Basic Principles of Protein Structures

ECS129
PATRICE KOEHL

Proteins

Proteins: The Molecule of Life

Proteins: Building Blocks

Proteins: Secondary Structures

Proteins: Tertiary and Quartenary Structure

Proteins: Geometry

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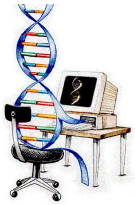
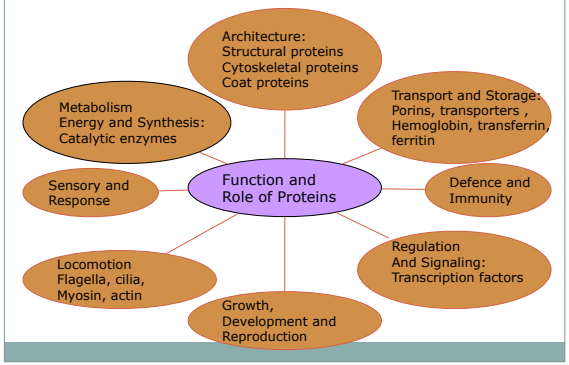
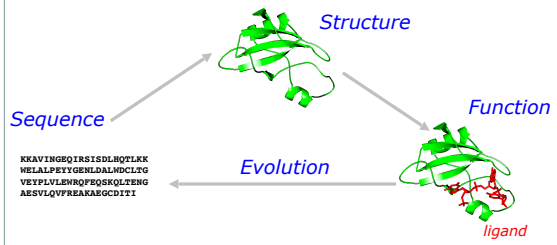


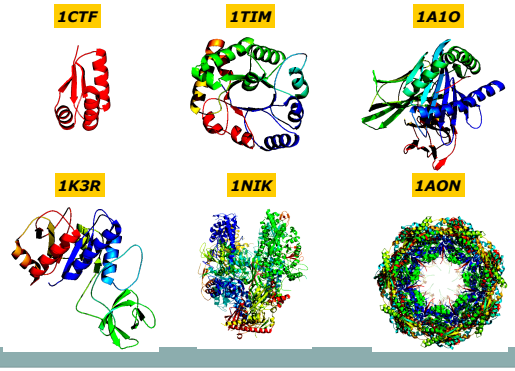
Why Proteins?



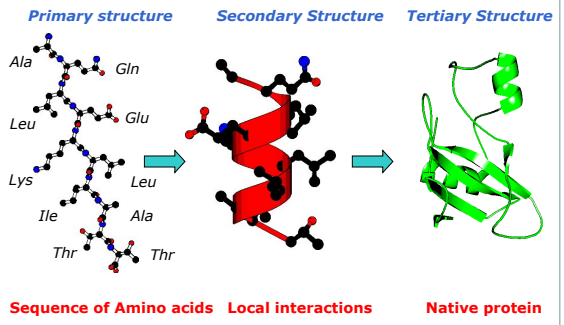
The Protein Cycle



Protein Structure Diversity



Protein Structure



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Review of Acid-Base Chemistry

What is an acid or a base?

An acid is a material that can release a proton (or hydrogen ion, H^+), and a base is a material that can donate a hydroxide ion (OH^-) (Arhennius definition), or accept a proton (Lowry Bronsted definition).

Note: It is important to notice that just because a compound has a hydrogen or an OH group does not mean that it can be an acid or a base!!

- The hydrogen of methane (CH4) and usually of methyl groups (-CH3) are all strongly attached to the carbon atom
- Glycerol has three OH groups (CH2OH – CHOH – CH2OH) and all 3 are alcoholic groups.

Review of Acid-Base Chemistry

Acid plus base makes water plus a salt:

AH + BOH → AB + H2O
(HCL + NaOH → NaCl + H2O)

The chemical dissociation of nitric acid is:

HNO3 → (NO3)- + H+

Which can be rewritten as:

HNO3 + H2O → (NO3)- + H3O+
acid base conjugate base conjugate acid

Review of Acid-Base Chemistry

pH is a measure of how acidic or alkaline (basic) a solution is. The pH of a solution is the negative log of the hydrogen ion concentration.

$$pH = -\log([H^+])$$
$$pOH = -\log([OH^-])$$
$$pH + pOH = 14$$

	[H+]	pH	pOH	[OH-]
Strong base	10^{-14}	14	0	1
Base	10^{-12}	12	2	10^{-2}
Weak base	10^{-9}	9	5	10^{-5}
Neutral	10^{-7}	7	7	10^{-7}
Weak acid	10^{-4}	4	10	10^{-10}
Acid	10^{-2}	2	12	10^{-12}
Strong acid	1	0	14	10^{-14}

Review of Acid-Base Chemistry

Dissociation of a weak acid:

HA → A- + H+

Equilibrium constant:

$$K_A = \frac{[H^+][A^-]}{[HA]}$$
$$pK_A = -\log(K_A)$$

Dissociation of a weak base:

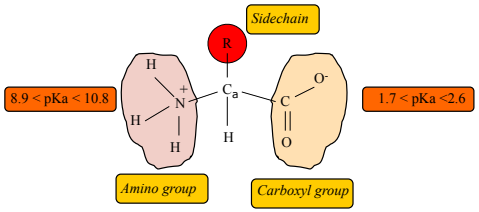
BOH → B+ + OH-

$$K_B = \frac{[B^+][OH^-]}{[BOH]}$$
$$pK_B = -\log(K_B)$$

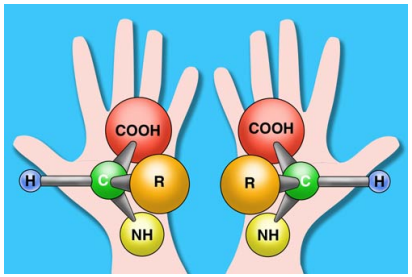
For an (acid,base) pair:

$$pK_A + pK_B = 14$$

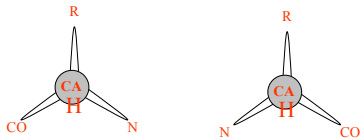
The Basic Block: Amino Acid



"zwitterion"



Amino Acid Chirality



L-form

(CORN rule)

D-form

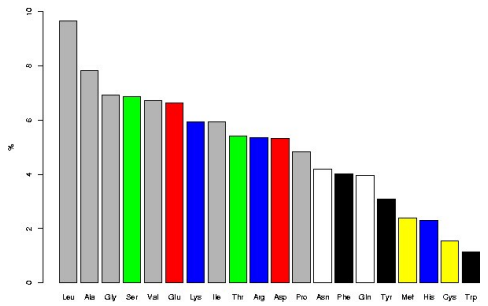
Amino acids in proteins are in the L-form

Threonine and Isoleucine have a second optical center which is also identical in all natural amino acids.

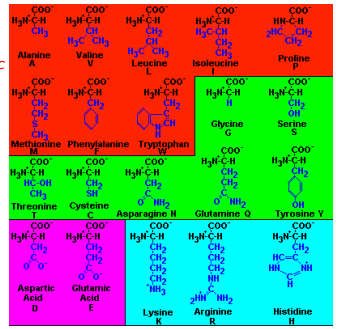
The 20 amino acids

1-letter	3-letter	Amino acid	1-letter	3-letter	Amino Acid
A	Ala	Alanine	M	Met	Methionin
C	Cys	Cysteine	N	Asn	Asparagine
D	Asp	Aspartic Acid	P	Pro	Proline
E	Glu	Glutamic Acid	Q	Gln	Glutamine
F	Phe	Phenylalanine	R	Arg	Arginine
G	Gly	Glycine	S	Ser	Serine
H	His	Histidine	T	Thr	Threonin
I	Ile	Isoleucine	V	Val	Valine
K	Lys	Lysine	W	Trp	Tryptophan
L	Leu	Leucine	Y	Tyr	Tyrosine

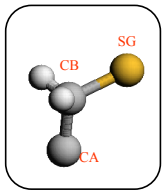
Amino Acids: Usage

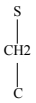


The 20 amino acids



Polar Amino acids: Cysteine





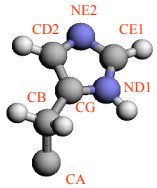
Names: Cys, C

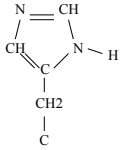
Occurrence: 1.8 %

pKa sidechain: 8.3

Can form disulphide bridges in proteins

Polar Amino acids: Histidine



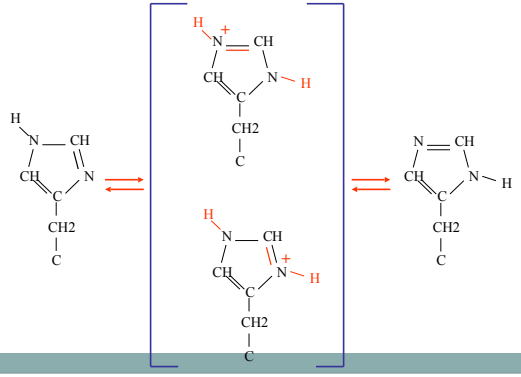


Name: His, H

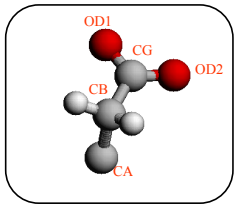
Occurrence: 2.2 %

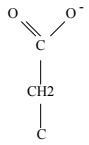
pKa sidechain: *6.04*

Different ionic states of Histidine



Charged Amino acids: Aspartic Acid



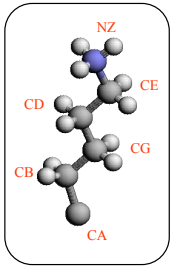


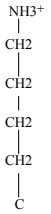
Names: Asp, D

Occurrence: 5.2 %

pKa sidechain: 3.9

Charged Amino acids: Lysine





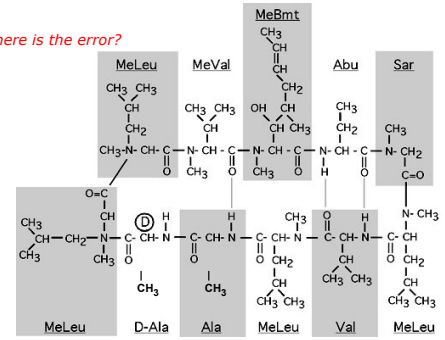
Names: Lys, K

Occurrence: 5.8 %

pKa sidechain: 9.2

Unusual Amino Acids: Cyclosporin

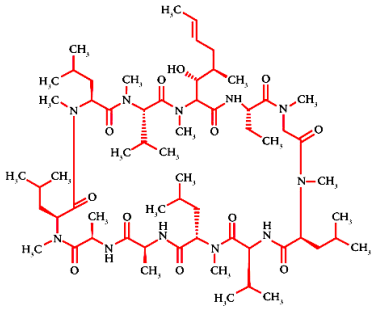
Where is the error?



http://purefixion.com/attention/2006_03_26_archive.html

Unusual Amino Acids: Cyclosporin

Correct!!



http://www.cellsignal.com/products/9973.html

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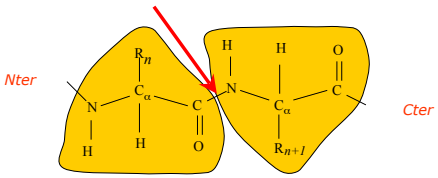
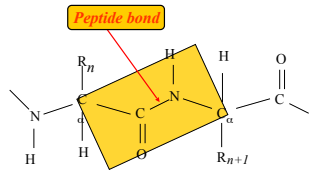
The Protein: A polymer of Amino acids

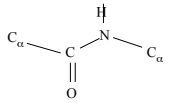
Peptide bond



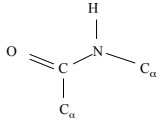
The Peptide Bond



The peptide bond is planar



Conformation "Trans"

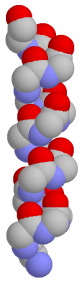


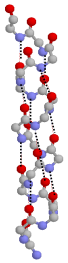
Conformation "Cis"

Helices

Cter

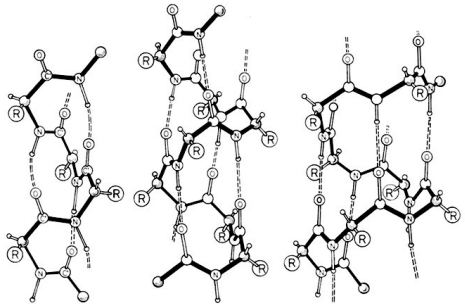
Nter





Hydrogen bonds: O (i) <-> N (i+4)

Helices



3_{10} helix | α-helix (4_{13}) | π-helix (5_{16})

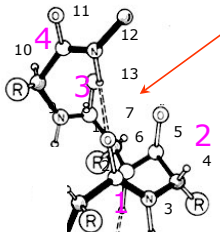
Helices

3_{10} helix — *"Thin"; 3.0 residues /turn; ~ 4 % of all helices*

π-helix (5_{16}) — *"Fat"; 4.2 residues /turn; instable*

α-helix (4_{13}) — *"Right"; 3.6 residues /turn; 5.4 Å /turn; most helices*

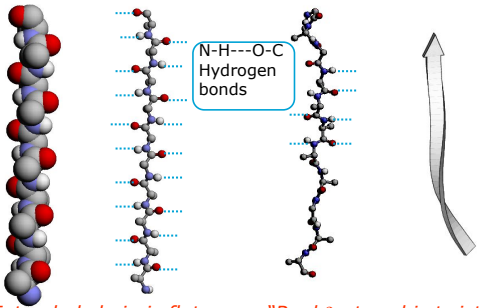
Identify Helix Type



1. *Find one hydrogen bond loop*
2. *Count number of residues (by number of C atoms in the loop). Here :* *4*
3. *Count number of atoms in the loop (including first O and last H). Here:* *13*

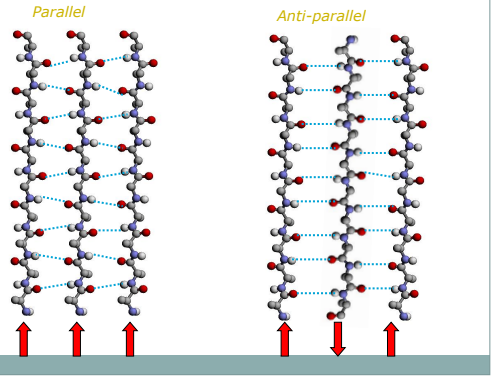
4_{13} helix = α-helix

The β-strand

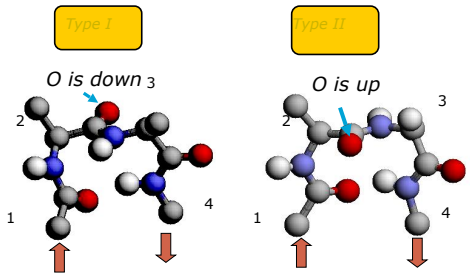


Extended chain is flat *"Real β-strand is twisted"*

Two types of β-sheets



β-turns

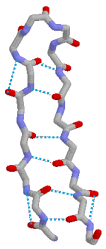


The chain changes direction by 180 degrees

Favorable /Unfavorable Residues In Turns

Turn	1	2	3	4
I	Asp, Asn, Ser, Cys	Pro	Pro	Gly
II	Asp, Asn, Ser, Cys	Pro	Gly, Asn	Gly

The β-hairpin



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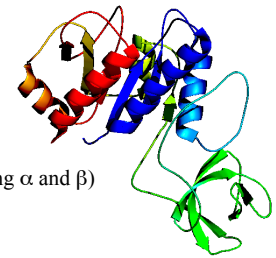
Protein Tertiary Structure

- All α proteins
- All β proteins
- Alpha and beta proteins:
  - α/β proteins (alternating α and β)
  - α + β proteins



All-Alpha topologies

- The lone helix

Glucagon (hormone involved Is regulating sugar metabolism)

PDB code : 1GCN

- The helix-turn-helix motif

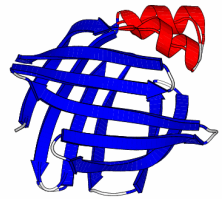
ROP: RNA-binding Protein

PDB code: 1ROP

The 2 helices are twisted

All Beta Topology

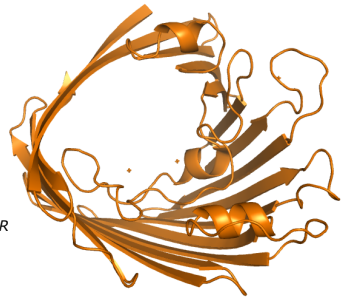
Beta sandwiches:



Fatty acid binding protein

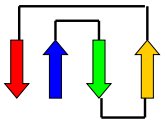
PDB code: 1IFB

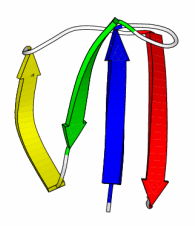
Closed Beta Barrel



PDB file: 2POR

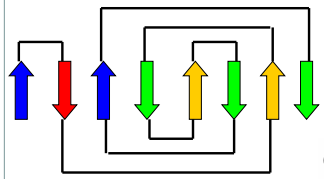
The Greek Key Topology





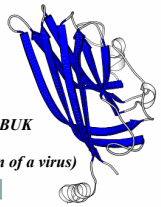
Folds including the Greek key topology include 4 to 13 strands.

The Jellyroll Topology



A Greek key with an

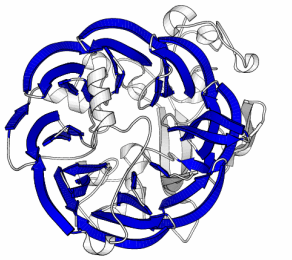
extra swirl



PDB code 2BUK

(coat protein of a virus)

The Beta Propellor



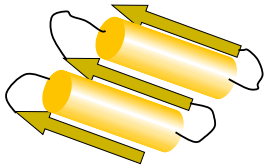
Eight-plated propellor:

Each plate is a four-stranded anti-parallel sheet

PDB code 4AAH

Alpha- Beta Topology

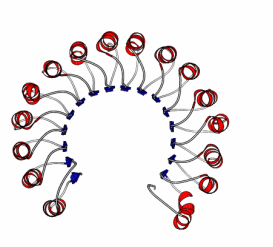
The Rossman fold:



Alternate beta / alpha motif

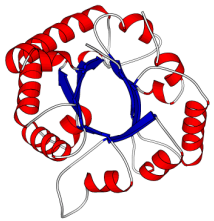
Always right handed

The Horseshoe



PDB code: 2BNH

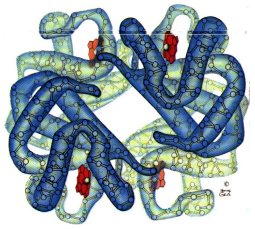
The alpha/beta barrel

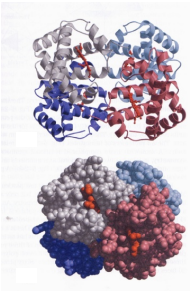


In a succession of alpha/beta motifs, if the first strand connects to the last, then the structure resembles a Barrel.

PDB code : 1TIM

Quaternary Structures
Assemblies of Protein Chains





Hemoglobin - 4 chains:
2-α chain, 2-β chain
(Heme- four iron groups)

Structural Bioinformatics: Proteins

Proteins: The Molecule of Life

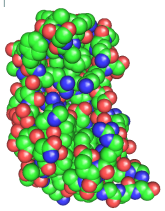
Proteins: Building Blocks

Proteins: Secondary Structures

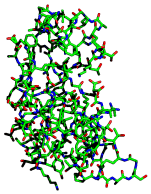
Proteins: Tertiary and Quartenary Structure

Proteins: Geometry

Protein Structure Representation



CPK: hard sphere model

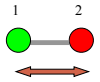


Ball-and-stick

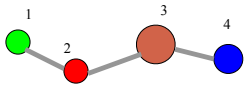
Cartoon

Degrees of Freedom in Proteins

Bond length

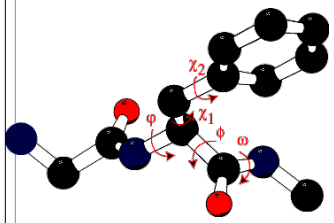


Dihedral angle



Bond angle

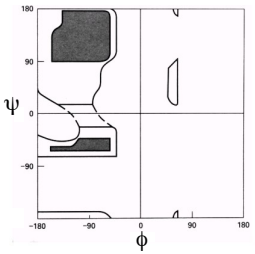
Protein Structure: Variables

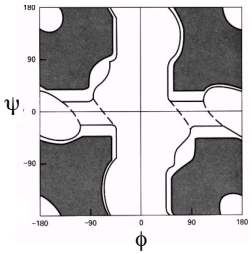


Backbone: 3 angles per residue : φ, ϕ and ω

Sidechain: 1 to 7 angles, χ; each χ has 3 favored values: 60°, -60°, 180°.

Ramachandran Plots





All residues, but glycine ***Glycine***

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What have we learnt?

- All proteins are polymers built up from 20 amino acids.
- All 20 amino acids have a similar structure: they all have a main-chain, consisting of an amino group and an acidic group, attached to a central carbon, named CA; the remaining atoms form the side-chain, that can be hydrophobic, polar or charged (acid or basic).
- The conformation of the backbone of amino acids is restricted, except for glycine that does not have a sidechain.
- There are 3 main graphical representations of proteins: space-filling, wireframe and cartoon.

What have we learnt?

- There are 3 major types of secondary structures: α-helices, β-sheets and β-turns.
- Most helices are α-helices, stabilized through a network of CO (i) --- HN (i+4) hydrogen bonds
- There are two types of β-sheets: parallel and anti-parallel
- β-turns correspond to 180 change in the backbone direction.

What have we learnt?

- There are three main classes of proteins: all Alpha, all Beta and Alpha + Beta. The latter can be divided in two, considering the alternating alpha/beta proteins as defining their own class.
- Bundles are common alpha-proteins
- Common beta folds include the greek key and the sandwiches. Immuno-globulins adopt a beta fold.
- The Rossman fold (alternating alpha/beta) is a common motif in proteins. It is found in the horseshoe, as well as in the TIM fold.