

# MS2MODELS



**P. Tufféry**

**Guillaume Postic**  
Postdoctoral fellow, IFB,  
RPBS



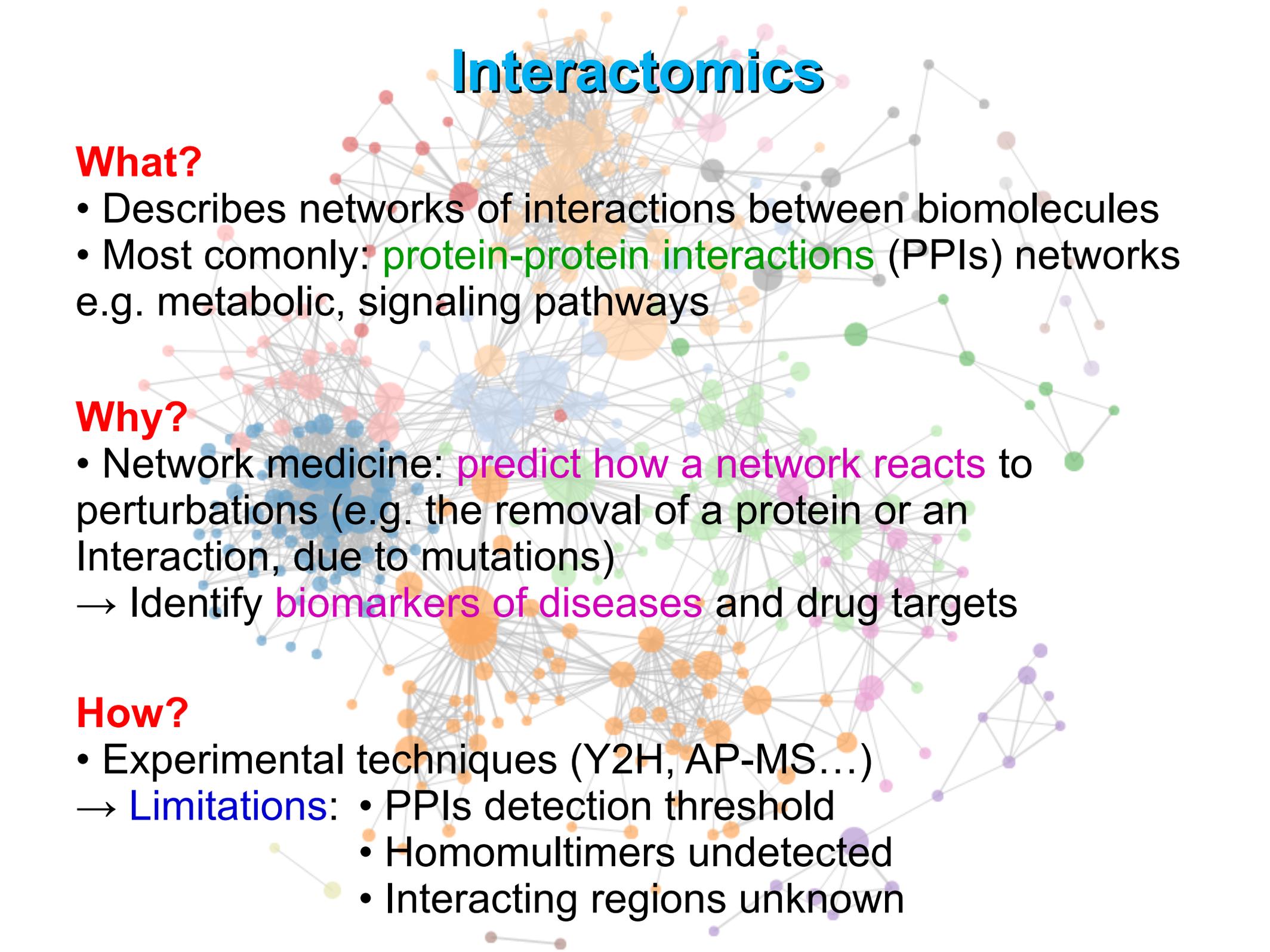
**G. Labesse**



**ProFI**  
PROTEOMICS

**O. Schiltz**

# Interactomics



## What?

- Describes networks of interactions between biomolecules
- Most commonly: **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

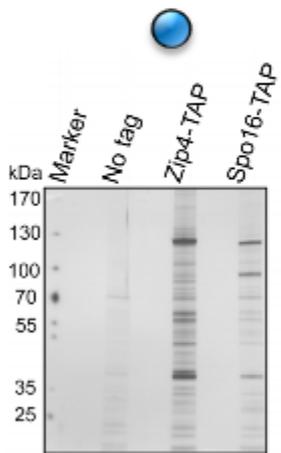
## How?

- Experimental techniques (Y2H, AP-MS...)  
→ **Limitations**:
  - PPIs detection threshold
  - Homomultimers undetected
  - Interacting regions unknown

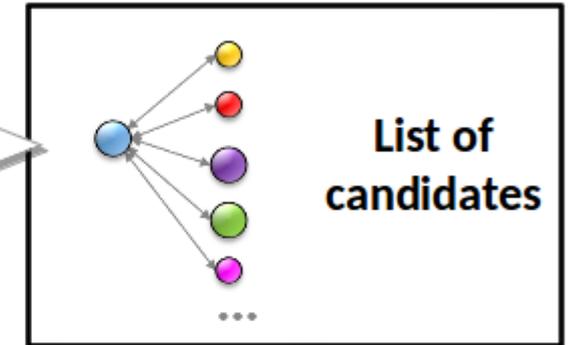
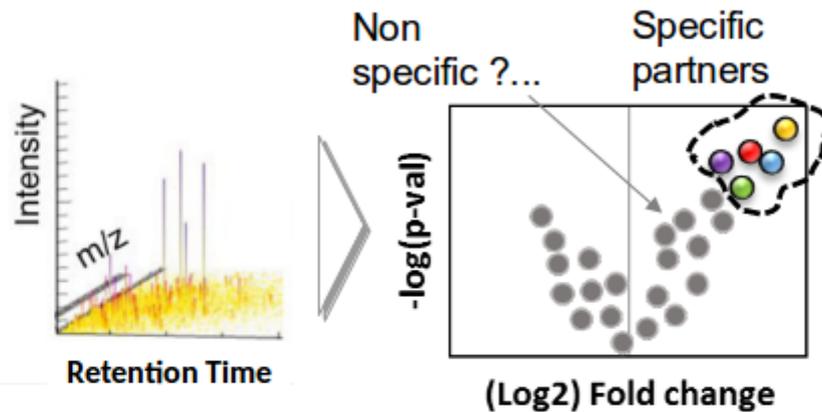
# Development of an Integrative Proteomics Pipeline

## Context

Fractionation  
or enrichment  
via bait  
protein

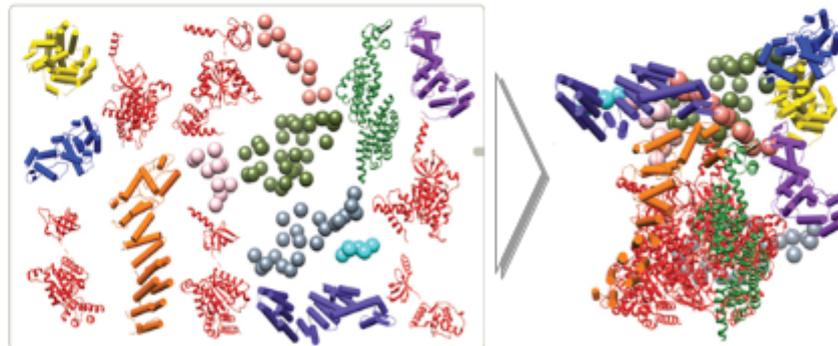


## ProFI: Mass Spectrometry



List of  
candidates

## FRISBI: Structural Biology



IFB

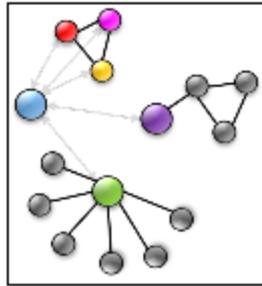
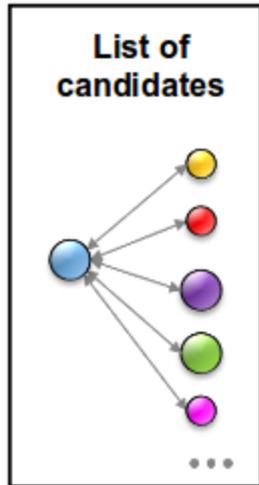


FRISBI → PROFI: Improve interactome analysis (focus on proteins with no known structure)

PROFI → FRISBI: Spatial constraints for structural biology

# Challenge: bioinformatics integration

## 1 → In-depth analysis of detected partners



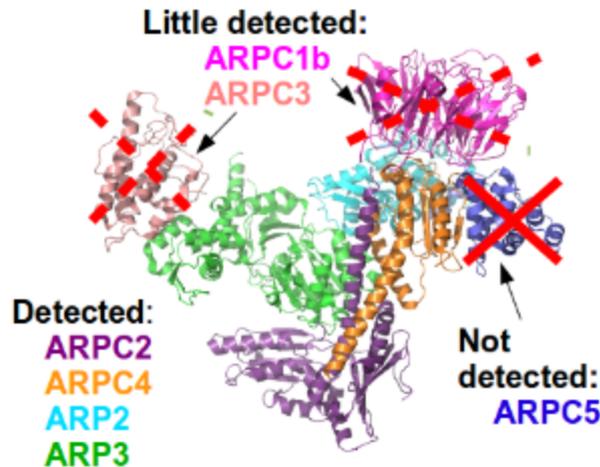
- Gene mapping, functional annotation, coupling with known interactomes

ProFI expertise : MS based proteomics resources, ProteoRE

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

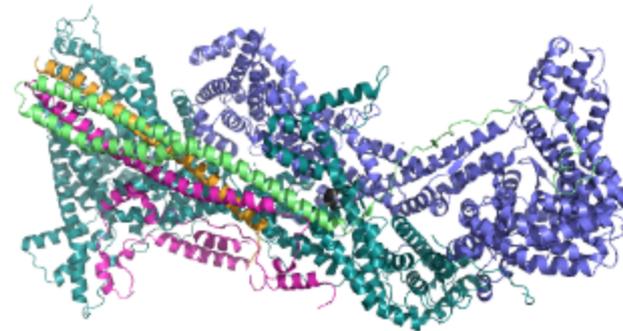
### Examples: Complexes partially detected by mass spectrometry

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 threshold):  
**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

The screenshot displays the RPBS Web portal interface. The top navigation bar includes the RPBS logo, the text "RPBS Web portal", and user options: "(guest)", "set email", "sign-in", "activate", "sign-out", and "refresh workspace". Below the navigation bar, there is a search bar and a menu with "Welcome", "Forms", "Data Bookmarks", "Jobs", and "Tutorials". The "Forms" tab is active, showing a tab for "MS2MODELS" with a close button. The main content area is titled "MS2MODELS 1.0" and includes the subtitle "Probing protein interaction networks by MS-based proteomics and structural data integration". There are buttons for "Run", "Reset", "Help pages", and "Advanced options". A section titled "Input Data" contains a checkbox for "Fill the service form with preset data" (checked) and a "Yes" button. A note states: "Note: MS2MODELS will load a pre-configured test case. Click the 'Reset' button above to reset the form." Below this is a "Query" section with tabs for "paste", "db", and "upload", and "edit" and "clear" buttons. A large text area is provided for "Enter your data below:". At the bottom of the input section, there are fields for "Organism" and "Graph layout" (set to "Circle"). The footer of the page includes the text "Article in preparation" and a list of authors: "Postic G, Andreani J, Guerois R, Bousquet M-P, Rey J, Marcoux J, Mouton-Barbosa E, Vandenbrouck Y, Cianferani S, Labesse G, Schiltz O, Tufféry P." with a link to "http://bioserv.rpbs.univ-paris-diderot.fr/services/MS2MODELS/".

Output: Tables and graphs

**Links to contents:**

- [Table 1: Detection of template structures for the modeling of each input protein](#)
- [Table 2: Detection of homomultimers](#)
- [Table 3: Direct interactions observed within the structural data](#)
- [Table 4: Identification of interaction motifs](#)

**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
1	<a href="#">ARP2_HUMAN</a>	<a href="#">1K8K_B</a>	Bos taurus	100	394	Crystal Structure of Arp2/3 Complex	X-RAY DIFFRACTION	2	1JCE_A 1JCF_A 1K8K_A 1K8K_B 1U...
2	<a href="#">ARP3_HUMAN</a>	<a href="#">1K8K_A</a>	Bos taurus	100	418	Crystal Structure of Arp2/3 Complex	X-RAY DIFFRACTION	2	1JCE_A 1JCF_A 1K8K_A 1K8K_B 1U...
3	<a href="#">ARPC2_HUMAN</a>	<a href="#">1K8K_D</a>	Bos taurus	100	299	Crystal Structure of Arp2/3 Complex	X-RAY DIFFRACTION	2	1K8K_D 3DXK_D 4XF2_W
4	<a href="#">ARPC4_HUMAN</a>	<a href="#">1K8K_F</a>	Bos taurus	100	168	Crystal Structure of Arp2/3 Complex	X-RAY DIFFRACTION	2	1K8K_F 3DXK_F 4XEI_F

**Table 2: Detection of homomultimers**[\[Top of Page\]](#)

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2	<a href="#">ARP3_HUMAN</a>	<a href="#">4BQL</a>	Homo 4-mer (A4)
3	<a href="#">ARPC2_HUMAN</a>	-	-
4	<a href="#">ARPC4_HUMAN</a>	-	-

**Table 3: Direct interactions observed within the structural data**[\[Top of Page\]](#)**C1** Average seq id% = 67.8 [\[Top of Table\]](#)

GROUP OF 4 INPUT PROTEINS (labeled p1, p2, ...) FOUND TOGETHER IN 2 STRUCTURES

- p1:[ARPC2\\_HUMAN](#)
- p2:[ARPC4\\_HUMAN](#)
- p3:[ARP3\\_HUMAN](#)
- p4:[ARP2\\_HUMAN](#)

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<a href="#">1K8K</a>	Hetero 7-mer (ABCDEFGF)	7	A;B;C;D;E;F;G;	p1:D p2:F p3:B p4:A	C ( <a href="#">ARC1B</a> ); E ( <a href="#">ARPC3</a> ); G ( <a href="#">ARPC5</a> );	Bos taurus	Crystal Structure of Arp2/3 Complex	X-RAY DIFFRACTION	2
<a href="#">3DXK</a>	Hetero 7-mer (ABCDEFGF)	7	A;B;C;D;E;F;G;	p1:D p2:F p3:B p4:A	C ( <a href="#">ARC1B</a> ); E ( <a href="#">ARPC3</a> ); G ( <a href="#">ARPC5</a> );	Bos taurus	Structure of Bos Taurus Arp2/3 Complex with Bound Inhibitor CK0944636	X-RAY DIFFRACTION	2.7

Facultative partners: -

**Table 4: Identification of interaction motifs**[\[Top of Page\]](#)

#Input	UniProt_name	Confirmed_partners	Undetected_partners
1	<a href="#">ARP2_HUMAN</a>	-	-
2	<a href="#">ARP3_HUMAN</a>	-	-
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# Comparative modelling possible?

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<a href="#">3DXK</a>	Hetero 7-mer (ABCDEFGF)	7	A;B;C;D;E;F;G;	p1:D p2:F p3:B p4:A	C ( <a href="#">ARC1B</a> ); E ( <a href="#">ARPC3</a> ); G ( <a href="#">ARPC5</a> );	Bos taurus	Structure of Bos Taurus Arp2/3 Complex with Bound Inhibitor CK0944636	X-RAY DIFFRACTION	2.7

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**Table 2: Detection of homomultimers**

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- p3:ARP3\_HUMAN
- p4:ARP2\_HUMAN

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3DXK	Hetero 7-mer (ABCDEFGF)	7	A;B;C;D;E;F;G;	p1:D p2:F p3:B p4:A	C ( <b>ARC1B</b> ); E ( <b>ARPC3</b> ); G ( <b>ARPC5</b> );	Bos taurus

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2	<a href="#">ARP3_HUMAN</a>	<a href="#">1K8K_A</a>	Bos taurus	100	418	Crystal Structure of Arp2/3 Complex	X-RAY DIFFRACTION	2	1JCE_A 1JCF_A 1K8K_A 1K8K_B 1U...
3	<a href="#">ARPC2_HUMAN</a>	<a href="#">1K8K_D</a>	Bos taurus	100	299	Crystal Structure of Arp2/3 Complex	X-RAY DIFFRACTION	2	1K8K_D 3DXK_D 4XF2_W
4	<a href="#">ARPC4_HUMAN</a>	<a href="#">1K8K_F</a>	Bos taurus	100	168	Crystal Structure of Arp2/3 Complex	X-RAY DIFFRACTION	2	1K8K_F 3DXK_F 4XEI_F

**Table 2: Detection of homomultimers**[\[Top of Page\]](#)

#Input	UniProt_name	PDB_ID	Stoichiometry
1	<a href="#">ARP2_HUMAN</a>	<a href="#">5LJV</a>	Homo 6-mer (A6)
2	<a href="#">ARP3_HUMAN</a>	<a href="#">4BQL</a>	Homo 4-mer (A4)
3	<a href="#">ARPC2_HUMAN</a>	-	-
4	<a href="#">ARPC4_HUMAN</a>	-	-

**Table 3: Direct interactions observed within the structural data**[\[Top of Page\]](#)**C1** Average seq id% = 67.8 [\[Top of Table\]](#)

GROUP OF 4 INPUT PROTEINS (labeled p1, p2, ...) FOUND TOGETHER IN 2 STRUCTURES

- p1:[ARPC2\\_HUMAN](#)
- p2:[ARPC4\\_HUMAN](#)
- p3:[ARP3\\_HUMAN](#)
- p4:[ARP2\\_HUMAN](#)

PDB_ID	Stoichiometry	Number_of_protein_chains	Names_of_chains	Proteins_found	Missing_partners	Species	Protein_structure_title	Method	Resolution
<a href="#">1K8K</a>	Hetero 7-mer (ABCDEFGF)	7	A;B;C;D;E;F;G;	p1:D p2:F p3:B p4:A	C ( <a href="#">ARC1B</a> ); E ( <a href="#">ARPC3</a> ); G ( <a href="#">ARPC5</a> );	Bos taurus	Crystal Structure of Arp2/3 Complex	X-RAY DIFFRACTION	2
<a href="#">3DXK</a>	Hetero 7-mer (ABCDEFGF)	7	A;B;C;D;E;F;G;	p1:D p2:F p3:B p4:A	C ( <a href="#">ARC1B</a> ); E ( <a href="#">ARPC3</a> ); G ( <a href="#">ARPC5</a> );	Bos taurus	Structure of Bos Taurus Arp2/3 Complex with Bound Inhibitor CK0944636	X-RAY DIFFRACTION	2.7

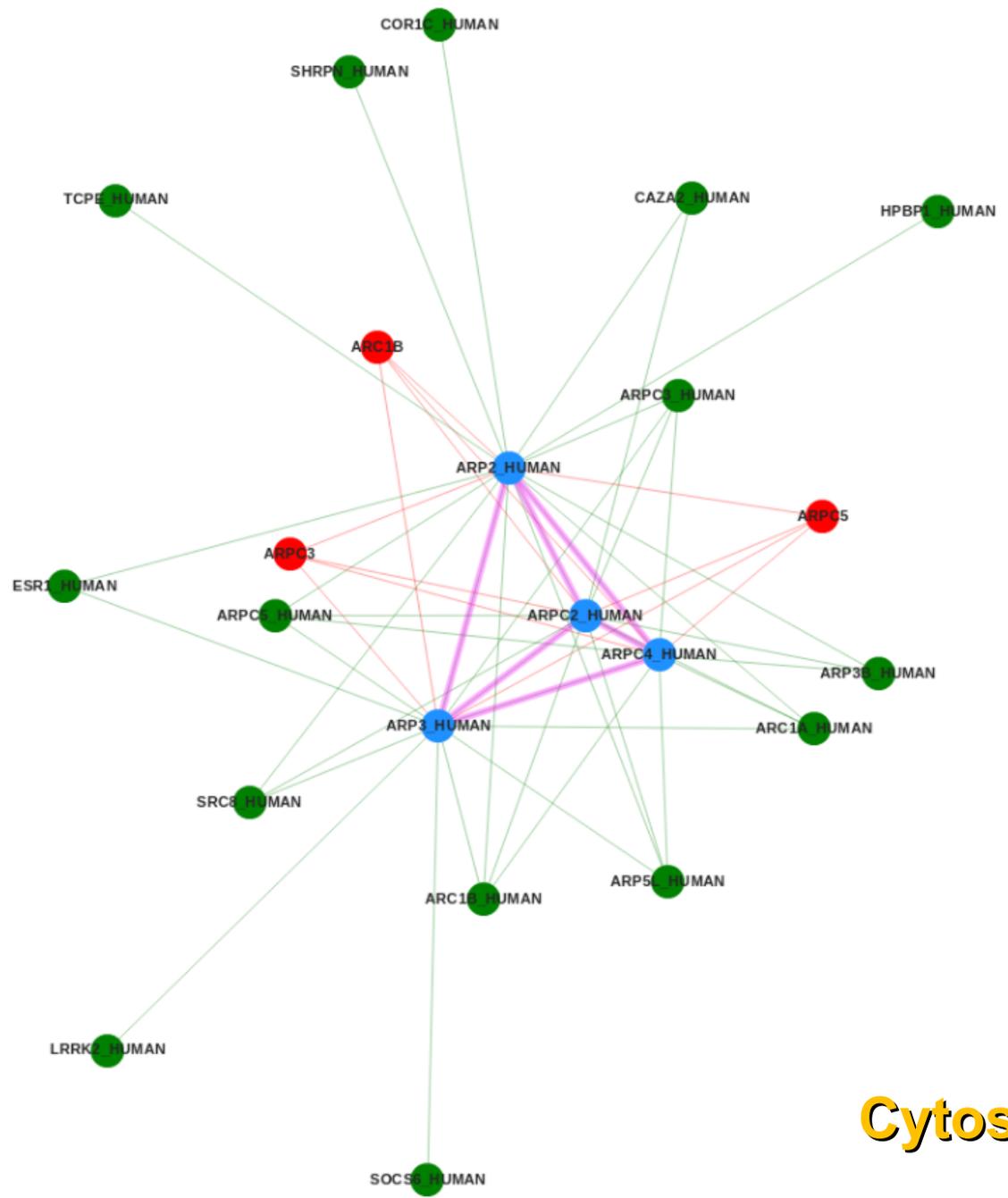
Facultative partners: -

**Table 4: Identification of interaction motifs**[\[Top of Page\]](#)

#Input	UniProt_name	Confirmed_partners	Undetected_partners
1	<a href="#">ARP2_HUMAN</a>	-	-
2	<a href="#">ARP3_HUMAN</a>	-	-
3	<a href="#">ARPC2_HUMAN</a>	-	-
4	<a href="#">ARPC4_HUMAN</a>	-	-

**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:        
 Nodes: MS (4)   Missing (3)   BioGRID (15)    
 Edges: Missing (12)   BioGRID (42)   Structural (6)



- Input proteins
- Missing partners
- BioGRID

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

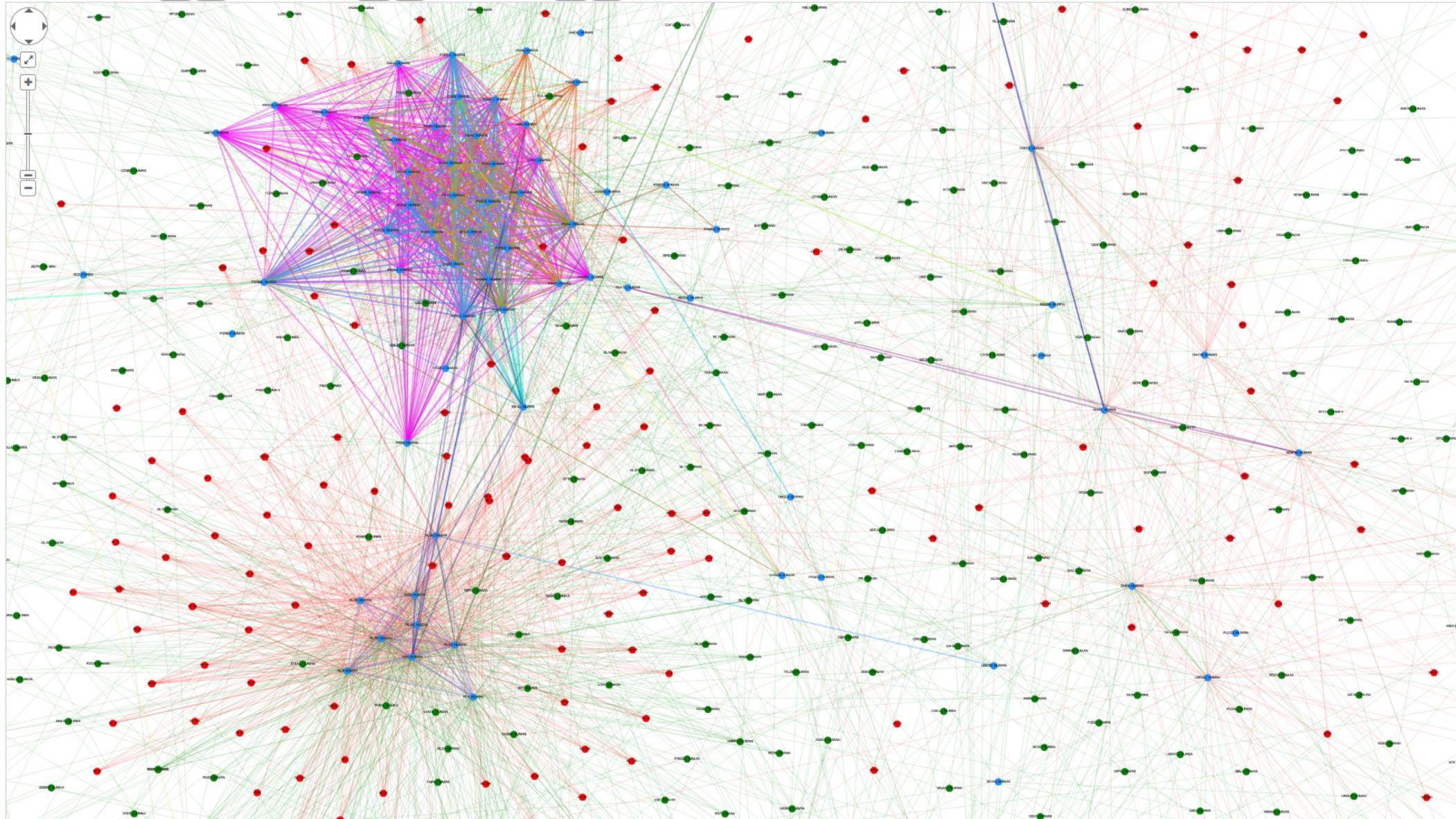
Nodes >1500; edges >5000

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

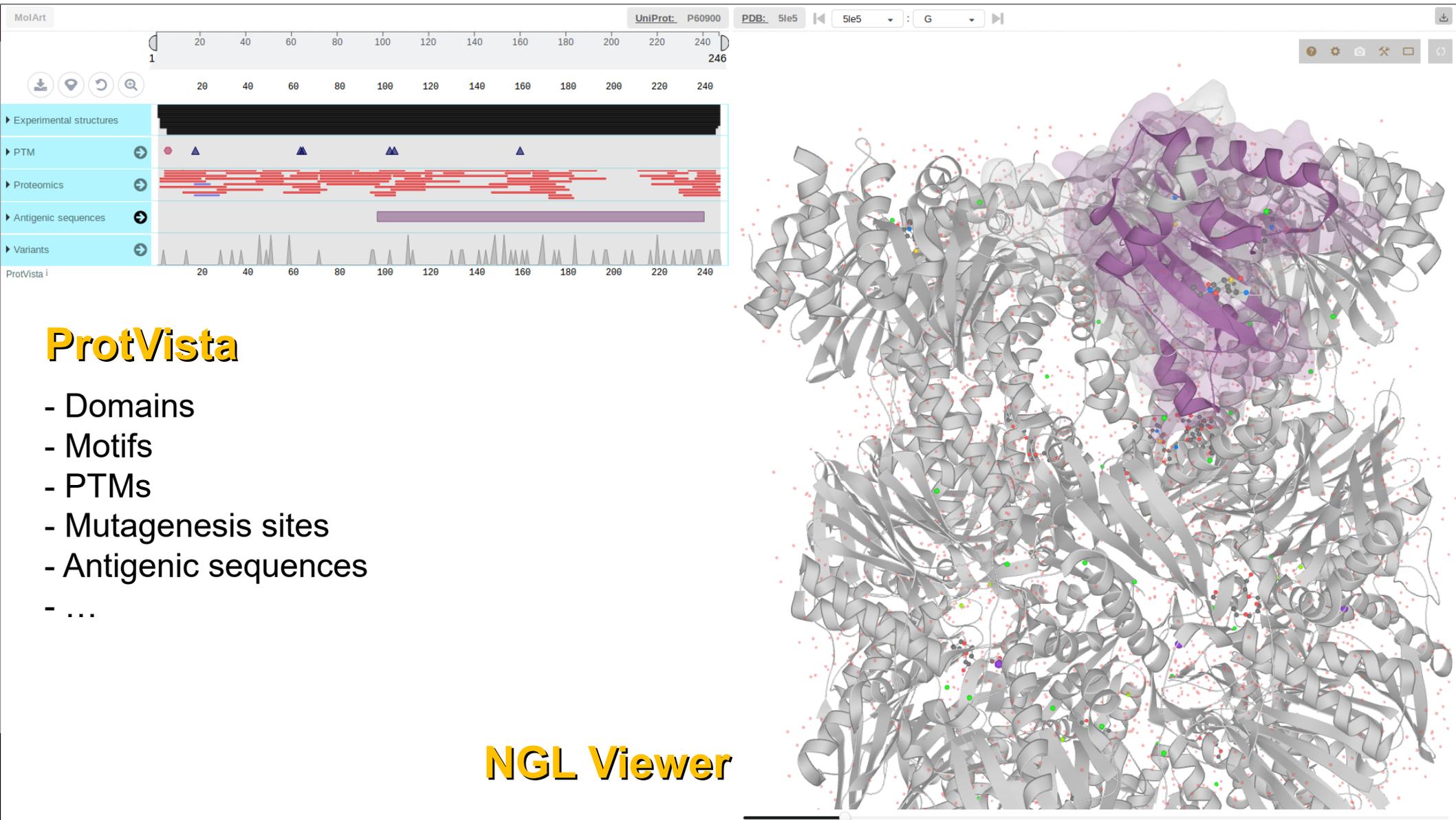
Selection:

Nodes: MS (192)  H  S Missing (197)  H  S BioGRID (1122)  H  S

Edges: Missing (1224)  H  S BioGRID (2803)  H  S Structural (974)  H  S



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



The image displays the MolArt web interface for protein visualization and annotation. The top panel shows a sequence viewer for UniProt P60900 (PDB: 5le5) with a scale from 1 to 246. Below the sequence, there are several tracks: Experimental structures, PTM (Post-Translational Modifications), Proteomics, Antigenic sequences, and Variants. The PTM track shows several modifications marked with colored triangles. The Proteomics track shows red horizontal bars representing protein abundance. The Antigenic sequences track shows a purple bar representing an antigenic region. The Variants track shows a line graph of variant frequencies. On the right, a 3D ribbon model of the protein structure is shown in grey, with a purple ribbon highlighting a specific region. The model is surrounded by numerous small red dots, likely representing mutations or variants. The interface includes navigation controls like zoom, pan, and download buttons.

## ProtVista

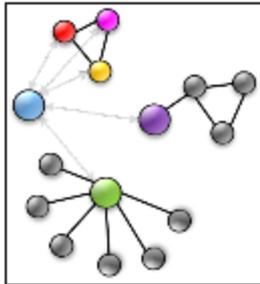
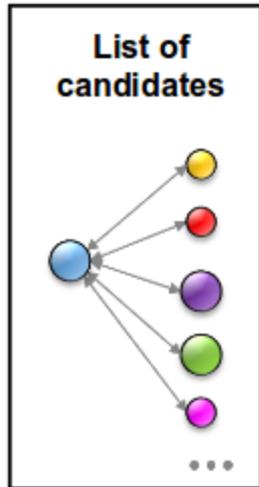
- Domains
- Motifs
- PTMs
- Mutagenesis sites
- Antigenic sequences
- ...

## 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

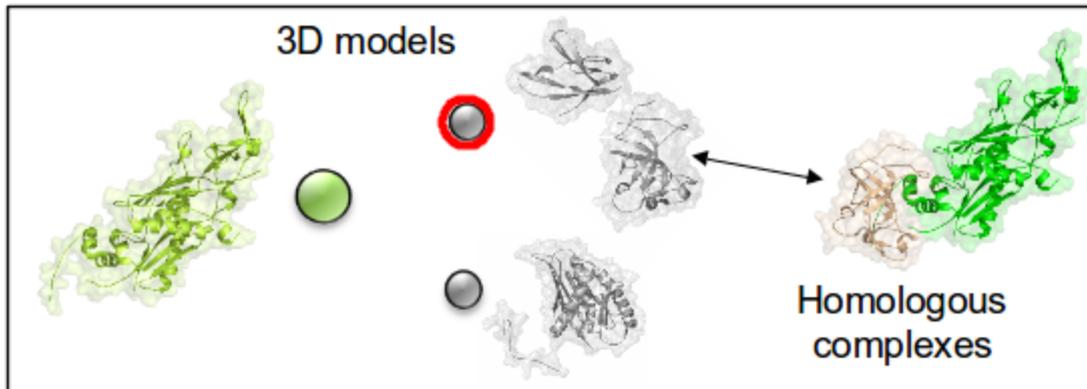


- Gene mapping, functional annotation, coupling with known interactomes

ProFI expertise : MS based proteomics resources, ProteoRE

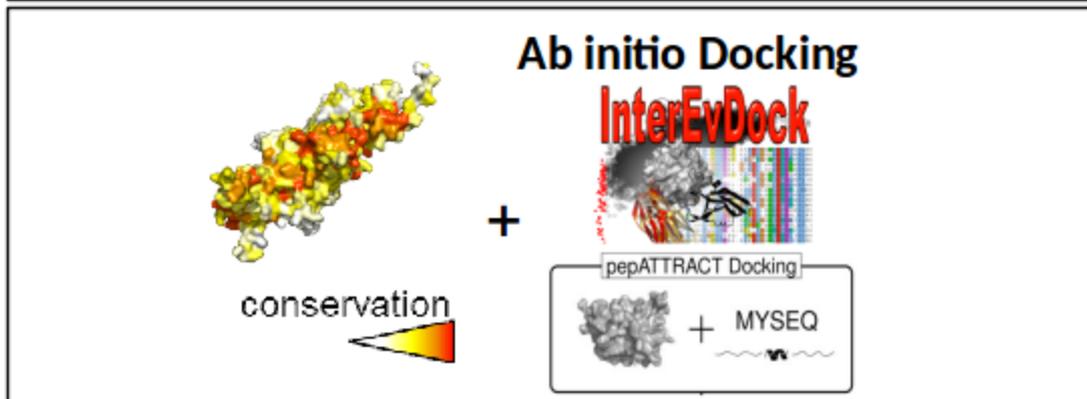
- Partner validation: **Reveal probable partners including those below the threshold.**

## 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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