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

Introduction

- 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

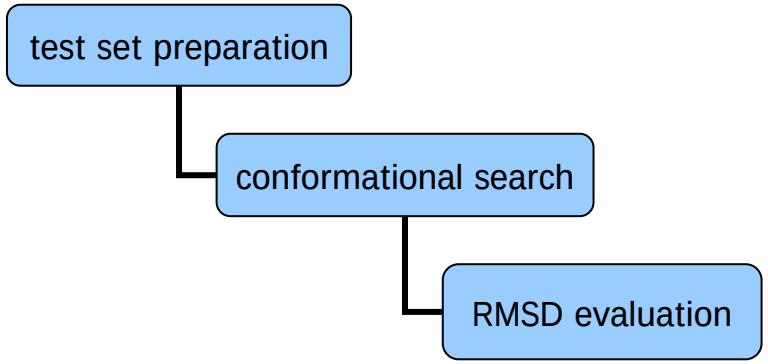
- bio-active conformation is not at the global energy minimum – many conformers within a certain energy range (~20 kcal/mol) to be investigated
- **make a representative sampling of conformational space with the smallest number of conformers that contains the bio-active conformation within the required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

Conformational Model Generators

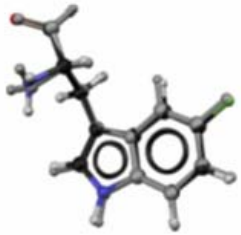
- **Catalyst 4.11** (Accelrys) www.accelrys.com
  - CHARMm force field
  - FAST: heuristic approach aiming at interactive speed
    - ring fragment library
  - BEST: Monte-Carlo like algorithm & poling
- **Omega 2.0** (OpenEye) www.eyesopen.com
  - rule-based approach using a fragment library
  - two 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

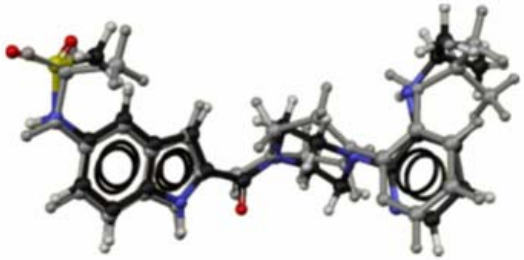


Results
What RMSD values denote...

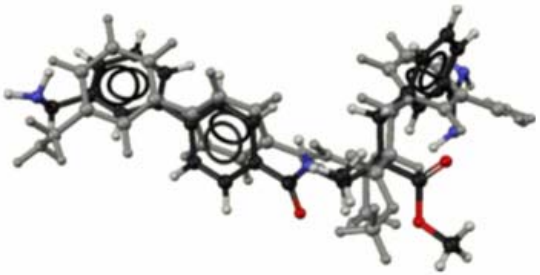


FTR-5FWG: RMSD = 0.089

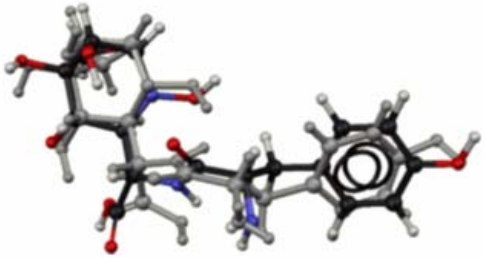
116-1HWJ: RMSD = 1.466



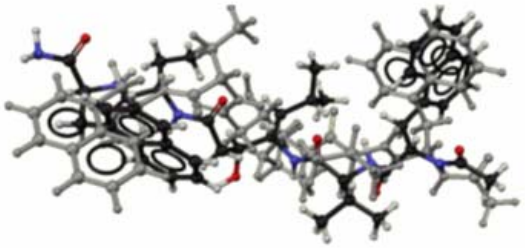
SPP-1KLM: RMSD = 0.499



RPR-1EZQ: RMSD = 1.984

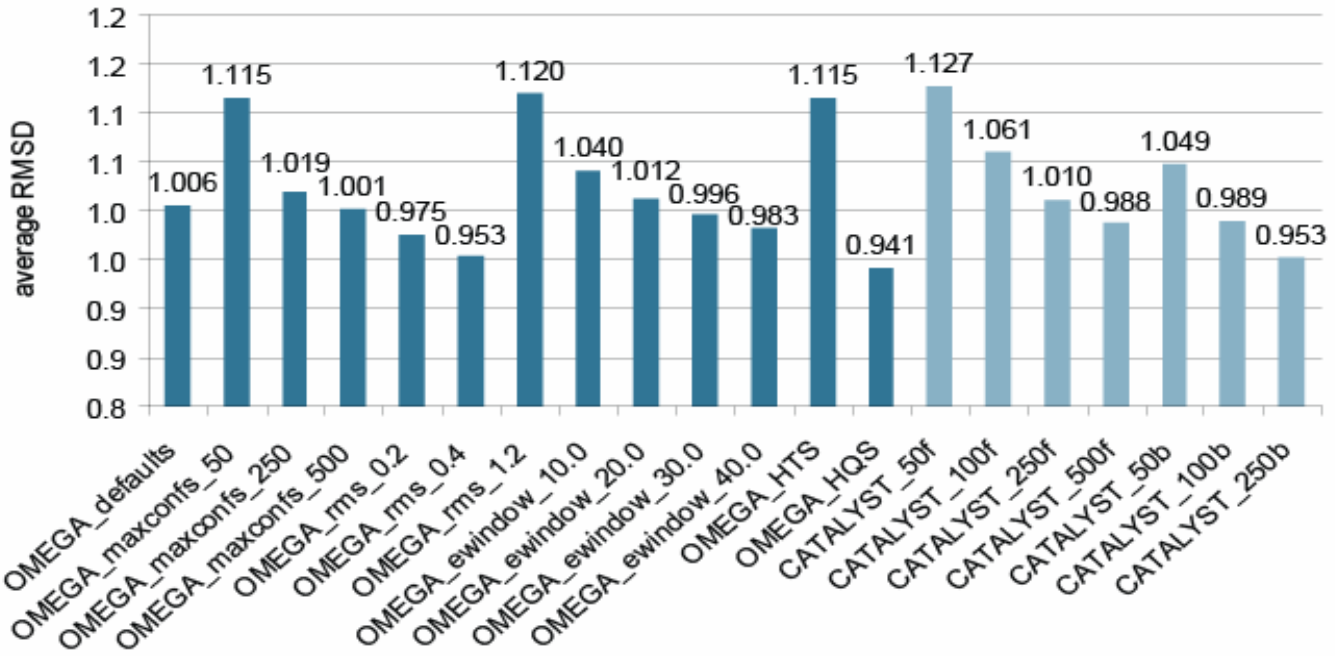


383-1JII. RMSD = 0.944



LP1-1ODY: RMSD = 2.932

Results
The average RMSDs



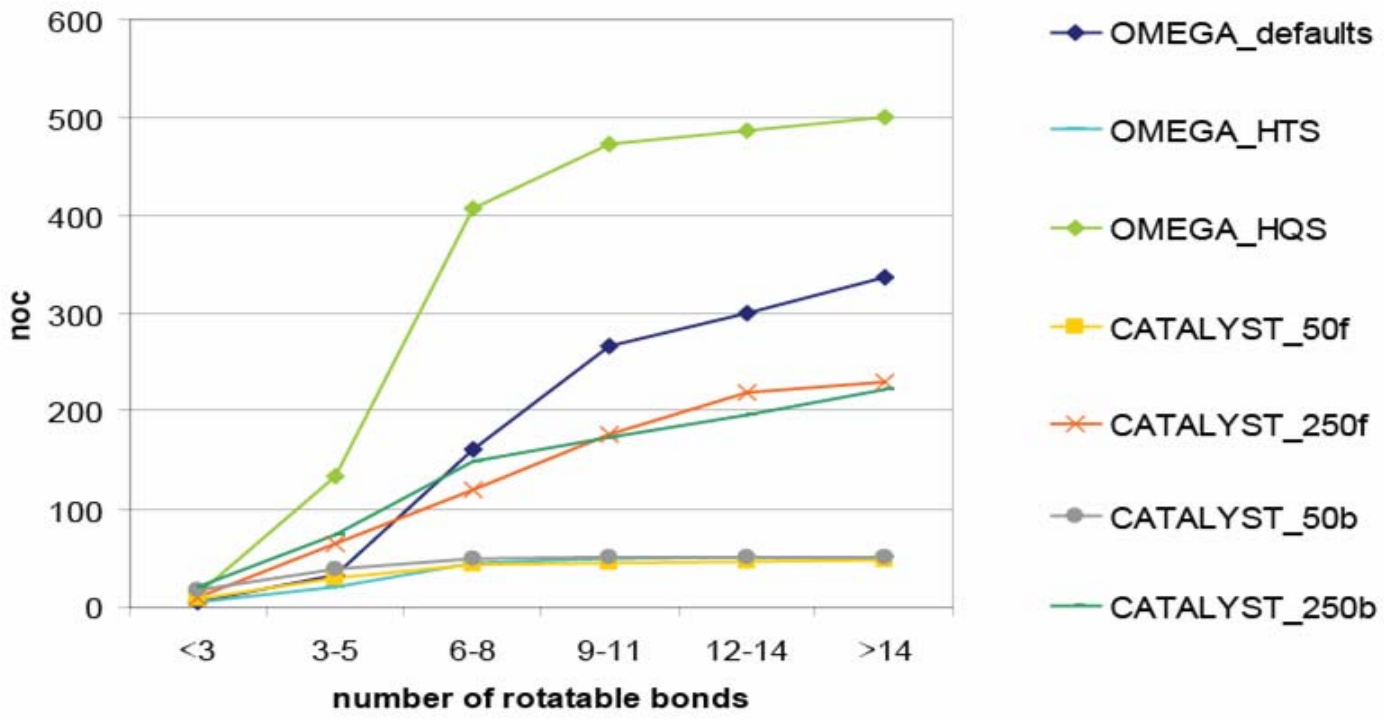
RMSD achieved with different settings:

- 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

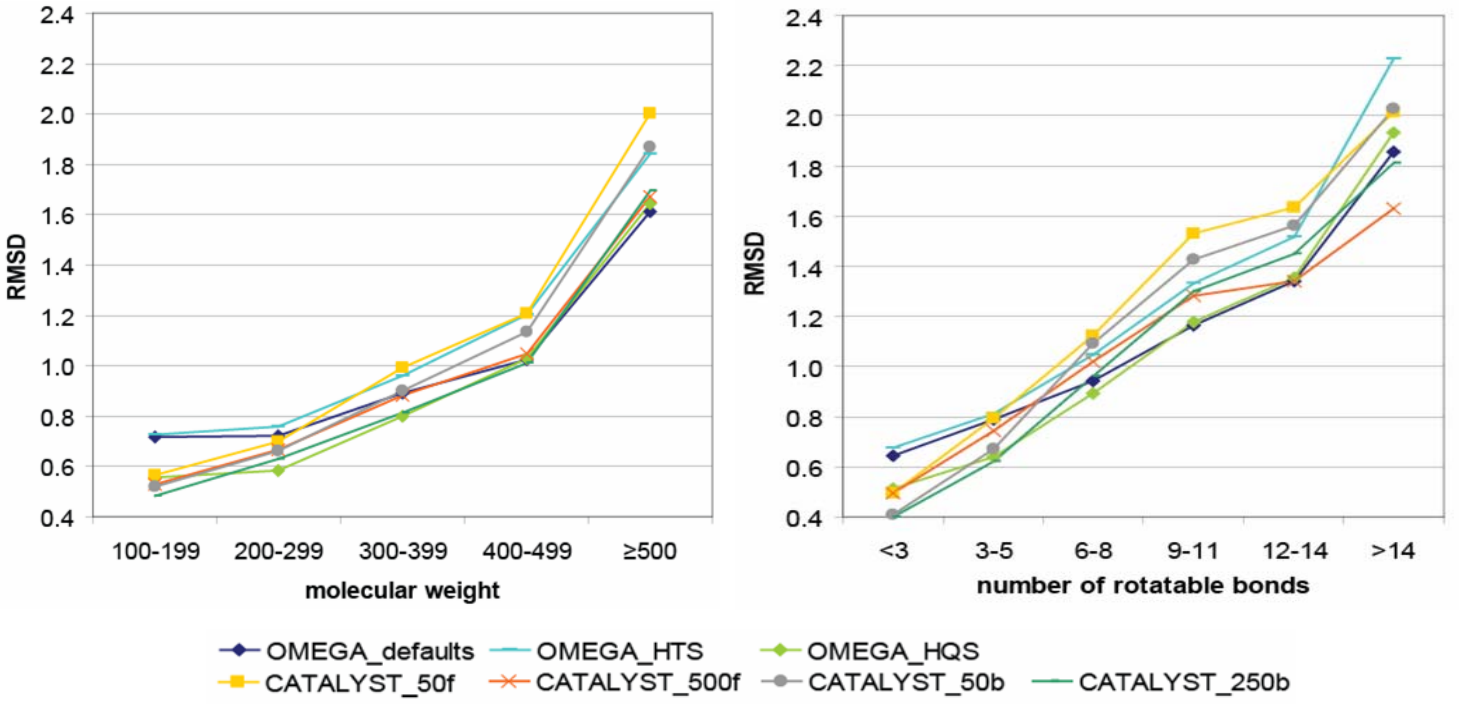
Results

Average NOC as a function of molecular flexibility



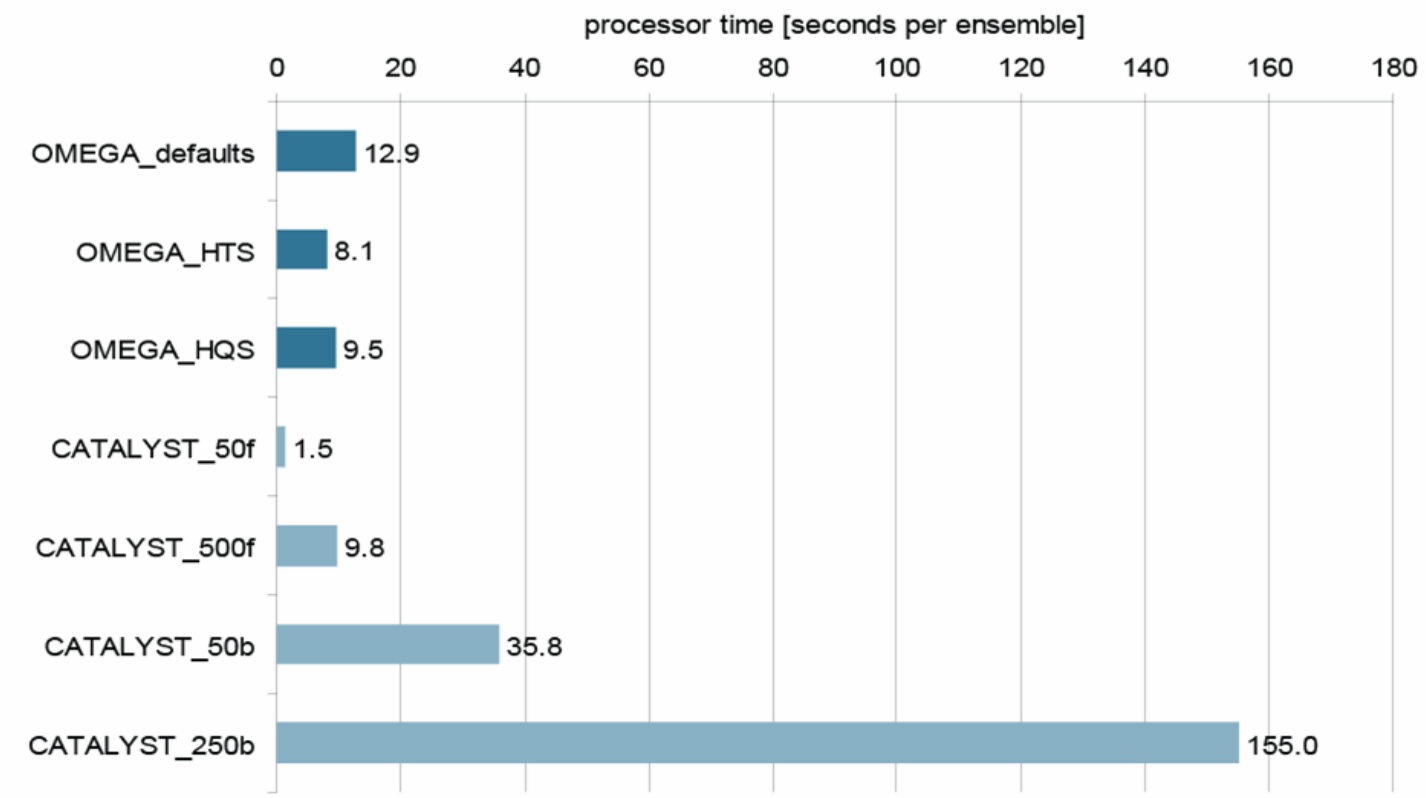
the number of generated conformers increases with flexibility and size of the compounds

Results
RMSD as a function of conformational space



the accuracy of conformational models is highly dependent on the size of conformational space

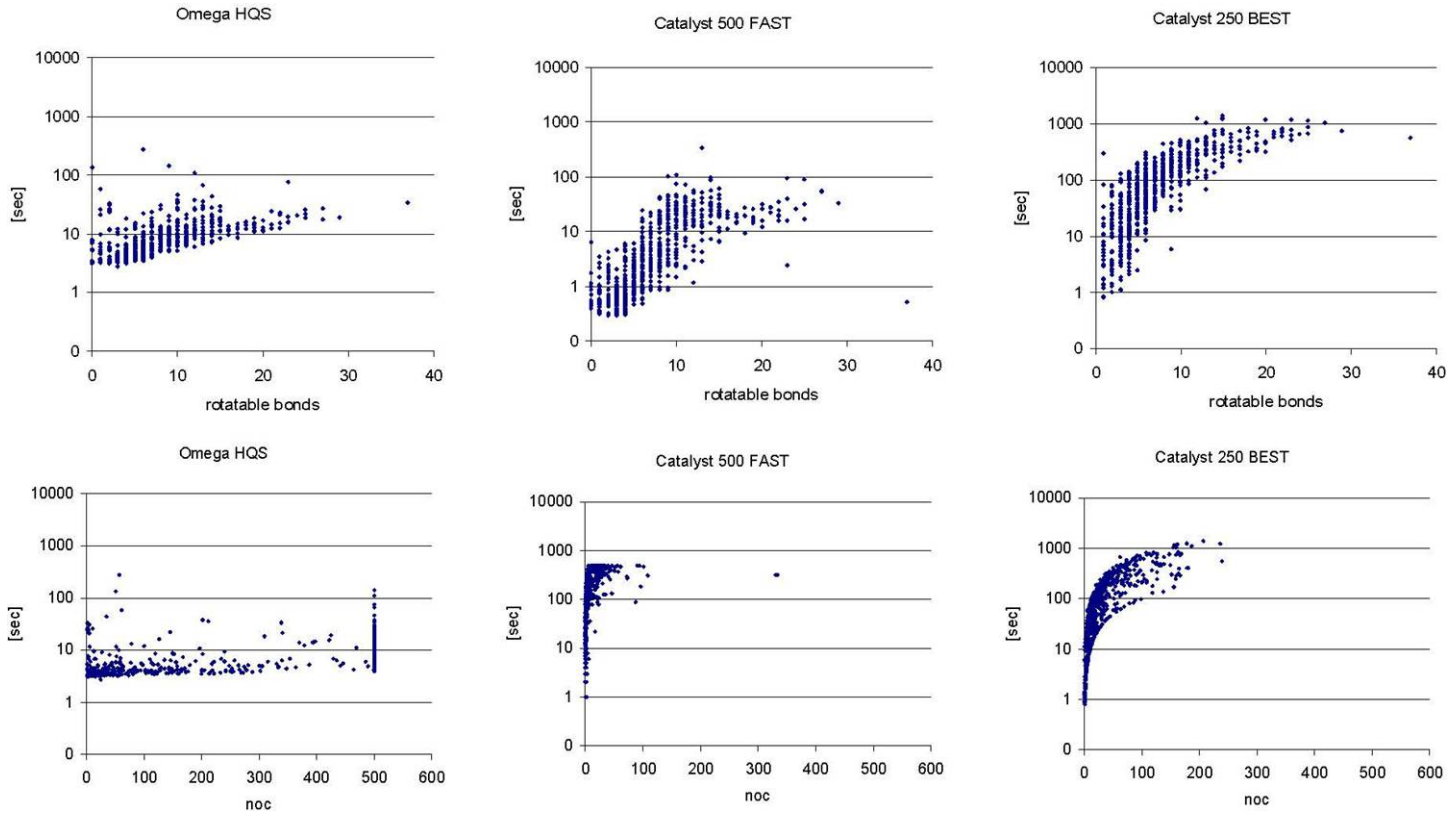
Results
Computational cost



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

Results

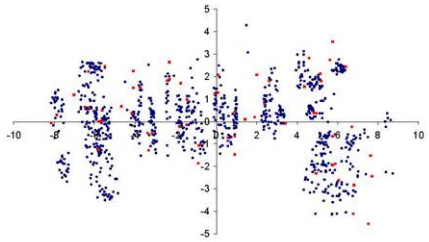
Computing time as a function of flexibility and ensemble size

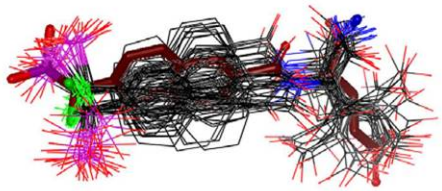


Catalyst BEST shows significant correlation between the size of conformational space and calculation time

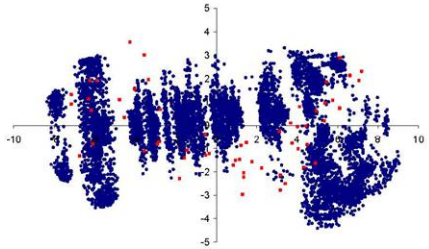
Results
Conformational space sub sampling

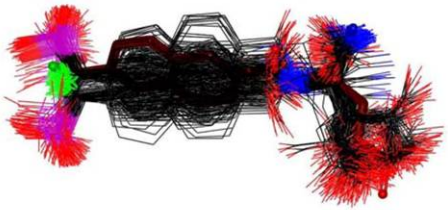
OMEGA HTS



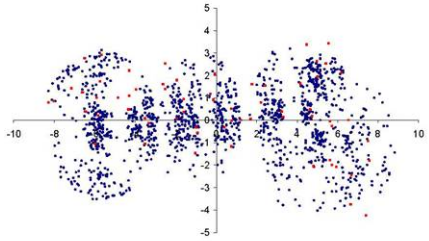


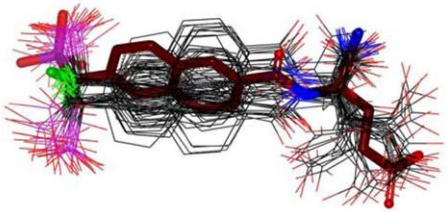
OMEGA HQS



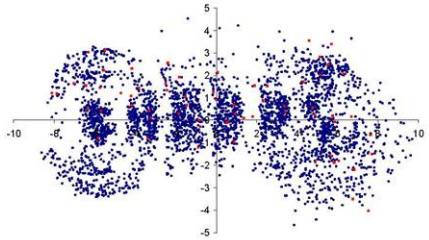


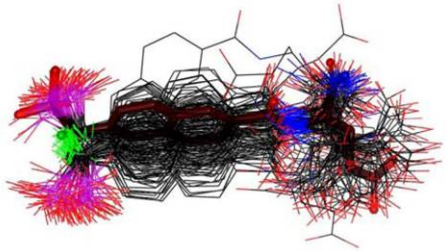
CATALYST 50F



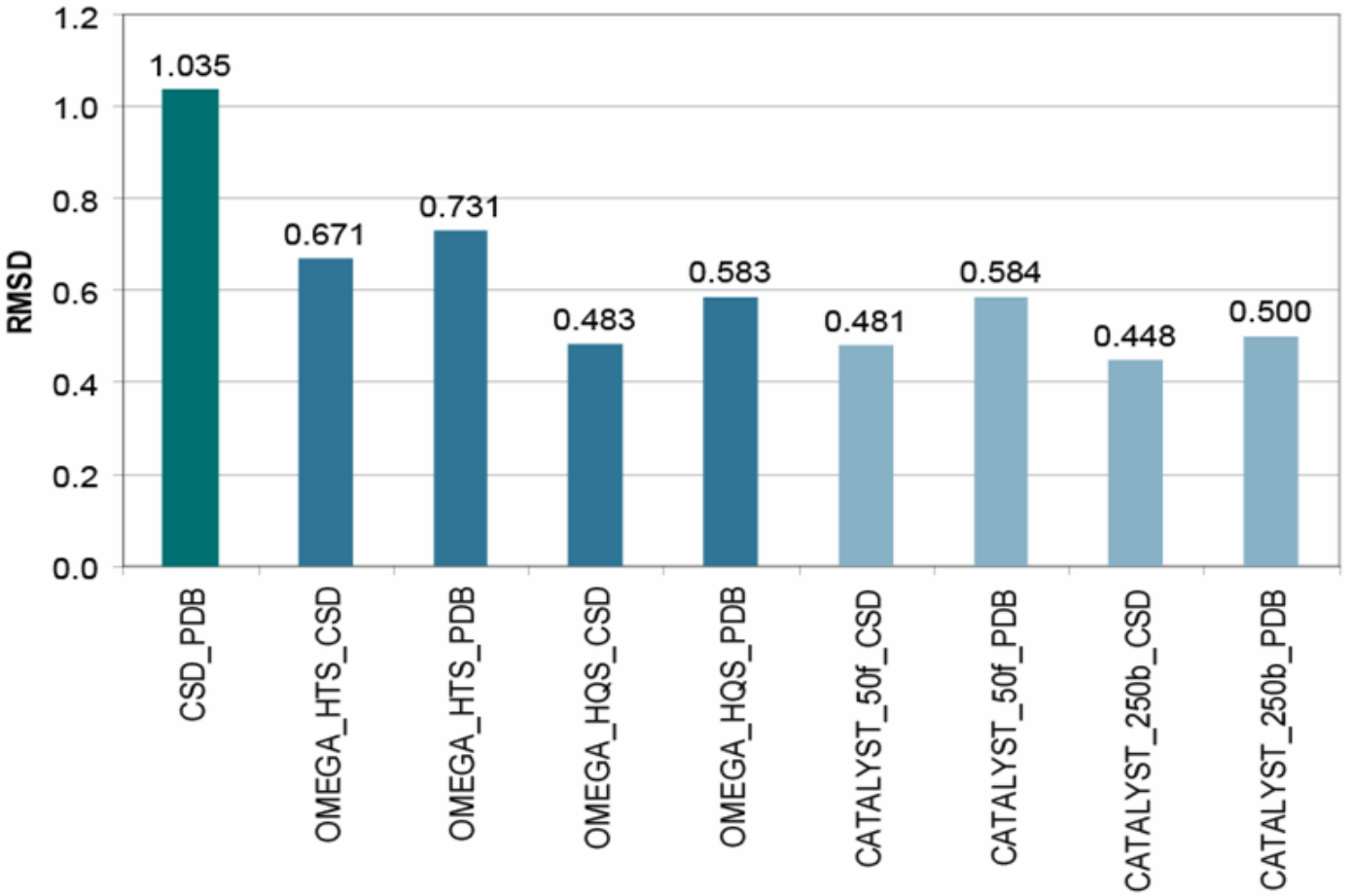


CATALYST 250B





Results
CSD vs. PDB conformations of 29 compounds



the average CSD RMSD values are 8% to 17% lower than the respective PDB conformation

A User-Guide for Best Performance...

Best performing settings:

	HTS	HQS
application scenario	database screening	flexible compounds cyclic scaffolds shape fitting alignments
Omega	maxconfs_50, bmmff94s_trunc rms_0.8	**maxconfs_500** **bmmff94s_trunc** **rms_0.4**
Catalyst	**50 FAST**	250 BEST

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

References...

Kirchmair J, Laggner C, Wolber G, Langer T

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J. Chem. Inf. Model. **2006**, *accepted*

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Gerhard Wolber, Ali Dornhofer, Fabian Bendix, Martin Biely, and Robert Kosara

Thank You for Your Attention!

- Introduction
- Conf. Model Generators
- Work Flow
- Results
- Generator User Guide
- Conclusions