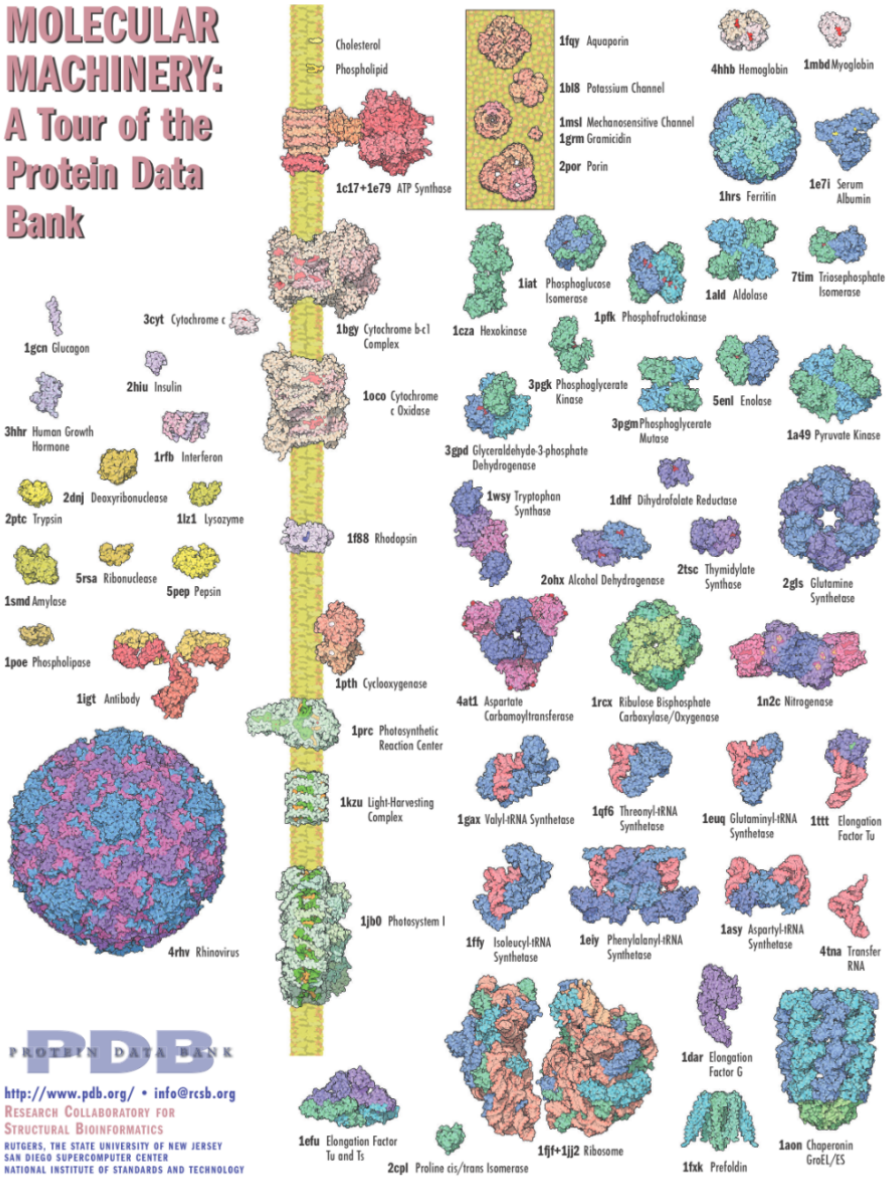
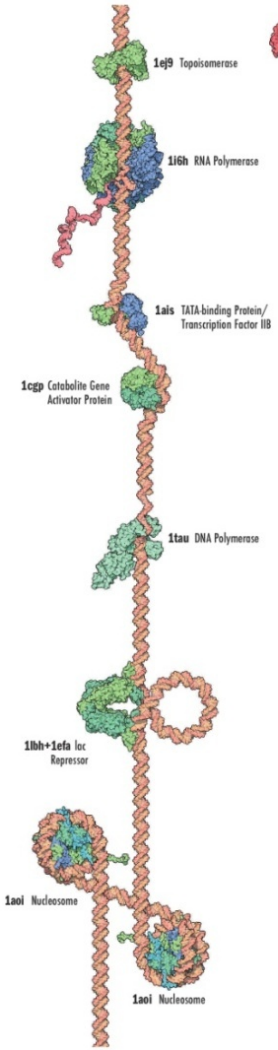
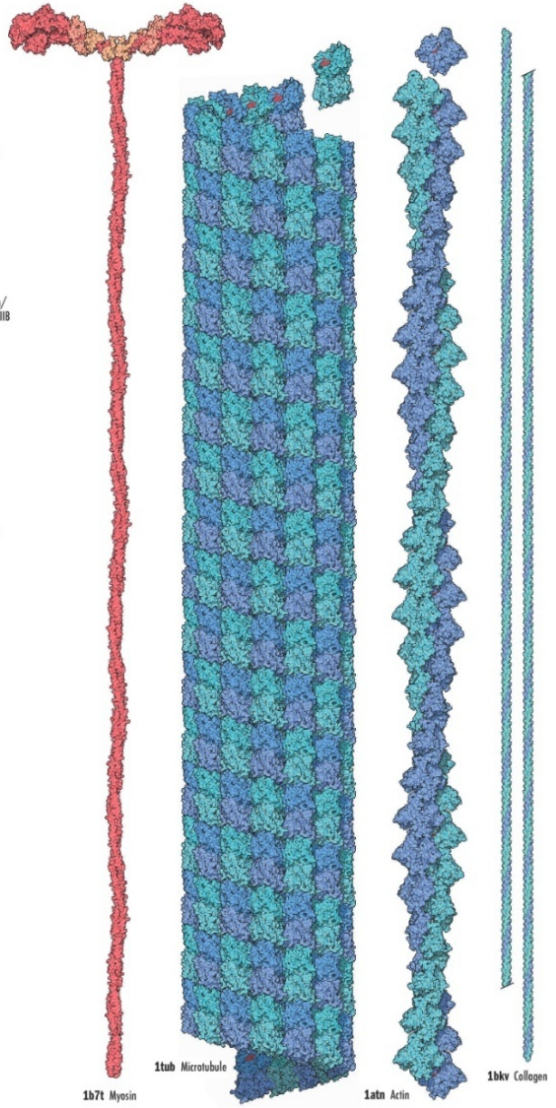
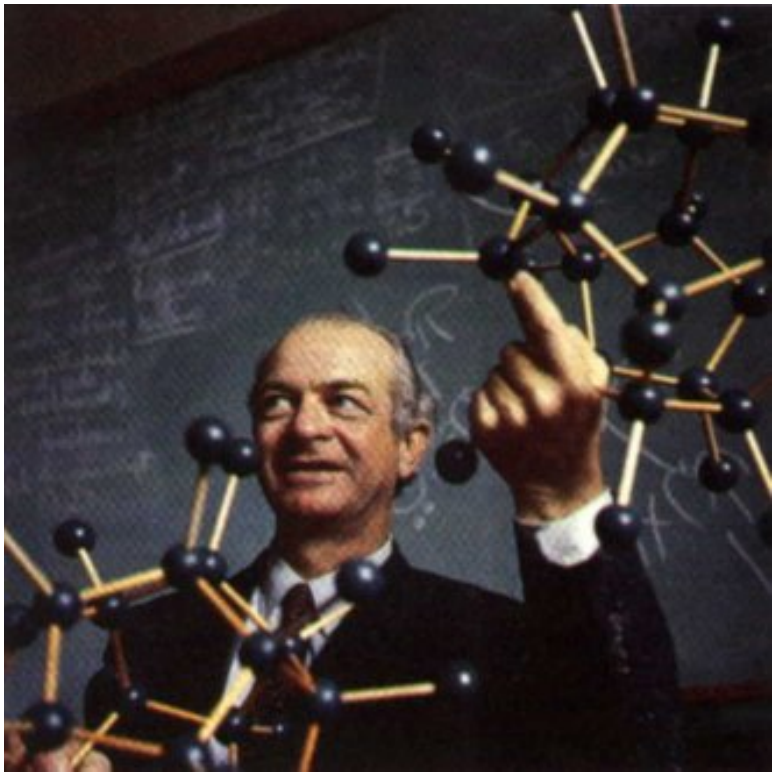
Proteins


MOLECULAR MACHINERY: A Tour of the Protein Data Bank
Cholesterol
Phospholipid
1c17+1e79 ATP Synthase
1fqy Aquaporin
1bl8 Potassium Channel
1msl Mechanosensitive Channel
1grm Gramicidin
2por Porin
4hhb Hemoglobin
1mbd Myoglobin
1hrs Ferritin
1e7i Serum Albumin
1bgy Cytochrome b-c1 Complex
1iat Phosphoglucose Isomerase
1cza Hexokinase
1pfk Phosphofructokinase
1ald Aldolase
7tim Triosephosphate Isomerase
3cyt Cytochrome c
1gcn Glucagon
2hiu Insulin
1oco Cytochrome c Oxidase
3pgk Phosphoglycerate Kinase
3pgm Phosphoglycerate Mutase
5enl Enolase
1a49 Pyruvate Kinase
3hhr Human Growth Hormone
1rfb Interferon
3gpd Glyceraldehyde-3-phosphate Dehydrogenase
2ptc Trypsin
2dnj Deoxyribonuclease
1lz1 Lysozyme
1wsy Tryptophan Synthase
1dhf Dihydrofolate Reductase
1f88 Rhodopsin
2ohx Alcohol Dehydrogenase
2tsc Thymidylate Synthase
2gls Glutamine Synthetase
1smd Amylase
5rsa Ribonuclease
5pep Pepsin
1poe Phospholipase
1pth Cyclooxygenase
1igt Antibody
4at1 Aspartate Carbamoyltransferase
1rcx Ribulose Bisphosphate Carboxylase/Oxygenase
1n2c Nitrogenase
1prc Photosynthetic Reaction Center
1kzu Light-Harvesting Complex
1gax Valyl-tRNA Synthetase
1qf6 Threonyl-tRNA Synthetase
1euq Glutaminyl-tRNA Synthetase
1ttt Elongation Factor Tu
4rhv Rhinovirus
1jb0 Photosystem I
1ffy Isoleucyl-tRNA Synthetase
1eiy Phenylalanyl-tRNA Synthetase
1asy Aspartyl-tRNA Synthetase
4tna Transfer RNA
PDB PROTEIN DATA BANK
http://www.pdb.org/ • info@rcsb.org
RESEARCH COLLABORATORY FOR STRUCTURAL BIOINFORMATICS
RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY
SAN DIEGO SUPERCOMPUTER CENTER
NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY
1efu Elongation Factor Tu and Ts
2cpl Proline cis/trans Isomerase
1fjf+1jj2 Ribosome
1dar Elongation Factor G
1fxk Prefoldin
1aon Chaperonin GroEL/ES


1ej9 Topoisomerase
1i6h RNA Polymerase
1ais TATA-binding Protein/ Transcription Factor IIB
1cgp Catabolite Gene Activator Protein
1tau DNA Polymerase
1lbh+1efa lac Repressor
1aoi Nucleosome
1aoi Nucleosome


1b7t Myosin
1tub Microtubule
1atn Actin
1bkv Collagen

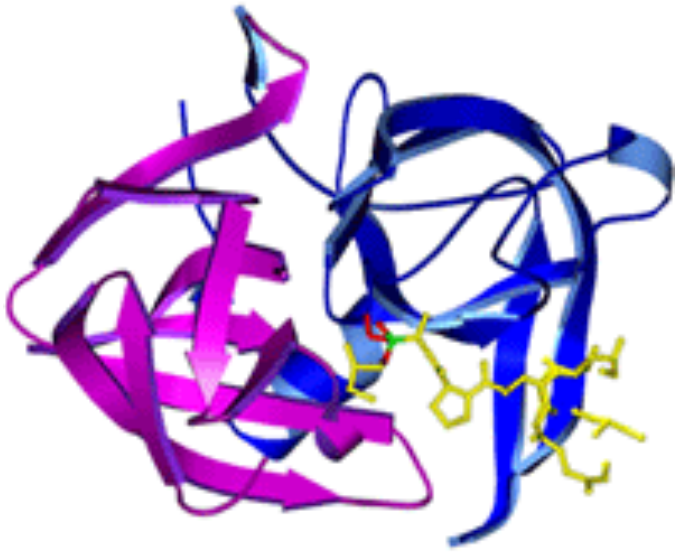
Linus Pauling
(1901-1994) Double Nobel
Laureat



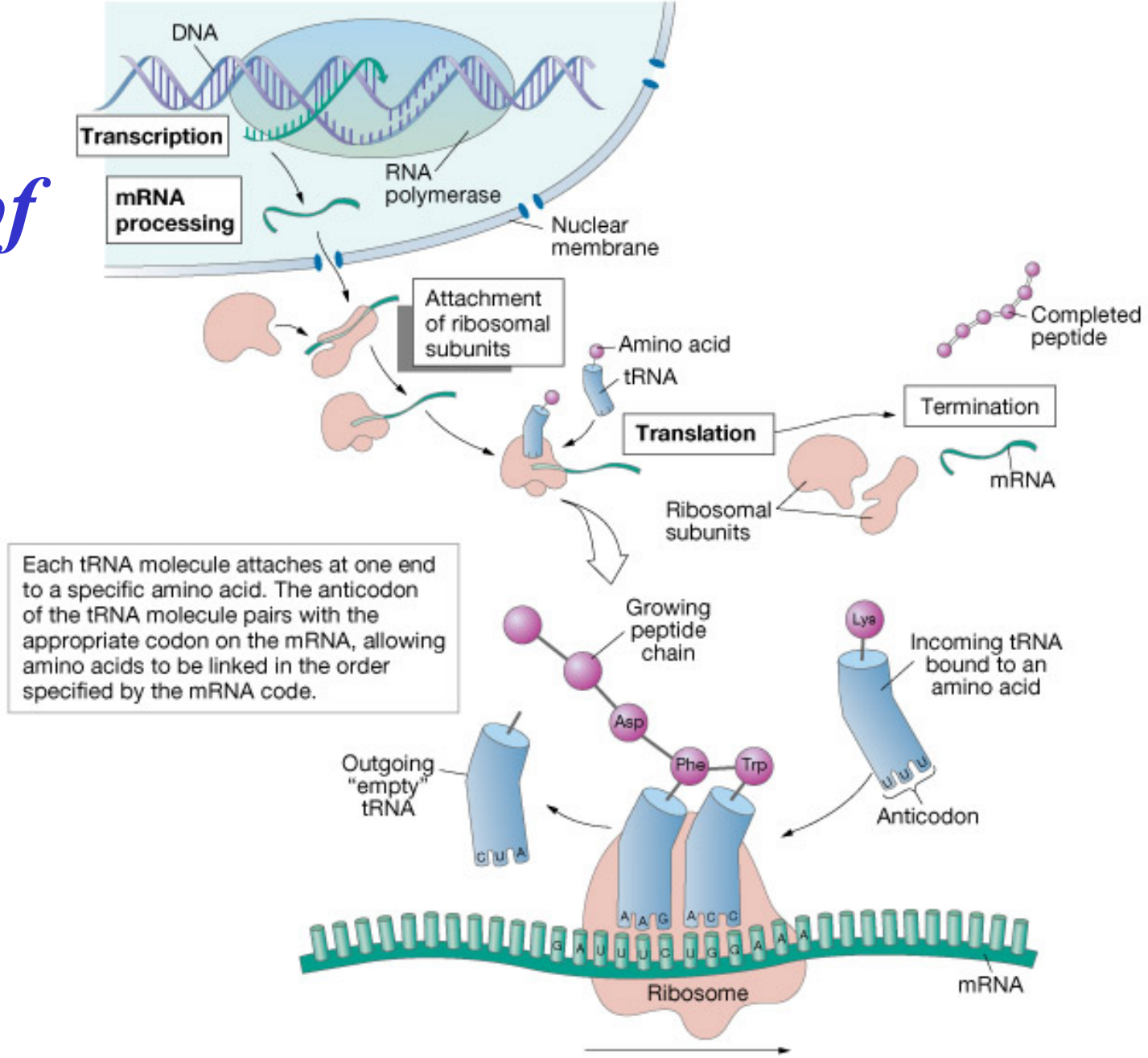
The father of "Structural Chemistry"

Proteins

Structurally complex functionally sophisticated long repeats of individual monomers (amino acid's)
15% of cell's dry mass

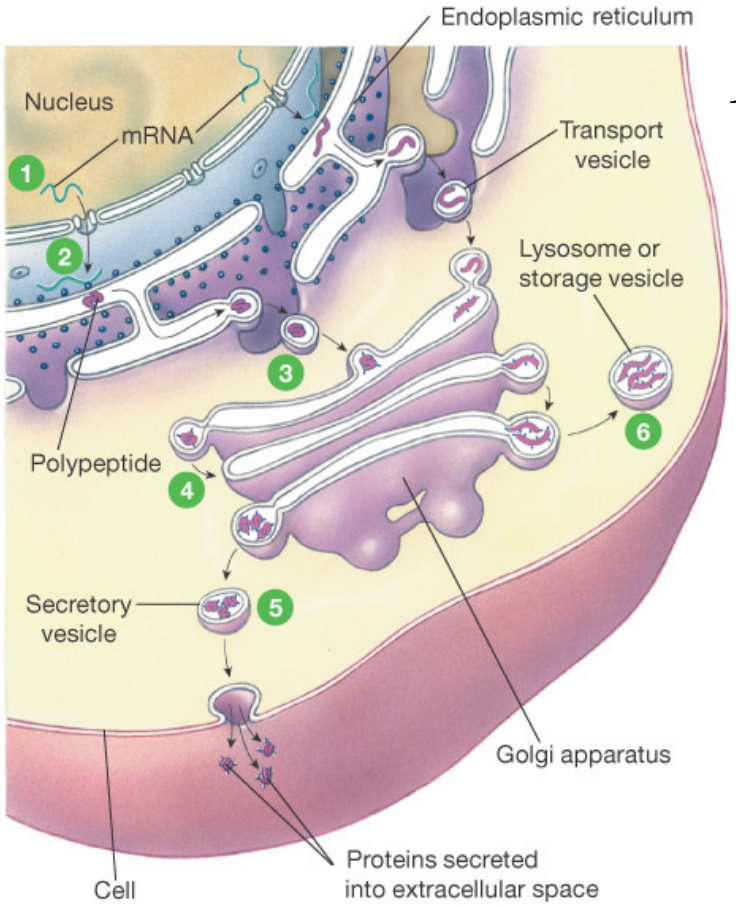


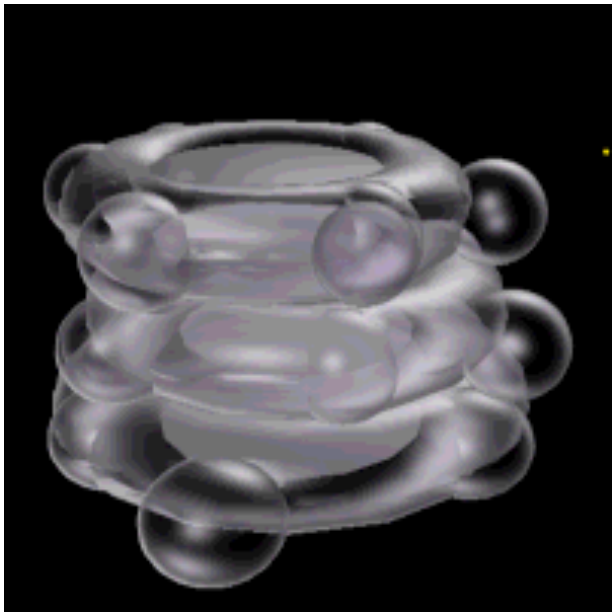
Main dogma of biology



Post–translational protein modificaitons

1. Newly transcribed mRNA goes to the cytoplasm.
2. mRNA on ribosomes is translated into a string of amino acids, which is directed into the lumen of the endoplasmic reticulum. Post-translation modification begins here.
3. Transport vesicles take proteins to the Golgi apparatus.
4. Post-translational modification continues in the Golgi.
5. Proteins that will leave the cell are packaged in secretory vesicles.
6. Proteins that remain in the cell are packaged in lysosomes or storage vesicles.





Complex Proteins

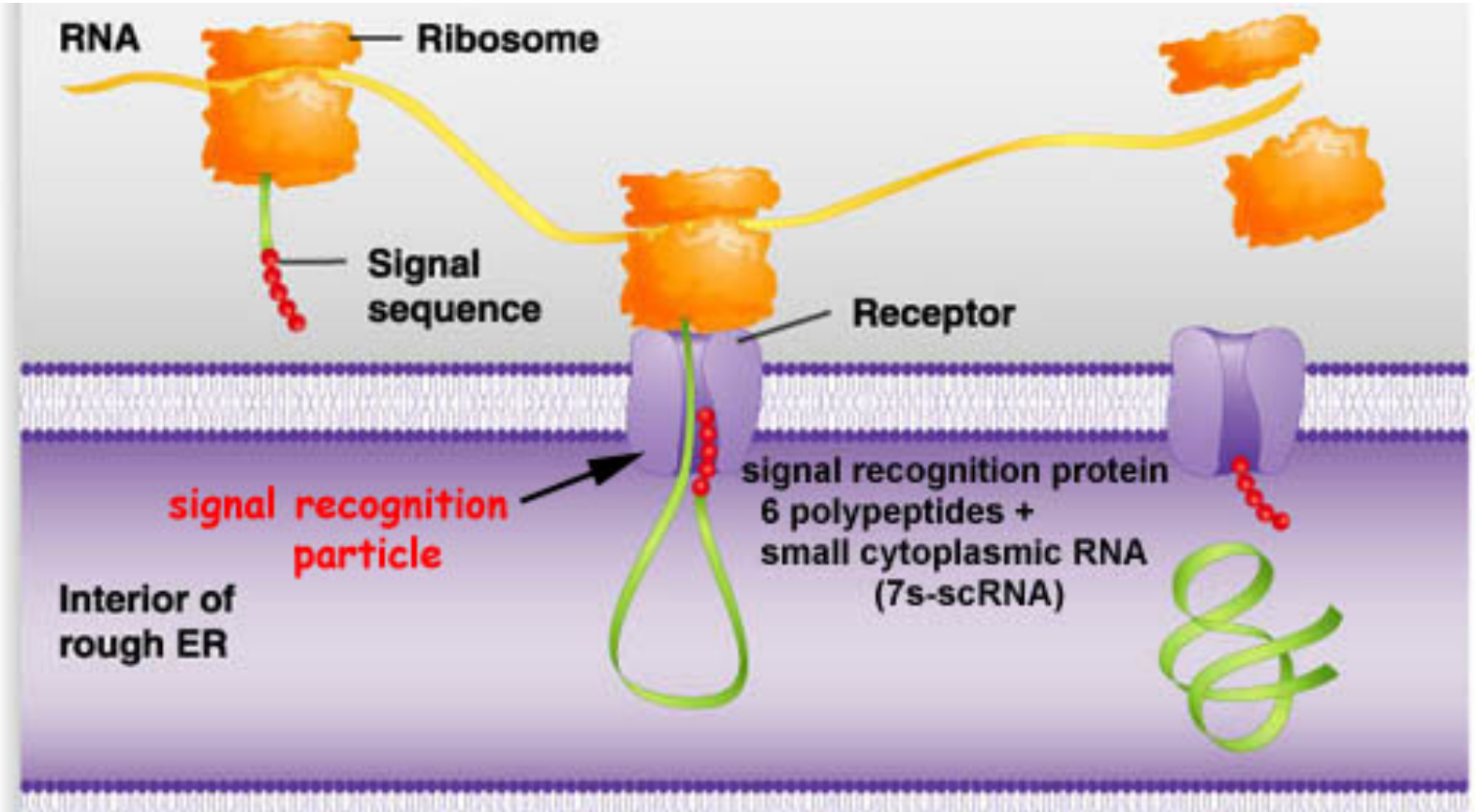
nucleoproteins - ribosomes & organelles

glycoproteins - antibodies, cell surface proteins

lipoproteins - blood, membrane, & transport proteins

Protein Sorting

- No signal sequence ⇒ protein stays in cell
- Signal sequence ⇒ protein destined for translocation into organelles or for export



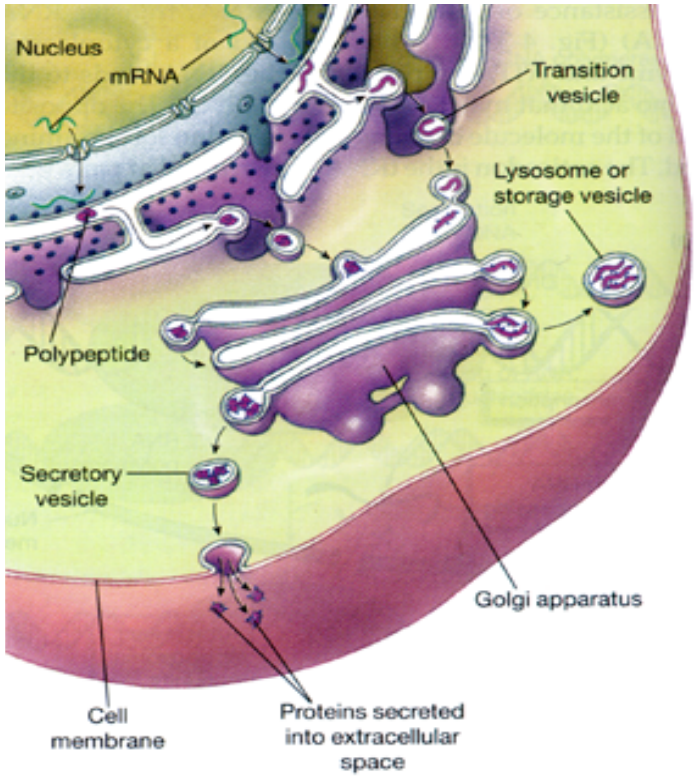
For “export proteins”: Signal sequence leads growing polypeptide chain across ER membrane into ER lumen

Modifications in ER

Transition vesicles to

Golgi apparatus for further modifications

Transport vesicles to cell membrane



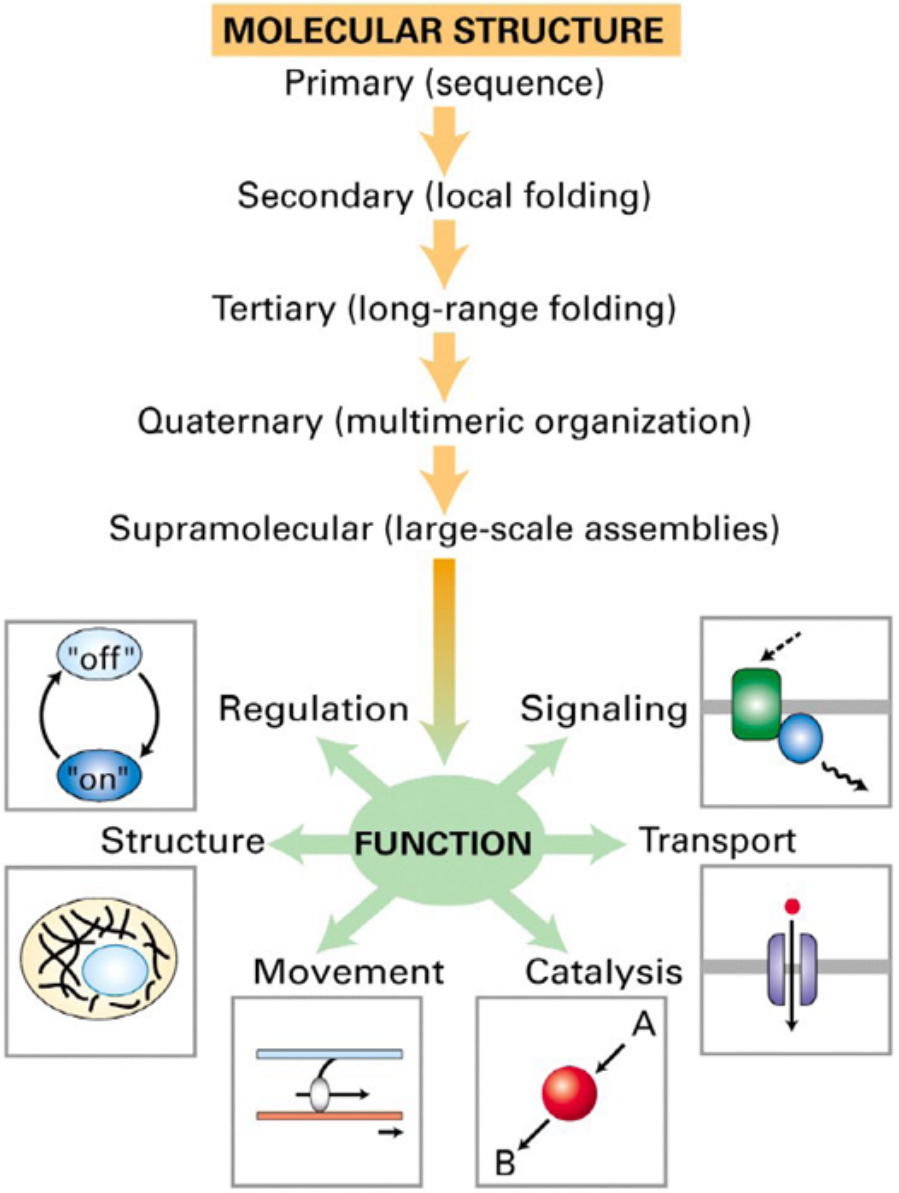
The Hierarchal Structure of Proteins

- **Primary Structure**:
  - Amino acid sequence from N- to C-terminus
  - Ultimately determines all higher order structure and function
  - Driven and stabilized by covalent bonds

- **Secondary Structure:**
  - Local, spatial interactions between functional groups of the protein backbone
  - Driven and stabilized by the hydrogen bond
  - Not usually a determinant of function

- **Tertiary Structure:**
  - Three-dimensional folding of a polypeptide
  - Driven and stabilized largely by weak, hydrophobic interactions
  - Often dictates biological activity

- **Quaternary Structure:**
  - Specific interactions between two or more proteins
  - Can be driven and stabilized by any combination of bond types



Hierarchy

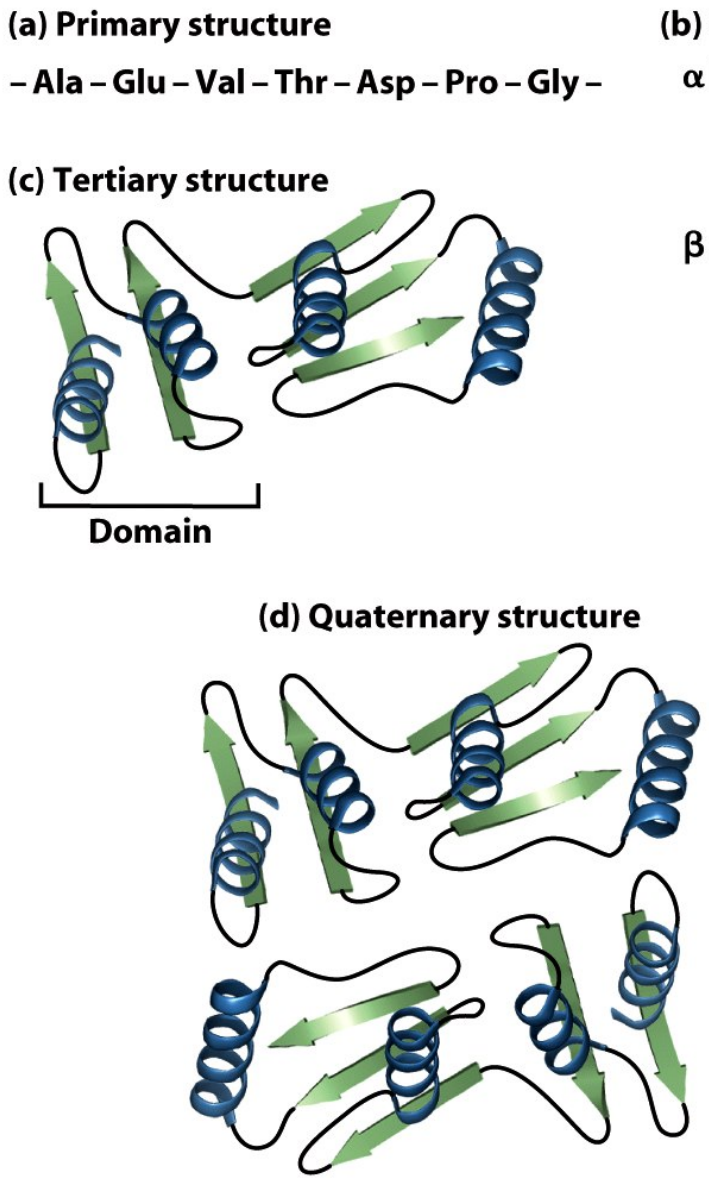


Figure 3-2
Molecular Cell Biology, Sixth Edition

Folding order

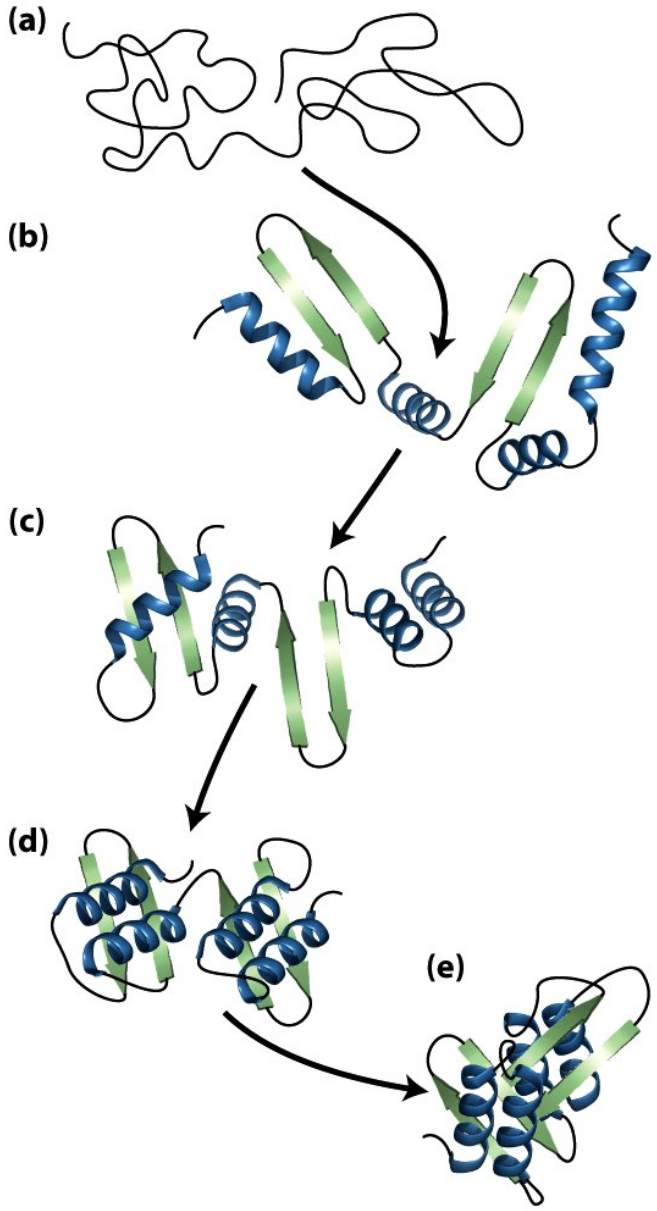
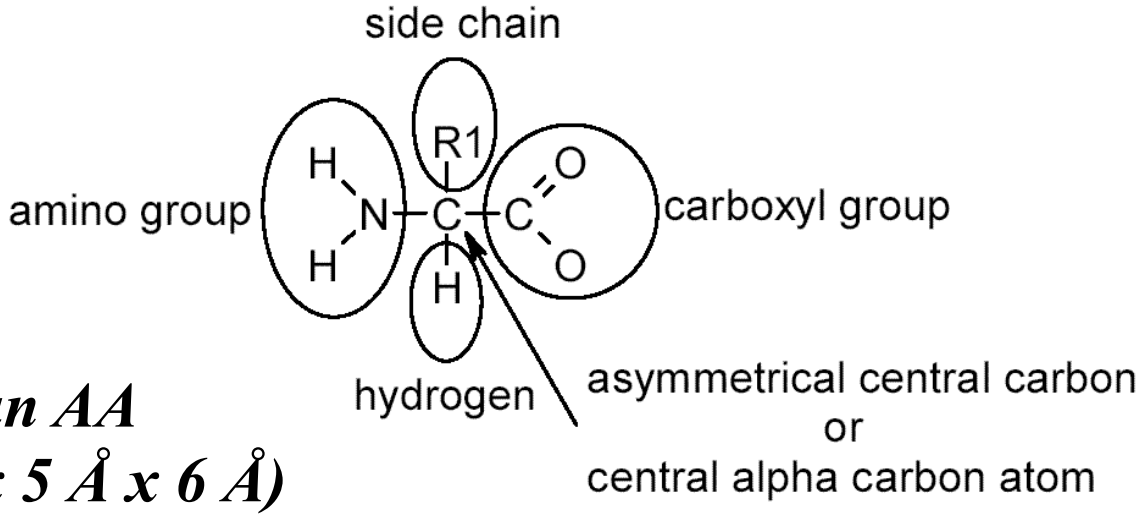


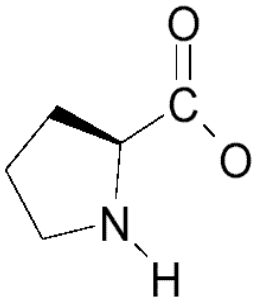
Figure 3-15
Molecular Cell Biology, Sixth Edition

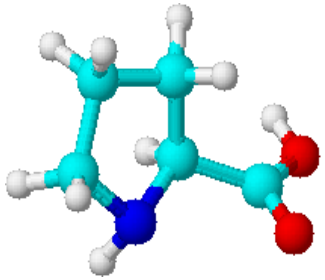
Primary structure

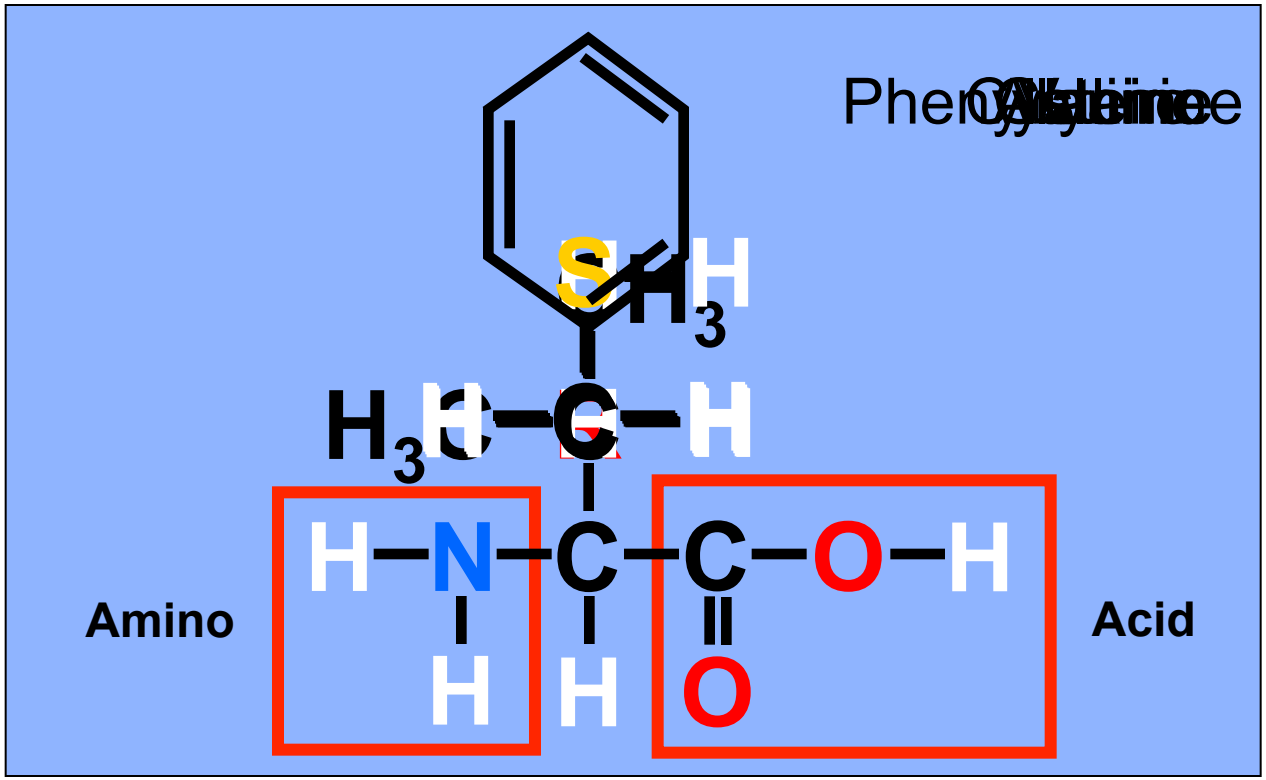
Amino Acids



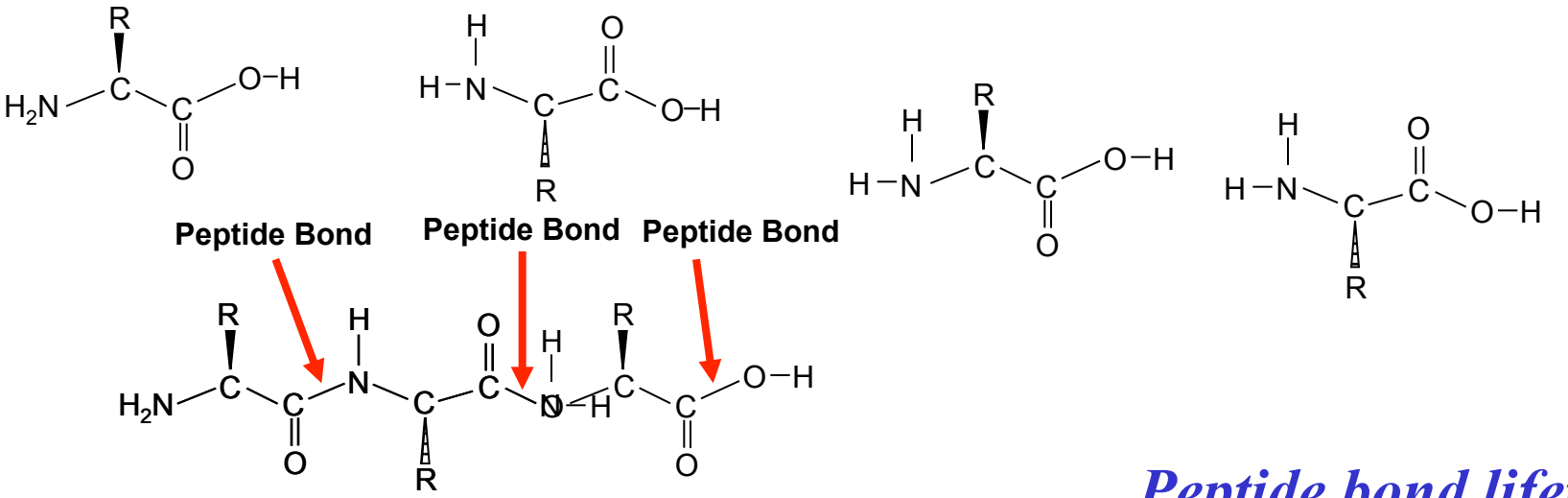
The average volume of an AA residue is 161 Å³ (5 Å x 5 Å x 6 Å)



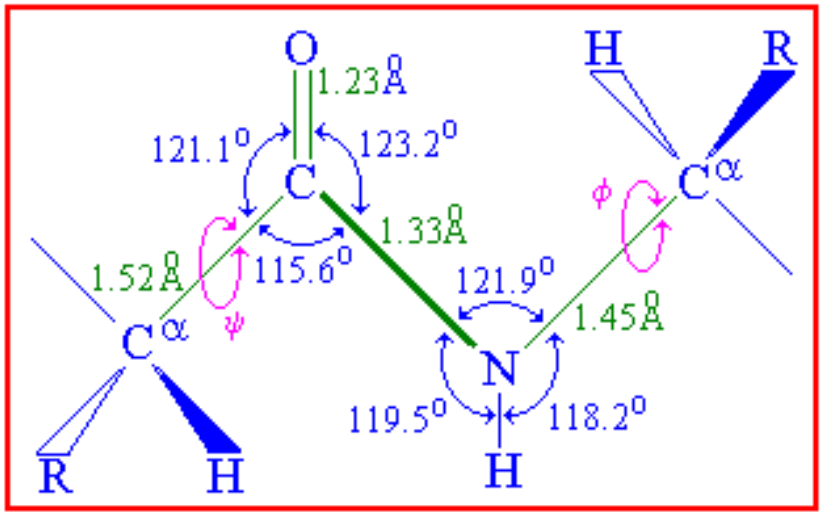




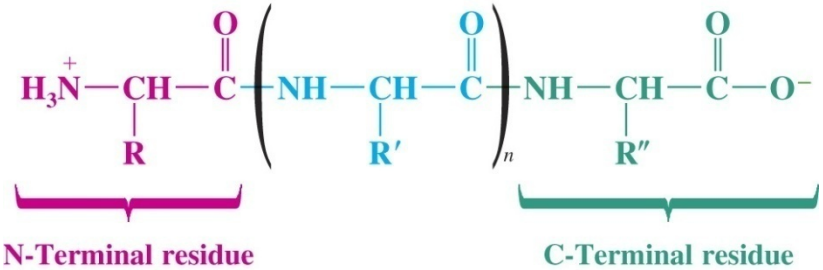
Polypeptide – condensation Reaction



Peptide bond lifetime – 7 years.
(pH = 7, T= 25 ^{0}C)

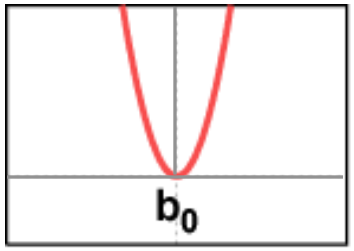


Polypeptides are customarily written with the N-terminal residue to the left



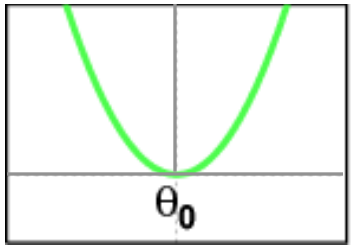
Potential function of macromolecules

U = Bond + Angle + Dihedral + van der Waals + Electrostatic



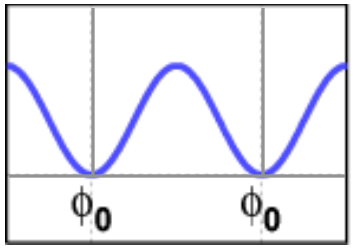
Bond

$$\sum_{i}^{bonds} K_{b,i}(b_i - b_{0,i})^2$$



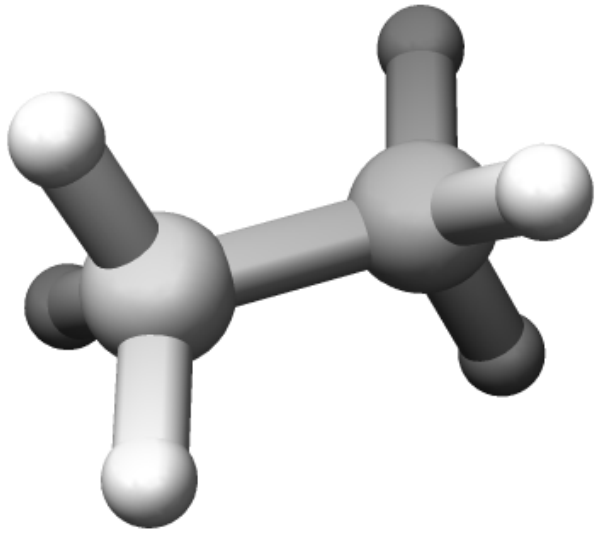
Angle

$$\sum_{i}^{\substack{bond \\ angles}} K_{\theta,i}(\theta_i - \theta_{0,i})^2$$



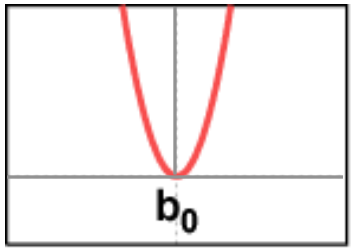
Dihedral

$$\sum_{i}^{\substack{torsion \\ angles}} K_{\phi,i}\{1 - \cos[n_i(\phi_i - \phi_{0,i})]\}$$



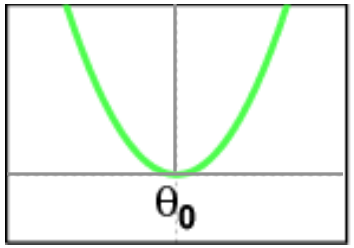
Potential function of macromolecules

U = **Bond + Angle + Dihedral + van der Waals + Electrostatic**



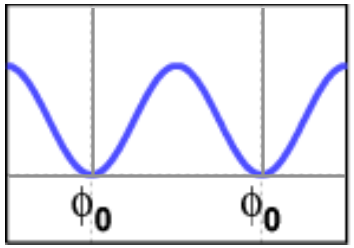
Bond

$$\sum_{i}^{bonds} K_{b,i}(b_i - b_{0,i})^2$$



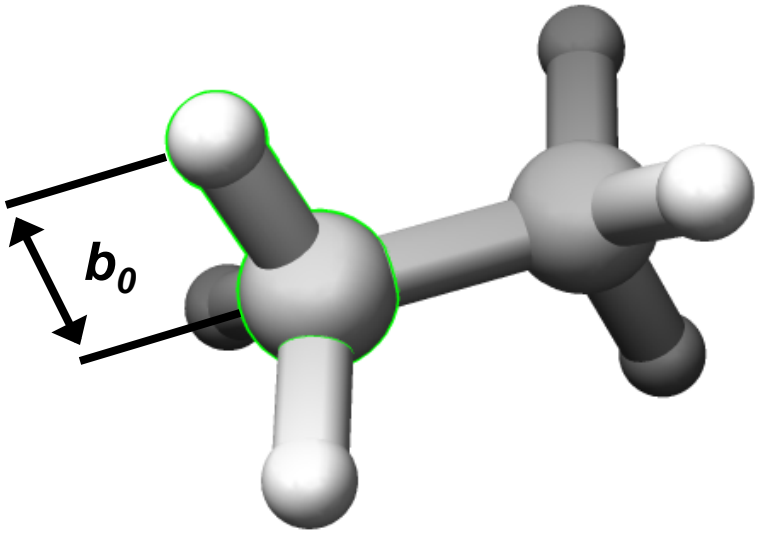
Angle

$$\sum_{i}^{\substack{bond \\ angles}} K_{\theta,i}(\theta_i - \theta_{0,i})^2$$



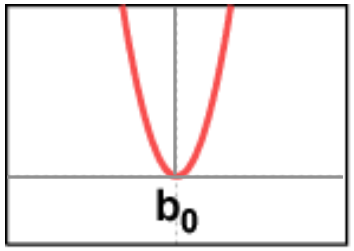
Dihedral

$$\sum_{i}^{\substack{torsion \\ angles}} K_{\phi,i}\{1 - \cos[n_i(\phi_i - \phi_{0,i})]\}$$



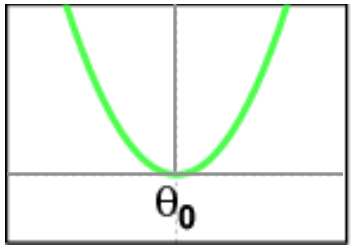
Potential function of macromolecules

U = **Bond + Angle + Dihedral** + van der Waals + Electrostatic



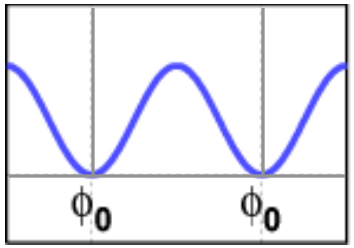
Bond

$$\sum_{i}^{bonds} K_{b,i}(b_i - b_{0,i})^2$$



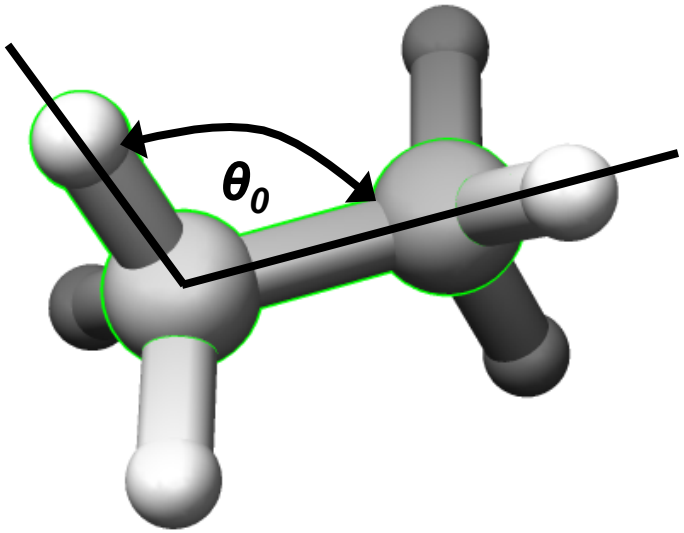
Angle

$$\sum_{i}^{\substack{bond \\ angles}} K_{\theta,i}(\theta_i - \theta_{0,i})^2$$



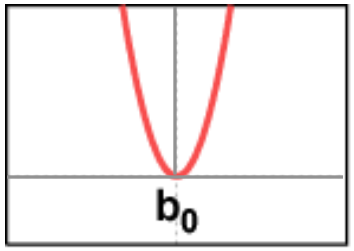
Dihedral

$$\sum_{i}^{\substack{torsion \\ angles}} K_{\phi,i}\{1 - \cos[n_i(\phi_i - \phi_{0,i})]\}$$



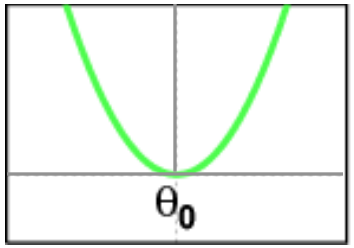
Potential function of macromolecules

U = **Bond + Angle + Dihedral** + van der Waals + Electrostatic



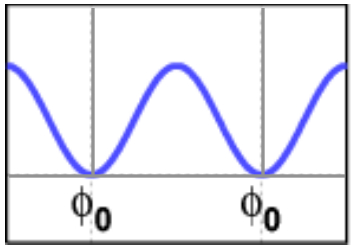
Bond

$$\sum_{i}^{bonds} K_{b,i}(b_i - b_{0,i})^2$$



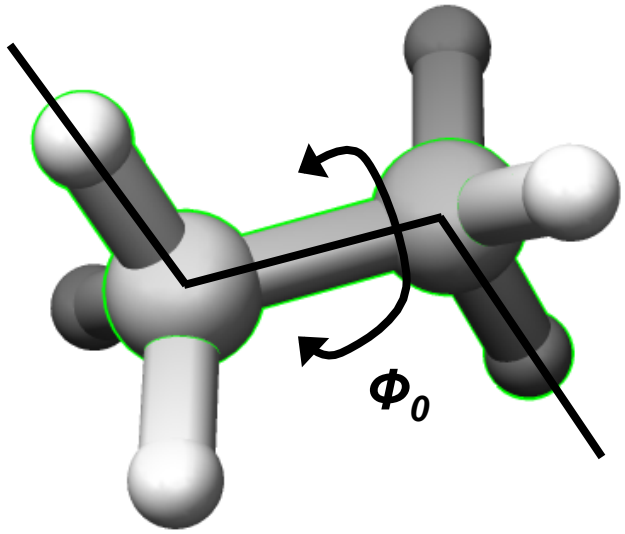
Angle

$$\sum_{i}^{\substack{bond \\ angles}} K_{,i}(\theta_i - \theta_{0,i})^2$$



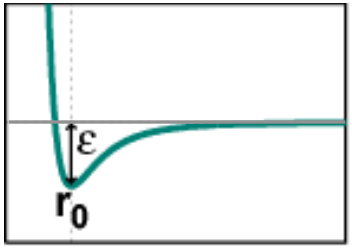
Dihedral

$$\sum_{i}^{\substack{torsion \\ angles}} K_{\phi,i}\{1 - \cos[n_i(\phi_i - \phi_{0,i})]\}$$



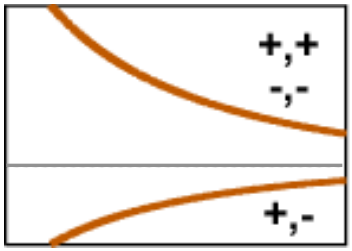
Non-bonded components of potential function

U_{nb} = van der Waals + Electrostatic



van der Waals

$$\sum_{pairs\cdot i,j} [\varepsilon_{ij} \left(\frac{r_{0,ij}}{r_{ij}} \right)^{12} - 2\varepsilon_{ij} \left(\frac{r_{0,ij}}{r_{ij}} \right)^{6}]$$



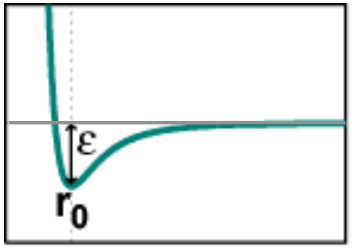
Electrostatic

$$332 \sum_{pairs\cdot i,j} \left(\frac{q_i q_j}{r_{ij}} \right)$$

To a large degree, macromolecule structure is dependent on non-bonded atomic interactions

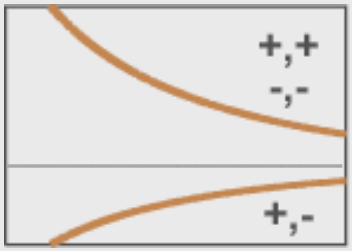
Non-bonded components of potential function

U_{nb} = van der Waals + Electrostatic



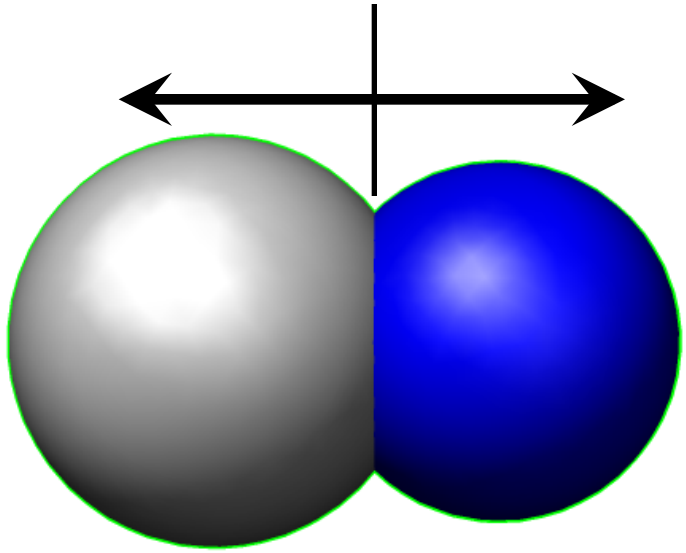
van der Waals

$$\sum_{pairs\cdot i,j} [\varepsilon_{ij}\left(\frac{r_{0,ij}}{r_{ij}}\right)^{12} - 2\varepsilon_{ij}\left(\frac{r_{0,ij}}{r_{ij}}\right)^{6}]$$



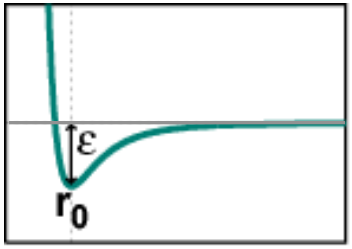
Electrostatic

$$332 \sum_{pairs\cdot i,j} \left(\frac{q_i q_j}{r_{ij}}\right)$$



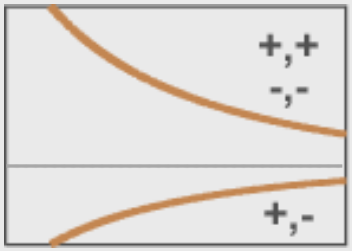
- **Non-bonded components of potential function**

U_{nb} = van der Waals + Electrostatic



van der Waals

$$\sum_{pairs\cdot i,j} [\varepsilon_{ij}\left(\frac{r_{0,ij}}{r_{ij}}\right)^{12} - 2\varepsilon_{ij}\left(\frac{r_{0,ij}}{r_{ij}}\right)^{6}]$$



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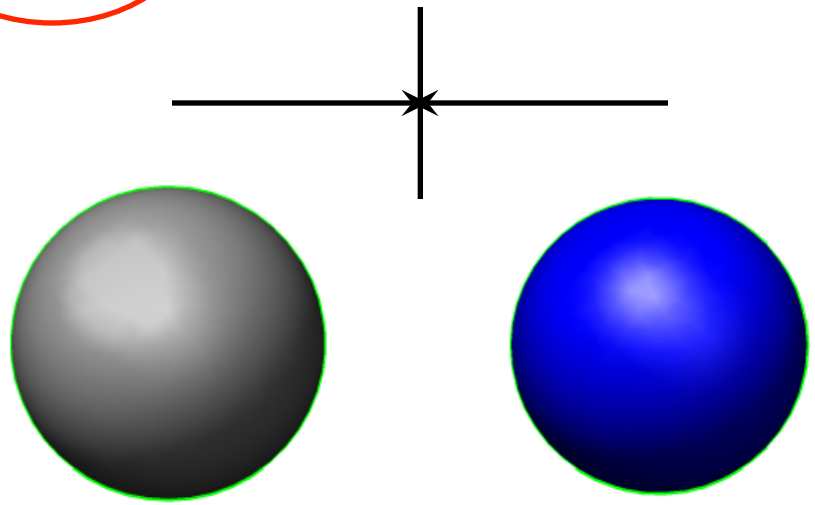

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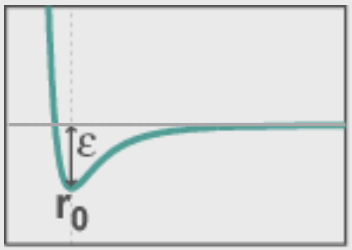
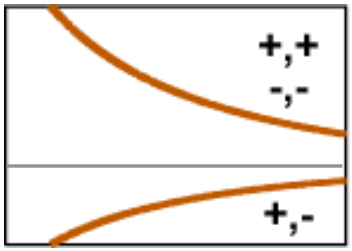


van der Waals

$$\sum_{pairs\text{-}i,j} [\varepsilon_{ij}\left(\frac{r_{0,ij}}{r_{ij}}\right)^{12} - 2\varepsilon_{ij}\left(\frac{r_{0,ij}}{r_{ij}}\right)^{6}]$$



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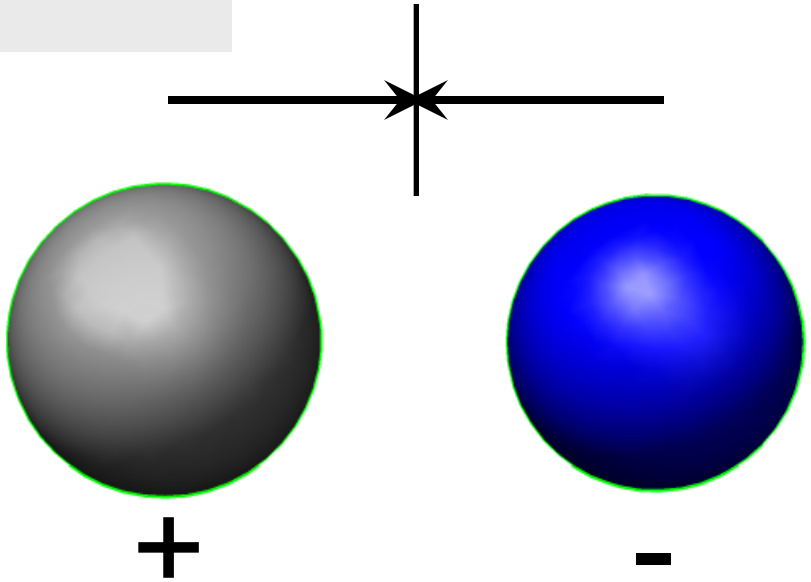

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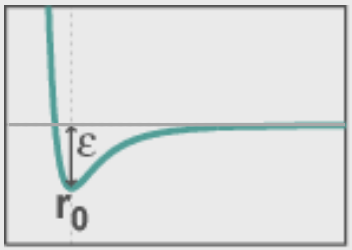
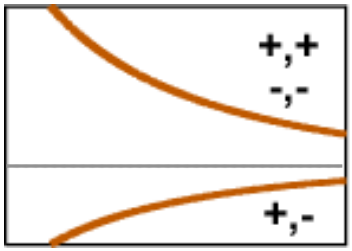
U_{nb} = van der Waals + Electrostatics



van der Waals

$$\sum_{pairs\text{-}i,j} [\varepsilon_{ij}\left(\frac{r_{0,ij}}{r_{ij}}\right)^{12} - 2\varepsilon_{ij}\left(\frac{r_{0,ij}}{r_{ij}}\right)^{6}]$$



Electrostatic

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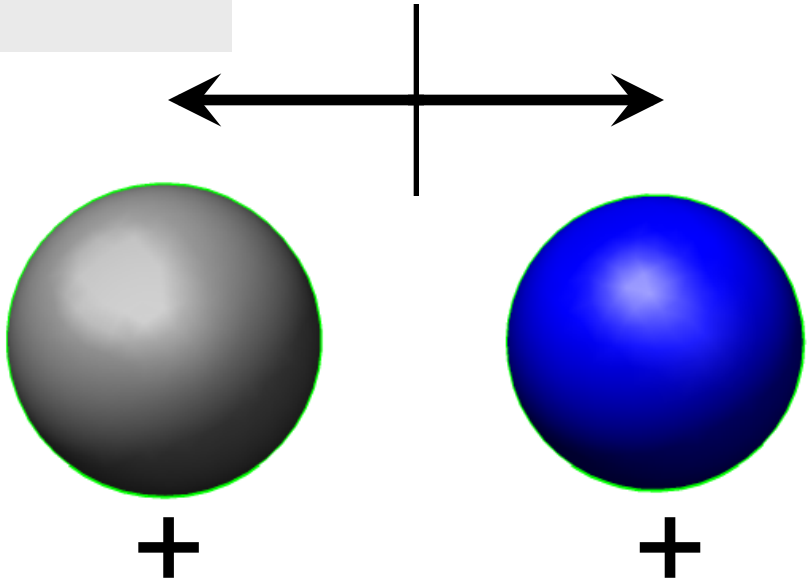
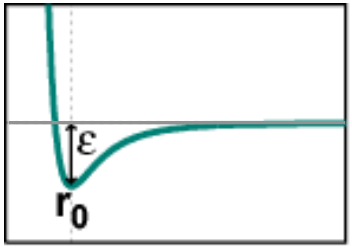


Molecular Dynamics

- **Non-bonded components of potential function**



van der Waals

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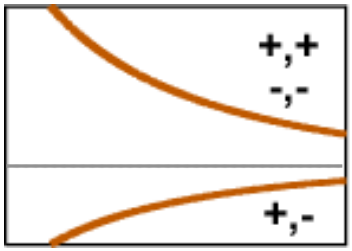


Electrostatic

$$332 \sum_{pairs\cdot i,j}\left(\frac{q_i q_j}{r_{ij}}\right)$$

NOTE:

Sum over all pairs of N atoms, or

$$\frac{N * N - 1}{2} \quad \textbf{pairs}$$

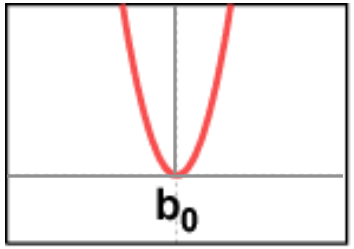
N is often between $5x10^5$ to $5x10^6$

For $5x10^5$ that is $1.25x10^{11}$ pairs

THAT IS A LOT OF POSSIBLE PAIRS!

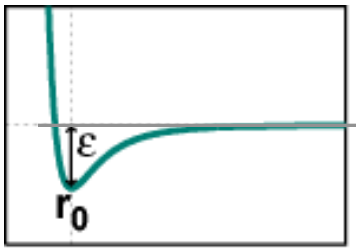
Molecular Dynamics

Potential functions



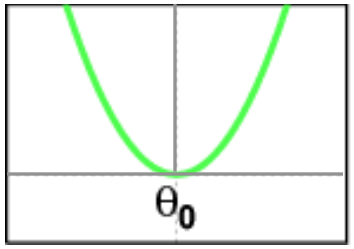
Bond

$$\sum_{i}^{bonds} K_{b,i}(b_i - b_{0,i})^2$$



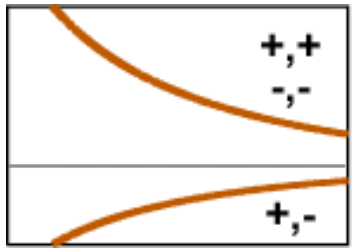
van der Waals

$$\sum_{pairs\text{-}i,j} [\varepsilon_{ij}\left(\frac{r_{0,ij}}{r_{ij}}\right)^{12} - 2\varepsilon_{ij}\left(\frac{r_{0,ij}}{r_{ij}}\right)^{6}]$$



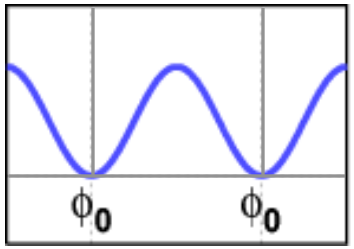
Angle

$$\sum_{i}^{\substack{bond \\ angles}} K_{\theta,i}(\theta_i - \theta_{0,i})^2$$



Electrostatic

$$332 \sum_{pairs\text{-}i,j} \left(\frac{q_i q_j}{r_{ij}}\right)$$

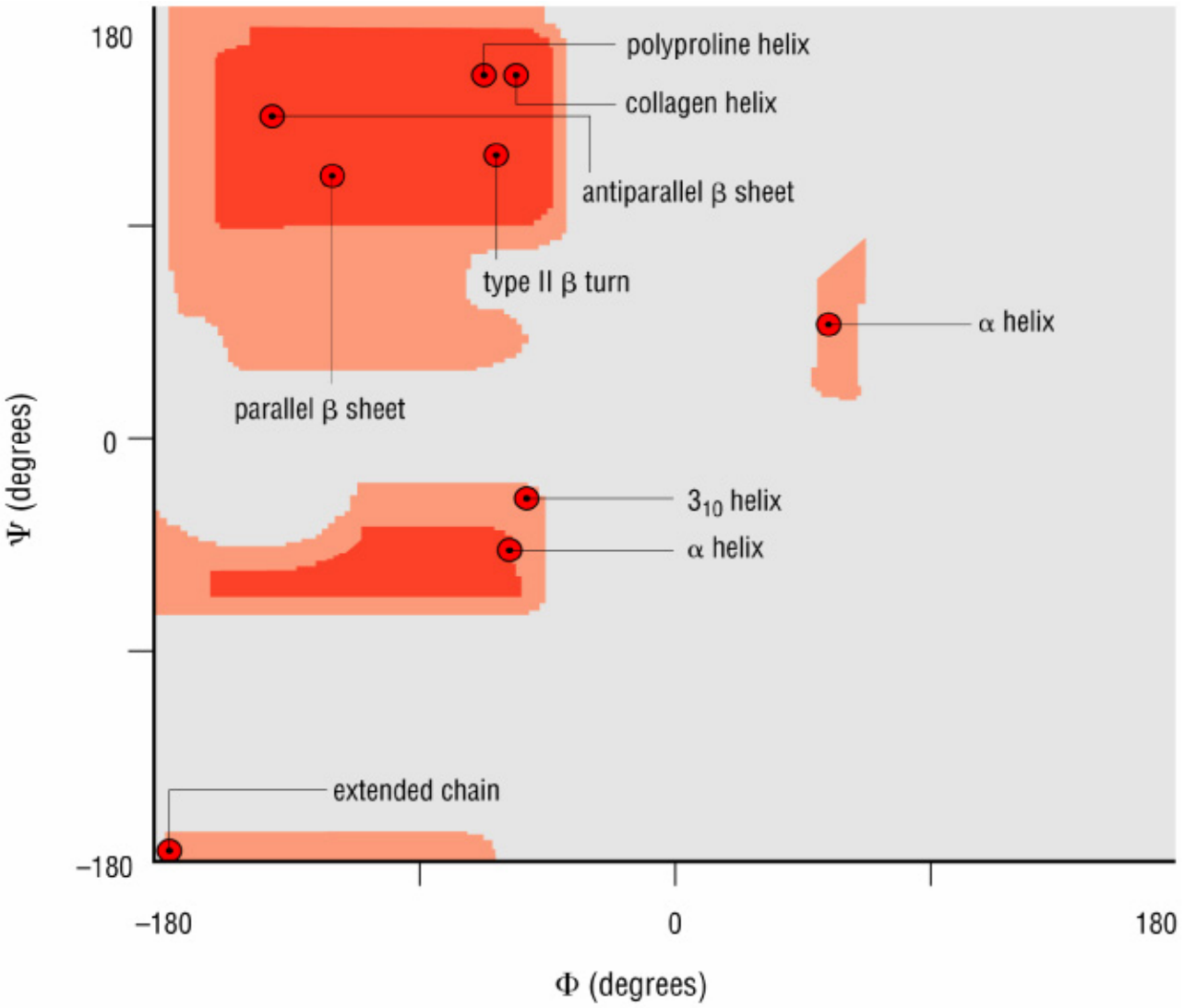


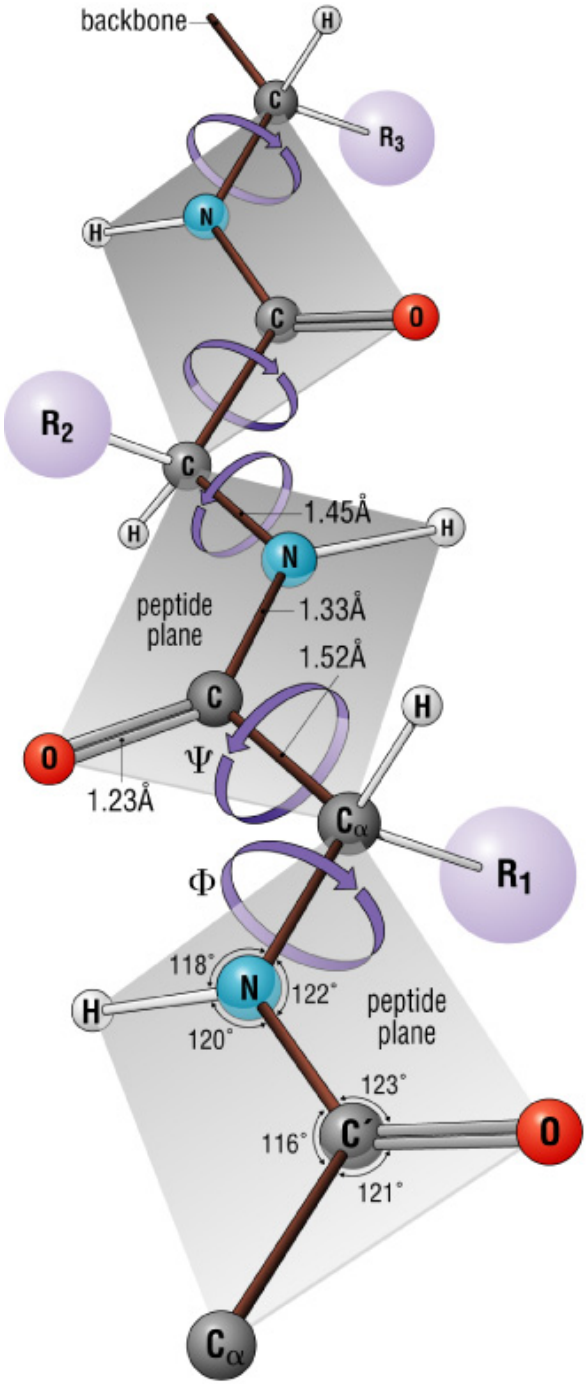
Dihedral

$$\sum_{i}^{\substack{torsion \\ angles}} K_{\phi,i}\{1 - \cos[n_i(\phi_i - \phi_{0,i})]\}$$

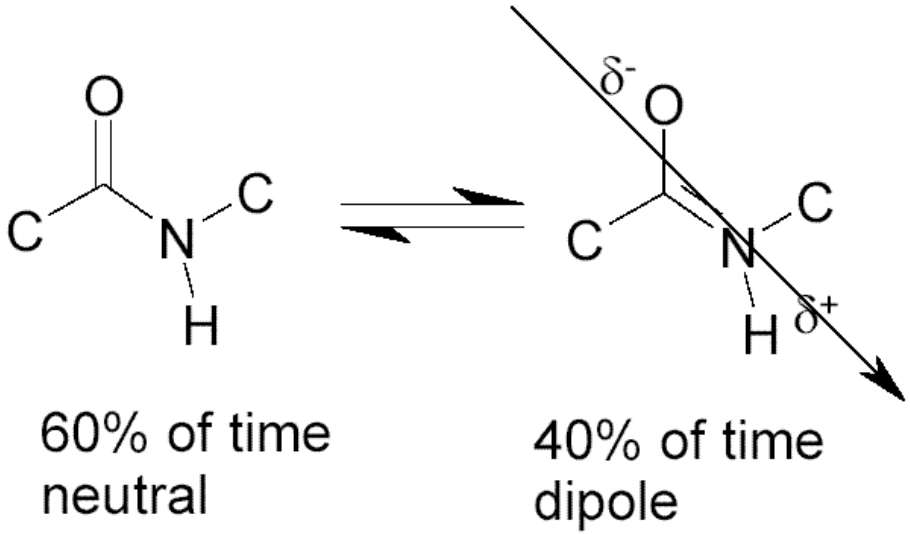
1. Levitt M. Hirshberg M. Sharon R. Daggett V. Comp. Phys. Comm. (1995) 91: 215-231
2. Levitt M. *et al.* J. Phys. Chem. B (1997) 101: 5051-5061

Backbone configuration is restricted by side chains





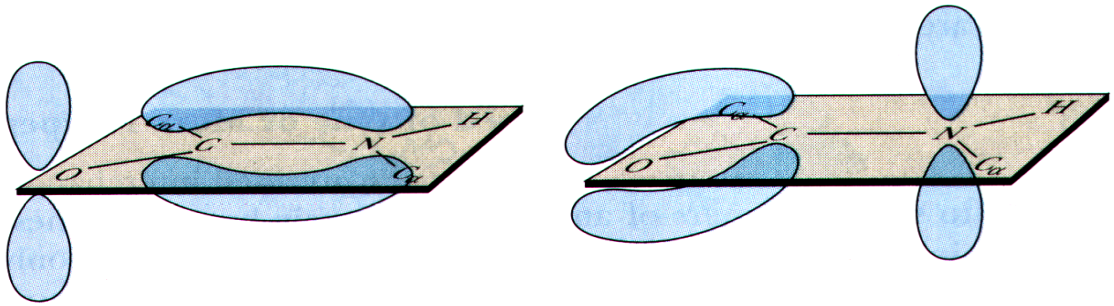
Peptide bonds properties



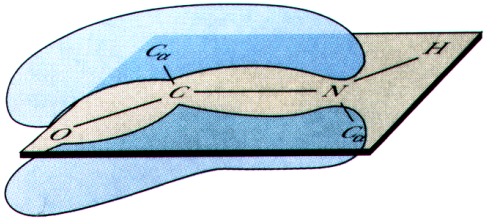
60% of time neutral

40% of time dipole

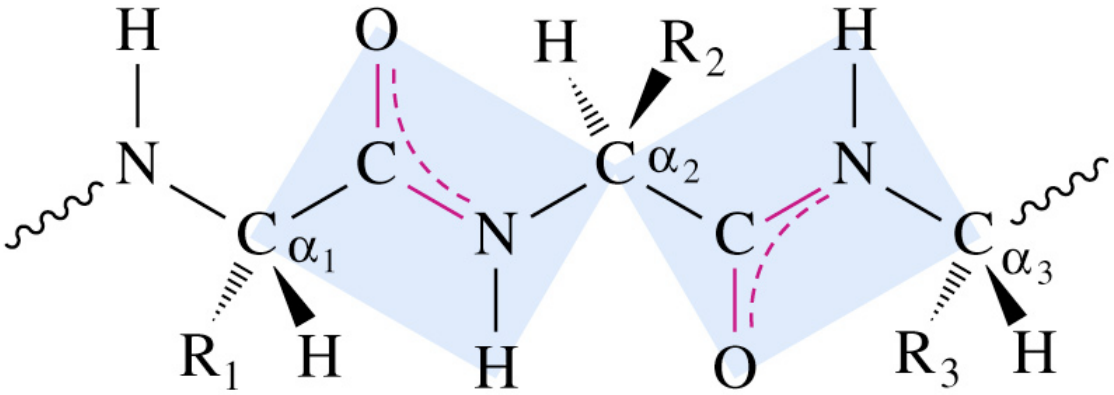
- Approximately 40% double bond character is due to thr resonance.
- Electrons are delocalized over three atoms: O, C, N



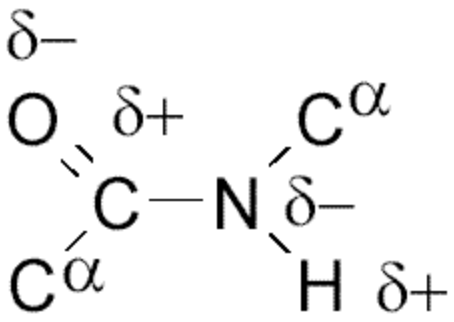
- Rigid, due to partial double bond character (resonance).



- It is planar

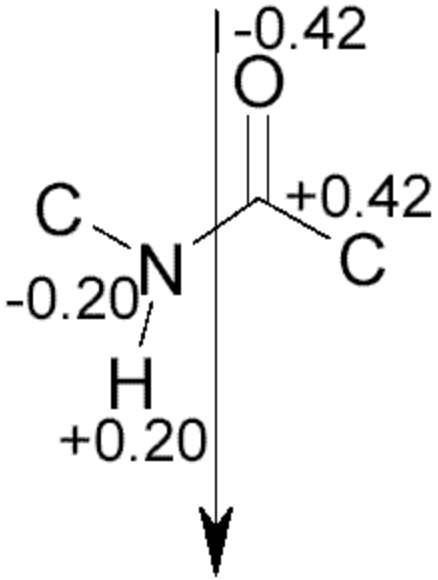


Dipole moment



δ^- = 0.42 electron units

δ + = 0.20 electron units

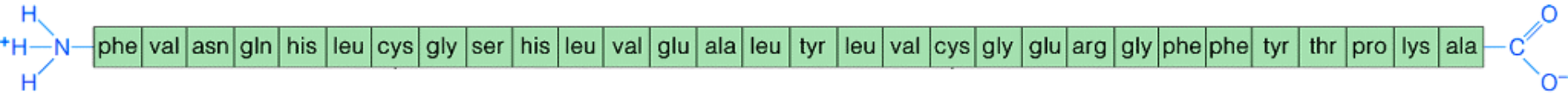


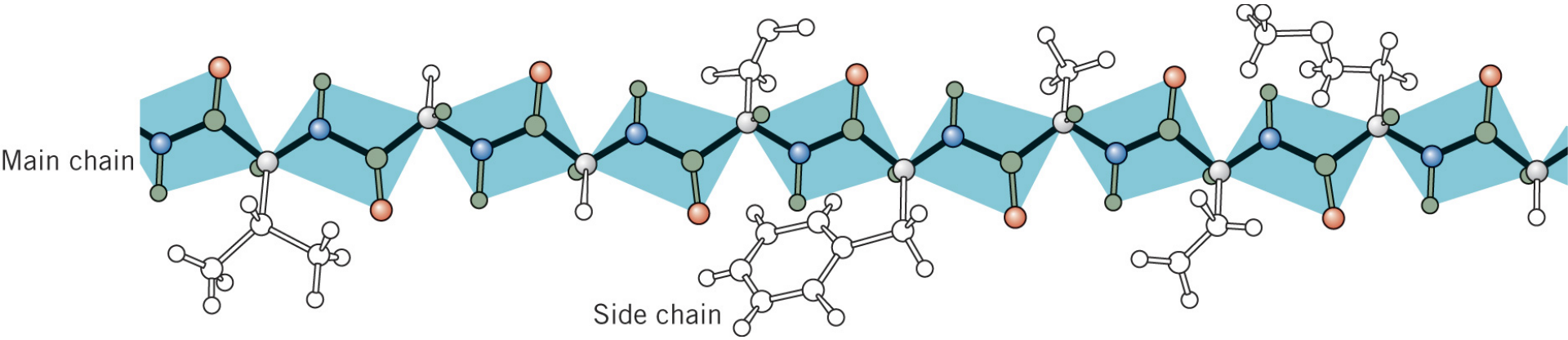
The **dipole moment** of the peptide bond = **3.5 D**
(D = Debye units, two charges separated by 1 Angstrom = 4.8 D)

The diploe moment of **water** is **1.85 D**.

The peptide backbone is usually not ionized!

Polar – can form at least two hydrogen bonds.



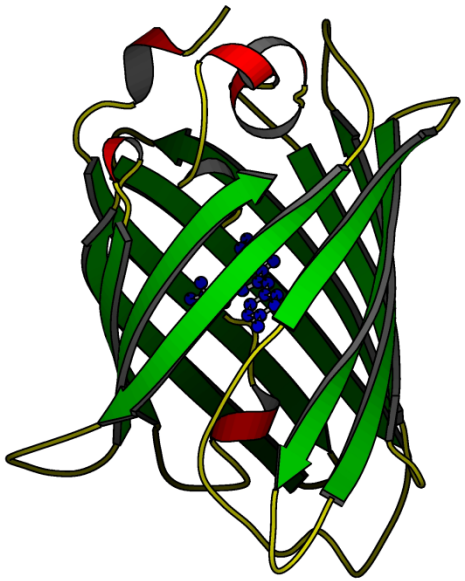


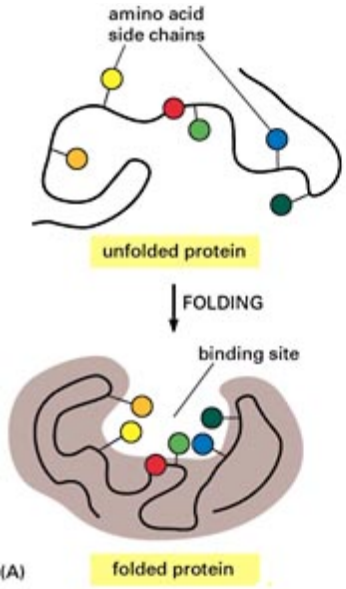
There are 20 possible AAs and if there are 100 AAs in the protein, this gives $(20)^{100} = 1.27 \times 10^{130}$ different protein of this length possible.

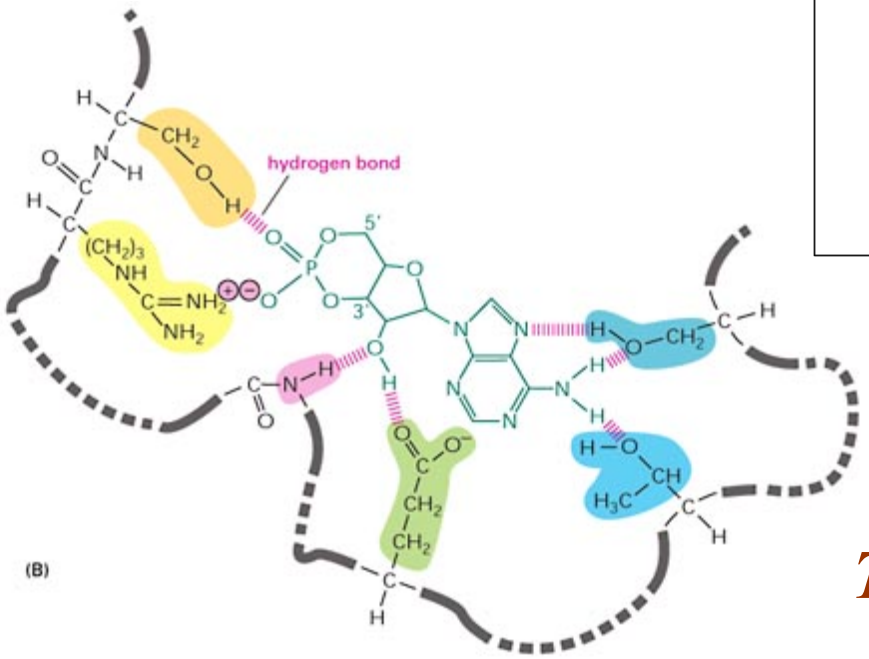
Noncovalent Forces in Protein Structure

- They act at short-range
- They are exceedingly numerous
- Noncovalent energies are 2 to 3 orders of magnitude lower than covalent bonds.

Green Fluorescent Protein

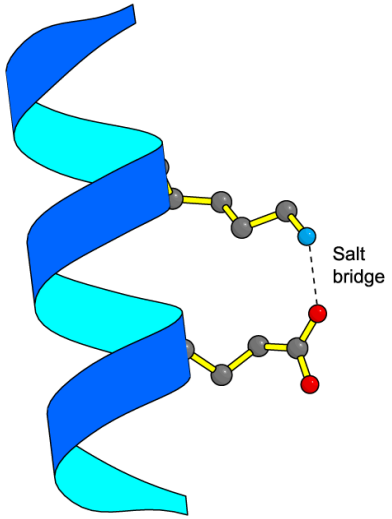






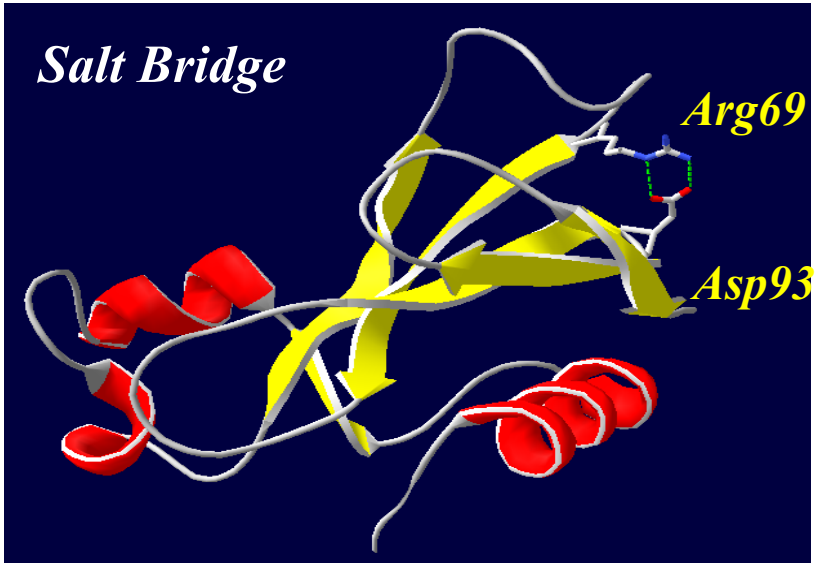
Thermal energy 25 ^{0}C is equal 0.6 kcal/mol

Ionic interactions are often called ***salt bridges*** and occur between carboxylate groups and lysines and arginines.



The potential energy of two charges separated by 4 Å is
≈ 1 kcal / mole in water
≈ 20 kcal / mole inside the protein.

If a charge is buried in the core of a protein, there is a large energetic advantage in burying a group of opposite charge nearby.

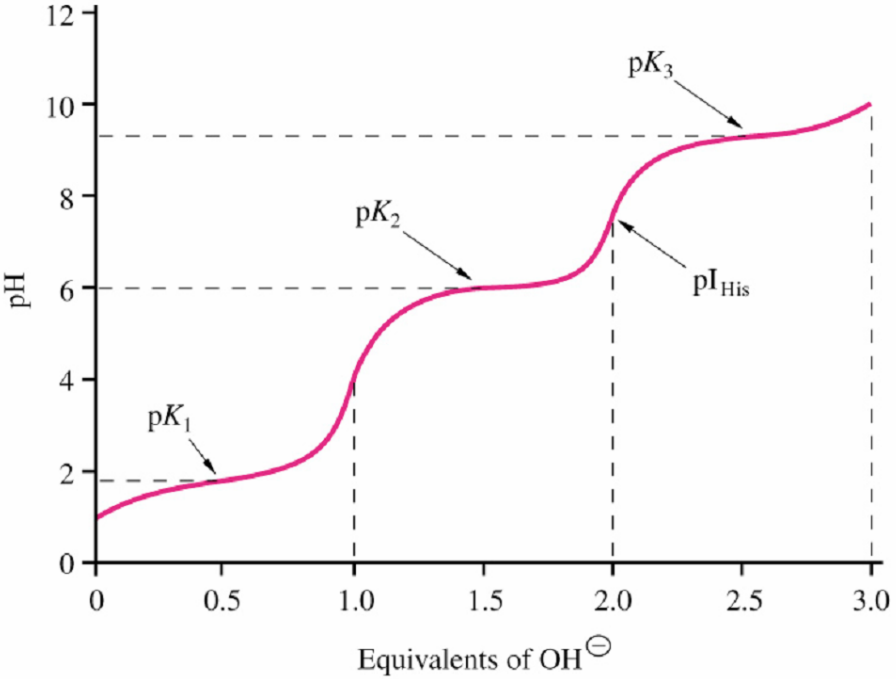


Titration curve for alanine

$pK_1 = 2.4$; $pK_2 = 9.9$

pI_{Ala} = isoelectric point – it is the pH at which net charge is zero.

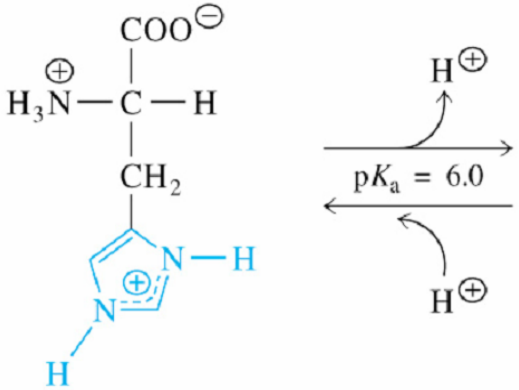
Titration curve of histidine



Typical ranges of pK_a values for ionizable groups *in proteins*

Ionizable group	pK_a range
α-carboxyl (any amino acid)	3.5 - 4.0
side-chain carboxyl (Asp, Glu)	4.0 - 4.8
α-amino (any amino acid)	8.0 - 9.0
side-chain amino (Lys)	9.8 - 10.4
sulfhydryl, -SH (Cys)	8.5 - 9.0
phenol, -OH (Tyr)	9.5 - 10.5
imidazole, -NH (His)	6.5 - 6.8
guanidinium (Arg)	12.0 - 12.5

$pK_1 = 1.8$; $pK_2 = 6.0$; $pK_3 = 9.3$



Imidazolium ion (protonated form) of histidine side chain

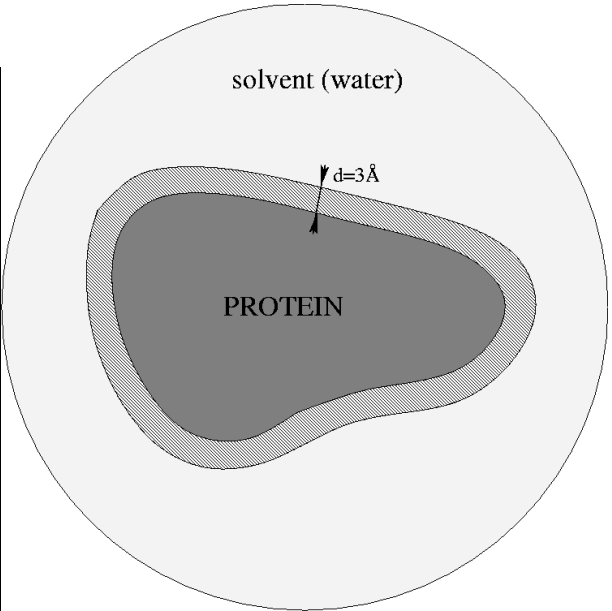
Imidazole (deprotonated form) of histidine side chain

Protein hydration

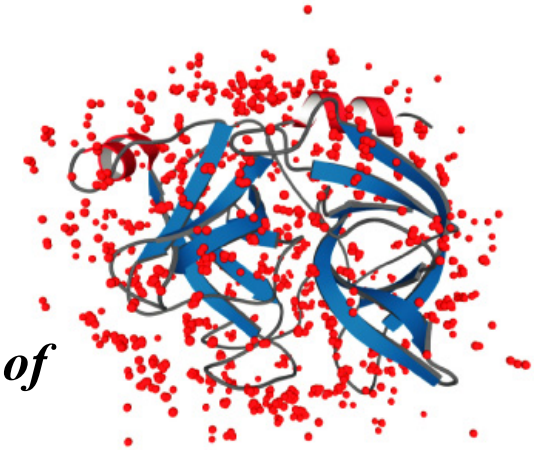
Water properties are different from that of the bulk.

- It is ordered
- It has high proton transfer rates
- The density is 10-20 % higher than bulk water
- It has a 15% greater heat capacity than bulk water.

Surface water molecules exchange with the bulk solvent on the 10^{-9} s timescale.



- There are differences in the directional rates of water diffusion perpendicular and parallel to the protein surface (maximal at about 6 Å).



Porcine pancreatic elastase showing the first hydration shell of Porcine pancreatic elastase.

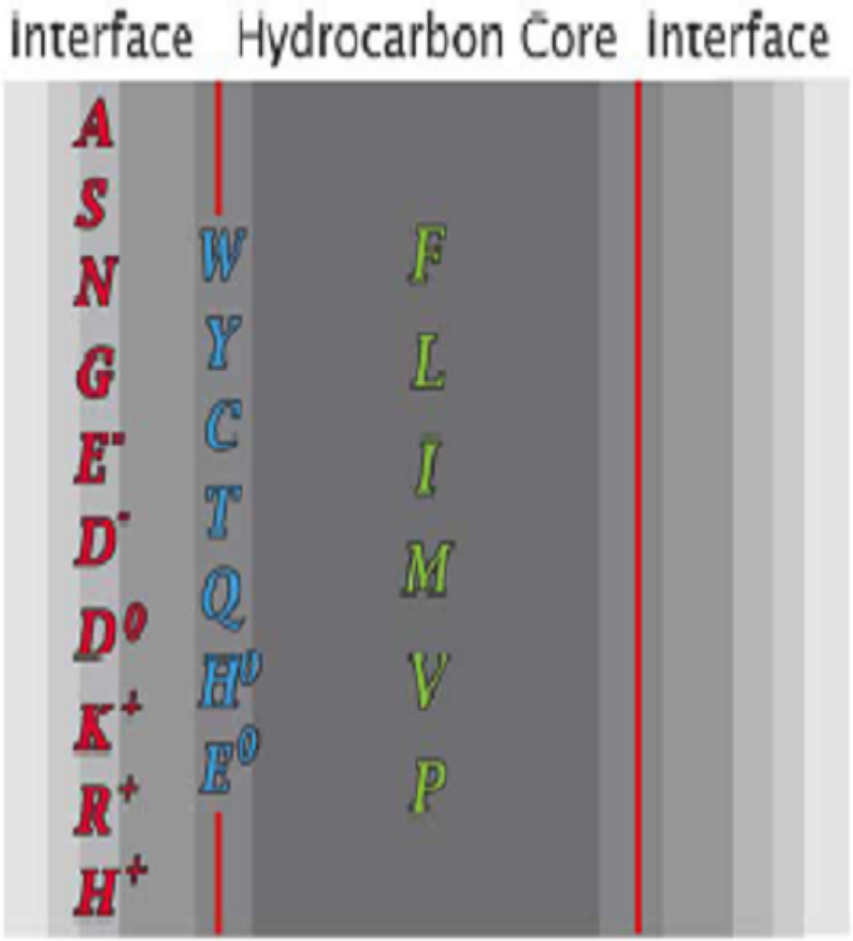
Hydrophobicity scales

It is composed of experimentally determined transfer free energies for each amino acid.

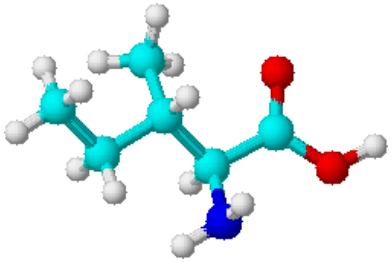
Two scales are needed:

- The transfer of unfolded chains from water to bilayer interface

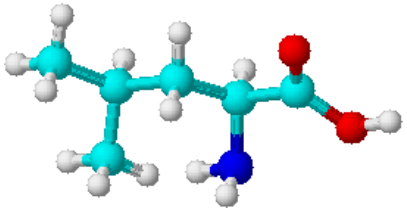
- The transfer of folded chains into the hydrocarbon interior.



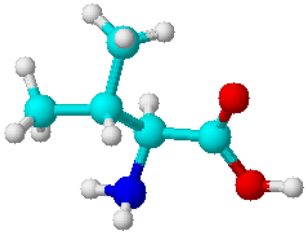
Hydrophobic residues - clathrate



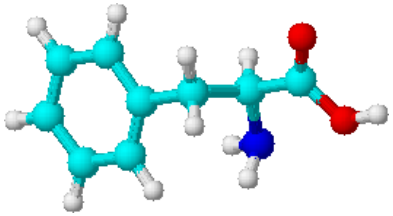
Isoleucine



Leucine

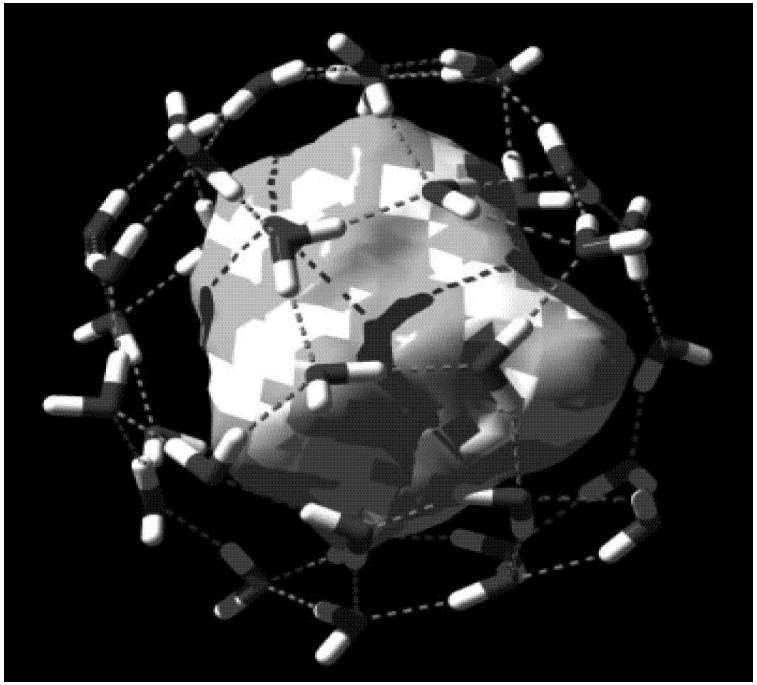


Valine



Phenylalanine

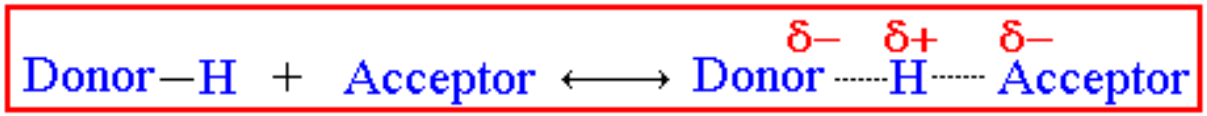
- Clathrate forms over hydrophobic areas maximizing non-bonded interactions without loss of H-bonds.



- Clathrate shells contain loosely held water with greater rotational freedom than in the bulk.

Hydrogen bonds

1 – 7 kcal/mole

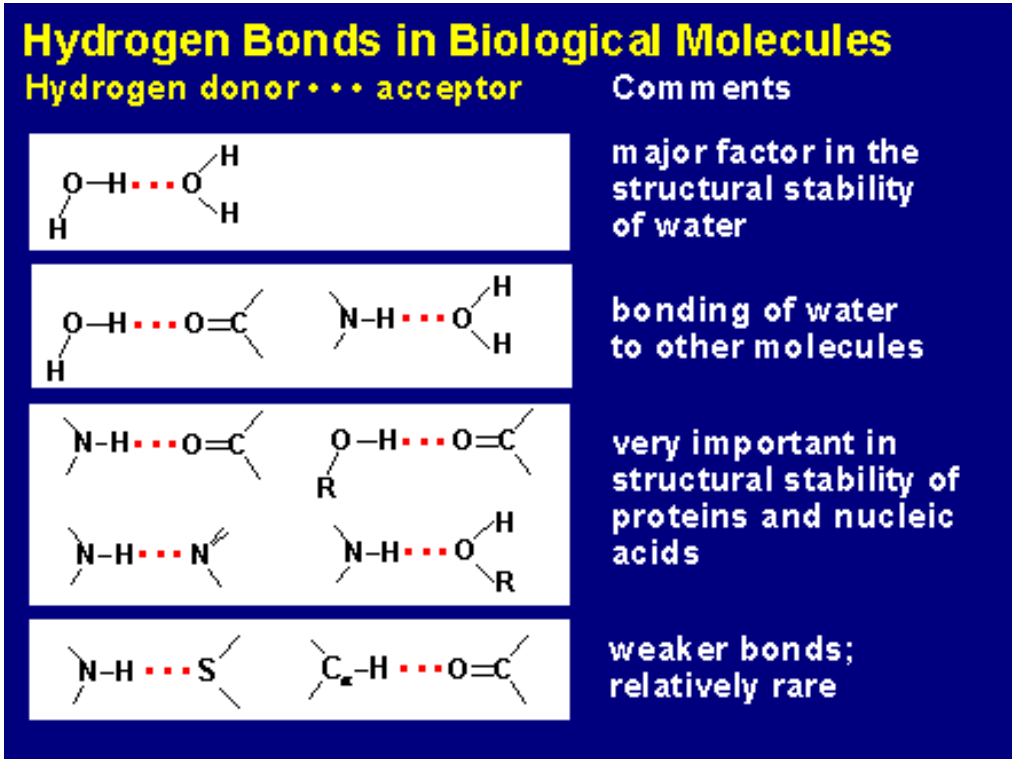


- A H-bond requires interatomic distances of < 3.5 Å, and should be linear.

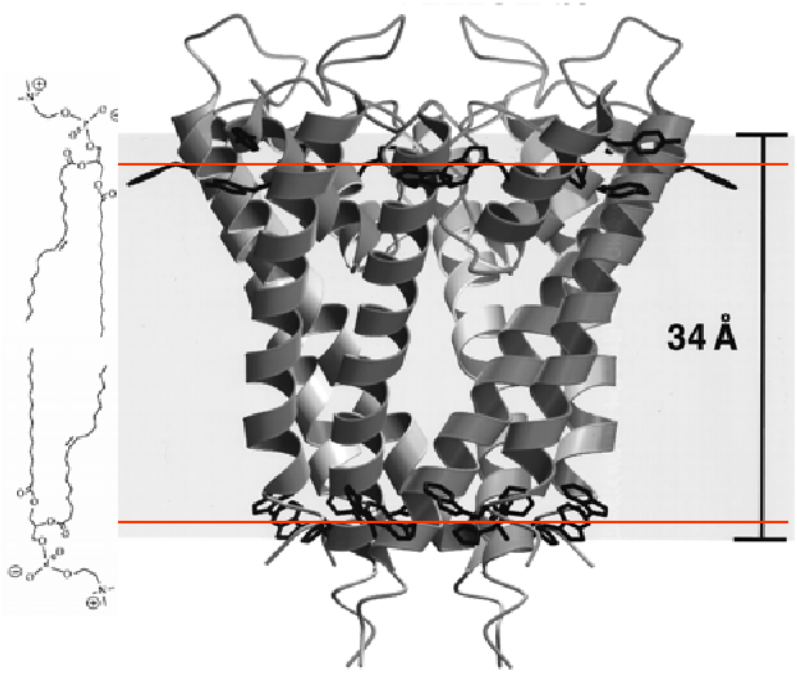
- The hydrogen-bonding groups form hydrogen bonds to water which are energetically similar to those formed within the protein. ***The hydrogen bonds in proteins are thermodynamically neutral.***

The donor – an oxygen or nitrogen atom with a covalently attached hydrogen atom.

The acceptor – either oxygen or nitrogen with partial negative charge.



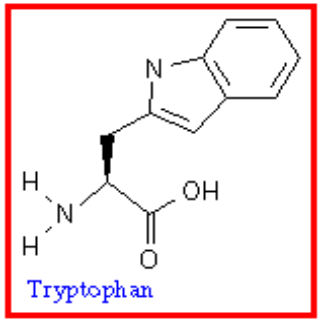
Aromatic amino acids

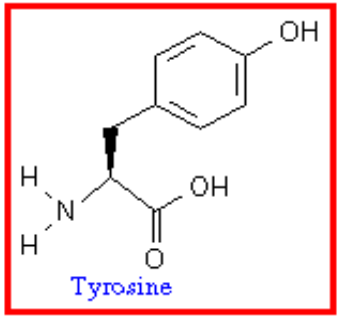


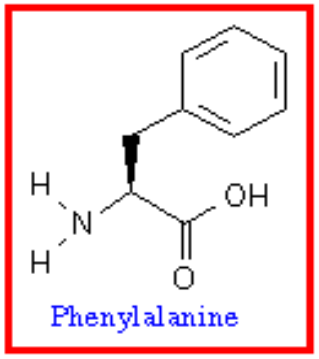
Chromophore	λ_{max}	*Molar extinction coefficient (ε)*
Tryptophan	280 219	5600 47000
Tyrosine	274 222 193	1400 8000 48000
Phenylalanine	257 206 188	200 9300 60000
Histidine	211	5900
Cysteine	250	300

Delocalized electrons in aromatic side chains can participate in weak electrostatic interactions

About 60% of the aromatic side chains (Phe, Tyr, and Trp), found in proteins are involved in aromatic pairings.

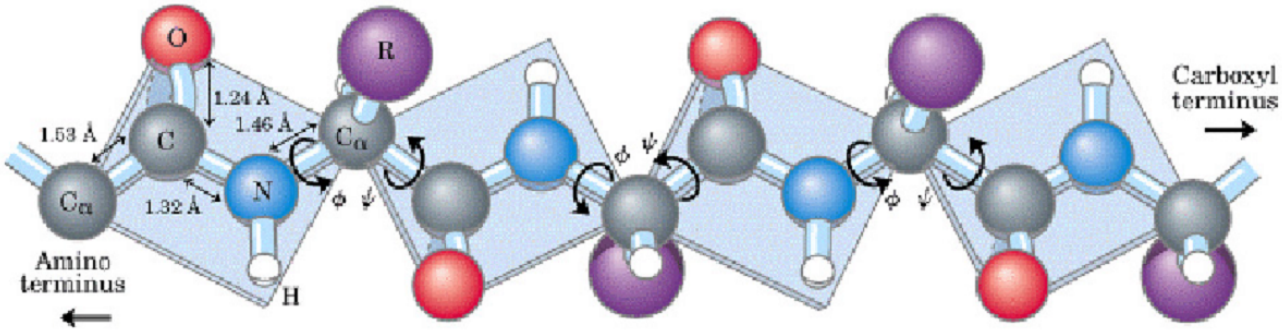


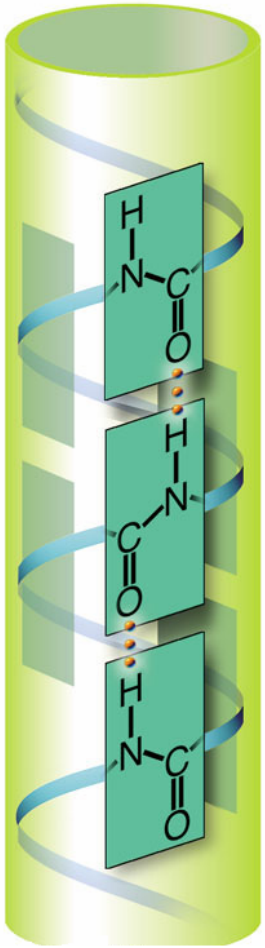


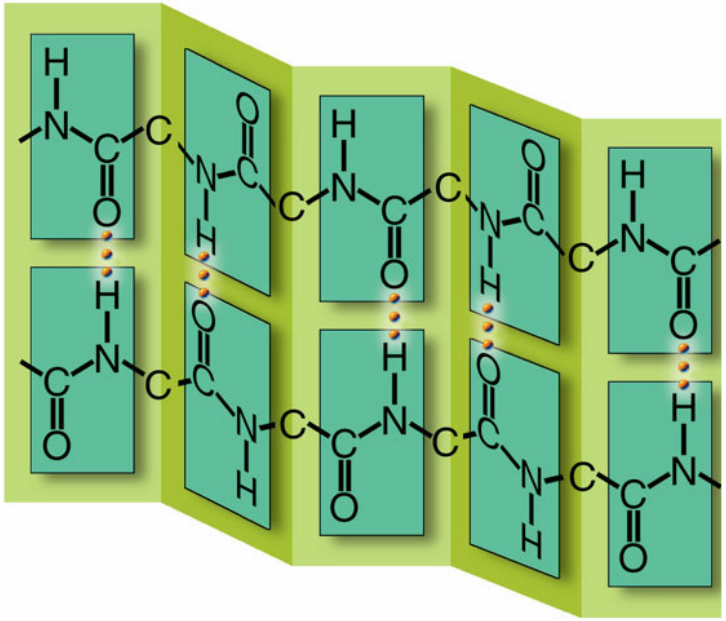


Studies with model compounds suggest that the optimal geometry is perpendicular.

Secondary Structures

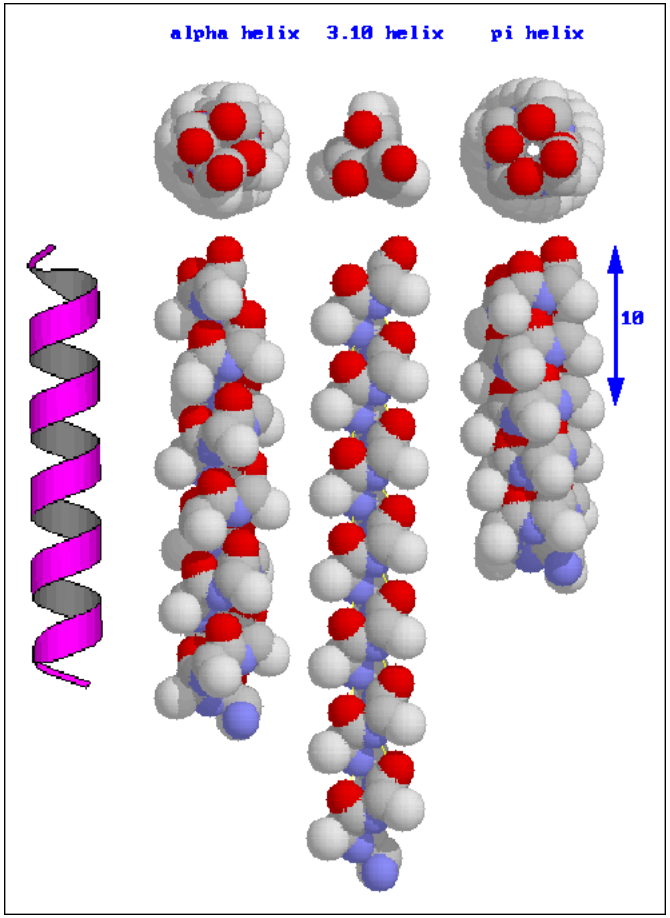




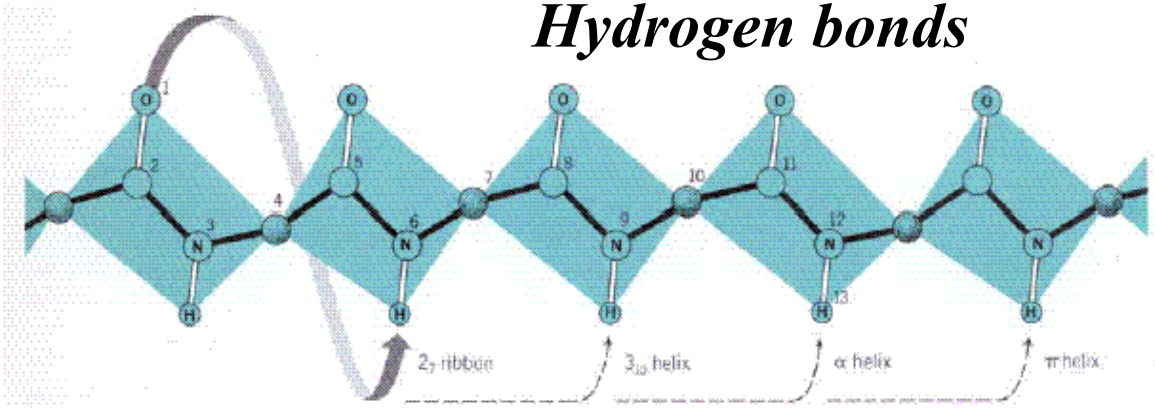


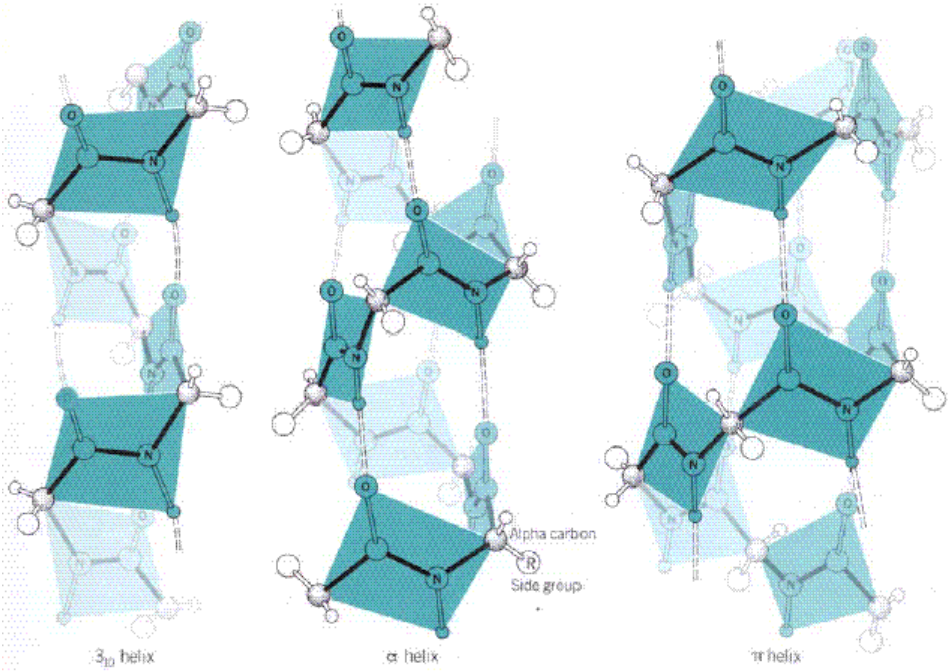
Secondary structure is stabilized by hydrogen bond.

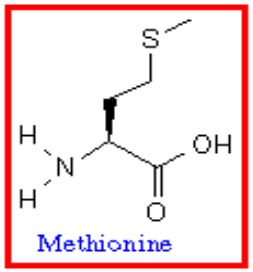
Helices - Types

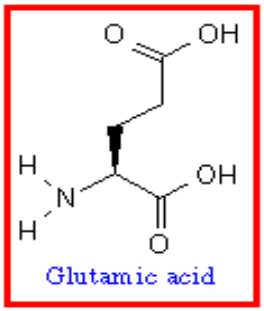


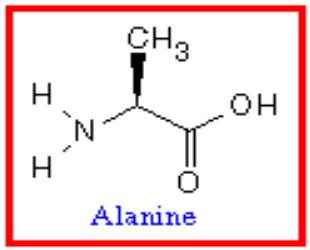
Hydrogen bonds

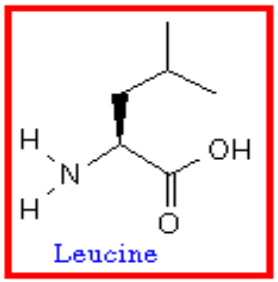






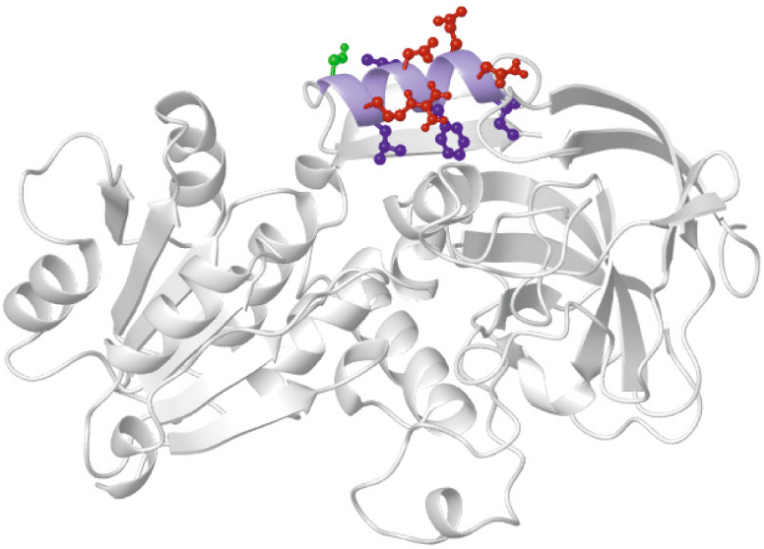


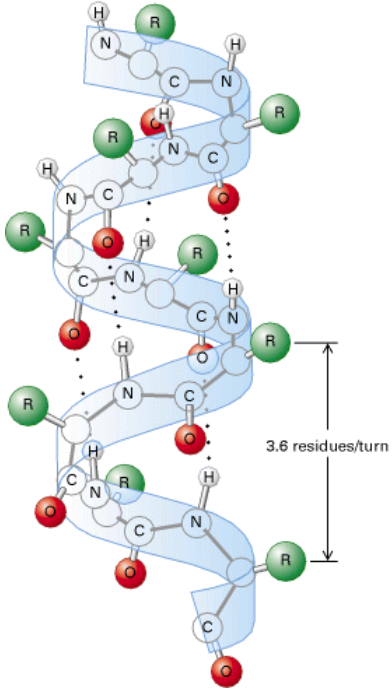


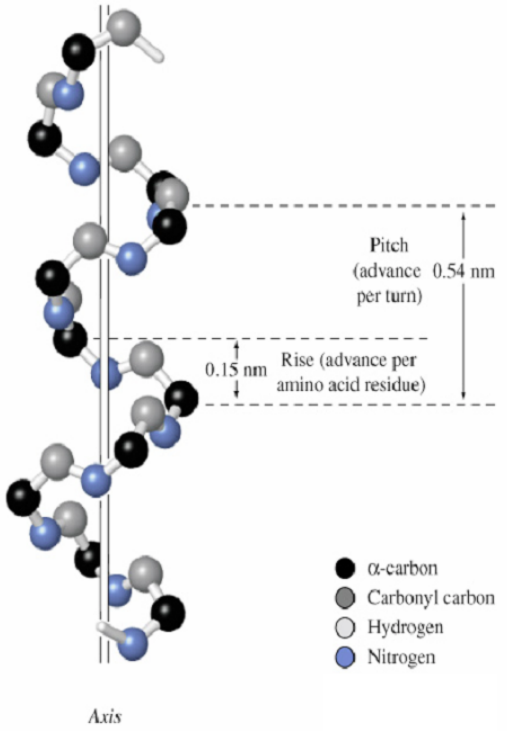


α-helices prefering residues.

The α-helix

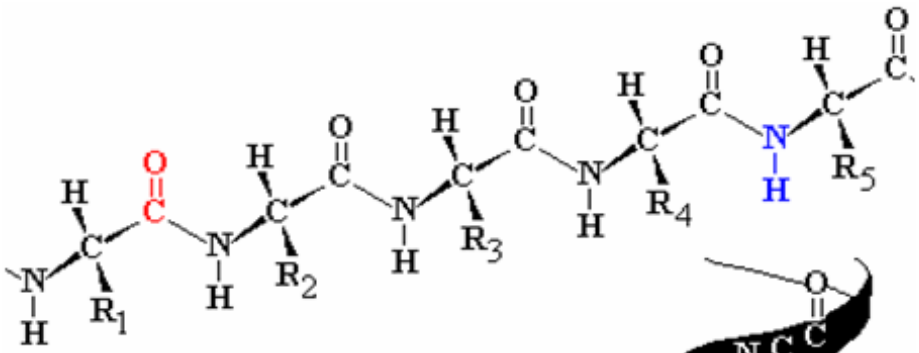


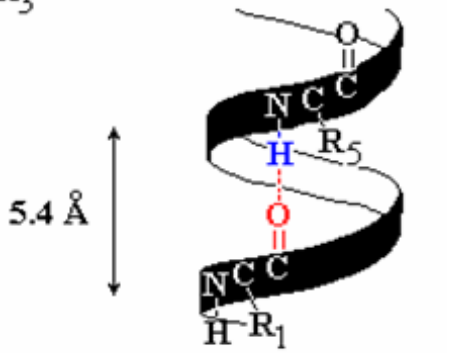




Horse liver alcohol dehydrogenase

Hydrophobic residues (blue) directed inward, hydrophilic (red) outward.

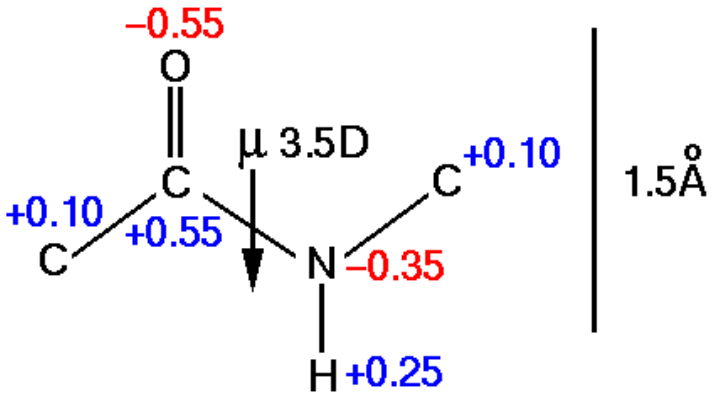


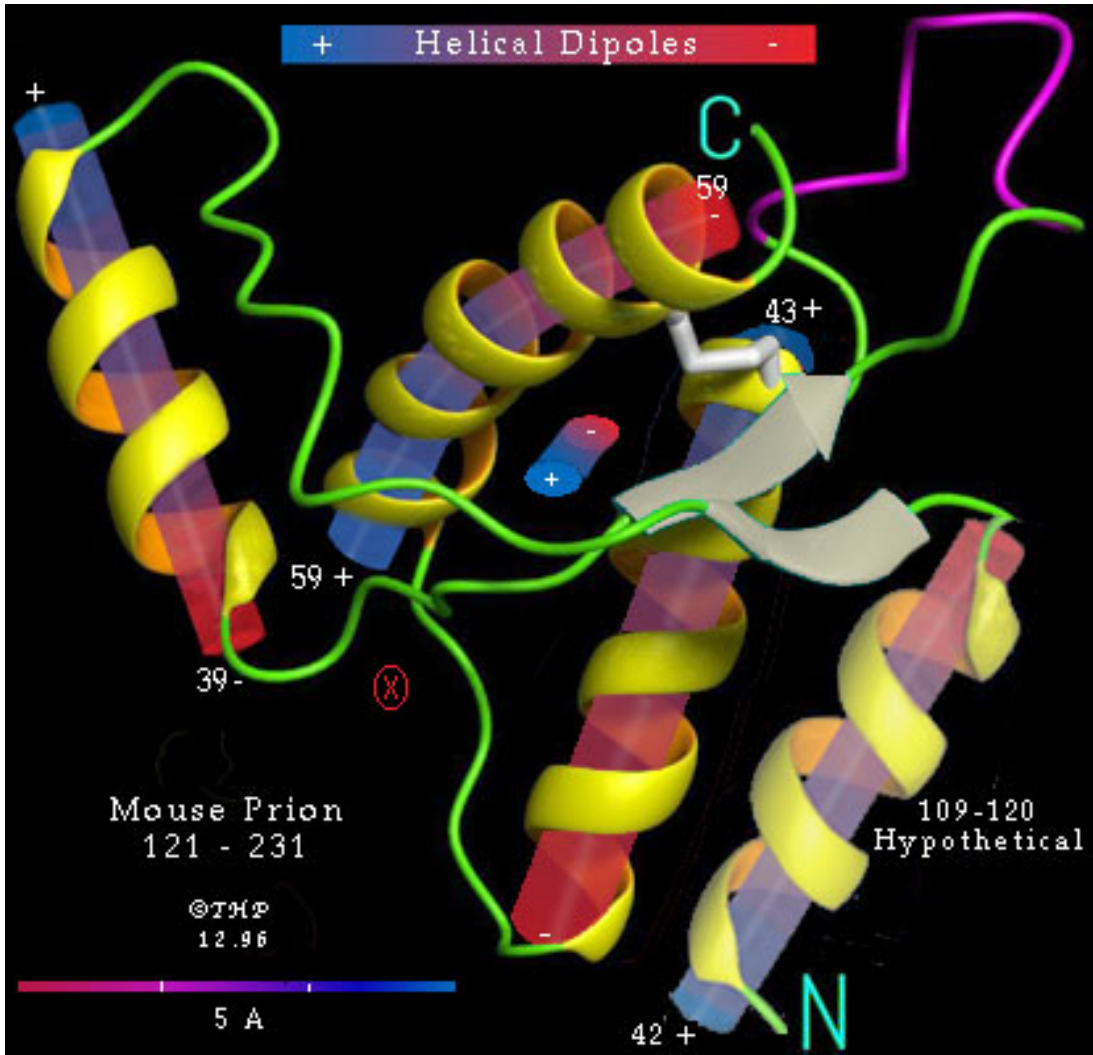


Every main-chain C=O and N-H group is hydrogen-bonded to a peptide bond 4 residues away (O(i) to N(i+4)).

Dipole moment

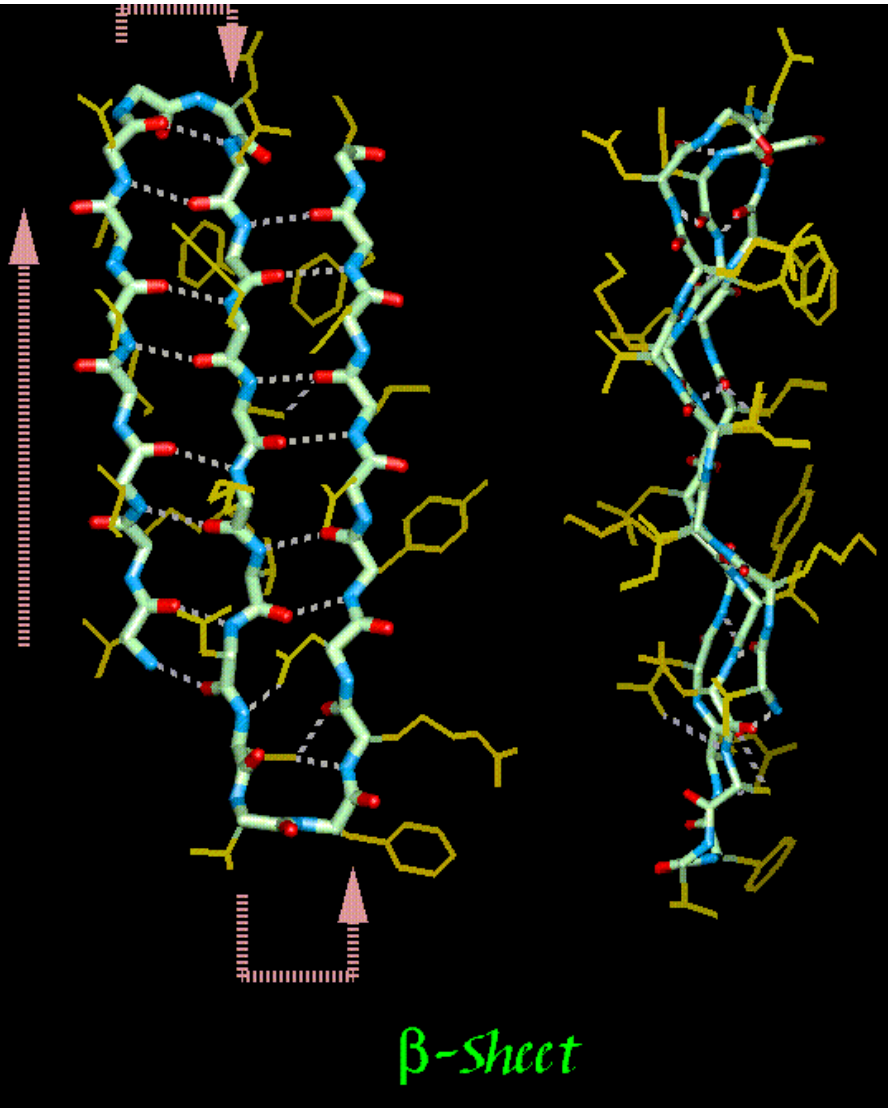
- „+” charge at N-terminii, „-” charge at COOH
- Negative molecules (PO_4^{2-} groups) bind at N-terminii

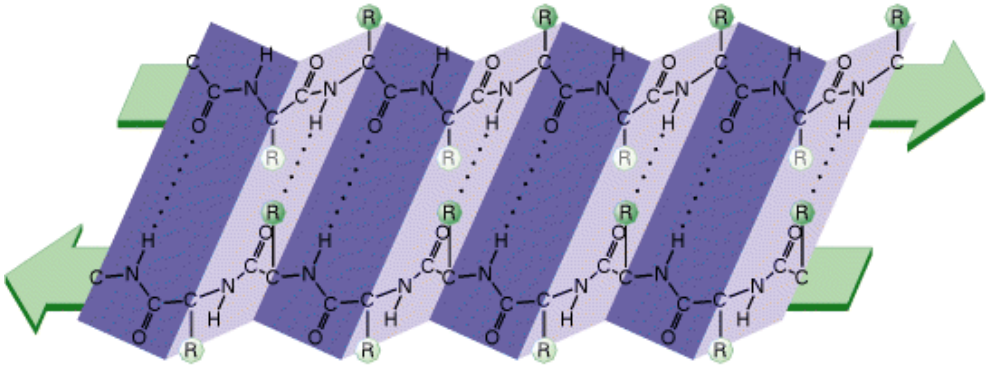


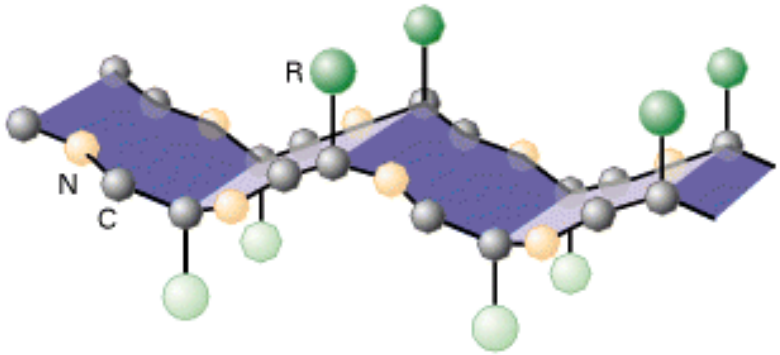


The β - strand and β - sheet

β-strands are usually 5-10 residues long and are in a fully extended conformation.



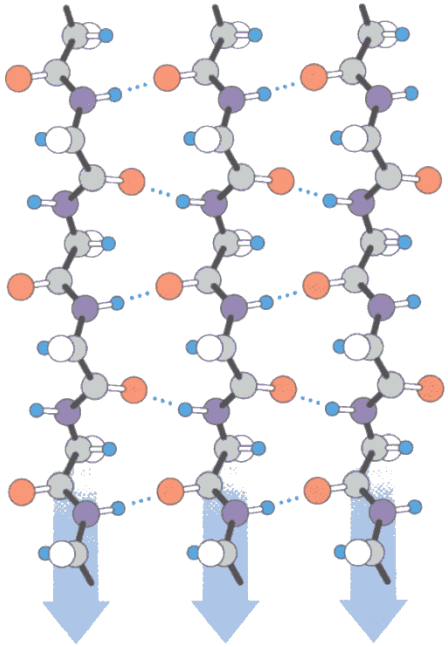


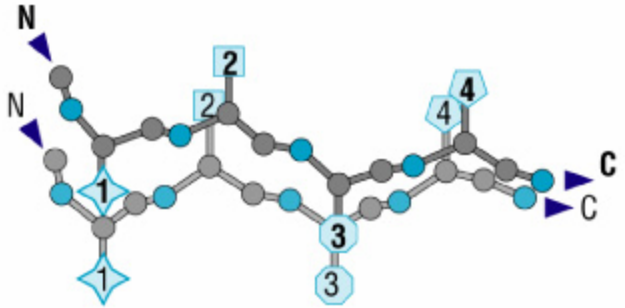


*Residues are **7.0 Å apart along** a strand **but 4.5 Å apart between** adjacent strands.*

Parallel – not stable

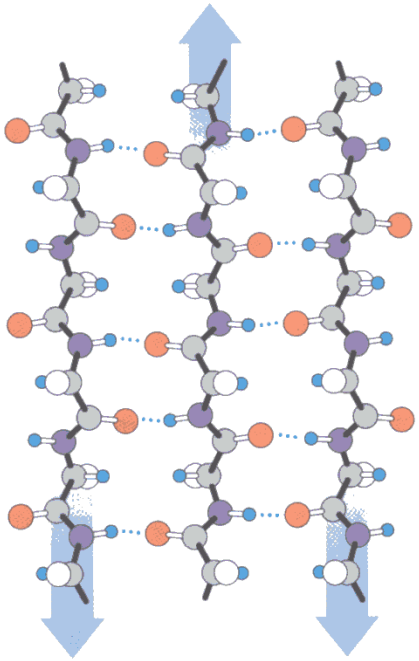
Rise per residue: 3.25 Å

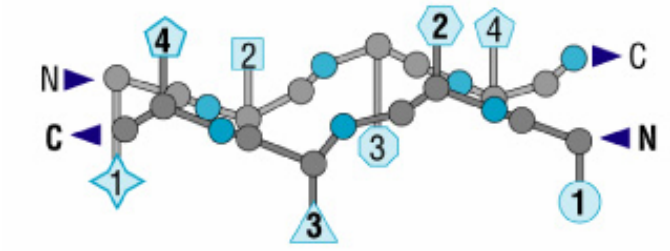




AntiParallel – stable

Rise per residue: 3.47 Å



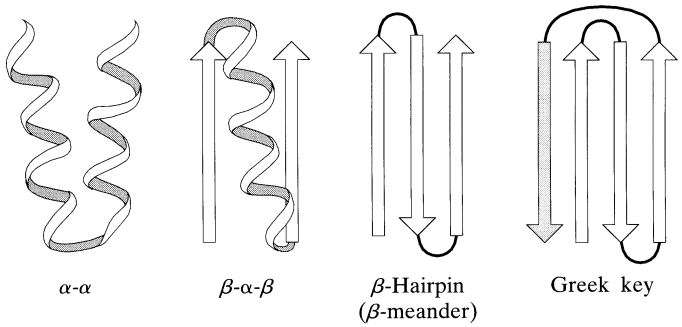


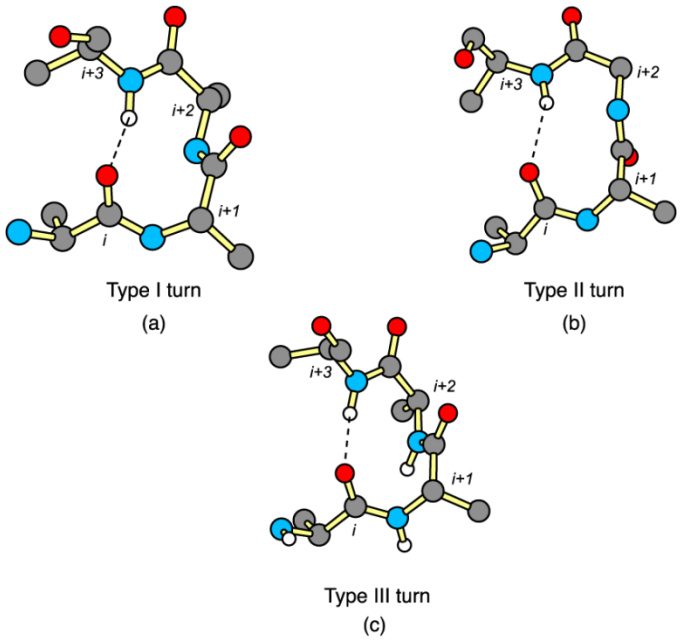
The dipole moments of the strands are also aligned in a β-sheet.

β-sheets of less than 5 strands are rare.

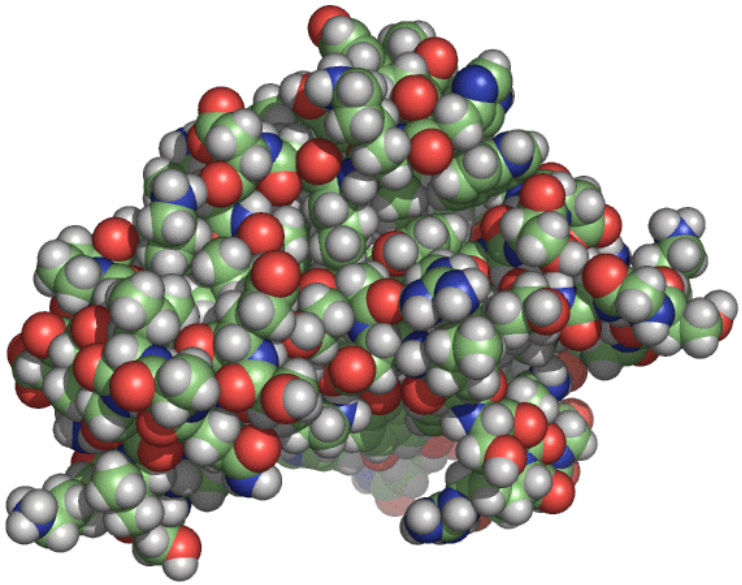
Turns

- Peptide fragments that connect regular secondary structure elements.
- Found often at the surface of globular proteins.
- Form hydrogen bonds with water.
- Are in general very flexible.
- Have a length of 2-16 residues.
- Very compact and well ordered.
- Glycine and Proline are common.



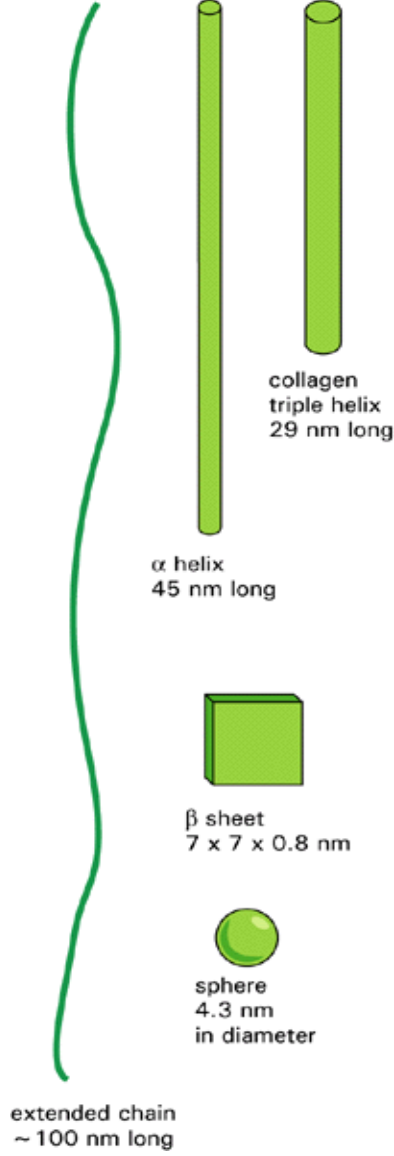


Barnase



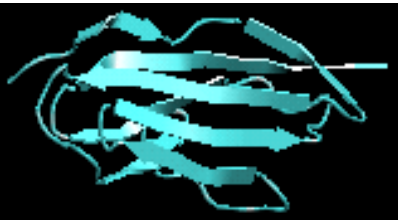
Tertiary Structure

A 300-residue polypeptide

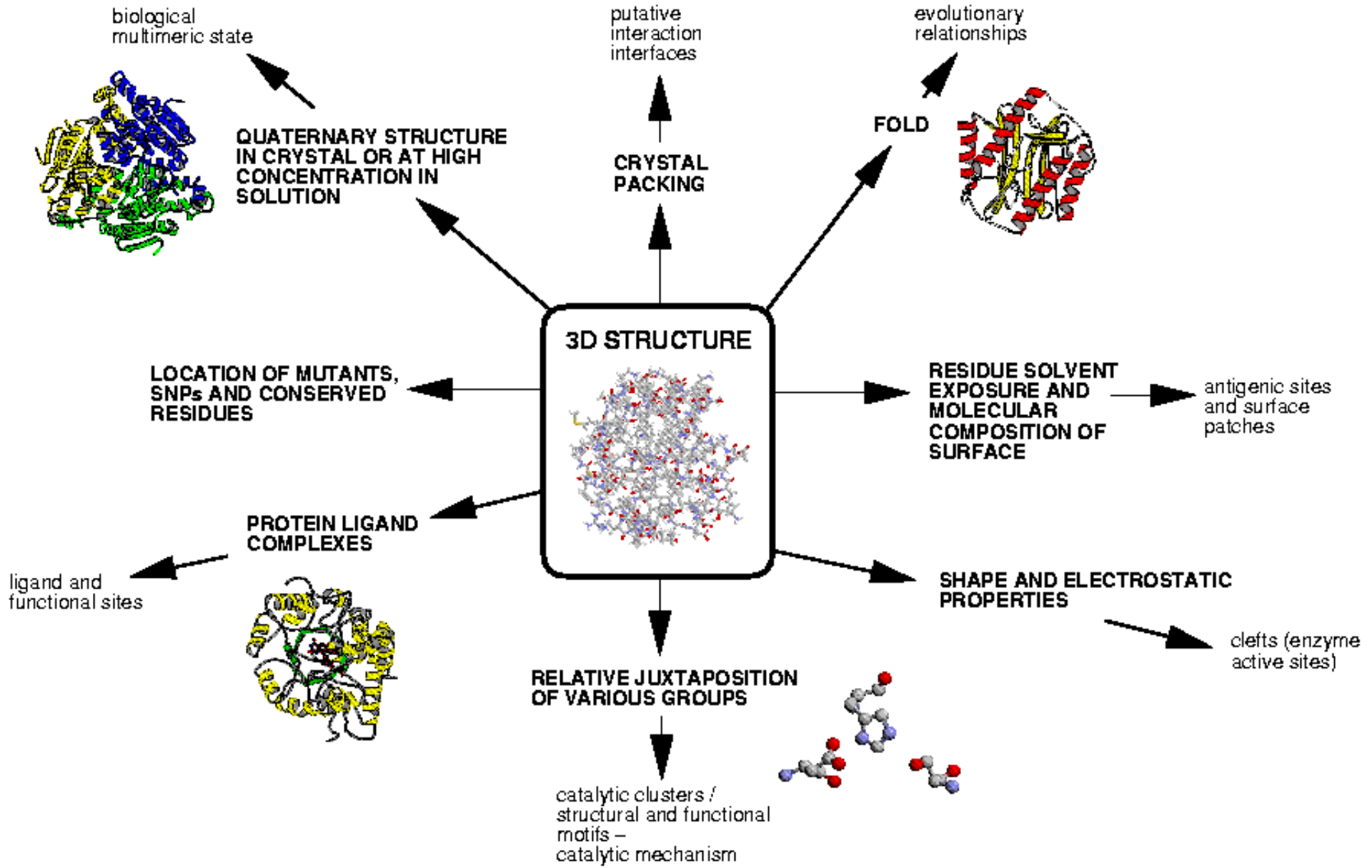


Tertiary structure is stabilized by hydrophobic effect, electrostatics, hydrogen bonds between polar side chains, and disulfide bonds.

Evolutionary, the 3D structure is more conserved than the sequence.

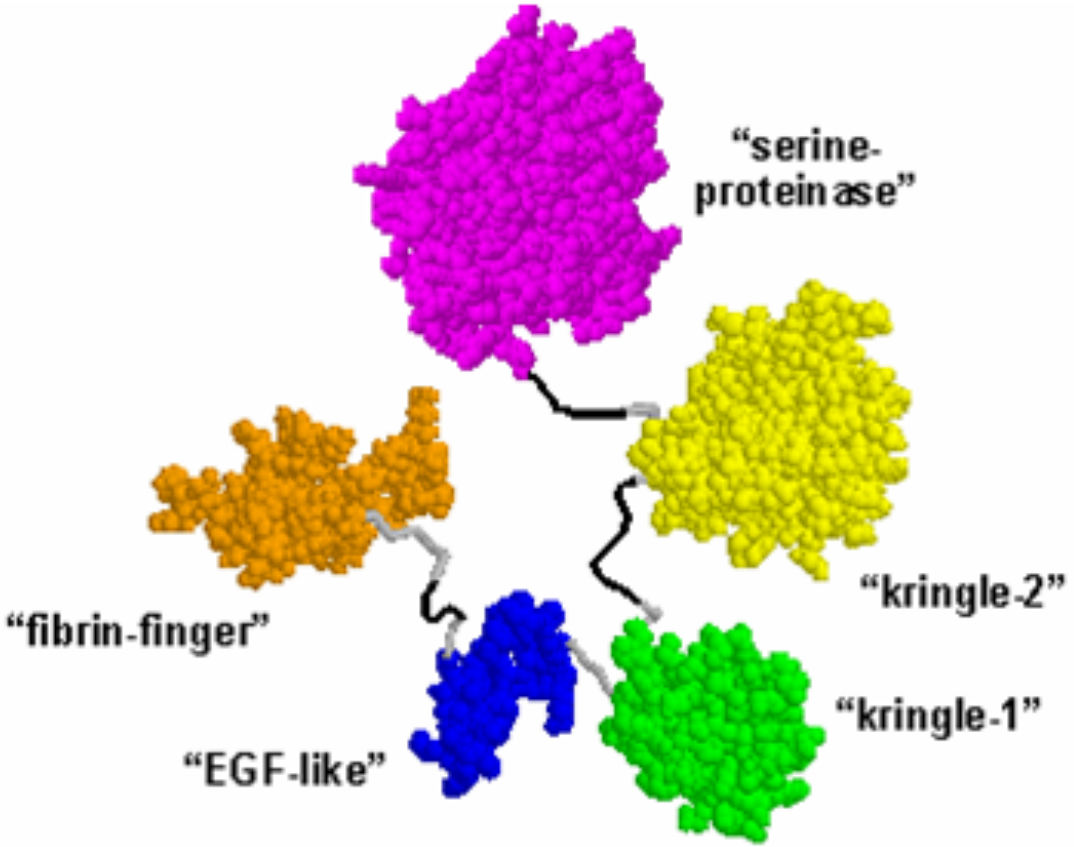


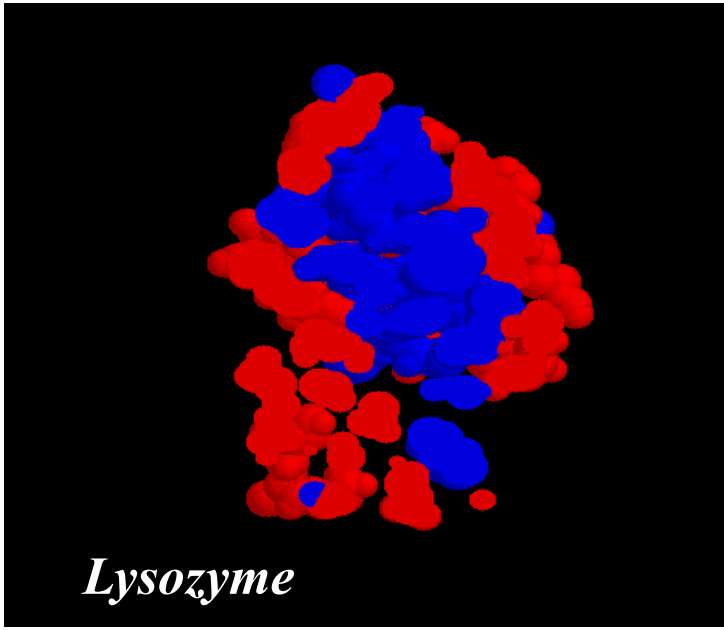
Protein 3D structure is critical for understanding its functioning



A domain - packing of secondary structure elements into a compact independently-folding spatial and/or functional unit.

- A region with a separate hydrophobic core.
- Typically 100-200 amino acids and an average diameter of 25 Å.

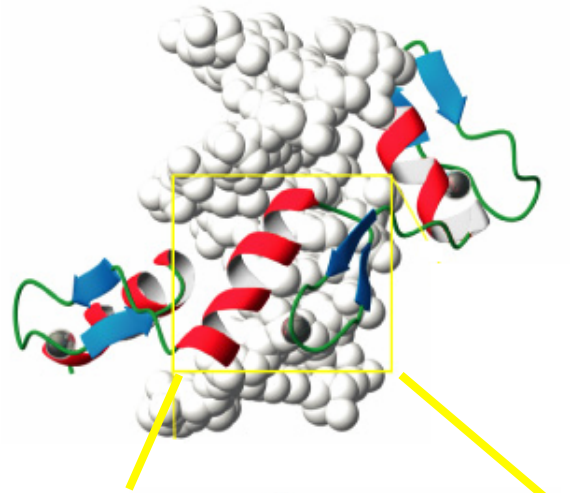


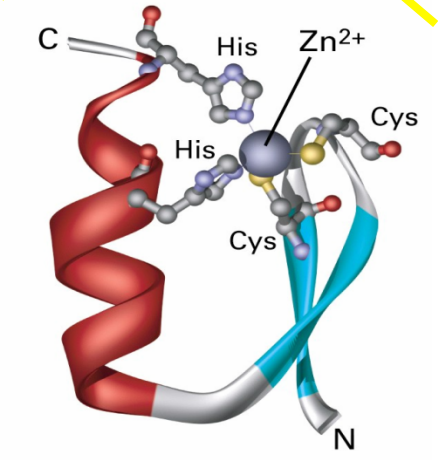


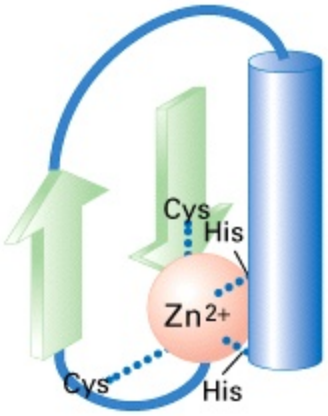
Lysozyme

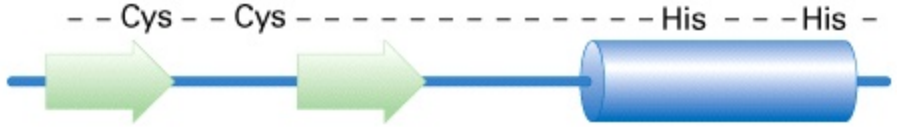
Human tissue plasminogen activator

Sequence motif – a particular amino-acid sequence that is characteristic of a specific biochemical function.







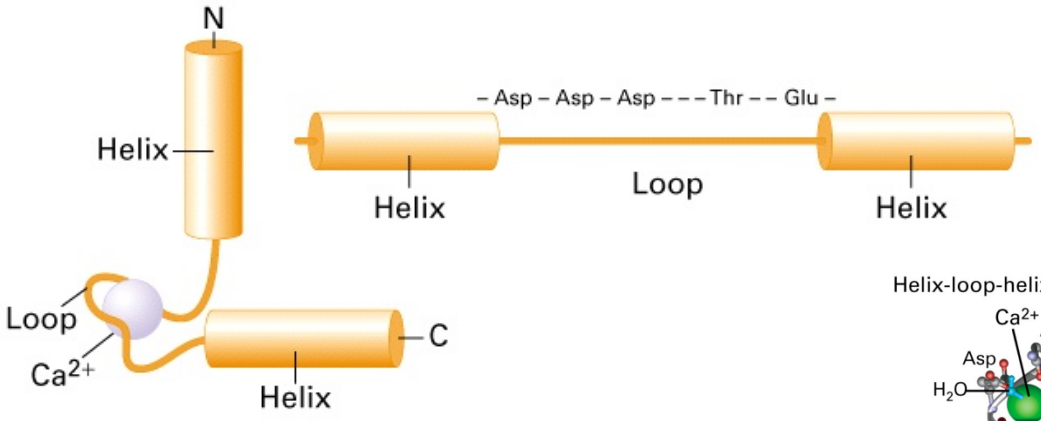


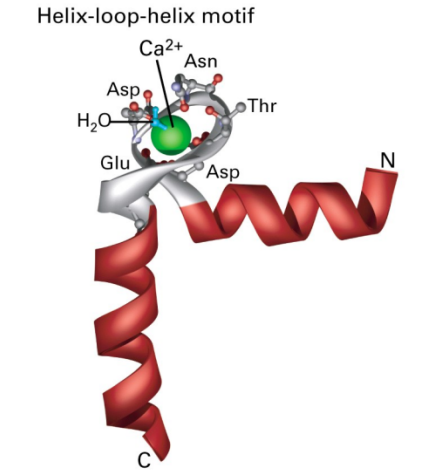
- An α-helix, two β strand with antiparallel orientation
- Zinc ion,
- Form a finger like bundle
- Two cysteines, two histidines
- DNA or RNA binding proteins

Zinc finger motif: proteins that bind nucleic acids
CXX(XX)CXXXXXXXXXXXXHXXXH

Structural Motif – a set of contiguous secondary structure elements that either have a particular functional significance or define a portion of an independently folded domain.

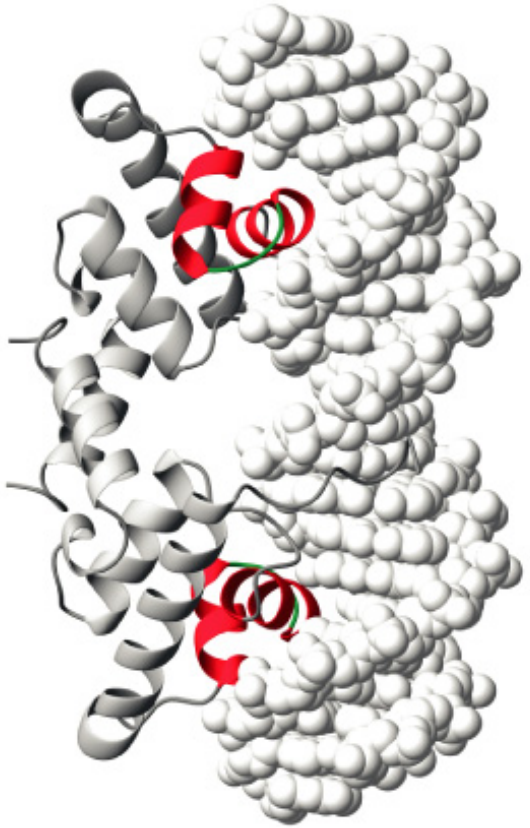
Helix-turn-helix





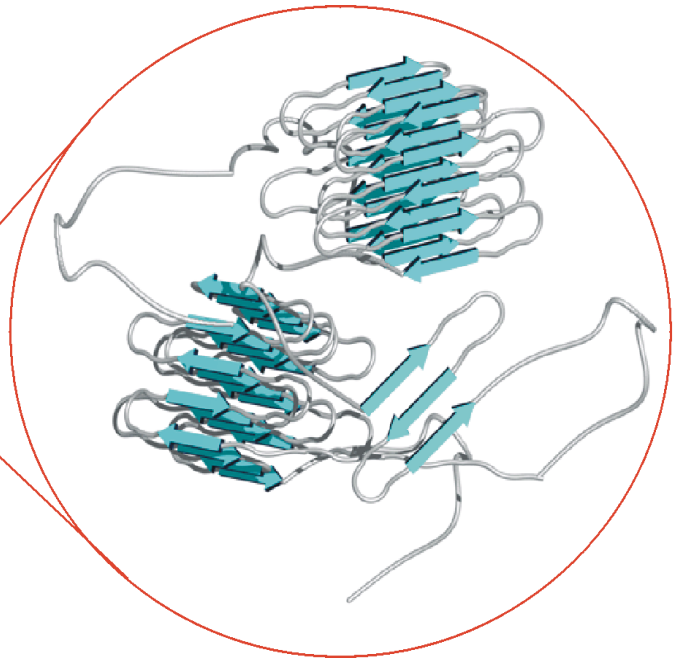
Consensus sequence:
D/N - D/N - D/N/S - [backbone O] - - - - E/D

- Certain hydrophilic residues at invariant positions in the loop,
- Ionic bonds,
- Called the EF hand
- Calcium binding proteins
- DNA binding proteins



The DNA-binding domain of the bacterial gene regulatory protein lambda repressor.

Silk - an all anti-parallel β-sheet protein



Polypeptide chain is fully extended and can't be stretched without breaking.

The silk is stronger weight for weight than steel!

Long stretches of silk are composed of the repeat

(- Gly-Ser-Gly-Ala-Gly-Ala-)$_n$

The soft and flexible properties come from the β-structure.

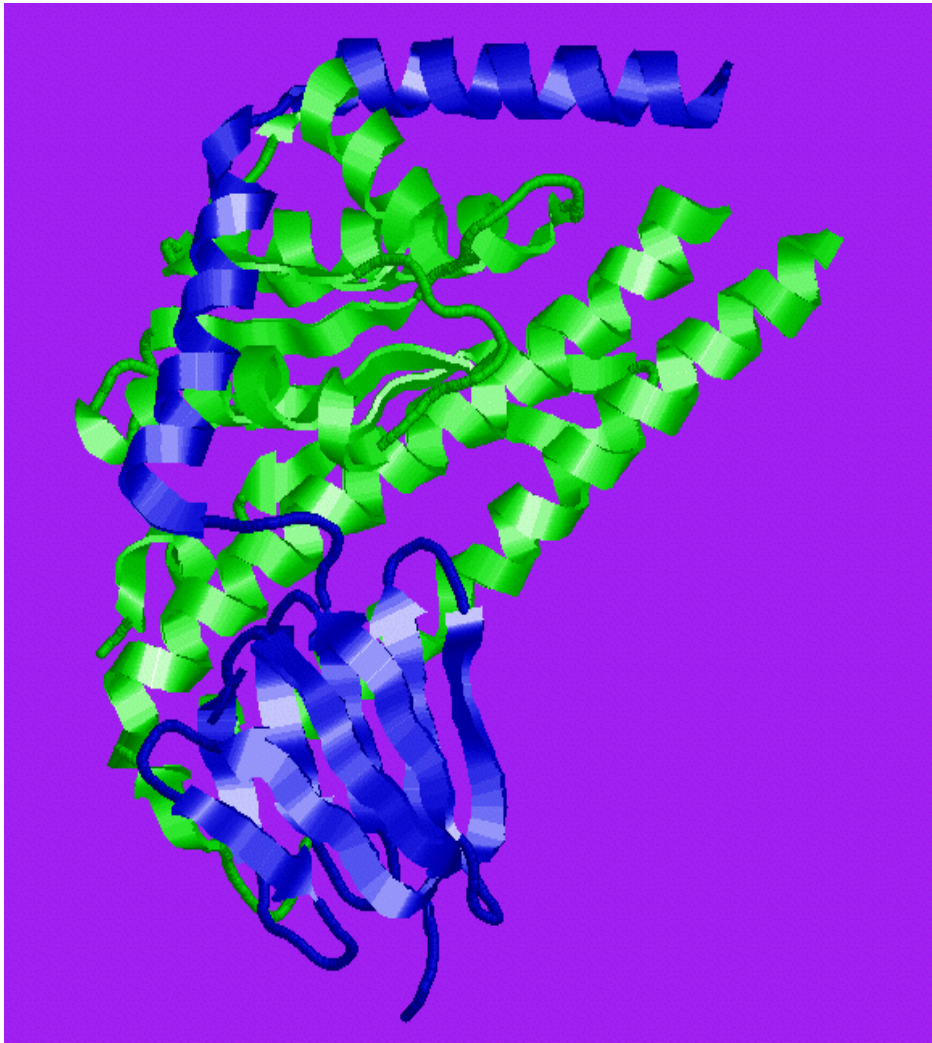
- *the strength comes from the covalent and hydrogen bonds within each β-sheet;*
- *the flexibility from the van der Waals interactions that hold the sheets together.*

Tertiary structure

Protein assumes its characteristic 3-D shape by the secondary structural elements folding on themselves.

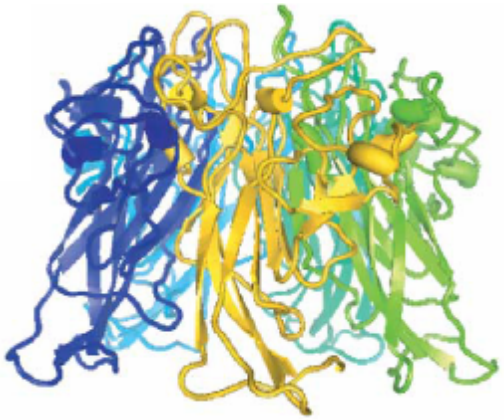
Quaternary structure

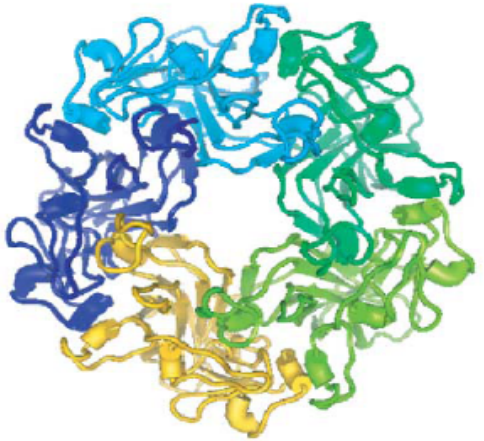
Refers to the organization of subunits in a protein with multiple subunits (an "oligomer")



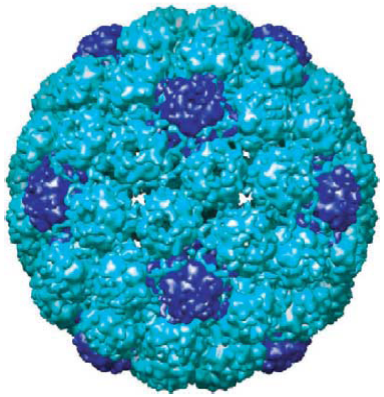
Quaternary structure

- They are formed by non-covalent subunits interactions.
- They may be stable (long-lived) or transitory
- Quaternary structure allows nature to do more with less (viruses for example).
- The buried hydrophobic surface area – ***the selforganization*.**
- *Provides a way for proteins to communicate.*





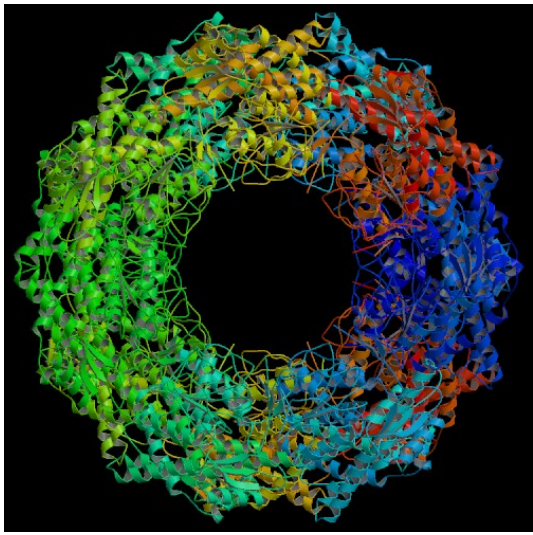
The architecture of a polyomavirus VLP



Advantages of quaternary structure

- Cooperativity and substrate feedback
  - *active site often located at subunit interface*
- Evolution
  - *Mutations are amplified*
  - *Bad mutations are hard to introduce*
- Genetic economy
  - *Saves the need for long transcripts*
- Reduces the error rate of synthesis
  - *If 1 error per 1000 residues: # correct copies*
  - *Single chain (1000 residues) = 37%*
  - *Four chains (250 residues each)= 78%*
- Reduce surface/volume
  - *buries portions of protein surface*
  - *reduce # ions needed to neutralize exposed charges*
  - *reduce # ordered waters for hydration*

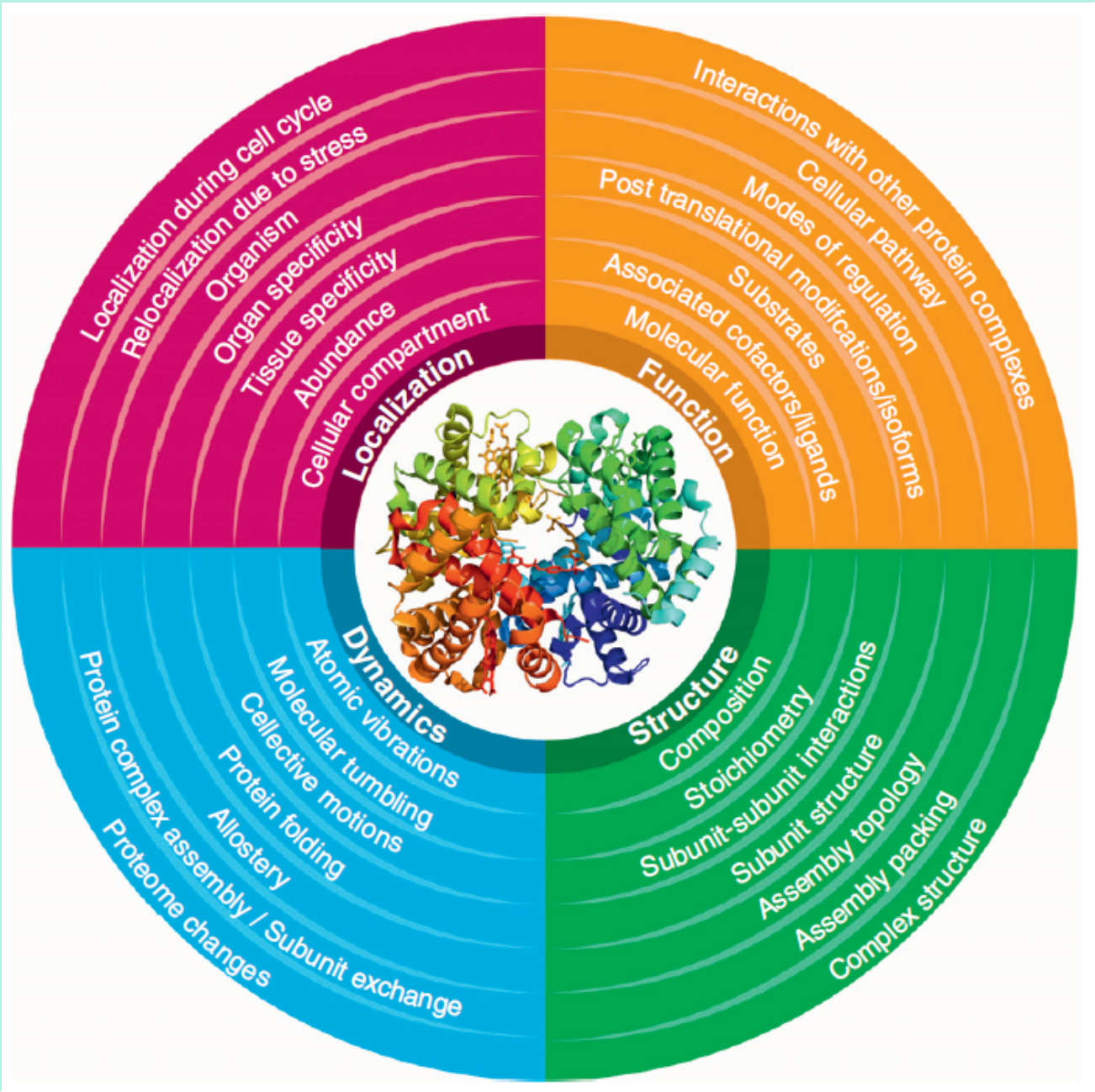
The monomer of chaperonin GroEl



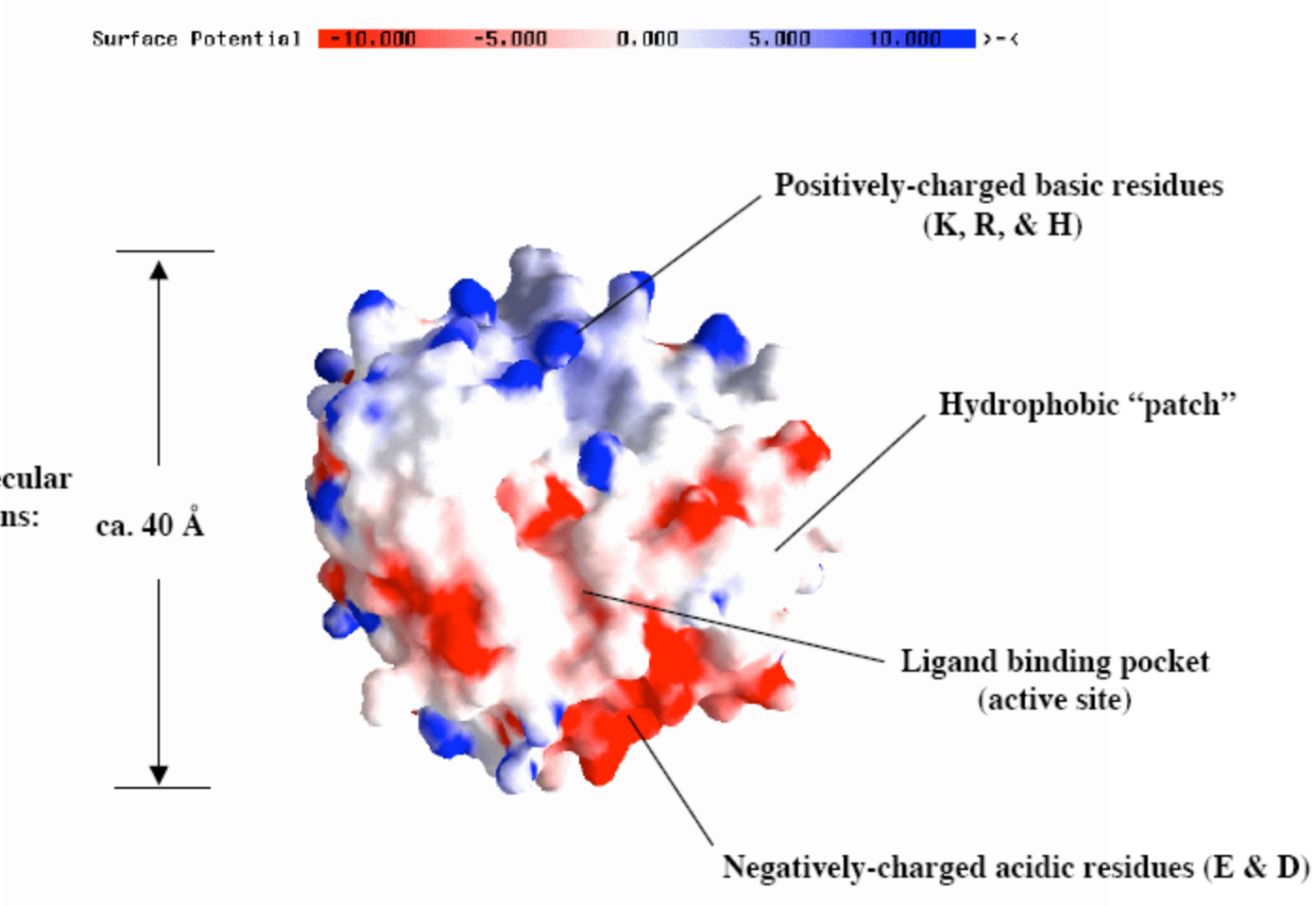
The tetradecamer

The layers of protein complexity.

The complete picture of a protein complex in action requires detailed information on;
its function, three dimensional structure,
dynamics, cellular localization.

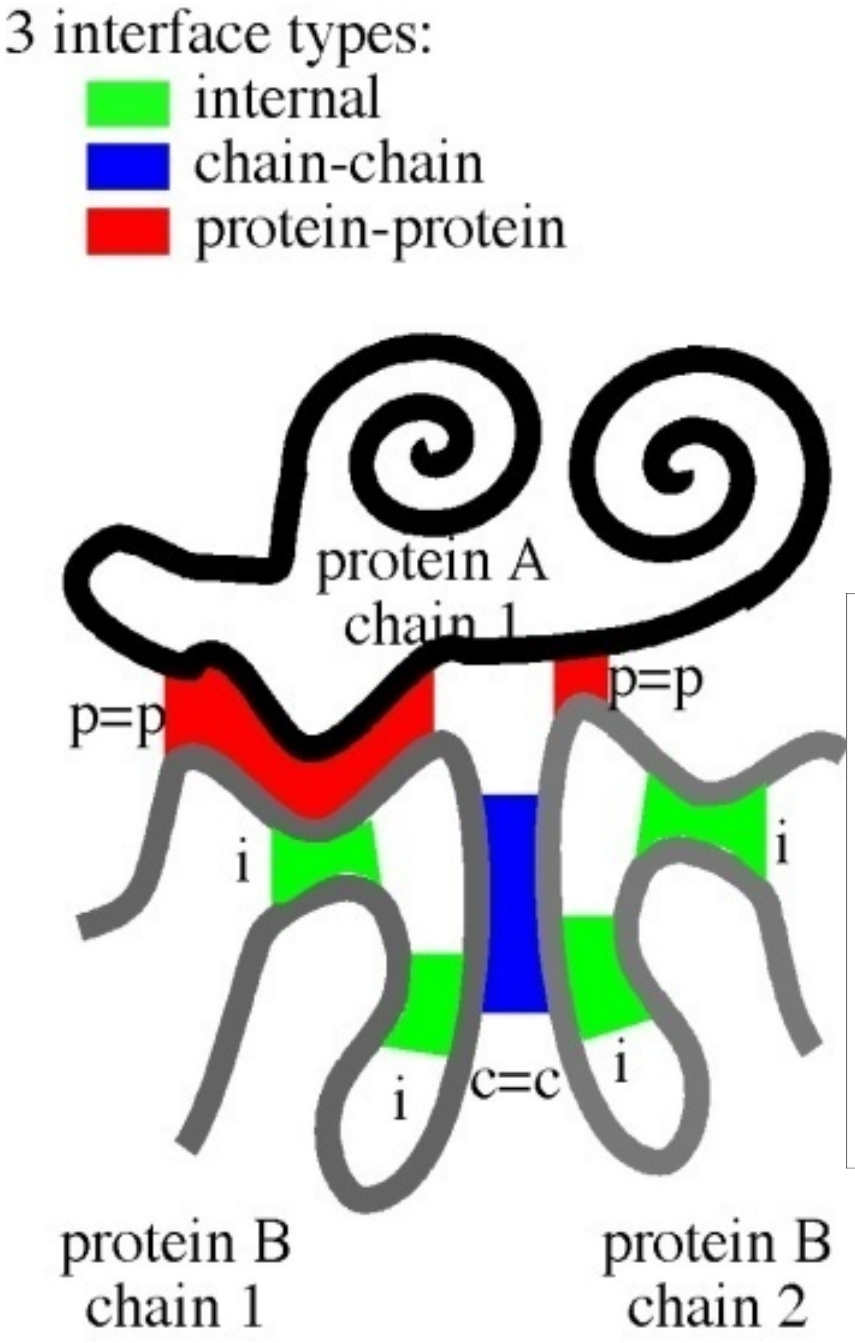


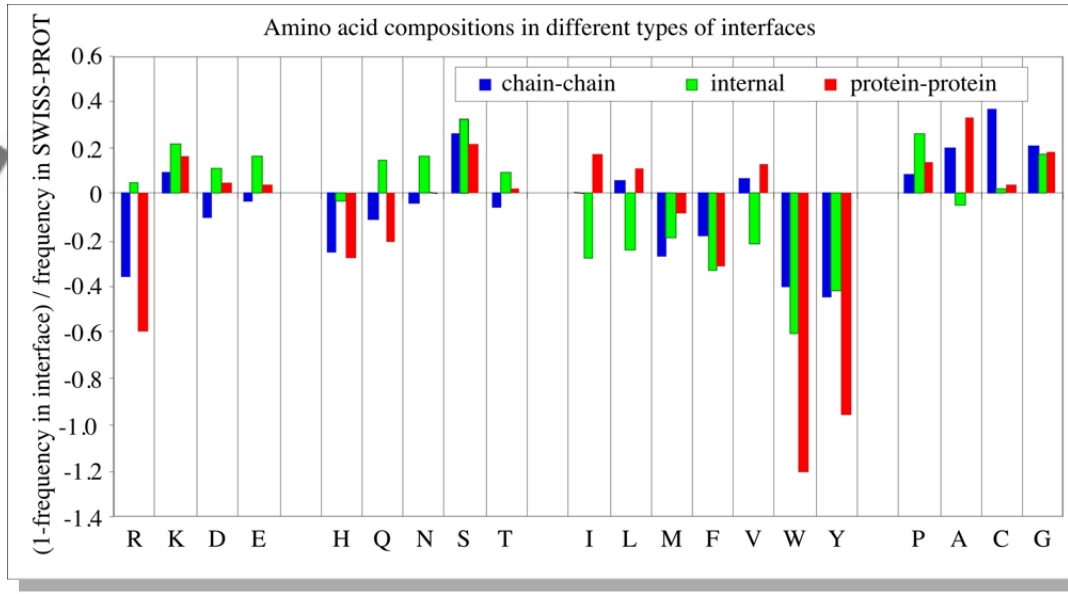
Proteins are Amphiphilic Macro-Ions



The charged groups, hydrophobic regions, size, and solvation affect the biophysical properties of the protein and largely determine its purification behavior.

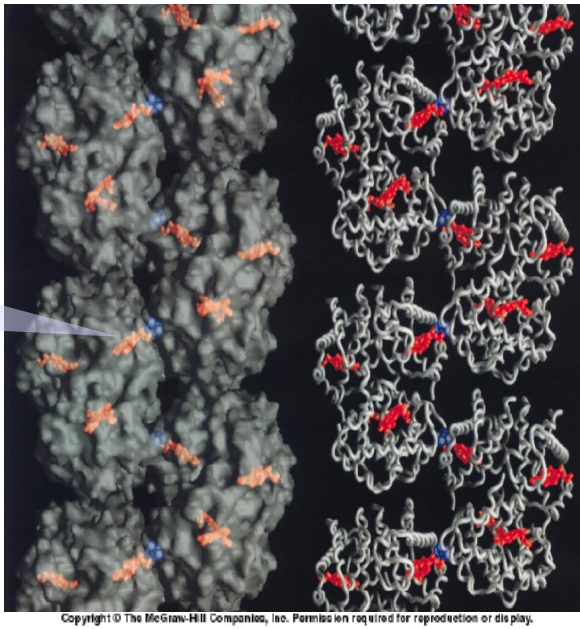
Functionally important residues and their stability



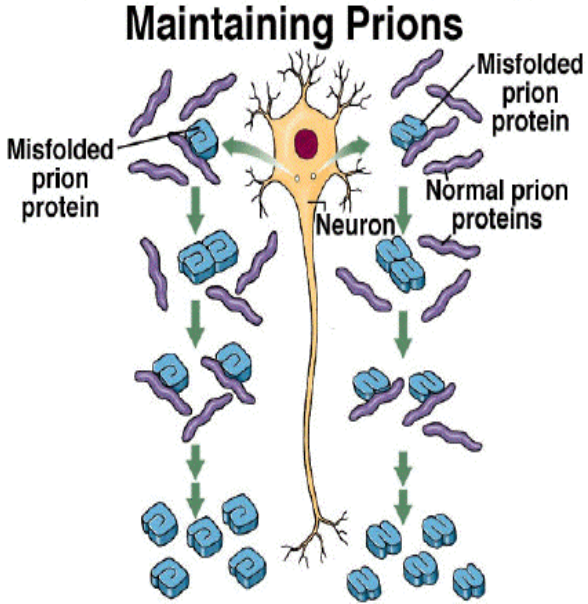


Natural proteins fold to a configuration in which they are soluble.

- *Natural protein, under abnormal conditions, form fibre-like insoluble aggregates (**Sickle cell anaemia**).*



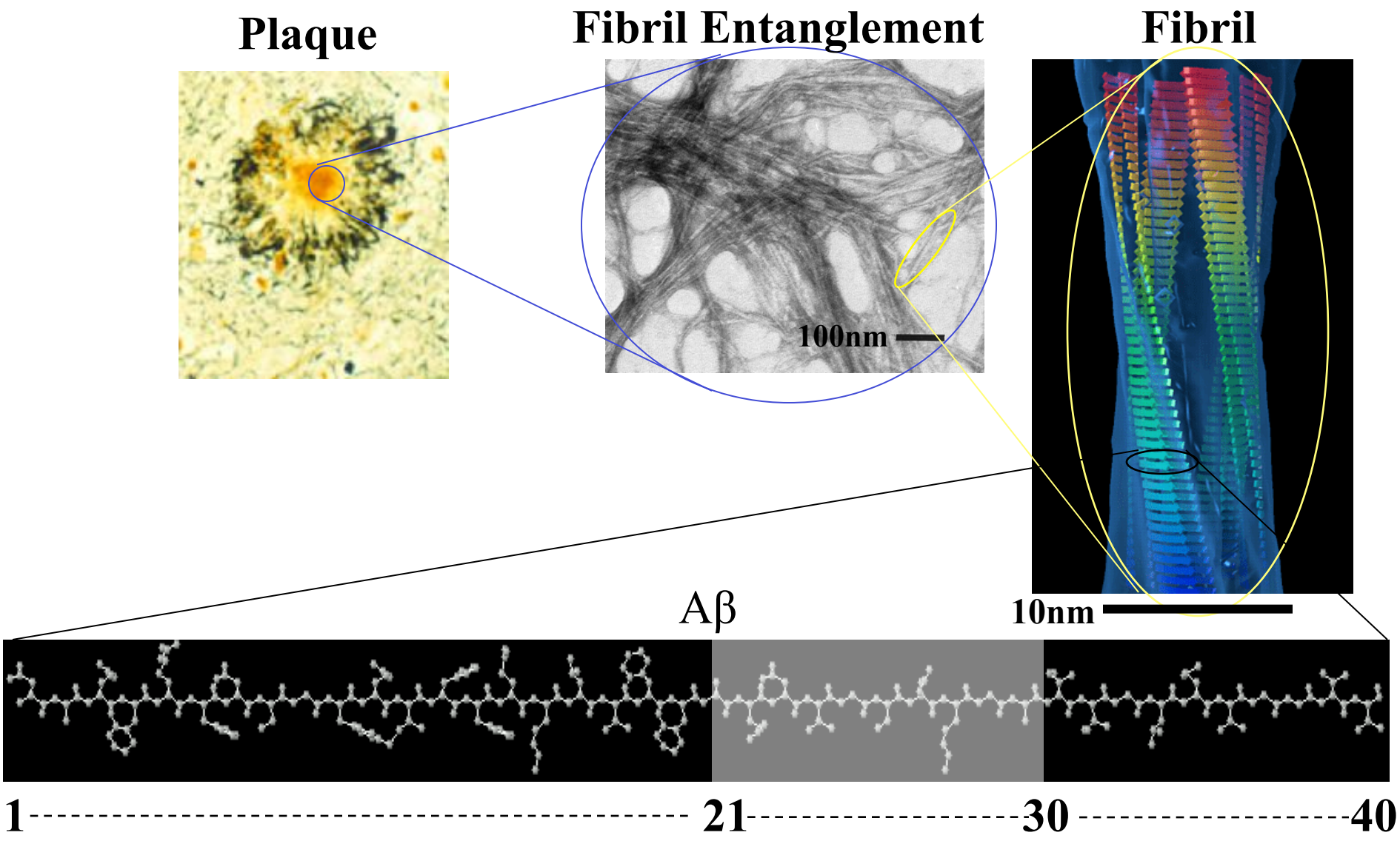
- *Their synthesis would continue and, because the fibres are not in solution, they would not be eliminated by the usual protective mechanisms.*

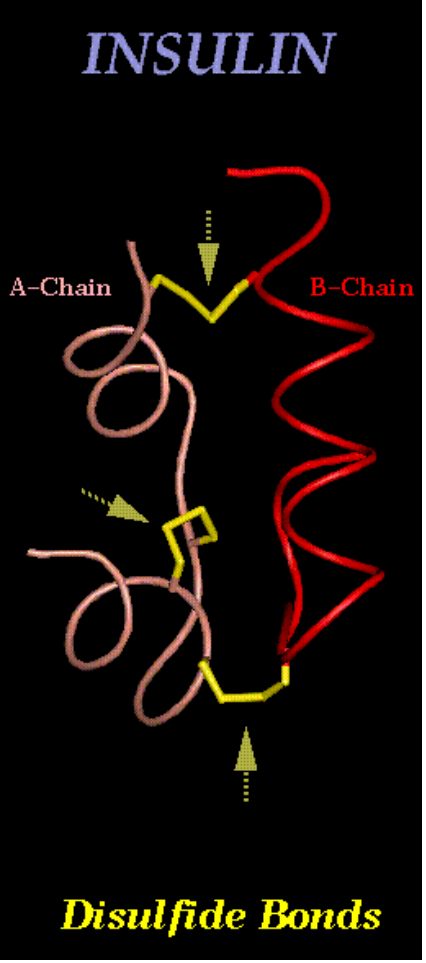


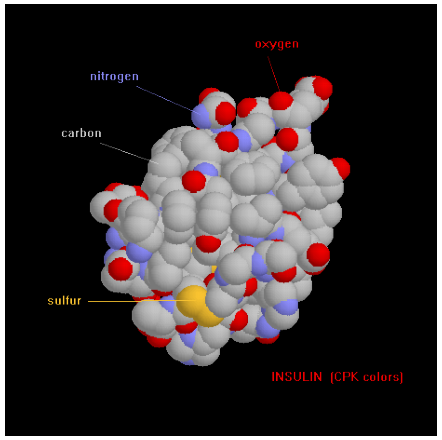
These insoluble fibres form the basis of the protein-folding diseases.

Alzeimer's and Type II diabetes

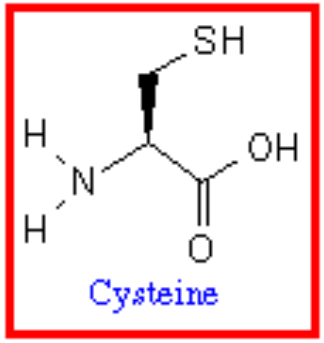
Aβ(21-30) and Alzheimer's Plaque



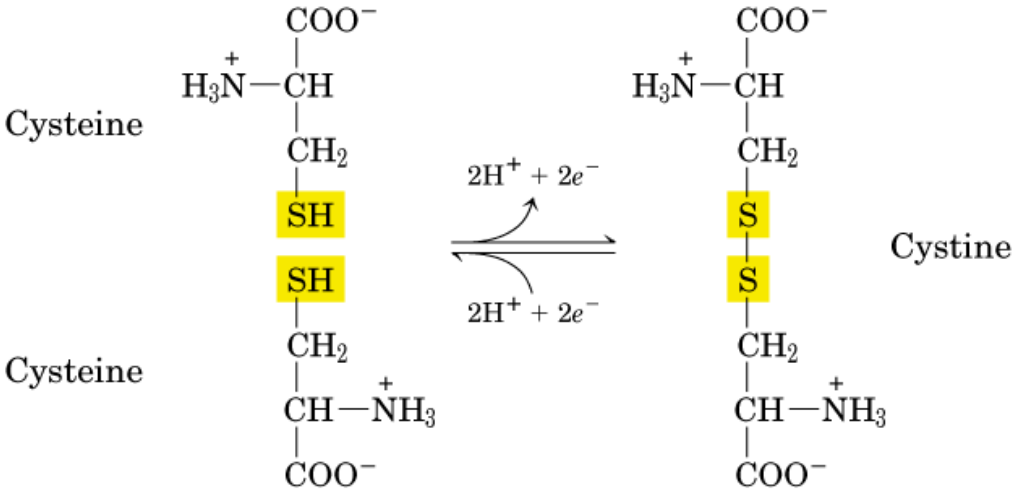


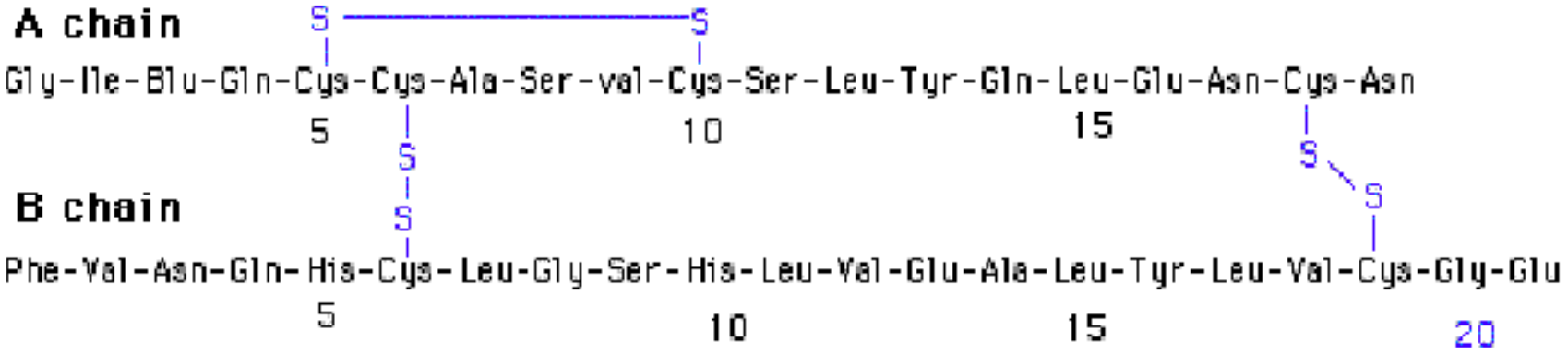


The disulphide bonds



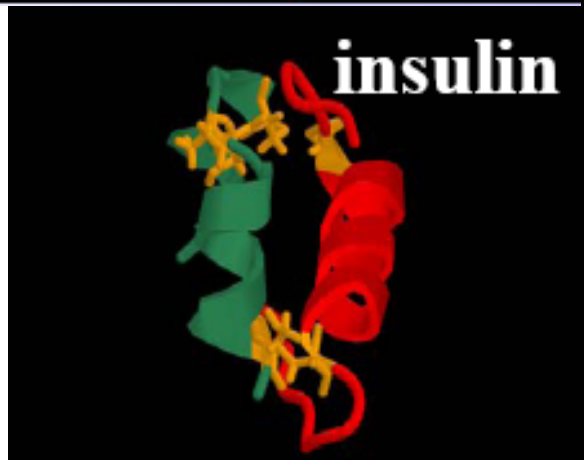
Only in extracellular proteins.



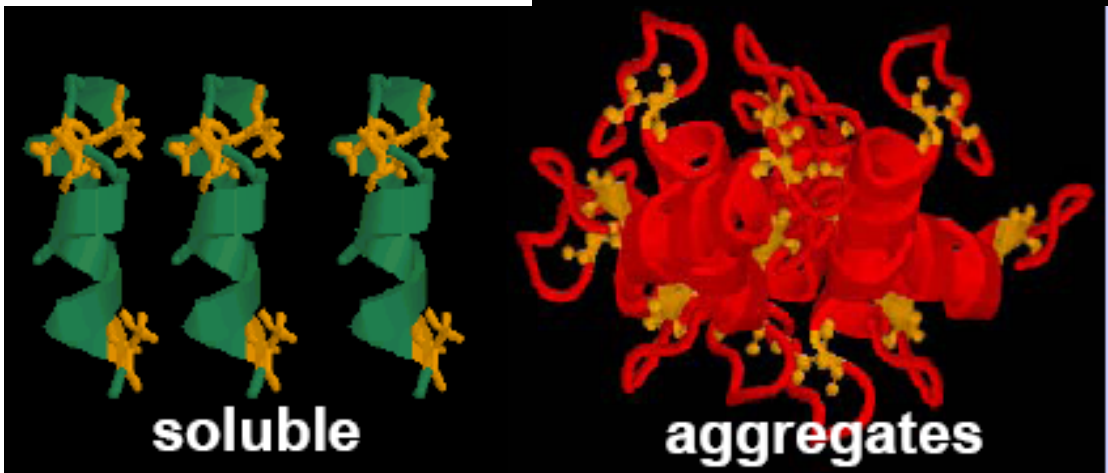


Insulin

protein assembly *-*
with regulation



protein aggregation *-*
irreversible assembly
without regulation



Protein activity may be regulated by multiple mechanisms

1. Phosphorylation
2. Binding to GTP
3. Allosteric regulation
4. Feedback inhibition