Is It Reliable to Take the Molecular Docking Top Scoring Position as the Best Solution without Considering Available Structural Data?

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Molecular docking is the most frequently used computational method for studying the interactions between organic molecules and biological macromolecules. In this context, docking allows predicting the preferred pose of a ligand inside a receptor binding site. However, the selection of the ?best? solution is not a trivial task, despite the widely accepted selection criterion that the best pose corresponds to the best energy score. Here, several rigid-target docking methods were evaluated on the same dataset with respect to their ability to reproduce crystallographic binding orientations, to test if the best energy score is a reliable criterion for selecting the best solution. For this, two experiments were performed: (A) to reconstruct the ligand-receptor complex by performing docking of the ligand in its own crystal structure receptor (defined as self-docking), and (B) to reconstruct the ligand-receptor complex by performing docking of the ligand in a crystal structure receptor that contains other ligand (defined as cross-docking). Root-mean square deviation (RMSD) was used to evaluate how different the obtained docking orientation is from the corresponding co-crystallized pose of the same ligand molecule. We found that docking score function is capable of predicting crystallographic binding orientations, but the best ranked solution according to the docking energy is not always the pose that reproduces the experimental binding orientation. This happened when self-docking was achieved, but it was critical in cross-docking. Taking into account that docking is typically used with predictive purposes, during cross-docking experiments, our results indicate that the best energy score is not a reliable criterion to select the best solution in common docking applications. It is strongly recommended to choose the best docking solution according to the scoring function along with additional structural criteria described for analogue ligands to assure the selection of a correct docking solution.

AutoDock

Cross-docking

Glide

Rigid molecular docking

RMSD

Scoring energy

ligand

protein

protein binding

biology

chemistry

metabolism

molecular docking

molecular model

procedures

X ray crystallography

Computational Biology

Crystallography, X-Ray

Ligands

Models, Molecular

Molecular Docking Simulation

Protein Binding

Proteins