Finding 'Bioactive' Conformations using Catalyst's Conformer Generation Algorithm

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Any conformation generation algorithm for the purposes of pharmacophore modeling needs to address two important points: adequate *coverage* of the energy landscape and *diversity* represented among the conformational models of the compound under consideration. Catalyst® allows conformation generation, within a user-defined energy threshold, through either a FAST method or a BEST method. The FAST method is a preferred method for generating Catalyst 3D compound databases, whereas the BEST method is recommended for generating conformers that would be used as input for developing automated hypotheses (HipHop, HypoGen, and HipHop Refine).[1]

The BEST conformation generation method uses the Poling algorithm, which attempts to generate diverse conformers in feature space.[2] In a recently published study, Kirchmair, *et al.* investigated Catalyst's ability to generate biologically relevant conformers using 510 protein-ligand complexes obtained from the PDB.[3] This work represents the most comprehensive external review focused on the quality of conformers generated in Catalyst and the effect of several parameters (FAST vs BEST methods, maximum numbers of conformers generated, and the choice of energy threshold).

The study reveals that the recommended settings of generating 255 conformers using the BEST method and a 20 kcal/mol produces conformations with RMS of less than 1 Å to the X-ray structure of the ligand. Both FAST and BEST methods provide best fitting conformers with RMS < 1.50 in more than 80% of all cases and with RMS < 2 in more than 93% cases. Commonly used force fields estimate that the energy of biologically active conformations are, in most of the cases, at a higher level than the computed global energy minimum and that Catalyst does well in predicting such conformers when the appropriate energy threshold values are chosen. These high quality conformers can be subsequently used for pharmacophore modeling and structure based drug design.

References

1. http://www.accelrys.com/products/catalyst/

2. Smellie, A., Teig, S. L. *et al.,* "Poling: Promoting Conformational Variation," *J. Comp. Chem.*, **1995**, *16*, 171-187.

3. Kirchmair J., Laggner C., Wolber G., and Langer T., "Comparative Analysis of Protein-Bound Ligand Conformations with Respect to Catalyst's Conformational Space Subsampling Algorithms," *J. Chem. Inform. Mod.*, **2005**, *45*, 422.
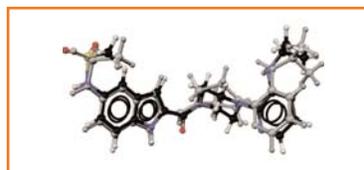
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An example fitting of bioactive conformation of 1KLM pdb ligand with the best fitting generated conformer. RMS=0.499 (Reproduced by permission of the author).

Flexibility of Catalyst conformational generation: Users can adjust the conformation generation process in Catalyst through the use of .Catalyst parameters.

"The aim of this large scale study was to evaluate Catalyst's conformational model generation with a large sample of 510 ligands and to develop a reliable protocol for the modeler on how to use Catalyst's ConFirm settings. The results show that the CHARMm force field implemented within Catalyst is a powerful tool which is able to produce high quality conformers that most of the times are well suited for in silico drug research."
—Kirchmair *et al.,* 2005