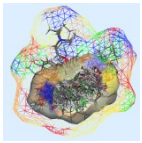

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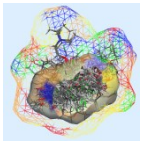
Computer Lab, Session 7



Virtual screening

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Download Thrombin_VS.tar.gz from course website to Lab7 folder.

Unzip and untar file:

tar zxf Thrombin_VS.tar.gz

Change into Thrombin_VS folder:

cd Thrombin_VS

and open all mol2 files in PyMOL:

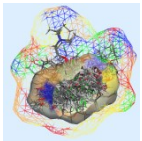
pymol *.mol2

Generate ligand library (as in Lab6):

AutoDockVina → Export ligand library and save as *Thrombin_VS* library

Next, perform docking with similar settings as in Lab6 (use again Lab6_0.pse file for protein template):

Virtual screening



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AutoDockVina Plugin

Choose target protein and ligand library for AutoDock simulation

Project definition name

Base directory: /home/student/Desktop/CADD_Lab/Lab8 Browse

Project subdirectory: project_VS

Ligand library

Path to ligand library: /home/student/AUTODOCK_library/Thrombin_VS Search and Import

Protein selection

Protein from file [PDB,MOL2,MOL]

Path to protein file: Full path to protein file Search and Import

File containing multiple protein structures [NMR-PDB]

Path to protein file: Full path to protein file Search and Import

Trajectory from Amber

Path to topology file: Full path to .top file Search and Import

Path to trajectory file: Full path to .trj file Search and Import

Protein in current PyMol session

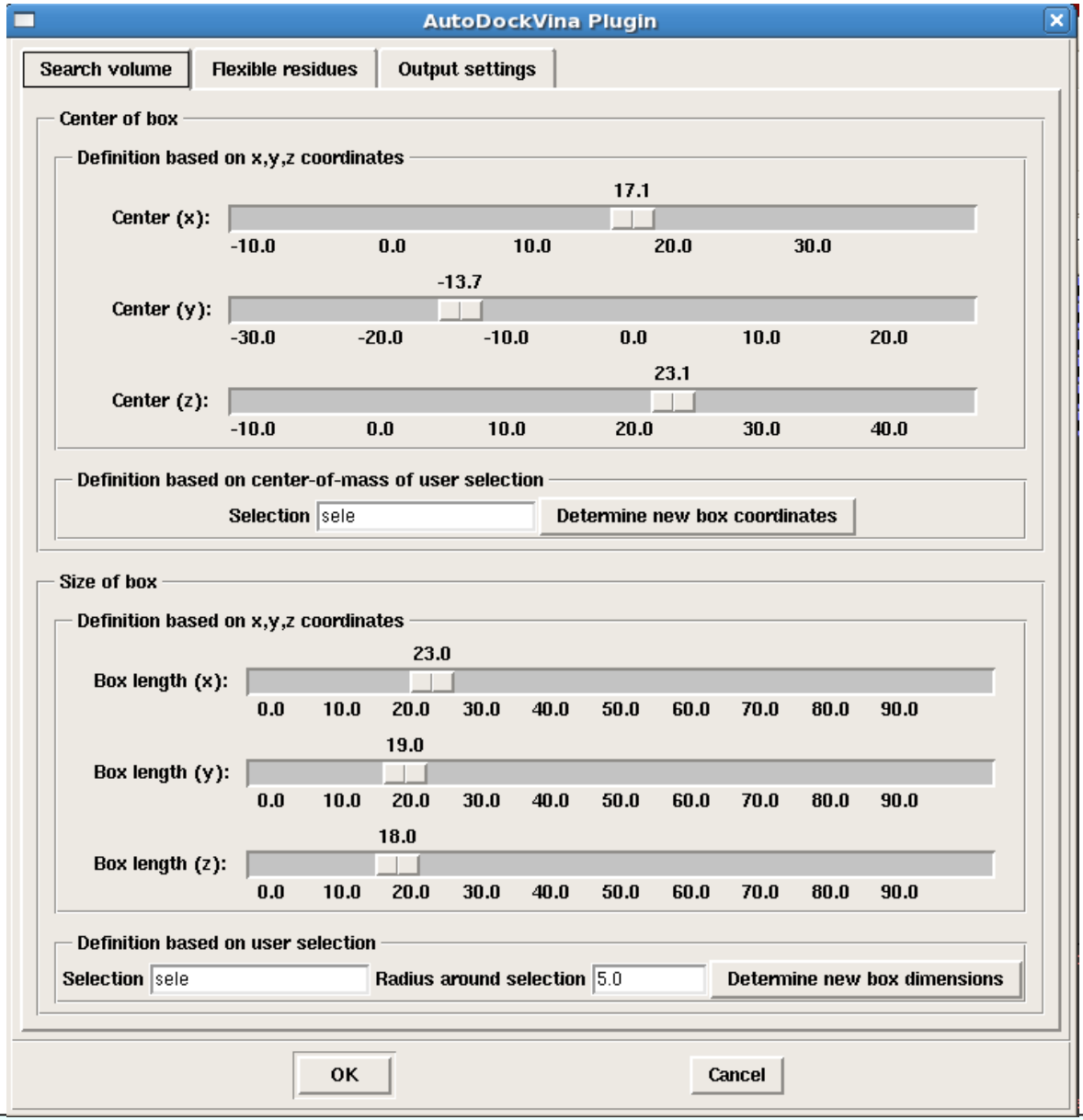
Objects to select from: 1MU6

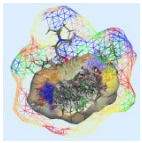
Protein preparation

Let autodock change protonation states

OK Cancel

Virtual screening





Virtual screening

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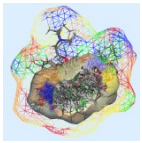
After docking simulations are finished import results:

AutoDockVina → Import results

select Monitor.aut in folder project_VS_client

For statistical analysis: Open Excel

Create Excel table with the following format using the AutoDock Results dialog:



Virtual screening

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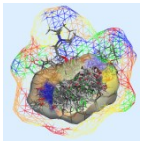
Excel table:

Active or decoy in ranked list	Rank %	Actives found at rank %	Ideal	Random
	0	0	0	0
0	6.666666	=# of actives in first column*100/5	20	6.666666
1	13.33333	…	40	13.33333
0	20.00000	…	60	20.00000
…	…	…	…	…

Plot “Actives found at rank %”, “Ideal”, “Random” as a function of “Rank %” and compute enrichment factor at 0, 6.66666%, 13.3333%, …



Discussion

Case study (**Use software from course**):

Based on the crystal structure of a thrombin-ligand complex (1mu6) you have virtually screened a library of 10000 compounds using Autodock Vina with a single solution as output. You want to identify possible new lead structures and optimize their binding affinity.

Please, discuss the following issues:

1. Propose ideas to validate the outcome of your screen; in particular, how can you decide how many compounds from the top-ranked list you should consider as possible active compounds? How can you refine the outcome of the screen?
2. Plan a possible strategy to optimize the affinity of the lead compound using discussed software. Take into consideration a reasonable balance between accuracy and efficiency.