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**

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

first half

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

PBOC Chapter 1.1, 1.2, 8.1, 8.4

last week

second half

- History of structure

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

Your mission:

Integrate information about the context of biomolecular structure.

- Open questions / challenges / goals of the field.

Name one open question in the field of biomolecular structure

Understand / explain the key developments in the field

- Human-sized vs. consortium-sized vs. field-sized breakthroughs

Give an example of a breakthrough described, and identify its "scale"

Classify "genre" of information sources

- expository: neutral, logical, balanced, objective
- argumentative: establishes an opinion, presents arguments to support as well as reasonable alternatives
- narrative: historical, tells a story or describes an experience

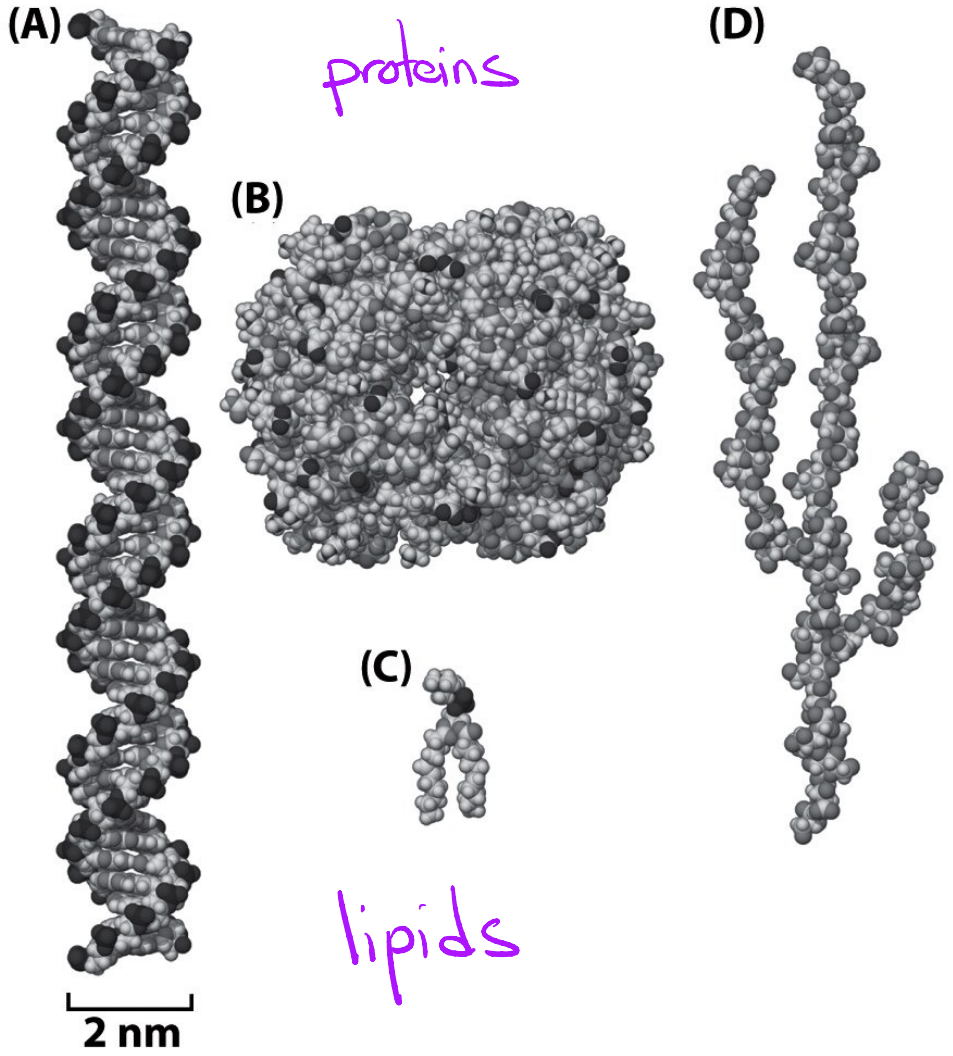
Identify the genre used in the media we listened to / watched

The stuff of life

What macromolecules are cells made of?

nucleic acids

(DNA
RNA)



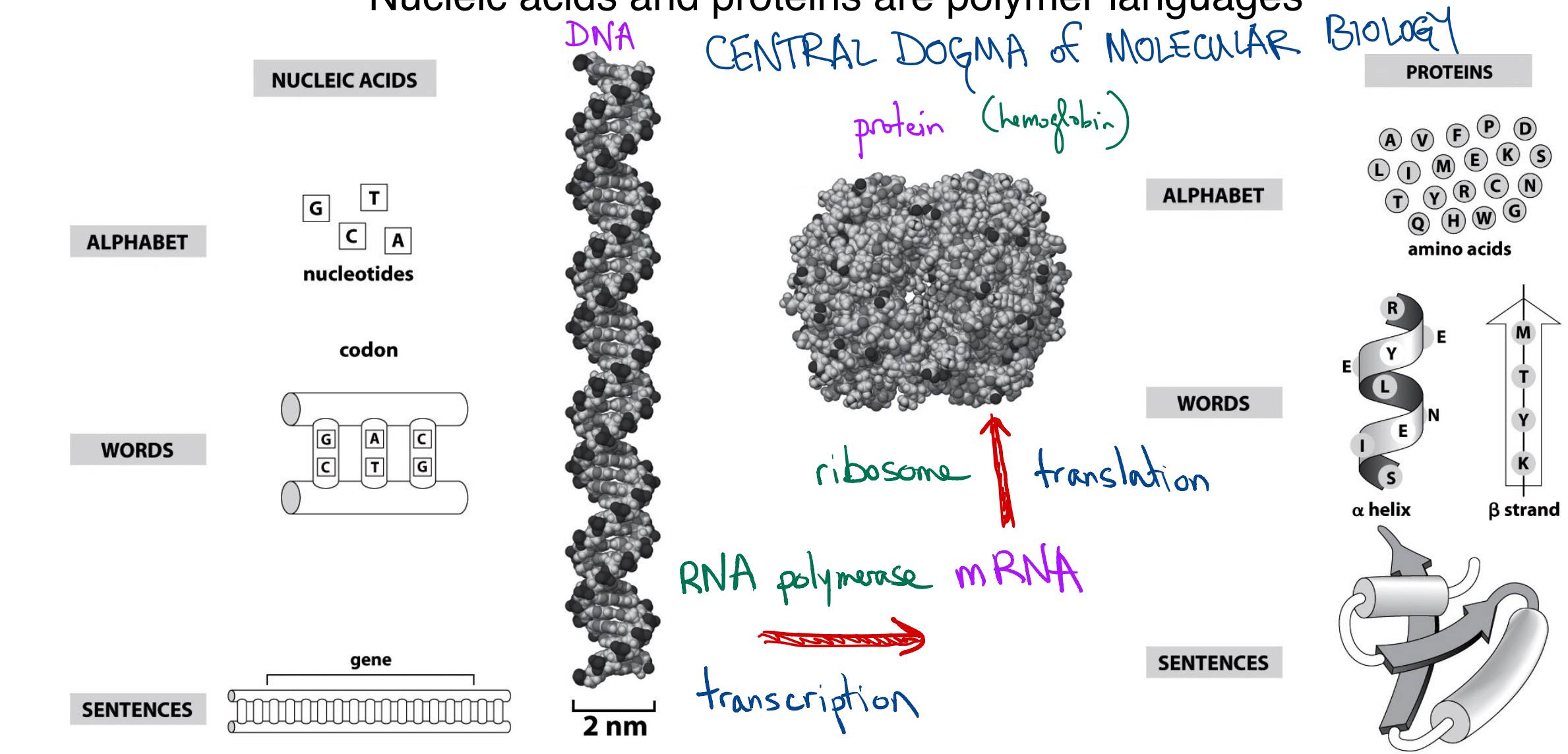
proteins

lipids

carbohydrates

The stuff of life

Nucleic acids and proteins are polymer languages



Why structure?

Structure-function relationship

- Example of hemoglobin.

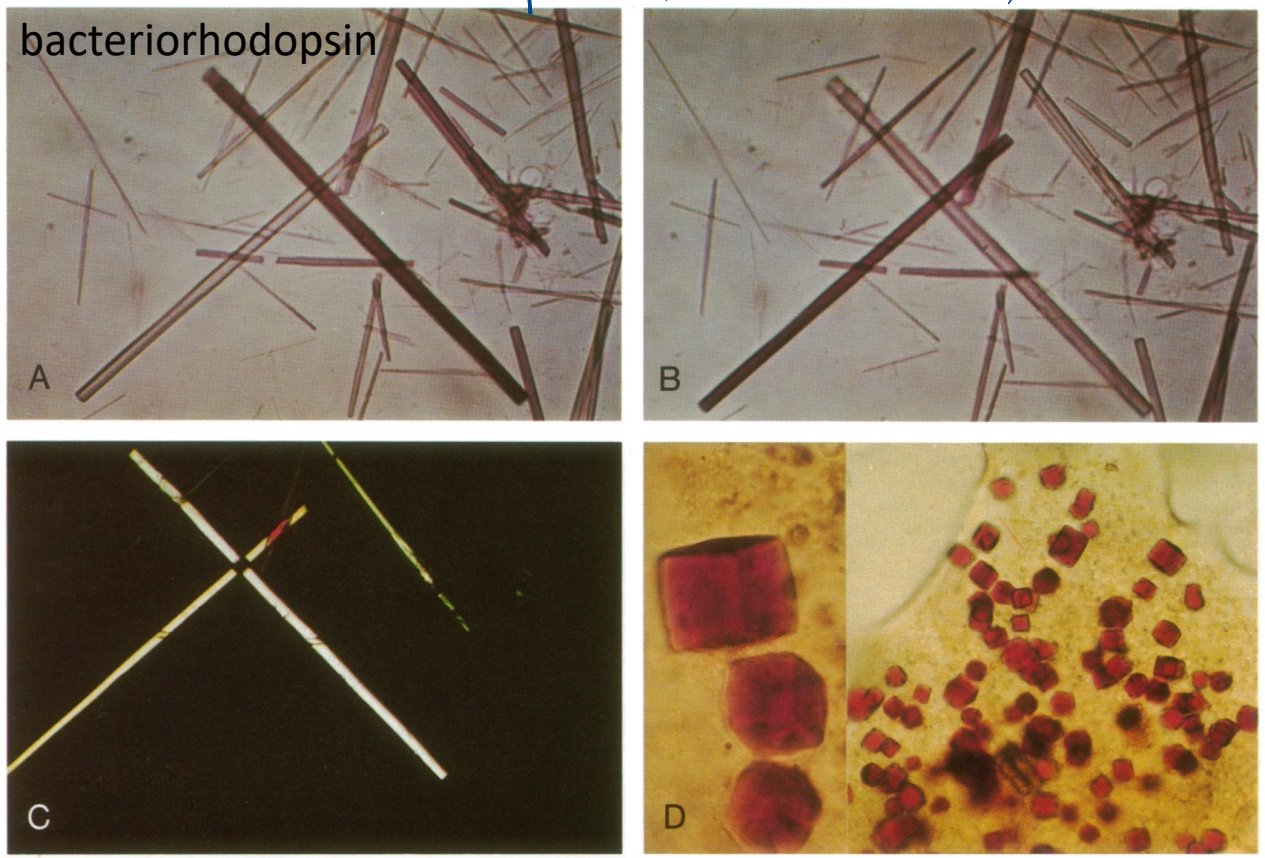
- Understand → fundamental curiosity
  - → engineer new functions
  - → treat disease

What is a structure?

Deterministic vs. statistical descriptions

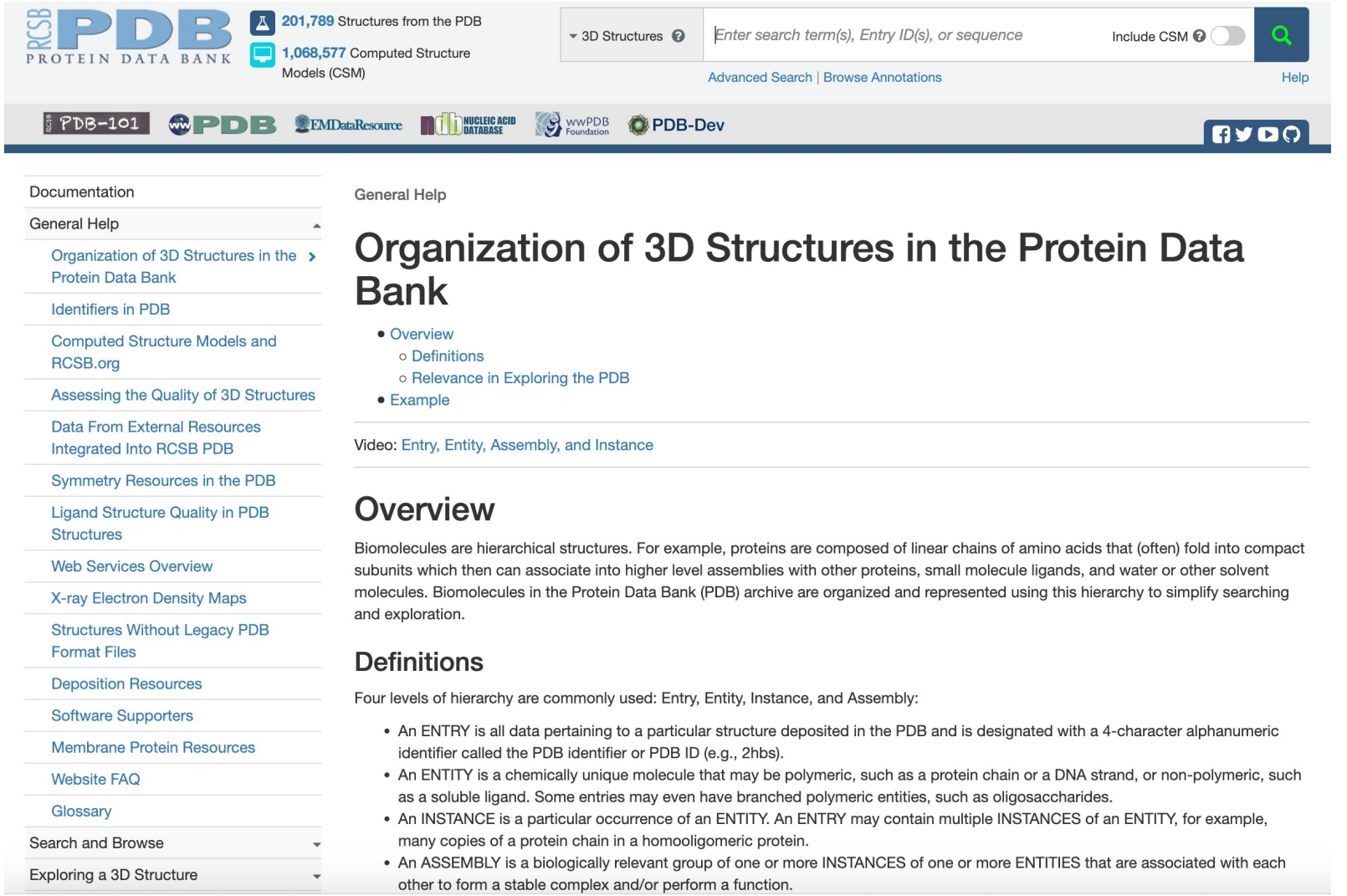
Crystal: regular packing of atoms into unit cells
Some proteins will form crystals

27 kDa protein, 248 amino acids, ~ 5000 atoms



What is a structure?

Protein data bank: repository of structures

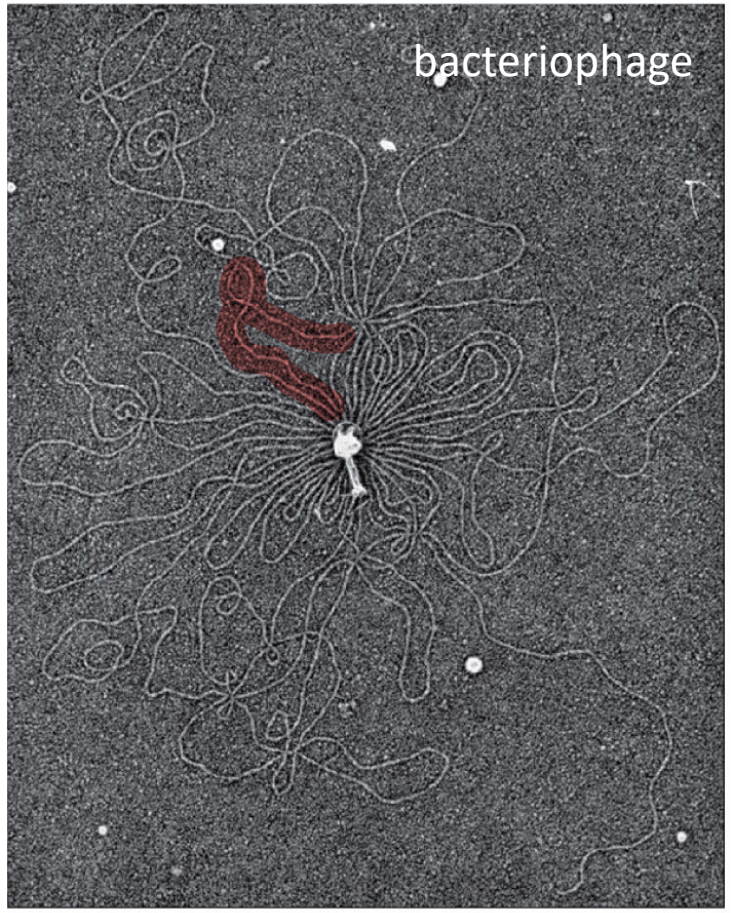


What is a structure?

Deterministic vs. **statistical** descriptions

PB.C 8.1

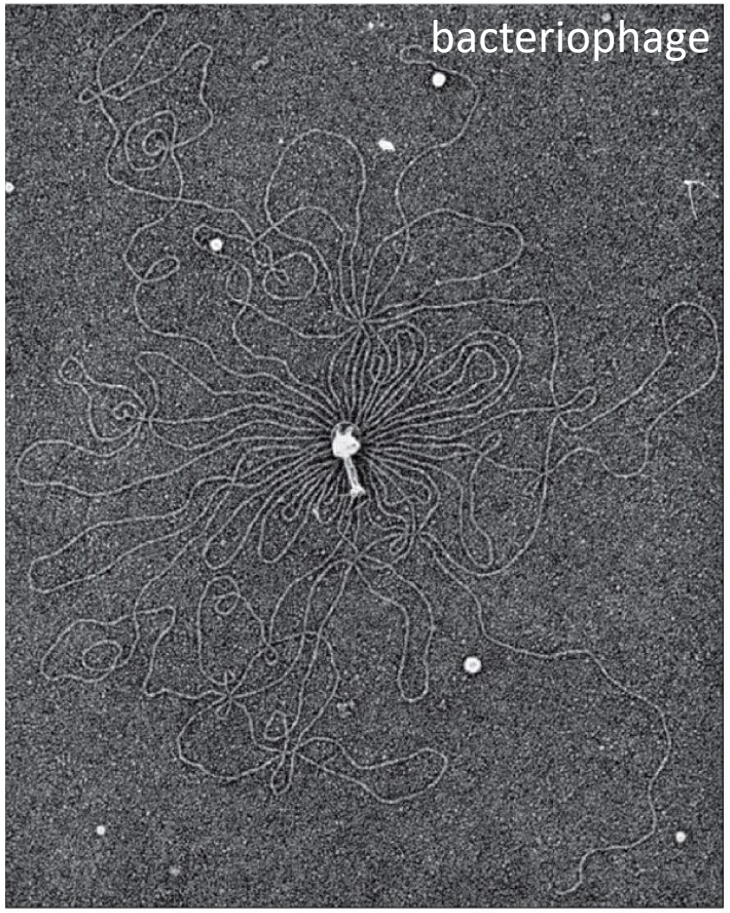
Average size and shape, fluctuations are important

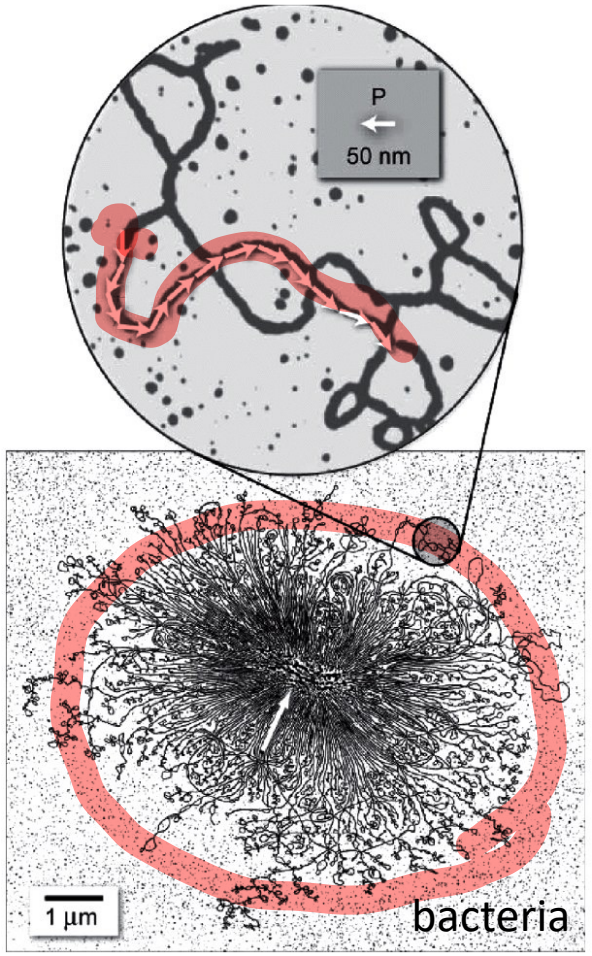


What is a structure?

Deterministic vs. **statistical** descriptions

Average size and shape, fluctuations are important





What can we learn about the molecule?

elasticity

$r \propto m^{n}$

"proportional to"

$n = \frac{1}{2}$ or $\frac{3}{5}$

random SAW

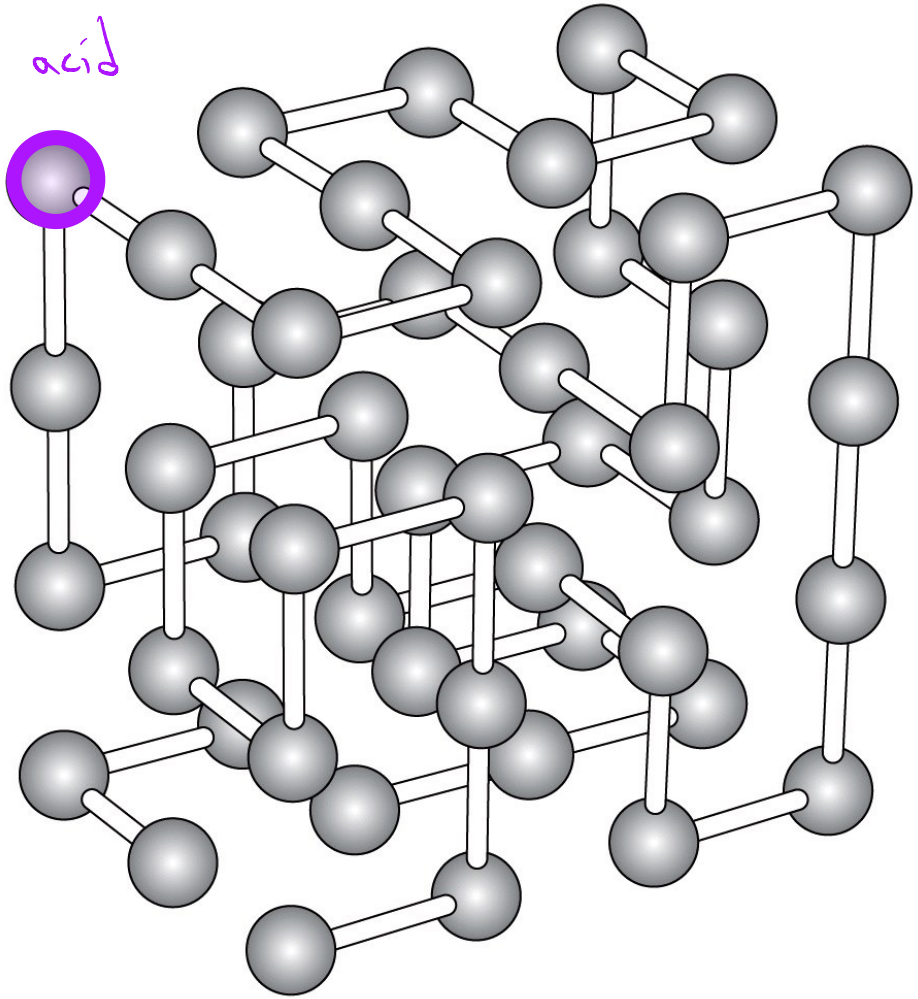
What is a structure?

Proteins as random walks

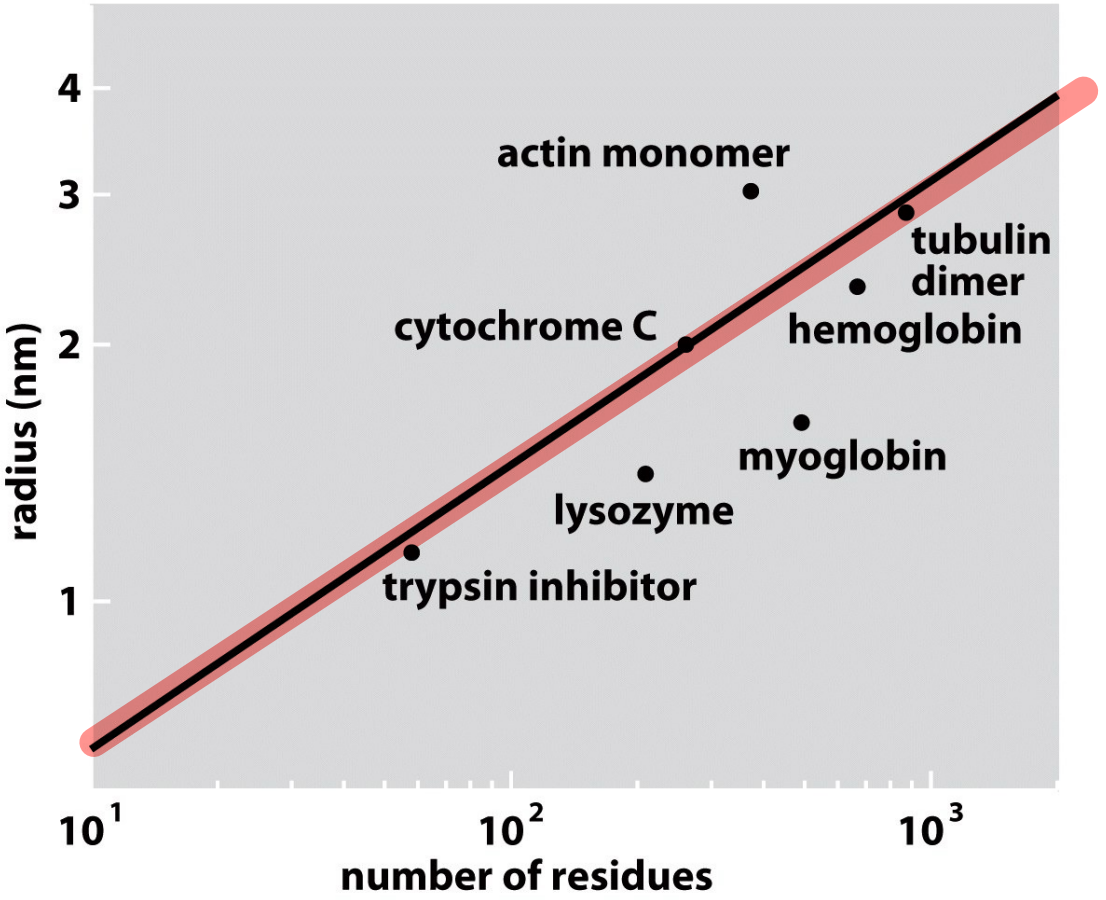
PBoC 8.4

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

amino acid



$V \propto m \Rightarrow r \propto m^{1/3}$



What is a structure?

HP model

consider the solvent, water

More complex model: Hydrophobic and polar residues

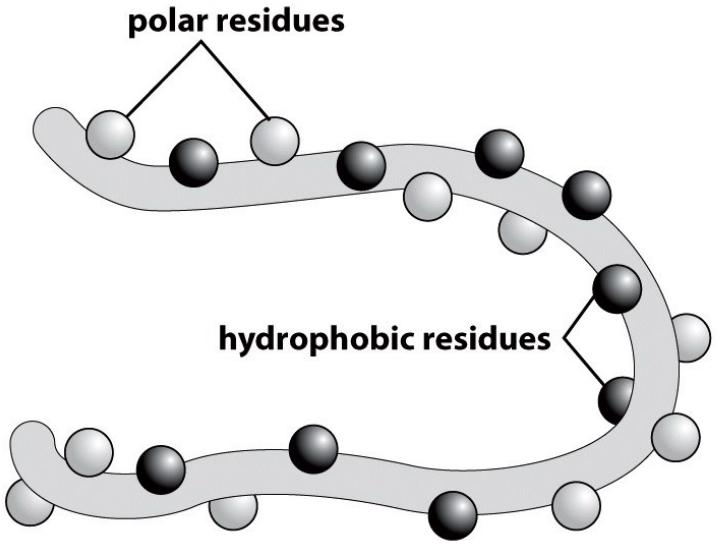
Number of possible 3D conformations is so large that a random search would take a long time:

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

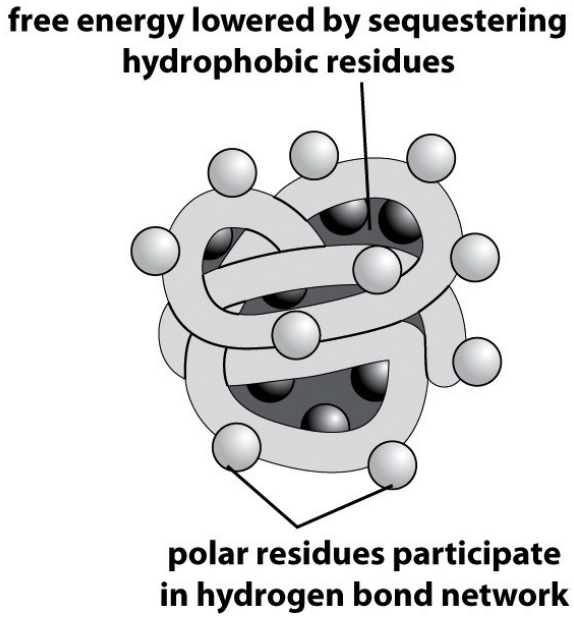
One structure per femtosecond
2×10^{55} years
Age of universe ~10^{10} years

One key: hydrophobicity

20 AA → HP



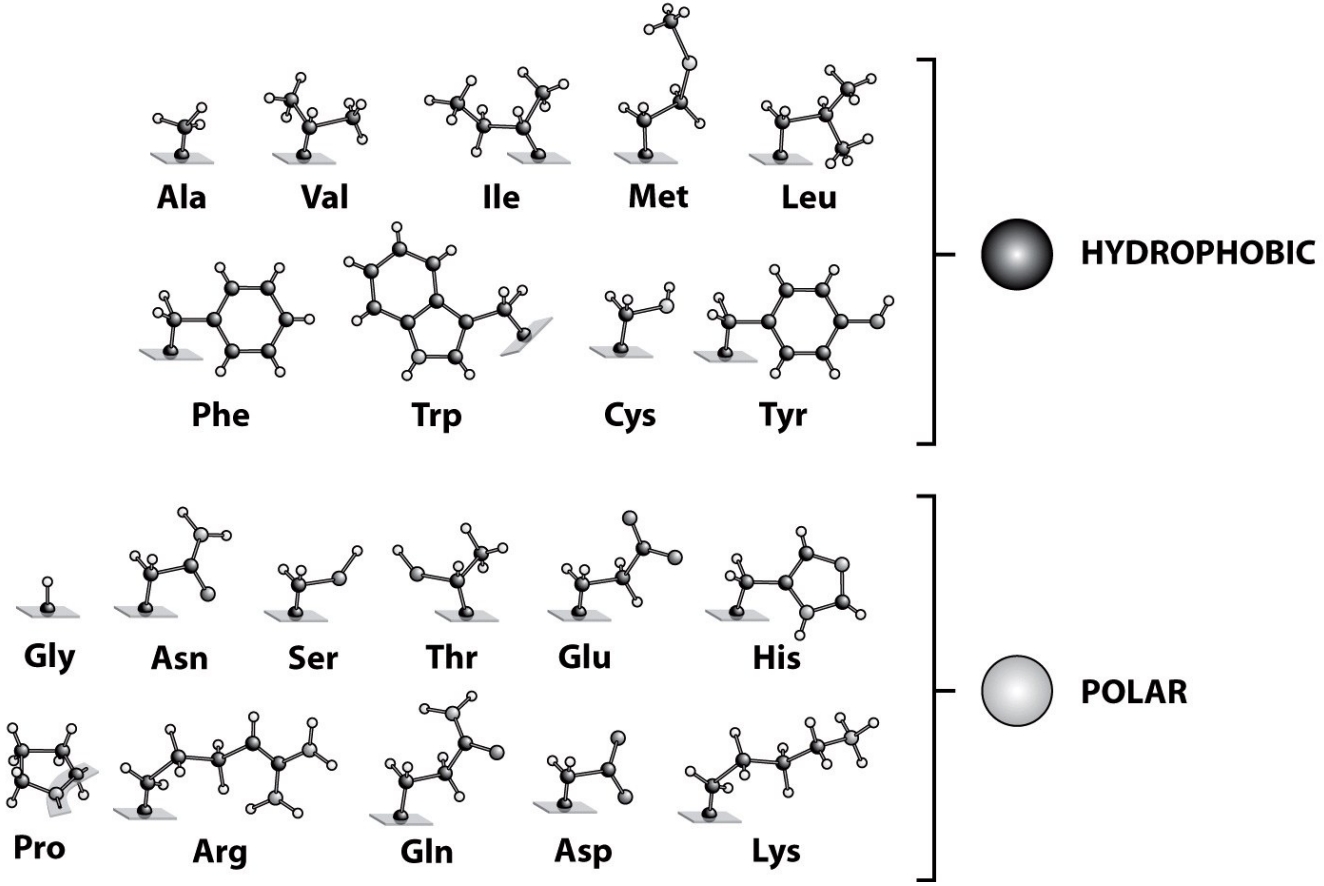
unfolded polypeptide



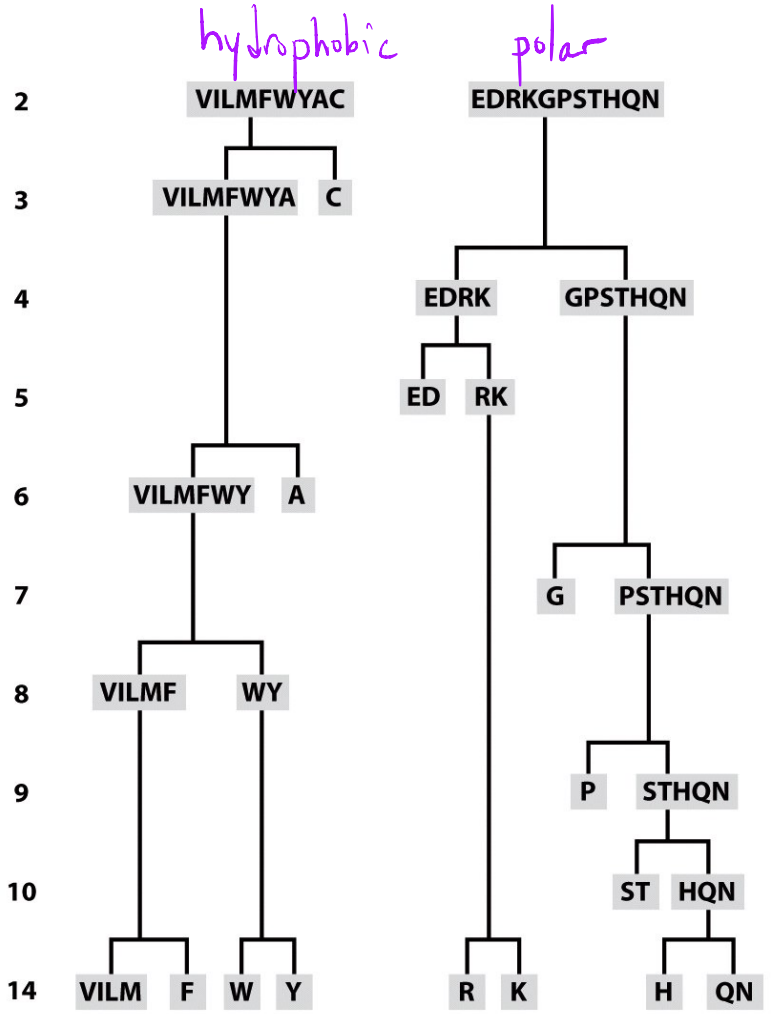
folded conformation in aqueous environment

What is a structure?

HP model



coarse-grained model: HP



hierarchy of classes

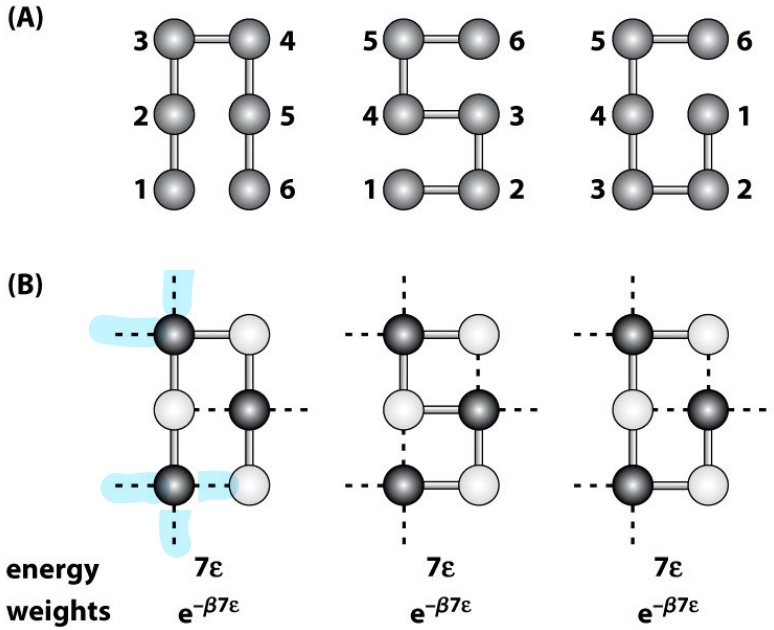
What is a structure?

HP model

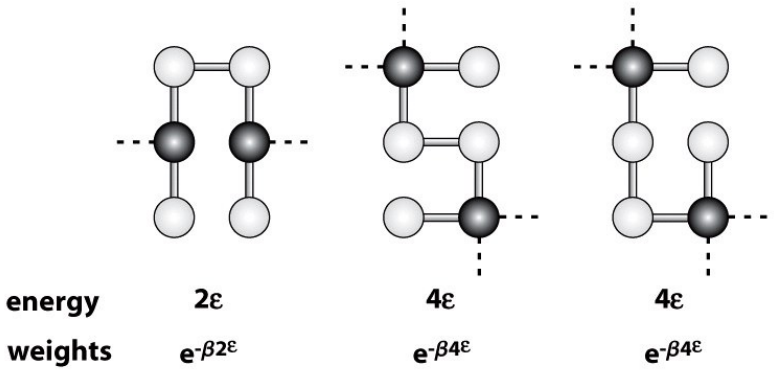
toy HP model:
6 monomers on a
3x2 lattice

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?

$$p_{\text{fold}} = \frac{e^{-2\beta\epsilon}}{e^{-2\beta\epsilon} + 2e^{-4\beta\epsilon}} = \frac{\text{Boltzmann factor for state}}{\text{partition function}}$$

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?

⋮

What sequences are protein-like?

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.*"

1895 Roentgen xrays

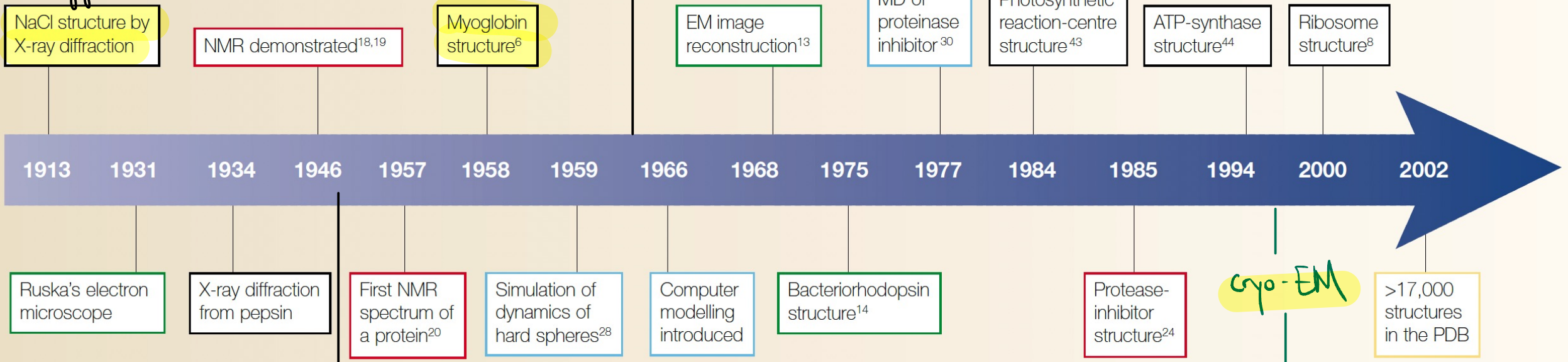
2020: AlphaFold

Dorothy Hodgkin penicillin

Timeline | **The march of structural biology**

Bragg

Perutz/Kendrew



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.

Watson/Crick/Franklin DNA

no crystallization required

Your mission:

Integrate information about the context of biomolecular structure.

Name one open question in the field of biomolecular structure

a priori structure prediction aa → 3D structure

Understand / explain the key developments in the field

Give an example of a breakthrough described, and identify its "scale"

- X-rays, fueled the field ~ human-scale ~ curiosity / accidental
  → impact on medical technology
- computational structure determination
- cryo-EM, no crystals needed!

Classify "genre" of information sources

- expository partially
- argumentative
- narrative primarily

Identify the genre used in the media we listened to / watched

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)