Lecture 3:
Mechanical and Chemical Equilibrium In the Living Cell

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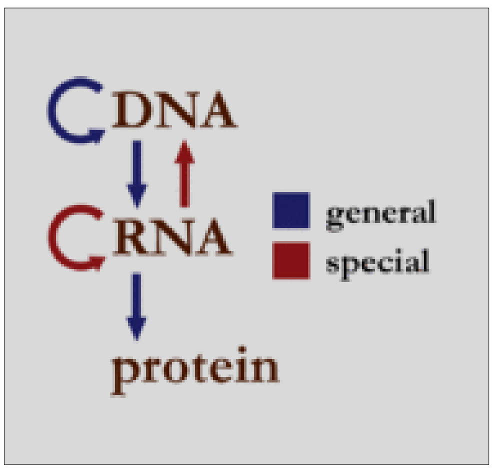
The Central Dogma Of Molecular Biology



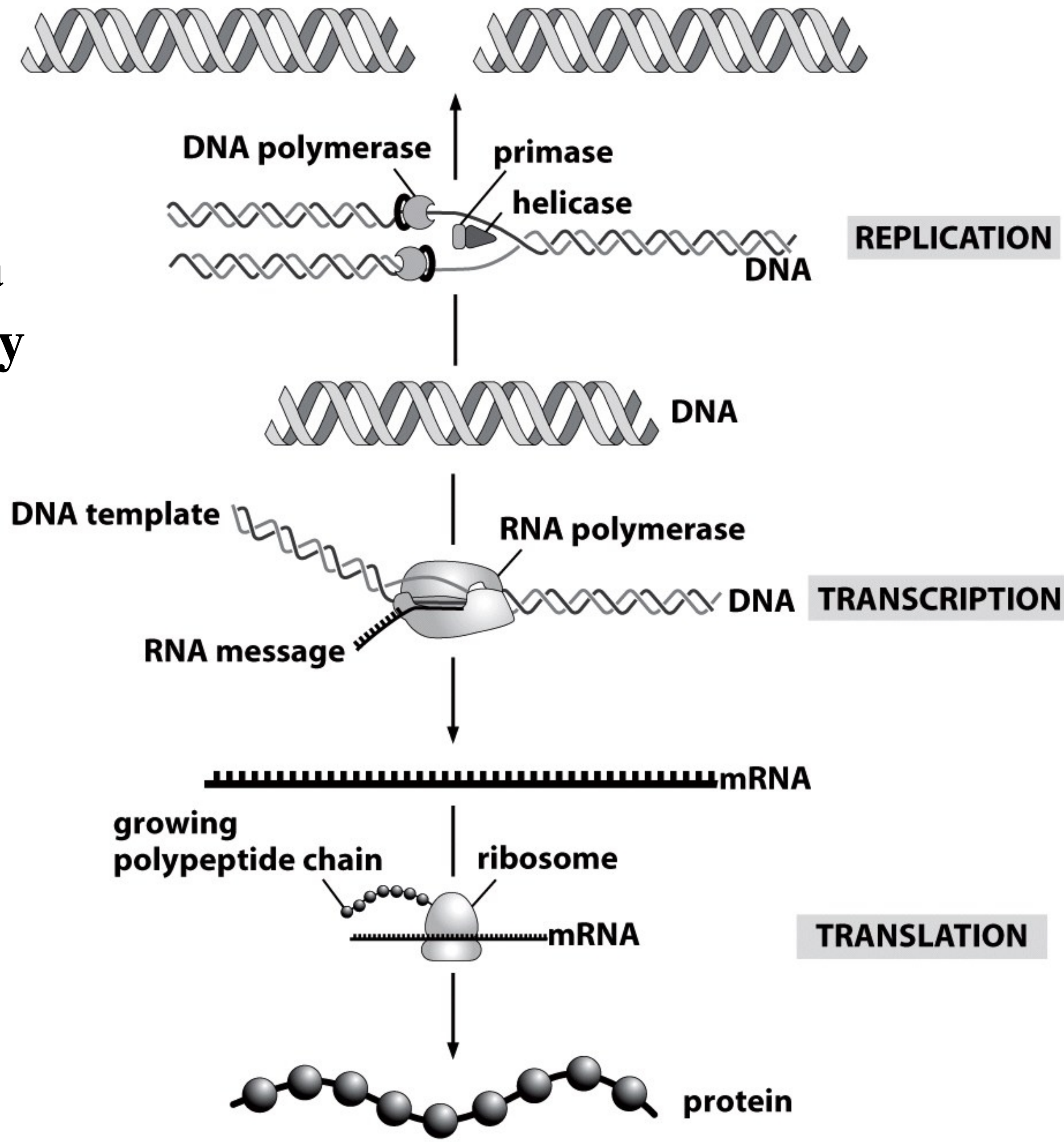


Figure 3.8 Physical Biology of the Cell (© Garland Science 2009)

The Bacterial Standard Ruler:
E. coli

- **prokaryotic cell (no compartments)**
- **minimal requirements for life:**
  - **-DNA based genome**
  - **-DNA → RNA transcription**
  - **-ribosomes (convert RNA into protein sequences)**

A) AMF image
B) electron micrograph
C) schematic picture

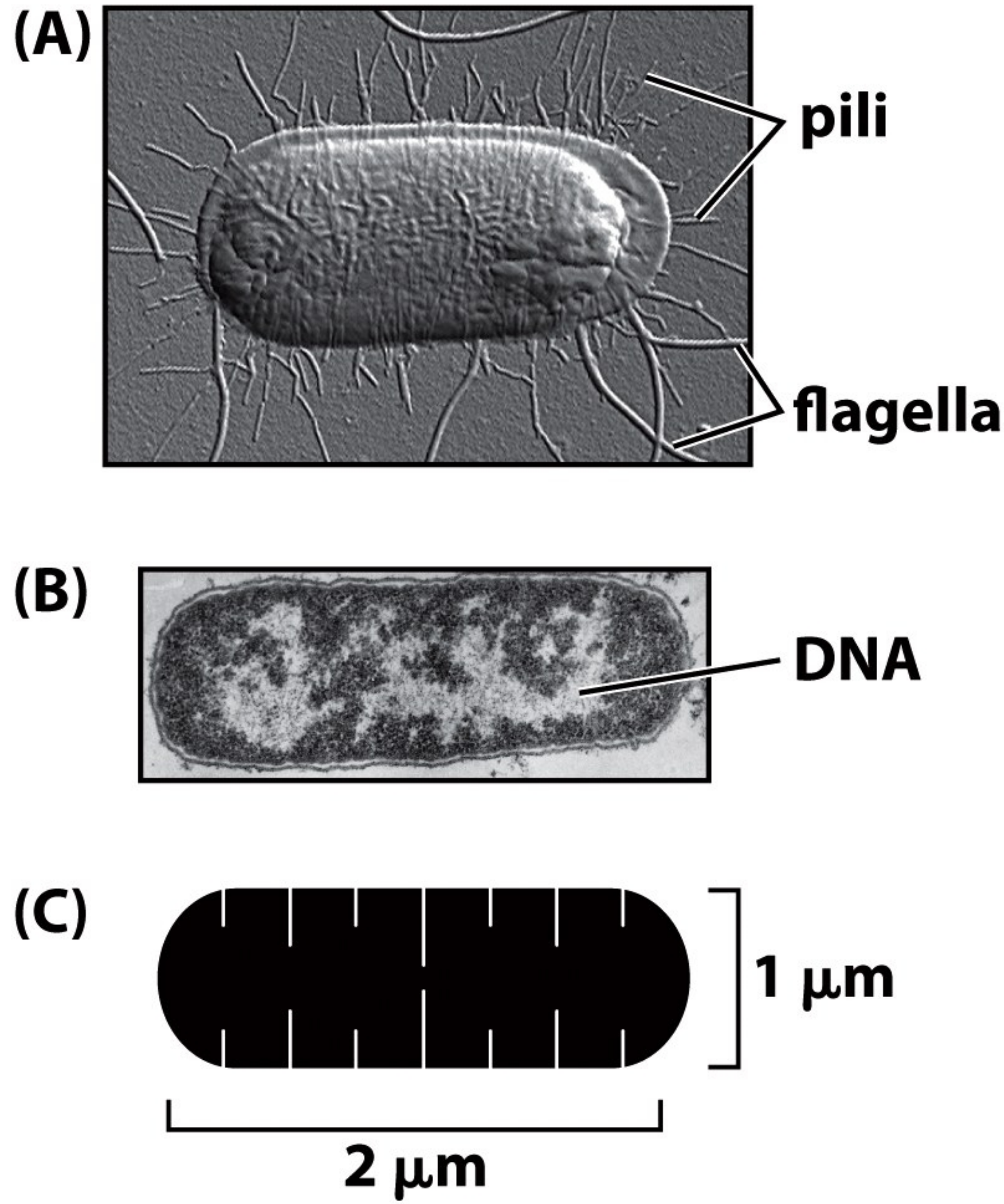


Figure 2.1 Physical Biology of the Cell (© Garland Science 2009)

What is the *E. coli's* intracellular environment like?
crowded with many macromolecules

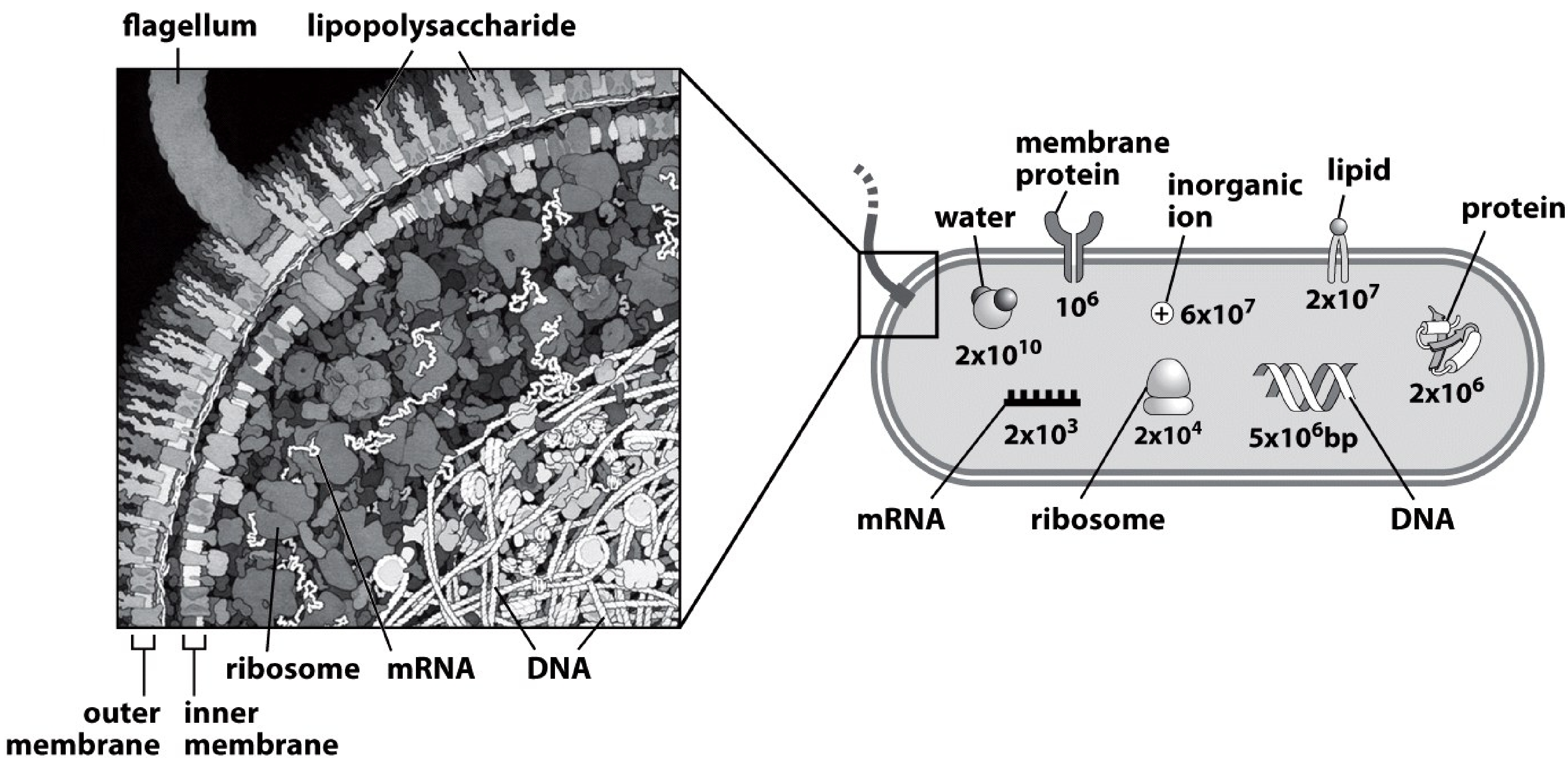


Figure 2.2 Physical Biology of the Cell (© Garland Science 2009)

Molecular census on *E. coli* (has 4 lipid layers):

- **volume: 1 fL = 10^{-15} L; mass: 1pg = 10^{-12} g; density: 1g/mL (H_2O)**
- **dry weight of the cell: ~30% of its total (0.30pg);**
  half of dry weight is protein (0.15 pg)
- **half of dry mass comes from the carbon content of E. coli, so there is ~10^{10} carbon atoms in a cell**
- **number of proteins: assume each protein ~300 amino acids and each amino acid 100 Da (30 kDa; 1 Da = 1.6 x 10^{-24} g), thus: 3 x 10^{6} proteins (1/3 of these within the membrane, 2/3 inside)**
- **number of ribosomes: the mass of each ribosome 2.5 Mda; each ribosome is consists 1/3 of protein and 2/3 of RNA; 20% of all proteins in the cell resides in ribosomes: 20,000 ribosomes (Total ribosomal protein mass/protein mass inside on ribosome)**
- **the diameter of ribosome is 20 nm: 10% cell volume**

An *E. coli* cell: Macromolecular census

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 Observed macromolecular census of an *E. coli* cell. (Data from F. C. Neidhardt et al., Physiology of the Bacterial Cell, Sunderland, Sinauer Associates Inc., 1990 and M. Schaechter et al., Microbe, Washington DC, ASM Press, 2006.)

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

(A) the protist *Giardia lamblia*
(B) a plant cell
(C) yeast cell (with a bud)
(D) red blood cell
(E) a fibroblast cell
(F) a nerve cell
(G) retinal rod cell

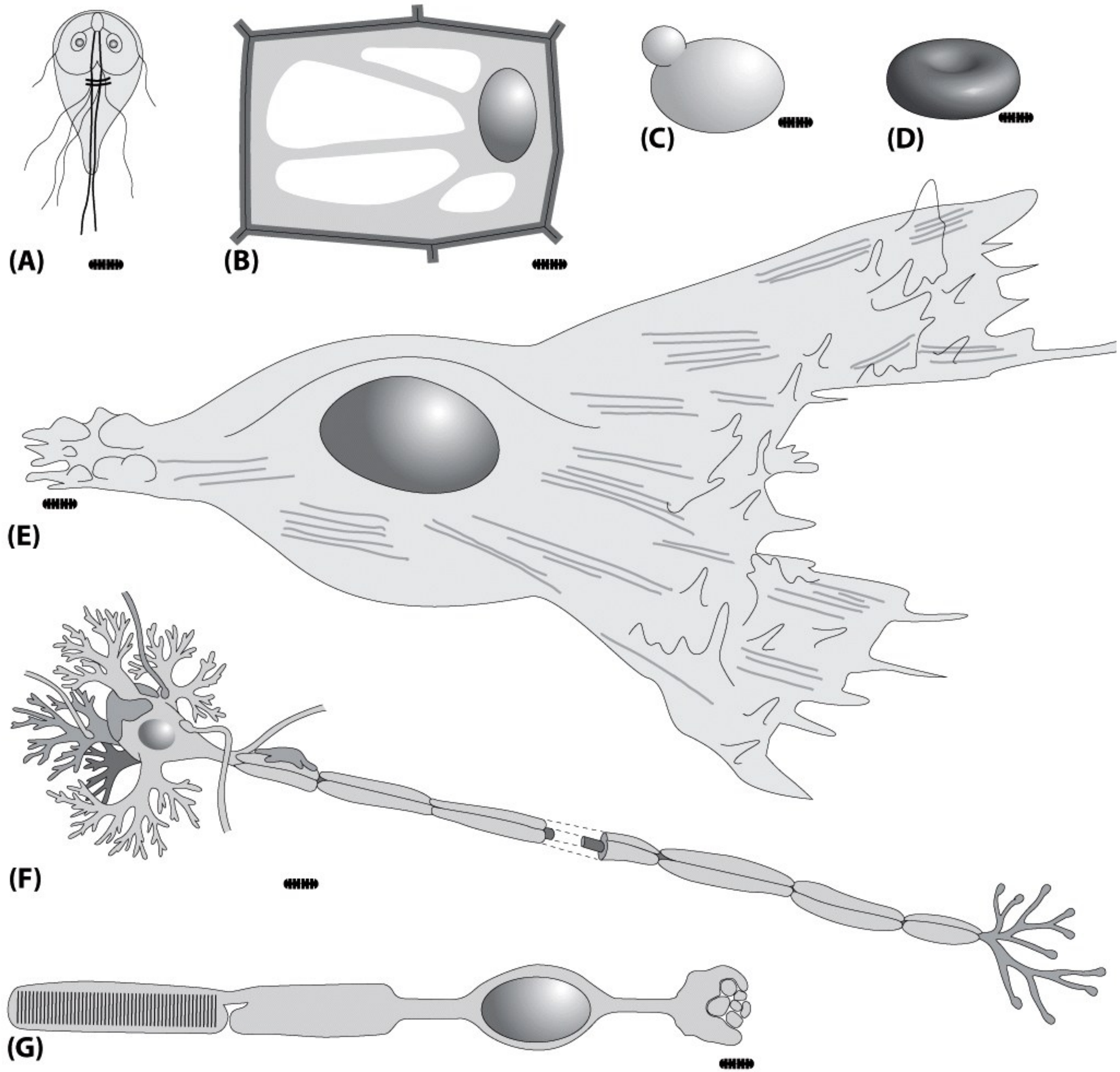


Figure 2.8 Physical Biology of the Cell (© Garland Science 2009)

Molecular census on a yeast cell:

- ➔ ***E. coli*** **volume:** $V_{E.\ Coli} = 1.0\ \mu m^3$ **(1 x 2** μ**m)**
- ➔ **Yeast: a sphere of diameter 5** μ**m:** $V_{yeast} = 65\ \mu m^3 \sim 60\ V_{E.\ Coli}$ **; surface area** $A_{yeast} \sim 80\ \mu m^2$ **; yeast nucleus a sphere of diameter 2** μ**m and volume ~ 4** μm^3 **with** 1.2×10^7 **base pairs (bp) of yeast genome (16 chromosomes)**
- ➔ **DNA packed into nucleosomes (histone-DNA complexes): 150 bp wrapped around a cylindrical core, histone octamer (radius 3.5 nm, height 6 nm, volume 230** nm^3**), with 50 bp spacers:**

$$N_{nucleosomes} \sim 60{,}000$$

(Exp. 80,000 nucleosomes with a mean spacing of ~170 bp)

- ➔ **volume of one bp ~ 1** nm^3 **& volume of all histones:** $14 \times 10^6\ nm^3$
- ➔ **the genomic DNA packing fraction** $\rho_{pack} \sim 3 \times 10^{-3}$

Chemical, mechanical, electromagnetic, thermal energy versus length scale

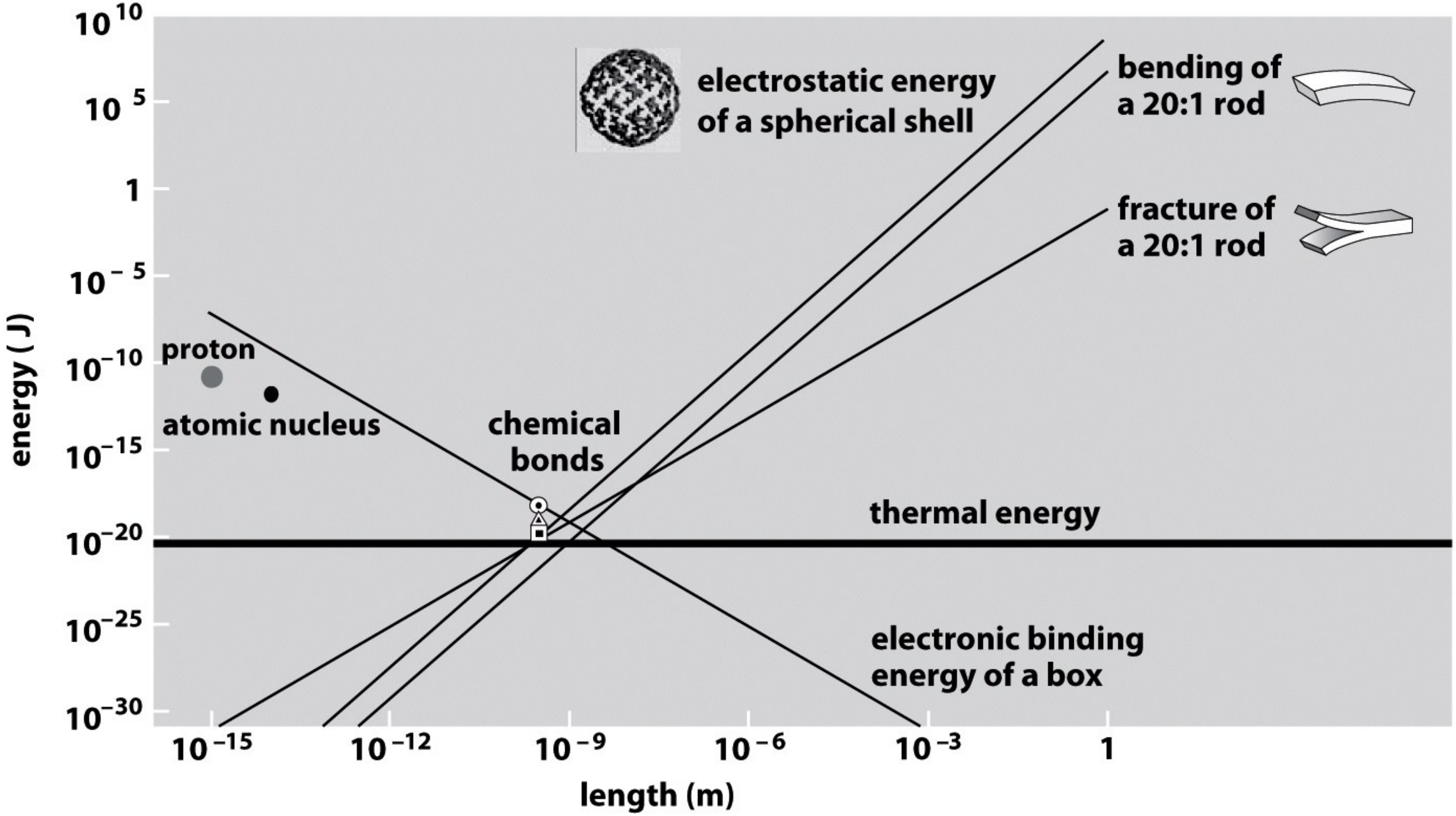


Figure 5.1 Physical Biology of the Cell (© Garland Science 2009)

Thermal energy at room temperature T = 300 K:

$k_B T = 1.38 \times 10^{-23}$ J/K x 300 K = 4.1 pN nm

= 25 meV = 2.5 kJ/mol = 0.6 kcal/mol

(Avogadro's number: $N_A = 6.022 \times 10^{23}$)

Brownian (thermal) motion: important for nm to μm length scales.
For macromolecules (DNA, proteins, lipids, and carbohydrates) ~ nm
Scale: thermal energy ~ energy needed for intramolecular rearrangement!

Discussion:

Where does the energy to sustain life come from?

- **food intake (animals eat plants and other animals, how about plants?)**

$$CO_2 + H_2O + \text{energy} \leftrightarrow \text{sugar} + O_2$$

- **plants requires input energy (through photosynthesis store some input EM energy (sunlight) into the chemical bonds of sugar)**

How is then sugar converted into the energy the cells need to be able to form the needed macromolecules? How do the cells store the energy?

Metabolic breakdown of glucose in a *glycolysis* pathway

metabolism … cellular transformation of one molecule into another

needs input energy (ATP)

produces more energy (ATP, NADH)

end product: two molecules of pyruvate

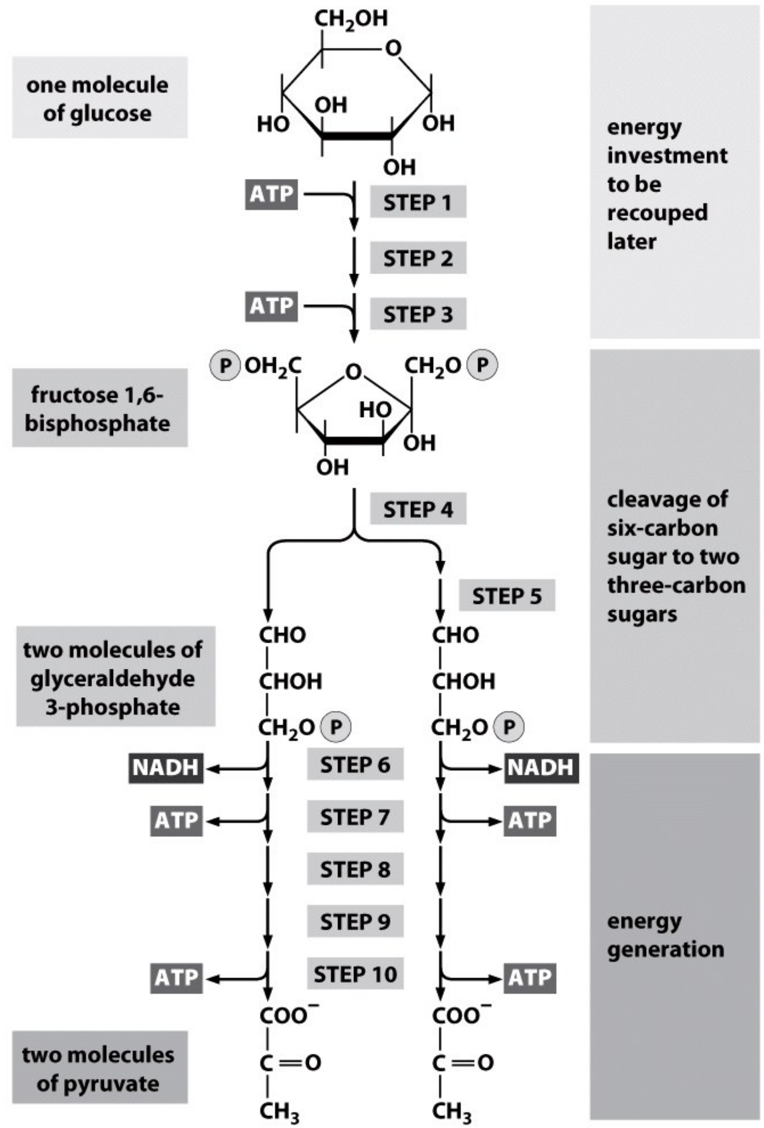
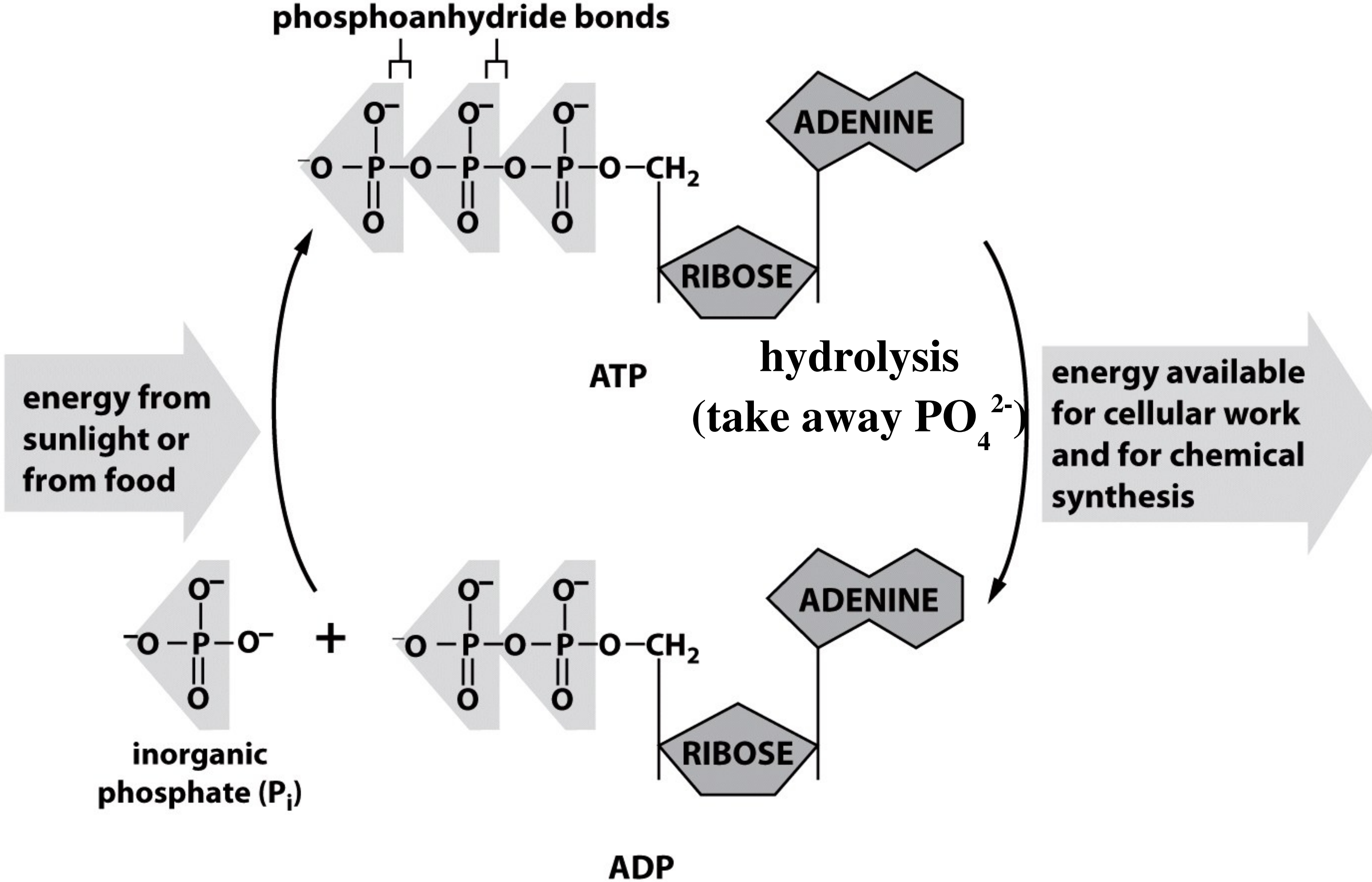


Figure 5.2 Physical Biology of the Cell (© Garland Science 2009)

1. ATP (conversion to ADP releases ~ 20 $k_B T$ energy; unit of energy in cell processes)

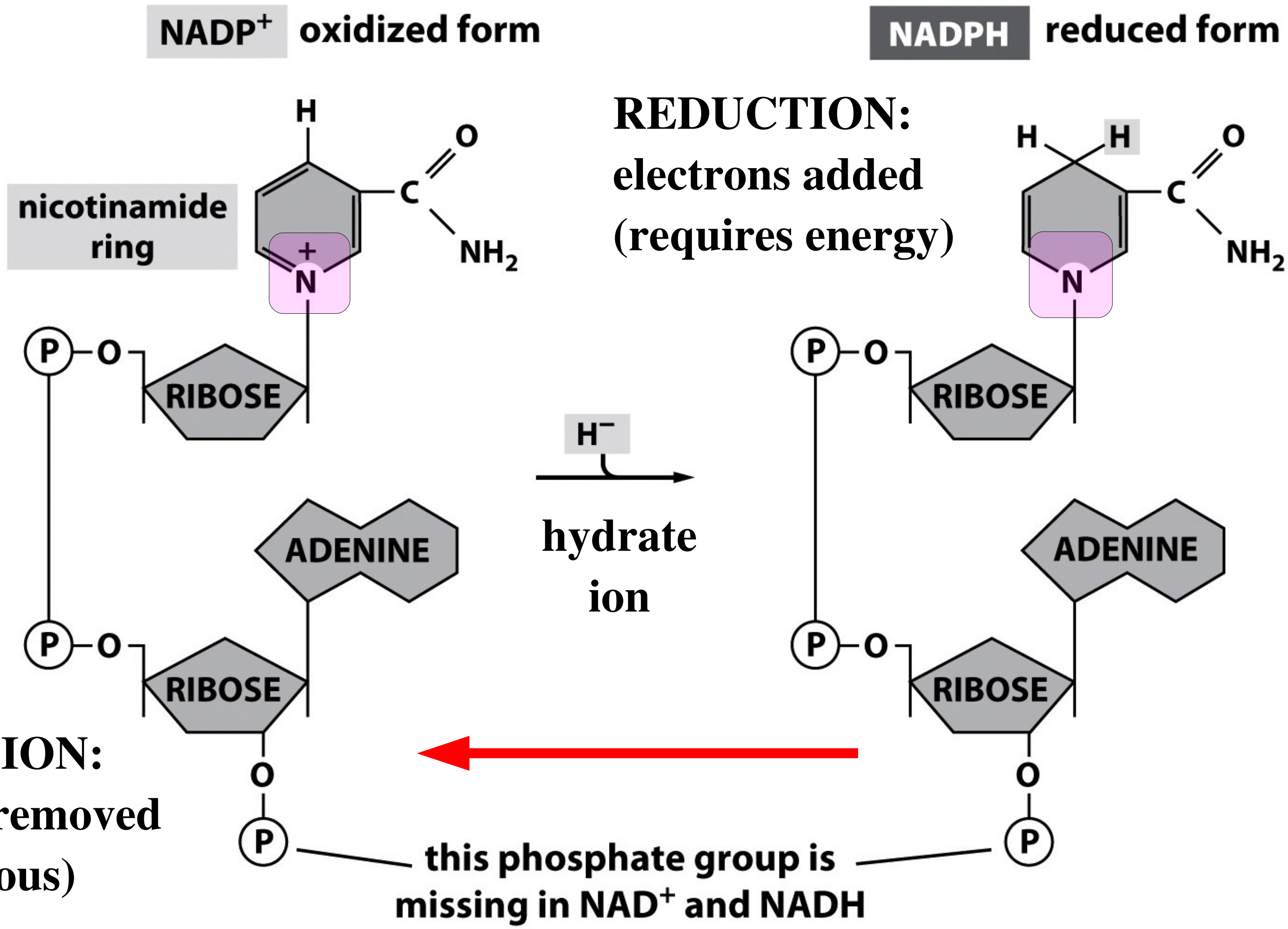


hydrolysis
(take away PO_4^{2-})

Figure 5.3a Physical Biology of the Cell (© Garland Science 2009)

2. Transferable electrons on NADH and NADPH:

NADPH gives up its hydrate ion and liberates energy



REDUCTION:
electrons added
(requires energy)

hydrate
ion

OXYDATION:
electrons removed
(spontaneous)

Figure 5.3b Physical Biology of the Cell (© Garland Science 2009)

3. Create H^+ gradients across the membrane (can be converted to ATP or NADH energy)

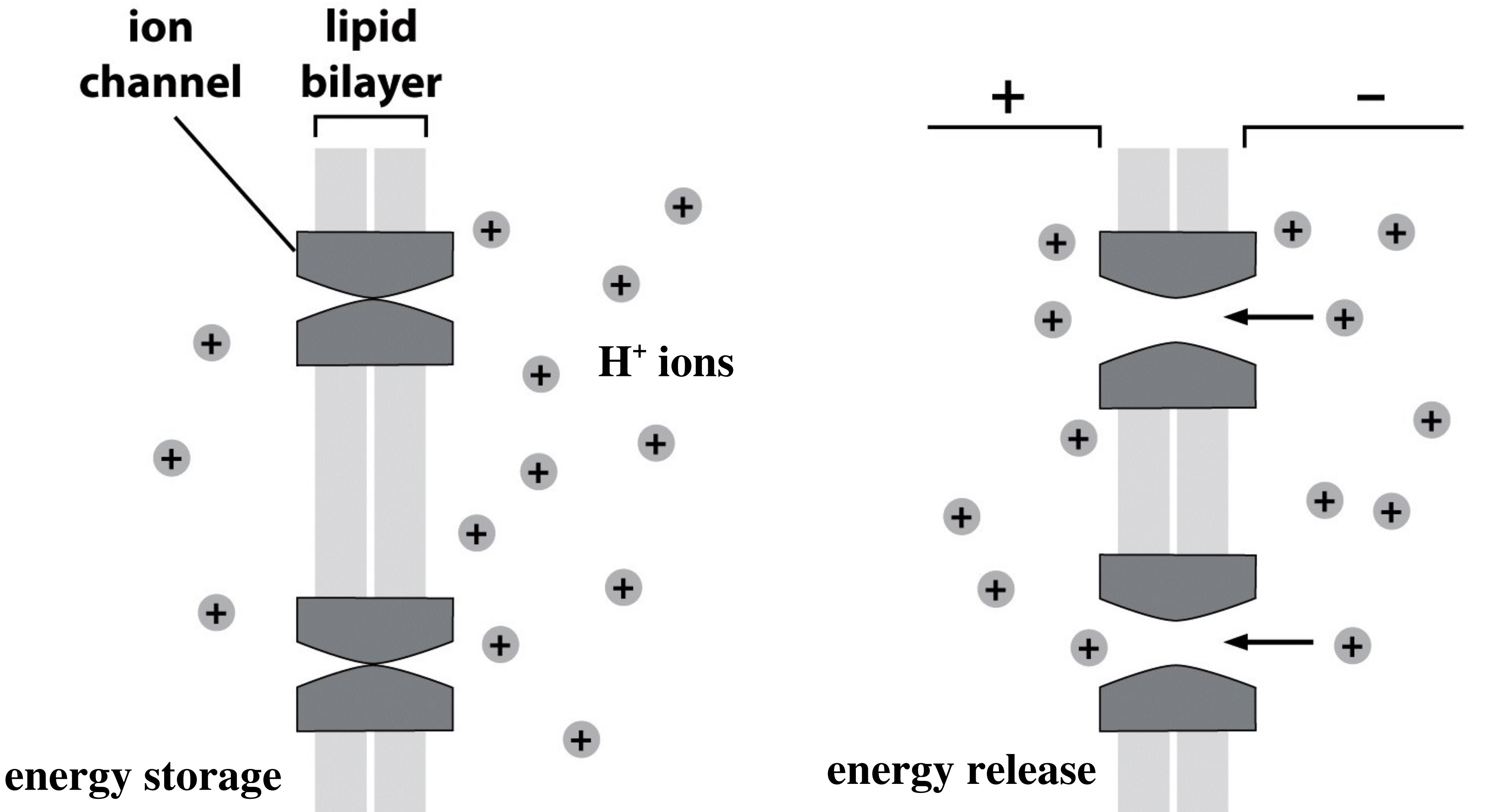


Figure 5.3c Physical Biology of the Cell (© Garland Science 2009)

Synthesis of Biological Molecules

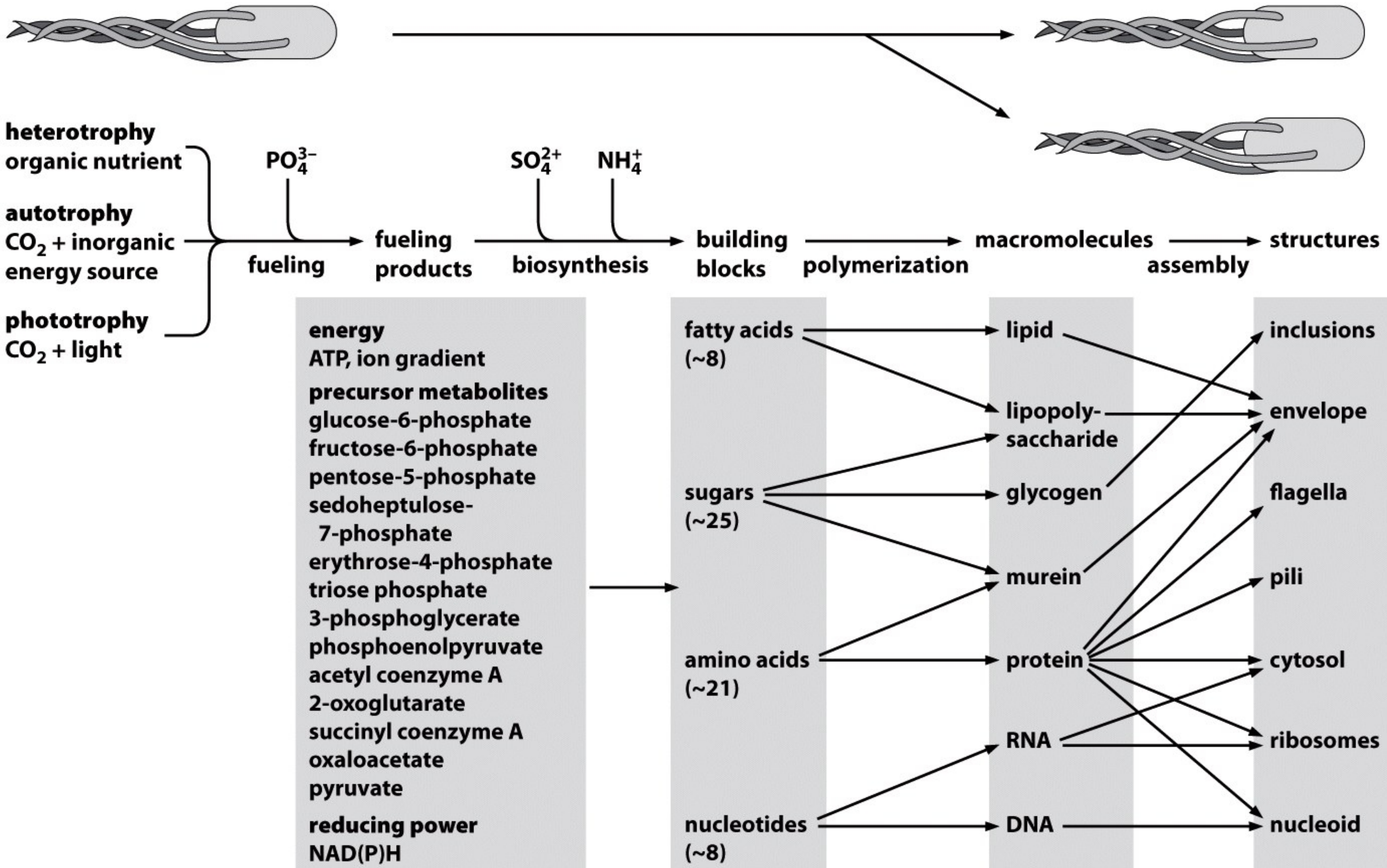


Figure 5.4 Physical Biology of the Cell (© Garland Science 2009)

Biosynthesis of proteins

- glucose as a sole carbon source: 10^{10} C-atoms in *E.coli* cell (6 C-atoms per glucose, need 2×10^{9} glucose molecules just to construct a cell)

- metabolic pathways for synthesis of 20 amino acids known but complex; connected to glycolytic pathway:
  (alanine from pyruvate in a single step by a single enzyme)

- an average energetic cost to synthesize an amino acid is:
  1.2 ATP equivalents aerobically
  4.7 ATP equivalents anaerobically

- Build a protein from amino acids: 4 ATP equivalents
  form peptide bonds
  attach amino acids to tRNA (carries one codon, 73-93 nucleotides)
  power the movement of ribosome

In total, to build a protein: 5.2 ATP equivalents per amino acid:

For the entire *E.coli* cell: 5.2 ATP x 300 x 3 x 10^6 =
4.5 x 10^9 ATP

How about DNA/RNA building?
- **to synthesize one nucleotide: 10-20 ATP**
- **cost of assembling nucleotides into polymers is small (10%)**

How much energy can one glucose generate?
- **under ideal growing conditions: 30 ATP (CO_2 waste product)**

Total cost of *E.coli* cell building: 10^{10} ATP or 6 x 10^8 glucose molecules (1/3 of the material required under ideal conditions and up to 10-fold in less efficient growth conditions)

Amino acid	Abundance (molecules per cell)	Glucose equivalents	ATP equivalents (aerobic)	ATP equivalents (anaerobic)
Alanine (A)	2.9×10^8	0.5	−1	1
Arginine (R)	1.7×10^8	0.5	5	13
Asparagine (N)	1.4×10^8	0.5	3	5
Aspartate (D)	1.4×10^8	0.5	0	2
Cysteine (C)	5.2×10^7	0.5	11	15
Glutamate (E)	1.5×10^8	0.5	−7	−1
Glutamine (Q)	1.5×10^8	0.5	−6	0
Glycine (G)	3.5×10^8	0.5	−2	2
Histidine (H)	5.4×10^7	1	1	7
Isoleucine (I)	1.7×10^8	1	7	11
Leucine (L)	2.6×10^8	1.5	−9	1
Lysine (K)	2.0×10^8	1	5	9
Methionine (M)	8.8×10^7	1	21	23
Phenylalanine (F)	1.1×10^8	2	−6	2
Proline (P)	1.3×10^8	0.5	−2	4
Serine (S)	1.2×10^8	0.5	−2	2
Threonine (T)	1.5×10^8	0.5	6	8
Tryptophan (W)	3.3×10^7	2.5	−7	7
Tyrosine (Y)	7.9×10^7	2	−8	2
Valine (V)	2.4×10^8	1	−2	2

Table 5.1 (part 2) Physical Biology of the Cell (© Garland Science 2009)

Seven major classes of macromolecular components

Table 5.2 Biosynthetic cost in ATP equivalents to synthesize the macromolecules of a single *E. coli* cell.

Class	Biosynthetic cost (aerobic) – ATP equiv.
Protein	4.5×10^9
DNA	3.5×10^8
RNA	1.6×10^9
Phospholipid	3.2×10^9
Lipopolysaccharide	3.8×10^8
Peptidoglycan	1.7×10^8
Glycogen	3.1×10^7

Table 5.2 Physical Biology of the Cell (© Garland Science 2009)

Biological Systems as Minimizers

➔ **mechanical and chemical equilibrium: minimization problems**

➔ **mechanical / chemical equilibrium: short time scales**

Example:

$$A \underset{k-}{\overset{k+}{\rightleftharpoons}} B \xrightarrow{r} C$$

if k+ and k- >> r (faster reactions), then A and B can be treated as if in chemical equilibrium

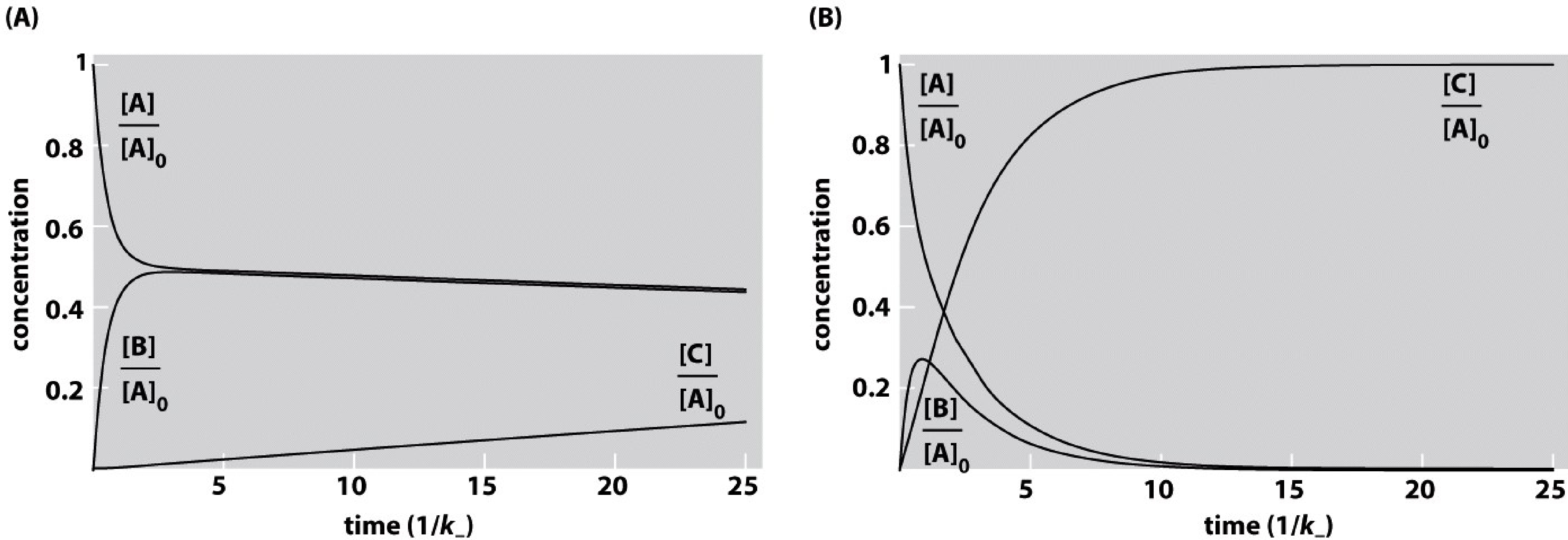


Figure 5.6 Physical Biology of the Cell (© Garland Science 2009)

Protein folding: Free energy minimization principle

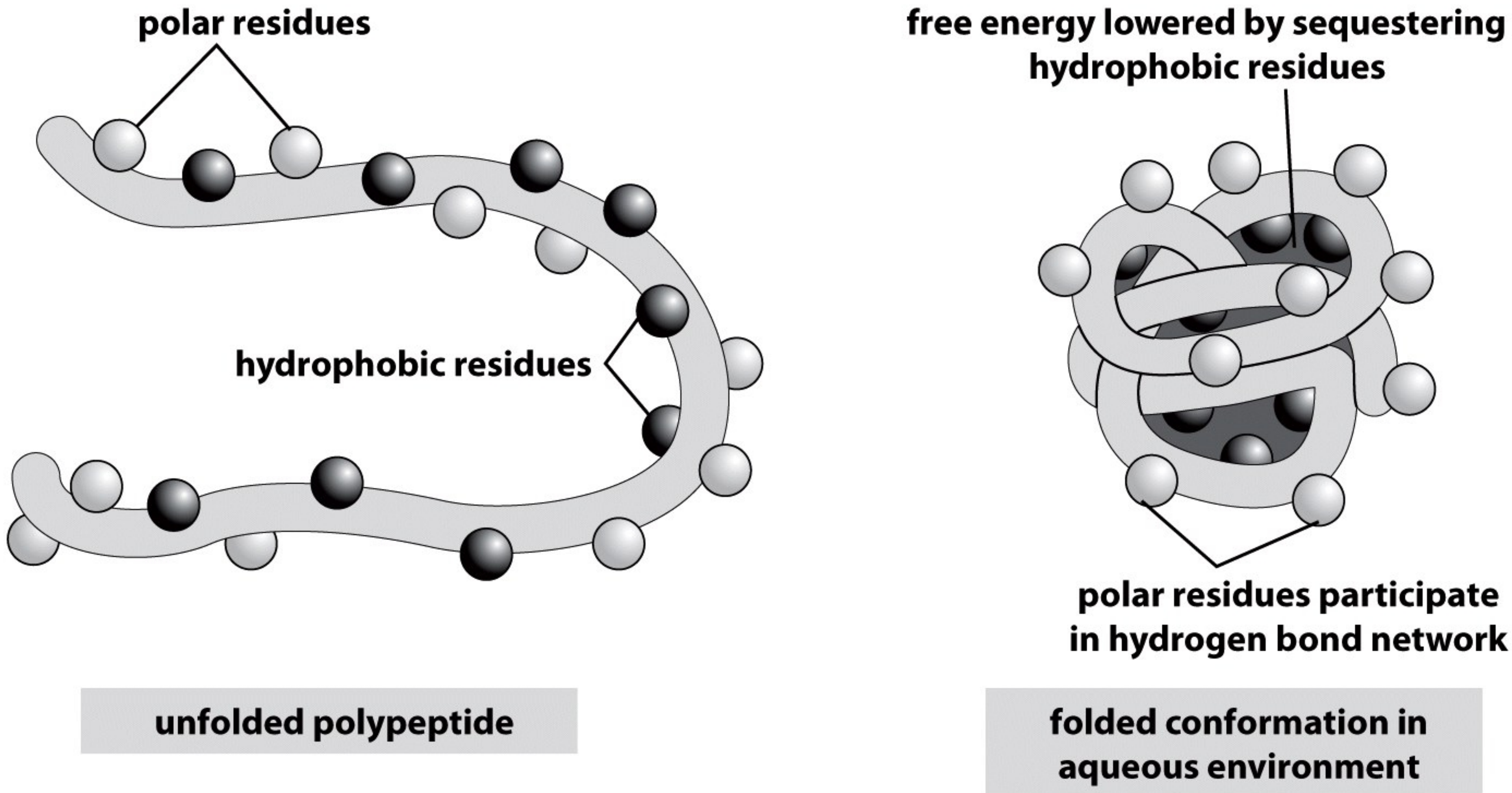


Figure 5.8 Physical Biology of the Cell (© Garland Science 2009)

Mechanical Equilibrium: Potential Energy Minimization

$$U(x) = k\,(x-x_0)^2/2 - mg\,(x - x_0)$$

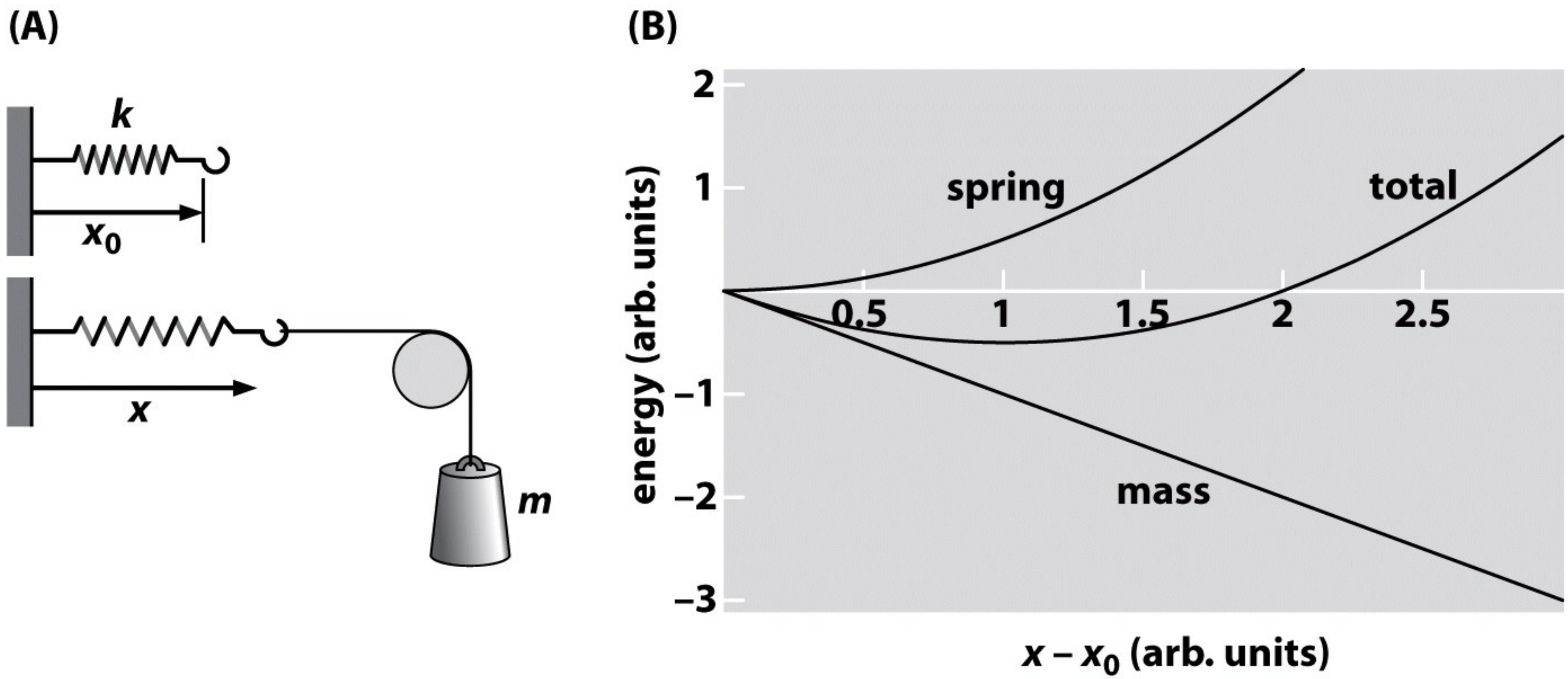


Figure 5.11 Physical Biology of the Cell (© Garland Science 2009)

Optical trap as a mass-spring system

→ **bead in an optical trap with DNA tether exerting a force:**

$$U(x) = k_{trap}\, x^2/2 - Fx$$

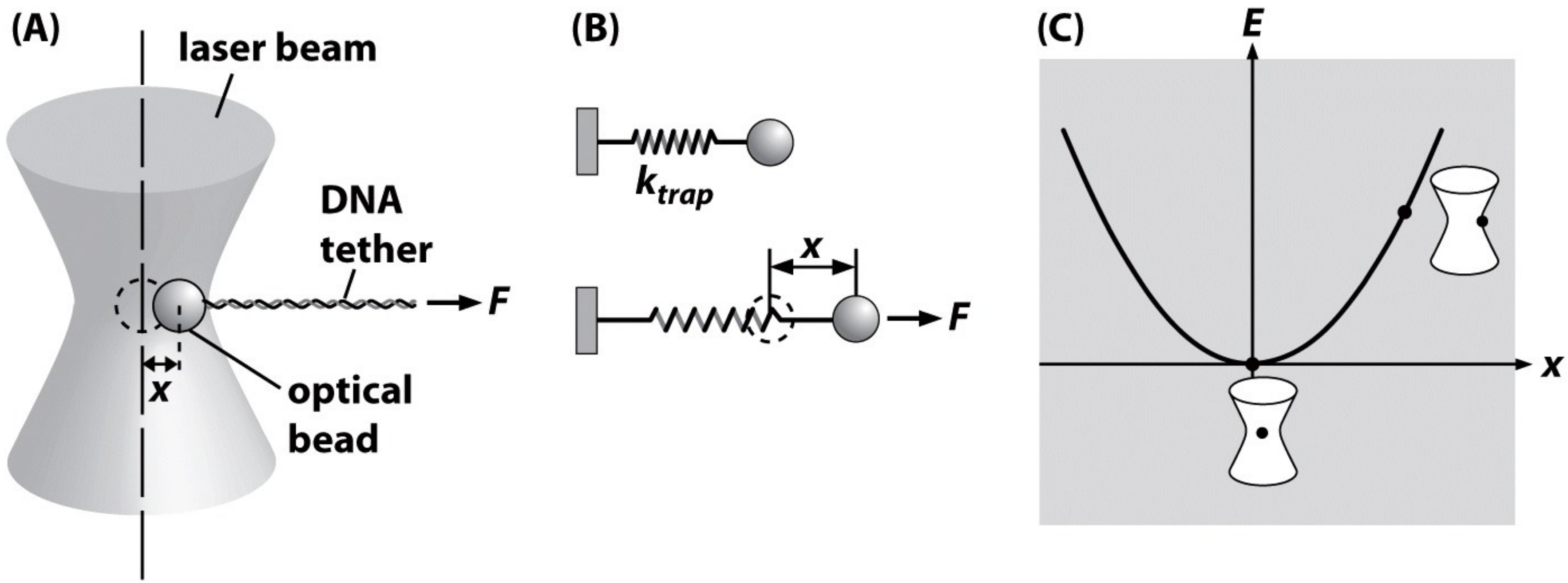


Figure 5.13 Physical Biology of the Cell (© Garland Science 2009)