Informatica Biomedica

lezione17

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Informatica Biomedica: Lezione 17

- Fundamentals of Protein Structure
- Primary Structure - Amino Acid Sequence
  - The Peptide Bond
- Secondary Structure is Local 3D Structure
  - α Helices
  - β Sheets
  - Other Secondary Structure
- Representations of protein structure
- Tertiary Structure - Global 3D Structure
  - Side Chains and Tertiary Structure
  - Domains and Motifs
  - Biochemical Classification of Folds
  - Structural Classification of Folds
- Quaternary Structure - Associations of Multiple Polypeptide Chains
  - Functional Relevance of Quaternary Structure

Fonte essenziale: J- Gu amp; P.E- Bourne, *Structural Bioinformatics*, Wiley (2009)

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- These large, complex molecules exhibit a remarkable versatility that allows them to perform a myriad of activities that are fundamental to life.
- No other type of biological macromolecule could possibly assume all of the functions that proteins have amassed over billions of years of evolution.

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- It is this precision that allows proteins to act as catalysts (enzymes) for an impressive variety of chemical reactions.
- Precise placement of chemical groups also allows proteins to play important structural, transport, and regulatory functions in organisms.
- Further, the functional diversity of proteins is expanded through the interaction of proteins with small molecules, as well as other proteins.

After discovery of structure of *myoglobin*

Lack of regularities

> *Perhaps the most remarkable features of the molecule are its complexity and its lack of symmetry- The arrangement seems to be almost totally lacking in the kind of regularities which one instinctively anticipates, and it is more complicated than has been predicated by any theory of protein structure.*

Discovery of myoglobin (1958)
– Kendrew et al.

Emerging regularities in protein structures

Despite these initial frustrations, subsequent studies of the myoglobin structure based on higher-quality data revealed that the protein did have some regularities; these regularities were also observed in other protein structures.

Decades of research have now yielded a coherent set of principles about the nature of protein structure and the way in which this structure is utilized to effect function-

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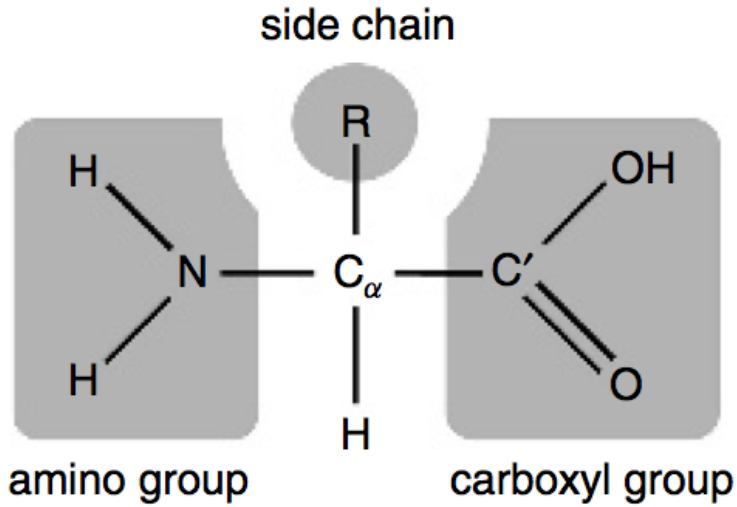

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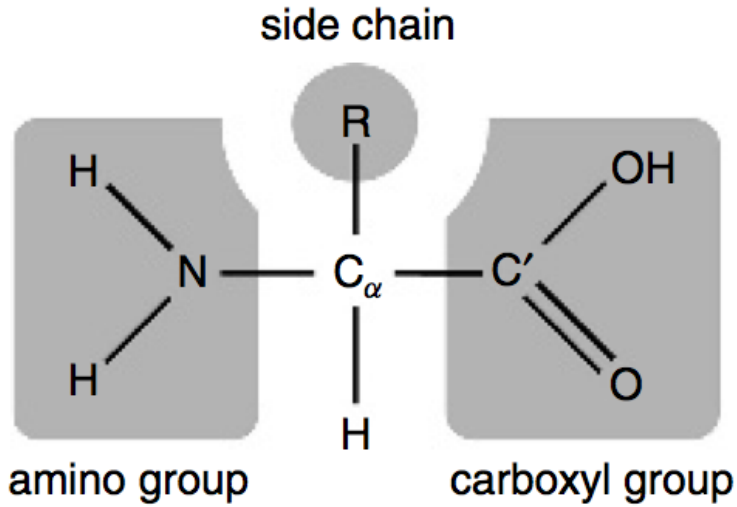

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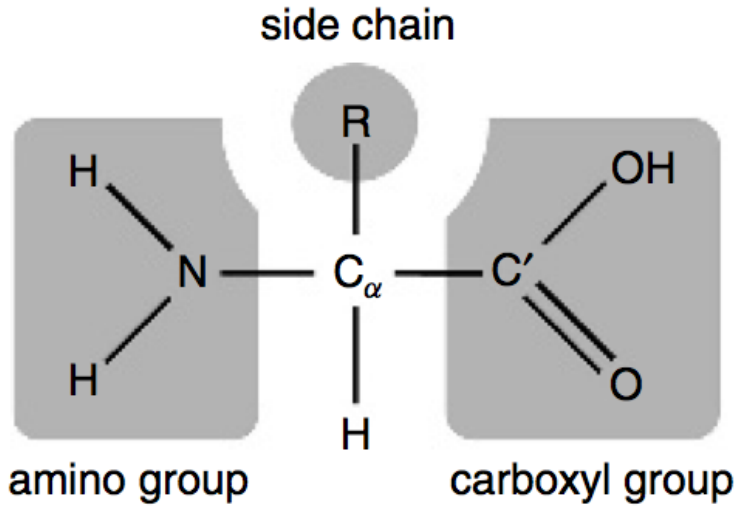

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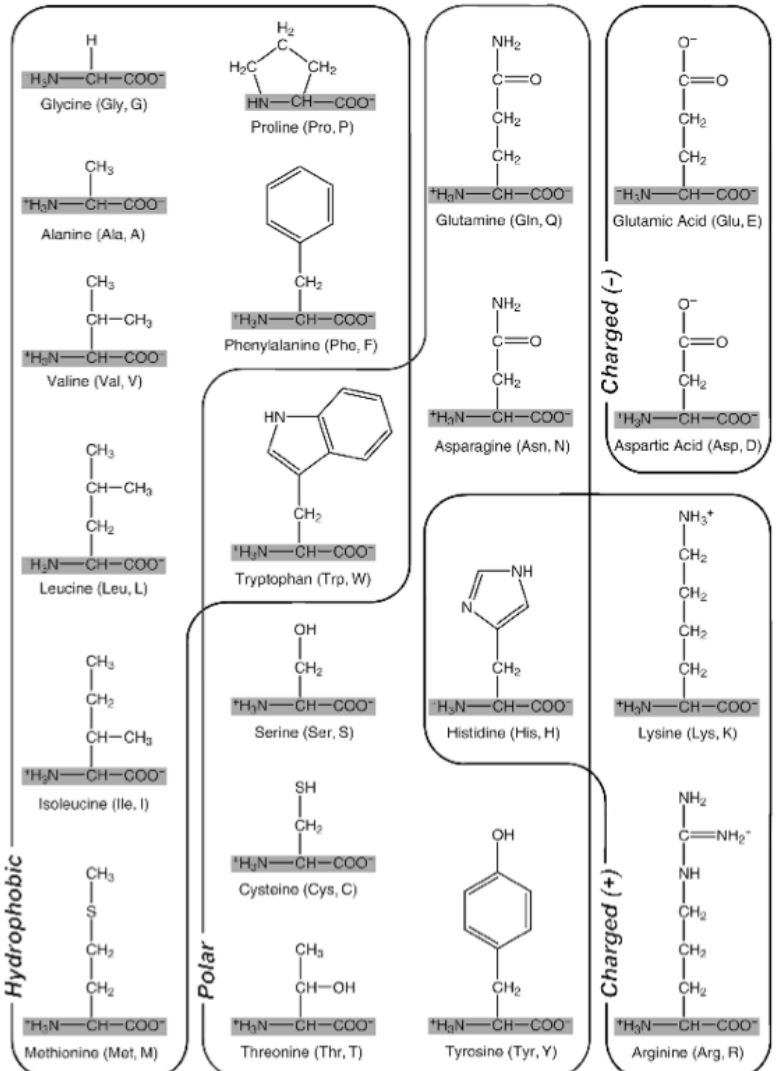

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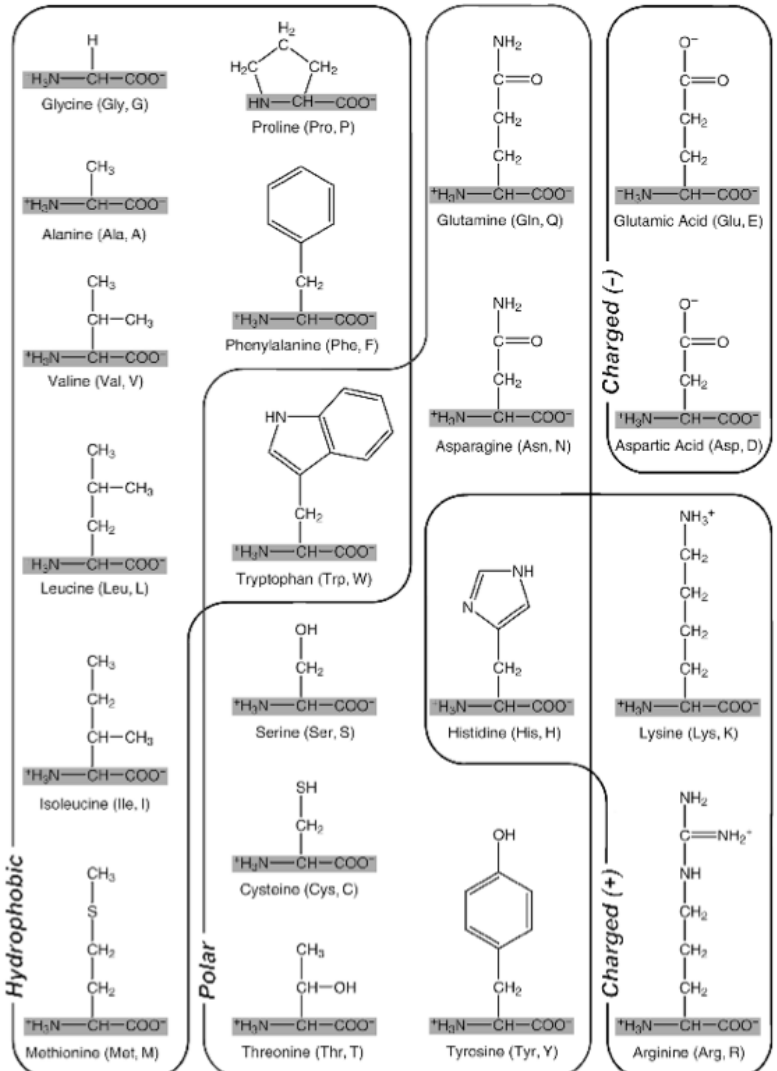

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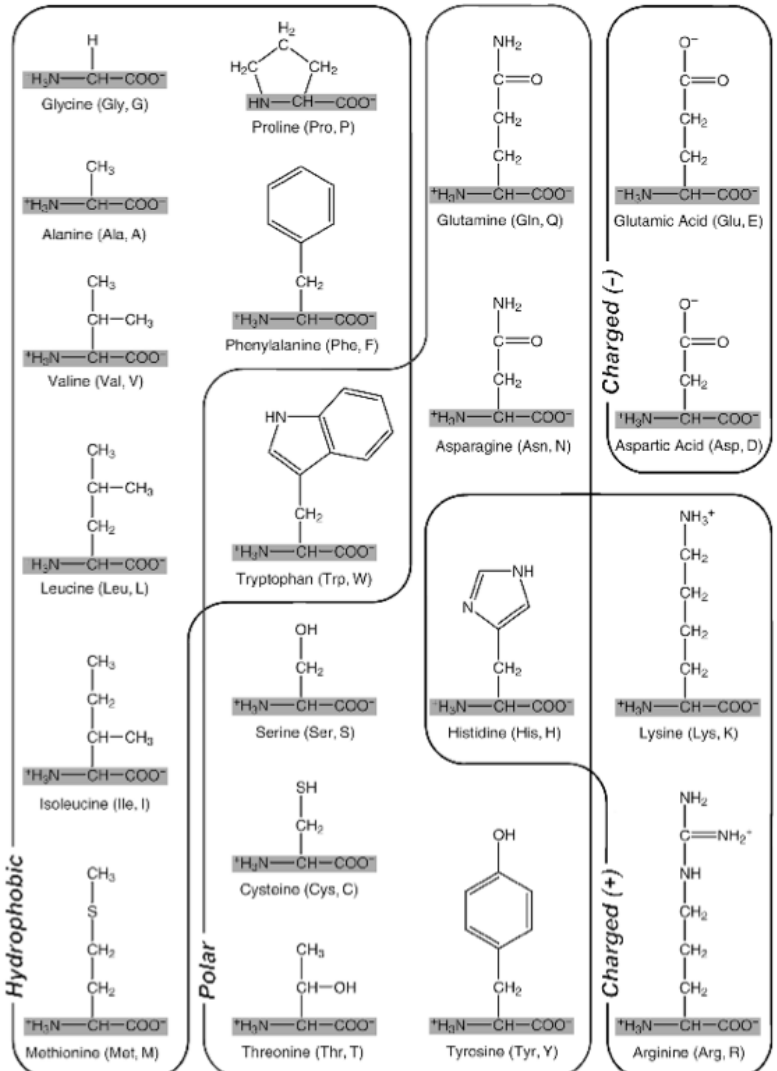

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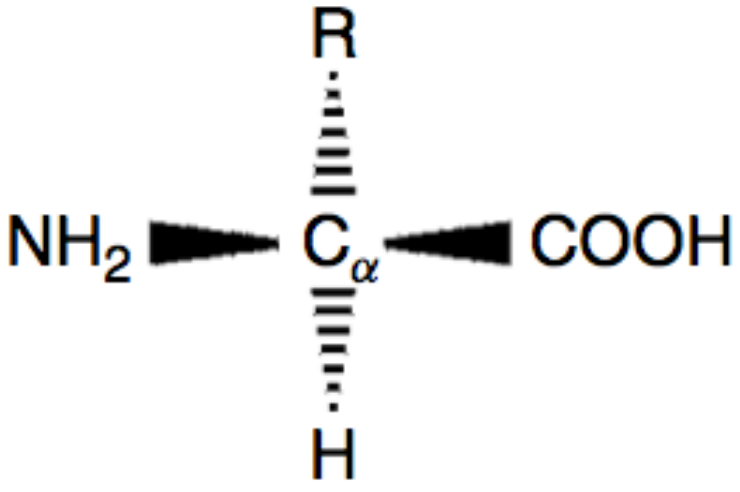
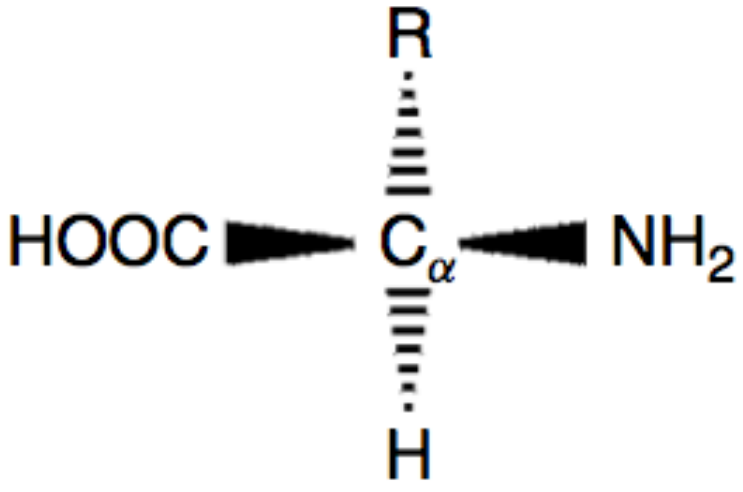
- The atoms involved in the peptide bond are referred to as the peptide backbone

Stereoisomers of a prototypical amino acid (1/2)



L-amino acid



D-amino acid

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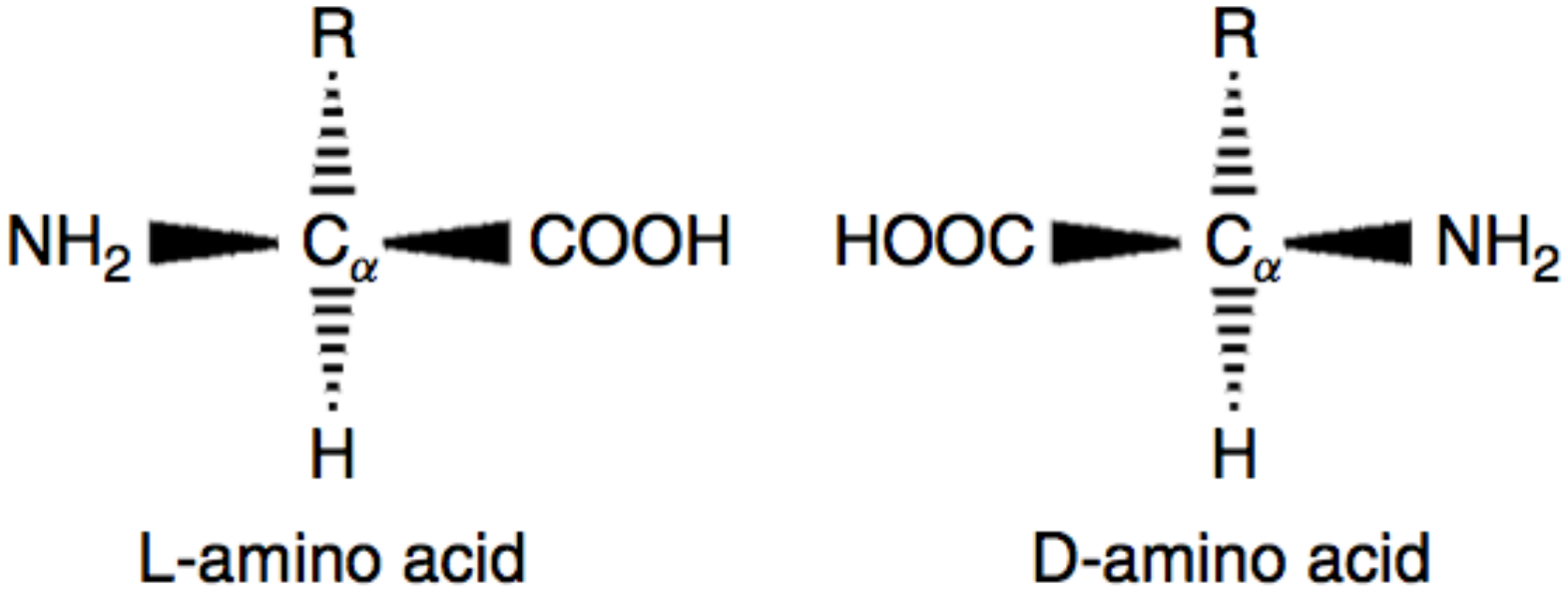

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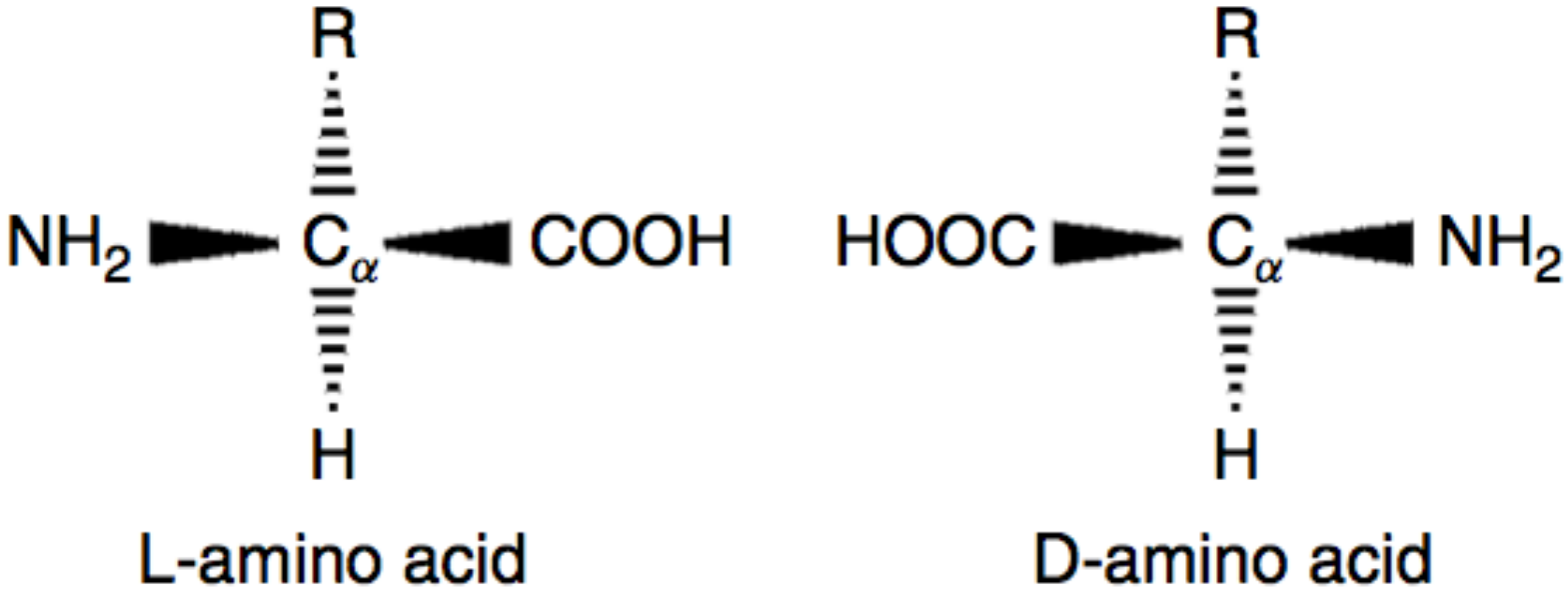
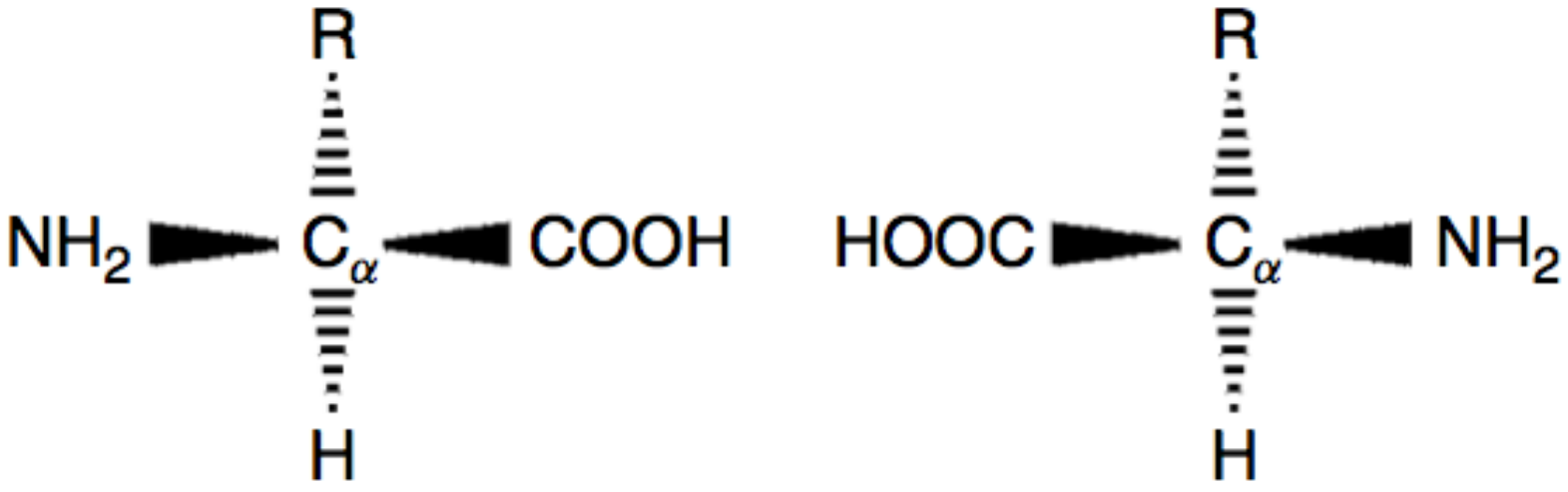


- These structures are mirror images of each other
- The L-form is the only type incorporated into proteins via the genetic machinery.

Stereoisomers of a prototypical amino acid (2/2)



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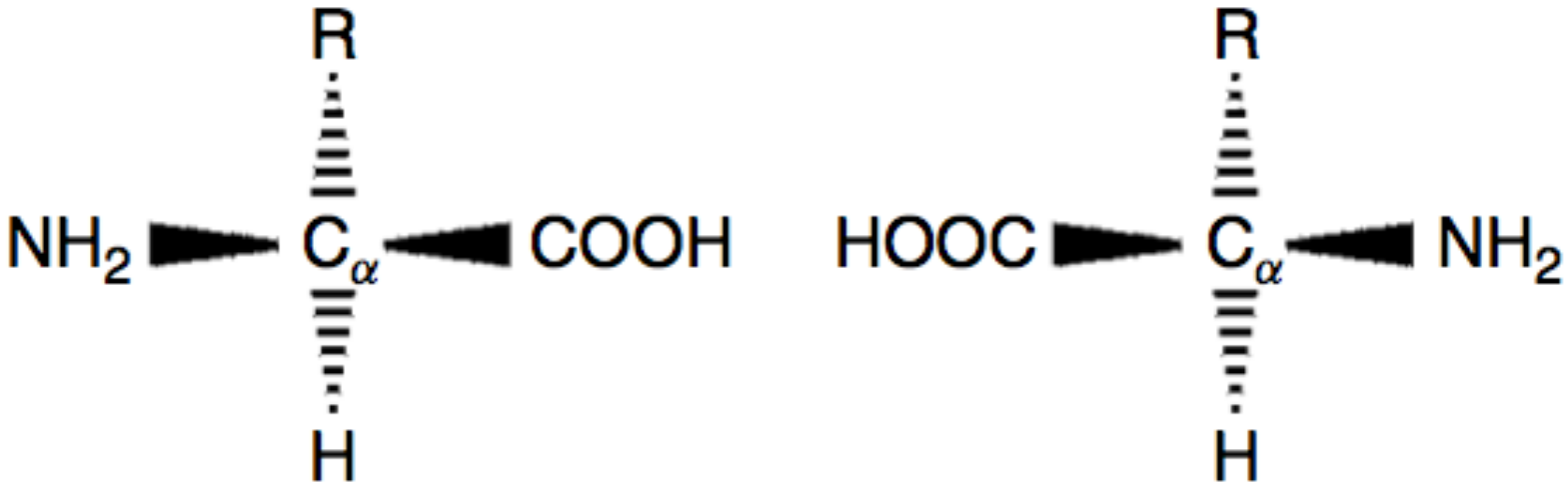

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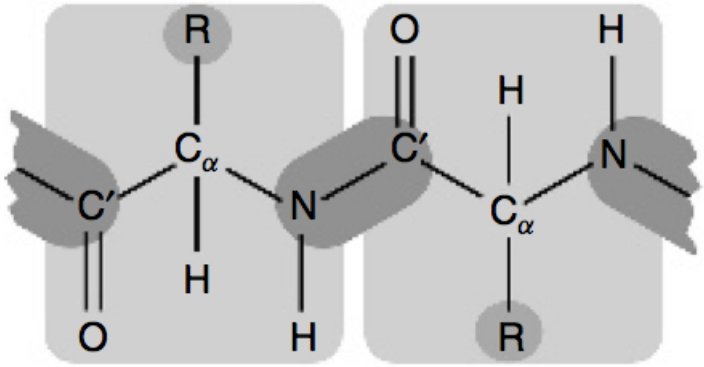

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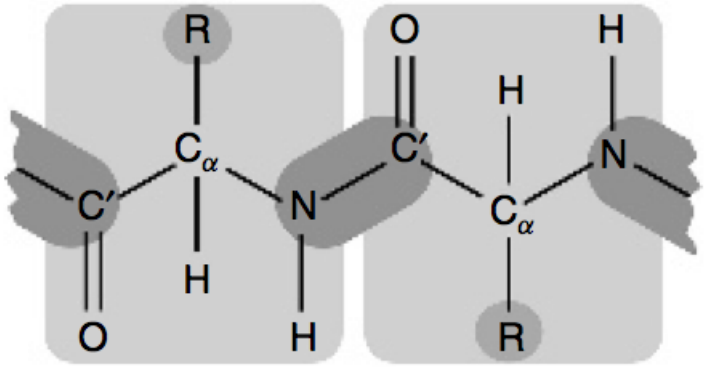

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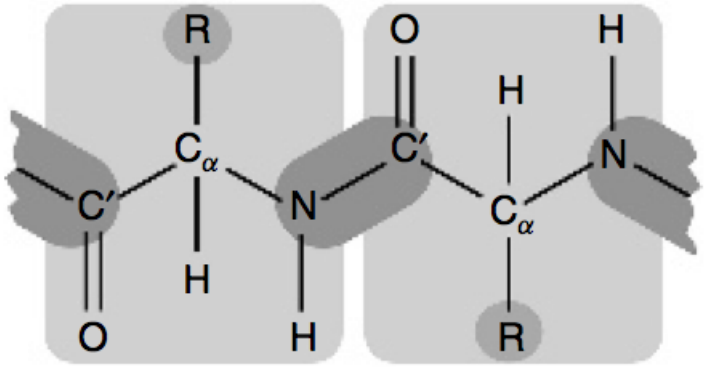

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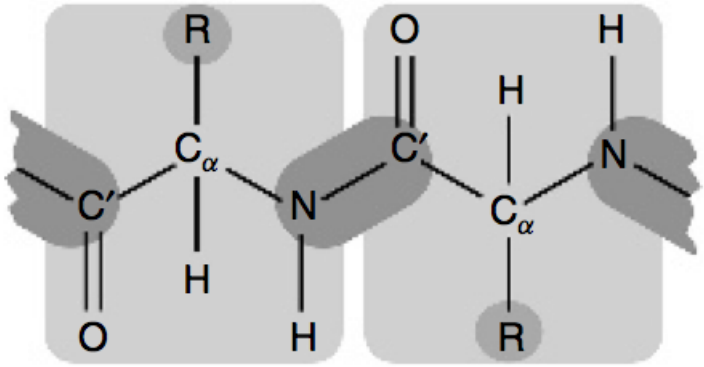

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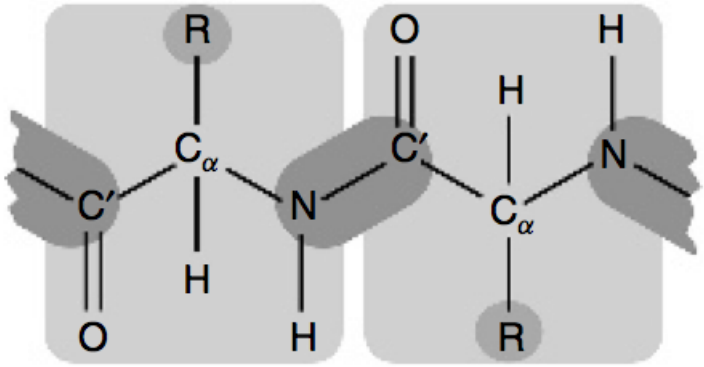

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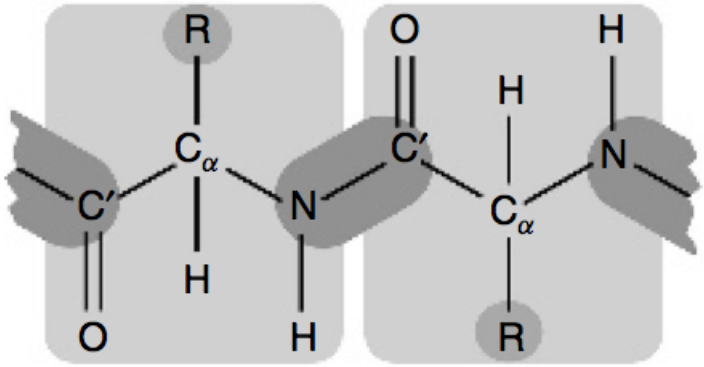

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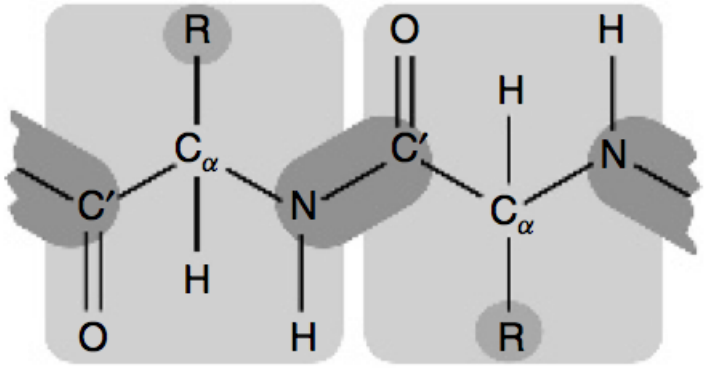

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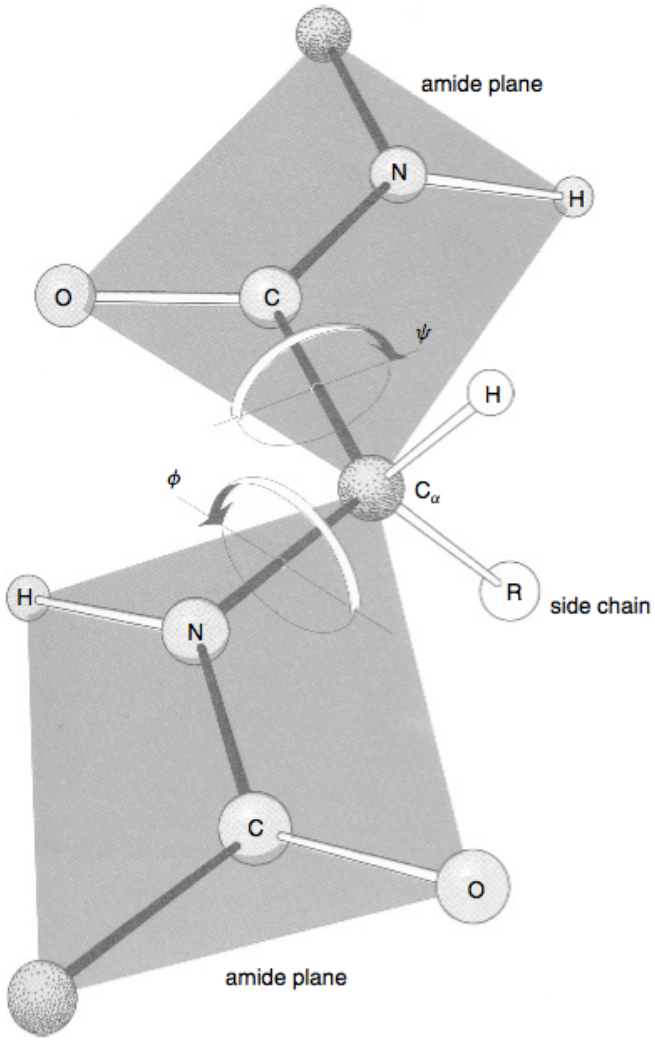
- Therefore, the polypeptide chain has rotational freedom only about the bonds formed by the α-carbons-

Rotation of the peptide backbone about the Cα atom.



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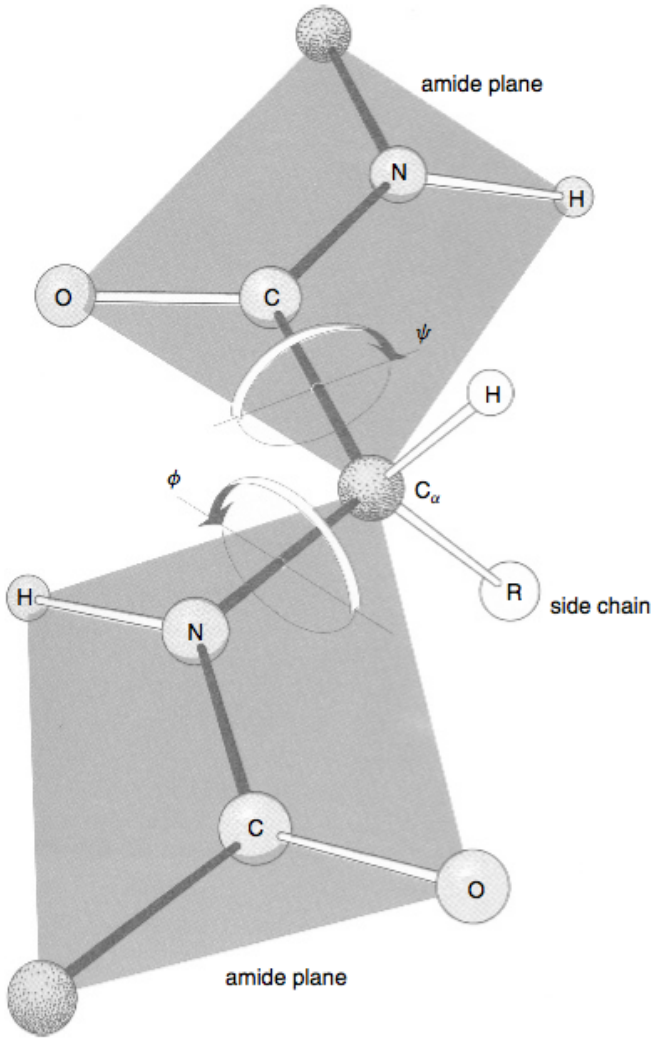

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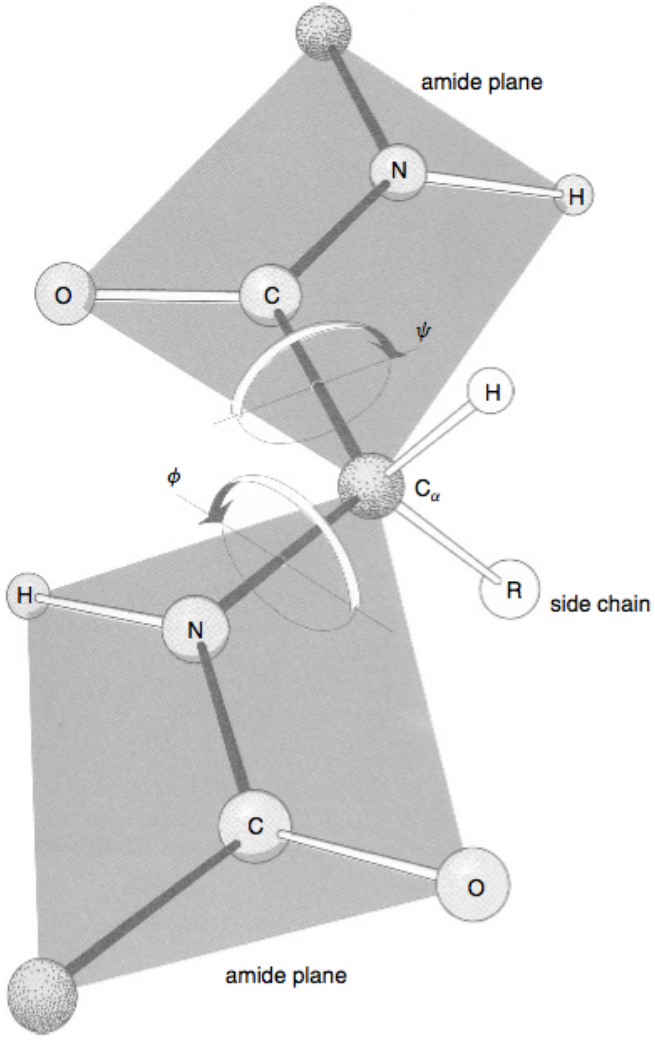

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- Arrows about the two angles show the positive rotation.

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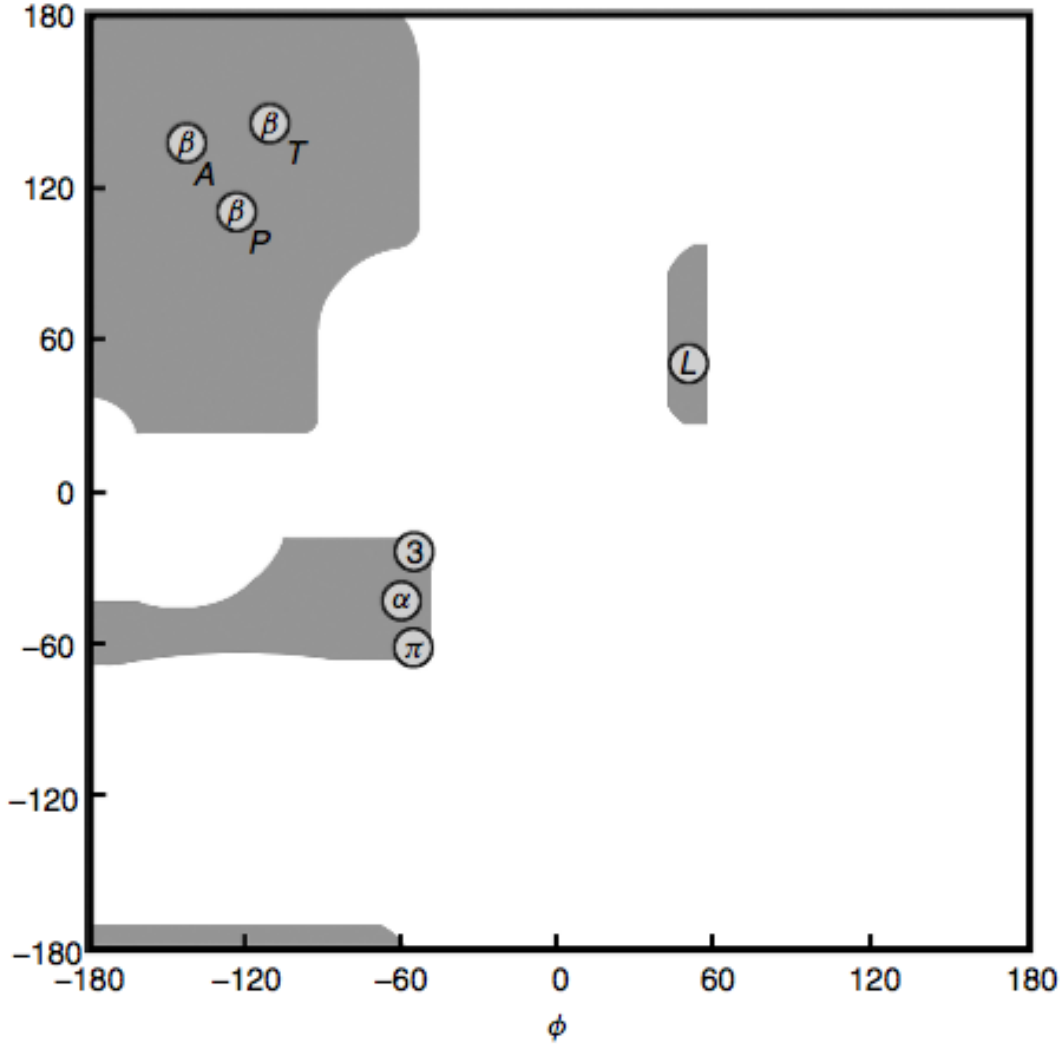
Ramachandran plot(ϕ vs ψ angles)



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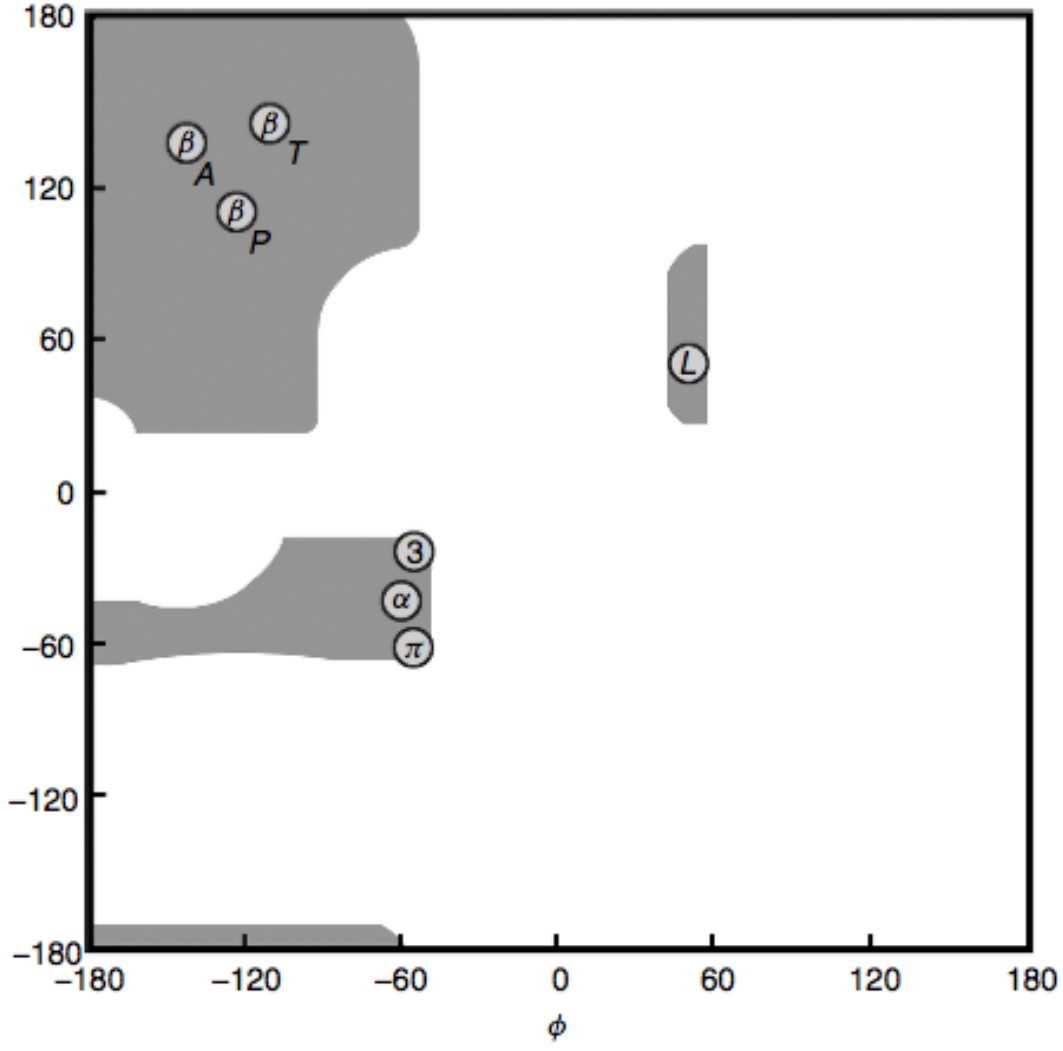

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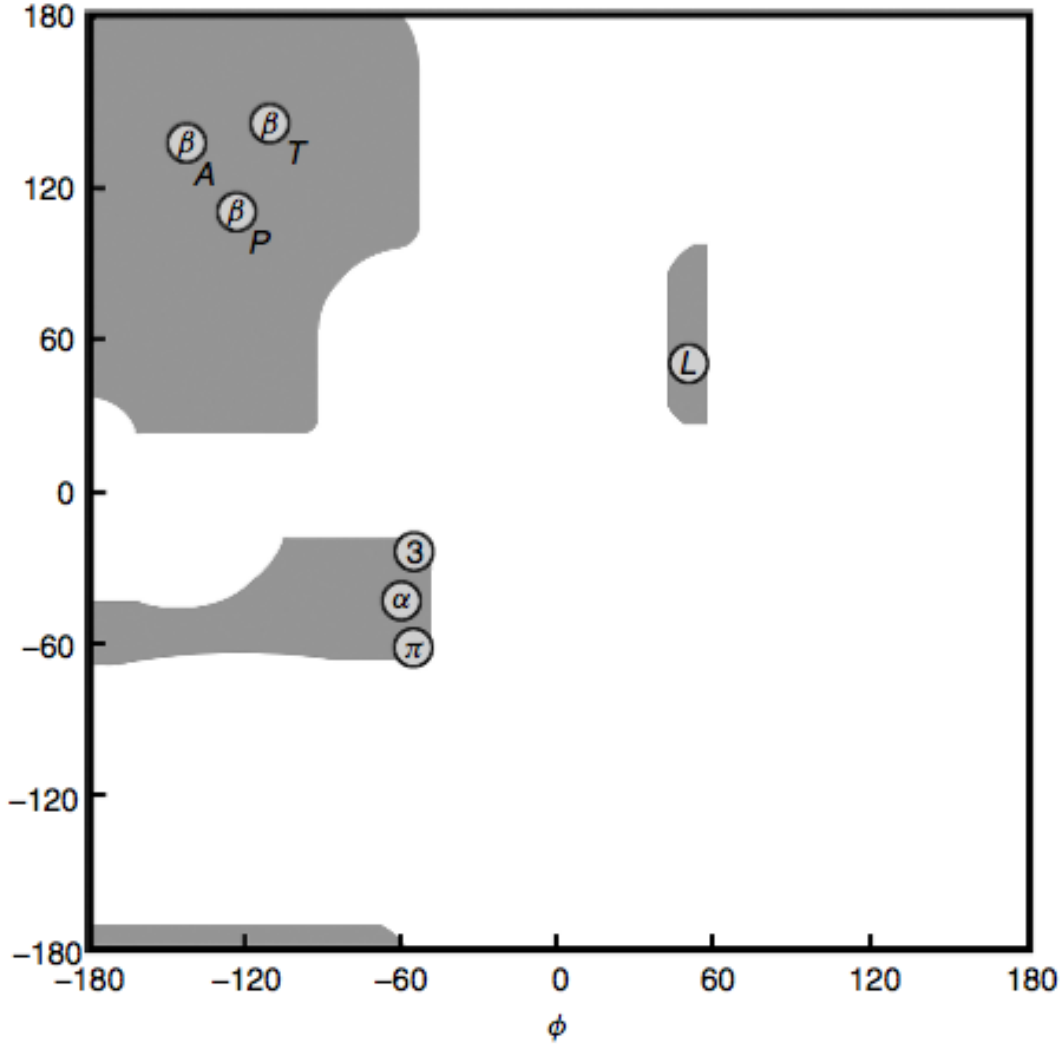

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- Circles denote the paired angle values of the secondary structures

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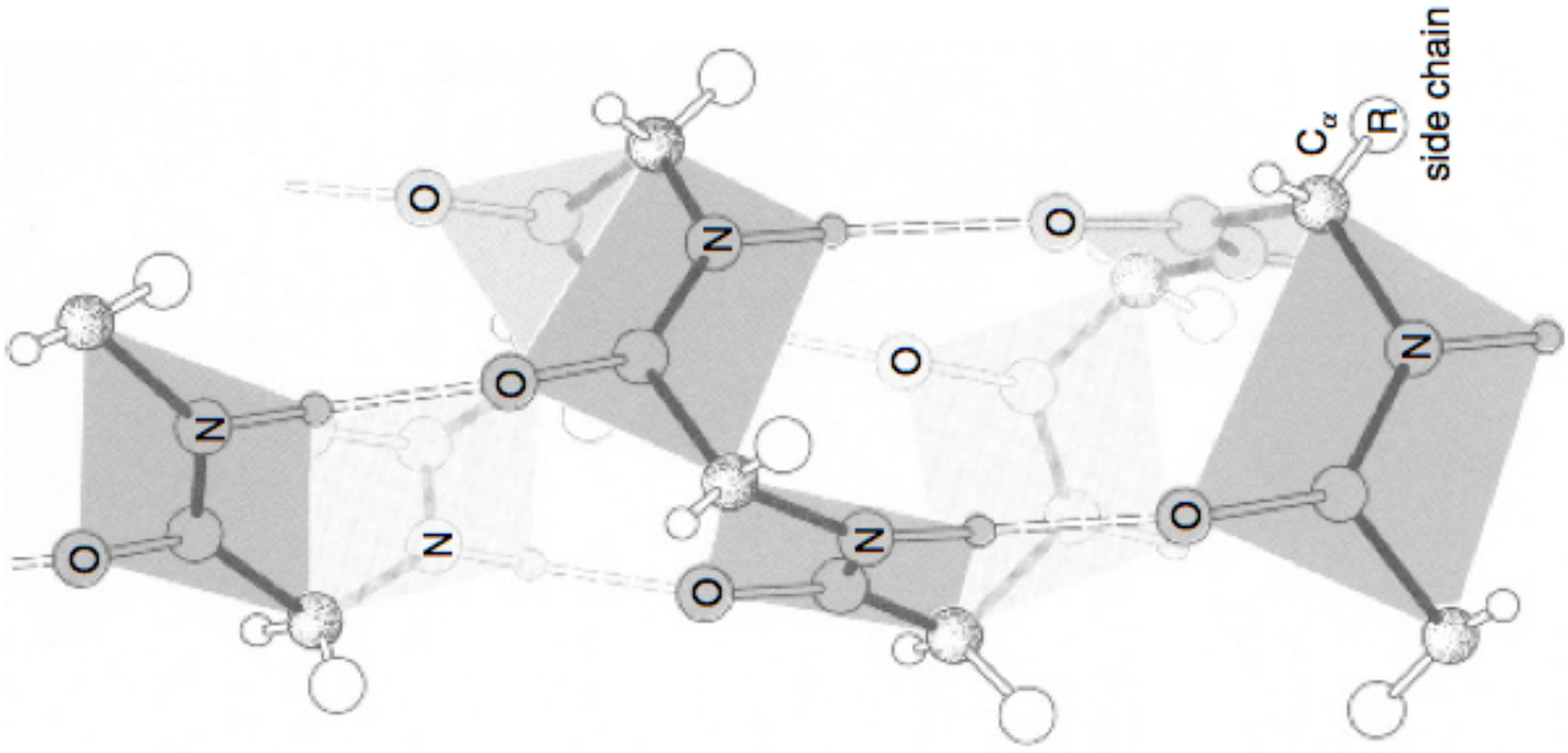
- Among the right-handed helices, the α helix is by far the most prevalent.

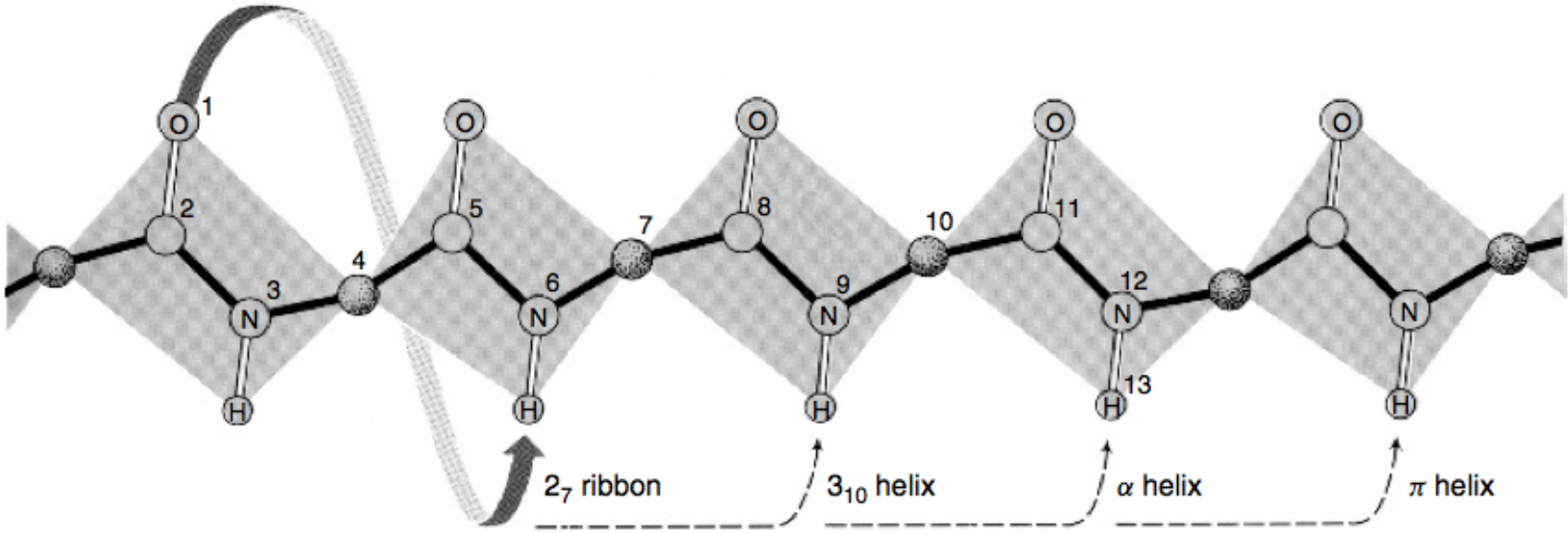
Helix stabilization



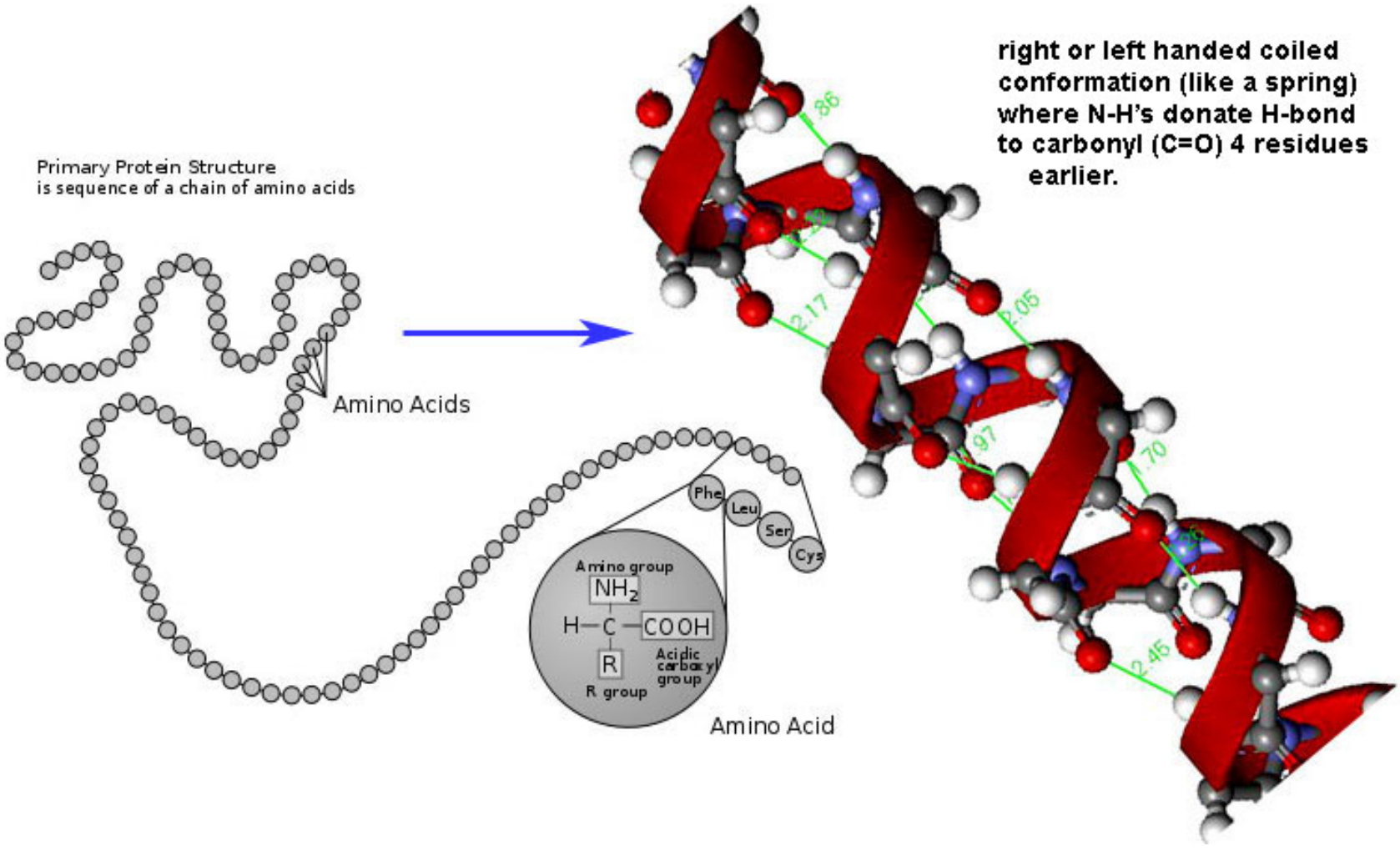
The α-helix is stabilized by internal hydrogen bonds formed between the carbonyl oxygen of each residue and the amide proton of the residue 4 residues ahead in the helix, shown here as dashed lines.

Hydrogen bonds

The hydrogen bonding patterns of different helical secondary structures-



Hydrogen bonds of α-helix



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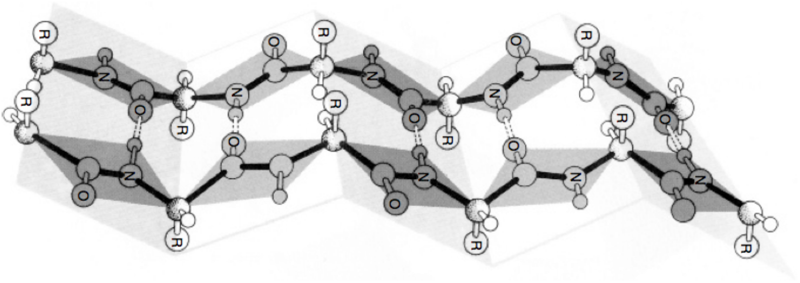
- β strands represent an extended conformation of the polypeptide chain, where the and angles are rotated (approximately) 180° with respect to each other
- This arrangement produces a sheet that is pleated, with the residue side chains alternating positions on opposite sides of the sheet.

β sheet configurations

Figure: Diagram of an antiparallel β sheet using a ball-and-stick model-



Two configurations of β sheet are possible: parallel and antiparallel.

Irregular structure regions

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ACTIVE SITE

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- Loop regions are usually present at the surface of the protein
- These regions are often simply transitions between regular structures, but they also can possess structural significance, and can be the location of the functional portion, or active site, of the protein.

ACTIVE SITE

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All-atom line representation

The N-terminal domain of eukaryotic protein kinase A (PKA; PDB-id 1APM) is shown using different representations.

Figure: All-atoms diagram of 1APM

This section of PKA contains a five-stranded antiparallel β sheet and three helices.

Topology diagram representation

It is difficult to determine the overall structural characteristics of a protein using the all-atom line representation

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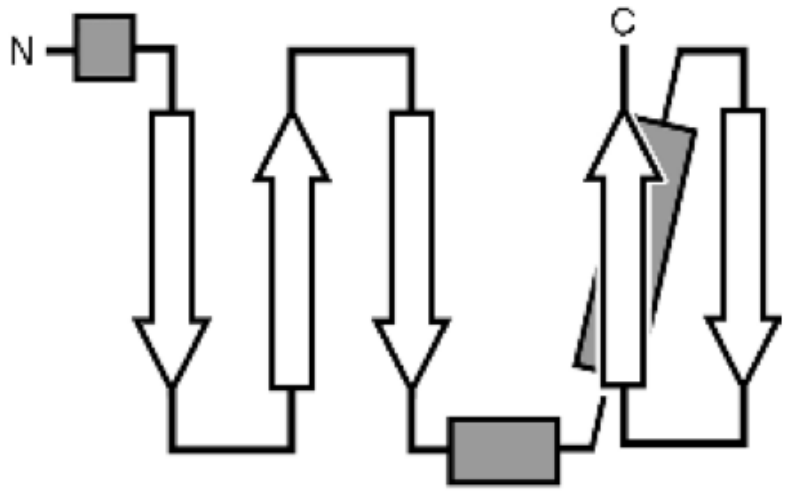
Figure: Topology diagram of 1APM



Topology diagram representation

It is difficult to determine the overall structural characteristics of a protein using the all-atom line representation

- Because proteins are often large and complex structures, views at the atomic level tend to obfuscate the important features.
- Simple topology diagrams are two-dimensional projections of the protein structure

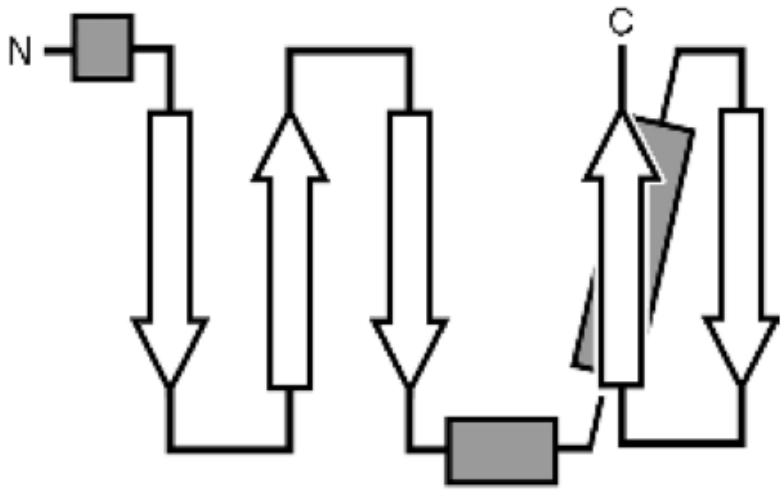


Figure: Topology diagram of 1APM

Cartoon diagram representation

These diagrams clearly illustrate the topology (connectivity) between the secondary structural elements and parallel or antiparallel nature of β sheets

Figure: cartoon diagram of 1APM

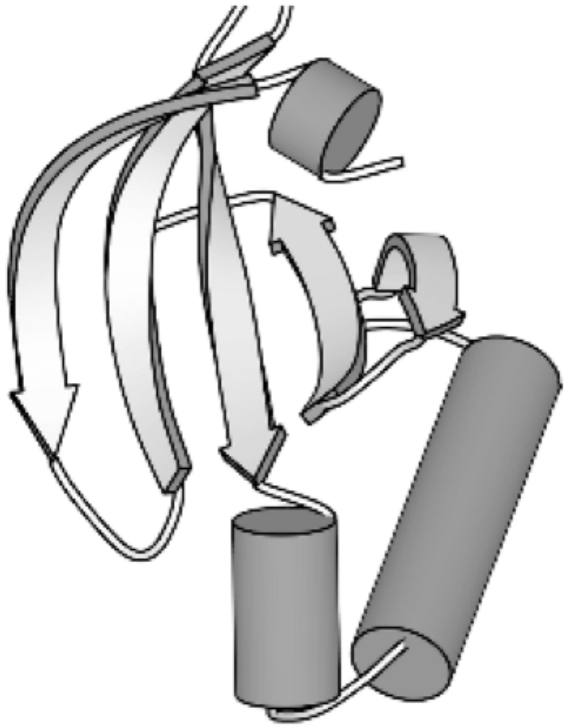
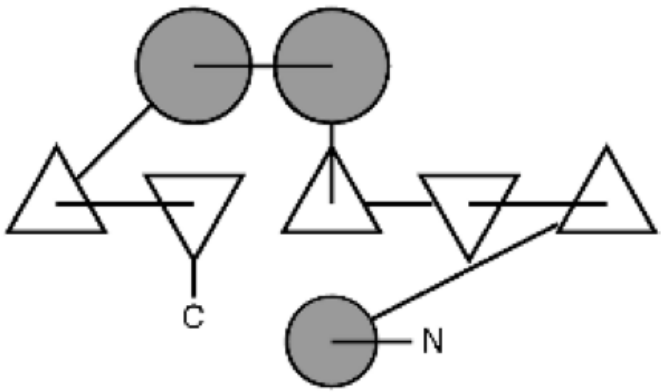


figure generated by MolScript package (Kraulis, 1991)

TOPS diagram representation

Figure: TOPS diagram of 1APM

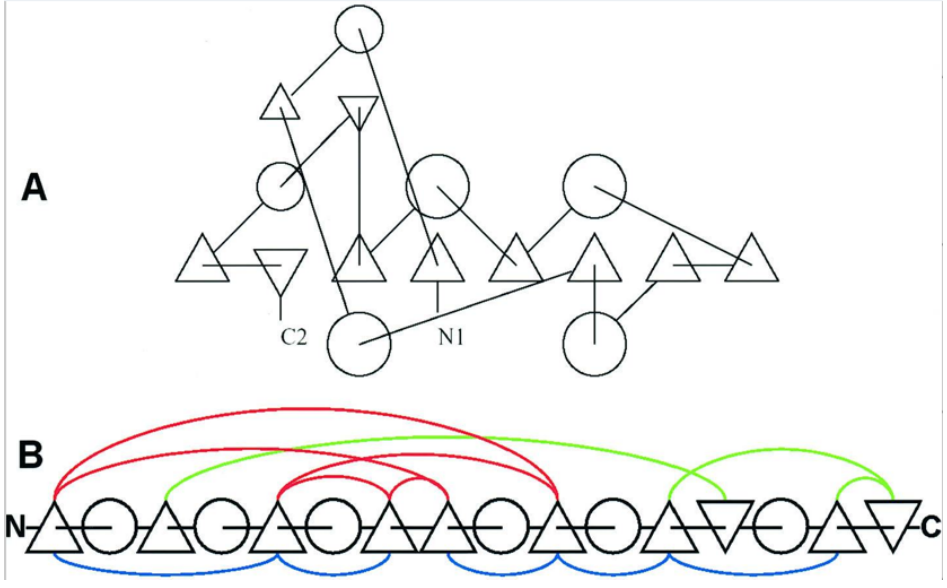


TOPS: an enhanced database of protein structural topology
Ioannis Michalopoulos et al., *Nucleic Acids Res.* 2004 January 1; 32(Database issue): D251–D254.

Abstract topological representation (1/2)

Consider a sequence of SSEs, i.e helices (circles) or strands (triangles), together with relationships like spatial adjacency within the fold and approximate orientation, neglecting details like the lengths of SSEs and loops

Figure: Abstract topology diagram: 1ra9



Abstract topological representation (2/2)

(A) 2D TOPS cartoon for of 1ra9 (dihydrofolate reductase)

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- TOPS cartoons are pseudo-2D schematic abstractions, where the third dimension is implied, since SSEs are considered to have an approximate direction of 'up' or 'down' (connecting lines drawn to the centre of the symbol indicate connection to the top, and those drawn to the edge indicate connection to the base)

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(B) TOPS diagram of 1ra9

- Hydrogen bonds and supersecondary chiralities are shown explicitly (parallel in red, anti-parallel in green, right-handed chiralities in blue).

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- As helices and sheets are units of secondary structure, so the domain is the unit of tertiary structure

Side Chains and Tertiary Structure

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- In contrast, backbone interactions are primarily responsible for the generation of secondary structure (particularly in the case of helices and sheets)
- The 3D tertiary structure of a protein is commonly referred to as its fold

Domains and Motifs

Tertiary Protein Structure and folds

Within the protein fold, domains and motifs can be recognized

Domains

are compact sections of the protein that represent structurally (and usually functionally) independent regions-

Motifs

(also referred to as supersecondary structure) are small substructures that are not necessarily structurally independent: generally, they consist of only a few secondary structural elements-

Specific motifs

Specific motifs are seen repeatedly in many different protein structures; they are integral elements of protein folds

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- Several motifs can combine to form specific domains.

Protein classification

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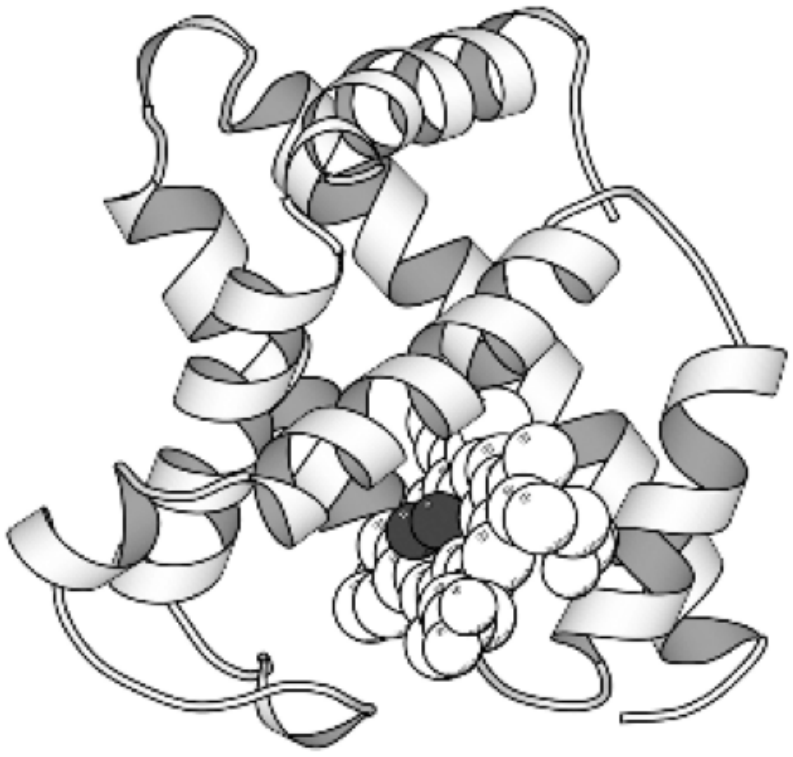
- fibrous (see Fibrous and Structural Proteins)

Globular protein

Globular proteins

Myoglobin

(PDB id 1A6M)

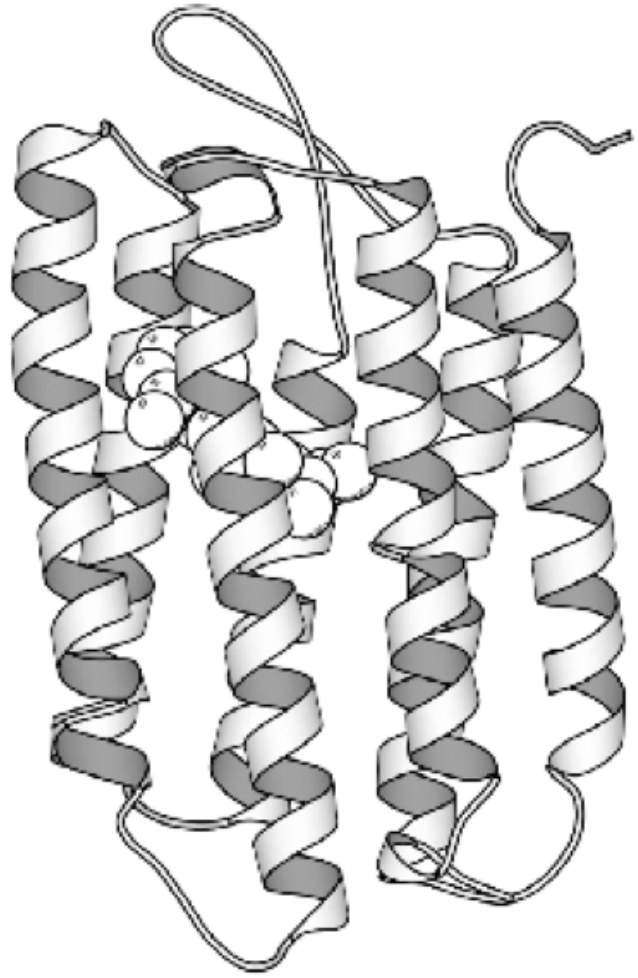


Membrane protein

Membrane proteins

Rhodopsin

(PDB id 1AT9)



Fibrous protein

Fibrous proteins

Collagen

(PDB id 1QSU)

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- This classification consisted of four groups: all α, all β, α/β, and $\alpha+\beta$

Predominant secondary structural element

all α proteins

as the name suggests, are based almost entirely on α helical structure

all β structures

are based almost entirely on β sheet

α/β structure

is based on a mixture of α helix and β sheet, often organized as parallel β strands connected by α helices

$\alpha + \beta$ structures

consist of discrete α helix and β sheet motifs that are not interwoven (as they are in α/β structure).

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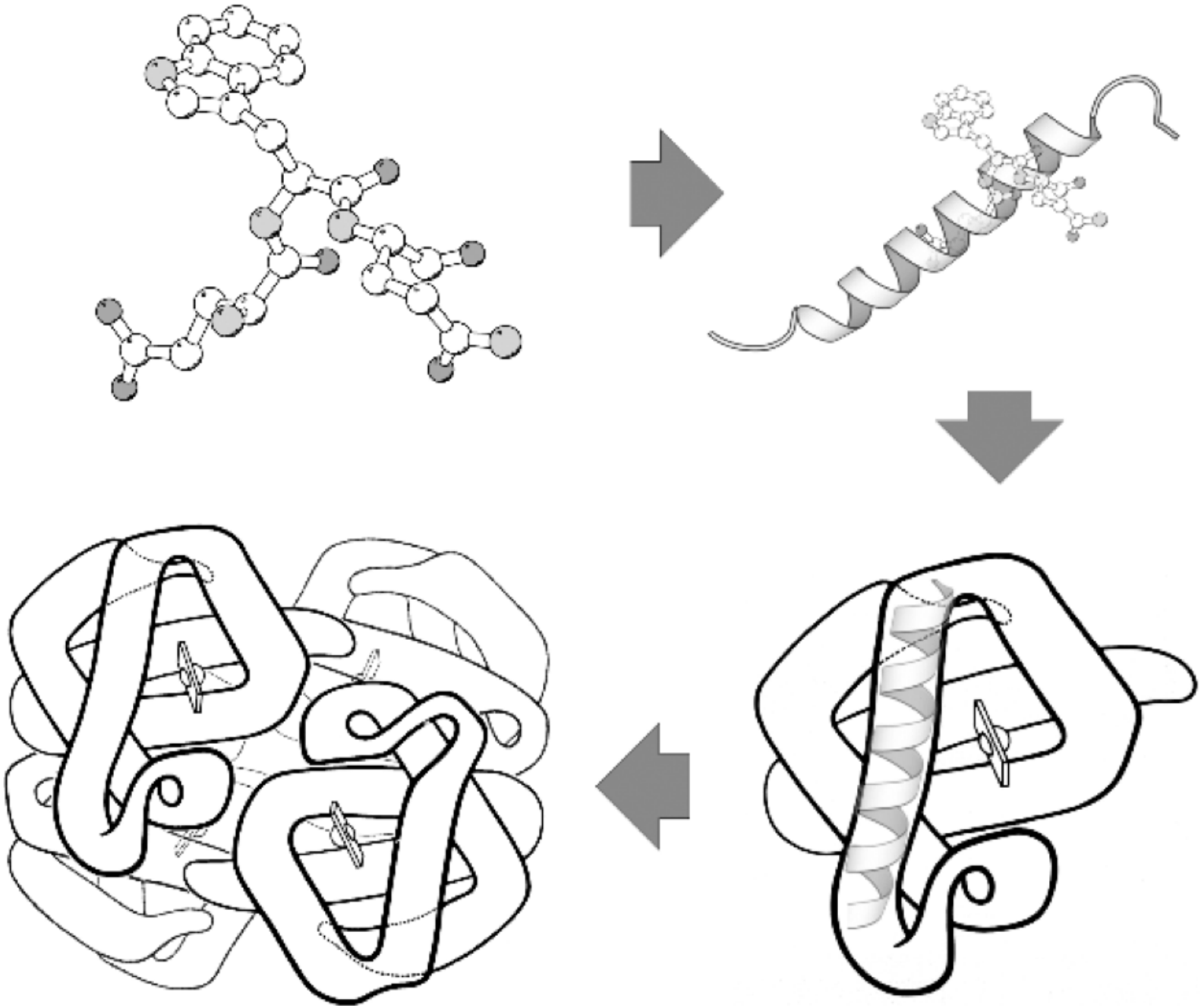
- *However, many proteins do not function as a single chain, or monomer*
- *Rather, they exist as a *noncovalent association of two or more independently folded polypeptides**
- *These proteins are referred to as multisubunit, or multimeric proteins and are said to have a quaternary structure*

The four-tiered hierarchy of protein structure (hemoglobin)



Functional Relevance of Quaternary Structure

Interestingly, most proteins are folded such that aggregation with other polypeptides is avoided (Richardson, 1992);

The formation of multisubunit proteins is therefore a very specific interaction.

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- The individual subunits are usually not covalently connected, but might be connected by a disulfide bond

Molecular chaperones that assist protein folding

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see Chaperonin Structure – The Large Multi-Subunit Protein Complex

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- These molecular machines use chemical energy, in the form of adenosine triphosphate (ATP), to promote protein folding in all cells.

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Cooperativity

Cooperativity
The association of subunits that bind the same substrate is often able to enhance binding capabilities of the multimer beyond what is possible with individual subunits. This cooperativity is realized through the ability of the subunits to influence each other based on their close proximity.

Hemoglobin

(PDB id 1A3N)

Co-localization of Function

Co-localization of Function

Different subunits can associate in order to confer multiple functions on a single protein. Often these functions involve distinct steps in the processing of a single substrate. Thus, the co-localization of function provided by a multisubunit complex can further enhance the abilities of a protein.

Tryptophan Synthase

(PDB id 1QOP)

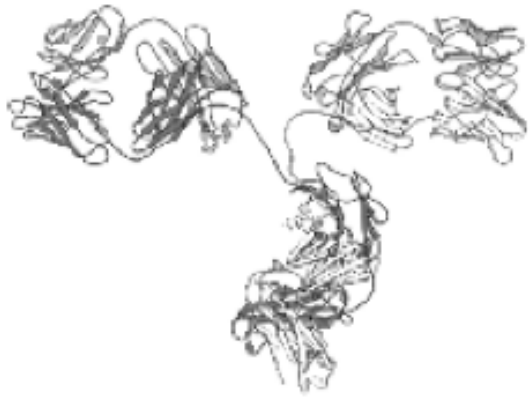
Combinations of Subunits

Combinations of Subunits

Combinatorial shifts in quaternary structure are able to bestow impressive versatility to protein function and regulation. Protein function can be altered by subunit swapping, and protein regulation can be achieved via interactions with different subunits.

Immunoglobulin

(PDB id 12E8)



Structural Assembly

Structural Assembly

Very large structural proteins are made possible by the association of a large number of small subunits. This component-based assembly simplifies the construction of such structures and allows the information required to code these proteins to be more concise.

Actin

(PDB id 1ALM)