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Sublinear ligand-based virtual screening using bitmap indices

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The contemporary standard approach for ligand-based virtual screening is based on a sequential screening pipeline which means that every compound of a given compound library has to be screened against a reference molecule. For tools based on small molecule alignments, this requires calculating superpositions between a reference ligand and each compound of the library to obtain a list of hit compounds.

As calculating molecular superpositions is computationally expensive, our new tool for ligand-based virtual screening named TrixS BMI tries to avoid the sequential screening pipeline of other ligand-based virtual screening tools by reducing the number of compounds to superimpose in a computationally much faster pre-processing step. This allows for sublinear runtimes with respect to the library size while still providing comparable enrichment and hit rates. TrixS BMI is an adaptation of the structure-based virtual screening tool TrixX BMI [1] and uses an approach based on descriptors containing pharmacophoric and shape information, as well as an indexed database. In addition, TrixS BMI allows user-defined pharmacophoric constraints and has a novel approach to handle partial shape similarity directly upon the indexed search process.

An outline of the workflow can be described as follows: as TrixS BMI does not decompose the compounds into smaller fragments, flexibility is handled by using a conformer generator, which calculates conformational ensembles for each compound of a given library. The ensembles are used to calculate descriptors, which are then stored in an indexed database. This is a one time effort. The same database is queried by descriptors calculated from a target molecule, which results in a preselection of compounds for the process of superpositioning.

Screening experiments on literature data show that TrixS BMI obtains comparable hit rates and enrichment values to standard alignment-based virtual screening tools like ROCS [2] and FlexS [3]. Computing times are in the range of 7 to 8 compounds per second in case of searching with drug-like target molecules.

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