

Design and Development of a Versatile Graphical User Interface for Assisting Consensus Docking analyses

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Introduction

Molecular Docking, and its application in high-throughput virtual screening (HTVS), has arisen over the years as one of the most used tools in Drug Discovery, which is important to eliminate much of the effort and to decrease costs of experimental assays. A comprehensive understanding of the system that is subject to docking and of its underlying structural principles, may need a parallel usage of Molecular Graphics Visualization Software to visualize bio-molecules, interactions and search spaces. The steps that must be carried on to complete a docking process, from the preparation of input files to the analyses of the results, usually take advantage of more than one platform. Although docking algorithms are usually implemented for a command-line usage only, just for some of them is currently available a graphical user interface (GUI) that may facilitate their usage. Furthermore, the already developed GUIs are limited to the implementation of a single docking algorithm but, it is a general opinion, that in some cases it is not enough to rely on a single one to reach accurate results, making it necessary the usage of more docking algorithms in parallel. To overcome these drawbacks, we have developed a versatile, user-friendly and cross-platform GUI for assisting the process in all its steps, which works as a plugin of the molecular visualization system PyMOL.

Consensus Docking

The plugin's peculiar feature, which is not found in any other GUI currently developed, is to be suited for the implementation and usage of more docking algorithms in parallel. Therefore, in order to truly reflect its purposes, we have both tested and implemented the “Consensus Scoring” scheme. This approach is primary useful to have a much more accurate ranking of the real bio-active molecules. Indeed it becomes necessary when dealing with Virtual Screening that, too often, lead to False Positives (FP) results.

Brief Overview of the GUI

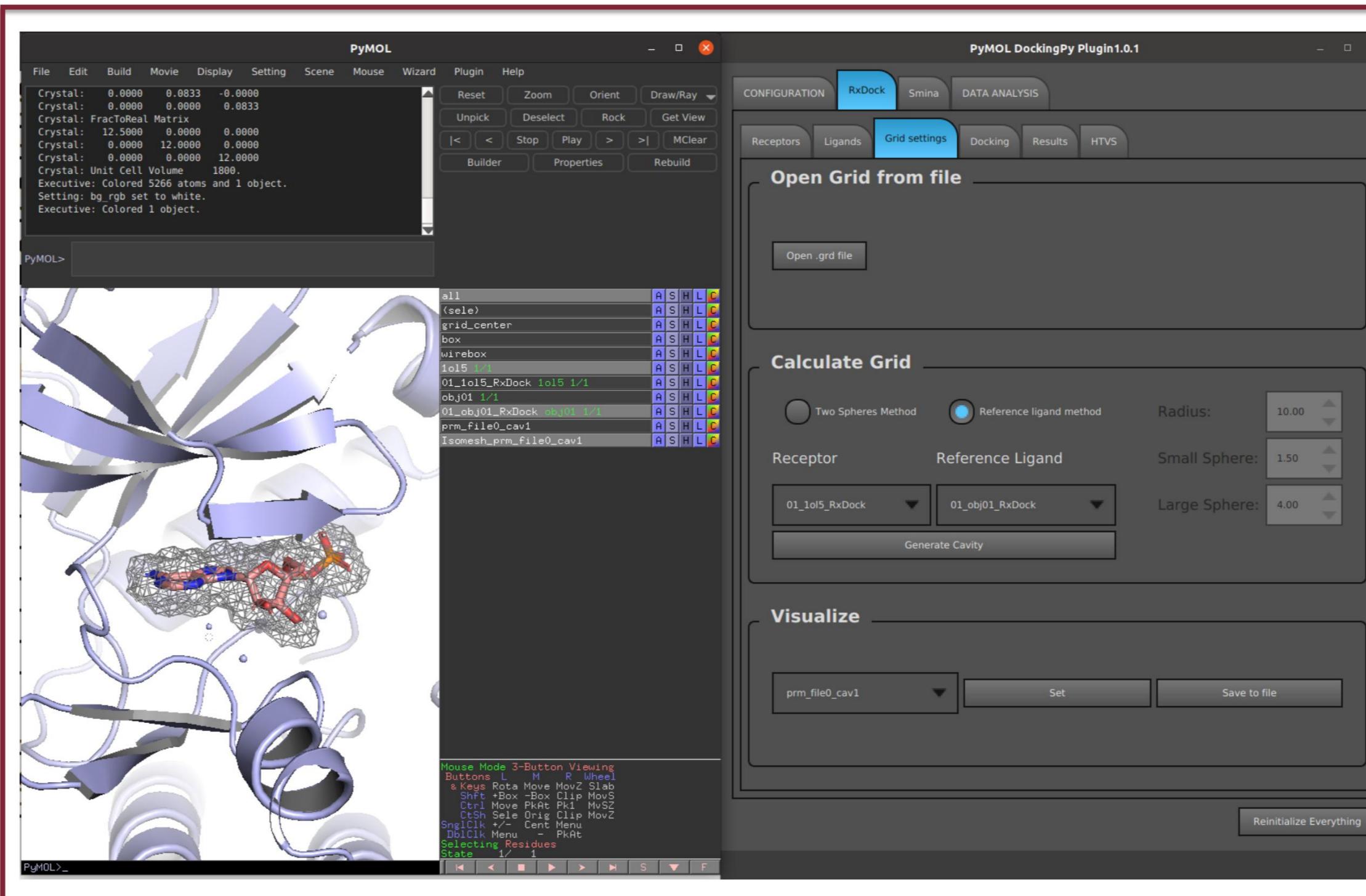


Figure 1. Image shows the Grid Settings tab peculiar of RxDock

Availability

“Structural
Bioinformatics
Group at
Sapienza”



A tab for the analyses of the results

Data Analyses:
in this section are provided the tools for the comparison of the results. It is possible to plot the distributions of RMSD values and to carry out a re-scoring with the “Consensus Scoring” approach.

A tab for each step of the docking workflow

Receptors/Ligands:
extrapolation of structural data,
proper formatting of chemical
properties, protonation.

Grid settings:
creation,
visualization and interactive
modification of the related
parameters

Docking: parameters settings

Results: visualization and RMSD
calculation

- Ensured compatibility, actively-developed and cross-platform
- Interactivity with PyMOL
- Projected on new algorithms
- User-friendly

An application: targeting Aurora-A for cancer treatment

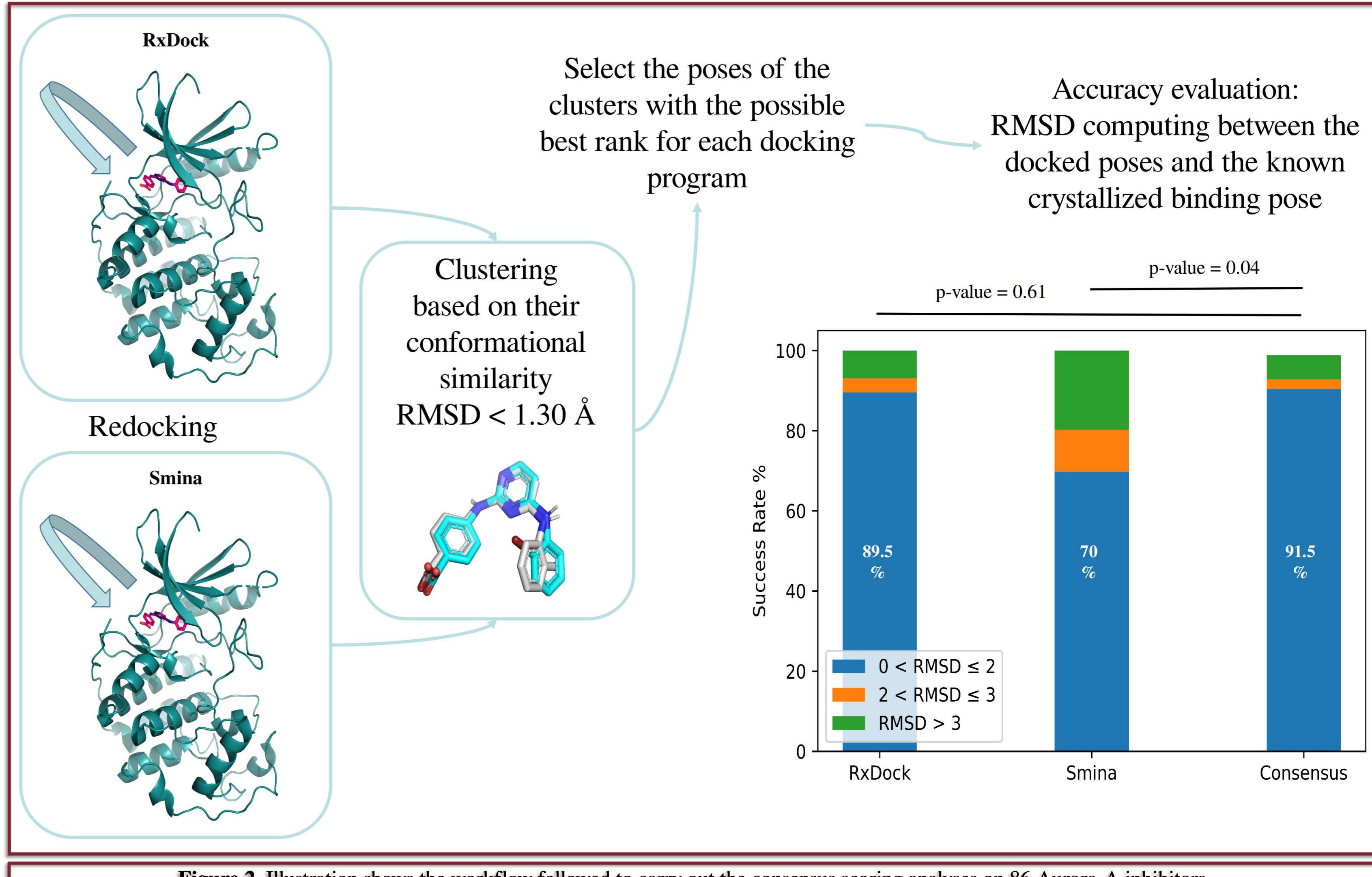
The biological interest was focused on Aurora-A protein, a Serine-Threonine Kinase involved in different Cell-Cycle related (CCR) processes, for which have been reported several mis-regulations that lead to the appearance of a neoplastic phenotype. By now, diverse types of compounds able to bind to the active site, impeding its catalytic activity, have been developed. But, when talking about kinases, off-target events and cell toxicity may arise because of the high structural similarity between member of this family of proteins. This feature makes the identification of new selective and potent inhibitors as the main challenge to be overcome. Therefore, it is needed the development of new methods to reach this aim. On these bases we have decided to evaluate the accuracy of “Consensus Scoring” method on Aurora-A.

Methods

Dataset: 86 crystal structures of human Aurora-A in complex with the inhibitor.

Accuracy evaluation: the information of the conformation adopted by the ligand in the x-ray crystallography experiment was used as a reference for RMSD computing.

Smina: exhaustiveness = 32. RxDock: default settings Protocol: as shown in Figure 2



Results

A significant improvement of the accuracy was found when the Consensus Scoring method has been applied to Smina. Although the method in some cases led to slight but not significant worsening of the results, the cases of deep error regard those ligands whose own redocking failed, thus concluding that the combination of scoring functions can be a good method when evaluating the results, as long as the individual algorithms are used with the parameters settings optimized for the system under study. Furthermore, the analysis was also useful to identify some issues in the scoring function of Smina since this algorithm was able to reproduce the correct binding conformation but not to properly rank it.

Conclusions

The fact that, when applied to Aurora-A, the “Consensus Scoring” method revealed both an improvement of accuracy and some scoring issues in the docking algorithms used, is a step forward of utmost importance for the identification of new protocols and scoring schemes potentially useful to improve the accuracy of HTVS campaign on Kinases. Furthermore, the PyMOL plugin provides the integration, in an easy-to-use environment, of the tools needed to carry out this type of analyses.

References

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