Hotspots API: A Toolkit for the Application of Fragment Hotspot Mapping to SBDD

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Introduction

We present the Hotspots API, a Python toolkit for the detection of small molecule binding hotspots and application of results to structure-based drug discovery (SBDD) methods.

Motivations

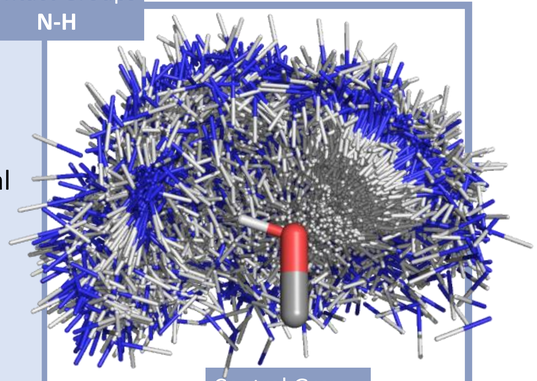
- Programmatic **access** to algorithm and integration
- Platform for **collaboration**
- Pathway for **productisation**.

1997

IsoStar

3D **scatterplots** that show the probability of occurrence and spatial characteristics of **interacting** functional groups from the CSD and PDB.

Bruno, I. J., *et al.* IsoStar : A library of information about nonbonded interactions *J. Comput. Aided Mol. Des.*, **11,** 525–537 (1997).

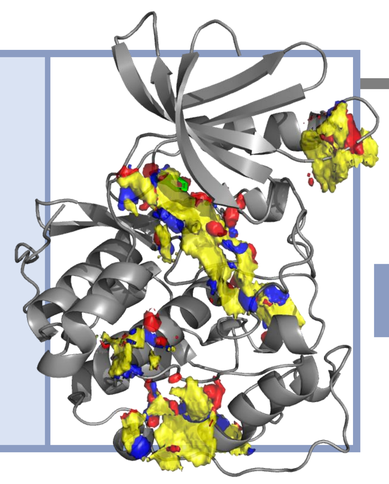


1999

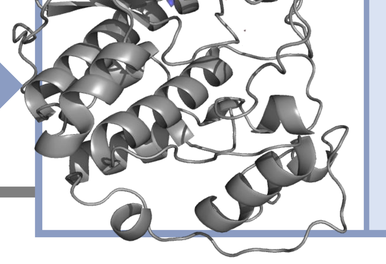
SuperStar

Using **IsoStar** data, interaction propensities are **mapped** to functional groups on the target molecule highlighting likely interactions.

Verdonk, M. L., *et al.* SuperStar : A Knowledge-based Approach for Identifying Interaction Sites in Proteins. *J. Mol. Bio,* **289**, 1093–1109 (1999).



Reduction in false positives



2016

Fragment Hotspot Maps

Predicts the location of small molecule binding hotspots in proteins. Weighs SuperStar by pocket **burial** and samples with **pseudomolecular probes**.

Radoux, C. J., *et al.* Identifying Interactions that Determine Fragment Binding at Protein Hotspots. *J. Med. Chem.* **59,** 4314–4325 (2016).

Hotspots API

- Programmatic access to hotspots.
- Growing support for SBDD applications.
- Built on top of the CSD Python API (CSD License required).
- Latest stable package on PyPI and GitHub.

Increasing Accessibility and Utility

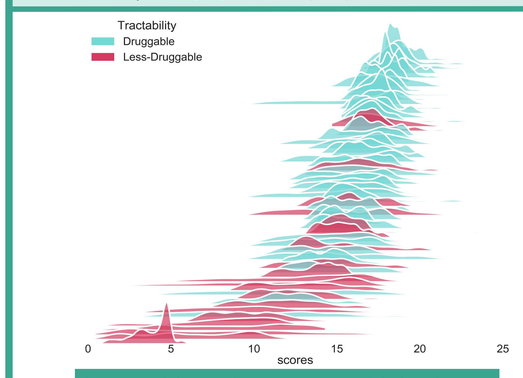
2018

Use Cases

1 Tractability Assessment

1. Calculate Maps
2. Restrict to “Drug” Volume ~500 A^3
3. Sort by median score value
4. Plot scores distributions

Krasowski, A., *et al.,* DrugPred : A Structure-Based Approach To Predict Protein Druggability Developed Using an Extensive Nonredundant Data Set. *J. Chem. Inf. Model.*, 51, 2829–2842 (2011).



‘Druggable and Less Druggable’ subset

2 Improving Docking with GOLD

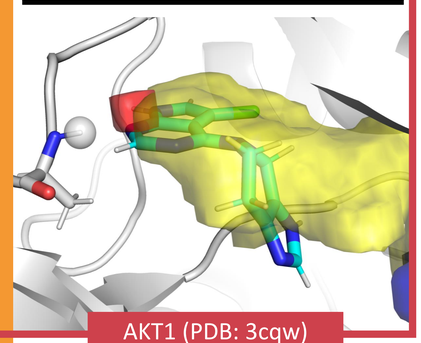
- Supports application of results to GOLD docking.
- Previous work has shown improved early enrichment when using hotspot H-bond constraints for VS.

Options:

1. H-Bond Constraint
2. Apolar fitting points
3. Rescore

Radoux, C. J. The Automatic Detection of Small Molecule Binding Hotspots on Proteins Applying Hotspots to Structure-Based Drug Design. PhD, University of Cambridge, UK (2018).

Constraint	EF 1%
No Constraint	9.9
1 constraint (penalty = 10)	12.7
1 constraint (penalty = 100)	15.7



AKT1 (PDB: 3cqw)

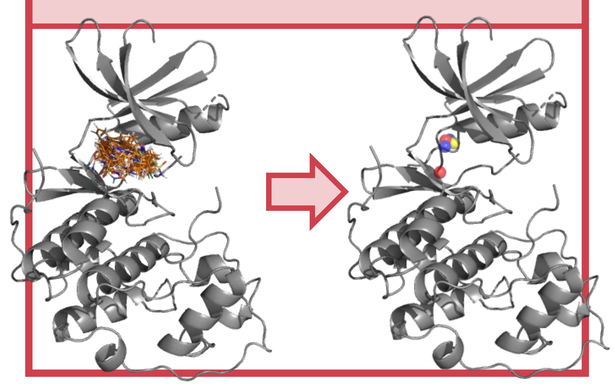
3 Pharmacophore Modelling

Pharmacophores can be created from:

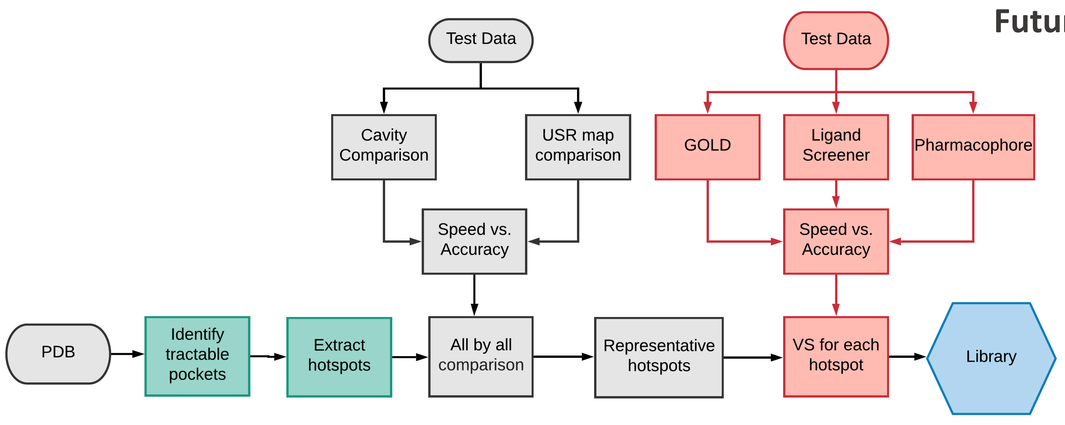
- overlaid ligands
- a hotspot result

Generated pharmacophore can be used to:

- search CSD & PDB with CSD-CrossMiner
- search ZINC with Pharmit



Future



Global Pharmacophoric Analysis

- The work on the Hotspot API supports futures objectives.
- Using PDB data, this project aims to map “global” pharmacophoric space of protein hotspots.
- Then, design a virtual small molecule screening library covering it.
- We aim to increase the biological relevance of screening libraries to improve HTS efficiency.

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