### Programme

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### Feedback Persons

![Feedback Persons Image]
Summary of Last Week

- Walk-through of course plan

Group Work

- MOTIVATION:
  - General qualification to be able to work with (almost) anybody.

- CHALLENGE:
  - Some students have not yet shown up and need to join other groups or form new.
  - Incompatibilities within groups.

- SOLUTION:
  - New groups can be formed when projects are initiated.
  - Define new set of group rules.
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Levels of Protein Structure
Primary to Quaternary Structure
Learning Objectives

- After today you should be able to:
  - Define the structural levels of proteins.
  - Identify the structural units of the protein backbone.
  - Create a model of a protein fragment given its backbone torsion angles.
  - Explain why some backbone conformations are “forbidden”, i.e. not found in natural proteins.
  - Name properties on which the amino acids can be grouped.
  - Name more amino acids than you could before 😊

- Tool
  - Amino acid quiz!

Amino Acids

- Proteins are built from amino acids
- Amino group and acid group
- Side chain at Cα
- Chiral, only one enantiomer found in proteins (L-amino acids)
- 20 natural amino acids

Methionine
The Amino Acids

- Ala (A)
- Val (V)
- Thr (T)
- Phe (F)
- His (H)
- Leu (L)
- Ser (S)
- Cys (C)
- Lys (K)
- Asp (D)
- Ile (I)
- Asn (N)
- Met (M)
- Lys (K)
- Glu (E)
- Gln (Q)
- Pro (P)
- Tyr (Y)
- Gly (G)
- Phe (F)
- Arg (R)
- Trp (W)
- Met (M)
- Leu (L)
- Ala (A)
- Val (V)
- Thr (T)
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- Pro (P)
- Tyr (Y)
- Gly (G)

How to Group Them?

- Many features
  - Charge +/-
    - Acidic vs. basic (pKₐ)
  - Polarity (polar/non-polar)
    - Type, distribution
  - Size
    - Length, weight, volume, surface area
  - Type (Aromatic/aliphatic)
The Amino Acids

http://www.ch.cam.ac.uk/magnus/molecules/amingo/

Grouping Amino Acids

Amino Acids
A alanine (ala)
R arginine (arg)
N asparagine (asn)
D aspartic acid (asp)
C cysteine (cys)
Q glutamine (gln)
E glutamic acid (glu)
G glycine (gly)
H histidine (his)
I isoleucine (ile)
L leucine (leu)
K lysine (lys)
M methionine (met)
F phenylalanine (phe)
P proline (pro)
S serine (ser)
T threonine (thr)
W tryptophan (trp)
Y tyrosine (tyr)

http://www.dreamingintechnicolor.com/InfoAndIdeas/AminoAcids.gif
The Evolution Way

- Based on Blosum62 matrix
- Measure of evolutionary substitution probability

Form vs. Function

- **Divergent evolution**
  - Common ancestor
  - New function

- **Convergent evolution**
  - Different ancestor
  - Same function

**Convergent** evolution

- Red panda
- Tree kangaroo
- Deer
- Red kangaroo

http://palaeo.gly.bris.ac.uk/palaeofiles/marsupials/Index.htm
Sequence vs. Function – I

- Trypsin
  - positive
- Chymotrypsin
  - large hydrophobic
- Elastase
  - Small hydrophobic

- Divergent evolution
  - Same fold
  - Different specificities
  - Small changes in binding pocket

Sequence vs. Function – II

- Subtilisin
- Trypsin

Convergent evolution
The Simple Aliphatic

Ala (A)

Val (V)

Leu (L)

Ile (I)

Met (M)

The Small Polar

Ser (S)

Cys (C)

Cysteine

Thr (T)

Cystine
The Unusual

- P, G
- Also aliphatic
- Structural impact

- Strictly speaking, proline is an imino acid

---

The Acidic and Their Derivatives

- Asp (D)
- Asn (N)
- Glu (E)
- Gln (Q)
The Basic

- Arg (R)
- Lys (K)
- His (H)

The Aromatic

- Phe (F)
- Trp (W)
- Tyr (Y)
- His (H)
Active Site Residues

Catalytically Active (or Modified)?

http://www.ch.cam.ac.uk/magnus/molecules/amino/
Links

- Amino acid properties (under construction)

- Amino acid quizzes

- Fun stuff
  - [http://wiki.bio.dtu.dk/teaching/index.php/Course27617#Fun_Staff](http://wiki.bio.dtu.dk/teaching/index.php/Course27617#Fun_Staff)

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Proteins Are Polypeptides

- The peptide bond
- A polypeptide chain

Torsion Angles
Ramachandran Plot

- Allowed backbone torsion angles in proteins

Small Exercise (5 minutes)

- For the polypeptide on the left discuss the following with your neighbour:
  - Why is the lower right quadrant a “forbidden” region in the Ramachandran plot?
  - What makes Gly a special amino acid when it comes to Ramachandran plots?
  - What about Pro?
Structure Levels

- **Primary structure** = Sequence (of amino acids)
- **Secondary Structure** = Helix, sheets/strands, bends, loops & turns (all defined by H-bond pattern in backbone)
- **Structural Motif** = Small, recurrent arrangement of secondary structure, e.g.
  - Helix-loop-helix
  - Beta hairpins
  - EF hand (calcium binding motif)
  - Many others...
- **Tertiary structure** = Arrangement of Secondary structure elements within one protein chain

Quaternary Structure

- **Assembly of monomers/subunits into protein complex**
  - Backbone-backbone, backbone-side-chain & side-chain-side-chain interactions:
    - Intramolecular vs. intermolecular contacts.
    - For ligand binding side chains may or may not contribute. For the latter, mutations have little effect.
- **Myoglobin**
- **Haemoglobin**
Hydrophobic Core

- Hydrophobic side chains go into the core of the molecule – but the main chain is highly polar.
- The polar groups (C=O and NH) are neutralized through formation of H-bonds.

Hydrophobic vs. Hydrophilic

- Globular protein (in solution)
- Membrane protein (in membrane)
Hydrophobic vs. Hydrophilic

- Globular protein (in solution)

- Membrane protein (in membrane)

Characteristics of Helices

- Aligned peptide units → Dipolar moment
- Ion/ligand binding
- Secondary and quaternary structure packing
- Capping residues
- The α helix (i→i+4)
- Other helix types! ($3_{10}$, π)
Helix Types

Helices
- Helix capping
- Amphiphilic residue patterns

Sheets
- Amphiphilic residue patterns
- Residue preferences at edges vs. middle

Special residues
- Proline
  - Helix breaker
- Glycine
  - In turns/loops/bends

Residue Patterns
**β-Sheets**

- Multiple strands → sheet
  - Parallel vs. antiparallel
  - Twist

- Flexibility
  - Vs. helices
  - Folding
  - Structure propagation (amyloids)
  - Other…
**β-Sheets**

- Multiple strands → sheet
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  - Structure propagation (amyloids)
  - Other…
**β-Sheets**

- **Multiple strands → sheet**
  - Parallel vs. antiparallel
  - Twist

- Strand interactions are **non-local**

- Flexibility
  - Vs. helices
  - Folding

**Turns, Loops & Bends**

- Between helices and sheets

- On protein surface

- Intrinsically “unstructured” proteins
Summary

- The backbone of polypeptides form regular secondary structures.
  - Helices, sheets, turns, bends & loops.

- These are the result of local as well as non-local interactions.

- Secondary structure elements are associated with specific residue patterns.

\[\alpha\]-sheets and \[\beta\]-helices

\[\alpha\]-sheet  \[\beta\]-helix

![Theoretical](image)

![Real](image)

1M8N
Break!

Be back @ 9.15

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M1 Protein

- Influenza protein.
- Covers the ribonucleoprotein capsid below the membrane.
- Helix bundle.

M1 for Exercise

- One helix per group
- Split in two parts, build then switch and check.
- Assist each other in connecting the helices when done!
Procedure

1. Build backbone in extended conformation (strand).
2. Twist to align all peptide units (look at the C=O groups).
3. Add H-bonds (i+4) to construct an ideal $\alpha$-helix.
4. Add side chains along the way (pointing “down”).
5. Adjust side chain torsion angles.

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