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PLATINUM: a web tool for analysis of hydrophobic/hydrophilic organization of biomolecular complexes

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ABSTRACT

Summary: The PLATINUM (Protein–Ligand ATtractions Investigation NUMerically) web service is designed for analysis and visualization of hydrophobic/hydrophilic properties of biomolecules supplied as 3D-structures. Furthermore, PLATINUM provides a number of tools for quantitative characterization of the hydrophobic/hydrophilic match in biomolecular complexes e.g. in docking poses. These complement standard scoring functions. The calculations are based on the concept of empirical Molecular Hydrophobicity Potential (MHP).

Availability: The PLATINUM web tool as well as detailed documentation and tutorial are available free of charge for academic users at http://model.nmr.ru/platinum/. PLATINUM requires Java 5 or higher and Adobe Flash Player 9.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 INTRODUCTION

Nowadays, automated receptor–ligand docking is widely used in studies of molecular mechanisms of protein—small compound interactions and in drug design (Moitessier *et al.*, 2008). However, the insufficient accuracy of the scoring functions may result in the loss of perspective ligands since near-native solutions may be underscored. Taking this into account, many docking methods apply a multi-step procedure where the preliminary list of putative docking poses is afterwards rescored using more accurate or system-specific criteria to throw out the majority of incorrect solutions.

The hydrophobic effect has long been recognized as an important factor driving the interactions between biological molecules. One of the most successful methods to describe the hydrophobic effect is the empirical concept of Molecular Hydrophobicity Potential—MHP (reviewed in Efremov *et al.*, 2007). Previously, we have demonstrated that in some particular cases, more effective results in docking can be achieved when a standard scoring function is complemented with the term of hydrophobic match at the protein–ligand interface (Pyrkov *et al.*, 2007b, 2008). Also, this approach was particularly efficient when re-scoring results of docking to a flexible protein target in our study of ATP—Ca–ATPase interactions (Pyrkov *et al.*, 2007a). The hydrophobicity-based ranking identified correct pose of the ligand in the binding site, while the scoring function implemented in the docking algorithm and based on hydrogen bonds, yielded random distribution of correct poses among the misleading ones.

To make this approach available to a broader community, we have designed the Protein–Ligand ATtractions Investigation NUMerically (PLATINUM) web interface. Besides protein–ligand complexes, PLATINUM can estimate hydrophobic complementarity in other systems, such as peptide–lipid bilayer (Polyansky *et al.*, 2009), etc., which can also be easily visualized online.

2 METHODS

The empirical MHP concept used in PLATINUM to calculate molecular hydrophobic/hydrophilic properties is based on atomic hydrophobicity constants derived from water–octanol log *P*-values for various organic compounds (Ghose *et al.*, 1998;). PLATINUM automatically assigns hydrophobicity constants according to this parameterization which comprises ~120 atom types based on molecular topology (including explicit hydrogens). Then atomic properties of a ligand and its receptor are projected onto the molecular surface of the former. Comparison of molecular MHP on the interfacial surface can give an understanding of the complementarity of the ligand to the receptor binding site in terms of hydrophobic interactions. Besides, PLATINUM can estimate the number of receptor–ligand hydrogen bonds and stacking interactions based on their geometry.

3 IMPLEMENTATION

The input to PLATINUM is a 3D structure of a receptor molecule in a separate file and a set of ligand poses. If more than one ligand was uploaded, e.g. when analyzing the results of docking—one of them can be selected as a reference (usually this is extracted from an X-ray structure). Currently, the multiple file upload module requires that Adobe Flash Player 9 has to be installed.

After molecules have been uploaded, the parameters of MHP can be settled. These parameters include selection of the MHP distance function, atomic hydrophobicity parameterization and the offset of the MHP scale. The latter is a unique feature of PLATINUM and makes it more flexible in calculating MHP as compared to other software (see the Supplementary Material for detailed description).

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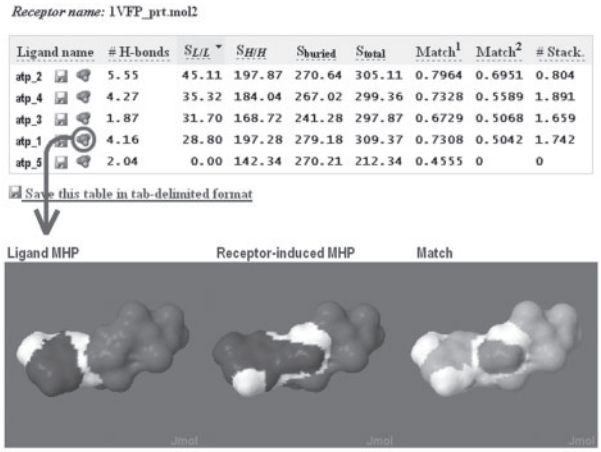

Fig. 1. Screenshot of the results page (top) and visualization (bottom) from the PLATINUM server. Interaction terms calculated for ATP poses docked to Ca–ATPase binding site. The ligand poses list can be sorted according to: (i) the number of hydrogen bonds; (ii) the lipophilic match surface $S_{L/L}$; (iii) the hydrophilic match surface $S_{H/H}$; (iv) the contact surface S_{buried}; (v) the total ligand surface S_{total}; (vi) the fraction of hydrophilic/lipophilic match surface Match[1]; (vii) the fraction of lipophilic match surface Match[2]; (viii) the number of stacking contacts; (ix) the number of cation-pi contacts with guanidinium group (see Supplementary Material for detailed description). On the visualization panel the hydrophobic/hydrophilic properties of ATP (left) and its binding site (middle) projected onto the surface of the ligand, and their match (right) are shown. Color scheme: (i) left-hand and middle panels: hydrophobic (dark grey), hydrophilic (light grey); (ii) right-hand panel: match (light grey), mismatch (moderate grey).

In our previous studies, we have demonstrated that in particular cases (e.g. for nucleobase-containing ligands) a moderate shift of ligand MHP scale to a more hydrophobic range can greatly improve representation of the spatial distribution of its properties (Pyrkov *et al.*, 2007b).

The output of PLATINUM is a table with ligand hydrophobic and hydrophilic match surface areas, stacking and hydrogen bonds listed for each of the uploaded ligand molecules. Figure 1 shows a representative output page from the PLATINUM server. The list of ligands can be sorted according to the magnitude of each of the interaction terms. This can be used to rerank the docking poses previously generated using a standard docking software. While the accuracy of scoring the docking solutions with the term of hydrophobic complementarity has been demonstrated in our previous studies, we must caution that this may not be applicable for every protein–ligand complex and a preliminary test would be desirable (Pyrkov *et al.*, 2008).

Also, additional output is provided for more detailed analysis of selected ligands/ligand poses which will be discussed below. To perform subsequent analysis, the MHP data for each ligand can be downloaded in one of the following formats.

(1) Simple text file where atoms are annotated according to the MHP atom type parameterization.

(2) The pdb file where either atomic hydrophobicity constants or surface MHP values are written to the B-factor column.

(3) Ligand molecular surface represented as a set of dots in pdb or InsightII (Molecular Simulations Inc., 2000) formats.

(4) Grid hydrophobic/hydrophilic potential in InsightII or MolMol (Koradi *et al.*, 1996) formats.

All these data can also be used for visualization of ligand and receptor hydrophobic/hydrophilic properties on the molecular surface of the former. Sliding MHP offset to more hydrophobic or hydrophilic range can produce a clearer picture (Pyrkov *et al.*, 2008). Besides, these properties along with their match/mismatch mapped onto the ligand surface can be instantly visualized in a Jmol applet implemented in the PLATINUM web service.

4 SUMMARY AND FUTURE DIRECTIONS

The PLATINUM web service provides flexible tools for calculation and visualization of molecular hydrophobic/hydrophilic properties in receptor–ligand complexes. These data can be used in such important area of molecular modeling as docking to improve the efficiency of standard scoring functions.

However, the user still has to perform preliminary tests to identify whether this method is applicable in each particular case. It would be desirable to simplify and automate this procedure. In future, we hope to incorporate into the PLATINUM interface some predefined scoring criteria for particular receptor/ligand classes as e.g. for ATP binding proteins (Pyrkov *et al.*, 2007b).

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