Reproducing Bio-Active Conformations with Catalyst and Omega

A careful assessment of conformational model generators

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http://pharmazie.uibk.ac.at/CAMD
Why do we need conformational models?

Are model generators able to represent the protein-bound ligand conformation?

How can the maximum performance be achieved with Omega and Catalyst?
Introduction

Importance of finding bio-active conformers

• Conformational models are needed for
  • pharmacophore modeling
  • rigid docking
  • shape fitting
  • 3D QSAR
  • virtual screening
  • …

• Any in silico 3D drug discovery approach depends on the accurate representation of low-energy conformations
  Aim: reproducing the bio-active conformation!
Search for Bio-Active Conformation
The need for reliable conformational models

- bio-active conformation is not at the global energy minimum – many conformers within a certain energy range (~20 kcal/mol) to be investigated
- make a representative sampling of conformational space with the smallest number of conformers that contains the bio-active conformation within the required accuracy
Conformational Model Generators

- **Catalyst 4.11** (Accelrys) [www.accelrys.com](http://www.accelrys.com)
  - CHARMM force field
  - FAST: heuristic approach aiming at interactive speed
    - ring fragment library
  - BEST: Monte-Carlo like algorithm & poling

- **Omega 2.0** (OpenEye) [www.eyesopen.com](http://www.eyesopen.com)
  - rule-based approach using a fragment library
  - two self-sufficient modules:
    - seed structure generator
    - torsion driver
  - highly user-adaptable
Work Flow Scheme
Assessment of 778 PDB complexes

- assembling of a representative ligand set
- conformational search
- evaluation:
  RMSD between the bio-active ligand conformation and the best fitting conformer
Results
What RMSD values denote...
RMSD achieved with different settings:

- Omega and Catalyst FAST achieve comparable accuracy
- Catalyst BEST surpasses Omega and FAST

**default:** ewindow 25.0 kcal/mol, maxconfs 400, rms 0.8, bmmff94s_noestat, smmff94s_noestat

**HTS:** maxconfs_50, bmmff94s_trunc, rms 0.8

**HQS:** maxconfs_500, bmmff94s_trunc, rms 0.4
the number of generated conformers increases with flexibility and size of the compounds
the accuracy of conformational models is highly dependent on the size of conformational space
### Computational cost

Catalyst FAST requires only 1.5 seconds for conformational ensembles of maximally 50 conformers.

<table>
<thead>
<tr>
<th>Generator</th>
<th>Processor Time (seconds per ensemble)</th>
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<tbody>
<tr>
<td>OMEGA_defaults</td>
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<tr>
<td>OMEGA_HTS</td>
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<td>OMEGA_HQS</td>
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<tr>
<td>CATALYST_50f</td>
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<tr>
<td>CATALYST_500f</td>
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<td>CATALYST_50b</td>
<td>35.8</td>
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<tr>
<td>CATALYST_250b</td>
<td>155.0</td>
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</table>

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Computing time as a function of flexibility and ensemble size

Catalyst BEST shows significant correlation between the size of conformational space and calculation time
Results

Conformational space sub sampling

Introduction
Conf. Model
Generators
Work Flow
Results
Generator User
Guide
Conclusions
CSD vs. PDB conformations of 29 compounds

the average CSD RMSD values are 8% to 17% lower than the respective PDB conformation
**Best performing settings:**

<table>
<thead>
<tr>
<th></th>
<th>HTS</th>
<th>HQS</th>
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<tbody>
<tr>
<td><strong>application scenario</strong></td>
<td>database screening</td>
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<td>alignments</td>
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<td>Omega</td>
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</tr>
<tr>
<td>Catalyst</td>
<td>50 FAST</td>
<td>250 BEST</td>
</tr>
</tbody>
</table>
Conclusions

• the quality of conformational models is always a trade-off between sampling depth and computational costs
• Omega & Catalyst are able to generate high quality conformational models
• Omega shows favorable results in HQS
• Catalyst FAST is the best choice for HTS
Kirchmair J, Laggner C, Wolber G, Langer T
Comparative Analysis of Protein-Bound Ligand Conformations with Respect to Catalyst’s Conformational Space Subsampling Algorithms.

Kirchmair J, Wolber G, Laggner C, Langer T
Comparative Performance Assessment of the Conformational Model Generators Omega and Catalyst: A Large-Scale Survey on the Retrieval of Protein-Bound Ligand Conformations.
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Thank You for Your Attention!