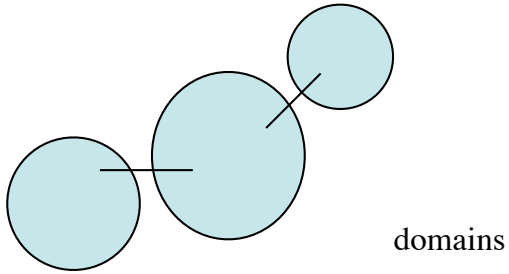
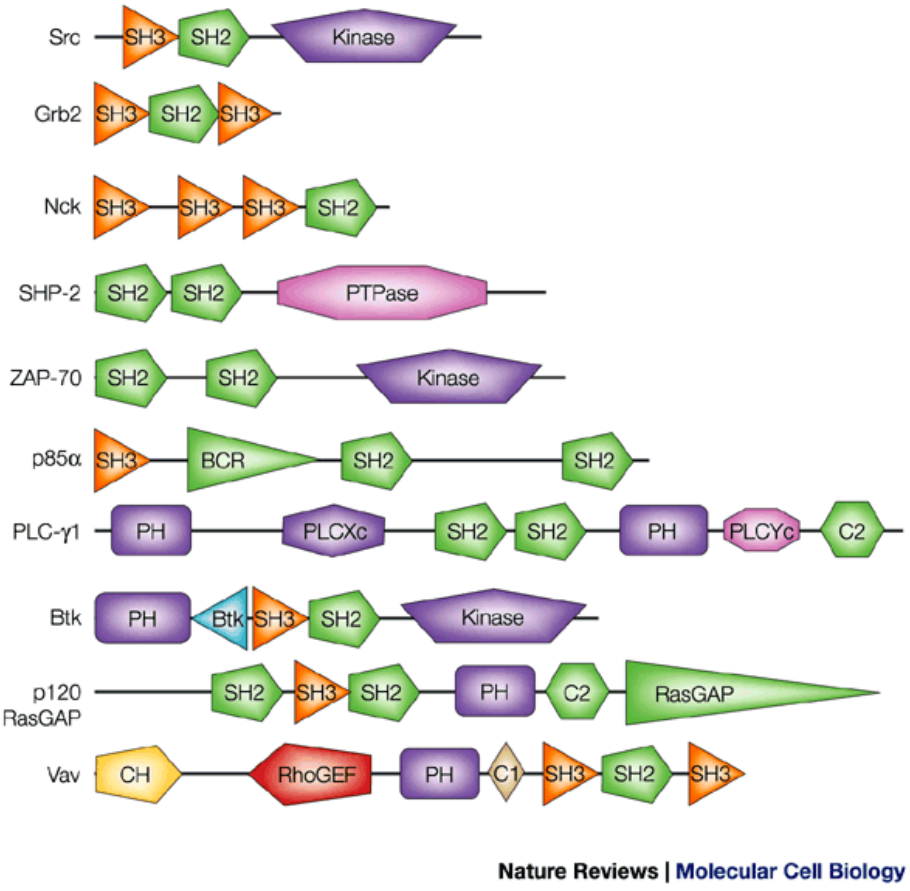
# Molecular Modeling 2021
# lecture 3 -- Tues Feb 2

Protein classification

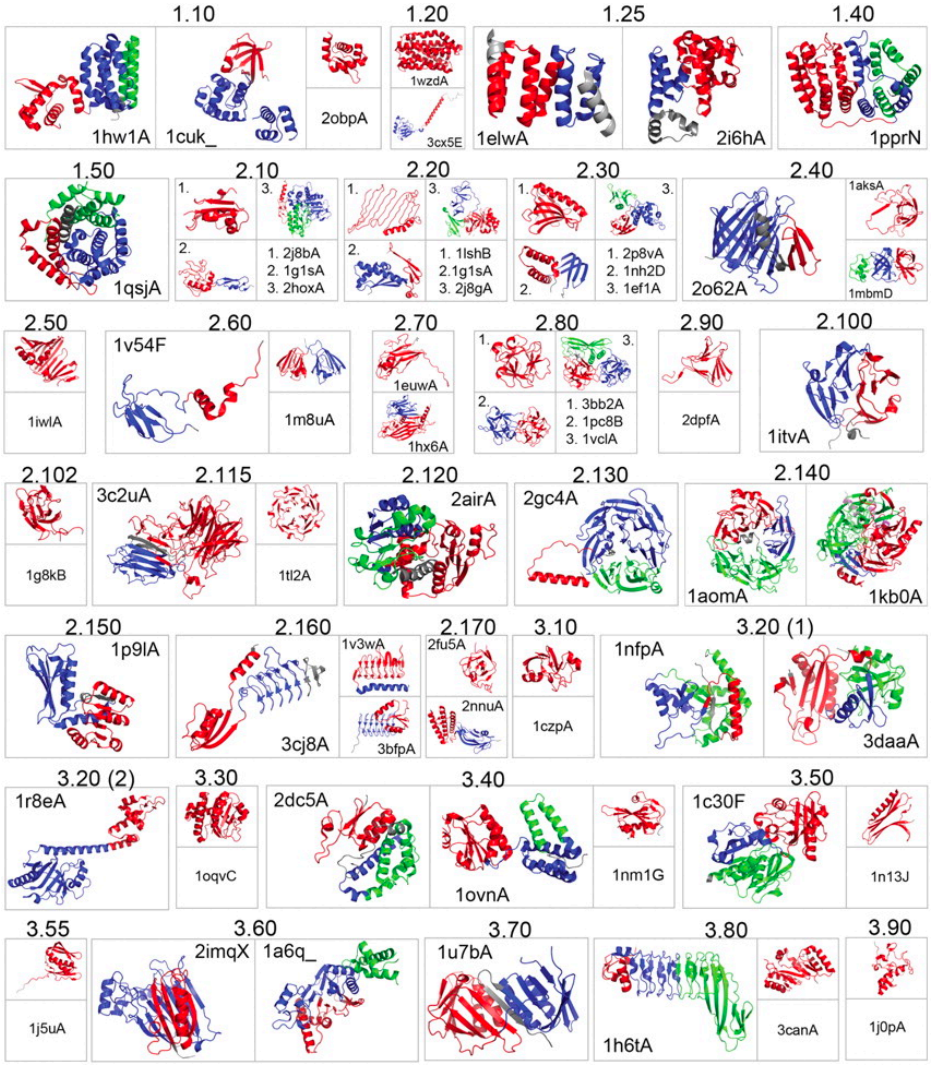
- SCOP
- TOPS
- Contact maps



# Domains




Nature Reviews | Molecular Cell Biology



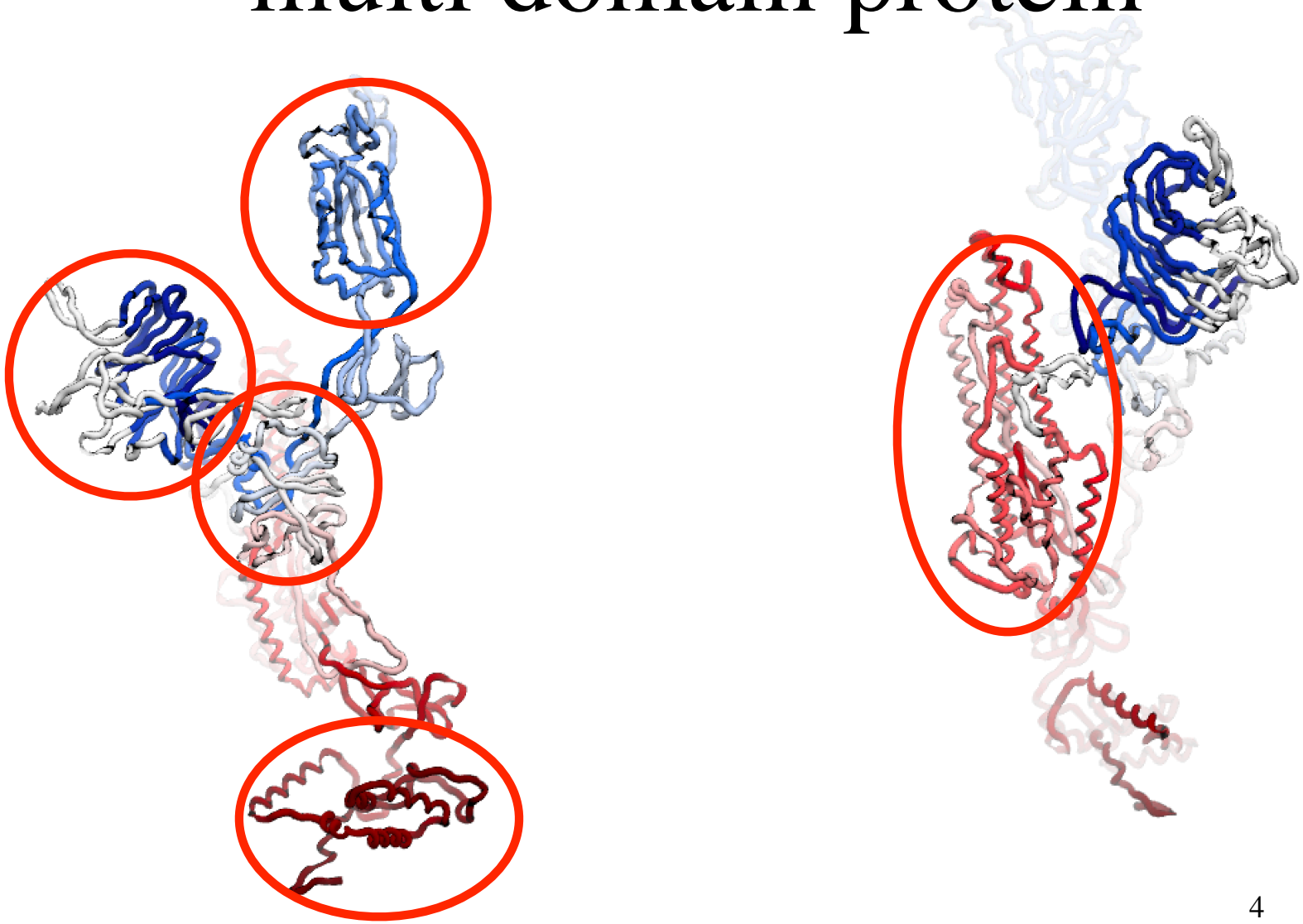

To a **cell biologist** a domain is a sequential unit within a gene, usually with a specific function.

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

# A domain is…

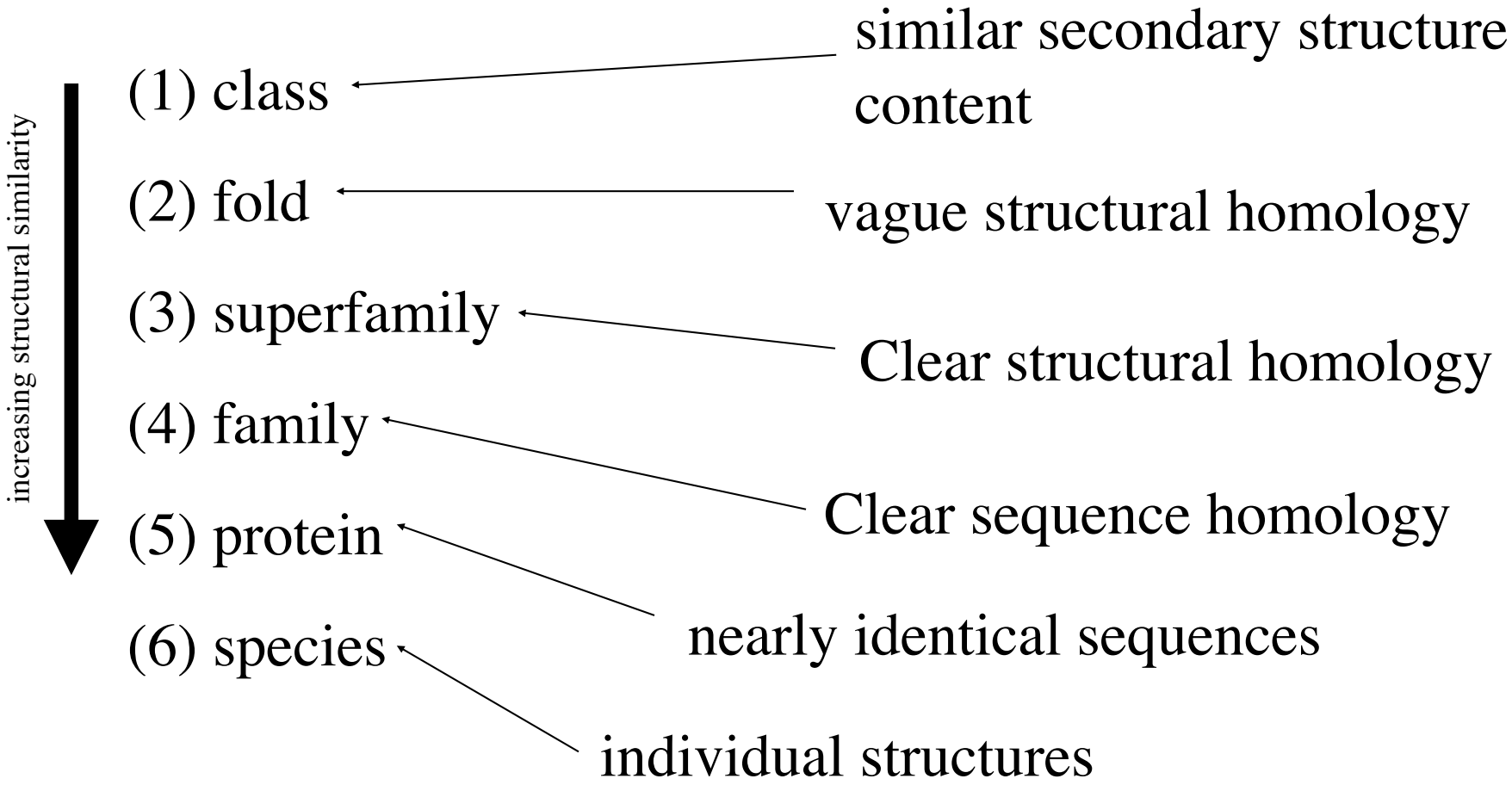
- … an autonomously-folding substructure of a protein.
- … > 30 residues, but typically < 200. May be bigger.
- …usually has a single hydrophobic core
- … usually composed of one chain (occasionally composed of multiple chains)
- …is usually composed on one contiguous segment (occasionally made of discontiguous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

# SARS-CoV-2 spike protein — a multi domain protein



# SCOPe -- classification of domains

- http://scop.berkeley.edu



# SCOPe -- 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

# SCOPe -- 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.

# fold level jargon

## example: α/β proteins: flavodoxin-like

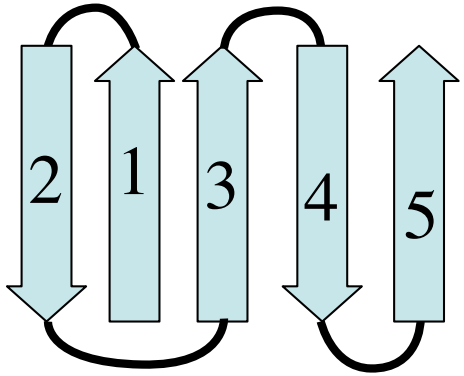
SCOP Description: 3 layers, α/β/α; parallel beta-sheet of 5 strand, order 21345

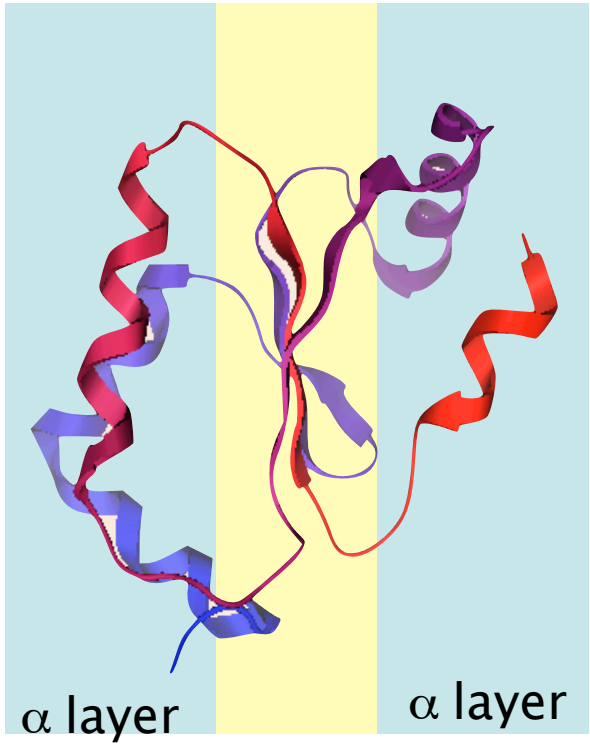
"*layers*"

Rough arrangements of secondary structure elements.

"*order*"

The sequential order of beta strands in a beta sheet.

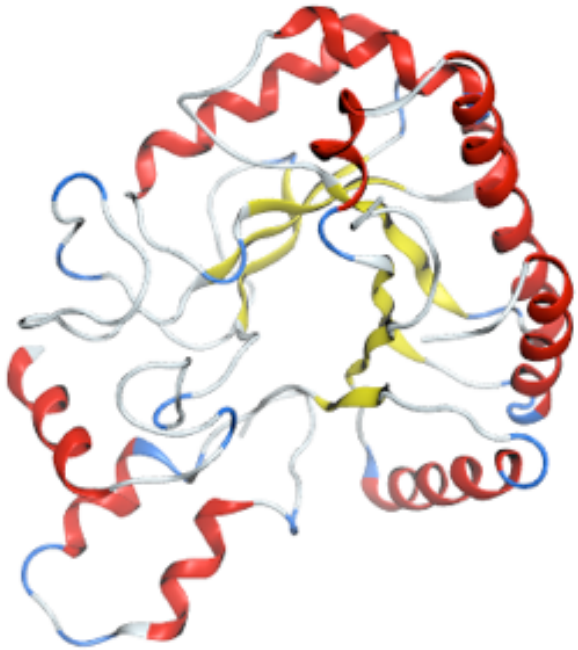


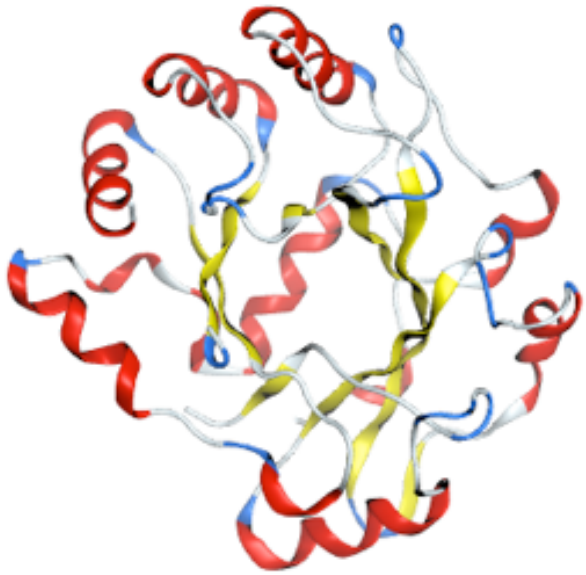
# **Fold**-level similarity

7-stranded alpha/beta barrel

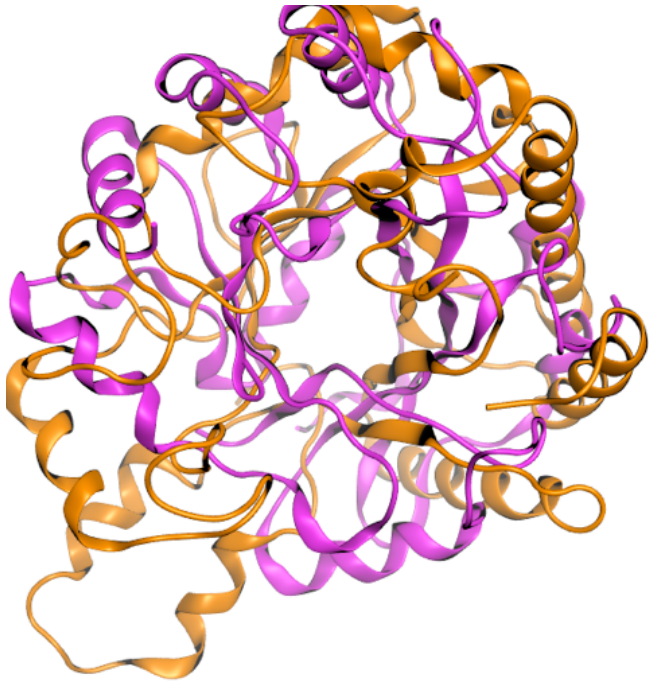
2bod



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

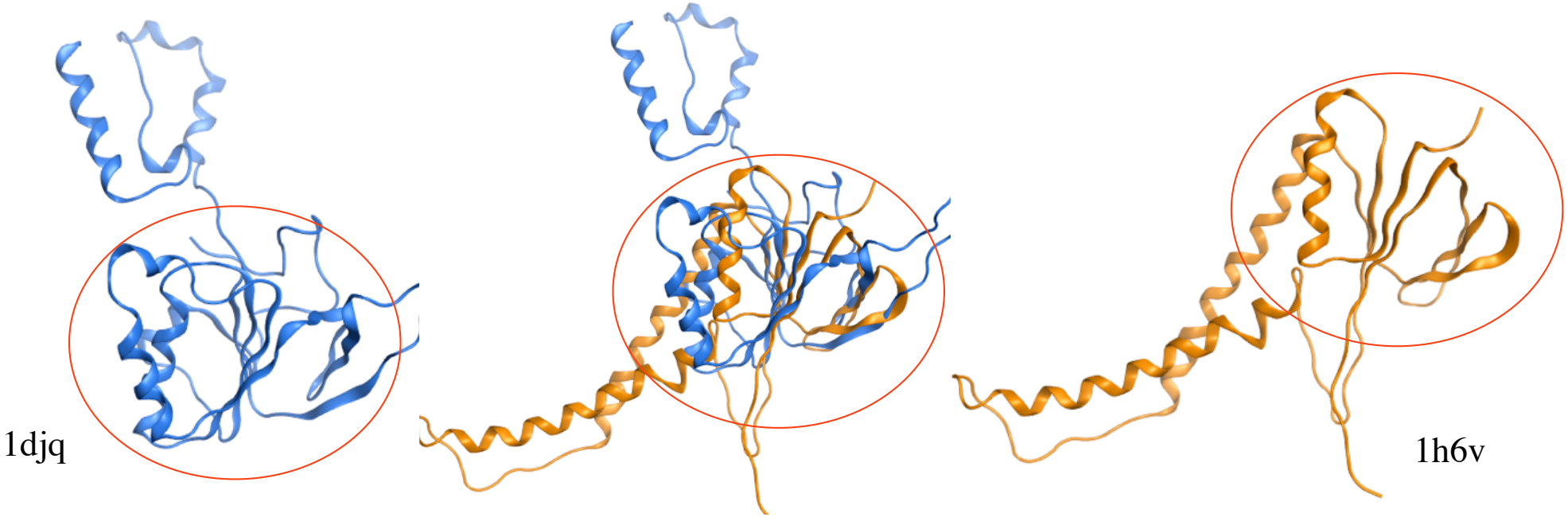


But the SSE do not superpose. Some superposition algorithms fail to superpose proteins of the same fold.

# Superfamily level similarity

is hard to see.

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



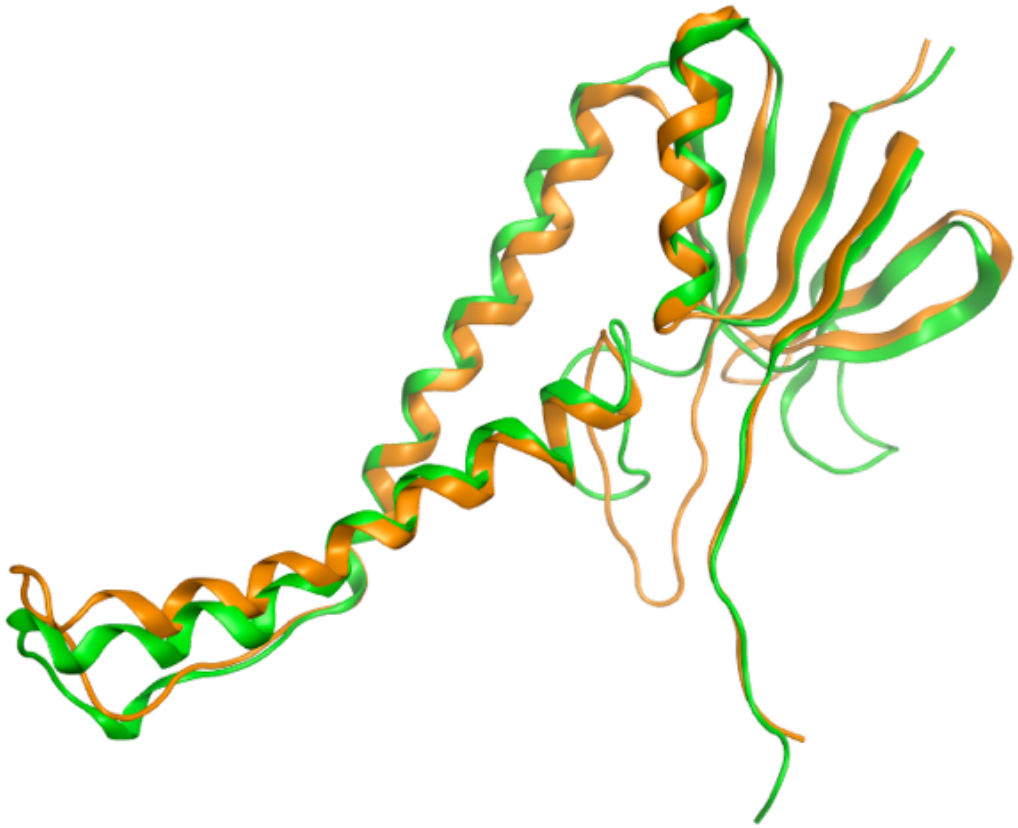

FAD-linked reductases

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

is obvious.

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



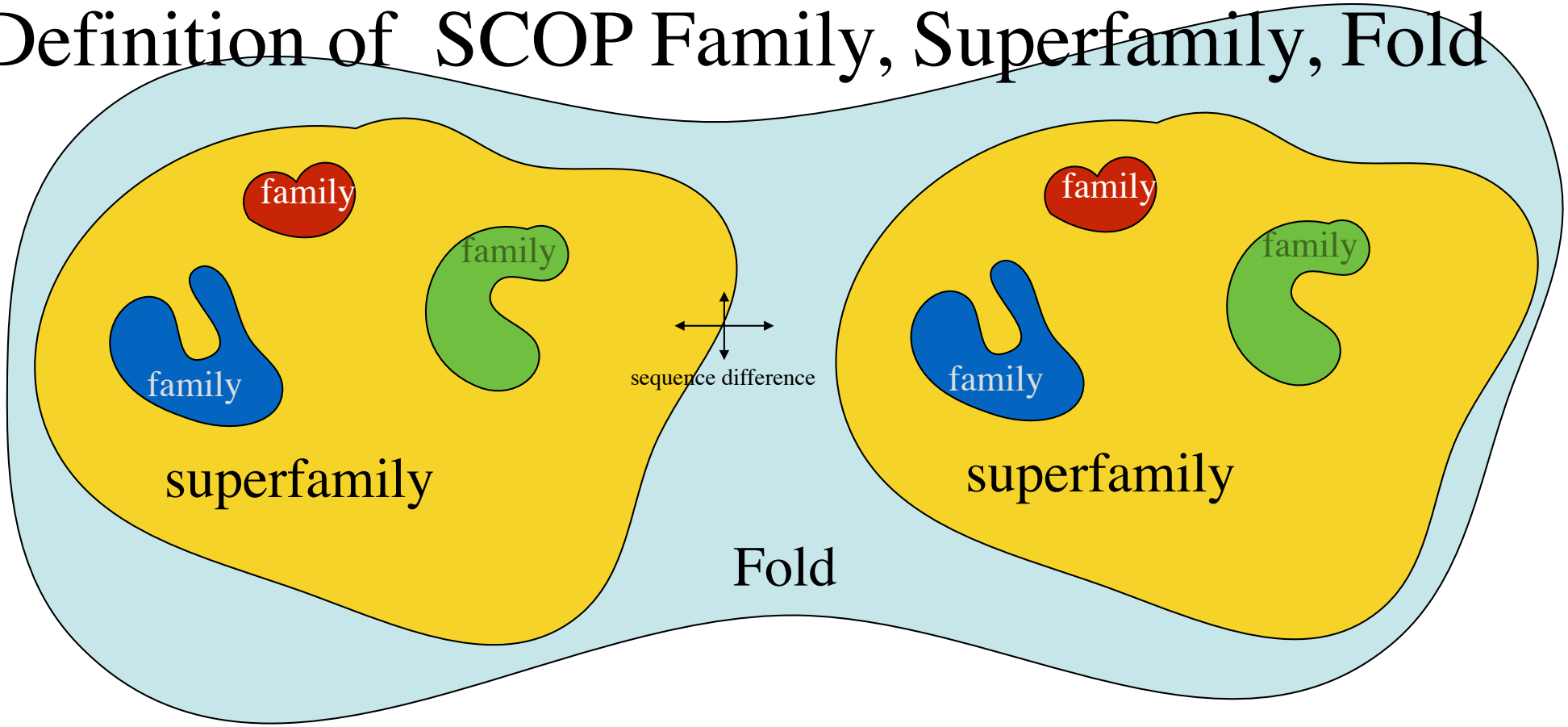
1h6v

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

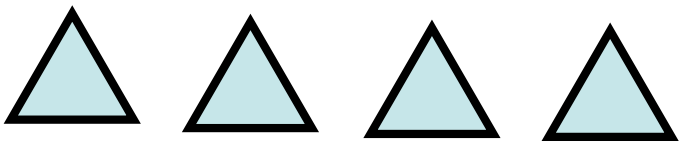
Secondary structure elements (SSE)

beta strand pointing up

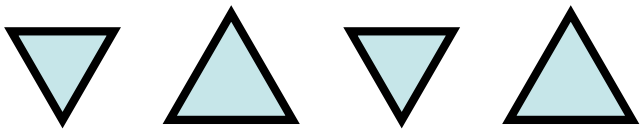
beta strand pointing down

alpha helix

connections



A parallel beta sheet

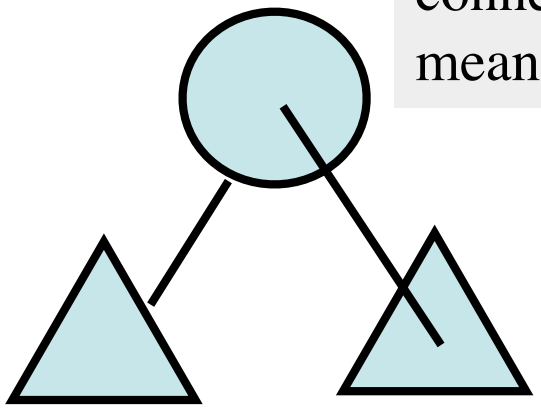


An anti- parallel beta sheet

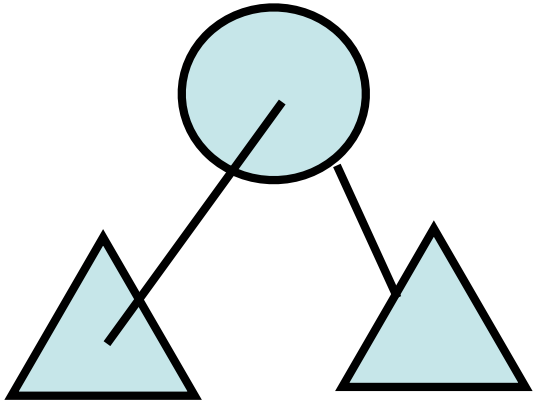
# TOPS topology cartoons

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

A right-handed βαβ unit



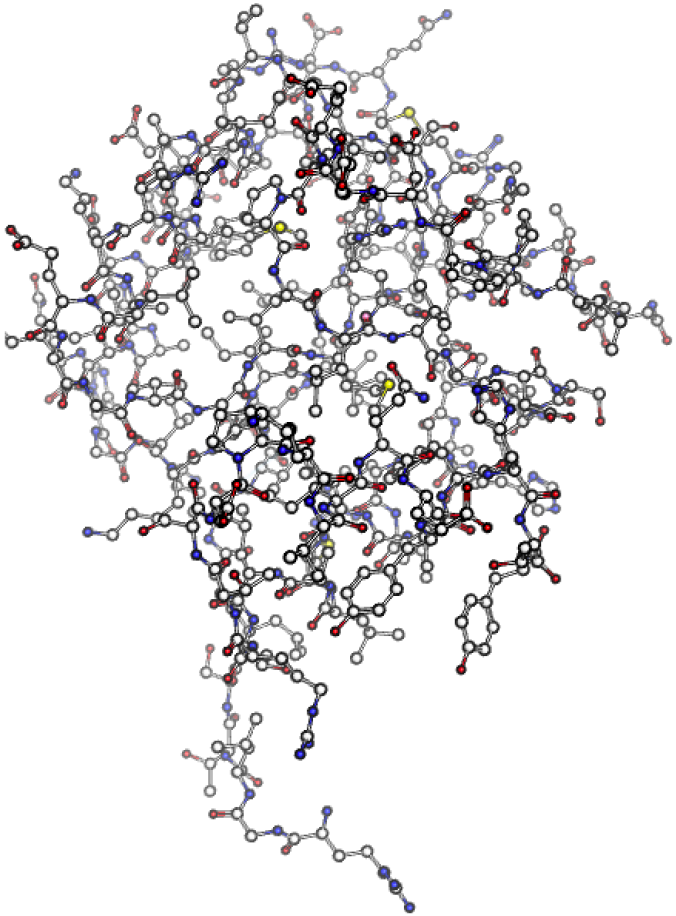
A left-handed βαβ unit (rare)

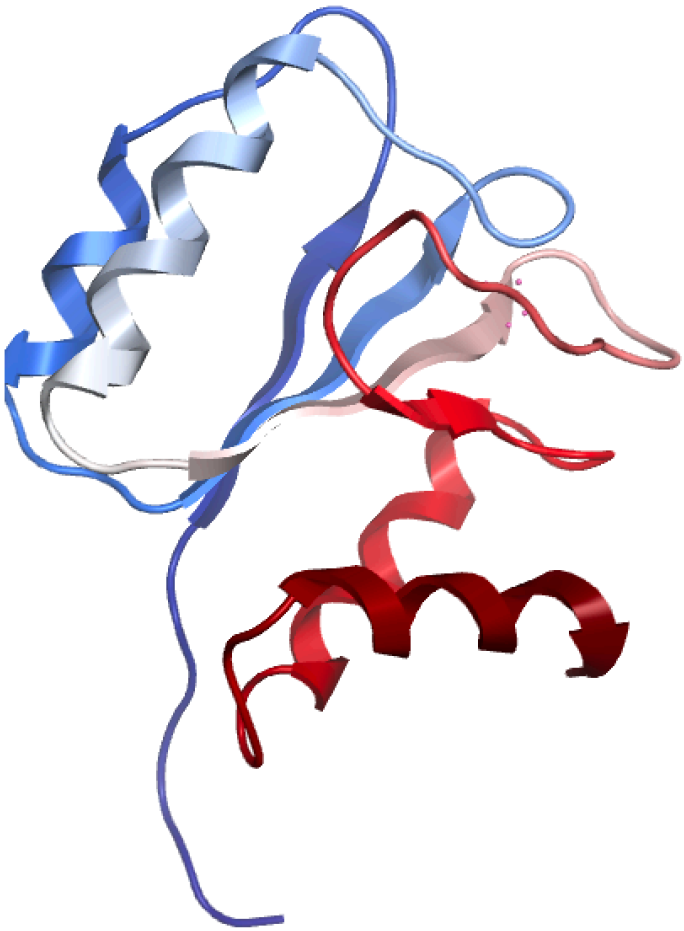


# How to draw TOPS

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.

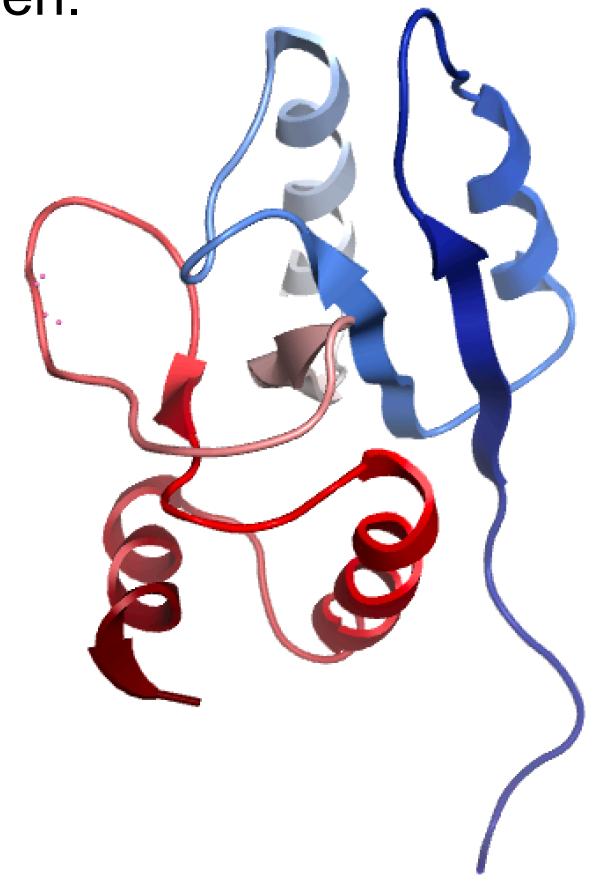




# How to draw TOPS

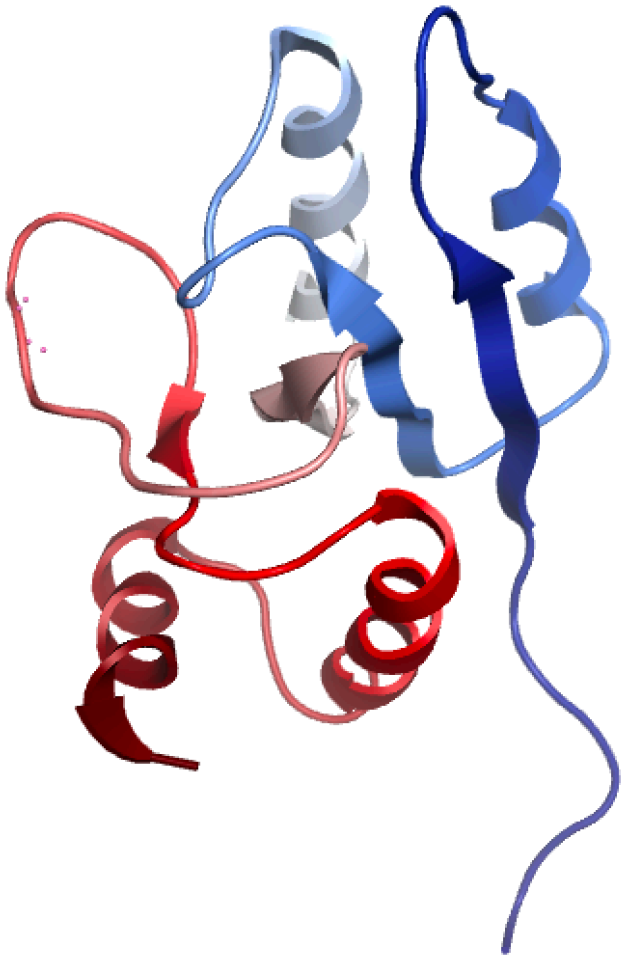
Line up the molecule along the beta sheet, if present.

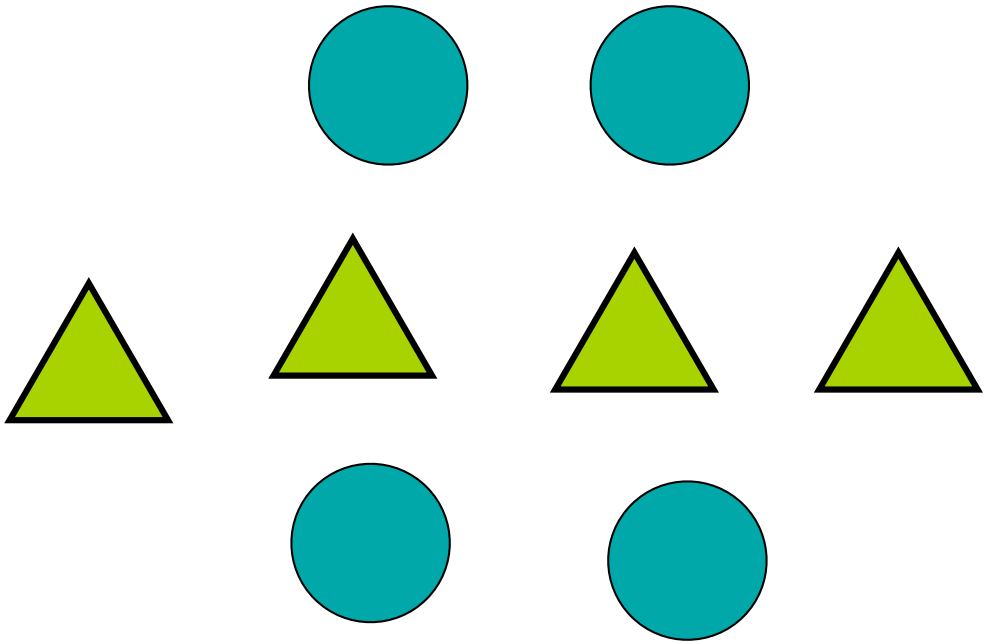
Otherwise choose a direction so that secondary structures are mostly perpendicular to the screen.



# TOPS diagram

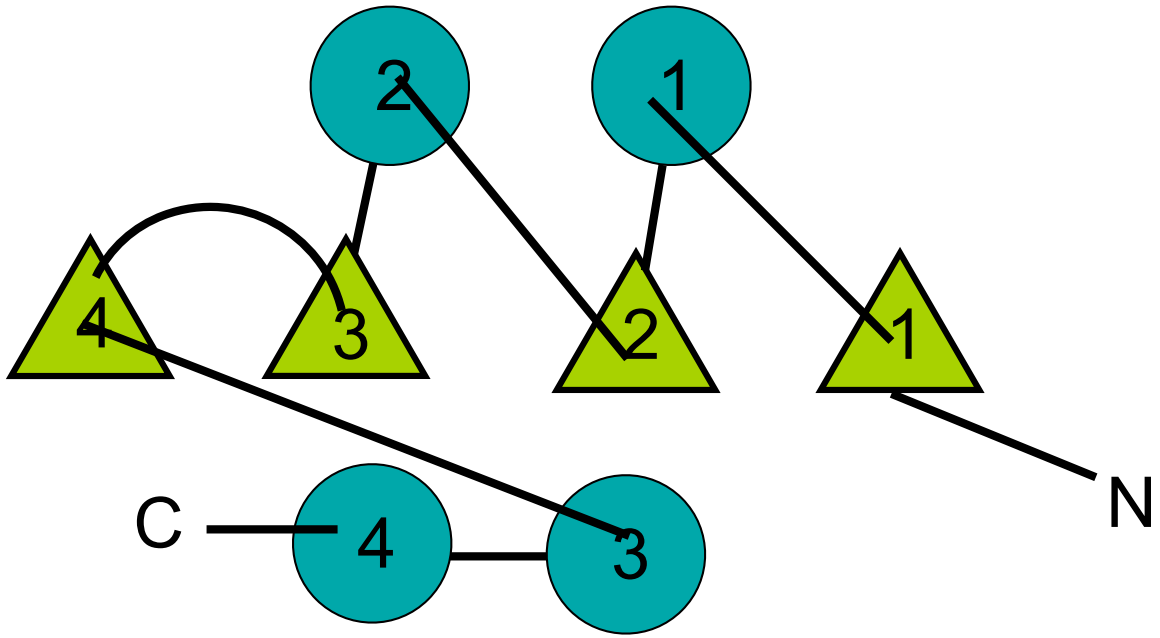
- Draw secondary structures first.





# TOPS diagram

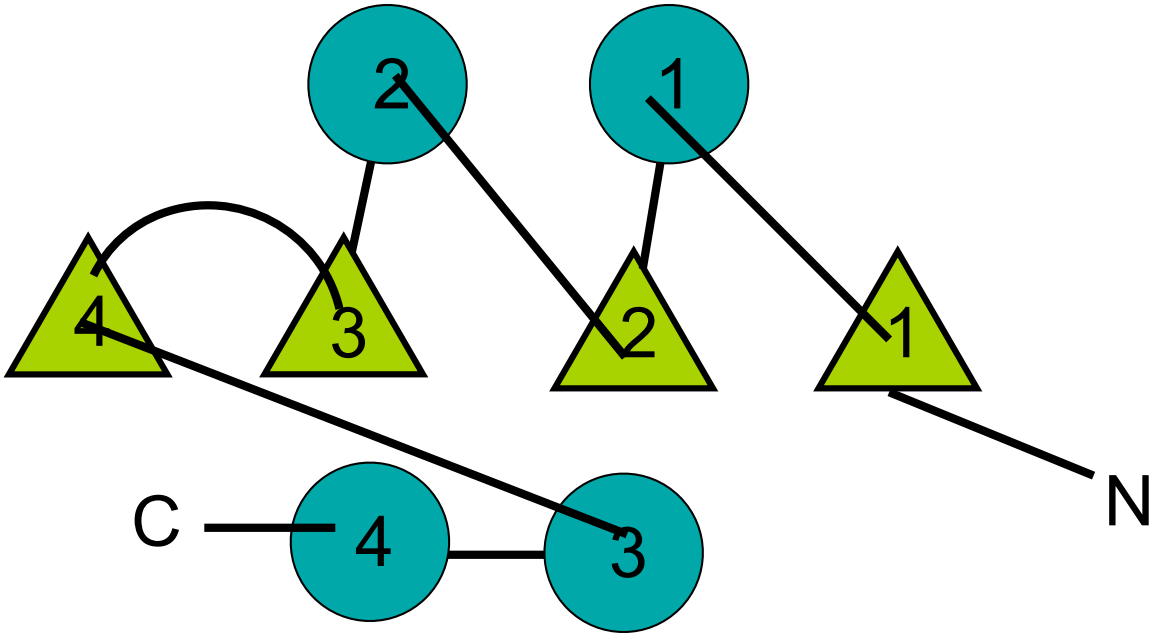
- number them and connect




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

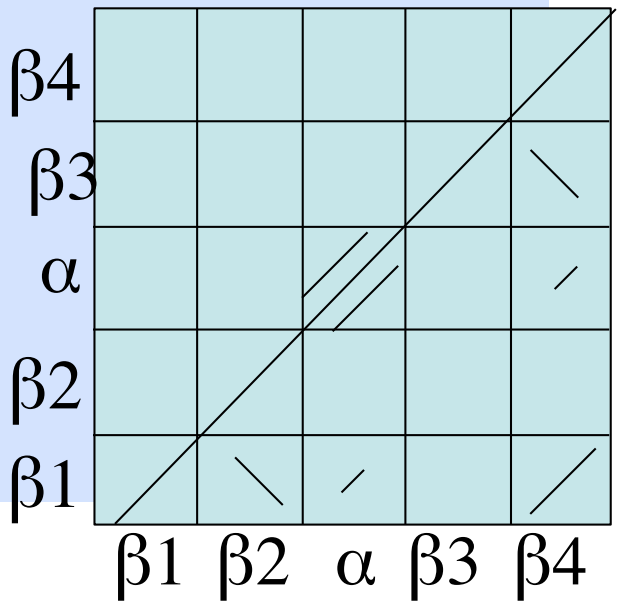
**Ribbon | Style: oval**

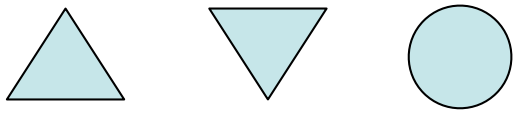
**Ribbon | Color : structure**

Identify SSEs. Draw triangles and circles

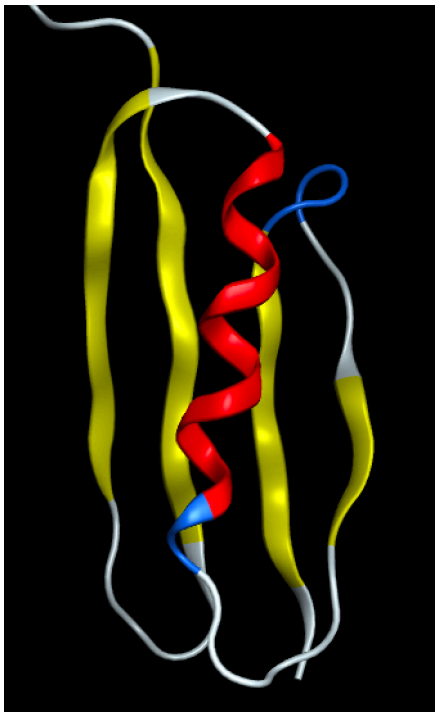
**Ribbon | Color : terminus**

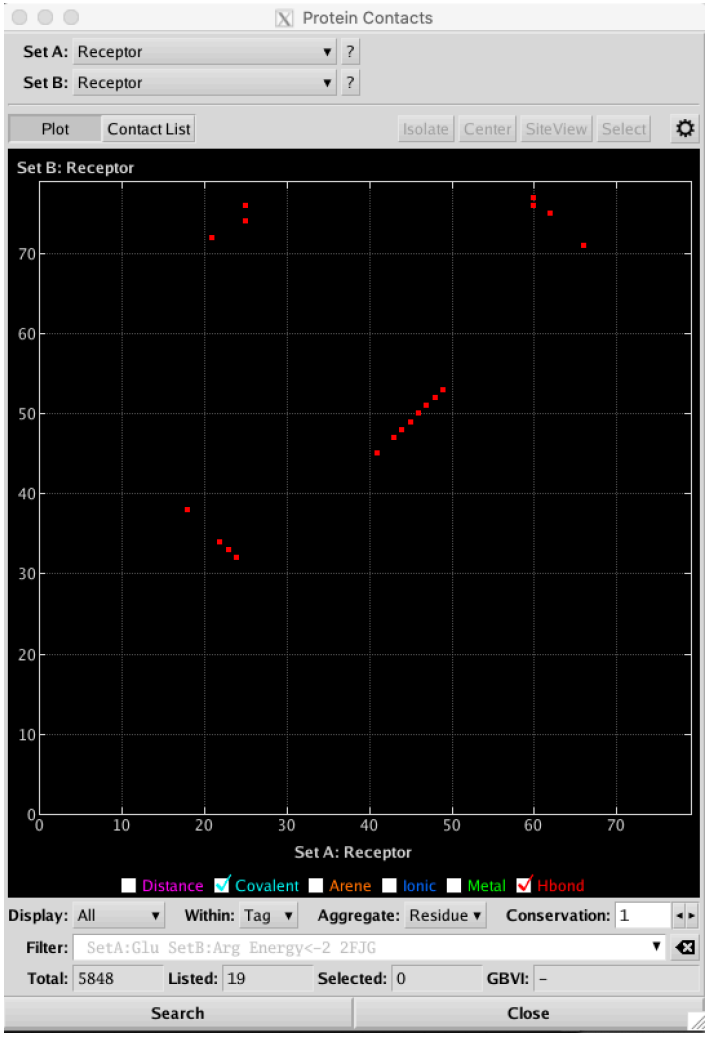
Number and connect SSEs.



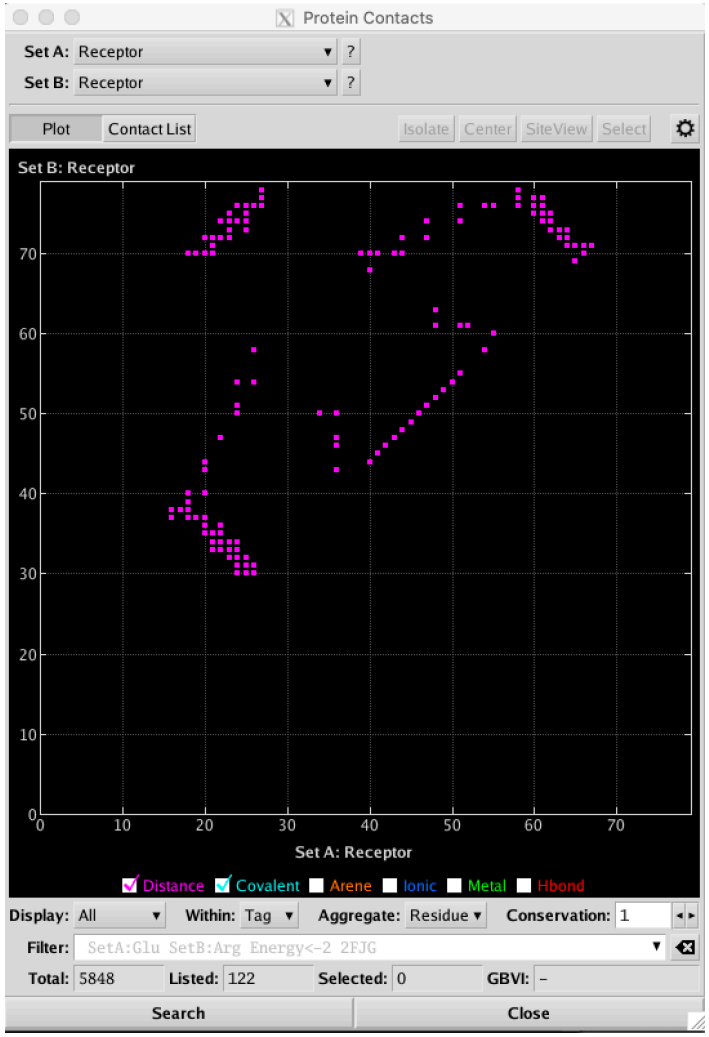



# 2ptl contact map






H-bonds

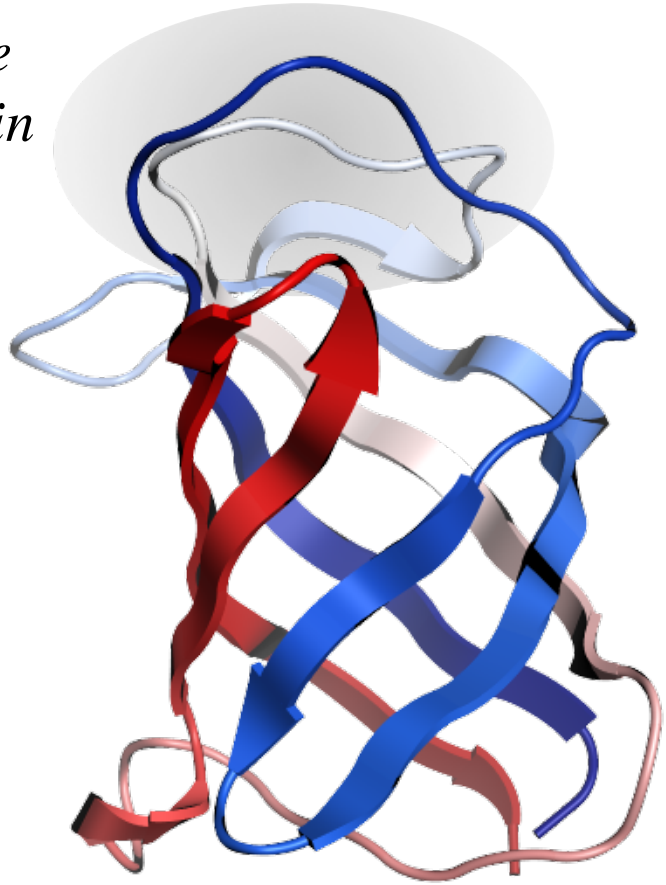


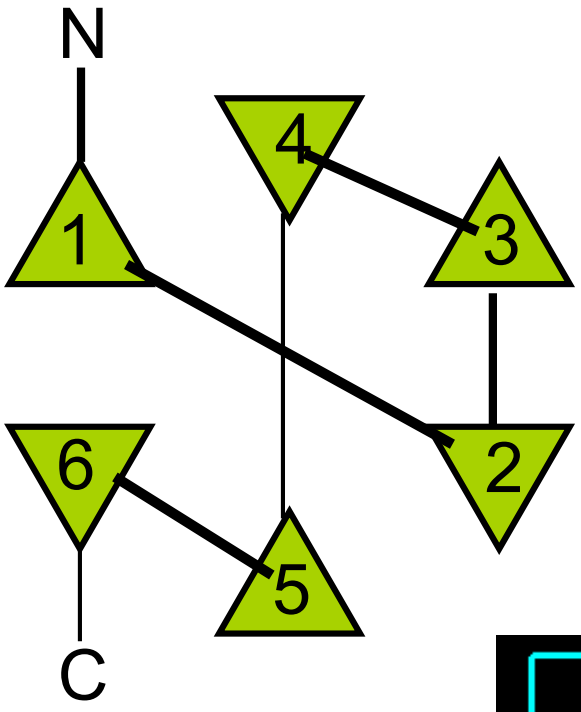

Distance cutoff

# TOPS diagram of a beta barrel

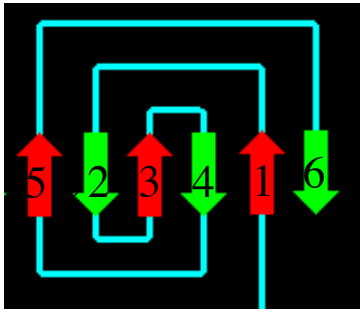
- *all anti-parallel barrel, closed; n=6, S=10; greek-key*

*loops are 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 3.3: TOPS cartoon of beta barrel

Open MOE. Open Green Fluorescent Protein

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

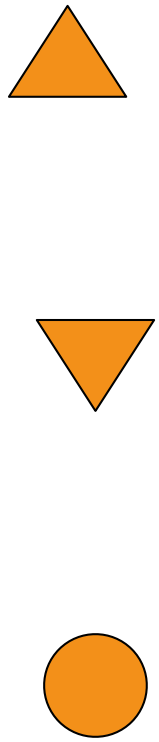
**Ribbon | Style: oval**

**Ribbon | Color : structure**

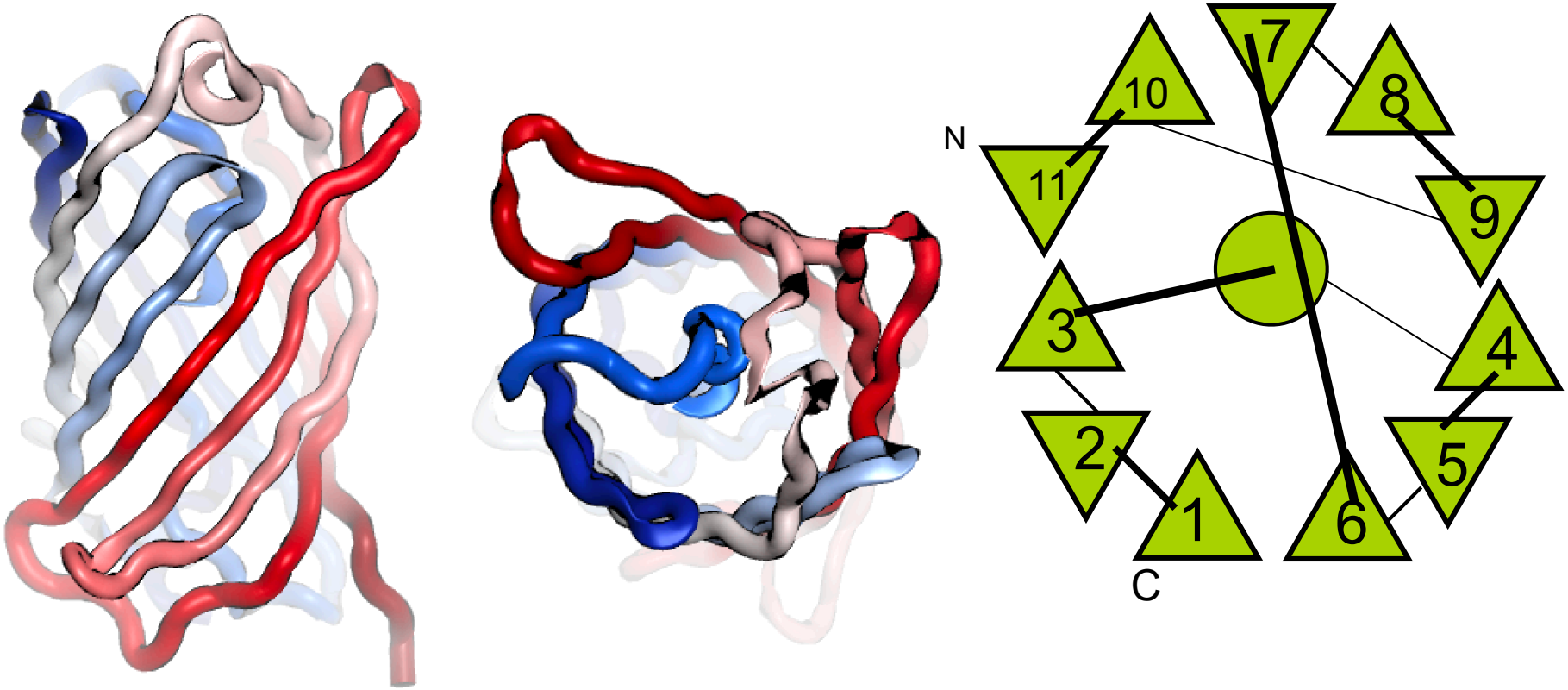
Identify SSEs. Draw triangles and circles

**Ribbon | Color : terminus**

Number SSEs. Draw connections. Label termini.

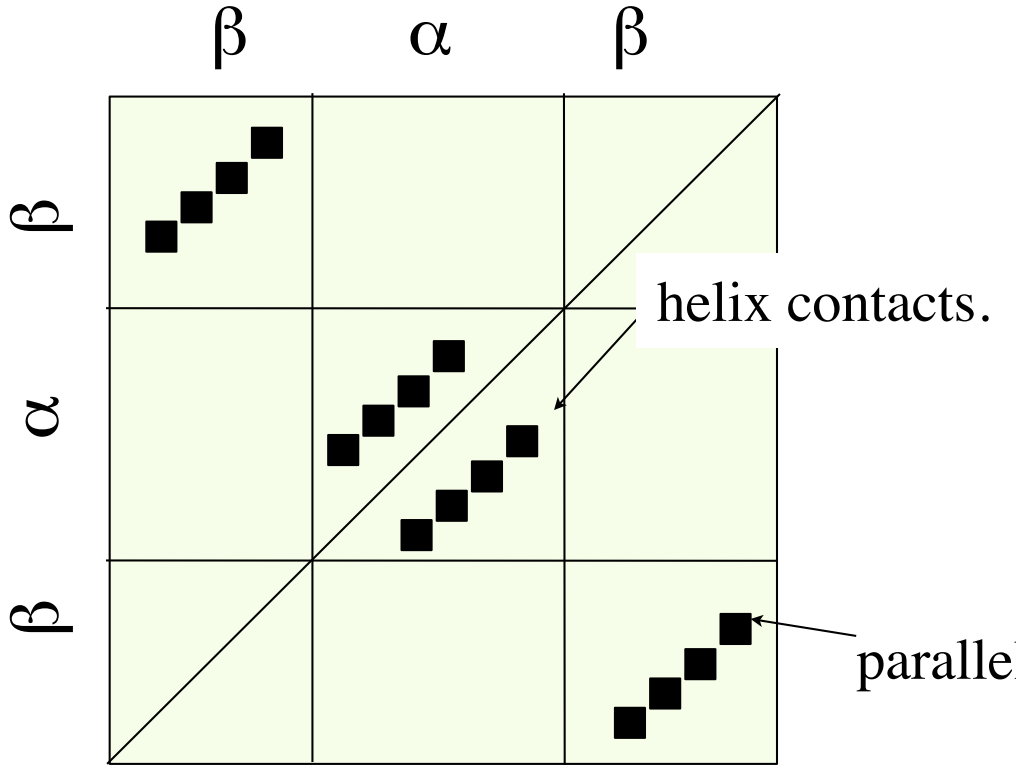


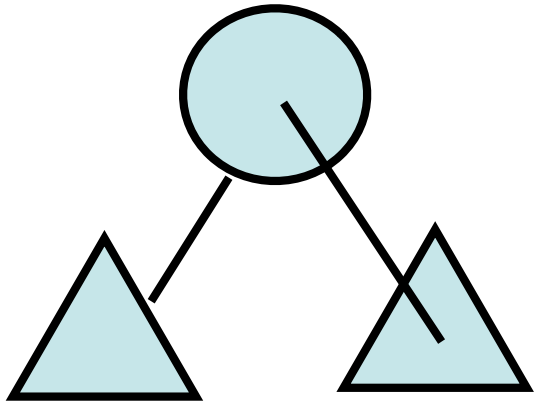
- *Mostly anti-parallel barrel, closed, containg a helix; n=11*
- *strand order 1 2 3 11 10 7 8 9 4 5 6*




GFP-like fluorescent proteins

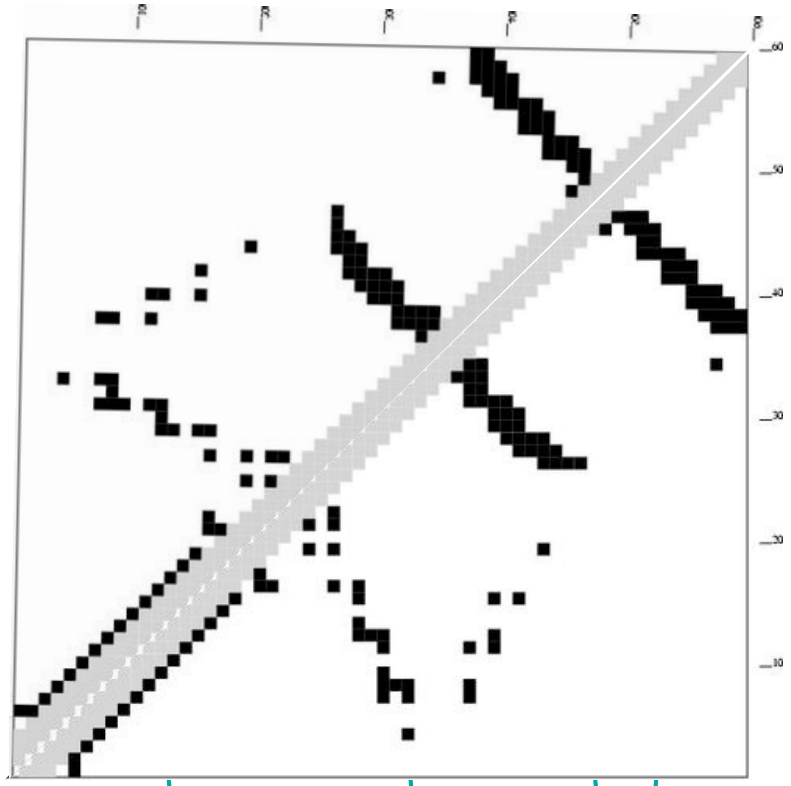
# TOPS and contact maps



A "contact map" for a βαβ unit.

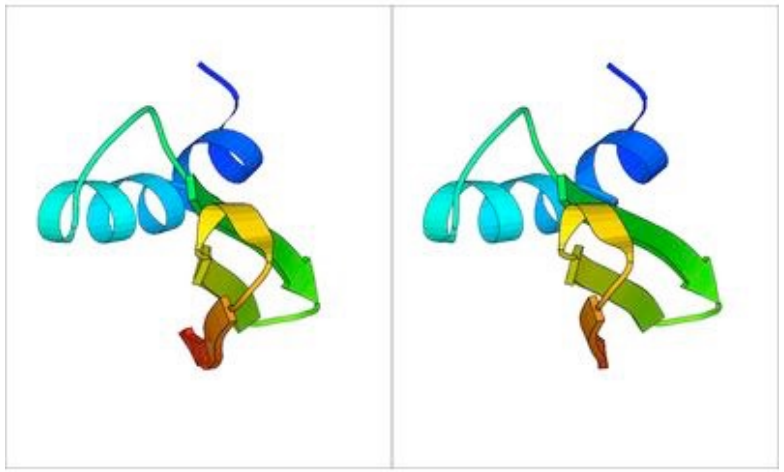
# Contact map for a small protein



alpha-helix

contacts between
helix and sheet

beta-hairpins

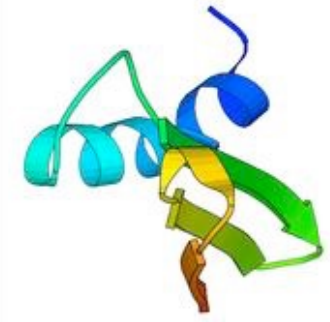


A contact map contains enough information to build the 3D structure within ~2Å RMSD.

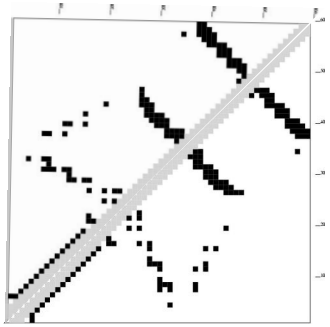
# A simplified contact map based on SSEs

(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.

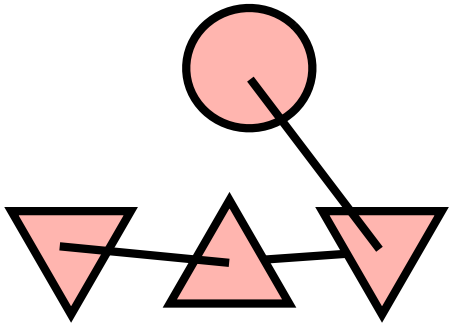
Structure



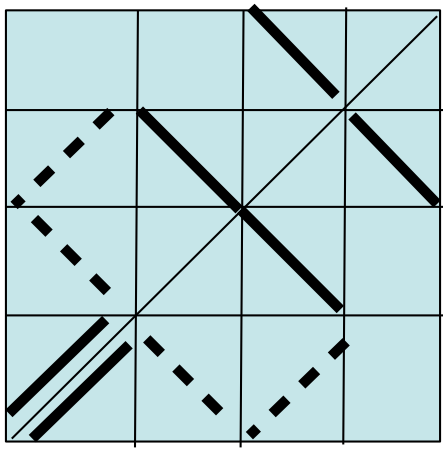
contact map



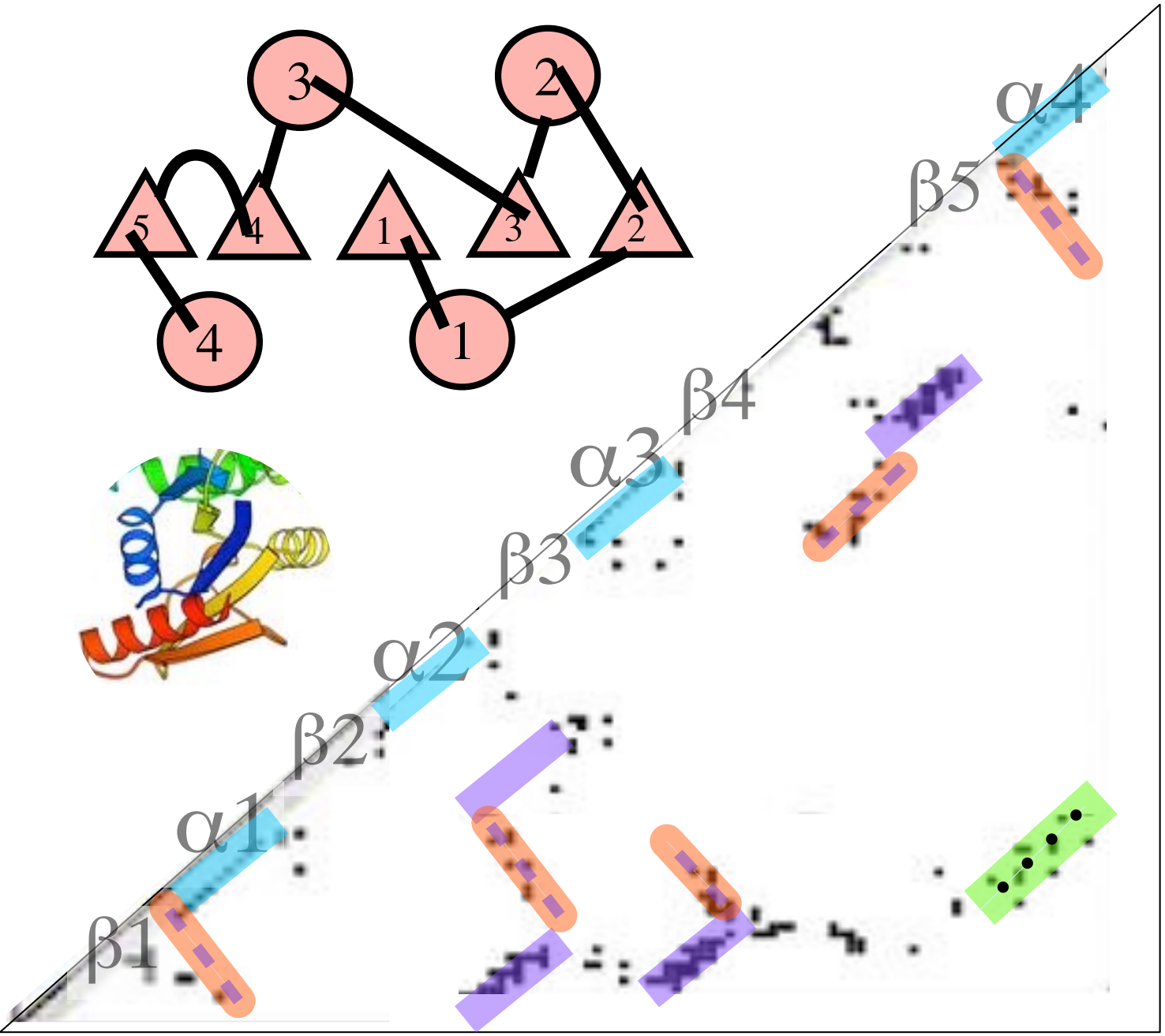
TOPS



simplified contact map



# Simplified contact map to TOPS diagram



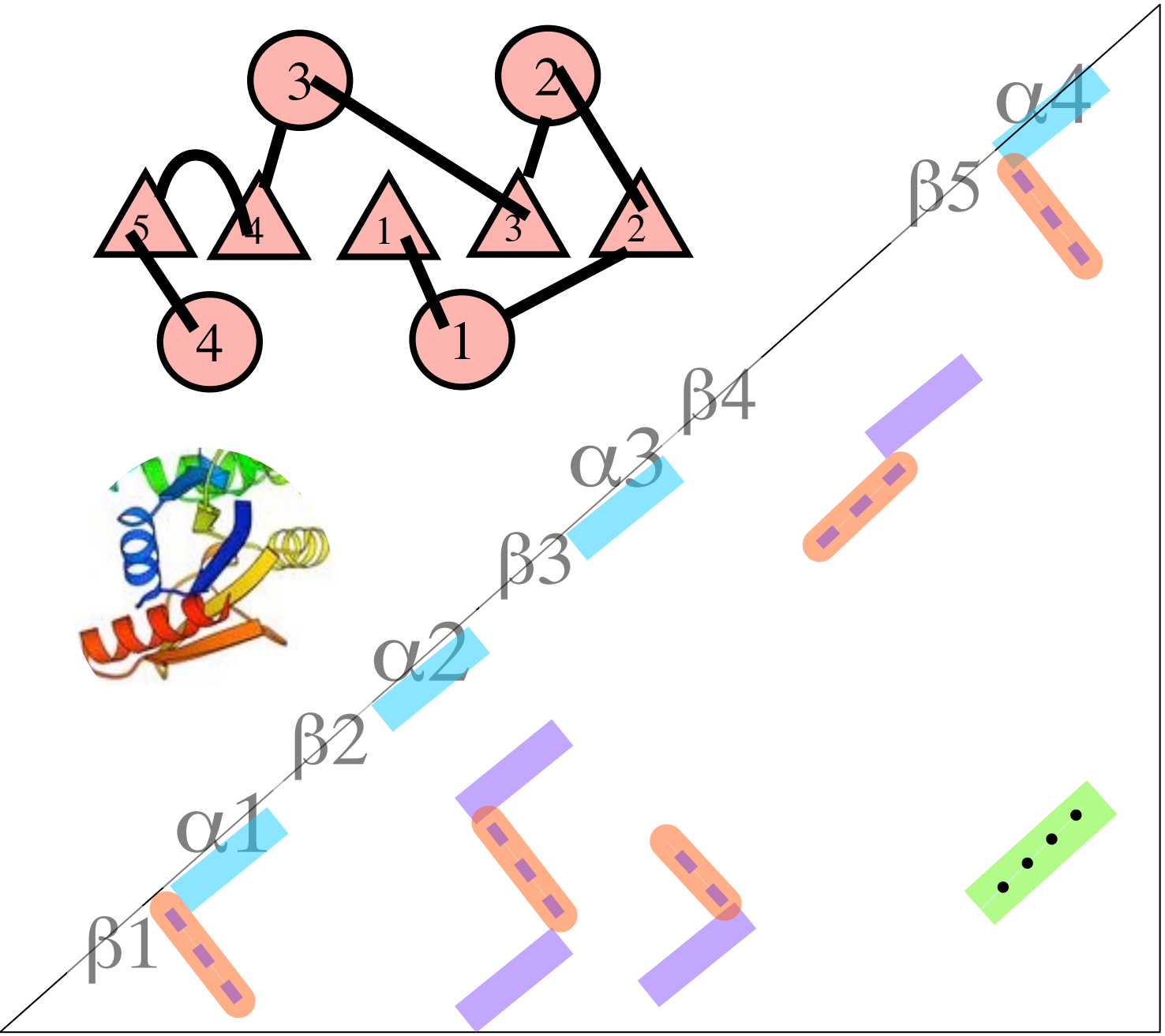

alpha i->i+4

beta-beta

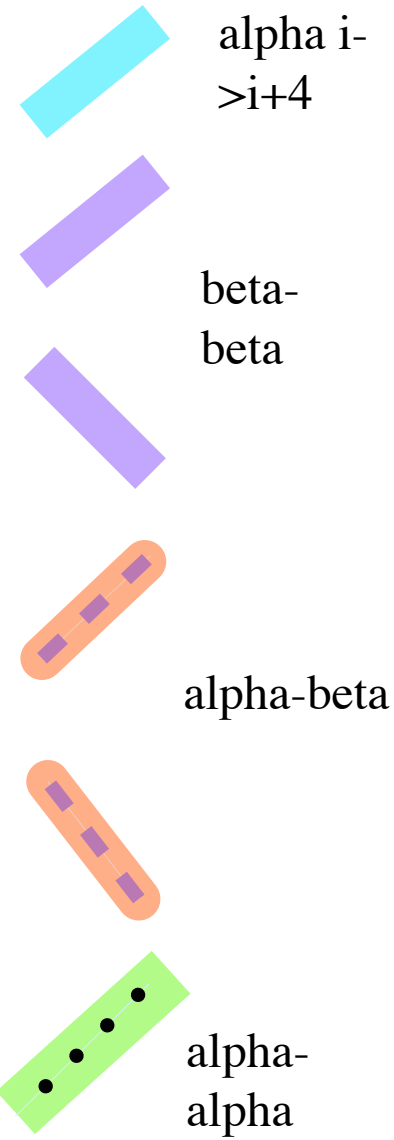
alpha-beta

alpha-alpha

# Simplified contact map to TOPS diagram

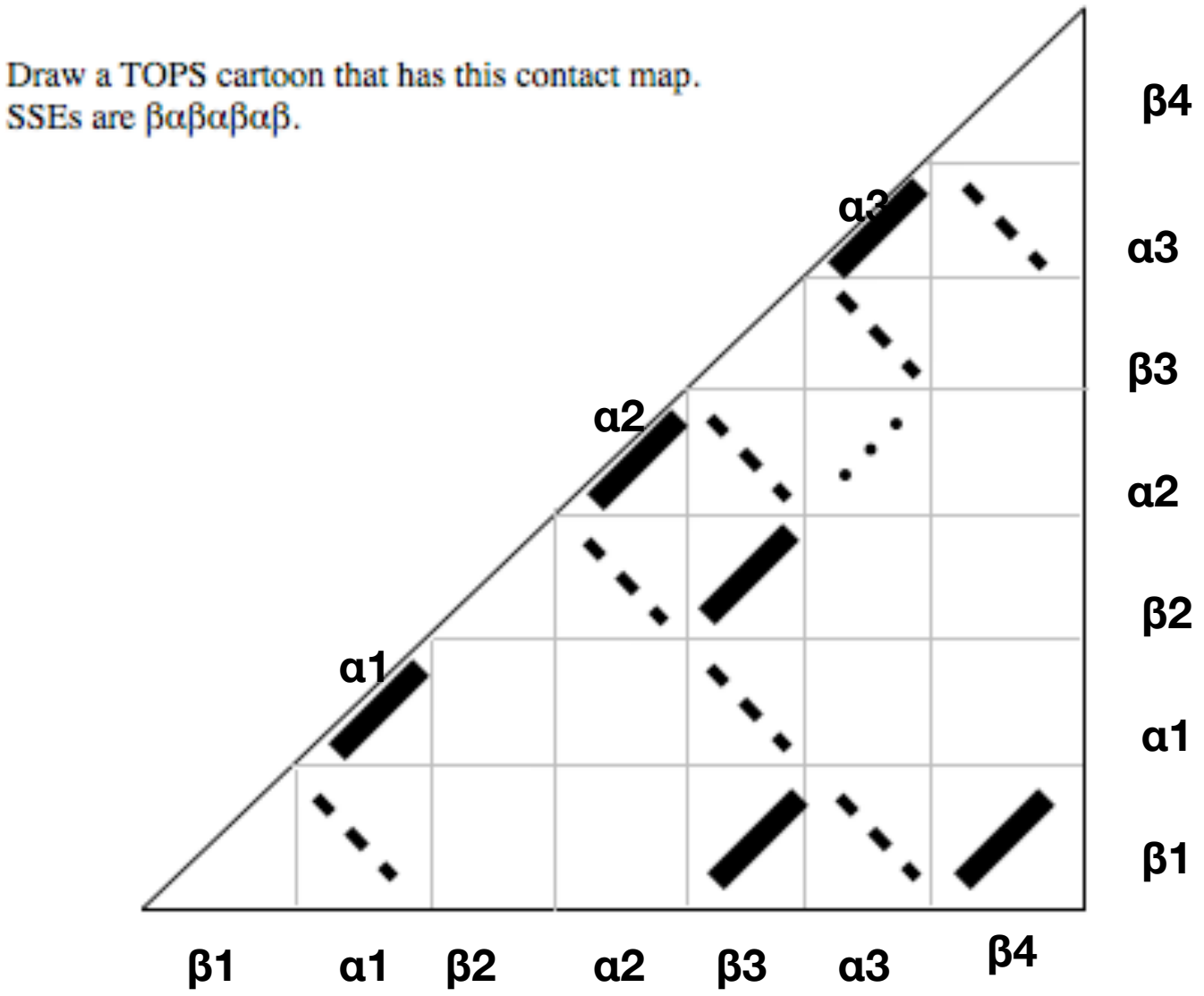




# Exercise 4.4: TOPS from contact map

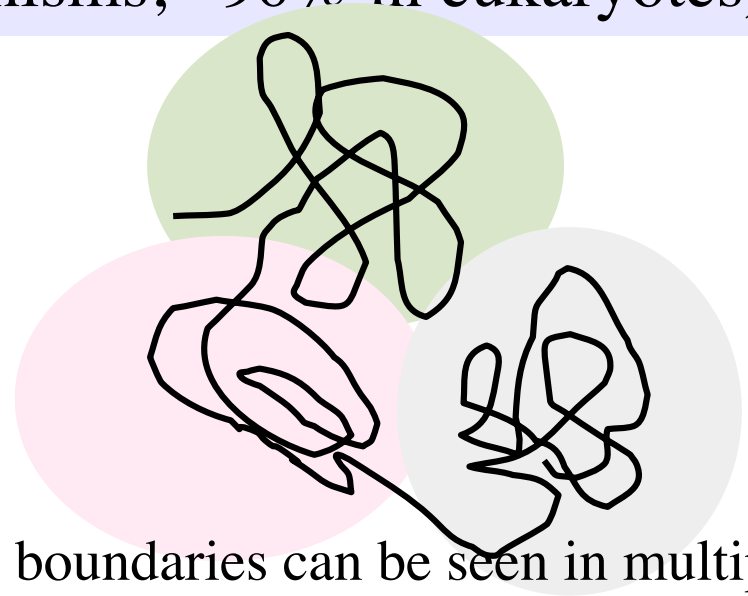
Do this on paper.



# Many 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).

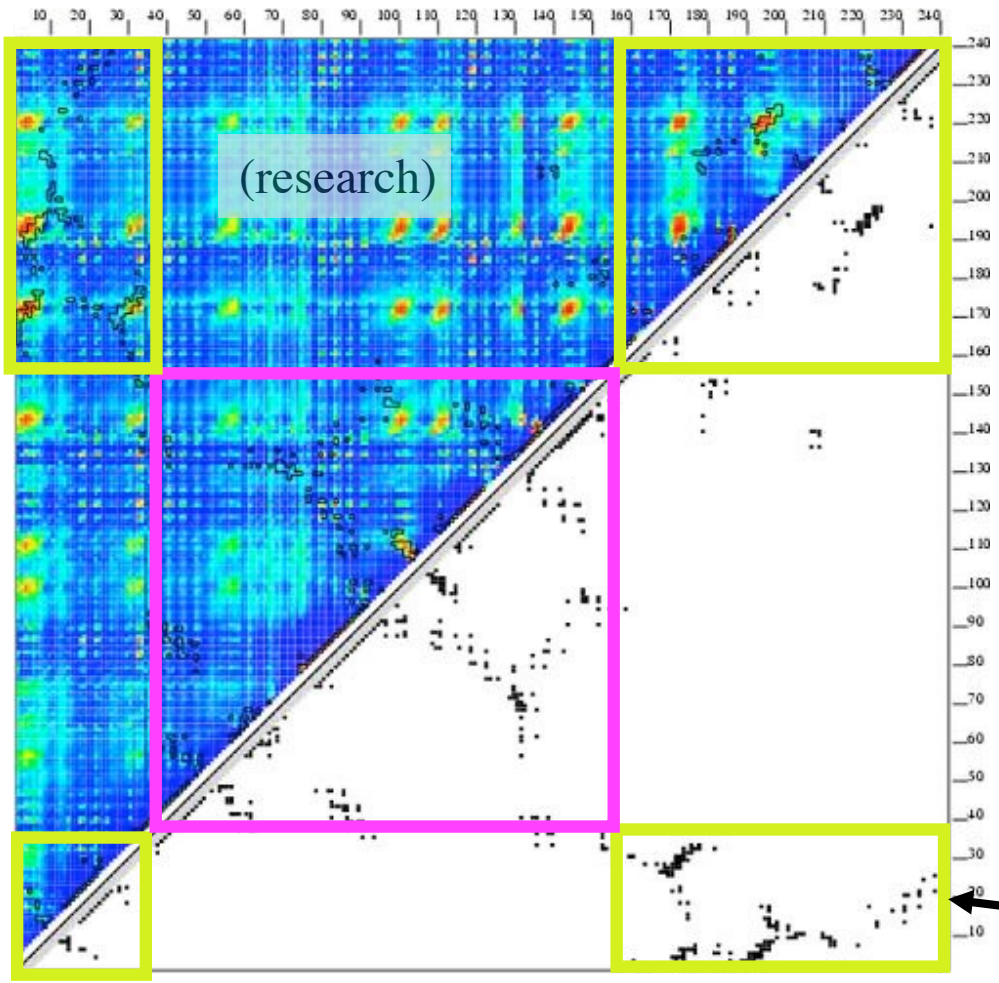


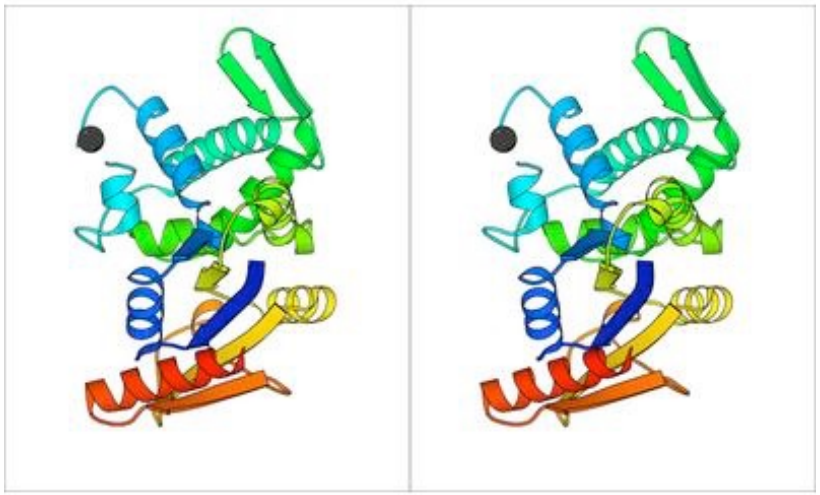
Domain boundaries can be seen as "weak" connections in the structure.

"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.

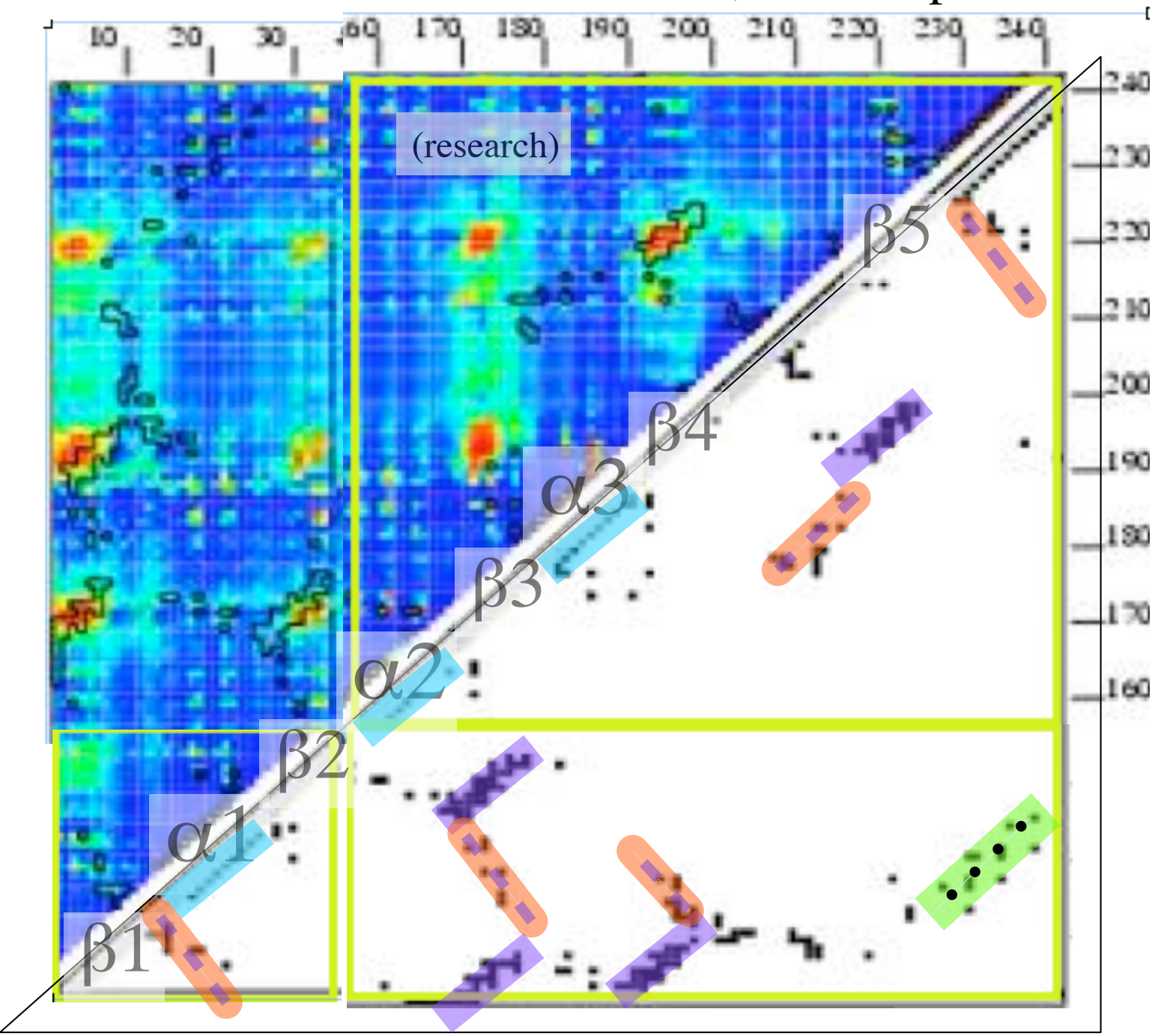
# Seeing two domains within a contact map



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 3.1: 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.

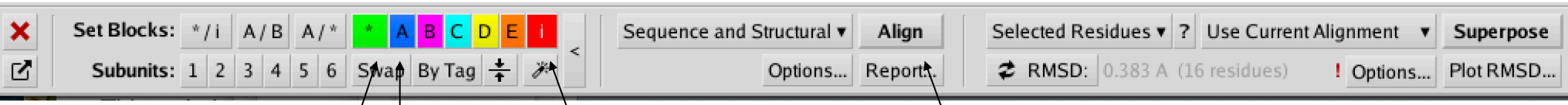
in-class

# Exercise 3.2: 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 3.3: 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 SARS-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 **homework1.pdf**
- Turn in on LMS as PDF file.

# 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

- Class
- Architecture
- Topology
- Homology

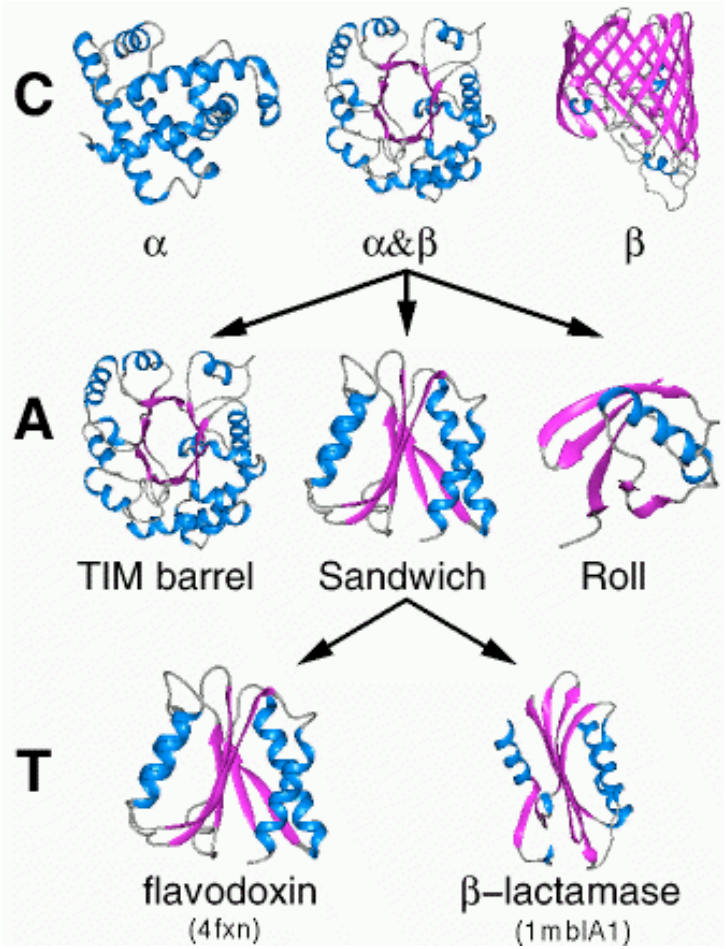
# CATH

**Class** = like SCOPe "Class"

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

**Topology** = like SCOPe "Fold".

**Homology** = like SCOPe "Superfamily".




https://www.cathdb.info/

# 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. |