DeCAF – Discrimination, Comparison, Alignment algorithm for small molecules.

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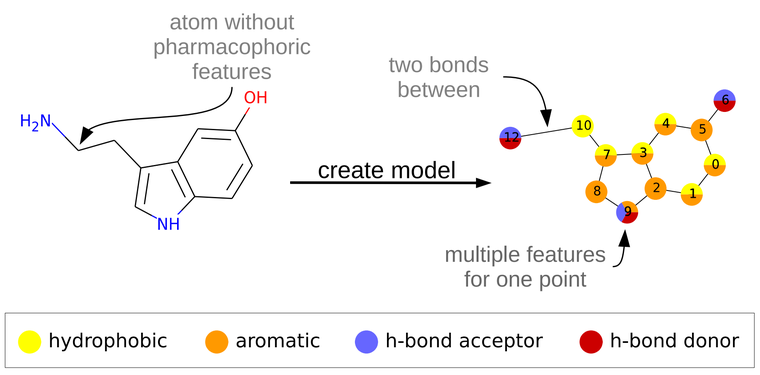
1. Introduction

Predicting biological activity of small molecules is a key element of computer-aided drug design. Existing methods often fail to identify ligands with similar physicochemical properties but different structures. Many of the current approaches rely on generating 3D conformations, which leads to sampling problems and unacceptably high computational costs for large sets of molecules. Herein we present DeCAF – a novel method for describing ligand properties and a fast and effective tool for comparing multiple molecules, and merging them into a single pharmacophore model. DeCAF is written as an open source Python module (**http://bitbucket.org/marta-sd/decaf**) and can be easily combined with RDKit to facilitate ligand-based drug design.

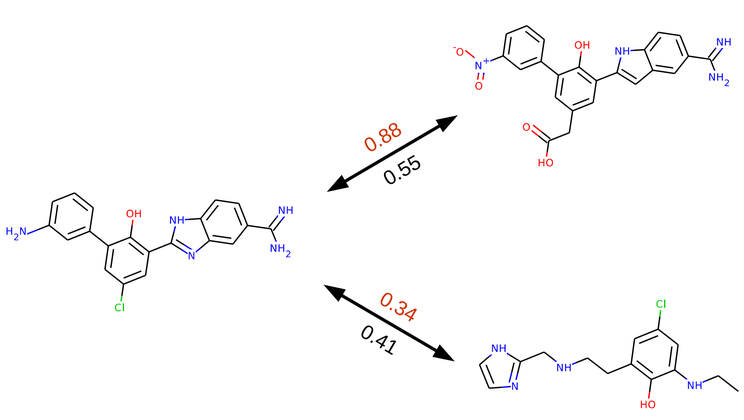
2. Pharmacophore model

To describe a molecule, DeCAF substitutes its functional groups with pharmacophoric points (hence the "F" in the algorithm's name). Points are organised into an undirected graph. Lengths of the edges in the graph represents the number of bonds between pharmacophoric points.



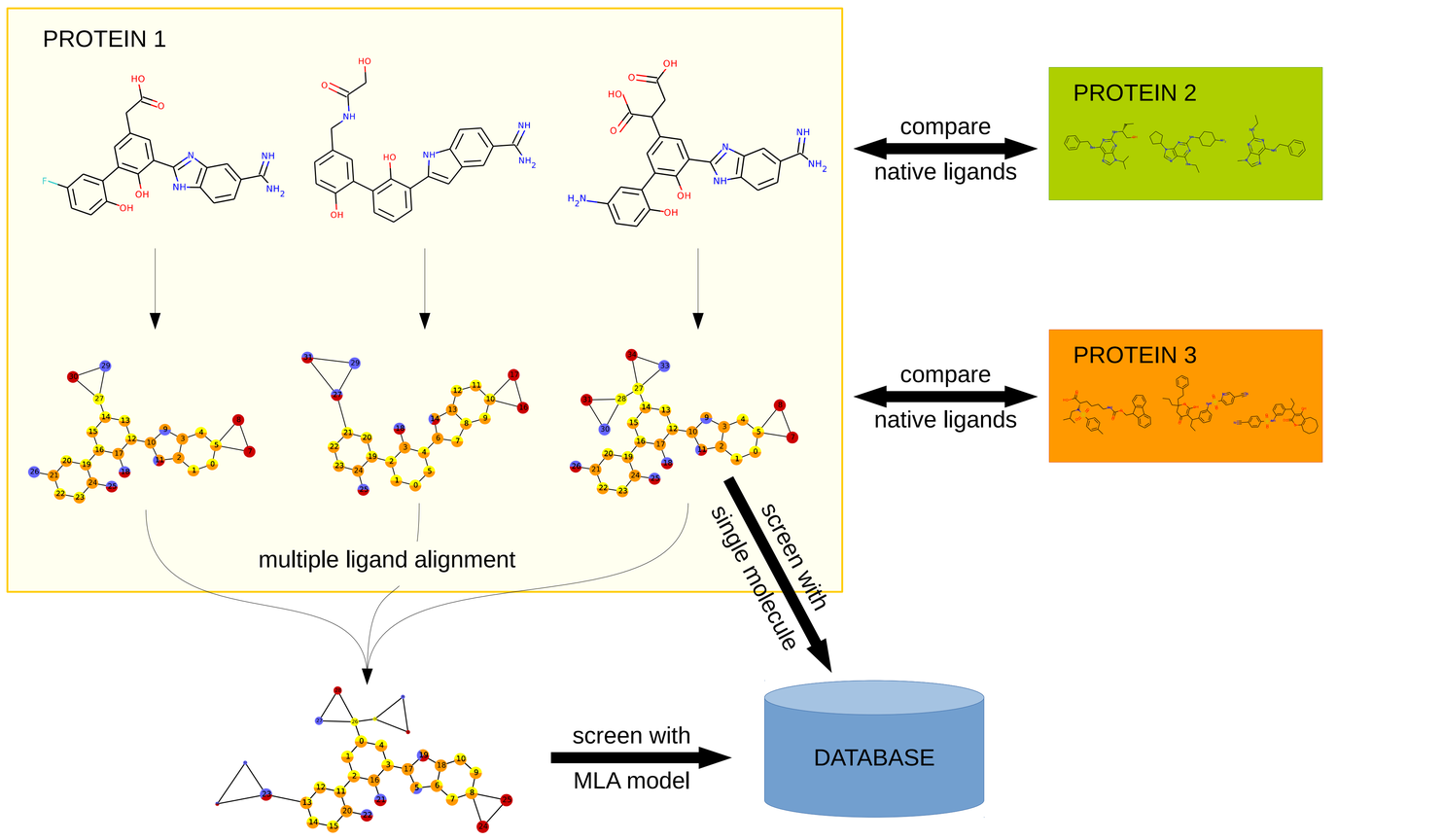
3. Similarity measure

To measure similarity of two molecules or to combine them into one model, DeCAF first finds their **maximum common substructure (MCS)**. To provide fast, but accurate method for solving MCS problem, we combined Generic Match Algorithm (GMA) [1] with backtracking algorithm proposed by Yiqun Cao [2].
Here we present comparison of molecules with similar and with different structures. DeCAF scores and **Tanimoto coefficient (Tc)** values are shown in red and black, respectively.

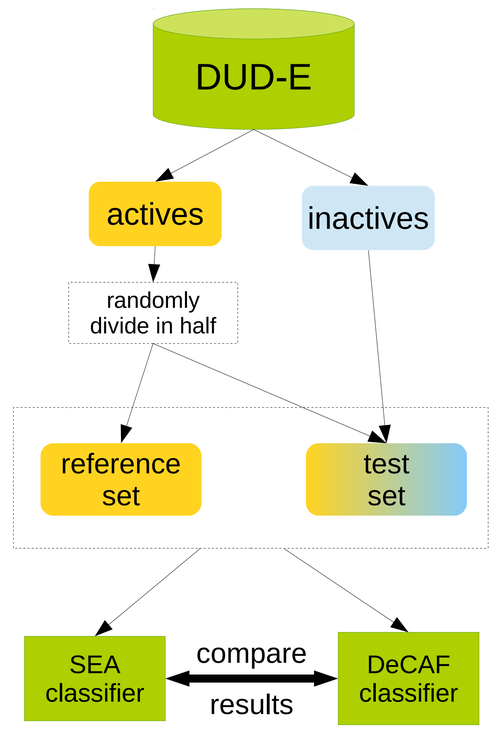


4. Applications

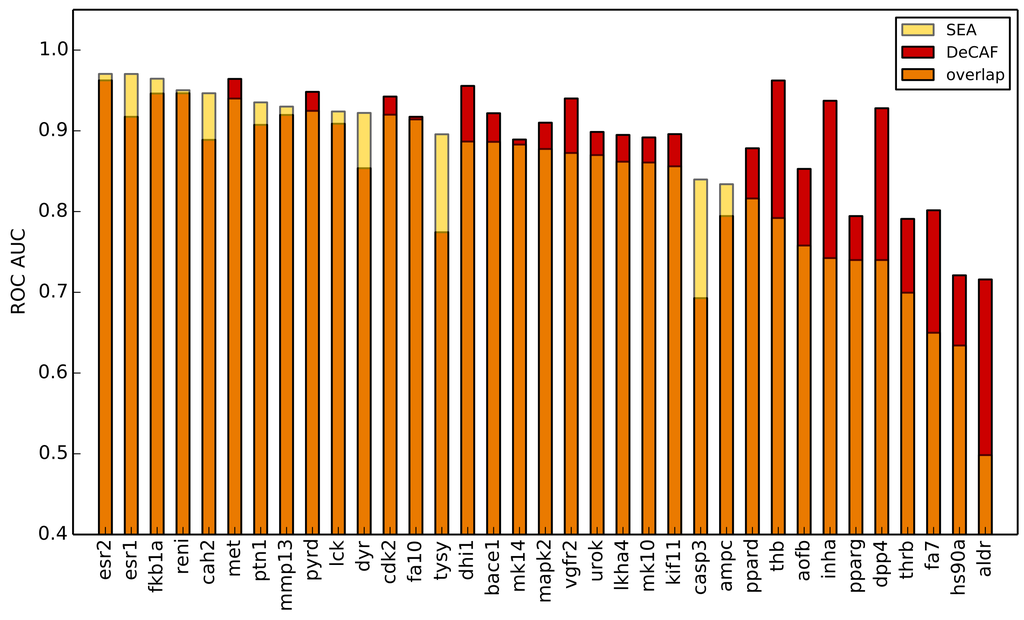
DeCAF is a versatile tool with many possible applications. It allows to compare two molecules or more complex models created from sets of ligands. Our method can be used to align multiple ligands and find crucial pharmacophoric features in a set of active compounds. Pharmacophore models can help in database screening for molecules with desired properties. DeCAF is also suitable for comparing entire sets of ligands, e.g. to analyse properties of proteins in drug repositioning process.



5. DeCAF vs. SEA



We tested DeCAF in 35 diverse targets taken from the DUD-E database, to evaluate its power to classify molecules as active or inactive. We compared DeCAF to the renowned **SEA (Similarity Ensemble Approach)** algorithm [3], which uses Tc as a similarity measure. Dataset preparation steps are shown on the left diagram. Comparison results (**ROC AUC** values for each receptor) are shown below.



6. Conclusions

We proved that DeCAF is a significant improvement over the SEA algorithm, a popular method for comparing sets of ligands.

1. DeCAF gives better results for 23 out of 35 receptors.
2. For targets with easily separable active and inactive datasets, SEA and DeCAF give similar results.
3. In cases in which SEA fails to identify active molecules, our method performs substantially better.

7. References

[1] Jun Xu. Gma: a generic match algorithm for structural homomorphism, isomorphism, and maximal common substructure match and its applications. *J. Chem. Inf. Comput. Sci.*, 36(1):25–34, 1996.

[2] Yiqun Cao, Tao Jiang, and Thomas Girke. A maximum common substructure-based algorithm for searching and predicting drug-like compounds. *Bioinformatics*, 24(13):i366–i374, 2008.

[3] Michael J Keiser, Bryan L Roth, Blaine N Armbruster, Paul Ernsberger, John J Irwin, and Brian K Shoichet. Relating protein pharmacology by ligand chemistry. *Nat. Biotechnol.*, 25(2):197–206, 2007.