Search fast, bridge scaffolds

BioSolveIT

The developers of FlexX

FTrees

FTrees is a highly efficient software tool for fuzzy similarity searching facilitating virtual HTS. The ability to detect novel molecular scaffolds is one of several features special to FTrees.

About FTrees

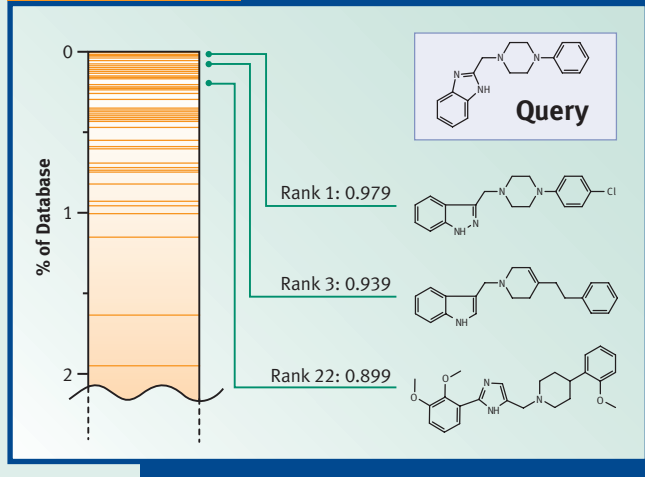
Its underlying topological descriptor (Feature Tree) captures connectivity and physico-chemical properties of functional groups [1]. The optimum similarity of two descriptors is defined by an alignment, so an SAR may be readily detected.

FTrees have been reported to be highly successful in numerous projects by various customers in (a) lead finding, (b) HTS analysis and (c) general virtual screening applications [2-4].

Advantages

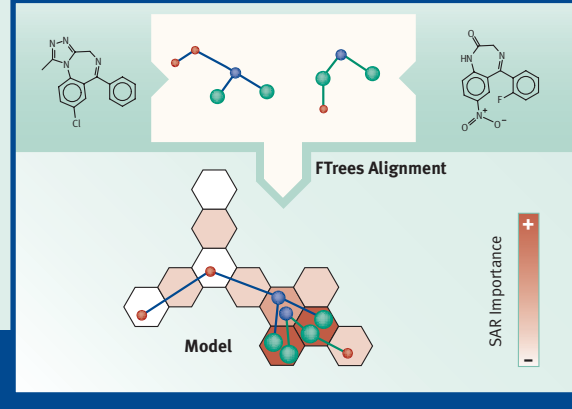
- Speed: Search a typical vendor catalog (e.g. Maybridge with currently about 60.000 compounds) within 15 seconds on a standard PC
- Bridge Scaffolds: Structurally diverse molecules (low fingerprint similarity) may be detected as highly similar Feature Trees
- Hit Rates: FTrees tops industry standards on a benchmark dataset
- Model Building: Multiple molecules may be aligned in a model to reveal conserved (or diverse) functional groups
- De Novo Design: FTrees facilitates *de novo* design via fragment space searches. 10^{18} virtual compounds can be processed within about 5 minutes

Bridge Scaffolds



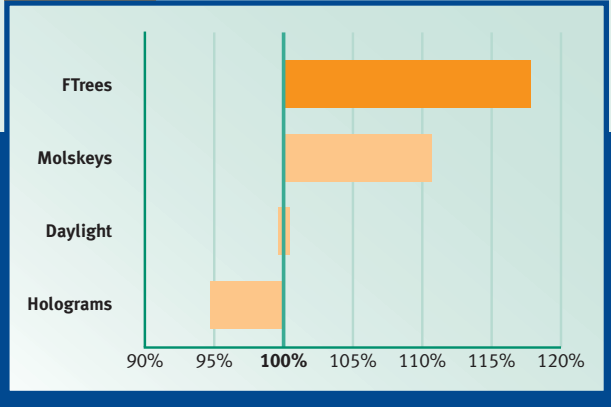
Due to the fuzziness of the Feature Trees descriptor different scaffolds may be detected at high similarity values

Model Building



Explain which groups cause activity to your synthetic department: Unlike fingerprint-type approaches Feature Trees retain both the topology and the nature of physics and chemistry of the compounds. This descriptor is built to learn about pharmacophore features

Hit Rates



Compared to industry standards (Daylight Fingerprints set to 100% as the reference), FTrees detects 17.7% more hits as a broad average across multiple activity classes [2]

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FTrees

Application Scenarios

What puts FTrees one step ahead of other software in a typical similarity-based virtual screen?

→ To compare two molecules, FTrees creates an alignment between them. This gives the immediate advantage that the chemist understands why the molecules were awarded a certain similarity. Also, the modeler can influence the alignment – do I want to focus on physicochemical properties or molecular shape and size?
In short, FTrees combines the scaffold hopping abilities of 3D descriptors with the performance of 2D descriptors.

OK, but I want to carry out more complicated experiments – for example, I have several active molecules displaying some diversity, what now?

→ FTrees is ideal for this scenario. We have already seen how it is possible to align molecules. Let's align the actives; they must have something in common to make them all active. This is possible with the FTrees model building facility. A model is built from a set of several aligned molecules and is in fact itself just another Feature Tree.

So my model tree describes the unified features of my actives but what is this good for?

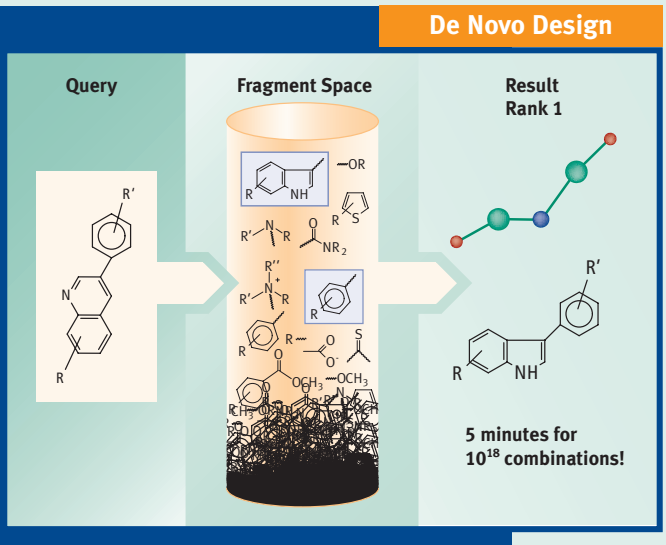
→ You can screen with the model Feature Tree just as easily as with a Feature Tree representing a single molecule. That will give just one result set instead of several. The results will highlight compounds that best match the common description of the set of actives.

I work on a daily basis with the in-house database – this contains millions of compounds these days, where do I start?!

→ Millions of compounds represent no problem to FTrees – 1/2 million Feature Trees can be handled at once (in memory) by the software.
In fact FTrees – in the form of a python module – is perfect for carrying out data reduction of large datasets. Starting with a small set of seed compounds, you can use FTrees to filter the dataset down to a size more manageable for more intensive modeling methods.

What about de novo *design?*

→ This is possible with an add-on called FTrees-FS.



A fragment space is a set of molecular building blocks with linker rules. FTrees can assemble and search highly similar molecules on the fly

Complementary to FTrees

There are more add-ons to the basic FTrees software that will enhance the integration of FTrees into your molecular modeling workplace:

FTrees-FS: Fragment Spaces module – extend your usage of FTrees to cover your combinatorial libraries. Indeed, 'shred' your own database to create a fragment space and carry out *de novo* style searching within it to generate new lead ideas.

HTSview: a tool originally developed from the FTrees software base for analyzing HTS data. Assign activity values and classes to molecules, calculate similarity matrices and clusterings, carry out statistical analyses of fragment occurrences, view your models in aligned 2D or 3D format...

pyFTrees: Plug FTrees into any python environment by importing pyftrees - the complete FTrees functionality contained in a python module.

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[1] Rarey, M. and Dixon, S. *JCAMD*, **12**, 471 (1998)
[2] Briem, H. and Lessel, U. *PD3*, **20**, 231 (2000)
[3] Rarey, M. and Stahl, M. *JCAMD*, **15**, 497 (2001)
[4] Zimmermann, M. *et al.* in *Proceedings EuroQSAR 2002*

Technical Requirements
Standard PC hardware is sufficient to run FTrees:
- 256MB or more RAM
- Only for pyFTrees: Python version 2.2 or later

Supported Operating Systems
- Linux, SGI/IRIX, SunOS, HP-UX, Windows NT/2000/XP

FTrees runs in parallel with PVM 3.4.4 or later on all above-mentioned operating systems

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