COSMOsim3D and COSMOsar3D Alignment and 3D-QSAR based on COSMO surfaces

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COSMOsim3D
Similarity assessment based on the polarity of a solvent accessible surface.

COSMOsar3D
Generates fields based on local σ-profiles for molecular field analysis.

Test Case: Sutherland Data Sets Alignment and 3D-QSAR
COSMOsim3D utilizes LSPs instead of chemical structure or pharmcophores to assess a molecule's similarity to a template molecule. This enables scaffold hopping and allows users to deal with datasets of different chemotypes.

Arrays of LSPs provide all information required for quantifying ligand-receptor interactions, including desolvation. In COSMOsar3D, this leads to:
• increased predictive accuracy
• outstanding robustness with regard to grid step size, grid positioning and random misalignment.

Test Case: Virtual Screening
Active ligands for 22 diverse biological targets, each with
• 2-3 ligands as alignment templates
• 4-30 known active ligands

Screening compounds:
• "Random": Rogner Screening Set selected from MDL Screening Compounds Directory (850 organic compounds)
• Drugs: active ligands of all 22 biological targets (253 known diverse drugs)

Linear Relationship of logK and LSPs
Consider a protein receptor R and its aqueous embedding as a locally slightly flexible matrix with locally varying σ-potential. The free energy of a ligand l in R, assuming that the receptor generates a position-dependent σ-potential, is

\[ \nu_l = c(R) + \sum_{i=1}^{3} a_i \sigma_i (l) \]

Similarly, the free energy of a solute X in a homogeneous solvent S is

\[ \nu_l = \sum_{i=1}^{3} a_i \sigma_i (l) + kT \ln \rho \]

Interpolating on a grid the position-dependent σ-potential of ligand l in receptor R gives:

\[ \nu_l = c(R) + \sum_{i=1}^{3} a_i \sigma_i (l) \]

The same holds for mu in water, even with a position-independent σ-potential \( \nu_m \).

→ Linear relationship to pK \( l \)

COSMOsar3D

• Pairwise Alignment and Similarity Assessment: LSPs instead of chemical structure or pharmcophores enable scaffold hopping and dealing with datasets of different chemotypes.
• Multi-template alignment: The superposition of multiple aligned template molecules can be used as a virtual template molecule.
• Ligand-Based Virtual Screening: Ranking potential ligand molecules according to their similarity to a single template or a virtual multi-template allows for enrichment of ligand sets with potential cognate drugs.

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