Two Coots and a Moorhen

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Nov 2023 @ CLS

Coot *vs.* Moorhen

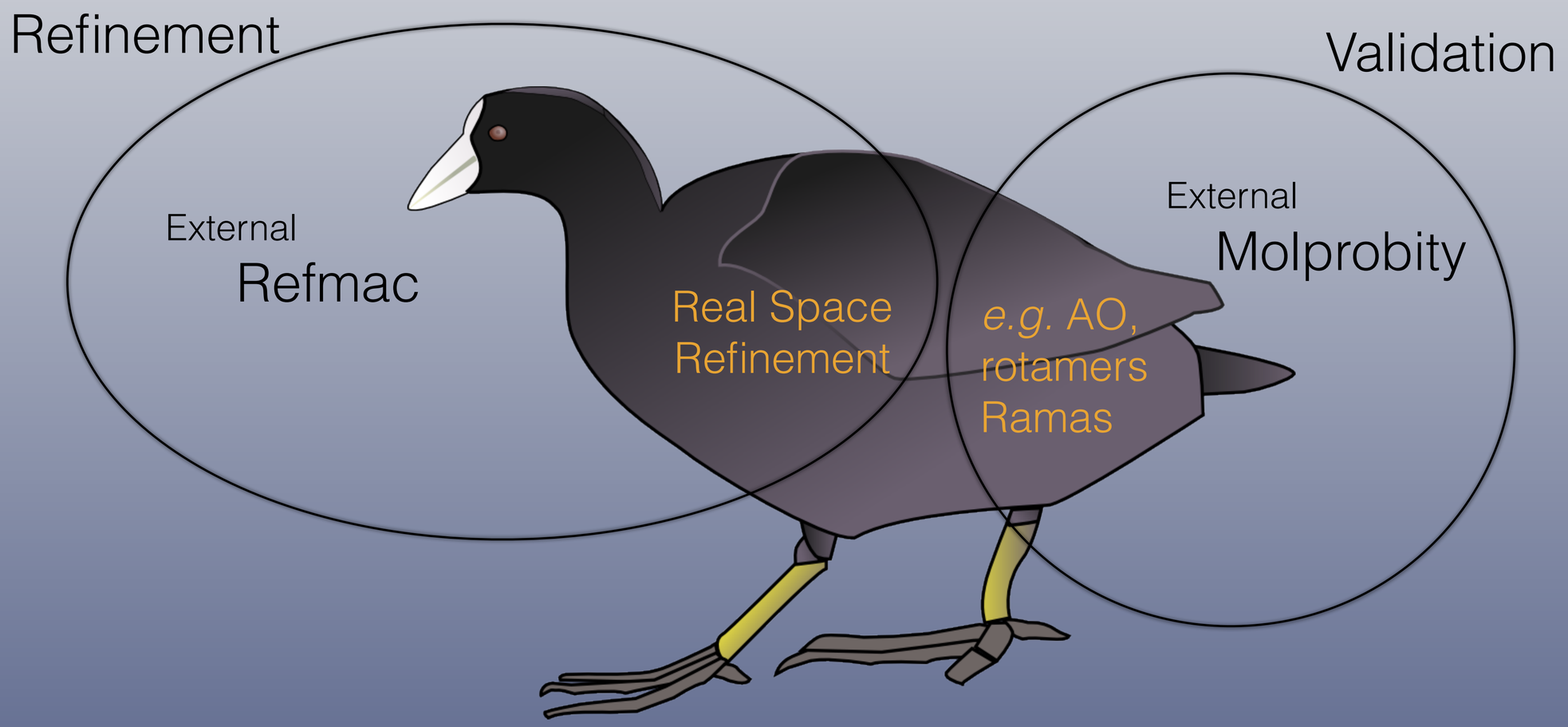
Coot

Moorhen

About This Presentation

- Part 1: *Coot* 0.9.x
- Part 2: *Coot* 1.x
- Part 3: Moorhen
- Part 4: *Coot* 1 demo

Coot Feature Integration



It is convenient & expeditious to use Model-building, Refinement and Validation together

Part 1: *Coot* 0.9.x

Coot 0.9.8.93

- “Backrub Rotamers”
  - “All-Chain”
- Geman-McClure Restraints
- “Proportional Editing”
- “Updating Maps”

Thanks to Tristan Croll

What is “Refinement”?

- The adjustment of model parameters (coordinates) so that the calculated structure factors more closely match the observations
  - In *Coot*, we sometimes don’t recalculate the map, so this translates to :
    - Move the atoms into as high density as possible while minimising geometric distortions

“Minimising Geometry”
What Prior Knowledge do we have?

- We know chemistry:
  - Bond lengths and uncertainties
  - Bond angles and uncertainties
  - Chiral Centres
  - Delocalisation and aromaticity
  - Torsions
- We combine the gradients from the minimisation of geometric deviations with the gradients derived from the map

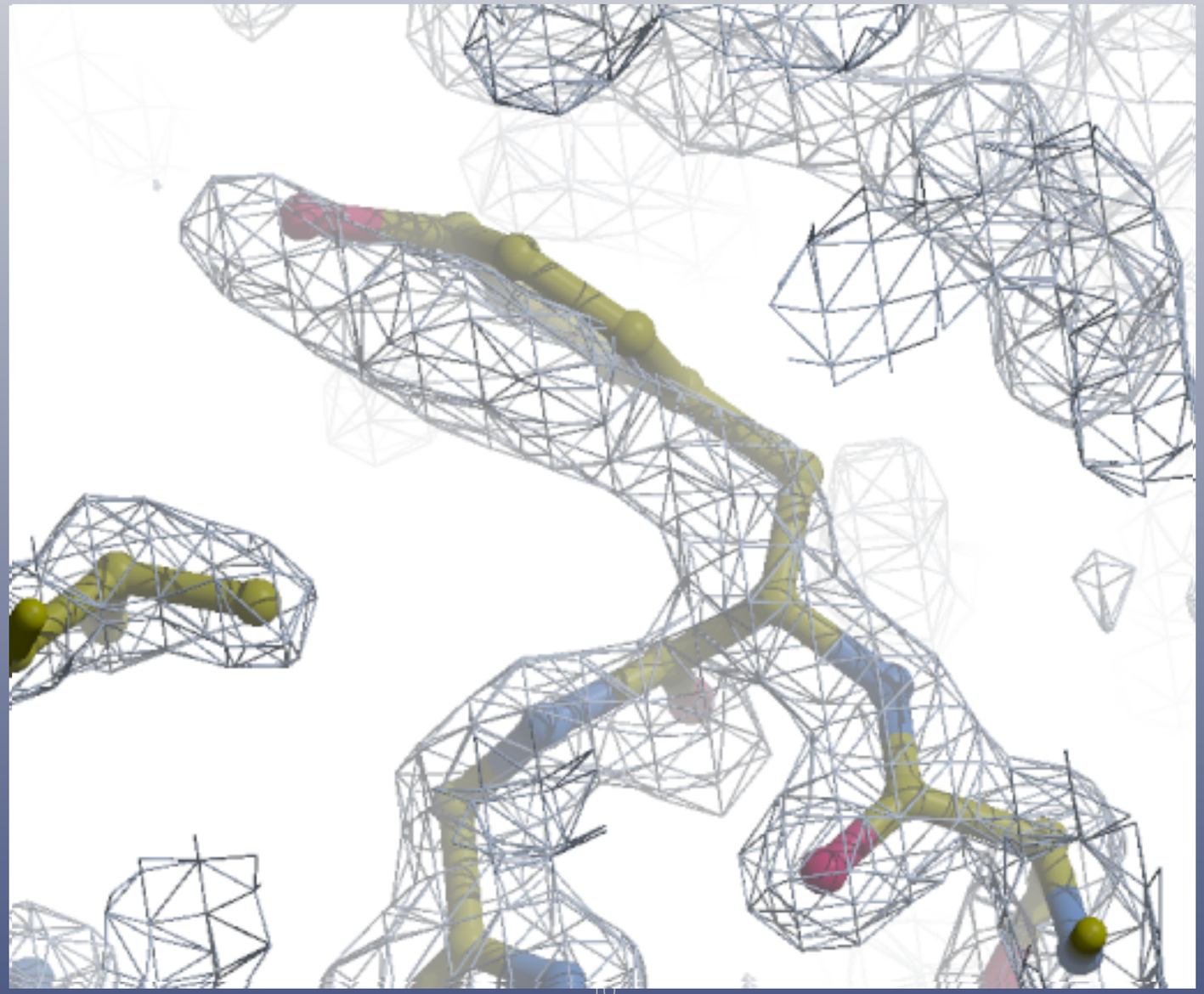
Minimisation

APPENDIX *A*
Regularization and refinement derivatives

The function that we are trying to minimize is S, where

$$S = S_{\text{bond}} + S_{\text{angle}} + S_{\text{torsion}} + S_{\text{plane}} + S_{\text{nbc}} + S_{\text{chiral}} - S_{\text{density}}$$

Minimisation



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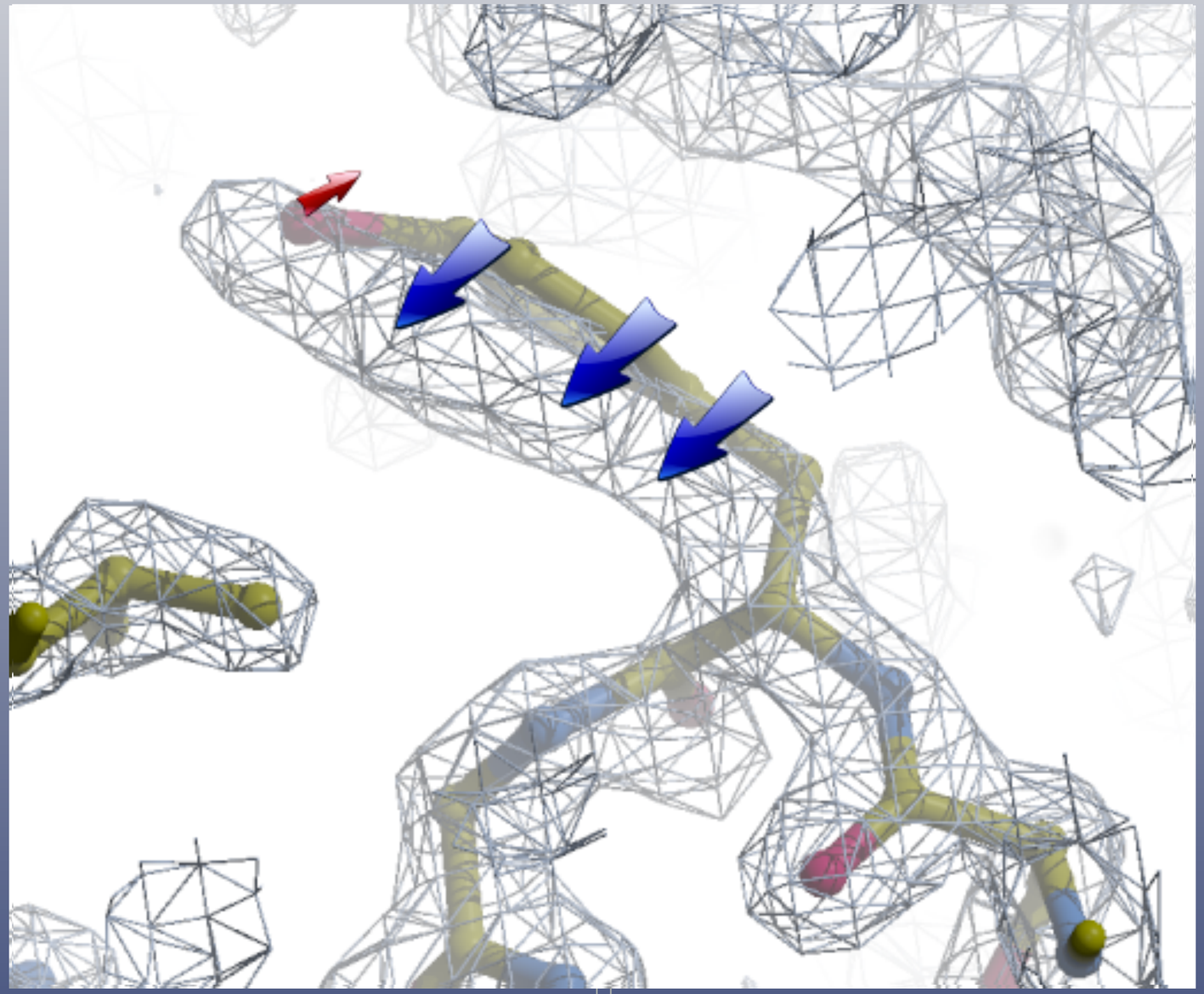

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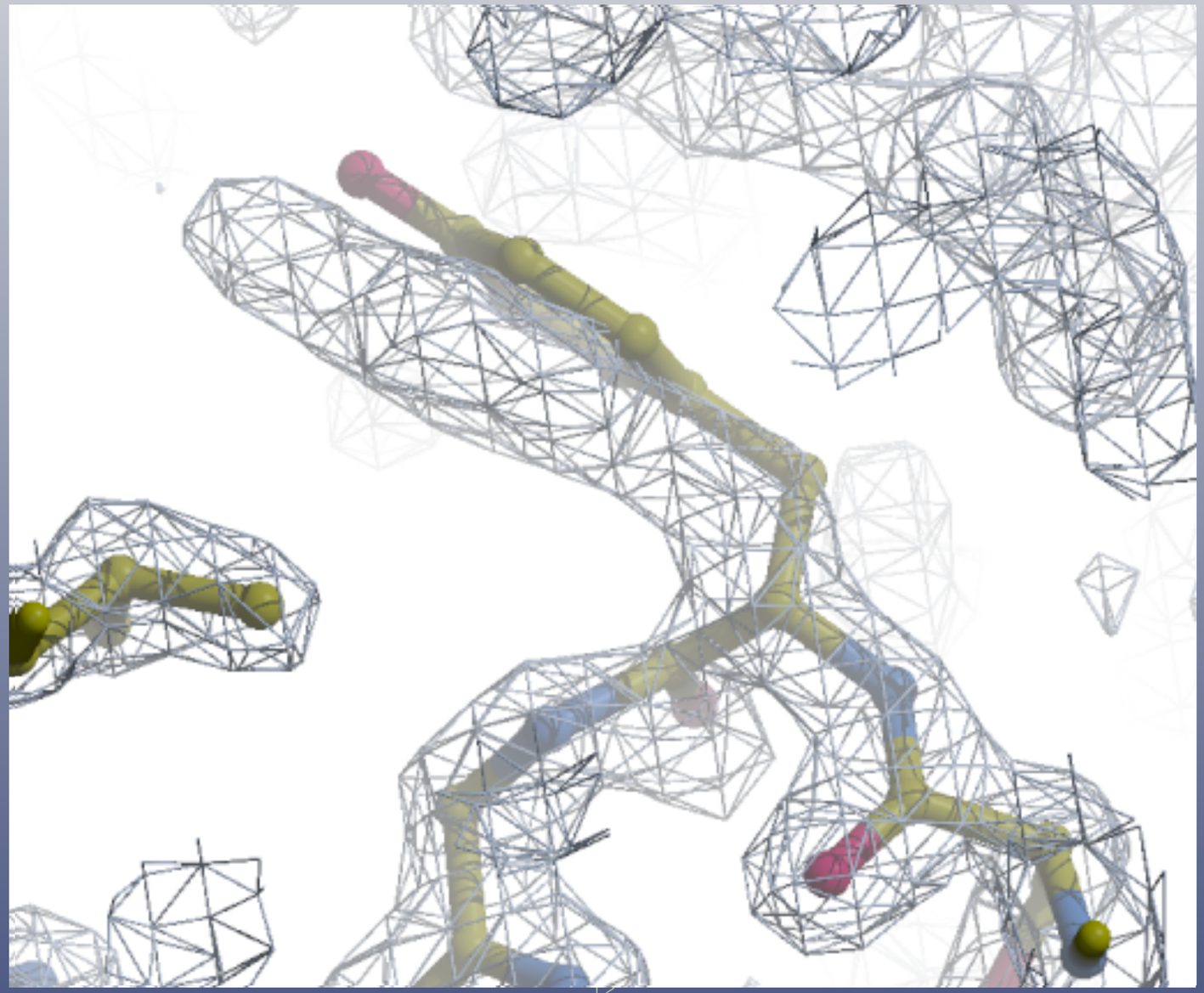

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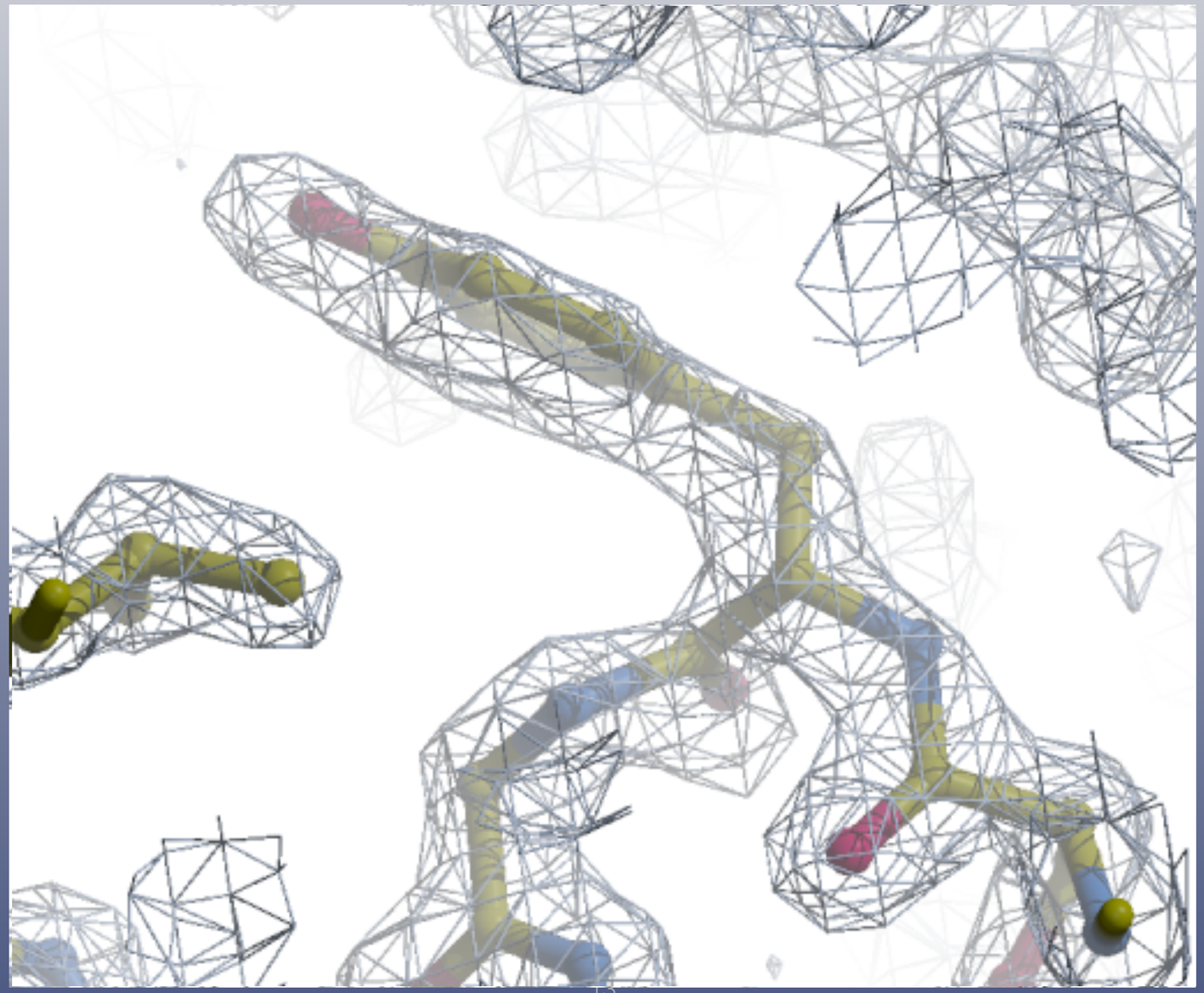
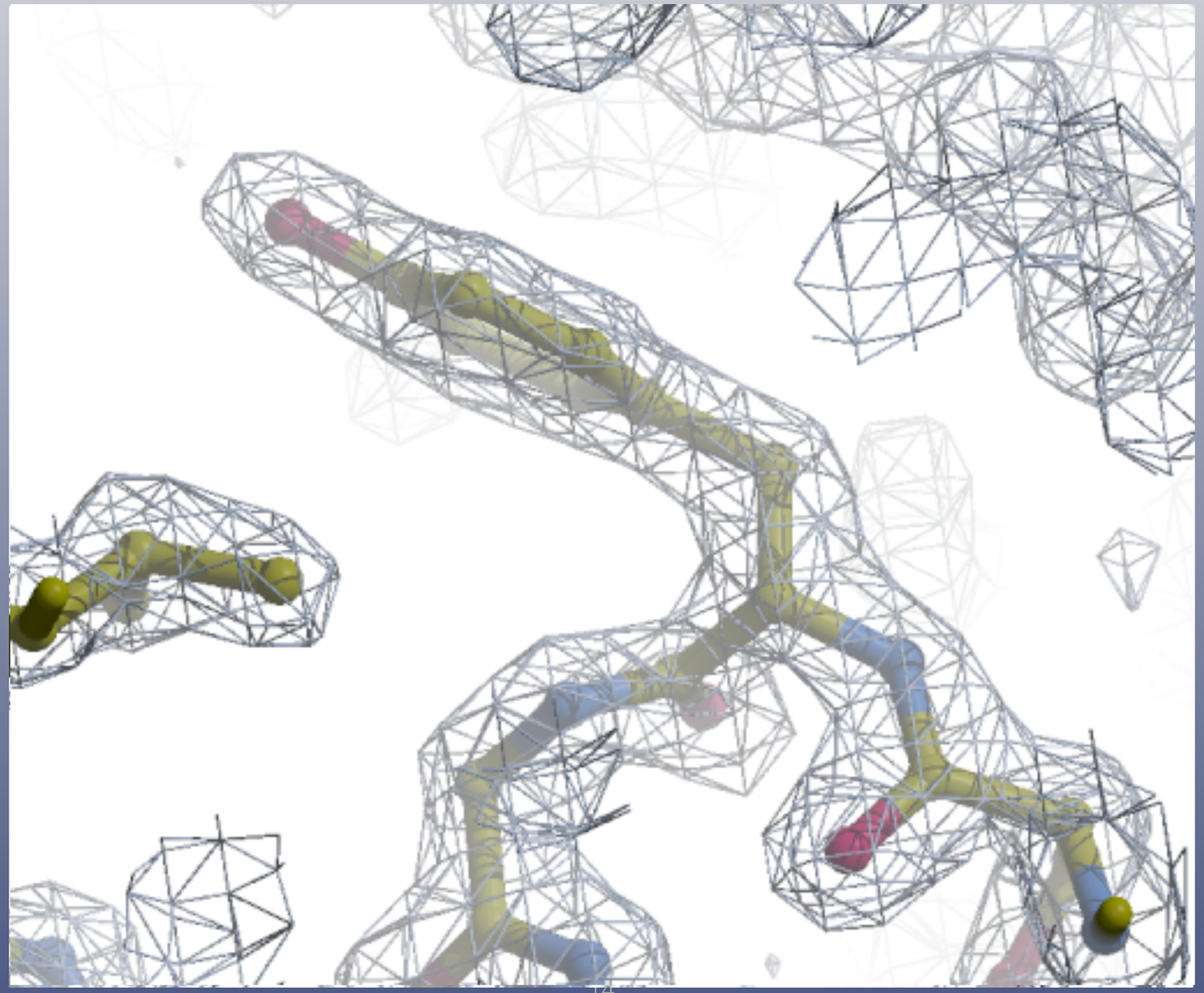
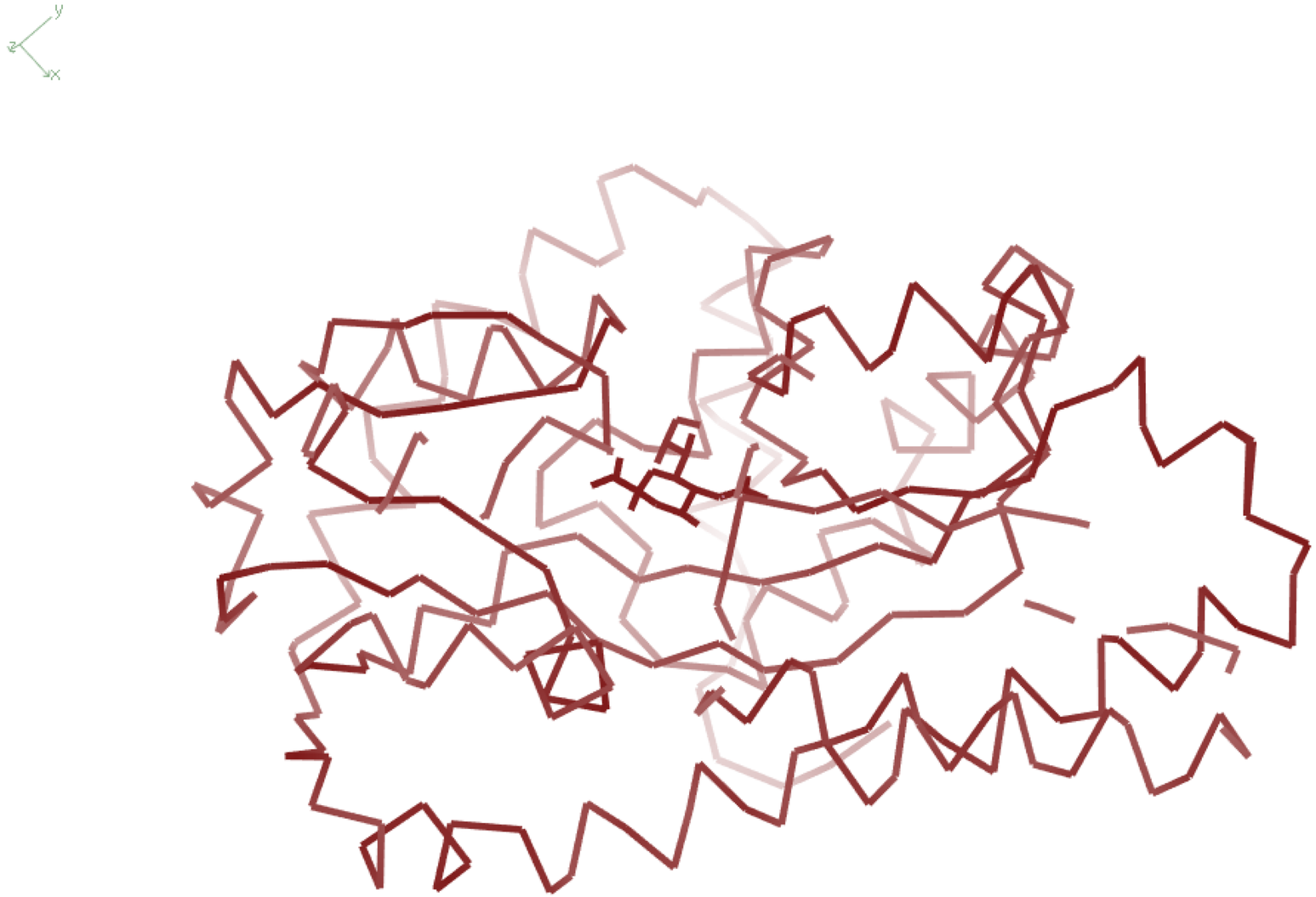


Minimisation

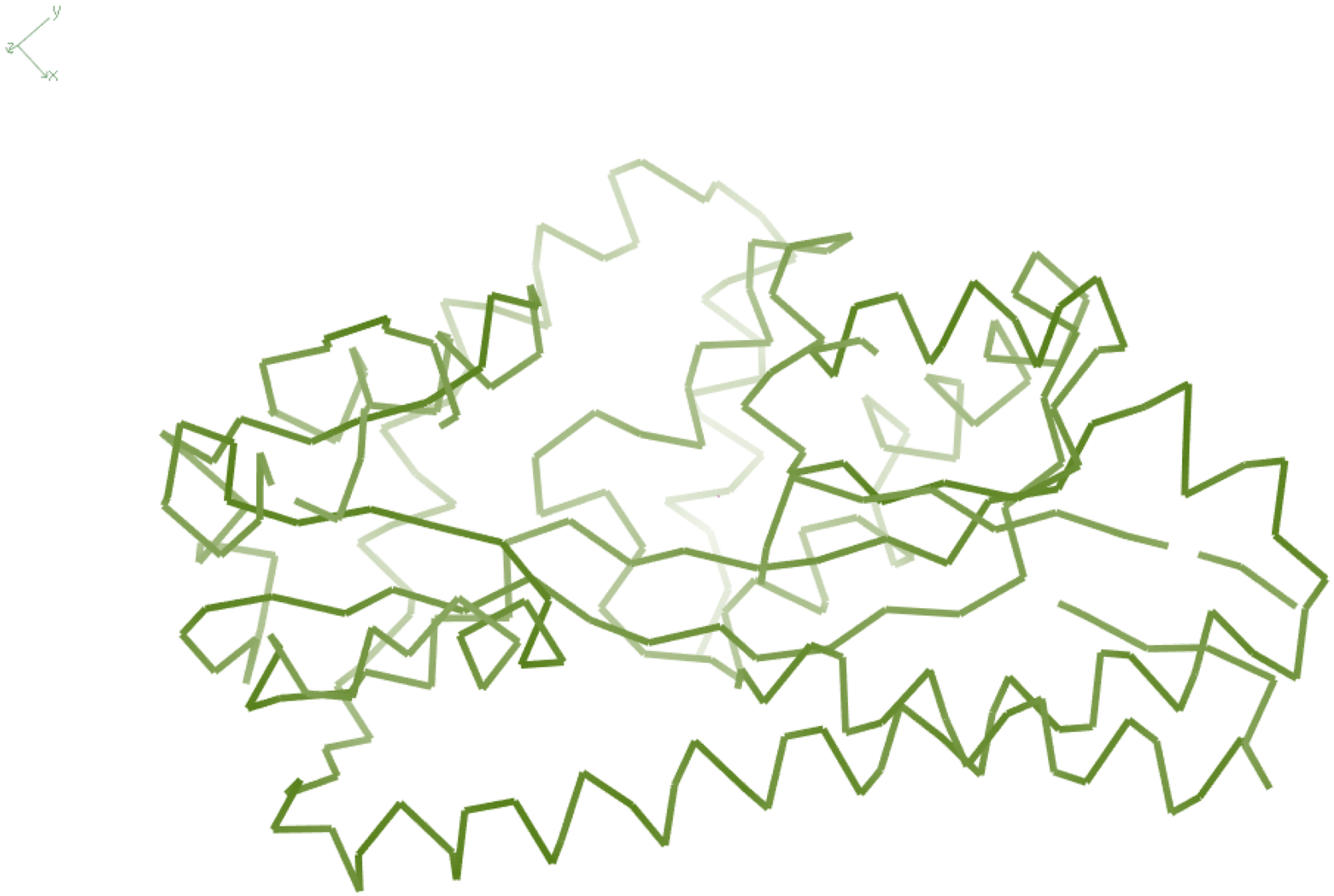


Additional Restraints

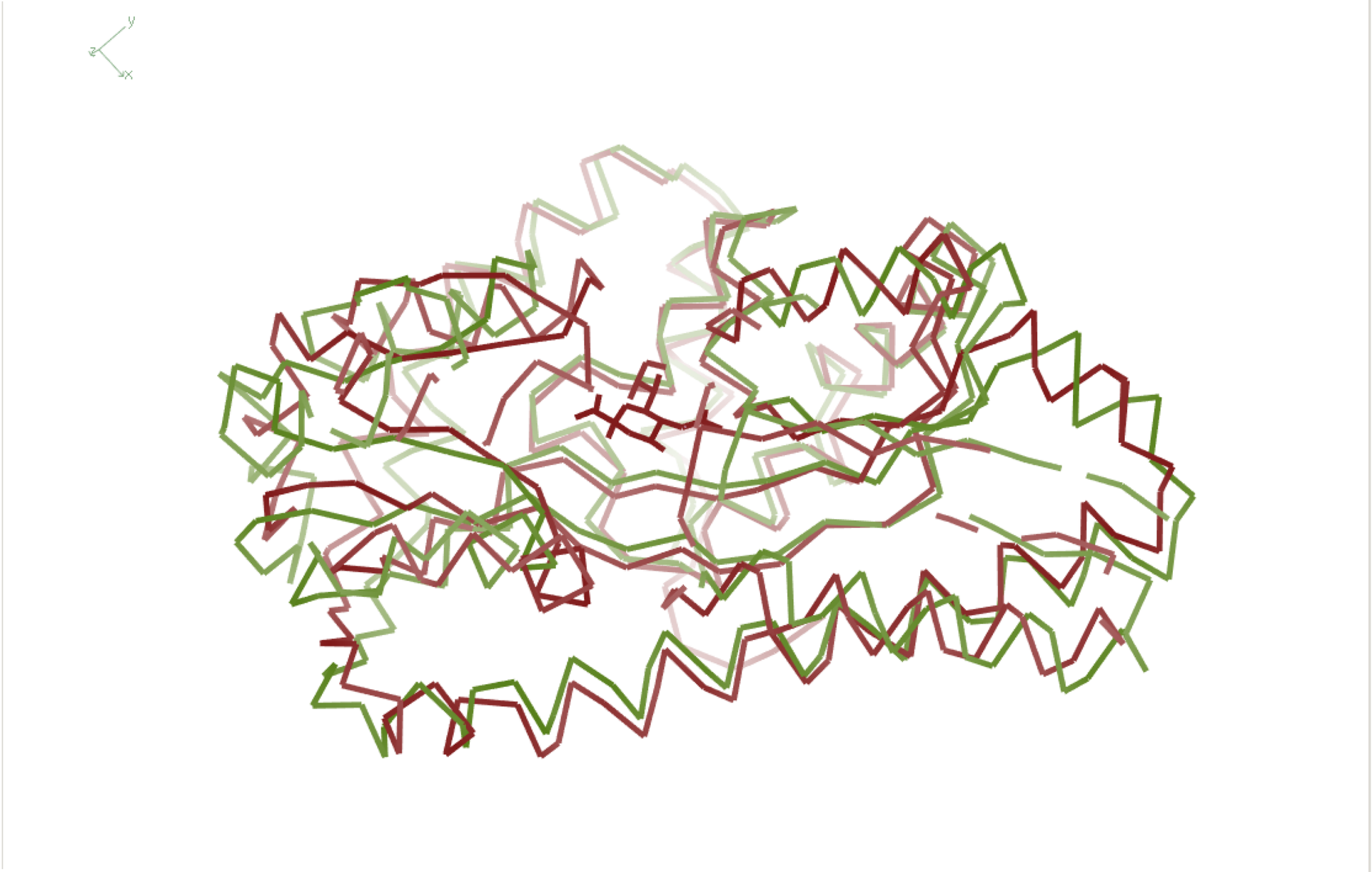
Local Distance Restraints
Prior Structure



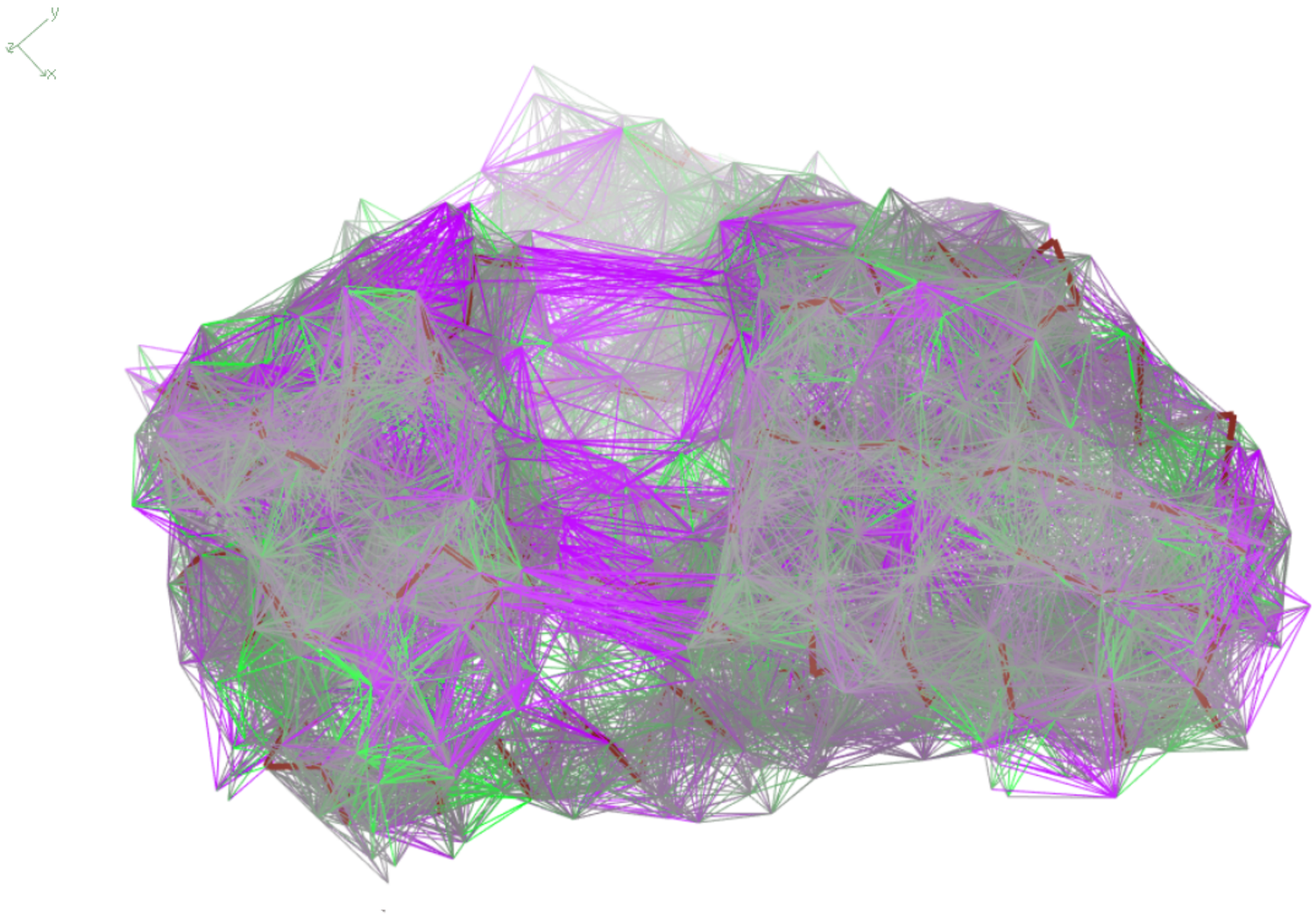
Local Distance Restraints
Today's Structure



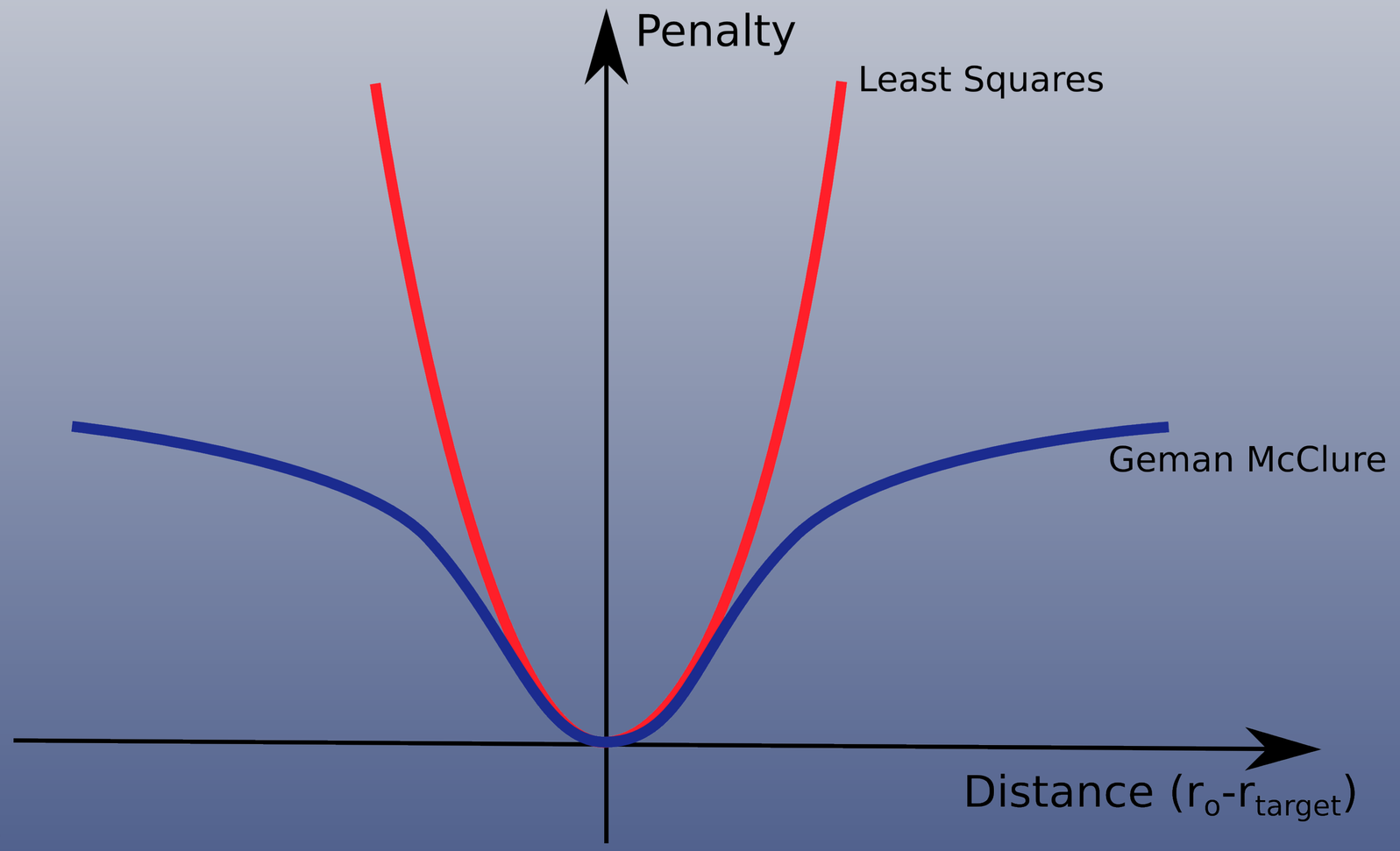
Local Distance Restraints
Today's Structure



Local Distance Restraints



Modified Target Function



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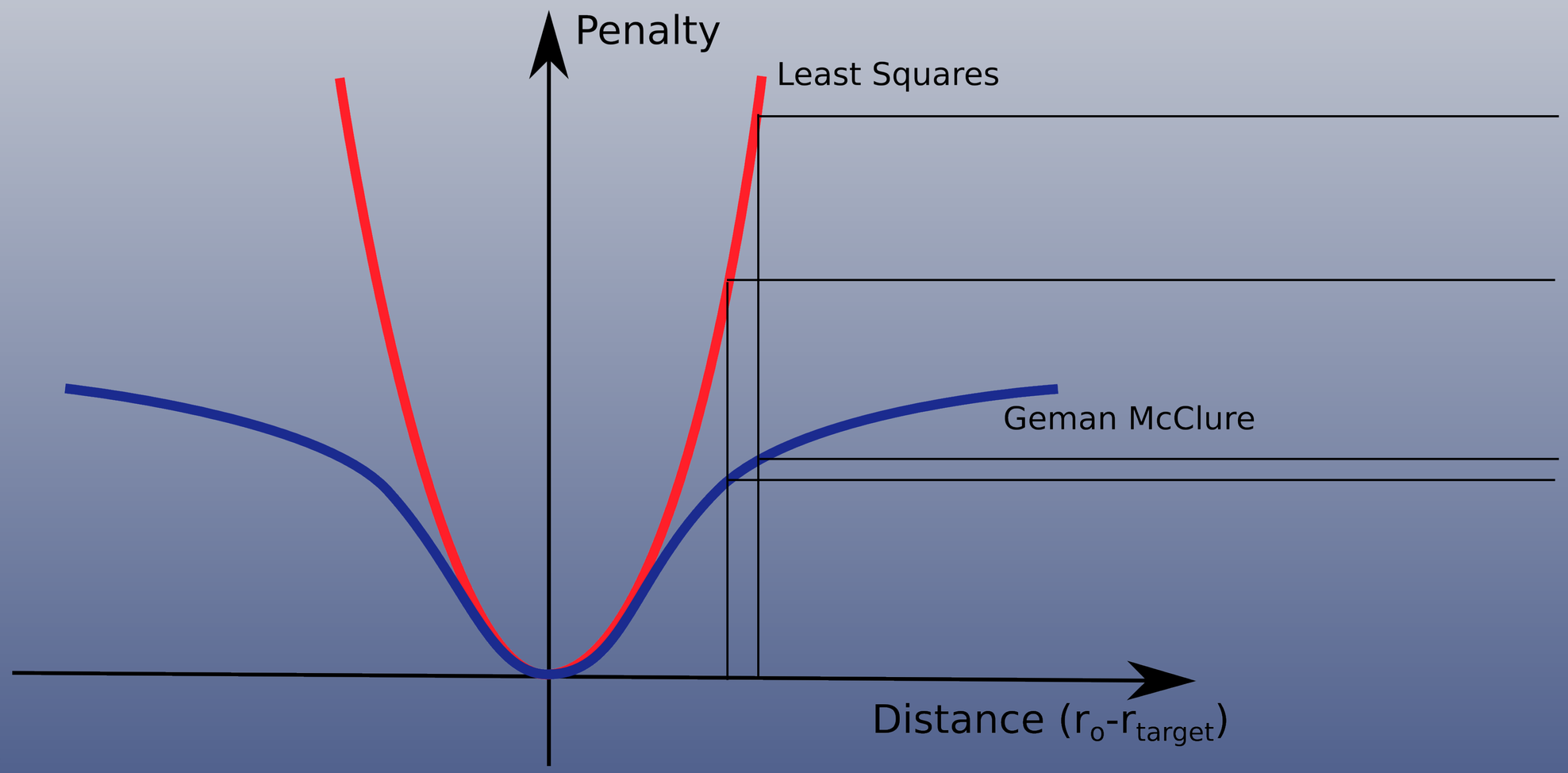

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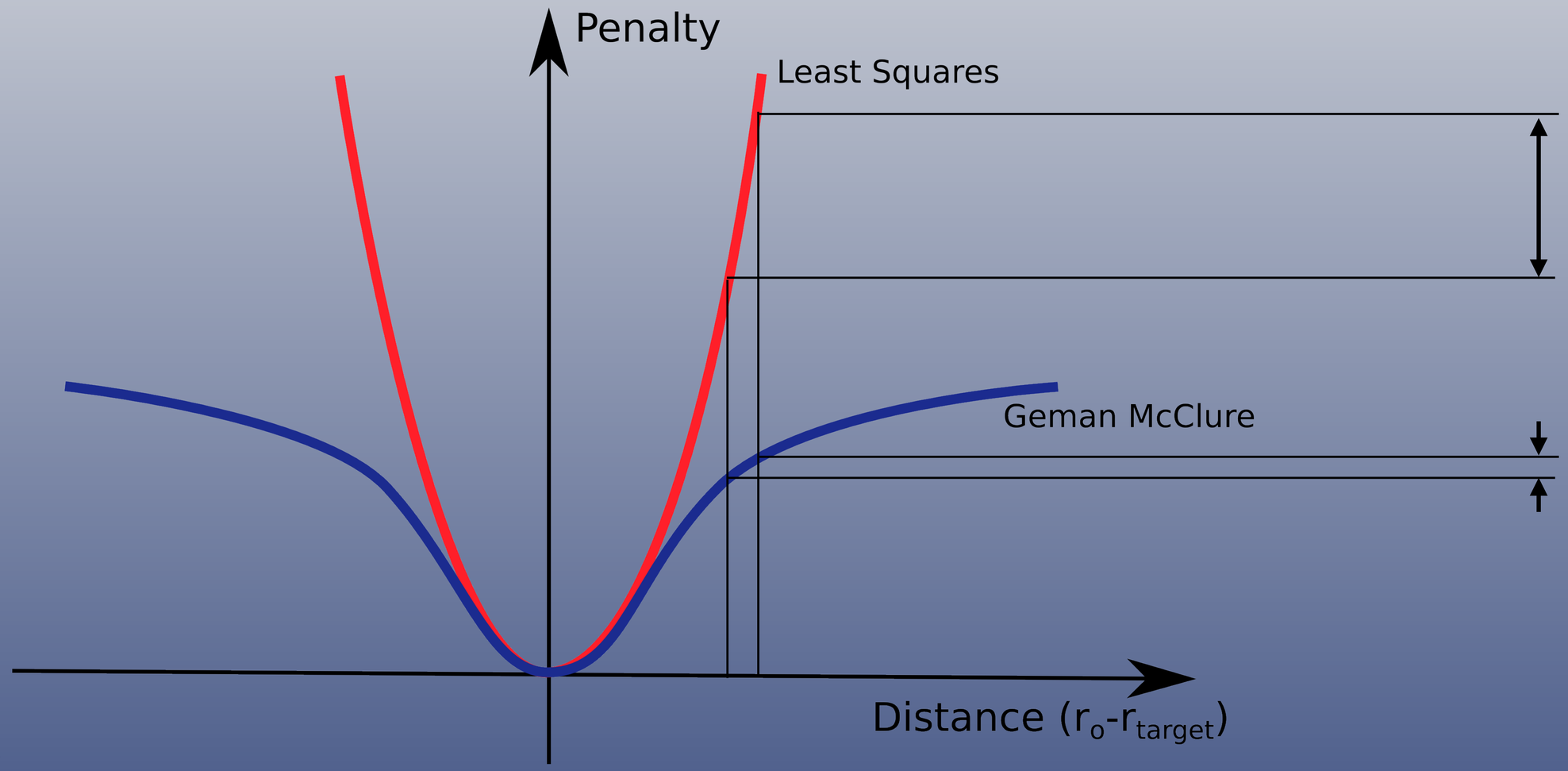

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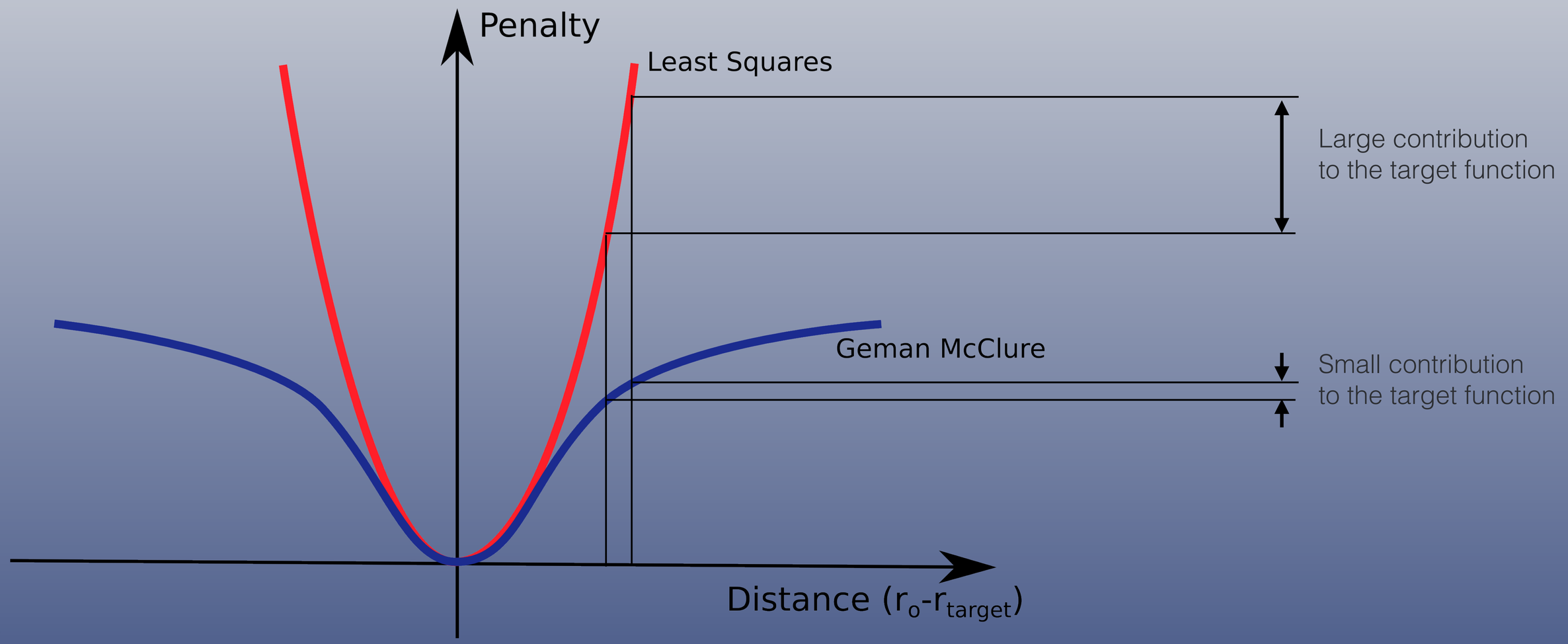
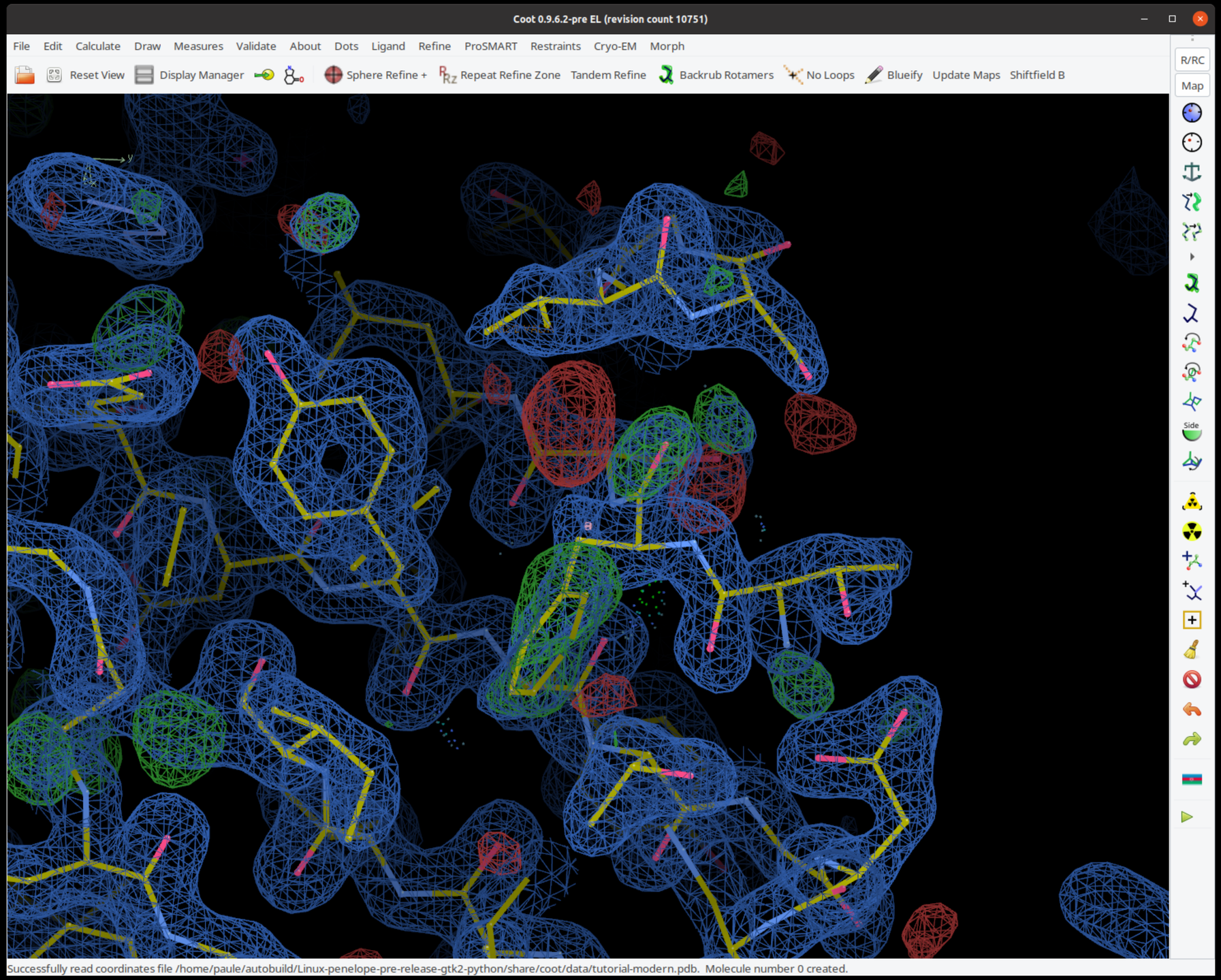


Coot Local Distance Restraints

- Demo

Updating Maps

- In the **Calculate** menu
  - Fobs needed (of course)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Cryo-EM
Morph
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Tandem Refine
Backrub Rotamers
No Loops
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Update Maps
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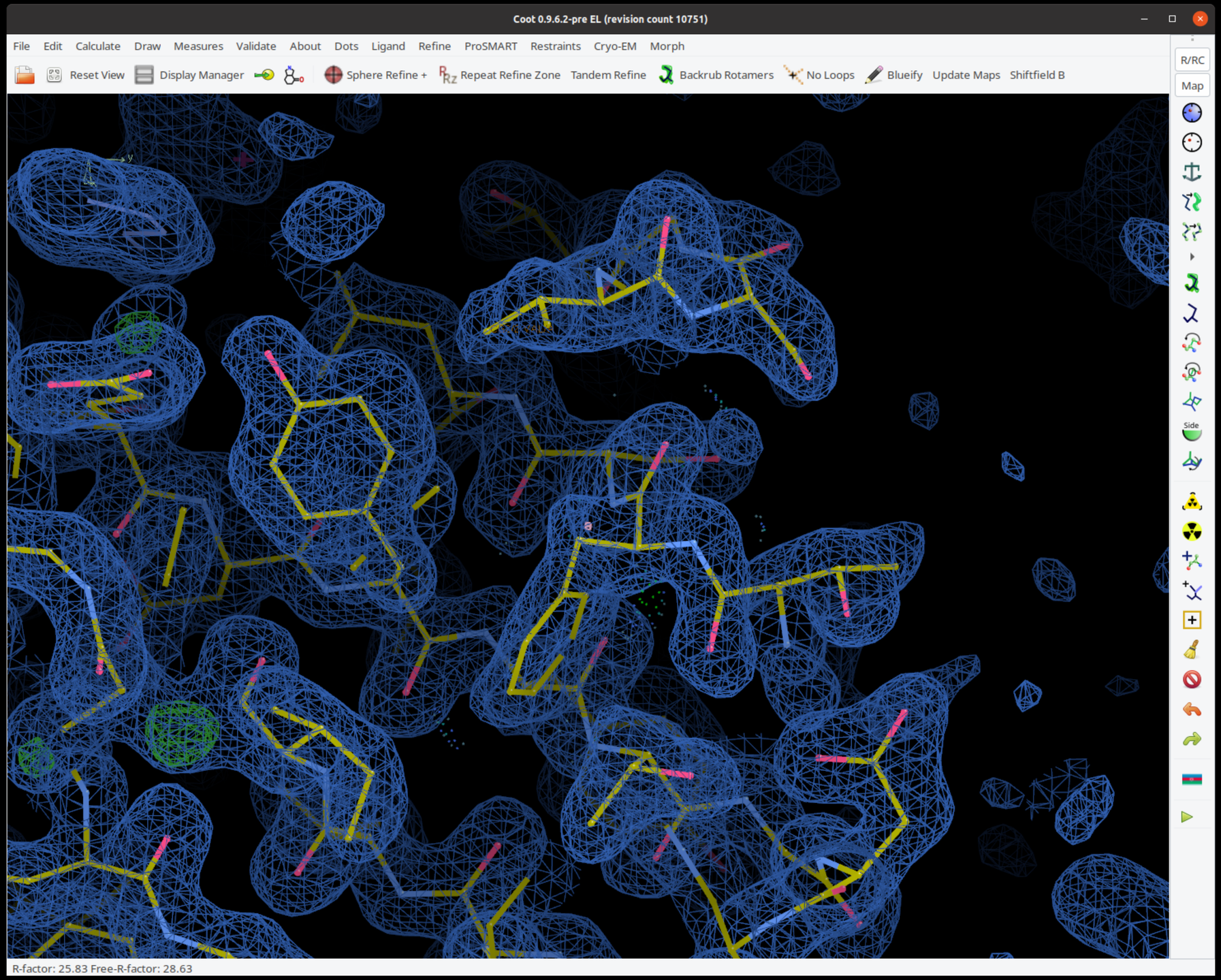
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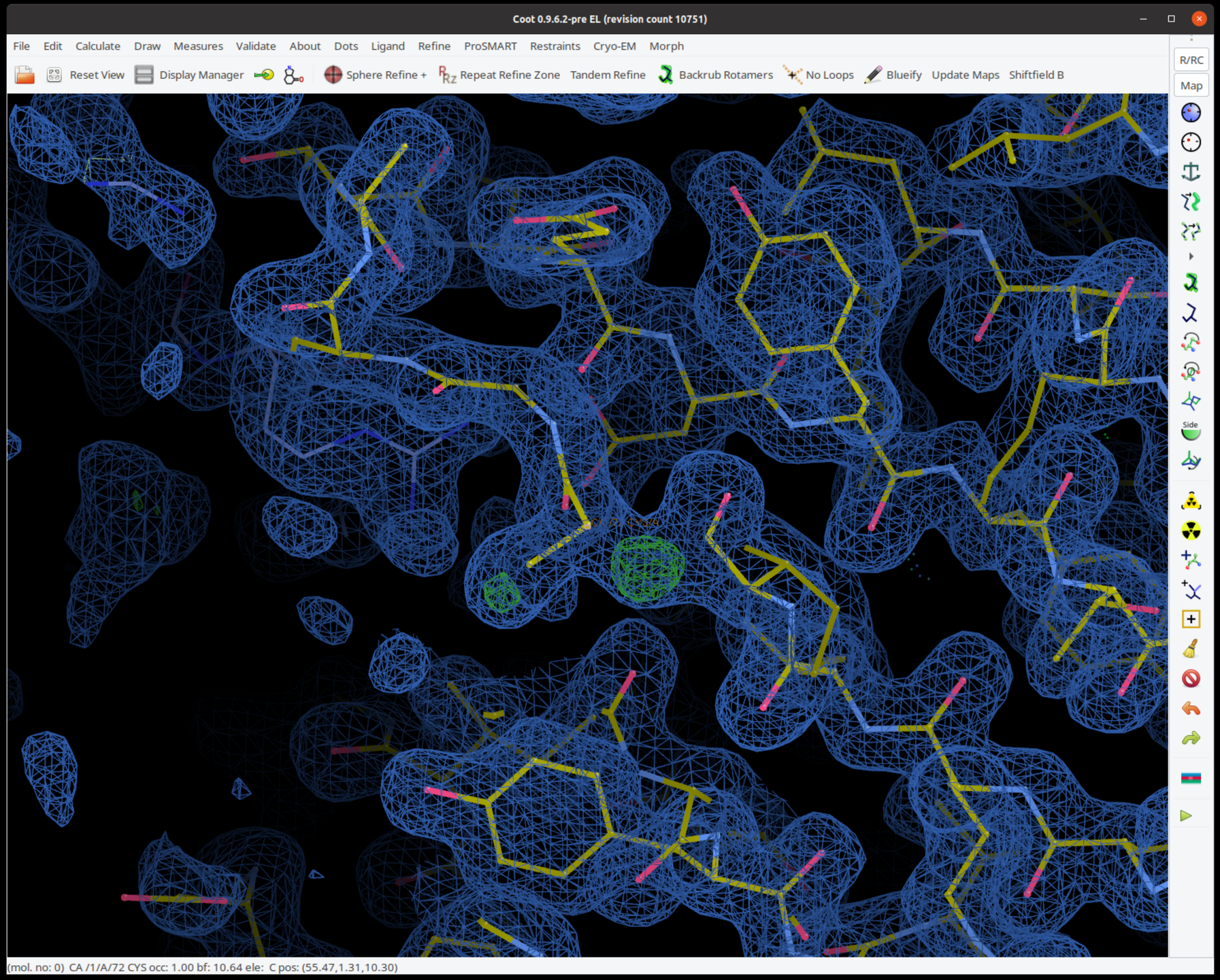
R-factor: 25.83 Free-R-factor: 28.63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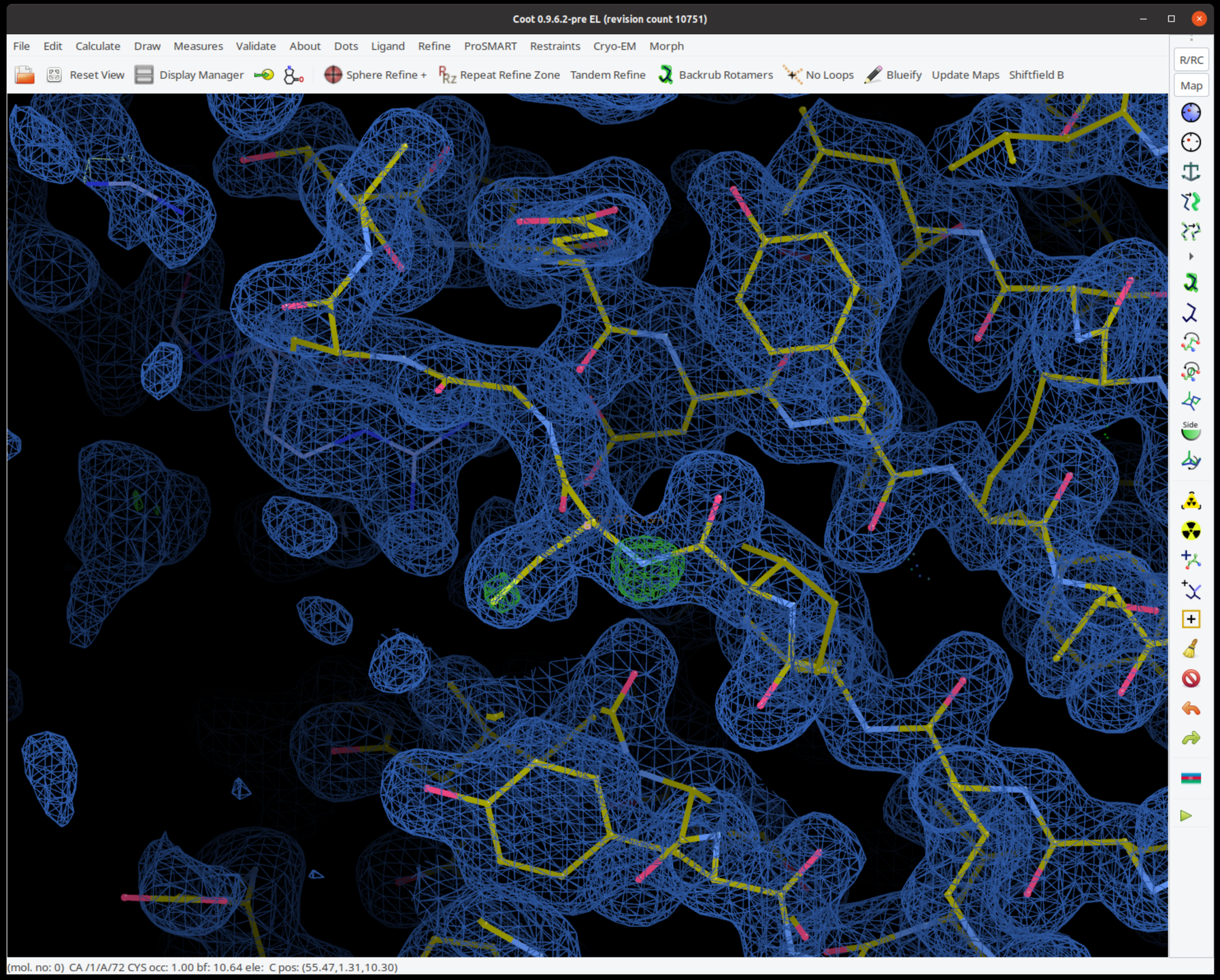
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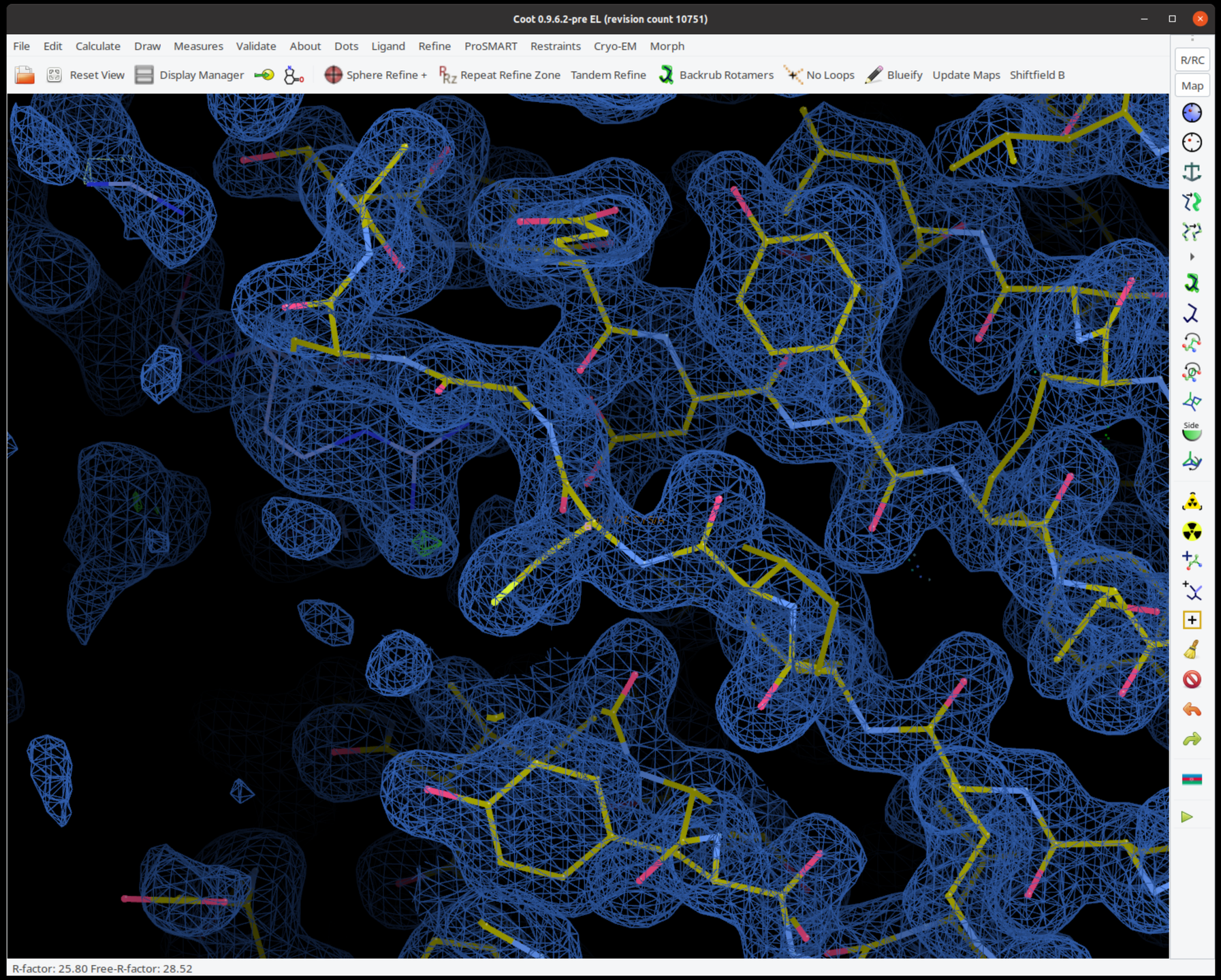
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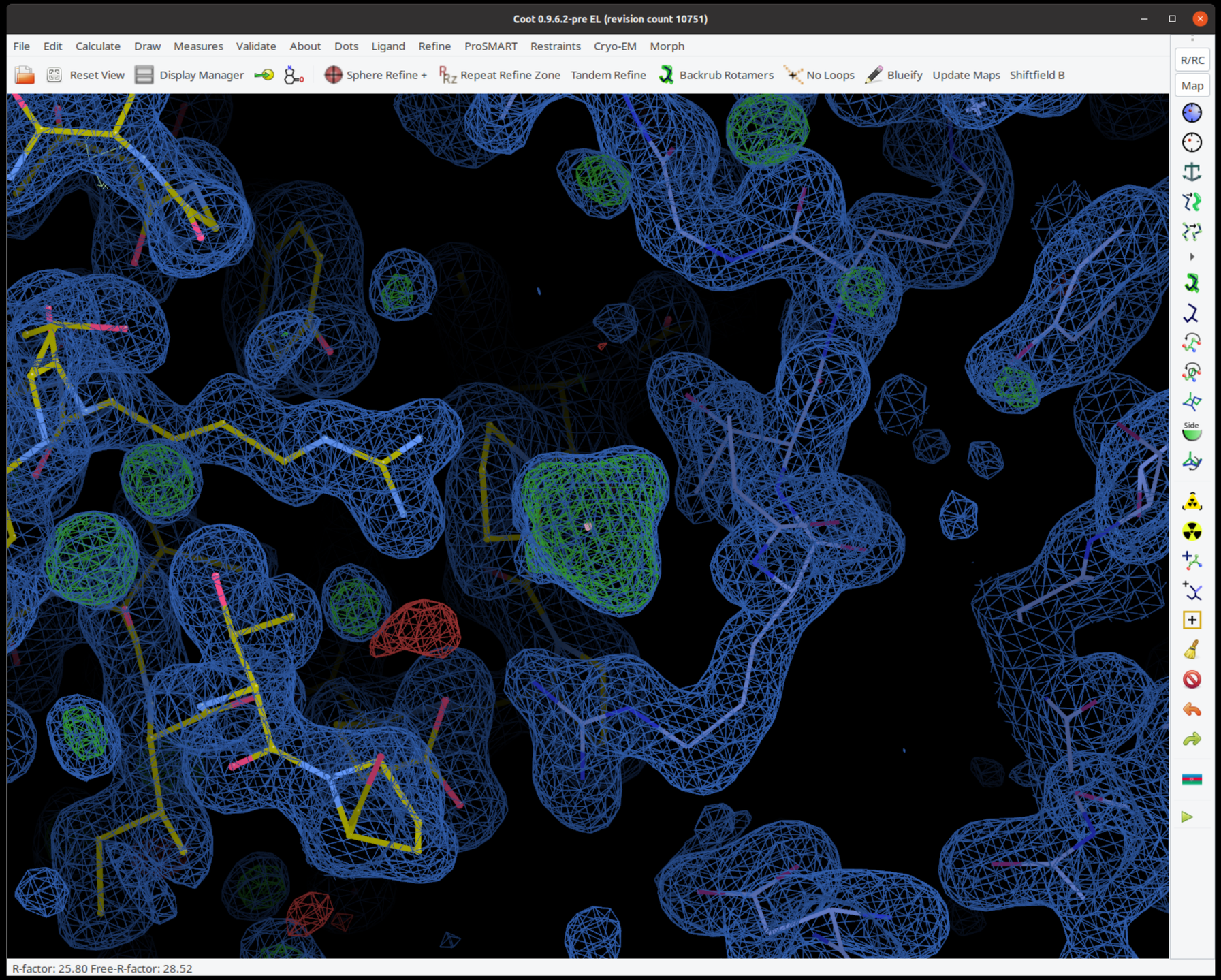
R-factor: 25.80 Free-R-factor: 28.52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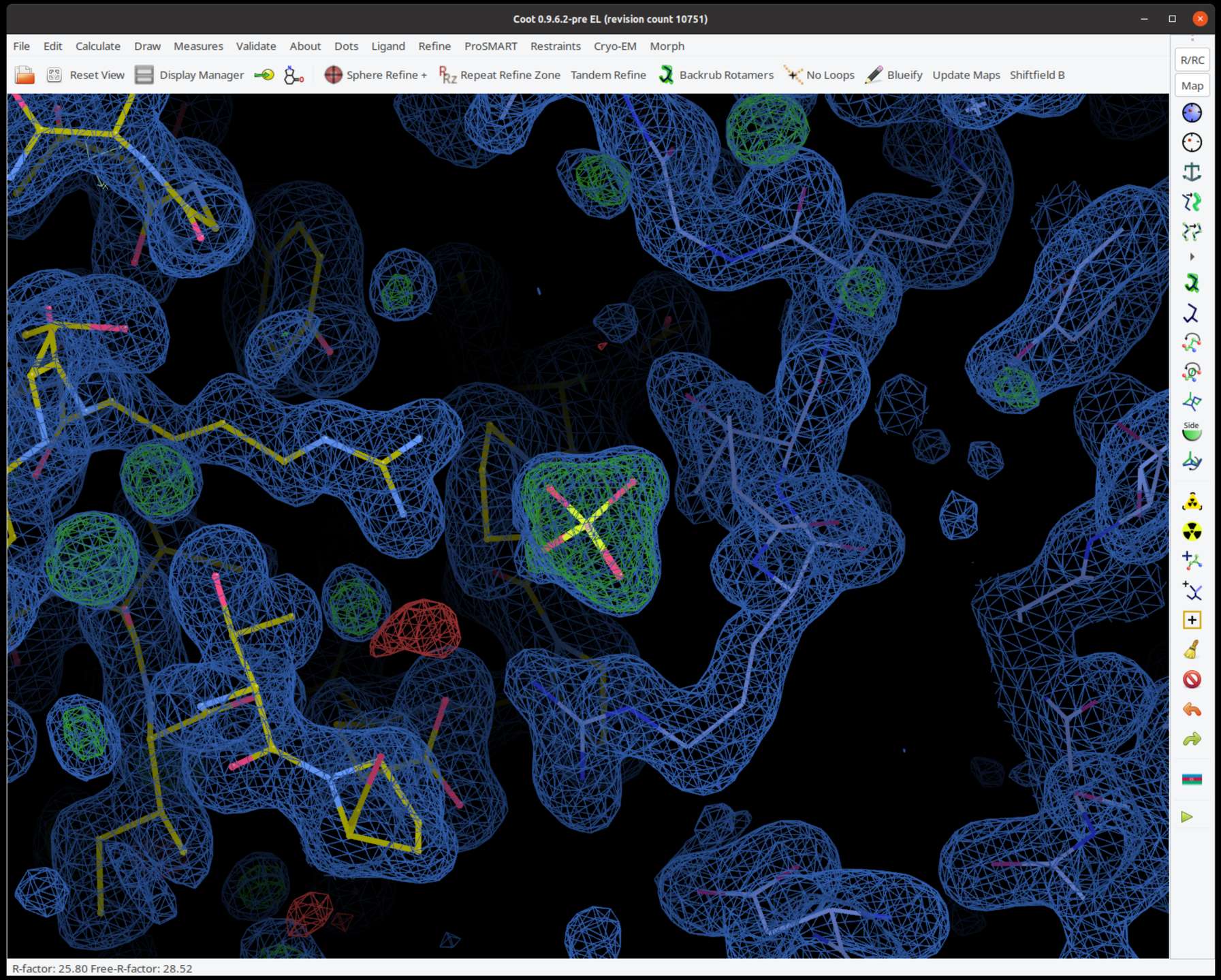
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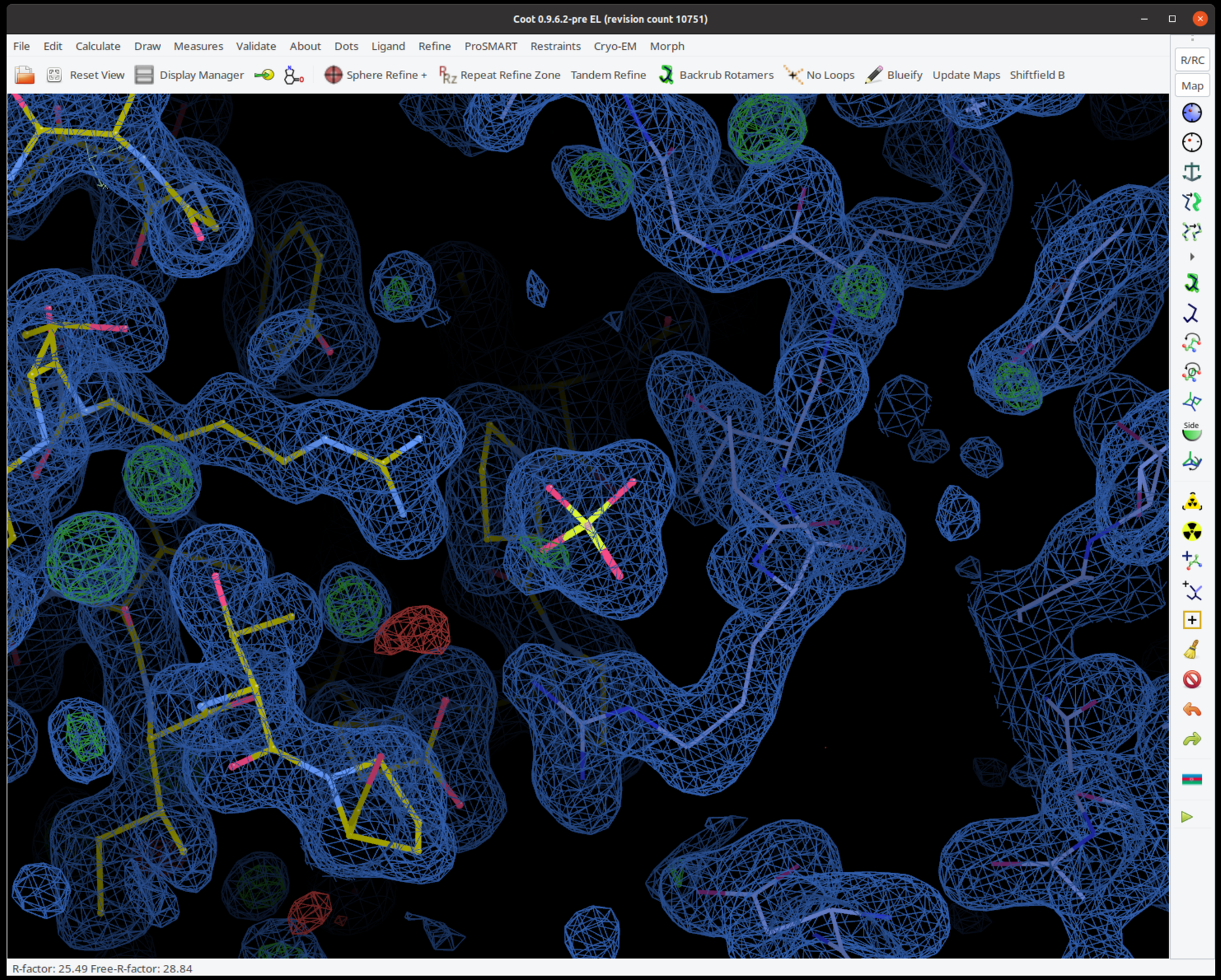
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Backrub Rotamers
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Side
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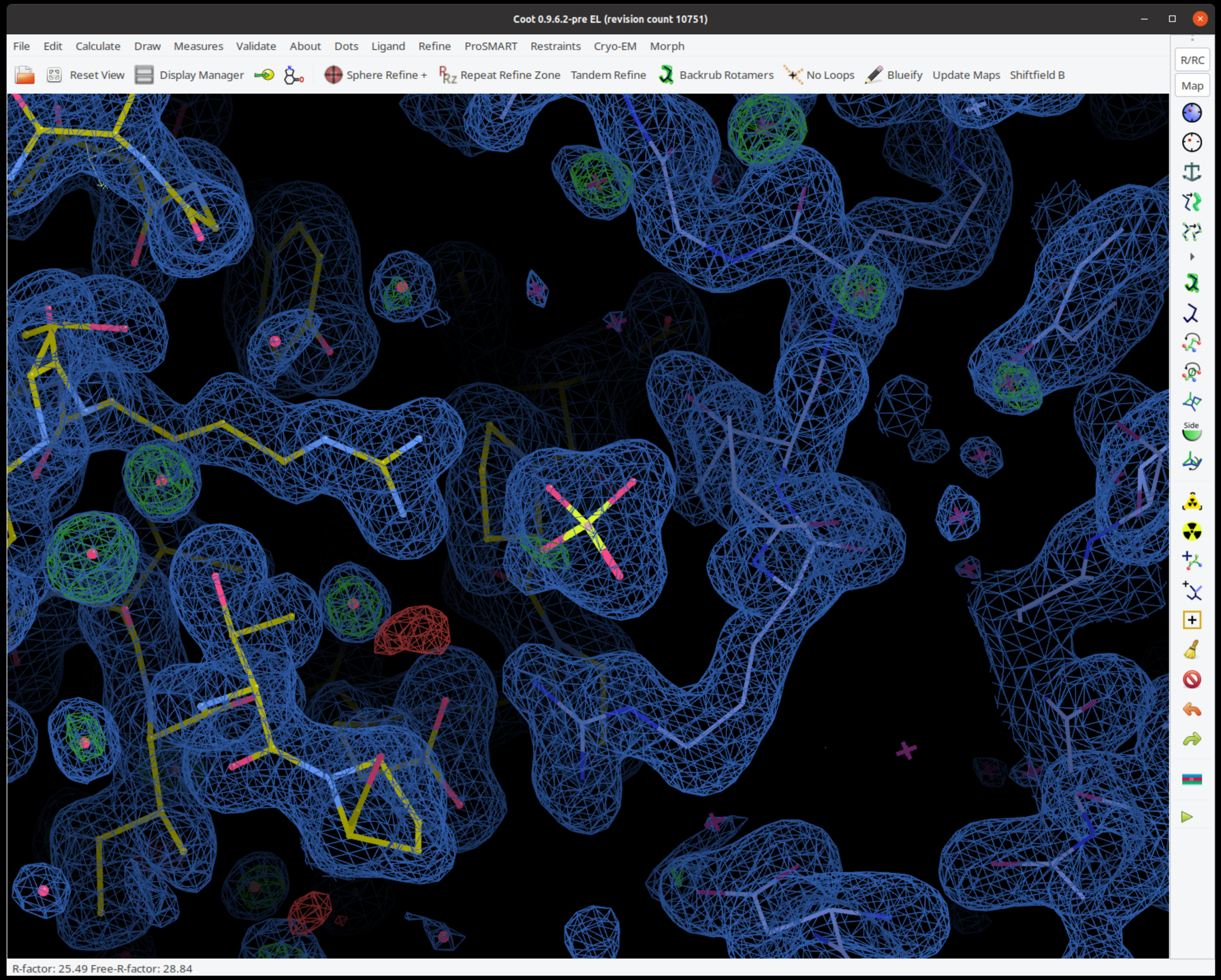
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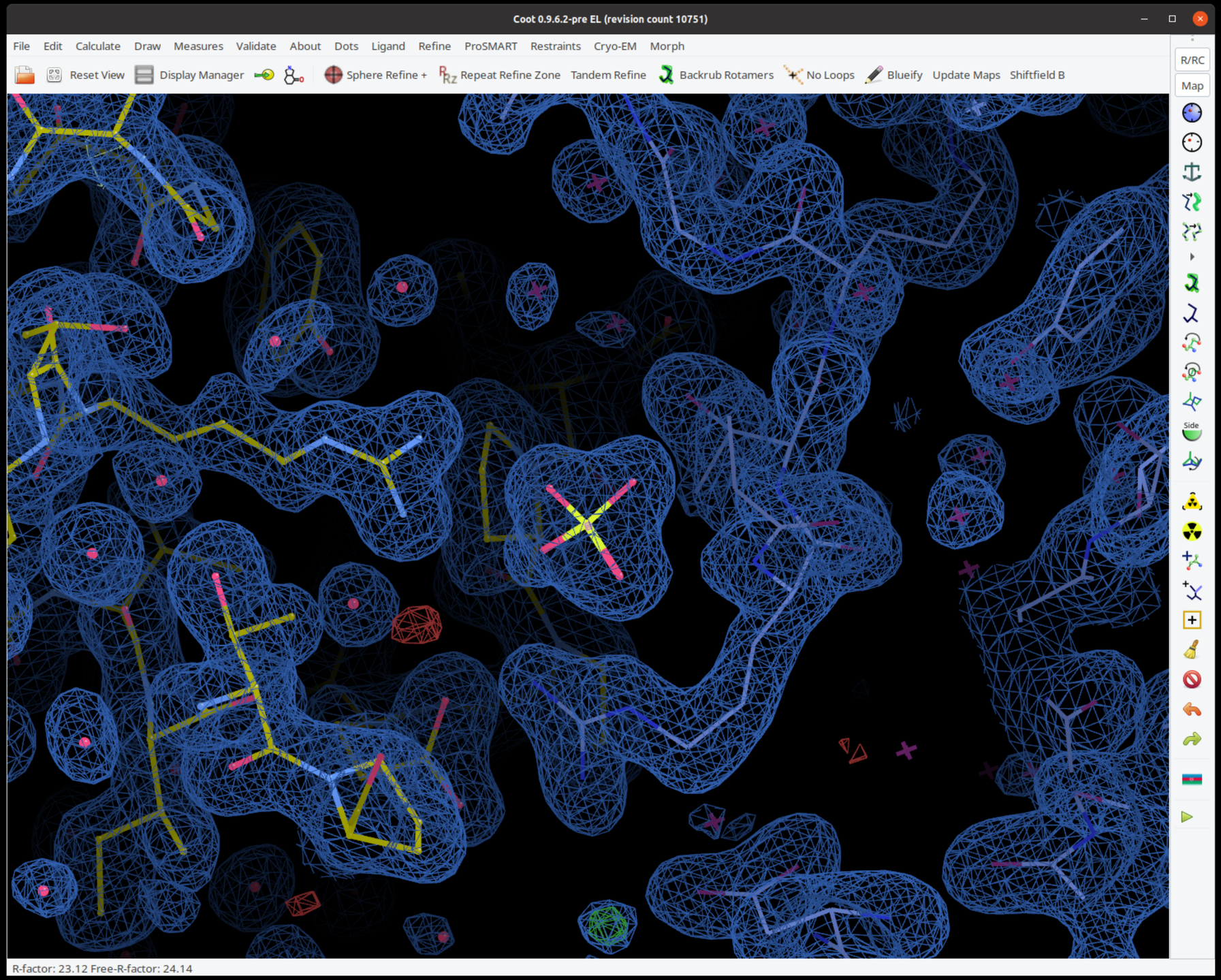
R-factor: 25.49 Free-R-factor: 28.84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Repeat Refine Zone
Tandem Refine
Backrub Rotamers
No Loops
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Update Maps
Shiftfield B
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Side
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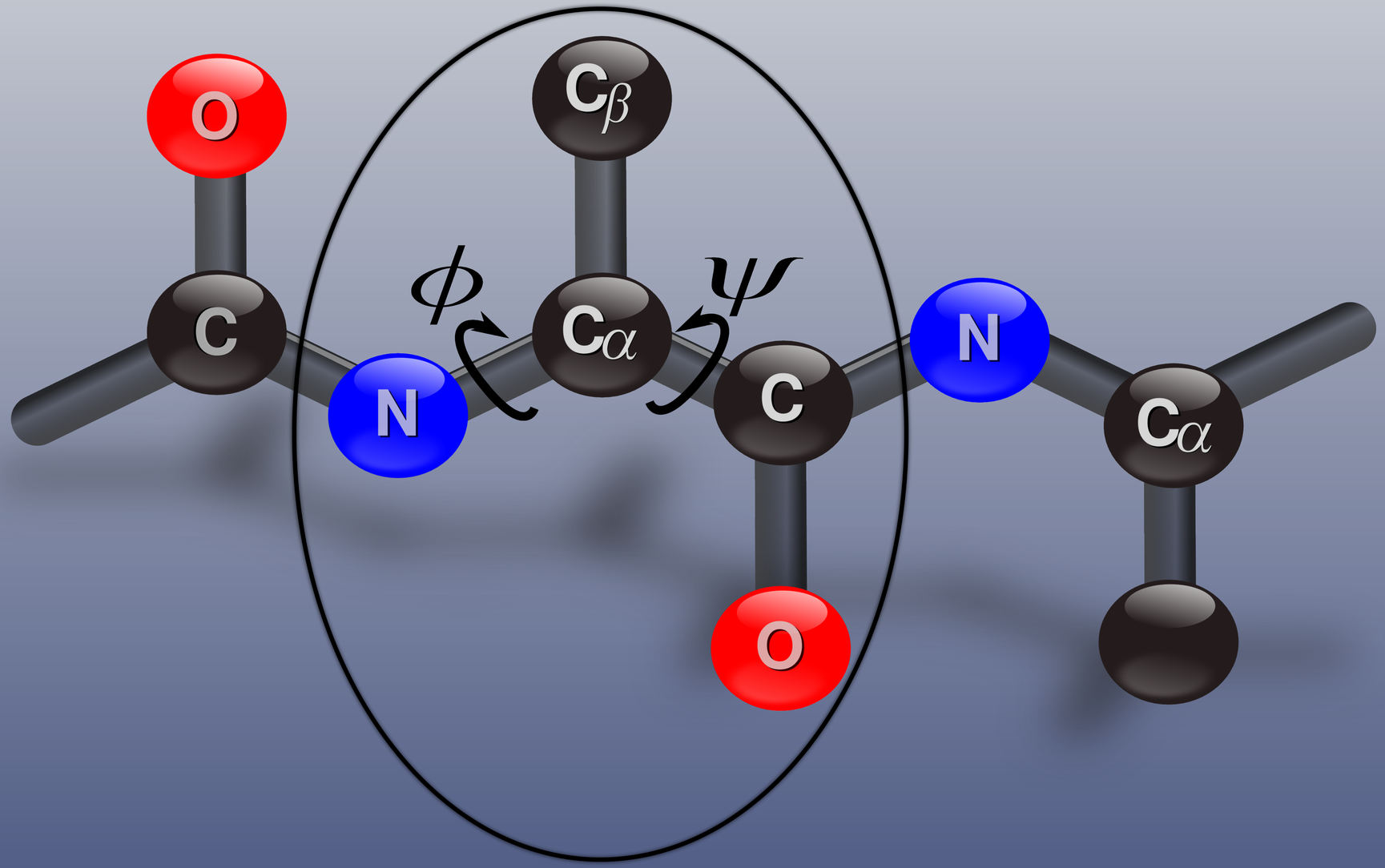
Proportional Editing

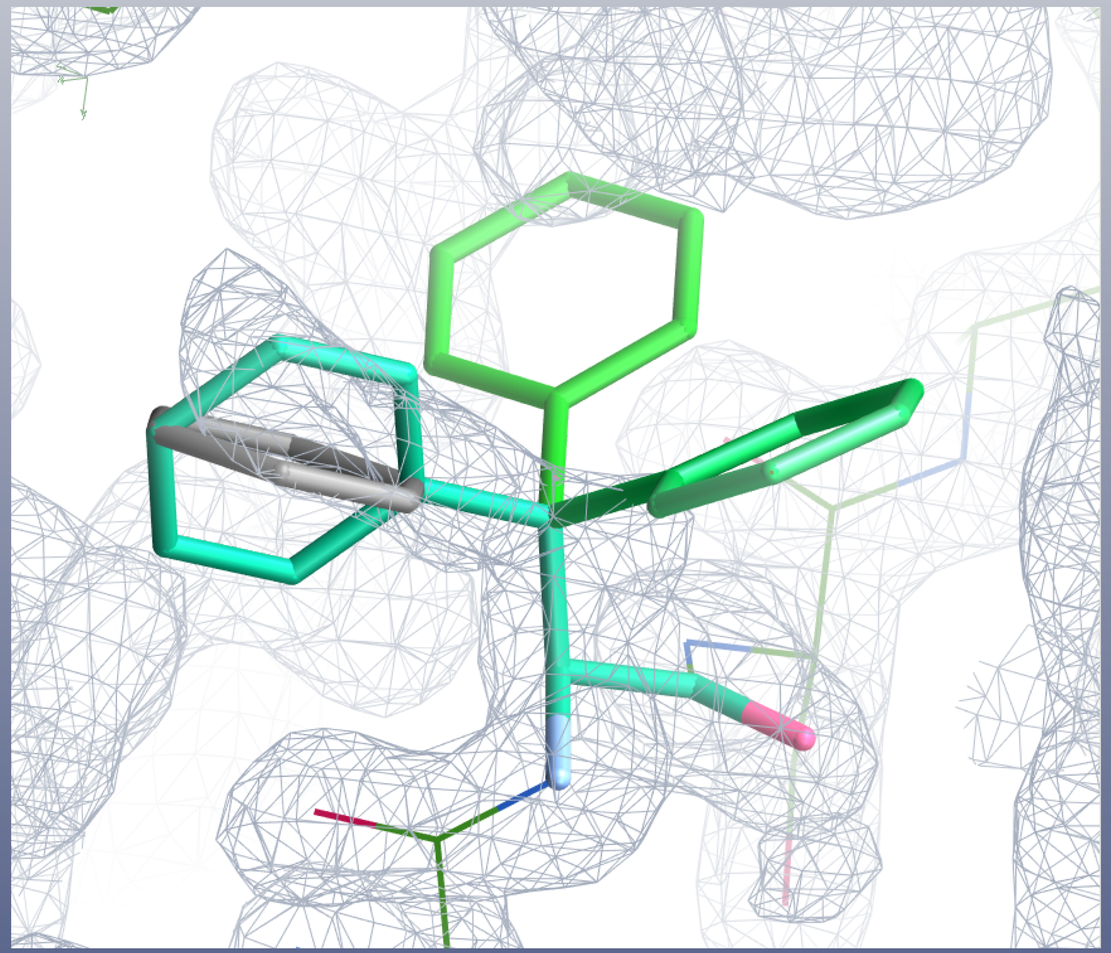
Rotamers

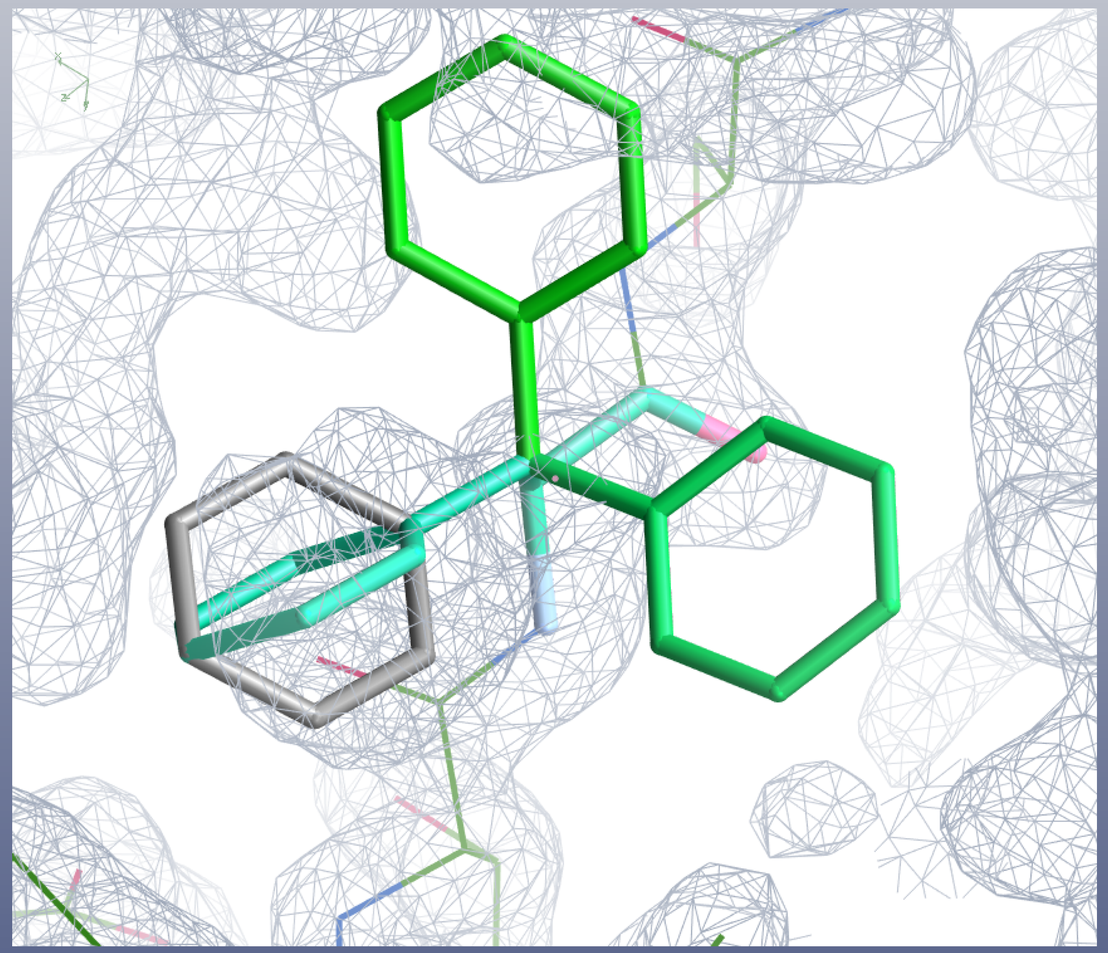


Rotamers

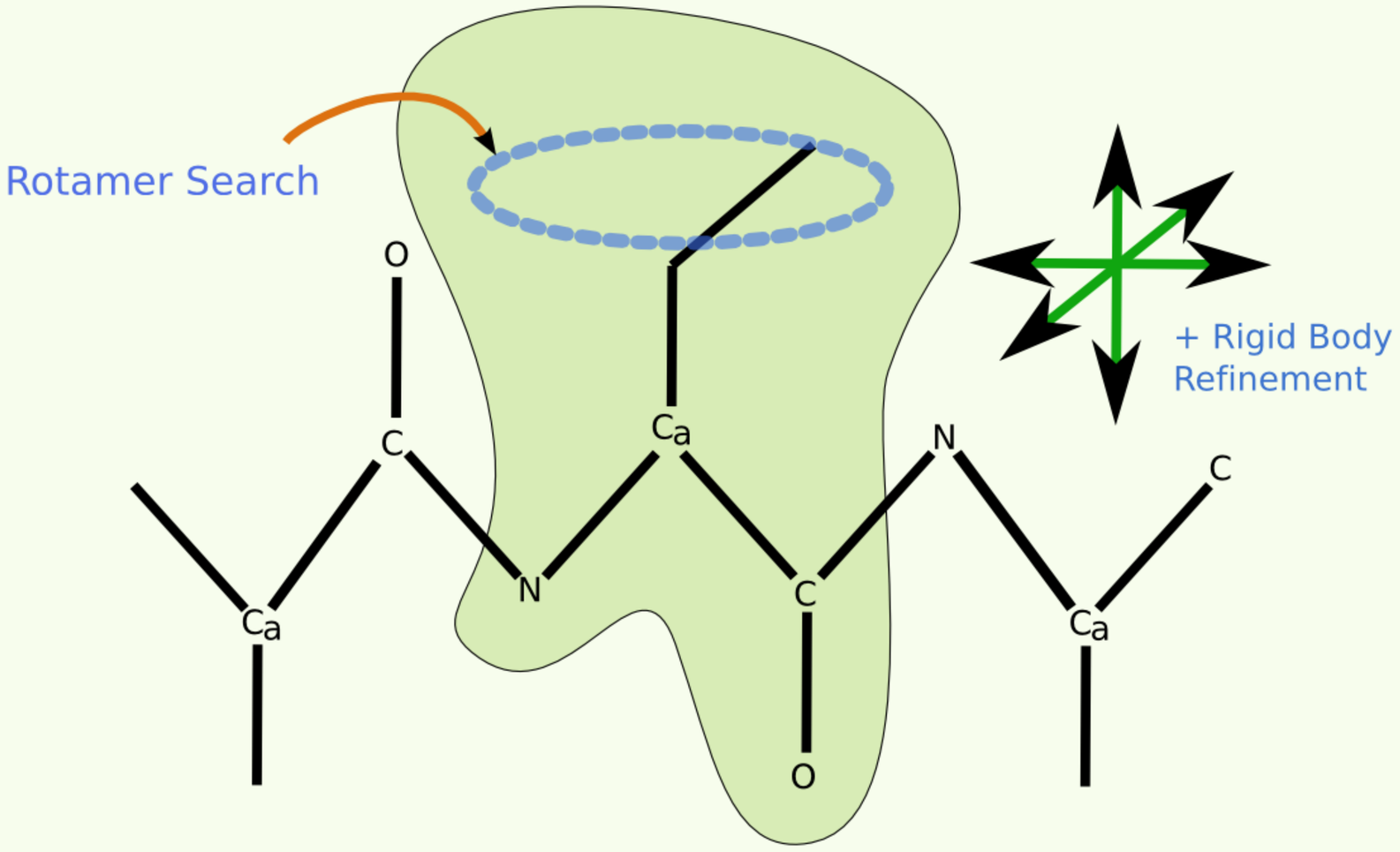
- Rotamers are preferred configurations of side-chains
- “preferred” because they appear (more) frequently in (a selection of) structures from the PDB
- Low energy conformations
- Databases of these distributions
  - “Son of the Penultimate Rotamer Library” is used in Coot

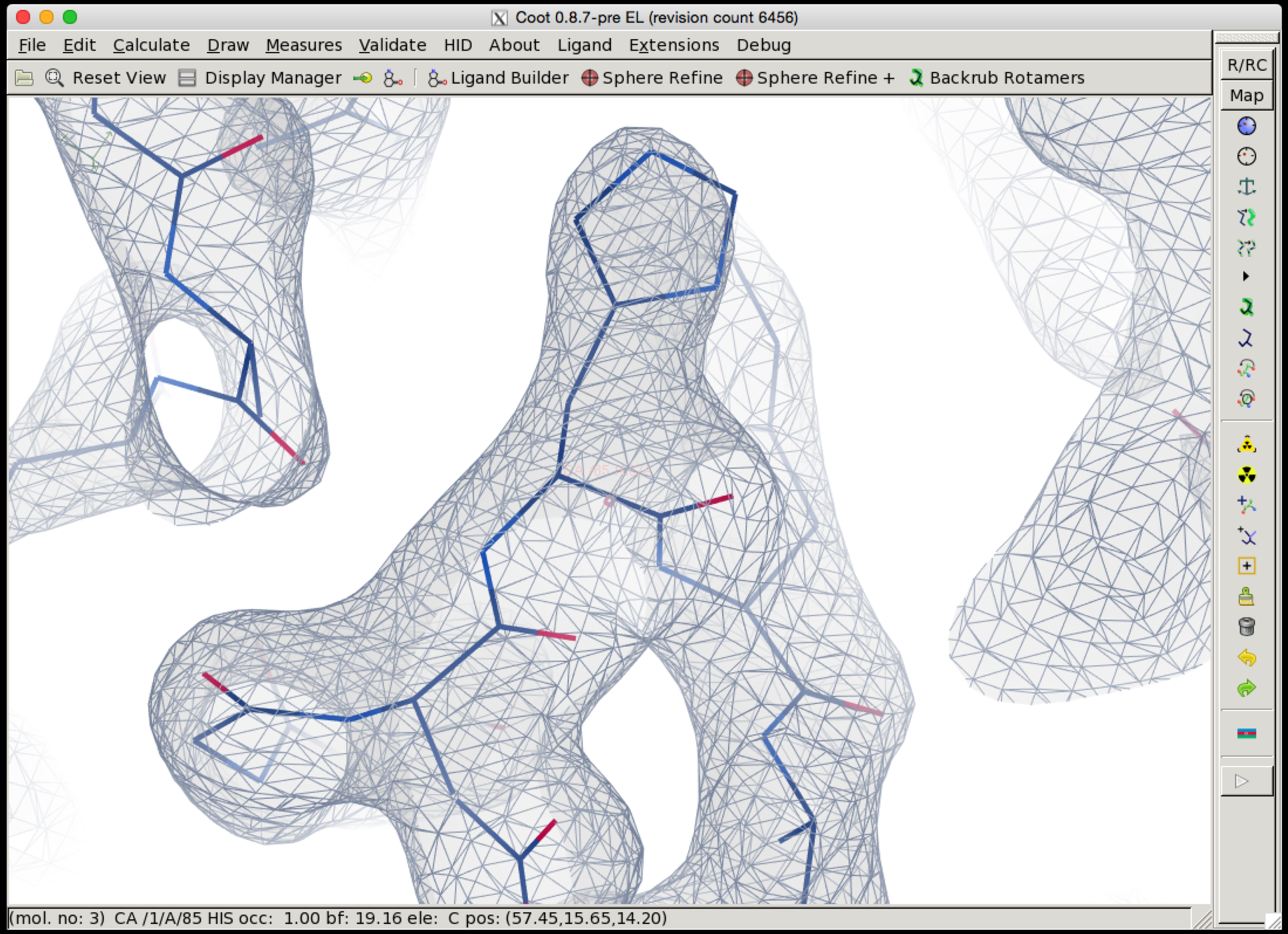
Rotamers example: PHE

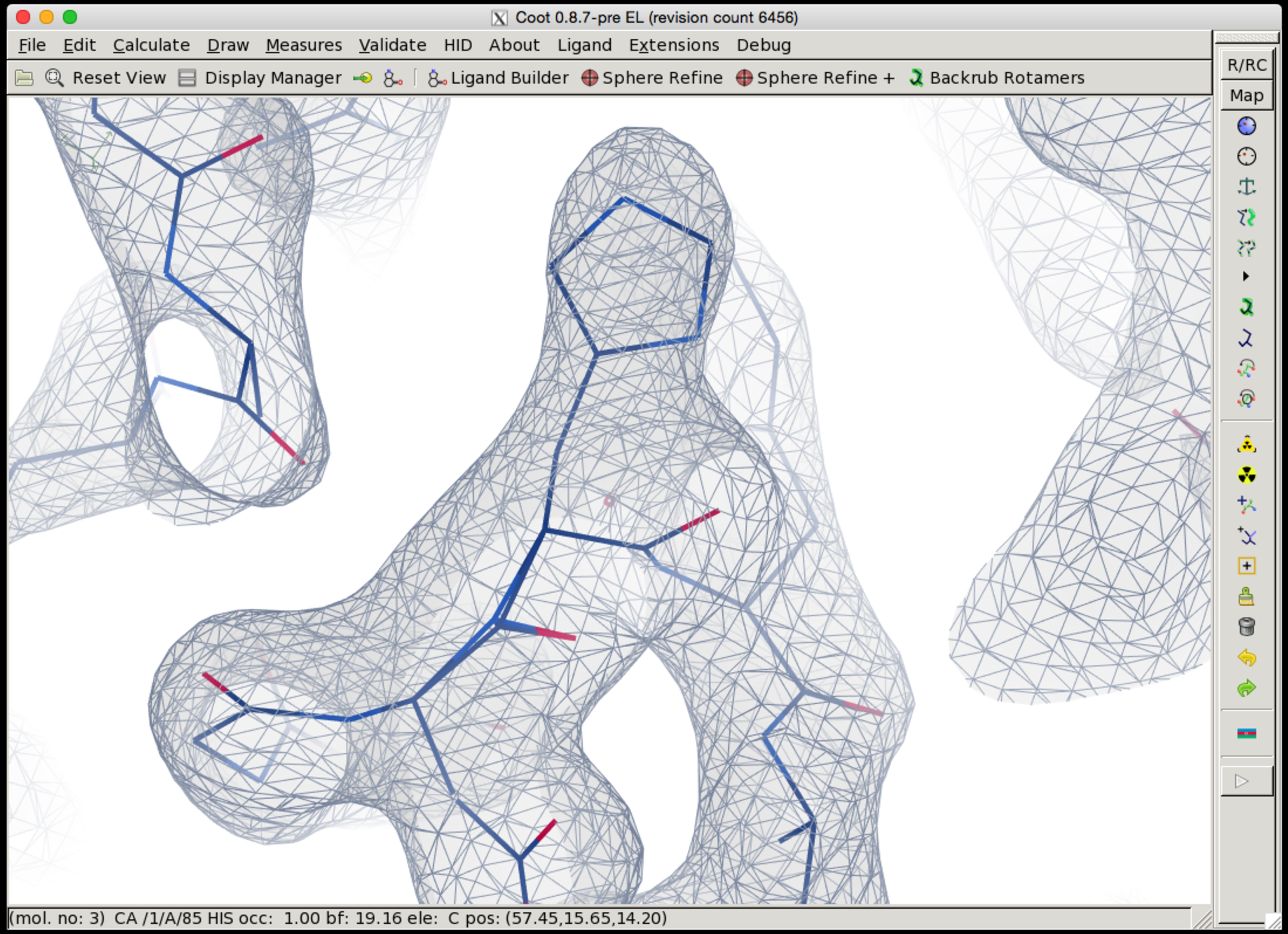




Current Low Resolution Rotamer Search




Coot 0.8.7-pre EL (revision count 6456)
File Edit Calculate Draw Measures Validate HID About Ligand Extensions Debug
Reset View
Display Manager
Ligand Builder
Sphere Refine
Sphere Refine +
Backrub Rotamers
R/RC
Map
(mol. no: 3) CA /1/A/85 HIS occ: 1.00 bf: 19.16 ele: C pos: (57.45,15.65,14.20)


Coot 0.8.7-pre EL (revision count 6456)
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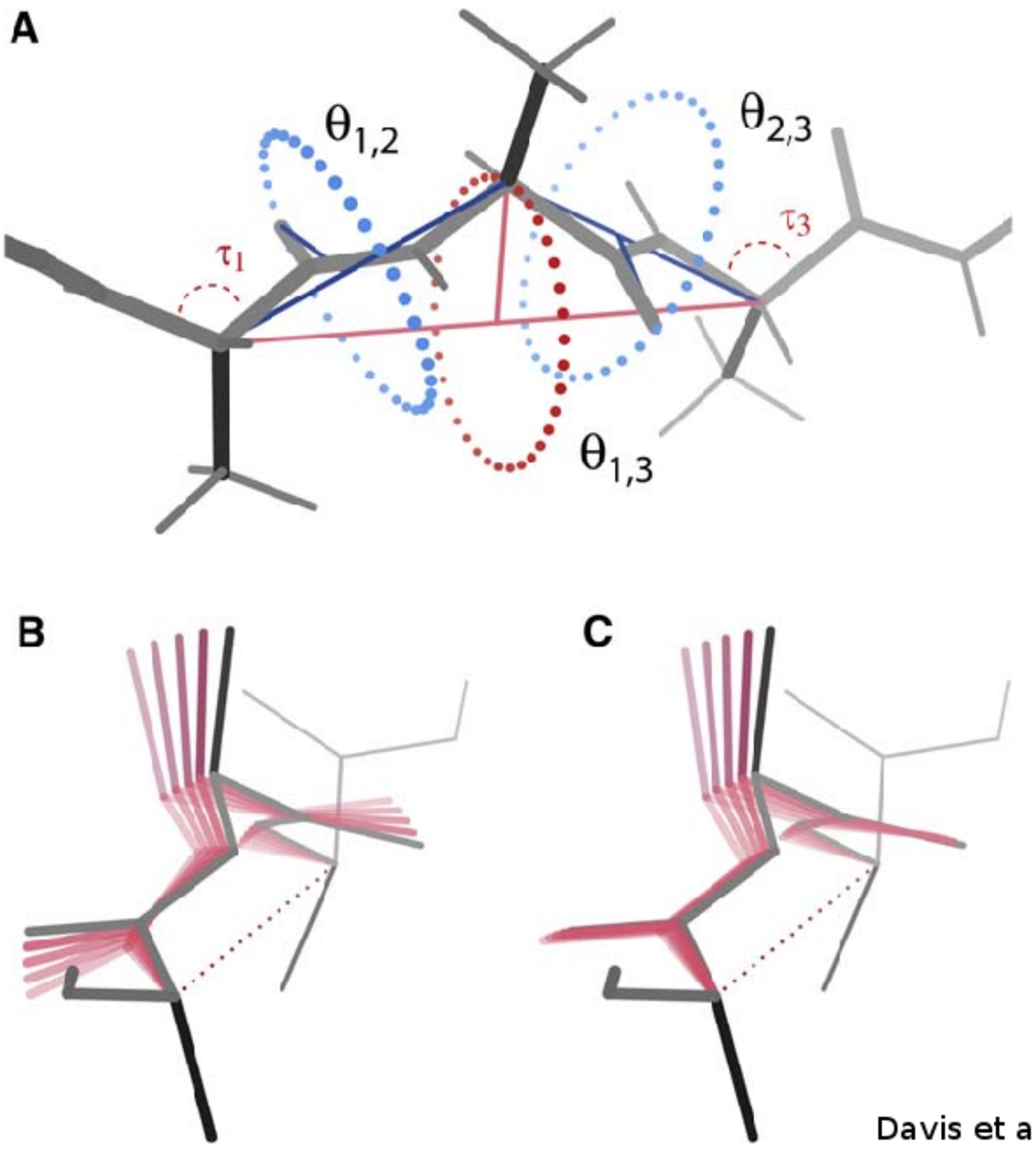
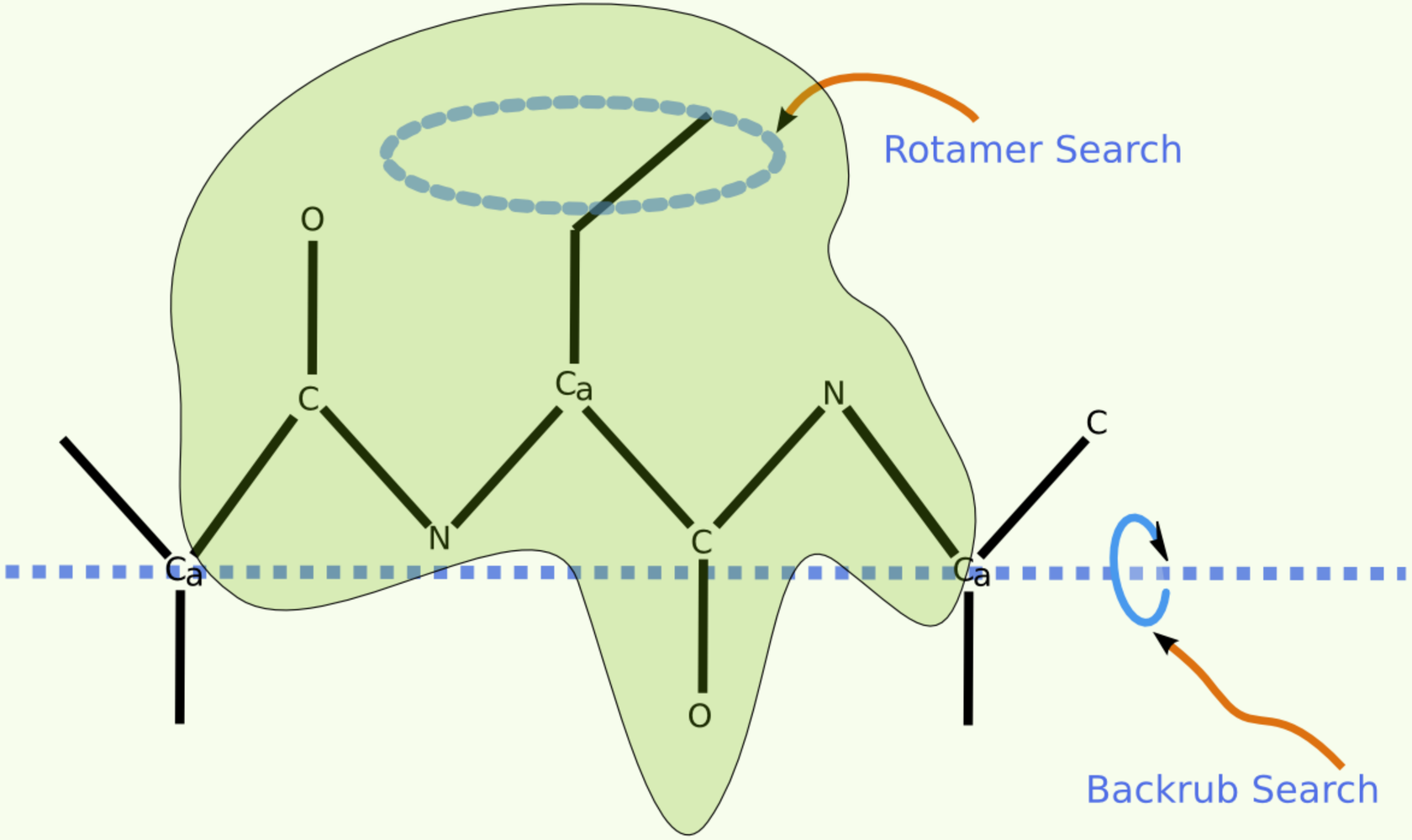
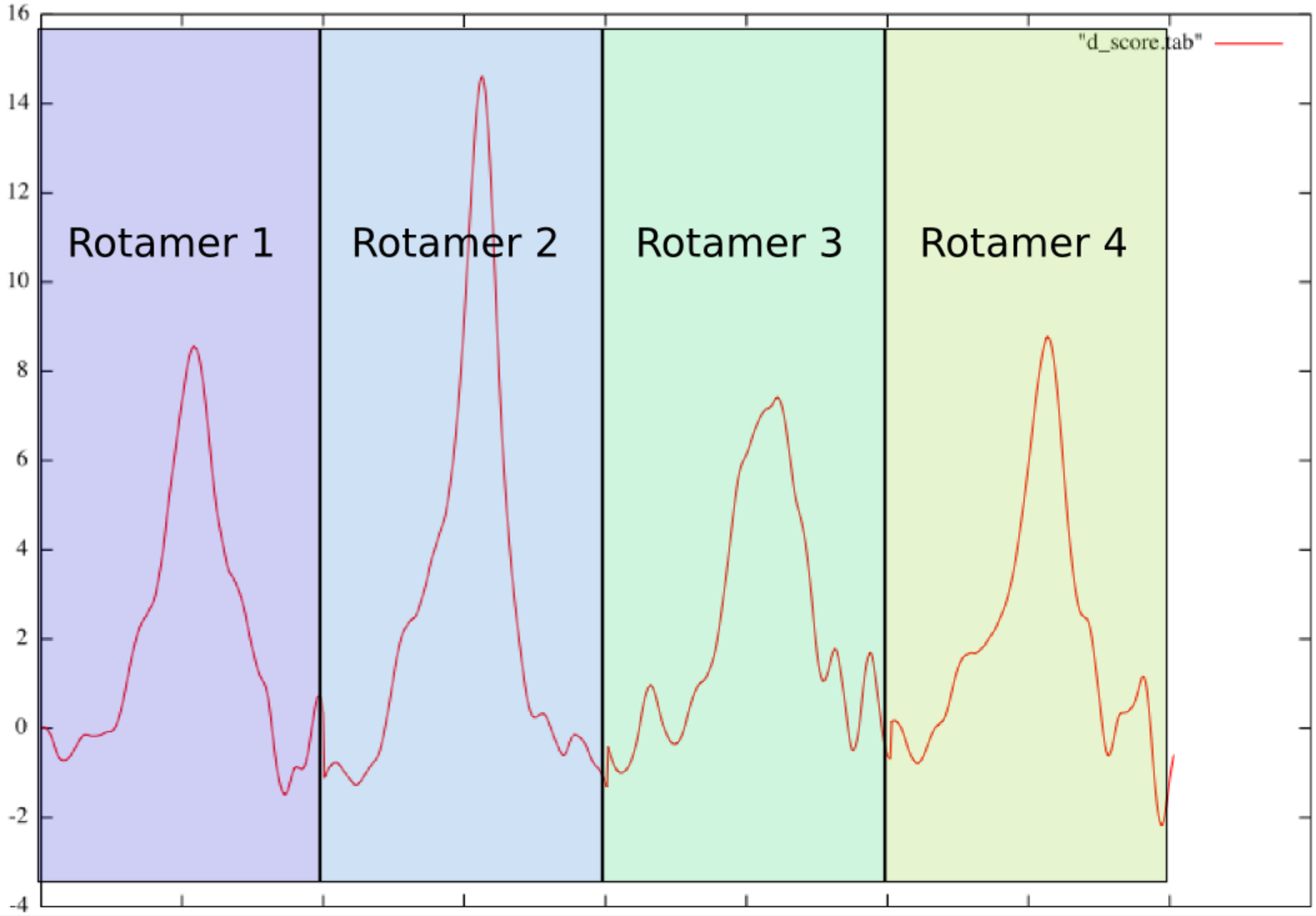


Davis et al. (2006) Structure

New Low Resolution Rotamer Search



After Fitting Tools in KING/Molprobity


16
14
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-2
-4
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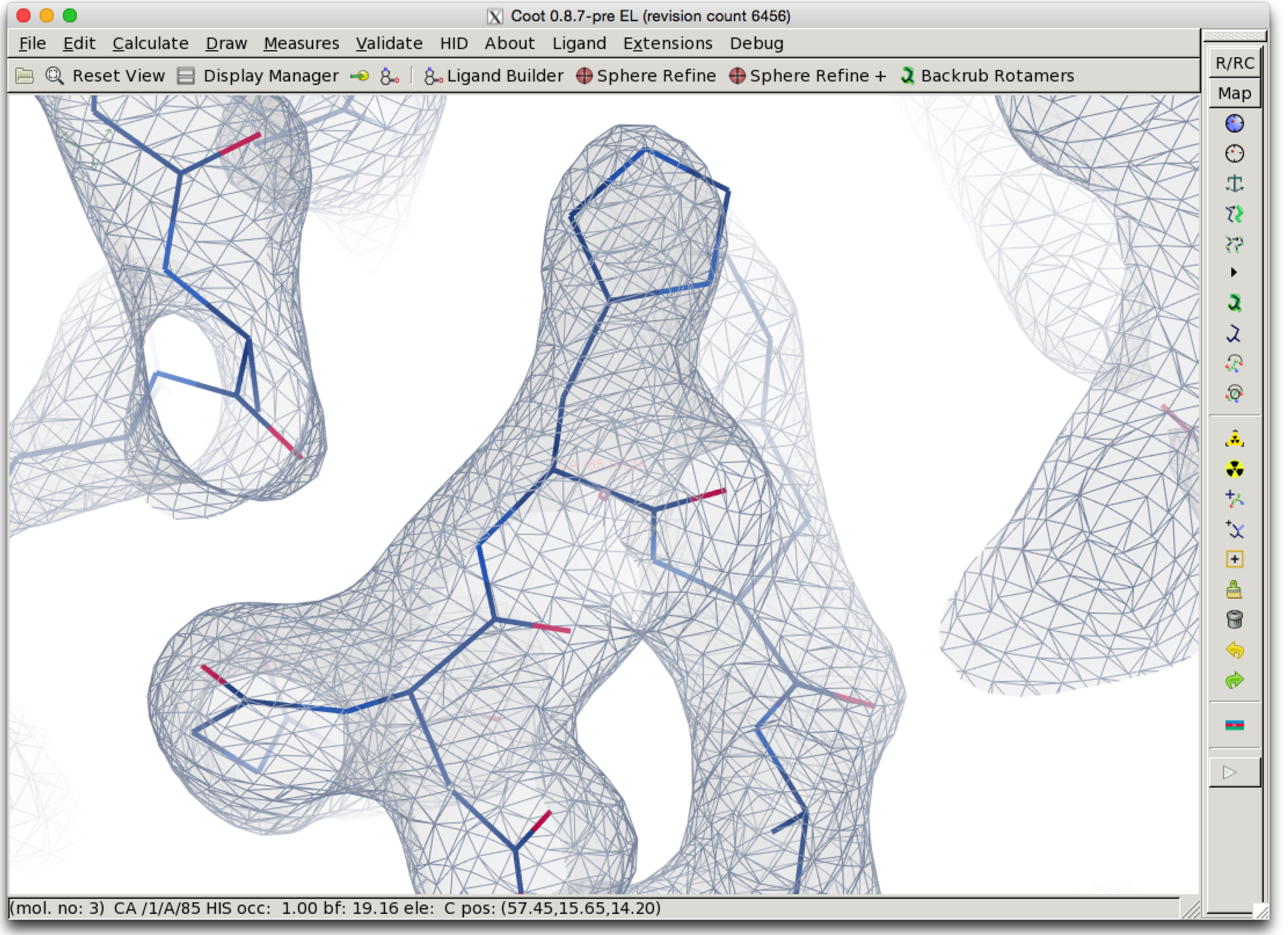
Rotamer 1
Rotamer 2
Rotamer 3
Rotamer 4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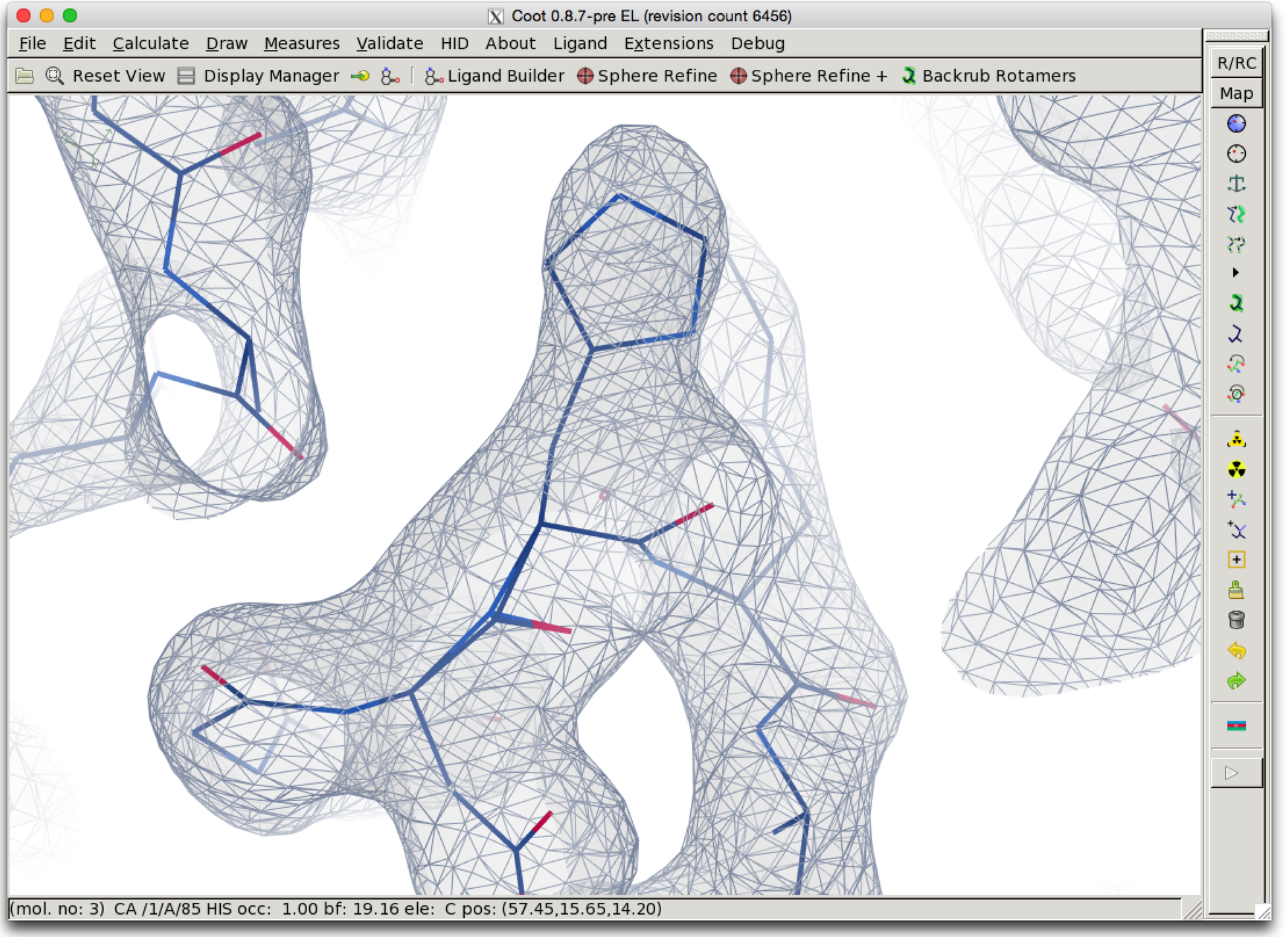
(mol. no: 3) CA /1/A/85 HIS occ: 1.00 bf: 19.16 ele: C pos: (57.45,15.65,14.20)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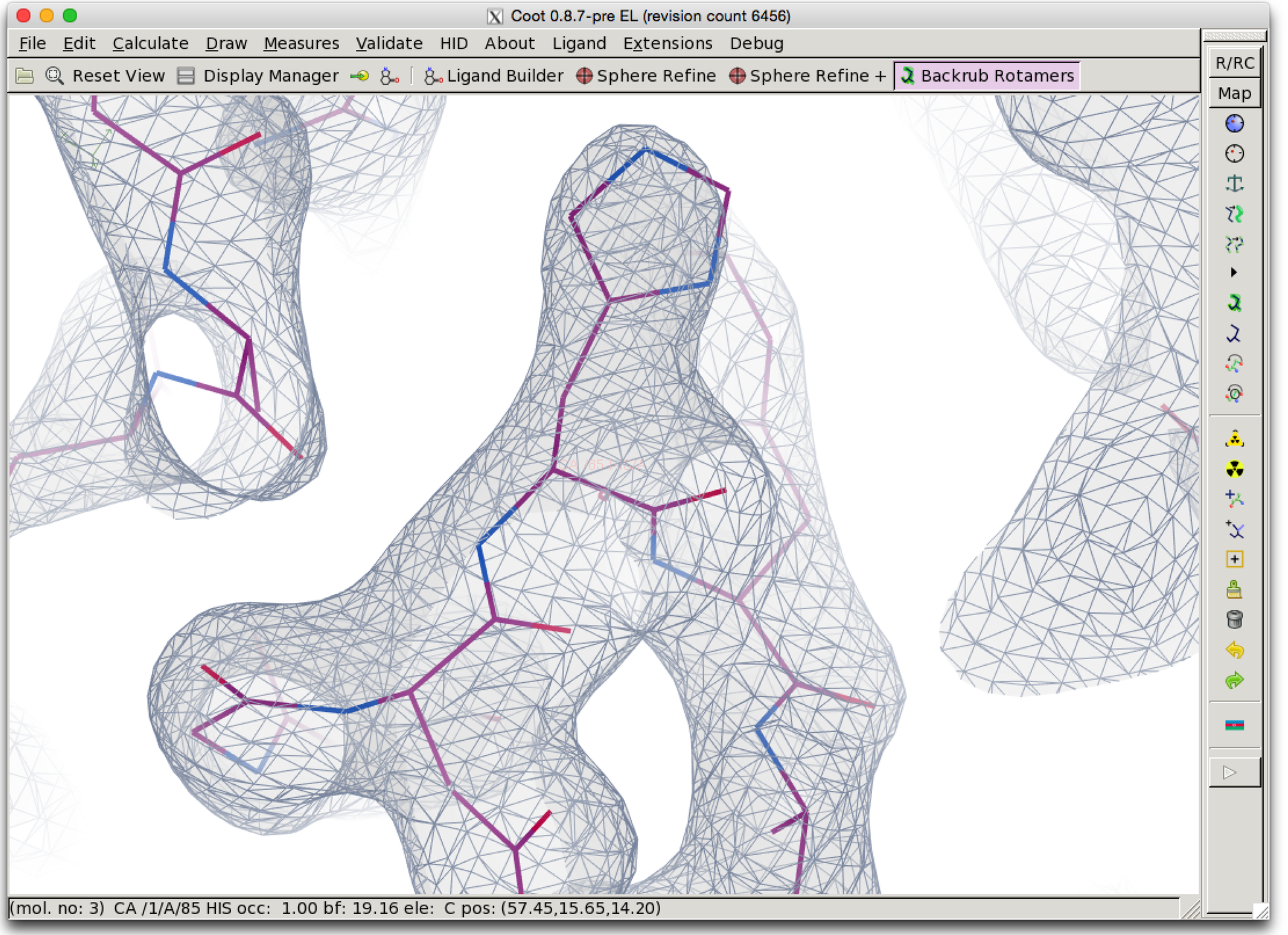
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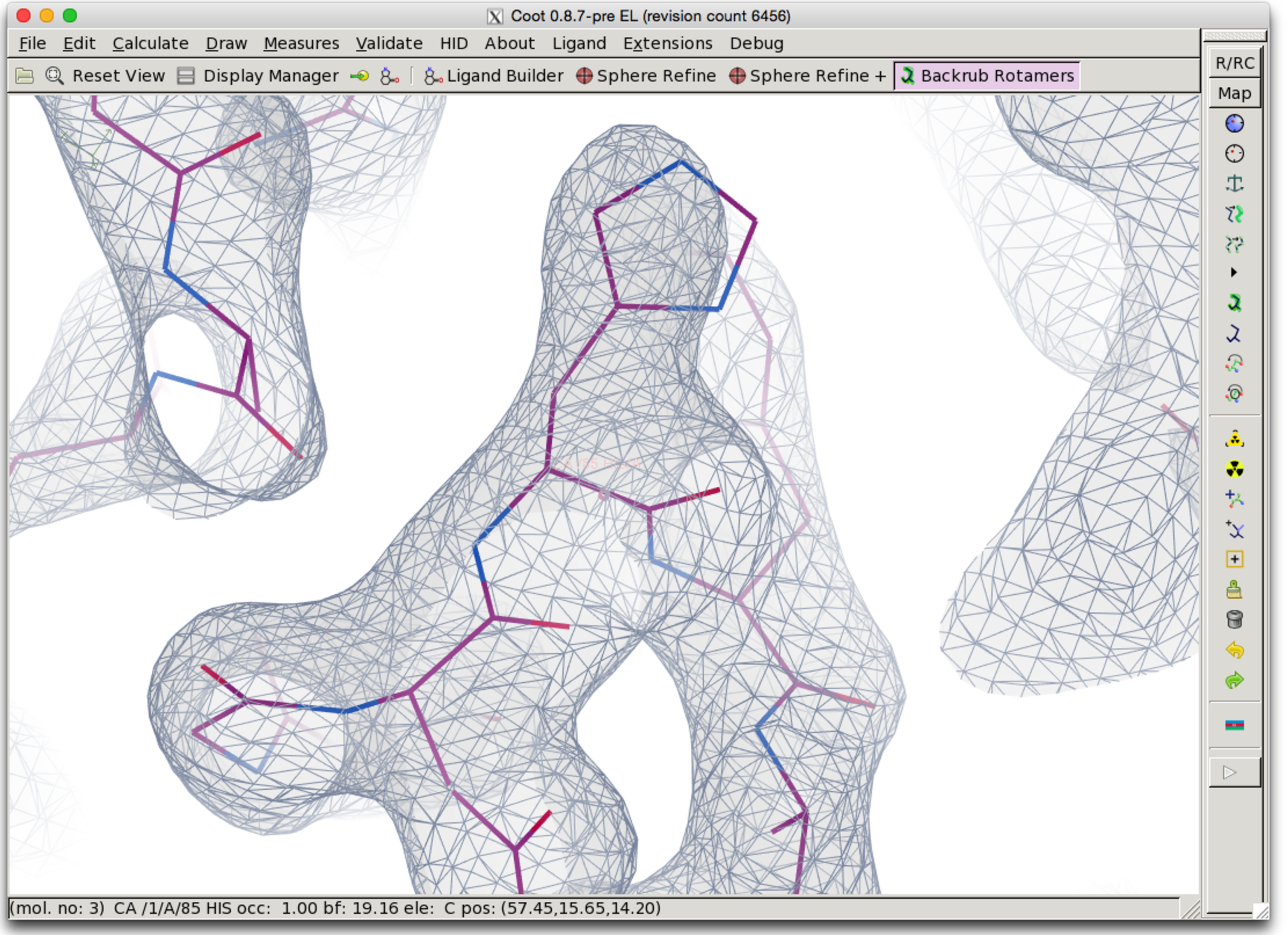
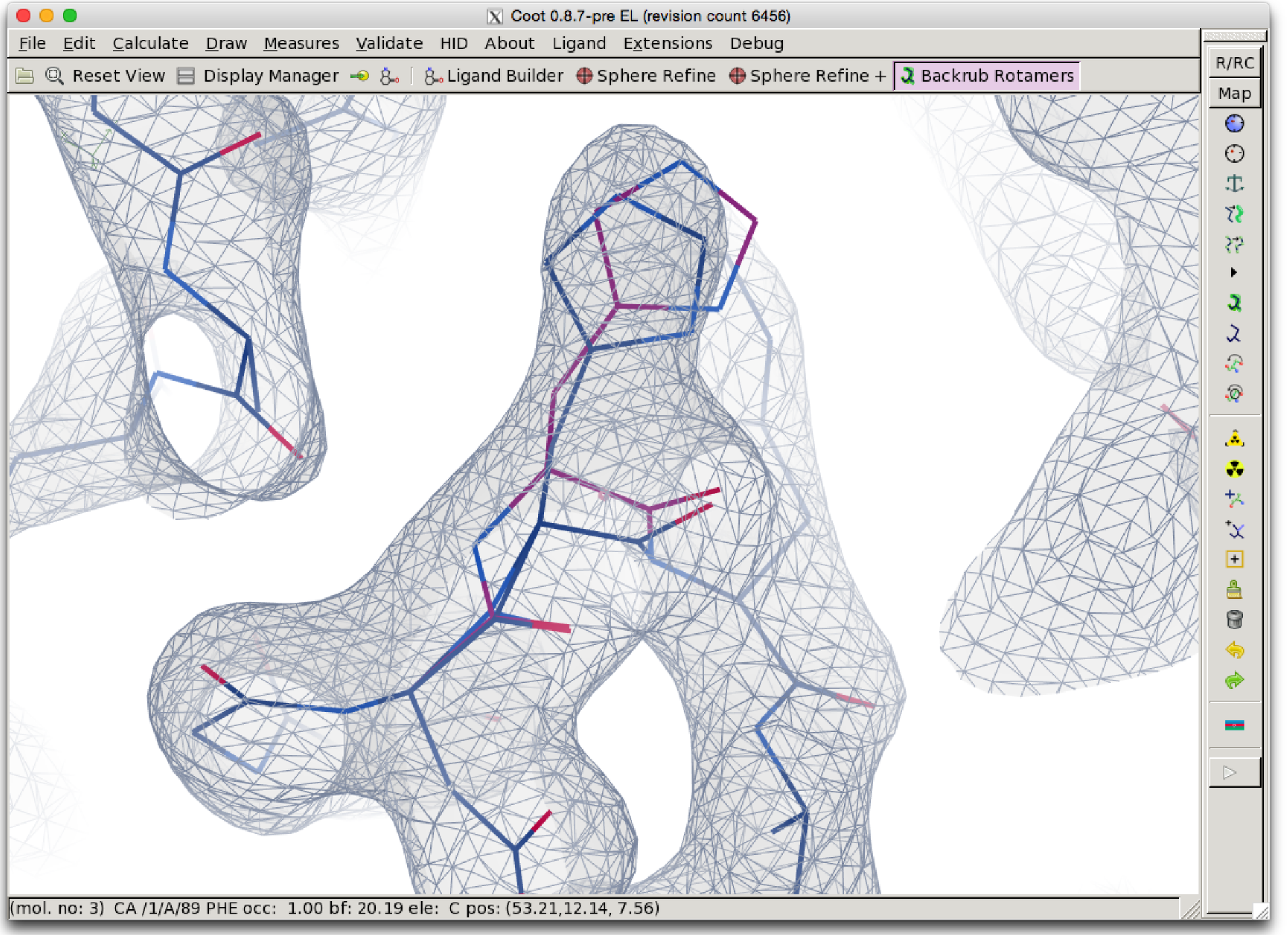
Map
(mol. no: 3) CA /1/A/85 HIS occ: 1.00 bf: 19.16 ele: C pos: (57.45,15.65,14.20)


Coot 0.8.7-pre EL (revision count 6456)
File Edit Calculate Draw Measures Validate HID About Ligand Extensions Debug
Reset View
Display Manager
Ligand Builder
Sphere Refine
Sphere Refine +
Backrub Rotamers
R/RC
Map
(mol. no: 3) CA /1/A/85 HIS occ: 1.00 bf: 19.16 ele: C pos: (57.45,15.65,14.20)


Coot 0.8.7-pre EL (revision count 6456)
File Edit Calculate Draw Measures Validate HID About Ligand Extensions Debug
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Ligand Builder
Sphere Refine
Sphere Refine +
Backrub Rotamers
R/RC
Map
(mol. no: 3) CA /1/A/89 PHE occ: 1.00 bf: 20.19 ele: C pos: (53.21,12.14, 7.56)

Part 2: *Coot* 1

Coot 1

- What has changed?
  - Technical:
    - Widgets (GTK4), 2⟶3 then 3⟶4
    - Python version (3.11), PyGObject
  - User Interface
  - Graphics
  - Libcootapi

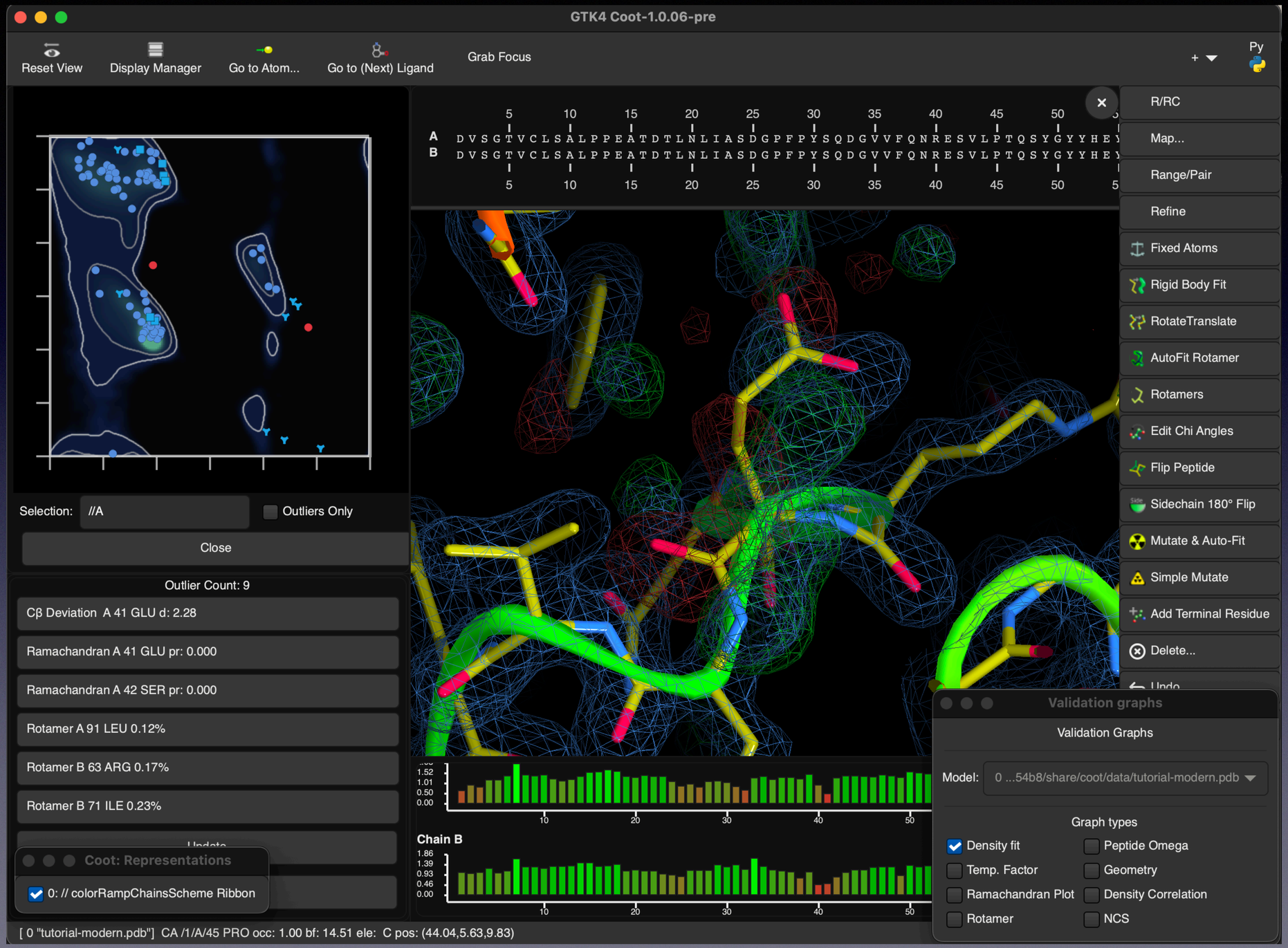
Coot 1 User Interface

- Modern “One Window” paradigm
- Remove dialogs or make them transient
- Use revealers, panes, overlays & popovers
- “Dark Mode”
- “Select First” - “Centering is selection”
- Right mouse for view rotation
- Left-mouse for clicking and picking

Coot 1 Graphics

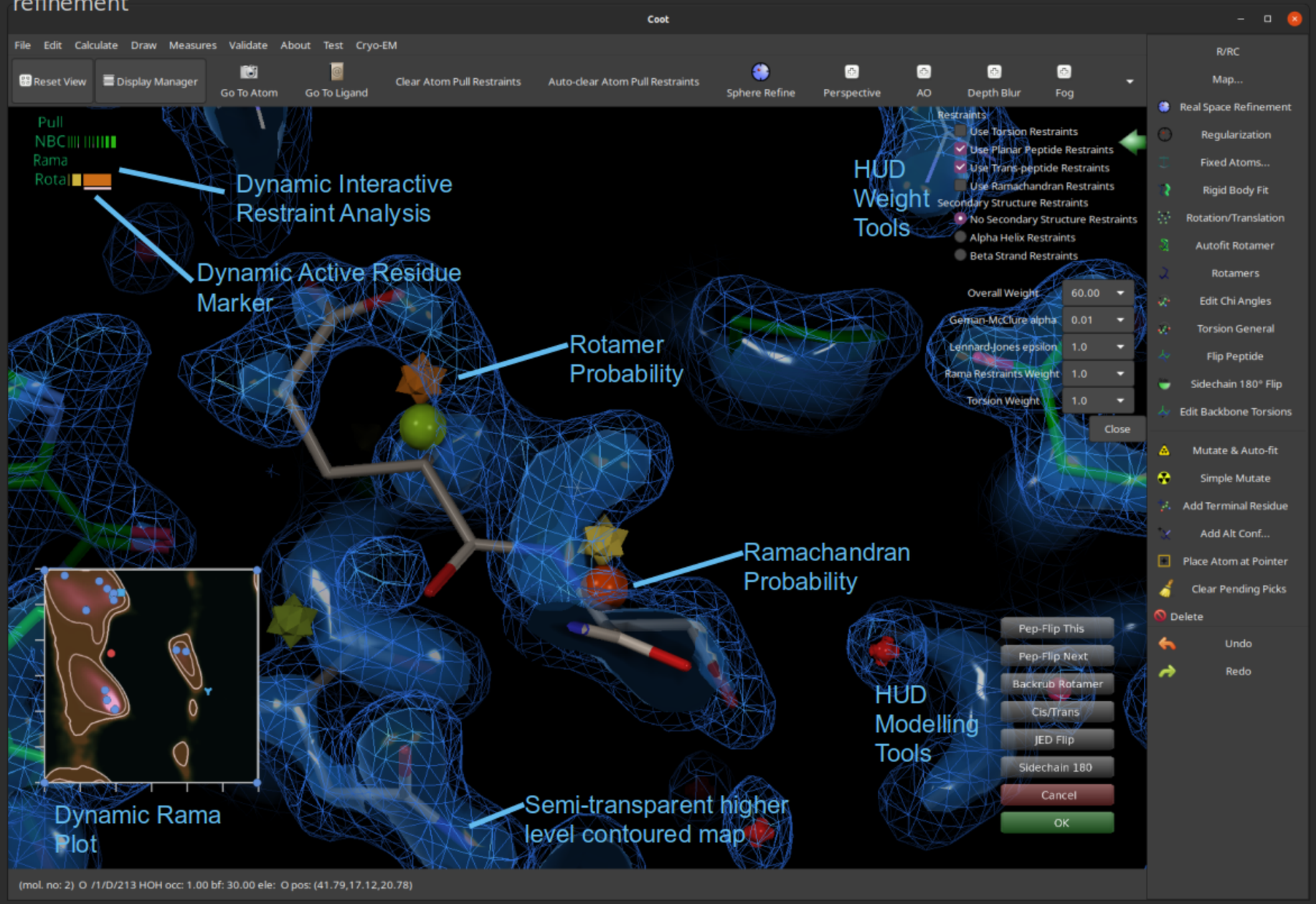
- Models and maps are now 3D objects and interact with the lighting
- Uses “instancing”
- Interactive validation
- vdW Contact texture, chiral centre texture
- Double click blobs
- Updating maps -> “Coot Points”

Coot 1.1 with Ramachandran Plot, Validation Graphs, and Dynamic Validation

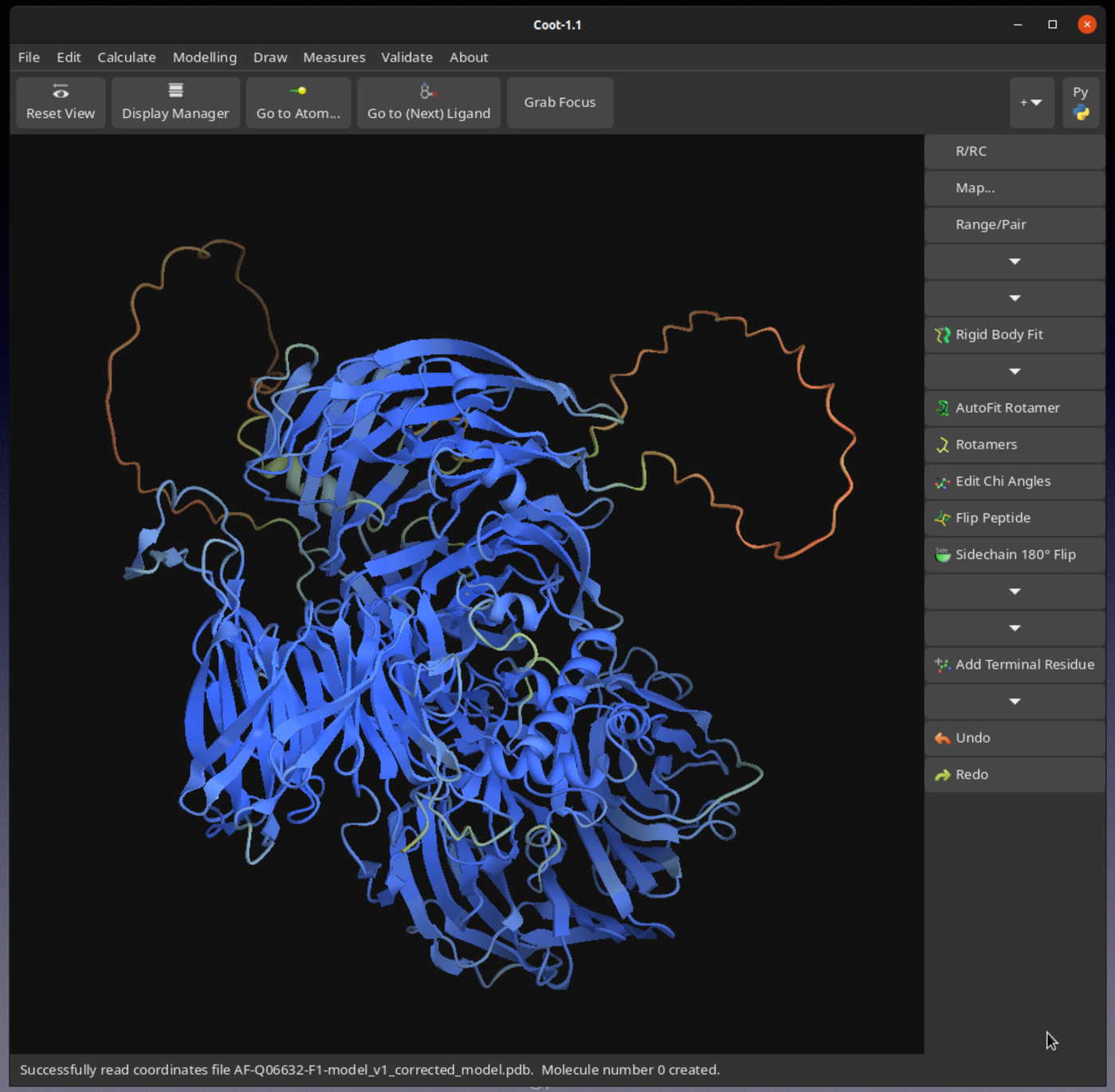


Real-Space Refinement of a mispositioned residue in modern Coot

The coloured bonds show the fixed original structure, the grey bonds show the refined atoms after real space refinement



Coot 1.1 with "User-defined" Colours - in this case, AlphaFold2 pLDDT



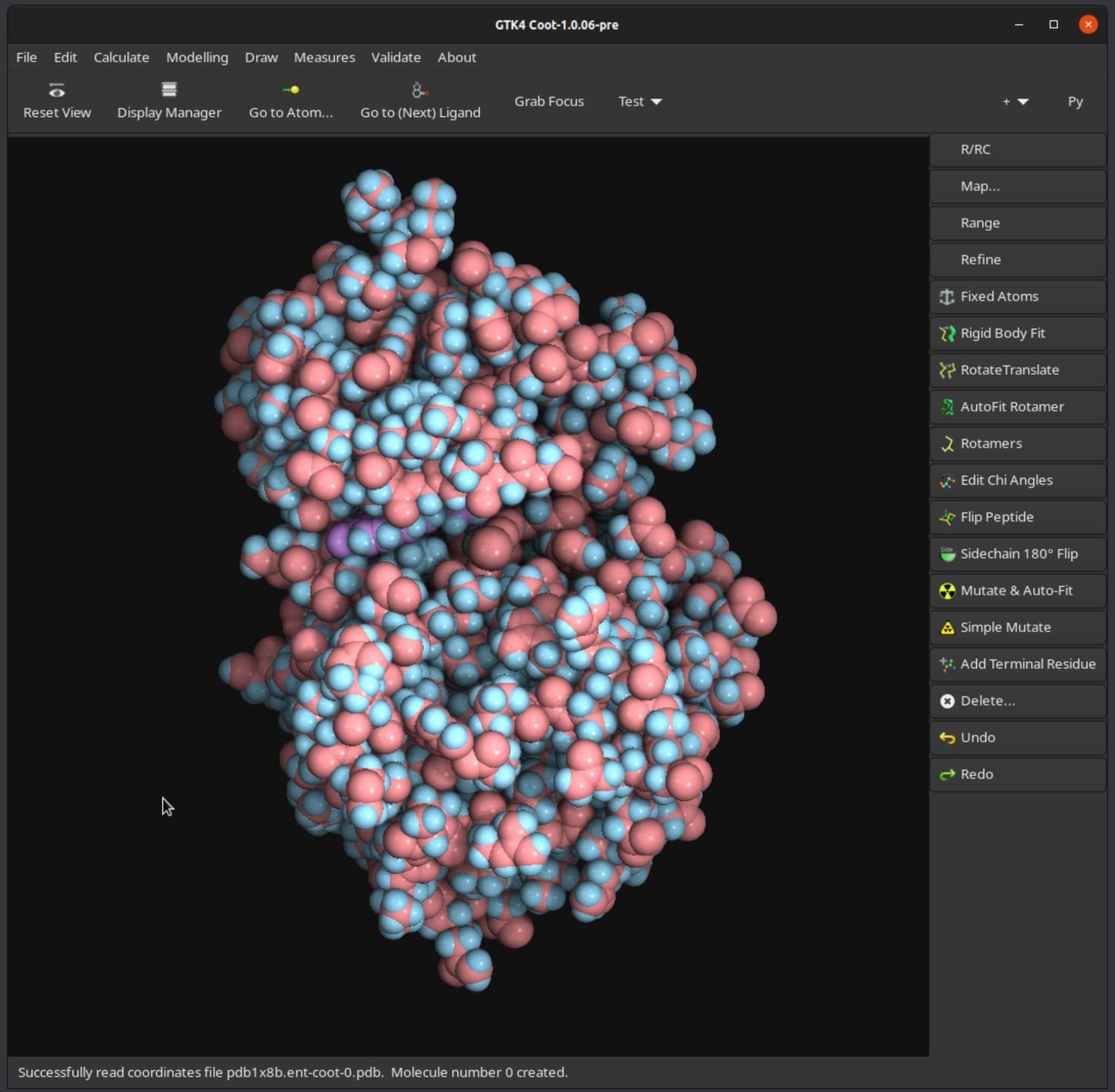
MoleculesToTriangles
Martin Noble

Coot 1 Graphics: Fancy Mode

- “Frame-buffer effects”
- Screen-space Ambient Occlusion (SSAO)
- Shadows
- Outlines and Blur

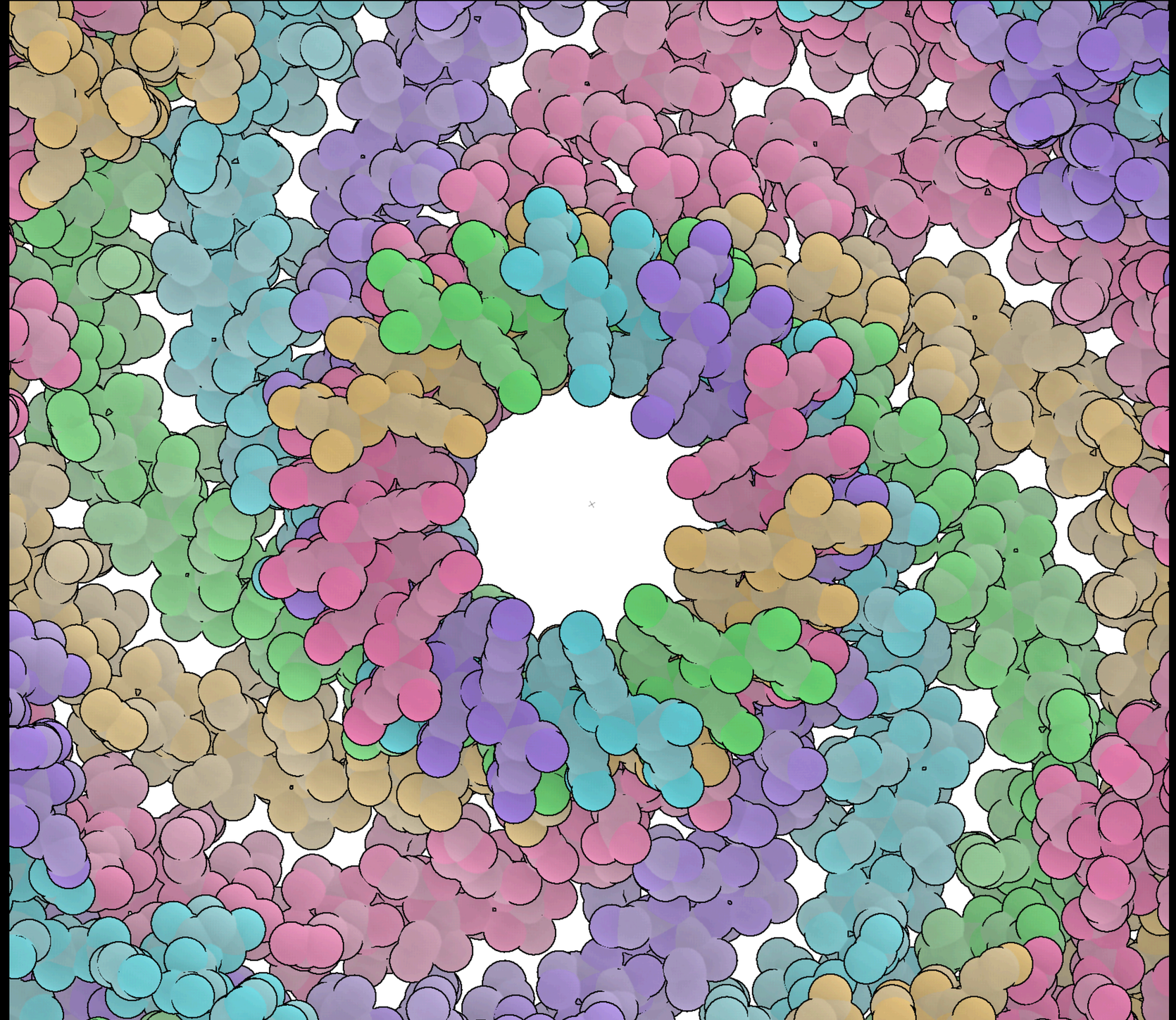
Coot 1.1

"User-defined"
Colours
with SSAO



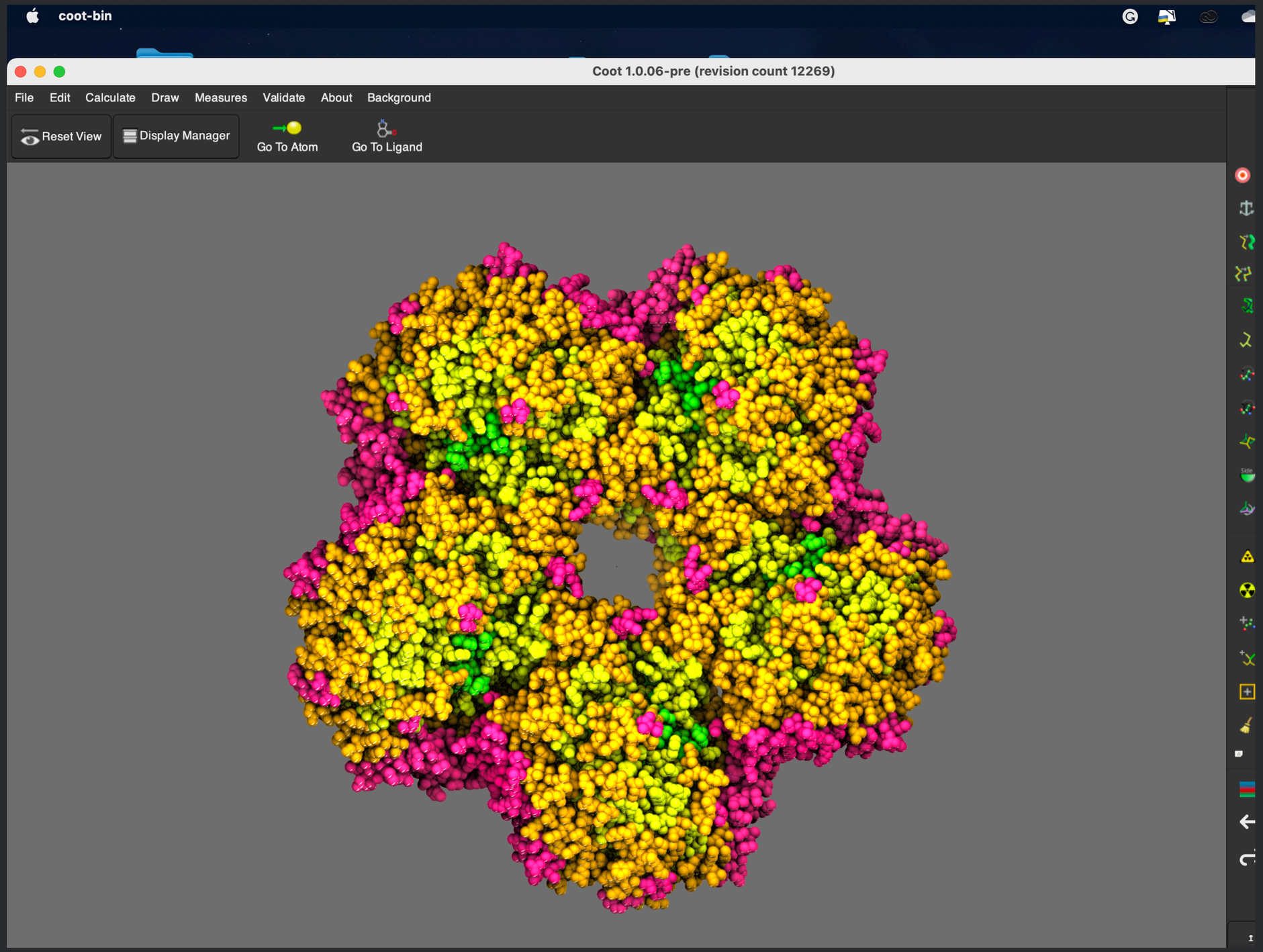
Coot 1.1

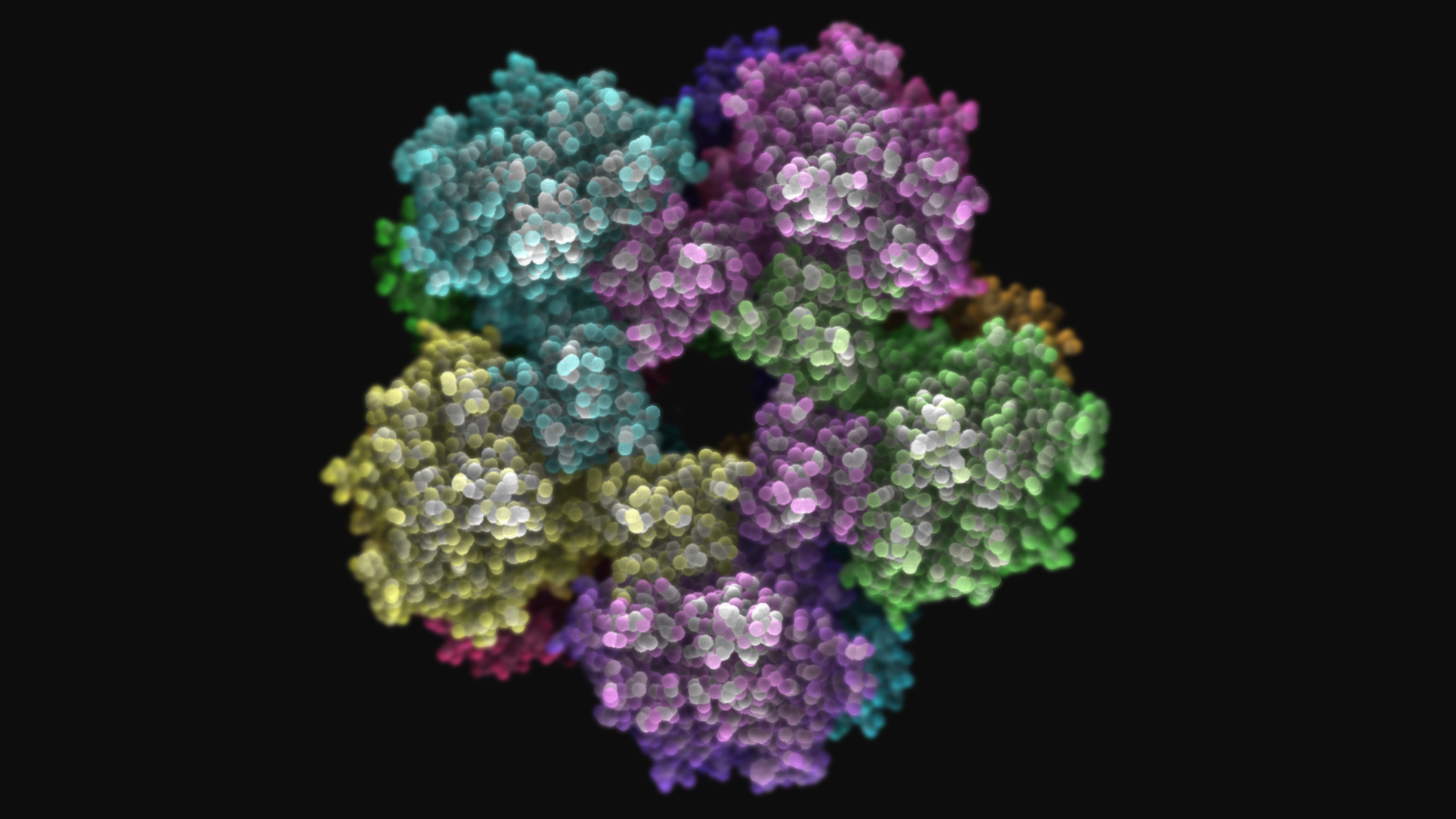
Goodsell-mode Colours



Coot 1.1

Colour-by-B-factor with SSAO





Coot 1.1
T4 bacteriophage

Colour-by-Chain
with SSAI

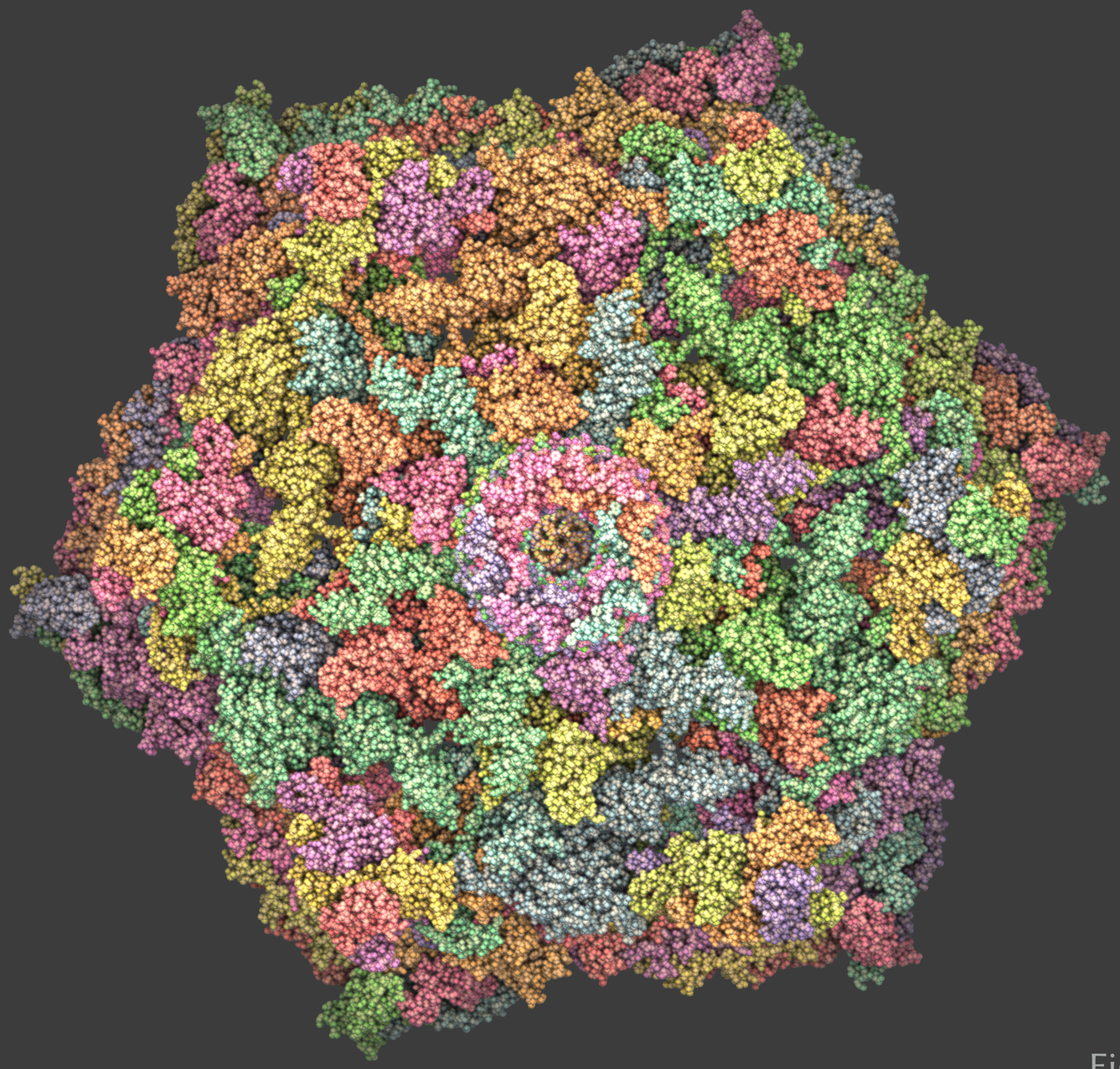
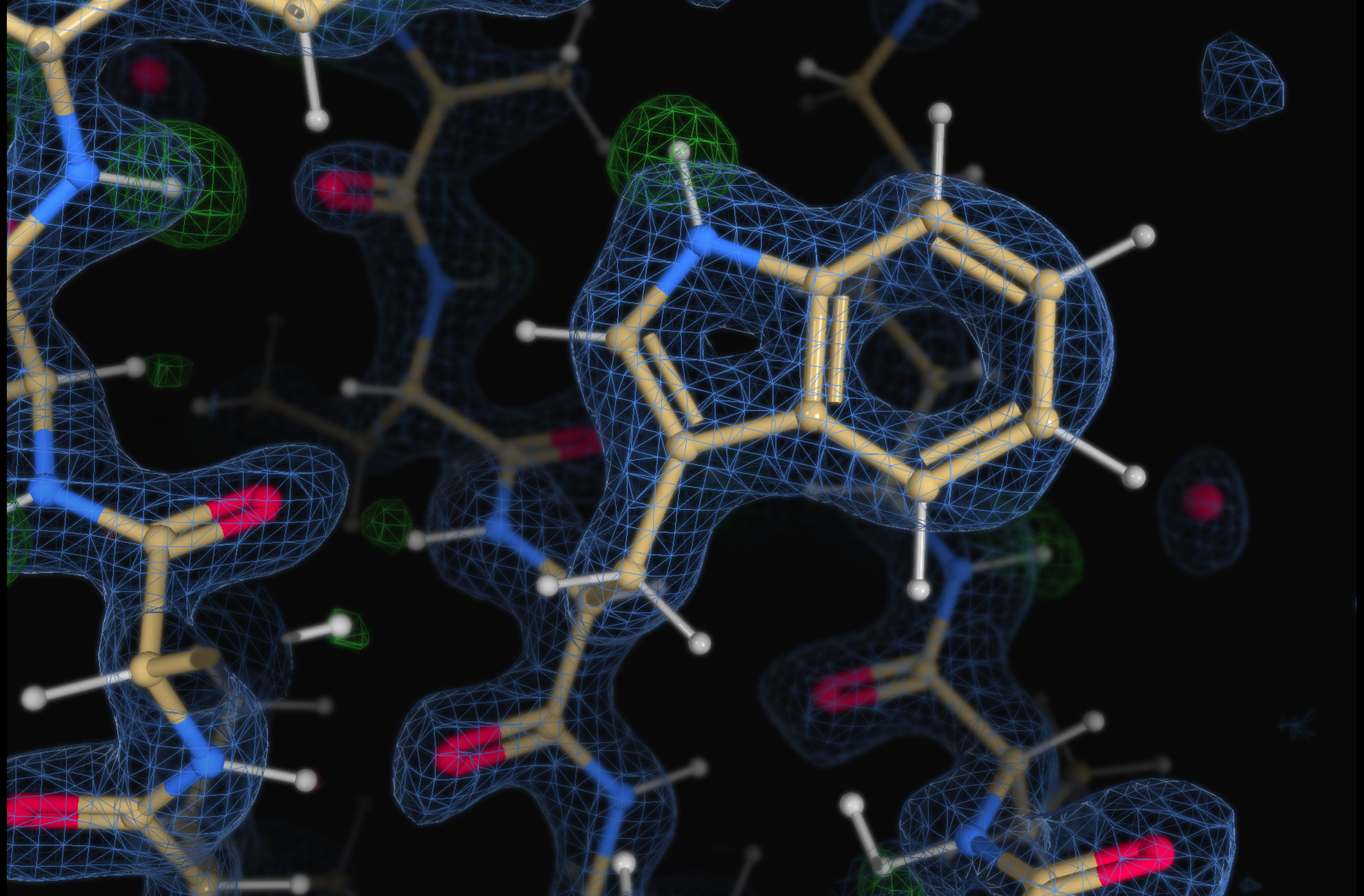
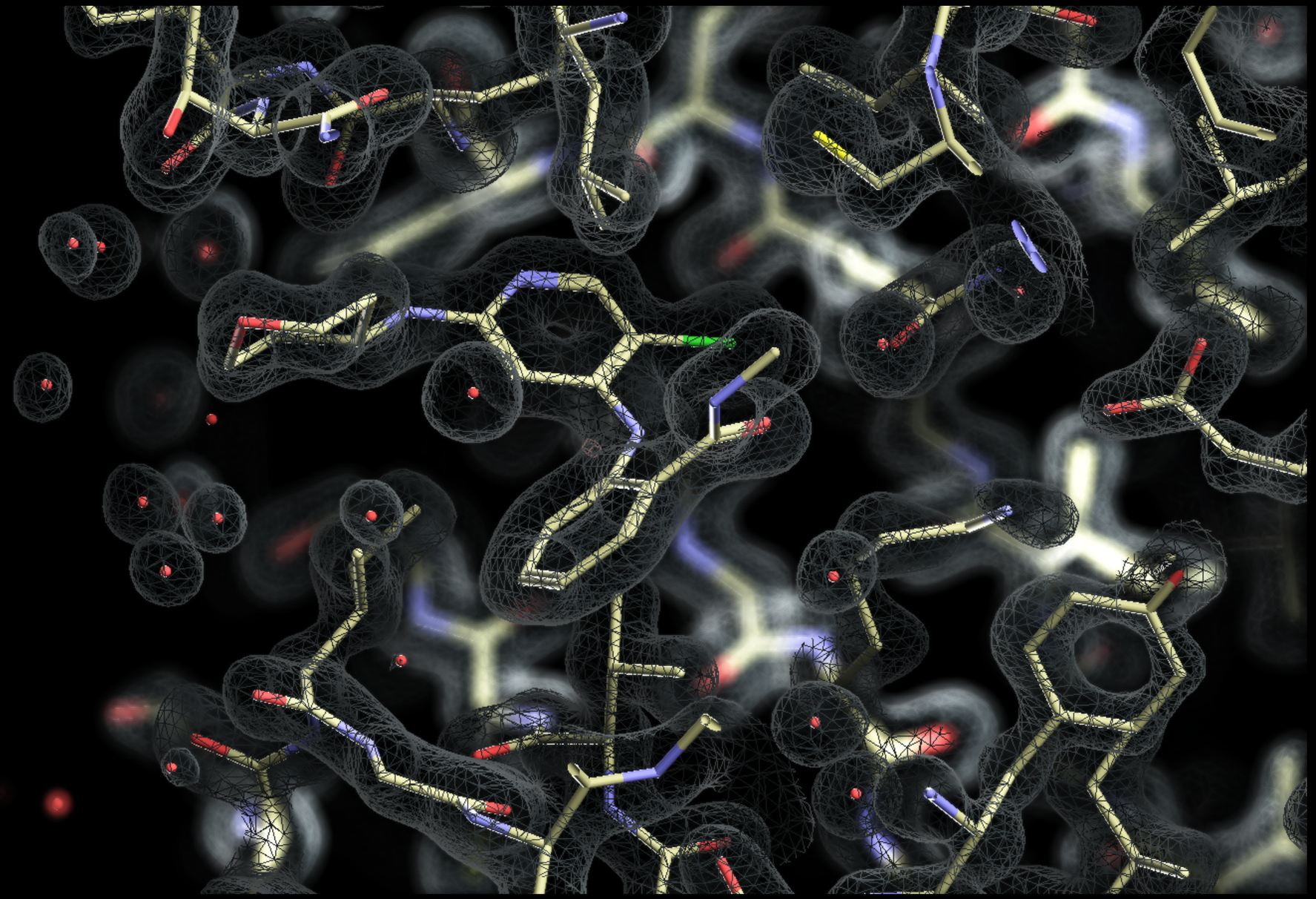


Figure by Lucrezia Catapano



Coot 1.1

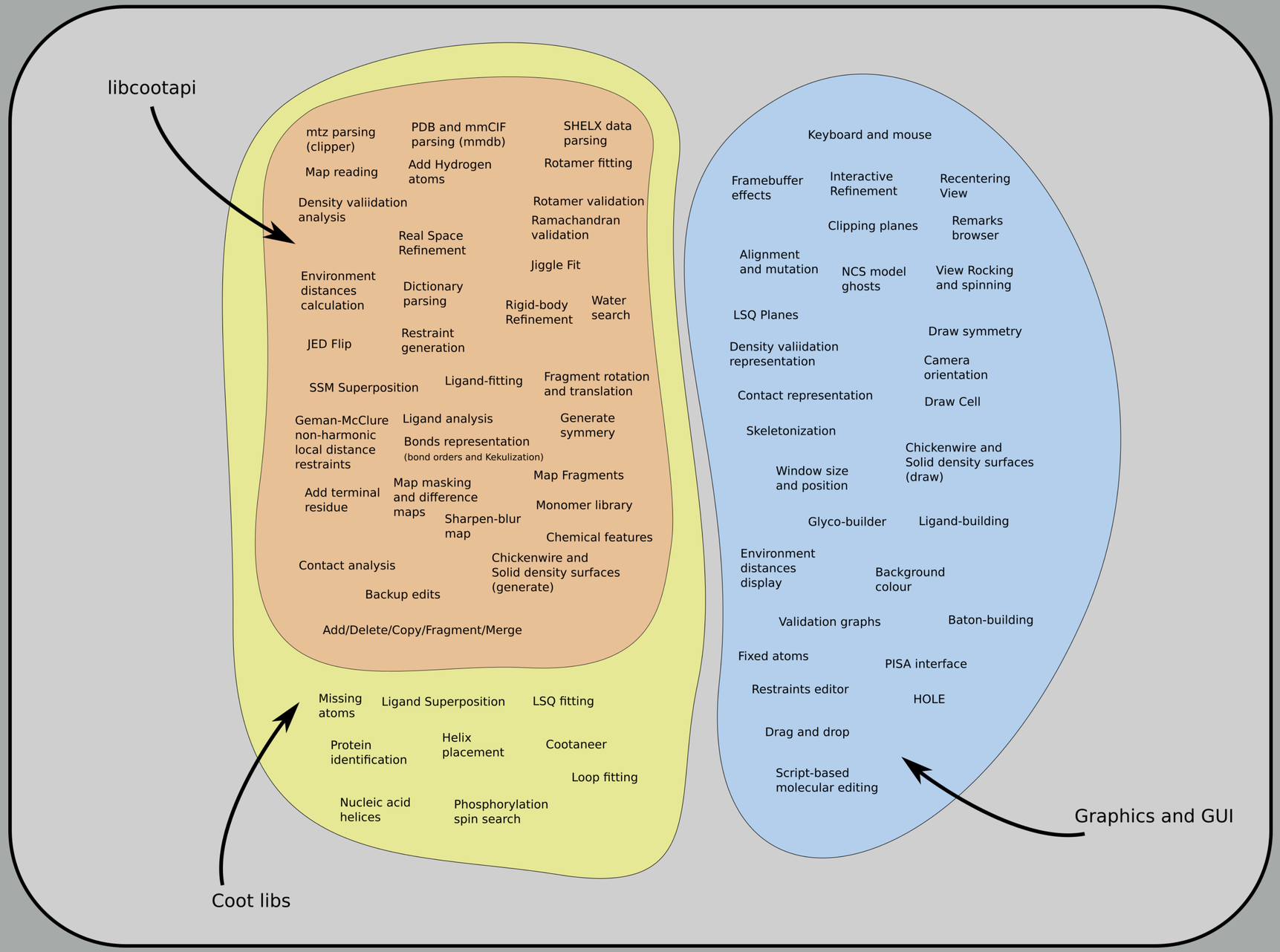
Fresnel lighting
4zzn



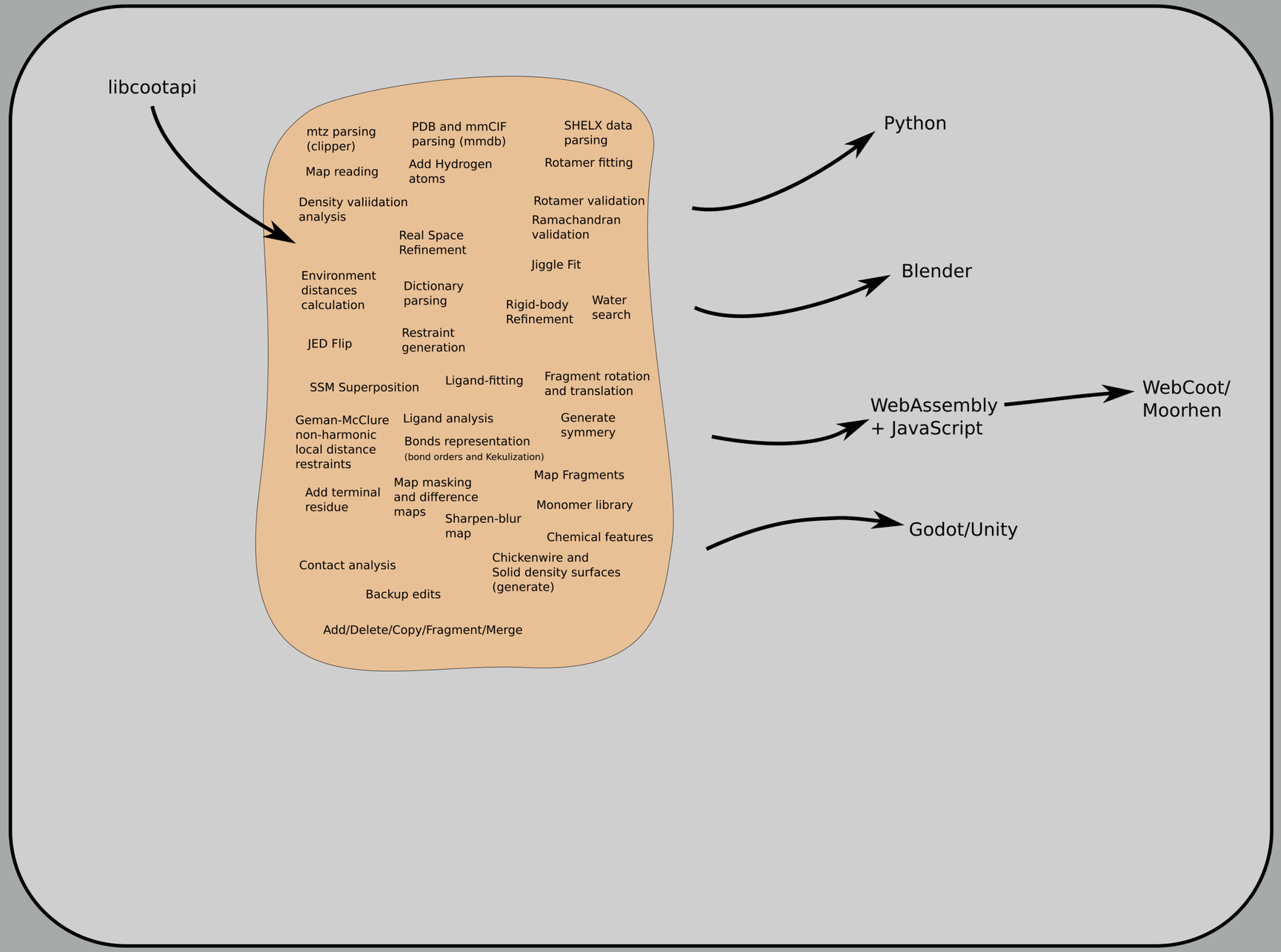
Coot 1 libcootapi

- An API for *Coot* functions that does not use the graphics
  - which increases the portability
  - Access via a molecules container outside the main/old container
  - Extended by use of nano-bind to provide a python module
  - BlendCoot

What is *Coot*?


libcootapi
mtz parsing (clipper)
PDB and mmCIF parsing (mmdb)
SHELX data parsing
Map reading
Add Hydrogen atoms
Rotamer fitting
Density valiidation analysis
Rotamer validation
Ramachandran validation
Real Space Refinement
Jiggle Fit
Environment distances calculation
Dictionary parsing
Rigid-body Refinement
Water search
JED Flip
Restraint generation
SSM Superposition
Ligand-fitting
Fragment rotation and translation
Geman-McClure non-harmonic local distance restraints
Ligand analysis
Generate symmery
Bonds representation
(bond orders and Kekulization)
Map Fragments
Add terminal residue
Map masking and difference maps
Monomer library
Sharpen-blur map
Chemical features
Contact analysis
Chickenwire and Solid density surfaces (generate)
Backup edits
Add/Delete/Copy/Fragment/Merge
Missing atoms
Ligand Superposition
LSQ fitting
Protein identification
Helix placement
Cootaneer
Loop fitting
Nucleic acid helices
Phosphorylation spin search
Coot libs
Keyboard and mouse
Framebuffer effects
Interactive Refinement
Recentering View
Clipping planes
Remarks browser
Alignment and mutation
NCS model ghosts
View Rocking and spinning
LSQ Planes
Draw symmetry
Density valiidation representation
Camera orientation
Contact representation
Draw Cell
Skeletonization
Chickenwire and Solid density surfaces (draw)
Window size and position
Glyco-builder
Ligand-building
Environment distances display
Background colour
Validation graphs
Baton-building
Fixed atoms
PISA interface
Restraints editor
HOLE
Drag and drop
Script-based molecular editing
Graphics and GUI

What is *Coot*?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PDB and mmCIF parsing (mmdb)
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Add Hydrogen atoms
Rotamer fitting
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Rotamer validation
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Real Space Refinement
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Environment distances calculation
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Rigid-body Refinement
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Restraint generation
SSM Superposition
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Fragment rotation and translation
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Monomer library
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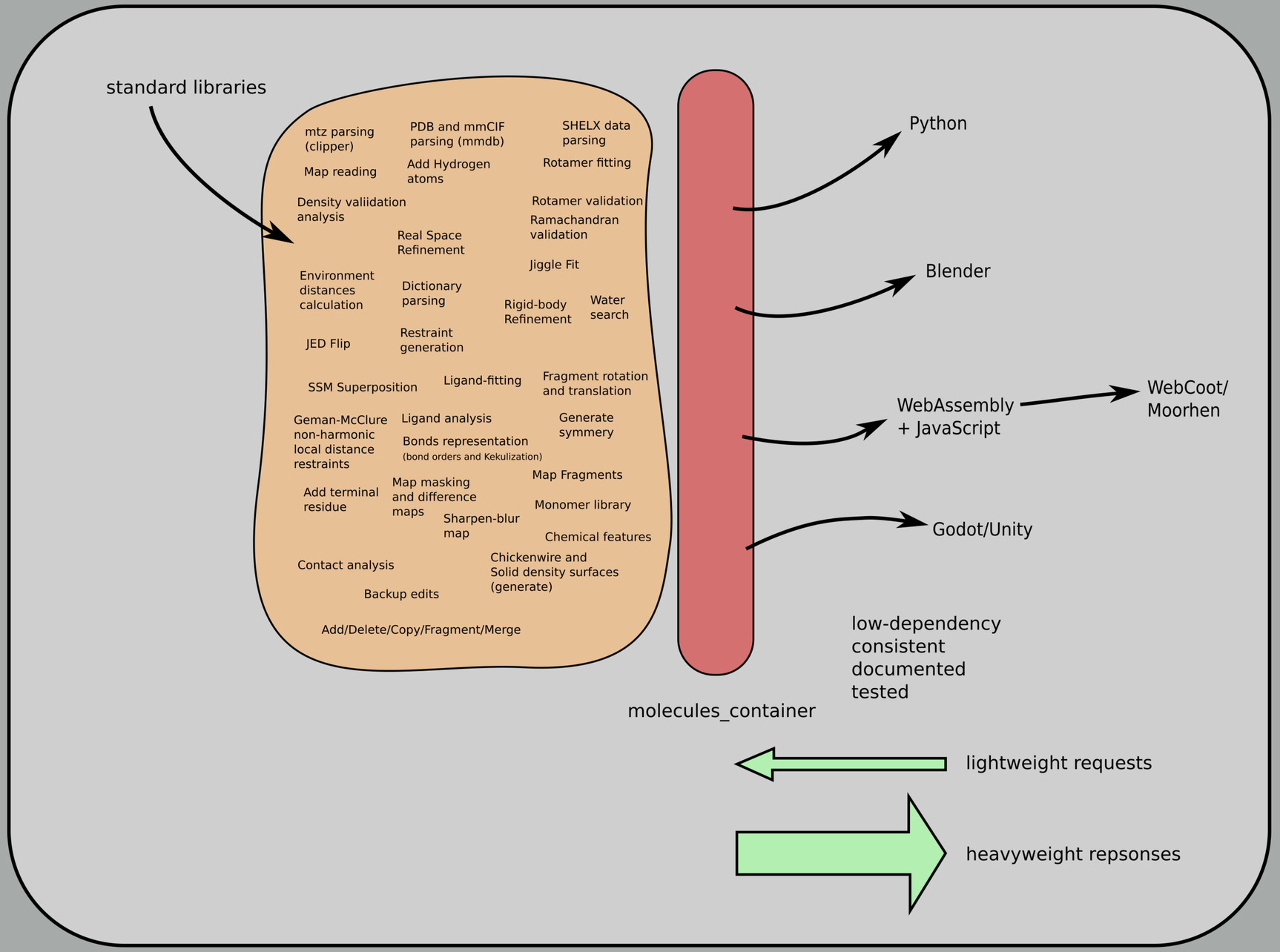
Contact analysis
Chickenwire and Solid density surfaces (generate)
Backup edits
Add/Delete/Copy/Fragment/Merge
Python
Blender
WebAssembly + JavaScript
WebCoot/ Moorhen
Godot/Unity


standard libraries
mtz parsing (clipper)
PDB and mmCIF parsing (mmdb)
SHELX data parsing
Map reading
Add Hydrogen atoms
Rotamer fitting
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Rotamer validation
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Backup edits
Add/Delete/Copy/Fragment/Merge
Python
Blender
WebAssembly + JavaScript
WebCoot/ Moorhen
Godot/Unity
low-dependency
consistent
documented
tested
molecules_container
lightweight requests
heavyweight repsonses

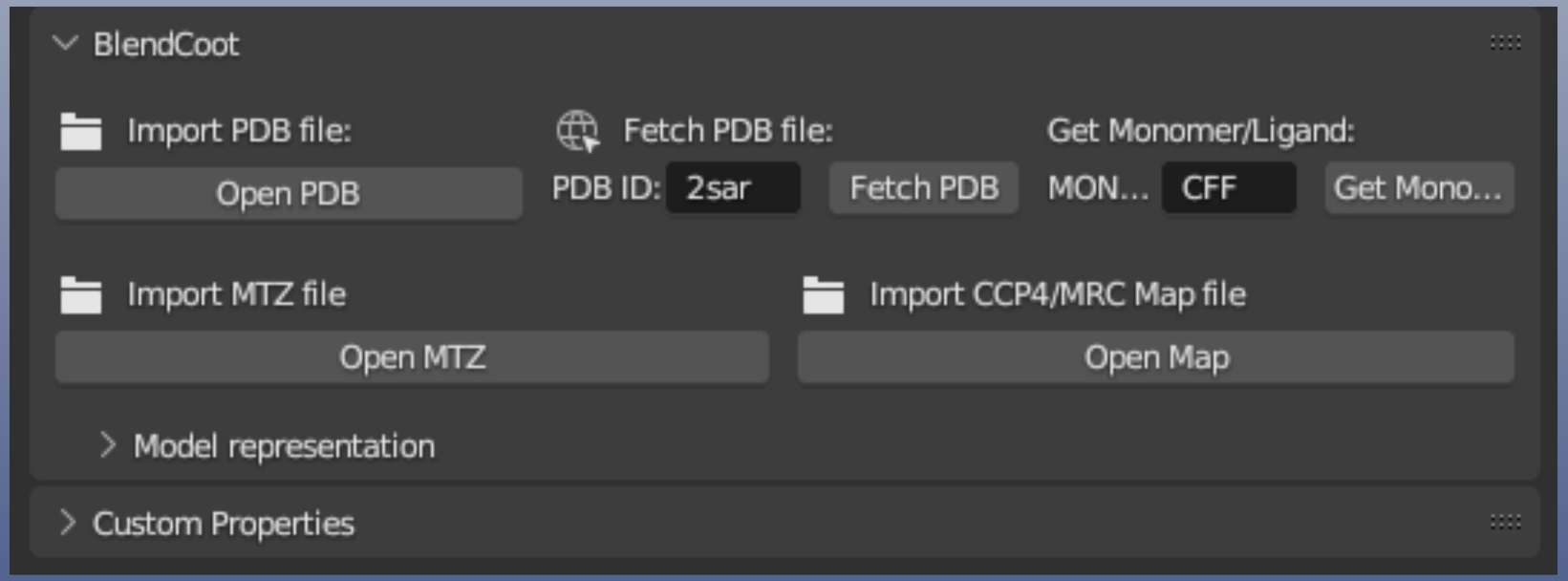
libcootapi/chapi in action

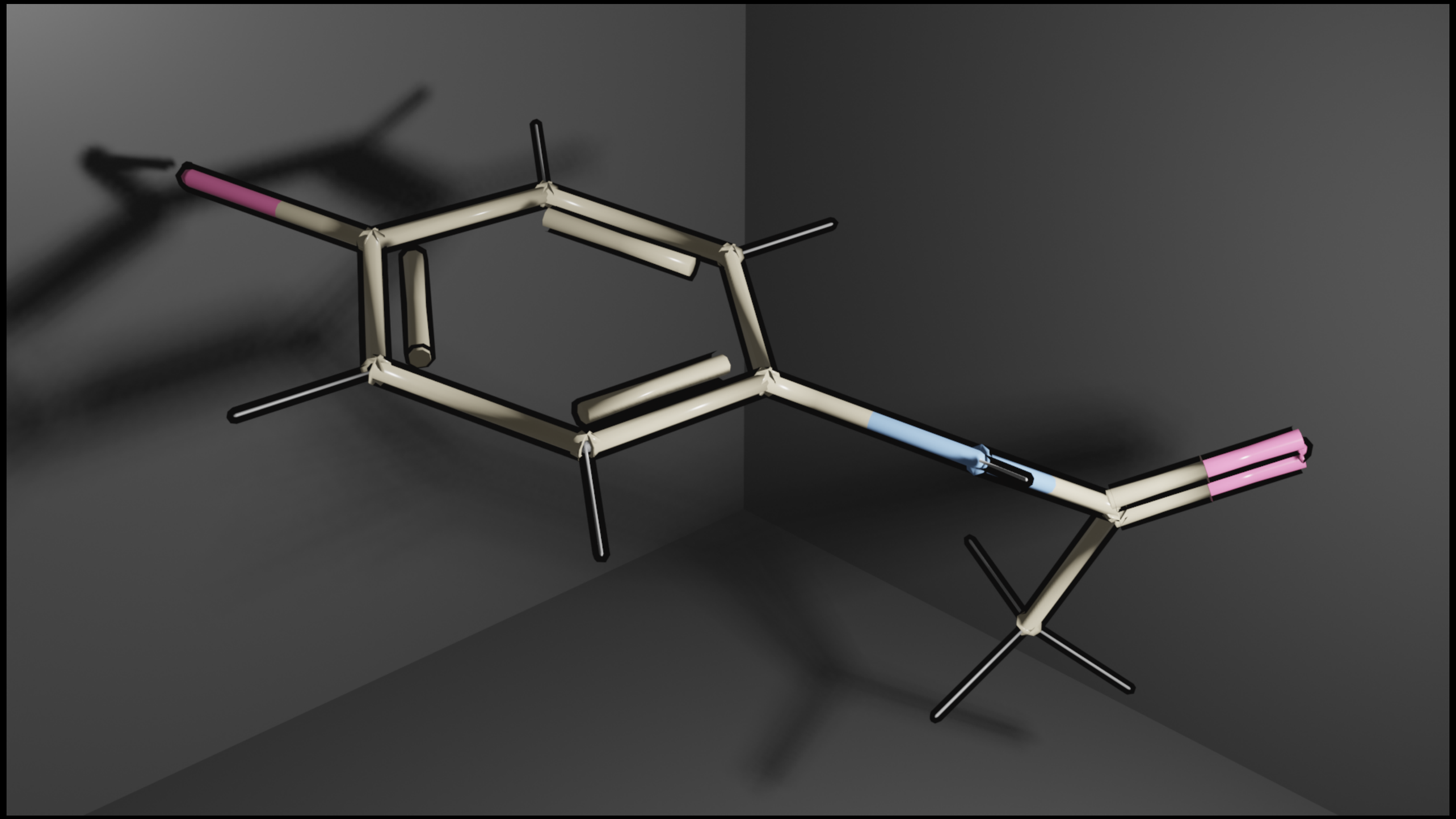
```
1
2   import coot_headless_api
3   chapi = coot_headless_api.molecules_container_t()
4
5   dist = 7.3
6   imol = chapi.read_pdb("tutorial-modern.pdb")
7   rnrl = chapi.get_residues_near_residue(imol, "//A/20", dist)
8
9   for r in rnrl:
10      print(r)
11
```

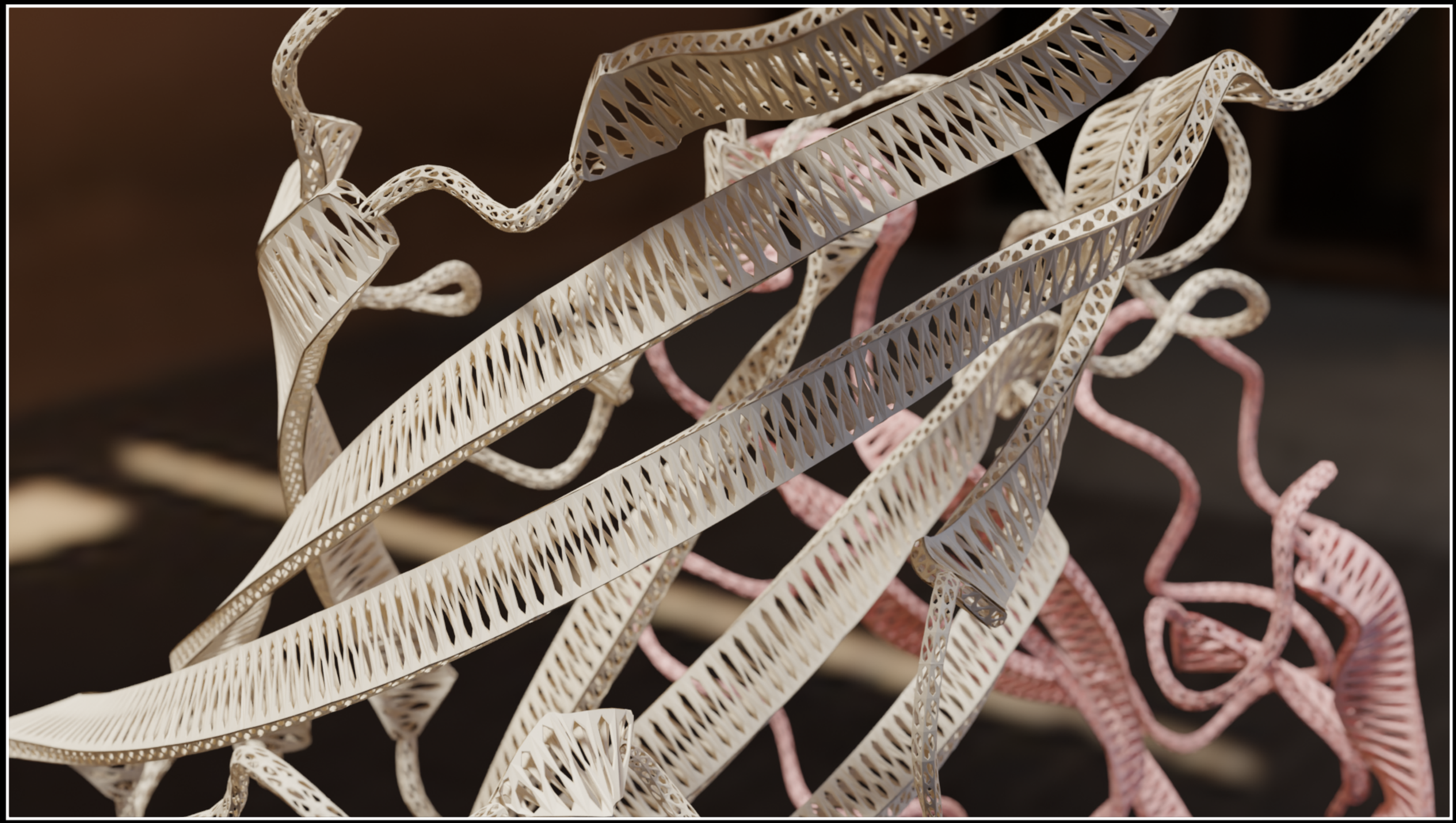
BlendCoot

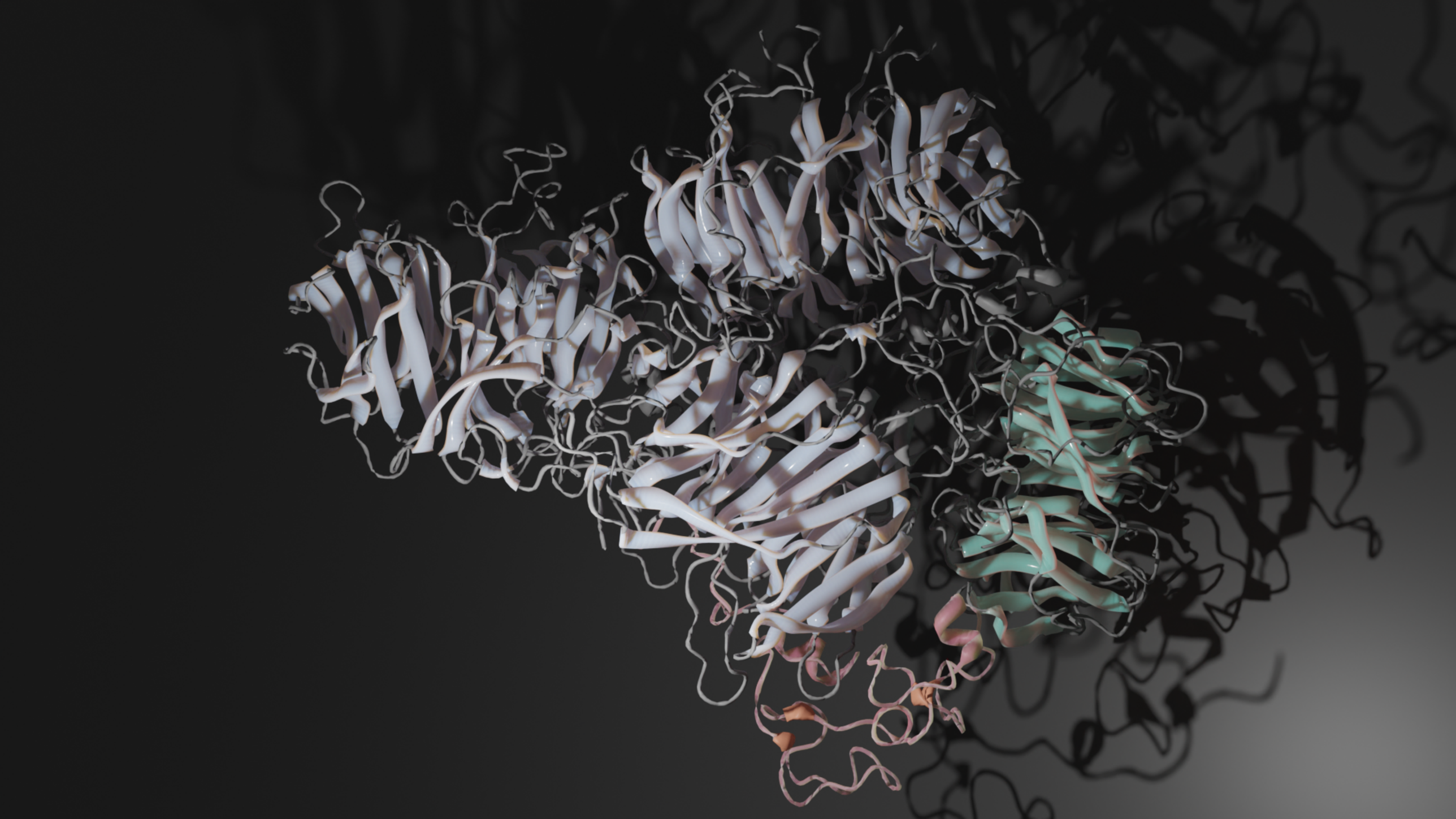
Lucrezia Catapano

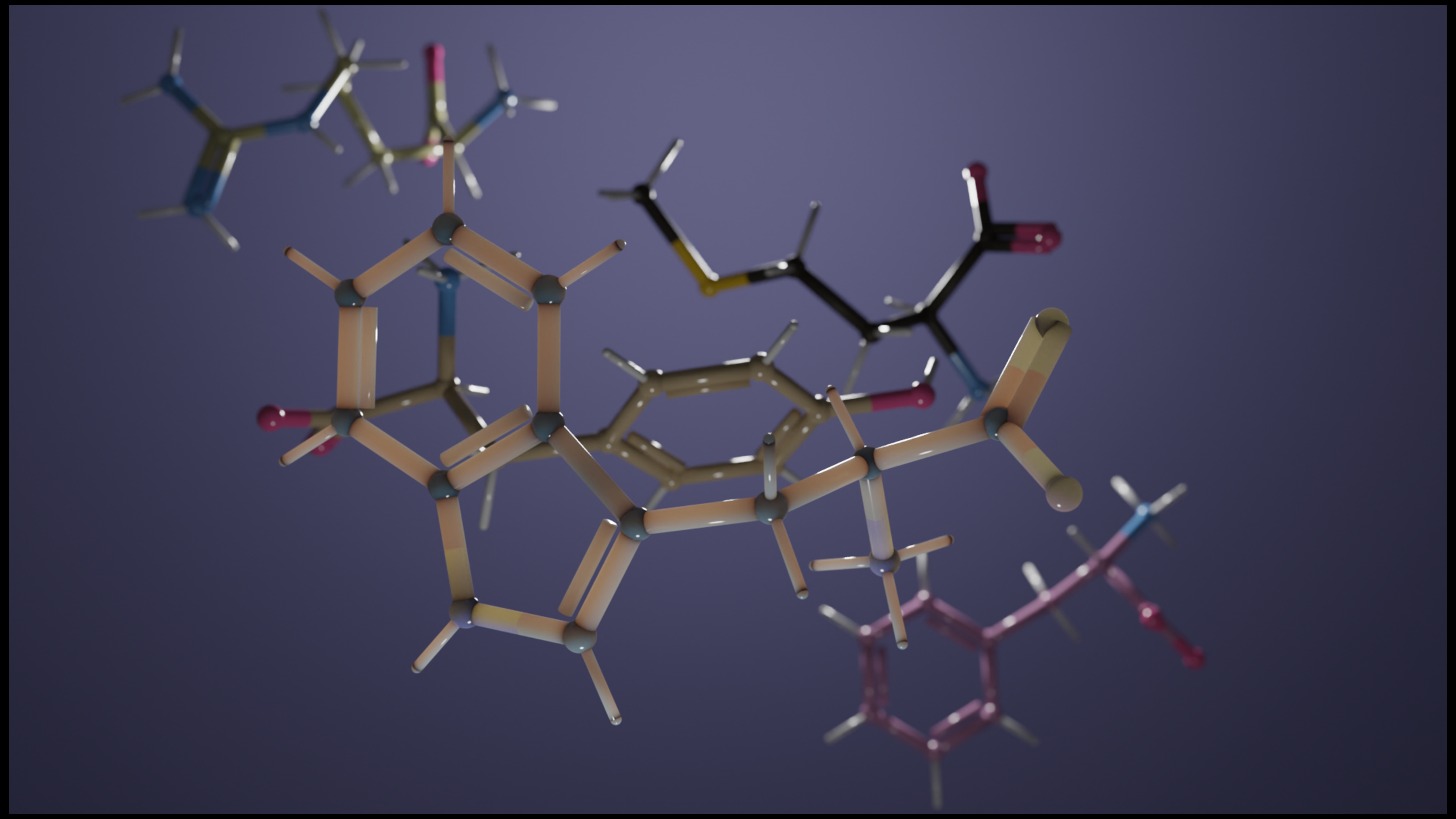
- Libcootapi with python bindings and Blender conversion utils

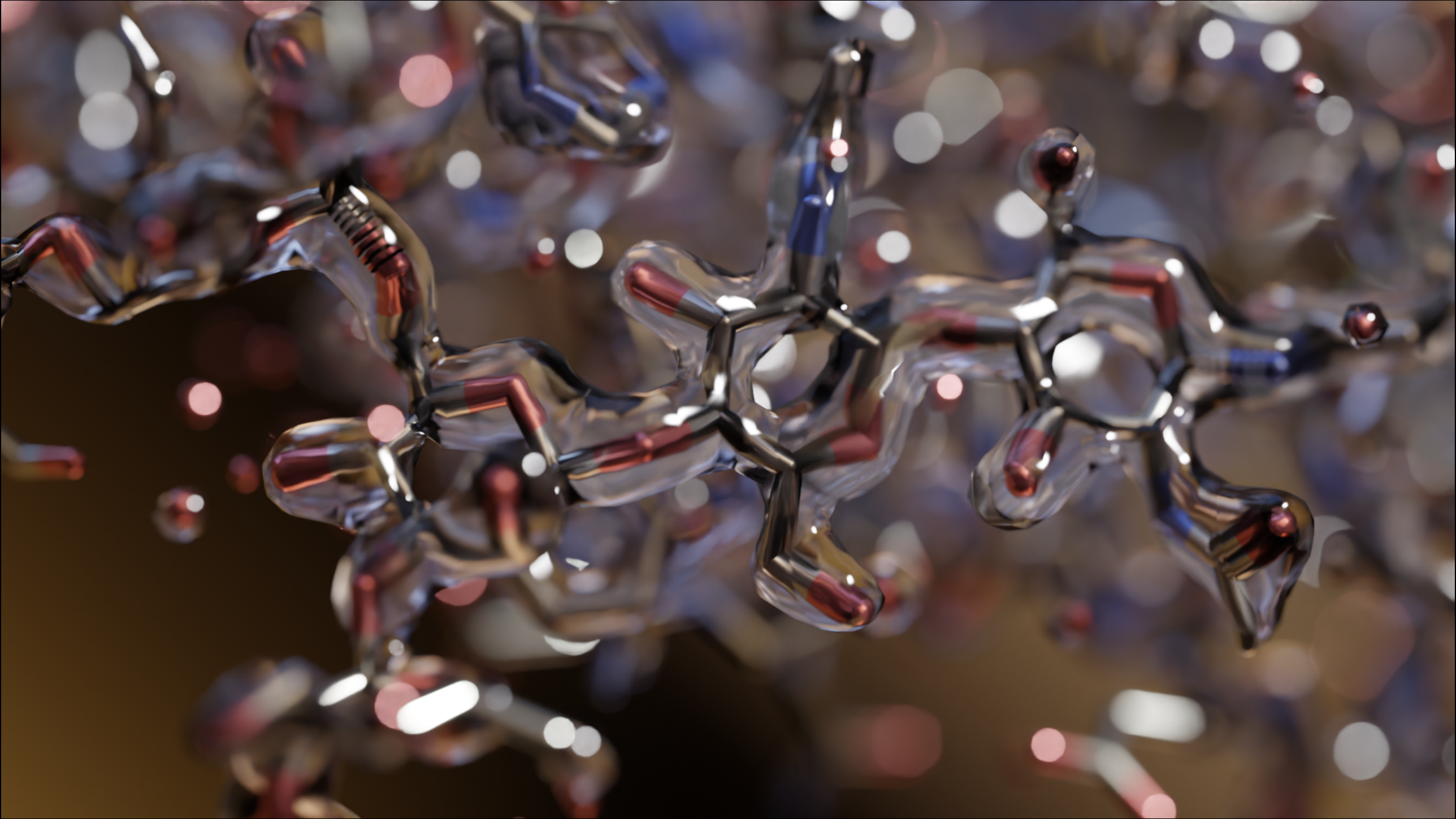


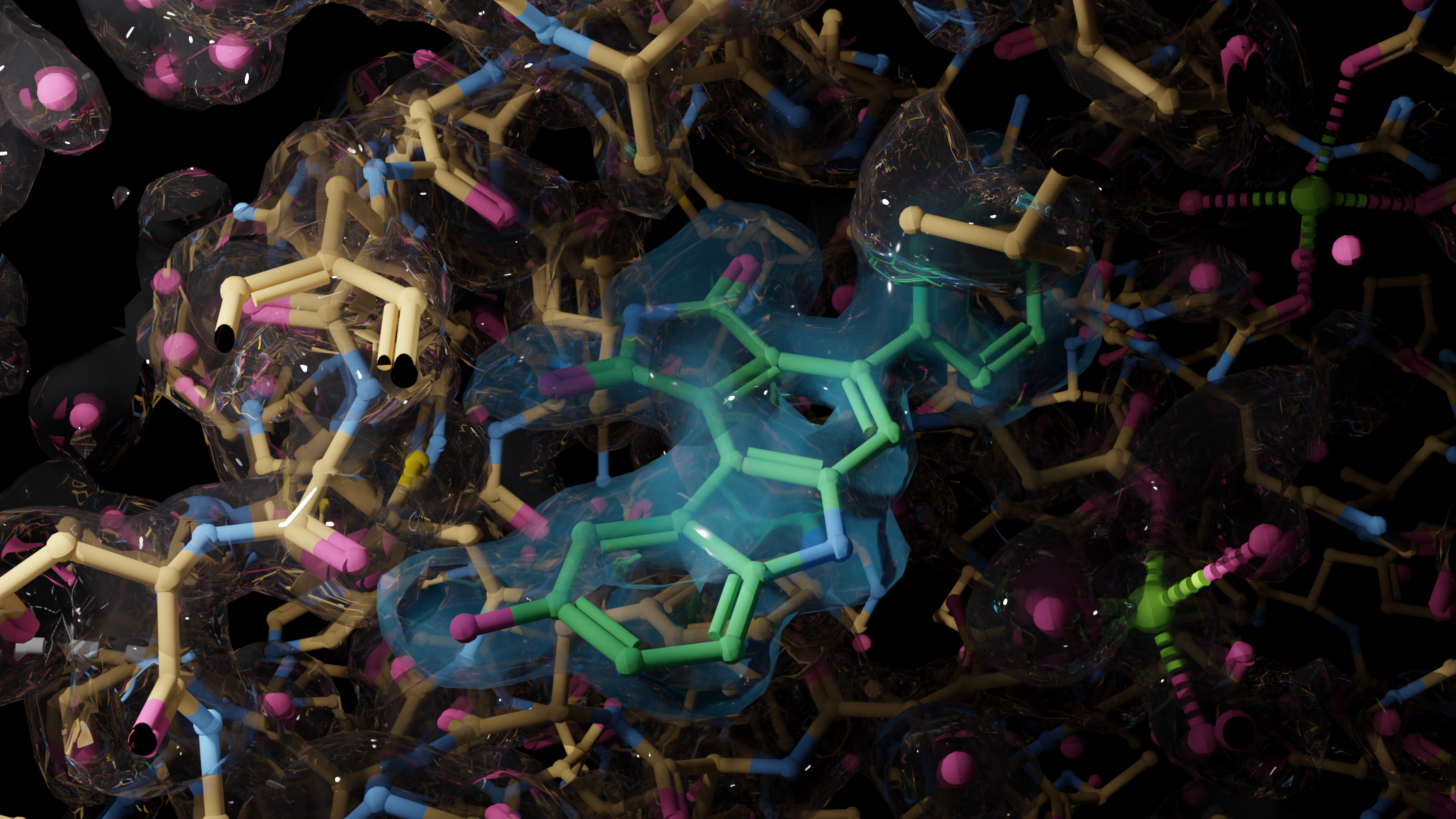


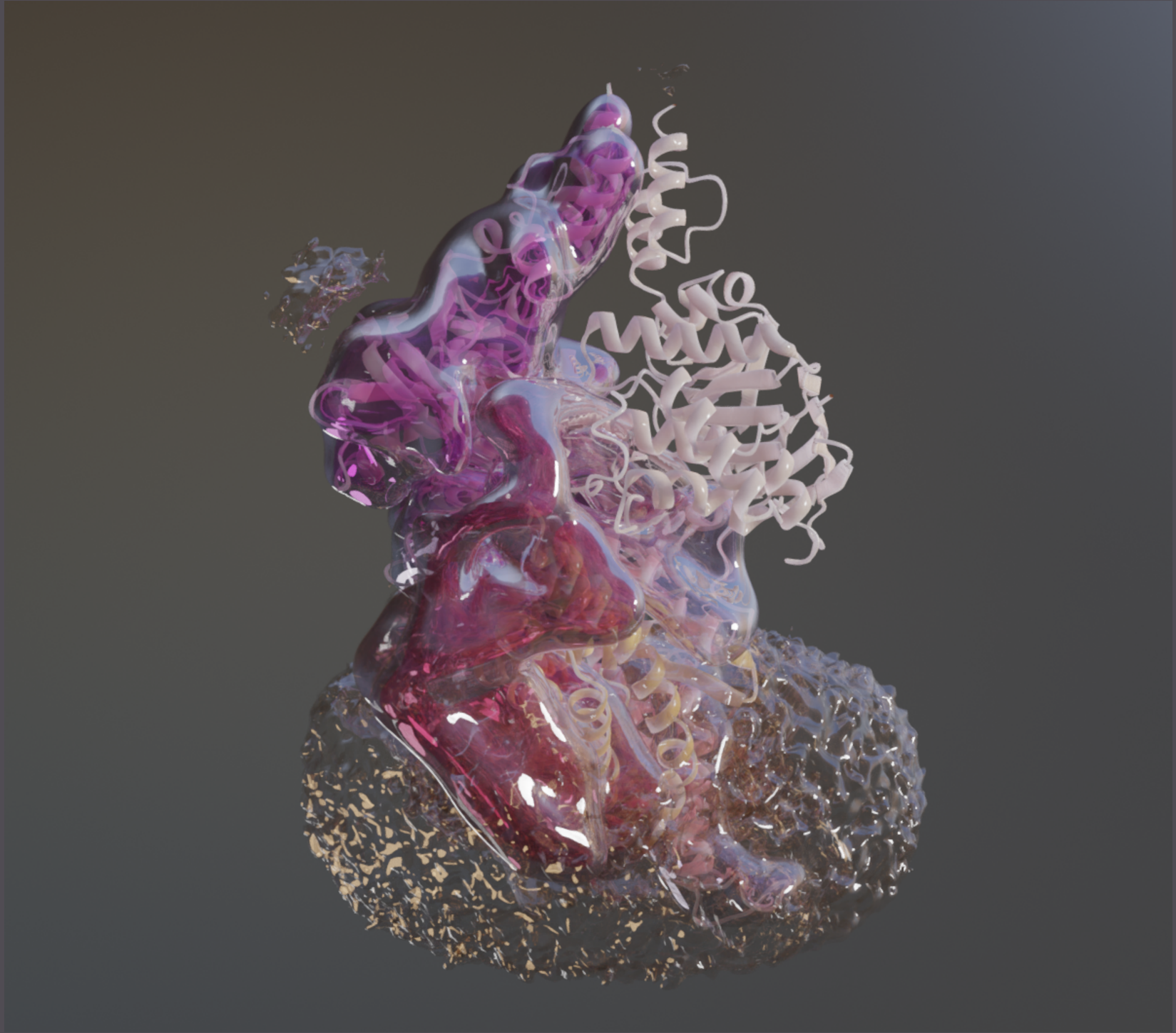


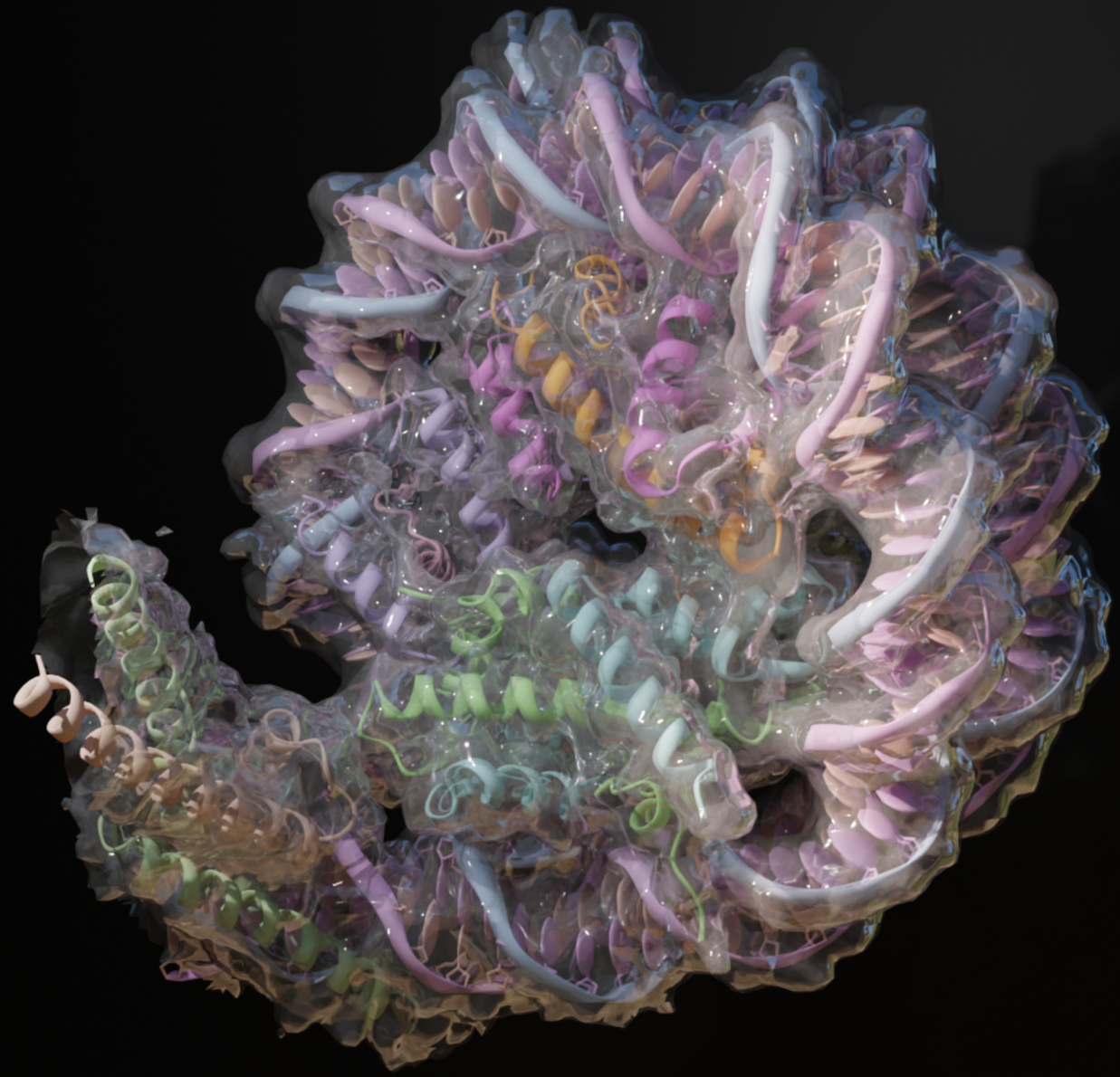












Ligands: Acedrg

- Acedrg is a generator of stereochemical descriptions
  - *i.e.* ligand (and polymer) dictionaries
- Derived from structures in the (Free) COD
  - exquisitely details atom types

Long *et al.* (2017)

https://doi.org/10.1107/S2059798317000067

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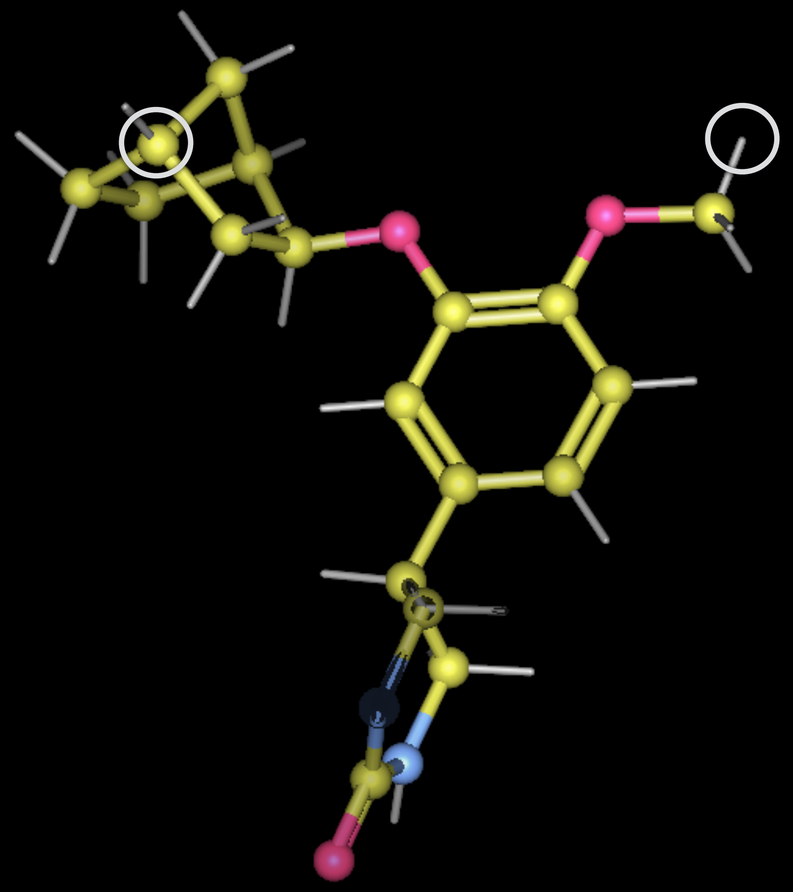
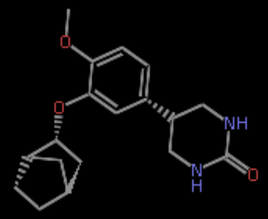
Acedrg: 2nd Order Neighbours



H1B: H(CHHO)
C9: C[5,5,6](C[5,5]CHH)(C[5,6]CHH)(C[5,6]CHO)(H)



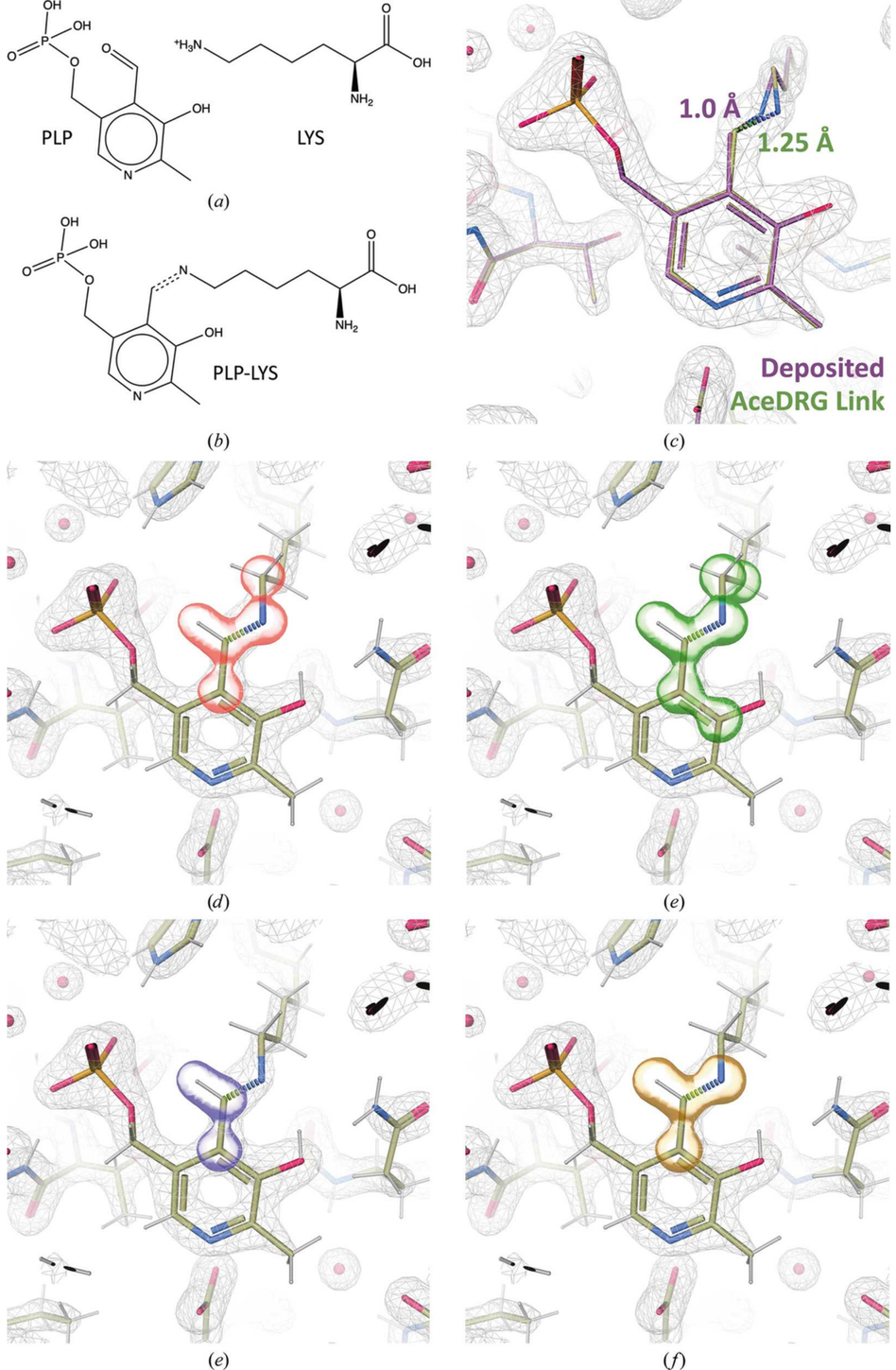
Links

- Modelling covalent interaction between compounds in macromolecular structures requires specialist knowledge/considerations
  - Previously used basic atom types and dictionary lookups
  - Now Acedrg does this for us automatically using COD atom types

- Modelling covalent linkages in CCP4
- Nicholls *et al.* (2021)
- https://doi.org/10.1107/S2059798321001753

Acedrg Link Mode in Action

Red: Bonds and Angles
Green: Torsion Angles
Blue:Planar Restraints Removed
Orange: Planar Restraints added



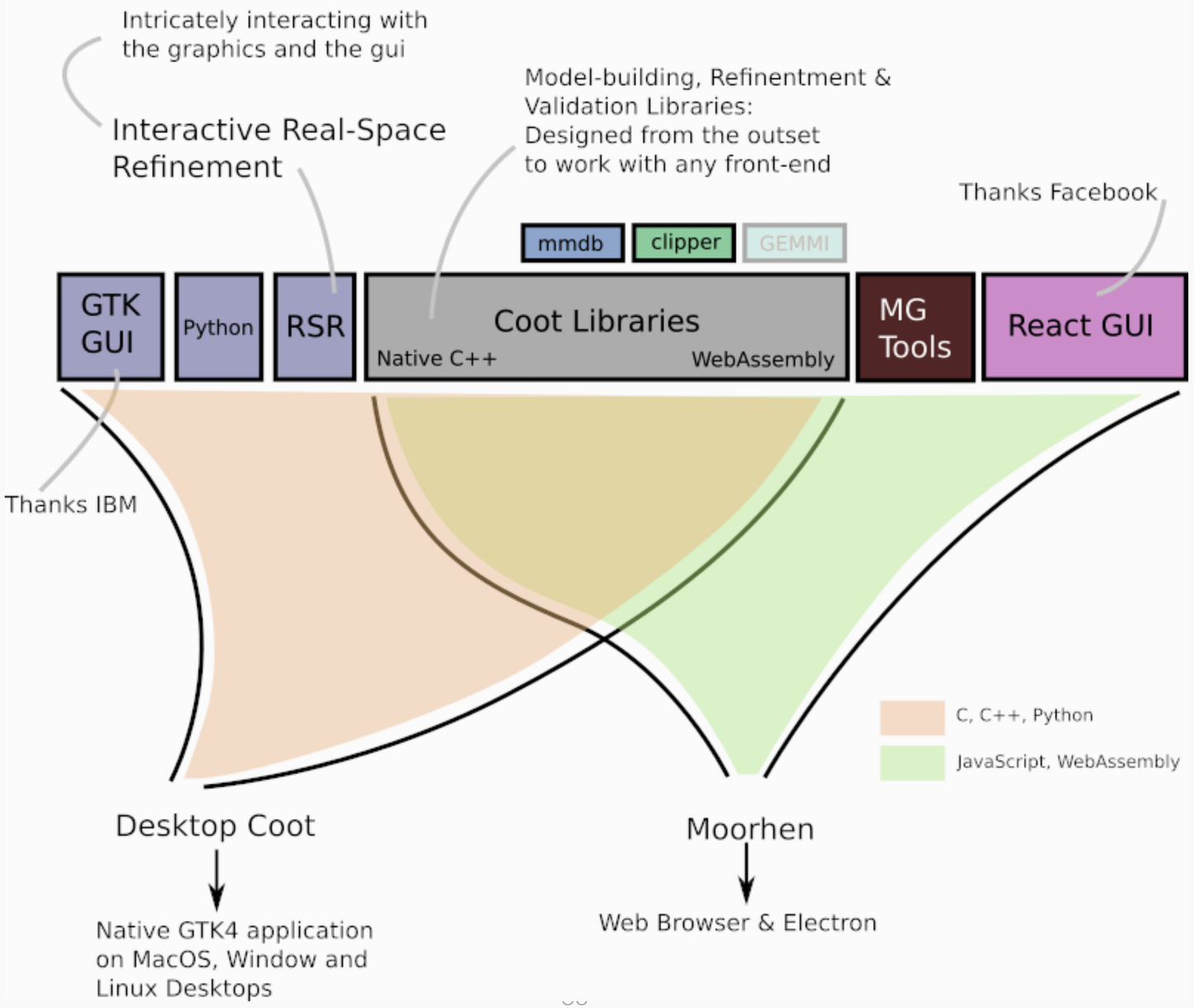
Nicholls *et al.*
Volume 77 | **Part 6** | June 2021 | Pages 712–726 | 10.11107/S2059798321001753

Part 3: Moorhen/webCoot

Moorhen/webCoot

- Moorhen is “Coot in the web browser”
- CCP4 Cloud needed interactive modelling tools
- Left-mouse for view rotation and picking
- Right-mouse for context menu
- User-interface is written in React
  - So it has a “modern” feel

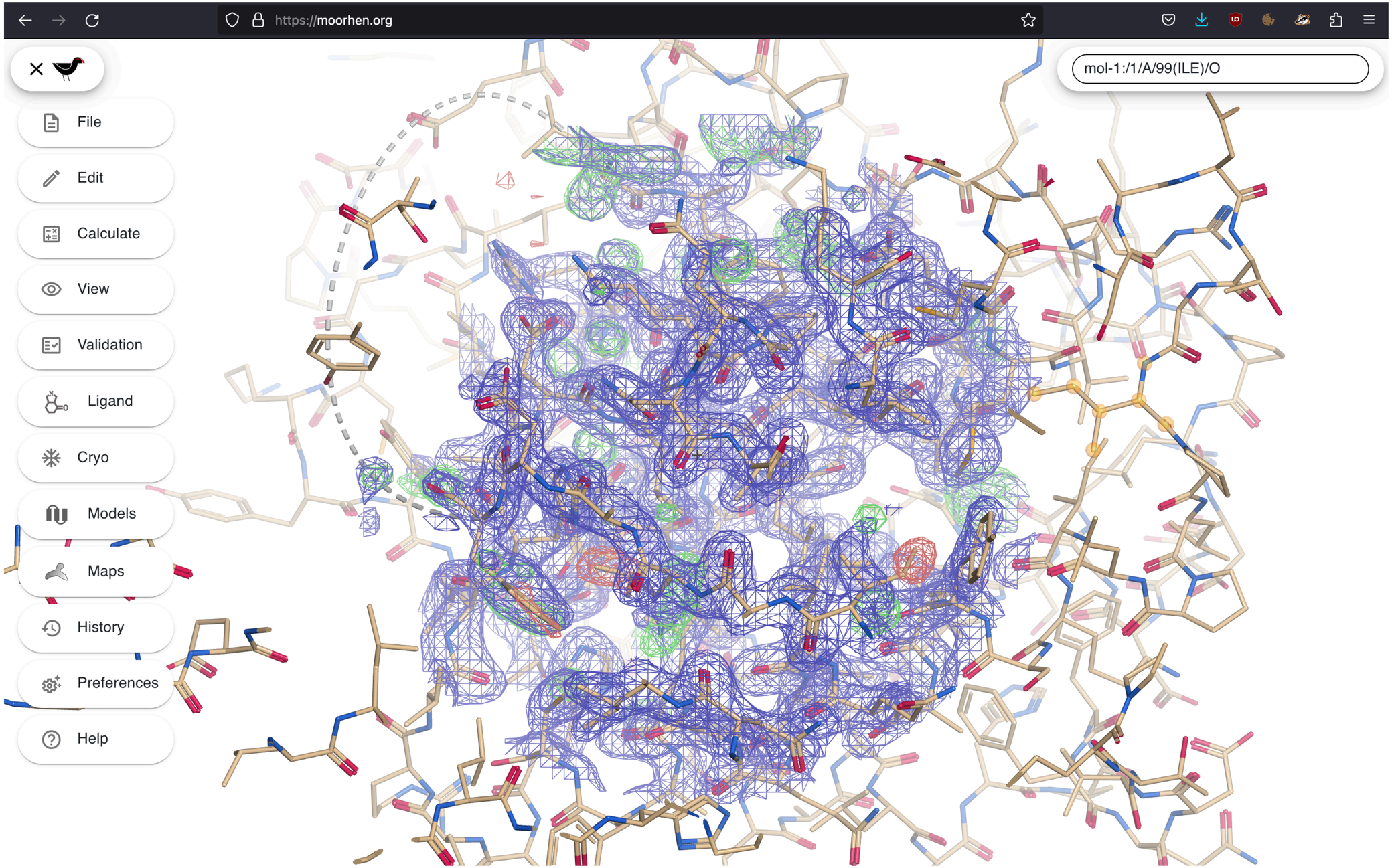
Coot *vs*. Moorhen



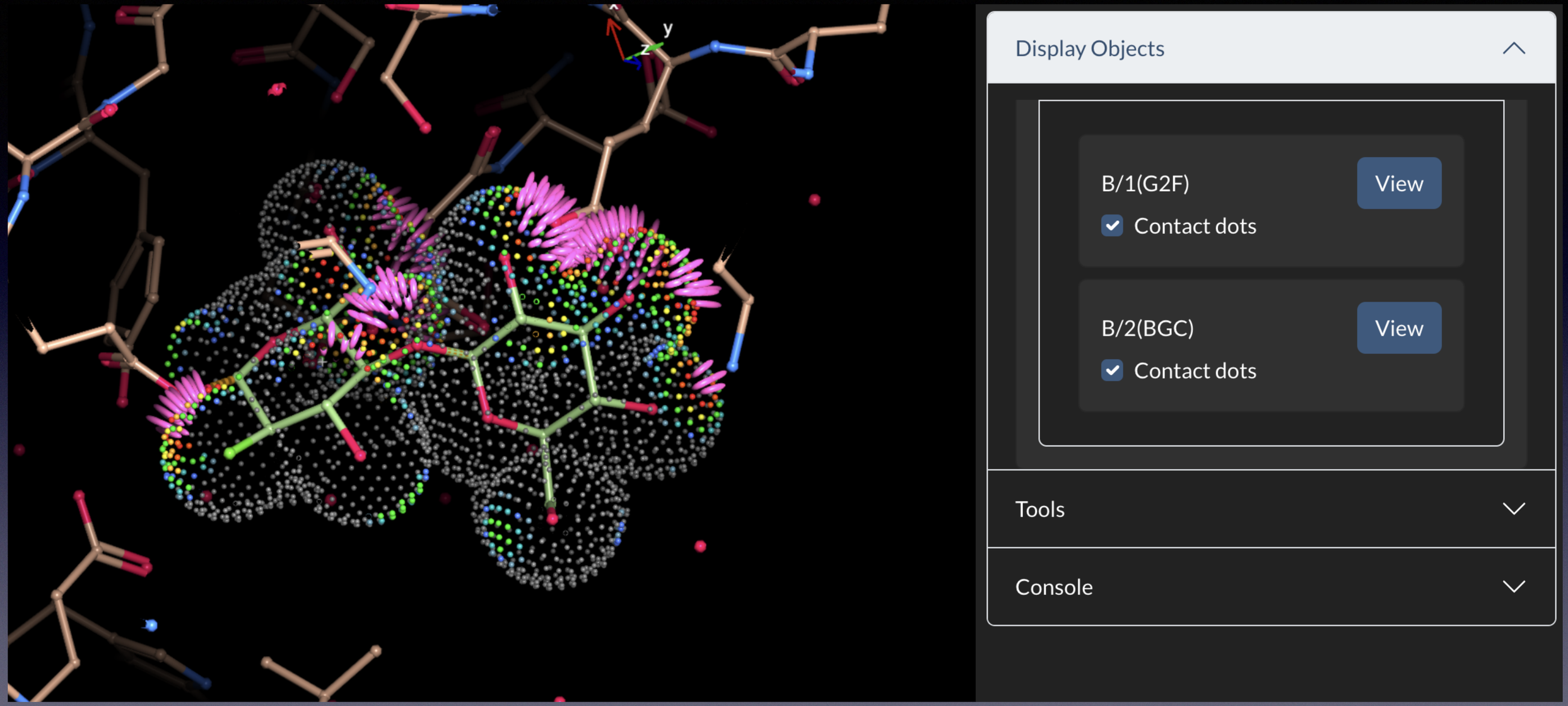
What can Moorhen do?

- Add, delete & mutate residue
- Real Space Refinement
- Rotamer fitting
- Peptide flipping
- Ligand fitting
- Add waters, validate waters
- Density and model validation

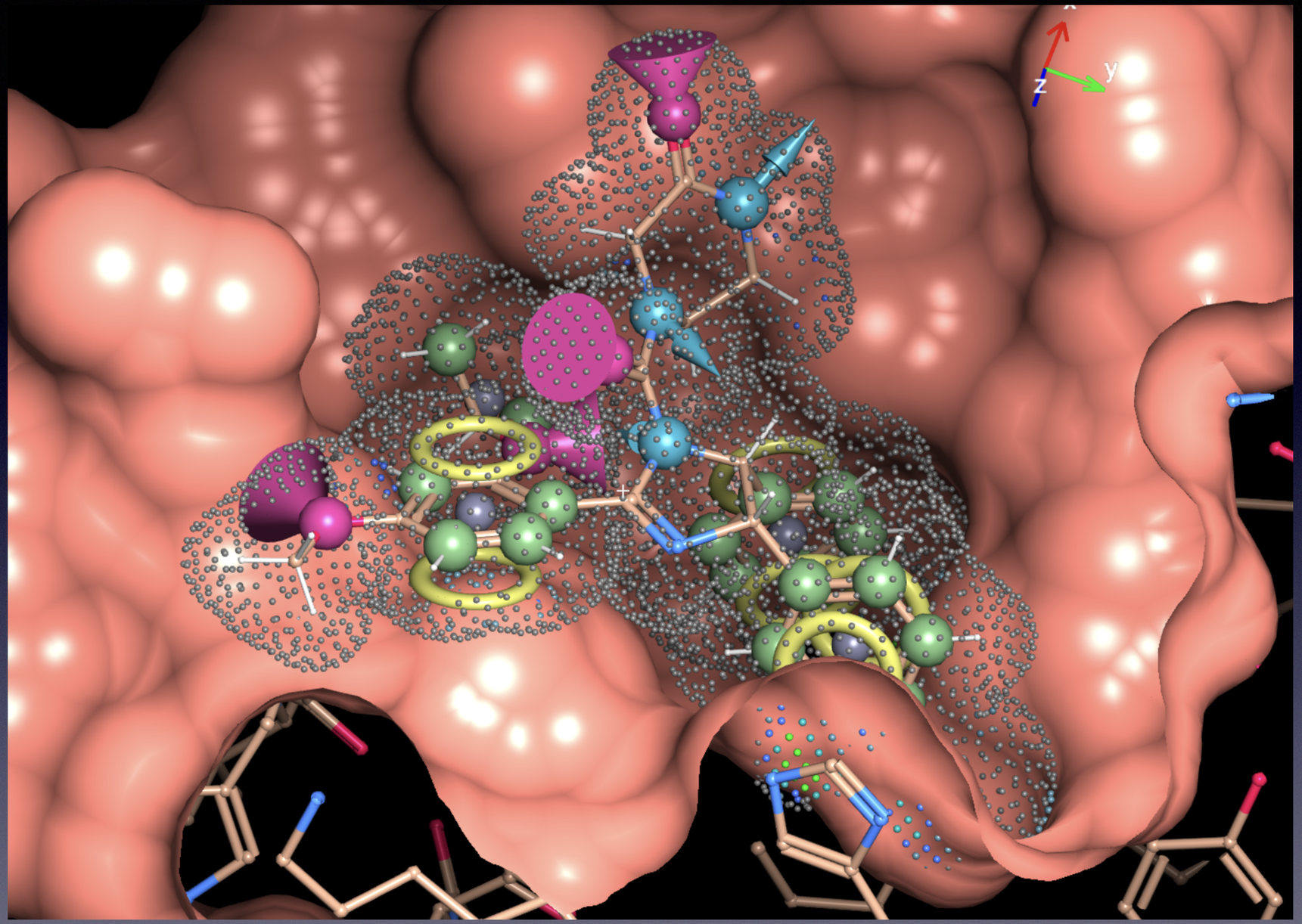
Moorhen on startup



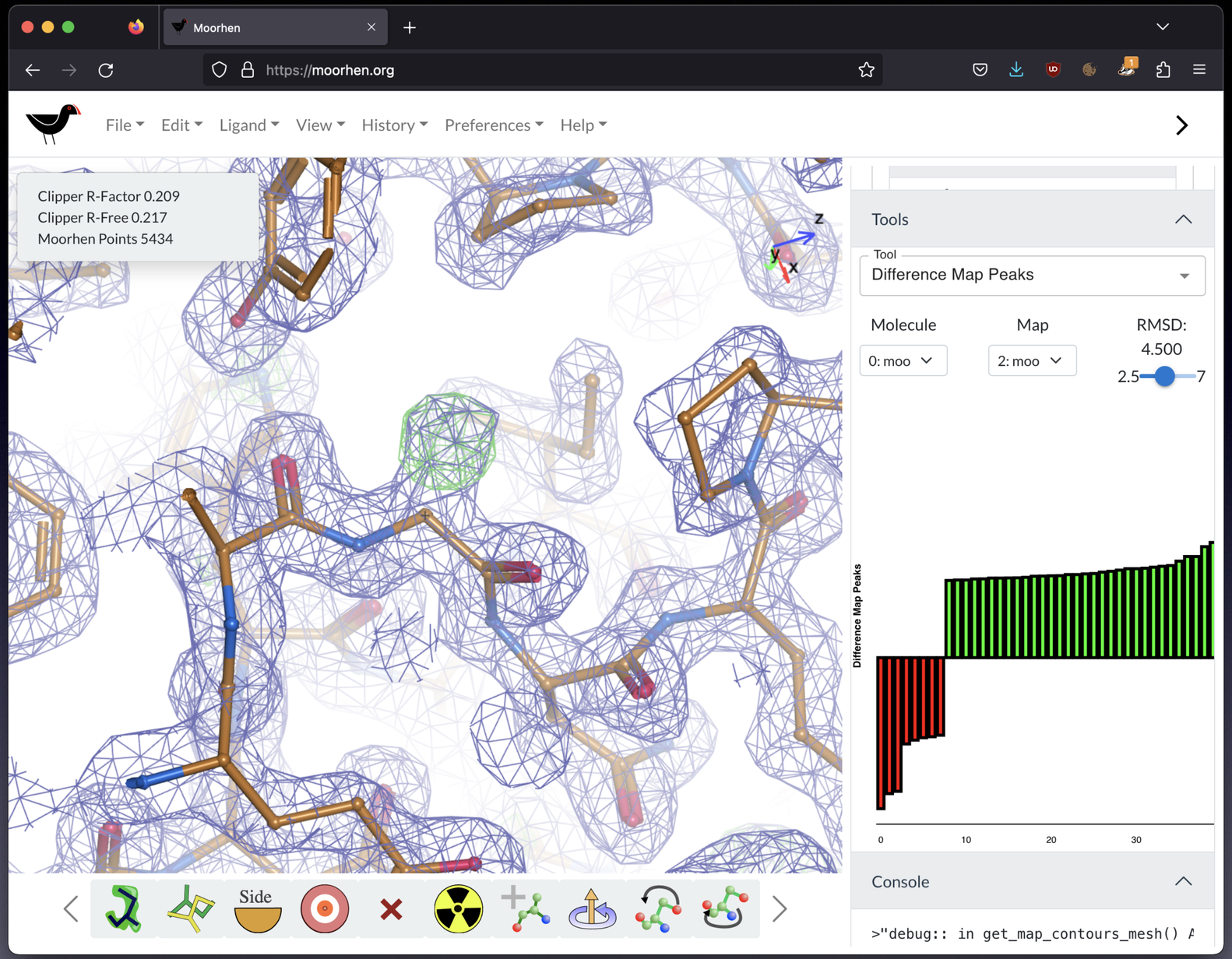
Moorhen Transparent Maps



Moorhen with contact dots



Moorhen with Ligand Chemical Features



Collecting “Moorhen Points” is fun

Acknowledgements

- **LMB**

Garib Murshudov

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- **Moorhen Team**

Stuart McNicholas

Filomeno Sanchez-Rodriguez

Martin Noble

Lucrezia Catapano

Moorhen Tutorials

- Part 1: Validation & Rebuilding
- Part 2: Making figures for publication