Fragment Hotspot Maps

Characterisation of small molecule binding hotspots

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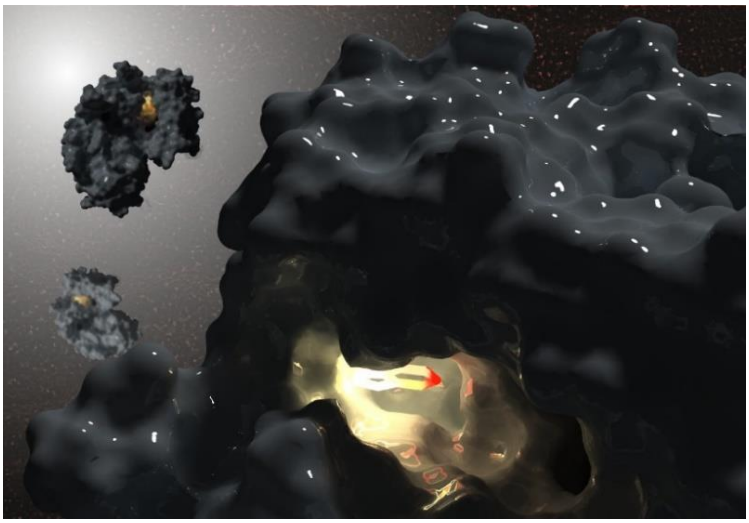
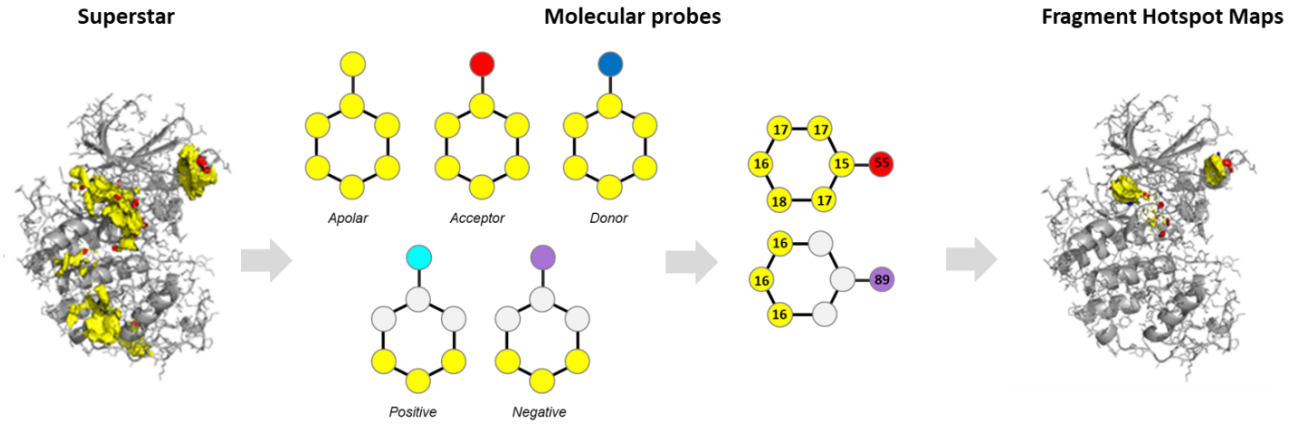
Overview

Fragment hotspot maps predicts the location and key interaction features of small molecule binding "hotspots" and provides valuable insights to guide the hit-to-lead phase of drug development. Built upon the vast quantity of interaction data in the CSD, fragment hotspot maps is able to rapidly detect hotspots from a global search of a protein.



Scientific Methodology

The probability of forming common intermolecular interactions (hydrogen-bonding, charged, apolar) is estimated using Superstar. Superstar fragments a protein and uses interaction libraries, abstracted from the CSD, to predict the likelihood of finding a probe atom at a given point. The following probes are used: “apolar”: Aromatic CH Carbon, “acceptor”: Carbonyl oxygen, “donor”: Uncharged NH Nitrogen, “negative”: Carboxylate, “positive”: Charged NH Nitrogen.



Although SuperStar does have some hydrophobic correction, the local protein environment is not fully considered. Consequently, large regions of the protein are scored highly (figure 1). Hotspots arise from enclosed, hydrophobic pockets that can form directional, polar interactions. Therefore, this method incorporates these physical characteristics into the detection of hotspots. This is done in two ways; weighting the SuperStar Maps by the degree of burial and sampling the weighted maps using hydrophobic molecular probes. This method was validated on a set of 21 fragment-to-lead progression. The median fragment atom scores were in the top 98% of all grid point scores.

Getting Started!

Install CSDS 2018 → Install Python packages: CSD-python-API (>= 2.0.0), Hotspots-API → Install Ghecom → Set env. variable: GHECOM_EXE = ~/src/ghecom