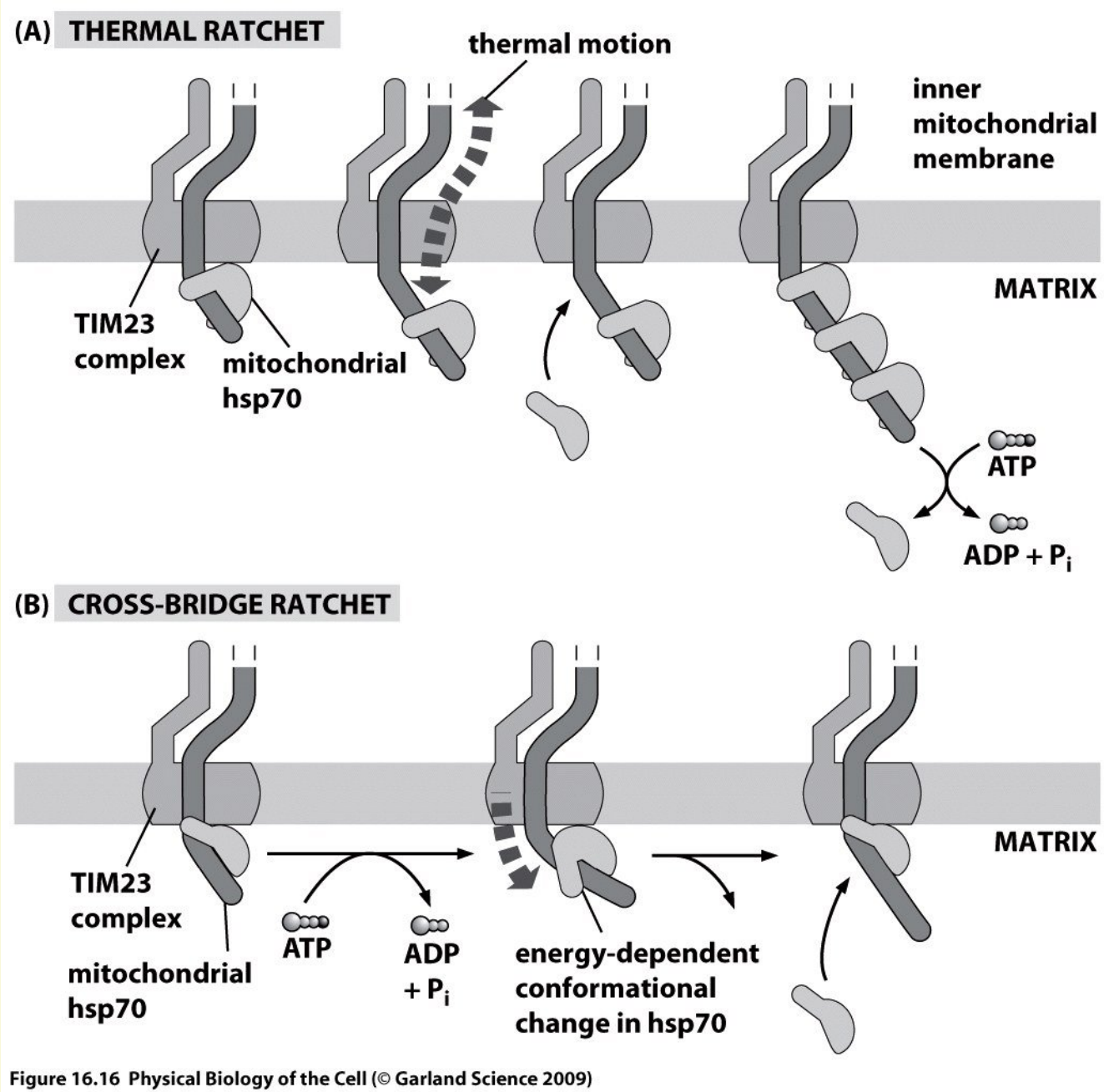


Figure 16.16 Physical Biology of the Cell (© Garland Science 2009)

Part II: Qualitative (toy) models, and ingredients in quantitative models.

Design principles for Brownian molecular machines: how to swim in molasses and walk in a hurricane

R. Dean Astumian*

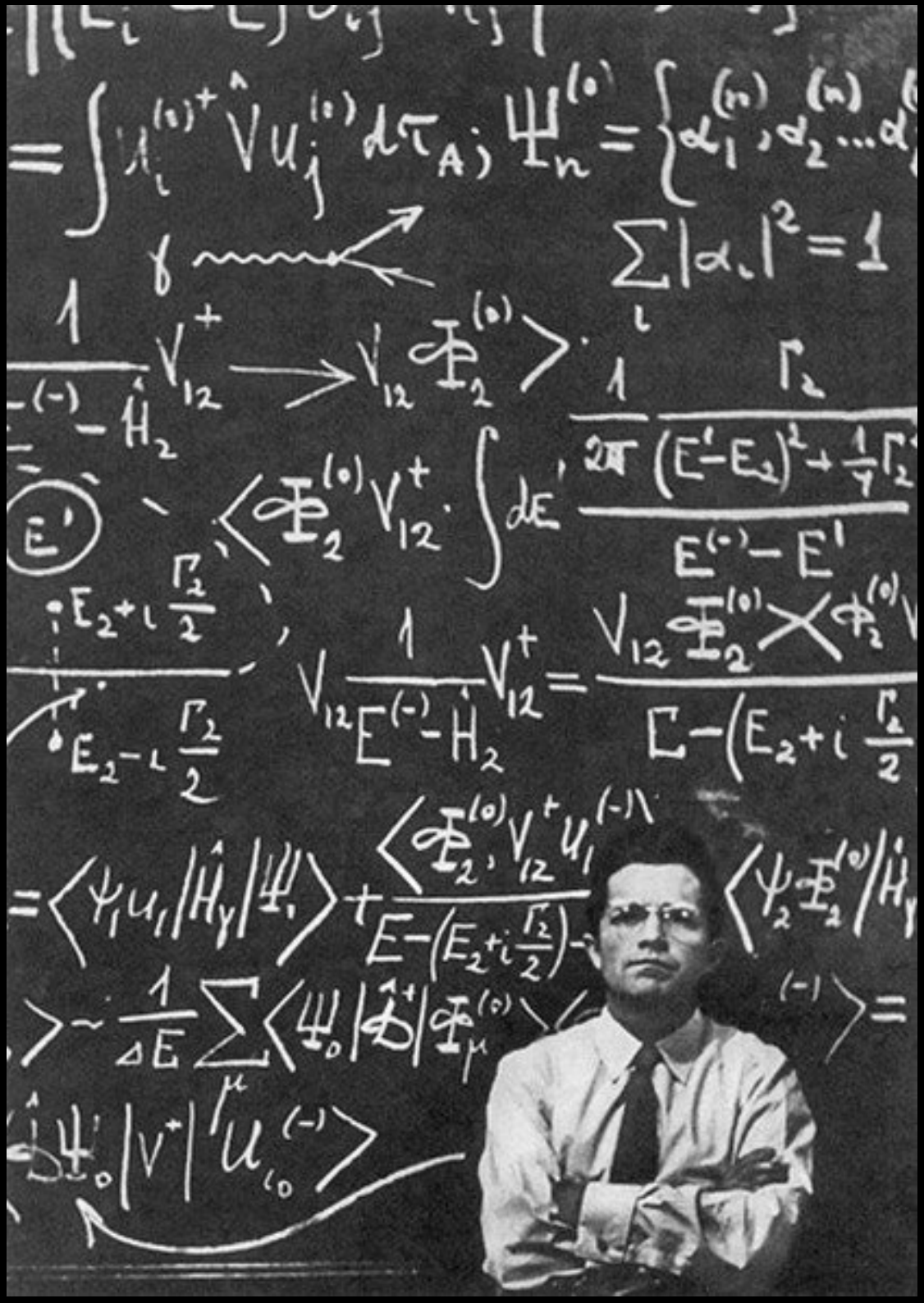
(Pun on a classic paper/talk by Purcell).

Life at low Reynolds number

E. M. Purcell
Lyman Laboratory, Harvard University, Cambridge, Massachusetts 02138
(Received 12 June 1976)

Motor proteins (and all other proteins) work under very noisy conditions.

How noisy...?



Trajectories of motors: The one-state model

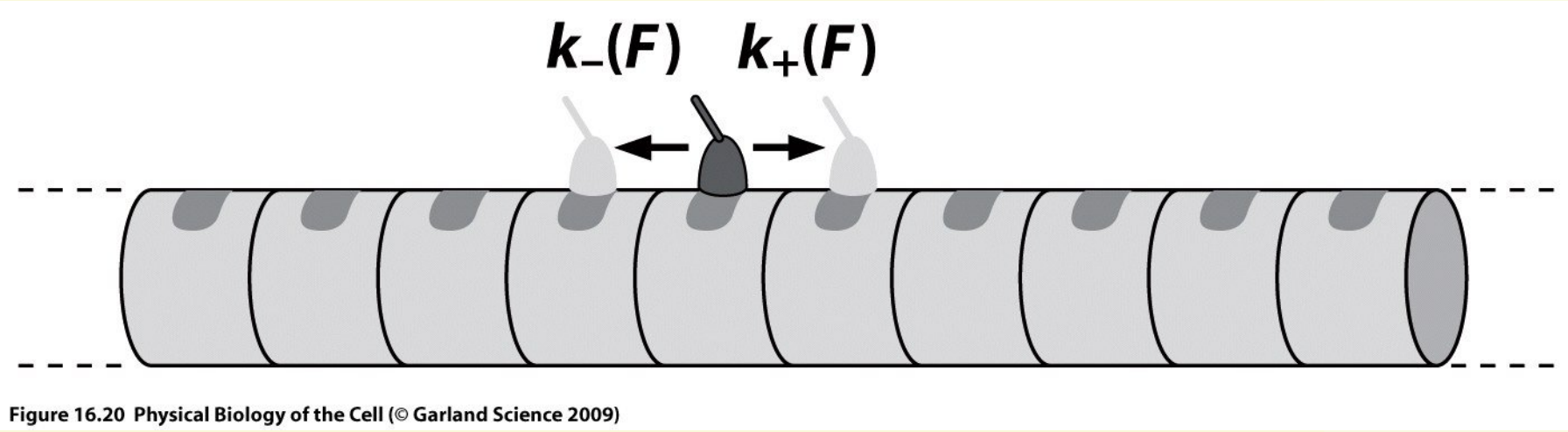


Figure 16.20 Physical Biology of the Cell (© Garland Science 2009)

- Simple, captures randomness and molecular discreteness of motors.
- Rationale: one transition (often) slowest
- Steps map to many examples

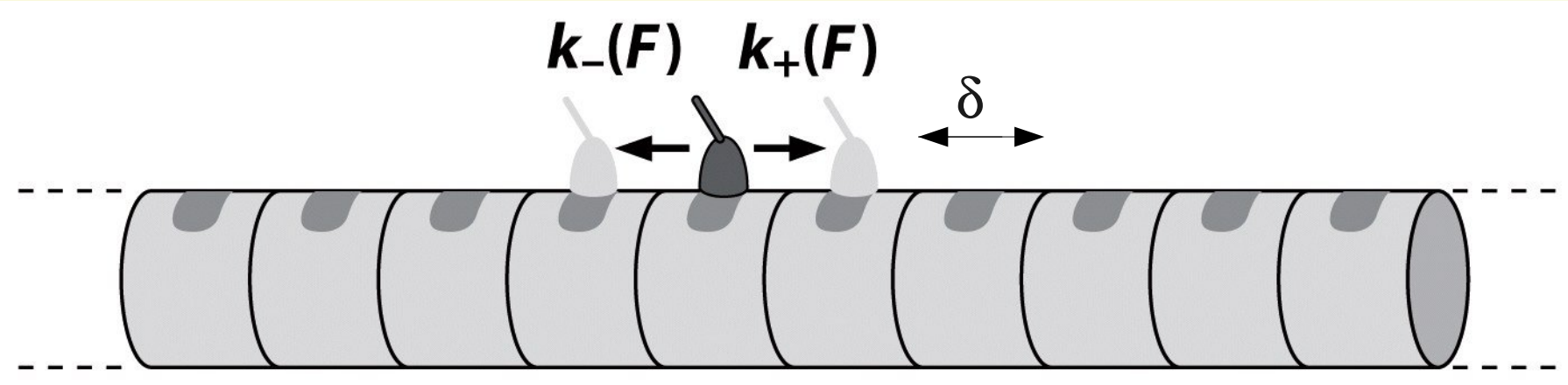
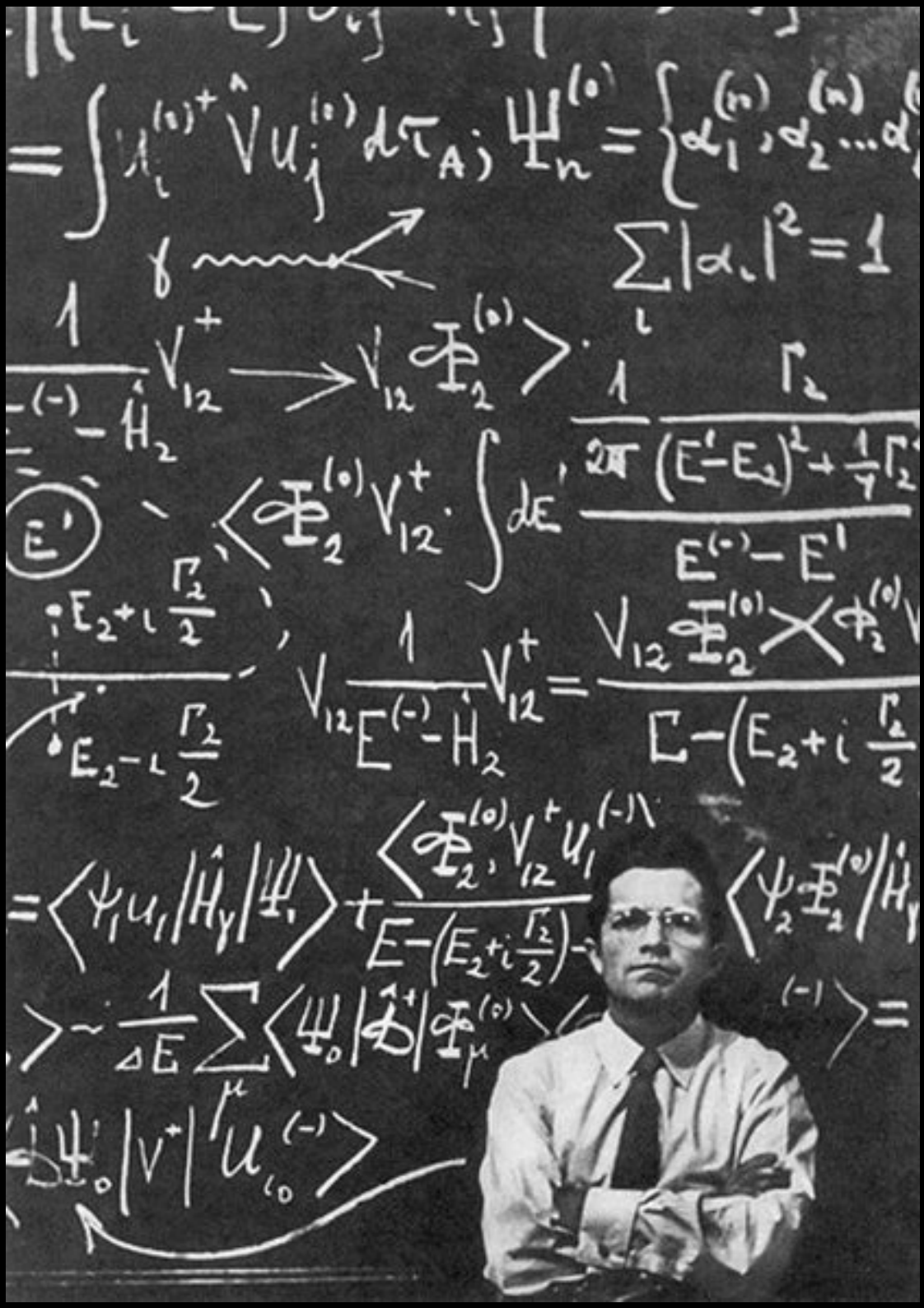


Figure 16.20 Physical Biology of the Cell (© Garland Science 2009)

- Mean velocity
- Effective diffusion constant
- Waiting time distribution: exponential (known?)
- Maximal force



'Effective' diffusion? What does it look like?

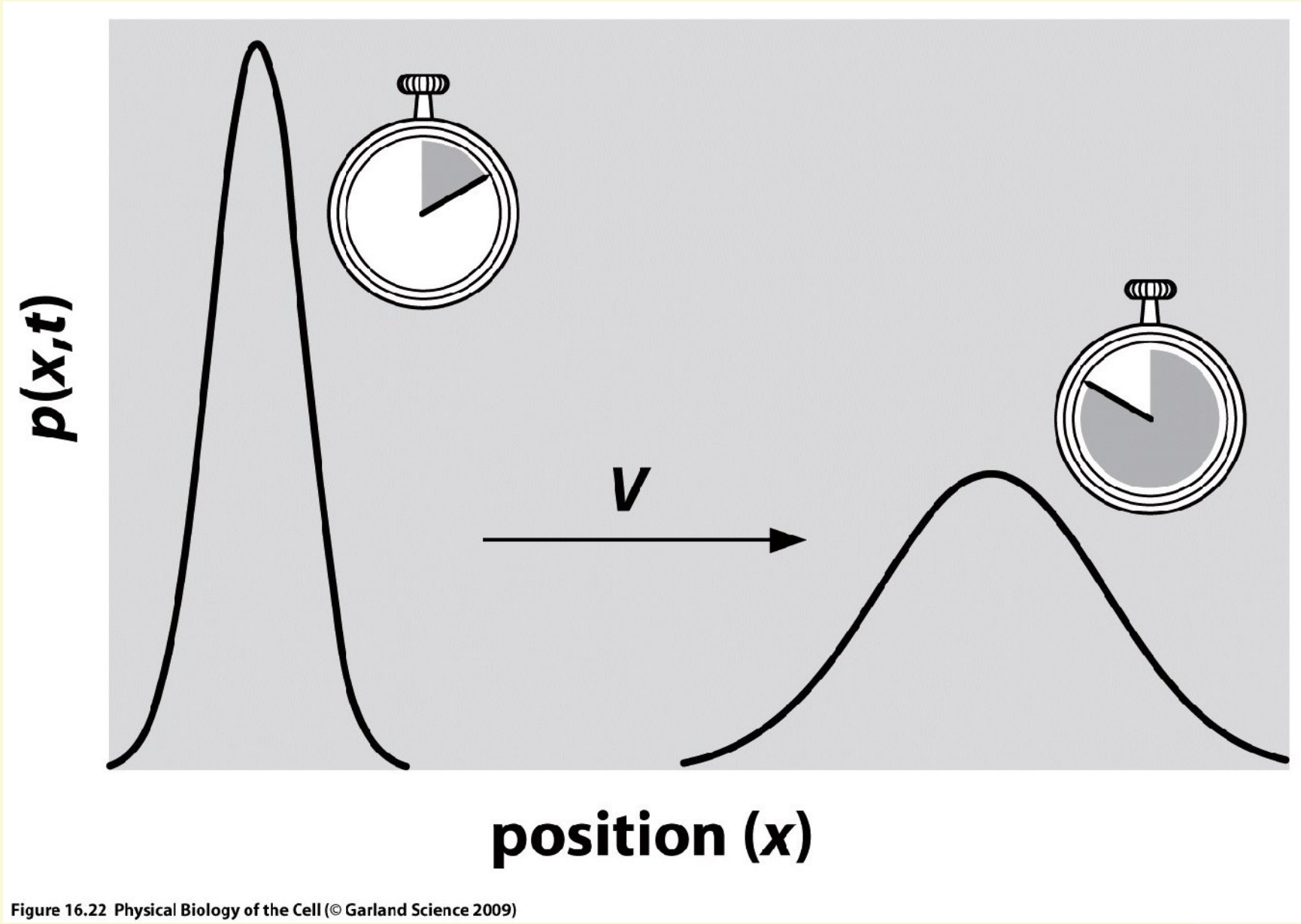
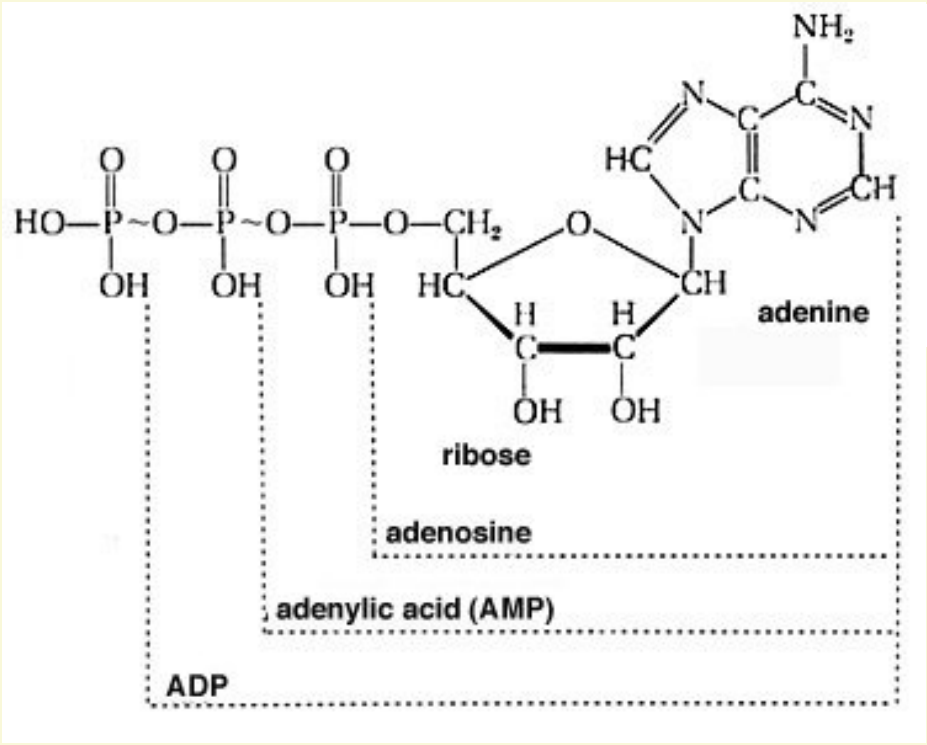


Figure 16.22 Physical Biology of the Cell (© Garland Science 2009)

Energy and force

- Energy content of molecular fuel
  - Maximum force?
- **Principle of detailed balance**
  - Force dependence of transition rates
- Free energy landscape, and what it means to understand the 'mechanism' of a motor protein.
- Force-velocity and [fuel]-velocity curves
- Calculation of first passage times

Free energy from ATP



$$\mu = \mu_0 + k_B T \ln(c/c_0)$$

$$\Delta G = \Delta G_0 - k_B T \ln \frac{[\mathrm{ADP}][\mathrm{P_i}]}{[\mathrm{ATP}]c_0}$$

c_0, G_0: standard conditions.

ΔG: distance from equilibrium

Bionumbers.com: $\Delta G_0 = -11\ k_B T$

Human muscle:

[ATP]~8.2 mM
[ADP]~9 .4 μM
[Pi]~3.7 mM

$\Delta G \sim -24\ k_B T$

Canonical value: $-20\ k_B T$

$$\mathrm{ATP} \rightleftharpoons \mathrm{ADP} + \mathrm{P_i}$$

Complications: several species
(ATP, ATP-Mg^{2+}, ...)

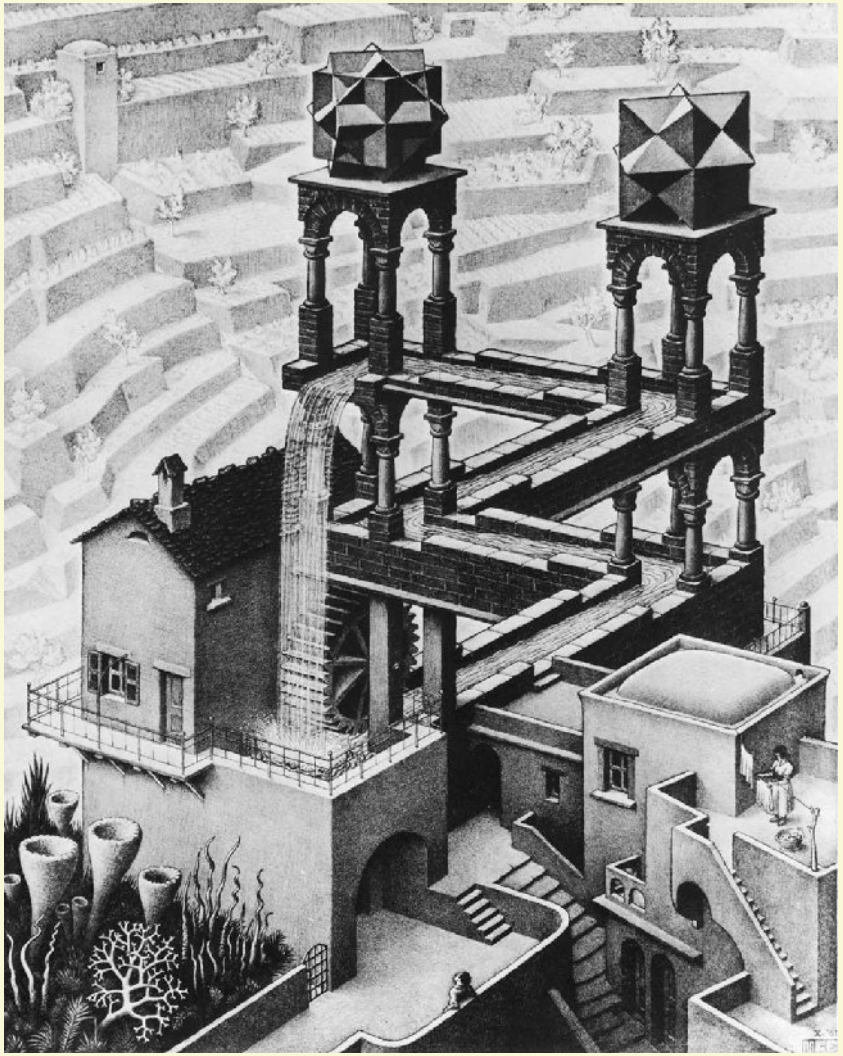
Maximal force from a single motor

$$F_{\max} = -\frac{\Delta G_{\mathrm{ATP}}}{\delta}$$

(rough estimate of upper limit)

- Kinesin: δ = 8.2 nm, F_{max} ~ 10 pN
  F_{stall} ~ 6-8 pN (in vitro)
- Myosin V: δ = 36 nm, F_{max} ~ 2.3 pN
  F_{stall} ~ 2-3 pN (in vitro)
- Many in vitro experiments are done far from physiological conditions (e.g., [ADP]~0).
- Why are these numbers so good...?

Principle of detailed balance



Consistency requirement: how to not model a perpetuum mobile.

$$\frac{k_{1\to 2}}{k_{2\to 1}} = \exp\left(-\frac{G_2 - G_1}{k_{\mathrm{B}}T}\right)$$

Applications

- Consistency check
- Motion implies force dependent rates
- Detect free energy transduction.

Motion implies force dependence

Reaction free energy under opposing load

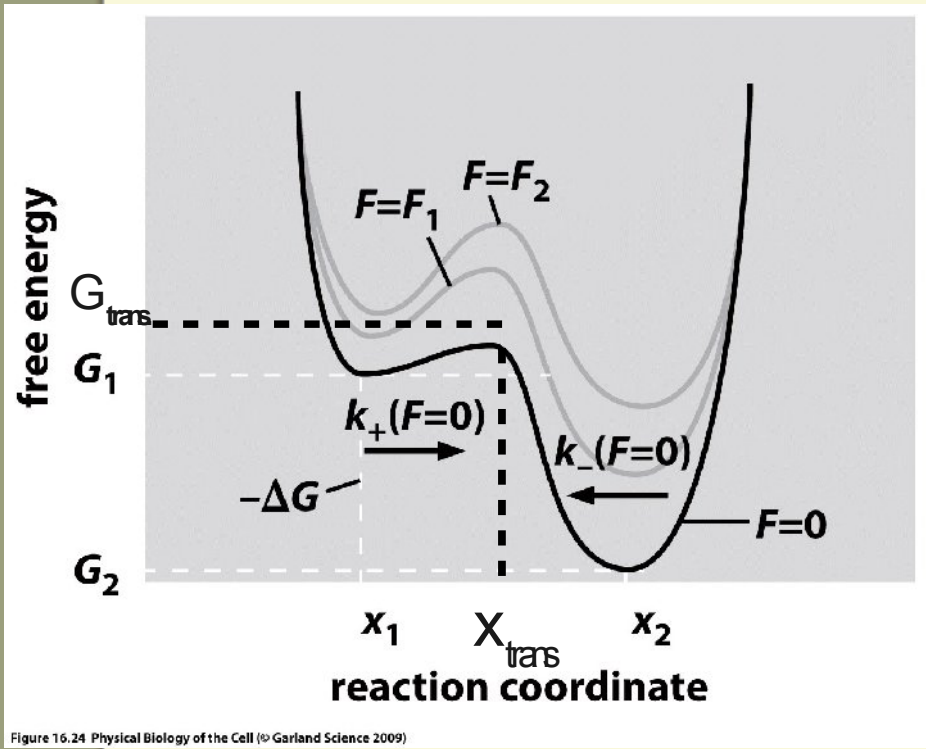


Figure 16.24 Physical Biology of the Cell (© Garland Science 2009)

Detailed balance:

$$\frac{k_{1\to 2}(\vec{F})}{k_{2\to 1}(\vec{F})} = \exp\left(-\frac{\Delta G(\vec{F}=0) + \vec{F}\cdot\Delta\vec{x}}{k_{\mathrm{B}}T}\right)$$

(If the wells have equal width...).

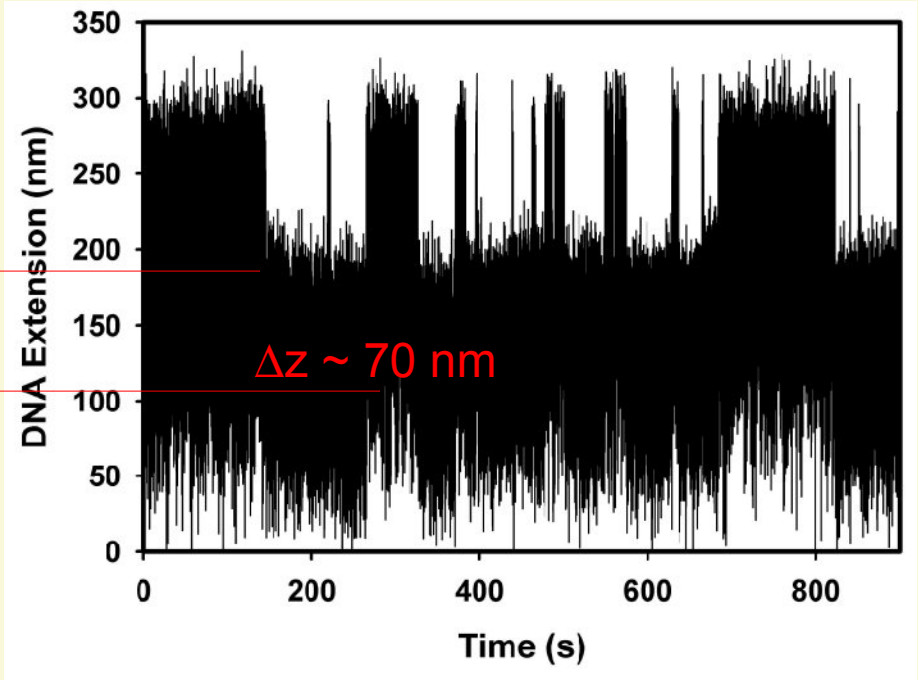
For a single rate

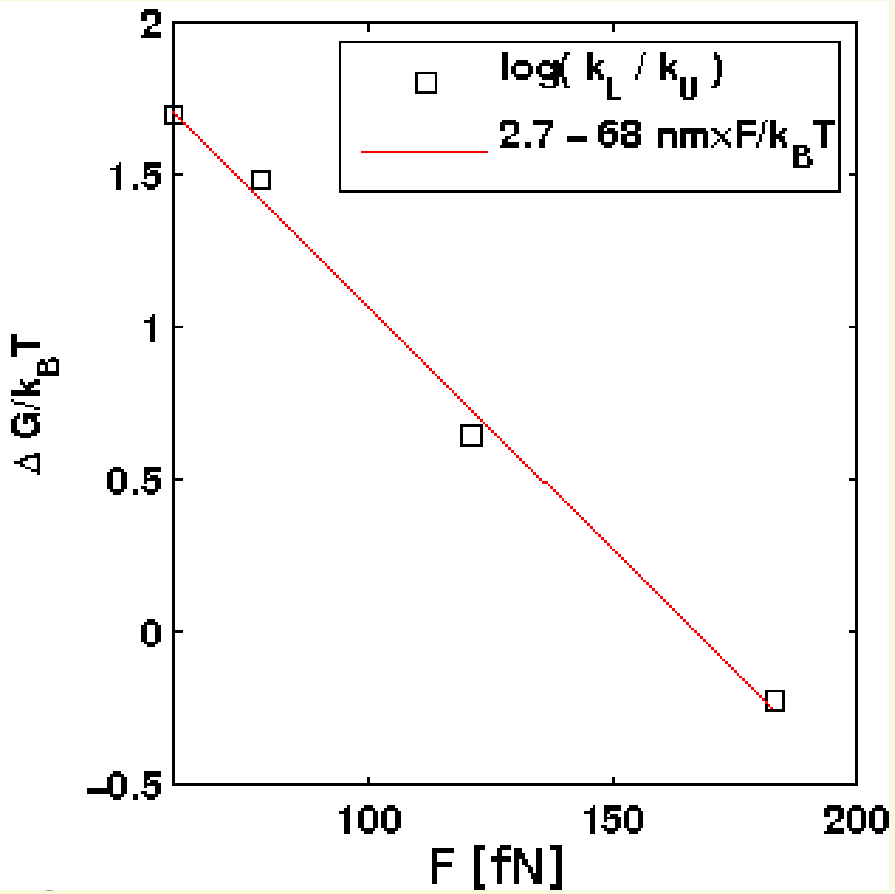
- Detailed balance only constrains the ratio.
- Common choice (quick&dirty): transition state theory

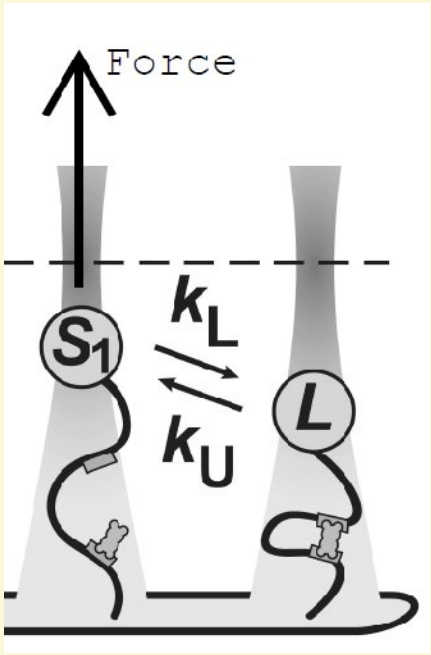
$$k(F) = k_0 e^{-\Delta G_{\mathrm{trans.}}/k_{\mathrm{B}}T}$$

$$k_{1\to 2}(\vec{F}) \approx k_{1\to 2}(0)\exp\left(-\frac{\vec{F}\cdot(\vec{x}_{\mathrm{trans.}} - \vec{x}_1)}{k_{\mathrm{B}}T}\right)$$

Detailed balance in action



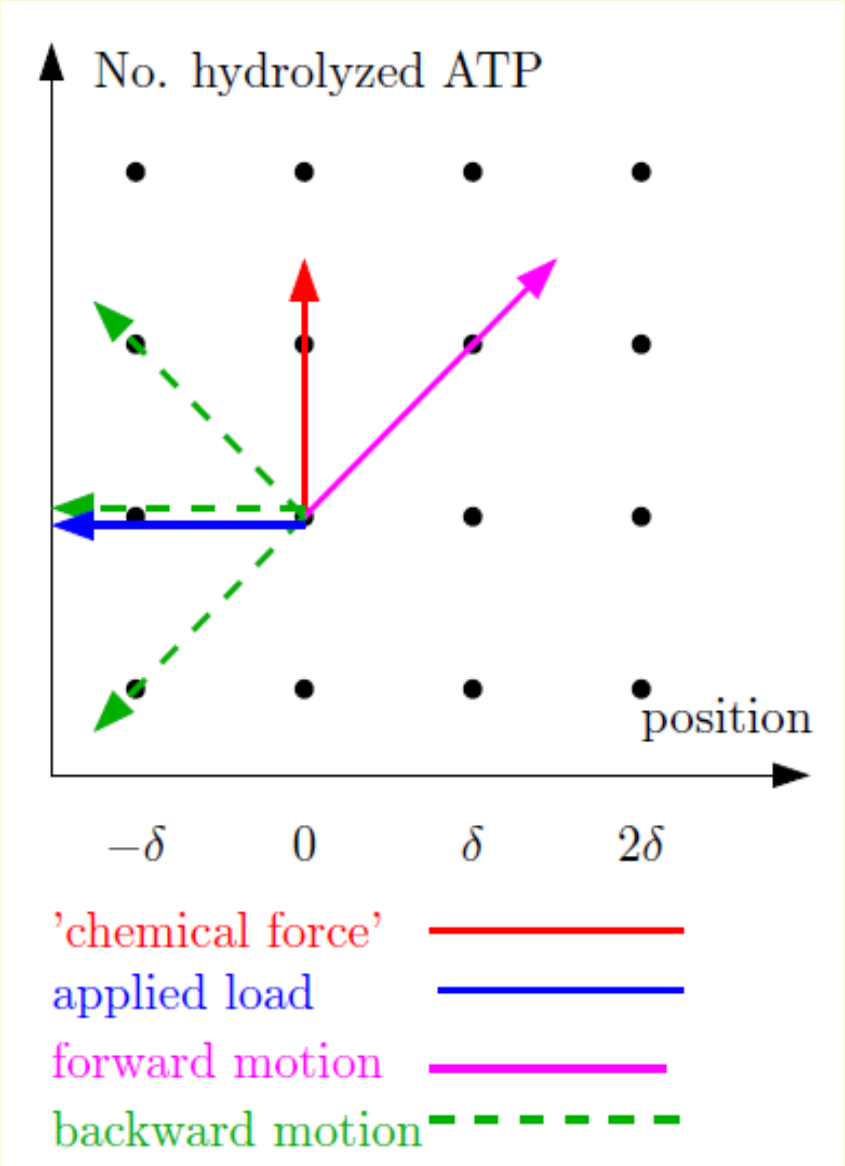




Meiners' lab
U Michigan

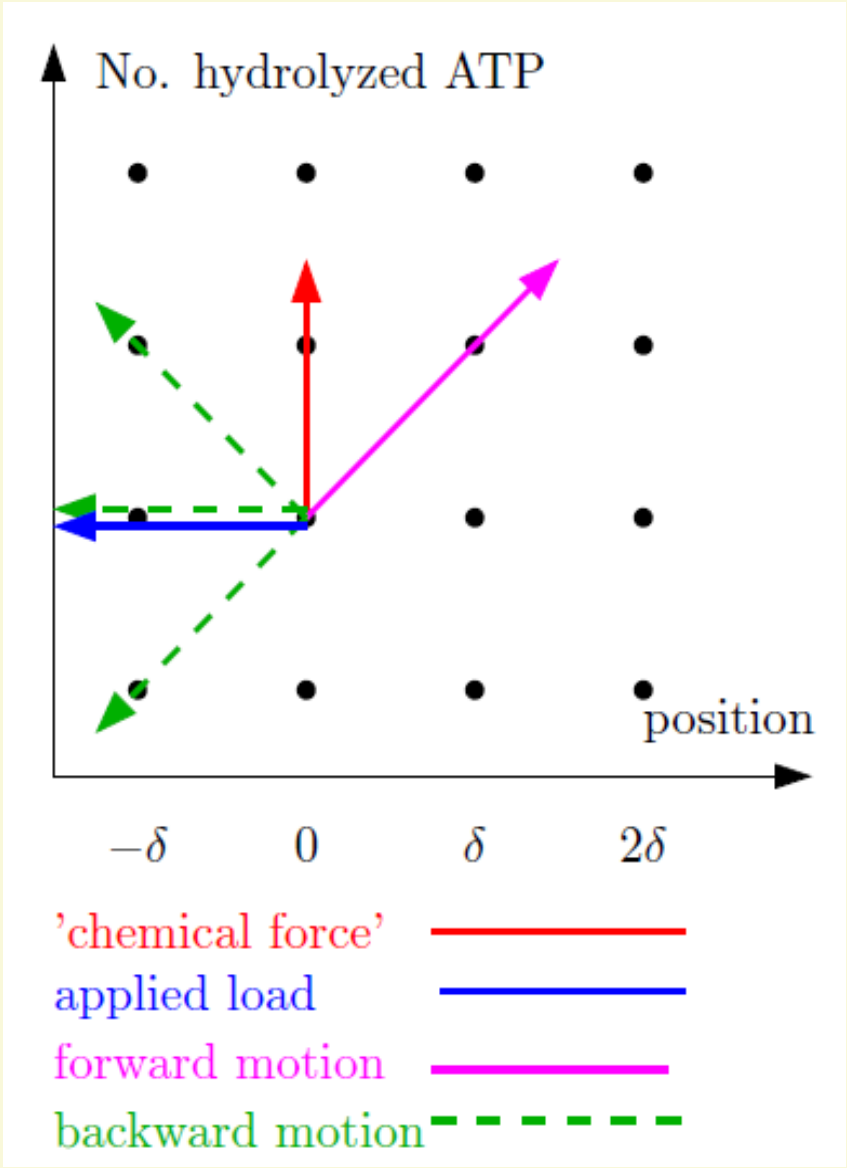
DNA looping: Binding and unbindi of looping protein is an equilibrium process.

Free energy landscape



- Keep track of position and fuel consumption independently.
- Direction of motion is not parallell to applied forces: some kinetic *"mechanism"* is at work.
- Backward steps are (somtimes) not reversed forward steps: no detailed balance in that case.
- Most useful for models with many states.

Free energy landscape

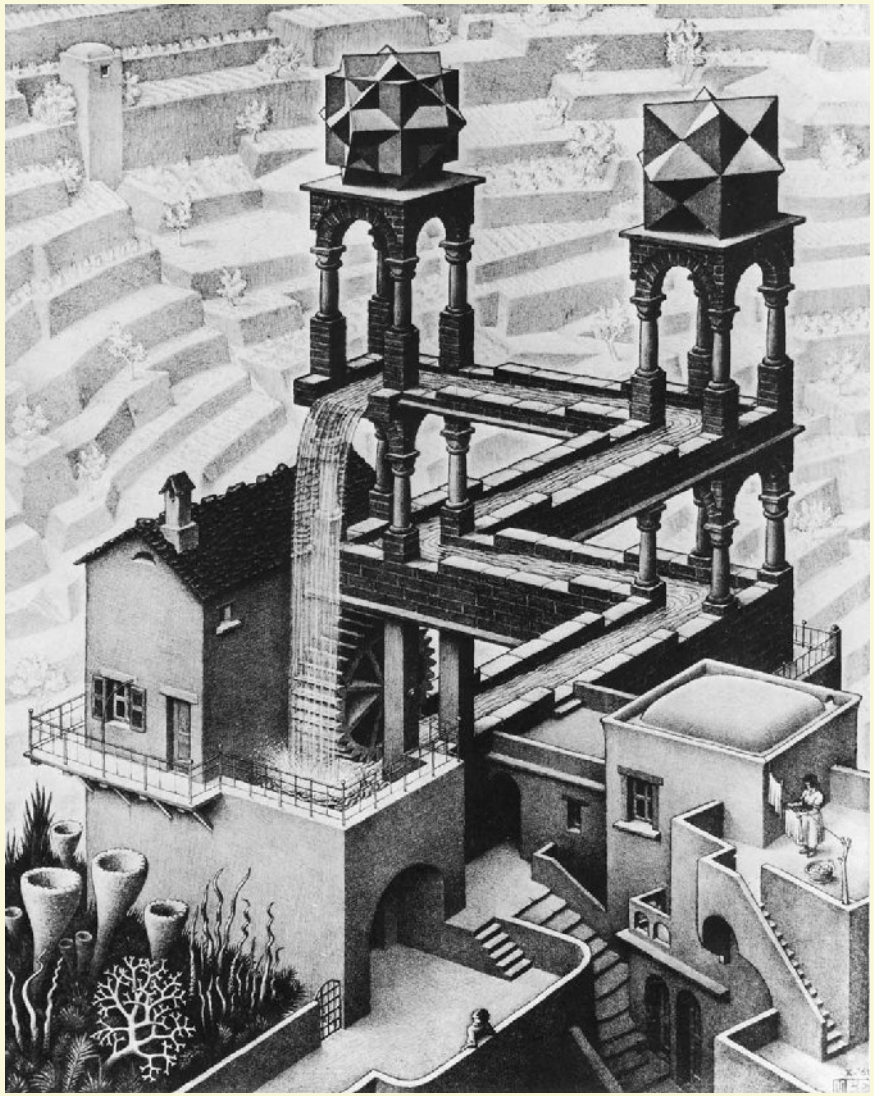


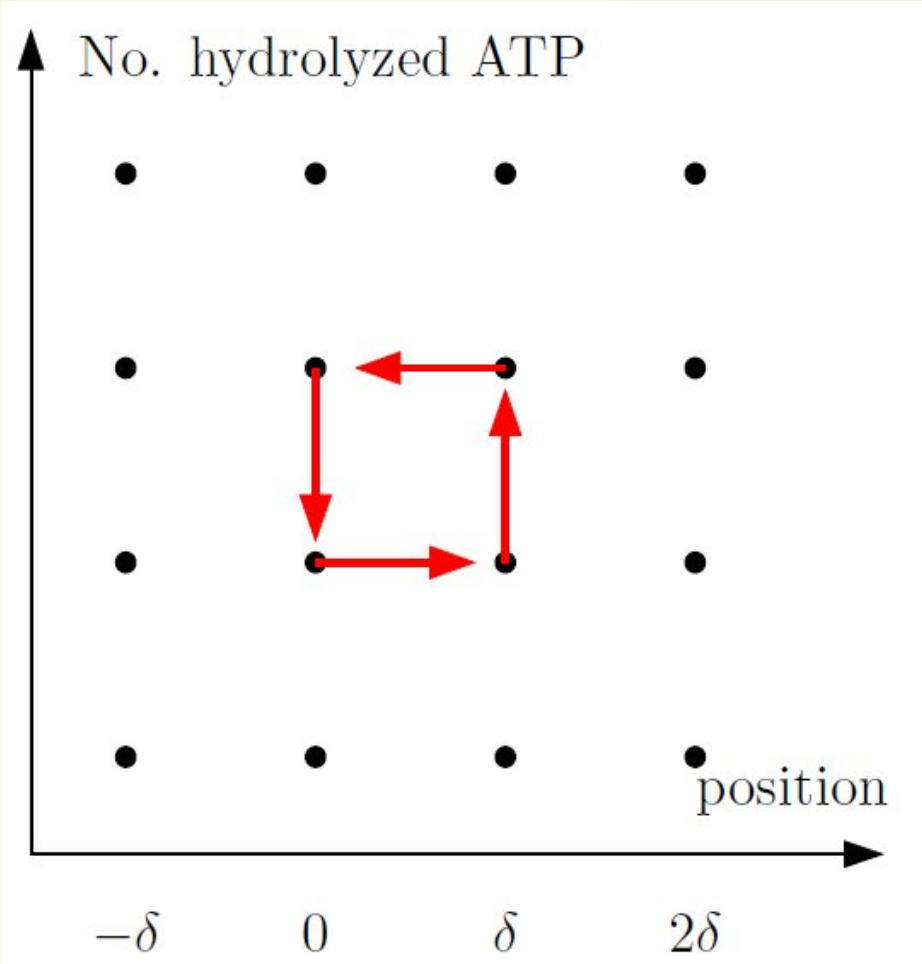
- Direction of motion is not sum of applied forces: some kinetic *"mechanism"* is needed.
- Stall force is pretty well described by the physiological ΔG_{ATP} , even far from physiological conditions. Why?

Speculation:

- Force is limited by kinetic mechanism, which is optimized for physiological conditions.

Escher and detailed balance...?





If the free energy change along a closed path is non-zero, then there is a 'hidden' driving force in the model. (This might be OK, just do not put it there by mistake.)

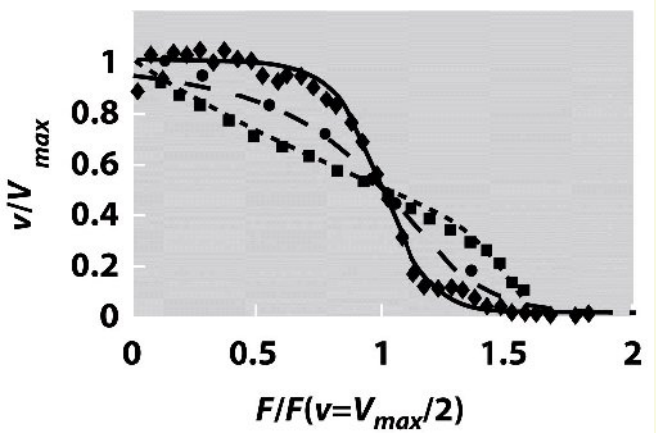
Beyond the 1-state model:

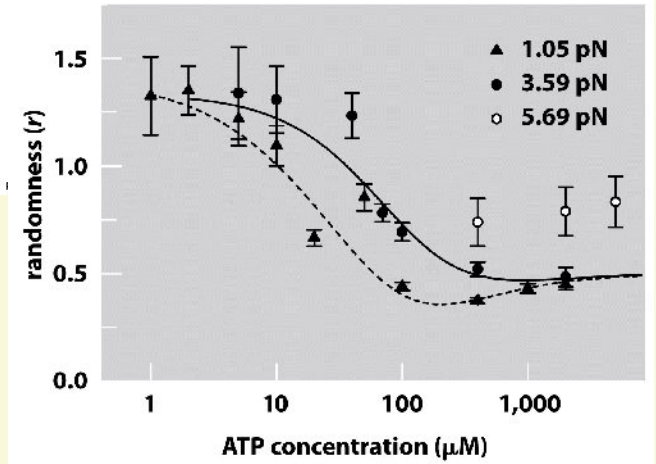
- Complex force-velocity relations

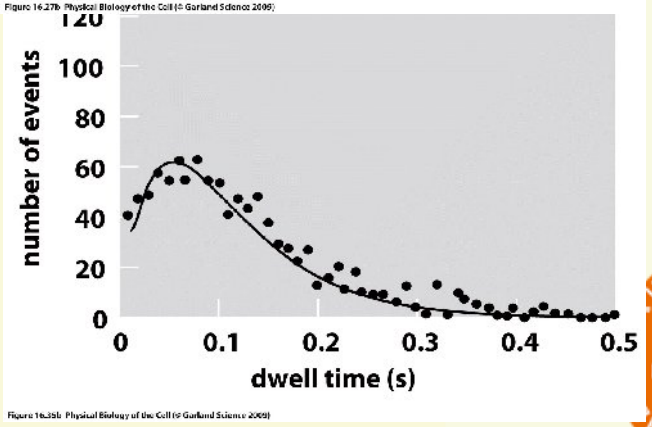
- Diffusion constant too low. 1-state prediction

$$r = \frac{2D}{v\delta} = \frac{k_+ + k_-}{k_+ - k_-} > 1$$

- Non-exponential waiting time distributions







III. First passage time calculations

- Workhorse: 2 state model.
- Non-exponential waiting times.
- Absorbing boundary vs adjoint equation.
- Moment generating functions.
- Several exits, . . ., (no time).

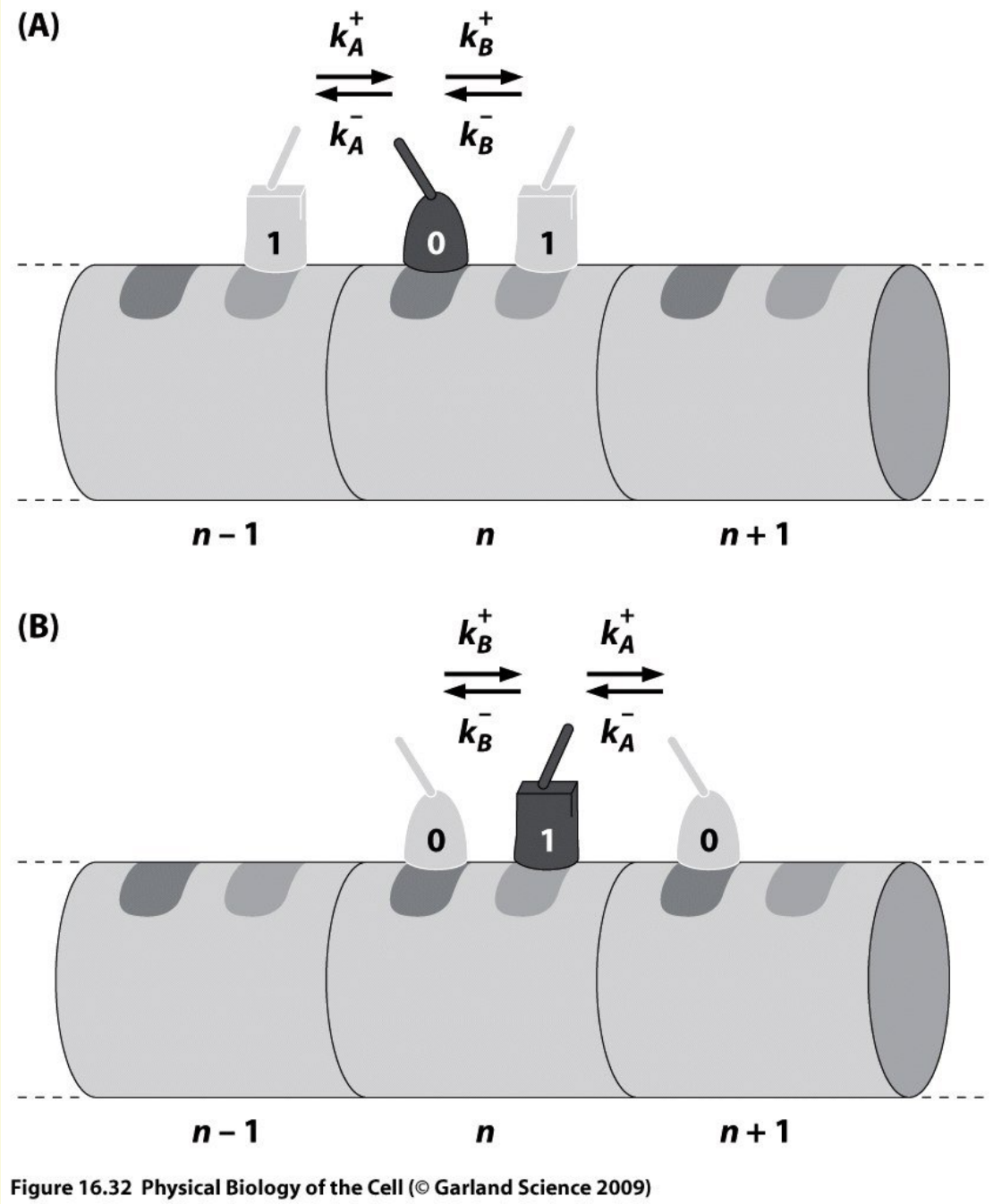
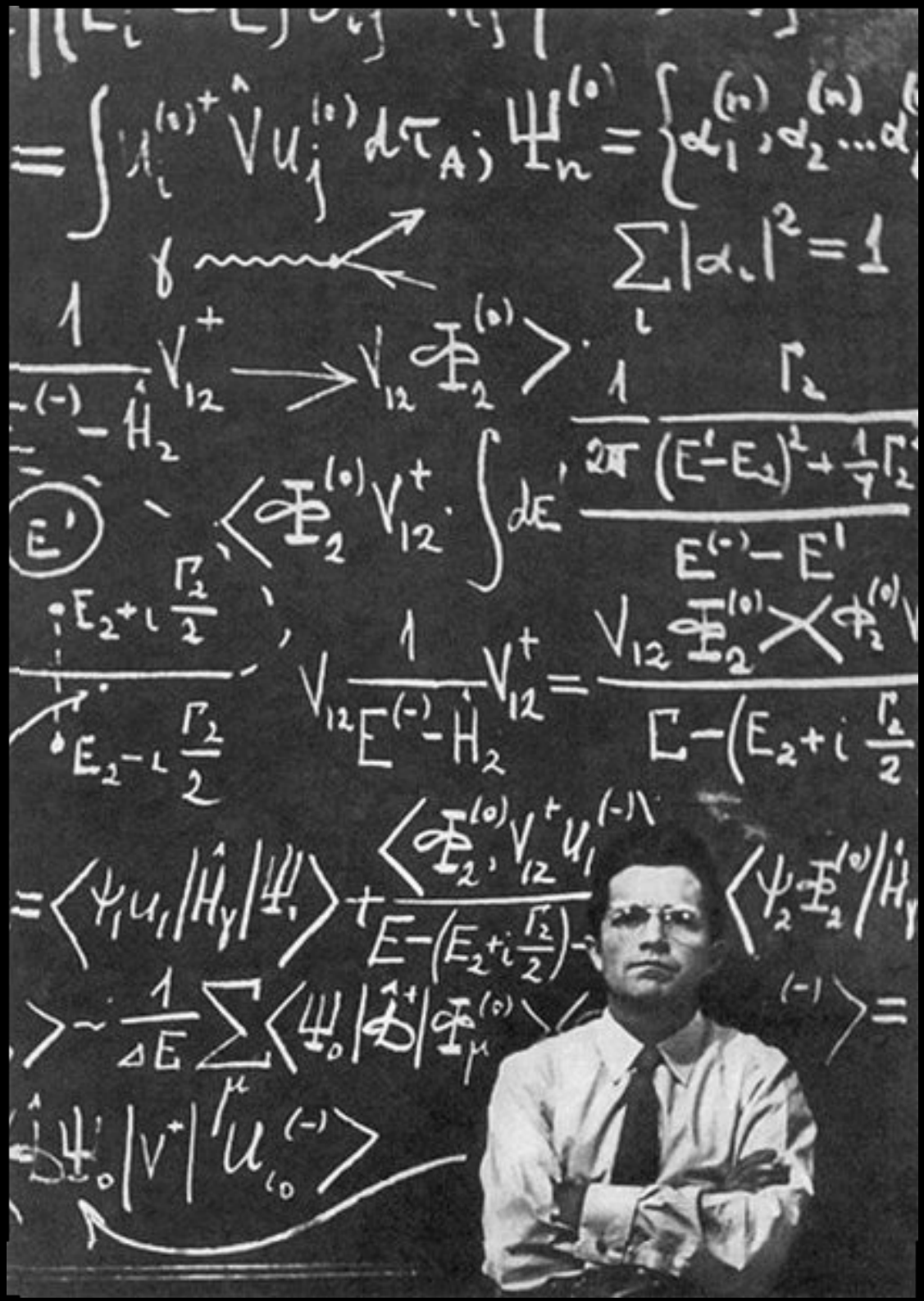


Figure 16.32 Physical Biology of the Cell (© Garland Science 2009)



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