HTP SurflexDock 1.2: Improving SBVS campaign by including a user defined post-processing stage

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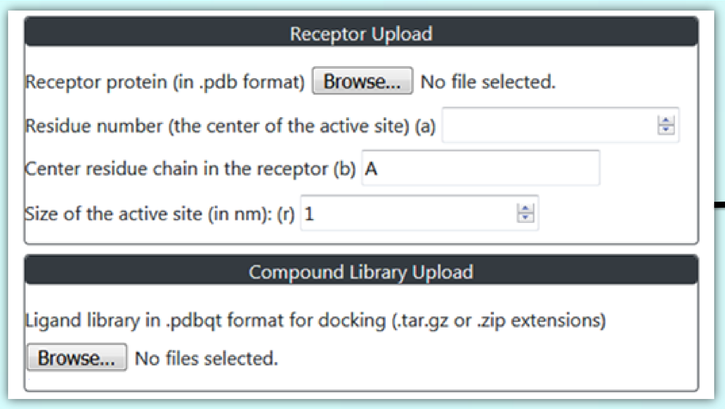
SPECIAL INTEREST GROUP

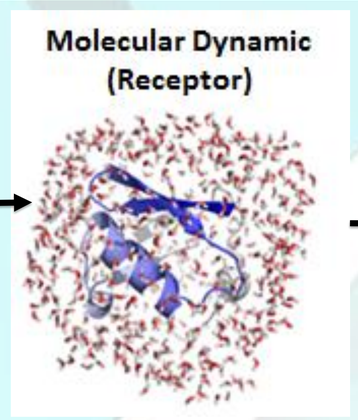
DRUG-DESIGN

Structure-Based Virtual Screening (SVBS) is an essential tool that may be used to define a sub-set of the more specific inhibitors for a receptor of interest during the early stages of drug discovery studies. We developed the HTP SurFlexDock, a web server that improves SBVS campaigns by the use of ensemble docking pipeline in order to simulate the protein receptor flexibility. However, like other SVBS tools, HTP SurflexDock uses a scoring function based on the ΔG of the best pose to classify the compounds. This function is subject to enrich poses with unnatural artifacts such as improper ligand torsions and malformed hydrogens bonds, among others. In this sense, we include a post-processing phase in the HTP SurflexDock, where the user can select up to 10 promising compounds from the initial classification to boost the exploratory of the active site conformational space. At this stage, the user is presented with up to 30 more poses per complex using AutoDock 4.2. Through qualitative analysis of the three-dimensional interactions of the obtained complexes in ensemble docking, the users takes a better picture of the sub-set of the compounds with better interactions and consequently choose the compounds that will go to future stages of the nest drug discovery experiments with greater reliability. The HTP SurFlexDock is freely available as a web service at http://biocomp.uenf.br:81.

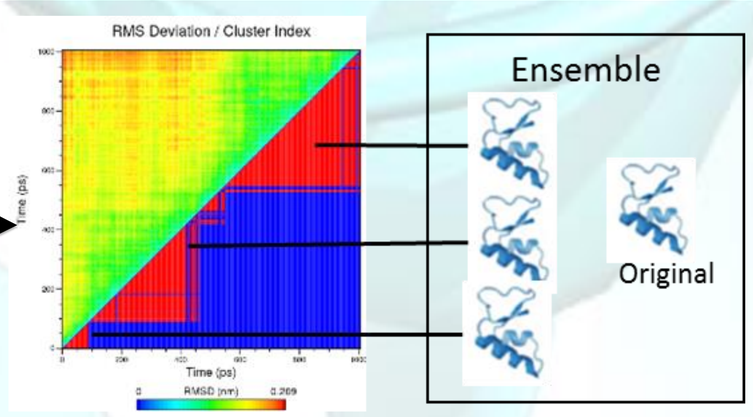
(I) Data Upload



(II) Ensemble Construction

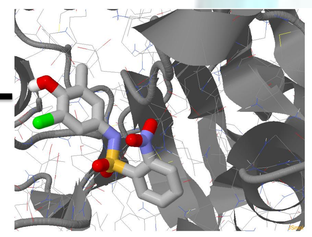


Clustering



(III) Virtual Screening Campaign

Docking Calculation



Ranked Result

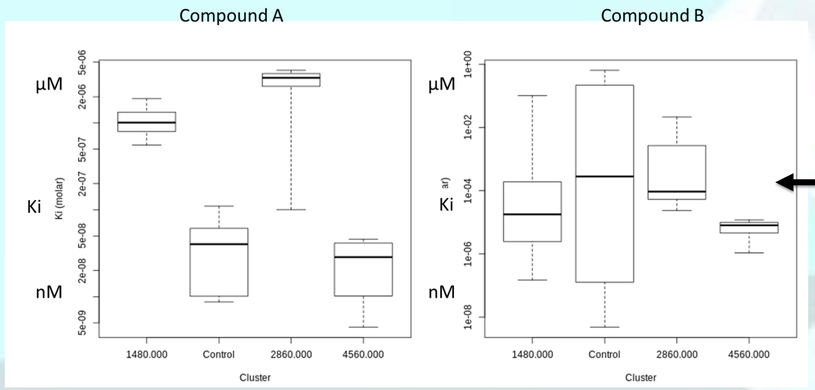
Compounds Ranking

View Complex	Compound	Ki	Conformation	Binding energy	Download complex	Refine
view	ZINC33813076.pdbqt	9.33e-06	Control	-6.86	Download!	
view	ZINC61542532.pdbqt	3.1251e-07	2160.000	-8.87	Download!	
view	ZINC13617629.pdbqt	5.656e-08	860.000	-9.89	Download!	
view	ZINC02522391.pdbqt	3.124e-08	3940.000	-10.24	Download!	

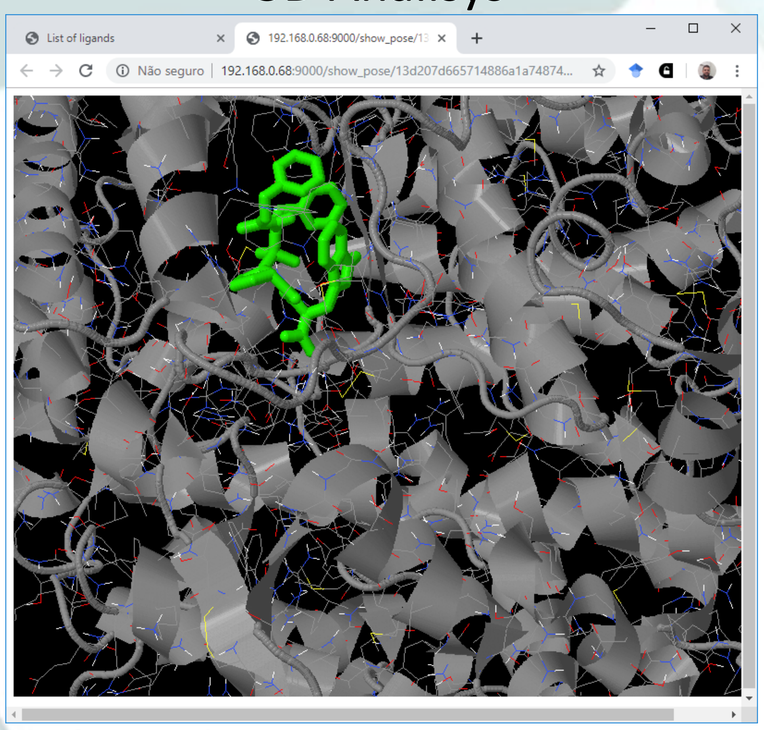
Up to 10 cpds

(IV) Post-processing Analisys

Binding energy Analisys



3D Analisys



HTP SurflexDock Pipeline. (I) The HTP SurflexDock home page allows you to load a druggable target and a library with drug candidates. (II) Representative conformations of the receptor are obtained from molecular simulation by clustering similar conformations. (III) The candidates are challenged against the ensemble through docking and scored according to the calculated ΔG. (IV) The new HTP SurflexDock feature allows you to qualitatively analyze the interaction of the most promising candidates through the analysis of three-dimensional interaction and binding energy of dozens of calculated poses for each complex.

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