Lecture 3:
Mechanical and Chemical Equilibrium
In the Living Cell

Lecturer:
Brigita Urbanc
Office: 12-909
(E-mail: brigita@drexel.edu)

Course website:
www.physics.drexel.edu/~brigita/COURSES/BIOPHYS_2011-2012/
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

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Figure 2.1 Physical Biology of the Cell (© Garland Science 2009)
What is the *E. coli*’s intracellular environment like? crowded with many macromolecules

![Diagram of E. coli](image)

Figure 2.2 Physical Biology of the Cell (© Garland Science 2009)
Molecular census on *E. coli* (has 4 lipid layers):

- volume: $1 \text{ fL} = 10^{-15} \text{ L}$; mass: $1\text{ pg} = 10^{-12} \text{ g}$; density: $1\text{ g/mL} (\text{H}_2\text{O})$

- dry weight of the cell: $\sim 30\%$ of its total ($0.30\text{ pg}$);
  half of dry weight is protein ($0.15 \text{ pg}$)

- half of dry mass comes from the carbon content of *E. coli*, so there is $\sim 10^{10}$ carbon atoms in a cell

- number of proteins: assume each protein $\sim 300$ amino acids and each amino acid $100 \text{ Da}$ ($30 \text{ kDa}$; $1 \text{ Da} = 1.6 \times 10^{-24} \text{ g}$), thus: $3 \times 10^6$ proteins ($1/3$ of these within the membrane, $2/3$ inside)

- number of ribosomes: the mass of each ribosome $2.5 \text{ Mda}$; 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 $20 \text{ nm}$: $10\%$ cell volume
An *E. coli* cell: Macromolecular census

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

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
Molecular census on a yeast cell:

→ *E. coli* volume: $V_{E.\,Coli} = 1.0 \, \mu m^3 \ (1 \times 2 \, \mu m)$

→ Yeast: a sphere of diameter $5 \, \mu m$: $V_{\text{yeast}} = 65 \, \mu m^3 \sim 60 \, V_{E.\,Coli}$; surface area $A_{\text{yeast}} \sim 80 \, \mu m^2$; yeast nucleus a sphere of diameter $2 \, \mu m$ and volume $\sim 4 \, \mu m^3$ with $1.2 \times 10^7$ base pairs (bp) of yeast genome (16 chromosomes)

→ DNA packed into nucleosomes (histone-DNA complexes): $150 \, \text{bp}$ wrapped around a cylindrical core, histone octamer (radius $3.5 \, \text{nm}$, height $6 \, \text{nm}$, volume $230 \, \text{nm}^3$), with $50 \, \text{bp}$ spacers:

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

(Exp. $80,000$ nucleosomes with a mean spacing of $\sim 170 \, \text{bp}$)

→ volume of one bp $\sim 1 \, \text{nm}^3$ & volume of all histones: $14 \times 10^6 \, \text{nm}^3$

→ the genomic DNA packing fraction $\rho_{\text{pack}} \sim 3 \times 10^{-3}$
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:

\[ k_B T = 1.38 \times 10^{-23} \text{ J/K} \times 300 \text{ K} = 4.1 \text{ pN nm} \]

\[ = 25 \text{ meV} = 2.5 \text{ kJ/mol} = 0.6 \text{ kcal/mol} \]

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

Brownian (thermal) motion: important for nm to \( \mu \text{m} \) length scales. For macromolecules (DNA, proteins, lipids, and carbohydrates) \( \sim \) nm Scale: thermal energy \( \sim \) 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?)

\[ \text{CO}_2 + \text{H}_2\text{O} + \text{energy} \leftrightarrow \text{sugar} + \text{O}_2 \]

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)
2. Transferable electrons on NADH and NADPH:
NADPH gives up its hydrate ion and liberates energy

[Diagram showing the structure of NADP⁺ and NADPH]

OXYDATION: electrons removed (spontaneous)

REDUCTION: electrons added (requires energy)

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)
Synthesis of Biological Molecules

heterotrophy
organic nutrient

autotrophy
$CO_2 +$ inorganic
energy source

phototrophy
$CO_2 +$ light

**energy**
- ATP, ion gradient
- precursor metabolites
- glucose-6-phosphate
- fructose-6-phosphate
- pentose-5-phosphate
- sedoheptulose-7-phosphate
- erythrose-4-phosphate
- triose phosphate
- 3-phosphoglycerate
- phosphoenolpyruvate
- acetyl coenzyme A
- 2-oxoglutarate
- succinyl coenzyme A
- oxaloacetate
- pyruvate
- reducing power
- NAD(P)H

**fatty acids**
- (~8)

**lipid**
- lipopolysaccharide
- glycogen
- murein

**sugars**
- (~25)

**flagella**
- envelope
- pili

**amino acids**
- (~21)

**murein**
- cytosol

**nucleotides**
- (~8)

**protein**
- ribosomes

**DNA**
- nucleoid

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 $2 \times 10^9$ 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: \(5.2 \text{ ATP} \times 300 \times 3 \times 10^6 = 4.5 \times 10^9 \text{ ATP}\)

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 (\(\text{CO}_2\) waste product)

Total cost of *E.coli* cell building: \(10^{10} \text{ ATP}\) or \(6 \times 10^8\) glucose molecules (1/3 of the material required under ideal conditions and up to 10-fold in less efficient growth conditions)
<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Abundance (molecules per cell)</th>
<th>Glucose equivalents</th>
<th>ATP equivalents (aerobic)</th>
<th>ATP equivalents (anaerobic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine (A)</td>
<td>$2.9 \times 10^8$</td>
<td>0.5</td>
<td>-1</td>
<td>1</td>
</tr>
<tr>
<td>Arginine (R)</td>
<td>$1.7 \times 10^8$</td>
<td>0.5</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Asparagine (N)</td>
<td>$1.4 \times 10^8$</td>
<td>0.5</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Aspartate (D)</td>
<td>$1.4 \times 10^8$</td>
<td>0.5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cysteine (C)</td>
<td>$5.2 \times 10^7$</td>
<td>0.5</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Glutamate (E)</td>
<td>$1.5 \times 10^8$</td>
<td>0.5</td>
<td>-7</td>
<td>-1</td>
</tr>
<tr>
<td>Glutamine (Q)</td>
<td>$1.5 \times 10^8$</td>
<td>0.5</td>
<td>-6</td>
<td>0</td>
</tr>
<tr>
<td>Glycine (G)</td>
<td>$3.5 \times 10^8$</td>
<td>0.5</td>
<td>-2</td>
<td>2</td>
</tr>
<tr>
<td>Histidine (H)</td>
<td>$5.4 \times 10^7$</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Isoleucine (I)</td>
<td>$1.7 \times 10^8$</td>
<td>1</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Leucine (L)</td>
<td>$2.6 \times 10^8$</td>
<td>1.5</td>
<td>-9</td>
<td>1</td>
</tr>
<tr>
<td>Lysine (K)</td>
<td>$2.0 \times 10^8$</td>
<td>1</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Methionine (M)</td>
<td>$8.8 \times 10^7$</td>
<td>1</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Phenylalanine (F)</td>
<td>$1.1 \times 10^8$</td>
<td>2</td>
<td>-6</td>
<td>2</td>
</tr>
<tr>
<td>Proline (P)</td>
<td>$1.3 \times 10^8$</td>
<td>0.5</td>
<td>-2</td>
<td>4</td>
</tr>
<tr>
<td>Serine (S)</td>
<td>$1.2 \times 10^8$</td>
<td>0.5</td>
<td>-2</td>
<td>2</td>
</tr>
<tr>
<td>Threonine (T)</td>
<td>$1.5 \times 10^8$</td>
<td>0.5</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Tryptophan (W)</td>
<td>$3.3 \times 10^7$</td>
<td>2.5</td>
<td>-7</td>
<td>7</td>
</tr>
<tr>
<td>Tyrosine (Y)</td>
<td>$7.9 \times 10^7$</td>
<td>2</td>
<td>-8</td>
<td>2</td>
</tr>
<tr>
<td>Valine (V)</td>
<td>$2.4 \times 10^8$</td>
<td>1</td>
<td>-2</td>
<td>2</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Class</th>
<th>Biosynthetic cost (aerobic) – ATP equiv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>$4.5 \times 10^9$</td>
</tr>
<tr>
<td>DNA</td>
<td>$3.5 \times 10^8$</td>
</tr>
<tr>
<td>RNA</td>
<td>$1.6 \times 10^9$</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>$3.2 \times 10^9$</td>
</tr>
<tr>
<td>Lipopolysaccharide</td>
<td>$3.8 \times 10^8$</td>
</tr>
<tr>
<td>Peptidoglycan</td>
<td>$1.7 \times 10^8$</td>
</tr>
<tr>
<td>Glycogen</td>
<td>$3.1 \times 10^7$</td>
</tr>
</tbody>
</table>

*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:

\[ A \xrightarrow[k^-]{k^+} B \xrightarrow{r} C \]

if \(k^+\) and \(k^-\) \(\gg r\) (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

\[ U(x) = k \frac{(x-x_0)^2}{2} - mg (x - x_0) \]
Optical trap as a mass-spring system

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

$$U(x) = k_{\text{trap}} \frac{x^2}{2} - Fx$$