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Application of Docking Methods: An Effective In Silico Tool for Drug Design

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Abstract

Using computational approaches we can dock small molecules into the structures of Macromolecular targets and then score their potential complementarity to binding sites is widely used in hit identification and lead optimization techniques. This review seeks to provide the application of docking in structure-based drug design (binding mode prediction, Lead Identification and Lead optimization), and also discussed how to manage errors in docking methodology in order to overcome certain limitations of docking and scoring algorithm.

Key words: Docking, Structure-Based Drug Design, Scoring Function

1. Introduction

Every drug companies are actively involved to identify the hit compounds and lead optimization process, computation methodologies plays a crucial role in drug discovery programs[1-4]. The number of proteins with a known 3D is increasing rapidly, and structures produced by structural genomics initiatives are beginning to become publicly available. The increase in the number of structural targets is in part due to improvements in techniques for structure determination, such as hight-hroughput X-ray crystallography. With large-scale structure-determination projects driven by genomics consortia, many current target proteins have been selected for their therapeutic potential. One key methodology docking of small molecules to protein binding sites was pioneered during the early 1980, and remains a highly active area of research[5]. Docking is the search for spatial transformations that fit two molecules together in energetically favorable configurations. It should accurately predict the structure of a ligand-receptor complex with respect to experiment and calculate a binding energy that can be used to correctly rank the ligands relative to experimentally measured binding affinities. If the ligand pose sampling is adequate, and the energy scoring function is sufficiently accurate, then the global minimum-energy position of the ligand in the receptor can be selected from the set of local energy minima. Docking is mostly applied to the systems of small molecule ligands and protein receptors; it has also been used to dock proteins and proteins, nucleic acids to proteins, and small molecules to nucleic acids. Although significant improvements in the speed and efficiency of the conformational search capabilities of docking algorithms have been obtained, only incremental improvements in the predictive capabilities of the scoring functions used by these algorithms have occurred. There are a number of excellent reviews of docking programs and algorithms that described in the field of docking program in a level of detail[6,7]; this review discussed the application of docking approaches in structure-based drug design.

2. Theoretical Aspects of Docking

For an enzyme and inhibitor, docking aims at correct prediction of the structure of the complex [E+I] = [EI] under equilibrium conditions (equation 1).

$$[EI]_{aq} \rightleftharpoons [E]_{aq} + [I]_{aq} \quad (1)$$

The free energy of binding (ΔG) is related to binding

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affinity by equations 2 and 3:

$$\Delta G = -RT\ln K_A \quad (2)$$

$$K_A = K_i^{-1} = \frac{[EI]}{[E][I]} \quad (3)$$

Prediction of the correct structural pose of the [E+I] complex does not require information about *K*A. However, prediction of biological activity (ranking) requires this information; scoring terms can therefore be divided in the following fashion. When considering the term [EI], the following factors are important: steric, electrostatic, hydrogen bonding, inhibitor strain (if flexible) and enzyme strain. When considering the equilibrium shown in equation 1, the following factors are also important: desolvation, rotational entropy and translational entropy.

3. Application of Docking Methods in Structure-Based Drug Design

Docking approaches is extremely useful in three broad categories: to predict the structure of a ligand-receptor complex accurately with respect to experiment (binding mode prediction), virtual screening for lead identification, and potency prediction for lead optimization.

4. Prediction of Binding Mode

Binding mode prediction involves two step processes: (1) a set of ligand conformations are generated. In docking algorithm, the ligand conformations are generated and modified within the environment of the binding site, (2) scoring algorithm is applied for the generated conformations, based on the best binding affinity the top conformer to be selected. The selected pose will be similar to the pose that would be seen crystallography. The docking algorithm should be able to identify successfully small molecule binding mode that are sufficiently correct to be useful for structure-based drug design[8].

5. Virtual Screening for Lead Identification

Docking algorithm is useful to screen large chemical database to find out potential lead for the interested protein target. Since the database usually contains 10^5-10^6 chemical compounds, so it's extremely important to consider about the computational time. To make the docking algorithm more efficient, the parameters of the algorithm modified or optimized to increase the speed of calculation. At the end of screening process, potential candidate could be identified using specific cutoff score, and further validated by experimental assay studies[9]. Docking methodology identifying that compounds with poor shape and chemical complementarity to the protein-binding site will score poorly and it will be at the bottom of the list of scored compounds. Most scoring functions have been designed to reproduce binding mode and affinities of true actives, for virtual screening the scoring function does not necessarily need to account correctly for all the features conferring affinity.

6. Potency Prediction for Lead Optimization

In addition to hit identification, docking techniques are increasingly used to support lead optimization efforts. Here, the scenario changes: to facilitate a hit-to-lead transition, the compound potency typically has to be increased by two to three orders of magnitude and relatively small chemical modifications can lead to significant changes in binding. The requirement to estimate the effects of relatively small chemical changes further complicates the calculations and therefore distinguishing a micromolar compound from a nanomolar analogue often requires much greater accuracy than typical docking and scoring can provide. However, once hits or leads have been co-crystallized with their targets and exact binding conformations have been established, docking of analogues can be facilitated by the application of algorithms such as 'anchored search' 24 that model compound modifications on pre-defined core fragments of leads.

Docking approaches are relatively successful to order the rank of a set of related compounds by affinity. Even though the scoring function has some limitations, it has modest progress towards the lead optimization. If a binding mode is identified accurately, scoring function can count favorable and unfavorable interactions and therefore predict relative potency. Current docking algorithms and scoring functions do not thoroughly account for contributions such as loss of conformational entropy during binding[10].

7. Absorption, Distribution, Metabolism and Excretion Properties

Docking techniques are currently also applied to aid in structure-based absorption, distribution, metabolism and excretion (ADME) evaluation. Cytochrome P450 isoforms are major drug-metabolizing enzymes and have become focal points in the study of rapid metabolism and drug-drug interactions[11,12]. Several groups have developed structure-based approaches for the prediction of compounds that would be metabolized by or inhibit P450s, and various homology models of human P450 isoforms have been generated for these purposes as templates for docking to predict drug metabolism[13-16]. Recently, a crystal structure was determined of a human P450 isoform in complex with warfarin. The inhibitor binds proximally to the iron-porphyrin system in the enzyme but had no direct interaction with the cofactor. These structural insights should help to further refine docking studies on human P450s and increase their predictive value.

8. Managing Errors in Docking

Because of large space of ligand-receptor complex configurations, approximate sampling and energy scoring are used when docking. Errors in the sampling methods and energy scoring methods can cause both complex structure prediction and docking application based on ligand database ranking to fail. Structure prediction failures can be classified as sampling failures or scoring failures. Sampling failures occur when the sampling algorithm fails to sample any ligand poses near the native ligand pose; increasing the amount of sampling usually eliminates these failures modes. Scoring failures occur when the predicted ligand pose has a more favorable energy score than the native co-crystal ligand pose. Because energy scoring function does include the calculation of binding entropy. To get more reliable docking results, it's very important that using higher accuracy of sampling and scoring functions when necessary.

9. Conclusion

This review has briefly discussed the application of docking approach in structure-based drug design. Even though, these methodologies have some pitfalls, but its useful application in drug discovery process. Virtual screening on protein templates, which differs from molecular similarity- and ligand-based virtual screening methods, provides an opportunity for the de novo identification of active compounds, without bias towards known hits or leads. The relationship between docking and scoring algorithm is quite complex, however the models produce better results in order to differentiate 'true ligand' from false positive. Although docking and scoring relies on many approximations, the application of these techniques during binding mode prediction, lead identification and optimization, quite useful in traditional approaches in structure-based design.

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