PHYSICS 177

Lecture 2
Physical Intuition of Cellular Environment and Macromolecules, Biological Timescales
Physical Properties of Biological Macromolecules

- **SEQUENCE**: 5’..TCAAGTCCGAT.. 3’
  3’..AGTTCAGGCTA.. 5’

- **BINDING SITE**

- **CHARGED ROD**

- **ELASTIC ROD**

- **RANDOM WALK**

*Figure 1.5 Physical Biology of the Cell © Garland Science 2009*
Figure 1.6 Physical Biology of the Cell (© Garland Science 2009)
Figure 1.7 Physical Biology of the Cell (© Garland Science 2009)
Figure 1.8 Physical Biology of the Cell (© Garland Science 2009)
Figure 1.9 Physical Biology of the Cell (© Garland Science 2009)
### Biology by Numbers

#### E. Coli

<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>$2.2 \times 10^6$</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>
</tbody>
</table>

\[
N_{protein} = \frac{\text{total protein mass}}{\text{mass per protein}} = \frac{0.15 \times 10^{-12} g}{30,000 \times 1.6 \times 10^{-24}} = 3 \times 10^6
\]

\[
N_{lipid} = \frac{\text{total area} \times \text{filling ratio} \times \text{lipid per area}}{\text{area per lipid}} = \frac{6 \times 10^6 \text{nm}^2 \times 0.5 \times 4}{0.5 \text{nm}^2} = 2 \times 10^7
\]
Concentration and Mean Spacing of Molecules

Mean spacing between proteins

\[ d = 13 \text{ nm}. \text{ Size of a typical protein is 2-5 nm}. \]
Yeast

• Yeast is a sphere of a diameter of 5 \( \mu m \).
• The volume is roughly 60 \( \mu m^3 \)
• One can fit 60 \textit{E.coli} cells inside a yeast cell.
• The area is 80 \( \mu m^2 \)
• Within nucleus, its genome is 12 million bases long.
• 150 DNA bp wraps around each nucleosome, with 50 bp spacer in between.
• Therefore yeast has roughly 60,000 nucleosomes.
• Total volume taken by each histone is 230 nm\(^3\) resulting a total volume of 14 million nm\(^3\).
• The volume per base is 1 nm\(^3\)

• DNA packing ratio would be

\[
\rho_{\text{pack}} = \frac{\text{volume of the genome}}{\text{volume of nucleus}} = \frac{1.2 \times 10^7 \text{bp} \times 1 \text{nm}^3/\text{bp}}{4 \times 10^9 \text{nm}^3} = 3 \times 10^{-3}
\]
<table>
<thead>
<tr>
<th>Quantity of interest</th>
<th>Symbol</th>
<th>Rule of thumb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell volume</td>
<td>$V_{E.\text{coli}}$</td>
<td>$\approx 1\ \mu m^3$</td>
</tr>
<tr>
<td>Cell mass</td>
<td>$m_{E.\text{coli}}$</td>
<td>$\approx 1\ pg$</td>
</tr>
<tr>
<td>Cell cycle time</td>
<td>$t_{E.\text{coli}}$</td>
<td>$\approx 3000\ s$</td>
</tr>
<tr>
<td>Cell surface area</td>
<td>$A_{E.\text{coli}}$</td>
<td>$\approx 6\ \mu m^2$</td>
</tr>
<tr>
<td>Genome length</td>
<td>$N_{E.\text{coli}}$</td>
<td>$\approx 5 \times 10^6\ (bp)$</td>
</tr>
<tr>
<td>Swimming speed</td>
<td>$V_{E.\text{coli}}$</td>
<td>$\approx 20\ \mu m/s$</td>
</tr>
<tr>
<td><strong>Yeast</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of cell</td>
<td>$V_{\text{yeast}}$</td>
<td>$\approx 60\ \mu m^3$</td>
</tr>
<tr>
<td>Mass of cell</td>
<td>$m_{\text{yeast}}$</td>
<td>$\approx 60\ pg$</td>
</tr>
<tr>
<td>Diameter of cell</td>
<td>$d_{\text{yeast}}$</td>
<td>$\approx 5\ \mu m$</td>
</tr>
<tr>
<td>Cell cycle time</td>
<td>$t_{\text{yeast}}$</td>
<td>$\approx 200\ min$</td>
</tr>
<tr>
<td>Genome length</td>
<td>$N_{\text{yeast}}$</td>
<td>$\approx 10^7\ (bp)$</td>
</tr>
<tr>
<td><strong>Organelles</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of nucleus</td>
<td>$d_{\text{nucleus}}$</td>
<td>$\approx 5\ \mu m$</td>
</tr>
<tr>
<td>Length of mitochondrion</td>
<td>$l_{\text{mito}}$</td>
<td>$\approx 2\ \mu m$</td>
</tr>
<tr>
<td>Diameter of transport vesicles</td>
<td>$d_{\text{vesicle}}$</td>
<td>$\approx 50\ nm$</td>
</tr>
<tr>
<td><strong>Water</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of molecule</td>
<td>$V_{H_2O}$</td>
<td>$\approx 10^{-2}\ nm^3$</td>
</tr>
<tr>
<td>Density of water</td>
<td>$\rho$</td>
<td>$1\ g/cm^3$</td>
</tr>
<tr>
<td>Viscosity of water</td>
<td>$\eta$</td>
<td>$\approx 1\ \text{centipoise}$</td>
</tr>
<tr>
<td>Hydrophobic embedding energy</td>
<td>$E_{\text{hydr}}$</td>
<td>$\approx 25\ \text{cal/ (mol A}^2\text{)}$</td>
</tr>
<tr>
<td><strong>DNA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length per base pair</td>
<td>$l_{bp}$</td>
<td>$\approx 1/3\ nm$</td>
</tr>
<tr>
<td>Volume per base pair</td>
<td>$V_{bp}$</td>
<td>$\approx 1\ nm^3$</td>
</tr>
<tr>
<td>Charge density</td>
<td>$\lambda_{\text{DNA}}$</td>
<td>$2\ e/0.34\ nm$</td>
</tr>
<tr>
<td>Persistence length</td>
<td>$\xi_p$</td>
<td>$50\ nm$</td>
</tr>
<tr>
<td><strong>Amino acids and proteins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radius of “average” protein</td>
<td>$r_{\text{protein}}$</td>
<td>$\approx 2\ nm$</td>
</tr>
<tr>
<td>Volume of “average” protein</td>
<td>$V_{\text{protein}}$</td>
<td>$\approx 25\ nm^3$</td>
</tr>
<tr>
<td>Mass of “average” amino acid</td>
<td>$M_{\text{aa}}$</td>
<td>$\approx 100\ Da$</td>
</tr>
<tr>
<td>Mass of “average” protein</td>
<td>$M_{\text{protein}}$</td>
<td>$\approx 30,000\ Da$</td>
</tr>
<tr>
<td>Protein concentration in cytoplasm</td>
<td>$c_{\text{protein}}$</td>
<td>$\approx 300\ mg/mL$</td>
</tr>
<tr>
<td>Characteristic force of protein motor</td>
<td>$F_{\text{motor}}$</td>
<td>$\approx 5\ \text{pN}$</td>
</tr>
<tr>
<td>Characteristic speed of protein motor</td>
<td>$v_{\text{motor}}$</td>
<td>$\approx 200\ nm/s$</td>
</tr>
<tr>
<td>Diffusion constant of “average” protein</td>
<td>$D_{\text{protein}}$</td>
<td>$\approx 100\ \mu m^2/s$</td>
</tr>
<tr>
<td><strong>Lipid bilayers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thickness of lipid bilayer</td>
<td>$d$</td>
<td>$\approx 5\ nm$</td>
</tr>
<tr>
<td>Area per molecule</td>
<td>$A_{\text{lipid}}$</td>
<td>$\approx \frac{1}{2}\ nm^2$</td>
</tr>
<tr>
<td>Mass of lipid molecule</td>
<td>$m_{\text{lipid}}$</td>
<td>$\approx 800\ Da$</td>
</tr>
</tbody>
</table>
Biological Timescales

- Sequoia lifespan, 3000 years \( \approx 10^{11} \text{ s} \)
- Galapagos tortoise lifespan, 150 years \( \approx 5 \times 10^9 \text{ s} \)
- Human embryonic stem cell line doubling time, 72 h \( \approx 3 \times 10^5 \text{ s} \)
- Mayfly adult lifespan, 1 day \( \approx 9 \times 10^4 \text{ s} \)
- E. coli doubling time, 20 min \( \approx 1.2 \times 10^3 \text{ s} \)
- Unstable protein half-life, 5 min \( \approx 300 \text{ s} \)
- Lysozyme turnover rate, \( \approx 0.5 \text{ s}^{-1} \)
- Carbonic anhydrase turnover rate, \( \approx 600,000 \text{ s}^{-1} \)
- Side chain rotation, \( \approx 500 \text{ ps} \)
- H-bond rearrangements in water, \( \approx 10 \text{ ps} \)
- Covalent bond vibration in water, \( \approx 1 \text{ fs} \)
development of *Drosophila*

1 day:
- egg → larva

2 days:
- larva → pupa

5 days:
- pupa → adult fly

early development of *Drosophila* embryo

hours:
- egg → embryonic shape
- embryonic shape → early larva
- early larva → late larva
- late larva → pupa

bacterial cell division

minutes:
- bacterial cell → cell division
- cell division → daughter cells

Figure 3.2c Physical Biology of the Cell (© Garland Science 2009)
gating of ion channels

lipid bilayer → closed ion channel → open ion channel → lipid bilayer

enzyme catalysis

substrate → enzyme → product

Figure 3.2h Physical Biology of the Cell (© Garland Science 2009)
## Methods to Measure Biological Time

<table>
<thead>
<tr>
<th>Method</th>
<th>Direct Observation</th>
<th>Fixed Time Points</th>
<th>Pulse-Chase</th>
<th>Product Accumulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical Time Scales</td>
<td>milliseconds to hours</td>
<td>microseconds to years</td>
<td>minutes to days</td>
<td>minutes to days</td>
</tr>
<tr>
<td>Types of Processes</td>
<td>Individual transformations</td>
<td>Population changes</td>
<td>Continuous (e.g., metabolism, transport)</td>
<td>Biosynthetic or enzymatic</td>
</tr>
<tr>
<td>Example</td>
<td>Cell crawling</td>
<td>Bacterial growth curve</td>
<td>Axonal transport</td>
<td>GFP expression</td>
</tr>
</tbody>
</table>
1. Procedural Time

- Chemical reactions are not instantaneous
- Multistep biological processes add up to determine the cell cycle.
- In *E. Coli*, two polymerases synthesize the DNA in opposite directions

![Diagram showing DNA replication, transcription, and translation](https://via.placeholder.com/150)

\[
t_{\text{replication}} = \frac{5 \times 10^6 \text{bp}}{2 \times 3000 \text{ sec}} = 1000 \text{ bp/sec}
\]

- Typical mRNA transcript is 1000 bases long, and RNA polymerases work at 40 bases/sec.

Takes 25 sec to make mRNA.
Internal Clocks: Cell Cycle Proteins

- Cyclin protein concentration rises over time.
- When it reaches a threshold, it activates CDK.
- CDK concentration increases rapidly, activates cyclin degradation pathway.
- Cyclin level falls, followed by reduction in CDK levels.
- Period of oscillation is equal to the cell cycle time.
2. Relative Time

- Some reactions cannot occur in parallel.
- Event A occurs before B, C has to wait for B.
3. Manipulated Time

• Cell does not have enough time for some slow processes to occur slowly.
• Finds creative ways to speed up the process.

\[ \tau_{\text{diffusion}} = \frac{x^2}{D}, \ D \text{ is diffusion constant.} \]

D of a protein of 5 nm in size is roughly 100 \(\mu\text{m}^2/\text{sec}\), so time to travel across E.coli is 0.01 sec.

• Diffusion of mitochondria (1 \(\mu\text{m}\) diameter) along axons (1 meter long)
• Takes 8 years!
• Diffusion won’t work in this case
Solution: Molecular Motors

- Motors haul cargos and carry them along cytoskeletal tracks.
- Typical speed is 1 μm/sec.
- Typical step size is 8 nm.
- How long would it take? How many steps will be taken?
Enzymes: Catalysts

- Even though a reaction can occur spontaneously, it takes a certain amount of time.

\[
\tau_{A\rightarrow B} = e^{-G_{\text{barrier}}/kT}
\]

- Enzyme lowers the energetic barrier through favorable charge interactions at the transition state, and increases the rate of reaction.
Floating Balls Analogy for Enzymes

uncatalyzed reaction—waves not large enough to surmount barrier

catalyzed reaction—waves often surmount barrier