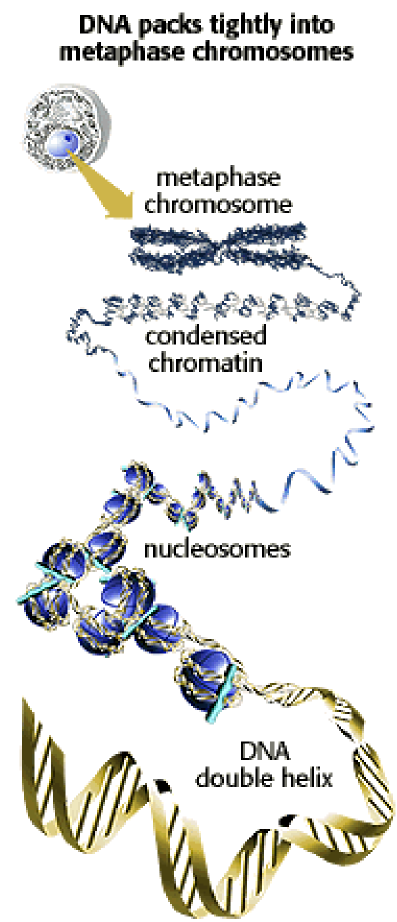
Introduction to Physical Biology: Models and Numbers



Boulder Lectures on Soft Matter Physics
July 2012
Yitzhak Rabin

R. Phillips, J. Kondev, J. Theriot, "*Physical Biology of the Cell*" (Garland, 2009)
A.D. Bates and A. Maxwell, "*DNA Topology*" (Oxford, 2005)

Building blocks of cells – 4 types of macromolecules made of simple repeat units:

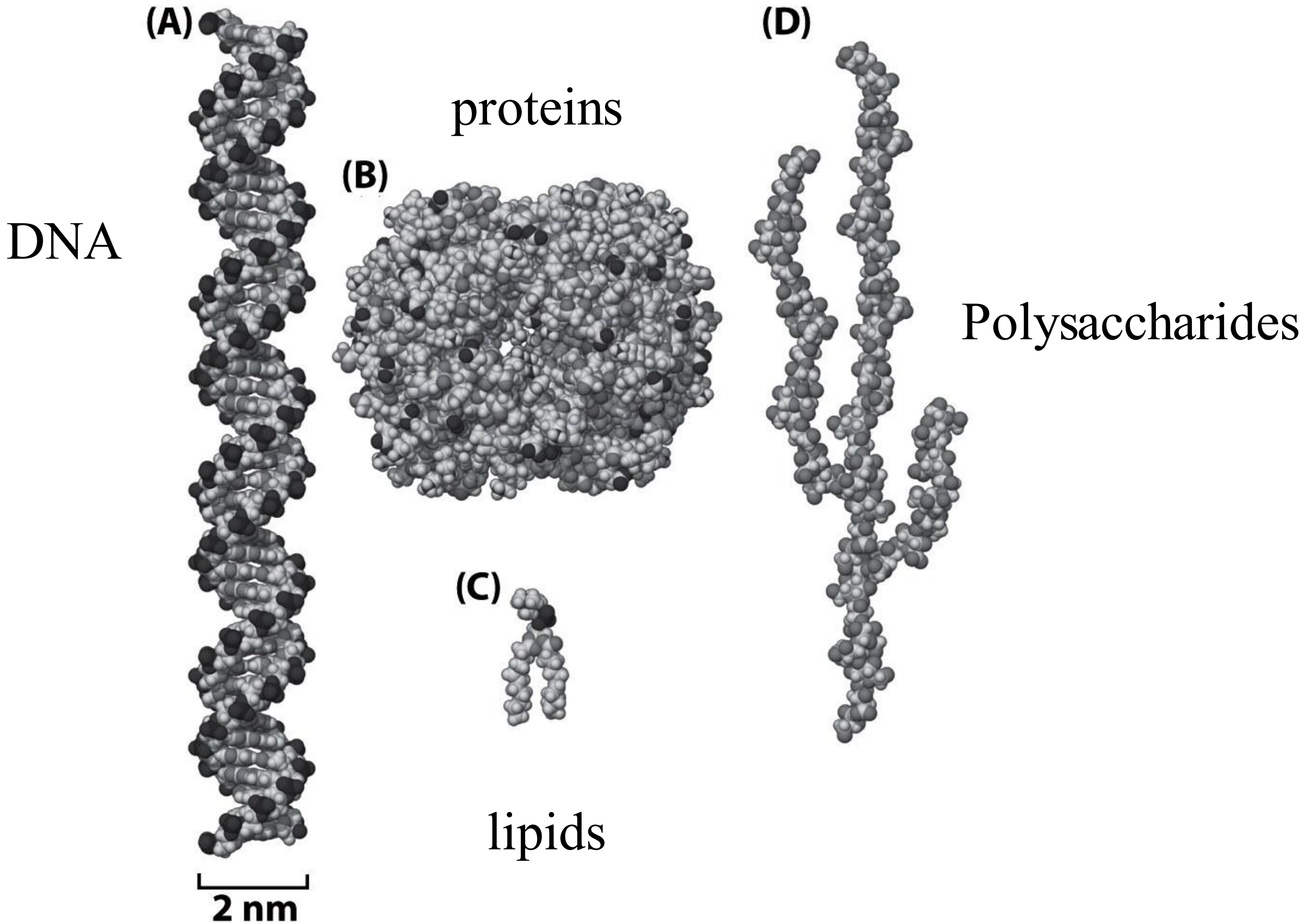


Figure 1.1 Physical Biology of the Cell (© Garland Science 2009)

Distribution of macromolecules in E. coli bacterium

Substance	% of total dry weight	Number of molecules
Macromolecule		
Protein	55.0	2.4×10^6
RNA	20.4	
23S RNA	10.6	19,000
16S RNA	5.5	19,000
5S RNA	0.4	19,000
Transfer RNA (4S)	2.9	200,000
Messenger RNA	0.8	1,400
Phospholipid	9.1	22×10^6
Lipopolysaccharide	3.4	1.2×10^6
DNA	3.1	2
Murein	2.5	1
Glycogen	2.5	4,360
Total macromolecules	**96.1**	
Small molecules		
Metabolites, building blocks, etc.	2.9	
Inorganic ions	1.0	
Total small molecules	**3.9**	

Table 2.1 Physical Biology of the Cell (© Garland Science 2009)

Language of DNA and proteins:

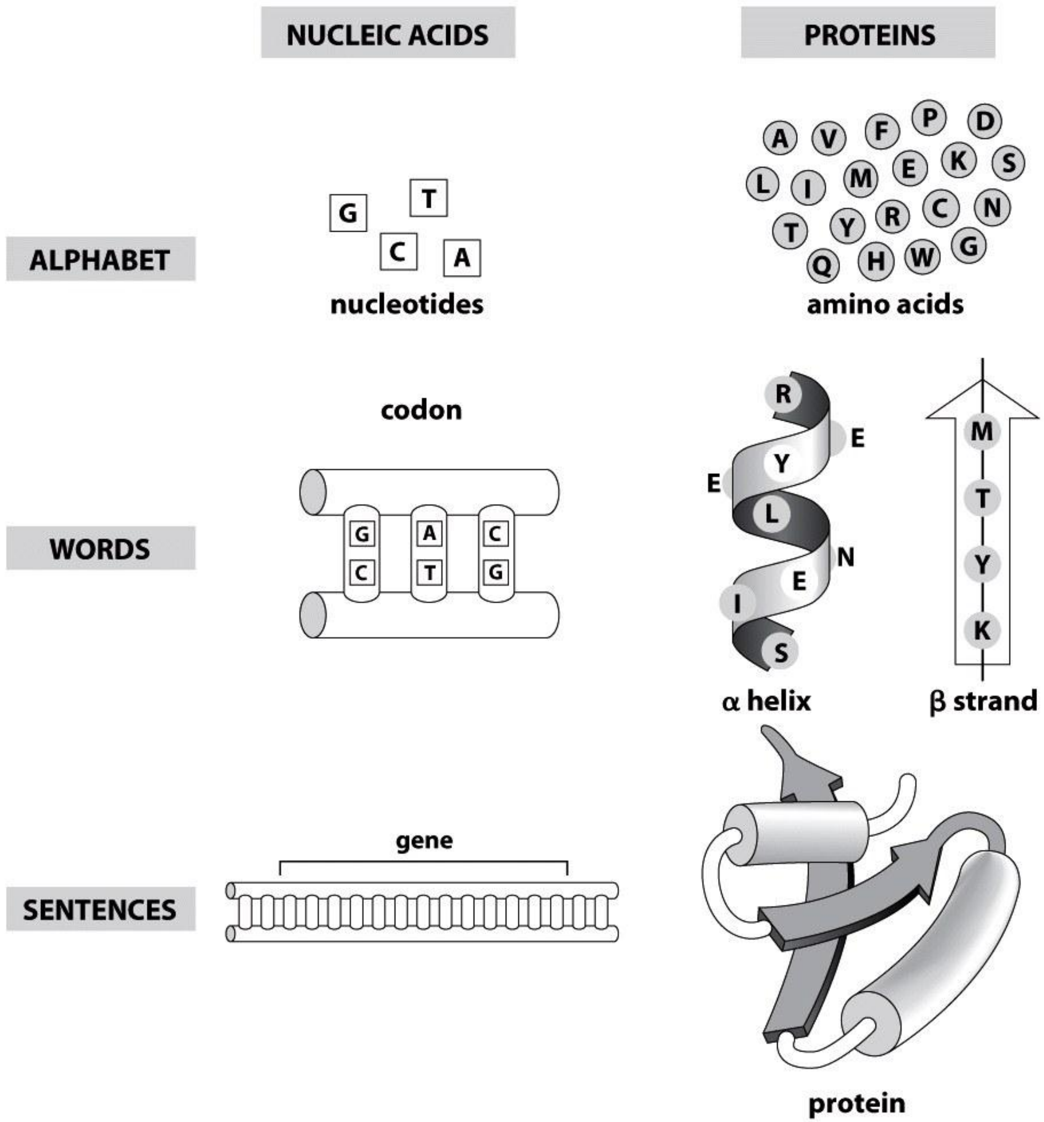


Figure 1.2 Physical Biology of the Cell (© Garland Science 2009)

Nucleotides:

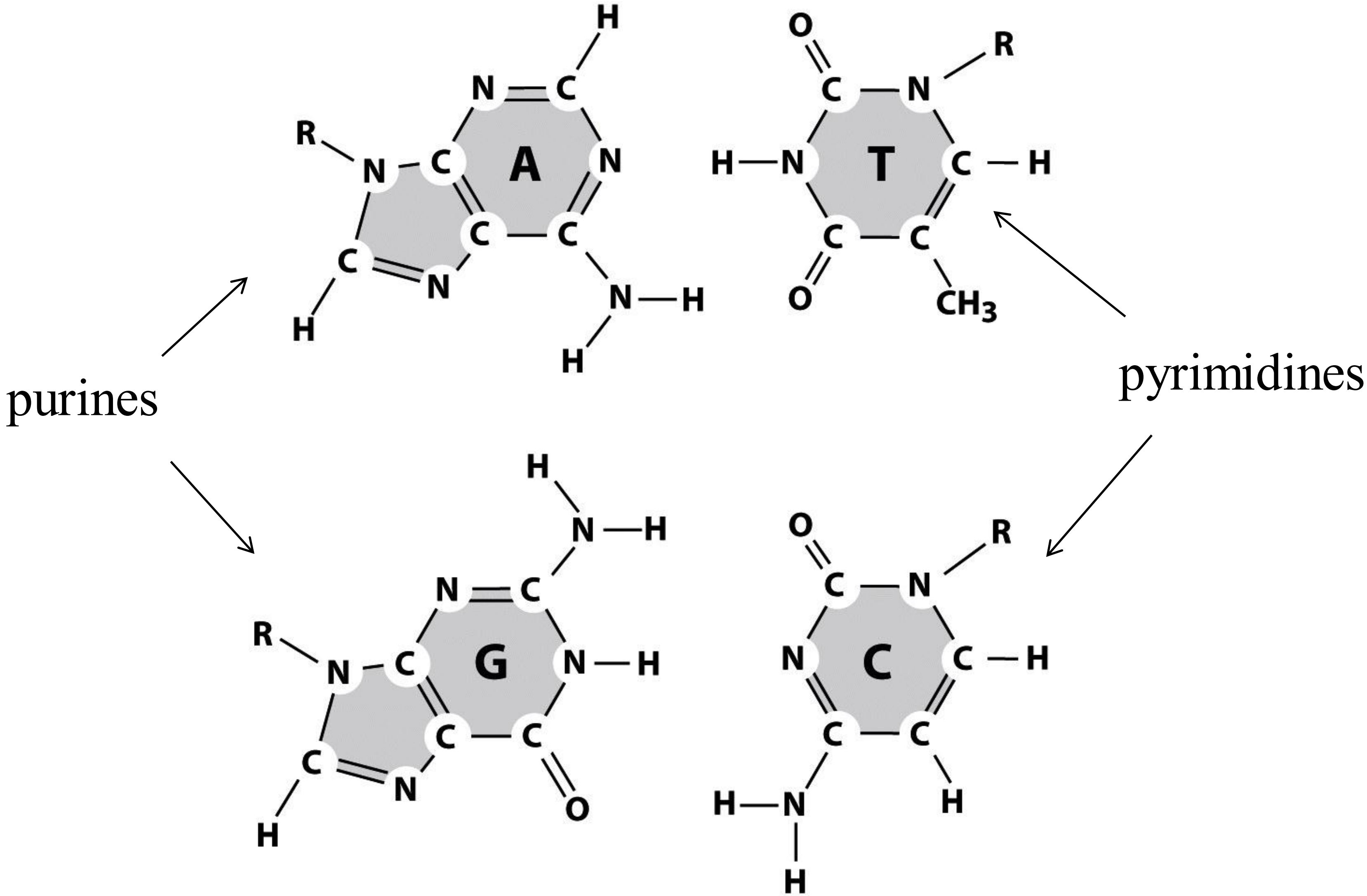


Figure 1.3a Physical Biology of the Cell (© Garland Science 2009)

Chemical structure of DNA

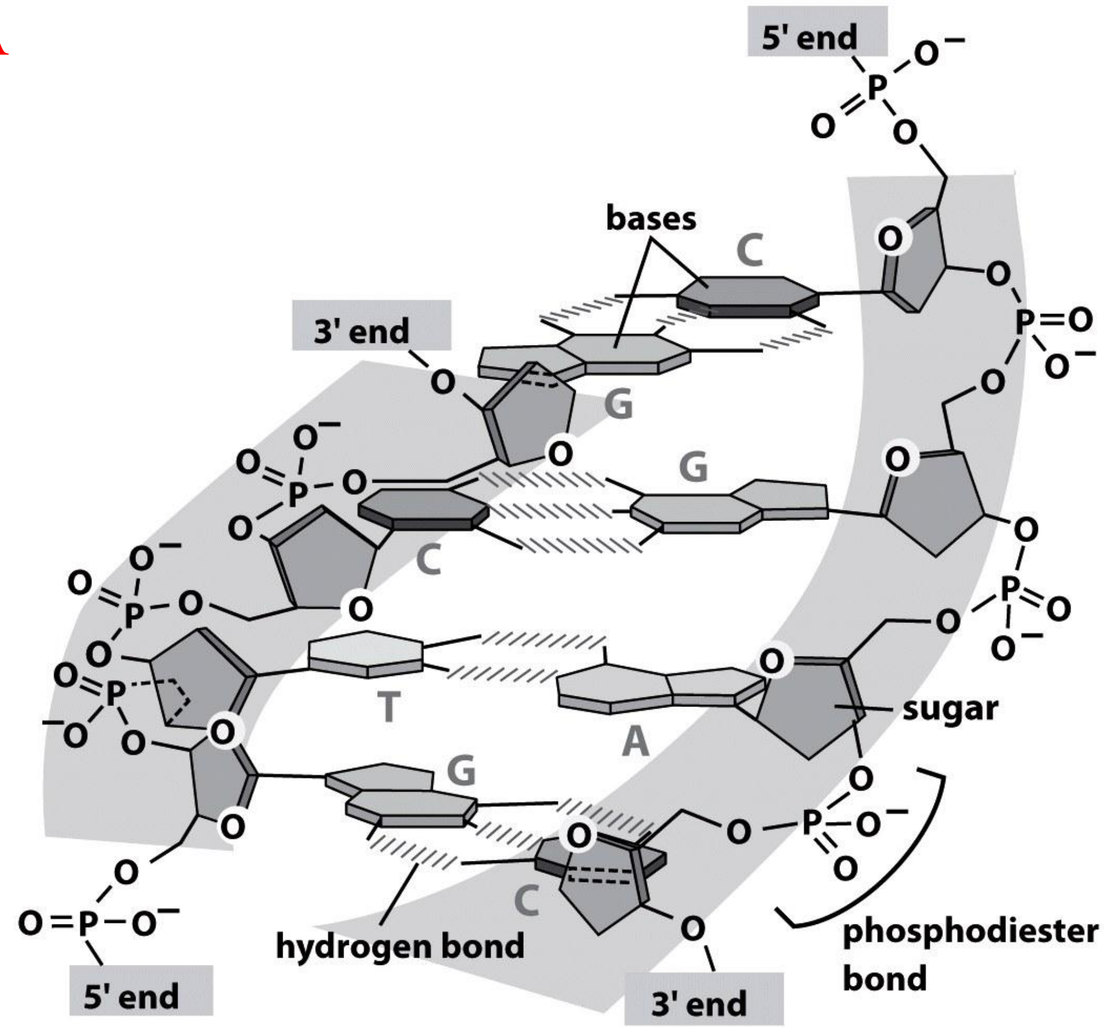


Figure 1.3b Physical Biology of the Cell (© Garland Science 2009)

Conclusions at a glance:

1. Each strand has a direction (3’ to 5’)
2. GC bp more stable than AT bp – 3 h-bonds instead of 2!
3. Bases turn inwards – how do proteins recognize sequence?

Standard B form of DNA

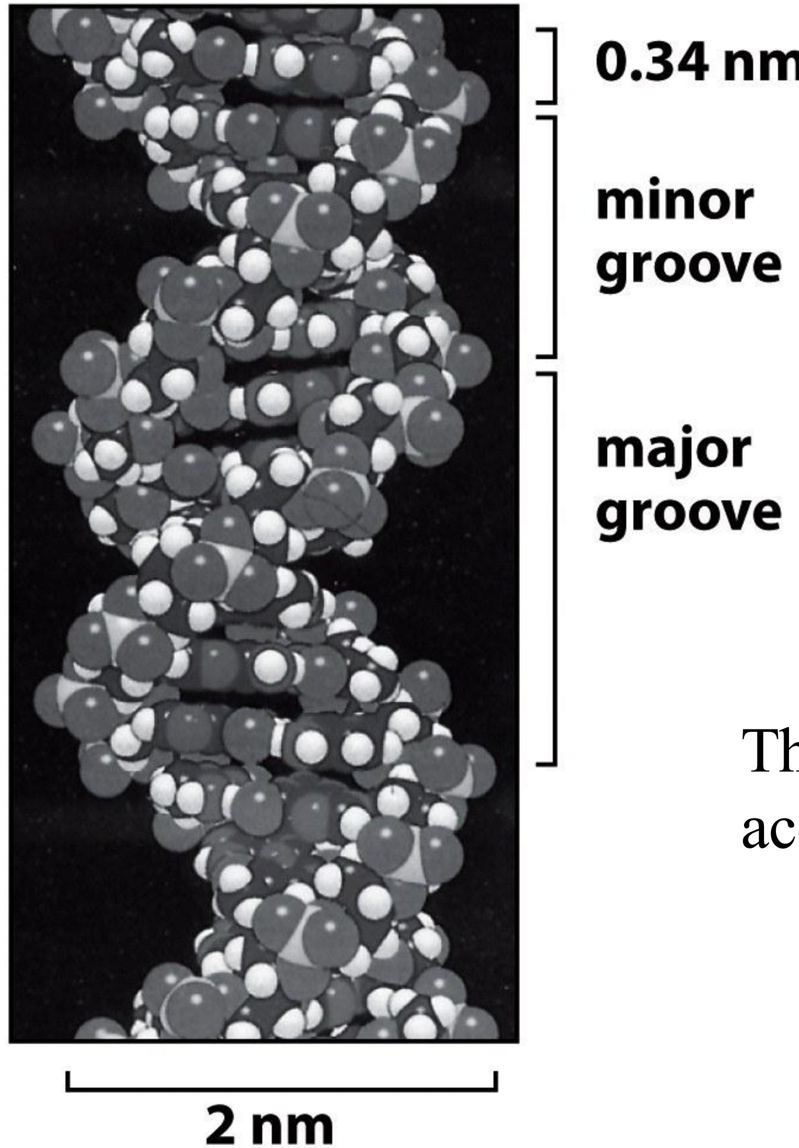


Figure 1.3c Physical Biology of the Cell (© Garland Science 2009)

The grooves allow access to proteins

Rosetta stone - translating bp code to aa sequence

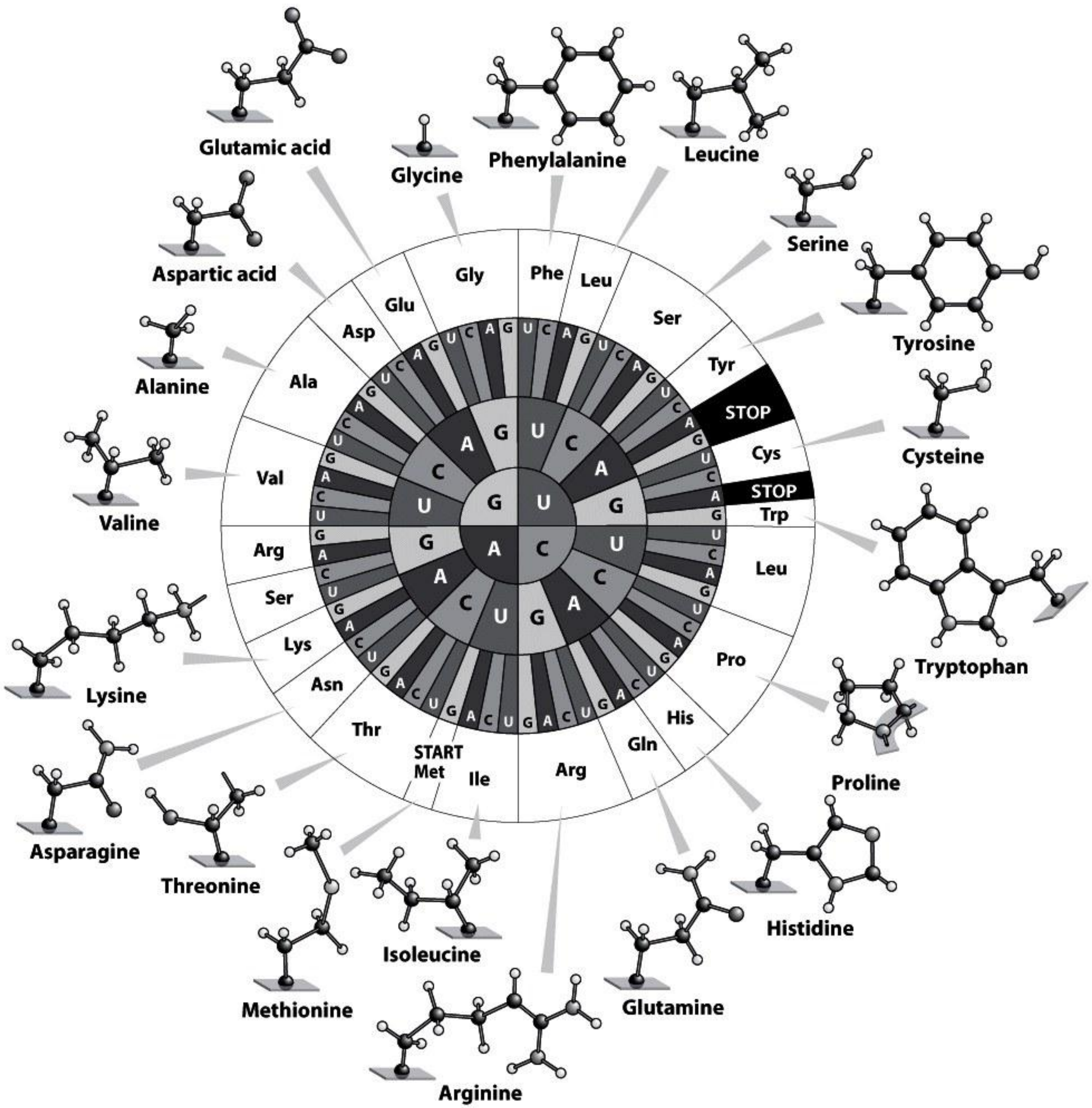


Figure 1.4 Physical Biology of the Cell (© Garland Science 2009)

Models of DNA – what is the question?

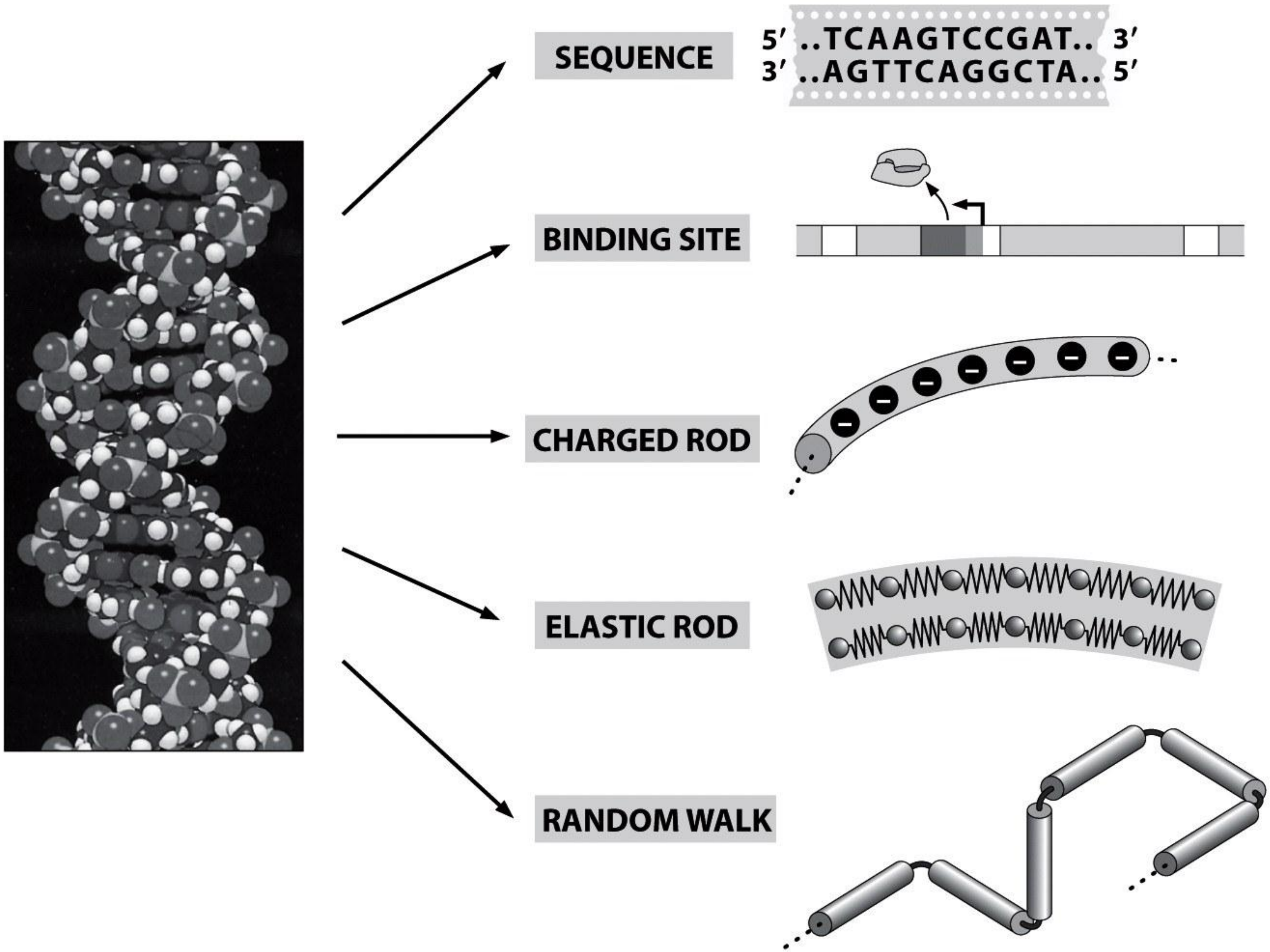


Figure 1.5 Physical Biology of the Cell (© Garland Science 2009)

Models of proteins:

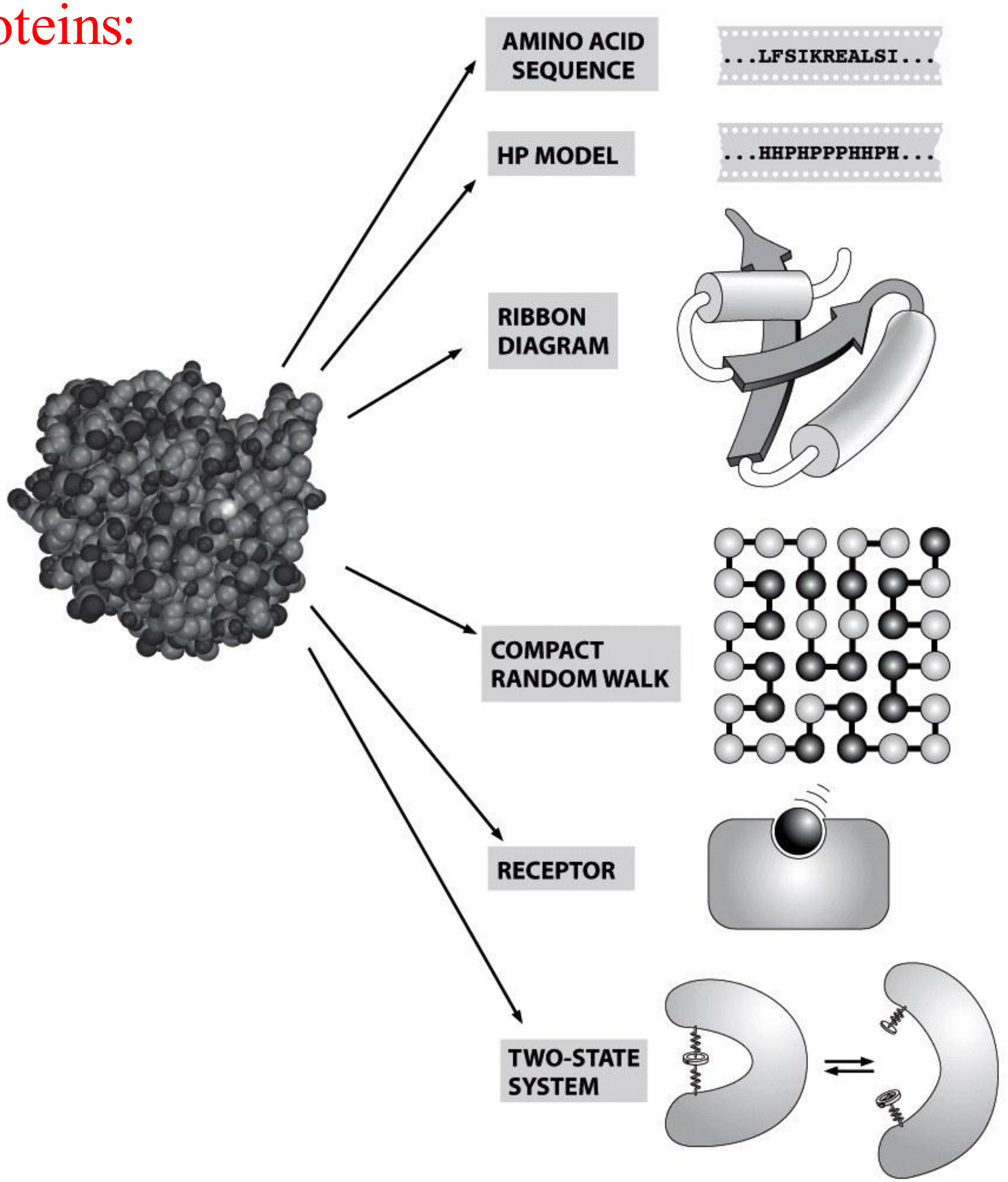


Figure 1.6 Physical Biology of the Cell (© Garland Science 2009)

Models of membranes:

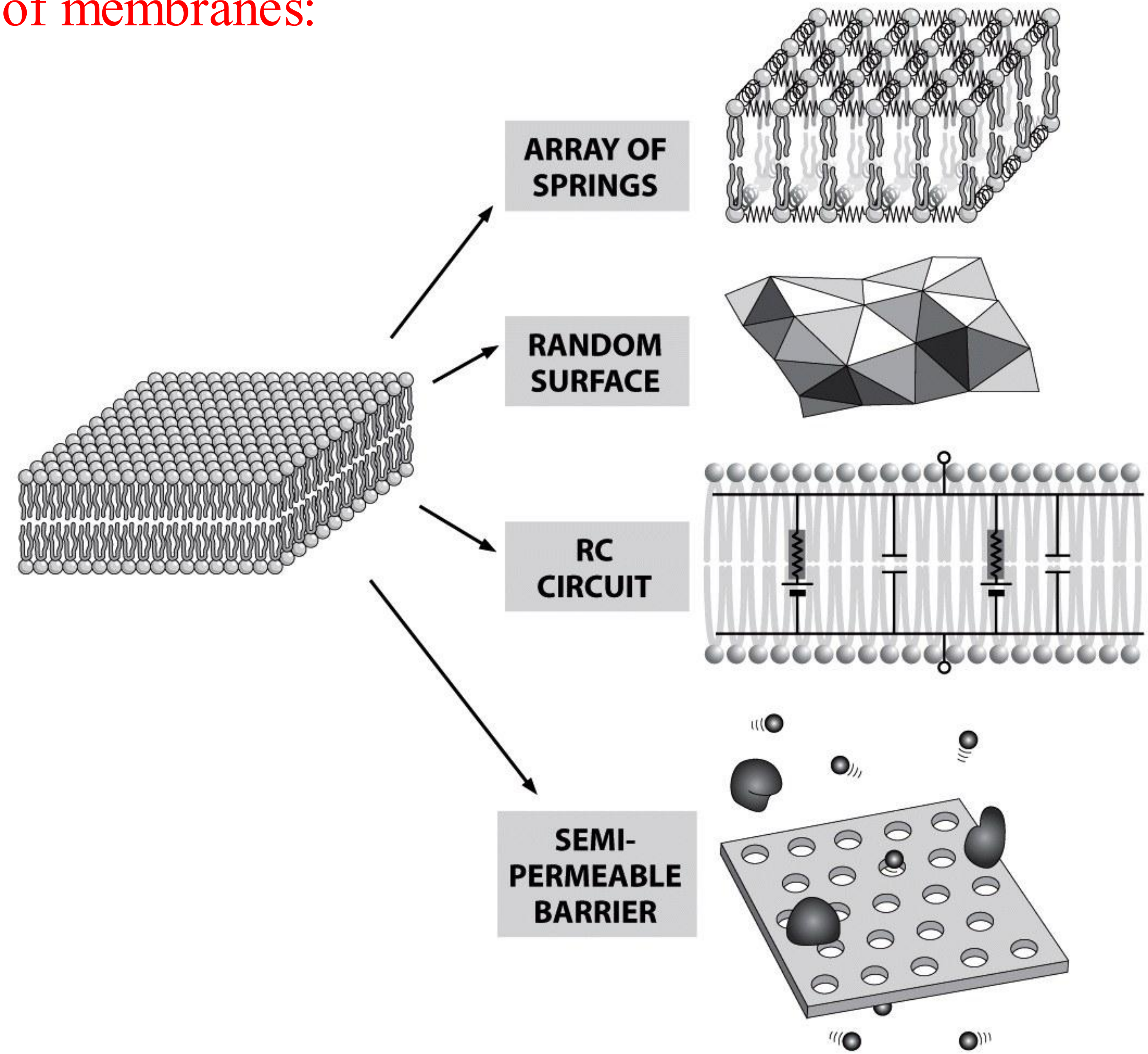


Figure 1.7 Physical Biology of the Cell (© Garland Science 2009)

Models of Bacteria

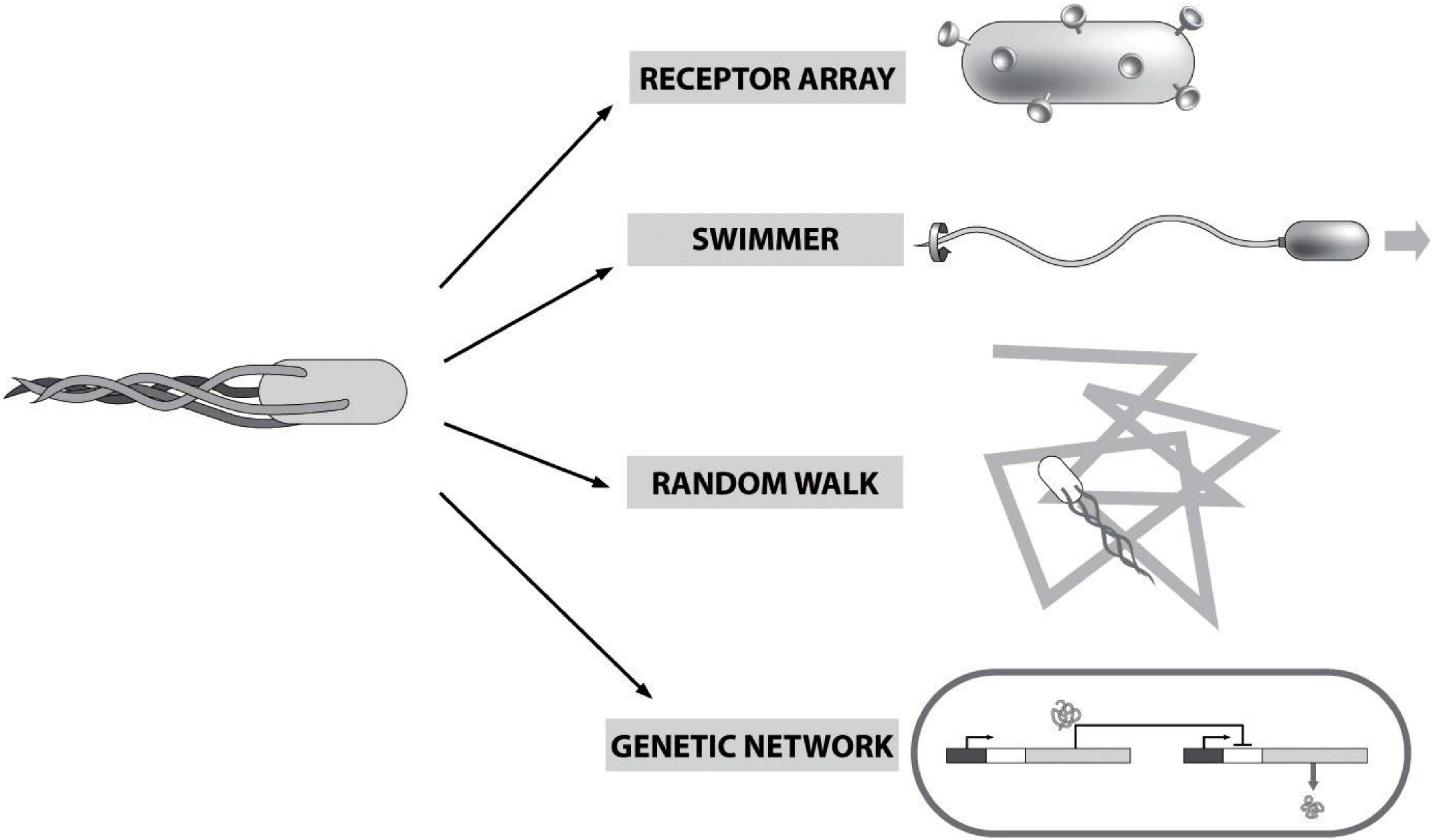


Figure 1.8 Physical Biology of the Cell (© Garland Science 2009)

Pictures are nice - but quantitative data requires quantitative models!

The toolbox of physics and chemistry:

Simple tools (we understand them well):

- Harmonic oscillator
- Ideal gas
- Two level systems (Ising model)
- Diffusion and random walks
- Polymer physics
- DH and PB models of charges in solution
- Elasticity of rods and plates
- Low Reynolds number hydrodynamics
- Rate equations
- Newton’s equations (MD simulations)

Complex tools (we do not understand them well enough):

- Non-linear dynamics (attractors)
- Reaction-diffusion equations
- Many body systems of complex elements
- Quantum chemistry of large molecules
- Topology
- ……

Example – simple applications of harmonic oscillator:

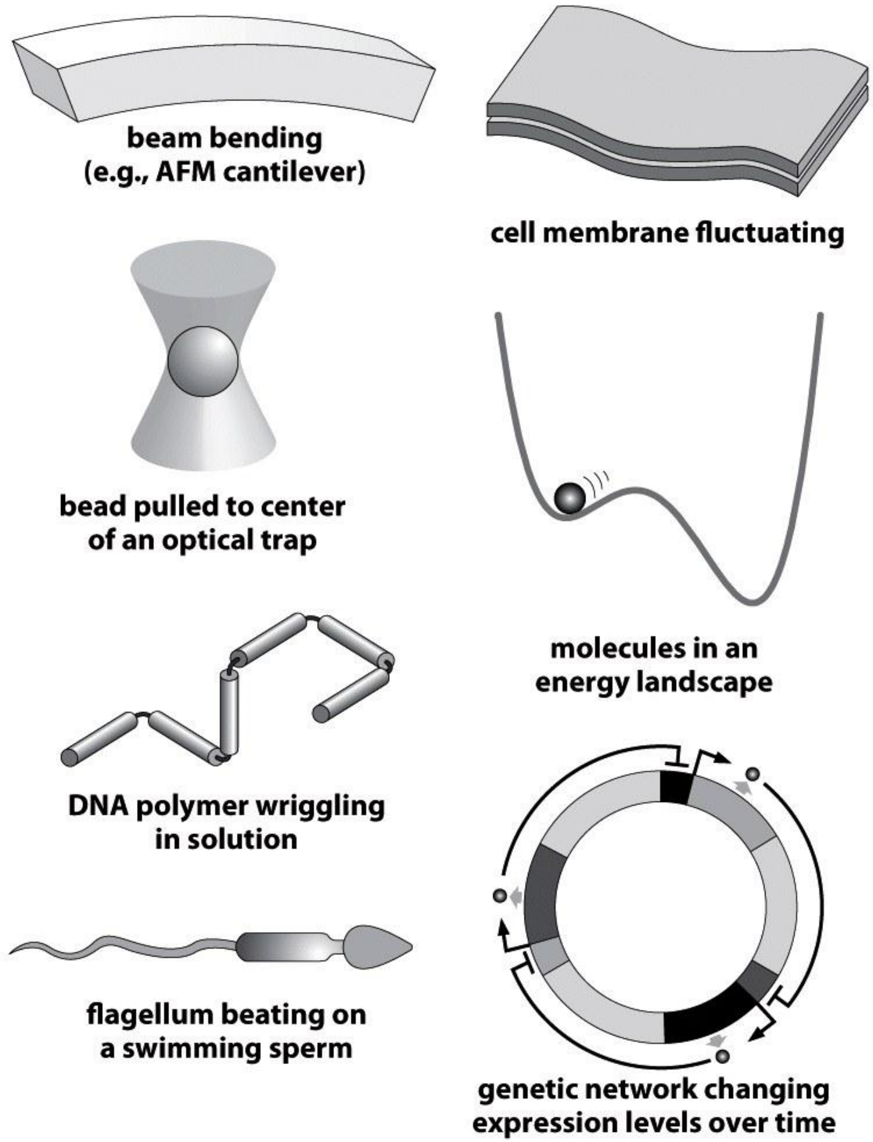


Figure 1.12b Physical Biology of the Cell (© Garland Science 2009)

Choice of model requires knowing the order of magnitude of some characteristic numbers!

Examples:

1. Is inertia important for bacterial propulsion?

Estimate the Reynolds number of E. coli's motion in water

Size: $L=1\mu m$, velocity: $V=10\mu m/s$, kinematic viscosity: $\nu=0.01 cm^2/s$

$$Re=\frac{V\cdot L}{\nu}=10^{-5}$$

Inertia is irrelevant – velocity is proportional to the force and responds instantaneously to it!

(Aristotle beats Newton for bacteria)

2. Confinement of DNA:

Estimate the radius of gyration of the lambda phage DNA:

Kuhn segment length of DNA: a=100nm;
Length of DNA: $L=5\cdot10^4$ bp · 0.3nm $=1.5\cdot10^4$nm

DNA radius of gyration in solution

$$R=(a\cdot L/6)^{1/2}=125 \text{ nm}$$

Radius of capsid: 27nm

Confinement ratio: $\frac{125^3}{27^3}$

100 fold confinement (by volume) – DNA will rapidly spread when capsid is removed

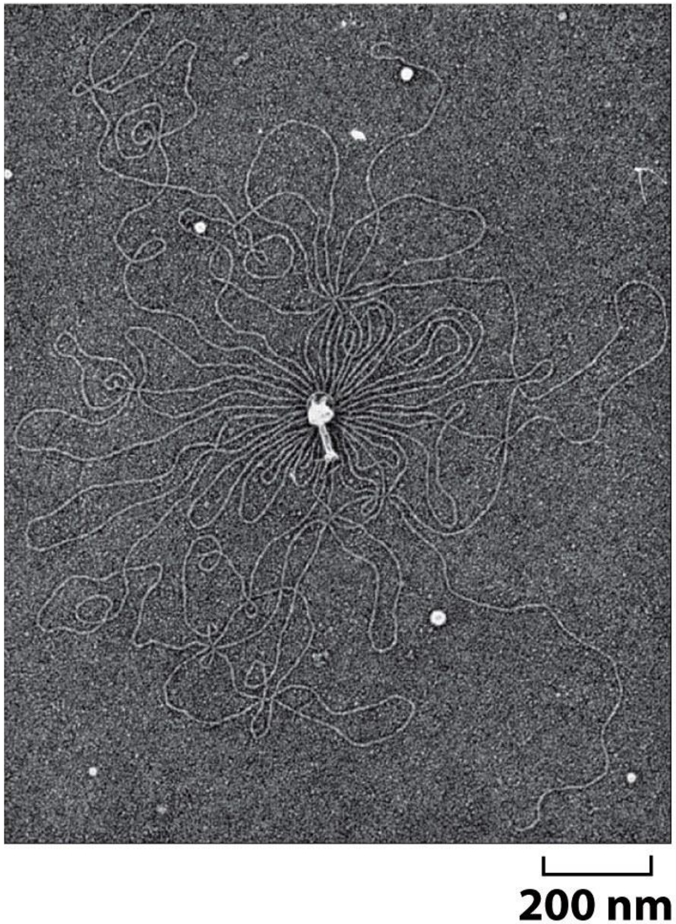


Figure 1.13 Physical Biology of the Cell (© Garland Science 2009)

What is the volume fraction occupied by DNA?

Volume per bp of DNA $=1\text{nm}^3$

Packing ratio: $$\nu_{\text{lambda}} = \frac{1 \cdot Nbp}{\frac{4\pi}{3} \cdot r^3}$$

Confining radii: $r_{\text{lambda}} = 27\text{nm}$; $r_{\text{nucleoid}} = 0.25\mu\text{m}$; $r_{\text{sperm head}} = 2.5\mu\text{m}$; $r_{\text{nucleus}} = 5\mu\text{m}$

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

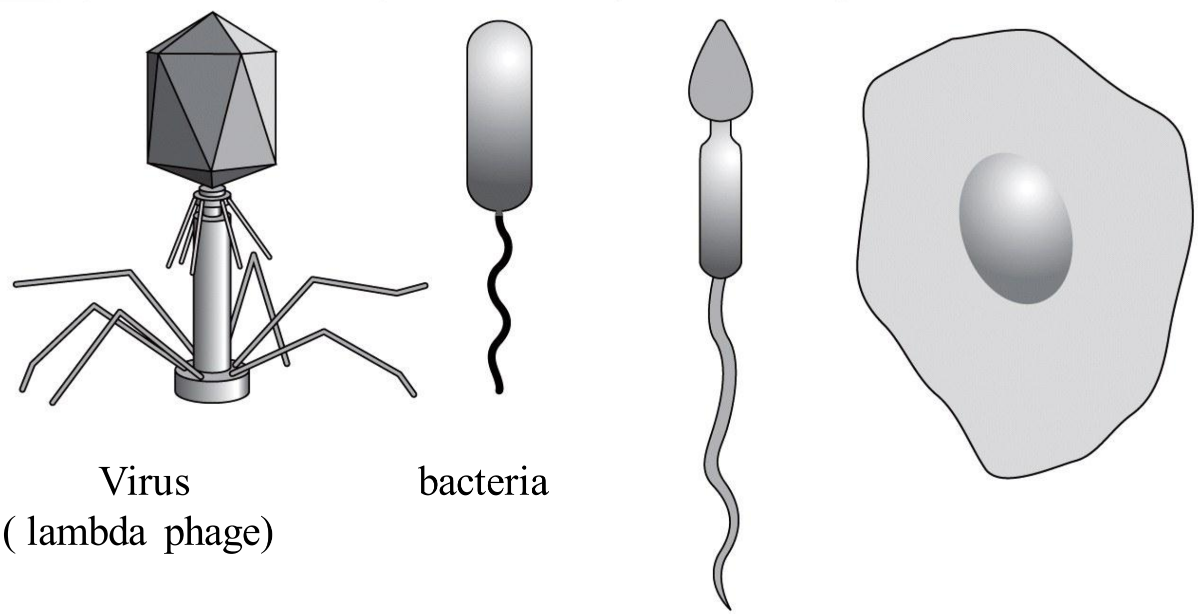


Figure 10.13 Physical Biology of the Cell (© Garland Science 2009)

How is the highly confined state of DNA maintained?

Viruses: crystal-like density and arrangement

- need motors for packing
- No proteins inside to balance electrostatic repulsion – Wigner crystal –type stabilization by walls

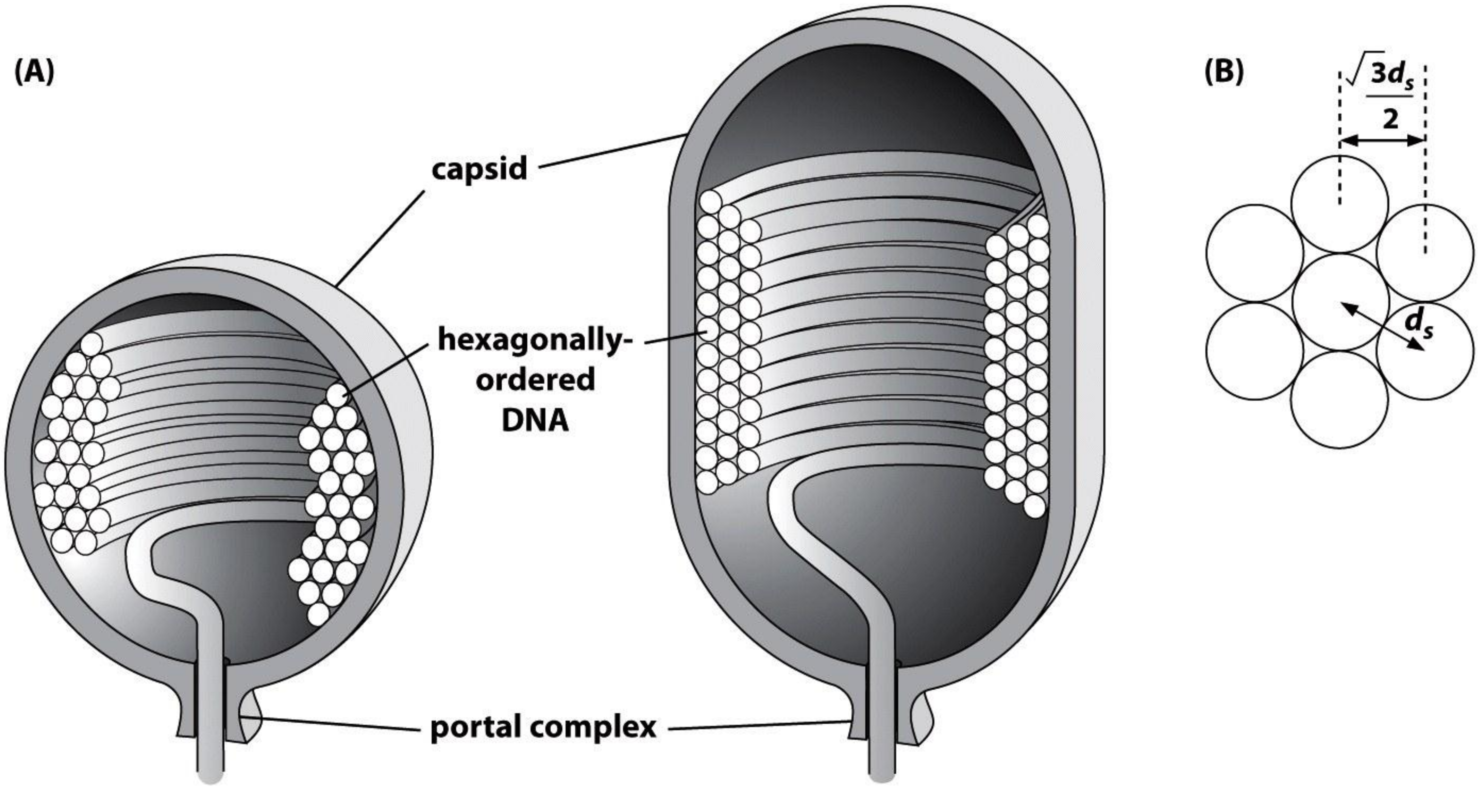
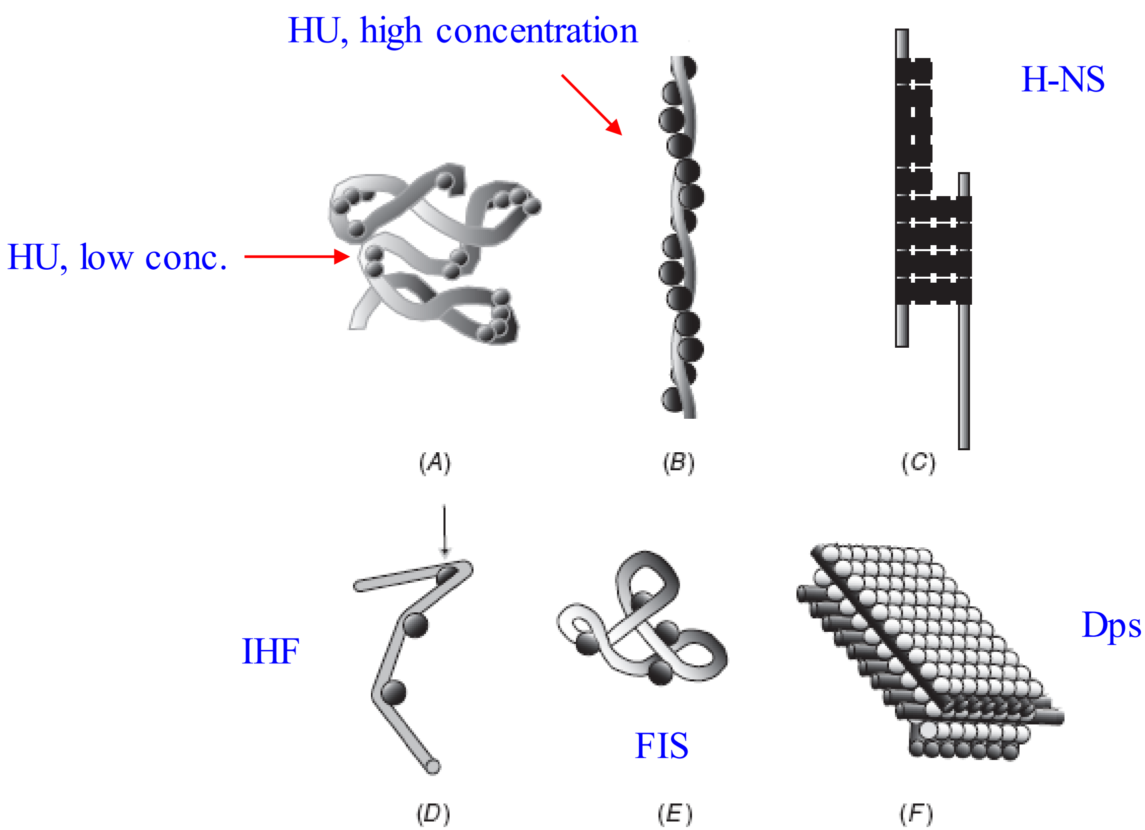


Figure 10.15 Physical Biology of the Cell (© Garland Science 2009)

Bacteria: single DNA is packed –without confining walls- in < 10% of bacterial volume – need attractions!

1. DNA is packaged by about a dozen of nucleoid-associated proteins that bend and twist it



2. Topology: bacterial DNA is circular –

conserved linking number   Lk = # of turns of double helix

Native linking number of DNA:

$$Lk_0 = \frac{\textit{length of DNA}}{\textit{helix repeat length}\ (3.4nm)} = \frac{N_{bp}}{10.4}$$

Topology-changing enzymes (gyrases, topoisomerases) can cut one DNA strand, overwind ($Lk > Lk_0$) or unwind ($Lk < Lk_0$) it, and glue it together again.

Bacterial DNA is typically underwound

$$\frac{Lk - Lk_0}{Lk_0} = -0.06$$

(this destabilizes the double helix – promotes recognition and reactivity of exposed bases?)

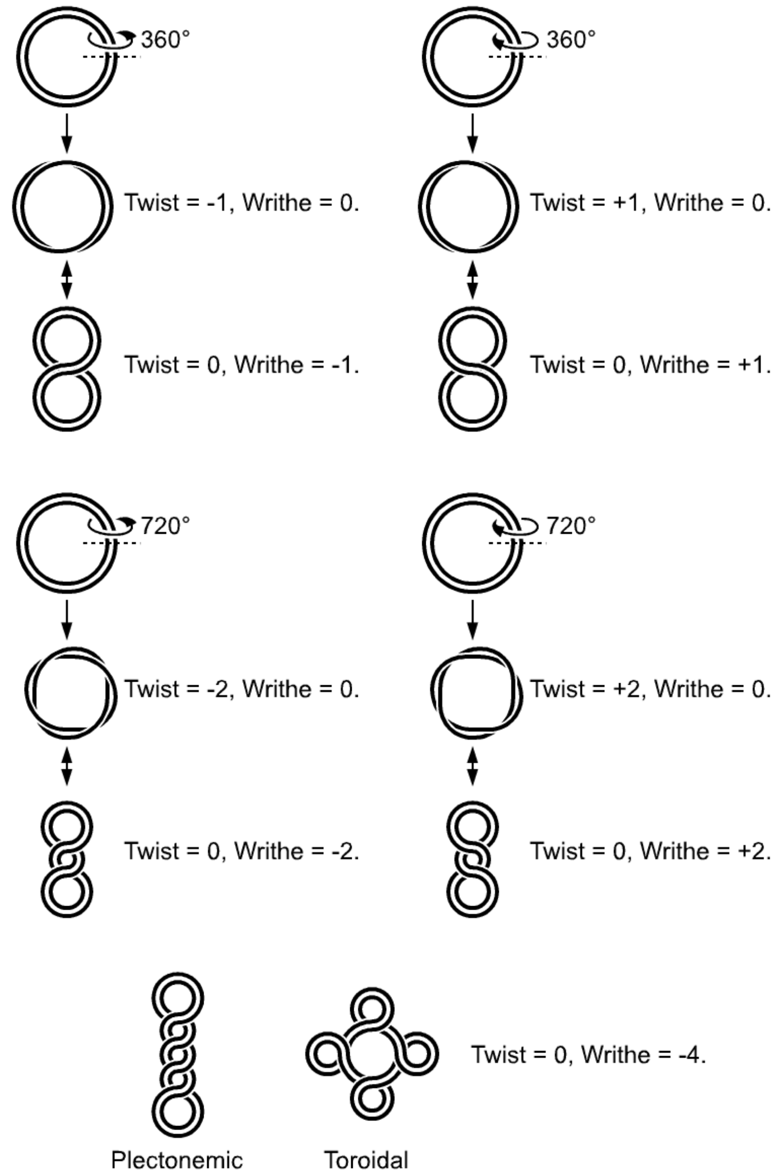
Linking number can be decomposed into twist and writhe:

$$L_k = Tw + Wr$$

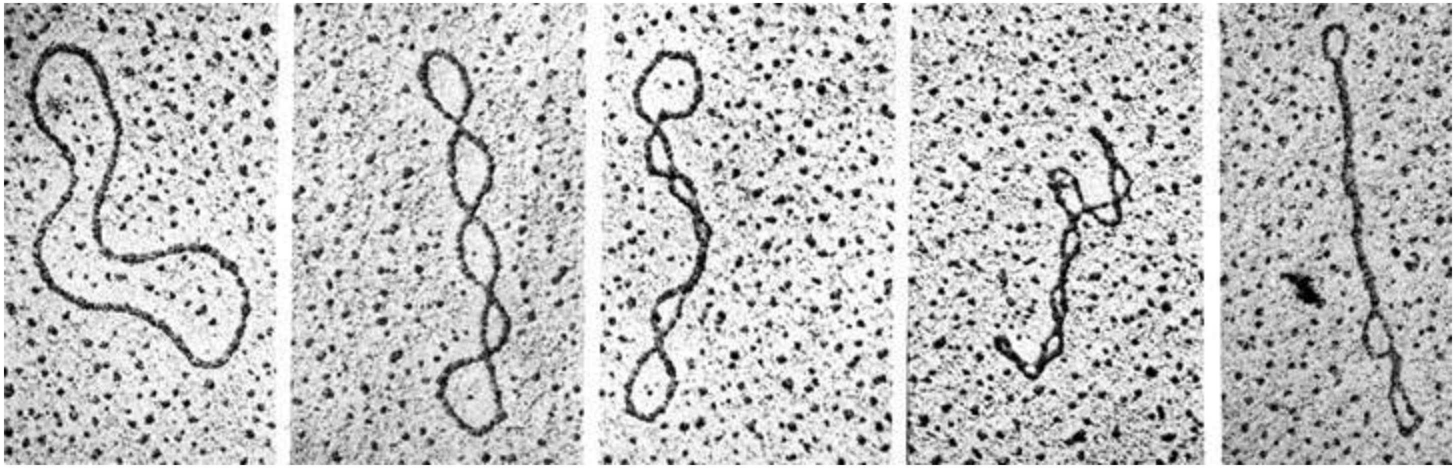
As there is energy penalty for twist

$$E_{tw}/kT = \frac{l_T}{2L} Tw^2$$

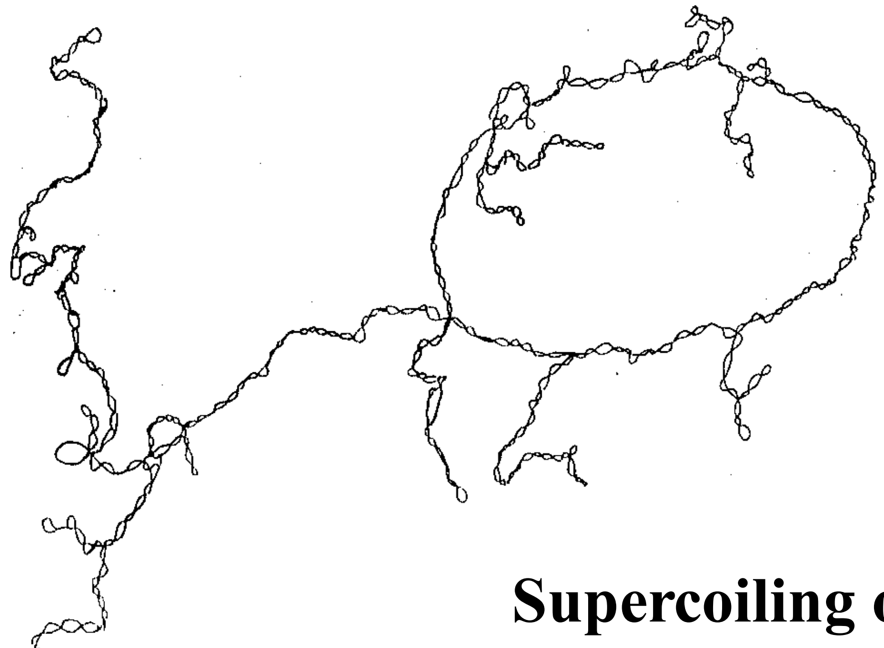
but no direct penalty for writhe, over/underwinding will generate high writhe configurations (supercoils, plectonemes)



Plasmids form right-handed (-) supercoils

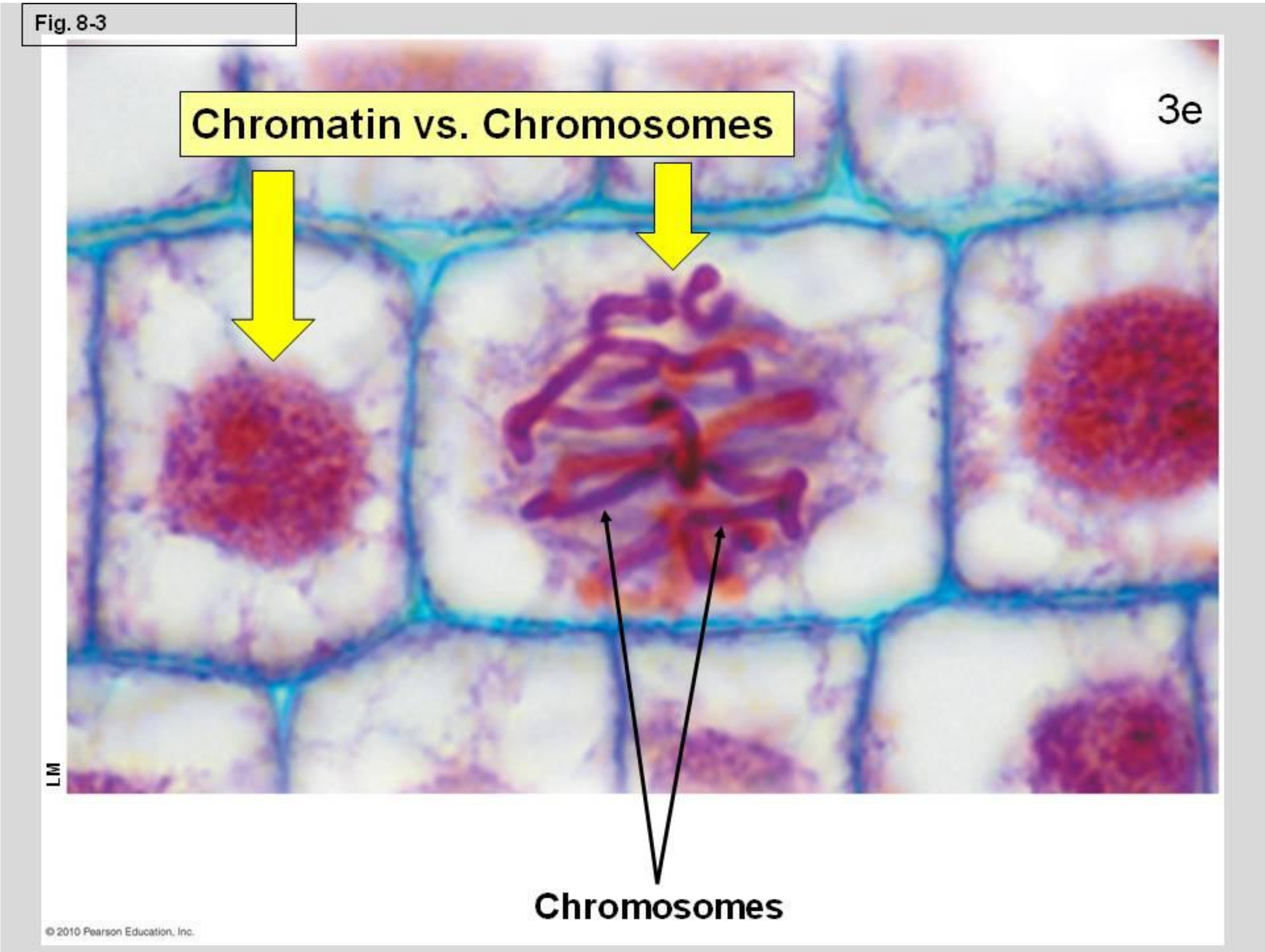


E.coli genome



Supercoiling of bacterial DNA helps with its packing?

Eukaryotic (human) cells: 46 DNA molecules inside nucleus



Chromosomes are segregated during mitosis– what about interphase chromatin?

Spaghetti soup "model" of chromatin?

Problem – numerous inter-chain entanglements for N > Ne (Ne=200)
-like a polymer melt!

Even a single DNA molecule confined in a nucleus ($R_G/R_{nucleus} > 10$) will be strongly self-entangled!

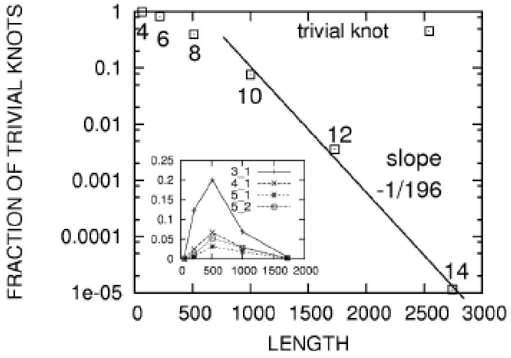


Fig. 2. Trivial knot probabilities for compact conformations of size $4\times4\times4$ to $14\times14\times14$. Inset shows the probabilities of the non-trivial knots 3_1 (trefoil), 4_1 (figure-eight), 5_1 (star), 5_2.

Lua et al, 2004

Solution I: entanglements and knots can be removed by topo II

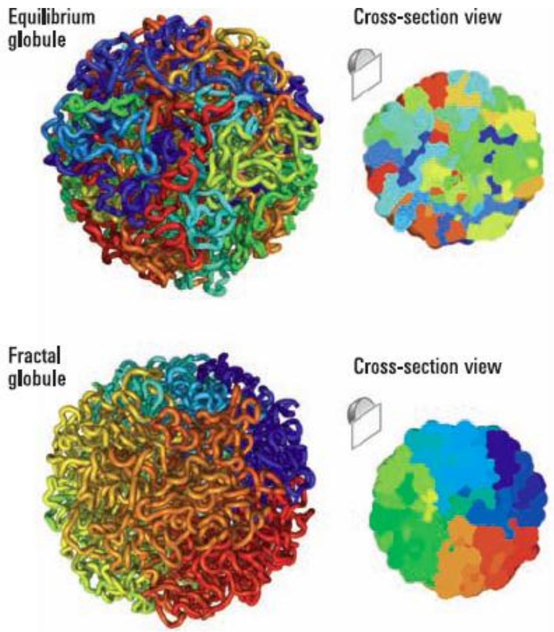
Sikorav and Janninck, C. R. Acad. Sci. Paris t. 316, serie II, p. 751, 1993

Solution II: DNA molecules are organized in crumpled globules and segregated in space

Grosberg et al, Europhys. Lett. **23**, 373, 1993

Crumpled (unknotted) globule: $d_f=3$

Equilibrium (knotted) globule: $d_f=2$



HiC experiments agree with crumpled/fractal globule:

$$R(s)=\text{const}\cdot s^{1/3}$$

Lieberman et al, *Science* **326**, 289 (2009)

Chromatin territories:

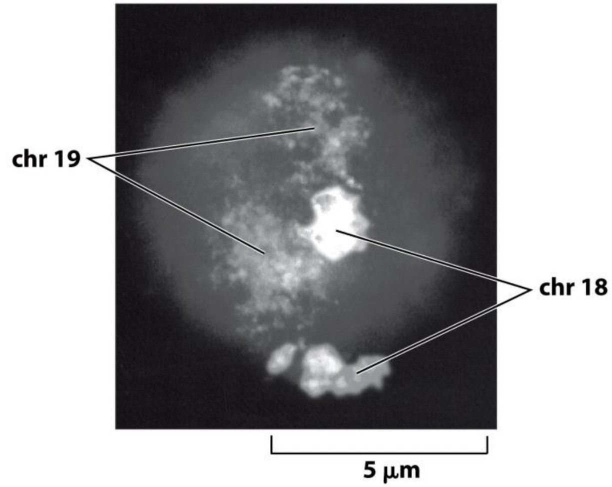
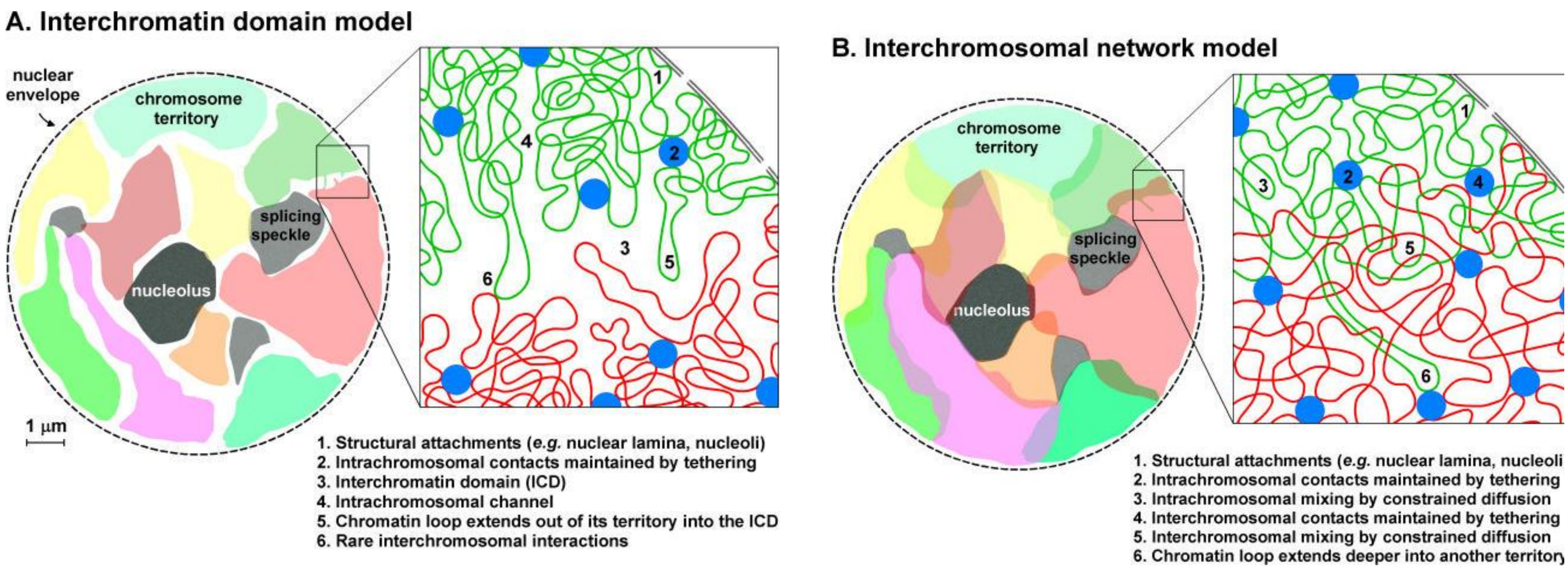


Figure 8.8 Physical Biology of the Cell (© Garland Science 2009)

Segregation vs interpenetration?



Small scale organization of chromatin

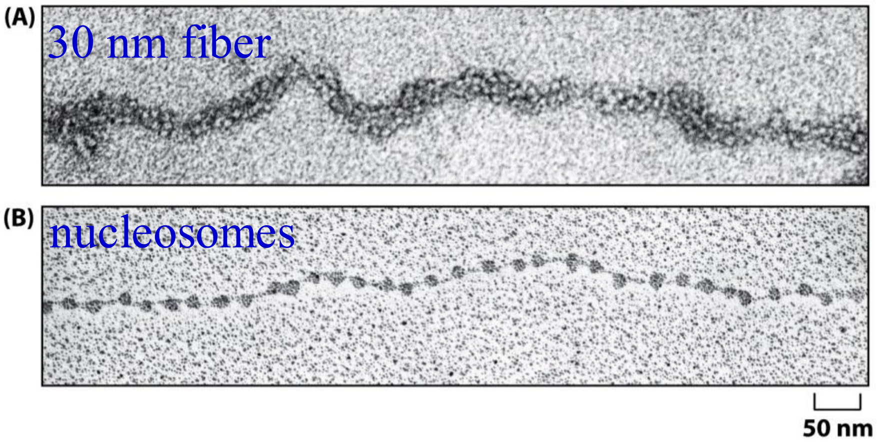


Figure 8.7 Physical Biology of the Cell (© Garland Science 2009)

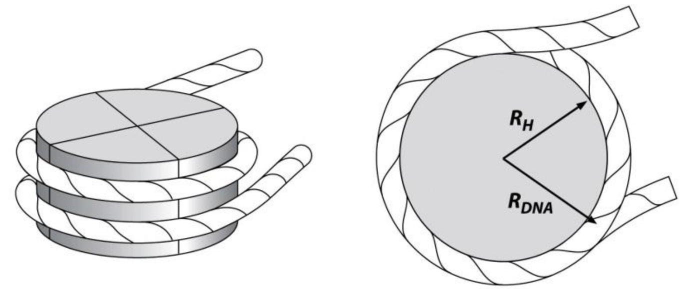


Figure 10.20c Physical Biology of the Cell (© Garland Science 2009)

Nucleosome chain– 147bp DNA wrapped around histone octamer with 50 bp linker

Number of nucleosomes in genome = $\frac{3 \cdot 10^9 bp}{200 bp} = 10^7$

Histone octamer: cylinder of r=3.5nm and h=6nm

Volume fraction of nucleosomes in nucleus: $\frac{\pi \cdot 3.5^2 \cdot 6 \cdot 10^7}{\frac{4\pi}{3} \cdot (5 \cdot 10^3)^3} = 0.5\ \%$

Very dilute!

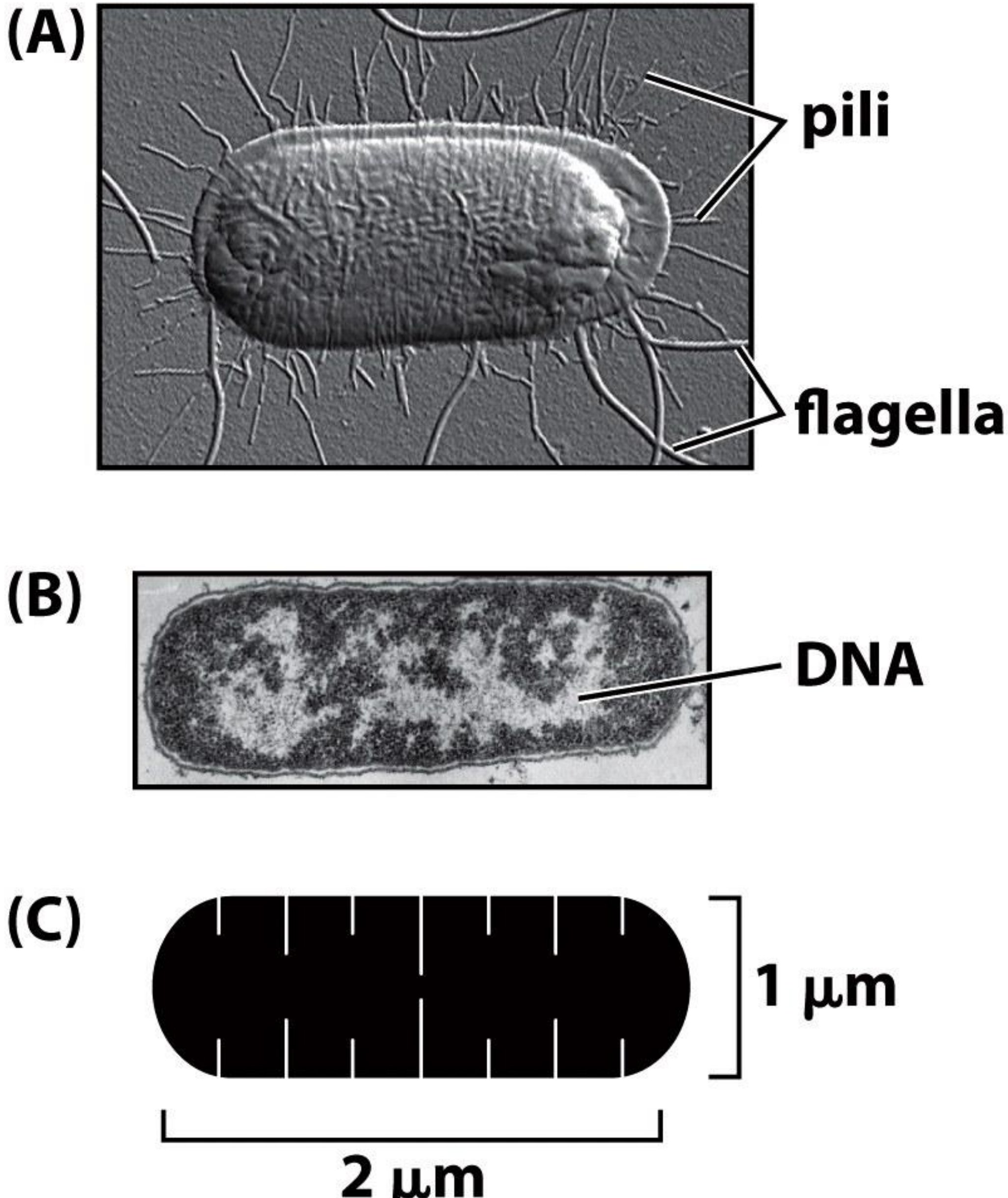


Figure 2.1 Physical Biology of the Cell (© Garland Science 2009)

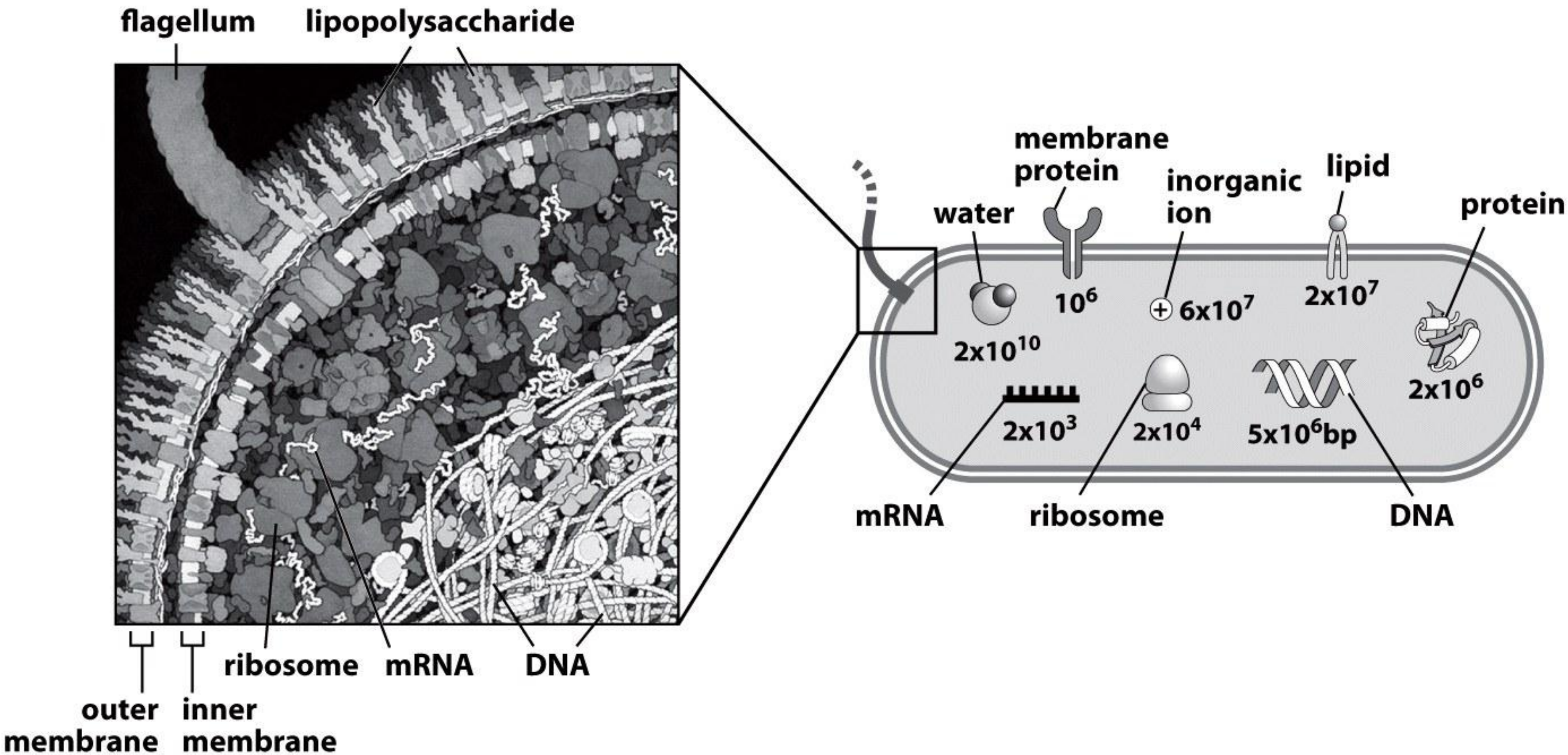


Figure 2.2 Physical Biology of the Cell (© Garland Science 2009)

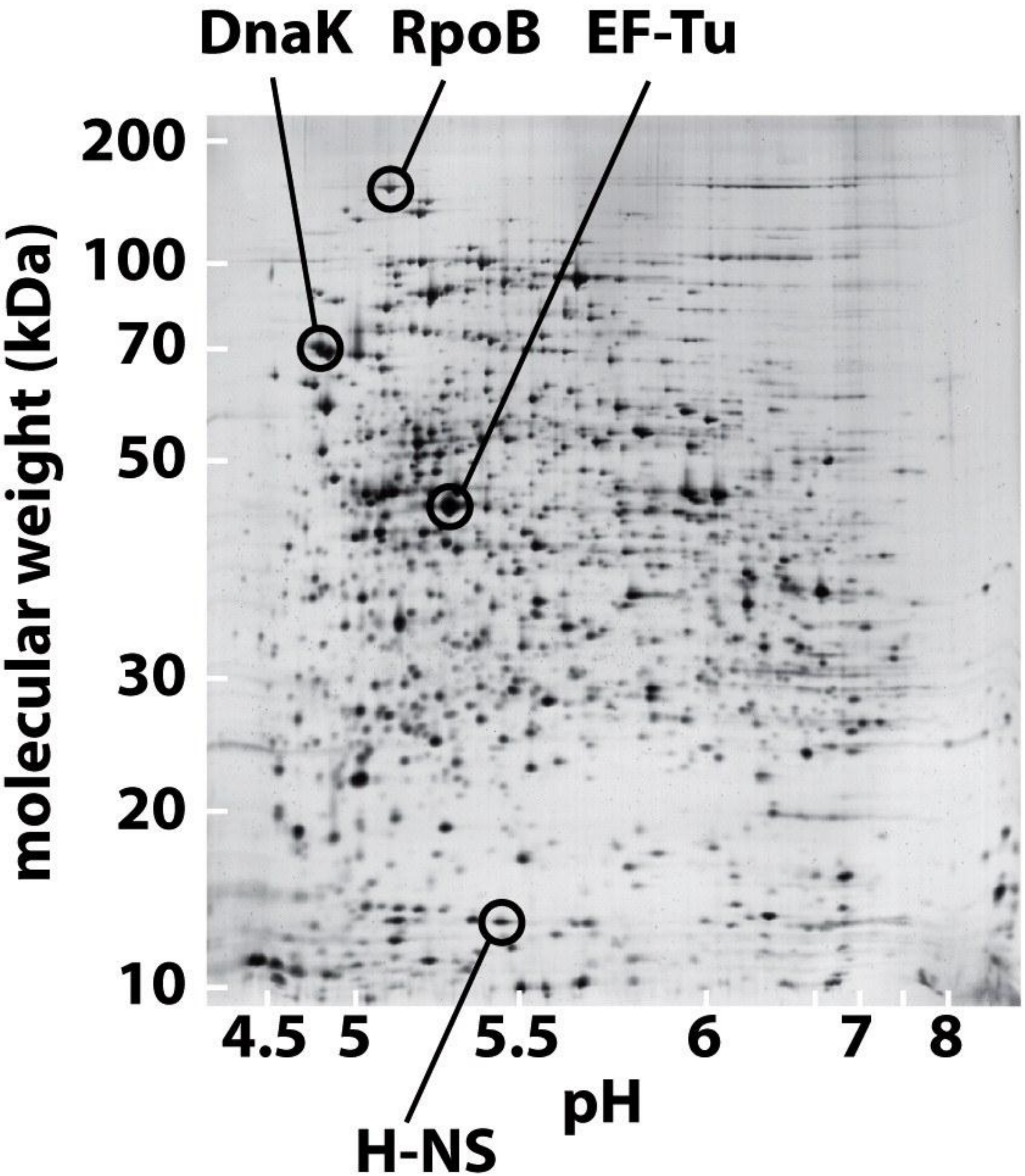


Figure 2.3 Physical Biology of the Cell (© Garland Science 2009)

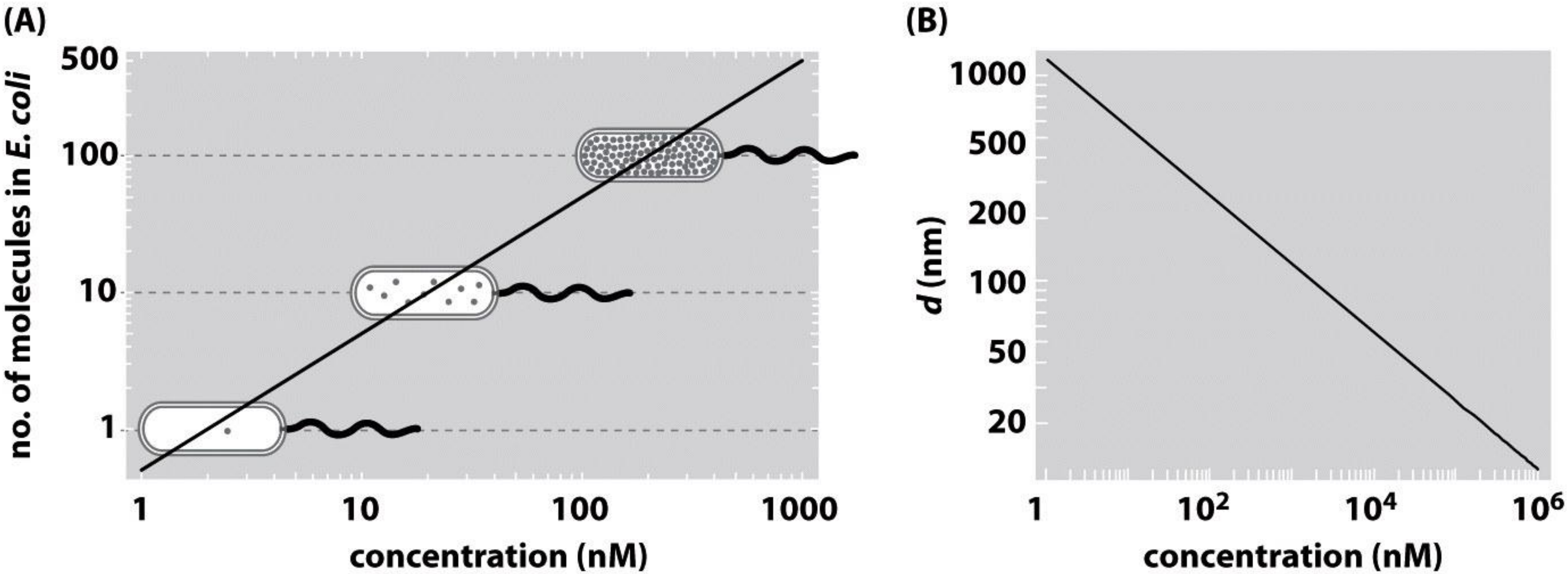


Figure 2.4 Physical Biology of the Cell (© Garland Science 2009)

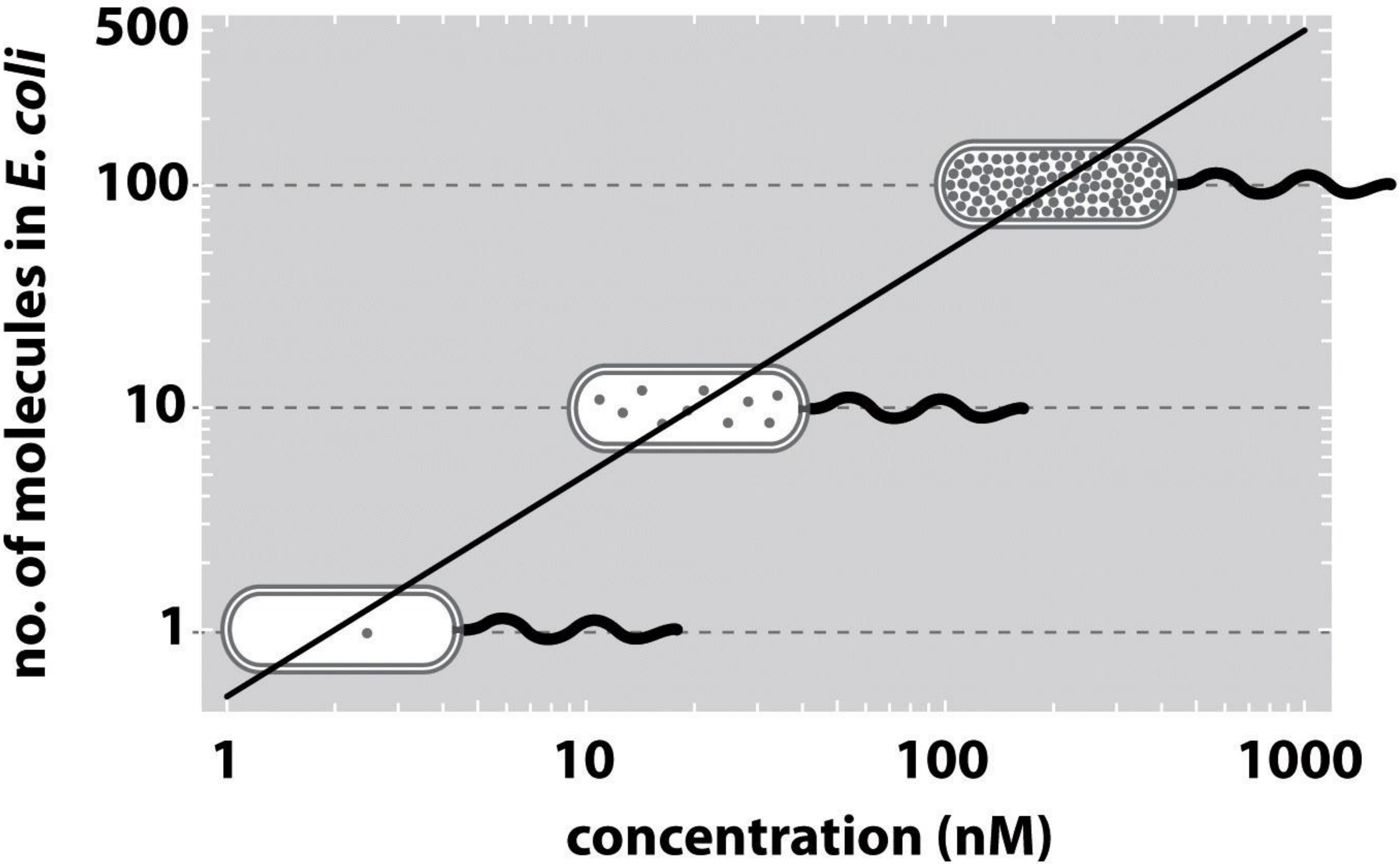


Figure 2.4a Physical Biology of the Cell (© Garland Science 2009)

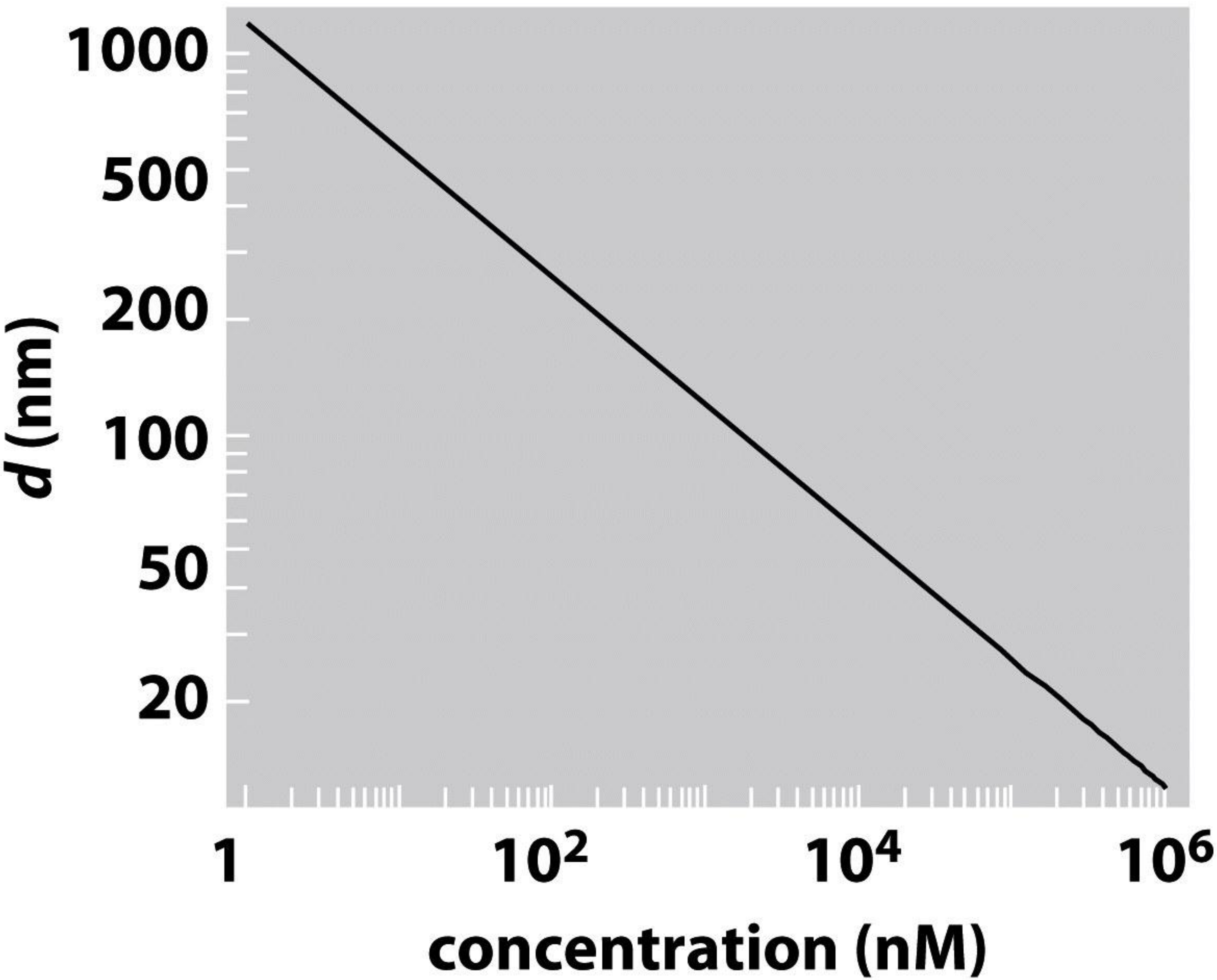


Figure 2.4b Physical Biology of the Cell (© Garland Science 2009)

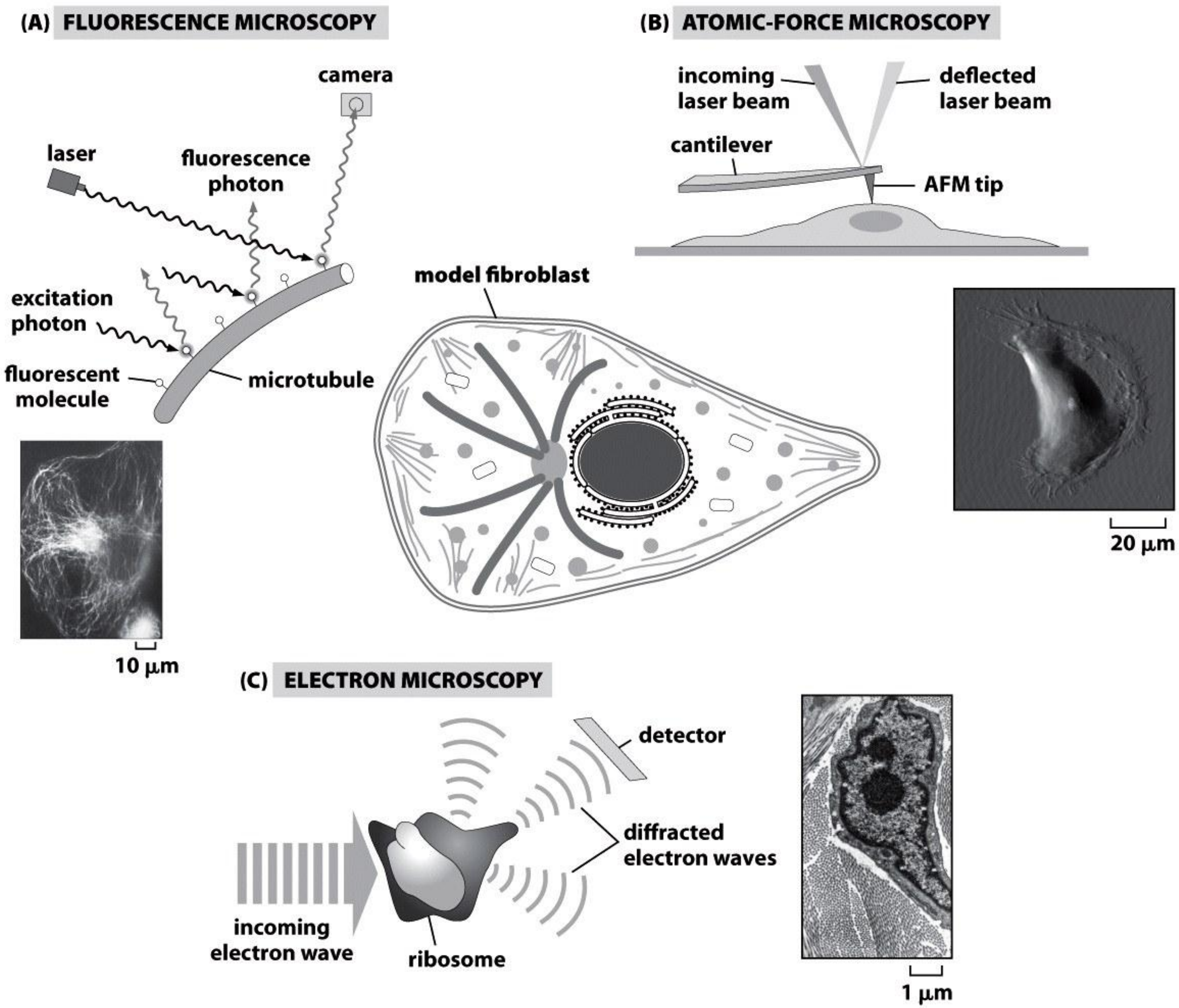


Figure 2.5 Physical Biology of the Cell (© Garland Science 2009)

FLUORESCENCE MICROSCOPY

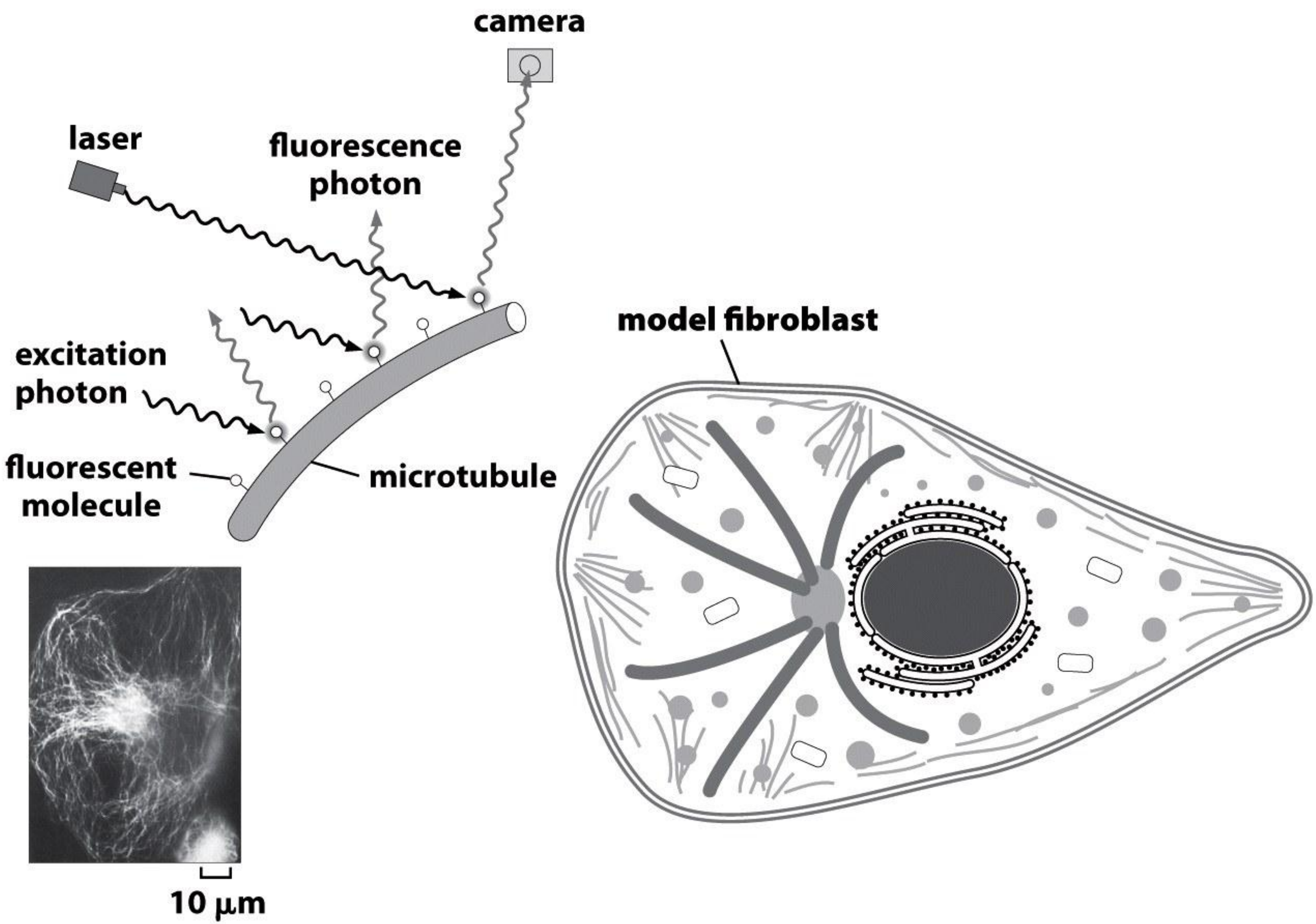


Figure 2.5a Physical Biology of the Cell (© Garland Science 2009)

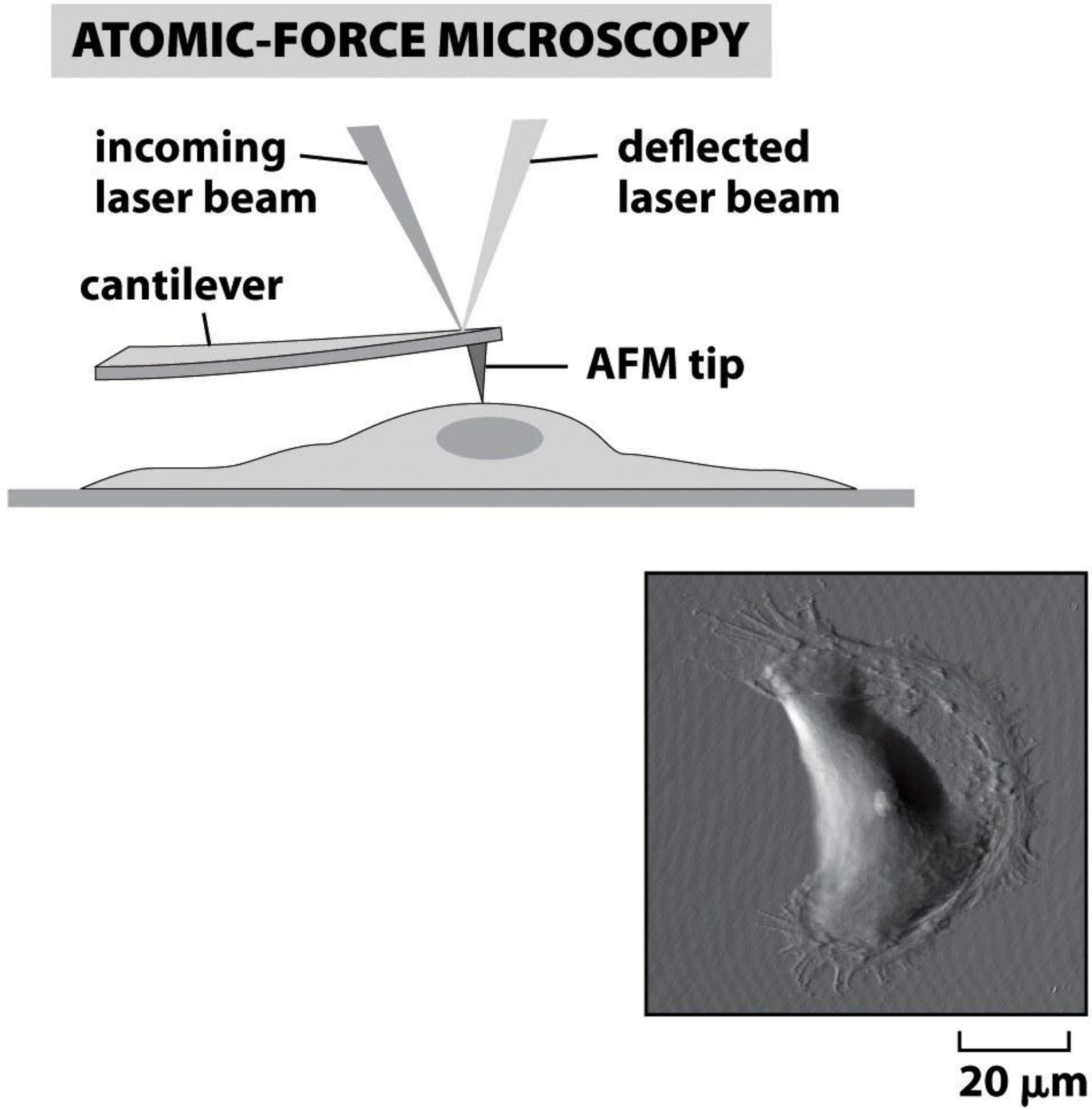


Figure 2.5b Physical Biology of the Cell (© Garland Science 2009)

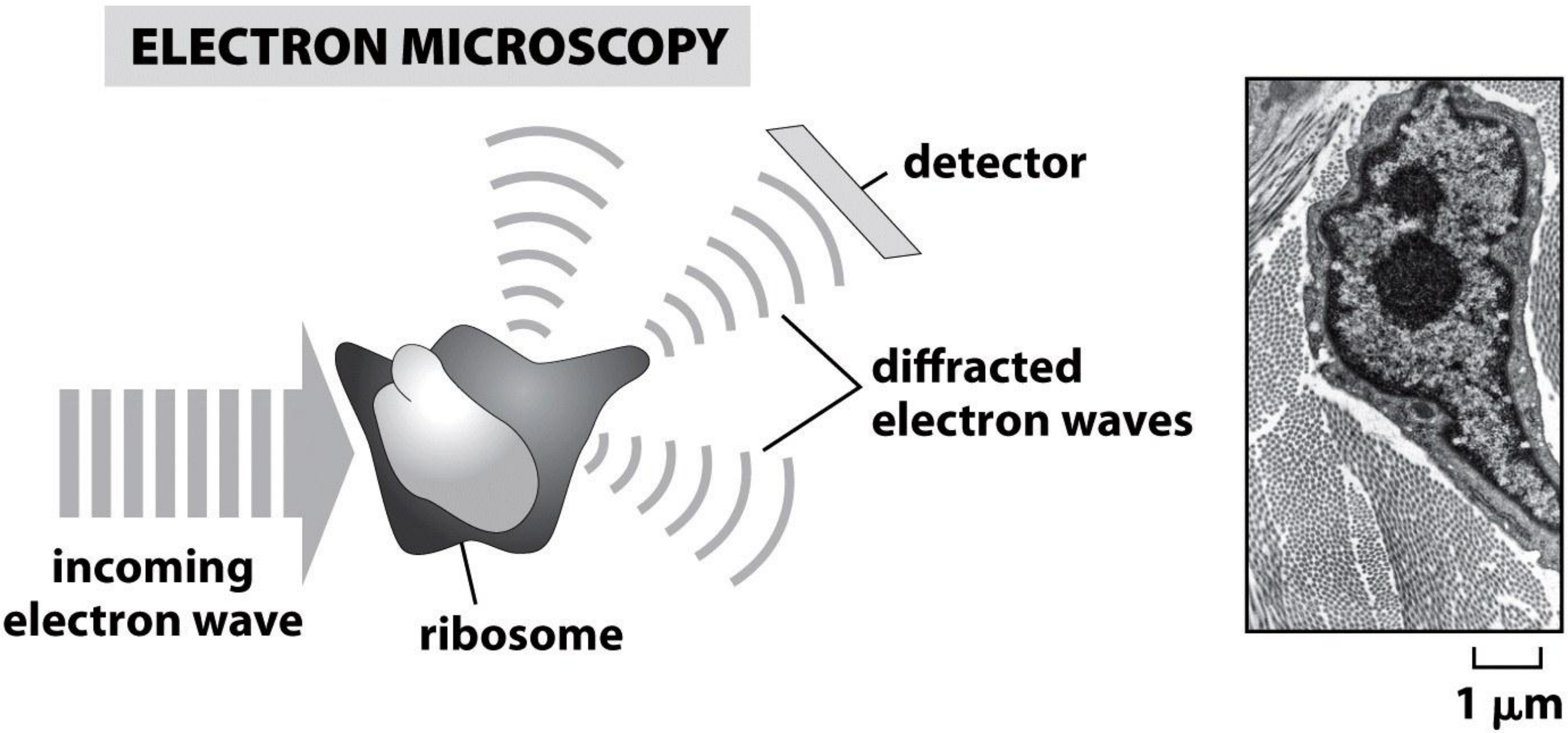


Figure 2.5c Physical Biology of the Cell (© Garland Science 2009)

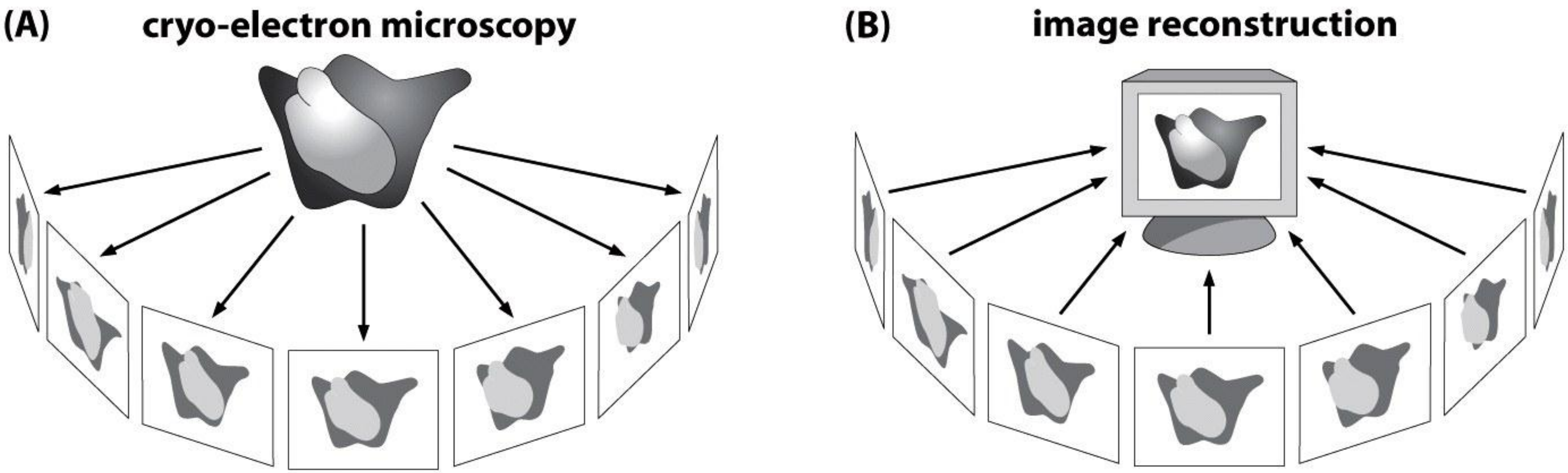


Figure 2.6 Physical Biology of the Cell (© Garland Science 2009)

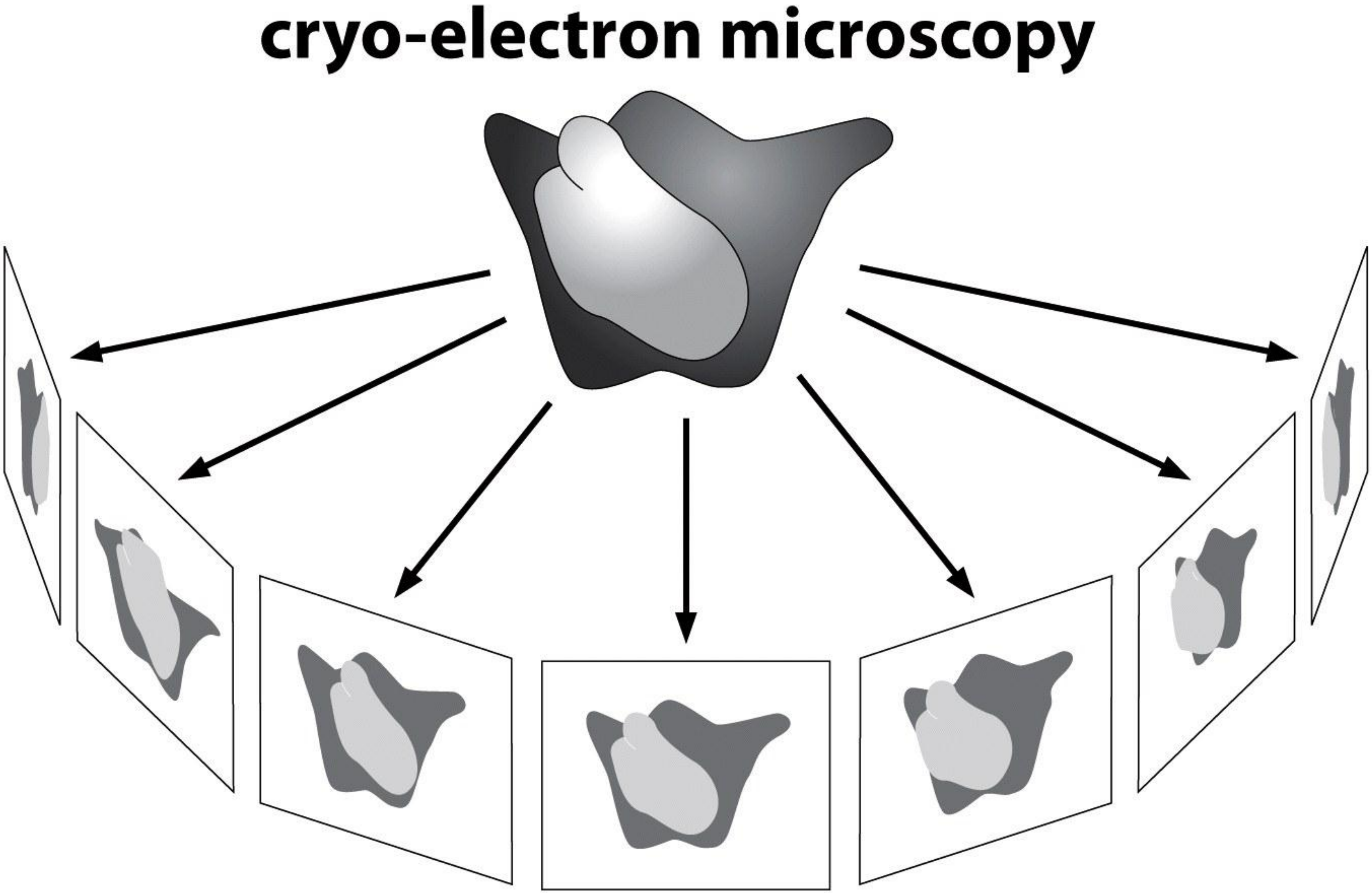


Figure 2.6a Physical Biology of the Cell (© Garland Science 2009)

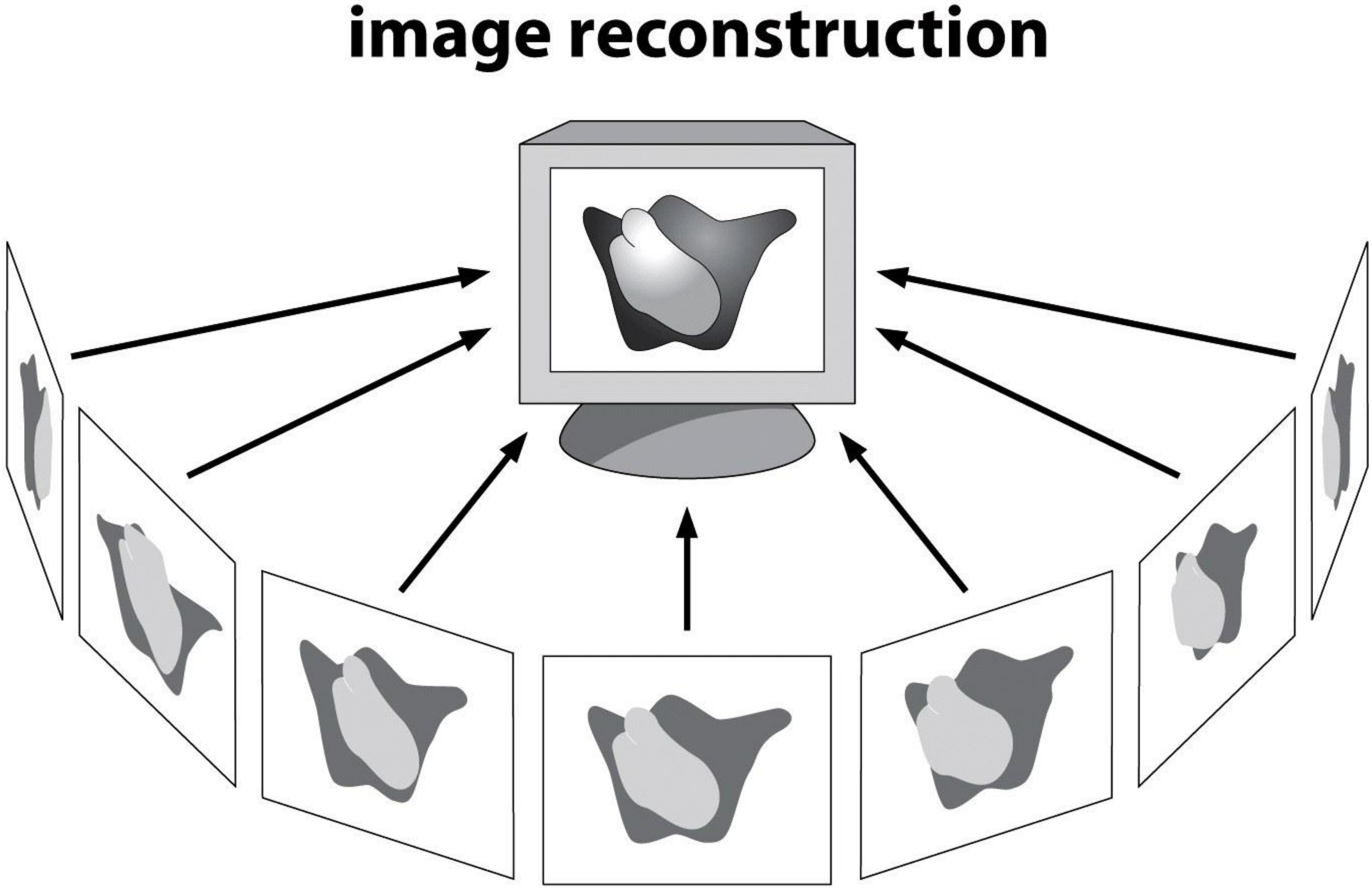


Figure 2.6b Physical Biology of the Cell (© Garland Science 2009)

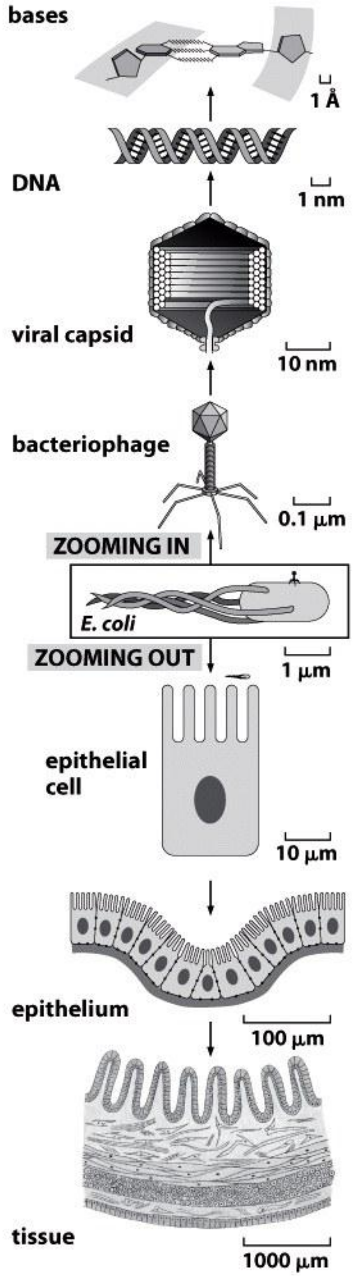


Figure 2.7 Physical Biology of the Cell (© Garland Science 2009)

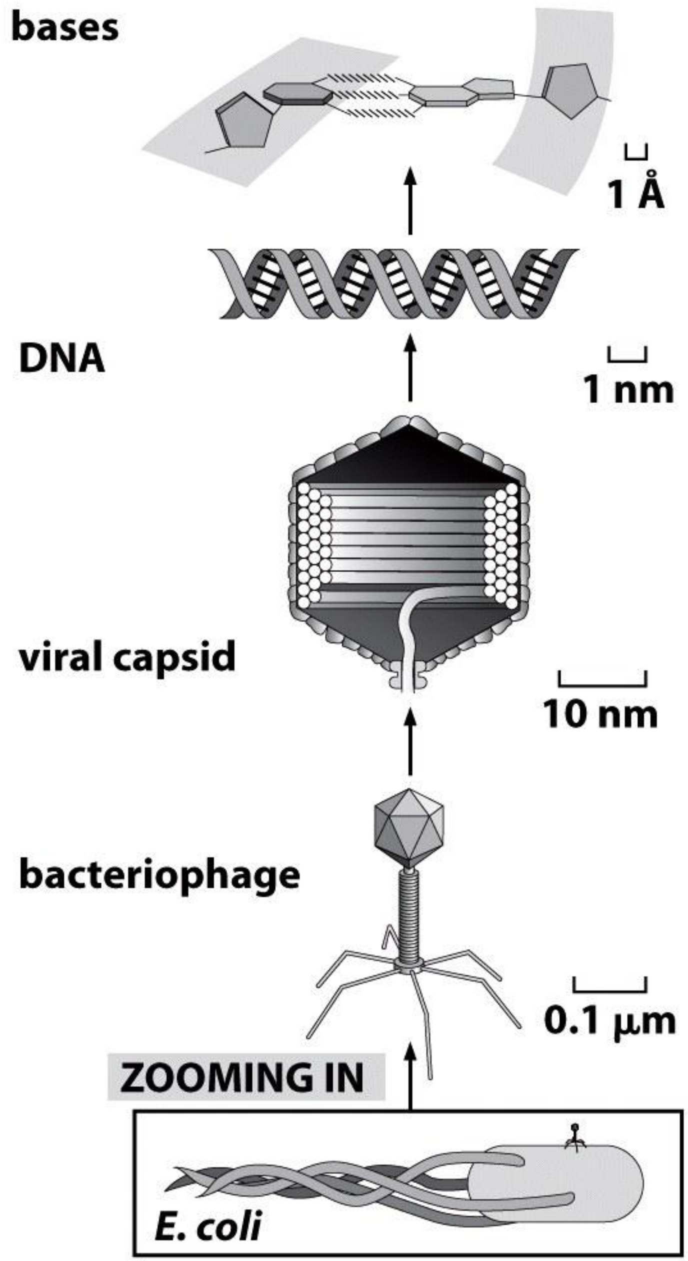


Figure 2.7 (part 1) Physical Biology of the Cell (© Garland Science 2009)

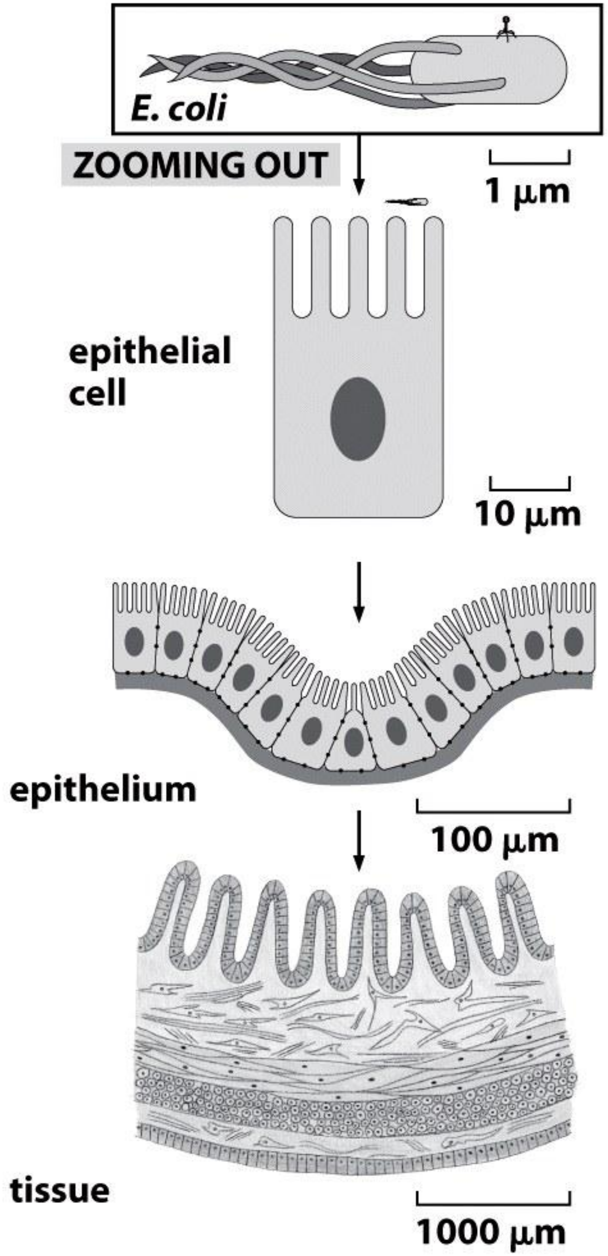


Figure 2.7 (part 2) Physical Biology of the Cell (© Garland Science 2009)

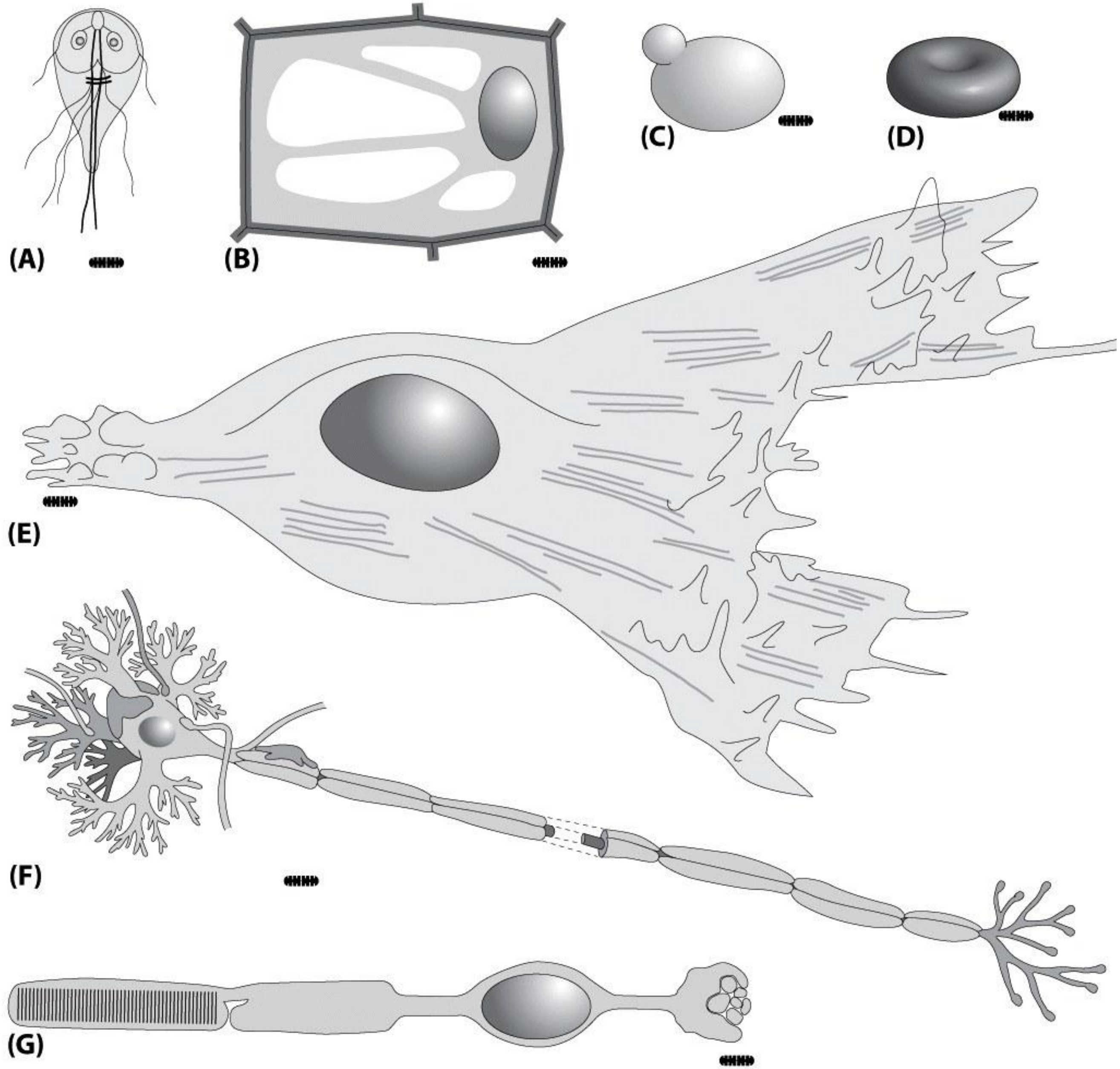


Figure 2.8 Physical Biology of the Cell (© Garland Science 2009)

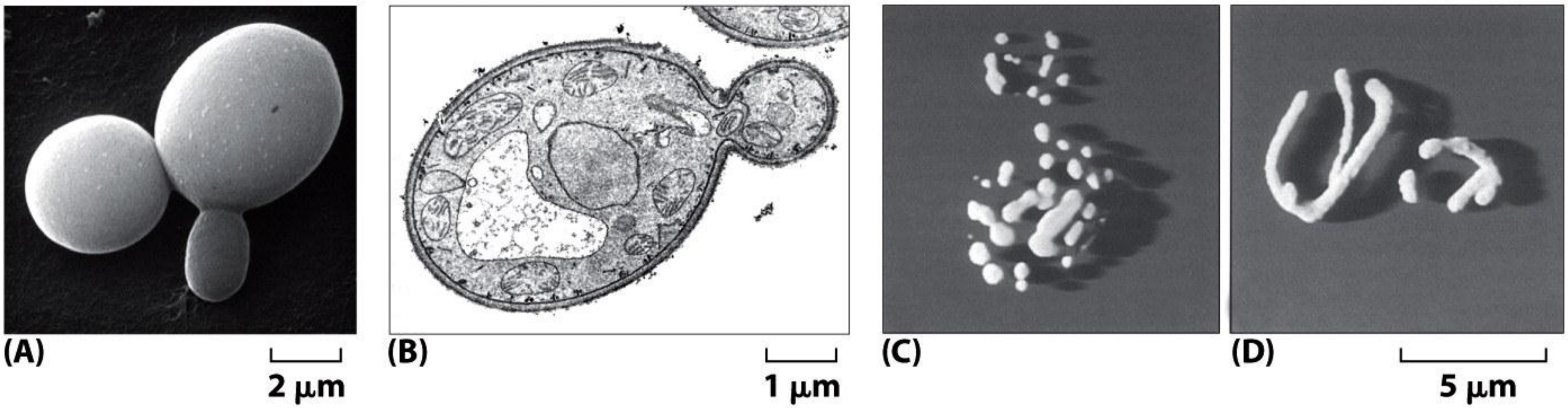


Figure 2.9 Physical Biology of the Cell (© Garland Science 2009)

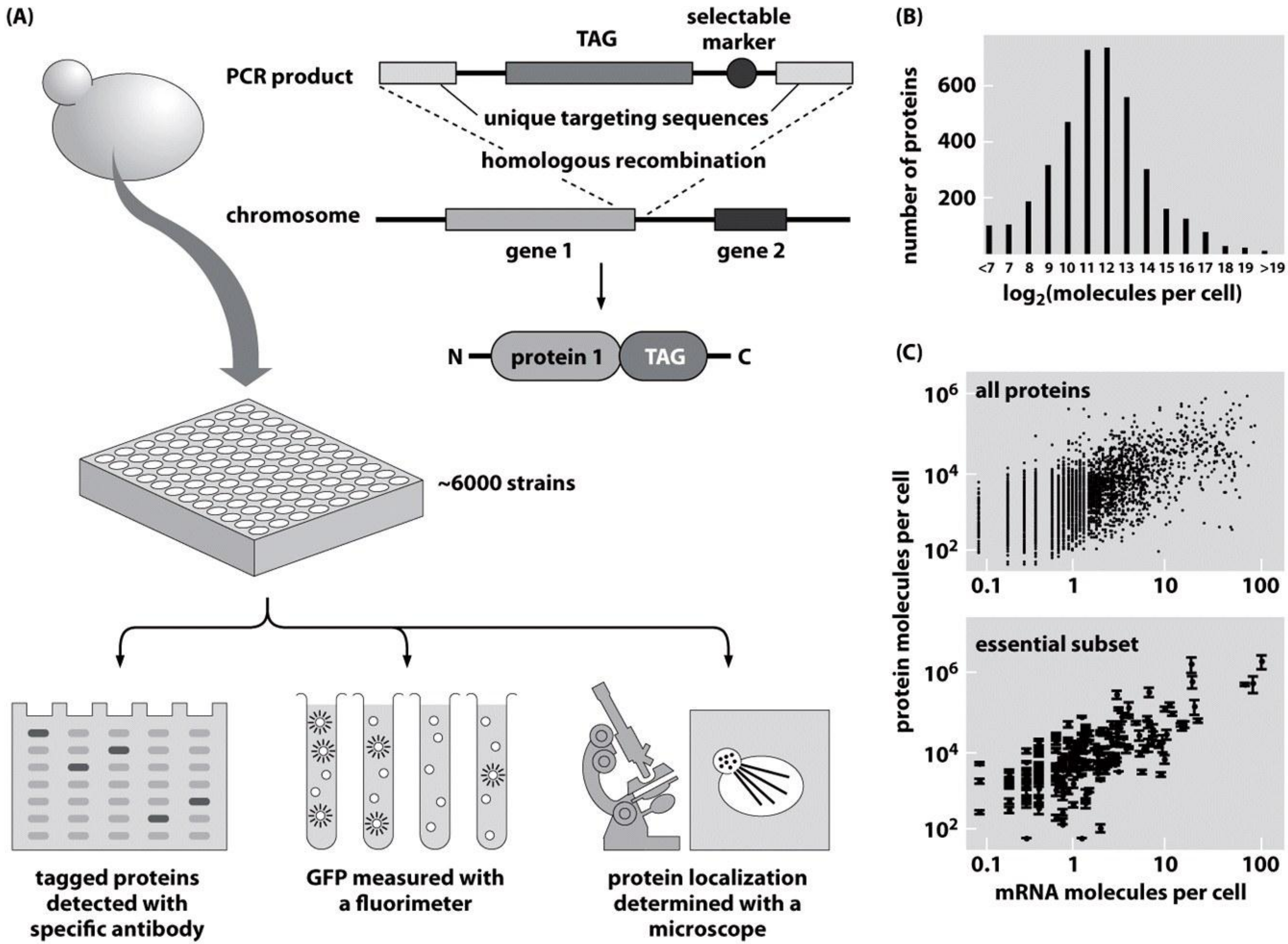


Figure 2.10 Physical Biology of the Cell (© Garland Science 2009)

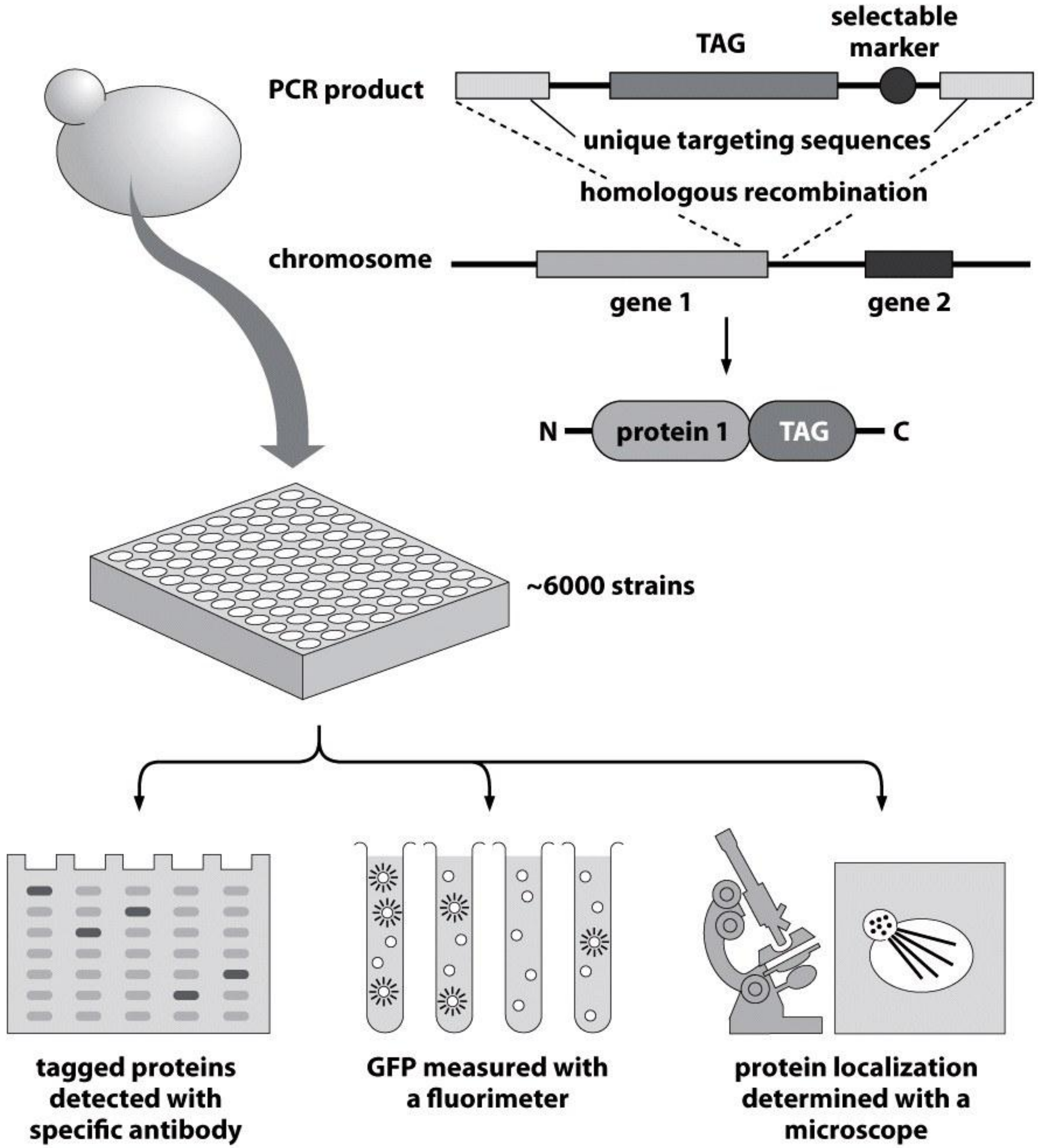


Figure 2.10a Physical Biology of the Cell (© Garland Science 2009)

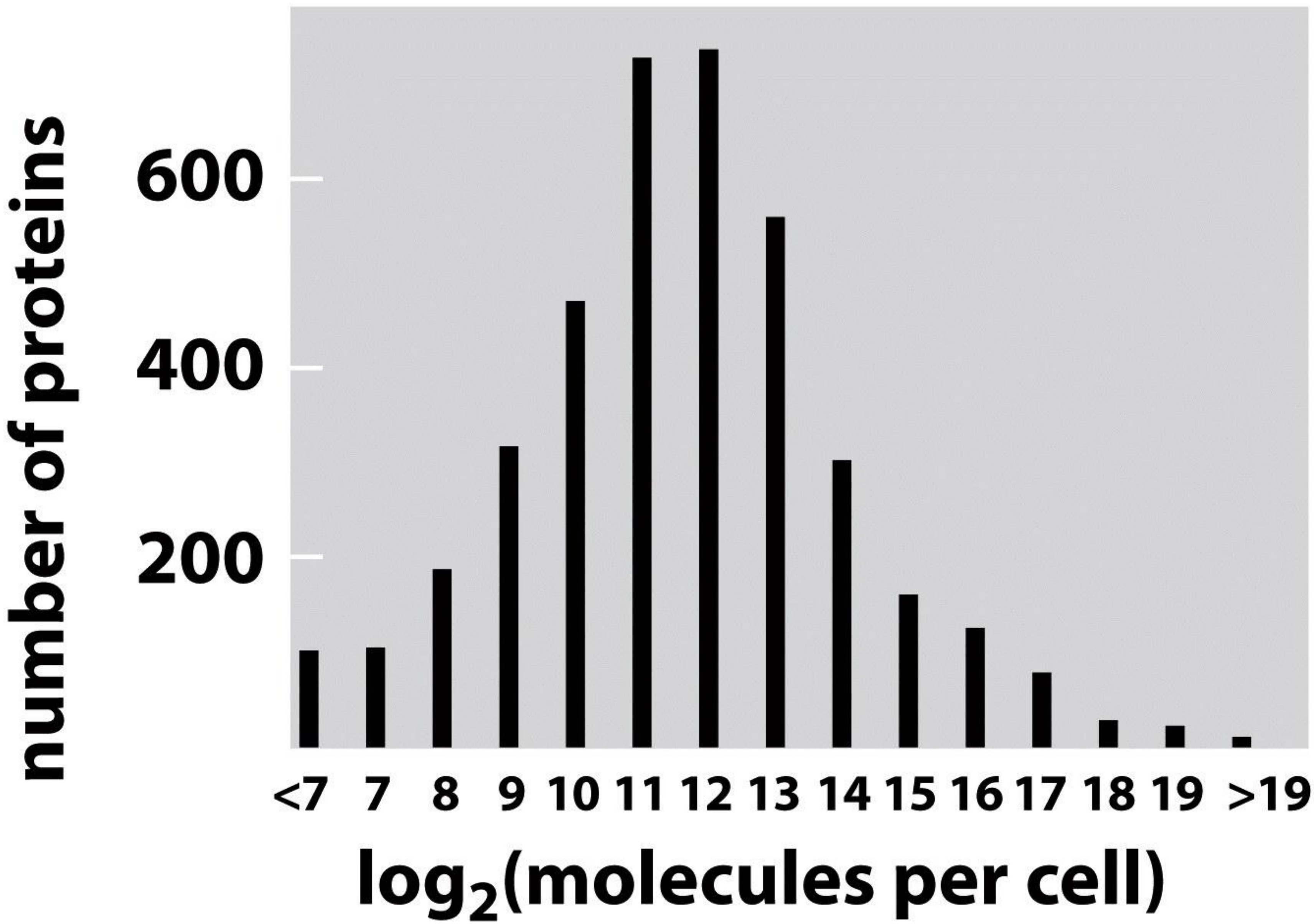


Figure 2.10b Physical Biology of the Cell (© Garland Science 2009)

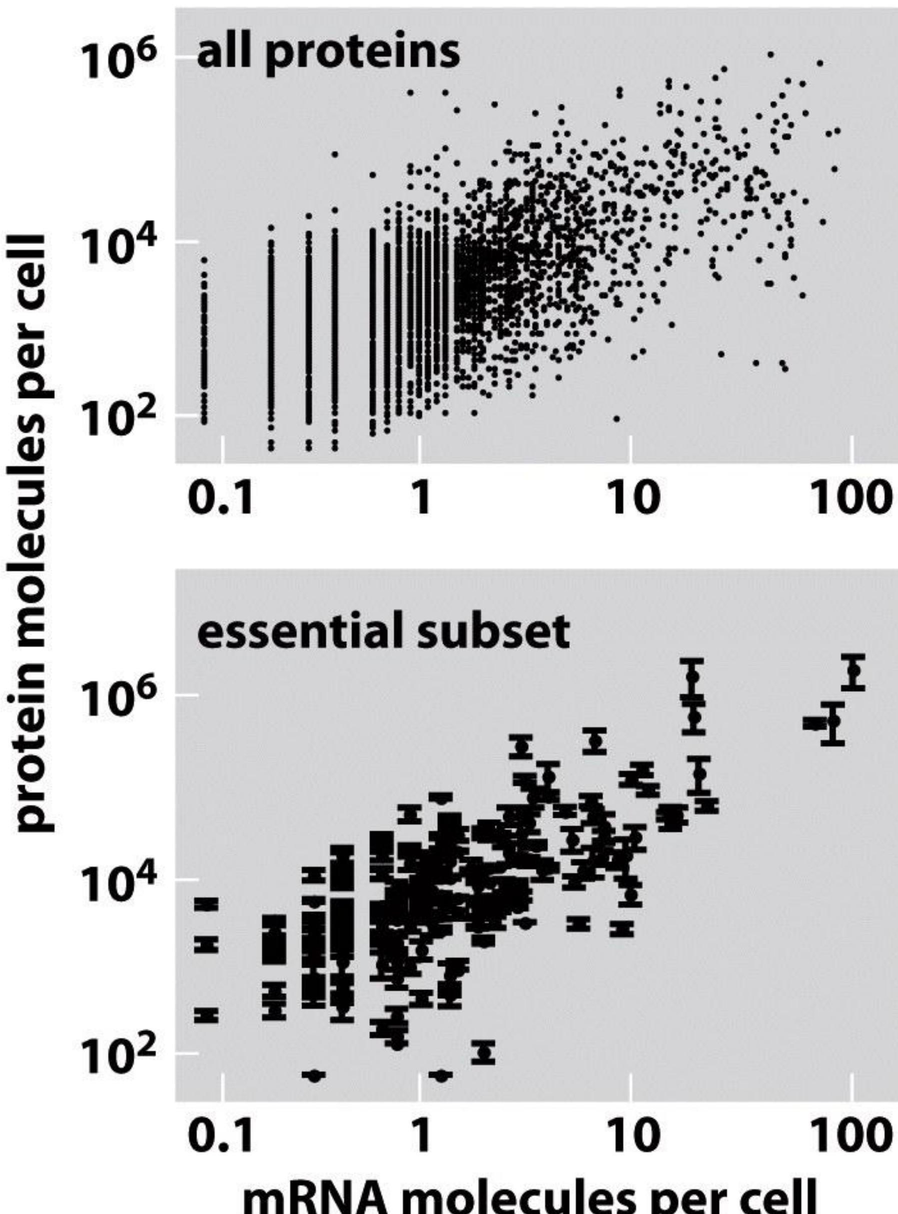


Figure 2.10c Physical Biology of the Cell (© Garland Science 2009)

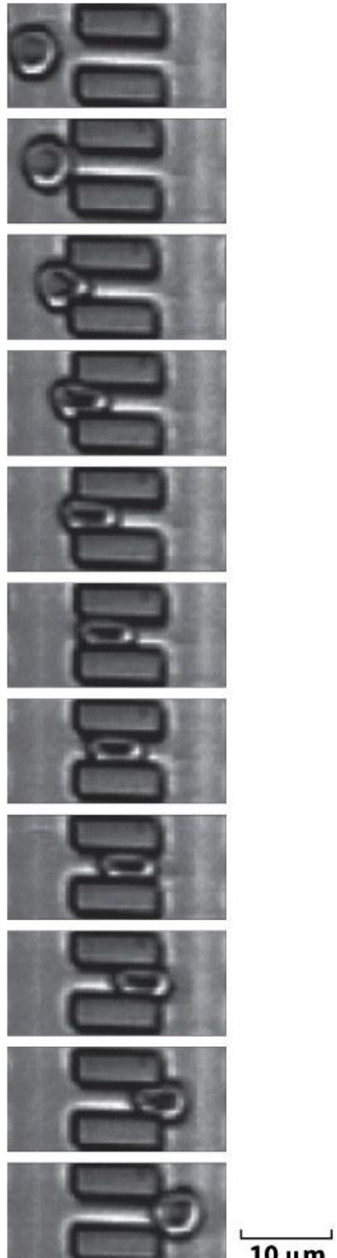


Figure 2.11 Physical Biology of the Cell (© Garland Science 2009)

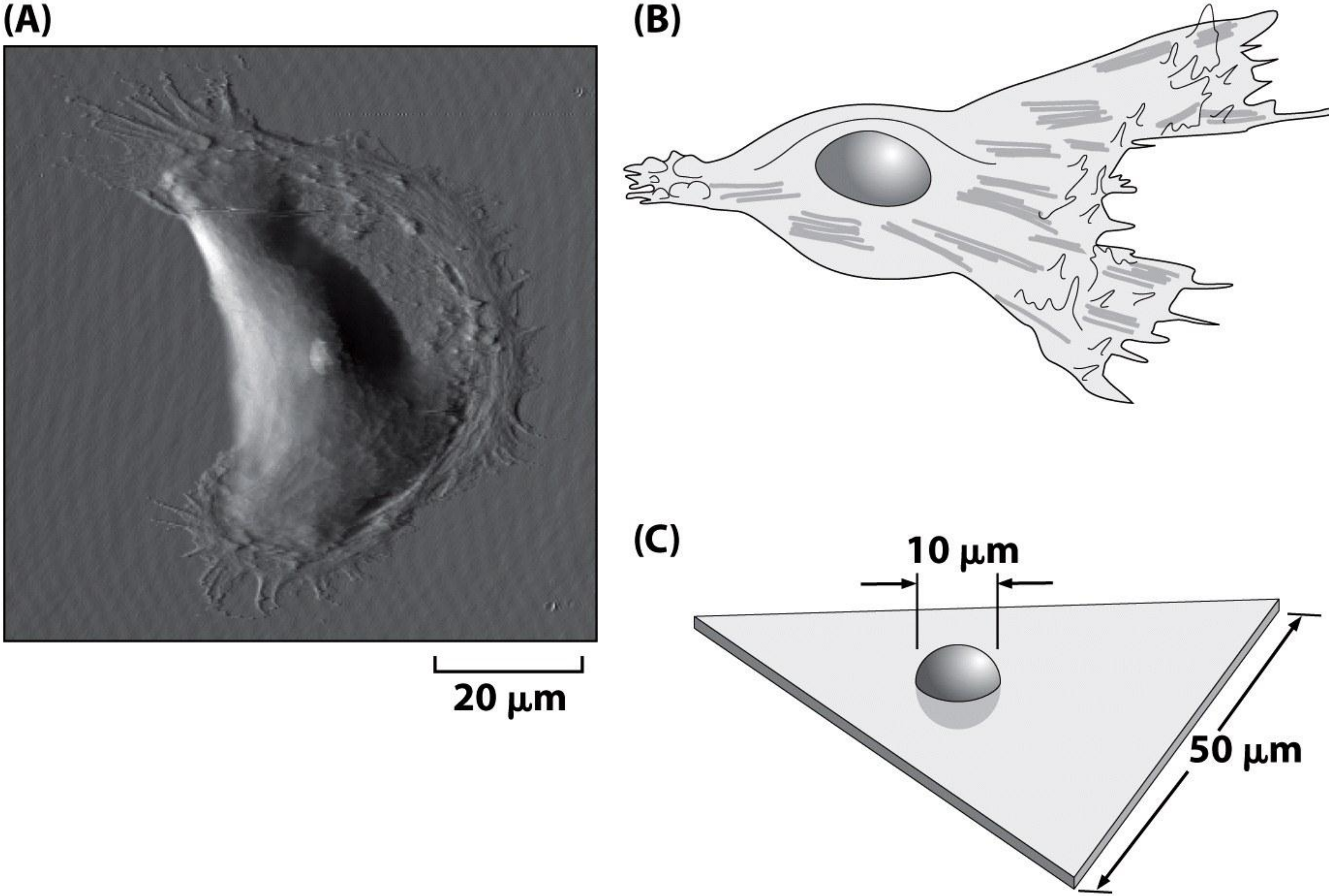


Figure 2.12 Physical Biology of the Cell (© Garland Science 2009)

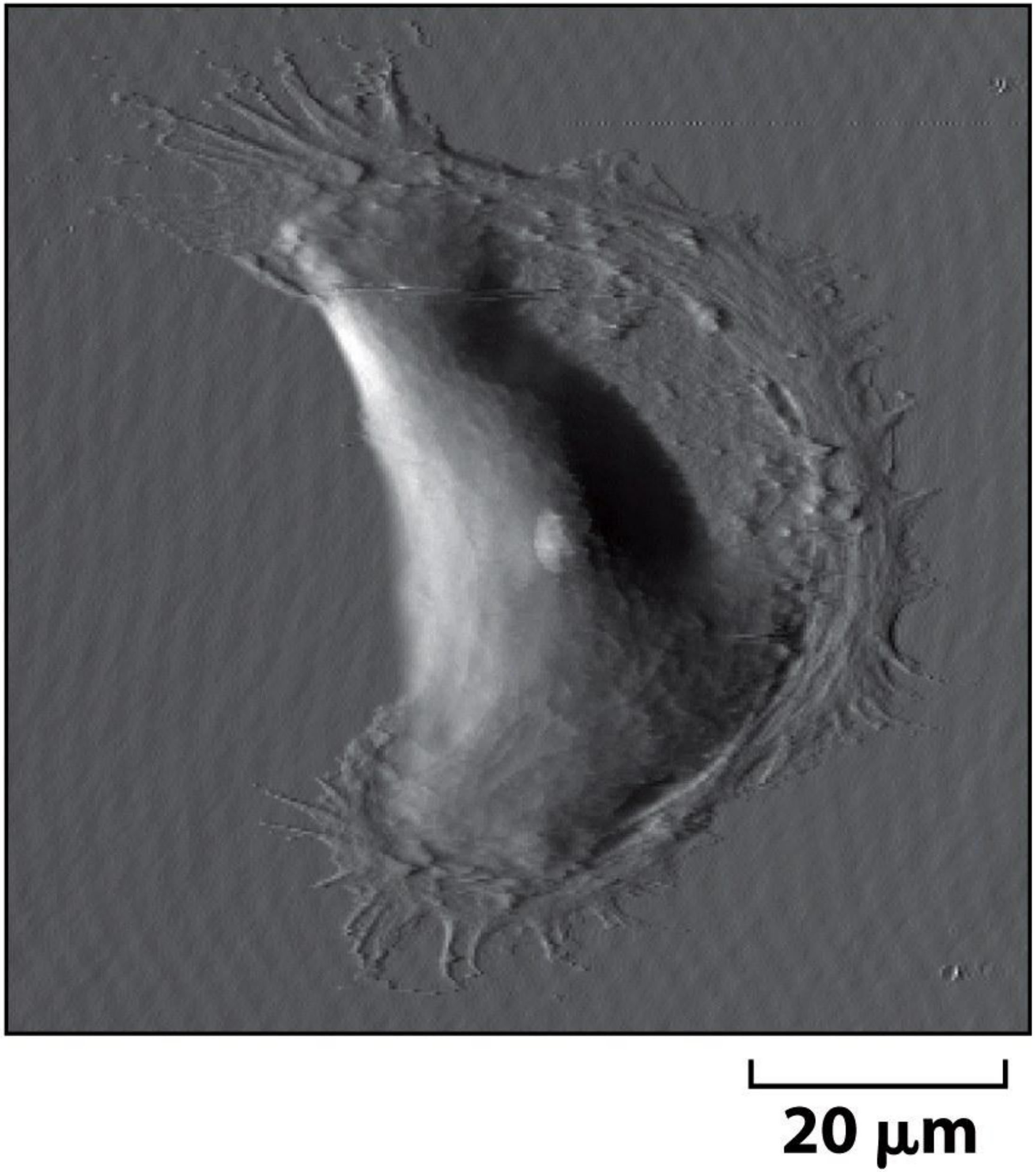


Figure 2.12a Physical Biology of the Cell (© Garland Science 2009)

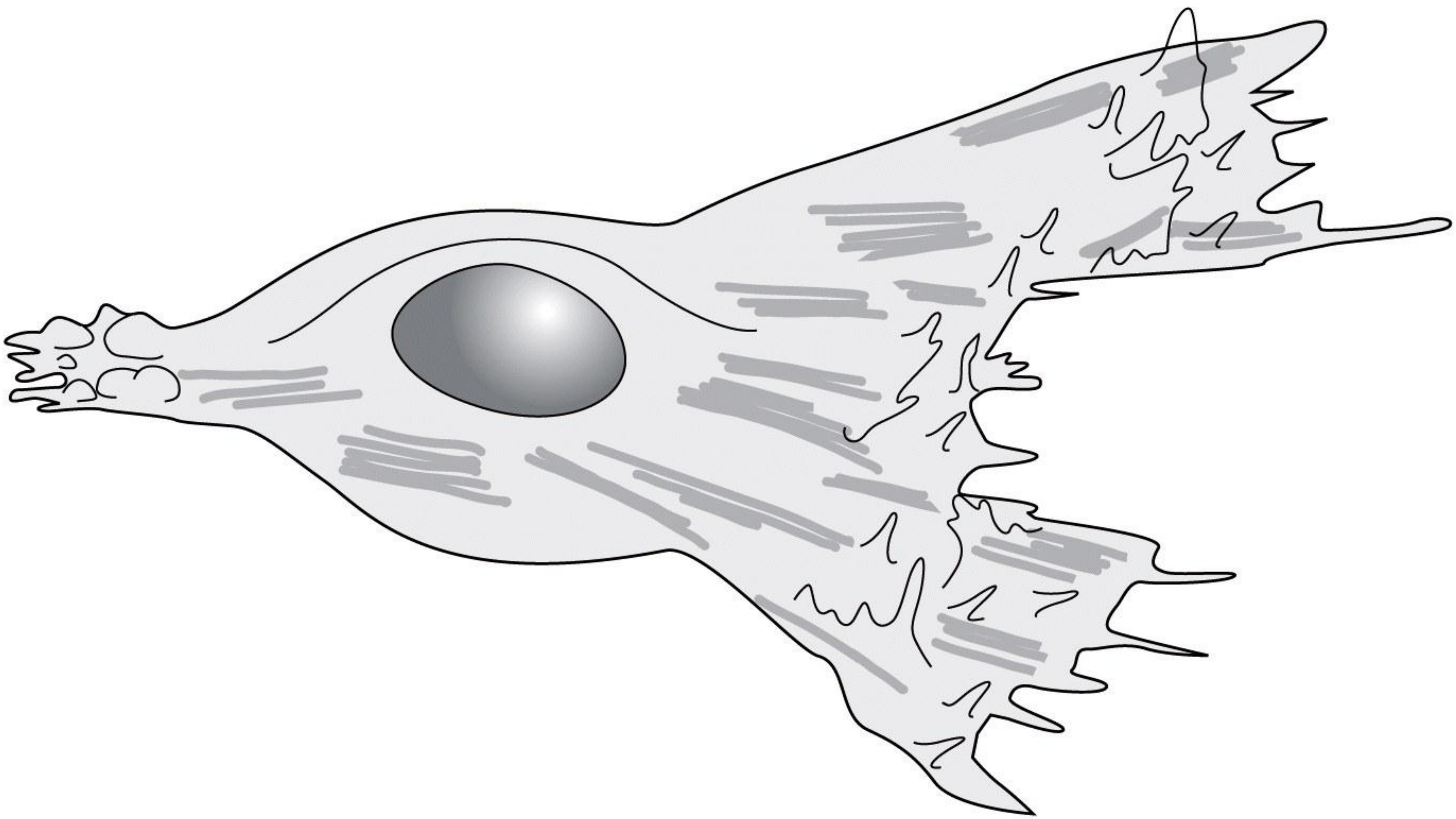


Figure 2.12b Physical Biology of the Cell (© Garland Science 2009)

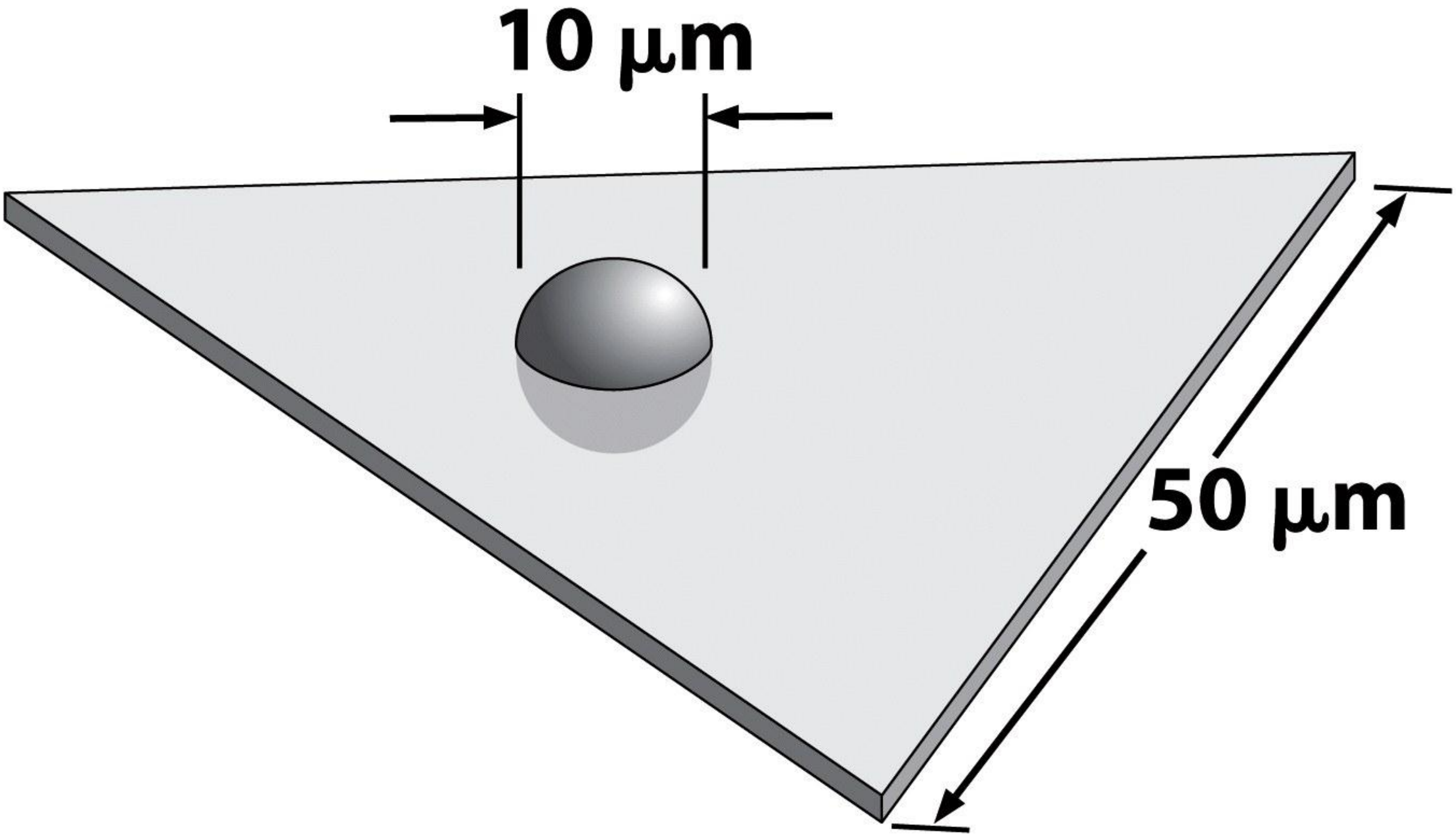


Figure 2.12c Physical Biology of the Cell (© Garland Science 2009)

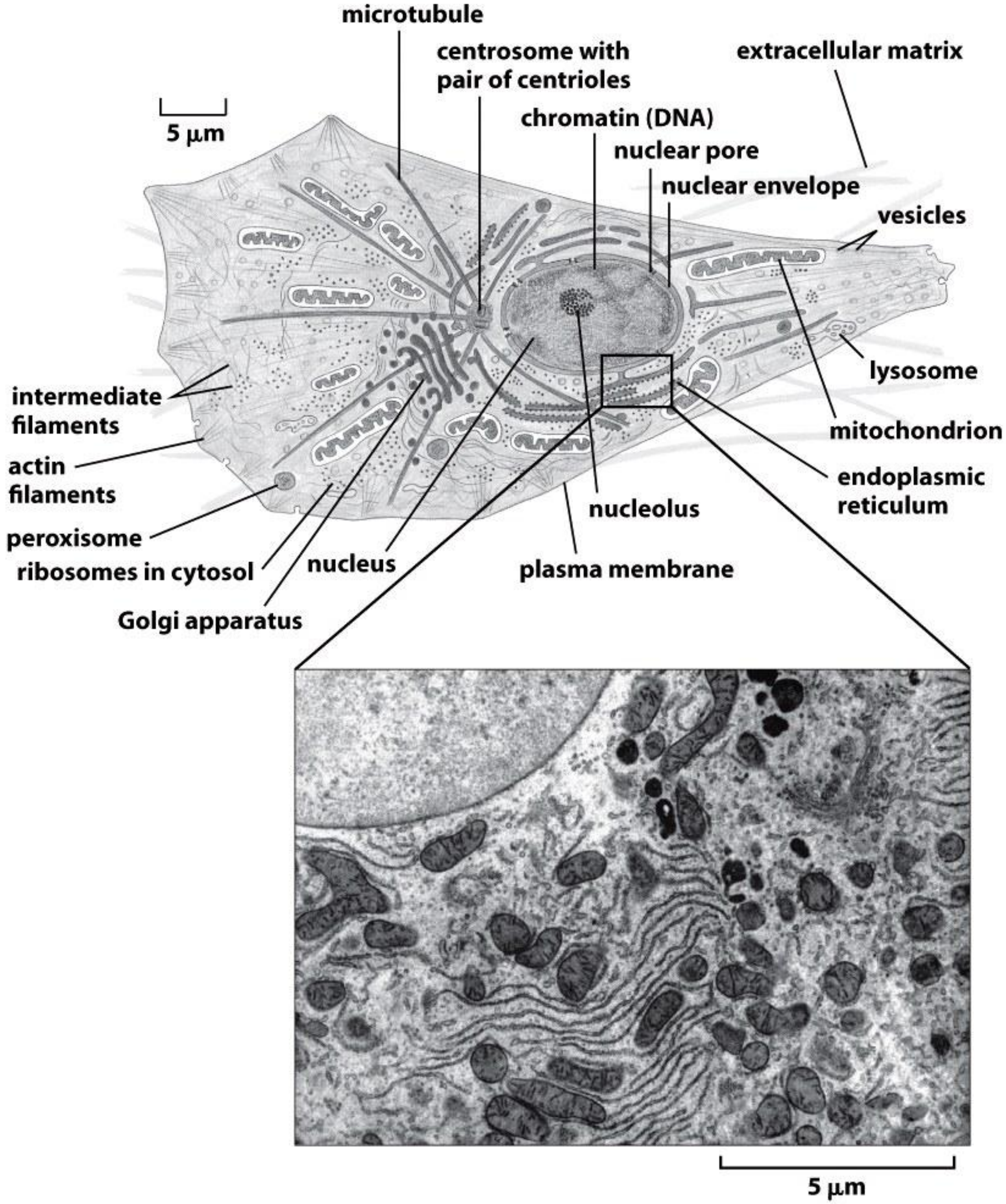


Figure 2.13 Physical Biology of the Cell (© Garland Science 2009)

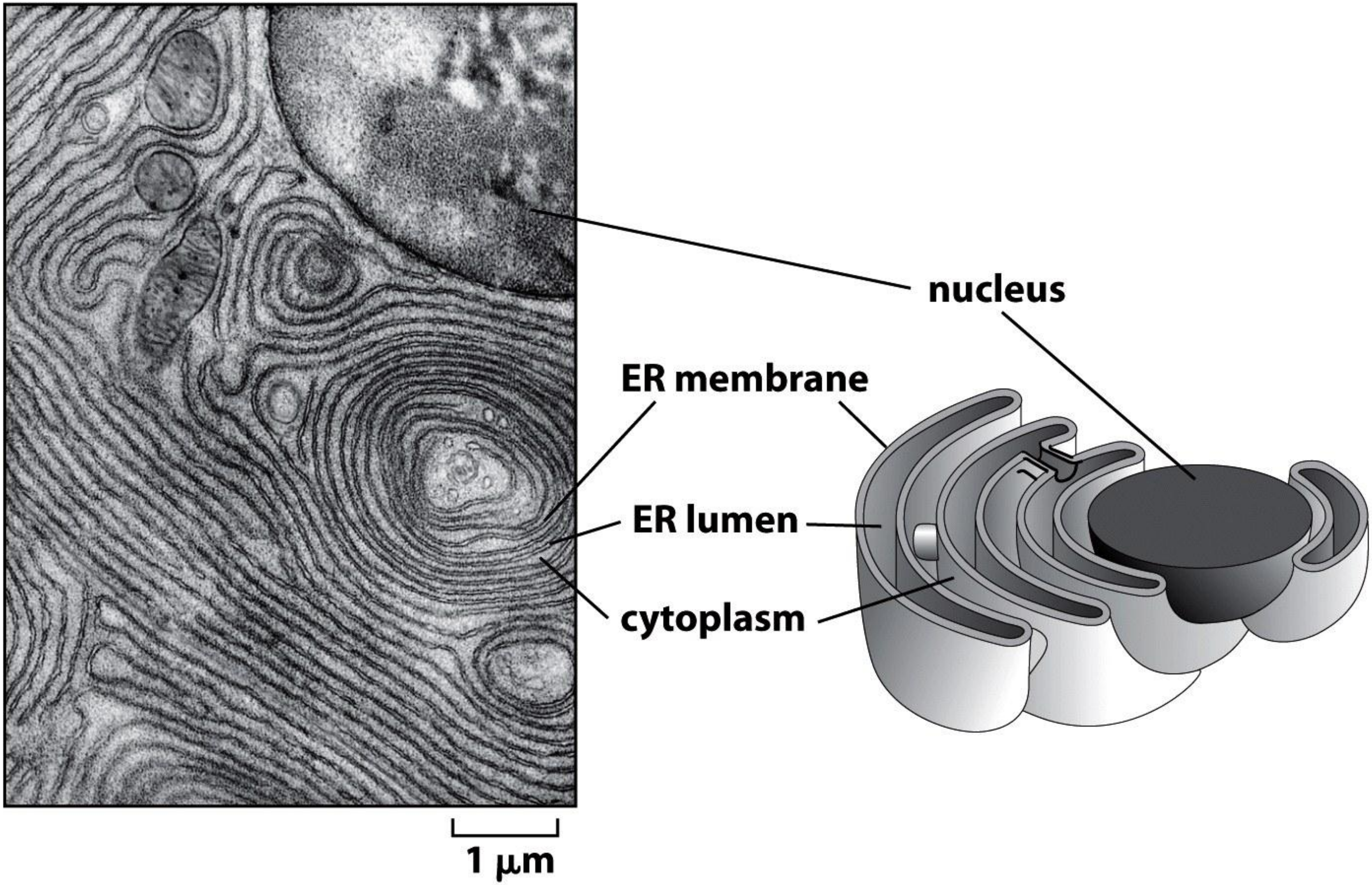


Figure 2.14 Physical Biology of the Cell (© Garland Science 2009)

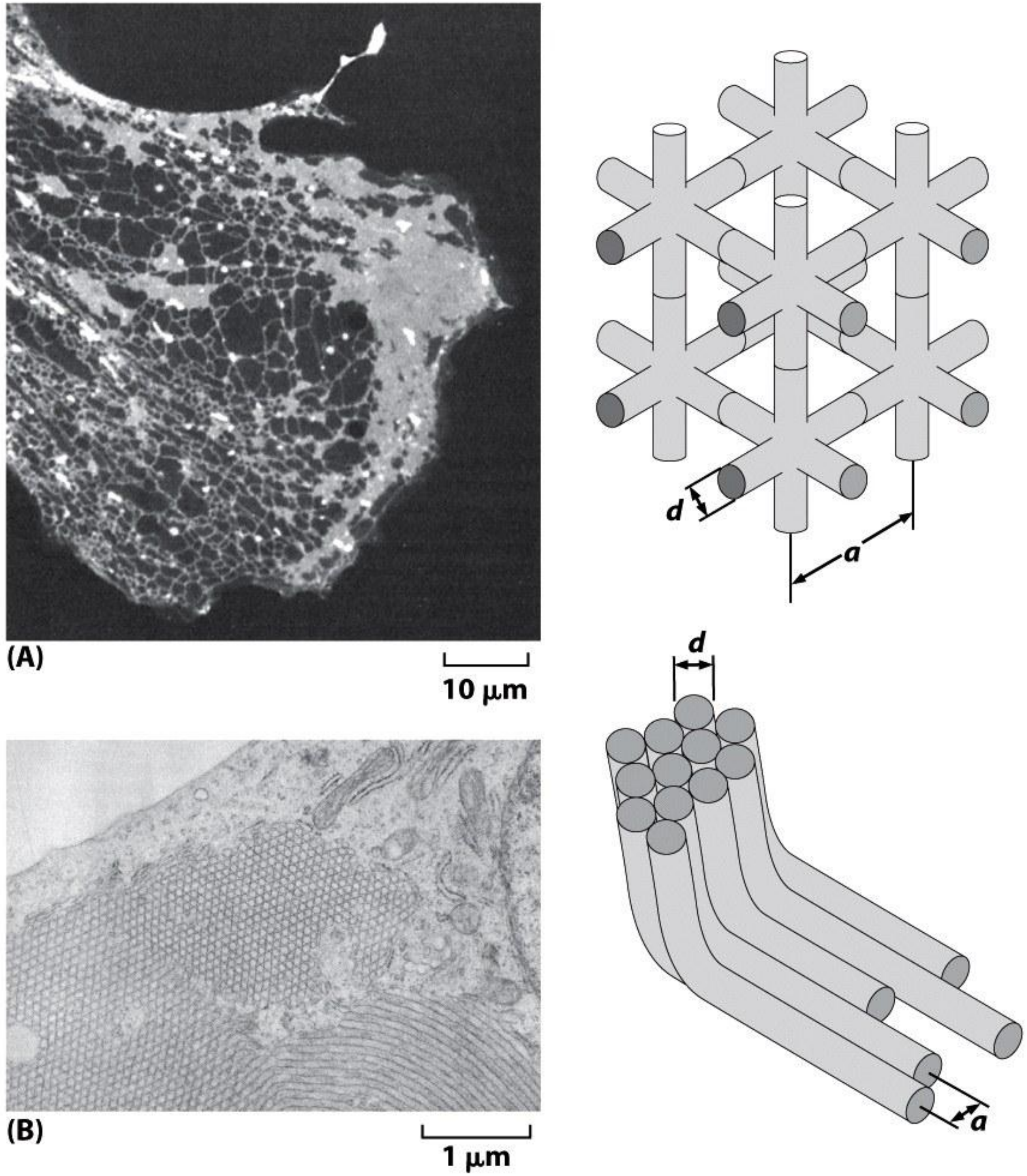


Figure 2.15 Physical Biology of the Cell (© Garland Science 2009)

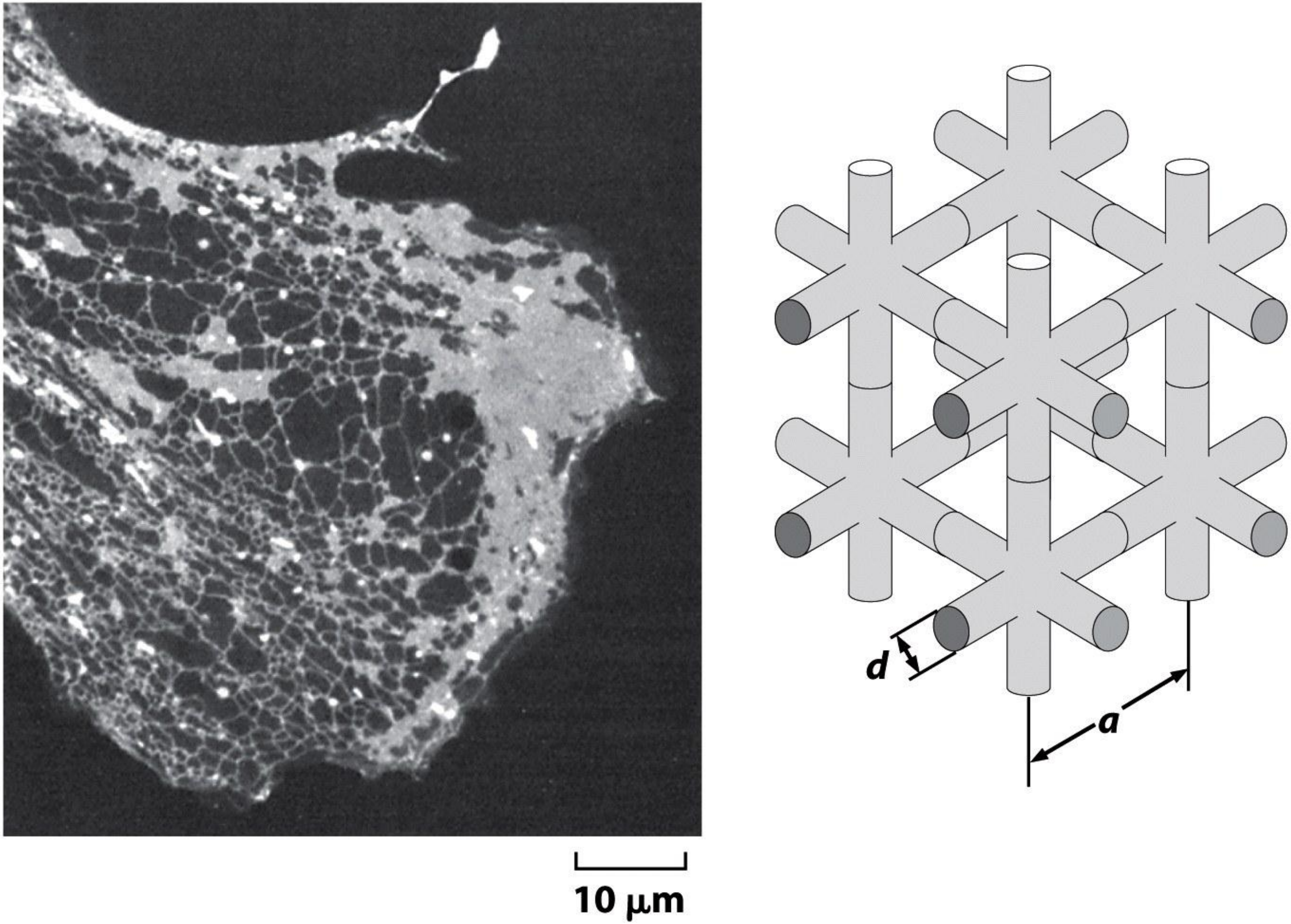


Figure 2.15a Physical Biology of the Cell (© Garland Science 2009)

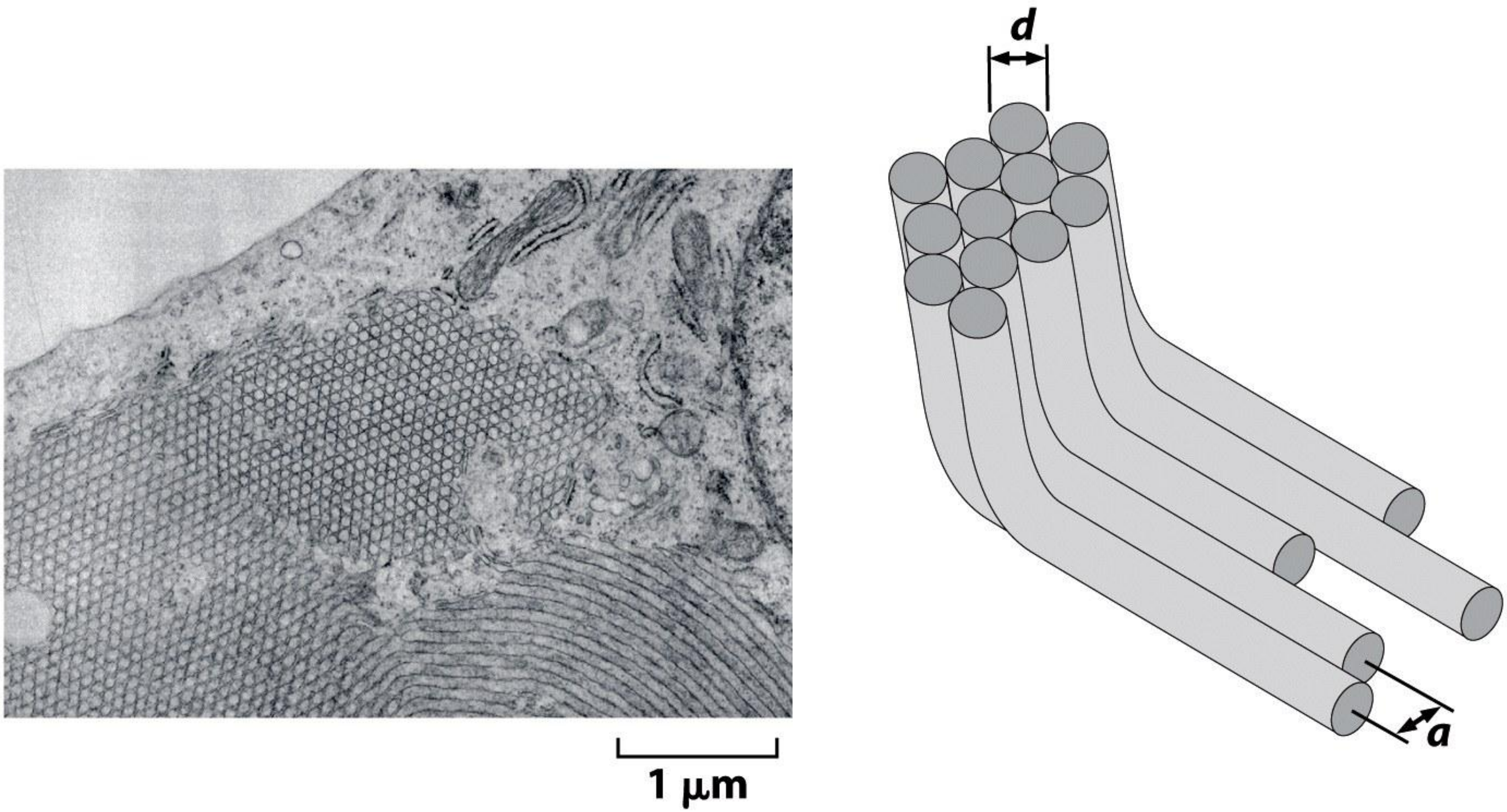


Figure 2.15b Physical Biology of the Cell (© Garland Science 2009)

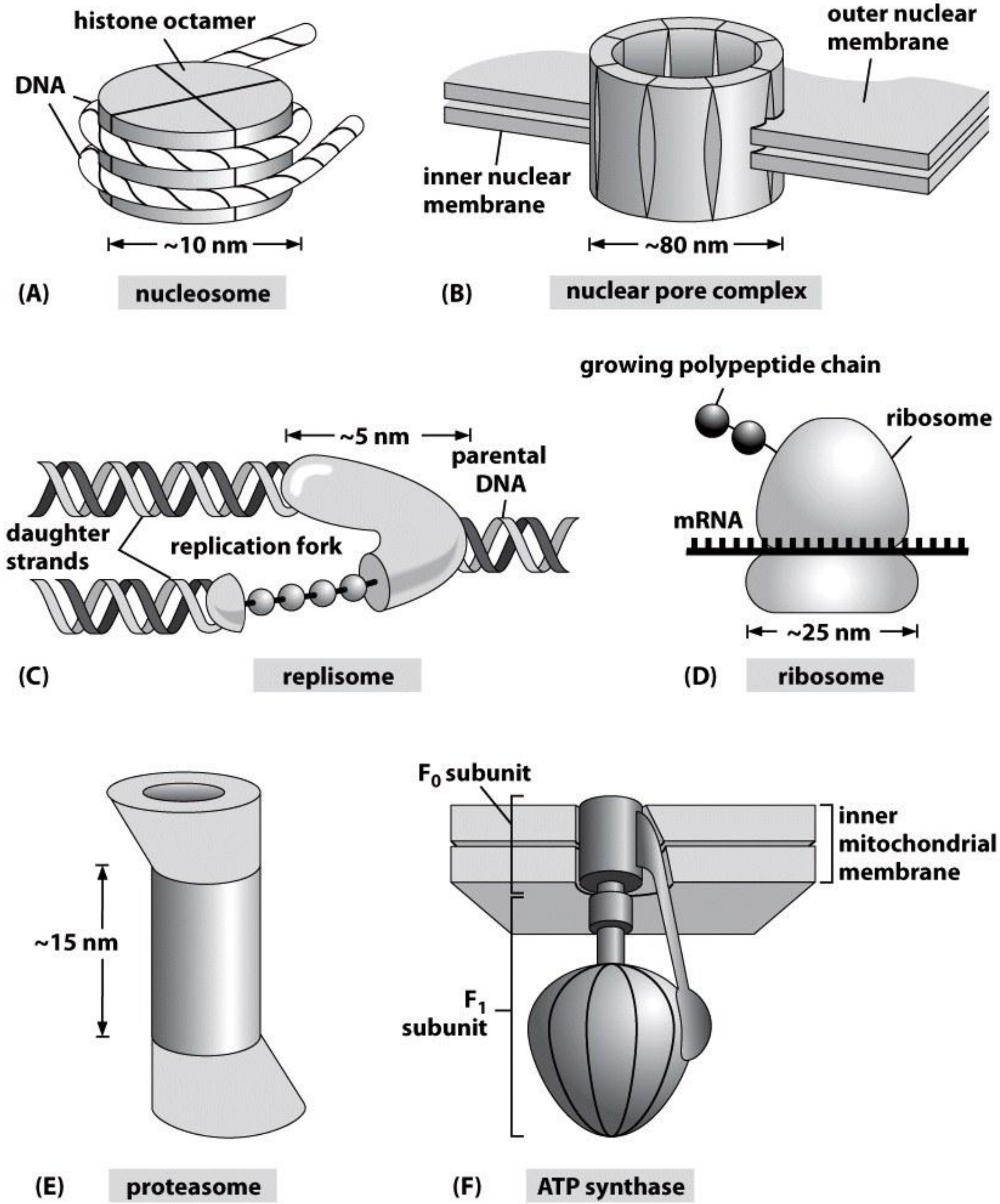
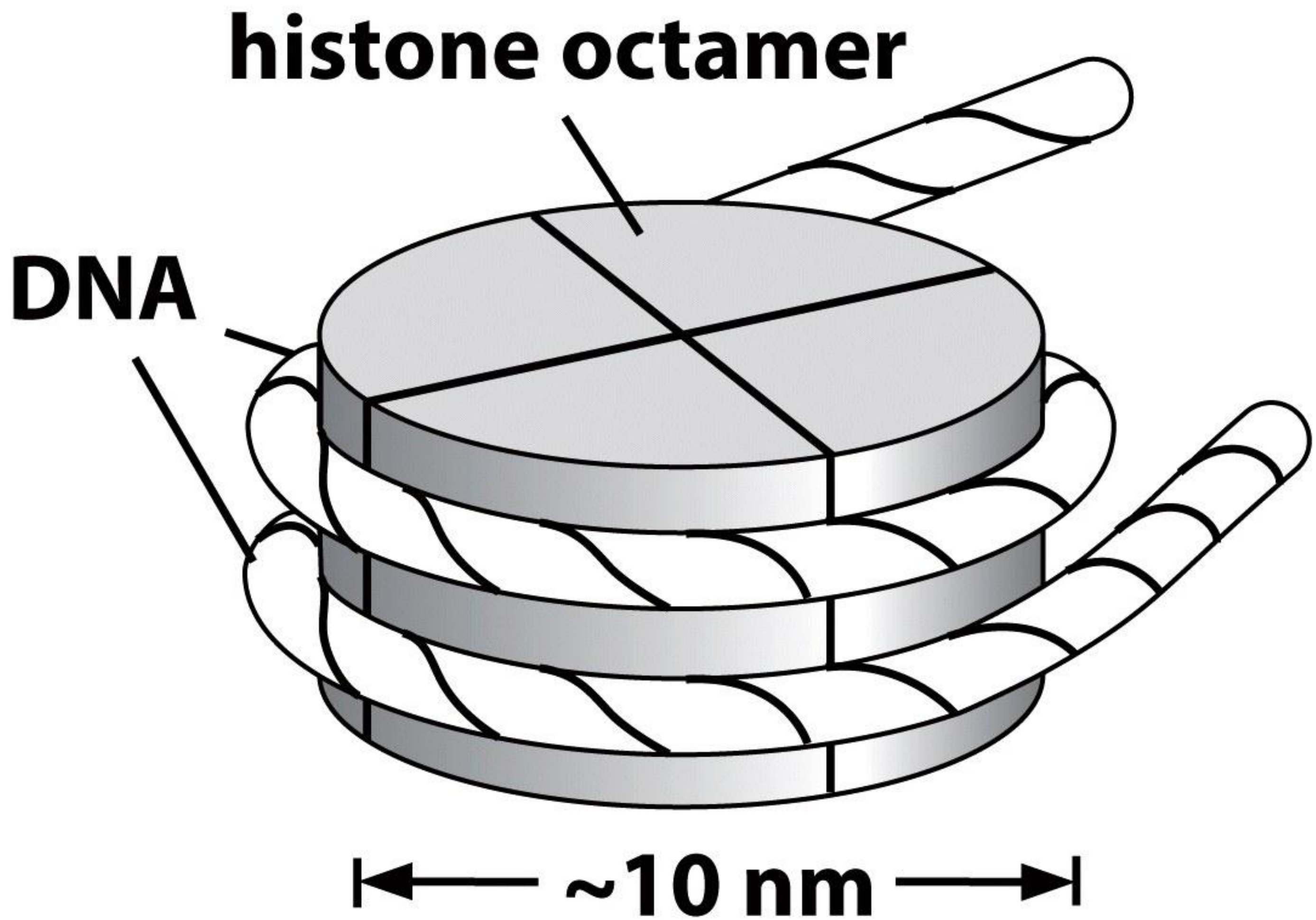


Figure 2.16 Physical Biology of the Cell (© Garland Science 2009)



nucleosome

Figure 2.16a Physical Biology of the Cell (© Garland Science 2009)

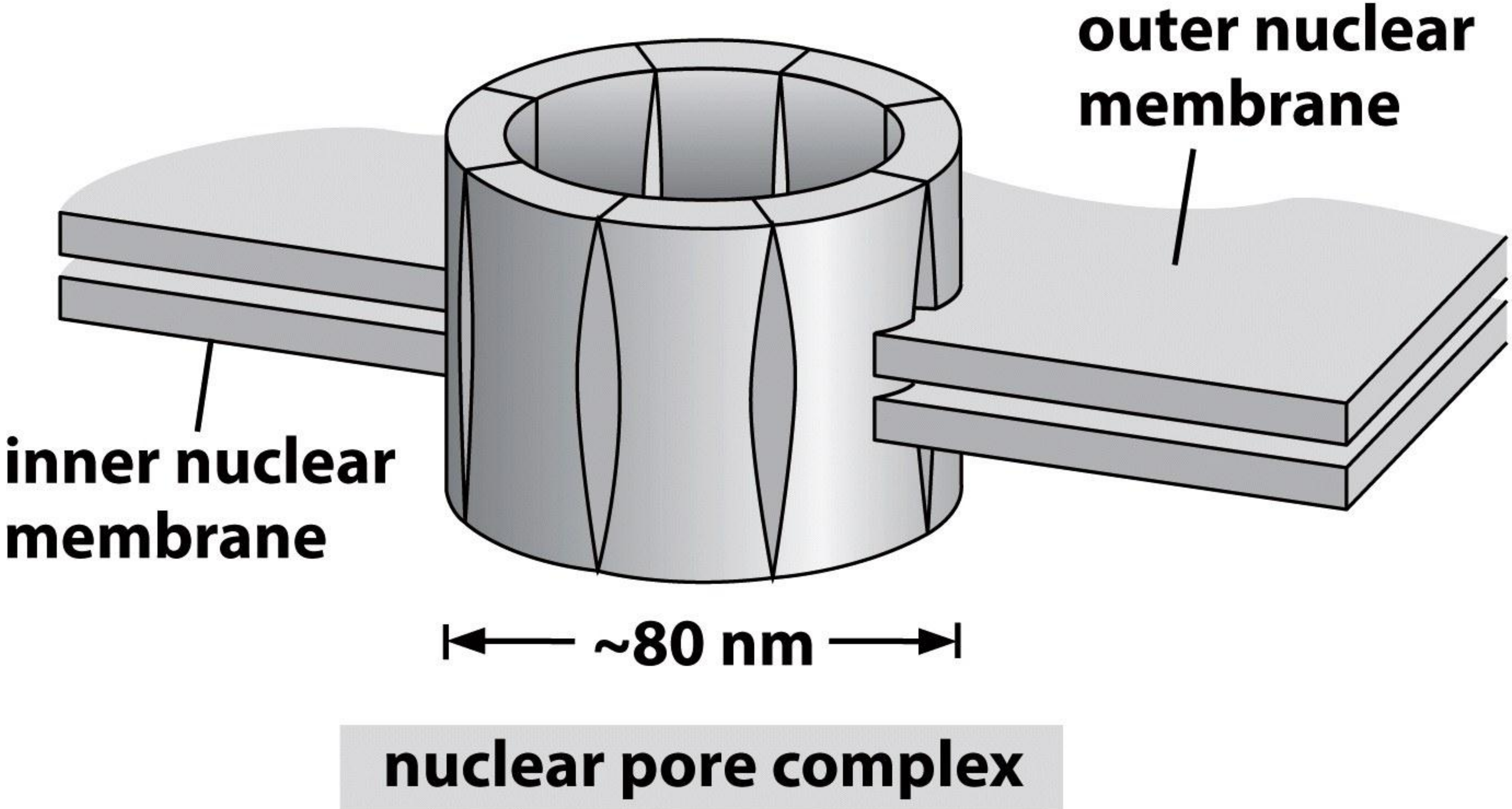


Figure 2.16b Physical Biology of the Cell (© Garland Science 2009)

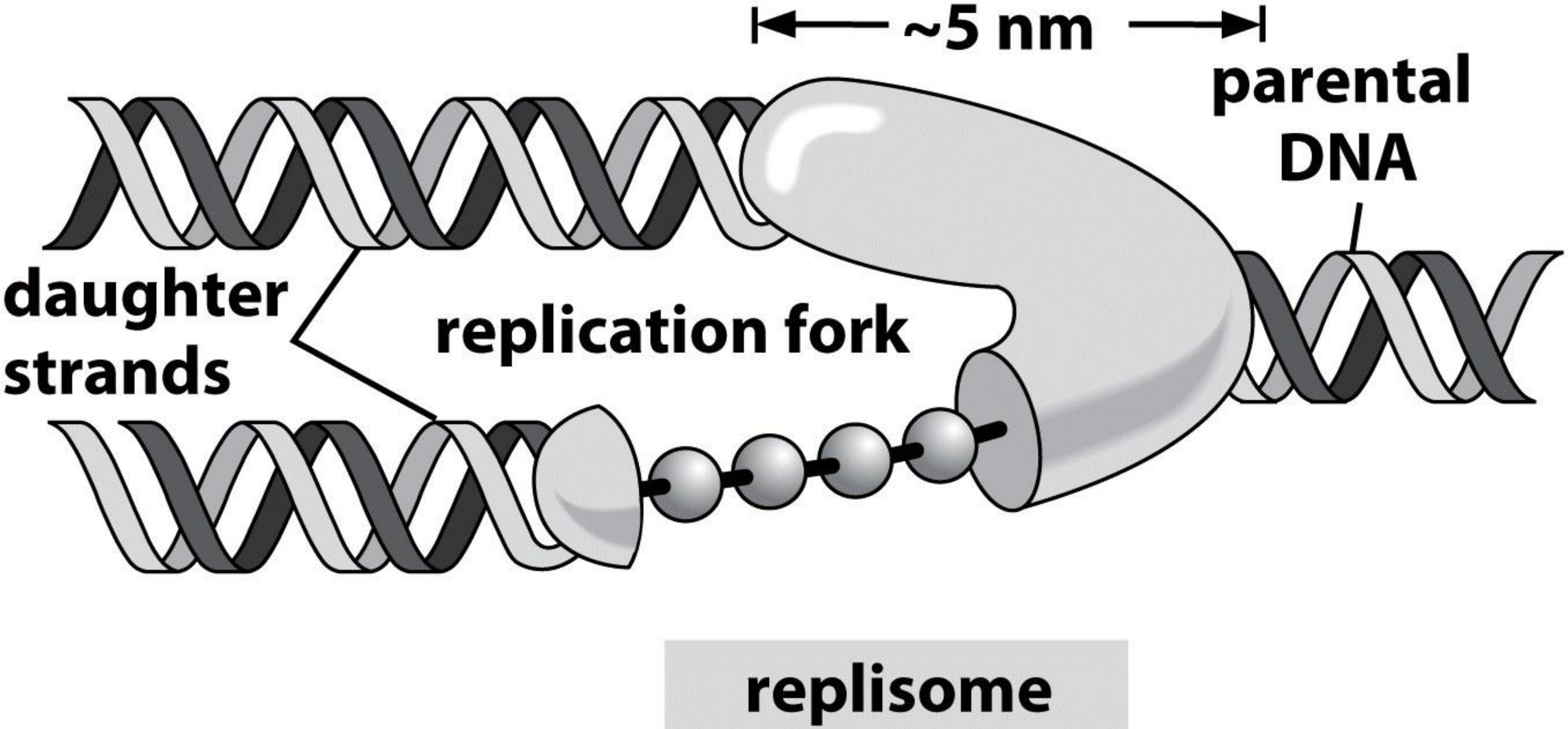
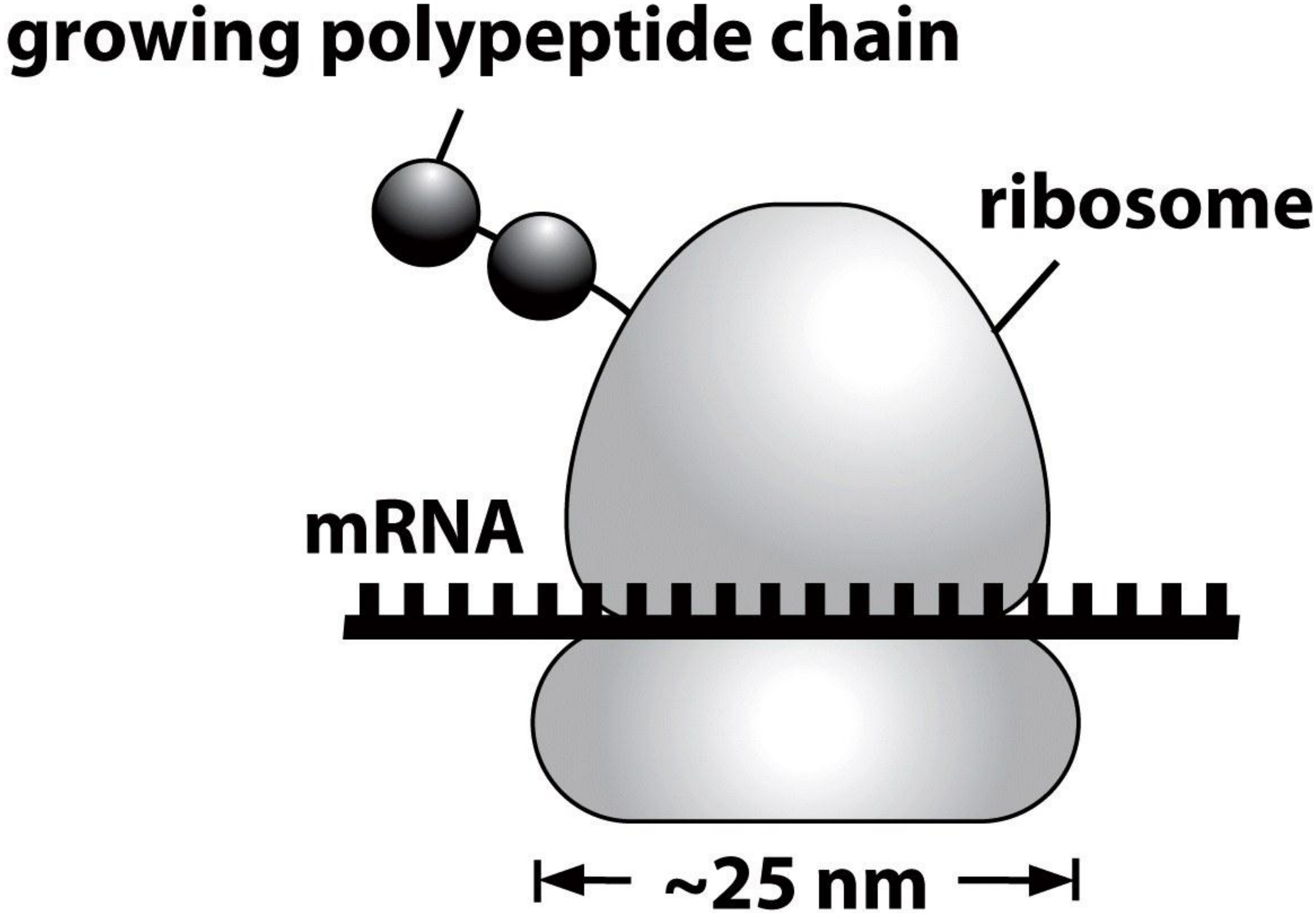


Figure 2.16c Physical Biology of the Cell (© Garland Science 2009)



ribosome

Figure 2.16d Physical Biology of the Cell (© Garland Science 2009)

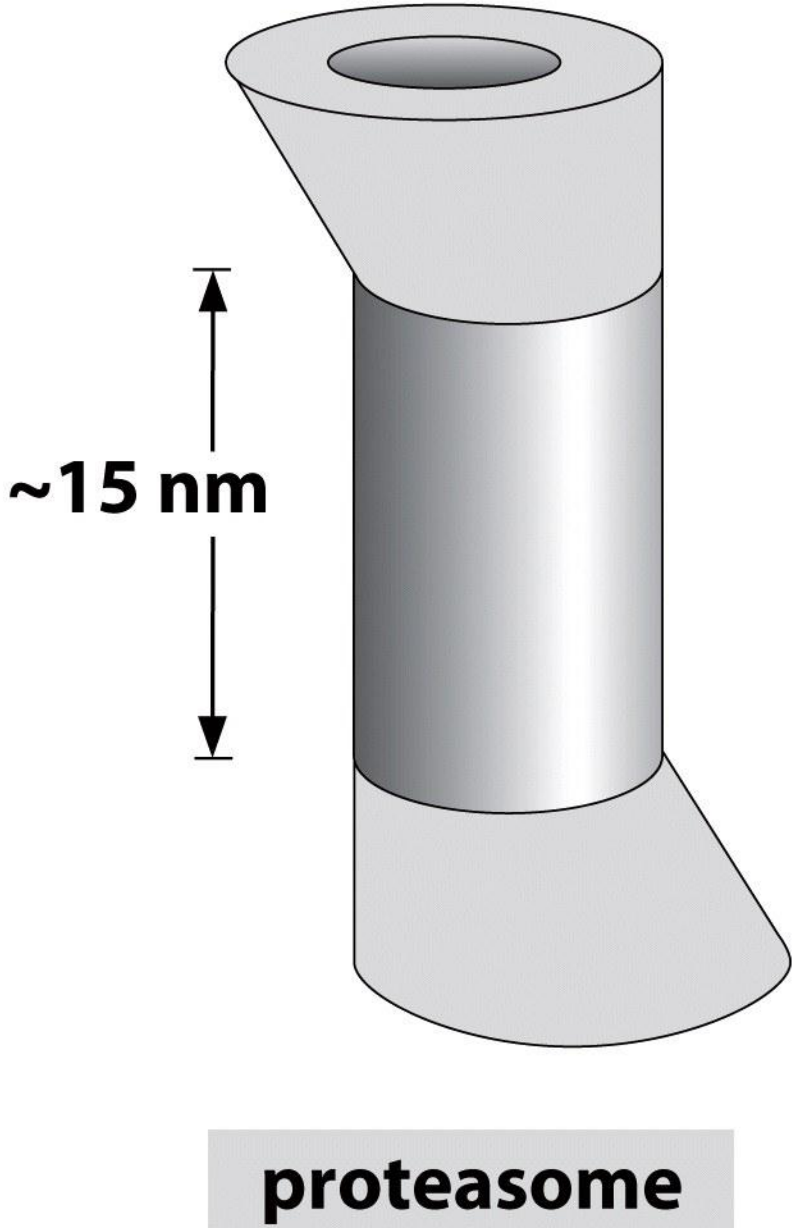
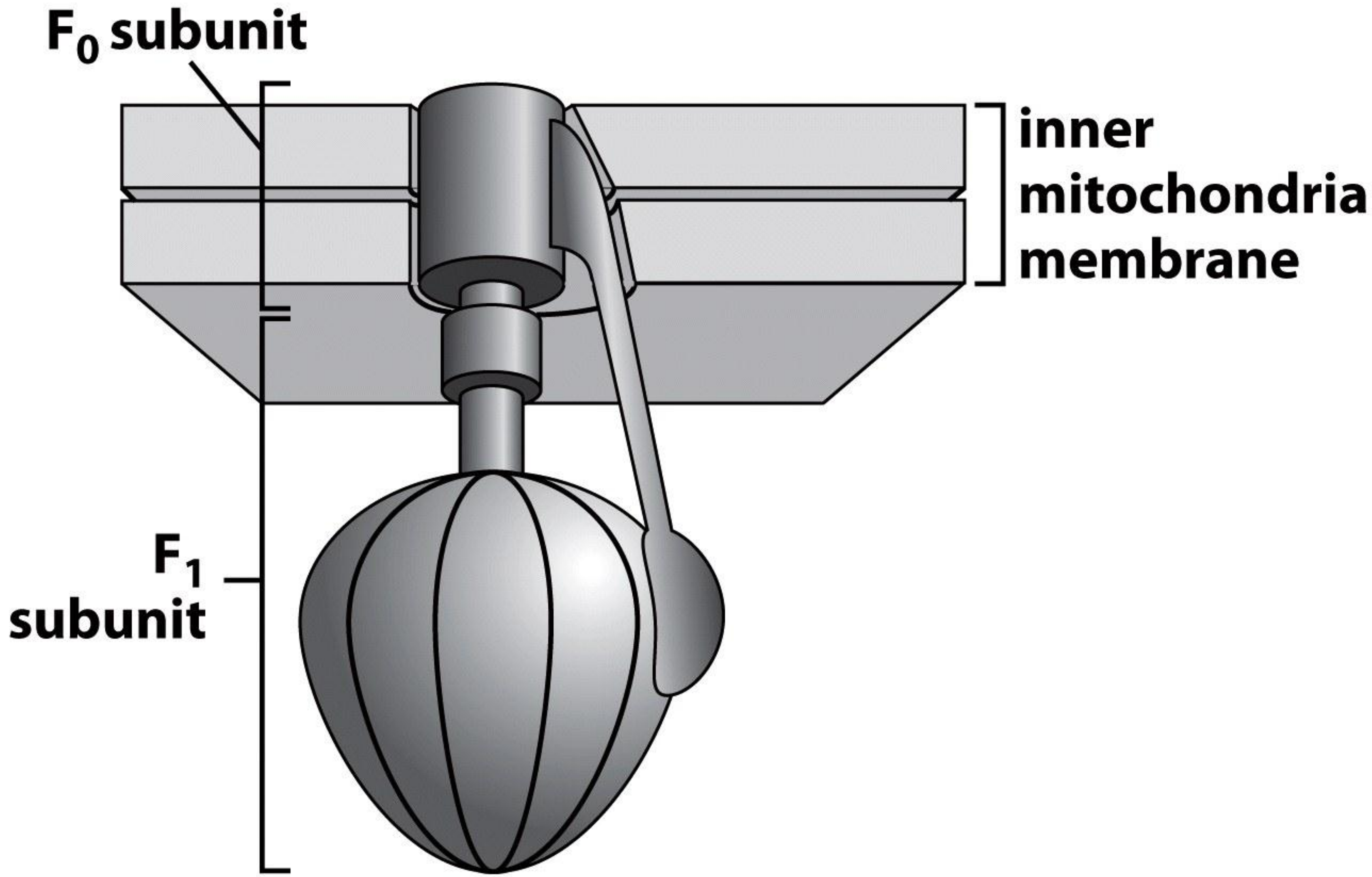


Figure 2.16e Physical Biology of the Cell (© Garland Science 2009)



ATP synthase

Figure 2.16f Physical Biology of the Cell (© Garland Science 2009)

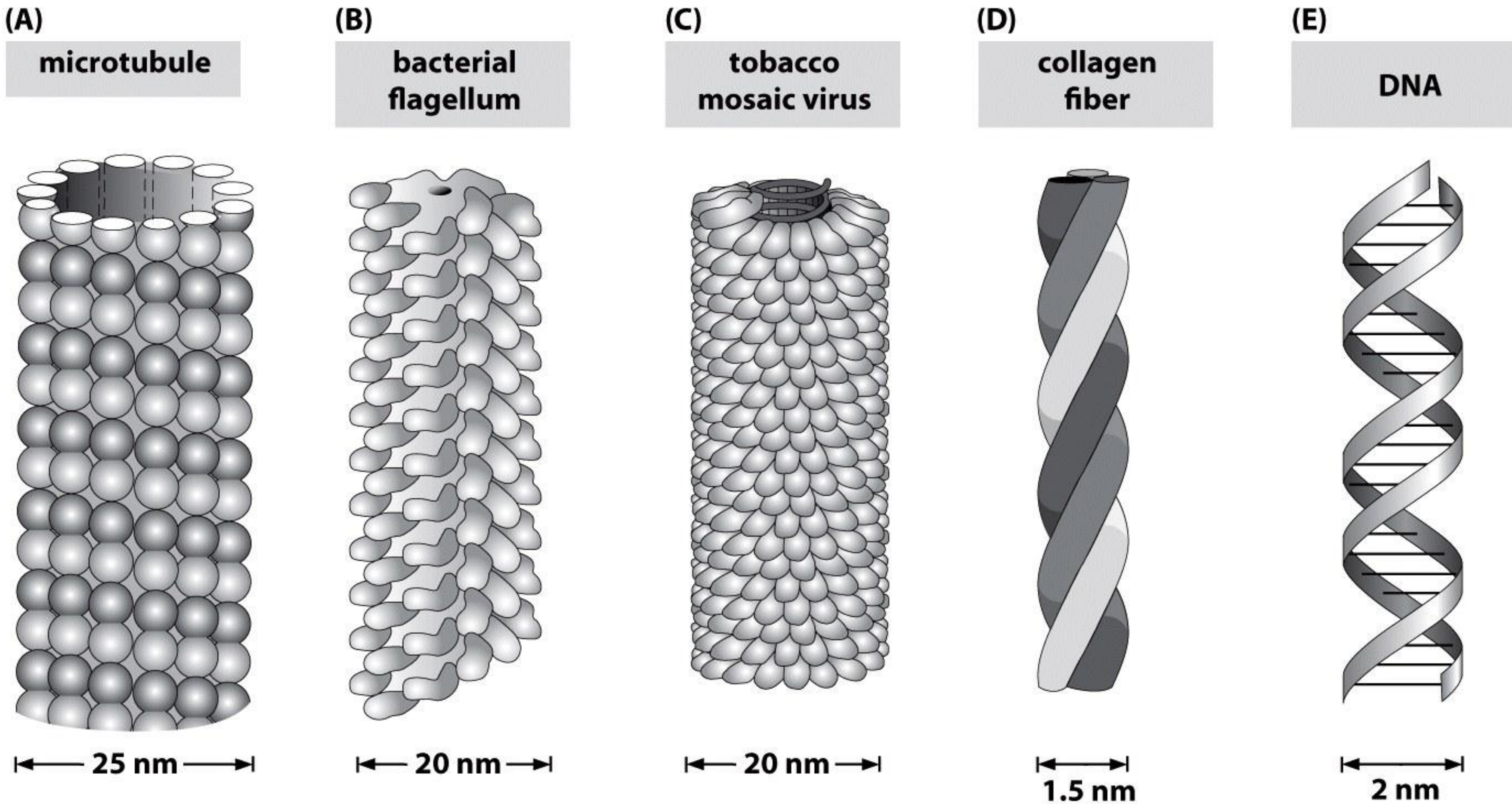


Figure 2.17 Physical Biology of the Cell (© Garland Science 2009)

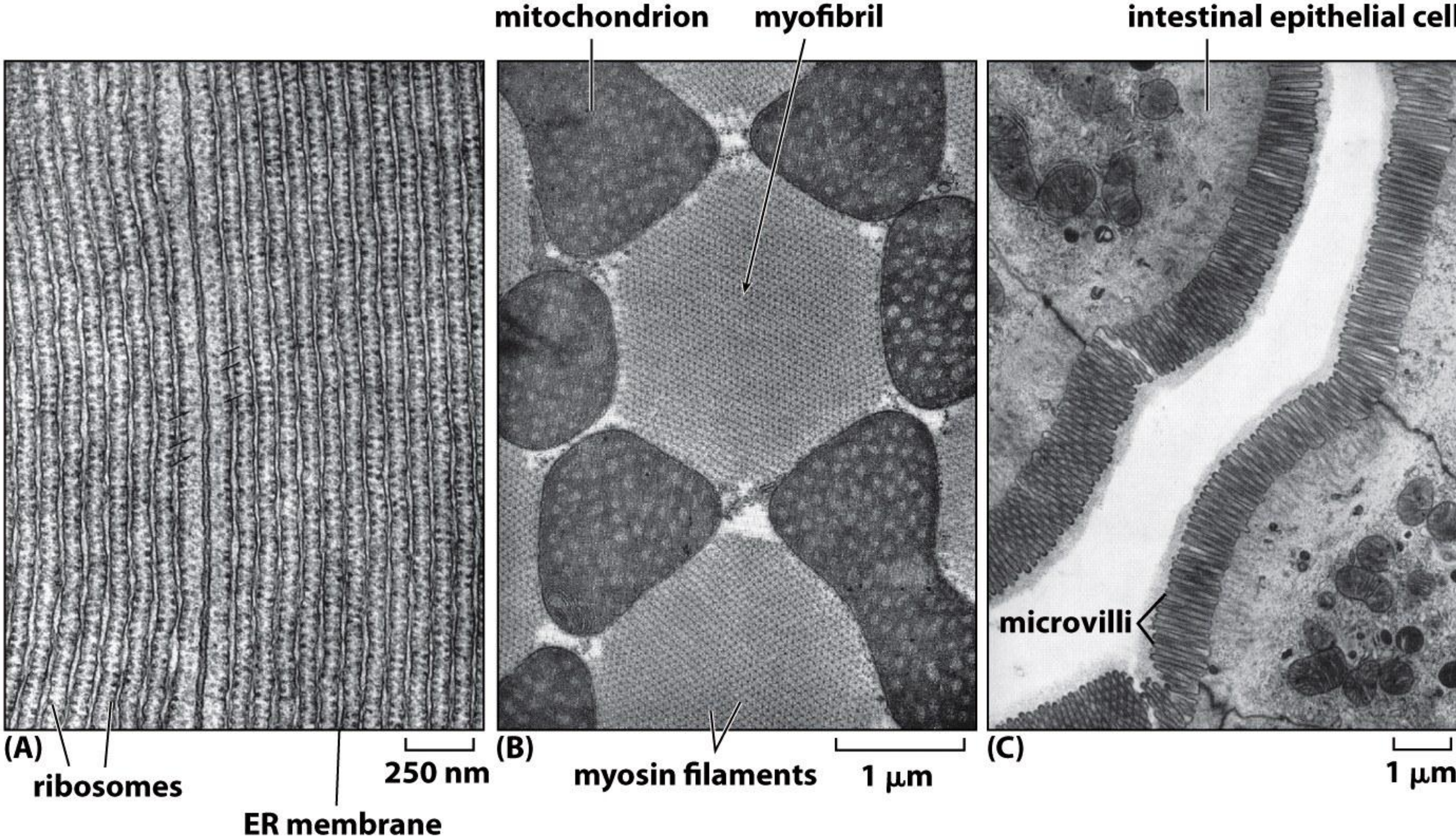


Figure 2.18 Physical Biology of the Cell (© Garland Science 2009)

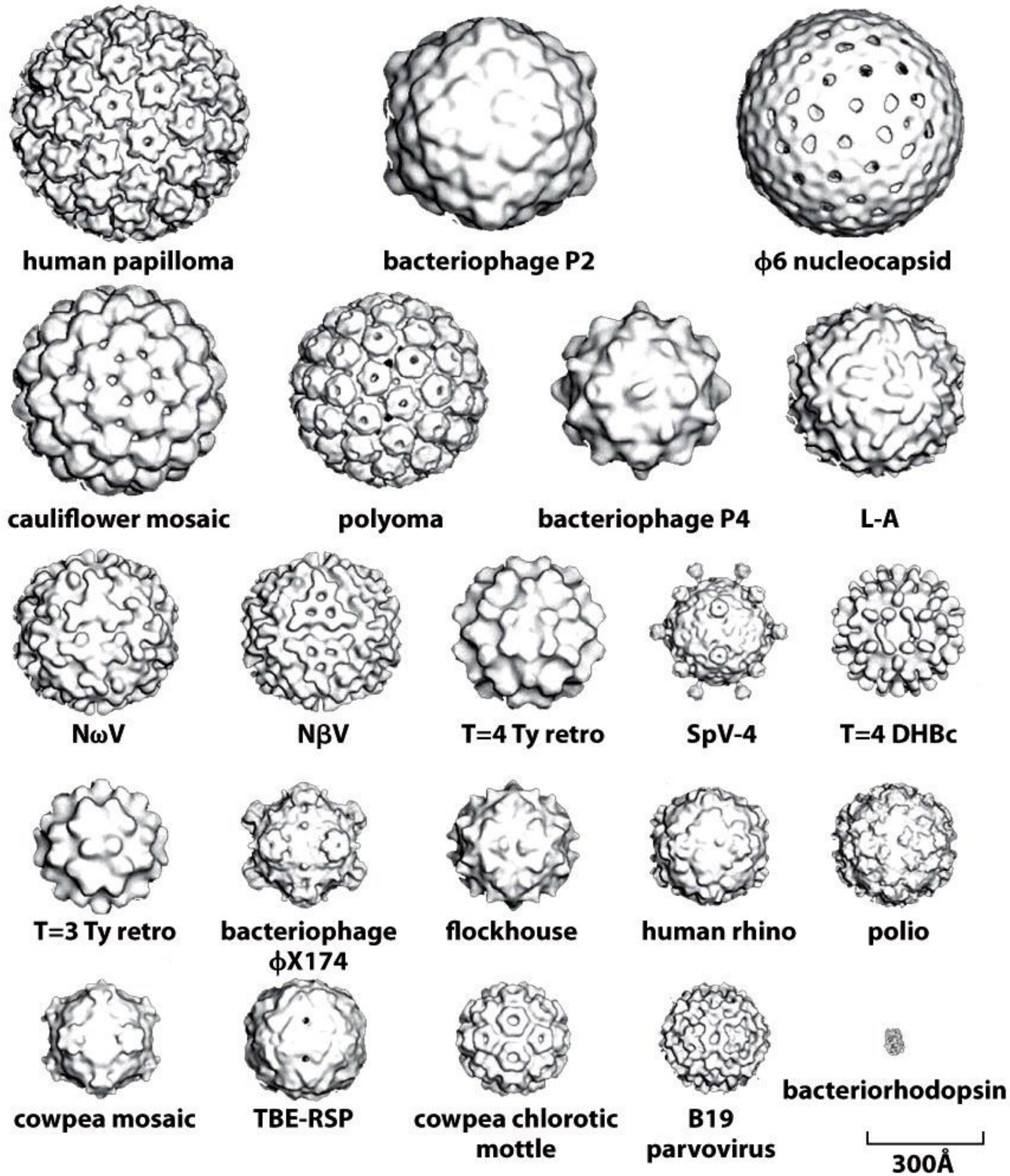


Figure 2.19 Physical Biology of the Cell (© Garland Science 2009)

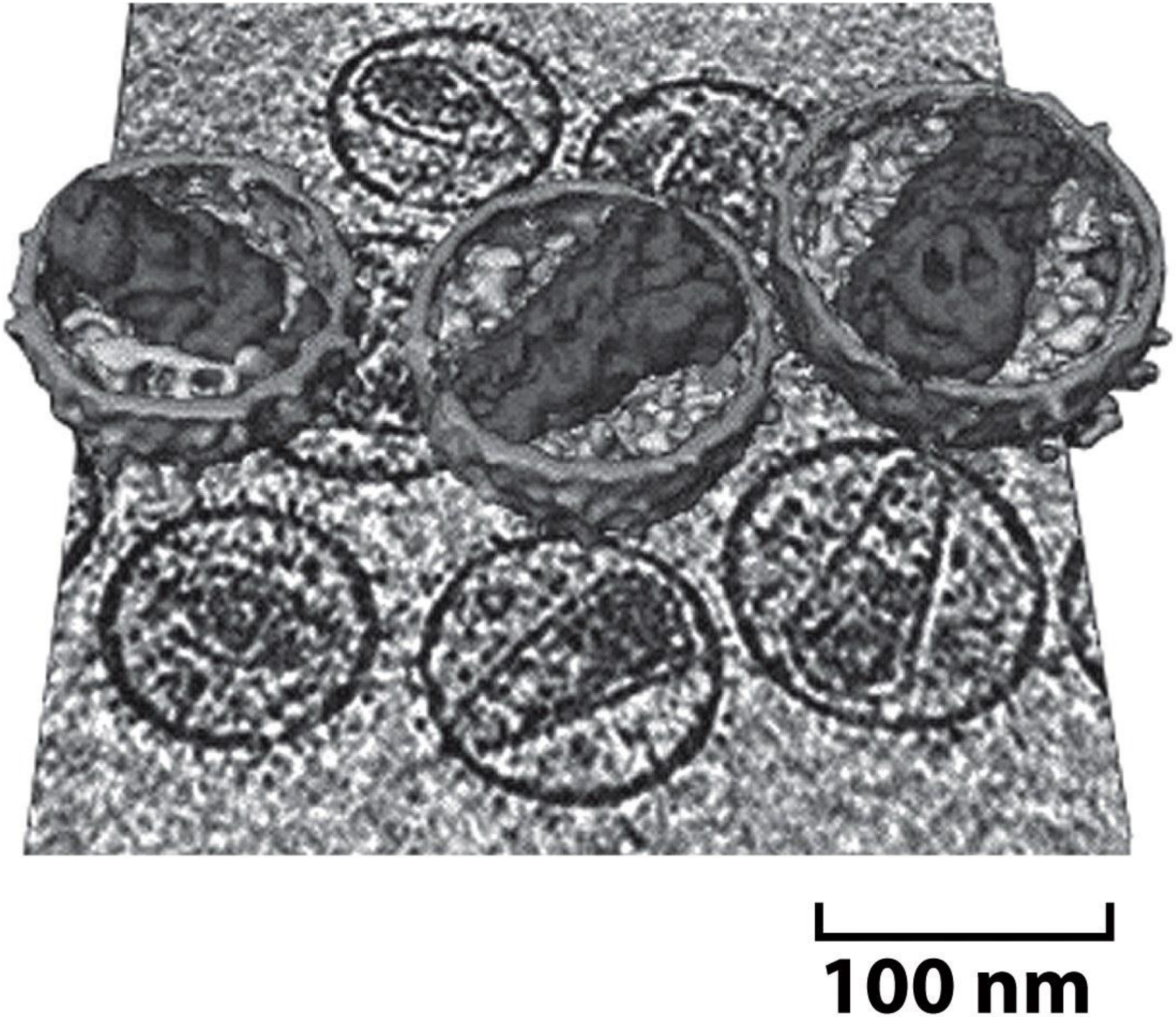


Figure 2.20 Physical Biology of the Cell (© Garland Science 2009)

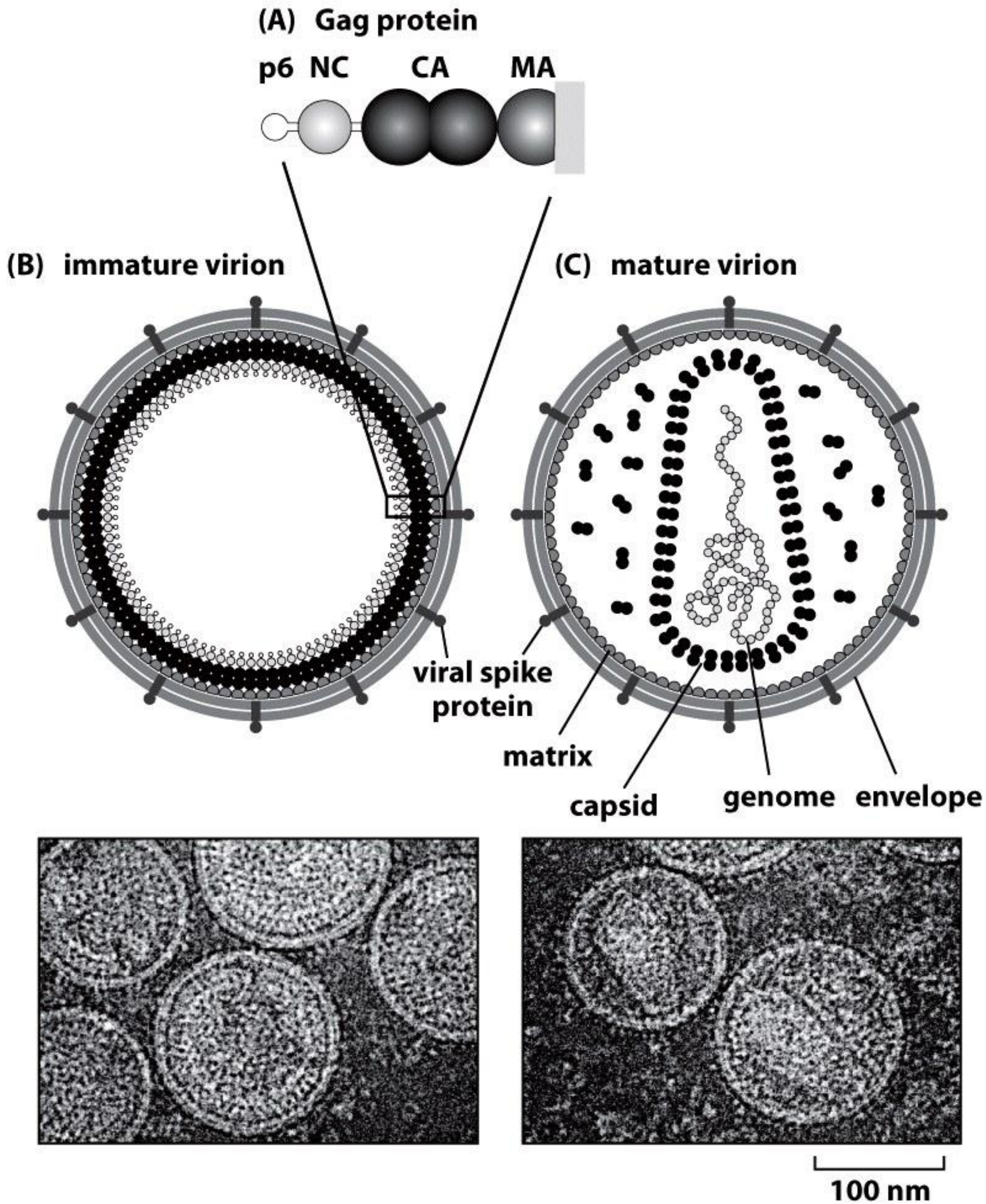


Figure 2.21 Physical Biology of the Cell (© Garland Science 2009)

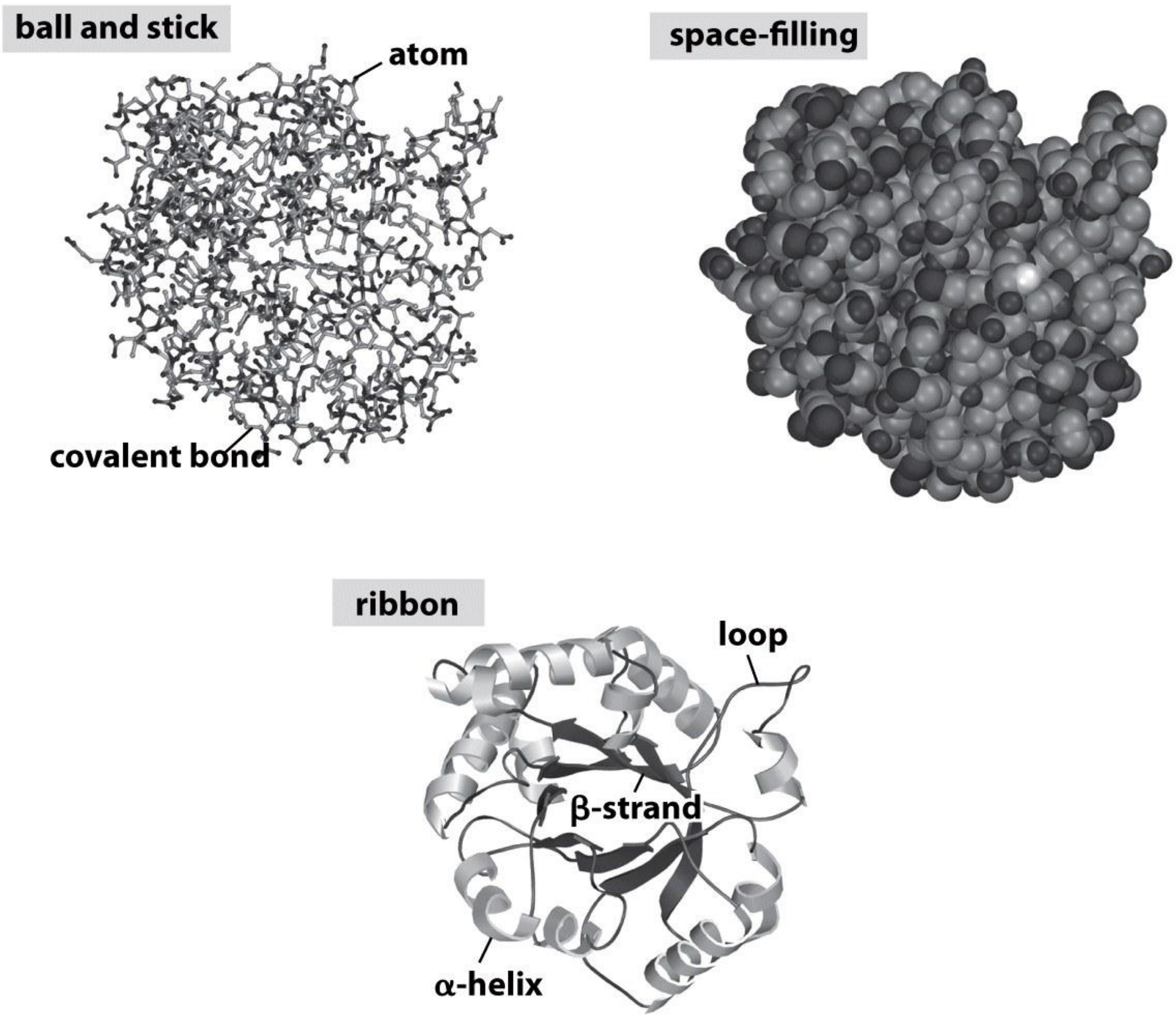


Figure 2.22 Physical Biology of the Cell (© Garland Science 2009)

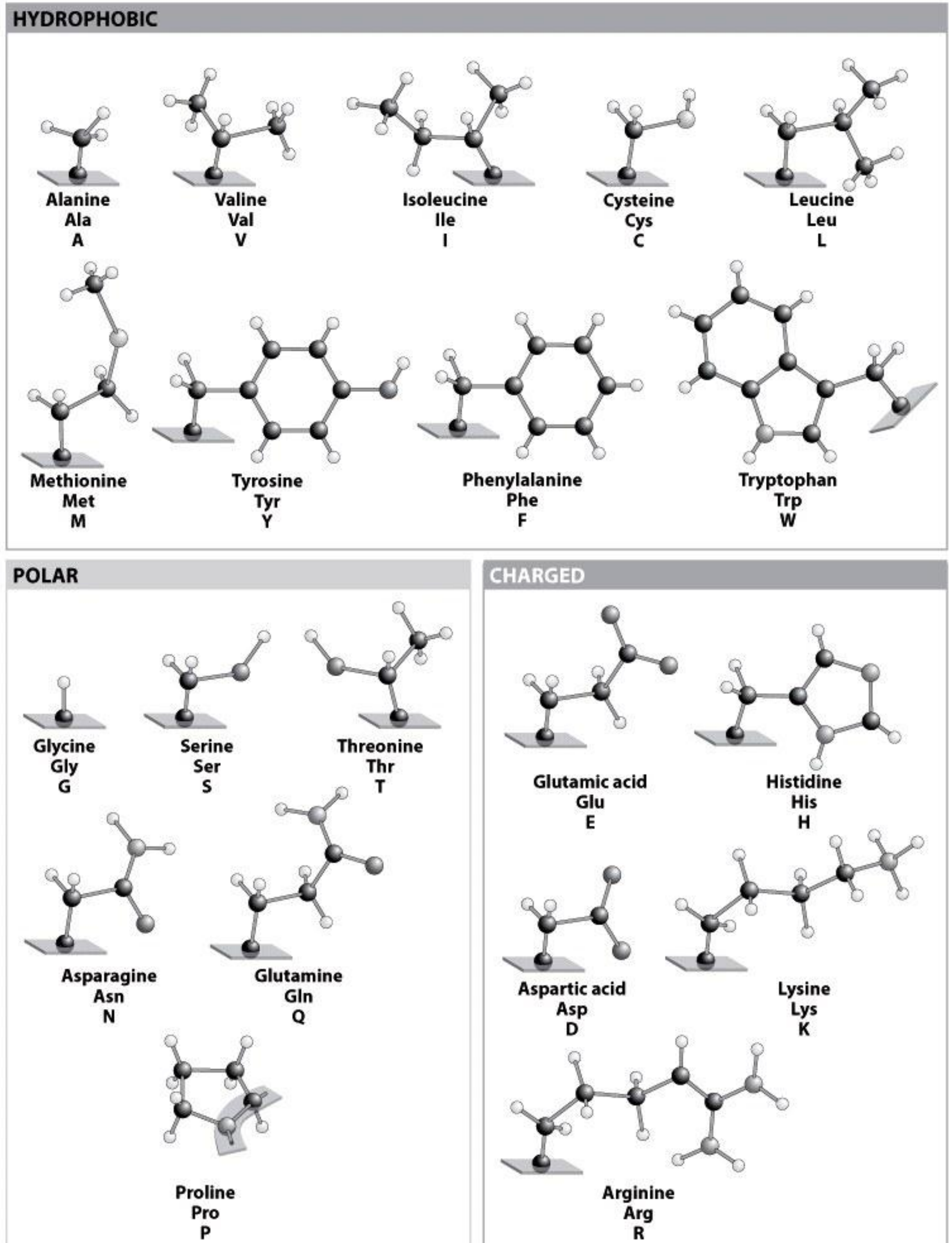


Figure 2.23 Physical Biology of the Cell (© Garland Science 2009)

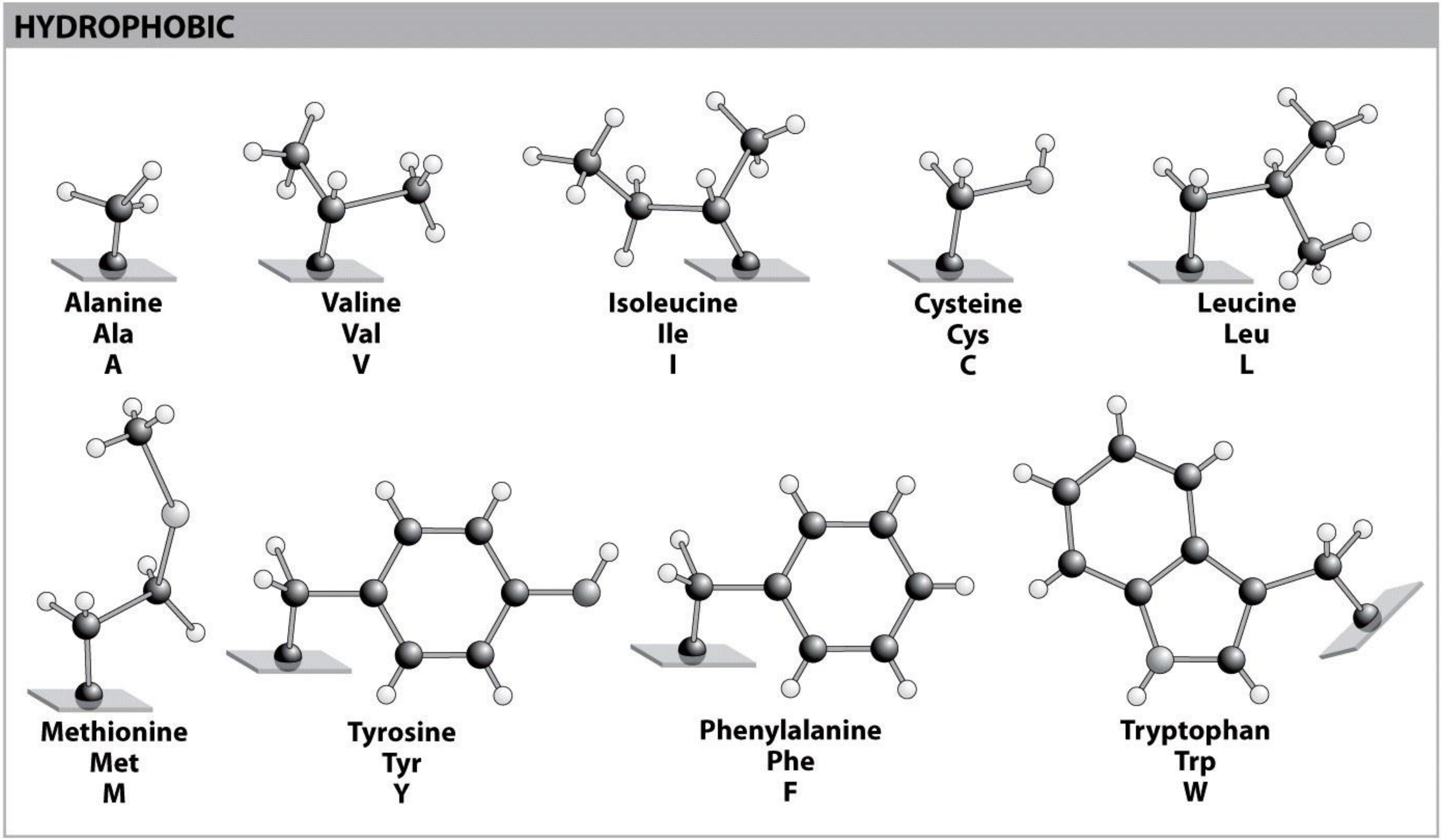


Figure 2.23 (part 1) Physical Biology of the Cell (© Garland Science 2009)

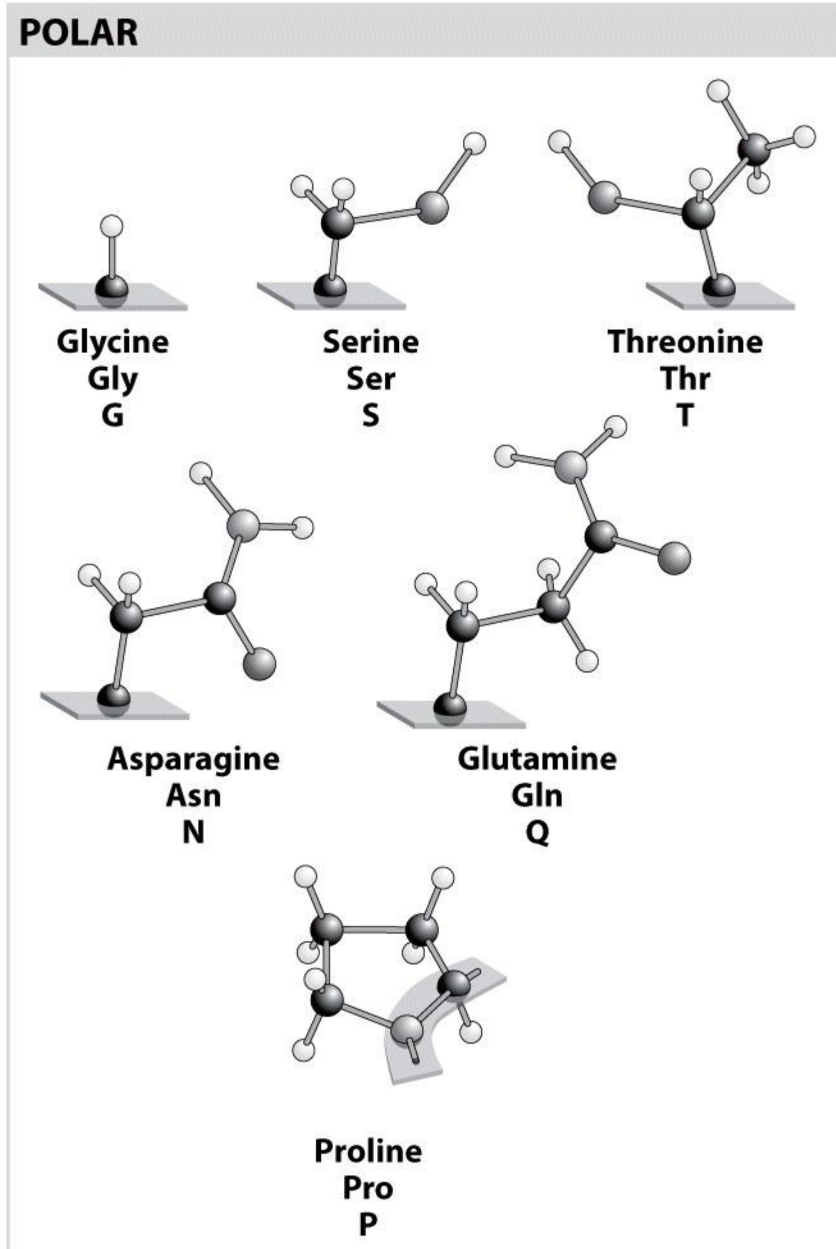


Figure 2.23 (part 2) Physical Biology of the Cell (© Garland Science 2009)

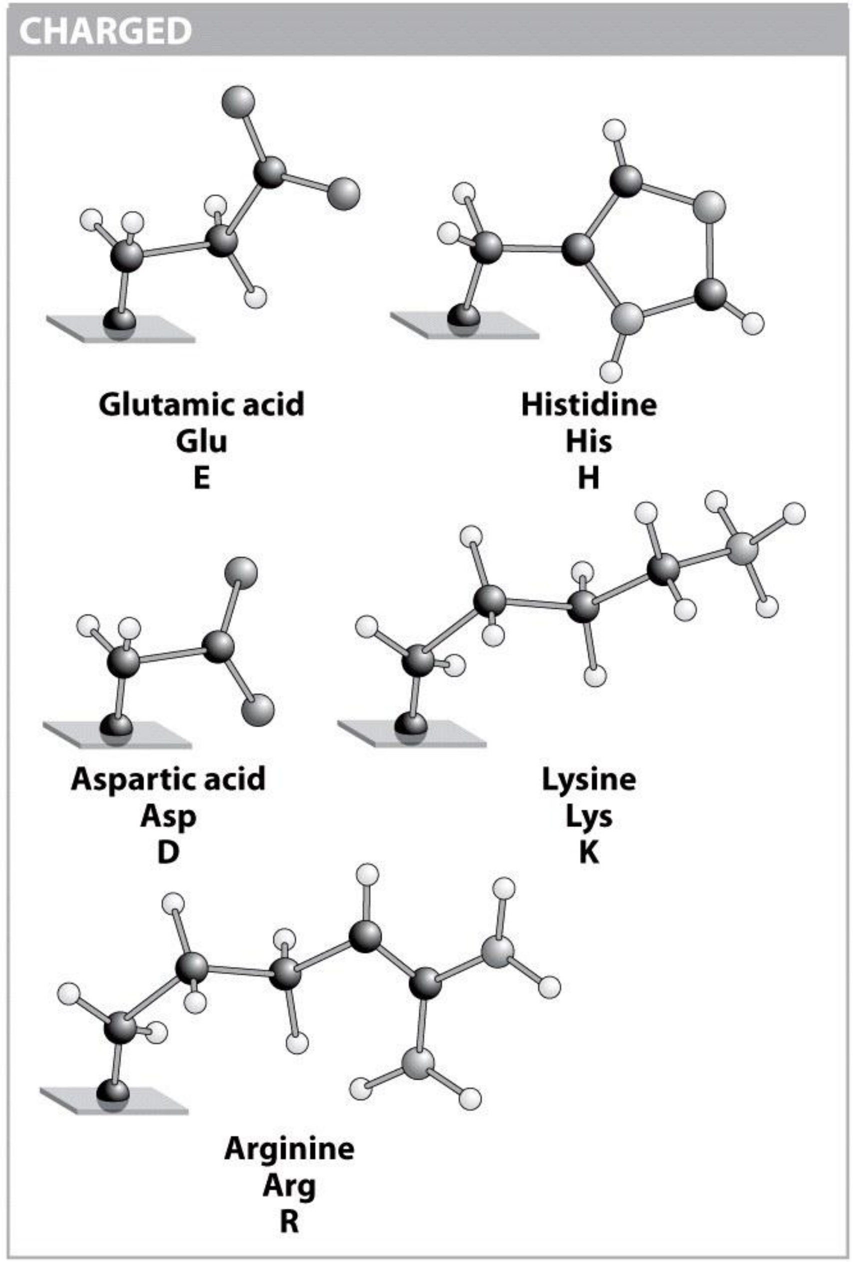


Figure 2.23 (part 3) Physical Biology of the Cell (© Garland Science 2009)

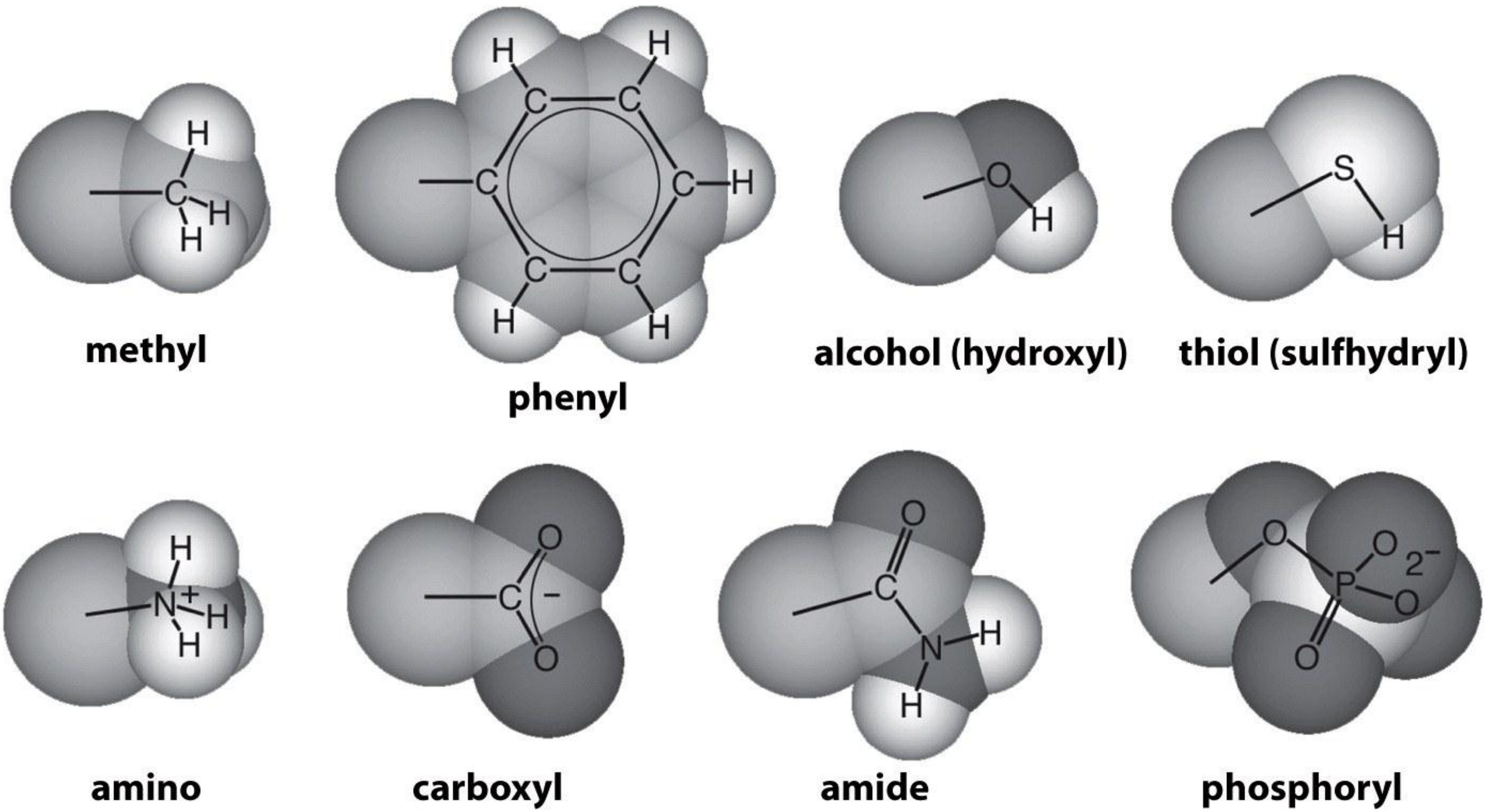


Figure 2.24 Physical Biology of the Cell (© Garland Science 2009)

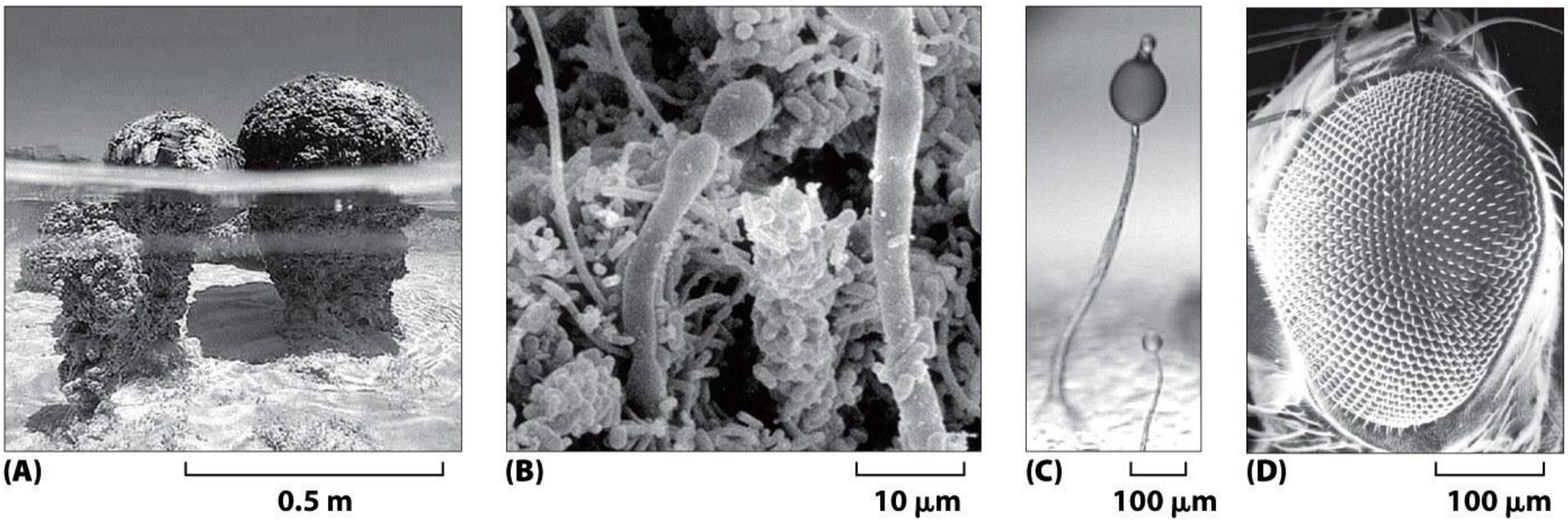


Figure 2.25 Physical Biology of the Cell (© Garland Science 2009)

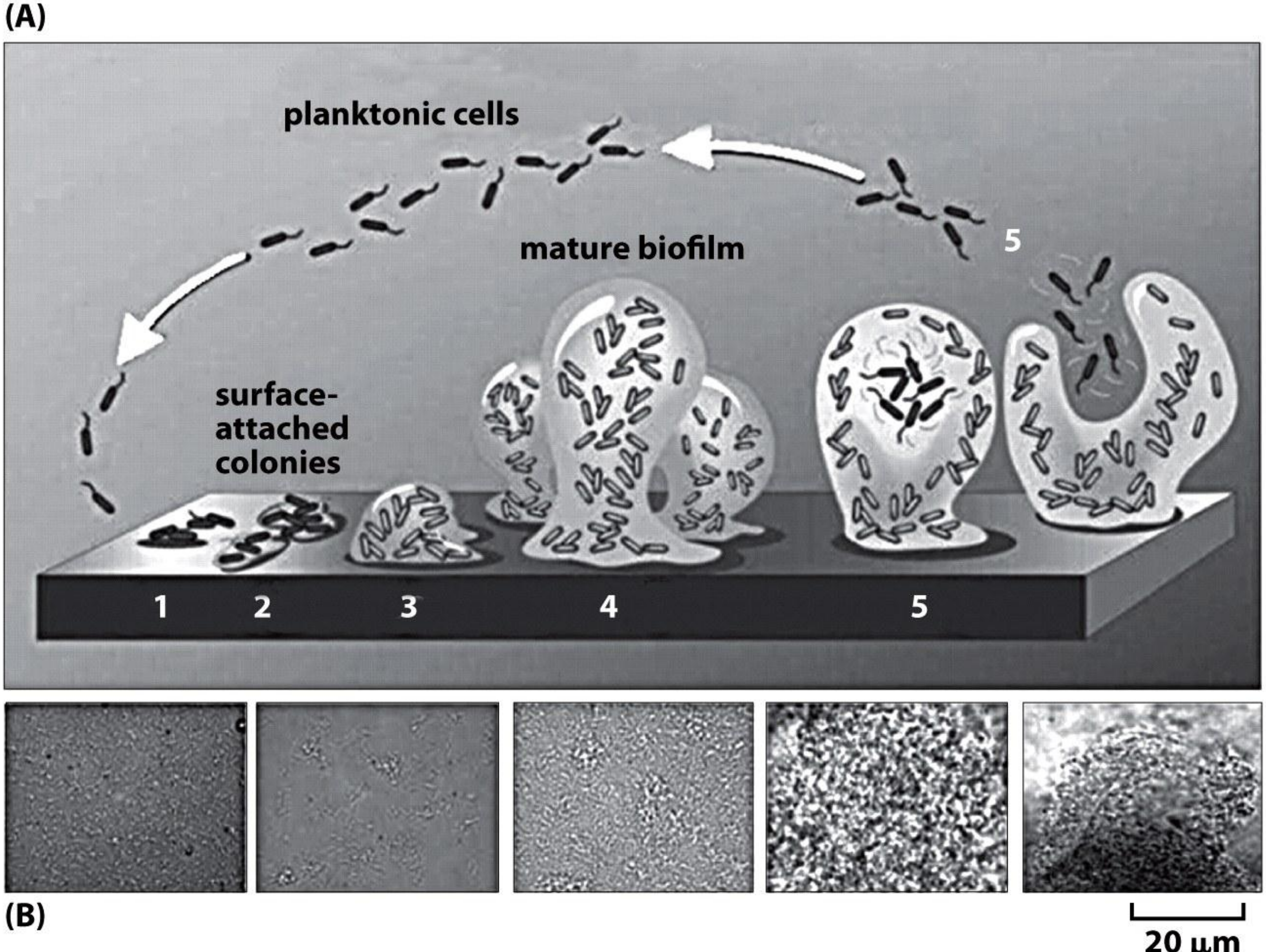


Figure 2.26 Physical Biology of the Cell (© Garland Science 2009)

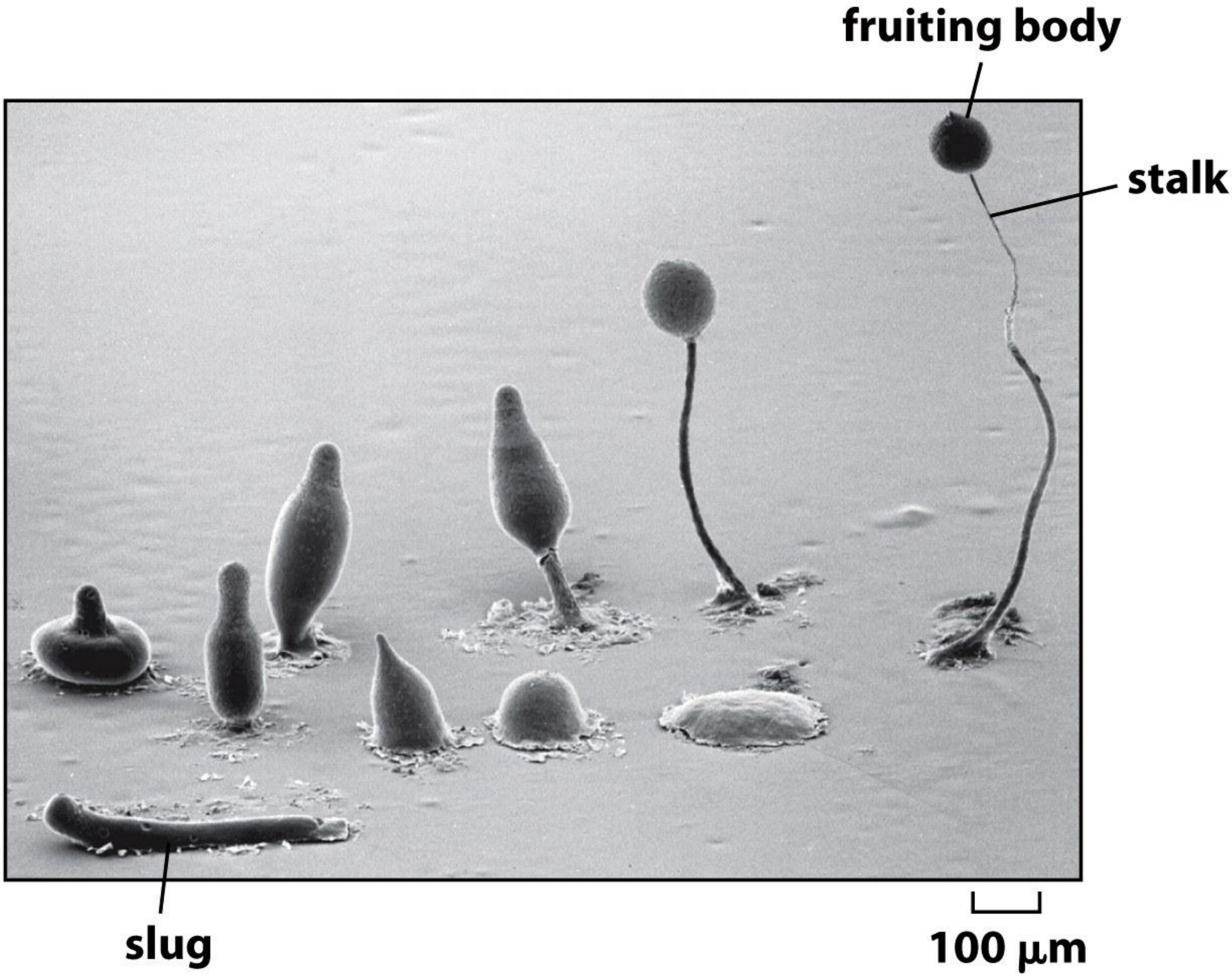


Figure 2.27 Physical Biology of the Cell (© Garland Science 2009)

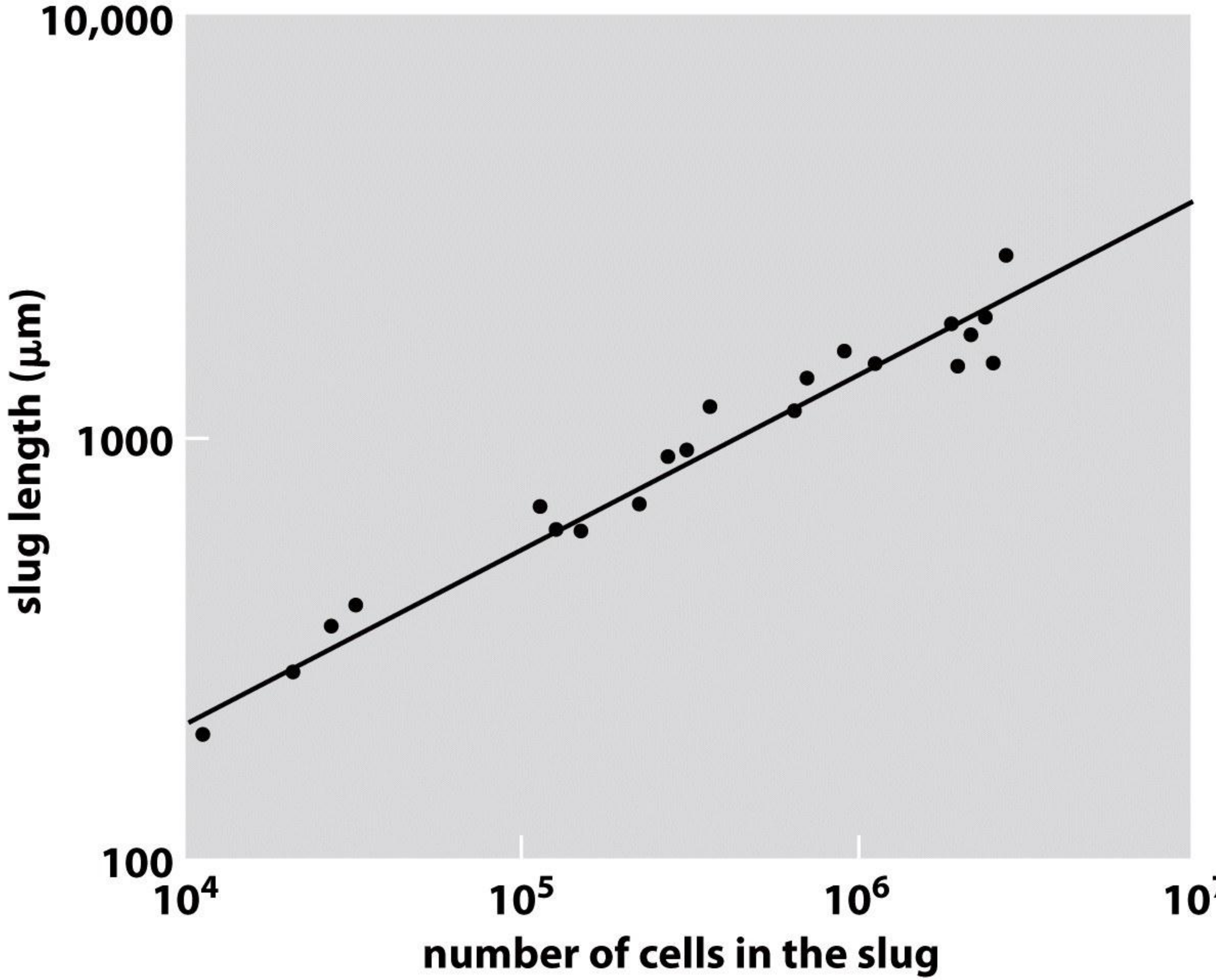


Figure 2.28 Physical Biology of the Cell (© Garland Science 2009)

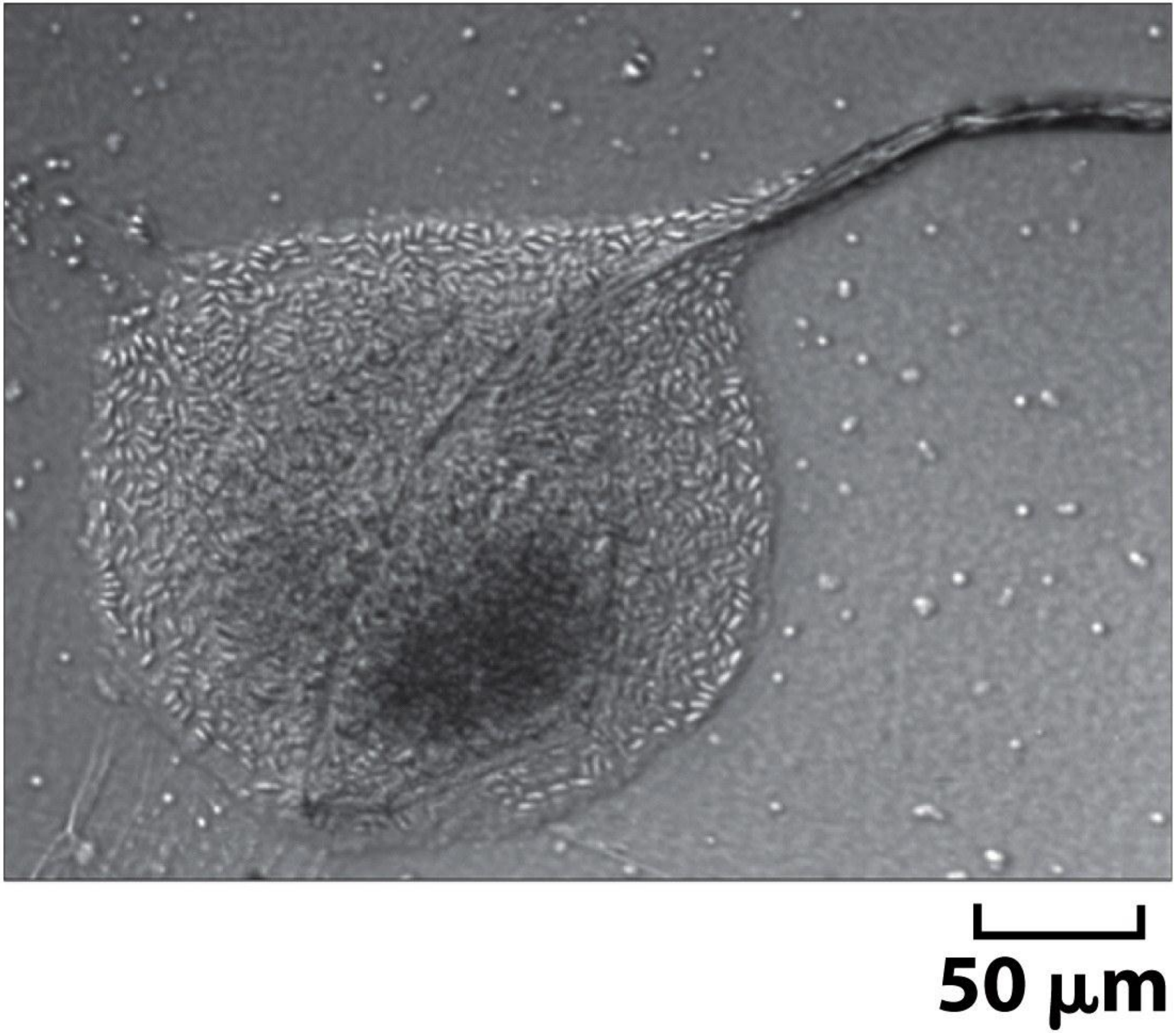


Figure 2.29 Physical Biology of the Cell (© Garland Science 2009)

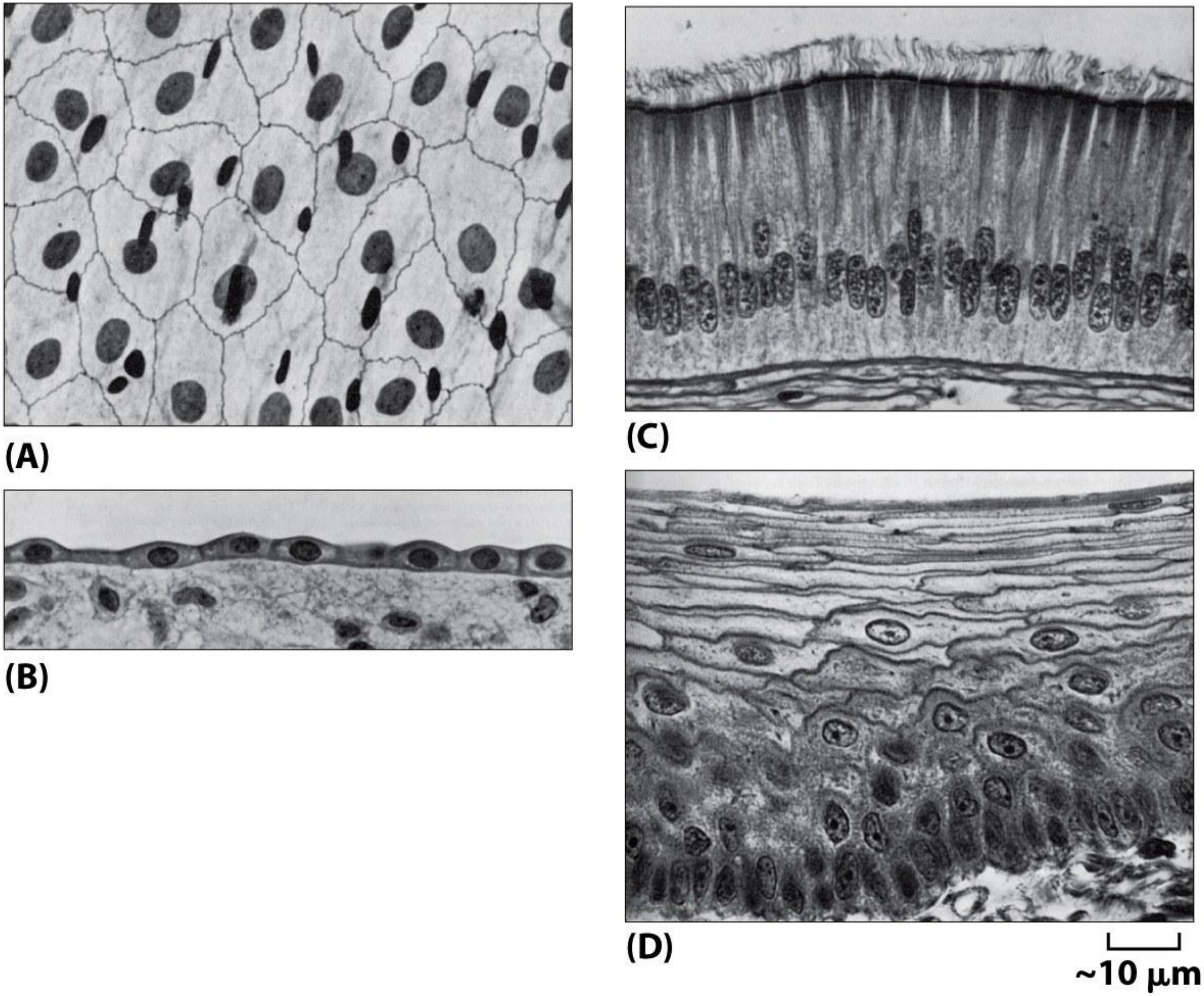


Figure 2.30 Physical Biology of the Cell (© Garland Science 2009)

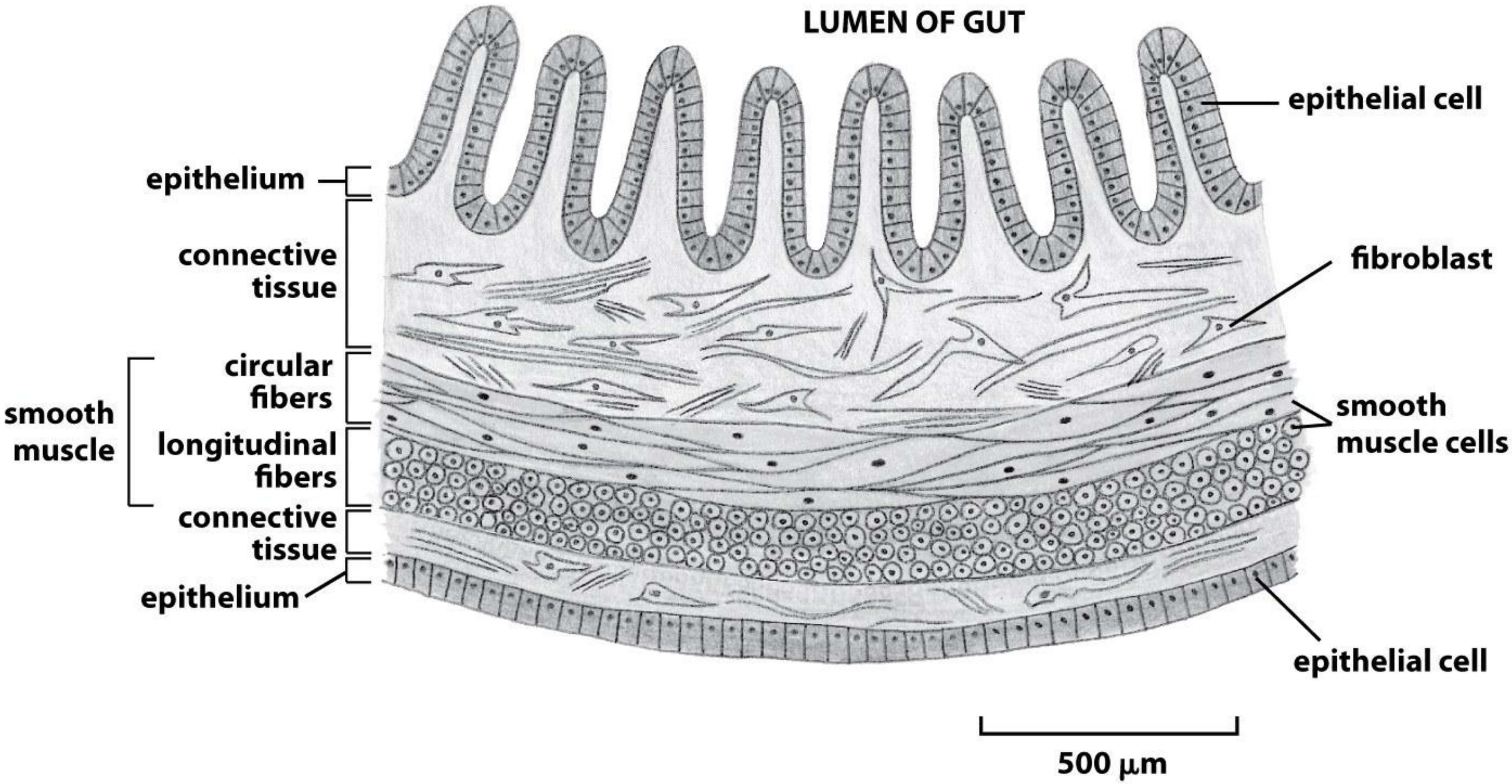


Figure 2.31 Physical Biology of the Cell (© Garland Science 2009)

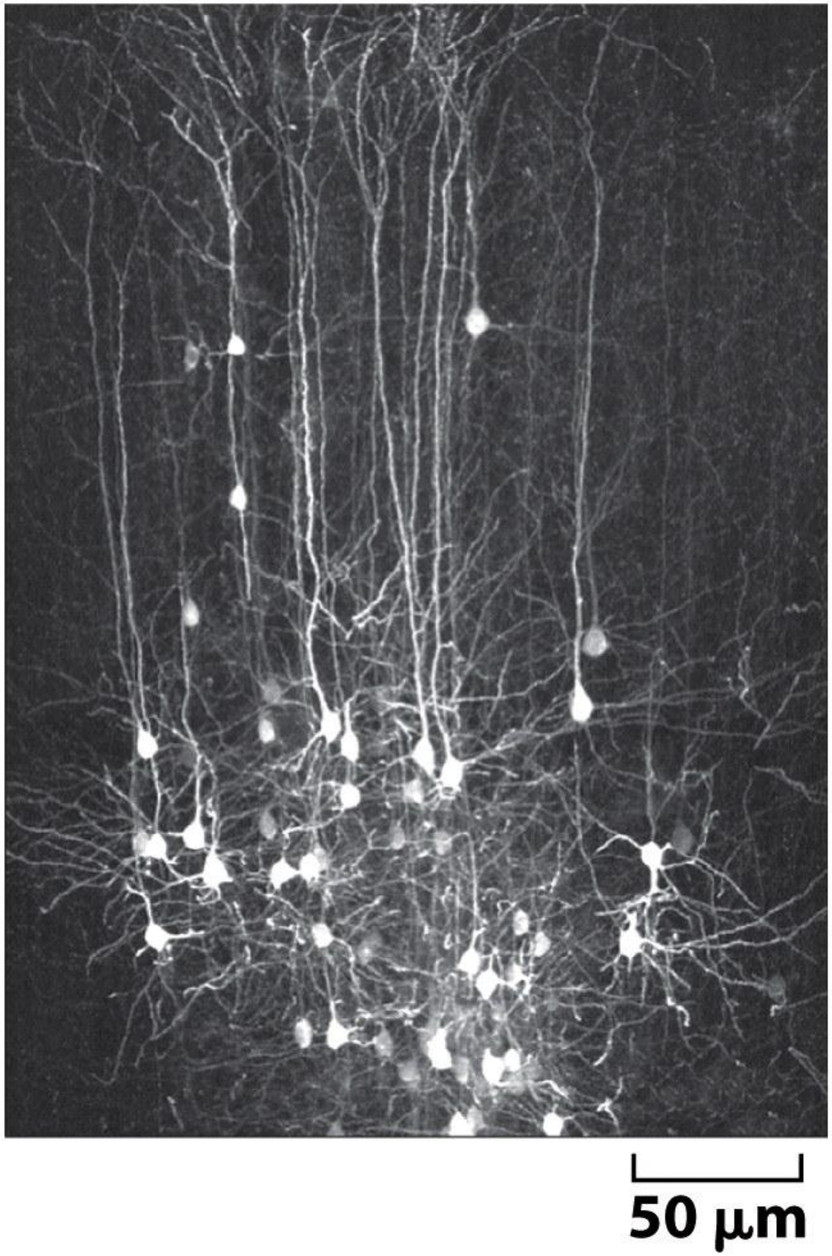


Figure 2.32 Physical Biology of the Cell (© Garland Science 2009)

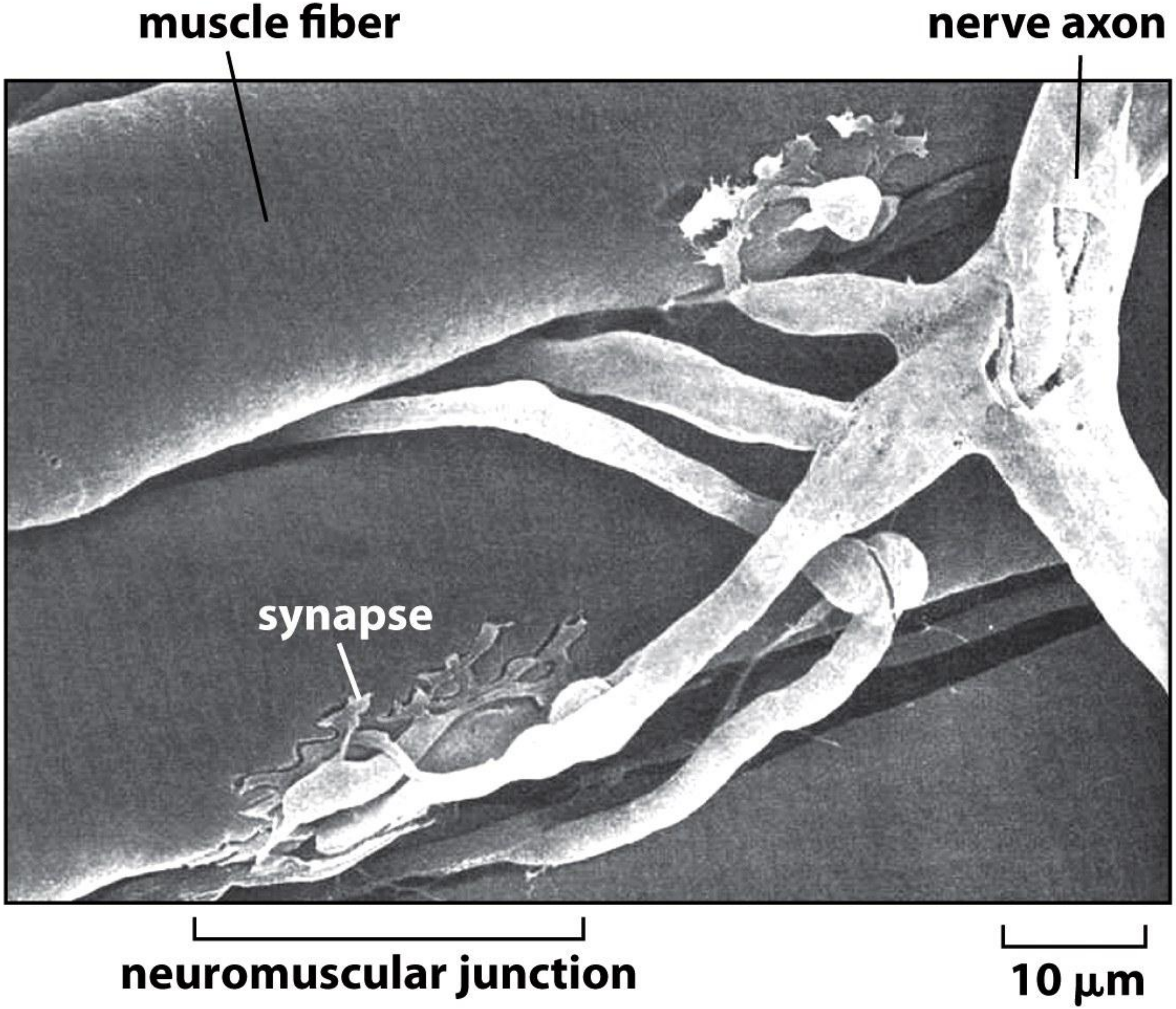


Figure 2.33 Physical Biology of the Cell (© Garland Science 2009)

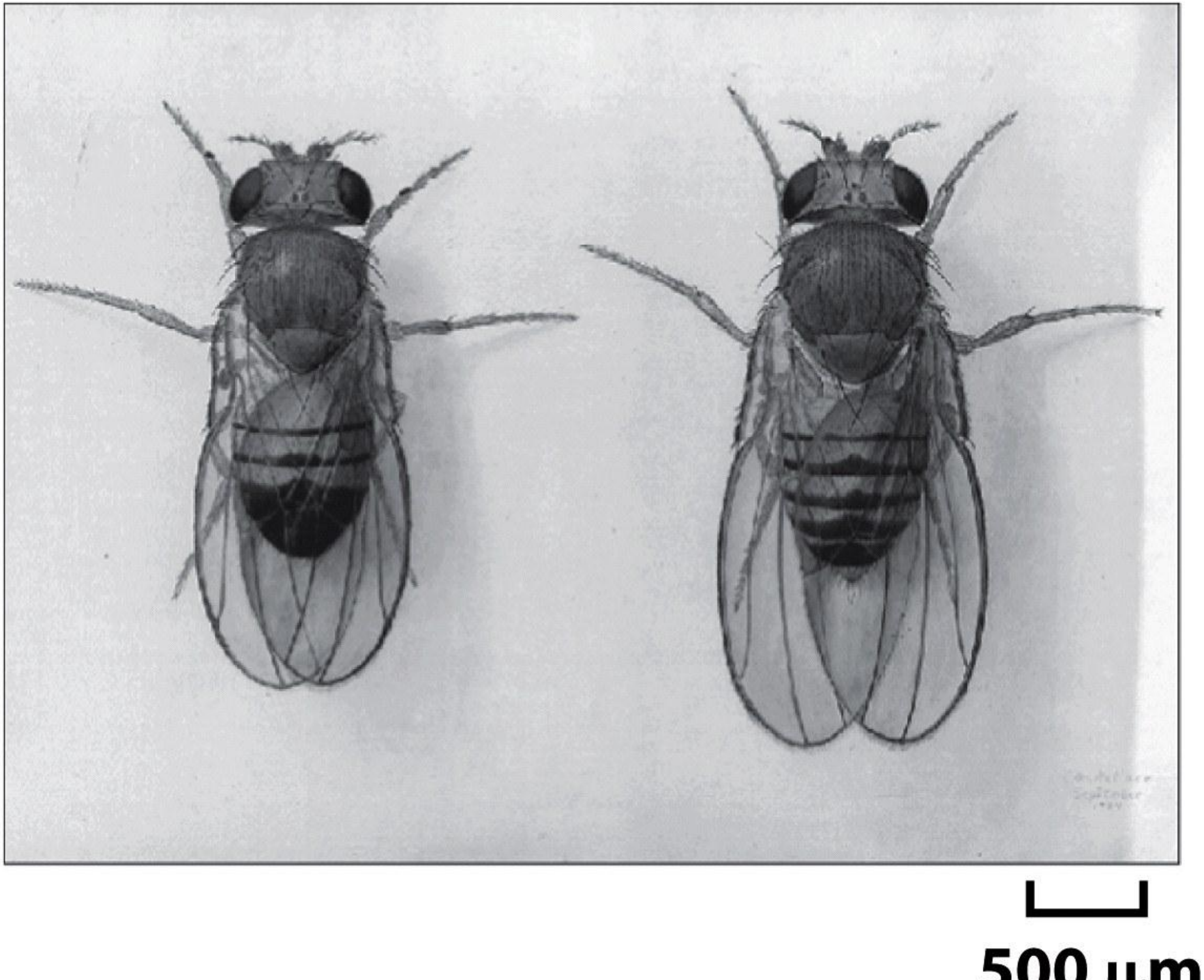


Figure 2.34 Physical Biology of the Cell (© Garland Science 2009)

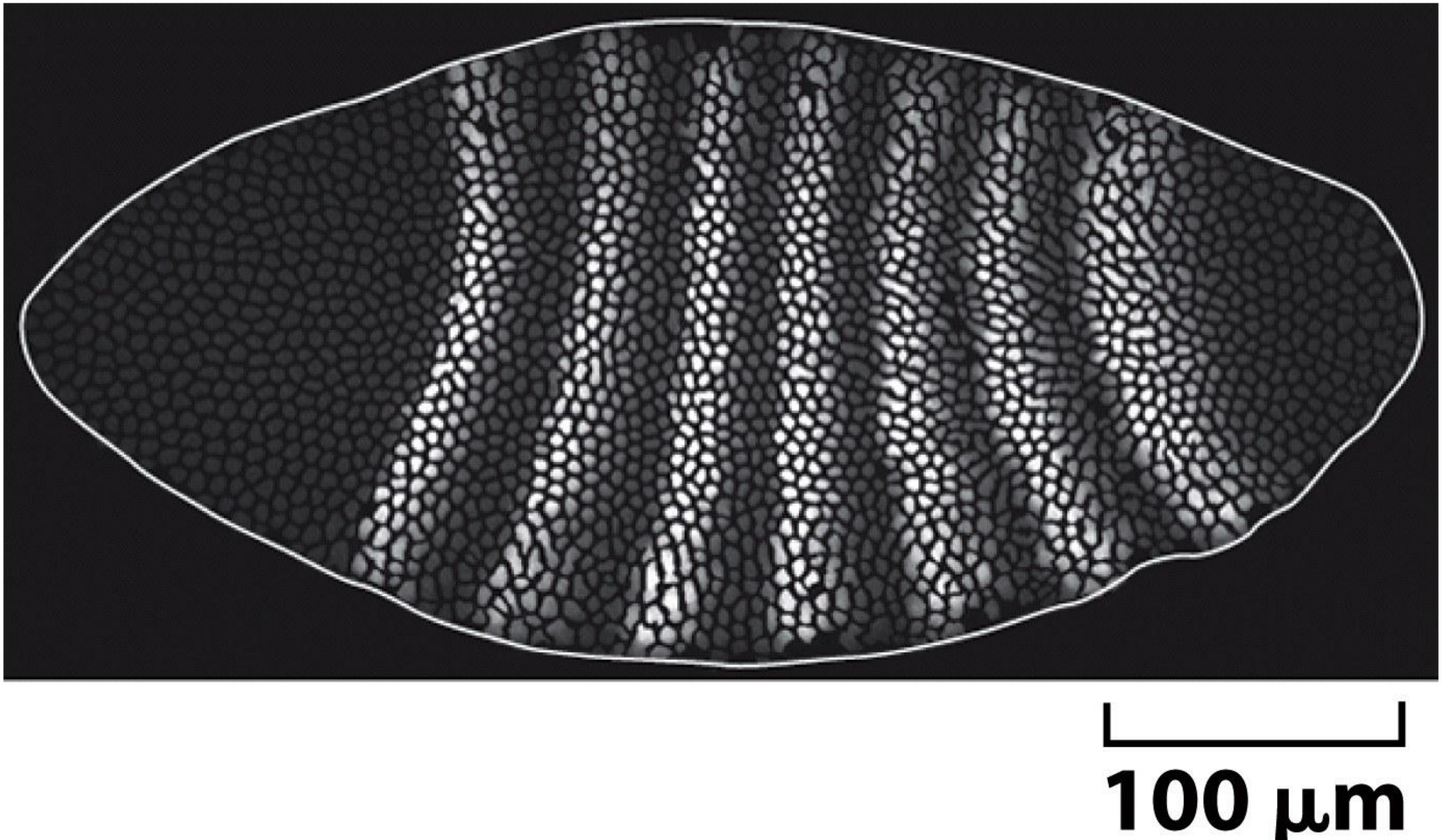


Figure 2.35 Physical Biology of the Cell (© Garland Science 2009)

Figure 2.36 Physical Biology of the Cell (© Garland Science 2009)

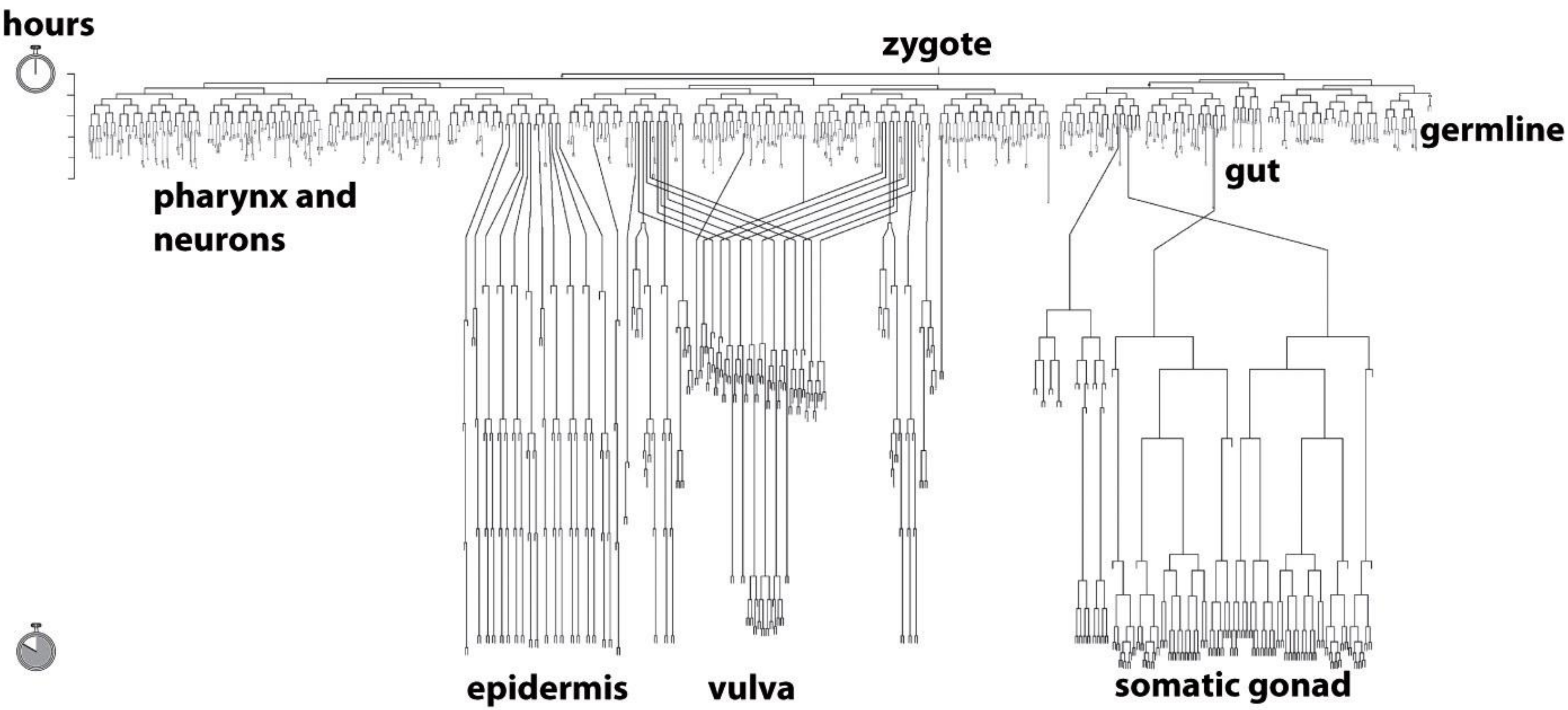


Figure 2.37 Physical Biology of the Cell (© Garland Science 2009)

Table 1.1 Rules of thumb for biological estimates

	Quantity of interest	Symbol	Rule of thumb
E. coli	Cell volume	$V_{E.\ coli}$	$\approx 1\ \mu m^3$
	Cell mass	$m_{E.\ coli}$	≈ 1 pg
	Cell cycle time	$t_{E.\ coli}$	≈ 3000 s
	Cell surface area	$A_{E.\ coli}$	$\approx 6\ \mu m^2$
	Genome length	$N_{bp}^{E.\ coli}$	$\approx 5 \times 10^6$ bp
	Swimming speed	$v_{E.\ coli}$	$\approx 20\ \mu m/s$
Yeast	Volume of cell	V_{yeast}	$\approx 60\ \mu m^3$
	Mass of cell	m_{yeast}	≈ 60 pg
	Diameter of cell	d_{yeast}	$\approx 5\ \mu m$
	Cell cycle time	t_{yeast}	≈ 200 min
	Genome length	N_{bp}^{yeast}	$\approx 10^7$ bp
Organelles	Diameter of nucleus	$d_{nucleus}$	$\approx 5\ \mu m$
	Length of mitochondrion	l_{mito}	$\approx 2\ \mu m$
	Diameter of transport vesicles	$d_{vesicle}$	≈ 50 nm
Water	Volume of molecule	V_{H_2O}	$\approx 10^{-2}\ nm^3$
	Density of water	ρ	$1\ g/cm^3$
	Viscosity of water	η	≈ 1 centipoise (10^{-2} g/(cm s))
	Hydrophobic embedding energy	$\approx E_{hydr}$	25 cal/(mol Å^2)
DNA	Length per base pair	l_{bp}	$\approx 1/3$ nm
	Volume per base pair	V_{bp}	$\approx 1\ nm^3$
	Charge density	λ_{DNA}	2 e/0.34 nm
	Persistence length	ξ_P	50 nm
Amino acids and proteins	Radius of "average" protein	$r_{protein}$	≈ 2 nm
	Volume of "average" protein	$V_{protein}$	$\approx 25\ nm^3$
	Mass of "average" amino acid	M_{aa}	≈ 100 Da
	Mass of "average" protein	$M_{protein}$	$\approx 30{,}000$ Da
	Protein concentration in cytoplasm	$c_{protein}$	≈ 300 mg/mL
	Characteristic force of protein motor	F_{motor}	≈ 5 pN
	Characteristic speed of protein motor	v_{motor}	≈ 200 nm/s
	Diffusion constant of "average" protein	$D_{protein}$	$\approx 100\ \mu m^2/s$
Lipid bilayers	Thickness of lipid bilayer	d	≈ 5 nm
	Area per molecule	A_{lipid}	$\approx \frac{1}{2}\ nm^2$
	Mass of lipid molecule	m_{lipid}	≈ 800 Da

Table 1.1 Physical Biology of the Cell (© Garland Science 2009)