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A Multi-objective Docking Method in Drug Molecular Design

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Abstract

The molecular docking problem is an optimization problem, which finds the optimal molecular orientation and conformation by minimizing the intermolecular interaction energy. It plays an important role in drug design. Being the object of the optimization problem, score functions (SFs) estimate binding affinities between ligands and proteins. The non-ideal efficacy of SFs is thought as the biggest barrier which hinders the improvement of the molecular docking method. The conflict between the accuracy and speed of SF is a difficult problem need to make great efforts in. Therefore, how to improve the docking accuracy with available SFs is a practical and urgent task.

Most docking methods are based on one single objective. However, due to the approximation adopted in the SF developing, deviations from the real binding energy are unavoidable. Based on this consideration, consensus scoring was developed by combining multiple SFs to reduce the deviations brought by individual SFs as possible. How to choose and combine the SFs, and design relevant optimization strategy to the multi-objective problem are crucial for improving the docking efficiency with consensus scoring.

In this work, a new multi-objective docking method is proposed to further improve the pose prediction with available SFs. The available scoring functions can generally be divided into the following three types: force-field-based, empirical-based and knowledge-based SFs. They focus on diverse aspects of ligand binding, and are derived from different principles. Therefore, three representative scoring functions from these three types are introduced as the objectives, and then a multi-objective optimization method is designed to optimize these three objectives simultaneously. Instead of simple combination of the multiple objectives with fixed weight factors, an aggregate function is introduced to approximate the real solution of the original multi-objective and multi-constraint problem, which will simultaneously smooth the energy surface of the combined scoring functions.

The publicly available GOLD test set containing 134 protein-ligand complexes is applied to evaluate the reliability of this method. The results indicate that the multi-objective method can enhance the pose prediction power of docking with the available SFs, and can be efficiently employed in molecular drug design.