Modeling and Parametrization of small molecules with Molefacture and ffTK

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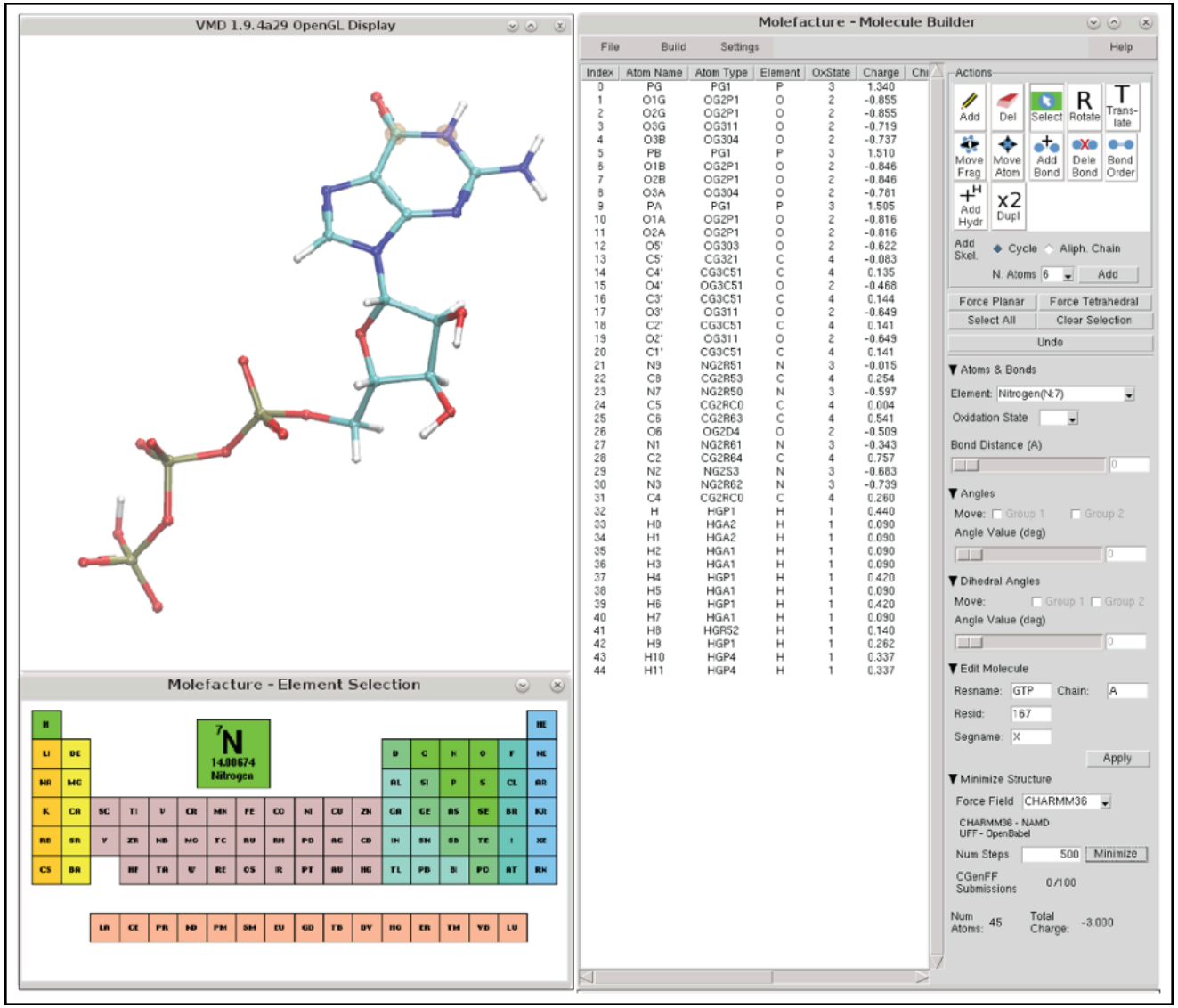
Molecular Builder and Editor: Molefacture

- 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.

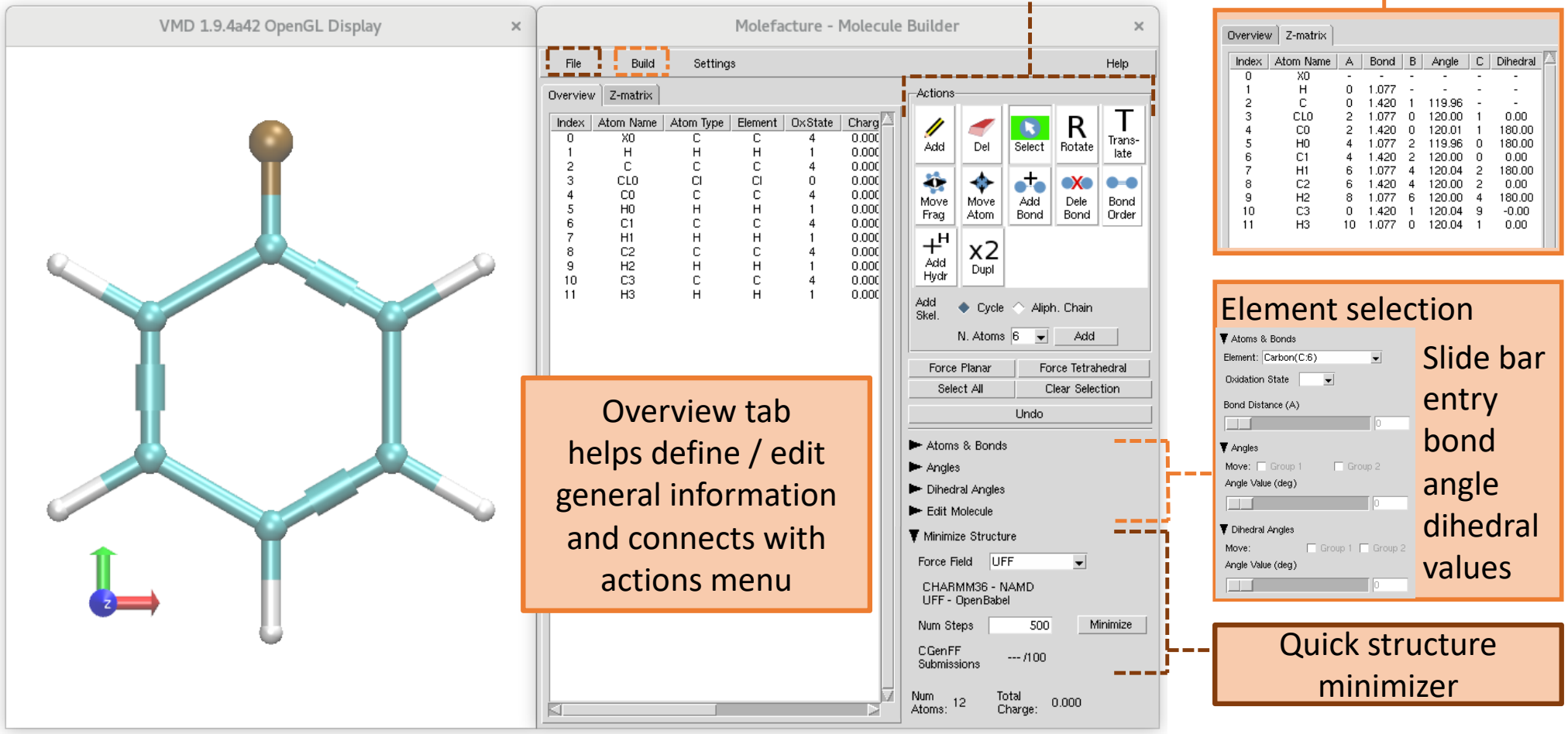
Molecular Builder and Editor: Molefacture

File menu to export into files / QMTool

Build menu to use library of fragments

Buttons for structure manipulation

Z-matrix editor



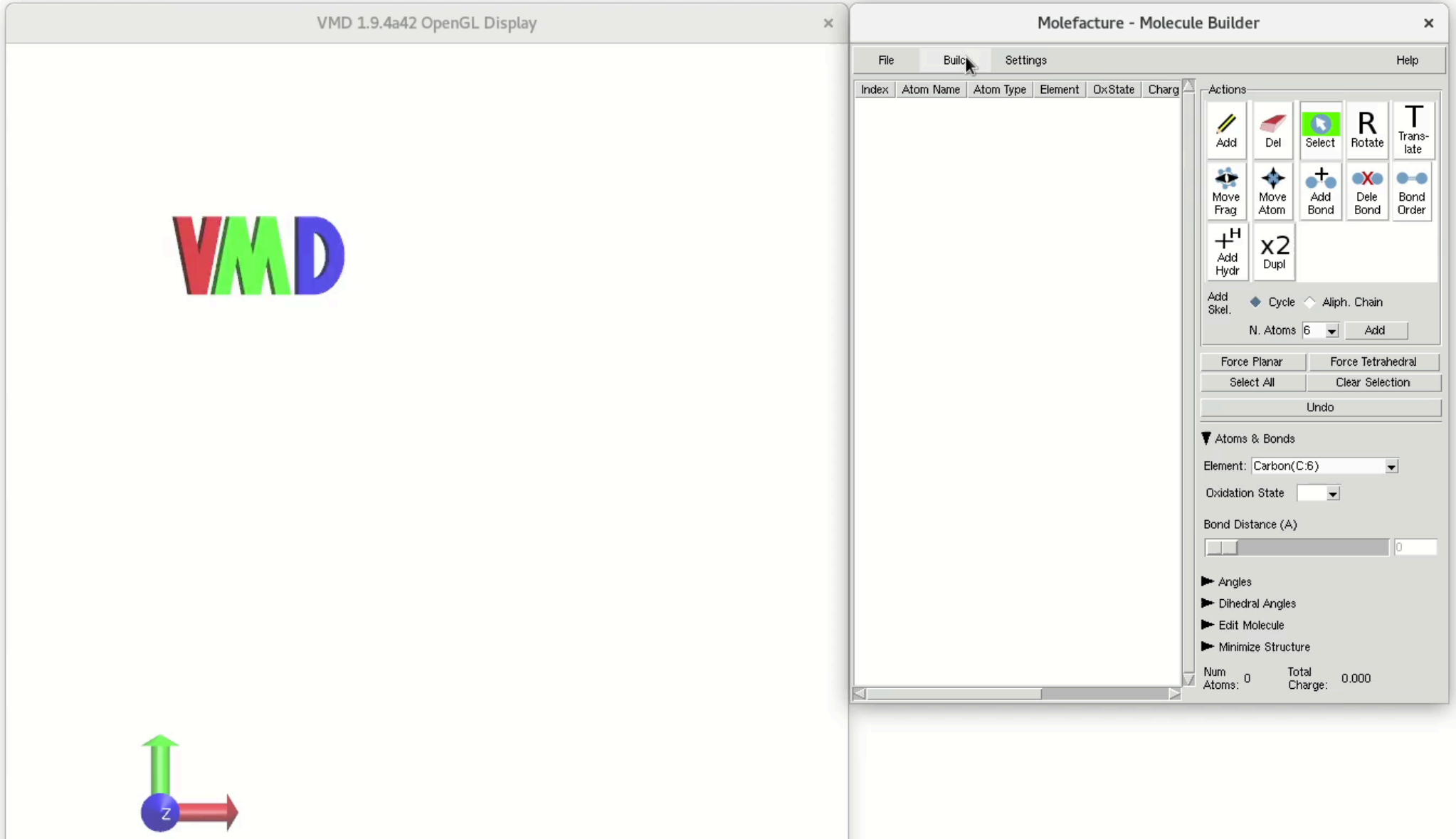
Overview tab helps define / edit general information and connects with actions menu

Element selection

Slide bar entry bond angle dihedral values

Quick structure minimizer

Molecular Builder and Editor: Molefacture



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)

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$$\sum_{impropers} k_\omega(\omega - \omega_0)^2 + \sum_{Urey-Bradley} k_u(u - u_0)^2 + \sum_{nonbonded} \epsilon_{ij}\left[\left(\frac{R_{min_{ij}}}{r_{ij}}\right)^{12} - \left(\frac{R_{min_{ij}}}{r_{ij}}\right)^{6}\right] + \frac{q_i q_j}{\epsilon r_{ij}}$$

Lennard-Jones / VdW *Coulomb/Electrostatics*

- **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 Mechanics simulations**

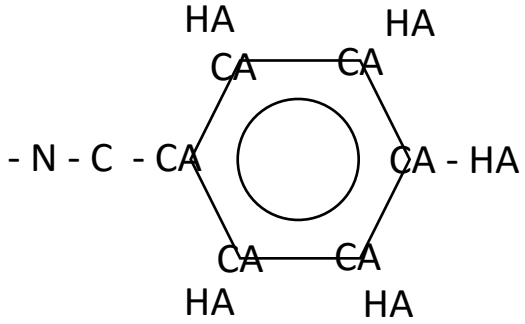
    GAAMP, **Force Field Toolkit**

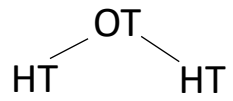
Force Field terms for MD (CHARMM)

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

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
```



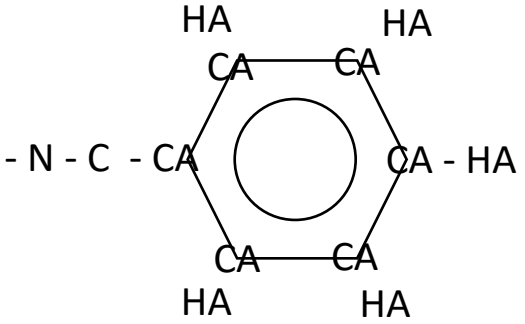


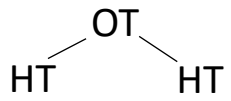
Force Field terms for MD (CHARMM)

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

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.
```



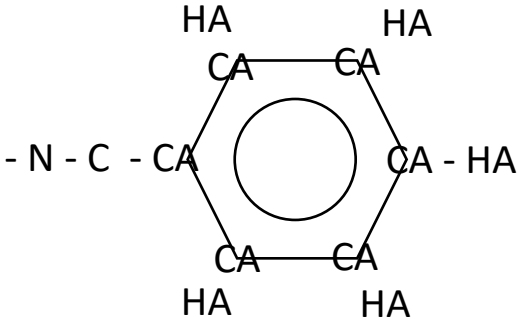


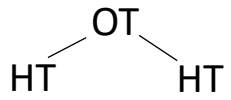
Force Field terms for MD (CHARMM)

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

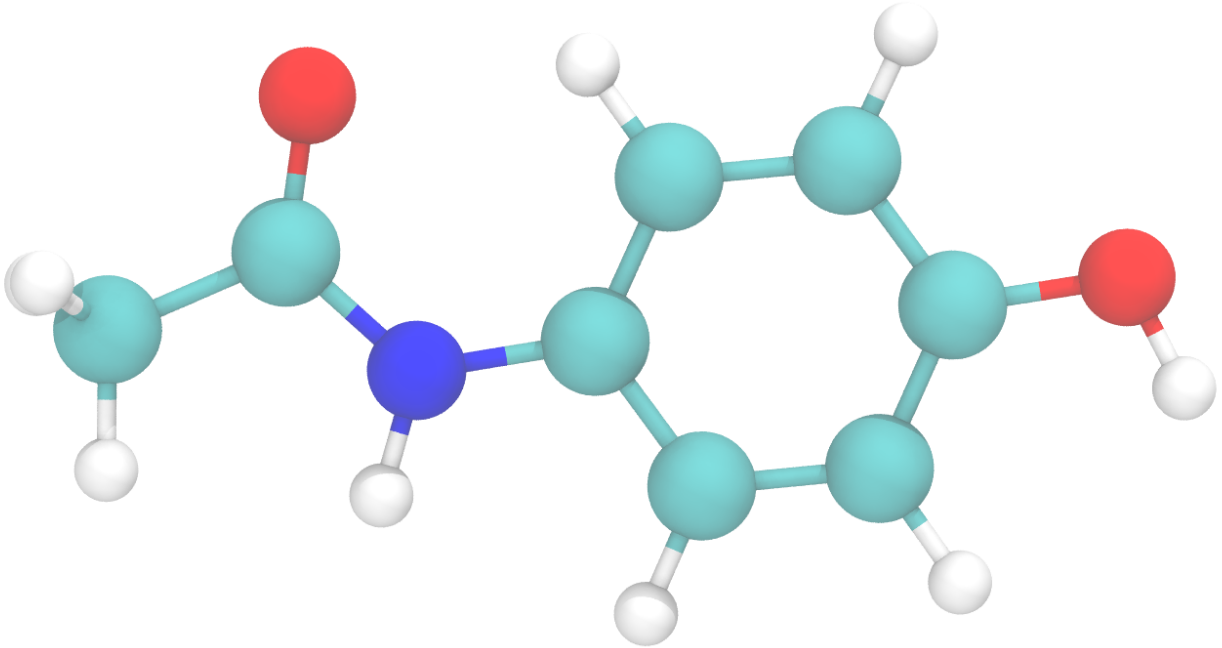
Parameter file

```
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
```



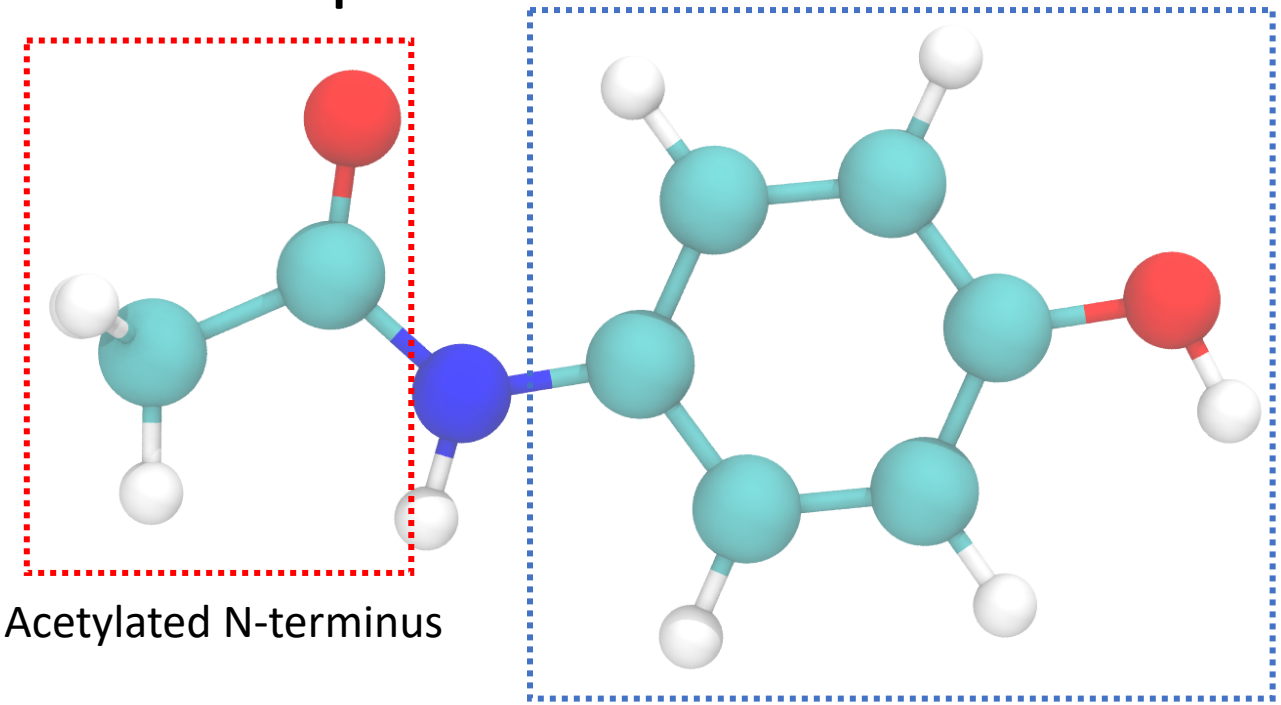


Example Case: Acetaminophen



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

Example Case: Acetaminophen



Acetylated N-terminus

Tyrosine side-chain

Topology for Ace-patch

```
PRES ACE          0.00 ! acetylated N-terminus
GROUP                  ! use in generate statement
ATOM CAY  CT3    -0.27 !
ATOM HY1  HA      0.09 !
ATOM HY2  HA      0.09 !
ATOM HY3  HA      0.09 !
GROUP                  !
ATOM CY   C       0.51 !
ATOM OY   O      -0.51 !
```

```
HY1 HY2 HY3
   \ | /
    CAY
     |
    CY=OY
     |
```

Name Type Charge

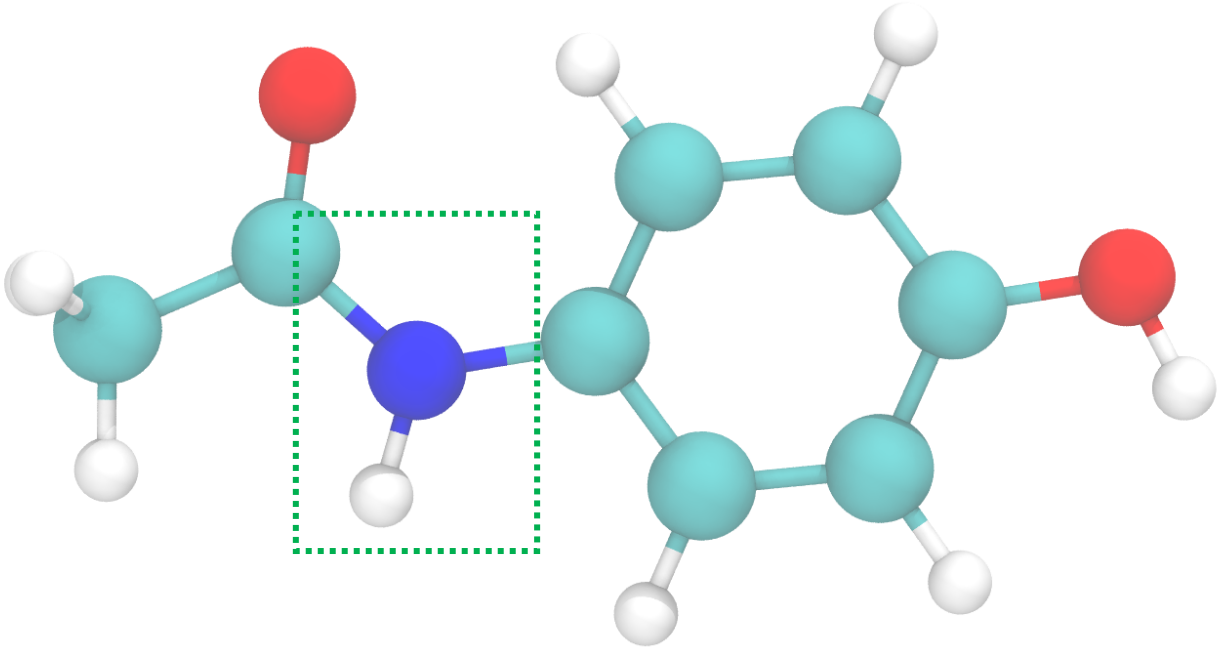
Topology file for Tyrosine

```
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
```

```
      |          HD1  HE1
HN-N             |    |
      |     HB1  CD1--CE1
      |     |   //      \\
HA-CA--CB--CG       CZ--OH
      |     |   \  __  /     \
      |     HB2  CD2--CE2     HH
   O=C             |    |
      |            HD2  HE2
```

Name Type Charge

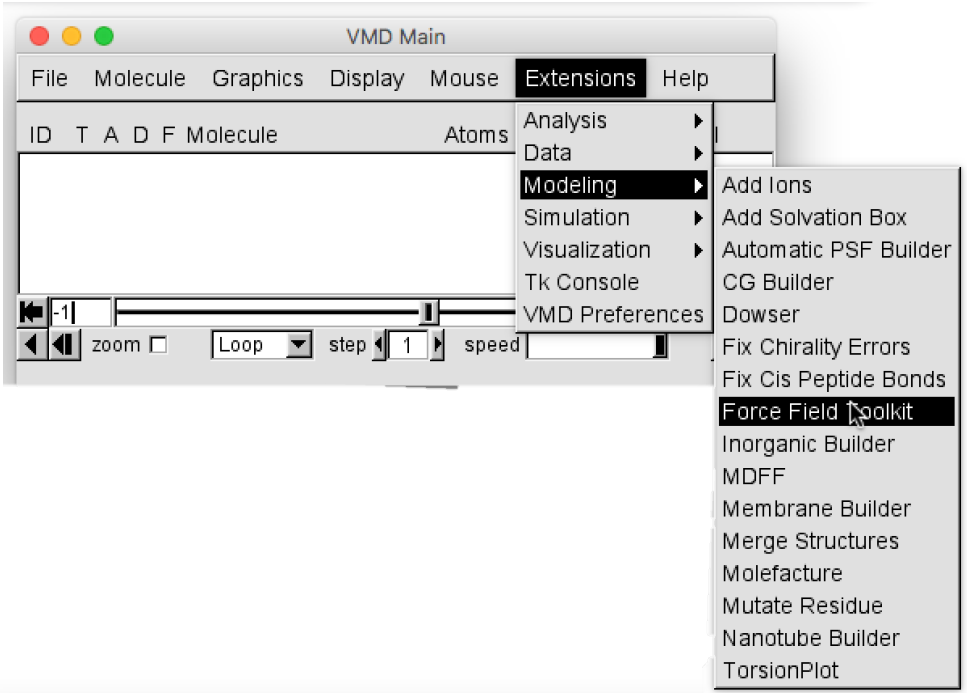
Example Case: Acetaminophen

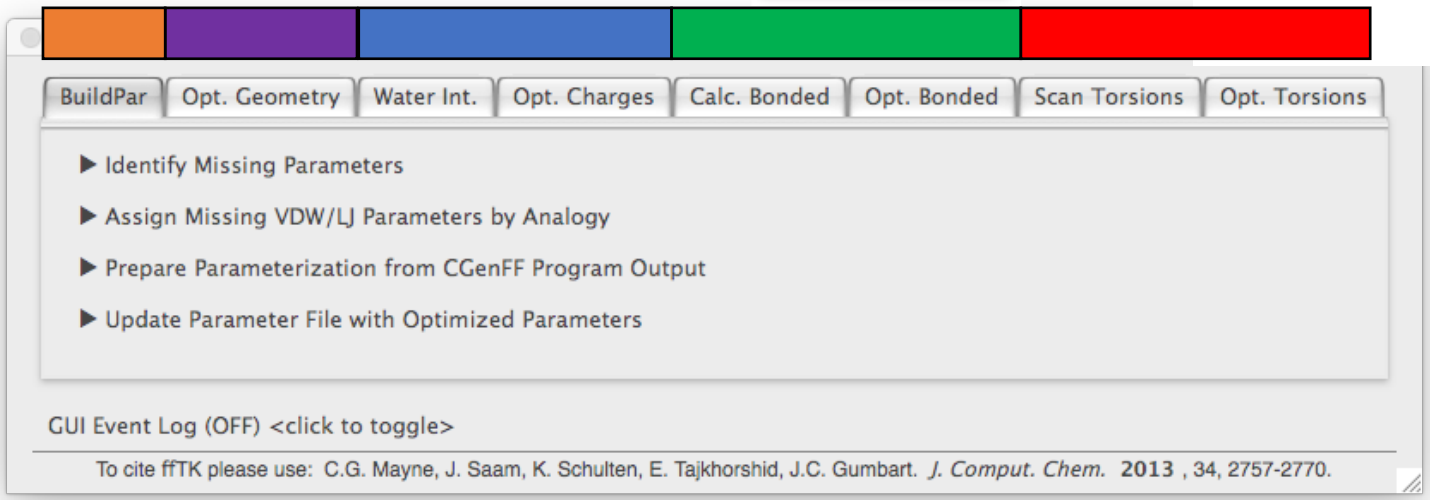


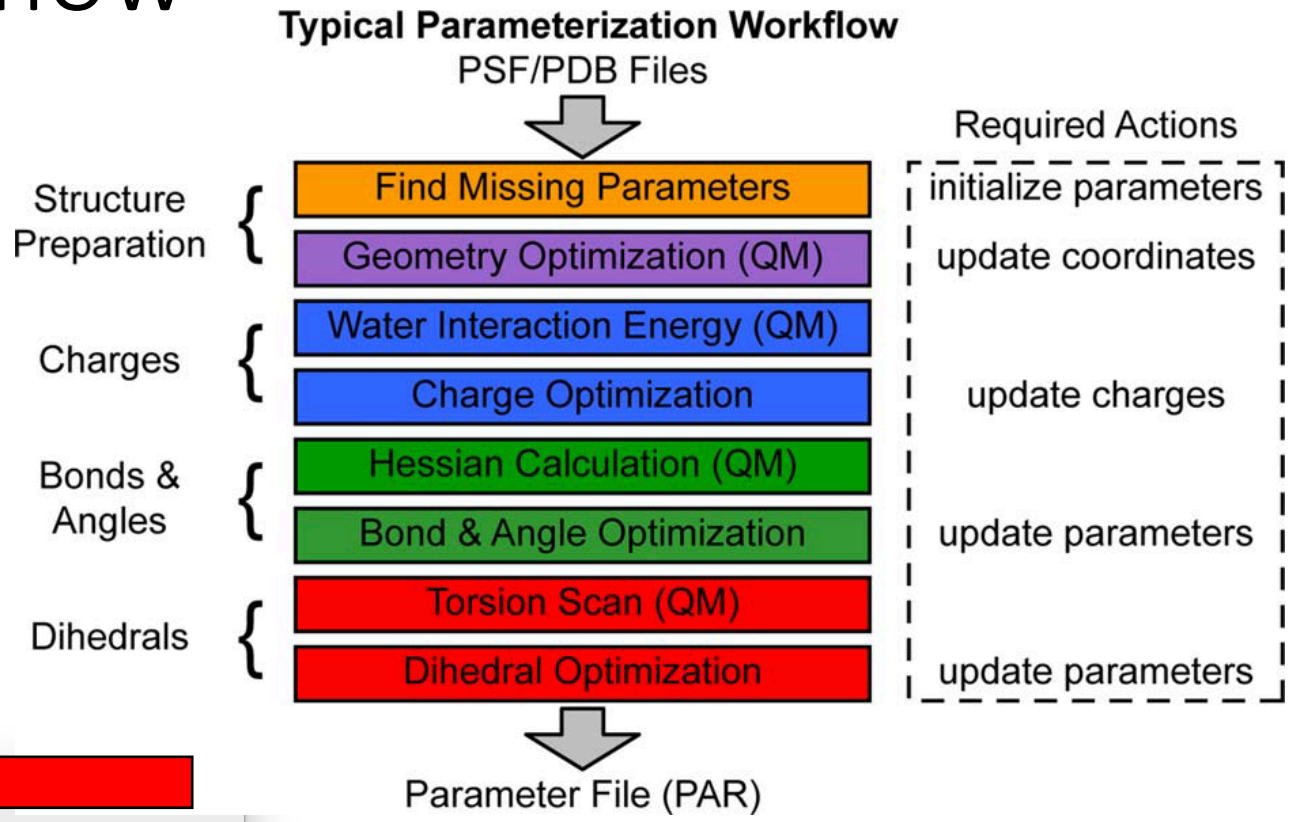
- Need to define new Atom types (N, H) and Charges: q_i
- Generate bond, angle and dihedral parameters: $(k_i^{bond}, r_0, k_i^{ang}, \theta_0, k_i^{dih}, n_i, \delta_i)$

Force Field Toolkit

Force Field Toolkit Workflow

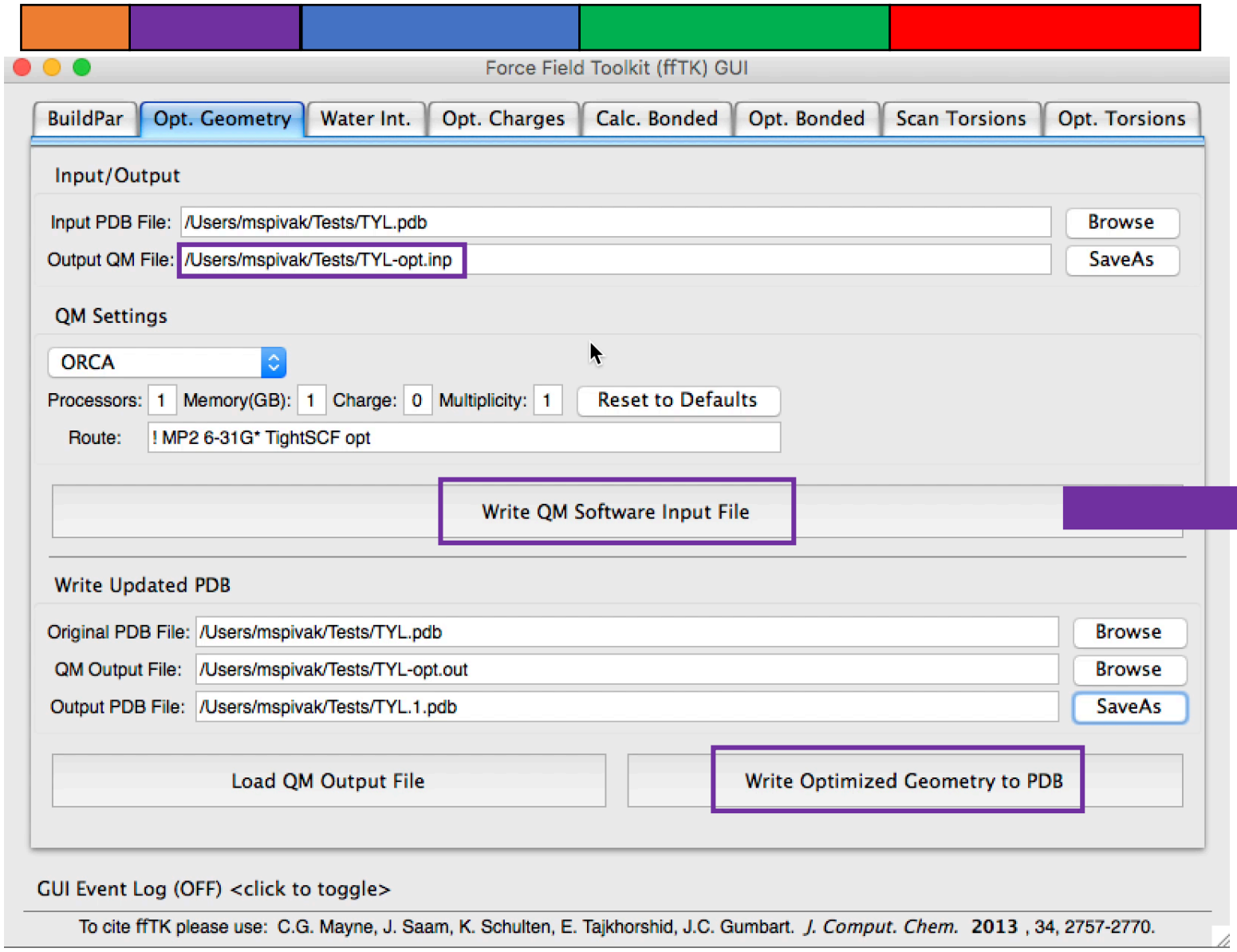






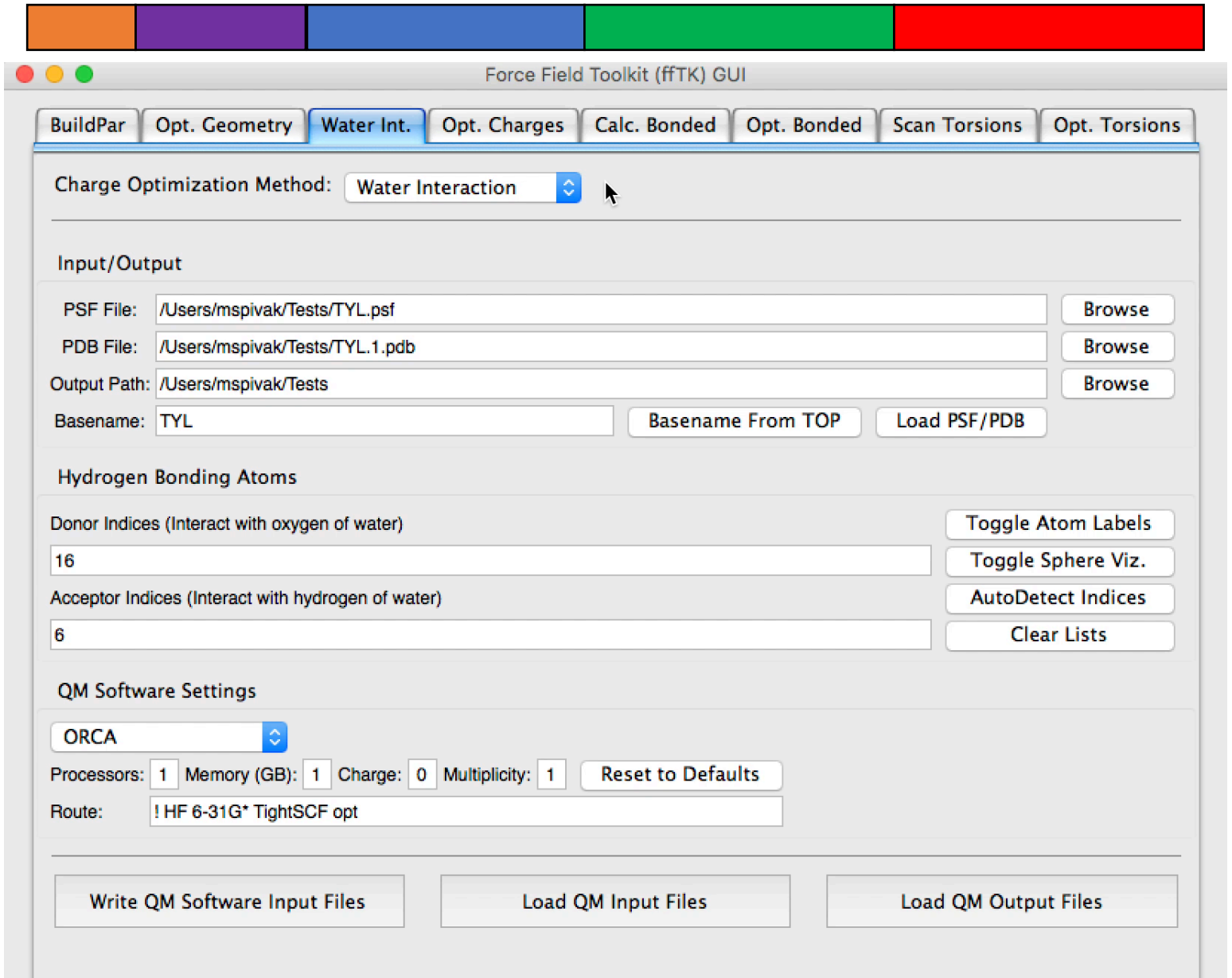
- FFTK generates all but the VDW/LJ Parameters
- Requires a Quantum Mechanics (QM) Software GAUSSIAN or ORCA (new)

Force Field Toolkit Workflow



Run QM Simulation externally

Force Field Toolkit Workflow

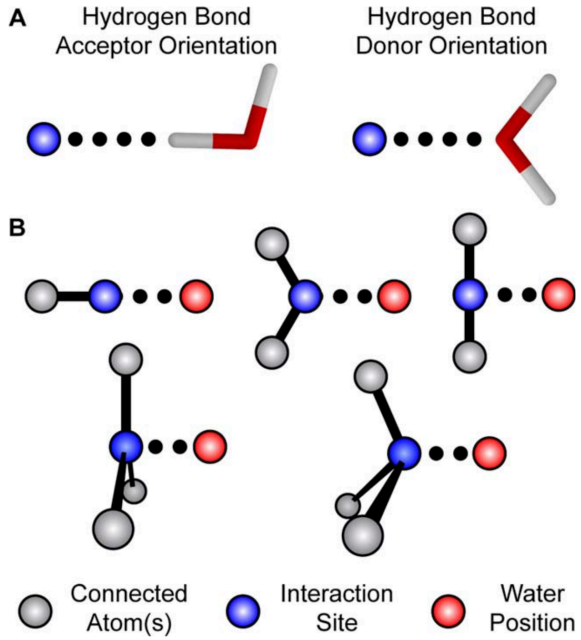


- AMBER: RESP Fitting

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.

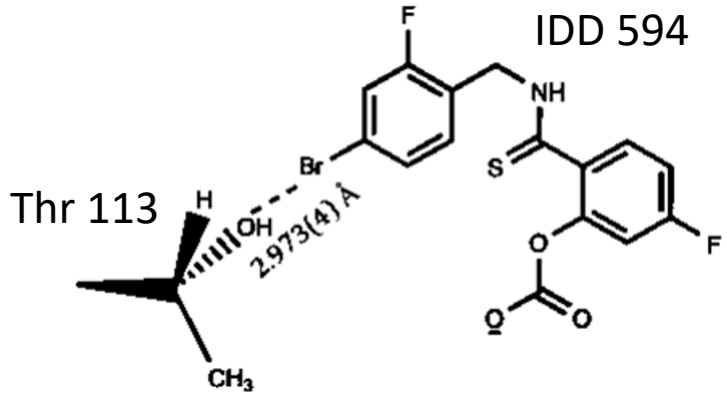


New Development: Halogen parametrization

- 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
A · · · H–D

Halogen bond
A · · · X–D

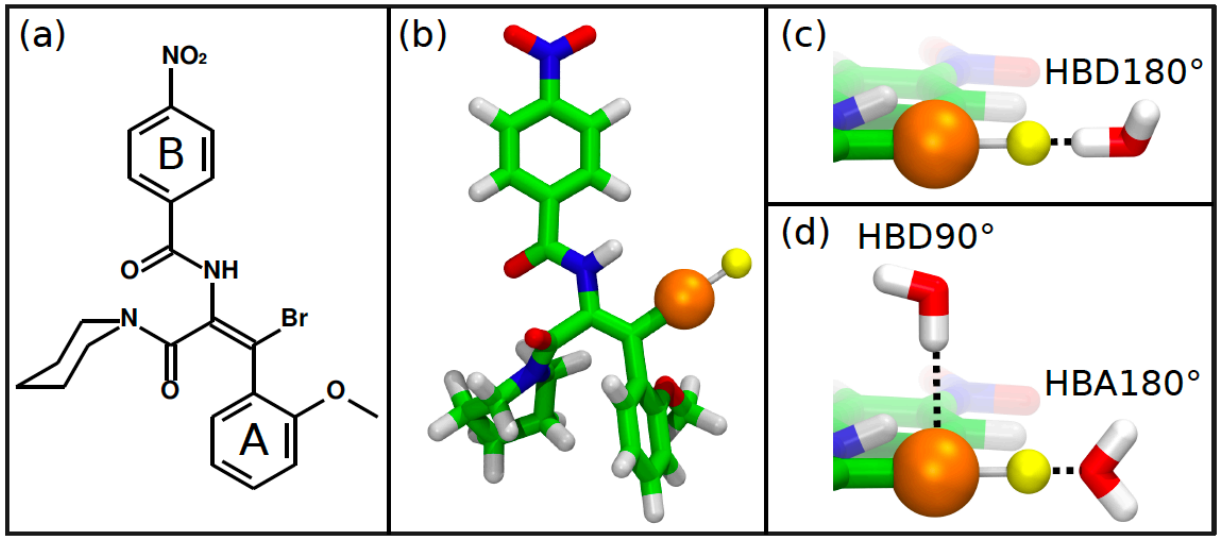


Human Aldose Reductase-Inhibitor complex

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.



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NAMD Scalable Molecular Dynamics

VMD Visual Molecular Dynamics

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