Structural bioinformatics

Practice 6: Protein-protein docking

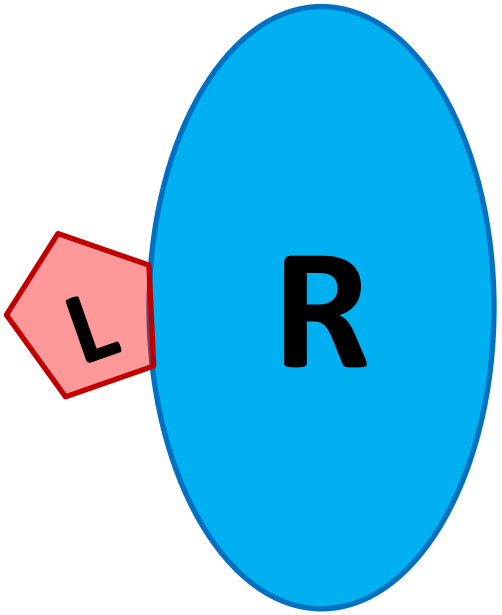
Course 2021-2022

Docking

Docking consists on exploring the conformational space of two interacting proteins

Ligand

Receptor



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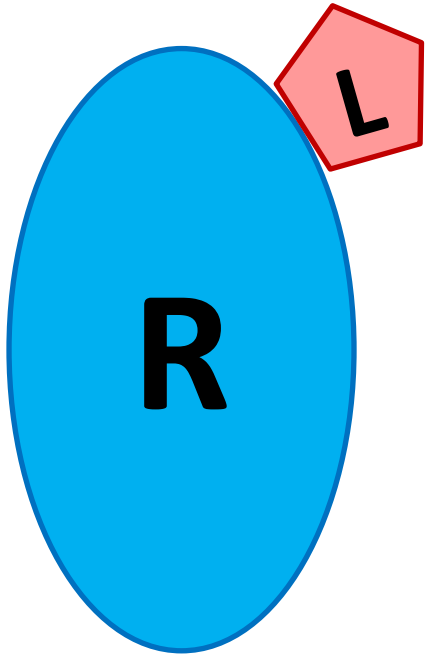

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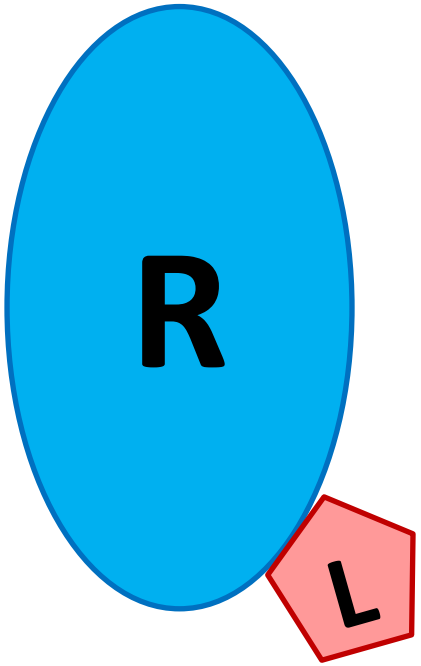


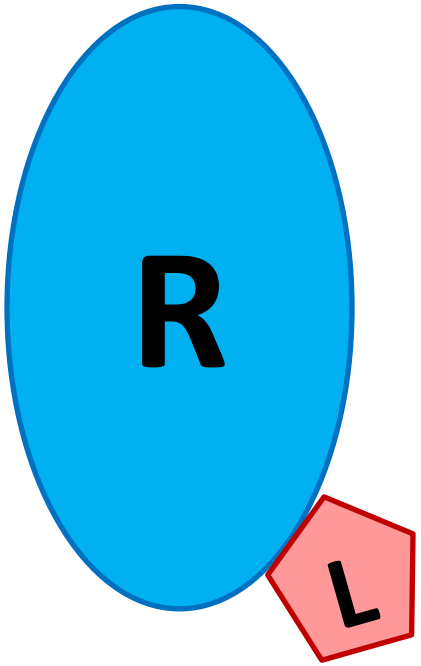
Docking

Docking programs generate lots of possible conformations for the interaction under study

Ligand

Receptor

Each of these docking conformations is called a <u>docking pose</u>



Docking

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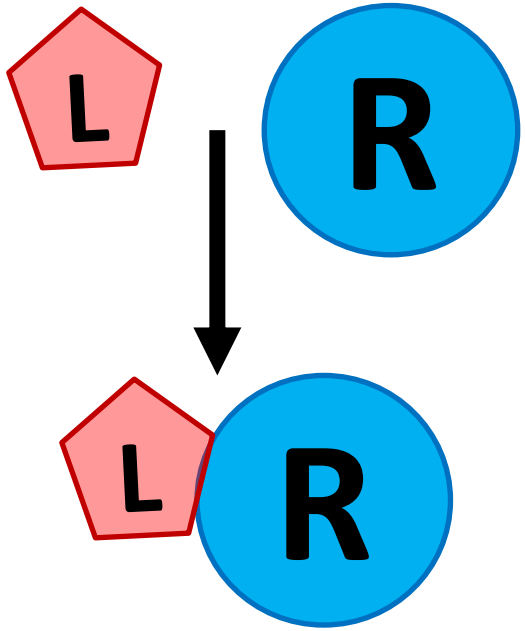
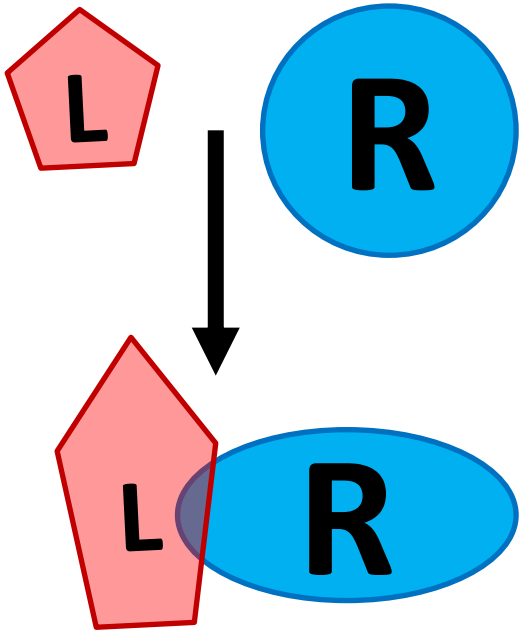
Rigid body docking



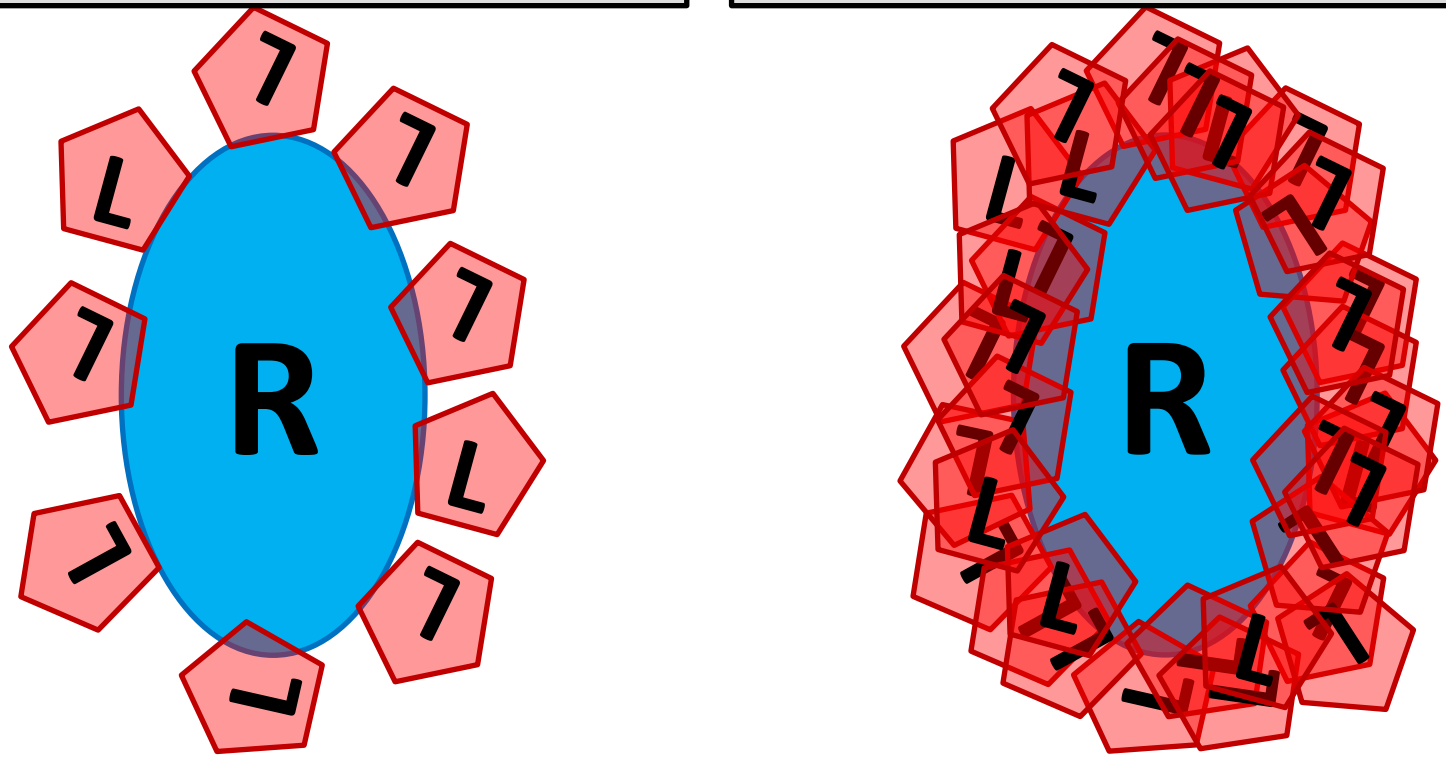
Flexible docking



Docking

Docking programs can explore the conformational space of the interaction with different levels of depth

Non exhaustive	Exhaustive



Docking

How can I know what is the right docking pose?

Docking

How can I know what is the right docking pose?

Using scoring functions

Statistical potentials

- Knowledge based

Physics/chemical scoring functions

- Electrostatics
- Solvatation

Docking

How can I know what is

But is not that easy…

- Electrostatics
- Solvatation

Docking

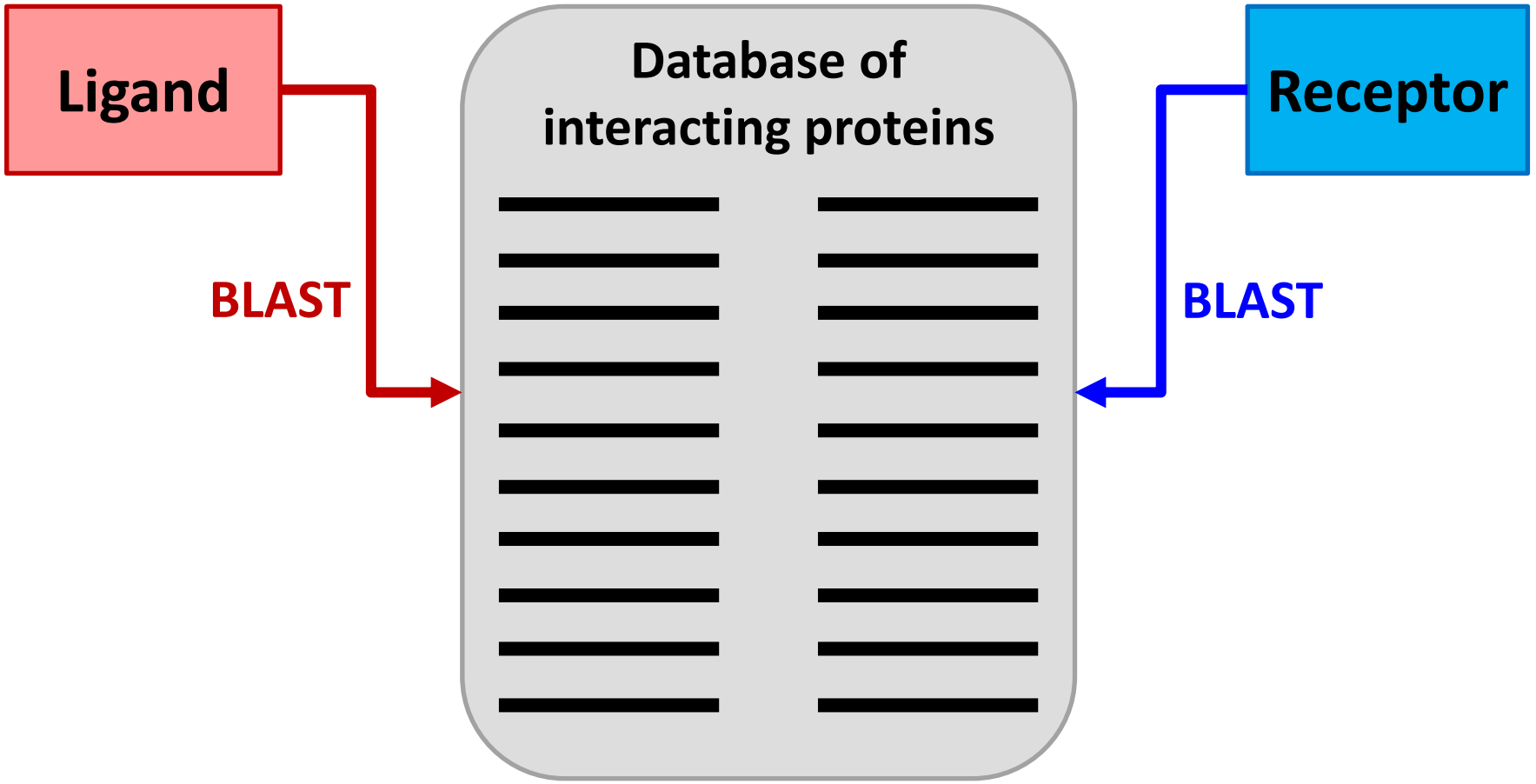
Step 1: Use pydock to reconstruct the interaction between RhoGAP and RAB1A

Docking

Step 2: Use pydock knowing that arginine 279 from RhoGAP is interacting with threonine 129 from RAB1A

Predicting protein-protein interfaces

iFrag is a program that predicts protein-protein interaction inferfaces from protein sequences



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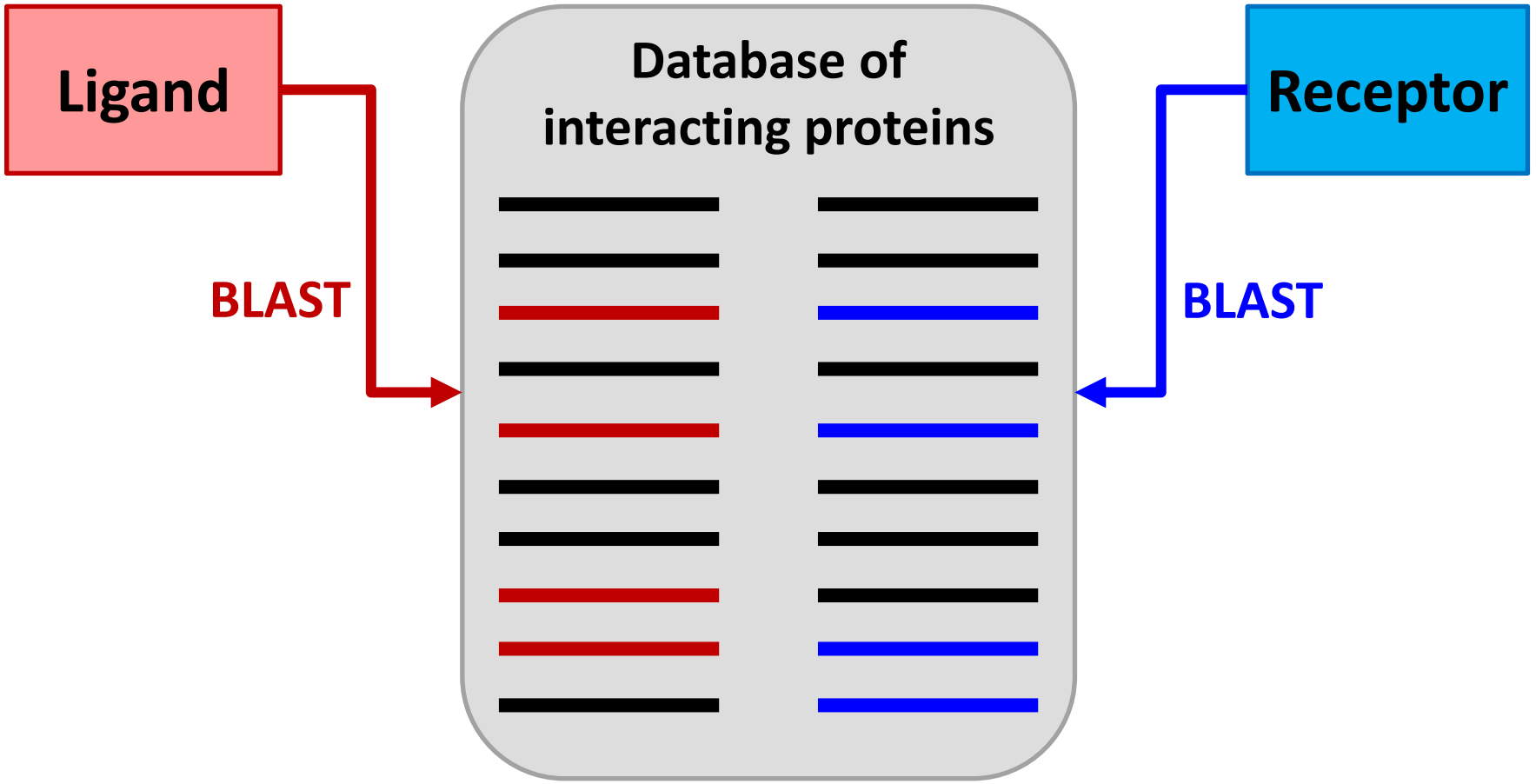

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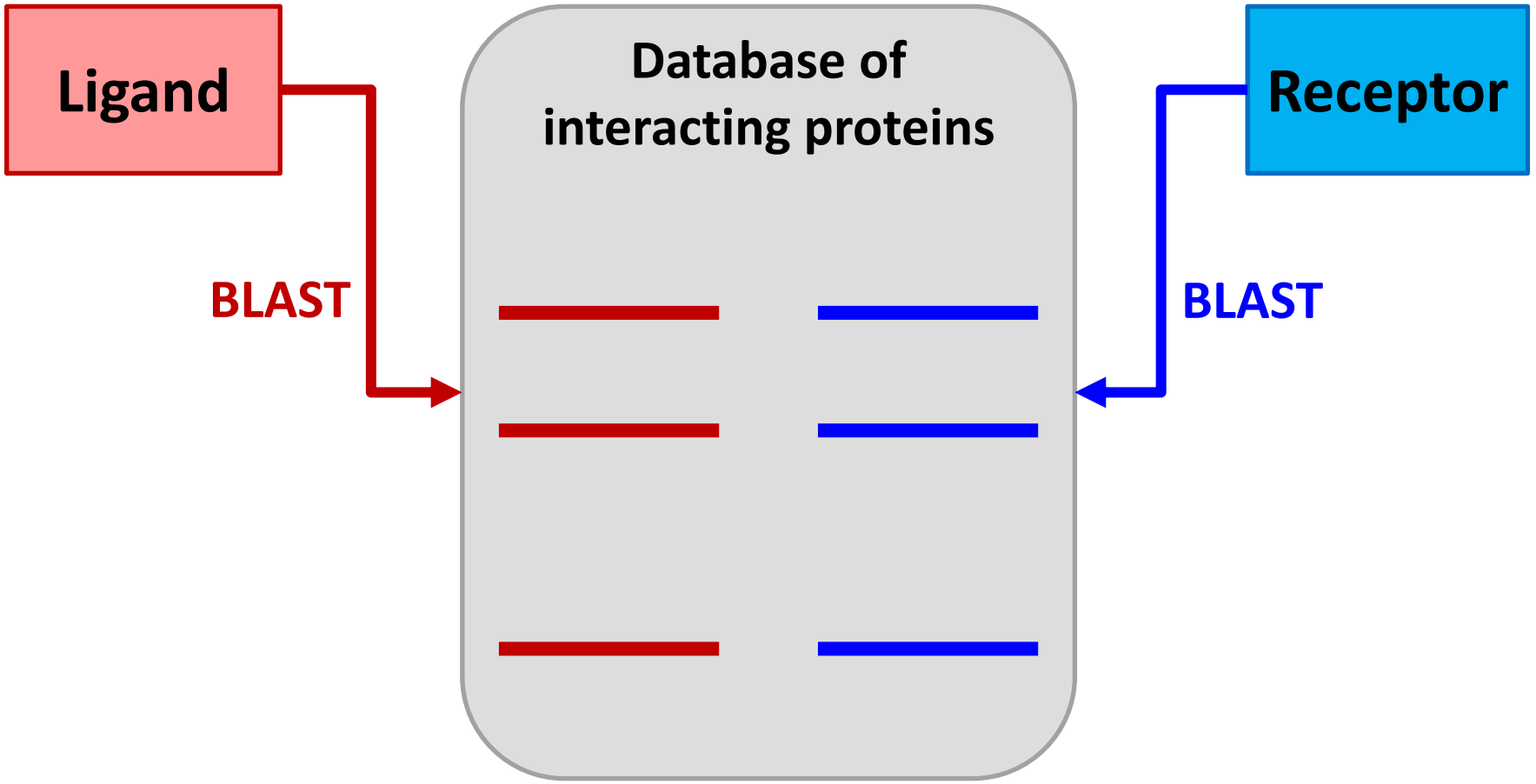

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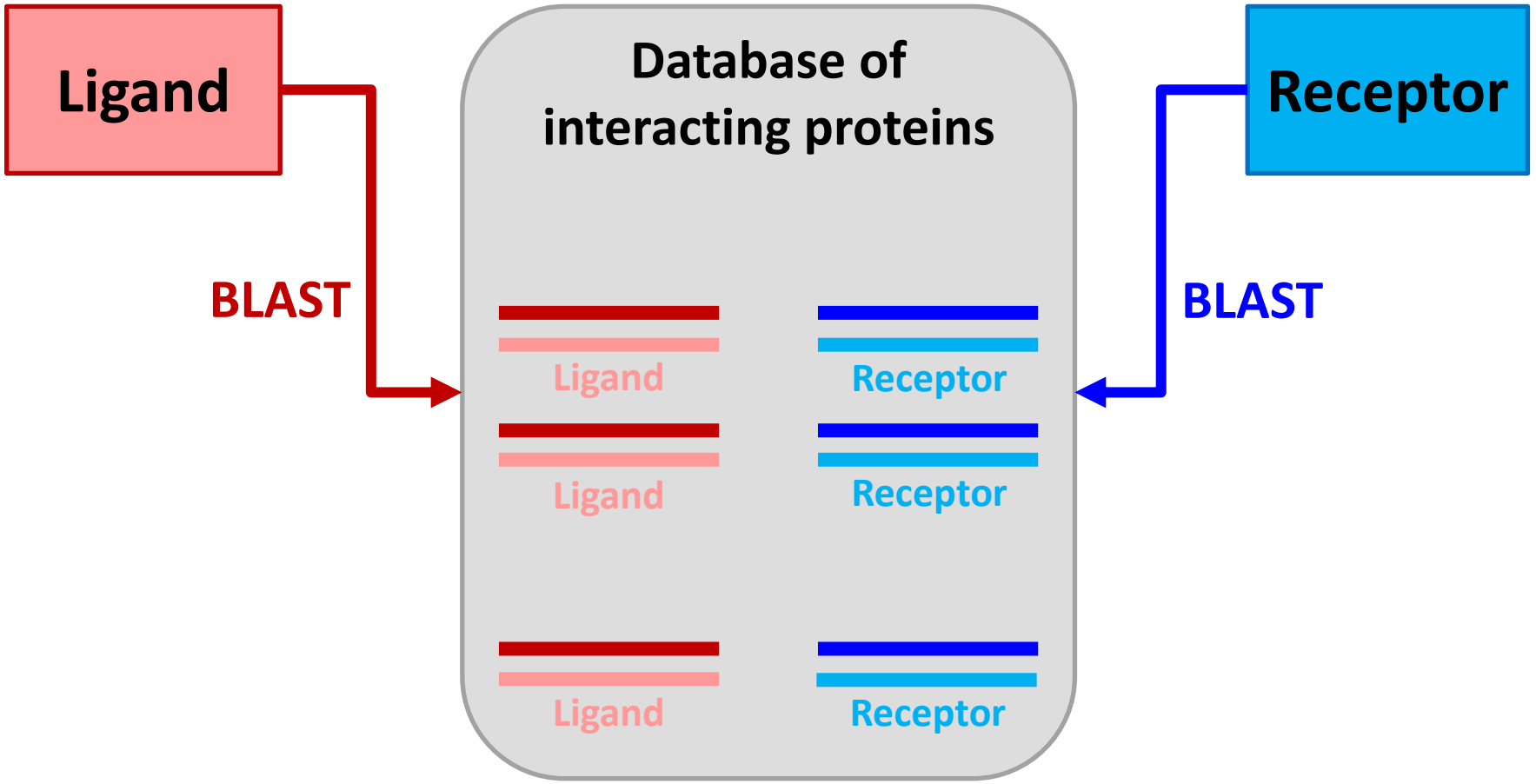

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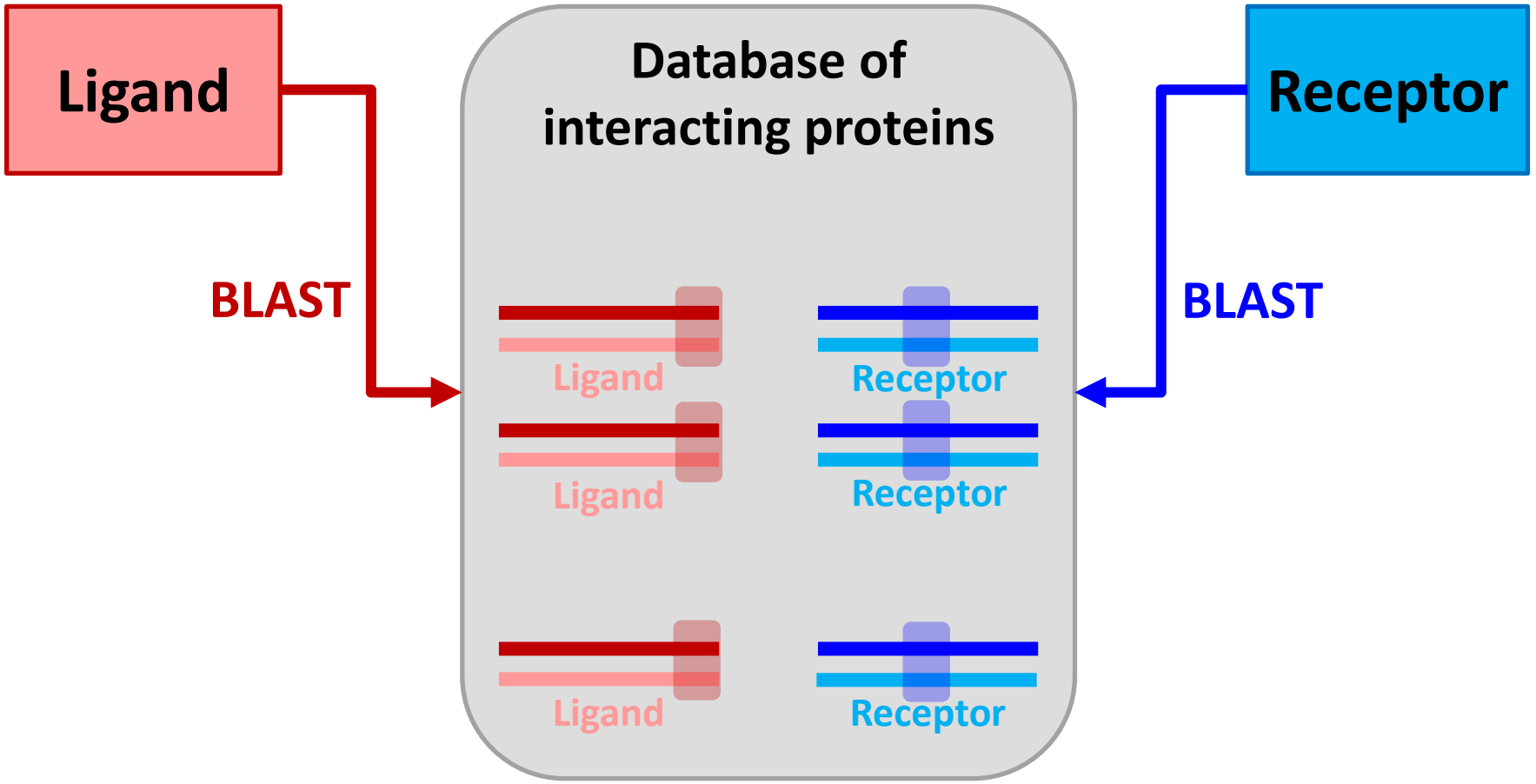

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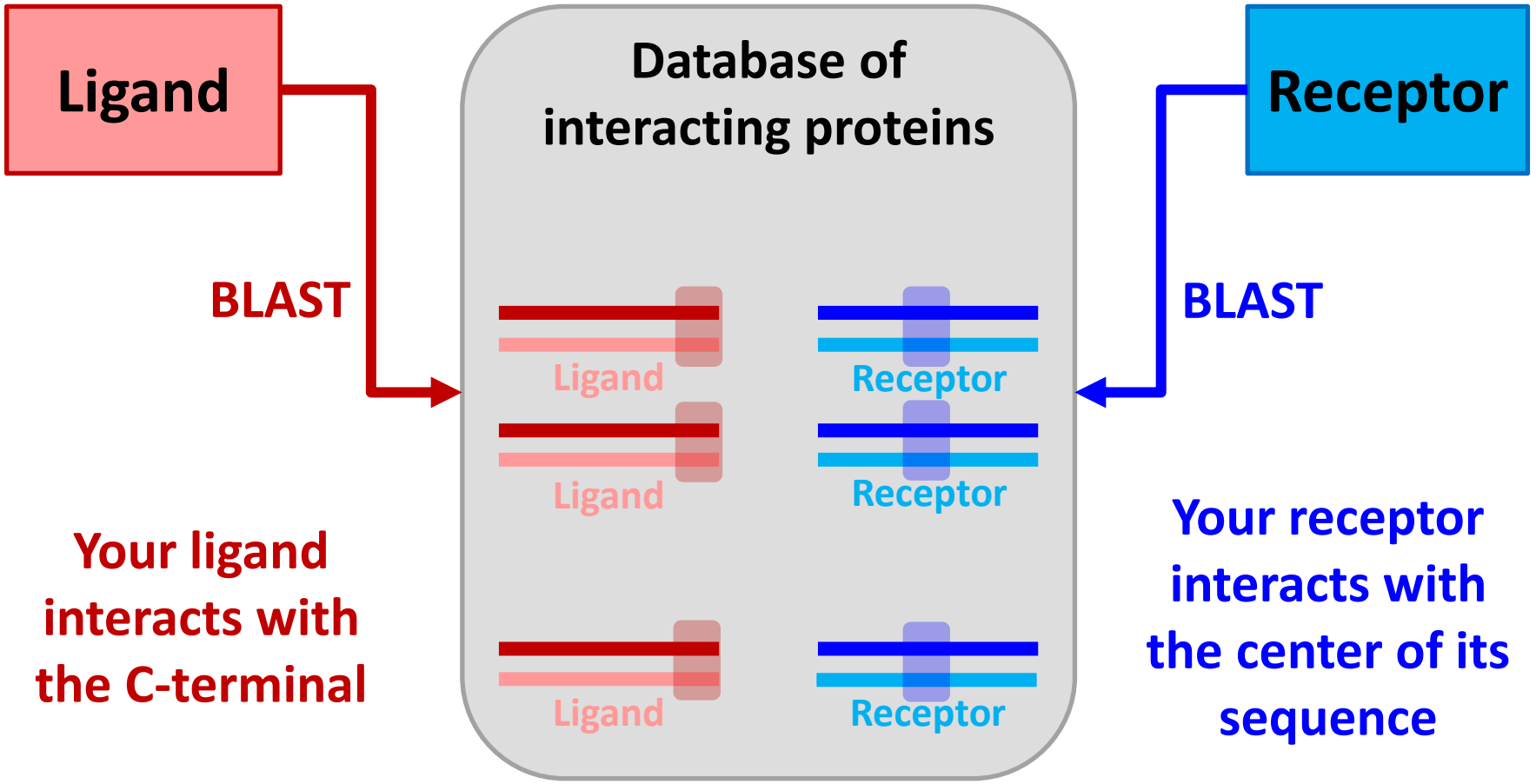
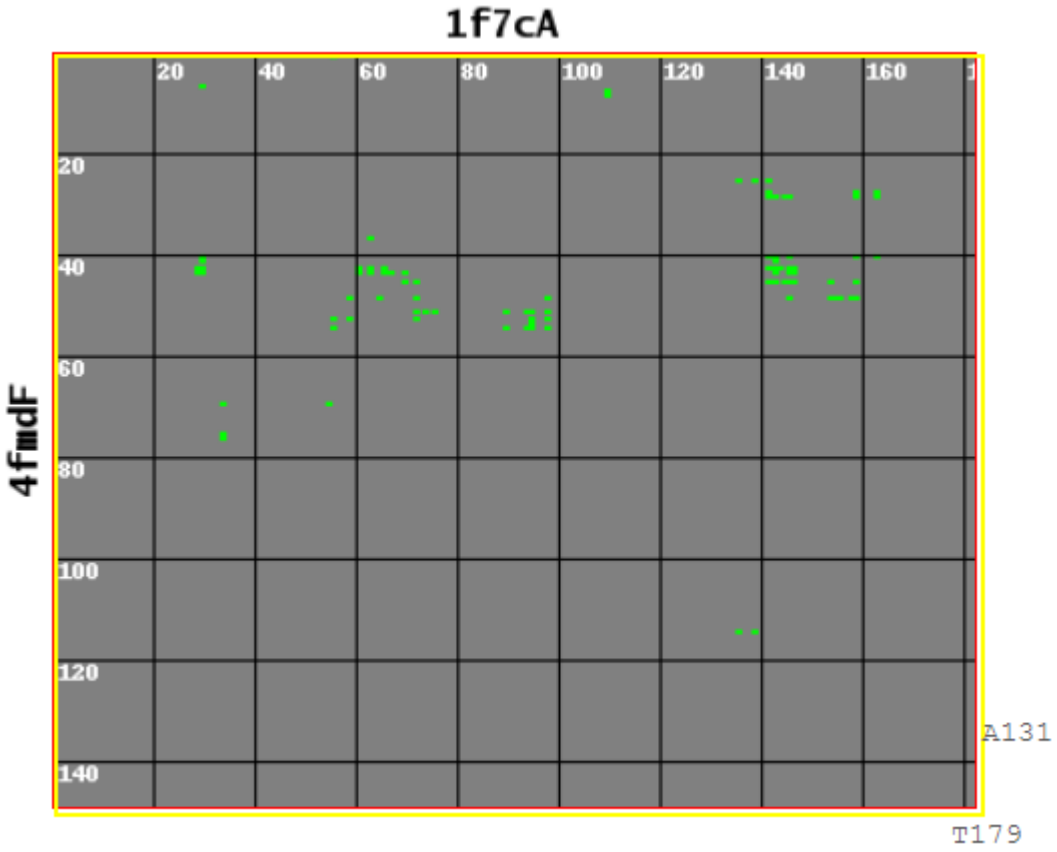


Predicting protein-protein interfaces

iFrag represents its results as a heatmap where each axis represents the amino acid sequence

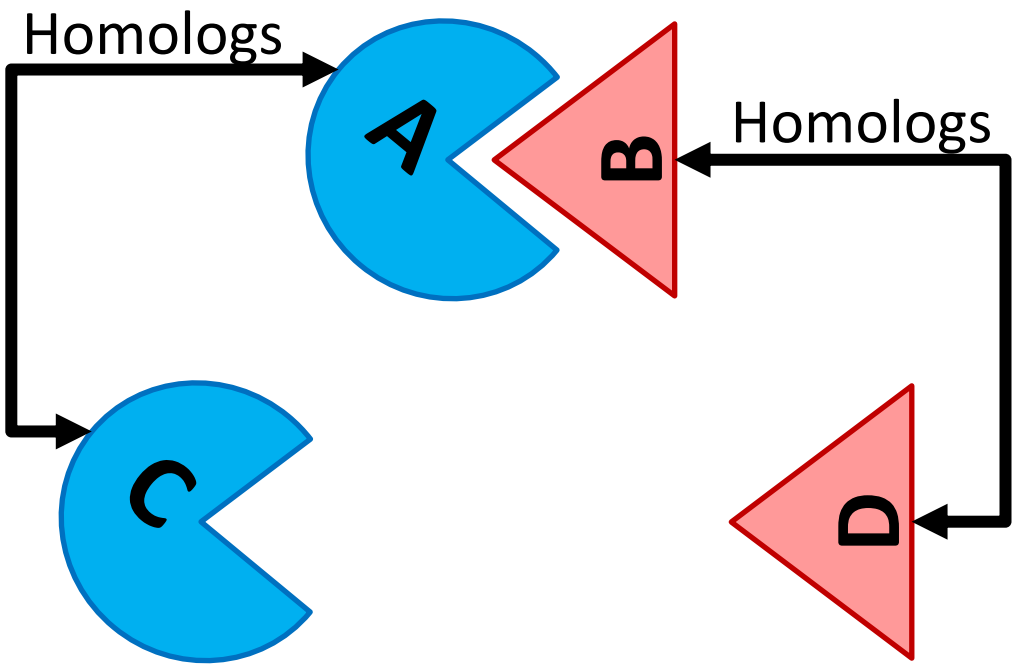


Docking

Step 3: Use the results of iFrag to select amino acids that should be included in the interacting interface and execute pydock

Template guided docking

This is what we did on practical 3: reconstructing protein interactions using superimposition



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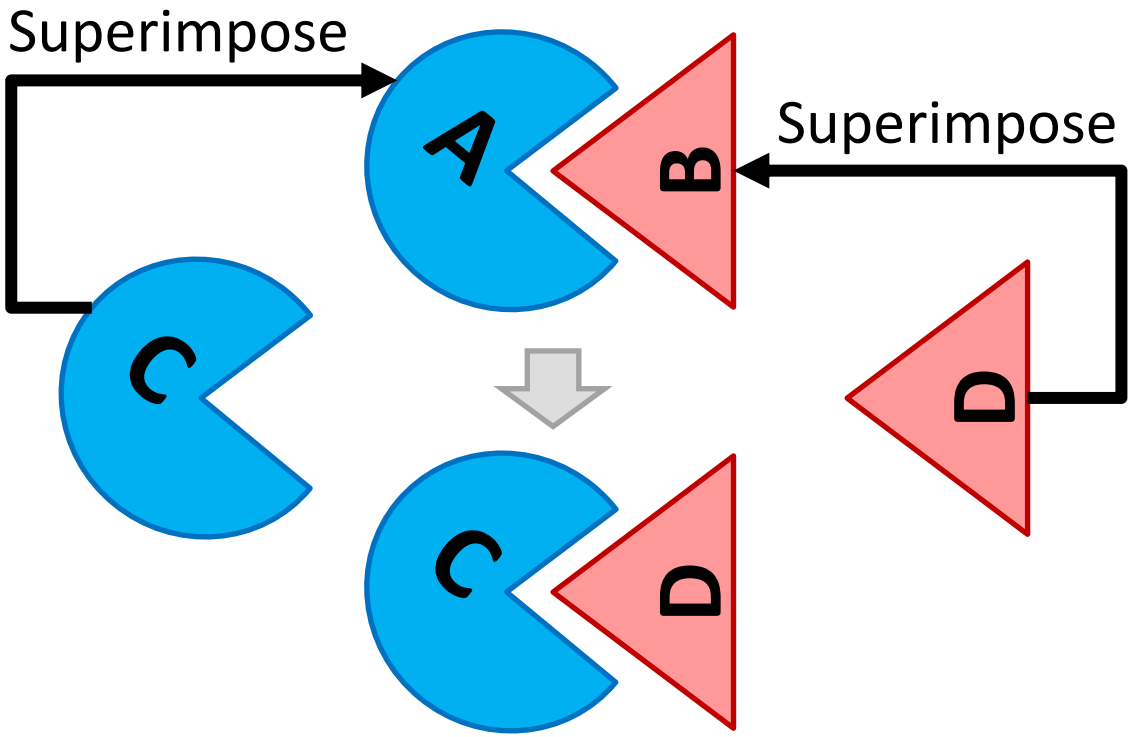


Template guided docking

Ab initio docking	Template guided docking
Not very reliable	Very reliable
Can be applied to any pair of proteins	Can only applied to protein interactions wih available templates

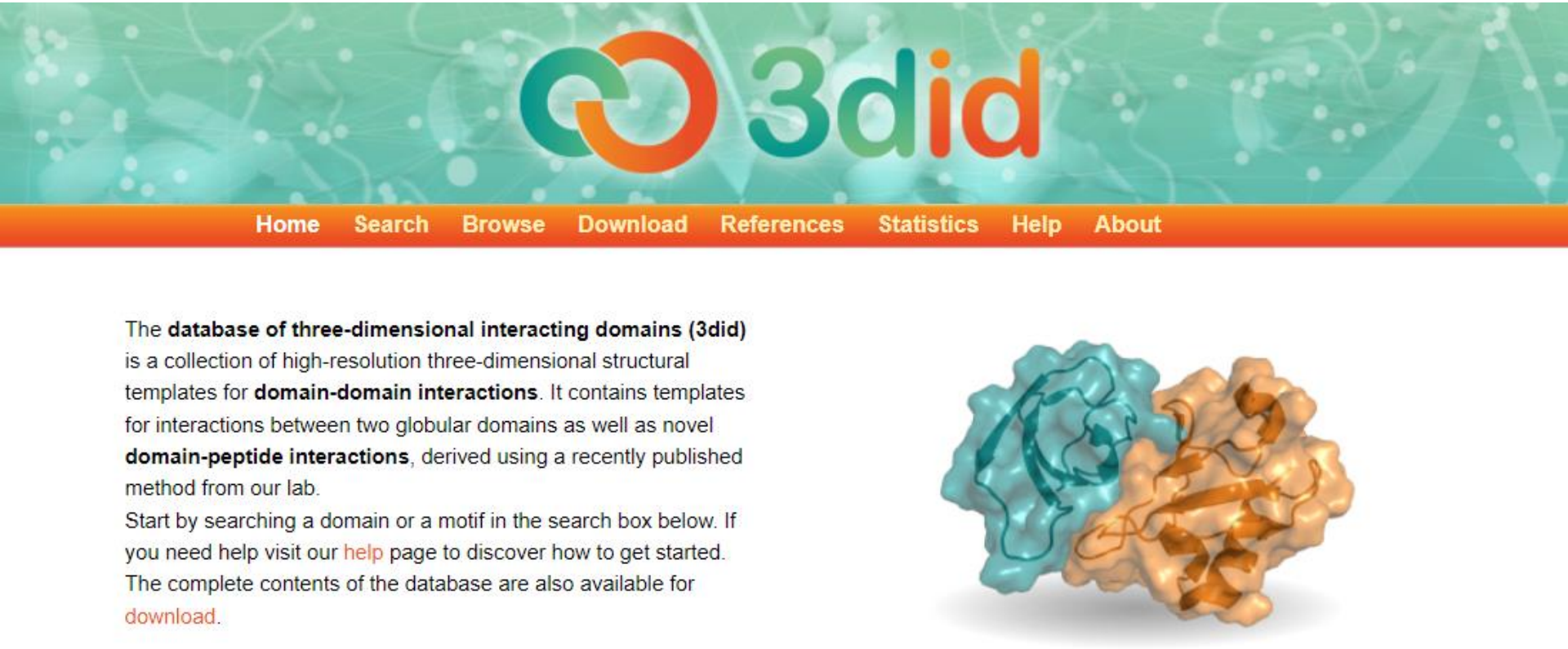
Template guided docking

Ab initio docking

Is there an easy way to find structural templates for protein-protein interactions???

Template guided docking

3did is a database for interacting protein domains



Template guided docking

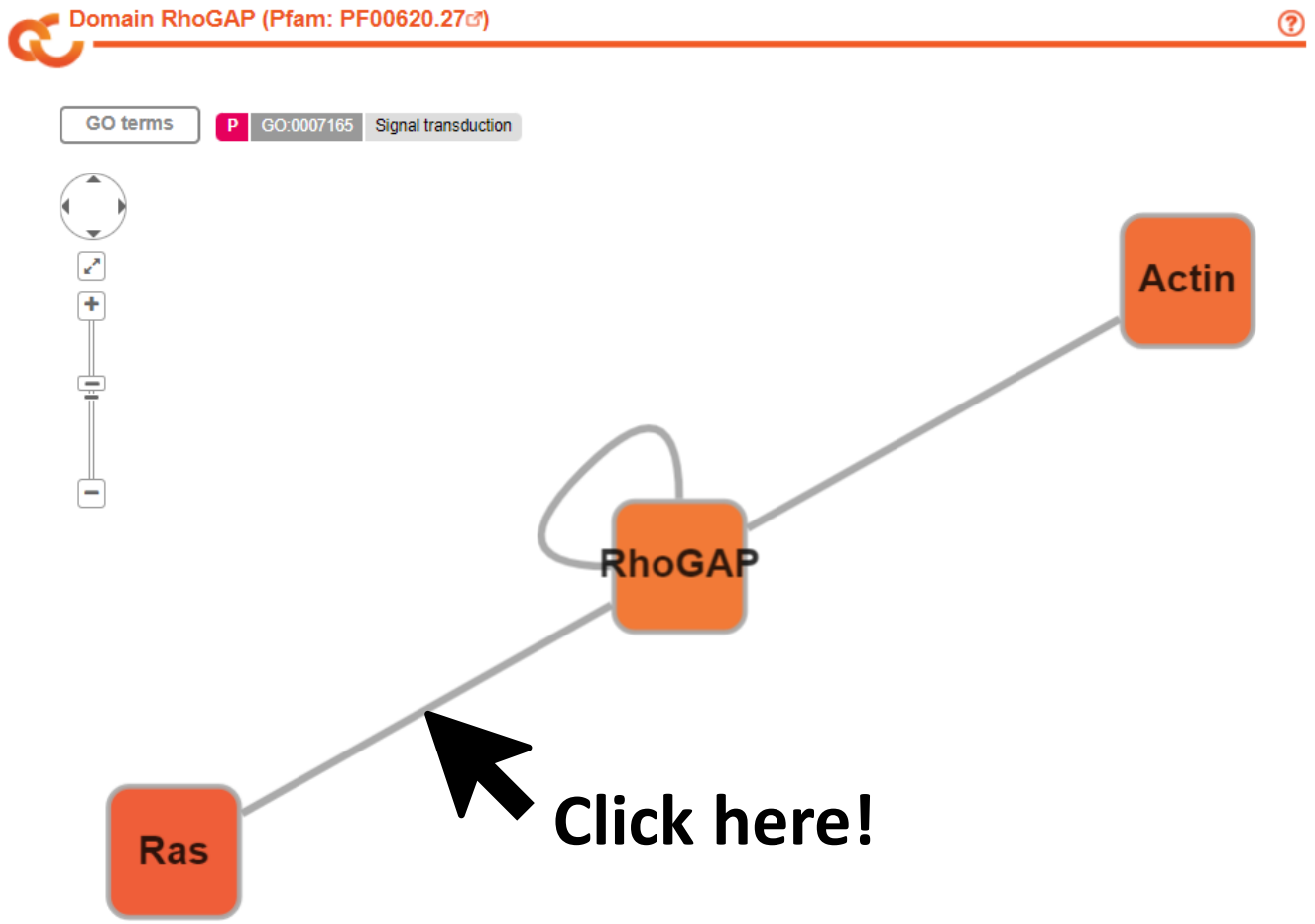
Upload the sequences of the proteins we are working with to the cluster and find what are their domains

```
hmmscan /shared/databases/pfam-3/Pfam-A.hmm 1f7cA.fa > 1f7cA.out
```

```
hmmscan /shared/databases/pfam-3/Pfam-A.hmm 4fmdF.fa > 4fmdF.out
```

Template guided docking

Search the RhoGAP domain in the 3did database



Template guided docking

Here you have the page for the interaction between RhoGAP and RAS domains

DDI interaction between RhoGAP and Ras

Interactor1 :: Domain RhoGAP

Pfam: PF00620.27

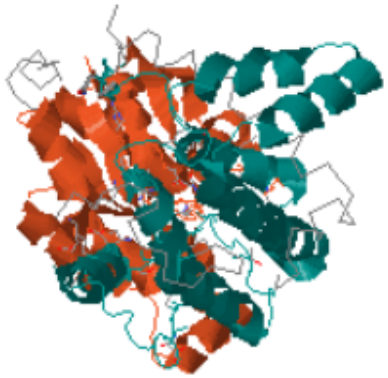
GO | P | GO:0007165 | Signal transduction

Interactor2 :: Domain Ras

Pfam: PF00071.22

GO | F | GO:0003924 | GTPase activity | F | GO:0005525 | GTP binding

5c2j B-A



Template guided docking

Check out the available templates for this interaction

This interaction has been found in the following PDB entries

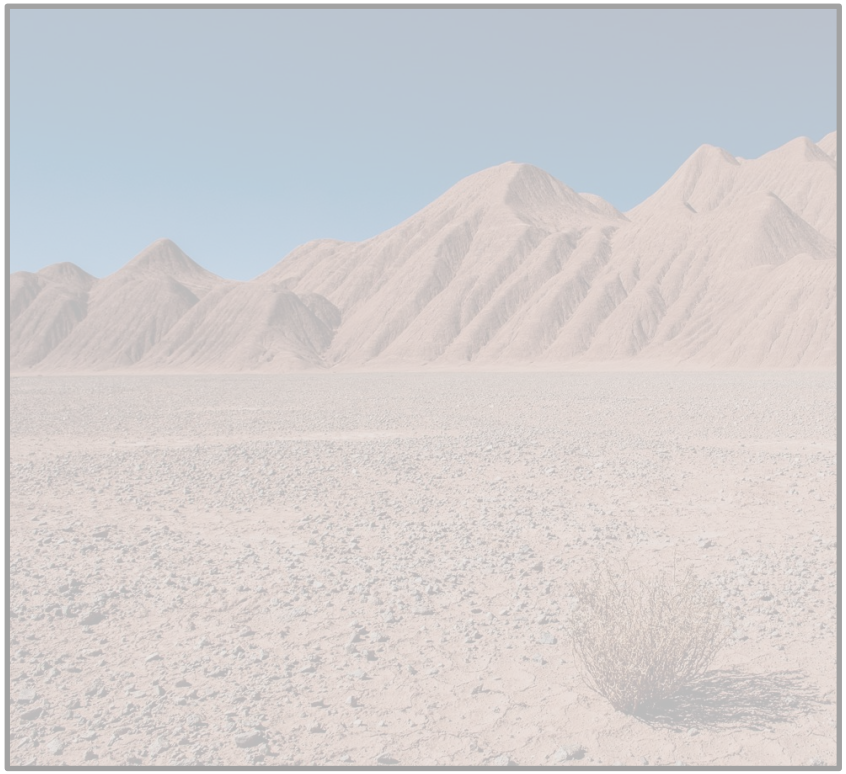
PDB ID	Chain1	Residues	Chain2	Residues	Score	Z-score	Topology	3did	Visualization
5c2j	B	5-178	A	363-511	13.24	5.92556	0:0	View	Jmol
5c2k	A	7-180	A	225-373	12.39	5.51575	0:0	View	Jmol
5hpy	B	7-180	A	213-367	13.48	5.85199	0:0	View	Jmol
5hpy	F	7-180	A	213-367	3.82	3.79582	2:3	View	Jmol
5hpy	F	7-180	D	213-366	13.42	5.69934	0:0	View	Jmol
5irc	D	7-180	B	1262-1414	16.05	6.10425	0:0	View	Jmol
5irc	F	7-180	A	1262-1414	17.48	6.41067	0:0	View	Jmol
5irc	F	7-180	B	1262-1414	1.56	2.24966	1:2	View	Jmol
5jcp	A	7-180	A	920-1073	7.84	5.06104	0:0	View	Jmol
5jcp	A	7-180	B	920-1073	1.53	1.77614	1:3	View	Jmol

Predicting protein affinity from docking poses

How do you imagine the cytoplasm of one cell?

Predicting protein affinity from docking poses

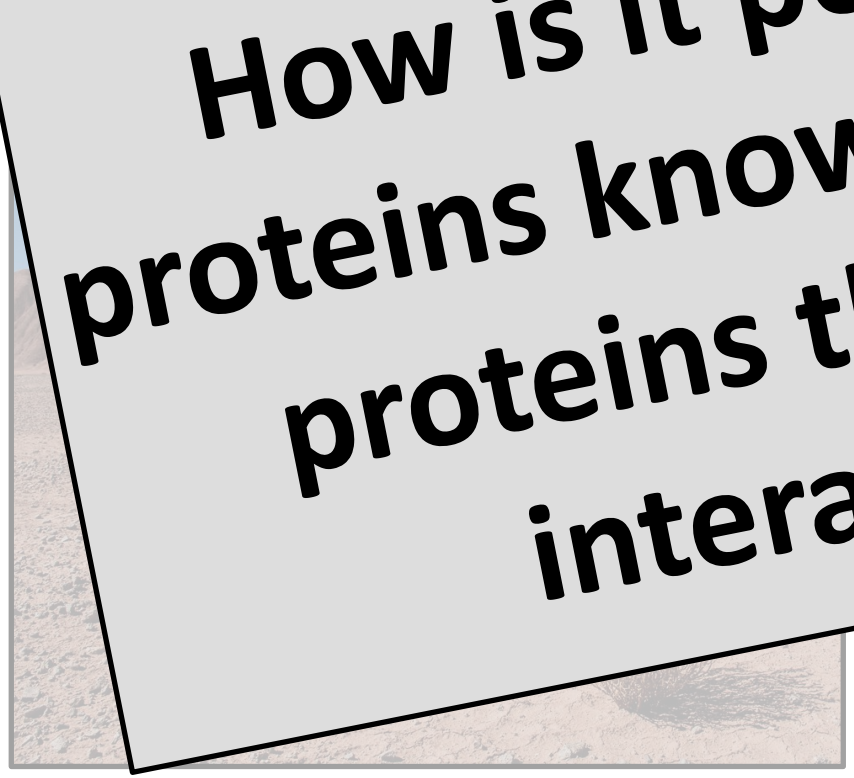
How do you imagine the cytoplasm of one cell?

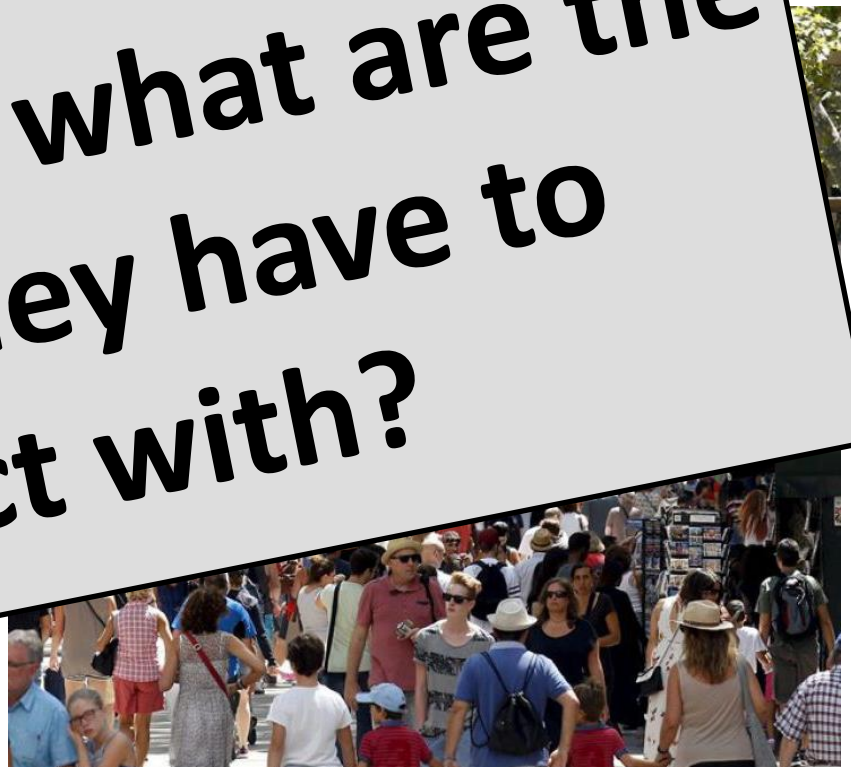


Predicting protein affinity from docking poses

How do you imagine th

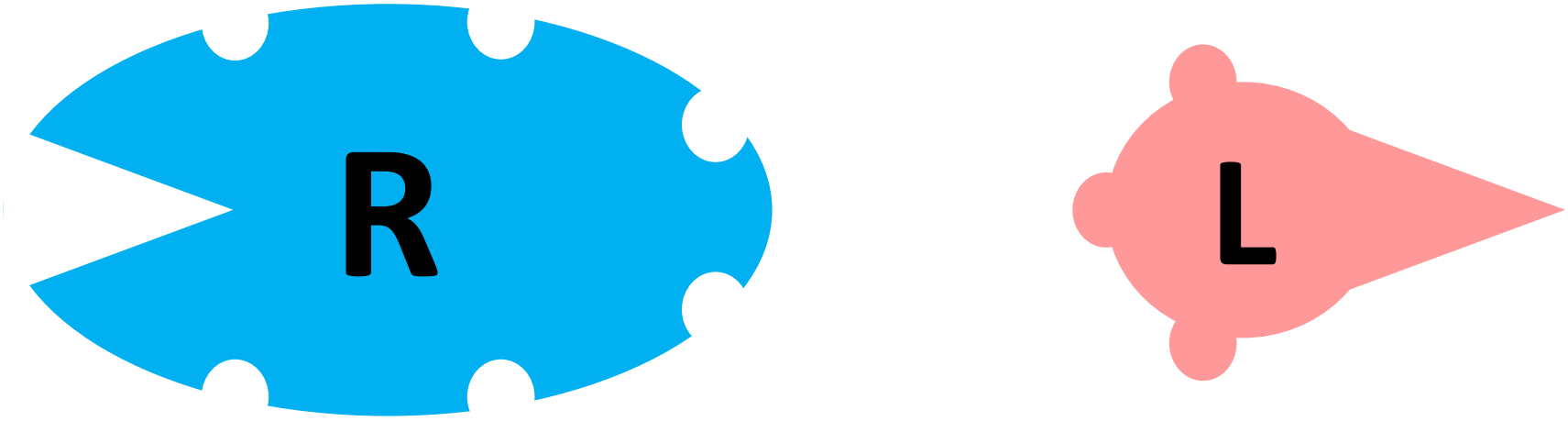
How is it possible that proteins know what are the proteins they have to interact with?





Predicting protein affinity from docking poses

One theory states that non-native conformations also contribute to the stablishment of the interaction



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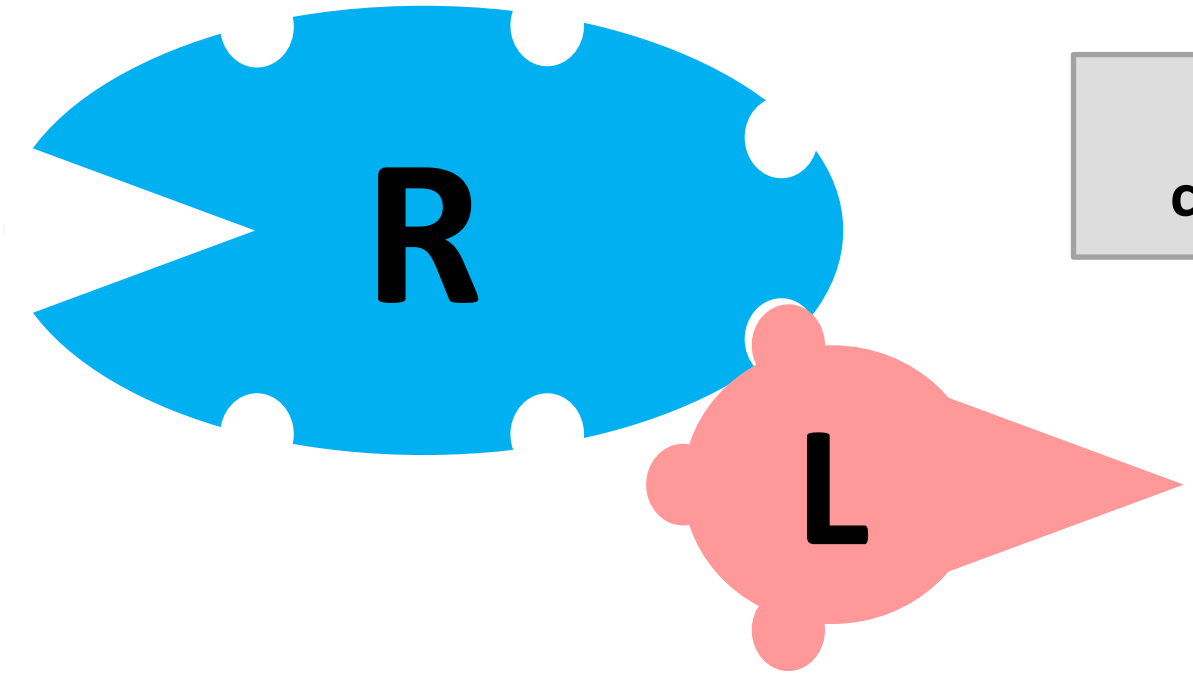

Non-native conformation

Predicting protein affinity from docking poses

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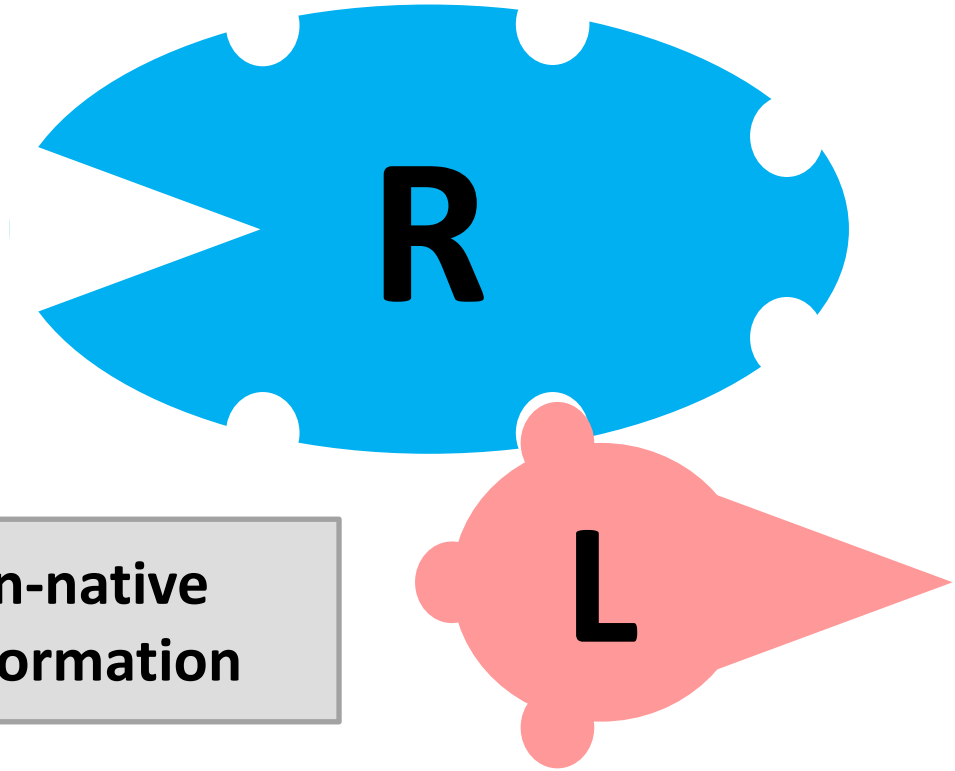

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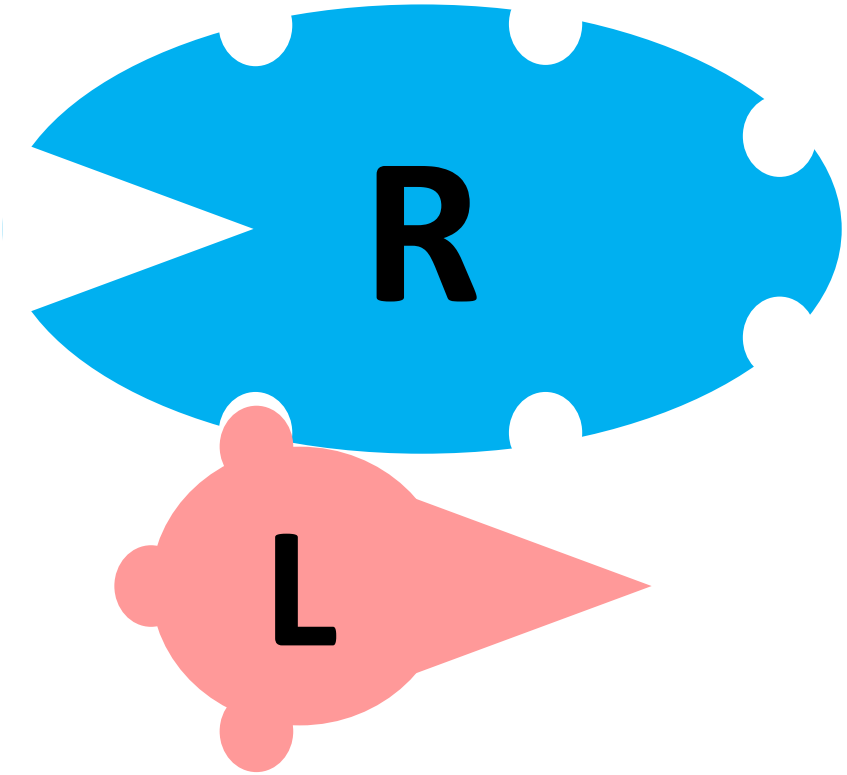

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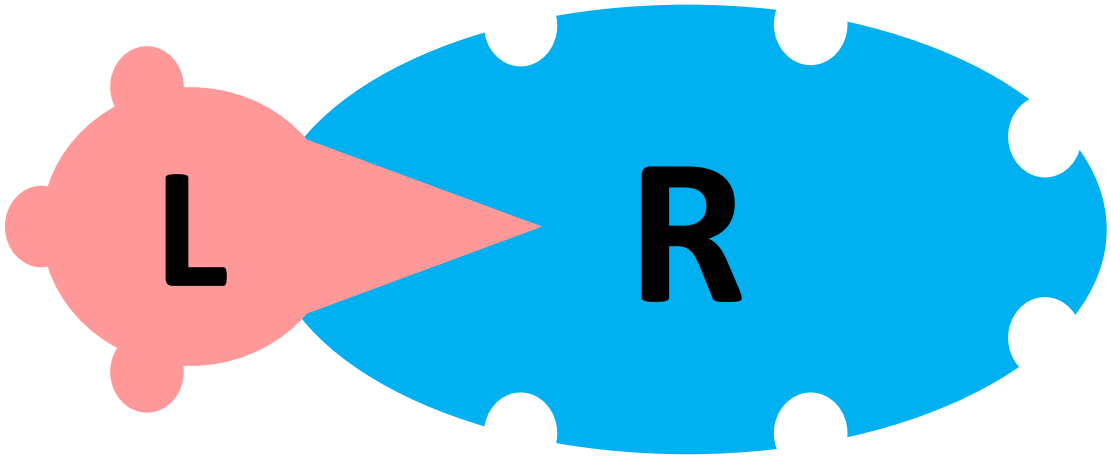
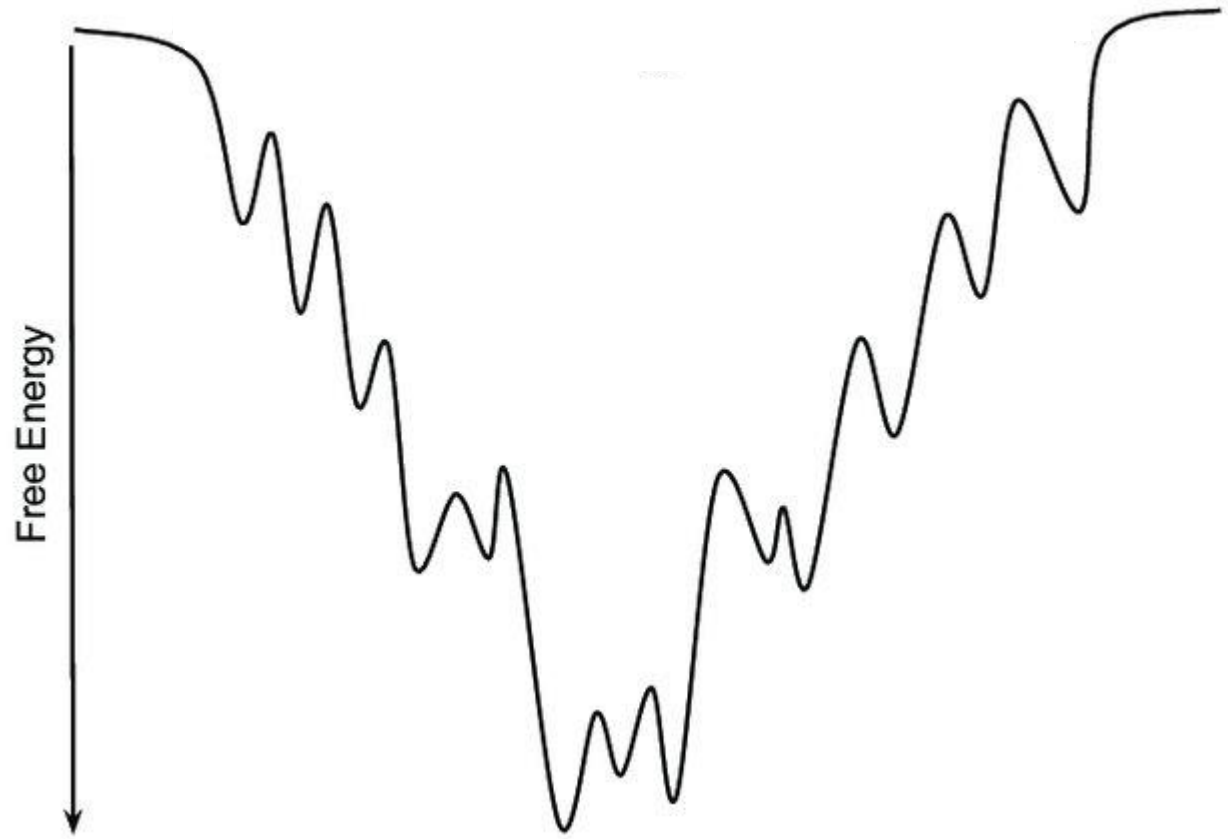


¡Native conformation!

Predicting protein affinity from docking poses

Similarly to the process of protein folding, the process of finding a native conformation can be represented as a funnel of energy



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