NATIONAL INSTITUTE OF CHEMISTRY

EURO SLING

Molecular Docking Calculations

Utilizing

Discovery Studio & Pipeline Pilot

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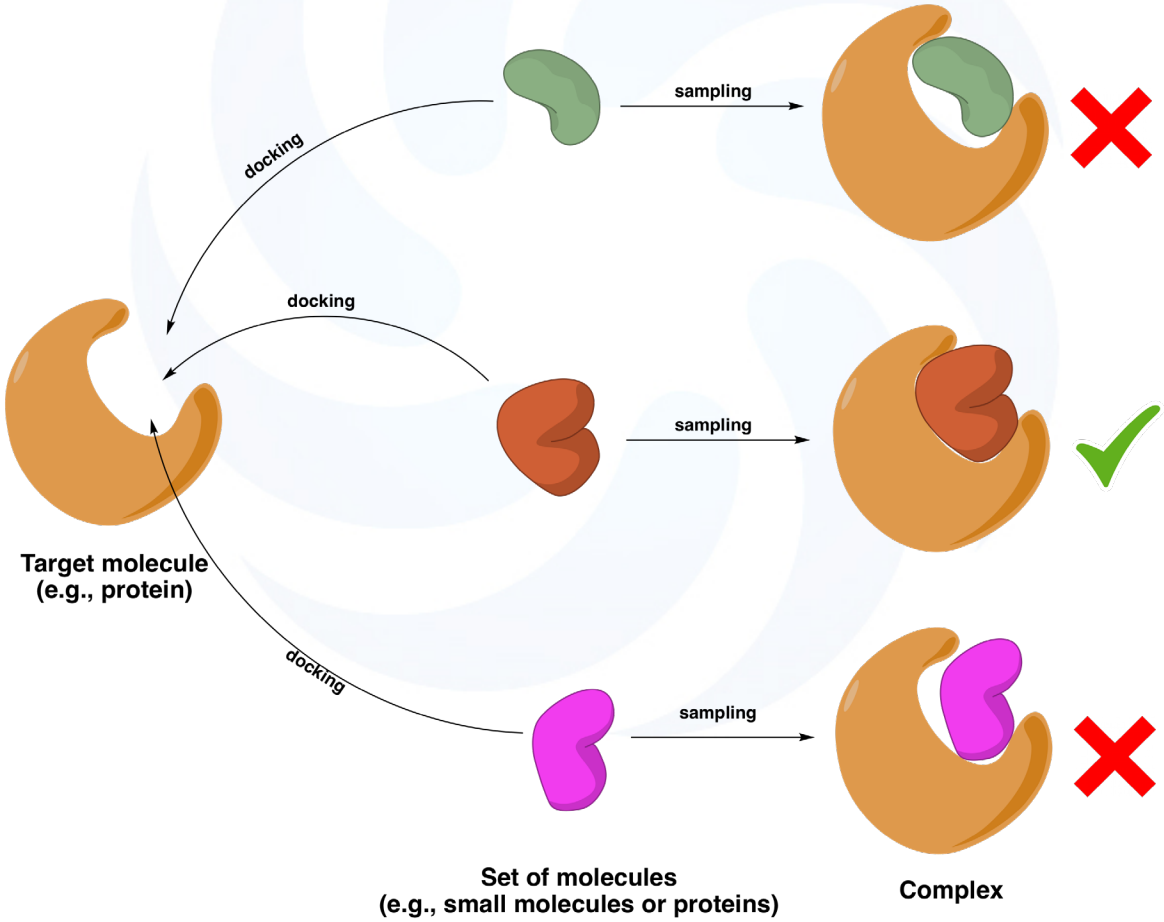
Outline

- Molecular docking: a general overview!
- How it looks in reality?!
- Types of molecular docking approaches
- A typical molecular docking workflow
- Experimental data for performing molecular docking
- Docking tools, algorithms & scoring functions
- Accelrys Enterprise Platform (AEP)
- Practical guidelines (step-by-step tutorial)

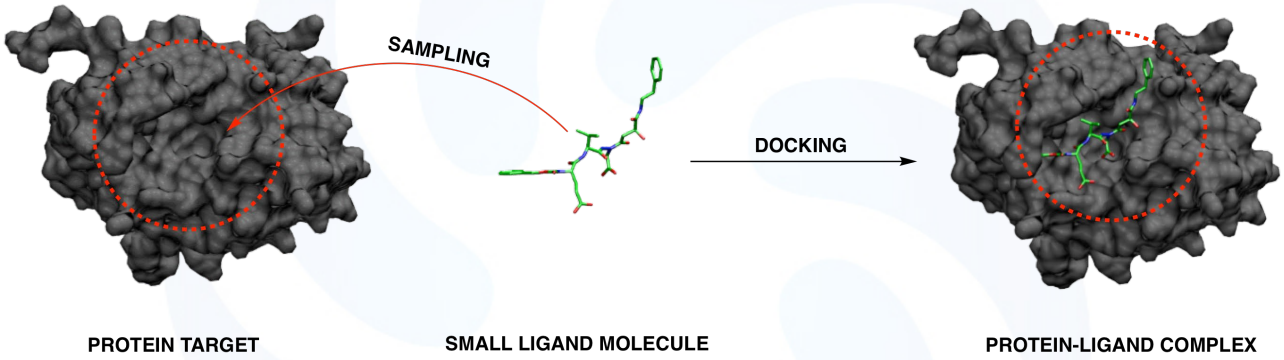
Molecular docking: a general overview

- A computational method for prediction of the favorable spatial orientation and conformation of one molecule bound to another forming a stable complex.
- In a simplified manner, the molecular docking can be compared to a puzzle.

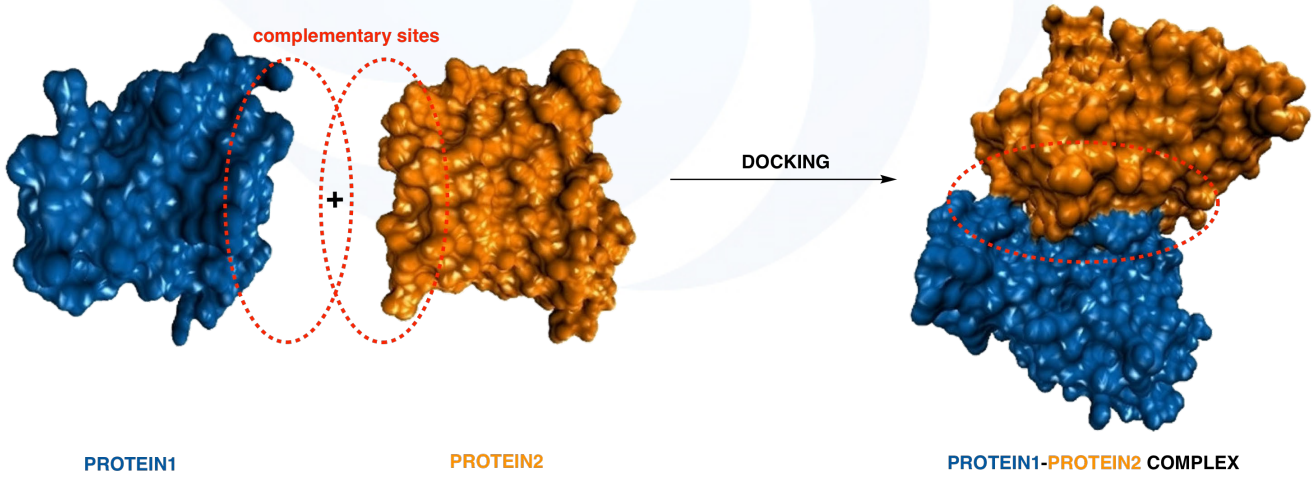


How it looks in reality?!

- Depending on the problem we want to solve:
  - Protein-ligand docking (e.g., an enzyme inhibitor, toxic compound, etc.).

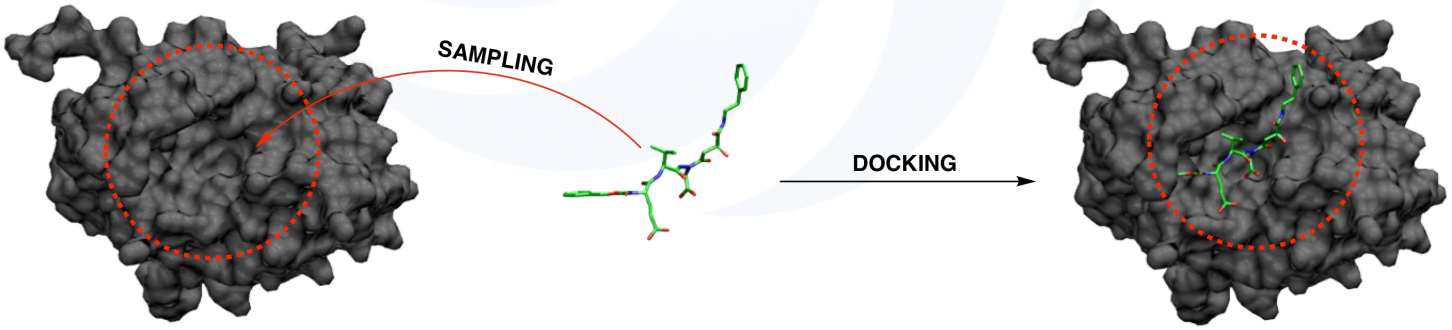


  - Protein-protein docking (e.g., antigen-antibody complex).

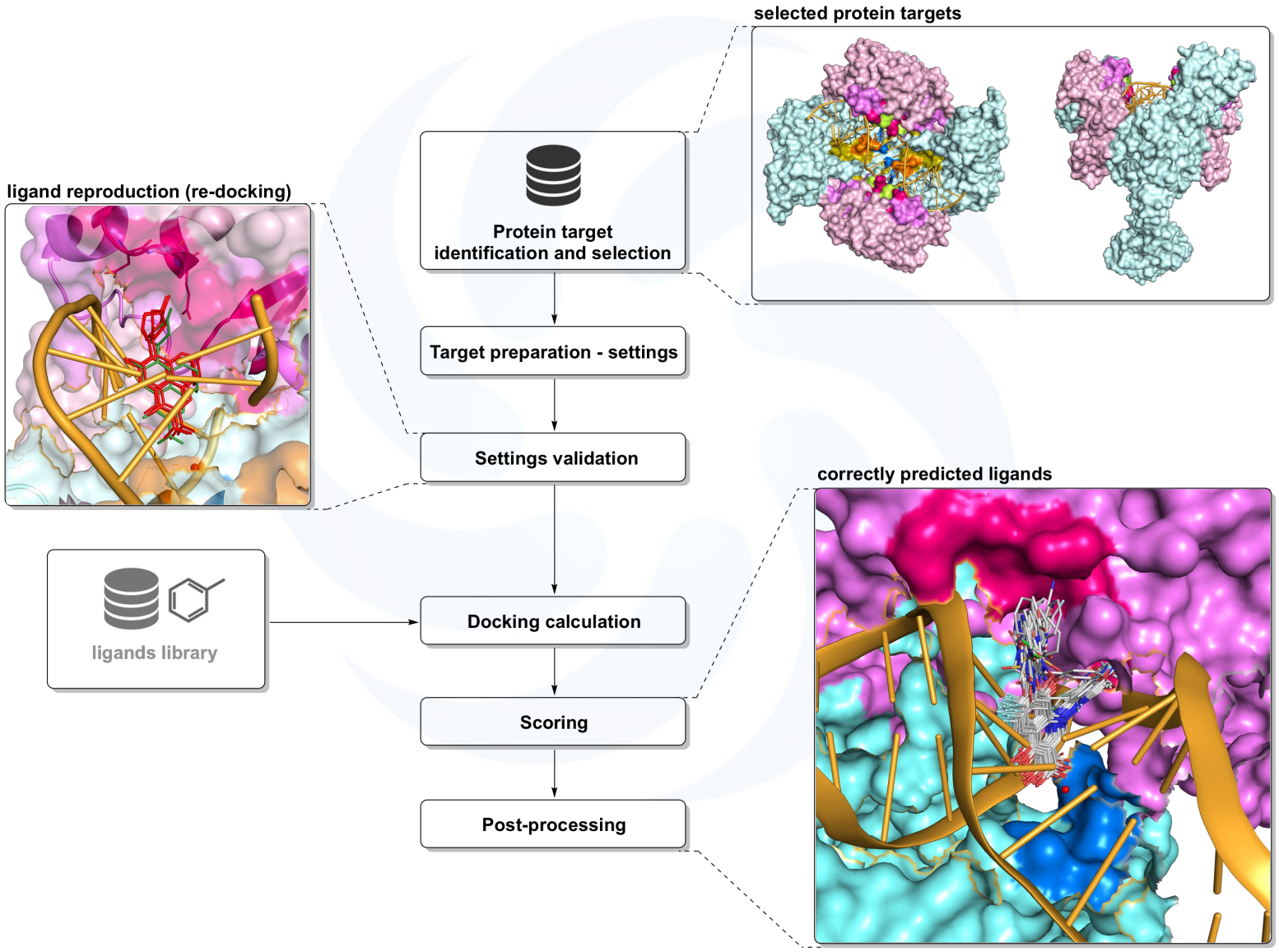


Types of molecular docking calculations

- Rigid-body docking calculations
  - The ligand is usually flexible, while the protein is rigid.
  - Useful for studying ligands orientations within the protein binding pocket.
  - Computationally inexpensive calculations (fast method).
- Flexible docking calculations
  - Both entities are flexible (e.g., simulations of induced-fit mechanisms).
  - Useful for studying ligands orientations and conformations (ligand binding).
  - The flexibility of the protein is limited to few amino acids.
  - Computationally more expensive calculations (slower method).



A typical molecular docking workflow



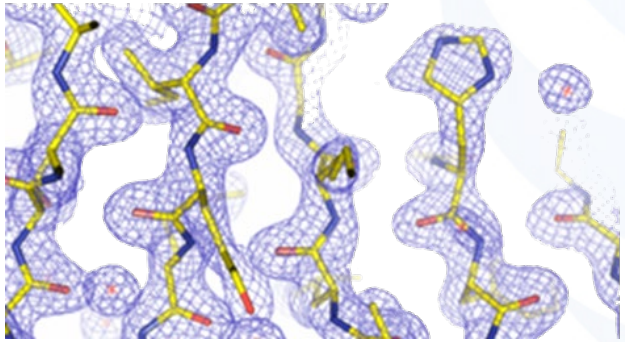
Experimental data for performing molecular docking

- **Online structural repositories**

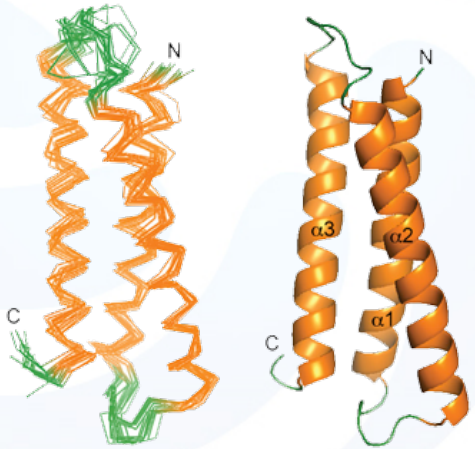
RCSB Protein Data Bank (http://www.rcsb.org).

EMBL-EBI Protein Data Bank in Europe (http://www.ebi.ac.uk/pdbe/).

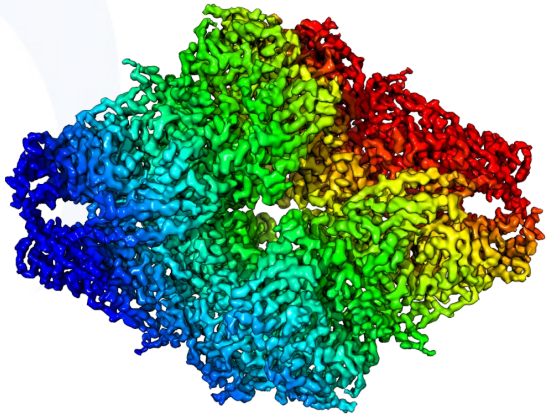
- **Experimental data solved by**



X-ray crystallography*



NMR**



CryoEM***

* http://teatree.lbl.gov/portal/page/94/

** https://www.creative-biostructure.com/nmr-services_28.htm

*** Bartesaghi, A. *et al.*, *Proc. Natl. Acad. Sci. U. S. A.*, **2014**, *111*(32), 11709-11714.

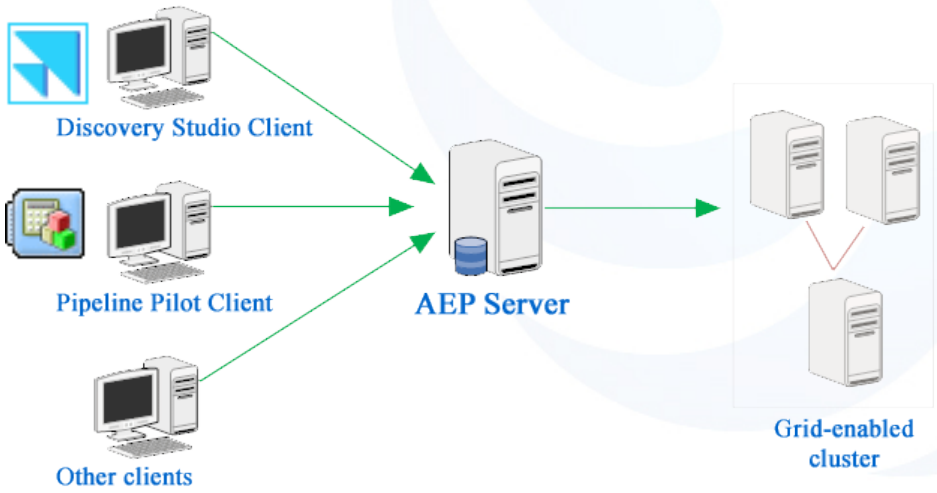
Docking tools, algorithms & scoring functions

- A plethora of available docking tools (free & commercial)
  - Open-source docking platforms
    - AutoDock/AutoDock Vina (GA-based sampling; scoring by ΔG_{bind} [kcal/mol])*
    - rDock (GA & Monte Carlo sampling; scoring by S_{total}, similar to ΔG_{bind})*
  - Commercial docking platforms
    - CCDC GOLD (GA-based sampling; scoring by GoldScore, ChemScore, etc.)*
    - CDOCKER (CHARMM-based MD sampling; scoring by -CDOCKER_ENERGY)*

* Trott, O. & Olson, A. J., *J. Comput. Chem.*, **2010**, *31*, 455-461.
* Ruiz-Carmona, S. *et al.*, *PLoS Comput. Biol.*, **2014**, *10*(4), e1003571.
* Jones, G. *et al.*, *J. Mol. Biol.*, **1997**, *267*(3), 727-748.
* Wu, G. *et al.*, *J. Comput. Chem.*, **2003**, *24*, 1549-1562.

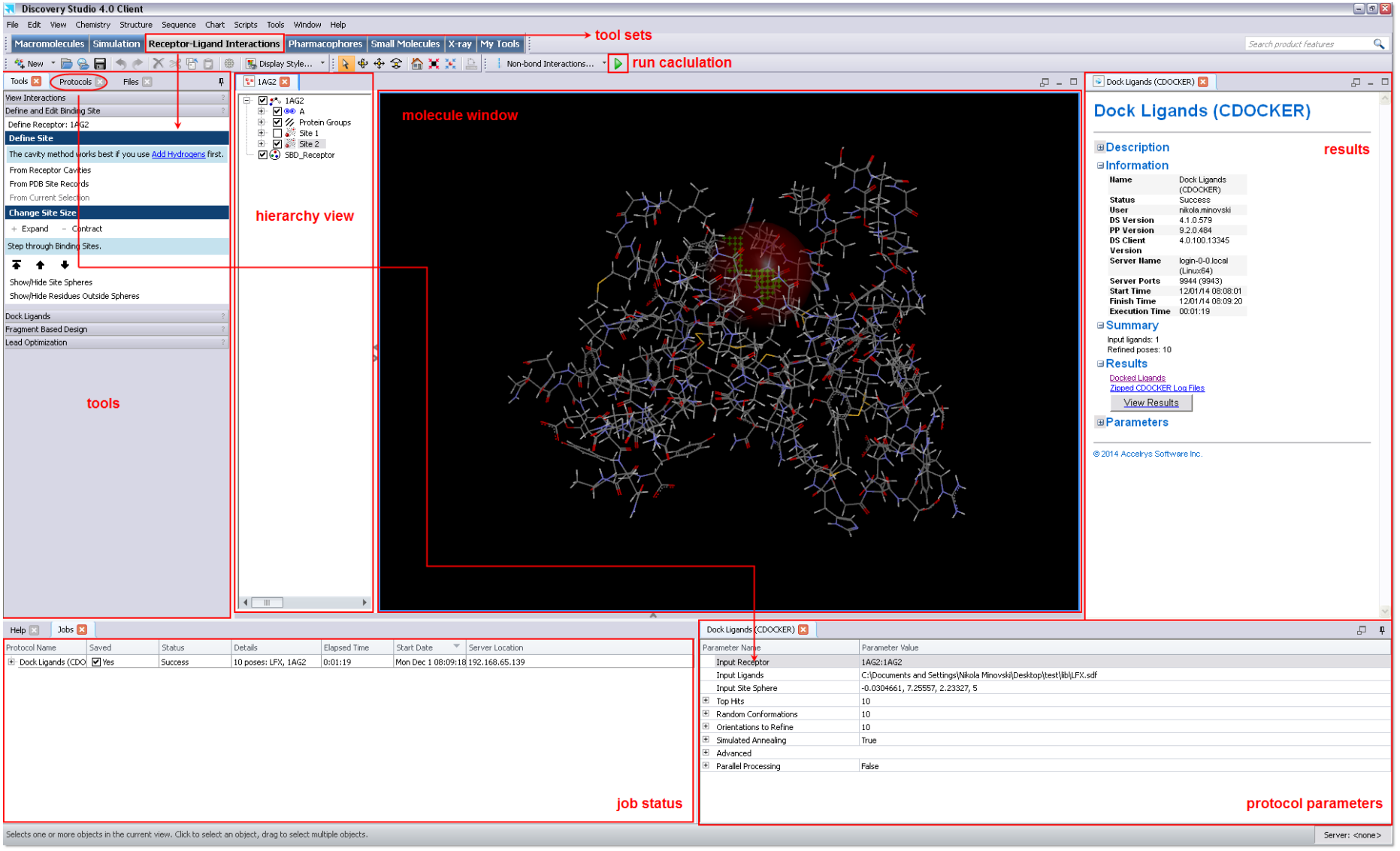
Accelrys Enterprise Platform (AEP)

- A comprehensive molecular informatics platform covering:
  - Molecular modeling, simulations, & analysis of complex molecular systems
  - Data workflow & automation
- Client-server integration technology

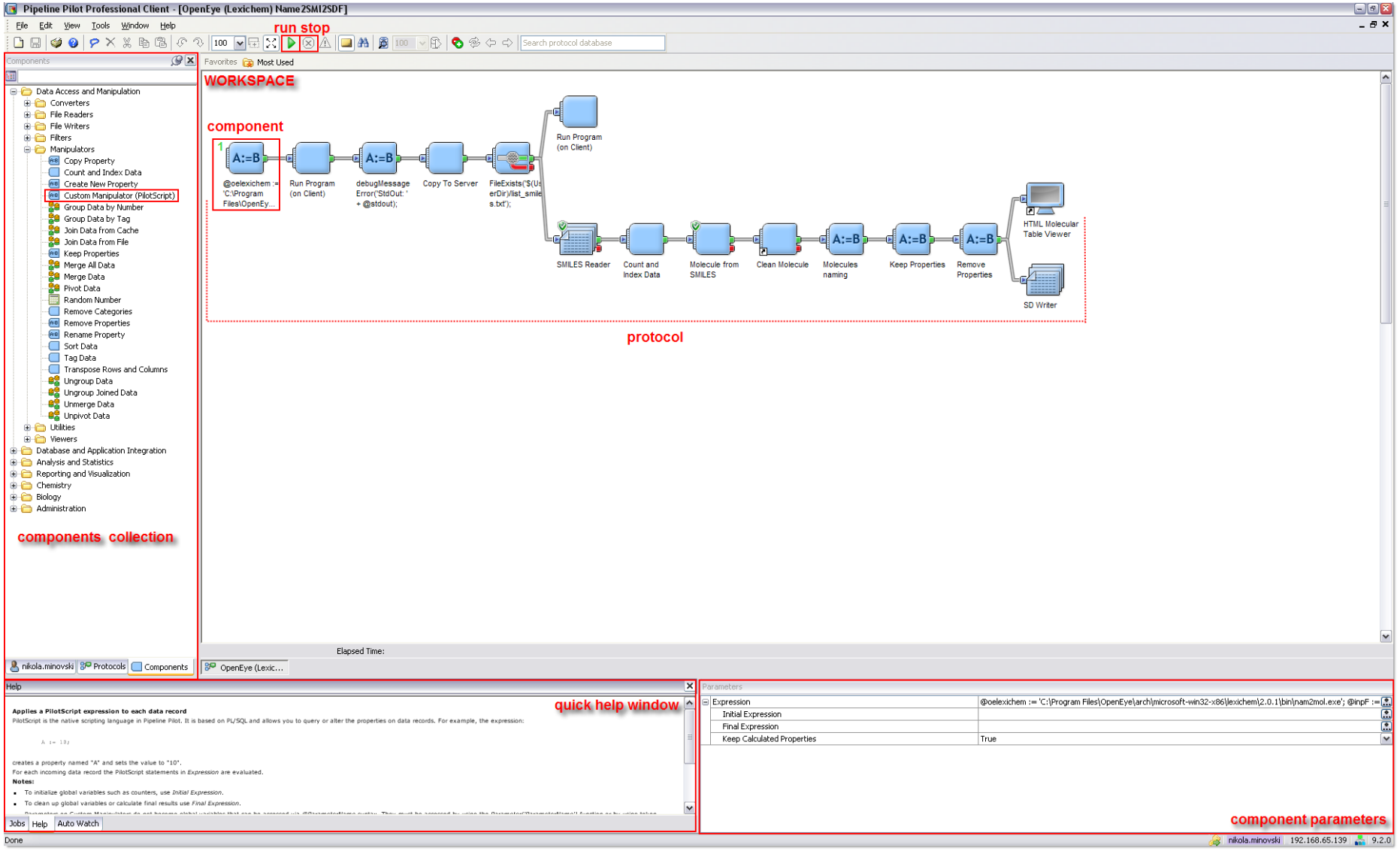


- Available AEP Clients:
  - Discovery Studio Client 4.1
  - Pipeline Pilot Client 9.2

Discovery Studio Client 4.1

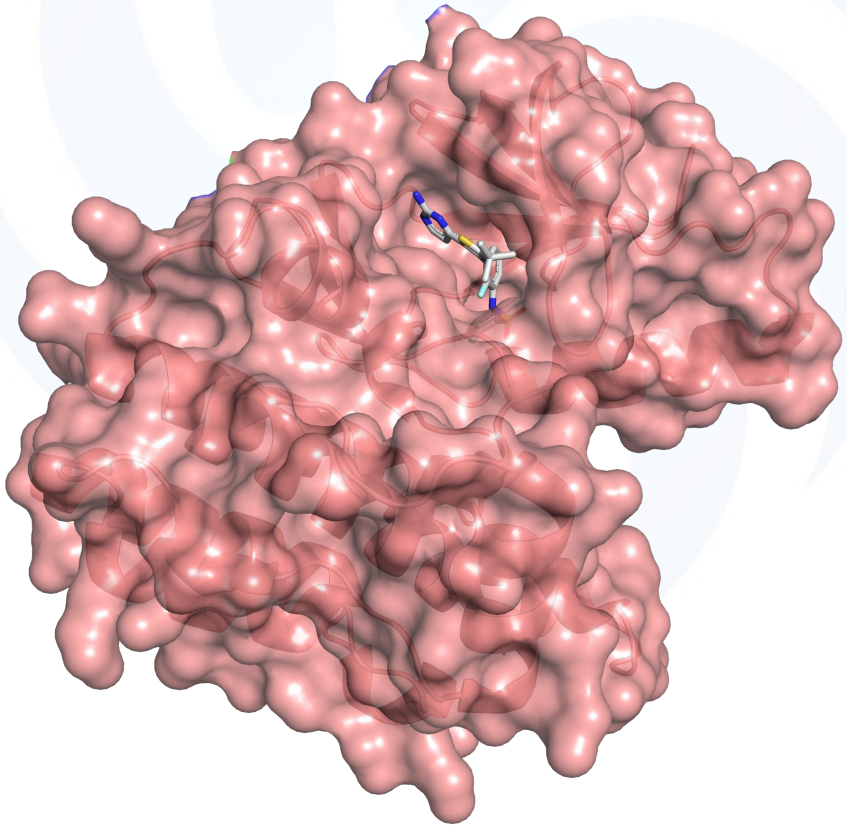


Pipeline Pilot Client 9.2



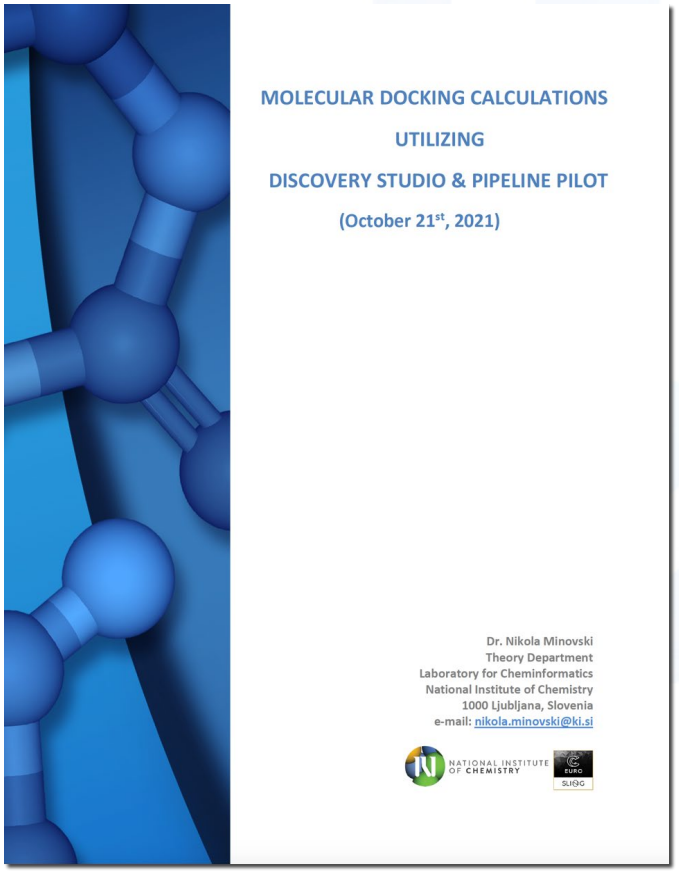
Practical guidelines (step-by-step tutorial)

- B-Raf protein target (PDB ID: 5CSW) for anticancer chemotherapy
  - B-Raf (kinase protein) - involved in a signaling pathway progressing to cell-growth
  - FDA approved B-Raf inhibitors (e.g., Dabrafenib, Vemurafenib, etc.)



Literature & further reading

- A detailed step-by-step tutorial (*.pdf format).
- Further reading (a chapter on integrated *in silico* methods, *.pdf format).



MOLECULAR DOCKING CALCULATIONS

UTILIZING

DISCOVERY STUDIO & PIPELINE PILOT

(October 21st, 2021)

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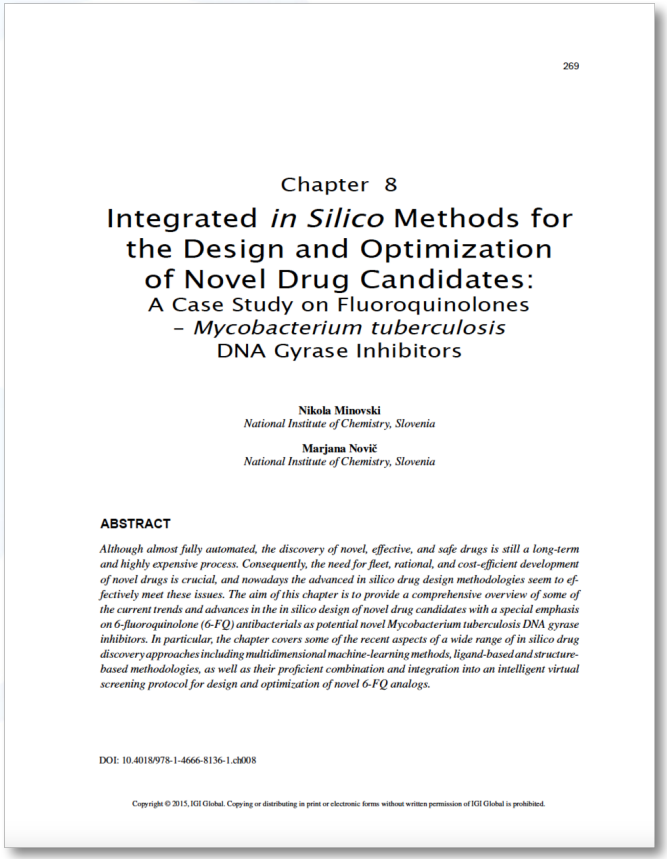

Chapter 8

Integrated *in Silico* Methods for the Design and Optimization of Novel Drug Candidates:
A Case Study on Fluoroquinolones – *Mycobacterium tuberculosis* DNA Gyrase Inhibitors

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ABSTRACT

Although almost fully automated, the discovery of novel, effective, and safe drugs is still a long-term and highly expensive process. Consequently, the need for fleet, rational, and cost-efficient development of novel drugs is crucial, and nowadays the advanced in silico drug design methodologies seem to effectively meet these issues. The aim of this chapter is to provide a comprehensive overview of some of the current trends and advances in the in silico design of novel drug candidates with a special emphasis on 6-fluoroquinolone (6-FQ) antibacterials as potential novel Mycobacterium tuberculosis DNA gyrase inhibitors. In particular, the chapter covers some of the recent aspects of a wide range of in silico drug discovery approaches including multidimensional machine-learning methods, ligand-based and structure-based methodologies, as well as their proficient combination and integration into an intelligent virtual screening protocol for design and optimization of novel 6-FQ analogs.

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Thank you
for your attention