SAPIENZA UNIVERSITÀ DI ROMA

PhD Life Sciences

EBERHARD KARLS UNIVERSITÄT TÜBINGEN

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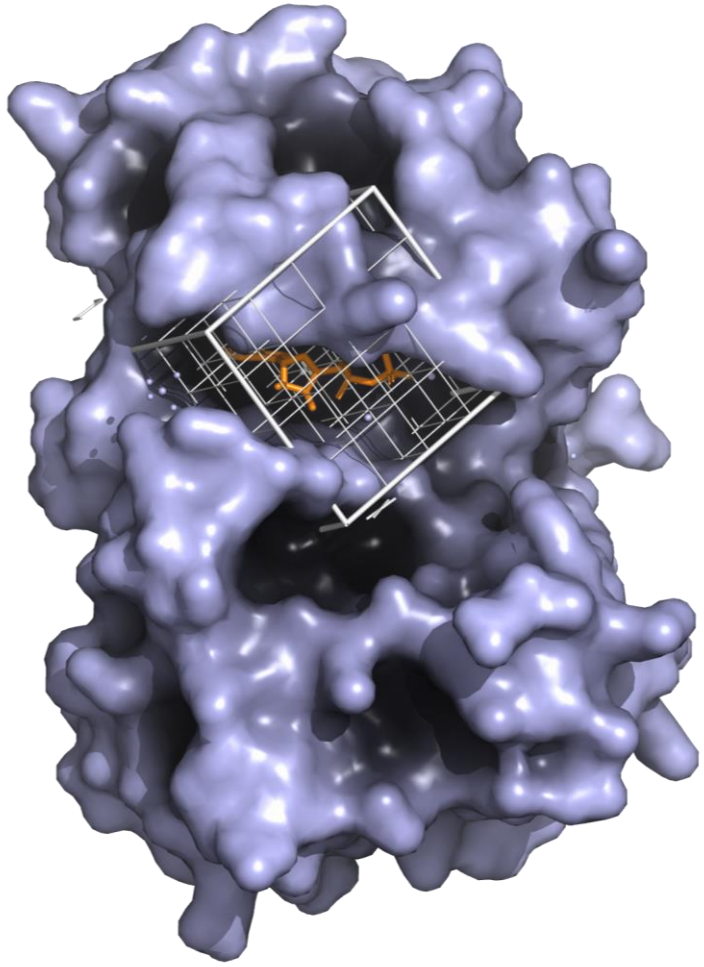
Bioinformatics tools to assess Protein/ligand binding and complexes

CIVIS A European Civic University

Summer School - Bioinformatics for non bioinformaticians - Computational analyses in health and life sciences

18-22 July 2022
Tübingen, Germany

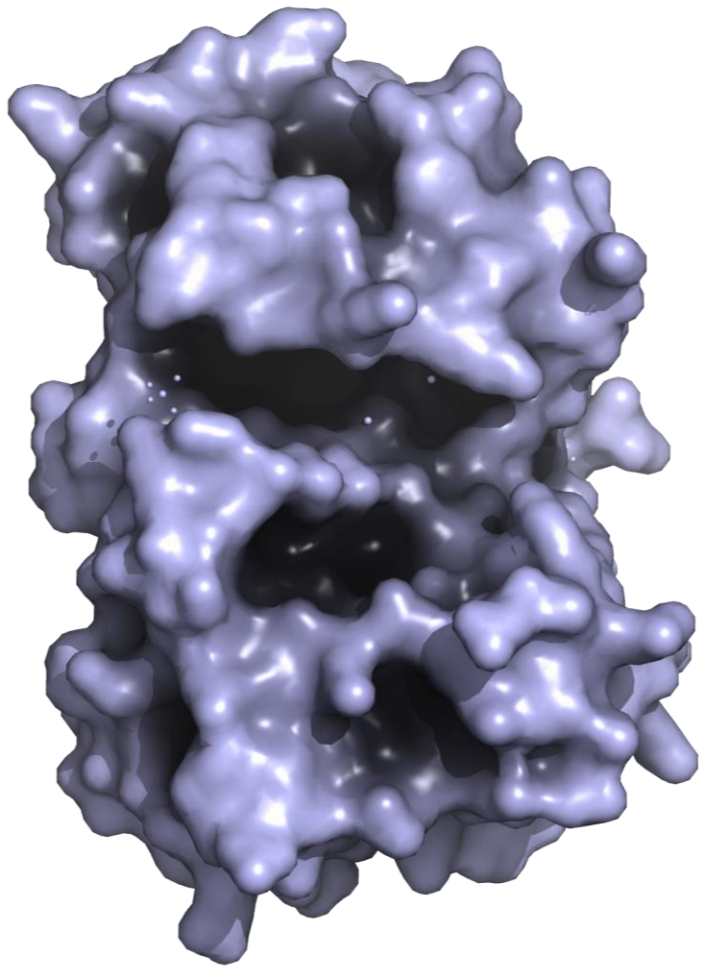


Molecular docking: An *In silico* method for the prediction of ligands' conformation and energy of binding in the interaction with the target

Identification of chemical and structural properties that are mandatory for the interaction to occur (both of the ligand and the target)

Rational design of new ligands with higher affinity for the target

Hypotesis about the mechanism of action (e.g. protein-inhibitor, enzyme-substrate)



Tridimensional Protein Structure

Experimentally determined (x-ray crystallography, nmr, cryo-EM)

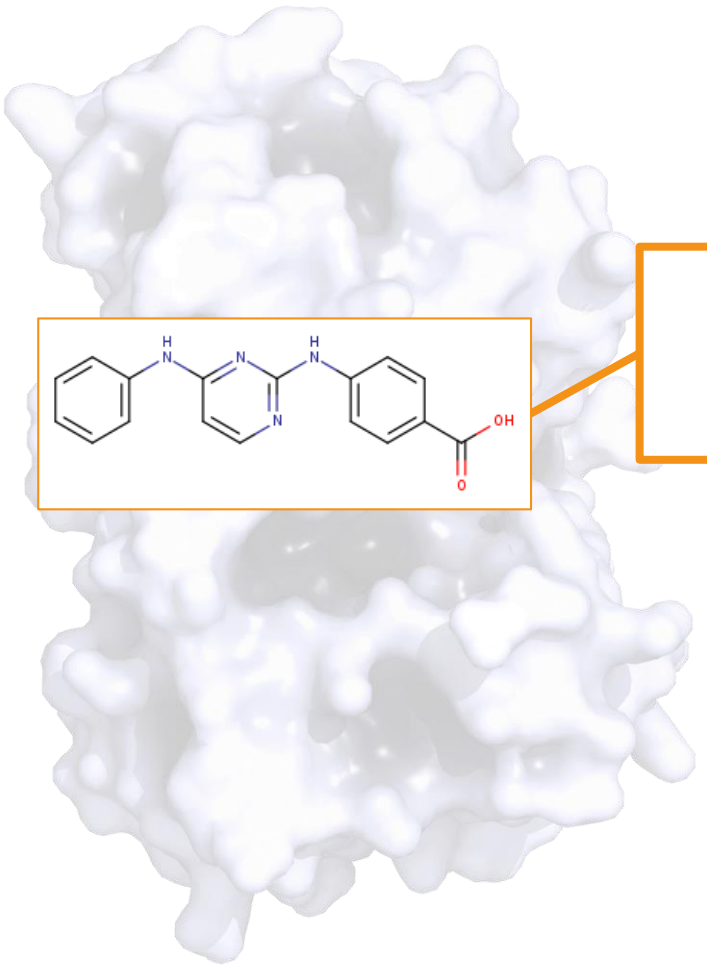
- Protein Data Bank (PDB)
- Electron Microscopy Data Bank (EMDB)

Computationally predicted (homology modeling or 'ab initio' methods)

- AlphaFold: modeled or retrieved from the AlphaFold Protein Structure Database.
- MODELLER implementation in Pymod

Control of proper formatting of chemical properties:
- protonation;
- assignment of partial charges;
- file format (e.g. mol2, pdb, pdbqt)

- Molecular Graphics Viewer with chemical modification tools (e.g. PyMOL)
- Command-line chemical modification tools (e.g. Openbabel)



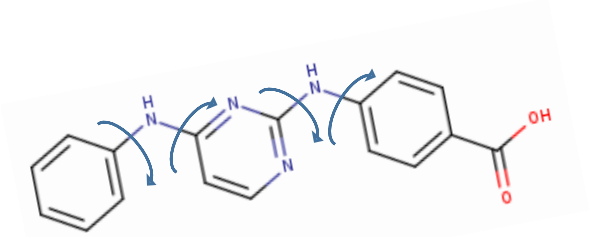
Ligand

Retrieved from databases

PubChem, PDB, ZINC

Drawn

PyMOL, MarvinSketch

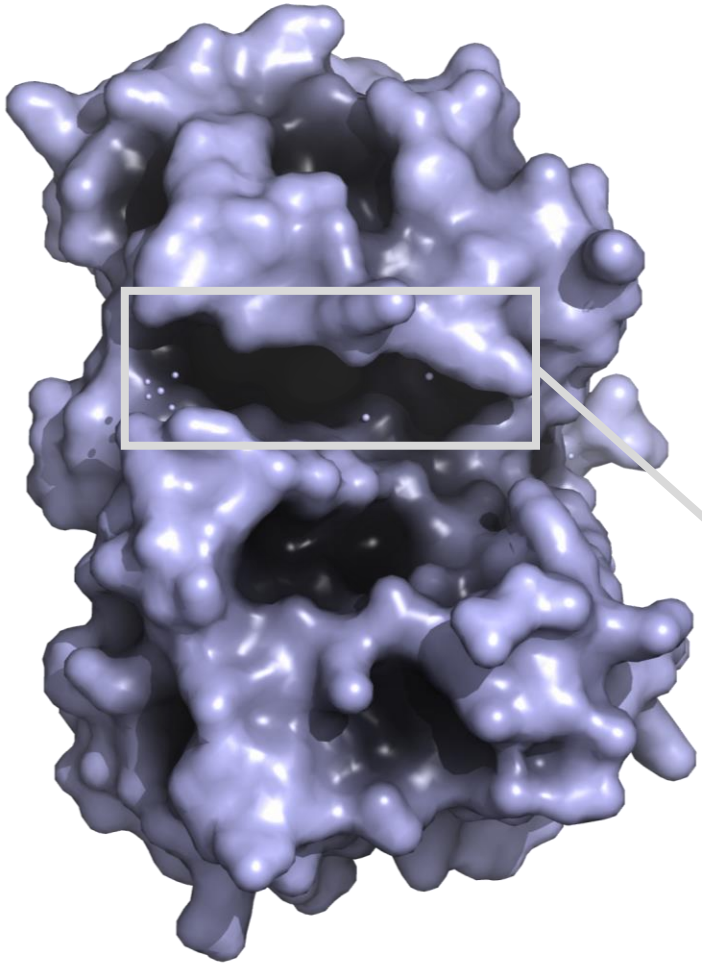


Active torsions: related to the degrees of freedom of the molecule (see next ...)

Control of proper formatting of chemical properties:

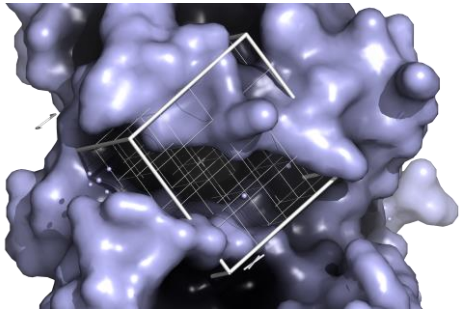
- protonation;
- assignment of partial charges;
- file format (e.g. sdf, pdb, pdbqt);
- assignment of active torsions

- Molecular Graphics Viewer with chemical modification tools (e.g. PyMOL)
- Command-line chemical modification tools (e.g. Openbabel)
- Manually modified file

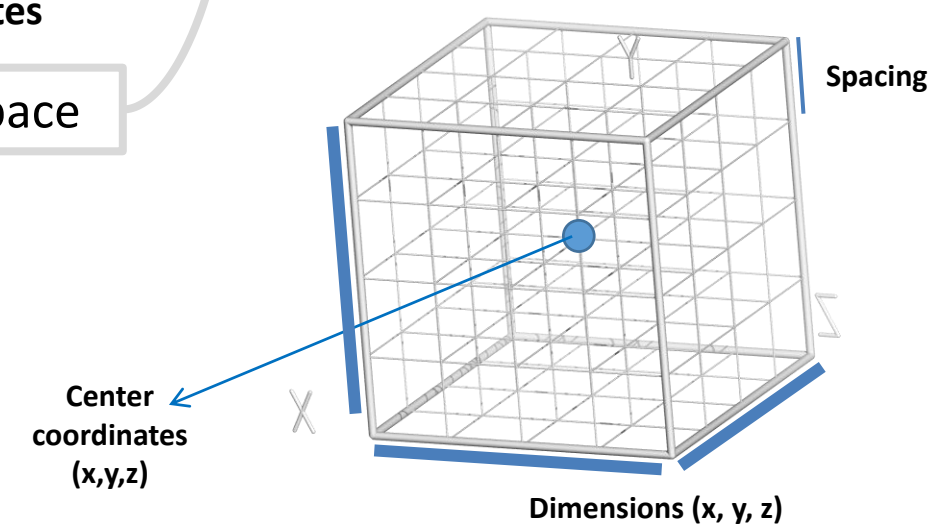


Identification of the protein moiety of interest, in terms of x,y,z coordinates

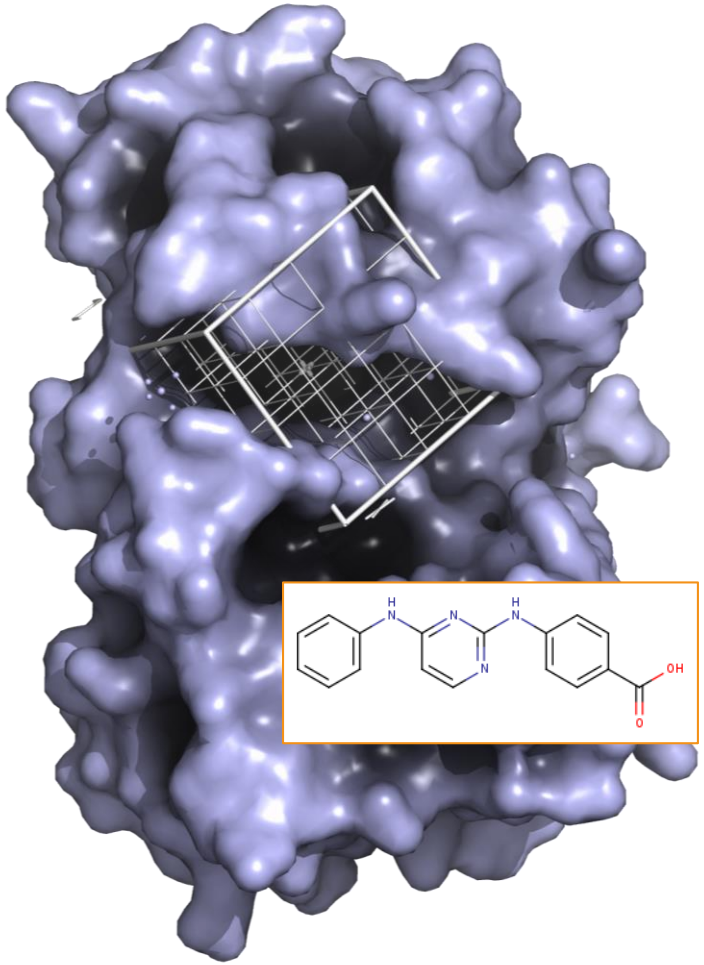
Search Space



Generation of the affinity grid map



Affinity grid map: a representation of the interaction energy as a function of a point in the space. For the entire search space, the interaction energy between any atom of the ligand and the receptor is computed and stored as a grid object.



- **Inputs**

Tridimensional Protein Structure

Ligand

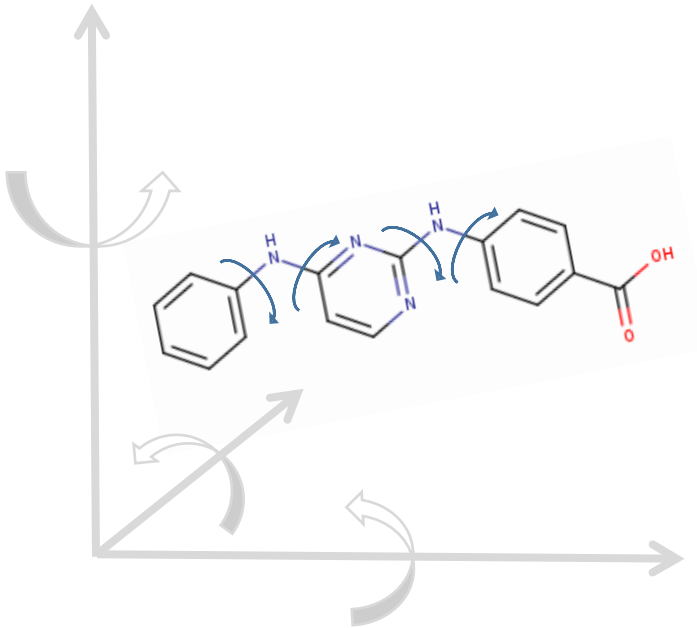
Grid Map

Run the docking algorithm

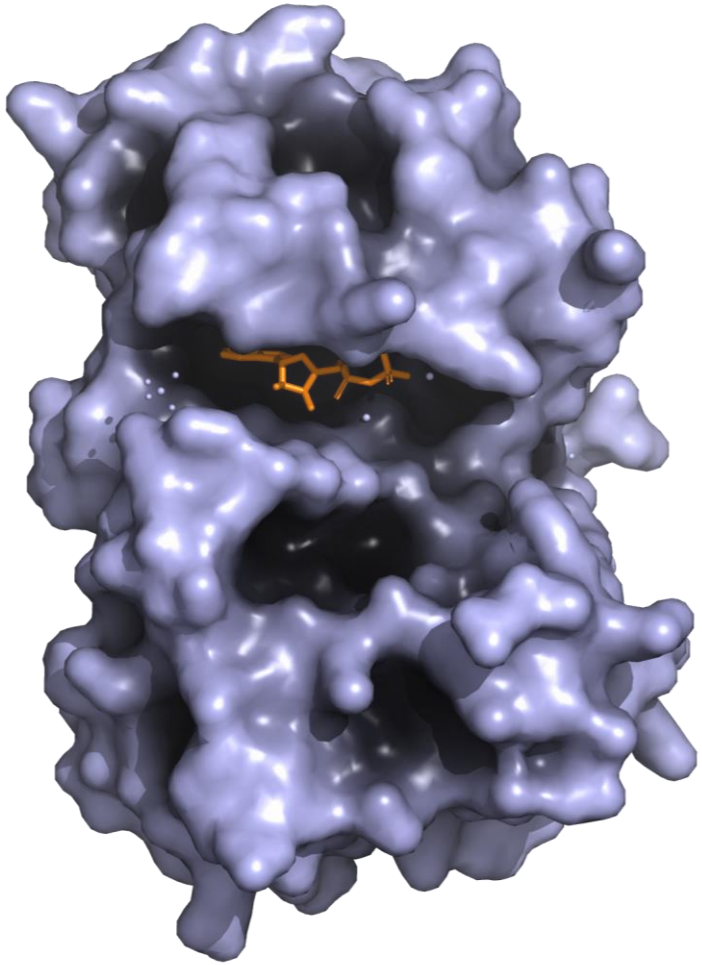
Translation and rotation vectors are applied to the initial conformation to make a new conformation that is evaluated for its interaction with the target.

Additional options:

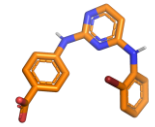
- the number of poses to generate
- protein side chains flexibility



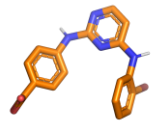
Degrees of Freedom: *number of independent variables (coordinates) that completely describe the position and conformation of a structure*



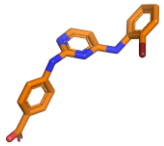
Conformation search



1° (Top-ranked)



2° Score

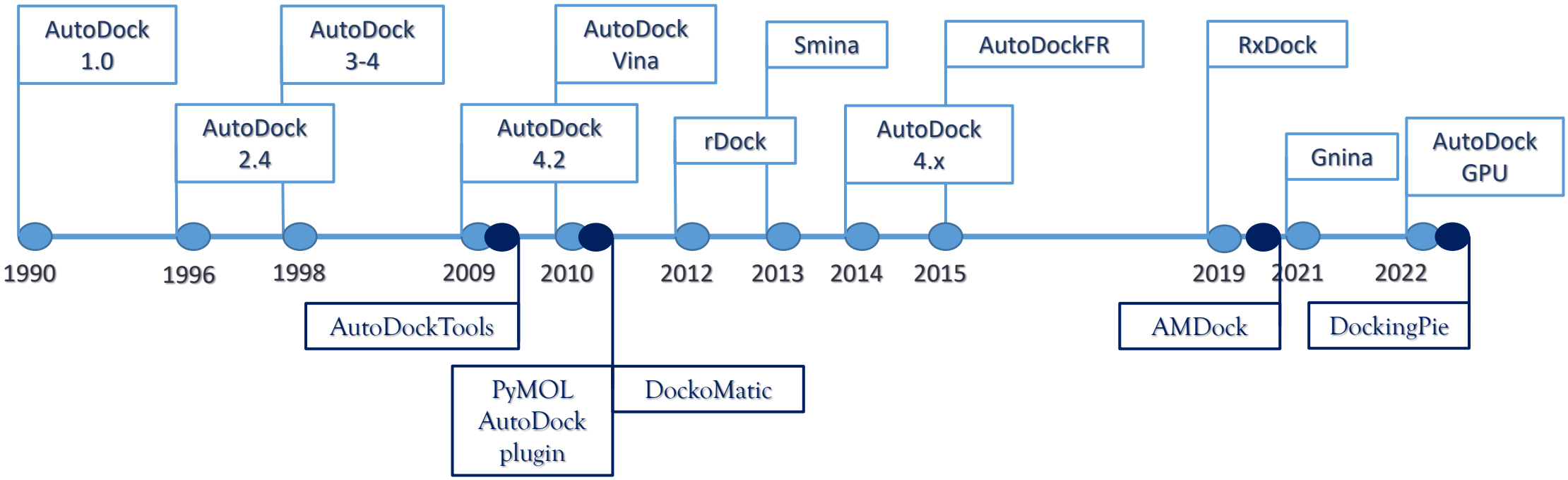


3° Score

Scoring

Results visualization

Molecular Graphics Viewer (e.g. PyMOL, Chimera, PMV)


AutoDock 1.0
AutoDock 2.4
AutoDock 3-4
AutoDock 4.2
AutoDock Vina
rDock
Smina
AutoDock 4.x
AutoDockFR
RxDock
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AutoDock GPU
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2021
2022
AutoDockTools
PyMOL AutoDock plugin
DockoMatic
AMDock
DockingPie