# 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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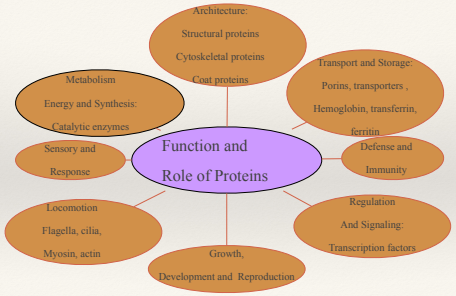
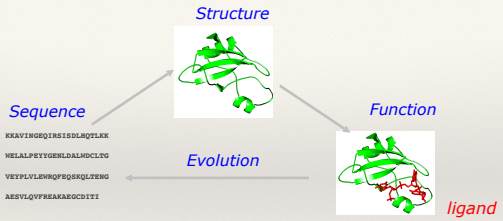
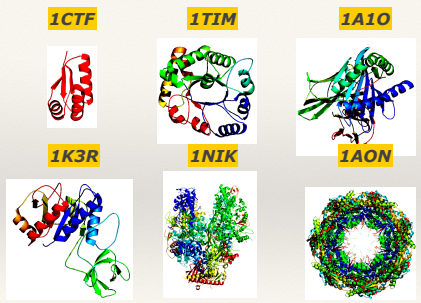
## Why Proteins?




## The Protein Cycle

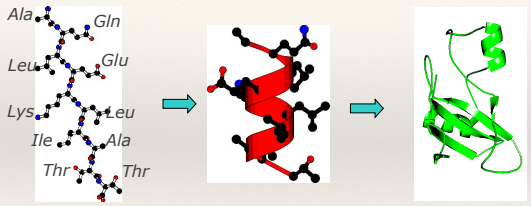



## Protein Structure Diversity



## Protein Structure

***Primary structure*** ***Secondary Structure*** ***Tertiary Structure***




**Sequence of Amino acids** **Local interactions** **Native protein**

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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 ($CH_4$) and usually of methyl groups ($-CH_3$) are all strongly attached to the carbon atom
- Glycerol has three OH groups ($CH_2OH - CHOH - CH_2OH$) 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 conjugate

## 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:***

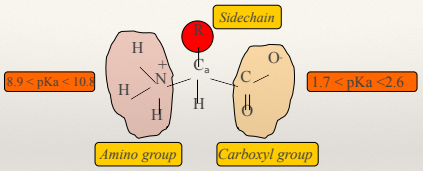
BOH → $B^+$ + $OH^-$

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

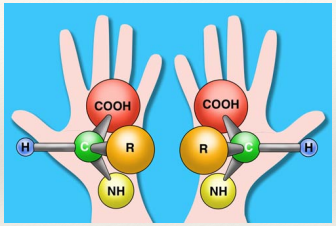
***For an (acid,base) pair:***

$$pK_A + pK_B = 14$$

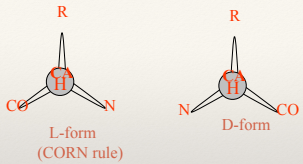
## The Basic Block: Amino Acid




*"zwitterion"*




## Amino Acid Chirality







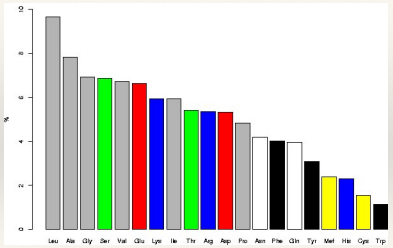
**Amino acids in proteins are in the L-form**

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

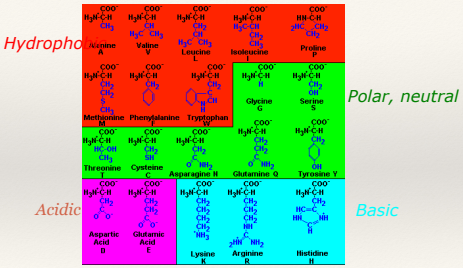
## The 20 amino acids

| 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 |

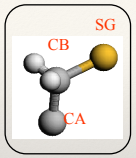
## Amino Acids: Usage




## The 20 amino acids



## Polar Amino acids: Cysteine





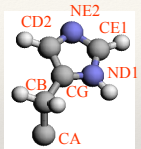
***Names:*** Cys, C

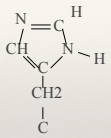
***Occurrence:*** 1.8 %

***pKa sidechain***: 8.3

*Can form disulphide bridges in proteins*


## Polar Amino acids: Histidine



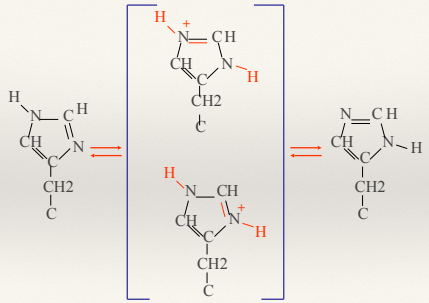




***Name:*** His, H

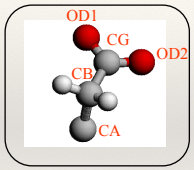
***Occurrence:*** 2.2 %

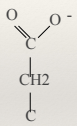
***pKa sidechain:*** ***6.04***

## Different ionic states of Histidine



## Charged Amino acids: Aspartic Acid



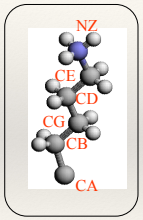



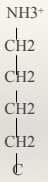

***Names:*** Asp, D

***Occurrence:*** 5.2 %

***pKa sidechain***: 3.9

## Charged Amino acids: Lysine



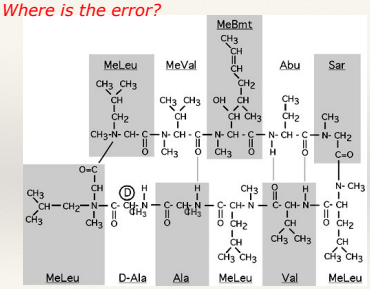

***Names:*** Lys, K

***Occurrence:*** 5.8 %

***pKa sidechain***: 9.2

## Unusual Amino Acids: Cyclosporin

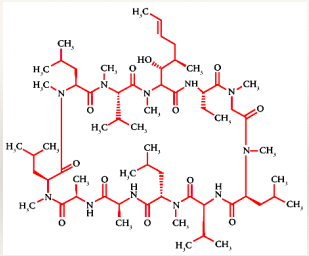
*Where is the error?*




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

## Unusual Amino Acids: Cyclosporin

*Correct!!*



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

## Proteins

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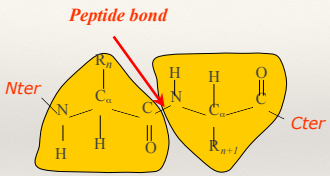
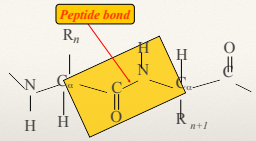
Proteins: Geometry

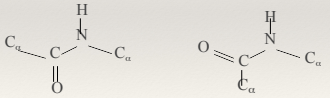
## The Protein: A polymer of Amino acids



## The Peptide Bond




*The peptide bond is planar*

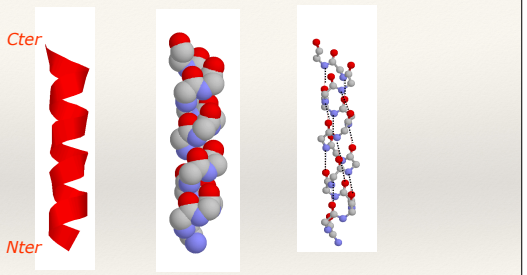


*Conformation "Trans"*



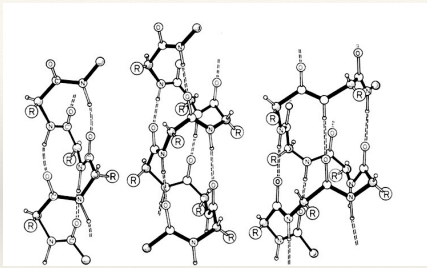
*Conformation "Cis"*

## Helices




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

## Helices



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

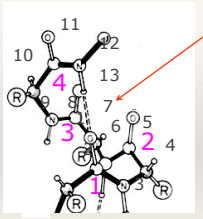
## Helices

$3_{10}$ 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*

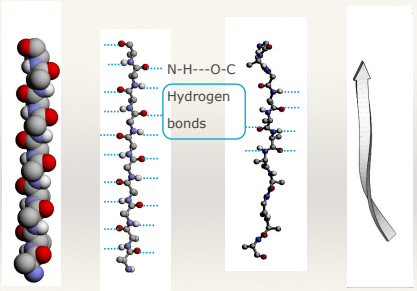
## Identify Helix Type




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

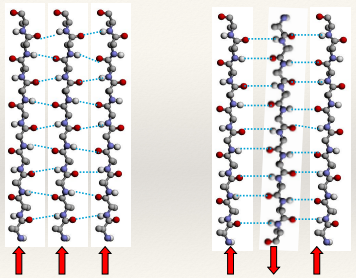
## The β-strand




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

## Two types of β-sheets

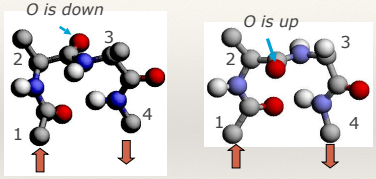
*Parallel* *Anti-parallel*



## β-turns

*Type I* *Type II*

*O is down* *O is up*

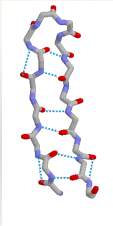



The chain changes direction by 180 degrees

## 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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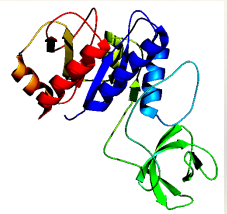
## Protein Tertiary Structure

- 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*

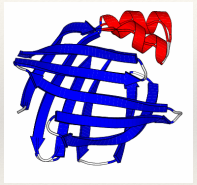
- The helix-turn-helix

*ROP: RNA-binding Protein*
*PDB code: 1ROP*

*The 2 helices*
*are twisted*

## All Beta Topology

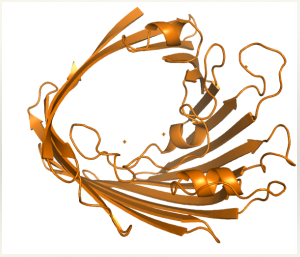
***Beta sandwiches:***



*Fatty acid binding protein*

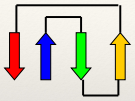
*PDB code: 1IFB*

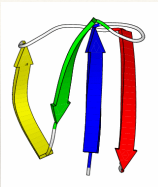
## Closed Beta Barrel



*PDB file: 2POR*

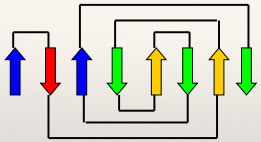
## The Greek Key Topology





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

## The Jellyroll Topology

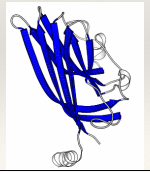


*A Greek key with an*

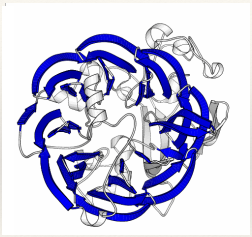
*extra swirl*

*PDB code 2BUK*

*(coat protein of a virus)*



## The Beta Propellor



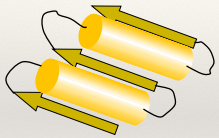
*Eight-plated propellor:*

*Each plate is a four-stranded anti-parallel sheet*

*PDB code 4AAH*

## Alpha- Beta Topology

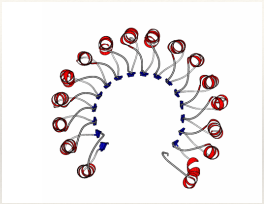
*The Rossman fold:*



***Alternate beta / alpha motif***

***Always right handed***

## The Horseshoe



***PDB code: 2BNH***

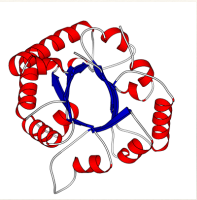
## The alpha/beta barrel

*motifs, if the first strand*

*connects to the last,*

*then the structure resembles a*

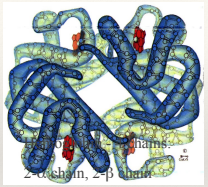
*Barrel.*



*PDB code : 1TIM*

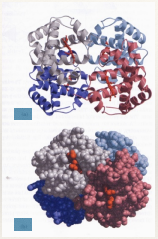
## Quaternary Structures

### Assemblies of Protein Chains



2 α chain, 2 β chain

(Heme- four iron groups)



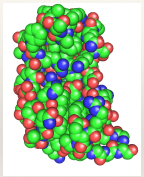
## Structural Bioinformatics: Proteins

Proteins: Secondary Structures

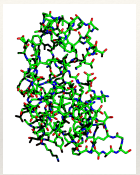
Proteins: Tertiary and Quartenary Structure

Proteins: Geometry

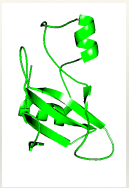
## Protein Structure Representation



CPK: hard sphere model

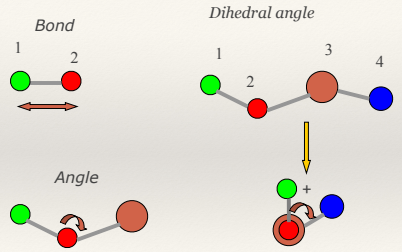


Ball-and-stick

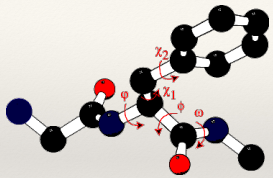


Cartoon

## Degrees of Freedom in Proteins



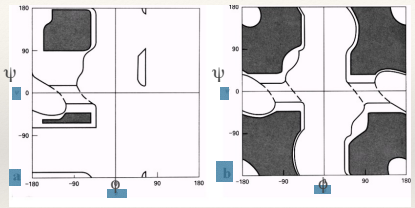

## Protein Structure: Variables




**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*

*Acta Cryst.* (2002). D**58**, 768-776

## 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.