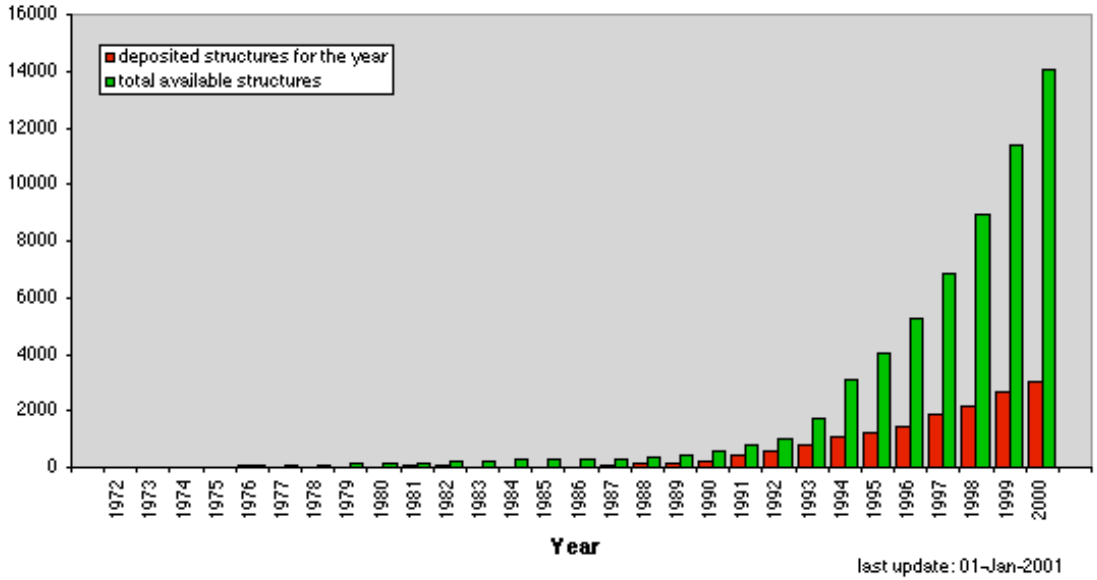
Principles of Protein Structure and Conformational Space (part 3)

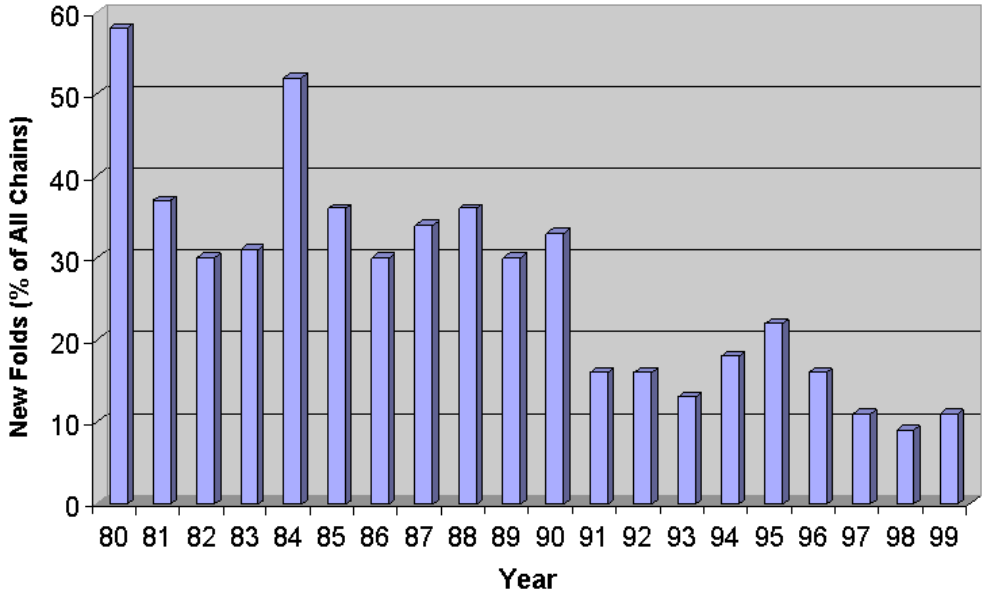
Protein structure

3. Soluble and globular proteins
    5. Principles observed in folds
    6. Classical folds (TIM & Rossman)
    7. All α
    8. All β
    9. α/β
    10. $\alpha+\beta$
4. Globular membrane proteins
    1. Definition
    2. Classification
        1. Integral
        2. Periferal

3. Soluble and globular proteins
5. Principles observed in folds



Geometric increase of the number of structures in PDB



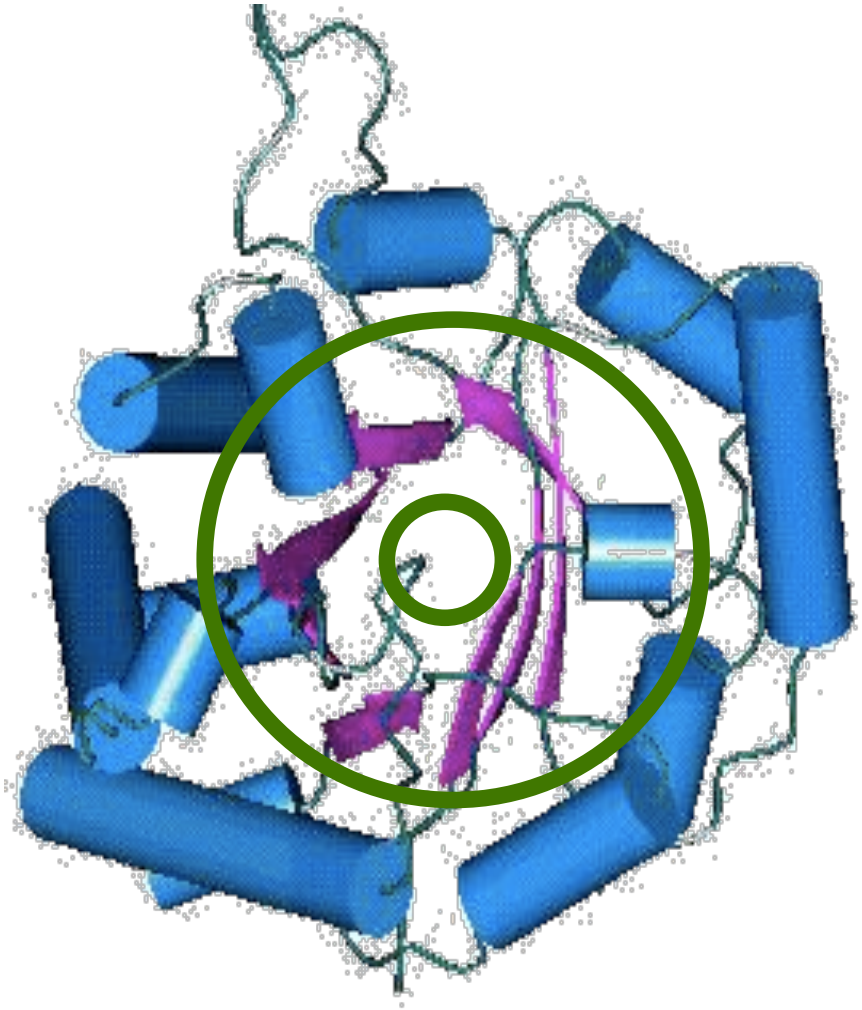
The % of new folds has reached a plateau and the tendency will be to decrease until no more new folds are found.

3. Soluble and globular proteins
5. Principles observed in folds

- Folds have a compact structure formed by the organization of regular secondary structures
- Folds have an hydrophobic core that stabilizes its conformation
- The hydrophobic core is formed by non-polar residues, while polar residues are mostly in the surface and active sites
- Structure is conserved among proteins with similar sequence
- The total number of folds is finite
- The structure of a protein an be build by joining several folds (this can be produced by gene fusion).

3. Soluble and globular proteins
6. Classical folds

Triose Phosphate Isomerase (TIM Barrel)



- Double hydrophobic core
- Highly stable
- Found in many proteins, mostly enzymes.
- It was recently proved that all of them have the same ancestor

3. Soluble and globular proteins

6. Classical folds

TIM Barrel Evolution

- A fusion gene is a hybrid gene formed from two previously separate genes. It can occur as the result of a translocation, interstitial deletion, or chromosomal inversion.

- Gene duplication plays an important role in enzyme evolution. It has been estimated that 50% of all genes in microorganisms are the result of duplication events, which are followed by diversification of the twin genes (Fani et al 1998, Lynch & Conery 2000).

- Gene duplication and fusion events that multiply and link functional protein domains are crucial mechanisms of enzyme evolution.

- The analysis of amino acid sequences and three-dimensional structures suggested that the (αβ)8-barrel, has evolved by the duplication, fusion, and mixing of (αβ)4-half-barrel domains (Höcker et al 2004).

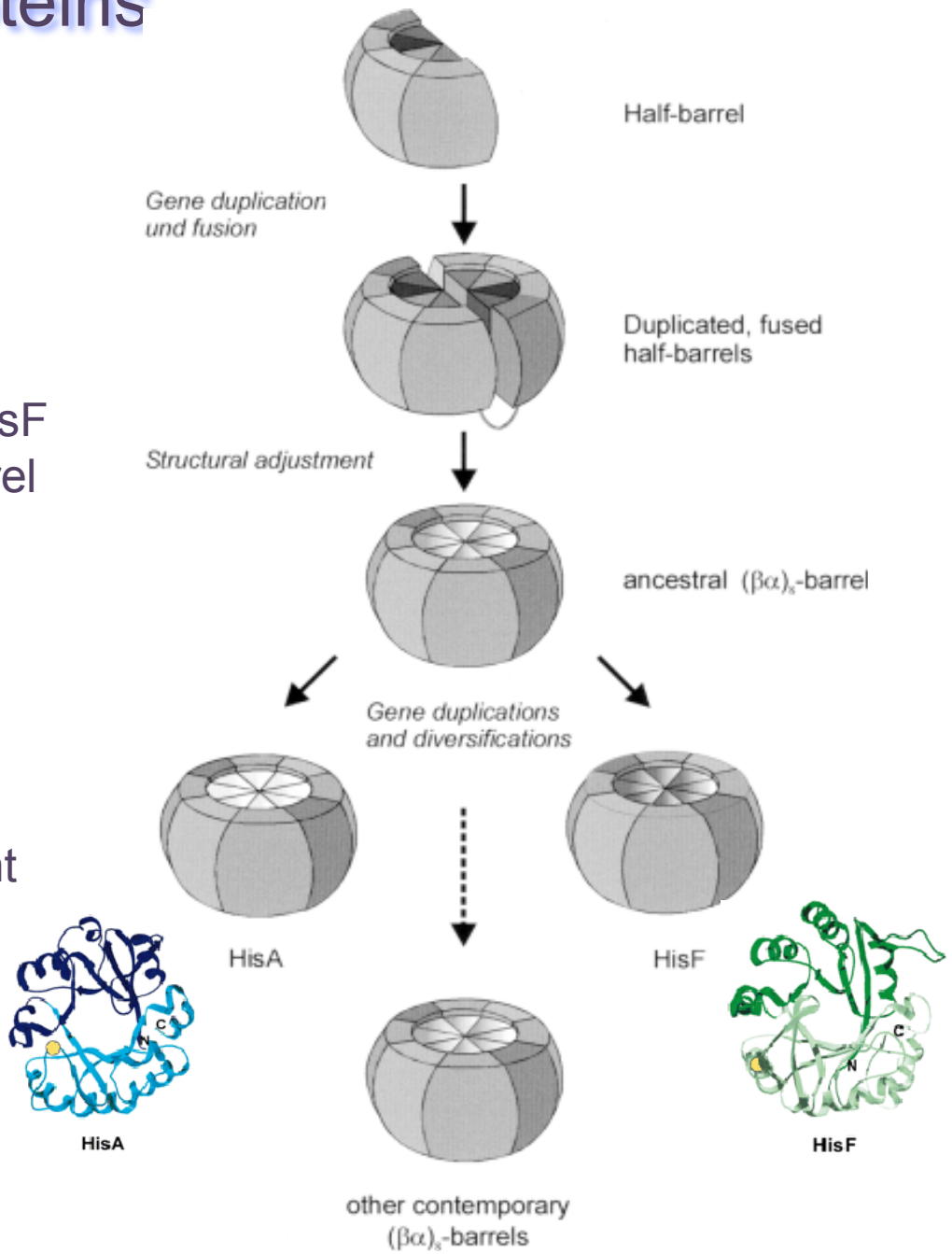
3. Soluble and globular proteins

6. Classical folds

TIM Barrel Evolution

It has been postulated that HisA and HisF evolved from a common (βα)4-half-barrel by a series of gene duplication and diversification events (Höcker et al 2004).

(βα)8-barrels were derived from 'half-barrels' will motivate the search for ancestral domains within other apparent single-domain protein folds (Petsko, 2000; Gerlt and Babbitt, 2001, Jürgens al 2000).



3. Soluble and globular proteins

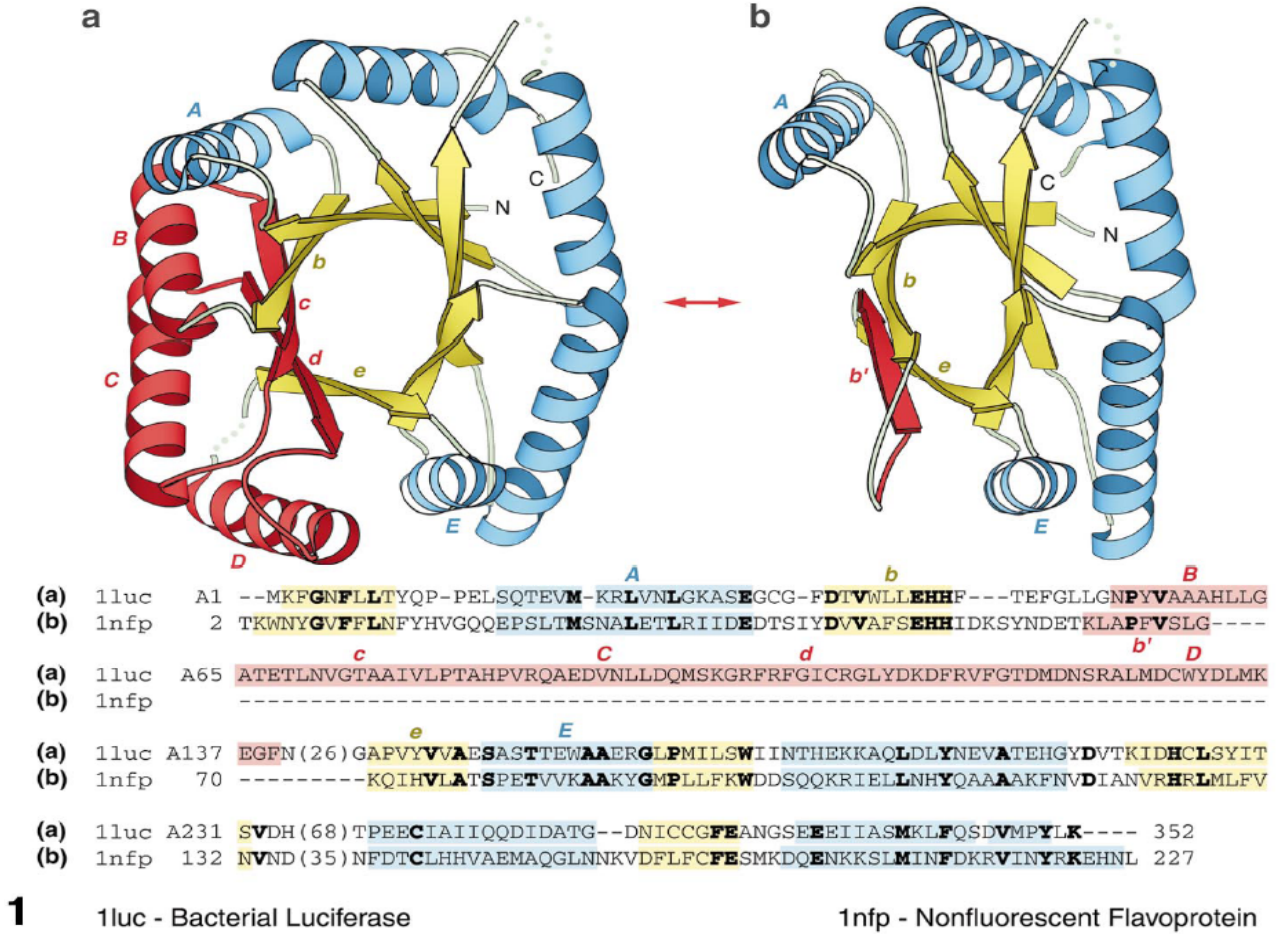
6. Classical folds

TIM Barrel Evolution

Insertion, deletion and substitution

Luciferase and NFP

- NFP deletes a 90-residue section αβαβα
- Missing segment is compensated by a single anti-parallel strand
- Shared regions are 30% identical



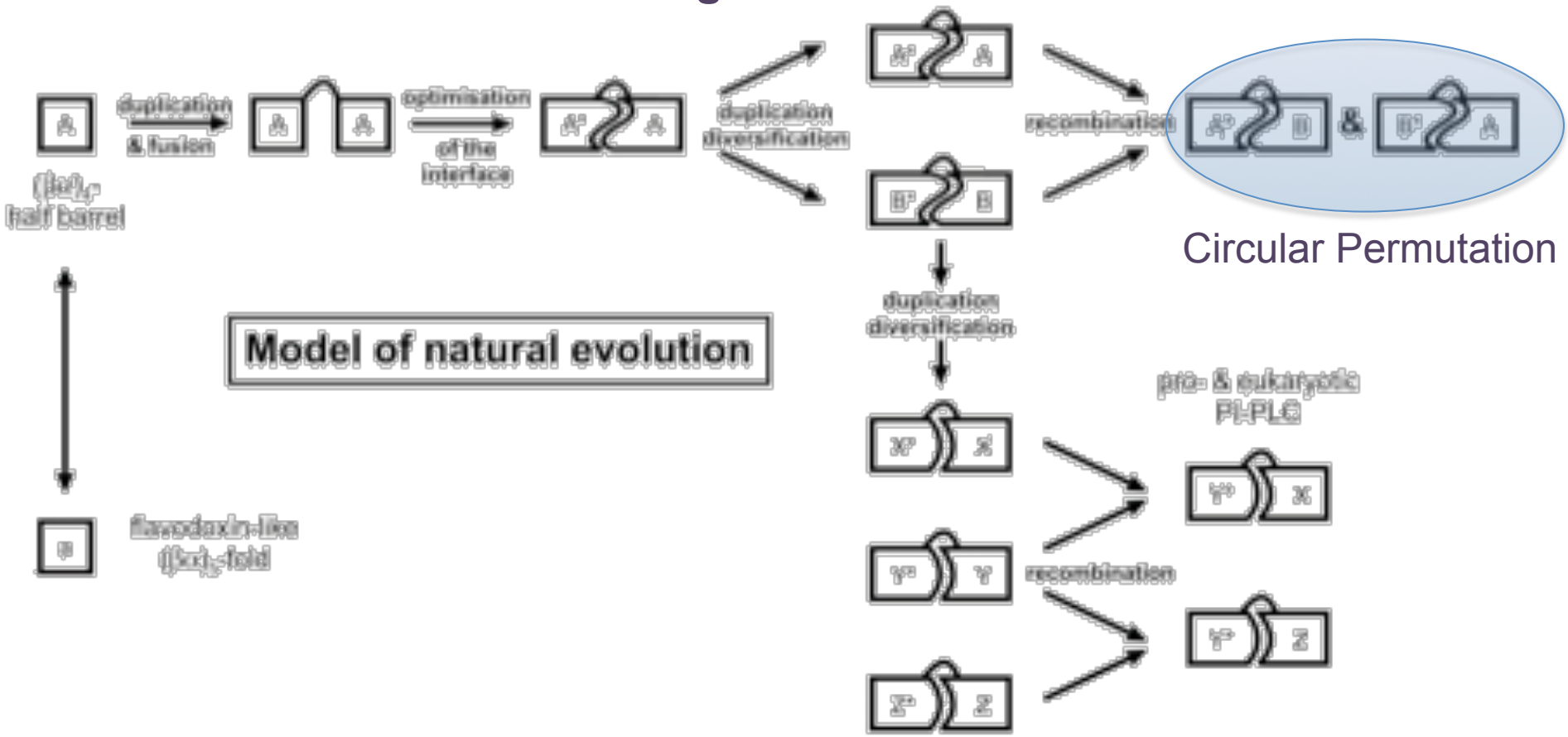
3. Soluble and globular proteins

6. Classical folds

TIM Barrel Evolution

Circular Permutation

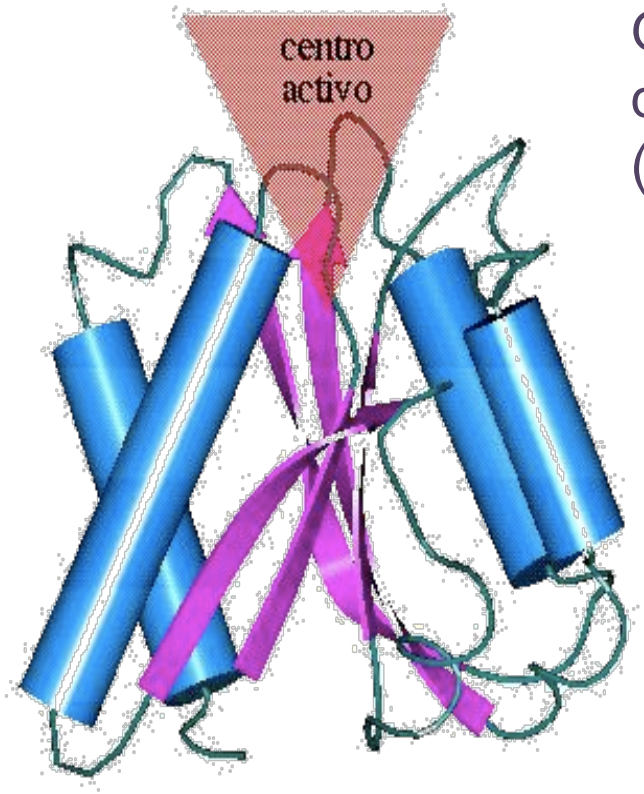
- Circular permutations can be detected when the N- and C-termini are near
- Similar structures are found but the alignment in the sequence is shifted.
- Example: between proteins of the super families **FAD-linked oxidoreductase** and **PLP-binding barrel**.



3. Soluble and globular proteins

6. Classical folds

Rossmann Fold



Rossman Fold of Flavodoxin

Often found as binding domain of mono-nucleotides (NAD, FAD, FMN, etc.).

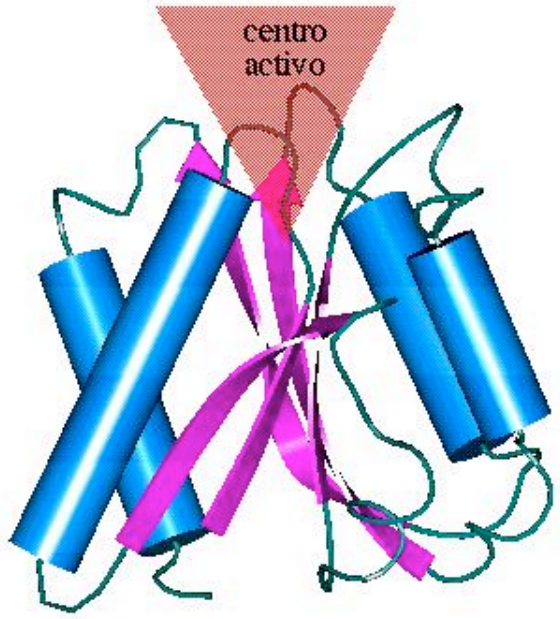
- Found in 1974 by Rossmann
- This domain appears in many proteins
- **Hypothesis**: many proteins have incorporated this domain by gene fusion, changing the activity by its interaction with mononucleotides

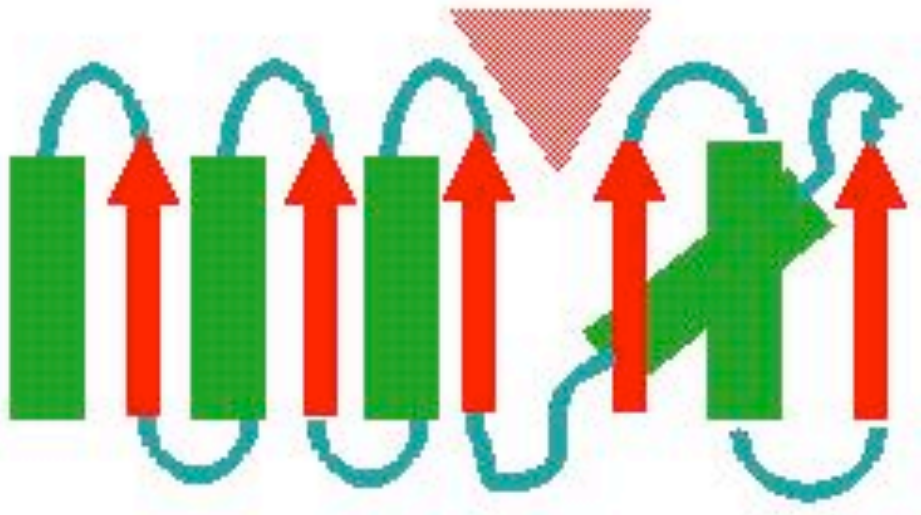
3. Soluble and globular proteins

6. Classical folds

Rossmann Fold

- The active site is located in a βα motif of the type NADP/FAD binding loop
- The location of the loop was often found in the change of orientation of the topological diagram. This is named **topological switch point**



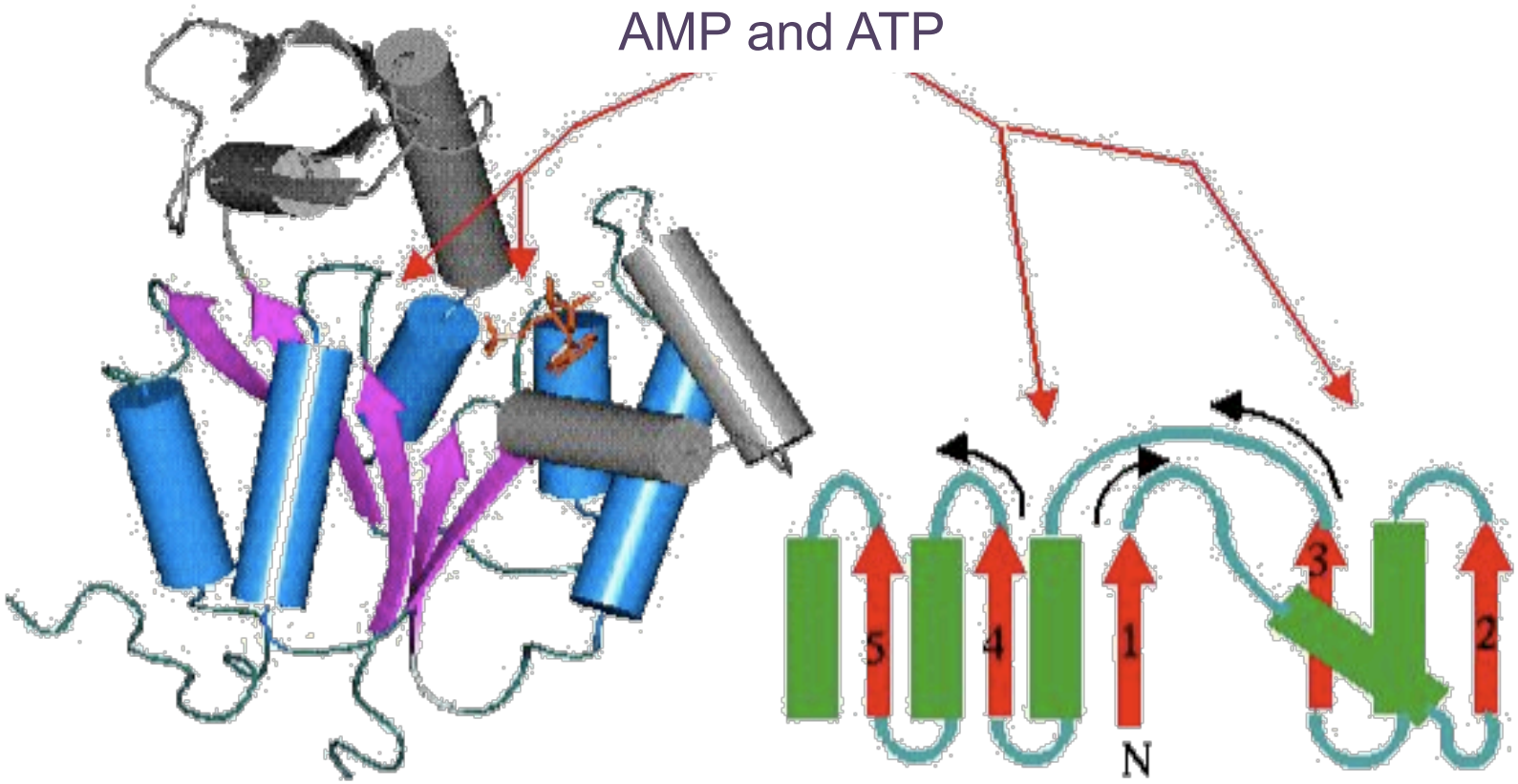


3. Soluble and globular proteins

6. Classical folds

Rossmann Fold

Active site has two binding sites for AMP and ATP

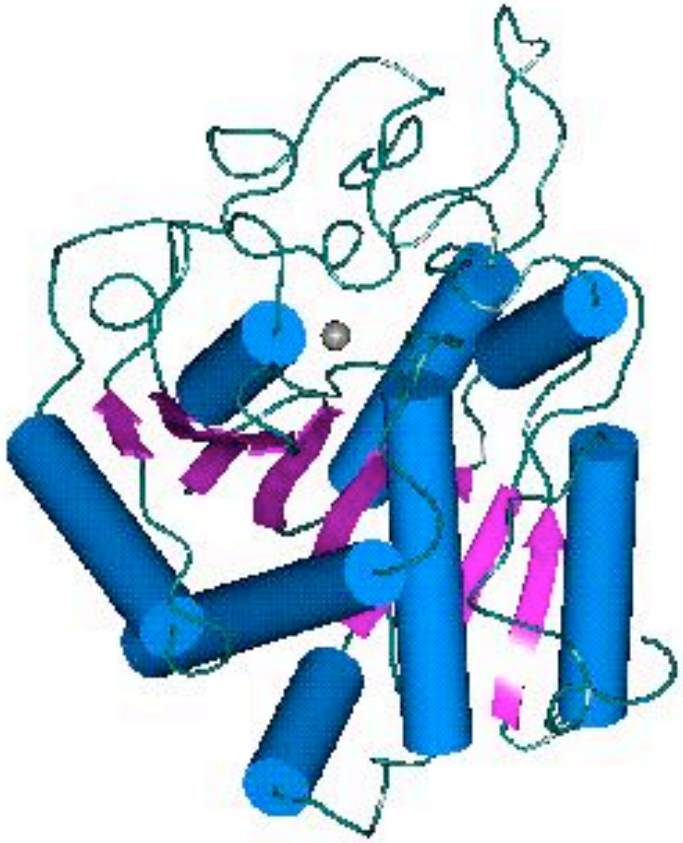


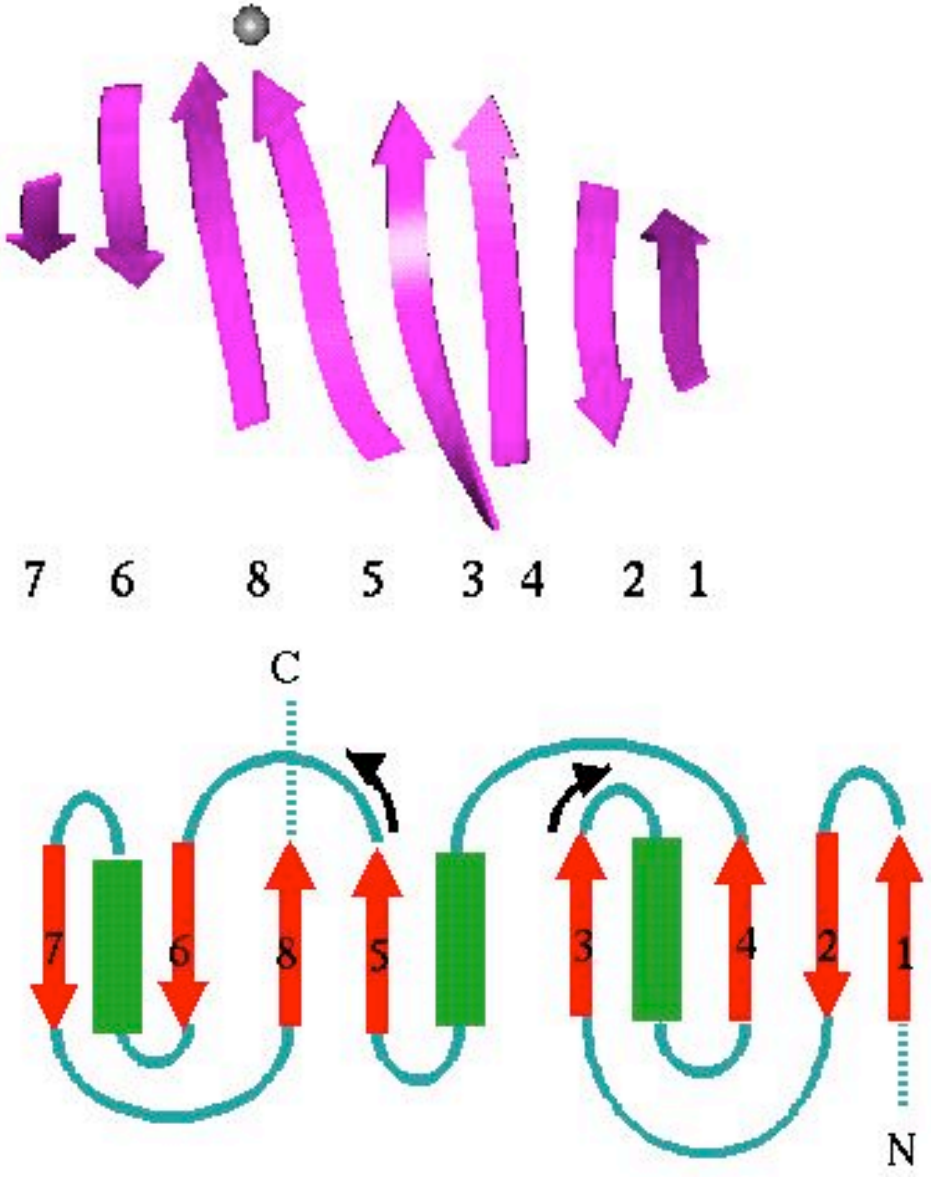
Adenilate Kinase

3. Soluble and globular proteins

6. Classical folds

Rossmann Fold



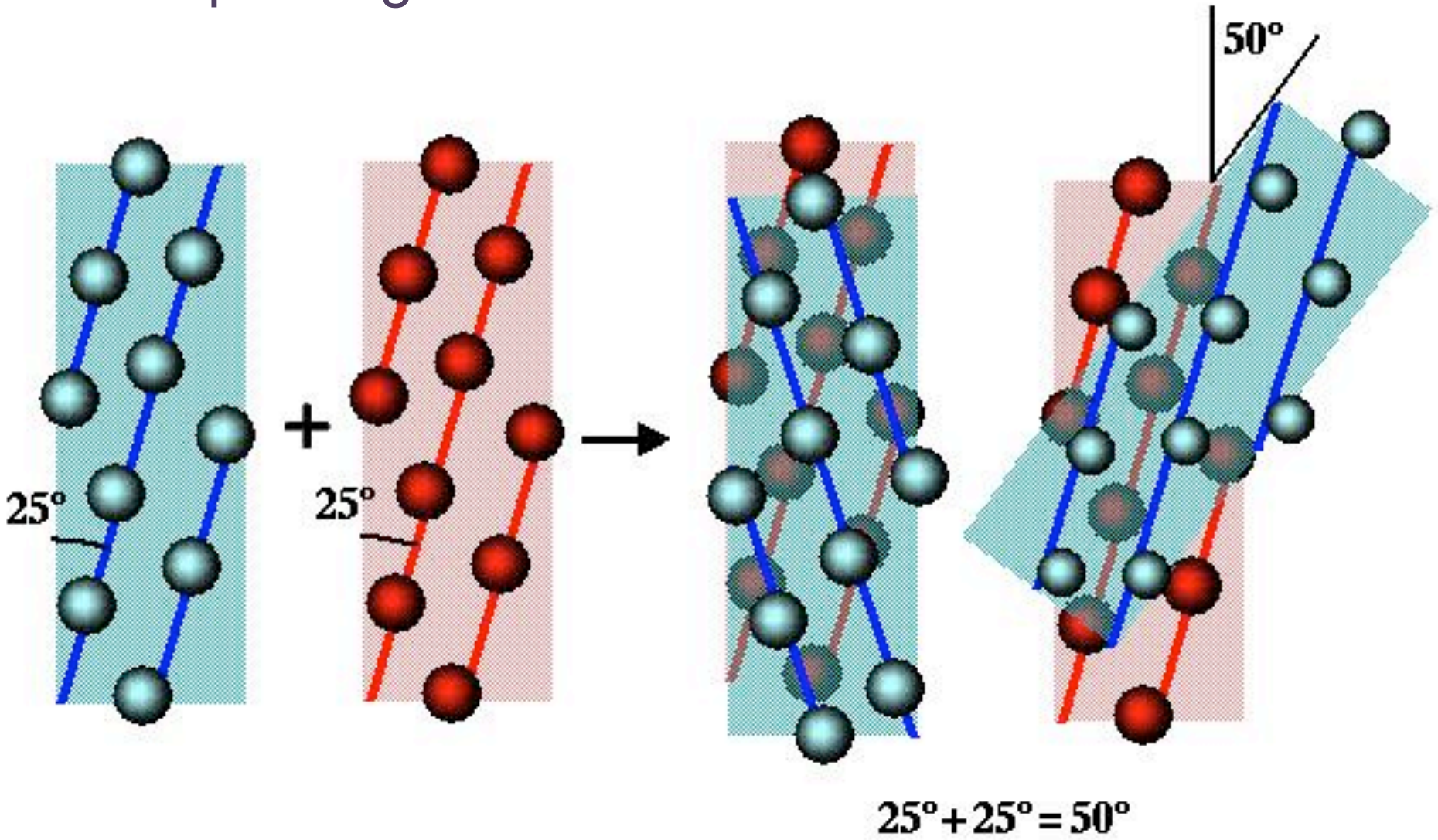


Carboxypeptidase

3. Soluble and globular proteins

7. All α

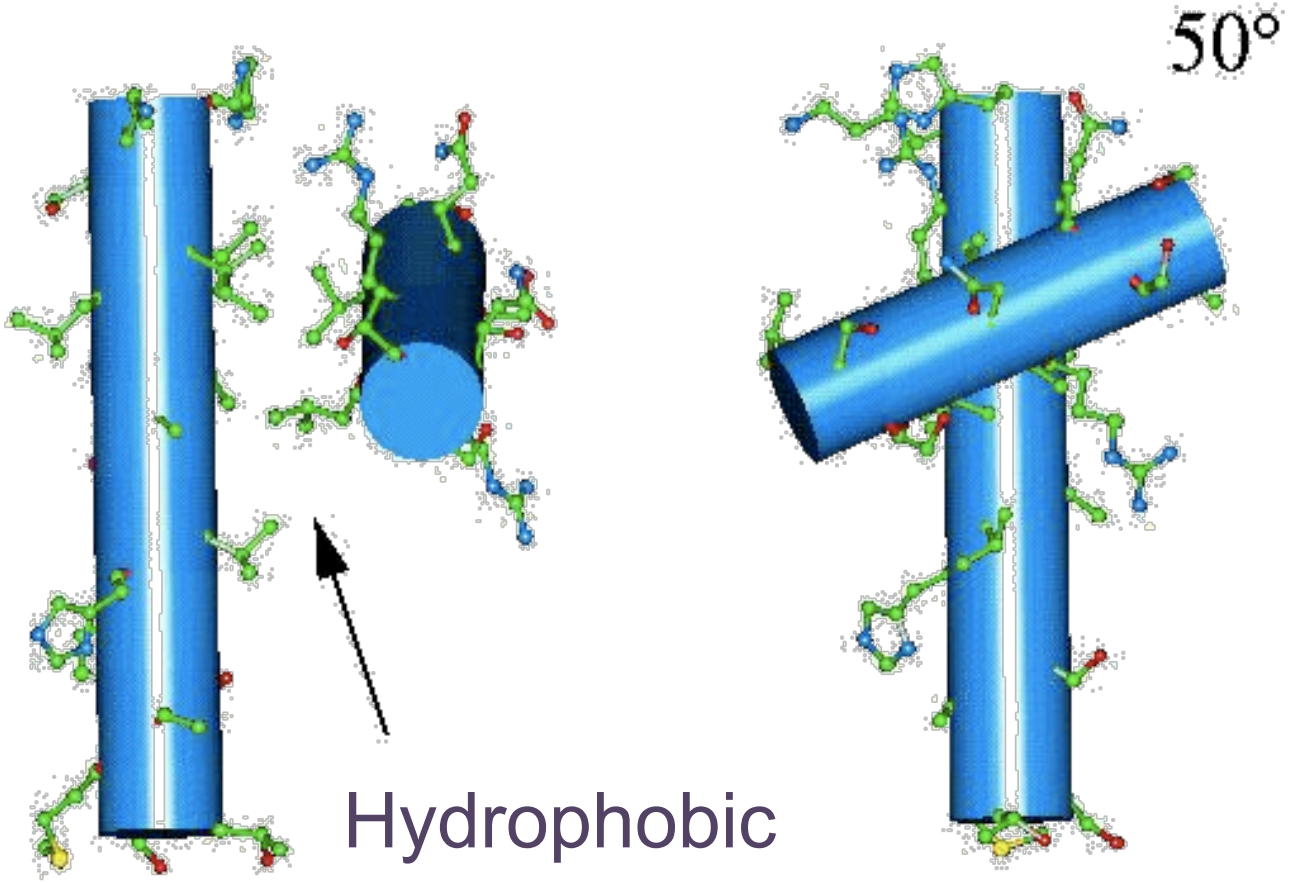
α-helix packing of two helices



3. Soluble and globular proteins

7. All α

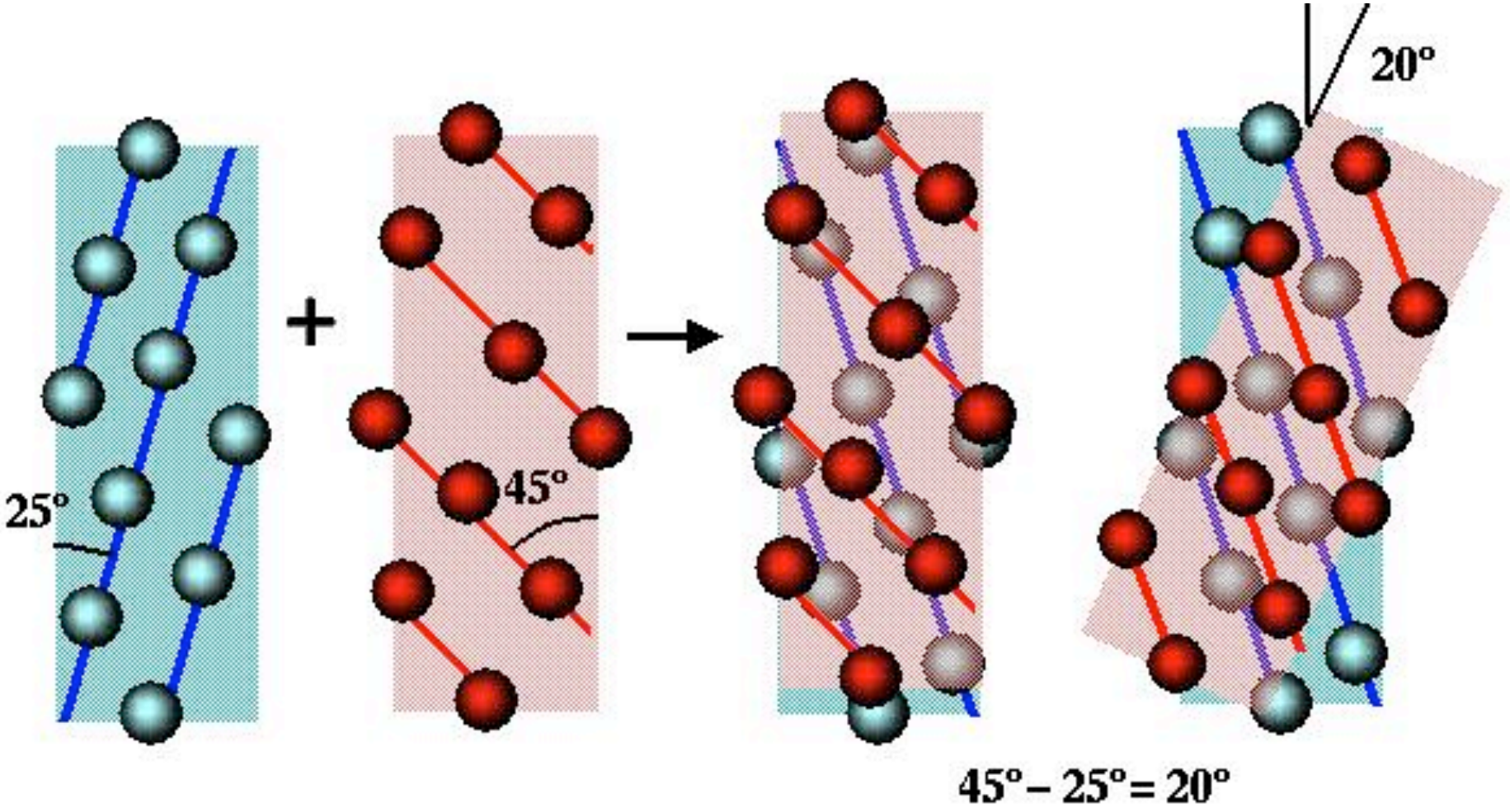
α-helix packing of two helices



3. Soluble and globular proteins

7. All α

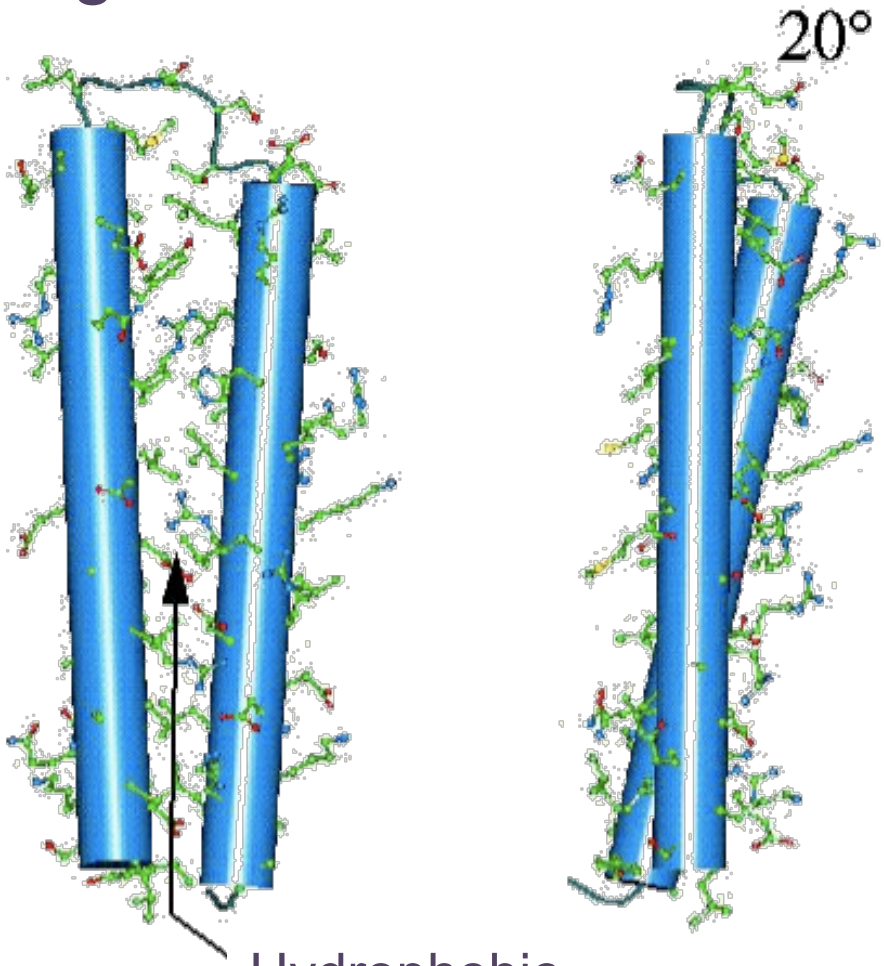
α-helix packing of two helices



3. Soluble and globular proteins

7. All α

α-helix packing of two helices



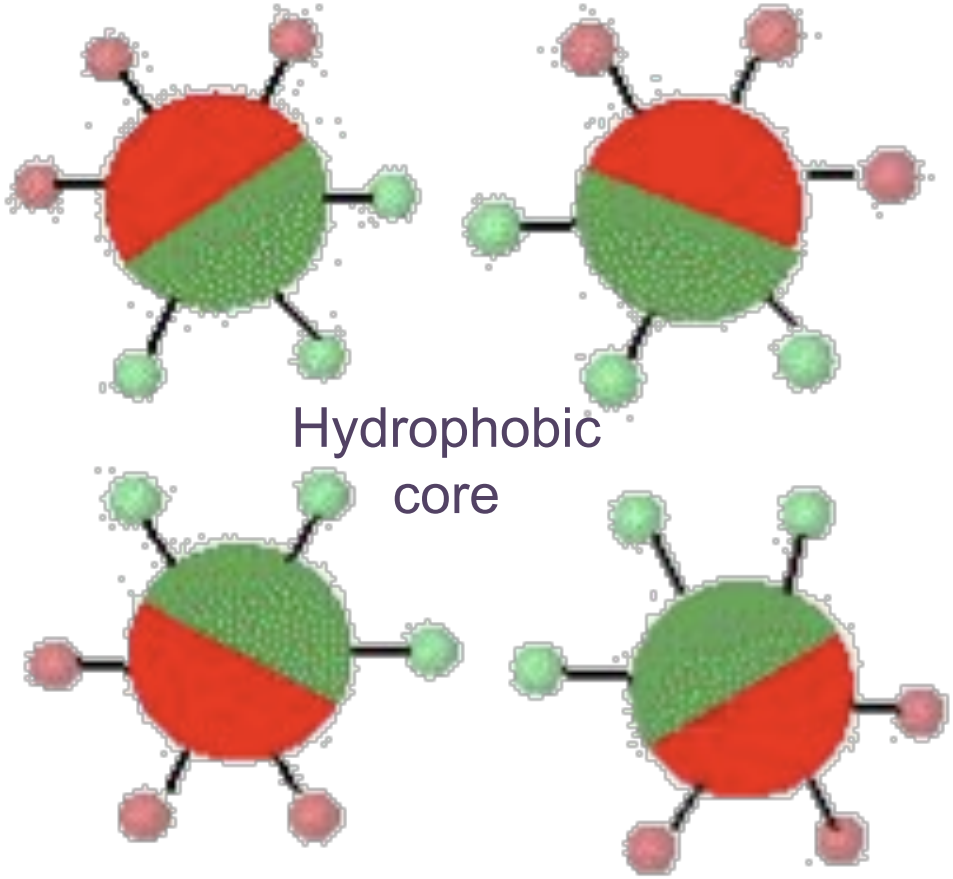
3. Soluble and globular proteins

7. All α

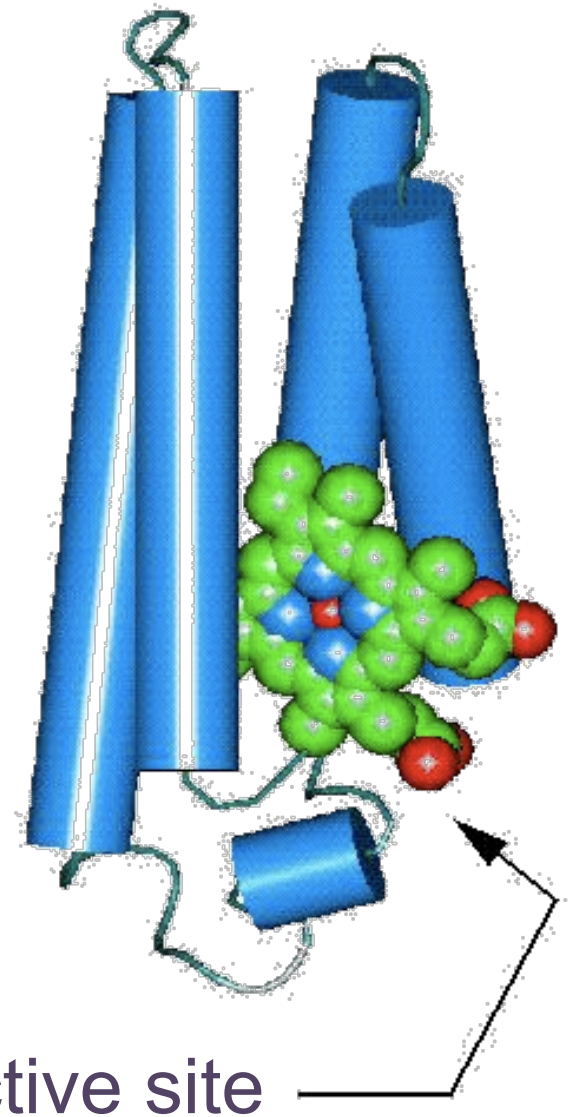
4 helix bundle

Polar residues

Non-polar residues



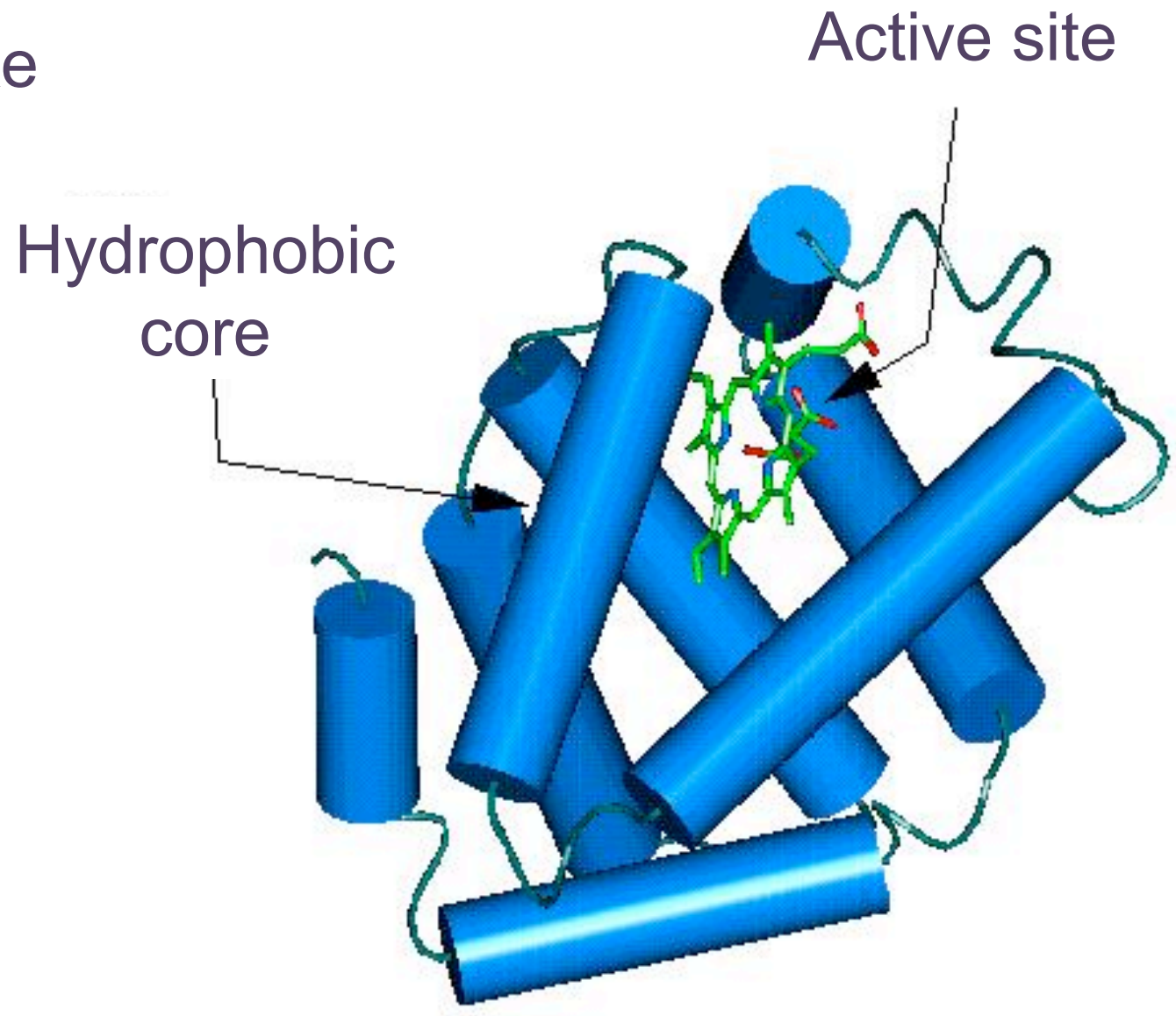
Cytochrome b_{562}



3. Soluble and globular proteins

7. All α

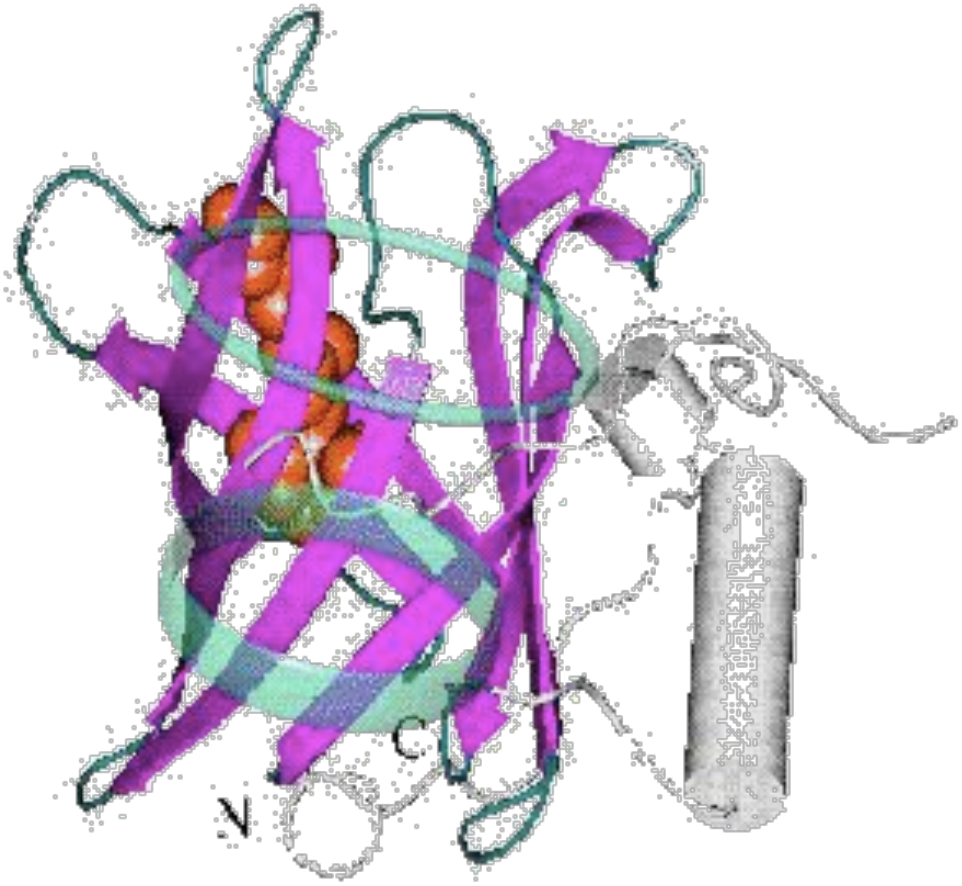
Globin-like



3. Soluble and globular proteins

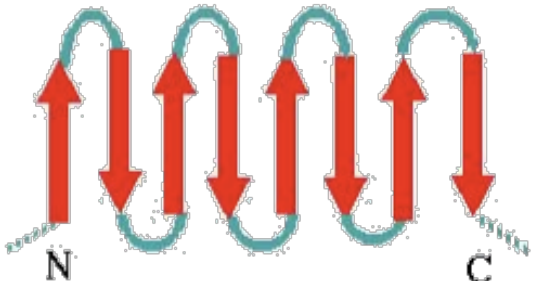
8. All β

Up & Down β−barrel

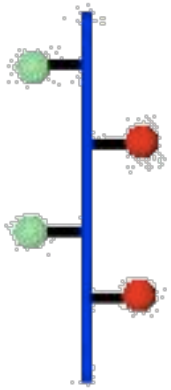


Retinol binding protein is a carrier of retinol (hydrophobic)

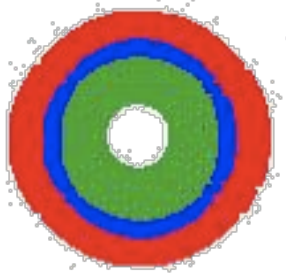
Topologic diagram

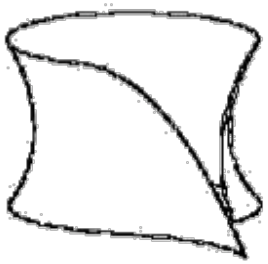


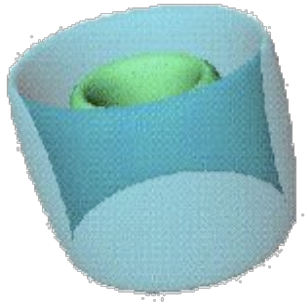
β-meanders are the main super-secondary structure



Hydrophobic core





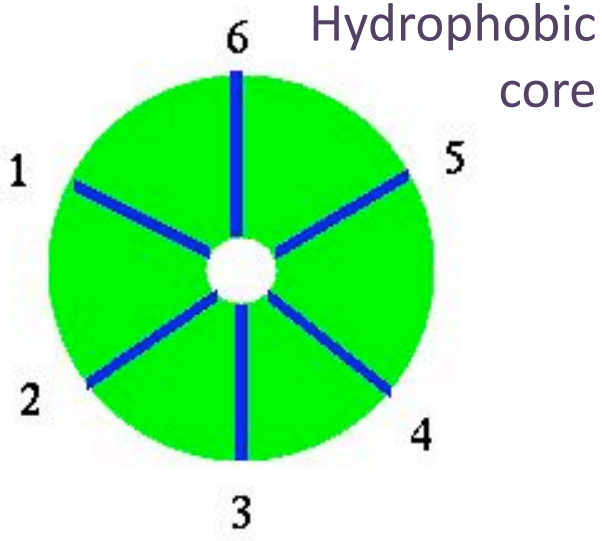


3. Soluble and globular proteins

8. All β

β−propeller (super barrel)

formed by N β-meanders placed as blades



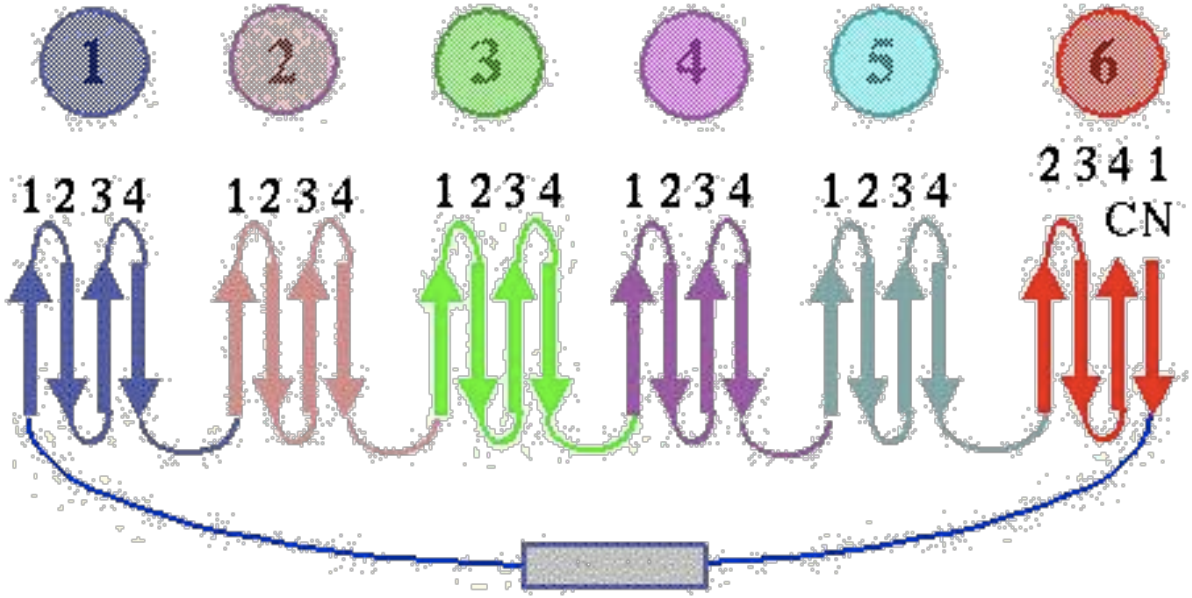
Hydrophobic core

3. Soluble and globular proteins

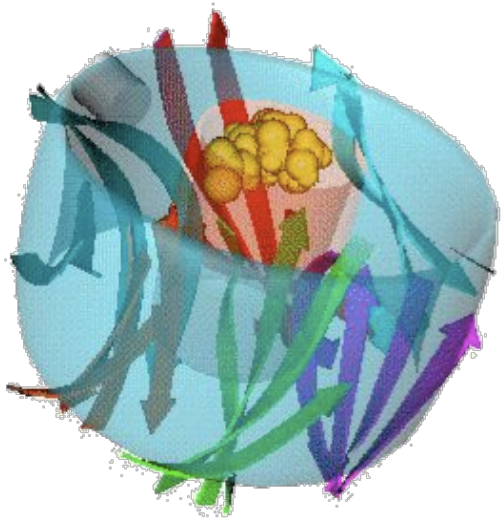
8. All β

β−propeller (super barrel)

Neuraminidase is a 6 β−meander β−propeller



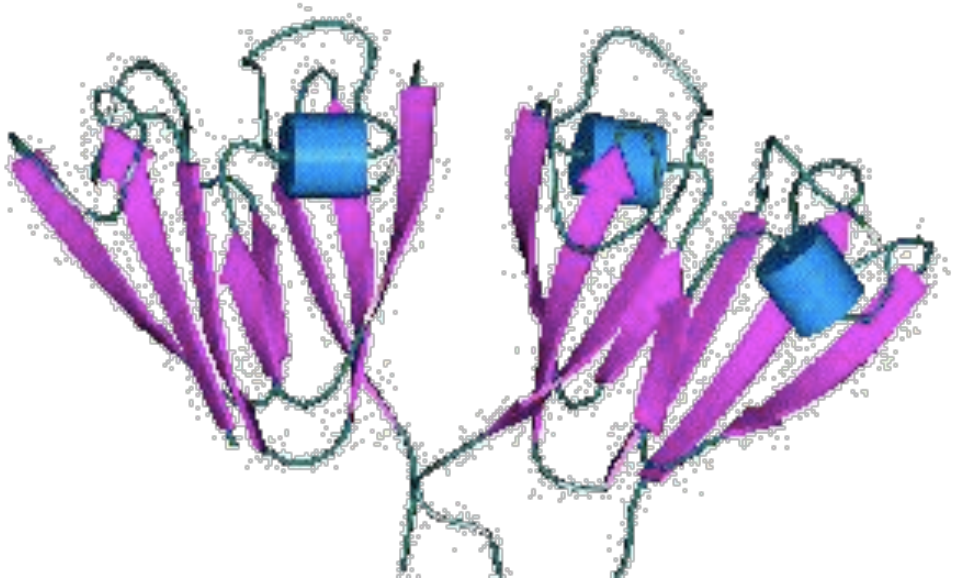
Active site



3. Soluble and globular proteins

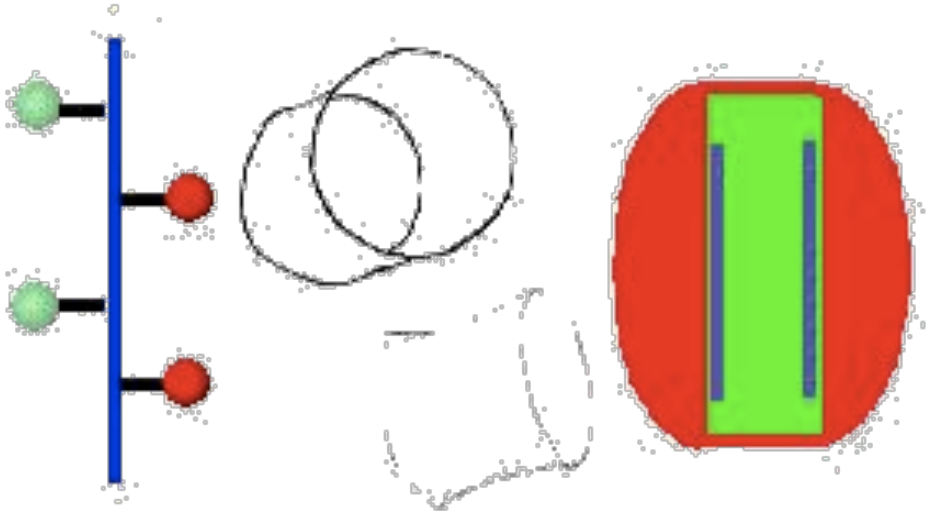
8. All β

Greek key β-sandwich



γ-cristallin

Hydrophobic core

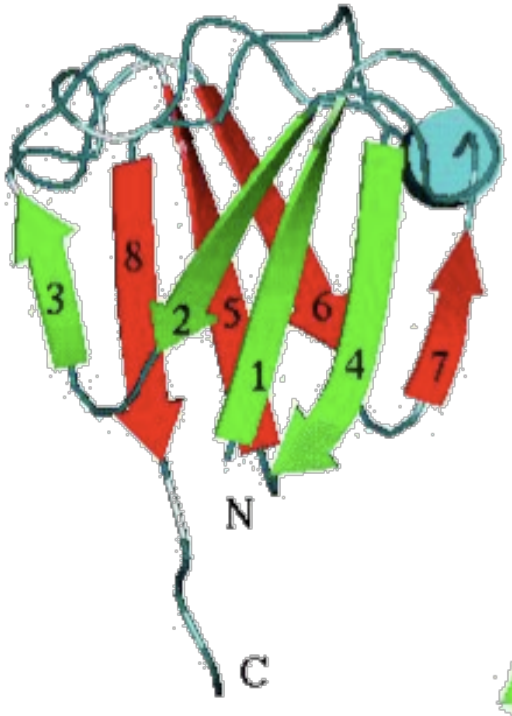


3. Soluble and globular proteins

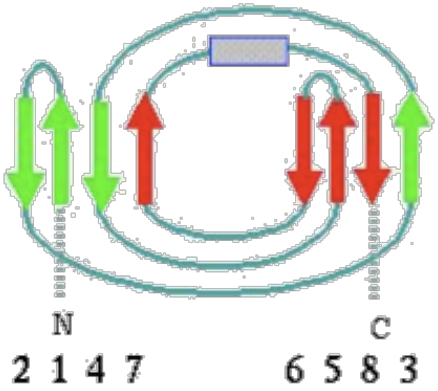
8. All β

Greek key β-sandwich

γ-crystallin domain

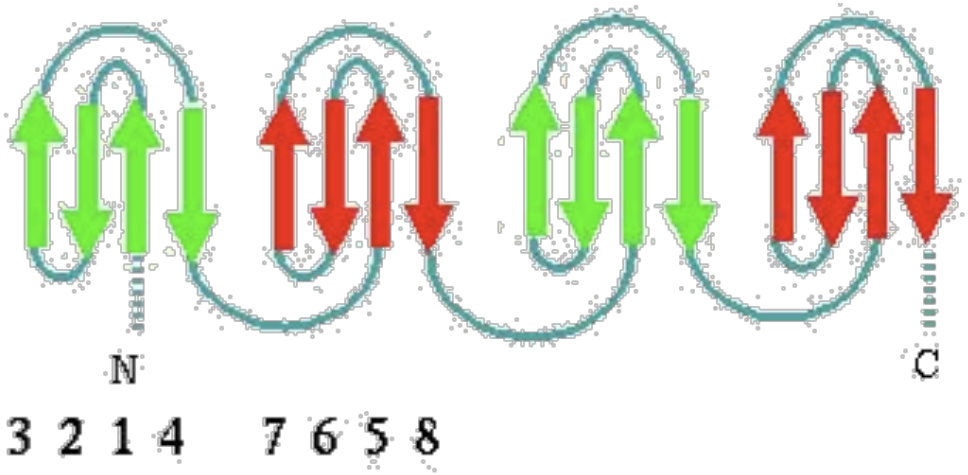


Topologic diagram



Topologic diagram rearranged

Domain 1 Domain 2

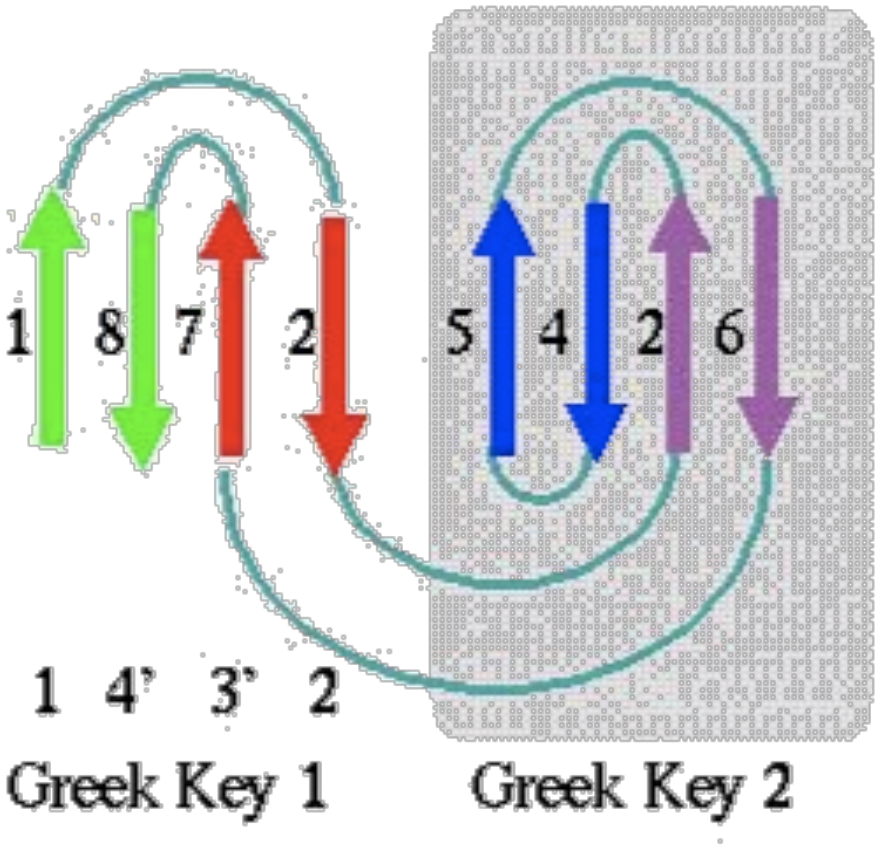


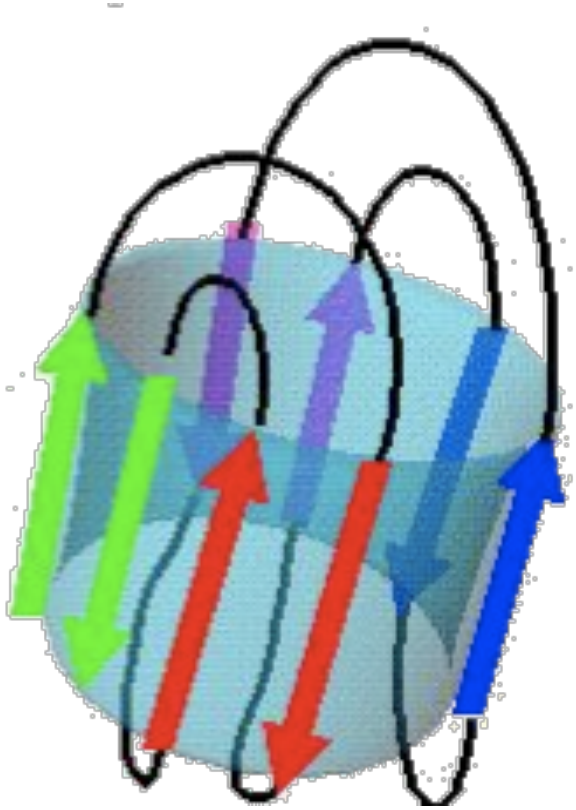
Hypothesis:
It was shown that the rearrangement coincides with the exons, then it was hypothesized that domains corresponds to exons.
Up to date the hypothesis is wrong

3. Soluble and globular proteins

8. All β

Greek key Jelly-Roll



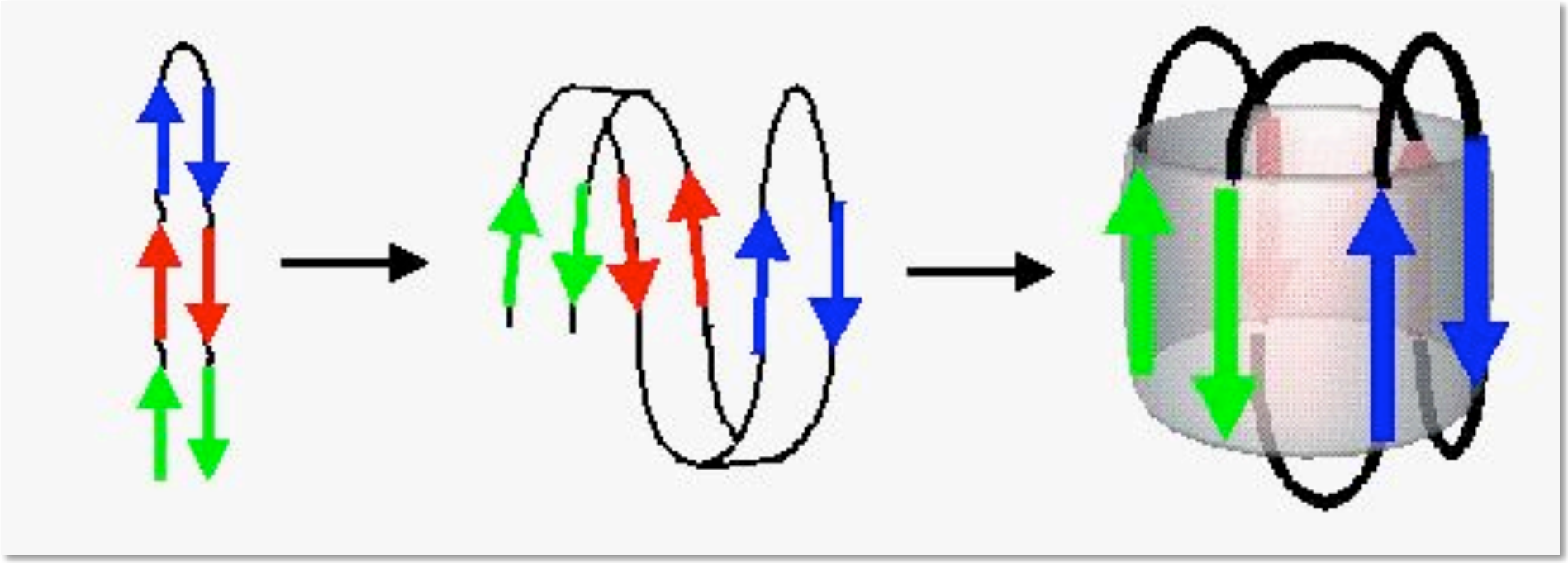


3. Soluble and globular proteins

8. All β

Greek key Jelly-Roll

Proposed mechanism of folding



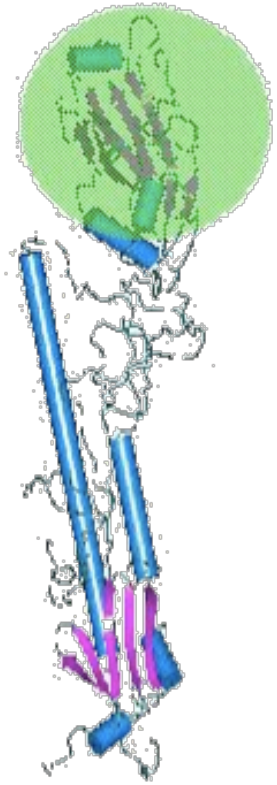
3. Soluble and globular proteins

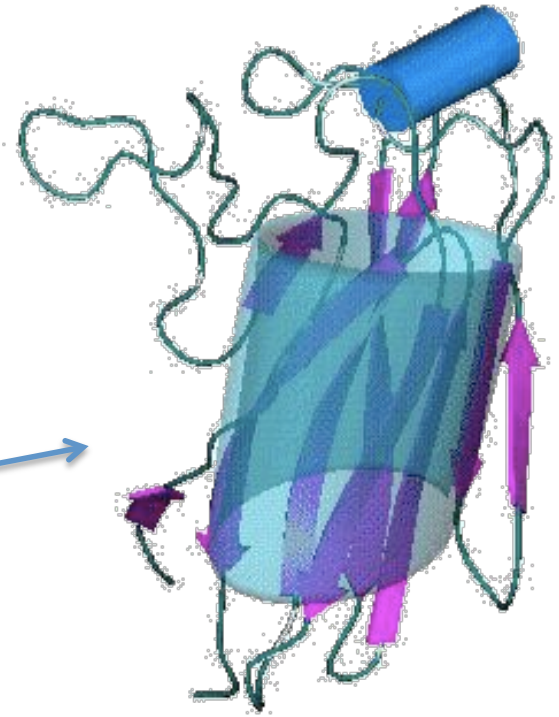
8. All β

Greek key Jelly-Roll

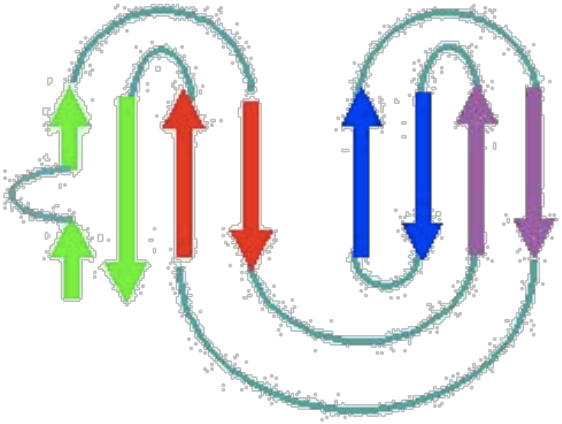
Hemaglutinin

Trimer of the capside of the virus of flu. Membrane fusion





Jelly-roll barrel

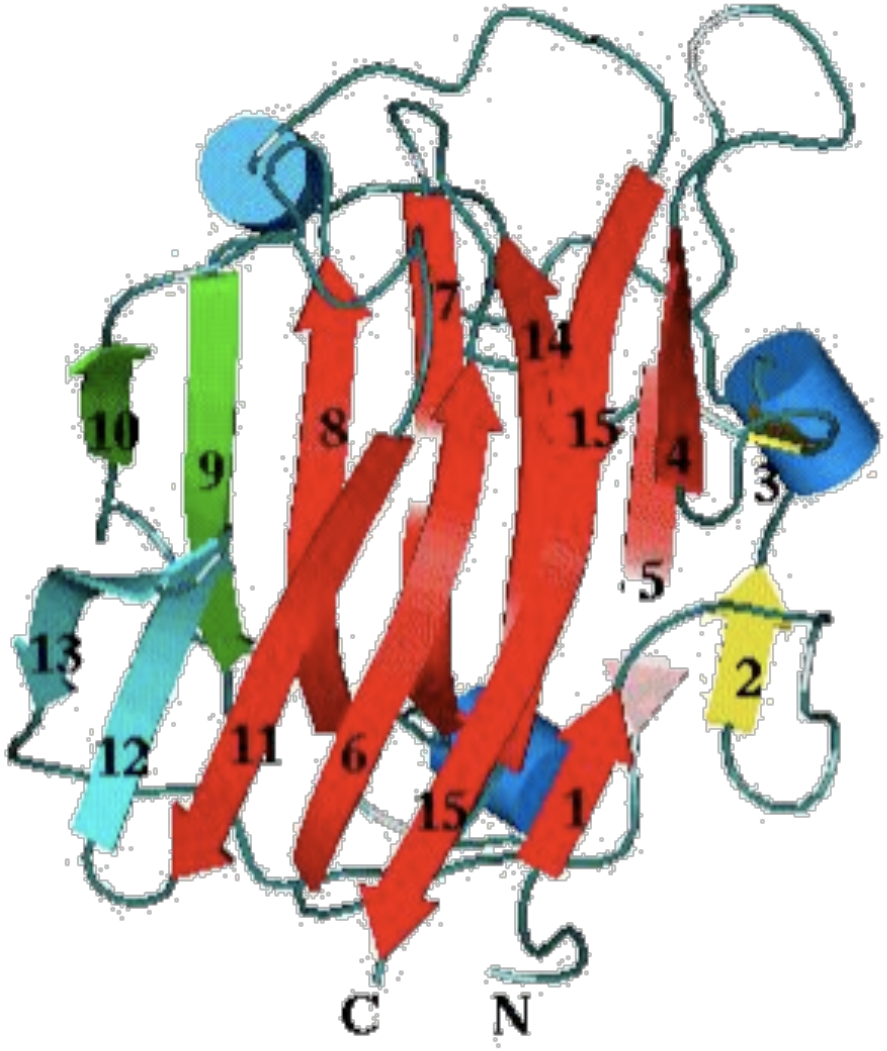


Topologic diagram

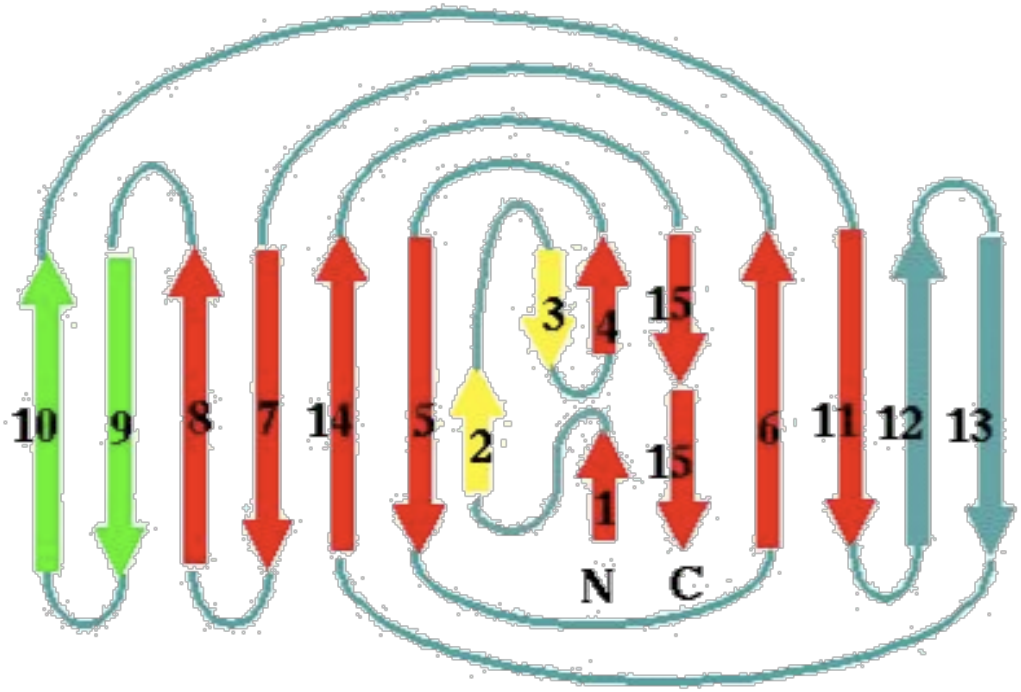
3. Soluble and globular proteins

8. All β

Greek key Jelly-Roll



Glucanase

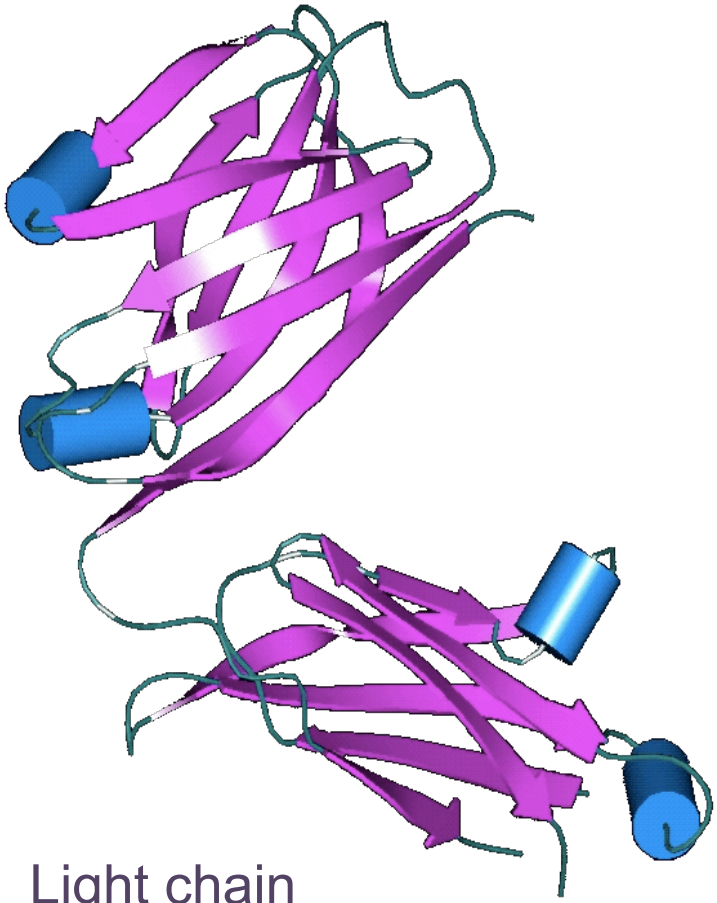


Topologic diagram

3. Soluble and globular proteins

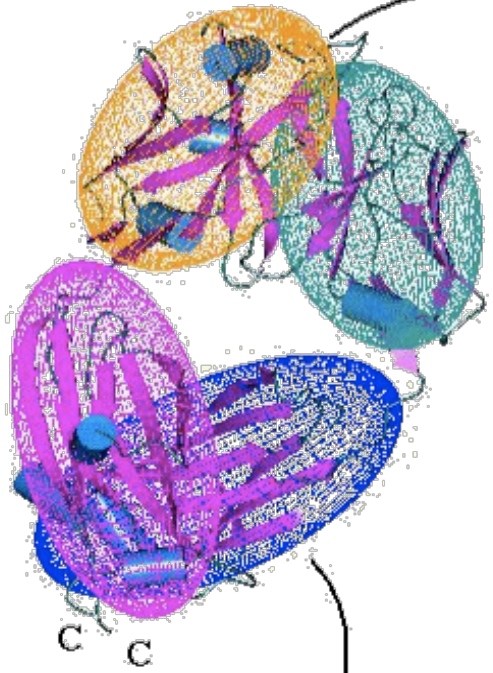
8. All β

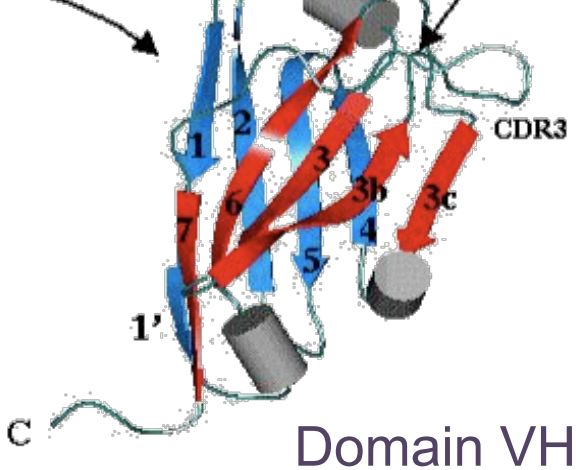
β-sandwich
Immunoglobulin-like



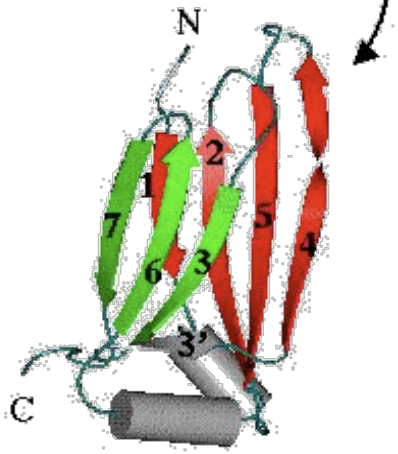
Light chain

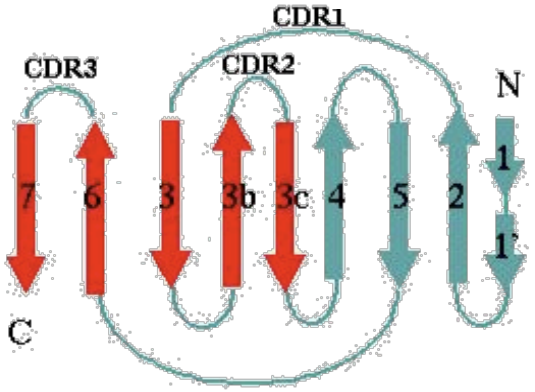
Fragment Fab

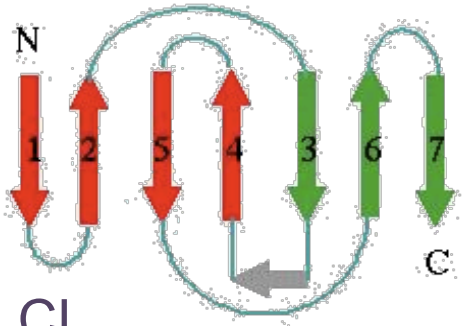




Domain VH





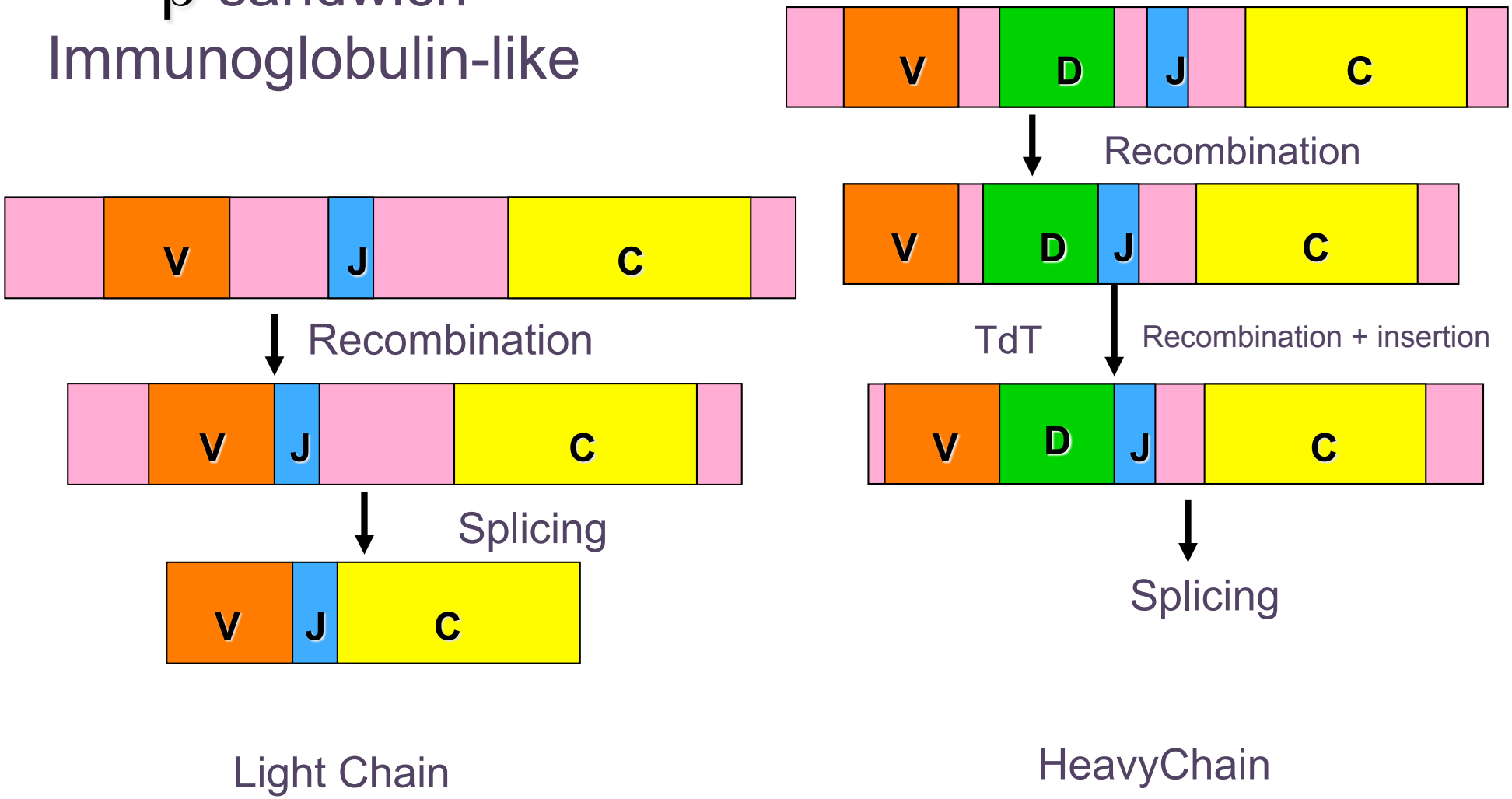


Domain CL

3. Soluble and globular proteins

8. All β

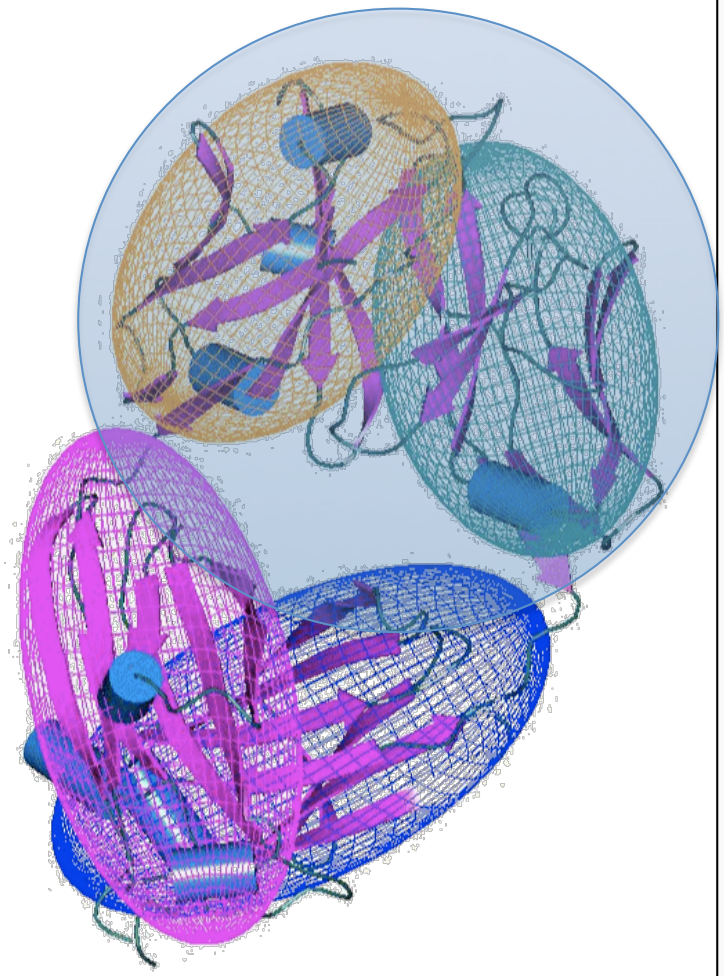
β-sandwich
Immunoglobulin-like



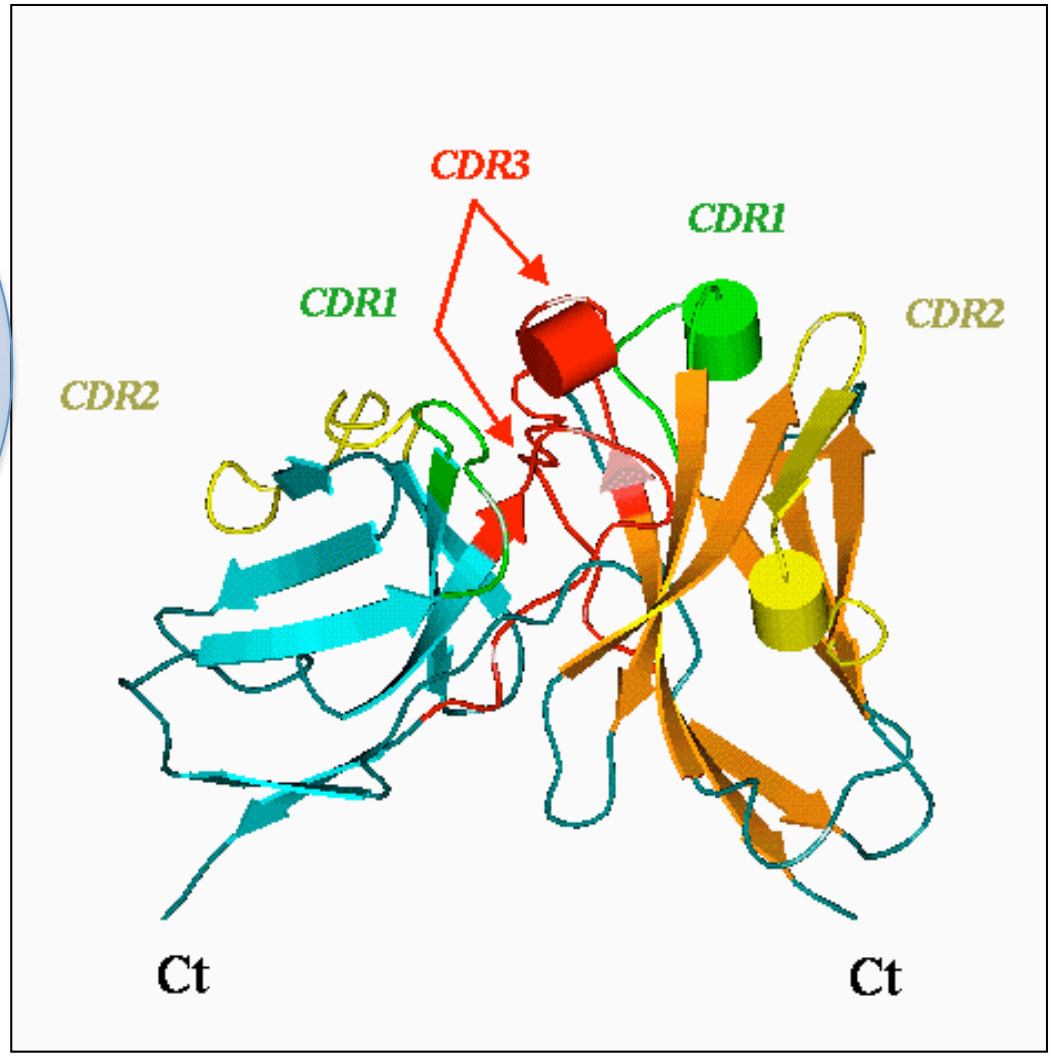
3. Soluble and globular proteins

8. All β

β-sandwich
Immunoglobulin-like



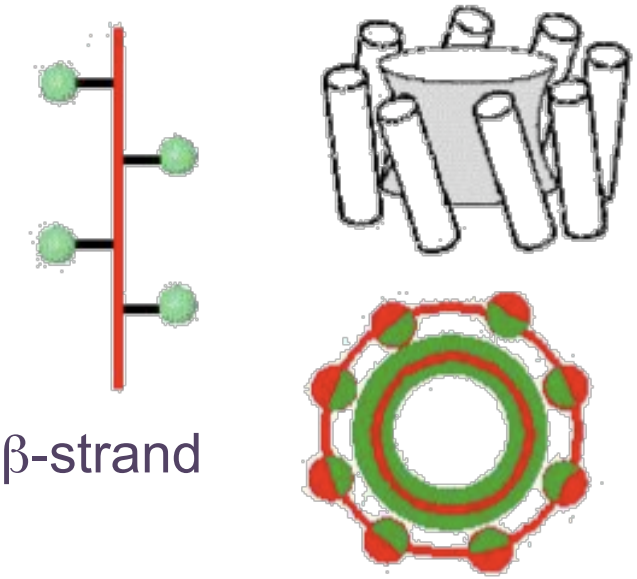
CDR loops



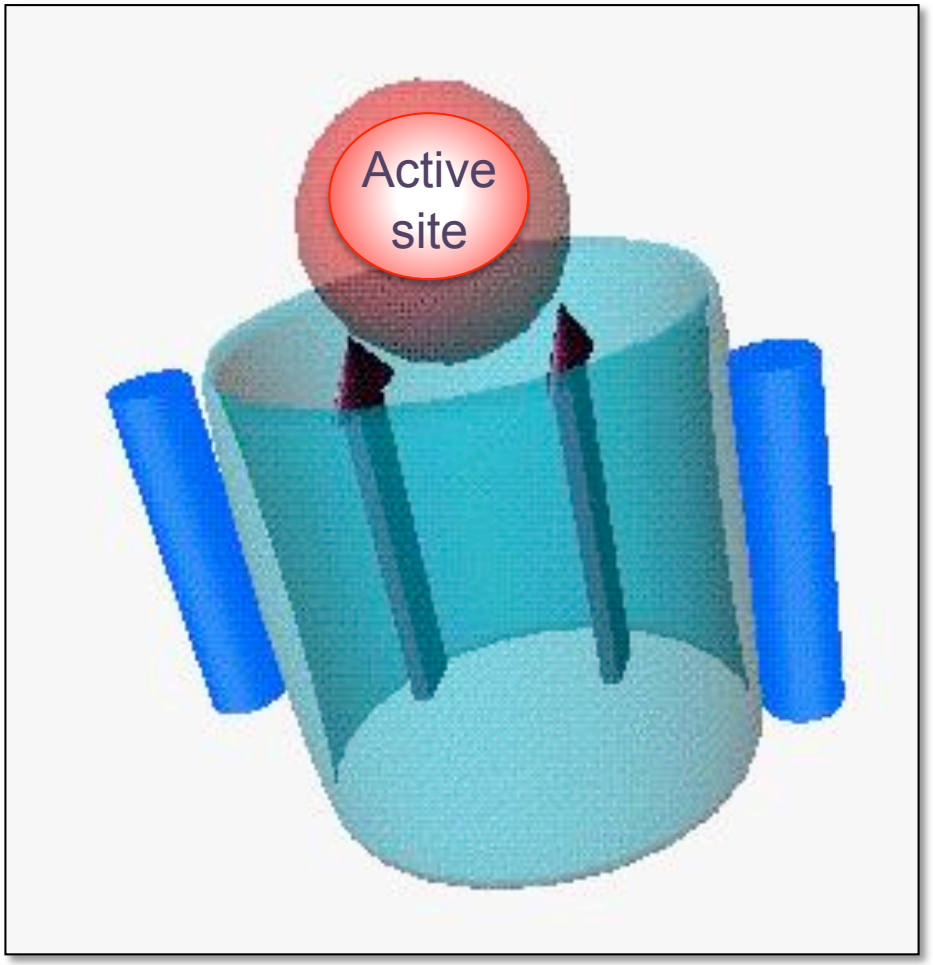
3. Soluble and globular proteins

9. α/β

TIM Barrel



β-strand

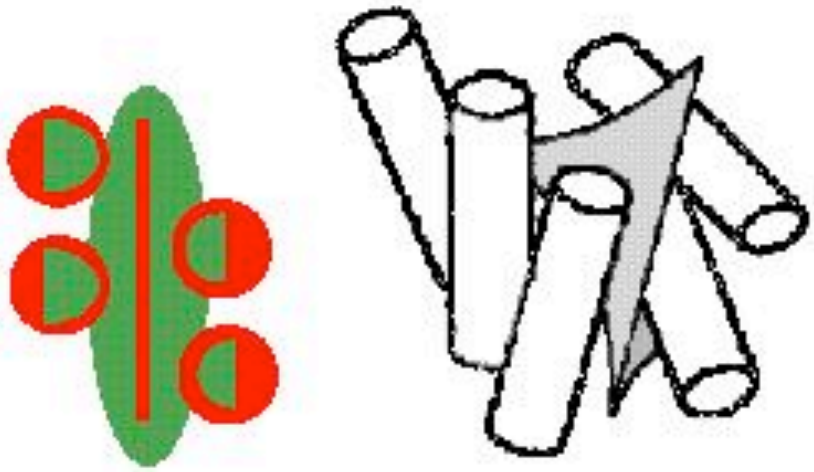


Highly stable structure due to the double hydrophobic core

3. Soluble and globular proteins

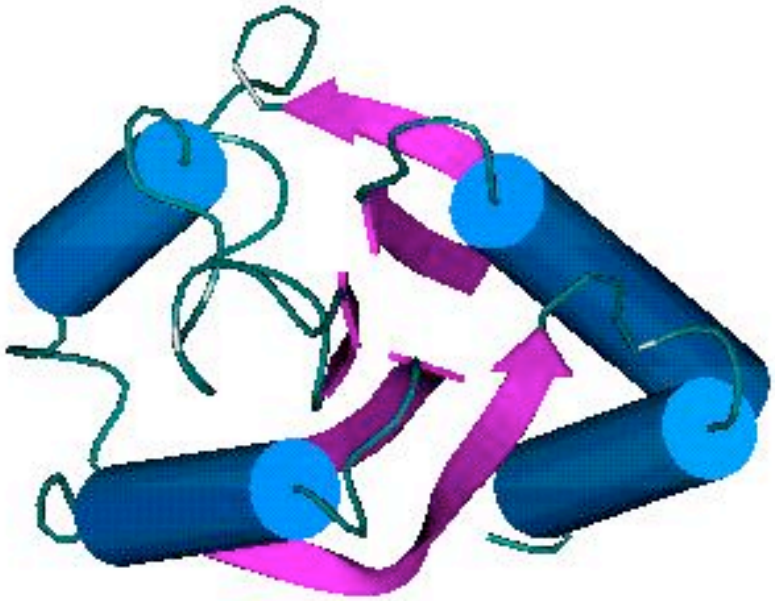
9. α/β

Rossmann Fold



Open sheet

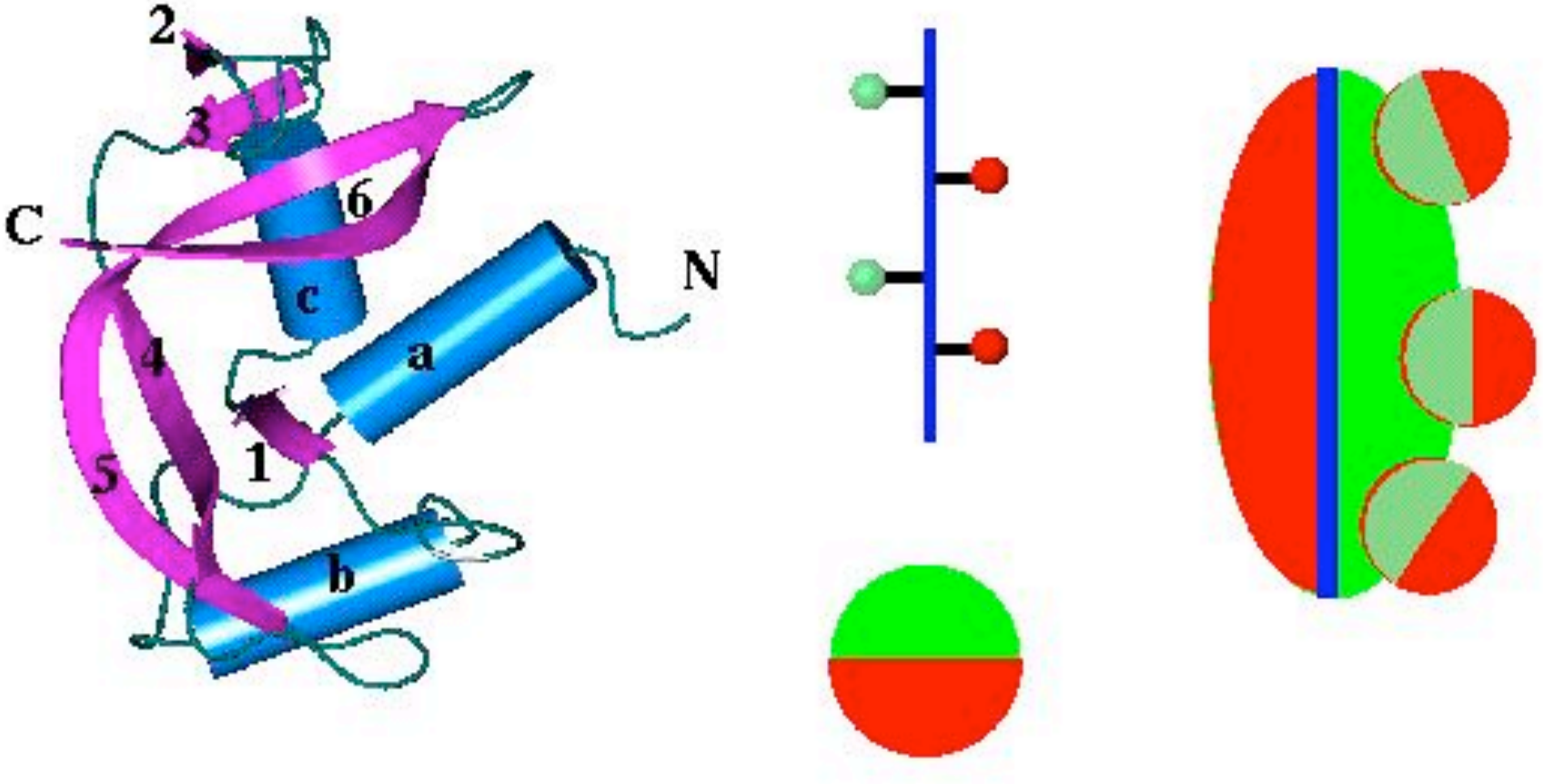
Flavodoxin



3. Soluble and globular proteins

10. α+β

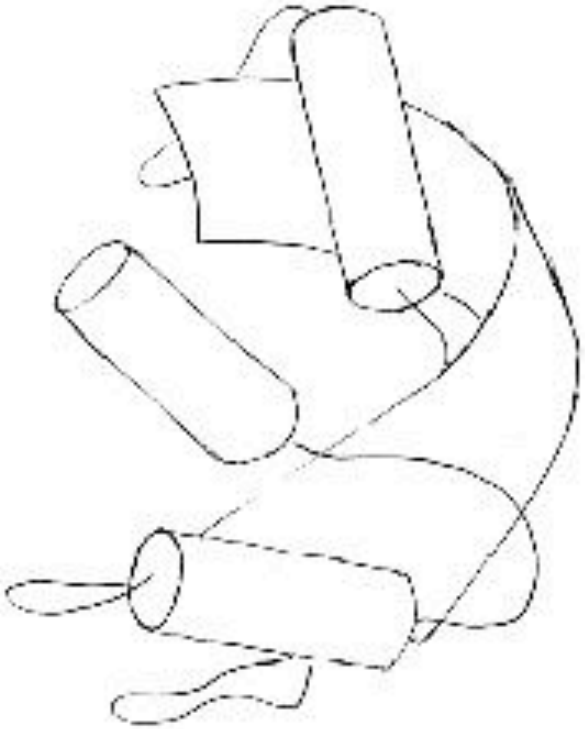
Ribonuclease



3. Soluble and globular proteins

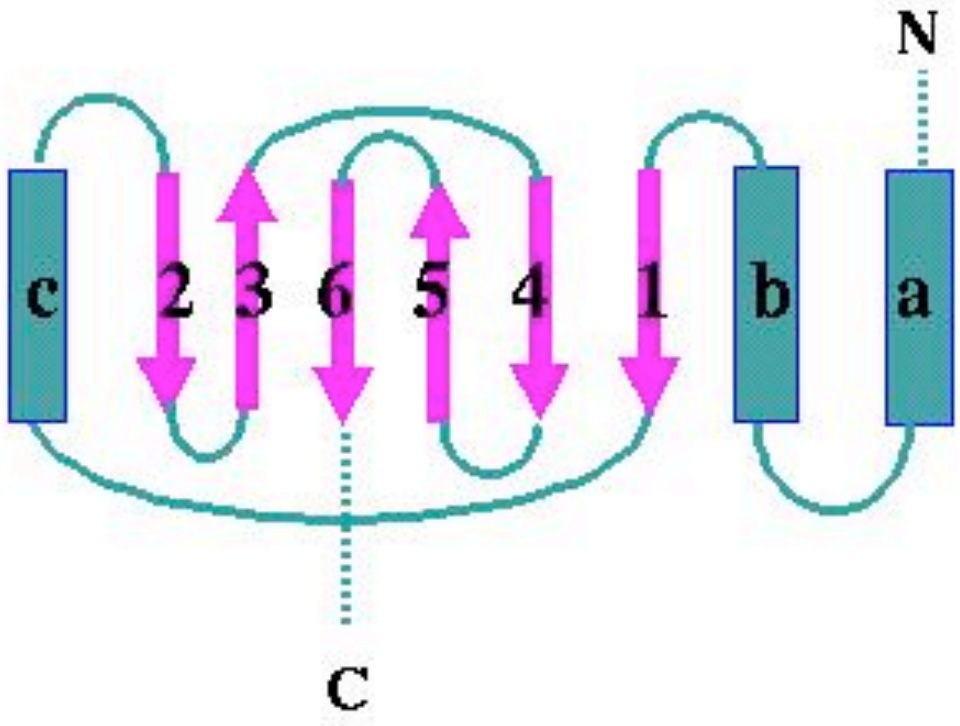
10. α+β

Ribonuclease



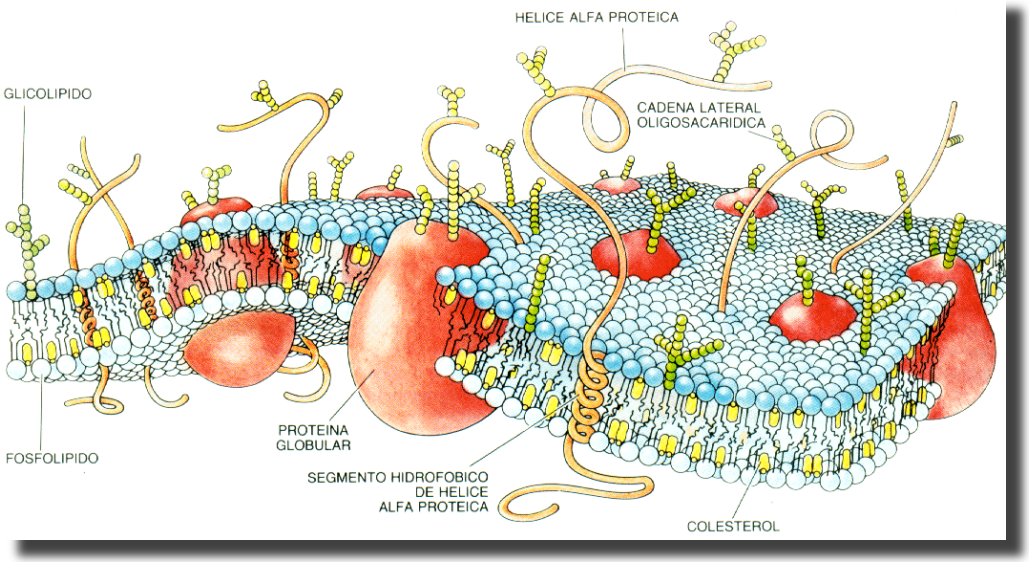
RNase A-like fold

α+β class segregates α and β regular secondary structures in 3D and in the topologic diagram



4. Globular membrane proteins

1. Definition

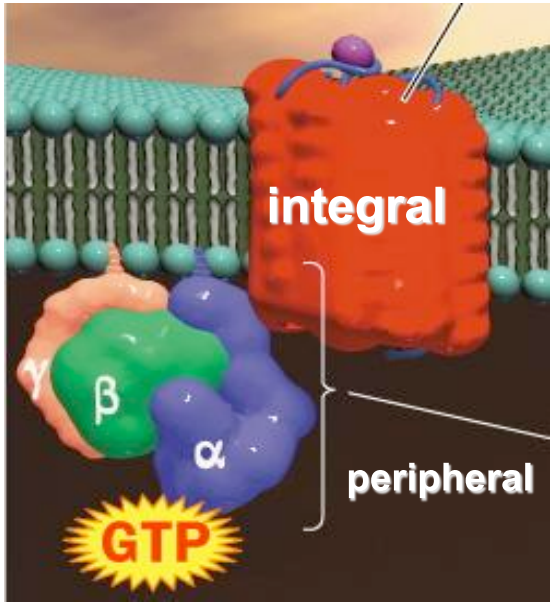


- Membrane proteins are protons bound to the membrane
- Membrane Proteins can be of two types: peripheral and integral
- Integral membrane proteins are inserted in the membrane, where the main bulk of the domain is buried inside the membrane
- Peripheral membrane proteins are only linked by few residues to the membrane
- The residues of the integral proteins are mostly non-polar, changing the rules of hydrophobicity patterns described for soluble domains.

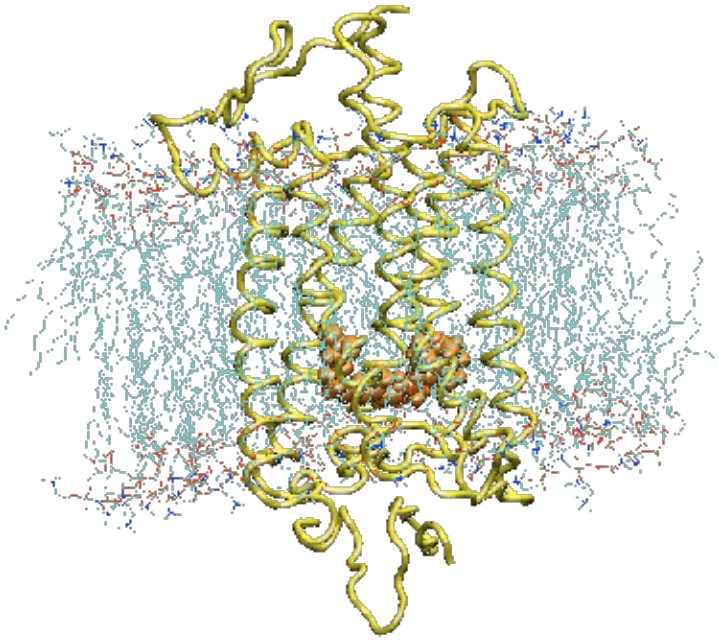
4. Globular membrane proteins

2. Classification

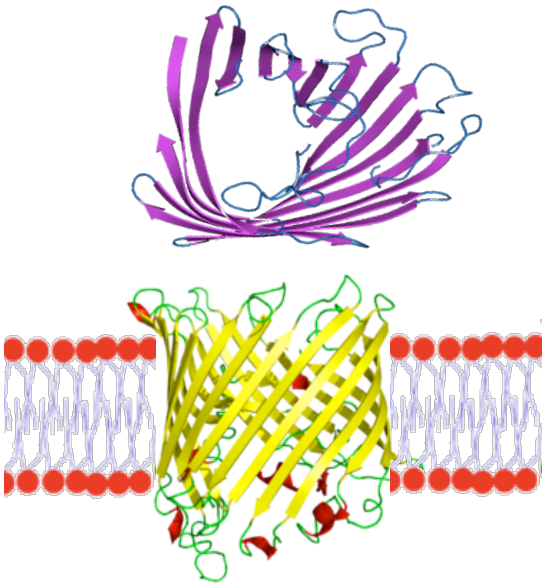
1. Integral



Two types of integral proteins:
α-helix transmembrane
β-sheet transmembrane



α-helix transmembrane
Rhodopsine



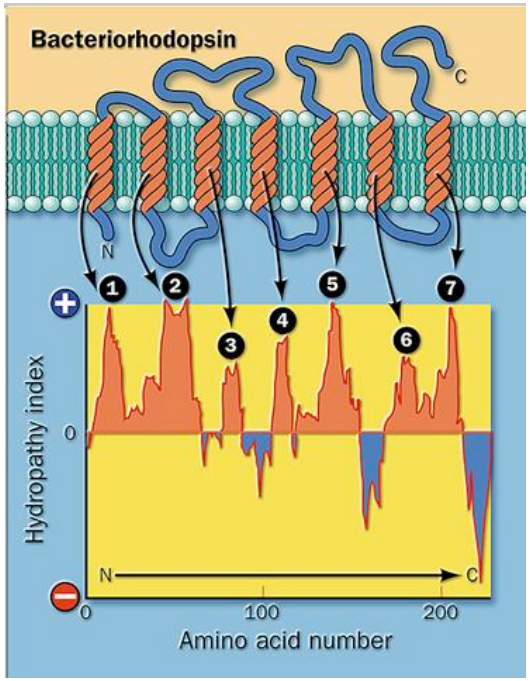
β-sheet transmembrane
Porin

4. Globular membrane proteins

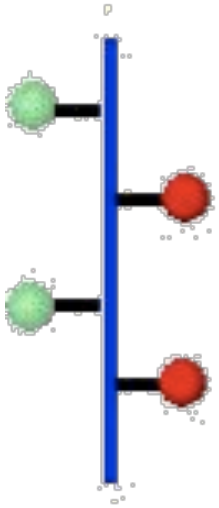
2. Classification

1. Integral

Hydrophobic properties



α-helix transmembrane
Rhodopsine



membrane

Inner channel

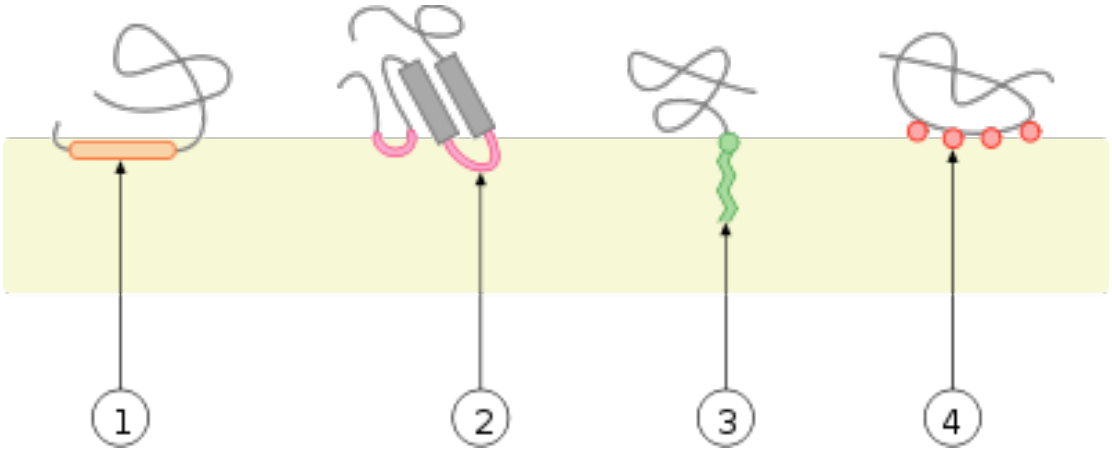
β-sheet transmembrane
Porin

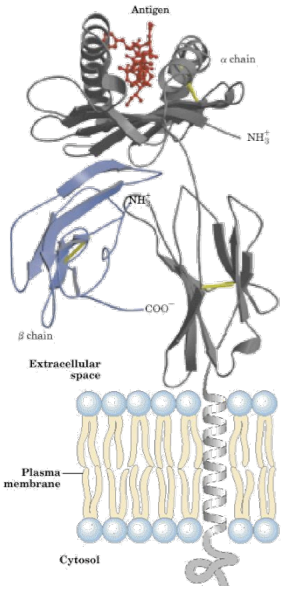
4. Globular membrane proteins

2. Classification

2. Peripheral

The main body of a peripheral membrane protein is out of the membrane. The protein is anchored by few residues to the membrane





5

Example of different types of interaction between membrane proteins and the cell membrane: 1. interaction by an amphipathic helix parallel to the membrane plane 2. interaction by a hydrophobic loop 3. interaction by a covalently bound membrane lipid (lipidation, i.e. myristilation) 4. electrostatic or ioinic interaction with membrane lipids (e.g. through a calcium ion) 5. hydrophobic helix transmembrane.

4. Globular membrane proteins

2. Classification

2. Peripheral

Some proteins have two main bodies one at each side of the membrane, an in general its function is to transfer a biochemical signal from one side to the other