BIO-4371
STRUCTURE-BASED DRUG DESIGN
Summer Term 2018

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Five Week Semester - Project

To be handed in by July 19th, 2018, 16:00 via ILIAS.

Introduction

In course of the practical assignment tasks you had the chance to train the basic steps that are required to perform a protein-ligand docking. Later in the lecture we will more deeply discuss the computer-based counterpart to HTS, namely Virtual Screening (VS or vHTS). The concept is easy to understand: screen numerous (10^3-10^6) compounds in order to identify the most promising candidates for binding to the target that should be tested in an experimental assay. This basically means to systematically perform a protein-ligand docking for every single compound against the common target and to rank the entire compound dataset according to a metric, which in case of docking usually is a predicted binding or docking score.

In this project you should perform VS for the given target. Based on a collection of known inhibitors and a set of so-called decoys, i.e. compounds assumed to be inactive on this target, you should demonstrate the ability to enrich active inhibitors. As you have probably recognized within the assignment tasks, a lot of parameters are available during protein and ligand preparation, receptor grid generation, and the protein ligand-docking itself. Please think about possible and promising modifications of these parameters in order to improve the VS performance compared to the default settings.

The performance of VS is often evaluated using ROC-curves, AUC as well as Enrichment Factors (EF). Please familiarize yourself with these performance measures and use them to evaluate and compare your VS trials [1,2].

The *baseline* to pass the project is to do the VS using standard settings. To achieve better grading you are required to demonstrate and discuss trials to improve the standard setting VS. We highly recommend to do literature research and to dive deeper into the Schrodinger manuals in order to identify and apply strategies to improve over standard VS.

Of course, you are also required to give a summary of your target!

Your Target

... can be found in PDB entry with ID 4zi1.

Please Note:

- As a small motivation: the team that is able to achieve the best improvement over baseline VS is awarded a bottle of sparkling wine or a non-alcoholic alternative! To compare performances we will use the ΔEF(5%).
- The Schrodinger installation has changed to improve performance. Additionally, the most recent version is also available. On the pool computers you can load the Schrodinger environment using
  `$ source /local/sbdd/schrodinger/201(7|8)-2/env.(bash|tcsh)`
- Please create a new Schrodinger working directory in `/local/sbdd/schrodinger/workdirs/` and use it for your work.
- Please write a scientific report using the PNAS Template as you have practiced in the assignment sheets of 5 to 7 pages.
- As usual Bundle your report, the Maestro Project(s) (including all files that where created during your work) and any supplementary files, in a `tar.gz`-archive and upload it to ILIAS.
- Be prepared to give a 10 minute presentation about your work and results on Thursday, July 26th (one week after handing in the projects).

References:

[1] Empereur-Mot, C. et al. (2015) *J. Cheminform.*, 7:52

[2] Lätti, S. et al. (2016) *J. Cheminform.*, 8:45

▷ Please use the ILIAS forum to discuss problems in the first place

▷ If you have unresolved questions, don't hesitate to drop by or write an eMail

▷ `sbdd18@informatik.uni-tuebingen.de`