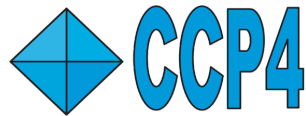


# **Cryo-EM Model Refinement**

## **CCP-EM Icknield Workshop – RAL/DLS**

11<sup>th</sup> October 2023

**Rob Nicholls**  
**nicholls@mrc-lmb.cam.ac.uk**



**REFMAC5**  
Macromolecular structure  
refinement engine

**SERVALCAT**  
Macromolecular structure  
refinement framework

**COOT**  
Visualization and  
model building

**EMDA**  
Cryo-EM map calculation  
and map/model validation

**AceDRG**  
Ligand restraint dictionary  
and conformer generation

**LibG**  
Nucleic acid  
restraint generation

**ProSMART**  
Restraint generation  
and comparative  
structural analysis

*A few key tools for  
model refinement*

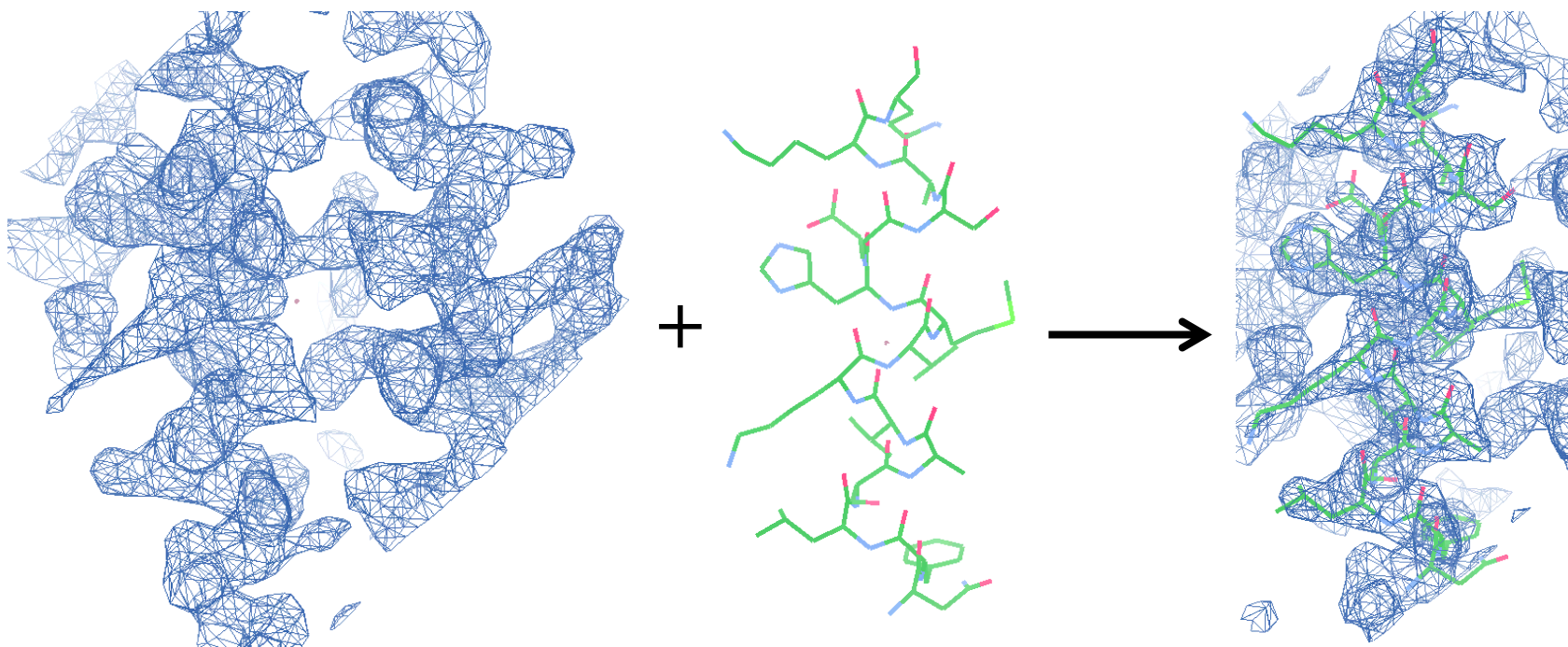
*MRC-LMB, Cambridge:*



# Purpose of Refinement

To fit an atomic model into observed data

- *Model should agree with the observed data*
- *Model must be chemically and structurally sensible*



Data

Atomic model

Fit and refine

Structure factors (reconstruction/map) are treated as observations...

# Model Refinement

Modern refinement programs use a Maximum Likelihood approach

Maximum Likelihood (ML) target:

$$P(\text{model}; \text{obs}) \rightarrow \max$$

$$P(\text{model}; \text{obs}) \propto P(\text{obs}; \text{model}) P(\text{model}) \rightarrow \max$$

likelihood:  $P(F_{\text{obs}}; F_{\text{calc}})$

prior

$$\log[P(\text{obs}; \text{model})] + \log[P(\text{model})] \rightarrow \max$$

$$-\log[P(\text{obs}; \text{model})] - \log[P(\text{model})] \rightarrow \min$$

*Objective - minimise the negative log-likelihood*

# Model Refinement

Modern refinement programs use a Maximum Likelihood approach

MX/Cryo-EM target functions have two components:

$$f_{\text{total}} = w f_{\text{data}} + f_{\text{geometry}}$$

likelihood of the data

probability of the model

We have:

- Data – to refine our model against
- Parameters to refine – describing the model

**We also need prior knowledge (restraints)**

*These help ensure chemical and structural integrity*

# Restraints

Standard restraints (used by default) include:

- Bond lengths
- Angles
- Chirals
- Planes
- Some torsion angles
- B-values
- VDW repulsions

These help to ensure that the model is chemically sensible

Note – we generally deal with restraints, not constraints

# Cryo-EM vs MX

*Tools designed for low-resolution MX have been repurposed for high-resolution cryo-EM*

## Some relevant differences:

- “Observations” are electrostatic potential maps
  - *In MX the observations are estimated diffraction spot intensities (usually converted to amplitudes)*
- Able to obtain phase information (although amplitudes and phases are noisy)
  - *map is not updated as model is refined*
- No crystallographic properties (e.g. space groups) or peculiarities (e.g. twinning).
- Point group or helical symmetry (instead of xtal symmetry).
- No fixed unit cell – boundaries are not enforced; artificial boxes are used
- Concept of “resolution”
  - *quoted resolution in MX is the diffraction limit (resolution of the largest Miller indices used)*
  - *In cryo-EM we can consider local resolution*
  - *local map quality varies greatly within and between reconstructions*

## One similarity:

- Scattering: High-resolution information loss
  - *most refinement methods developed for MX can be transferred to cryo-EM*

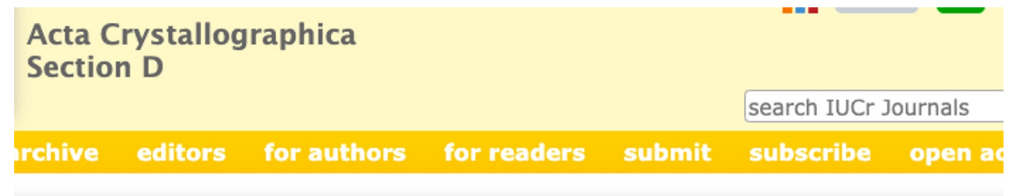
# Cryo-EM Model Refinement

*Uses REFMAC5 for refinement, just like in MX... but*

MX	Optimise agreement between SF amplitudes	– R-factor
Cryo-EM	Optimise agreement between SFs	– FSC

*Wrapped by Servalcat:*

- Symmetry constraints
- Map masking & trimming
- Difference maps



STRUCTURAL  
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## Cryo-EM single-particle structure refinement and map calculation using *Servalcat*

Keitaro Yamashita,<sup>a\*</sup> Colin M. Palmer,<sup>b</sup> Tom Burnley<sup>b</sup> and Garib N. Murshudov<sup>a\*</sup>

<sup>a</sup>MRC Laboratory of Molecular Biology, Francis Crick Avenue, Cambridge CB2 0QH, United Kingdom, and <sup>b</sup>Scientific Computing Department, UKRI Science and Technology Facilities Council, Rutherford Appleton Laboratory, Harwell Campus, Didcot OX11 0FA, United Kingdom

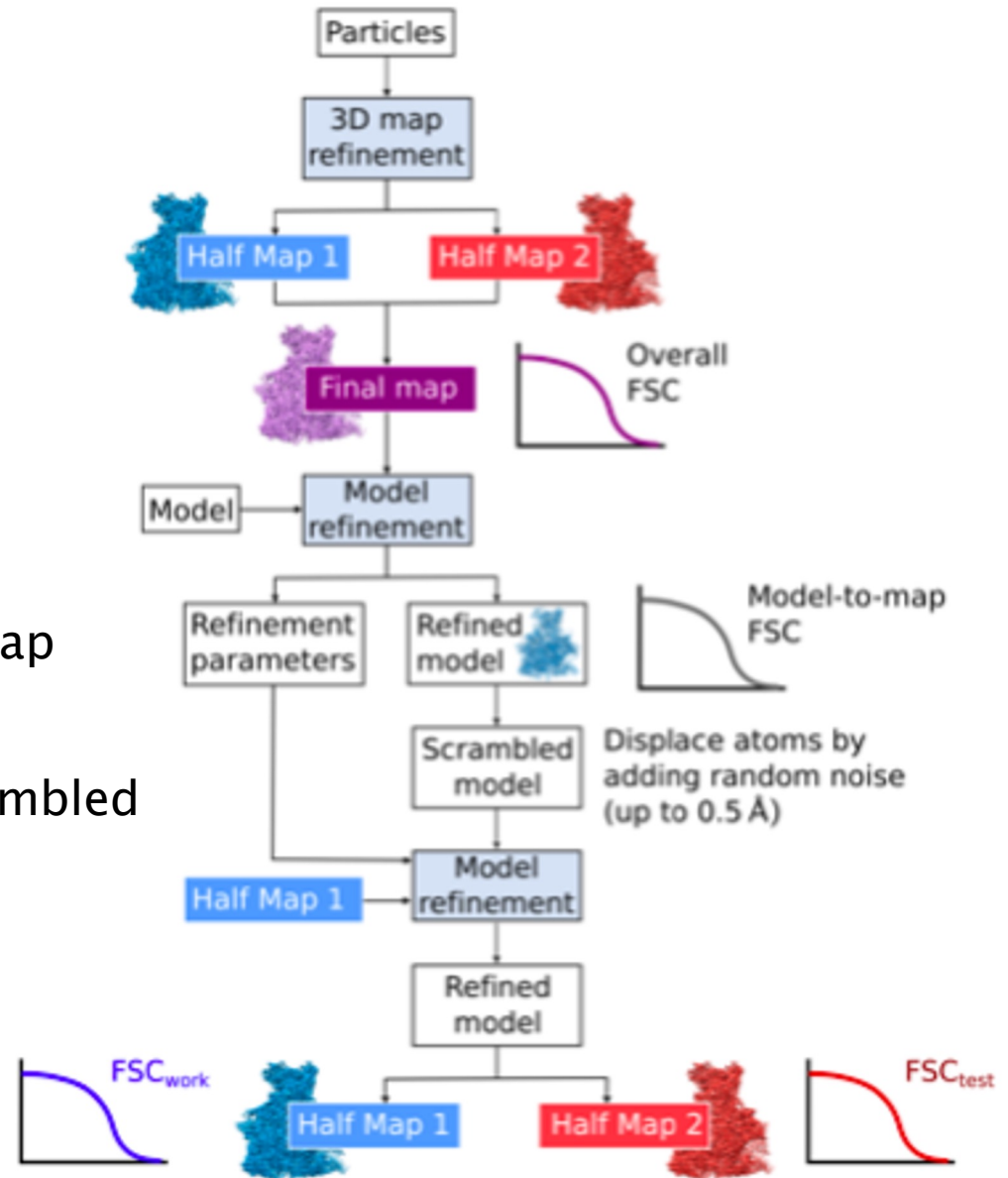
\*Correspondence e-mail: [kyamashita@mrc-lmb.cam.ac.uk](mailto:kyamashita@mrc-lmb.cam.ac.uk), [garib@mrc-lmb.cam.ac.uk](mailto:garib@mrc-lmb.cam.ac.uk)



# Cryo-EM Model Refinement

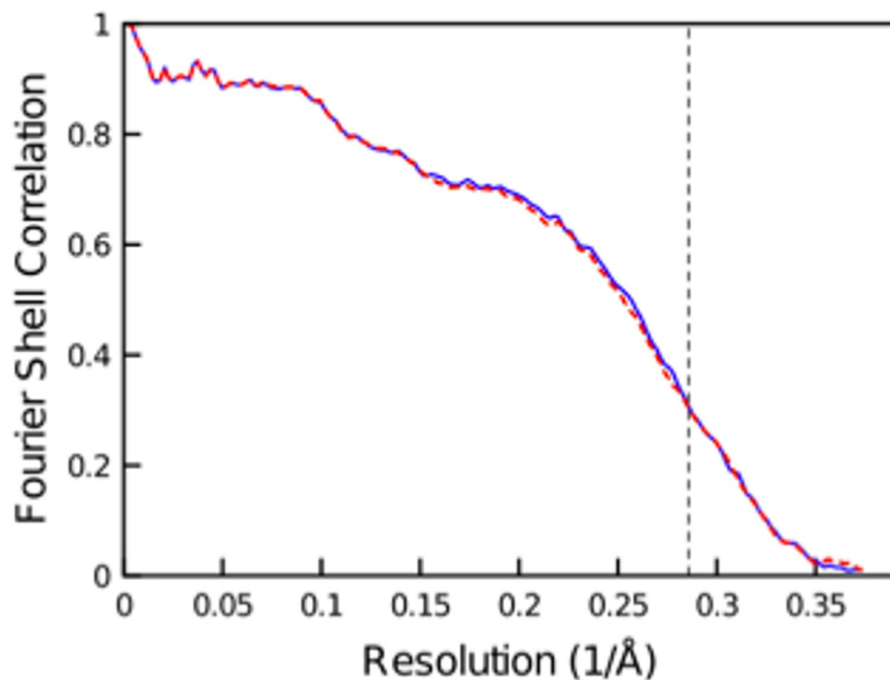
## *Half-map cross-validation:*

1. Initial refinement using full map
2. Second refinement using scrambled model and half map 1
3. Compare model vs map for:
  - a. Half-map 1 - work
  - b. Half-map 2 - test

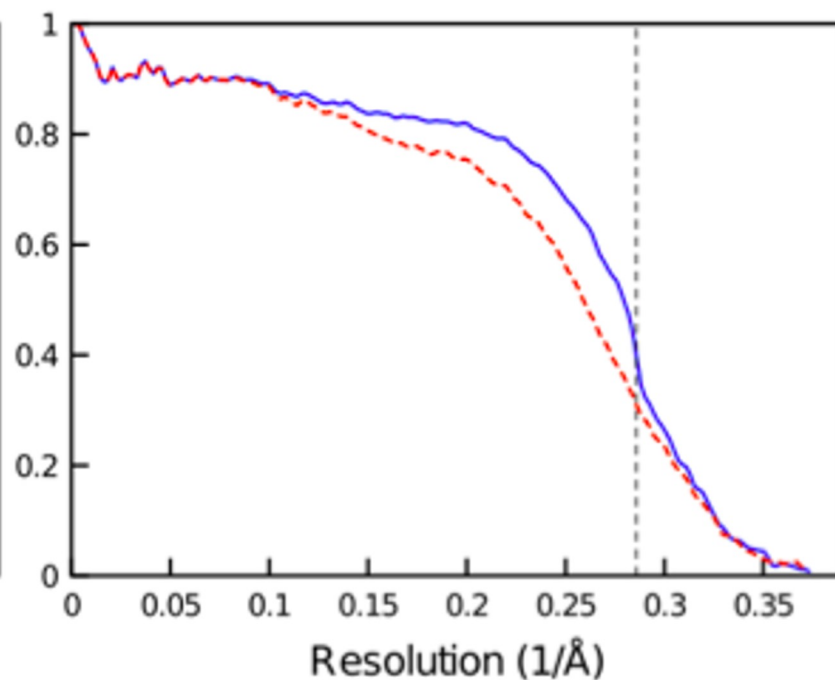


# Half-Map Cross-Validation

Not overfitted



Overfitted



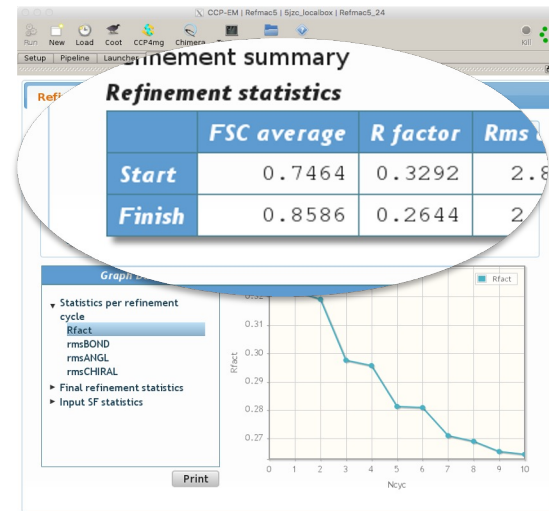
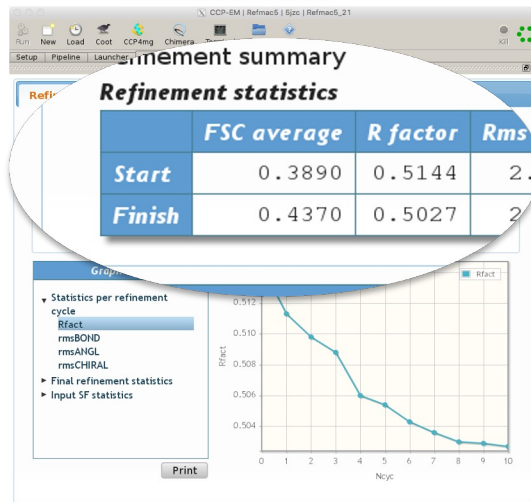
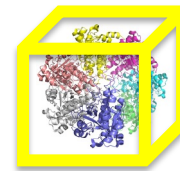
$FSC_{work}$  : model refined against half-map 1; compared to half-map 1  
 $FSC_{free}$  : model refined against half-map 1; compared to half-map 2

# Servalcat Masking & Trimming

Box size is arbitrary, unlike in MX



Helical filament 5jzc (4.2 Å)

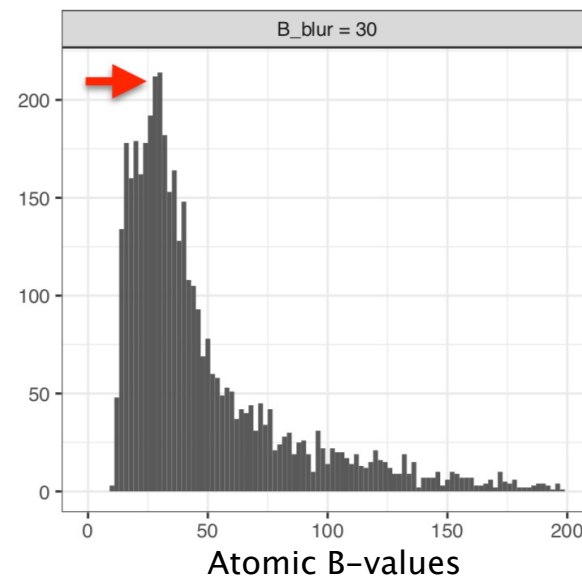
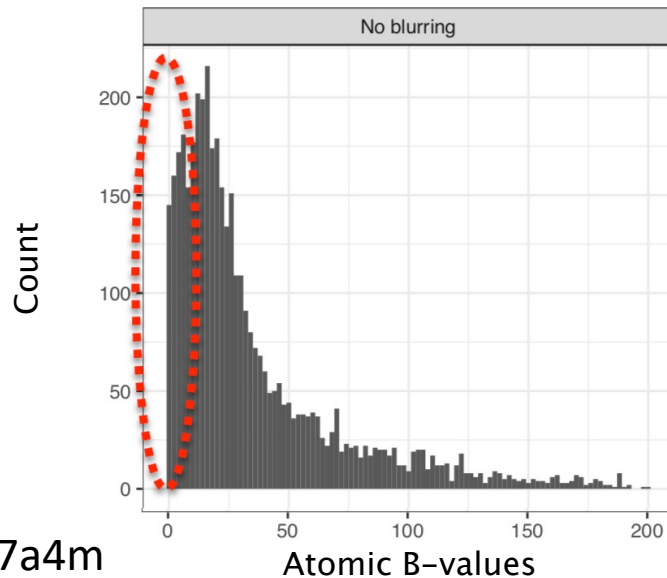
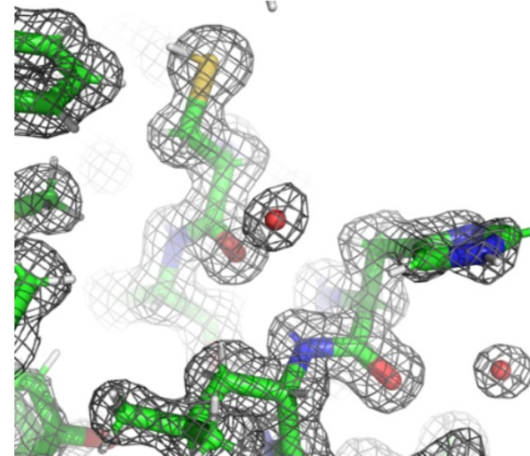
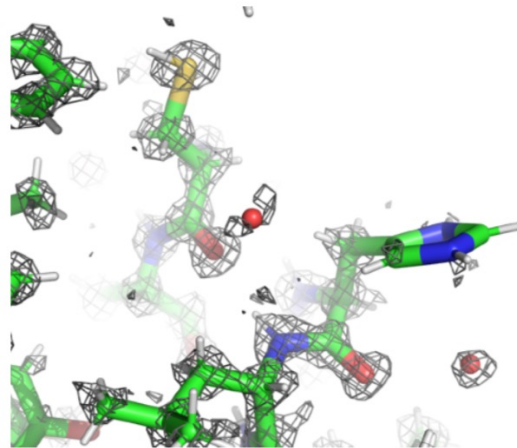


## *Applied to half-maps:*

- Sharpen map – to avoid blurring of signal
- Mask map around modelled atoms
- Blur map – using the same B-factor as for sharpening

# Unsharpened Unweighted Half-Maps

Maps often oversharpened – negatively affects refinement; causes incorrect B-values  
So always refine against unsharpened, unweighted half-maps

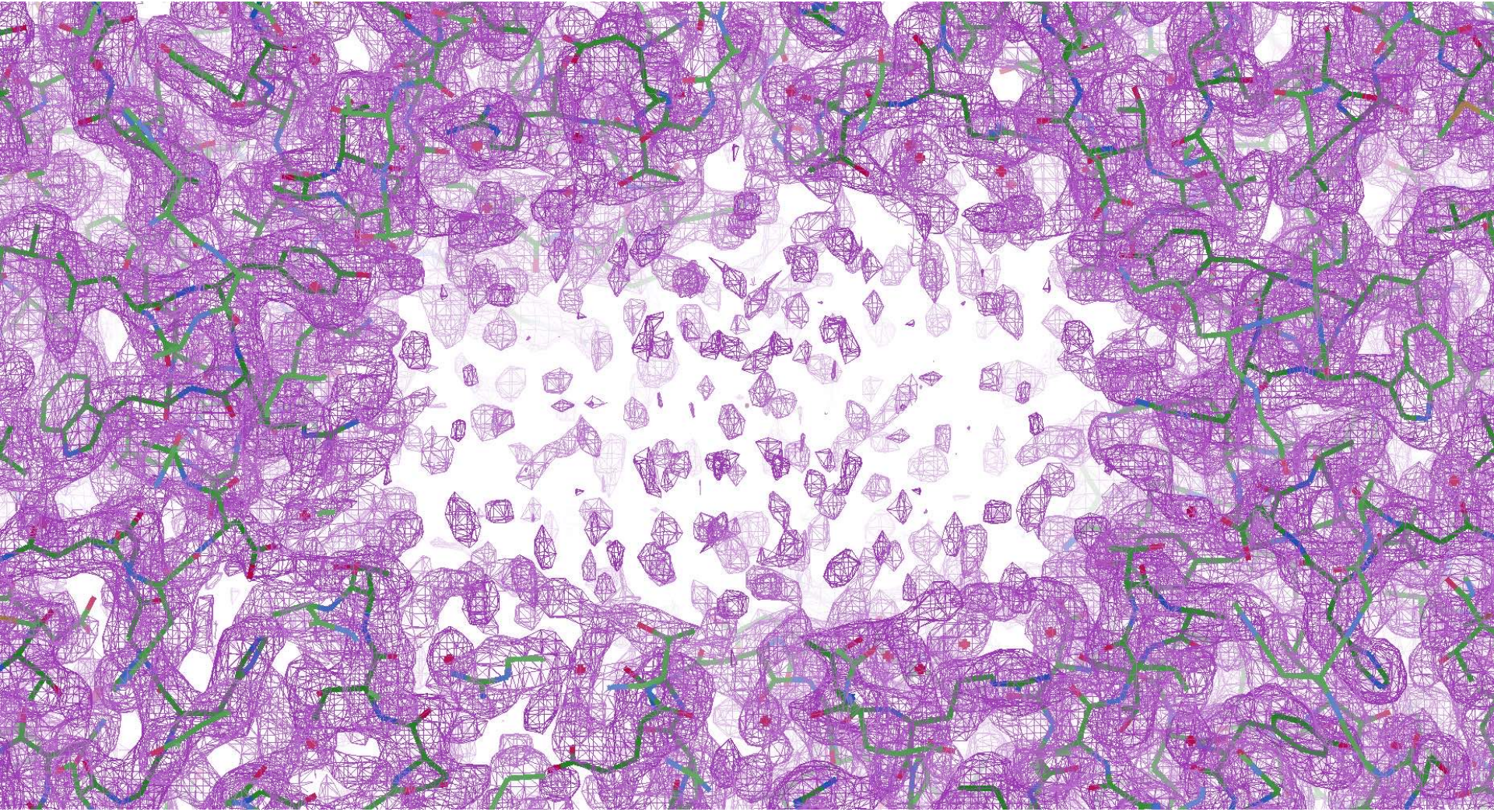


EMD-11638, 7a4m

# Map Sharpening/Blurring

Default map

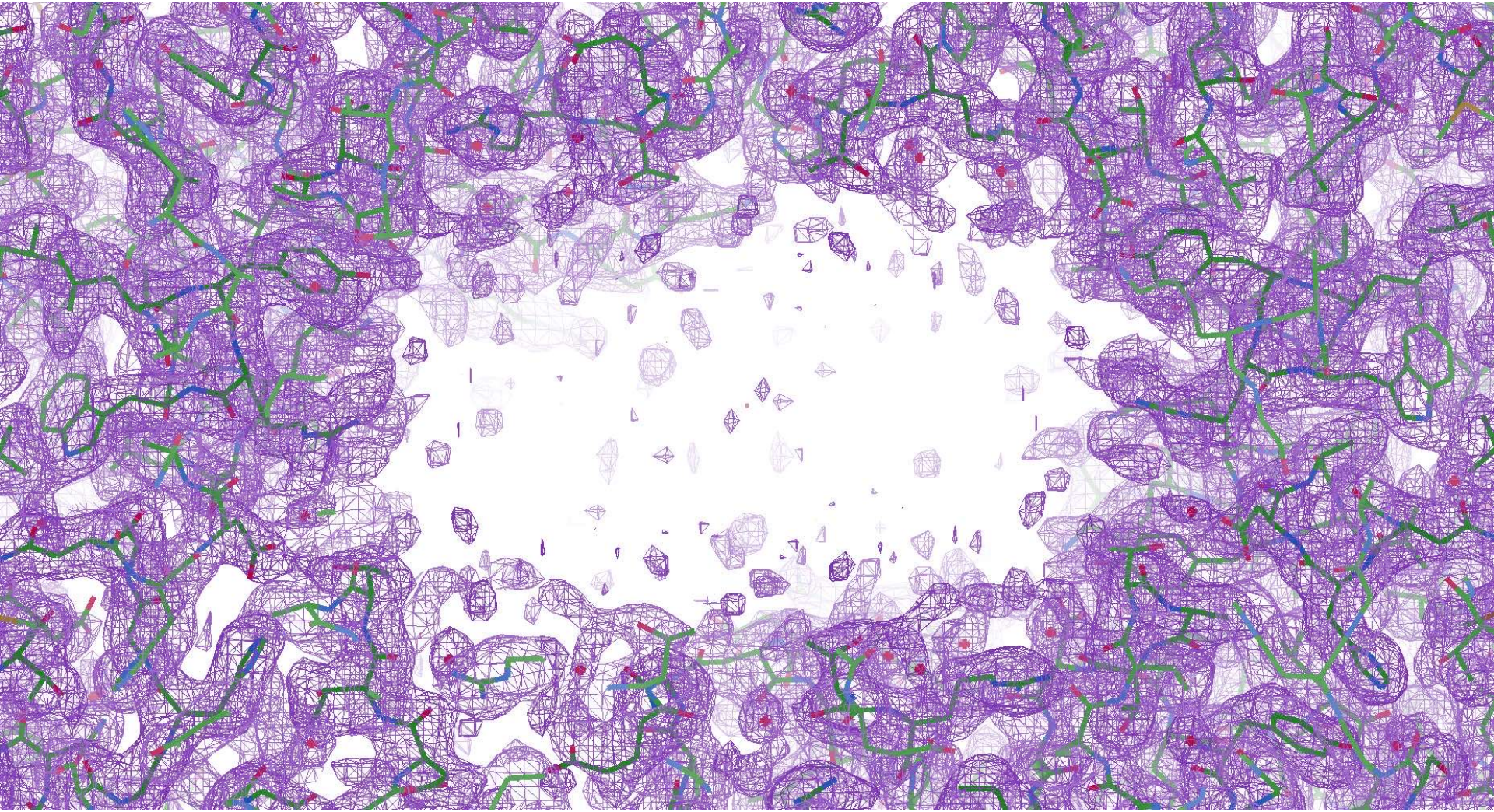
5a1a (2.2Å)



# Map Sharpening/Blurring

Blur 20 Å<sup>2</sup>

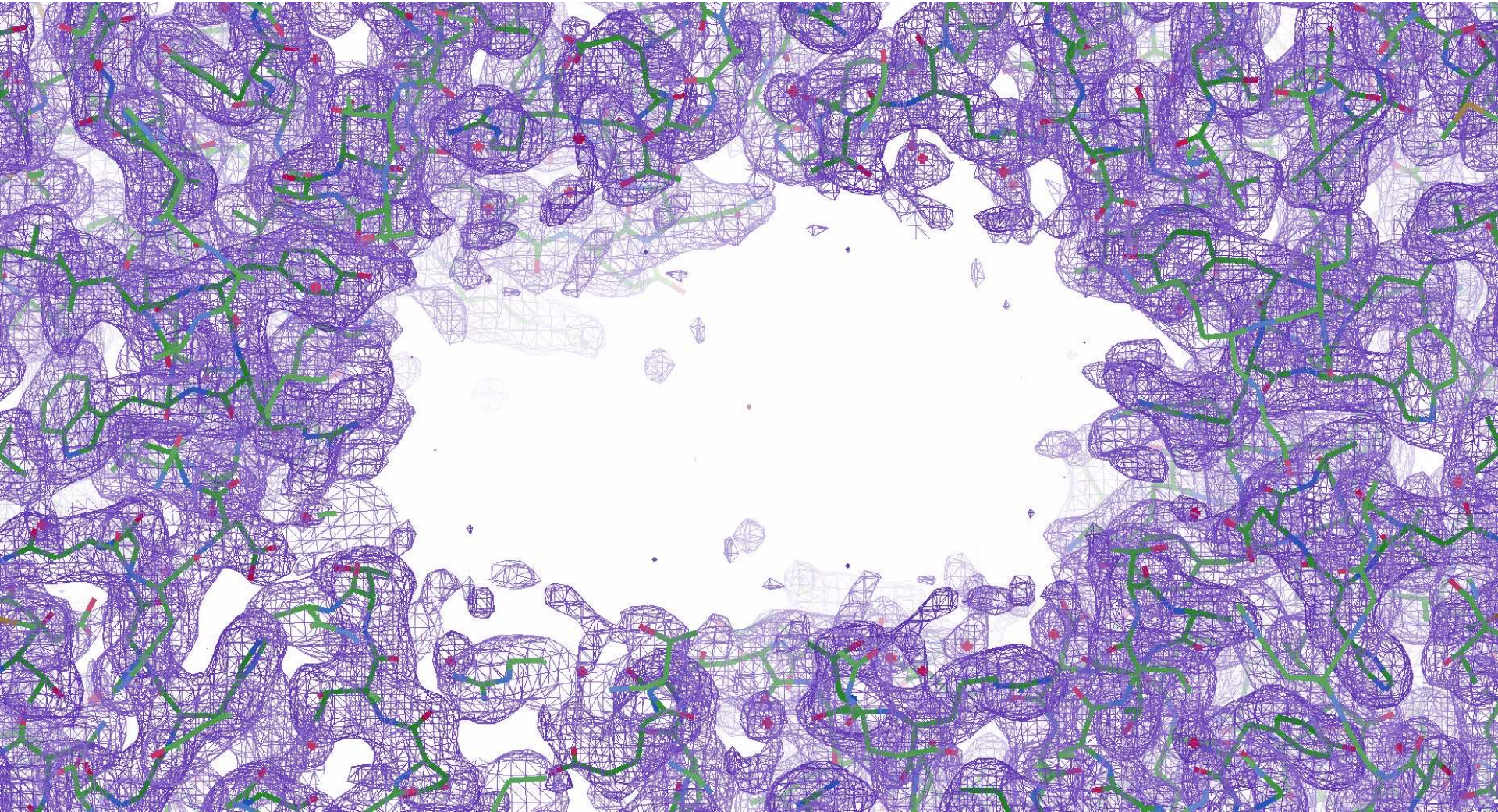
5a1a (2.2Å)



# Map Sharpening/Blurring

Blur 40 Å<sup>2</sup>

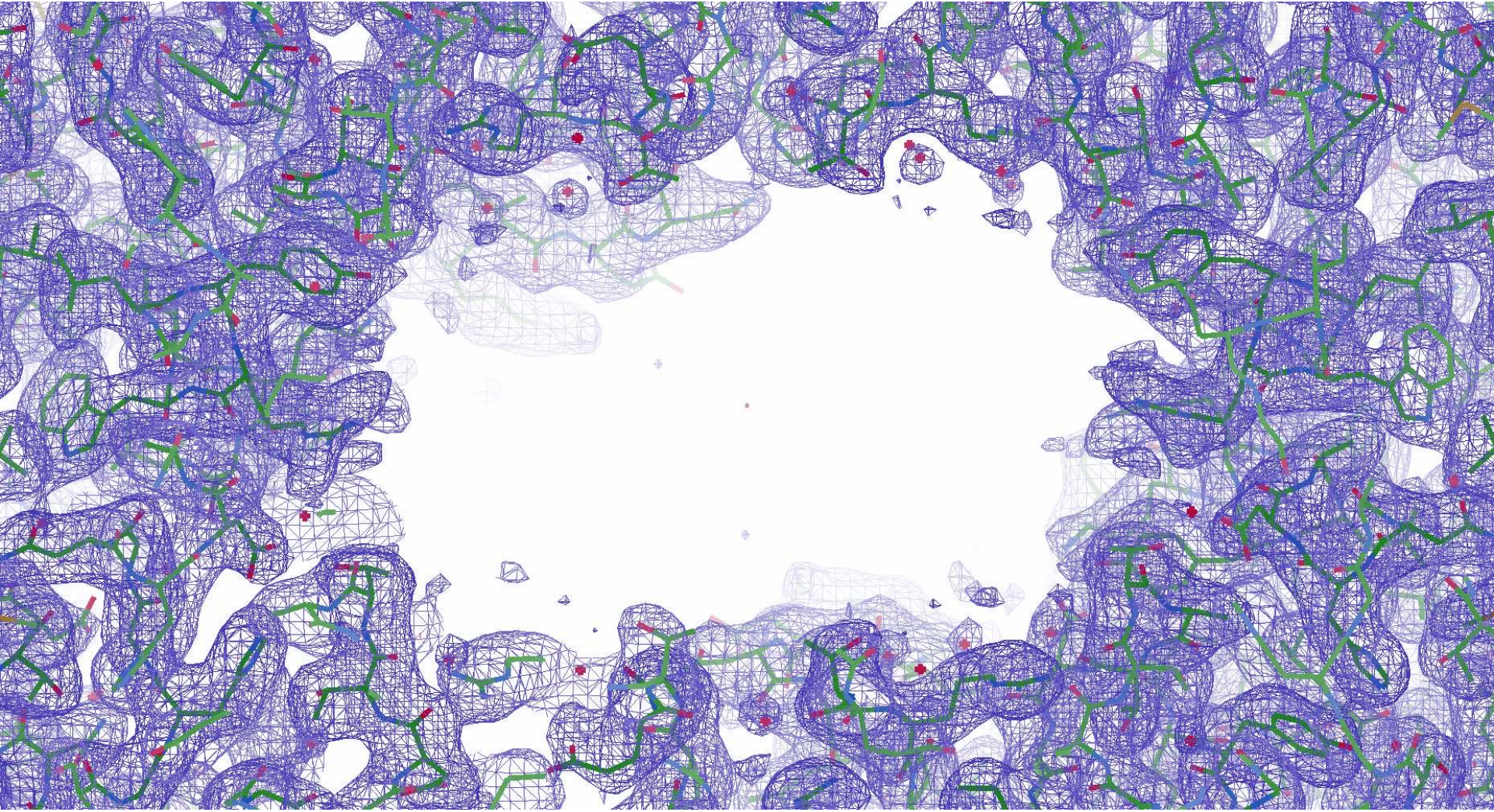
5a1a (2.2Å)



# Map Sharpening/Blurring

Blur 60 Å<sup>2</sup>

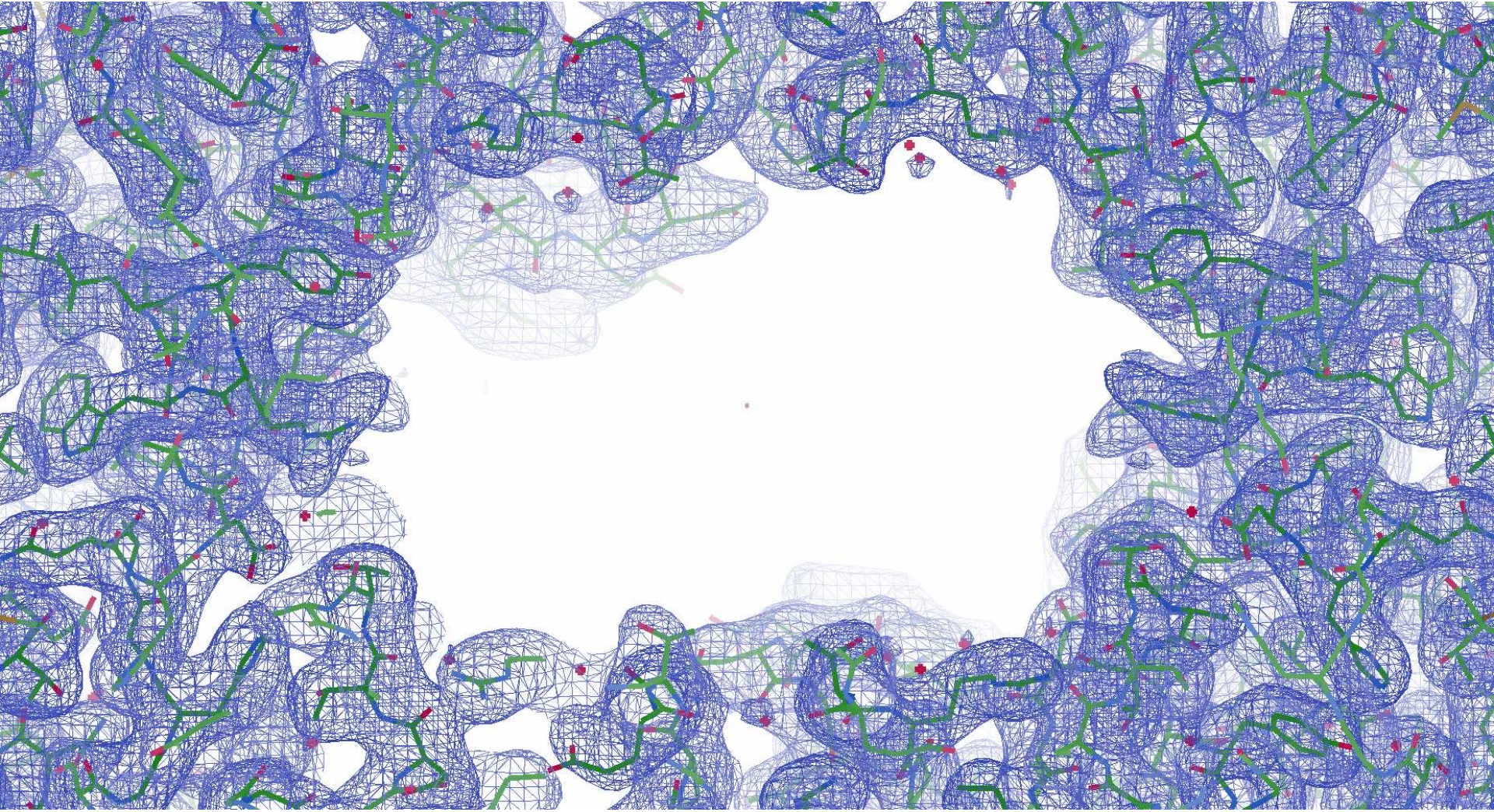
5a1a (2.2Å)



# Map Sharpening/Blurring

Blur 80 Å<sup>2</sup>

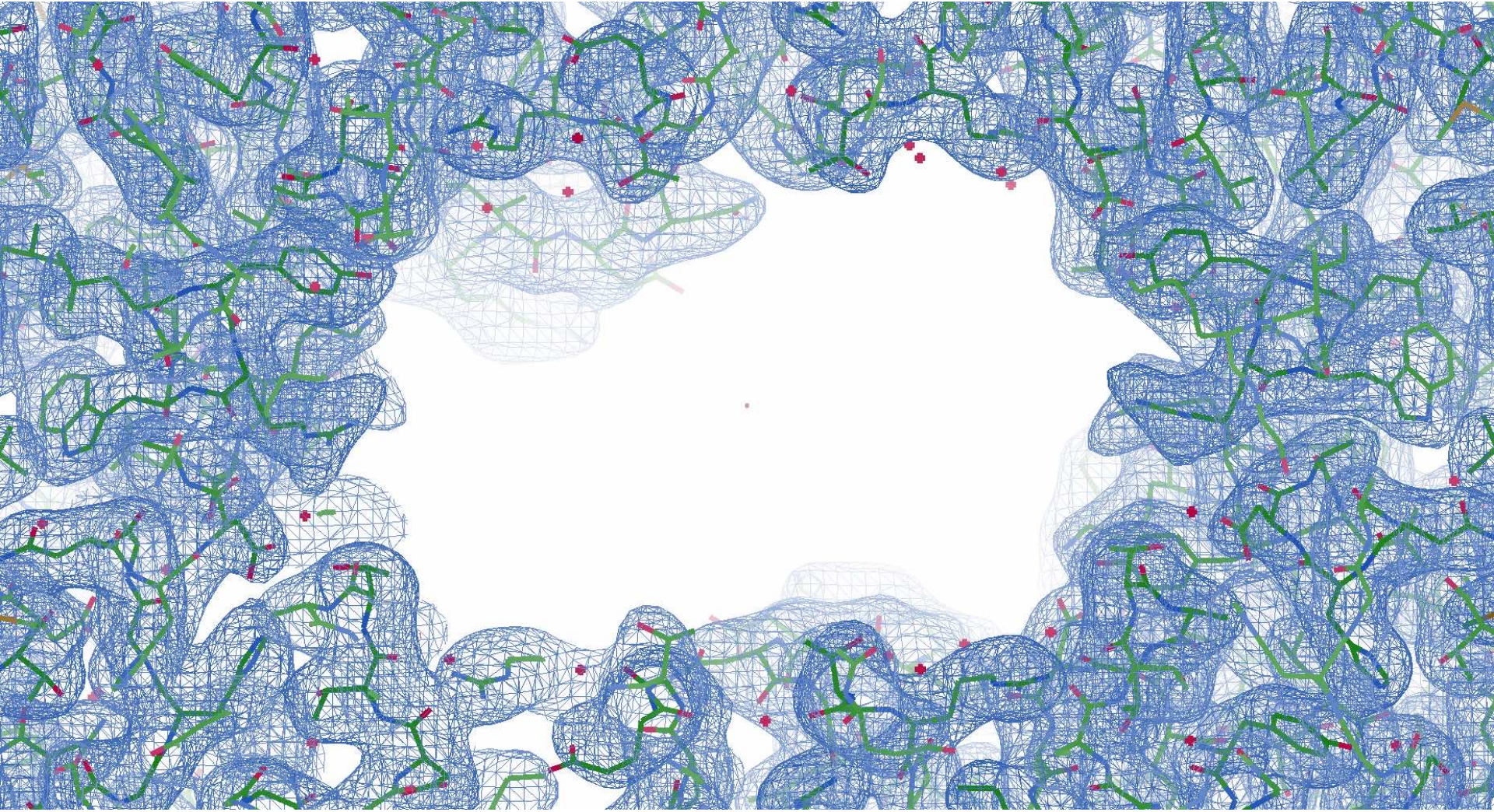
5a1a (2.2Å)



# Map Sharpening/Blurring

Blur 100 Å<sup>2</sup>

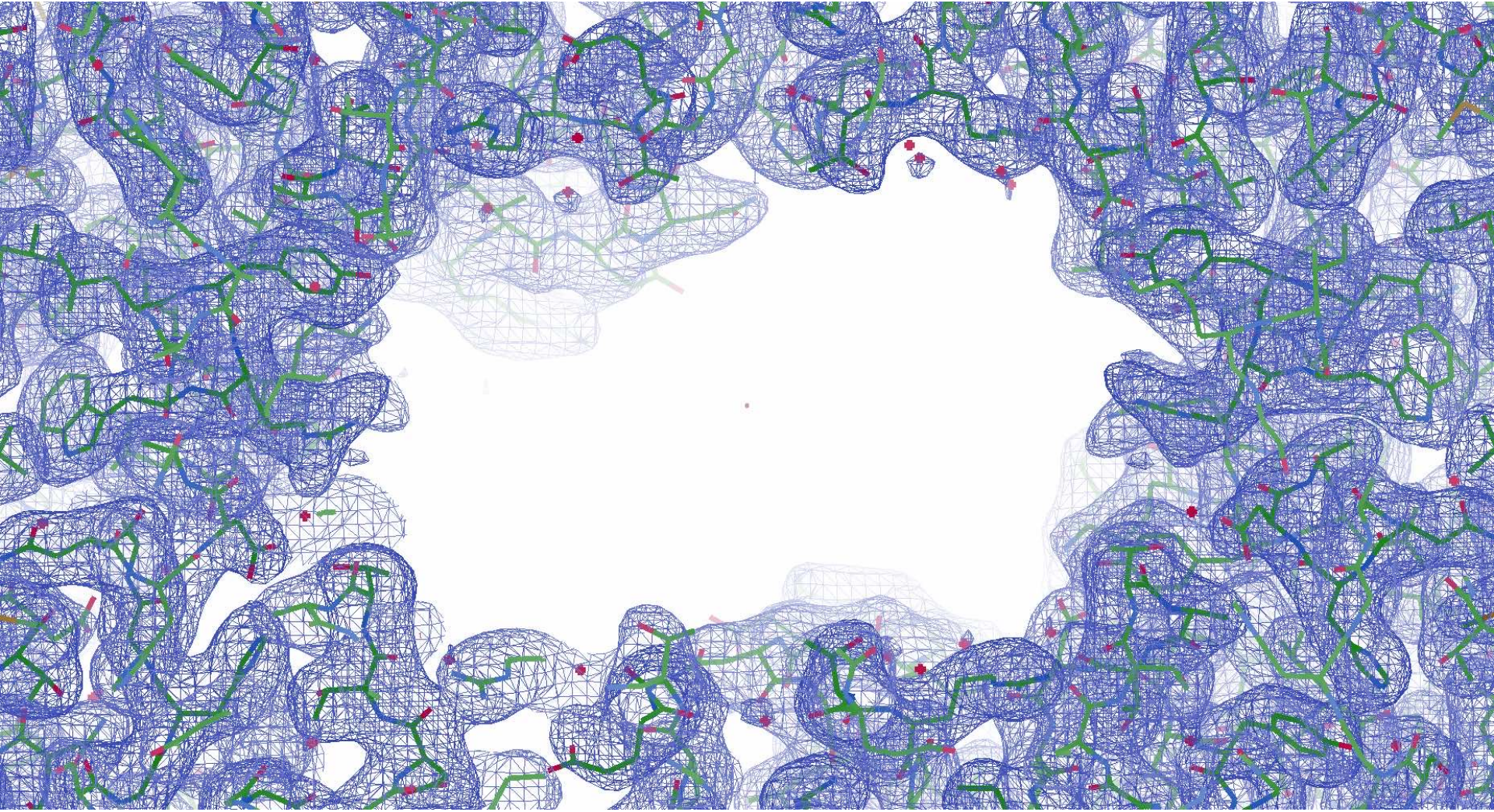
5a1a (2.2Å)



# Map Sharpening/Blurring

Blur 80 Å<sup>2</sup>

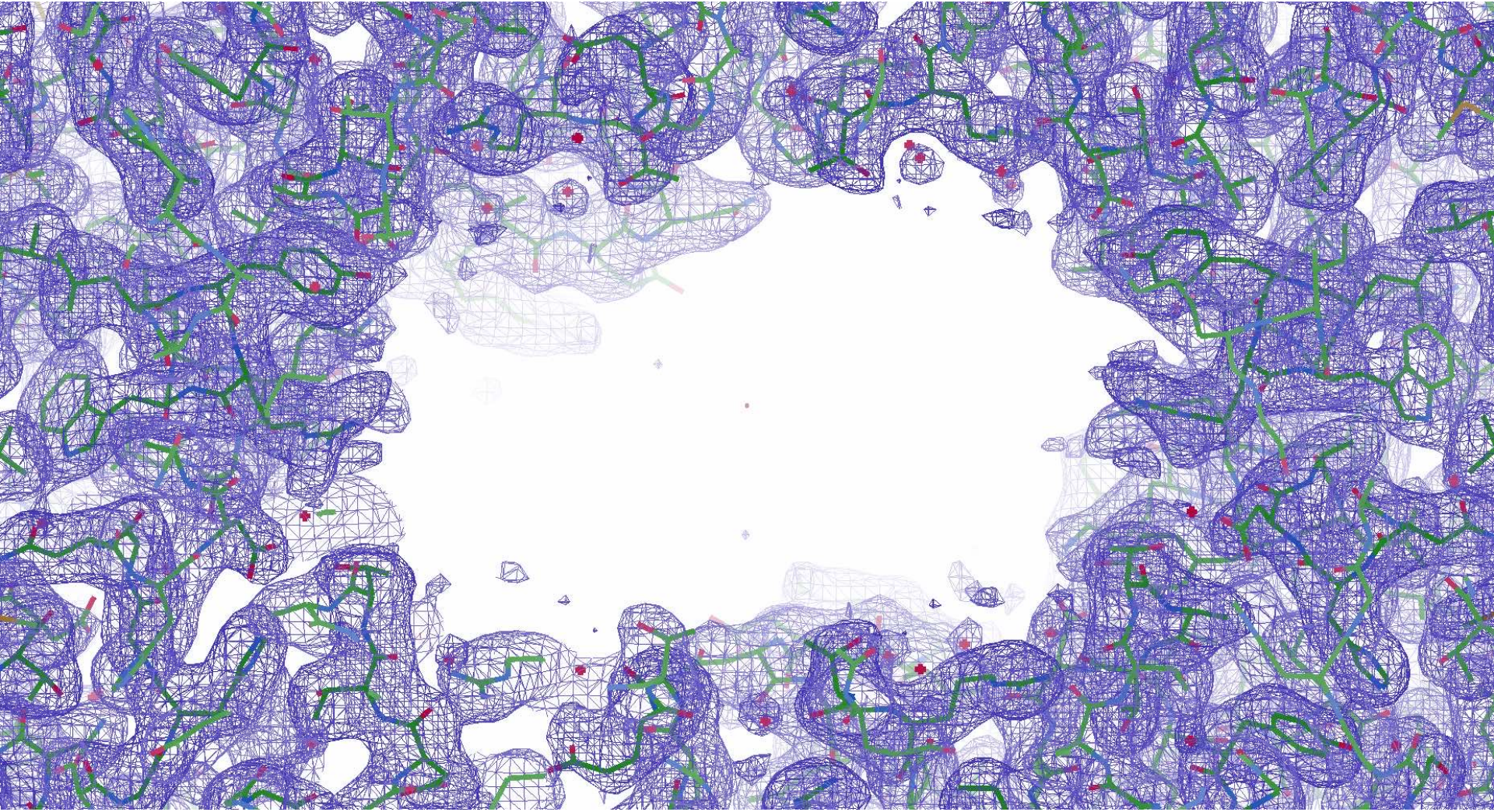
5a1a (2.2Å)



# Map Sharpening/Blurring

Blur 60 Å<sup>2</sup>

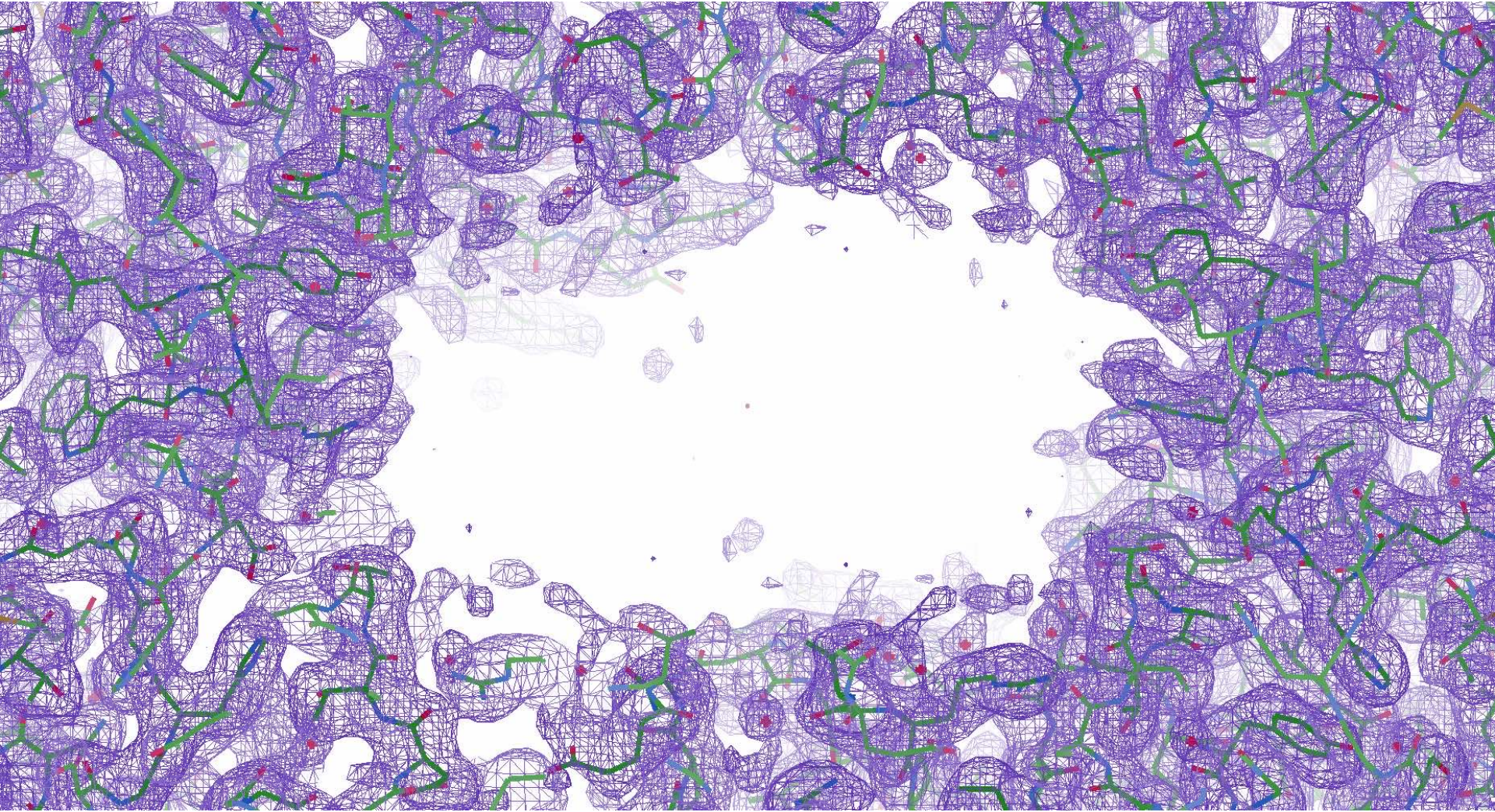
5a1a (2.2Å)



# Map Sharpening/Blurring

Blur 40 Å<sup>2</sup>

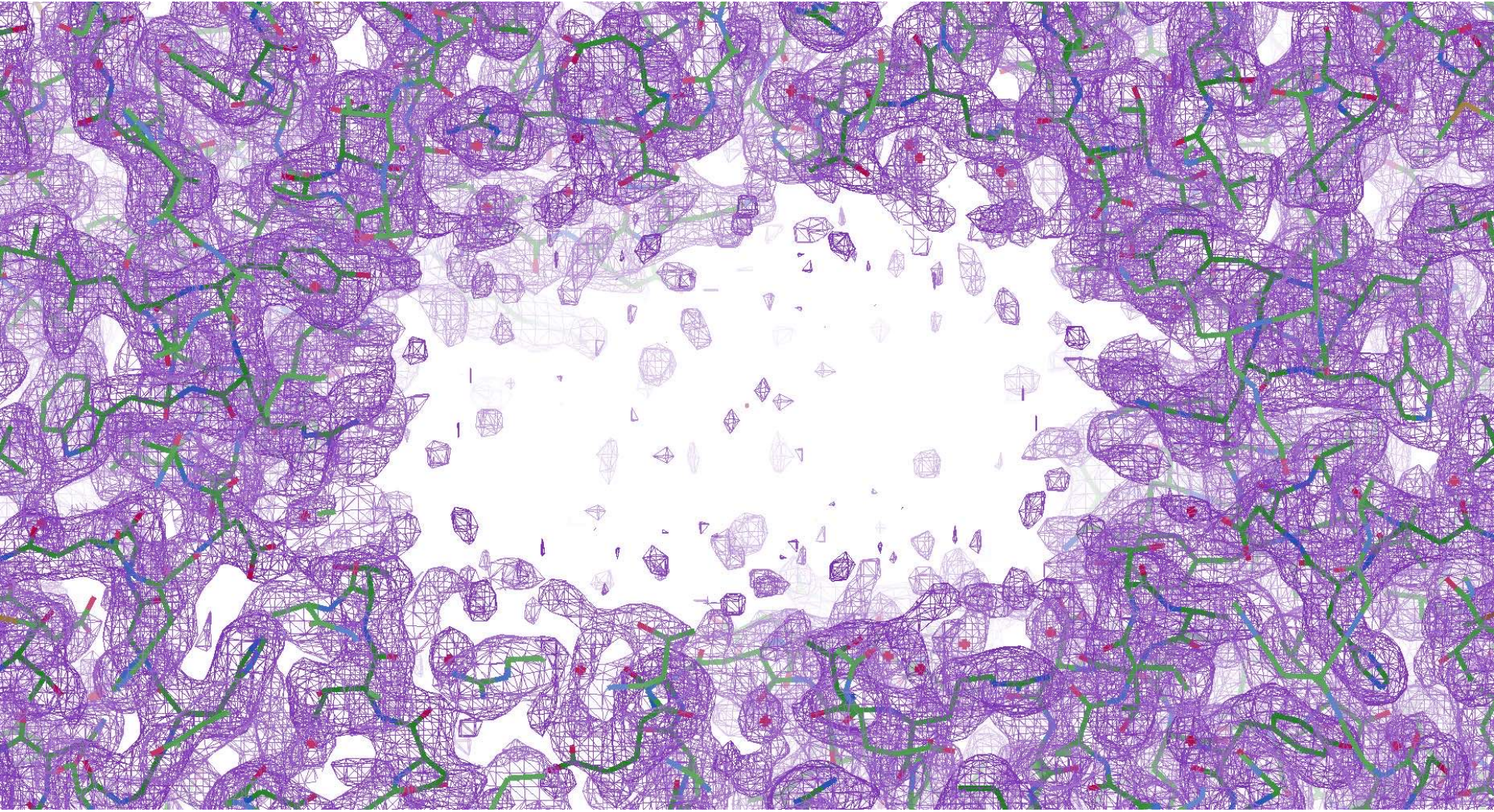
5a1a (2.2Å)



# Map Sharpening/Blurring

Blur 20 Å<sup>2</sup>

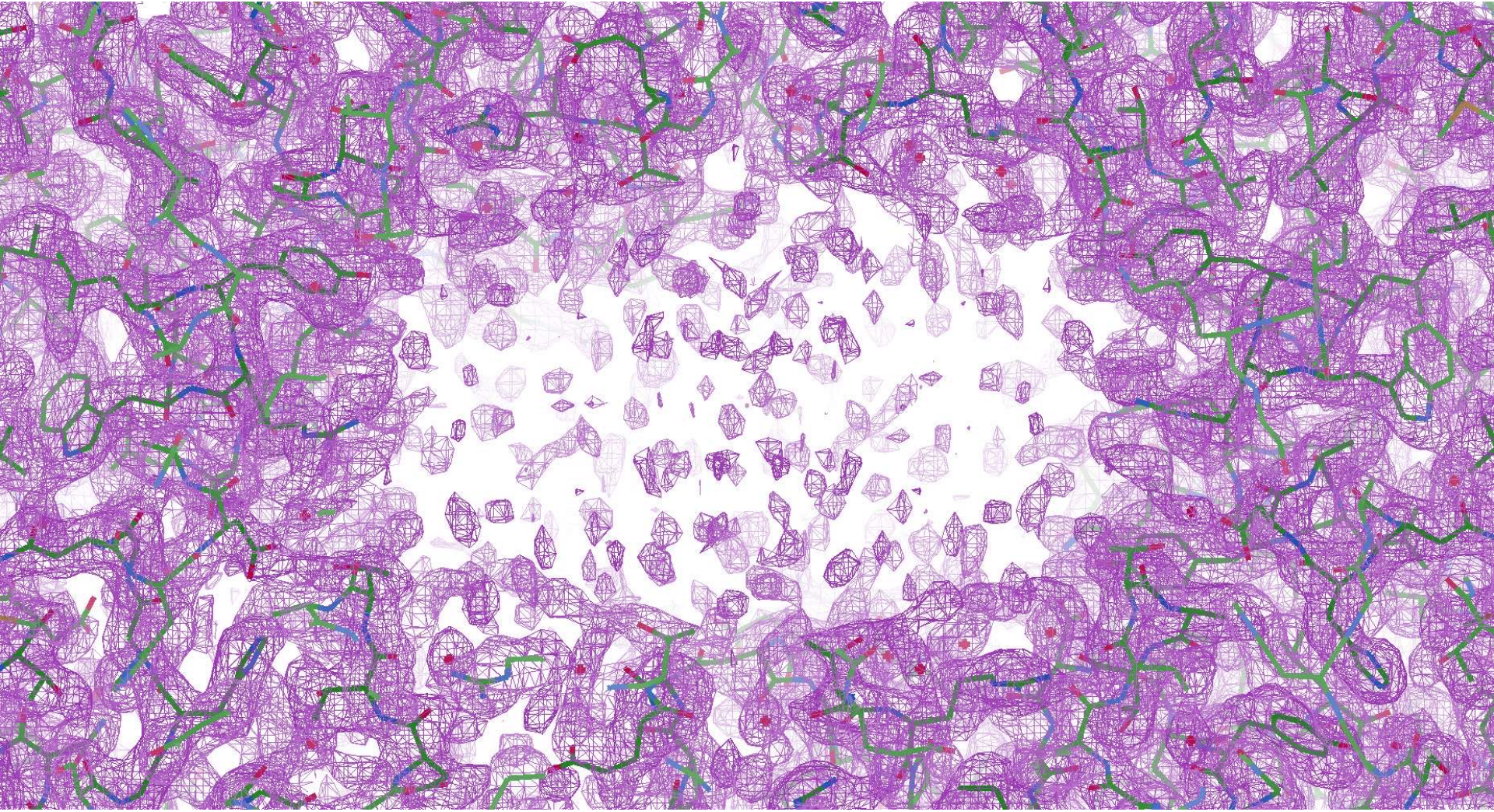
5a1a (2.2Å)



# Map Sharpening/Blurring

Default map

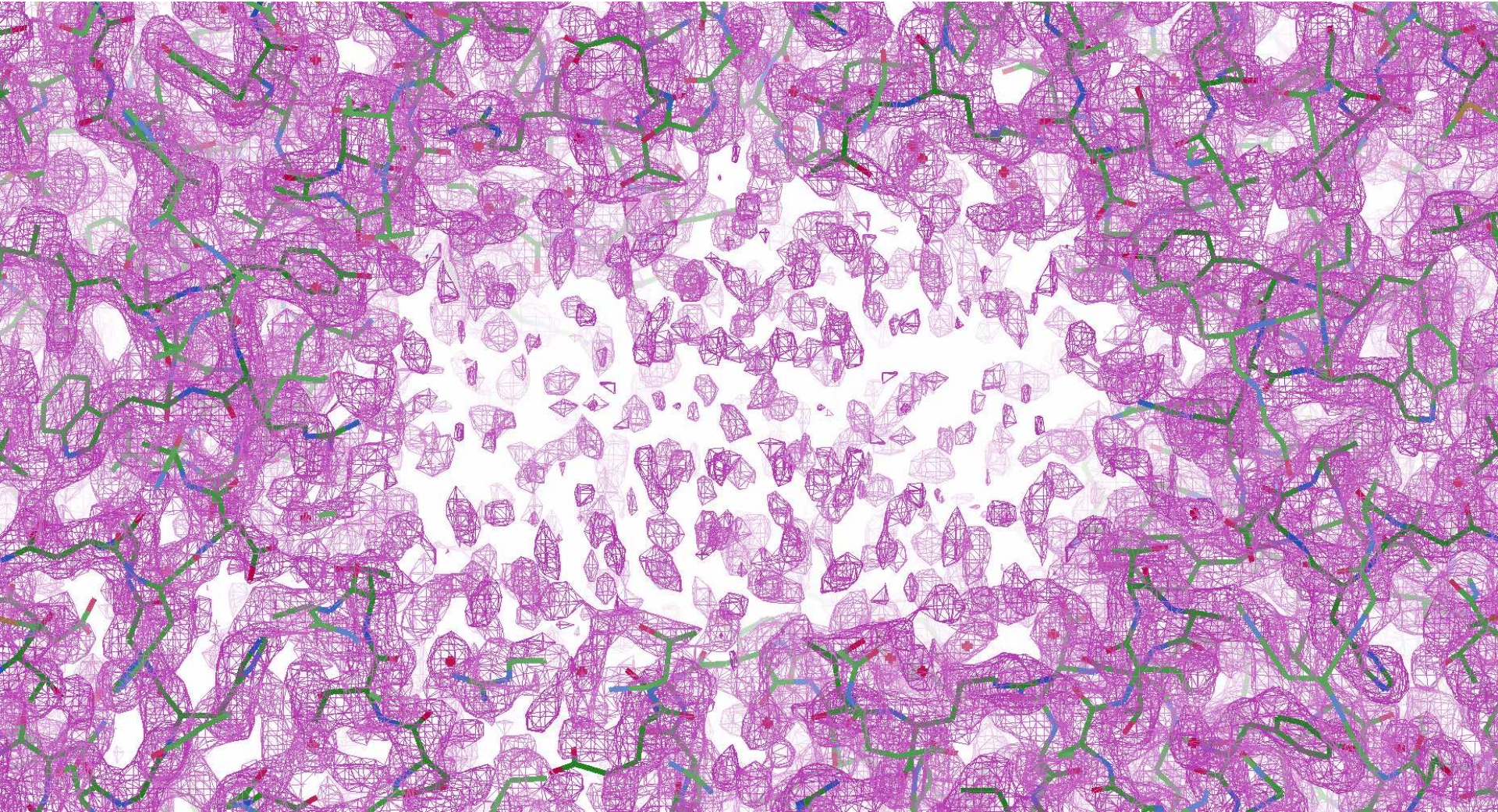
5a1a (2.2Å)



# Map Sharpening/Blurring

Sharpen 20 Å<sup>2</sup>

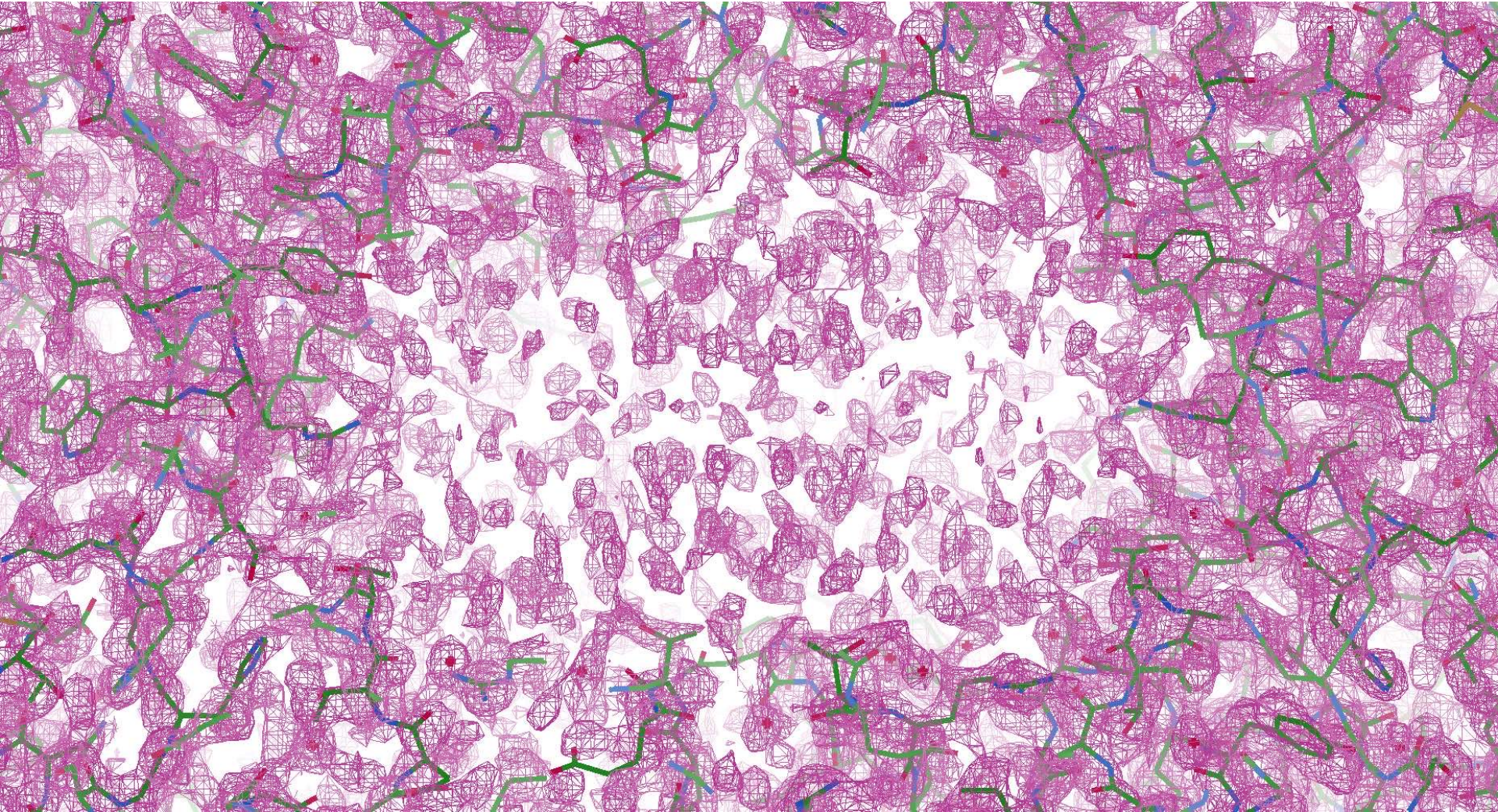
5a1a (2.2Å)



# Map Sharpening/Blurring

Sharpen 40 Å<sup>2</sup>

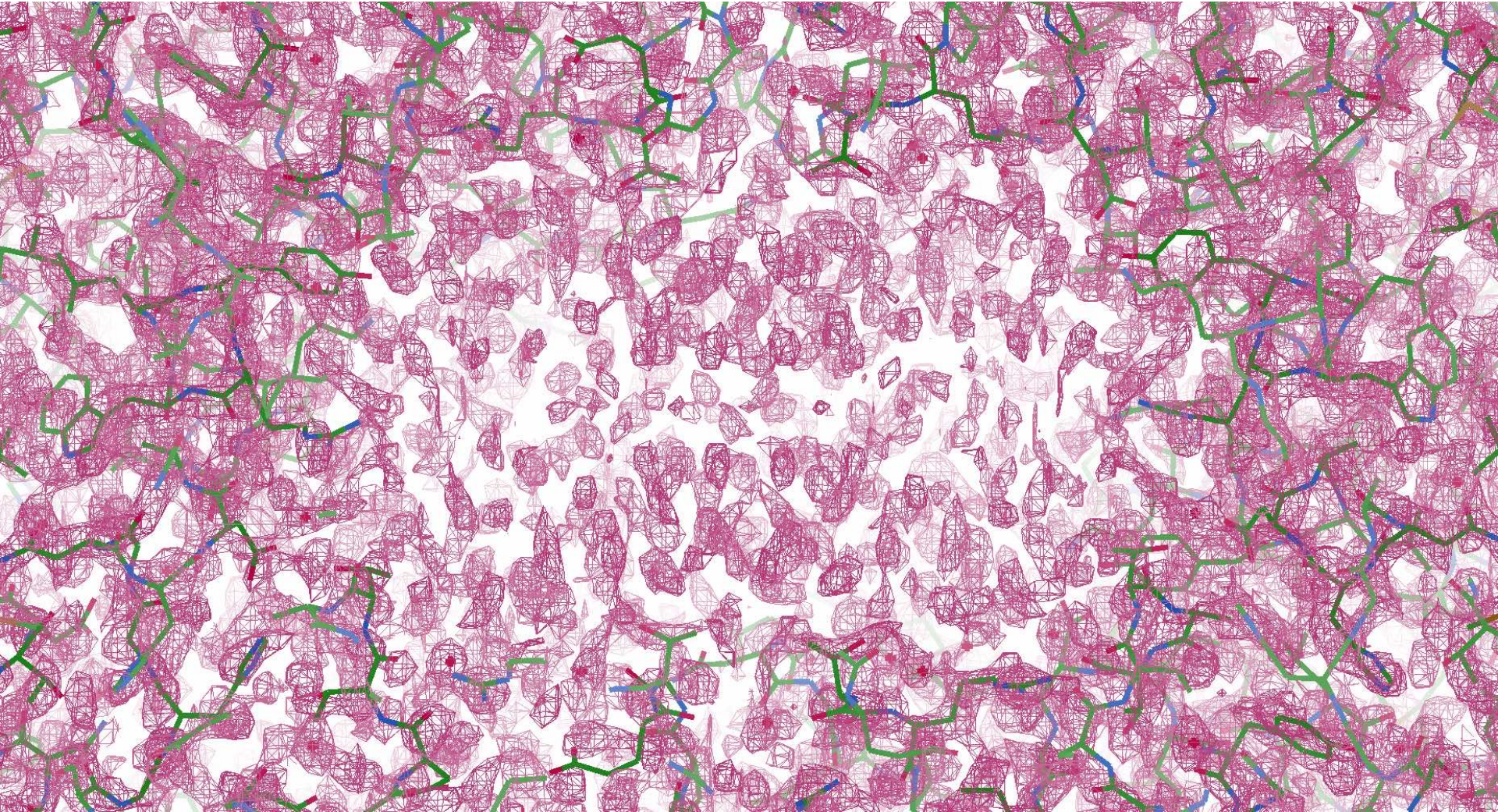
5a1a (2.2Å)



# Map Sharpening/Blurring

Sharpen 60 Å<sup>2</sup>

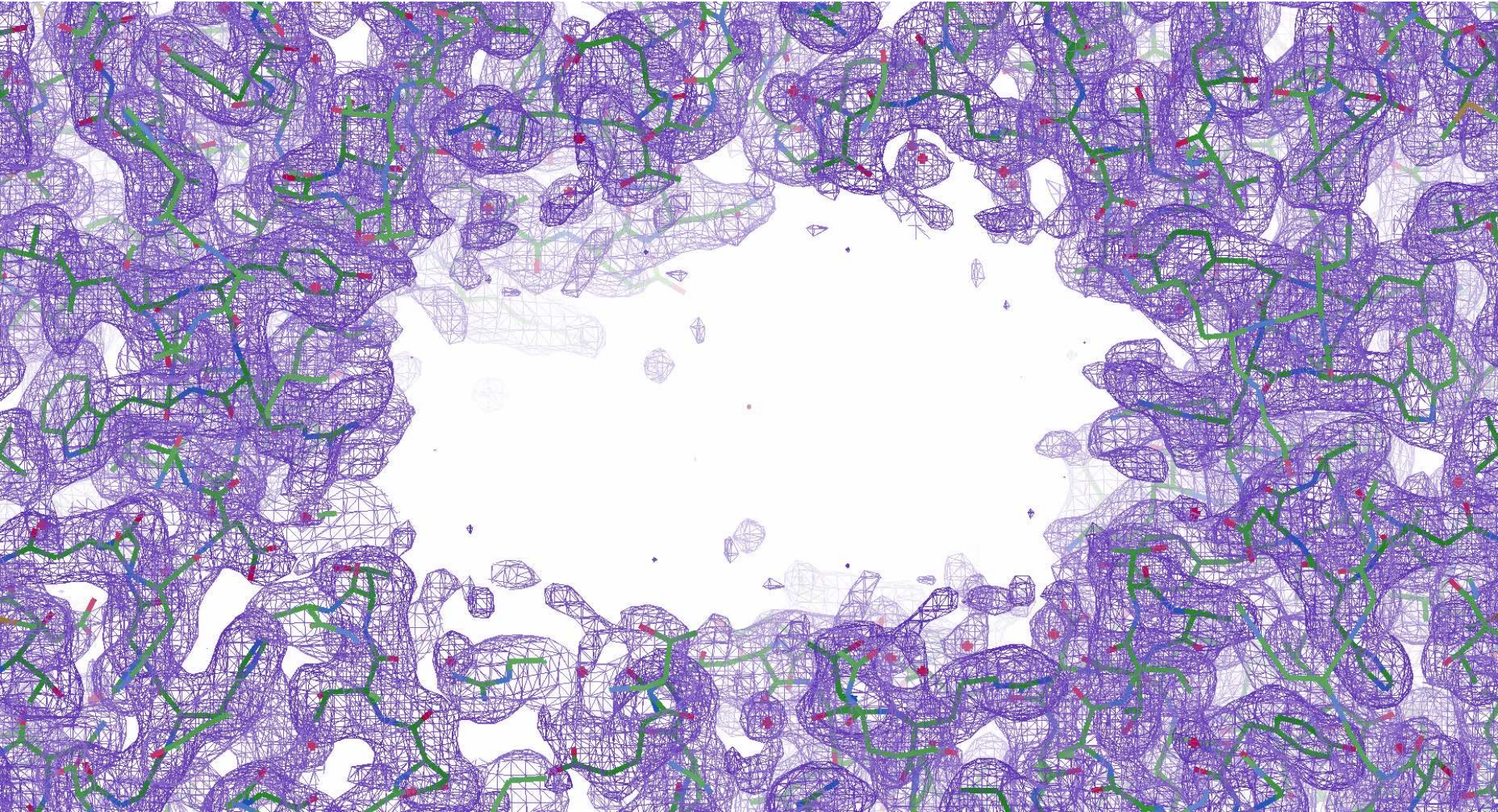
5a1a (2.2Å)



# Map Sharpening/Blurring

Blur 40 Å<sup>2</sup>

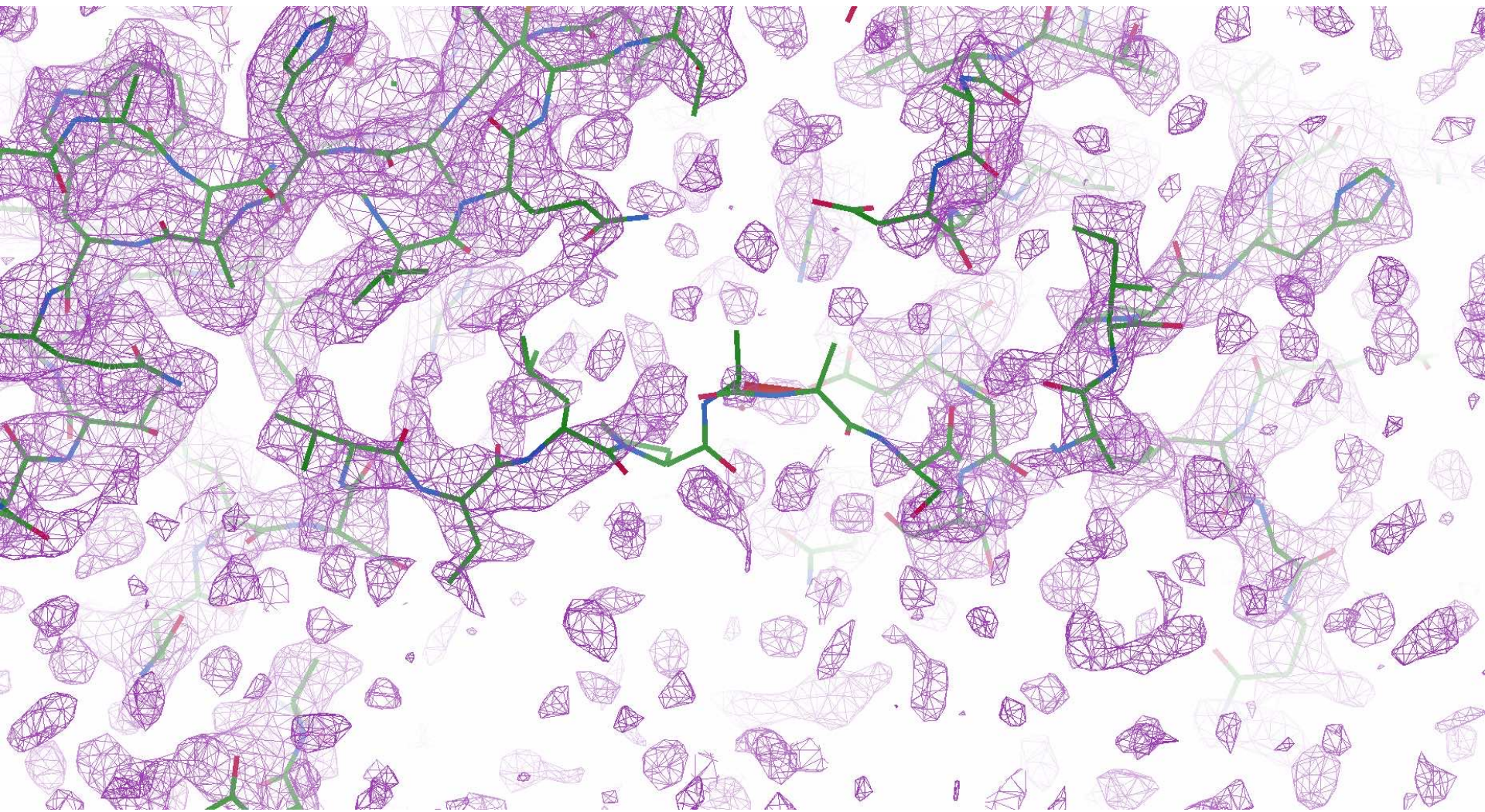
5a1a (2.2Å)



# Blurring / Sharpening

Default map

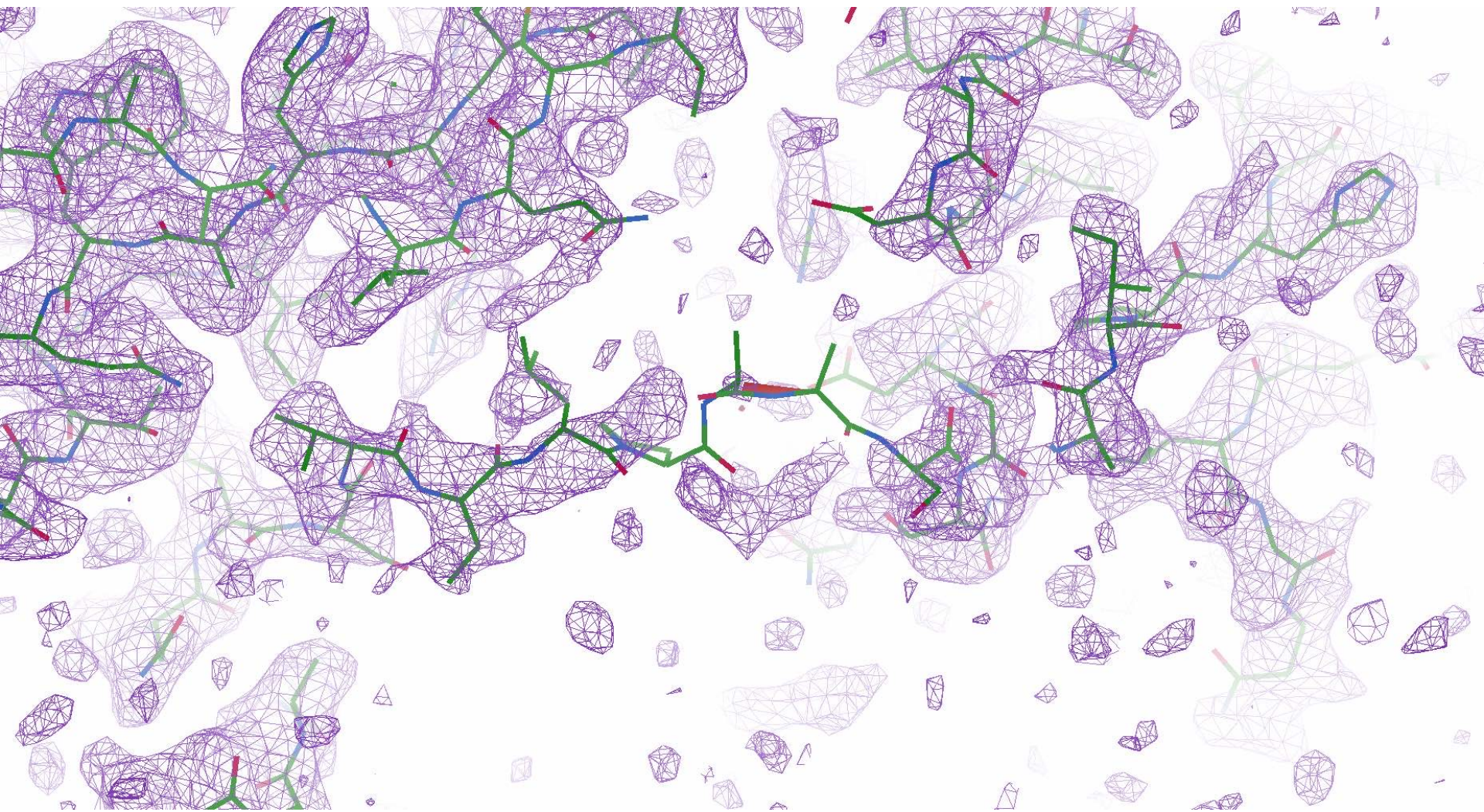
5a1a (2.2Å)



# Blurring / Sharpening

Blur 20 Å<sup>2</sup>

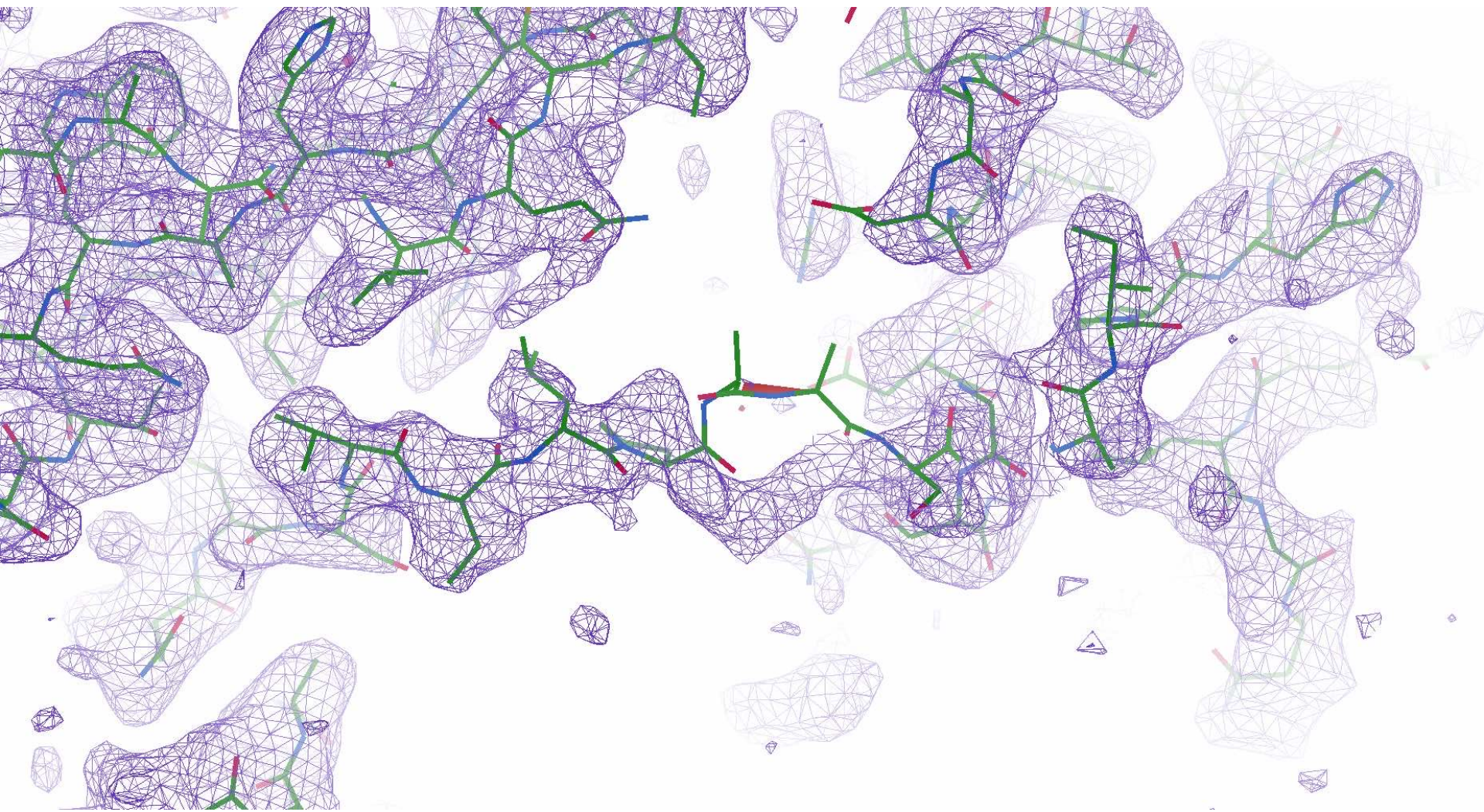
5a1a (2.2Å)



# Blurring / Sharpening

Blur 40 Å<sup>2</sup>

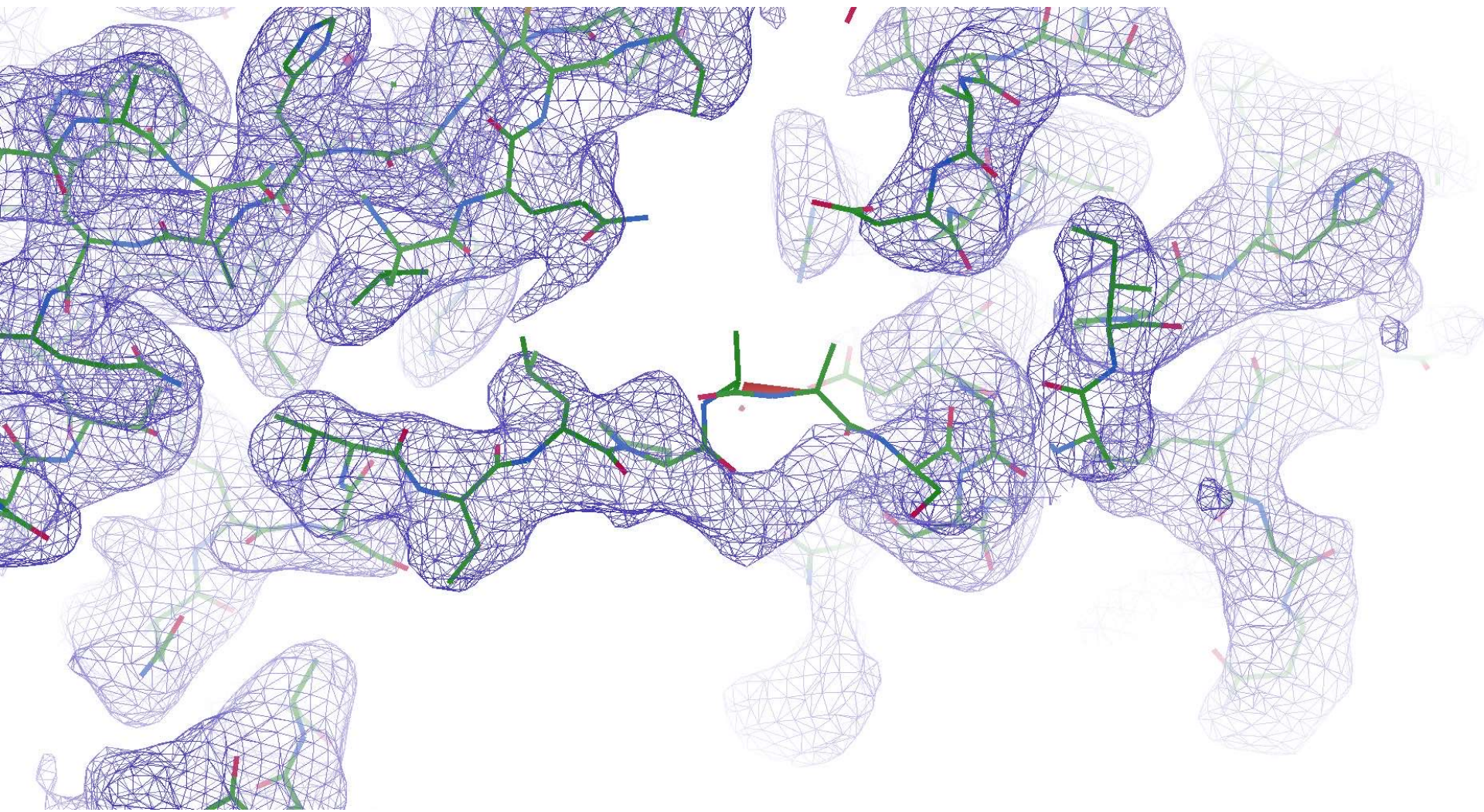
5a1a (2.2Å)



# Blurring / Sharpening

Blur 60 Å<sup>2</sup>

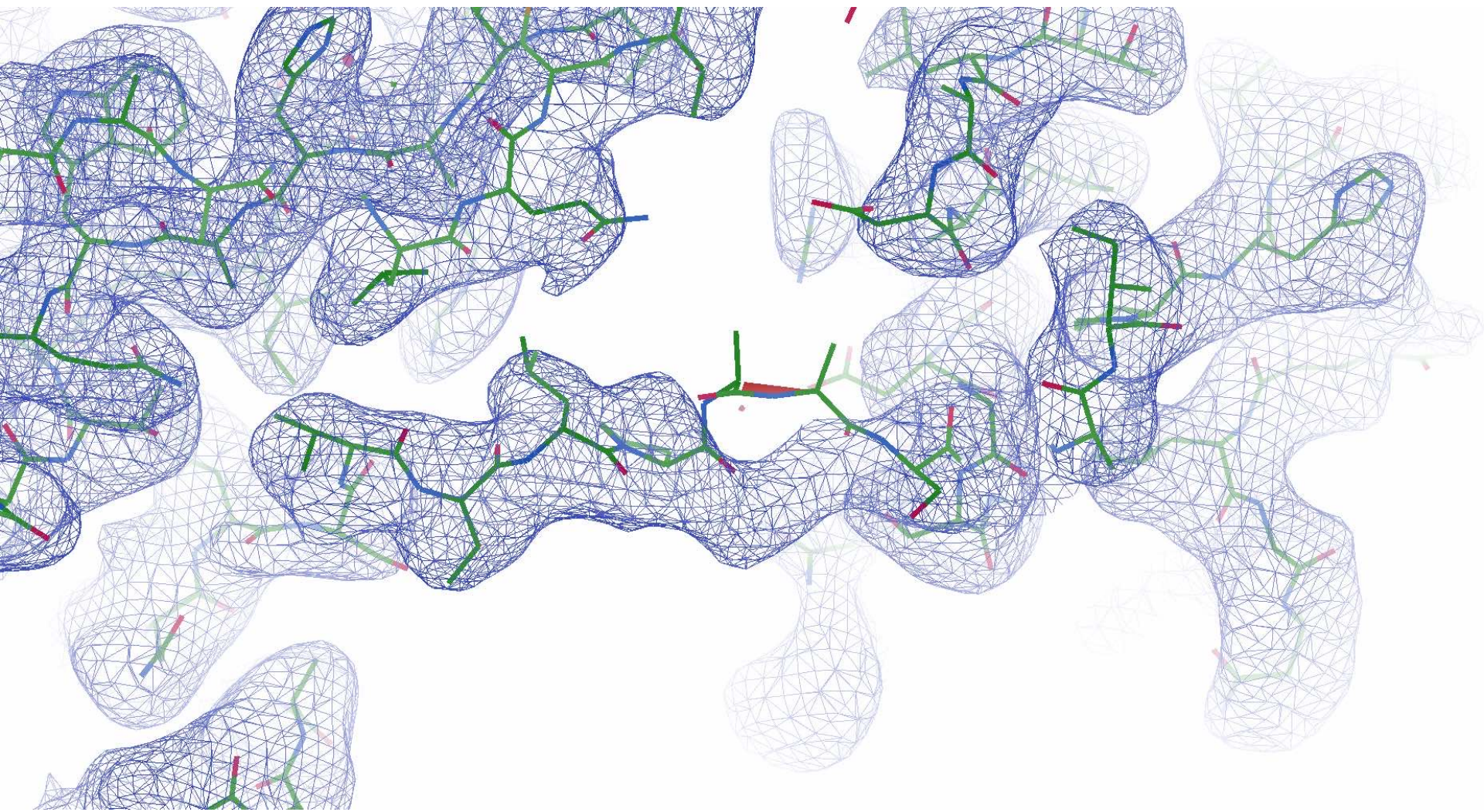
5a1a (2.2Å)



# Blurring / Sharpening

Blur 80 Å<sup>2</sup>

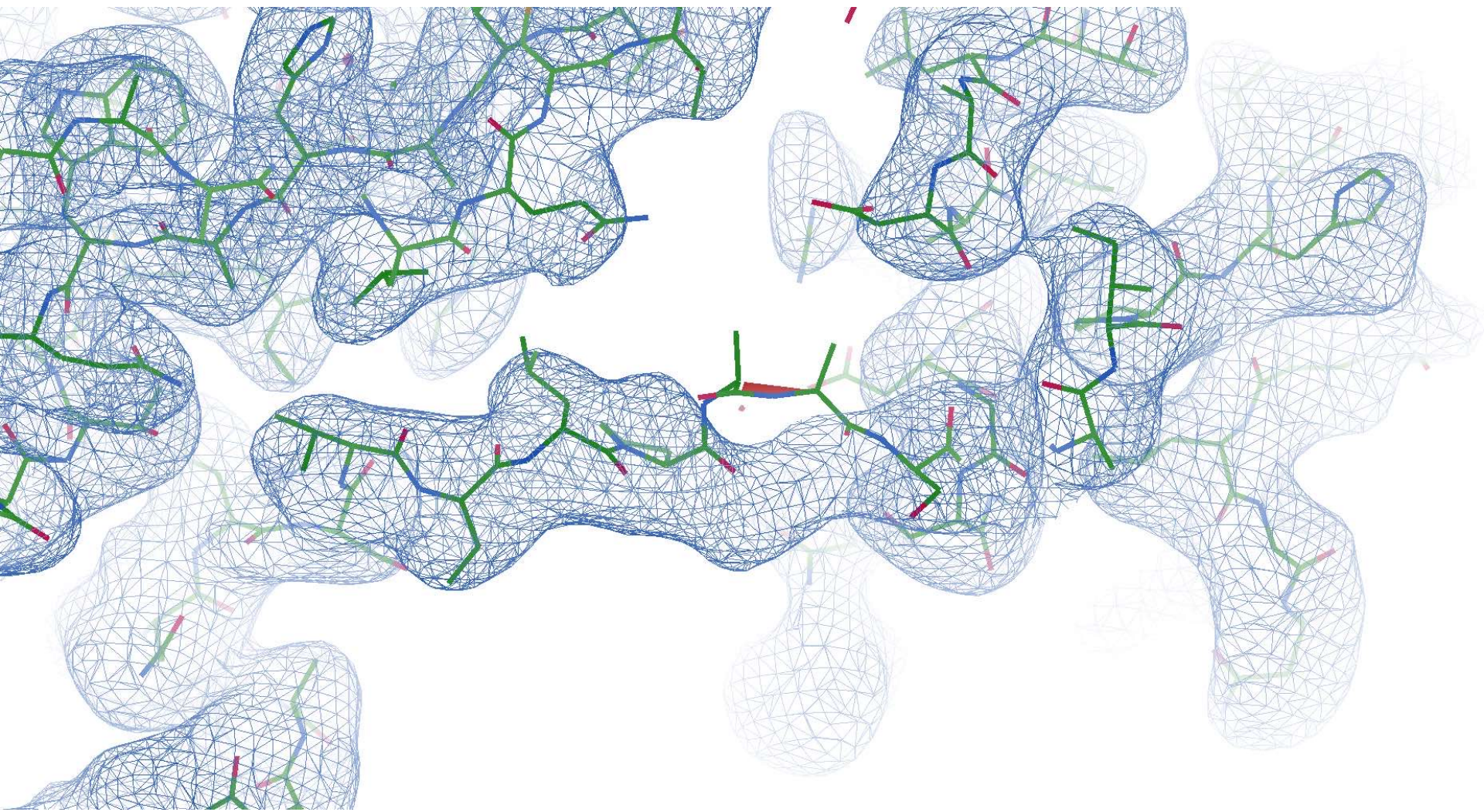
5a1a (2.2Å)



# Blurring / Sharpening

Blur 100 Å<sup>2</sup>

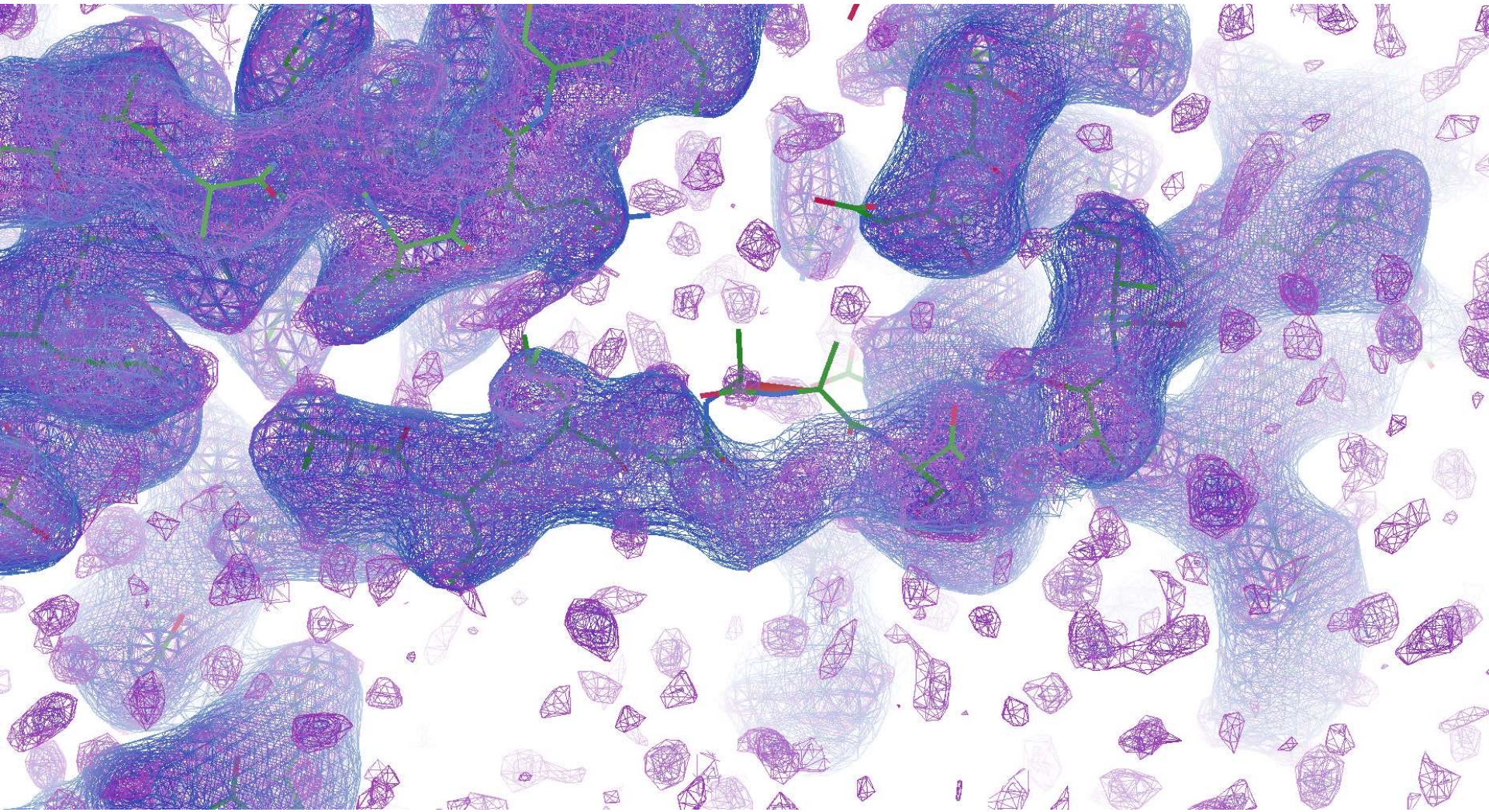
5a1a (2.2Å)



# Blurring / Sharpening

Blur 0–100 Å<sup>2</sup>

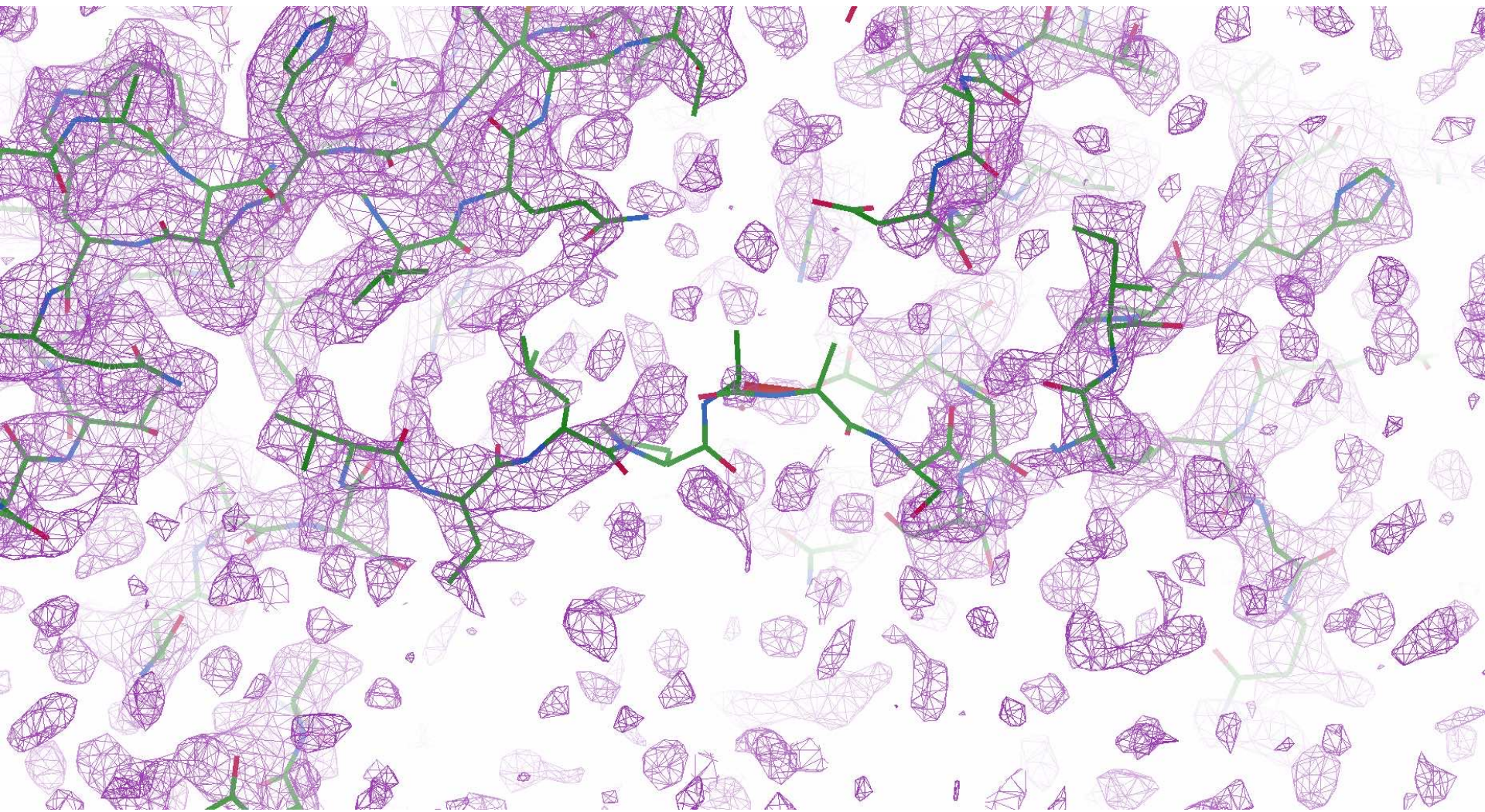
5a1a (2.2Å)



# Blurring / Sharpening

Default map

5a1a (2.2Å)



# Servalcat Difference Maps

**Map Input:** Unweighted half-maps – for refinement

**Map Output:** Weighted sharpened maps – for visualisation

## ***Difference map calculation:***

Variance of noise:

Calculated from half-maps in res bins

$$\sigma_n^2 = \frac{\text{var}(F_{o1} - F_{o2})}{4}.$$

Used to calculate SF weightings:

Proportion of unexplained signal vs signal+noise

(unexplained signal estimated using ML)

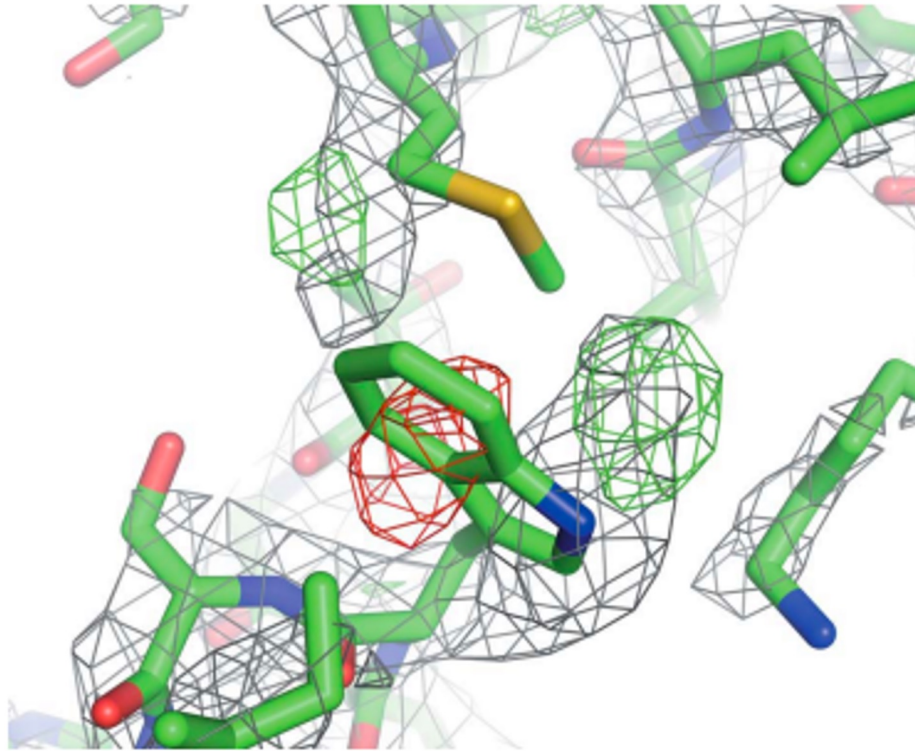
$$w = \frac{\sigma_{U,T}^2}{\sigma_{U,T}^2 + \sigma_n^2}.$$

Final scaling sharpens the map (~removes B):

$$F_{\text{diff}} = \frac{w}{(\text{FSC}_{\text{full}} \langle |F_o|^2 \rangle)^{1/2}} (F_o - DF_c).$$

# Servalcat Difference Maps

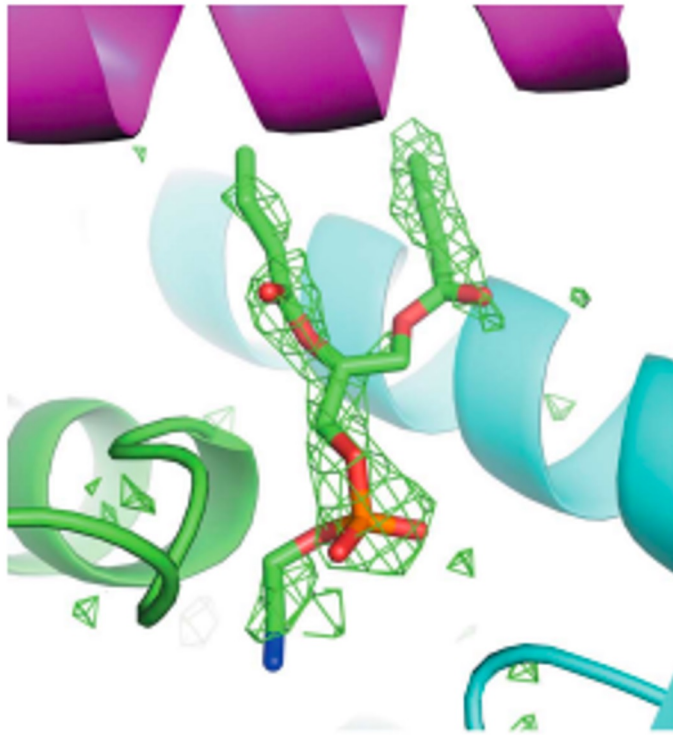
*Model Improvement -  $F_o - F_c$  map:*



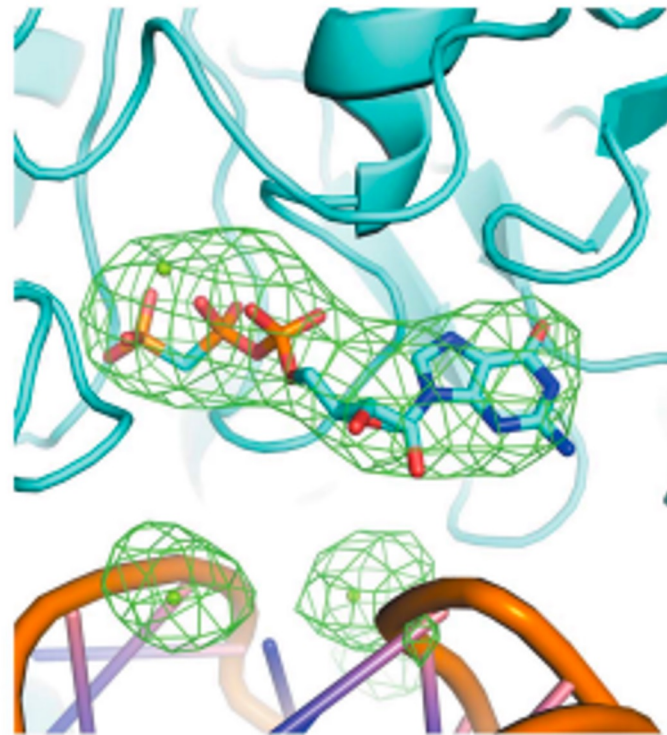
Killifish Calcium homeostasis modulator  
EMD-0919 (2.7 Å)

# Servalcat Difference Maps

*Ligand Inspection -  $F_o - F_c$  omit maps:*



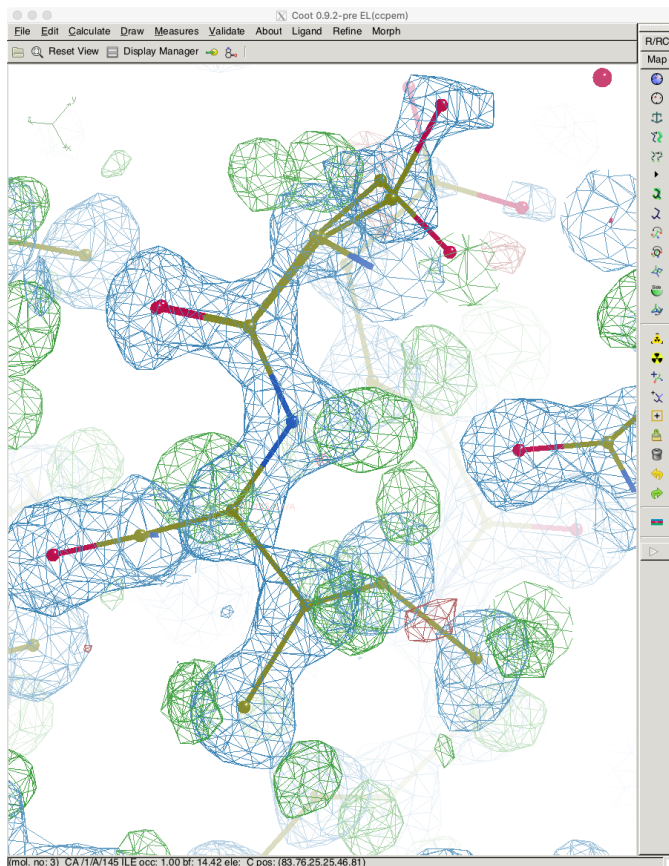
SARS-CoV-2 3a ion channel  
EMD-22898 (2.1 Å)



Kluyveromyces lactis 80S ribosome  
EMD-8123 (3.6 Å)

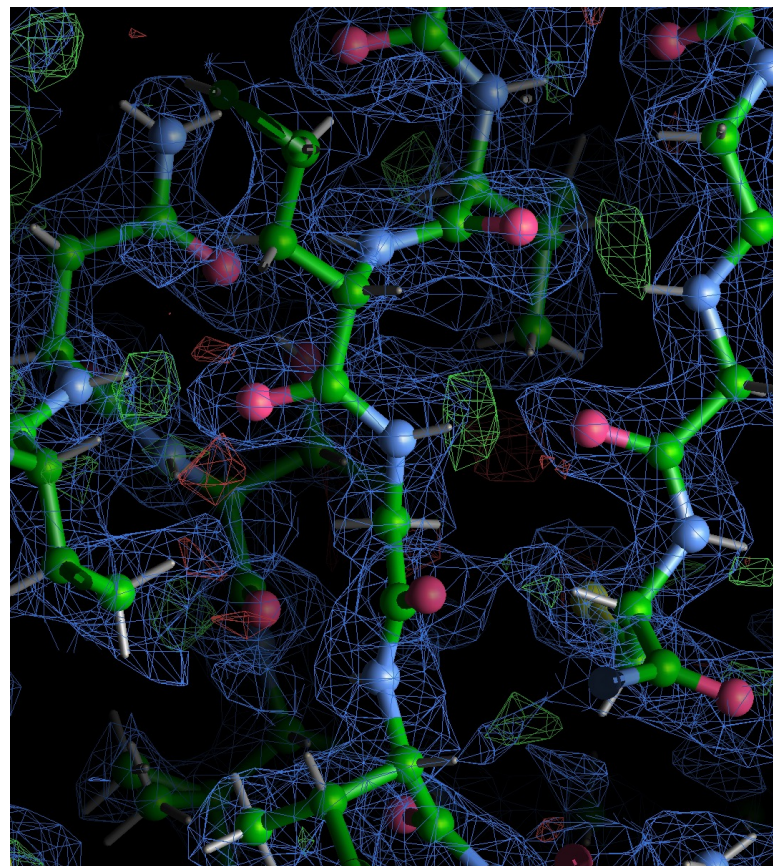
# Servalcat Difference Maps

*Hydrogen inspection –  $F_o - F_c$  hydrogen omit map:*



Apoferritin

EMD-11638, PDB: 7a4m (1.22 Å)



$\beta$ -galactosidase

EMD-10109, PDB: 6s6z (2.0 Å)

# EMDA Validation Tools

**Fourier Shell Correlation (FSC) calculation:** *EMDA internally masks around the input map*

- Half map FSC
- Map-to-map FSC
- Map-to-model FSC

**Local real space correlation:**

*Correlation within a sphere*

- Map-to-map
- Map-to-model

*E.g. "full map correlation" - between half maps*

**Map calculation:**

*Involves likelihood-based scaling*

- Map averaging
- Difference map calculation

**Other utilities:**

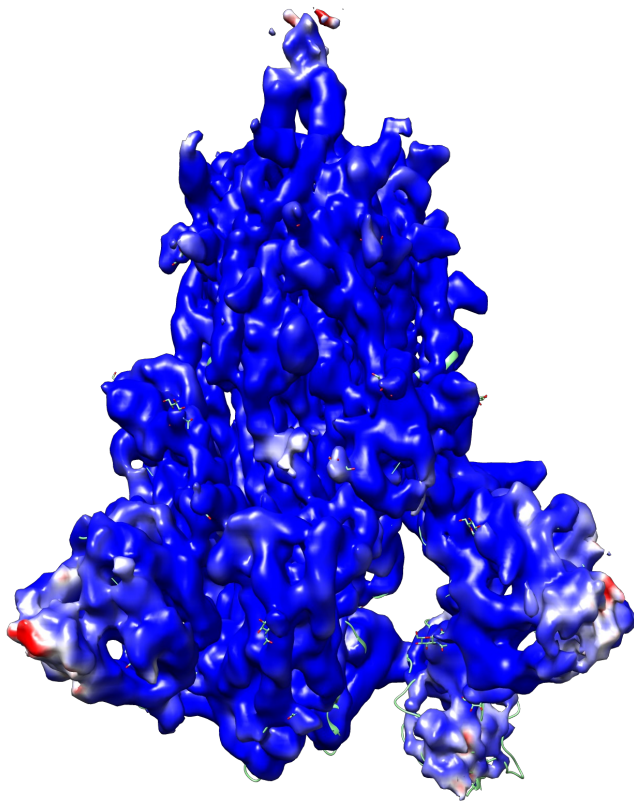
- Map fitting
- Magnification refinement

# EMDA Local Real Space Correlation

*Visualised by colouring the "standard" full map by calculated correlation*

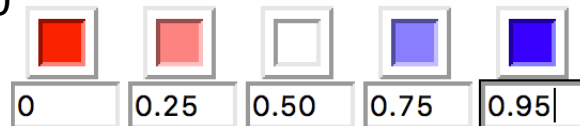
**Full map correlation**

*local correlation between half maps*



Average CC: 0.70

EMD-22162 (4.0 Å)



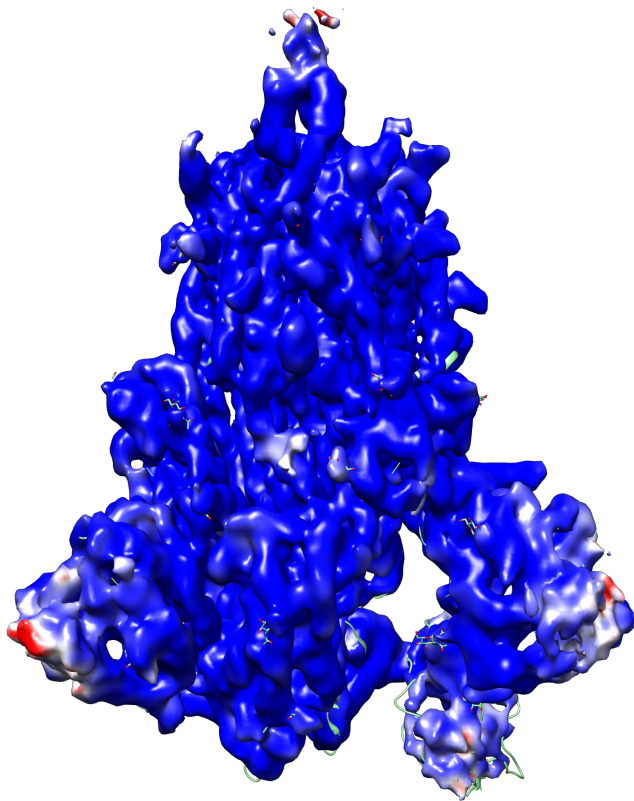
# EMDA Local Real Space Correlation

*Visualised by colouring the "standard" full map by calculated correlation*

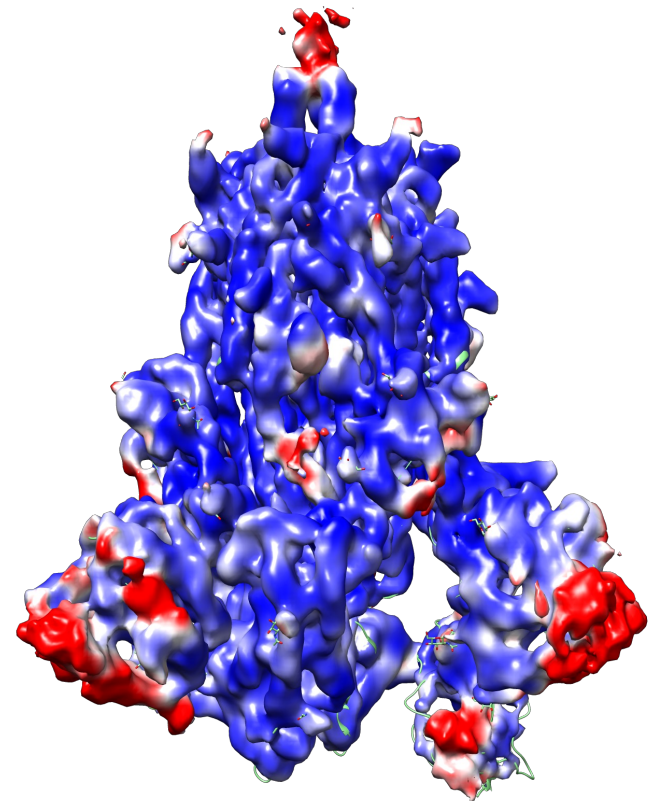
**Full map correlation**

*local correlation between half maps*

**Map-model correlation**

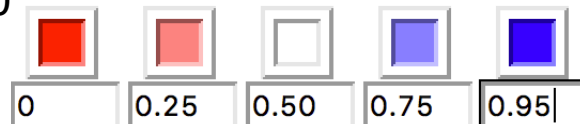


Average CC: 0.70



Average CC: 0.48

EMD-22162 (4.0 Å)



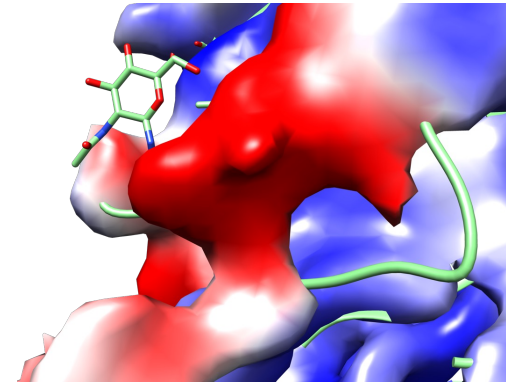
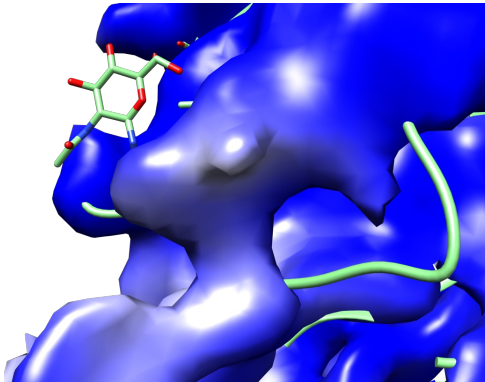
# EMDA Local Real Space Correlation

*Visualised by colouring the “standard” full map by calculated correlation*

**Full map correlation**

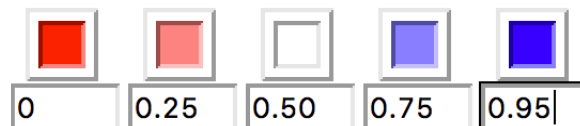
*local correlation between half maps*

**Map-model correlation**



C/135 - 140

EMD-22162 (4.0 Å)

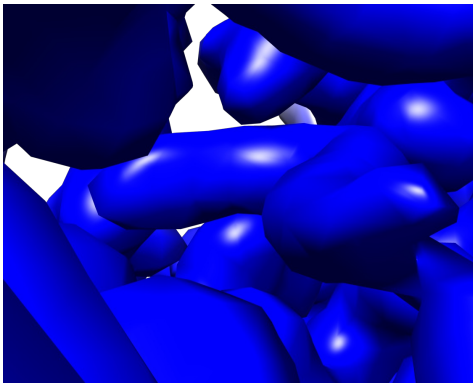


# EMDA Local Real Space Correlation

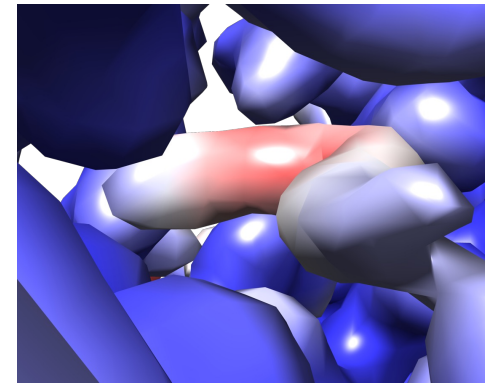
*Visualised by colouring the “standard” full map by calculated correlation*

**Full map correlation**

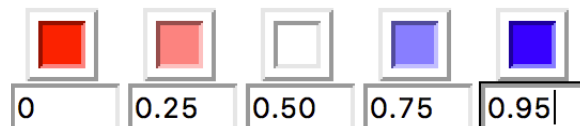
*local correlation between half maps*



**Map-model correlation**



EMD-11203 (2.6 Å)

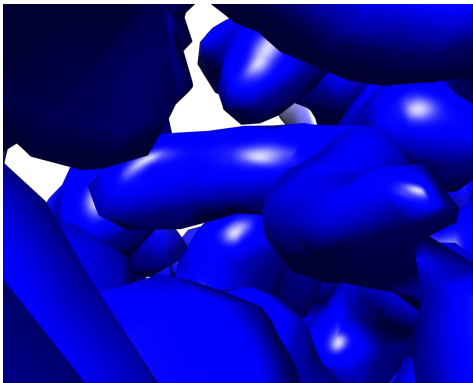


# EMDA Local Real Space Correlation

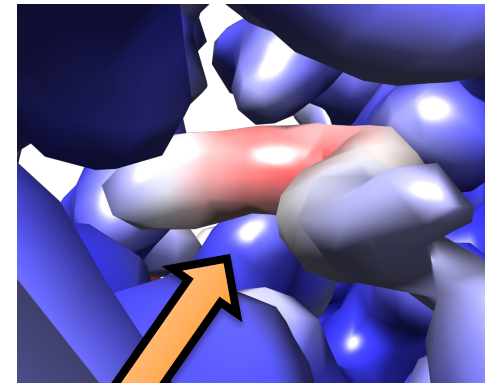
*Visualised by colouring the "standard" full map by calculated correlation*

**Full map correlation**

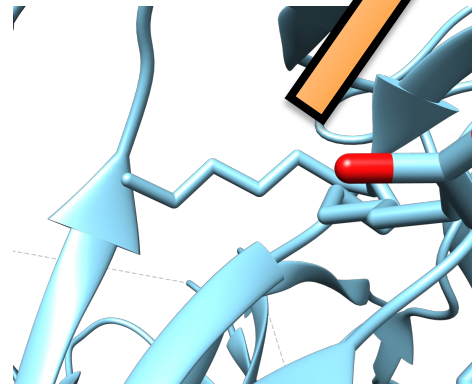
*local correlation between half maps*



**Map-model correlation**



Homolog: 6z5b (1.9 Å)  
Linoleic acid



EMD-11203 (2.6 Å)

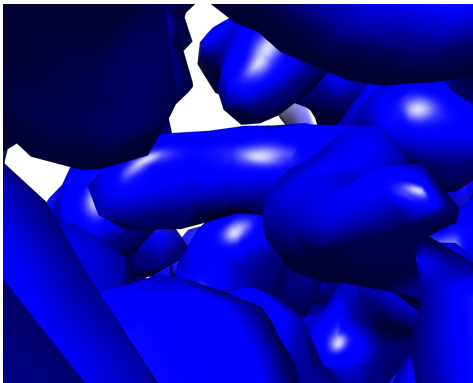


# EMDA Local Real Space Correlation

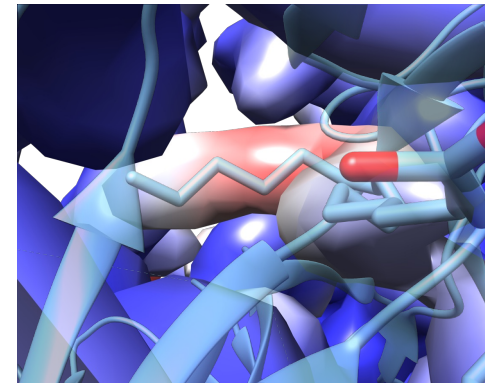
*Visualised by colouring the "standard" full map by calculated correlation*

**Full map correlation**

*local correlation between half maps*

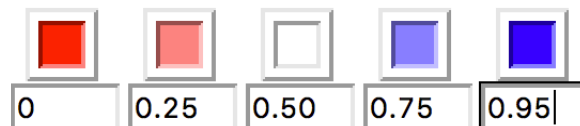


**Map-model correlation**



Homolog 6z5b superposed  
Linoleic acid seems to fit

EMD-11203 (2.6 Å)



# EMDA Difference Map Calculation

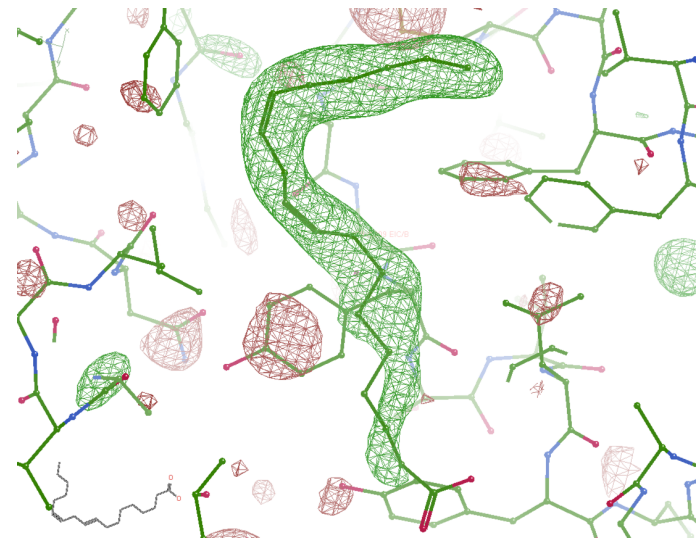
Aim: to represent differences between a map and a model

- Analogous to the  $F_o - F_c$  map in MX
- Structure factors are normalised so that they are on the same scale (by default)
- Structure factors are weighted according to FSC – avoid high-resolution noise
- Can weight according to the signal-to-noise ratio (requires half maps)

Difference map between  
EMD-11203 and PDB-6zge



Homolog 6z5b superposed

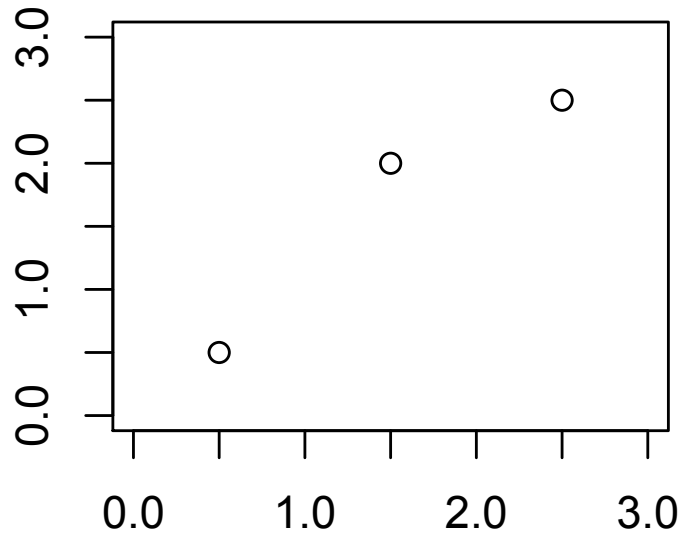


Linoleic acid

# Restrains

Why introduce so many restraints?

Answer: to improve the observation:parameter ratio.

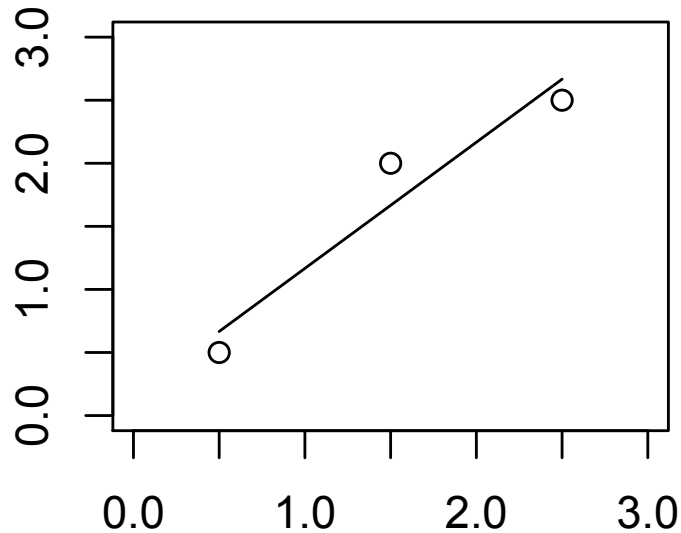


Example: Fitting a line  $y = a + bx$

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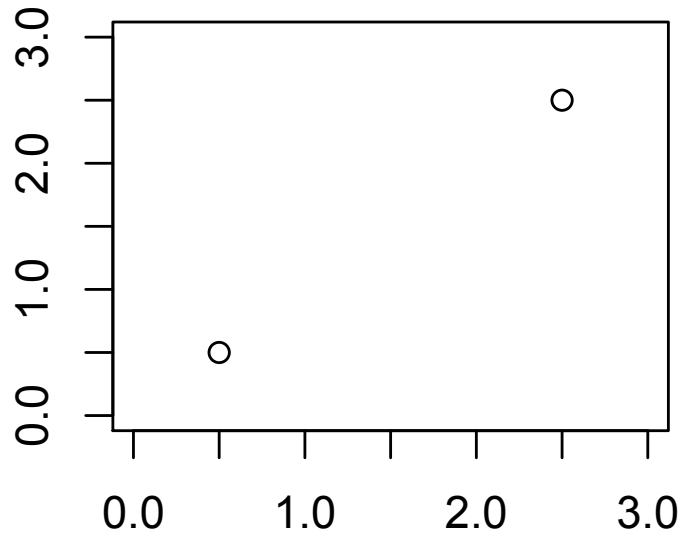


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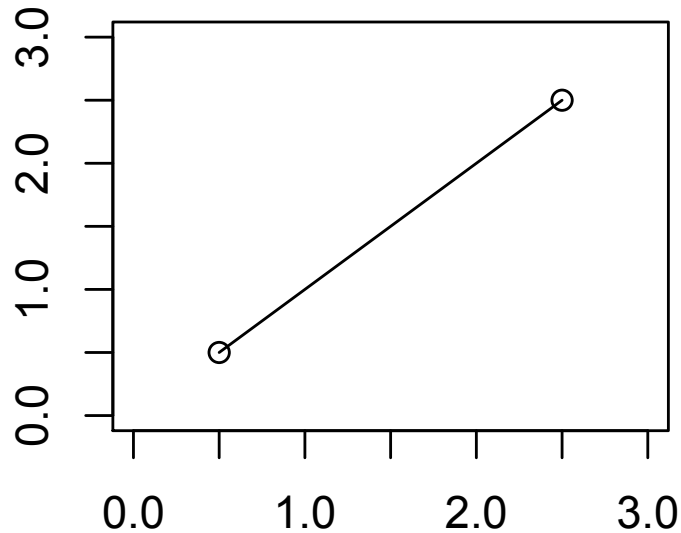
# Restraints

Why introduce so many restraints?

Answer: to improve the observation:parameter ratio.

Can fit a line

Line is unreliable



Overfitting  
Model Bias

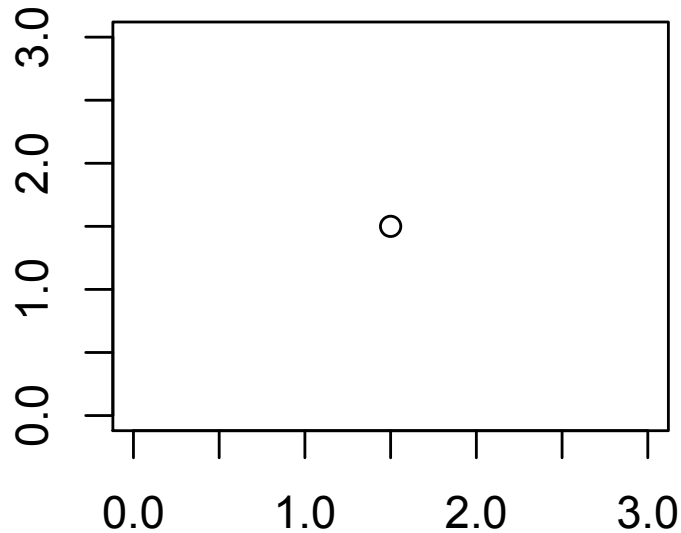
Example: Fitting a line

$$y = a + bx$$

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Example: Fitting a line  $y = a + bx$

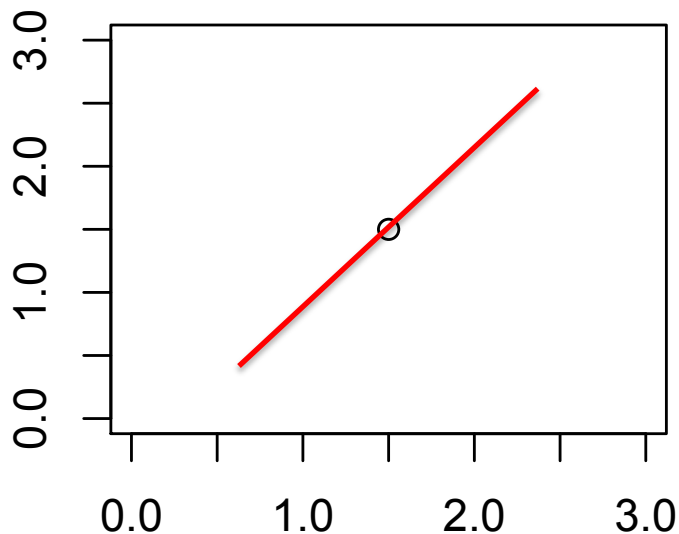
# Restraints

Why introduce so many restraints?

Answer: to improve the observation:parameter ratio.

Insufficient  
observations!

Unstable  
refinement



Ill-posed  
problem

Example: Fitting a line

$$y = a + bx$$

# Restraints

How can we improve the observation:parameter ratio?

1. Reduce number of parameters

Typically 4 parameters per atom:

- Coordinates – 3 parameters
- B-factor – 1 parameter

Alternatively:

- Rigid body refinement – 9 parameters per body

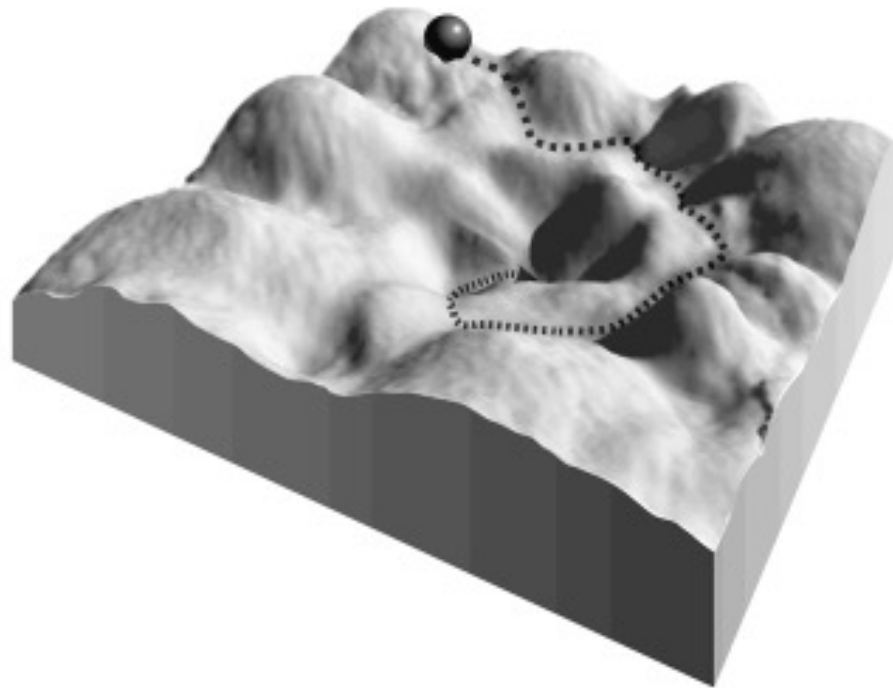
# Restraints

How can we improve the observation:parameter ratio?

1. Reduce number of parameters
2. Increase number (and strength) of restraints
  - B-value restraints
  - NCS restraints
  - H-bond and secondary-structure restraints
  - Restraints to homologous known structures
  - Nucleic acid base-pair and base-stacking restraints
  - Jelly-body restraints

Use of **prior knowledge** to stabilize refinement – *Regularisation*

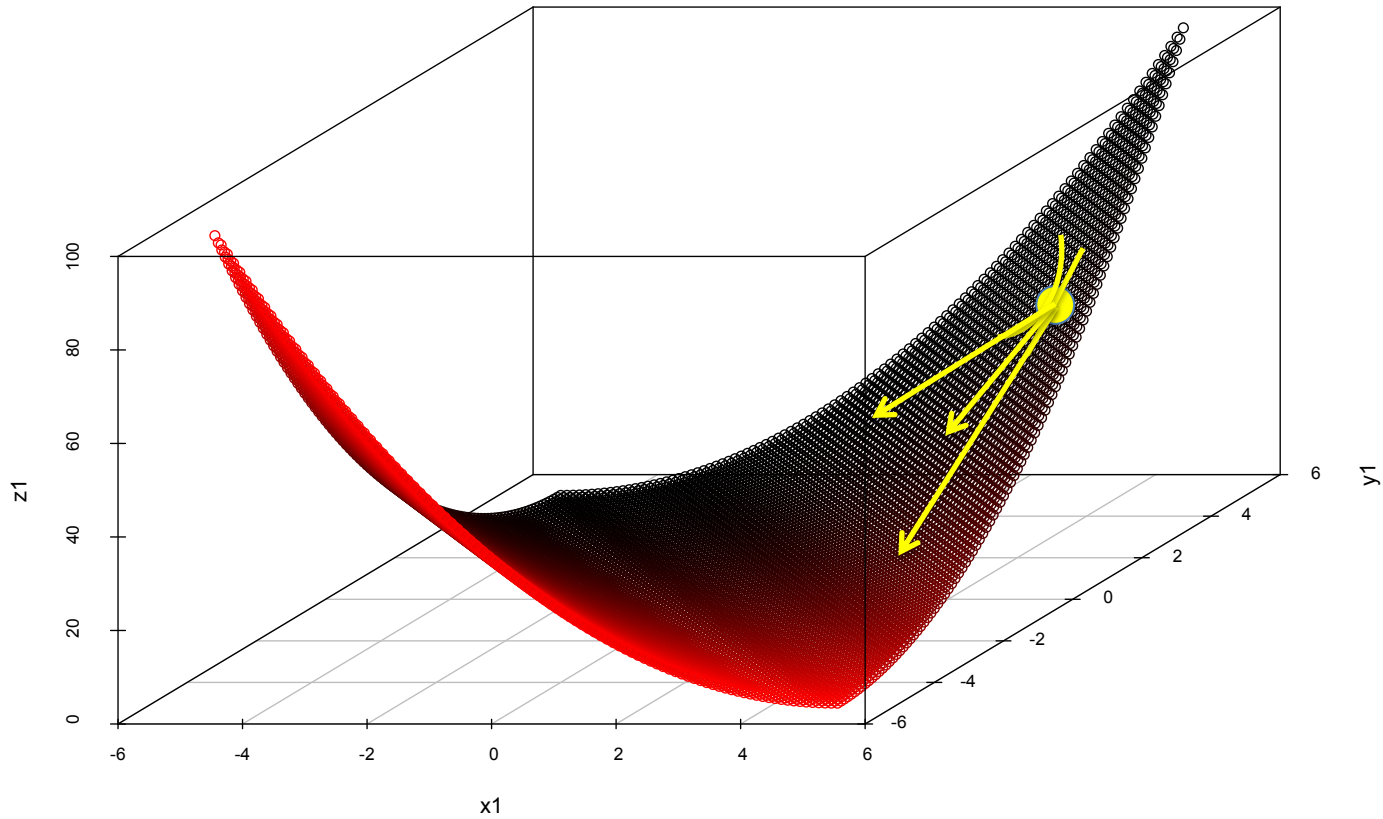
# Regularisation



# Regularisation

Example:

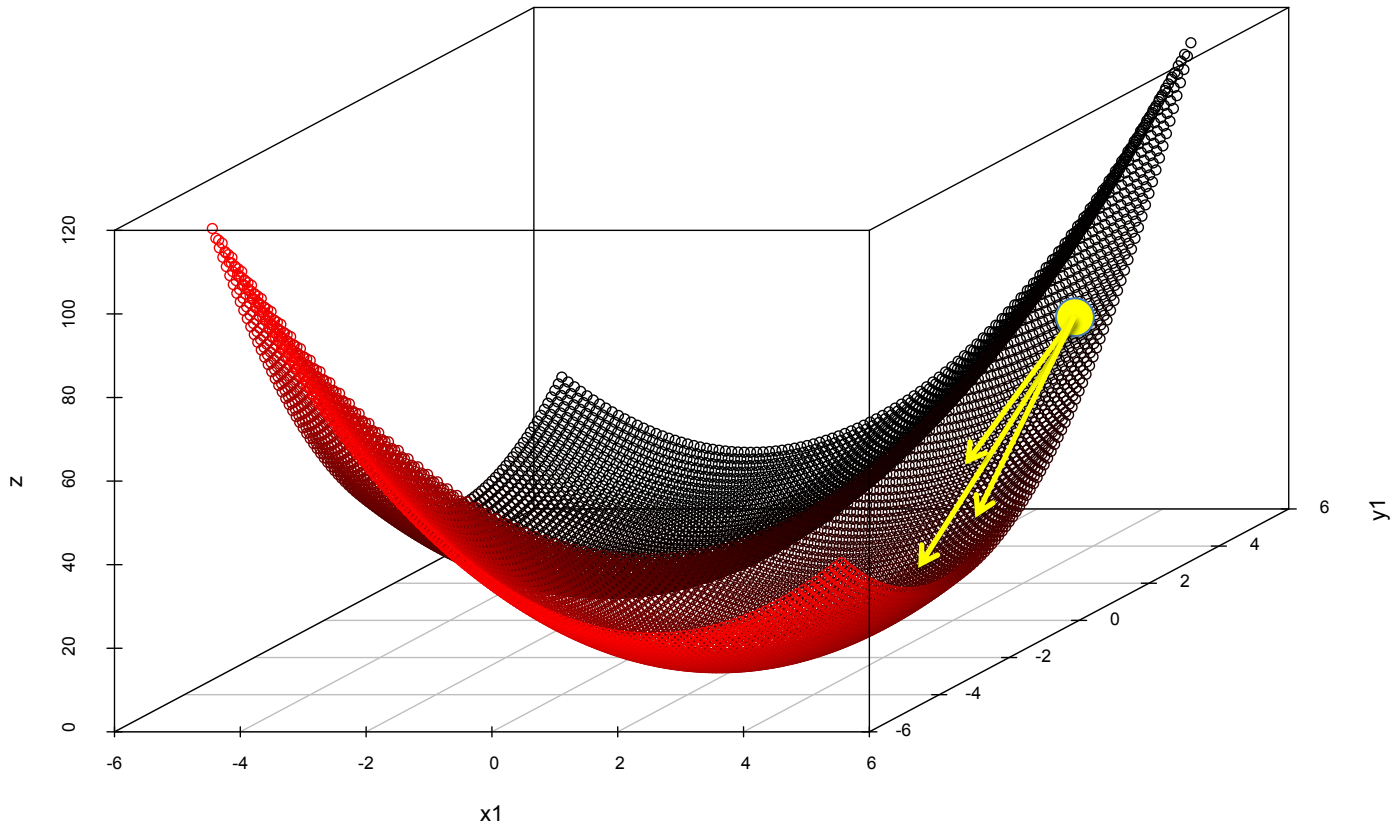
$$z = (x + y)^2$$



# Regularisation

Example:

$$z = (x + y)^2 + (|x - y| - 4)^2$$



Regularise using prior information:

$$|x - y| = 4$$

# Regularisation

## Use of available knowledge (prior information):

### *High–low resolution:*

- Geometry restraints (chemical information)

### *Medium–low resolution:*

- Local NCS restraints
- B-value restraints
- Jelly body restraints

### *Low resolution (and medium–low resolution model building):*

- External restraints

# Regularisation

Use of available knowledge (prior information):

*High–low resolution:*

- **Geometry restraints (chemical information)**

*Medium–low resolution:*

- **Local NCS restraints**
- **B–value restraints**
- Jelly body restraints

*Low resolution (and medium–low resolution model building):*

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**Regularisers with a target value**

# Regularisation

Use of available knowledge (prior information):

*High–low resolution:*

- Geometry restraints (chemical information)

*Medium–low resolution:*

- Local NCS restraints
- B–value restraints
- **Jelly body restraints**

*Low resolution (and medium–low resolution model building):*

- External restraints

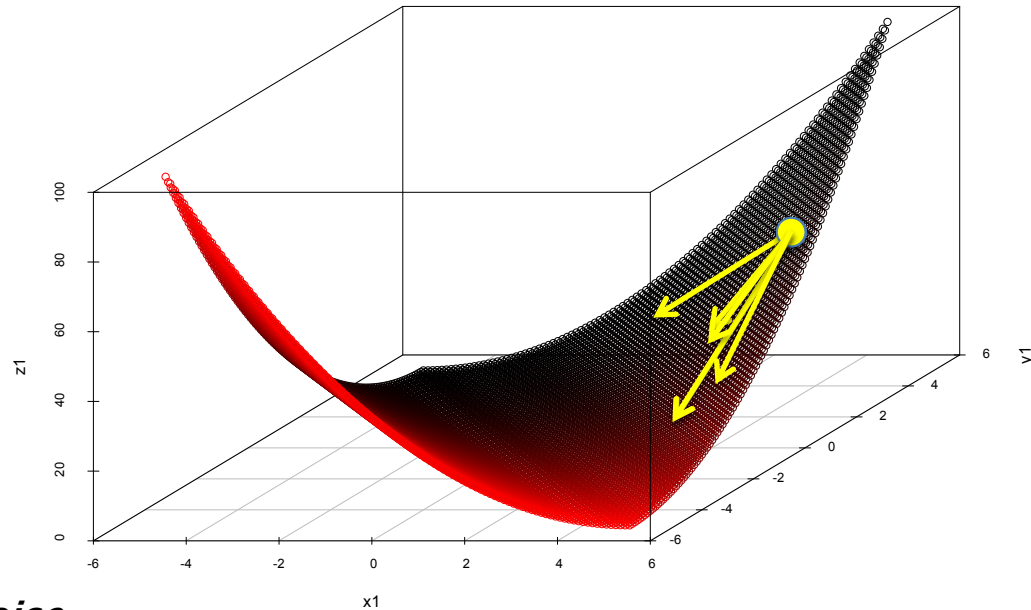
**Regularisers without an external target value**

# Jelly Body Restraints

Regularisers without a target:

$$f = \sum_{\text{close atom pairs}} \frac{1}{\sigma^2} (d - d_{\text{current}})^2$$

$d$  : interatomic distance  
 $d_{\text{current}}$  : current interatomic distance  
 $\sigma$  : restraint standard deviation



Does not change likelihood function.  
Does not change derivative.  
Does change 2<sup>nd</sup> derivative – curvature.

***Model should be less prone to fitting into noise***

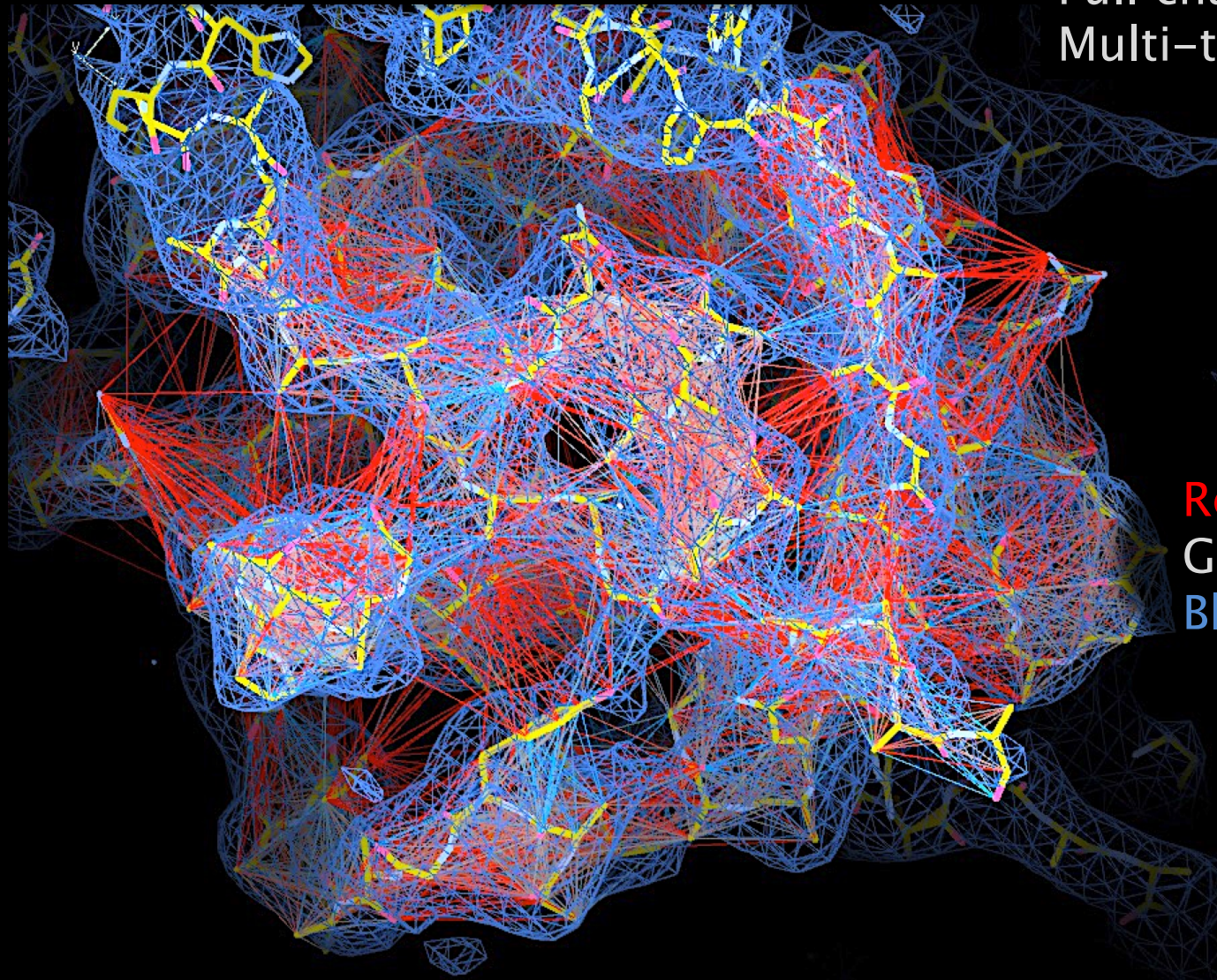
Will only work if parameters are near the minima (model is already good)

Typical:  $\sigma = 0.01-0.02$

Distance threshold:  $4.2\text{\AA}$

# ProSMART Restraints in Coot

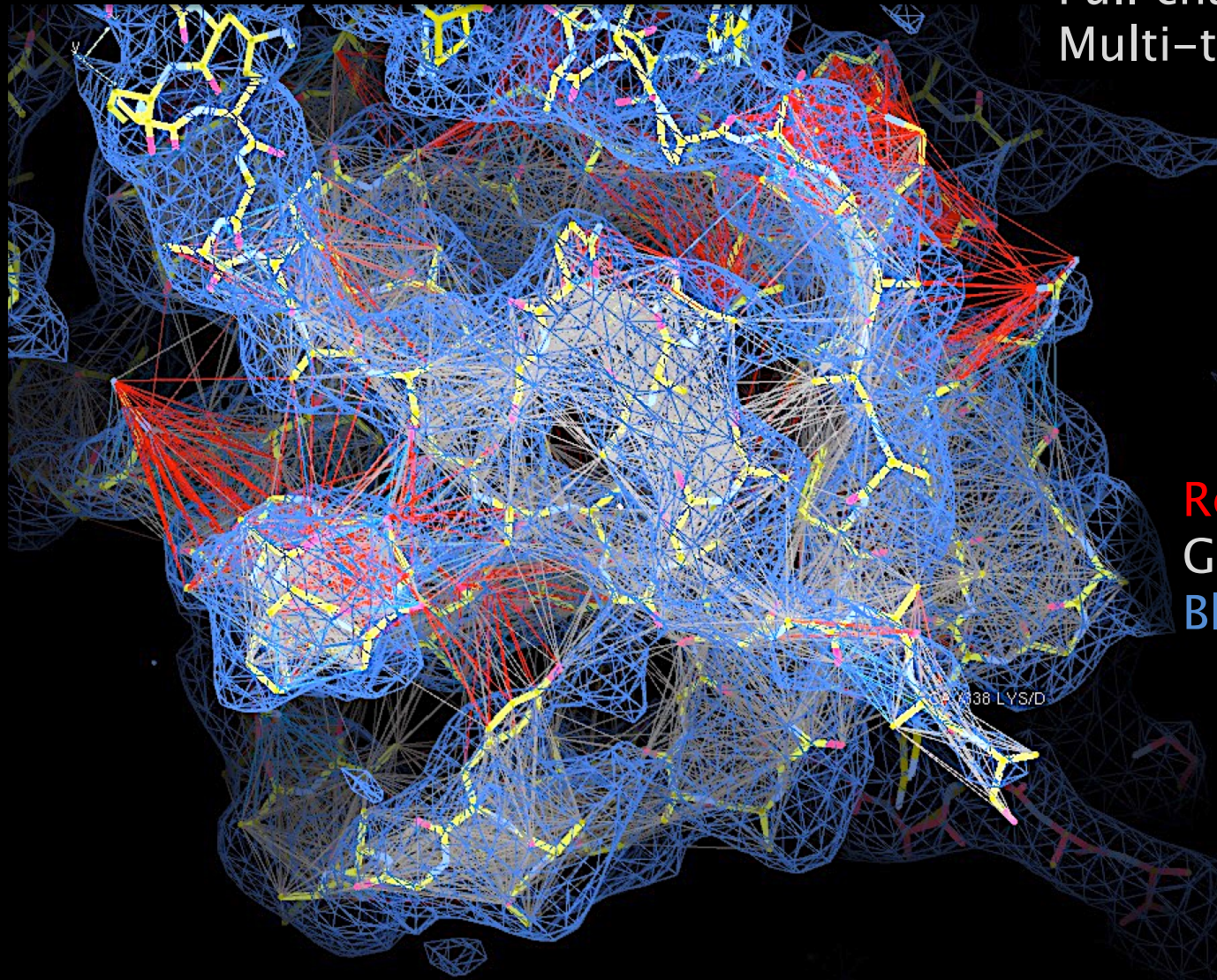
Full chain refine  
Multi-threaded



Red: long  
Grey: similar  
Blue: short

# ProSMART Restraints in Coot

Full chain refine  
Multi-threaded



Red: long  
Grey: similar  
Blue: short

338 LYS/D

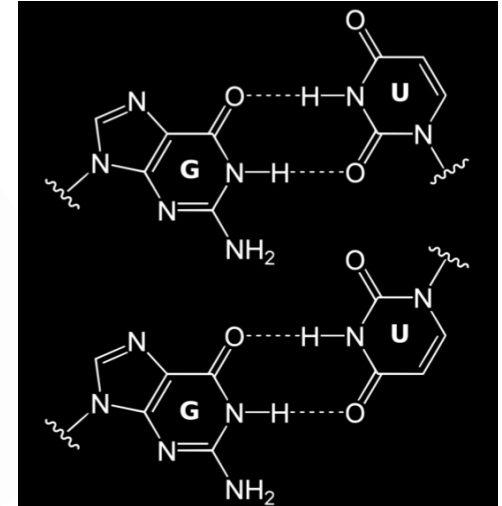
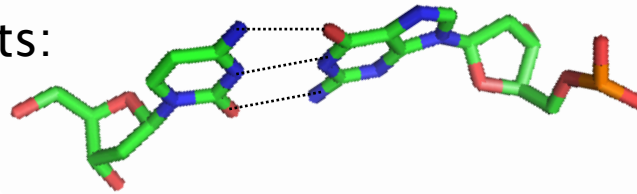
# What if there are no high-resolution homologues?

But we still need to stabilise refinement...

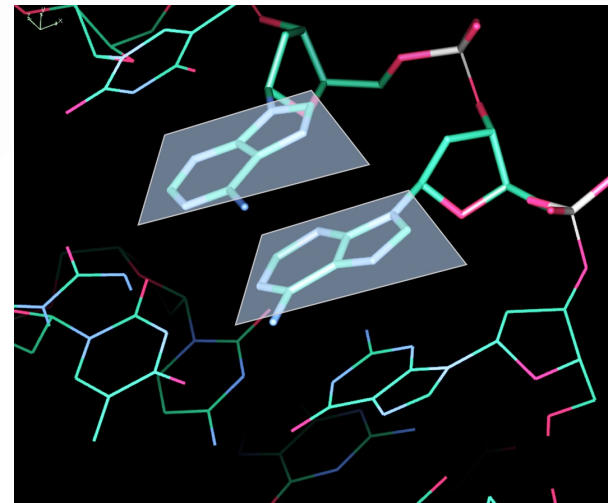
- Jelly-body restraints
- ProSMART – Alphafold restraints
- Generic external restraints:
  - ProSMART – protein  
(secondary structure h-bonds)
  - LibG – DNA/RNA  
(base-pair, base-stacking)

# LibG Nucleic Acid Restraints

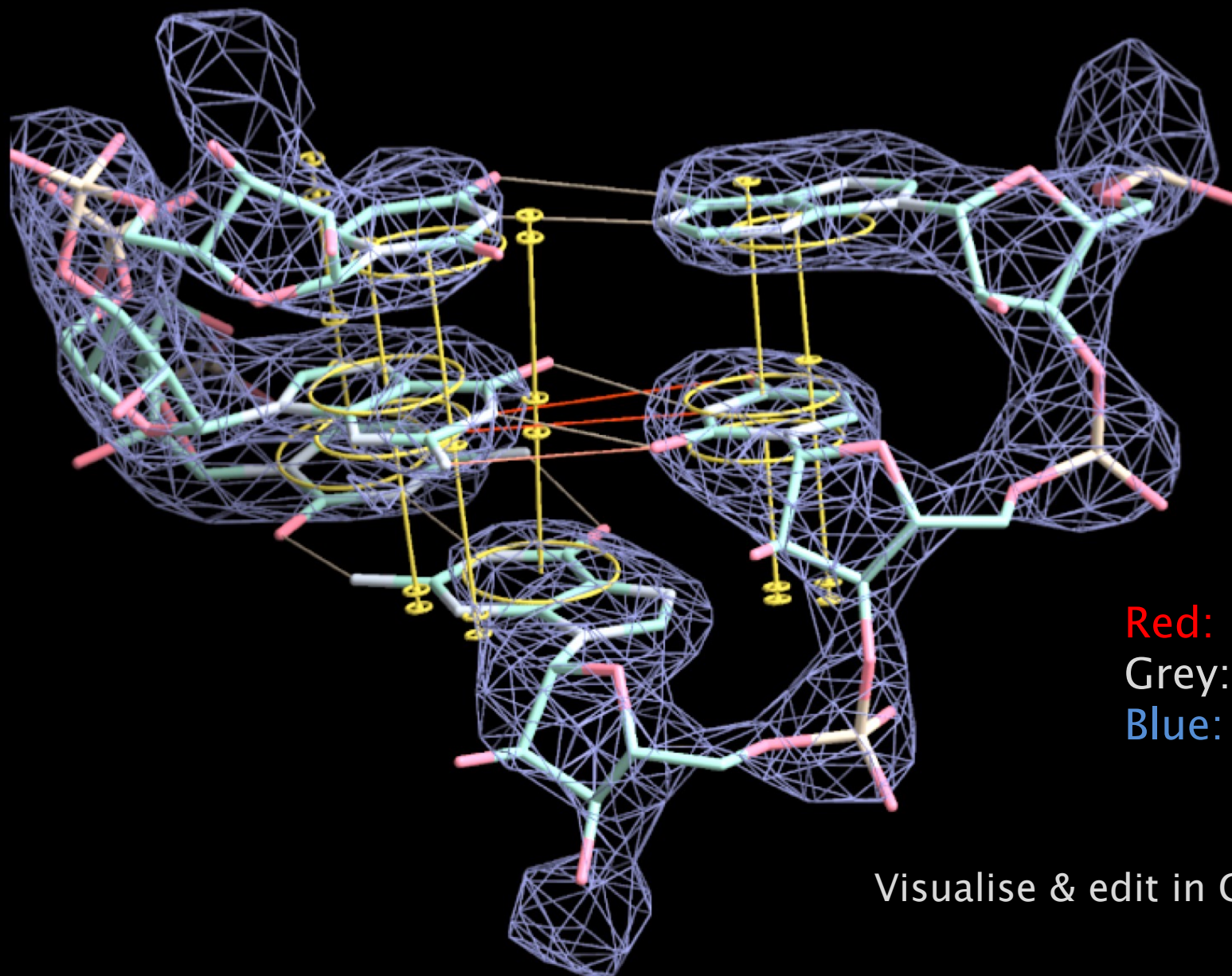
1) Base-pair restraints:



2) Parallel plane restraints:



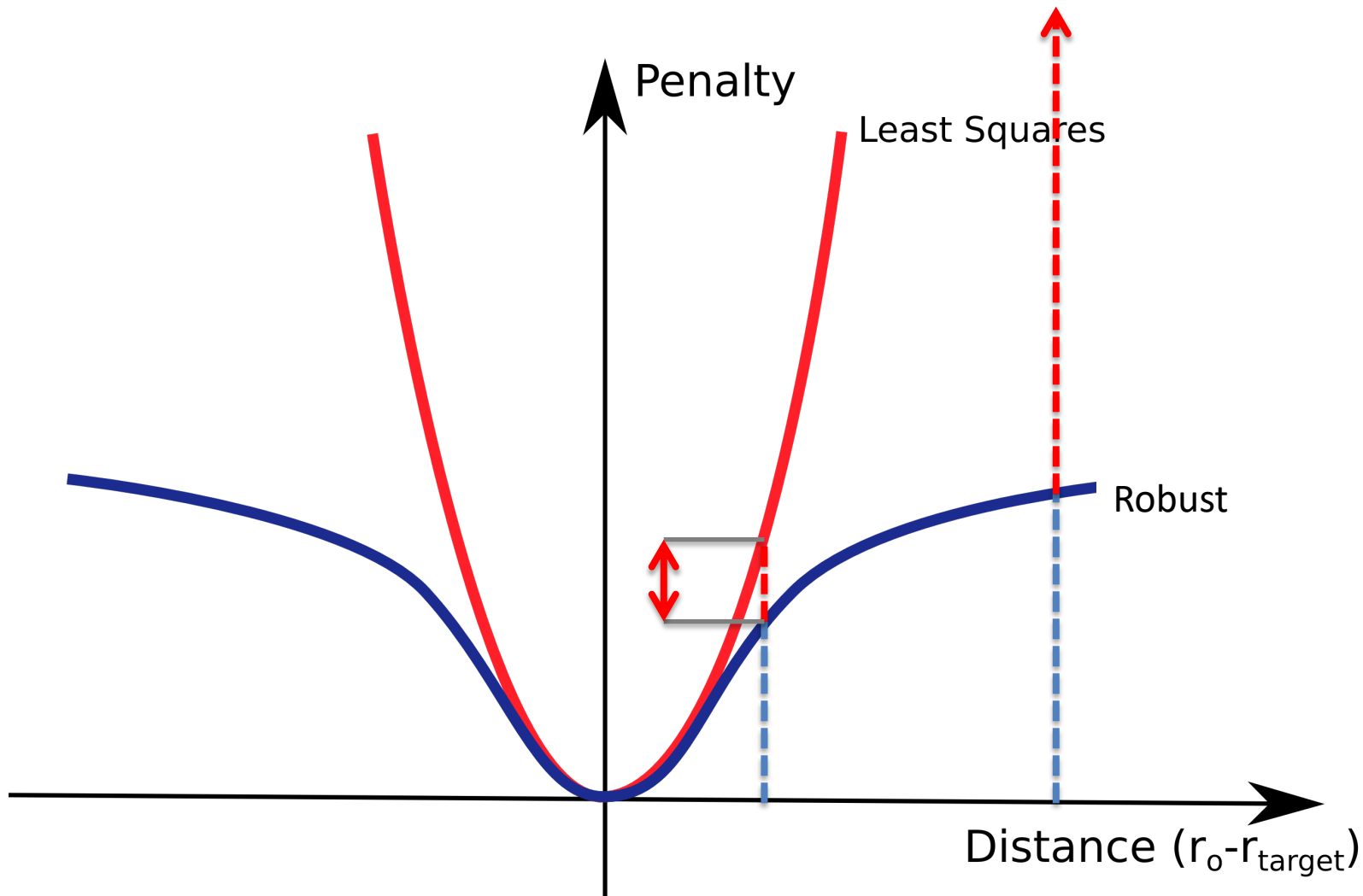
# LibG Nucleic Acid Restraints



Red: long  
Grey: similar  
Blue: short

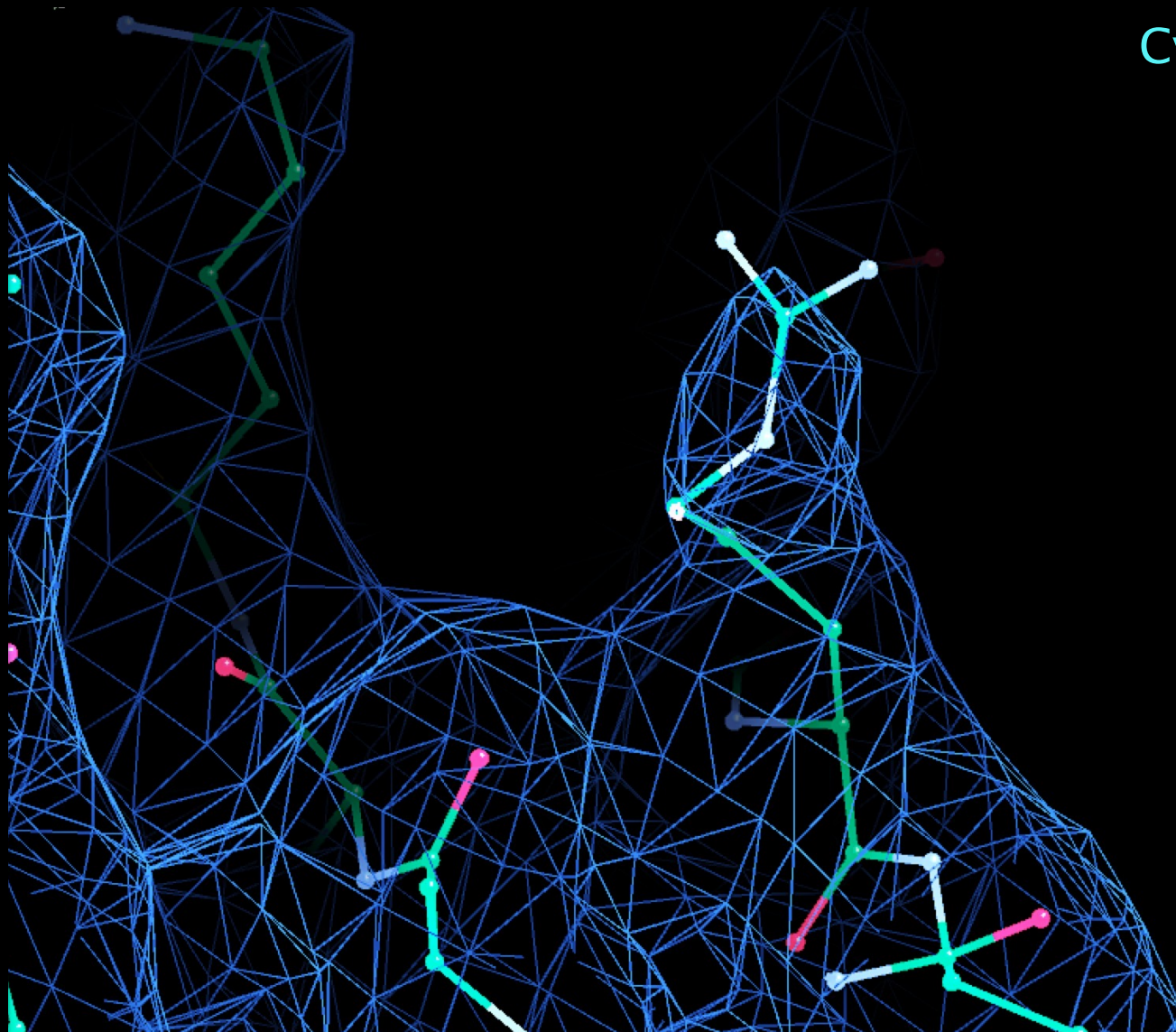
Visualise & edit in Coot

# Robust Estimation



# Robust Estimation

Cyan: original

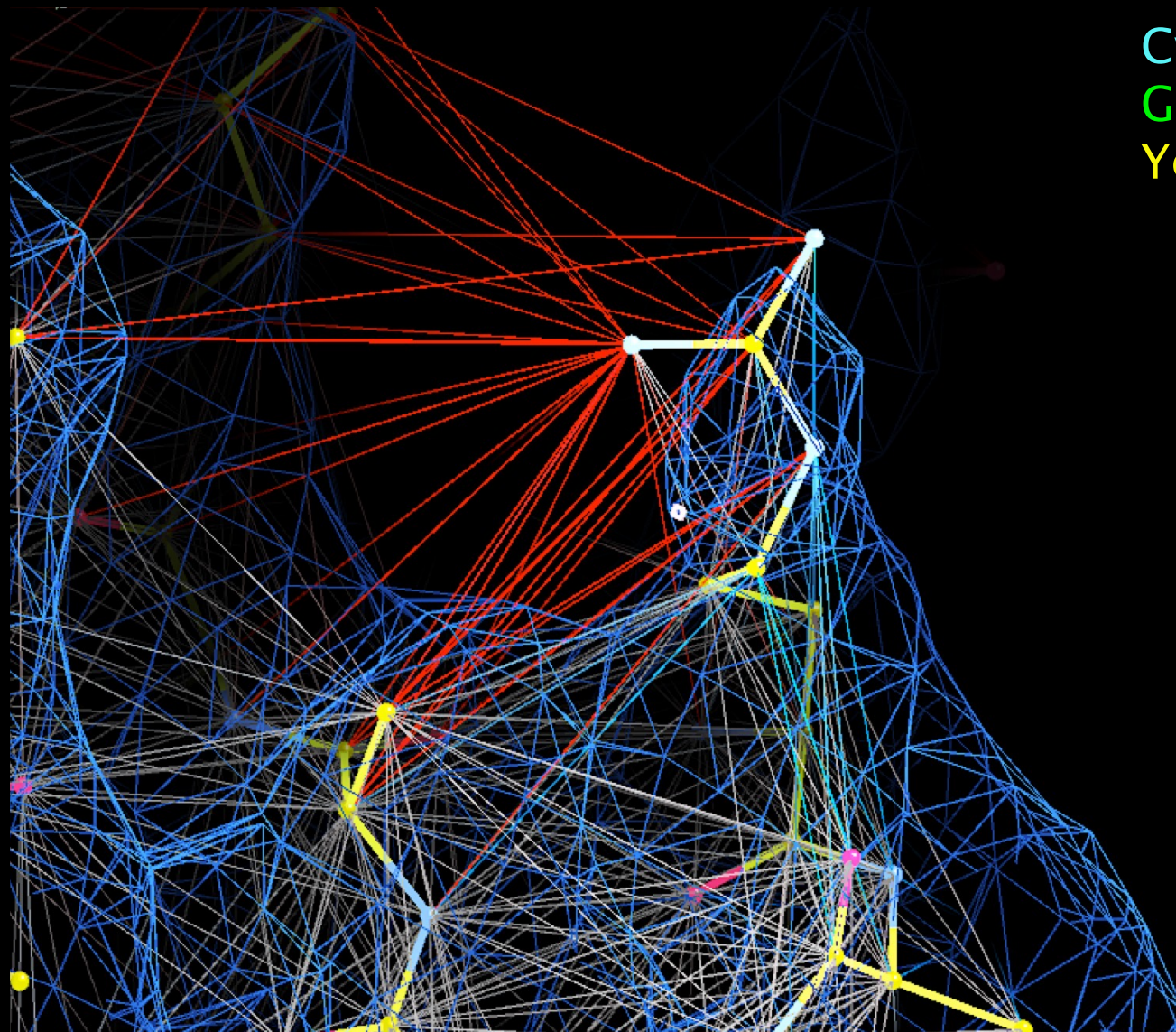


# Robust Estimation



Cyan: original  
Green: homolog

# Robust Estimation



Cyan: original  
Green: homolog  
Yellow: refined

Red: long  
Grey: similar  
Blue: short

# Robust Estimation

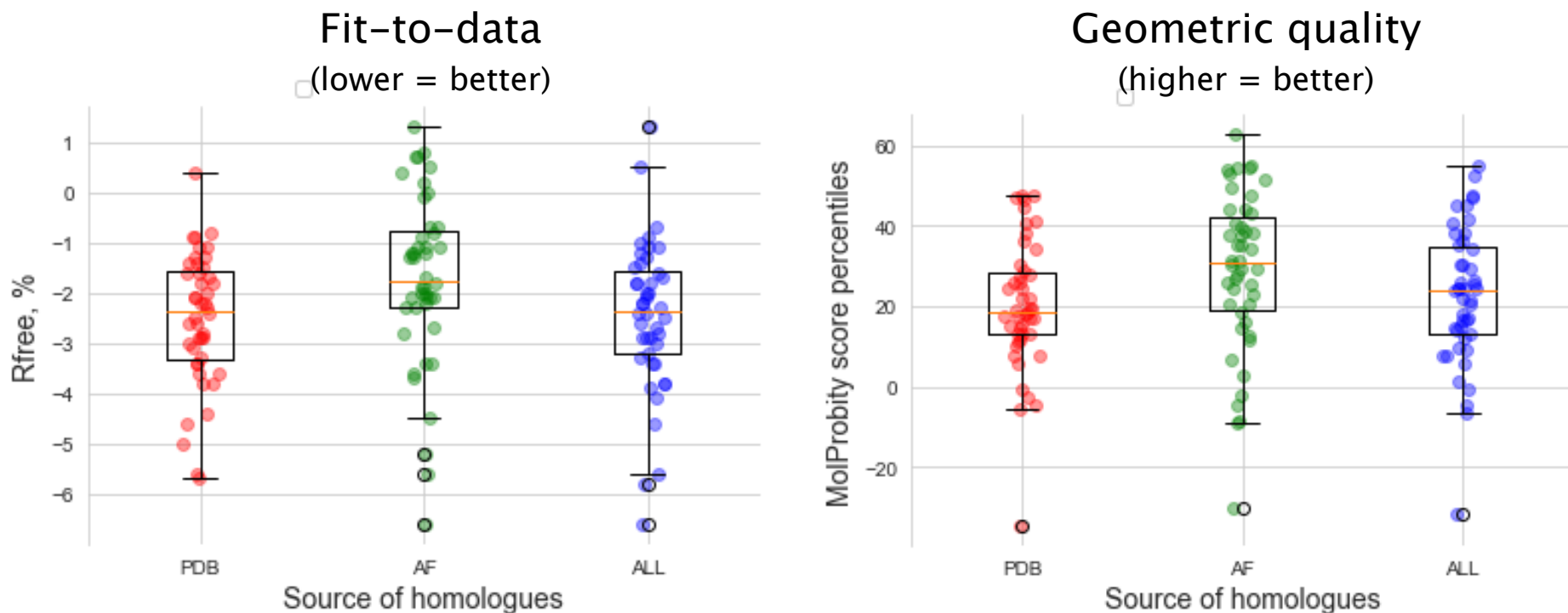


Cyan: original  
Green: homolog  
Yellow: refined

Red: long  
Grey: similar  
Blue: short

# Utilising Predicted Structures

LORESTR performance vs original model – restraints from PDB/AF2 models



- AlphaFold2 models can be used for external restraint generation.
- Close homologues usually perform better, if available; try both.
- LORESTR automatically gets and prepares AF2 models ready for ProSMART.

*(unpublished; thanks to Oleg Kovalevskiy)*

# Importance of Phases

*“Phases are more important than amplitudes”*

$\rho_C$  = current map

$\rho_t$  = ideal (true) map

$$\text{cor}(\rho_t, \rho_C) = \text{cor}(F_t, F_C) = \frac{\sum |F_t| |F_C| \cos(\varphi_t - \varphi_C)}{\sqrt{\sum |F_t|^2 \sum |F_C|^2}}$$

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In a given shell:

$$FSC = \frac{1}{N} \sum |E_t| |E_C| \cos(\varphi_t - \varphi_C)$$

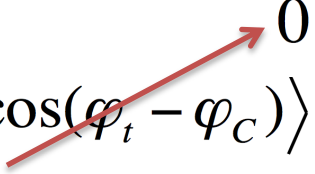
FSC : Fourier Shell Correlation

$$FSC = \langle |E_t| |E_C| \cos(\varphi_t - \varphi_C) \rangle$$

(under certain assumptions)

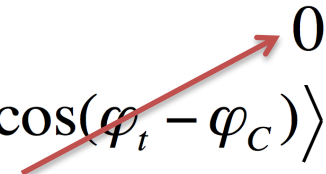
# Importance of Phases

Case 1: *phases are random; amplitudes are exact:*

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$$= 0$$

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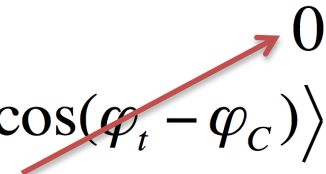
Case 2: *phases are exact; amplitudes are random:*

$$FSC = \langle |E_t| |E_C| \cos(\varphi_t - \varphi_C) \rangle$$
$$= \langle |E_t| |E_C| \rangle$$
$$\approx 0.785 \quad \text{(Under simple assumptions)}$$

Conclusions: 1. Phases are more important than amplitudes

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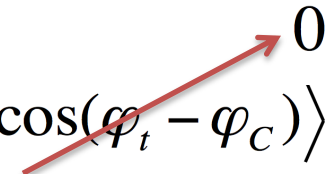
Case 3: *phases are exact; amplitudes are random - replace with expectation:*

$$|E_C| = \langle |E_C| \rangle$$
$$FSC \approx 0.886$$

- Conclusions:
1. Phases are more important than amplitudes
  2. Justification for “free lunch” approach

# Importance of Phases

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$$= 0$$

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Case 3: *phases are exact; amplitudes are random - replace with expectation:*

$$|E_C| = \langle |E_C| \rangle$$
$$FSC \approx 0.886$$

Conclusions:

1. Phases are more important than amplitudes
2. Justification for “free lunch” approach
3. Only use if cor. between current and “true” E-values is high

# Correlation between $F_{\text{obs}}$ and $F_{\text{calc}}$

*More practically... a warning:*

There is an upper limit:  $\text{cor}(F_{\text{obs}}, F_{\text{calc}}) \leq \left( \frac{2FSC_{1/2}}{1 + FSC_{1/2}} \right)^{1/2}$

E.g. if  $FSC_{1/2} = 0.5$  then  $\text{cor}(F_{\text{obs}}, F_{\text{calc}}) \leq 0.82$

Observe correlation higher than this  $\rightarrow$  further investigation is required

(denoted  $CC_{1/2}$  for SFs in Cryo-EM,  $CC^*$  for intensities in MX)

# Relevant Publications

Yamashita *et al.* (2021) Cryo-EM single-particle structure refinement and map calculation using Servalcat. *Acta Cryst D77*, 1282-91.

Casanal *et al.* (2020) Current developments in Coot for macromolecular model building of electron cryo- microscopy and crystallographic data. *Protein Science* 29(4), 1055-64.

Nicholls *et al.* (2018) Current approaches for the fitting and refinement of atomic models into cryo-EM maps using CCP-EM. *Acta Cryst.* D74, 492-505.

Burnley *et al.* (2017) Recent developments in the CCP-EM software suite. *Acta Cryst D73*.

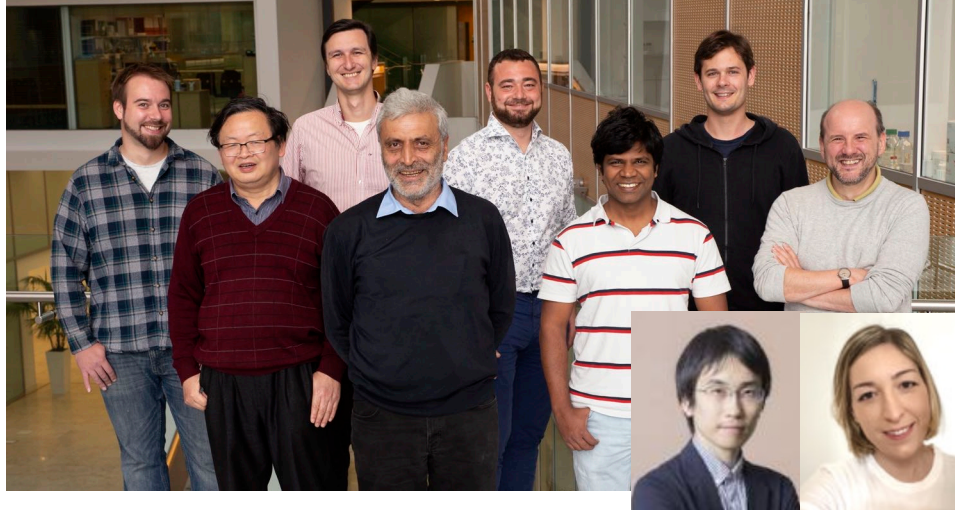
Murshudov (2016) Refinement of atomic structures against cryo-EM maps. *Methods in Enzymology*, 277-305.

Brown *et al.* (2015) Tools for macromolecular model building and refinement into electron cryo-microscopy reconstructions. *Acta Cryst.* D71, 136-53.

# Acknowledgements

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[www2.mrc-lmb.cam.ac.uk/groups/murshudov/](http://www2.mrc-lmb.cam.ac.uk/groups/murshudov/)

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Oleg Kovalevskiy  
Garib Murshudov  
Michal Tykac  
Rangana Warshamanage  
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Ronan Keegan  
Ville Uski  
Maria Fando

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### ***Computing***

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Toby Darling

All colleagues from  
MRC-LMB, CCP4, CCP-EM  
Users for feedback!