

Pharmacophore Modeling

- Pharmacophore Elucidation
- Query Editor
- Volume Constraints
- Feature Expressions
- Receptor Based Queries
- Fast 3D Database Search
- High Throughput Conformational Search
- Pharmacophore Consensus

MOE™'s pharmacophore modeling methodology is a powerful means to generate and use 3D geometric information to search for novel active compounds, particularly when no receptor geometry is available. Pharmacophore methods use a generalized ligand representation and geometric constraints to bypass the structural or chemical class bias of 2D methods. MOE's pharmacophore applications are powerful, intuitive and easy to use, both for experts and occasional users.

Pharmacophore Elucidation. Generate pharmacophore queries from a collection of input compounds (possibly with activity data) by considering all possible discrete geometries and all possible combinations of feature query expressions. A build-up strategy is used to avoid combinatorial explosion. Enforce limits on feature counts and add custom query expressions. Each pharmacophore query is scored based on known active compound coverage, statistical activity enrichment and atomic overlap of matching conformations. The resulting scores and induced molecular alignments of high-scoring pharmacophore queries are written to a MOE molecular database for further analysis.

Pharmacophore Search. Rapidly search a conformational database for compound conformations that satisfy a pharmacophore query. Search multiple databases, a sub-range of molecules or a database of docked compounds. Output data consists of molecules that satisfy the 3D pharmacophore query (either all conformations or just the conformations that satisfy the query). Partial matches, output of all symmetric matches and specification of essential features are supported.

High Throughput Conformational Analysis. Use MOE's High Throughput Conformational Search methodology to construct conformation databases for virtual screening. Conformational databases are constructed using a parallelized fragment-based approach. Molecules are subdivided into overlapping fragments each of which is subjected to a rigorous stochastic search. The fragment conformations are rapidly assembled by superposing the overlapping atoms. A database of fragments is maintained (and augmented as the search proceeds) making conformation generation of combinatorial libraries very fast.

Pharmacophore Query Editor. Use an interactive editor to construct a 3D query from a molecular alignment or macromolecular structure. Use the query to filter a conformational database in an effort to determine candidate active compounds that satisfy the pharmacophore model. Refine the query to contain locations of Boolean expressions of pharmacophore features as well as restrictions on shape by using union-of-spheres for included, excluded and exterior volumes each containing an optional SMARTS chemical pattern.

Pharmacophore Consensus suggests possible pharmacophore queries based on a set of aligned active compounds. A consensus calculation requires a set of aligned input molecules, a tolerance radius, the consensus score threshold and the consensus score mode. Pharmacophore consensus is particularly useful when starting from a few highly active compounds.

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