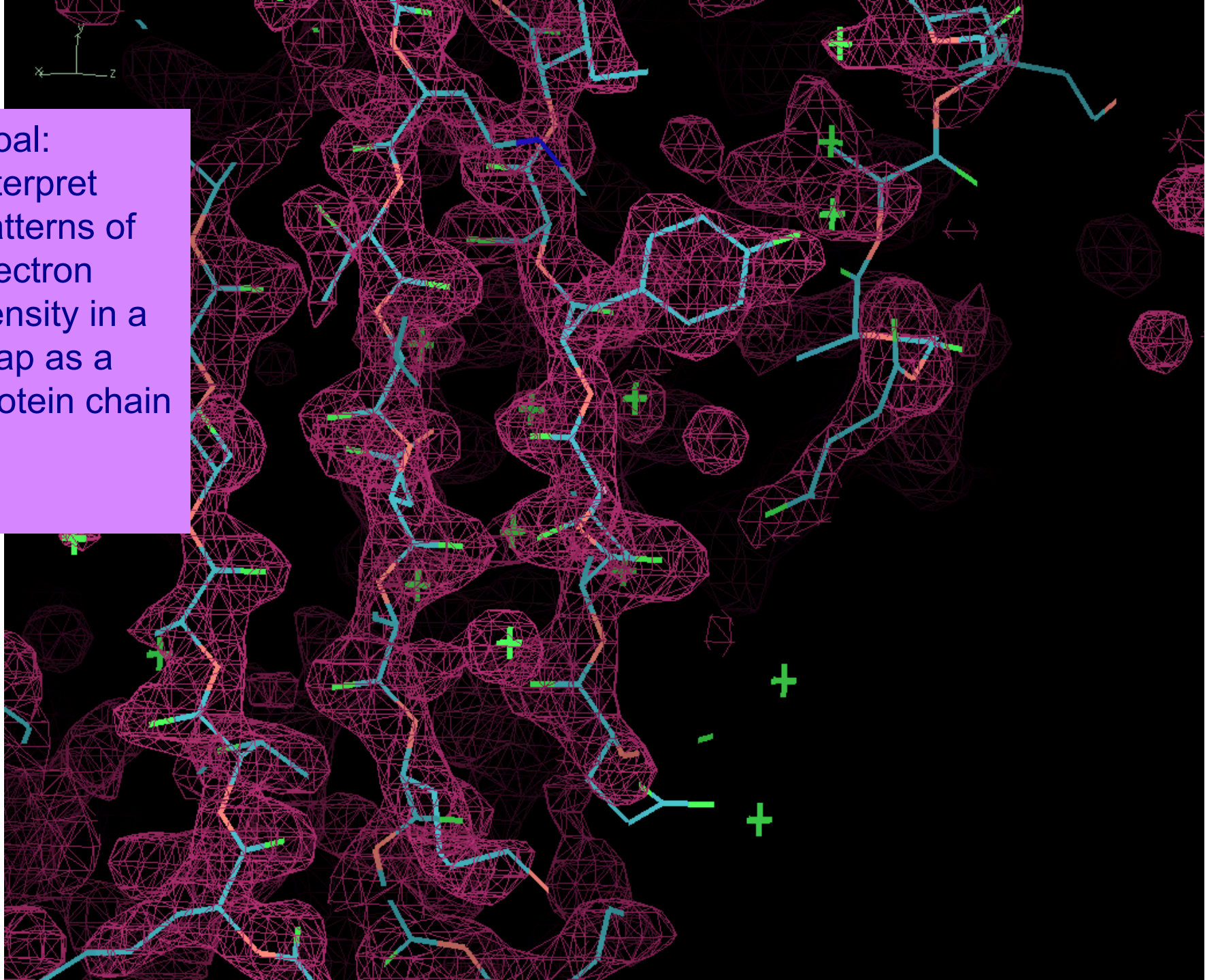# Model-building with PHENIX and Rosetta
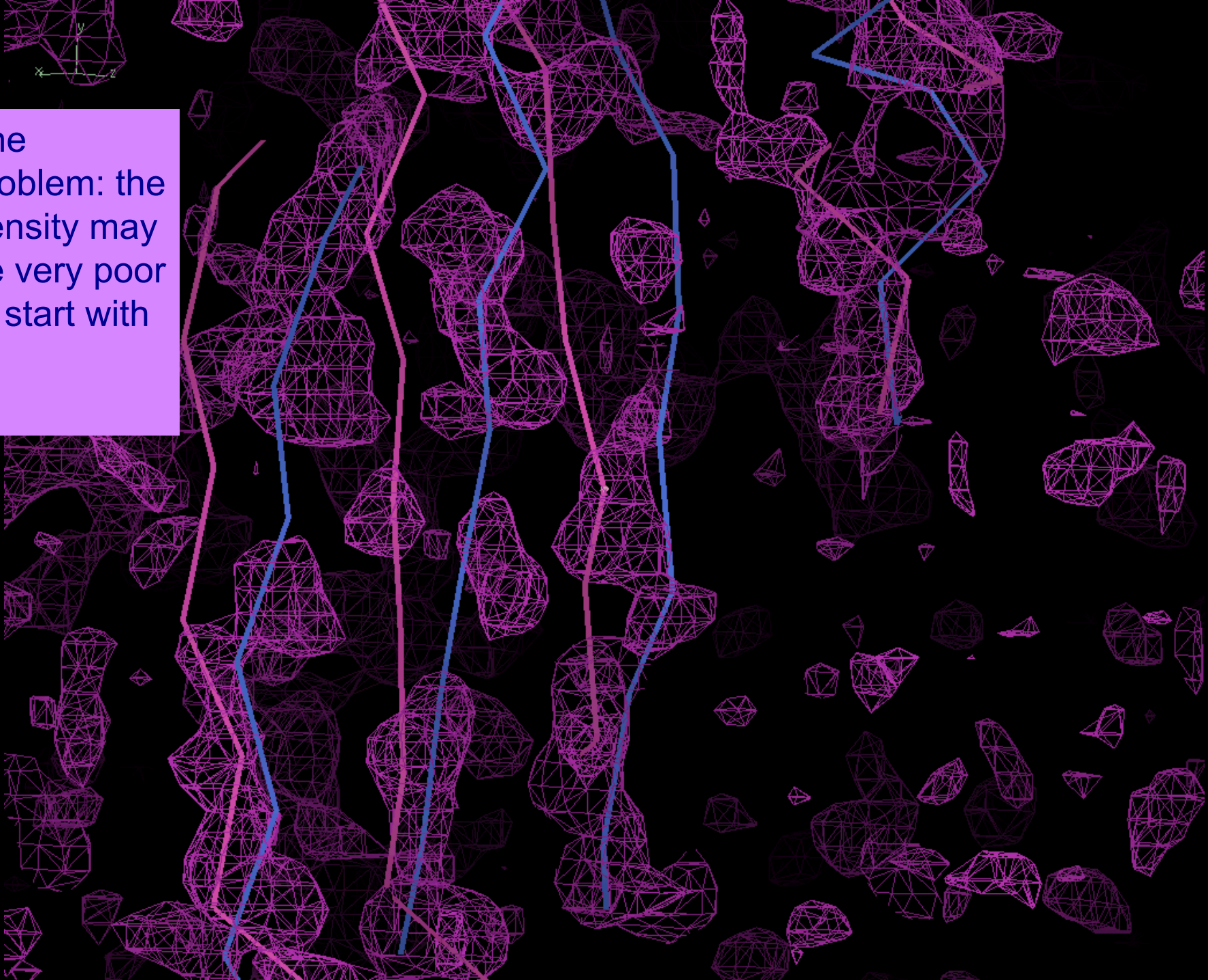
Duke University
Jan 11, 2011

Tom Terwilliger (Los Alamos National Laboratory)
Randy Read (Cambridge University), David Baker,
Frank DiMaio (University of Washington)

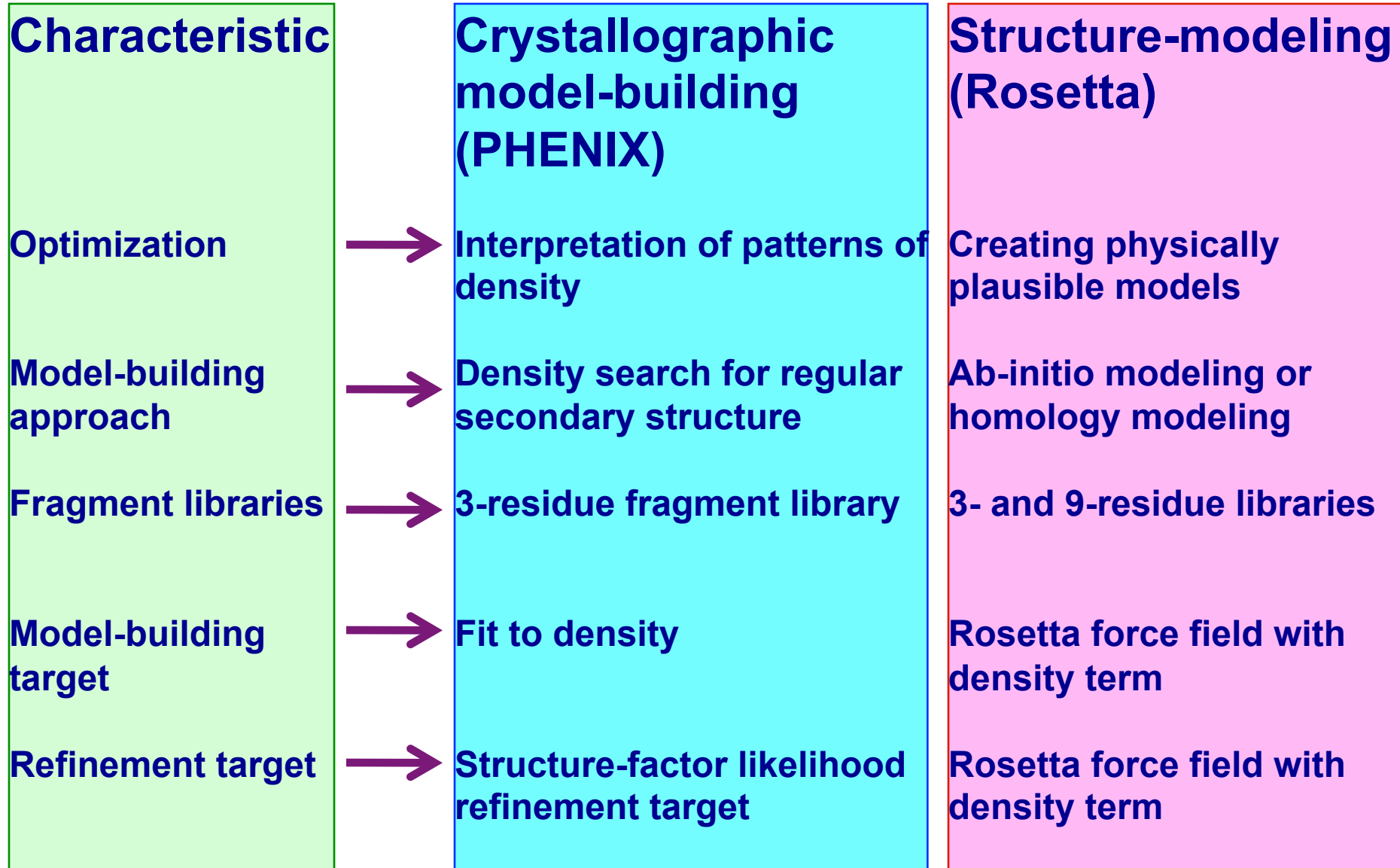Goal: interpret patterns of electron density in a map as a protein chain

The
problem: the
density may
be very poor
to start with

Complementarity of PHENIX and Rosetta model-building
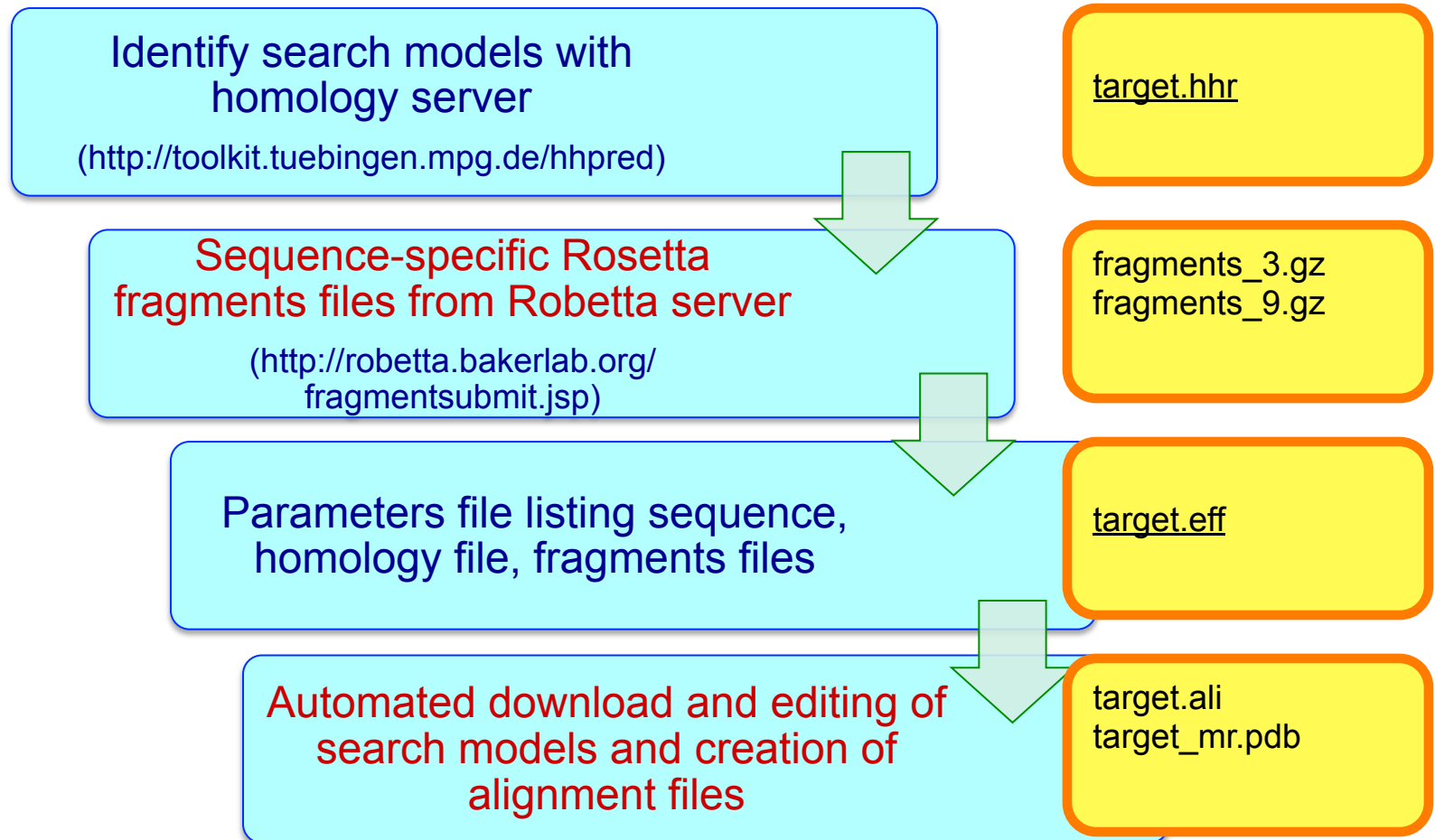(Randy Read, David Baker, Frank DiMaio)

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

Combining structure-modeling with crystallographic model-building
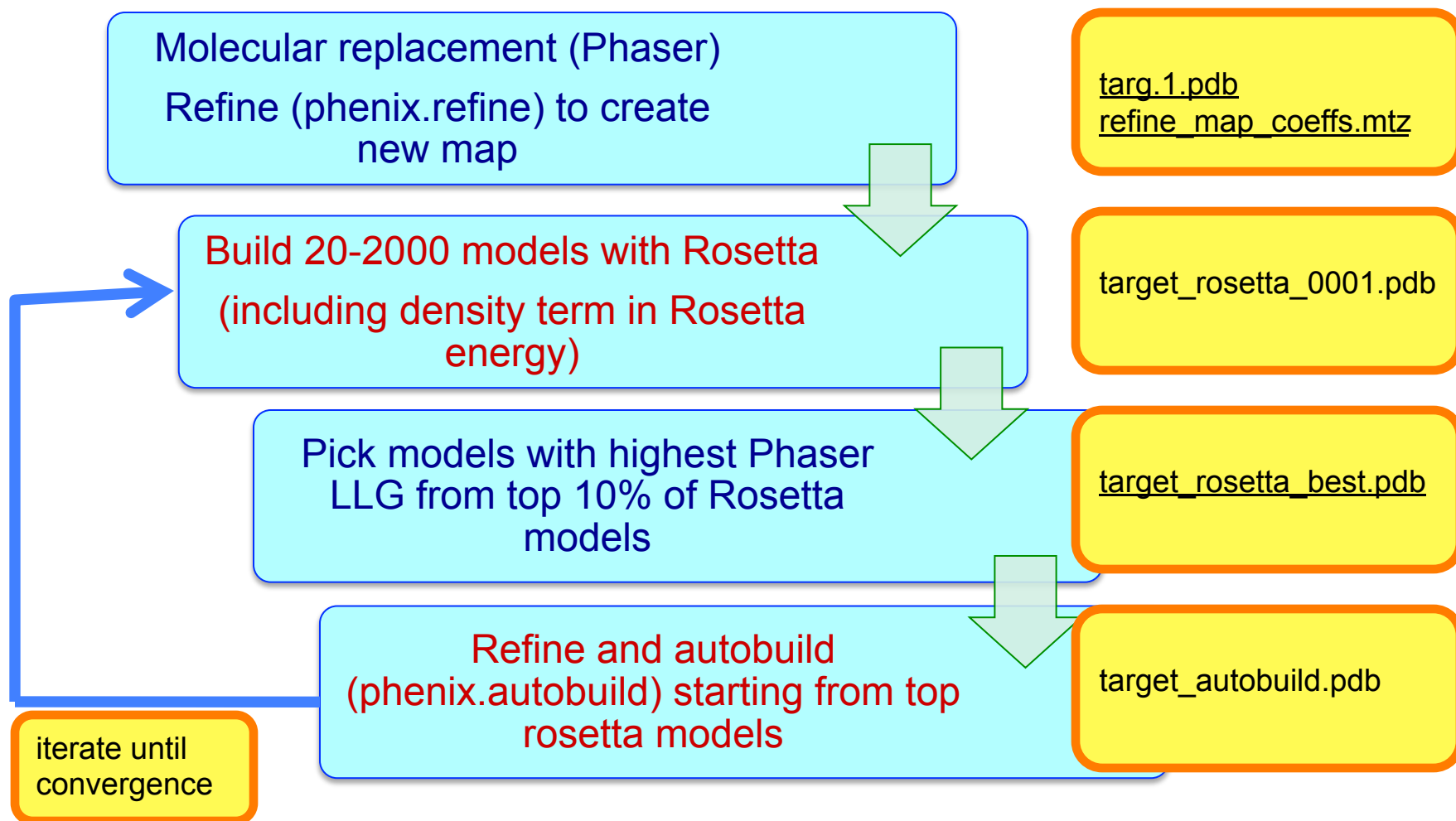
20 templates for 1XVQ from PDB (optimally superimposed)
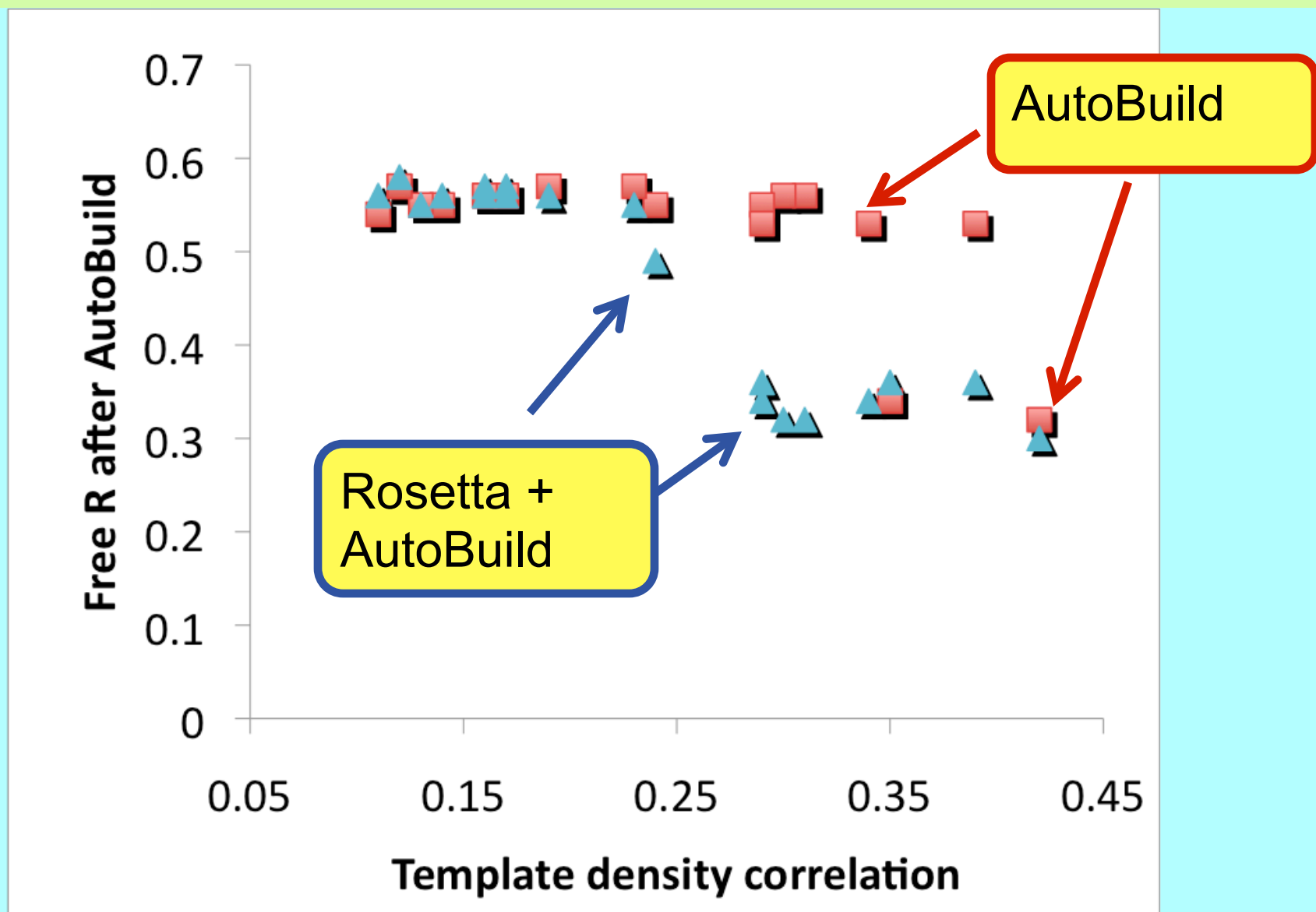
Molecular replacement using distant homology models with PHENIX and Rosetta (phenix.mr_rosetta)

Setup and model preparation

Identify search models with homology server

(http://toolkit.tuebingen.mpg.de/hhpred)

target.hhr

Sequence-specific Rosetta fragments files from Robetta server

(http://robetta.bakerlab.org/fragmentsubmit.jsp)

fragments_3.gz
fragments_9.gz

Parameters file listing sequence, homology file, fragments files

target.eff

Automated download and editing of search models and creation of alignment files

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

targ.1.pdb
refine_map_coeffs.mtz

Build 20-2000 models with Rosetta

(including density term in Rosetta energy)

target_rosetta_0001.pdb

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

target_rosetta_best.pdb

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

target_autobuild.pdb

iterate until convergence

Structure determination of cab55348 (using template supplied by user)

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

MR model: blue, Final model: green
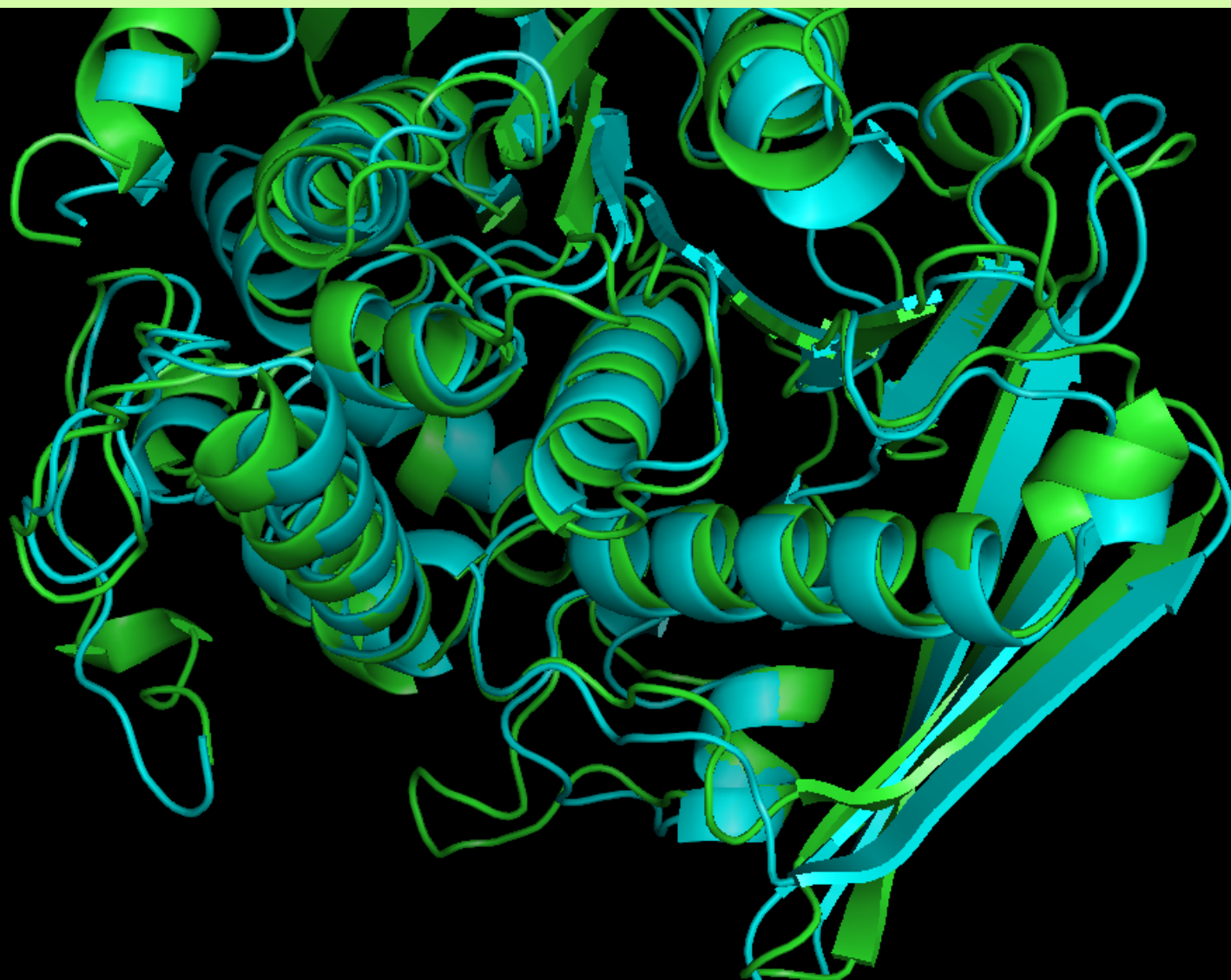
MR model: blue   Best-scoring Rosetta model: pink

Map CC: 0.16   Map CC: 0.40

Overall changes and map correlations during mr_rosetta,

MR model: blue Best-scoring Rosetta model: pink, Final model: green

Map CC: 0.16   Map CC: 0.40

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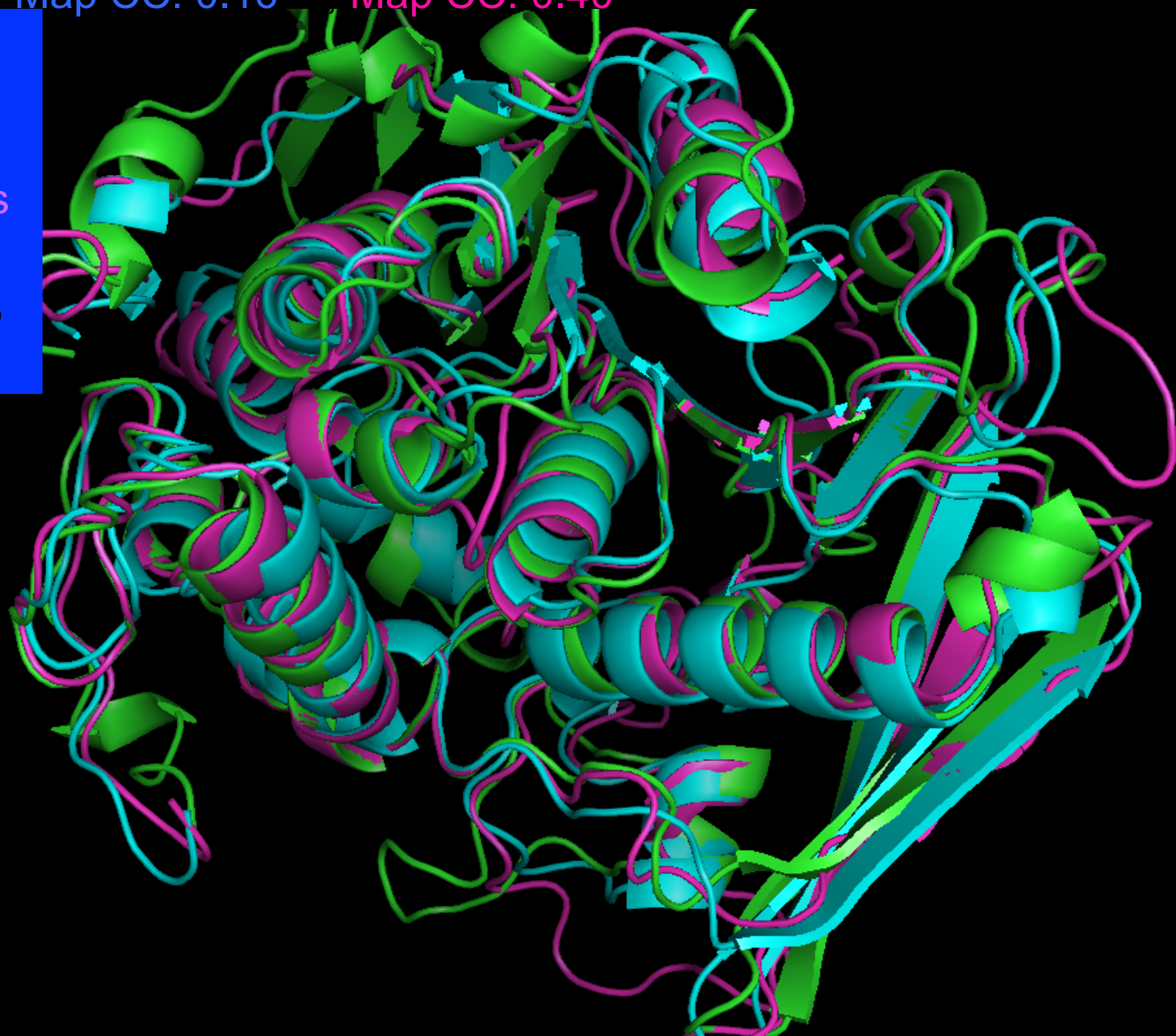
Best-scoring Rosetta model: pink, AutoBuild model: yellow

Map CC: 0.40   Map CC: 0.74

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,
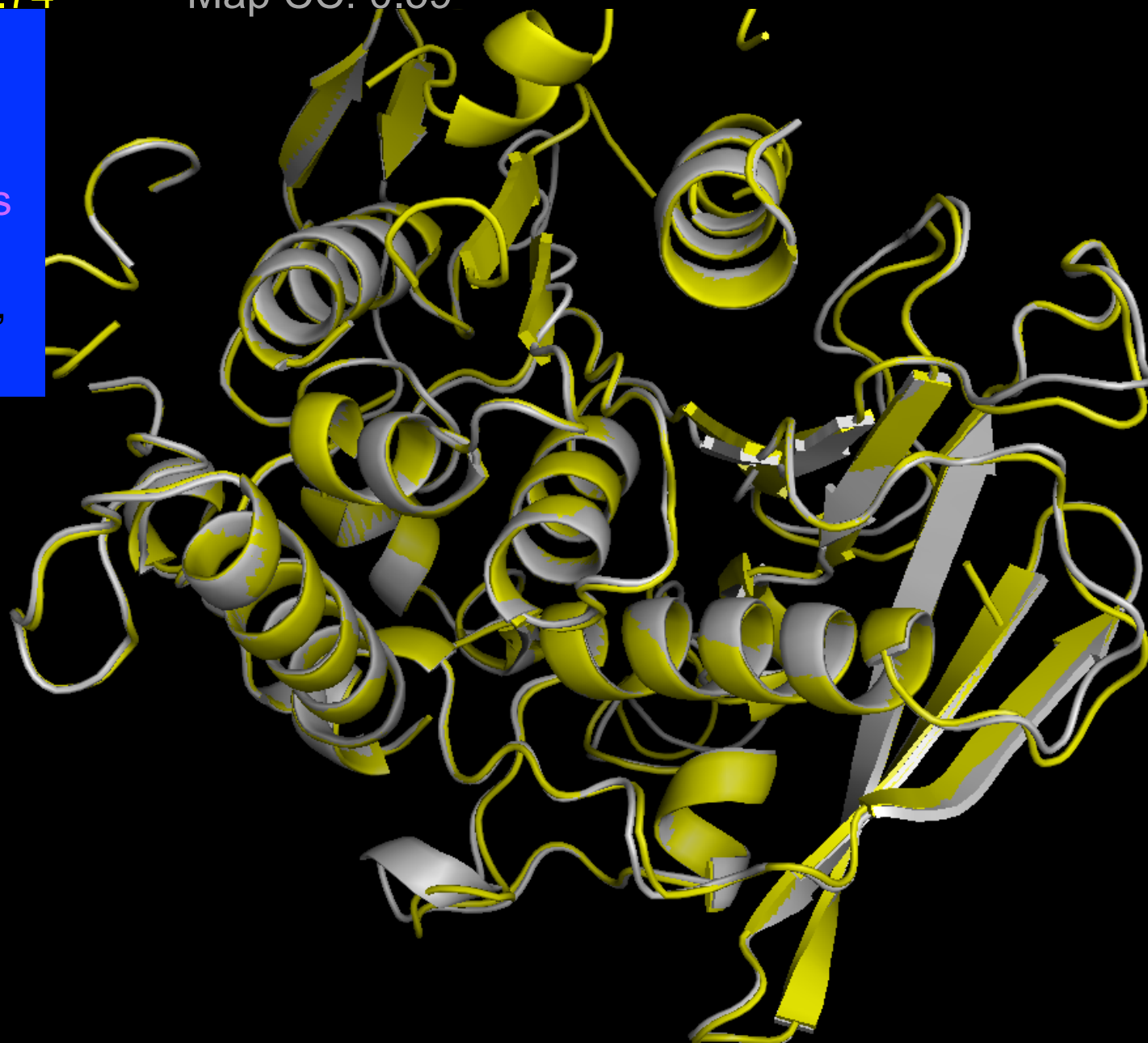
AutoBuild model cycle 1: yellow, AutoBuild model cycle 2: blue

Map CC: 0.74   Map CC: 0.78

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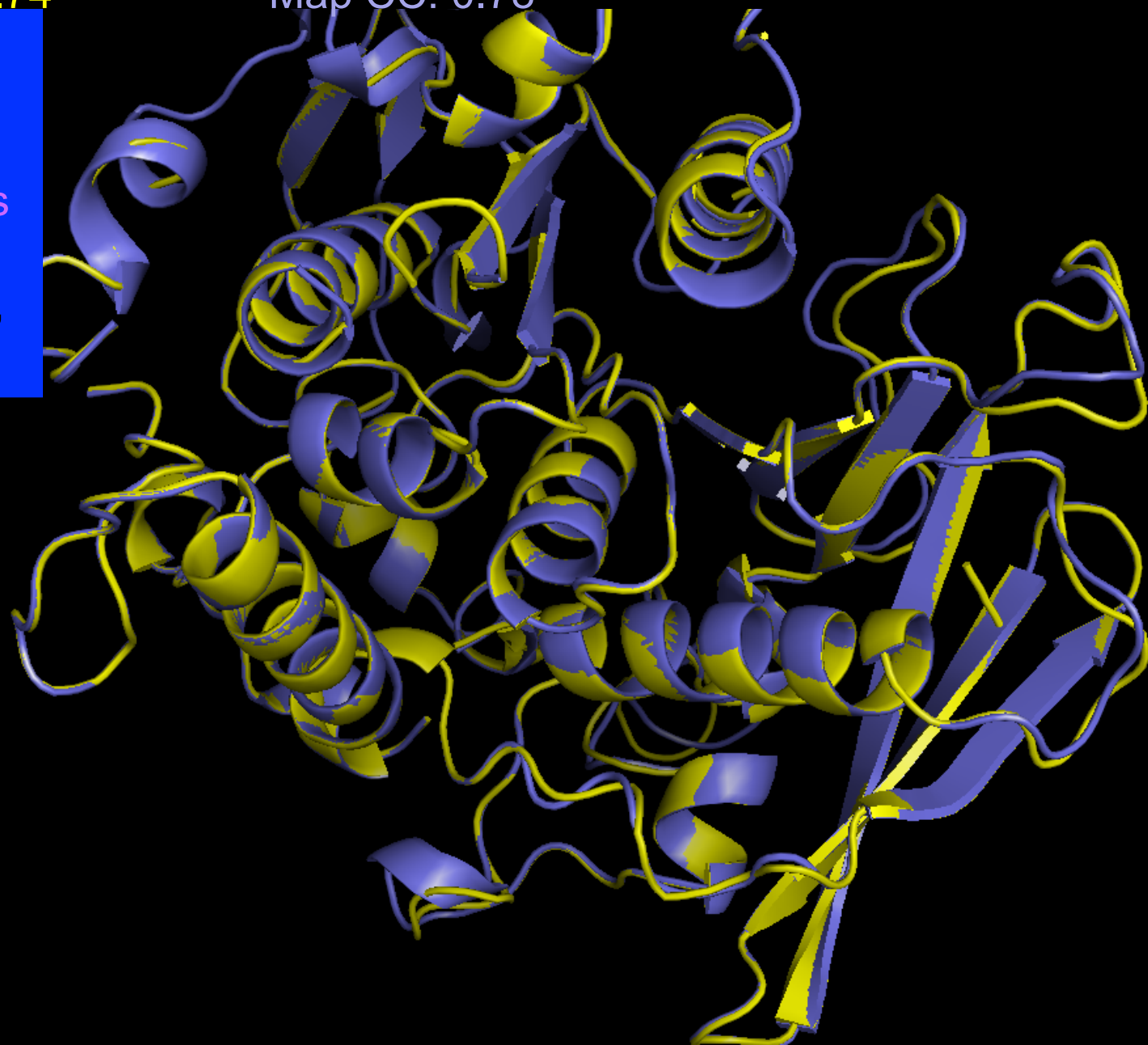
AutoBuild model cycle 2: blue Final model: green

Map CC: 0.78   R/Rfree = 0.26/0.31

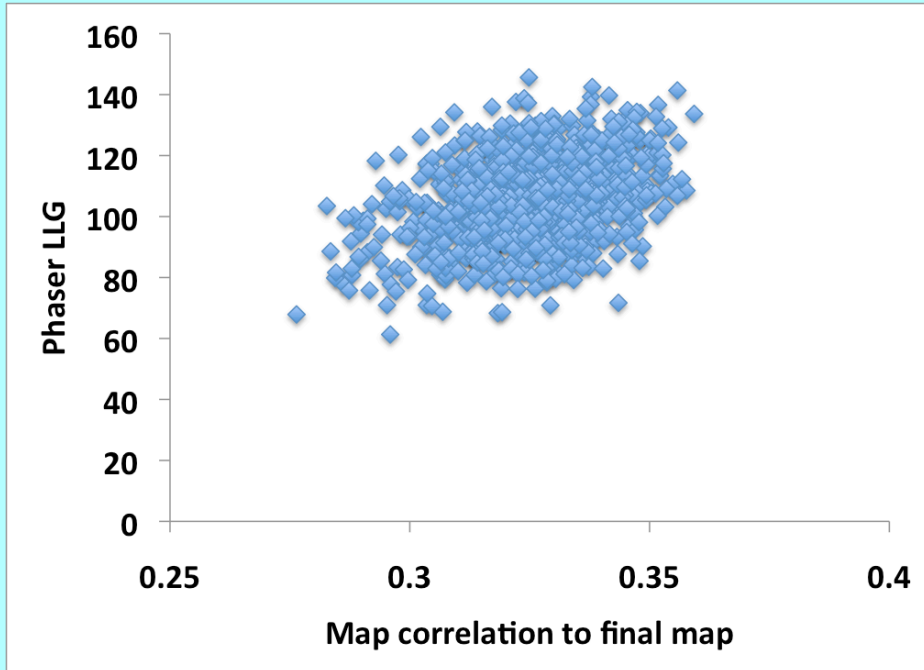Overall changes and map correlations during mr_rosetta,
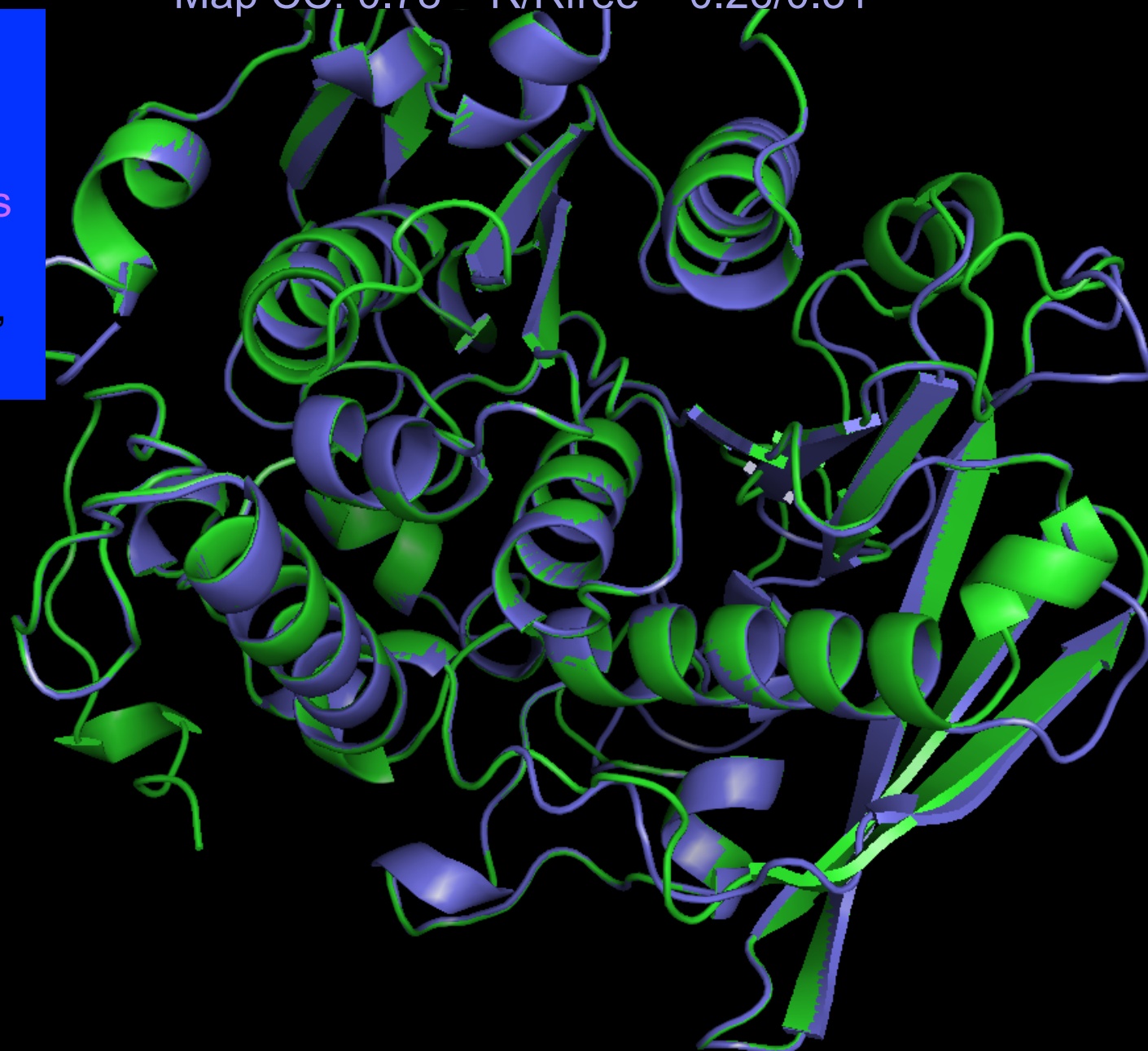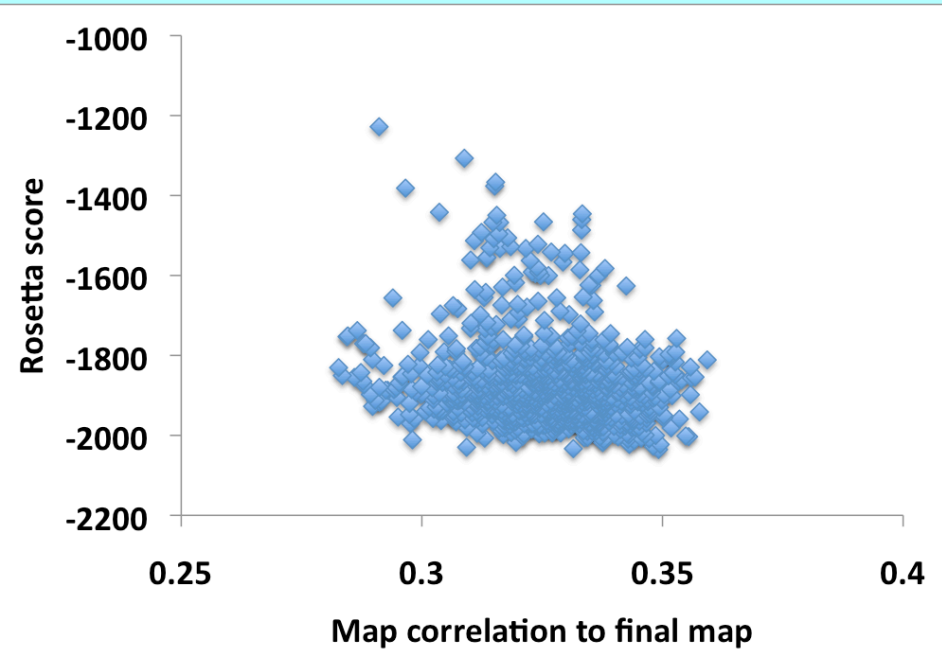
MR model : blue   Final model: pink

Rosetta models cycle 1: green

Sample
Rosetta
models in
cycles 1 and
2,
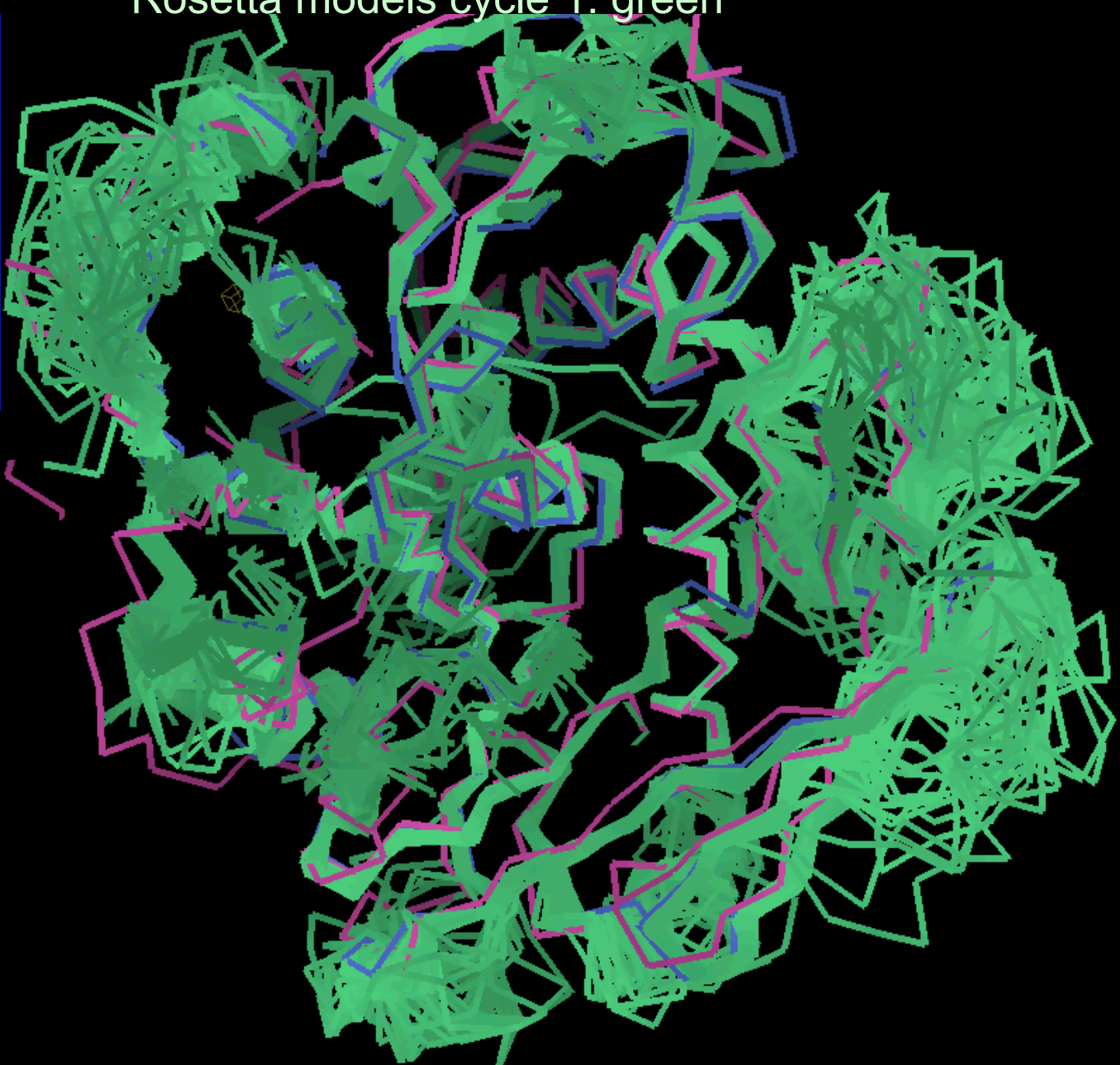
Evaluating Rosetta models with Rosetta score and LLG

MR model : blue   Final model: pink

Rosetta models cycle 2: yellow
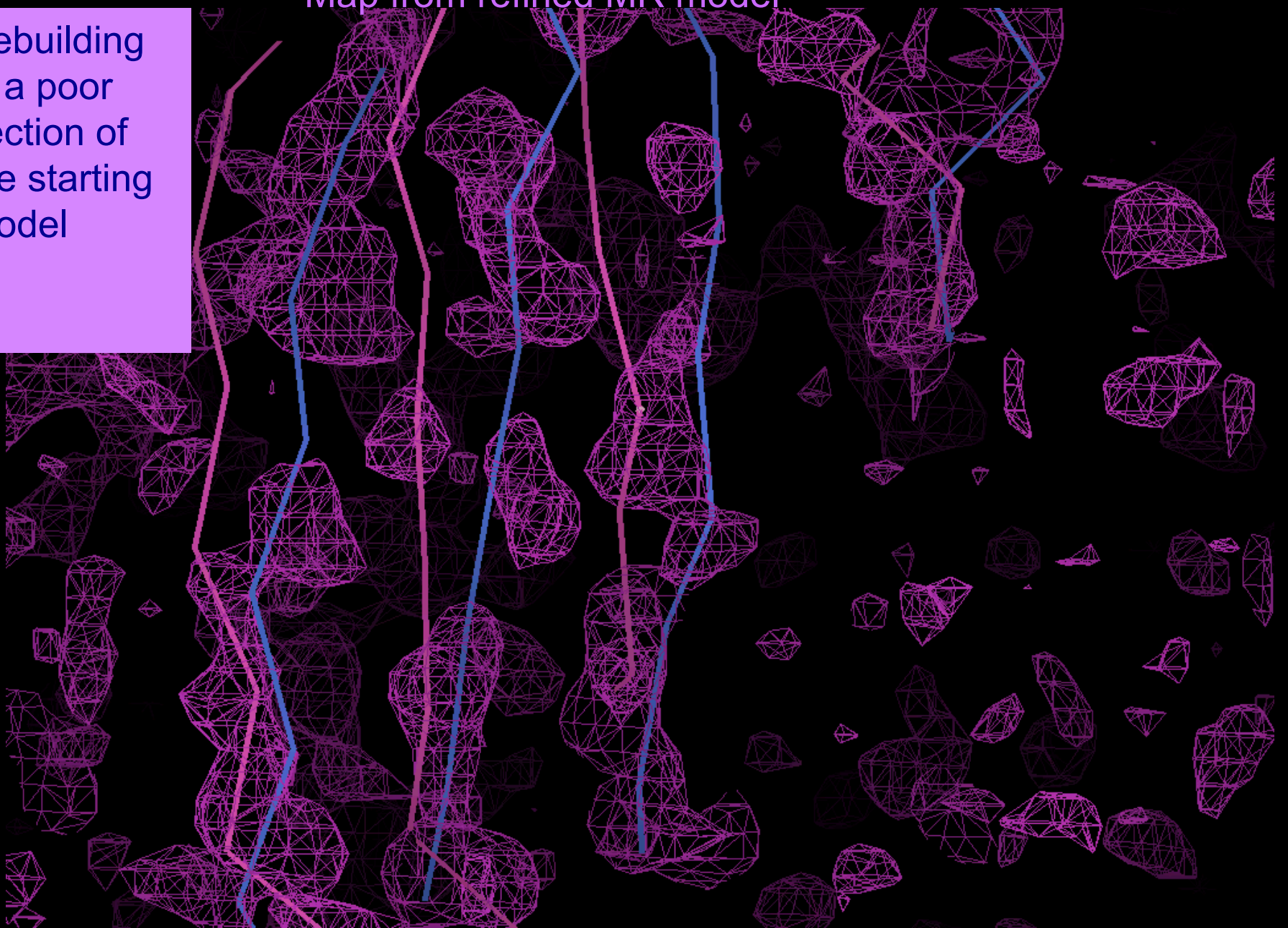
Sample
Rosetta
models in
cycles 1 and
2,

MR model : blue   Final model: pink

Map from refined MR model

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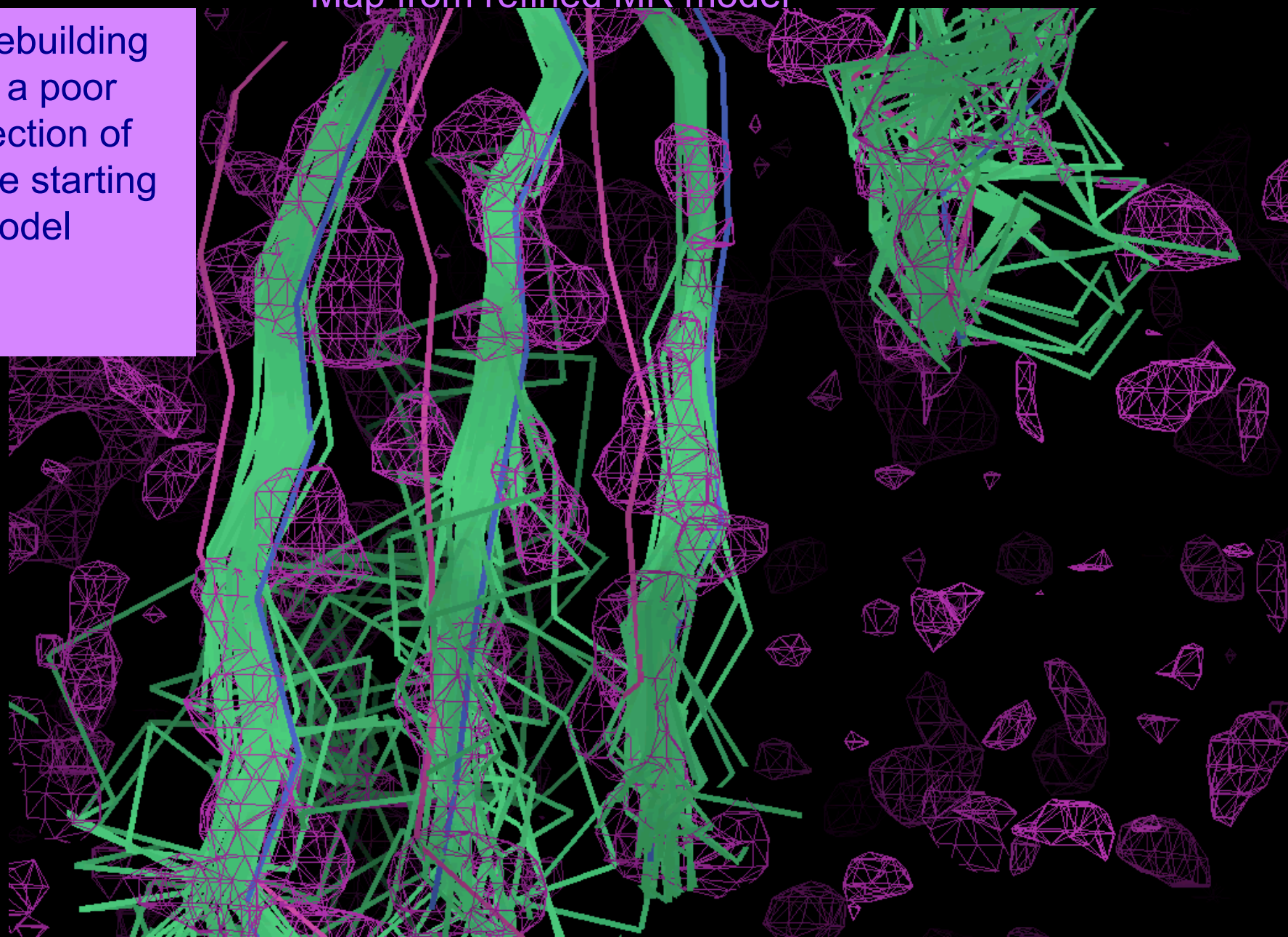
MR model : blue   Final model: pink   Rosetta models cycle 1: green

Map from refined MR model

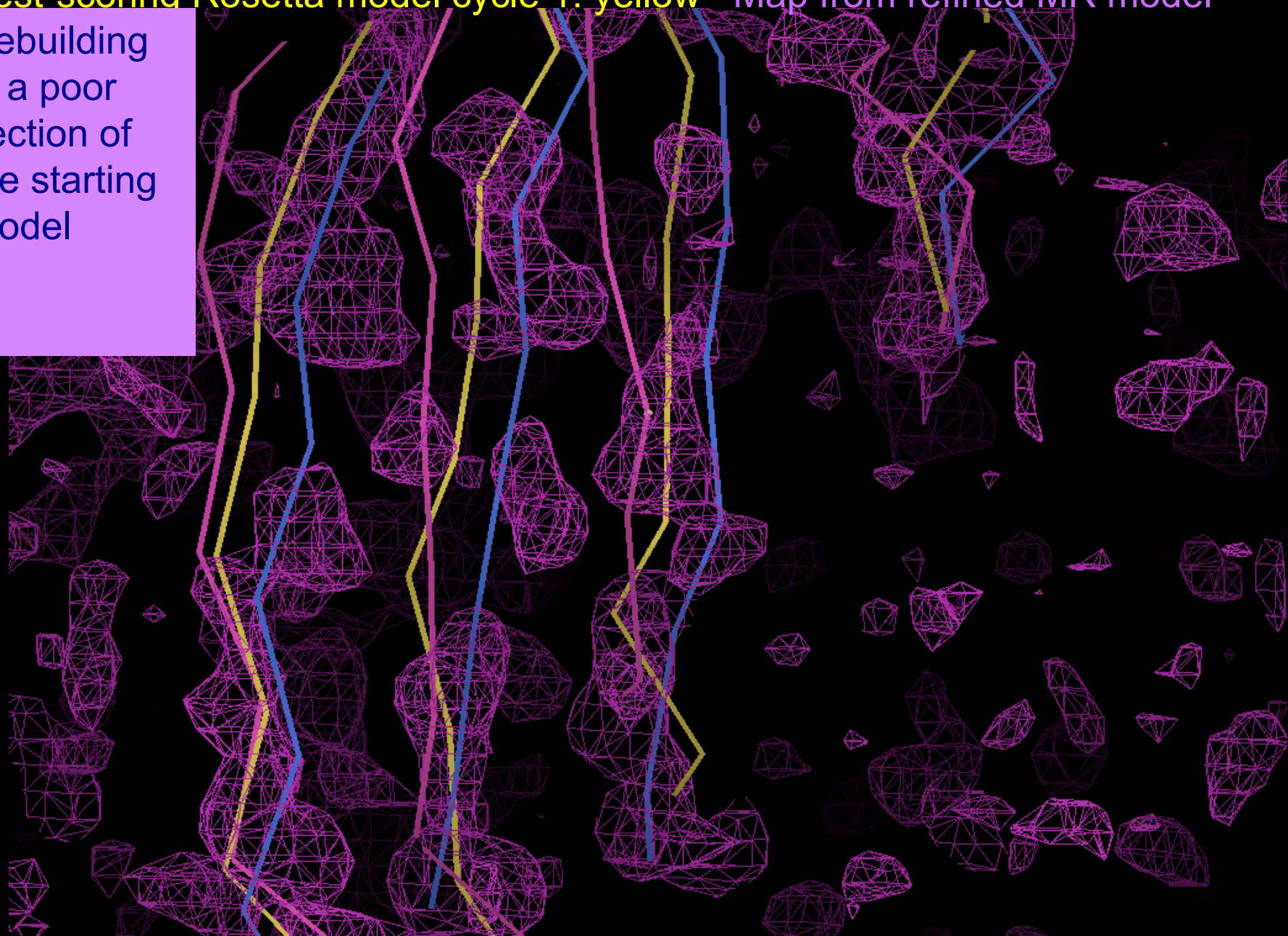Rebuilding in a poor section of the starting model

MR model : blue   Final model: pink

Best-scoring Rosetta model cycle 1: yellow   Map from refined MR model
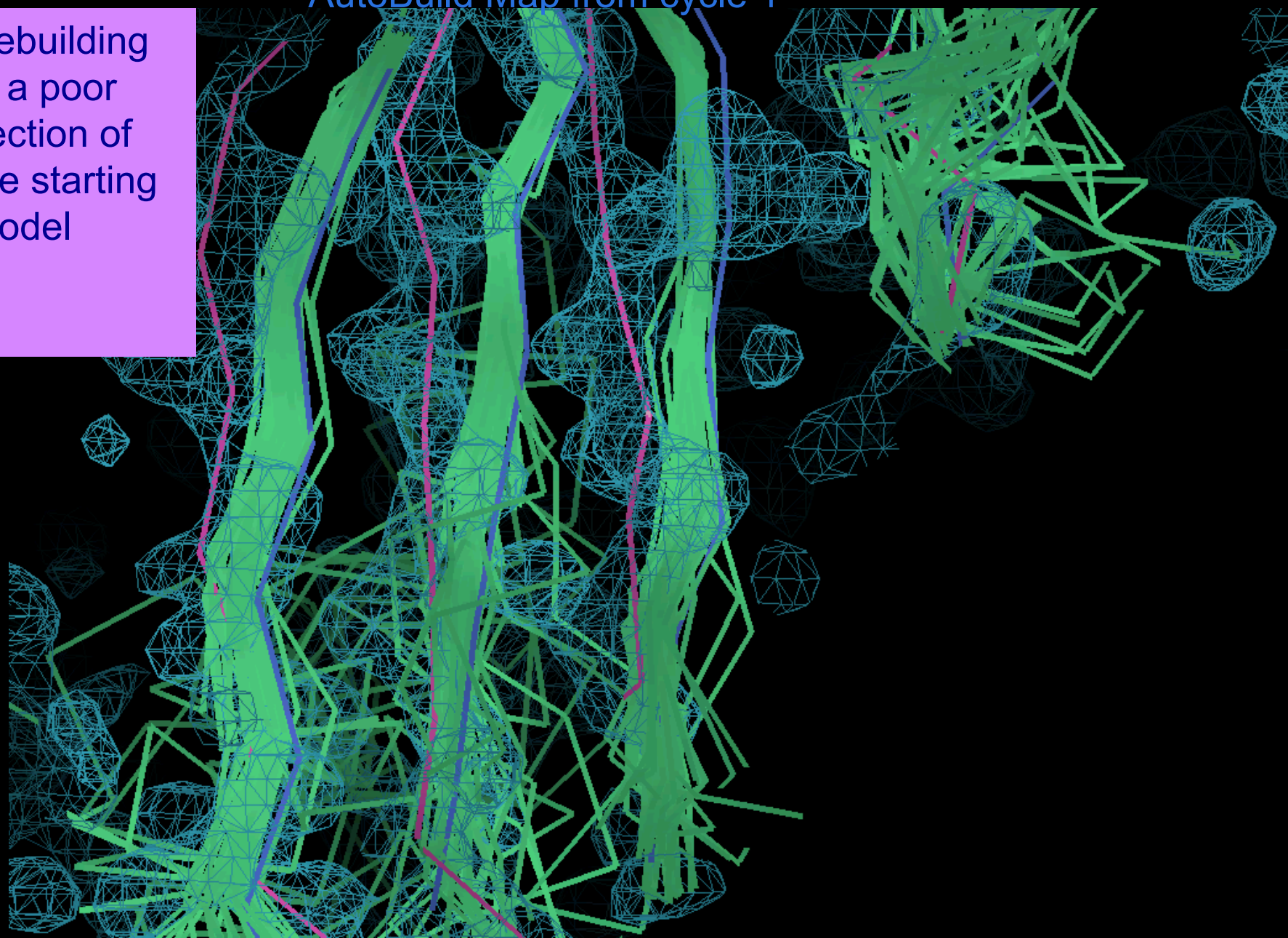
Rebuilding in a poor section of the starting model

MR model : blue   Final model: pink   Rosetta models cycle 1: green

AutoBuild Map from cycle 1

Rebuilding
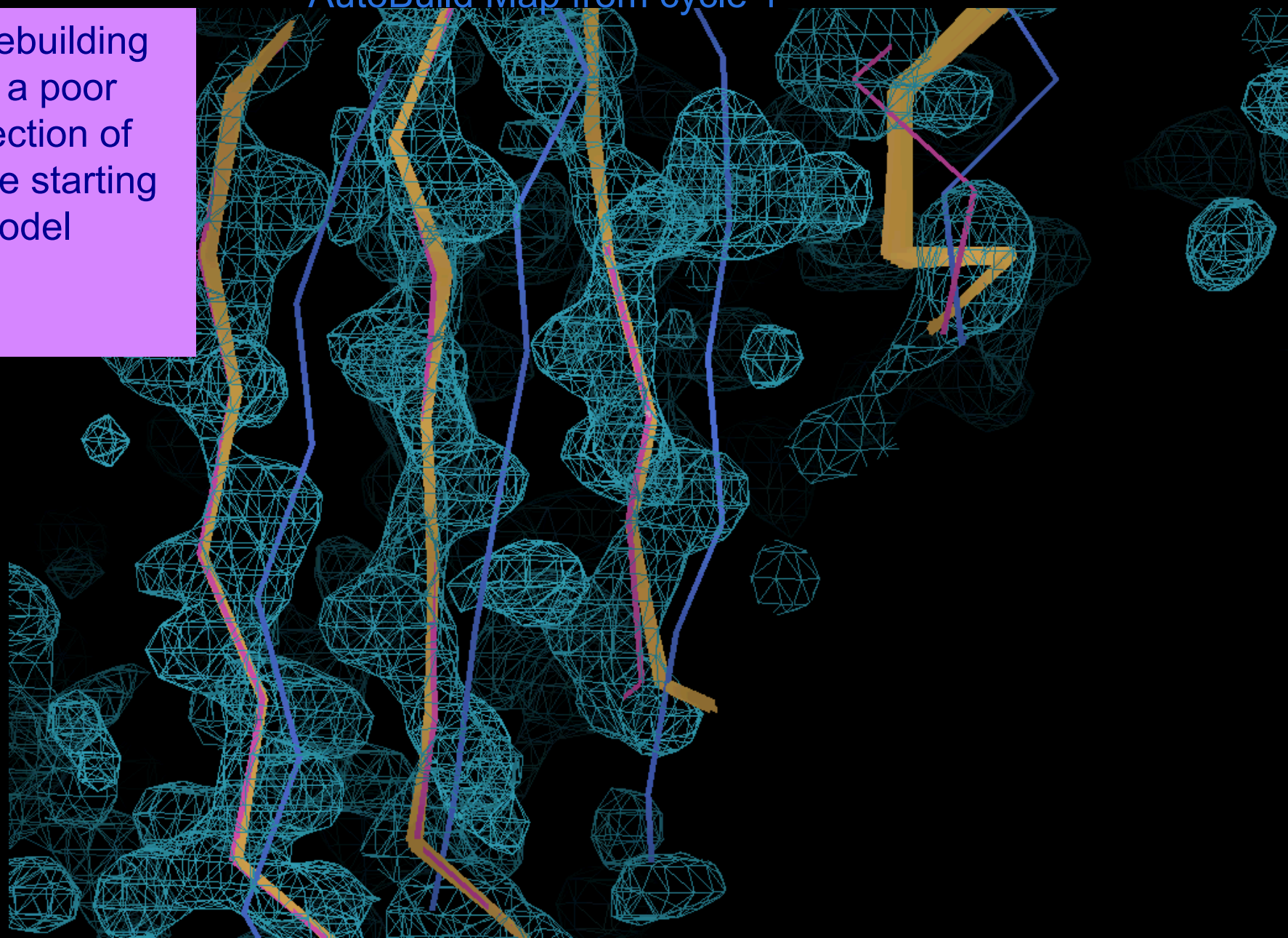in a poor
section of
the starting
model

MR model : blue   Final model: pink   Rosetta models cycle 2: yellow
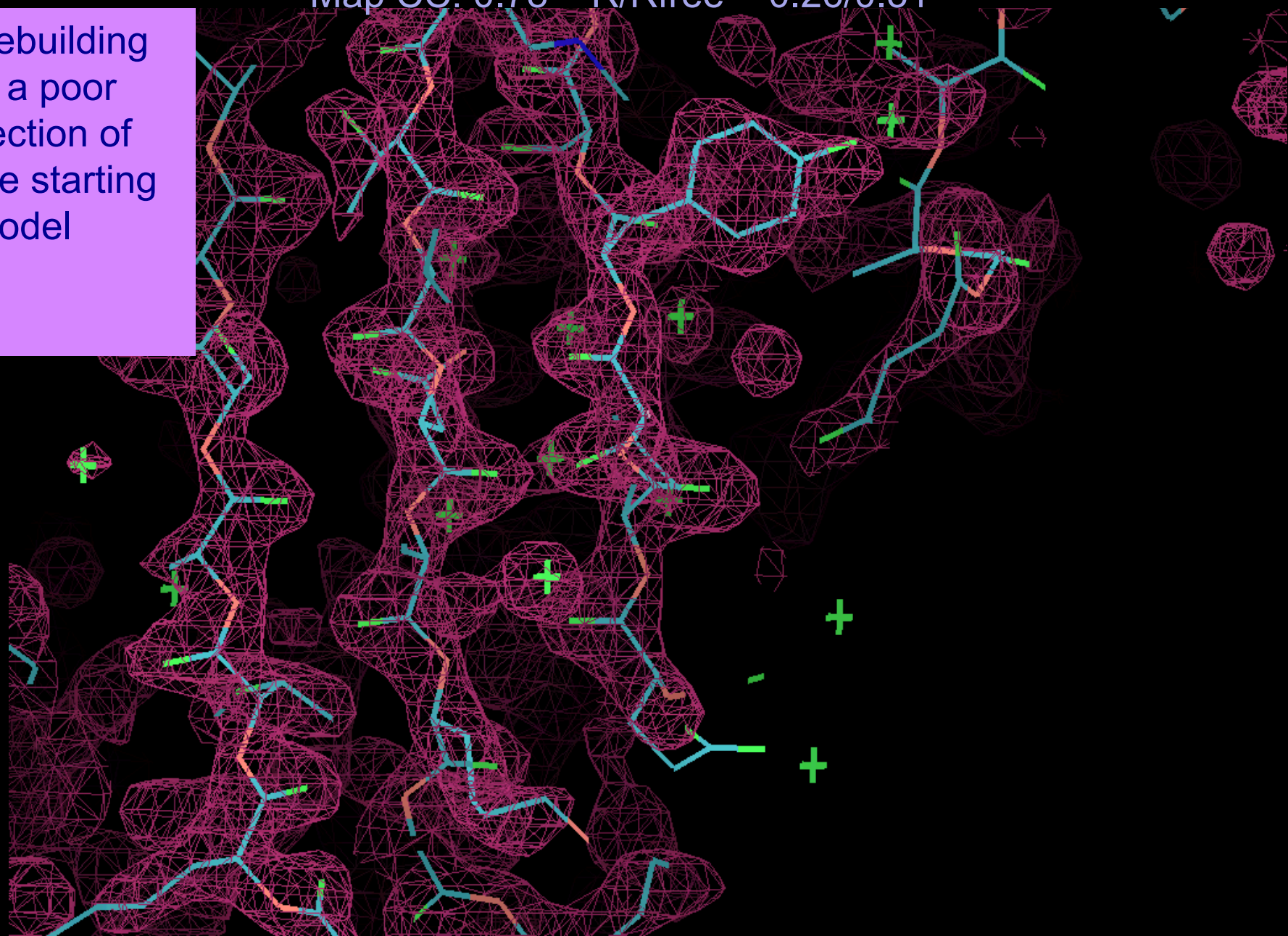
AutoBuild Map from cycle 1

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

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