Finding ligands in electron-density maps

Tom Terwilliger
Los Alamos National Laboratory
Automated fitting of flexible ligands

A difference electron-density map

...and a flexible ligand to be fitted

2-Aryl-2,2-Difluoroacetamide FKBP12
Ligand generation in PHENIX

1. Parse SMILES
2. Topology
   - Generate 3D structure (cctbx & AM1)
3. Read Mol2D
4. Read Mol3D
5. Read PDB
   - Coordinates
   - Refinement Restraints

Electronic Ligand Builder and Optimization Workbench
Auto-generated ligands

Alanine

ATP

Strychnine

Lipitor
Fitting a flexible ligand (following ideas of Klei)

Where is the ligand?
Choose the largest region of contiguous density

What are rotatable bonds? Analyze ligand for allowed rotations

What is the orientation of the ligand? Fit core of ligand

What is the conformation of the ligand? Trace the ligand from core
Fitting Fo-Fc density at resolutions from 0.95 Å to 4.5 Å

FAD (0.95 Å, 1N1P)

8-(2,5-DIMETHOXY-BENZYL)-2-FLUORO-9-PENT-9H-PURIN-6-YLAMINE (2.2 Å 1UYI)
Fitting Fo-Fc density at resolutions from 0.95 Å to 4.5 Å

ATP (3 Å, 1NBM)

(1-(4-IODOBENZOYL)-5-METHOXY-2-METHYL-INDOLE-3-ACETIC ACID (4.5 Å, 1PGF)

(Ligand conformation from 1PGF in green)
Fitting ligand density in the PDB

Ligand in PDB (1JUT, 2.8 Å)

Fo-Fc density map

Fit ligand (cc= 0.73)

Compare with original (rmsd=0.7 Å)
### Fitting ligand density in the PDB

Based on 6209 PDB entries with 9319 ligands

<table>
<thead>
<tr>
<th></th>
<th>Ligands in PDB fitting Fo-Fc map with CC ≥ 0.75</th>
<th>All Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ligands</td>
<td>6590</td>
<td>9319</td>
</tr>
<tr>
<td>Mean CC of ligand in PDB</td>
<td>0.85</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean CC of fitted ligand (unrefined)</td>
<td>0.76</td>
<td>0.72</td>
</tr>
<tr>
<td>Rmsd ≤ 1.0 Å</td>
<td>2715 (41%)</td>
<td>3004 (32%)</td>
</tr>
<tr>
<td>Rmsd ≤ 2.0 Å</td>
<td>4666 (71%)</td>
<td>5421 (58%)</td>
</tr>
<tr>
<td>Rmsd &gt; 10 Å</td>
<td>310 (5%)</td>
<td>1417 (15%)</td>
</tr>
</tbody>
</table>
phenix.find_all_ligands – 1J4R (3 molecules of FKB12)

FKB12

Peptide decoy

Site 1

Site 2

Site 3
The PHENIX Project

An NIH/NIGMS funded Program Project

Lawrence Berkeley Laboratory

Paul Adams, Ralf Grosse-Kunstleve, Pavel Afonine, Nat Echols, Nigel Moriarty, Jeff Headd, Nicholas Sauter, Peter Zwart

Los Alamos National Laboratory

Tom Terwilliger, Li-Wei Hung

Cambridge University

Randy Read, Airlie McCoy, Gabor Bunkoczi, Rob Oeffner

Duke University

Jane & David Richardson, Vincent Chen, Chris Williams, Bryan Arendall, Laura Murray