Mechanics of molecules and biological structures

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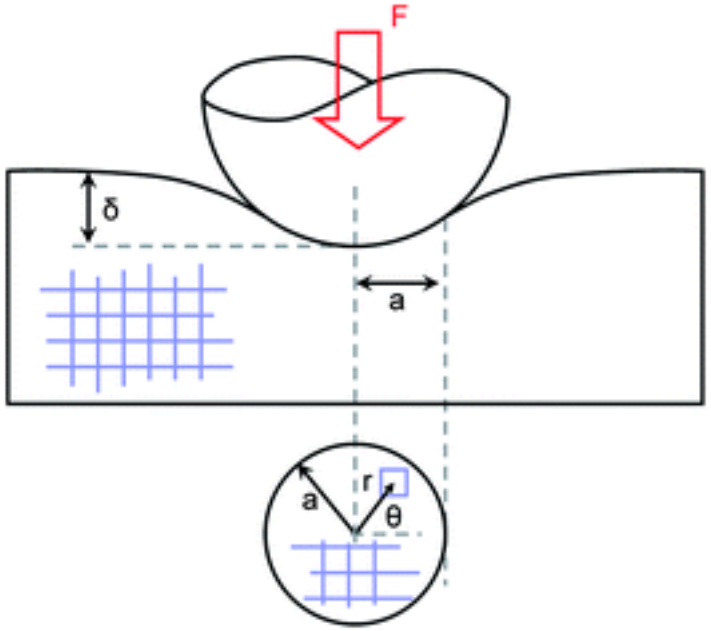
Acknowledgements:
- *Phillips, Kondev, Theriot, "Physical Biology of the Cell"*
- *Tom Duke († 2012)*

Mechanics



Rahmat et al. (2012). *Nanoscale* 4, 157-16

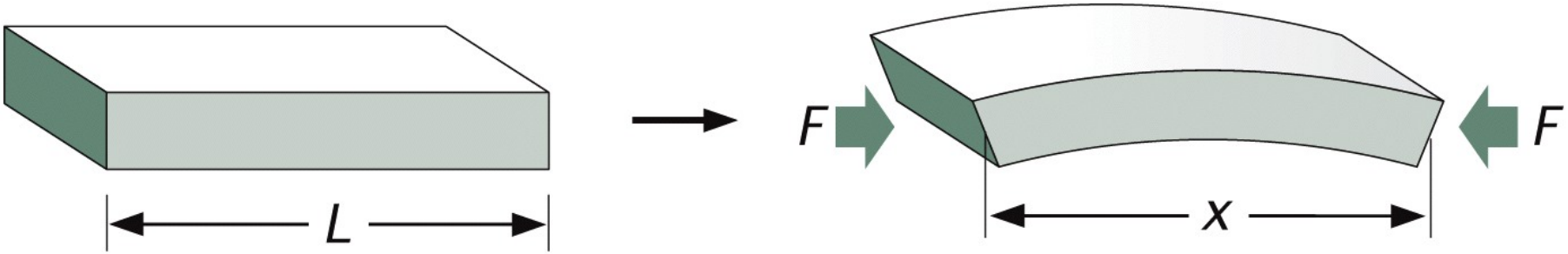
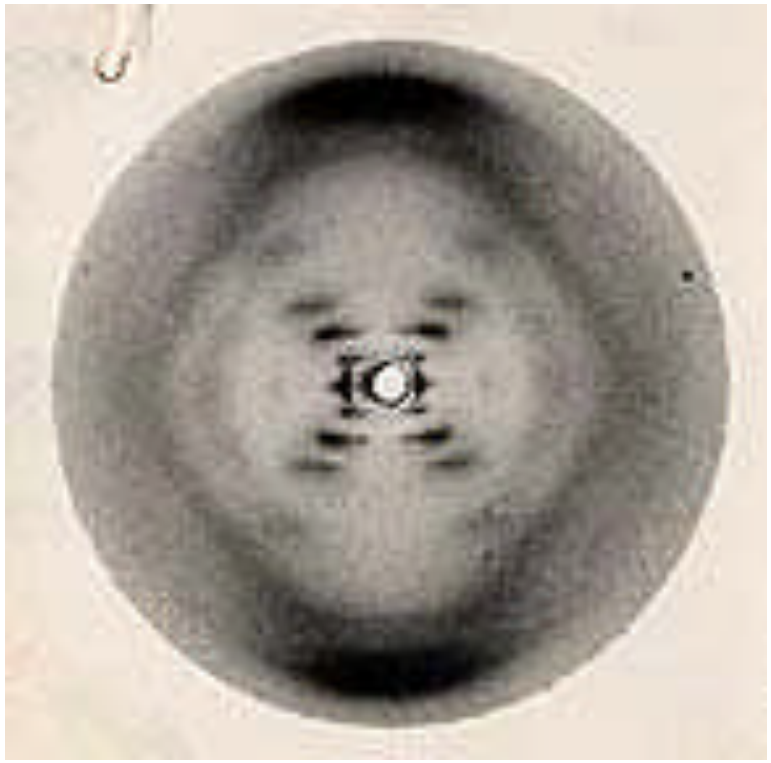
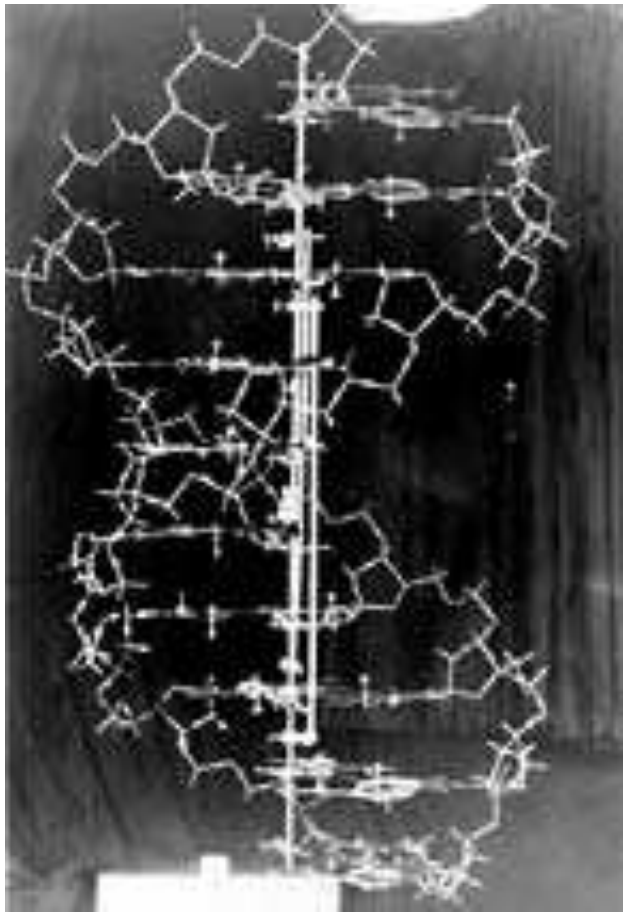


Figure 10.33a Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Nanotechnology mid-20th century



X-ray diffraction



Biological molecules are not typically restricted to one particular state

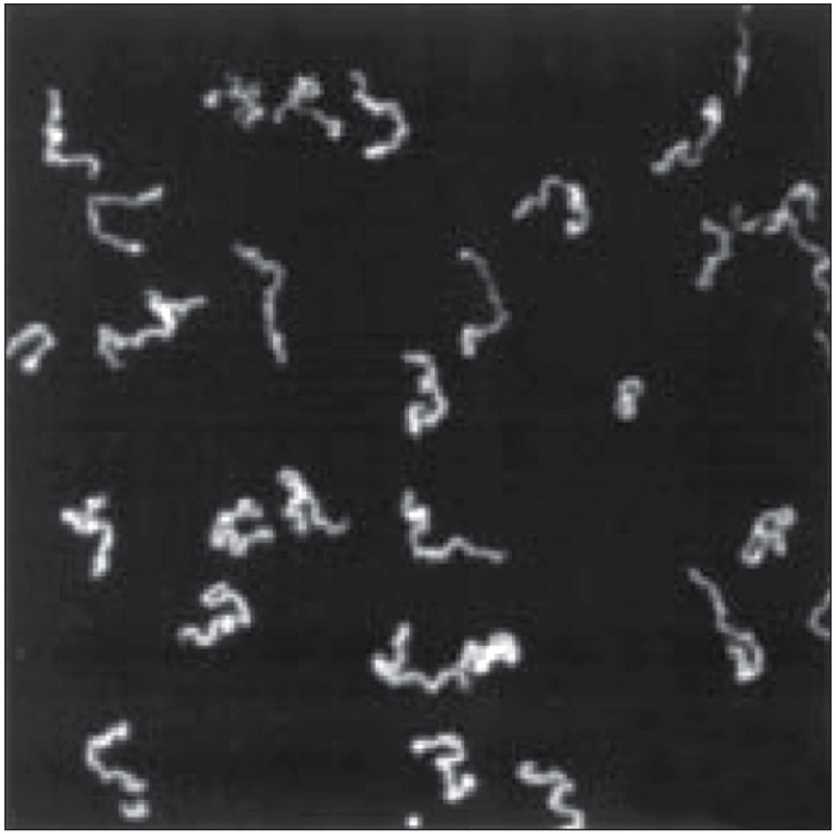
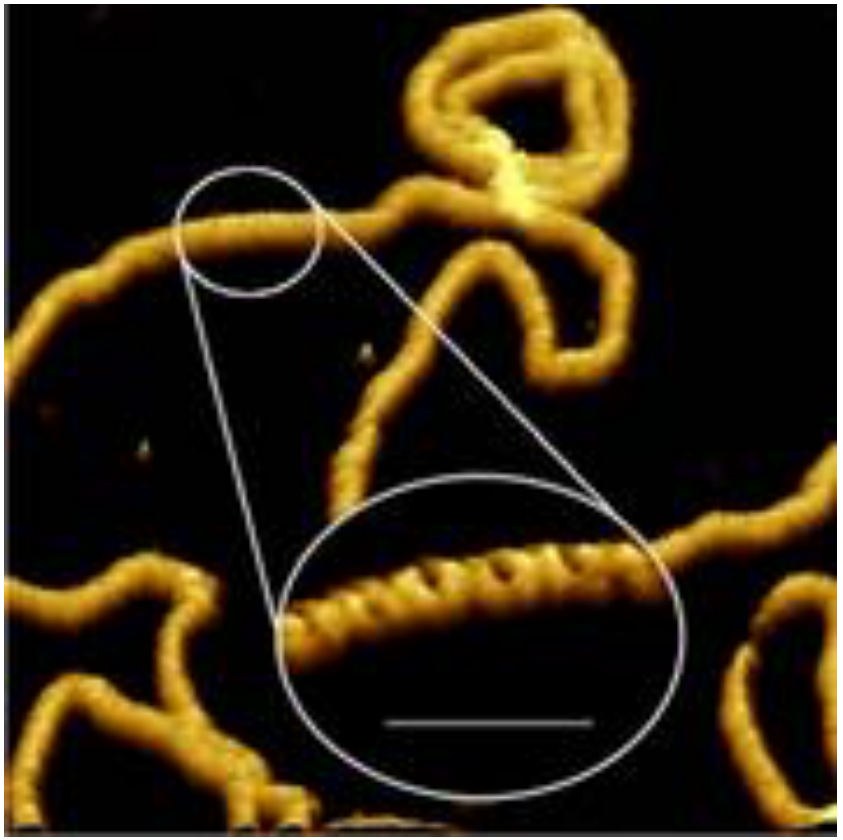


Figure 6.2a Physical Biology of the Cell, 2ed. (© Garland Science 2013)



Pyne et al., Small (2014).

Notes 1-2

Boltzmann distribution

Probability p of a system being in a state with energy E

$\propto \exp(-E/k_B T)$

Examples, for oxygen molecule:

p(Grenoble)/p(London) = 98%

p(Everest)/p(London) = 33%

When considering (macro-)molecular mechanics, we need not only consider the molecular (bending or stretching) energy, but the molecular *free* energy

Mechanics of molecules and biological structures

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August 6, 2015

These notes provide some more technical and mathematical details and background material for the lecture *Mechanics of Molecules and Biological Structures* at the *European School on Nanosciences & Nanotechnologies*, Grenoble.

1 Boltzmann distribution

The Boltzmann distribution prescribes that

$$\text{the probability of being in a state of energy } E \propto \exp\left(-\frac{E}{k_\mathrm{B}T}\right) , \tag{1.1}$$

where k_B is Boltzmann's constant (1.38×10^{-23} J/K) and T is the absolute temperature. At room temperature (about 300 K), $k_\mathrm{B}T \approx 4.1 \times 10^{-21}$ J $= 4.1$ pN nm.

The general derivation of the Boltzmann distribution can be found in textbooks on statistical mechanics. To make Eq. 1.1 plausible, I will here derive it in the special case of the distribution of gas molecules as a function of height. In that case, the energy of a a gas molecules is given by

$$E(h) = mgh\,, \tag{1.2}$$

as you may remember from secondary school, where m is the mass of a molecule, $g \approx 9.8$ m s^{-2} the gravitational acceleration, and h the height above a reference surface.

You may also remember the ideal gas law,

$$PV = nRT\,, \tag{1.3}$$

with

P the pressure of the gas;

V the volume of the gas;

n the amount of gas (in moles);

$R = k_\mathrm{B}N_A$ the gas constant, with N_A ($\approx 6.0 \times 10^{23}$ mole^{-1}) the Avogadro constant;

T is the absolute temperature as previously.

This allows us to write

$$P = \left(\frac{n}{V}\right) RT = \left(\frac{nN_A}{V}\right) k_{\mathrm{B}} T = n_V \, k_{\mathrm{B}} T \,, \tag{1.4}$$

where we define n_V as the number of gas molecules per unit volume.

Assuming that T does not depend on the height, we can take the derivative

$$\frac{\mathrm{d}P}{\mathrm{d}h} = \left(\frac{\mathrm{d}n_V}{\mathrm{d}h}\right) k_{\mathrm{B}} T \,. \tag{1.5}$$

To derive the Bolzmann distribution in this case, we also calculate $\mathrm{d}P/\mathrm{d}h$ in a different way, as follows.

Given a gas volume of cross section A and height $\mathrm{d}h$, the amount the molecules in this volume is $n_V A \mathrm{d}h$, which translates to a force

$$|\mathrm{d}F| = (mg)(n_V A \mathrm{d}h) \tag{1.6}$$

that is exerted on the gas column below it. Since the pressure $P = F/A$, we can thus derive that an height increment $\mathrm{d}h$ leads to a change in pressure

$$\mathrm{d}P = \frac{1}{A}\mathrm{d}F = mgn_V \times (-\mathrm{d}h) \,, \tag{1.7}$$

where the minus sign refers to the fact that the pressure will go down with increasing height. Rearranging and equating to the earlier result for $\mathrm{d}P/\mathrm{d}h$, Eq. 1.5, we find

$$\frac{\mathrm{d}P}{\mathrm{d}h} = -mgn_V = \left(\frac{\mathrm{d}n_V}{\mathrm{d}h}\right) k_{\mathrm{B}} T \,. \tag{1.8}$$

Hence,

$$\frac{\mathrm{d}n_V}{\mathrm{d}h} = \left(-\frac{mg}{k_{\mathrm{B}} T}\right) n_V \,, \tag{1.9}$$

which is a differential equation with solution

$$n_V \propto \exp\left(-\frac{mgh}{k_{\mathrm{B}} T}\right) = \exp\left(-\frac{E(h)}{k_{\mathrm{B}} T}\right) \,. \tag{1.10}$$

This proves the Boltzmann formula Eq. 1.1 in the special case of an ideal gas, if we realise that the probability to find a molecule at height h is proportional to the average number of molecules that can be found at that height, *i.e.*, $p(h) \propto n_V(h)$.

2 Free energy

To understand the concept of free energy, it is useful to again consider the case of molecules in an ideal gas. As derived in Section 1, the probability of a gas molecule being at height h is

$$p(h) \propto \exp\left(-\frac{E(h)}{k_{\mathrm{B}}T}\right) . \tag{2.1}$$

With $E(h) = mgh$ and recalling the respective altitudes of Grenoble and London, it thus follows that

$$\frac{\text{probability to find a gas molecule in Grenoble}}{\text{probability to find a gas molecule in London}} = \frac{\exp(-mg \times 214 \text{ meter}/k_{\mathrm{B}}T)}{\exp(-mg \times 115 \text{ feet}/k_{\mathrm{B}}T)} . \tag{2.2}$$

Since 115 feet corresponds to 35 m and since an O_2 molecule has a mass of $(32 \text{ g/mol})/N_A = 5.3 \times 10^{-26}$ kg, the probability to find an an oxygen molecule in Grenoble is

$$\frac{p(\text{Grenoble})}{p(\text{London})} = \exp\left(-\frac{5.3 \times 10^{-26} \text{ kg} \times 9.8 \text{ m s}^{-2} \times (214 - 35) \text{ m}}{4.1 \text{ pN nm}}\right) \tag{2.3}$$

$$= \exp\left(-\frac{5.3 \times 9.8 \times 179 \times 10^{-5} \text{ pN nm}}{4.1 \text{ pN nm}}\right) \tag{2.4}$$

$$= \exp\left(-\frac{0.093 \text{ pN nm}}{4.1 \text{ pN nm}}\right) = 98\% \tag{2.5}$$

of the probability of finding it in London, which is probably the reason why you feel a only moderately asphyxiated by now.

Looking at this in another way, we can observe that $k_{\mathrm{B}}T$ is large compared to the difference in potential energy between Grenoble and London, 4.1 pN nm $\gg 0.093$ pN nm in Eq. 2.5, *i.e.*, thermal fluctuations dominate gravitation as far as the O_2 distribution is concerned. If this were not the case, the trip from London to Grenoble would represent a significant health-and-safety hazard.

For comparison, the same calculation — ignoring any difference in temperature — gives us a difference in potential energy of 4.6 pN nm between an O_2 molecule on Mount Everest and one in London. This is very similar to the energy of thermal fluctuations, and leaving us with a rather hazardous result of only 33%.

To understand the concept of free energy, let us compare the probability of finding a gas molecule in a CNRS seminar room in Grenoble with the probability of finding a gas molecule in a tiny lecturer's office in London. Now we will not only have to take into account the difference in (gravitational) energy, but also the difference in room size, *i.e.*,

$$\frac{\text{probability of gas molecule in seminar room}}{\text{probability of gas molecule in lecturer's office}} = \frac{V_{\text{seminar room}}}{V_{\text{lecturer's office}}} \frac{\exp(-E_{\text{Grenoble}}/k_{\mathrm{B}}T)}{\exp(-E_{\text{London}}/k_{\mathrm{B}}T)} , \tag{2.6}$$

where E_{Grenoble} and E_{London} refer to the potential energy of a gas molecule in Grenoble and London, respectively, and $V_{\text{lecturer's office}}$ and $V_{\text{seminar room}}$ to the respective sizes of the seminar room and the lecturer's office.

To make this result more general, we can assume that a gas molecule occupies a (small) volume ν, such that we can define its total number of distinguishable positions $W = V/\nu$ for a macroscopic volume V. With $W_{\text{Grenoble}} = V_{\text{seminar room}}/\nu$ and With $W_{\text{London}} = V_{\text{lecturer's office}}/\nu$, we can write

$$\frac{\text{probability of molecule in seminar room}}{\text{probability of molecule in lecturer's office}} = \frac{\exp(-(E_{\text{Grenoble}} + Tk_{\text{B}} \ln W_{\text{Grenoble}})/k_{\text{B}}T)}{\exp(-(E_{\text{London}} + Tk_{\text{B}} \ln W_{\text{London}})/k_{\text{B}}T)} \tag{2.7}$$

$$= \frac{\exp(-F_{\text{Grenoble}}/k_{\text{B}}T)}{\exp(-F_{\text{London}}/k_{\text{B}}T)}\,, \tag{2.8}$$

where

$$F = E - Tk_{\text{B}} \ln W = E - TS \tag{2.9}$$

is the Helmholtz free energy, and

$$S = k_{\text{B}} \ln W \tag{2.10}$$

the entropy.

In this particular example $V_{\text{seminar room}} \gg V_{\text{lecturer's office}}$, such that it is much more likely to find a molecule in the seminar room in Grenoble than it is to find a molecule in the lecturer's office in London, even though the molecule in Grenoble has a higher potential energy.

Summarising, if the energy difference between two states is small compared to the energy of thermal fluctuations ($k_{\text{B}}T$), probabilities are dominated by the number of possible configurations (positions) for the molecule at each particular energy. Hence, entropy is important, and in general the most favourable state is the one with the lowest *free* energy.

1. Effect of fluctuations on mechanics

a. Single-molecule mechanics

Single molecule mechanics: experiments

Atomic Force Microscopy

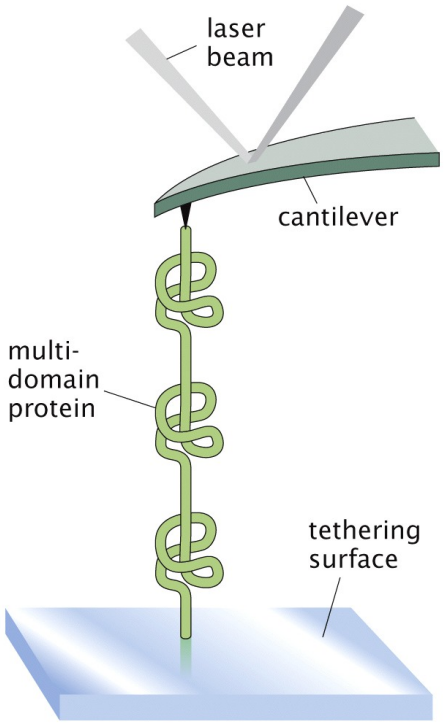
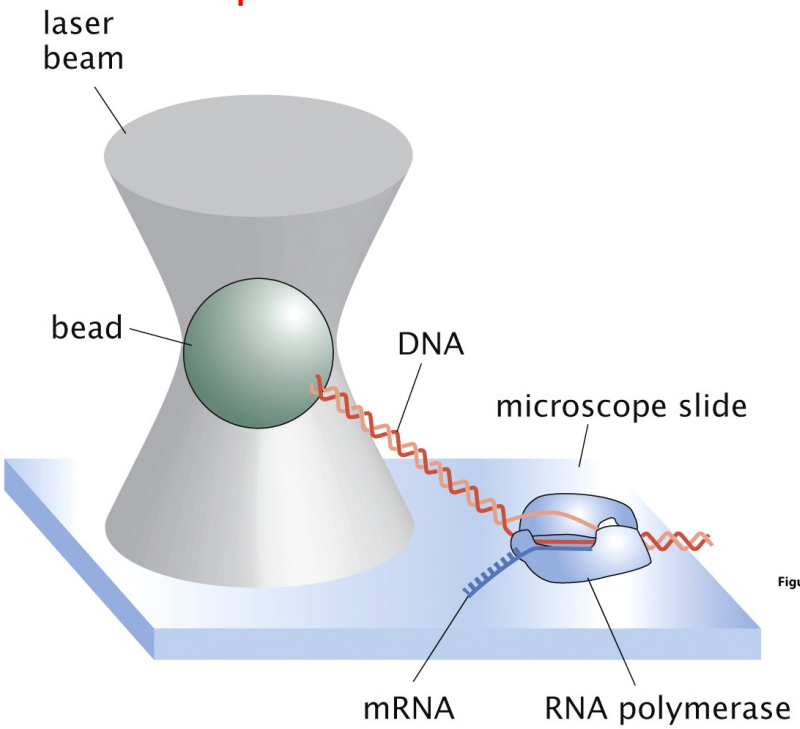


Figure 8.21a Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Optical Tweezers



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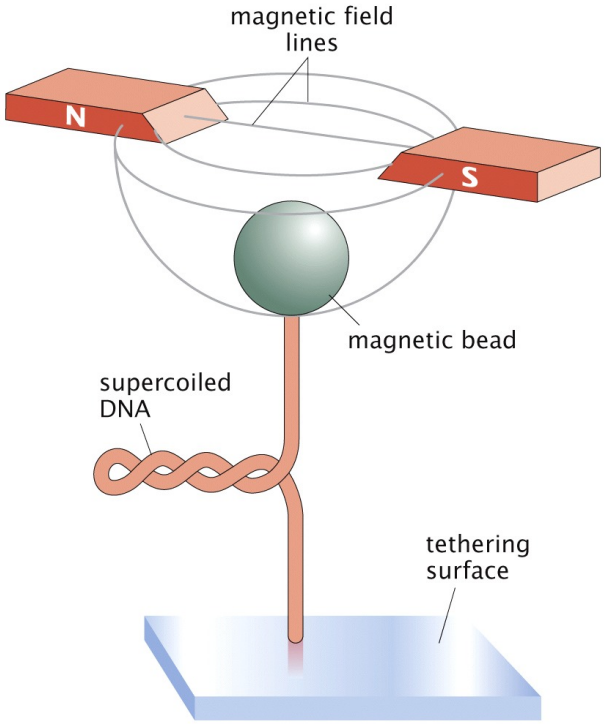
Magnetic Tweezers



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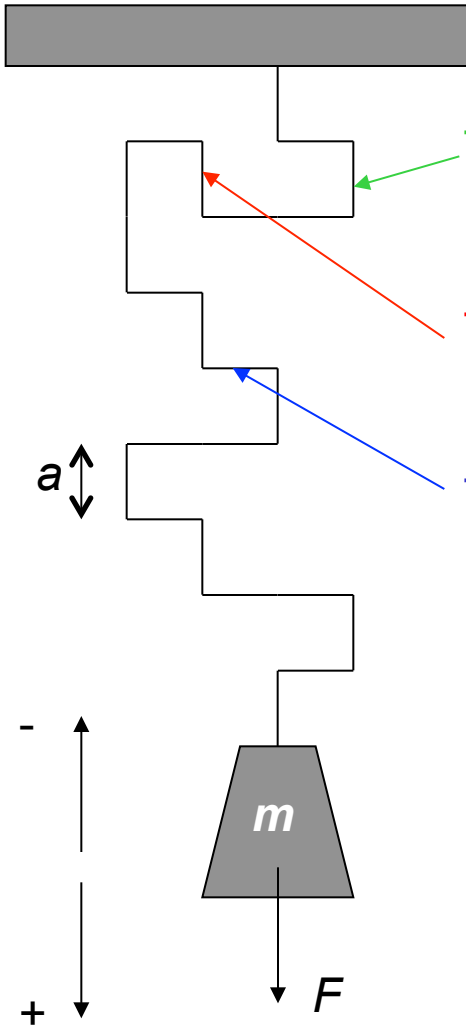
Molecular stretching on a 3D lattice



This orientation (down) lowers the potential energy by *Fa*

This orientation (up) raises the potential energy by *Fa*

This orientation does not change the potential energy

$$\langle L_1 \rangle = \frac{-a \exp(-Fa/k_B T) + a \exp(+Fa/k_B T) + 0 + 0 + 0 + 0}{\exp(-Fa/k_B T) + \exp(+Fa/k_B T) + 4 \exp(0)}$$

$$\frac{\langle L \rangle}{L_{tot}} = \frac{2 \sinh(Fa/k_B T)}{4 + 2 \cosh(Fa/k_B T)} \approx \frac{Fa}{3 k_B T} \quad \text{for } Fa << k_B T$$

3 Gaussian spring

The Boltzmann distribution can help us to predict the force-extension relation for a molecular-scale chain of paperclips, as a model for, e.g., DNA. If this chain is stretched by a force F along the z direction and we assume for simplicity that each paperclip can only be oriented parallel to the three axes (x, y and z) of a cartesian coordinate system, we can derive the average end-to-end distance of the chain

$$\langle L \rangle = N \langle L_1 \rangle \,, \tag{3.1}$$

where N is the number of paperclips on the chain, and $\langle L_1 \rangle$ the average projection of a paperclip along the pulling direction,

$$\langle L_1 \rangle = \frac{a \exp(Fa/k_\mathrm{B}T) - a \exp(-Fa/k_\mathrm{B}T)}{4 + \exp(Fa/k_\mathrm{B}T) + \exp(-Fa/k_\mathrm{B}T)} \,. \tag{3.2}$$

Here a is the paperclip length such that $L_\mathrm{tot} = Na$ is the stretched length of the chain. Hence

$$\langle L \rangle = \frac{\exp(Fa/k_\mathrm{B}T) - \exp(-Fa/k_\mathrm{B}T)}{4 + \exp(Fa/k_\mathrm{B}T) + \exp(-Fa/k_\mathrm{B}T)} \times L_\mathrm{tot} \,. \tag{3.3}$$

A similar result can be derived if one lets the paperclips be oriented in arbitrary direction, *i.e.*, not limited to the cartesian axes. We can now consider three special cases:

- $Fa \gg k_\mathrm{B}T$, such that $\langle L \rangle \approx \exp(Fa/k_\mathrm{B}T)/\exp(Fa/k_\mathrm{B}T) \times L_\mathrm{tot} = L_\mathrm{tot}$, *i.e.*, the chain is completely straightened.
- $F = 0$, which implies that $\langle L \rangle = 0$, *i.e.*, without a force, the two ends of the chain are on average at the same position.
- $Fa \ll k_\mathrm{B}T$, such that for small forces, the average end-to-end distance can be approximate by a Taylor expansion, and begins to deviate from zero according to

  $$\langle L \rangle \approx \frac{(1 + Fa/k_\mathrm{B}T) - (1 - Fa/k_\mathrm{B}T)}{4 + (1 + Fa/k_\mathrm{B}T) + (1 - Fa/k_\mathrm{B}T)} \times L_\mathrm{tot} \approx \frac{2Fa/k_\mathrm{B}T}{6} L_\mathrm{tot} \,. \tag{3.4}$$

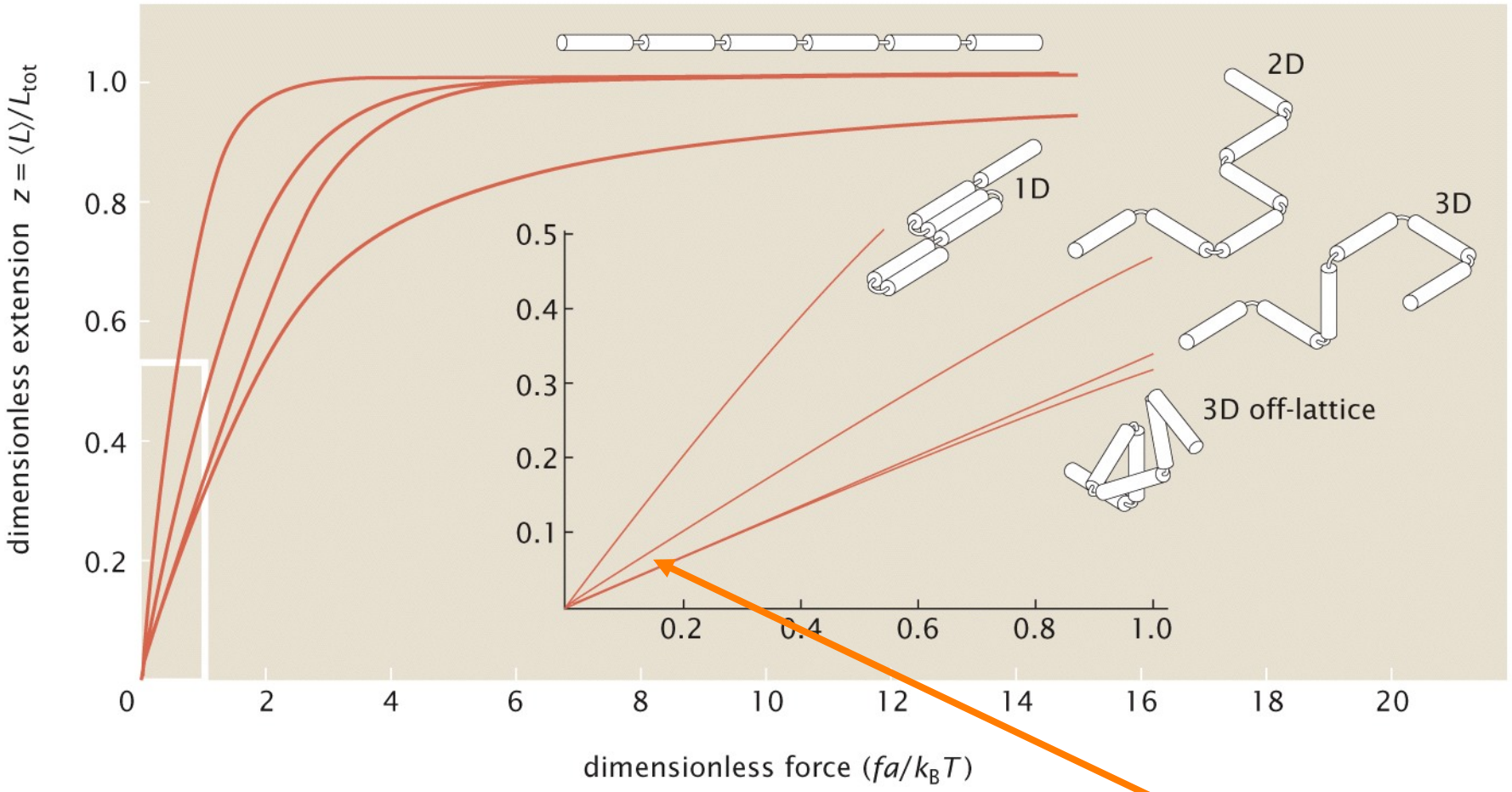
  This can be rewritten as

  $$F \approx \frac{3k_\mathrm{B}T}{aL_\mathrm{tot}} \langle L \rangle = k_L \langle L \rangle \,, \tag{3.5}$$

  which is identical to Hooke's law if we take $\langle L \rangle$ as an extension and $k_L = 3k_\mathrm{B}T/(aL_\mathrm{tot})$ as a spring constant.

This chain of paperclips will thus behave as flexible cord that already starts behaving as a (so-called Gaussian) spring when its two ends are very close together, and that only at much larger forces may behave as an elastic cord under tension, going from completely straightened to over-stretched.

Force-extension experiments



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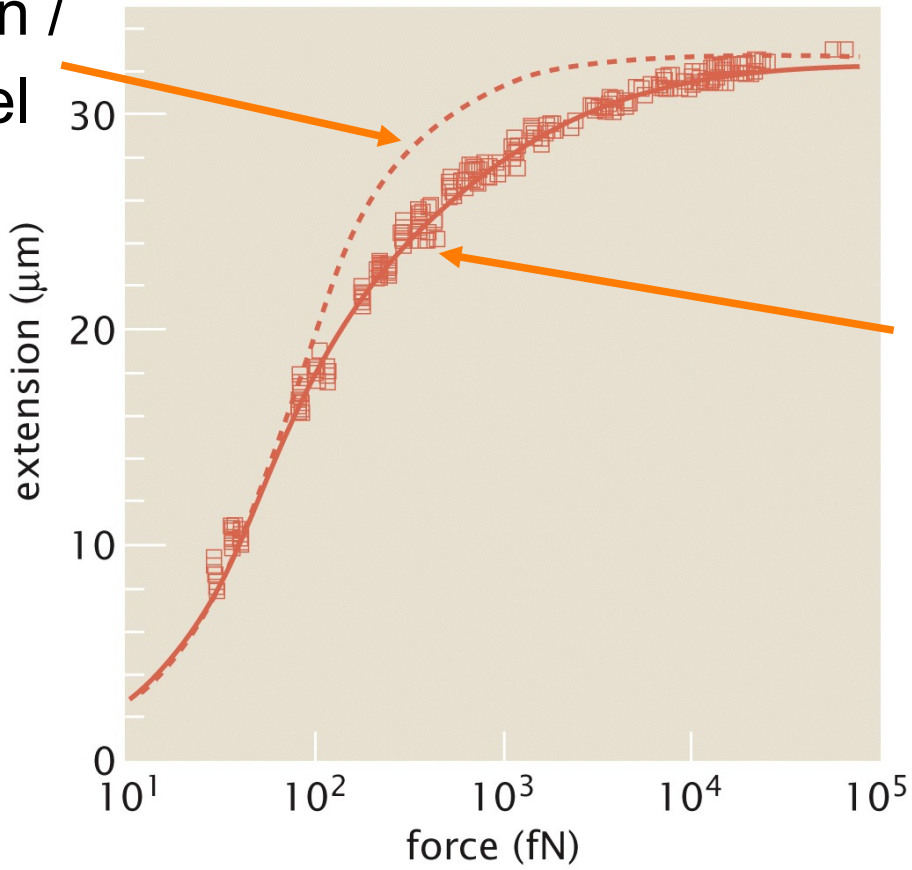
Force-extension curve for dsDNA

Freely jointed chain / random walk model



Experiment & "worm-like chain"

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Random-walk models (without applied force)

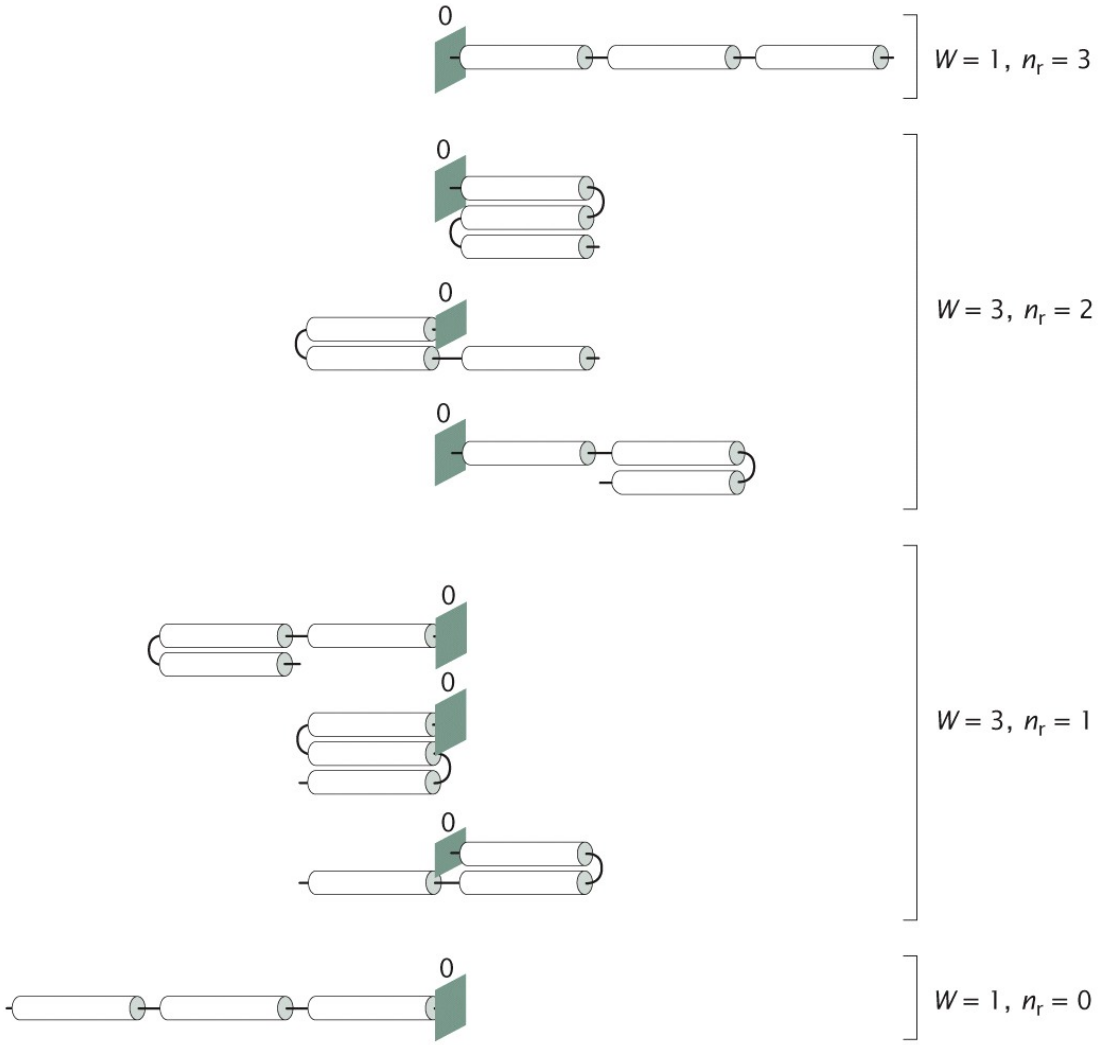


Figure 8.3 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Number of ways W to have n_r of the total N segments pointing to the right, in 1D:

$$W(n_r;N) = \frac{N!}{n_r\,!(N-n_r)!}$$

Probability:

$$p(n_r;N) = W(n_r;N)\,(½)^N$$

End-to-end distance:

$$R = (n_r - n_l)\,a$$

Notes 4

Probability distribution for end-to-end distance of a macromolecule

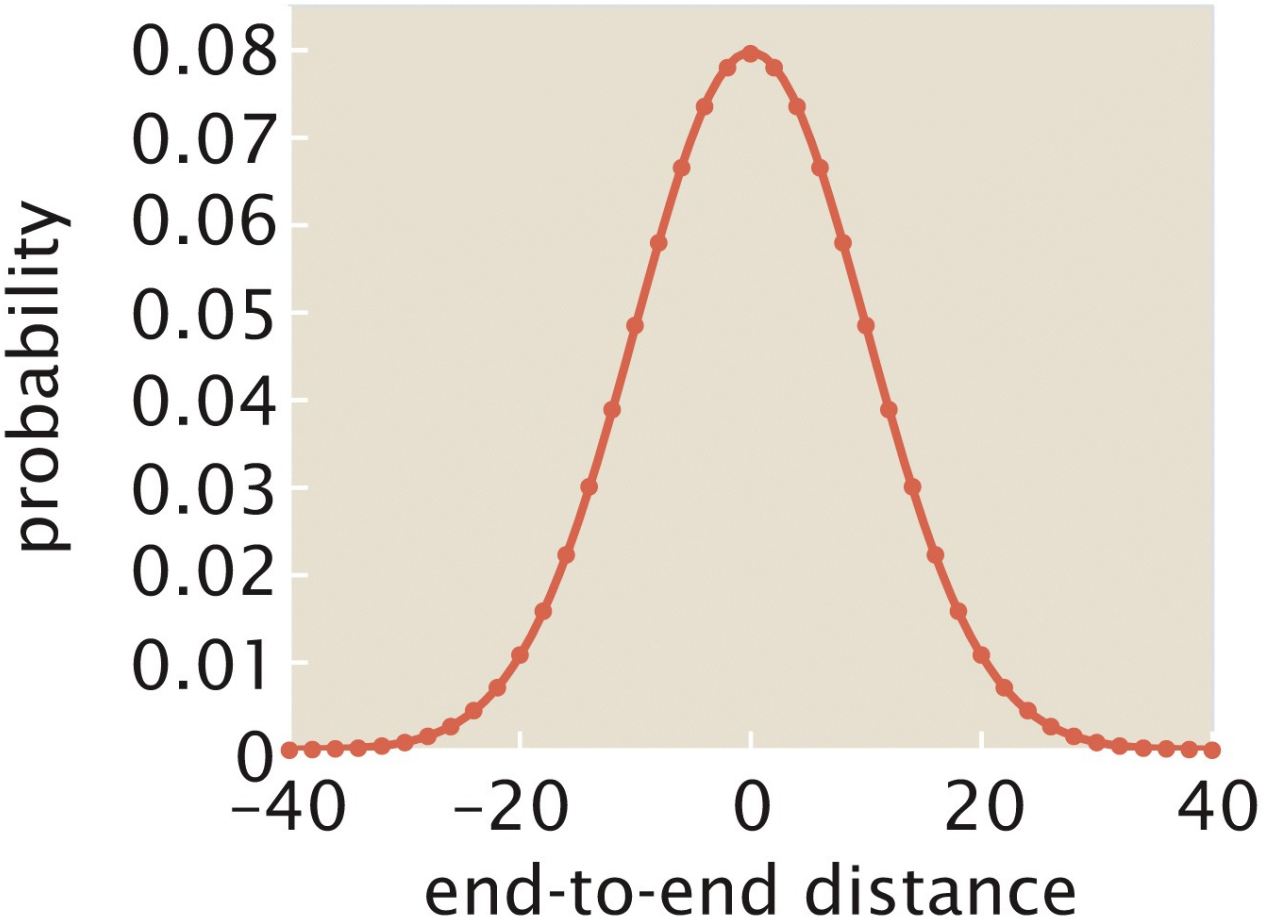


Figure 8.4 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Note:

$\langle R \rangle = 0$

$\langle R^2 \rangle \neq 0$

4 Macromolecules as random walks

The random-walk model is a commonly used to describe the behaviour of polymers and flexible macromolecules. It considers a polymer as a chain of segments (cf. chain of paperclips) that can freely rotate with respect to each other. These segments are of a length a over which the polymer can be considered roughly straight, are considered as steps in a random walk. To illustrate the principle, I will here derive the probability distribution for the end-to-end distance R of a one-dimensional random walk, where it is understood that R can both be positive and negative.

In one dimension, each step (or polymer segment) can be either to the right or to the left. Let us define n_r as the total number of steps to the right, n_l the total number of steps to the left, and $N = n_r + n_l$ the total number number of steps such that the contour length of the polymer $L = Na$. The end-to-end distance is thus given by

$$R = (n_r - n_l)\, a\,. \tag{4.1}$$

Since $n_l = N - n_r$ and N is fixed, we only need to know n_r to determine R for any particular configuration. We thus need to calculate the probability $p(n_r; N)$ that of the N segments, n_r are pointing to the right. This probability follows from

$$\begin{aligned} p(n_r; N) = &\text{(the probability of any particular sequence of steps or segment orientations)} \\ &\times \text{(the number of these sequences that contain } n_r \text{ steps to the right, } W(n_r; N))\ . \end{aligned} \tag{4.2}$$

If there is no external force applied to the polymer, there are equal probabilities ($\frac{1}{2}$) for a segment to point to the right or to the left. Hence

$$p(n_r; N) = \left(\tfrac{1}{2}\right)^N \times W(n_r; N) = \left(\tfrac{1}{2}\right)^N \frac{N!}{n_r!(N - n_r)!}\,. \tag{4.3}$$

where $W(n_r; N)$ follows from the total number of ways $N!$ to arrange N segments all in different orientations, and next taking into account that of these N segments, n_r have identical, indistinguishable orientations, and similar for $n_l = N - n_r$.

The next steps of the derivation involve (i) substituting $n_r = \frac{N}{2}(1 + R/(Na))$, (ii) making use of the Sterling approximation for $n \gg 1$, $\ln n! \approx n \ln n - n + \frac{1}{2}\ln(2\pi n)$, (iii) Taylor expansions for terms including $(1 \pm R/(NA))$ for $R/(NA) \ll 1$, and normalisation such that $\int p(R; N)\mathrm{d}R = 1$, to yield the final result

$$p(R; N) \approx \frac{1}{\sqrt{2\pi N a^2}} \exp\left(-\frac{R^2}{2Na^2}\right)\,, \tag{4.4}$$

which is a normal distribution.

Using this distribution, we can calculate

$$\langle R \rangle = \int_{-\infty}^{+\infty} p(R; N) R \mathrm{d}R = 0 \tag{4.5}$$

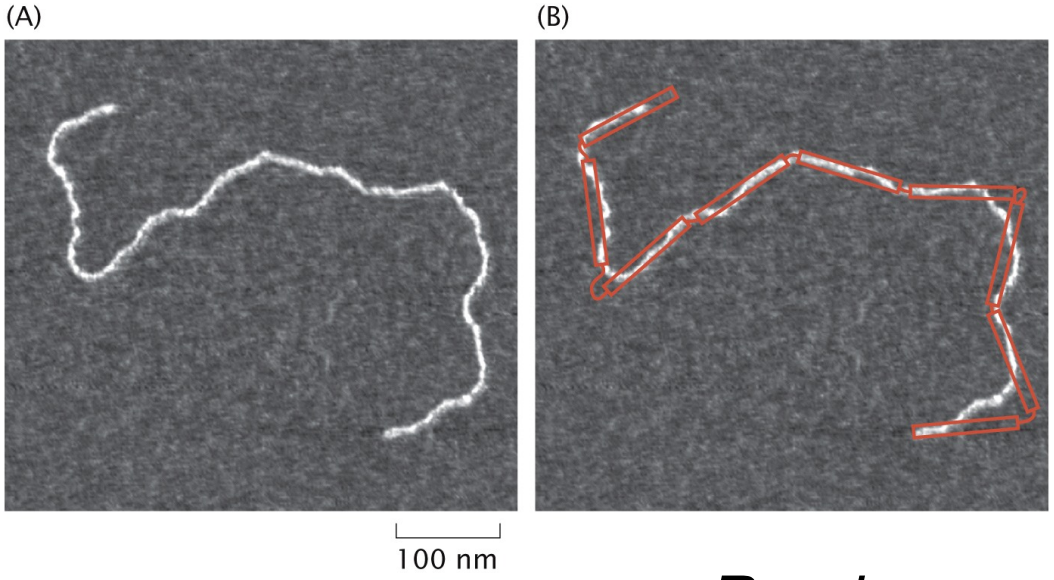
and the variance

$$\langle R^2 \rangle = \int_{-\infty}^{+\infty} p(R; N) R^2 \mathrm{d}R = Na^2 = La\,, \tag{4.6}$$

which provides a measure of the average *absolute* end-to-end distance.

1. **Effect of fluctuations on mechanics**
   a. **Single-molecule mechanics**
      - DNA size in solution

Relevant length scales of macromolecule



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- Persistence length ξ_p
- Contour length L
- Kuhn length: length of step a

Random walk model:

$a = 2\xi_p$

$L = Na$

Kuhn length = a

How long is DNA in solution?

- DNA: persistence length $\xi_p \approx 50$ nm
- Contour length $L \approx 0.34$ nm x $N_{base\ pairs}$
- $\sqrt{\langle R^2 \rangle} = \sqrt{(2L\xi_p)} \approx 0.82 \sqrt{(N_{base\ pairs}\xi_p)}$ nm

- Alternative measure of polymer size: radius of gyration R_G
- $\langle R_G^2 \rangle = 1/N \sum \langle (R_i - R_{CM})^2 \rangle \approx 0.34 \sqrt{(N_{base\ pairs}\xi_p)}$ nm
- R_{CM} = centre of mass

Typical human chromosome: ~ 10^8 bp
Contour length ~ 3 cm
$\sqrt{\langle R^2 \rangle}$ ~ 60 µm

Size of DNA in solution

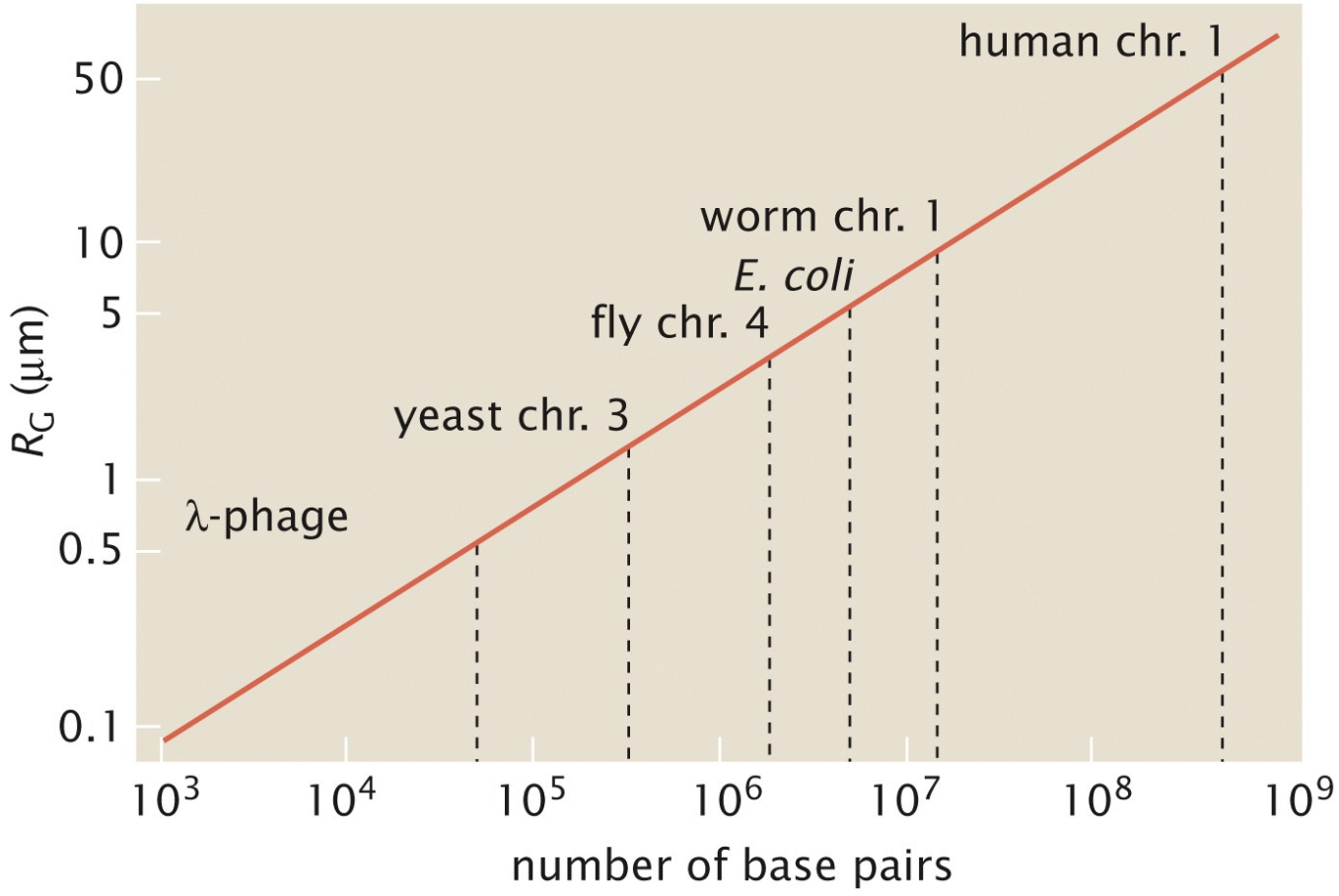
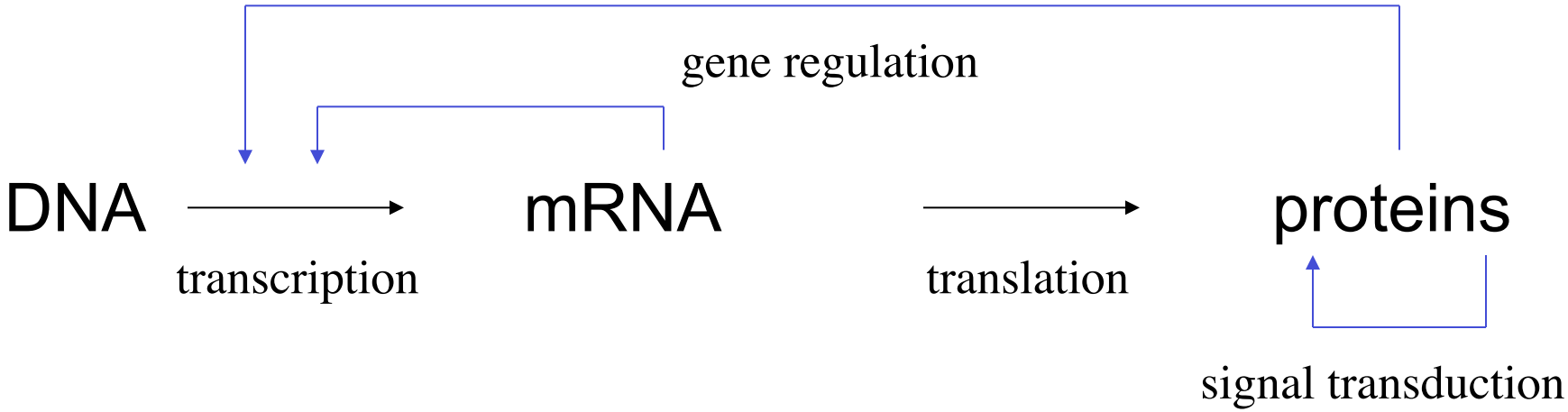


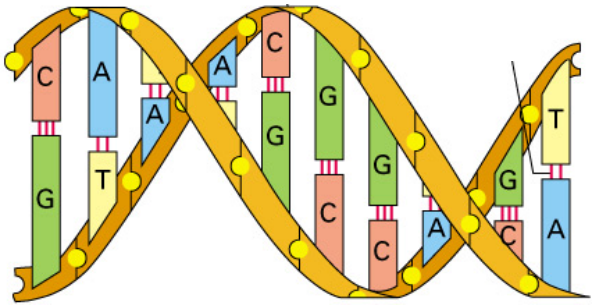
Figure 8.6 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

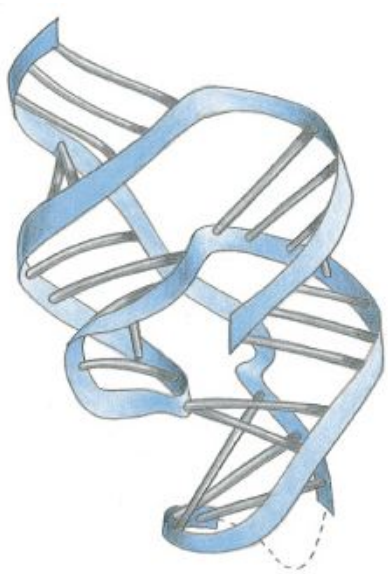
Size of "average" nucleus in mammalian cells: ~ 6 μm !

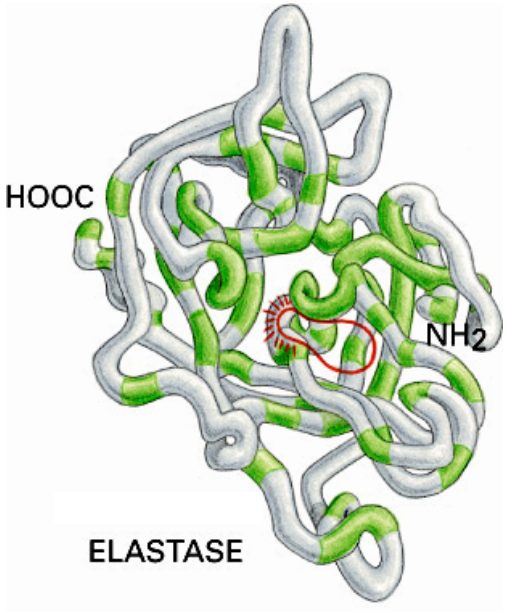
1. **Effect of fluctuations on mechanics**
   a. **Single-molecule mechanics**
      - DNA size in solution
      - **Gene repression**

Central dogma









Regulation of gene expression

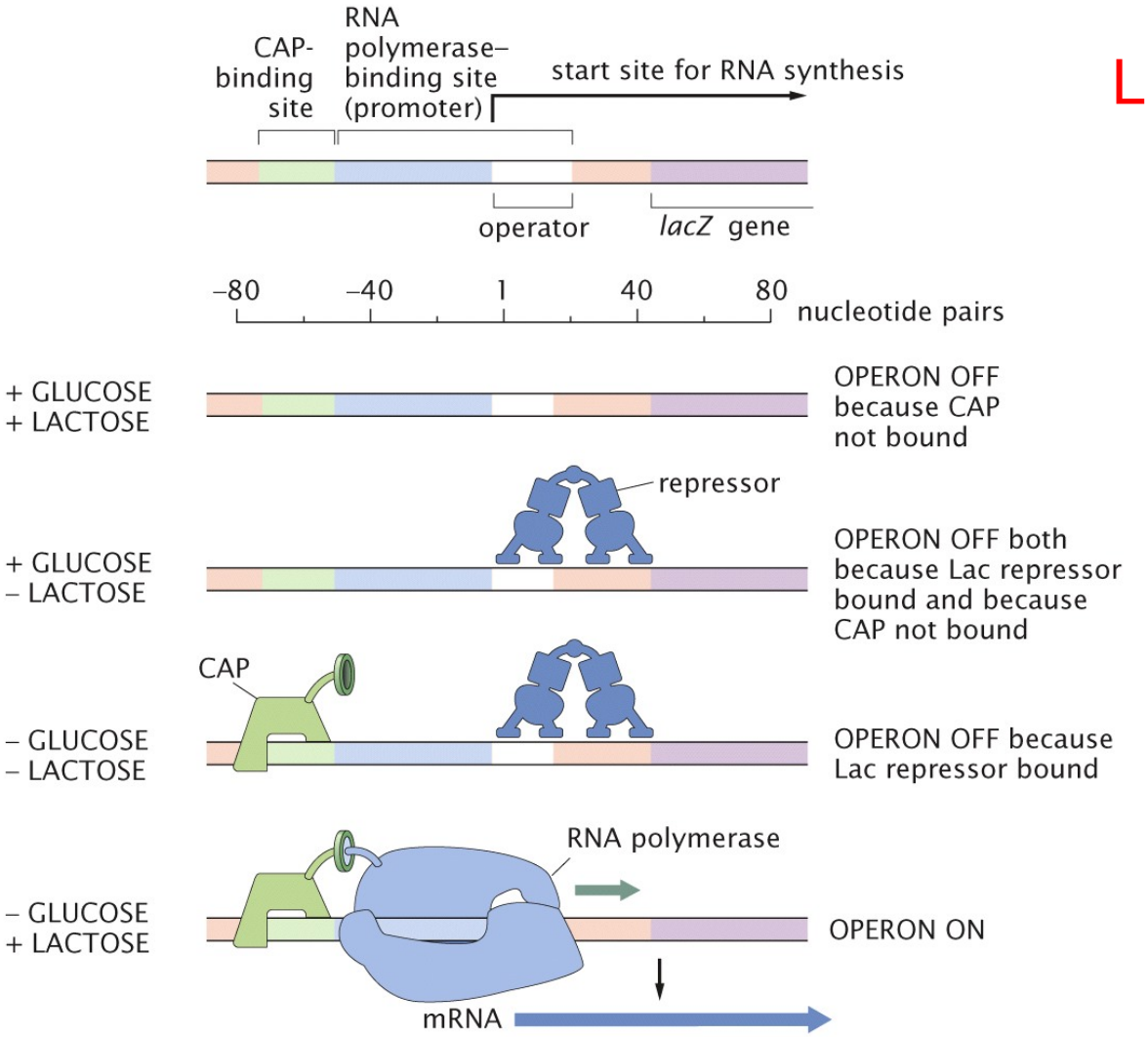


Figure 4.15 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Lac repressor prevents expression of proteins that are necessary for digestion of lactose

Probability of loop formation

Number of ways W to make a loop in chain of N segments in 1D model =>

$n_r = n_l = N/2$

$$W(N/2,N) = \frac{N!}{(N/2)!\ (N/2)!}$$

Probability:

$p_{loop} = W(N/2,N)\ (½)^N$

If $N>>1$,

$P_{loop} \approx \sqrt{(2/\pi N)}$

$= \sqrt{(2a/\pi)}\ 1/\sqrt{(Na)}$

$\propto 1/\sqrt{(\text{loop length})}$

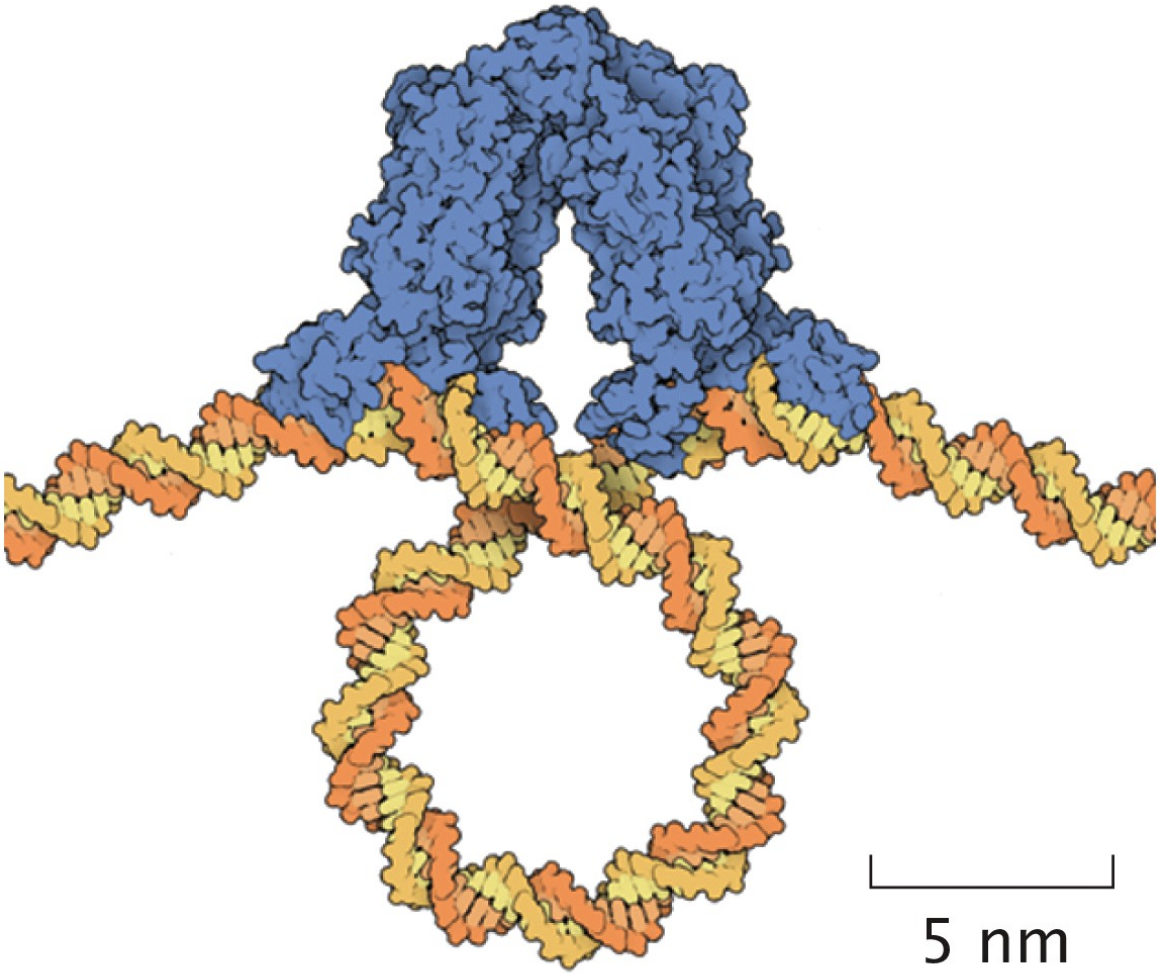


Figure 8.19 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Probability of loop formation

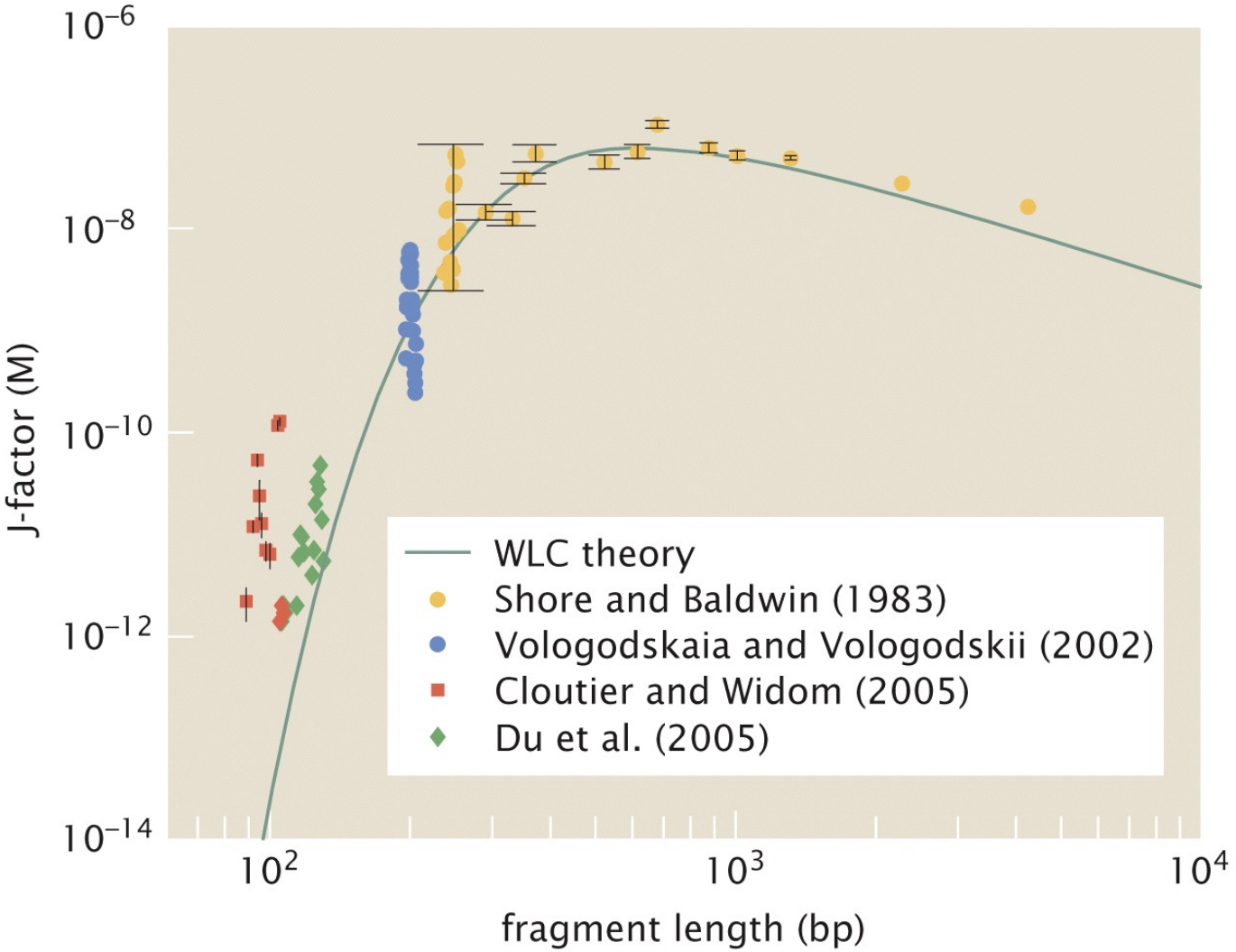
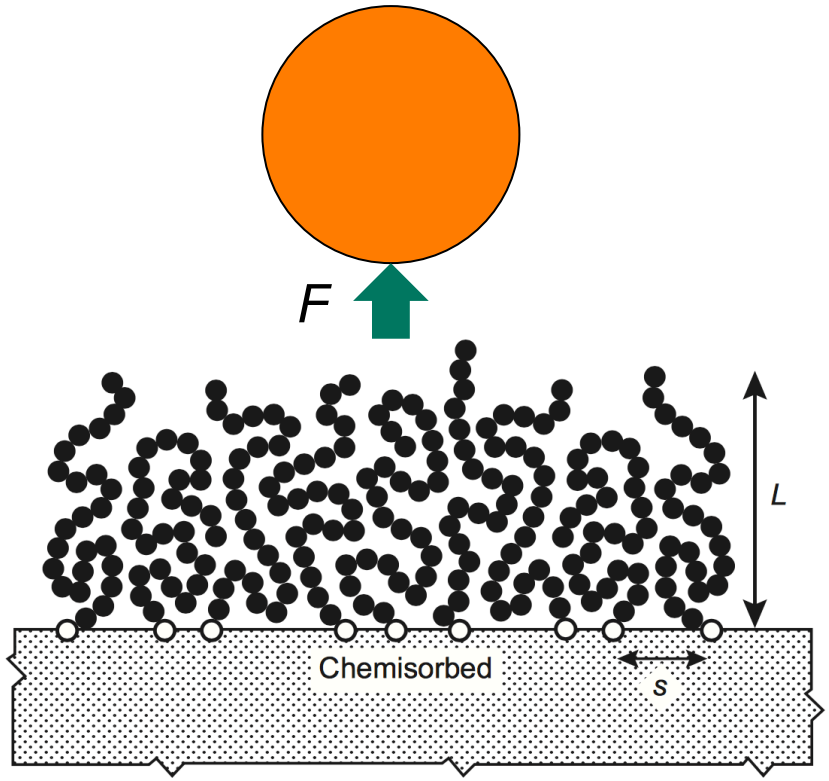


Figure 10.12 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

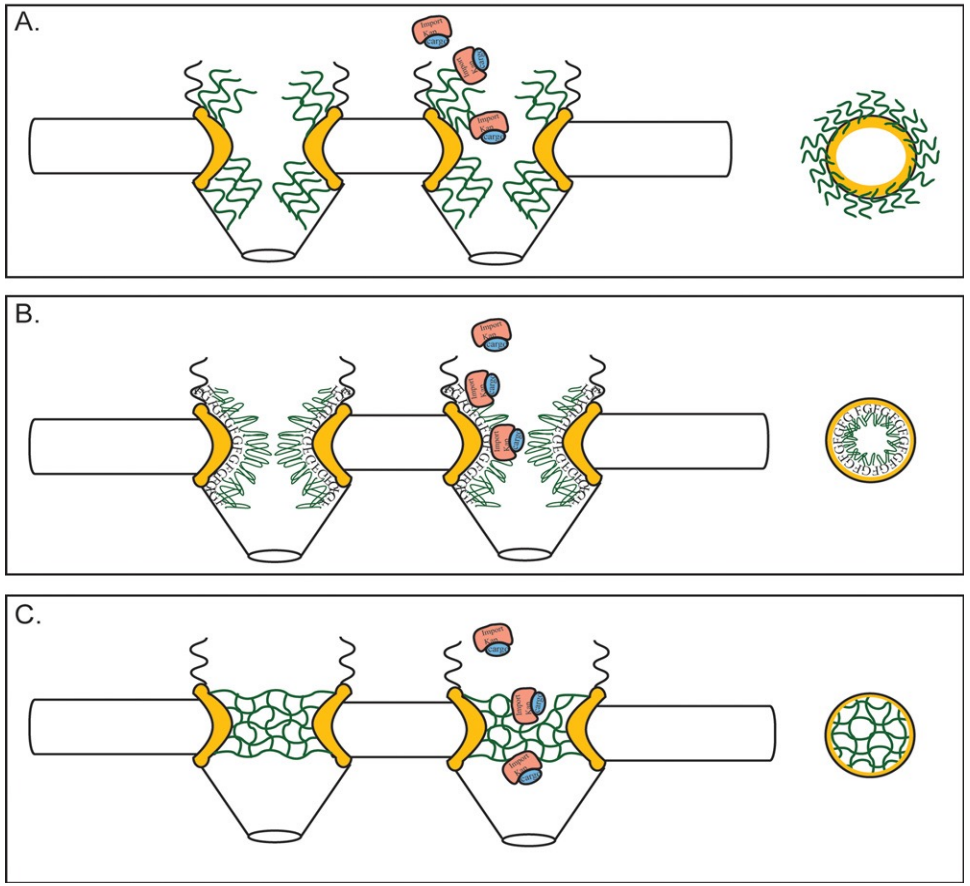
1. **Effect of fluctuations on mechanics**
   a. **Single-molecule mechanics**
      - **DNA size in solution**
      - **Gene repression**
   b. **Multi-molecule mechanics**
      - **Polymer brush & nuclear pores**

Polymer brush



Israelachvili (2011). *Intermolecular and surface forces*, 3° ed.

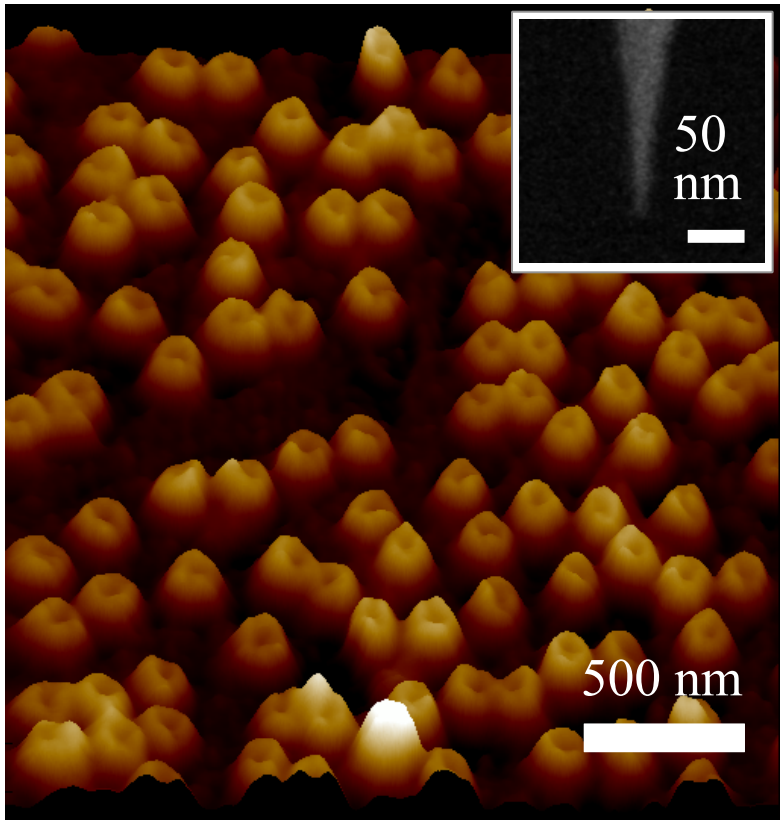
Nuclear pore complex

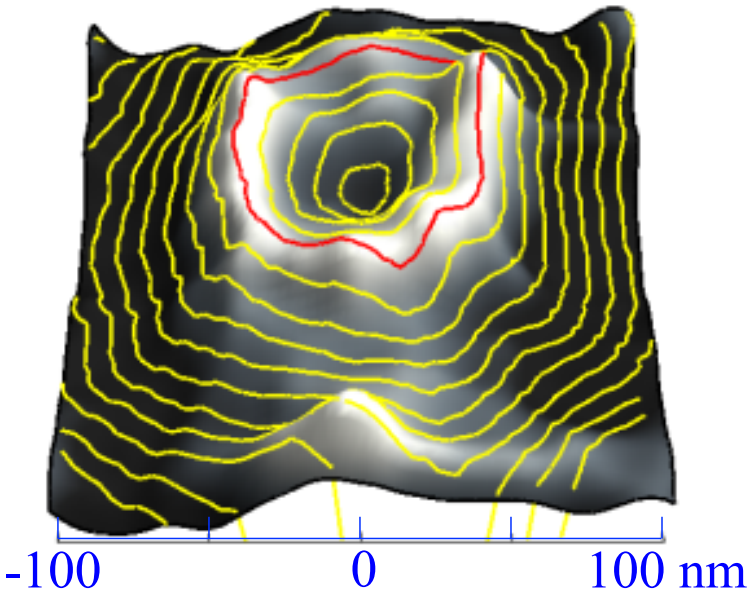


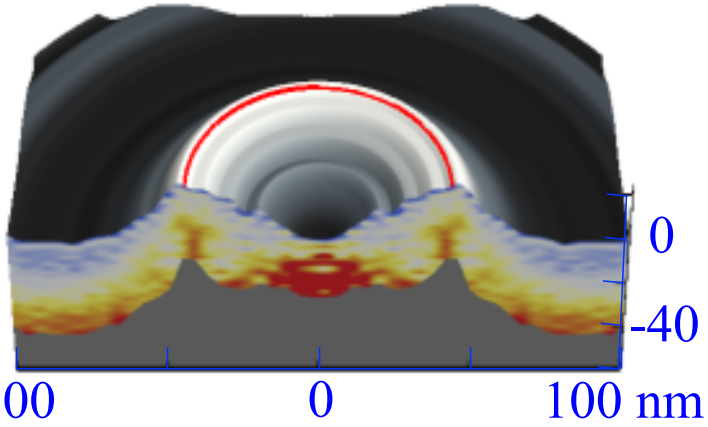
Terry, L. J. & Wente, S. R. Eukaryot (2009). Cell 8, 1814–27.

Nuclear pore nanomechanics

Bestembayeva, Kramer et al.
Nature Nanotechnol. (2015)



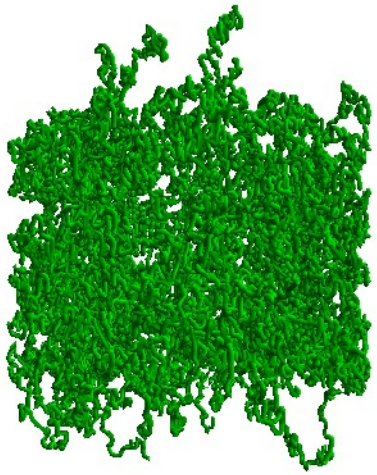




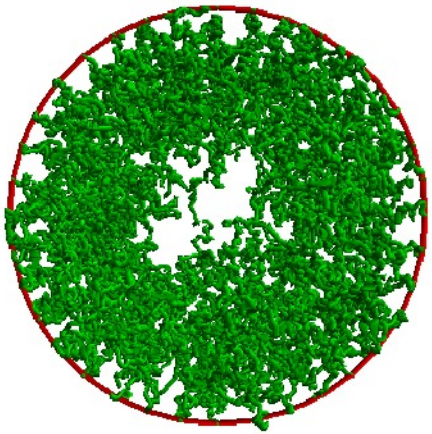
Height: 0 80 nm

Stiffness: 0 16 pN/nm

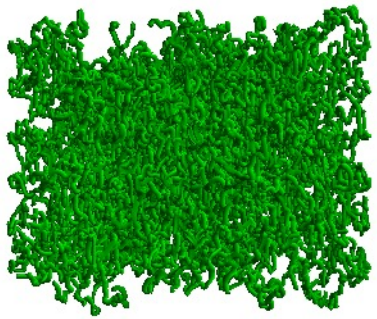
In-silico indentation of nuclear pores

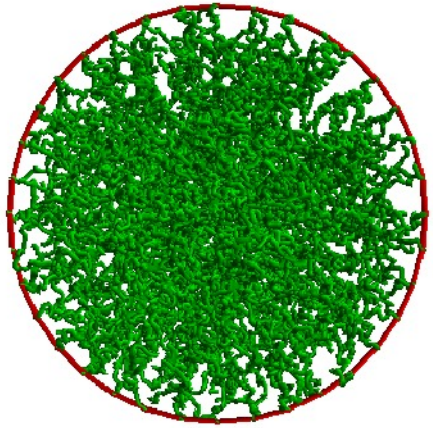


Side View

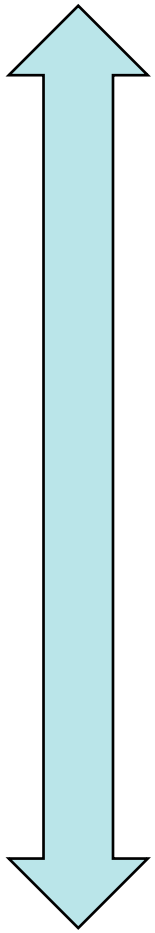


Top View

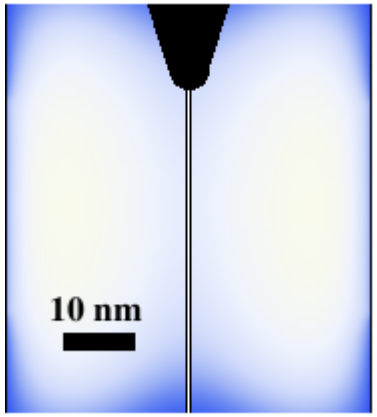


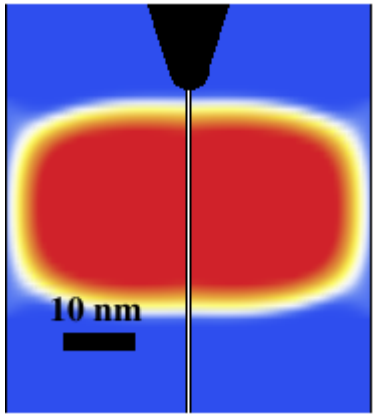


Entropic brush

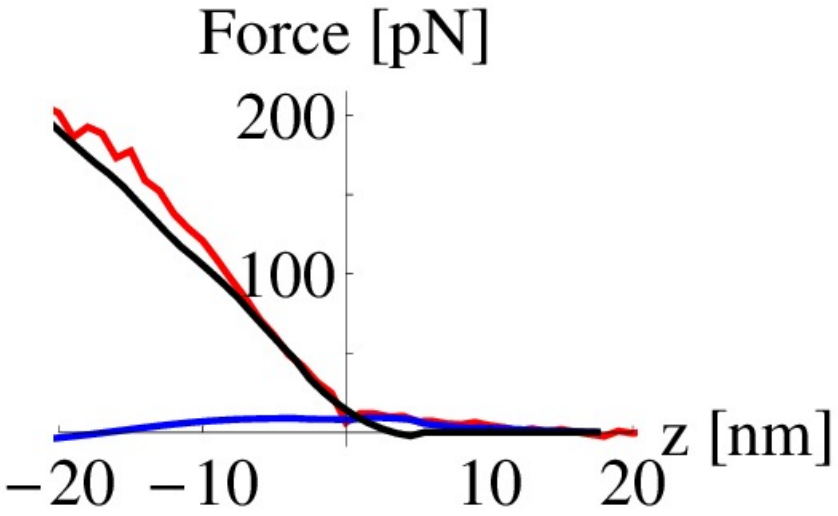


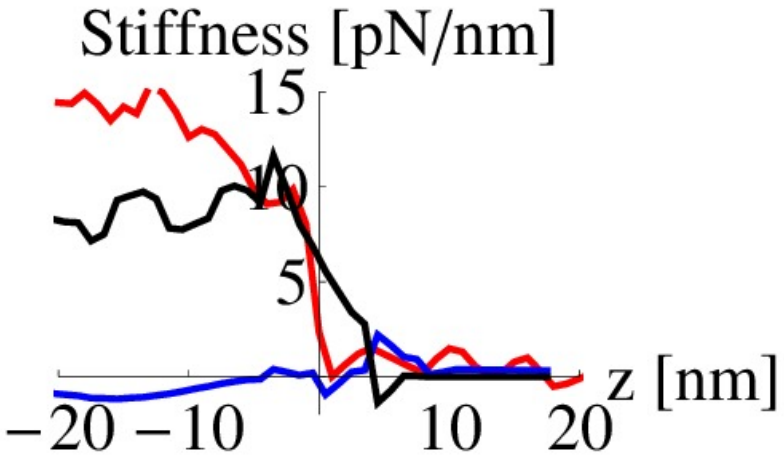
Gel





Comparison with experiment





"Entropic brush" scenario

"Gel" scenario

Experimental data

1. **Effect of fluctuations on mechanics**
   a. **Single-molecule mechanics**
      - **DNA size in solution**
      - **Gene repression**
   b. **Multi-molecule mechanics**
      - **Polymer brush & nuclear pores**
   c. **Mechanics of 2D assemblies**
      - **Membrane pore formation**

Lipid membranes

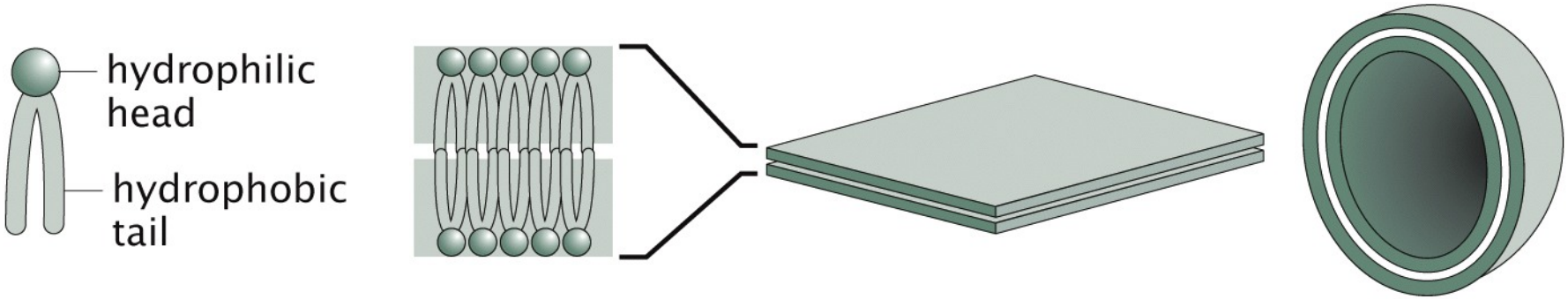


Figure 11.1a Physical Biology of the Cell, 2ed. (© Garland Science 2013)

What is the cost of drilling a hole in such a membrane?

The answer: Entropy & hydrophobicity

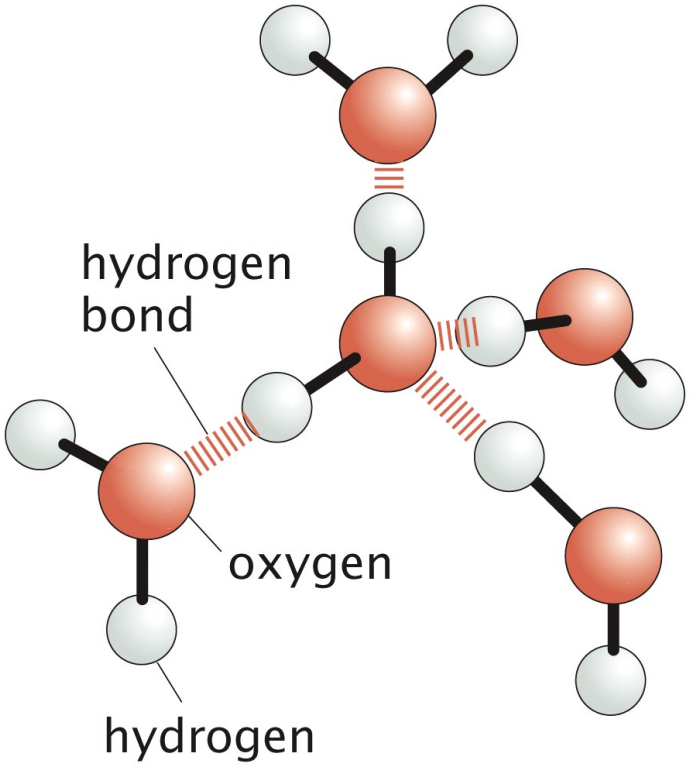


Figure 5.27 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

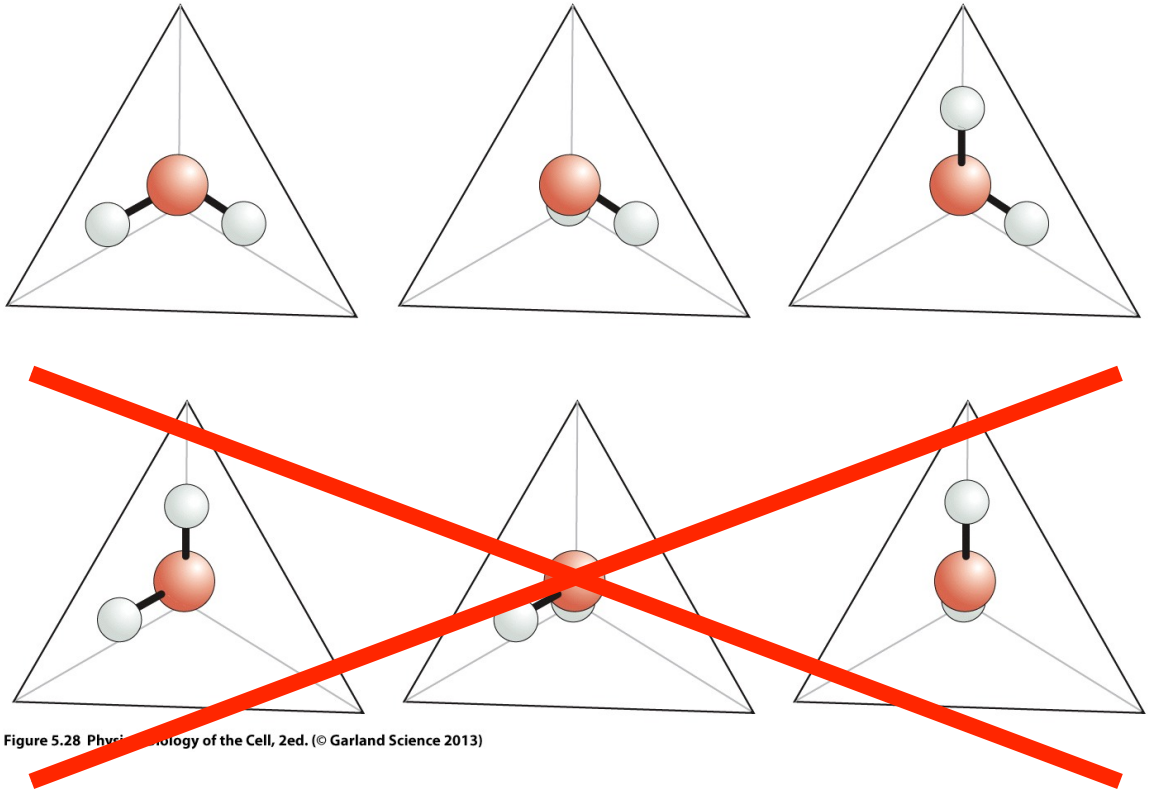
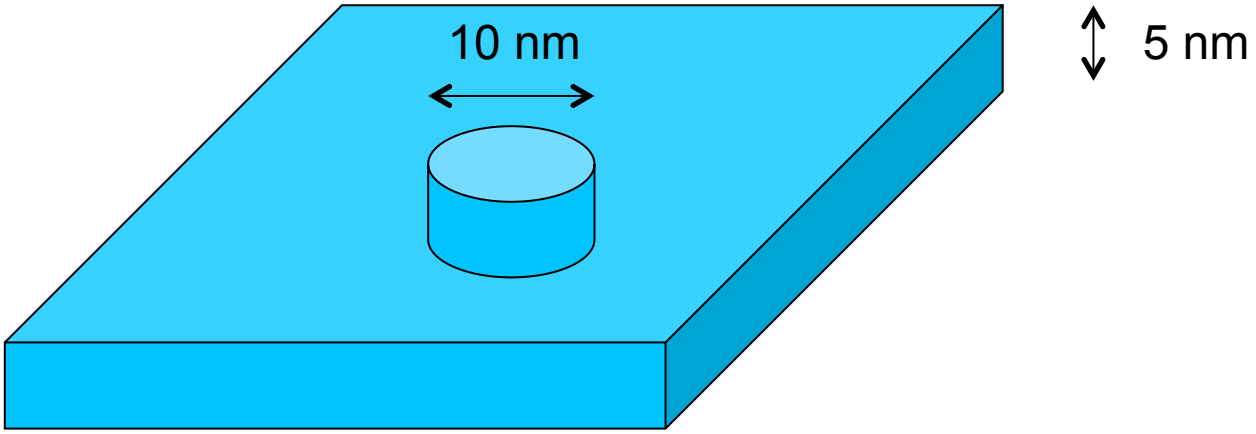


Figure 5.28 Phys[illegible]ology of the Cell, 2ed. (© Garland Science 2013)

$S = k_B \ln[\text{number of configurations}]$

$\Delta S = k_B \ln 3 - k_B \ln 6 = - k_B \ln 2$, per H_2O molecule

Free energy cost of 10 nm hole…



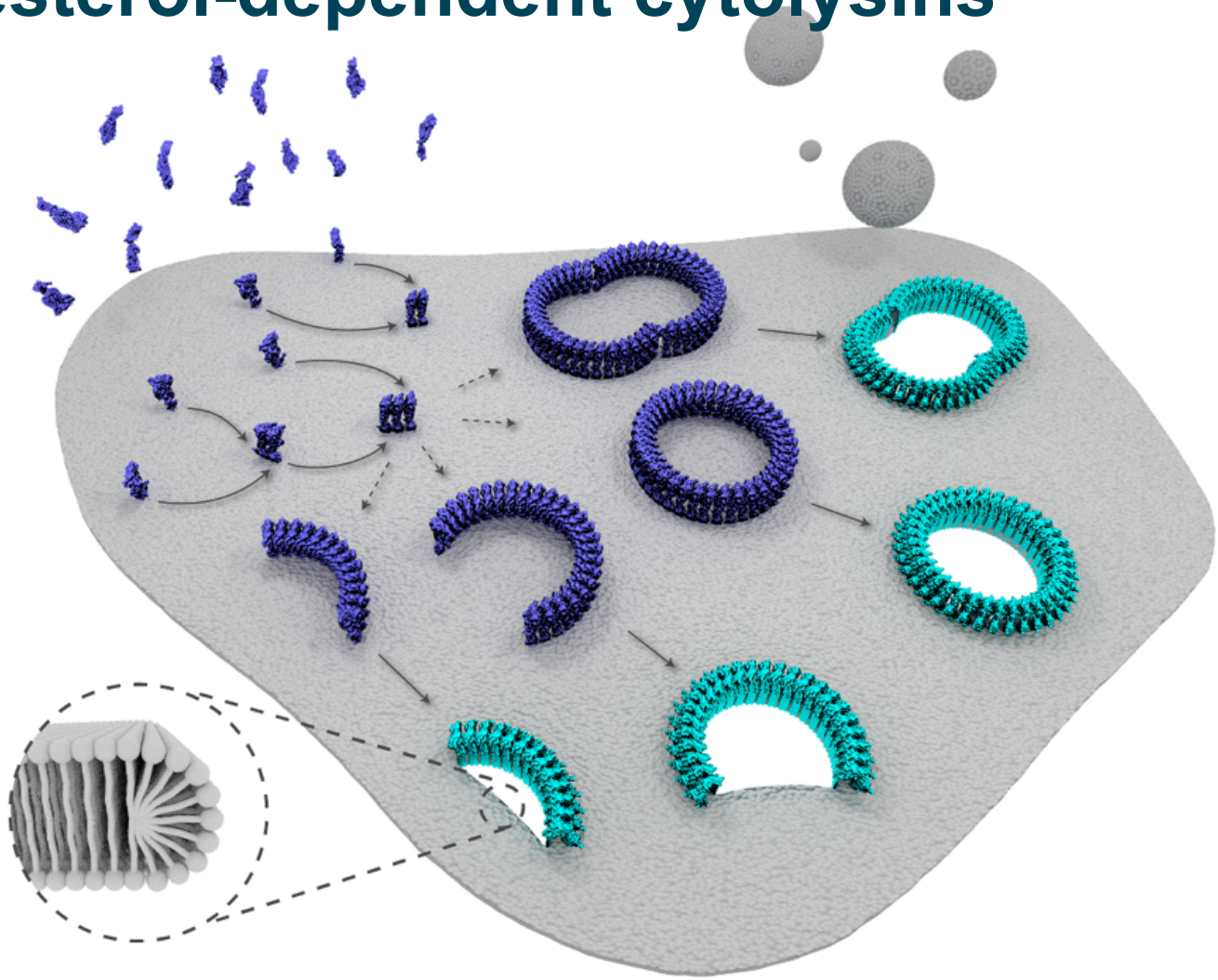
Hydrophobic tails of lipids exposed over an area corresponding to the side wall of the pore: 2π (5 nm) (5 nm) = 50π nm^2

~10 H_2O molecules nm^{-2} =>

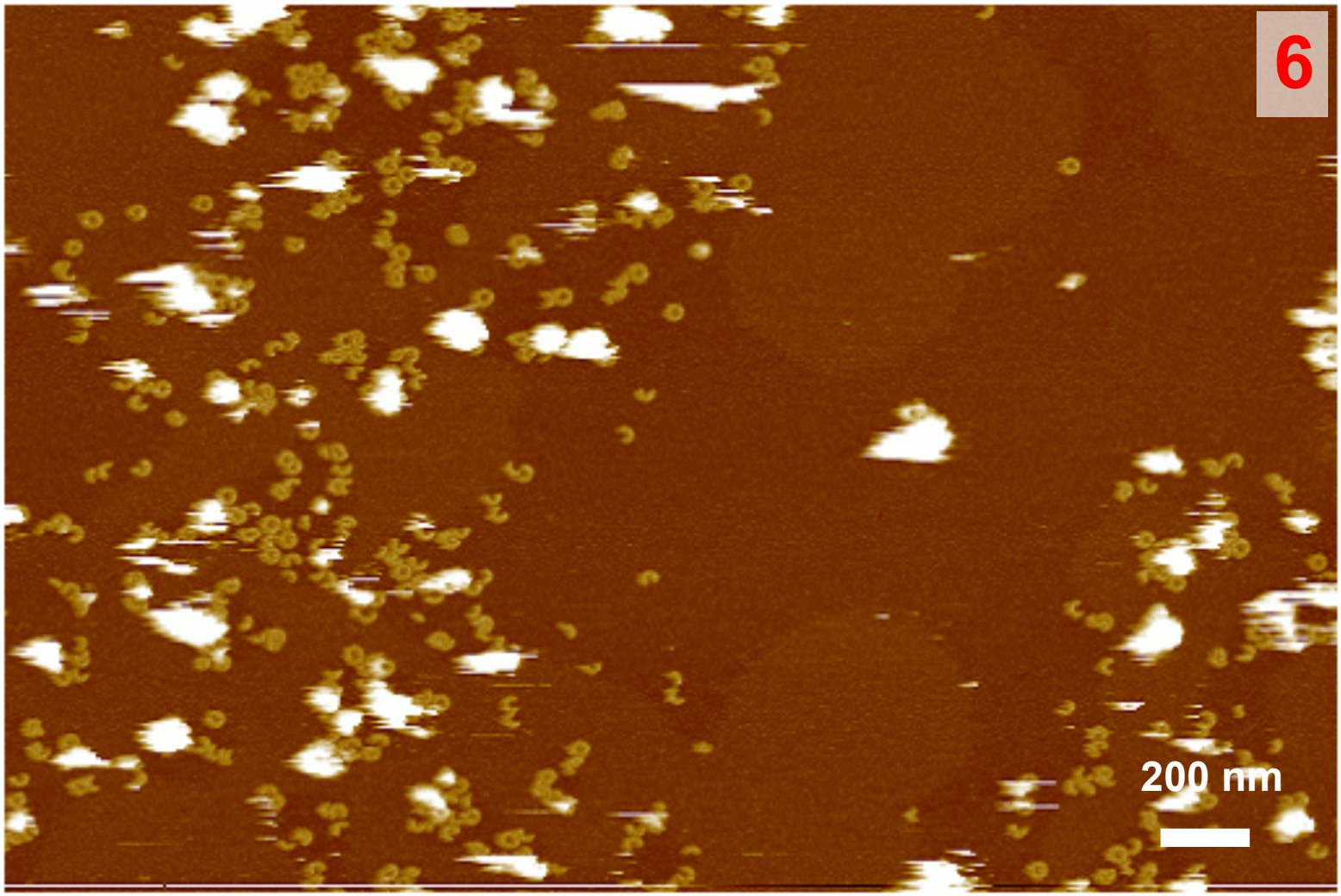
Free energy = - $T\Delta S$ = (10 nm^{-2}) × $k_B T$ ln 2 ≈ 7 $k_B T$ nm^{-2}

Free energy cost of hole: $50\pi \times 7\ k_B T \approx 10^3\ k_B T$!!!

Bacterial nanodrills: Cholesterol-dependent cytolysins



Bacterial (suilysin) nanodrills at work

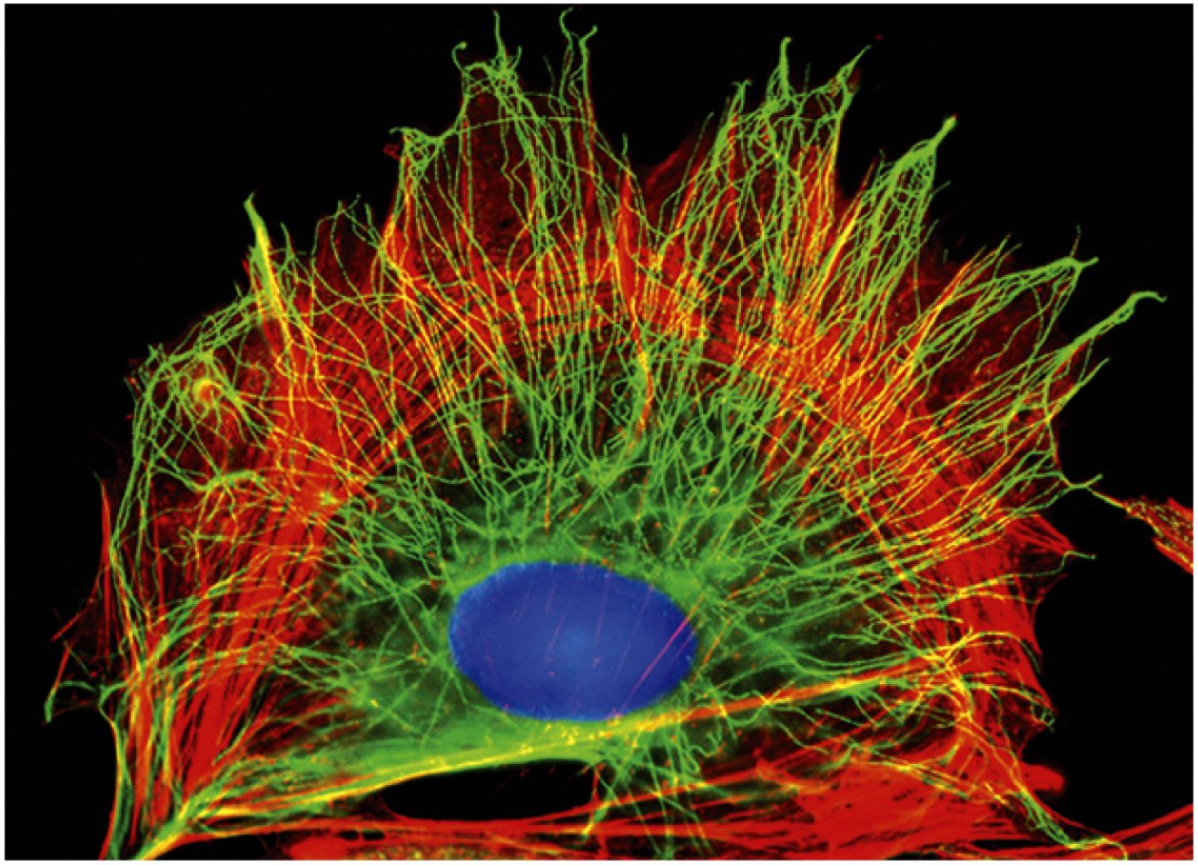


Leung, Dudkina, et al. eLife (2014)

1. Effect of fluctuations on mechanics
   a. Single-molecule mechanics
      - DNA size in solution
      - Gene repression
   b. Multi-molecule mechanics
      - Polymer brush & nuclear pores
   c. Mechanics of 2D assemblies
      - Membrane pore formation

2. Active mechanical components

Cytoskeleton: The cell's spatial organisation

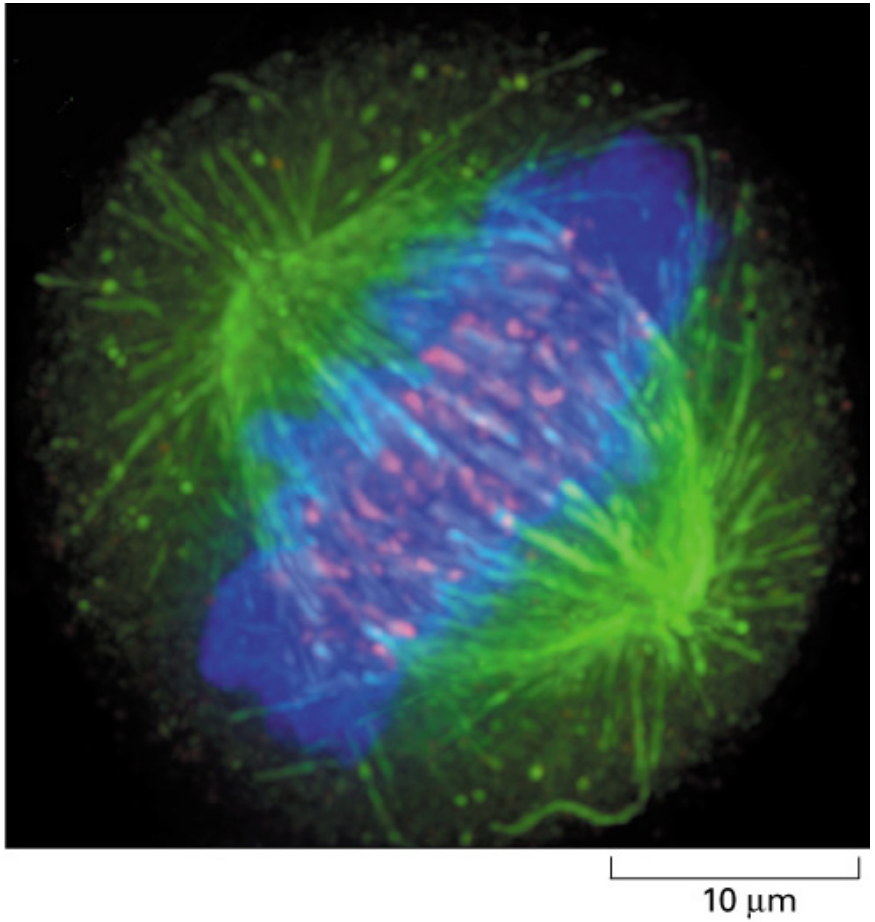


Green:
- Microtubules

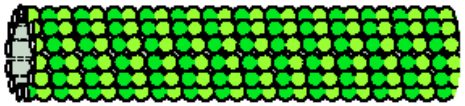
Red:
- Actin filaments

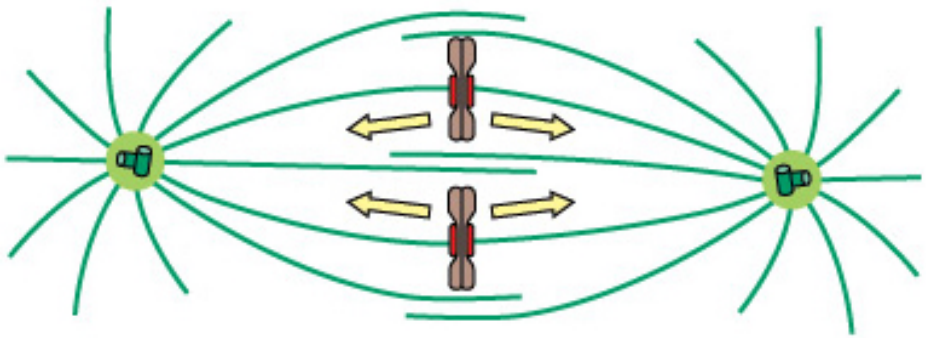
Blue:
- Nucleus

Separating chromosomes during mitosis



- chromosomes
- microtubules
- centromeres

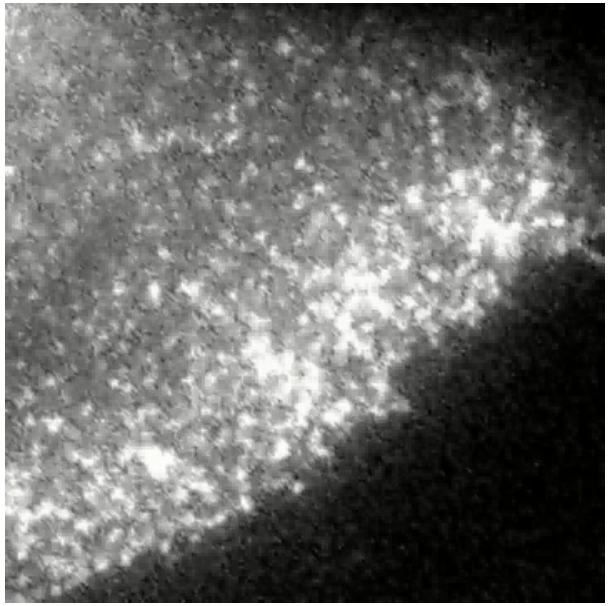


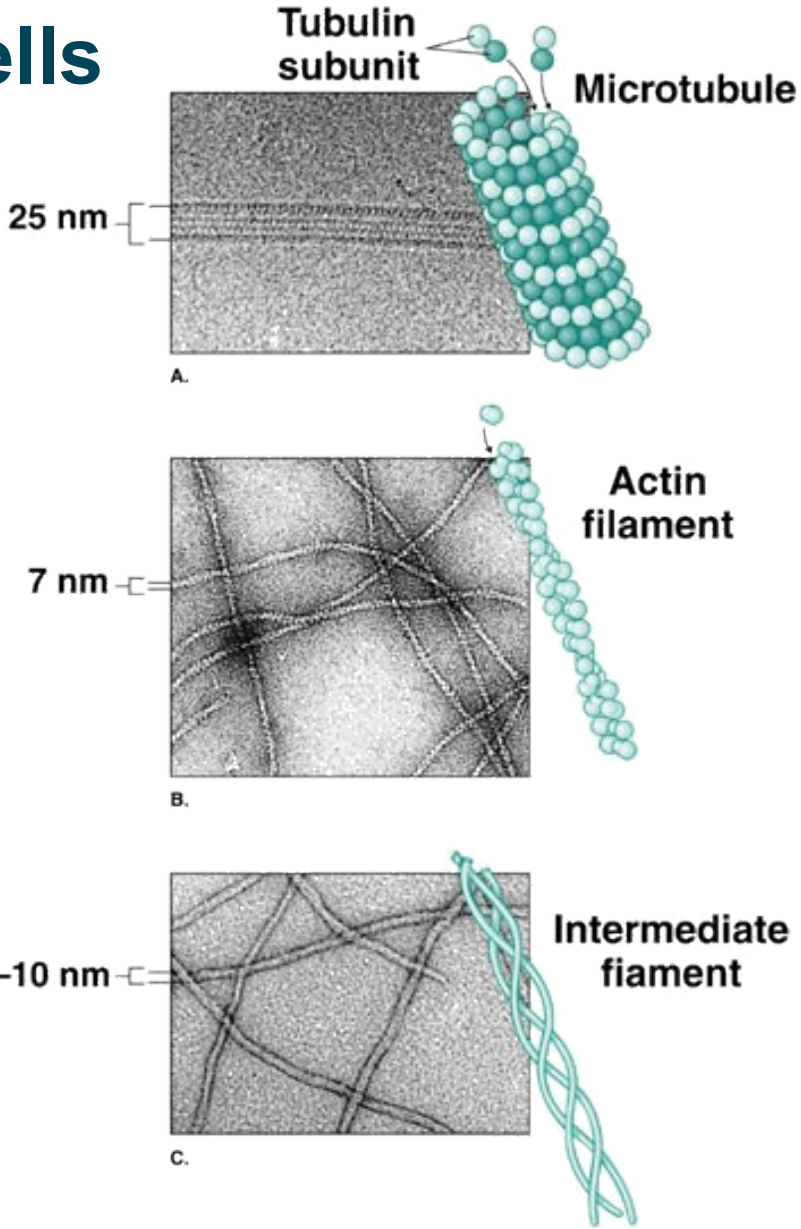


mitotic spindle

Filamental structures in cells

Actin speckles in the leading edge of an XTC cell (Naoki Watanabe, Kyoto)

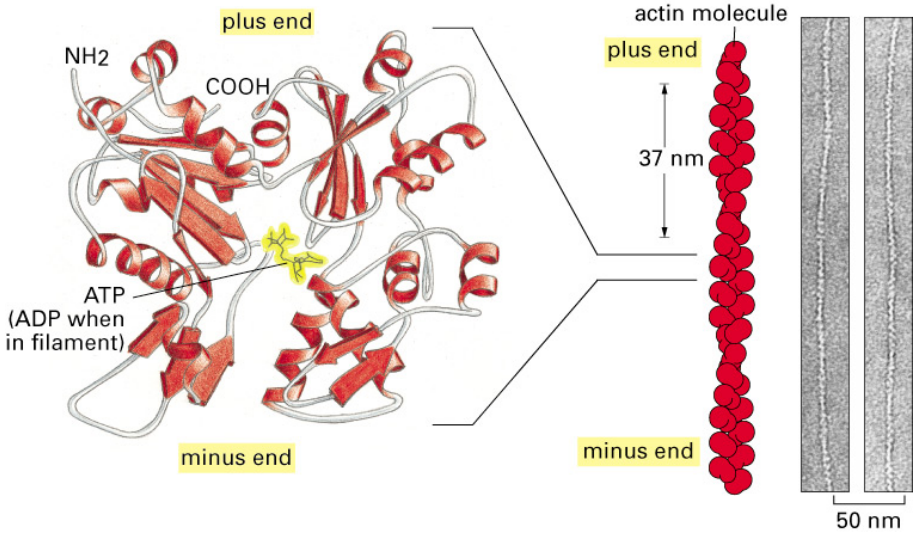




Persistence lengths:

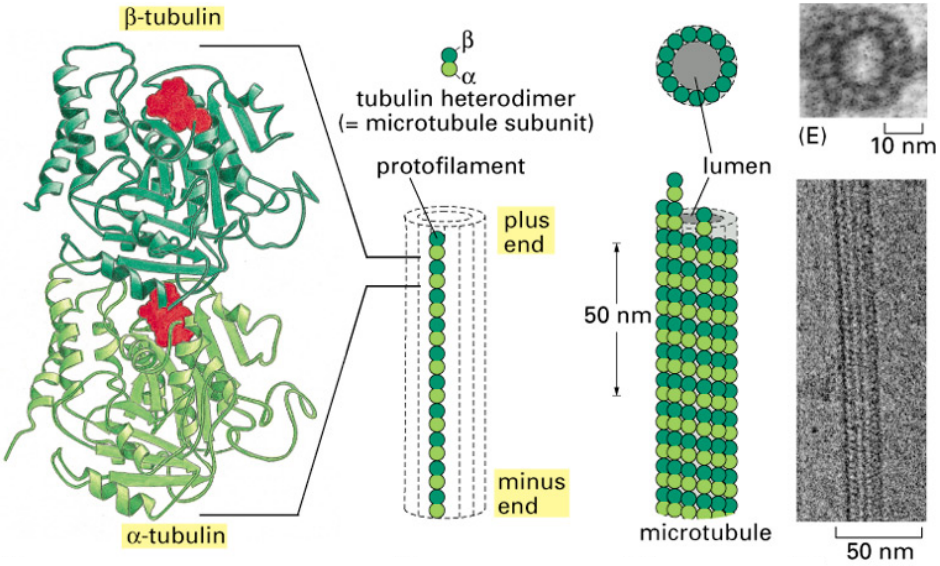
$\xi_{p\ \text{tubulin}} \sim 1\text{mm}$
$\xi_{p\ \text{actin}} \sim 10\ \mu\text{m}$
$\xi_{p\ \text{IF}} < 1\ \mu\text{m}$

Actin filaments



$\xi_p = 15\ \mu m$

Microtubules



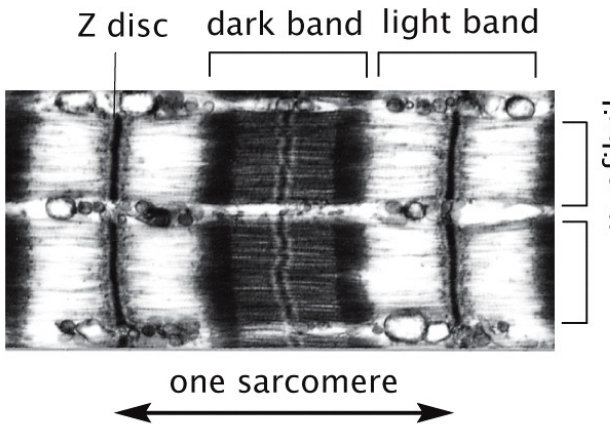
$\xi_p = 6\ mm$

Figure 16–6. Molecular Biology of the Cell, 4th Edition.

1. Effect of fluctuations on mechanics

2. Active mechanical components
   a. Molecular motors
      - Muscles
      - Example of myosin V
      - Diffusion / Smoluchowksi equation

A look inside a muscle



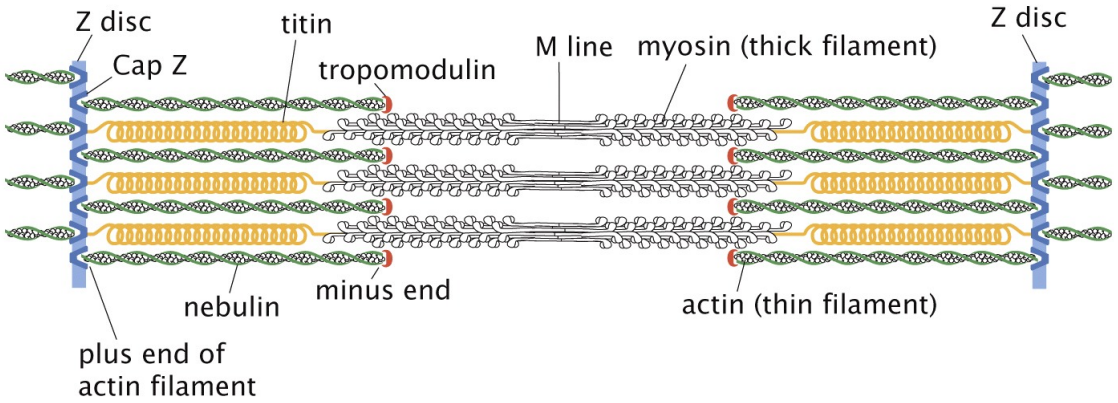


Figure 16.7b Physical Biology of the Cell, 2ed. (© Garland Science 2013)

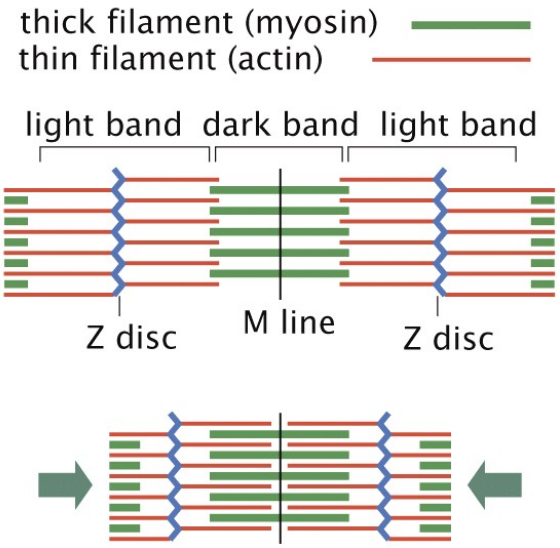


Figure 16.7a Physical Biology of the Cell, 2ed. (© Garland Science 2013)

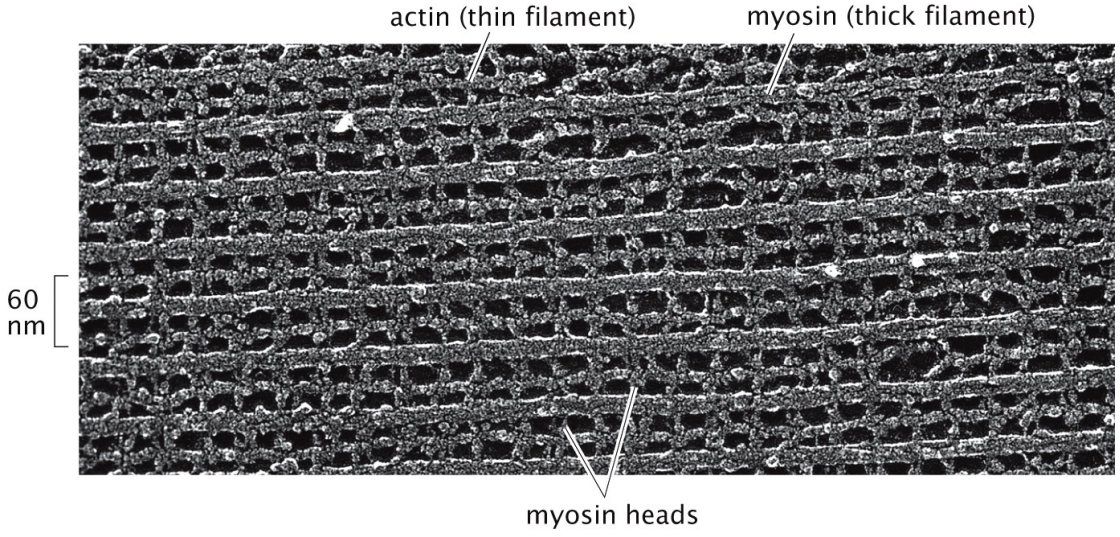
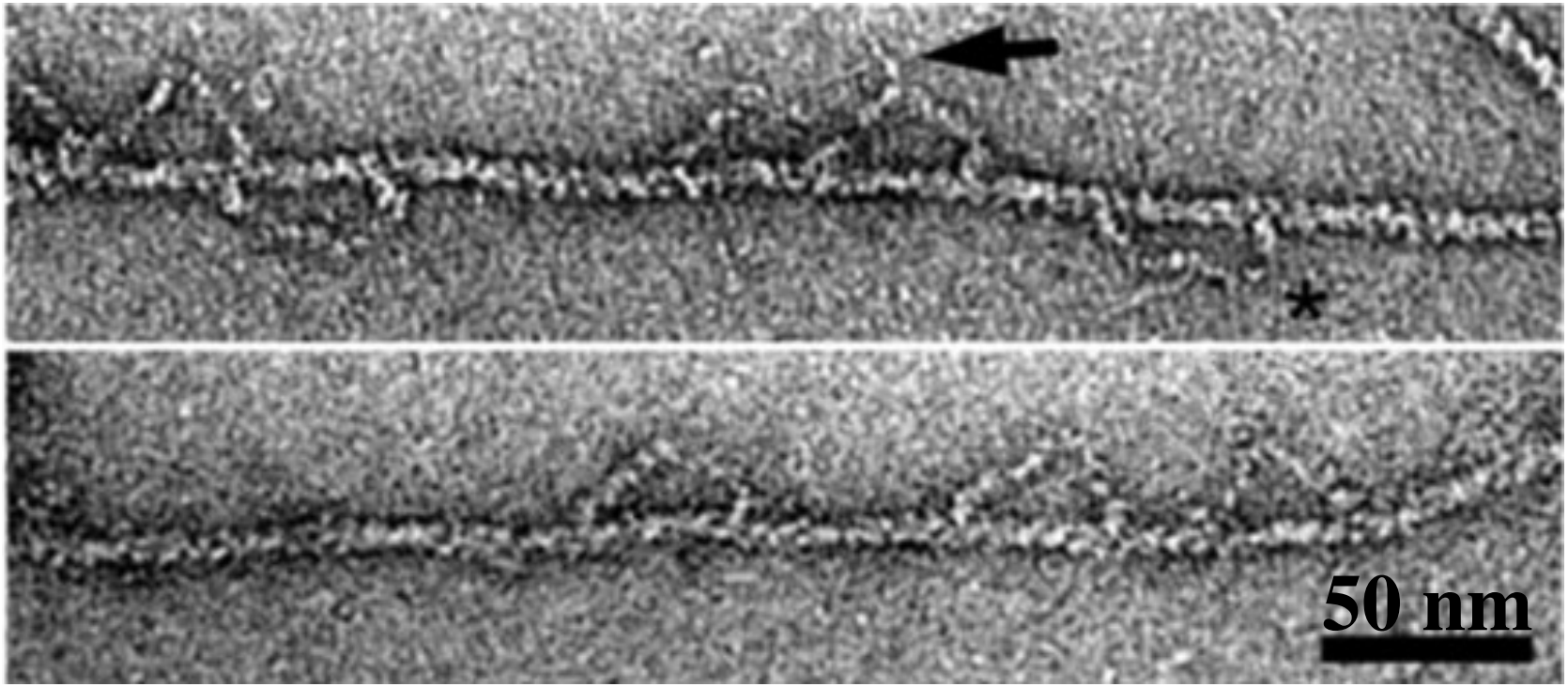


Figure 16.7c Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Electron microscopy



Walker *et al*., Nature (2000)

Some translational motors

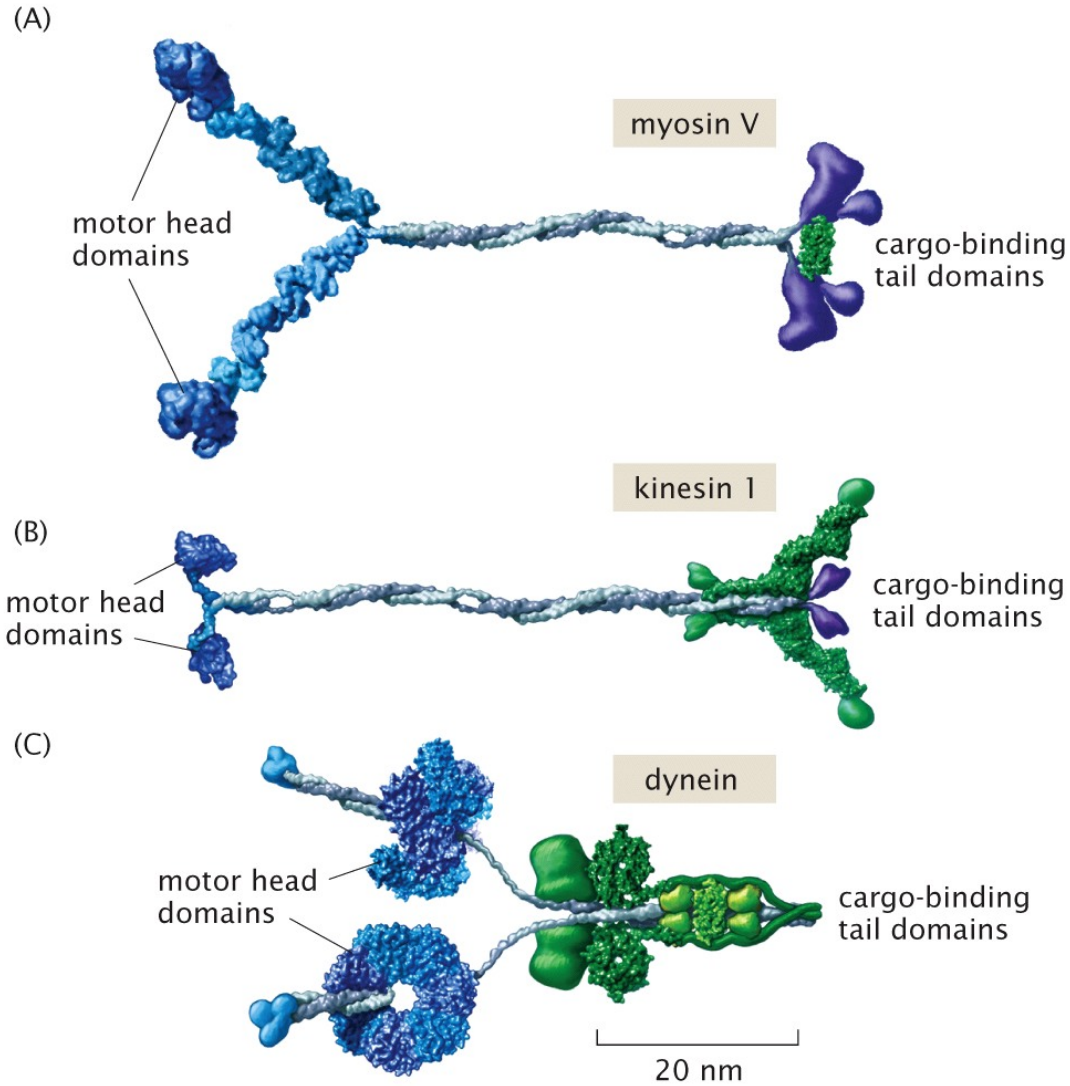


Figure 16.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Molecular motors, example of Myosin V

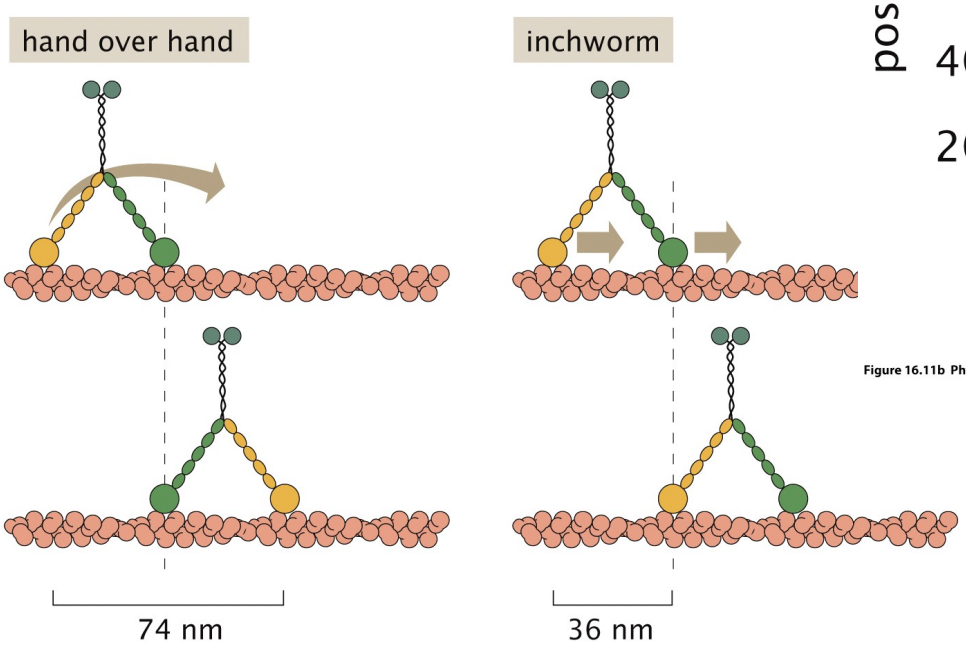


Figure 16.11a Physical Biology of the Cell, 2ed. (© Garland Science 2013)

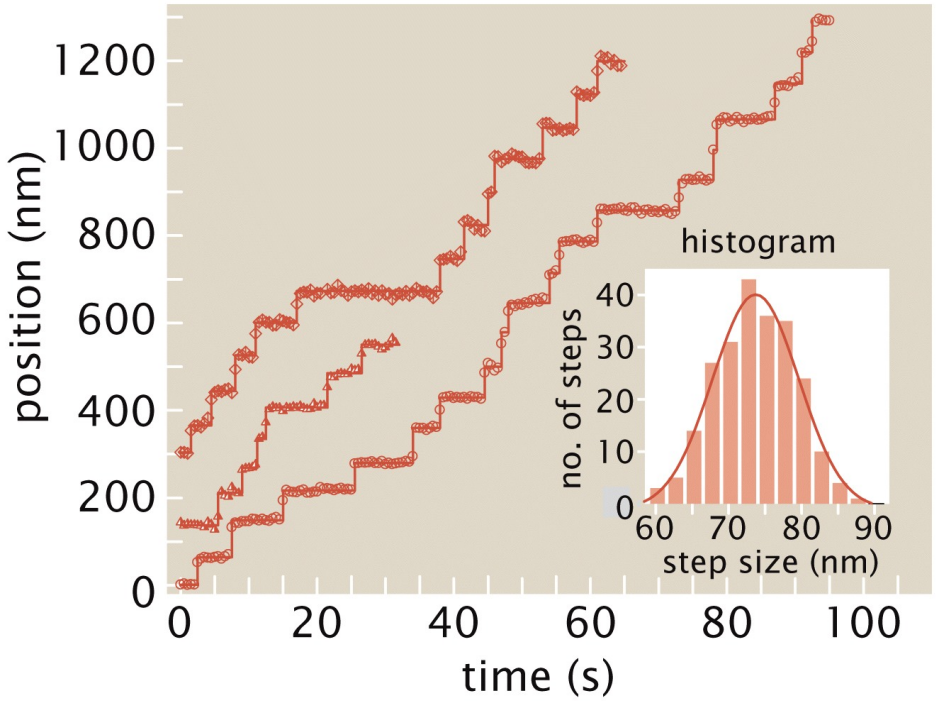
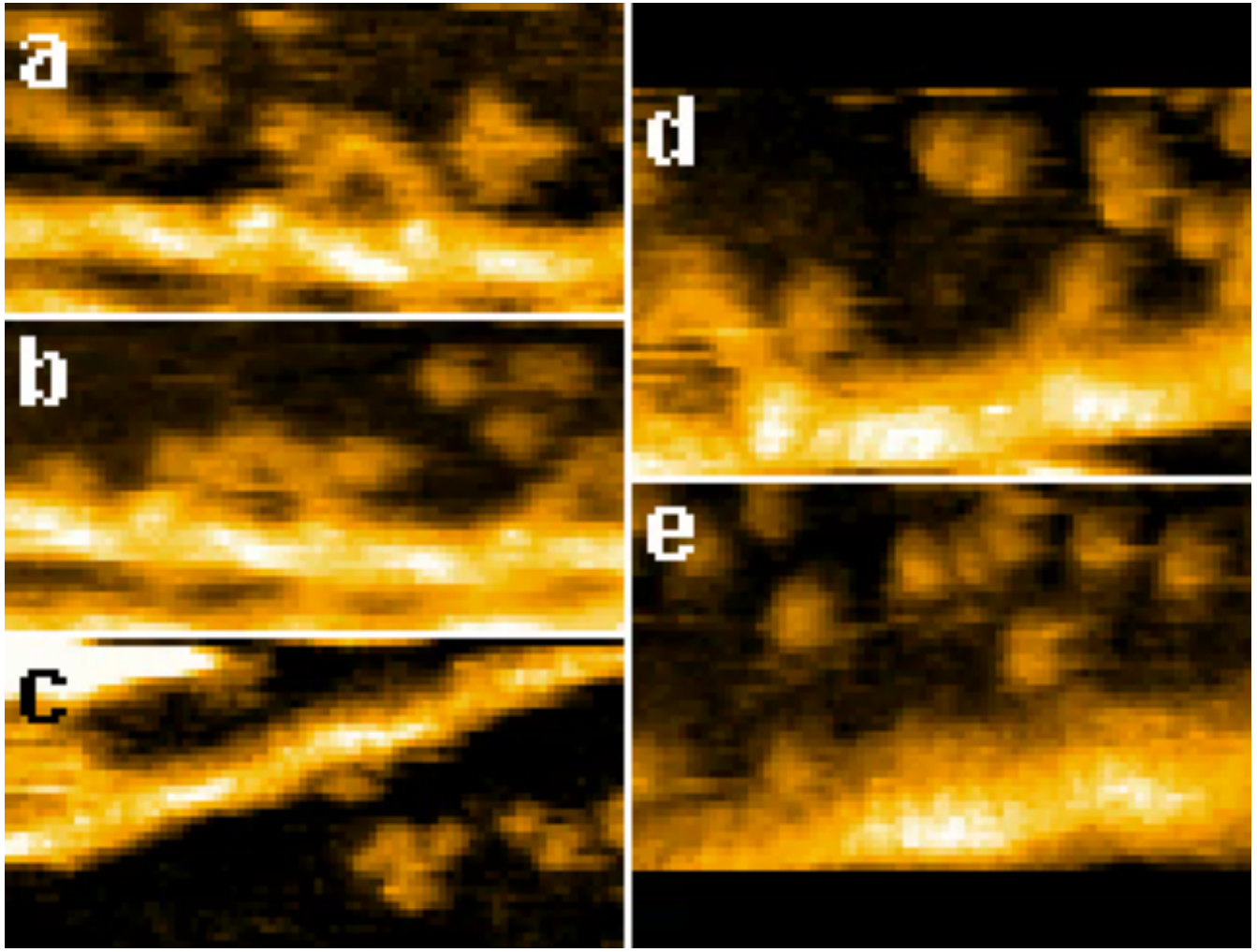


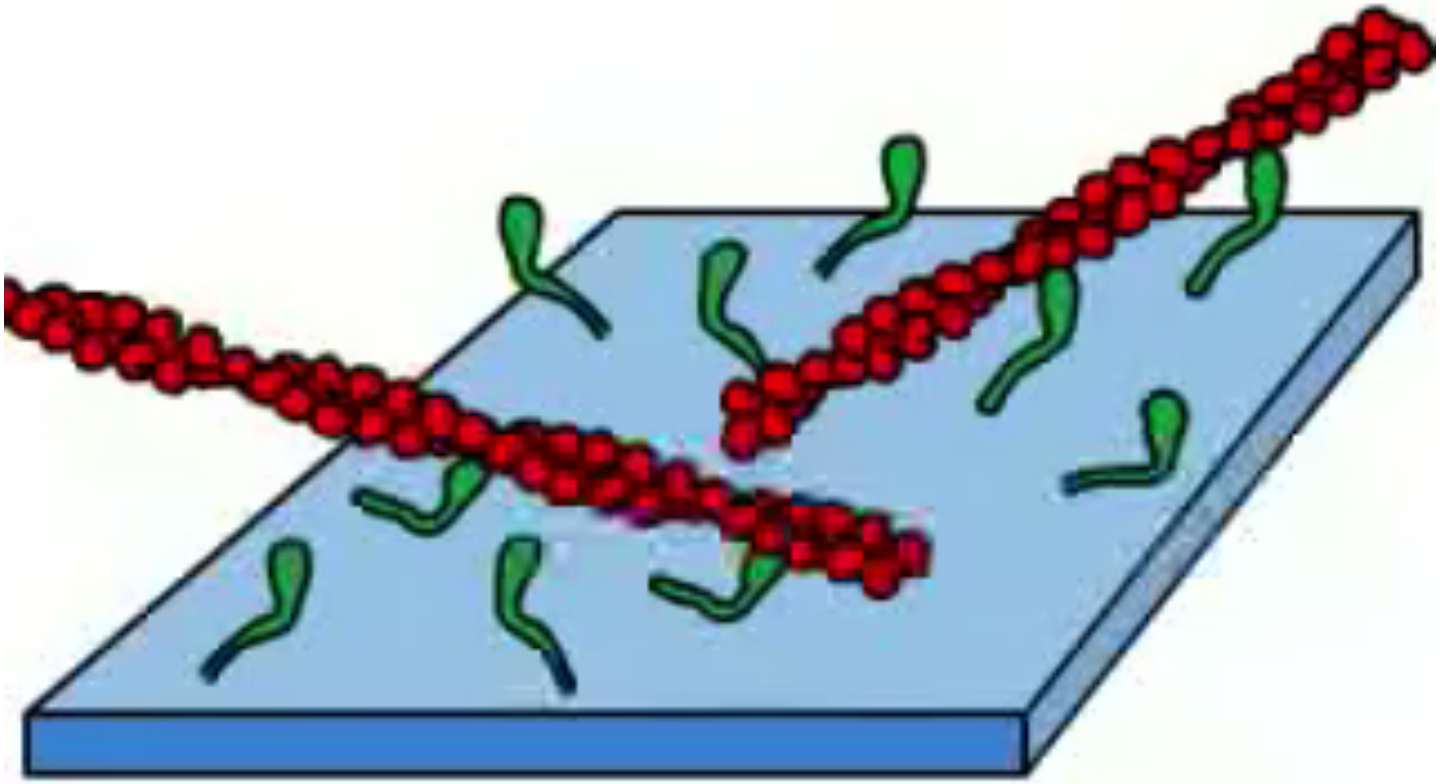
Figure 16.11b Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Actin fixed, myosin moves…



Kodera *et al*., Nature (2010)

Myosins fixed, actin moves…



Notes 5

One-state model

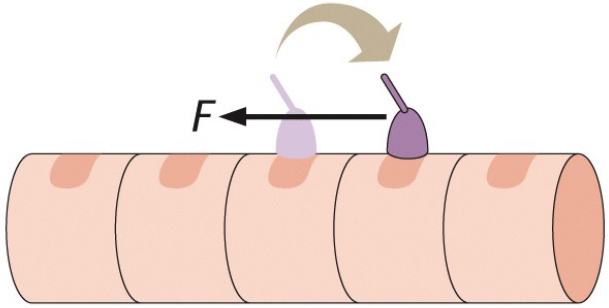
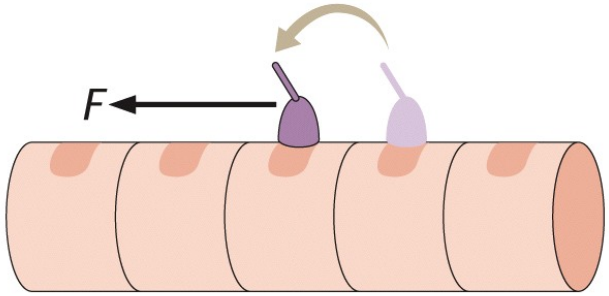
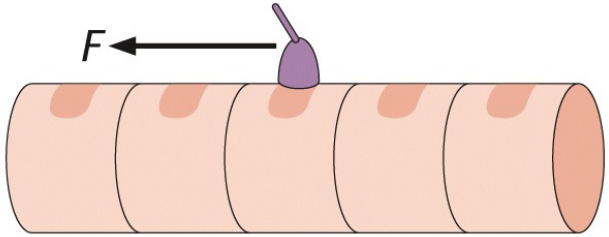
TRAJECTORY	WEIGHT
	$k_+(F)\Delta t$
	$k_-(F)\Delta t$
	$1 - [k_+(F) + k_-(F)]\Delta t$

Figure 16.22 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

5 Random walking, diffusion, and Smoluchowski equation

Random walks can be described in various ways and have wide applicability. For example, we can consider a molecular motor walking along a one-dimensional filament with steps of length a. For simplicity, we consider only a so-called one-state model of such a motor, *i.e.*, at each position the motor can only be in a single state. Such a motor is equivalent to a random walker that can take a step forward or backward, where — unlike the random walk model used for a polymer previously — we do not assume that the probabilities for for forward and backward stepping are equal.

We can then define $k_+\Delta t$ and $k_-\Delta t$ as the probability for a given motor to move one step to the right and to the left, respectively, in a time interval Δt, and next write a probability for the motor to be found at a position x at a time $t + \Delta t$:

$$p(x, t+\Delta t) = \underbrace{k_+\Delta t\, p(x-a,t)}_{\text{Motor moved from } (x-a)\to x} + \underbrace{k_-\Delta t\, p(x+a,t)}_{\text{Motor moved from } (x+a)\to x} + \underbrace{(1-k_+\Delta t - k_-\Delta t)p(x,t)}_{\text{Motor stayed where it was}}, \tag{5.1}$$

where $p(x \pm a, t)$ and $p(x, t)$ represent the probabilities, respectively, that the motor was at position $x \pm a$ and x, at time t.

This can be rearranged to give

$$\frac{p(x, t+\Delta t) - p(x,t)}{\Delta t} = k_+\, p(x-a,t) + k_-\, p(x+a,t) - k_+\, p(x,t) - k_-\, p(x,t)\,. \tag{5.2}$$

Without loss of generality, we can let $\Delta t \to 0$, allowing us to write

$$\lim_{\Delta t\to 0} \frac{p(x, t+\Delta t) - p(x,t)}{\Delta t} = \frac{\partial p(x,t)}{\partial t}\,, \tag{5.3}$$

and next approximate $p(x \pm a, t)$ by the Taylor expansion

$$p(x \pm a, t) \approx p(x,t) \pm a\frac{\partial p(x,t)}{\partial x} + \frac{a^2}{2}\,\frac{\partial^2 p(x,t)}{\partial x^2}\,. \tag{5.4}$$

We can thus rewrite Eq. 5.2 in terms of $p(x, t)$ and its partial derivatives. Noting that the terms with $k_\pm p(x, t)$ at the right hand side cancel, we find

$$\frac{\partial p(x,t)}{\partial t} = -a(k_+ - k_-)\frac{\partial p(x,t)}{\partial x} + \frac{a^2}{2}(k_+ + k_-)\frac{\partial^2 p(x,t)}{\partial x^2}\,. \tag{5.5}$$

Finally, defining a drift velocity $v = a(k_+ - k_-)$ and a diffusion coefficient $D = (a^2/2)(k_+ + k_-)$, this yields the so-called Smoluchowski equation

$$\frac{\partial p(x,t)}{\partial t} = -v\frac{\partial p(x,t)}{\partial x} + D\frac{\partial^2 p(x,t)}{\partial x^2}\,. \tag{5.6}$$

In the case of $v = 0$, this reduces to the *diffusion equation*, a very general equation that, e.g., describes the diffusion of molecules in solution or the spreading of heat in a material, with $p(x, t)$ replaced by, respectively, a concentration $c(x, t)$ or temperature $T(x, t)$.

Diffusion & Smoluchowski equation

$$\partial p(x,t)/\partial t = -v\, \partial p(x,t)/\partial x + D\, \partial^2 p(x,t)/\partial x^2$$

Solution: $p(x,t) = 1/\sqrt{(4\pi Dt)}\, \exp[-(x-vt)^2/4Dt]$

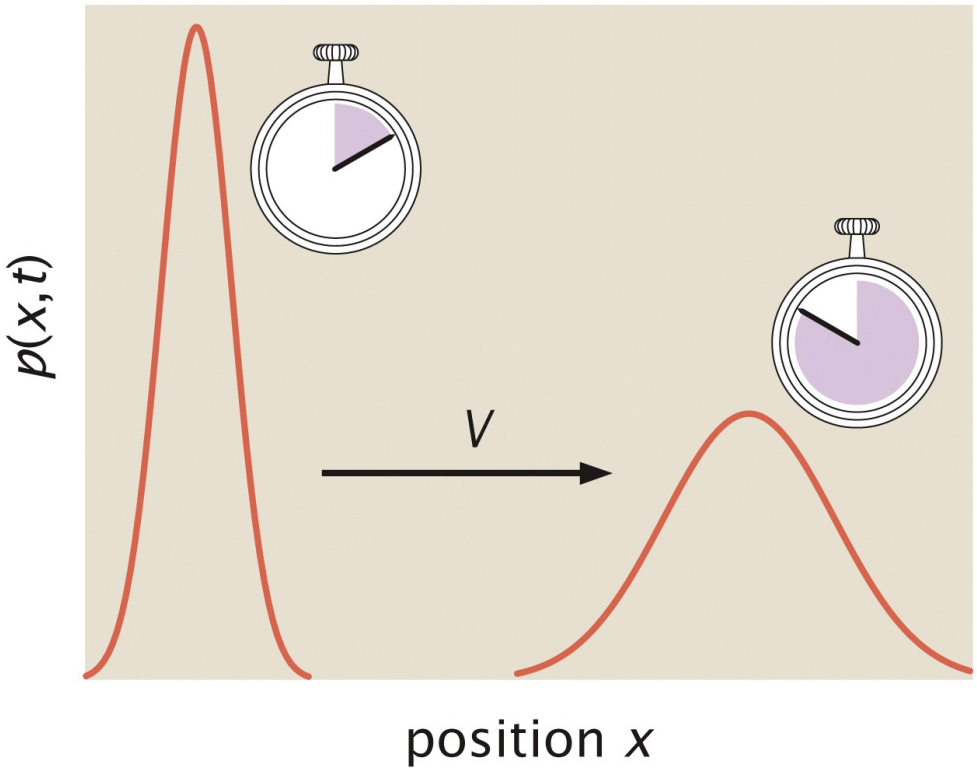


Figure 16.23 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Generally, we need multi-state models…

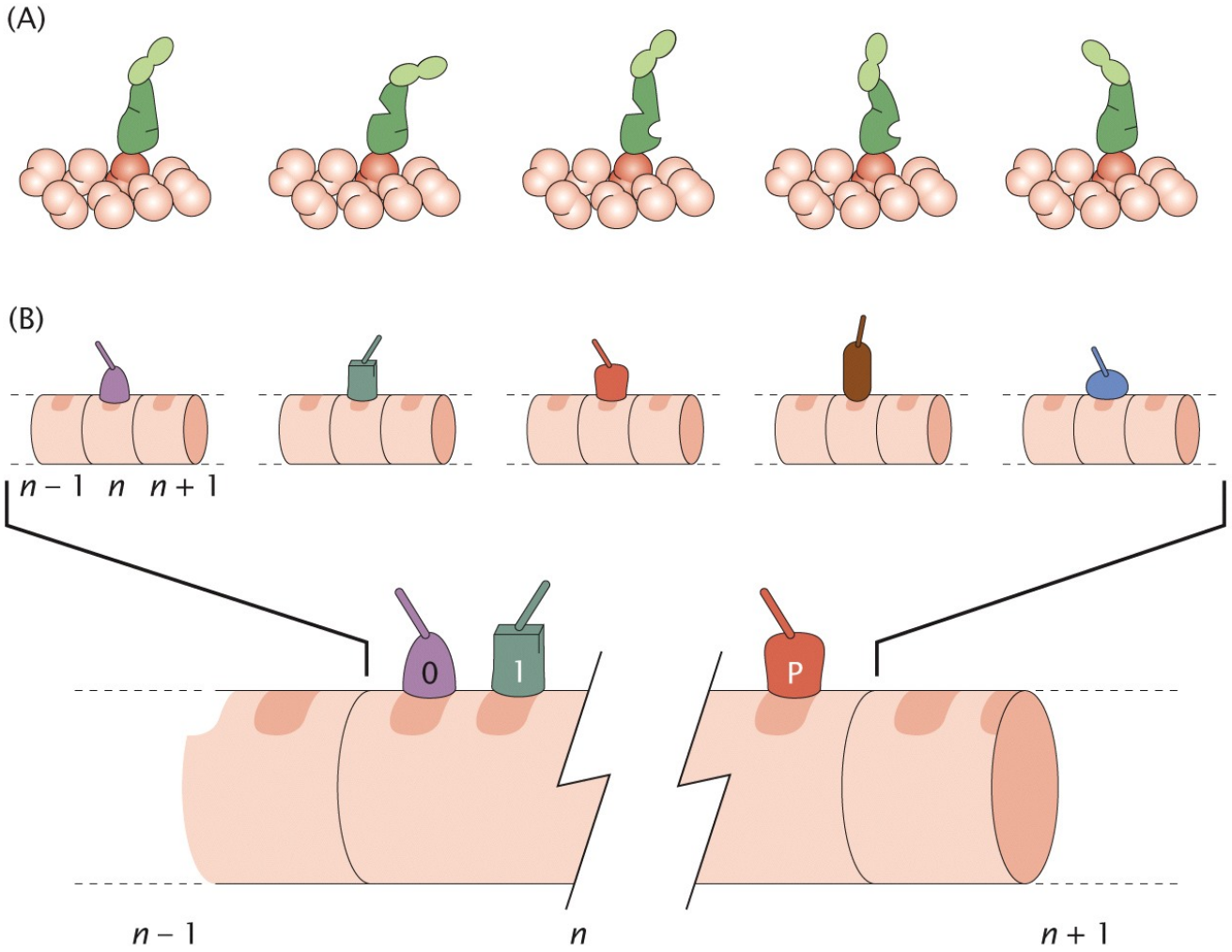
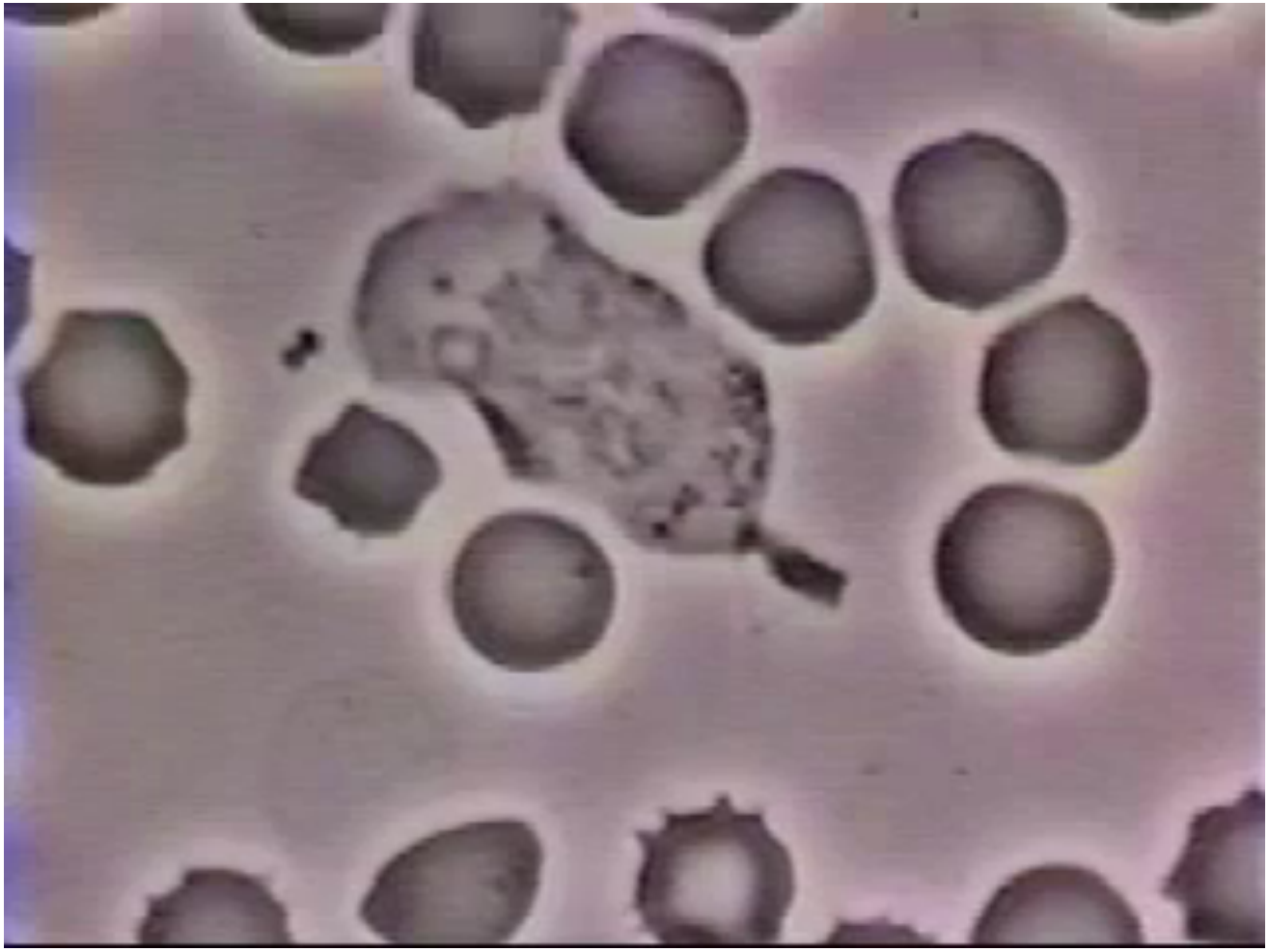


Figure 16.20 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

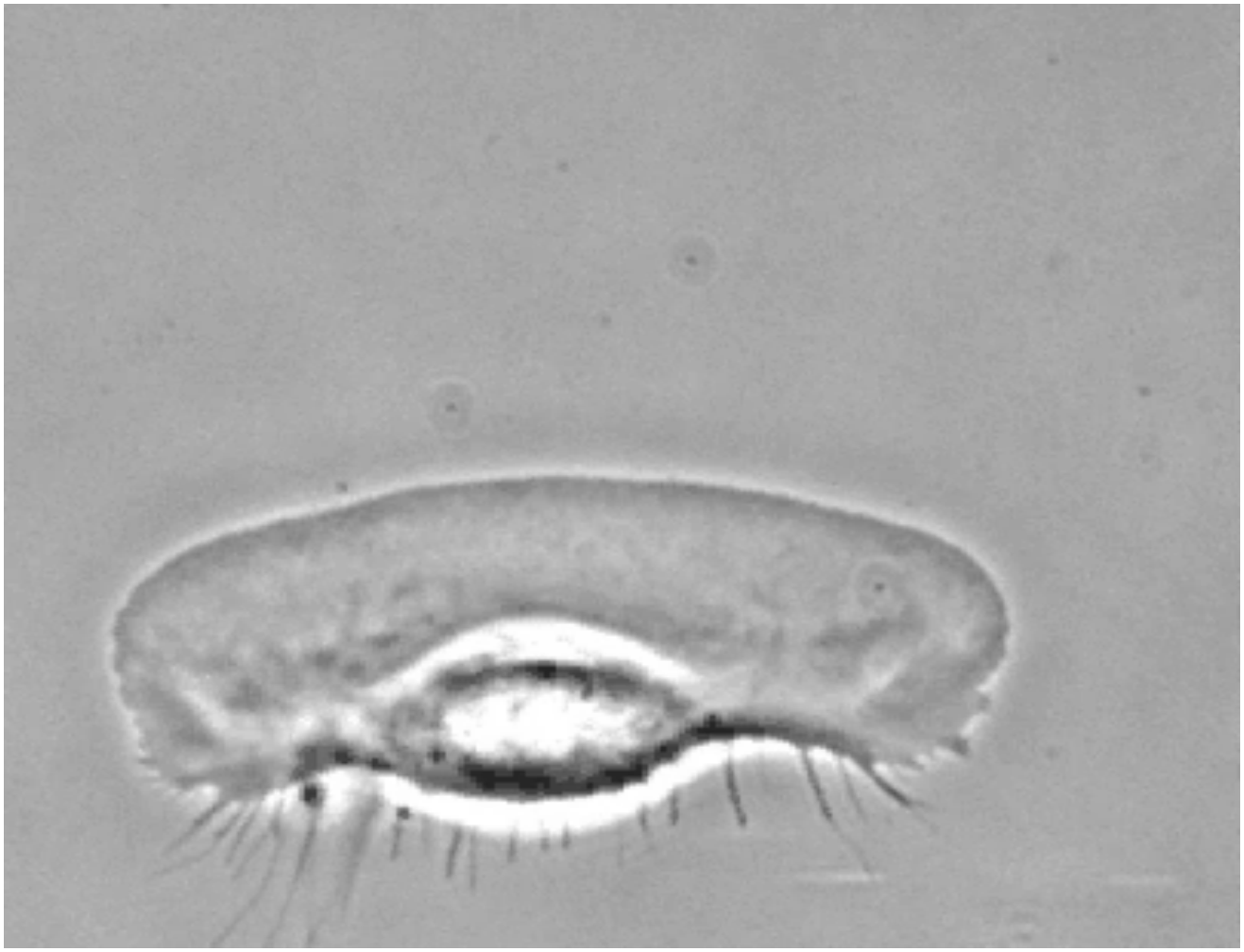
1. Effect of fluctuations on mechanics

2. Active mechanical components
   a. Molecular motors
      - Muscles
      - Example of myosin V
      - Diffusion / Smoluchowksi equation
   b. Polymerisation motors
      - Moving cells
      - Simple models

Cells are not static structures



They crawl around…



Actin polymerisation

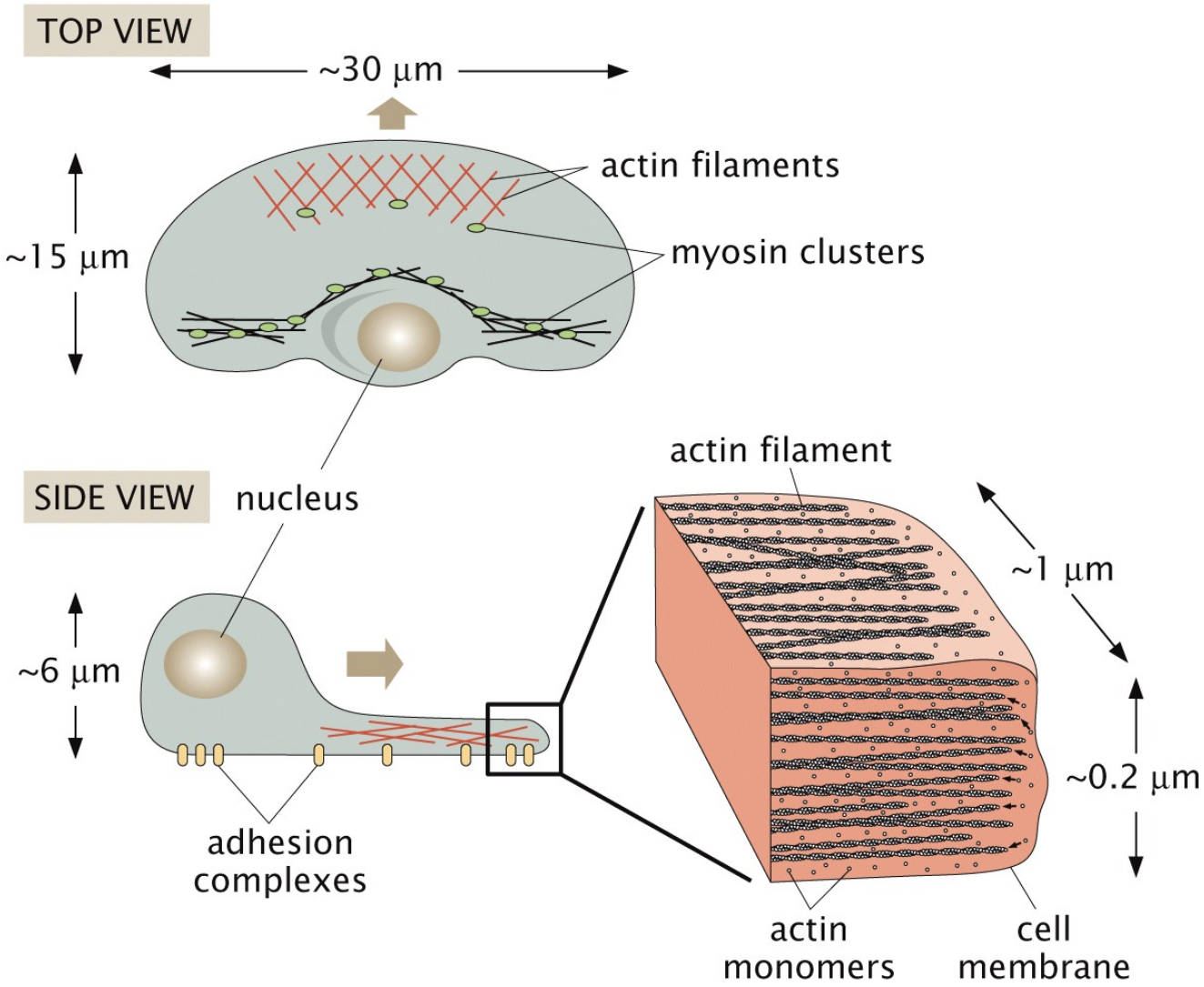


Figure 15.2b Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Polymerisation motor pushing against wall

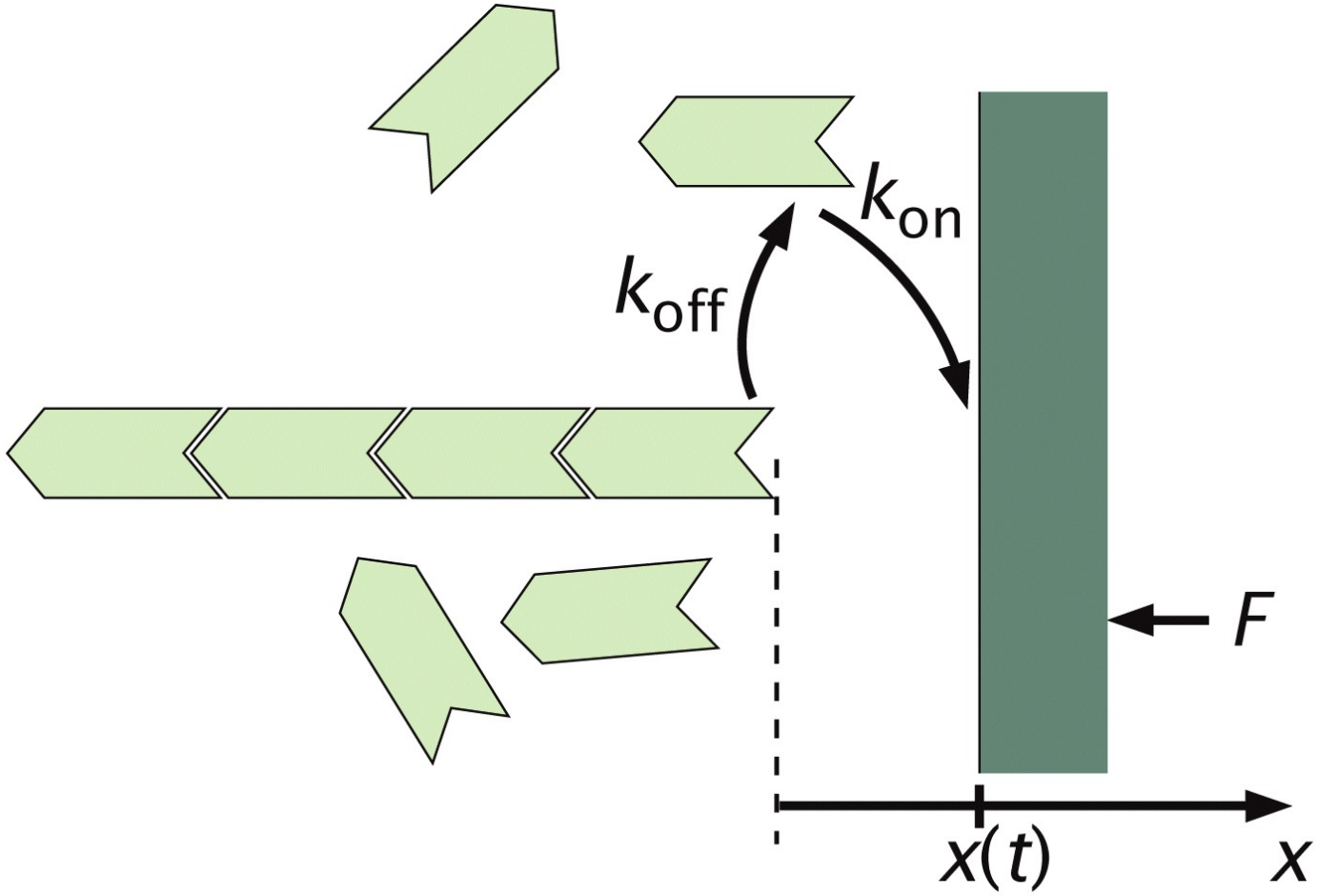


Figure 16.45 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

What determines rate?

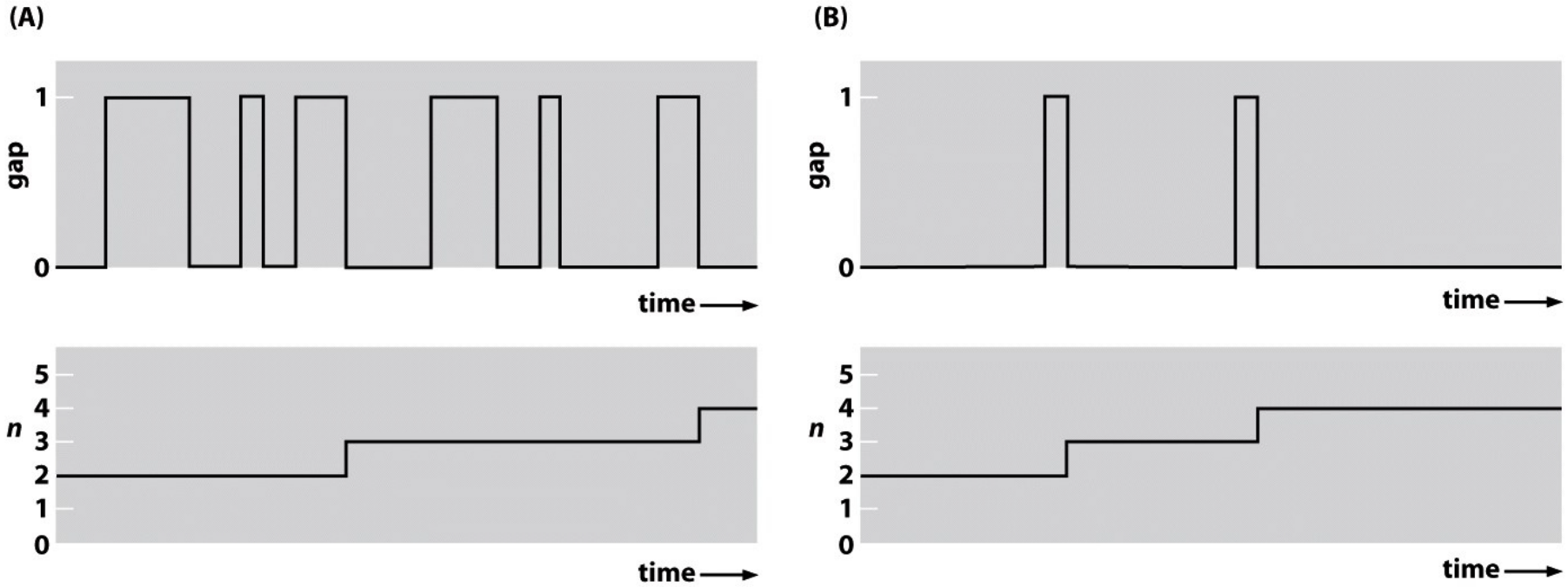


Figure 16.45 Physical Biology of the Cell (© Garland Science 2009)

Monomer-addition limited

Gap-opening limited

Polymerisation motor (gap-opening limited)

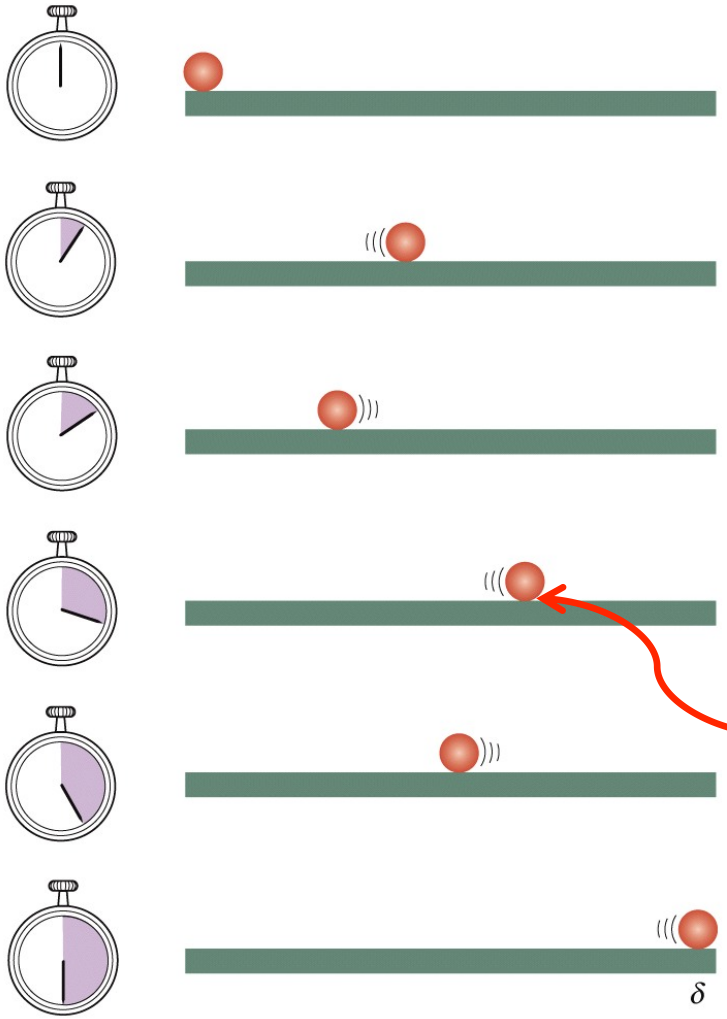


Figure 16.47 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

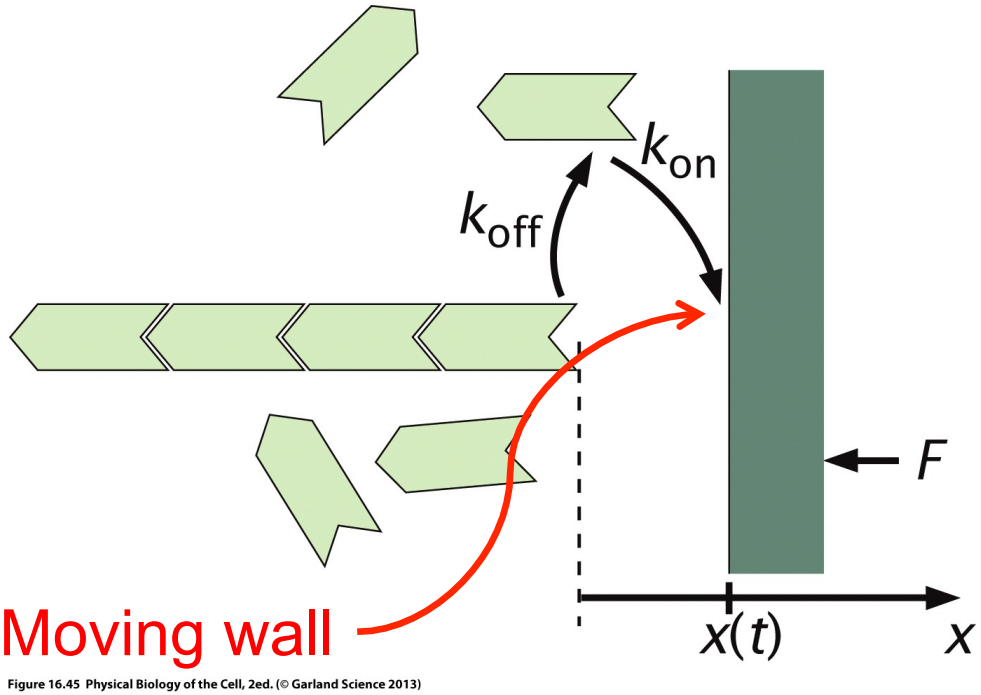


Figure 16.45 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Diffusion wall arrives at δ =>
insert monomer and reset $x \rightarrow 0$

Solving the Smoluchowski equation

$$\partial p(x,t)/\partial t = -F/\gamma \, \partial p(x,t)/\partial x + D \, \partial^2 p(x,t)/\partial x^2$$

Einstein relation : $\gamma D = k_B T$

Boundary conditions : $p(\delta) = 0$ and $\int_0^{\delta} p(x)\mathrm{d}x = 1$

Solution : $v = D/\delta \quad (F\delta/k_B T)^2/(\exp[F\delta/k_B T] - 1 - F\delta/k_B T)$

Low force : $v = 2D/\delta$

High force : $v = D/\delta \, (F\delta/k_B T)^2 \exp[-F\delta/k_B T]$

Measure the polymerisation force

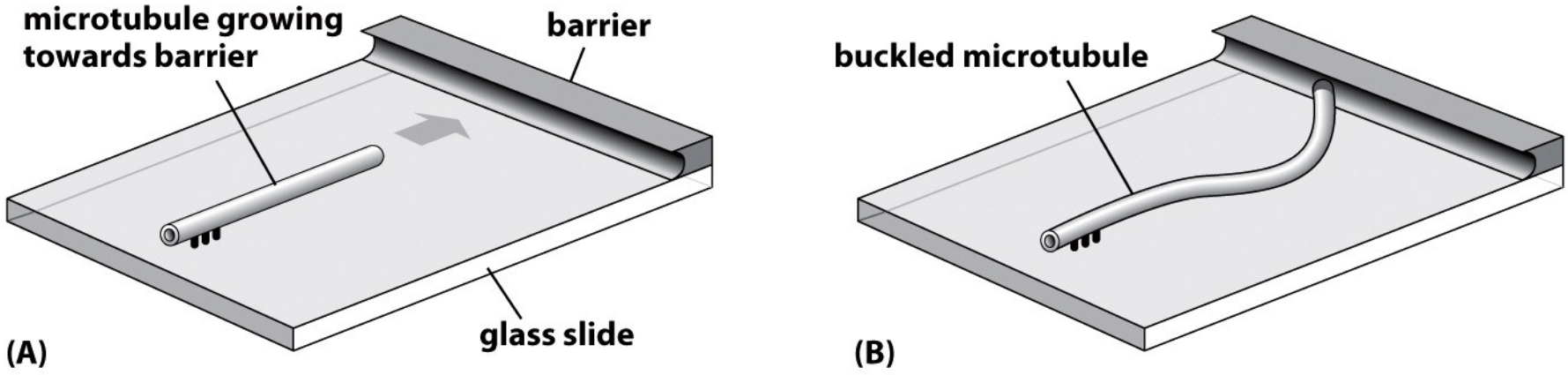


Figure 10.33 Physical Biology of the Cell (© Garland Science 2009)

Dogterom & Yurke, Science 278, 856 (1997)

Experiments to detect polymerisation force

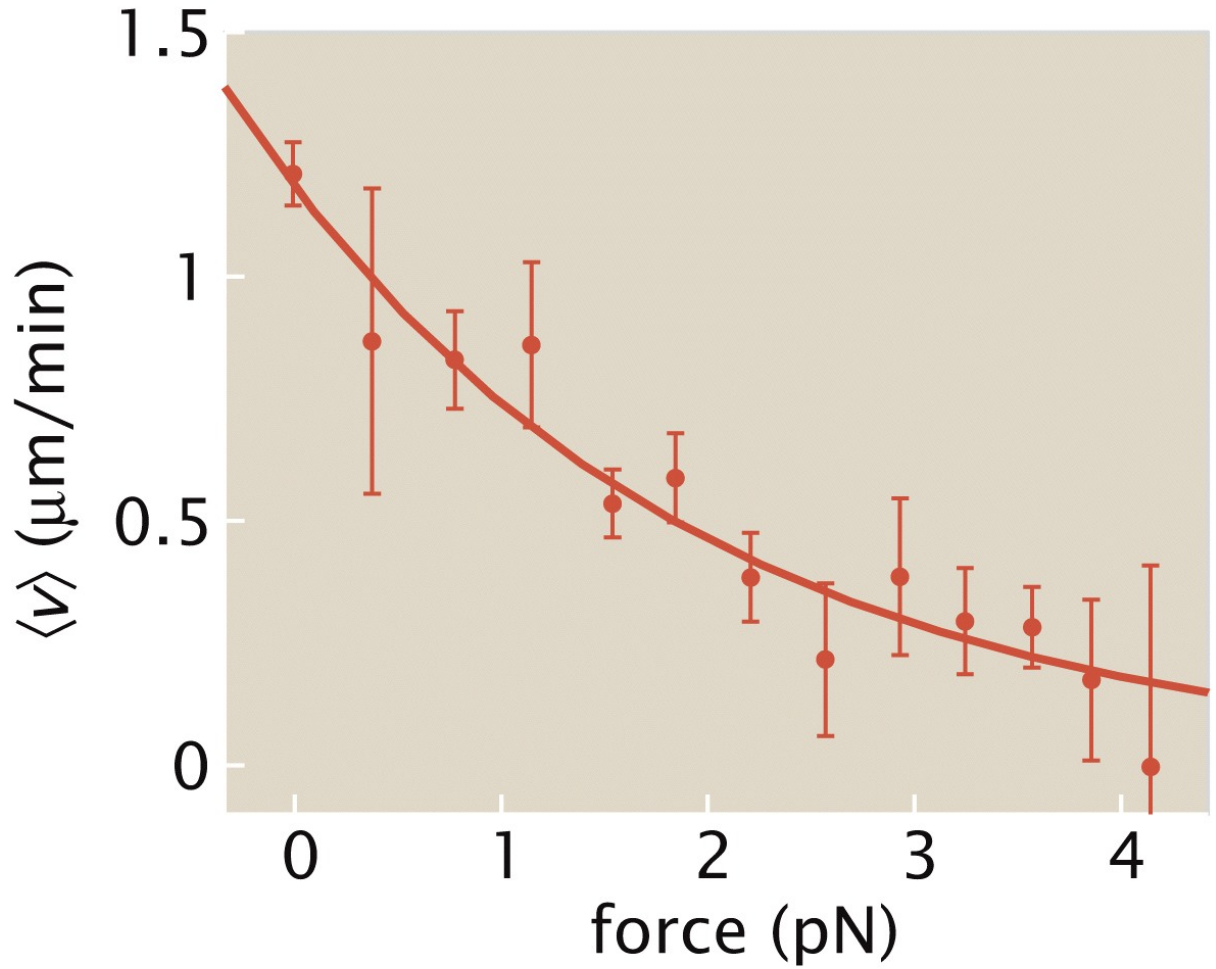


Figure 16.48 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

1. Effect of fluctuations on mechanics

2. Active mechanical components
   a. Molecular motors
      - Muscles
      - Example of myosin V
      - Diffusion / Smoluchowksi equation
   b. Polymerisation motors
      - Moving cells
      - Simple models
      - More cytoskeleton dynamics

Cytoskeletal polymerisation

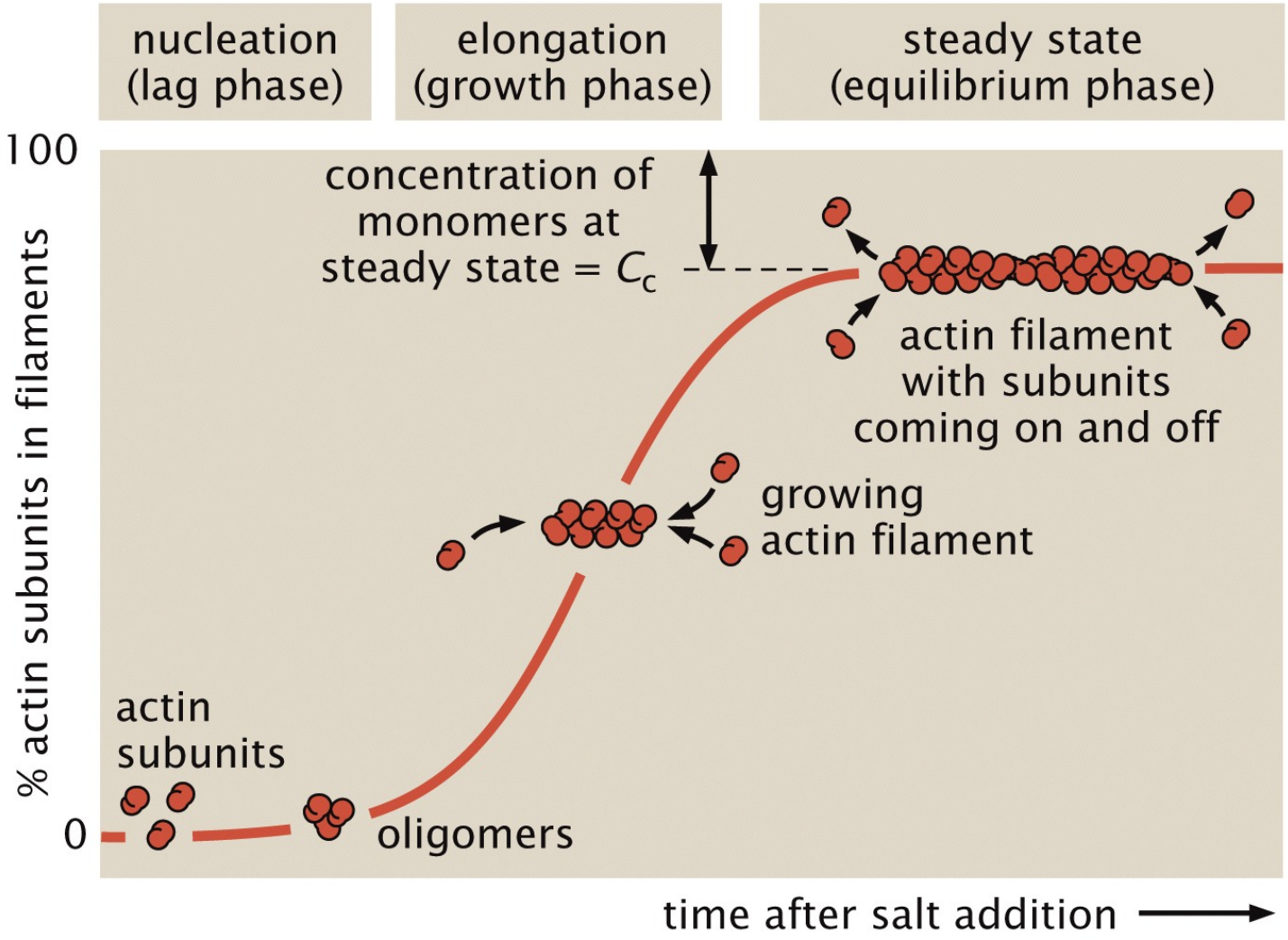


Figure 15.19a Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Polymer in equilibrium

- $P_n + P_1 \leftrightarrow P_{n+1}$
- $K_d = [P_n][P_1]/[P_{n+1}]$

Assume now K_d independent of n:

- $K_d = [P_1][P_1]/[P_2] \Rightarrow [P_2] = [P_1]^2/ K_d$
- $K_d = [P_2][P_1]/[P_3] = [P_1]/[P_3]\ [P_1]^2/ K_d \Rightarrow [P_3] = [P_1]^3/ K_d^2$
- $[P_n] = K_d ([P_1]/ K_d)^n = K_d \exp[n \ln[[P_1]/ K_d]] = K_d e^{-\alpha n}$

Probability distribution:

$\langle n \rangle = \int_0^\infty n\, e^{-\alpha n}\, dn \,/\, \int_0^\infty e^{-\alpha n}\, dn = 1/\alpha = 1/ \ln[K_d /[P_1]]$

Distribution of actin filament lengths

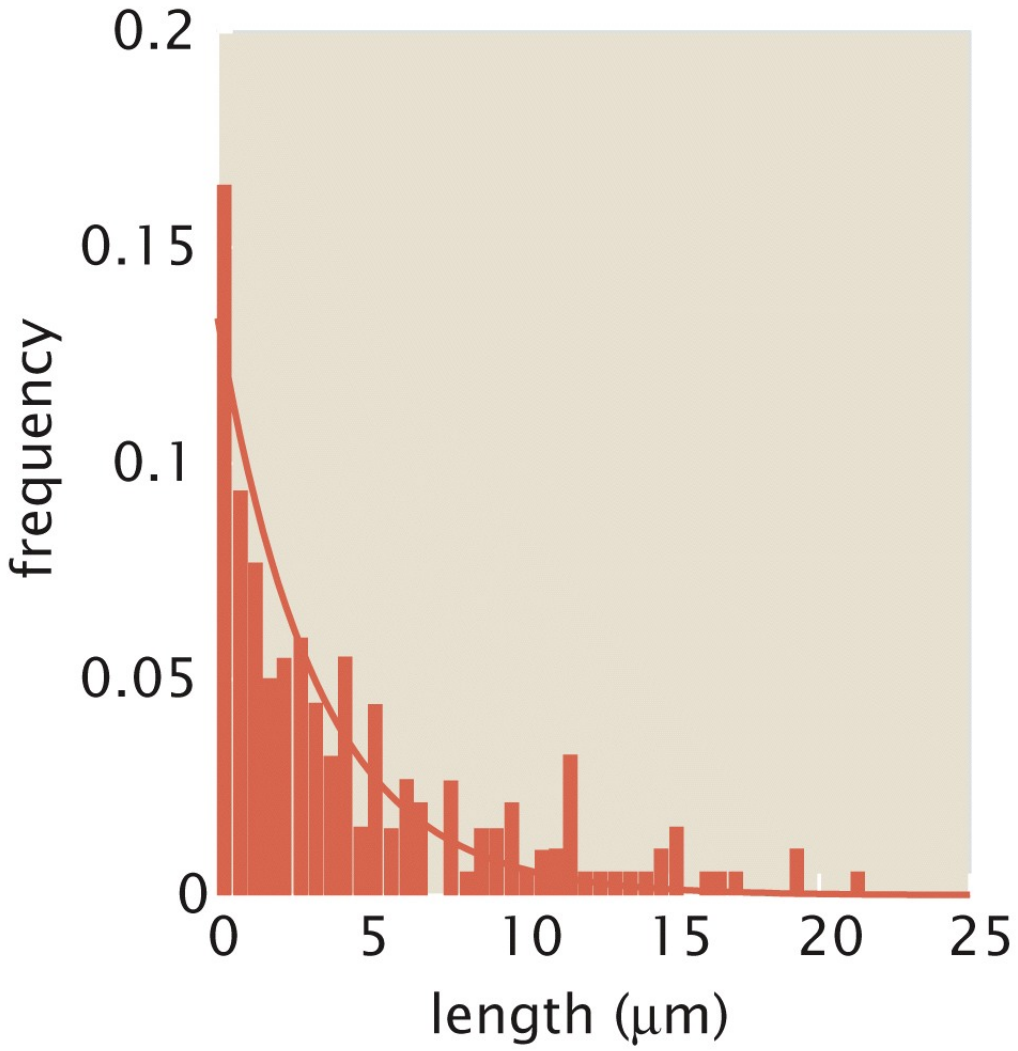


Figure 15.23 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Cytoskeletonal filaments are not static

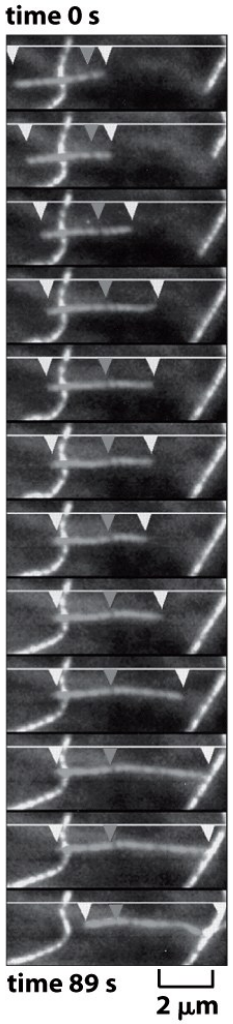


Figure 15.34 Physical Biology of the Cell (© Garland Science 2009)

Mircotubule "treadmilling"

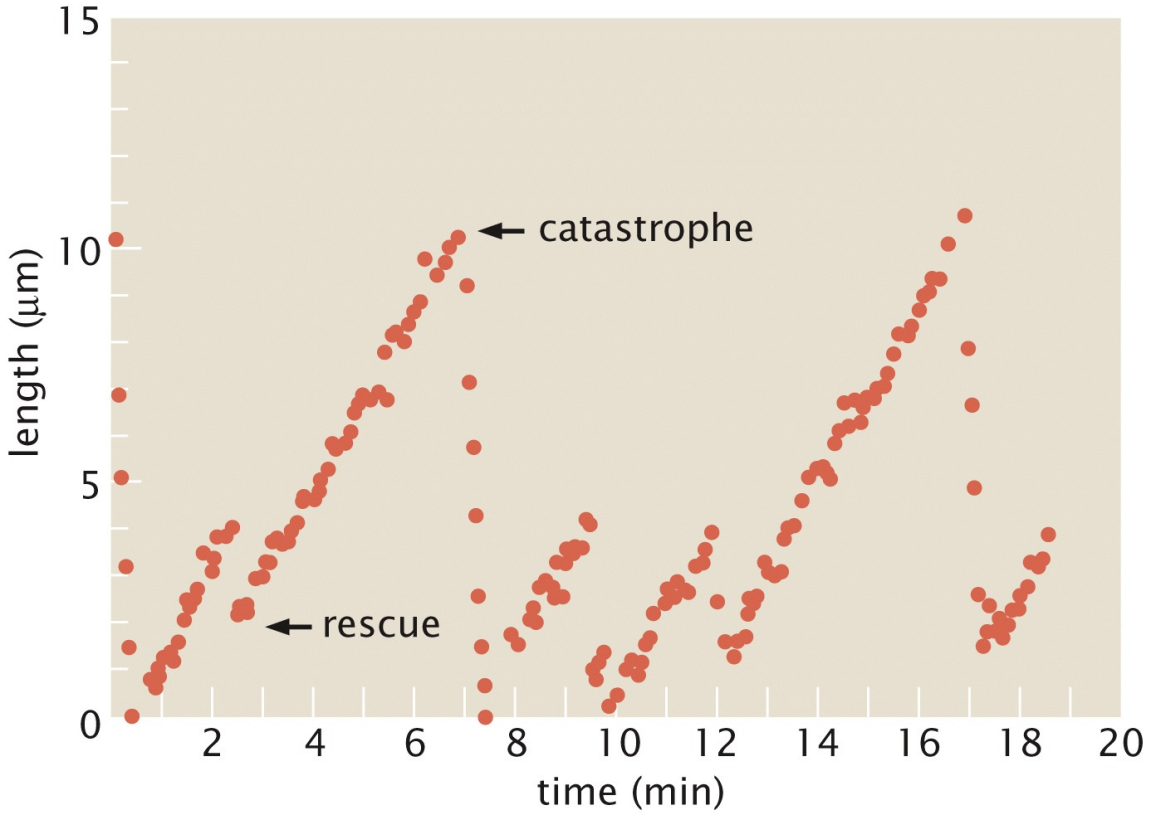


Figure 15.34 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

"Dynamic instability" of microtubules

Models for polymerisation

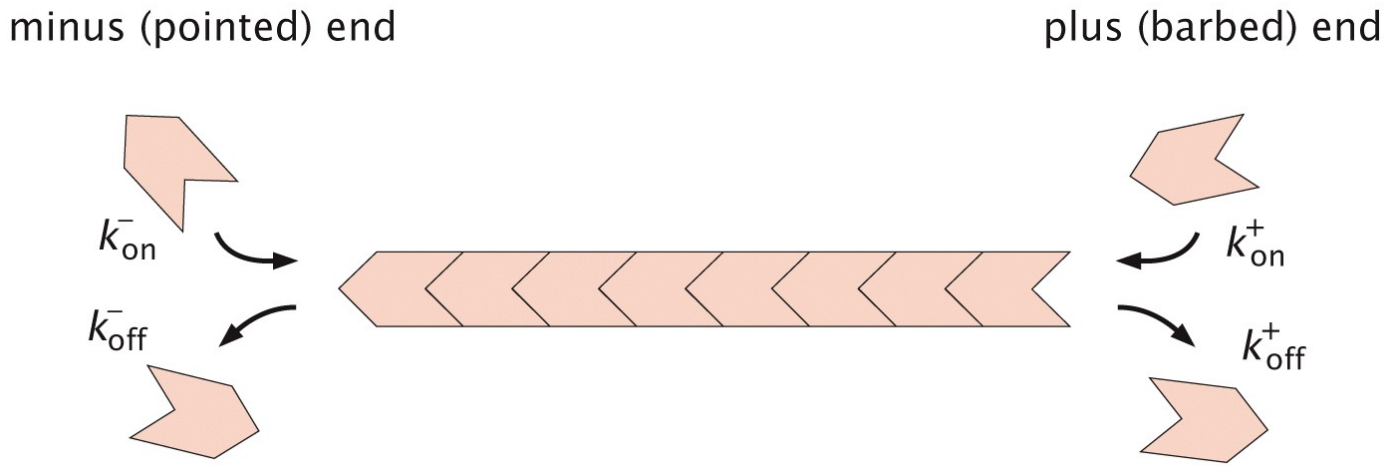


Figure 15.21b Physical Biology of the Cell, 2ed. (© Garland Science 2013)

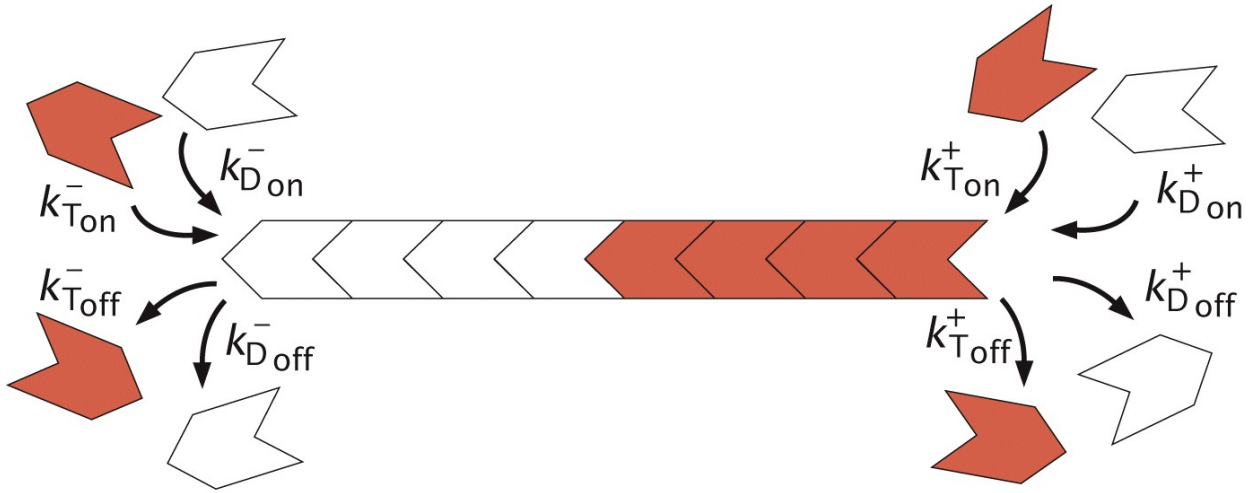


Figure 15.21c Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Dynamic instability

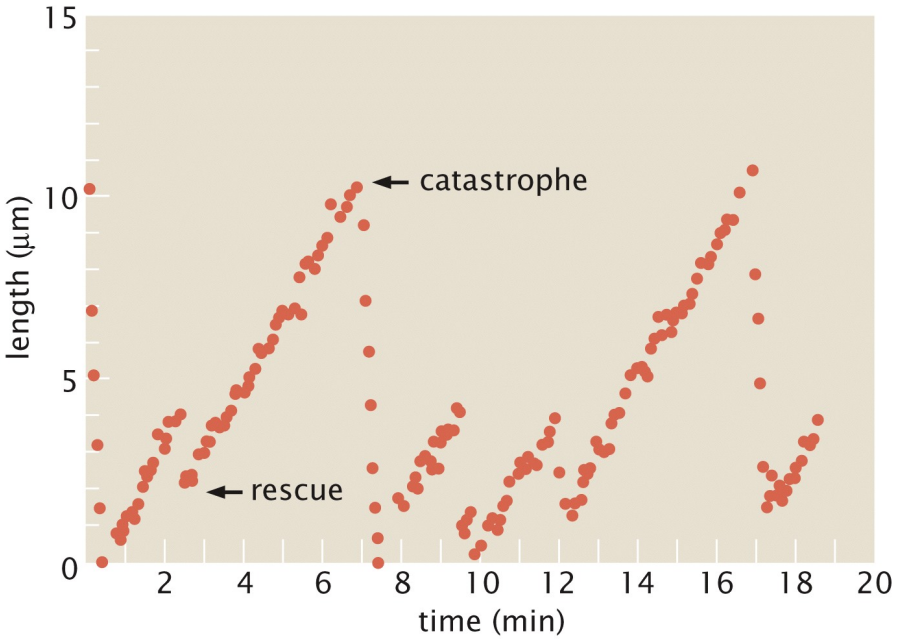


Figure 15.34 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

At cap end :

ATP or GTP bound monomers (unhydrolysed) => Growth

ADP or GDP bound monomers (hydrolysed) => Shrinkage

Model :

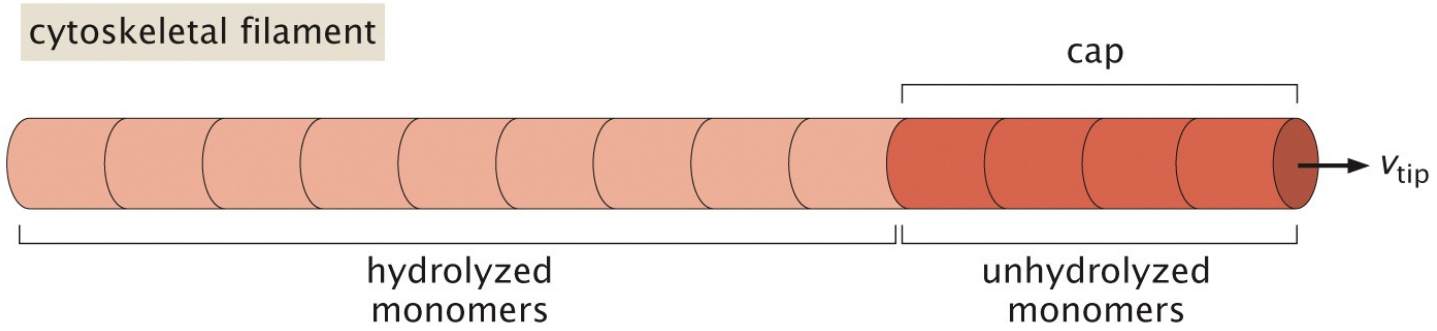


Figure 15.35 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Catastrophe rate

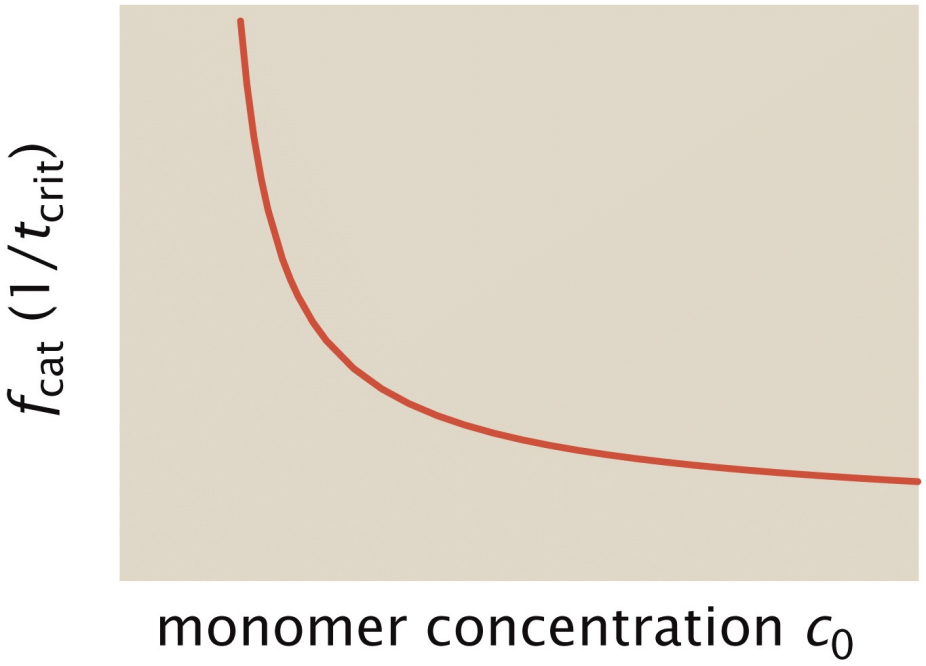


Figure 15.37a Physical Biology of the Cell, 2ed. (© Garland Science 2013)

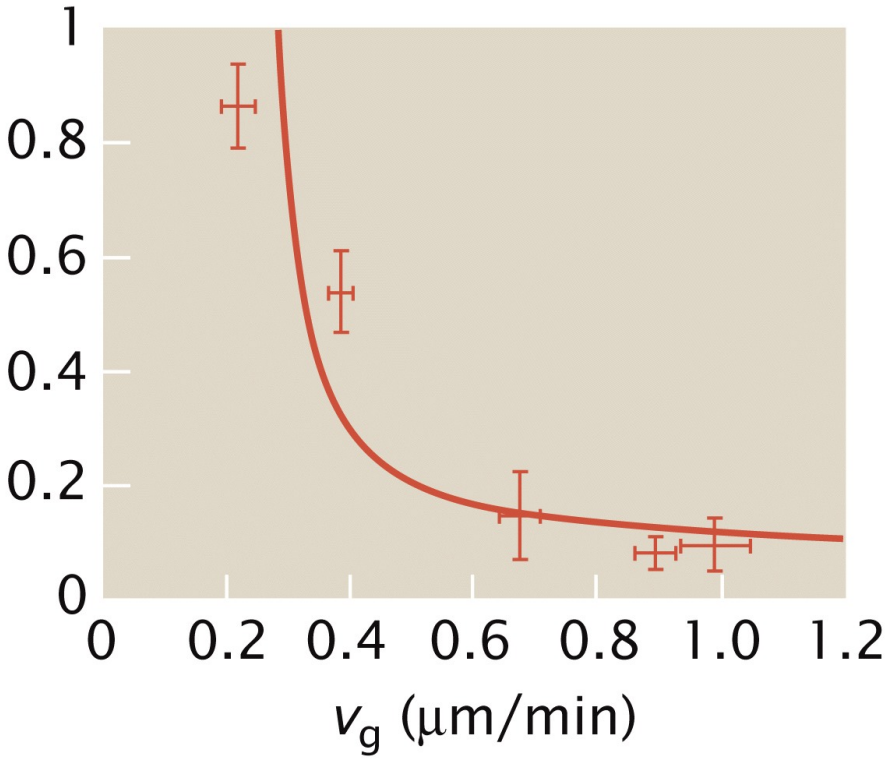


Figure 15.37b Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Proportional to [monomer]

1. Effect of fluctuations on mechanics

2. Active mechanical components
   a. Molecular motors
      - Muscles
      - Example of myosin V
      - Diffusion / Smoluchowksi equation
   b. Polymerisation motors
      - Moving cells
      - Simple models
      - More cytoskeleton dynamics
   c. Other motors (rotation, translocation, …)

3. Viscous fluids

Optical tweezers experiments

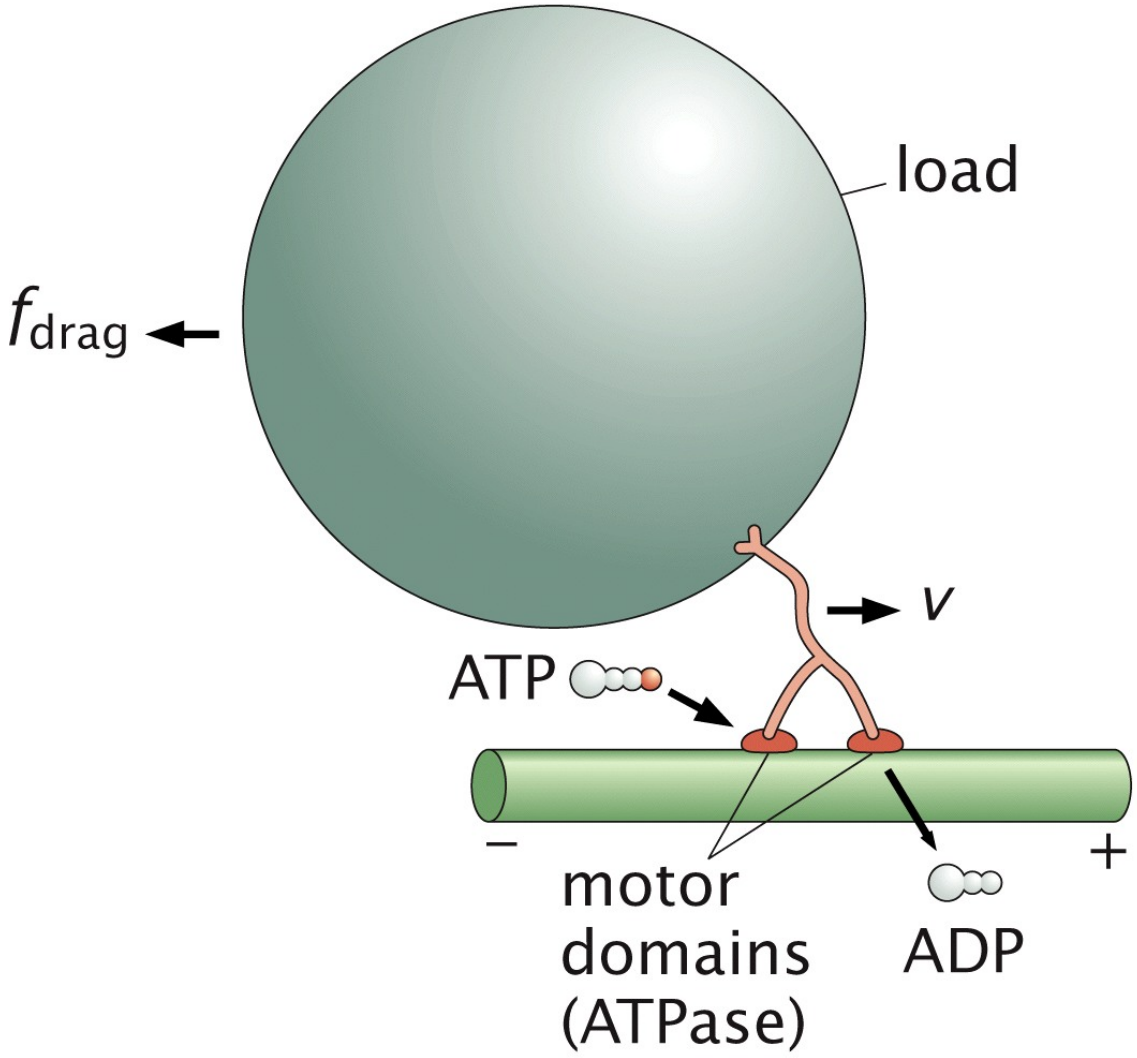


Figure 12.13 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Bead ~ 1 μm

Molec. motor ~ 1 nm

For comparison:

Earth ~ 10^4 km

Mt. Everest ~ 10 km

Jiggling water molecules cause friction

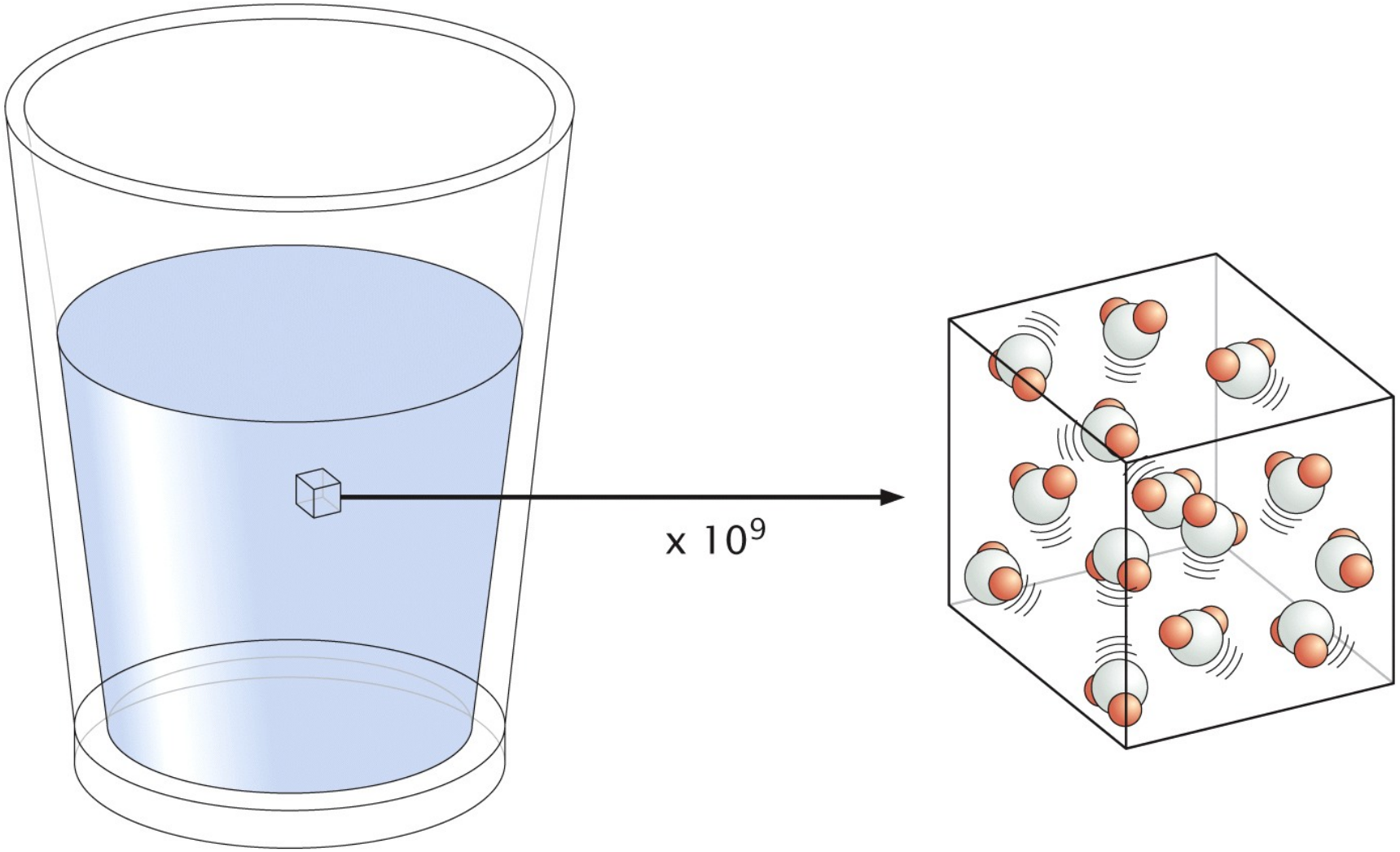


Figure 12.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Navier-Stokes equation: Flow around sphere

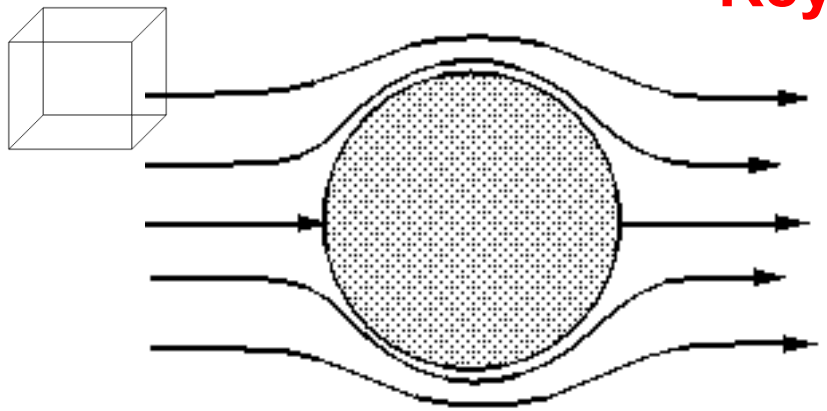
ρ = mass density

$\boldsymbol{v}$ = velocity

p = pressure

η = viscosity

∇ = differential



Reynolds number

$$\rho\, \partial \boldsymbol{v} / \partial t + \rho\, (\boldsymbol{v} \bullet \nabla)\boldsymbol{v} = -\nabla p + \eta\, \nabla^2 \boldsymbol{v}$$

$$\sim \rho\, v^2/R + \sim \rho\, v^2/R = -\nabla p + \sim \eta\, v/R^2$$

$$\sim \rho v R/\eta + \sim \rho v R/\eta = -(\nabla p) R^2/\eta v + \sim 1$$

inertial terms

viscous term

Aristotle's mechanics

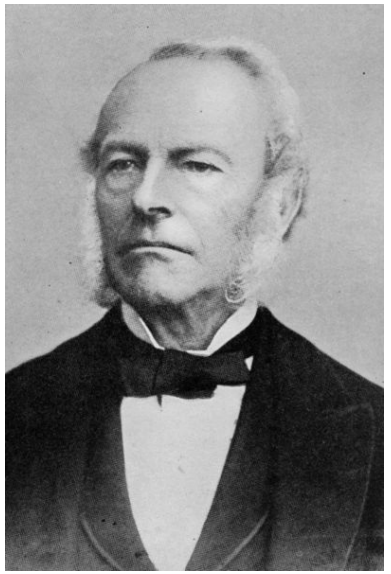
Aristotle (ca. 350 BC):

“velocity proportional to force”

Galileo, Newton *et al*. (ca. 1600 AD):

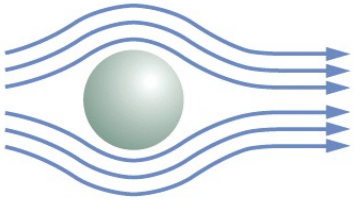
$\boldsymbol{F} = m\,\boldsymbol{a}$

$\boldsymbol{F} = 0 \iff \boldsymbol{v} = \text{const.}$

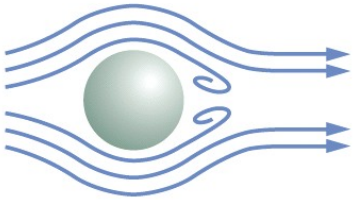


Stokes (ca. 1850 AD) and low Reynolds number (- 2015): $\boldsymbol{F} = \text{const.}\ \boldsymbol{v}$

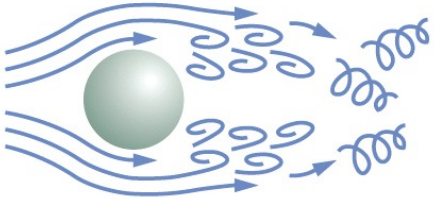
Reynold's number



Re < 10
Laminar flow



Re 10–40
Vortices form and are maintained



Re 40–20,000
Vortices form and are periodically shed

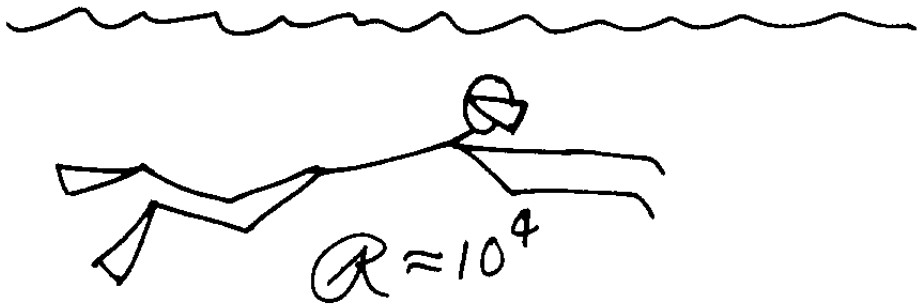


Figure 12.12 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Optical tweezers experiments

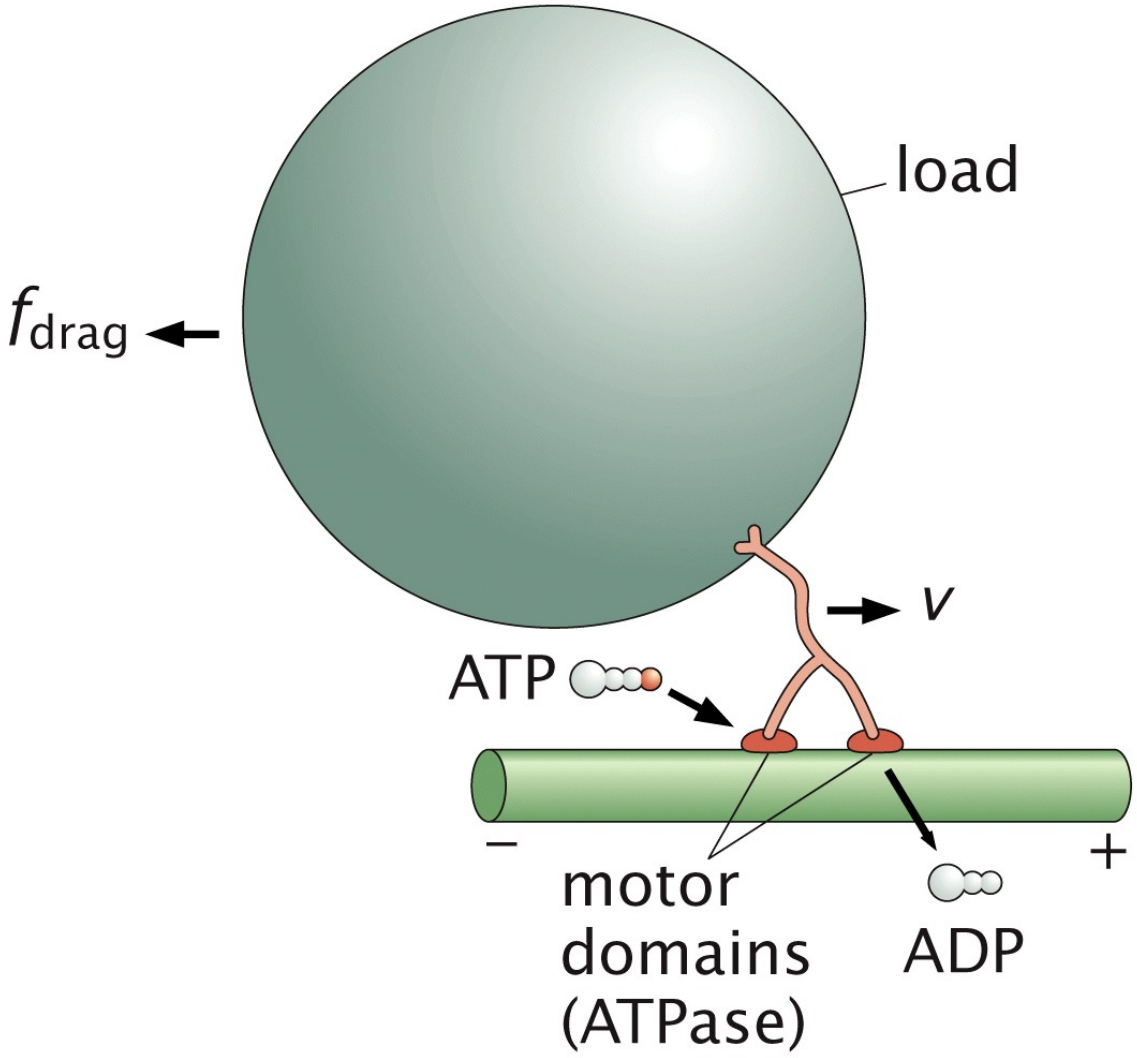


Figure 12.13 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Stokes law:

$F = 6 \pi \eta R v$

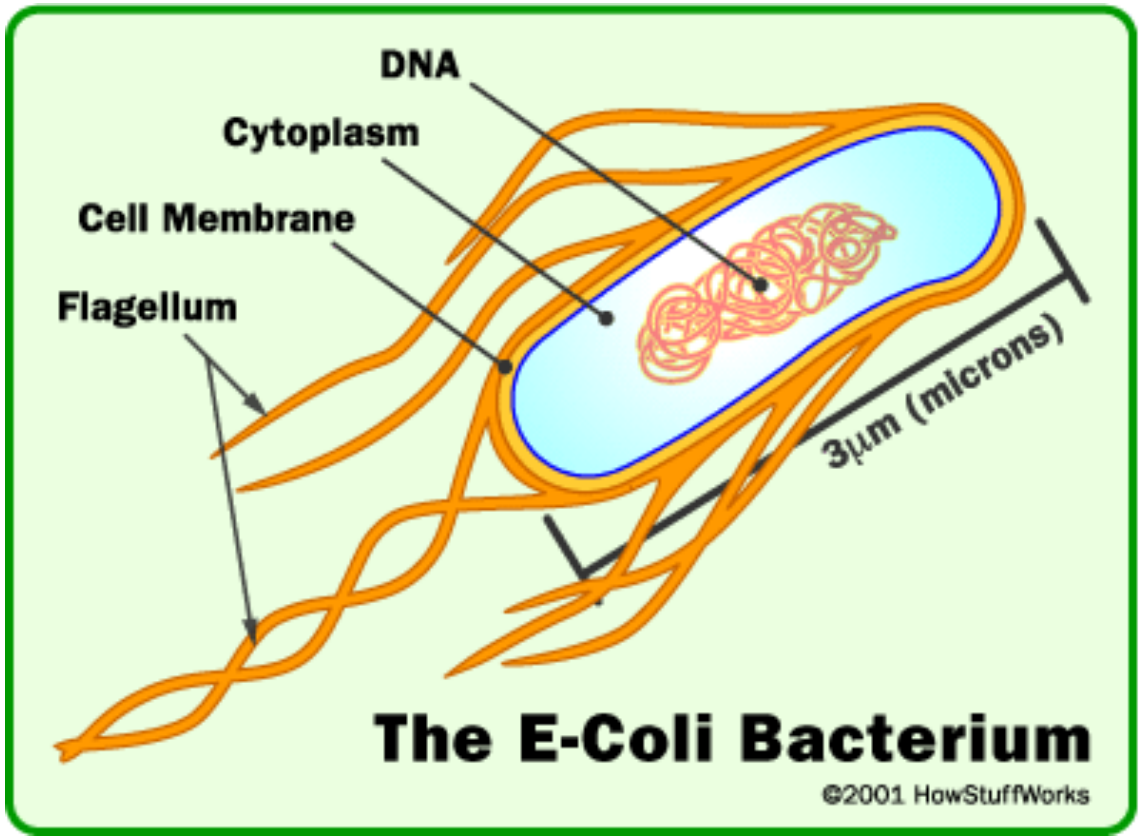
$= 6 \pi * 10^{-3}$ Ns/m^2 *

0.5 μm * 10^{-6} m/s

~ 10^{-2} pN

Motor force ~ 5 pN

Stopping distance of a bacterium



Stopping distance versus size (in water)

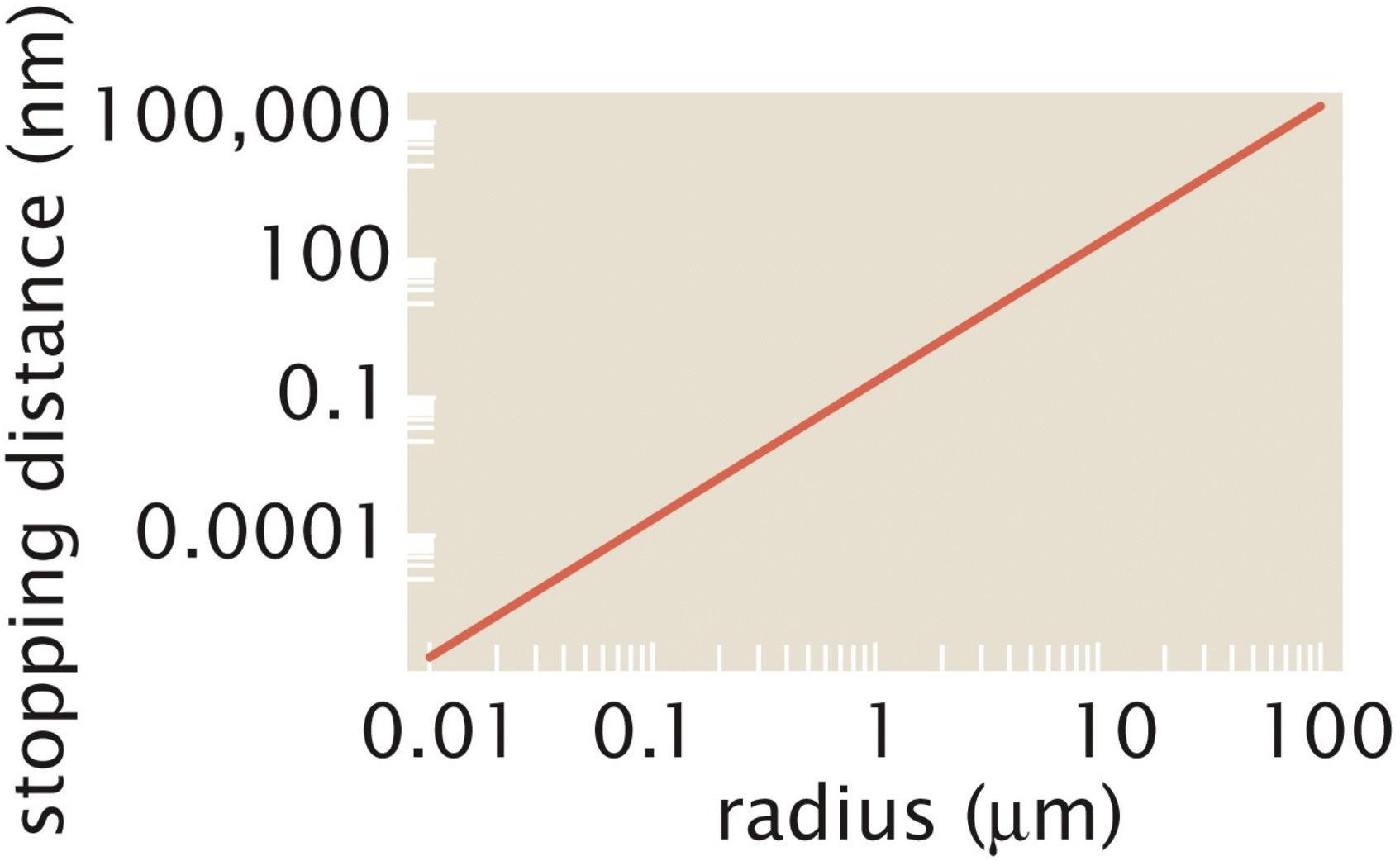


Figure 12.15 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

How far does a bacteria need to swim to outrun (out-swim) diffusion?

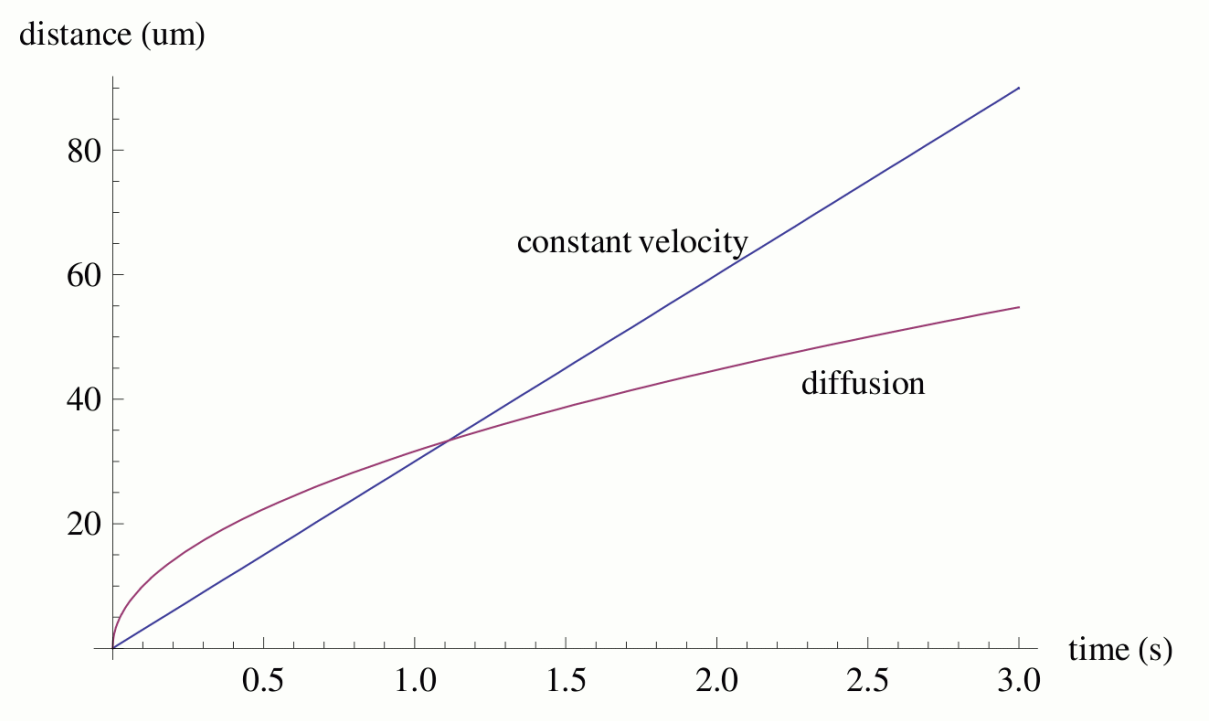
Bacterial velocity:

v = 30 μm/s

Diffusion of molecule

in water:

D = 500 μm^2/s



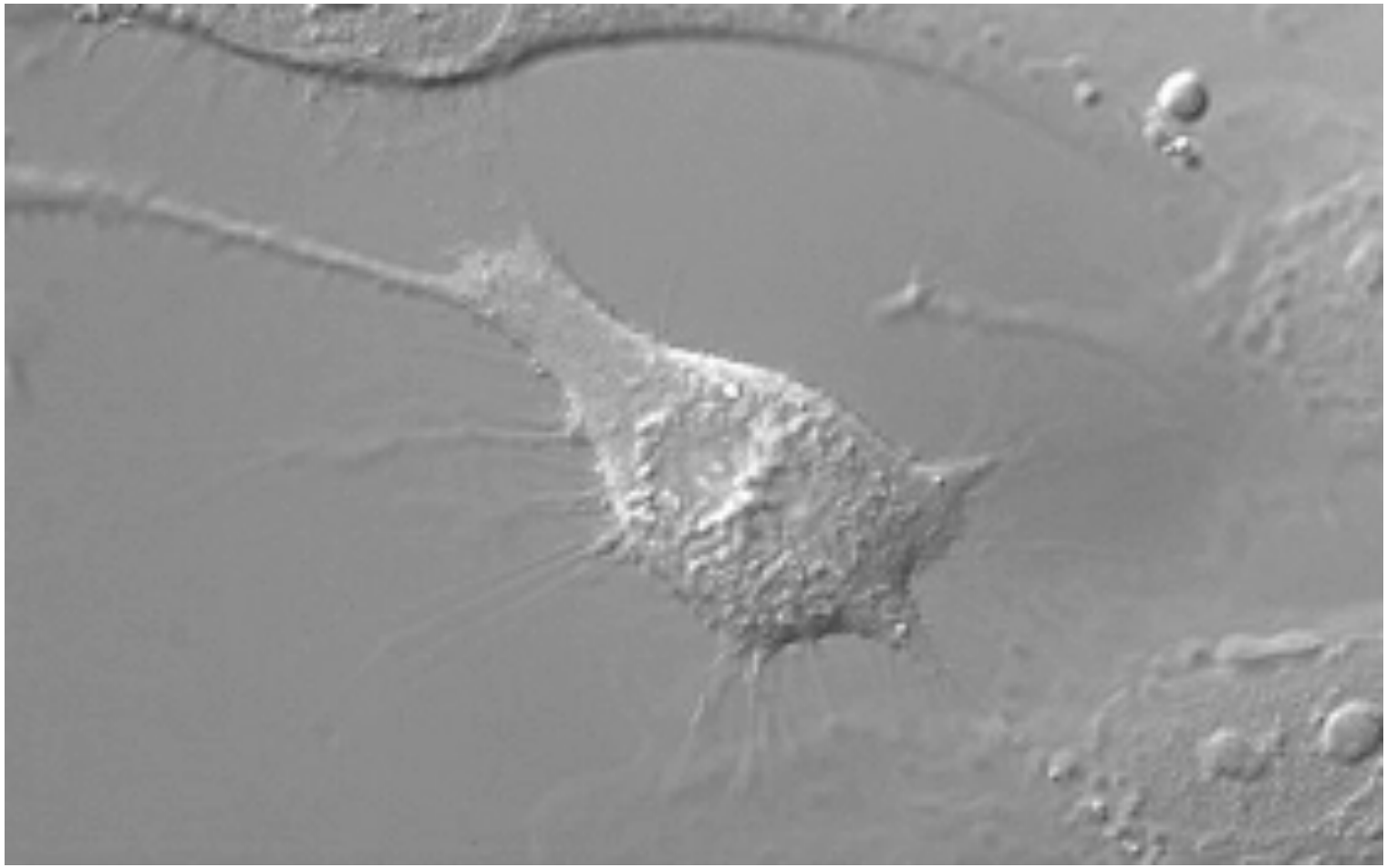
Recall polymer $\langle R^2 \rangle = L\,a$, with L "path length" ~ time

1. Effect of fluctuations on mechanics

2. Active mechanical components

3. **Viscous fluids**
   - Navier-Stokes equation
   - Reynolds number
   - Inertial does not matter here
   - Friction does

More and more complex…



1. Effect of fluctuations on mechanics

2. Active mechanical components

3. **Viscous fluids**
   - Navier-Stokes equation
   - Reynolds number
   - Inertial does not matter here
   - Friction does

   Bonus material: Purcell paper (1976)

Life at low Reynolds number

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

Editor's note: This is a reprint (slightly edited) of a paper of the same title that appeared in the book *Physics and Our World: A Symposium in Honor of Victor F. Weisskopf*, published by the American Institute of Physics (1976). The personal tone of the original talk has been preserved in the paper, which was itself a slightly edited transcript of a tape. The figures reproduce transparencies used in the talk. The demonstration involved a tall rectangular transparent vessel of corn syrup, projected by an overhead projector turned on its side. Some essential hand waving could not be reproduced.

This is a talk that I would not, I'm afraid, have the nerve to give under any other circumstances. It's a story I've been saving up to tell Viki. Like so many of you here, I've enjoyed from time to time the wonderful experience of exploring with Viki some part of physics, or anything to which we can apply physics. We wander around strictly as amateurs equipped only with some elementary physics, and in the end, it turns out, we improve our understanding of the elementary physics even if we don't throw much light on the other subjects. Now this is that kind of a subject, but I have still another reason for wanting to, as it were, needle Viki with it, because I'm going to talk for a while about viscosity. Viscosity in a liquid will be the dominant theme here and you know Viki's program of explaining everything, including the heights of mountains, with the elementary constants. The viscosity of a liquid is a very tough nut to crack, as he well knows, because when the stuff is cooled by merely 40 degrees, its viscosity can change by a factor of a million. I was really amazed by fluid viscosity in the early days of NMR, when it turned out that glycerine was just what we needed to explore the behavior of spin relaxation. And yet if you were a little bug inside the glycerine, looking around, you wouldn't see much change in your surroundings as the glycerine cooled. Viki will say that he can at least predict the *logarithm* of the viscosity. And that, of course, is correct because the reason viscosity changes is that it's got one of these activation energy things and what he can predict is the order of magnitude of the exponent. But it's more mysterious than that, Viki, because if you look at the Chemical Rubber Handbook table you will find that there is almost no liquid with viscosity much lower than that of water. The viscosities have a big range *but they stop at the same place.* I don't understand that. That's what I'm leaving for him.[1]

Now, I'm going to talk about a world which, as physicists, we almost never think about. The physicist hears about viscosity in high school when he's repeating Millikan's oil drop experiment and he never hears about it again, at least not in what I teach. And Reynolds's number, of course, is something for the engineers. And the *low* Reynolds number regime most engineers aren't even interested in—except possibly chemical engineers, in connection with fluidized beds, a fascinating topic I heard about from a chemical engineering friend at MIT. But I want to take you into the world of very low Reynolds number—a world which is inhabited by the overwhelming majority of the organisms in this room. This world is quite different from the one that we have developed our intuitions in.

I might say what got me into this. To introduce something that will come later, I'm going to talk partly about how microorganisms swim. That will not, however, turn out to be the only important question about them. I got into this through the work of a former colleague of mine at Harvard, Howard Berg. Berg got his Ph.D. with Norman Ramsey, working on a hydrogen maser, and then he went back into biology which had been his early love, and into cellular physiology. He is now at the University of Colorado at Boulder, and has recently participated in what seems to me one of the most astonishing discoveries about the questions we're going to talk about. So it was partly Howard's work, tracking *E. coli* and finding out this strange thing about them, that got me thinking about this elementary physics stuff.

Well, here we go. In Fig. 1, you see an object which is moving through a fluid with velocity v. It has dimension a. In Stokes's law, the object is a sphere, but here it's anything; η and ρ are the viscosity and density of the fluid. The ratio of the inertial forces to the viscous forces, as Osborne Reynolds pointed out slightly less than a hundred years ago, is given by $av\rho/\eta$ or av/ν, where ν is called the *kinematic* viscosity. It's easier to remember its dimensions: for water, $\nu \approx 10^{-2}\ \mathrm{cm}^2/\mathrm{sec}$. The ratio is called the Reynolds number and when that number is small the viscous forces dominate. Now there is an easy way, which I didn't realize at first, to see who should be interested in small Reynolds numbers. If you take the viscosity η and square it and divide by the density, you get a force (Fig. 2). No other dimensions come in at all. η^2/ρ is a force. For water, since $\eta \approx 10^{-2}$ and $\rho \approx 1$, $\eta^2/\rho \approx 10^{-4}$ dyn. That is a force that will tow *anything,* large or small, with a Reynolds number of order of magnitude 1. In other words, if you want to tow a submarine with Reynolds number 1 (or strictly speaking, $1/6\pi$ if it's a spherical submarine) tow it with 10^{-4} dyn. So it's clear in this case that you're interested in small Reynolds number if you're interested in *small forces* in an absolute sense. The only other people who are interested in low Reynolds number, although they usually don't have to invoke it, are the geophysicists. The Earth's mantle is supposed to have a viscosity of 10^{21} P. If you now work out η^2/ρ, the force is 10^{41} dyn. That is more than 10^9 times the gravitational force that half the Earth exerts on the other half! So the conclusion is, of course, that in the flow of the mantle of the Earth the Reynolds number is *very* small indeed.

Now consider things that move through a liquid (Fig. 3). The Reynolds number for a man swimming in water might be 10^4, if we put in reasonable dimensions. For a goldfish or a tiny guppy it might get down to 10^2. For the animals that we're going to be talking about, as we'll see in a mo-

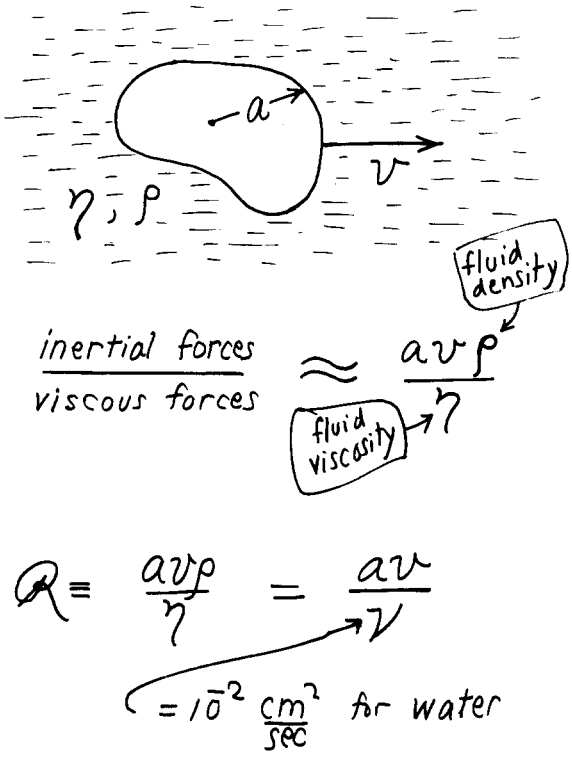


Figure 1.

ment, it's about 10^{-4} or 10^{-5}. For these animals inertia is totally irrelevant. *We* know that $F = ma$, but they could scarcely care less. I'll show you a picture of the real animals in a bit but we are going to be talking about objects which are the order of a micron in size (Fig. 4). That's a micron scale, not a suture, in the animal in Fig. 4. In water where the kinematic viscosity is 10^{-2} cm/sec these things move around with a typical speed of 30 μm/sec. If I have to push that animal to move it, and suddenly I stop pushing, how

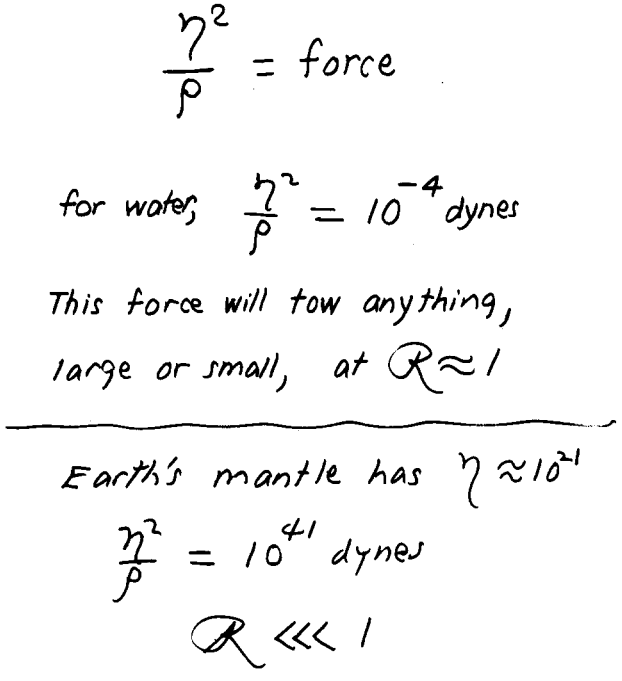


Figure 2.

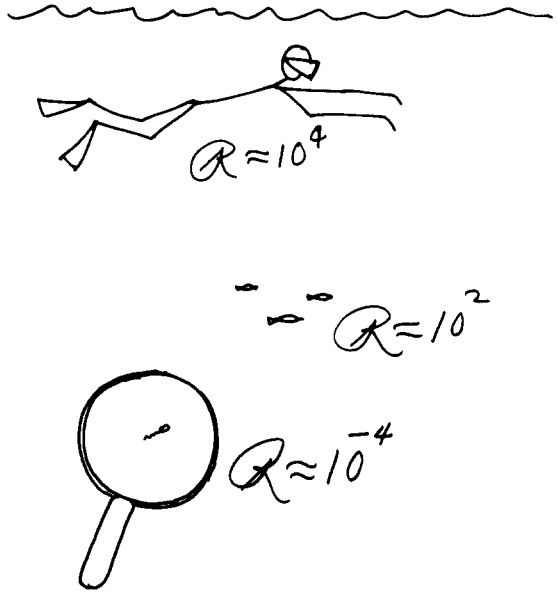


Figure 3.

far will it coast before it slows down? The answer is, about 0.1 Å. And it takes it about 0.6 μsec to slow down. I think this makes it clear what low Reynolds number means. Inertia plays no role whatsoever. If you are at very low Reynolds number, what you are doing at the moment is entirely determined by the forces that are exerted on you *at that moment,* and by nothing in the past.[2]

It helps to imagine under what conditions a man would be swimming at, say, the same Reynolds number as his own sperm. Well, you put him in a swimming pool that is full of molasses, and then you forbid him to move any part of his body faster than 1 cm/min. Now imagine yourself in that condition: you're under the swimming pool in molasses, and now you can only move like the hands of a clock. If under those ground rules you are able to move a few meters in a couple of weeks, you may qualify as a low Reynolds number swimmer.

I want to talk about swimming at low Reynolds number in a very general way. What does it mean to swim? Well, it means simply that you are in some liquid and are allowed to deform your body in some manner. That's all you can do.

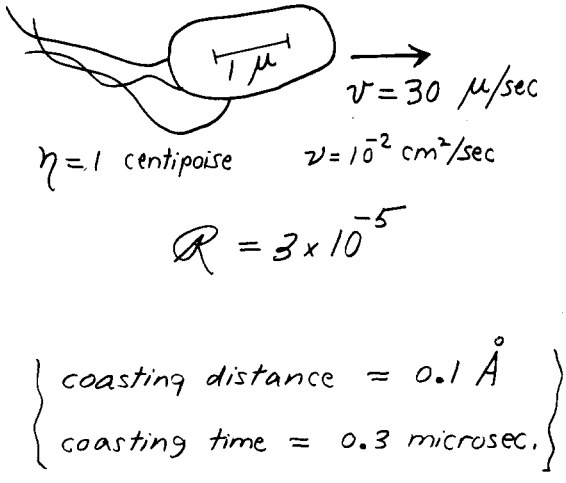


Figure 4.

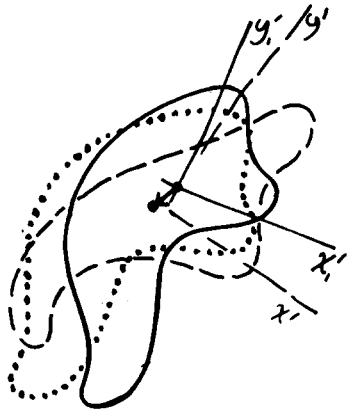


Figure 5.

Move it around and move it back. Of course, you choose some kind of cyclic deformation because you want to keep swimming, and it doesn't do any good to use a motion that goes to zero asymptotically. You have to keep moving. So, in general, we are interested in cyclic deformations of a body on which there are no external torques or forces except those exerted by the surrounding fluid. In Fig. 5, there is an object which has a shape shown by the solid line; it changes its shape to the dashed contour and then it changes back. When it finally gets back to its original shape, the dotted contour, it has moved over and rotated a little. It has been swimming. When it executed the cycle, a displacement resulted. If it repeats the cycle, it will, of course, effect the same displacement, and in two dimensions we'd see it progressing around a circle. In three dimensions its most general trajectory is a helix consisting of little kinks, each of which is the result of one cycle of shape change.

There is a very funny thing about motion at low Reynolds number, which is the following. One special kind of swimming motion is what I call a reciprocal motion. That is to say, I change my body into a certain shape and then I go back to the original shape by going through the sequence in reverse. At low Reynolds number, everything reverses just fine. Time, in fact, makes no difference—only configuration. If I change quickly or slowly, the pattern of motion is exactly the same. If you take the Navier–Stokes equation and throw away the inertia terms, all you have left is $\nabla^2 v = p/\eta$, where p is the pressure (Fig. 6). So, if the animal tries to swim by a reciprocal motion, it *can't go anywhere.* Fast or slow, it exactly retraces its trajectory and it's back where it started. A good example of that is a scallop. You know, a scallop opens its shell slowly and closes its shell fast, squirting out water. The moral of this is that the scallop at low Reynolds number is no good. It can't swim because it only has one hinge, and if you have only one degree of freedom in configuration space, you are bound to make a reciprocal motion. There is nothing else you can do. The simplest animal that can swim that way is an animal with two hinges. I don't know whether one exists but Fig. 7 shows a hypothetical one. This animal is like a boat with a rudder at both front and back, and nothing else. This animal can swim. All it has to do is go through the sequence to configurations shown, returning to the original one at S_5. Its configuration space, of course, is two dimensional with coordinates θ_1, θ_2. The animal is going around a loop in that configuration space, and that enables it to swim. In fact, I worked this one out just for fun and you can prove from symmetry that it goes along the direction shown in the figure. As an exercise for the student, what is it that distinguishes that direction?

You can invent other animals that have no trouble swimming. We had better be able to invent them, since we know they exist. One you might think of first as a physicist, is a torus. I don't know whether there is a toroidal animal, but whatever other physiological problems it might face, it clearly could swim at low Reynolds number (Fig. 8). Another animal might consist of two cells which were stuck together and were able to roll on one another by having

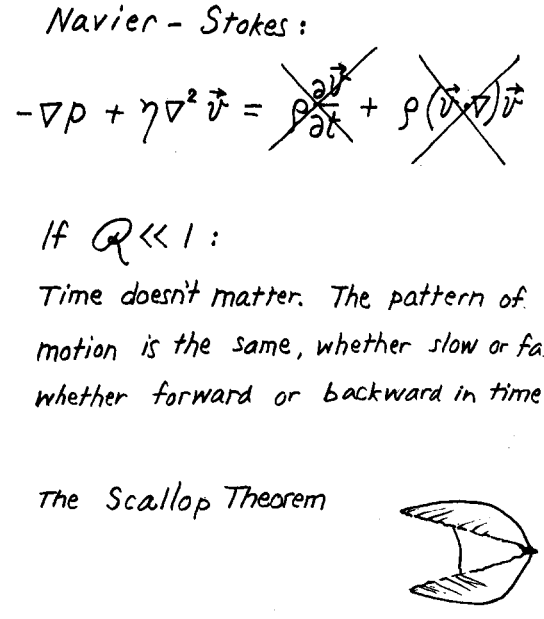


Figure 6.

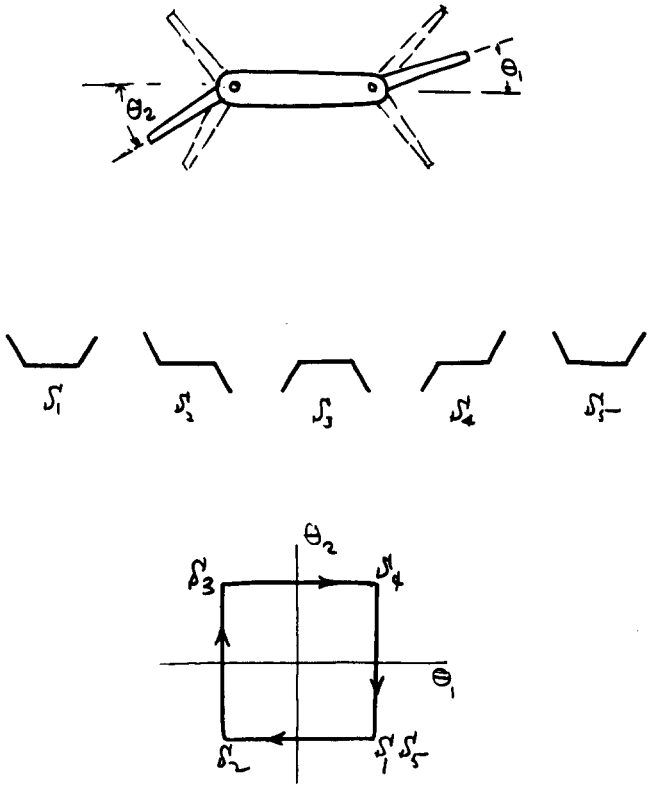


Figure 7.

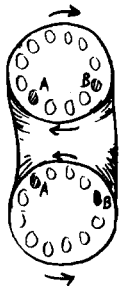
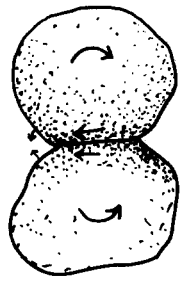


Figure 8.



some kind of attraction here while releasing there. That thing will "roll" along. I described it once as a combination caterpillar tractor and bicycle built for two, but that isn't the way it really works. In the animal kingdom, there are at least two other more common solutions to the problem of swimming at low Reynolds number (Fig. 9). One might be called the flexible oar. You see, you can't row a boat at low Reynolds number in molasses—if you are submerged—because the stiff oars are just reciprocating things. But if the oar is flexible, that's not true, because then the oar bends one way during the first half of the stroke and the other during the second half. That's sufficient to elude the theorem that got the scallop. Another method, and the one we'll mainly be talking about, is what I call a corkscrew. If you keep turning it, that, of course, is not a reciprocal change in configuration space and that will propel you. At this point, I wish I could persuade you that the direction in which this helical drive will move is *not* obvious. Put your-

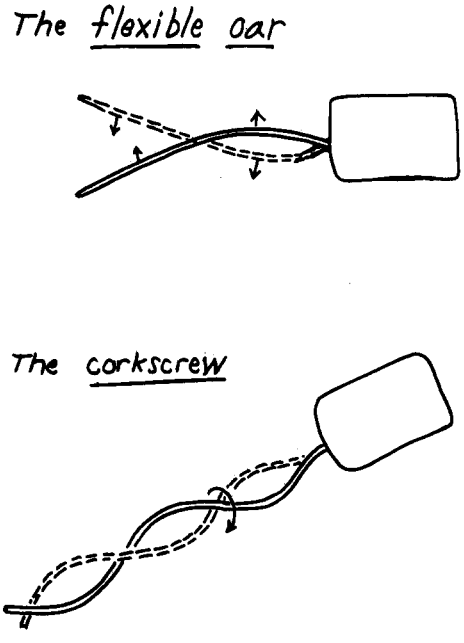


Figure 9.

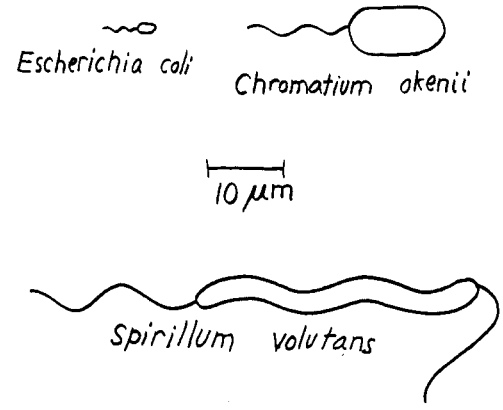


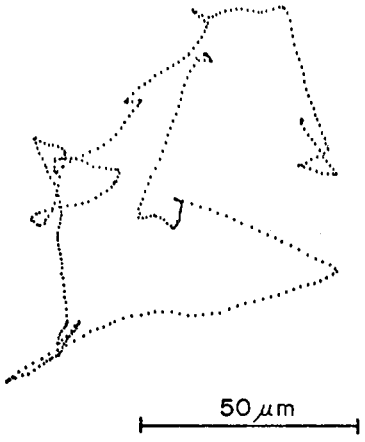
Figure 10.

self back in that swimming pool under molasses and move around very, very slowly. Your intuitions about *pushing water backwards* are irrelevant. That's not what counts. Now, unfortunately, it turns out that the thing does move the way your naive, untutored, and actually incorrect argument would indicate, but that's just a pedagogical misfortune we are always running into.

Well, lets look at some real animals (Fig. 10). This figure I've taken from a paper of Howard Berg that he sent me. Here are three real swimmers. The one we're going to be talking about most is the famous animal, *Escherichia coli,* at A, which is a very tiny thing. Then there are two larger animals. I've copied down their Latin names and they may be old friends to some of you here. This thing (*S. volutans*) swims by waving its body as well as its tail and roughly speaking, a spiral wave runs down that tail. The bacterium *E. coli* on the left is about 2 μm long. The tail is the part that we are interested in. That's the flagellum. Some *E. coli* cells have them coming out the sides; and they may have several, but when they have several they tend to bundle together. Some cells are nonmotile and don't have flagella. They live perfectly well, so swimming is not an absolute necessity for this particular animal, but the one in the figure does swim. The flagellum is only about 130 Å in diameter. It is much thinner than the cilium which is another very important kind of propulsive machinery. There is a beautiful article on cilia in this month's *Scientific American.*[3] Cilia are about 2000 Å in diameter, with a rather elaborate apparatus inside. There's not room for such apparatus inside this flagellum.

For a long time there has been interest in how the flagellum works. Classic work in this field was done around 1951, as I'm sure some of you will remember, by Sir Geoffrey Taylor, the famous fluid dynamicist of Cambridge. One time I heard him give a fascinating lecture at the National Academy. Out of his pocket at the lecture he pulled his working model, a cylindrical body with a helical tail driven by a rubber-band motor inside the body. He had tested it in glycerine. In order to make the tail he hadn't just done the simple thing of having a turning corkscrew, because at that time nearly everyone had persuaded themselves that the tail doesn't rotate, it waves. Because, after all, to rotate you'd have to have a rotary joint back at the animal. So he had sheathed the turning helix with rubber tubing anchored to the body. The body had a keel. I remember Sir Geoffrey Taylor saying in his lecture that he was embarrassed that he hadn't put the keel on it first and he'd had to find out that

Figure 11.



ıe needed it. There has since been a vast literature on this ıubject, only a small part of which I'm familiar with. But ıt that time G. I. Taylor's paper in the *Proceedings of the Royal Society* could conclude with just three references: H. Lamb, *Hydrodynamics;* G. I. Taylor (his previous ɔaper); G. N. Watson, *Bessel Functions.* That is called ɜetting in on the ground floor.

To come now to modern times, I want to show a picture ɔf these animals swimming or tracking. This is the work of Howard Berg, and I'll first describe what he did. He started ɔuilding the apparatus when he was at Harvard. He was nterested in studying not the actual mechanics of swimming at all but a much more interesting question, namely, why these things swim and where they swim. In particular, ıe wanted to study chemotaxis in *E. coli*—seeing how they ɔehave in gradients of nutrients and things like that. So he ɔuilt a little machine which would track a single bacterium n *x, y, z* coordinates—just lock onto it optically and track t. He was able then to track one of these bacteria while it was behaving in its normal manner, possibly subject to the influence of gradients of one thing or another. A great advantage of working with a thing like *E. coli* is that there are ɜo many mutant strains that have been well studied that you ɔan use different mutants for different things. The next picture (Fig. 11) is one of his tracks. It shows a projection ɔn a plane of the track of one bacterium. The little dots are ıbout 0.1 sec apart so that it was actually running along one ɔf the legs for a second or two and the speed is typically 20–40 μm/sec. Notice that it swims for a while and then ɜtops and goes off in some other direction. We'll see later what that might suggest. A year ago, Howard Berg went ɔut on a limb and wrote a paper in *Nature*[4] in which he ırgued that, on the basis of available evidence, *E. coli* must ɜwim by *rotating* their flagella, not by waving them. Within the year a very elegant, crucial experiment by Silverman and Simon at UC–San Diego showed that this fact is the case.[5,6] Their experiment involved a mutant strain of *E. coli* bacteria which don't make flagella at all but only make something called the proximal hook to which the flagella would have been attached. They found that with antihook antibodies they could cause these things to glue together. And once in a while one of the bacteria would have its hook glued to the microscope slide, in which case the whole body rotated at constant angular velocity. And when two hooks glued together, the two bodies counter-rotated, as you would ɛxpect. It's a beautiful technique. Howard was ready with his tracker and the next picture[7] (Fig. 12) shows his tracker

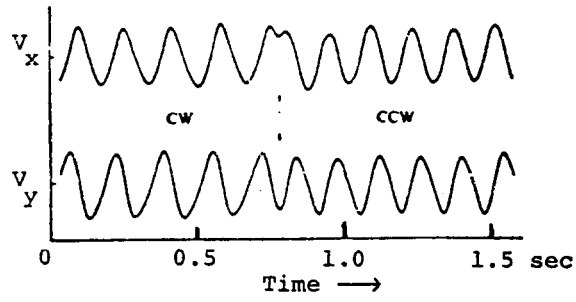


Figure 12.

following the end of one of these tethered *E. coli* cells which is stuck to the microscope slide by antibody at the place where the flagellum should have been. Plotted here are the two velocity components V_x and V_y. The two velocity components are 90° out of phase. The point being tracked is going in a circle. In the middle of the figure, you see a 90° phase change in one component, a reversal of rotation. They can rotate hundreds of revolutions at constant speed and then turn around and rotate the other way. Evidently the animal actually has a rotary joint, and has a motor inside that's able to drive a flagellum in one direction or the other, a most remarkable piece of machinery.

I got interested in the way a rotating corkscrew can propel something. Let's consider propulsion in one direction only, parallel to the axis of the helix. The helix can translate and it can rotate; you can apply a force to it and a torque. It has a velocity v and an angular velocity Ω. And now remember, at low Reynolds number everything is linear. When everything is linear, you expect to see matrices come in. Force and torque must be related by matrices with constant coefficients, to linear and angular velocity. I call this little 2×2 matrix the propulsion matrix (Fig. 13). If I knew its elements A, B, C, D, I could then find out how good this rotating helix is for propelling anything.

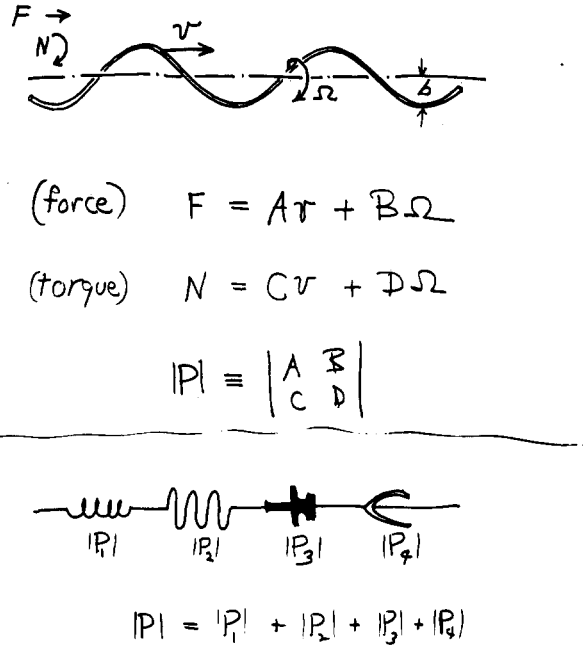


Figure 13.

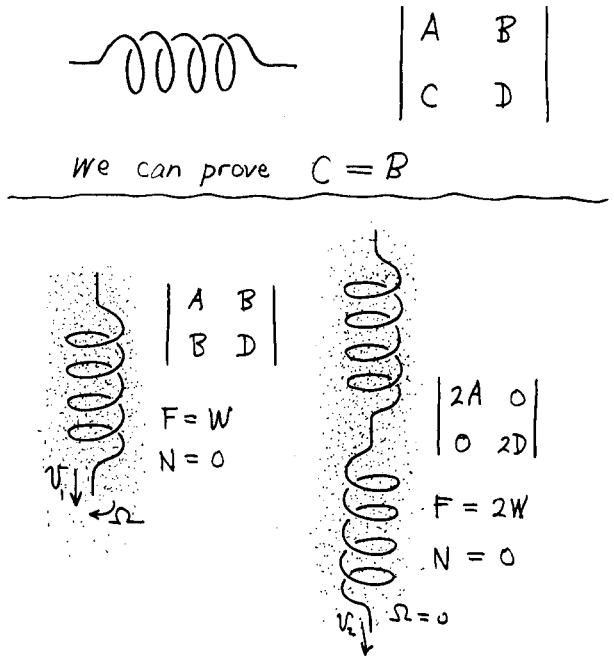


Figure 14.

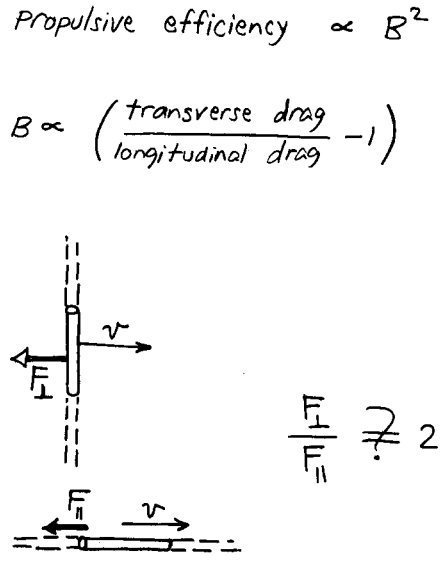


Figure 15.

Well, let's try to go on by making some assumptions. If two corkscrews or other devices on the same shaft are far enough from one another so that their velocity patterns don't interact, their propulsive matrices just add. If you allow me that assumption, then there is a very nice way, which I don't have time to explain, of proving that the propulsion matrix must be symmetrical (Fig. 14). So actually the motion is described by only three constants, not four, and they are very easily measured. All you have to do is make a model of this thing and drop in a fluid at you are interested in or not, because these constants are independent of that. And so I did that and that's my one demonstration. I thought this series of talks ought to have one experiment and there it is. We're looking through a tank not of glycerine but of corn syrup, which is cheaper, quite uniform, and has a viscosity of about 50 P or 5000 times the viscosity of water. The nice part of this is you can just lick the experimental material off your fingers.

Motion at low Reynolds number is very majestic, slow, and regular. You'll notice that the model is actually rotating but rather little. If that were a corkscrew moving through a cork of course, the pattern in projection wouldn't change. It's very very far from that, it's *slipping*, so that it sinks by several wavelengths while it's turning around once. If the matrix were diagonal, the thing would not rotate at all. So all you have to do is just see how much it turns as it sinks and you have got a handle on the off-diagonal element. A nice way to determine the other elements is to run two of these animals, one of which is a spiral and the other is two spirals, in series, of opposite handedness. The matrices add and with two spirals of opposite handedness, the propulsion matrix must be diagonal (Fig. 14). That's not going to rotate; it better not.

The propulsive efficiency is more or less proportional to the square of the off-diagonal element of the matrix. The off-diagonal element depnds on the difference between the drag on a wire moving perpendicular to its length and the drag on a wire moving parallel to its length (Fig. 15). These are supposed to differ in a certain limit by a factor of 2. But for the models I've tested that factor is more like 1.5. Since it's that factor minus 1 that counts, that's very bad for efficiency. We thought that if you want something to rotate more while sinking, it would be better not to use a round wire. Something like a slinky ought to be better. I made one and measured its off diagonal elements. Surprise, surprise, it was no better at all! I don't really understand that, because the fluid mechanics of these two situations is not at all simple. In each case there is a logarithmic divergence that you have to worry about, and the two are somewhat different in character. So that theoretical ratio of two I referred to is probably not even right.

When you put all this in and calculate the efficiency, you find that it's really rather low even when the various parameters of the model are optimized. For a sphere which is driven by one of these helical propellers (Fig. 16), I will

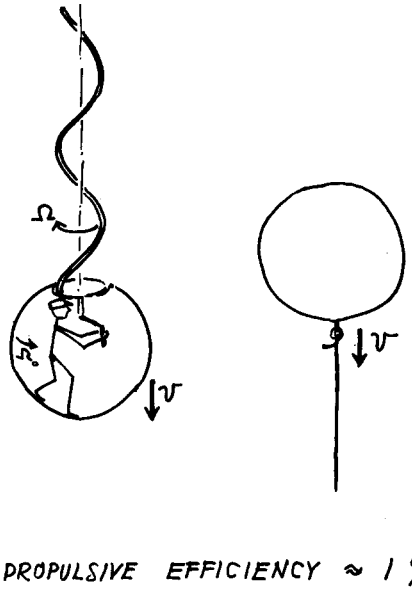


Figure 16.

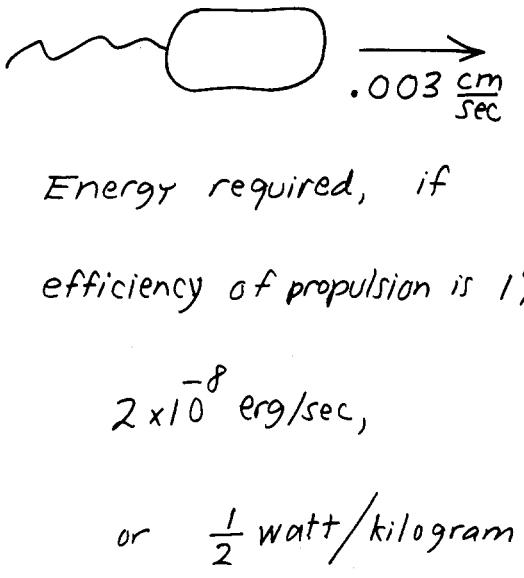


Figure 17.

define the efficiency as the ratio of the work that I would have to do just to pull that thing along to what the man inside it turning the crank has to do. And that turns out to be about 1%. I worried about that result for a while and tried to get Howard interested in it. He didn't pay much attention to it, and he shouldn't have, because it turns out that efficiency is really not the primary problem of the animal's motion. We'll see that when we look at the energy requirement. How much power does it take to run one of these things with a 1% efficient propulsion system, at this speed in these conditions? We can work it out very easily. Going 30 μm/sec, at 1% efficiency will cost us about 2×10^{-8} ergs/sec at the motor. On a per weight basis, that's a 0.5 W/kg, which is really not very much. Just moving things around in our transportation system, we use energy at 30 or 40 times that rate. This bug runs 24 h a day and only uses 0.5 W/kg. That's a small fraction of its metabolism and its energy budget. Unlike us, they do not squander their energy budget just moving themselves around. So they don't care whether they have a 1% efficient flagellum or a 2% efficient flagellum. It doesn't really make that much difference. They're driving a Datsun in Saudi Arabia.

So the interesting question is not how they swim. Turn anything—if it isn't perfectly symmetrical, you'll swim. If the efficiency is only 1%, who cares. A better way to say it is that the bug can collect, by diffusion through the surrounding medium, enough energetic molecules to keep moving when the concentration of those molecules is 10^{-9} M. I've now introduced the word diffusion. Diffusion is important because of another very peculiar feature of the world at low Reynolds number, and that is, stirring isn't any good. The bug's problem is not its energy supply; its problem is its environment. At low Reynolds number you can't shake off your environment. If you move, you take it along; it only gradually falls behind. We can use elementary physics to look at this in a very simple way. The time for transporting anything a distance l by stirring, is about l divided by the stirring speed v. Whereas, for transport by diffusion, it's l^2 divided by D, the diffusion constant. The ratio of those two times is a measure of the effectiveness of stirring versus that of diffusion for any given distance and diffusion constant. I'm sure this ratio has someone's name but I don't know the literature and I don't know whose number that's called. Call it S for *stirring number*.[8] It's just lv/D. You'll notice by the way that the Reynolds number was lv/ν. ν is the kinematic viscosity in cm^2/sec, and D is the diffusion constant in cm^2/sec, for whatever it is that we are interested in following—let us say a nutrient molecule in water. Now, in water the diffusion constant is pretty much the same for every reasonably sized molecule, something like 10^{-5} cm^2/sec. In the size domain that we're interested in, of micron distances, we find that the stirring number S is 10^{-2}, for the velocities that we are talking about (Fig. 18). In other words, this bug can't do anything by stirring its local surroundings. It might as well wait for things to diffuse, either in or out. The transport of wastes away from the animal and food to the animal is entirely controlled locally by diffusion. You can thrash around a lot, but the fellow who just sits there quietly waiting for stuff to diffuse will collect just as much.

At one time I thought that the reason the thing swims is that if it swims it can get more stuff, because the medium is full of molecules the bug would like to have. All my instincts as a physicist say you should move if you want to scoop that stuff up. You can easily solve the problem of diffusion in the velocity field represented by the Stokes flow around a sphere—for instance, by a relaxation method. I did so and found out how fast the cell would have to go to increase its food supply. The food supply if it just sits there is $4\pi aND$ molecules/sec, where a is the cell's radius (Fig. 19) and N is the concentration of nutrient molecules. To increase its food supply by 10% it would have to move at a speed of 700 μm/sec, which is 20 times as fast as it can swim. The increased intake varies like the square root of the bug's velocity so the swimming does no good at all in that respect. But what it can do is find places where the food is better or more abundant. That is, it does not move like a cow

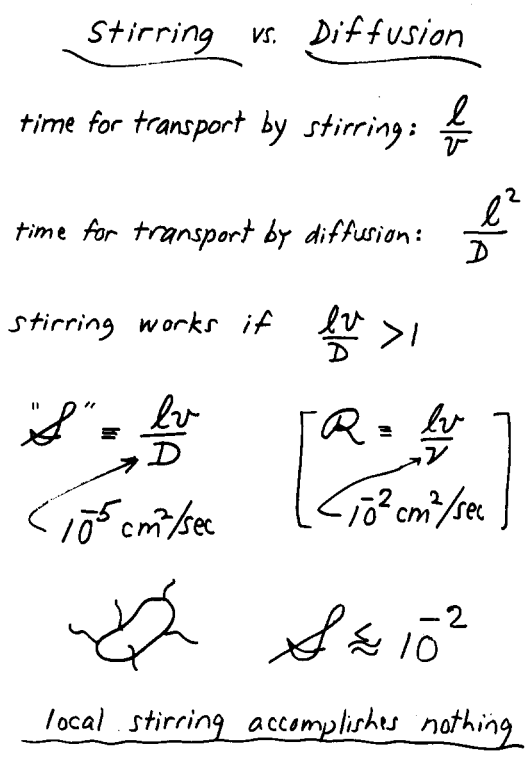


Figure 18.

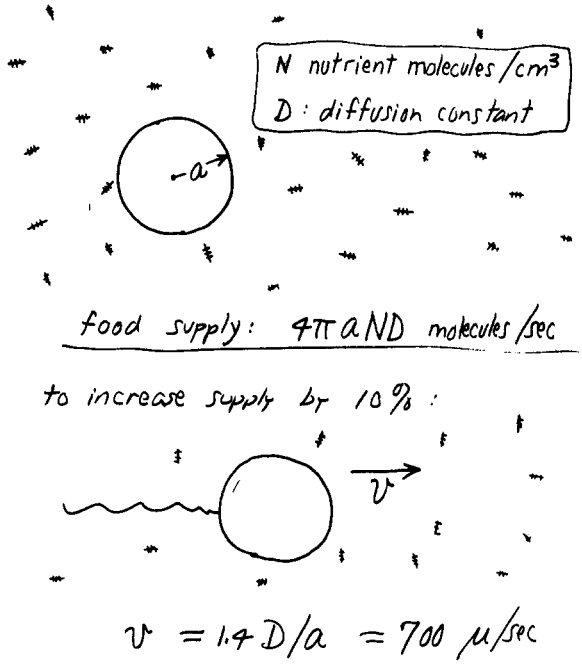


Figure 19.

that is grazing a pasture—it moves to find *greener pastures.* And how far does it have to move? Well, it has to move far enough to outrun diffusion. We said before that stirring wouldn't do any good locally, compared to diffusion. But suppose it wants to run over there to see whether there is more over there. Then it must outrun diffusion, and how do you do that? Well, you go that magic distance, D/v. So the rule is then, to outswim diffusion you have to go a distance which is equal to or greater than this number we had in our S constant. For typical D and v, you have to go about 30 μm and that's just about what the swimming bacteria were doing. If you don't swim that far, you haven't gone anywhere, because it's only on that scale that you could find a difference in your environment with respect to molecules of diffusion constant D (Fig. 20).

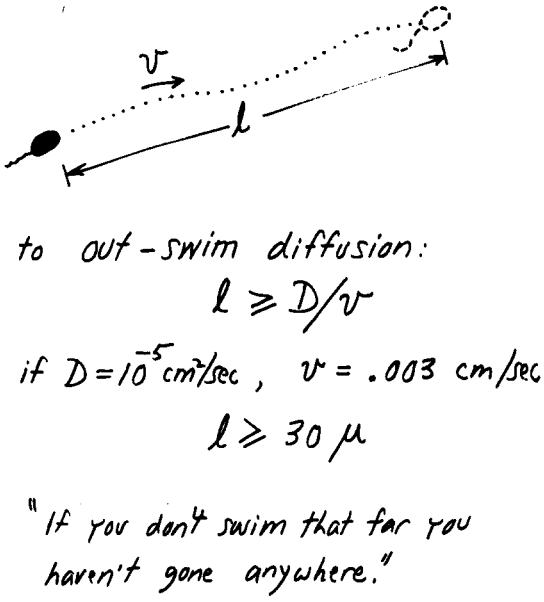


Figure 20.

Let's go back and look at one of those sections from Berg's track (Fig. 11). You'll see that there are some little trips, but otherwise you might ask why did it go clear over here and stop. Why did it go back? Well, my suggestion is, and I'd like to put this forward very tentatively, that the reason it does is because it's trying to outrun diffusion. Otherwise, it might as well sit still, as indeed do the mutants who don't have flagella. Now there is still another thing that I put forward with even more hesitation because I haven't tried this out on Howard yet. When he did his chemotaxis experiments, he found a very interesting behavior. If these things are put in a medium where there is a gradient of something that they like, they gradually work their way upstream. But if you look at how they do it and ask what rules they are using, what the algorithm is to use the current language, for finding your way upstream, it turns out that it's very simple. The algorithm is: if things are getting better, don't stop so soon. If, in other words, you plot, as Berg has done in some of his papers, the distribution of path lengths between runs and the little stops that he calls "twiddles," the distribution of path lengths if they are going *up* the gradient gets longer. That's a very simple rule for working your way to where things are better. If they're going down the gradient, though, they don't get shorter. And that seems a little puzzling. Why, if things are getting worse, don't they change sooner? My suggestion is that there is no point in stopping sooner. There is a sort of bedrock length which outruns diffusion and is useful for sampling the medium. Shorter paths would be a ridiculous way to sample. It may be something like that, but as I say, I don't know. The residue of education that I got from this is partly this stuff about simple fluid mechanics, partly the realization that the mechanism of propulsion is really not very important except, of course, for the physiology of that very myserious motor, which physicists aren't competent even to conjecture about.

I come back for a moment to Osborne Reynolds. That was a very great man. He was a professor of engineering, actually. He was the one who not only invented Reynolds number, but he was also the one who showed what turbulence amounts to and that there is instability in flow, and all that. He is also the one who solved the problem of how you lubricate a bearing, which is a very subtle problem that I recommend to anyone who hasn't looked into it. But I discovered just recently in reading in his collected works that toward the end of his life, in 1903, he published a very long paper on the details of the *submechanical universe,* and he had a complete theory which involved small particles of diameter 10^{-18} cm. It gets very nutty from there on. It's a mechanical model, the particles interact with one another and fill all space. But I thought that, incongruous as it may have seemed to put this kind of stuff in between our studies of the submechanical universe today, I believe that Osborne Reynolds would not have found that incongruous, and I'm quite positive that Viki doesn't.

[1](1976 footnote) As no one will be surprised to hear, Professor Weisskopf has recently shown me how this can be explained. I hope he will communicate it to AJP readers.

[2](1976 footnote) In that world, Aristotle's mechanics is *correct!* See A. Franklin, Am. J. Phys. **44,** 527–528 (1976).

[3]P. Satir, Sci. Am. **231,** 45 (October 1974).
[4]H. C. Berg and R. A. Anderson, Nature **245,** 380 (1973).
[5]M. Silverman and M. Simon, Nature **249,** 73 (1974).
[6]S. H. Larson, R. W. Reader, E. N. Kort, W-W. Tso, and J. Adler, Nature **249,** 74 (1974).
[7]H. C. Berg, Nature **249,** 77 (1974).
[8]I've recently discovered that its official name is the *Sherwood number,* so S is appropriate, after all! There is a list of all the dimensionless ratios that have acquired names—an astonishingly long list—in the *McGraw-Hill Encyclopedia of Science and Technology* (1971).

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TEACHING

So how do you go about teaching them something new? By mixing what they know with what they don't know. Then, when they see vaguely in their fog something they recognize, they think, "Ah, I know that." And then it's just one more step to, "Ah, I know the whole thing." And their mind thrusts forward into the unknown and they begin to recognize what they didn't know before and they increase their powers of understanding.

—Picasso, in *Life with Picasso* by Francoise Gilot and Carlton Lake (Nelson, London, 1965), p. 66.