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DrugScore^{FP}: profiling protein-ligand interactions using fingerprint simplicity paired with knowledge-based potential fields

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Scoring functions used in structure-based drug design are often inefficient in reliably placing near-native geometries on the first scoring rank. Furthermore, there is no means to incorporate protein-specific information which additionally captures interaction details of different experimentally observed binding modes with the target protein under consideration.

Here, we present a vector-based extension of the DrugScore^{CSD} formalism [1], called DrugScore Fingerprints (DrugScore^{FP}), to rescore docking results. The original DrugScore of a docked inhibitor is partitioned into per-atom scores resulting in a 1D vector. Simple distance metrics allow the determination of similarities between fingerprints of docked compounds and reference fingerprints derived from crystal structures. Furthermore, DrugScore^{FP} allows the generation of family-based fingerprint profiles similarly implemented in SIFT [2,3][4]. Therefore, a weighted consensus vector is derived from a given set of co-crystallized inhibitors with the target protein. Thus, DrugScore^{FP} binding profiles capture similarities and dissimilarities with respect to drug targets for which a large amount of structural data is available.

We have applied DrugScore^{FP} to handle the following tasks in structure-based drug design:

The recognition of near-native docking-poses was improved compared to DrugScore^{CSD} and SIFT using the Wang dataset [5]. DrugScore^{FP} places geometries <0.5Å rmsd on the first scoring rank in 94% of the cases. This indicates an improvement compared to the original DrugScore^{CSD} of 6% and SIFT of 18%. Furthermore, cross-validation studies on different consensus fingerprints were performed with respect to a trypsin dataset consisting of 61 co-crystallized ligand structures. In a leave-one-out experiment, DrugScore^{FP} showed better recognition rates of crystal structures than docked compounds in 75% of the cases. As a final step, GOLD was used to dock 1800 compounds from the National Cancer Institute Diversity Set (NCI; http://www.nci.nih.gov) into trypsin and HIV-1 protease. DrugScore^{FP} shows superior ROC-AUCs of up to 99% compared to GOLD-Score (72%) and DrugScore^{CSD} (85%), using a fingerprint profile constructed from 61 and 22 co-crystallized ligands as query for the trypsin and the HIV-1 protease screen, respectively.

Finally, the results prove that DrugScore^{FP} can be used as a powerful filter, identifying similar binding profiles. It could also be shown that DrugScore^{FP} is stable with respect to cross-validations. It reliably discriminates near-native poses from widely spread decoys and retrieves active compounds diluted in a large dataset almost perfectly.

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