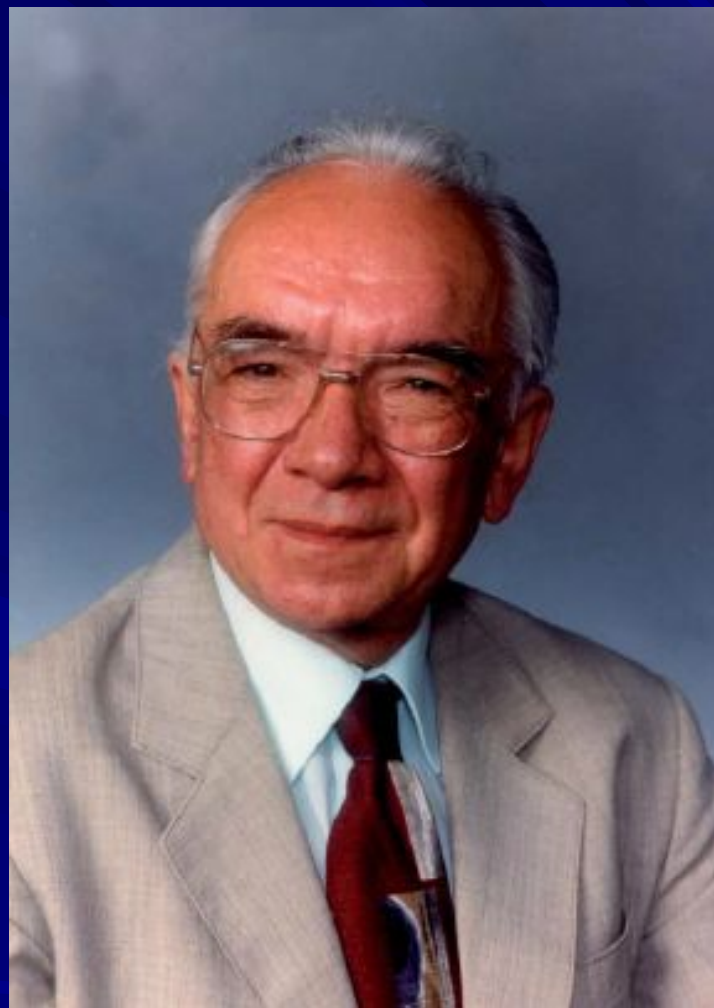


PROTEIN PHYSICS

1. Introduction & overview
2. Structure elements & elementary interactions
3. Transitions: thermodynamics & kinetics
4. Secondary structures
5. Protein structures
6. Protein denaturation & folding
7. Protein structure prediction, engineering, design
8. Proteins in action

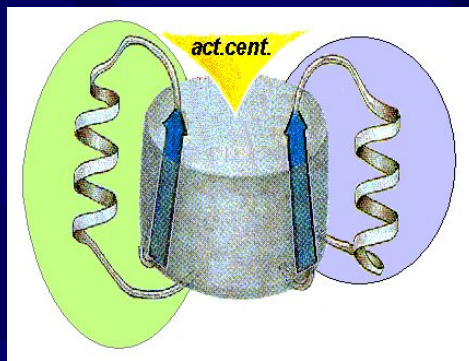


**Олег Борисович Птицын
(1929-1999)**

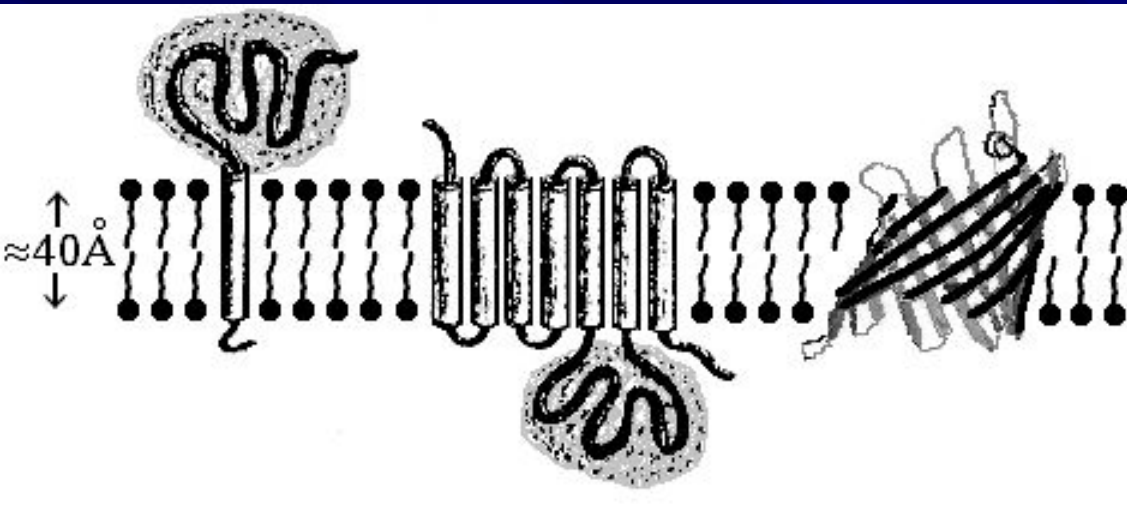
PROTEIN PHYSICS

LECTURE 1

Introduction & overview



Globular proteins



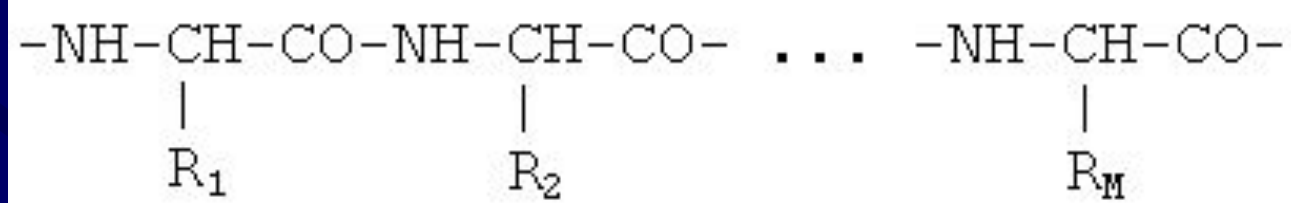
Membrane proteins



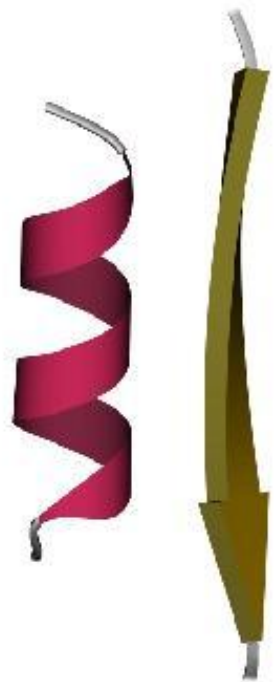
Fibrous proteins

H-bonds (NH:::OC) & hydrophobic forces

Protein chain
(gene-encoded
sequence)

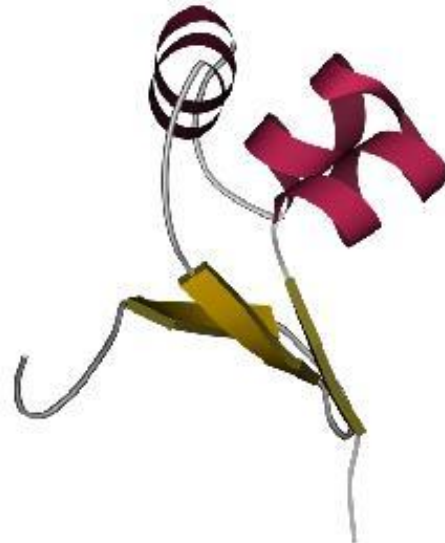


Primary ...- *Gly-Val-Tyr-Gln-Ser-Ala-Ile-Asn*-...

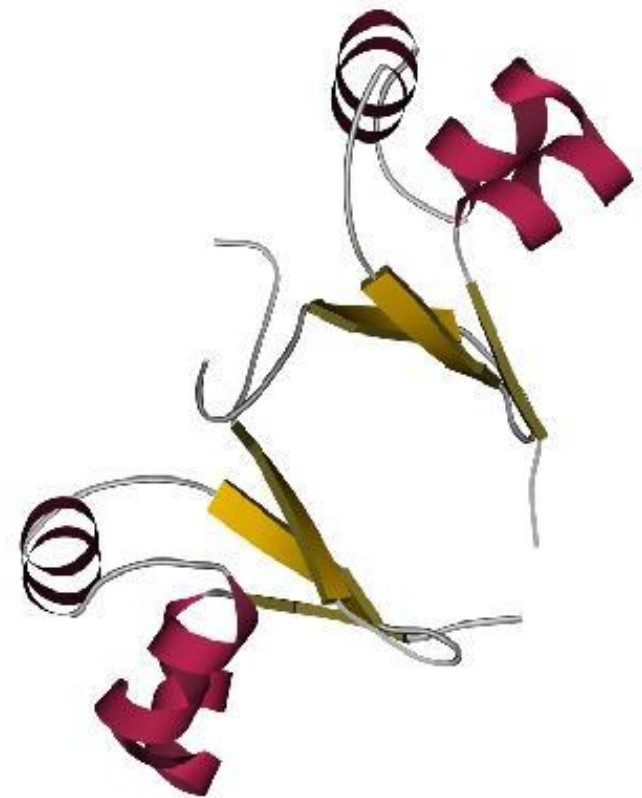


α β

Secondary



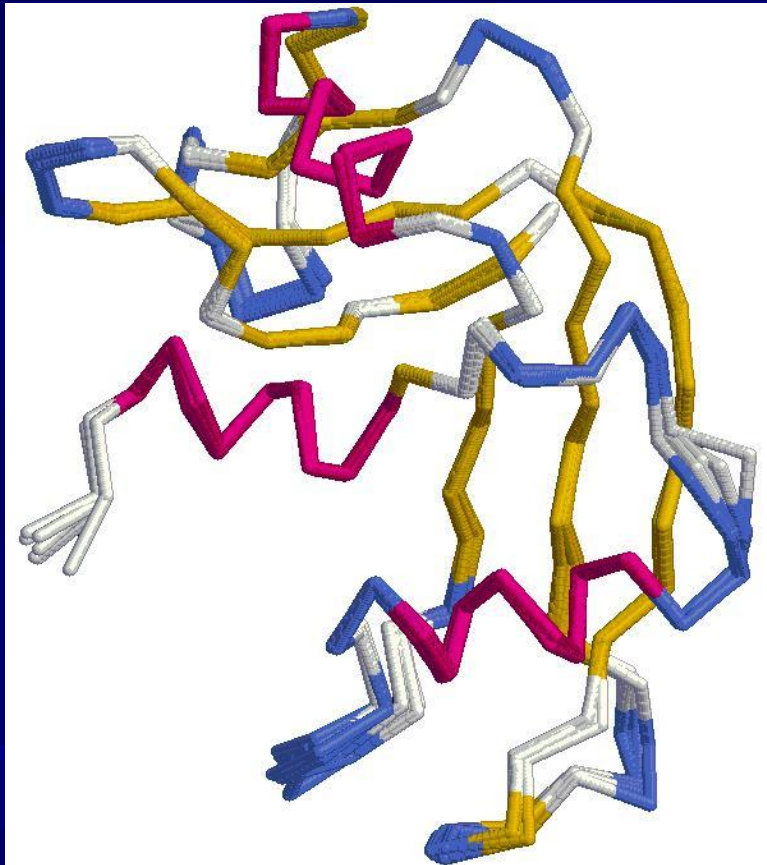
Tertiary



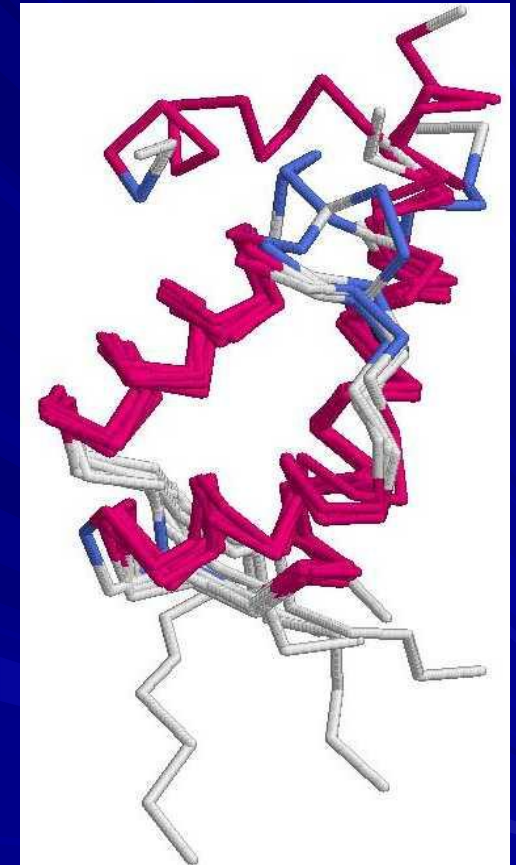
Quaternary

PROTEIN HAS DEFINITE 3D STRUCTURE

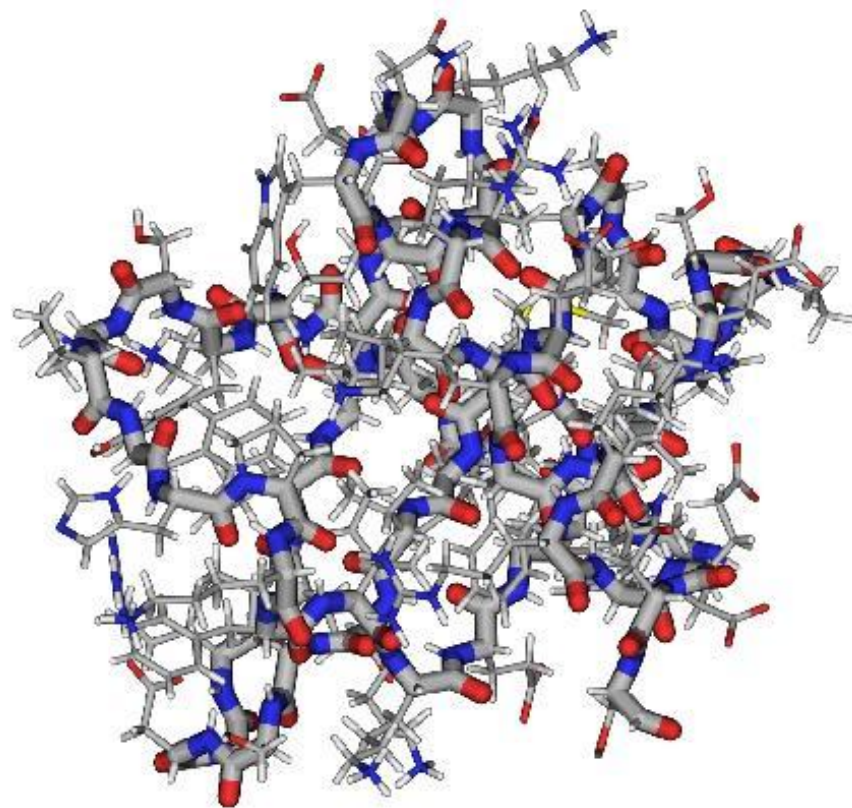
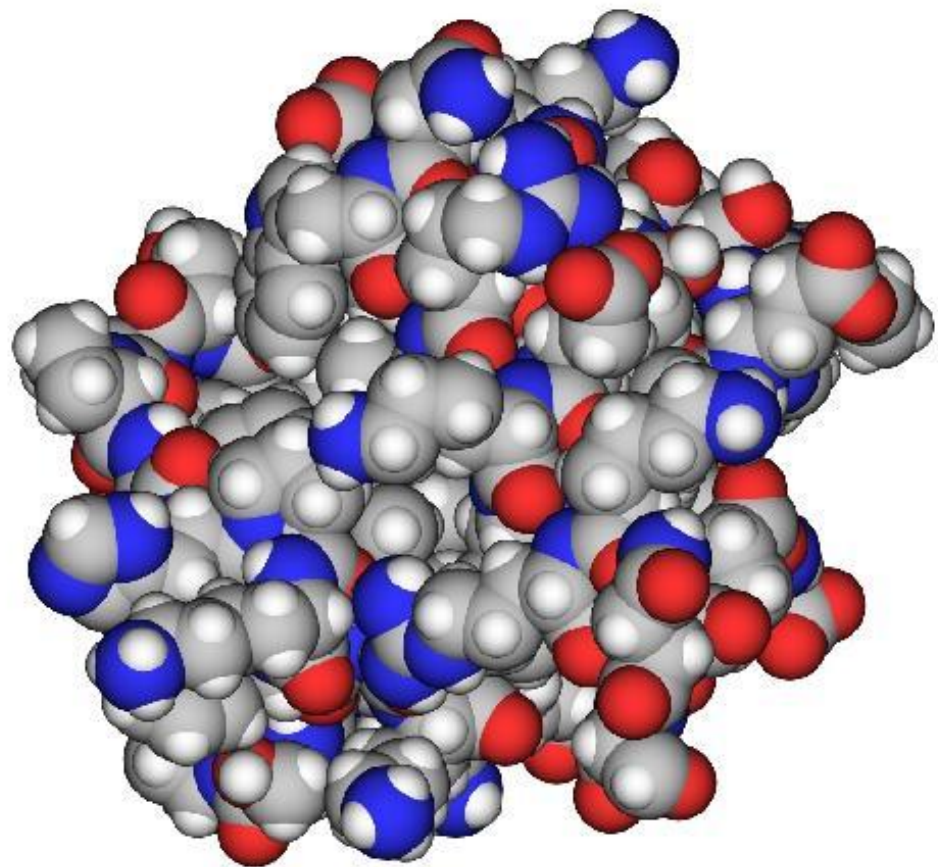
One protein - various crystallization, NMR

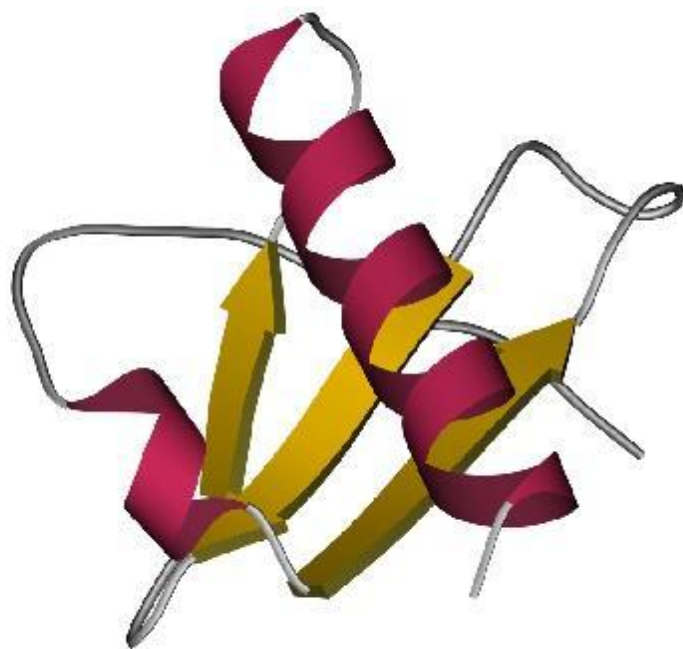
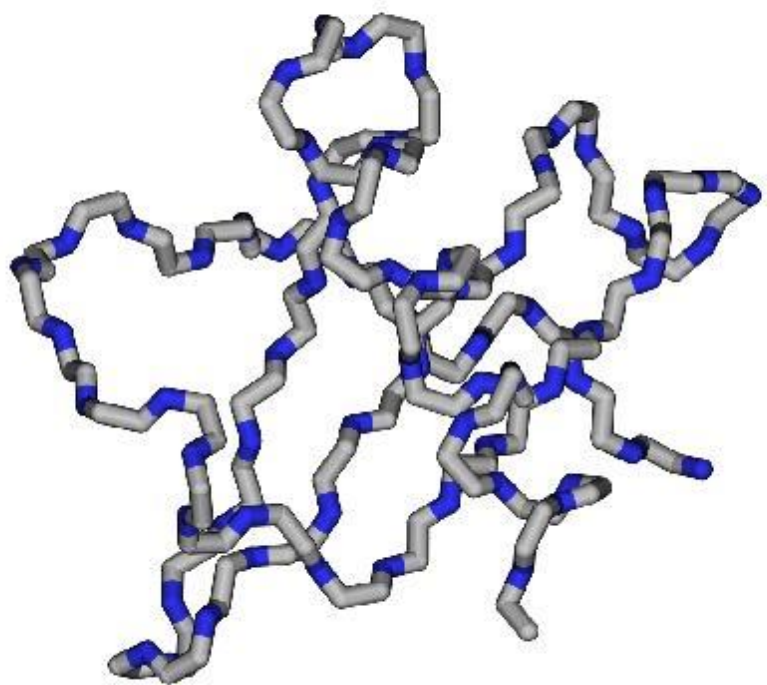


Homologous
(closely related)
proteins

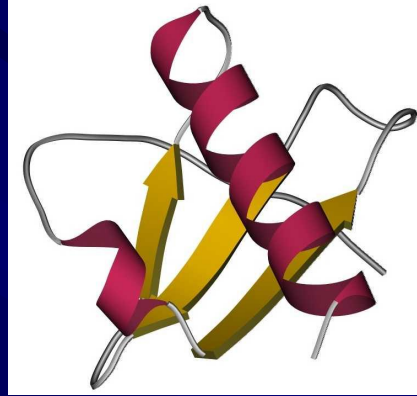


Secondary structures (α -helices, β -strands)
are most conserved structural elements.
They form a basis of protein classification





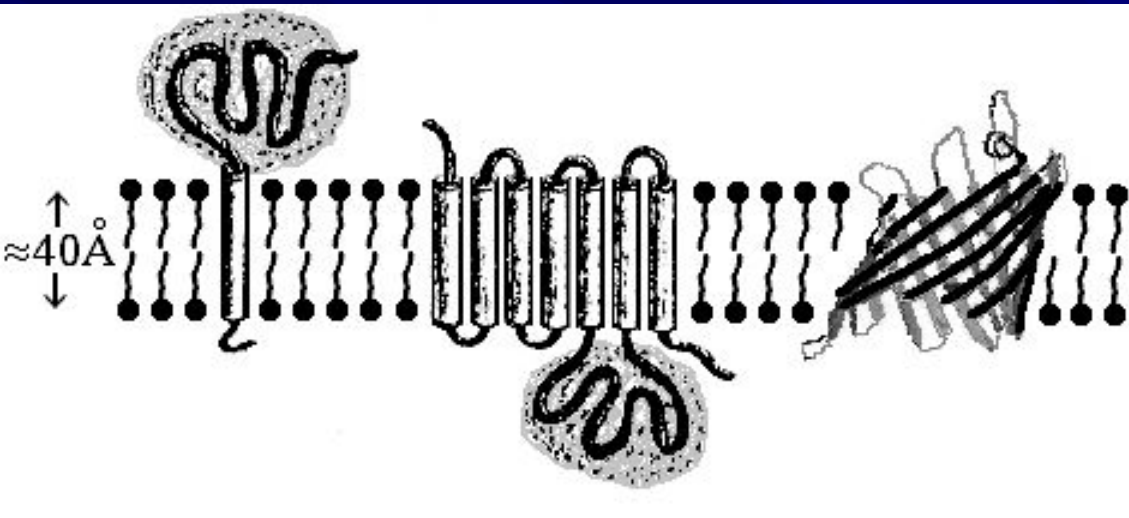
Sequence & Structure



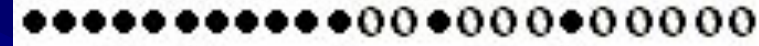
Globular proteins



quasi-random



Membrane proteins

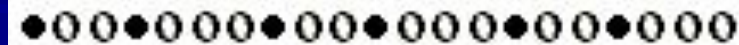


Hydro-
phobic
block

Hydro-
philic
block



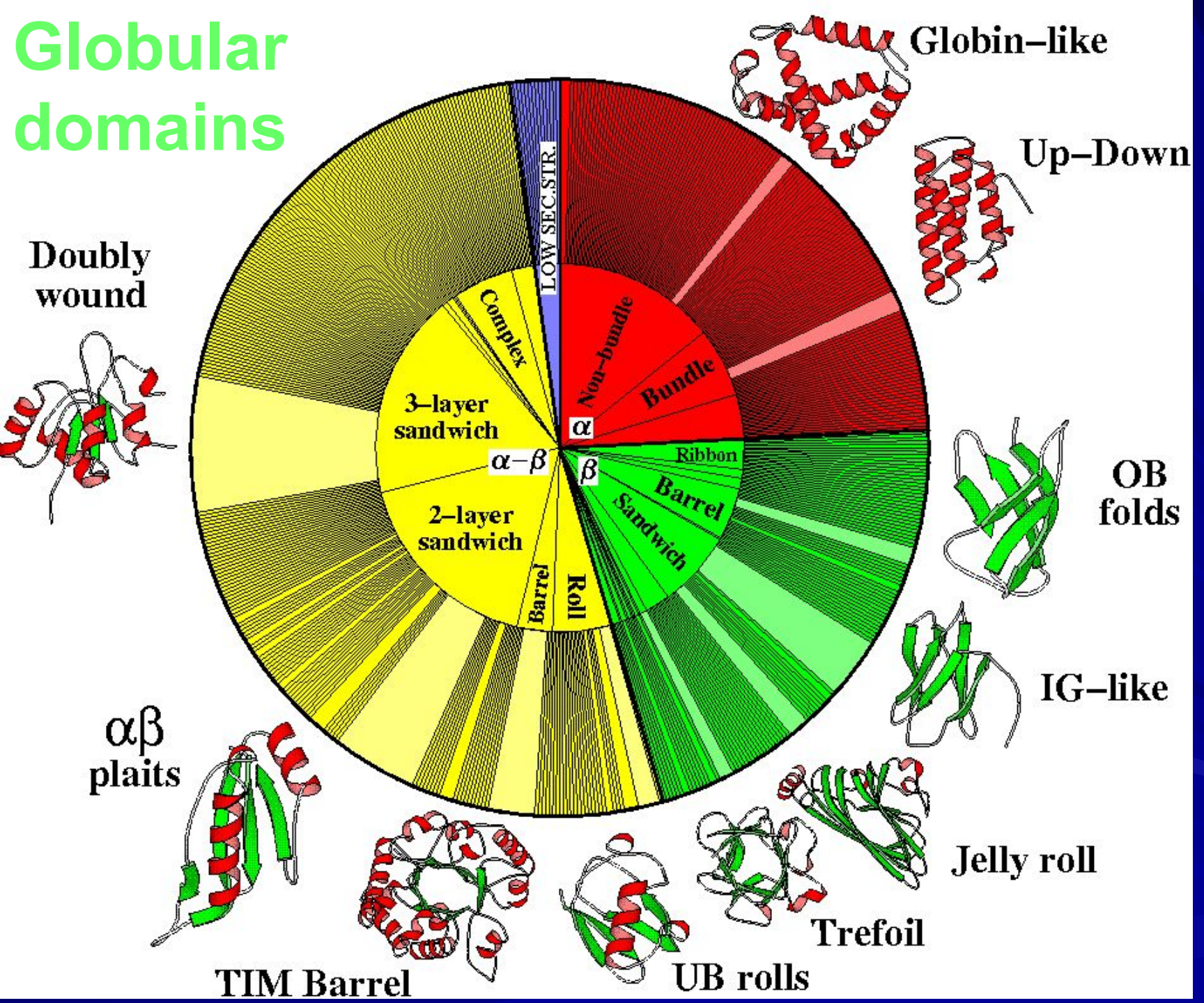
Fibrous proteins



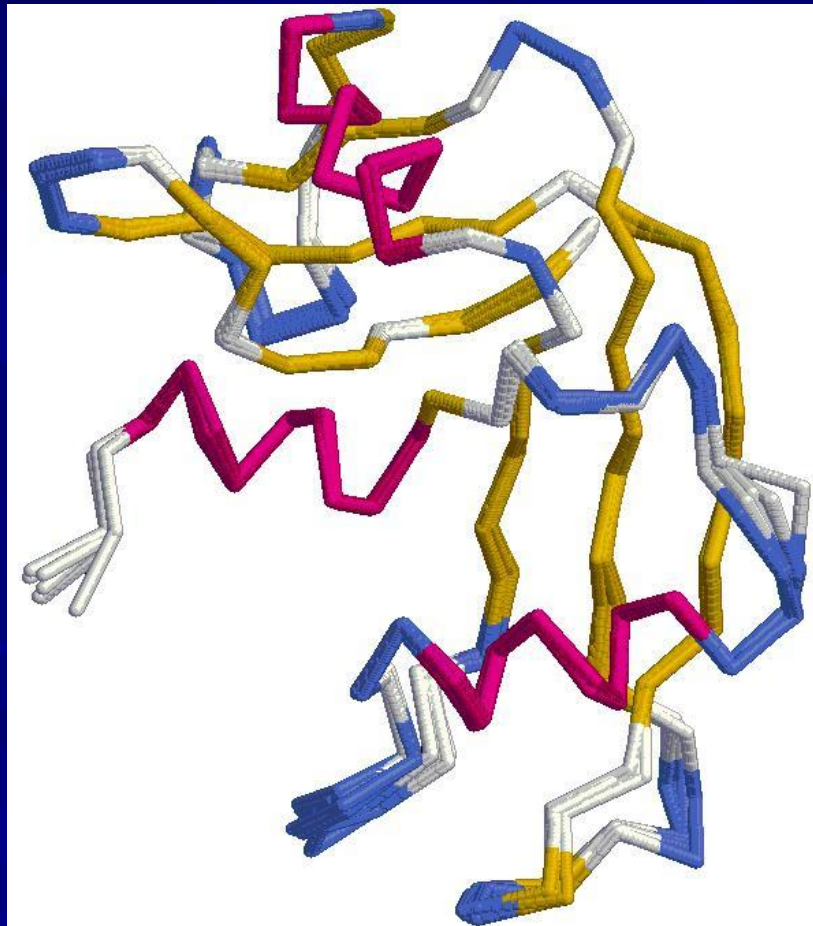
repeat | repeat |

H-bonds (NH:::OC) & hydrophobic forces

Globular domains

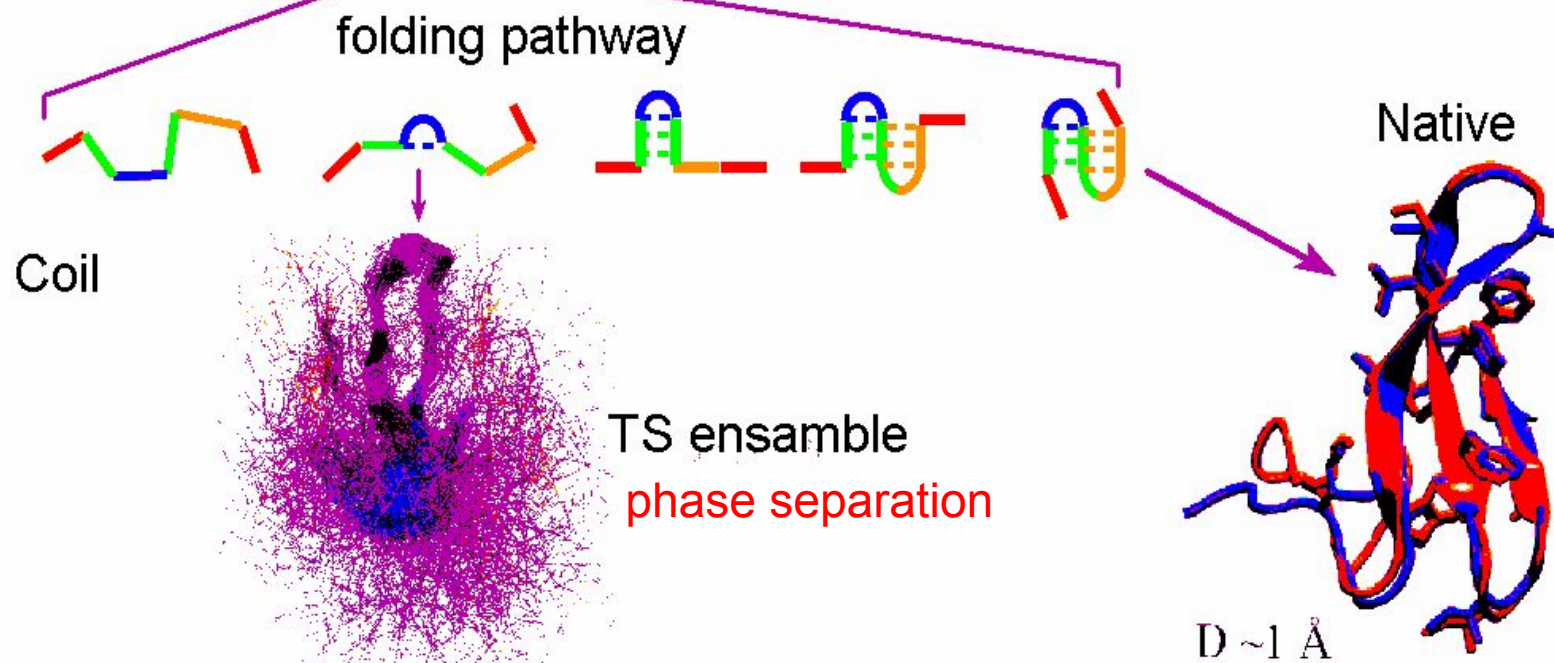
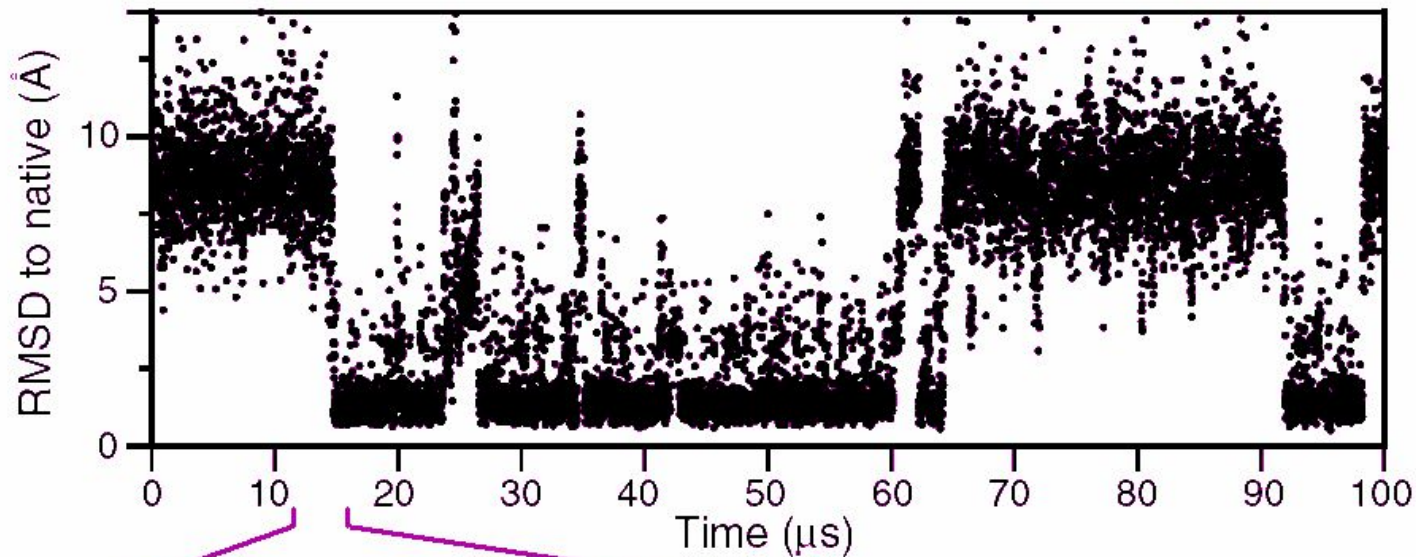


**PROTEIN CHAIN
CAN FORM ITS UNIQUE 3D STRUCTURE
SPONTANEOUSLY
*IN VITRO***



FIP35 protein: simulation of folding

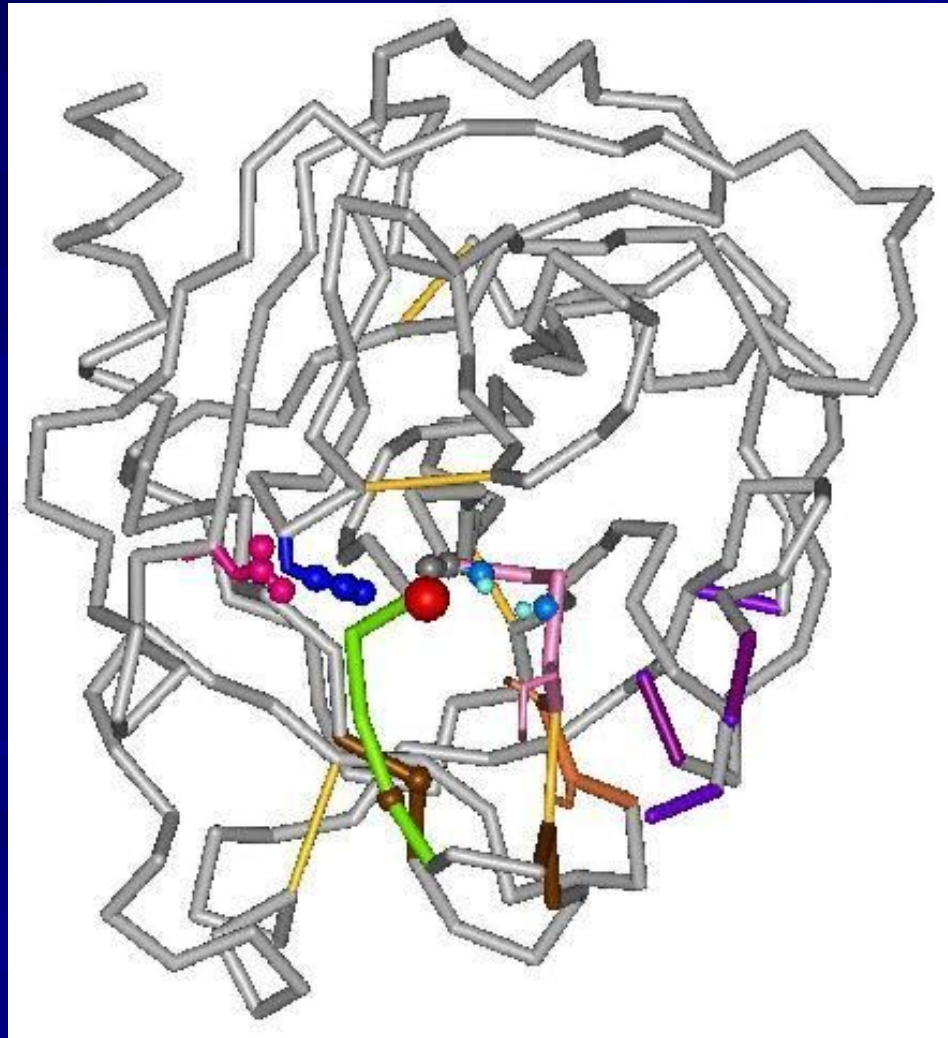
D.E. Shaw et al., Oct. 2010, *Science* **330**, 341



BIND □ TRANSFORM □ RELEASE:

ENZYMES (chymotrypsin)

Note small active site



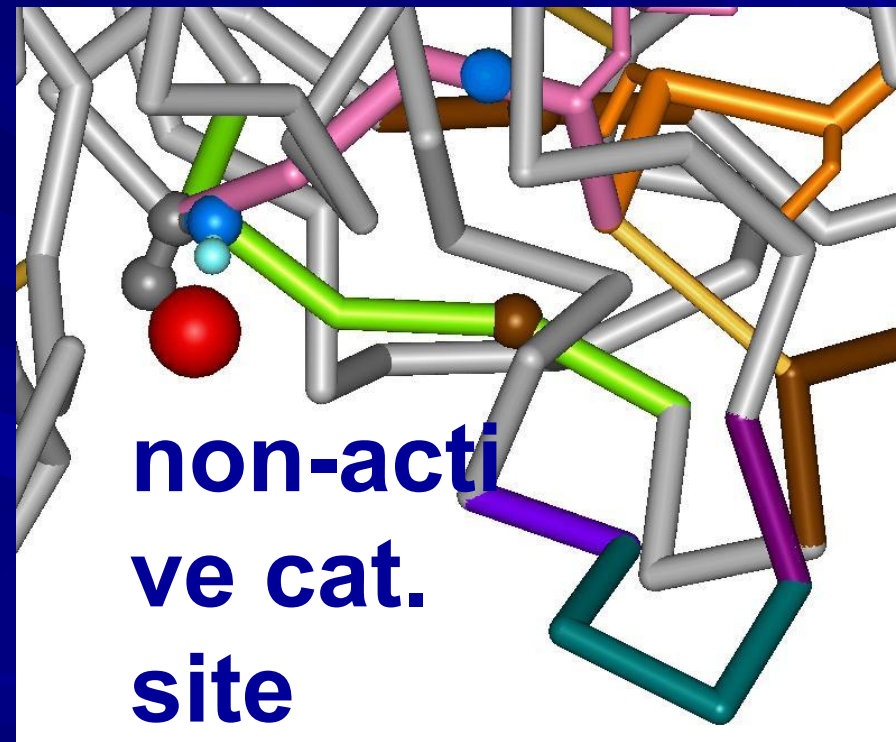
POST-TRANSLATIONAL MODIFICATIONS

Sometimes,

CHAIN CUT-INDUCED DEFORMATION
MAKES ENZYME ACTIVE



Chymotrypsin



Chymotrypsinogen

POST-TRANSLATIONAL MODIFICATIONS:

(especially in eukaryotes):

PROTEIN CHAIN CUTS (proteolysis),

- **SPLICING (inteins)**

- **CYCLIZATION**

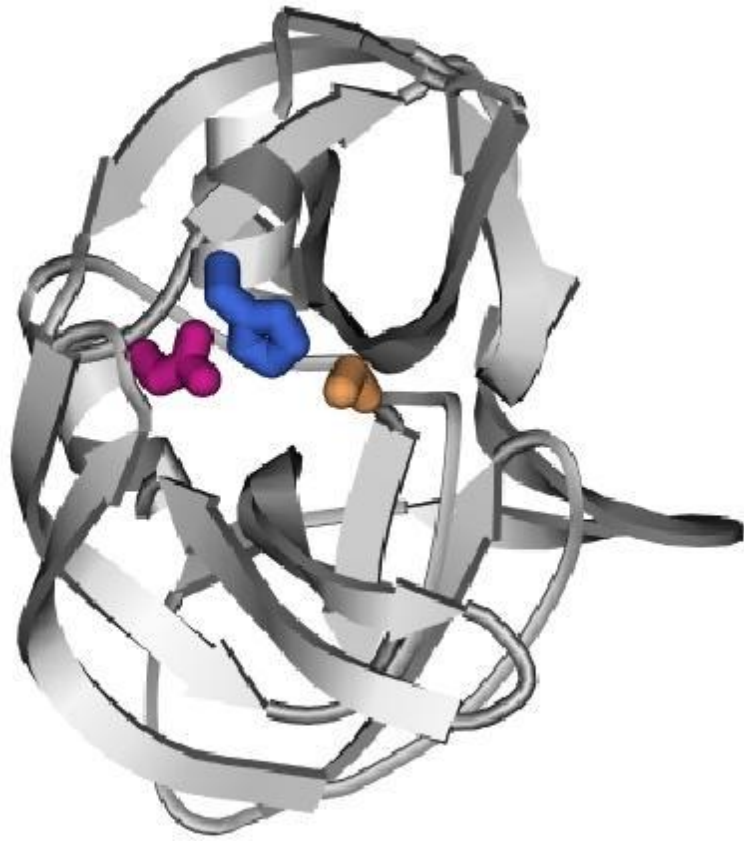
- **INTERNAL CHEM. TRANSFORMATION**

GLYCOSYLATION, etc.

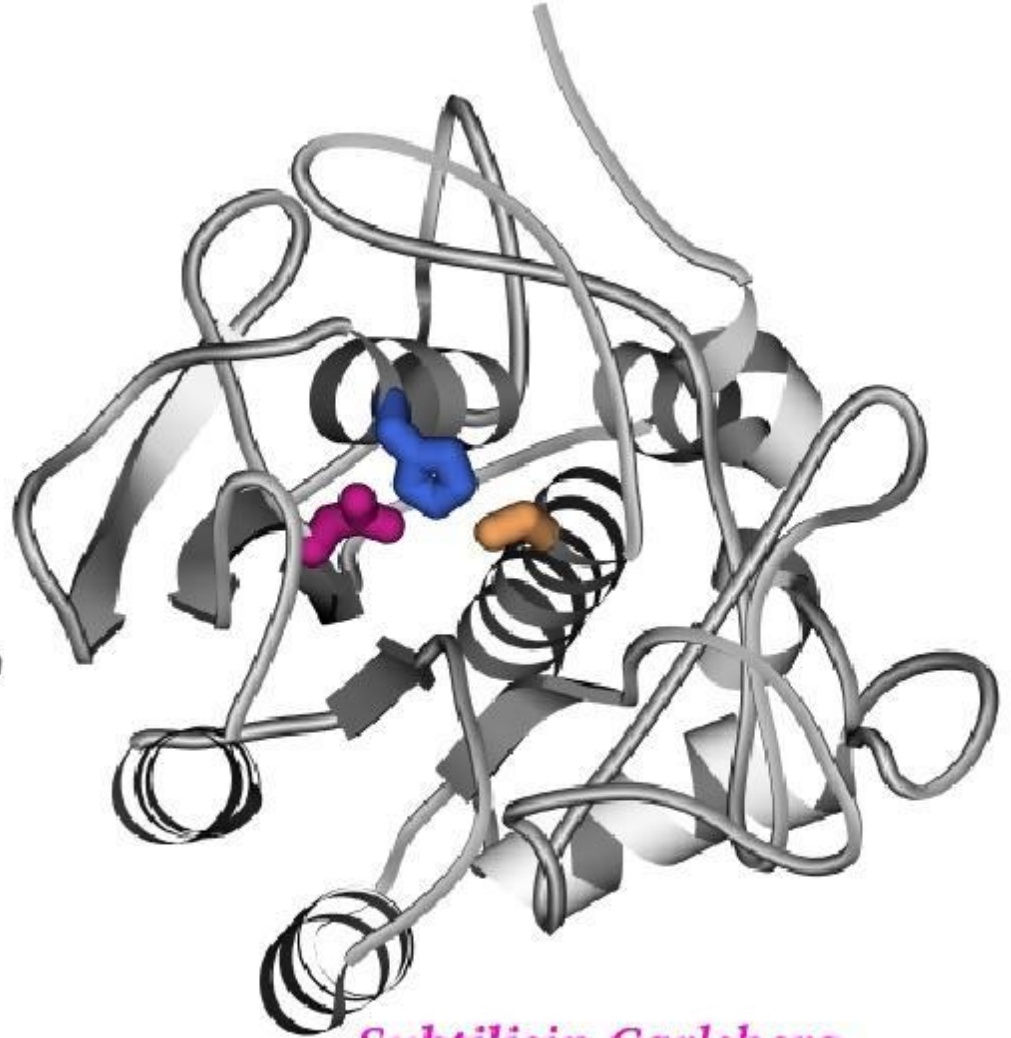
MODIFICATION OF ENDS (acetylation, etc.)

**MODIFICATION OF SIDE CHAINS (S-S bonding,
phosphorilation, etc.)**

COFACTORS ...



α -Chymotrypsin



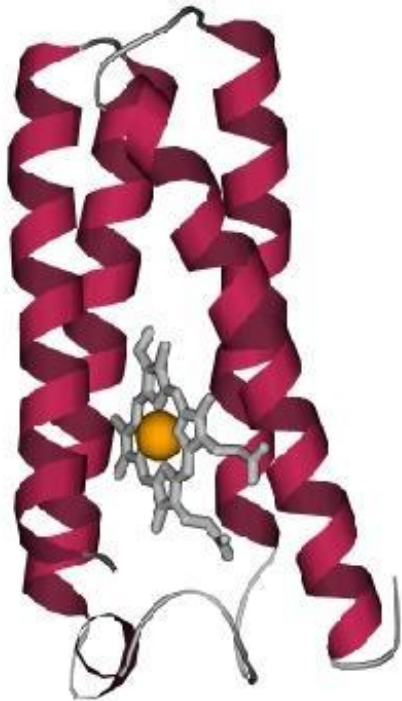
Subtilisin Carlsberg

Sometimes:

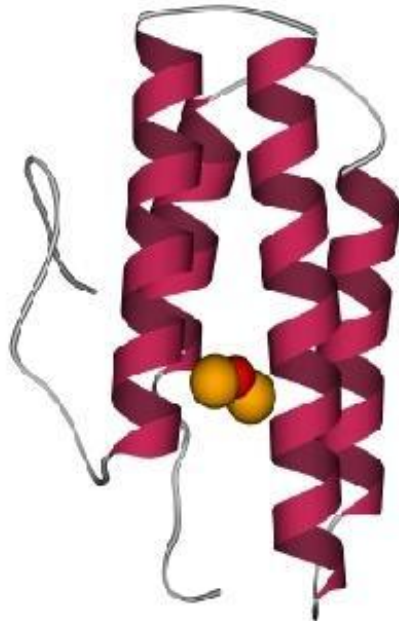
**Different folds with the same active site:
the same biochemical function**

4-helix bundle

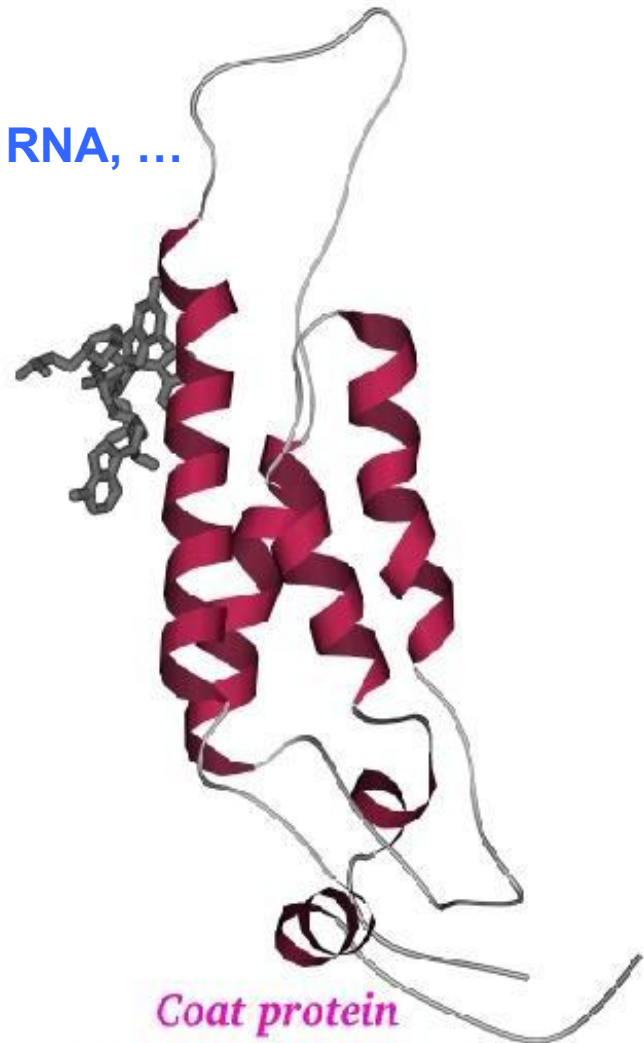
COFACTORS: HEME, 2Fe, RNA, ...



Cytochrome c'



Hemerythrin

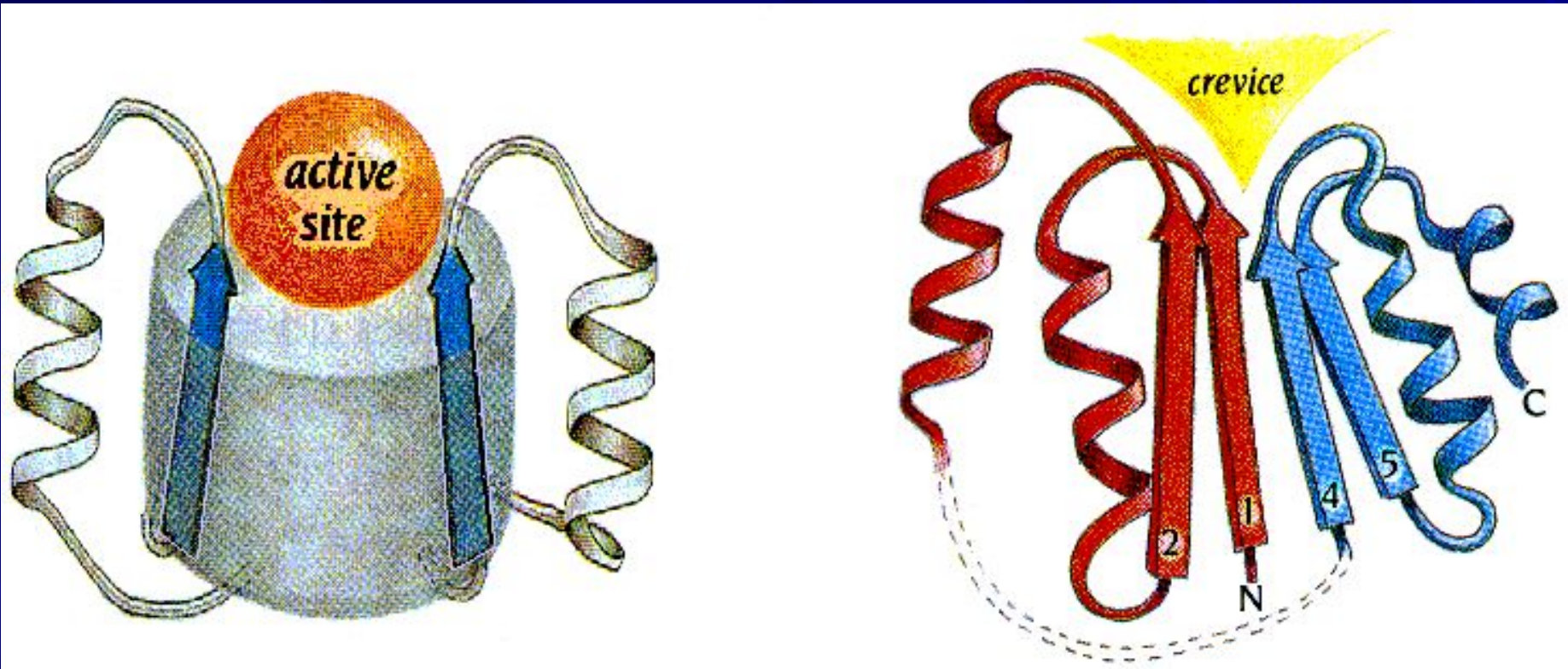


Coat protein
Tobacco mosaic virus

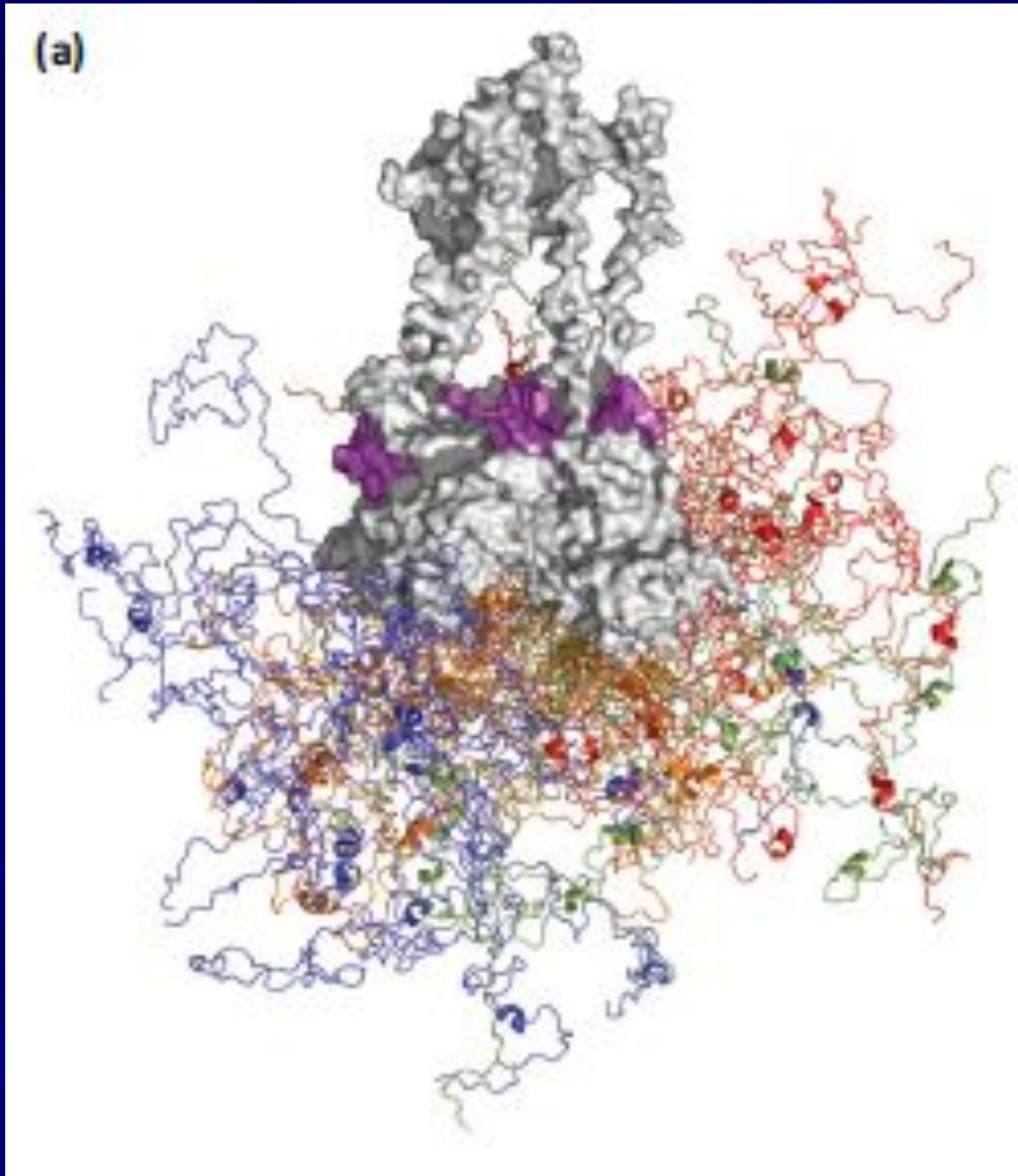
Sometimes:

**Similar folds with different active sites:
different biochemical function**

Standard positions of active sites in protein folds

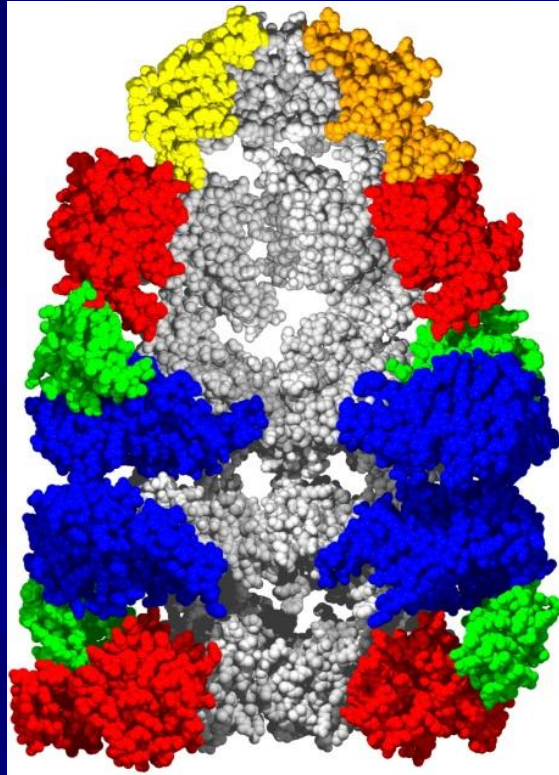


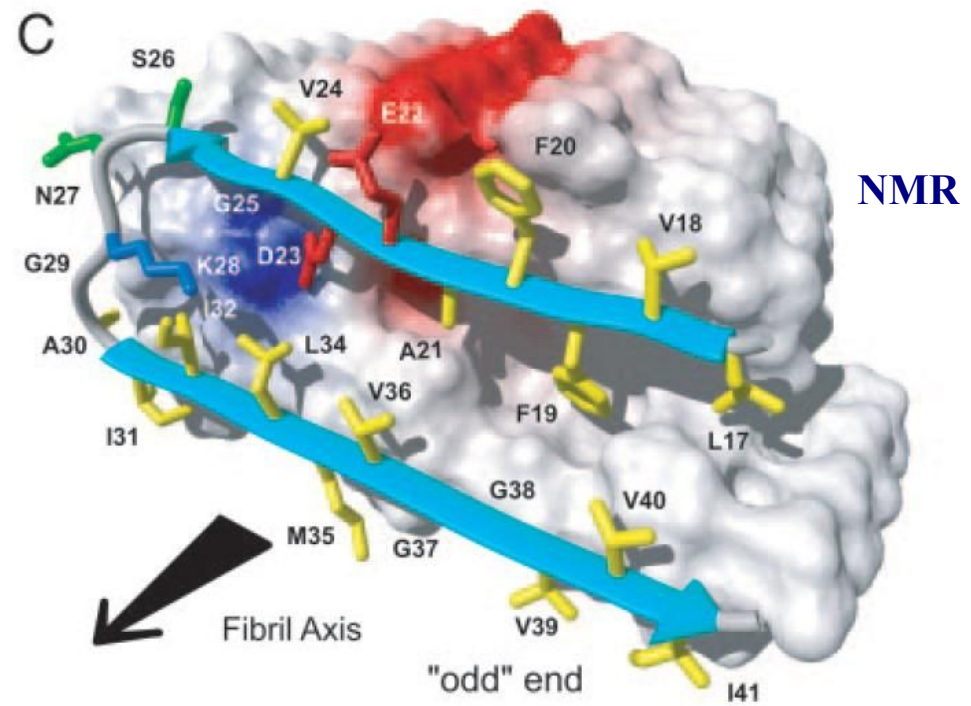
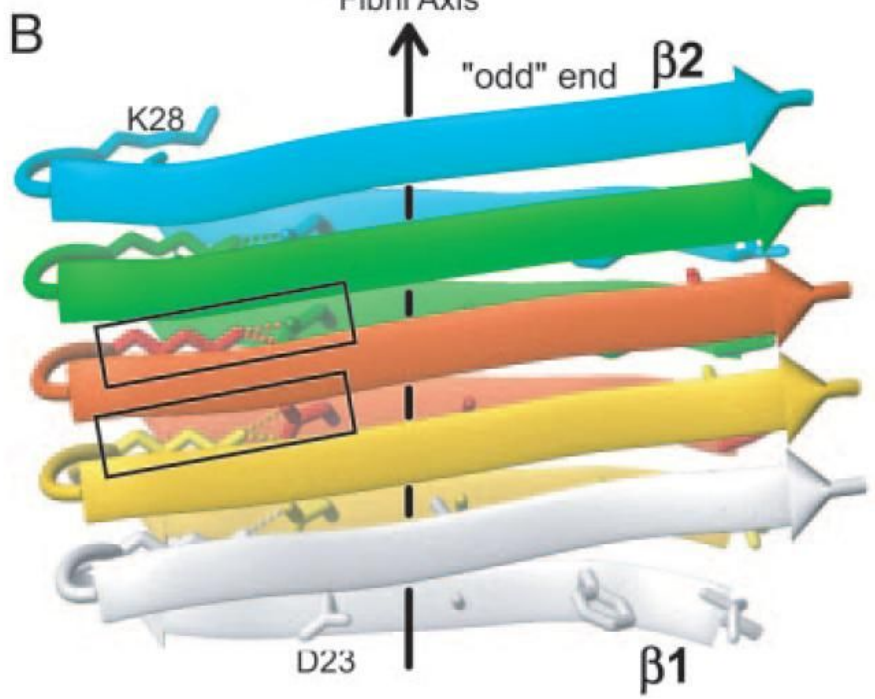
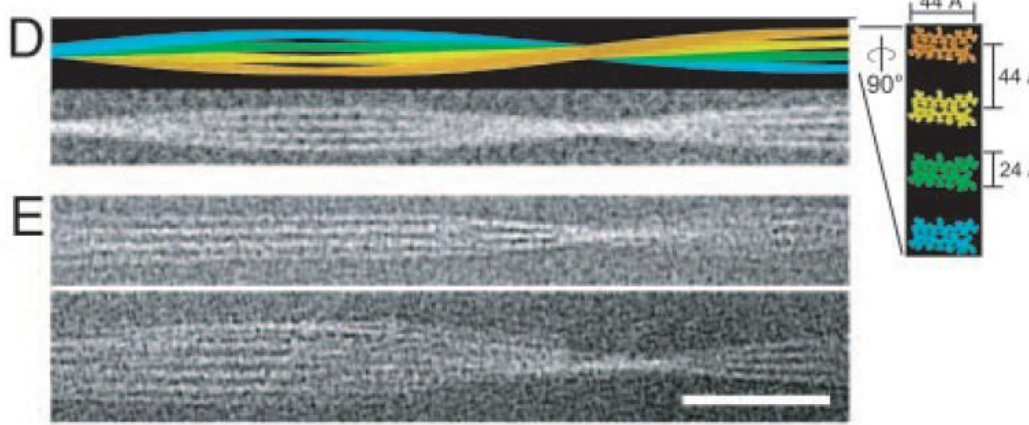
Natively disordered protein:



X-ray
+
SAXS
+
NMR
+
MD simulations

Chaperone GroEL



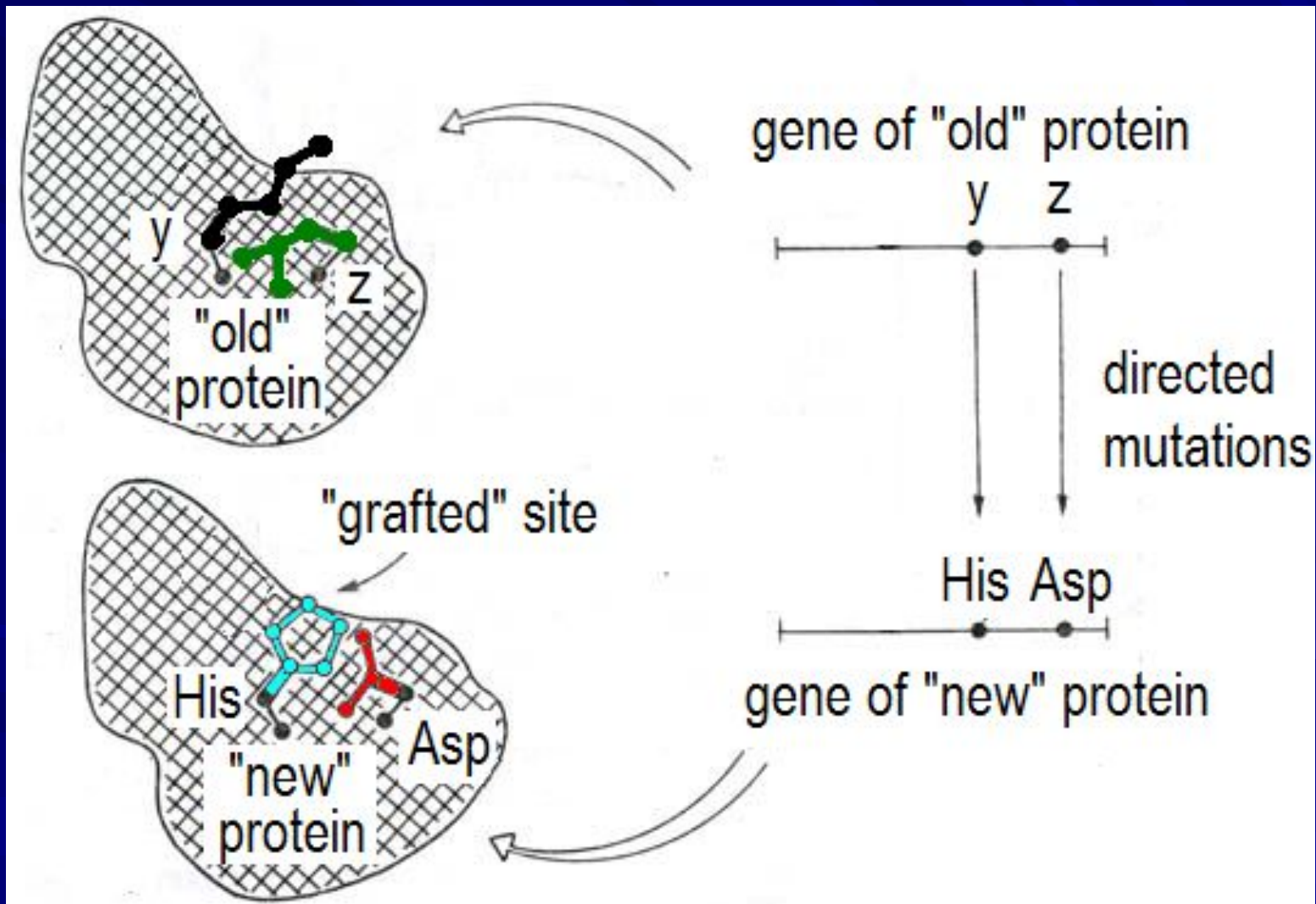


3D structure of Alzheimer's amyloid- $\beta(1-42)$ fibrils

T.Lührs, C.Ritter, M.Adrian, D.Riek-Loher, B.Bohrmann, H.Döbeli, D.Schubert, R.Riek. *PNAS* 102:17342-17347 (2005)

Protein engineering

Wanted: new protein with additional salt bridge
(e.g., His⁺:::Asp⁻)



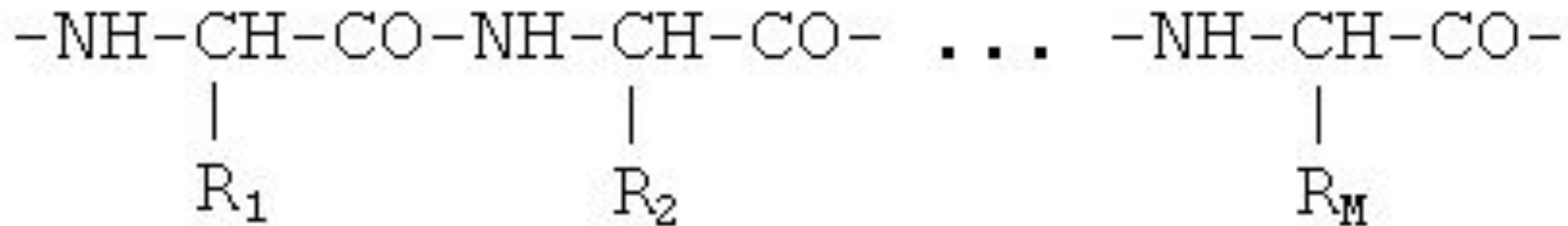
PROTEIN PHYSICS

LECTURE 2

**Elementary interactions:
covalent**

Protein chain:

regular backbone
&
gene-encoded sequence
of side chains

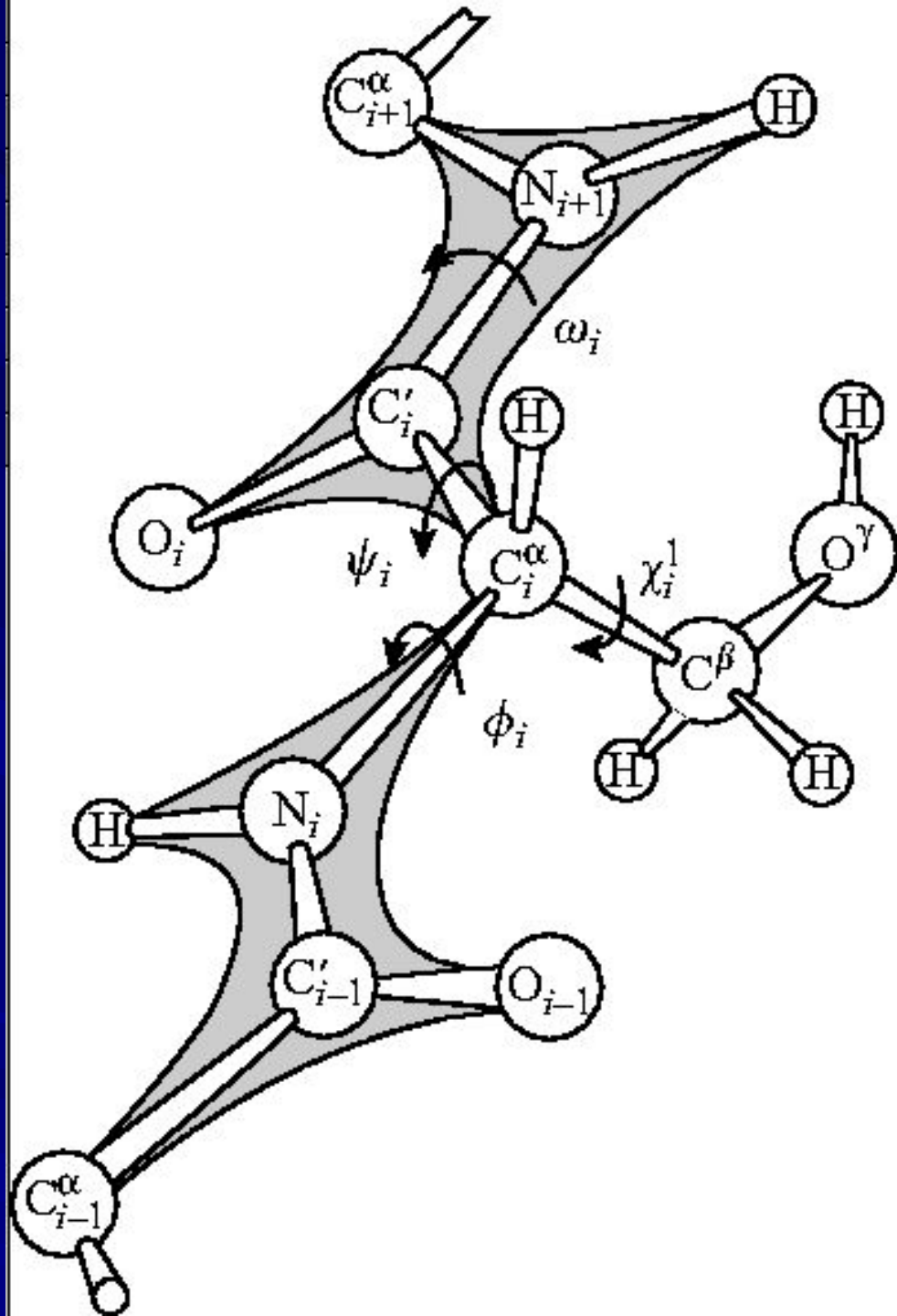


Protein chain

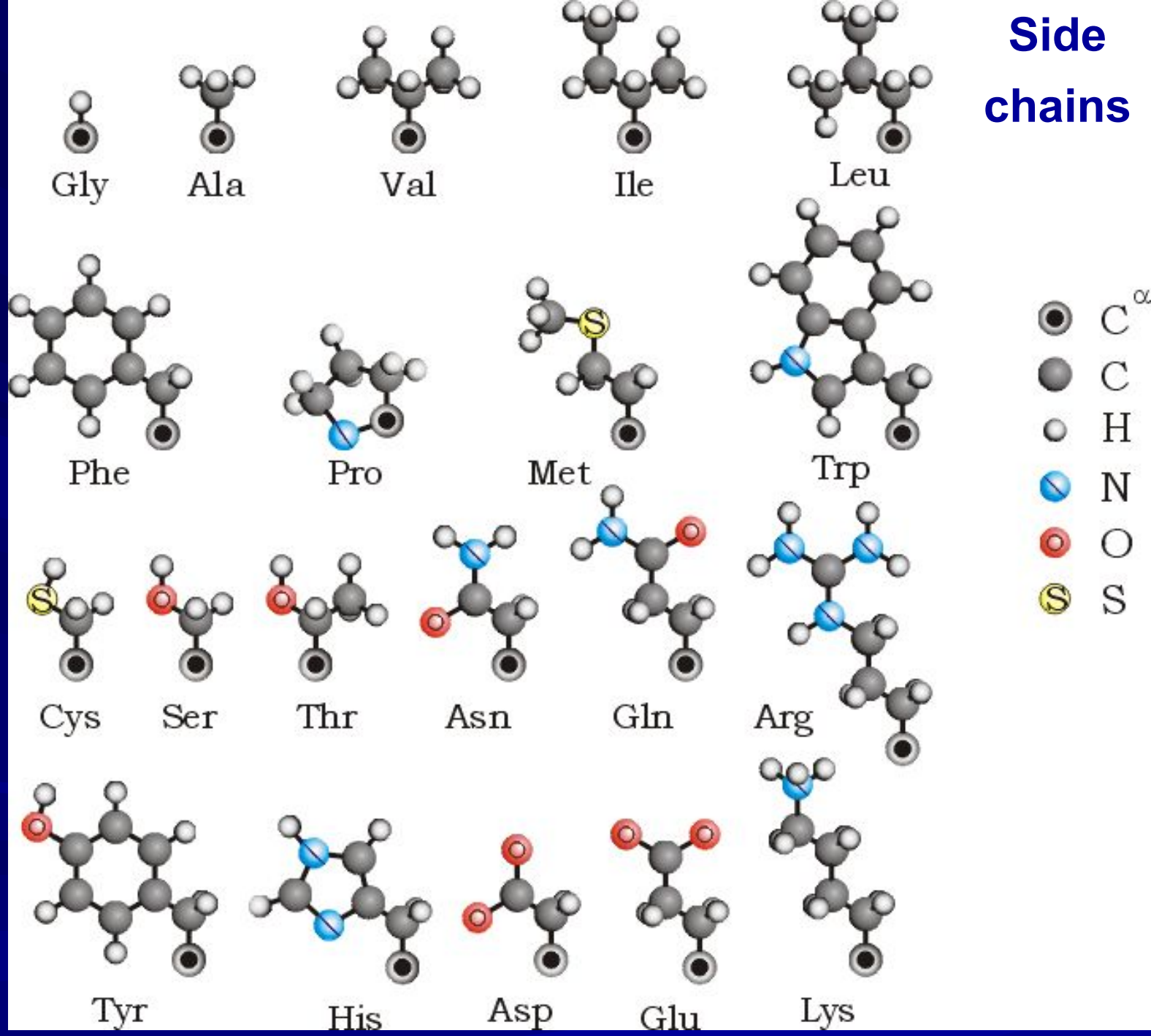
Covalent bond
lengths:
0.9 – 1.8 Å

Covalent bond
angles:
109° – 120°

Atom radii:
1 – 2 Å



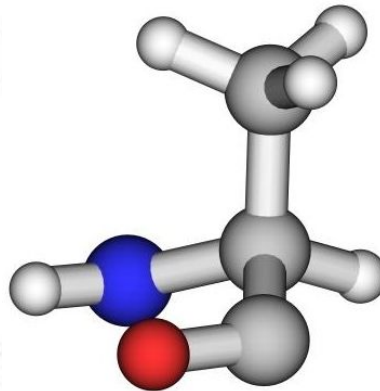
Side chains



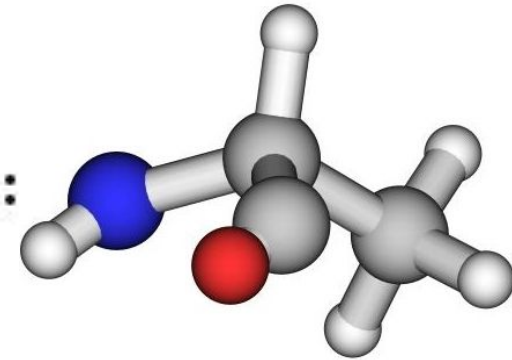
Protein chain

Side chains:
L
amino acids

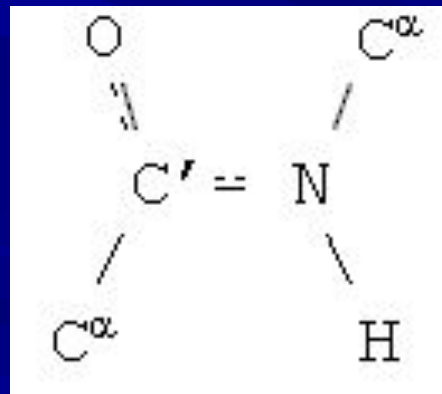
L:



D:

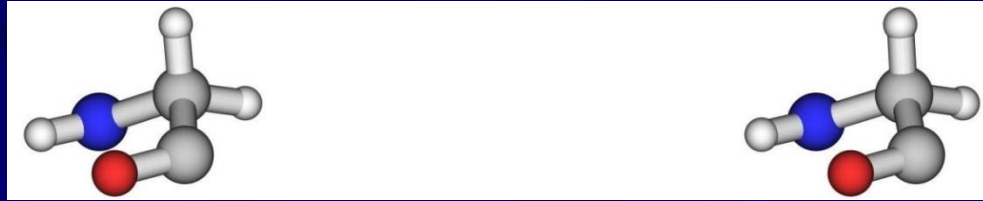


Main-chain:
peptide group:
flat & rigid



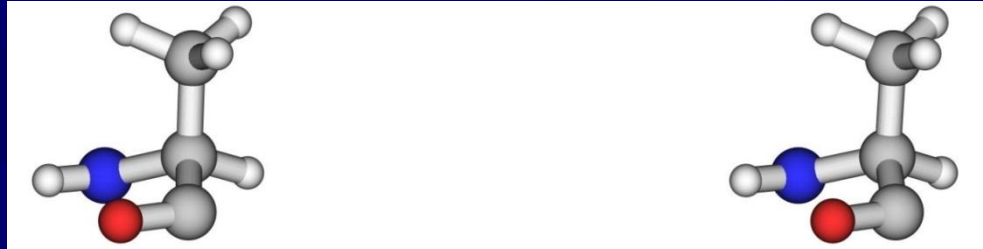
Stereo images

Symmetric



Gly

**Asymmetric
backbone-to-
side_chain:**



Ala_L

**Two
asymmetric
side
chains:**



Thr



Ile

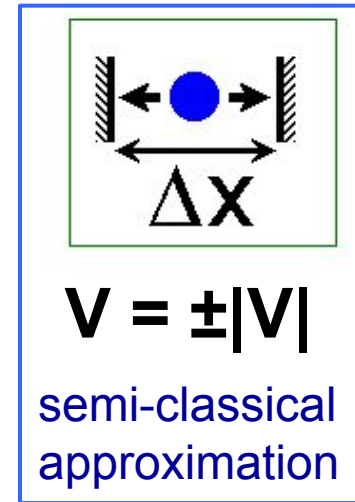
COVALENT BONDING: quantum effect

1. Heisenberg's uncertainty:

$$\Delta(mv) \cdot \Delta x \cong \hbar \text{ Planck's const}$$

Energy of localization in Δx :

$$E = mv^2/2 \sim (\hbar^2/m)/(\Delta x^2)$$



DELOCALIZED **e** IS MORE STABLE

2. Pauli exclusion principle: $e^{\uparrow} \uparrow e \leq 2 e$

COVALENT BOND: $e \cdot + e \cdot \rightarrow e^{\uparrow} \cdot \cdot \downarrow e$

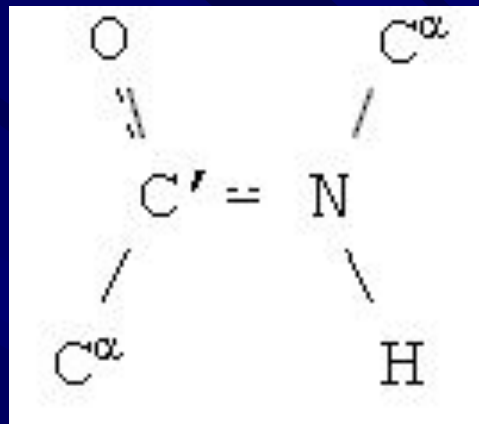


Werner Karl Heisenberg (1901-76)
— Nobel Prize 1932

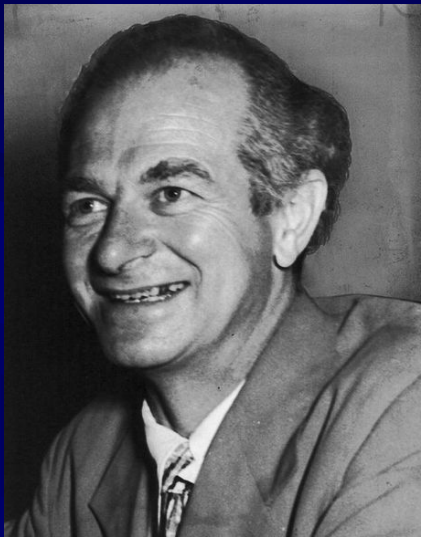


Wolfgang Ernst Pauli) (1900-58)
— Nobel Prize 1945

Peptide group: flat & rigid

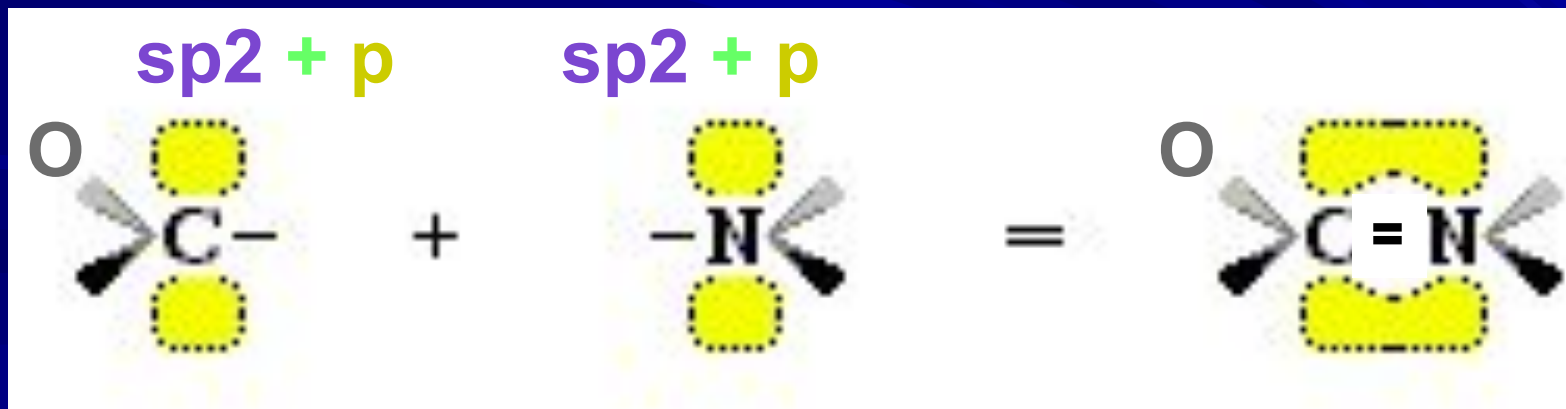


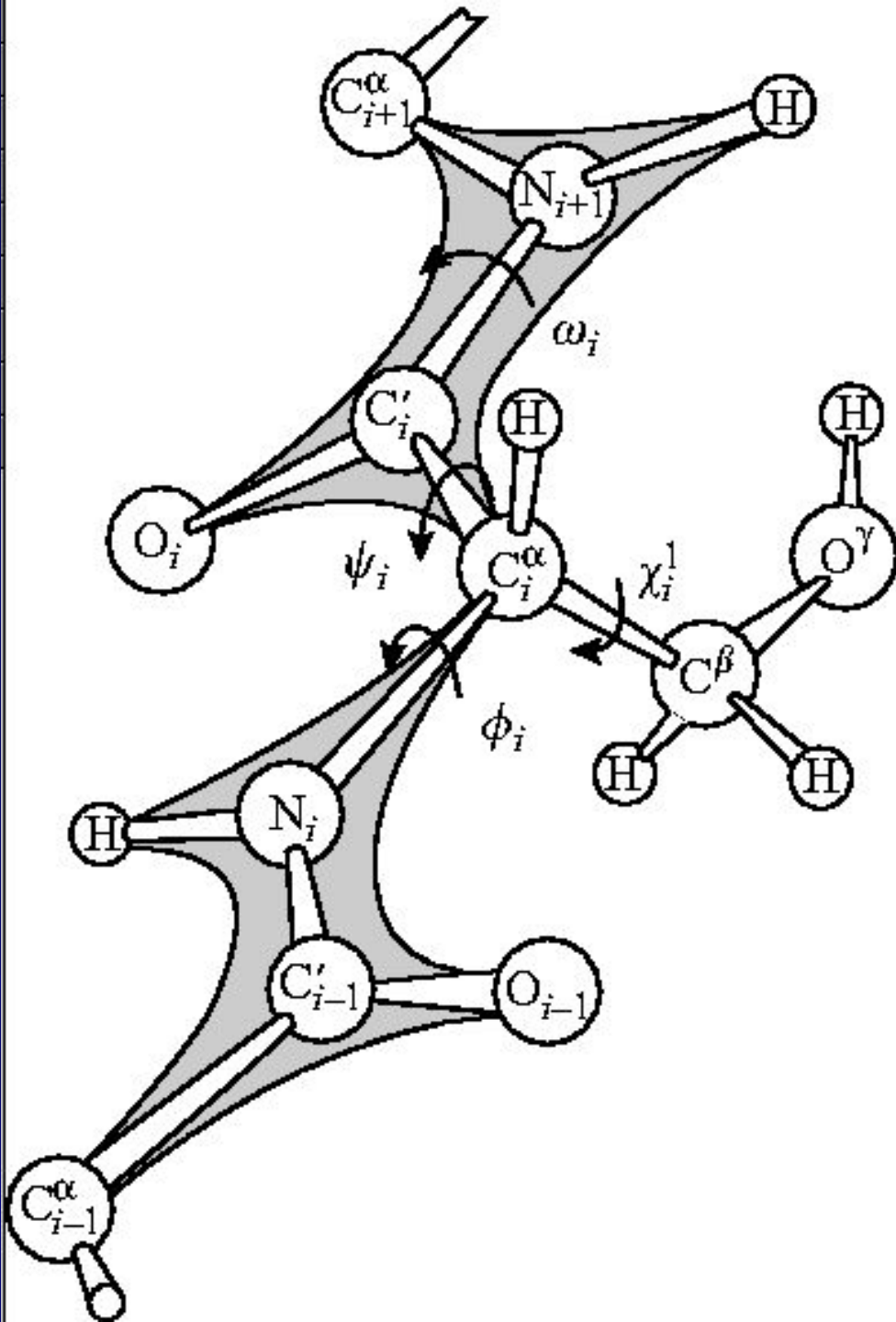
Pauling resonance
theory of $\text{--}\equiv$ bonds:



Linus Carl
Pauling
(1901-94)
— Nobel Prizes:
1954, 62

Covalent bonding in peptide group:





Main-chain:

ϕ (N-C α),

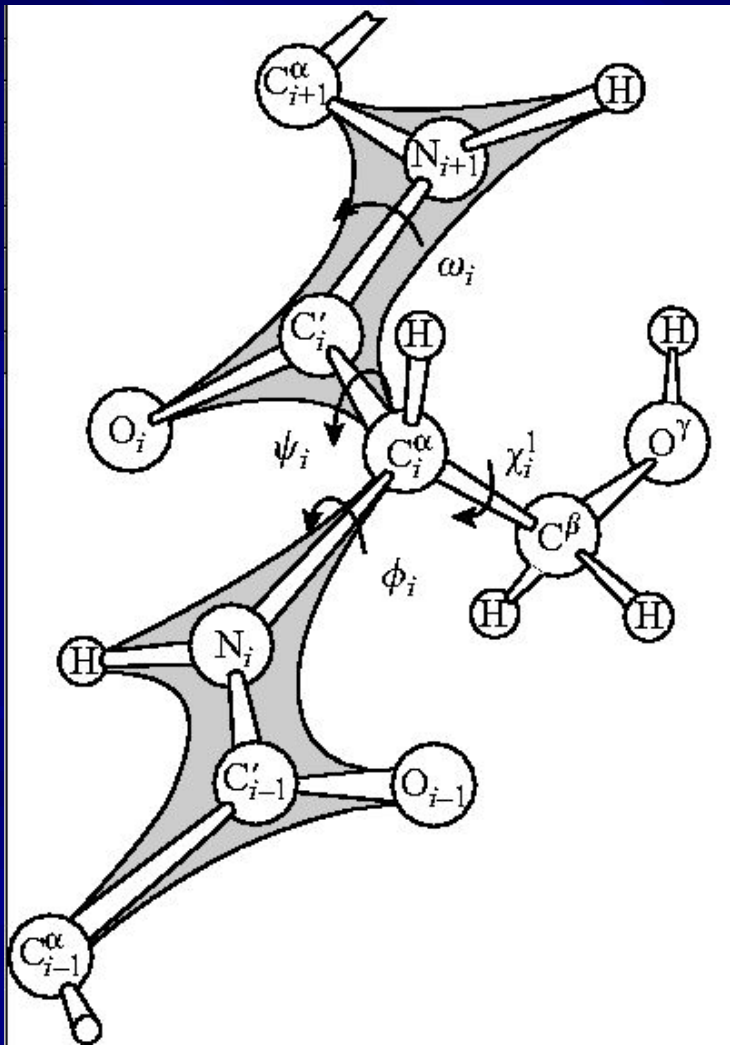
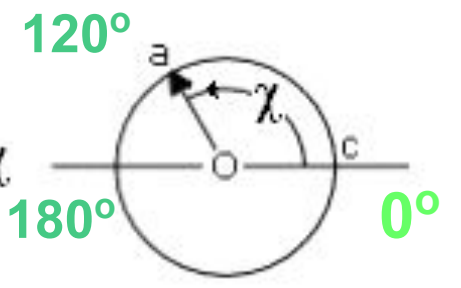
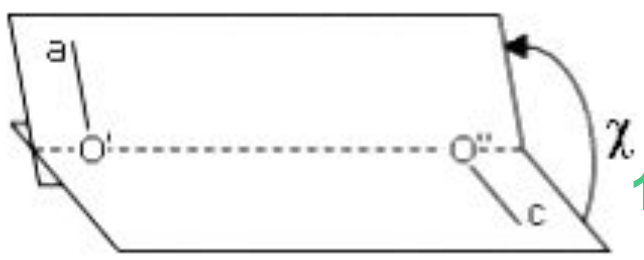
ψ (C α -C $^{\prime}$),

ω (C $^{\prime}$ =N)

Side-chain:

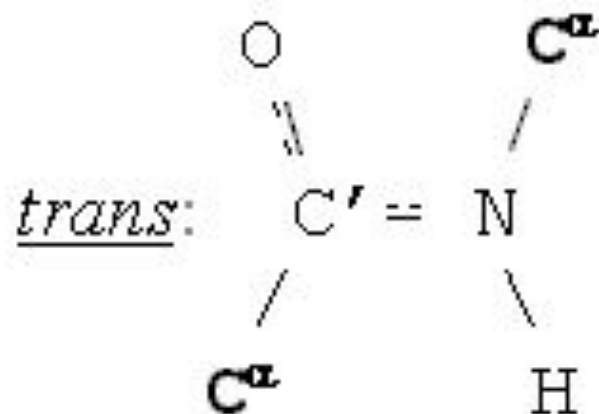
χ^1, χ^2, \dots

Counting angles:

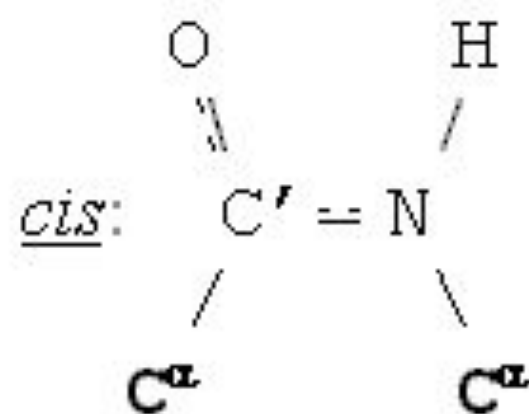


sp² - sp² (ω)

Typical:

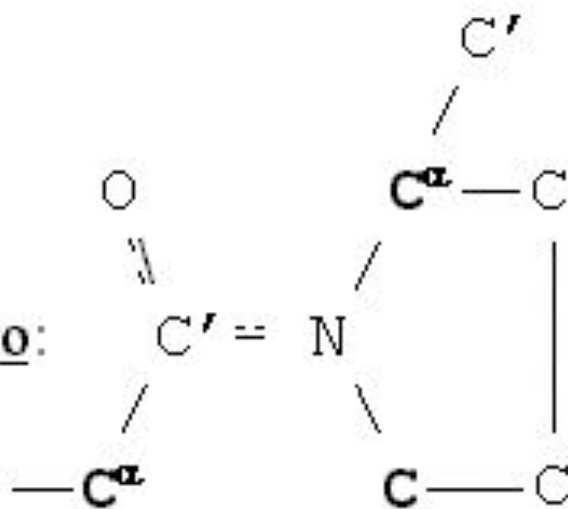


$$\omega = 180^\circ$$

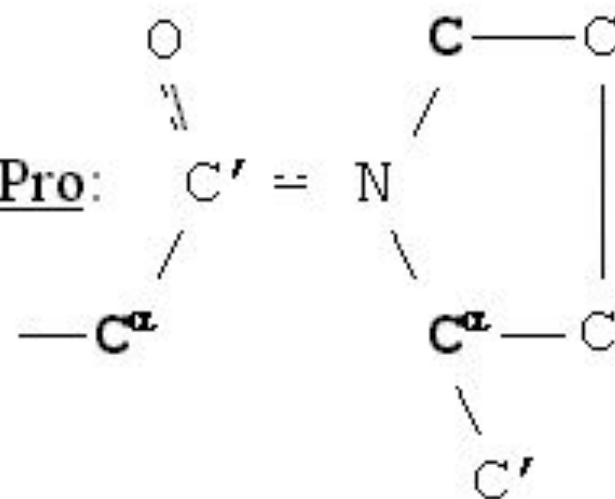


$$\omega = 0^\circ$$

trans Pro:



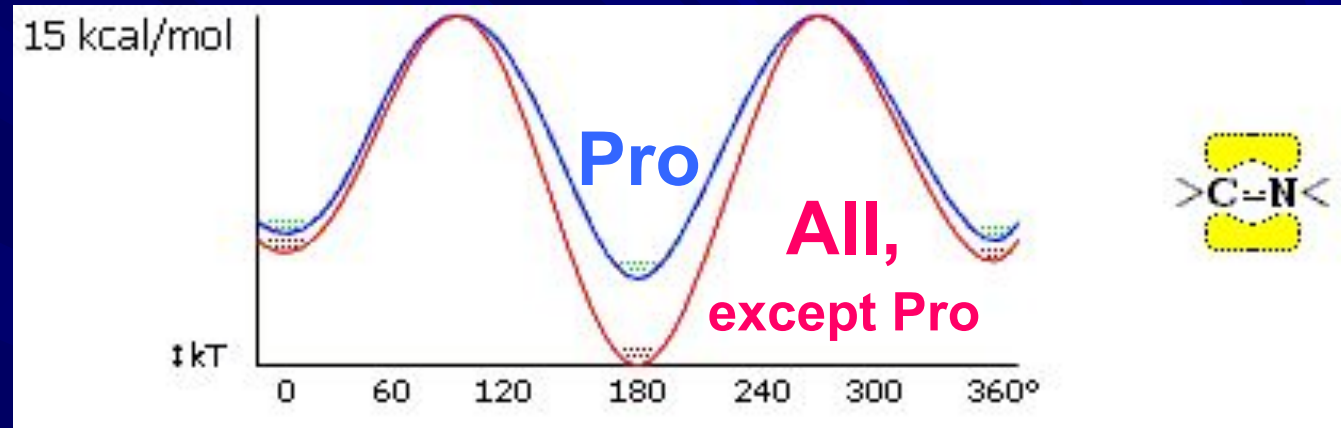
cis Pro:



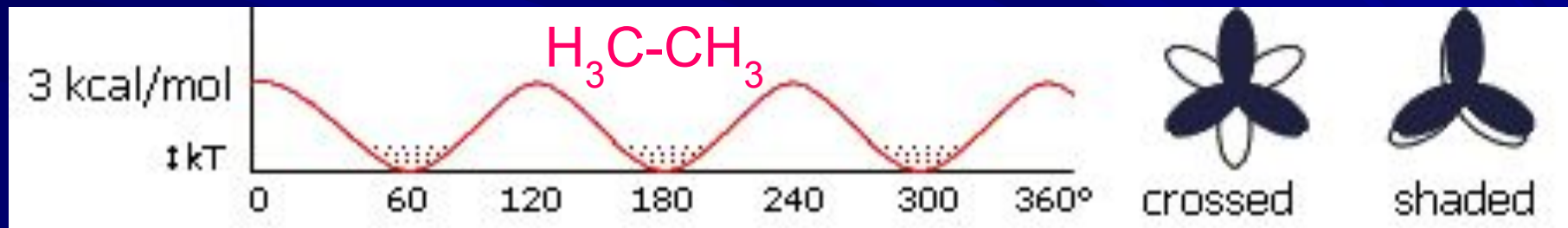
Potentials: from IR spectra of vibrations

classical

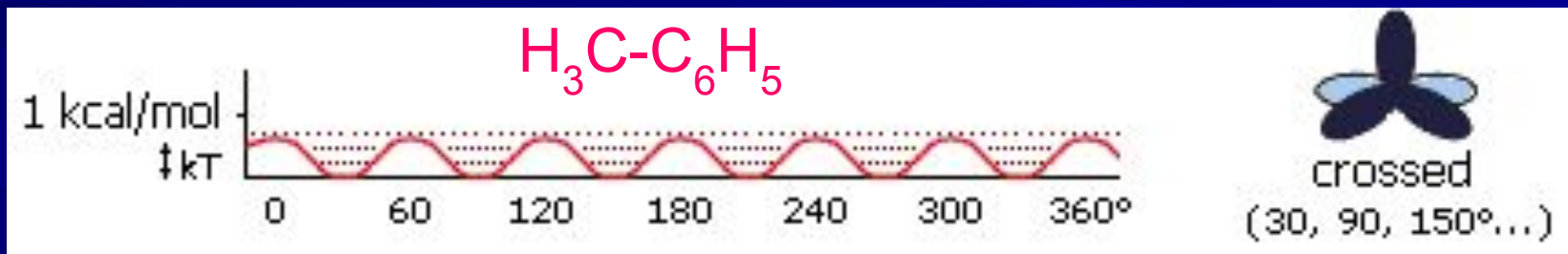
$sp^2 - sp^2$ (ω)



$sp^3 - sp^3$ (χ)



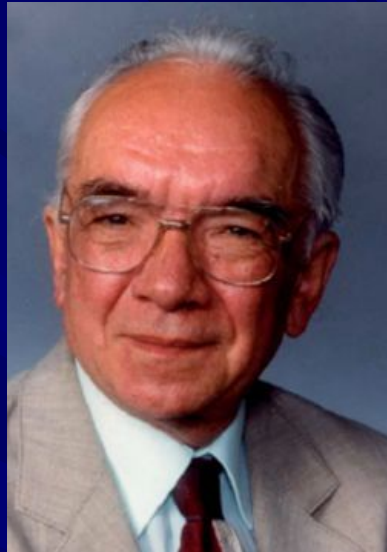
$sp^2 - sp^3$ (ϕ, ψ)



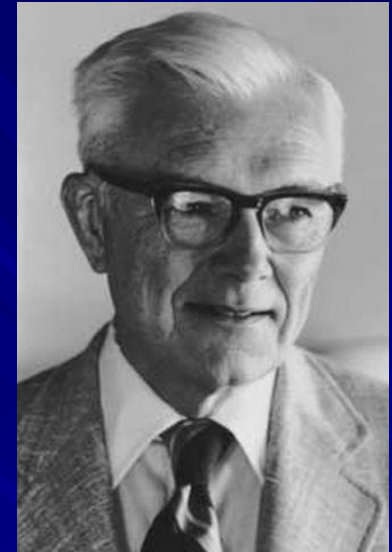
Поворотно-изомерная теория полимеров



Михаил Владимирович
Волькенштейн (1912-92)



Олег Борисович
Птицын (1929-99)

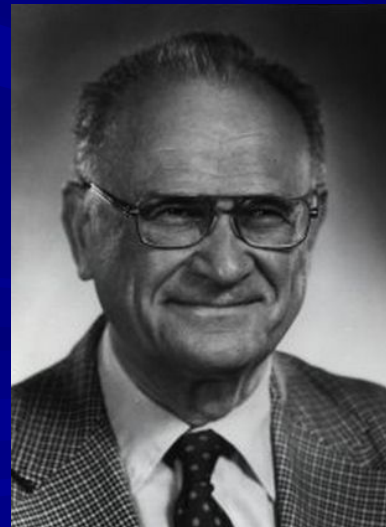


Paul John Flory (1910-85)
— Nobel Prize 1974

Конформационный анализ



Александр
Исаакович
Китайгородский
(1914–1985)



Harold
Abraham
Scheraga
(1921)

The Nobel Prize in Chemistry 2013



Martin Karplus



Michael Levitt



Arieh Warshel

***"for the development of multiscale models
for complex chemical systems"***

(conformational & quantum-mechanical methods)