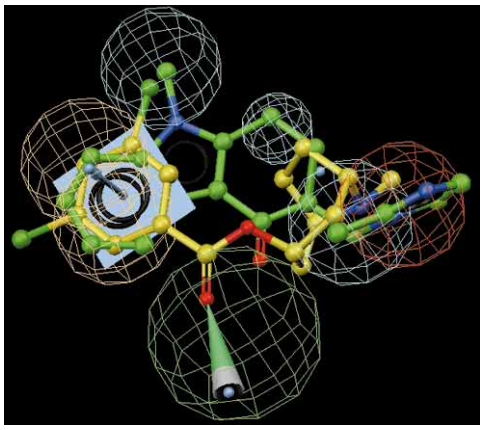
Specify hypotheses in terms of chemical features that are likely to be important for binding to an active site

Generate general interaction hypotheses that explain variations in activity across sets of molecules

Catalyst Datasheet

Pharmacophore Identification Using Catalyst

A pharmacophore is a representation of generalized molecular features including 3-dimensional (3D) (hydrophobic groups, charged/ionizable groups, hydrogen bond donors/acceptors), 2D (substructures), and 1D (physical or biological) properties that are considered to be responsible for a desired biological activity. Catalyst develops 3D models called hypotheses from a collection of molecules possessing a range of diversity in both structures and activities. You can use these hypotheses as queries to search 3D databases to retrieve structures that fit the hypothesis, or as models to predict the activities of novel compounds.



▲ *Two 5-HT3 antagonists (green and yellow) mapped on to a six-feature hypothesis.*

How Does Catalyst Pharmacophore Identification Work?

Given only available experimental information such as 2D structures and biological activities of a set of molecules, you can use Catalyst to identify possible binding features between a receptor and a set of ligands that can explain variations in their activity.

Catalyst specifies hypotheses in terms of chemical features[1] that are likely to be important for binding to the active site. Each hypothesis consists of four parts:

Chemical Features

The list of functions includes hydrophobes, charged/ionizable groups, and hydrogen bond donors/acceptors. You can refine (edit) the default chemical functions or define your own, which gives you more flexibility and independent analysis. Catalyst checks surface accessibility, so that it only considers those hydrophobic groups or hydrogen bond donors and acceptors that are available for interaction with the receptor.

Location and Orientation in 3D Space

Catalyst defines the position of different features (and excluded volumes) by absolute coordinates rather than by inter-feature distances alone. This produces hypotheses that allow you to discriminate between enantiomers and provides significant performance improvements to the underlying algorithms.

Tolerance in Location

Each chemical function is graphically represented by colored spheres. For example, donors and acceptors are represented by two spheres describing the locations of the heavy-atom ends of the hydrogen bond in the ligand and the projected location in the active site. The size of the spheres represents the precision necessary for location of a particular feature or excluded volume. A small sphere means that the function must be more precisely located for the molecule to be predicted active, while a larger sphere means that the precise location is less important. This allows you to distinguish which locations of features are the most crucial to a compound's activity.

Weight

Each chemical function includes a weight that describes its relative importance in conferring activity. The numerical value of the weight represents the order of magnitude increase in activity that can be expected from using that function fully as opposed to missing it entirely.

Once Catalyst has identified a hypothesis, it uses

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this hypothesis as a query to search Catalyst-formatted chemical databases such as Available Chemicals Directory (ACD), Derwent World Drug Index (WDI), BioByteMasterFile, National Cancer Institute database (NCI), and Maybridge catalog, for similar compounds that match the hypothesis.

Catalyst performs pharmacophore-based alignments of molecules and best-fit correlations that enable you to prioritize hit lists and focus on the best drug candidates. You can use the search results to refine your model, then search the databases again for more information.

HipHop

HipHop provides feature-based alignment of a collection of compounds without considering activity. HipHop matches the chemical features of a molecule, against drug candidate molecules. The resulting hypotheses can be used to iteratively search chemical databases to find new lead candidates.

How HipHop Works

HipHop takes a collection of conformational models of molecules and a selection of chemical features, and produces a series of molecular alignments in a variety of standard file formats. Catalyst gives you the freedom to supplement the chemical features that HipHop supports by allowing you to define your own customized chemical functions to cover alternative chemical concepts such as basic nitrogens[1].

HipHop begins by identifying configurations of features common to a set of molecules. A configuration consists of a set of relative locations in 3D space, and associated feature types. A molecule matches the configurations if it possesses conformations and structural features that can be superimposed within a certain tolerance from the corresponding ideal locations.

HipHop also maps partial features of molecules in the alignment set. This provision gives you the option to use partial mapping during the alignment. Partial mapping allows you to identify larger, more diverse, and more significant hypotheses and alignment models without the risk of missing compounds that do not map to all of the pharmacophore features.

Hypogen

This algorithm generates an activity-based pharmacophore model which can be used to estimate activities of new compounds.

How Is a Hypothesis Used to Estimate Activity of New Compounds?

Based on the structure/activity relationship developed from the molecules in the training set, Catalyst will estimate an activity for the new molecule based on the connection between (1) how well a compound can fit a hypothesis, (2) the number and placement of features that comprise a hypothesis, and (3) the estimated activity.

Highlights

- Constructs multiple hypotheses for a given hypothesis generation run, that explain the structure/activity data.
- Visualizes hypothesis features making it possible for you to see common features
- Clusters and merges hypotheses for developing more selective models
- Includes algorithms that can process larger numbers of conformations and molecules faster than previously existing methods- HipHop's pharmacophore identification technology[2] allows you to quickly and robustly handle flexible compounds that require exploration of a large number of conformational models[3]
- Thoroughly considers potential hydrogen bonding directionality, not just ideal lone pair positions
- Identifies conformationally dependent features and checks surface accessibility
- Ranks alignment hypothesis models by clustering to rank these configurations according to a cost function that estimates the uniqueness and/or selectivity of each hypothesis

Required Software

- HypoGen
- HipHop
- ConFirm
- Catalyst/VISUALIZER
- Catalyst/COMPARE

References

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