Lecture 05:

Structure and Dynamics of Cellular Molecules

Basics of Cell Biology Literature Reading
Outline

• Review: chemical composition of a cell
• Review: chemical bonds of cellular molecules
• A brief introduction to protein structures
• A brief introduction to protein folding
• Basics of cell biology literature reading
Outline

• Review: chemical composition of a cell
  • Review: chemical bonds of cellular molecules
  • A brief introduction to protein structures
  • A brief introduction to protein folding

• Basics of cell biology literature reading
Cells are made mostly of macromolecules, which define the physics and chemistry of a cell.

Table 2–3 Approximate Chemical Compositions of a Typical Bacterium and a Typical Mammalian Cell

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>PERCENT OF TOTAL CELL WEIGHT</th>
<th>E. COLI BACTERIUM</th>
<th>MAMMALIAN CELL</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O</td>
<td>70</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Inorganic ions (Na⁺, K⁺, Mg²⁺, Ca²⁺, Cl⁻, etc.)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous small metabolites</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Proteins</td>
<td>15</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>RNA</td>
<td>6</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>DNA</td>
<td>1</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Phospholipids</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Other lipids</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total cell volume</td>
<td>2 × 10⁻¹² cm³</td>
<td>4 × 10⁻⁹ cm³</td>
<td></td>
</tr>
<tr>
<td>Relative cell volume</td>
<td>1</td>
<td>2000</td>
<td></td>
</tr>
</tbody>
</table>
Chemical Compositions of Cells (II)

- Macromolecules in cells are usually polymers.

- **Polymer:** a natural or synthetic compound of large molecules that are formed by a linked series of repeated structural units.

Table 2–2 The Approximate Chemical Composition of a Bacterial Cell

<table>
<thead>
<tr>
<th>Component</th>
<th>Percent of Total Cell Weight</th>
<th>Number of Types of Each Molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>70</td>
<td>1</td>
</tr>
<tr>
<td>Inorganic ions</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Sugars and precursors</td>
<td>1</td>
<td>250</td>
</tr>
<tr>
<td>Amino acids and precursors</td>
<td>0.4</td>
<td>100</td>
</tr>
<tr>
<td>Nucleotides and precursors</td>
<td>0.4</td>
<td>100</td>
</tr>
<tr>
<td>Fatty acids and precursors</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Other small molecules</td>
<td>0.2</td>
<td>~300</td>
</tr>
<tr>
<td>Macromolecules (proteins, nucleic acids, and polysaccharides)</td>
<td>26</td>
<td>~3000</td>
</tr>
</tbody>
</table>

Alberts *MBoC* 5e
Outline

- Review: chemical composition of a cell
- **Review: chemical bonds of cellular molecules**
- A brief introduction to protein structures
- A brief introduction to protein folding
- Basics of cell biology literature reading
Outline of Intramolecular and Intermolecular Interactions

- **Intramolecular interactions**
  - Covalent bonds
  - Noncovalent bonds
    - Electrostatic attractions
      (including ionic bond)
    - Hydrogen bond
    - Van der Waals bond

- **Intermolecular interactions**
  - Electrostatic attractions
  - Hydrogen bond
  - Van der Waals bond
  - Hydrophobic force

Table 2-1 Covalent and Noncovalent Chemical Bonds

<table>
<thead>
<tr>
<th>BOND TYPE</th>
<th>LENGTH (nm)</th>
<th>STRENGTH (kcal/mole)</th>
<th>IN VACUUM</th>
<th>IN WATER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncovalent: ionic*</td>
<td>0.15</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>80</td>
<td>80</td>
<td>3</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>0.30</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Van der Waals attraction (per atom)</td>
<td>0.35</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*An ionic bond is an electrostatic attraction between two fully charged atoms.
Atoms Forming a Cell & Chemical Bonds

• All living organisms are fundamentally chemical systems.

• Cells are made primarily of a few chemical elements.
  - Organic chemistry; biochemistry
  - Statistical mechanics, thermodynamics

• Cell chemistry is based overwhelmingly on carbon compounds and reactions in water.

• Atoms that make up a molecule are joined together by different chemical bonds, which define boundaries between molecules.
Chemical Bonds of Cellular Molecules (I)

• Covalent bonds are abundant in cellular molecules.

• There are different types of covalent bonds.
  - single bonds, double bonds
  - polar covalent bonds vs nonpolar covalent bonds

• Polar covalent bonds allow cellular molecules to interact through electrostatic forces.
Chemical Bonds of Cellular Molecules (II)

- **Hydrogen bonds**: An electropositive hydrogen is shared by two electronegative atoms.
  - Highly directional
  - Example: nucleotide base pairing

- **Nonpolar atoms** can become dipoles transiently due to the fluctuation of their electron cloud.

- **van der Waals attractions** result from attraction of atoms of opposite transient dipoles

- Water weakens hydrogen bonds but not van der Waals attractions.
Chemical Bonds of Cellular Molecules (III)

- Water molecules are polar.

- Water molecules form hydrogen bonds with each other.

- Functions
  - A solvent for most cellular molecules.
  - Reactant or product in cellular biochemical reactions

- Water molecules forms hydrogen binds with many cellular molecules and generates functionally important complexes.
  - e.g. ion-water complex can affect ion permeability
Chemical Bonds of Cellular Molecules (IV)

- Molecules can be hydrophilic or hydrophobic.
  - hydrophilic: polar or charged molecules/groups that dissolve easily in water
  - hydrophobic: nonpolar molecules/groups that are insoluble in water

- Nonpolar surfaces tend to be pushed out of the water molecule network → Hydrophobic force

- Hydrophobic effect stabilizes biological structure.
Outline

• Review: chemical composition of a cell
• Review: chemical bonds of cellular molecules
• A brief introduction to protein structures
• A brief introduction to protein folding
• Basics of cell biology literature reading
Proteins: Overview

- Proteins are the predominant structural and functional components of all cells.
- Proteins vary widely in length, typically in the range of 100~1000 amino acids.
- Determination of protein sequence
  - Genetic approach
  - Mass spectrometry
Protein Primary Structure (I)

- 20 naturally occurring amino acids
- Amino acids differ in side chains
Protein Primary Structure (II)

- Amino acids can be hydrophobic, hydrophilic, or amphipathic

- Amphipathic: residues that have both polar and unpolar properties and are ideal for forming interfaces.
Protein Primary Structure (III)
How Protein Structures are Determined

1. Structure data interpretation is not unambiguous. Information from multiple sources is often required to fully determine the structure.

2. The structure is solved for a purified protein.

X-ray crystallography

Nuclear magnetic resonance

© 1999-2004 New Science Press
Protein Structure Overview

• **A structural hierarchy**
  - primary structure
  - secondary structure
  - tertiary structure
  - quarternary structure

• **Different representations**
  - wire diagram
  - ribbon
  - ball-and-stick
  - space filling
  - surface
Secondary Structure (I)

- Secondary structure
  - Local structures of repeated residue conformation
  - Two primary types of secondary structure elements (i.e. folding patterns: alpha helix, beta sheet.
- Alpha helix was first discovered in hair protein keratin.
- Beta sheet was first discovered in fibroin, the silk protein.
- Both patterns result from hydrogen bonding between N-H and C=O group of the backbone.
Secondary Structure (II)

- Many cellular proteins contain extensive regions of beta sheets, which provide structural rigidity.

- Alpha helix are abundant in membrane proteins.

- Many proteins contain a hydrophobic core.

- Secondary structure consists of extensive network of hydrogen bonds and contributes significantly to the stabilization of the overall protein structure.
Tertiary Structure (I)

- Tertiary structure
  - The three dimensional conformation of a protein is its native folded state; i.e. the global organization of secondary structures.

- Tertiary structures are not regular. Proteins with similar secondary structure elements can have very different tertiary structures.

Left: triosephosphate isomerase
Right: dihydrofolate
Tertiary Structure (II)

- The folded structure of a protein is directly determined by its primary structure.

- Condensing of multiple secondary structural elements leads to tertiary structure.

- Computational predication of folding is not yet reliable.

- Most folded proteins are marginally stable to allow flexibility.

- Conformation changes tend to be local.
Quarternery Structure (I)

- Many proteins have more than one polypeptide chain.
- Individual polypeptide chains are referred to as monomers.
- Quaternary structure is the arrangement of different polypeptide chains.

From *Protein Structure and Function* by Gregory A. Petsko and Dagmar Ringe

(a) homodimer: a₂
(b) heterodimer: ab
(c) heterotetramer: a₂b₂
(d) heteropentamer a₂bcd

© 1999-2004 New Science Press
Quaternery Structure (II)

- Irregular protein surfaces enables specific binding.
- Specific intermolecular interactions depend on complementarity.
- Protein binding can trigger large conformational changes

Alpha helical coiled coil
Protein Interactions (I)

- Selectivity and affinity of protein binding depend on weak noncovalent bonds.

- Surface conformation of a protein defines its chemistry.

- The most common way of protein interaction is through precise matching of surfaces.

- Protein interactions often require catalysis by enzymes.
Protein Interactions (II)

- Protein interactions often require catalysis by enzymes.

(A) enzyme binds to two substrate molecules and orients them precisely to encourage a reaction to occur between them

(B) binding of substrate to enzyme rearranges electrons in the substrate, creating partial negative and positive charges that favor a reaction

(C) enzyme strains the bound substrate molecule, forcing it toward a transition state to favor a reaction
Protein Interactions (III)

- A complex network of protein interactions underlies cell function.
- Proteins are highly dynamic in the intracellular environment.
Outline

- Review: chemical composition of a cell
- Review: chemical bonds of cellular molecules
- A brief introduction to protein structures
- A brief introduction to protein folding
- Basics of cell biology literature reading
Protein Folding: the Energy Landscape Theory

- First proposed by Joseph Bryngelson and Peter Wolynes.

- **Principle of minimal frustration**: the native folded state is favored by evolution.

- The energy landscape is encoded by the amino acid sequence and represents all the possible energy states.

Protein Folding in Cells

- Protein folding in cells can happen before the completion of synthesis (co-translational).

- Complex protein structures often fold after exit from ribosomes.

- Incorrectly fold proteins are detected by a quality-control mechanism and sent for degradation.

Chaperone-Assisted Protein Folding

- Chaperons increase the efficiency of protein folding by avoiding unfavorable folding paths.

- Typical functions
  - To prevent aggregations.
  - To prevent interference
Structure of DNA and RNA

• DNA secondary structure
  - Purine: adenine (A) guanosine (G)
  - Pyrimidines: thymine (T) cytosine (C)

• RNA secondary structure
  - Purine: adenine (A) guanosine (G)
  - Pyrimidines: uracil (U) cytosine (C)
The Cytoplasm

- The global view: the cytoplasm is densely populated.

- Only correctly folded proteins have long-term stability.

http://mgl.scripps.edu/people/goodsell/
Some Comments

• **Biochemistry**
  - The level of molecular details really depends on the question to be addressed.

• **Structural biology**
  - Provides critical insights into cellular processes.
  - Needs to be integrated with other approaches.
  - Structural genomics aims to determine the primary and tertiary structures of all proteins of a given organism.
References

Petsko & Ringe
New Science, 2004

Nelson & Cox
W.H. Freeman, 2008

Dill & Bromberg,
Garland Sciences, 2002
Outline

• Review: chemical composition of a cell
• Review: chemical bonds of cellular molecules
• A brief introduction to protein structures
• A brief introduction to protein folding

• Basics of cell biology literature reading
Why Focus on Literature Reading

- Biology is a scientific discipline undergoing rapid development.
- Reading primary research literature is essential for in-depth understanding of biology.
- Much more about biology can be learned from literature reading.
An Overview of Cell Biology Literature

- Journals
  - General purpose journals
    - Science
    - Nature
    - PNAS
  - Specialized journals
    - Cell
    - Journal of Cell Biology
    - Nature associated journals

- Commercial vs noncommercial journals

- Review journals and review articles
How to Read Cell Biology Papers (I)

• To be able to critically read and evaluate contemporary biology papers - Why so critical?

• General guidelines
  - Fundamentally, it is about original data and ideas
  - Not that different from a mathematical proof: Logical coherence and rigor

• Highly stereotyped structures of biology papers

• Organization (I): biology papers are result-driven
  - Introduction: However, …
  - Results: To…, we did …
  - Discussion: We speculate …
How to Read Cell Biology Papers

• Organization (II):
  - Every figure must tell
  - Logical flow: connection between result sections

• Our aims
  - To be able to effectively read papers in cell biology
  - To be able to effectively communicate cell biology research results
Process of Publication

• Journal selection
  - What are the messages: short vs long format
  - Usually several comparable journals to choose from
    Similar paper formats
    Similar review standards
  - Keep a rational perspective: vanity journals
  - Keep doing good science, your record will show

• Submission and review process
  - Pre-submission inquiry: usually for vanity journals
  - Editorial review
  - External review
  - Outcome I: preliminary acceptance
    Point-to-point response to reviews
  - Outcome II: rejection
  - Peer-review system not perfect but generally works
Small Molecules

- Definition of small molecules is not firm.
- Can be natural or synthesized. Not a polymer.
- Low molecular weight permits fast permeation across membranes.
- Used to induce immediate functional perturbations.
- Important targets of pharmacology and chemical biology research.

**Table 2–2 The Approximate Chemical Composition of a Bacterial Cell**

<table>
<thead>
<tr>
<th></th>
<th>PERCENT OF TOTAL CELL WEIGHT</th>
<th>NUMBER OF TYPES OF EACH MOLECULE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>70</td>
<td>1</td>
</tr>
<tr>
<td>Inorganic ions</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Sugars and precursors</td>
<td>1</td>
<td>250</td>
</tr>
<tr>
<td>Amino acids and precursors</td>
<td>0.4</td>
<td>100</td>
</tr>
<tr>
<td>Nucleotides and precursors</td>
<td>0.4</td>
<td>100</td>
</tr>
<tr>
<td>Fatty acids and precursors</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Other small molecules</td>
<td>0.2</td>
<td>~300</td>
</tr>
<tr>
<td>Macromolecules (proteins, nucleic acids, and polysaccharides)</td>
<td>26</td>
<td>~3000</td>
</tr>
</tbody>
</table>


Terminology

- **Genome**: all the genetic information encoded in a cell. → Genomics
- **Proteome**: the complete set of proteins expressed in a cell. → Proteomics
- **Backbone**: the regularly repeating part of a polymer.
- **Residue**: the basic building block of a polymer.
- **Sidechain**: the chemical group that protrudes from the backbone.
- **Polypeptide**: a linear polymer of amino acids.
- **Homologs**: Different forms of a gene/protein that are similar in sequence as a result of derivation from the same ancestral gene.
- **Isoforms**: Different forms of a protein that may be produced from different genes, or from the same gene by alternative splicing in the same cell.