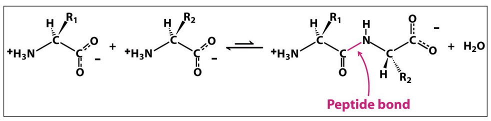
Chem 452 – Lecture 2
Protein Structure
Part 3

Question of the Day: Most proteins are made from a repertoire of 20 different amino acids. A small protein contains around 100 amino acids strung together in a polypeptide chain. How many different possible chains, containing 100 amino acids each, can be made when there are 20 different options for each of the amino acid in a chain?

Protein Primary Structure

- The amino acids combine to form polymers of amino acids.
  - Polymers of amino acids are called **polypeptides**

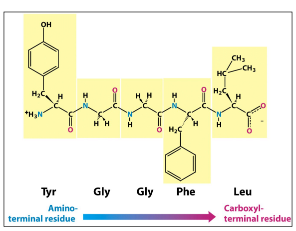


Question

Based on the number of amino acid residues it contains

A) how would you classify the oligopeptide shown below?

B) What is the predicted mass for this oligopeptide?



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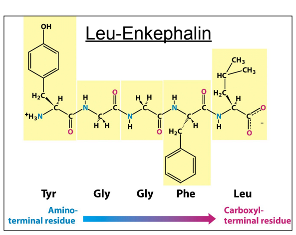
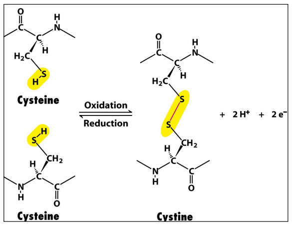


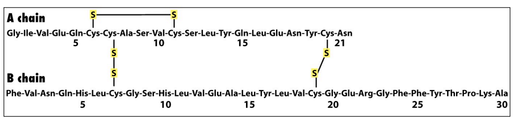
Protein Primary Structure

- While polypeptides are linear polymers, they can form cross links.



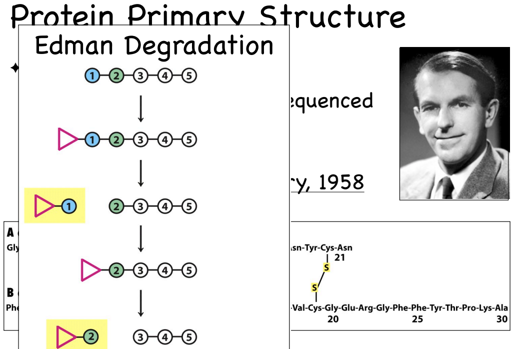
Protein Primary Structure

- Protein Sequencing
  - The first protein to be sequenced was insulin
  - Frederick Sanger (1953)
    - Nobel Prize in Chemistry, 1958



Human Insulin

Protein Primary Structure



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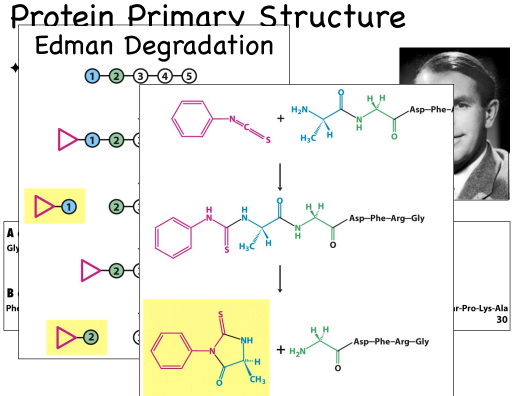
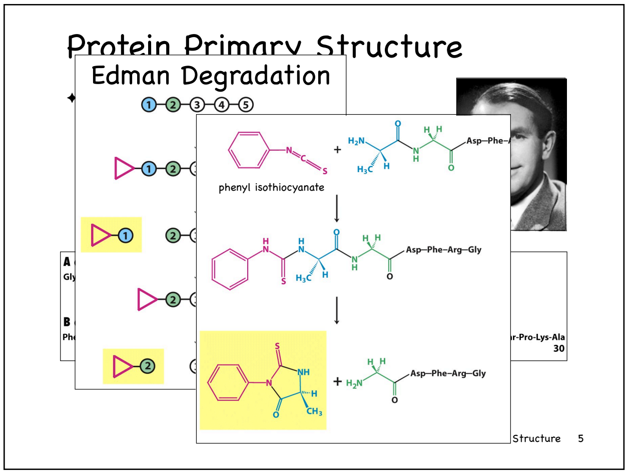
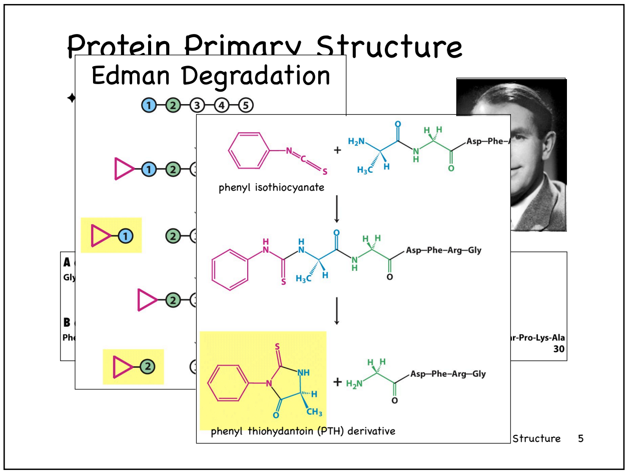



Protein Primary Structure
Edman Degradation
phenyl isothiocyanate
Asp–Phe–Arg–Gly
Asp–Phe–Arg–Gly
Structure 5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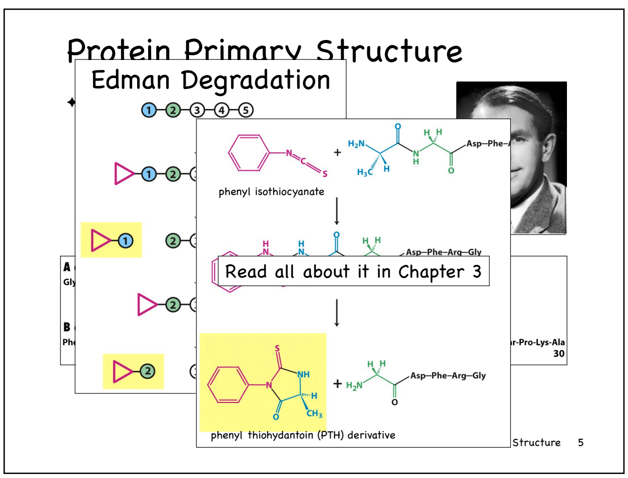
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Read all about it in Chapter 3
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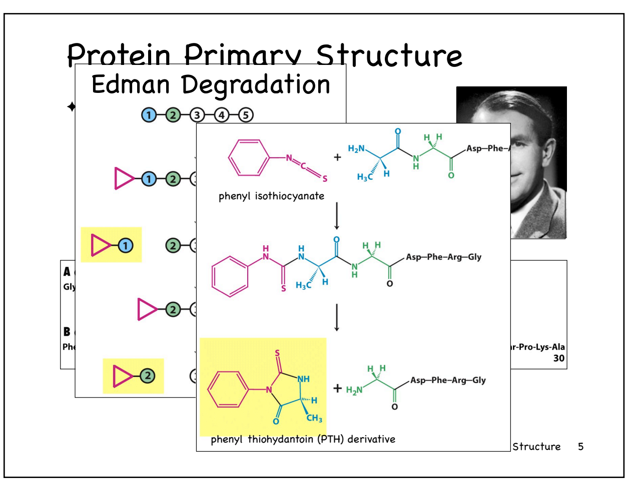
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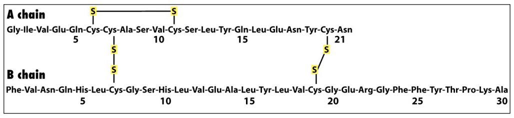
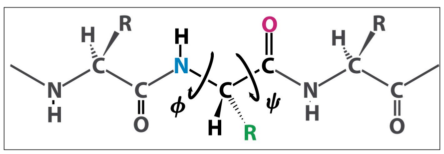


Human Insulin

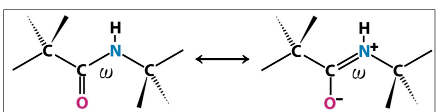
Polypeptide Conformations

- Polypeptides are conformationally flexible.
  - Rotation is possible about the ϕ and ψ bonds.



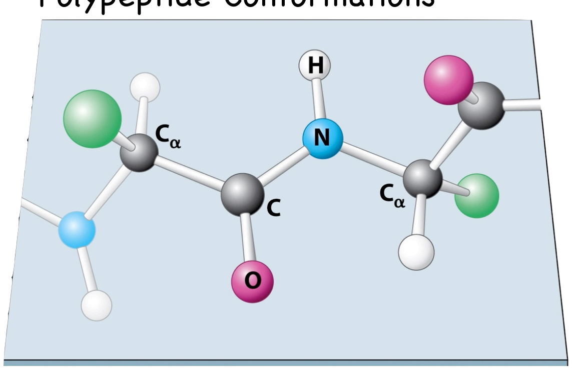
Polypeptide Conformations

- Rotation about the peptide (ω) bond is restricted to 0° and 180°.
  - The ω bond behaves like a double bond
    - cis (0°) or trans (180°)



Peptide-bond resonance structures

Polypeptide Conformations



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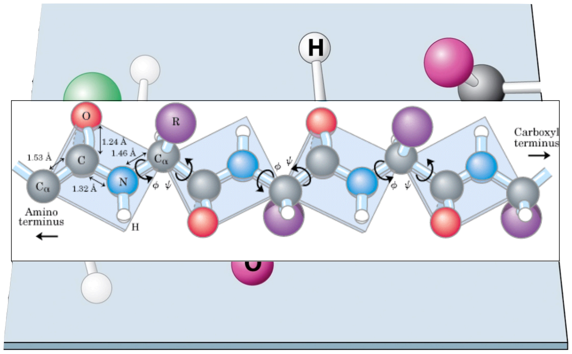

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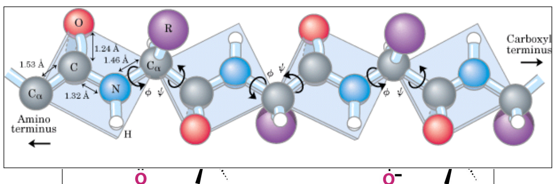

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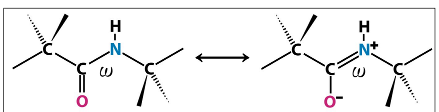

Peptide-bond resonance structures

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- Rotation about the peptide (ω) bond is restricted to 0° and 180°.
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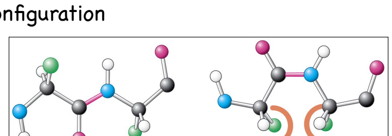
    - **cis** (0°) or **trans** (180°)
  - **trans** is the sterically more favorable configuration



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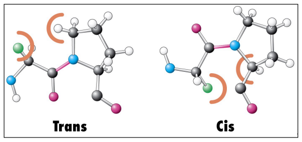
  - The ω bond behaves like a double bond
    - **cis** (0°) or **trans** (180°)
  - For peptide bonds involving proline, both **cis** and **trans** configurations are possible.



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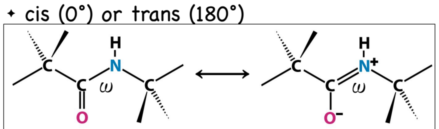

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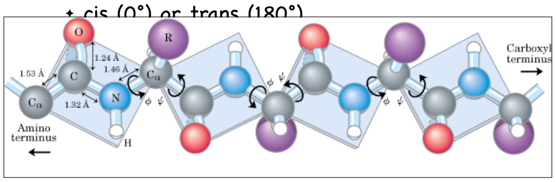

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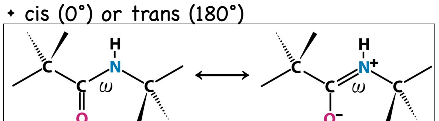
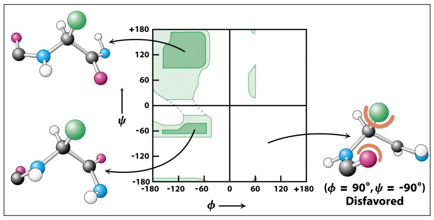


Peptide-bond resonance structures

Polypeptide Conformations

- Ramachandran determined the sterically most favorable combinations of ϕ and ψ angles.



Primary -> Secondary -> Tertiary

- We will consider proteins structure hierarchically:

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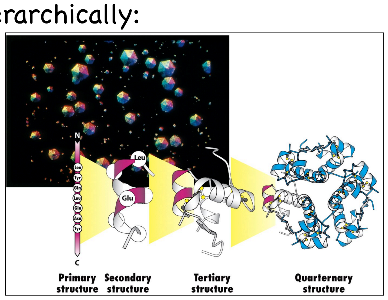

Question

The functional diversity of proteins results from the large number of possible polypeptides that can be built using the 20 different amino acids

Question: What is the minimum mass it would take to construct one molecule each of all of the possible polypeptides that contain 100 amino acids?

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View the polypeptides as beads on a string, with one of 20 possible types of beads at each position

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13

Thinking of the Possibilities

The Earth weighs 6.0 x 10^{27} g, how many Earths would it take?

14

Thinking of the Possibilities

The Sun weighs 2.0 x 10^{33} g, how many Suns would it take?

15

Thinking of the Possibilities

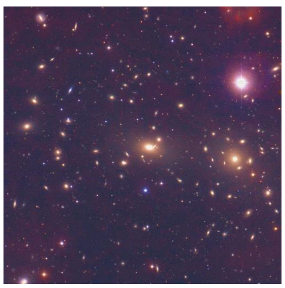
The Milky Way galaxy weighs 1.2×10^{45} times the mass of the sun

A) $(1.2 \times 10^{45}$ suns$)(2.0 \times 10^{33}$ g/sun$) = 2.4 \times 10^{78}$ g

B) How may galaxies would it take?

Thinking of the Possibilities

The Coma galaxy cluster contains several thousand galaxies, how many ...?

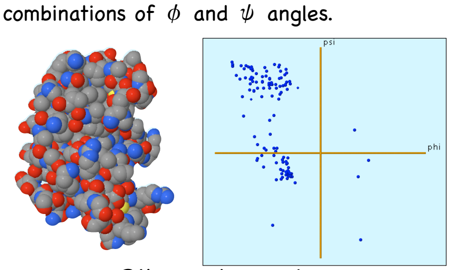


Thinking of the Possibilities

Number of polypeptides (20^{100})	1.26×10^{130}
Avg. Mass of each polypeptide	1.83×10^{-22} g
Total mass needed	2.32×10^{108} g
Number of Earths	3.9×10^{80}
Number of Suns	1.2×10^{75}
Number of Galaxies	9.7×10^{29}

Protein Tertiary Structure

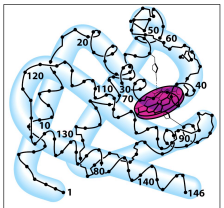
- The amino acid residues in a folded, globular protein, generally adopt these favorable combinations of ϕ and ψ angles.



Ribonuclease A

Protein Tertiary Structure

- The first 3-dimensional structure of a protein were published in the late 1950's by John Kendrew (myoglobin) and Max Perutz (hemoglobin).



Beta chain of hemoglobin

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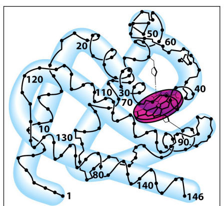

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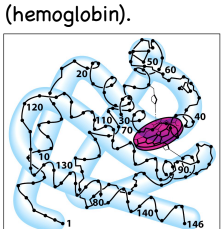
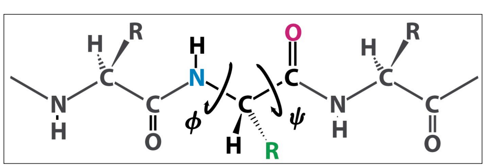


Beta chain of hemoglobin

Interior or folded proteins is packed almost exclusively with non-polar amino acid side chains.

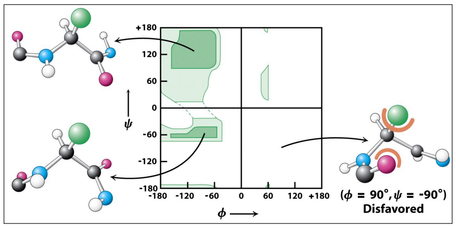
Protein Tertiary Structure

- What effect does the polar backbone have on folding?



Protein Secondary Structure

- Looking at the sterically favorable ϕ and ψ angles.



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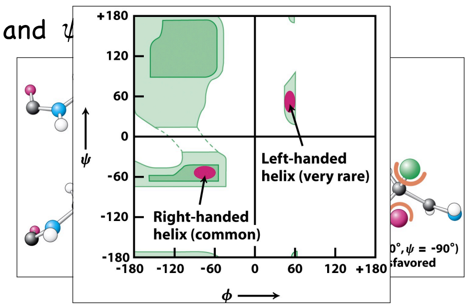
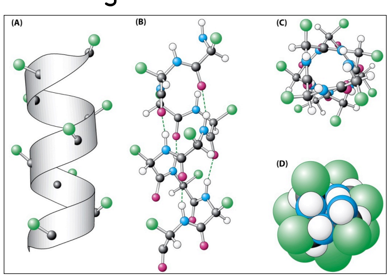


Protein Secondary Structure

- α-helix region



α-helix

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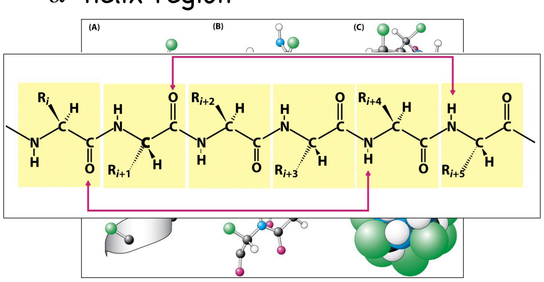

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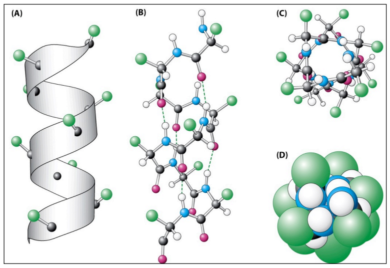

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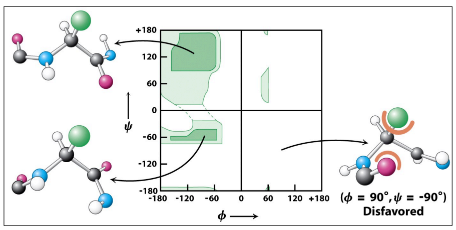
Protein Secondary Structure

- Looking at the sterically favorable ϕ and ψ angles.



Protein Secondary Structure

- Looking at the sterically favorable ϕ

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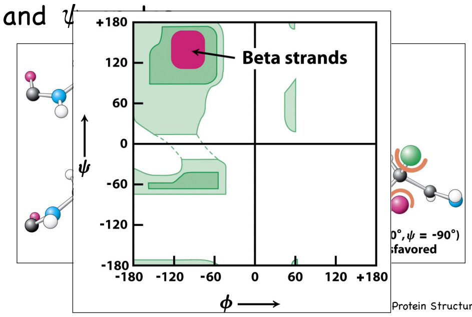
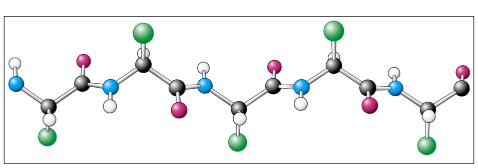


Protein Secondary Structure

- β-sheet region



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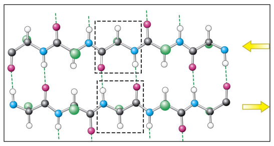
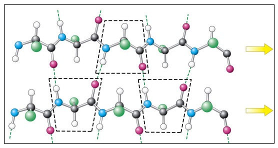


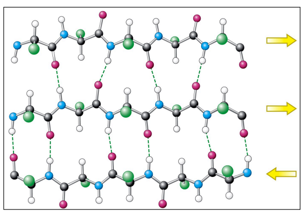
Antiparallel
β-sheet



Parallel
β-sheet

Protein Secondary Structure

- β-sheet region
  - Can also have mixed parallel and antiparallel β-sheets



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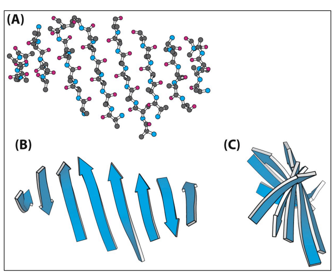
- β-sheet region



Protein Secondary Structure

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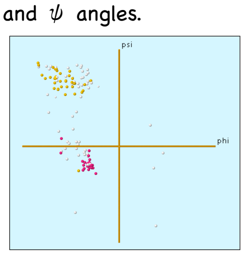
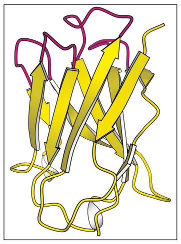
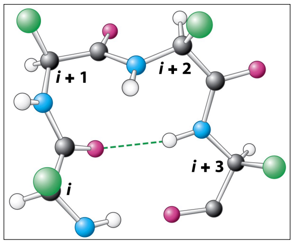


Ribonuclease A

Protein Secondary Structure

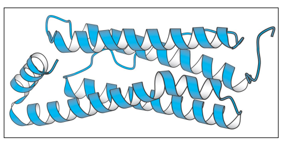
- Loops and β-turns



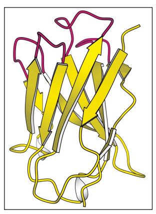


Protein Secondary Structure

- Proteins vary in their α-helix and β-sheet content.



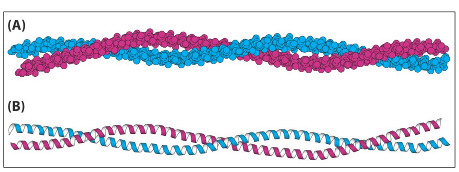
Ferritin (1aew)



Antibody (7fab)

Fibrous Proteins

- Some fibrous proteins lack tertiary but have quaternary structure.



α-helical coiled coils

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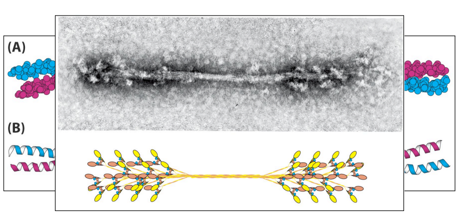

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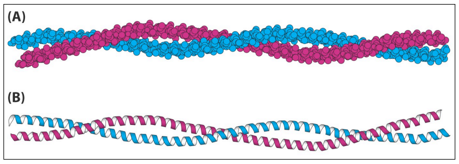

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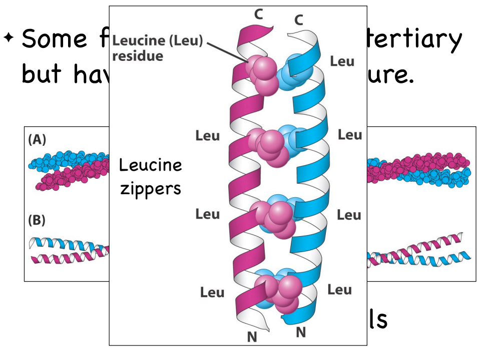

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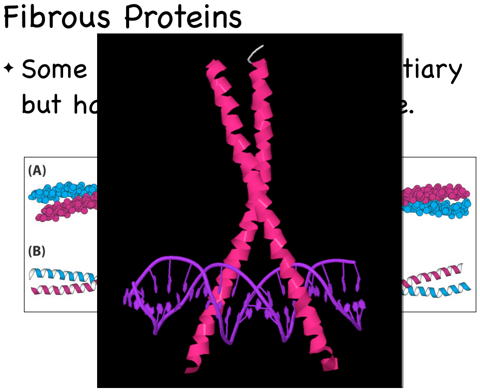

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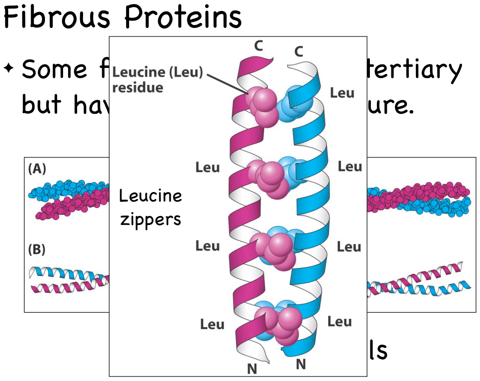

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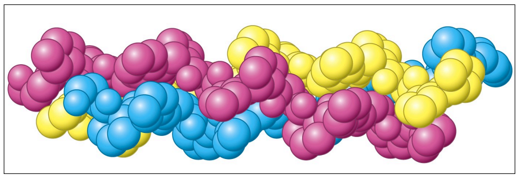

Collagen
(polyproline triple helix)

Fibrous Proteins

- Some fibrous proteins lack tertiary but have quaternary structure.

Collagen
(polyproline triple helix)

Fibrous Proteins

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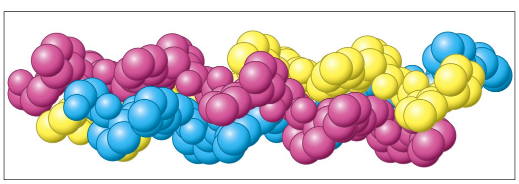

Collagen
(polyproline triple helix)

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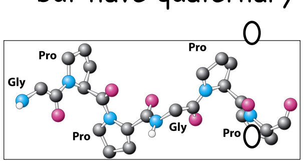

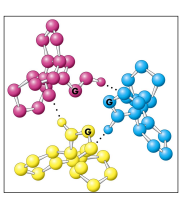

Collagen
(polyproline triple helix)

Fibrous Proteins

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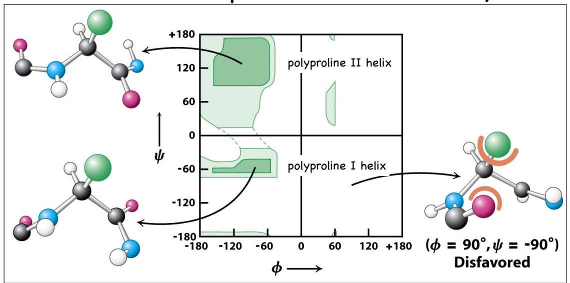

(polyproline triple helix)

Fibrous Proteins

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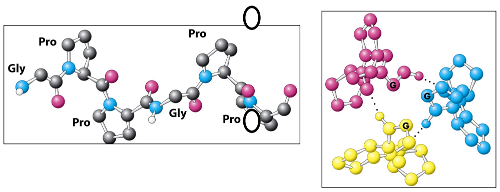
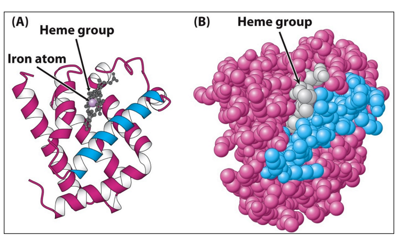


Collagen
(polyproline triple helix)

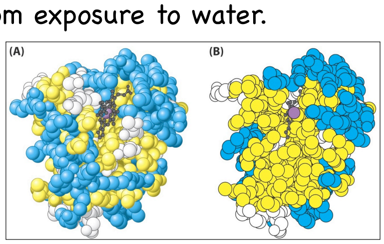
Protein Tertiary Structure

- The 3-dimensional fold of a single polypeptide



Protein Tertiary Structure

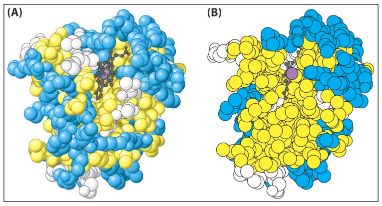
- Polypeptides fold to remove hydrophobic amino acid side chains from exposure to water.



surface interior

Protein Tertiary Structure

- Polypeptides fold to remove hydrophobic amino acid side chains from exposure to water.

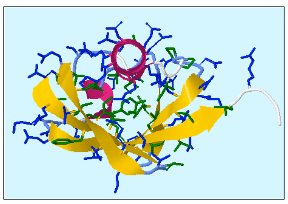


yellow - hydrophobic
blue - charged
white - other

surface interior

Protein Tertiary Structure

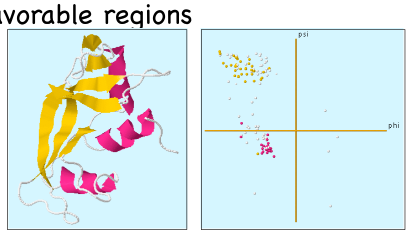
- Formation of secondary structure allows for the polar backbone to be buried as well.



Ubiquitin

Protein Tertiary Structure

- Most of the amino acid residues have ϕ and ψ angles in the sterically favorable regions



Ribonuclease A

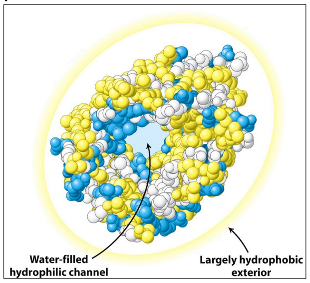
Protein Tertiary Structure

- Disulfide bonds help cement the tertiary fold.

Ribonuclease A

Protein Tertiary Structure

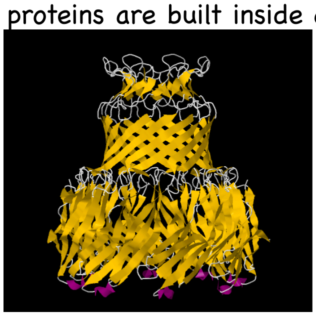
- Some proteins are built inside out



Porin, a membrane protein

Protein Tertiary Structure

- Some proteins are built inside out



Porin, a membrane protein

Protein Tertiary Structure

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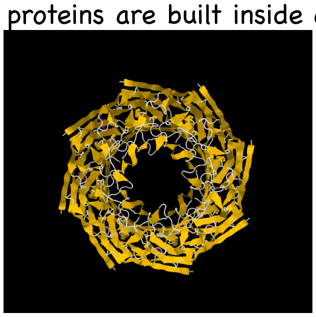
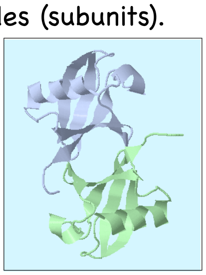


Porin, a membrane protein

Protein Quaternary Structure

- Some proteins have multiple polypeptides (subunits).



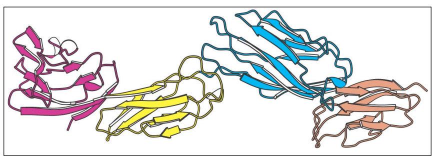
Ubiquitin

Protein Quaternary Structure

- Quaternary structures are stabilized by the same interactions that stabilize tertiary structures.
  - Non-covalent interactions involving primarily the amino acid side chains.

Protein Quaternary Structure

- Some tertiary structures have multiple folding domains, which give them the appearance of having quaternary structure



CD4 protein

Hierarchy of Protein Structure

- Primary
- Secondary
- Tertiary
- Quaternary

Phosphofructokinase I

Next up

- Protein folding and misfolding.
- **Question of the Day:** How is online video game-playing is being used to help find cures for diseases?