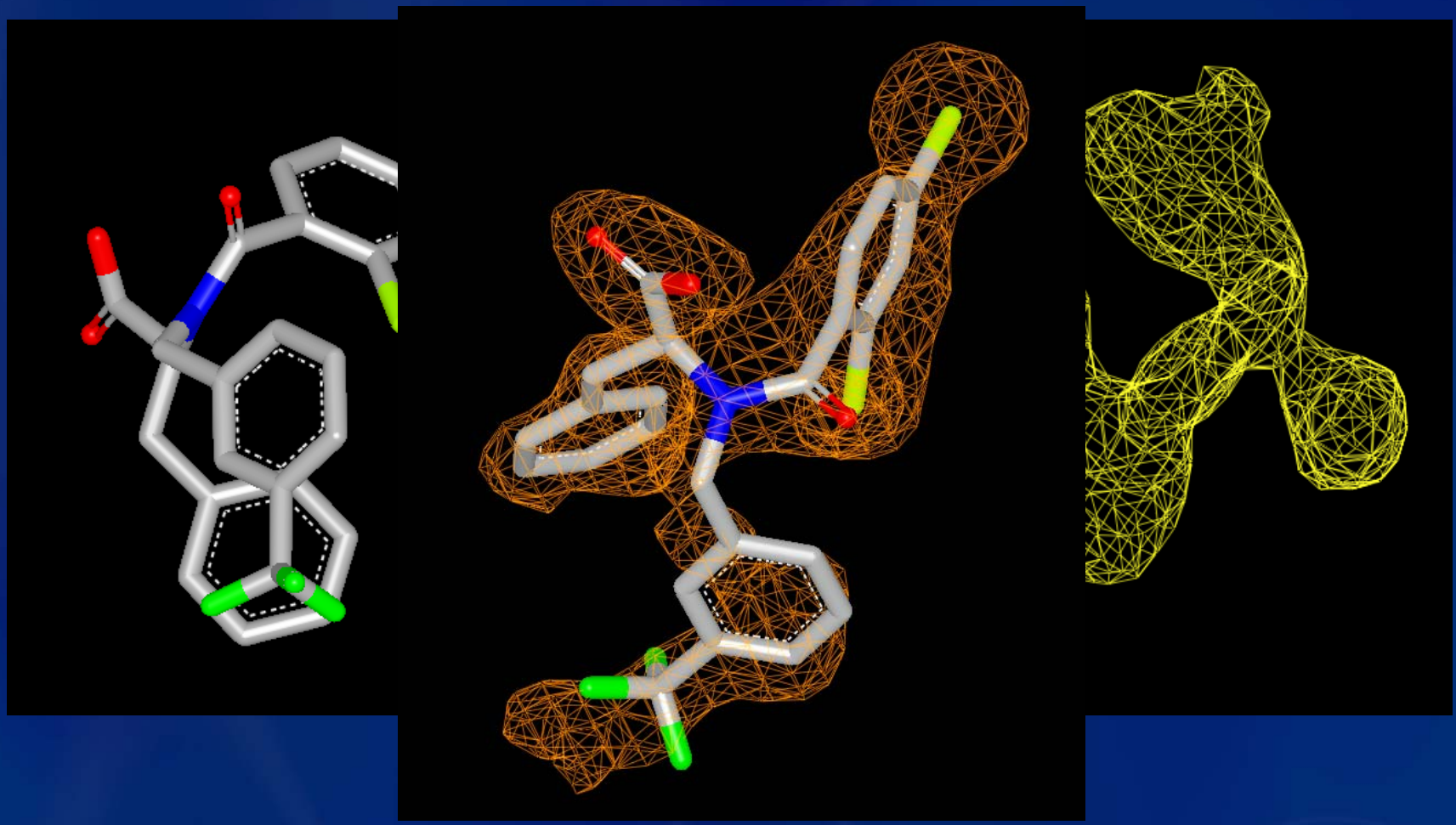
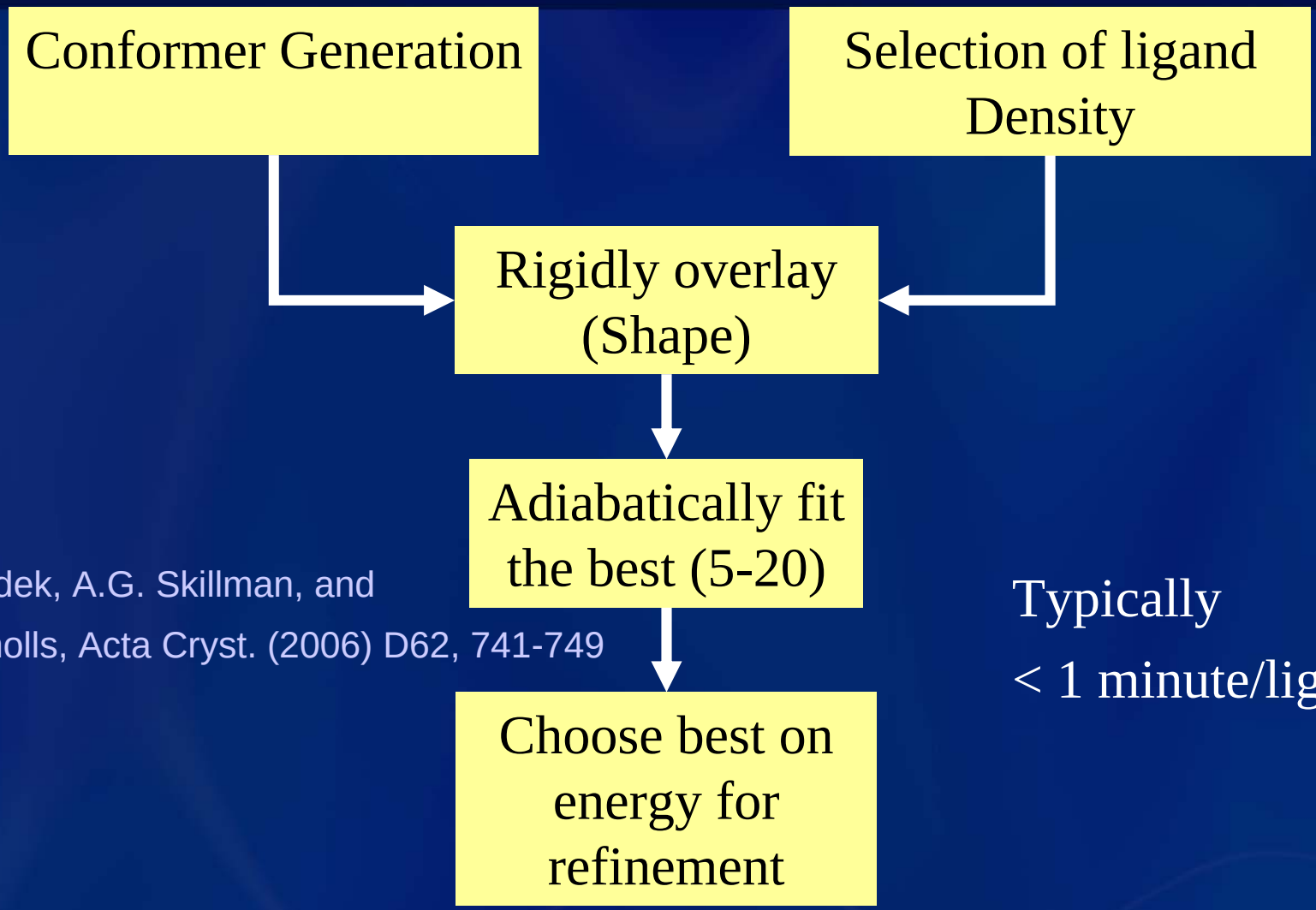
Overview of Afitt

Gregory L Warren
Senior Applications Scientist

Fitting Ligands to Density



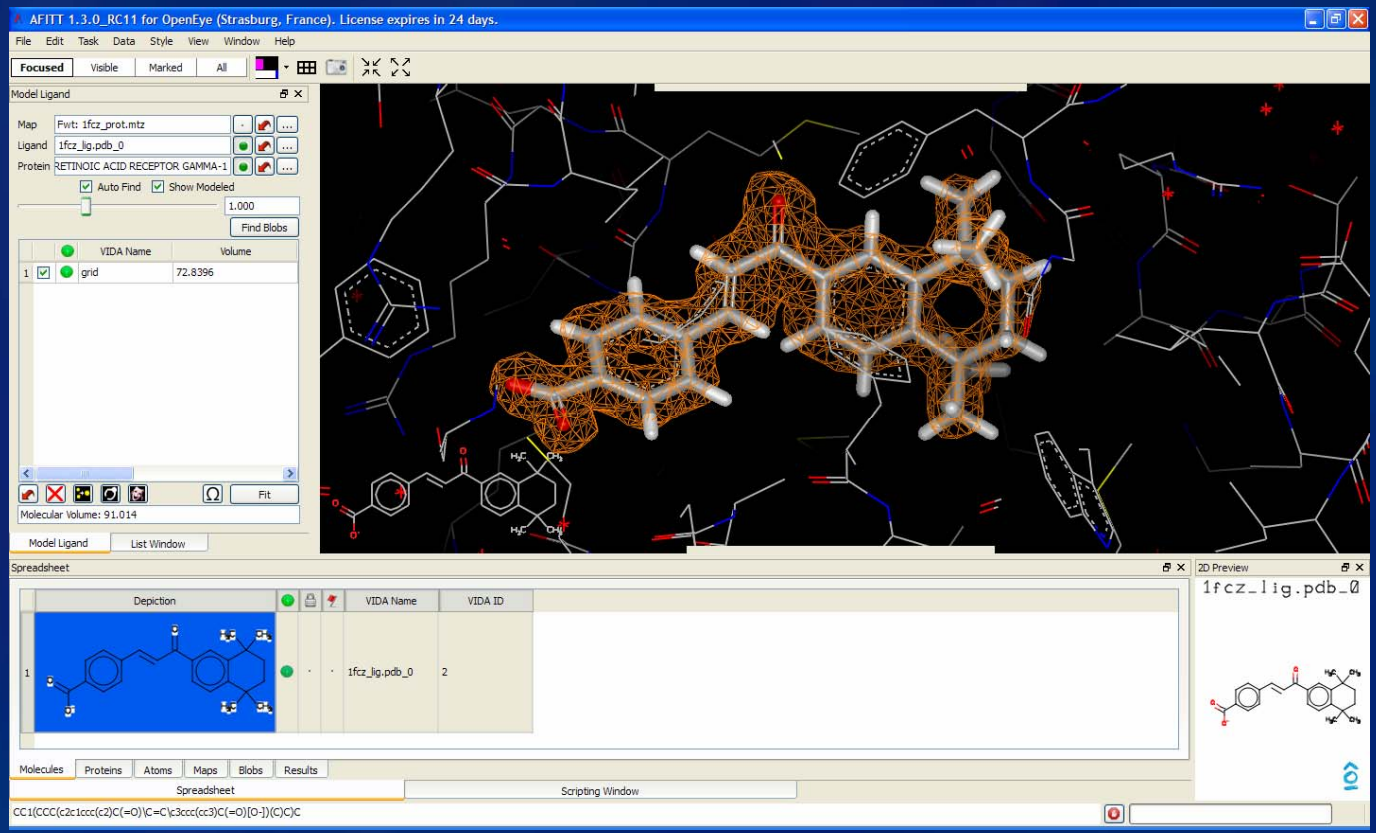
AFITT - Ligand Fitting Workflow



S. Wlodek, A.G. Skillman, and A. Nicholls, Acta Cryst. (2006) D62, 741-749

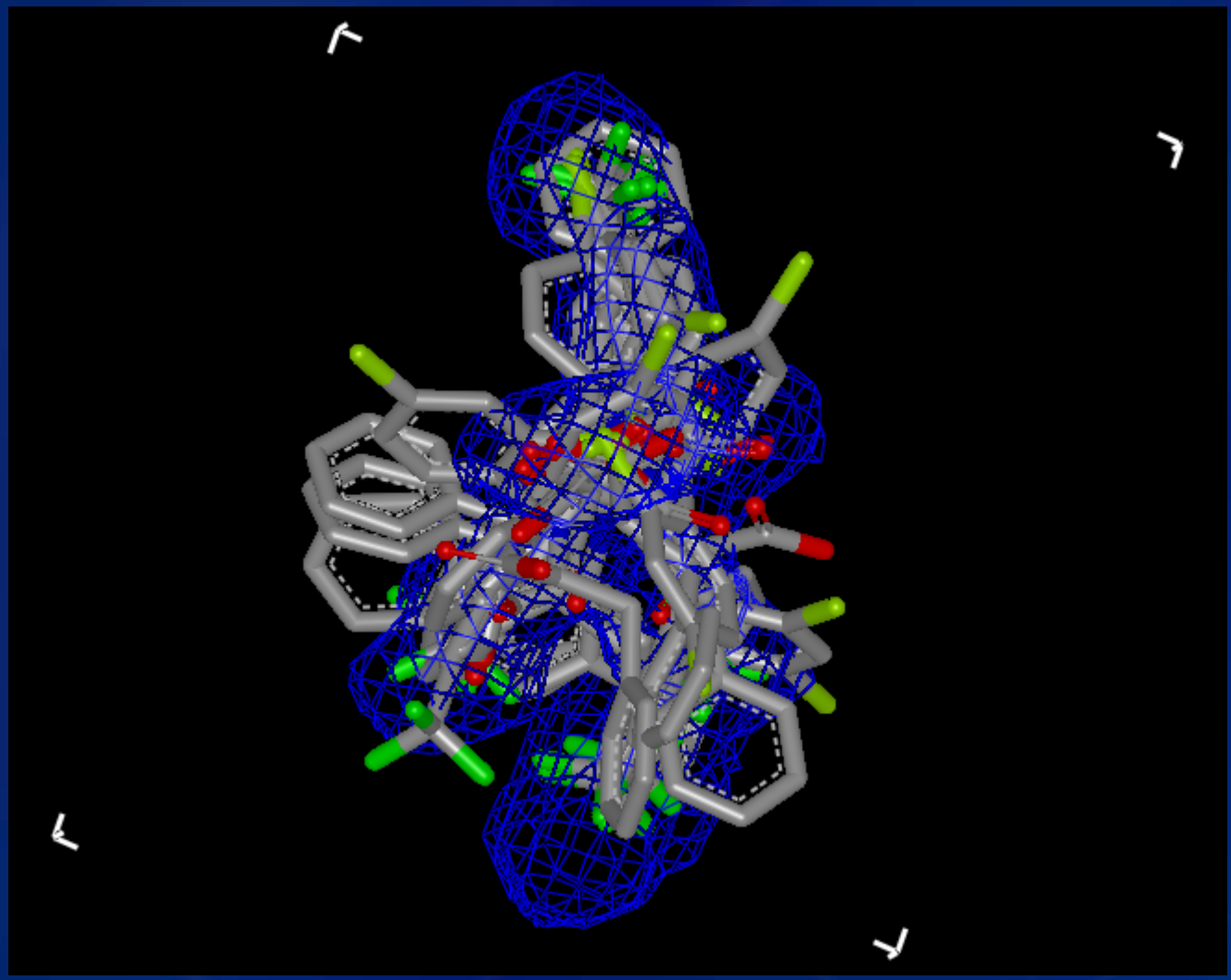
Typically
< 1 minute/ligand

Afitt - Fitting Ligands To Density

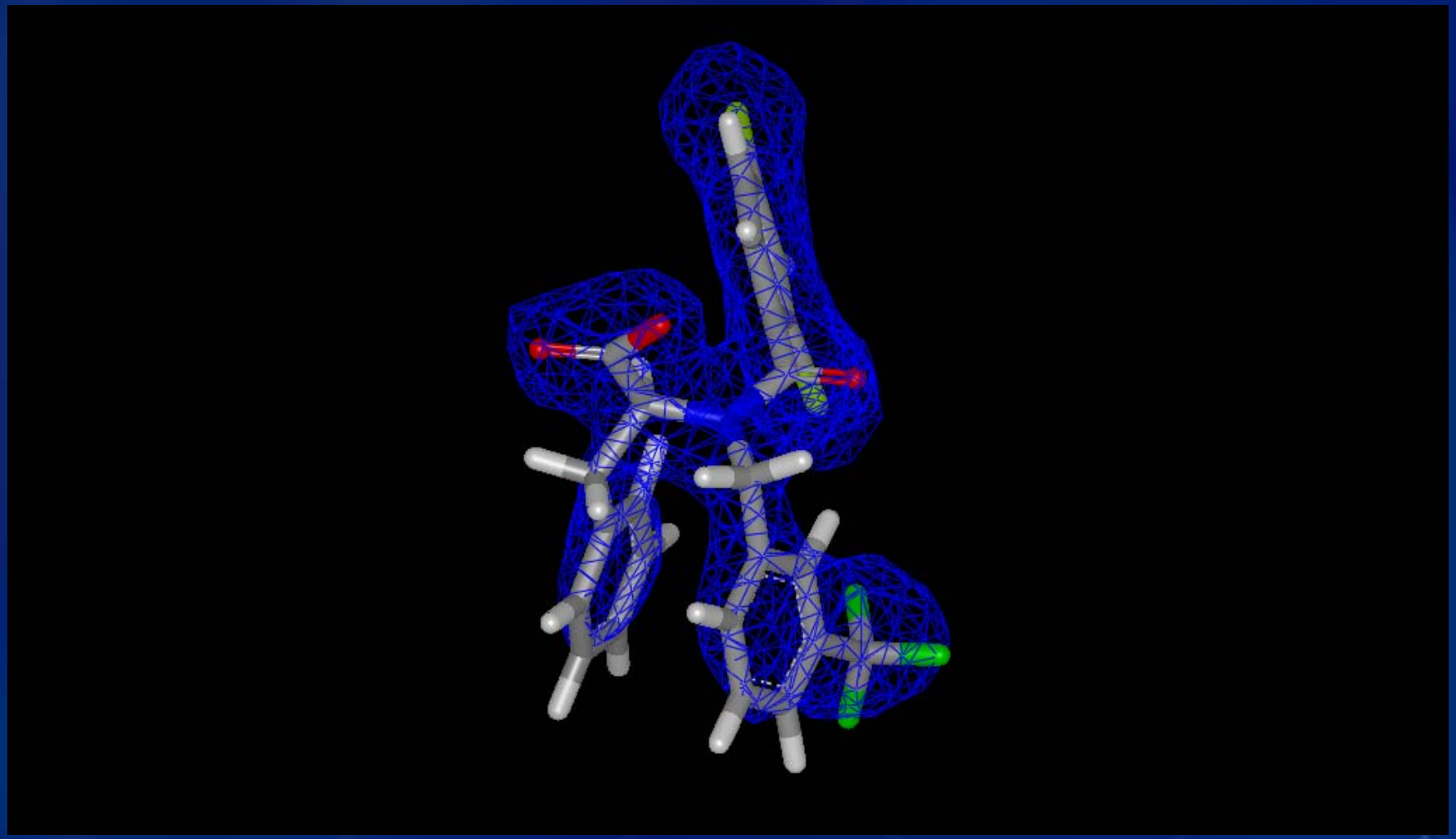


- Automatic
  - Blob (density) Finding
- Automated
  - Fitting
  - Scoring
  - thousands of poses

Multiple Solutions Generated and Scored



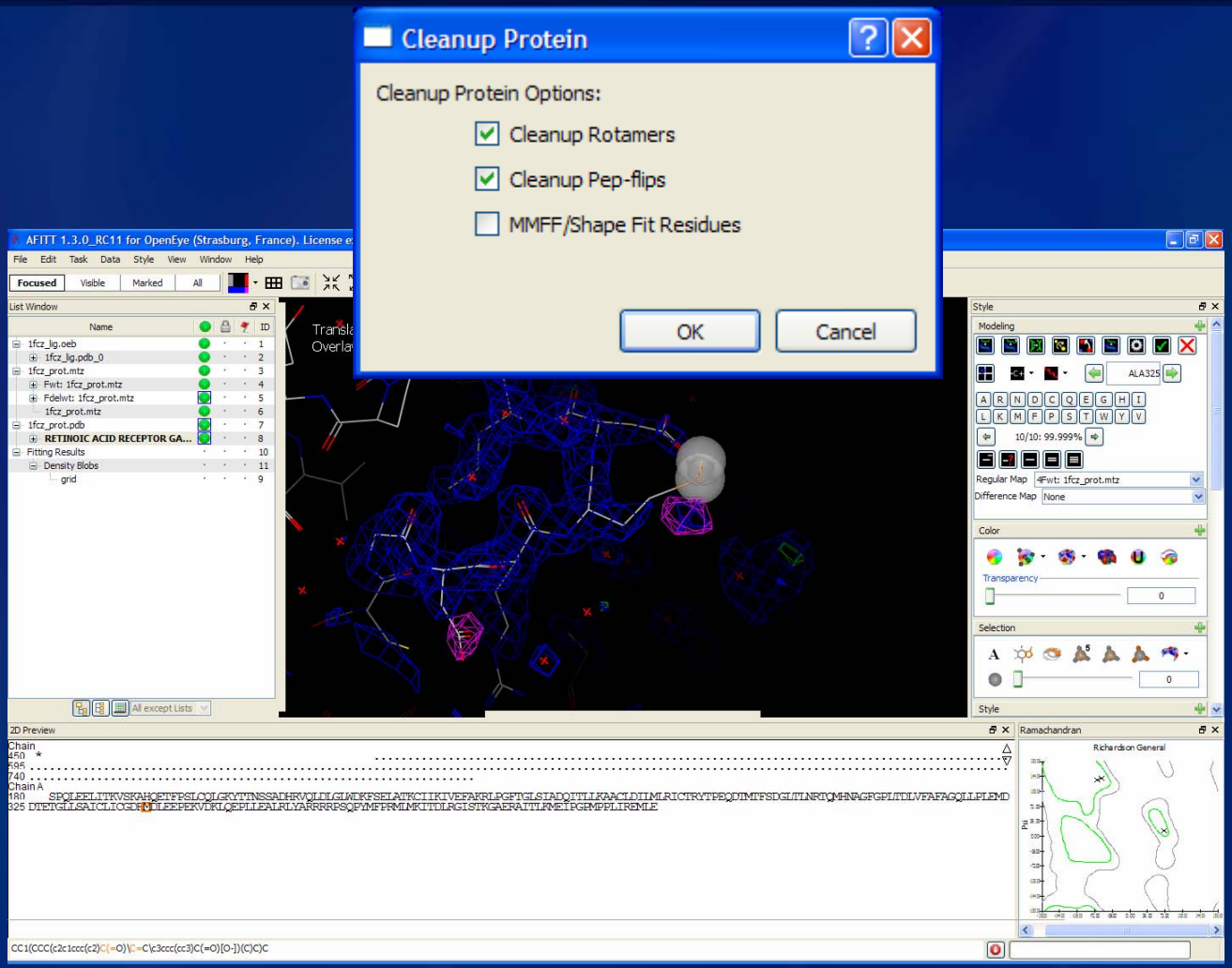
A Single Solution Selected



After initial ligand fit

- Refinement programs can change the ligand conformation
  - Poor refinement dictionaries
- AFITT writes out refinement dictionaries for popular refinement programs
  - REFMAC, CNX
  - Covalent ligands
- Fitted ligand conformation from AFITT is passed on to the next round of refinement

Automated Protein Fitting



MMFF + Shape

Rigid Shape Refinement

Best Rotamer

Automated Cleanup

Command line tools

- Flynn
- Writedict
- Coot integration

Flynn

- Command line ligand fitting
  - flynn –in ligand.smi –map density.grd –prot protein.pdb –out results.sdf
- Control blob or box
- Control map type
  - Fo-Fc, 2Fo-Fc, Fwt, Fdelwt
  - Automatic column detection (manual as well)
- Fully enumerate all stereochemistry

Writedict

- A command line tool for writing refinement dictionary

  writedict

  -in

  -out

  -assignCCP4

  -includeRotors

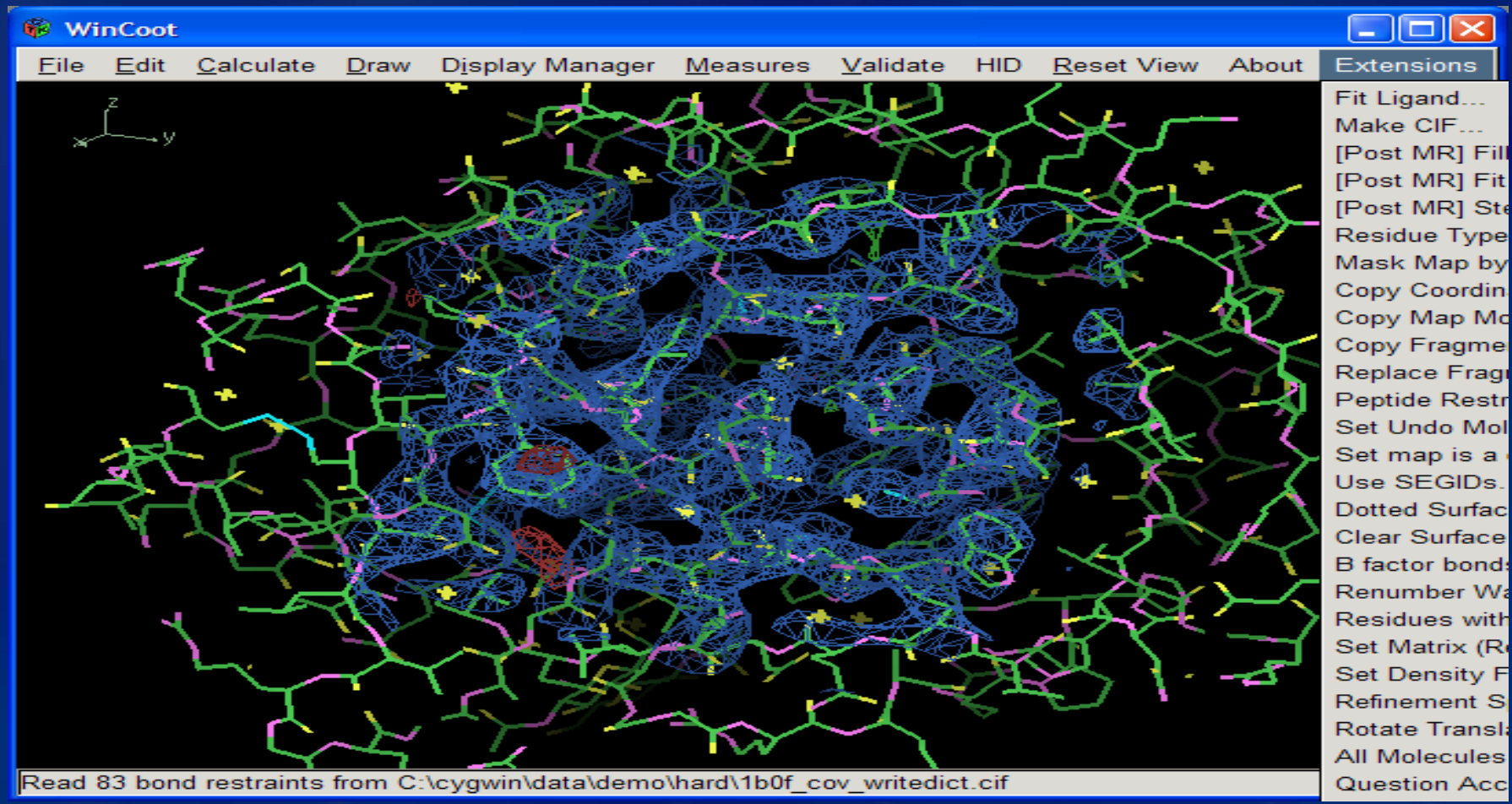
  -suppressH

  -type (CCP4, XPLOR/CNX)

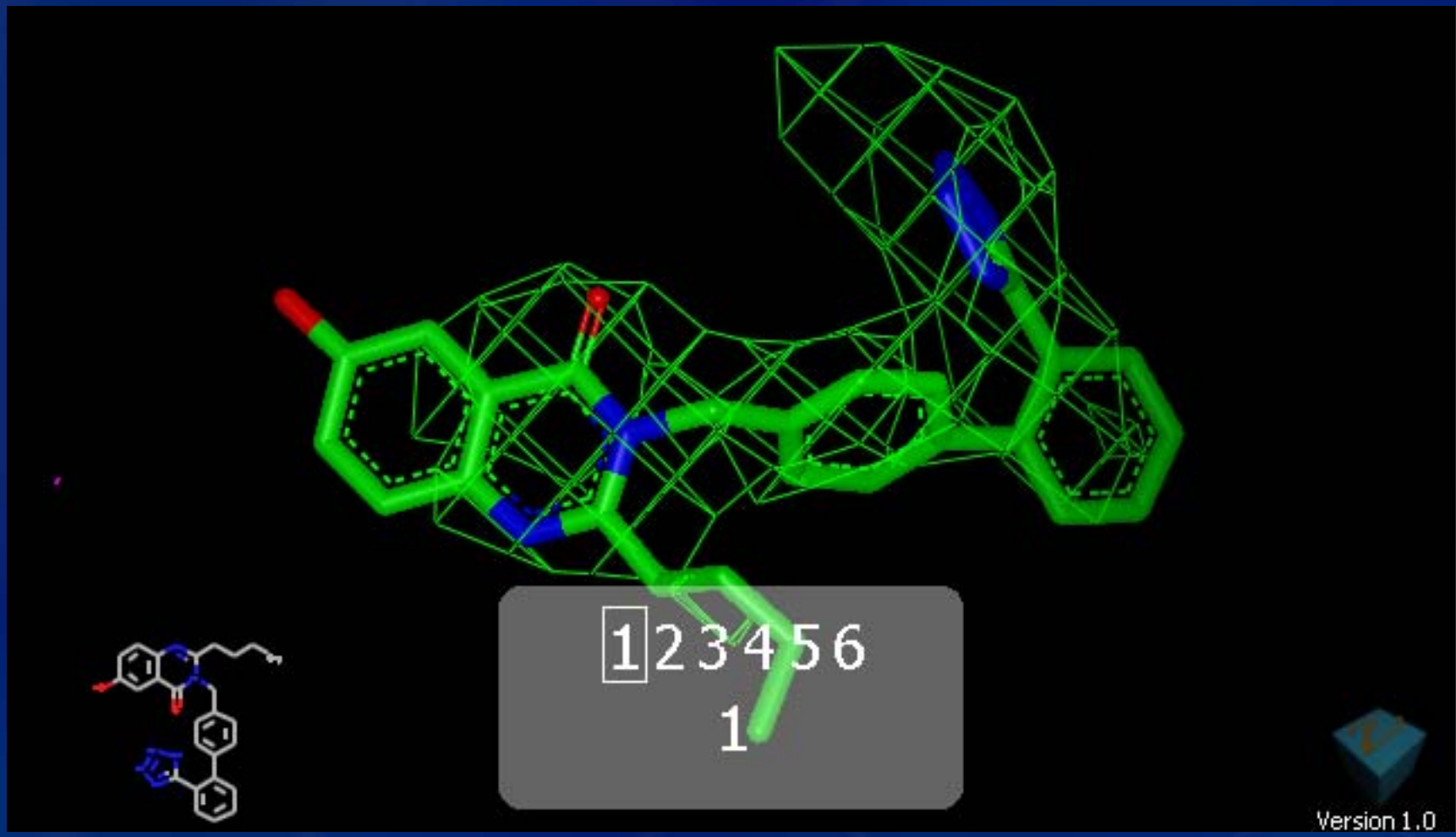
Coot integration

- Command line tools
  - Provide a method for integration
- OpenEye provides an integration for Coot and WinCoot
  - Fit Ligand
    - Runs Flynn and imports the results into the coot window
  - Make CIF
    - Generates a refinement dictionary for the selected coordinate set
    - Caveat - Does not work for covalent ligands

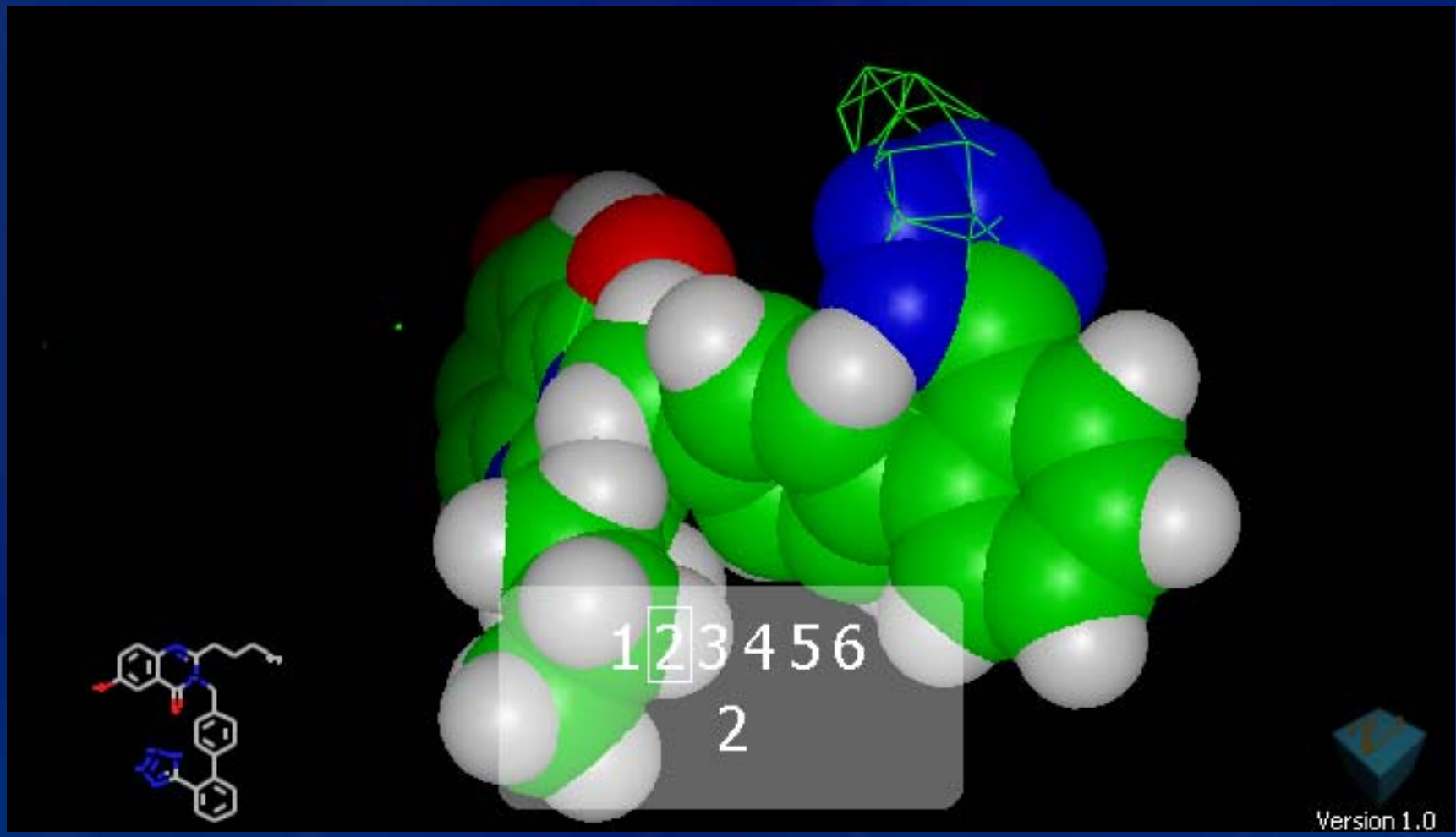
Coot integration



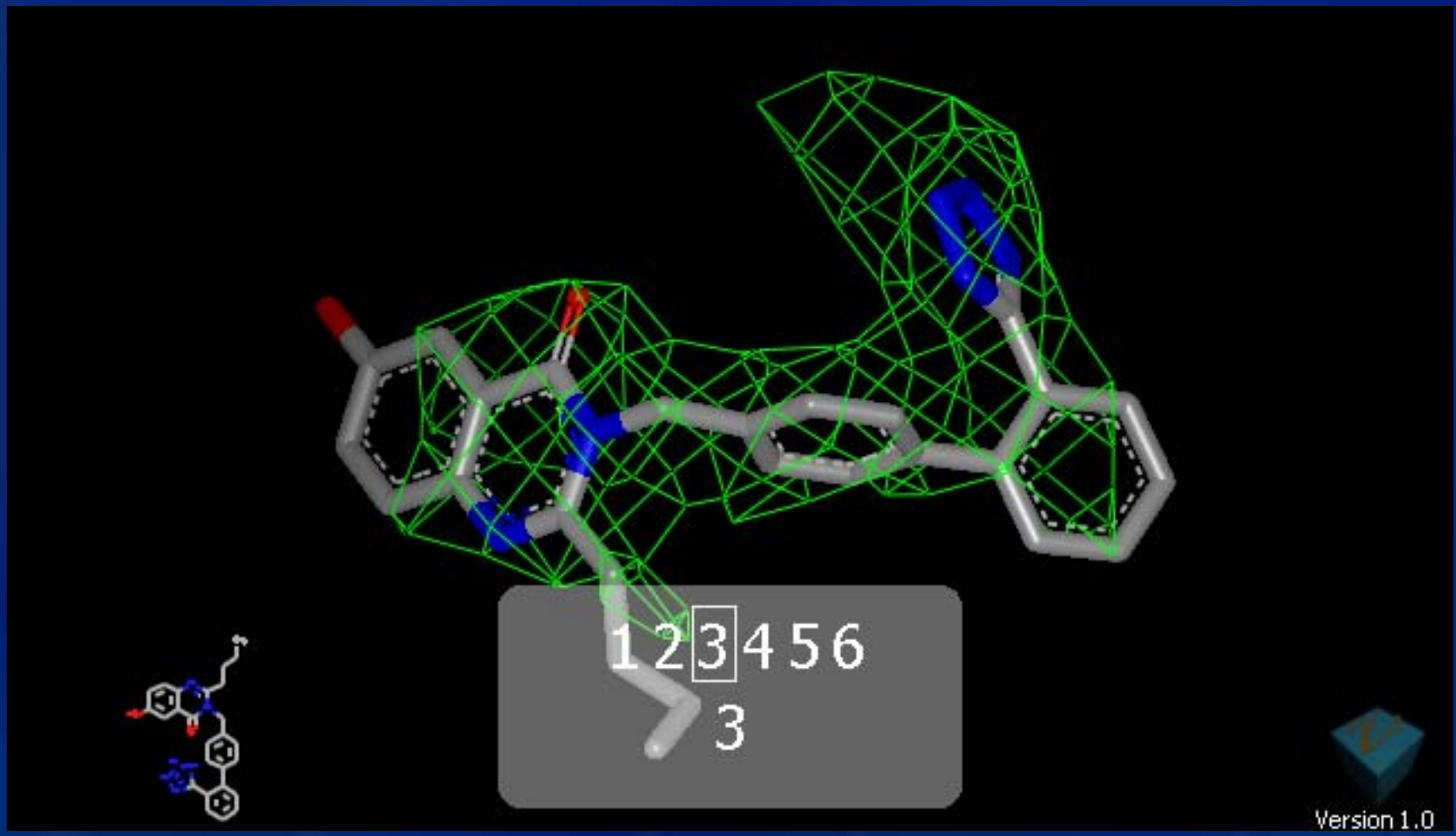
1a8t (RMSD = 0.65) ΔE=2.814



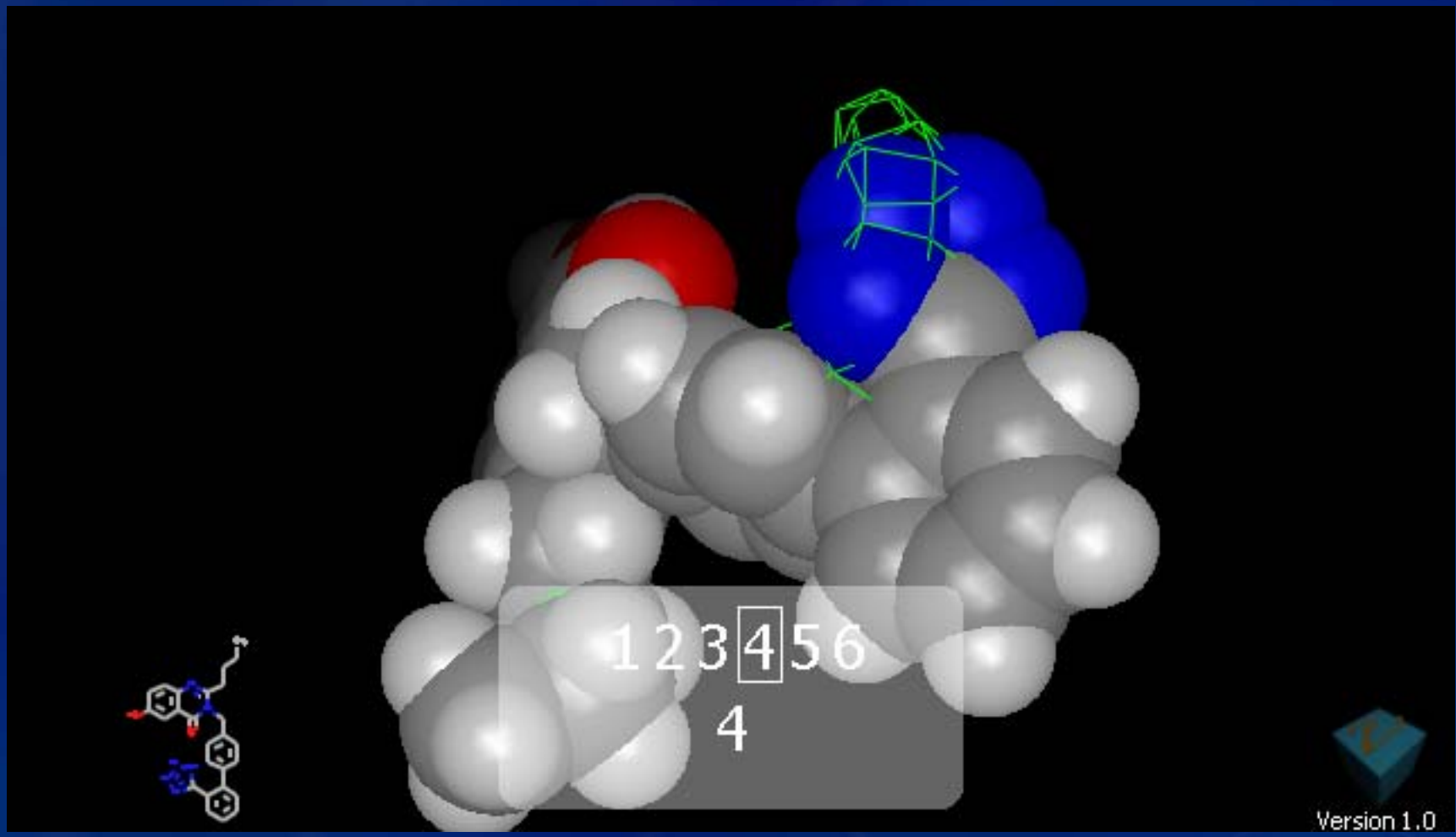
ΔE=28.4



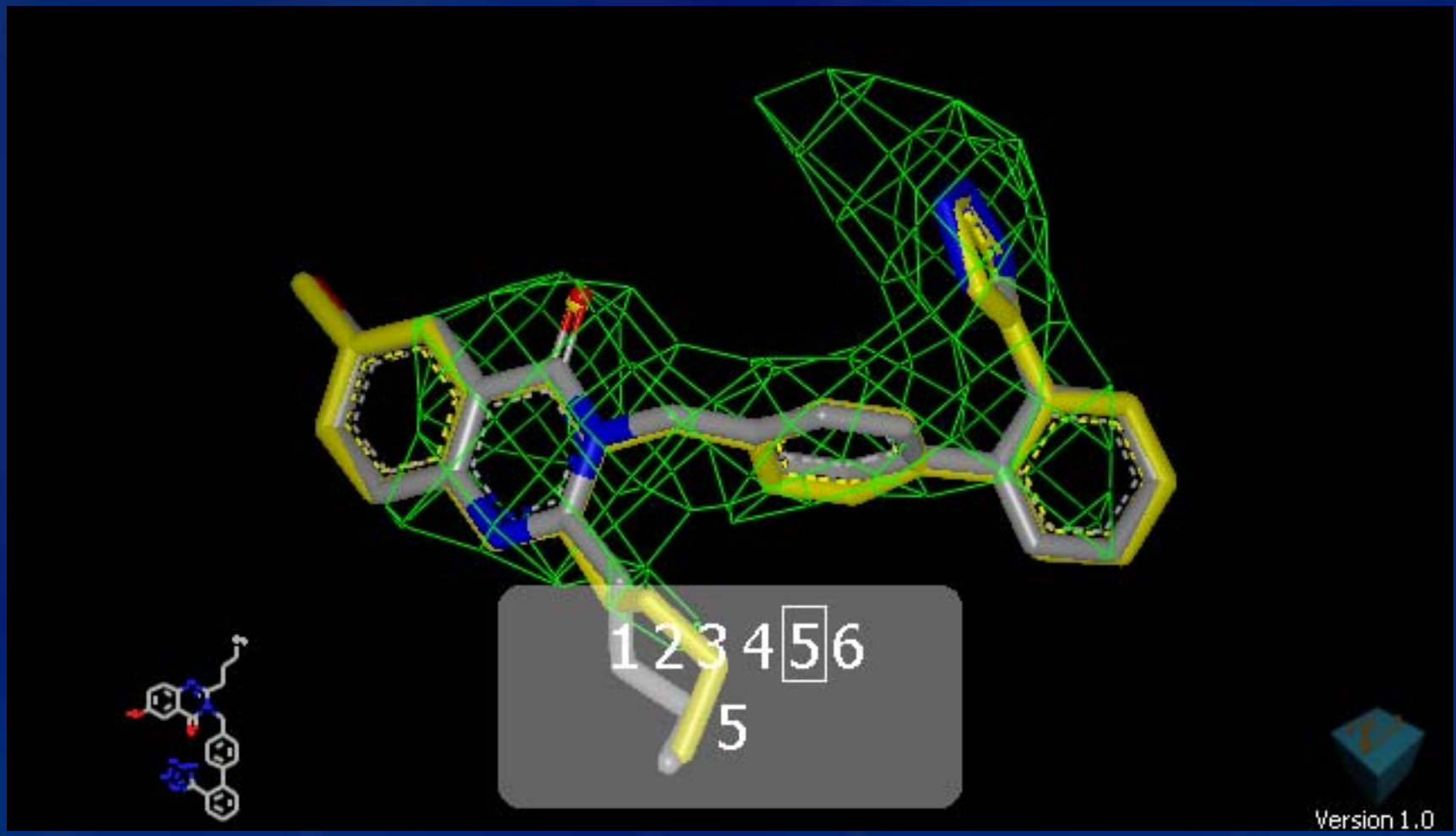
ΔE=28.4



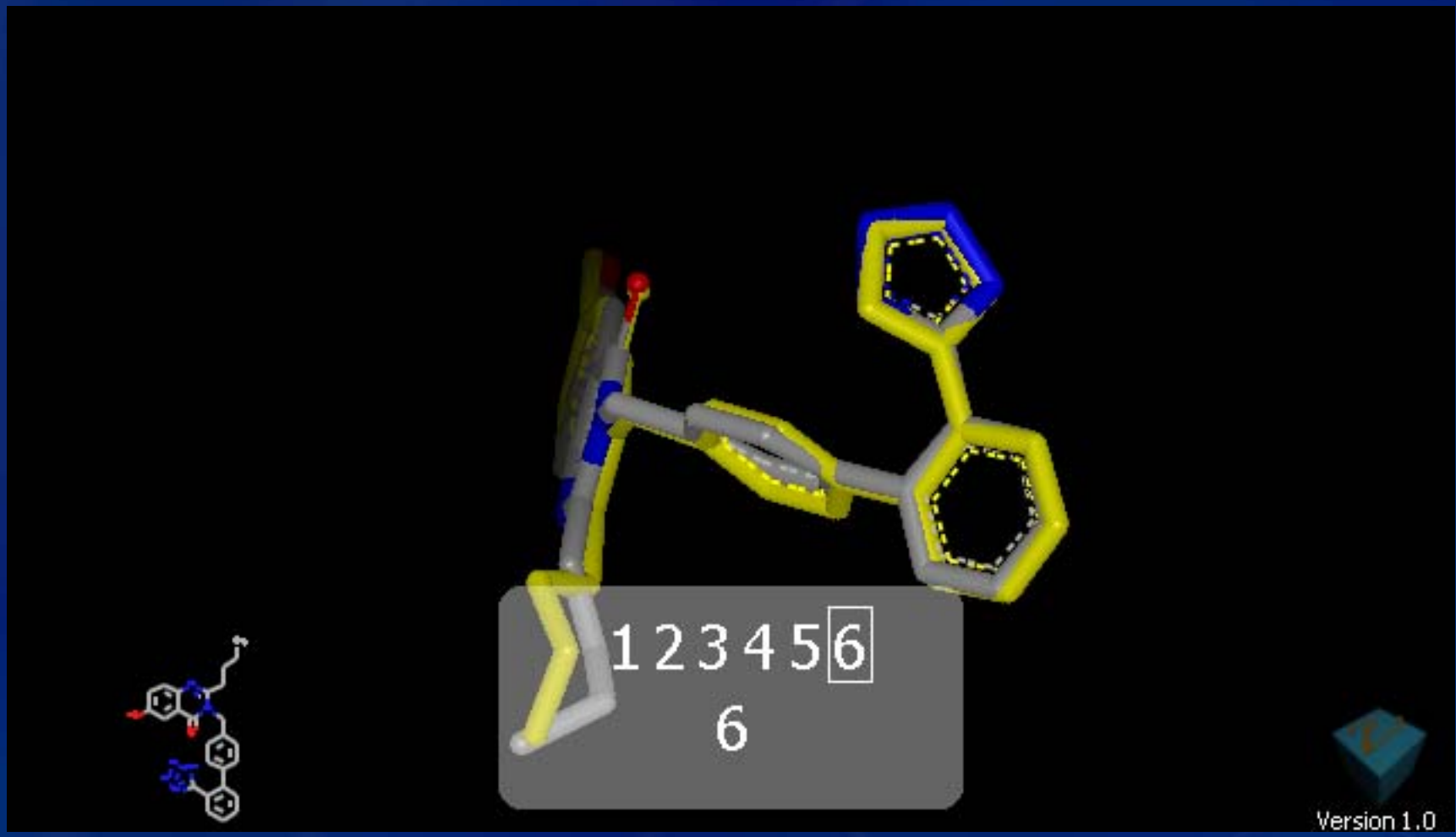
ΔE=28.4



ΔE=1.4



ΔE=1.4



Afitt – Summary

- Fitting to electron density
  - Ligand
    - Automated
      - Find ligand density
      - Generate a good ligand conformation
      - Fit ligand to density
      - Generate a good refinement dictionary
    - Manual
      - Fit ligand to density
  - Protein
    - Automated
      - Side chain rotamer search
      - Peptide flipping
    - Manual
      - Torsion angle rotation

Acknowledgements

- Brian Kelley
  - Jon Christopher
  - Tom Peat
- Matt Stahl
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