Dynamic Virtual Screening: reducing the search space within a ligand library

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What is DVS ?

Virtual screening is a far-reaching technique used in drug discovery which can substitute time-consuming *in vitro* assays to identify inhibitors for a protein. Molecular libraries which can be used for virtual screening contain over 35 million drug-like molecules [1]. Usually brute-force-technique are employed i.e all compounds are docked one after the other. This is a time-consuming process considering the scale of data available[2]. To optimize the technique and accelerate the virtual screening process we are developing a rational approach called **dynamic virtual screening(DVS)**.

Aim

To reduce the time taken by **High-throughput screening (HTS**). In order to achieve this, we reduce the size of library to be screened by defining rationally a set of dynamic ranges of physicochemical properties. Further improvement using pharmacophore modelling to search for molecules which share structural features will be pursued.

Compound library

The ligand library was generated with **ChemicalToolBoX**[3] by merging several compound databases, which yielded more than 9 million molecules[2]. We used **QikProp** (Schrödinger, LLC) to predict the physicochemical properties of the compounds.

SP Docking of compounds

SP Docking evaluates *in silico* the affinity of a protein–ligand complex. We have used this parameter to sort and select putative binders. SPDocking is computed for few compounds which arbitrarily represent the whole library.

Top-scored compounds

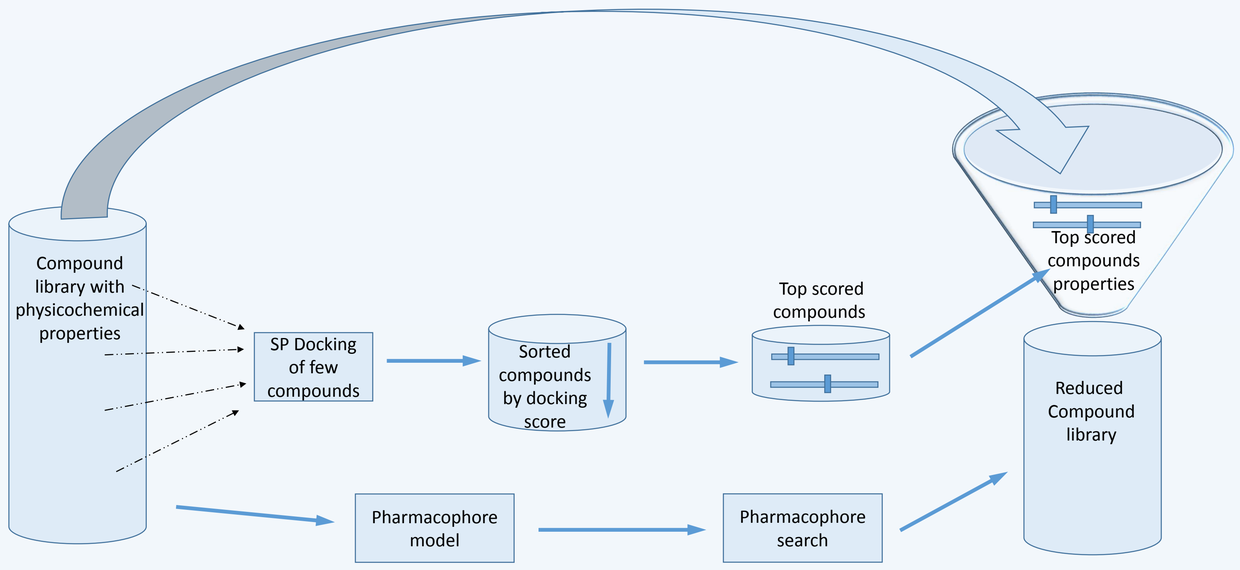
The physicochemical properties of top-ranked compounds are collected and used to define appropriate ranges for the filtering.

Physicochemical properties

Guiding properties are selected by their **Shannon entropy.** It is an information theory metric, which indicates dispersion of the physicochemical property. In our method we have taken properties which have **Shannon entropy <0.7**.

"Knowledge-driven library filtering"

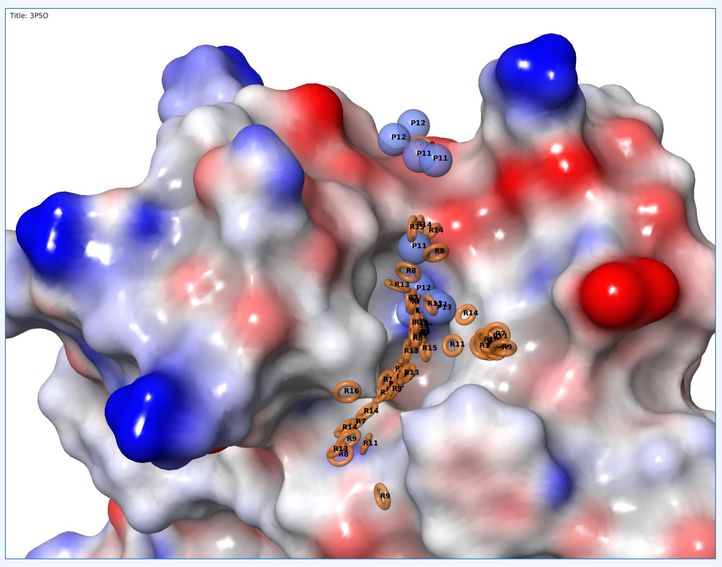
"Sharpen your resources while hunting for inhibitors"



Reduced compound library

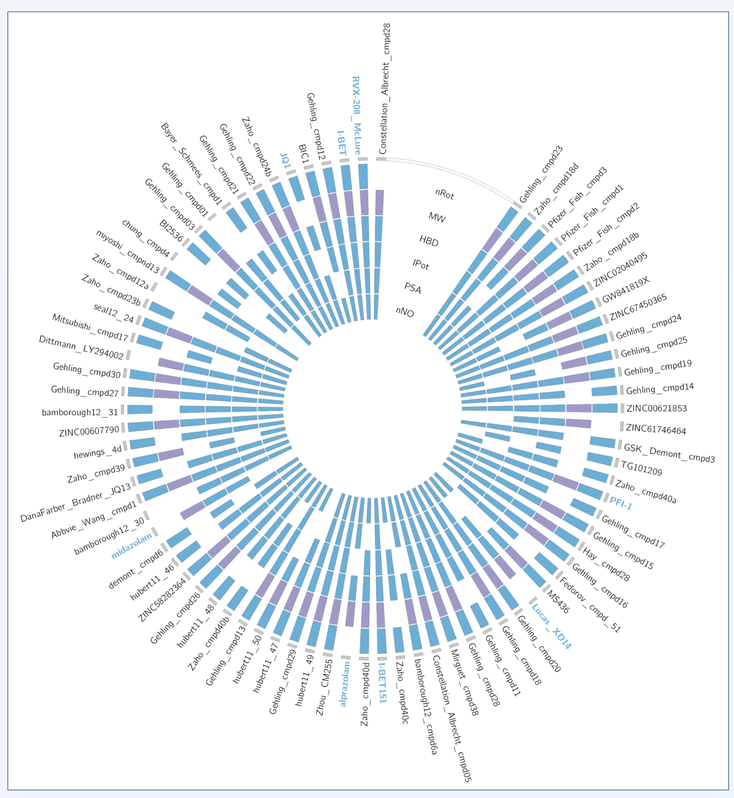
Reduced compound library which is obtained after applying filter is reduced by 18% with the help of initial algorithms. However there is still scope of improving the algorithm.

Pharmacophore model



Pharmacophores of known binders of **BRD4**. The shown models of positively charged groups as well as the rings are grouped at well-defined areas of the binding pocket. DVS aims at identifying these properties with randomly docked compounds. Such models can be the integrated in a subsequent pharmacophore-based library screening.

Benchmark using know bromodomain inhibitors



The graph shows how the method performed against **Bromodomain** inhibitors. It is interesting to see that Molecular weight did not play modest role compared to nRot, HBD, IPot, PSA, and nN+O.

Discussion & Outlook

The results indicate that planned approach did not yield the expected results. In the subsequent step of DVS we will consider pharmacophore information to include 3D conformation and develop a pharmacophore model, which will be used for pharmcophore searches of compounds with similar features.

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[1] Irwin, JJ, et al.: *J. Chem. Inf. Model*. **2012**, 52(7): 1757-1768
[2] Lucas, X., Wohlwend D., et al.*: Angew. Chem. Int. Ed*. *Eng*. **2013**, 52(52): 14055-14059
[3] http://ctb.pharmaceutical-bioinformatics.org

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