

TOPOMER SEARCH

EXCEPTIONALLY FAST LIGAND-BASED LEAD HOPPING



Topomer Search is an exceptionally fast 3D ligand-based virtual screening tool that has been demonstrated to be effective for both lead hopping and scaffold hopping. Topomer Search can search millions of structures overnight on a single processor, allowing you to screen very large collections of compounds and avoid the risk of missing important leads because of subsetting. Screen for whole molecules, side chains, or scaffolds using conformationally independent topomer similarity.

KEY FEATURES

EFFECTIVE

- Effective for Virtual Screening as demonstrated by numerous publications
- Effective for Lead Hopping and Scaffold Hopping
- Use Topomer Search in concert with Topomer CoMFA® to identify the substituents and R-groups that are predicted to optimize the activity of your compounds

FAST

- Screen millions of structures overnight
- Screen large collections without the need for subsetting - avoid the risk of missing leads
- Use all known leads as queries because multiple query searches are fast and efficient

EASY

- Virtually independent of query and database conformations
- No feature mapping input or guidance is required
- Requires no template definition
- No protein preparation is needed

Lead hopping and scaffold hopping - generating novel IP

Traditional virtual screening methodologies have a number of drawbacks. Receptor-based virtual screening requires a receptor structure and a defined binding site, but many important targets don't have a receptor structure available. Pharmacophore-based virtual screening requires a validated pharmacophore model to have been developed, which can be time-consuming. Fingerprint-based screening finds structures that are chemically as well as biologically similar, and hence does not tend to generate novel IP. Additionally, shape-based virtual screening usually relies on prior knowledge of the active structures' conformation. Topomer Search is simple to use and does not require significant preparation or model building.

Speed is also an issue: virtual screening methods like docking are relatively slow, and often can only be applied to a subset of the compounds available for screening, hence risking missing important hits and leads.

Topomer Search is very fast, and capable of screening millions of compounds overnight.

Virtual screening based on topomer similarity to known ligands can be very effective for all types of projects where one or more active compounds is available. Topomer Search ligand-based screening can be used as an adjunct to docking for receptor-based projects and as the primary virtual screening tool for lead-hopping when receptor information is not available. Topomer Search is exceptionally fast and is capable of screening millions of compounds overnight, so you avoid the need to select a subset of your compounds and thus the risk of missing important hits and leads. Unlike other methods, multiple queries (from existing known leads) can be added to improve the quality of your search with relatively little performance impact, and no prior knowledge of the bioactive conformation of your known leads

is needed. Topomer Search can also be used to search using R-groups for lead optimization or scaffolds for more focused scaffold hopping. Topomer Search is effective for whole molecule searching, for lead hopping, or for R-group or scaffold searching.

Conformer selection and alignment with topomer technology is entirely objective and automated, so Topomer CoMFA QSAR models can be used for virtual screening by Topomer Search; allowing you to use your compound collection as a source of structural fragments and to identify R-groups or substituents that would be predicted to optimize the biological properties of your series. This is something you just can't do with traditional 3D QSAR models based on manual alignments.

Prospective and Retrospective Validation¹

In a truly prospective study, 13 compounds active against different targets were selected from the weekly World Drug Alert service, and used as queries for a Topomeric Search of 80,000 LeadQuest™ compounds. For 11 out of 13 of the targets (85%), Topomerically similar confirmed actives were true 'Lead Hops'; ie they were significantly dissimilar using 2D fingerprints (average Tanimoto distance between query-active pairs was 0.36). 9 of the targets had no structural information available for the receptor and as such would not have been accessible to docking.

In a retrospective study, all World Drug Index structures from the 20 largest biological classes were used as query structures to search 8832 structures with reported biological mechanism, using both Topomer Search and 2D fingerprint similarity. Topomer Search yielded an average hit rate of 62% (44x better than random) compared with 48% for 2D fingerprint similarity at the usual 0.85 Tanimoto threshold, suggesting that Topomers are 34% more effective than 2D fingerprints on average.

HARDWARE AND SOFTWARE REQUIREMENTS

Topomer Search is available as a standalone application and through the SYBYL graphical interface, version 7.3.4 or above. It runs on IRIX® (SGI®) and Linux® (x86).

Target	Query (IC ₅₀ , i M)	Topomer Search Hit (IC ₅₀ , i M)
Adenosine A1	 (0.0066)	 (20.2)
PDE4	 (0.025)	 (2.9)
SERT	 (0.0038)	 (0.12)

Selected examples of leadhopping from query structures to LeadQuest hits using Topomer Search

REFERENCES & FURTHER READING

1. Cramer, R.D., Jilek, R.J., Guessregen, S., Clark, S.J., Wendt, B., Clark, R.D. (2004). 'Lead-Hopping'. Validation of topomer similarity as a superior predictor of similar biological activities. *J. Med. Chem.*, 47, 6777-6791.
2. Cramer, R.D. (2006). Leadhopping - and beyond. *Expert Opin. Drug Discov*, 1, 311-321.
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4. Jilek, R.J., Cramer, R.D., Topomers: A Validated protocol for their self-consistent generation. *J. Chem. Inf. Comp. Sci.* (2004) 44:1221-1227.
5. Cramer, R.D., Jilek, R.J., Andrews, K.M. (2002). dbtop: Topomer Similarity Searching of Conventional Databases. *J. Mol. Graph. Modeling*, 20, 447-462.
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7. Cramer, R.D., Poss, M.A., Hermsmeier, M.A., Caulfield, T.J., Kowala, M.C., Valentine, M.T. (1999). Prospective identification of biologically active structures by topomer shape similarity searching. *J. Med. Chem.* 42, 3919-3933.
8. R.D. CRAMER & R.D. CLARK (2007). Computer-implemented method of generating and characterizing representative three dimensional conformations of reactant molecules. US Patent No. 7,184,893.
9. R.D. Cramer et al. (2003). Method for searching heterogeneous compound databases using topomeric shape descriptors and pharmacophoric features. US Patent Application 2003/0060982 (allowed but has not yet issued).

Complementary Software

Topomer CoMFA®	Surflex-Sim™
Concord®	Surflex-Dock™
	UNITY 3D™