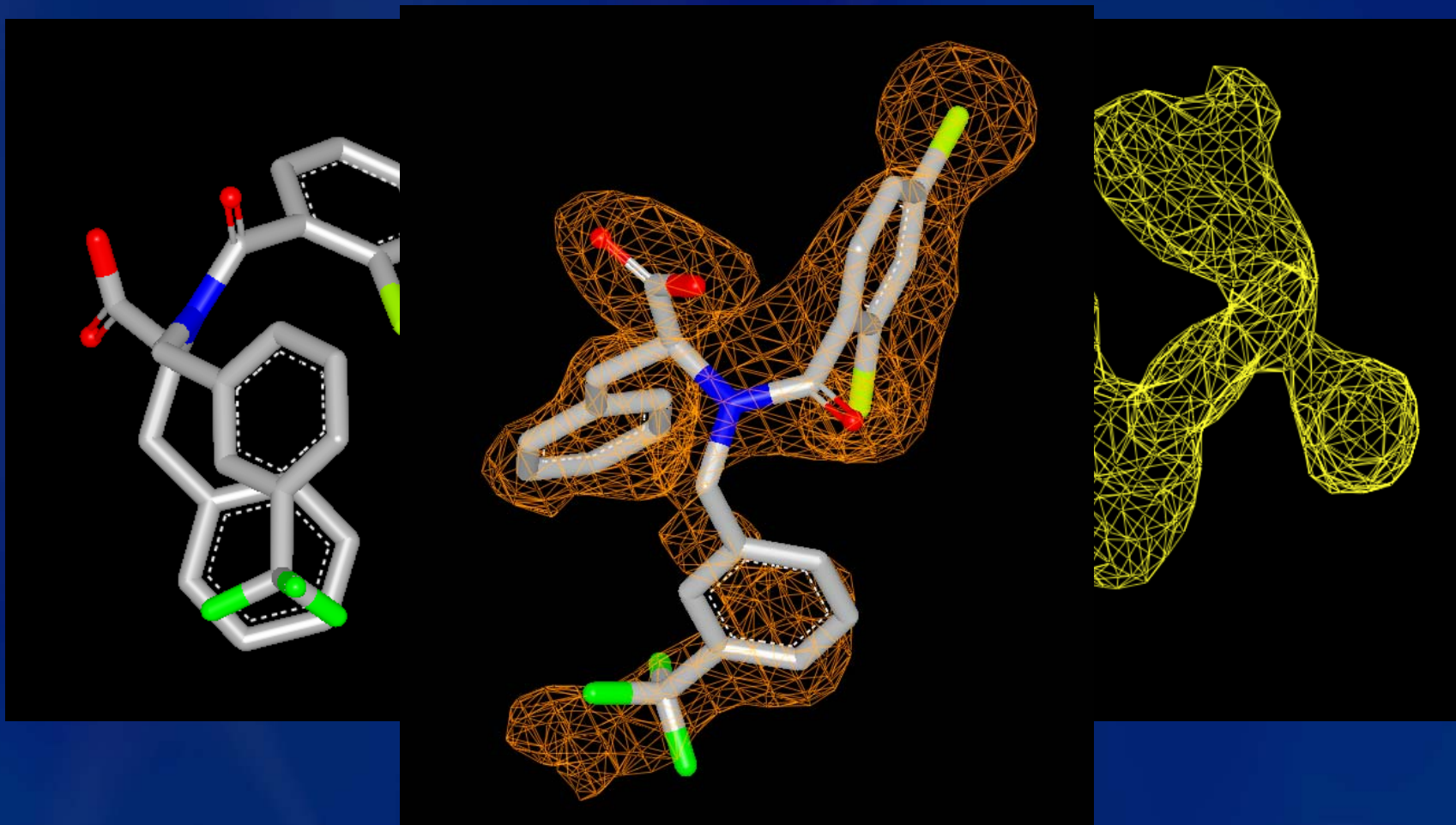


# Overview of Afitt

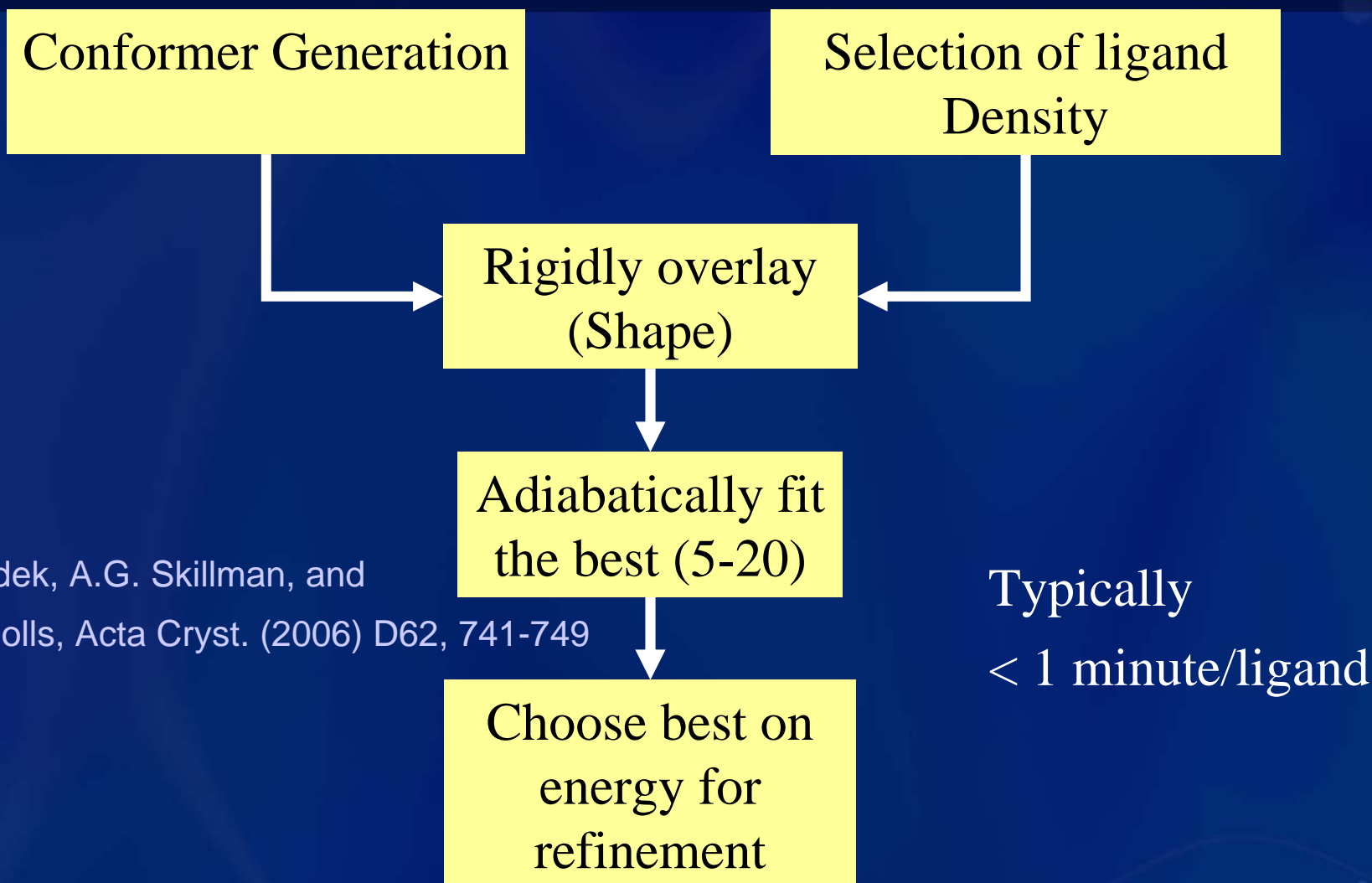
Gregory L Warren  
Senior Applications Scientist



# Fitting Ligands to Density



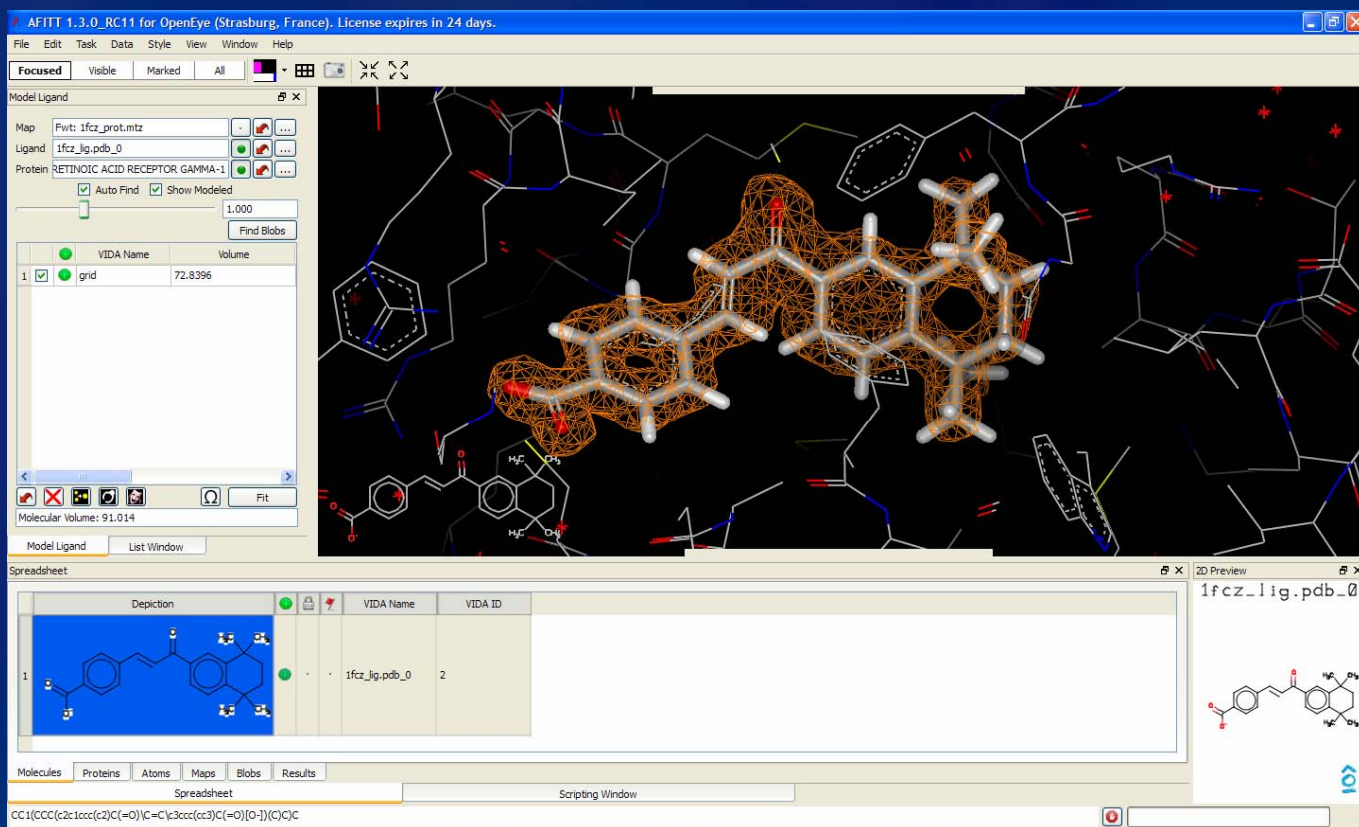
# AFITT - Ligand Fitting Workflow



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

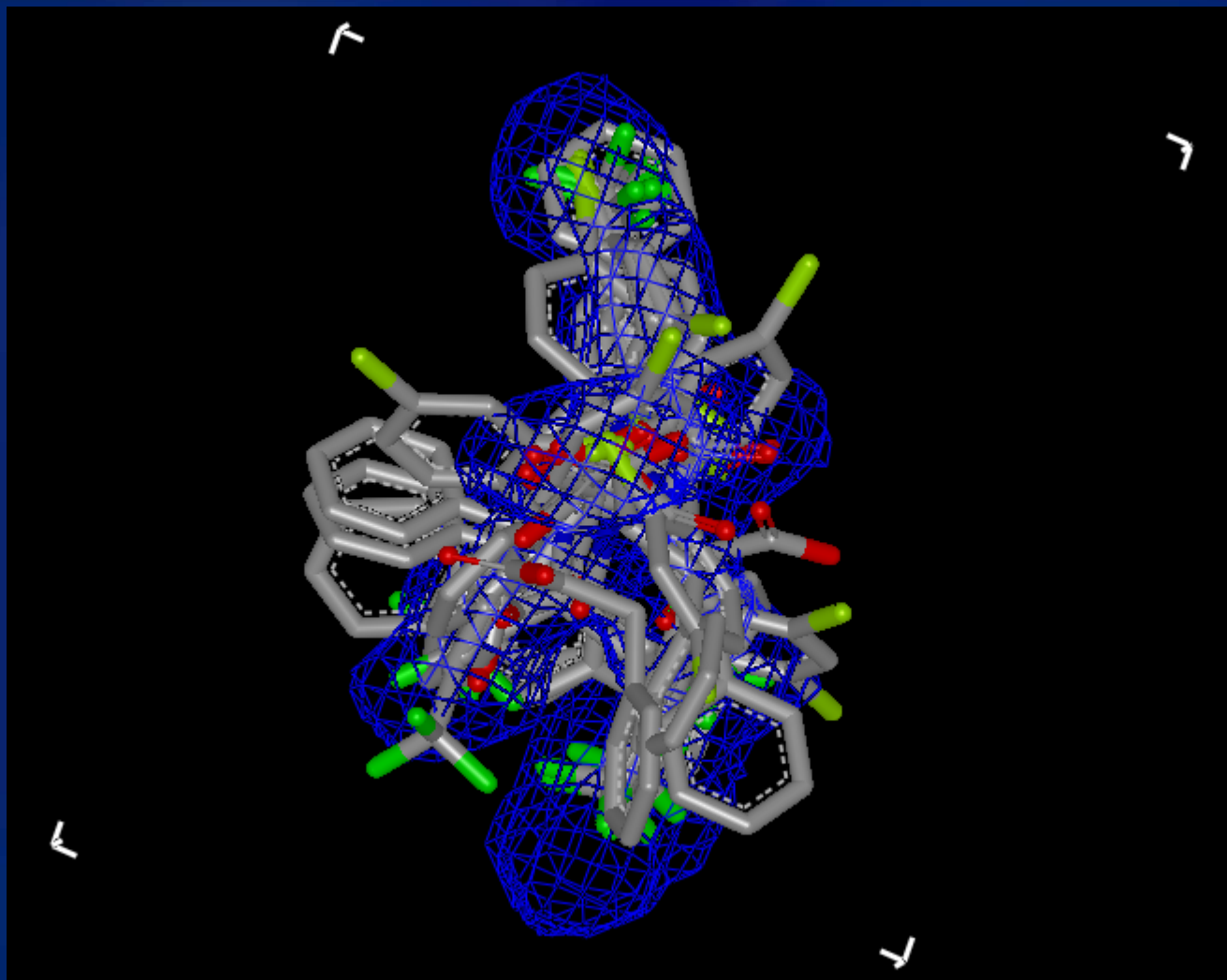
Typically  
< 1 minute/ligand

# Afitt - Fitting Ligands To Density

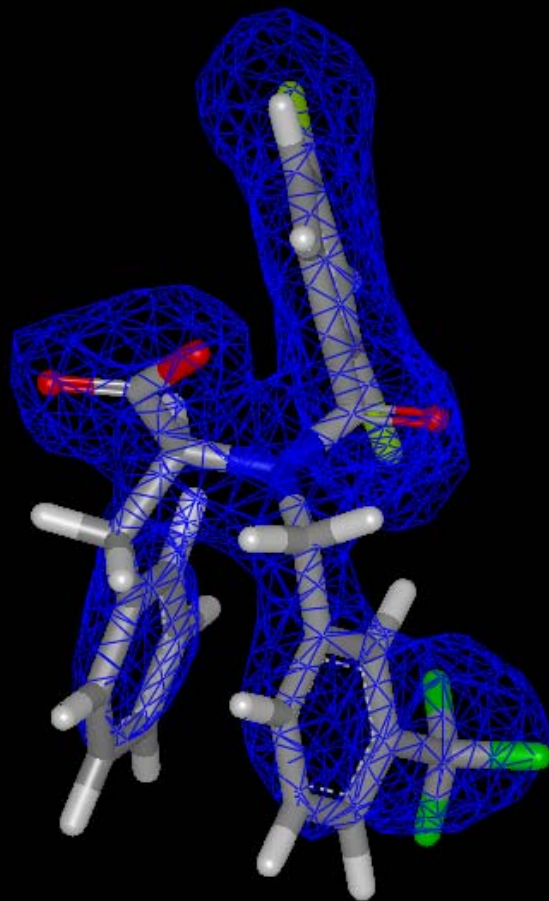


Automatic  
Blob (density)  
Finding  
Automated  
Fitting  
Scoring  
thousands  
of poses

# 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

The screenshot displays the AFITT 1.3.0 software interface. A central dialog box titled "Cleanup Protein" is open, showing the following options:

- Cleanup Rotamers
- Cleanup Pep-flips
- MMFF/Shape Fit Residues

Buttons for "OK" and "Cancel" are visible at the bottom of the dialog. The background shows a 3D molecular model of a protein structure. Other windows include a "List Window" with a table of items, a "Style" window with modeling tools and a sequence editor, a "2D Preview" window with a sequence viewer, and a "Ramachandran" window with a plot.

Name	ID
1fcz_lig.oeb	1
1fcz_lig.pdb_0	2
1fcz_prot.mtz	3
Fwit: 1fcz_prot.mtz	4
Fdelvt: 1fcz_prot.mtz	5
1fcz_prot.mtz	6
1fcz_prot.pdb	7
RETINOIC ACID RECEPTOR GA...	8
Fitting Results	10
Density Blobs	11
grid	9

Sequence viewer content:

```
Chain A
160  SPQLEELITKVSKGHPPTFSLCOLKVTINSSADHRVQLDLGLNDKPSFLATYCHIKIVFAKRLPSPFGLSPADQIILLKGAQLDILMLRACITRYTFPQDQIMFSDGLITLNRQMAHQGFPLITLIVFAFAGQLLEFLMD
325  DTEIGLLSATLIGDSDLEEPKRVKQCEPILLEALRLVARRFRSPQYMFRRMIMKTTDLRGLSITRGAERATILRVEYFGEMPHLIREMLE
```



# 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)

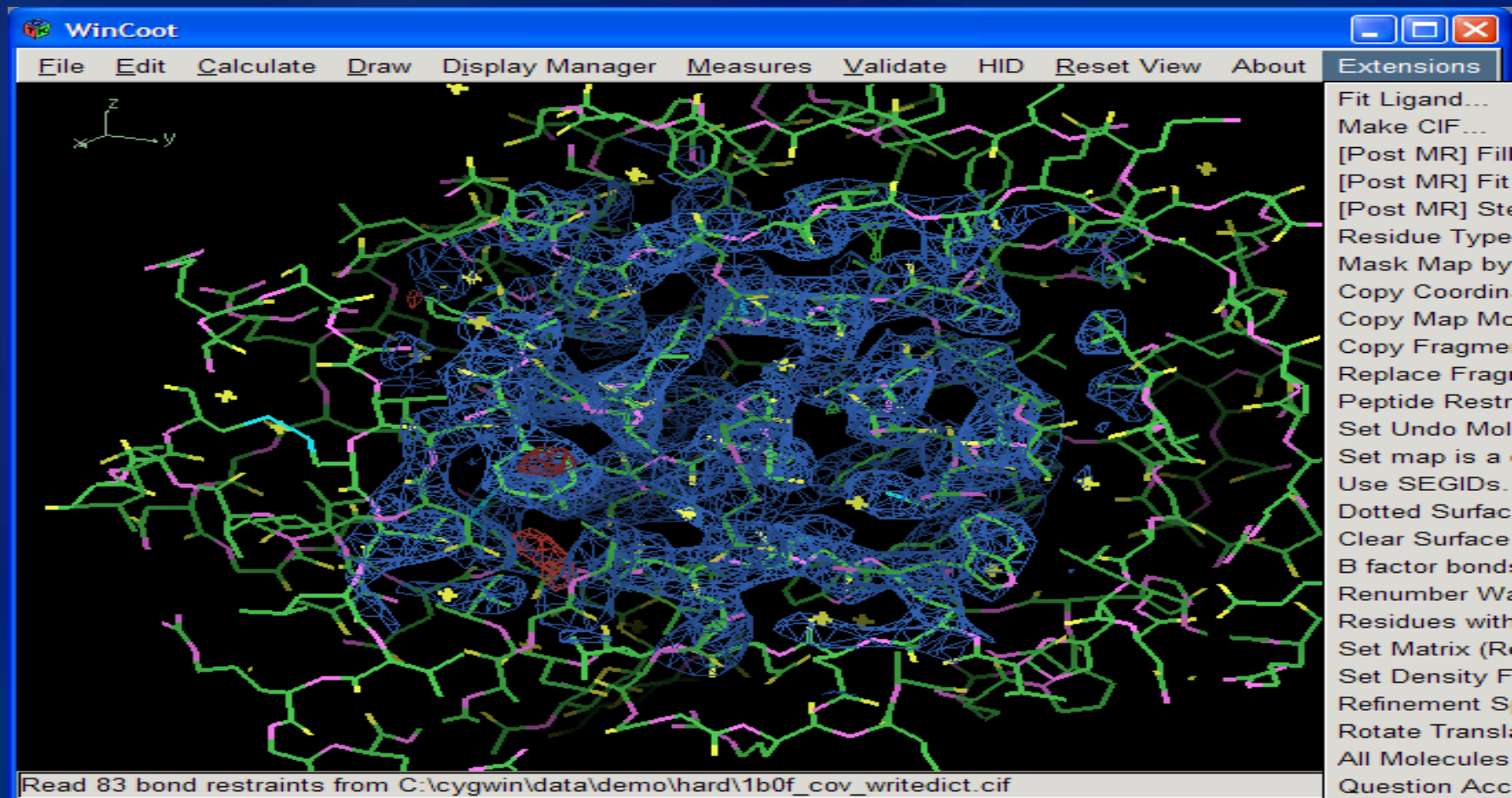


# Coot integration

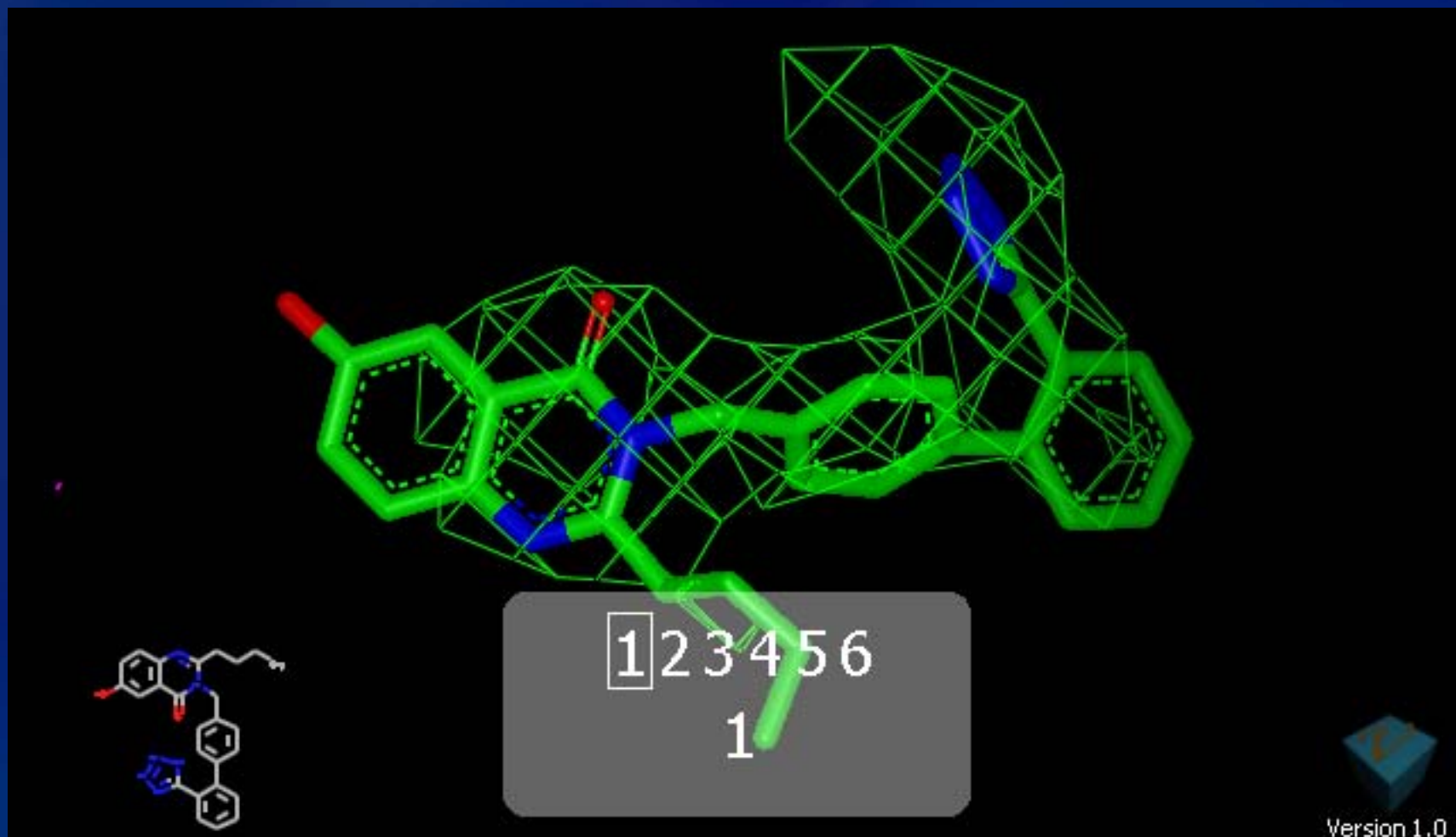
- Command line tools
  - Provide a method for integration
- OpenEye provides an integration for Coot and WinCoot
  - Fit Ligand
    - Runs Flynn and imports the results into the coot window
  - Make CIF
    - Generates a refinement dictionary for the selected coordinate set
    - Caveat - Does not work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



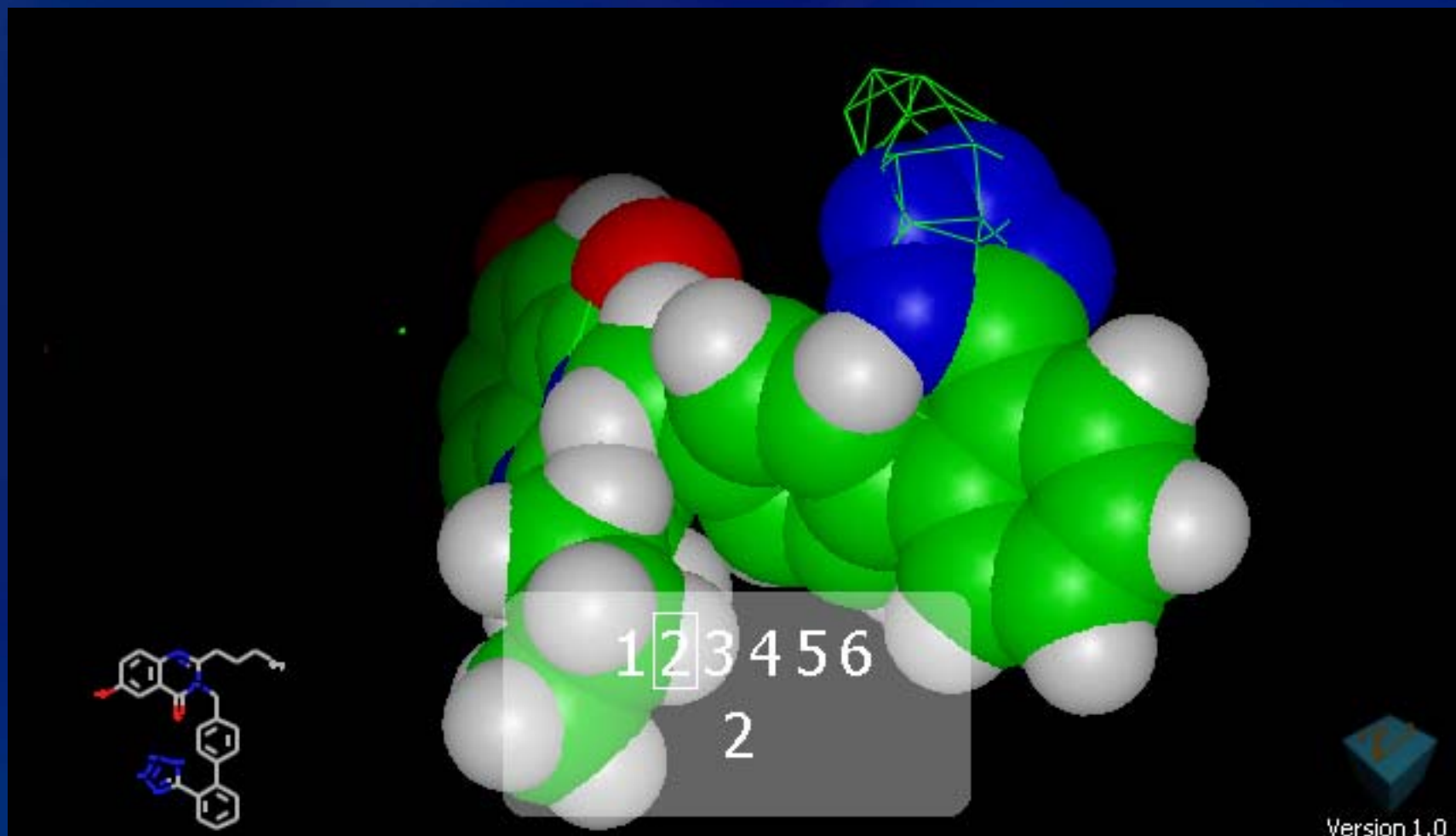
# Coot integration



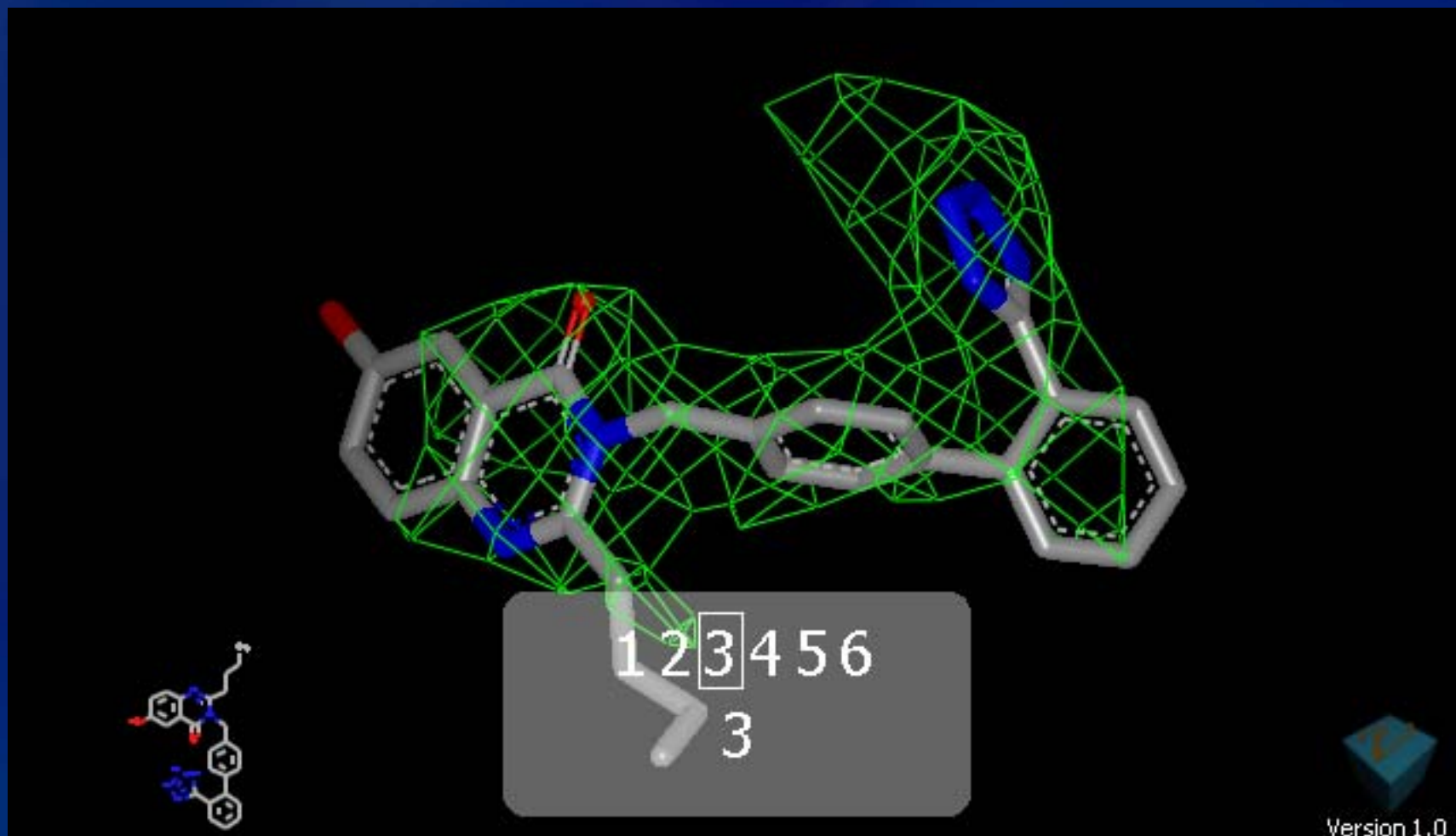
1a8t (RMSD = 0.65)  $\Delta E=2844$



$\Delta E=28.4$



$\Delta E=28.4$

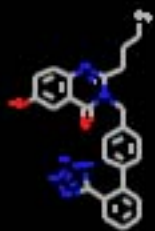
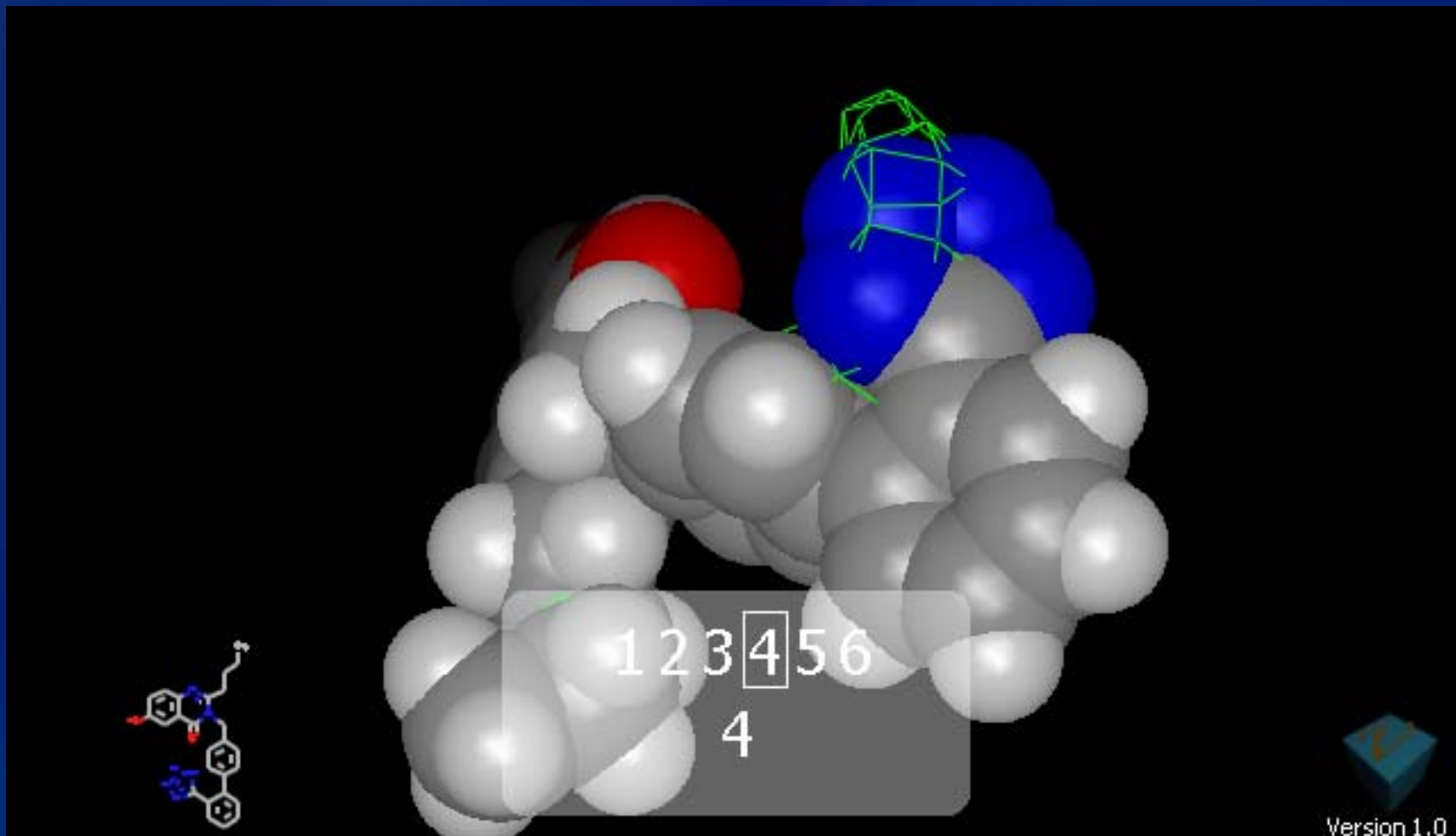


Version 1.0





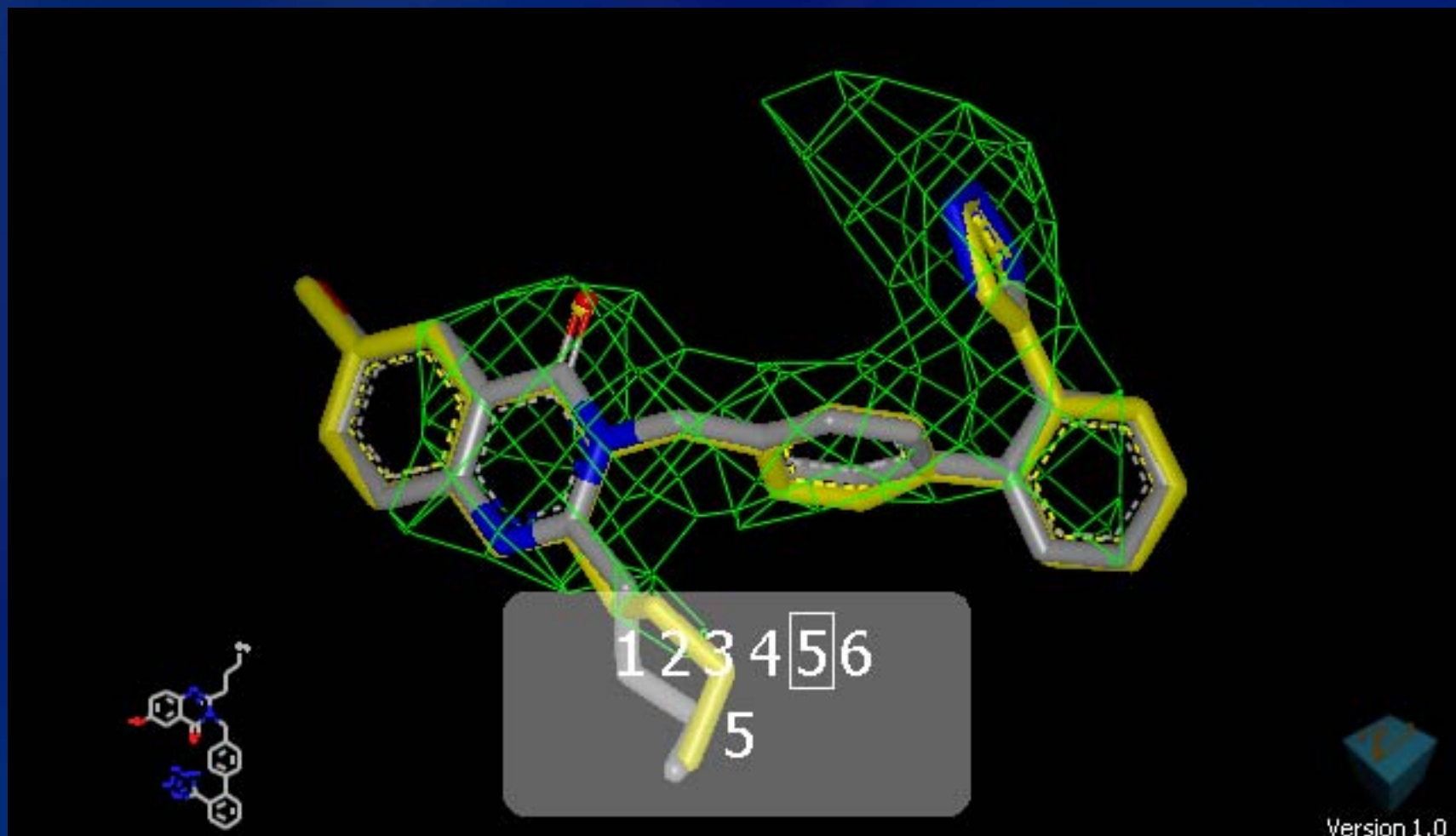
$\Delta E=28.4$



Version 1.0



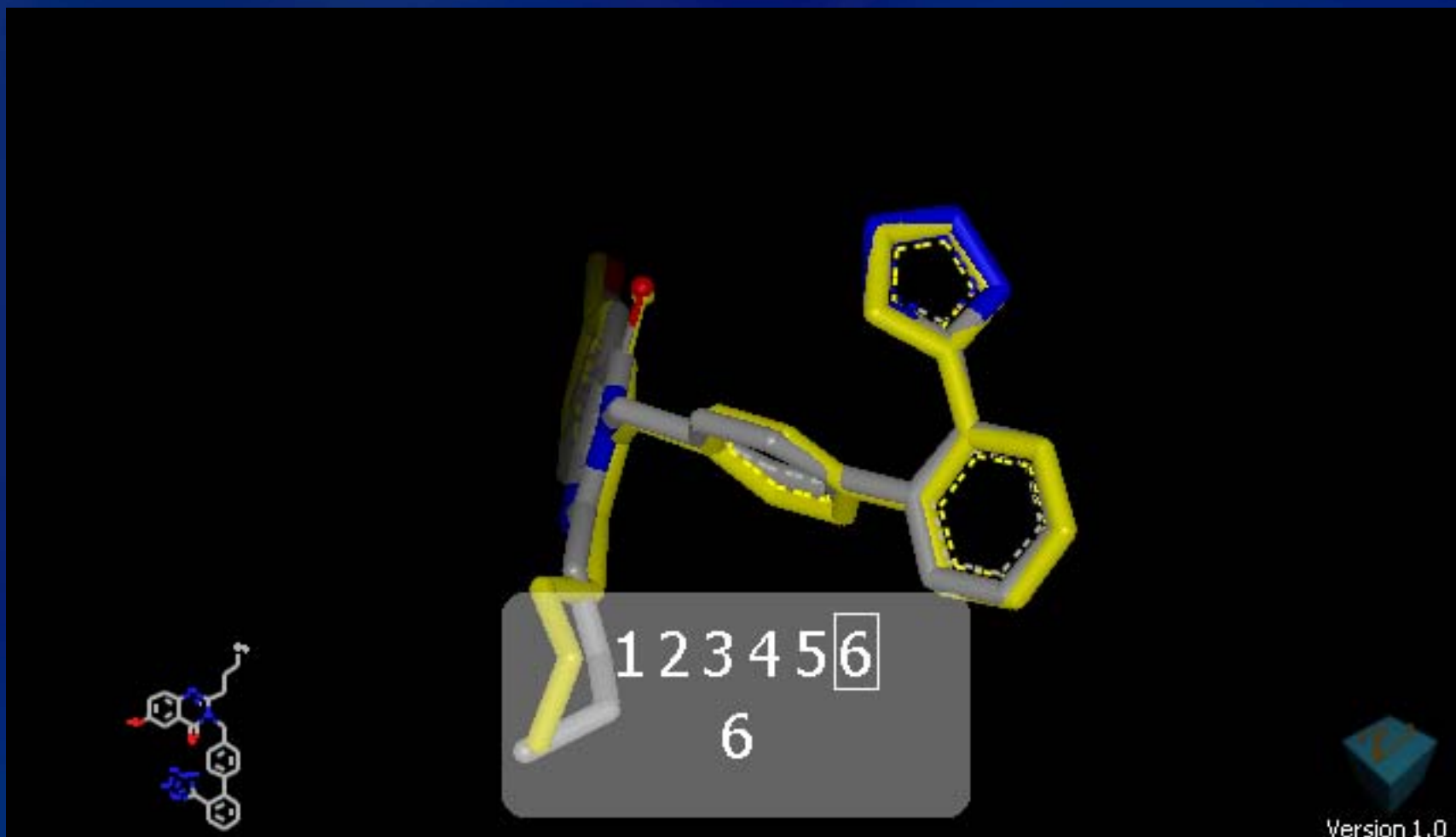
$\Delta E=1.4$



Version 1.0



$\Delta E=1.4$



# 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
- Geoff Skillman
- Stan Wlodek
- Roger Sayle
- Anthony Nicholls

