

MOLECULAR SIMILARITY BY PATTERN RECOGNITION: FAST CALCULATION OF 3D PHARMACOPHORE RESEMBLENCE

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Chemical-feature based pharmacophore models have been established as state-of-the-art technique describing interactions of small molecules with macromolecules and virtual screening [1, 2]. While there are already many approaches for molecular similarity in general, available similarity measures are commonly based on topological resemblance, atom pair coding or on n-point pharmacophores derived from subsets of chemical feature distances. If used for pharmacophoric similarity, these methods suffer from a topological bias to specified structure classes or by the combinatorial explosion occurring in the comparison algorithms if distance multiplets are involved.

We present a novel approach describing molecular similarity by multi-conformationally overlaying all their possible pharmacophoric features using pattern recognition and parts of our 3D alignment algorithm presented earlier [3]. The new similarity calculation method is based on a rotationally and translationally independent, but conformation-dependent representation of a molecule consisting of all chemical feature locations. Distance shells with feature proximity counts are derived from pharmacophore point locations, which are then paired and subtracted using a bipartite matching algorithm. The matching approach using distance shells, a method that has its original application in pattern recognition, bears the advantage of polynomial computational complexity and therefore allows for fast similarity measure calculation for conformational ensembles.

The use of pharmacophore points allows for a broader application scope such as measuring similarities between pharmacophore models. Applications for clustering and ligand-based pharmacophore creation are discussed.

References:

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3. G. Wolber, A. Dornhofer, T. Langer. Efficient overlay of small organic molecules using 3D pharmacophores. *J. Comput. Aided Mol. Des.*; **2007**; 20(12); 773-788.