

**Secondary Structure Calculation & Structure Classification**

Introduction to Structural Bioinformatics

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**Overview**

- Secondary Structure Calculation
  - Kabsch & Sander
- Structure Classification
  - SCOP
  - CATH

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**Secondary Structure Calc.**

- 4 major methods:
  - P-Curve [Sklenar et al. (1989), Proteins 6: 46-60]
  - DEFINE [Richards & Kundrot (1988), Proteins 3: 71-84]
  - STRIDE [Frishman & Argos (1995), Proteins 23: 566-579]
  - DSSP [Kabsch & Sander (1983), Biopolymers 22: 2577-2637]
- Most widely used: DSSP!

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## DSSP Algorithm

- "Define Secondary Structure of Proteins"
- Automated processing of PDB files and archived at <ftp://ftp.sdsc.edu/pub/sdsc/biology/dssp>
- Defines elementary hydrogen-binding patterns "turn" and "bridge"
- Defines cooperative 2°structure as repeats of elementary units:
  - Multiple Turns := "helices"
  - Multiple Bridges := "ladders"
  - Interconnected Ladders := "sheets"
- Also defines geometric structure (torsion and curvature) as well as solvent exposure

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## DSSP [2]

- Hierarchical definition of patterns:
  - H-bonds
  - Turns & bridges
  - $\alpha$ -helices,  $\beta$ -ladders, kinks & bulges
- Additionally: bends, chirality, SS bonds, and solvent exposure
- Structural features are defined independently
- Single state assigned to each residue after resolving overlaps

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## H-bonds

- Described by electrostatic model only:

$$E = q_1 q_2 \left( \frac{1}{r(ON)} + \frac{1}{r(CH)} - \frac{1}{r(OH)} - \frac{1}{r(CN)} \right) \cdot f \quad [kcal/mol]$$

$r(AB)$  =: distance between A and B

$$q_1(C,O) = 0.42e; q_2(N,H) = 0.20e; f = 332$$

- Good bond energy: -3 kcal/mol
- Threshold:  $E < -0.5$  kcal/mol

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## H-bonds [2]

- Problems:
  - Where are H placed??
  - What about quantum-mechanics??
- Ergo: no perfect answer, only good approximation!
- Need also allow for coordinate errors!

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## Turns

- Basic pattern: single H-bond between residues  $i$  and  $i+n$  “ $(i, i+n)$ ”
- Assigned for H-bonds between CO( $i$ ) and CN( $i+n$ )
- $n=3,4$  or 5
- Residues between and including H-bonding ones are denoted as “T” unless part of helix

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## Bridges

- Two non-overlapping triplet patterns of H-bond types  $(i-1,i,i+1)(j-1,j,j+1)$
- Parallel bridge( $i,j$ ) =:  $[(i-1,j) \& (j, i+1)]$  or  $[(j-1,i) \& (i, j+1)]$  -> lower case
- Antiparallel bridge ( $i,j$ ) =:  $[(i,j) \& (j,i)]$  or  $[(i-1,j+1) \& (j-1,i+1)]$  -> upper case

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## Helices

- Minimal helix is defined as two  $n$ -turns:  
 $n$ -helix( $i, i+2$ ) =: [ $n$ -turn( $i-1$ ) &  $n$ -turn( $i$ )]
- Longer helices:
  - $3_{10}$ -helix =: long 3-helix -> "G"
  - $\alpha$ -helix =: long 4-helix -> "H"
  - $\pi$ -helix =: long 5-helix -> "I"

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## Ladders & Sheets

- Ladder =: one or more consecutive bridges of the same type
- Sheet =: set of one or more ladders connected by shared residues
- Single bridges (ladders of length 1) -> "B"
- Extended ladders -> "E" ( $\beta$ -strands)

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## Irregularities

- Implicit for helices:
  - Overlapping helices
  - missing H-bonds (kinks due to Pro ?)
- Explicit for bridges:
  - Bulge-linked ladder: 2 (perfect) ladders or bridges of the same type connected by one single residue on one strand and less than 5 residues on other
- Both are marked as consecutive in one line summary!

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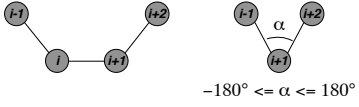
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### Geometric Structure

- Bends ("S"):
 
$$\text{Bend}(i) = \left[ \Phi \left\{ \begin{matrix} (x) \\ y \\ z \end{matrix} \right\}_{C\alpha(i)} \begin{matrix} (x) \\ -y \\ z \end{matrix} \right\}_{C\alpha(i-2)} \begin{matrix} (x) \\ -y \\ z \end{matrix} \right\}_{C\alpha(i+2)} \begin{matrix} (x) \\ -y \\ z \end{matrix} \right\}_{C\alpha(i)} \right] > 70^\circ$$
- Chirality: sign of dihedral angle  $\alpha$ 


$-180^\circ \leq \alpha \leq 180^\circ$

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### Geometric Structure [2]

- Most helices are "right handed", i.e. of positive chirality
- Most sheets are "left handed", i.e. of negative chirality
- Exceptions: thermolysin (only "-" helices)

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### Structure Summary

- Given as single line aligned with sequence
- Priorities for overlaps:  
H > B > E > G > I > T > S
- Blanks: no H-bonds, low curvature
- Most people forget to look at detailed description!!

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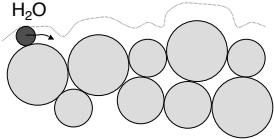
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### Solvent Exposure

□ “Rolling sphere” surface:



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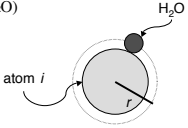
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### Solvent Exposure [2]

□ Mathematically:

$$\int f(x) d(x) \text{ with } f(x) = \begin{cases} 1 & \text{if water sphere at } x \text{ does not intersect other atoms} \\ 0 & \text{if it does} \end{cases}$$

$x =$  all points on sphere with radius  $r$  around atom  $i$   
 $r = r(\text{atom}) + r(\text{H}_2\text{O})$



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### Solvent Exposure [3]

□ Algorithm:

- Sum over 20, 80 or 320 approximately equal triangles
- use triangle centers as points  $x$  and area of triangle as weight
- Generate polyhedron iteratively:
  - ◊ Start with icosahedron
  - ◊ Dived each triangle into 4 by connecting midpoints and project the 3 new vertices onto sphere

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### Solvent Exposure [4]



- ❑ First iteration gives 20 points, next 80, next 320
- ❑ Accuracy: within  $4\text{\AA}^2$  for 80, within  $1\text{\AA}^2$  for 320 points

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### Solvent Exposure [5]

- ❑ Average number of water:
 
$$W = \frac{\text{Surface Area}}{V(\text{H}_2\text{O})^{2/3}} \approx \frac{\text{Surface Area}}{10}$$
- ❑ Since Area  $\approx$  Volume  $\approx$  ave. # of  $\text{H}_2\text{O}$  and  $V(\text{H}_2\text{O}) = 30\text{\AA}^3$  ( $30^{2/3} \approx 10$ )
- ❑ NOTE: solvent area differs between monomers and dimer!

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### Evolution of Structure

- ❑ Evolutionarily related proteins retain memory of relationship through sequence, structure and function
- ❑ Strong sequence similarity considered sufficient evidence for common ancestry
- ❑ Close structural and functional similarity **together** also evidence common ancestry
- ❑ Structure is more conserved than sequence in distantly related proteins

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### Protein Folds

- ❑ Similarities in secondary structure element assembly
- ❑ Topological units of polypeptide chains
- ❑ Regularities arise from intrinsic physical and chemical properties
- ❑ Folds are the units of protein function, structure, and evolution
- ❑ Examples: propeller, horseshoe, TIM barrel...

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### SCOP

- ❑ Structure Classification of Proteins
- ❑ Based on evolutionary relationships
- ❑ Generated through visual comparison and inspection of automated structure alignments
- ❑ Provides links to coordinates of domains, images and sequence data
- ❑ <http://scop.mrc-lmb.cam.ac.uk/scop/>

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### SCOP Hierarchy

- ❑ Class
  - ❑ secondary element composition
  - ❑ All  $\alpha$ , all  $\beta$ ,  $\alpha/\beta$ ,  $\alpha+\beta$ , some others
- ❑ Folds
  - ❑ Common core structures
  - ❑ 138, 93, 97 & 184 respectively for each class
- ❑ Superfamily
  - ❑ Share common structure and function
- ❑ Family
  - ❑ Share clear common evolutionary origin

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## SCOP Hierarchy [2]

- ❑ Fold classification most difficult step
- ❑ Differences between mixed classes:
  - ❑  $\alpha\beta$ 
    - ◊ Principally single  $\beta$ -sheet with  $\alpha$ -helices joining the individual strands
    - ◊ Two subclasses:  $\beta$ -sheet barrel surrounded by  $\alpha$ -helices and planar  $\beta$ -sheet flanked on either side by  $\alpha$ -helices
  - ❑  $\alpha+\beta$ 
    - ◊  $\alpha$  and  $\beta$  units largely separated
    - ◊ Antiparalell strands usually joined by hairpins
    - ◊ Small clusters of helices tightly packed against sheet

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## CATH

- ❑ Class, Architecture, Topology and Homologous Superfamily
- ❑ Also based on evolutionary relationships
- ❑ Automated generation with validation of ambiguities in assignments
- ❑ [http://www.biochem.ucl.ac.uk/bsm/cath\\_new/index.html](http://www.biochem.ucl.ac.uk/bsm/cath_new/index.html)

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## CATH Hierarchy

- ❑ Class
  - ❑ Determined by secondary structure composition and packing
  - ❑ mainly- $\alpha$ , mainly- $\beta$  and  $\alpha$ - $\beta$ .
- ❑ Architecture
  - ❑ Description of orientation of secondary structures regardless of connectivity
  - ❑ Assigned manually

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### CATH Hierarchy [2]

- Topology
  - Regards both secondary structure orientation and connectivity
- Homologous Superfamily
  - Evolutionary grouping based on structure, sequence and/or functional similarity
  - Proteins are clustered into sequence families at different levels of sequence identity (35%, 60%, 95%, 100%)

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### CATH Update Strategy

1. Identify close relatives using pairwise sequence alignments
2. Detect distant relatives using sequence profiles and structure comparisons
3. Examine unclassified structures using both automatic and manual procedures to determine domain boundaries
4. Reiterate over steps 2 and 3
5. Manual assignment to existing or new architectures

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### Hands-On/Homework

- Pet protein project:
  - Add general information
  - Add Rasmol generated images
  - Add a section on SCOP and CATH classifications including images of the domain(s) in your structure
- Review lectures 1 and 2, specifically SCOP and CATH
- Read chapters 4, 5 & 19

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