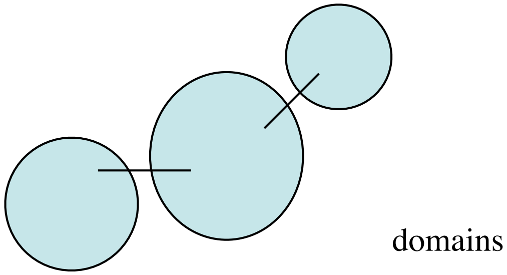
Molecular Modeling 2020
lecture 16 -- Tues Mar 16

Protein classification

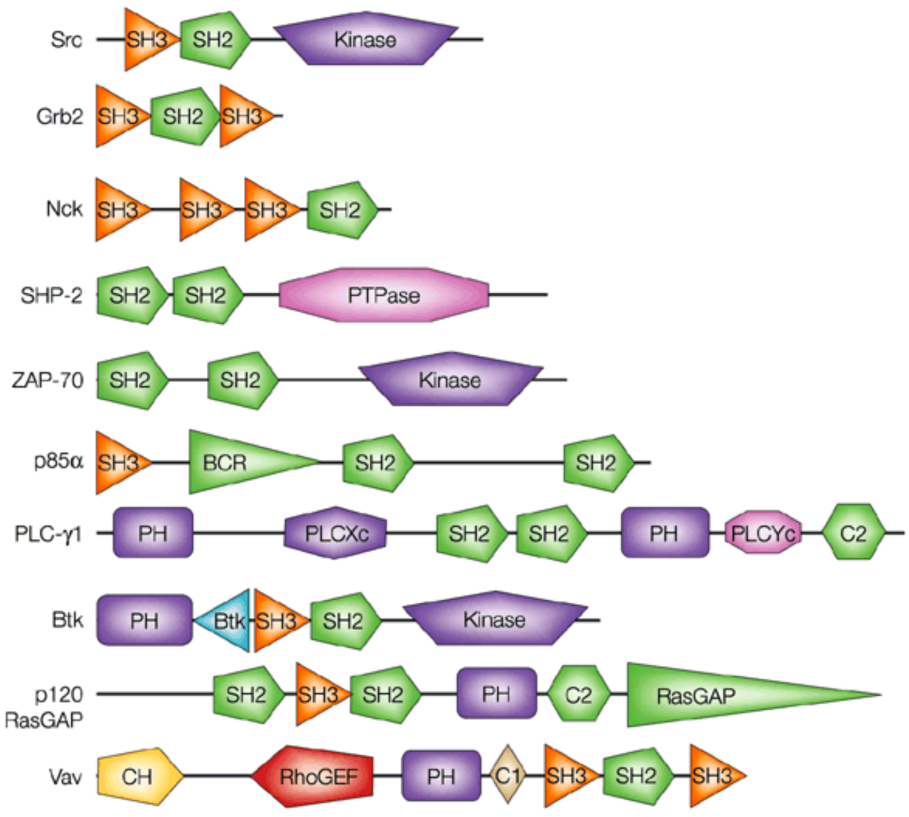
SCOP

TOPS

Contact maps



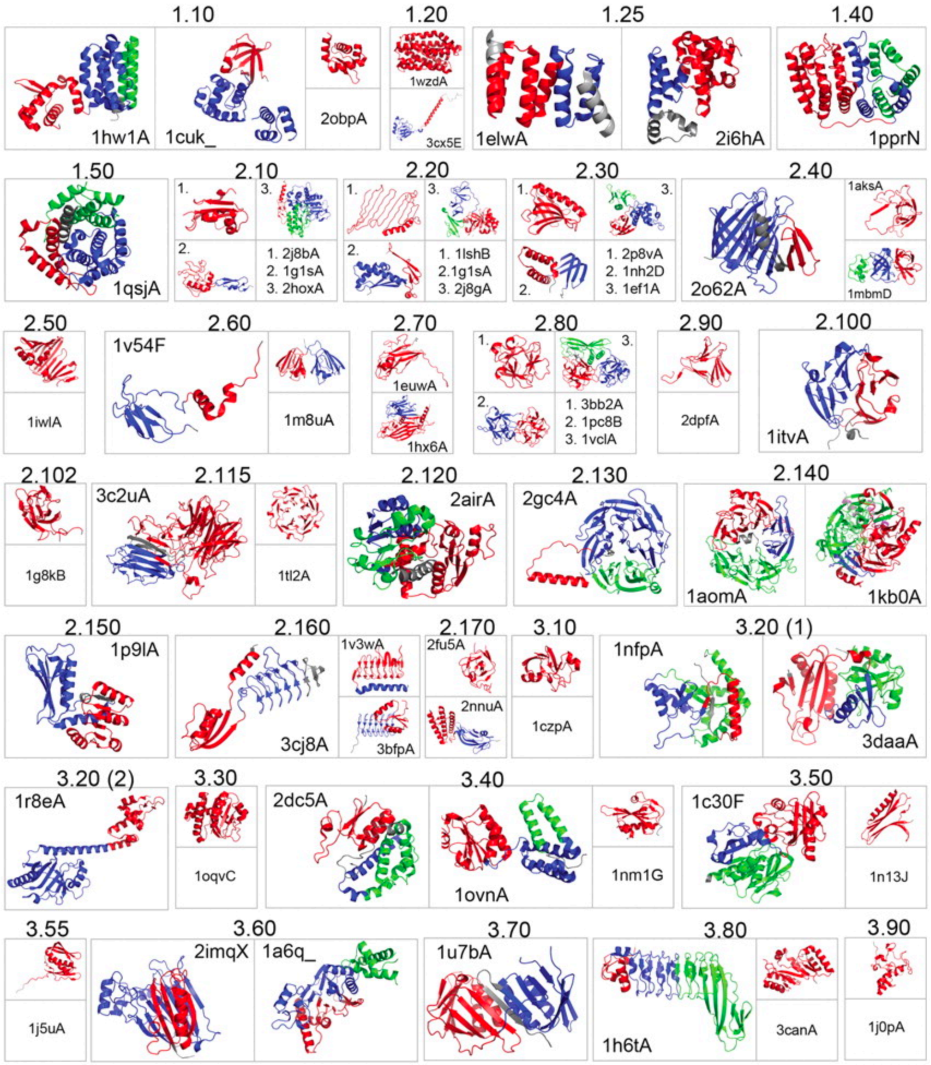
Domains



Nature Reviews | Molecular Cell Biology

To a **cell biologist** a domain is a sequential unit within a gene, usually with a specific function.

Domains

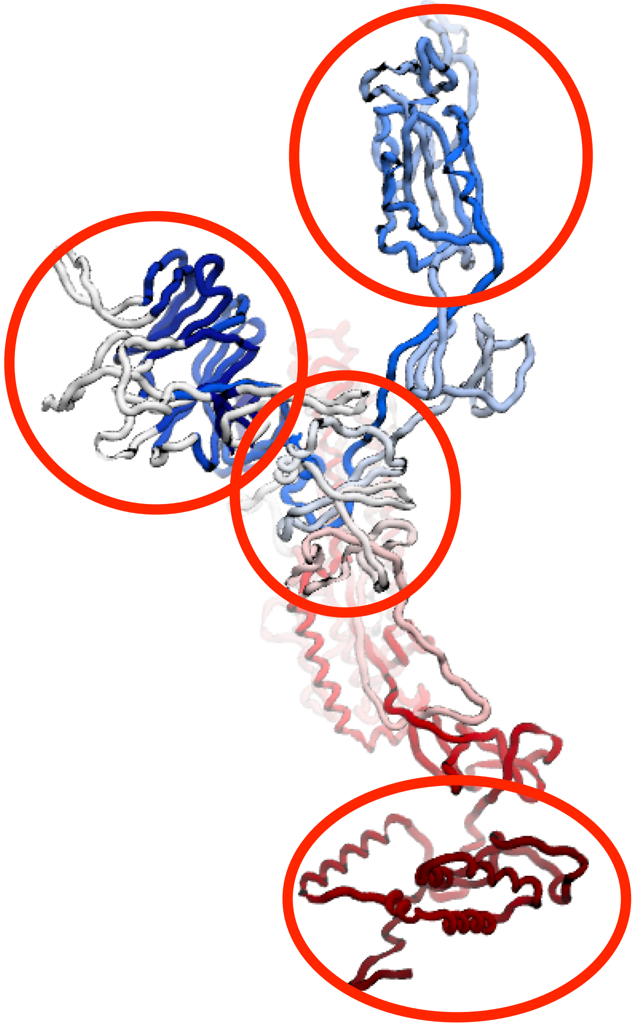


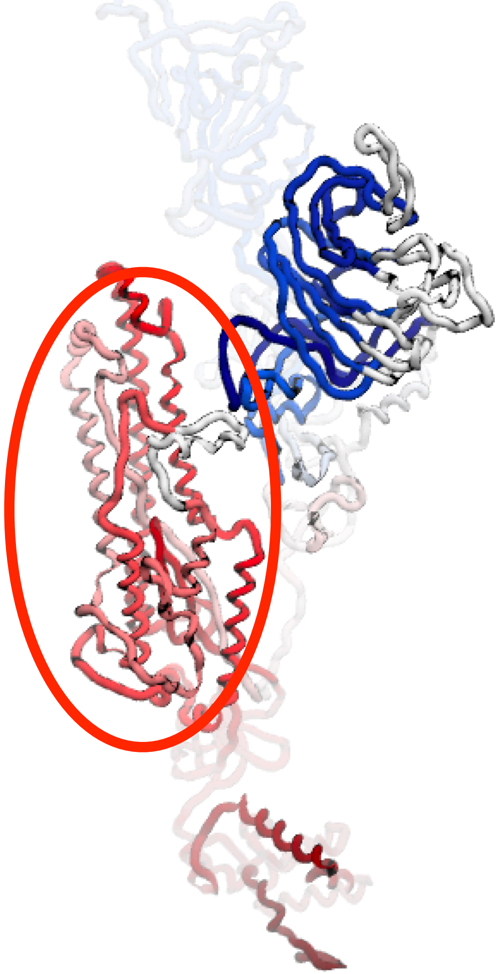
To a **structural biologist** a domain is a compact globular unit within a protein, classified by its 3D structure.

A domain is...

- ... an autonomously-folding substructure of a protein.
- ... > 30 residues, but typically < 200. May be bigger.
- ...usually has a single hydrophobic core
- ... usually composed of one chain (occasionally composed of multiple chains)
- ...is usually composed on one contiguous segment (occasionally made of discontiguous segments of the same chain)

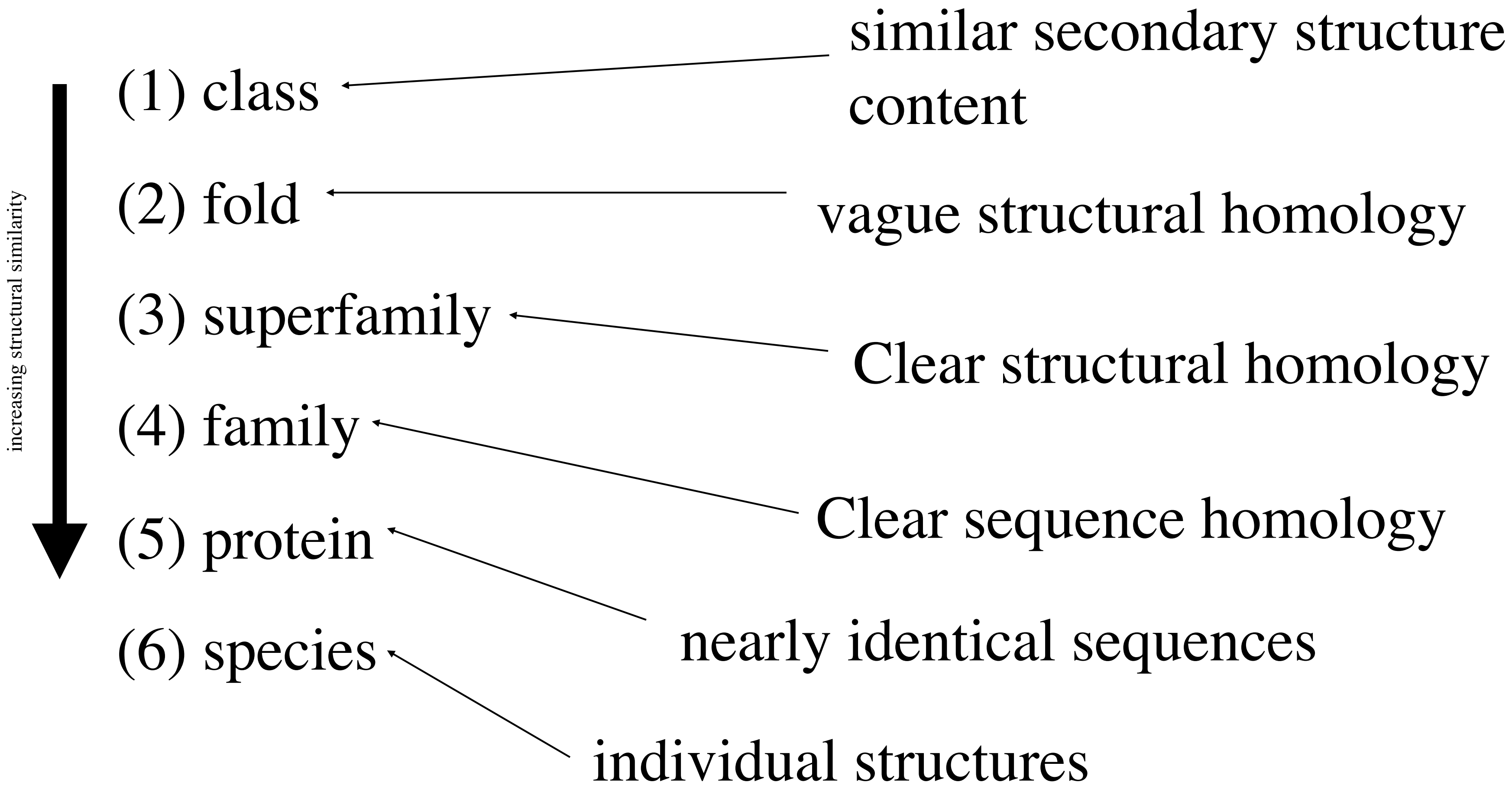
SAR-2 spike protein — a multi domain protein





SCOP -- a hierarchy

- http://scop.berkeley.edu



increasing structural similarity

(1) class

(2) fold

(3) superfamily

(4) family

(5) protein

(6) species

similar secondary structure content

vague structural homology

Clear structural homology

Clear sequence homology

nearly identical sequences

individual structures

SCOP -- class

1. all α (289)
2. all β (178)
3. α/β (148)
4. α+β (388)

classes of domains

5. multidomain (71)
6. membrane (60)
7. small (98)
8. coiled coil (7)
9. low-resolution (25)
10. peptides (148)
11. designed proteins (44)
12. artifacts (1)

Not true classes of globular protein domains

Proteins of the same class conserve secondary structure content

SCOP -- fold level

within α/β proteins -- Mainly parallel beta sheets (beta-alpha-beta units)

TIM-barrel (22)

swivelling beta/beta/alpha domain (5)

spoIIaa-like (2)

flavodoxin-like (10)

restriction endonuclease-like (2)

ribokinase-like (2)

chelatase-like (2)

Many folds have historical names. "TIM" barrel was first seen in TIM. These classifications are done *by eye*, by experts.

Proteins of the same Fold conserve topology.

SCOP fold level jargon

example: α/β proteins: flavodoxin-like

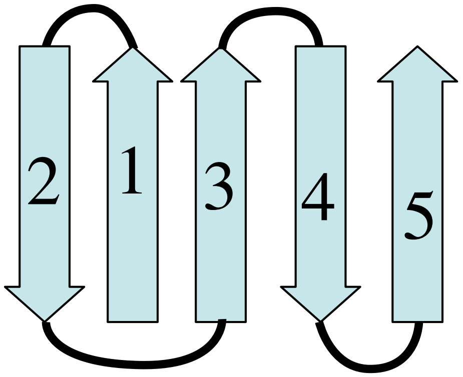
SCOP Description: 3 layers, α/β/α; parallel beta-sheet of 5 strand, order 21345

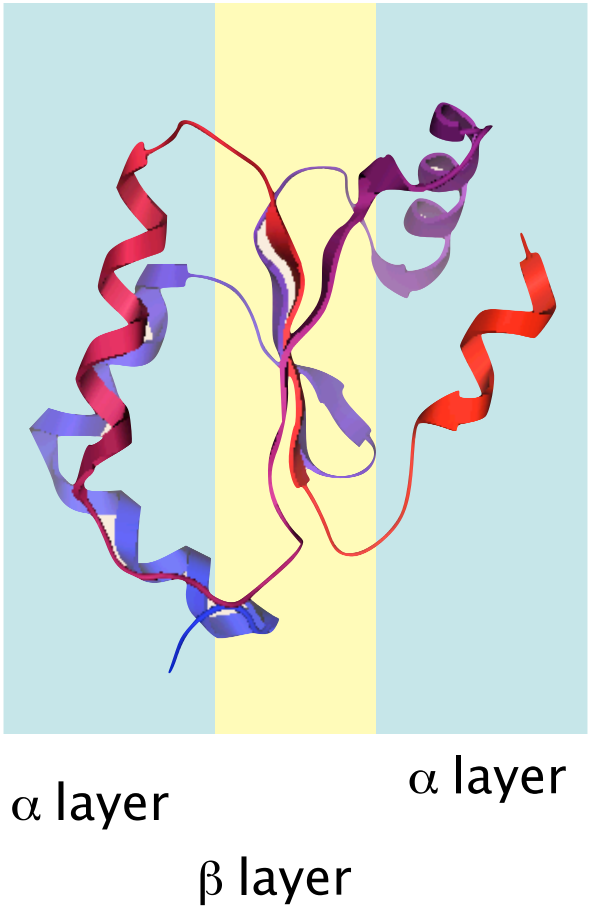
Note the term: “*layers*”

Rough arrangements of secondary structure elements.

Note the term: “*order*”

The sequential order of beta strands in a beta sheet.

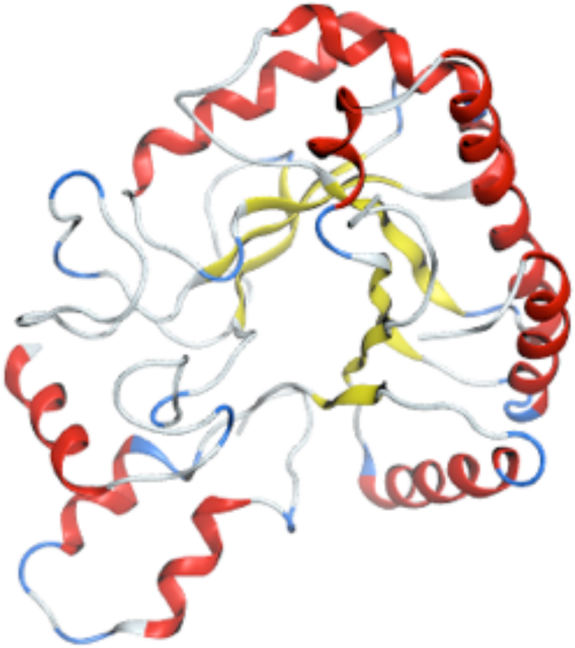




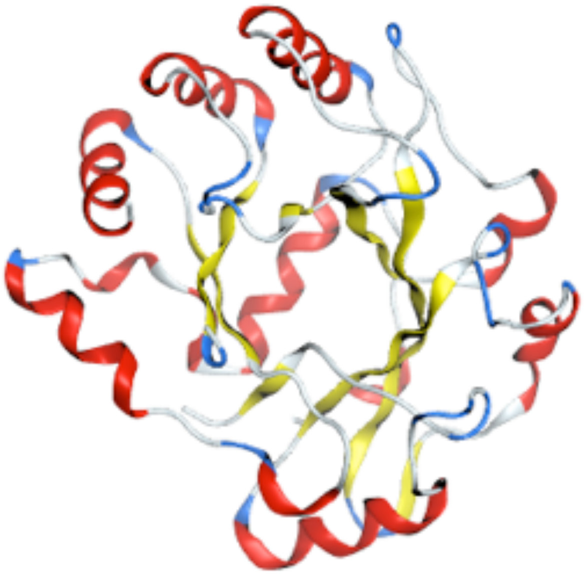
Fold-level similarity

7-stranded alpha/beta barrel

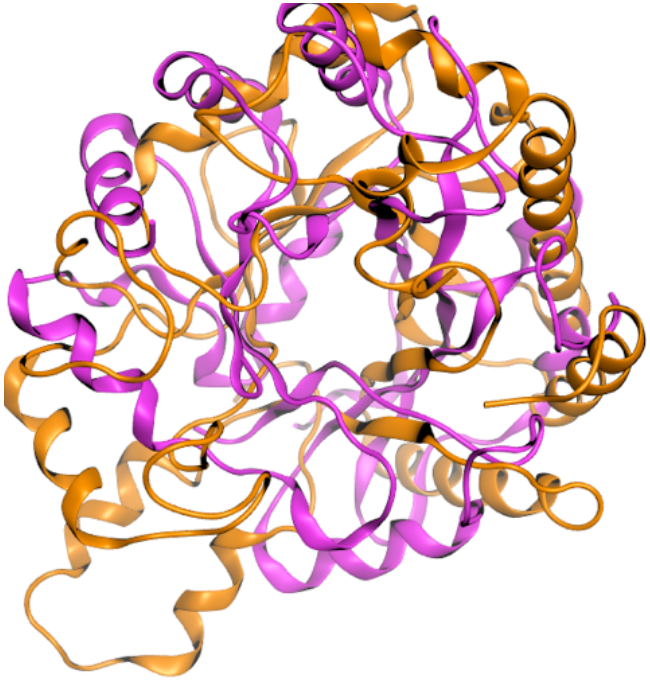
2bod



1m65



SSE are in the same order along the chain, and trace roughly the same path through space. Similarity is evident when viewed side-by-side

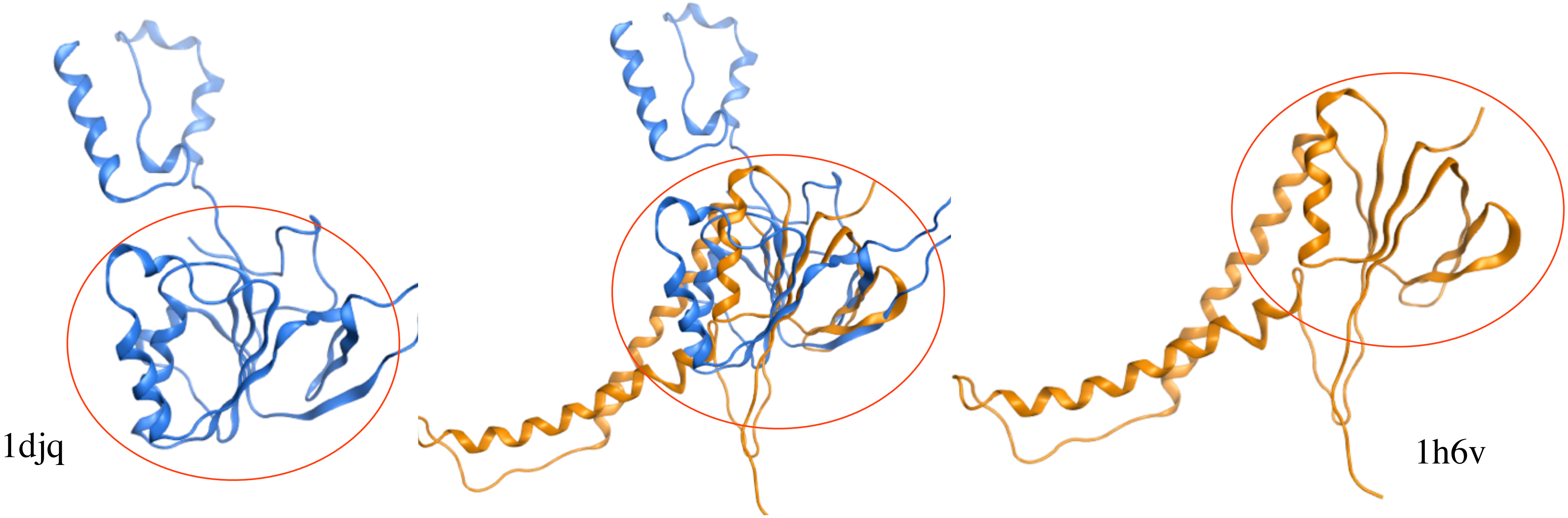


But the SSE do not superpose. Some superposition algorithms fail to superpose proteins of the same fold.

Superfamily level similarity

FAD-linked reductases

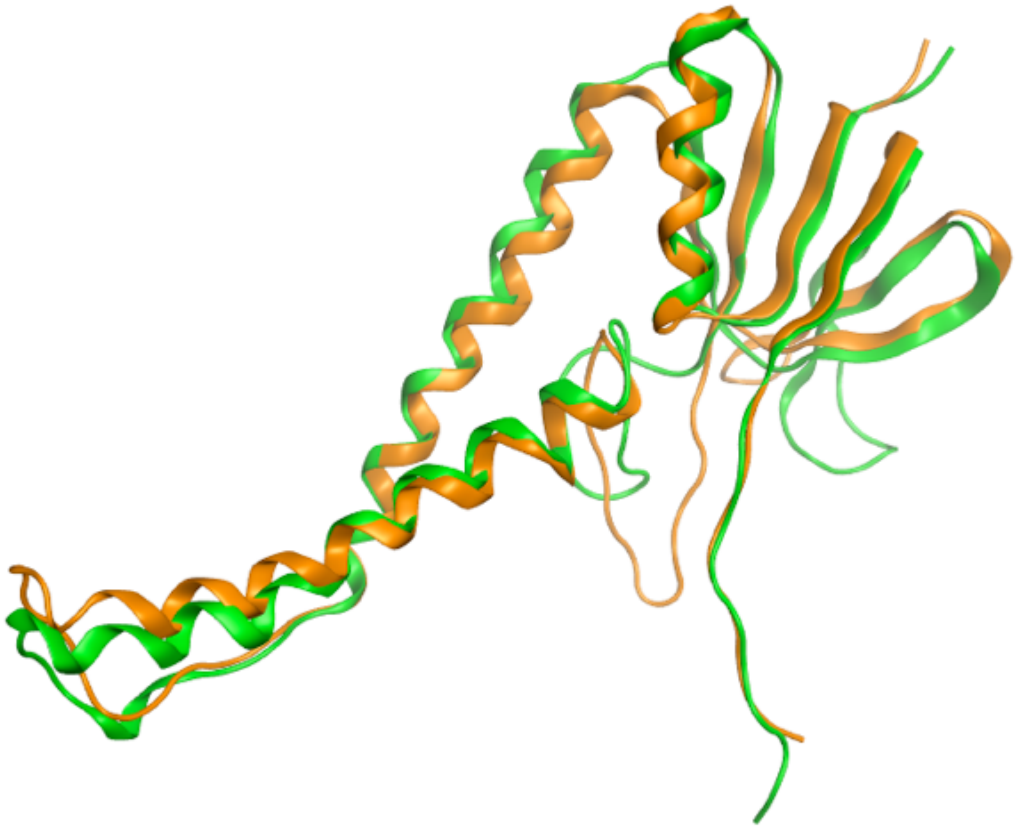
Members of the same superfamily cannot usually be found in a BLAST search. But can be identified by structural superposition.



Proteins in the same superfamily may look completely different, but upon close inspection they contains a superposable domain of secondary structure elements.

Family level similarity

FAD/NAD-linked reductases, N-terminal and central domains [51943]



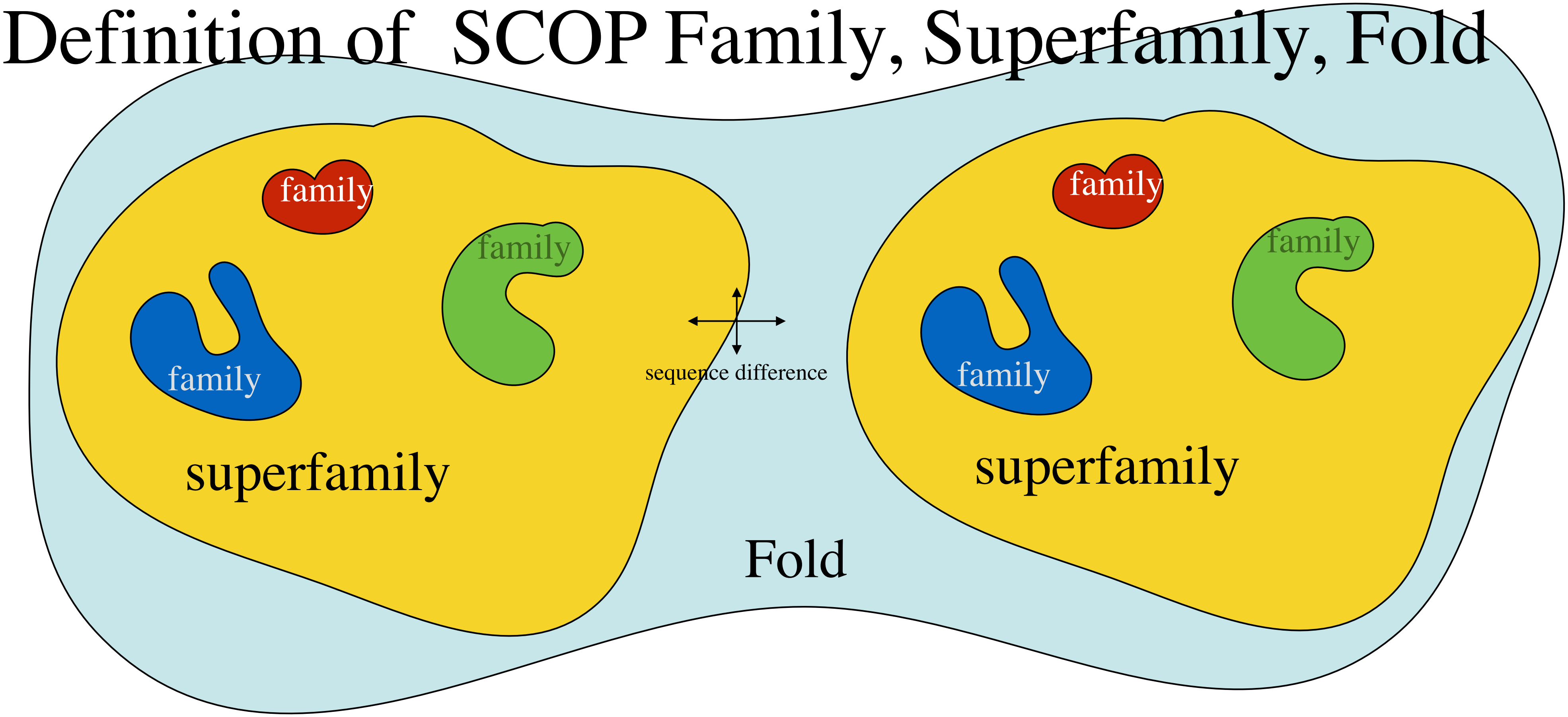
1h6v

1fec

Different members of the same family superimpose well. At this level, a structure may be used as a *molecular replacement model* for Xray crystallography.

A BLAST search using one family member finds all other family members.

Definition of SCOP Family, Superfamily, Fold



A **Family** is the set of homologs we can find by BLAST sequence database search.

A **Superfamily** is a set of distant homologs that cannot be easily found by BLAST search, but can be recognized by sophisticated fold recognition algorithms

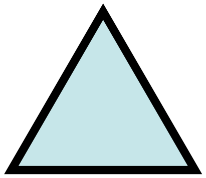
A **Fold** is an even more distant homologous relationship, recognizable only when the structure is known

A **Class** is not a homologous relationship but just a statement of the gross secondary structure content.

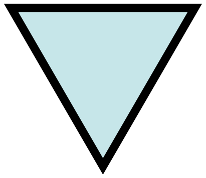
Contact maps and TOPS diagrams

TOPS topology cartoons

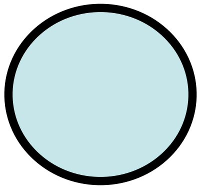
Secondary structure elements (SSE)



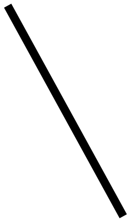
beta strand pointing up



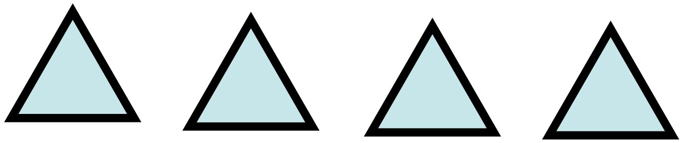
beta strand pointing down



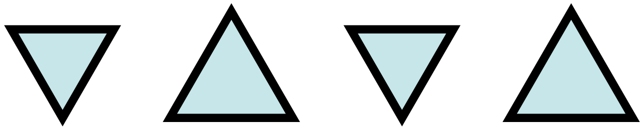
alpha helix



connections



A parallel beta sheet

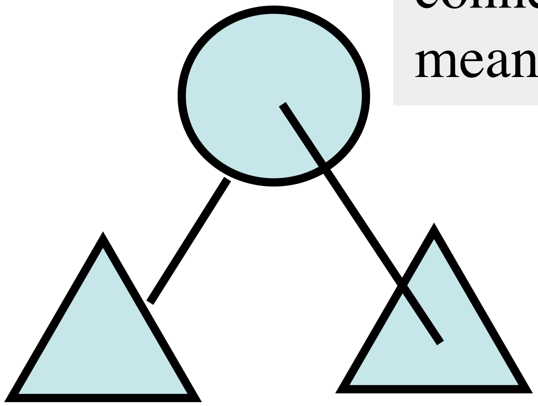


An anti- parallel beta sheet

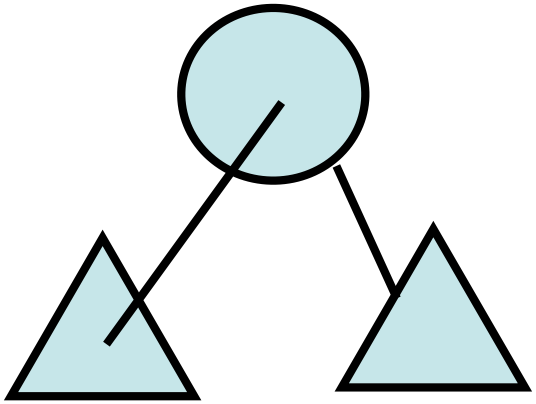
TOPS topology cartoons

connection in middle means on top. connection on side means on bottom.

A right-handed βαβ unit



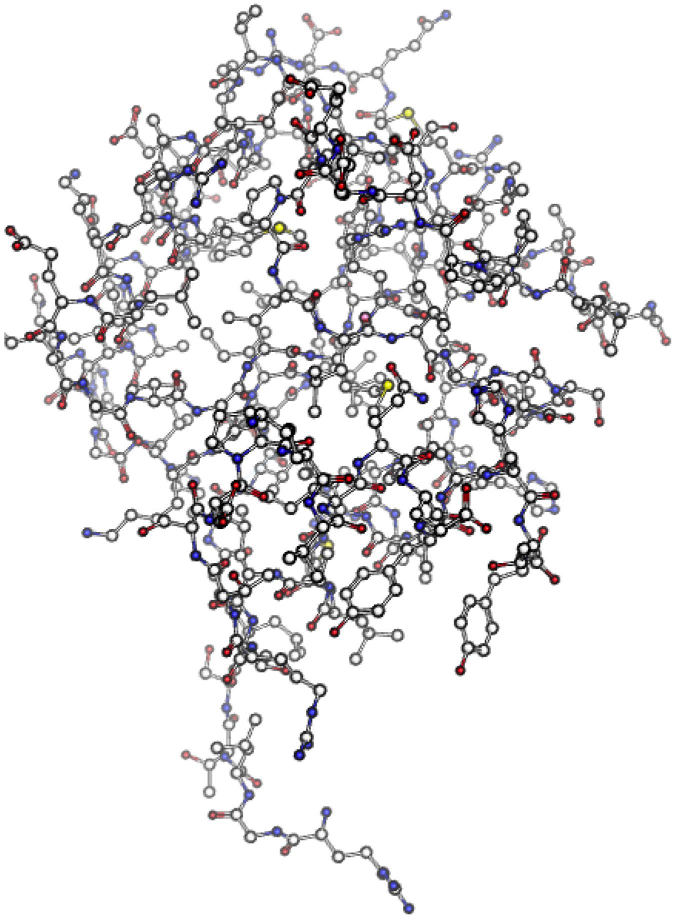
A left-handed βαβ unit (rarely seen)

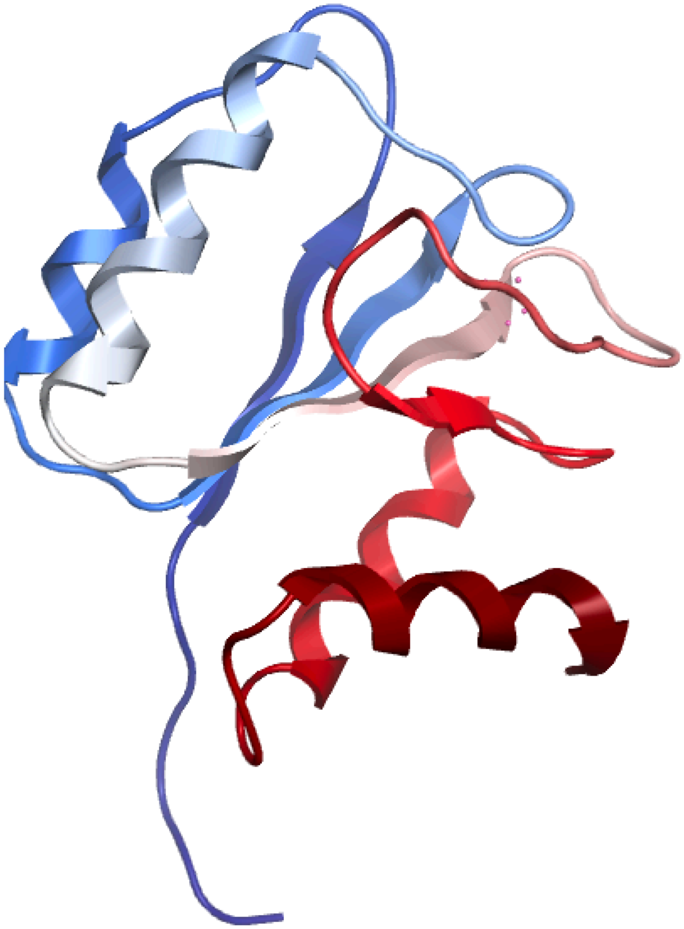


How to draw TOPS

To do this on your own, find the link "**TOPS practice**" (tops_practice.moe) on the course web site. Download. Open it in moe.

Or just follow along as I guide you through it. Get pen and paper.

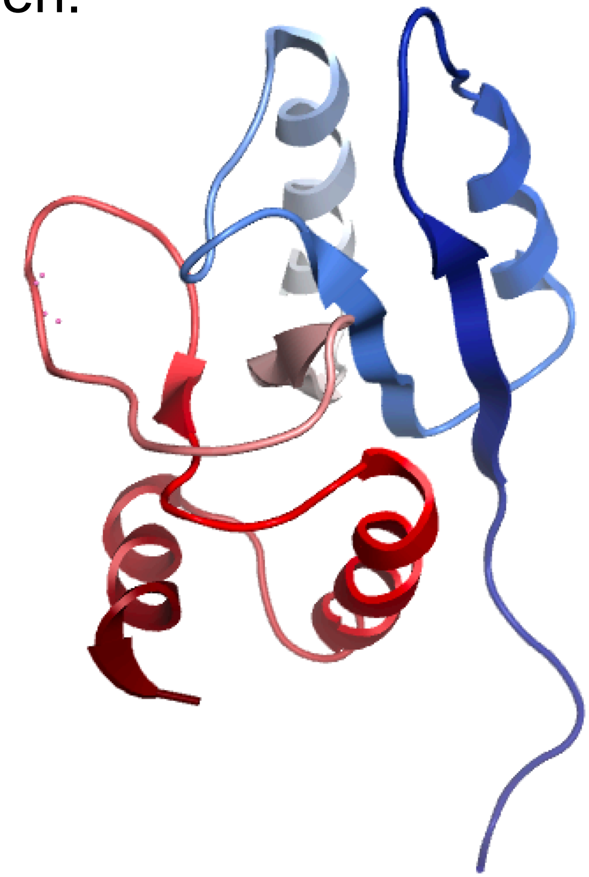




How to draw TOPS

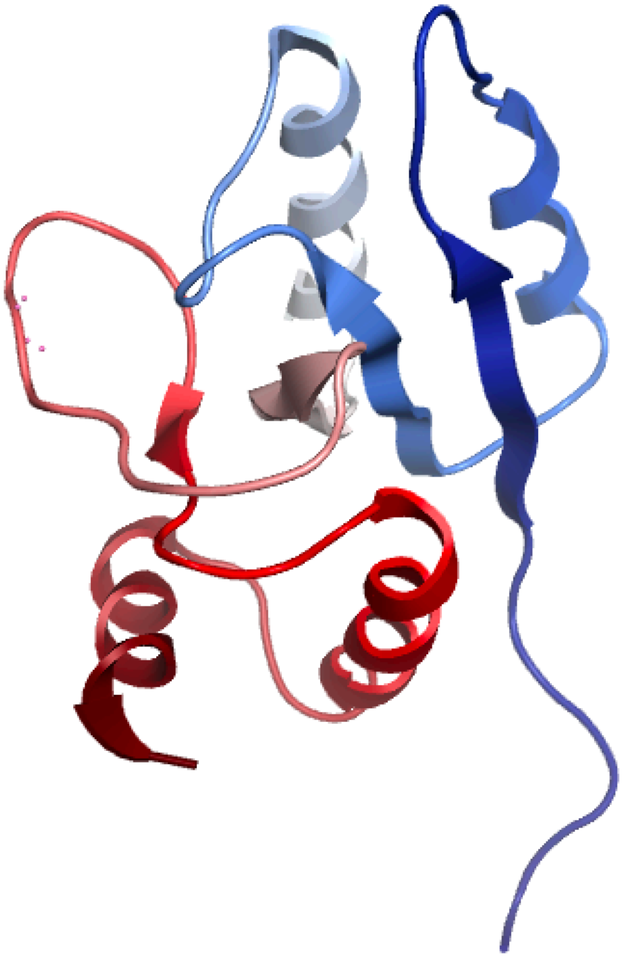
Line up the molecule along the beta sheet, if present.

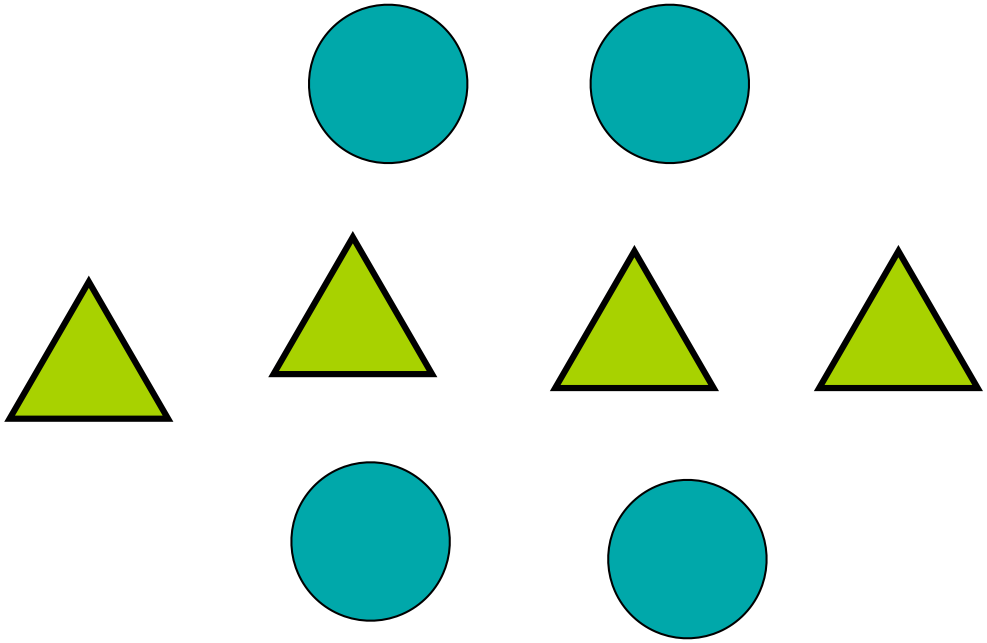
Otherwise choose a direction so that secondary structures are mostly perpendicular to the screen.



TOPS diagram

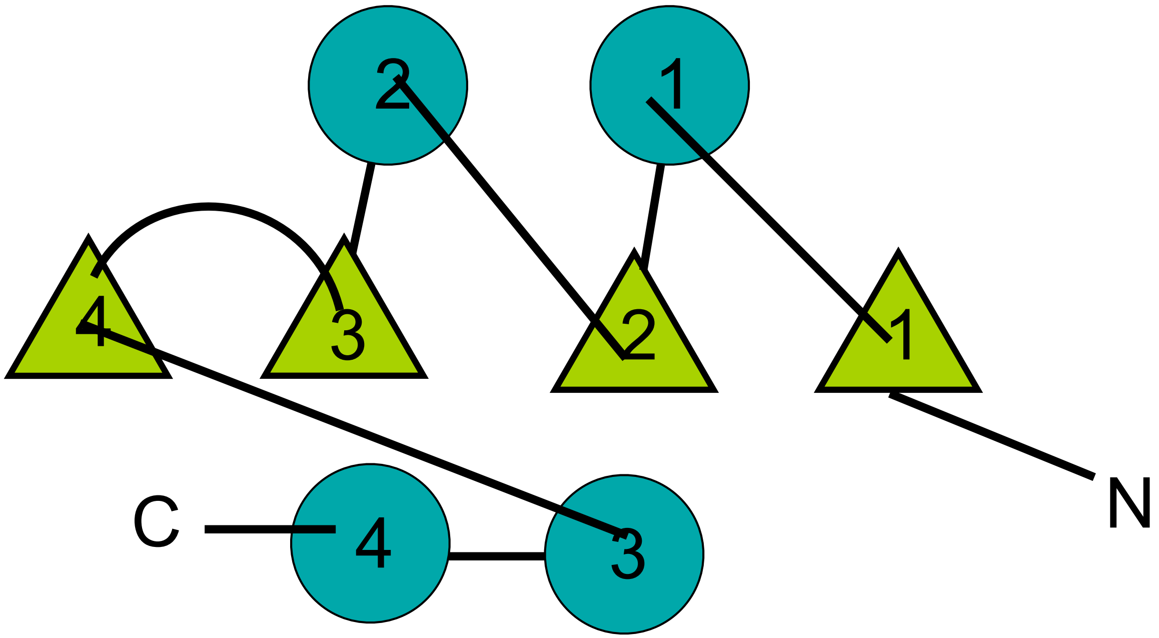
- Draw secondary structures first.





TOPS diagram

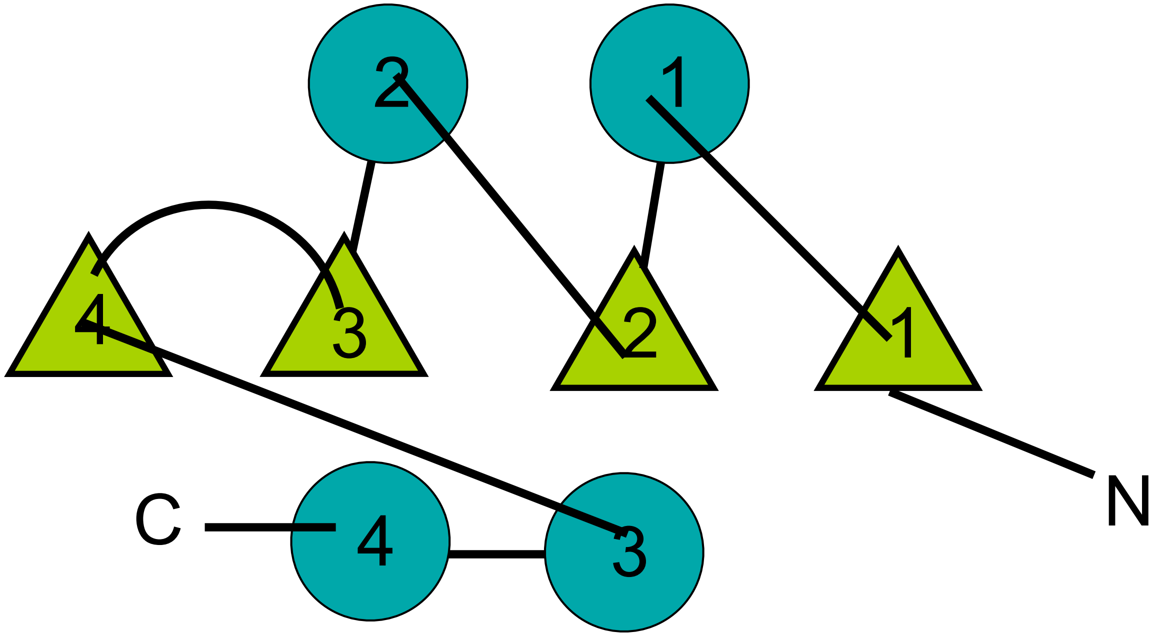
- number them and connect



Be careful to draw connections to the center or side, when it is in front or in back, respectively.

Name it. SCOP-style.

- 3 layers, 2-4-2 αβα, all parallel, 1234



Exercise 16.2: contact map and TOPS cartoon

Open MOE

File | Open: **RCSB PDB: codes:** 2ptl

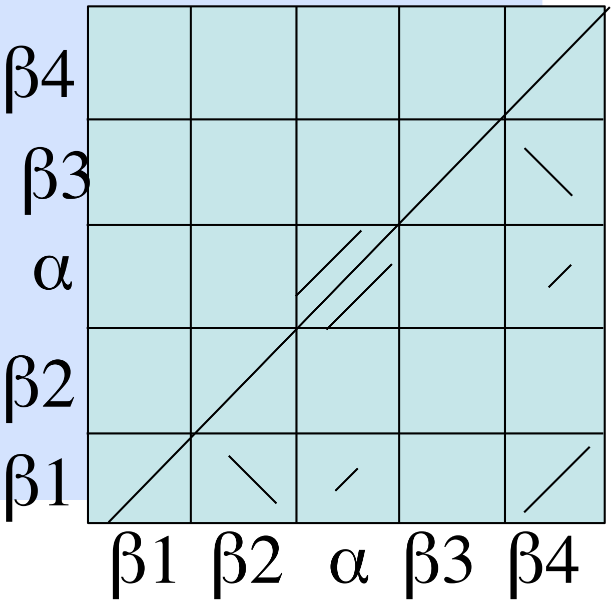
Ribbon | Style: oval

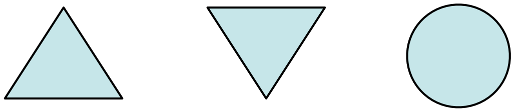
Ribbon | Color : structure

Identify SSEs. Draw triangles and circles

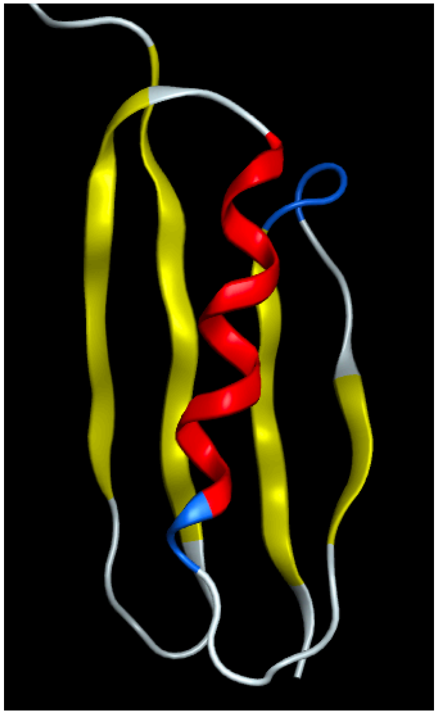
Ribbon | Color : terminus

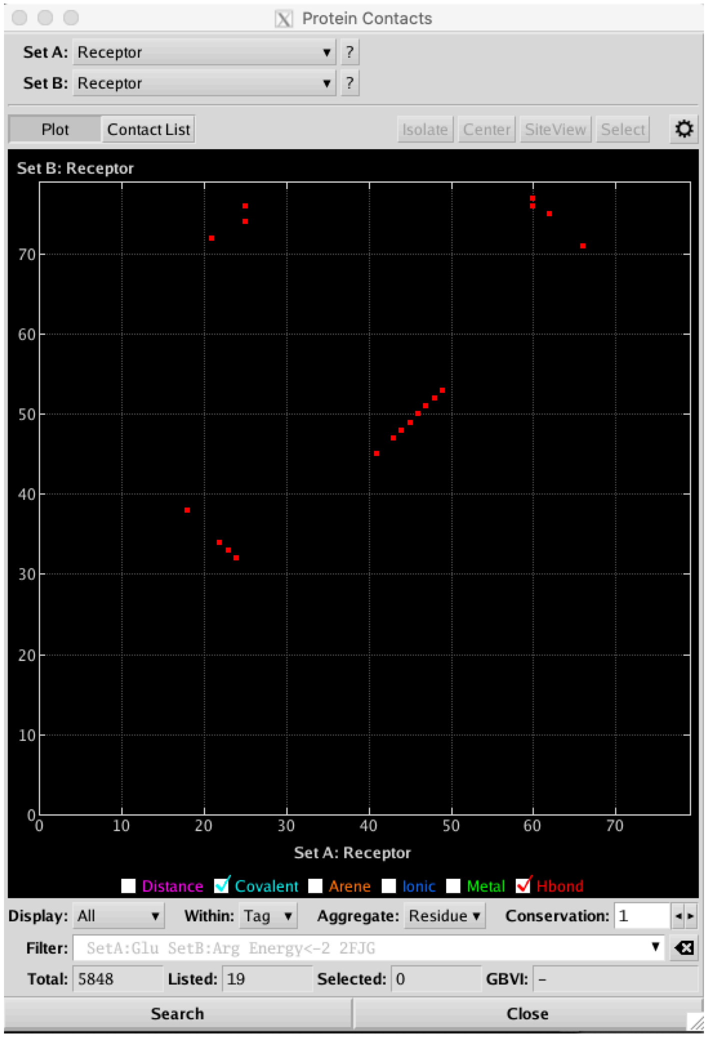
Number and connect SSEs.





2ptl contact map





Set A: Receptor

Set B: Receptor

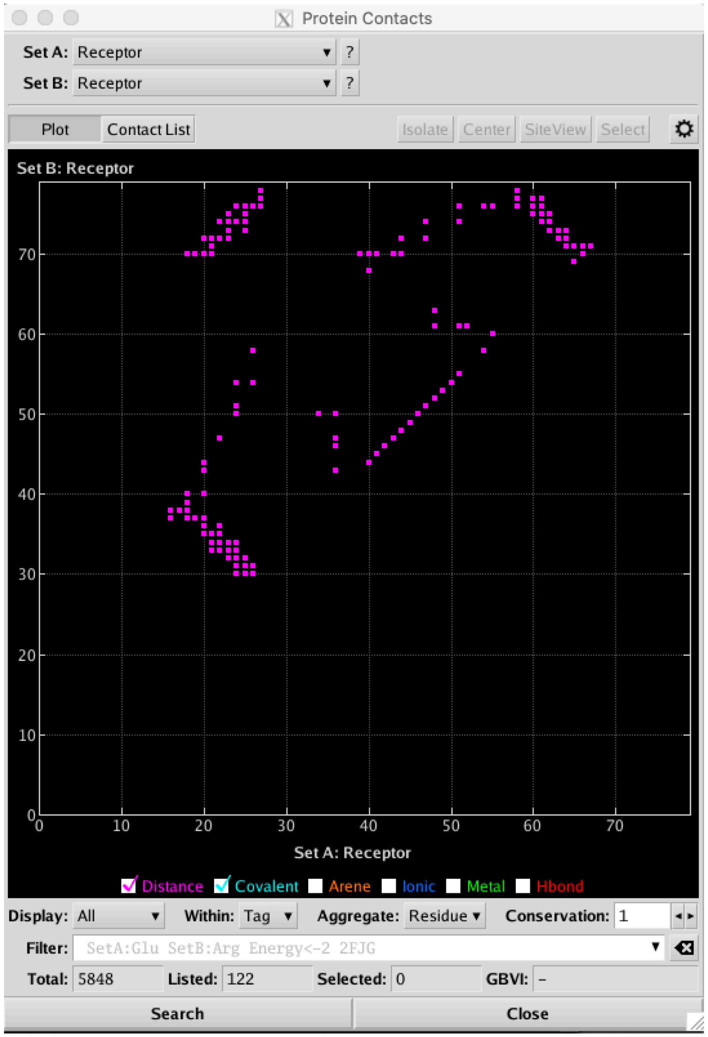
□ Distance ☑ Covalent □ Arene □ Ionic □ Metal ☑ Hbond

Display: All Within: Tag Aggregate: Residue Conservation: 1

Filter: SetA:Glu SetB:Arg Energy<-2 2FJG

Total: 5848 Listed: 19 Selected: 0 GBVI: –

H-bonds



Set A: Receptor

Set B: Receptor

☑ Distance ☑ Covalent □ Arene □ Ionic □ Metal □ Hbond

Display: All Within: Tag Aggregate: Residue Conservation: 1

Filter: SetA:Glu SetB:Arg Energy<-2 2FJG

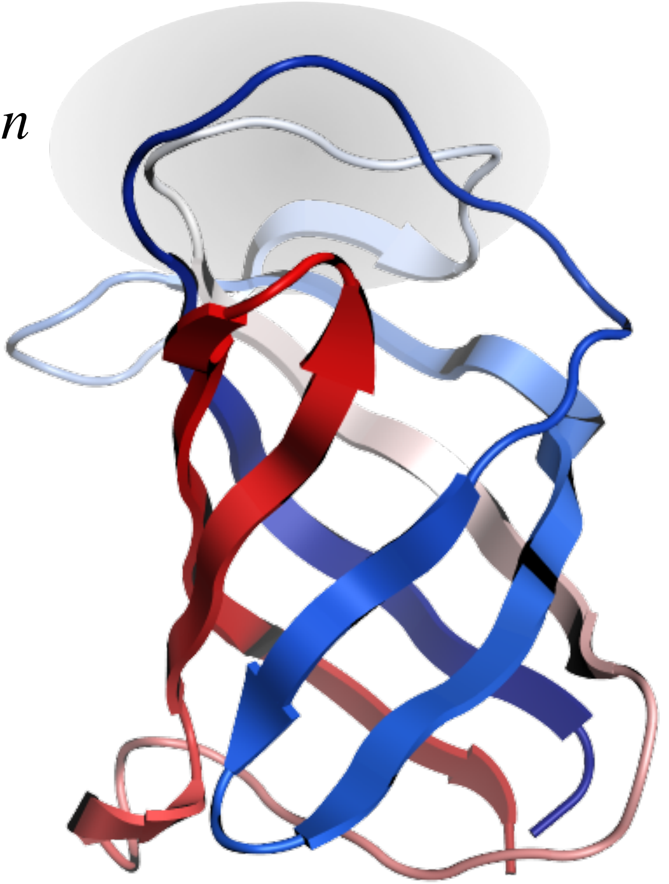
Total: 5848 Listed: 122 Selected: 0 GBVI: –

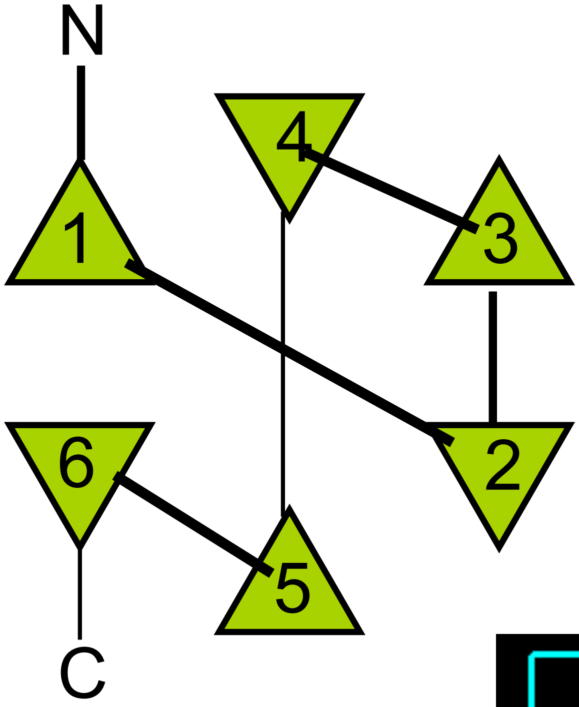
Distance cutoff

TOPS diagram of a beta barrel

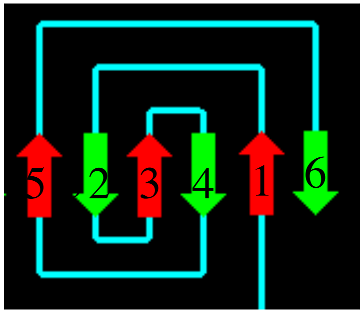
- *all anti-parallel barrel, closed; n=6, S=10; greek-key*

loops ignored in naming





loops drawn as simple lines or curves



it's a greek-key barrel!

To draw a barrel, determine strand neighbors, up or down, arrange triangles in a **circle**. Draw connector lines in front, or in back, of triangles.

Exercise 16.3: TOPS cartoon of beta barrel

Open MOE. Open Green Fluorescent Protein

File | Open: **RCSB PDB: code:** 2b3p

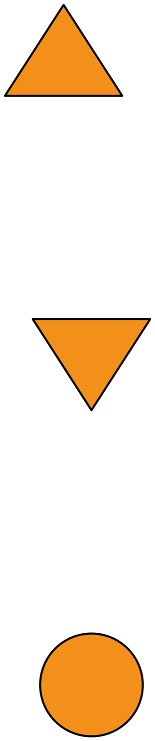
Ribbon | Style: oval

Ribbon | Color : structure

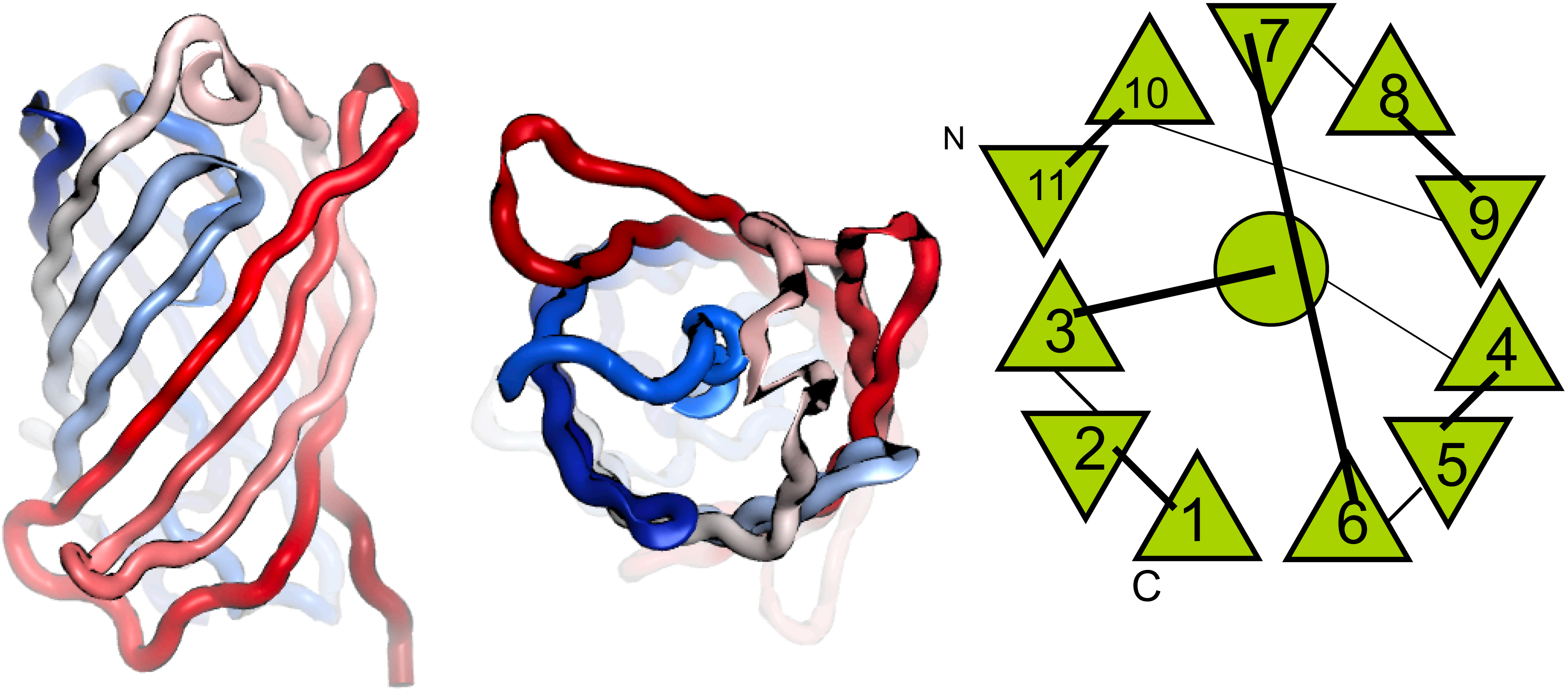
Identify SSEs. Draw triangles and circles

Ribbon | Color : terminus

Number SSEs. Draw connections. Label termini.



- *Mostly anti-parallel barrel, closed, containg a helix; n=11*
- *sheet order 1 2 3 11 10 7 8 9 4 5 6*

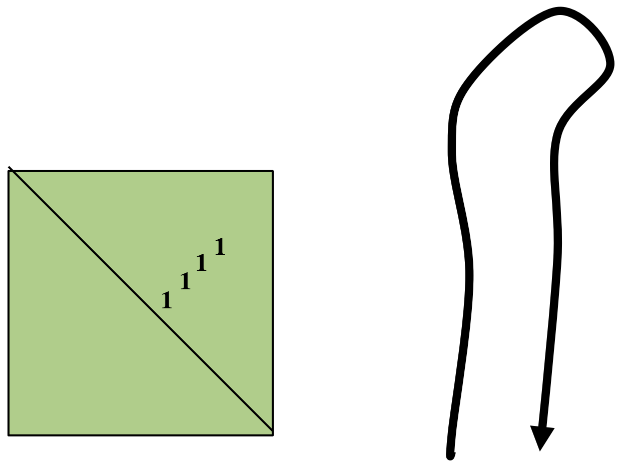


GFP-like fluorescent proteins

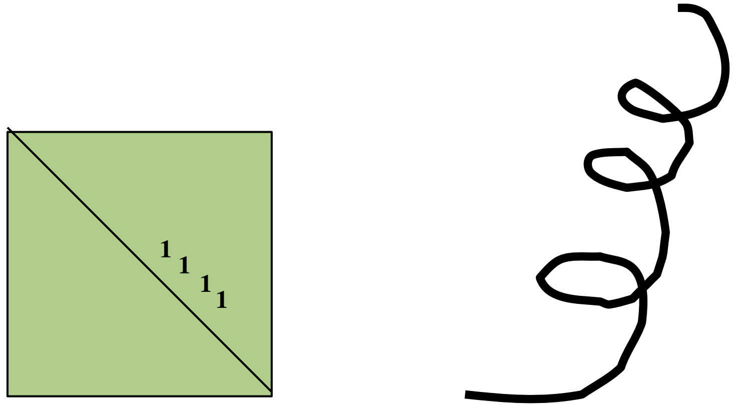
Contact maps: proteins in 2D

In a Contact Map: “1” = $D_{ij} < 8Å$

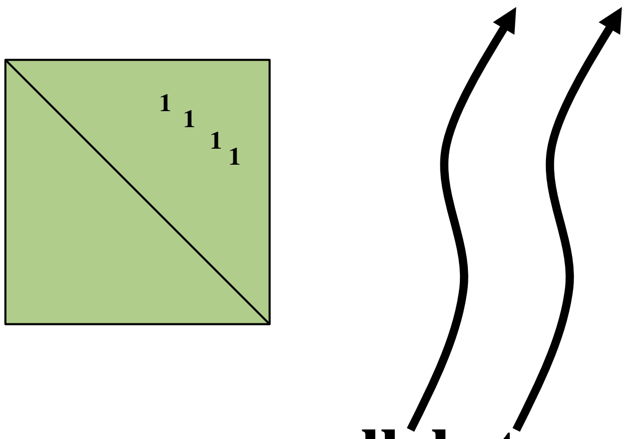
“0” = $D_{ij} > 8Å$



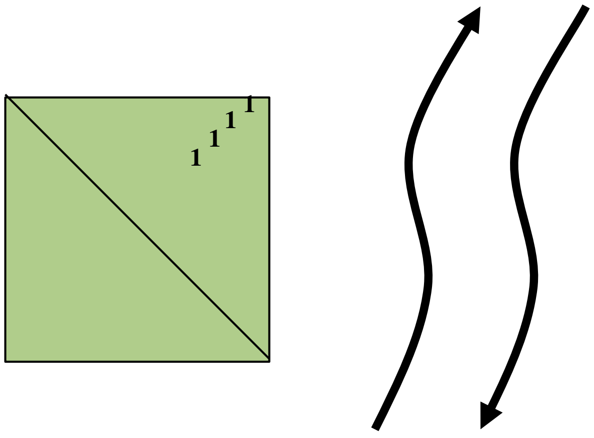
hairpin



helix

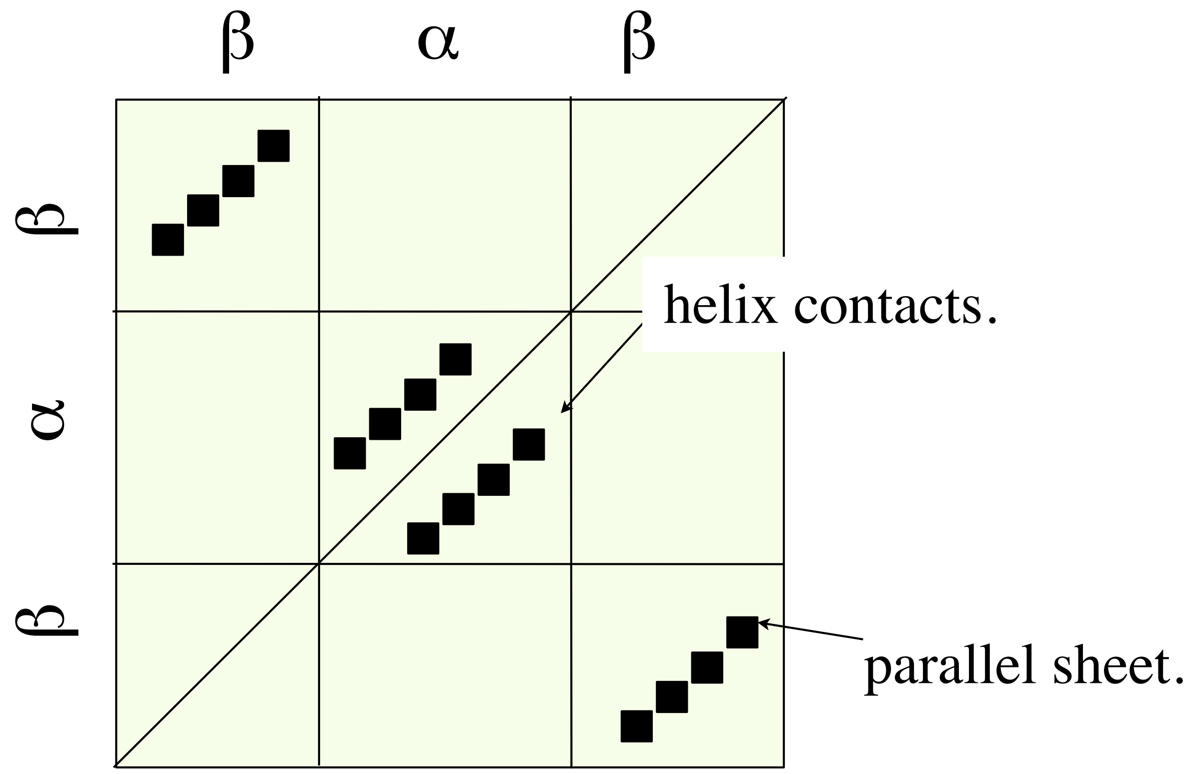


parallel strands



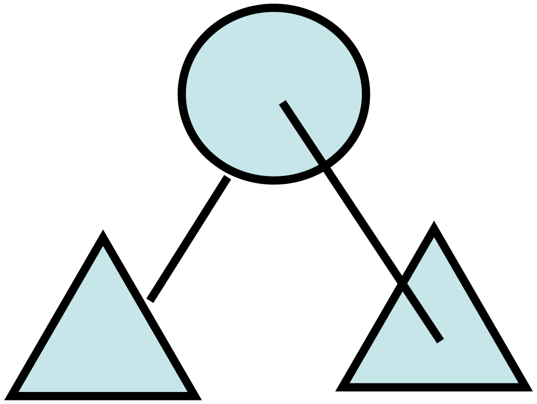
anti-parallel strands

TOPS and contact maps



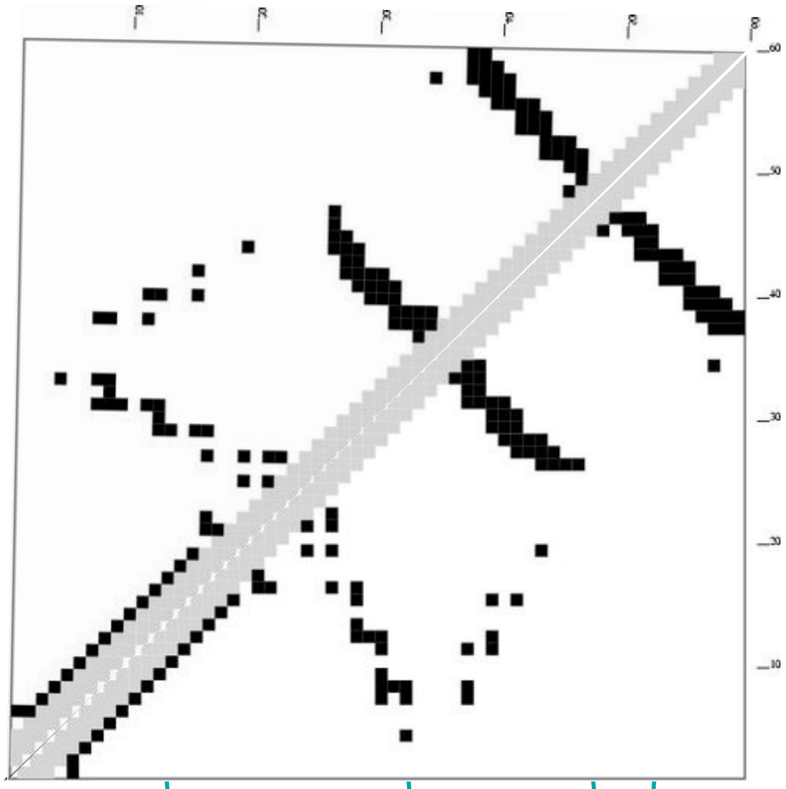
helix contacts.

parallel sheet.



A "contact map" for a βαβ unit.

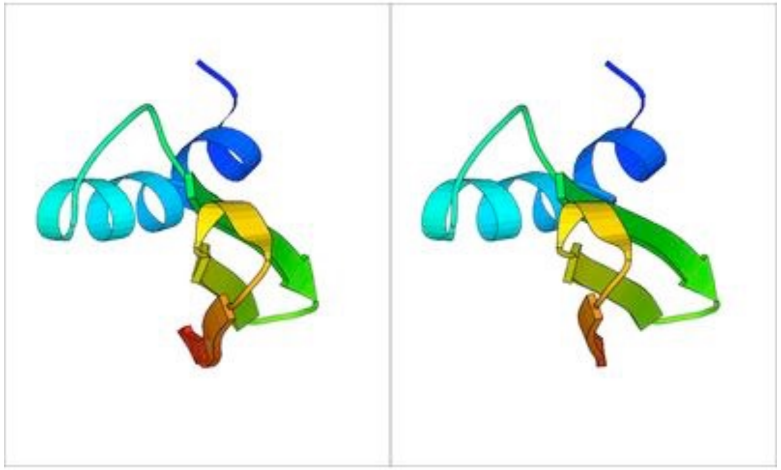
Contact map for a small protein



alpha-helix

contacts between helix and sheet

beta-hairpins



A contact map contains enough information to build the 3D structure within ~2Å RMSD.

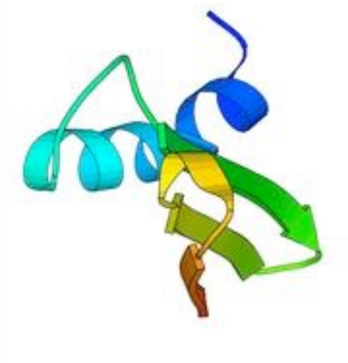
A simplified contact map based on SSEs

(1) Arrange the SSEs along the sequence (a line) in both directions

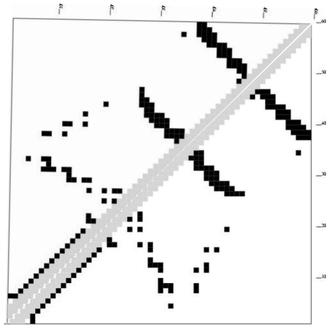
(2) Draw a line parallel to the diagonal for each helix

(3) For any two SSEs that touch, draw a line parallel to the diagonal if the contacts are parallel, draw a line perpendicular to the diagonal if the contacts are anti-parallel. Draw a dotted line if a helix is involved.

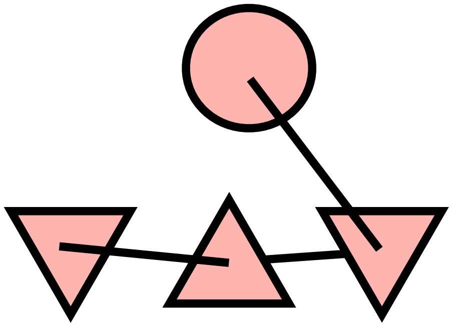
Structure



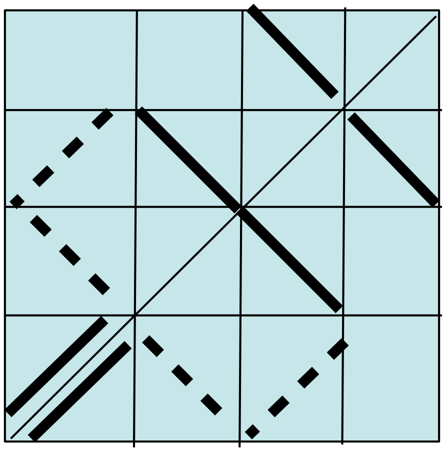
contact map



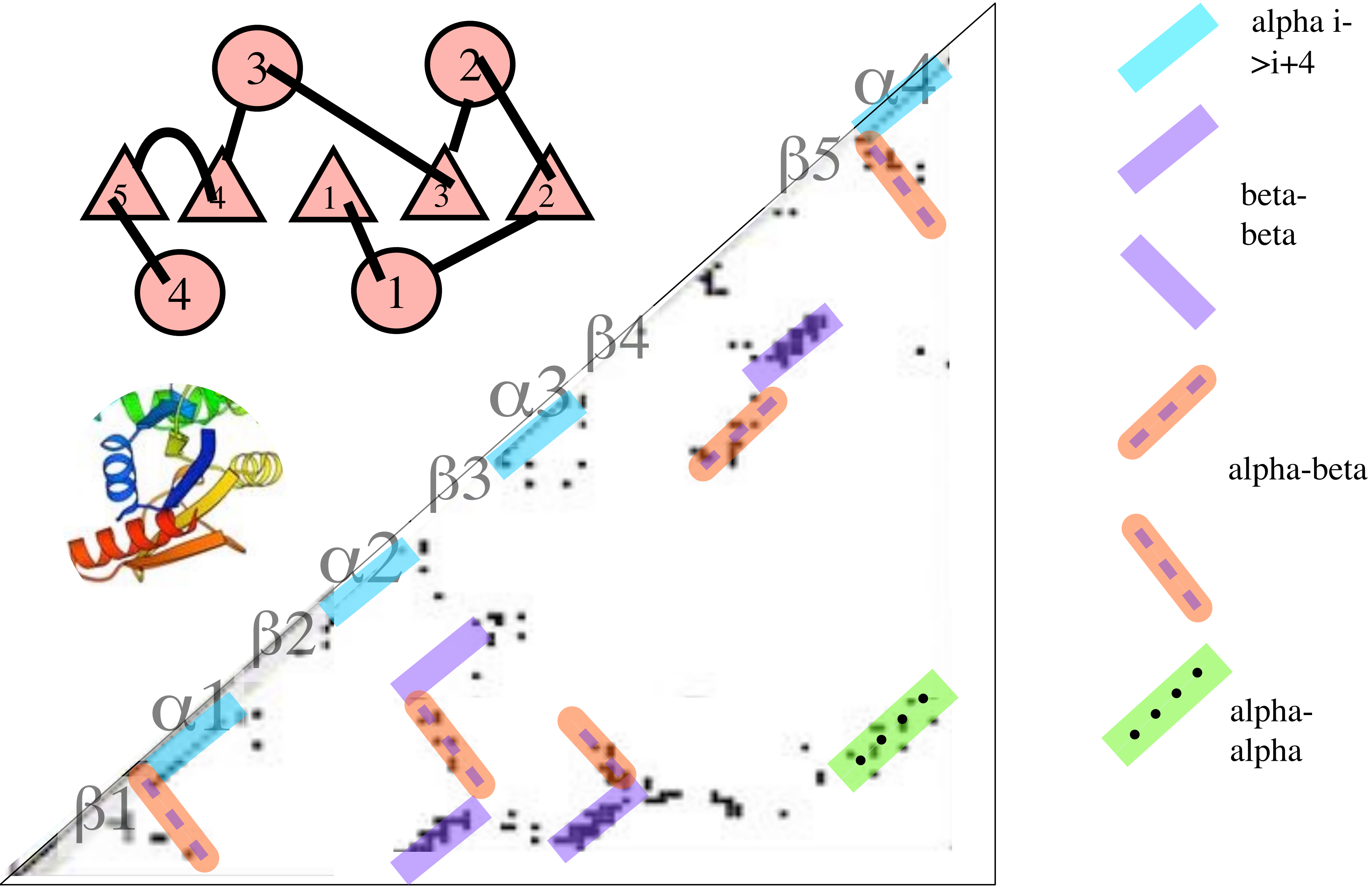
TOPS



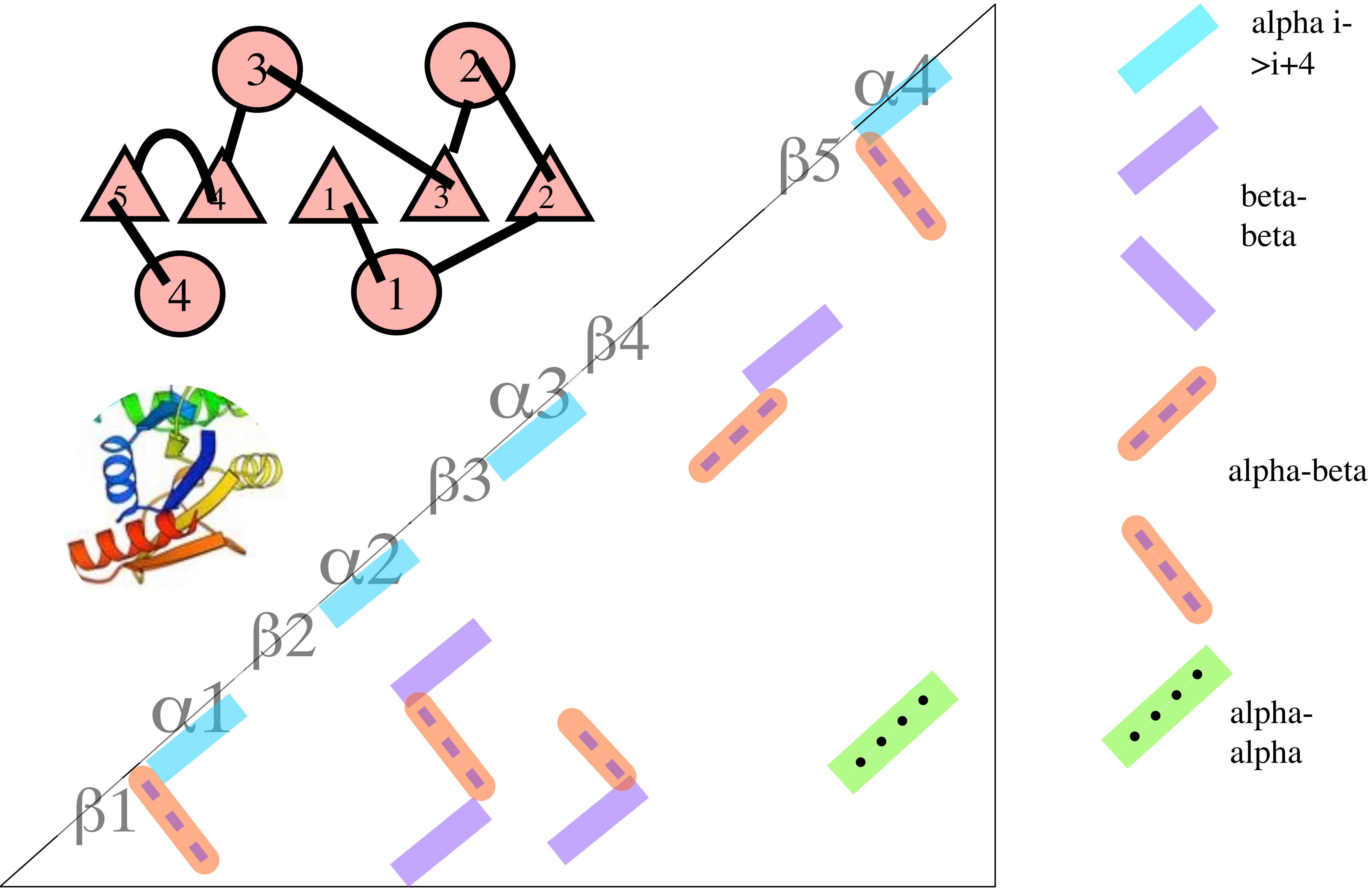
simplified contact map



Simplified contact map to TOPS diagram

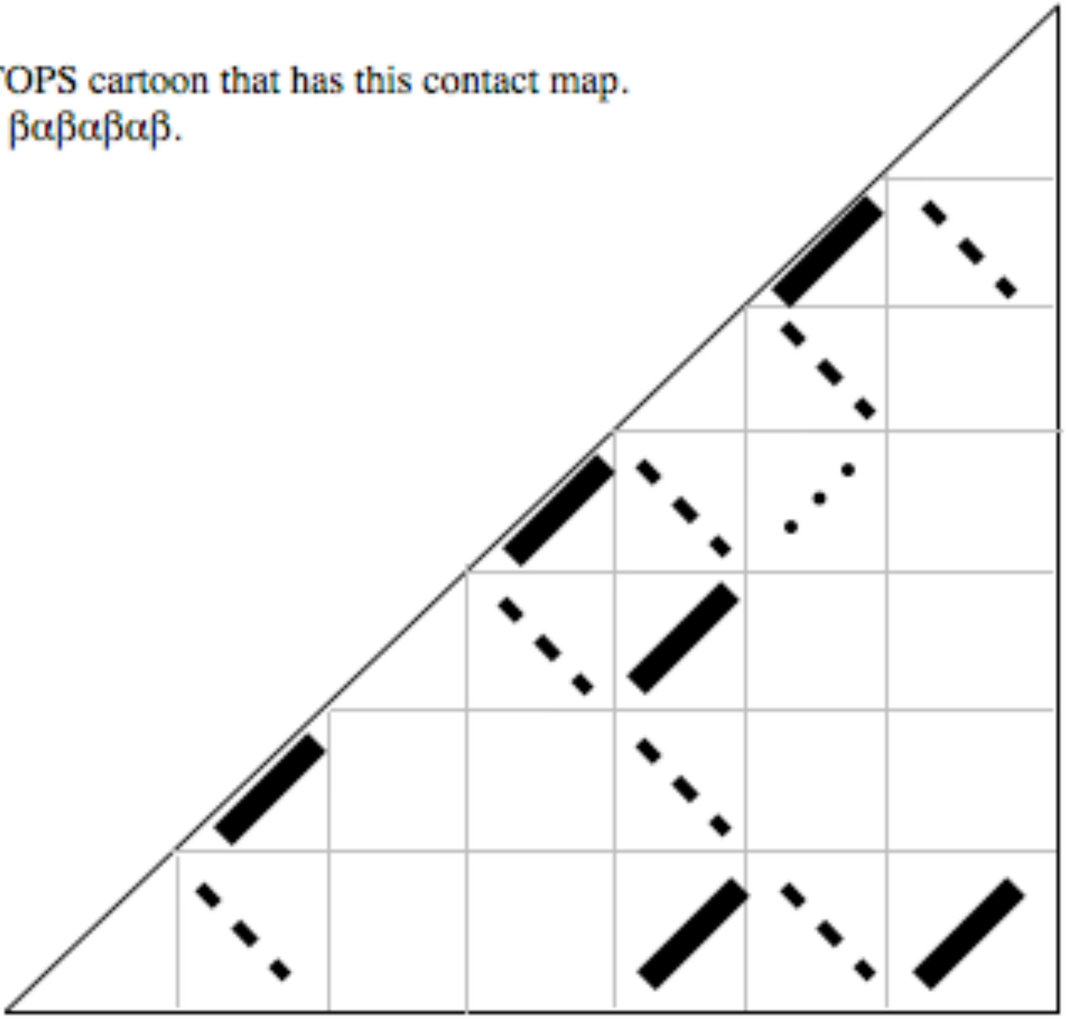


Simplified contact map to TOPS diagram



Exercise 16.4: TOPS from contact map

Do this on paper.

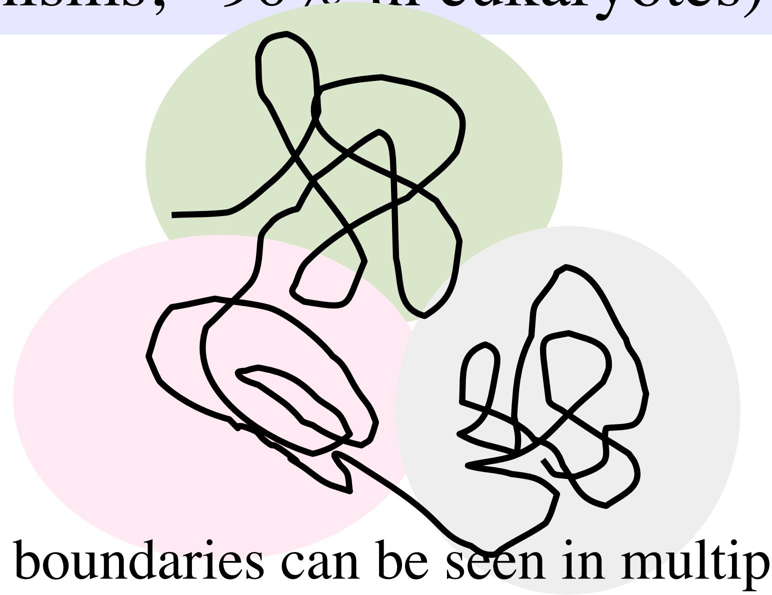


Draw a TOPS cartoon that has this contact map.
SSEs are βαβαβαβ.

Most genes represent multidomain proteins

~40% of known structures (crystal, NMR) are multidomain proteins, but

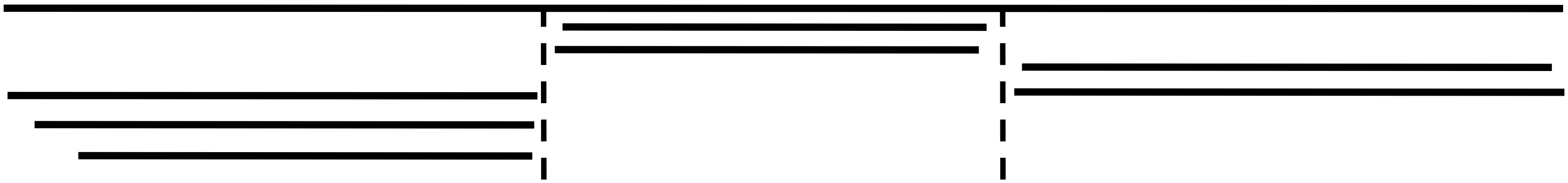
Most of all proteins are multidomain.(~60% in uncellular organisms, ~90% in eukaryotes).



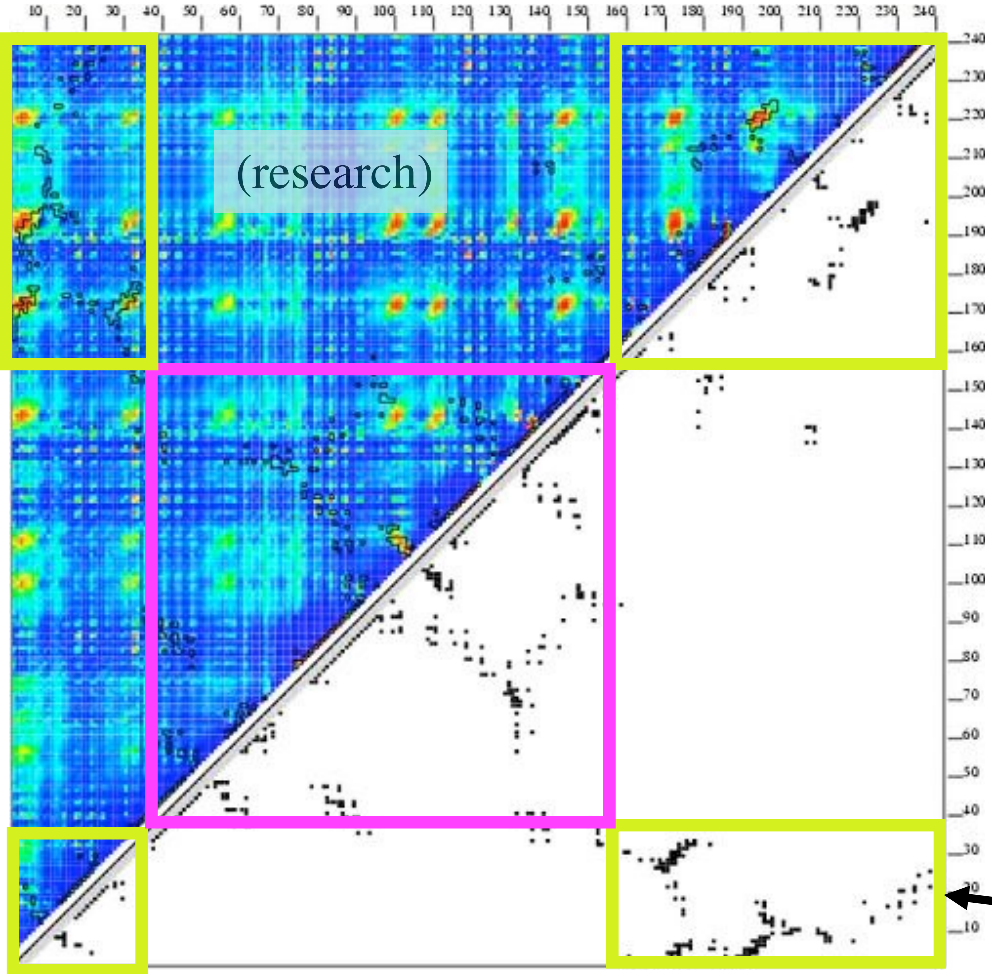
Domain boundaries can be seen as "weak" connections in the structure.

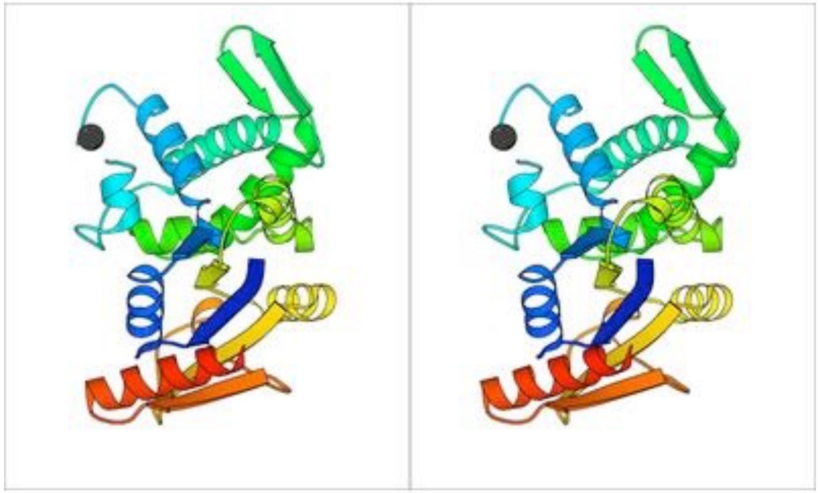
"Weak" means few contacts and few chain cross-overs.

Domain boundaries can be seen in multiple sequence alignments if the alignments are of whole genes.



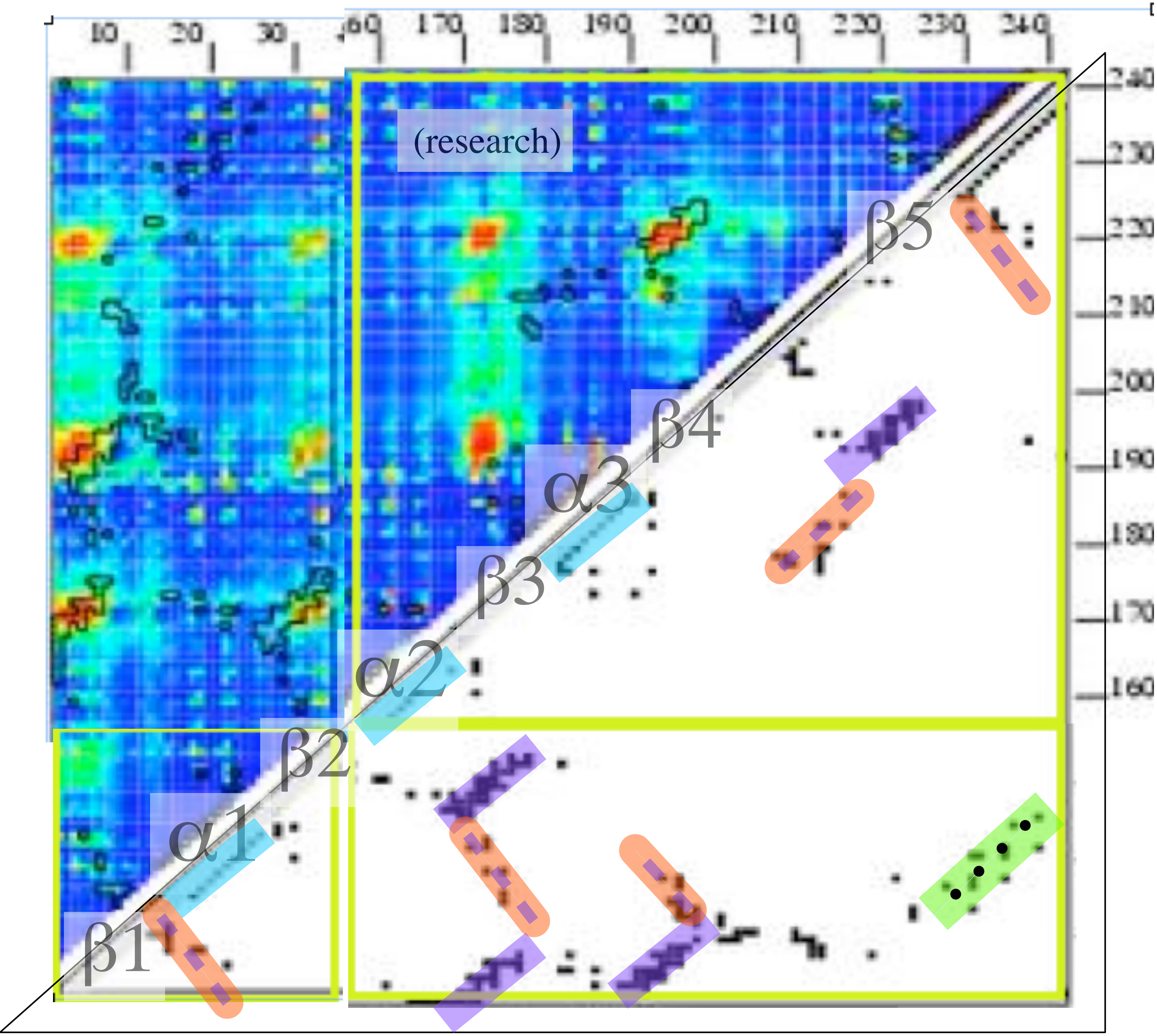
Example of two, discontiguous domains seen using a contact map





Contacts are mostly within domains, not between domains. One domain consis of N and C-terminal parts

C/N-Terminal domain, cut-and-pasted



in-class

Exercise 16.1: Superimpose by hand

Do this pair: 1WFA.A vs 1WFA.B (2 chains of the same PDB structure)

File | Open: RCSB PDB: code: 1WFA
Ribbon | Style: oval, Color: chain or **terminus**
Select | synchronize (check if not already checked)
In **SEQ** window (cntl-Q)
    Double-click on chain label to select one molecule.
In **MOE** window (cntl-M) practice these moves. Superpose the chains.
    Rotate selected : **meta-middlemouse-drag**.
    Translate selected : **shift-meta-middlemouse-drag**
    *Rotate all***: middlemouse-drag**
    *Translate all***: shift-middlemouse-drag**

Share screen to show me your superposition.

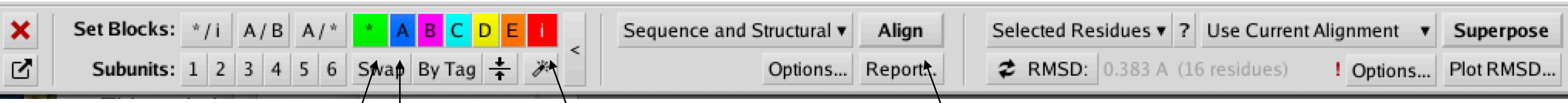
in-class

Exercise 16.2: Superimpose automatically

Same chains: 1WFA.A vs 1WFA.B

Do these steps.

1. **SEQ | Alignment|Align/Superpose**
2. **Open setup chains. Select waters** (click on chain name)**, set to "i" (ignore)**



Ignore selected chains

Align

Group chains

Align individual chains

3. Align (sequence and structural)

4. Inspect by showing straight-line trace ribbon.

5. **Superpose**. (explore options). Try selecting the C-terminal half (either MOE | left-mouse drag or SEQ | left-mouse drag along "ruler"), in menu set **Selected Residues**, then **Superpose** again. Do same after selecting N-terminal half. What is happening?

Share screen to show me your superposition.

Exercise 16.5: domain boundaries

6vsb. — Coronavirus spike protein, a multi domain protein.

File | Open | PDB: 6vsb

Double-click 1st chain. Select | invert. Delete. Display ribbon, colored by Terminus. Hide all atoms.

Where are the domains? What kind are they?

Select atoms of each domain. Color domains differently.

Homework 1 -- domains in coronavirus spike protein

- Align and superpose the three protein chains of SAR-2 spike (6vsb)
- Why doesn't the whole molecule superpose well?
- Superpose based on the receptor domain only ACE2 binding domain, residues 330-440
- Draw a TOPS diagram.
- Some loops are missing!
- Do http://www.bioinfo.rpi.edu/bystrc/courses/biol4550/homework1.pdf
- Turn in as PDF file: http://www.bioinfo.rpi.edu/bystrc/courses/biol4550/homework.html

test drive the homework server

- Goto http://www.bioinfo.rpi.edu/bystrc/courses/biol4550/homework.html
- Upload a file for homework 1. It can be any file. (I will delete it)
- Problems? Send me email.

Review questions

- What is a domain?
- What is a sequence “family” according to SCOP?
- What does “strand order” mean w/respect to SCOP naming?
- What defines a sequence “superfamily”?
- What characterizes a “fold”?
- Draw a beta-alpha-beta unit using TOPS.
- Draw a simplified contact maps based on a TOPS diagram.
- Find domain boundaries using a contact map.
- How can we infer domain boundaries using a multiple sequence alignment?
- In a TOPS diagram, what does a triangle pointing up mean?

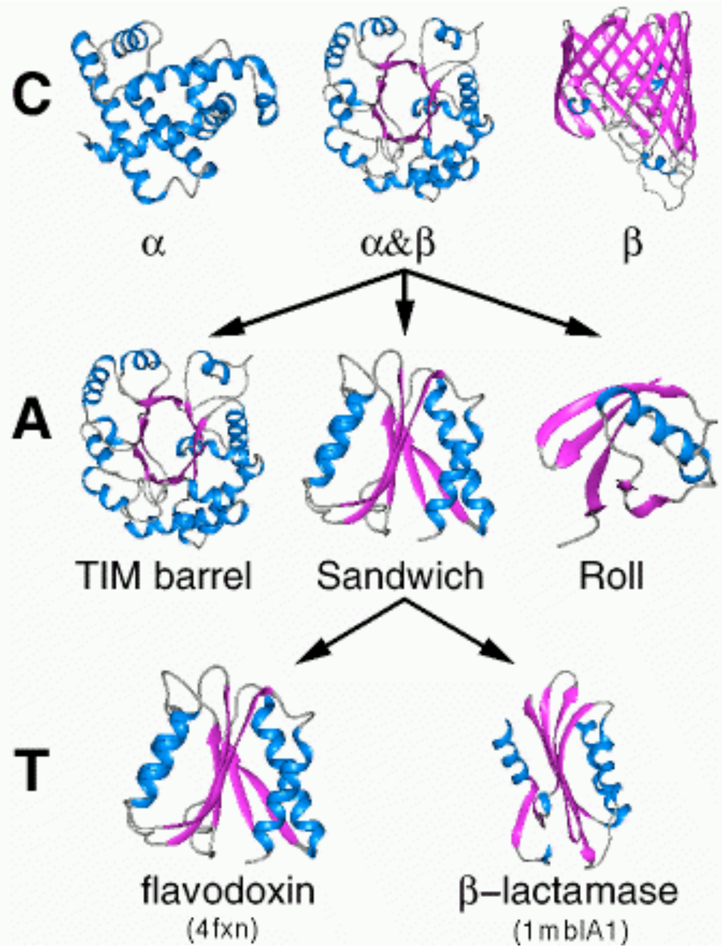
Supplementary slides

CATH

- Class
- Architecture
- Topology
- Homology

Architecture = conserves arrangement of SSE (secondary structural elements) but not sequential order.

Topology = like SCOP Fold.



http://www.biochem.ucl.ac.uk/bsm/cath_new/index.html

protein structure and representation - a hierarchy or a continuum?

Structure --	**representation.**
Secondary structure--	1D, three states
Local structure --	motifs, backbone angles.
Super-secondary structure --	TOPS.
Inter-residue distances --	2D contact maps
Tertiary structure --	3D backbone
Side chain conformation --	rotamers
Domain-domain interactions --	interface maps
Quaternary structure --	poses, interaction maps.