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From screening to searching: an index-driven approach to structure-based lead identification

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The standard approach to structure based high-throughput virtual screening nowadays is a sequential procedure. Each molecule of a given library is individually docked into the target protein in order to produce a ranked hit list. With the TrixX approach, we introduce a new paradigm avoiding the iterative process of virtual screening while yielding comparable re-docking results and enrichment rates.

TrixX BMI uses a descriptor capable to cover pharmacophoric as well as shape information to perform index-driven virtual screening. In contrast to TrixX [1] we use rigid body docking of pre-processed conformational ensembles of small molecules or molecular fragments with up to ten rotatable bonds. Furthermore we extended the original descriptor by introducing an 80 dimensional steric bulk vector. We kept the promising idea of splitting virtual screening into disjoint phases. During Data Pre-Processing descriptors based on conformational ensembles are computed and stored in a database. This is a one-time effort. In the Virtual High-Throughput Screening phase, a given protein active site is used to generate complementary descriptors as query templates which are used to identify potential hit candidates within the database. Query matches are then translated into initial fragment placements. Because of the enormous amount of descriptors and their high-dimensional content there is the need for an efficient decision support system. This functionality is realized using compressed bitmap indices supplied by Fastbit [2].

Re-docking experiments on the Astex Diverse Set [3] demonstrate that TrixX BMI achieves comparable results to current docking tools while improving the runtime by about one order of magnitude. Enrichment experiments on four targets (CDK2, DHFR, ER(agonists), ER(antagonists)) from the DUD [4] dataset further support this data and demonstrate that TrixX BMI is especially suited for structure-based virtual screening of lead-like compounds under pharmacophoric constraints. A large test set consisting of 1.7 million random lead-like compounds together with pharmacophores from the literature is used to show TrixX BMI's scalability. TrixX BMI is able to finish the VHTS runs on all four targets in less than 30 minutes on a 96 CPU compute cluster.

References

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