

Surflex-Sim

MOLECULAR ALIGNMENT AND MORPHOLOGICAL SIMILARITY



Surflex-Sim¹ generates molecular alignments and hypotheses of bioactive ligand conformations for 3D ligand-based design and virtual screening. Surflex-Sim uses a Morphological Similarity² algorithm based on the molecules' shape, H-bonding, and electrostatic properties.

Selected Features

■ Pairwise Alignments and Morphological Similarity^{2,3}

Surflex-Sim rapidly optimizes the pose of a query to maximize three-dimensional similarity to an object molecule. No input for mapping or guidance is necessary. Molecules judged to be similar tend to bind to the same proteins.

■ Optimal Ensemble Alignment³

Surflex-Sim produces an optimal superposition for a small number of competitive ligands, maximizing pairwise similarities while minimizing total volume.

■ Drug and Target Similarities³

It is possible to rationalize off-target effects of drugs and to predict them. Drug pairs sharing a target have significantly higher similarity than drug pairs sharing no target, and target pairs with no overlap in annotated drug specificity share lower similarity than pairs with increasing overlap.

■ Ligand-Based Virtual Screening³

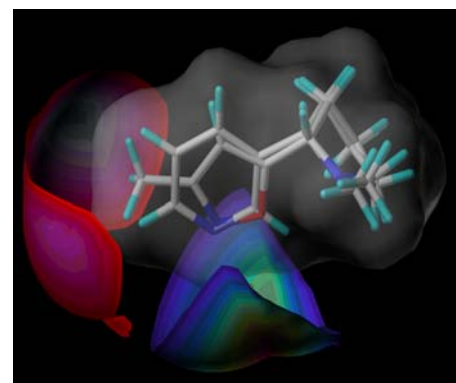
Superpositioning multiple molecules forms a hypothesis as to their preferred binding mode to a target. Surflex-Sim functions as a similarity program to rank a set of input molecules according to their degree of fit to the hypothesis. Models generated with Surflex-Sim have the ability to identify cognate drugs from a background of other drug molecules, producing fewer false positives and more true hits.

Molecular Alignment

The majority of drug targets for small molecule therapeutics are proteins whose three-dimensional structure is not known to sufficient resolution to permit structure-based design⁴. Complementary three-dimensional ligand-based design approaches require some hypothesis of bioactive ligand conformation and alignment. Predictions of molecular activity critically depend on this binding site hypothesis and its similarity to known bioactive ligands. Traditional molecular alignment utilizes the superposition of atoms or pharmacophoric features⁵⁻⁷. These methods rely on a good mapping of a large number of occurring bioisosteric features and appropriate coverage of the conformational space in order to align the correct conformations. In the absence of either, they are bound to fail.

Morphological Similarity²

Surflex-Sim rapidly and automatically optimizes the alignment of molecules maximizing their three-dimensional similarity. Recognition of small molecules by proteins depends on the three-dimensional molecular surface complementarities. Surflex-Sim uses a surface-based morphological similarity function coupled with quantitative pressure to minimize overall molecular volume of the aligned structures. The method generates hypotheses of bioactive conformations and alignments of sets of small molecules, which can be used for three-dimensional ligand-based design and virtual screening. This approach has been demonstrated to outperform previously dominant techniques based on two-dimensional chemical structure, which in turn had outperformed most three-dimensional techniques in comparisons of correlation to biological activity.



Optimal superposition of nicotine and a competitive oxazole derivative by morphological similarity. The translucent grey surface represents the overall molecular volume of the aligned molecules. Differences in measurements made of nicotine and the oxazole derivative from the observation points in space are shown. The red surface indicates differences in the hydrophobic surfaces being observed, the blue and green surface indicates the high degree of electrostatic potential overlap between the two molecules. The major difference arises from the protruding methyl on the oxazole, not the difference in 2D substructure of the oxazole and pyridine.

Scaffold Hopping

Classical medicinal chemistry has been very successful to develop congeneric molecular series to optimize the biological activity profile of lead compounds. These methods are of limited use to find alternative chemical scaffolds without the same toxicity and potential intellectual property issues as the given lead.

The morphological similarity approach of Surflex-Sim effectively facilitates scaffold hopping, thus allowing the user to address these limitations and to identify novel lead series with truly distinct properties while preserving those structural properties that are essential for biological activity.

Validation

Surflex-Sim has been extensively validated on 59 different datasets across a wide variety of targets^{3,8}.

Complementary Software

- **Concord[®]** - for generating accurate 3D conformations.
- **QSAR with CoMFA[®]** - for building predictive structure-activity and structure-property models.
- **MOLCAD[™]** - for visualizing molecular surfaces and molecular properties.
- **Surflex-Dock** - for receptor-based virtual screening and molecular docking
- **UNITY[®]** - for locating compounds in databases that match a pharmacophore hypothesis.

The Algorithm¹

Surflex-Sim utilizes a morphological similarity approach to generate putative alignments of molecules. Morphological similarity is defined as a Gaussian function of the differences in the molecular surface distances of two molecules at weighted observation points on a uniform grid. The computed surface distances include both distances to the nearest atomic surface and distances to donor and acceptor surfaces. This function is dependent on the relative alignment of the molecules, and consequently their alignment and conformation must be optimized.

The conformational optimization problem is solved by fragmentation, conformational search, alignment, and scoring, followed by incremental reconstruction from high-scoring aligned fragments.

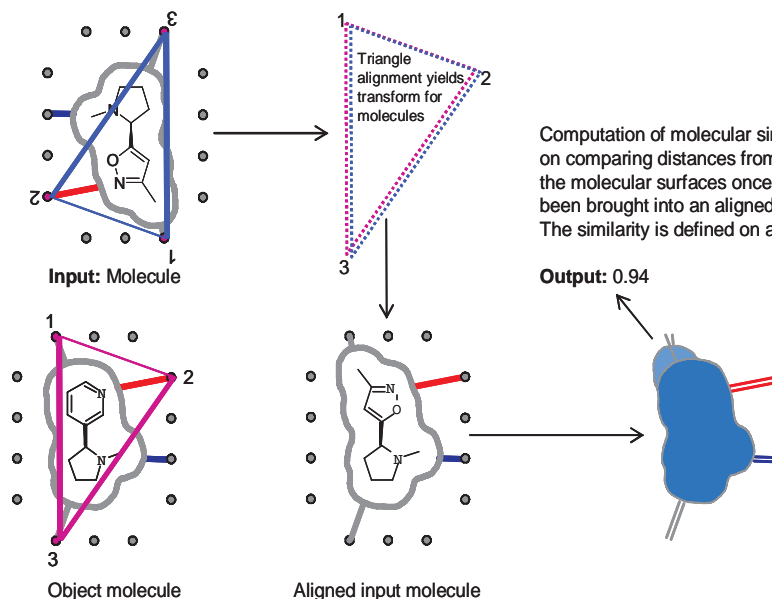
The alignment problem is addressed by exploiting the fact that two unaligned molecules or molecular fragments which have some degree of similarity will have some corresponding set of observers that are seeing the same things. Optimization of the similarity of two unaligned molecules or molecular fragments is performed by finding similar sets of observers of each molecule that form triangles of the same size.

Performance

On average 17s per ligand (~3s per rotatable bond).

Hardware and Software Requirements

Surflex-Sim 2.0 is available through the SYBYL interface and as such runs on IRIX[®] (SGI[®]) or Linux[®] (x86). Command-line versions are available for IRIX[®] (SGI[®]), Linux[®] (x86) and Windows[®].



Computation of molecular similarity is done based on comparing distances from observer points to the molecular surfaces once the molecules have been brought into an aligned coordinate frame. The similarity is defined on a scale of 0 to 1.

Molecular Alignment and Similarity (see the text for details).

Acknowledgements

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