Fred

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Binding site characteristics in structure-base virtual screening: evaluation of current docking tools.

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Objectives

- Scoring Functions
- Brief Fred Background
- Analysis

Several types of docking algorithms exist.

- FlexX – an incremental construction algorithm
  - A rigid base fragment is placed by specific directional interactions. Fragments of the ligand are then added to the base fragment.
- Fred (OpenEye) – a multiconformer algorithm
  - First a conformational analysis is carried out, then all relevant low-energy conformations are placed rigidly in the binding site. Then only the 6 remaining rotational and translational degrees of freedom are left to explore.

Scoring Functions

- Scoring functions play an important role in these algorithms.
  - They help to differentiate between the diverse poses of a single ligand in the binding site.
  - They are needed to estimate binding affinities of different receptor-ligand complexes as well as to rank order the compounds.

Scoring Functions

- Empirical Functions
  - Most important
  - Approximate free energy of binding as weighted sum of terms.
- Force Field Functions
  - Binding affinity estimated by summing up the electrostatic and van der Waals interactions.
- Knowledge-based Functions
  - Derived from statistical analysis of experimentally determined protein-ligand x-ray structures.
  - Omitted from this study.

Scoring Function Classifications

- Soft Scoring Functions
  - Contain no directional (angular) terms and have large distance cutoffs
  - PLP, and Gaussian Shape Fitting (OpenEye)
- Hard Scoring Functions
  - Contain angular terms for hydrogen bond interactions
  - Emphasize directed interactions more strongly
  - ChemScore, FlexX Scoring Function, Force Field Functions
- ScreenScore
  - Developed as a compromise between the hard FlexX function and the softer PLP function

Fred Docking
ligand preparation

- Fred's inputs are a multiconformer library/database of a ligand, a target protein file, and a box defining the binding site of the target.
- The ligand must be preprocessed using another program, either OpenEye's Omega or another conformer generating programs

Fred Docking
Exhaustive Docking

- First step is to generate all the poses. This is done by enumerating the rigid rotations and translations of each conformer in the active site.
  - Translations are systematically generated independent of the ligand shape.
  - Rotations are systematically generated, but are dependent on the ligand shape.

Fred Docking
Exhaustive Docking

- The second step is to filter out any pose that has one or more atom that fall out of a negative image.
  - The negative image is designed to complement the shape of the active site.
  - The shape of the image is carved out of the box defining the active site.
    - Any place where ligand atom clashes with the protein is cut out and any place where a probe atom has a worse Gaussian score than a specified value is cut out.
  - The speed of Fred depends is related to the size of the image, the larger the negative image the longer docking takes.

Fred Docking
Ranking

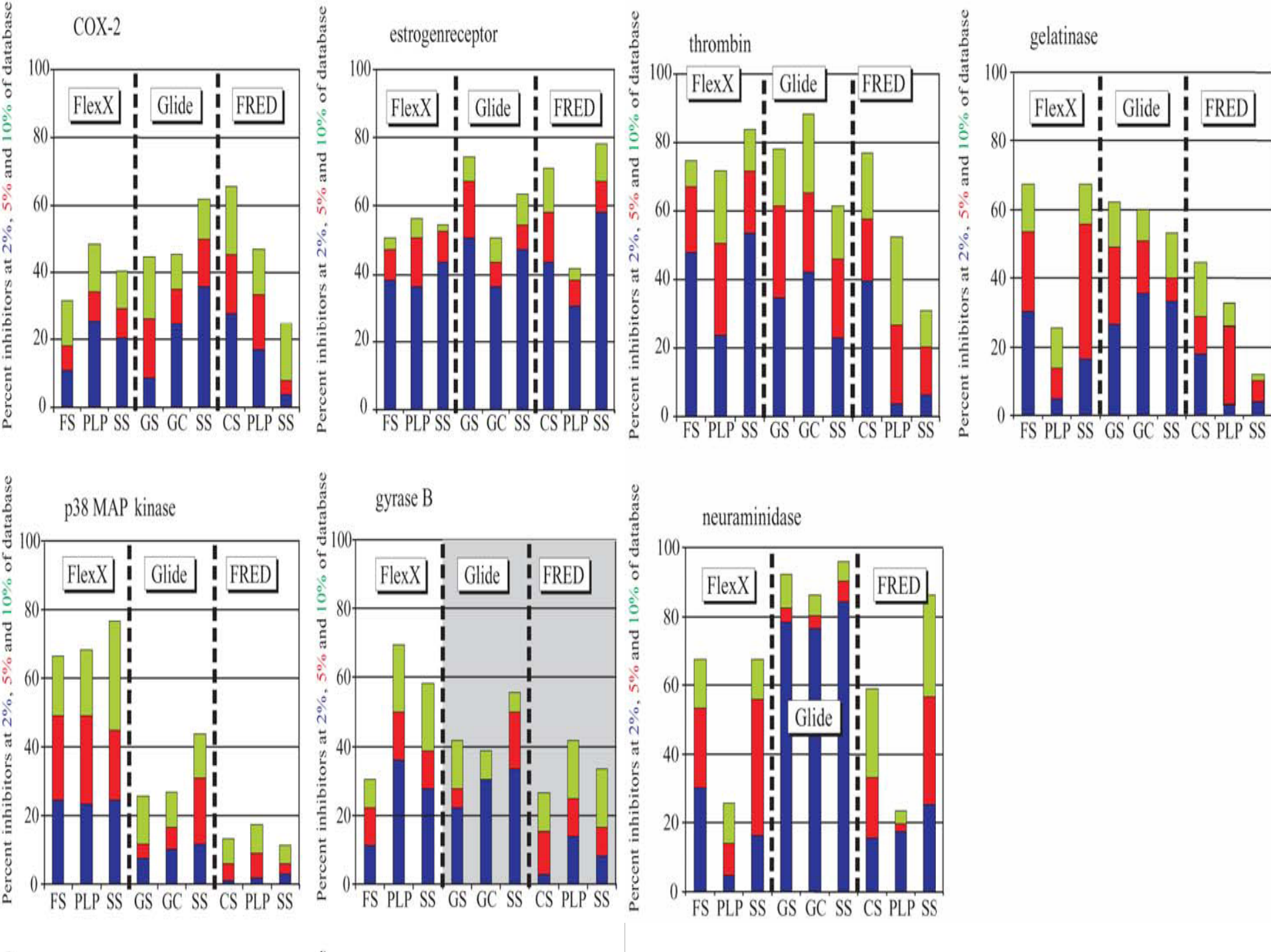
- Screening Process
  - Surviving conformations can then be passed through up to three scoring functions.
  - Optimizations for the scoring functions are optimization of hydroxyl group rotamers, rigid body optimization, torsion optimization, and reduction of number of poses passed on.
  - Available scoring functions in Fred are, ChemScore, PLP, ScreenScore, and Gaussian shape fitting.

Objective function and Scoring Function differentiation

- Objective function
  - Estimates the receptor-ligand interaction energy, used and minimized during the docking process
- Scoring function
  - Function used for rank ordering of ligands
- For Fred, the Gaussian shape function was the objective function

Analysis

- Fred, FlexX and Glide in combination of various scoring functions were evaluated against seven proteins
- Proteins can be divided into three categories
  - Buried, lipophilic binding site
    - Cox-2 and estrogen receptor
  - Intermediate polarity
    - p38 MAP kinase, gyrase B, and thrombin
  - Very polar, solvent-exposed binding site
    - neuraminidase, and gelatinase A


COX-2
estrogenreceptor
thrombin
gelatinase
p38 MAP kinase
gyrase B
neuraminidase
FlexX
Glide
FRED
Percent inhibitors at 2%, 5% and 10% of database
0
20
40
60
80
100
FS PLP SS GS GC SS CS PLP SS

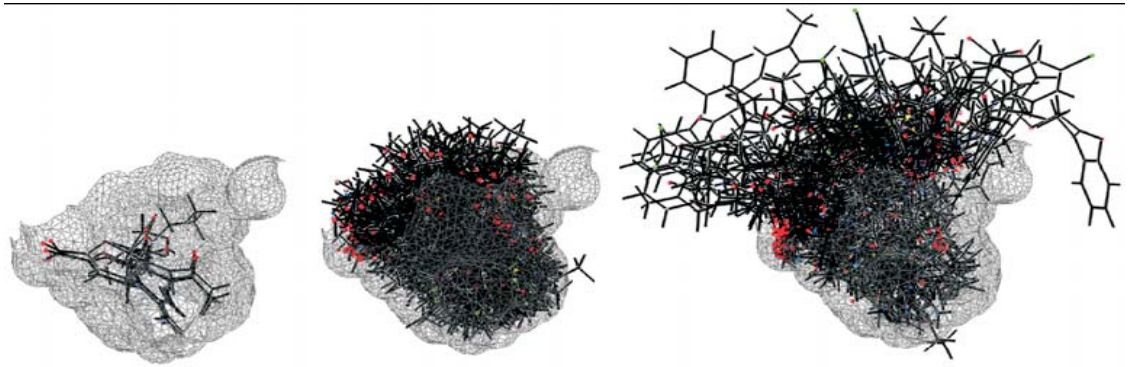
Analysis

- Cox-2 and estrogen receptor
  - Fred along with Gaussian shape fitting alone can lead to satisfactory enrichment of known inhibitors.
- p38 MAP kinase, gyrase B, thrombin, gelatinase A, and neuraminidase
  - Since these are more solvent exposed, pure shape fitting often leads to the selection of the wrong binding mode.
  - Good performance is only obtained if all the poses generated in the shape fitting are passed to the screening process with a different scoring function.

Binding Site Definition

- Success of the docking calculations depend on the specification of the binding site.
- Fred – the binding site is defined by a rectangular box oriented parallel to the main axes of the coordinate system.
- FlexX – You have to define a set of atoms that are part of the binding site.

- The neuraminidase binding site is relatively shallow and solvent exposed.
  - The boxes used by Fred act as filters to remove poses whose center of mass extends into the solvent region compared to the incremental construction of FlexX that allows solutions to grow into the solvent exposed regions.
- p38 is the opposite extreme. Its binding site is relatively narrow
  - The Fred bounding box cannot trim the solution space significantly and thus there is no easy way to orient the box to enclose only the relevant region of the cavity.



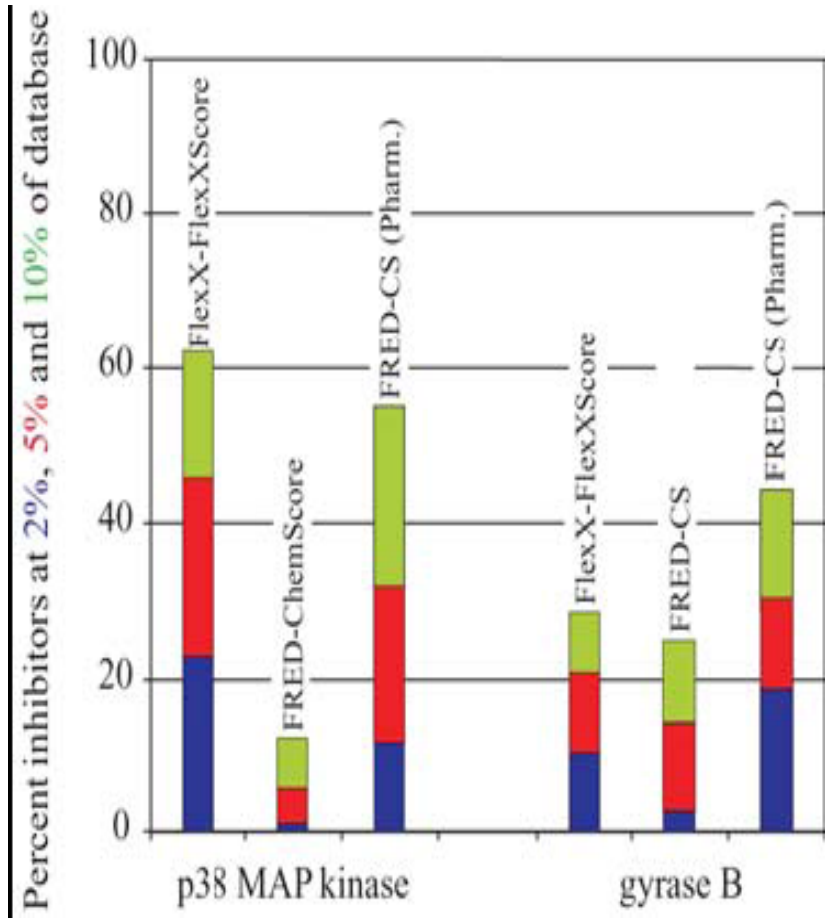
Pharmacophore Site

- “a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity” – Peter Gund

(Gund. *Prog. Mol. Subcell. Biol.* 1977, 5: pp 117–143)

Docking under pharmacophore constraints

- Useful for the inclusion of hydrogen bonding constraints in Fred.
- For p38 and gyrase B, the selection of a pharmacophore site greatly improved the results.



Wrap up

- Using a soft objective function, followed by optimization with restrictive repulsive and angular terms proved to be a good general strategy for Fred.
- Fred in combination of ChemScore for the scoring function was found to be a good general method for structure-based virtual screening.
- FlexX and Fred were found to complement each other well.
  - Where Fred was suboptimal, FlexX has specific strengths.

Reference

- Binding site characteristics in structure-based virtual screening, evaluation of current docking tools: Schulz-Gasch, T., and Stahl, M., J. Mol. Model. 2003, 9:47-57.

- http://www.eyesopen.com/products/applications/fred.html