REPRODUCING BIO-ACTIVE CONFORMATIONS WITH CATALYST AND OMEGA

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Following our recent study on the conformational space sub-sampling algorithm of Catalyst 4.8 [1], we investigated the quality of conformational models generated by Catalyst 4.11 [2] and Omega 2.0 [3]. Multi-conformer generation algorithms are typically assessed in terms of how accurate generated conformers correspond to low-energy conformations. For virtual screening using 3D methods, the reproduction of protein-bound ligand conformations is more interesting: We therefore geometrically compared generated poses to bound bio-active conformations from X-ray structures. We examined a sample of 768 PDB complexes representing pharmacologically relevant drug targets with reasonable quality and resolution. The ligands were extracted using our pharmacophore management and visualization tool LigandScout [4], and subsequently generated conformational models were retrieved from the respective isomeric SMILES strings. RMS deviation between the best fitting conformer of the generated ensemble and the bioactive conformation stored in the PDB database was used as a benchmark. Several user-adaptable algorithm parameters were analyzed to provide comprehensive guidelines for best generator performance.

[1] Kirchmair J, Laggner C, Wolber G, Langer T. Comparative Analysis of Protein-Bound Ligand Conformations with Respect to Catalyst's Conformational Space Subsampling Algorithms. J. Chem. Inf. Comput. Sci. 2005; 45:422-430.

[2] Catalyst, Version 4.11; Accelrys, Scranton Road, San Diego, CA

[3] Omega 2.0. OpenEye Scientific Software, 3600 Cerrillos Rd., Santa Fe, NM 87507

[4] Wolber G, Langer T. LigandScout: 3-D Pharmacophores Derived from Protein-Bound Ligands and Their Use as Virtual Screening Filters J. Chem. Inf. Model. 2005; 45:160-169.