Model Refinement

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Refinement tools in *Phenix*

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Reading

D RESEARCH PAPERS

Acta Cryst. (2018). D**74**, 531-544 https://doi.org/10.1107/S2059798318006551 Cited by 672

Part of CCP-EM Spring Symposium 2017



Real-space refinement in *PHENIX* for cryo-EM and crystallography

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Structure refinement in a nutshell

Initial (poor) model

Refinement

Improved (refined) model

Structure refinement: black box?



Structure refinement: black box?

• Does it always work?

 Is it always as easy as giving a 'black box' input files and hoping it produces a good model?

Structure refinement: black box?

- Does it always work?
- Is it always as easy as giving a 'black box' input files an hoping it produces a good model?
 - No. Because:
 - Parametrizing refinement is too complex
 - Default settings suit most common scenario

Structure refinement: lots of jargon

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Structure refinement: default doesn't cover all!

 Default refinement is parameterized and optimized to work with typical model and data

- Low-, high-, ultra-low-, ultra-high- resolution data need special attention
- Incomplete models need special attention
- Specialized fine-tuning of complete models may be needed
- AlphaFold predicted models may need special treatement

Structure refinement: decision-making variables

- Crystal
 - Mosaicity
 - Twining
 - Solvent content
 - Symmetry

- Data
 - Resolution
 - Errors
 - Completeness
 - Processing

- Model
 - Stage
 - Source
 - Parameterization
 - Fit to data

Refinement in a nutshell (II)



Refinement – optimization process of fitting model parameters to experimental data

Restraints in refinement

$$T = T_{\text{DATA}}(F_{\text{OBS}}, F_{\text{MODEL}}) + wT_{\text{RESTRAINTS}}$$

 $T_{RESTRAINTS} = T_{BOND} + T_{ANGLE} + T_{DIHEDRAL} + T_{PLANARITY} + T_{NONBONDED} + T_{CHIRALITY}$

 Restraints (extra information) are needed because data are not perfect (errors, resolution, etc)







Structure refinement: decision-making variables

- Crystal
 - Mosaicity
 - Twining
 - Solvent content
 - Symmetry

- Data
 - Resolution
 - Errors
 - Completeness
 - Processing

- Model
 - Stage
 - Parameterization
 - Fit to data

• Weight (w) in

$$T = T_{\text{DATA}}(F_{\text{OBS}}, F_{\text{MODEL}}) + wT_{\text{RESTRAINTS}}$$

is additional complication

Bottom line

• Refinement is hard (read impractical) to automate fully

• User involvement is needed

How you know...

- ... refinement worked ?
- ... you did it correctly ?
- ... the model you got is good enough to publish ?

Validation





Validation = checking model, data and model-to-data fit are all make sense and obey to prior expectations

Summary

- Refinement is highly automated but user decision-making is almost always needed
- Knowing about model and data guides decision-making
- Use model parameterization that is appropriate for the data quality and stage of refinement
- Use optimization method that is appropriate for the refinement stage
- Do validation throughout the process of structure solution

Feedback, asking for help, etc...

• Feedback, questions

phenixbb@phenix-online.org bugs@phenix-online.org help@phenix-online.org

- Reporting a problem, bug or asking for help:
 - We can't help you if you don't help us to understand your problem
 - Send us:
 - 1) PHENIX version;
 - 2) Command and parameters used;
 - 3) Input and output files;
 - 4) Clearly explain the problem.

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Project

Lawrence Berkeley Laboratory

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Los Alamos National Laboratory New Mexico Consortium



Jane & David Richardson, Christopher Williams, Vincent Chen





Liebschner D, *et al.*, Macromolecular structure determination using X-rays, neutrons and electrons: recent developments in *Phenix*. Acta Cryst. 2019 **D75**:861–877