Discovering the general architecture of protein families with OverProt

MUNI SCI National Centre for Biomolecular Research

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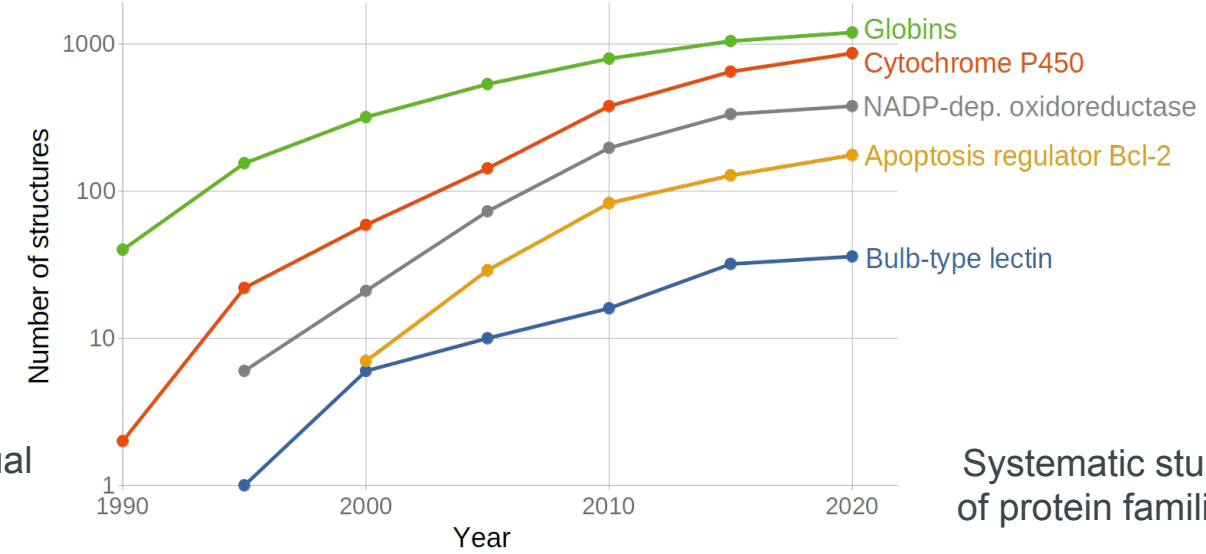
Introduction

- Protein structures → help us understand the function
  - Today > 190 000 experimental structures
- Similar protein structures form **protein families**
  - CATH database – 6 631 families
  - Families are getting bigger

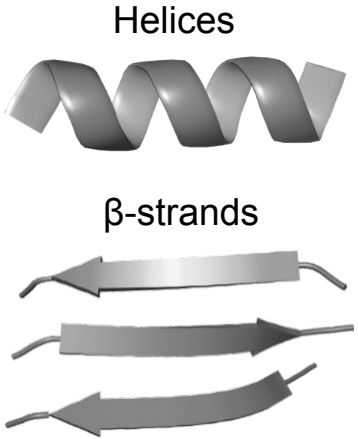


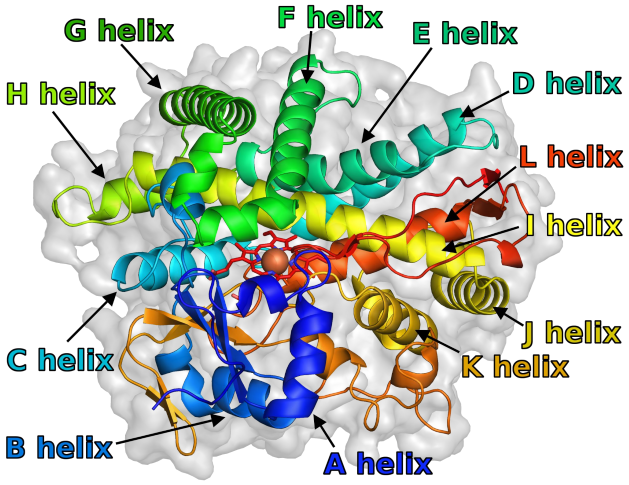
Study of individual structures

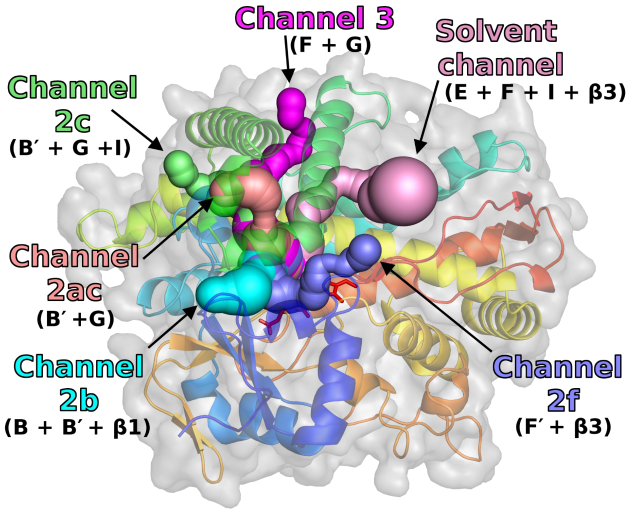
Systematic study of protein families

Secondary structure elements (SSEs)

- Characteristic arrangement in each protein family
  - ➜ “General architecture” of the family
- Can serve as landmarks
  - Help us orient in the structures
  - Help us locate the key regions (active sites, channels…)





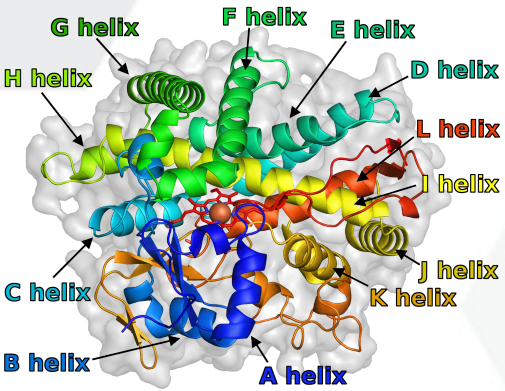


SecStrAnnotator

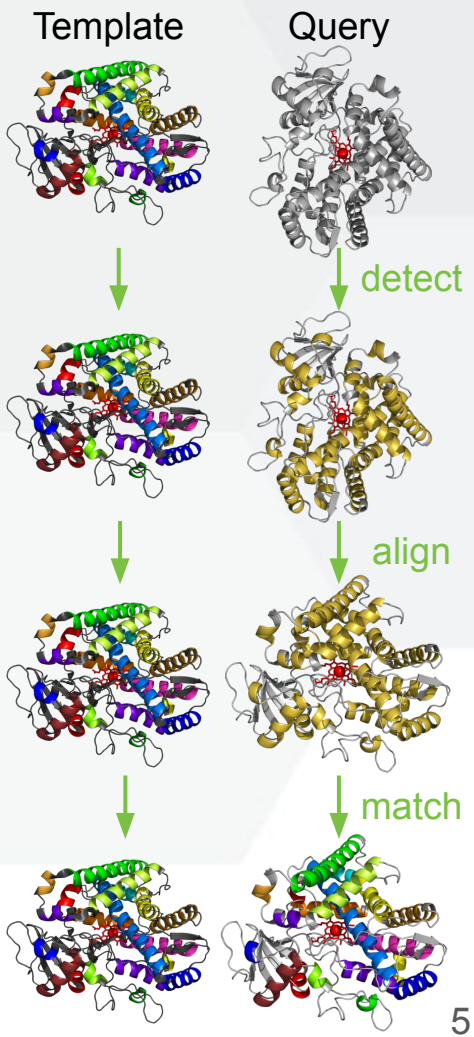
SSE annotation

= Labelling of SSEs, consistent throughout the family

- Many protein families have traditional annotations
  - Performed manually :(



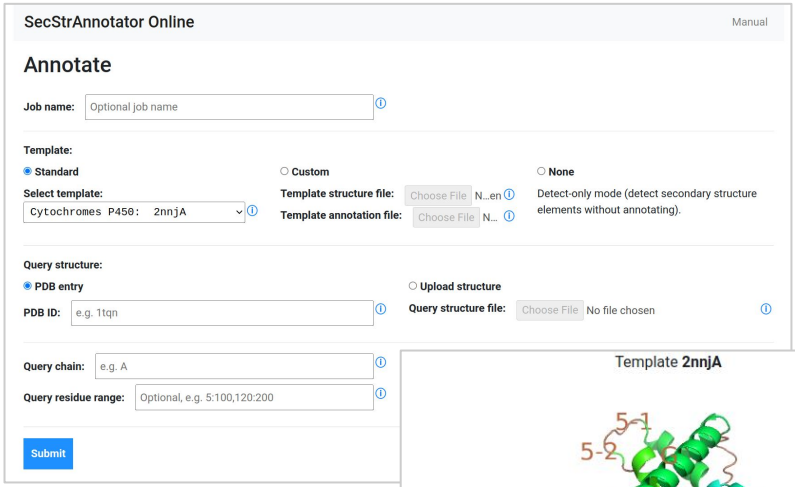
- Our solution – **SecStrAnnotator**
  - Annotation based on a provided template

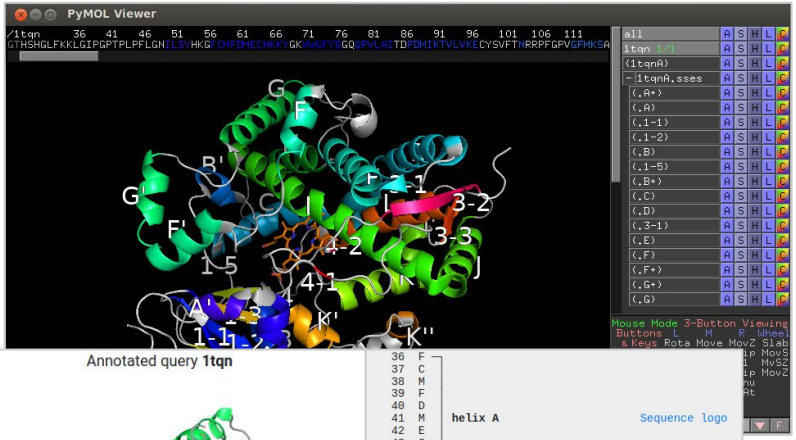


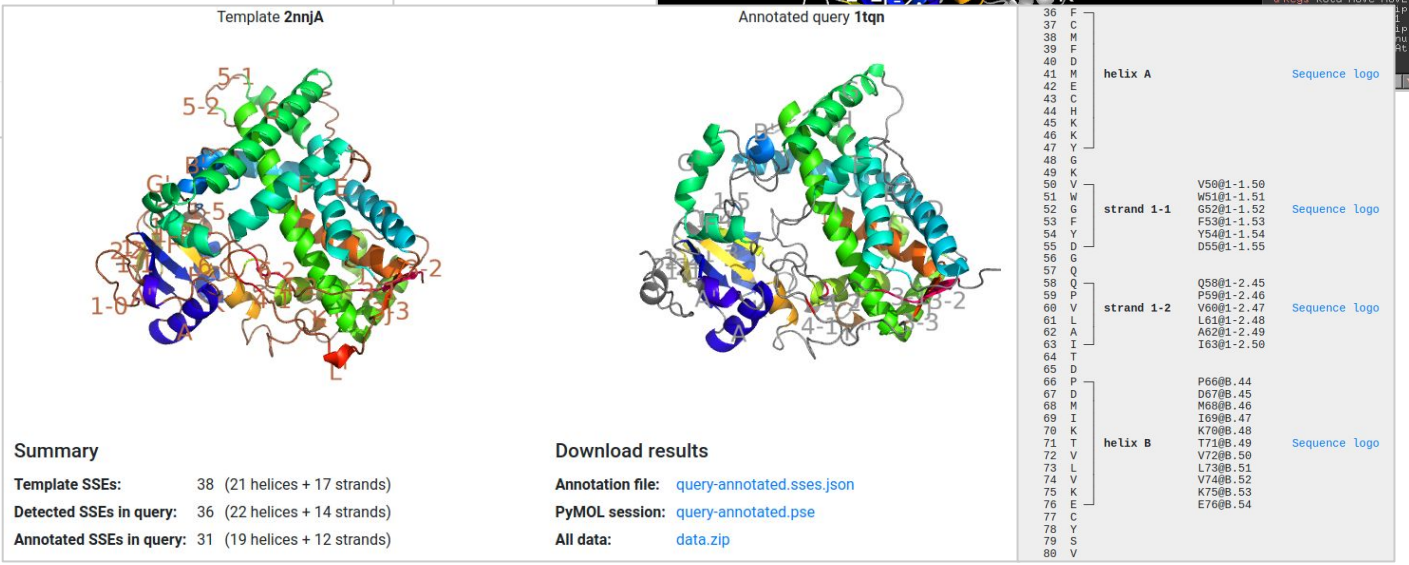
Midlik A. et al. (2019) Automated family-wide annotation of secondary structure elements. In Kister A.E. (ed.) *Protein Supersecondary Structures*, vol. 1958, pp. 47–71.

Midlik A. et al. (2021) Uncovering of cytochrome P450 anatomy by SecStrAnnotator. *Scientific Reports*, **11**, 12345.

SecStrAnnotator online – sestra.ncbr.muni.cz



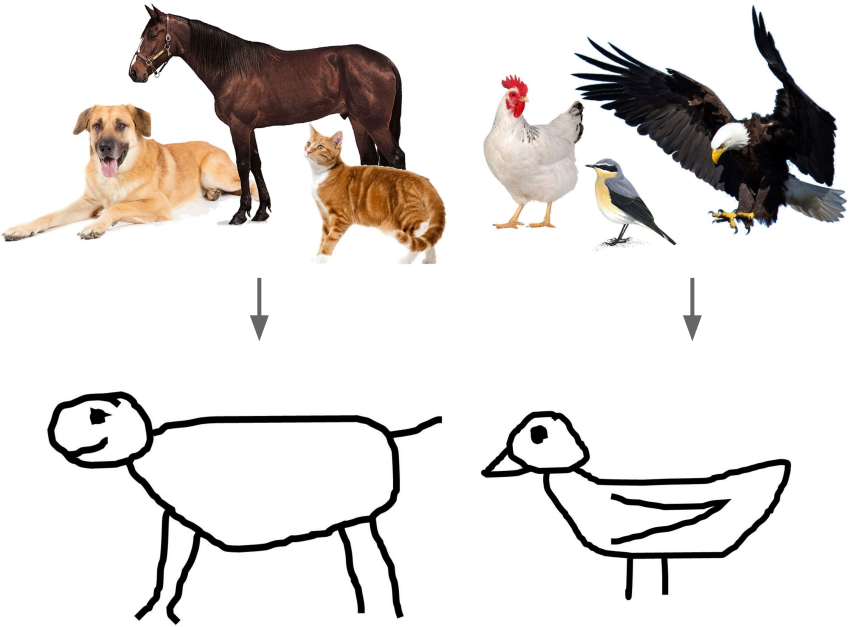




OverProt

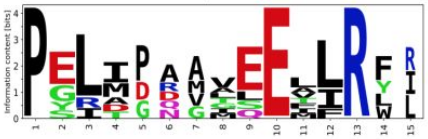
What is the “general architecture” of a family?

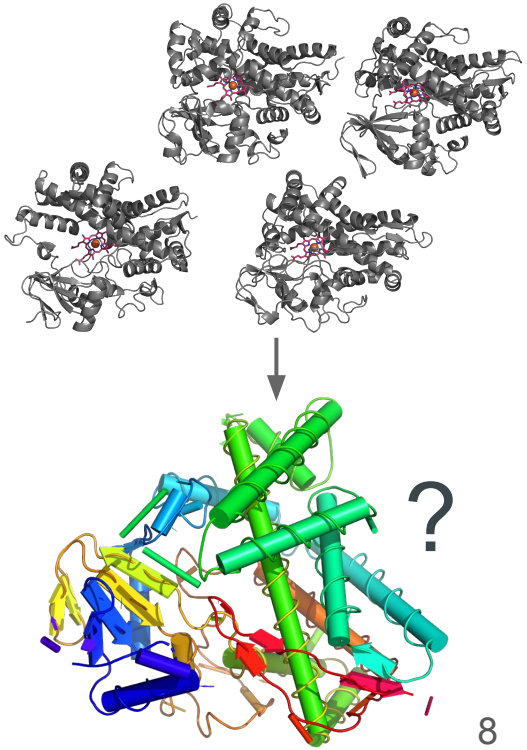
- Task: extract and visualize the characteristic features of a family



PGLIPAMVSETIRWL
ERIDAATEELLR
PELANAAEEVLRW
PYLDQVMQEILRLI
PELMGEEALRFR

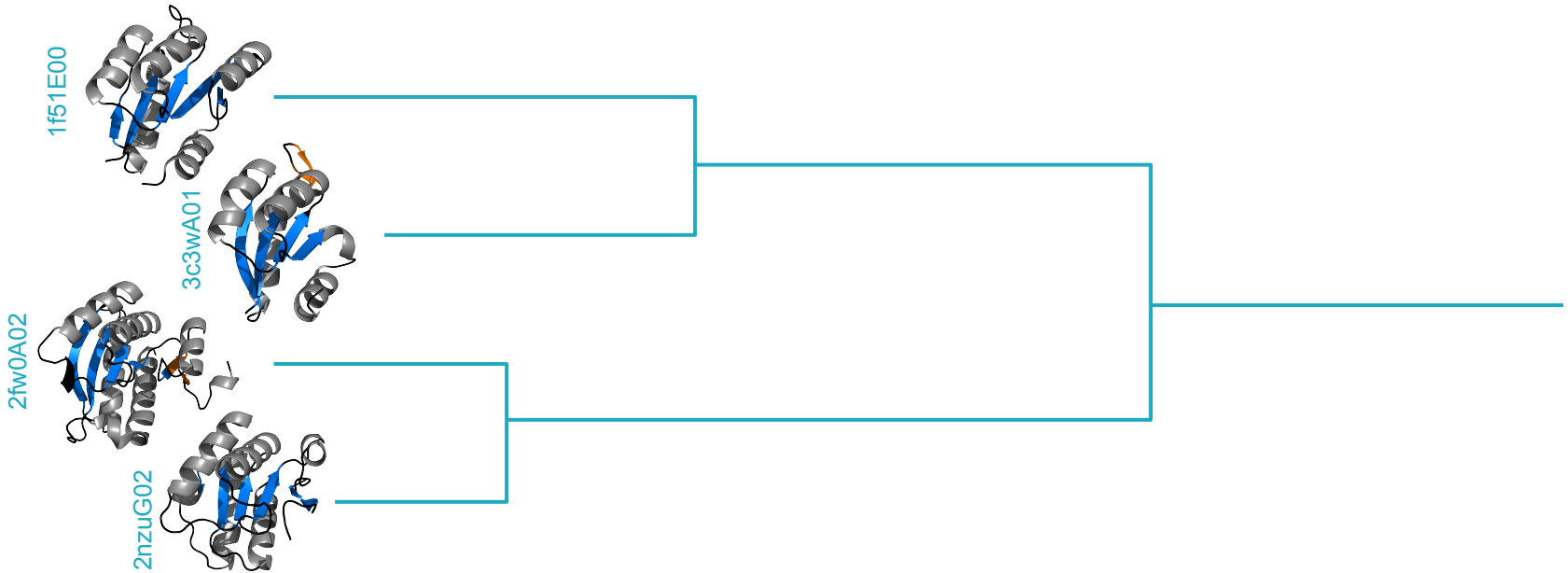
PGLIPAMVS**E**TI**R**WL
-ERIDAATE**E**LL**R**--
PELA-NAAE**E**VL**R**W-
PYLD-QVMQ**E**IL**R**LI
PELM---GE**E**AL**R**FR





Our solution: OverProt

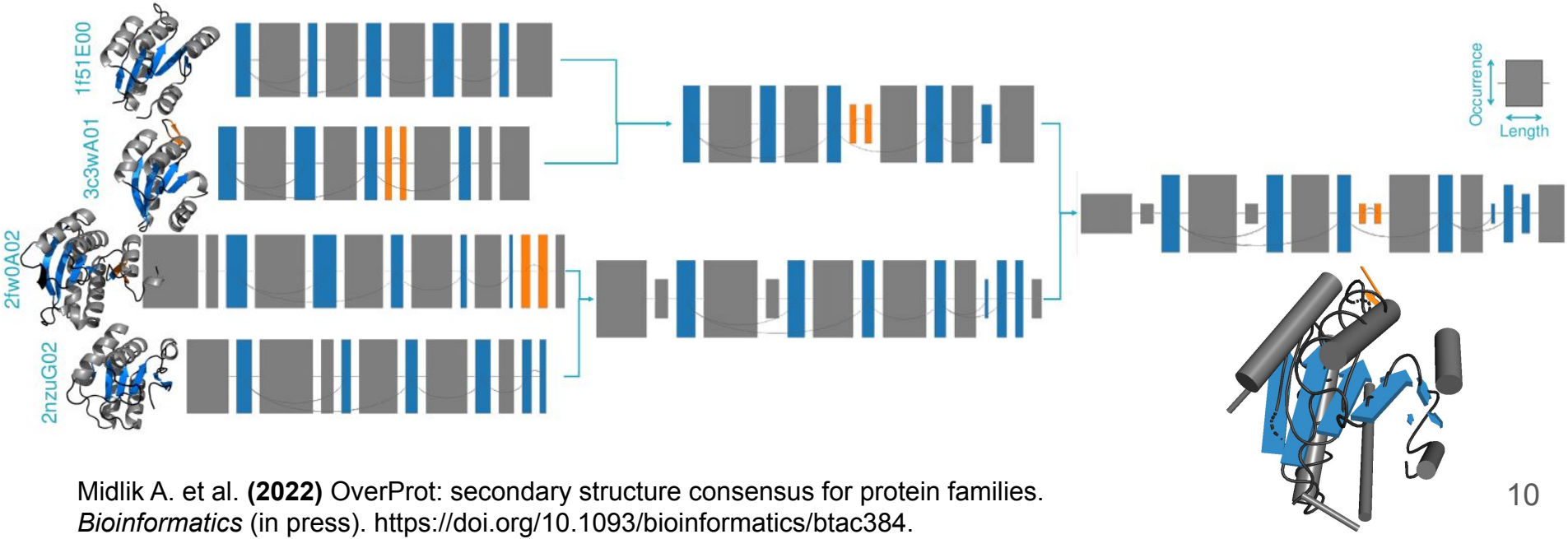
- Step 1: Align
- Step 2: Build the guide tree (agglomerative clustering of 3D domains)



Midlik A. et al. **(2022)** OverProt: secondary structure consensus for protein families. *Bioinformatics* (in press). https://doi.org/10.1093/bioinformatics/btac384.

Our solution: OverProt

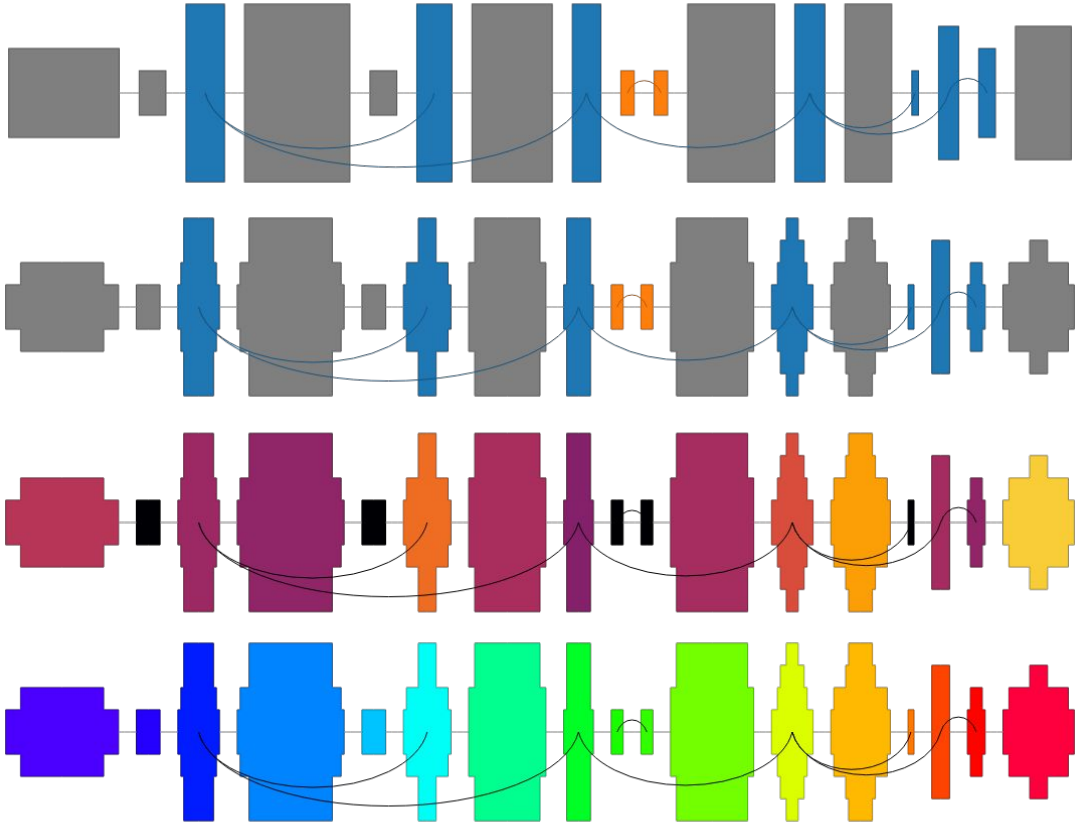
- Step 1: Align
- Step 2: Build the guide tree (agglomerative clustering of 3D domains)
- Step 3: Merge the SSEs through the guide tree



Midlik A. et al. **(2022)** OverProt: secondary structure consensus for protein families. *Bioinformatics* (in press). https://doi.org/10.1093/bioinformatics/btac384.

Alternative visualizations

- Classic
- Length distribution
- 3D variability
- Chainbow



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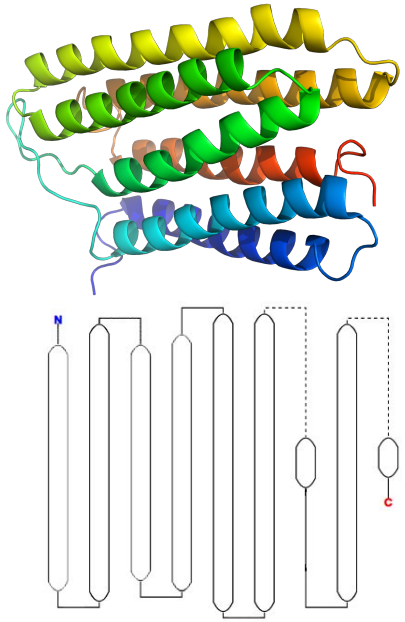
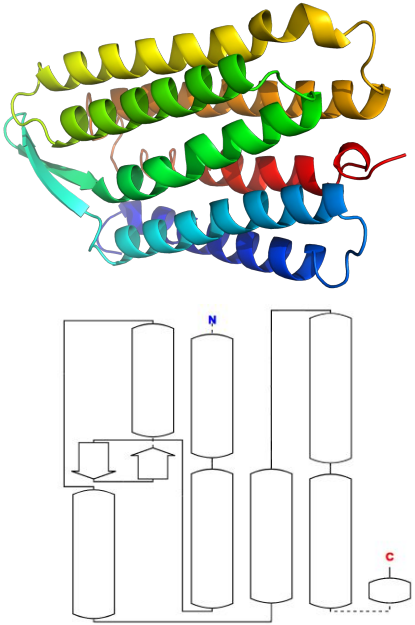
2DProts

SSE visualization in 2D diagrams

- Existing diagrams in PDBe:
  - Ignore 3D arrangement
  - Ignore protein similarity

1at9



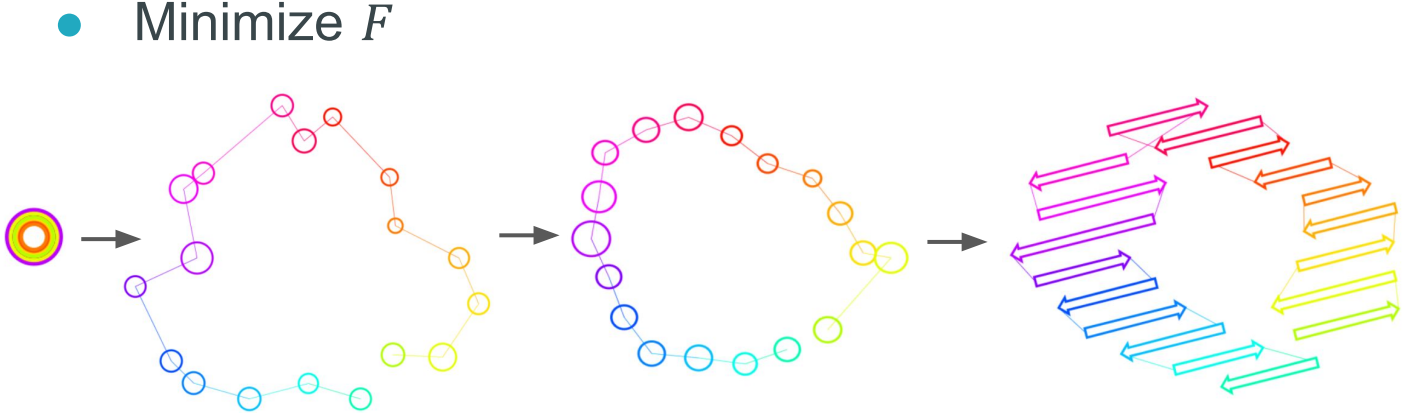


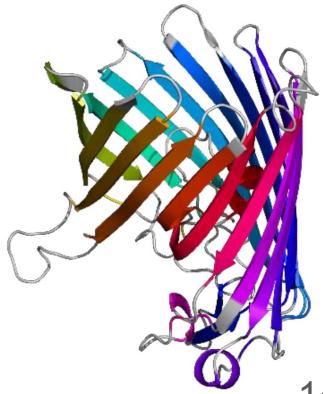
5zim

Our solution: 2DProts

- Preparation
  - OverProt creates SSE consensus for the family → annotation template
  - SecStrAnnotator annotates all protein domains in the family
- Objective function $F = \sum_{s_1,s_2 \in S_p} |d_{3D}(s_1,s_2) - d_{2D}(s_1,s_2)| \left(L(s_1) + L(s_2)\right) + \sum_{s \in S_p \cap S_0} |r(s) - r_0(s)|\, L(s) \frac{|S_p|}{20}$

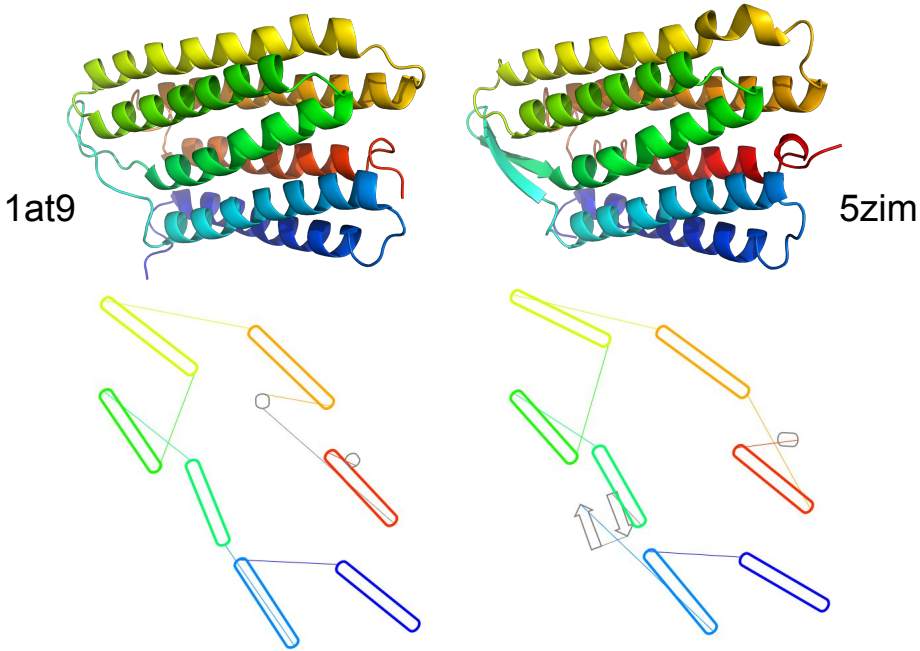
  Deviation of 2D vs 3D — Deviation of 2D vs family template 2D
- Minimize F



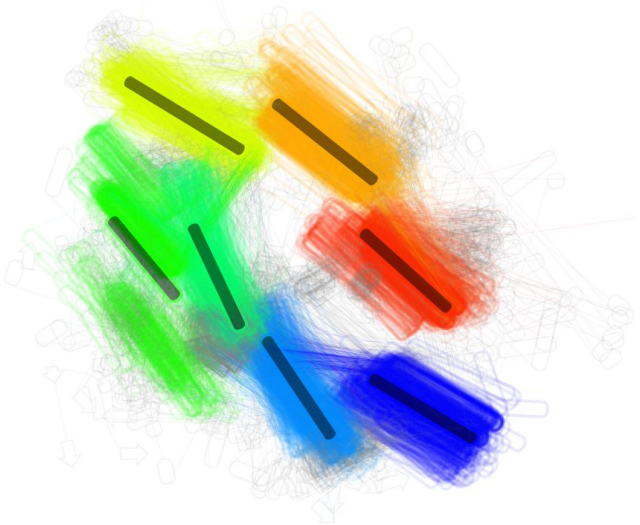


Example family

- 1.20.1070.10 Rhodopsin 7-helix transmembrane proteins



Family multi-diagram

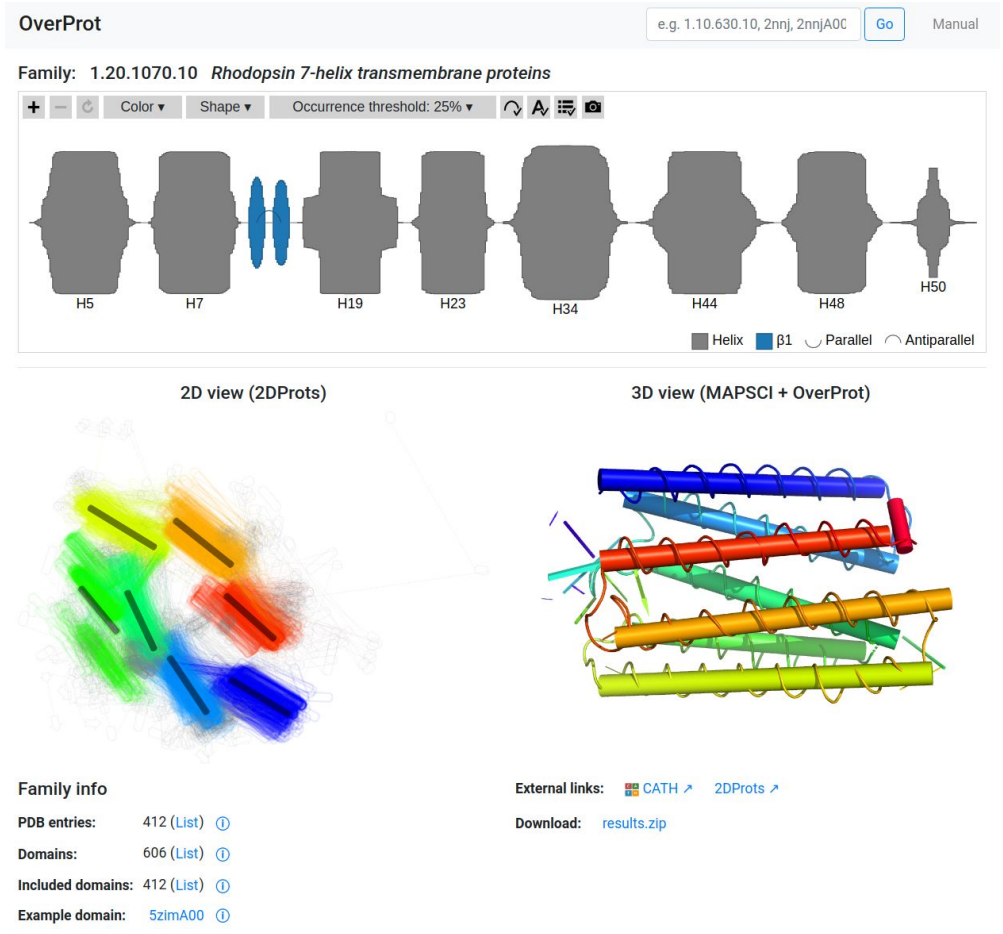


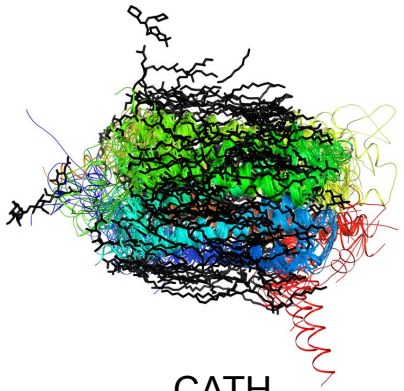
Hutařová Vařeková I. et al. (2021) 2DProts: database of family-wide protein secondary structure diagrams. *Bioinformatics*, **37**, 4599–4601.

Availability

	SecStrAnnotator	OverProt	2DProts
Desktop version	gitlab.com/midlik/SecStrAnnot2 (all platforms via .NET 6.0)	gitlab.com/midlik/overprot (all platforms via Docker/Podman)	
Online version	sestra.ncbr.muni.cz – Cytochrome P450 template – Custom template – Detect SSEs (no annotation)	overprot.ncbr.muni.cz Job calculations up to 500 protein domains	2dprots.ncbr.muni.cz Job calculations up to 30 protein domains
Database	1 family 1 855 domains	6 631 families > 470 000 domains (2.5 CPU days)	6 631 families > 470 000 domains (25 CPU days)
Integrations			CATH cathdb.info

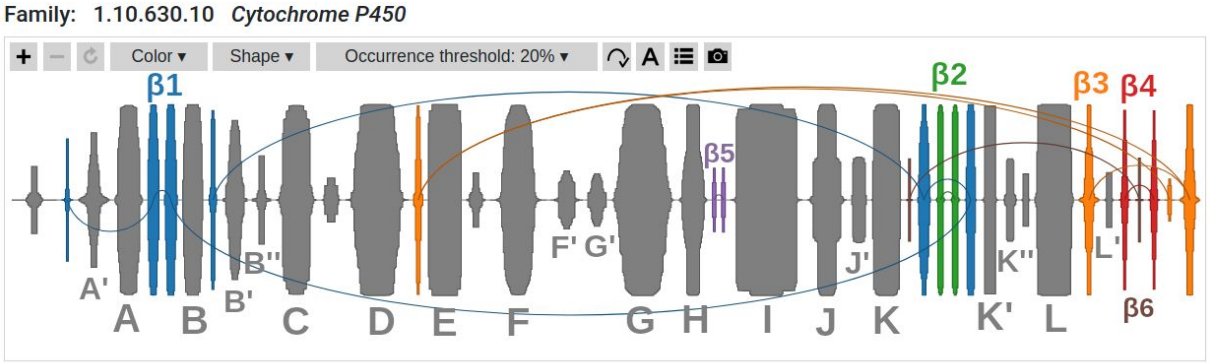
All together – overprot.ncbr.muni.cz

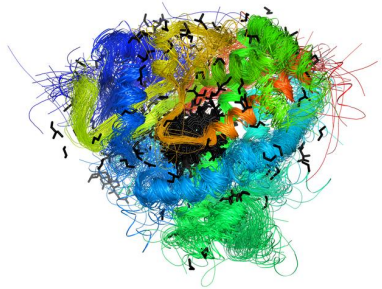




CATH superimposition

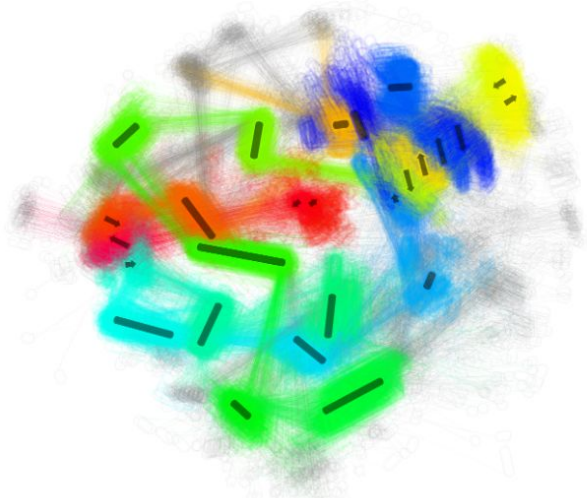
All together – overprot.ncbr.muni.cz



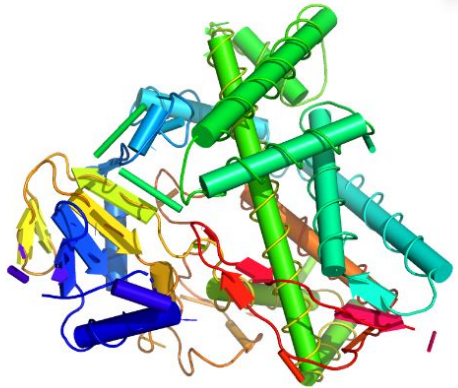


CATH superimposition

2D view (2DProts)

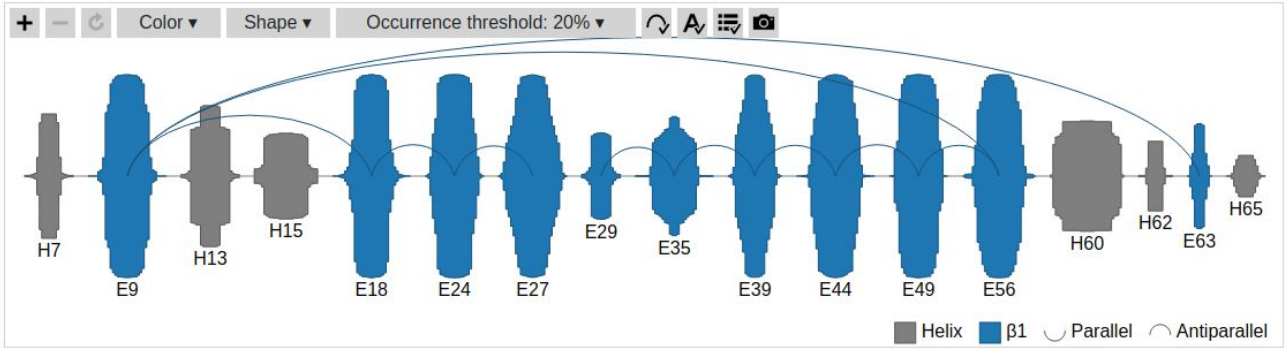


3D view (MAPSCI + OverProt)



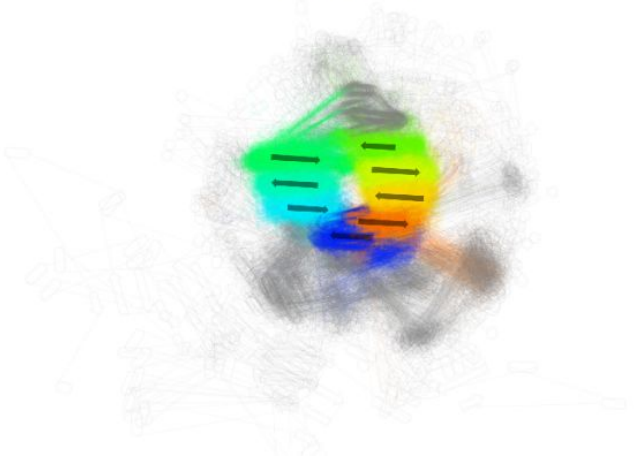
All together – overprot.ncbr.muni.cz

Family: 2.40.128.20 *Calycin beta-barrel core domain*

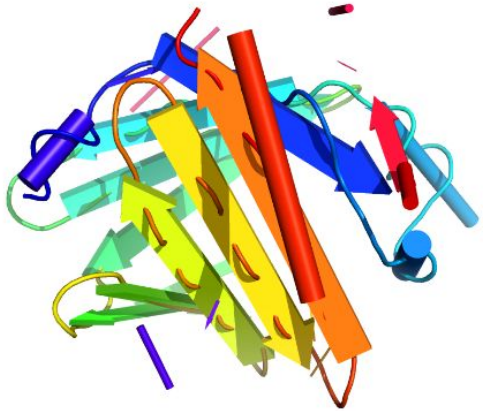


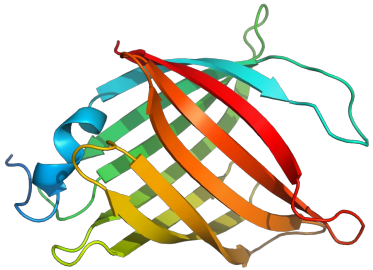
8-stranded subgroup (3k3l)

2D view (2DProts)



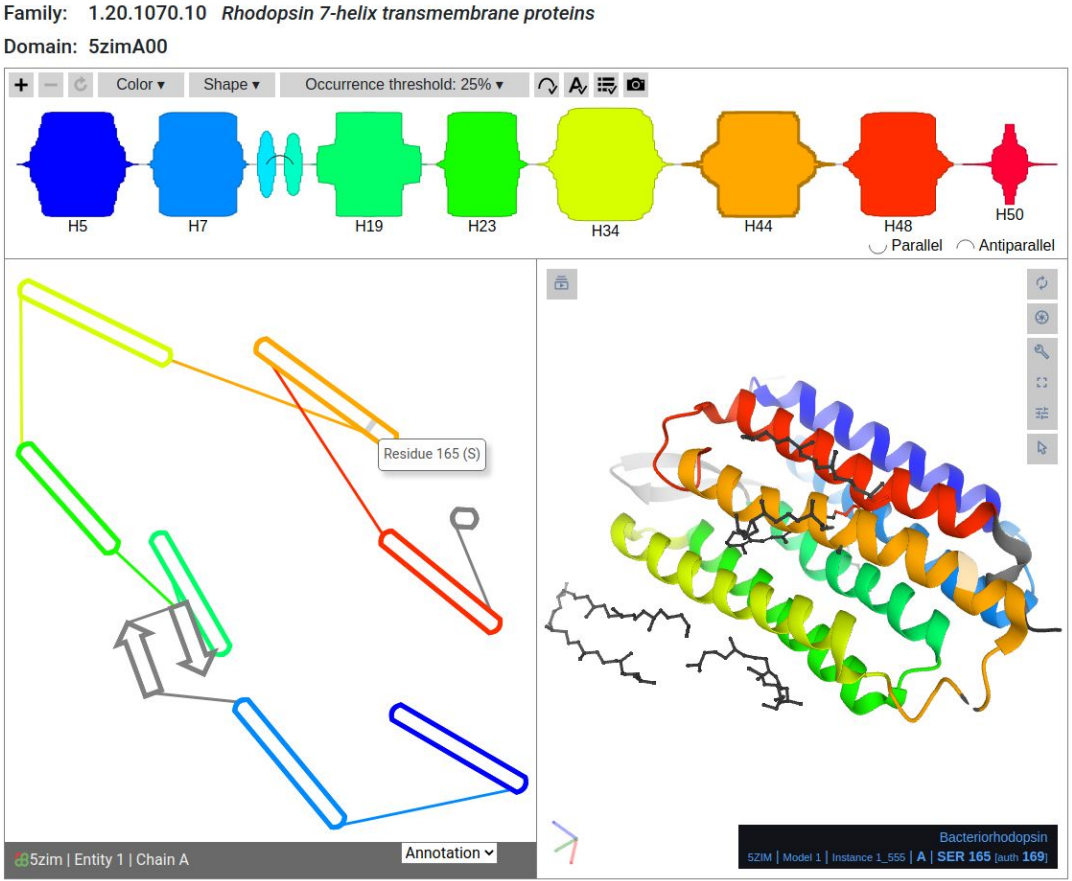
3D view (MAPSCI + OverProt)





10-stranded subgroup (3wjb)

Integrated view



← Family consensus

← Selected domain

https://overprot.ncbr.muni.cz/domain_view?family_id=1.20.1070.10&domain_id=5zimA00

Conclusion

- **SecStrAnnotator** – SSE annotation
- **OverProt** – SSE consensus + 1D visualization
- **2DProts** – SSE 2D visualization

Future plans

- **OverProt** – Integration with PDBe-KB, CATH
- **2DProts** – Inclusion of ligands
- Integration of AlphaFold DB via CATH cooperation

Acknowledgement

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Structural bioinformatics group, Masaryk University

- Ivana Hutařová Vařeková, Jan Hutař – **2DProts**
- Aliaksei Chareshneu – **Integrated view**
- Radka Svobodová, Jaroslav Koča

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Palacký University

- Karel Berka

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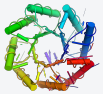
CATH

Thank you for your attention



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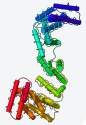

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