Ligand based virtual screening using Screen3D

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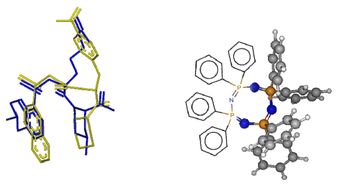
ChemAxon
Solutions for Cheminformatics

ChemAxon in 3D

3D Structure generation: Marvin Sketch, Marvin Space

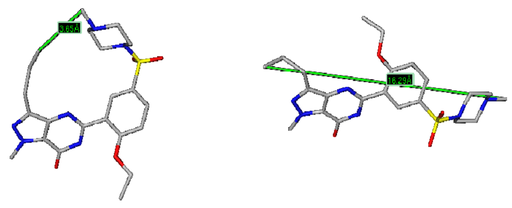
3D Alignment: Marvin Sketch, pseudo-docking in Marvin Space

- Flexible and rigid shape alignment
- Extended atom types/Pharmacophore types
- More than 2 molecules in a single run (2~6)

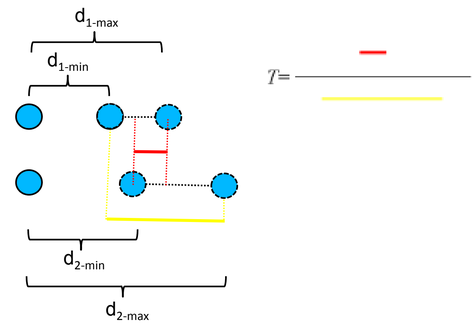


3D Similarity Screening: Screen3D

Minimal, maximal distance



Distance range



Flexible alignment

Quaternion hybrid method

Stepwise optimisation of dihedrals by a proprietary MDS-CG method

(Farkas, Ö., Schlegel, H.B.. J. Mol. Structure: THEOCHEM 2003, 666, 31-39.)

In every iteration, the translation and rotation step is delegated to rigid quaternion fit:

- minimises RMSD on selected atom pairs (best alignment)
- incorporates analytic solution of the equation

Pros:

- very fast
- robust: finds the best alignment

Cons:

- only quadratic constraints can be handled by this method
- two molecules per alignment

These are prerequisites to solve the atom/atom mapping

- exhaustive enumeration of all permutations of atom pairs
- excluding inappropriate ones in the early stage of search
- „cheap" geometrical constarint is aware of conformational flexibility

Atom – atom matching & alignment

Preprocessing

- Preprocessing has to be done once in the life of a molecule
- Preprocessing includes generation of colors (extended atom types / pharmacophore types)
- Ring centers are determined (aromatic, aliphatic)
- Minimal, maximal internal distance ranges are calculated (~ 10 s/mol)
- Atomic histograms for selected atoms are generated

Backtracking with constraints

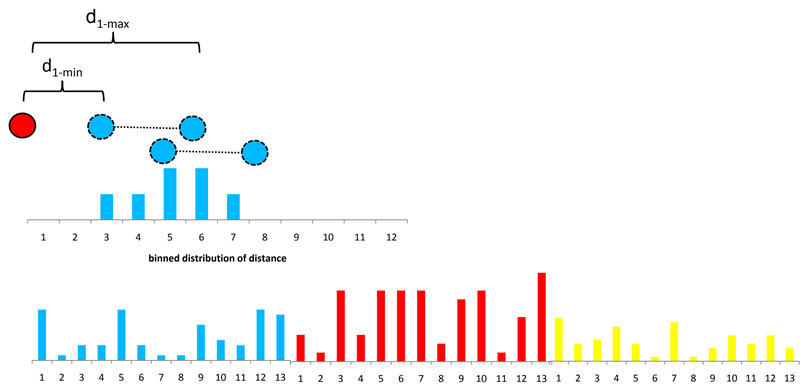
- It is investigated if colors of atoms are the same for the pairs
- Distance ranges are checked for any pairs of mapped atoms
- Triangle inequality for any triplet of maps is checked
- Quaternion Flexible Hybrid Alignment on map is executed

Output Result

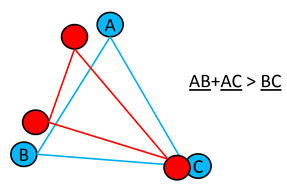
- Atom/atom mapping
- Molecules aligned
- Score: Tanimoto like coefficient is sum of atomic contributions

Guaranteed: No good solution of the conformational space is lost!

Atomic histogram based on Tanimoto similarity

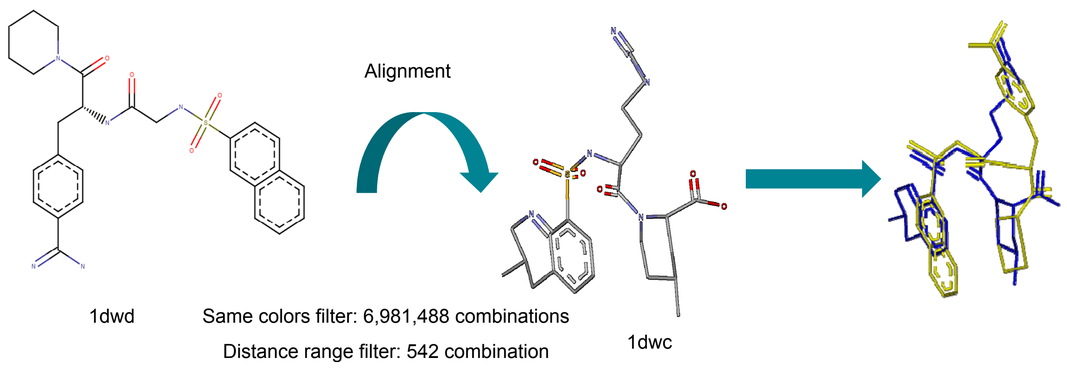


Triangle inequality



Flexible alignment of Thrombin inhibitors

Pseudo-docking in Marvin Space



Testing Screen3D on DUD datasets

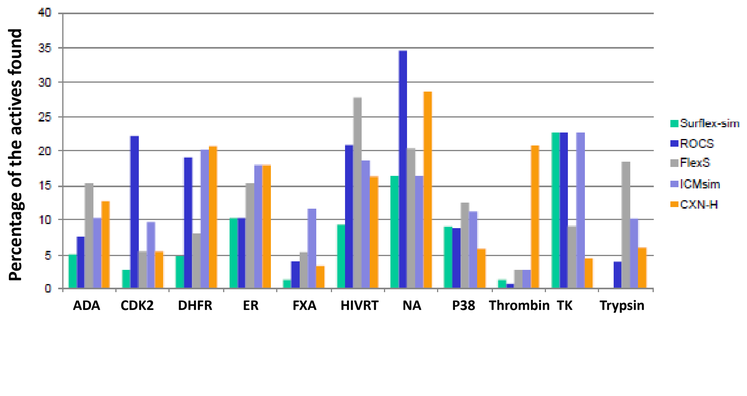
ADA	Adenosine deaminase	39/927
CDK2	Cyclin dependent kinase 2	72/2074
DHFR	Dihydrofolate reductase	410/8367
ER	Estrogen receptor antagonist	39/1448
FXA	Factor Xa	146/5745
HIVRT	HIV reverse transcriptase	43/1519
NA	Neuraminidase	49/1874
P38	P38 mitogen activated protein kinase	454/9141
THR	Thrombin	72/2456
TK	Thymidine kinase	22/891
TRY	Trypsin	49/1664

DOCK
Surflex-Dock
FRED
FlexX
ICM

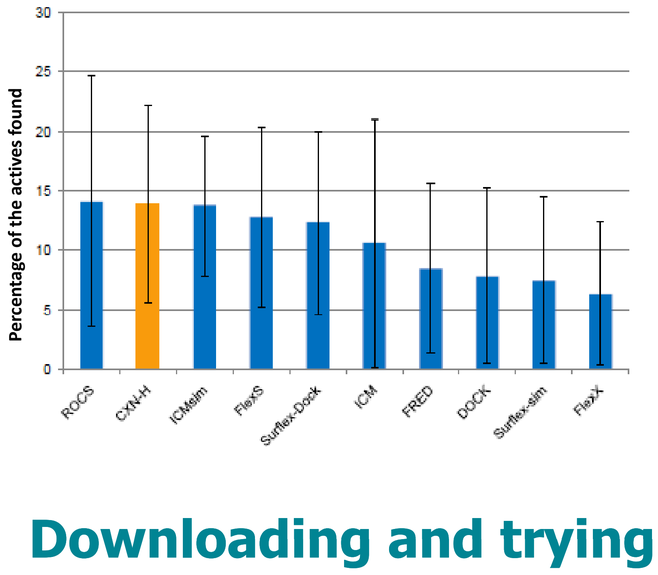
ROCS
Surflex-sim
FlexS
ICMsim

Giganti et al. J. Chem. Inf. Model. 2010, 50, 992

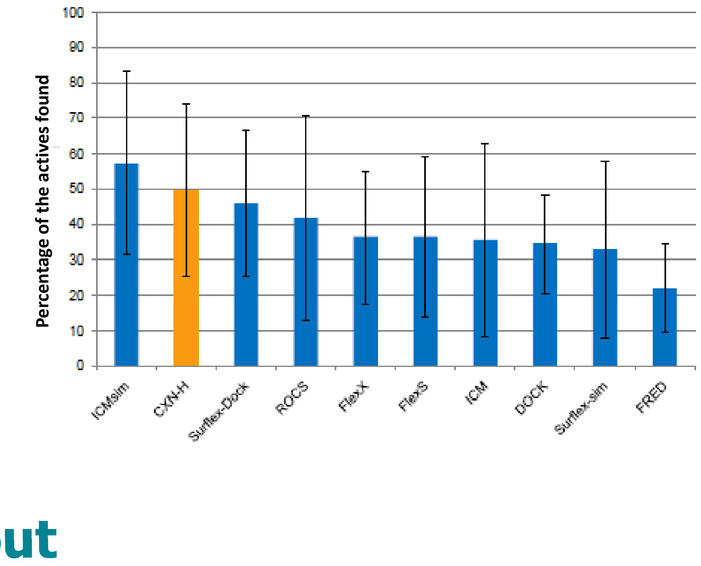
1% Enrichment



Average of 1% Enrichment factors



Average of 1% Enrichment factors



Speed

average time per compound (s)		
CXN-H	0.07	Intel Q6600 2.4 GHz
ROCS	0.5	Intel Xeon 2.4 GHz
FRED	1.0	
ICMsim	2.4	
Surflex-sim	6.7	
FlexS	6.9	
Surflex-dock	14.6	
FLEXX	15.6	
ICM	17.7	

Downloading and trying out

Functionality included within Screen product package:

- Screen 2D: similarity searches and various fingerprints
- Screen 3D: fast 3D similarity search

ChemAxon