Phenix

Improving molecular replacement with morphing

NECAT Workshop on Advances in Moderate to Low Resolution Phasing and Refinement
Sept. 19, 2011, Rockefeller University

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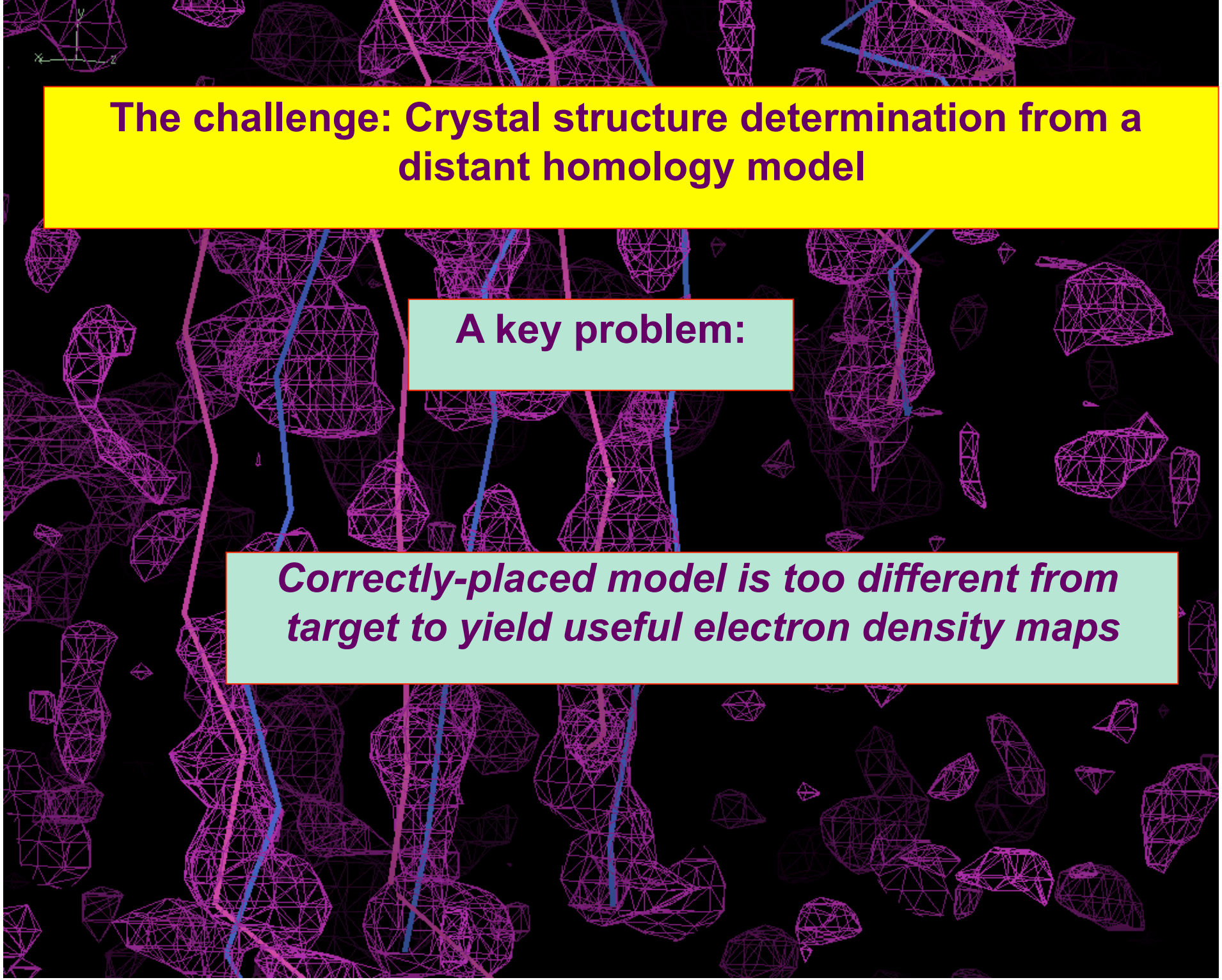
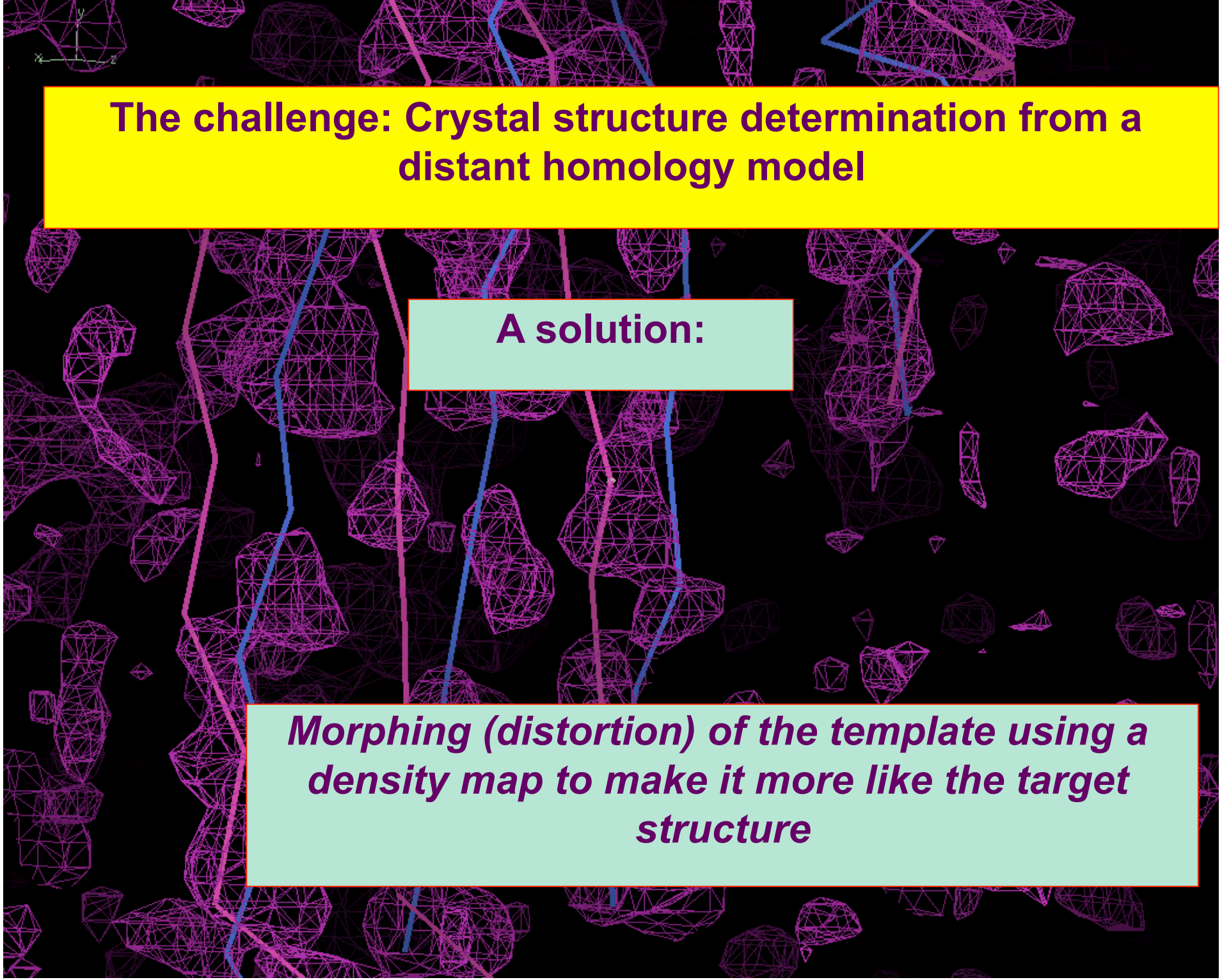

The challenge: Crystal structure determination from a distant homology model
A key problem:
Correctly-placed model is too different from target to yield useful electron density maps

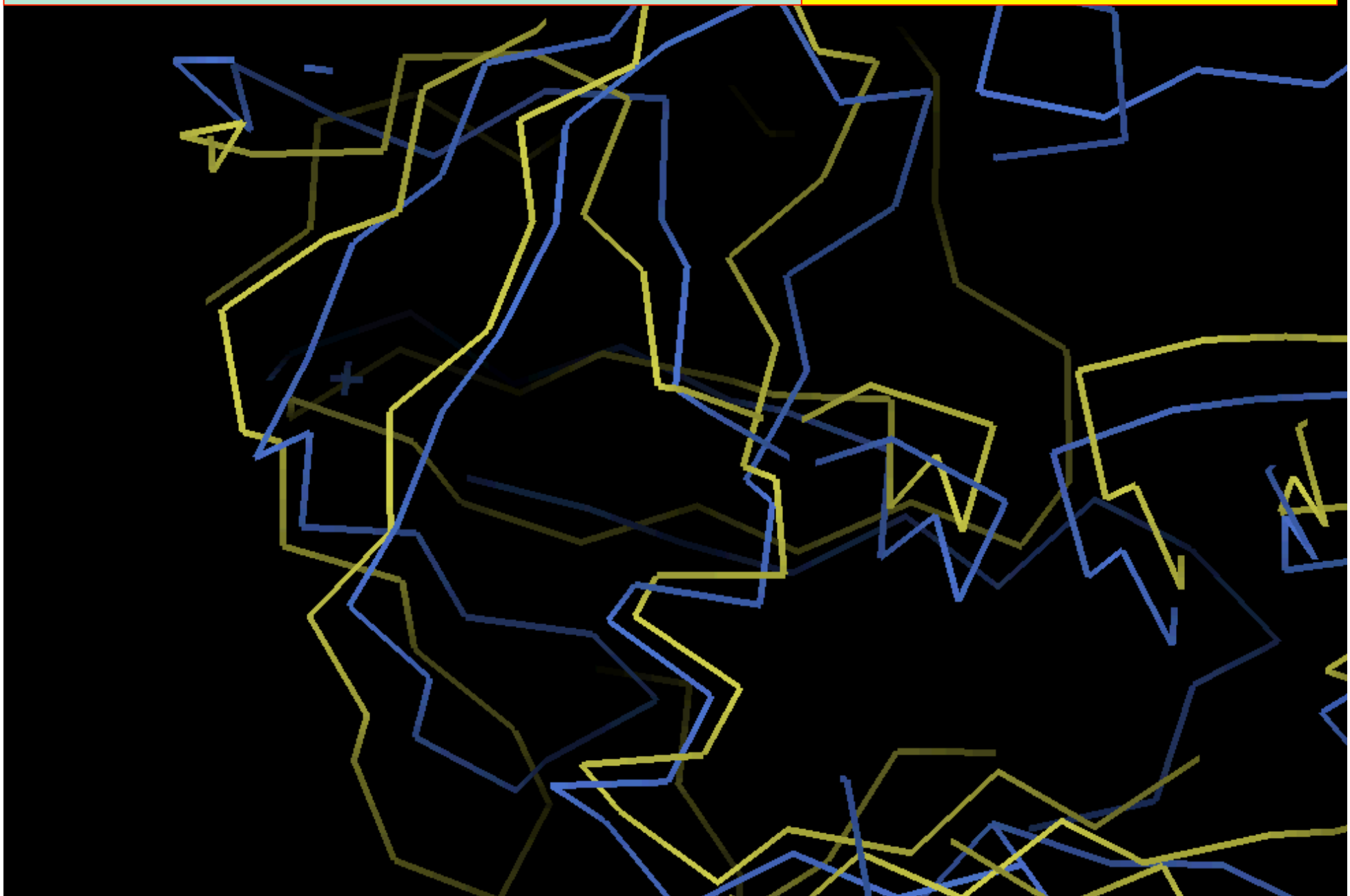

The challenge: Crystal structure determination from a distant homology model
A solution:
Morphing (distortion) of the template using a density map to make it more like the target structure

Related structures often have high local similarity

ag9603; approximate NMR model as template in pink

Related structures often have high local similarity

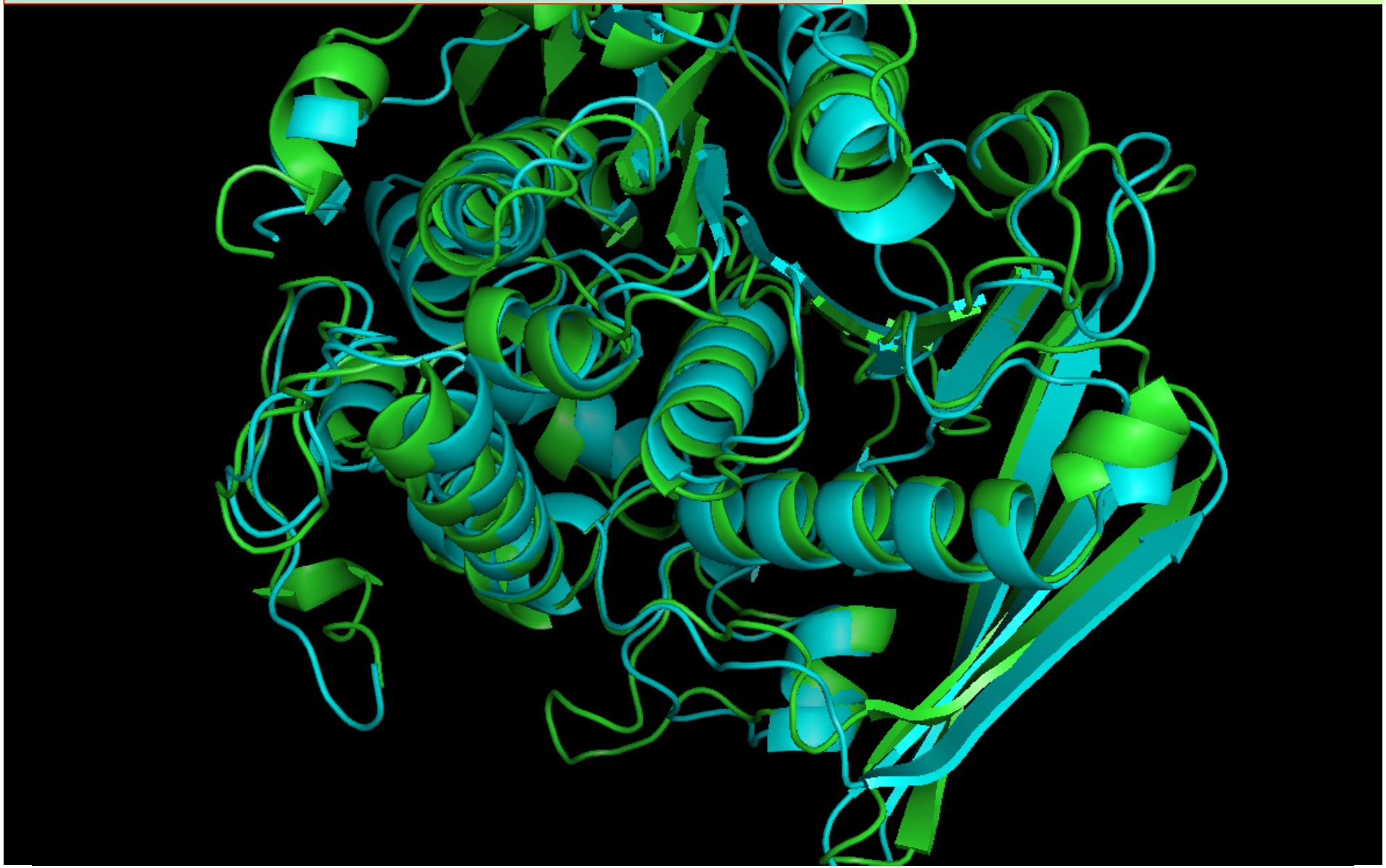
***XMRV PR*, 30% identity template (2hs1) in blue**



Related structures often have high local similarity

cab55348

32% identical template (Cip2) in blue



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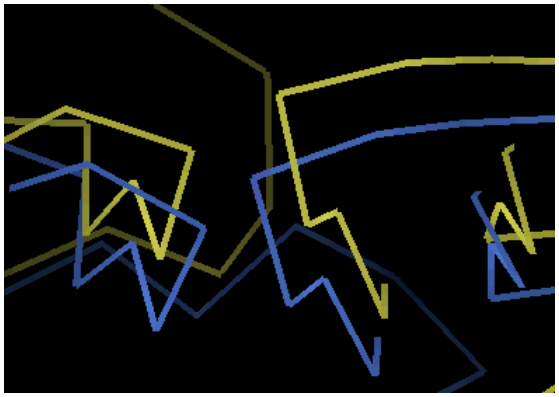
Taking advantage of local similarities of homologous structures



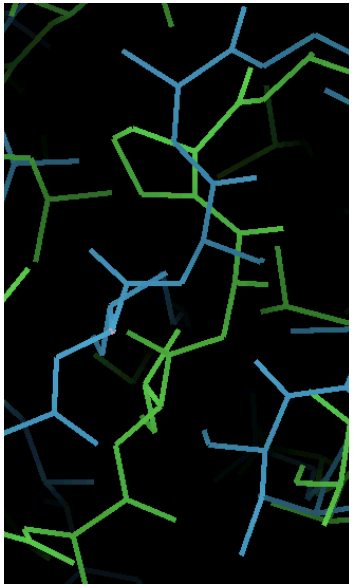
Rigid-body refinement of segments

Fragment searches (FFFEAR, ESSENS)

DEN or jelly-body refinement

Rosetta modeling

Morphing



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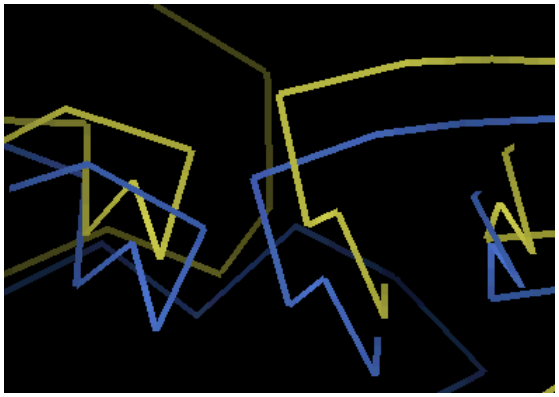
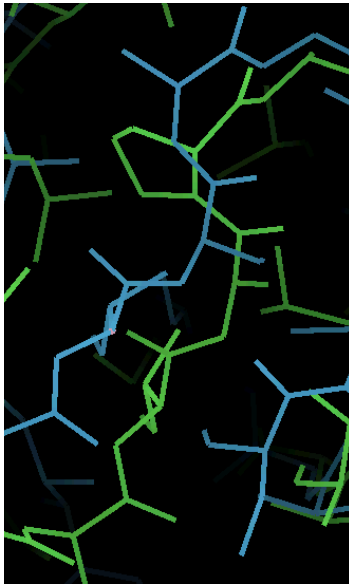
Morphing



Local structures may superimpose very closely

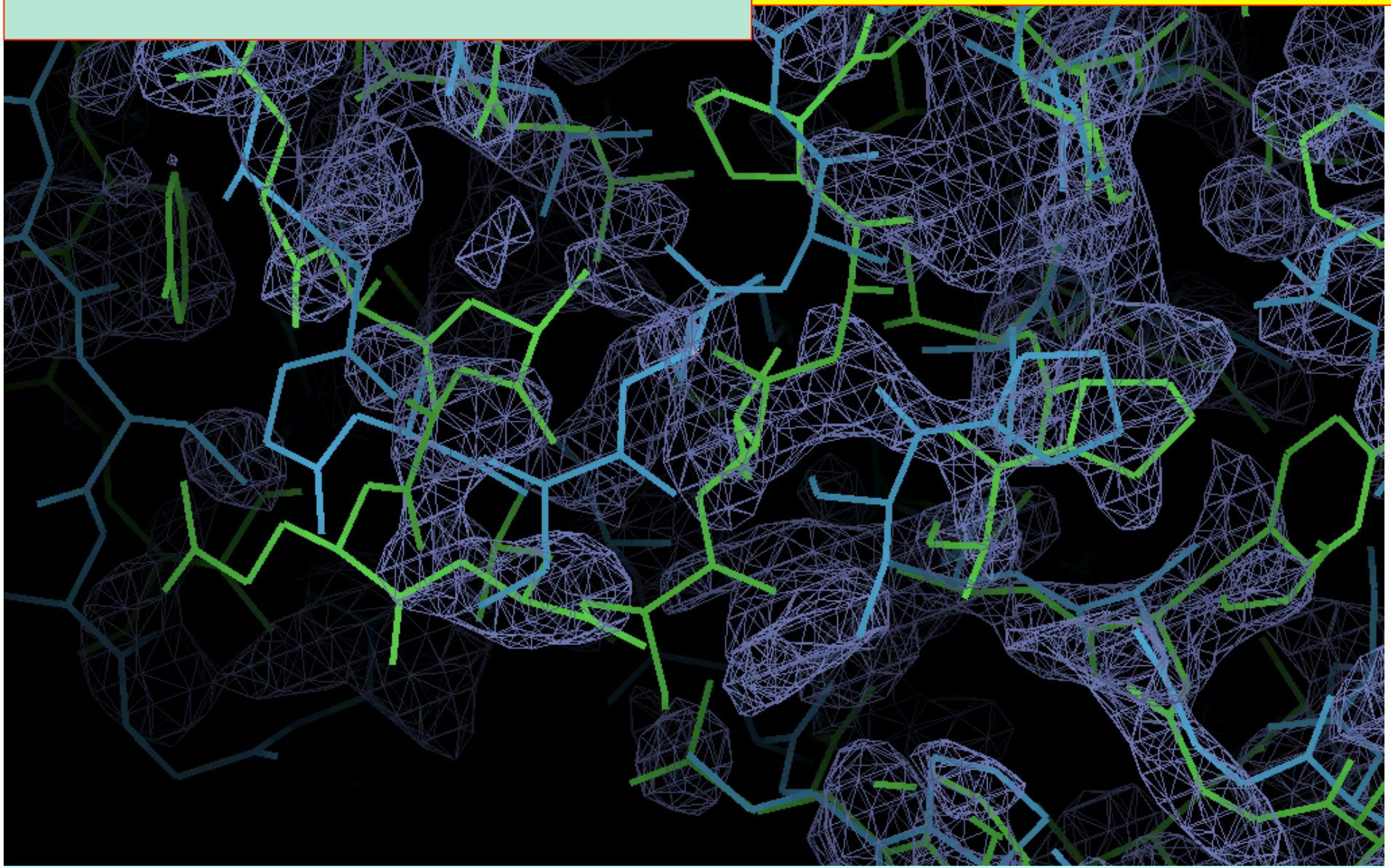
The position of a large group of atoms can be identified accurately with a poor map



Relationship between structures may be a simple distortion

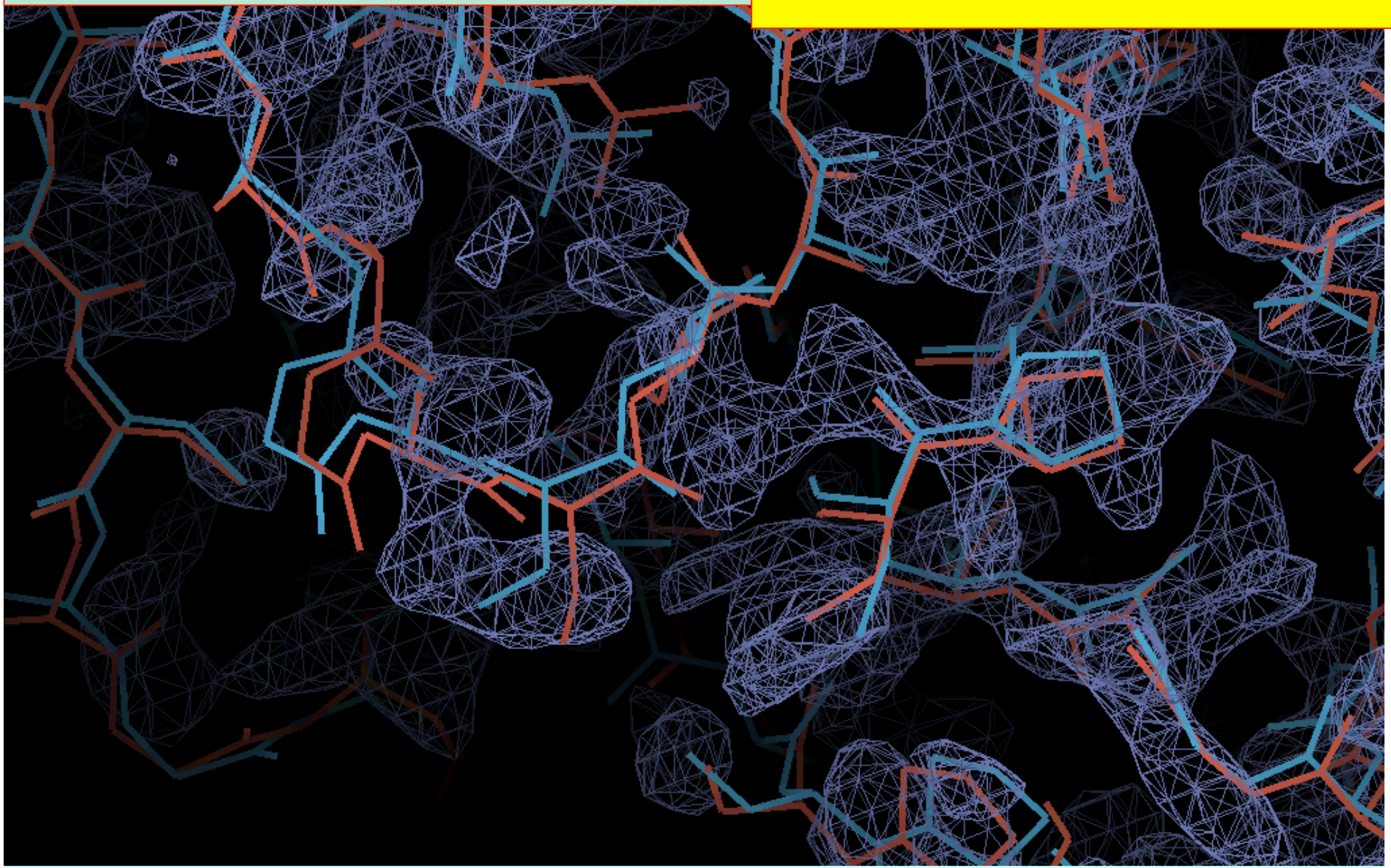
A challenging morphing problem:
How can we use this map to identify the shifts needed?

cab55342: final model green
3PIC (32% identity) in blue



Standard refinement does not move the structure very much..

cab55342:
3PIC (32% identity) in blue
Refined template in orange



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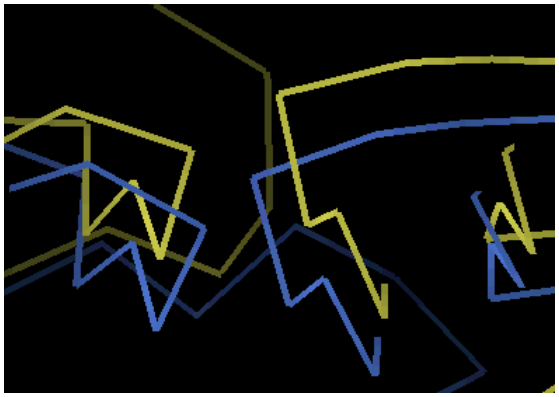
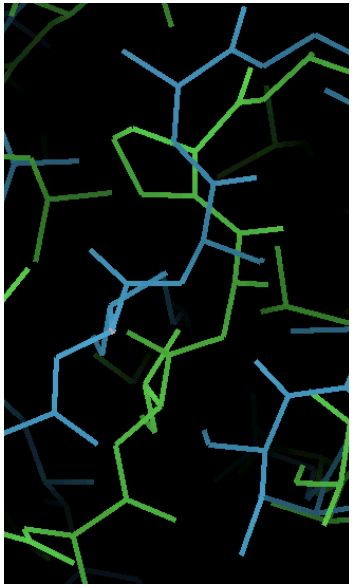
Steps in morphing



A. Identify local translation to apply to one C_α atom and nearby atoms

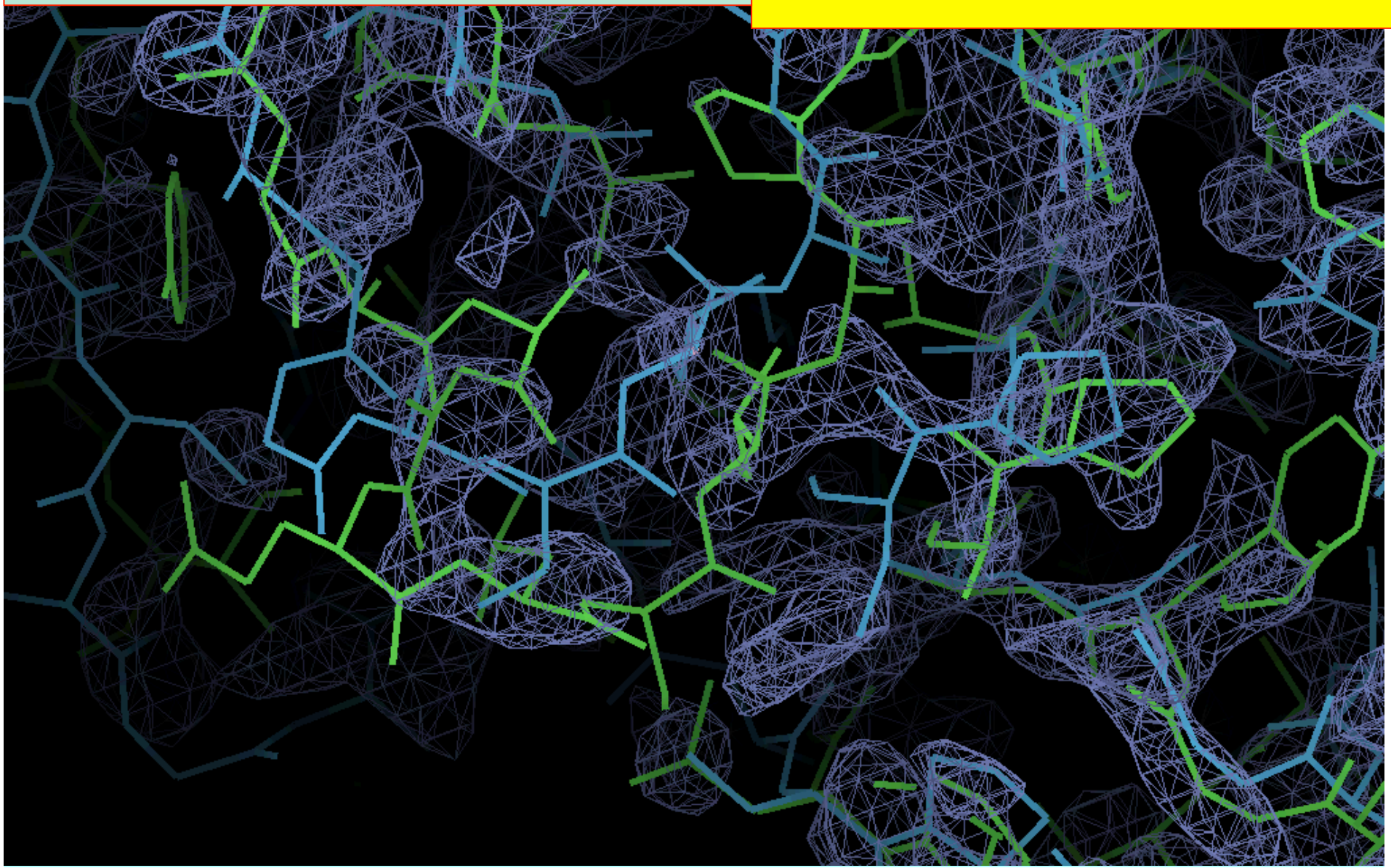
B. Smooth the local translations in window of 10 residues



C. Apply the smoothed translation to all atoms in the residue

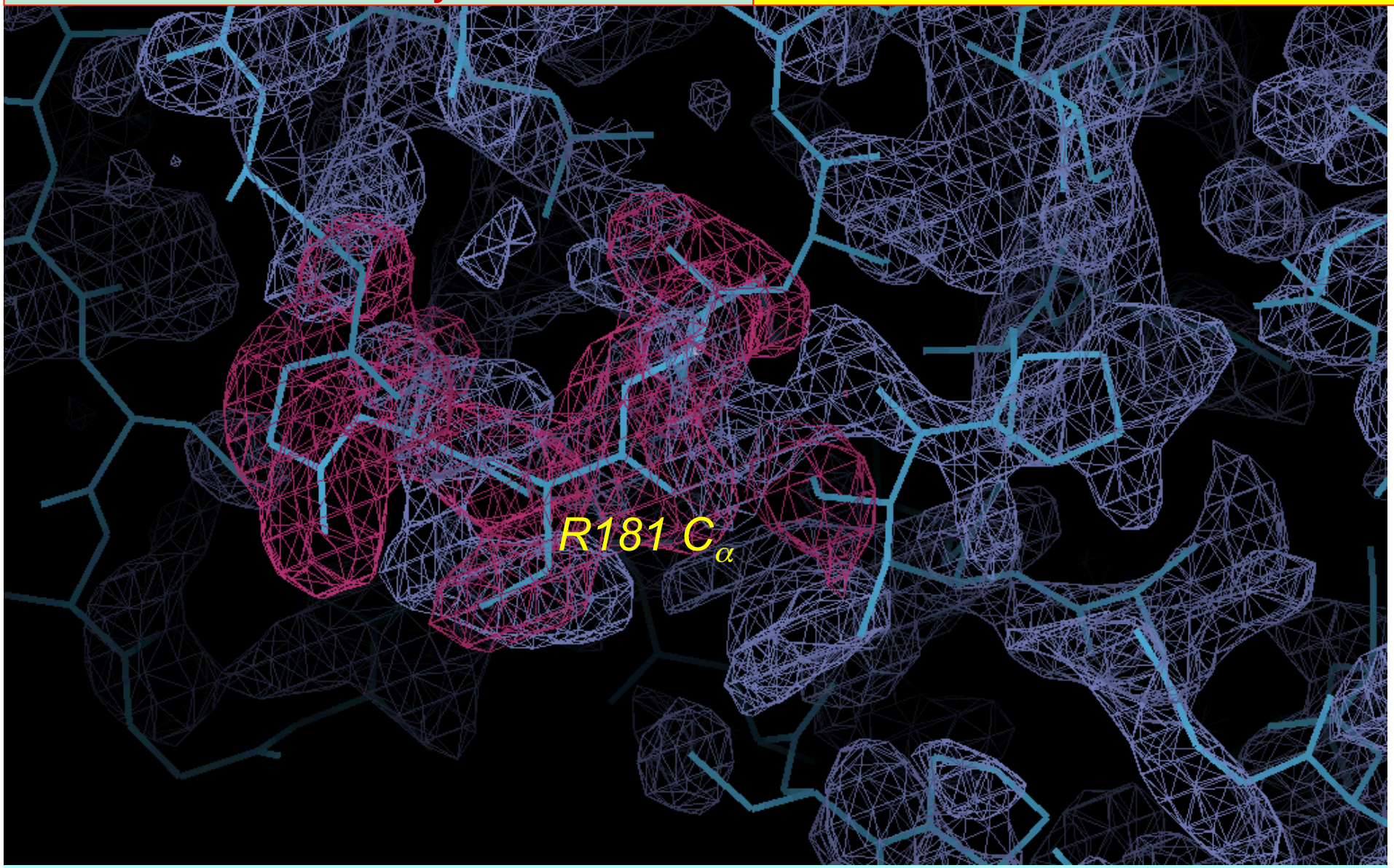
Identify local translation to apply to one C_α atom and nearby atoms

cab55342: final model (green)
3PIC (32% identity, blue)
prime-and-switch map (blue)



Identify local translation to apply to one C_α atom and nearby atoms
Model density in red

cab55342:
3PIC (32% identity, blue)



Identify local translation to apply to one C_α atom and nearby atoms
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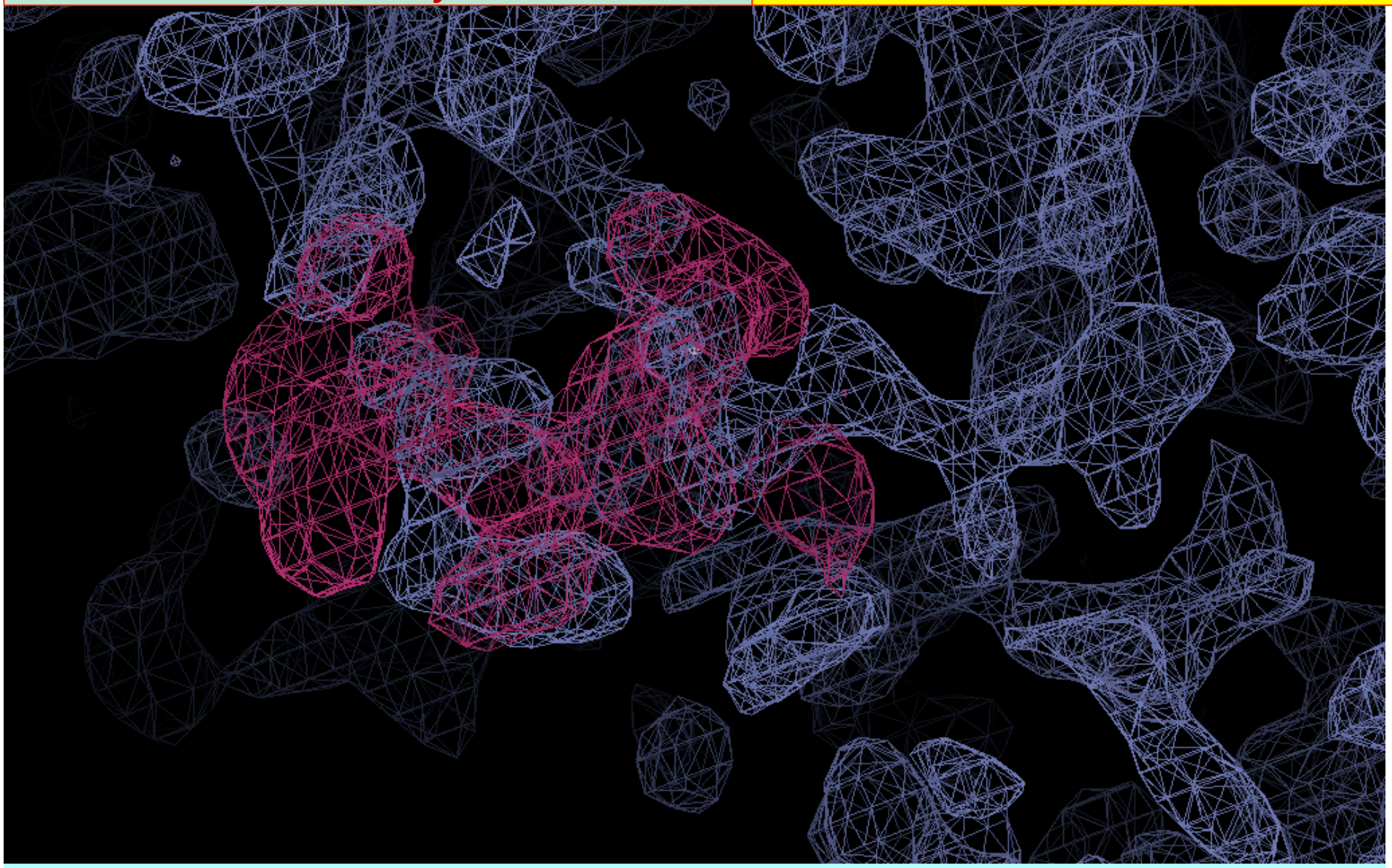
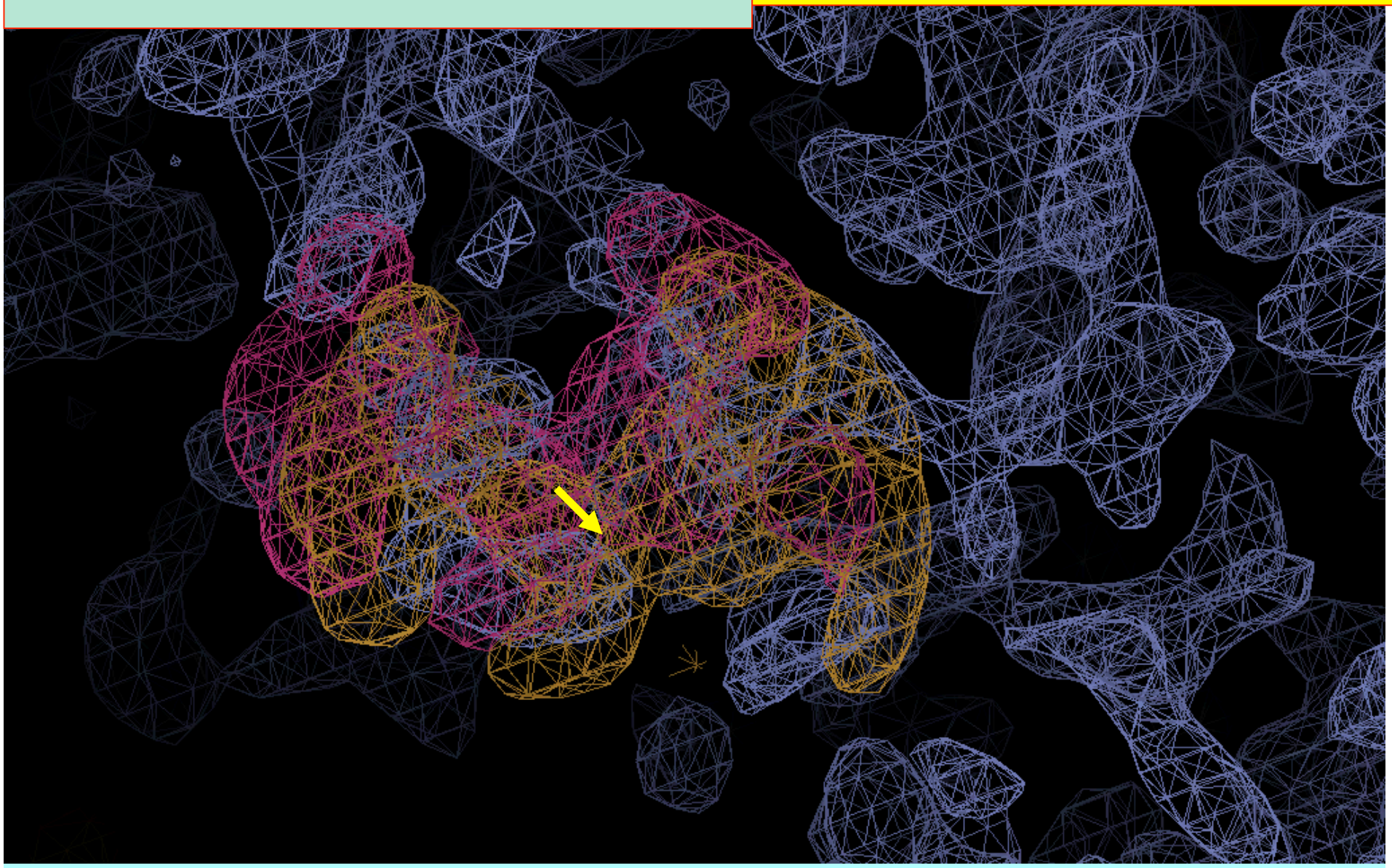


Identify local translation to apply to one C_α atom and nearby atoms
Model density offset to match map

cab55342:
3PIC (32% identity, blue)



Identify local translation to apply to one C_α atom and nearby atoms
Model density offset to match map

cab55342:
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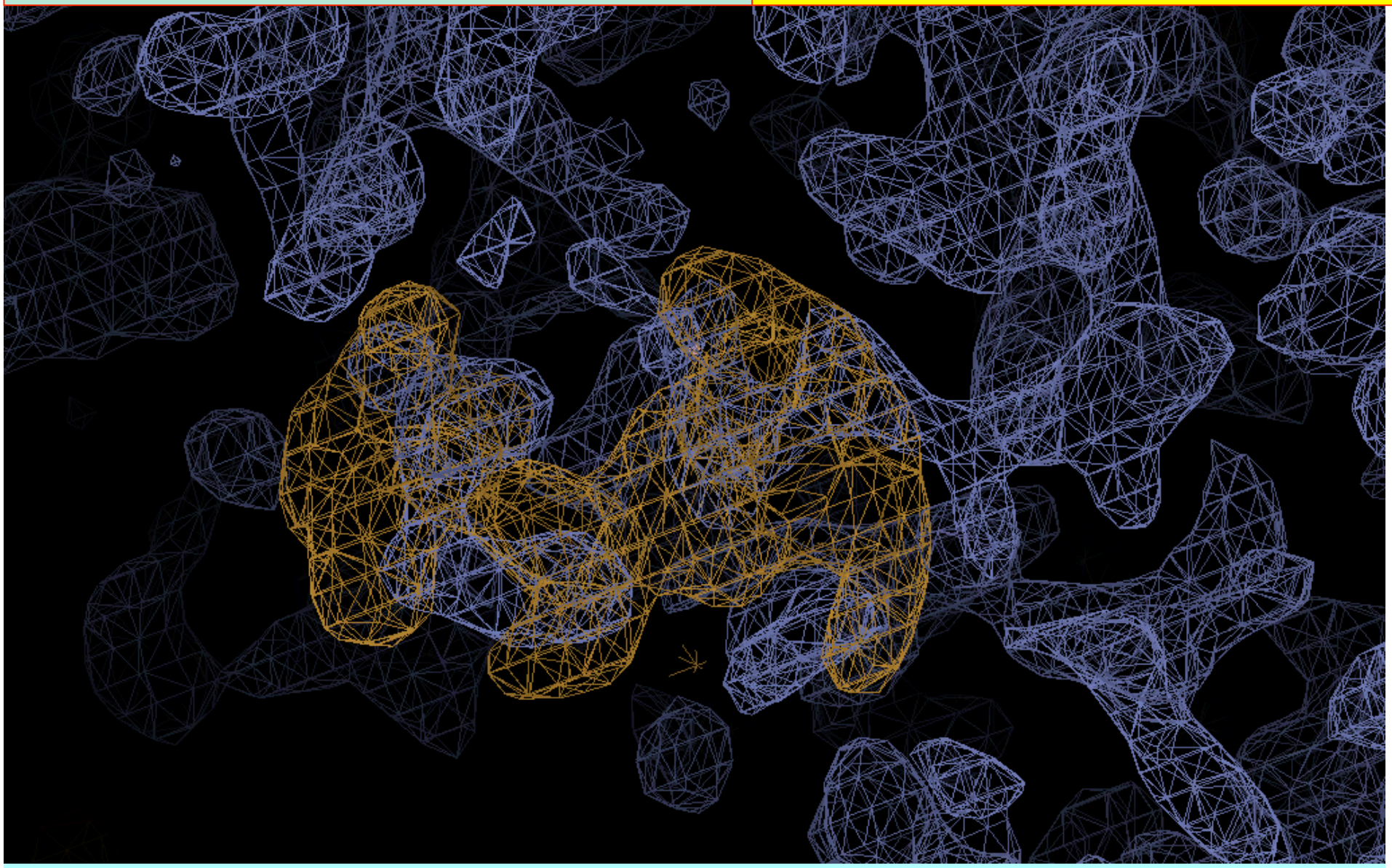
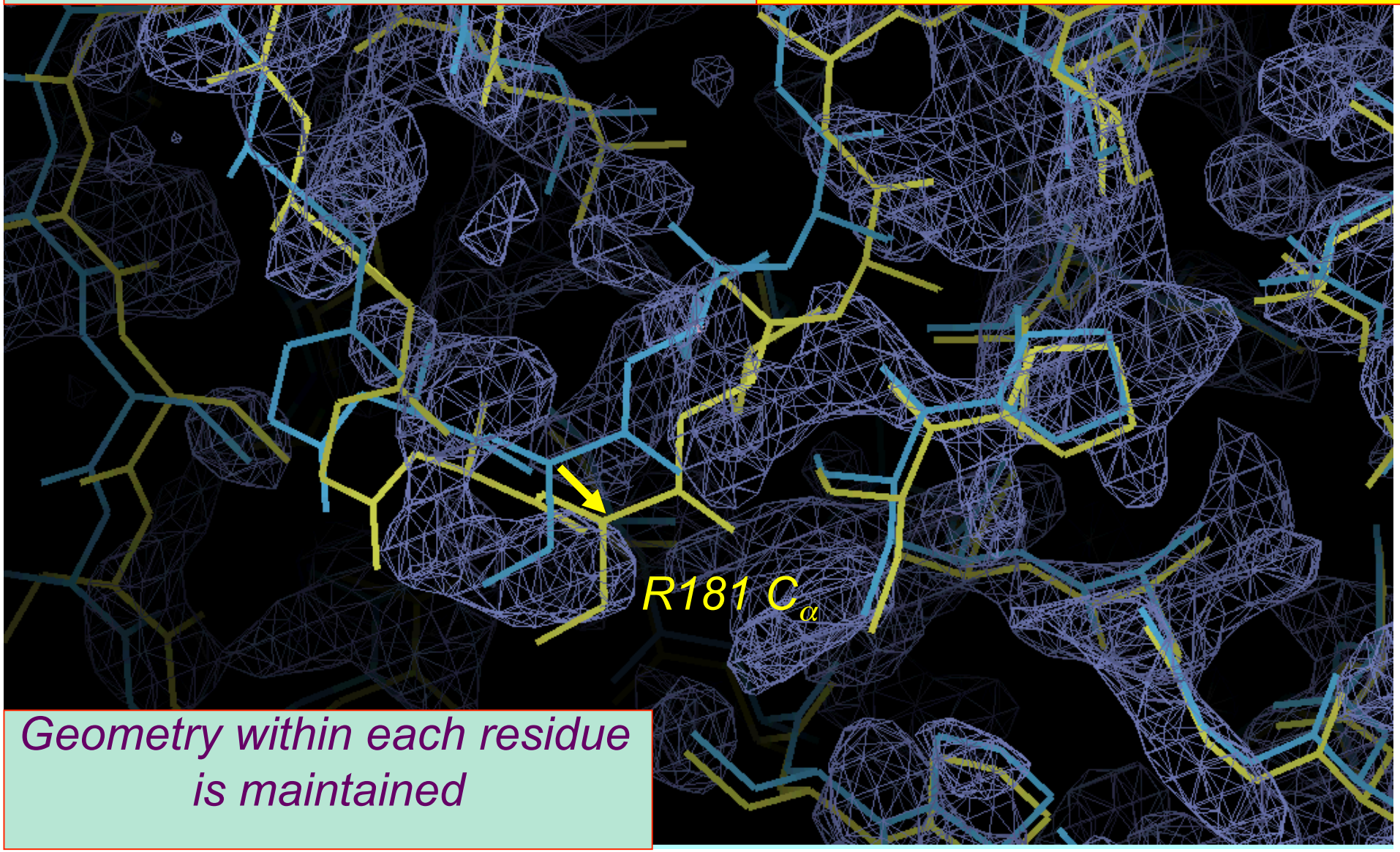


Smooth offset over nearby residues and apply to all atoms in the residue

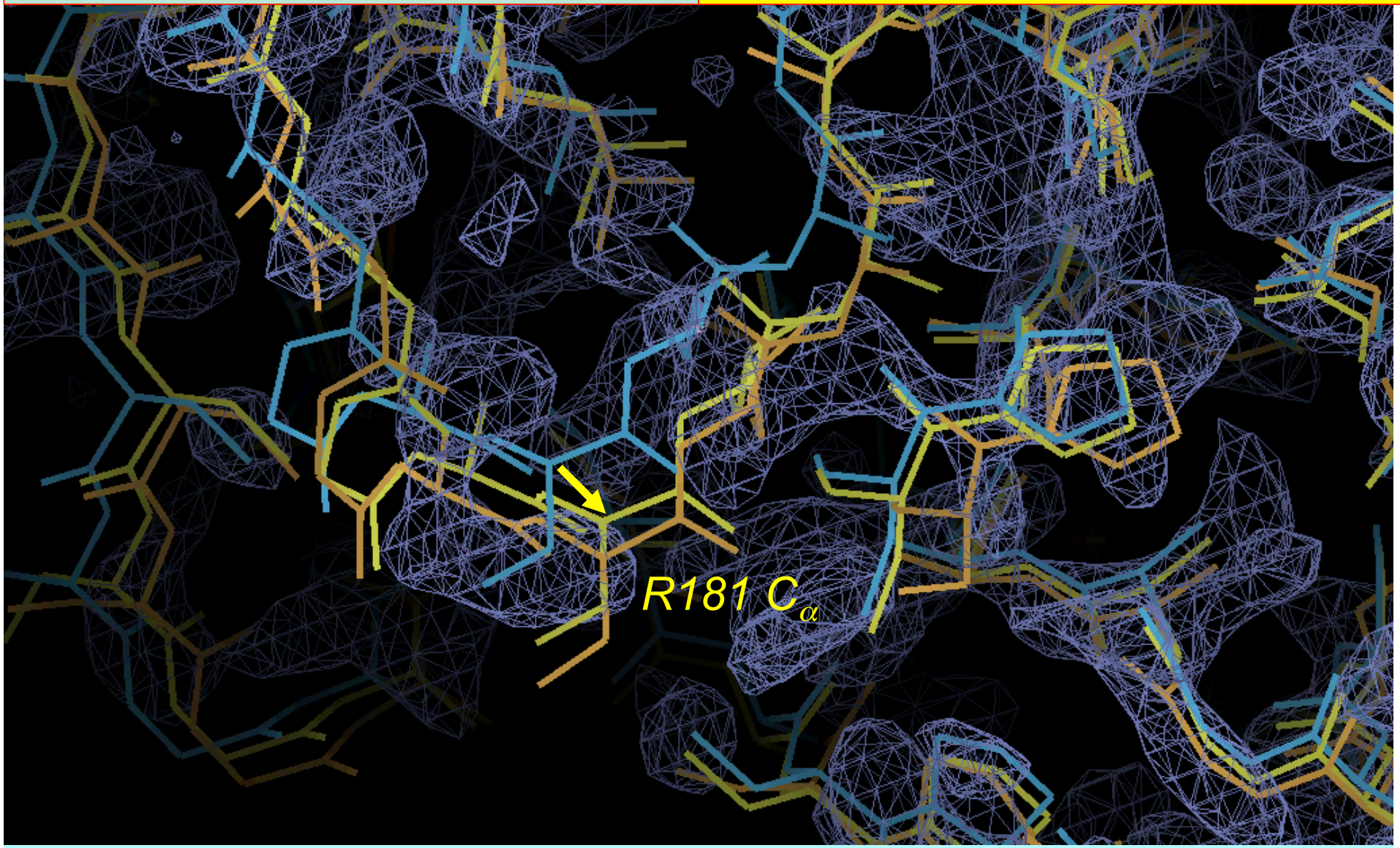
cab55342:
3PIC (32% identity, blue)
Morphed model (yellow)



Geometry within each residue is maintained

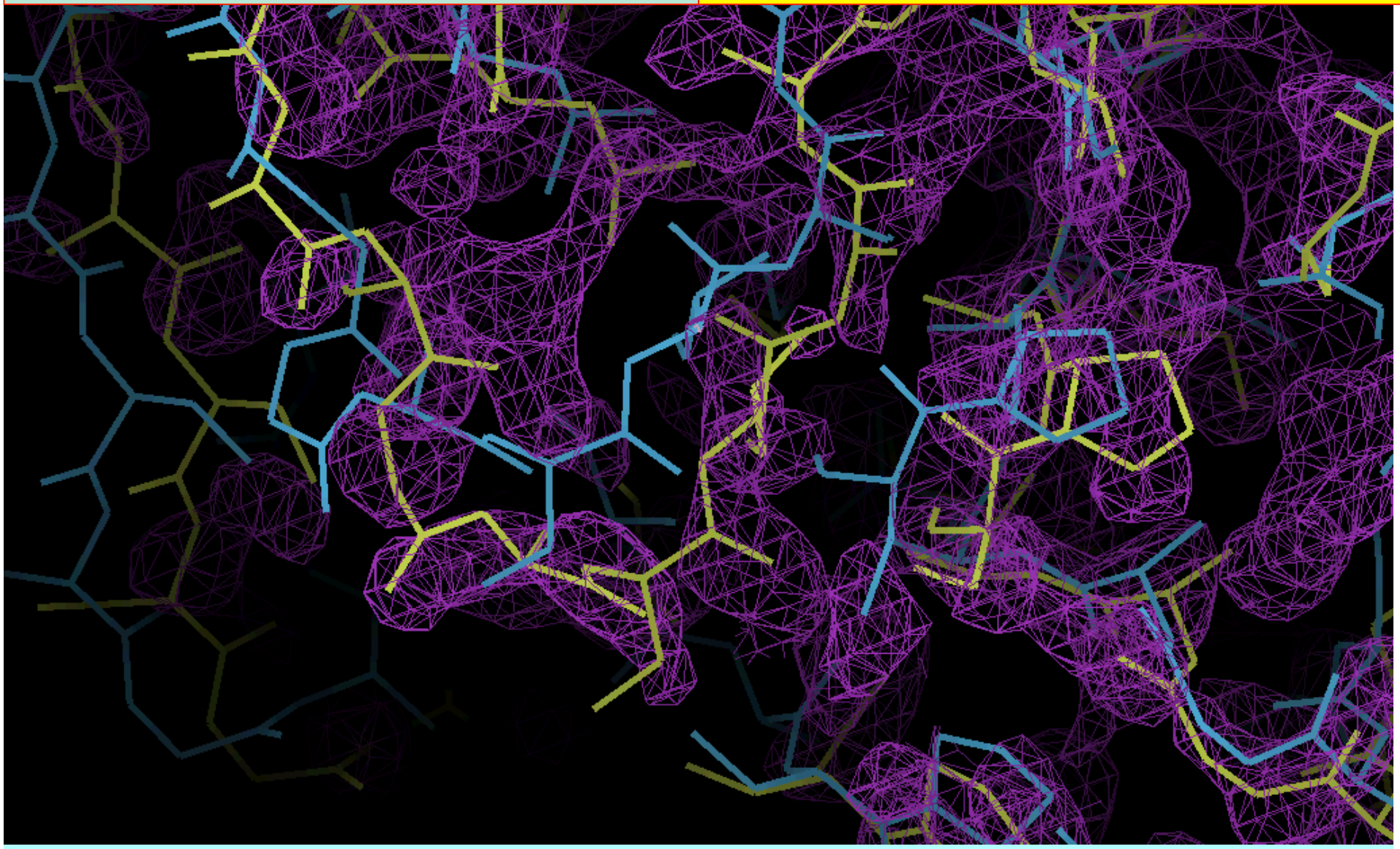
Refine morphed model

3PIC (32% identity) in blue
Morphed model (yellow)
Refined morphed model (orange)



Get new map
Repeat morphing 6 times...

3PIC (32% identity) blue
Refined morphed model (yellow)
prime-and-switch map (purple)



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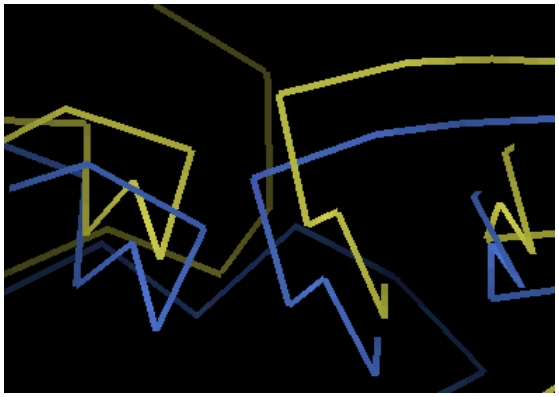
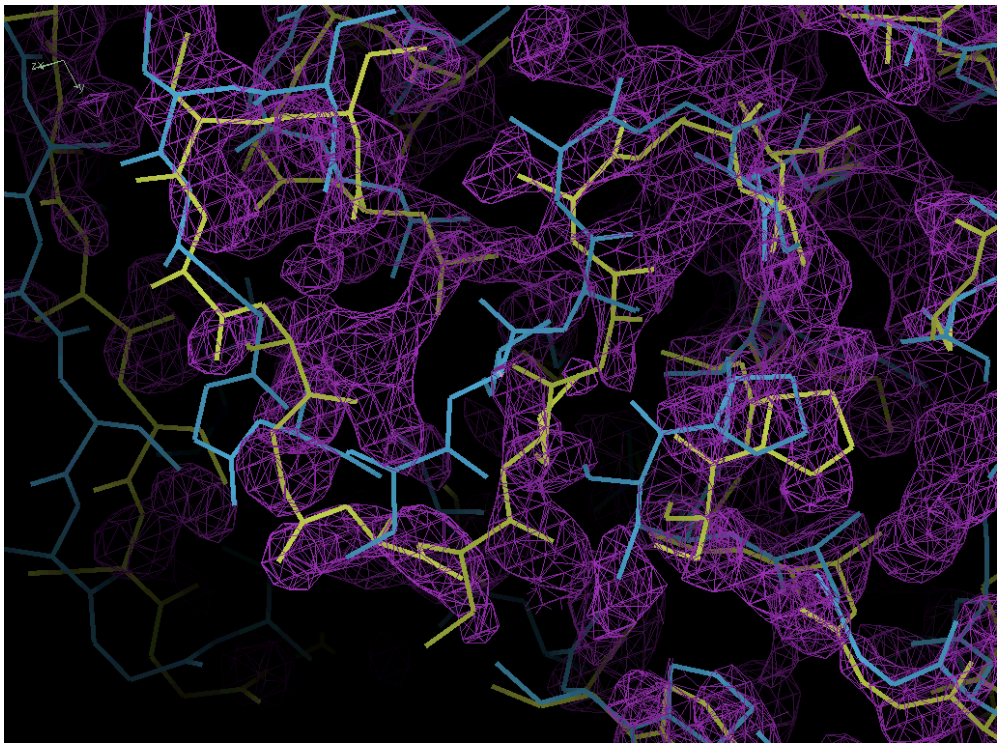
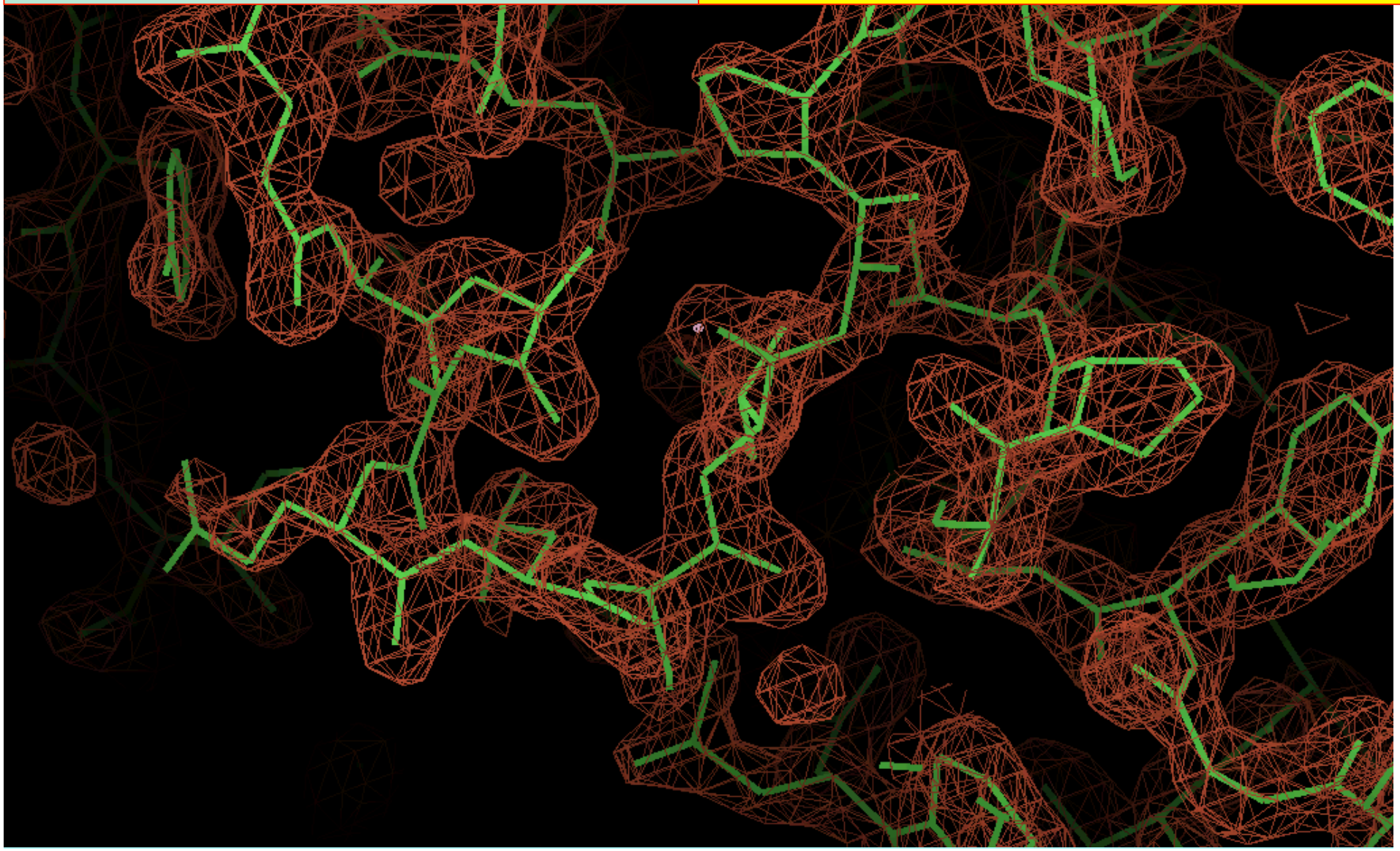
Autobuilding after morphing





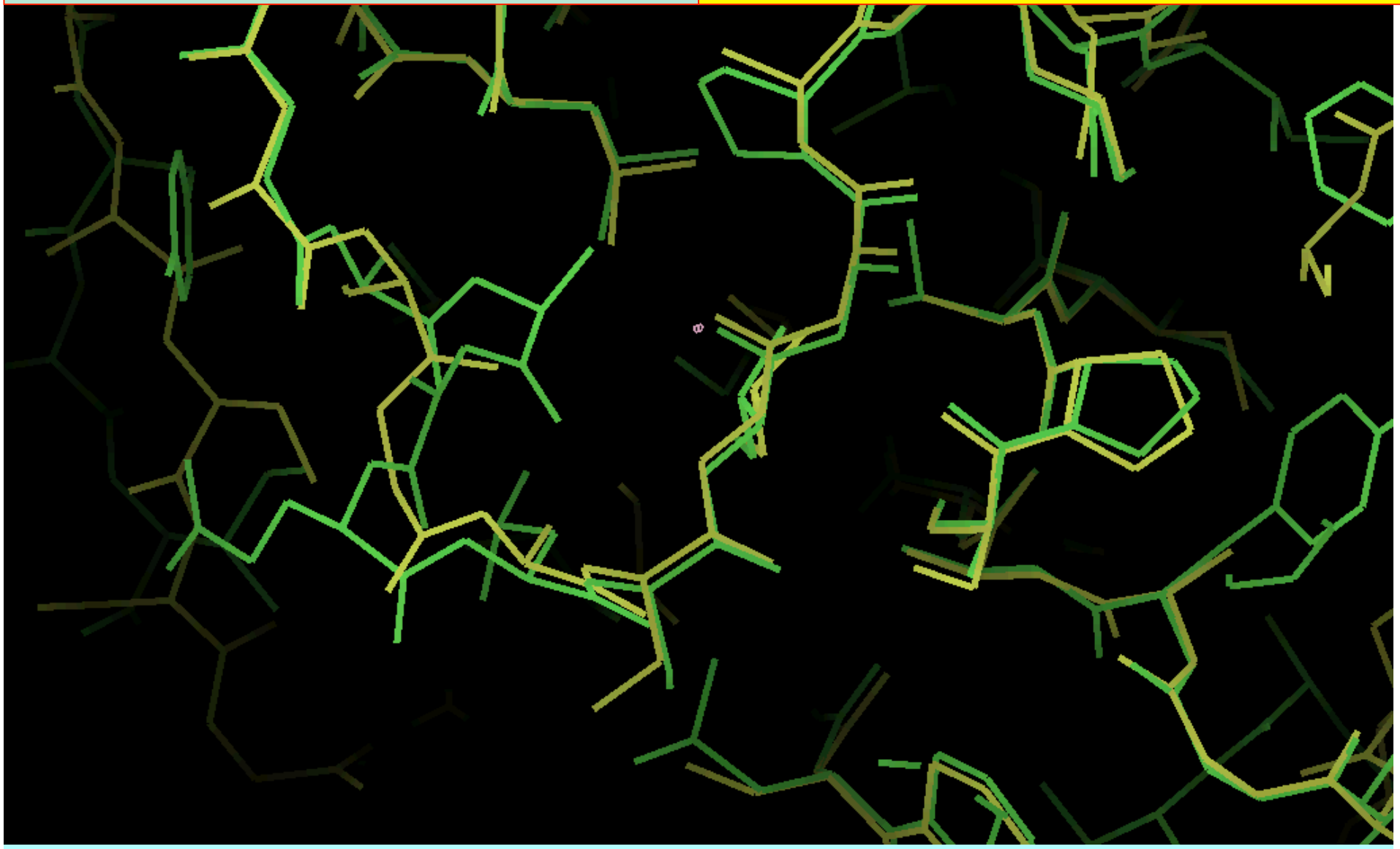
Autobuilding starting with morphed model

cab55342
Autobuild model
Density-modified map



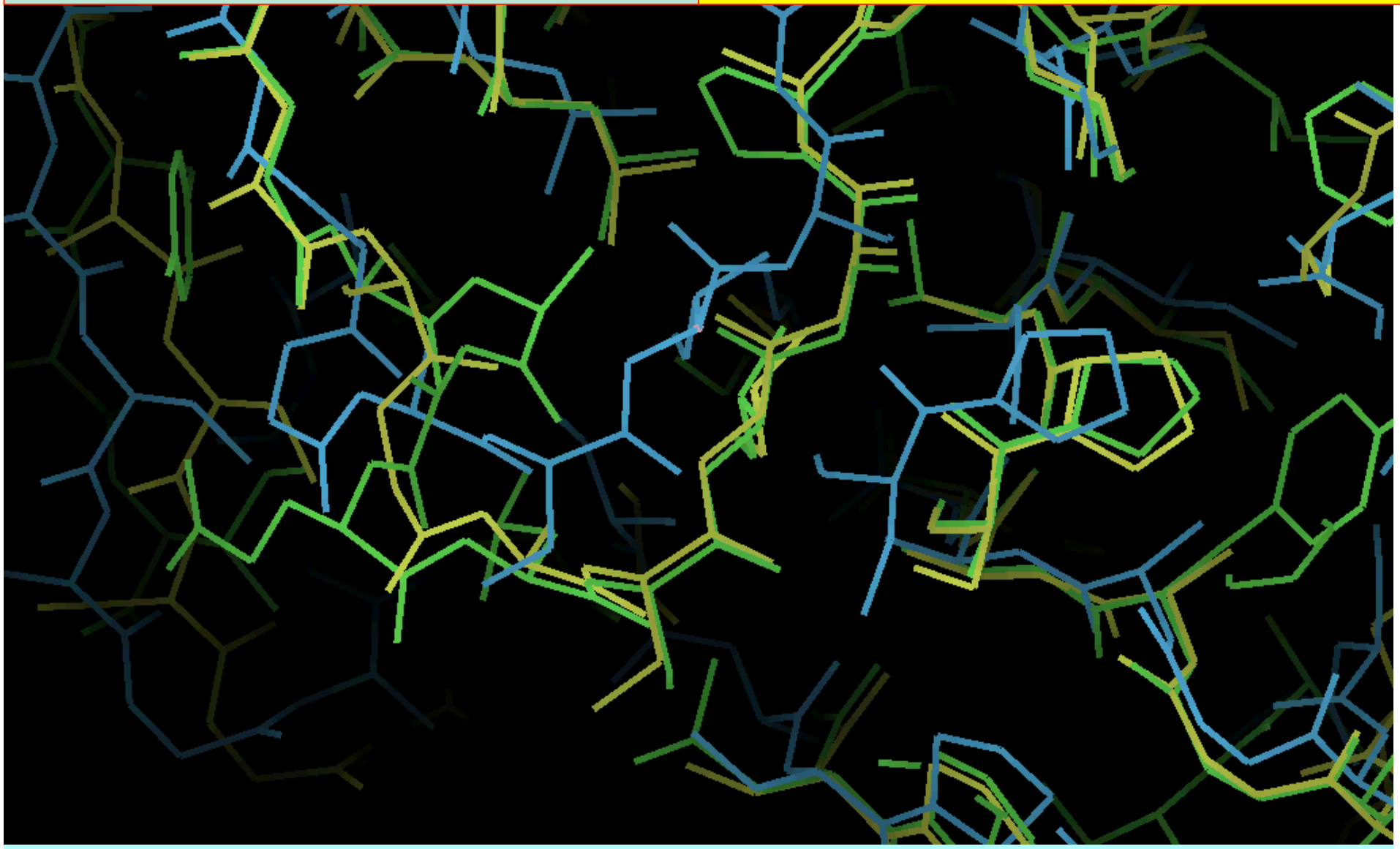
Autobuilding starting with morphed model

cab55342
Morphed model (yellow)
Autobuild model (green)



Autobuilding cab55342 starting with morphed model

3PIC (32% identity, blue)
Morphed model (yellow)
Autobuild model (green)



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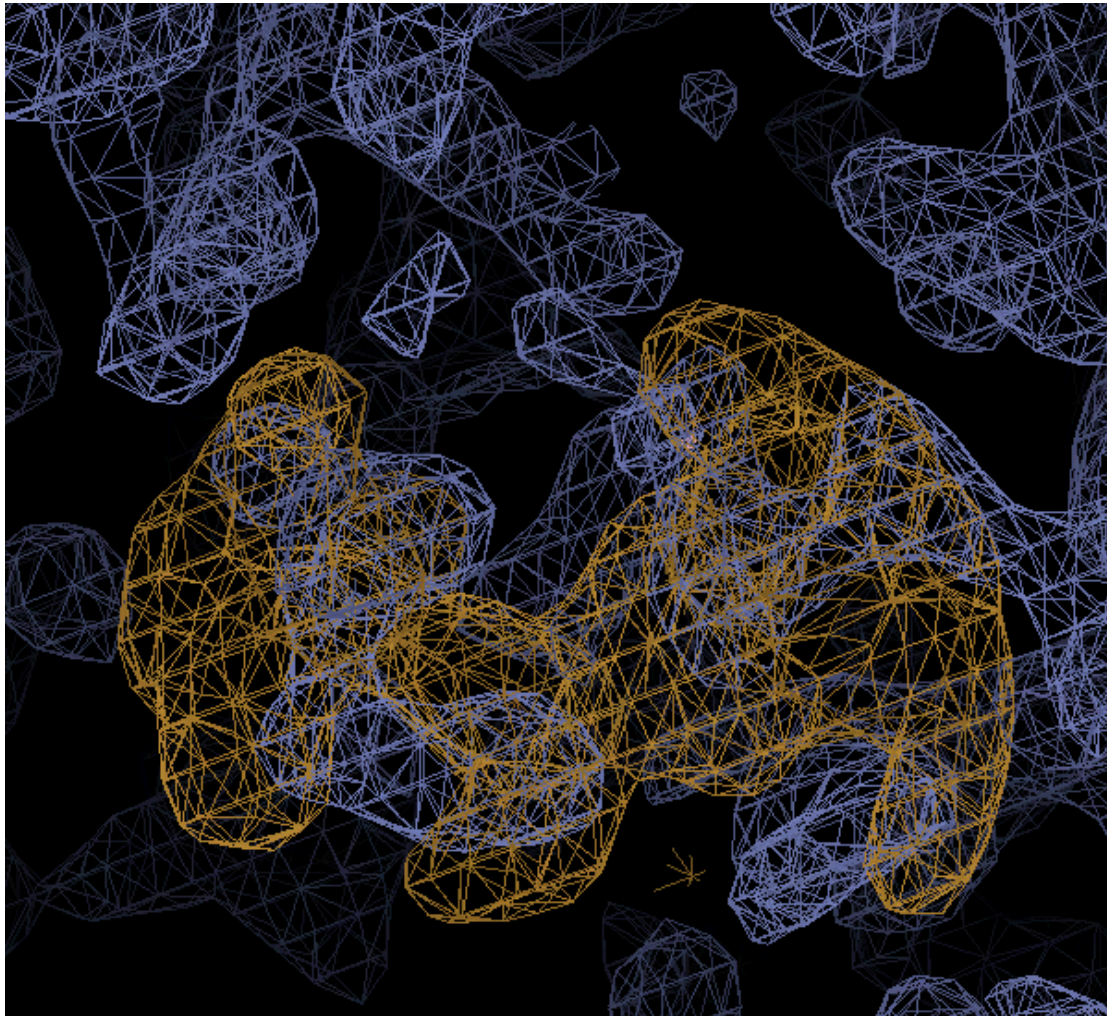
What is the best map for morphing?

Test structures from DiMaio et al. (2011). *Improving molecular replacement by density and energy guided protein structure optimization.* *Nature* 473, 540-543.

(Structures that could be solved by AutoBuild excluded)



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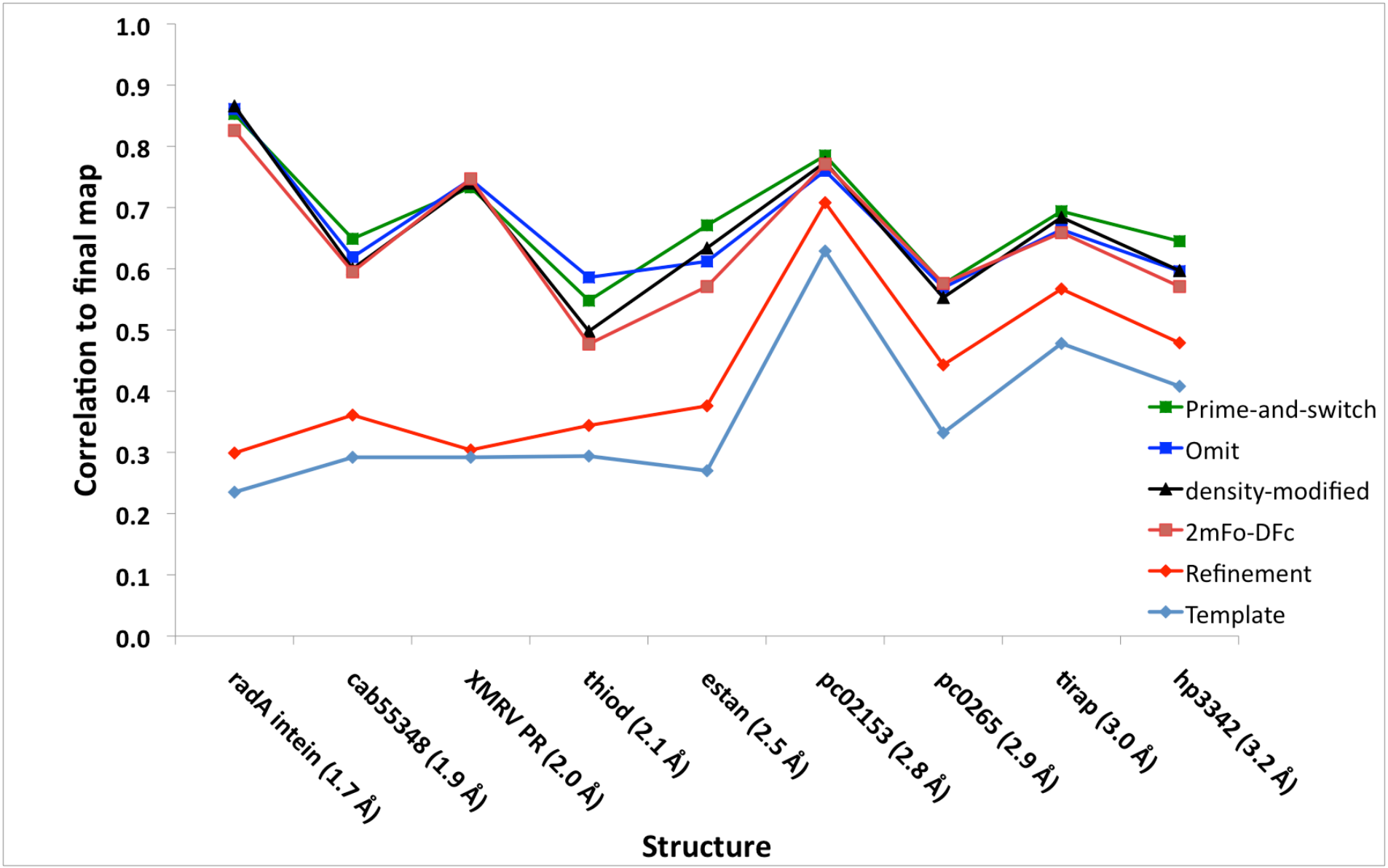
Comparison of maps for morphing



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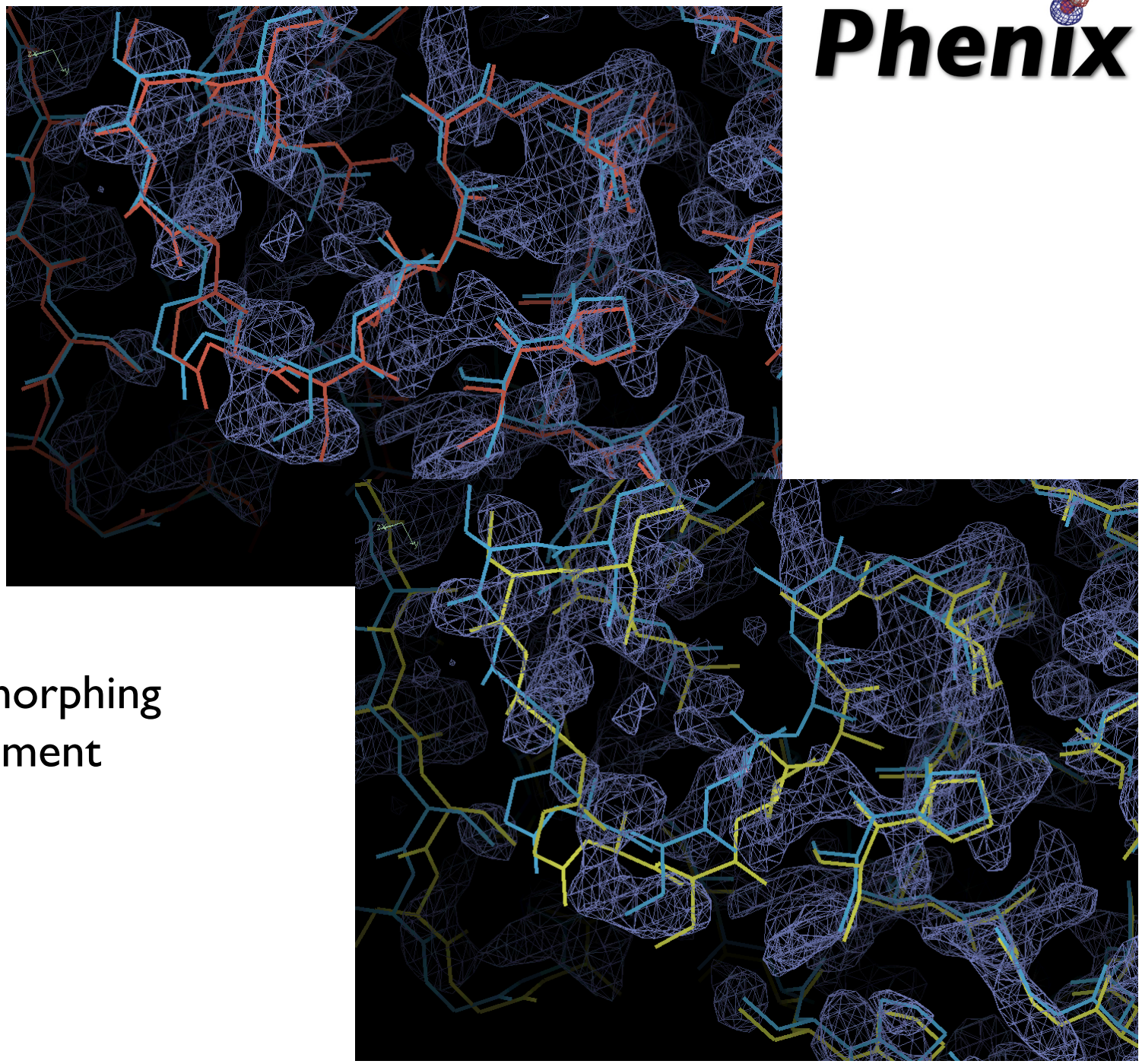

Comparing morphing
and refinement

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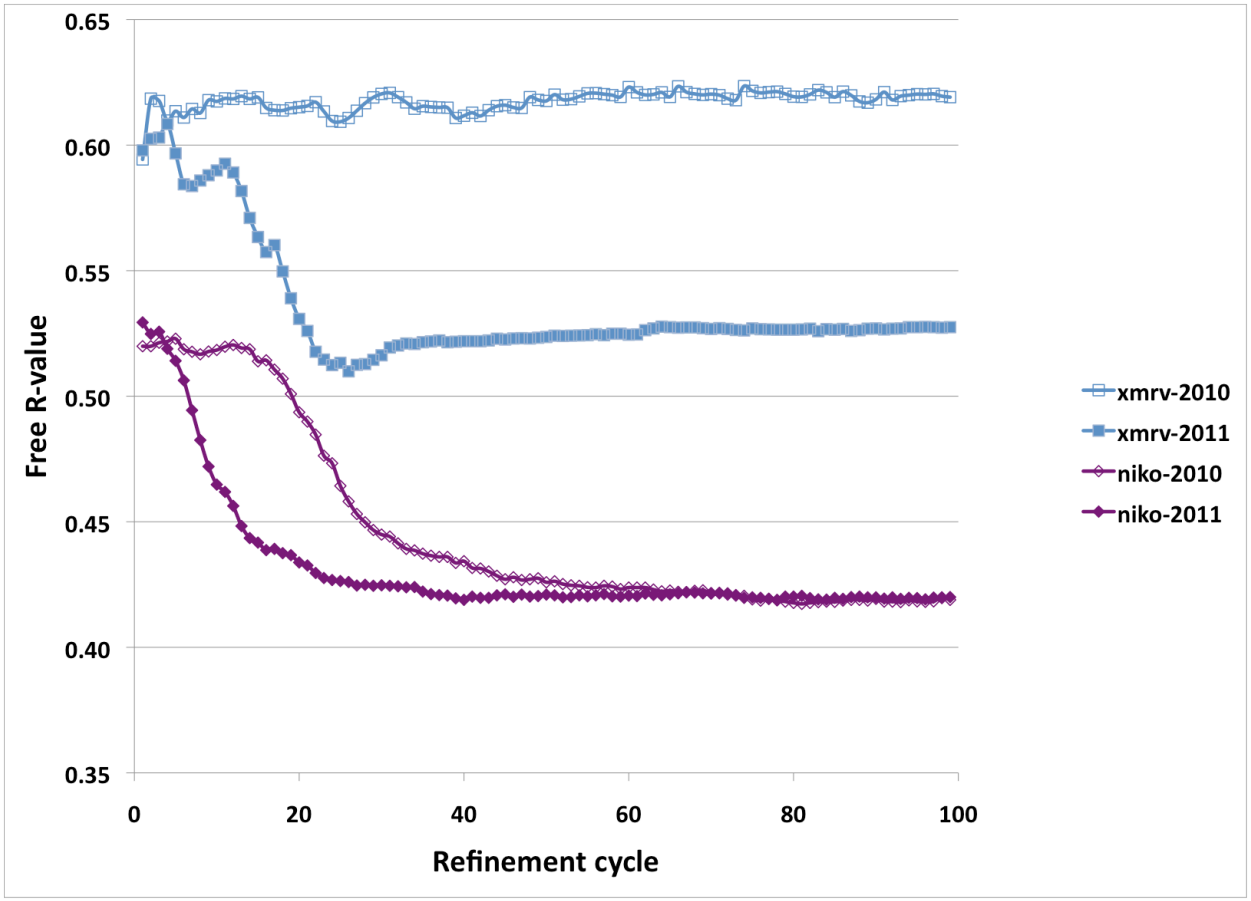
What to use as a baseline?

Major improvements in *phenix.refine* since 2010



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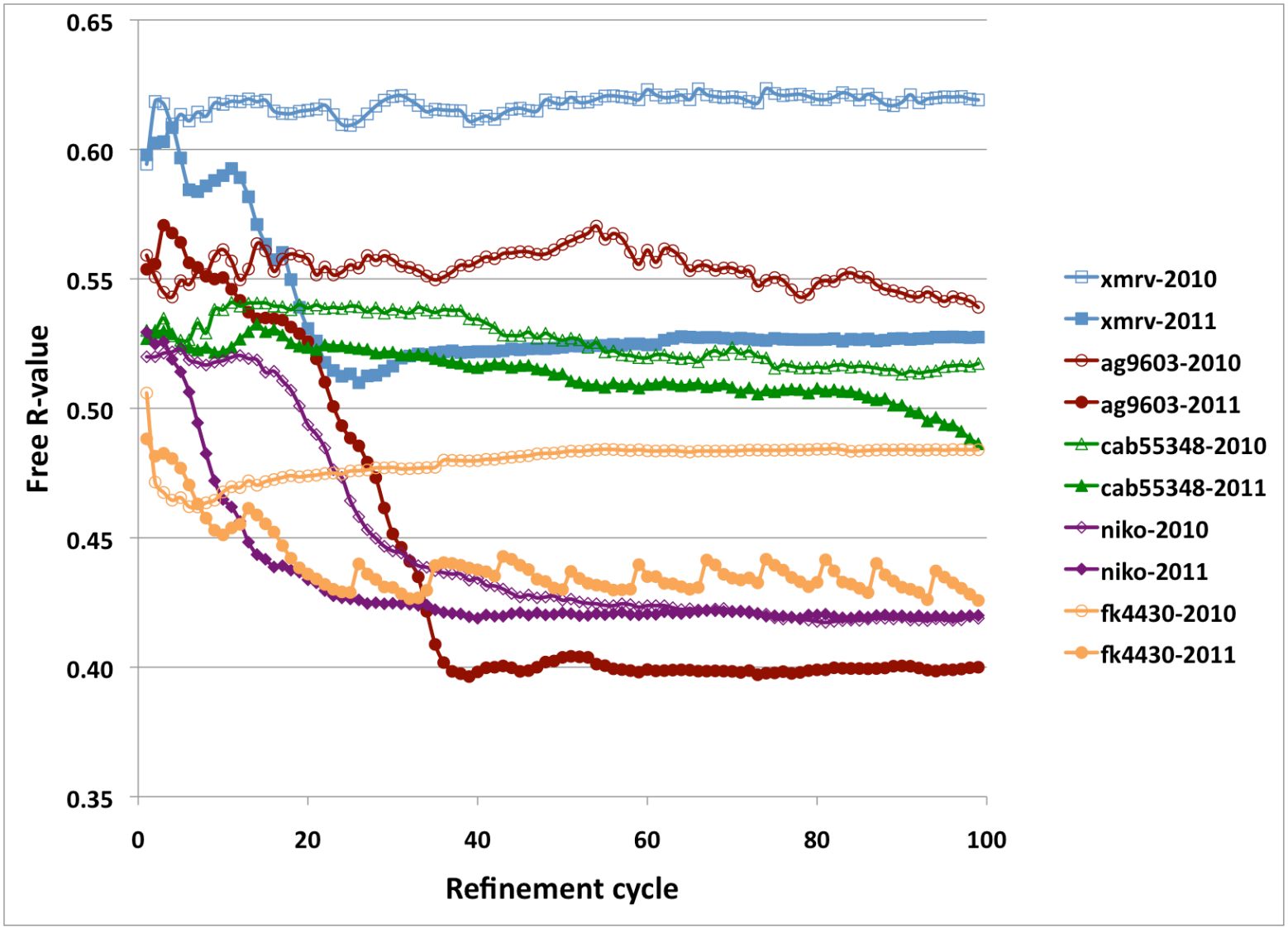
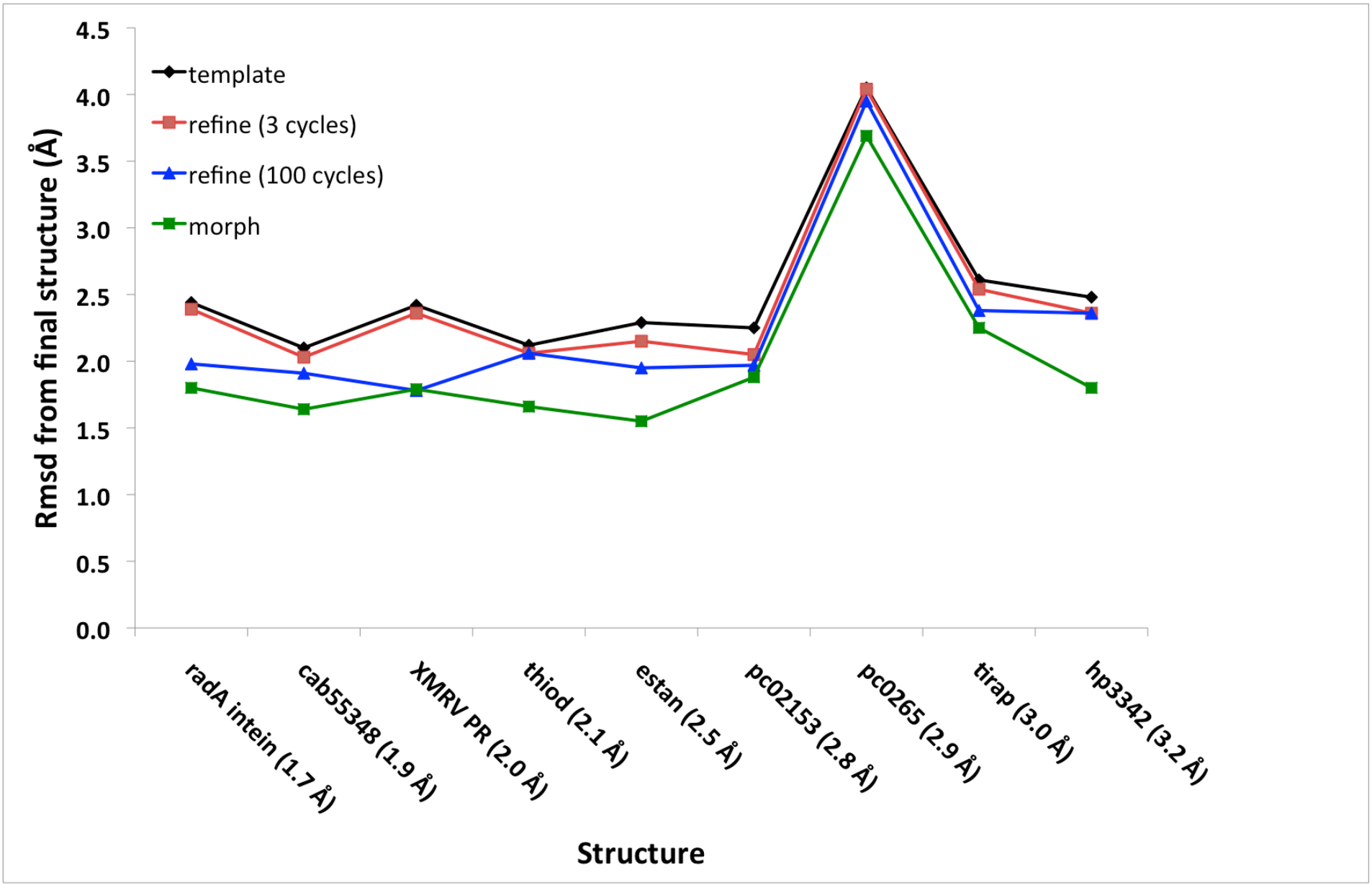
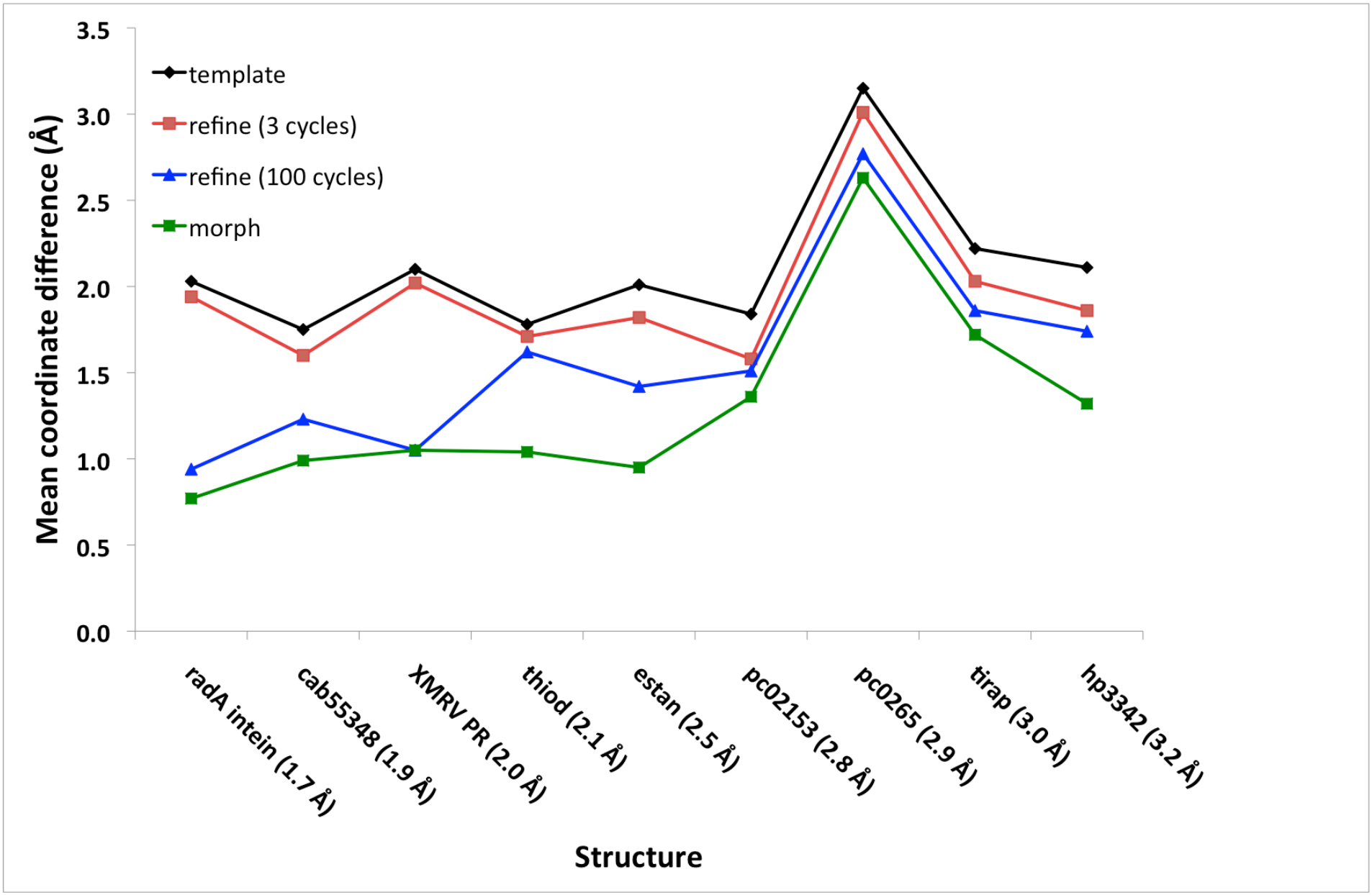
Extensive refinement can be effective



Morphing compared to refinement



Morphing compared to refinement



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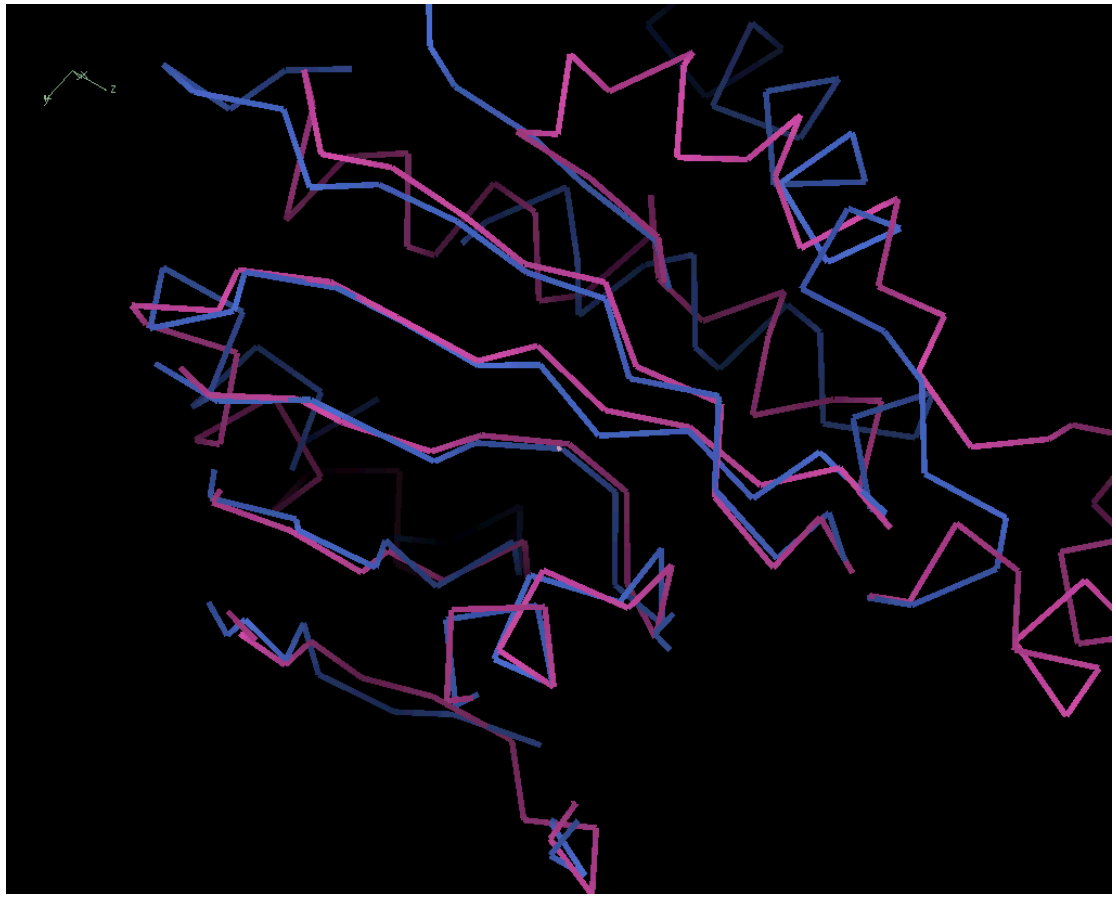
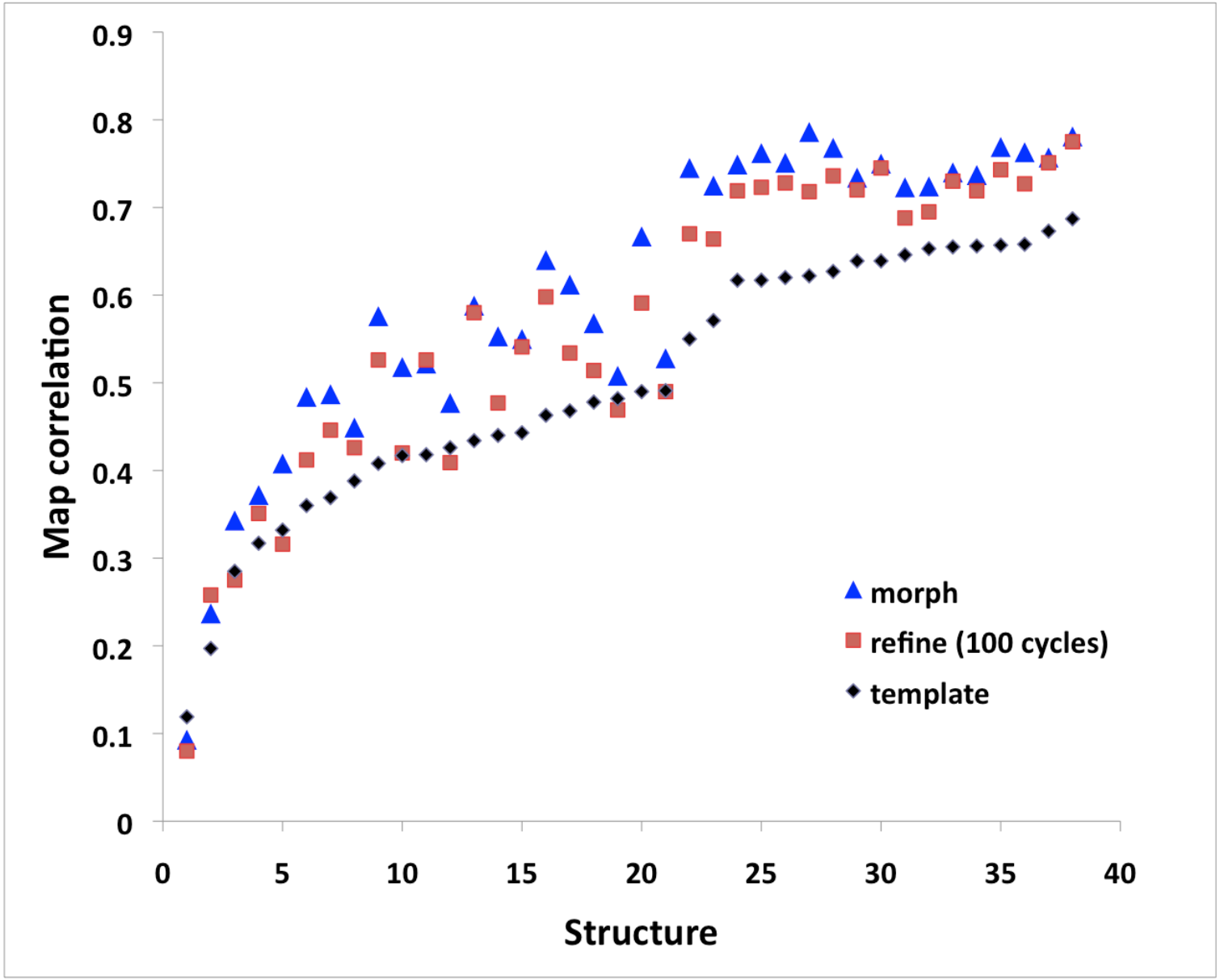
Tests of morphing with a series of templates with varying similarity to target structure



Phenix

Morphing on a series of templates



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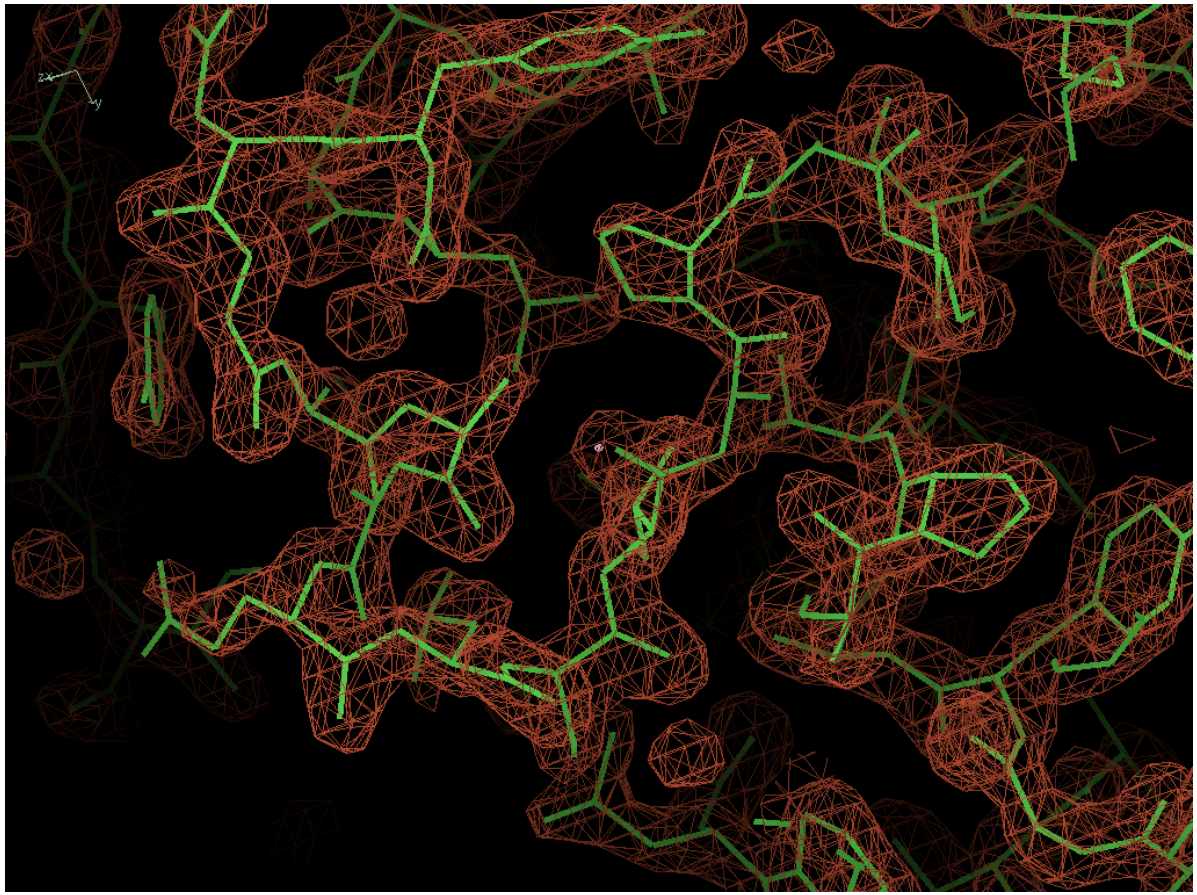
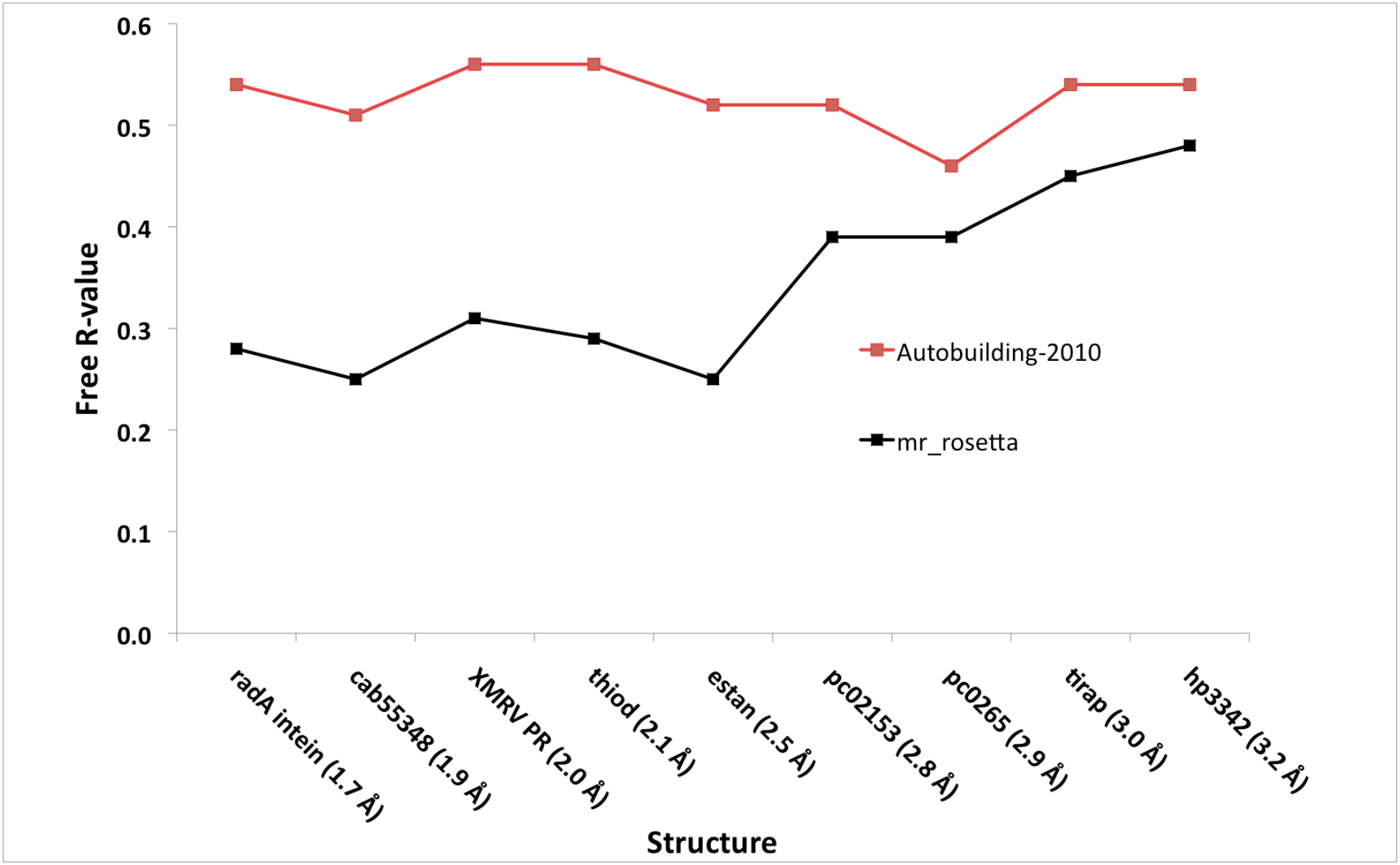
Tests of Autobuilding after morphing

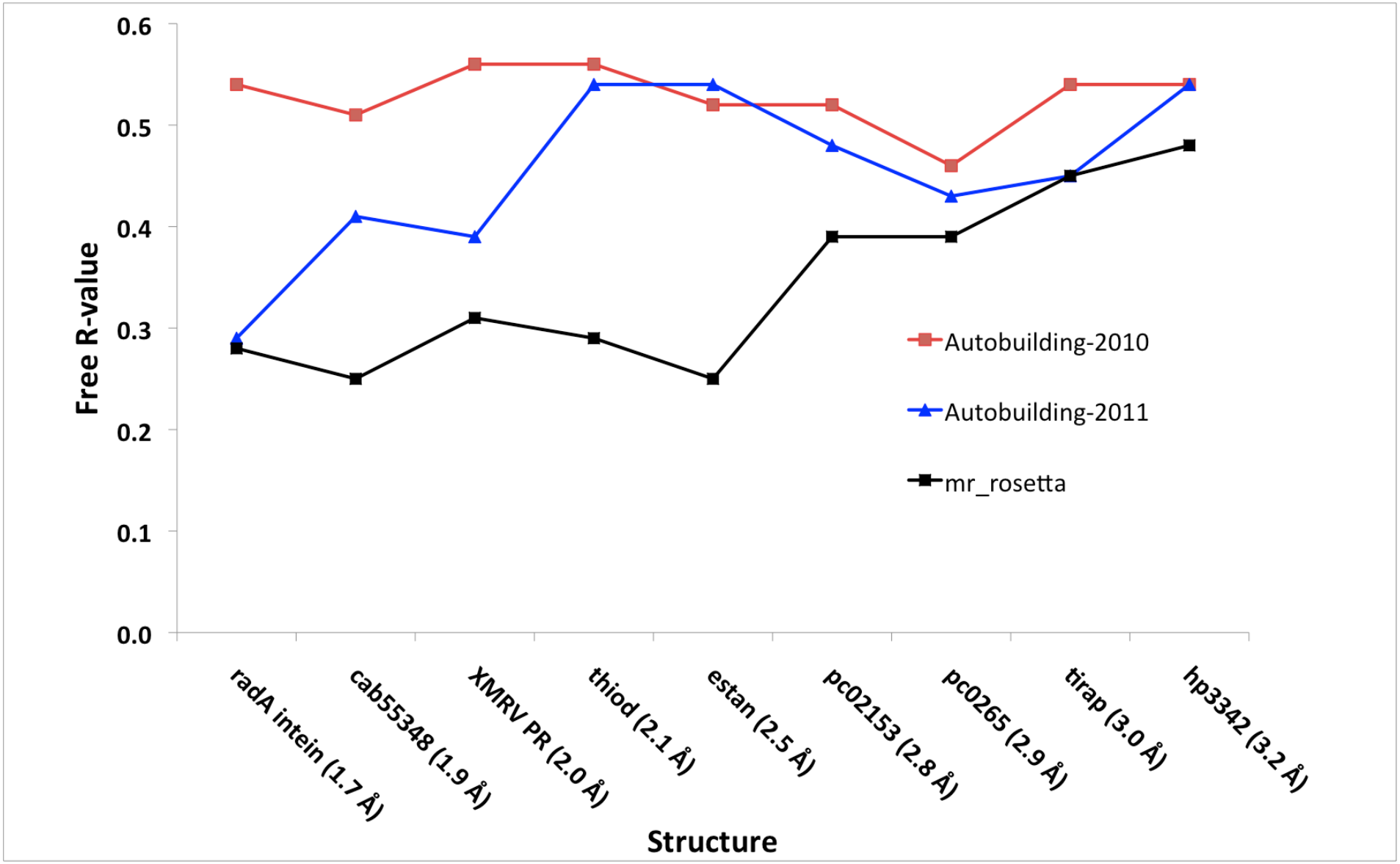
Comparison with *phenix.mr_rosetta*



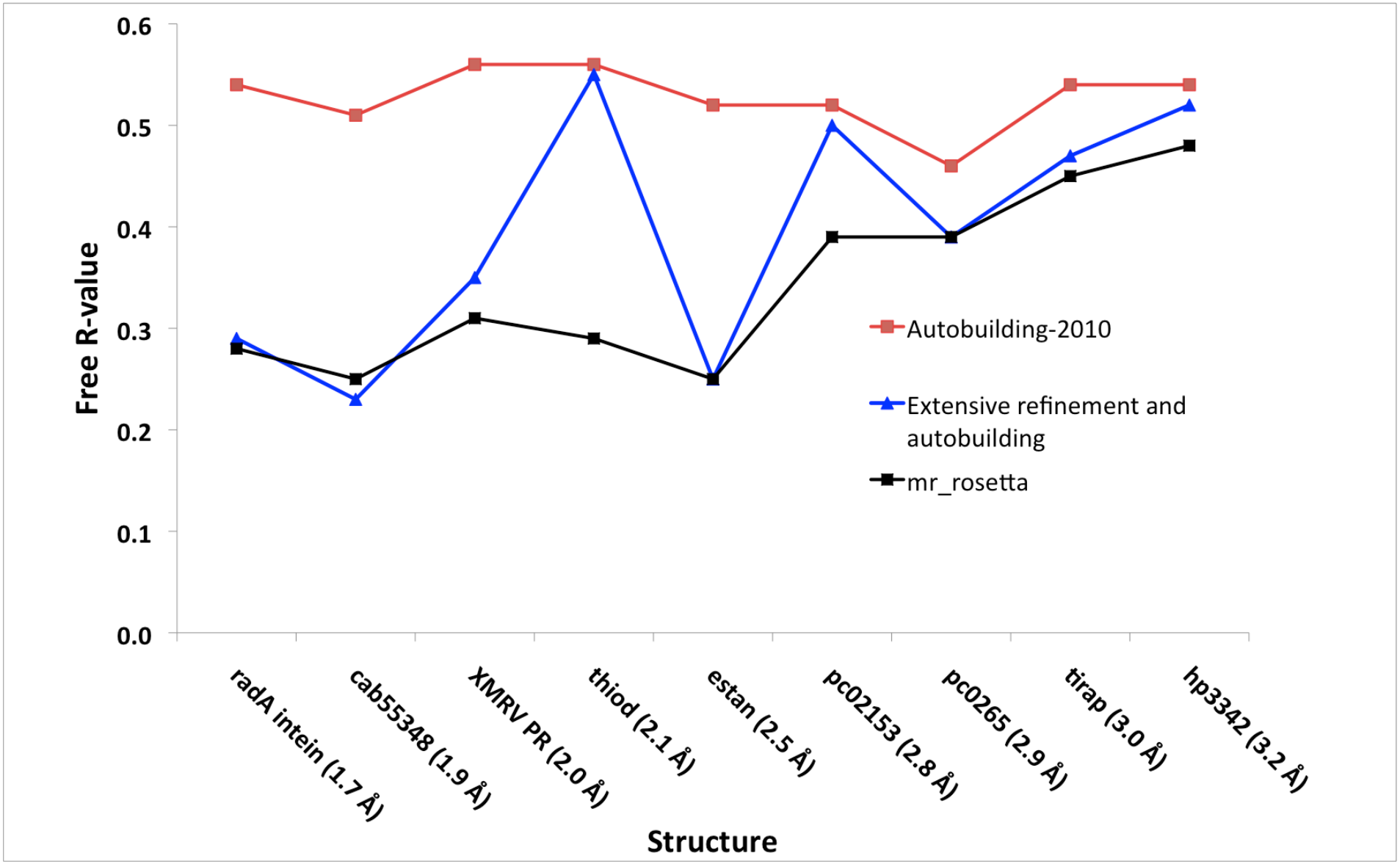
Morphing combined with autobuilding



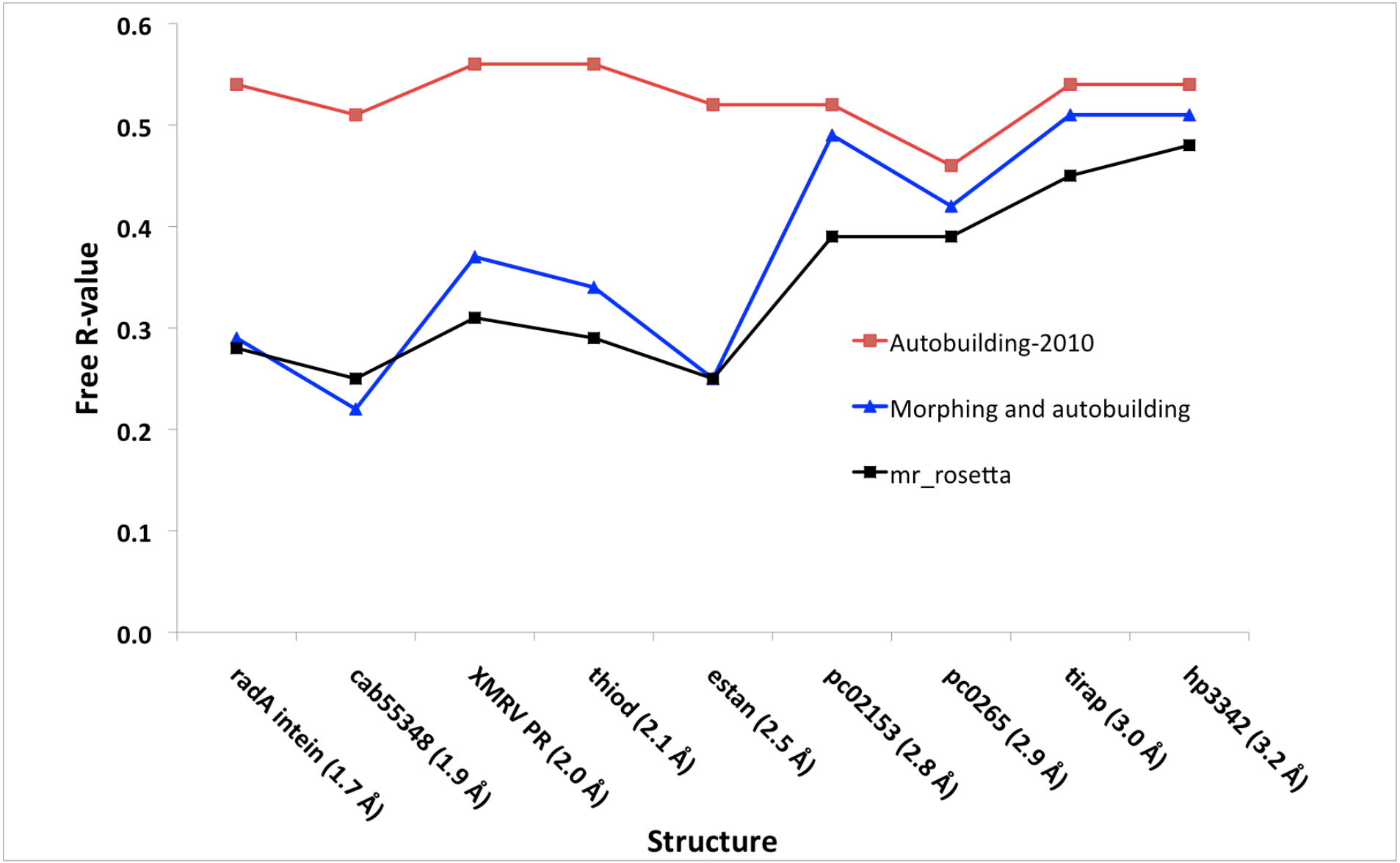
Morphing combined with autobuilding



Morphing combined with autobuilding



Morphing combined with autobuilding



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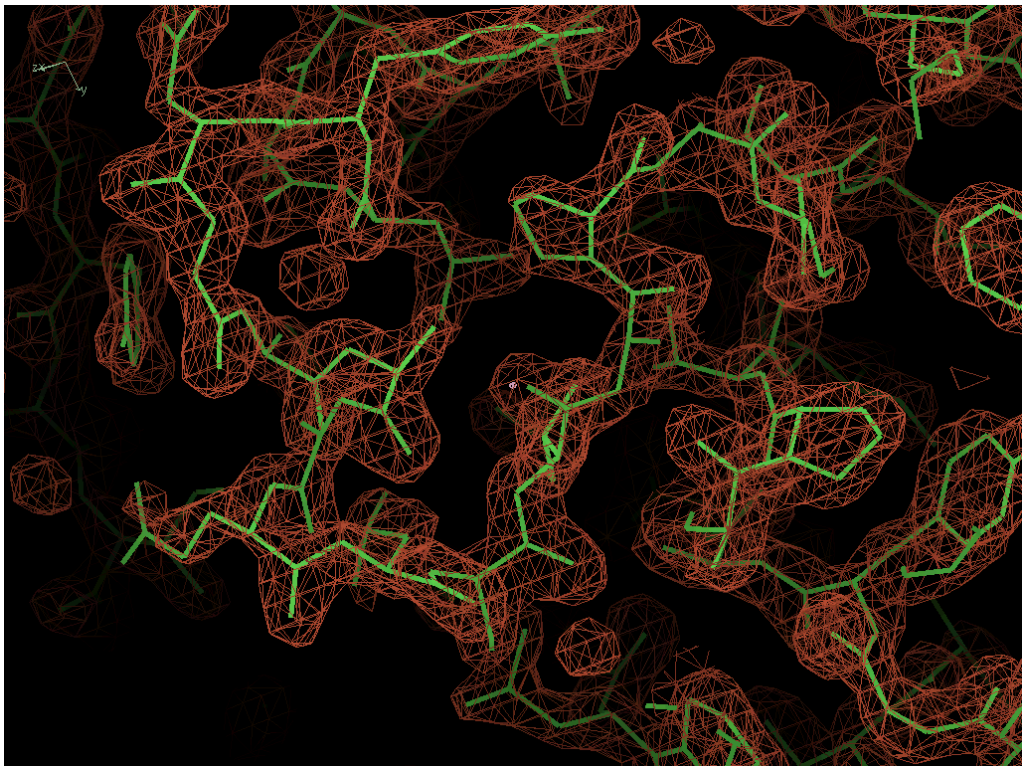
Applications for morphing

Molecular replacement templates that close but distorted

Building models into experimental electron density maps when a distant related structure is available



Thanks for data to...

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Sergey M. Vorobiev, NESG
Hideo Iwai, Univ. of Helsinki
P. Raj Pokkuluri, Argonne National Laboratory

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Scripts and documentation for phenix.morph_model are available at...

http://www.phenix-online.org

The PHENIX Project

Phenix

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Los Alamos National Laboratory

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