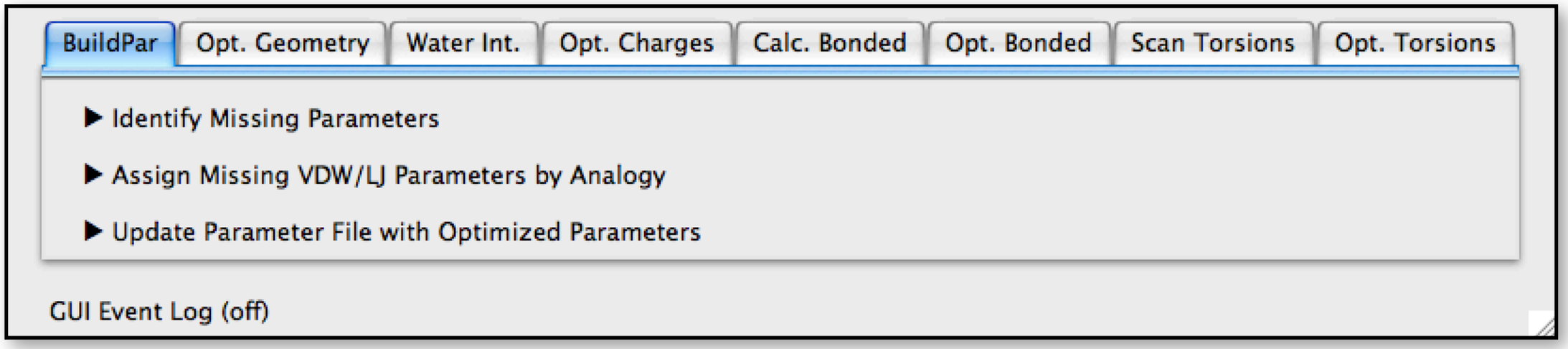
Parameterizing Small Molecules Using:

The Force Field Toolkit (*ff*TK)



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NIH Hands On Workshop | TCBG | November 19th, 2013

MD Simulations of Biological Systems

Molecular Mechanics Force Fields

$$U = \underbrace{U_{bonds} + U_{angles} + U_{dihedrals}}_{\text{bonded}} + \underbrace{U_{vdW} + U_{coulombic}}_{\text{non-bonded}}$$

The CHARMM Force Field

$$U = \sum_{bonds} k_i^{bond}(r_i - r_0)^2 + \sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2 +$$

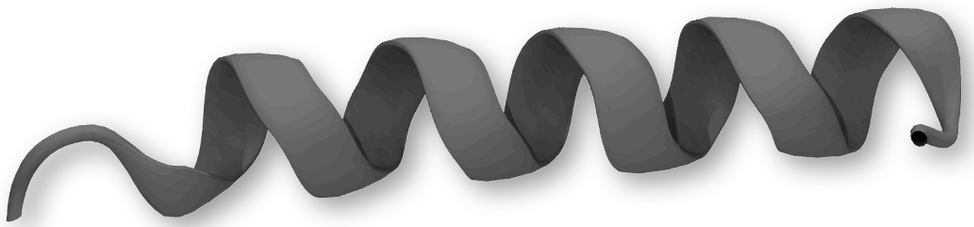
$$\sum_{dihedrals} k_i^{dihedral}[1 + \cos(n_i\phi_i + \delta_i)] +$$

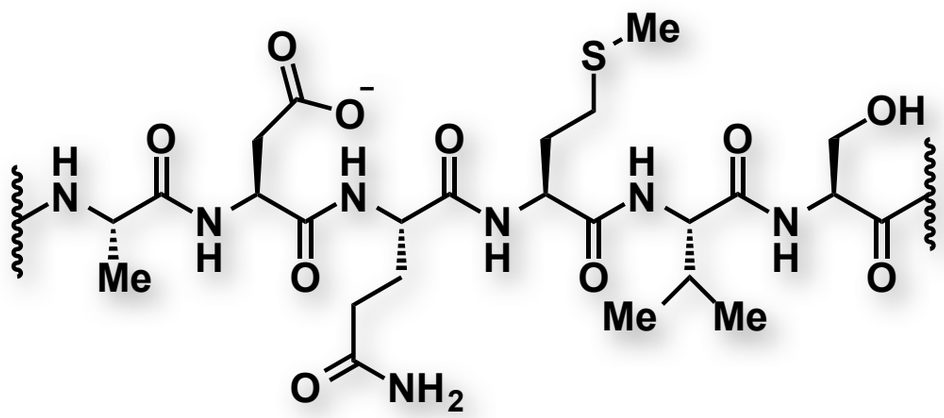
$$\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{r_{ij}}$$

Parameter Transferability In Biopolymers

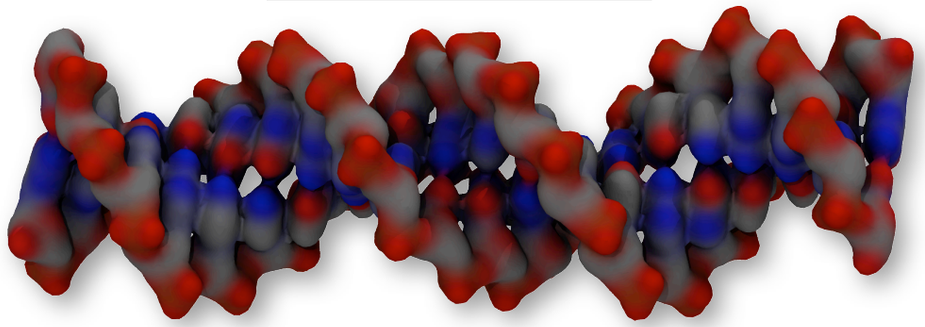
Parameter set describes molecular behavior in varied chemical (connectivity) and spatial (conformation) contexts

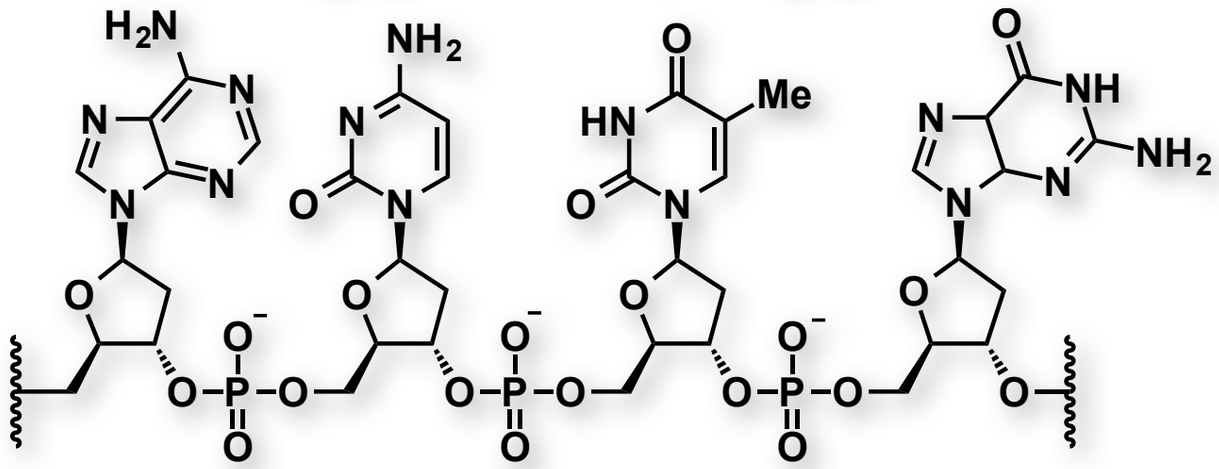
Peptides and Proteins



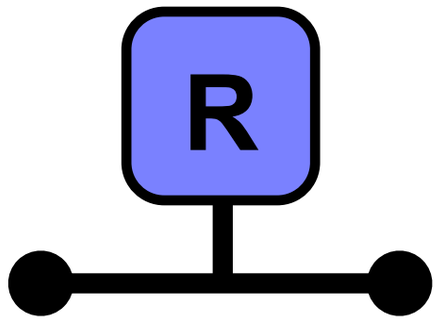


Nucleic Acids





Key Features:

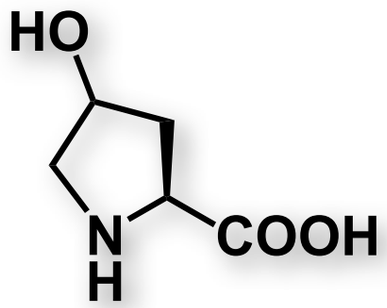


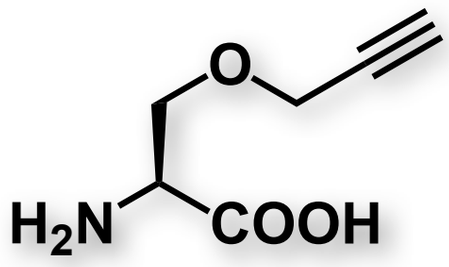
limited set of isolated building blocks

repetitive backbone unit

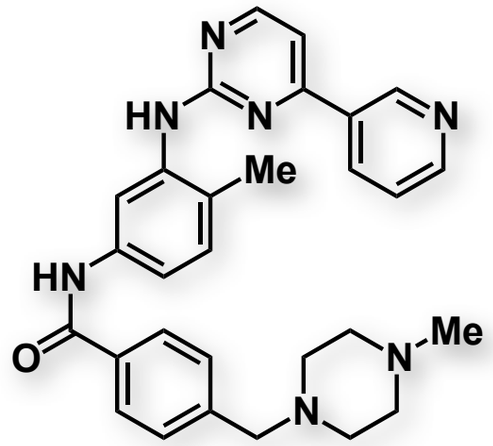
Parameterization as an Impasse

non-standard or engineered amino acids

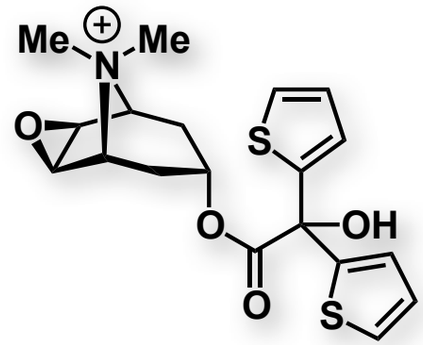




small molecule ligands

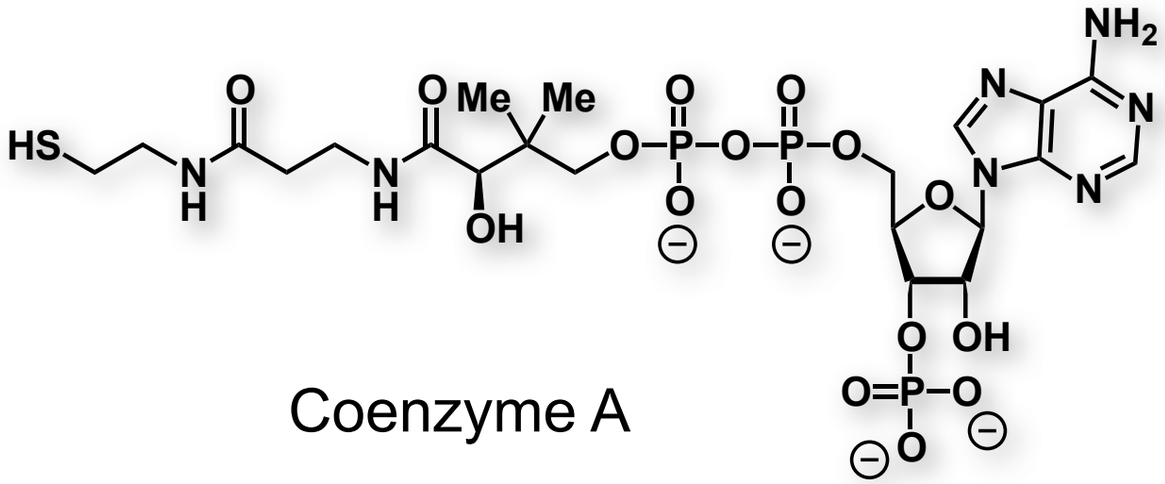


Imatinib (Gleevec)



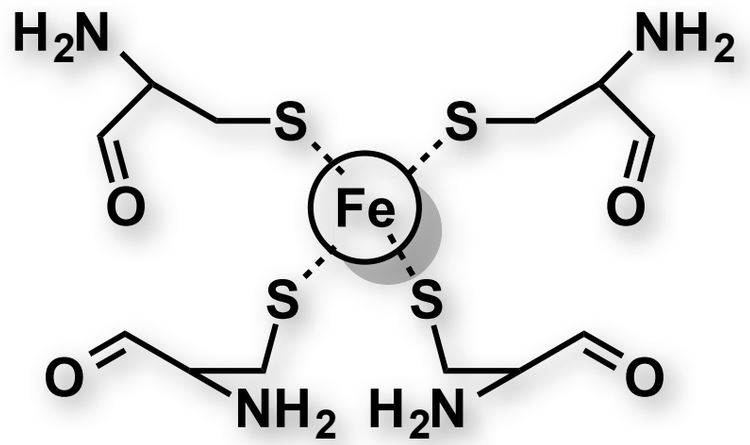
Tiotropium (Spiriva)

cofactors

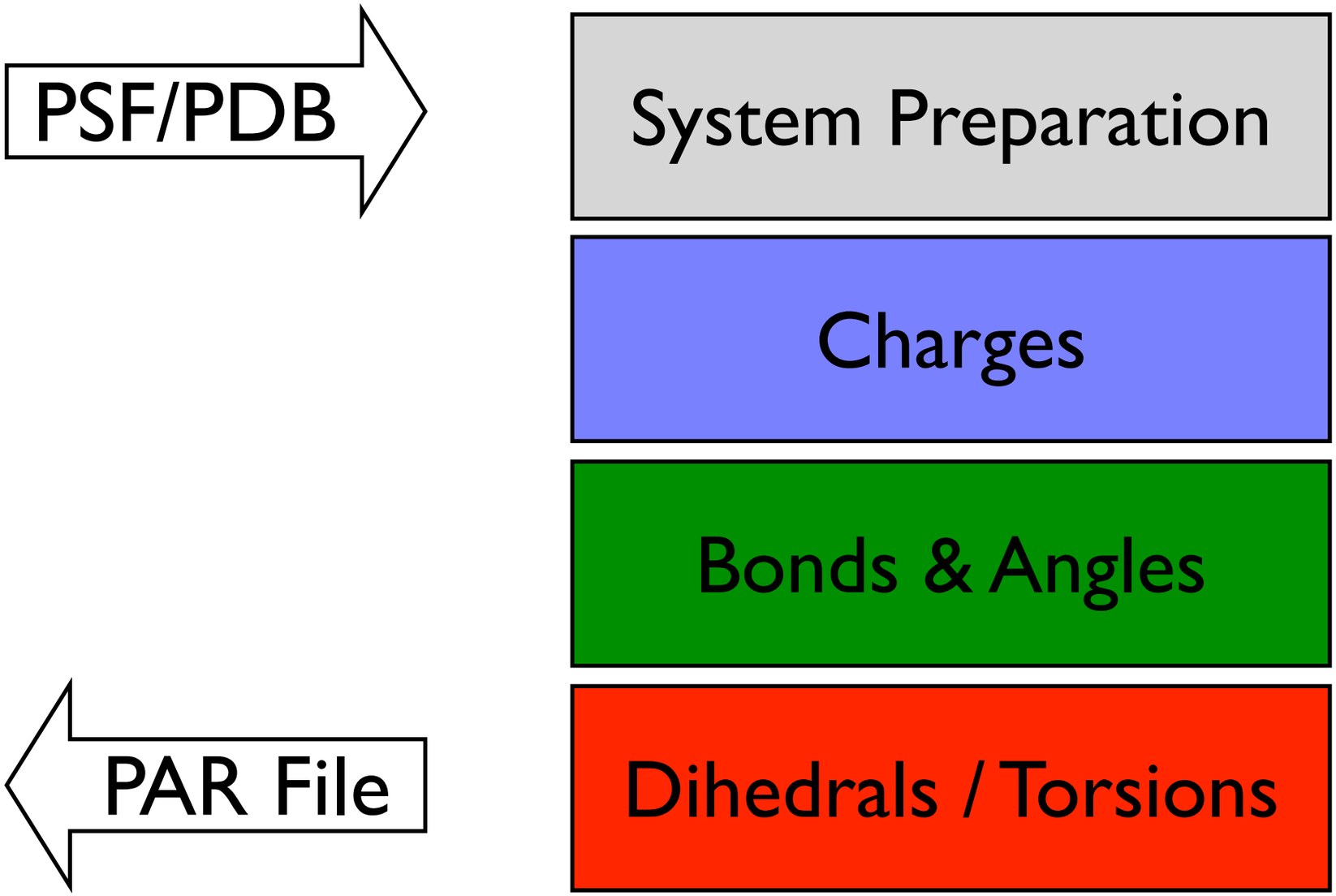


Coenzyme A

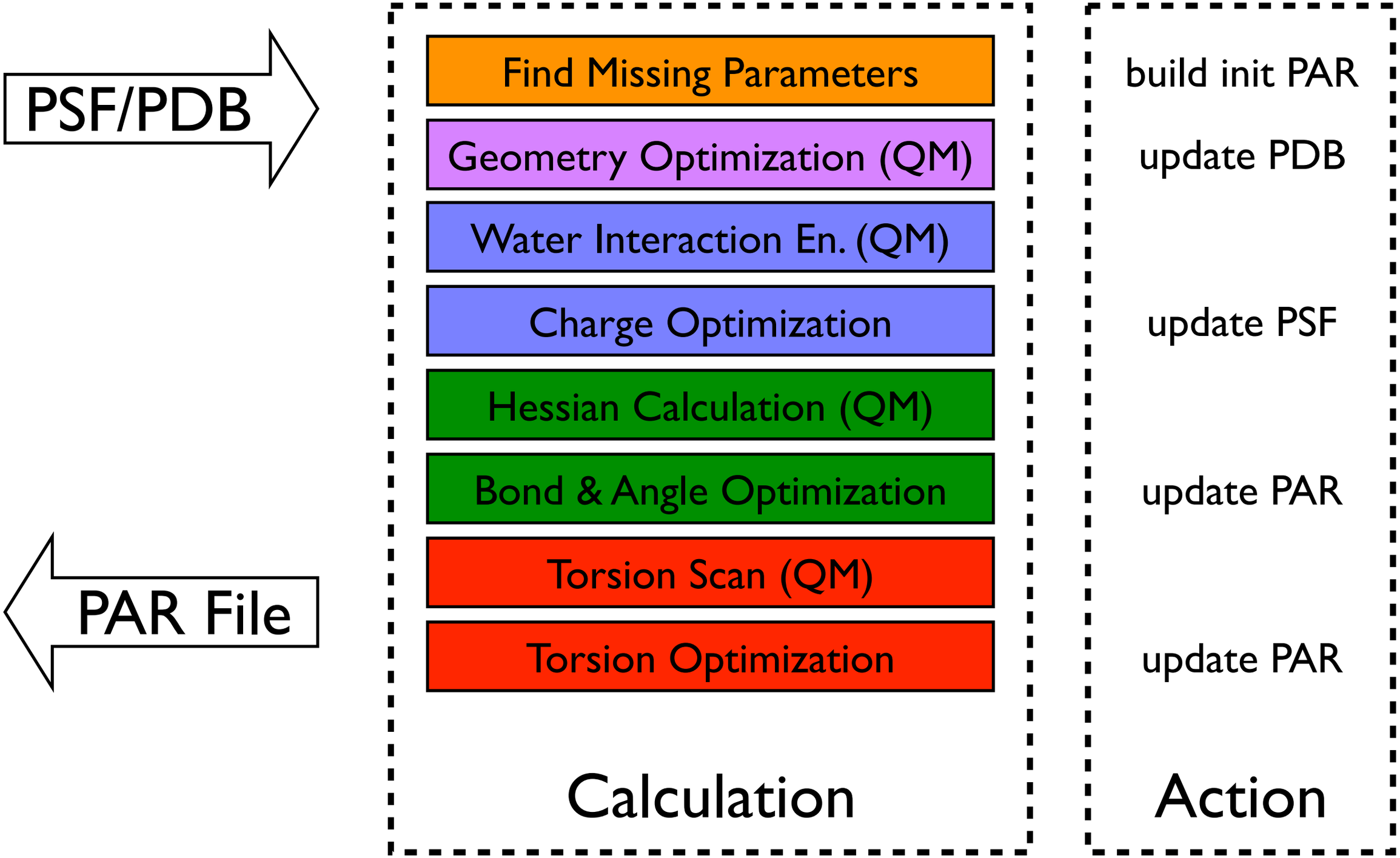
metal centers



General Parameterization Workflow

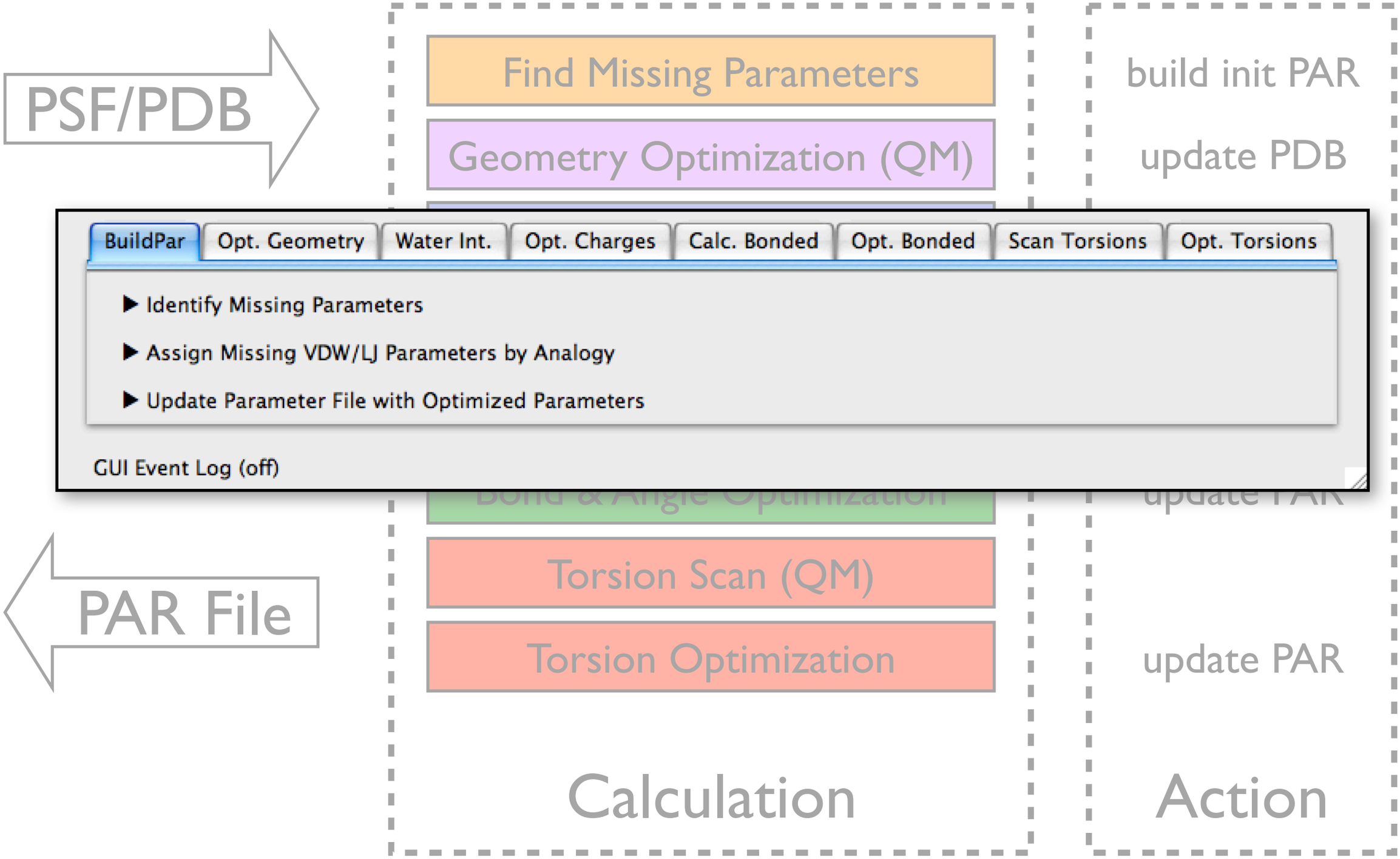


CGenFF Parameterization Workflow



K. Vanommeslaeghe *et al.*, *J. Comput. Chem.* **2010**, 31, 671-690.

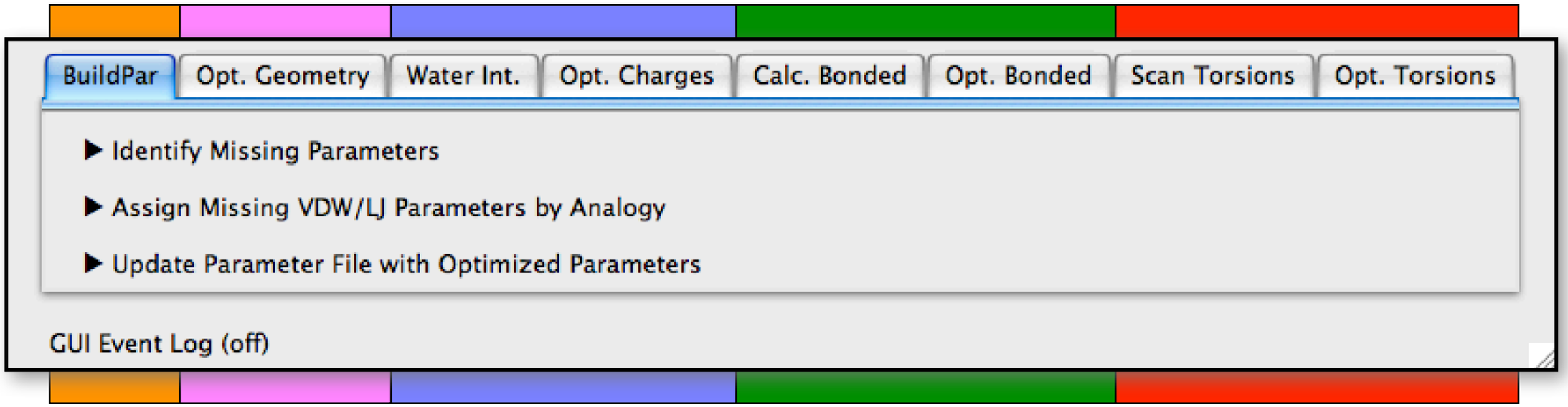
CGenFF Parameterization Workflow



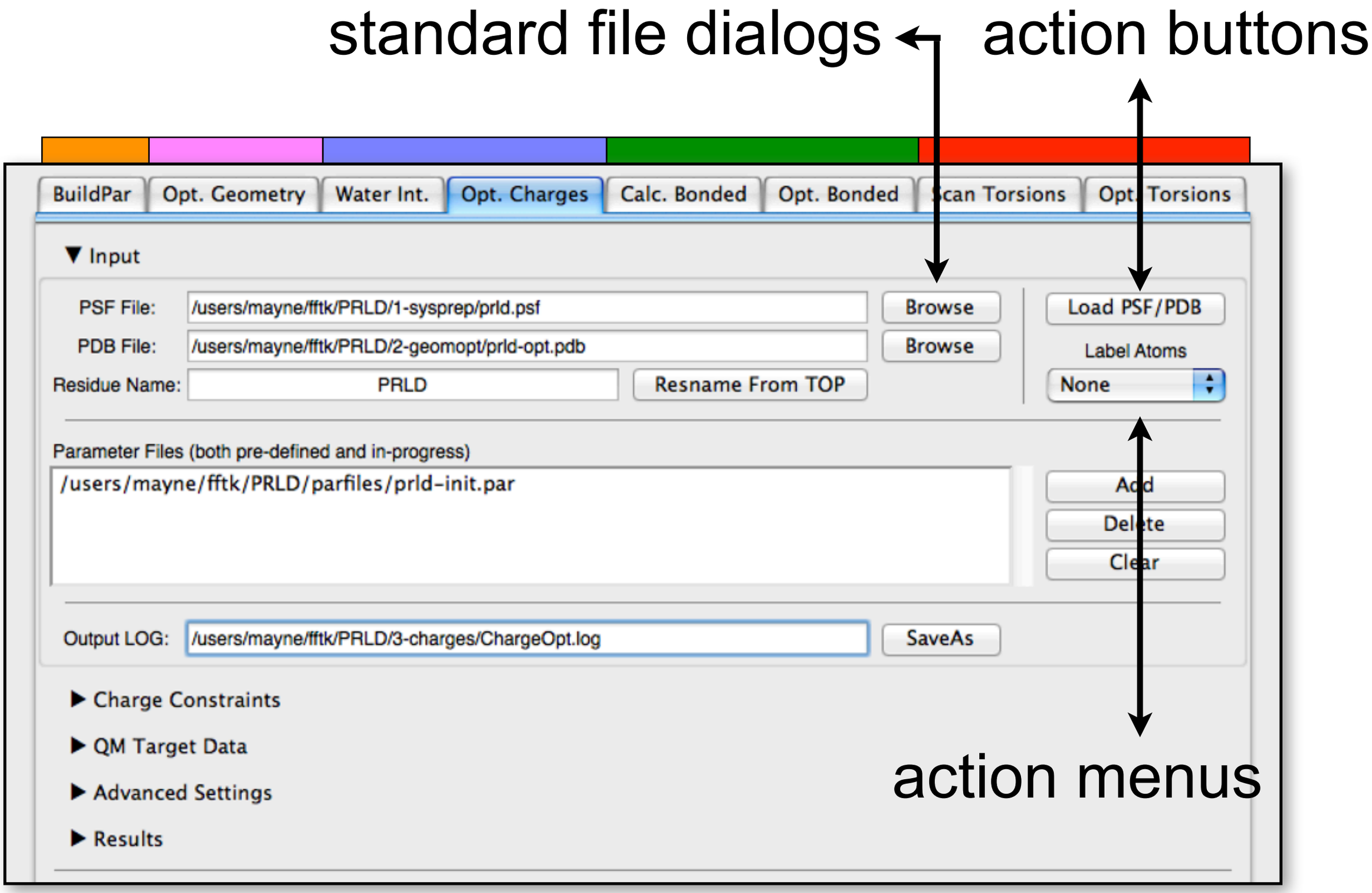
C.G. Mayne *et al.*, *J. Comput. Chem.* **2013**, 34, 2757-2270.

*ff*TK Interface

tasks organized under tabs



*ff*TK Interface



Functionality Provided by *ff*TK

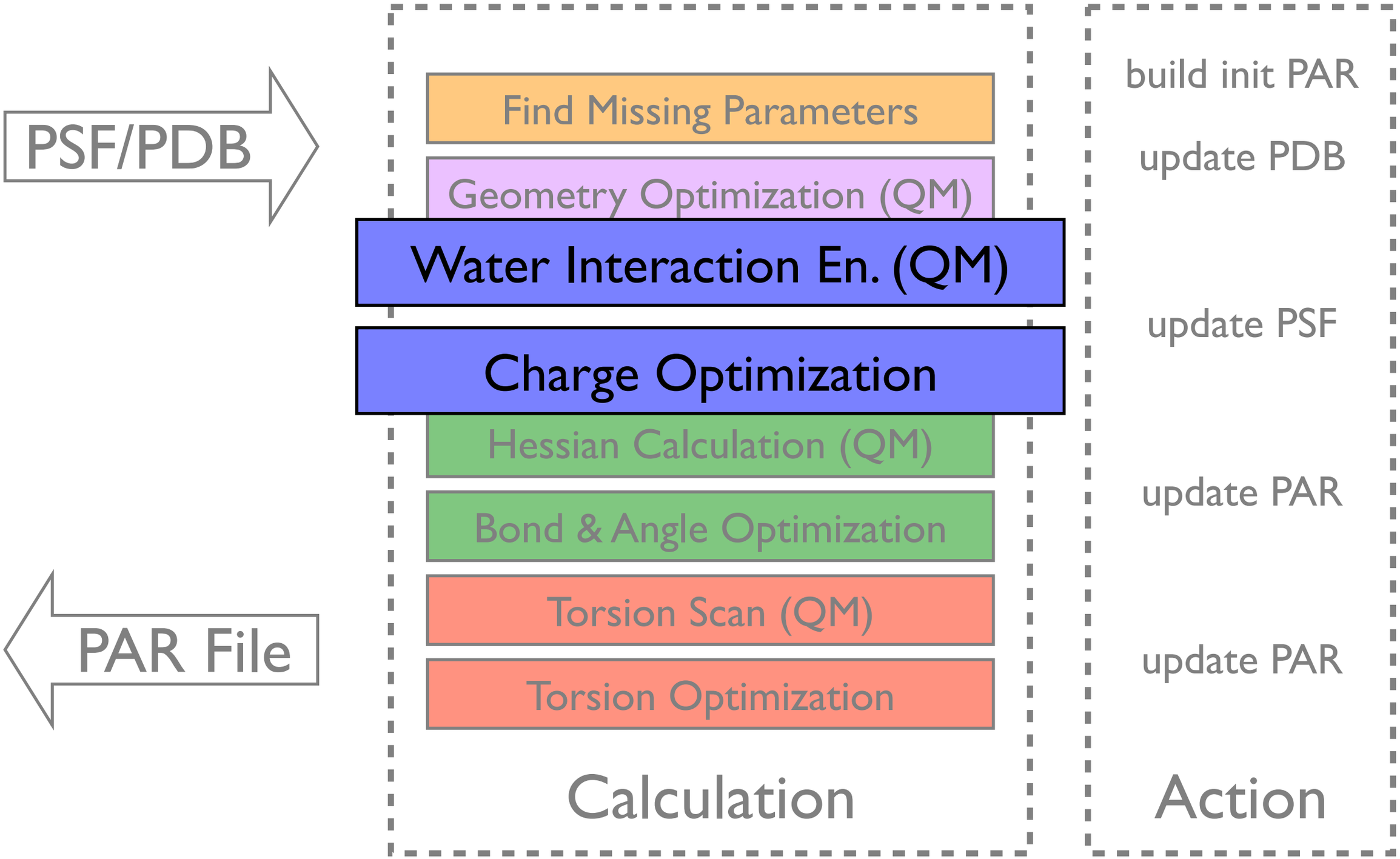
Core Functions

- Setup & Perform Multi-dimensional Optimizations
- Abstraction of Gaussian I/O (QM)
- Assess Performance of Parameters by Visualizing Optimization Data

Support Functions

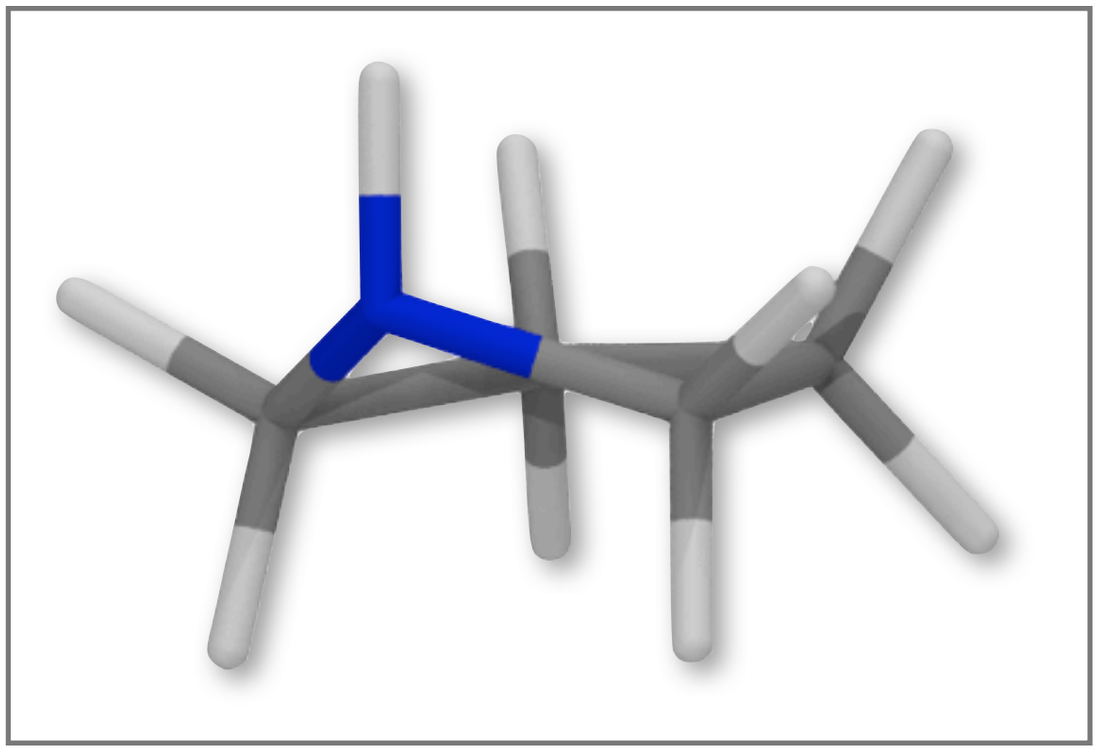
- Auto-detect Water Interaction Sites
- Auto-detect Charge Groups
- Auto-detect Non-redundant Torsions
- Build & Update Parameter Files
- Browse Existing Parameter Sets
- Write Updated Charges to PSF
- Reset Opt. Input from Output
- Visualize Target Data in VMD
- Create Graphic Objects in VMD
- Label Atoms in VMD
- Read Input Parameters from File
- Read/Write Data From Opt. Logs
- Export Plot Data to File
- Monitor Optimization Progress

*ff*TK Exemplified by Charge Optimization



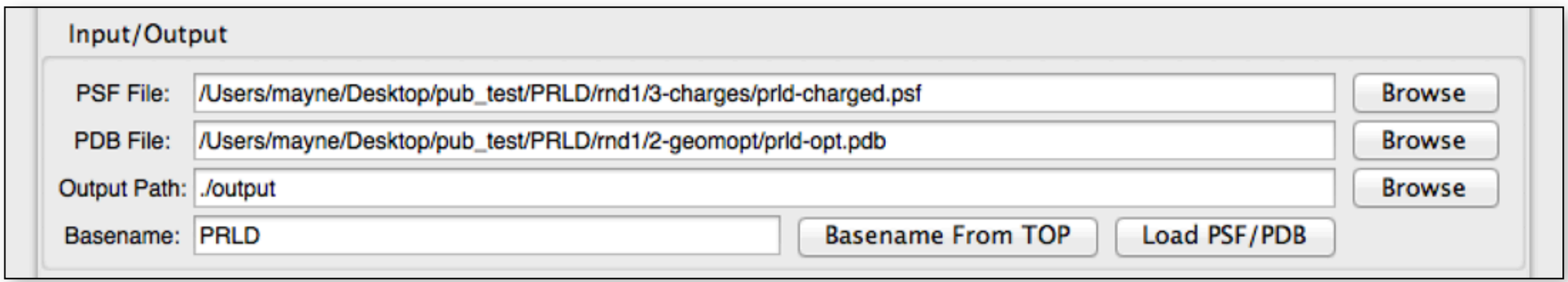
Generating Charge Optimization Target Data

Load QM optimized geometry | Auto-detect interaction sites | Genera



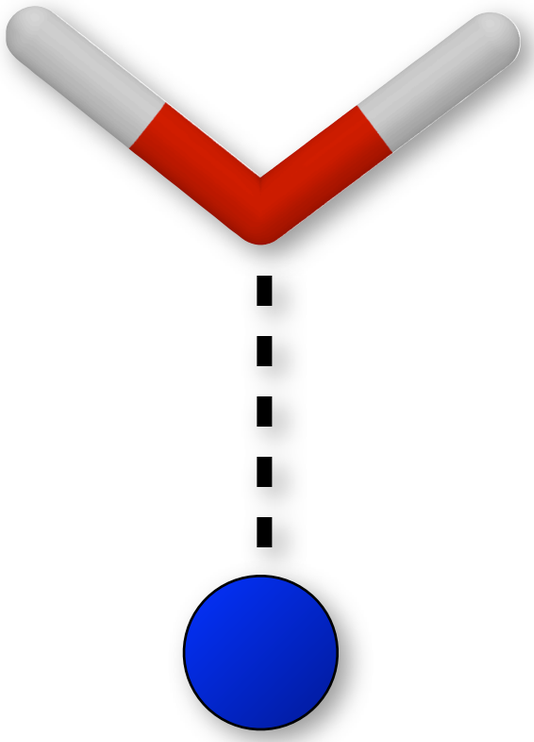
VMD main window

*ff*TK GUI

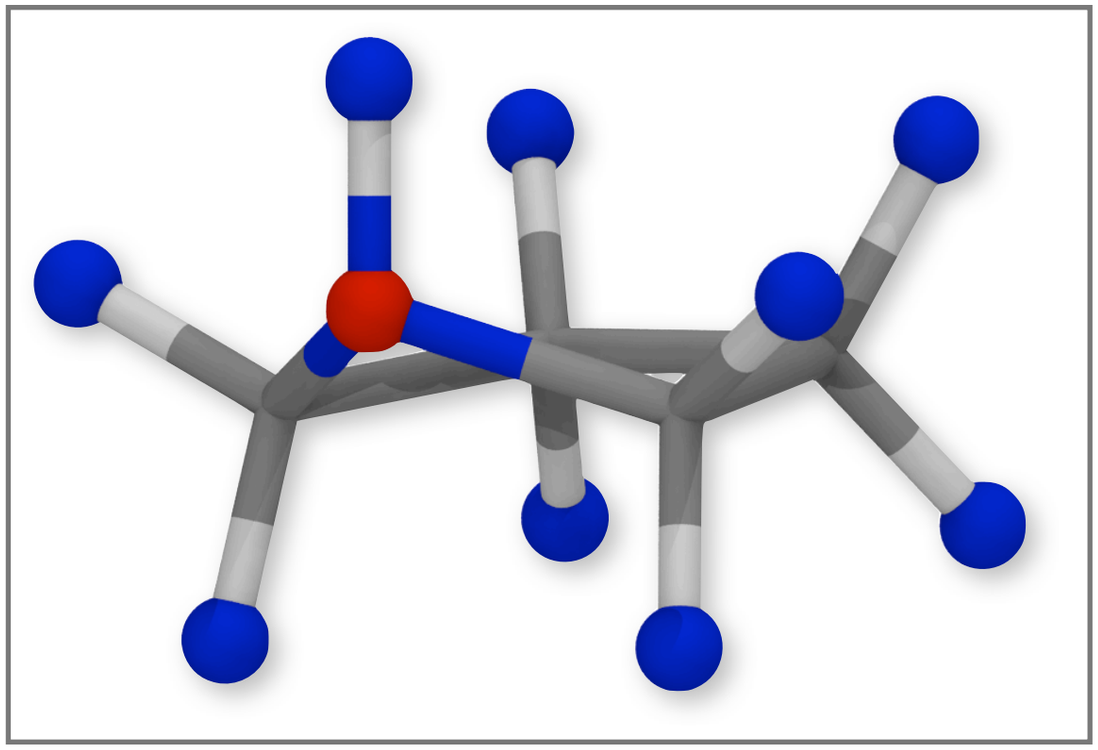


Generating Charge Optimization Target Data

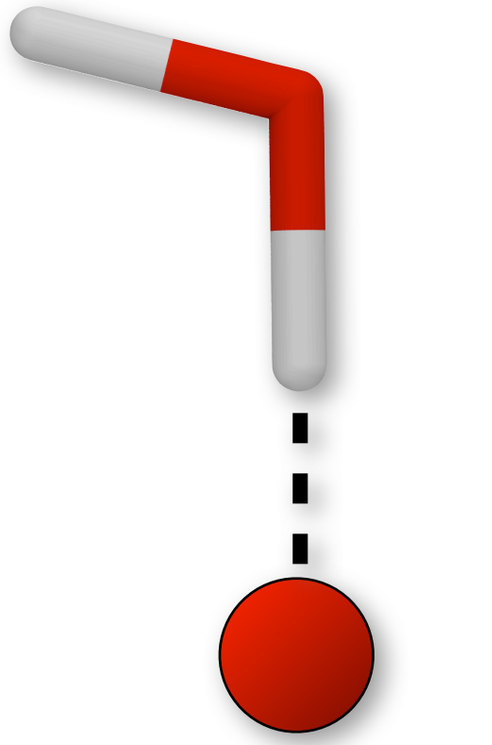
geometry | Auto-detect interaction sites | Generate Gaussian Input Files | Run



Donor

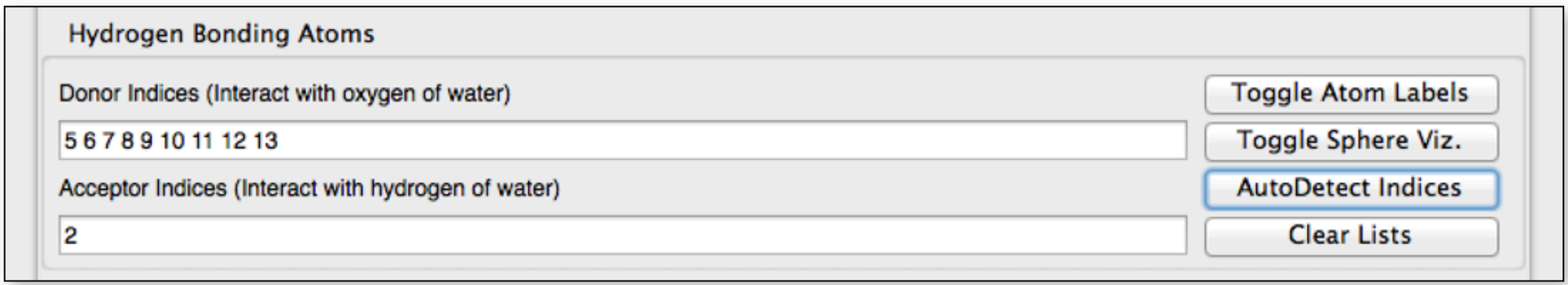


VMD main window



Acceptor

*ff*TK GUI

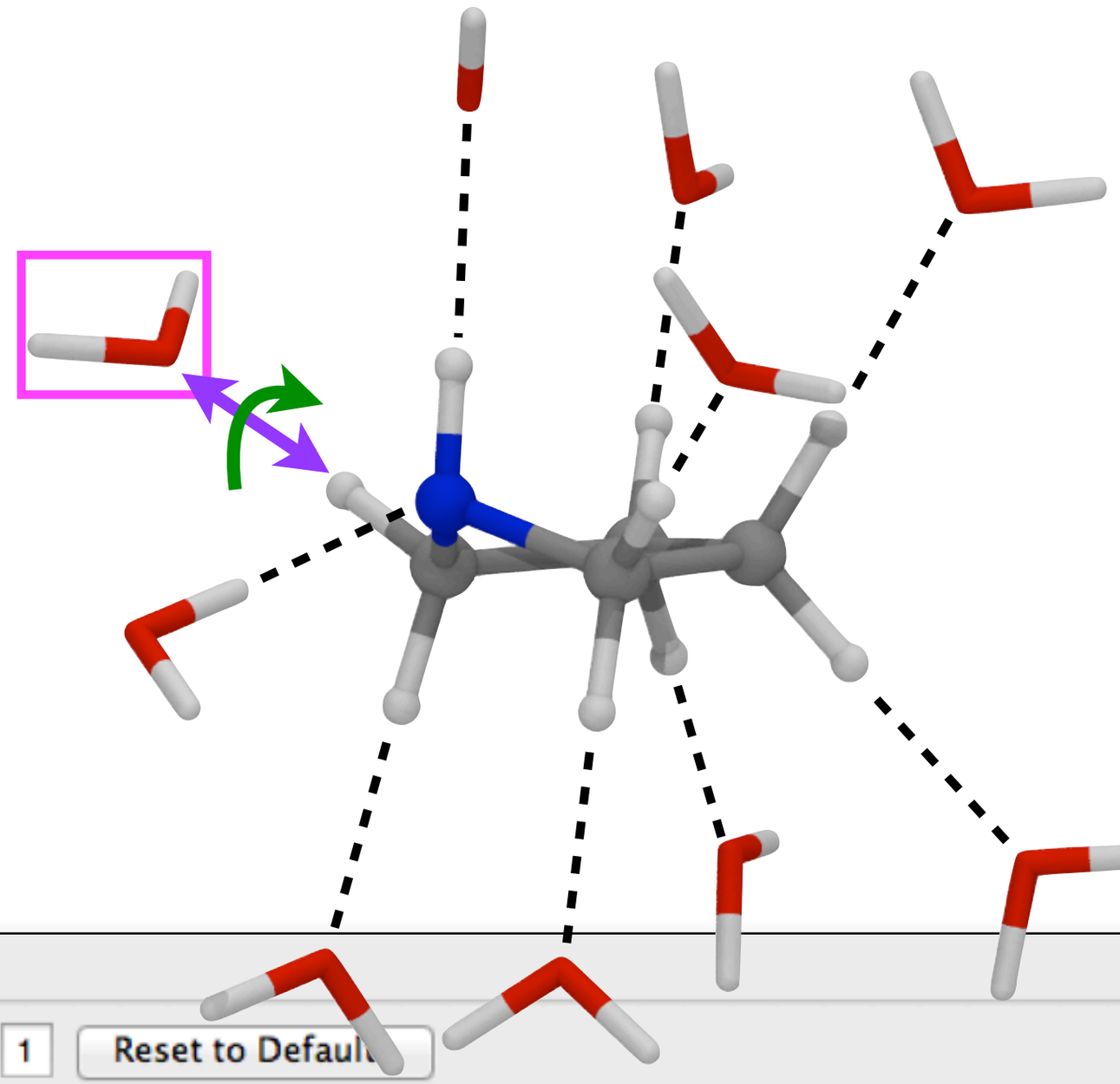


Generating Charge Optimization Target Data

on sites | Generate Gaussian Input Files | Run QM | Inspect water optimization

Compute water position

Optimize
distance & rotation



ffTK GUI

Gaussian Settings

Processors: 1 Memory (GB): 1 Charge: 0 Multiplicity: 1 Reset to Default

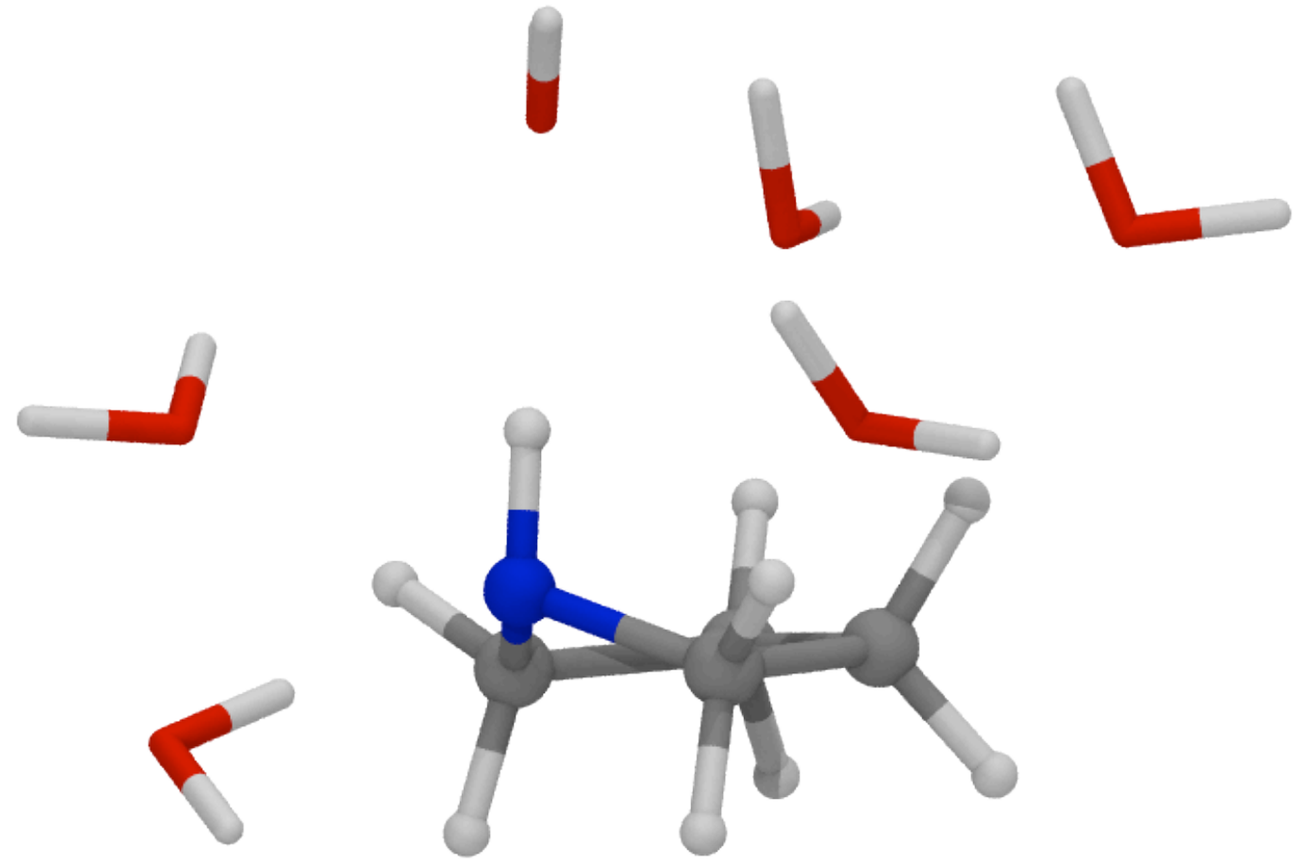
Route: # HF/6-31G* Opt=(Z-matrix,MaxCycles=100) Geom=PrintInputOrient

Write Gaussian Input Files | Load GAU Files | Load LOG Files

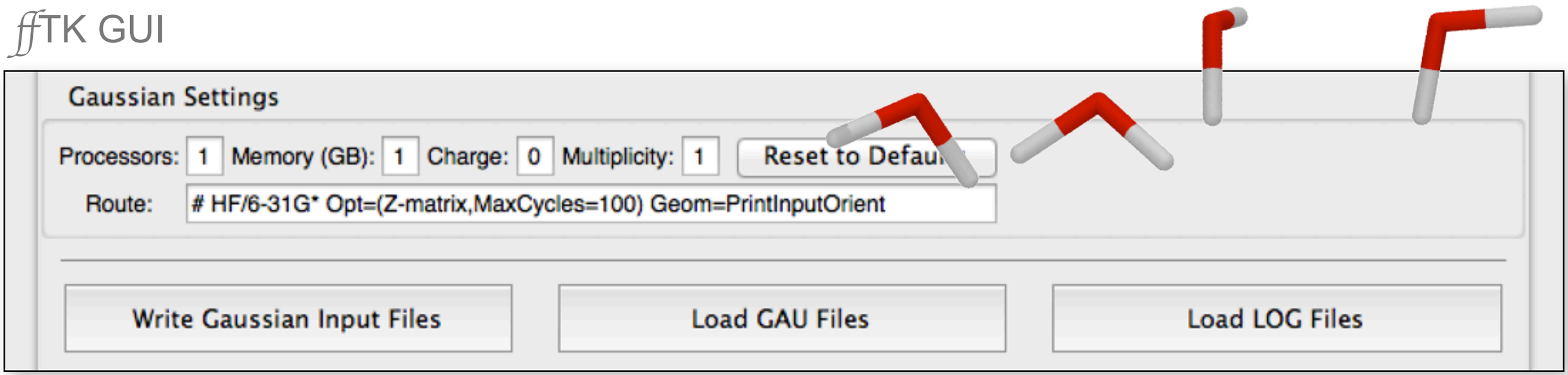
Generating Charge Optimization Target Data

| Run QM | Inspect water optimization

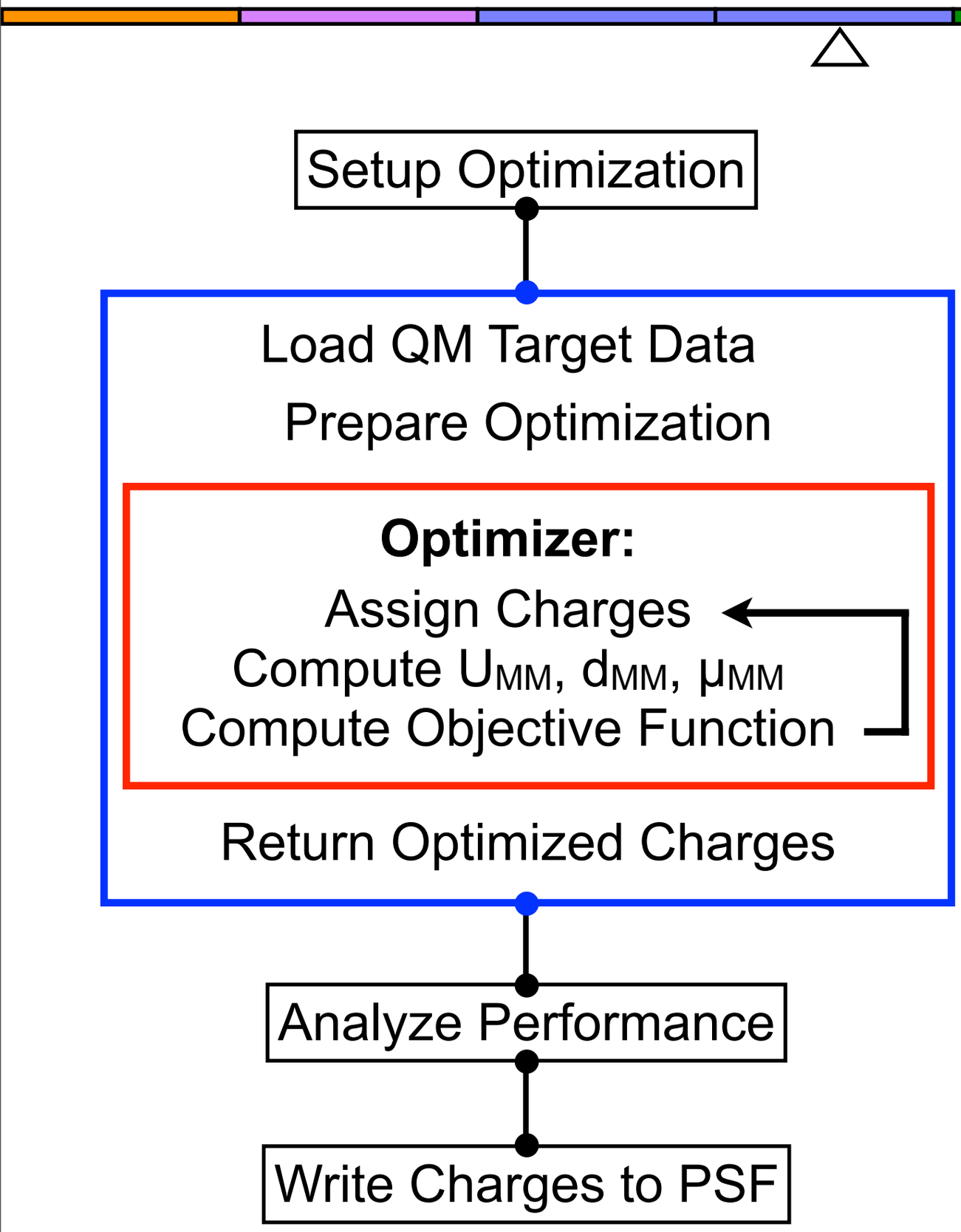
Visually assess QM-optimized water position(s)



*ff*TK GUI



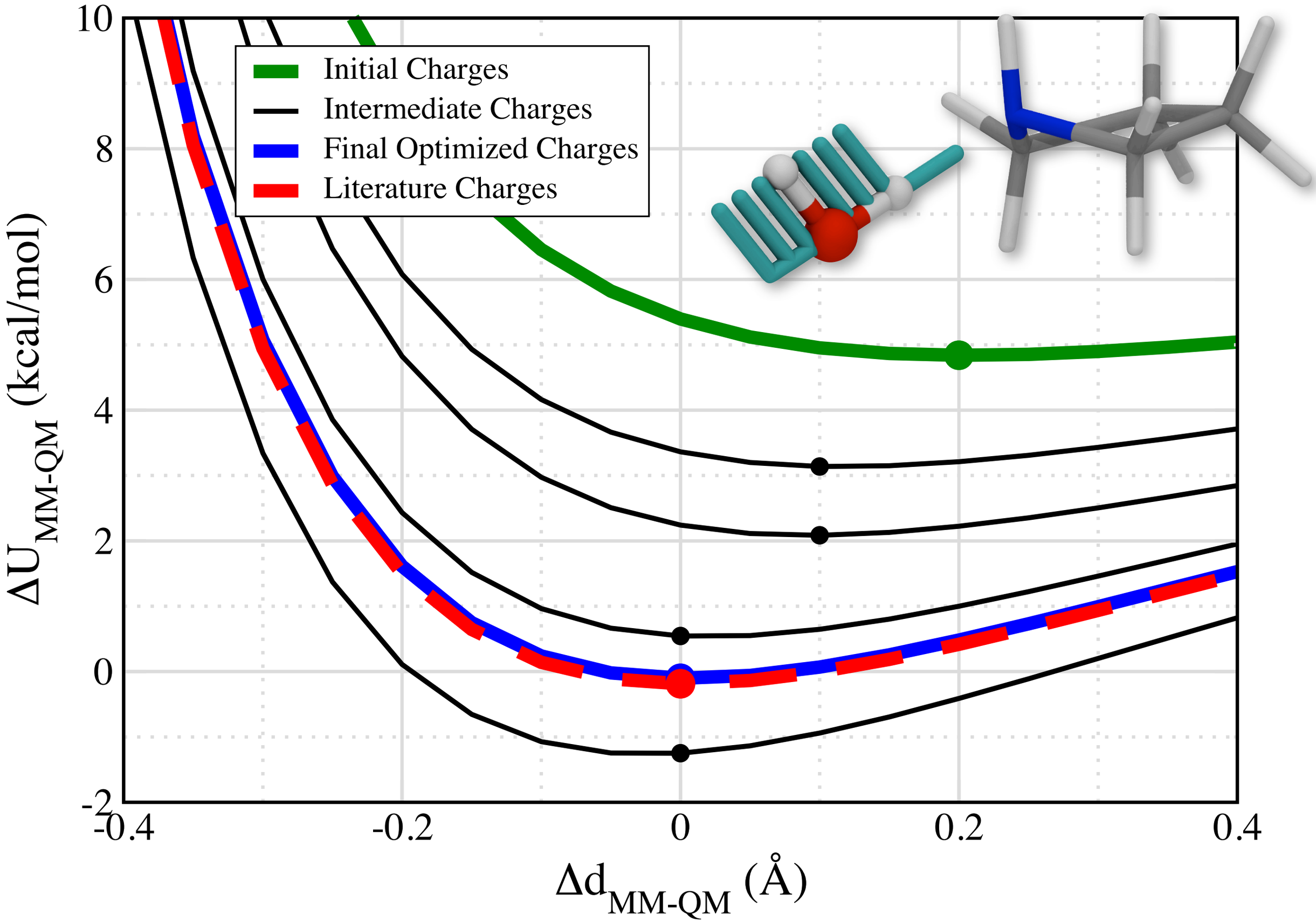
Charge Optimization



Objective Function

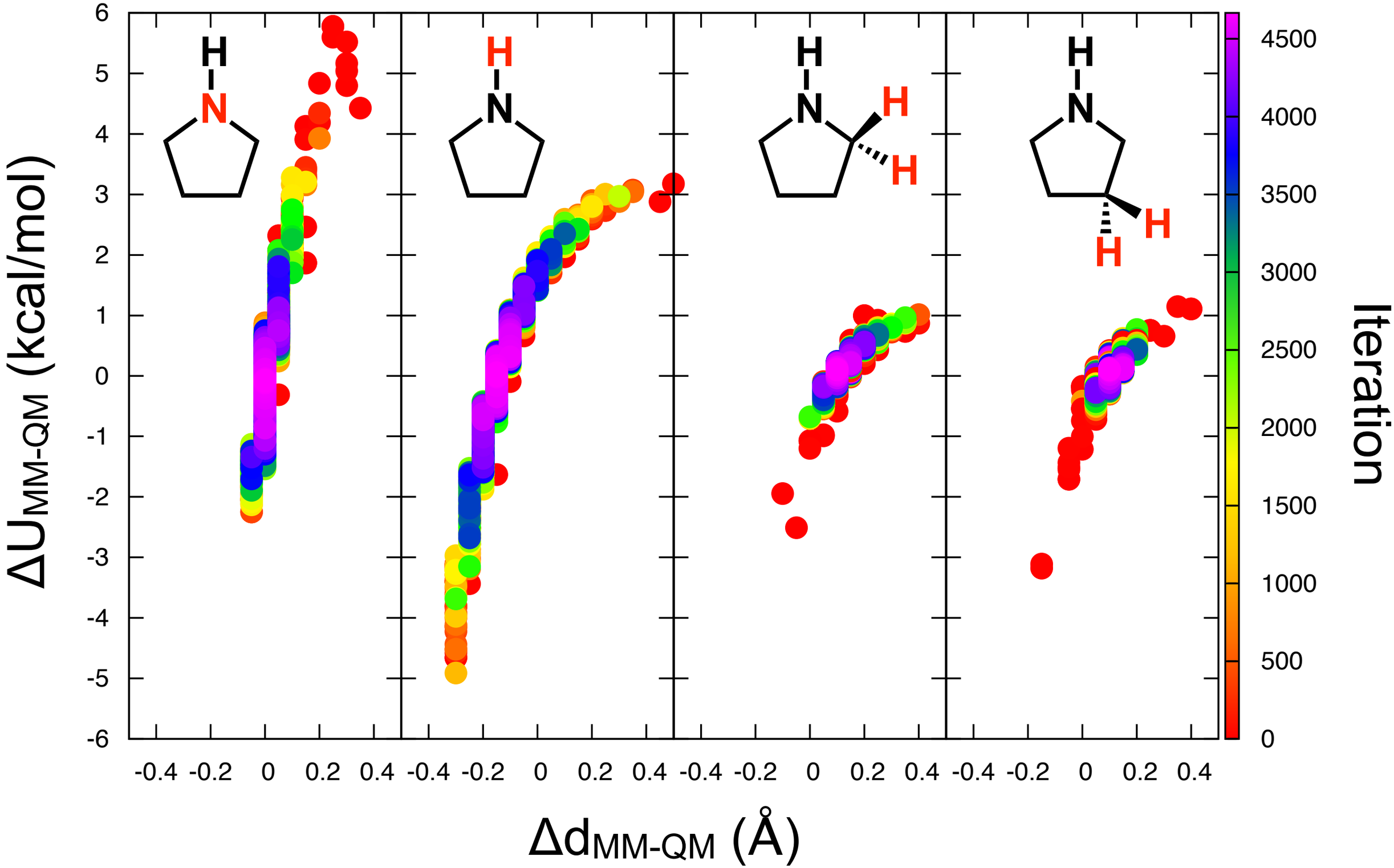
$$\sum_{\text{wat. int.}} f(U_{MM}\text{-}U_{QM}) + \sum_{\text{wat. int.}} f(d_{MM}\text{-}d_{QM}) + f(\mu_{MM}\text{-}\mu_{QM})$$

Assessing MM Water-Interaction Profiles

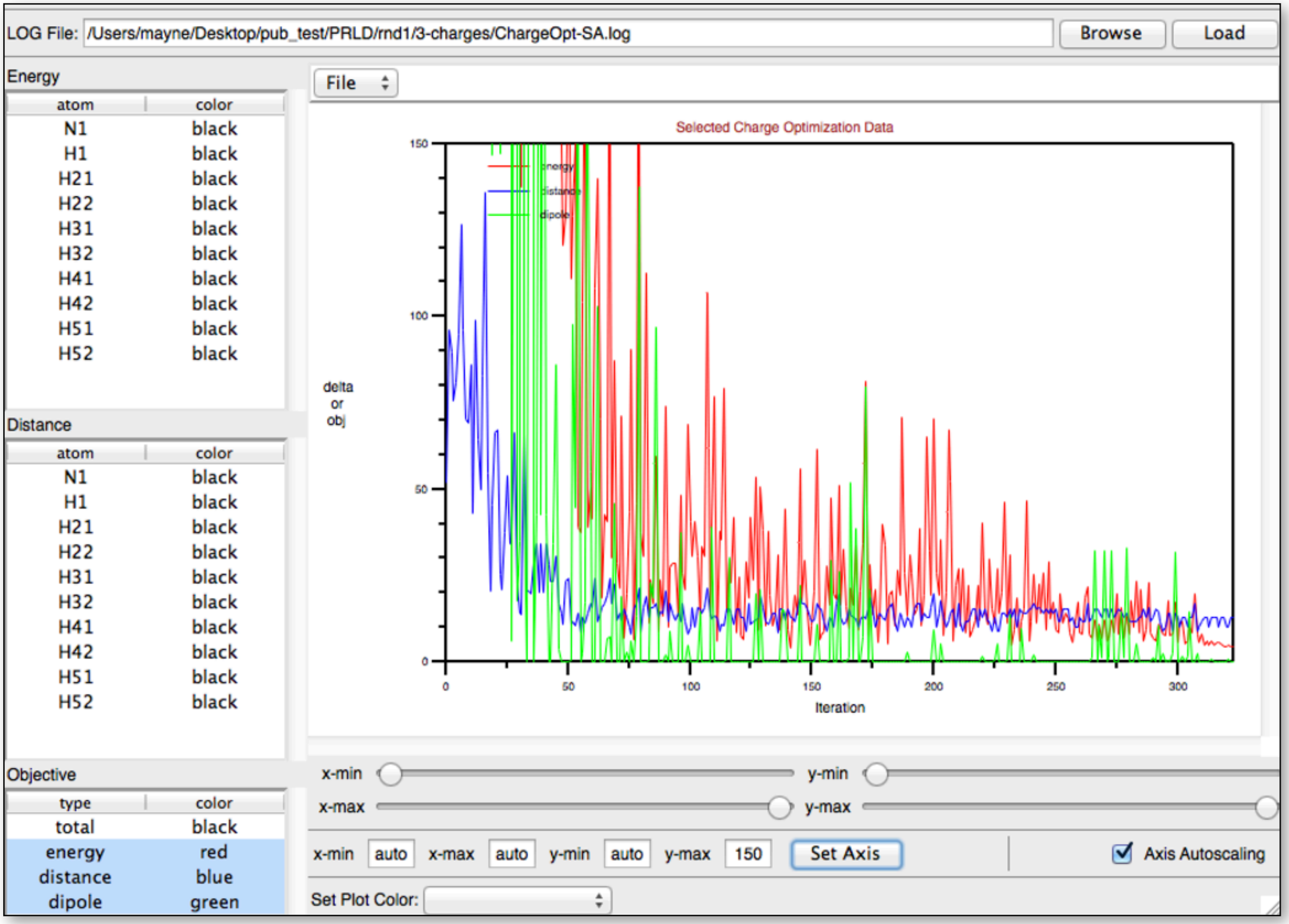


Sampling MM Water-Interaction Profiles

Mode: Simulated Annealing



Plotting Charge Optimization Data



Plotting Charge Optimization Data

LOG File: /Users/mayne/Desktop/pub_test/PRLD/rnd1/3-charges/ChargeOpt-SA.log

File

export data

Energy

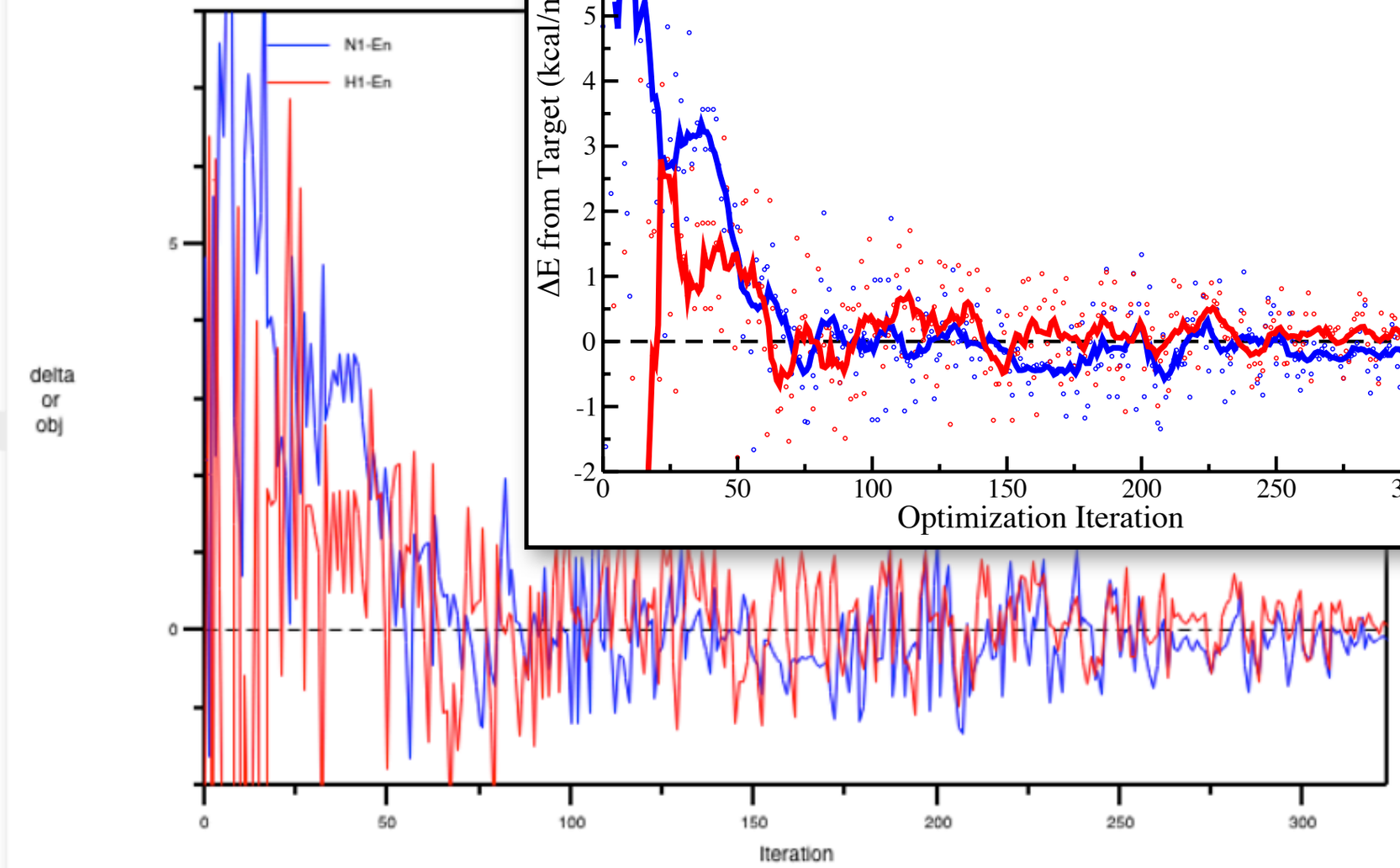
atom	color
N1	blue
H1	red
H21	black
H22	black
H31	black
H32	black
H41	black
H42	black
H51	black
H52	black

Distance

atom	color
N1	black
H1	black
H21	black
H22	black
H31	black
H32	black
H41	black
H42	black
H51	black
H52	black

Objective

type	color
total	black
energy	red
distance	blue
dipole	green



x-min y-min

x-max y-max

x-min auto x-max auto y-min -2 y-max 8 Set Axis

Axis Autoscaling

Set Plot Color: red

Conclusions

Find Missing Parameters

Geometry Optimization (QM)

Water Interaction En. (QM)

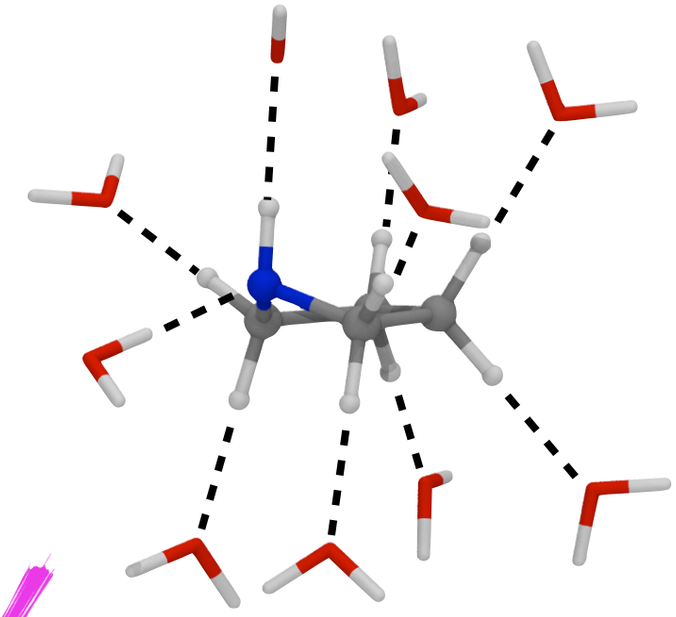
Charge Optimization

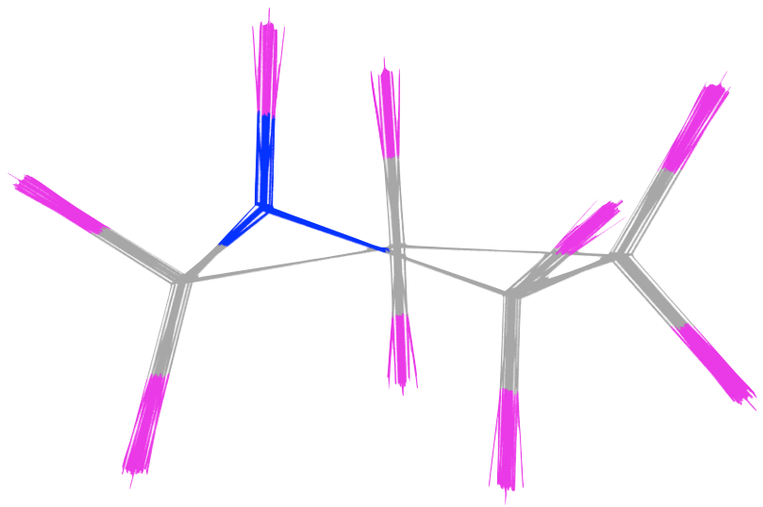
Hessian Calculation (QM)

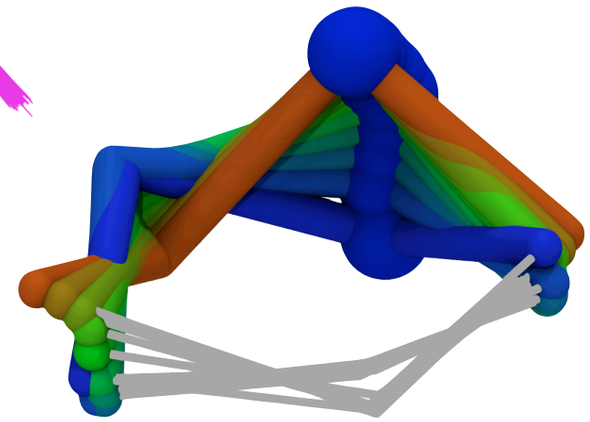
Bond & Angle Optimization

Torsion Scan (QM)

Torsion Optimization







*ff*TK:

- Simplifies the parameterization workflow
- Offers opportunity for extensive customization
- Provides analytical tools to assess parameter performance

www.ks.uiuc.edu/Research/vmd/plugins/fftk

Future Directions

Investigate forcefield performance

Support additional force fields (e.g. AMBER)

Improve optimization speed

Expand analysis tools

Support multiple QM packages

www.ks.uiuc.edu/Research/vmd/plugins/fftk

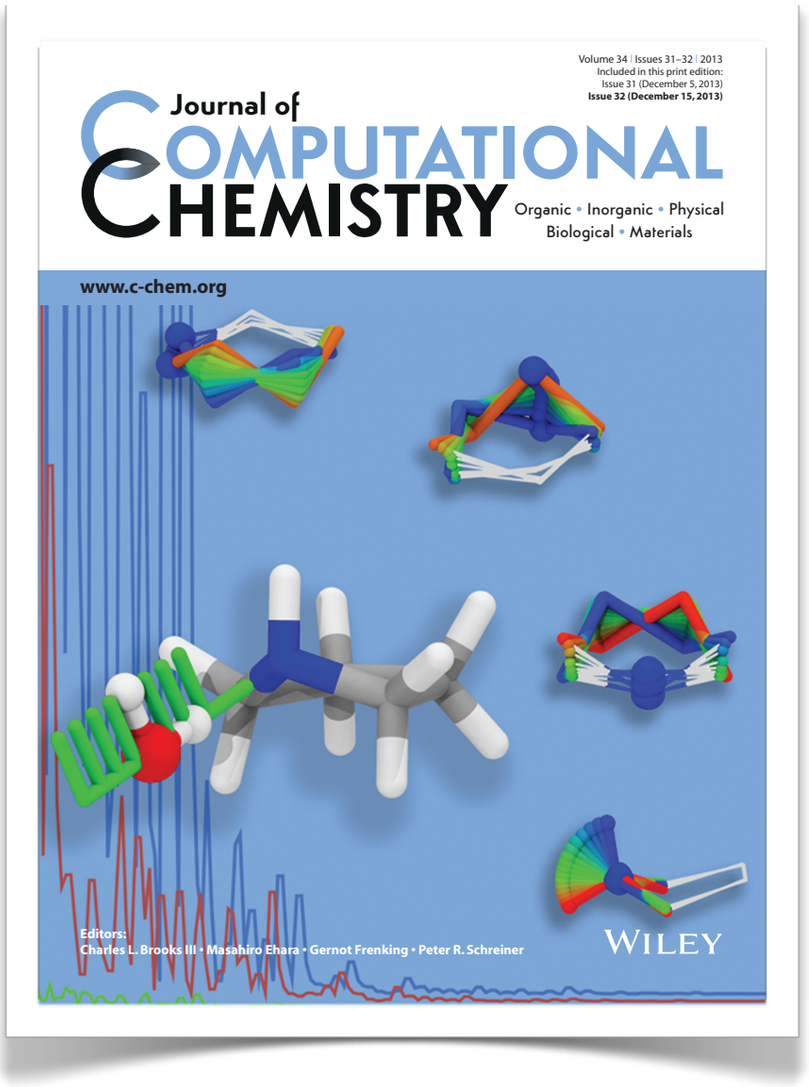
Office: 3011 in Innovation Courtyard II

*ff*TK

Mayne *et al.; J. Comp. Chem.* **2013,** 34, pp. 2757-2770

*ff*TK is available as a VMD Plugin (1.9.1 or newer)

http://www.ks.uiuc.edu/Research/vmd/plugins/fftk



Questions?