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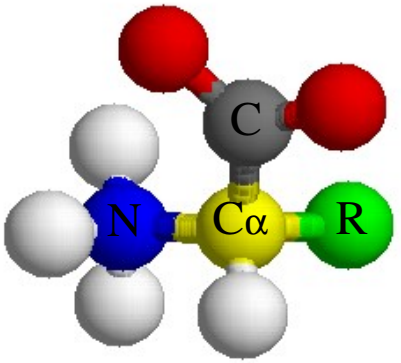
Physiochemical Properties of Residues

Various Sources



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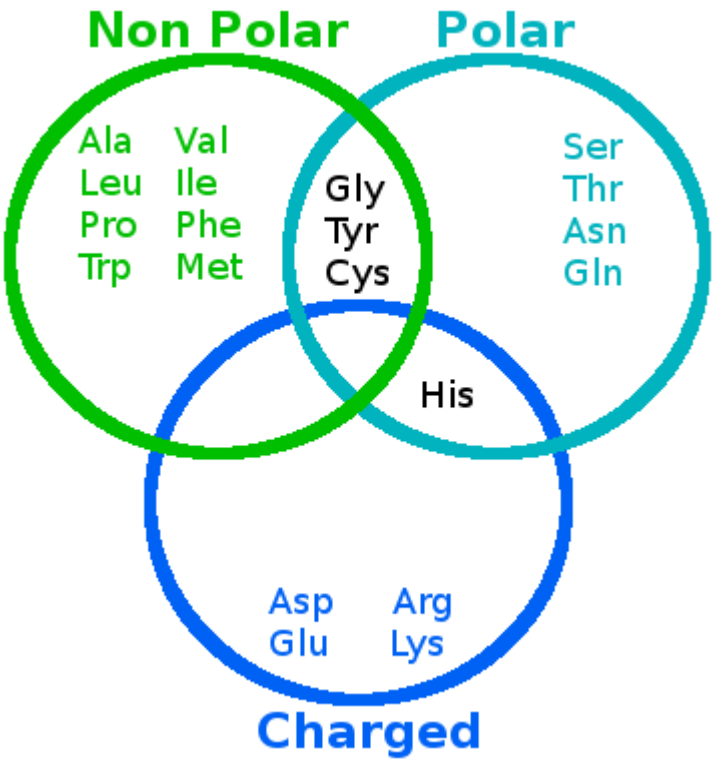
Conformational Propensities

Conformational Propensity is the frequency in which a residue adopts a given conformation (in a polypeptide)

- applies to main-chain (ie. secondary structure) and side-chain atoms
- Primarily dependent upon residue physiochemical properties
- Can depends upon sequence context (flanking residues)

- Derived from residue conformations in known structures
  - Circular Dichroism (original method) and Computational Simulations (newer approach) are also used to identify residue conformation



Amino acids grouped by Polarity (at neutral pH).

Conformational Propensities
(main chain)

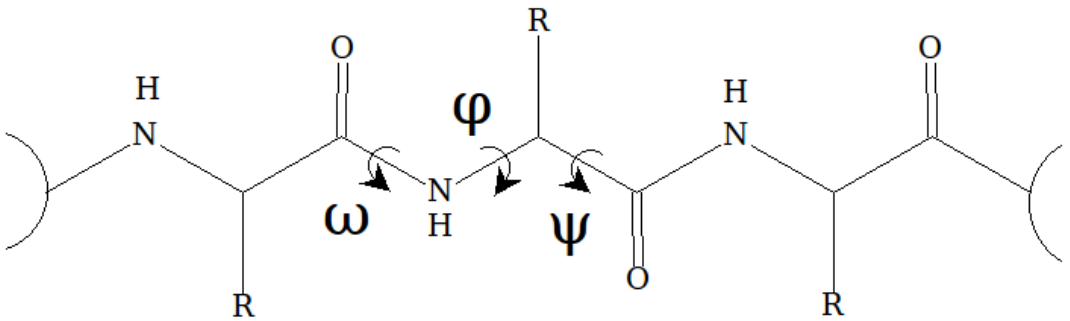
Main-chain conformations of amino acids are described by ϕ, ψ (and ω; peptide bond) torsion angles

- **Helix, sheet and loop propensities are calculated**
  - **Loop propensities are sometimes separated into turn and loop propensities**

Simple Logic

- **Physiochemical properties (size, shape, charge) of a given side chain prefer one secondary structure**
- **Significance: Propensity either dictates local structure OR Local structure dictates propensity**
  - **Useful in either case**

Example (extreme): Pro side-chain cannot be accomodated in an α-helical structure



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Calculated Propensities

Basic Approaches

Chou-Fasman (original)

- Calculate single propensity for each secondary structure
- No accounting for sequence 'context'

Example:

P_{α} (Glu) ≈ % Glu_{helix} / % All $Residues_{helix}$

GOR (Garnier-Osguthorpe-Robson)

- Accounts for sequence context by calculating propensities within a 17 residue window
- Improvement though requires more computational time

Amino Acid	P_{α}	P_{β}	P_t
Glu	1.51	0.37	0.74
Met	1.45	1.05	0.60
Ala	1.42	0.83	0.66
Val	1.06	1.70	0.50
Ile	1.08	1.60	0.50
Tyr	0.69	1.47	1.14
Pro	0.57	0.55	1.52
Gly	0.57	0.75	1.56

Chou-Fasman residue propensities (probabilities) for each secondary structure

> 1.00	preferred structure
1.00	no preference
< 1.00	unfavourable conformation

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Looking at Propensities

Helices
- Glu (helix cap), Met (rare), Ala (helix cap)

Sheets
- C_β branched and Tyr

Turns
- Pro, Gly and small polar/charged residues

Remaining Non-polar Residues
- Favour secondary structures over turns

Remaining Polar/Charged Residues
- No real preferences

… -Pro-Gly-Pro-Glu-Met-Leu-Phe-Leu-Ala-Ala-Tyr-Asp-Lys- …

----turn---- ----------helix---------- -----turn----

Amino Acid	P_α	P_β	P_t
Glu	1.51	0.37	0.74
Met	1.45	1.05	0.60
Ala	1.42	0.83	0.66
Val	1.06	1.70	0.50
Ile	1.08	1.60	0.50
Tyr	0.69	1.47	1.14
Thr	0.83	1.19	0.96
Pro	0.57	0.55	1.52
Gly	0.57	0.75	1.56
Asp	1.01	0.54	1.46
Asn	0.67	0.89	1.56
Ser	0.77	0.75	1.43
Leu	1.21	1.30	0.59
Phe	1.13	1.38	0.60
Trp	1.08	1.37	0.96
Arg	0.98	0.93	0.95
Cys	0.70	1.19	1.19
Glu	1.11	1.10	0.98
His	1.00	0.87	0.95
Lys	1.14	0.74	1.01

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How do the prediction methods perform?

Chou-Fasman (no sequence context)

- **< 60% of residues correctly predicted as Helix, Sheet or Loop**
- **80% of residues correctly predicted as Helix**

GOR (addition of sequence context)

- **~ 65% of residues correctly predicted**
- **Improved detection of Sheet and Loop conformations**

Homology-based GOR (not applicable in all cases)

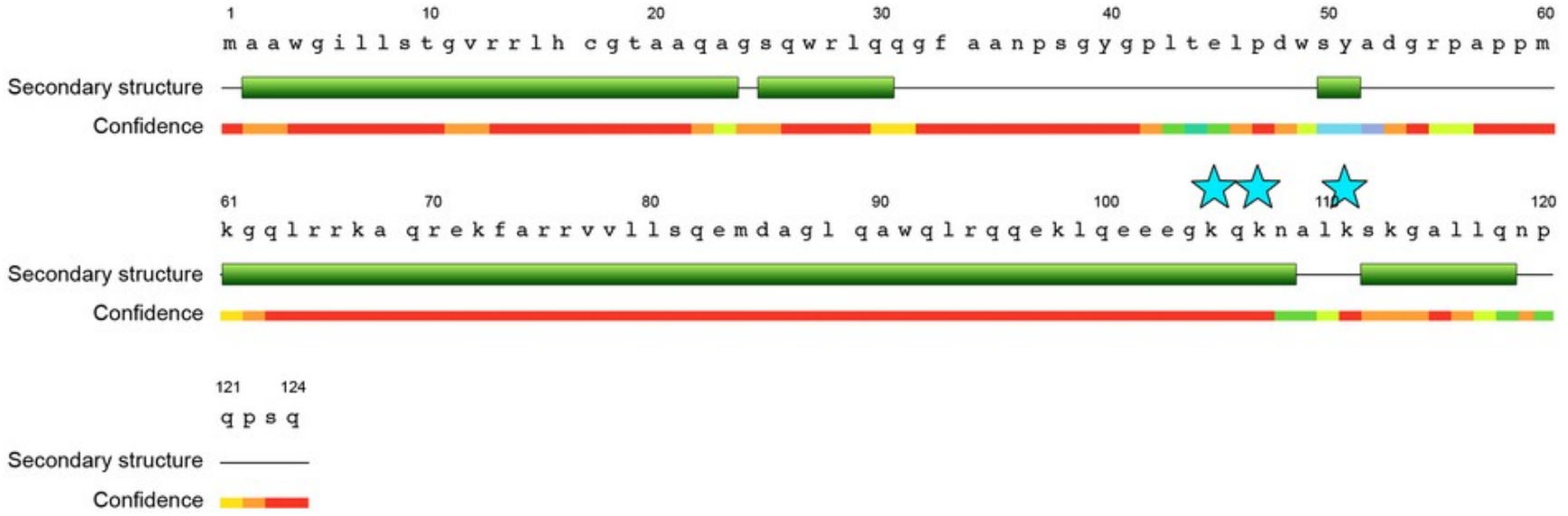
- **< 75% of residues correctly predicted**
- **Propensities are derived from a set of known structures of homologs**

Improving propensity-based predictions

Less than 75% accuracy …

- **Not (quite) as bad as it seems as most predictions provide "confidence estimates"**
- **Regions with low confidence estimates are often poorly predicted**

Require more representative protein structure database OR additional experimental evidence (eg. Circular Dichroism) to significantly improve current methods



Conformational Propensities
(side chain)

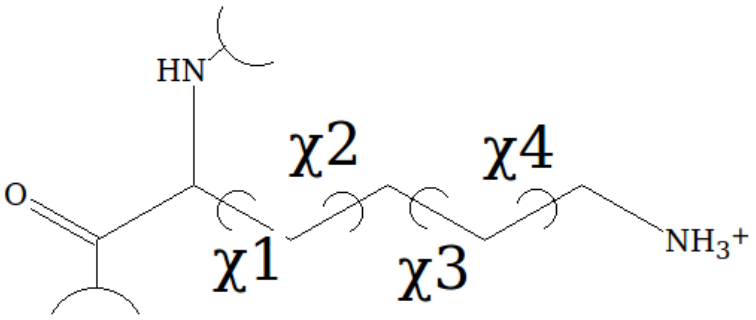
Side-chain conformations of amino acids are described by the $\chi 1$, $\chi 2$, etc torsion angles

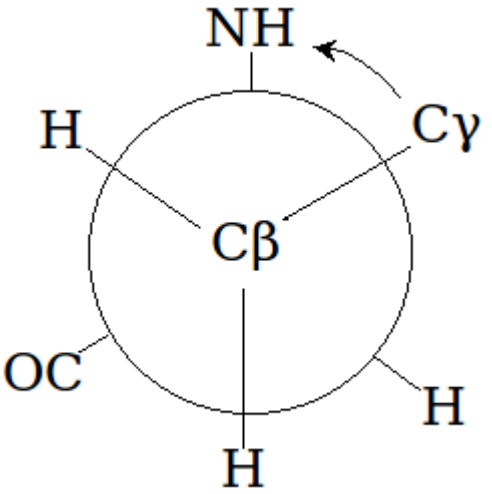
- **Preferred conformations of side chains from Newman Projection**

Newman Projection

- **Bonds between sp^3 hybridized atoms**

  Example: Cα -Cβ bond of Lys
- **$\chi 1$ has a preferred torsion angle of -60º**





Side chain atoms are named using greek letters in alphabetical order

eg. Cα, Cβ, Cγ, Cδ, Cε, Cζ, Cη

Conformational Propensities
(side chain)

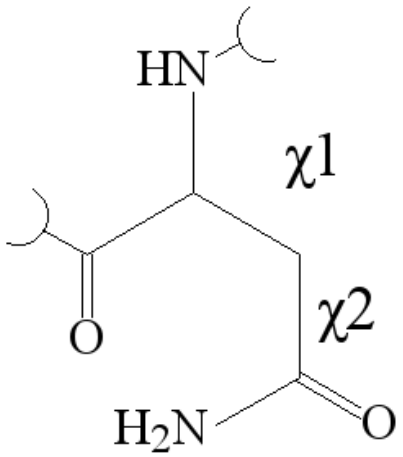
Side-chain conformations of amino acids are described by the χ1, χ2, etc torsion angles

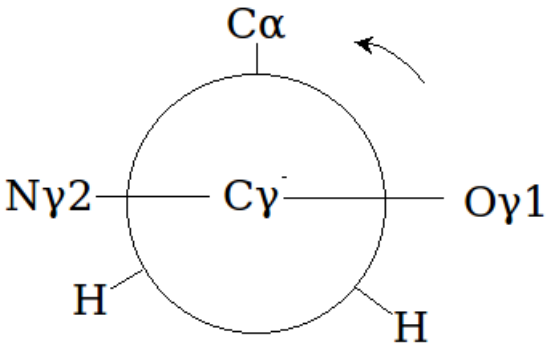
- **Preferred conformations of side chains from Newman Projection**

Simple Logic

- **Bonds between sp^3 and sp^2 hybrid atoms**

  Example: Cβ-Cγ bond of Asn
- **Asn has preferred χ2 of -90º (Newman Projection)**





Side chain atoms are named using greek letters in alphabetical order

eg. Cα, Cβ, Cγ, Cδ, Cε, Cζ, Cη

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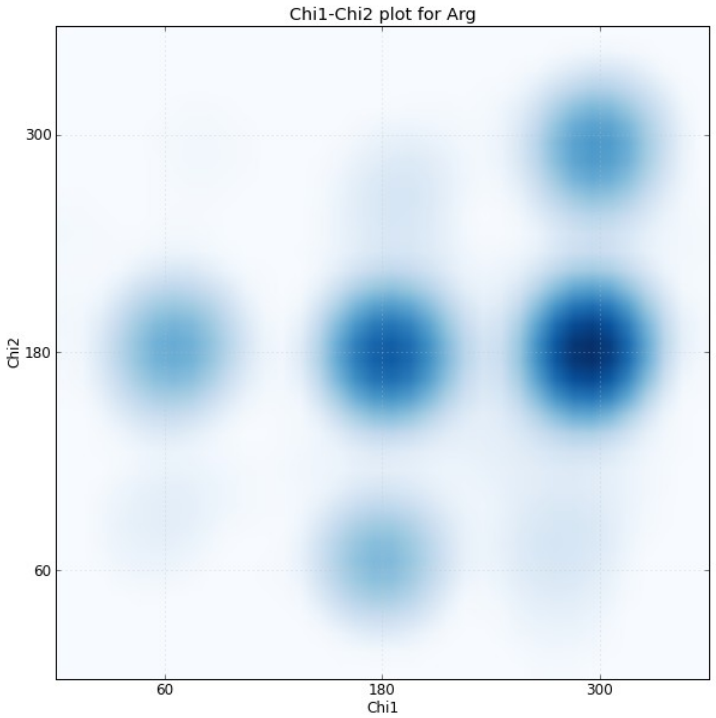
Chi1 (χ1) – Chi2 (χ2) plots
(side chain)

Chi1-Chi2 plots for selected residue side chains

- **Conformation propensity derived from known structures**

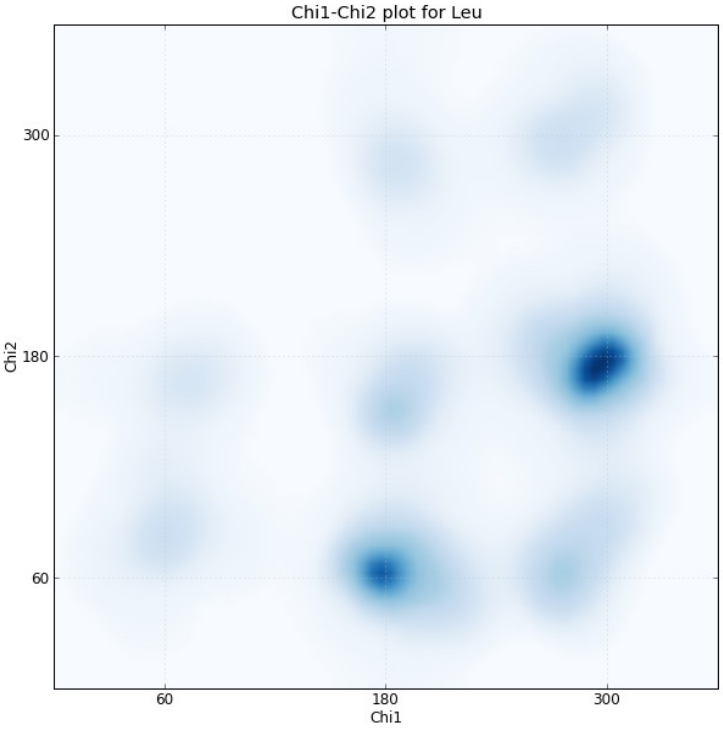
X-axis (Chi1) in degrees
Y-axis (Chi2) in degrees
Color Intensity is reflects number of residues at each Chi1-Chi2 value



Chi1 (sp3-sp3 atoms)
preferred torsion of -60º

Chi2 (sp3-sp3 atoms)
preferred torsion of 180º

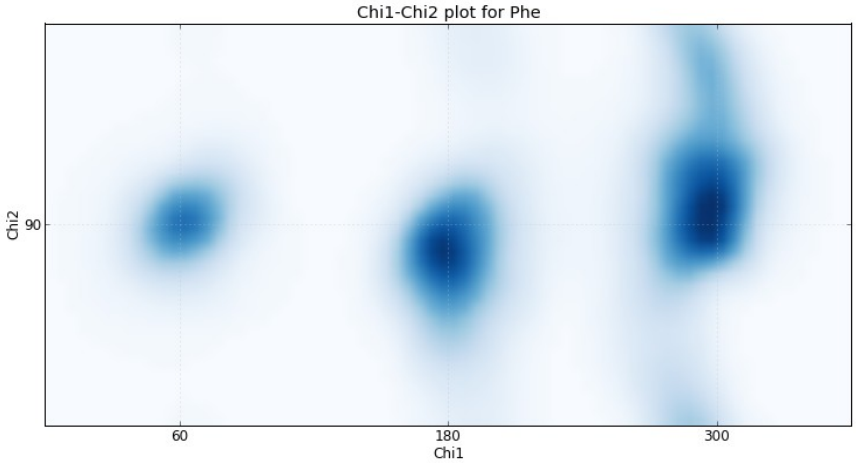
Agrees with predictions from Newman projections

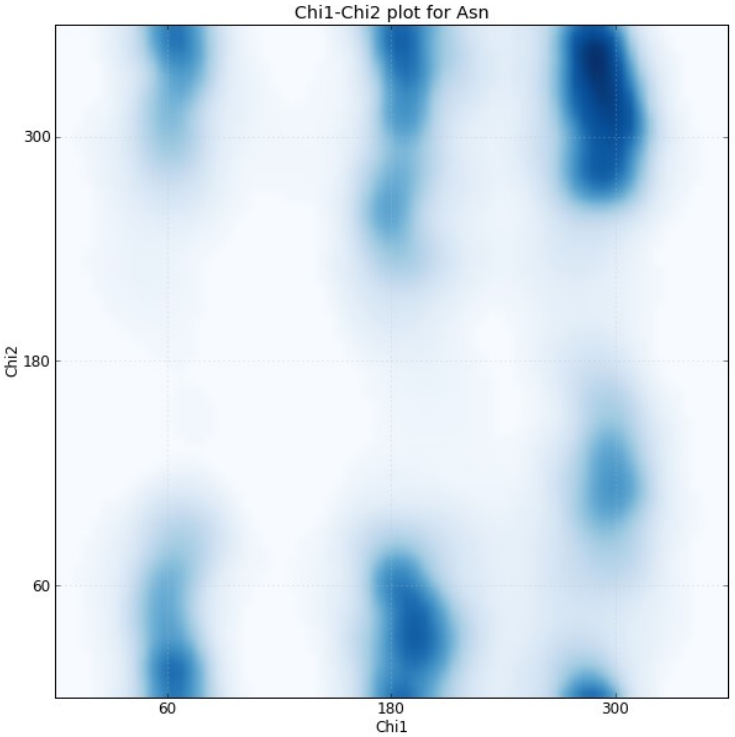


Chi1 (χ1) – Chi2 (χ2) plots
(side chain)

Chi1-Chi2 plots for selected residue side chains

- **Conformation propensity derived from known structures**



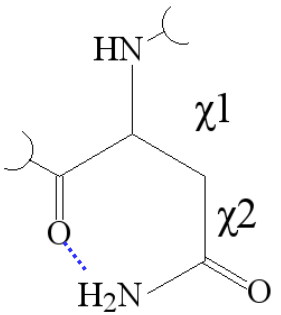


Chi2 does NOT agree with predictions from Newman projections !!!

Chi1 (sp3-sp3 atoms)
preferred torsion of -60º

Chi2 (sp3-sp2 atoms)
preferred torsion of 90º

Agrees with predictions from Newman projections



Chi2 torsion angles of +30º/-30º allow an 'intraresidue' H-bond to form

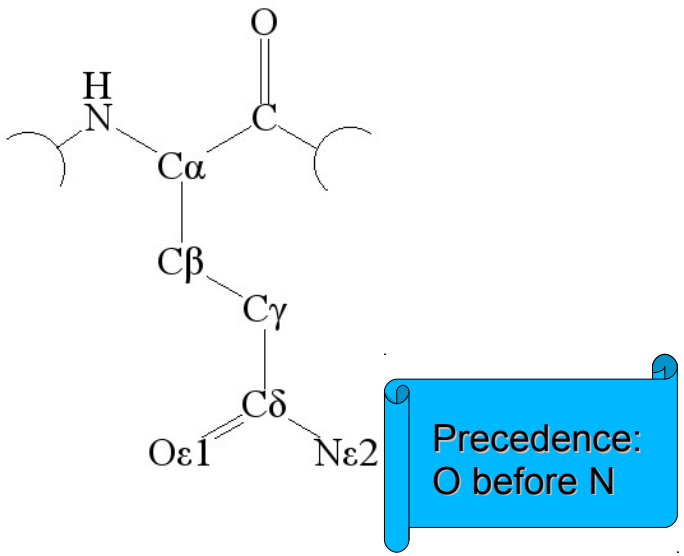
Atom Nomenclature
(amino acids)

Amino acid atom nomenclature

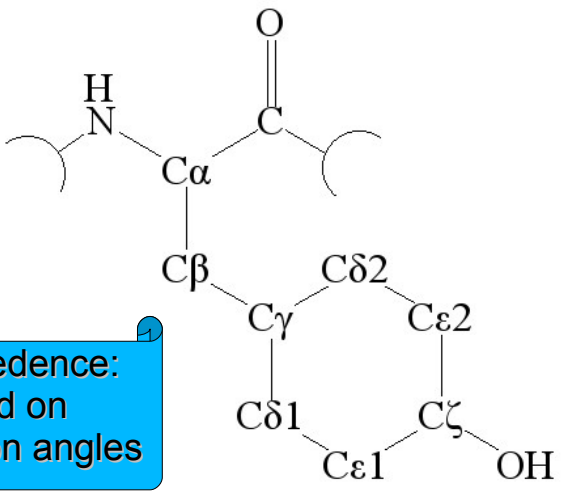
- Require nomenclature system that uniquely identifies each atom in a residue

Simple rules

(1) Greek letters (alphabetical order) identify distance from main-chain
(2) Branched side-chains are assigned a numeric counter with precedence given to atoms with larger atom numbers
(3) When branched side-chains have equal precedence, the atom with a torsion angle nearest 0° is given precedence
Note: One naming exception: Tyr -OH



Precedence:
O before N



Precedence:
Based on
torsion angles

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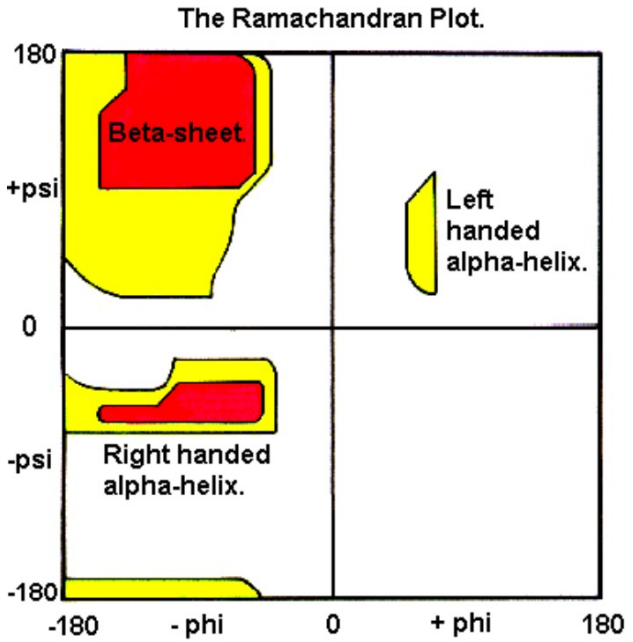
Secondary Structures
(revisited)

Ramachandran Plot describes the allowed backbone conformations of non-Gly residues (disallowed regions soley due to steric clashes)

Secondary structures are regular, repeating local backbone conformations (or H-bonding pattern)

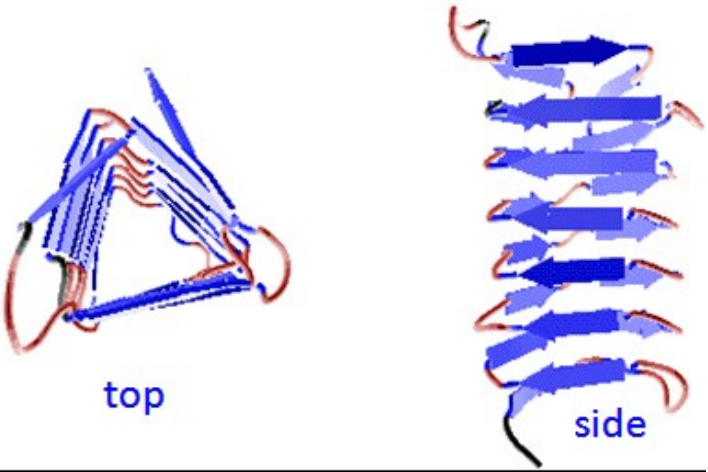


Bchm2000 (introductory level Bchm)

- Considered α-helices and β-Sheets; the most common and best studied secondary structures

Bchm4000

- New helical and sheet secondary structures
- Turns as secondary structures
- Simple loop classifications



β-trefoil folds contain 'flat', parallel β-sheets

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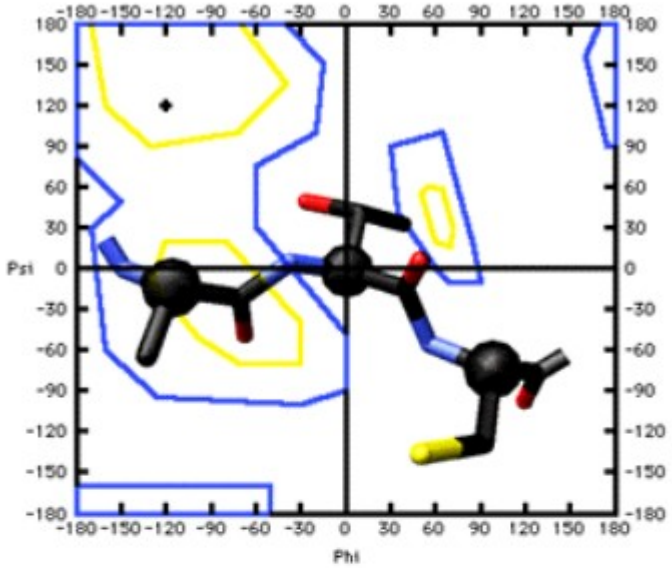
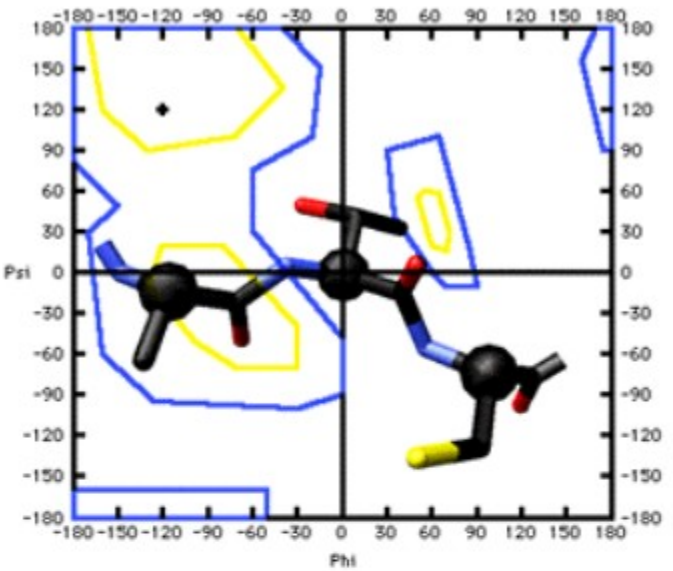
Effect of Phi-Psi changes
(Ramachandran plot)

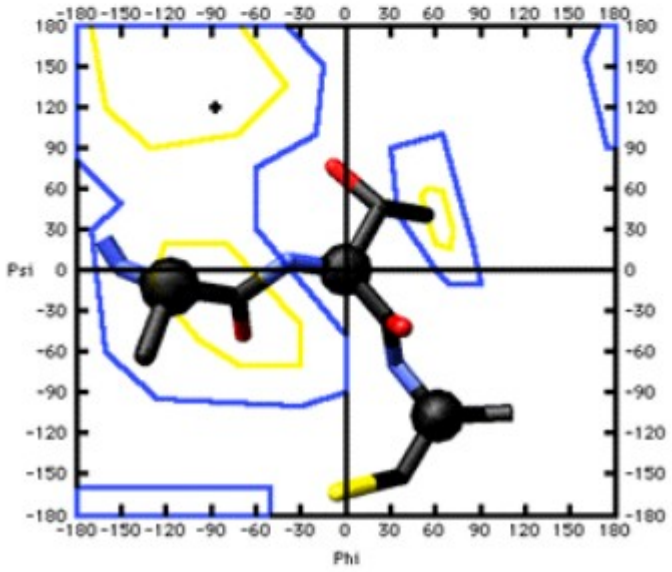


Left

Structural change arising from changing the phi torsion angle:

-120 (top) to -90º (bottom)

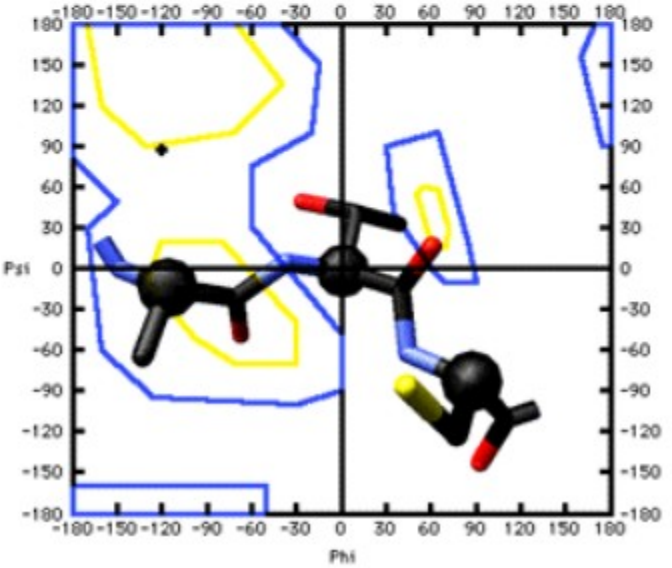




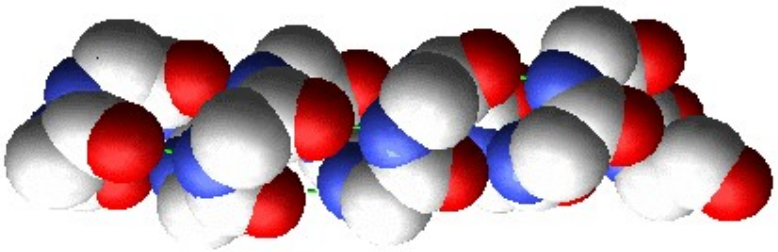
Right

Structural change arising from changing the psi torsion angle:

120º (top) to 90º (bottom)

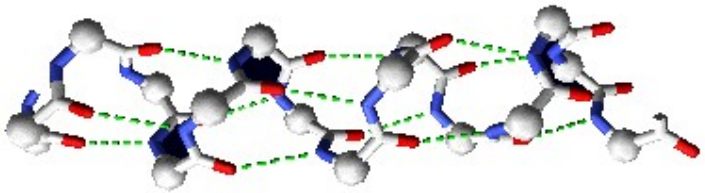


α-Helices



Properties

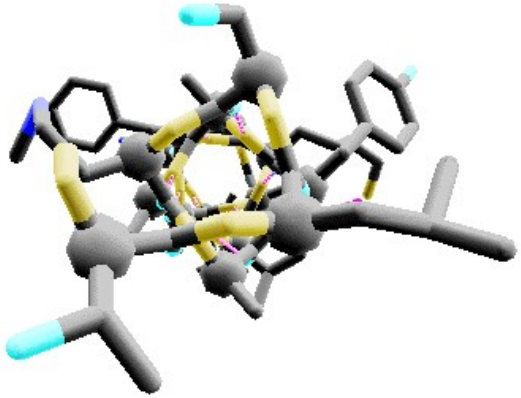
Structure repeats every 5.4 Å
3.6 residues / turn of helix (or 1.5 Å rise / residue)



Torsion angles with negative phi (near -60º) and psi (near -50º)

All main-chain CO and NH groups are hydrogen bonded (ie. O_i to N_{i+4})

Peptide planes are all roughly parallel to the helix axis and side chains radiate outwards and towards the N-terminal end



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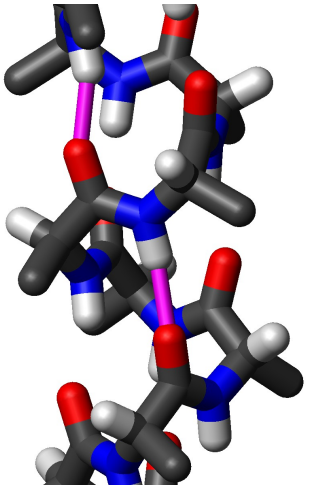
More Helices

Alternative helices can be identified by their H-bonding pattern



4_{13}

α-helix (4_{13}- helix)

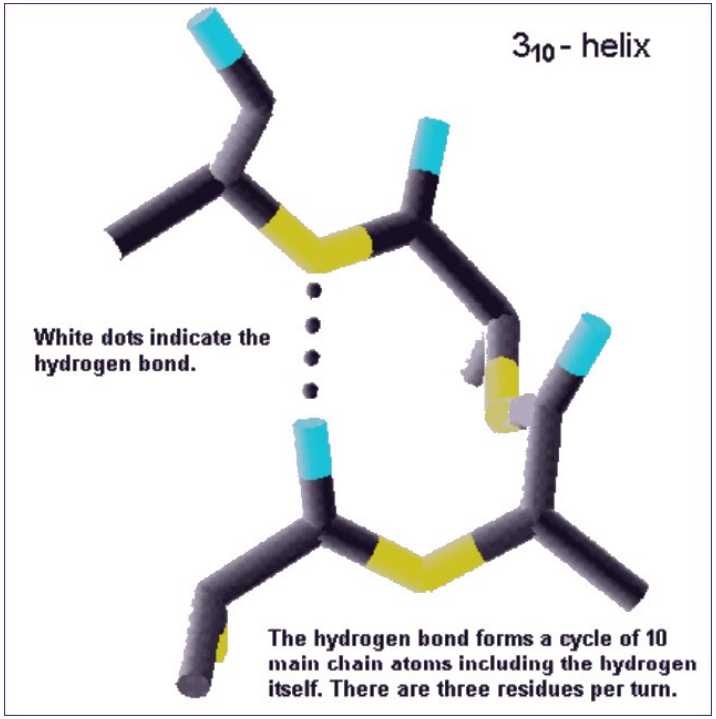
- 4 refers to the number of residues separating the H-bonded atoms (ie. O_i to N_{i+4})
- 13 refers to the number of atoms (including H) separating the H-bonded atom

3_{10}- helix (phi ~ -50° psi ~ -40°)

- 3 residues per turn (H-bonds between O_i to N_{i+3})
- Weaker H-bonding and packing (typically single turn only)
- Present at the terminii of many α-helices (cap)

5_{16}- helix (Π helix)

- 5 residues per turn (H-bonds between O_i to N_{i+5})
- rare except as turn subtype



Note: Colors of atoms inverted in bottom figure (O is blue, N is yellow)

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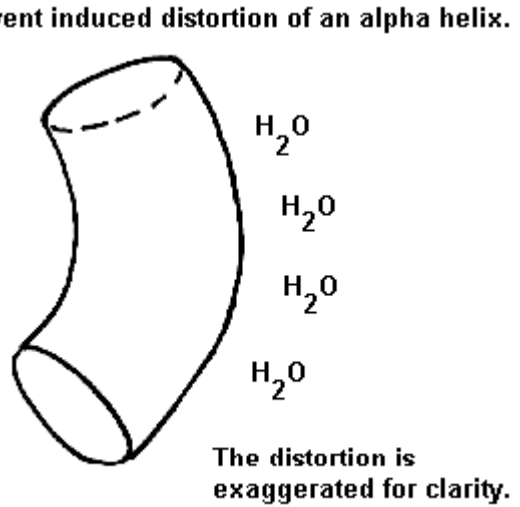
Distorted α-Helices



Majority of α-helices in proteins are distorted

Several factors account for the distortion of the classical Corey-Pauling α-helix

1) Packing of helices against other secondary structures within core

2) Pro can occur in longer 'bent' α-helices.

- **Pro induces a 20º bend while disrupting two hydrogen bonding interactions. This accounts for its occurrence within longer (ie. more stable) helices**

3) Solvent induced distortions of surface α-helices

- **Small rotation of peptide group allows CO to form additional 'bidentate' H-bonds with solvent**

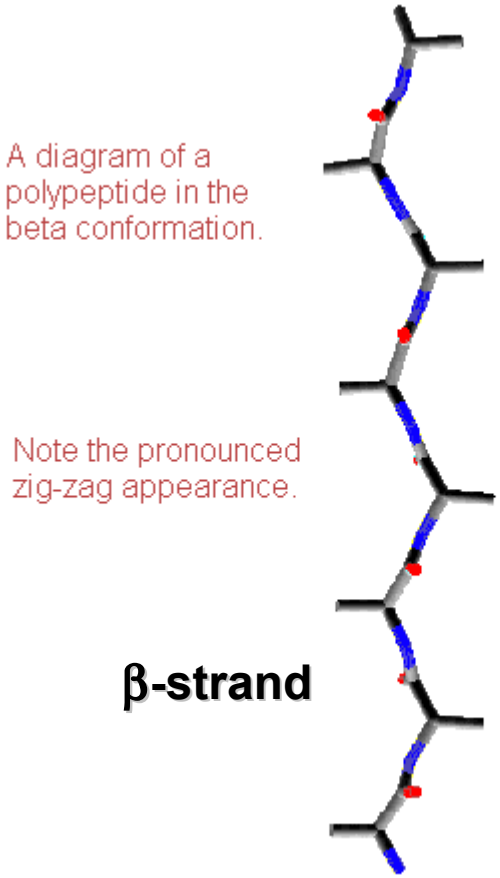
β-Strands

β-strands

Torsion angles near
phi = -140º and psi = +130º

3D structure repeats every 2 residues

distance between residues is 3.5 Å
pitch (distance between repeats) is 7.0 Å



β-strand

Side chains are orthogonal to the axis of the β-strand (minimizes steric clashes)

- **Allows β-strands to accommodate side chains with branches at Cβ (unlike helices)**

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β-Sheets

Composed of 2 or more β-strands

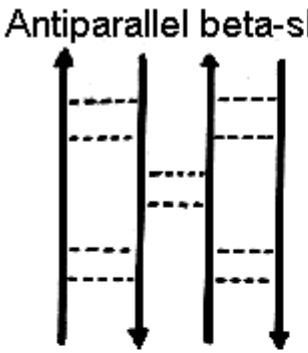
- Parallel and antiparallel β-sheets are equally common
  - Mixed sheets are less common

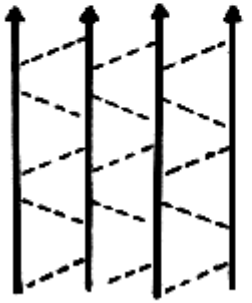
Parallel β-sheets

- 4-6 strands
- Always buried in hydrophobic core
- Weaker (bent) H-bonds
- Smaller sheet twist

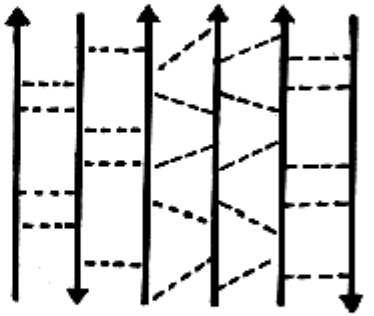
Antiparallel β-sheets

- 2-6 strands
- Stronger (linear) H-bonds
- Larger sheet twist
- β-bulge (distortion) is common

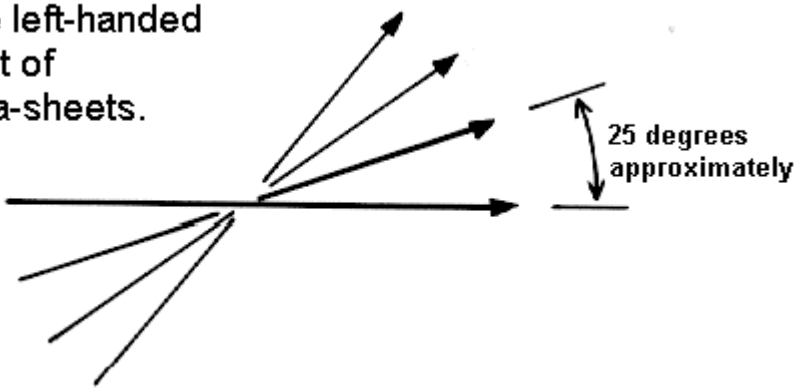




The different types of beta-sheet. Dashed lines indicate main chain hydrogen bonds.



The left-handed twist of beta-sheets.



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β-Bulges

β-bulge – single residue disruption of β-sheet hydrogen bonding

Common in antiparallel sheets (~95% of all bulges)

Classes of β-bulges (Kabsch and Sanders, 1983)

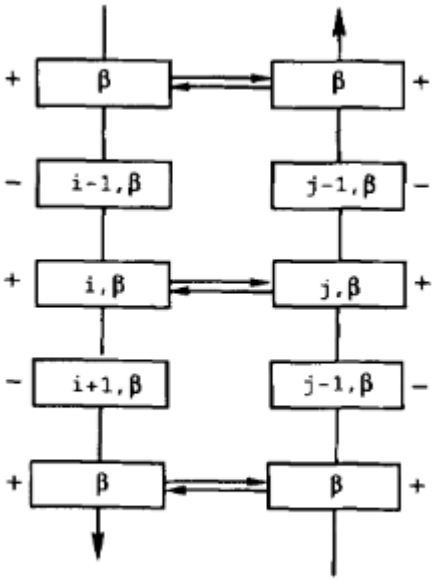
a) **Classic** (90% of antiparallel & 60% of parallel)
b) Wide
c) Bent
d) Special

Classification are based on the hydrogen bonding pattern at site of disruption

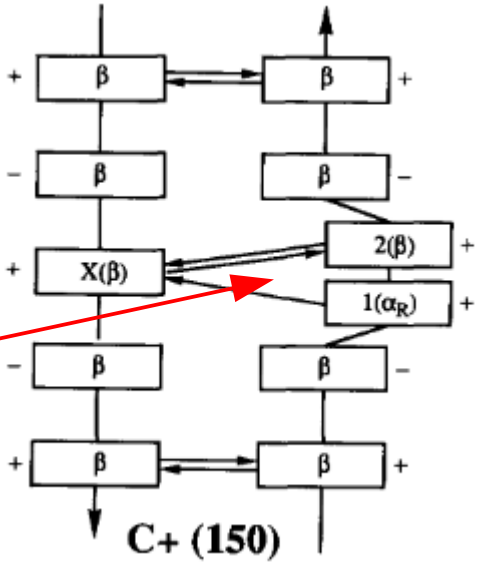
Introduces large twist

Classic bulge (antiparallel)

Schematic of H-bonding in β-sheets



Antiparallel



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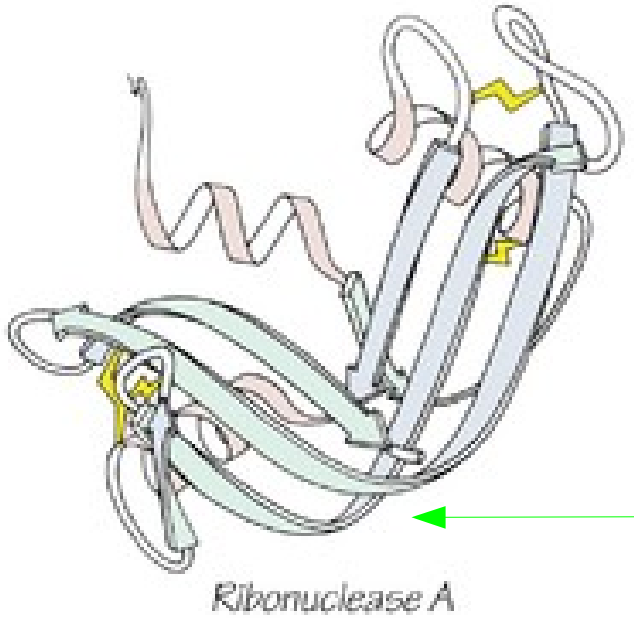
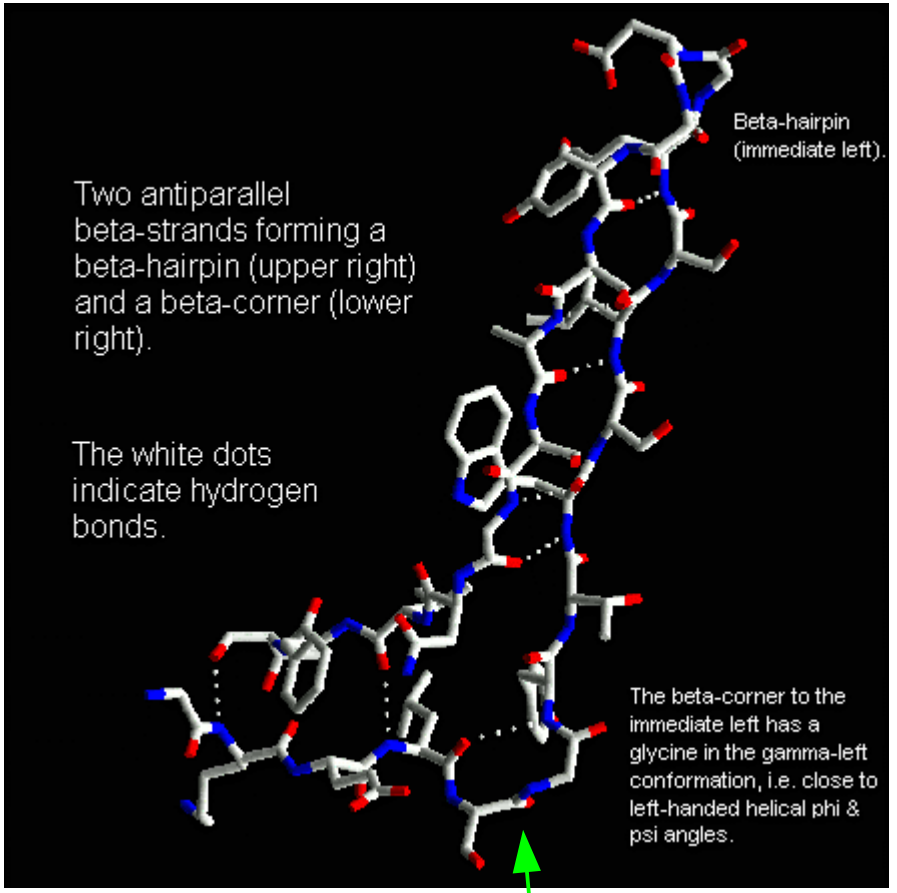
β-Corner

β-corner – two residue disruption of β-sheet hydrogen bonding

Disruption forms type I' turn (i to i+3 H-bond)

Introduces 90° bend and twist in one strand





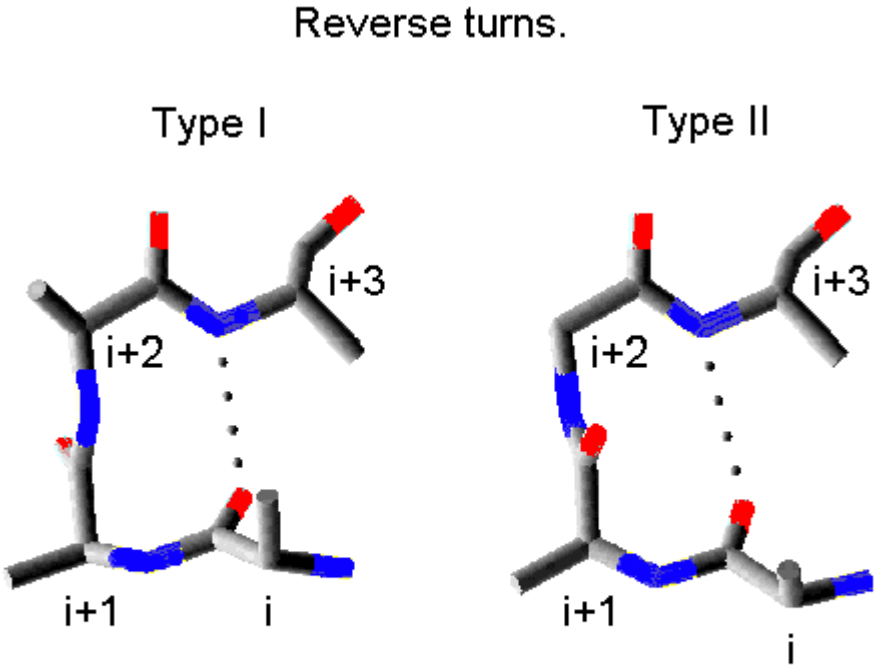
Antiparallel sheet with β-corner

Reverse Turns

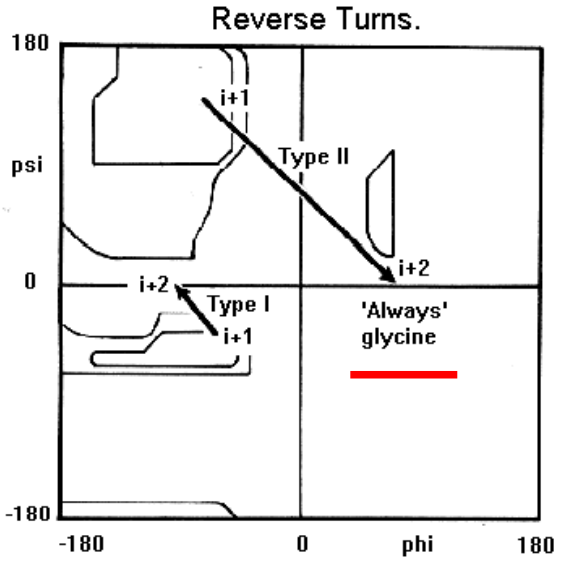
Reverse Turn: Non-helical regions of polypeptide with an O_i to N_{i+3} H-bond

- Reverse turns between β-strands are a special class of turn (β-hairpins)
- Reverse turns are abundant in globular proteins and have been implicated as folding nucleation centers

Reverse turns are classified according to the phi-psi torsion angles of residue i+1 and i+2



Two most common reverse turns differ in the orientation of the peptide bond between residues i+1 and i+2



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Supersecondary Structures (Motifs)

Supersecondary Structures (Motifs): Combinations of secondary structures in specific geometric arrangements

- Simple supersecondary structures consisting of 3 or fewer secondary structures considered here
- Large supersecondary structures (ie. Greek Key a
  more than 3 secondary structures will be conside
  structures and folds
  - Why? Large supersecondary structures can be domains.

Helix-turn-helix

Simple supersecondary structures are typically composed of two secondary structures (ie. strands or helices) and a turn (or loop)

Helix-turn-helix DNA binding motif

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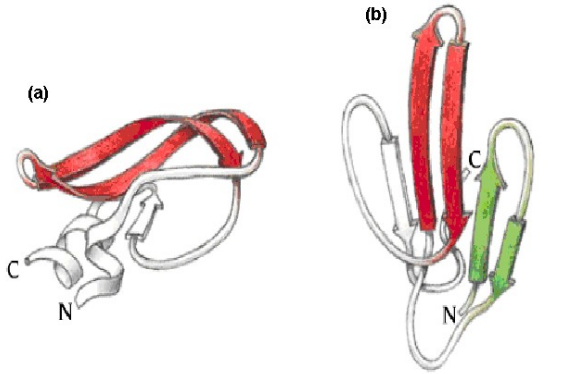
β-hairpin

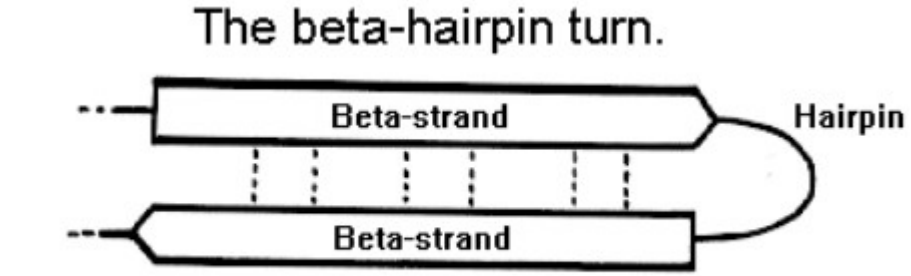


Bovine Trypsin Inhibitor Snake Venom Erabutoxin

Simple and Common supersecondary structure

β-hairpin Turn: Short loop segment joining two antiparallel β-strands

- **Hairpin turns are a special case of Reverse turns**
- **Favor type I' and II' turns in contrast to reverse turns which favor type I and II**
- **Small supersecondary structure (typically less than 10 residues)**



The dashed lines indicate main chain hydrogen bonds.

Two most common reverse turns differ in the orientation of the peptide bond between residues i+1 and i+2

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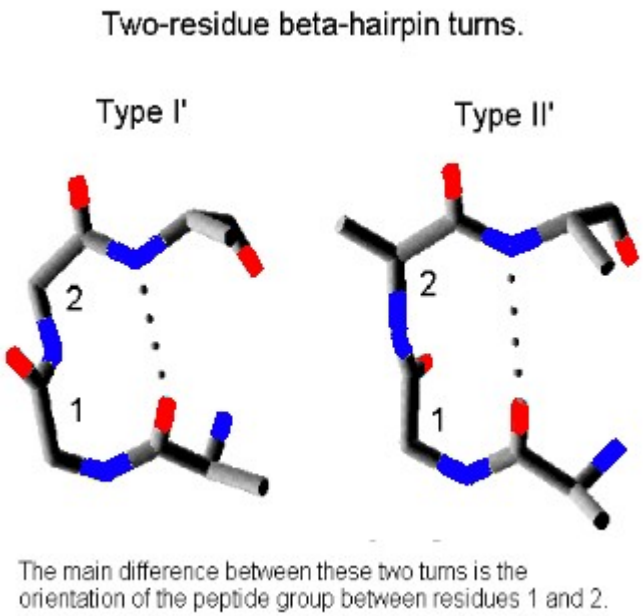
2 Residue β-hairpins



The main difference between these two turns is the orientation of the peptide group between residues 1 and 2.

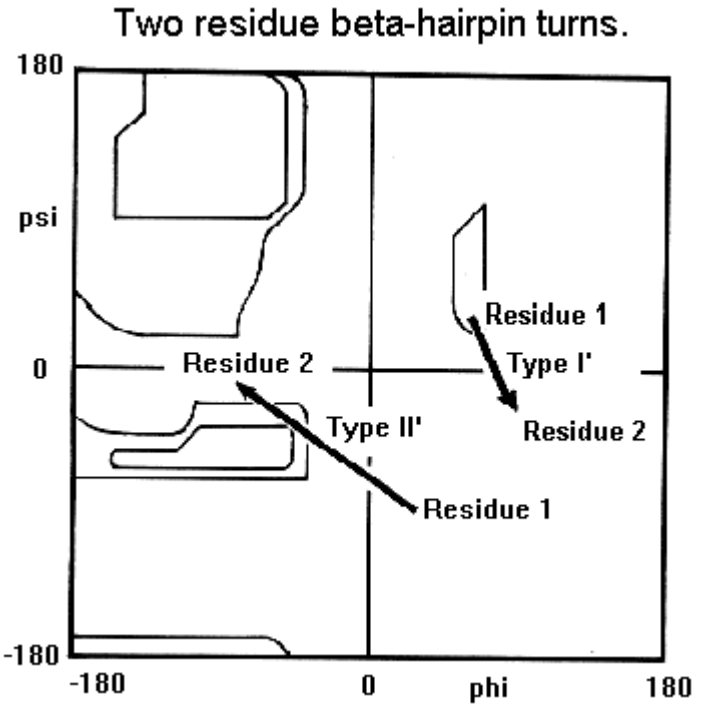
β-hairpin turn is a Type I' or Type II' (right)

Type I'

- **Residue 1 (left-handed helix) favors Gly, Asp or Asn (High turn propensity)**
- **Residue 2 is almost always Gly (disallowed region of Ramachandran for non-Gly)**

Type II'

- **Residue 1 is almost always Gly**
- **Residue 2 favors small polar (Ser, Thr)**



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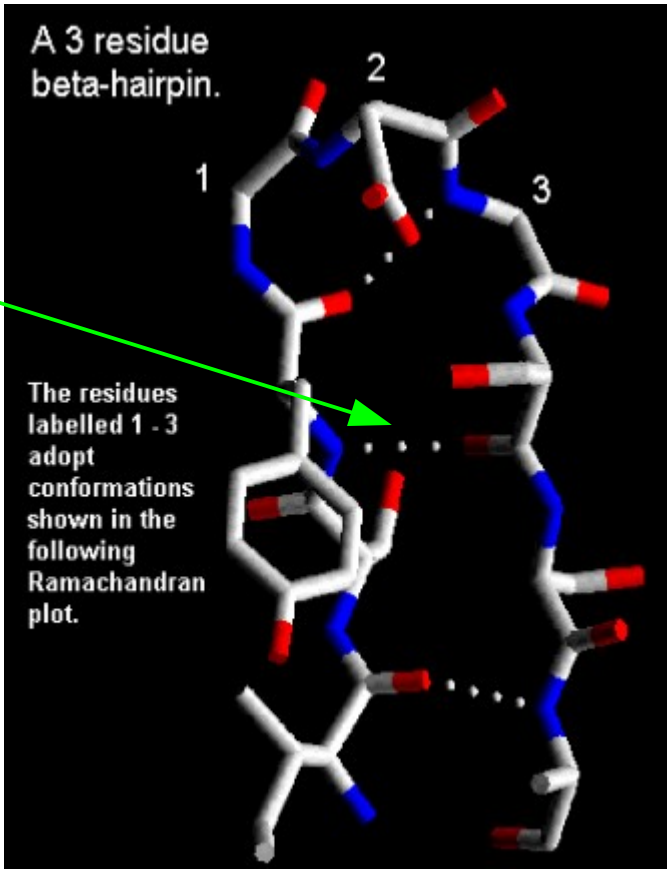
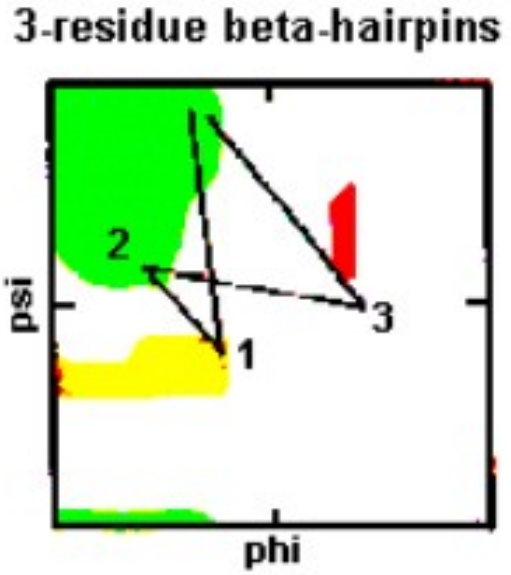
3 Residue β-hairpins



Residues at ends of β-sheets often make 1 (not 2) H-bonds

Intervening 3 residues have distinct conformational preferences

- **Residue 1** right-handed helical conformation
- **Residue 2** bridge region between helix and sheet
- **Residue 3** left-handed helical conformation (favors Gly, Asn, Asp)



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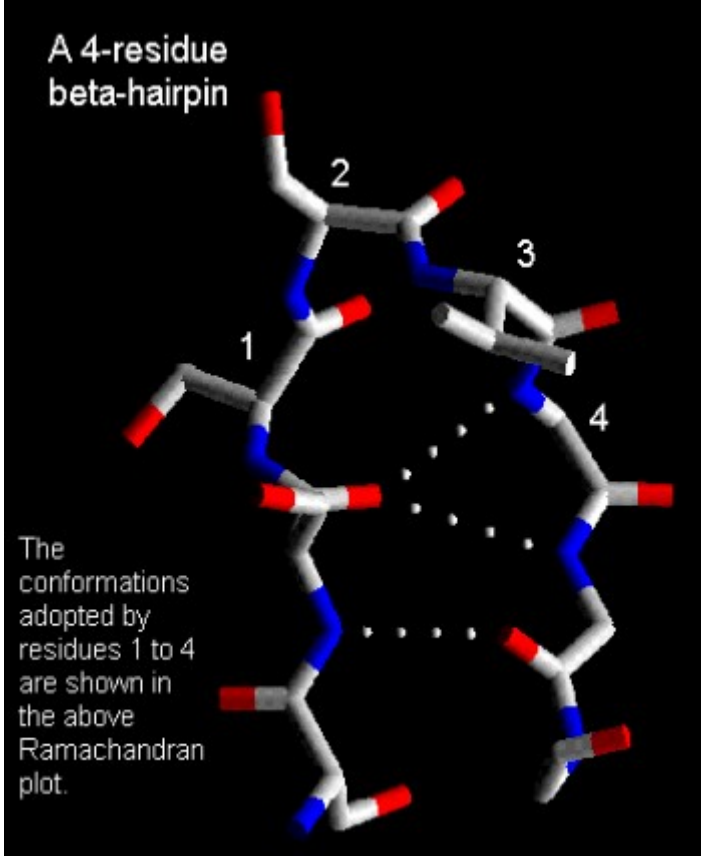
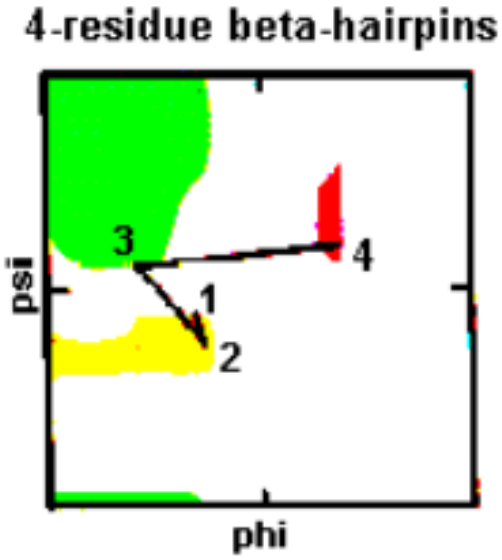
4 Residue β-hairpins



Last common β-hairpin

Intervening 4 residues have preferred conformations

- **Residue 1** right-handed helical conformation
- **Residue 2** right-handed helical conformation
- **Residue 3** bridge region between helix and sheet
- **Residue 4** left-handed helical conformation (favors Gly, Asn, Asp)



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Long Loop β-hairpins

Wide-range of conformations

Long loop β-hairpins are special case of ω loops

Often referred to as 'random coil'

- **Consecutive antiparallel β-strands joined by long loop β-hairpins are referred to as a β-meander supersecondary structure**