



Search and navigate in Chemical Spaces and find new scaffolds in a flash with FTrees.

How does FTrees work?

FTrees represents a molecule as a tree structure. Such a tree is composed of nodes (representing functional groups) connected such as to represent the overall topology. Each node carries a profile of the physics-chemical properties of the sub structure that it represents. The following attributes are captured:

- Spatial volume
- Ring or not
- Pharmacophore profile (donor, acceptor, amide-like, aromatic, hydrophobic)

Two trees are then aligned with each other, similar to a sequence alignment. The alignment provides a mapping of corresponding nodes on either tree (as illustrated by the same coloring of corresponding substructures). Mapped nodes are compared based on their property profiles resulting in a "Local Similarity". The "Global Similarity" is essentially an overall average, it can be used to categorize multiple molecules as to how similar they are, where 0 is dissimilar, and 1 is identical.

The coloring of the substructures helps the user to identify which substructure of the query is matched onto which one of the hit molecule. The alignment (or mapping) found by FTrees is among all the one with the highest "Global Similarity".

Advantages

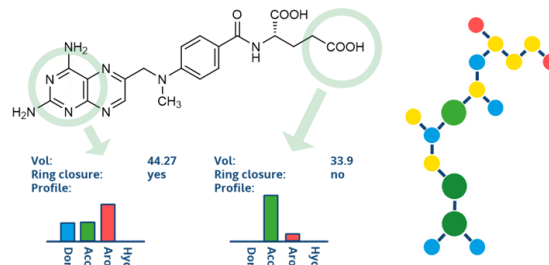
- Understand similarity: alignment of the molecules and an intuitive color code visualizes similarity.
- Literally billions of molecules can be searched in 5 minutes.

Scaffold hopping

The primary use case for FTrees is: "Find me a molecule with similar properties, but a different scaffold". For this purpose, large libraries are virtually screened, and the top-x compounds taken to be looked at. As you go down such a hit-list, molecules appear with less and less structural similarity. Typically, in the range between 0.7 to 0.9 you will find the most interesting results — similar enough in terms of pharmacophore properties but highly enriched with scaffold hops.

Orthogonality

FTrees have been shown to be orthogonal to other 2D descriptors. This means that one method likely picks up what other methods would not, and vice versa.



By looking at the molecules "fuzzily" it sees them more like a target as pharmacophore features in a certain topological arrangement, rather than structurally.

Template-based docking

Congeneric compound series can easily be docked. FlexX can superimpose a part of a ligand to dock onto a known crystal structure of a ligand. Template-based docking is performed by determining the Maximum Common Substructure (MCS) between the template and the compound-to-dock. Based on the MCS multiple overlays are generated to preserve the binding mode of the common core. The template needs to have at least 5 heavy atoms.

Literature

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Several presentations held during the NIH Workshop on Ultra-Large Chemical Spaces featuring the FTrees technology can be found [here](#).