Secondary structure restraints in low-resolution refinement

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Restraints and data resolution

- **Refinement target -** a weighted sum of experimental data (E_{data}) and *a priori* chemical knowledge terms (restraints; $E_{restraints}$): $E_{total} = w * E_{data} + E_{restraints}$

- **Choice of restraints** depends on data quality (resolution, fro example):
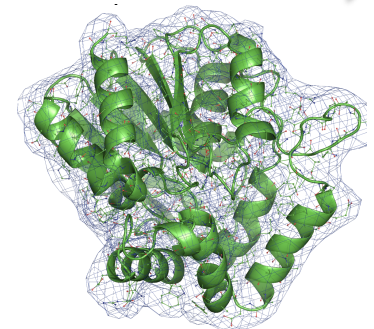
<1Å: unrestrained refinement
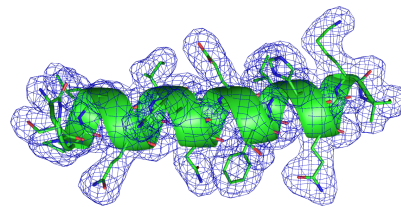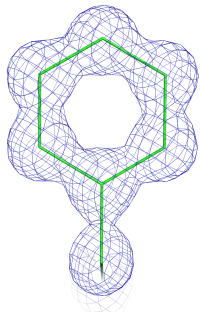
>3Å: more extra restraints needed

$$E_{restraints} = ... + E_{Ramachandran} + E_{NCS} + E_{ReferenceModel} + E_{SecondaryStructure} + ...$$

High   Resolution   **Low**

1-3Å: _**standard**_ restraints are necessary

$$E_{restraints} = E_{bond} + E_{angle} + E_{dihedral} + E_{nonbonded} + E_{planarity} + E_{chirality}$$
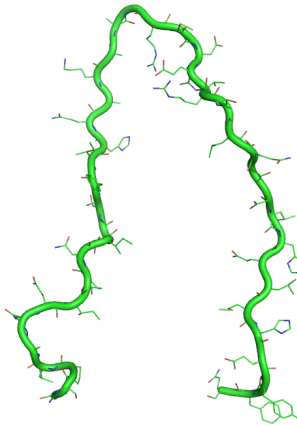
Illustration of insufficiency of standard restraints
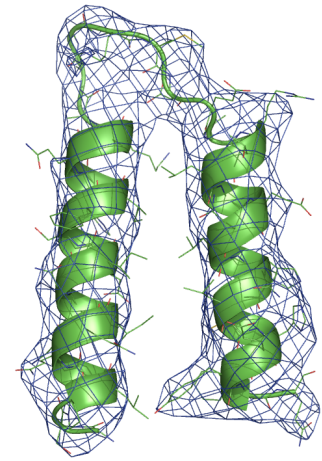
INPUT

Low resolution map (6Å)
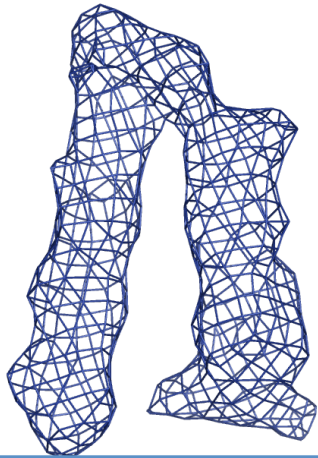
Poor initial model

Knowledge about secondary structure

2 alpha helices:
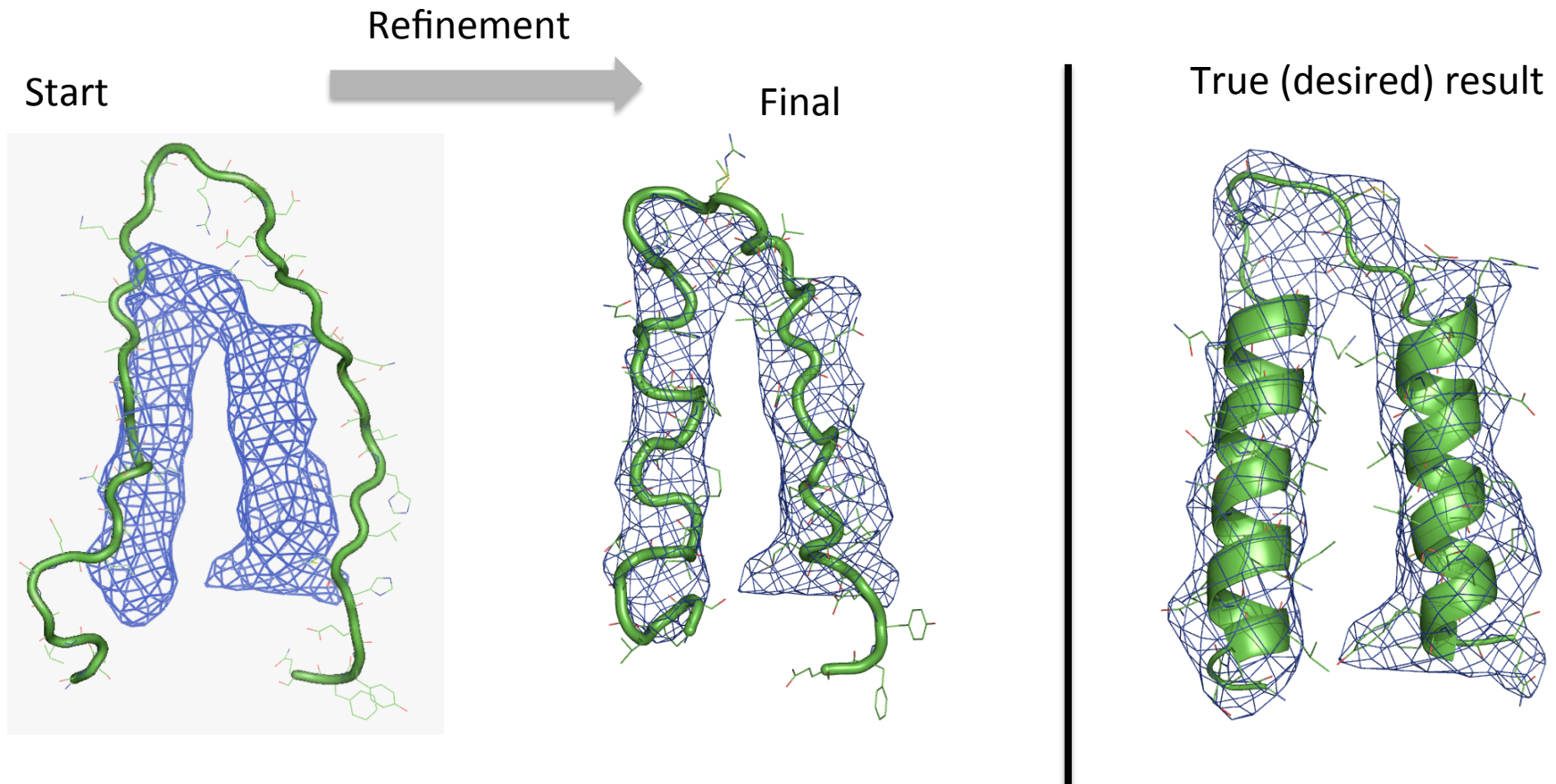resseq 2:19
resseq 27:42

DESIRED OUTPUT

- Best density fit
- Correct secondary structure (SS)

Illustration of insufficiency of standard restraints

- Refinement with standard restraints fits the model into map well but secondary structure is poor
  - This is because map is not detailed enough and no a priori knowledge was introduced into refinement

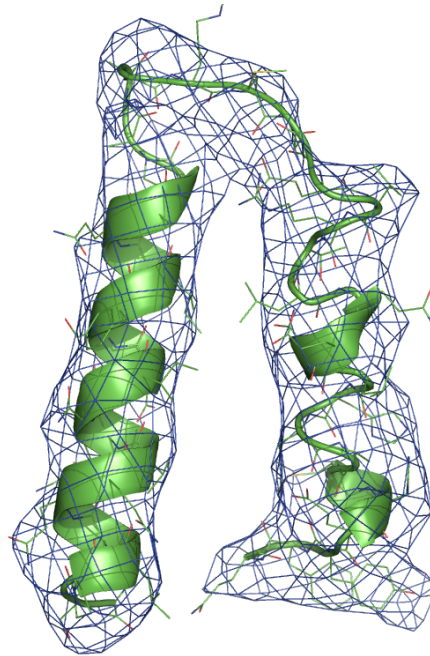# Complimenting standard restraints with SS restraints may not be sufficient

- Refined model with SS restraints (Final):
  - Model fits map well
  - Some model parts fold into expected secondary structure
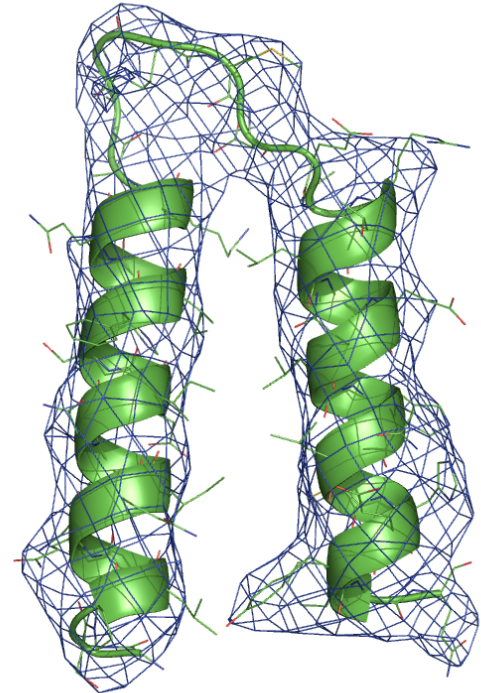 - Some model parts are trapped into local minima and have poor geometry
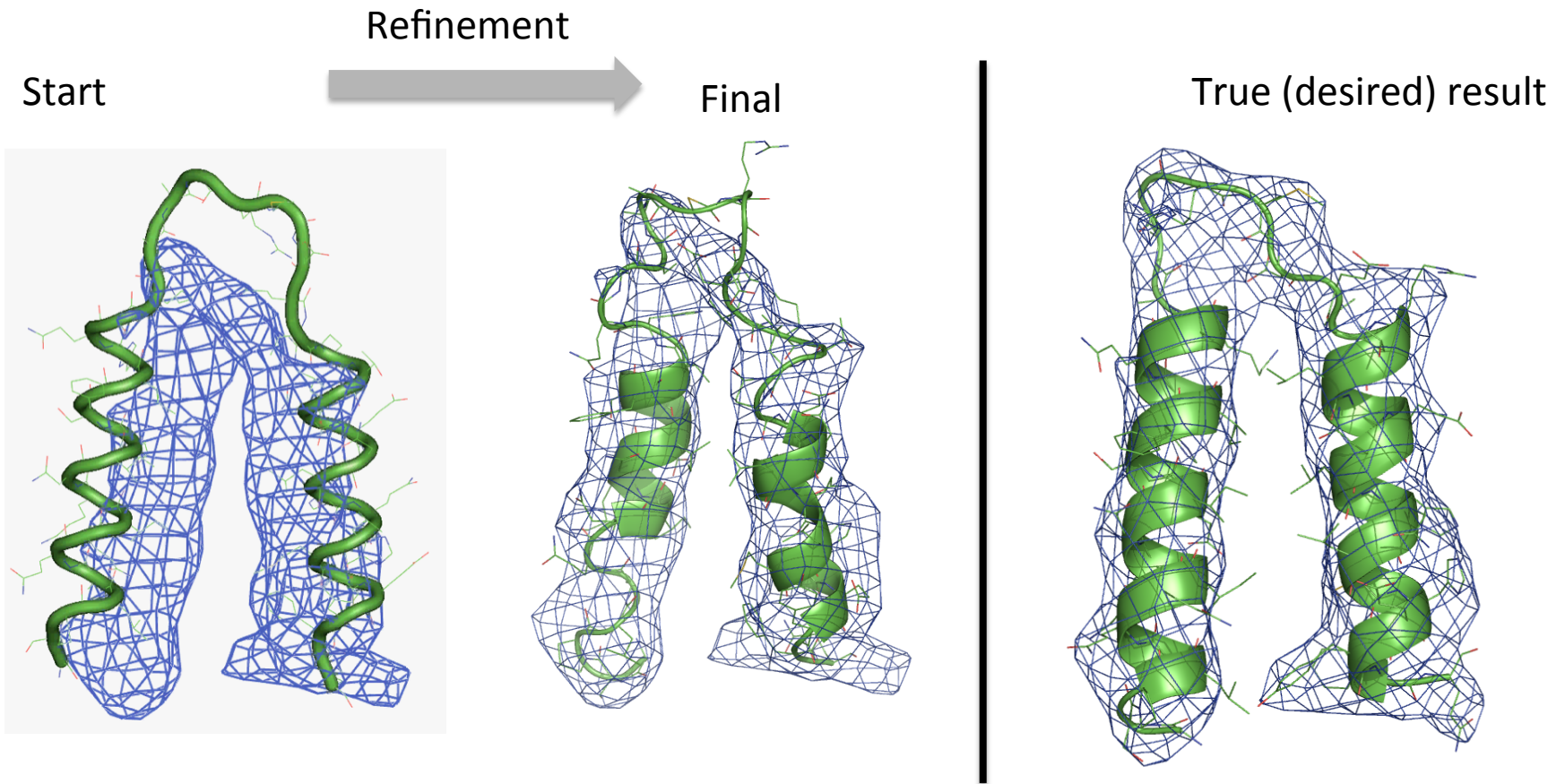
- Refined good starting model without SS restraints (Final):
    - Model fits map well
    - Some model parts fold into expected secondary structure
   - Some model parts are distorted due to low-res and lack of SS restraints

Refinement

Start   Final   True (desired) result

Solutions in Phenix

Improving use of SS restraints by idealizing initial model

- Generate idealized SS fragments (from sequence or other model)
- Replace existing (poor) parts of model with idealized ones
- Close gaps in main chain
- Use ideal SS as reference model restraints in torsion angle space
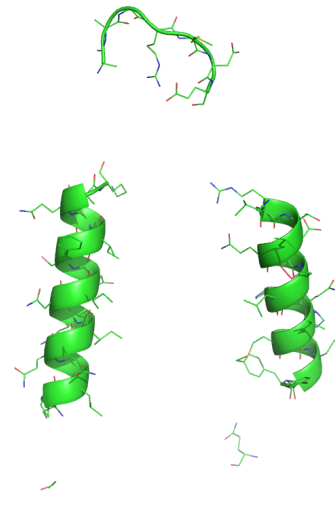
- Example:
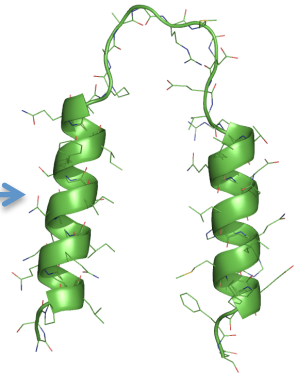
2 alpha helices:
resseq 2:19
resseq 27:42
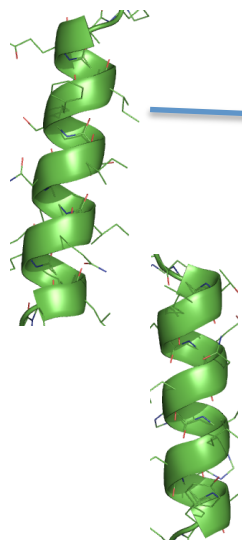
Poor starting model
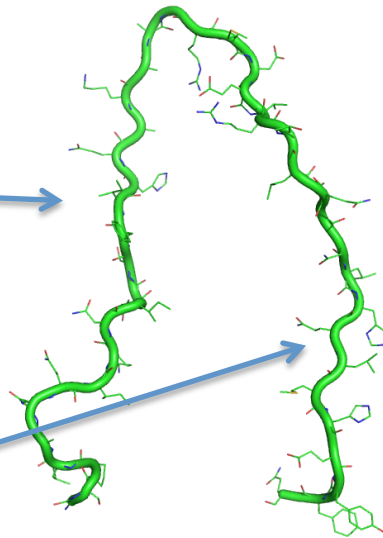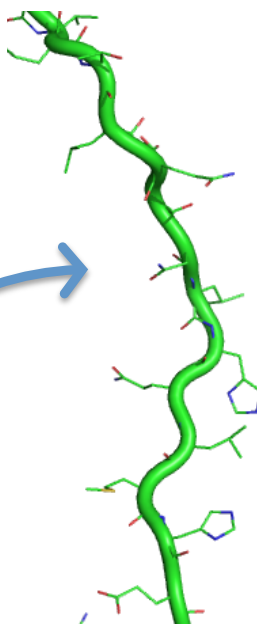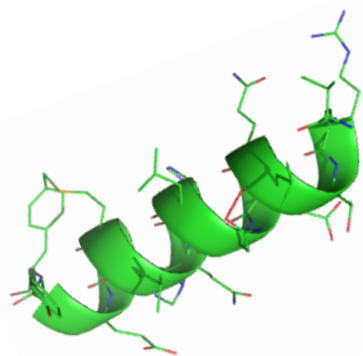
SS substituted

Good starting model

Improving use of SS restraints by idealizing initial model
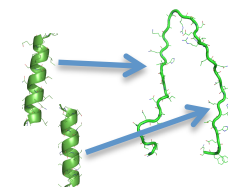
Ideal SS element

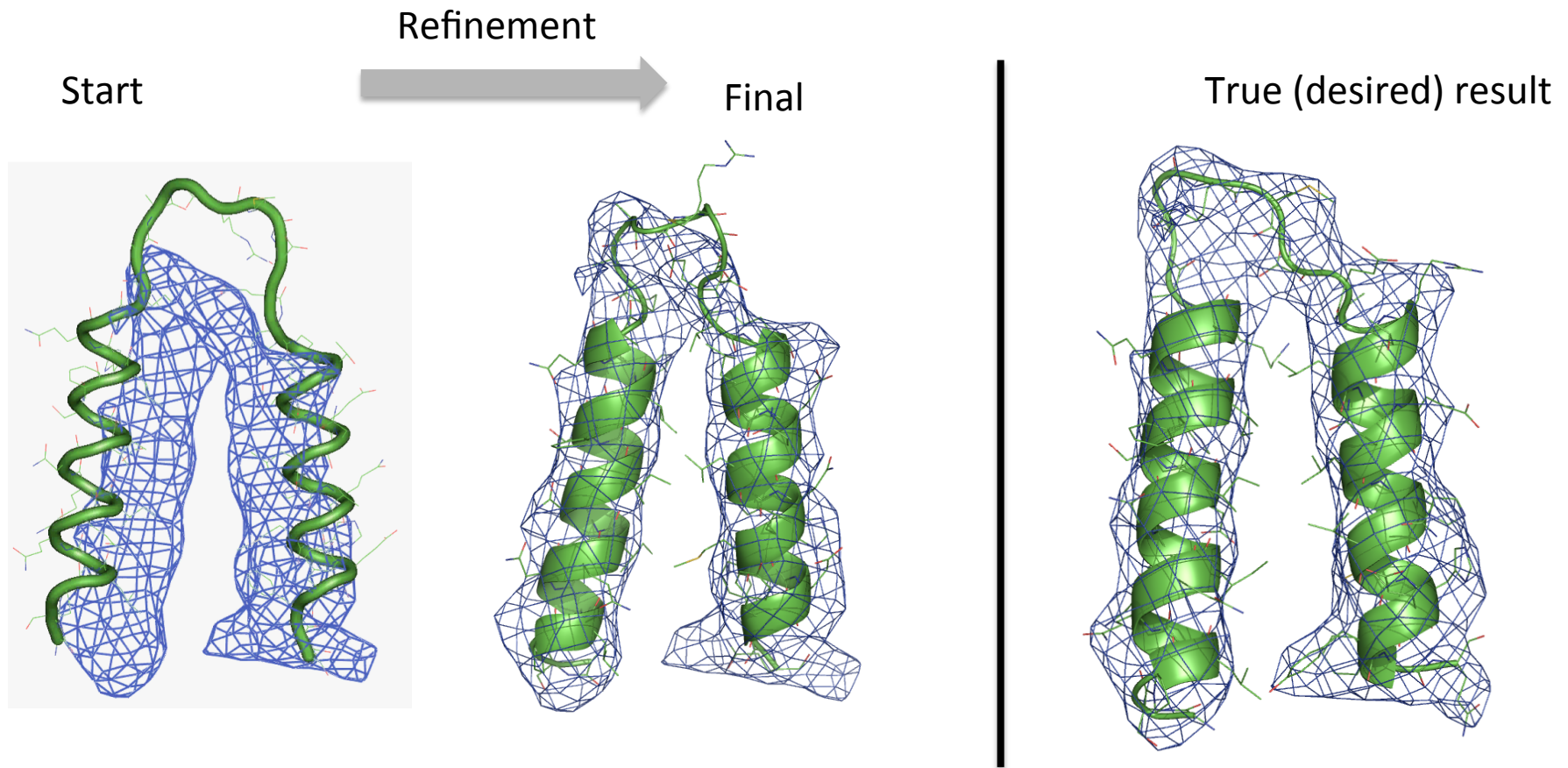Model fragment

Aligned element

Rigid body alignment onto model fragment

Replacement of model fragment with idealized SS fragment

Result: refinement of good starting model with SS restraints

- Refined good starting model with SS restraints (Final):
  - Model fits map well
  - Model possess expected SS

Refinement

Start

Final

True (desired) result

Implementation in Phenix

- Will be available soon in:
  - phenix.refine
  - phenix.real_space_refine
  - phenix.geometry_minimization
  - Stand-alone tool