

Turning 3D-QSAR weakness into strength with

Open3DALIGN & Open3DQ SAR

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Validation #1

- Scramble the original alignment
- Apply each of the three **Open3DALIGN** algorithms
- Compute RMSD from the original

Open3DALIGN

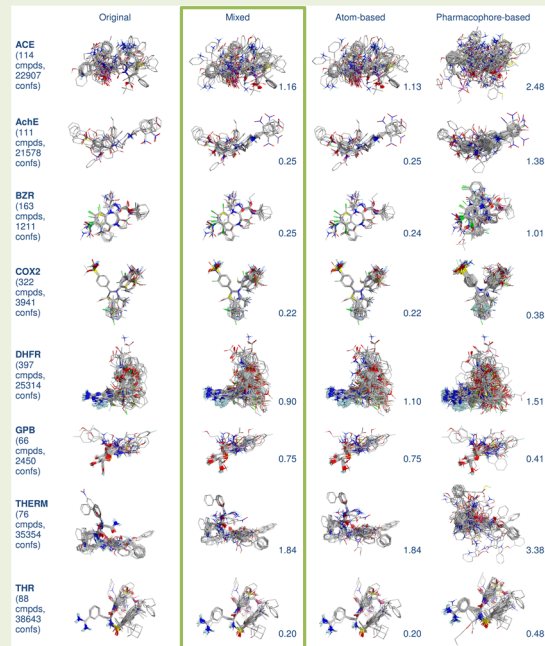
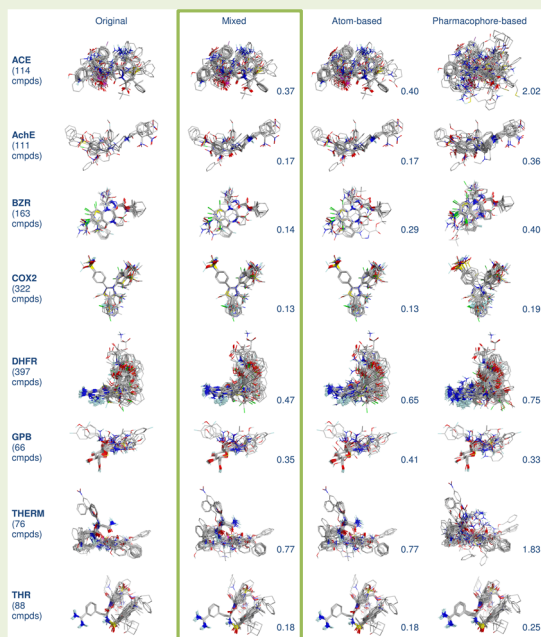
Open-source conformer generation and alignment

<http://open3dalign.org>

- QMD conformational searches use **TINKER** as the MMFF94/MMFF94s, GBSA-enabled molecular mechanics engine
- Single and multi-conformation superimpositions on one or more templates
- Atom-based (built-in, LAMDA-like algorithm), pharmacophore-based (through Pharo) and mixed alignments
- Validated on eight datasets (Sutherland et al., *J. Med. Chem.* 2004)
- Effective
- Fast (multi-threaded)
- Unsupervised
- Scriptable
- Open-source
- Same interface and file formats as **Open3DQ SAR** and **Open3DGRID**
- Highly suited for automated cheminformatics workflows

Validation #2

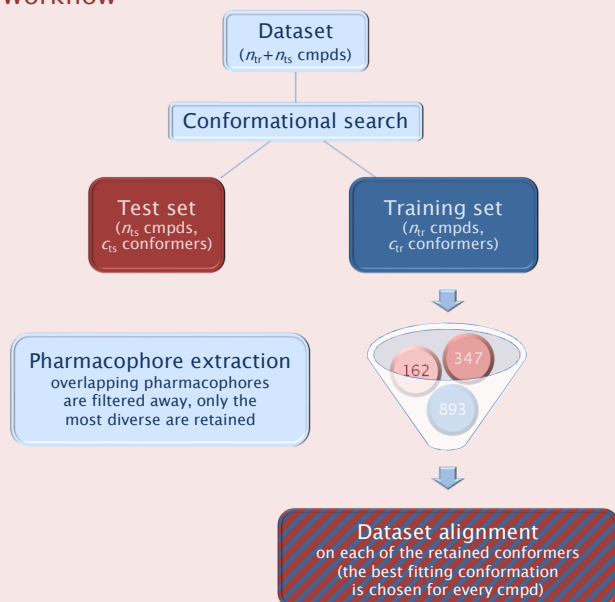
- Run a 5–ns QMD search on each compound
- Pick the conformer which best matches the template with each **Open3DALIGN** method
- Compute RMSD from the original



The challenge

- Find a putative binding mode for each dataset based only on the conformational preferences of the ligands, without using structural information from the target
- Compare these alignments and their 3D-QSAR performance with the original literature, in which datasets were flexibly aligned on crystallographic template(s)

Workflow



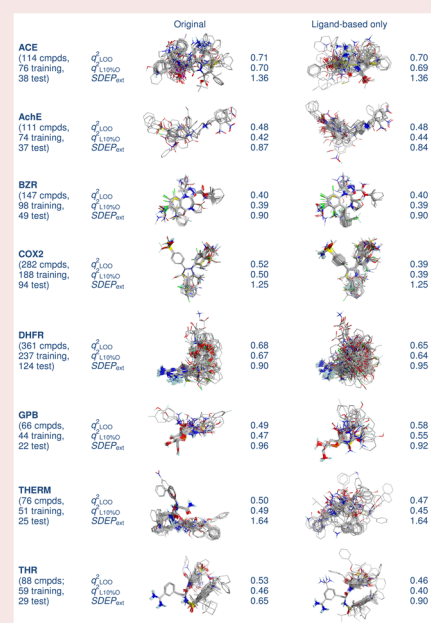
Open3DQ SAR

Open-source MIF computation and chemometric analysis

<http://open3dqsar.org>

- All conformers of training set compounds lying in a 3-log unit pIC₅₀ range from the most active one were considered as possible templates
- Pharmacophores were extracted with Pharo, then the ones overlapping with or being subsets of other pharmacophores were discarded
- Each of the conformers corresponding to the retained pharmacophores was used as a possible template to generate an alignment with the combined atom/pharmacophore-based algorithm
- A 3D-QSAR model was built on each alignment
- 3D-QSAR models were ranked according to a consensus score based on the quality of the alignment, on q^2_{LOO} and on $SDEP_{ext}$
- Best-ranked models have a predictive power (both internal and external) comparable to the original alignment
- For the most flexible datasets the alignment is quite different from the original one

Alignments and 3D-QSAR models



Acknowledgments

Open3DALIGN and Open3DQ SAR depend on

