MS2MODELS

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RPBS

G. Labesse

ProFI
PROTEOMICS

O. Schiltz

Interactomics

What?

• Describes networks of interactions between biomolecules

• Most comonly: protein-protein interactions (PPIs) networks e.g. metabolic, signaling pathways

Why?

• Network medicine: predict how a network reacts to perturbations (e.g. the removal of a protein or an Interaction, due to mutations)

→ Identify biomarkers of diseases and drug targets

How?

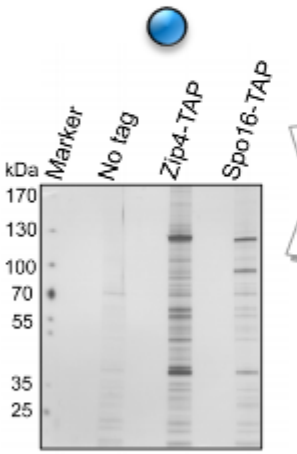
• Experimental techniques (Y2H, AP-MS…)

→ Limitations:
- PPIs detection threshold
- Homomultimers undetected
- Interacting regions unknown

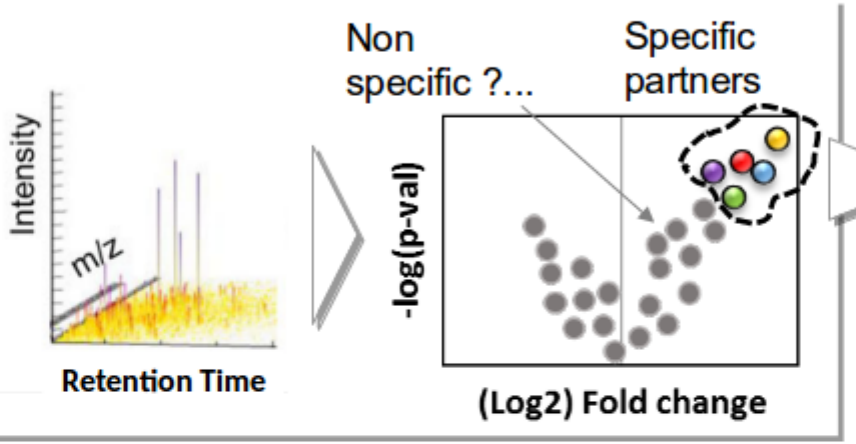
Development of an Integrative Proteomics Pipeline

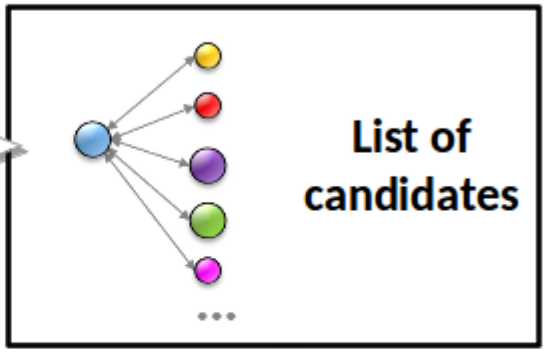
Context

Fractionation or enrichment via bait protein

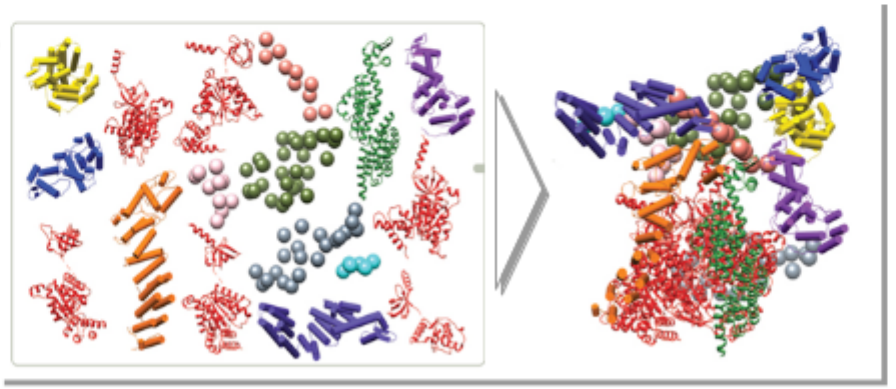


ProFI: Mass Spectrometry





FRISBI: Structural Biology

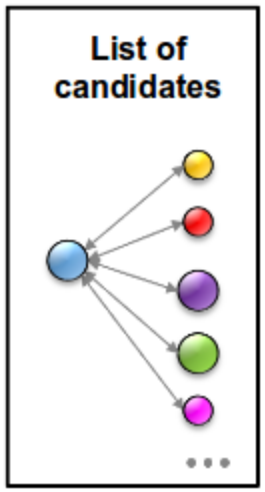


→ **IFB**

IFB **FRISBI → PROFI: Improve interactome analysis** (focus on proteins with no known structure)

PROFI → FRISBI: Spatial constraints for structural biology

Challenge: bioinformatics integration



1 ➔ In-depth analysis of detected partners

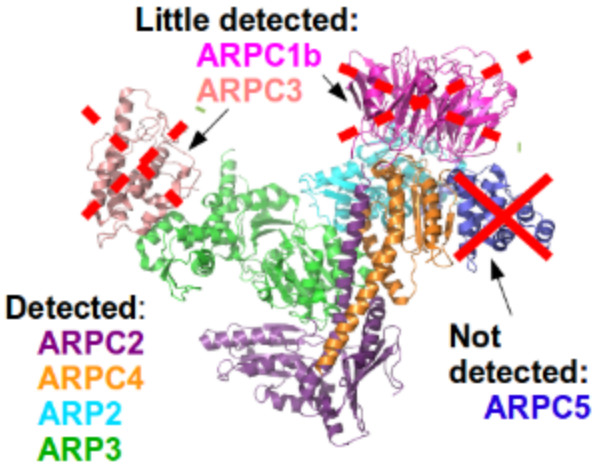
- Gene mapping, functional annotation, coupling with known interactomes

ProFI expertise : MS based proteomics resources, ProteoRE

- Partner validation: Reveal probable partners including those below the threshold.

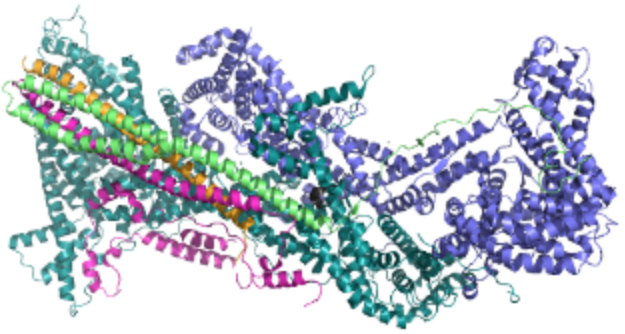
Examples:
Complexes partially detected by mass spectrometry

Arp2/3 complex (Actin-related protein)



PDB structure: 1K8K

WAVE regulatory complex



Detected:
CyFip1 (or CyFip2)
Nap1 (or Hem1)
Abi1 (or Abi2 or 3)

Detected (below treshold):
WAVE1/SCAR

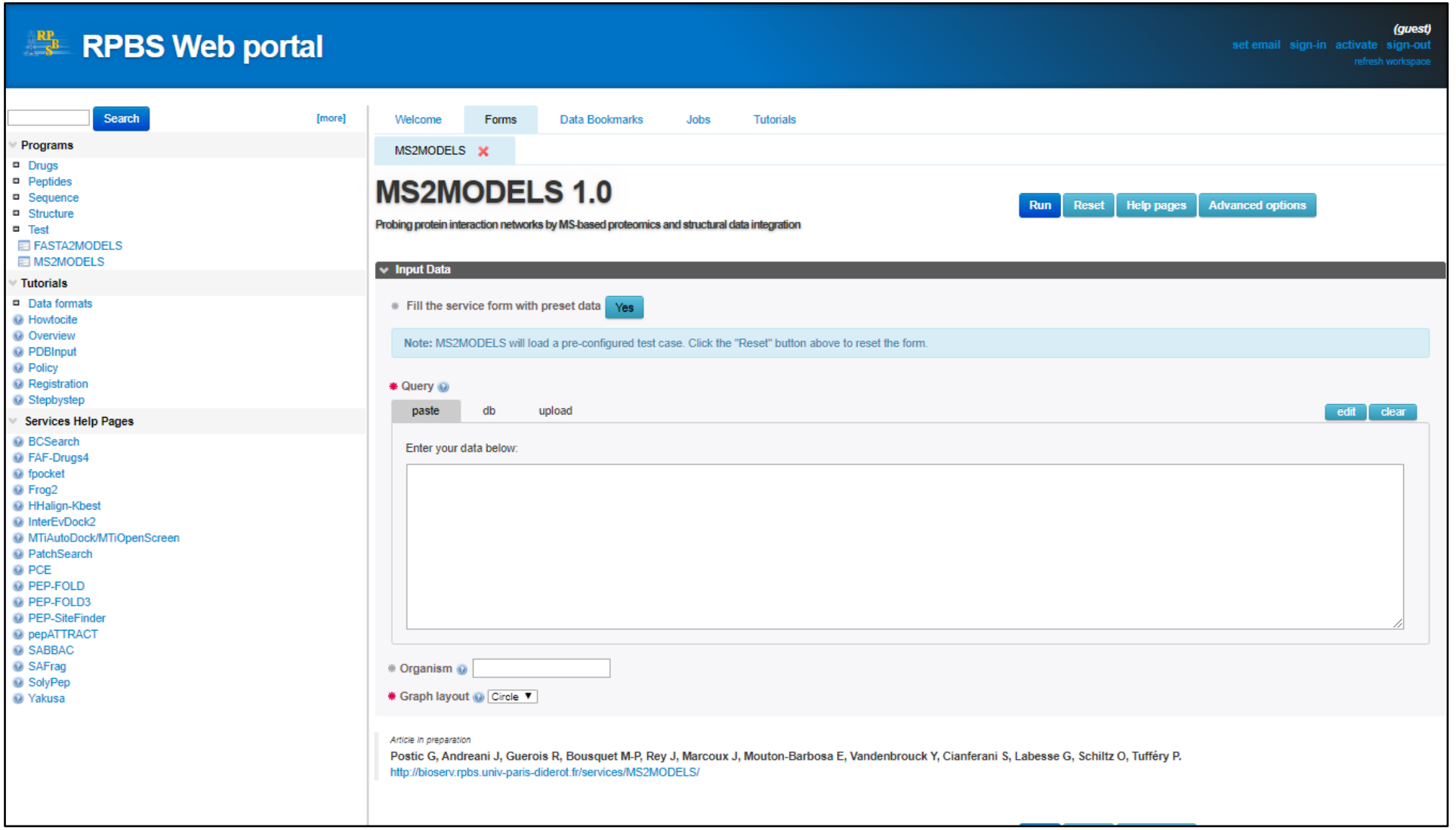
Not detected:
HSPC300/Brick1

PDB structures: 4N78, 3P8C

→ Fully detected by the MS2MODELS pipeline

Web server @ RPBS platform

Input: list of FASTA sequences



Output: Tables and graphs

Links to contents:

Table 1: Detection of template structures for the modeling of each input protein

#Input	UniProt_name	Template	Species	%Identities	Sequence_coverage	Protein_structure_title	Method	Resolution	Other_templates
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Table 2: Detection of homomultimers

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4	ARPC4_HUMAN	-	-

Table 3: Direct interactions observed within the structural data

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C1 Average seq id% = 67.8 [Top of Table]

GROUP OF 4 INPUT PROTEINS (labeled p1, p2, ...) FOUND TOGETHER IN 2 STRUCTURES
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- p3:ARP3_HUMAN
- p4:ARP2_HUMAN

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Facultative partners: -

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Comparative modelling possible?

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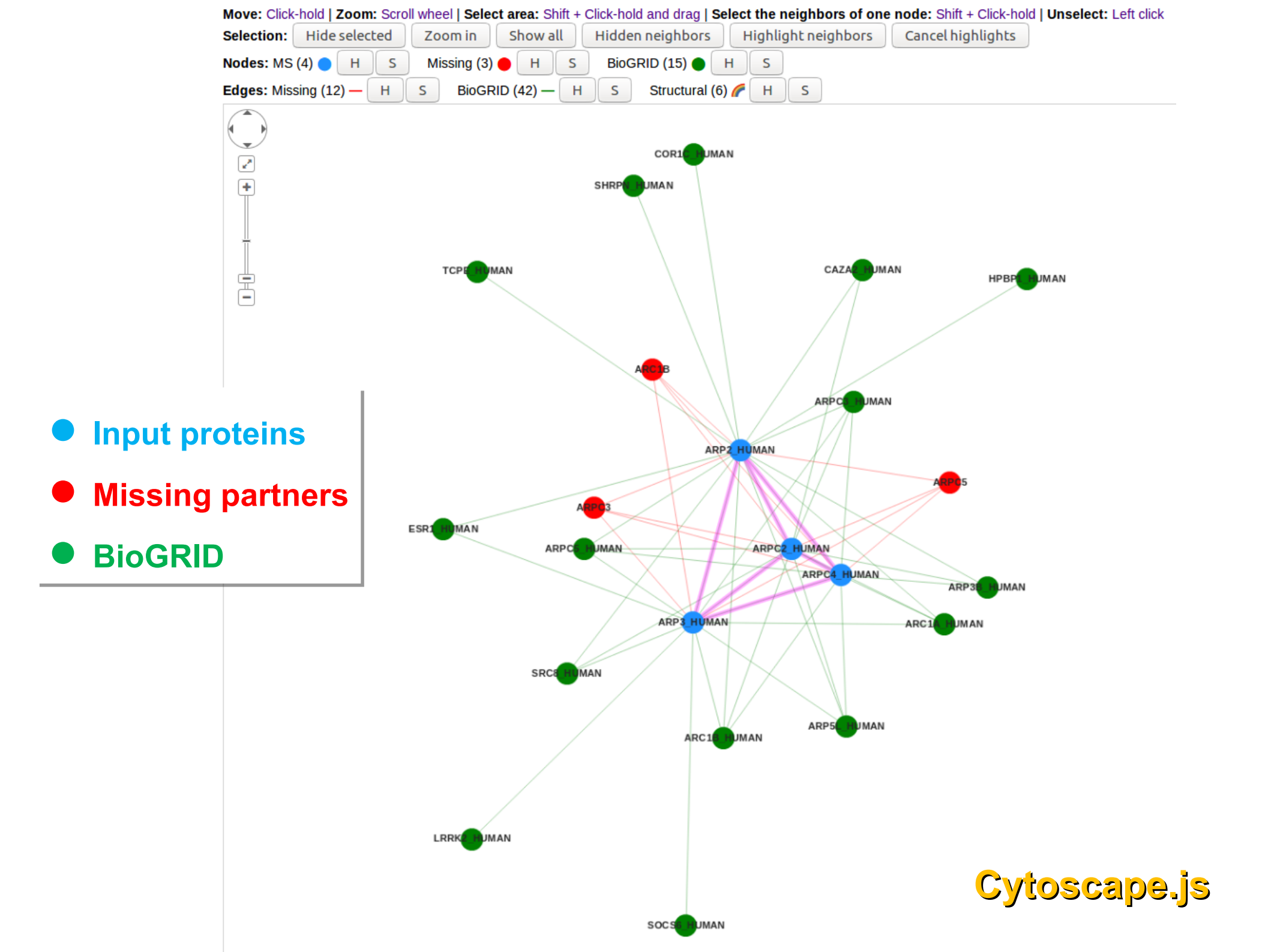
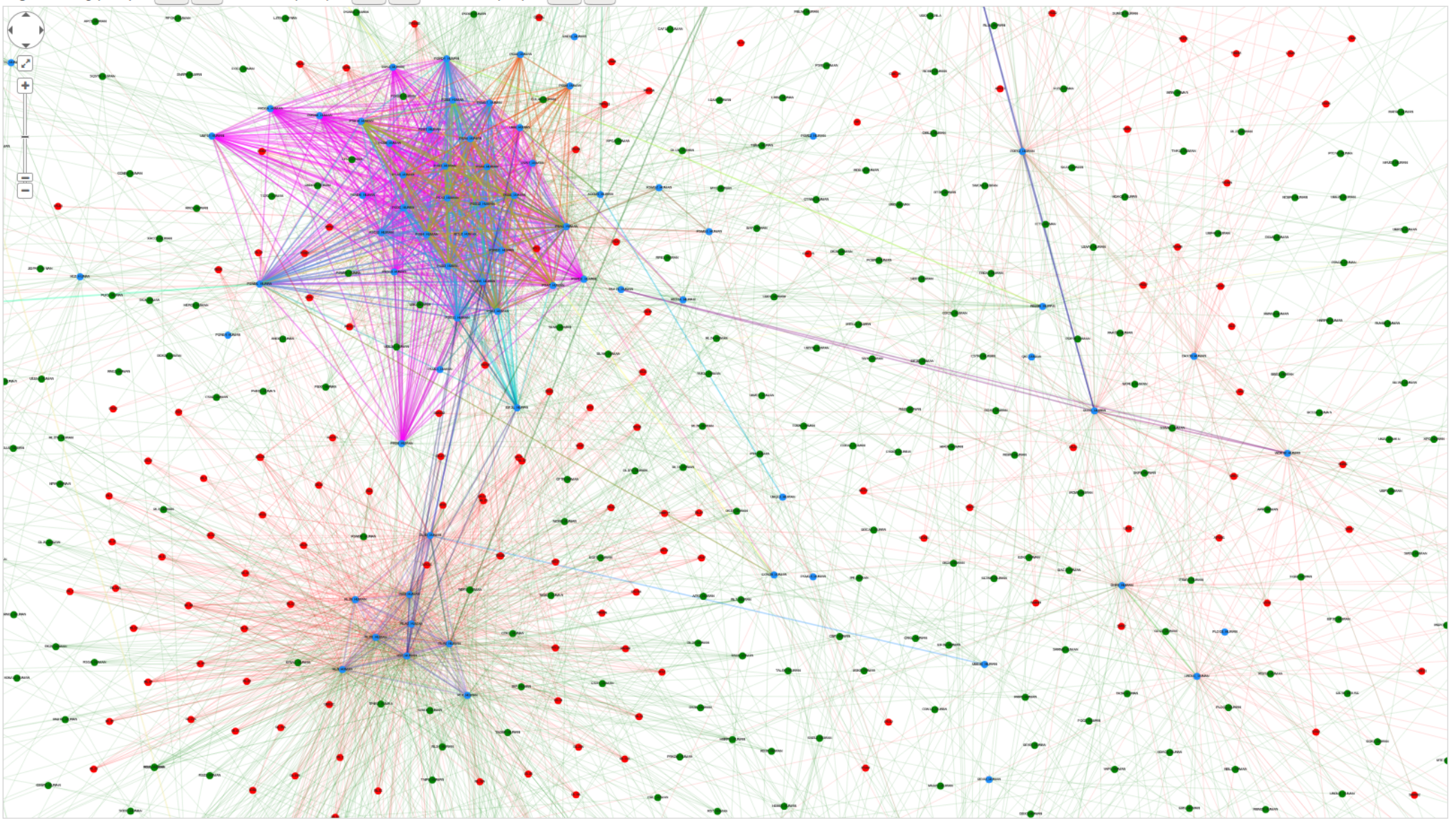
Additional partners?
→ Eukaryotic Linear Motif (ELM) resource

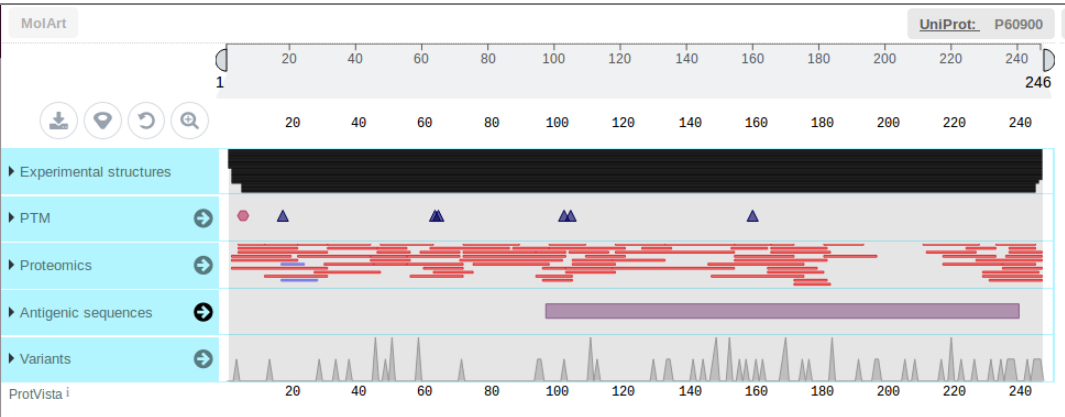

Move: Click-hold | Zoom: Scroll wheel | Select area: Shift + Click-hold and drag | Select the neighbors of one node: Shift + Click-hold | Unselect: Left click
Selection: Hide selected Zoom in Show all Hidden neighbors Highlight neighbors Cancel highlights
Nodes: MS (4) H S Missing (3) H S BioGRID (15) H S
Edges: Missing (12) H S BioGRID (42) H S Structural (6) H S
COR1C_HUMAN
SHRP1_HUMAN
TCPE_HUMAN
CAZA2_HUMAN
HPBP1_HUMAN
ARC1B
ARPC1_HUMAN
ARP2_HUMAN
ARPC5
ARPC3
ESR1_HUMAN
ARPC5_HUMAN
ARPC2_HUMAN
ARPC4_HUMAN
ARP3C_HUMAN
ARP3_HUMAN
ARC1A_HUMAN
SRC8_HUMAN
ARP5C_HUMAN
ARC1B_HUMAN
LRRK2_HUMAN
SOCS6_HUMAN
Input proteins
Missing partners
BioGRID
Cytoscape.js

Example of interactome: 20S proteasome (n = 192 input proteins)

Nodes >1500; edges >5000

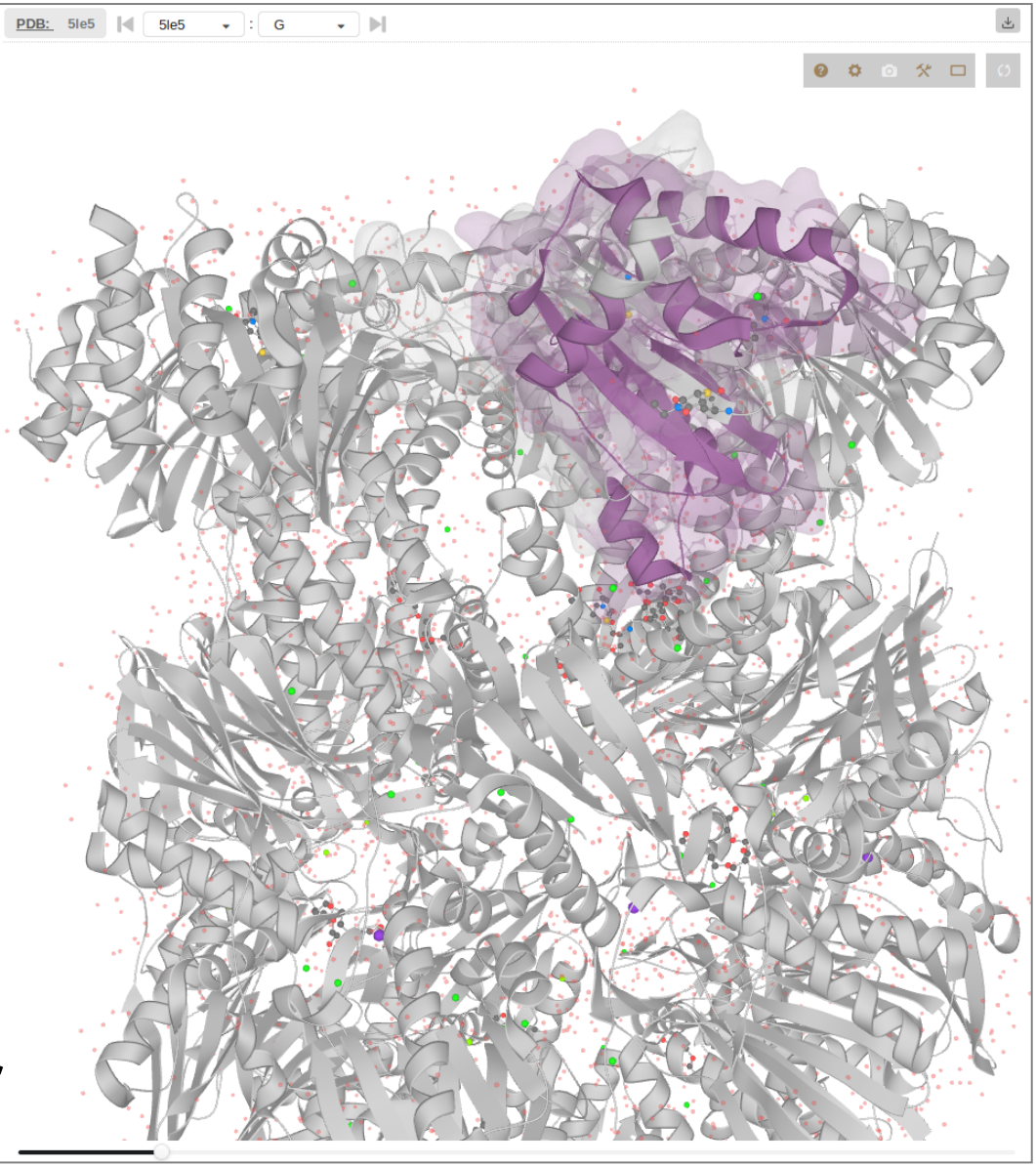


For each node (protein chain): annotations and 3D viewing



ProtVista

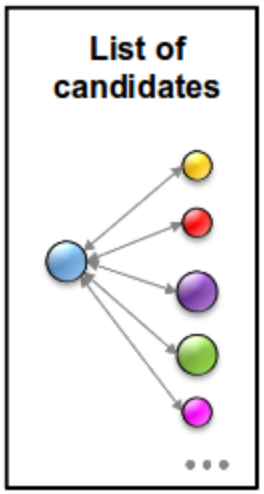
- Domains
- Motifs
- PTMs
- Mutagenesis sites
- Antigenic sequences
- …



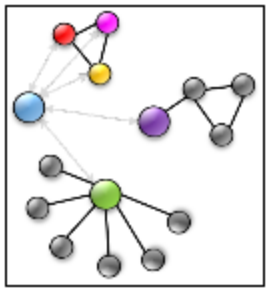
NGL Viewer

Hoksza, D., Gawron, P., Ostaszewski, M., & Schneider, R. (2018).
MolArt: a molecular structure annotation and visualization tool.
Bioinformatics, 34(23), 4127-4128.

Challenge: bioinformatics integration



1 ➔ In-depth analysis of detected partners

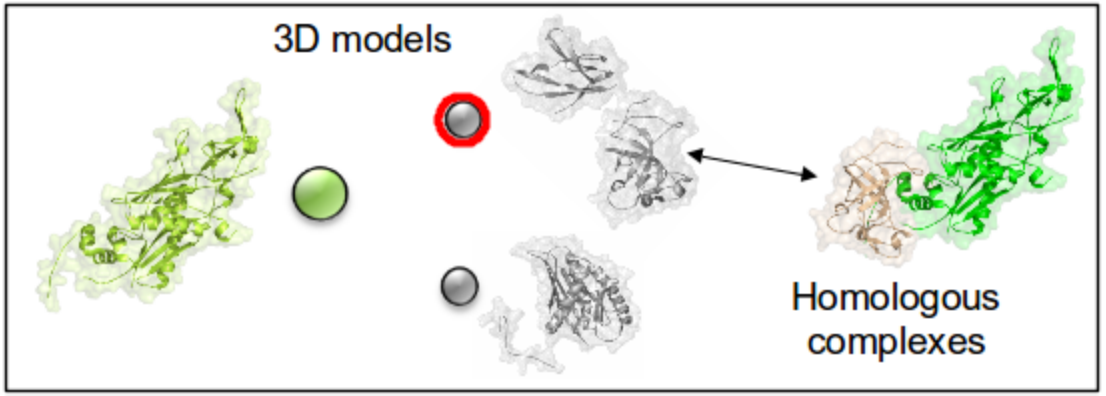


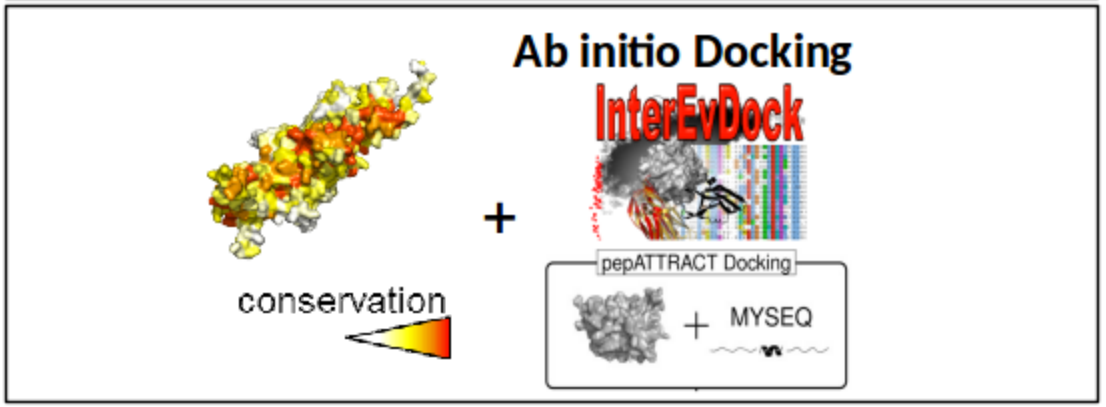
- Gene mapping, functional annotation, coupling with known interactomes

ProFI expertise : MS based proteomics resources, ProteoRE

- Partner validation: Reveal probable partners including those below the threshold.

2 ➔ Structural annotation → High-throughput modeling





➔ Partner search

➔ In absence of obvious partners: Prediction of interfaces by coevolution.

Applications:

➔ Functional dissection of interactomes

➔ Mutation design

➔ SNP interpretation

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