

Modeling and Parametrization of small molecules with Molefacture and ffTK

Mariano Spivak Ph.D.

NIH Center for Macromolecular Modeling and Bioinformatics
Theoretical and Computational Biophysics Group
University of Illinois at Urbana-Champaign

www.ks.uiuc.edu/~mariano

mspivak@Illinois.edu

 **ILLINOIS**

 National Institutes of Health

Molecular Builder and Editor: Molefacture

- Design Molecules from Scratch
- Edit Existing Molecules
- Templates for Quick Design
- Molecule / Functional Groups Library
- Quick Structure Minimizer
- Export Structure to:
 - PSF/PDB
 - MOL2
 - XYZ
- Interface with FFTK, QwikMD and QMTool



Peter Freddolino Ph.D.



João Ribeiro Ph.D.

The screenshot displays the Molefacture - Molecule Builder interface. On the left, a 3D ball-and-stick model of a complex organic molecule is shown in a VMD 1.9.4a29 OpenGL Display window. Below it is the Molefacture - Element Selection window, which features a periodic table with the element Nitrogen (N) highlighted in green. On the right, the Molefacture - Molecule Builder window is open, showing a table of atom properties and various control panels.

Index	Atom Name	Atom Type	Element	OxState	Charge	Chr
0	PG	PG1	P	3	1.340	
1	O1G	OG2P1	O	2	-0.855	
2	O2G	OG2P1	O	2	-0.855	
3	O3G	OG311	O	2	-0.719	
4	O3B	OG304	O	2	-0.737	
5	PB	PG1	P	3	1.510	
6	O1B	OG2P1	O	2	-0.846	
7	O2B	OG2P1	O	2	-0.846	
8	O3A	OG304	O	2	-0.781	
9	PA	PG1	P	3	1.505	
10	O1A	OG2P1	O	2	-0.816	
11	O2A	OG2P1	O	2	-0.816	
12	O5'	OG303	O	2	-0.622	
13	C5'	CG321	C	4	-0.083	
14	C4'	CG3C51	C	4	0.135	
15	O4'	OG3C51	O	2	-0.468	
16	C3'	CG3C51	C	4	0.144	
17	O3'	OG311	O	2	-0.649	
18	C2'	CG3C51	C	4	0.141	
19	O2'	OG311	O	2	-0.649	
20	C1'	CG3C51	C	4	0.141	
21	N8	NG2R51	N	3	-0.015	
22	C8	CG2R53	C	4	0.254	
23	N7	NG2R50	N	3	-0.597	
24	C5	CG2RC0	C	4	0.004	
25	C8	CG2R63	C	4	0.541	
26	O6	OG2D4	O	2	-0.509	
27	N1	NG2R61	N	3	-0.343	
28	C2	CG2R64	C	4	0.757	
29	N2	NG2S3	N	3	-0.663	
30	N3	NG2R62	N	3	-0.739	
31	C4	CG2RC0	C	4	0.260	
32	H	HGP1	H	1	0.440	
33	H0	HGA2	H	1	0.090	
34	H1	HGA2	H	1	0.090	
35	H2	HGA1	H	1	0.090	
36	H3	HGA1	H	1	0.090	
37	H4	HGP1	H	1	0.420	
38	H5	HGA1	H	1	0.090	
39	H6	HGP1	H	1	0.420	
40	H7	HGA1	H	1	0.090	
41	H8	HGR52	H	1	0.140	
42	H9	HGP1	H	1	0.262	
43	H10	HGP4	H	1	0.337	
44	H11	HGP4	H	1	0.337	

Molecular Builder and Editor: Molefacture

File menu to export into files / QMTool

Build menu to use library of fragments

Buttons for structure manipulation

Z-matrix editor

Overview

Index	Atom Name	Atom Type	Element	Ox:State	Charge
0	XO	C	C	4	0.000
1	H	H	H	1	0.000
2	C	C	C	4	0.000
3	ClO	Cl	Cl	0	0.000
4	CO	C	C	4	0.000
5	HO	H	H	1	0.000
6	C1	C	C	4	0.000
7	H1	H	H	1	0.000
8	C2	C	C	4	0.000
9	H2	H	H	1	0.000
10	C3	C	C	4	0.000
11	H3	H	H	1	0.000

Actions

Force Planar Force Tetrahedral

Select All Clear Selection

Undo

Atoms & Bonds

Angles

Dihedral Angles

Edit Molecule

Minimize Structure

Force Field: UFF

CHARMM36 - NAMD
UFF - OpenBabel

Num Steps: 500 Minimize

C GenFF Submissions: --- /100

Num Atoms: 12 Total Charge: 0.000

Overview tab helps define / edit general information and connects with actions menu

Overview Z-matrix

Index	Atom Name	A	Bond	B	Angle	C	Dihedral
0	XO	-	-	-	-	-	-
1	H	0	1.077	-	-	-	-
2	C	0	1.420	1	119.96	-	-
3	ClO	2	1.077	0	120.00	1	0.00
4	CO	2	1.420	0	120.01	1	180.00
5	HO	4	1.077	2	119.96	0	180.00
6	C1	4	1.420	2	120.00	0	0.00
7	H1	6	1.077	4	120.04	2	180.00
8	C2	6	1.420	4	120.02	2	0.00
9	H2	8	1.077	6	120.00	4	180.00
10	C3	0	1.420	1	120.04	9	-0.00
11	H3	10	1.077	0	120.04	1	0.00

Element selection

Atoms & Bonds

Element: Carbon(C:6)

Oxidation State: [dropdown]

Bond Distance (A): [slider] 0

Angles

Move: Group 1 Group 2

Angle Value (deg): [slider] 0

Dihedral Angles

Move: Group 1 Group 2

Angle Value (deg): [slider] 0

Slide bar entry bond angle dihedral values

Quick structure minimizer

Molecular Builder and Editor: Molefactory

The image shows two overlapping windows from the VMD software. The left window, titled "VMD 1.9.4a42 OpenGL Display", contains the VMD logo (the letters "VMD" in red, green, and blue) and a 3D coordinate system with a blue sphere at the origin and red, green, and blue axes. The right window, titled "Molefactory - Molecule Builder", is a control panel with a menu bar (File, Build, Settings, Help) and a table with columns: Index, Atom Name, Atom Type, Element, OxState, and Charge. Below the table is an "Actions" panel with icons for Add, Del, Select, Rotate, Translate, Move Frag, Move Atom, Add Bond, Dele Bond, and Bond Order. There are also buttons for "Add Hydr" (with an H⁺ symbol) and "x2 Dupl". Below these are "Add Skel." options for "Cycle" and "Aliph. Chain" with a "N. Atoms" dropdown set to 6 and an "Add" button. Further down are "Force Planar", "Force Tetrahedral", "Select All", "Clear Selection", and "Undo" buttons. The "Atoms & Bonds" section includes a dropdown for "Element" (Carbon(C:6)), an "Oxidation State" dropdown, and a "Bond Distance (A)" slider. A list of expandable sections includes "Angles", "Dihedral Angles", "Edit Molecule", and "Minimize Structure". At the bottom, it shows "Num Atoms: 0" and "Total Charge: 0.000".

Force Field terms for MD (CHARMM)

$$V = \sum_{bonds} k_b (b - b_0)^2 + \sum_{angles} k_\theta (\theta - \theta_0)^2 + \sum_{dihedrals} k_\phi [1 + \cos(n\phi - \delta)] +$$
$$\sum_{impropers} k_\omega (\omega - \omega_0)^2 + \sum_{Urey-Bradley} k_u (u - u_0)^2 + \sum_{nonbonded} \epsilon_{ij} \left[\left(\frac{R_{min_{ij}}}{r_{ij}} \right)^{12} - \left(\frac{R_{min_{ij}}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{\epsilon r_{ij}}$$

Lennard-Jones / VdW *Coulomb/Electrostatics*

Force Field terms for MD (CHARMM)

$$V = \sum_{bonds} k_b (\mathbf{b} - \mathbf{b}_0)^2 + \sum_{angles} k_\theta (\theta - \theta_0)^2 + \sum_{dihedrals} k_\phi [1 + \cos(n\phi - \delta)] +$$
$$\sum_{impropers} k_\omega (\omega - \omega_0)^2 + \sum_{Urey-Bradley} k_u (\mathbf{u} - \mathbf{u}_0)^2 + \sum_{nonbonded} \epsilon_{ij} \left[\left(\frac{R_{minij}}{r_{ij}} \right)^{12} - \left(\frac{R_{minij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{\epsilon r_{ij}}$$

Lennard-Jones / VdW *Coulomb/Electrostatics*

- **Coordinates from pdb or trajectory files**
- **Parameters from the topology and parameters files**
 - **Can be obtained by Analogy (similar structures)**
CGenFF, SwissParam, MATCH
 - **Developed from Quantum Chemical calculations**
GAAMP, Force Field Toolkit

Force Field terms for MD (CHARMM)

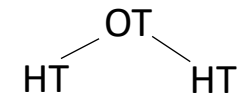
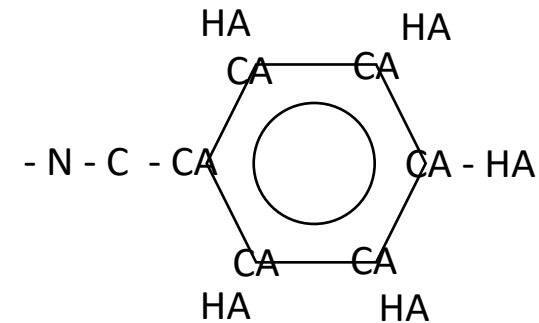
$$V = \sum_{\text{bonds}} k_b (b - b_0)^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} k_\phi [1 + \cos(n\phi - \delta)] +$$

Parameter file

```

BONDS
!
!V(bond) = Kb(b - b0)**2
!
!Kb: kcal/mole/A**2
!b0: A
!
!atom type Kb          b0
!
C      C      600.000    1.3350 ! ALLOW ARO HEM
! Heme vinyl substituent (KK, from propene (JCS))
CA     CA     305.000    1.3750 ! ALLOW  ARO
! benzene, JES 8/25/89
HA     CA     340.000    1.0830 ! ALLOW ARO
! trp, adm jr., 10/02/89
N      C      260.000    1.3000 ! ALLOW PEP POL ARO PRO
! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93
OT     HT     450.000    0.9572 ! ALLOW  WAT
! FROM TIPS3P GEOM

```



Force Field terms for MD (CHARMM)

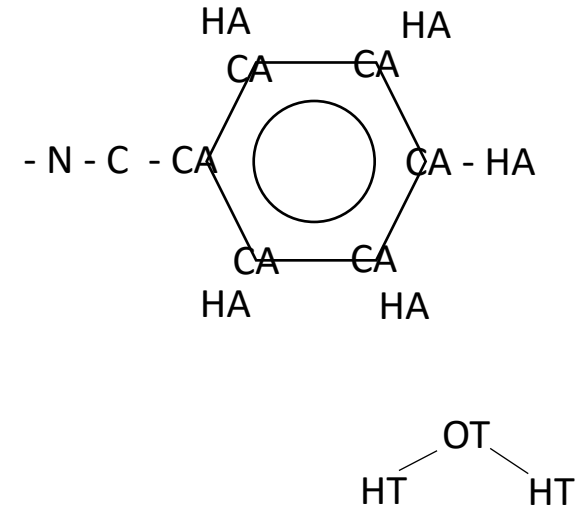
$$V = \sum_{bonds} k_b(b - b_0)^2 + \sum_{angles} k_\theta(\theta - \theta_0)^2 + \sum_{dihedrals} k_\phi[1 + \cos(n\phi - \delta)] +$$

Parameter file

```

ANGLES
!
!V(angle) = Ktheta(Theta - Theta0)**2
!
!V(Urey-Bradley) = Kub(S - S0)**2
!
!Ktheta: kcal/mole/rad**2
!Theta0: degrees
!Kub: kcal/mole/A**2 (Urey-Bradley)
!S0: A
!
!atom types      Ktheta   Theta0   Kub      S0
!
CA  CA  CA  40.000   120.00   35.00    2.41620 ! ALLOW  ARO
! JES 8/25/89
HA  CA  CA  29.000   120.00   25.00    2.15250 ! ALLOW  ARO
! trp, adm jr., 10/02/89
HT  OT  HT  55.000   104.5200 ! ALLOW  WAT
! TIP3P GEOMETRY, ADM JR.

```



Force Field terms for MD (CHARMM)

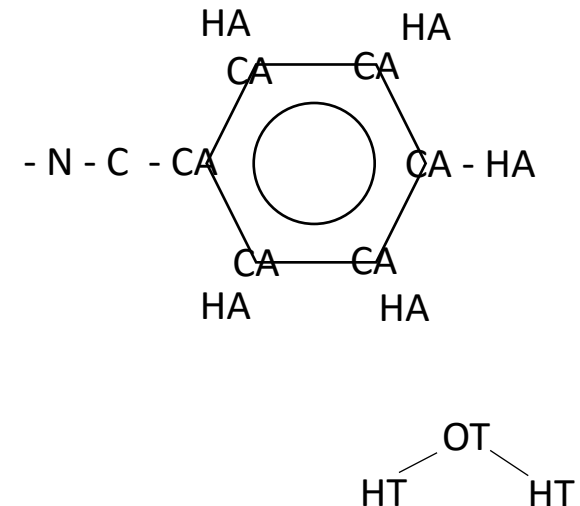
$$V = \sum_{bonds} k_b(b - b_0)^2 + \sum_{angles} k_\theta(\theta - \theta_0)^2 + \sum_{dihedrals} k_\phi[1 + \cos(n\phi - \delta)] +$$

Parameter file

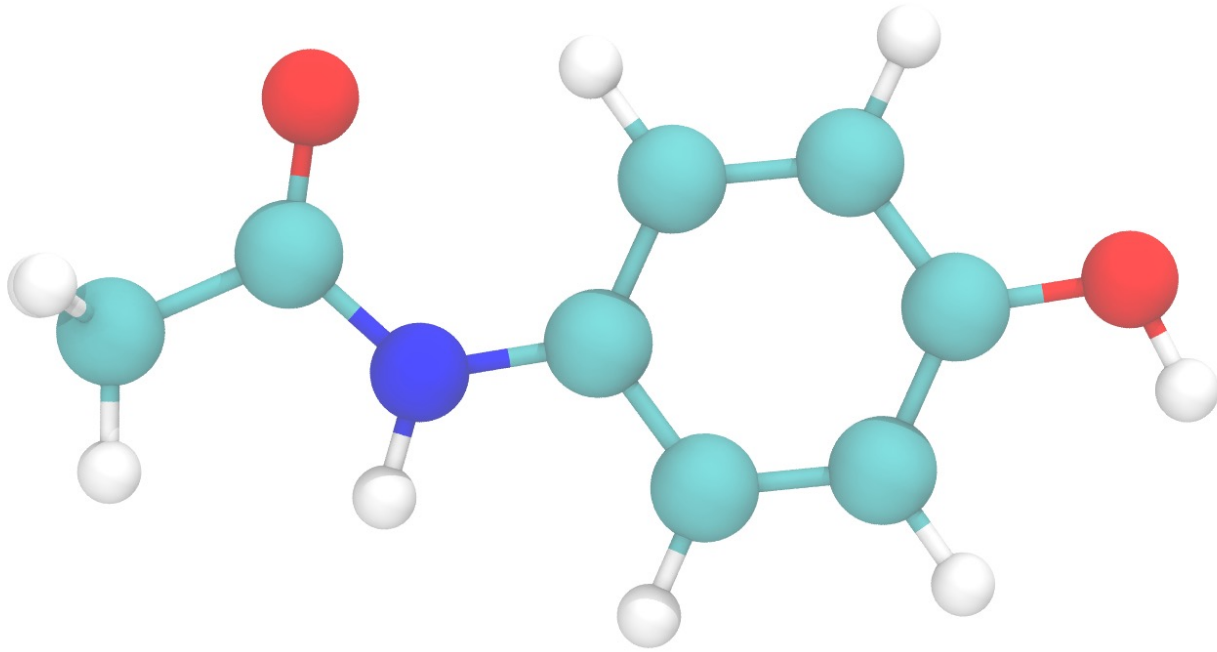
```

DIHEDRALS
!
!V(dihedral) = Kchi(1 + cos(n(chi) - delta))
!
!Kchi: kcal/mole
!n: multiplicity
!delta: degrees
!
!atom types          Kchi    n    delta
!
CA  CA  CA  CA      3.1000  2   180.00 ! ALLOW  ARO
! JES 8/25/89
HA  CA  CA  CA      3.5000  2   180.00 ! ALLOW  ARO
! adm jr., 10/02/89
HA  CA  CA  HA      2.5000  2   180.00 ! ALLOW  ARO
! ADM JR., 10/02/89
CT1 C   N   CP3     2.7500  2   180.00 ! ALLOW  PRO
! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93

```

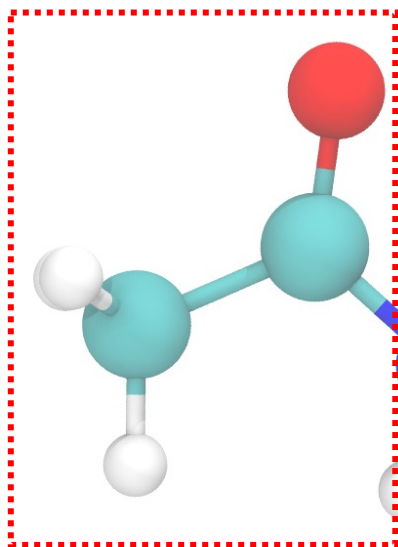


Example Case: Acetaminophen

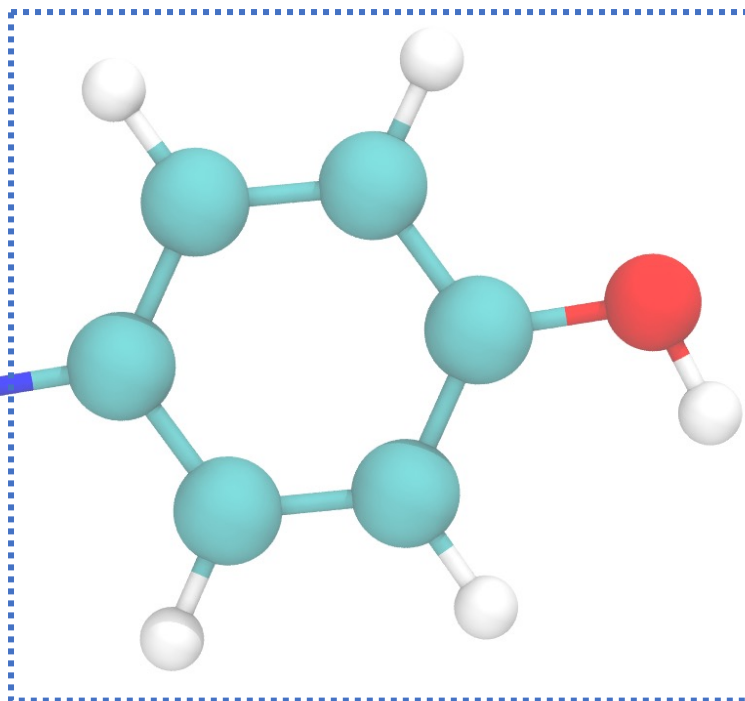


- Also known as Paracetamol or APAP
- Widely used medication to treat fever and pain

Example Case: Acetaminophen



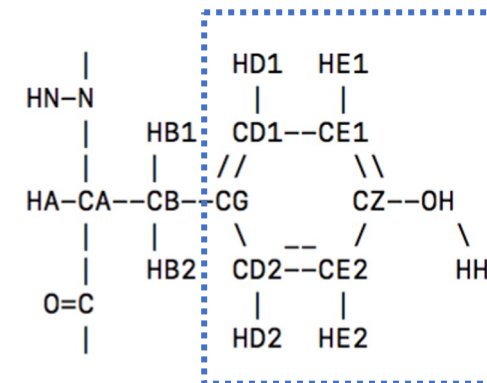
Acetylated N-terminus



Tyrosine side-chain

Topology file for Tyrosine

```
RESI TYR      0.00
GROUP
ATOM N      NH1  -0.47 !
ATOM HN     H    0.31 !
ATOM CA     CT1  0.07 !
ATOM HA     HB   0.09 !
GROUP
ATOM CB     CT2 -0.18 !
ATOM HB1    HA   0.09 !
ATOM HB2    HA   0.09 !
GROUP
ATOM CG     CA   0.00
GROUP
ATOM CD1    CA  -0.115
ATOM HD1    HP   0.115
GROUP
ATOM CE1    CA  -0.115
ATOM HE1    HP   0.115
GROUP
ATOM CZ     CA   0.11
ATOM OH     OH1 -0.54
ATOM HH     H    0.43
GROUP
ATOM CD2    CA  -0.115
ATOM HD2    HP   0.115
GROUP
ATOM CE2    CA  -0.115
ATOM HE2    HP   0.115
```



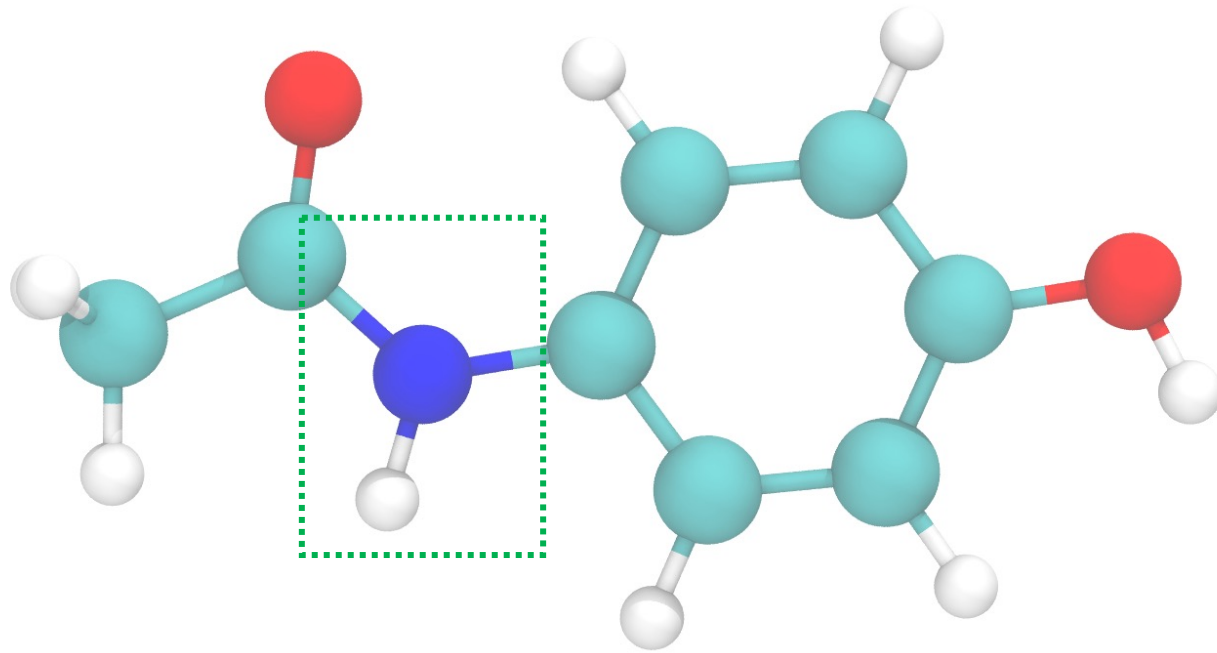
Topology for Ace-patch

```
PRES ACE      0.00 ! acetylated N-terminus
GROUP
ATOM CAY     CT3 -0.27 !
ATOM HY1     HA   0.09 ! HY1 HY2 HY3
ATOM HY2     HA   0.09 ! \ | /
ATOM HY3     HA   0.09 !   CAY
GROUP
ATOM CY      C    0.51 !   |
ATOM OY      O   -0.51 !   |
```

Name Type Charge

Name Type Charge

Example Case: Acetaminophen

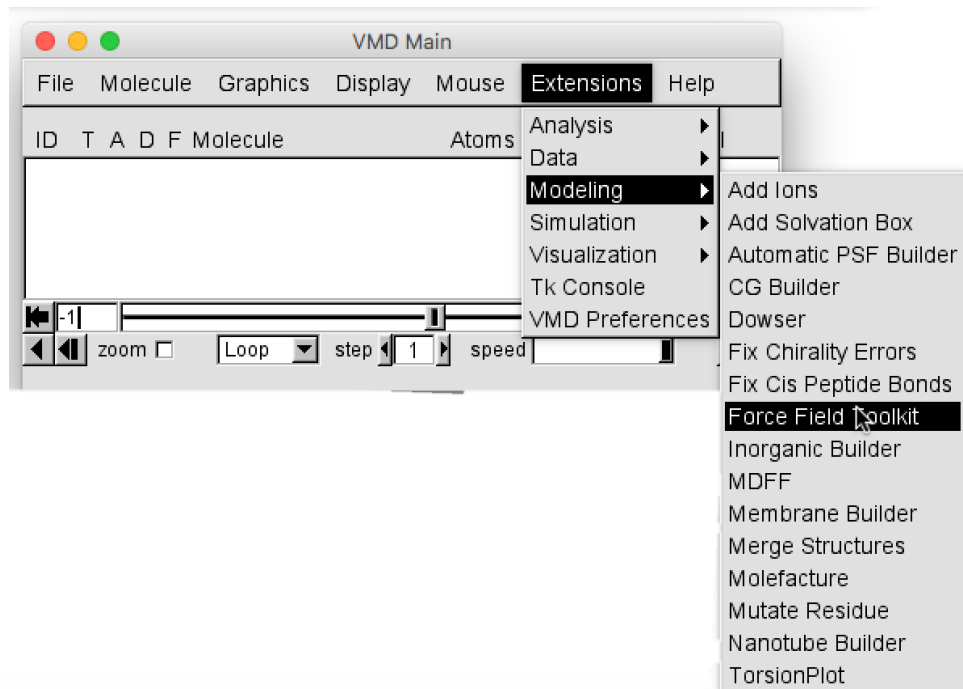


- Need to define new Atom types (N, H) and Charges: q_i
- Generate bond, angle and dihedral parameters: $(k_i^{bond}, r_0, k_i^{ang}, \theta_0, k_i^{dih}, n_i, \delta_i)$

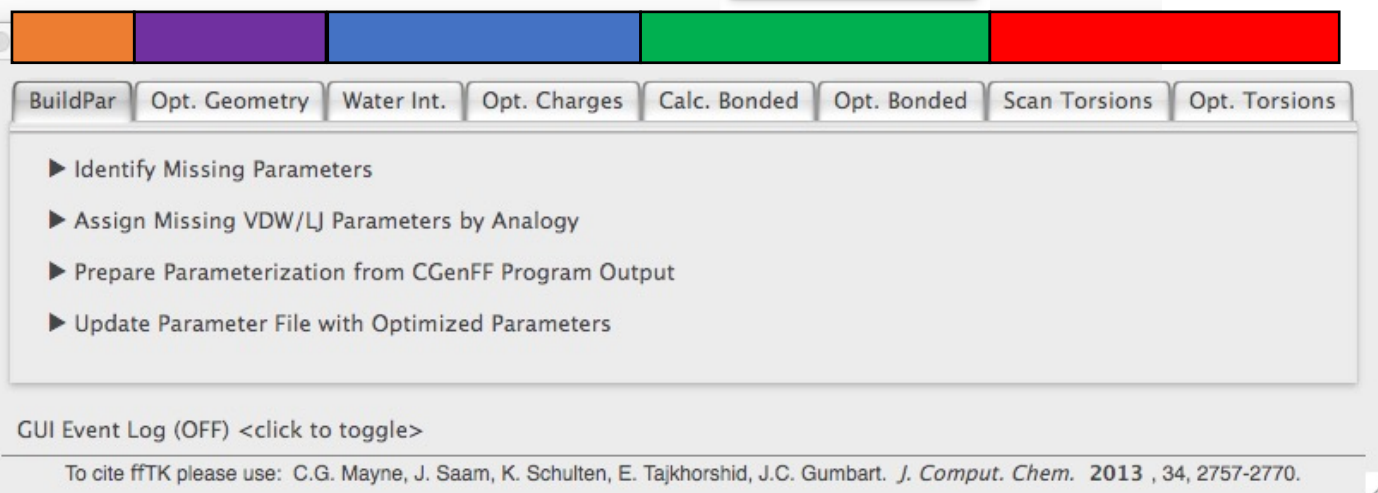
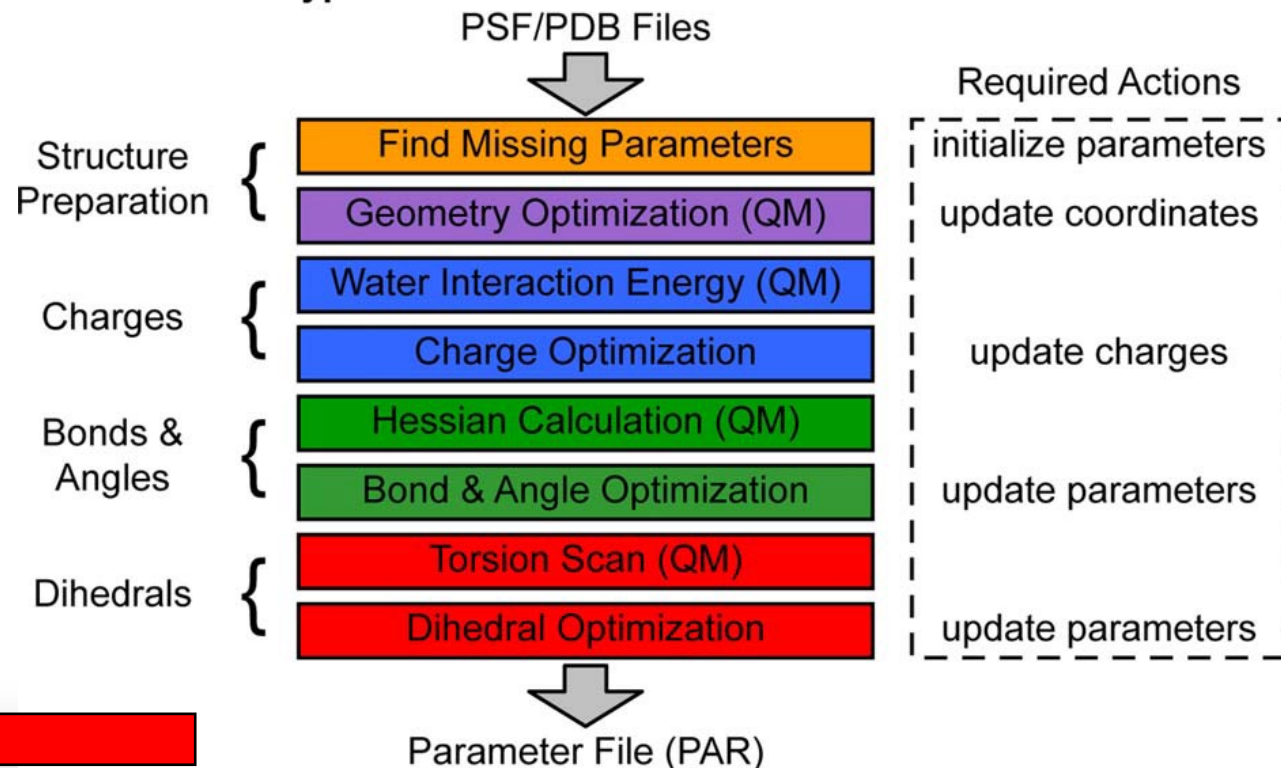


Force Field Toolkit

Force Field Toolkit Workflow



Typical Parameterization Workflow



- FTK generates all but the VDW/LJ Parameters
- Requires a Quantum Mechanics (QM) Software GAUSSIAN or ORCA (new)

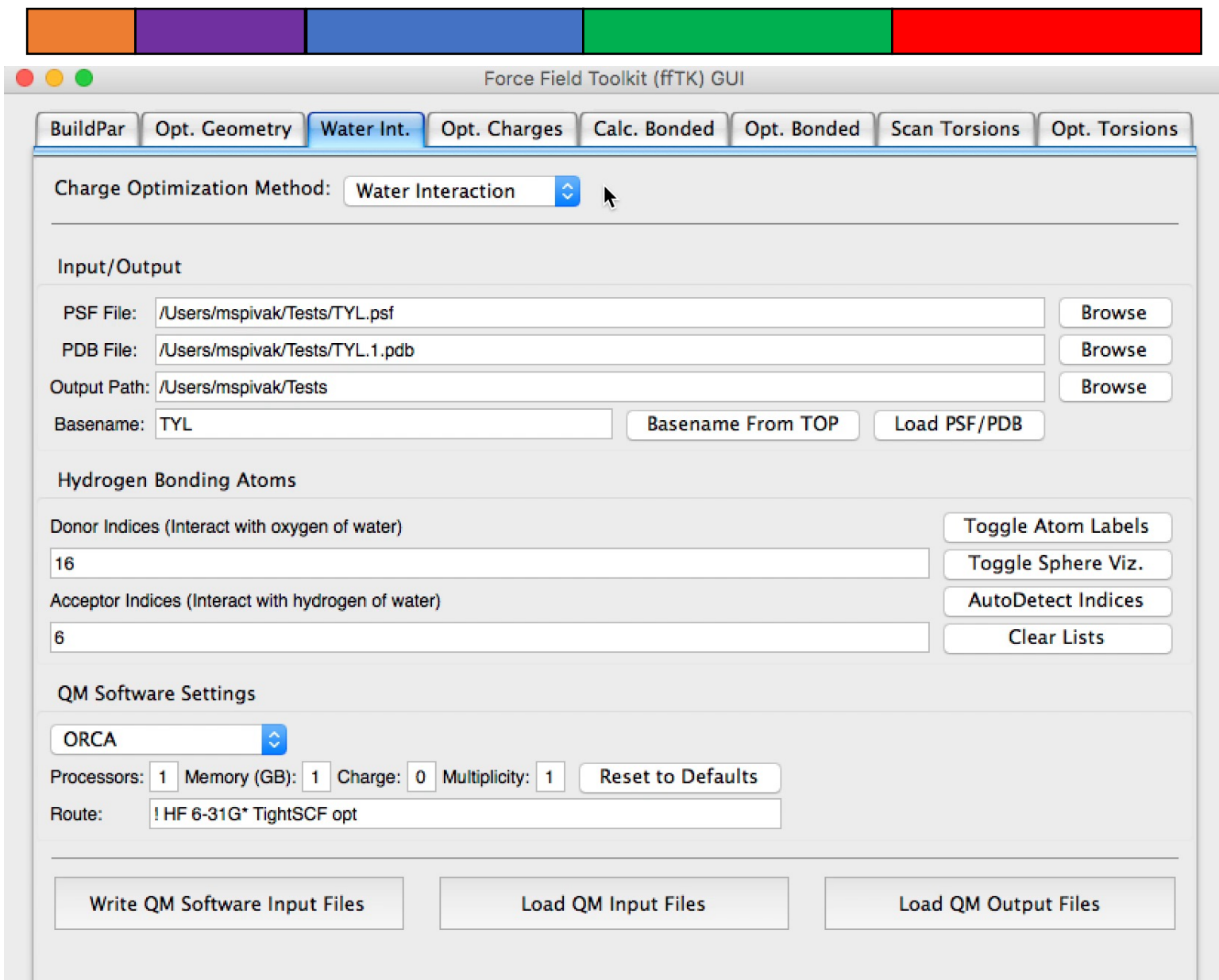
Force Field Toolkit Workflow

The screenshot displays the Force Field Toolkit (ffTK) GUI with the following components:

- Navigation Tabs:** BuildPar, Opt. Geometry (selected), Water Int., Opt. Charges, Calc. Bonded, Opt. Bonded, Scan Torsions, Opt. Torsions.
- Input/Output:** Input PDB File: /Users/mspivak/Tests/TYL.pdb; Output QM File: /Users/mspivak/Tests/TYL-opt.inp.
- QM Settings:** ORCA (selected), Processors: 1, Memory(GB): 1, Charge: 0, Multiplicity: 1, Route: !MP2 6-31G* TightSCF opt.
- Buttons:** Write QM Software Input File, Write Updated PDB, Load QM Output File, Write Optimized Geometry to PDB.
- GUI Event Log:** (OFF) <click to toggle>

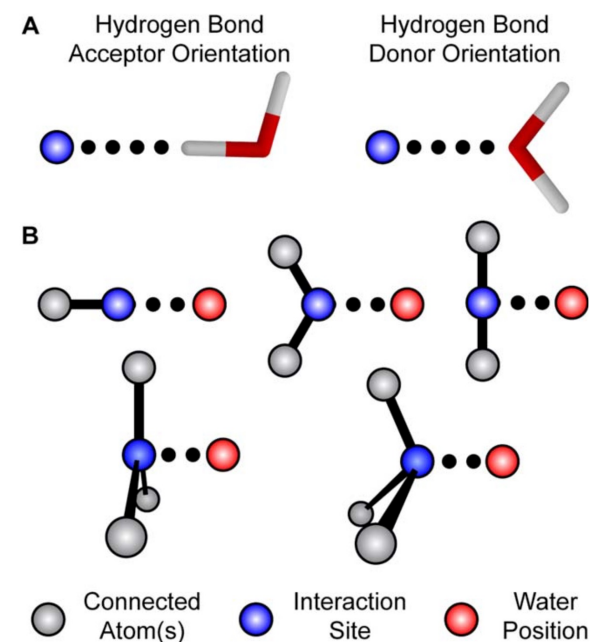
Run QM Simulation externally

Force Field Toolkit Workflow



- AMBER: RESP Fitting
Generates charges that fit the electrostatic potential around the molecule.

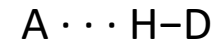
- CHARMM: Water Interaction
Generates charges that fit the QM interactions between water and a donor/acceptor atom.



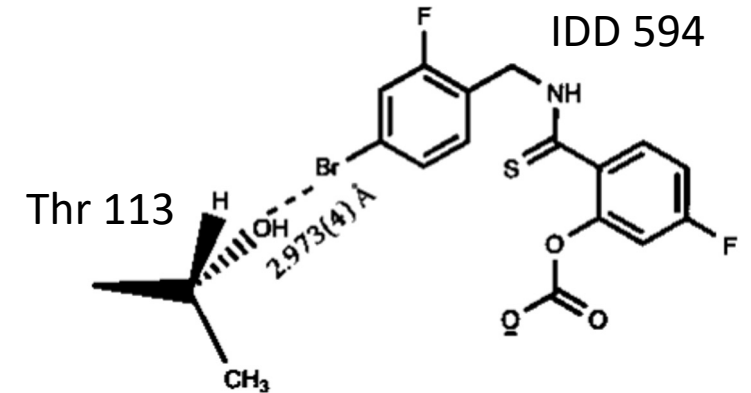
New Development: Halogen parametrization

- Many drug molecules have added halogen atoms to optimize binding affinities, absorption or enhance blood-brain barrier permeation
- New CHARMM force field includes “ σ -hole particle” to improve treatment of **halogen bonds** in ligand-protein interaction

Hydrogen bond



Halogen bond



Human Aldose Reductase-Inhibitor complex

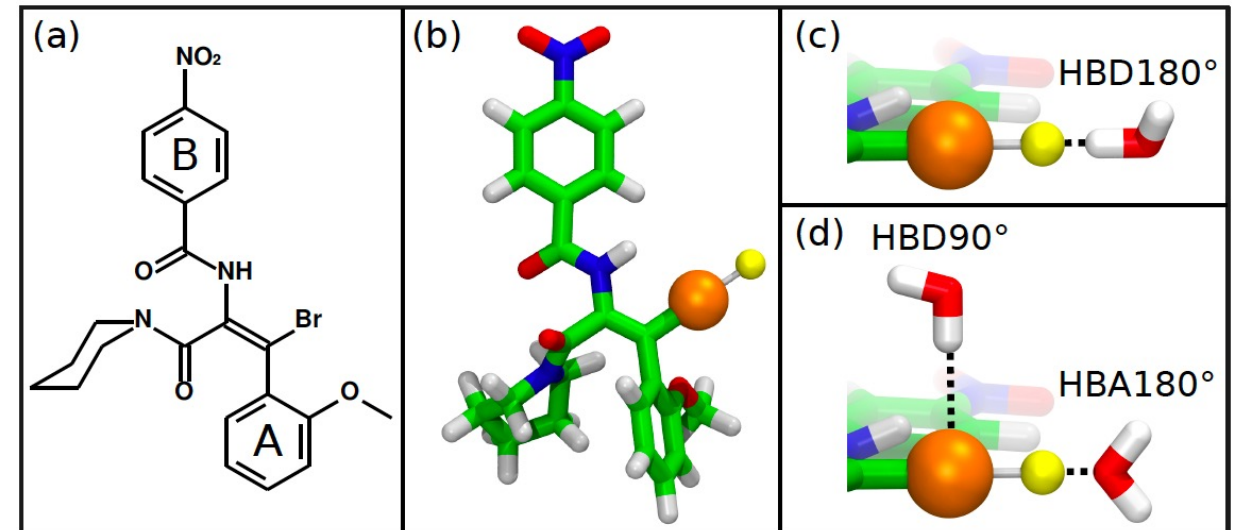
Soteras, Lin, Vanommeslaeghe, Lemkul, Armacost, Brooks, MacKerell, *Bioorg Med Chem.* 2016; 24(20): 4812–4825 doi:10.1016/j.bmc.2016.06.034

- Latest FFTK 2.0 includes charge parametrization for halogens following CHARMM recipe

- FFTK setups water interaction around halogen

- Publication with validation:

Pang, Pavlova, Tajkhorshid, Gumbart. Parameterization of a drug molecule with a halogen σ -hole particle using fftk: Implementation, testing and comparison. (2020) *J. Chem. Phys.* In press.





Theoretical and Computational Biophysics Group
NIH Center for Macromolecular Modeling & Bioinformatics Beckman Institute,
University of Illinois at Urbana-Champaign

