Proteins can be seen from space
Form follows function

- Examples of proteins
- Where is the relevance to physicists/chemists?
- Building blocks (beads on a string)
- Peptide bond, bb – Ramachandran diagram
- Side chain types,
- Primary, Secondary, Tertiary, Quarternary Structure
- Energetics (H-bonds, hydrophobic effect, salt bridges, aromatic stacking) (outside hydrophilic, inside hydrophobic)
- Methods to determine structure (NMR, X-ray, prediction)
Examples of protein structures

- Collagen
- Hormone Receptor bound to DNA
- Alcohol Dehydrogenase bound to ethanol
- Hemoglobin bound to oxygen
Physicists and Chemists are good at this!
Protein structure is hierarchical

Primary structure = amino acid sequence
Protein structure is hierarchical

Secondary structure = sequence of helices and sheets
Protein structure is hierarchical

Tertiary structure = three dimensional arrangement of atoms
Ribosomes synthesize proteins
Amino acids are polymerized

Amino acid $i$

Amino acid $i+1$
20 kinds of R groups

NH$_3^+$

amino group

C$_\alpha$

amino acid

R

H

carboxyl group

O

O$-$

Figure 1.28 The Molecules of Life (© Garland Science 2013)
residues with polar groups

Asparagine
Asn
N

Cysteine
Cys
C

Glutamine
Gln
Q

Amide

Thiol

Neutral Histidine
His
H

Imidazole

Hydroxyl

Serine
Ser
S

Indole

Threonine
Thr
T

Tryptophan
Trp
W

Tyrosine
Tyr
Y

Figure 1.29 (part 1 of 4) The Molecules of Life (© Garland Science 2013)
positively charged, hydrophilic residues

Figure 1.29 (part 2 of 4) The Molecules of Life (© Garland Science 2013)
nonpolar, hydrophobic residues

alanine
Ala
A

isoleucine
Ile
I

glycine
Gly
G

leucine
Leu
L

methionine
Met
M

phenylalanine
Phe
F

proline
Pro
P

valine
Val
V

Figure 1.29 (part 3 of 4) The Molecules of Life (© Garland Science 2013)
negatively charged, hydrophilic residues

Aspartate (Asp, D)

Glutamate (Glu, E)
Proteins are unbranched polymers.
Proteins are unbranched polymers

amino acid + amino acid → H₂O

Amino (N) - terminus

Carboxy (C) - terminus
The peptide chain has local structure
The peptide bond is planar

Keto-Enol tautomerism is responsible for planar peptide bond and short C-N distance.
Peptide bond can be *cis*- or *trans*

*Trans* is 1000-fold more favored than *cis*.
Exception proline: *trans* is only 3-fold more common
How does the peptide chain access a well determined 3D structure?
Two rotational bonds at $C\alpha$ define orientation of planar peptide bonds.

Towards C-terminus

Towards N-terminus

Figure 4.17 The Molecules of Life (© Garland Science 2013)
Some combinations of $\phi$ and $\psi$ clash
Ramachandran diagram defines permitted $\phi$ and $\psi$ combinations.

After G.N. Ramachandran, a physicist!

Figure 4.20 The Molecules of Life (© Garland Science 2013)
Ramachandran diagram defines permitted combinations

More than 95% of experimentally observed $\phi$ and $\psi$ angles fall into the predicted regions.
Ramachandran diagram defines permitted combinations

Glycine in multiple structures

Ramachandran plots are amino acid specific

Figure 4.20 The Molecules of Life (© Garland Science 2013)
Potential energy representation of Ramachandran diagram
Secondary structures are formed when consecutive residues adopt similar $\phi$ and $\psi$ angles.
Secondary structures are formed when consecutive residues adopt similar $\phi$ and $\psi$ angles.
β-sheets are stabilized by hydrogen bonds
α-helices are stabilized by hydrogen bonds and they are polarized.
Secondary structural elements arrange to form tertiary structures
Secondary structural elements arrange to form tertiary structures
Hydrophobic residues are in the interior
Hydrophilic residues tend to be on the surface

**Positive** (Arg, Lys)
**Negative** (Asp, Glu)
**Polar** (Asn, Gln, His, Ser, Thr, Trp, Tyr)
Membrane proteins are stuck in oil

Positive (Arg, Lys)
Negative (Asp, Glu)
Polar (Asn, Gln, His, Ser, Thr, Trp, Tyr)
Membrane proteins are stuck in oil
Where are the membranes?
Individual domains can be combined

Protein domains are independently folding and evolving protein structures
Individual domains can be combined

Protein domains are independently folding and evolving protein structures
Protein domains are reshuffled during evolution.
Similar domains in different proteins

Figure 4.6 The Molecules of Life (© Garland Science 2013)
Quaternary Structure: Proteins can form larger functional complexes

Makino et al (Nature 2013)
Methods to determine protein structures

Nuclear Magnetic Resonance spectroscopy

X-ray crystallography
X-ray crystallography

protein purification

crystal

diffraction pattern

phases

electron density map

refinement

fitting

atomic model
Nuclear Magnetic Spins
Alignment in external field
Sensitive to local chemistry
NMR resonance assignment
NOE experiments yield structural information

assigned protein sequence
NOE experiments yield structural information

assigned protein sequence

structural constraints

Nuclear Overhauser Effect Experiments
NOE experiments yield structural information

assigned protein sequence

Nuclear Overhauser Effect Experiments

structural constraints

Calculation of Models that satisfy constraints

Structure
Ab initio structure prediction

- Many different approaches
- If interested see David Baker and Rosetta (http://depts.washington.edu/bakerpg)

Skolnick Biophys J. 2007
Can you answer this?

• Can you name three major classes of proteins?
• What are the fundamental units of tertiary structure?
• How do hydrogen bonds stabilize secondary structure?
• Can you draw the tripeptide: Ala-Pro-Gly?
• How are amino acids distributed in the structure of the protein?
• Why is the rotation around the peptide bond hindered?
• What conformation can the peptide bond obtain and which conformation is more stable?
• What does the Ramachandran diagram show?
Further reading

• **Kuriyan, Konforti, Wemmer:** *The Molecules of Life* (Garland Science, 2012)

• **Petsko, Ringe:** *Protein Structure and Function* (Oxford University Press, 2004)

• **Braenden, Tooze:** *Introduction to Protein Structure* (Garland Science, 1999)

• **Tanford, Reynolds:** Nature’s Robots: A History of Proteins (Oxford Univ. Press, 2001)