Using PyMOL and its Plugins as a Molecular Modeling and Drug-design Platform

*Sophie Taraglio, Francesca Manganiello and Alessandro Paiardini**

Department of Biochemical Sciences "A. Rossi Fanelli", Sapienza University, Rome, Italy.

*E-mail: alessandro.paiardini@uniroma1.it

Over the years, the number of available structural Bioinformatics pipelines, in the form of command-line commands, programming libraries, plugins or GUI-based software, started to increase exponentially. This expansion has now profiled the field as a tangled network of methods, algorithms and user interfaces. The Molecular Graphics Environment PyMOL is one of the most popular software environments for visualization and analysis of biomolecules and is widely used by the scientific community. Recently, PyMOL started to play a key role in providing an easy and integrated way for supporting such pipelines. These lectures outline the features and the tools recently developed by our group (i.e., PyMod, DockingPie) that can easily turn PyMOL into a complete platform for supporting molecular modeling and drug-design analyses.

Project Detail - Analysis of the interaction between MT-SP1 and benzamidine/HAI-1

MT-SP1 (matriptase/ST14; EC 3.4.21) was first isolated by Shi et al. 1993, as a novel proteinase that was expressed by human breast cancer cells. MT-SP1 is highly expressed in prostate, breast, and colorectal cancers *in vitro* and *in vivo*, and inhibition of this enzyme suppresses both primary tumour growth and metastasis in a rat model of prostate and colon cancer. This protease has been shown to cleave and activate hepatocyte growth factor/scattering factor, and urokinase plasminogen activator, which suggest the function of this protease as an epithelial membrane activator for other proteases and latent growth factors. Using the three-dimensional model of the catalytic domain of human MT-SP1, obtained by sequence homology, we will study the interaction between this protein and its inhibitors (small molecule and protein):

Project A

A. Modeling the MT-SP1 Macromolecule with PyMod 3
B. Using PyMOL to build the benzamidine molecule
C. Using the DockingPie plugin of PyMOL to dock the benzamidine molecule into MT-SP1
D. Using PyMOL for rational, structure-based Drug Optimization
E. Using the DockingPie plugin of PyMOL to dock the molecule into the crystal structure of MT-SP1
F. Using the PHARMIT server to carry out a pharmacophore-based Virtual Screening on MT-SP1

Project B
A. Modeling the MT-SP1 Macromolecule with PyMod 3
B. Modeling the HAI-1 Macromolecule with PyMod 3
C. Evolutionary conservation analysis on MT-SP1 and its inhibitor HAI-1
D. Protein-protein docking between MT-SP1 and its inhibitor HAI-1 with HADDOCK
E. Protein-protein docking between MT-SP1 and its inhibitor HAI-1 with LZerD

Requirements

- ## PyMOL

  PyMOL is an open source, proprietary molecular visualization system created by Warren Lyford DeLano. It is a tool universally accessible to scientific and educational communities.

  Please, download and install PyMOL 2.5 from the following link:
  https://pymol.org/2/#download

  The first time you launch PyMOL, you'll be asked for a license file.
  Please, download it from:

  http://schubert.bio.uniroma1.it/temp/Medils/pymol-edu-license.lic

  (Save it as a **.lic** file; to install the license, open PyMOL, go to the "Help" menu -> Install new License File -> Browse for License File). (Note the PyMOL licenses can be obtained for educational and research purposes here: https://pymol.org/edu/)

  Please, also notice that you are strongly advised to use **a three-buttons mouse** during the practical part of these lessons.

- ## PyMod 3

  PyMod 3 (*Janson and Paiardini, 2021*) is an open source PyMOL plugin, designed to act as an interface between PyMOL and several bioinformatics tools (for example: BLAST+, HMMER, Clustal Omega, MUSCLE, PSIPRED and MODELLER). Please, download PyMod 3 from the following link:

  https://github.com/pymodproject/pymod/releases/download/v3.0/pymod3.zip
  (don't decompress the .zip file)

  INSTALLATION: PyMod 3 can be installed as any other PyMOL plugin.

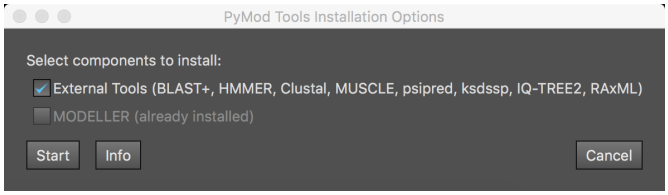
  1. Download the PyMod 3 plugin file (a ZIP file named pymod3.zip, see the link above)

  2. Launch PyMOL and use the PyMOL plugin manager (*Plugin -> Plugin Manager* from the menu of its main window) to install it.

CONFIGURATION

3. The first time you launch PyMod 3, You will be asked to give the path of the directory in which to install the plugin files. Just select the default option if you are unsure about what to do (the location of the plugin files does not make any difference when running the plugin).

4. The external tools of PyMod 3 are mandatory and can be obtained and configured through an easy-to-use installer dialog which can be launched by the plugin.
Open PyMOL, then *Plugin -> PyMod 3*. In the new window, go to *Help -> Install PyMod Components* from the main menu of the plugin). Check "External Tools" and "MODELLER", then click on start:



The license key of MODELLER is **MODELIRANJE** (uppercase)

- ## DockingPie

DockingPie (*Rosignoli and Paiardini, 2022*) is a plugin of the popular molecular graphics system PyMOL that offers a versatile and user-friendly graphical user interface for assisting molecular and consensus docking analyses. At the current, and first release, the implemented docking programs are Smina, Autodock Vina, RxDock and ADFR.

Download DockingPie ZIP file from:
https://github.com/paiardin/DockingPie →Green button Code → Download ZIP
OR
https://github.com/paiardin/DockingPie/releases/download/versioning/DockingPie.zip
(don't decompress the .zip file)

INSTALLATION: DockingPie is installed, as any other PyMOL plugin, via the PyMOL plugin manager.

1. Launch PyMOL and use the *Plugin → Plugin Manager* command from the main menu of PyMOL. The plugin manager window of PyMOL will open.

2. Click on Install *New Plugin → Choose File...* button. Select the DockingPie **ZIP file** which you have downloaded before. You will be asked to give the path of the directory in which to install the plugin files. Just select the default option if you are unsure about what to do (the location of the plugin files does not make any difference when running the plugin).

CONFIGURATION

3. DockingPie currently integrates four different docking tools: RxDock, Vina, Smina and ADFR; several chemoinformatics python modules (i.e. AutoDockTools, Openbabel, sPyRMSD) and other external tools like sdsorter. The "CONFIGURATION" tab provides an easy way for the installation of the needed tools from within the plugin in two steps, as reported next.
4. Configure external tools: "CONFIGURATION" tab → Configure → Start Download → Finish Download

5. Install external tools: If the needed tools were not previously installed by the user, the Install button is enabled and it can be used to install the external components.

- PHARMIT

PHARMIT (https://pharmit.csb.pitt.edu) provides an online, interactive environment for the virtual screening of large compound databases using pharmacophores, molecular shape and energy minimization.

No installation is necessary, BUT you're strongly advised to use the FIREFOX browser.