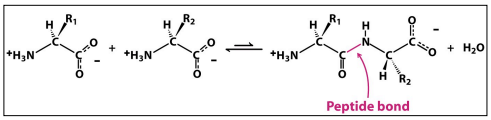
Chem 452 - Lecture 2
Protein Structure
110923

Proteins are the workhorses of a living cell and involve themselves in nearly all of the activities that take place in a cell. Their wide range of structures are manifested by the wide range of 3-dimensional structures that they are able to possess. Proteins are linear polymers of amino acids, whose sequence is determined by the sequence of DNA base pairs in their corresponding gene. The connection between this linear sequence of amino acids for a protein and its 3-dimensional structure will be the focus of this lecture.

Protein Primary Structure

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

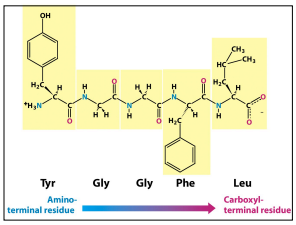


Question

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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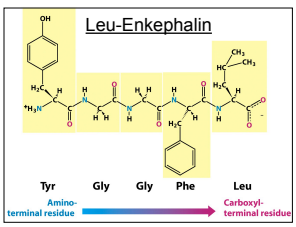
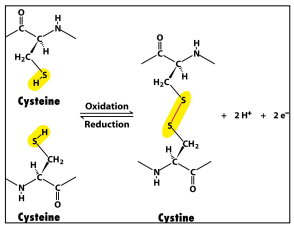


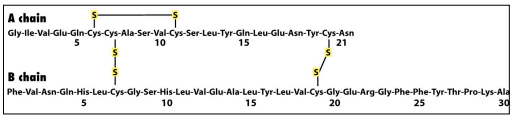
Protein Primary Structure

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



Protein Primary Structure

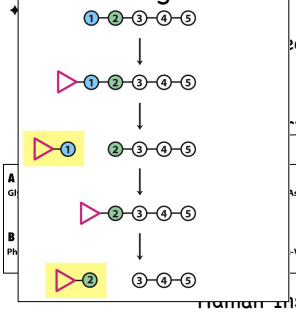
- Protein Sequencing
  - The first protein to be sequenced was insulin
  - Frederick Sanger (1953)
    - Nobel Prize in Chemistry, 1958



Human Insulin

Protein Primary Structure

Edman Degradation



Protein Primary Structure

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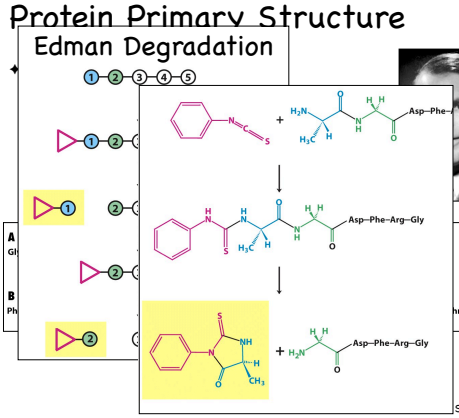

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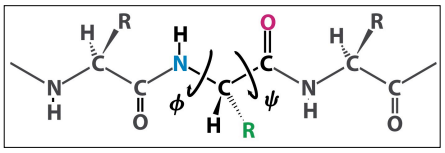
Human Insulin

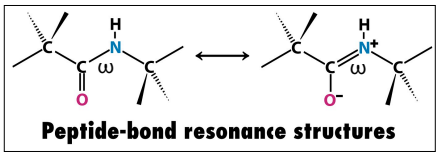
Protein Primary Structure

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



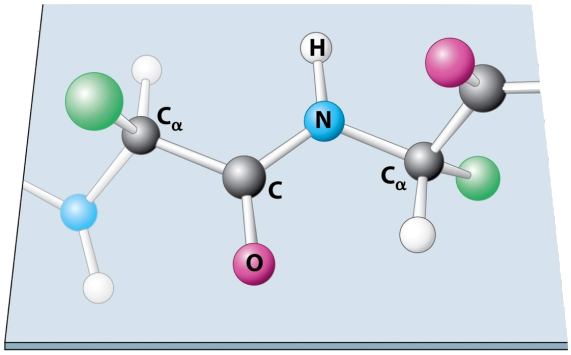
Protein Primary Structure

- 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

Protein Primary Structure



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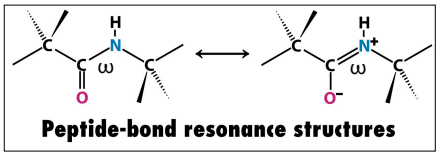
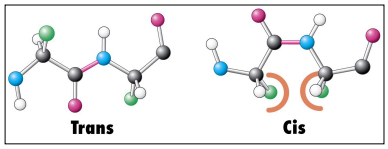


Peptide-bond resonance structures

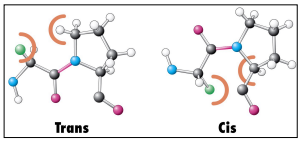
Protein Primary Structure

- 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°)
  - **trans** is the sterically more favorable configuration



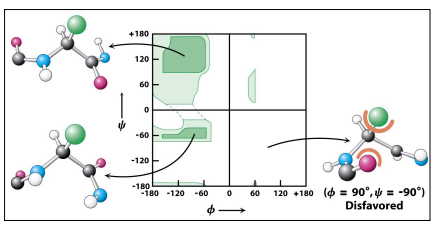
Protein Primary Structure

- 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°)
  - For peptide bonds involving proline, both **cis** and **trans** configurations are possible.



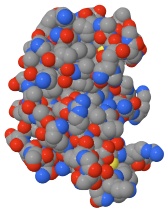
Protein Primary Structure

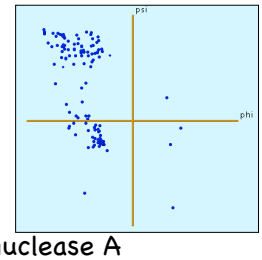
- Ramachandran determined the sterically most favorable combinations of φ and ψ angles.



Protein Tertiary Structure

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

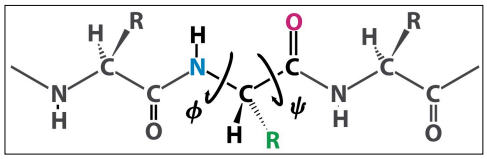




Ribonuclease A

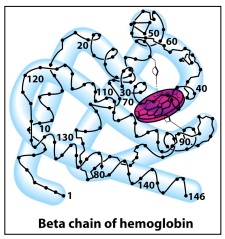
Protein Tertiary Structure

- What effect does the polar backbone have on folding?



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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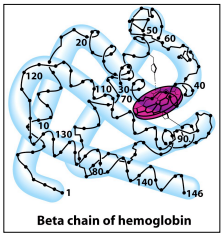

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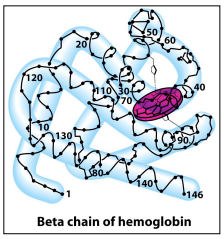
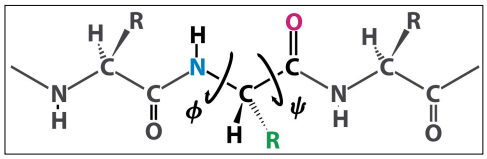


Beta chain of hemoglobin

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

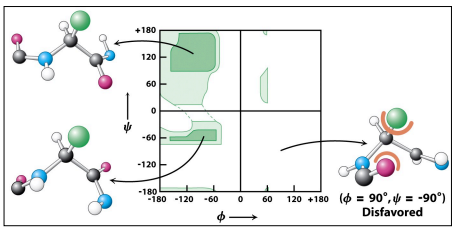
Protein Tertiary Structure

- 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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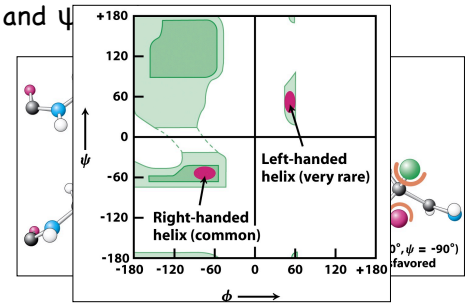
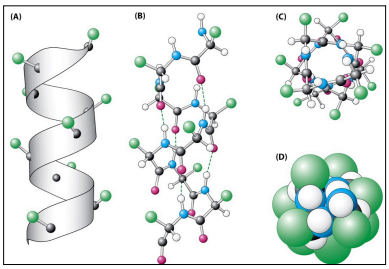


Protein Secondary Structure

- α-helix region



α-helix

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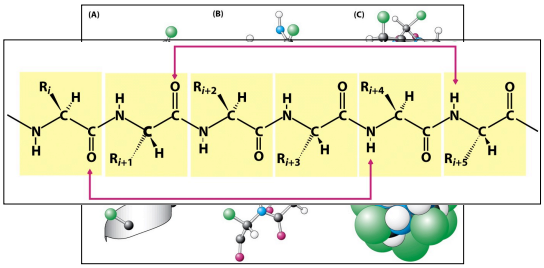

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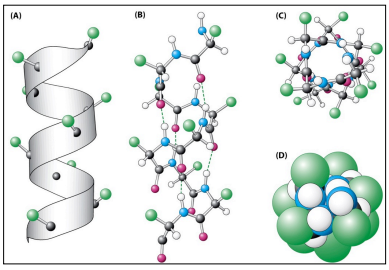

α-helix

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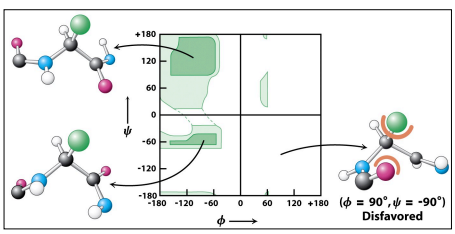

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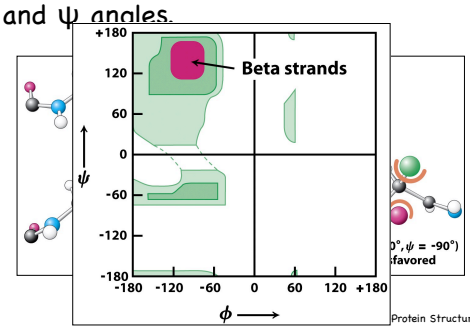
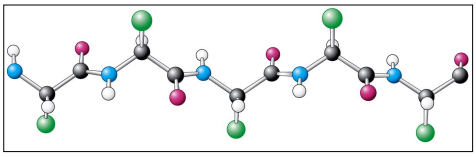


Protein Secondary Structure

- β-sheet region



Protein Secondary Structure

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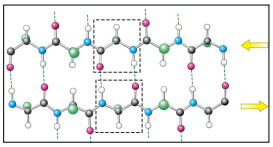
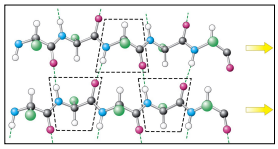


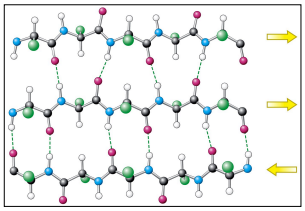
Antiparallel
β-sheet



Parallel
β-sheet

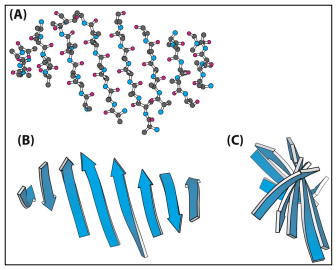
Protein Secondary Structure

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



Protein Secondary Structure

- β-sheet region



Protein Secondary Structure

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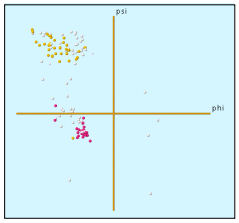
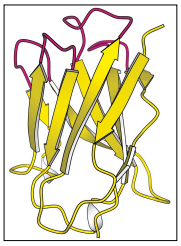
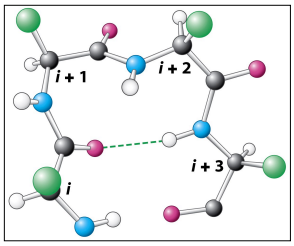


Ribonuclease A

Protein Secondary Structure

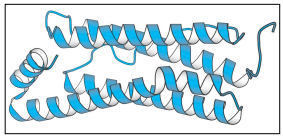
- Loops and β-turns

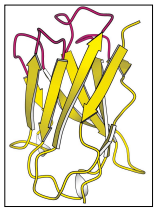




Protein Secondary Structure

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



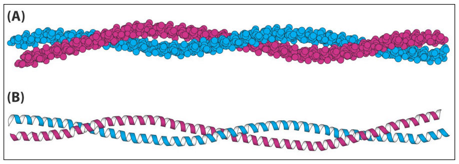


Ferritin (1aew)

Antibody (7ftp)

Fibrous Proteins

- Some fibrous proteins lack tertiary but have quaternary structure.



α-helical coiled coils

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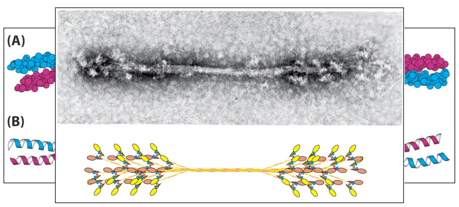

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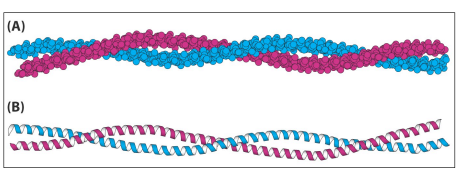

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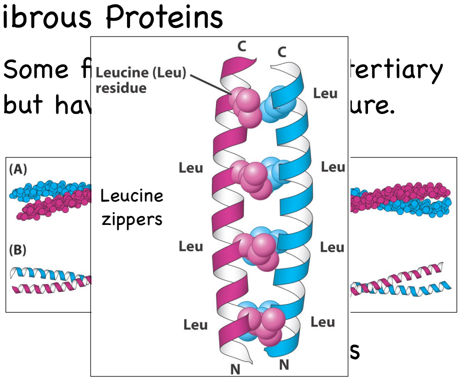

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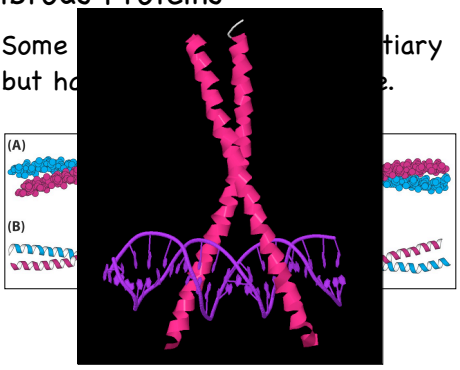

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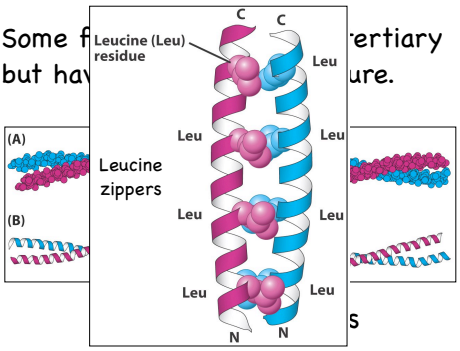

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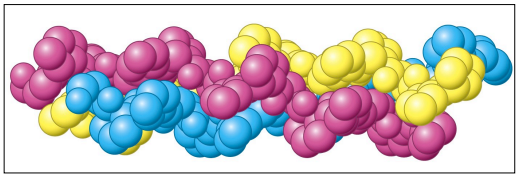

Collagen
(polyproline triple helix)

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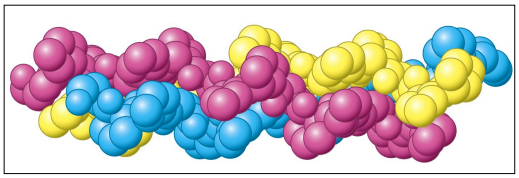

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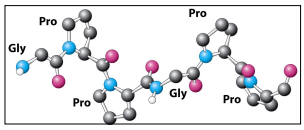

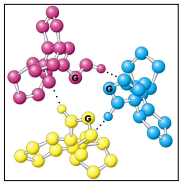

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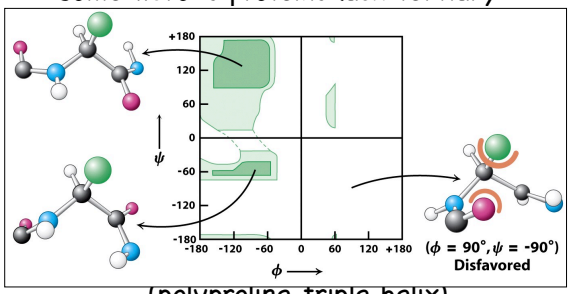

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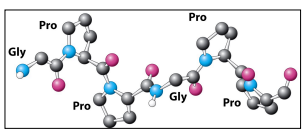
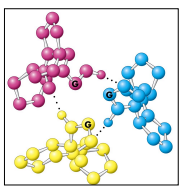
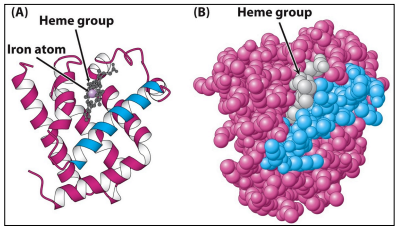




Collagen
(polyproline triple helix)

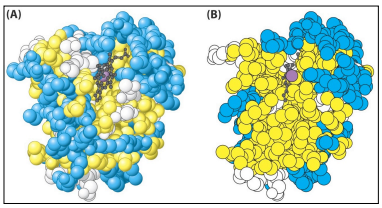
Protein Tertiary Structure

- The 3-dimensional fold of a single polypeptide



Protein Tertiary Structure

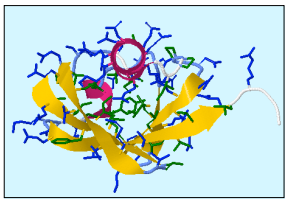
- Polypeptides fold to remove hydrophobic amino acid side chains from exposure to water.



surface interior

Protein Tertiary Structure

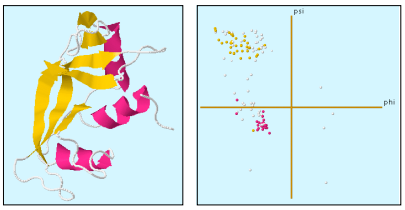
- Formation of secondary structure allows for the polar backbone to be buried as well.



Ubiquitin

Protein Tertiary Structure

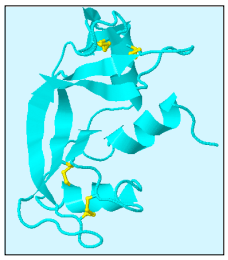
- Most of the amino acid residues have φ and ψ angles in the sterically favorable regions



Ribonuclease A

Protein Tertiary Structure

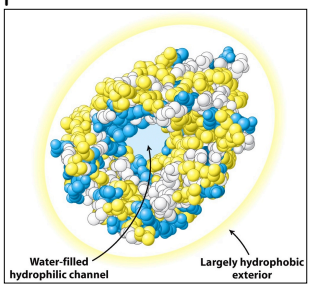
- Disulfide bonds help cement the tertiary fold.



Ribonuclease A

Protein Tertiary Structure

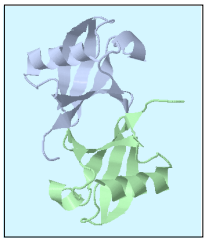
- Some proteins are built inside out



Porin, a membrane protein

Protein Quaternary Structure

- Some proteins have multiple polypeptides (subunits).



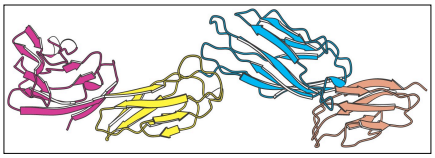
Ubiquitin

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

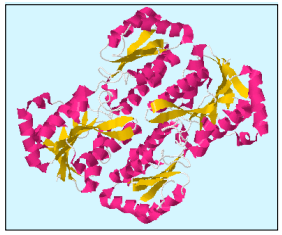
- Some tertiary structures have multiple folding domains, which give them the appearance of having quaternary structure



CD4 protein

Hierarchy of Protein Structure

- Primary
- Secondary
- Tertiary
- Quaternary



Phosphofructokinase I

Next up

- Protein folding and misfolding.