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# Optimization of *in silico* generated ligand geometries within a binding pocket using drugscore potentials

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The scoring function DrugScore (CSD) [1], developed in our group, is a knowledge-based scoring function that uses distance dependent pair potentials to evaluate ligand geometries in complex with a target protein. The currently applied potentials are derived from non-bonded interactions in small molecule crystal packings. DrugScore (CSD) was shown to perform particularly good in recognizing near-native ligand geometries from a set of wide spread docking solutions.

In this study we present an approach where the DrugScore potentials are not only used to evaluate ligand poses, but rather to optimize and thereby relax a ligand conformation under the influence of these potentials. Therefore a global minimization strategy based on local surface smoothing [2] was implemented into the program MiniMuDS (**Mini**mizing **M**olecules **u**sing **D**rug**S**core potentials). The variables to be optimized during minimization are the torsion angles about the rotatable ligand bonds as well as a free translation and rotation of the ligand molecule on the whole. The protein is treated as rigid. In the used energy model the DrugScore potentials represent all intermolecular interactions from the ligand to the protein. In addition Van-der-Waals interactions and knowledge-based torsion angle potentials account for the intramolecular interactions in the ligand.

To validate our optimization approach we used a subset of the Wang data set [3], which contains 100 crystal structures of protein-ligand complexes plus another 100 decoy docking solutions for each of these structures. We evaluated how much MiniMuDS drives a given crystal structure away from the native conformation, and on the other hand, how much a docking pose can be moved towards the native state. This influence is quantified by the scoring and rmsd values before and after minimization, and we compared these results to those produced by a minimization under the MAB force field as implemented in the program Moloc [4].

## References

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