The Use of Generalised Protein-Ligand Interaction Motifs in Docking

Suzanne Brewerton and Marcel Verdonk
Astex Therapeutics Ltd., 436 Cambridge Science Park, Milton Road, Cambridge, CB4 0QA, UK

BACKGROUND

The interactions that are formed between a ligand and the target receptor binding site can be represented as a fingerprint. Mason et al. use pharmacophoric fingerprints to describe complementary site-points to a protein binding site [1,2]. More recent approaches have focussed on reusing the wealth of data available in the structural databases to generate interaction fingerprints to describe the interactions made in known protein-ligand complexes at the protein binding site. The individual fingerprints have been used to visualise and analyse protein-ligand complexes [3] and also have been combined to form fingerprint profiles representing groups of complexes which can be used to inform rescoring approaches in docking and virtual screening [4-6].

AIM

To represent the interaction information derived from protein-fragment crystal structures resulting from Astex initial fragment screening as a group of ‘motifs’ and to incorporate these into the GOLD docking software to predict binding modes of larger ‘drug-like’ molecules and to enrich virtual screening databases for active molecules.

ASTEX MOTIFS

[Diagram showing different motifs]

VIRTUAL SCREENING

- For each target databases of ‘inactives’ were generated.
  - Inactives were within a minimum distance of actives. Distance is described by the following equation:
    \[ \text{dist} = \sqrt{\left(\text{HAC} + \text{HAC}^2\right) + \left(\text{MDL} + \text{MDL}^2\right) + \left(\text{HAC} + \text{MDL}\right)} \]
  - Inactives were also chosen to be aromatic.
  - 99 inactives were chosen per active.

CONCLUSIONS

Several factors make the docking performed here a difficult experiment. The actives chosen were diverse, a single target (i.e. non-native) structure was chosen for docking, all charge states and tautomers were generated and docked for each ligand, the database of ‘inactives’ chosen was focussed around the actives. However docking success was greatly improved by using Astex Motif Restraints to guide the docking and rank the compounds.

REFERENCES

9. For advice and guidance Gianni Chessa, Valerio Bertini, Chris Murray. Data provided by Structural Biology, Medicinal Chemistry and Assay Biology Groups at Astex.

GOLD

As part of the Pyramid™ process Astex applies computational chemistry and informatics technology to perform in silico docking on a large scale, to support its structure-based design approaches. A collaboration with the Cambridge Crystallographic Data Centre (CCDC) allows access to the source code for the GOLD docking software [9].

TABLE 2 : Docking success rates where success is the top-ranked docking pose within 2Å of the native target-ligand complex.

<table>
<thead>
<tr>
<th>Target</th>
<th>Baseline</th>
<th>Astex Motif Restraint</th>
<th>GOLD H-Bond Constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC Kinase</td>
<td>29.7 (2.4)</td>
<td>70.8 (1.5)</td>
<td>79.0 (1.0)</td>
</tr>
<tr>
<td>CDK2</td>
<td>50.0 (1.6)</td>
<td>78.7 (2.5)</td>
<td>64.9 (1.6)</td>
</tr>
<tr>
<td>FGFR</td>
<td>28.0 (4.0)</td>
<td>52.0 (2.3)</td>
<td>44.0 (2.3)</td>
</tr>
</tbody>
</table>