Surflex docking derived 3D topological descriptors improves virtual screening performance of Inhibitors of Protein-Protein Interactions

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Protein-Protein Interactions (PPIs) play a vital role in cellular function. However, the large, flat, and less distinguished binding sites of protein complexes impedes the rational design of novel therapeutic agents. [1,2] Here, we report the benchmarking of several post-docking derivatized scoring metrics to modulate complex PPI with small molecules. First, an automated structure-based KNIME workflow was used to guide the selection of protein structures of eleven diverse PPI interfaces based on binding site dissimilarity. Next, we curated and standardized the compounds for each target, retrieved from ChEMBL [3] and PubChem [4] repositories. The virtual screening protocol of Surflex [5] was employed to generate the protein-ligand docking poses. The best-ranked binding poses were post-processed to generate Structural Interaction Fingerprint (SIFt) metric and Solvent Accessible Surface Srea (SASA) descriptors. Also, the poses were evaluated for shape similarity and deviation from the geometric center of the co-crystallized ligand. Early database enrichments using 3D descriptors were found comparable or superior when used alone or in combination with Surflex docking scoring function. Importantly, SASA and SIFt descriptors display remarkable robustness to produce reasonable early enrichments for several PPI sites. The described methodology may have important implications in hit finding programs targeting PPIs as well as classical drug targets.

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