



NATIONAL INSTITUTE
OF CHEMISTRY



Molecular Docking Calculations Utilizing Discovery Studio & Pipeline Pilot

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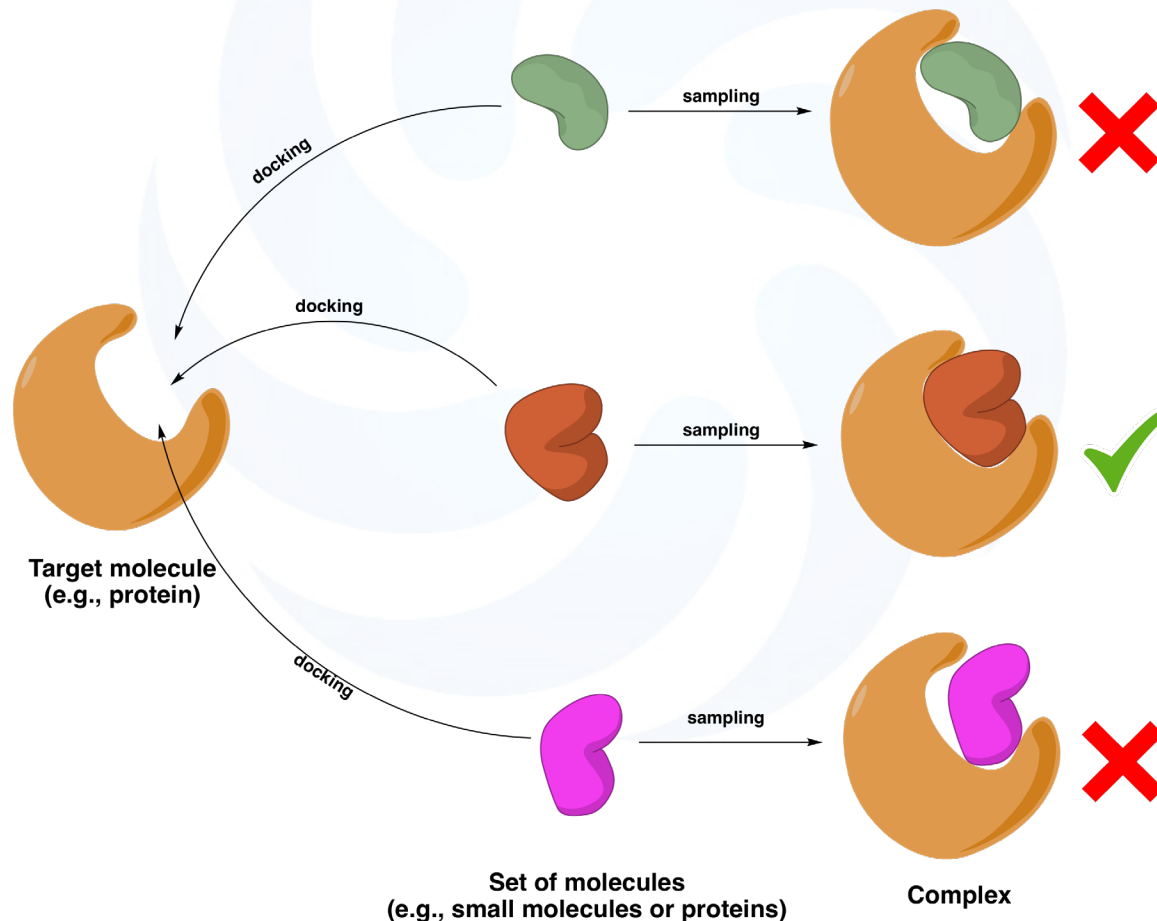


Outline

- 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)

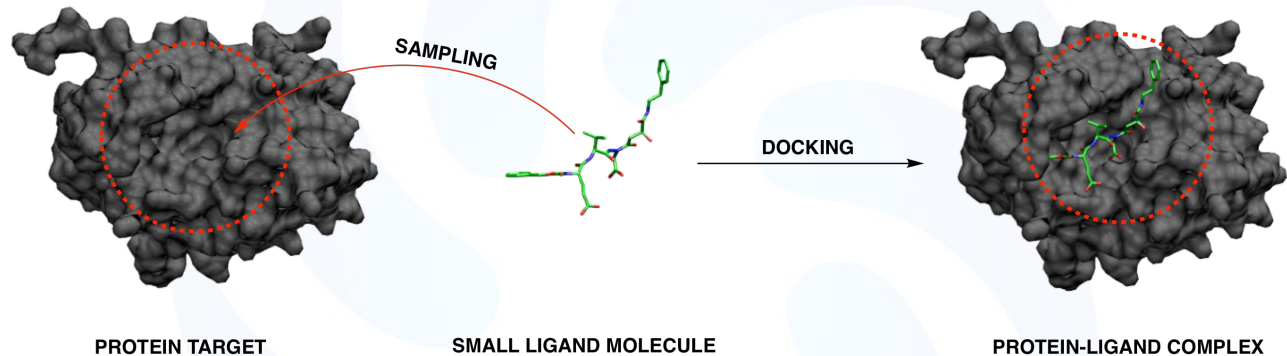
Molecular docking: a general overview

- 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.

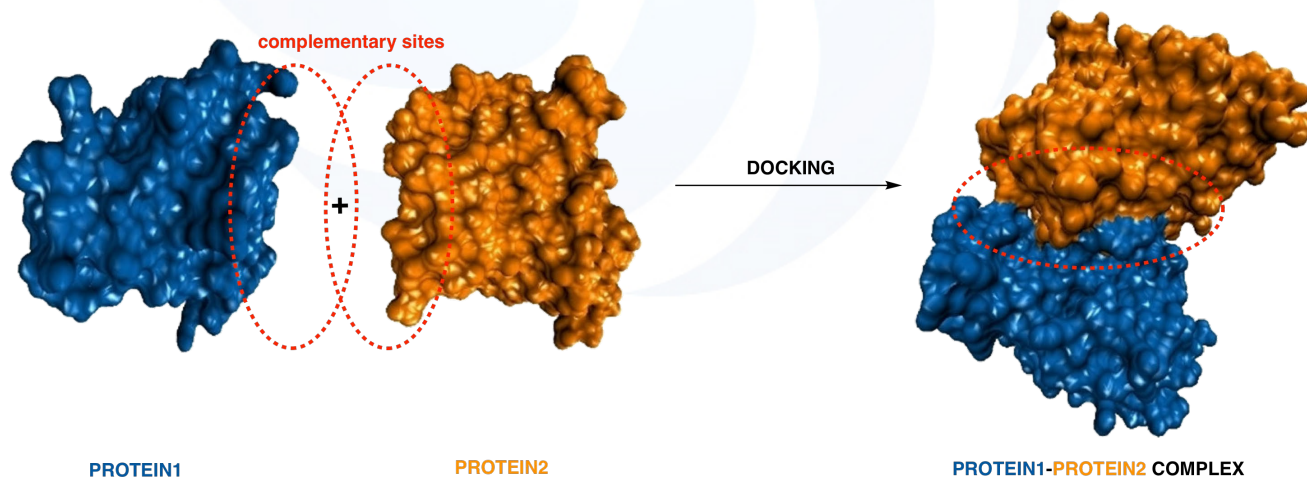


How it looks in reality?!

- 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).



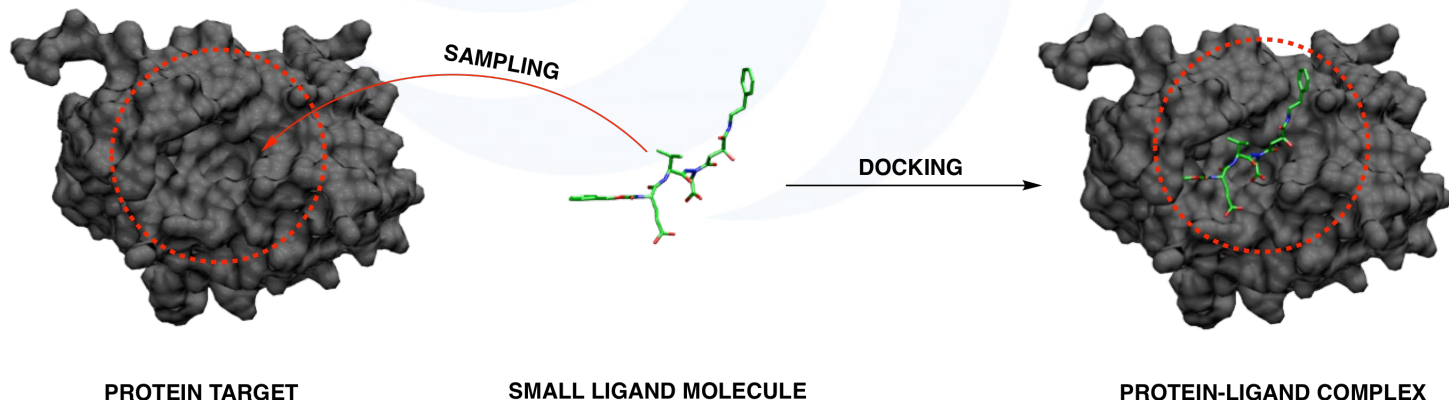
Types of molecular docking calculations

- Rigid-body docking calculations

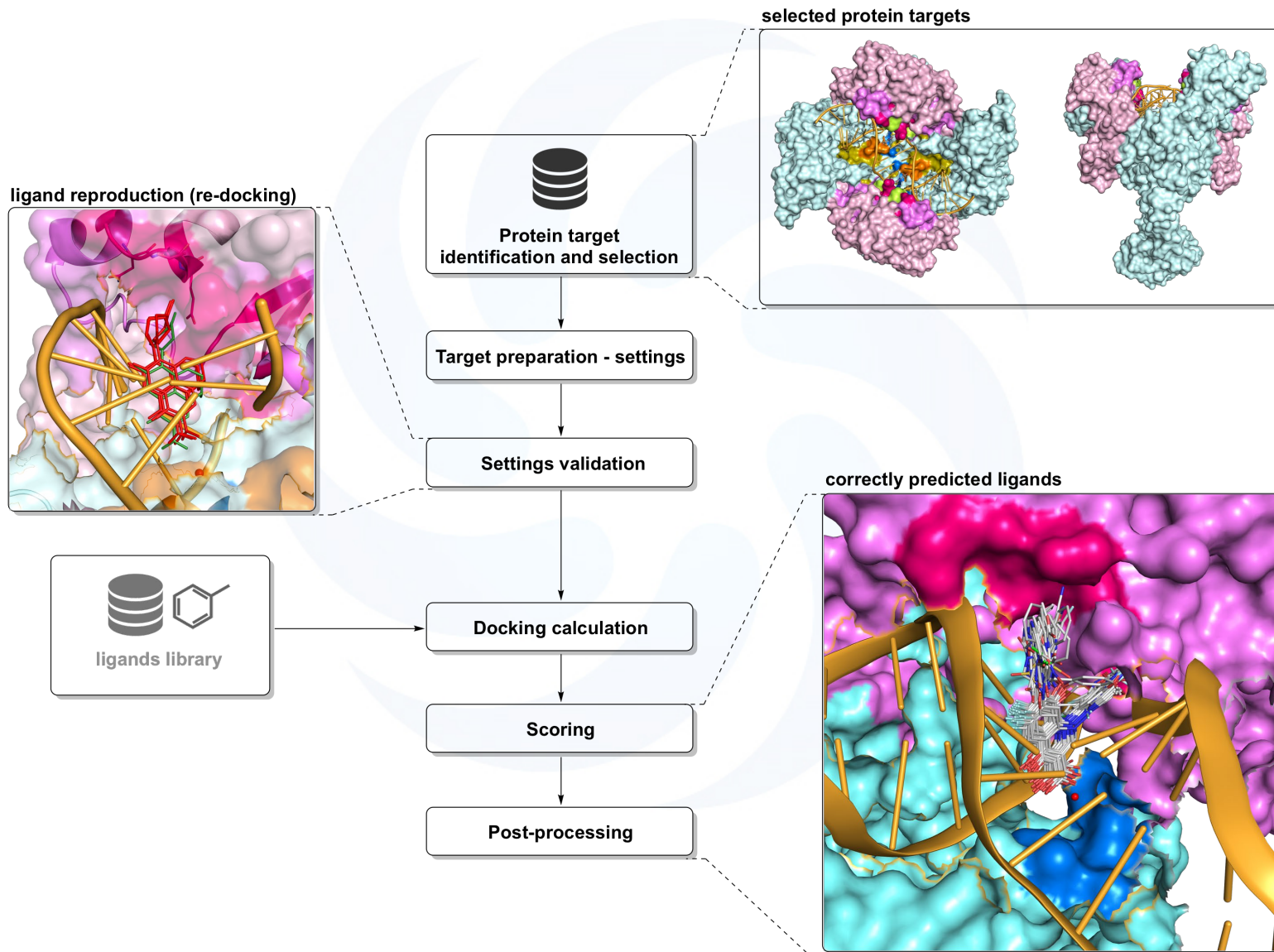
- The ligand is usually flexible, while the protein is rigid.
- Useful for studying ligands orientations within the protein binding pocket.
- Computationally inexpensive calculations (fast method).

- 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

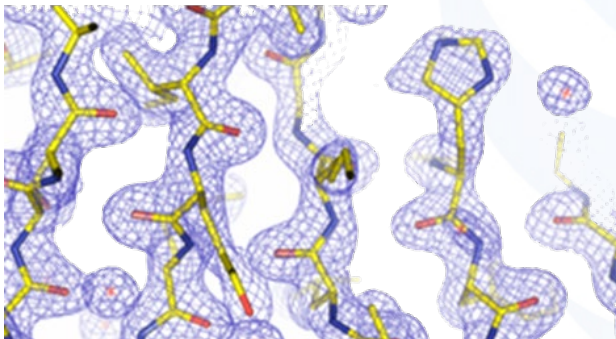


RCSB Protein Data Bank (<http://www.rcsb.org>).

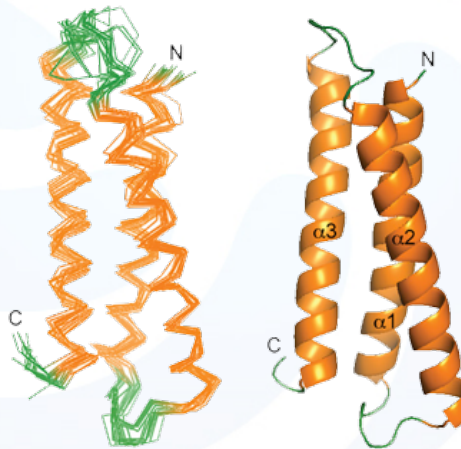


EMBL-EBI Protein Data Bank in Europe (<http://www.ebi.ac.uk/pdbe/>).

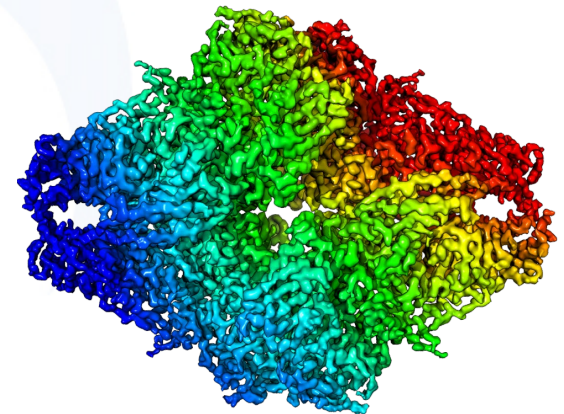
— Experimental data solved by



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.

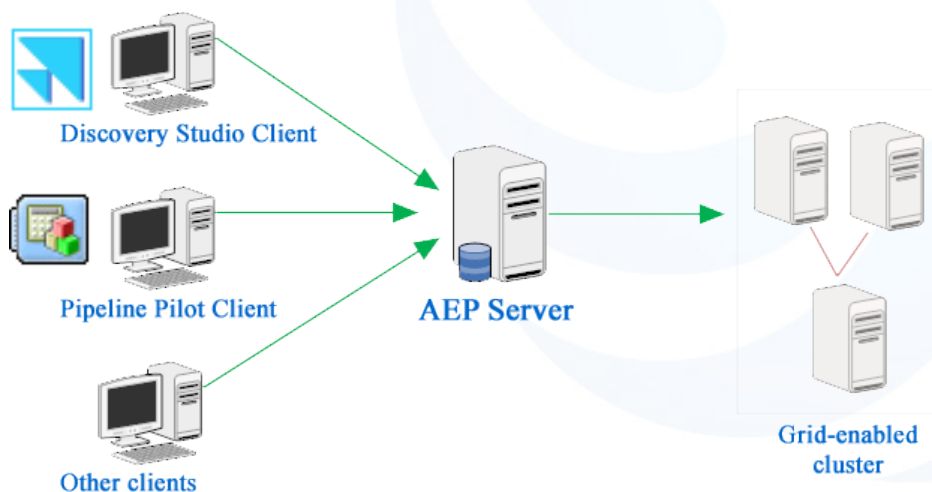
* Ruiz-Carmona, S. *et al.*, *PLoS Comput. Biol.*, **2014**, 10(4), e1003571.

* 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

Discovery Studio 4.0 Client

File Edit View Chemistry Structure Sequence Chart Scripts Tools Window Help

Macromolecules Simulation Receptor-Ligand Interactions Pharmacophores Small Molecules X-ray My Tools

tool sets

run calculation

Tools Protocols Files

View Interactions

Define and Edit Binding Site

Define Receptor: 1AG2

Define Site

The cavity method works best if you use [Add Hydrogens](#) first.

From Receptor Cavities

From PDB Site Records

From Current Selection

Change Site Size

+ Expand - Contract

Step through Binding Sites.

Show/Hide Site Spheres

Show/Hide Residues Outside Spheres

Dock Ligands

Fragment Based Design

Lead Optimization

hierarchy view

molecule window

Dock Ligands (CDOCKER)

Description

Information

Name Dock Ligands (CDOCKER)

Status Success

User nikola.minovski

DS Version 4.1.0.579

PP Version 9.2.0.494

DS Client 4.0.100.13345

Version

Server Name login-0-0.local (Linux64)

Server Ports 9944 (9943)

Start Time 12/01/14 08:08:01

Finish Time 12/01/14 08:08:20

Execution Time 00:01:19

Summary

Input ligands: 1

Refined poses: 10

Results

[Docked Ligands](#)

[Zipged CDOCKER Log Files](#)

[View Results](#)

Parameters

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Help Jobs

Protocol Name	Saved	Status	Details	Elapsed Time	Start Date	Server Location
Dock Ligands (CDO)	<input checked="" type="checkbox"/> Yes	Success	10 poses: LFX, 1AG2	0:01:19	Mon Dec 1 08:09:18	192.168.65.139

job status

Dock Ligands (CDOCKER)

Parameter Name	Parameter Value
Input Receptor	1AG2:1AG2
Input Ligands	C:\Documents and Settings\Nikola Minovski\Desktop\test\lib\LFX.sdf
Input Site Sphere	-0.0304661, 7.25557, 2.23327, 5
Top Hits	10
Random Conformations	10
Orientations to Refine	10
Simulated Annealing	True
Advanced	
Parallel Processing	False

protocol parameters

Server: <none>

Select one or more objects in the current view. Click to select an object, drag to select multiple objects.

Pipeline Pilot Client 9.2

Pipeline Pilot Professional Client - [OpenEye (Lexichem) Name2SMILES]

File Edit View Tools Window Help

run stop

100 100 Search protocol database

COMPONENTS

- Data Access and Manipulation
 - Converters
 - File Readers
 - File Writers
 - Filters
 - Manipulators
 - Copy Property
 - Count and Index Data
 - Create New Property
 - Custom Manipulator (PilotScript)**
 - Group Data by Number
 - Group Data by Tag
 - Join Data from Cache
 - Join Data from File
 - Keep Properties
 - Merge All Data
 - Merge Data
 - Pivot Data
 - Random Number
 - Remove Categories
 - Remove Properties
 - Rename Property
 - Sort Data
 - Tag Data
 - Transpose Rows and Columns
 - Ungroup Data
 - Ungroup Joined Data
 - Unmerge Data
 - Unpivot Data
 - Utilities
 - Viewers
- Database and Application Integration
- Analysis and Statistics
- Reporting and Visualization
- Chemistry
- Biology
- Administration

WORKSPACE

component

1 A:=B

@oelexichem := 'C:\Program Files\OpenEye\...

Run Program (on Client)

debugMessage Error('StdOut: ' + @stdout);

Copy To Server

FileExists('\${UserDir}\list_smiles.txt');

Run Program (on Client)

SMILES Reader

Count and Index Data

Molecule from SMILES

Clean Molecule

Molecules naming

A:=B

A:=B

A:=B

HTML Molecular Table Viewer

SD Writer

protocol

components collection

Elapsed Time:

nikola.minovski Protocols Components

OpenEye (Lexic...

quick help window

Apply a PilotScript expression to each data record

PilotScript is the native scripting language in Pipeline Pilot. It is based on PL/SQL and allows you to query or alter the properties on data records. For example, the expression:

```
A := 10;
```

creates a property named "A" and sets the value to "10".

For each incoming data record the PilotScript statements in Expression are evaluated.

Notes:

- To initialize global variables such as counters, use *Initial Expression*.
- To clean up global variables or calculate final results use *Final Expression*.

Parameters

Expression	@oelexichem := 'C:\Program Files\OpenEye\arch\microsoft-win32-x86\lexichem\2.0.1\bin\nam2mol.exe'; @inpF :=
Initial Expression	
Final Expression	
Keep Calculated Properties	True

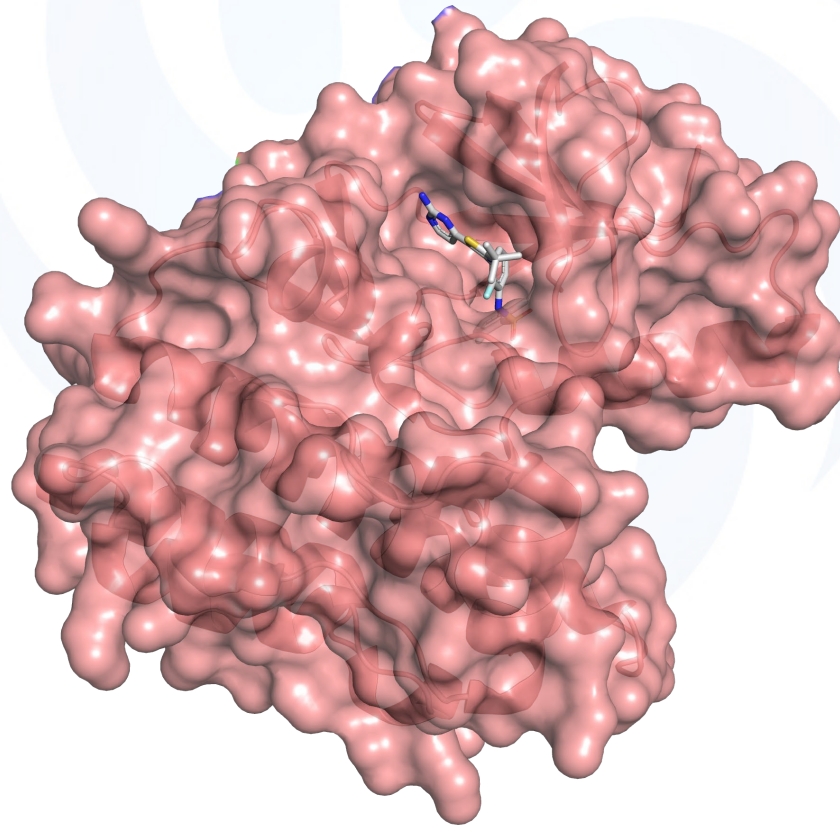
component parameters

Done

nikola.minovski 192.168.65.139 9.2.0

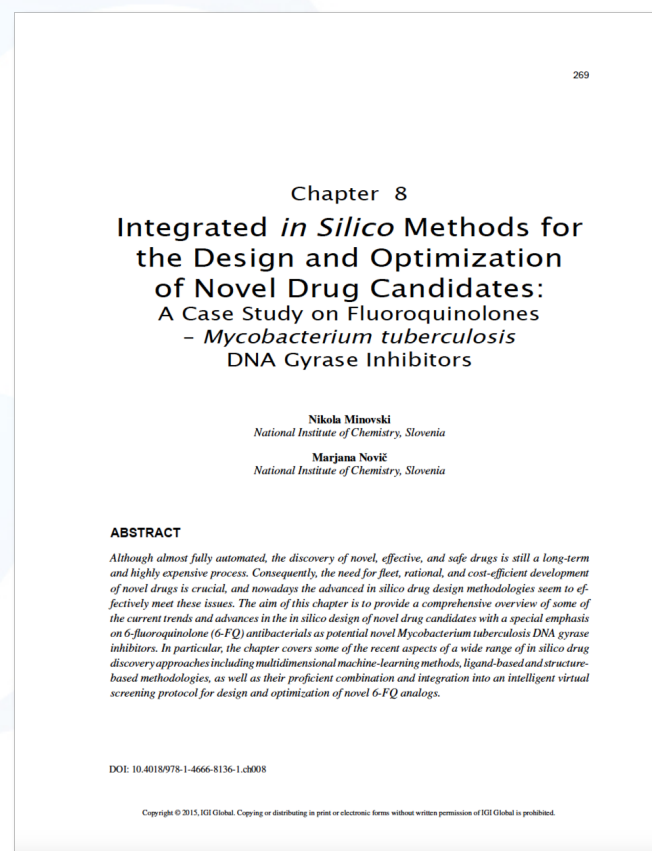
Practical guidelines (step-by-step tutorial)

- 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).





**Thank you
for your attention**