Lectures 14-15:
Beam Theory: Architecture for Cells and Skeletons

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Beam Theory:

- macromolecules can be viewed as networks of one-dimensional elements (chains of amino acids, chains of base pairs, …)
- beam theory addresses the mechanics of these networks
- a bead treated as a rod with elastic properties

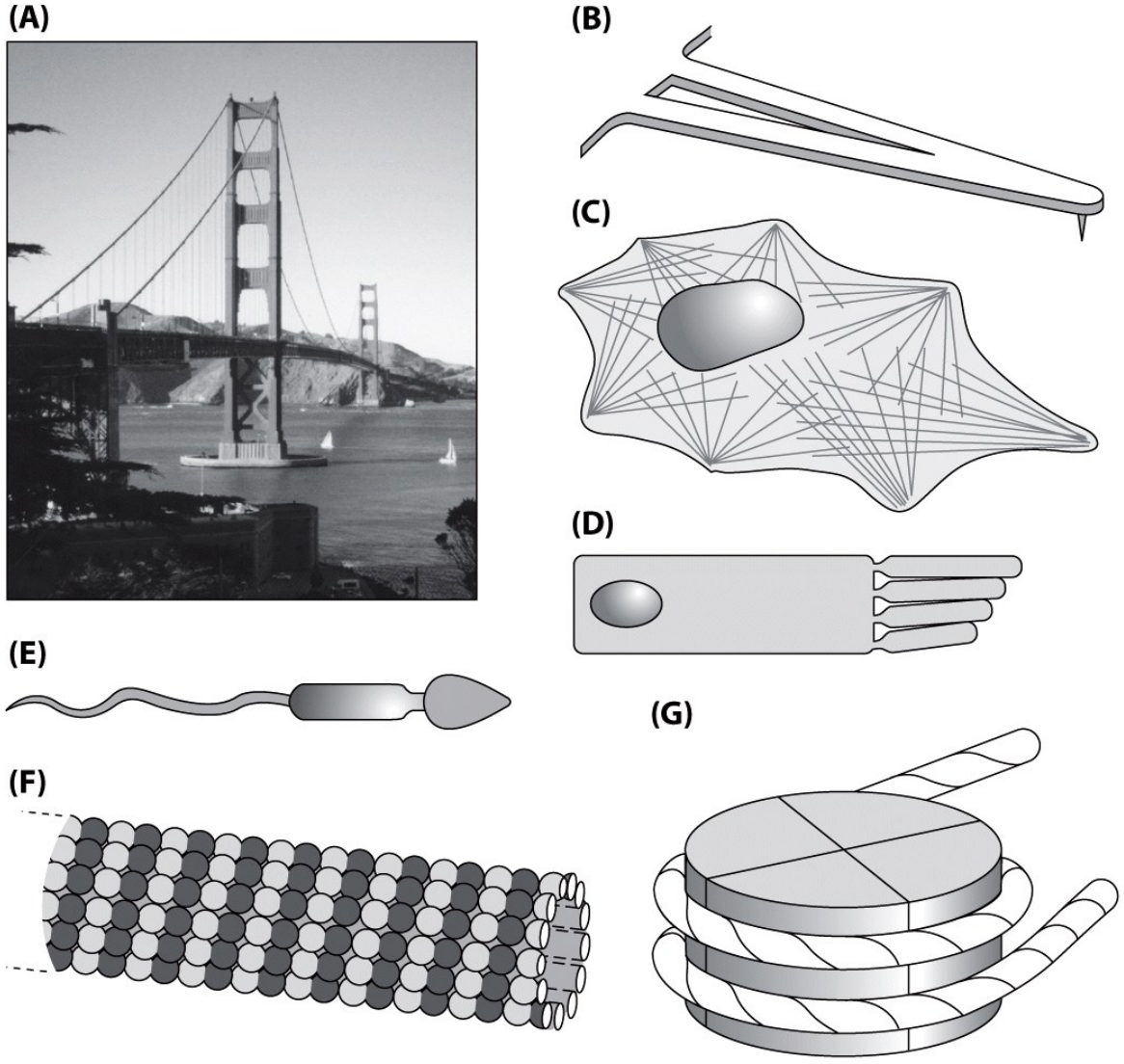


Figure 10.1 Physical Biology of the Cell (© Garland Science 2009)

Three types of deformations

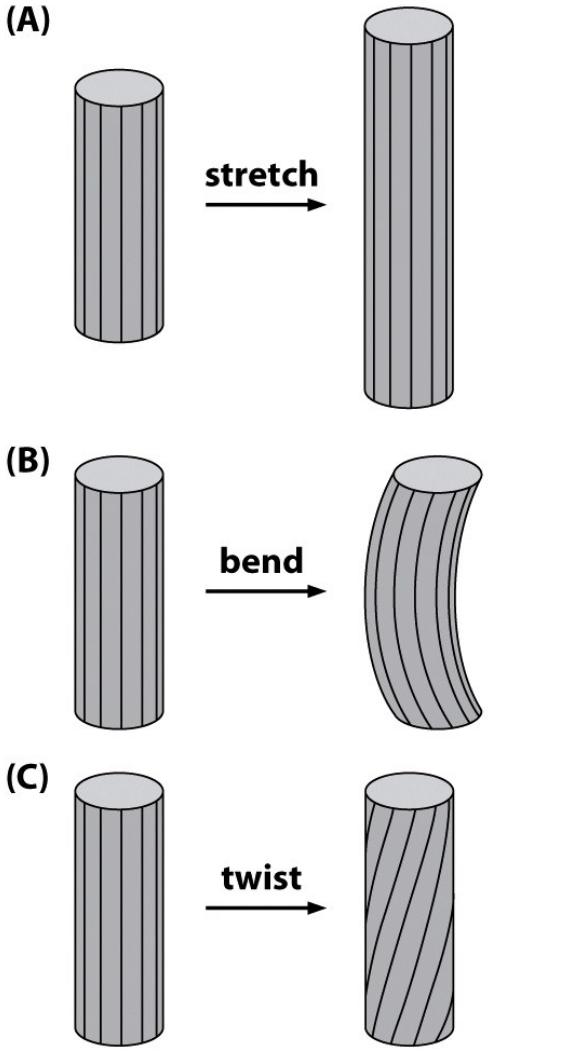


Figure 10.2 Physical Biology of the Cell (© Garland Science 2009)

Bending of a beam: a neutral plane

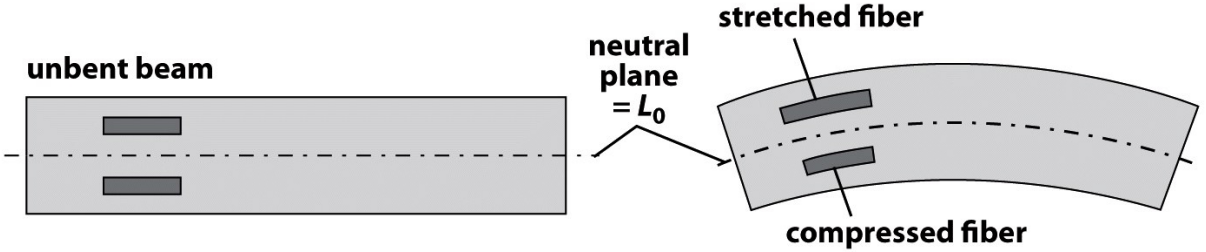


Figure 10.3 Physical Biology of the Cell (© Garland Science 2009)

Microscopic interpretation of bending

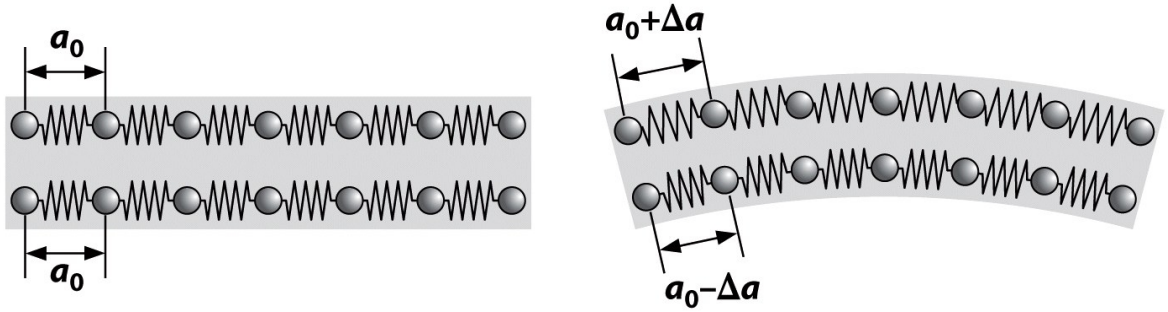


Figure 10.5 Physical Biology of the Cell (© Garland Science 2009)

Imagine a beam split up in segments each with own curvature

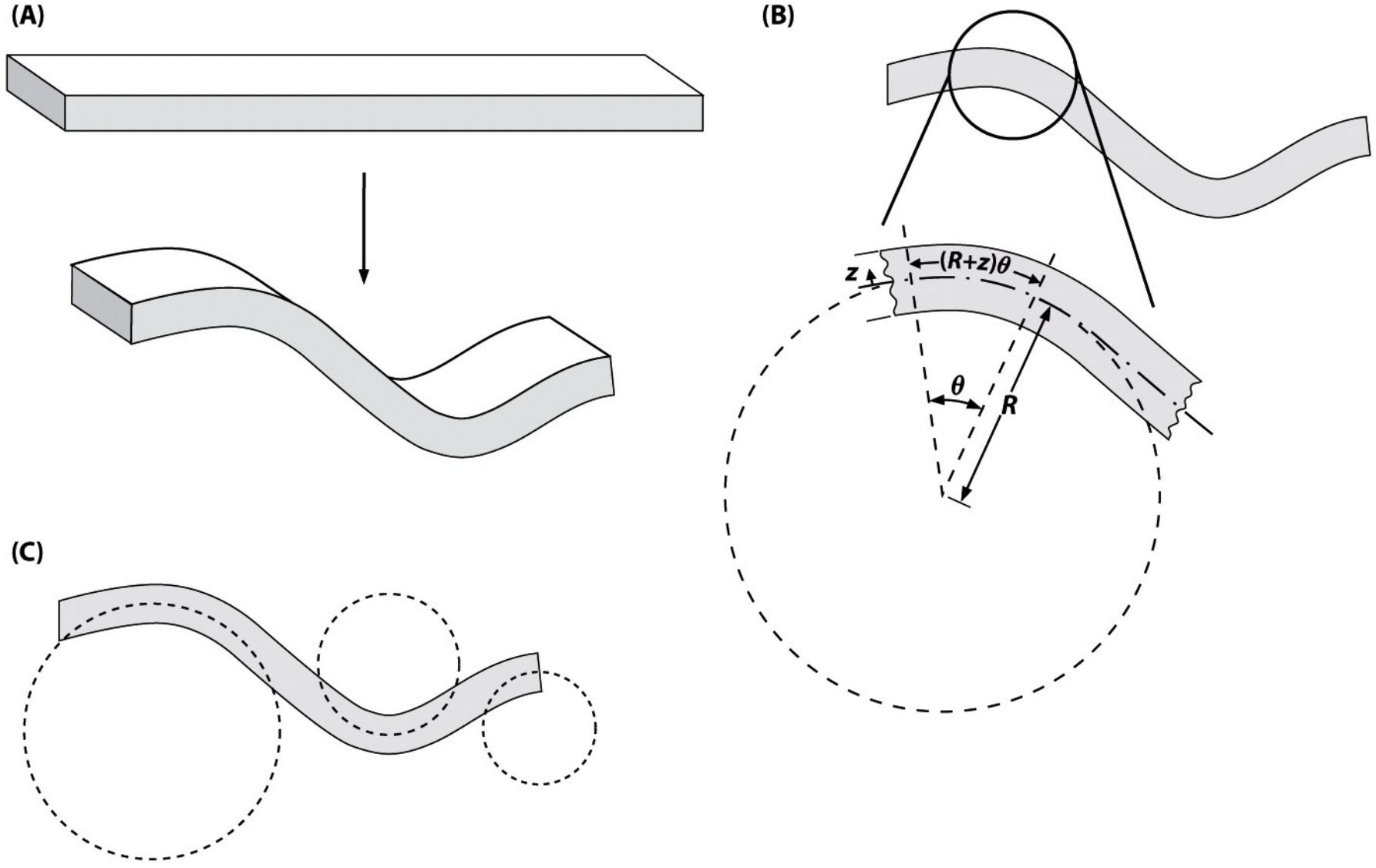


Figure 10.4 Physical Biology of the Cell (© Garland Science 2009)

Note that the extent of extension or compression is a linear function of the distance from the neutral plane z:

$$\theta = \frac{L_0}{R} \qquad L(z) = (R+z)\theta = \frac{(R+z)L_0}{R}$$

$$\Delta L(z) = L(z) - L_0 = (R+z)\frac{L_0}{R} - L_0 = z\frac{L_0}{R}$$

Extensional strain $\varepsilon(z)$ at a distance z is defined as:

$$\varepsilon(z) = \frac{\Delta L(z)}{L_0} = \frac{z}{R}$$

such that material above the neutral axis is stretched, $\varepsilon(z) > 0$, and material below the neutral axis is compressed, $\varepsilon(z) < 0$.

The energy cost is a quadratic function of the strain (Hooke's law):

$$W(\varepsilon) = \frac{1}{2}E\varepsilon^2 = \frac{1}{2}E\left(\frac{\Delta L}{L_0}\right)^2 \qquad E \ldots \text{the Young modulus}$$

A more precise calculation of the total strain energy of the beam:

$$E_{bend} = L_0 \int_{\partial\Omega} dA \frac{E}{2R^2} z^2 = \frac{EIL}{2R^2}$$

$$I = \int_{\partial\Omega} z^2 dA \qquad I \ldots \text{geometric moment}$$

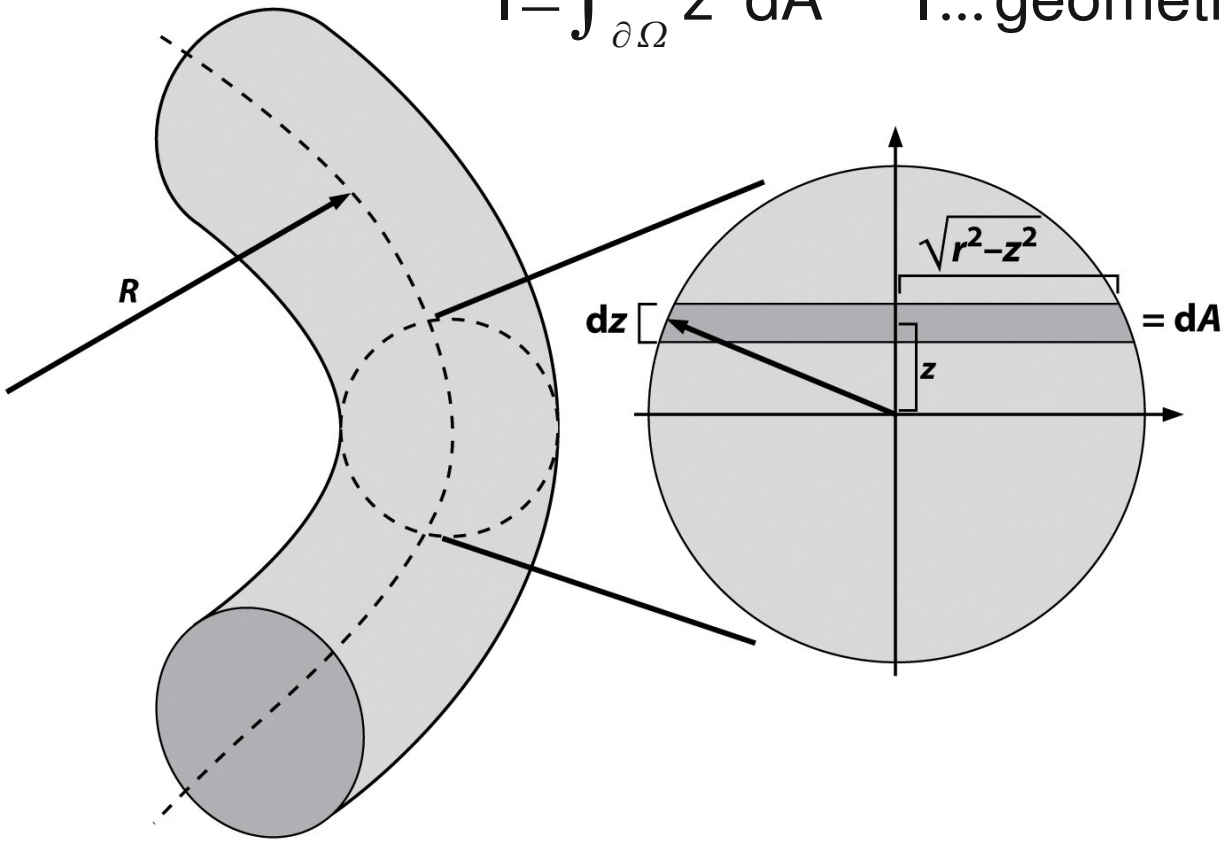


Figure 10.6 Physical Biology of the Cell (© Garland Science 2009)

$$E_{bend} = \frac{EIL}{2R^2} \qquad \text{For } L = 2\pi R, \text{ we get:} \quad E_{loop} = \frac{\pi EI}{R}$$

We can introduce flexural rigidity: $K_{eff} = EI$

Then the energy of bending is: $$E_{bend} = \frac{K_{eff}}{2}\int_0^L ds \frac{1}{R(s)^2}$$

In general, we can express the bending energy in terms of a curvature:

$$\kappa = \frac{1}{R(s)}$$

And we finally get:

$$E_{bend} = \frac{K_{eff}}{2}\int_0^L \left|\frac{dt}{ds}\right|^2 ds \qquad \left|\frac{dt}{ds}\right| \ldots \text{derivative of the tangent vector}$$

Persistence Length and Stiffness

- ***persistence length*** **is a measure of the competition between the entropy ("randomizer") and energy cost of bending**

- **equate the deterministic energy cost to thermal energy:**

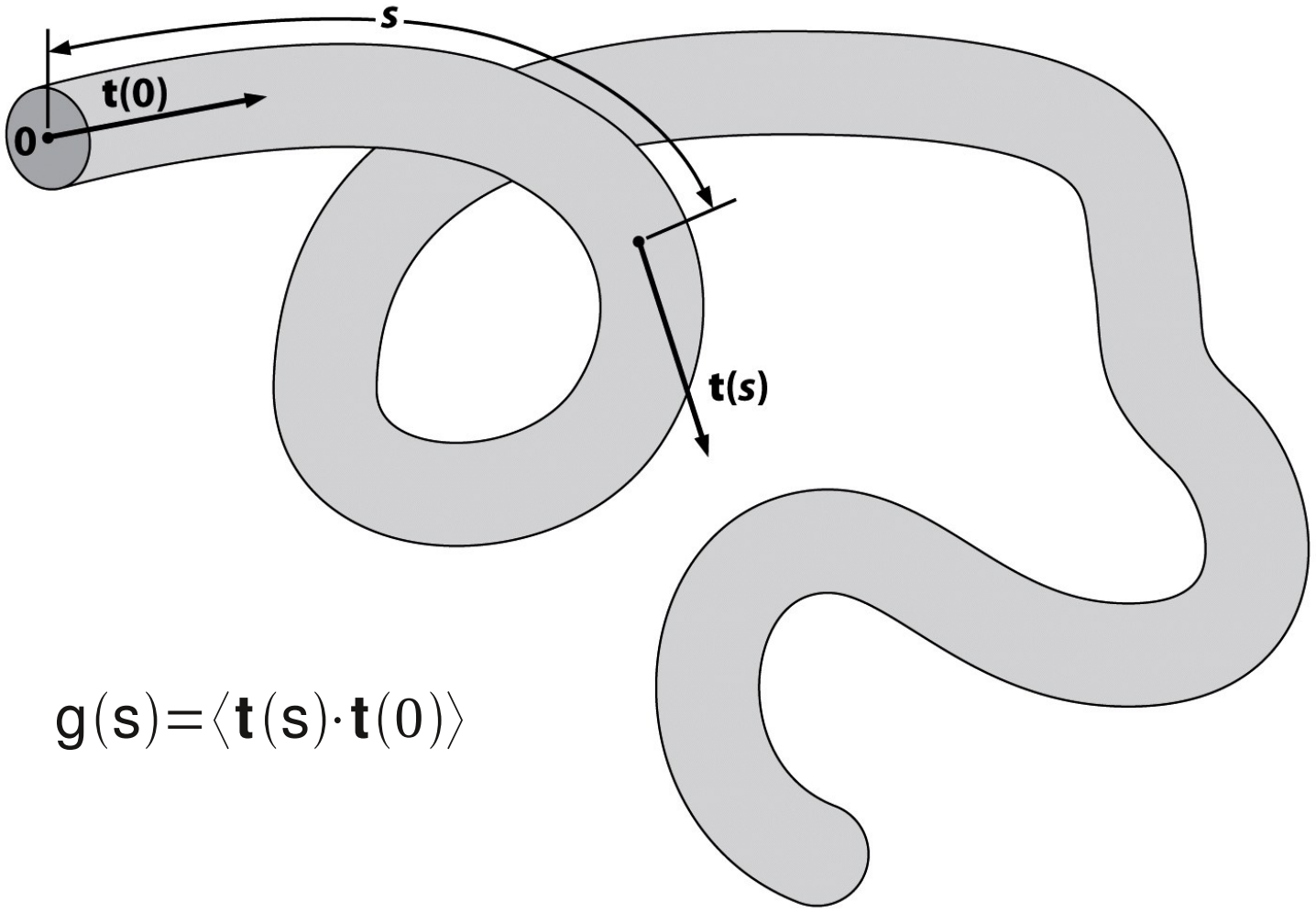
$$k_B T \approx \frac{EIL}{2R^2}$$

- **persistence length is the length of a polymer for which the radius of curvature is equal to the length of polymer itself:** $\xi_P \approx R \approx L$

- **estimate of the persistence length:**

$$\xi_P \approx \frac{EI}{2k_B T}$$

Persistence length characterizes the correlations in the tangent vectors at different positions along the polymer



$$g(s) = \langle \mathbf{t}(s) \cdot \mathbf{t}(0) \rangle$$

Figure 10.7 Physical Biology of the Cell (© Garland Science 2009)

General properties of the tangent-tangent correlation function:

$$g(s=0)=1 \qquad g(s\to\infty)=0$$

$$g(s)=\langle \mathbf{t}(s)\cdot\mathbf{t}(0)\rangle = e^{-s/\xi_P}$$

Relationship between flexural rigidity and persistence length:

- **short beam of length:** $L\approx s \ll \xi_P$
- **short beam is only slightly bent:** $E_{bend}=\frac{EIL}{2R^2}\approx\frac{EI}{2s}\theta^2 \quad (s=R\theta)$
- **if a tangent at s=0 points in the z-direction, then:**

$$g(s)=\langle\cos\theta(s)\rangle \qquad \theta\ll 1 \;\Rightarrow\; \cos\theta\approx 1-\frac{1}{2}\theta^2$$

$$g(s)\approx 1-\frac{1}{2}\langle\theta^2\rangle$$

Calculate: $$\langle\theta(s)^2\rangle=\frac{1}{Z}\int_0^{2\pi} d\Phi\int_0^{\pi} d\theta\sin\theta\,\theta^2 e^{-(EI/2k_BTs)\theta^2}$$

$$Z=\int_0^{2\pi} d\Phi\int_0^{\pi} d\theta\sin\theta\, e^{-(EI/2k_BTs)\theta^2}$$

We apply the same trick as before:

$$\langle\theta(s)^2\rangle=-\frac{1}{Z}\frac{2k_BTs}{I}\frac{\partial Z}{\partial E}$$

Thus, the only integral we really need to calculate is:

$$Z=\int_0^{2\pi} d\Phi\int_0^{\pi} d\theta\sin\theta\, e^{-(EI/2k_BTs)\theta^2}\approx\int_0^{2\pi} d\Phi\int_0^{\pi} d\theta\,\theta\, e^{-(EI/2k_BTs)\theta^2}$$

where we used the Taylor expansion for $\sin\theta\approx\theta$

$$Z=\frac{2\pi k_BTs}{EI}\int_0^{\infty} du\, e^{-u}=\frac{2\pi k_BTs}{EI}\qquad \frac{1}{Z}\frac{\partial Z}{\partial E}=-\frac{1}{E}$$

$$\langle\theta(s)^2\rangle=\frac{2k_BTs}{EI}\qquad \langle g(s)\rangle\approx 1-\frac{k_BT}{EI}s=1-\frac{s}{\xi_P}\qquad \xi_P=\frac{EI}{k_BT}=\frac{K_{eff}}{k_BT}$$

The Worm-Like Chain Model

- **contains both the entropic and elastic bending contributions to the free energy**

- **concept: chains are cylinders connected by flexible links**

(A)
- no bending (optimal E)
- non-optimal S

(B)
- bending (non-optimal E)
- more optimal S

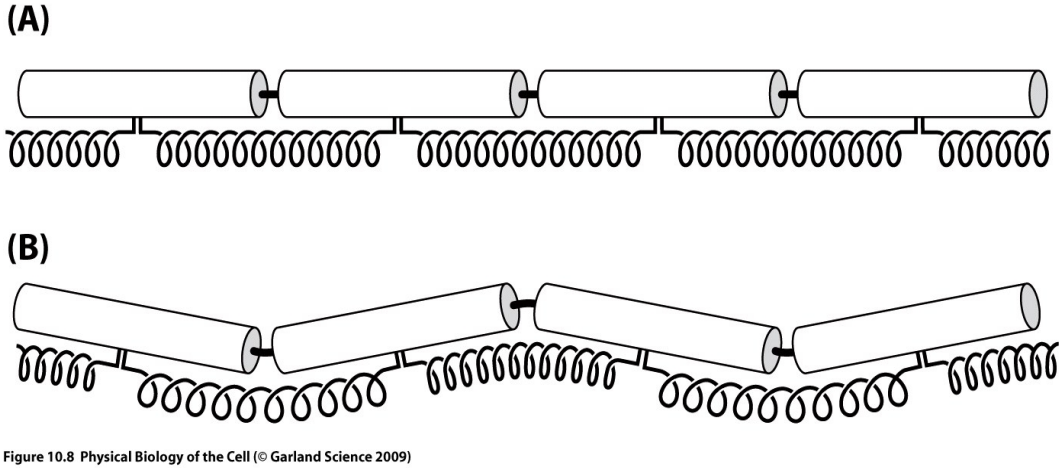


Figure 10.8 Physical Biology of the Cell (© Garland Science 2009)

$$Z = \int \mathcal{D}\mathbf{t}(s)\, \exp\left(-\frac{\xi_P}{2}\int_0^L \left|\frac{d\mathbf{t}}{ds}\right|^2 ds\right)$$

Sum over all possible $\mathbf{t}(s)$ curves of length L:
Feynman Path Integral

To calculate the force-extension curve, we need to include the work done by the external force F (along the z-direction), which adds:

$$-F\int_0^L t_z\,ds$$

such that an average change extension can be calculated as:

$$\langle z\rangle=\frac{1}{Z(f)}\int \mathcal{D}\mathbf{t}(s)\,z\exp\left(\frac{-\xi_P}{2}\int_0^L\left|\frac{d\mathbf{t}(s)}{ds}\right|^2 ds+f\int_0^L t_z\,ds\right)$$

$Z(f)$ **… partition function in the presence of the force**

$F = k_B T\, f$ **(**f **has a unit of inverse length)**

Again, the same trick can be used to avoid a calculation of two path integrals:

$$\langle z\rangle=\frac{d\ln Z(f)}{df}\rightarrow \text{approx. solution: } f\xi_P=\frac{z}{L}+\frac{1}{4(1-z/L)^2}-\frac{1}{4}$$

$$(\text{Appendix of Ch. } 10)$$

Force-Extension Curve for a Worm-Like Chain Model

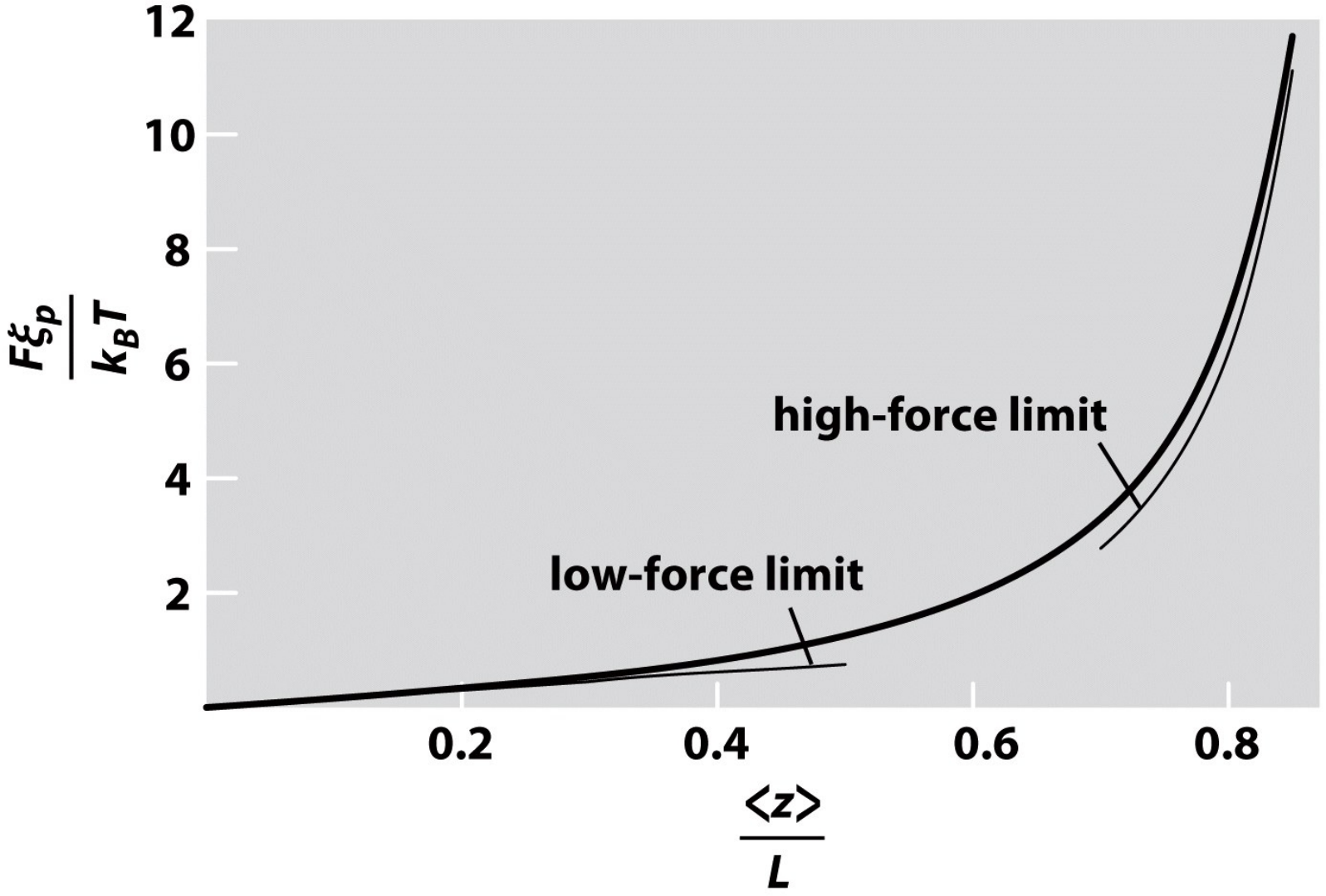


Figure 10.38 Physical Biology of the Cell (© Garland Science 2009)

The mechanics of transcriptional regulation

- ***lac* operon: genetic network that regulates the lactose metabolism in *E. coli***
- **consider lac repressor, a protein, which represses transcription by binding to DNA and initiating DNA loop formation**
- **Lac repressor: a tetrameric protein with three specific binding sites: O1, O2, and O3; loops can be either 401 or 92 bp long (401 x 0.34 nm = 136 nm; 92 x 0.34 nm = 31 nm < 50 nm)**
- **in eukaryotes, there are cis-regulatory regions that control developmental process by DNA loop formation**
- **bending of a DNA fragment that is smaller than the persistence length ξ_P!**

cis-regulatory region of DNA

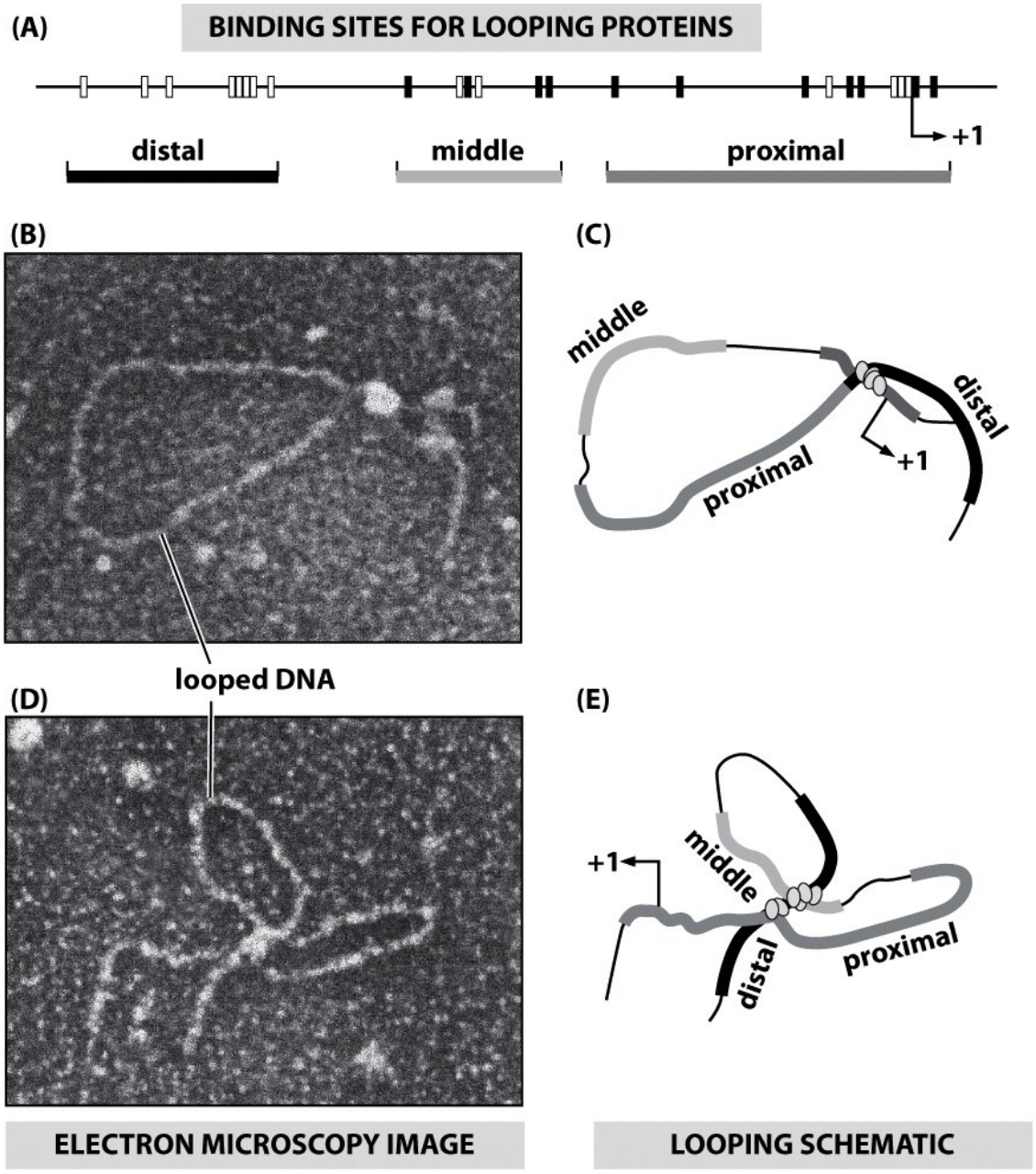


Figure 10.9 Physical Biology of the Cell (© Garland Science 2009)

Energetics of DNA looping

Bending energy of a loop with a radius R was calculated already:

$$E_{loop} = \frac{\xi_P \pi k_B T}{R}$$

For a DNA loop of length L, we take into account the following:

$$L = 2\pi R \quad \rightarrow \quad R = \frac{L}{2\pi} = \frac{\delta N_{bp}}{2\pi} \quad \text{where } \delta = 0.34\,\text{nm}$$

to obtain a more convenient bending energy of a DNA loop:

$$\frac{E_{loop}}{k_B T} = \frac{2\pi^2}{N_{bp}} \left(\frac{\xi_P}{\delta} \right) \approx \frac{3000}{N_{bp}}$$

expressed in terms of the number of base pairs. We used the estimate for the persistence length:

$$\xi_P = 50\,\text{nm}$$

The bending energy of DNA loops as a function of the number of base pairs in the DNA

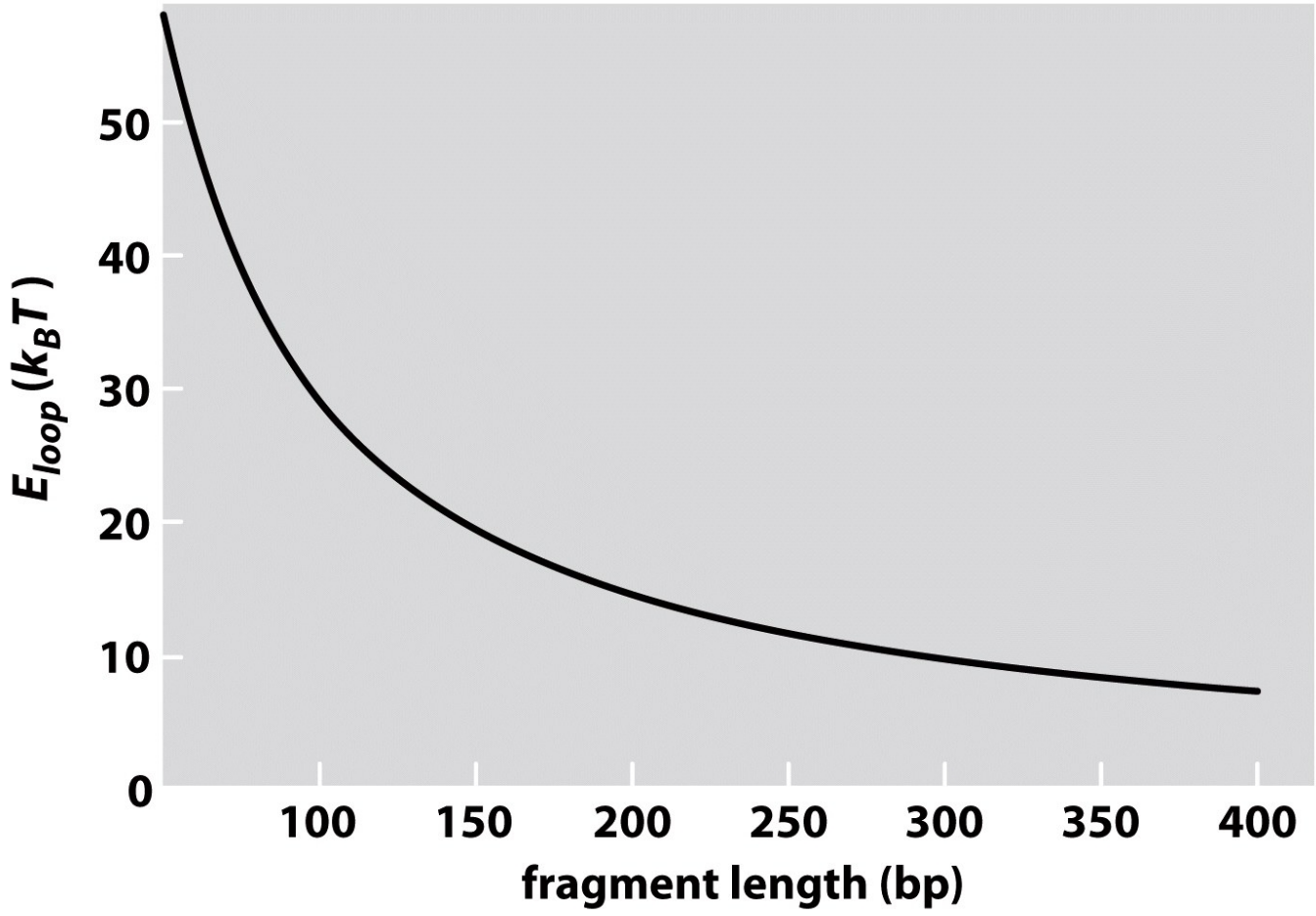


Figure 10.10 Physical Biology of the Cell (© Garland Science 2009)

Free Energy Estimate for DNA Looping: Elastic Energy Combined with Entropic Contribution

- **long DNA fragments: entropic contribution unfavorable**
- **short DNA fragment: bending contribution unfavorable**
- **elastic and entropic contributions:**

$$\Delta E_{loop} \approx \frac{3000\, k_B T}{N_{bp}}$$

$$p_0 \propto \frac{1}{\sqrt{N_{bp}^3}} \;\rightarrow\; \Delta S_{loop} = k_B \ln p_0 = -k_B \left(\frac{3}{2} \ln N_{bp} + \text{const}\right)$$

- **result in the total free energy change upon DNA looping:**

$$\Delta G_{loop} = \Delta E_{loop} - T S_{loop} \approx k_B T \left(\frac{3000}{N_{bp}} + \frac{3}{2} \ln N_{bp} + \text{const}\right)$$

The looping free energy as a function of the number of base pairs as derived within a simple toy model

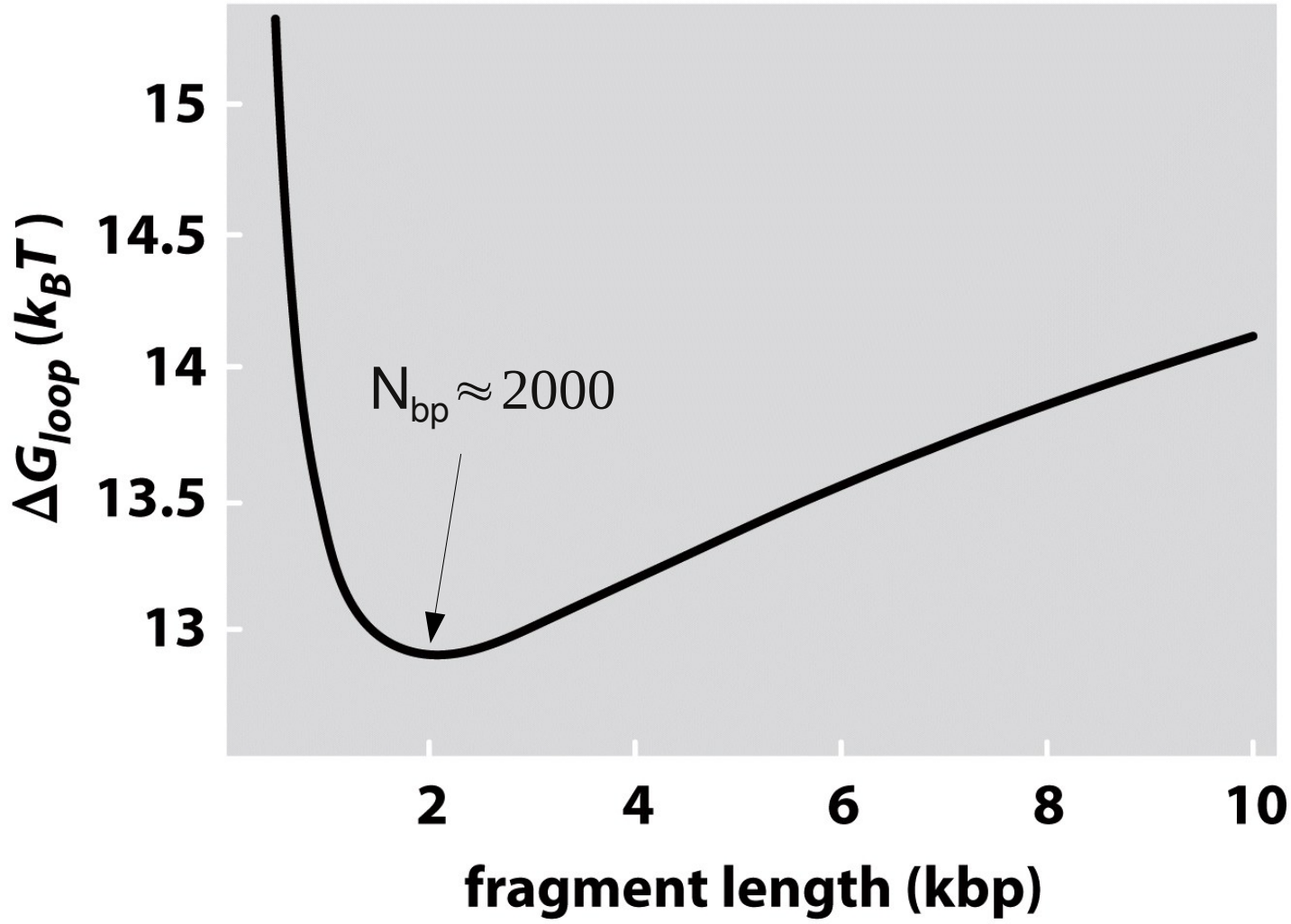


Figure 10.11 Physical Biology of the Cell (© Garland Science 2009)

Experimental data and the worm-like chain (WLC) model predict a slightly smaller favorable loop length

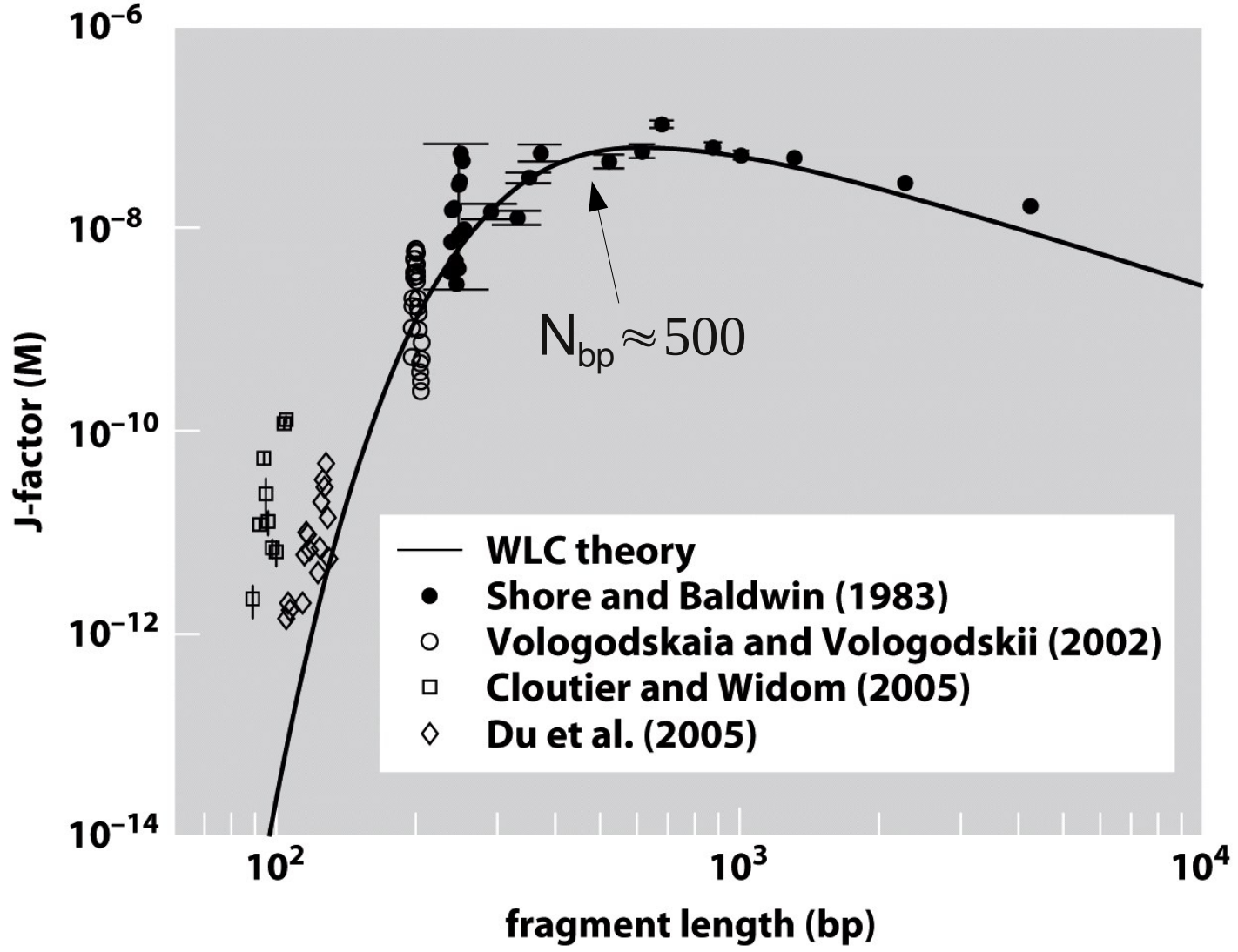


Figure 10.12 Physical Biology of the Cell (© Garland Science 2009)

What is the J-factor?

Cyclization experiments report a quantity J [in units of Concentration]:

$$J \propto e^{-\beta \Delta G_{loop}}$$

So that the minimum of the free energy of looping is equivalent to the maximum of J.

DNA Packing: From Viruses to Eukaryotes

$$\text{volume fraction } \nu = \frac{\Omega_{\text{genome}}}{\Omega_{\text{container}}} \approx \frac{N_{\text{bp}} \times 1\,\text{nm}^3}{\Omega_{\text{container}}\,[\text{nm}^3]}$$

L_{genome}	5×10^4 bp	5×10^6 bp	10^9 bp	10^9 bp
ν	0.6	0.1	0.02	0.002

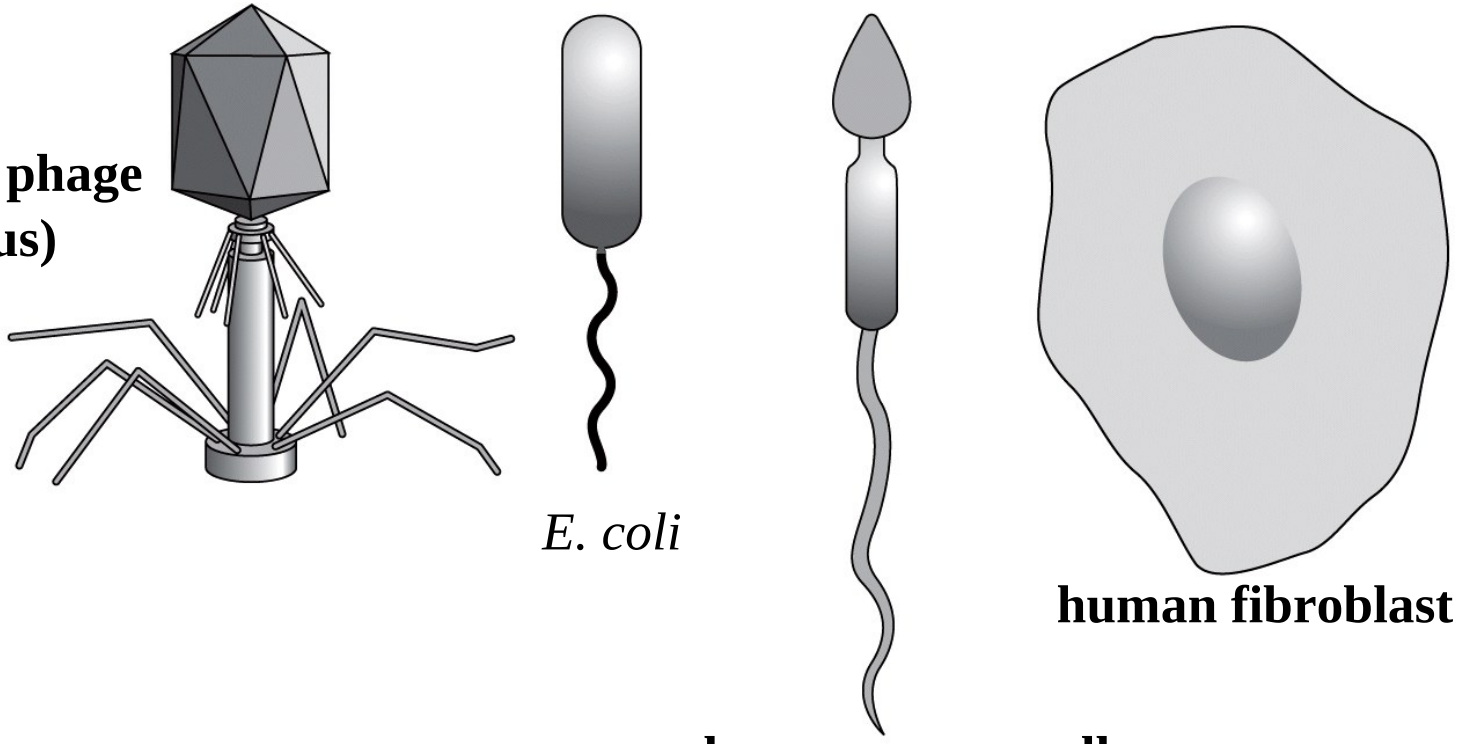


Figure 10.13 Physical Biology of the Cell (© Garland Science 2009)

The DNA Packing Compaction Ratio

a) lambda phage with spherical capsid of radius of 27 nm holding 48,500 base pairs:

$$\nu = \frac{N_{bp}\,nm^3}{\frac{4}{3}\pi R^3 nm^3} \approx \frac{5\times10^4}{4\times27^3} \approx 0.6$$

b) bacterial nucleoid: a sphere of radius 0.25 μm holding 5 x 10^6 base pairs:

$$\nu \approx \frac{5\times10^6}{4\times250^3} \approx 0.1$$

c) human sperm cell with a spherical nucleus of radius of 2.5 μm holding 10^9 base pairs:

$$\nu \approx \frac{10^9}{4\times2500^3} \approx 0.02$$

d) human fibroblast nucleus of radius of 5 μm holding 10^9 base pairs:

$$\nu \approx \frac{10^9}{4\times5000^3} \approx 0.002$$

The Problem of Viral DNA Packing
(check “viper.com” for a databank of viral structures)

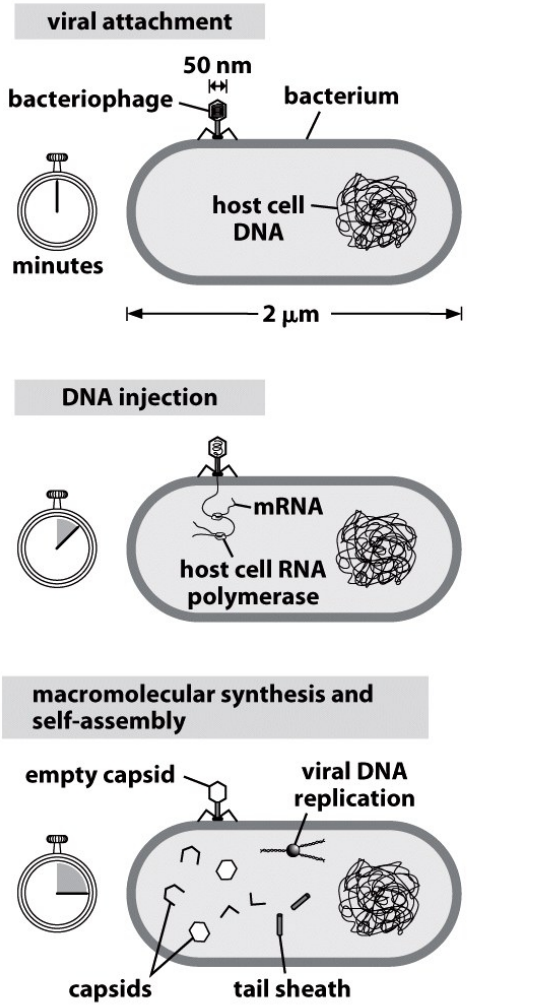
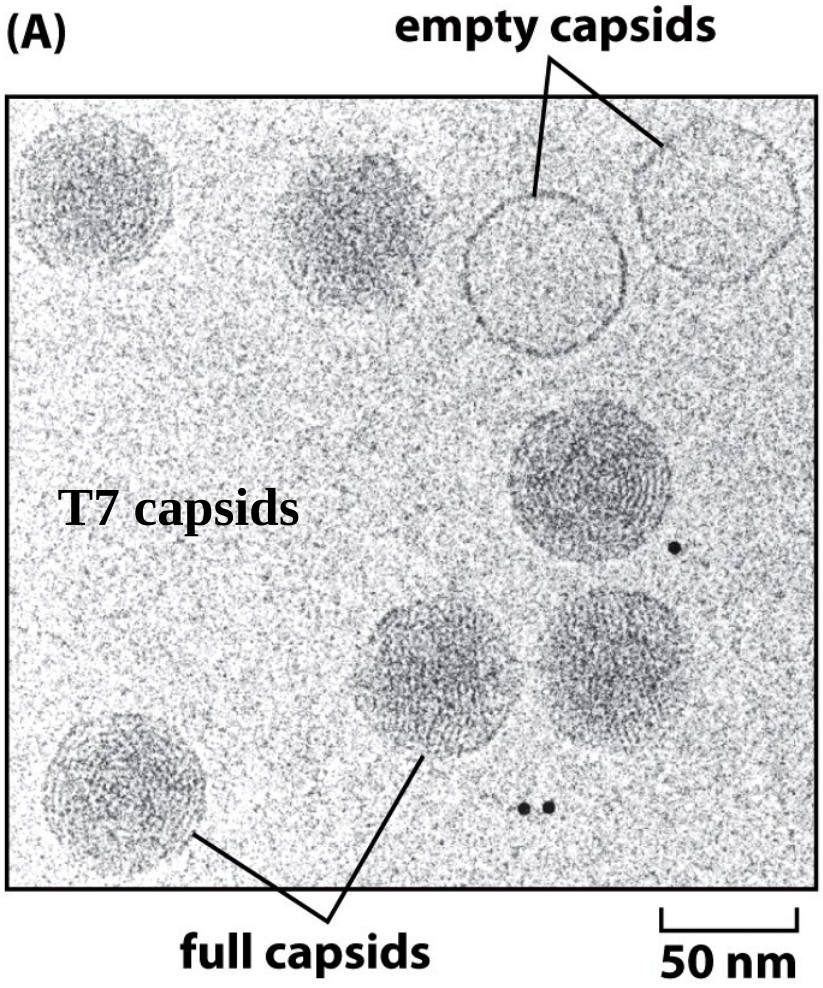
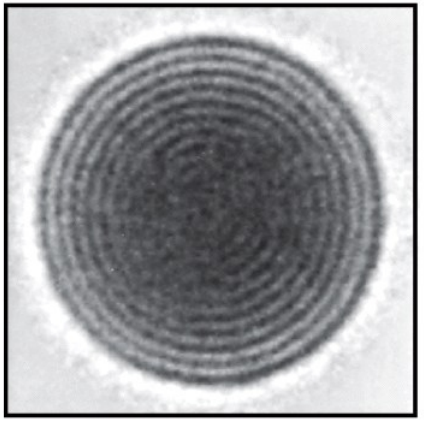


Figure 3.20 Physical Biology of the Cell (© Garland Science 2009)

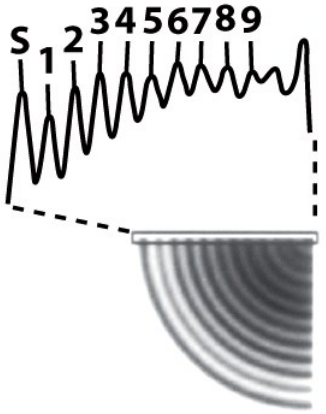
Why is the DNA packing in viruses a problem&

Cryo-electron microscopy images of packaged DNA





A single capsid with rings of packaged DNA

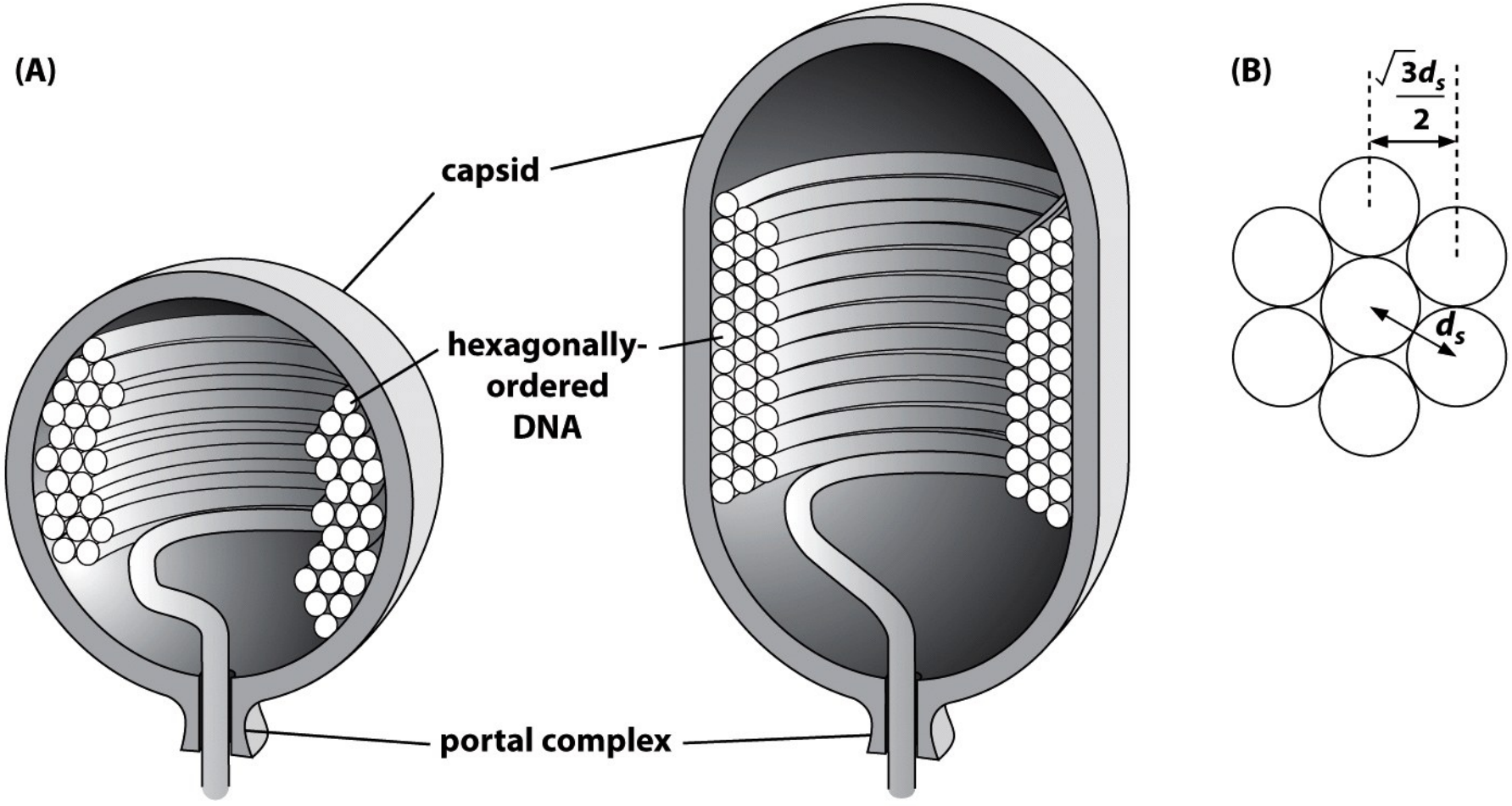


DNA shells

Highly ordered structures!

Figure 10.14 Physical Biology of the Cell (© Garland Science 2009)

$$\text{capsid volume}: V_{\text{capsid}} \approx L_{\text{DNA}}\, d_S^2 \quad \rightarrow \quad d_S \propto \frac{1}{L_{\text{DNA}}^{1/2}}$$



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Approximately correct scaling, though not on a large range

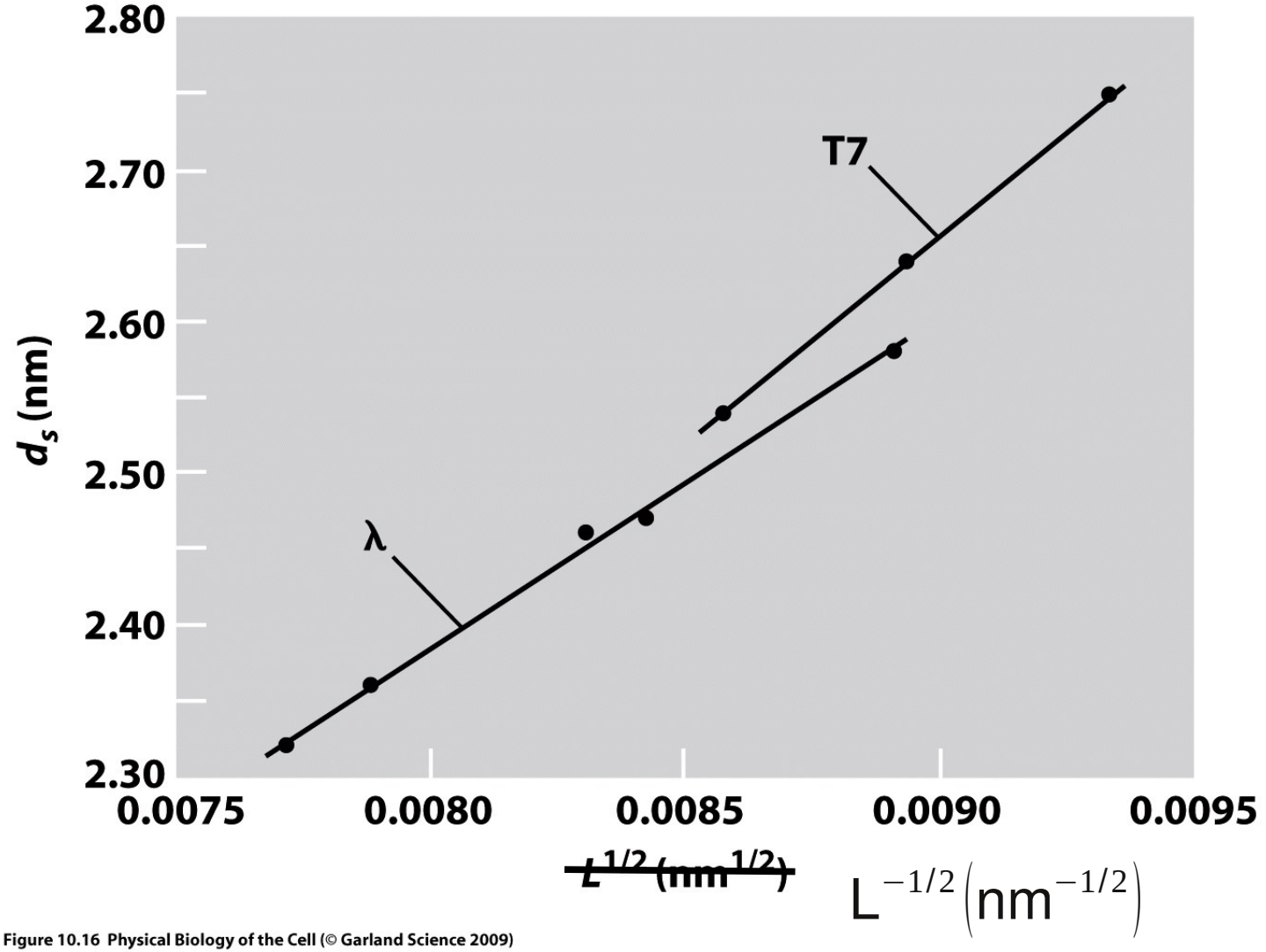


Figure 10.16 Physical Biology of the Cell (© Garland Science 2009)

Why does the DNA packing in viruses require energy?

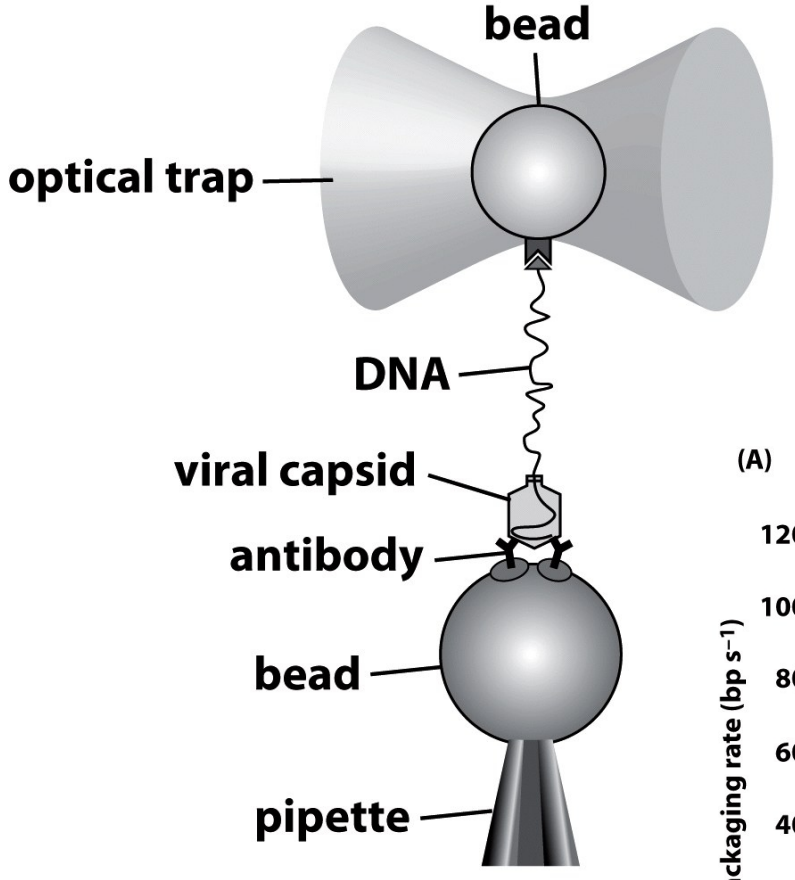
- **the entropic spring effect (DNA tends to spread out)**
- **elastic bending on the scale smaller than the persistence length of 50 nm**
- **strongly negatively charged DNA (tends to avoid itself)**
- **the entropic contribution is about 10-times smaller than the bending and electrostatic free energy associated with DNA packing (in viruses):**

$$G_{tot}(d_s, L) \approx G_{bend}(d_s, L) + G_{charge}(d_s, L)$$

- **the force that resists the packing is then:**

$$F = \frac{-dG_{tot}(d_s, L)}{dL}$$

How can we measure the force needed to pack the DNA?



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Optical tweezers: pulling DNA against the ATP-consuming motor

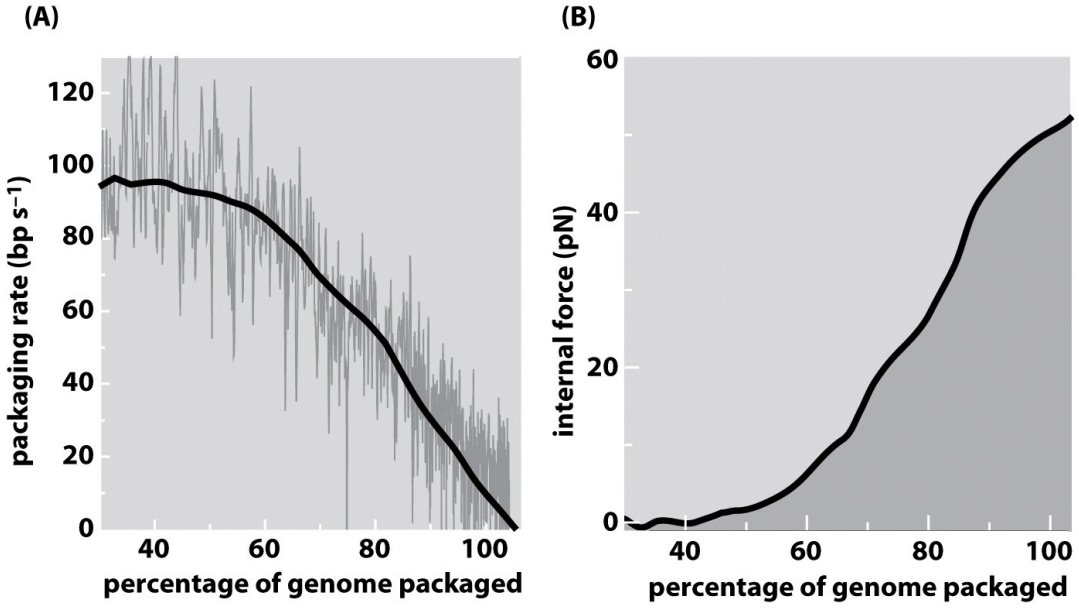

Figure 10.18 Physical Biology of the Cell (© Garland Science 2009)

Elastic Bending Contribution to the Free Energy: Circular Hoops

$$E_{loop} = \frac{\pi E I}{R} = \frac{\pi \xi_P k_B T}{R} \quad \rightarrow \quad G_{bend} = \pi \xi_P k_B T \sum_i \frac{N(R_i)}{R_i}$$

$$\sum_i \rightarrow \frac{2}{\sqrt{3} d_s} \int dR' \qquad \frac{\sqrt{3}}{2} d_s \ldots \text{distance between DNA strands}$$

$$G_{bend} = \frac{2\pi \xi_P k_B T}{\sqrt{3} d_s} \int_R^{R_{out}} \frac{N(R')}{R'} dR'$$

$$\text{DNA length}: L = \frac{2}{\sqrt{3} d_s} \int_R^{R_{out}} 2\pi R' N(R') dR'$$

cylindrical capsid of height z, radius R_{out}:

$$G_{bend}(R) = \frac{2\pi \xi_P k_B T z}{\sqrt{3} d_s^2} \ln\left(\frac{R_{out}}{R}\right) \qquad L(R) = \frac{2\pi z}{\sqrt{3} d_s^2} (R_{out}^2 - R^2)$$

The second equation for L(R) can be used to express R:

$$R = R_{out}\sqrt{1-\frac{\sqrt{3}\,d_s^2 L}{2\pi z R_{out}^2}}$$

And the final expression for the free energy of bending:

$$G_{bend} = \frac{-\pi \xi_P k_B T z}{\sqrt{3}\,d_s^2}\ln\left(1-\frac{\sqrt{3}\,d_s^2 L}{2\pi z R_{out}^2}\right)$$

And the force associated with accumulated bending energy:

$$f(L) = \frac{-dG_{bend}}{dL} = \frac{-\frac{\xi_P k_B T}{2R_{out}^2}}{1-\frac{\sqrt{3}\,d_S^2 L}{2\pi z R_{out}^2}}$$

Electrostatic Contribution to the Free Energy of DNA Packing In Viruses

- **experiment that measures osmotic pressure versus DNA spacing** d_s
- **assume that parallel strands interact via a pair potential per unit length (only nearest neighbors):** $\nu(d_s)$
- **if we experimentally determine the pressure, we can compute the interaction energy and obtain the pair potential** $\nu(d_s)$

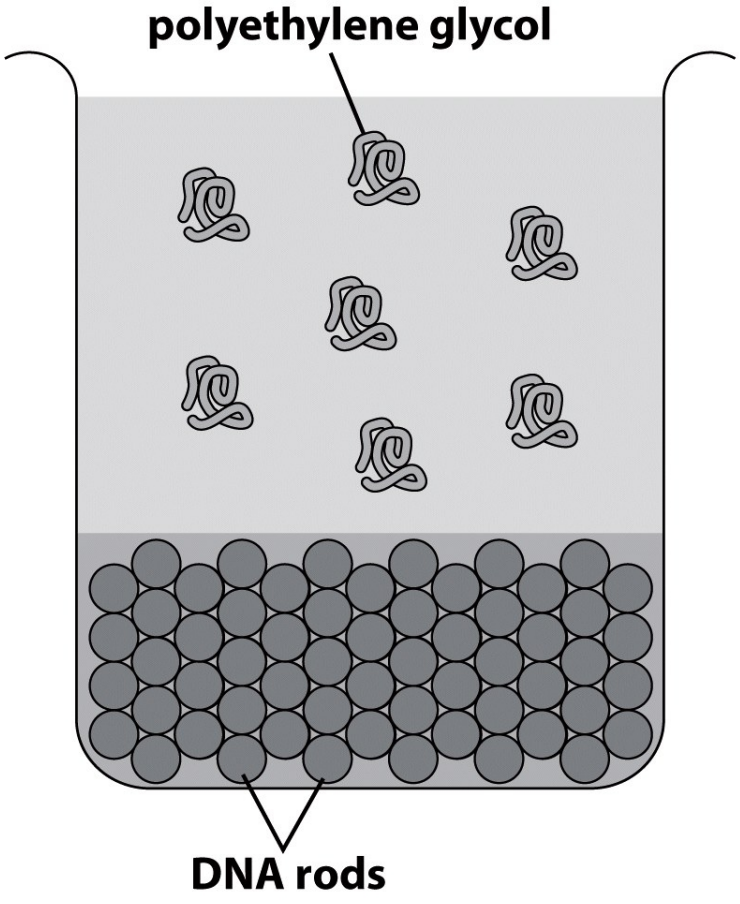

Figure 6.22 Physical Biology of the Cell (© Garland Science 2009)

Consider N parallel strands of length l, each packed into a hexagonal array with a spacing d_s : $G_{charge} = 3 N l \nu(d_s)$

(a factor of 3 = 1/2 x 6 for 6 nearest neighbors in the array)

The volume of the assembly is: $V = \frac{\sqrt{3}}{2} N d_s^2 l$

The pressure can be calculated as:

$$p(d_s) = \frac{-dG_{charge}}{dV}, \quad dV = N l \sqrt{3} d_s \, dd_s$$

So that the force is:

$$f(d_s) = \frac{d\nu(d_s)}{dd_s} = \frac{1}{\sqrt{3}} p(d_s) d_s$$

Experimental observation was (Textbook, page 245):

$$p(d_s) = F_0 e^{-d_s/c}$$

Which leads us to the final expressions:

$$\nu(d_s)=\frac{1}{\sqrt{3}}F_0(c^2+c\,d_s)\,e^{-d_s/c}$$

$$G_{charge}=\sqrt{3}\,F_0(c^2+c\,d_s)\,L\,e^{-d_s/c},\qquad L=N\,l\ldots\text{total DNA length}$$

This electrostatic contribution can be experimentally controlled Through ionic concentration, which affects the energy through F_0 **whereas** $c\approx 0.27\,\text{nm}$ **is more or less constant over a wide range of salt conditions.**

The total energy associated with DNA packing in viruses is:

$$G_{tot}=G_{bend}+G_{charge}$$

$$G_{tot}=\frac{-\pi\,\xi_P\,k_B\,T\,z}{\sqrt{3}\,d_s^2}\ln\left(1-\frac{\sqrt{3}\,d_s^2\,L}{2\pi\,z\,R_{out}^2}\right)+\sqrt{3}\,F_0(c^2+c\,d_s)\,L\,e^{-d_s/c}$$

We need to find the optimal spacing by minimizing the total free energy (at fixed DNA length) with respect to the spacing:

$$\frac{\partial G_{tot}}{\partial d_s} = 0 \qquad \rightarrow \qquad d_s = d_s(L)$$

Then use this relationship in the expression for the force F(L):

$$F(L) = \frac{-\partial G_{tot}}{\partial L}$$

Forces for bacteriophage viruses T4, T7, HK97, lambda, and Φ29

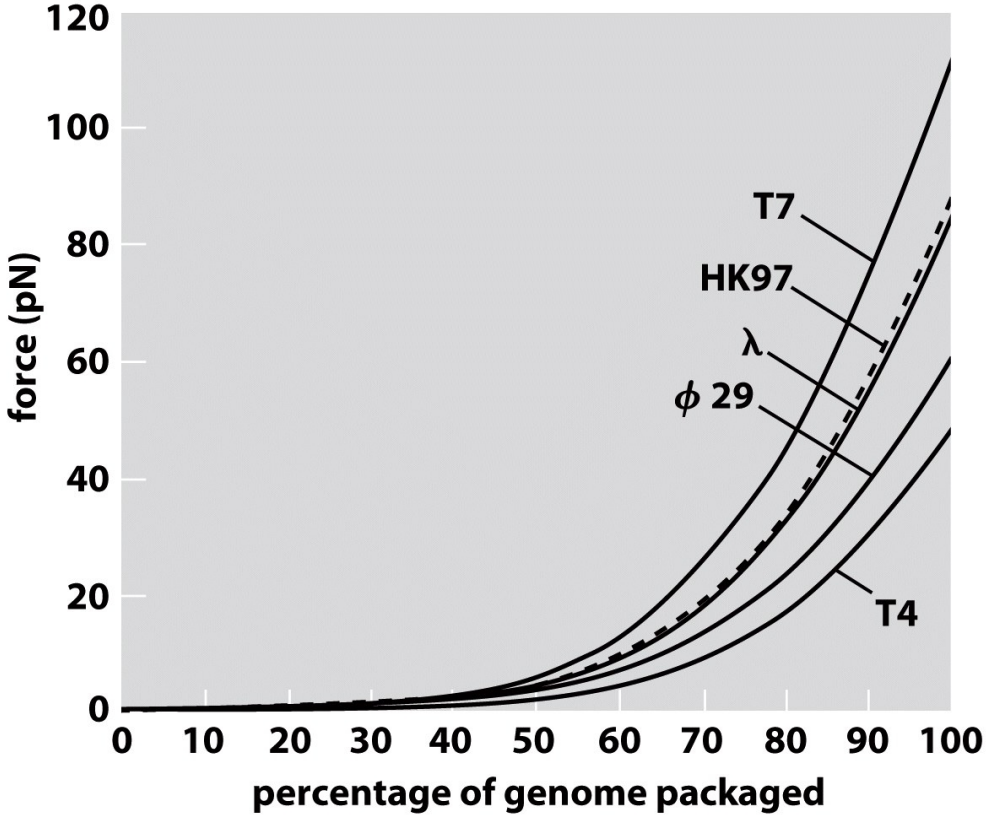

Figure 10.19 Physical Biology of the Cell (© Garland Science 2009)