Bioinformatics, 35(10), 2019, 1777–1779
doi: 10.1093/bioinformatics/bty879
Advance Access Publication Date: 17 October 2018
Applications Note

Structural bioinformatics

farPPI: a webserver for accurate prediction of protein-ligand binding structures for small-molecule PPI inhibitors by MM/PB(GB)SA methods

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Associate Editor: Alfonso Valencia

Received on July 20, 2018; revised on September 20, 2018; editorial decision on October 11, 2018; accepted on October 15, 2018

Abstract

Summary: Protein-protein interactions (PPIs) have been regarded as an attractive emerging class of therapeutic targets for the development of new treatments. Computational approaches, especially molecular docking, have been extensively employed to predict the binding structures of PPI-inhibitors or discover novel small molecule PPI inhibitors. However, due to the relatively 'undruggable' features of PPI interfaces, accurate predictions of the binding structures for ligands towards PPI targets are quite challenging for most docking algorithms. Here, we constructed a non-redundant pose ranking benchmark dataset for small-molecule PPI inhibitors, which contains 900 binding poses for 184 protein-ligand complexes. Then, we evaluated the performance of MM/PB(GB)SA approaches to identify the correct binding poses for PPI inhibitors, including two Prime MM/GBSA procedures from the Schrödinger suite and seven different MM/PB(GB)SA procedures from the Amber package. Our results showed that MM/PBSA outperformed the Glide SP scoring function (success rate of 58.6%) and MM/GBSA in most cases, especially the PB3 procedure which could achieve an overall success rate of ~74%. Moreover, the GB6 procedure (success rate of 68.9%) performed much better than the other MM/GBSA procedures, highlighting the excellent potential of the GBNSR6 implicit solvation model for pose ranking. Finally, we developed the webserver of Fast Amber Rescoring for PPI Inhibitors (farPPI), which offers a freely available service to rescore the docking poses for PPI inhibitors by using the MM/PB(GB)SA methods.

Availability and implementation: farPPI web server is freely available at http://cadd.zju.edu.cn/farppi/.

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

1 Introduction

Developing small molecules capable of modulating PPIs that can serve as therapeutic agents has become a tremendously active field in both academia and industry (Milroy *et al.*, 2014). In addition to the conventional methods, a variety of specialized screening techniques, such as fragment-based screening and improved virtual screening (VS), have been presented to facilitate the identification of small-molecule PPI inhibitors. To our knowledge, these methods

have allowed us to identify weakly active hits targeting PPIs in a relatively short time, but they are still inefficient when it comes to obtaining lead compounds with necessary selectivity and potency. From a medicinal chemistry perspective, high-resolution co-crystal structures of the initial hits in complex with the PPI targets can guide a structure-based optimization to design improved inhibitors with higher specificity and potency, implying that the acquisition of the accurate three-dimensional structures of protein-ligand complexes is of great importance for the discovery of drug-like small-molecule PPI inhibitors.

Protein-ligand docking, as one of the most common methods in structure-based drug design (SBDD), has been widely used to predict protein-ligand binding modes ever since the early 1980s. However, previous studies have shown that the sampling algorithms of popular docking programs are effective to obtain near-native ligand binding poses by generating a diverse conformational ensemble, while the scoring functions still have problems to distinguish the correct poses from decoy poses because most of them were developed with many approximations on the sake of high computational efficiency (Carlson *et al.*, 2016). In other words, although continuous efforts have been dedicated to improve the scoring functions, the issue that how to correctly identify the near-native binding pose, as the top-ranking pose still has not been well solved by current docking programs.

On the one hand, different optimized scoring functions, such as PoseScore (Fan *et al.*, 2011), SQM/COSMO filter (Pecina *et al.*, 2016), and GRIM method (Gomes *et al.*, 2018), have been developed to improve the accuracy of recognizing near-native binding geometries of ligands from the other poses. On the other hand, more rigorous methods, especially Molecular Mechanics/Poisson Boltzmann Surface Area (MM/PBSA) and Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) methods, have been well evaluated and regarded as better solutions for ranking docked poses (detailed examples shown in Supplementary Material) (Hou *et al.*, 2011). Given the increasing importance of PPI targets and the outstanding performance of MM/PB(GB)SA methods for near-native binding pose recognition, we believe that a benchmark is required to reveal the actual performance of MM/PB(GB)SA methods on the identification of near-native binding poses of small-molecule PPI inhibitors. Here we present our latest work on evaluating the performance of different MM/PB(GB)SA calculation procedures on recognizing near-native binding poses of small-molecule PPI inhibitors. Briefly, our work can be divided into three parts: (i) constructing a non-redundant pose ranking benchmark dataset for small-molecule PPI inhibitors that contains 194 protein-ligand complexes; (ii) evaluating the pose ranking performance of two Prime MM/GBSA calculation procedures implemented in the Schrödinger suites and seven different MM/PB(GB)SA calculation procedures implemented in the Amber package; and (iii) developing a web server, termed as Fast Amber Rescoring for PPI Inhibitors (farPPI), which offers a freely available service for rescoring docking poses using the MM/PB(GB)SA methods with different procedures.

2 Materials and methods

2.1 Dataset construction

Based on the $2P2I_{DB}$ (http://2p2idb.cnrs-mrs.fr), a ready-to-dock dataset which contains 194 protein-ligand complexes for 30 PPI targets was prepared for docking pose generation. Then, a dataset contains 900 docking poses from 184 PPI-inhibitor entries was constructed for the pose ranking performance benchmark. The detailed process flow involved in constructing the datasets and the compositions of the datasets can be found in Supplementary Material. The datasets can be downloaded from the farPPI website (http://cadd.zju.edu.cn/farppi/).

2.2 Pose ranking power benchmark

In addition to the Glide SP scoring function, two Prime MM/GBSA procedures from the Schrödinger suite (Prime $MM/GBSA_{OPLS2005}$ and Prime $MM/GBSA_{OPLS3}$) and seven MM/PB(GB)SA procedures from the Amber package (PB1, PB3, PB4, GB1, GB2, GB5, and GB6) were tested against the ready-to-rescore dataset (Supplementary Table S1). The performance of each method on the whole dataset as well as its different subclasses were analyzed (Supplementary Table S3 and Supplementary Fig. S3). Furthermore, the pose ranking powers of seven MM/PB(GB)SA procedures on different targets were also compared and discussed with the purpose of providing proper guidance value for a specific target (Supplementary Table S5). The detailed methods and results can be found in Supplementary Material.

2.3 Quality metrics

For each ligand, all docking poses were sorted by their scores. The heavy-atom root-mean-squared deviation (RMSD) between the top-scored pose and the native binding pose was calculated by the *obrms* utility in the Open Babel (O'Boyle *et al.*, 2011). It should be noted that the coordinates of docking poses were changed after rescoring due to the unrestricted minimization, thus the RMSD need to be recalculated. If the final RMSD between the minimized top-scored docking pose and native pose is no more than 2.0 Å (2.0 is an arbitrary cutoff, which is used in many other docking studies), it will be regarded as a case of successful pose ranking. The pose ranking success rate was benchmarked as a percentage of correctly ranked ligands.

3 Web server implementation

The web server of farPPI was designed for rescoring the results of a docking run using the MM/PB(GB)SA methods with different procedures. It was developed with Python based on Django web framework (https://www.djangoproject.com/). The AmberTools17 (Case *et al.*, 2005; Salomon-Ferrer *et al.*, 2013), Open Babel (O'Boyle *et al.*, 2011), and several in-house scripts were integrated to automate the calculation process. The overall workflow implemented in the farPPI server is shown in Supplementary Figure S1. Briefly, users can upload the results of a docking run (a file containing ligand docking poses and a file containing protein structure) as the input data; then each pose will be rescored within the binding site of protein using the MM/PB(GB)SA methods after a quick structural minimization; finally, two formatted results files (a csv file and a pdf file) and several log files are generated and zipped as the output data for downloading. A case study is provided in Supplementary Material.

4 Conclusion

In this study, we constructed a non-redundant pose ranking benchmark dataset for PPI inhibitors, which contains 184 protein-ligand complexes (900 docking poses) covering 29 different PPI targets. Then, it was used to assess the pose ranking power of two Prime MM/GBSA procedures and seven MM/PB(GB)SA procedures. Based on the comparison studies, several useful conclusions can be obtained: (i) The pose ranking power of MM/PBSA method outperformed Glide SP scoring function and MM/GBSA method in most cases, especially the PB3 procedure that can achieve an overall success rate of about 74%; (ii) The GB6 procedure performed much

better than the other MM/GBSA procedures, largely indicating that the excellent potential of the GBNSR6 implicit solvation model for pose ranking; and (iii) Using an appropriate rescoring procedure can significantly improve the success rate of near-native pose identification for a special target, but how to determine an appropriate rescoring method still needs to be studied. Finally, the farPPI web server (http://cadd.zju.edu.cn/farppi/) was developed to efficiently assist non-expert rescoring docking poses using the MM/PB(GB)SA methods with different procedures.

Funding

This study was supported by the National Key R&D Program of China (2016YFA0501701, 2016YFB0201700), and the National Science Foundation of China (21575128, 81773632).

Conflict of Interest: none declared.

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