Introduction to Antechamber

CTBP Summer School 2009
Molecular Simulations and Modeling

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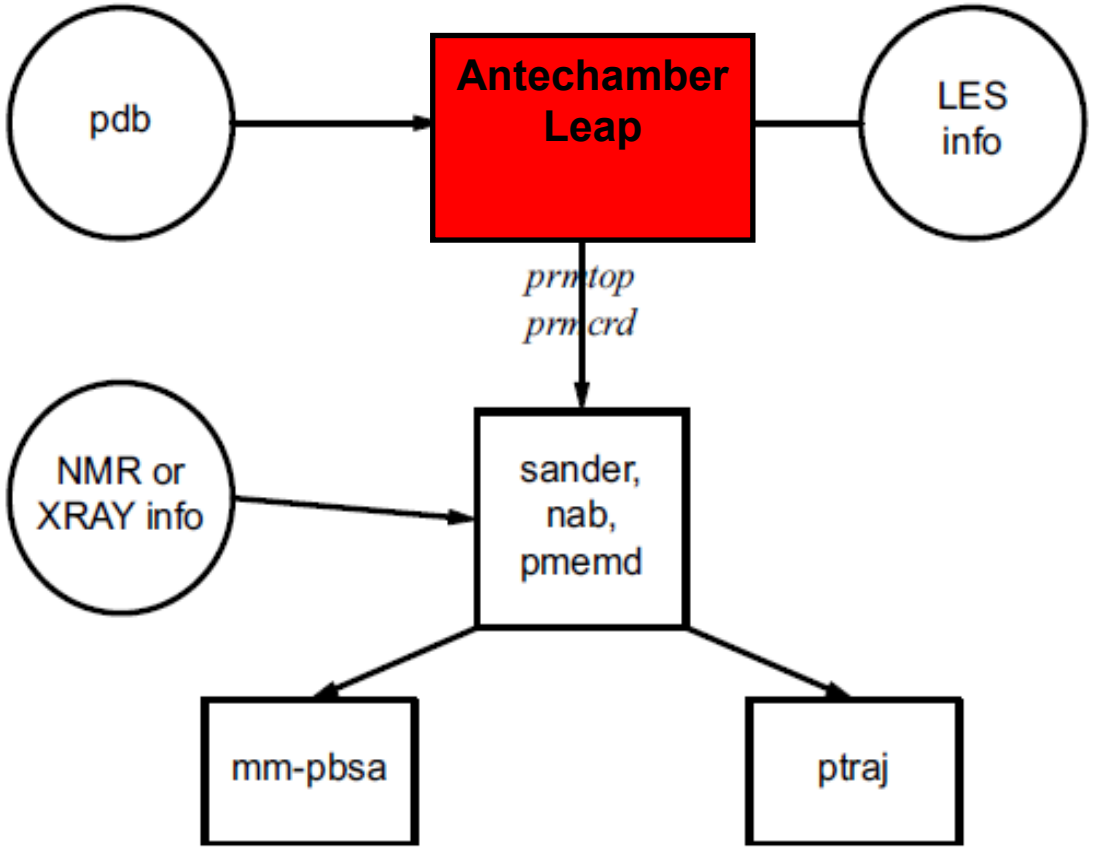
Antechamber in AMBER



General Amber Force Field (GAFF)

- Developed for general ligands
- Compatible with the AMBER force field
- Function form: $$E_{pair} = \sum_{\text{Bonds}} K_r (r - r_{eq})^2 + \sum_{\text{Angles}} K_\theta (\theta - \theta_{eq})^2 + \sum_{\text{Dihedrals}} \frac{V_n}{2}\left[1 + \cos(n\phi - \gamma)\right] + \sum_{i<j}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}}\right]$$
- Bond/Angle/Dihedral Parameterizations
  - Experimental Data and high level ab initio calculations

Atom types:

  - lower case, covers the organic chemical space

- Charge approach: RESP or AM1-BCC

Wang, J., Wolf, R.M., Caldwell, J. W., Kollman, P.A., Case, D.A., J Comput Chem, 25(9), 2004.

What can Antechamber do?

- Needed for non-standard residues
- Assign atom types from GAFF
- Generate empirical/semiempirical charges
  - AM1-BCC, Mulliken, Gasteiger…
- Extract QM charges from output
  - Gaussian and Jaguar outputs
- Prepare input mol2 file for leap
  - Convert different file formats to mol2 file

What can Antechamber do?

- File Conversions

file format type	abbre.	index	file format type	abbre.	index
Antechamber	ac	1	Sybyl Mol2	mol2	2
PDB	pdb	3	Modified PDB	mpdb	4
AMBER PREP (int)	prepi	5	AMBER PREP (car)	prepc	6
Gaussian Z-Matrix	gzmat	7	Gaussian Cartesian	gcrt	8
Mopac Internal	mopint	9	Mopac Cartesian	mopcrt	10
Gaussian Output	gout	11	Mopac Output	mopout	12
Alchemy	alc	13	CSD	csd	14
MDL	mdl	15	Hyper	hin	16
AMBER Restart	rst	17	Jaguar Cartesian	jcrt	18
Jaguar Z-Matrix	jzmat	19	Jaguar Output	jout	20
Divcon Input	divcrt	21	Divcon Output	divout	22
Charmm	charmm	23			

Build your own residue library

For simple molecules:

- Define a topology

Use Antechamber to:

- Choose atom types
- Calculate a set of partial charges
- Generate forcefield parameters

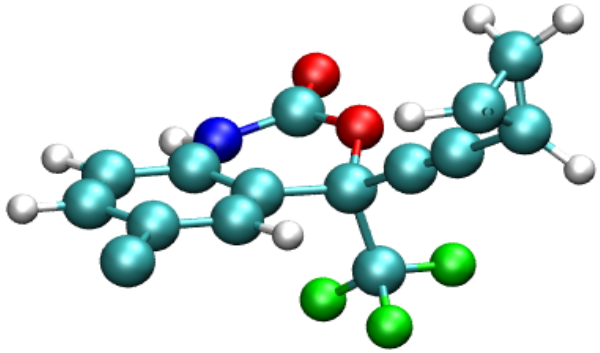
Use Leap to:

- Create a new residue library

Define a topology

- Extract it from an existing pdb
  - Search for topology from www.rcsb.org
  - Add hydrogens using “reduce”.
- Build it from any molecular builder

  xleap, chimera, maestro, etc.
- Save as pdb and visualize



Example: Sustiva (Efavirenz)

Choose atom types from GAFF

```
$AMBERHOME/exe/antechamber -i sustiva.pdb -fi pdb -o sustiva.mol2 \
 -fo mol2 -c bcc -s 2
```

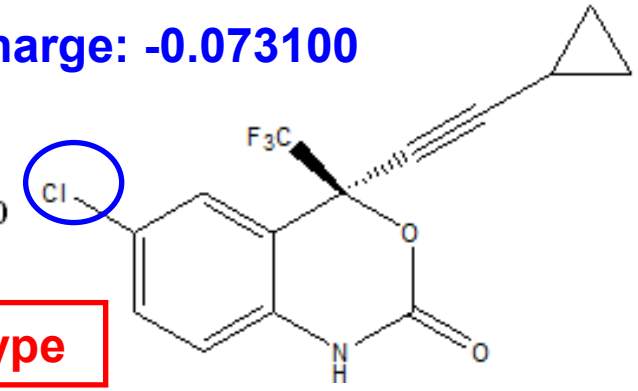
```
@<TRIPOS>MOLECULE
SUS
   30     32      1      0      0
SMALL
bcc


@<TRIPOS>ATOM
      1 CL      -4.6850  -32.7250   25.2220 cl      999 SUS     -0.073100
      2 F1      -0.7550  -36.6320   25.6970 f       999 SUS     -0.231400
      3 F2       1.0780  -37.0430   24.6720 f       999 SUS     -0.221400
      4 F3      -0.7840  -37.1770   23.6260 f       999 SUS     -0.216800
      5 O1       1.5240  -34.9340   20.9100 o       999 SUS     -0.573600
      6 O2       0.9890  -34.8800   23.0580 os      999 SUS     -0.371900
      7 N       -0.6810  -34.9710   21.4340 n       999 SUS     -0.459500
      8 C1      -1.6620  -34.4140   22.3130 ca      999 SUS      0.084700
      9 C2      -2.9150  -33.9470   21.8430 ca      999 SUS     -0.167000
     10 C3      -3.8380  -33.4230   22.7710 ca      999 SUS     -0.069500
     11 C4      -3.5330  -33.3730   24.1190 ca      999 SUS     -0.025500
```

Atom Names

GAFF Atom Types

Assign partial charges

Charge: -0.073100




```
@<TRIPOS>MOLECULE
SUS
    30     32      1      0
SMALL
bcc
@<TRIPOS>ATOM
      1 CL          -4.6850   -32.7250    25.2220 cl      999 SUS    -0.073100
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```

Charge Type

Atomic charges

Determine Partial Charges

- RESP Charges
  - Generate electrostatic potential
  - Fit point charges to potential
  - Equal charges for topologically equivalent atoms
  - Requires QM programs (Gaussian, Gamess, Jaguar, etc)
- AM1-BCC Charges
  - Fast, empirical generation
  - Emulate RESP charges
  - Can be directly generated from antechamber

Bayly, C.I., Cieplak, P., Cornell, W., Kollman, P.A., J Phys Chem B., 97, 10269, 1993.

Jakalian, A., Bush, B.L, Jack, D.B., Bayly, C.I., J Comput Chem, 21, 132, 2000.

Check forcefield parameters

- Check if there are missing parameters:
  Use the “check” command in leap
- Missing parameters can be:

a) Generated using “parmchk” utility
   (Problematic parameters generates warnings:
   “Attn, need revision.”)

b) Derived by “similarity” to existing parameters

c) Determined from QM calculations

Generate force field parameters

```
remark goes here
MASS

BOND

ANGLE
ca-c3-c1    64.784      110.735    Calculated with empirical approach
c1-c1-cx    56.400      177.990    same as c1-c1-c3
c1-cx-cx    64.200      111.590    same as c1-c3-c3
c1-cx-hc    48.300      109.750    same as c1-c3-hc

DIHE

IMPROPER
c -ca-n -hn          1.1          180.0          2.0
ca-ca-ca-n           1.1          180.0          2.0
ca-ca-ca-ha          1.1          180.0          2.0
n -o -c -os         10.5          180.0          2.0

NONBON
```

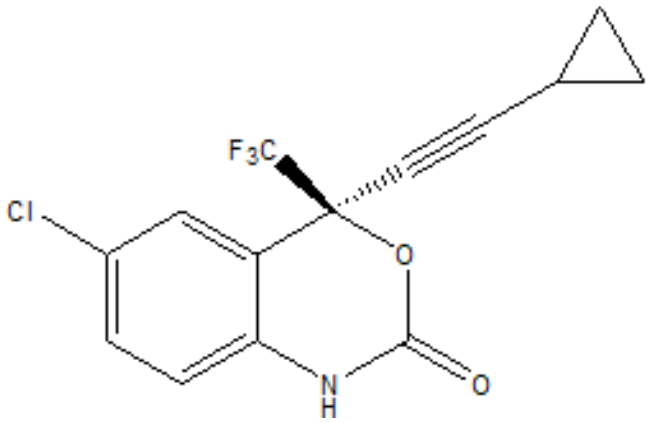
Angle Parameters generated from PARMCHK

Torsion Parameters generated from PARMCHK

Build a library file

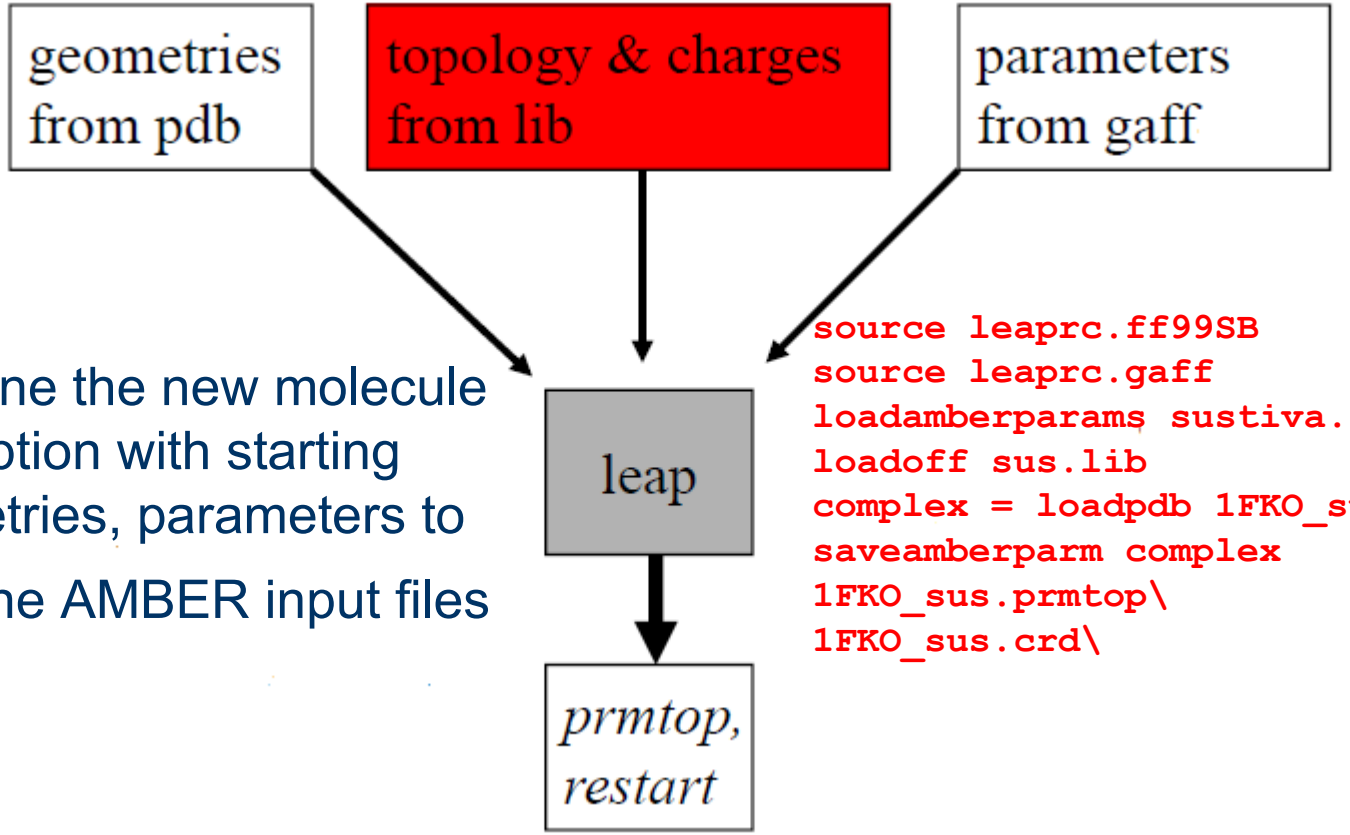
- Completely defines a molecule in AMBER terms
- Includes information on atom names, types, charges and topology

```
!!index array str
 "SUS"
!entry.SUS.unit.atoms table str name str type int typex int resx int flags int seq int elmnt dbl chg
 "CL" "cl" 0 1 131072 1 6 -0.073100
 "F1" "f" 0 1 131072 2 9 -0.231400
 "F2" "f" 0 1 131072 3 9 -0.221400
 "F3" "f" 0 1 131072 4 9 -0.216800
 "O1" "o" 0 1 131072 5 8 -0.573600
 "O2" "os" 0 1 131072 6 8 -0.371900
 "N" "n" 0 1 131072 7 7 -0.459500
 "C1" "ca" 0 1 131072 8 6 0.084700
 "C2" "ca" 0 1 131072 9 6 -0.167000
 "C3" "ca" 0 1 131072 10 6 -0.069500
 "C4" "ca" 0 1 131072 11 6 -0.025500
 "C5" "ca" 0 1 131072 12 6 -0.040200
 "C6" "ca" 0 1 131072 13 6 -0.163900
 "C7" "c3" 0 1 131072 14 6 0.315500
 "C8" "c1" 0 1 131072 15 6 -0.193300
```



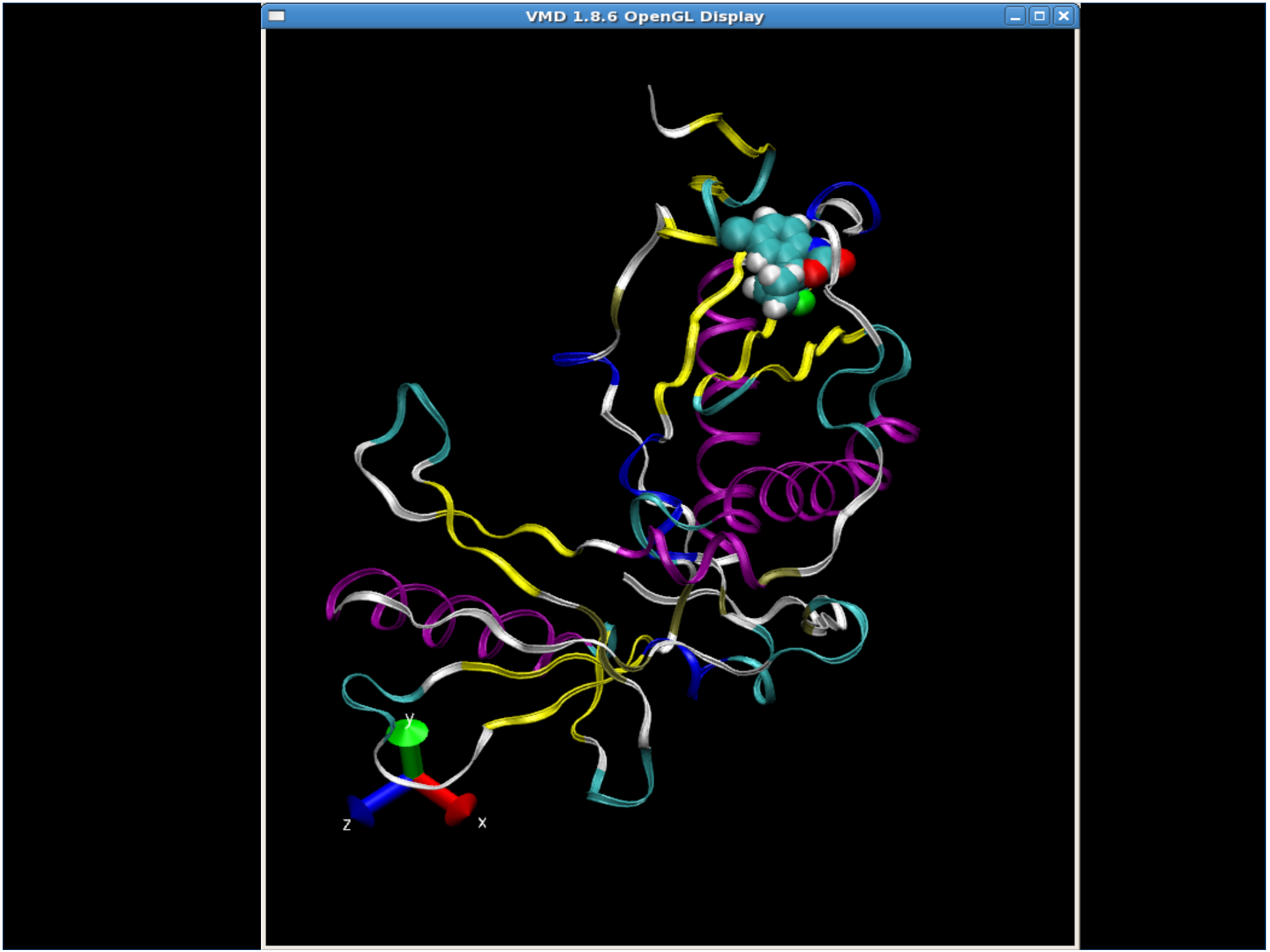
Sustiva

Use your new residue



- Combine the new molecule description with starting geometries, parameters to build the AMBER input files

```
source leaprc.ff99SB
source leaprc.gaff
loadamberparams sustiva.frcmod
loadoff sus.lib
complex = loadpdb 1FKO_sus.pdb
saveamberparm complex
1FKO_sus.prmtop\
1FKO_sus.crd\
```

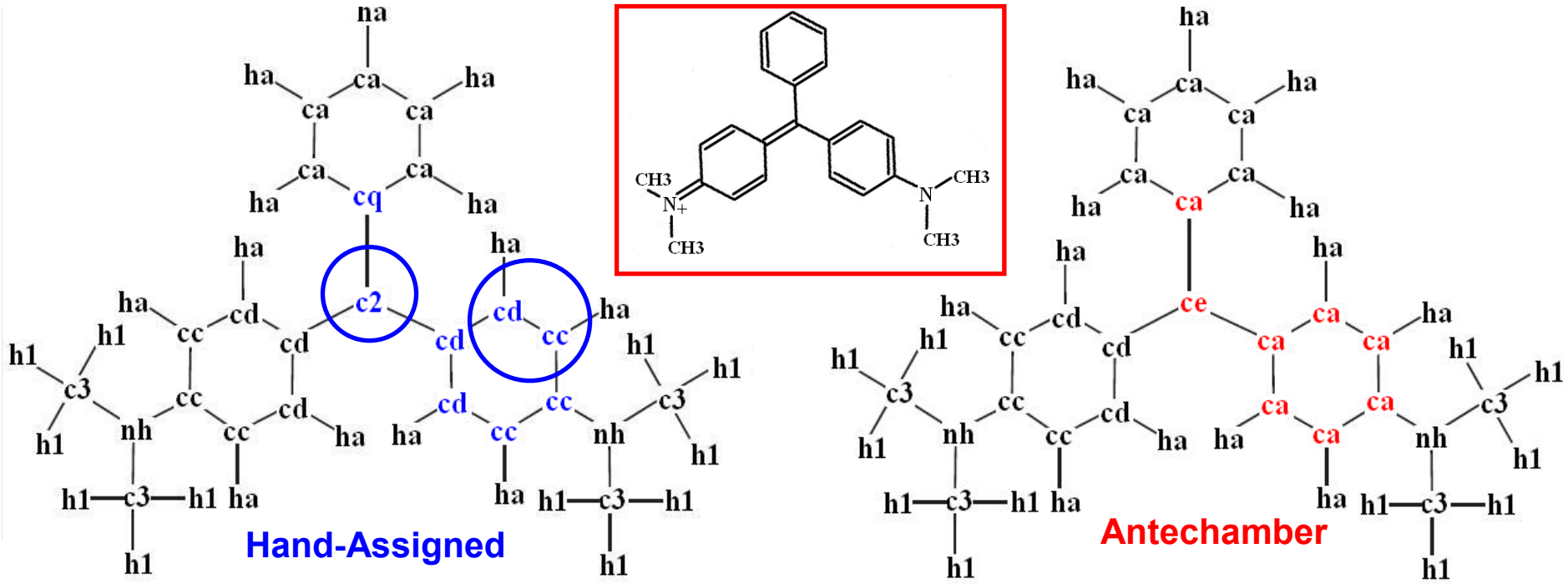

VMD 1.8.6 OpenGL Display
y
z
x

When running Antechamber, Make Sure that …

- Your pdb file has the correct geometry and connectivity.
- The atom names in your molecule are unique.
- Your molecule does not have open valence.
- The correct net charge of your molecule is specified.
- Your molecule does not contain multiple fragments
- The atom names and residue name of the coordinates. match the created library file.

Use Antechamber with caution: Malachite Green

- Reassign trivalent central carbon
- Describe elongated aromatic ring



Mark Williamson, Ph.D Thesis, Imperial College, London.

Where to find predefined libraries: The contributed parameter database

- Check here first:

http://www.pharmacy.manchester.ac.uk/bryce/amber

- Cofactors:GDP, GTP, ADP, ATP, FADH, NADH, NADPH
- Lipids: DMPC, DOPC
- Ions, organic molecules, modified AAs…

How to derive RESP charges: Use of R.E.D

- **R**ESP **E**SP Charge **D**erive
  - Check this: http://q4md-forcefieldtools.org/RED
- Database with RESP-charged mol2 files:
  - http://q4md-forcefieldtools.org/REDDB
  - Organic solvent: acetonitrile, benzene, toluene, etc.
  - New AA/RNA/DNA fragments…
- Server for deriving new RESP/ESP charges.
- Automated procedure for RESP fitting.