# [P11] Rescoring docking poses by graph matching of protein–ligand interactions: lessons learned from the D3R Grand Challenges

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Molecular docking is a widely-used technique to predict the three-dimensional (3D) atomic coordinates of a protein-ligand complex. However, correctly scoring the docking solutions is a major issue and limitation of current scoring functions[1]. The docking community has therefore organized several resources to aid computational chemists to refine both their methods and protocols. One of them is the Drug Design Data Resource (D3R) that periodically proposes challenges aimed at predicting protein-ligand coordinates and binding energies prior to the release of their crystal structures and related experimentally determined affinity data. The D3R Grand Challenges were a good opportunity to test our algorithm GRIM[2] to rank docking poses. GRIM uses a knowledge-based approach to convert protein-ligand complexes in interaction pattern graphs and score docking solutions by similarity of predicted interaction patterns to that already visited in the Protein Data Bank. Here we summarize the results achieved in two D3R Grand Challenges[3,4] (2015 and 2016) and discuss the strengths and the limitations of our method. When applied to the HSP90α data set, for which many protein-ligand X-ray structures were already available, GRIM provided very high quality solutions (mean rmsd = 1.06 Å, n = 6) as top-ranked poses, and significantly outperformed a state-of-the-art scoring function. In the case of MAP4k4 and FXR inhibitors, the accuracy of GRIM poses decayed due to two main factors: (i) scarce preexisting 3D knowledge and higher chemical diversity and (ii) hydrophobic nature of the active site. Nevertheless, GRIM still outperformed the docking energy-based scoring functions with a mean rmsd of 3.18 Å (n=30) for MAP4K4 and 3.25 Å (n=35) for FXR. Despite the limitations, our rescoring method is quite simple to implement, independent from a docking engine, and applicable to any target for which at least one holo X-ray structure is available. In addition to pose prediction, we established a simple scheme to rank 102 FXR agonists in the second challenge. Using GRIM to select the best pose and HYDE[5] to estimate the Gibbs free energy of binding, we provided a fast protocol, yielding the third most accurate ranking method among 57 contributions. This protocol is accurate enough and could be applied to post-process virtual screening data.

Bibliography:

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