

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

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## Introduction

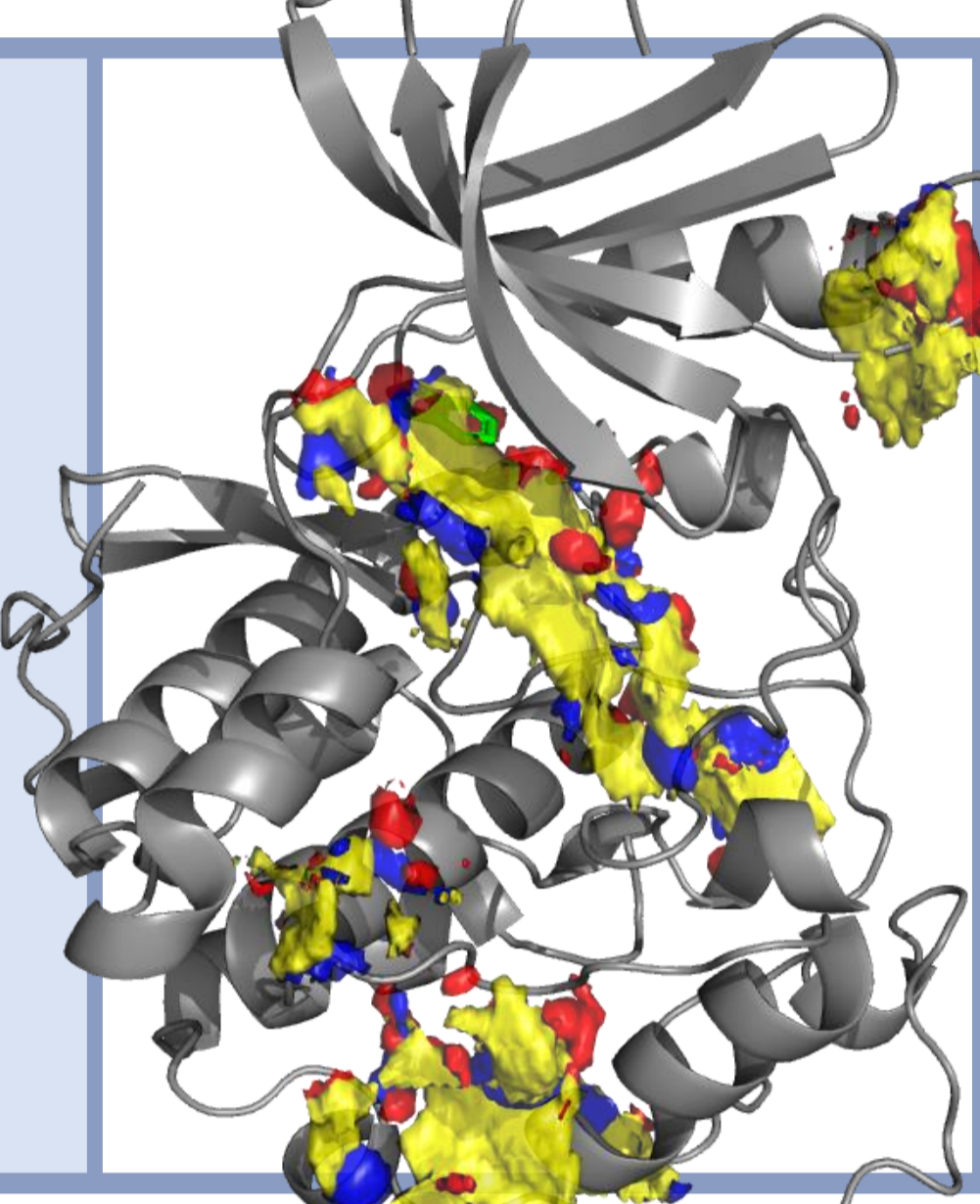
We present the Hotspots API, a Python toolkit for the detection of small molecule binding hotspots and application of results to structure-based drug discovery (SBDD) methods.

### Motivations

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

**SuperStar**

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

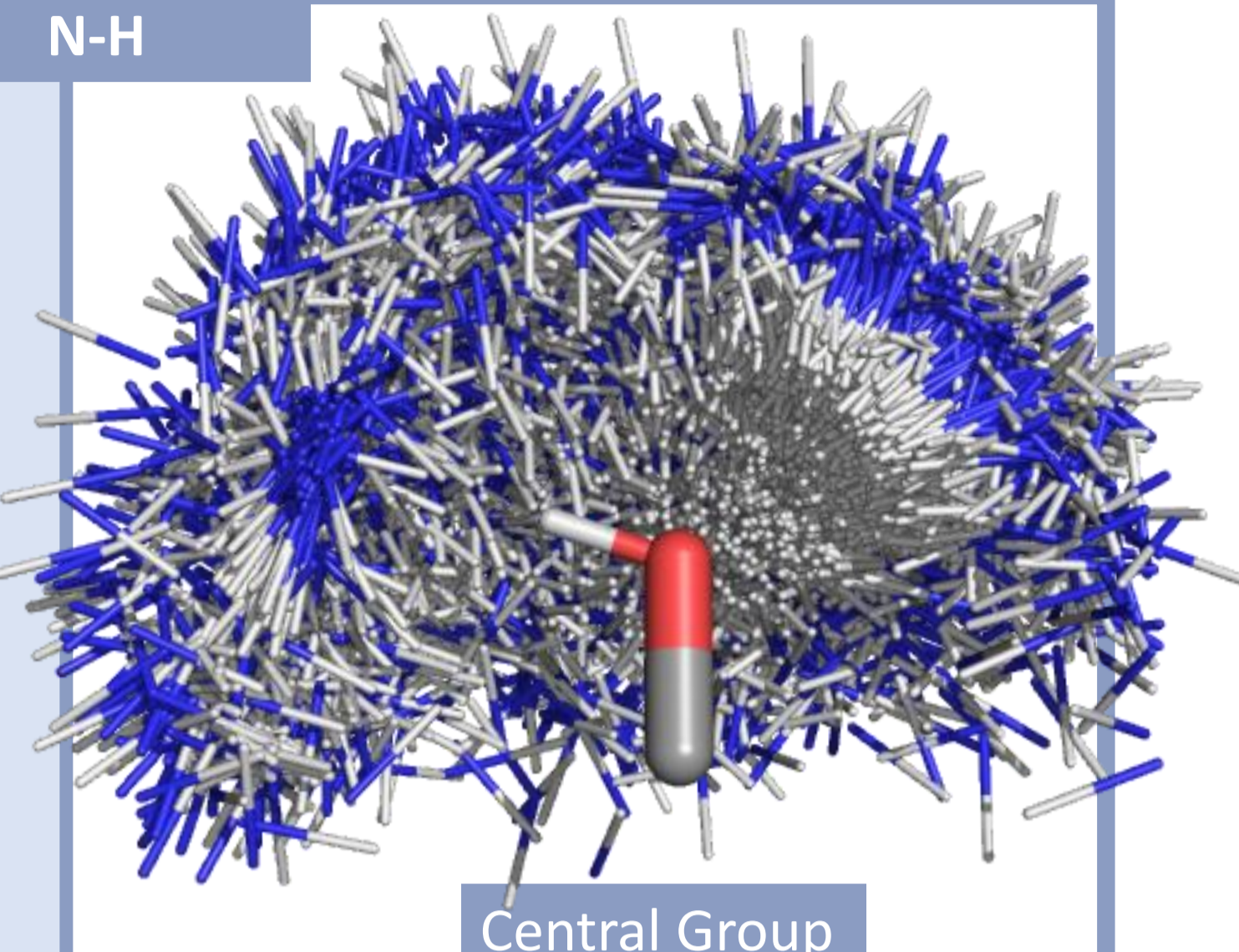


Verdonk, M. L., et al. SuperStar: A Knowledge-based Approach for Identifying Interaction Sites in Proteins. *J. Mol. Bio.* **289**, 1093–1109 (1999).

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).

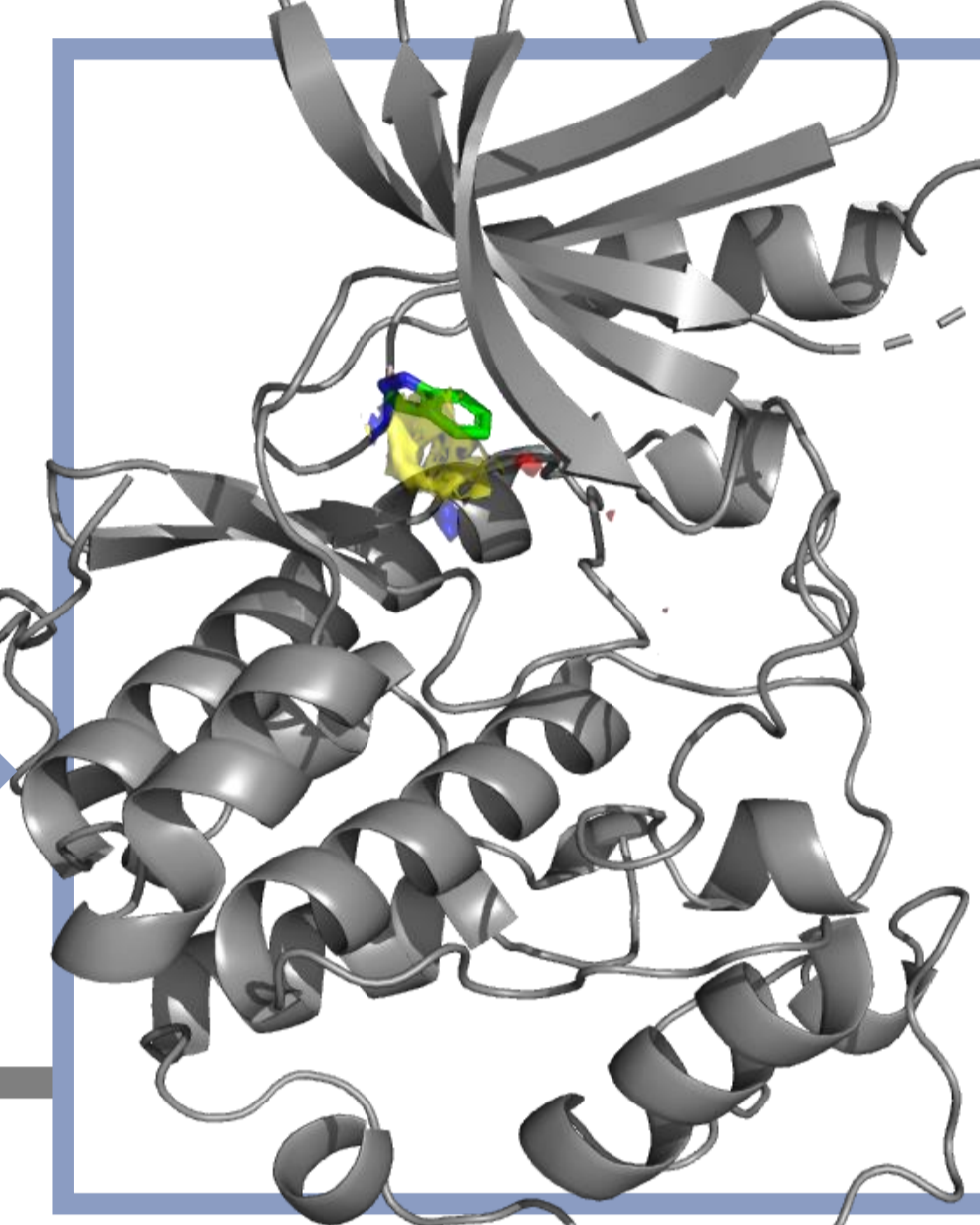
1999

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



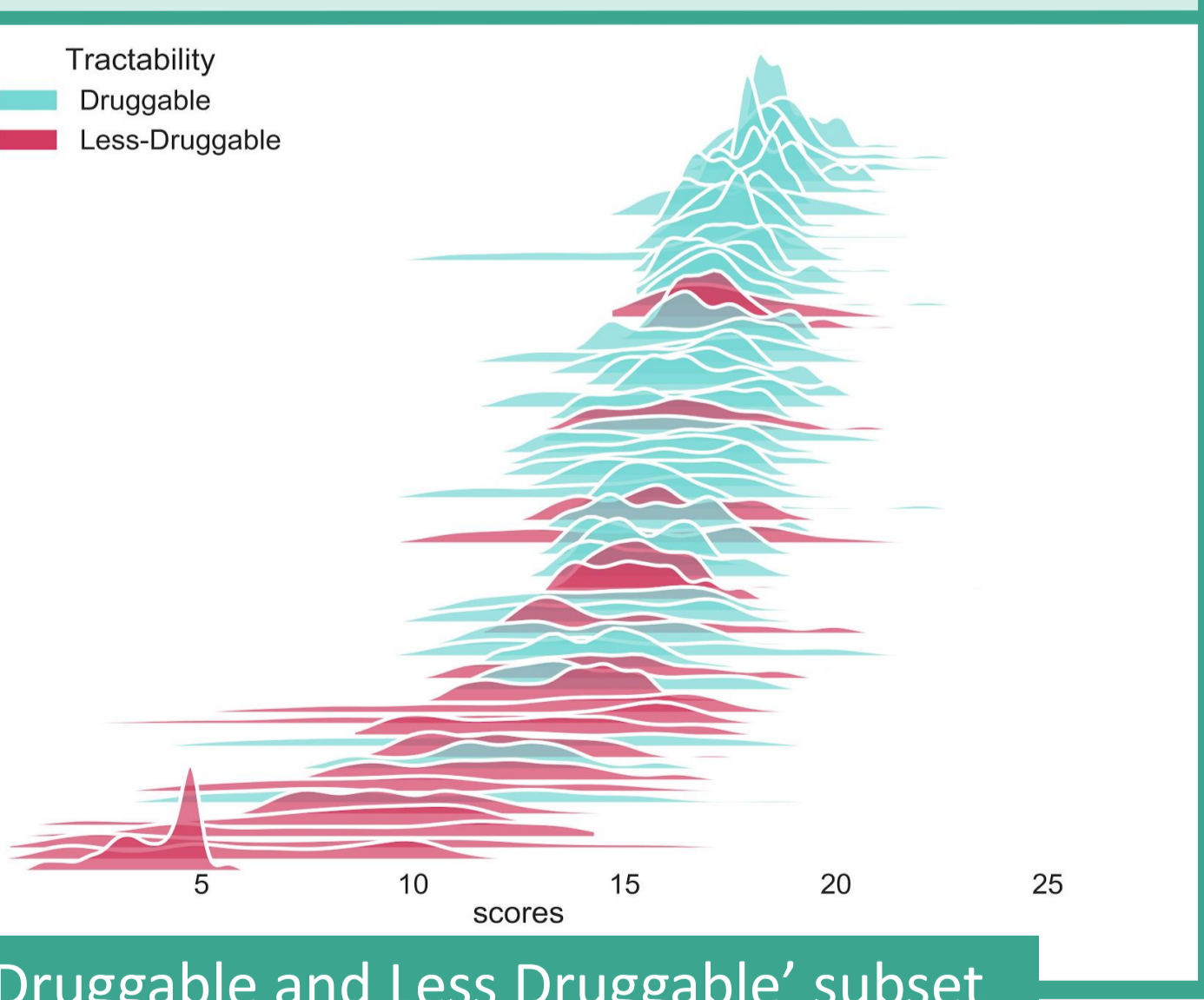
Increasing Accessibility and Utility

## Use Cases

**1 Tractability Assessment**

1. Calculate Maps
2. Restrict to "Drug" Volume ~500 Å<sup>3</sup>
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

2018

**2 Improving Docking with GOLD**

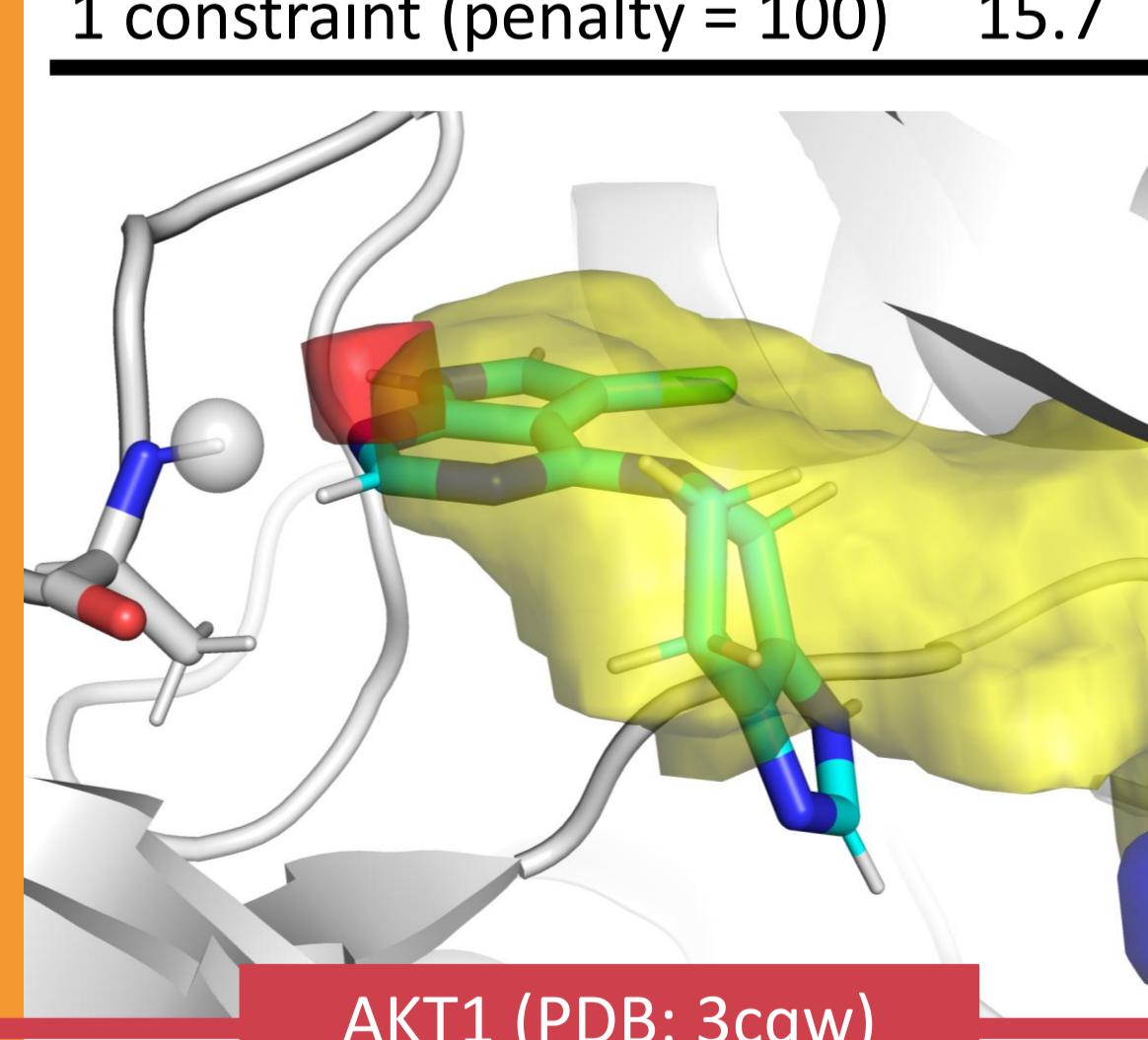
- Supports application of results to GOLD docking
- Previous work has shown improved early enrichment when using hotspot H-bond constraints for VS

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

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).



AKT1 (PDB: 3cqw)

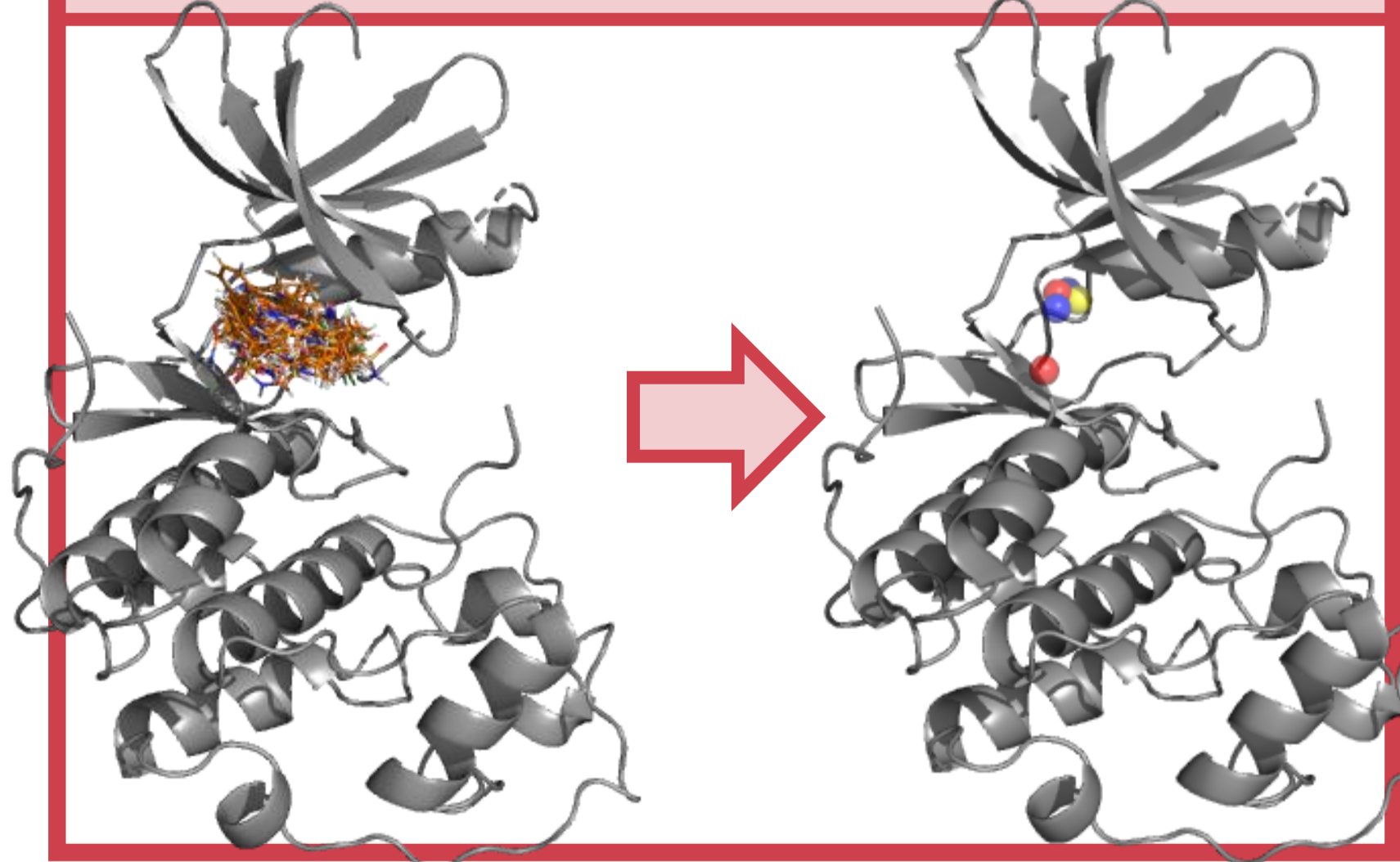
**3 Pharmacophore Modelling**

Pharmacophores can be created from:

- overlaid ligands
- a hotspot result

Generated pharmacophore can be used to:

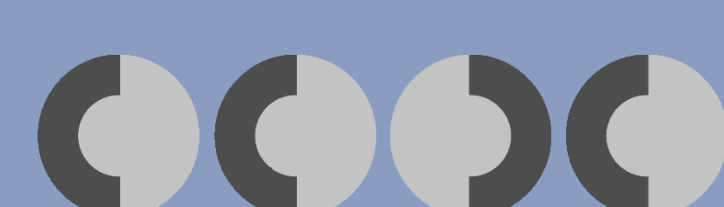
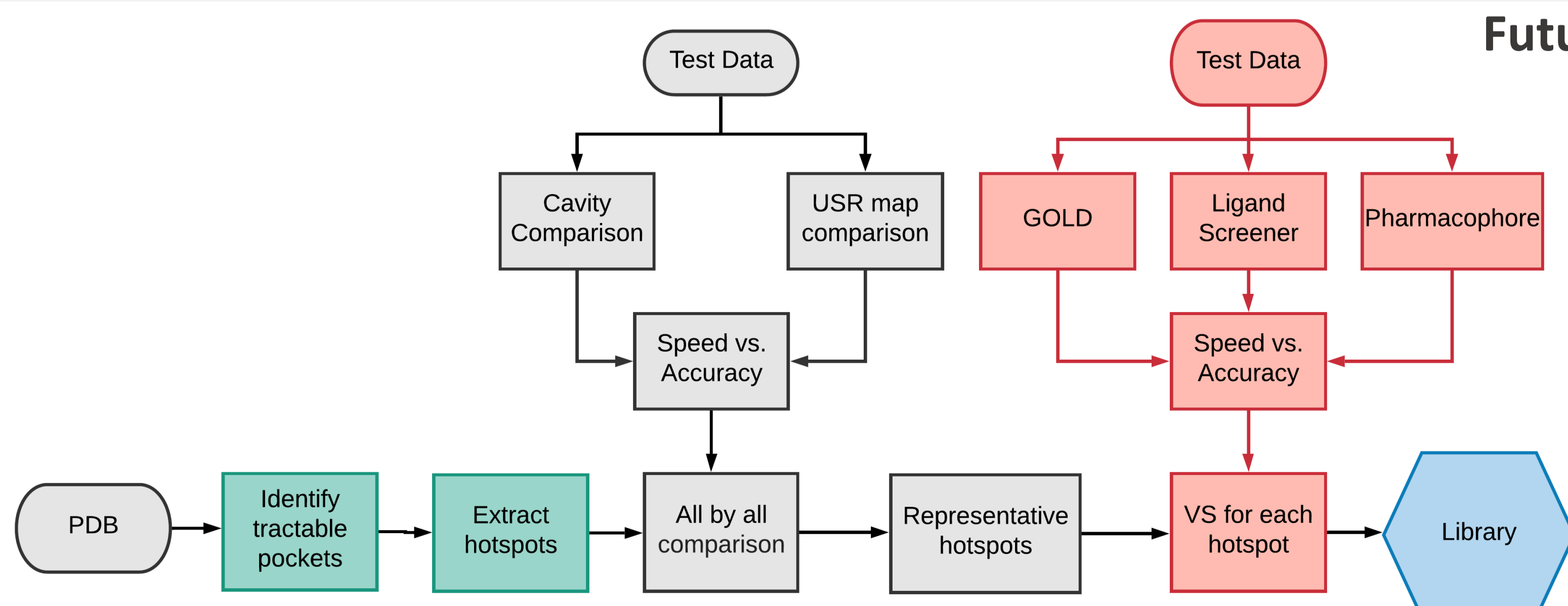
- search CSD & PDB with CSD-CrossMiner
- search ZINC with Pharmit



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



github.com/prcurran



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