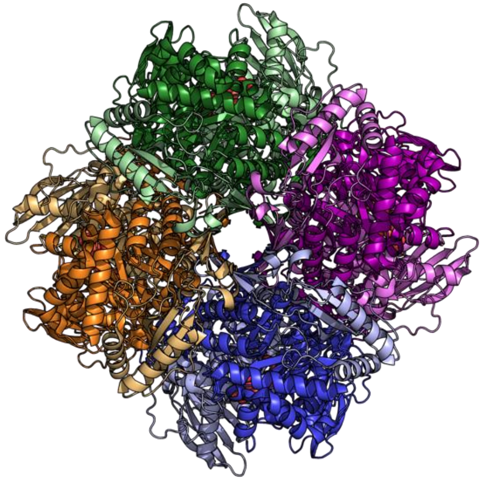
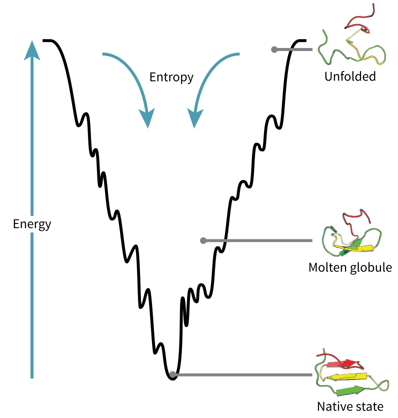
Protein Structure & Thermodynamics

Workshop

10th February 2025





Dr. Amanda Souza Câmara, *IPK*
Dr. Victor H. Rabesquine Nogueira, *IPK*
Prof. Dr. Antônio José da Costa Filho, *University of São Paulo*

In Silico Genebank Proteomics

POST DOC BOARD IPK

Programme

Monday 10th 13:00 – 17:00 – Welcome to the workshop, physics in biology, introduction to protein structure with atomic models

Tuesday 11th 08:30 – 12:00 – Introduction to protein thermodynamics

Wednesday 12th 08:30 – 12:00 – Continuing protein thermodynamics

13:00 – 14:00 - Vavilov Seminar by Prof. Dr. Antônio José da Costa Filho

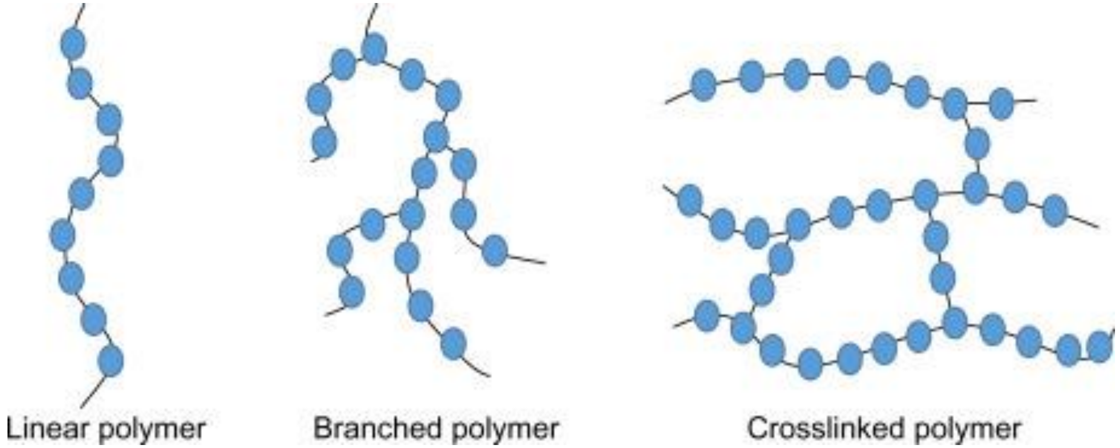
Thursday 13th 08:30 – 12:00 – *In silico* analyses of protein structure with PyMOL, AlphaFold3 prediction and docking

Friday 14th 08:30 – 12:00 – Molecular dynamics simulation

Introduction round

- Who are you?
- What is your background?
- Why are you interested in protein structure and thermodynamics?

A protein is a linear polymer



A protein is a linear polymer

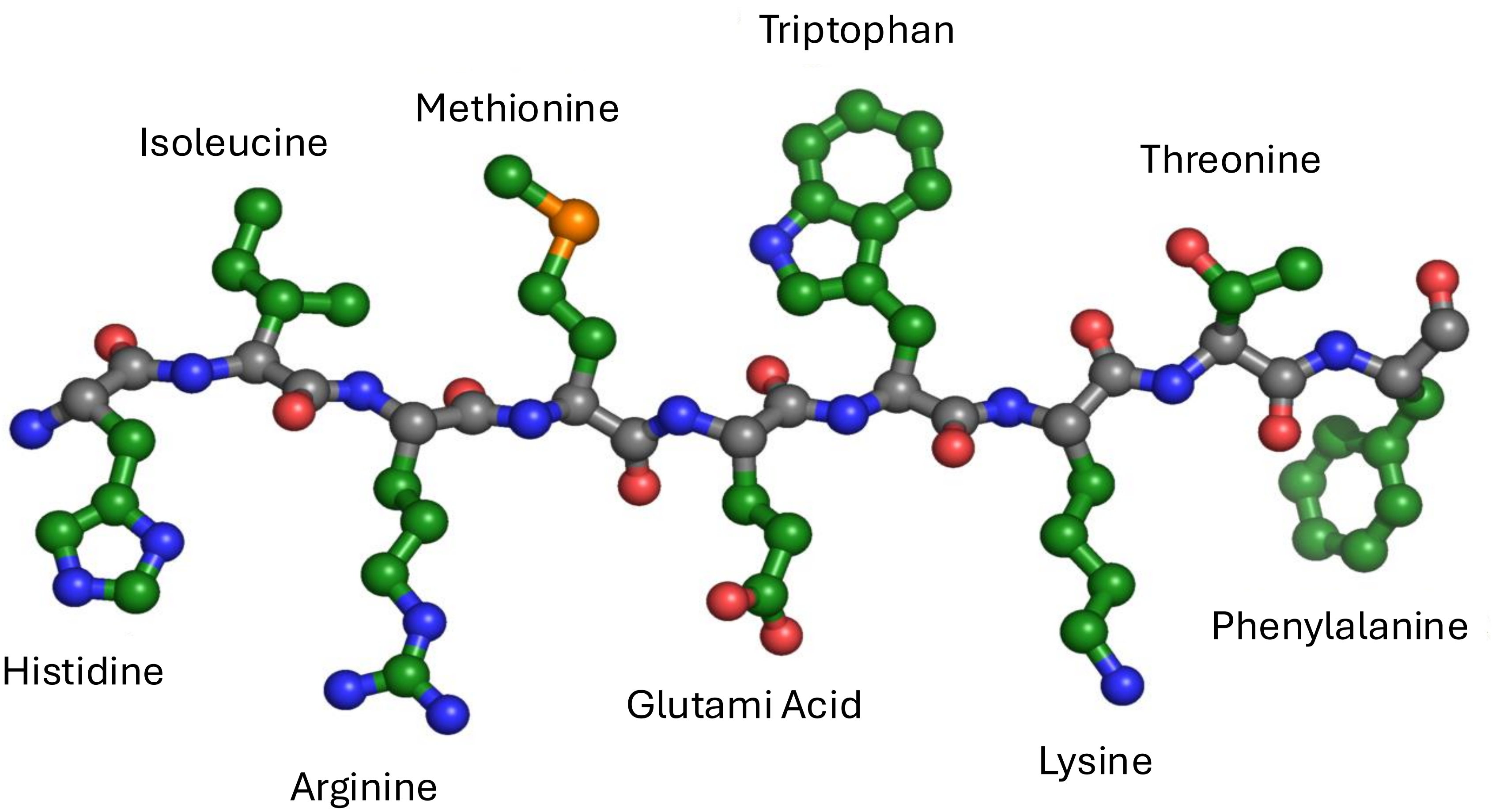
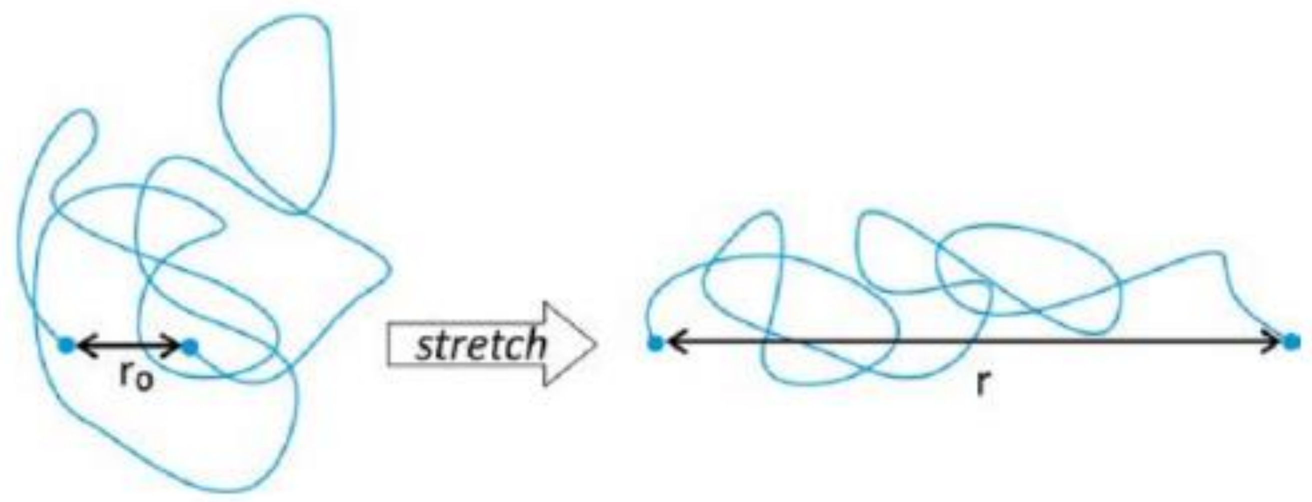


Figure by Richard Garratt

Conformations of a linear polymer

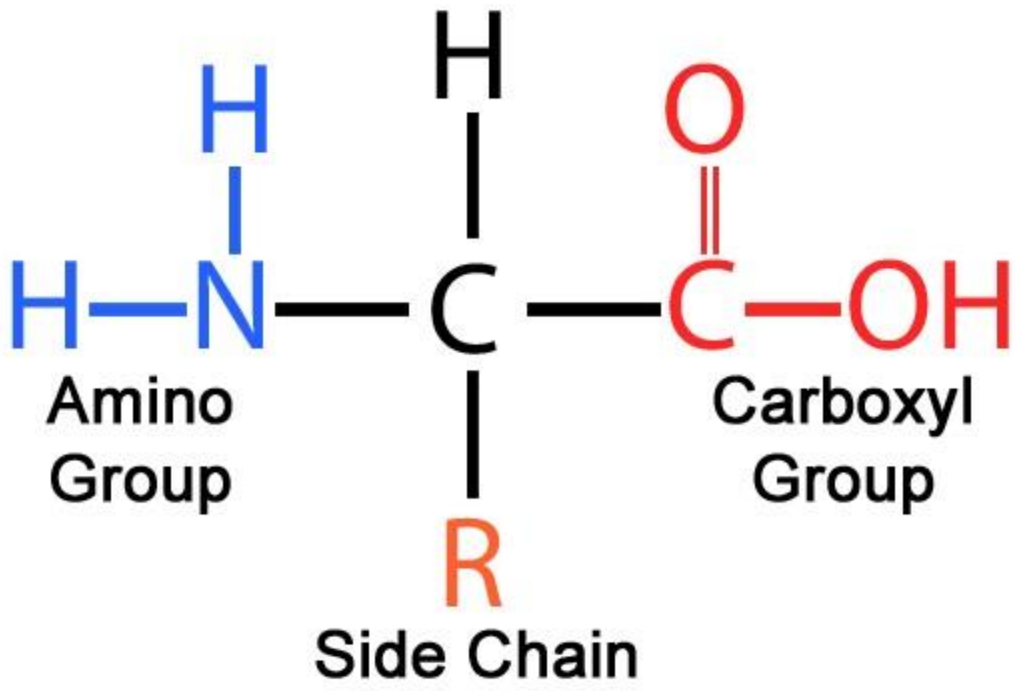


The completely stretched conformation is just one among countless possibilities.
But these conformations have restrictions!

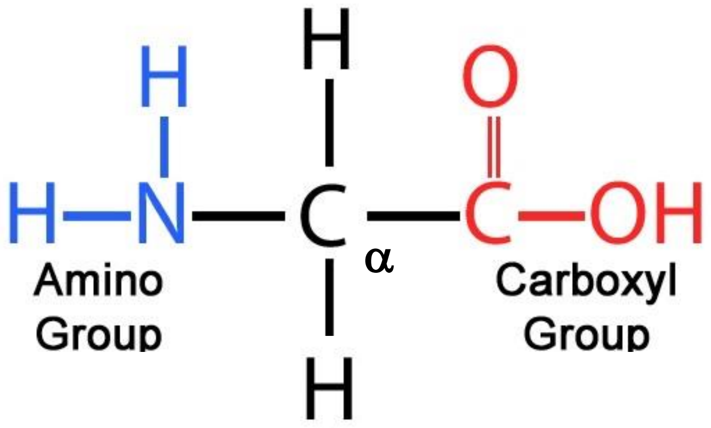
Our GitHub page

- https://github.com/InsilicoGenebankProteomics/Protein-Structure-and-Thermodynamics-Workshop-2025

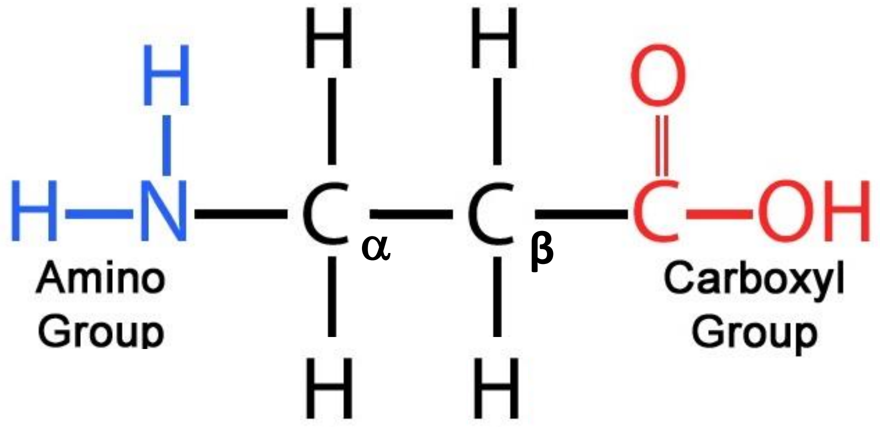
Building an amino acid



Building an α amino acid

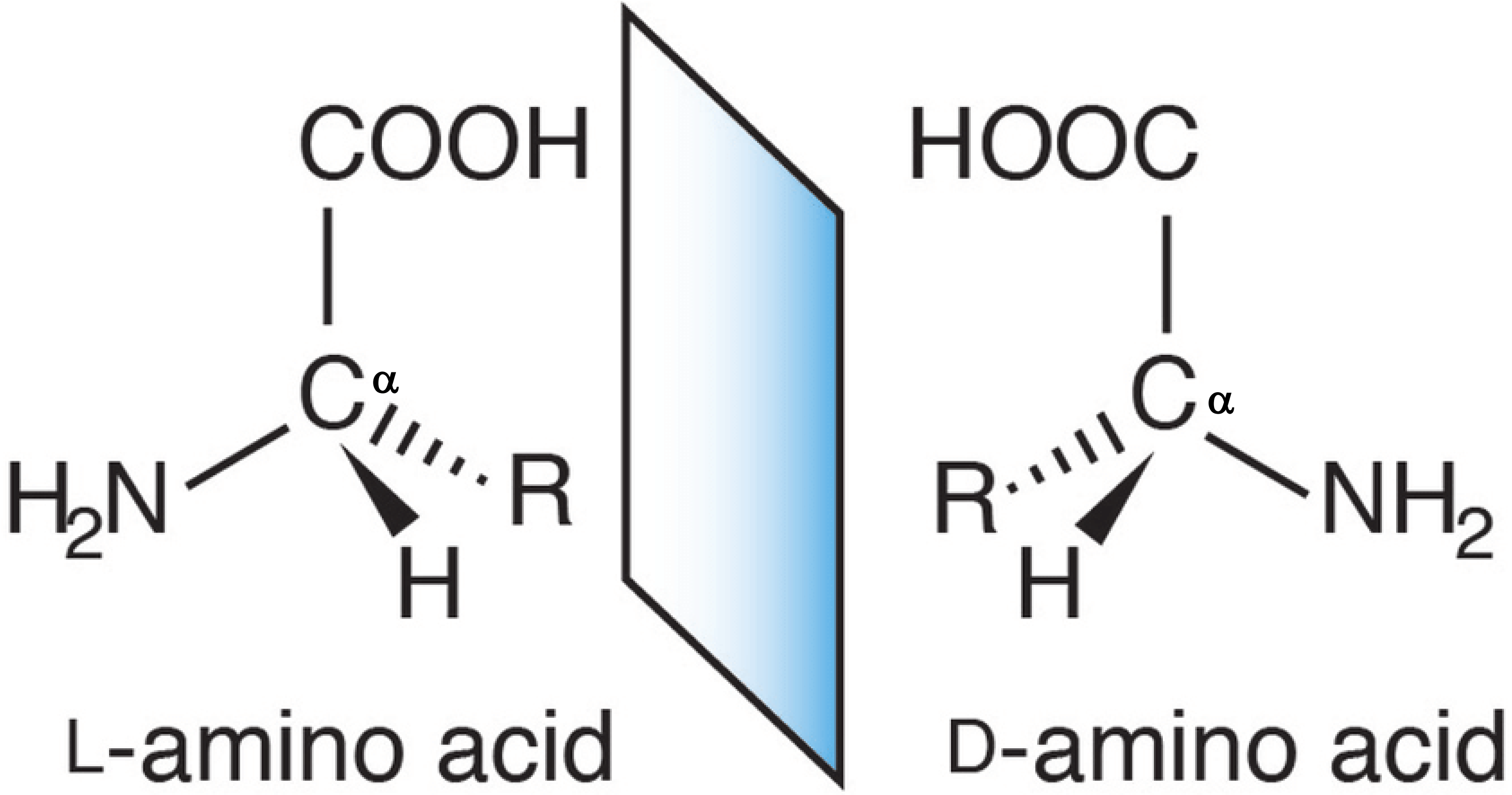


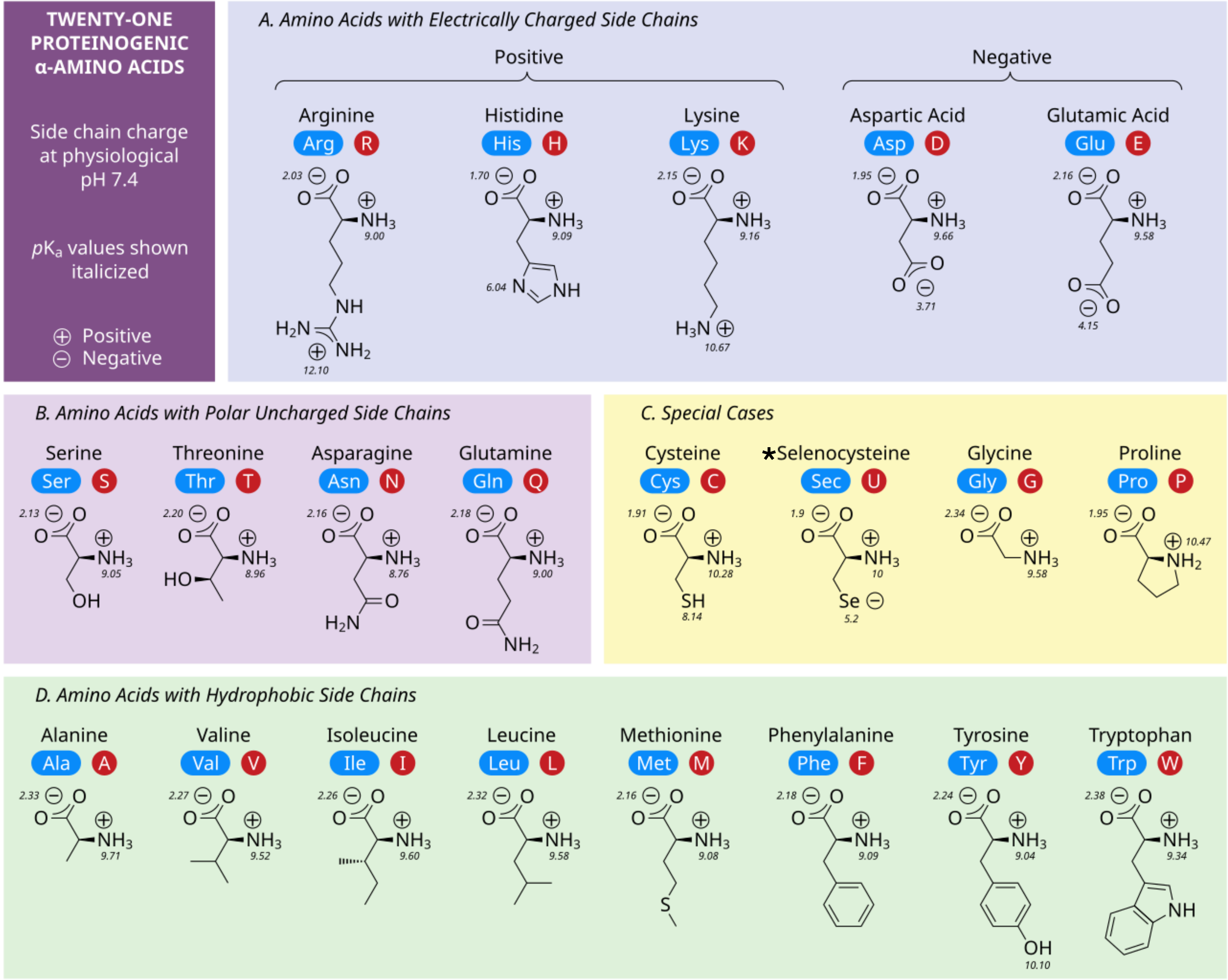
α amino acid



β amino acid

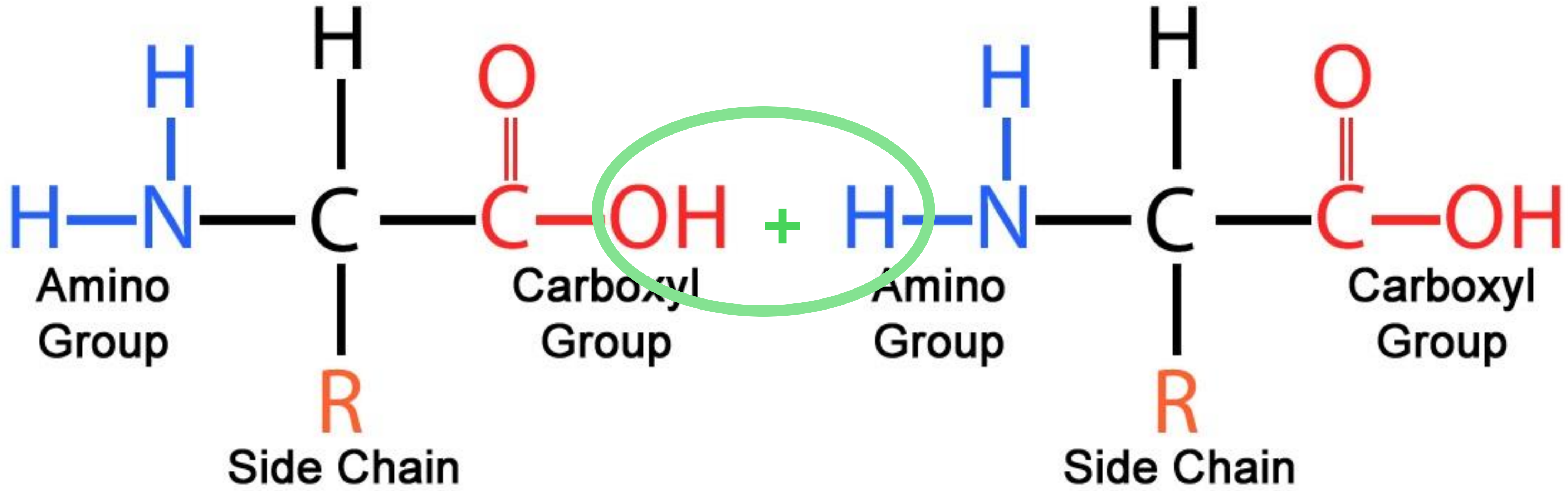
α carbons are chiral centers



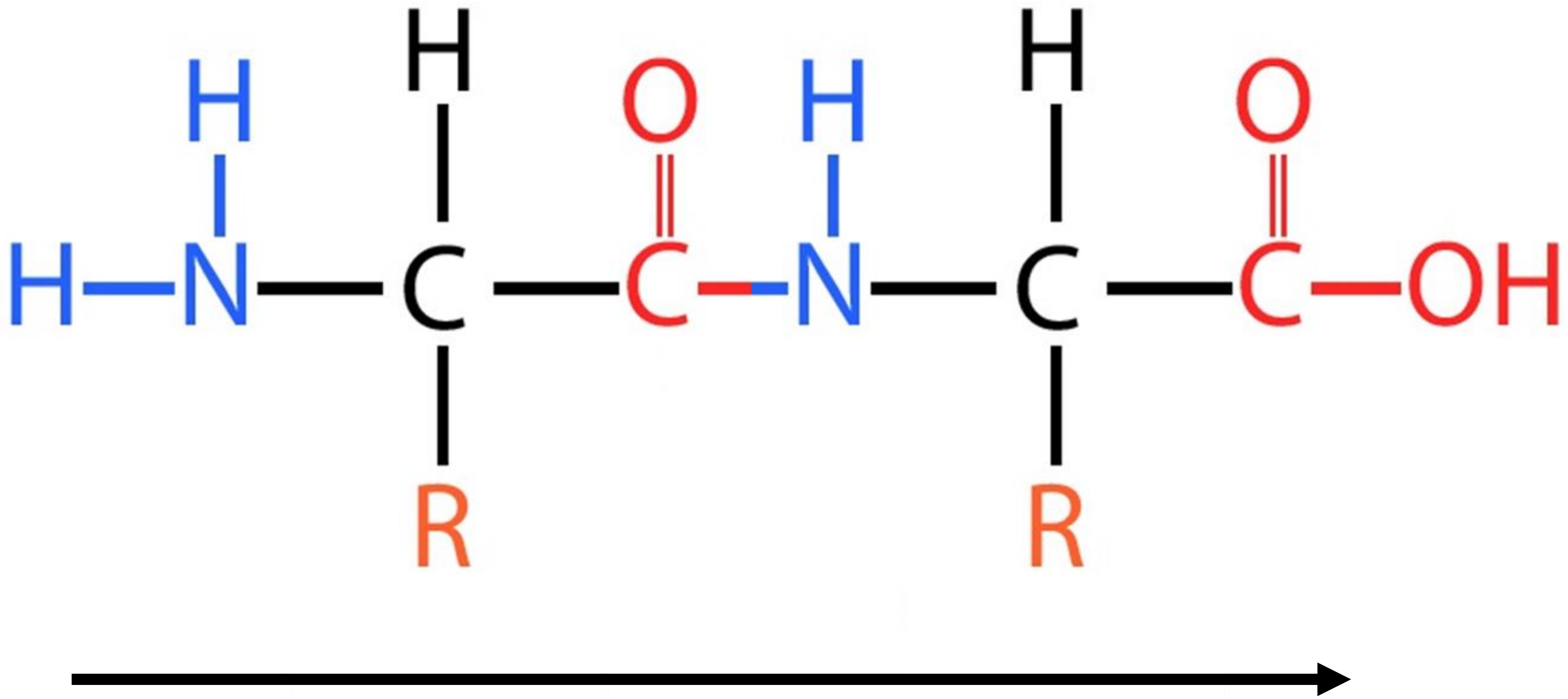


*Selenocysteine needs translational recoding.

The peptide bond

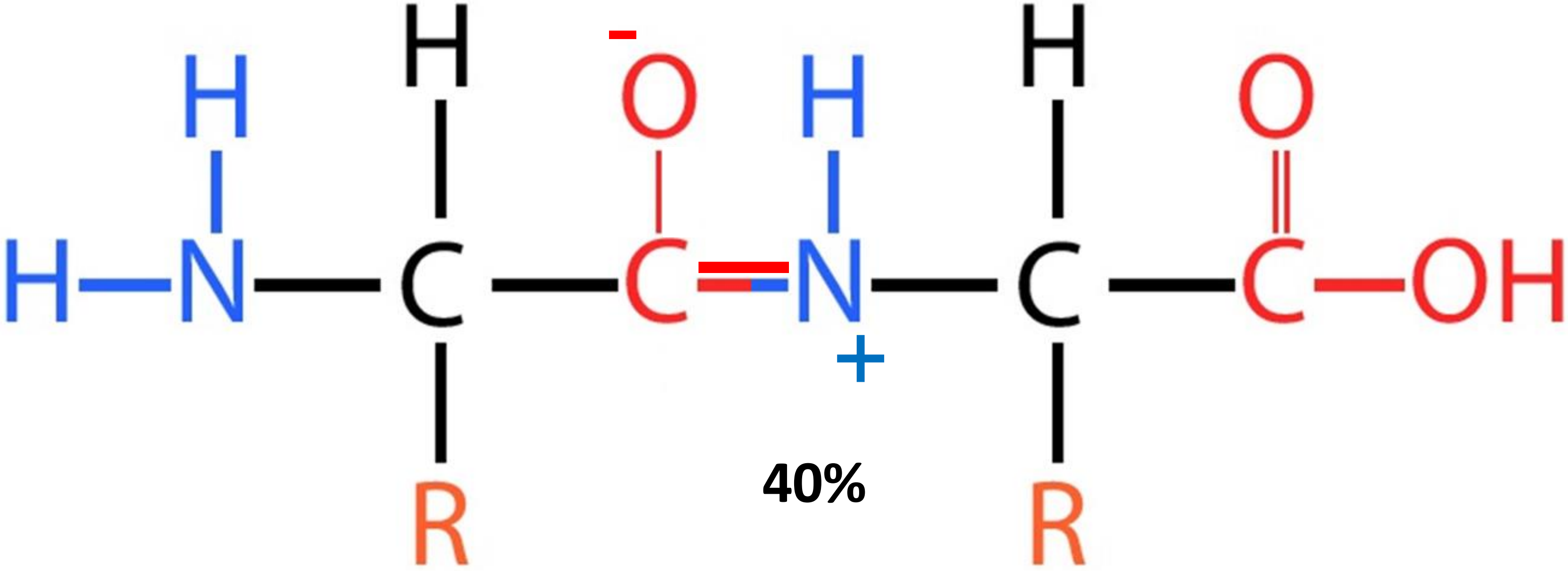


The peptide bond



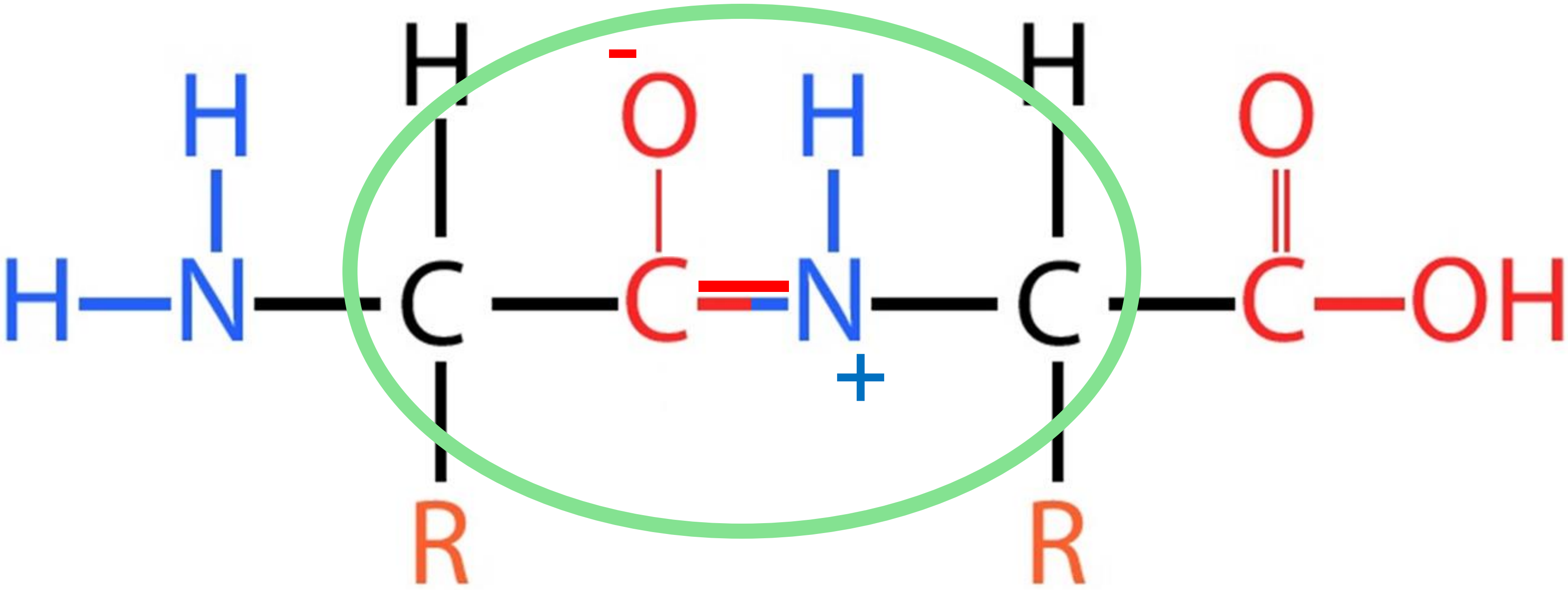
From the amino-terminal end to the carboxyl-terminal end

The peptide bond has two resonance structures

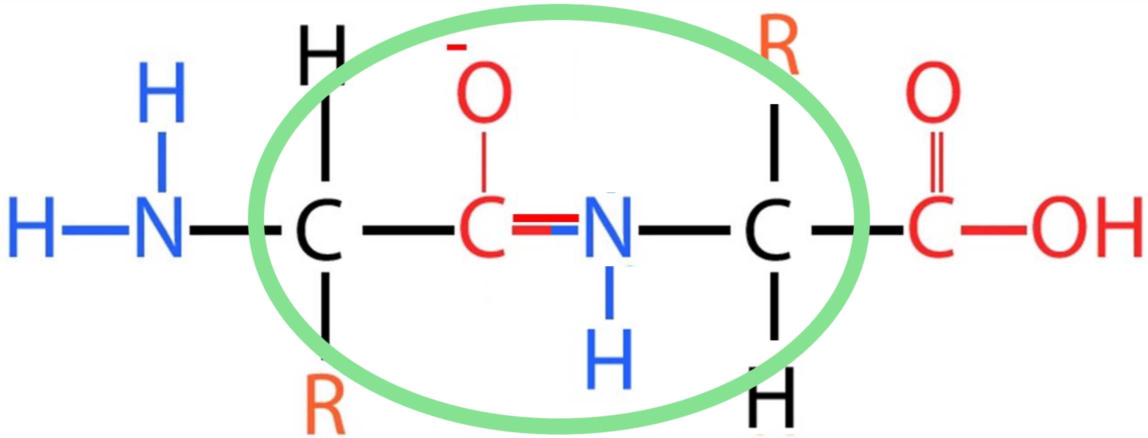


40%

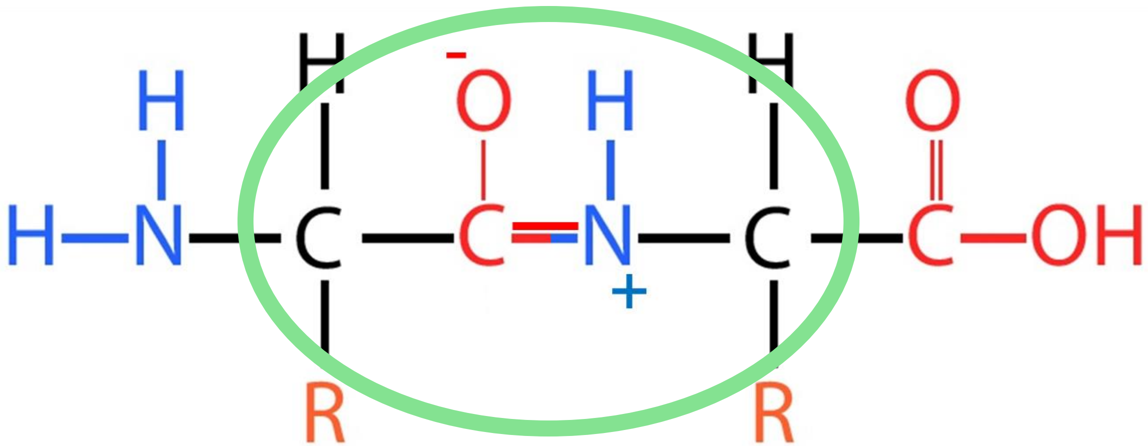
The peptide bond makes a plane



The peptide bond, cis or trans conformations

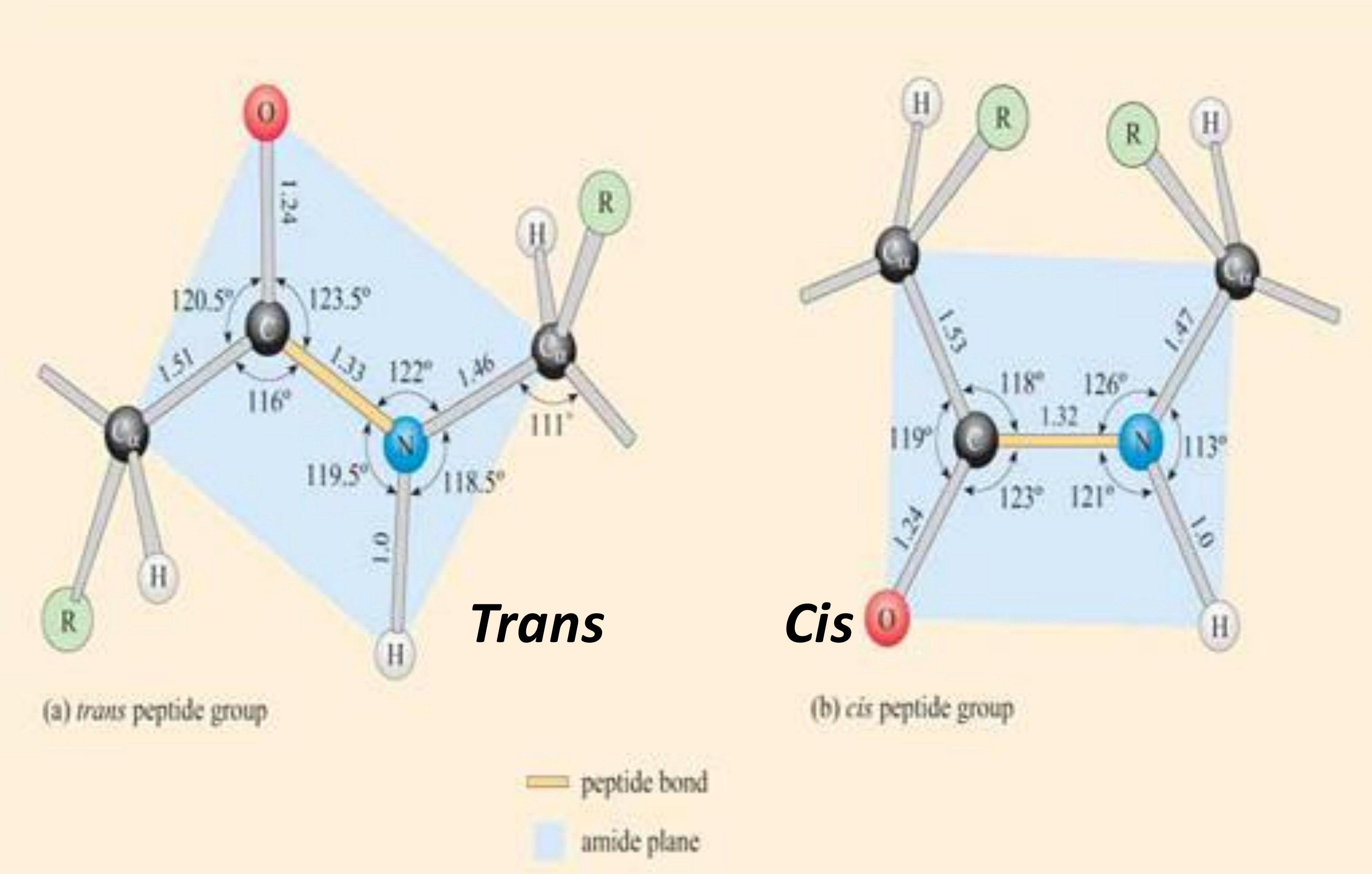


trans

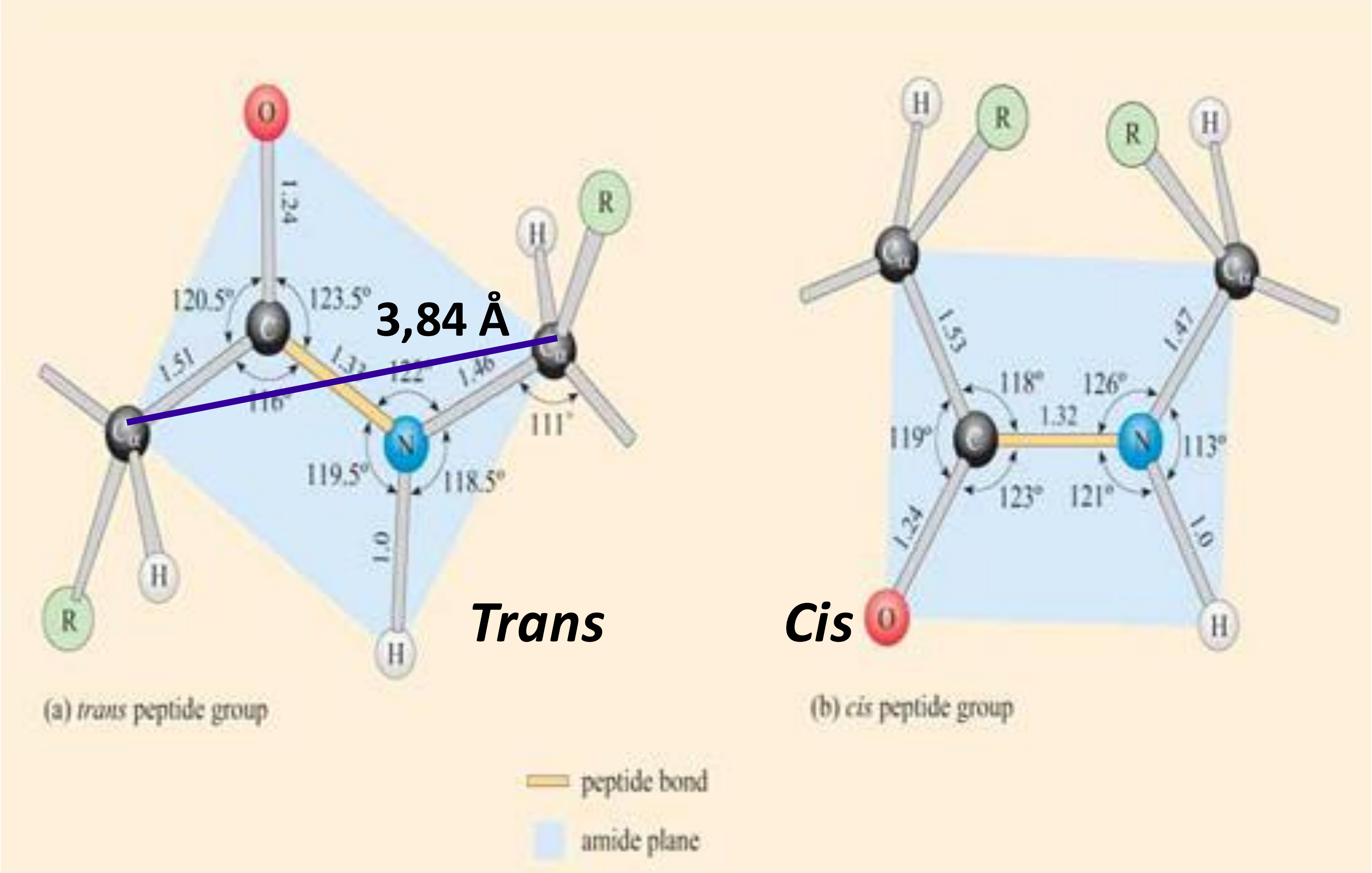


cis

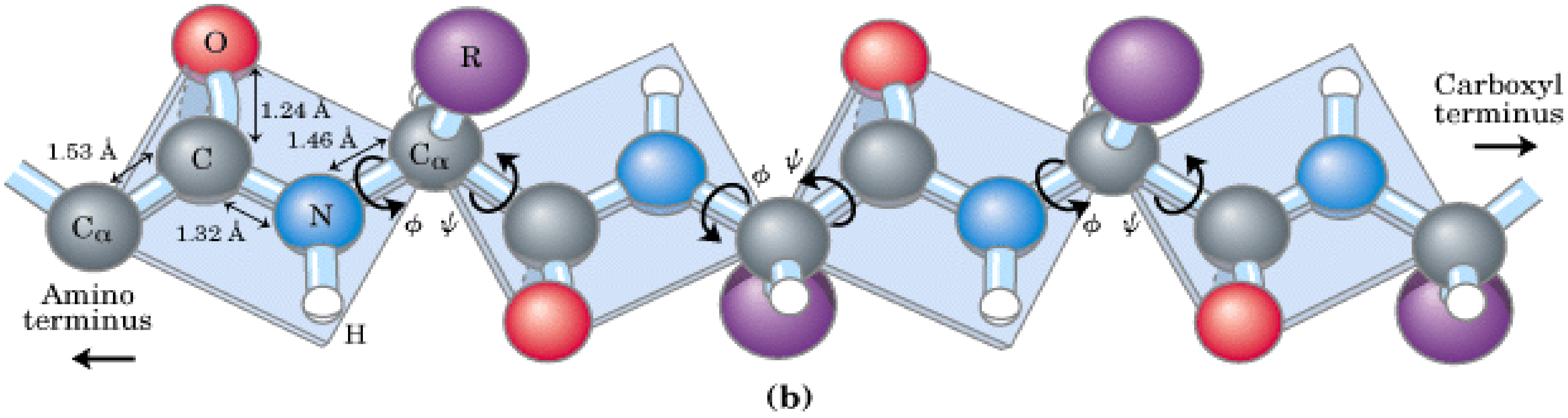
The peptide bond, cis or trans conformations



The peptide bond, cis or trans conformations

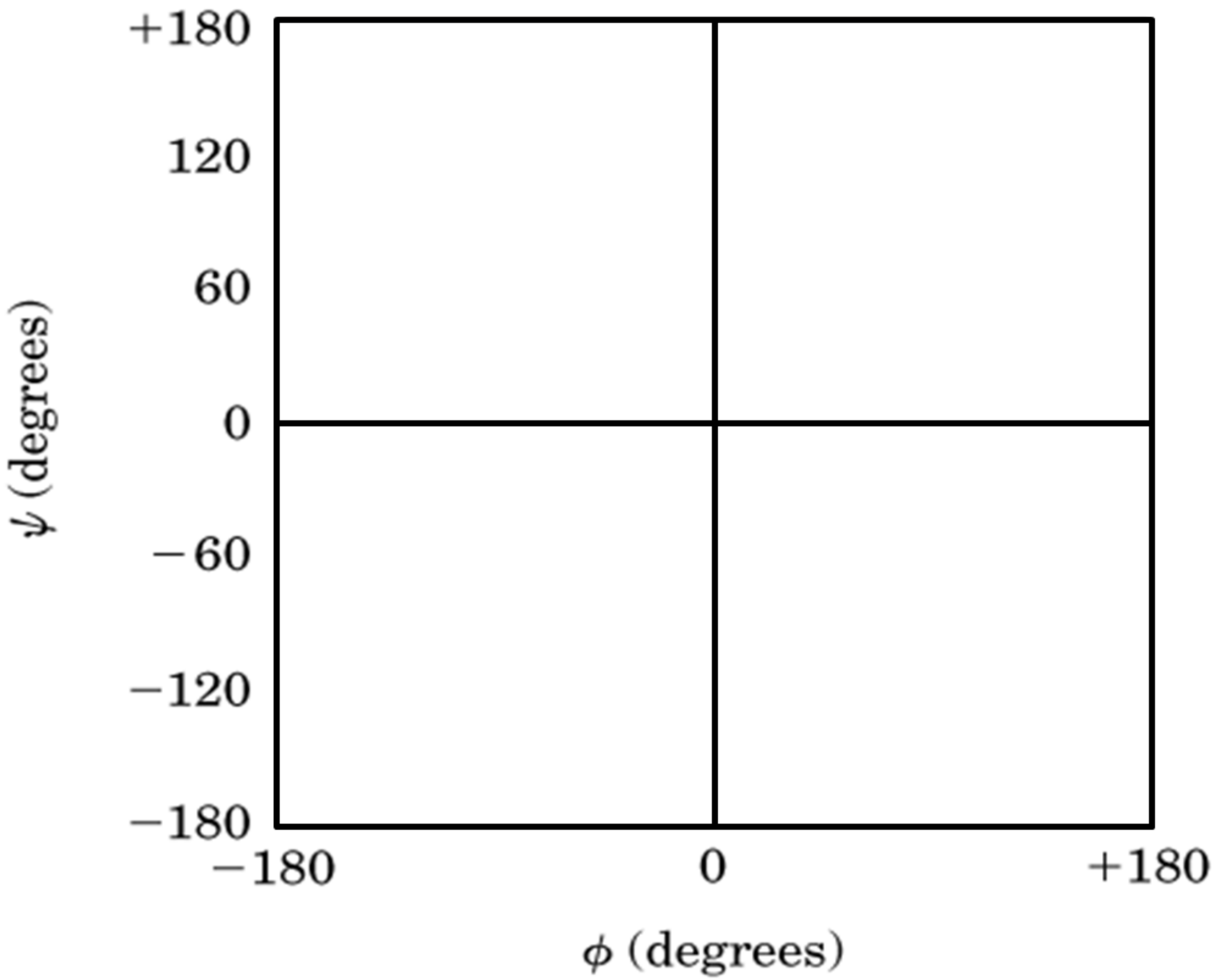


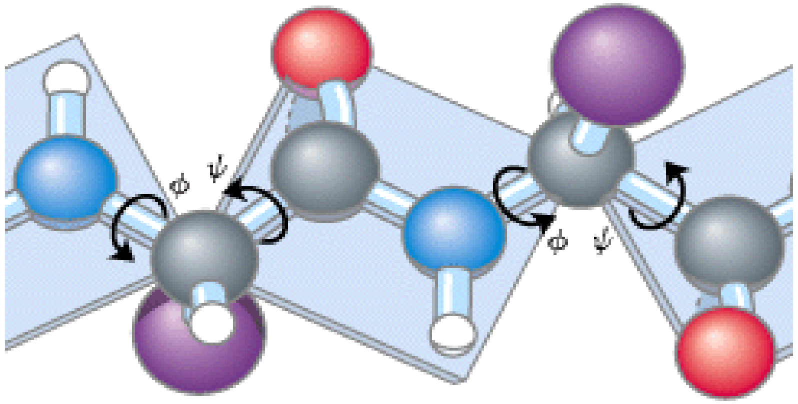
Between peptide planes are two torsion angles



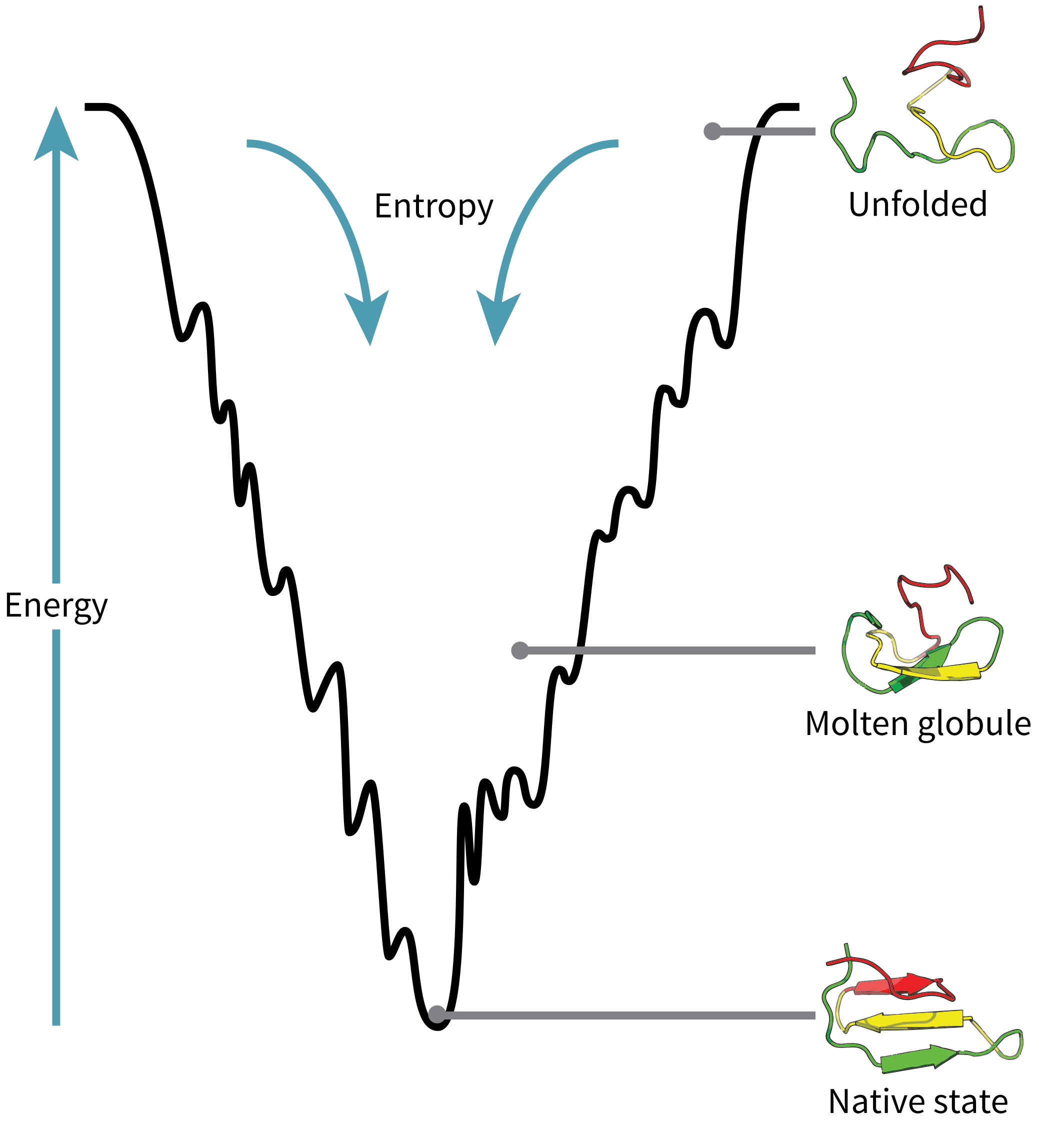
Only the ϕ and ψ angles are free to rotate
And the positions of the main-chain atoms can be entirely defined by them.

The Ramachandran plot





(b)



Extended conformations have low probability and high energy

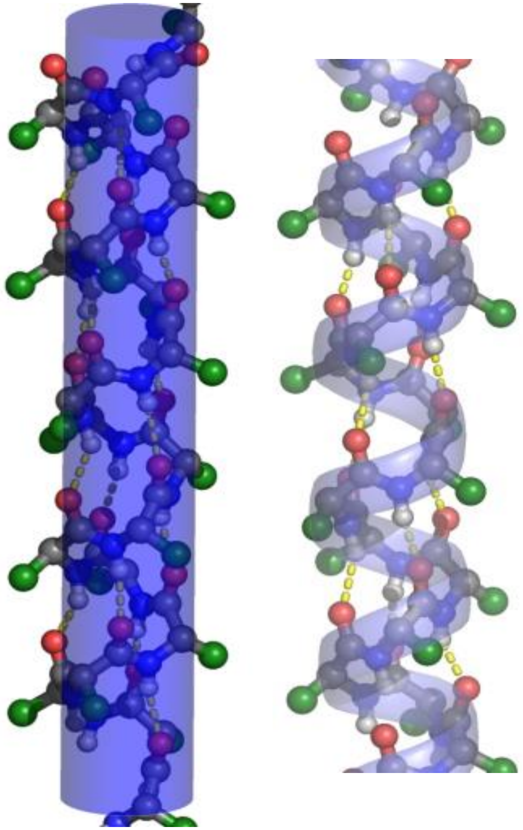
Globular conformations have a hydriphobic core

Lacking water, polar groups of the main chain make hydrogen bonds with each other, forming Secondary Structures (helices and sheets)

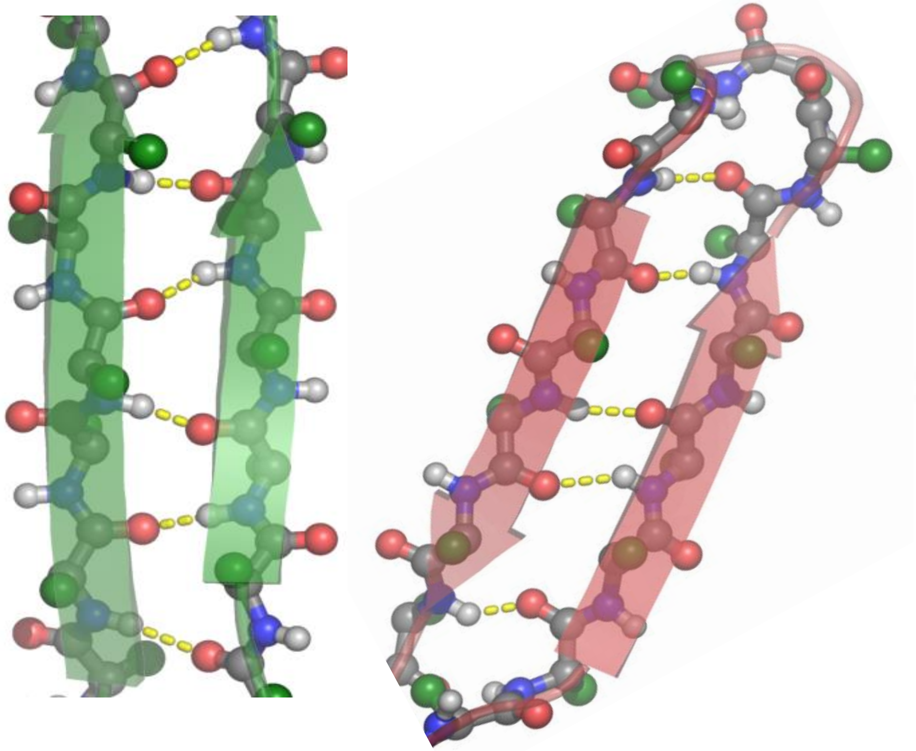
Secondary Structures arrange into motives and domains, which arrange into Tertiary Structures

Other protein chains arrange to form Quaternary Structures

Secondary structure



α-helices



β-sheets

Ramachandran plot

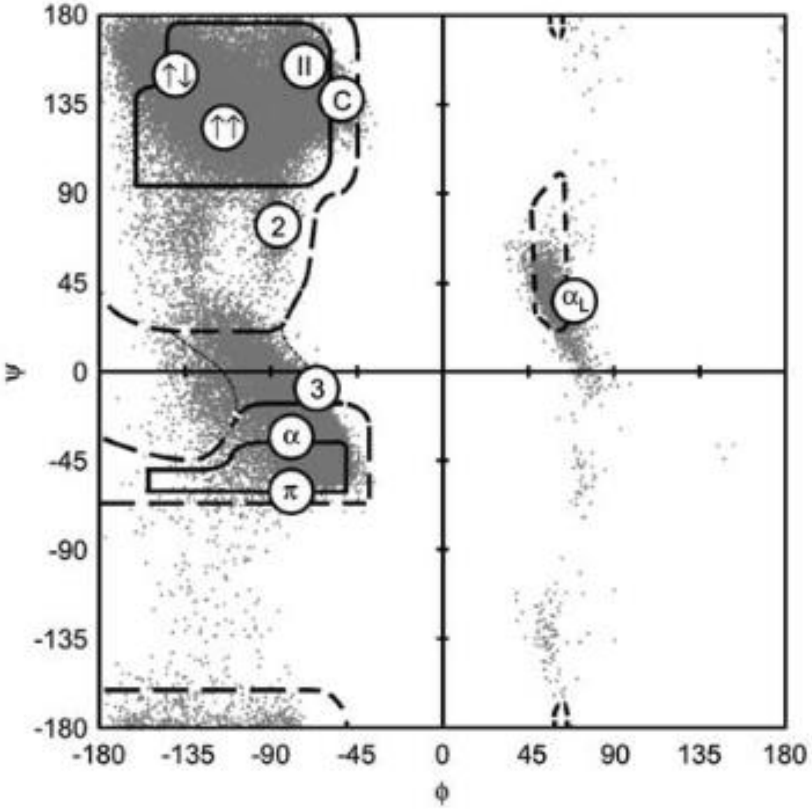
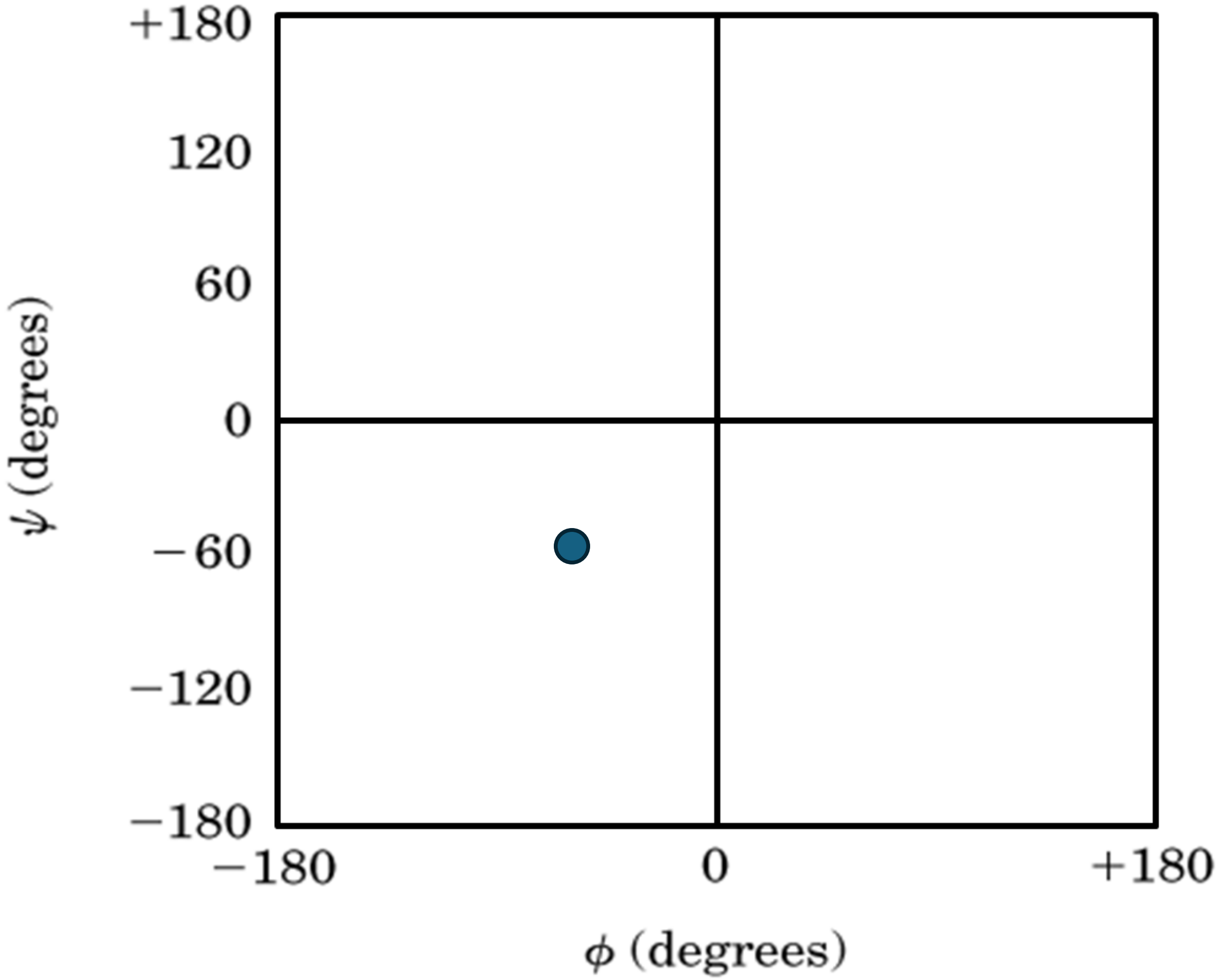
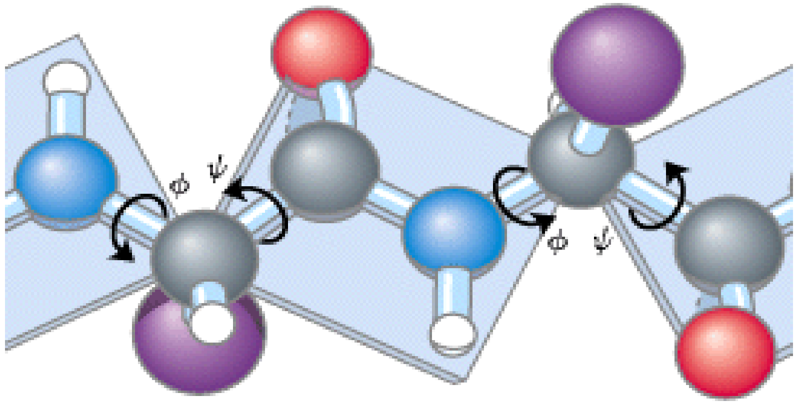


Figure by Richard Garratt

α-helices





(b)

α-helices

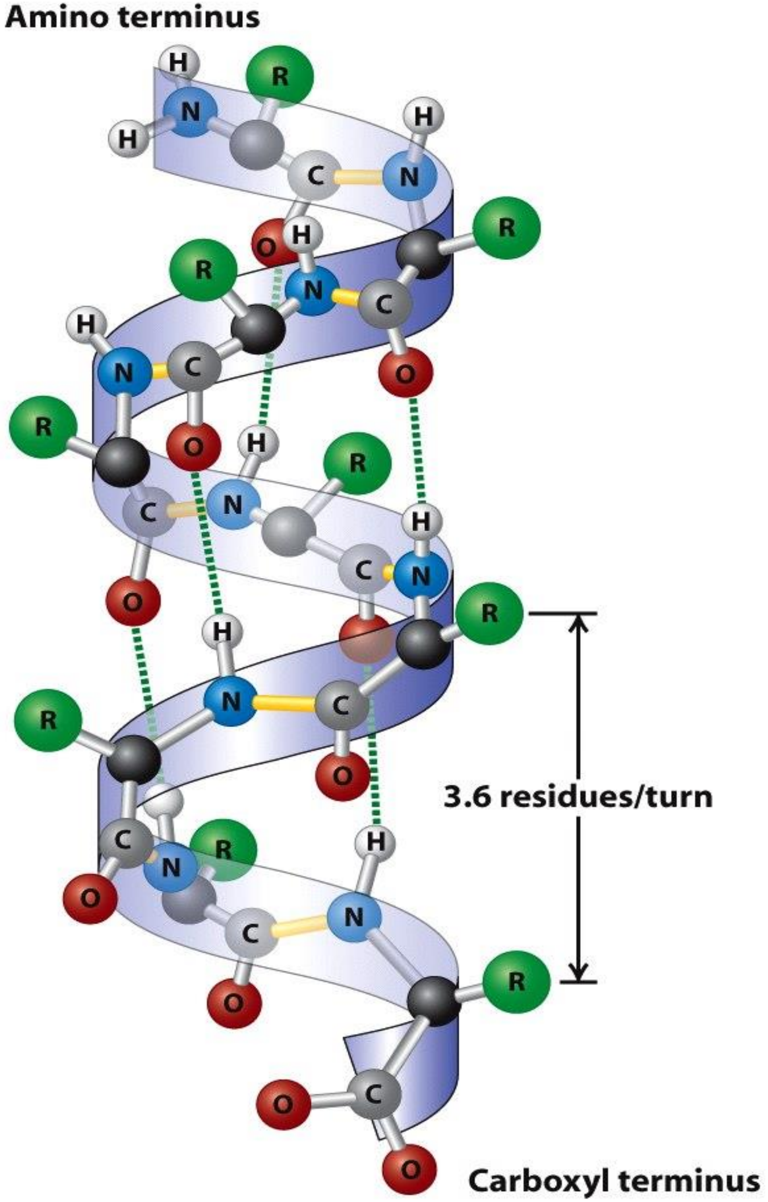
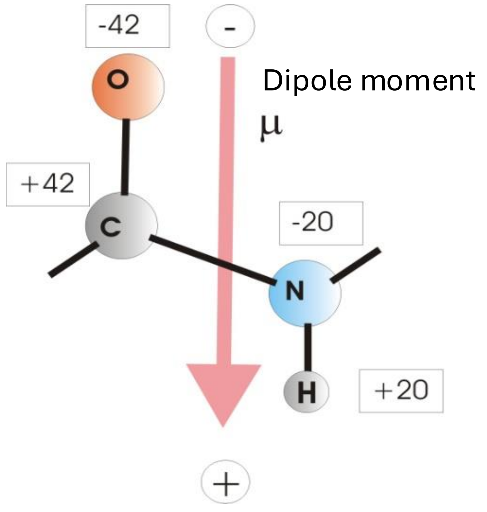
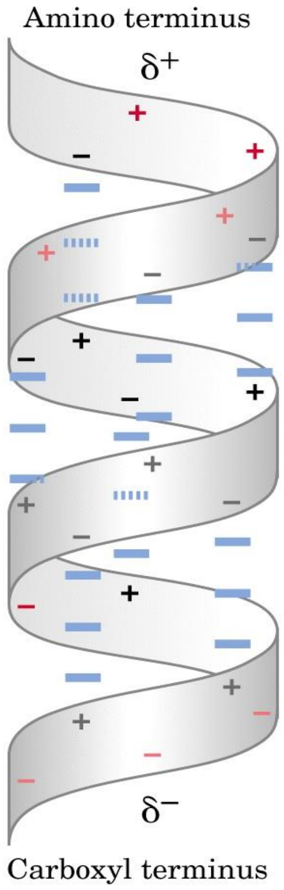


Figure 3-4
Molecular Cell Biology, Sixth Edition

Electrical dipole





Biological Function

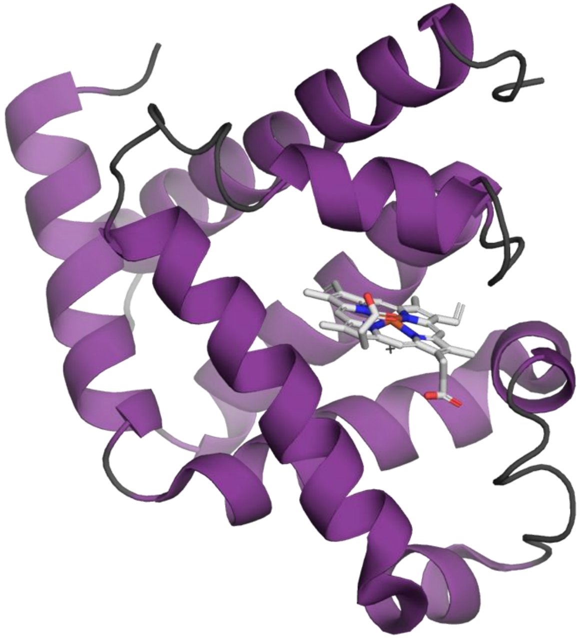
•Help in binding charged cofactors

• Long range attraction (K^+ and Cl^- channels)

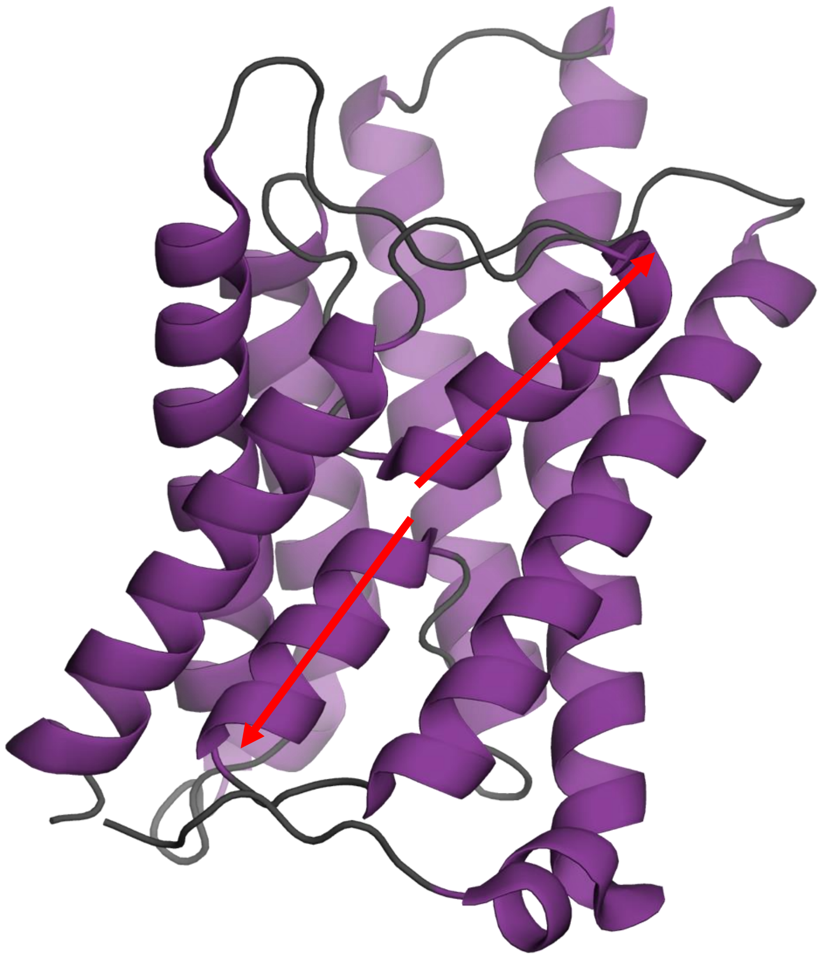
• Change the nucleophilic properties of neighbouring residues for catalysis

Slide by Richard Garratt

All alpha protein example

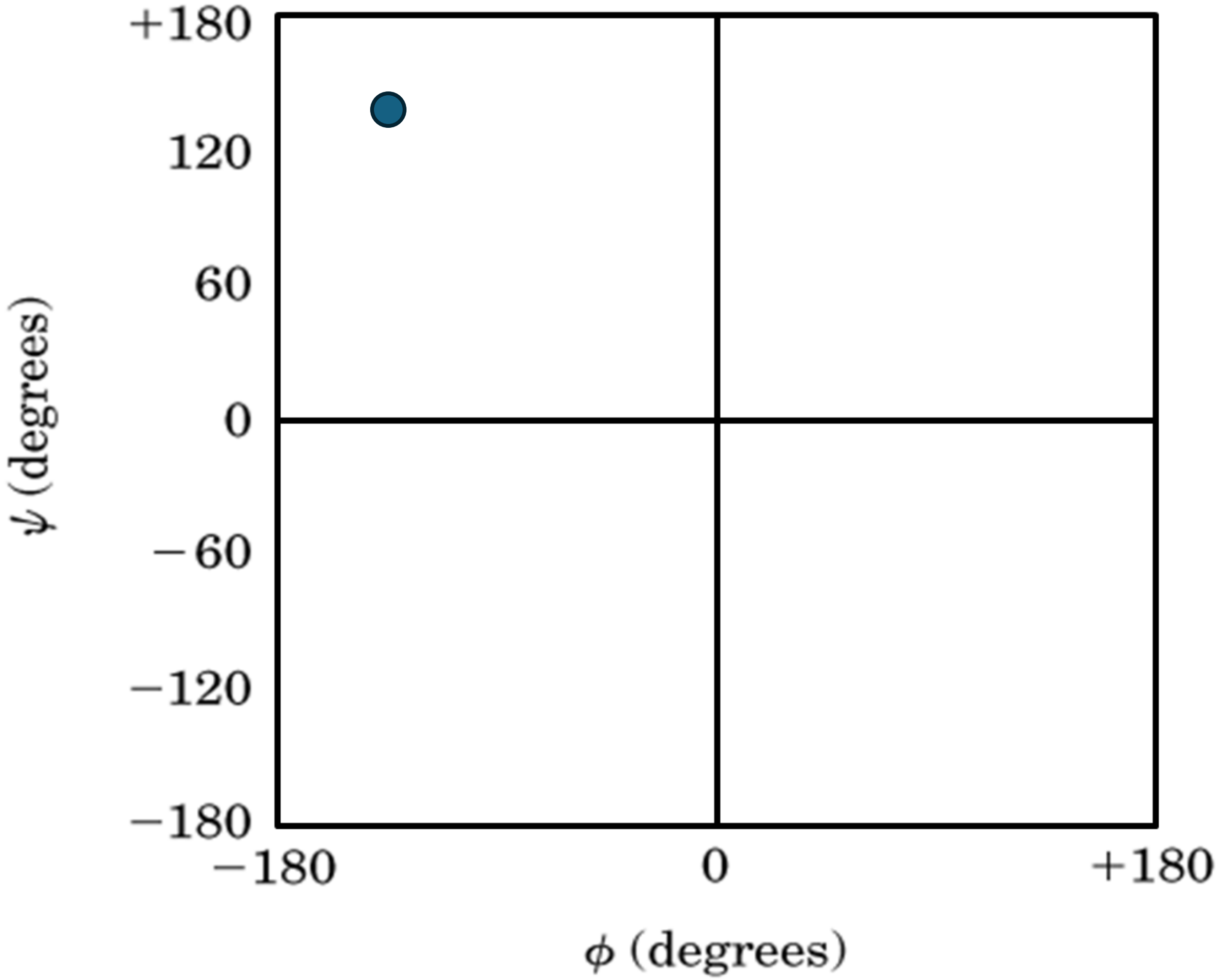


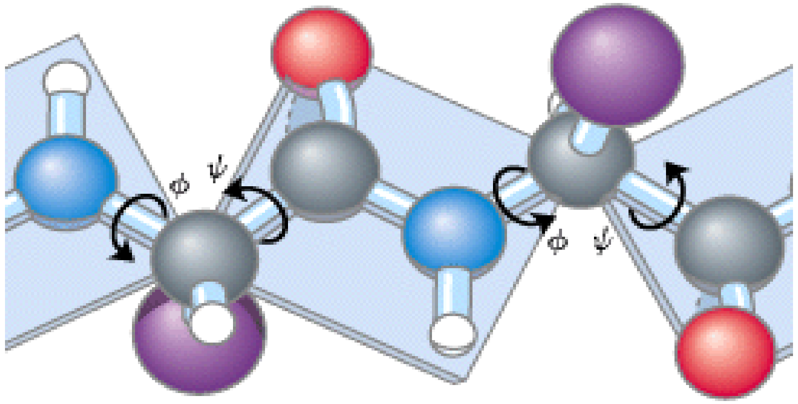
Myoglobin, 1976



Aquaporin

β-strands

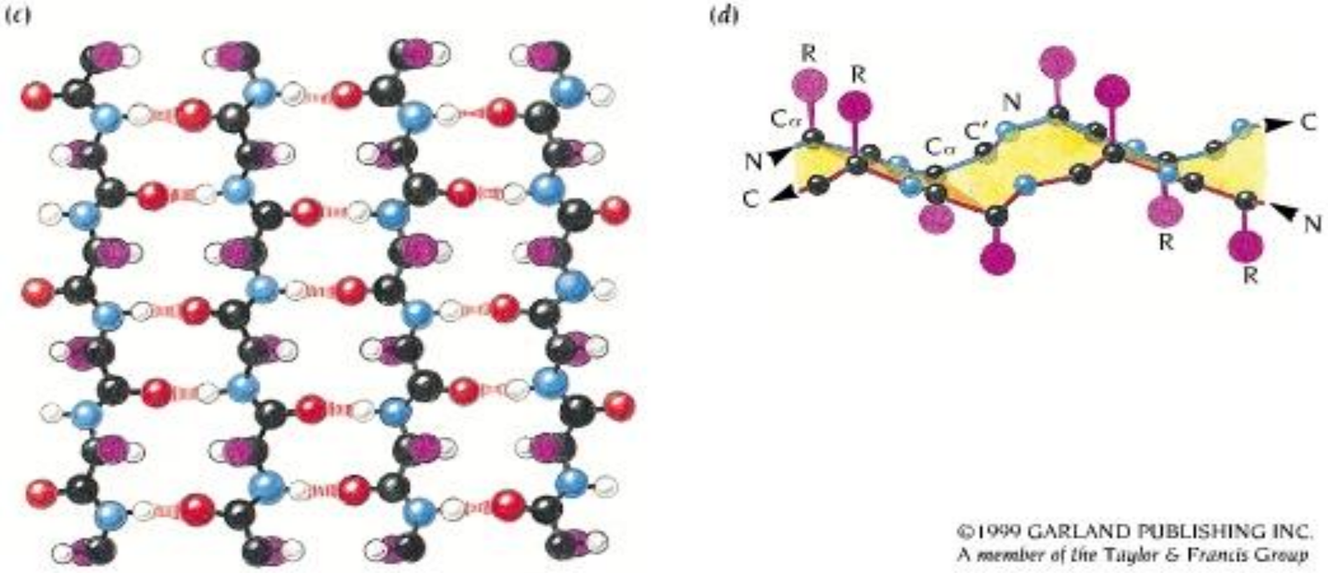




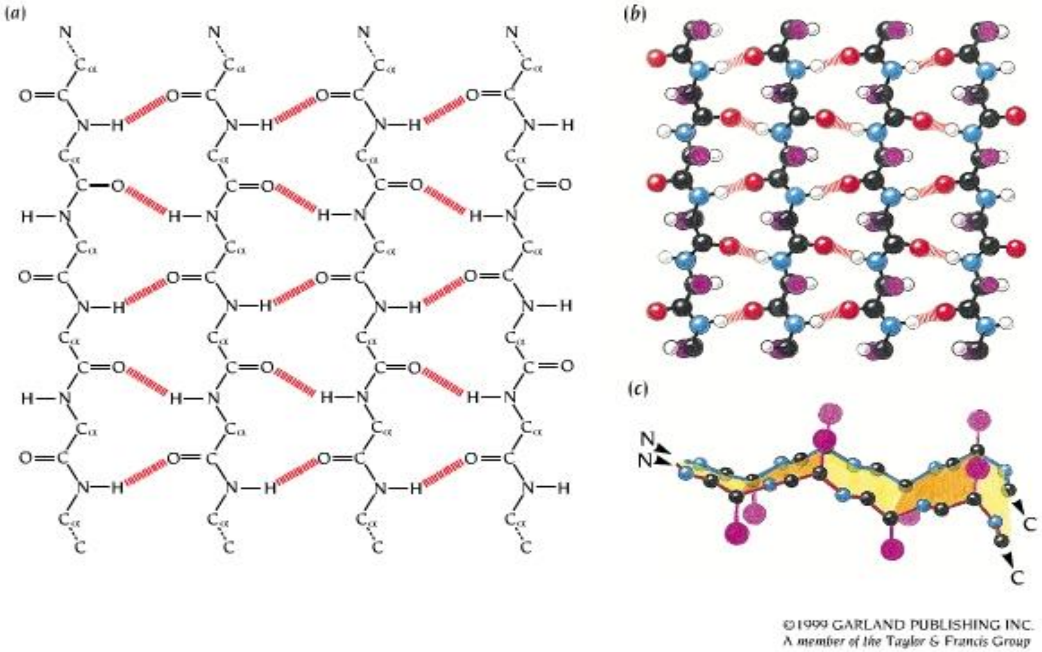
(b)

β-sheets

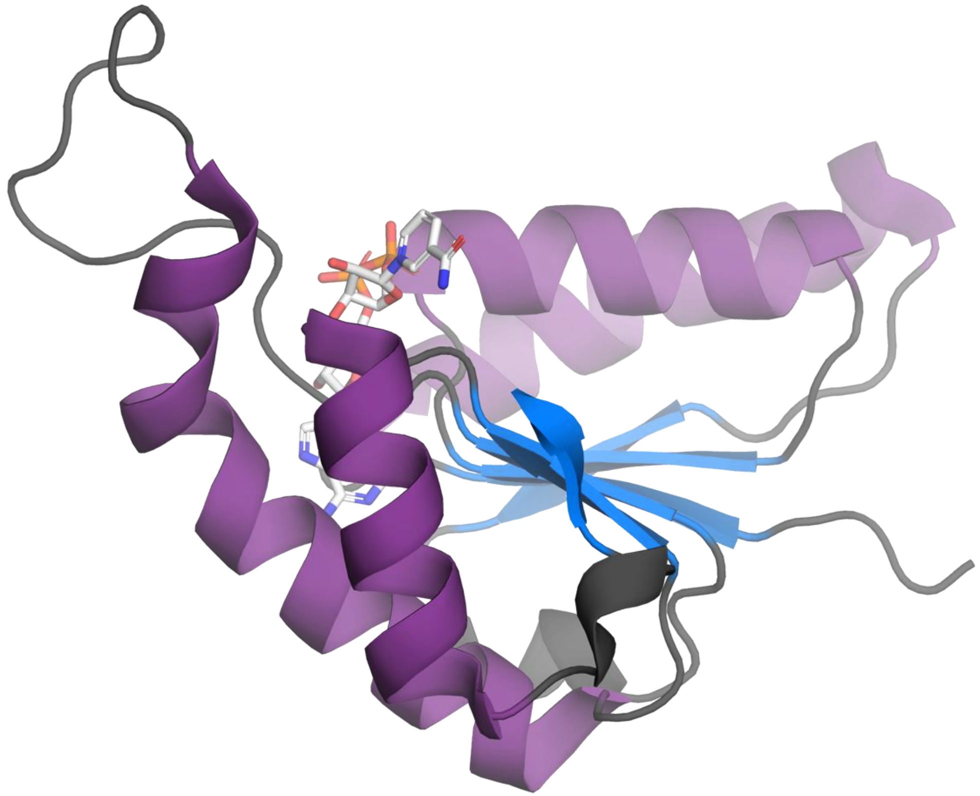
Anti-parallel β-sheet

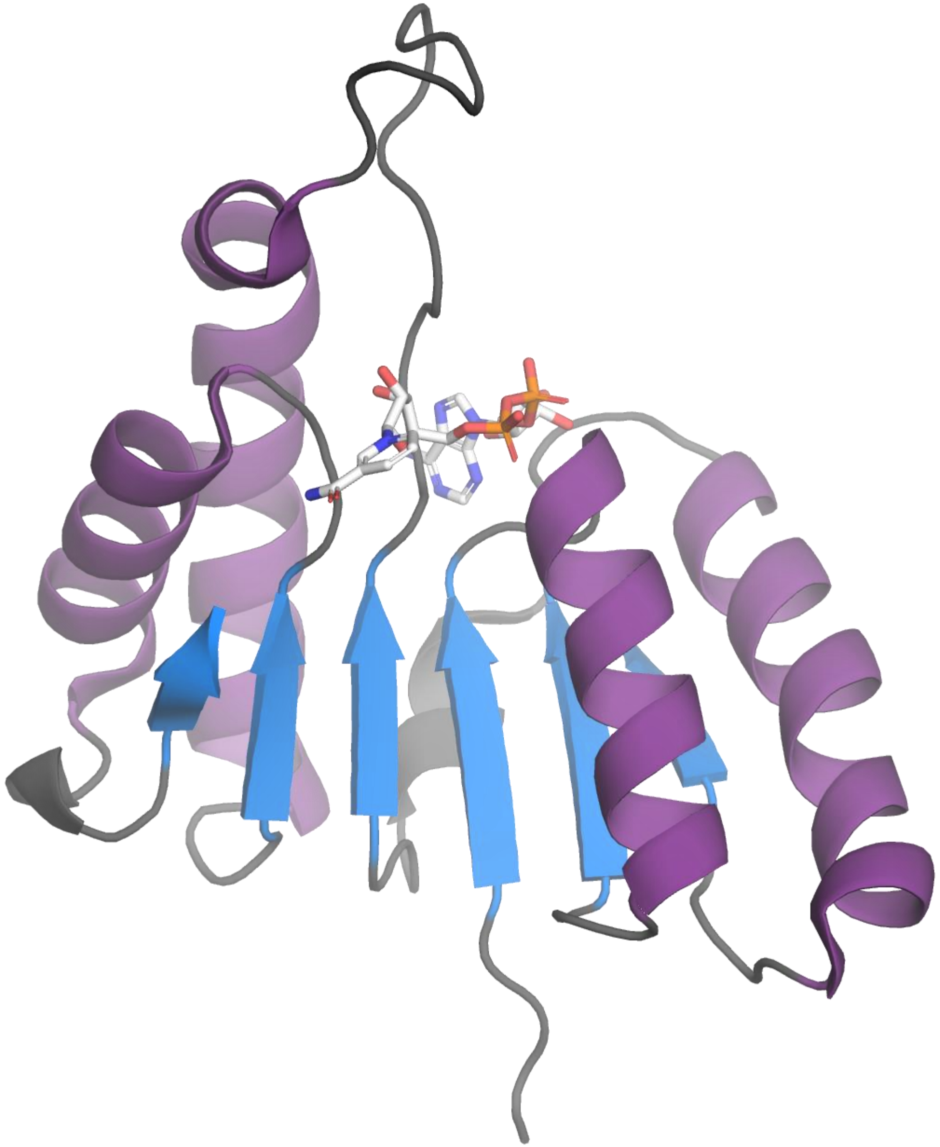


Parallel β-sheet

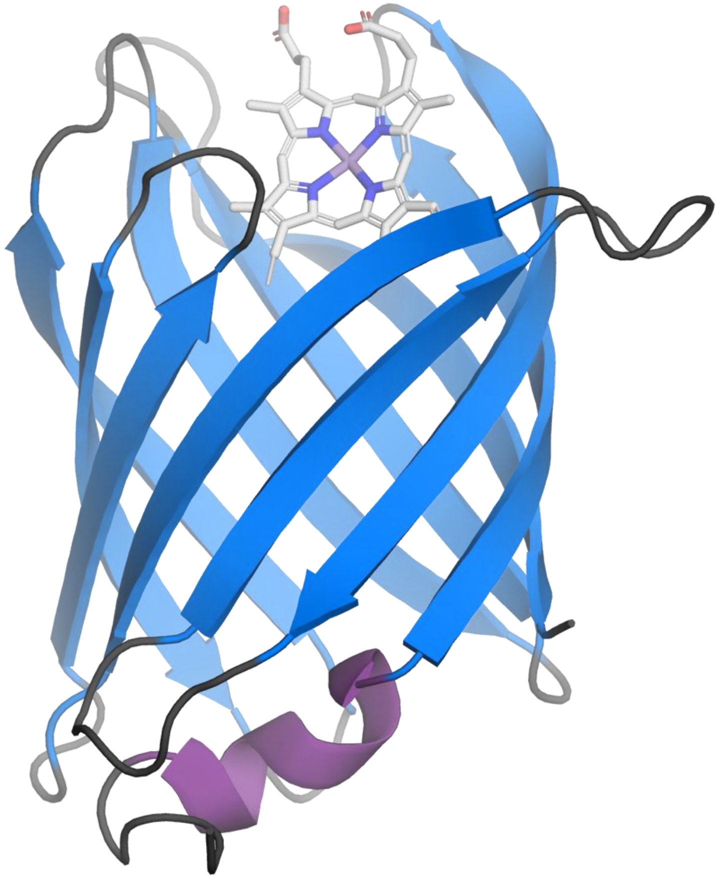


Example of beta sheet with twisted beta strands



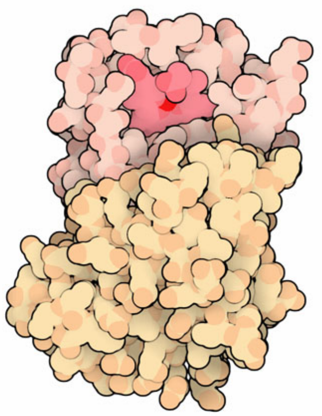


Example of a beta sheet with twisted beat strands



Nitrobindin

December 2010



Proteins perform most of the nanoscale tasks inside of cells, but occasionally, they need help from more exotic molecules. For instance, very small molecules like oxygen are difficult to capture, and proteins like hemoglobin use a heme to trap them. Heme is used in many other capacities as well, including the management of electrons and the capture of other gas molecules such as nitric oxide. So, when researchers at CESG discovered a new heme-containing protein in the plant Arabidopsis, they were faced with an exciting challenge: what is the heme doing?

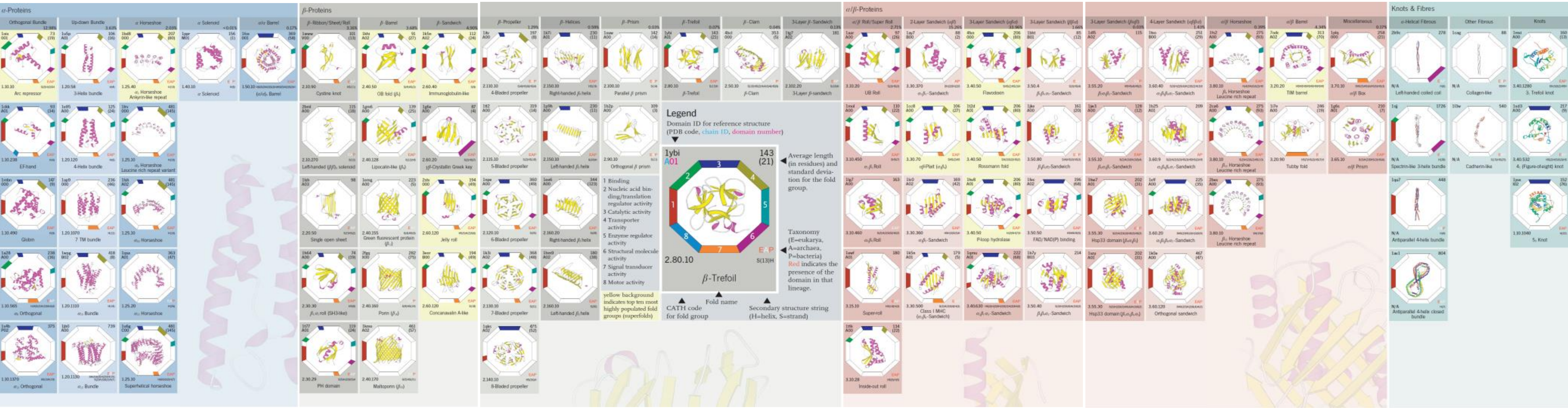
Heme Exposed

The heme in nitrobindin (PDB entry 3emm) is unusual in that the iron atom is rather exposed to solvent. In many heme proteins, the heme is buried deep within the protein, with perfectly-placed amino acids guarding access to the iron atom. For instance, globins have a histidine on one side of the heme, which positions the iron in the proper place, and a histidine or glutamine on the other side, leaving just enough room for oxygen to bind. Nitrobindin, on the other hand, has a similar histidine coordinated directly to the iron, but the other side of the iron is free to interact with water. This has an unusual consequence: in the presence of oxygen, the iron atom is rapidly oxidized and shows only a weak interaction with oxygen.

Managing Nitric Oxide

Testing revealed, however, that the reduced form of the protein binds to nitric oxide (NO) with substantial affinity. This has posed a mystery about the function of the protein. Nitric oxide, in spite of its significant toxicity, is widely used in animal cells as a hormone, in particular, in the local control of blood flow. It plays a similar role in plant cells as part of a complex signaling network that decides what to do when cells are infected or wounded. One clue to the function of nitrobindin is provided by the similar NO-binding protein nitrophorin. Nitrophorin is made by blood-sucking insects and used to deliver NO to their victims, where it dilates the blood vessels and provides more blood for the insect. Nitrobindin may play a similar role in plants, providing a way to store NO safely until it is needed.

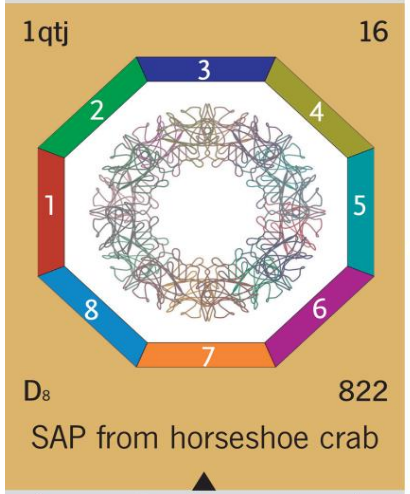
A summary of everything



Legend

PDB code for reference structure

Number of subunits



Protein name

Point group symmetry (Schoenflies nomenclature)

Point group symmetry (International nomenclature)

1 Multiple sites, cross-linking, membrane association
2 Cooperativity/allosterism
3 Cavities, channels and pores
4 Functional (active) site formation
5 Size and stability
6 Economy of genetic material
7 "Rulers" (exact separation between binding sites)
8 Multiple functions (in hetero-oligomers)

Yellow background indicates dihedral symmetry

Gray background indicates cubic/icosahedral symmetry

WILEY-VCH

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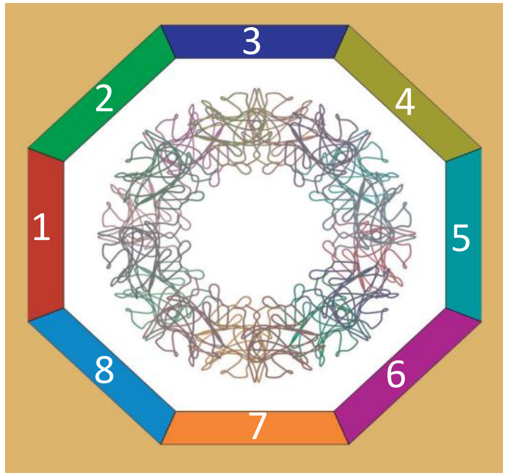
Why be oligomeric?

1) Multiple sites, cross-links, membrane association
2) Cooperativity/Alosterism
3) Cavities, channels and pores
4) Formation of functional sites (ative sites)
5) Size and Stability
6) Economy of genetic material
7) “Rulers” - exact eperation between active sites
8) Multiple functions (in the case of hetero-oligomers)



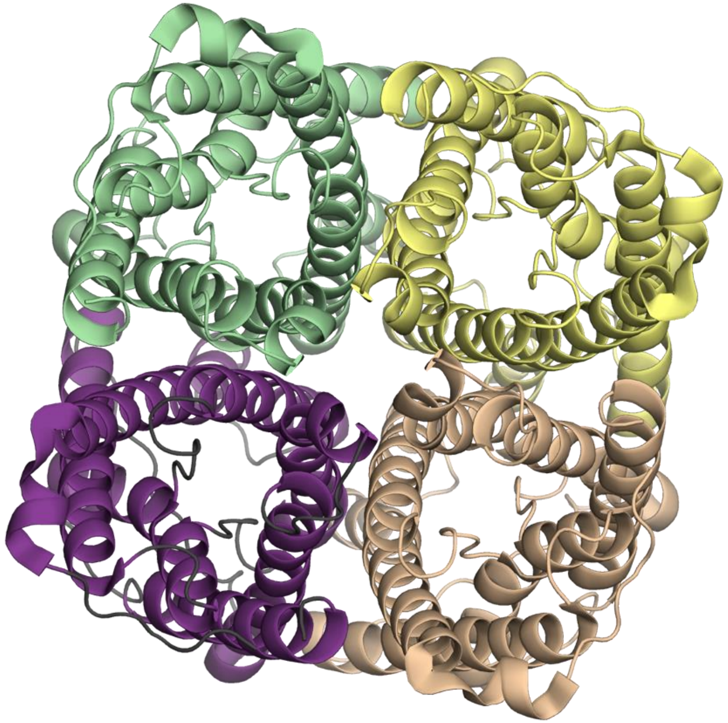
Slide by Richard Garratt

Oligomers distribution in *E. coli*

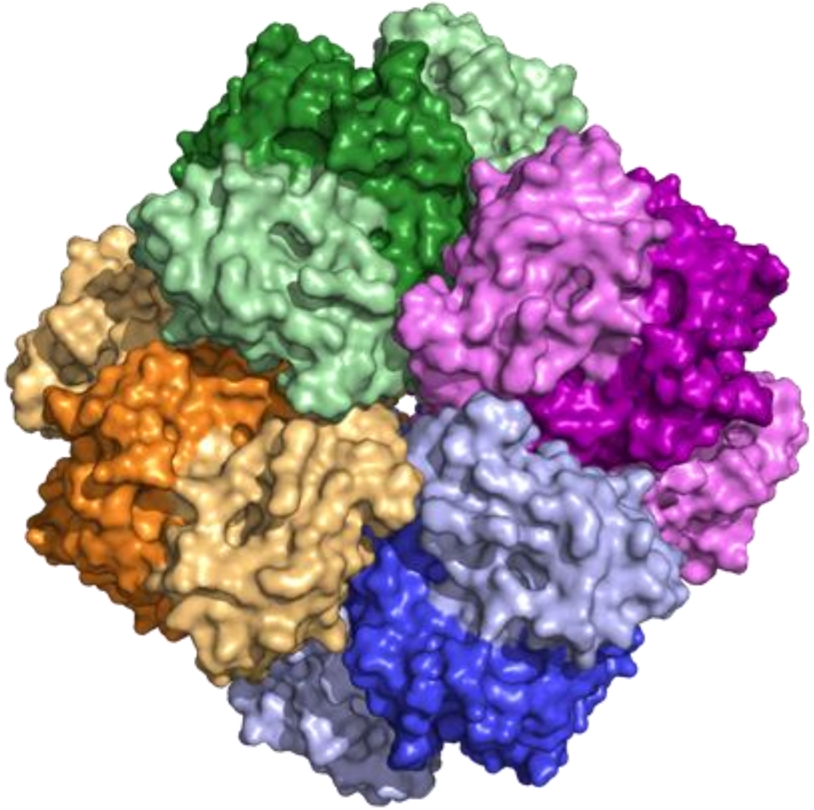
# subunits	% proteins
1	19.4
2	38.2
3	5.4
4	21.0
5	0.1
6	5.6
7	0.1
8	2.4
9	0.0
10	0.0
11	0.0
12	1.6
>12	2.2
Polimers	2.7

Slide by Richard Garratt

Oligomers



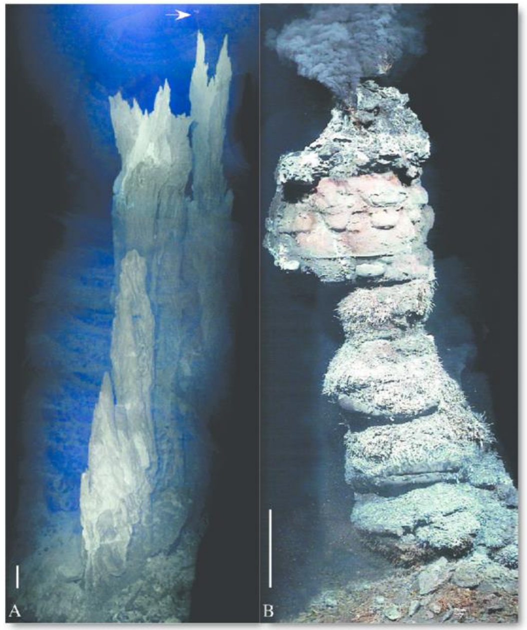
Aquaporin



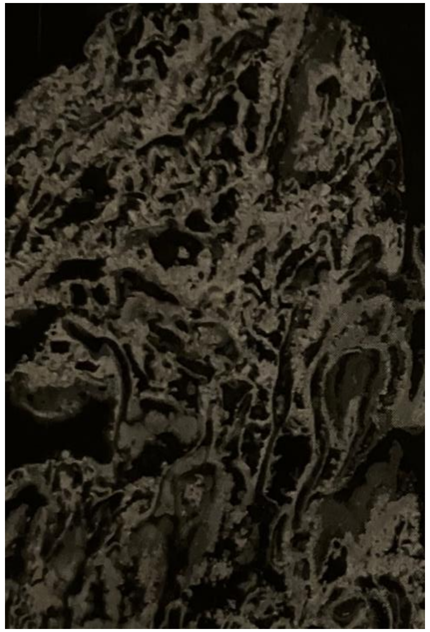
Rubisco

Why exactly these 20 amino acids?

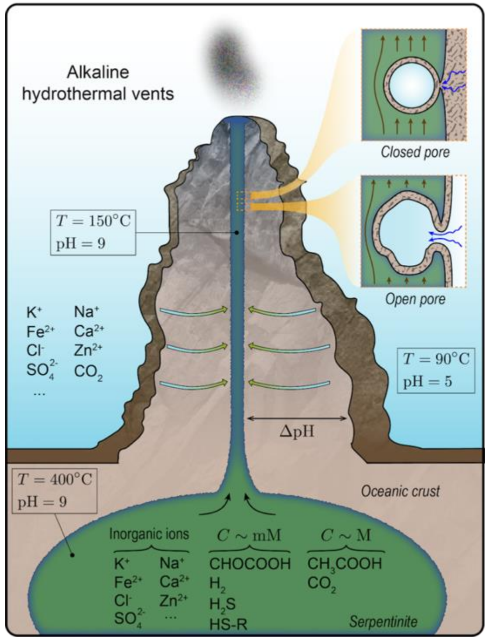
Hypothetical codons of 2 base pairs: 4 x 4 = 15 possible amino acids + stop
Codons of 3 base pairs: 4 x 4 x 4 = 20 possible amino acids + stop and redundancy



Lane, 2015



Lane, Life ascending



Akbari and Palsso, 2023

1^{st} letter – shared precursor
2^{nd} letter – degree of solubility
3^{rd} letter - degeneracy