Course content

Topics (lectures)**:**
1. **Introduction** (1)
2. **Structure** (2-5)
3. **Single molecule mechanics** (6-9)
4. **Collective/emergent properties** (9-11)
5. **Student presentations** (11-13)

Course structure:
1. **Introduction to topic**
2. **Awardees (1-2 per week)**
    - **History, first-person, second-person accounts (C)**
    - **Article, analysis of scientific work (E)**
3. **Discussion of topic, outlook**

Why is the course designed this way?
Explore the way science is done and who scientists are
Access resources beyond textbooks, to gain insights and experience

Recap of last time + loose ends

Philosophy of science and scientific breakthroughs:
- Kuhn
- Alternatives to Kuhn

What information do we need to decide if something is a breakthrough?
- context
- details about the work (facts)
- impact
    - citations on a topic before and after
    - scientific landscape before and after

What makes a breakthrough?
- nonlinear change in understanding / paradigm shift
- fills a knowledge gap
    - which was unfilled for a long time
    - better than other attempts by some-fold
- opens a new direction or create a new field. creative.

Lecture 2: Introduction to structure

Today's goal: Biomolecules, history of structure

- The stuff of life
- What is a structure
- Proteins as random walks

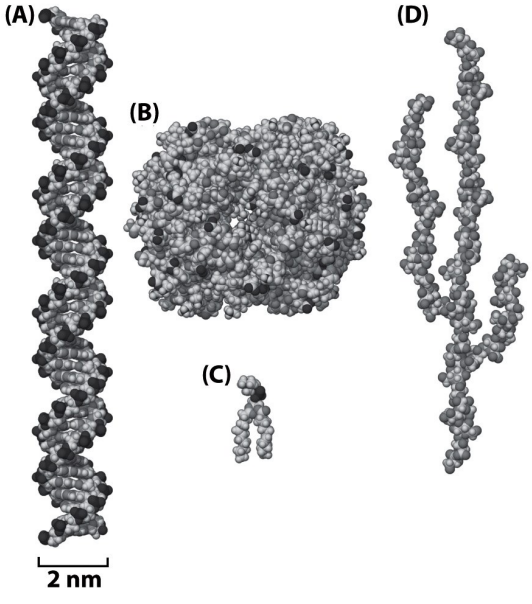
PBOC Chapter 1.1, 1.2, 8.1, 8.4

- History of structure

https://knowablemagazine.org/article/living-world/2022/structural-biology-how-proteins-got-their-closeup

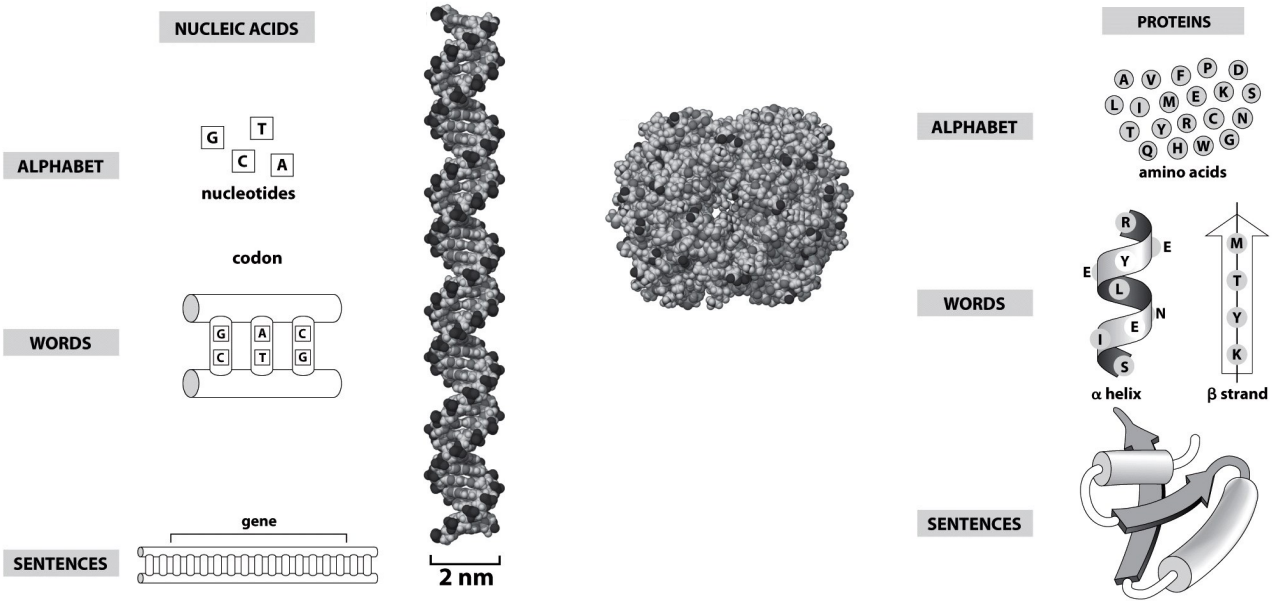
The stuff of life

What macromolecules are cells made of?



The stuff of life

Nucleic acids and proteins are polymer languages



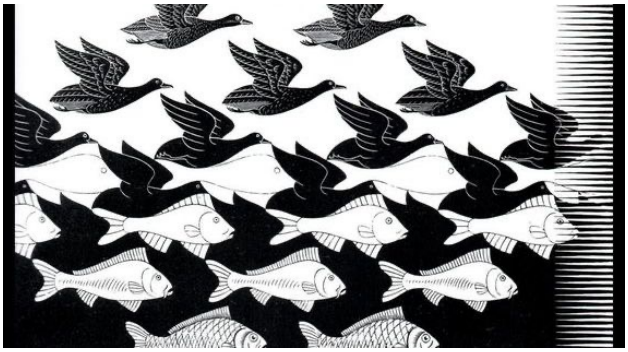
Why structure?

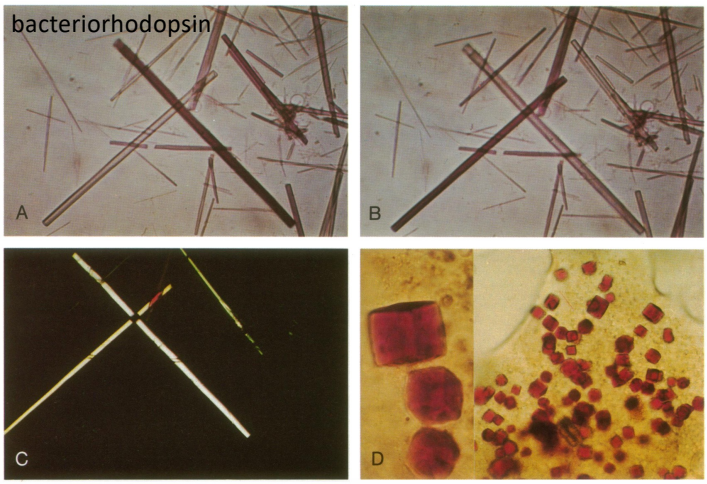
Structure-function relationship

What is a structure?

Deterministic vs. statistical descriptions

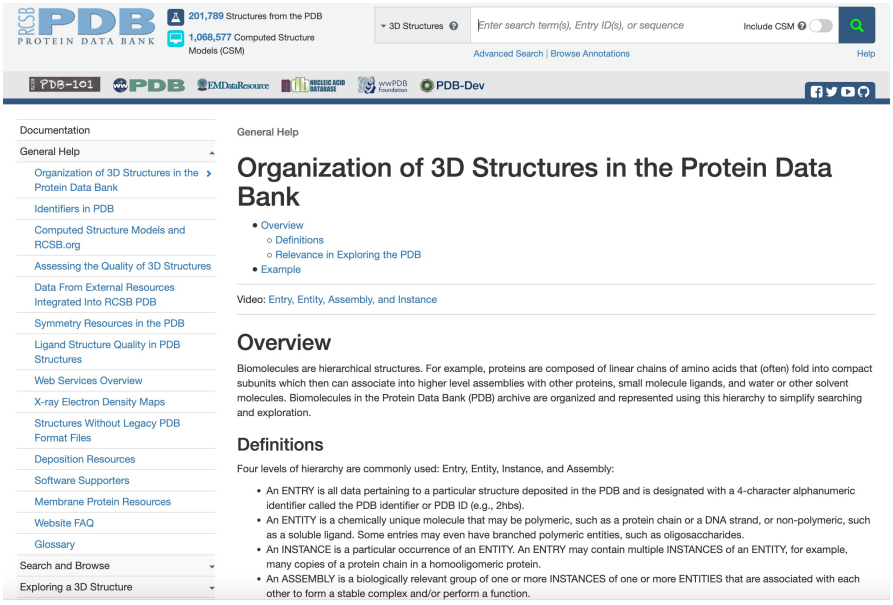
Crystal: regular packing of atoms into unit cells
Some proteins will form crystals





What is a structure?

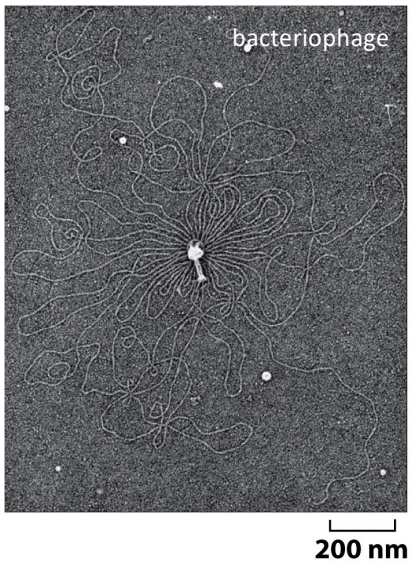
Protein data bank: repository of structures



What is a structure?

Deterministic vs. **statistical** descriptions

Average size and shape, fluctuations are important



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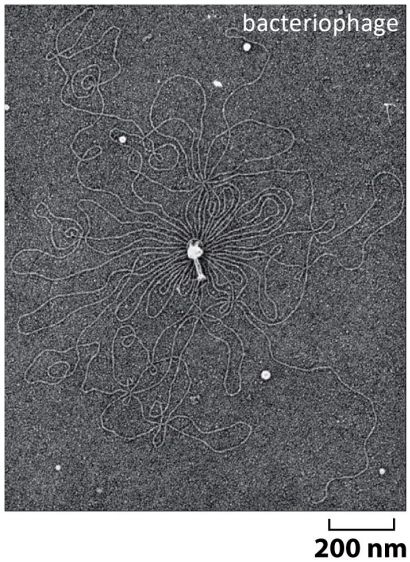
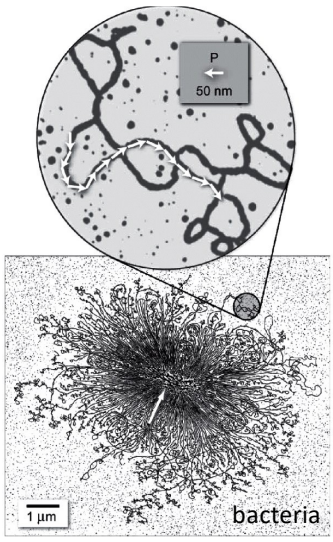
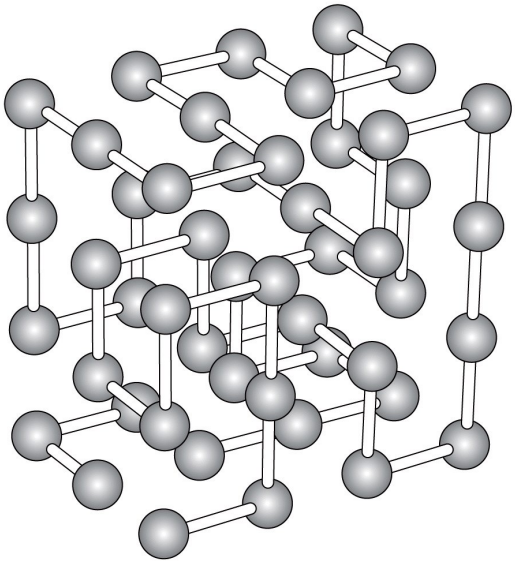


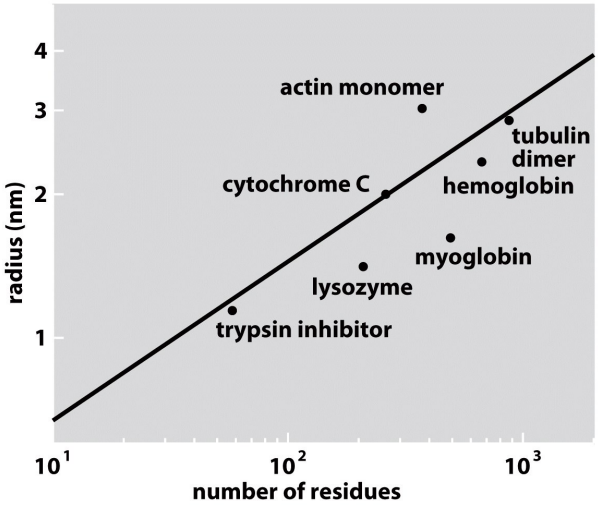


What is a structure?

Proteins as random walks

Simple model: Self-avoiding, compact random walk on a cubic lattice





What is a structure?

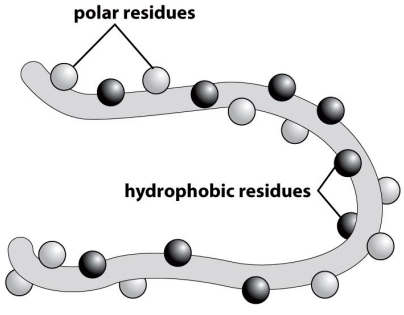
HP model

More complex model: Hydrophobic and polar residues

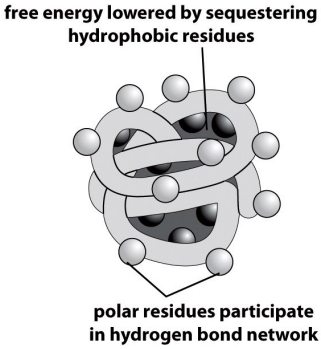
Number of possible 3D conformations is so large that a random search would take a long time:

100-monomer chain
$6^{100} = 6.5 \times 10^{77}$

One structure per femtosecond
2×10^{55} years
Age of universe ~10^{10} years



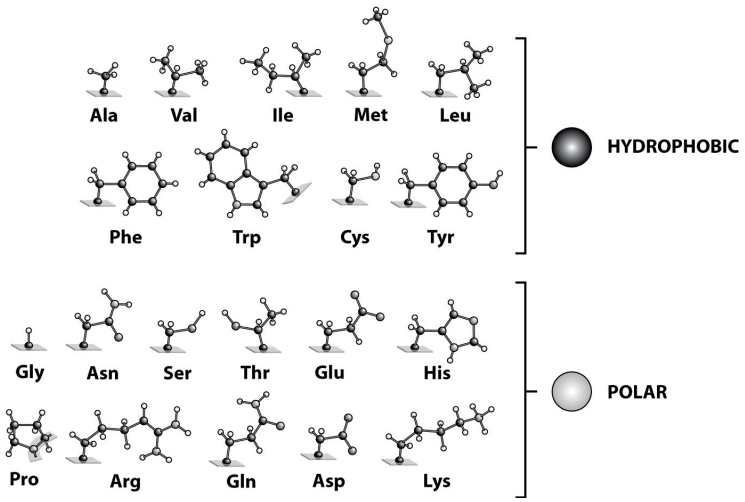
unfolded polypeptide



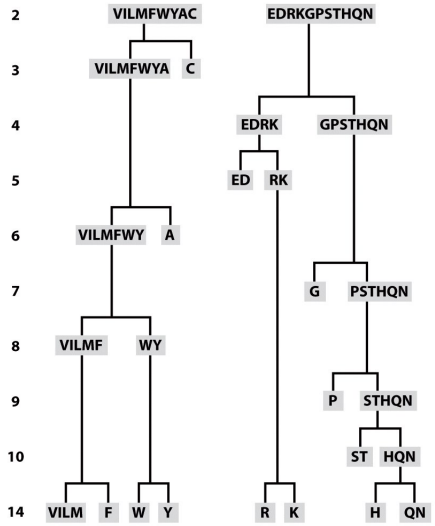
folded conformation in aqueous environment

What is a structure?

HP model



coarse-grained model: HP



hierarchy of classes

What is a structure?

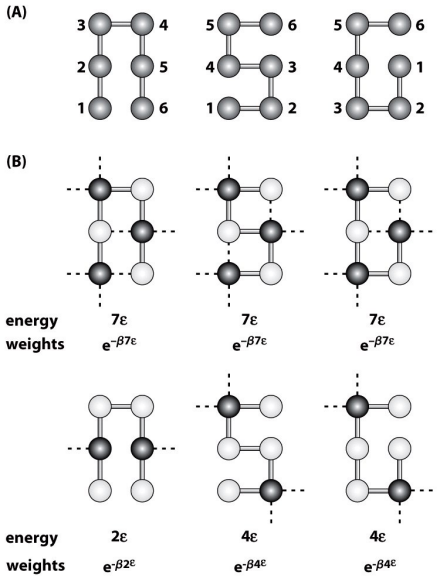
HP model

toy HP model:
6 monomers on a
3x2 lattice

sequences: $2^6 = 64$

sequence HPHPHP

sequence PHPPHP



number of unique structures: 3

interaction model: assign free energy penalty for H-P or H-solvent interactions (---)

Given an HP sequence, which of the possible structures minimizes the total free energy?

$$p_{\text{fold}} = \frac{e^{-2\beta\epsilon}}{e^{-2\beta\epsilon} + 2e^{-4\beta\epsilon}}$$

Protein folding problem

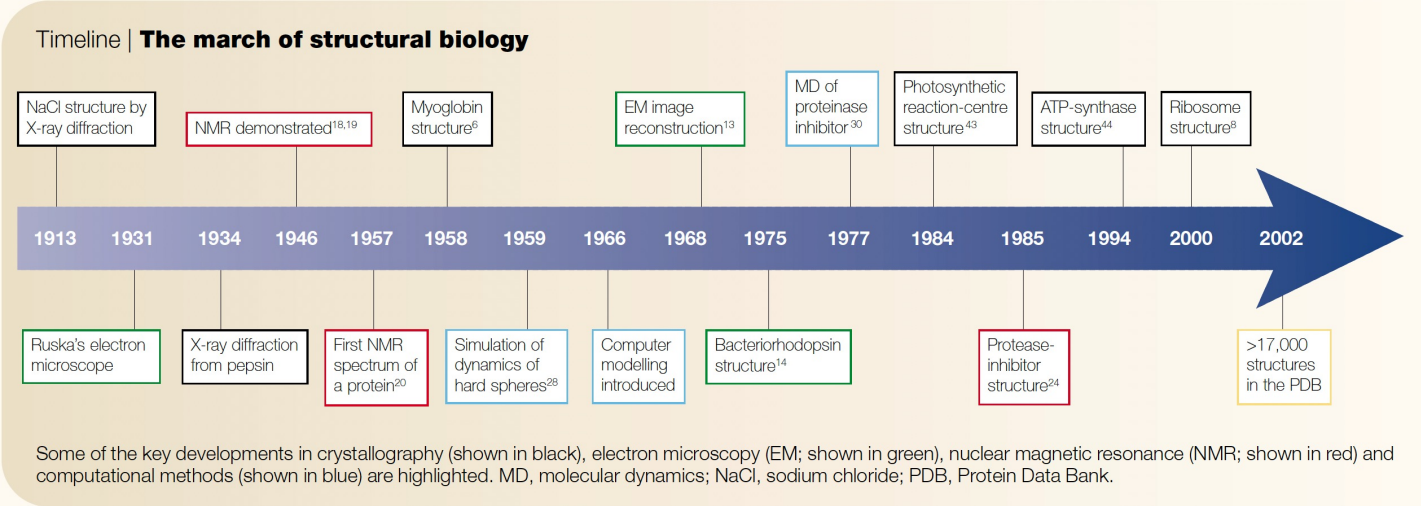
(i) What is the physical code by which an amino acid sequence dictates a protein's native structure?
(ii) How can proteins fold so fast?
(iii) Can we devise a computer algorithm to predict protein structures from their sequences?

Lectures 3, 4, 5

• Roderick Clayton: Purification of photosynthetic reaction center (1968)
• George Feher: Reaction center structure (1974)
"*For his many contributions to the understanding of the physics of photosynthesis; specifically, for his role in the pioneering of the concept of reaction enters in photosynthetic bacteria, their isolation, their spectroscopy and their structural characterization.*" (1982)

• Peter Wolynes: Protein folding, energy landscape (1987)
"*For his conceptual breakthroughs in protein dynamics and protein folding, and his critical insights toward the understanding of how proteins work at the most fundamental level.*" (2004)

• Jose Onuchic: Protein folding routes (1995)
• Ken Dill:
"*For independent contributions to a new view of protein folding, from the introduction and exploration of simple models, to detailed confrontations between theory and experiment.*"



Some of the key developments in crystallography (shown in black), electron microscopy (EM; shown in green), nuclear magnetic resonance (NMR; shown in red) and computational methods (shown in blue) are highlighted. MD, molecular dynamics; NaCl, sodium chloride; PDB, Protein Data Bank.

Lecture 3: Photosynthetic reaction centers

Clayton & Feher

- Roderick Clayton: Purification of photosynthetic reaction center (1968)
- George Feher: Reaction center structure (1974)

"*For his many contributions to the understanding of the physics of photosynthesis; specifically, for his role in the pioneering of the concept of reaction enters in photosynthetic bacteria, their isolation, their spectroscopy and their structural characterization.*" (1982 Delbruck Prize)