Model-building with PHENIX and Rosetta

Duke University
Jan 11, 2011

Tom Terwilliger (Los Alamos National Laboratory)
Randy Read (Cambridge University), David Baker,
Frank DiMaio (University of Washington)
Goal: interpret patterns of electron density in a map as a protein chain
The problem: the density may be very poor to start with.
## Complementarity of PHENIX and Rosetta model-building

*(Randy Read, David Baker, Frank DiMaio)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crystallographic model-building (PHENIX)</th>
<th>Structure-modeling (Rosetta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimization</td>
<td>Interpretation of patterns of density</td>
<td>Creating physically plausible models</td>
</tr>
<tr>
<td>Model-building approach</td>
<td>Density search for regular secondary structure</td>
<td>Ab-initio modeling or homology modeling</td>
</tr>
<tr>
<td>Fragment libraries</td>
<td>3-residue fragment library</td>
<td>3- and 9-residue libraries</td>
</tr>
<tr>
<td>Model-building target</td>
<td>Fit to density</td>
<td>Rosetta force field with density term</td>
</tr>
<tr>
<td>Refinement target</td>
<td>Structure-factor likelihood refinement target</td>
<td>Rosetta force field with density term</td>
</tr>
</tbody>
</table>
Combining structure-modeling with crystallographic model-building

20 templates for 1XVQ from PDB (optimally superimposed)
Molecular replacement using distant homology models with PHENIX and Rosetta (phenix.mr_rosetta)

Setup and model preparation

- Identify search models with homology server (http://toolkit.tuebingen.mpg.de/hhpred)
- Sequence-specific Rosetta fragments files from Robetta server (http://robetta.bakerlab.org/fragmentsubmit.jsp)
- Parameters file listing sequence, homology file, fragments files
- Automated download and editing of search models and creation of alignment files

Files:
- target.hhr
- fragments_3.gz
- fragments_9.gz
- target.eff
- target.ali
- target_mr.pdb
Molecular replacement using distant homology models with PHENIX and Rosetta (phenix.mr_rosetta)

Molecular replacement and model-building

- Molecular replacement (Phaser)
- Refine (phenix.refine) to create new map

Build 20-2000 models with Rosetta (including density term in Rosetta energy)

Pick models with highest Phaser LLG from top 10% of Rosetta models

Refine and autobuild (phenix.autobuild) starting from top rosetta models

Iterate until convergence

- target_1.pdb
- refine_map_coeffs.mtz
- target_rosetta_0001.pdb
- target_rosetta_best.pdb
- target_autobuild.pdb
Structure determination of **cab55348** (using template supplied by user)

1.9 Å, 28% sequence identity (AutoMR alone fails with R/Rfree=0.47/0.53)

MR model: blue, Final model: green
MR model: blue
Map CC: 0.16
Overall changes and map correlations during mr_rosetta,

Best-scoring Rosetta model: pink
Map CC: 0.40
Overall changes and map correlations during mr_rosetta,
Best-scoring Rosetta model: pink, AutoBuild model: yellow

Map CC: 0.40

Overall changes and map correlations during mr_rosetta,
AutoBuild model: yellow, Cycle-2 Best-scoring Rosetta model: grey

Map CC: 0.74
Map CC: 0.59

Overall changes and map correlations during mr_rosetta,
AutoBuild model cycle 1: yellow, AutoBuild model cycle 2: blue

Map CC: 0.74

Map CC: 0.78

Overall changes and map correlations during mr_rosetta,
AutoBuild model cycle 2: blue Final model: green

Map CC: 0.78 R/Rfree = 0.26/0.31

Overall changes and map correlations during mr_rosetta,
Sample Rosetta models in cycles 1 and 2,
Evaluating Rosetta models with Rosetta score and LLG
Sample Rosetta models in cycles 1 and 2.
MR model: blue

Final model: pink

Map from refined MR model

Rebuilding in a poor section of the starting model
MR model: blue  
Final model: pink  
Rosetta models cycle 1: green

Map from refined MR model

Rebuilding in a poor section of the starting model
MR model: blue  
Final model: pink  

Best-scoring Rosetta model cycle 1: yellow  

Map from refined MR model  

Rebuilding in a poor section of the starting model
AutoBuild Map from cycle 1

Rebuilding in a poor section of the starting model
MR model: blue
Final model: pink
Rosetta models cycle 2: yellow

Rebuilding in a poor section of the starting model
AutoBuild model cycle 2

Map CC: 0.78    R/Rfree = 0.26/0.31

Rebuilding in a poor section of the starting model
The PHENIX 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

An NIH/NIGMS funded Program Project