

***In silico* High-Throughput Screening by Hierarchical Chemical DB Search by 3D Pharmacophore Model**

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Recent advances in '-omics' technologies enable us to discover more diverse disease-relevant target proteins, which encourages us to find out more target-specific novel lead compounds as new drug candidates. Therefore, high-throughput screening (HTS) becomes an essential tool in this area. Among many HTS tools, *in silico* HTS is a very fast and cost-effective tool to try to derive a new lead compound for any new targets, especially when the target protein structures are known or readily modeled.

In order to discover a new lead compound or a novel core chemical structure for further optimization by combinatorial chemistry, one can quickly evaluate the biological activities of those compounds selected by *in silico* HTS tool among the millions of small organic molecules that are commercially available. There are now many approaches in *in silico* HTS such as 3D docking, QSAR, substructure similarity search, etc. Each has its own pros and cons.

Recently, we have developed our own *in silico* HTS system, called IDPharmo, which is a linux-based, very fast, and fully-automated tool for a new lead compound discovery among millions of commercially available chemical libraries. IDPharmo has several related modules.

In IDPharmo, PharmoMap module is a tool for the active-site modeling of target protein either by automatic or manual assignment of the potential binding pocket. PharmoMap scans accessible binding pockets and picks up potentially important interaction sites by using probe map search. After automatic analysis of the distribution of these interaction sites, PharmoMap gives us the number of desirable combinations among the interaction sites, which will be a model of the pharmacophore between ligand and binding pocket.

PharmoScan is a search tool which scans all the chemicals' 3D structures in the precompiled database, called PharmoDB, against each of the PharmoMaps. PharmoScan is a hierarchical chemical DB search engine. For a given PharmoMap, PharmoScan filters out, in one dimensional (1D) fashion,

any chemicals that do not fit to the chosen PharmoMap in terms of the number or the properties of the features in the PharmoMap. In the 2D filter in PharmoScan, all the inter-chemical feature distances of each chemical are compared to the inter-feature distances of the PharmoMap, so that only such chemicals with certain inter-feature distance patterns can pass through. In 3D scan and higher order scan, each chemical is challenged to superimpose to the PharmoMap by root-mean-square (RMS) fitting, and the fitness of docked structure is evaluated by scoring measurement.

Our chemical library database, PharmoDB, is precompiled according to this hierarchical search strategy. For example, maximum 150 possible 3D conformations of each chemical are pre-computed based on the conformation energy minimization, all the corresponding features to PharmoMap features are pre-assigned for each conformation, and all the distances matrices are pre-calculated and stored as binary compressed formats.

Currently, we have about 4 million non-redundant chemical libraries in PharmoDB and PharmoScan can search whole PharmoDB within 8 hours for a given target binding site by using 8-nodes linux cluster. In this seminar, some benchmark results of IDPharmo, as well as further detail strategy in *in silico* HTS application, will be discussed.