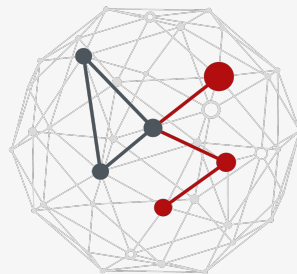


1222-2022  
800  
ANNI



UNIVERSITÀ  
DEGLI STUDI  
DI PADOVA

 DIPARTIMENTO  
MATEMATICA



**DATA SCIENCE**  
UNIVERSITY OF PADOVA

# Residue Interaction Network Generator - RING -

Master of Science in Data Science

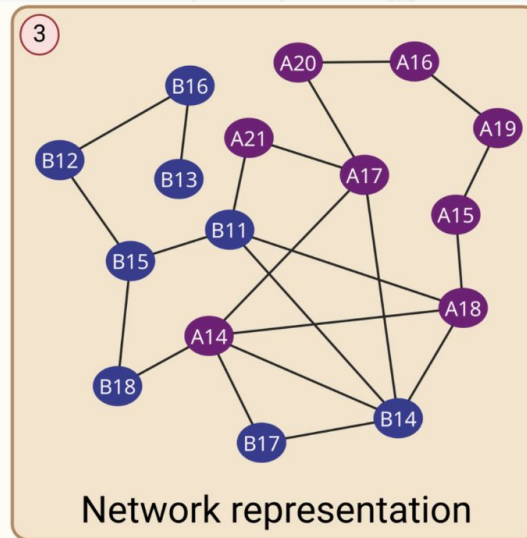
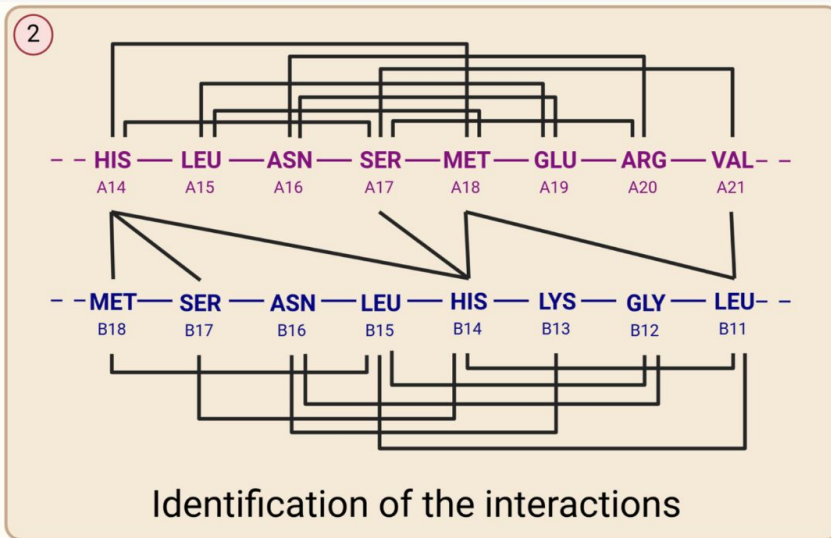
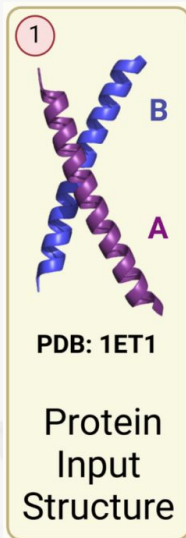
Damiano Piovesan



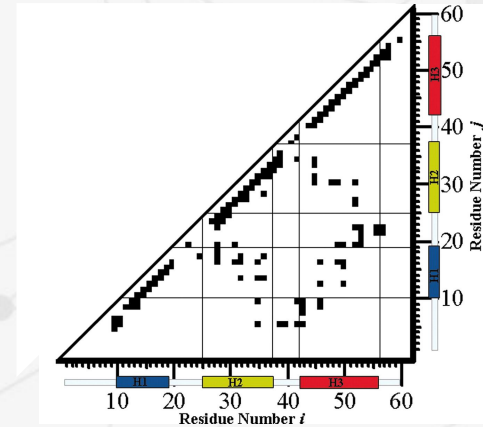
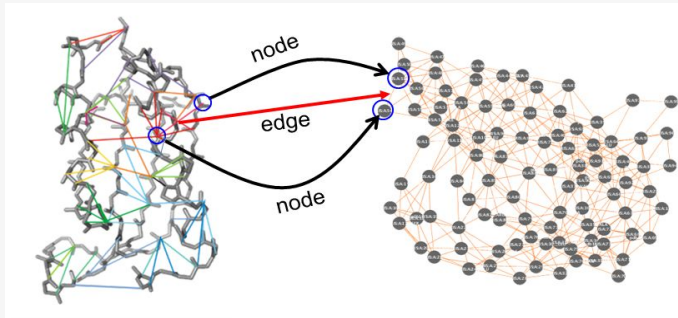
# Concept

A graph representation of a protein structure, where:

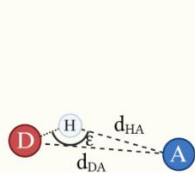
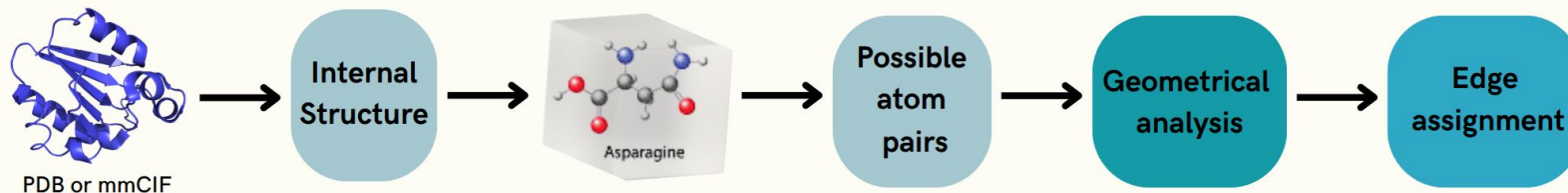
- Residues → Nodes
- Interactions → Edges



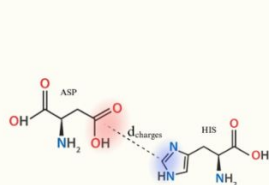
# RIN and contact maps



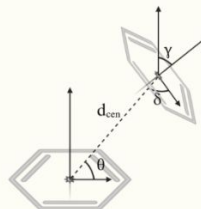
# Possible interactions



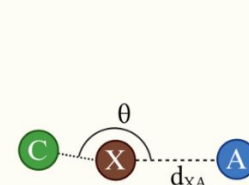
H-bond



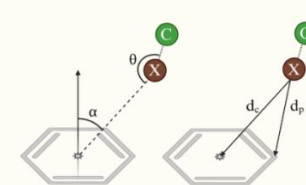
Ionic Bond



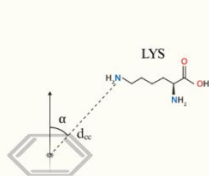
$\pi$ - $\pi$  stacking



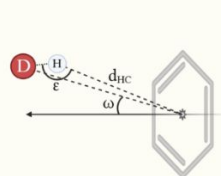
Halogen-acceptor bond



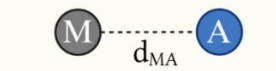
Halogen- $\pi$  bond



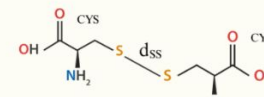
$\pi$ -cation bond



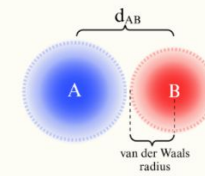
$\pi$ -H bond



Metal-ion coordination



Disulphide bond

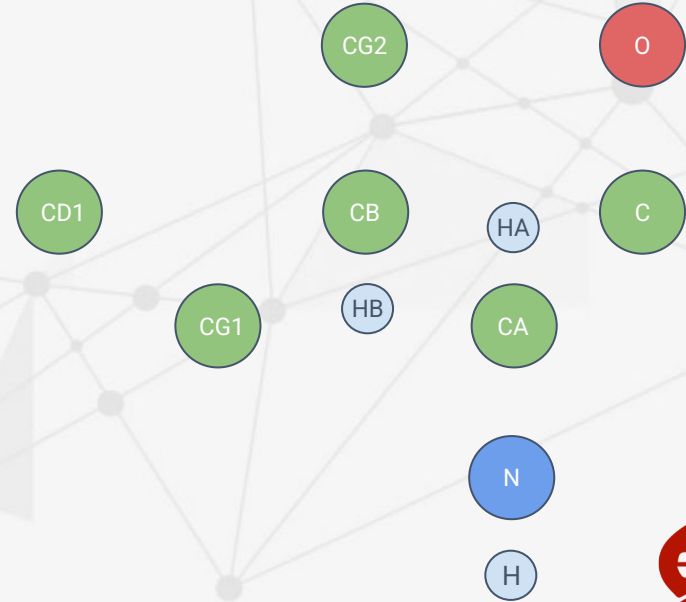


VdW forces

# How to build the protein structure

	<i>id</i>	<i>type_symbol</i>	<i>atom_id</i>	<i>comp_id</i>	<i>asym_id</i>	<i>seq_id</i>	<i>x</i>	<i>y</i>	<i>z</i>
→	ATOM 61	N	N	ILE	A	1 5 ?	-28.199	-33.564	-15.366
→	ATOM 62	C	CA	ILE	A	1 5 ?	-27.521	-32.693	-16.369
→	ATOM 63	C	C	ILE	A	1 5 ?	-26.502	-31.786	-15.674
→	ATOM 64	O	O	ILE	A	1 5 ?	-26.618	-31.493	-14.501
→	ATOM 65	C	CB	ILE	A	1 5 ?	-28.641	-31.864	-16.998
→	ATOM 66	C	CG1	ILE	A	1 5 ?	-28.041	-30.881	-18.008
→	ATOM 67	C	CG2	ILE	A	1 5 ?	-29.379	-31.084	-15.908
→	ATOM 68	C	CD1	ILE	A	1 5 ?	-27.509	-31.651	-19.217
→	ATOM 69	H	H	ILE	A	1 5 ?	-28.909	-33.198	-14.799
→	ATOM 70	H	HA	ILE	A	1 5 ?	-27.038	-33.293	-17.123
→	ATOM 71	H	HB	ILE	A	1 5 ?	-29.335	-32.521	-17.502
→	ATOM 72	N	N	GLN	A	1 6 ?	-25.505	-31.340	-16.389

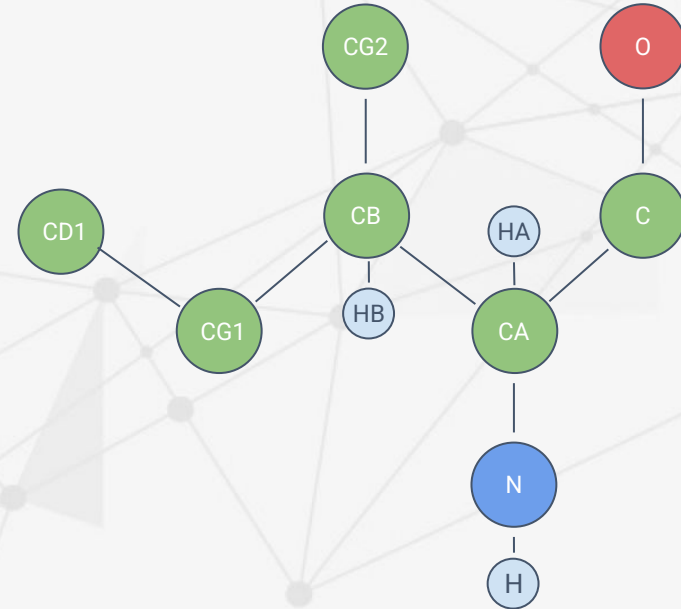
Isoleucine ?



# How to build the protein structure

Connect the atoms using the  
**chemical component dictionary - CCD**

RESIDUE	ILE					
→ CONECT	N	CA	H			
→ CONECT	CA	N	C	CB	HA	
→ CONECT	C	CA	O			
→ CONECT	O	C				
→ CONECT	CB	CA	CG1	CG2	HB	
→ CONECT	CG1	CB	CD1			
→ CONECT	CG2	CB				
→ CONECT	CD1	CG1				
→ CONECT	H	N				
→ CONECT	HA	CA				
→ CONECT	HB	CB				
END						
FORMUL	ILE	C6	H13	N	O2	



# How to build the protein structure

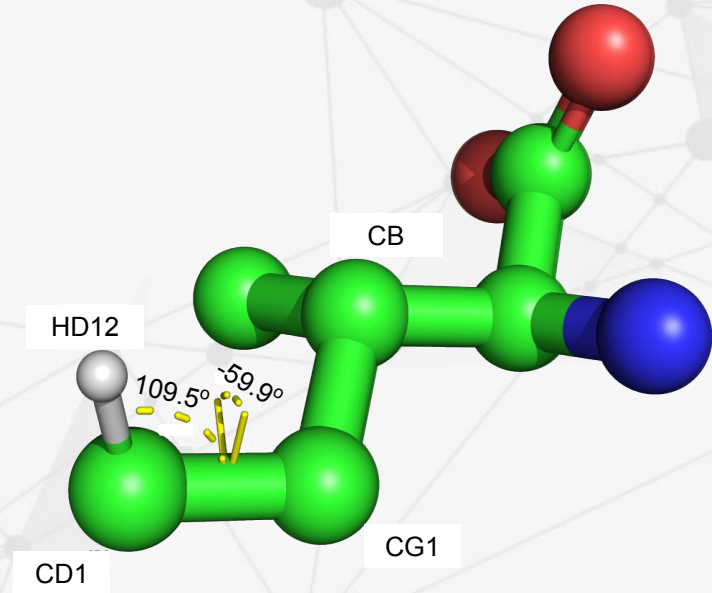
Add the hydrogens

ILE

→ HD12 CD1 CG1 109.5 CB -59.9

The algorithm converts the internal representation (z-matrix) to cartesian with some trigonometry formulas based on

- Bond length
- Bond angle
- Dihedral angle



# How to build the protein structure

Find aromatic rings (Depth First Search)

**Visited**

[CB]

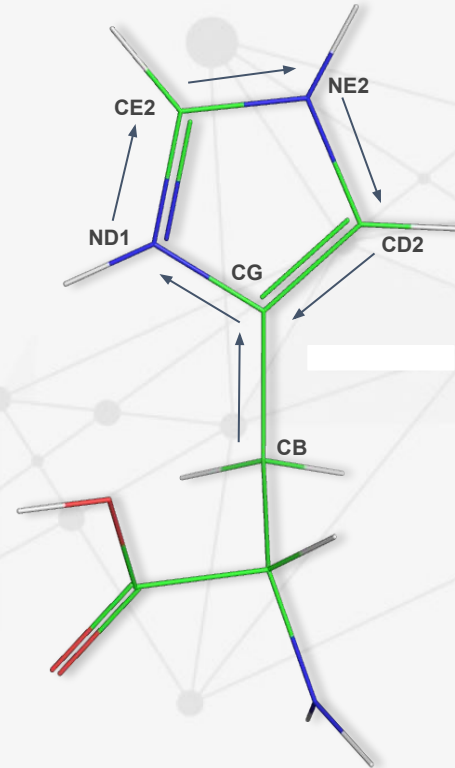
. . .

[CB, **CG**, ND1, CE2, NE2, CD2, **CG**]

Additional filters

- **Coplanarity** of ring atoms using the dot product
- Atoms names in extracted dictionary from the **CCD**

Histidine



# How to build the protein structure

Find aromatic rings (Depth First Search)

**Visited**

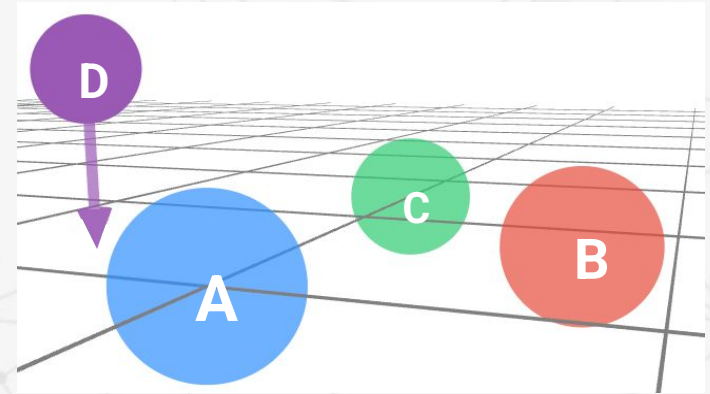
[CB]

...

[CB, **CG**, ND1, CE2, NE2, CD2, **CG**]

Additional filters

- **Coplanarity** of ring atoms using the dot product
- Atoms names in extracted dictionary from the **CCD**



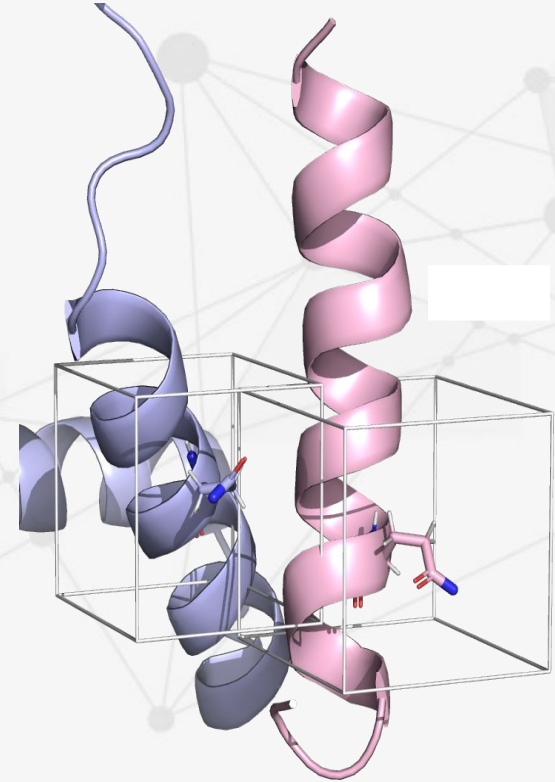
# Calculate the interactions

## An all vs all calculation?

Interactions have a maximum range (to be relevant). We can use this knowledge and the structural information to skip a lot of calculations and **reduce runtime**

## Use bounding boxes

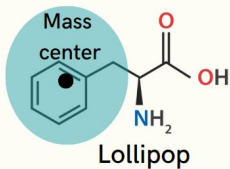
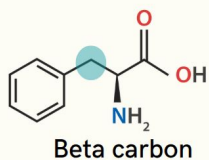
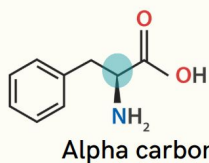
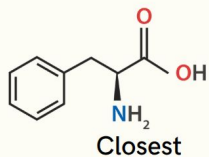
- At chain level
- Residue level



# Nodes definition and edge cardinality

## NODES

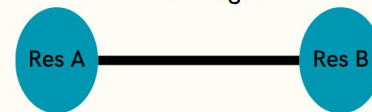
Not IAC



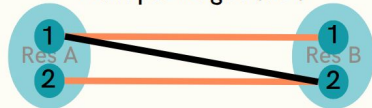
IAC

## EDGES

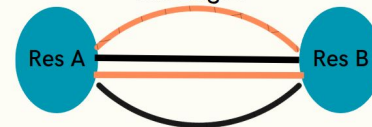
One edge



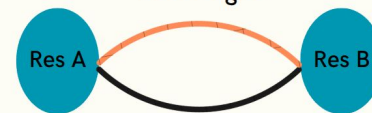
Multiple Edges (def)



All Edges



Best Edges



# Contacts in high-resolution PDB structures

Interaction partners	Intra-chain				Inter-chain					
	AA-AA		AA-Ligand <sup>^</sup>		AA-AA		AA-Ligand		AA-Nucleic acid	
Number of PDBs	30 244		3166		12 605		25 062		462	
Number of contacts	9 431 609		33 074		300 687		324 296		9311	
Hydrogen bond	8 442 301	89.5%	31 410	95.0%	229 295	76.3%	229 855	70.9%	8517	91.5%
$\pi$ - $\pi$ stacking	620 405	6.6%	1475	4.5%	36 301	12.1%	33 175	10.2%	608	6.5%
$\pi$ -cation	87 262	0.9%	102	0.3%	7278	2.4%	2836	0.9%	180	1.9%
Ionic bond	234 741	2.5%	–	–	25 025	8.3%	–	–	–	–
Disulfide	23 526	0.2%	–	–	890	0.3%	–	–	–	–
$\pi$ -hydrogen bond*	23 374	0.2%	35	0.1%	1898	0.6%	962	0.3%	6	0.1%
Halogen bond*	–	–	43	0.1%	–	–	831	0.3%	–	–
Metal ion coordination*	–	–	–	–	–	–	56 637	17.5%	–	–

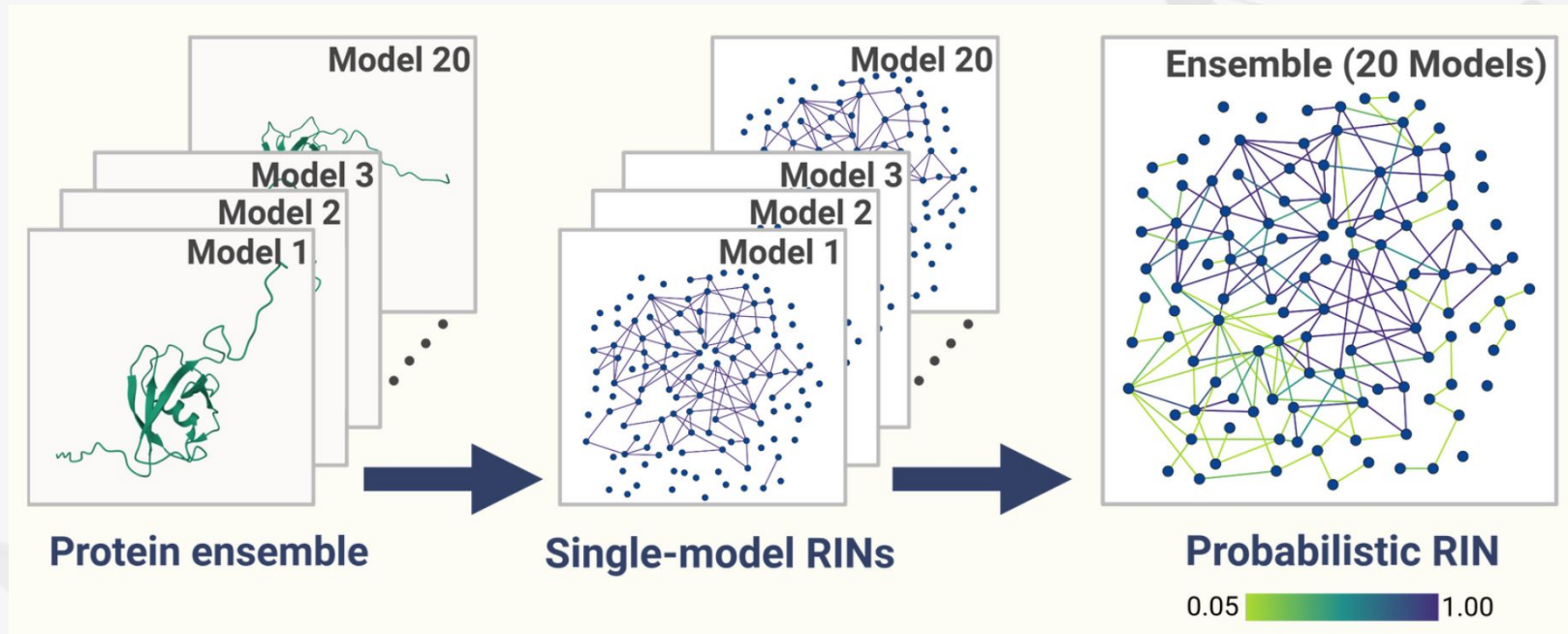
Del Conte et al.

**RING 4.0: faster residue interaction networks with novel interaction types across over 35,000 different chemical structures**

NAR



# Probabilistic RIN



# How to use RING

## CLI

```

> ring -h
RING $ -- Residue Interaction Network Generator - Version v4.0-4-gfca5770

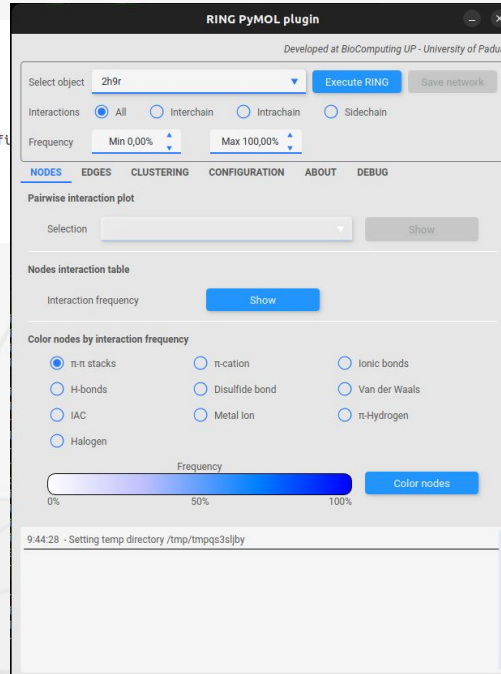
Input options:
-i <filename> Input PDB/mmCIF file
-I <filename> Input text file with a list of PDB/mmCIF files, absolute path needs to be specified
--all_models Executes RING on all models (default false)
-m <number> Model number to use (default first model)
-c <id> Chain identifier to read (default all chains)

Output options:
--out_dir <dirname> Output node and edges to the selected dir. (default input dir)
--export_structure Export the internal structure representation of RING to mmCIF/PDB

Network options:
-n <string> Network policy to define a contact between 2 groups/residues
Options: closest, lollipop, ca, cb (default closest)
-g <number> Network distance threshold for the specified network type (default 5.0)
-s <number> Sequence separation (gap) between residues (default 3)
--get_iac Include generic Inter-Atomic Contacts (IAC) (default false)
--no_het Skip calculation of hetero atoms connections (default false)
--water Include water molecules (default false)
--no_specific Skip calculation of bond specification (default false)
--energy Calculates TAP and FRST potentials for each residue, slower. (default false)
--no_add_H Skip the addition of H atoms to amino acids and nucleotides (default false)

Edges options:
default: Return multiple edges for a pair of nodes, those that should be the most int
--all_edges Return all edges found for a pair of nodes. (default false)
--best_edge Return only the most valuable connection between two nodes (default false)
  
```

## PyMOL plugin



## Web server

Upload File

Examples: [2H9R](#) [1K47](#) [P04637](#)

Example: Test with open conformation

**Nodes**

Closest  
  Lollipop  
  C $\alpha$   
  C $\beta$

Strict  
  Relaxed  
  Manual

Show advanced

**Edges**

Multiple  
  All  
  One

**Other options**

Add hydrogens  
 Only amino acids  
  Include water

Hydrogen bond donor-acceptor dista... A

3.9

pi-pi stacking centers distance A

6.5

Ionic bond distance A

4

Metal ion coordination distance A

2.8

pi-Hydrogen donor-ring center distan... A

4.3

Hydrogen bond H-acceptor distance A

2.5

pi-Cation distance A

5

Disulphide bonds distance A

2.5

van Der Waals radii intersection fracti... A

0.01

Submit 
Reset

# Command Line Interface

## Geometric parameters

- Strict
- Relaxed
- Manual
  - Distance thresholds
  - Angles

## Additional settings

- Gap between residues (default 3)
- IAC?
- Water molecules?
- Hydrogen adding (default True)

# OUTPUT FILES

## RING representation

- Plain text file. Similar to the original PDB input file, but containing the structure as used by RING.
- Can be opened with Pymol for visualization.
- Useful for checking hydrogen placement.

## Nodes file

- Plain text file. Contains information about the nodes.
- Organized in columns: NodeId, Chain, Position, Residue, Type, DSSP, **Degree**, Bfactor\_CA, Coordinates, pdbFileName, Model.

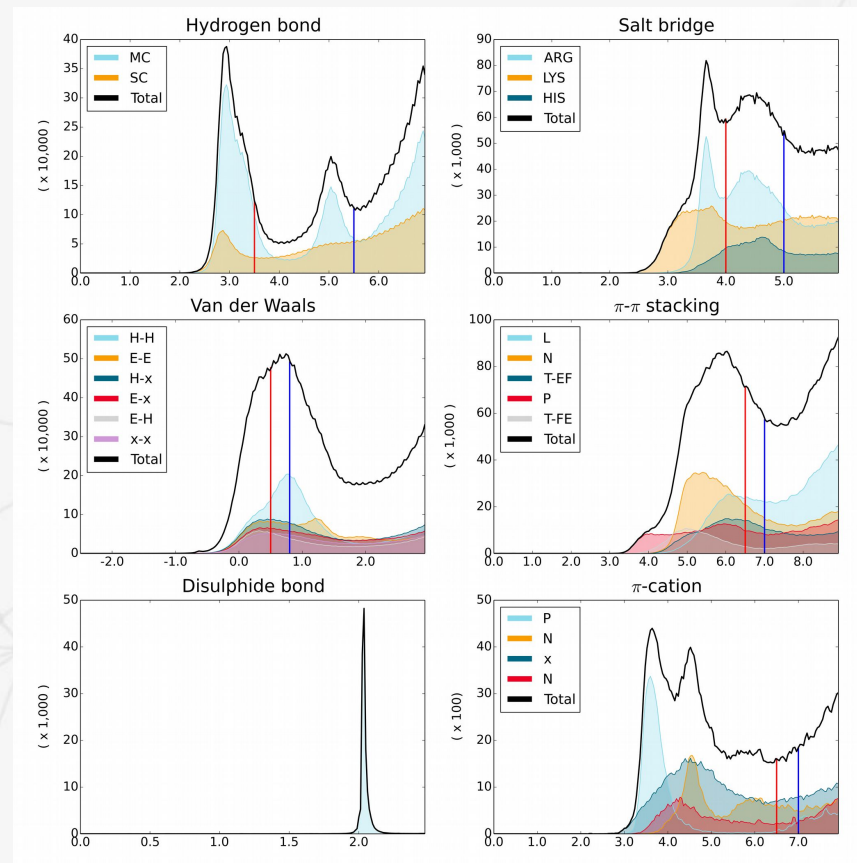
## Edges File

- Plain text file. Contains information about the edges.
- Indicates: interacting nodes and atoms, interaction type, geometrical parameters, model number.

# Distance cutoff


- Relaxed
- Strict (default)

*The RING-2.0 web server for high quality residue interaction networks.* Piovesan D, Minervini G, Tosatto, SCE. **NAR**, 2016, 44(W1), W367-74



# Web server

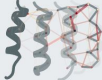
<https://ring.biocomputingup.it/>

**RING** Home Jobs About Help Login 

## Residue Interaction Network Generator Light Dark


The **Residue Interaction Network Generator (RING)** identifies non-covalent interactions at the atomic level in protein structures. RING processes **multi-state structures**, including molecular dynamics and structural ensembles, generating probabilistic networks and conformational-dependent contact maps with remarkable speed, scaling linearly with input size. The result page provides a synchronized and interactive side-by-side view of the structure and network. Users can **log in** through ORCID to save analyses for future use.

The new version of RING has advanced capabilities, **connecting the structure of all chemical components** found in the PDB by using the PDB HET dictionary. This integration includes the definition of hydrogen atom donors and acceptors, addition of hydrogen atoms with correct nomenclature and placement, generalized aromatic ring detection, and calculation of new interactions such as  $\pi$ -hydrogen, metal ion coordination, and halogen bonds. RING supports the **calculation of interactions with over 35,000 chemical components**. The web app now allows users to visualize structures with added hydrogens and explore various interactions calculated by RING, with detailed information displayed directly on the structure, along with many other components for **different representations of the contacts**.



For questions and comments, please [contact us](#). RING output can also be generated with the [RING standalone package](#) (available as pre-build for Linux and MacOS systems).

**ATTENTION:** We discovered a bug that was introduced on February 12th, 2025. It has now been fixed, but we strongly recommend rerunning any analyses performed between February 12th and April 23rd, 2025.

Structure ID (PDB or AlphaFold) or Upload File 

Examples: [2u9B](#) [3k67](#) [P04637](#)


Job description  Email (optional)

Example: Test with open conformation

Chain (all if empty)  Model (all if empty)  Sequence separation



Nodes  Closest  Lollipop  Ca  C $\beta$

Edges  Multiple  All  Best  One

Thresholds   Strict  Relaxed  Manual  Show advanced

Other options  Add hydrogens  Only amino acids  Include water  Prefer label\_asym\_id




Hydrogen bond donor-acceptor distance	A	Hydrogen bond H-acceptor distance	A	$\pi$ -stacking centers distance	A
3.9		2.5		6.5	
$\pi$ -Cation distance	A	Ionic bond distance	A	Disulphide bonds distance	A
5		4		2.5	
Metal ion coordination distance	A	van Der Waals radii intersection fraction	A	$\pi$ -Hydrogen donor-ring center distance	A
2.8		0.01		4.3	

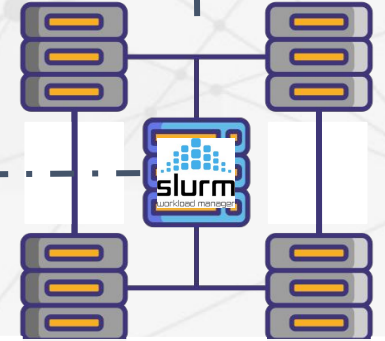
Submit  Reset 

For very large molecular dynamics simulations (>500 models) or huge structures (>200 MB) please consider using the [RING standalone package](#). You can find more information on how RING works in the [about](#) page. A brief overview and a description of the inputs, outputs and available APIs is available in the [help](#) page.

**RING 4.0: faster residue interaction networks with novel interaction types across over 35,000 different chemical structures**  
Alessio Del Conte, Giorgia F Camagni, Damiano Clementel, Giovanni Minerini, Alexander Miguel Monzon, Carlo Ferrari, Damiano Piovesan, Silvio C E Tosatto (2024) *Nucleic Acids Research*<sup>®</sup>

BioComputing UP - Department of Biomedical Sciences - University of Padua, Italy - 2023  
[license & disclaimers](#)

BioComp cluster



# Web server



Authenticate

Verify  
authentication

Port:443 (HTTPS)



- Creates an interface with the DRM
- Sends the jobs to the DRM
- Retrieves the status of the jobs
- Download the results
- Manage permissions



Web Browser

# RING-PyMol (not working with latest PyMol)

Repo and Wiki

<https://github.com/BioComputingUP/ring-pymol>

Plugin code archive

<https://biocomputingup.it/shared/ring-plugin/>



# Which is best?

## Local RING

- ✓ FAST
- ✓ Great for very large structures and huge ensembles
- ✓ Great for large scale analysis
- ✗ Limited output for single-model analysis
- ✗ Not very user friendly
- ✗ Network can't be directly imported to Cytoscape

## Web Server

- ✗ Slow(er)
- ✗ Not suitable for very large structures and huge ensembles
- ✗ Not suitable for large scale analysis
- ✓ Comprehensive output
- ✓ USER FRIENDLY
- ✓ Network can be directly imported to Cytoscape as a JSON file



