Comparison of Alignment Methods: FieldAlign and ROCS

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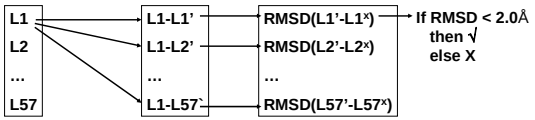
Introduction

The accuracy of three dimensional molecular alignments is dependent on several factors, such as the alignment method, the method of conformer generation and the choice of template molecule. Recently a comparison has been reported between ROCS and FlexS for molecular alignment [1]. Here we extend this study to include the first comparative study involving the FieldAlign [2] program which is compared with ROCS [3] in both rigid and flexible modes. We used both XedeX [2] and OMEGA [3] for conformer generation.

Methodology

Alignment Procedure: For each protein family, each ligand was taken in turn as template and all other ligands aligned to it. A correct alignment was one with RMSD < 2.0Å of the X-ray-based alignment. An accuracy rate was calculated for each ligand as the number of correct alignments.



Accuracy rate = percentage of alignments within 2Å

Data set	# cmpds	Av Rot Bonds
CDK2	57	4.1
HIV	28	16.0
ESR1	13	3.9
P38	13	3.5
Thermolysin	12	8.3
Rhinovirus	8	9.4
Elastase	7	8.4
Trypsin	7	2.9

Data Sets

The study was carried out on 158 X-ray complexes of nine protein targets [1].

Up to 500 conformers were generated from the CONCORD conformation using:

XedeX: average number of conformers 104 (SD 117)

OMEGA (v2.1): average number of conformers 132 (SD 180)

Progammes and Protocols

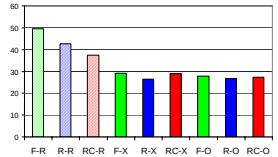
ROCS v2.0 was run in two modes
Shape only: options: *-rankby tanimoto*
Shape and Chemical Forcefield:
options: *-chemff ImplicitMillsDean –optchem -rankby combo*
FieldAlign v1.0.0 was run in default mode

Conformational flexibility was handled as follows:

Rigid: X-ray conformation of template and matching ligand
OMEGA: X-ray conformation of template; OMEGA conformations of matching ligands
XedeX: X-ray conformation of template; XedeX conformations of matching ligands

Alignment Method	Label
FieldAlign-Rigid	F-R
FieldAlign-XedeX	F-X
FieldAlign-Omega	F-O
ROCS-Shape-Rigid	R-R
ROCS-Shape-XedeX	R-X
ROCS-Shape-OMEGA	R-O
ROCS-Chem-Rigid	RC-R
ROCS-Chem-XedeX	RC-X
ROCS-Chem-OMEGA	RC-O

Results



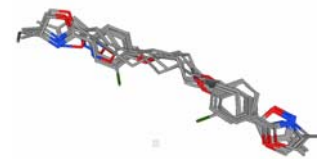
The average accuracy rates over all protein classes is shown with FieldAlign in green, ROCS-Shape in blue and ROCS-Chem in red.

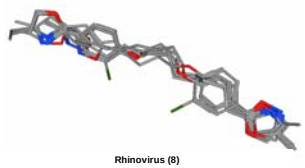
Rigid Alignments

Although the rigid alignments indicate a relative performance of FieldAlign > ROCS Shape > ROCS Chem:

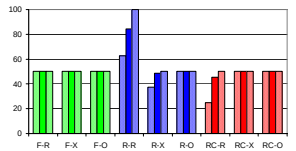
- ❖ the difference is significant for 3 targets only (Rhinovirus, ESR1 and Thermolysin);
- ❖ the rigid searches are unrealistic since they are based on X-ray bound conformations which are usually unknown.

Rhinovirus



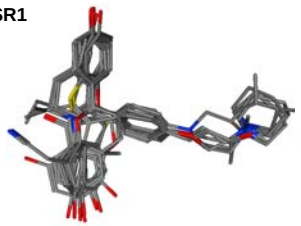


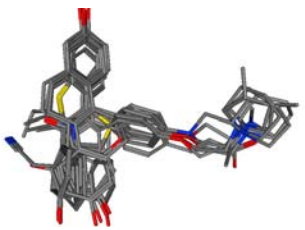
Rhinovirus (8)



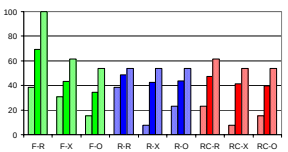
X-ray alignment (left) and ROCS-Shape-Rigid alignment of the 8 Rhinovirus ligands against *2rs3 as* template. All alignments have RMSD < 2.0 Å. The plot shows the worst (shaded), average (solid) and best (shaded) result for all methods.

ESR1





ESR1 (13)

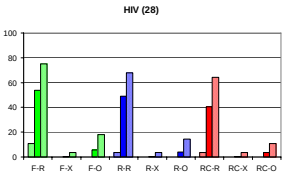


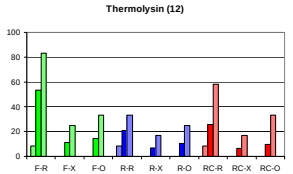
X-ray alignment (left) vs FieldAlign Rigid alignment (right) of the 13 ESR1 ligands. All alignments have RMSD < 2.0 Å. The plot shows the worst (shaded), average (solid) and best (shaded) result for all methods.

Flexible Alignments

On average, the more realistic flexible alignments for both FieldAlign and ROCS are much poorer. This is especially significant for the ligands with a higher average number of rotatable bonds (HIV and Thermolysin). The worst (shaded), average (solid) and best (shaded) results are shown for HIV.

OMEGA vs XedeX: FieldAlign performs slightly better for the XedeX-generated conformers than the OMEGA-generated conformers: ROCS is less sensitive to the conformational analysis method.



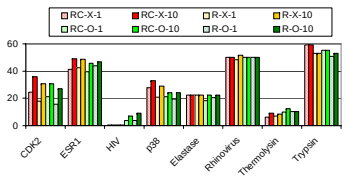


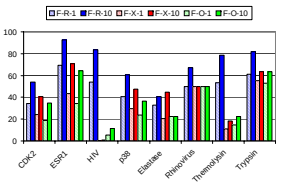
Importance of Template

In all data sets, except for Rhinovirus, there is a significant dependence of the overlay accuracy results on the choice of the template and aligned molecules (89% of the cases). The worst (shaded), average (solid) and best (shaded) results are shown for Thermolysin.

Best Alignment in Top Ten

Looking for the best alignment in the top 10 significantly improves the accuracy rate.





ROCS-Shape vs ROCS-Chem

There is little difference between the Shape-only and Shape and Chemical Forcefield combined versions of ROCS except for the rigid searches on the Rhinovirus and HIV datasets where Shape-only performs better (results not shown).

Conclusions

- Both FieldAlign and ROCS perform much better for rigid alignments than for flexible alignments.
- The quality of the alignment depends strongly on the choice of template molecule.
- The choice of conformer generation method is less important than that of the template molecule
- We find no significant difference between FieldAlign and ROCS for the flexible alignment of molecules.

References

[1]. Chen, Q.; Higgs, R. E.; Vieth, M.. *J. Chem. Inf. Model*. 2006, *46*, 1996-2002.

[2]. Cresset Biomolecular Discovery Ltd. Letchworth, UK, 2006

[3]. Openeye Scientific Software: Santa Fe, NM, 2005.

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