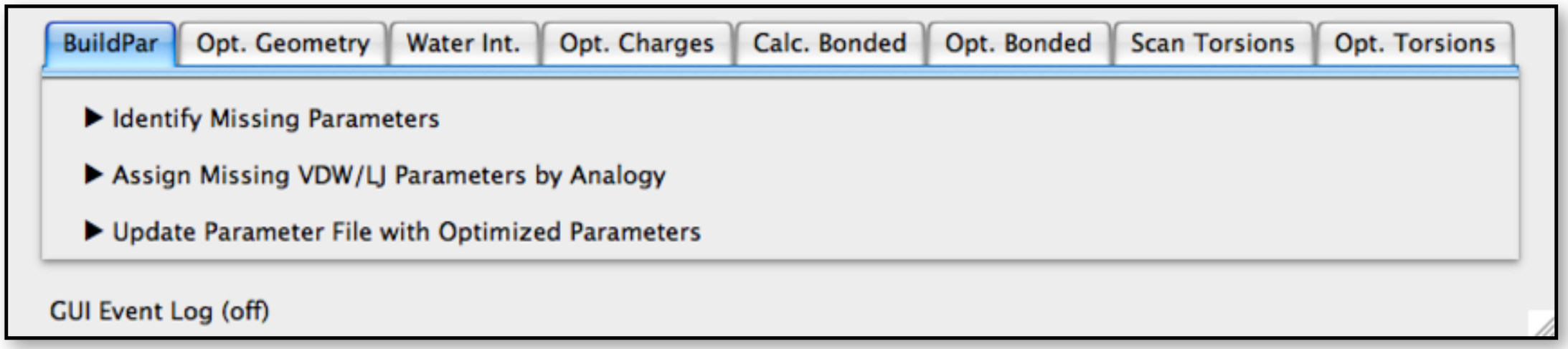
Parameterizing Small Molecules Using:

The Force Field Toolkit (*ff*TK)



Christopher G. Mayne, Emad Tajkhorshid
Beckman Institute for Advanced Science and Technology
University of Illinois, Urbana-Champaign

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Georgia Institute of Technology

NIH Hands On Workshop | TCBG | April 7th, 2015

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

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

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

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

MD Simulations of Biological Systems

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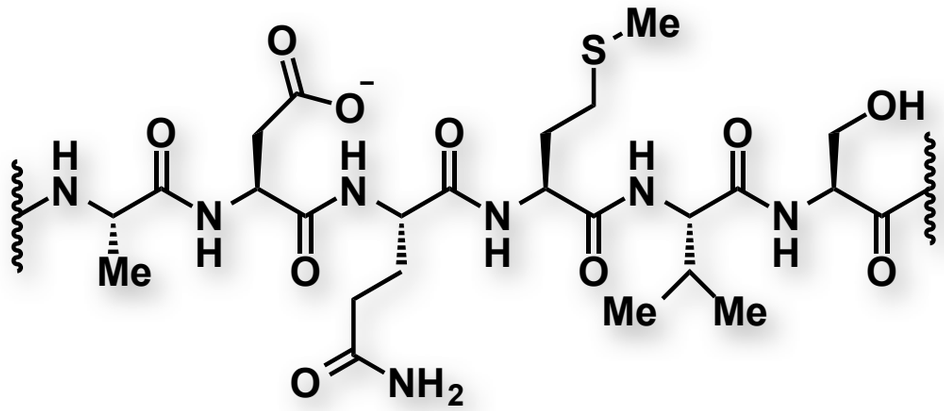
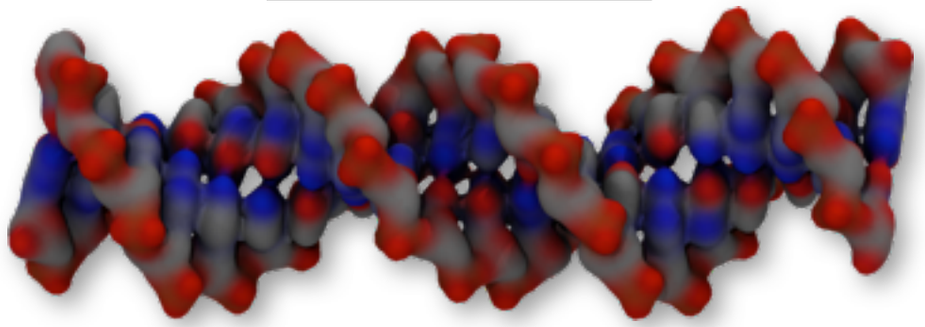
Parameter Transferability In Biopolymers

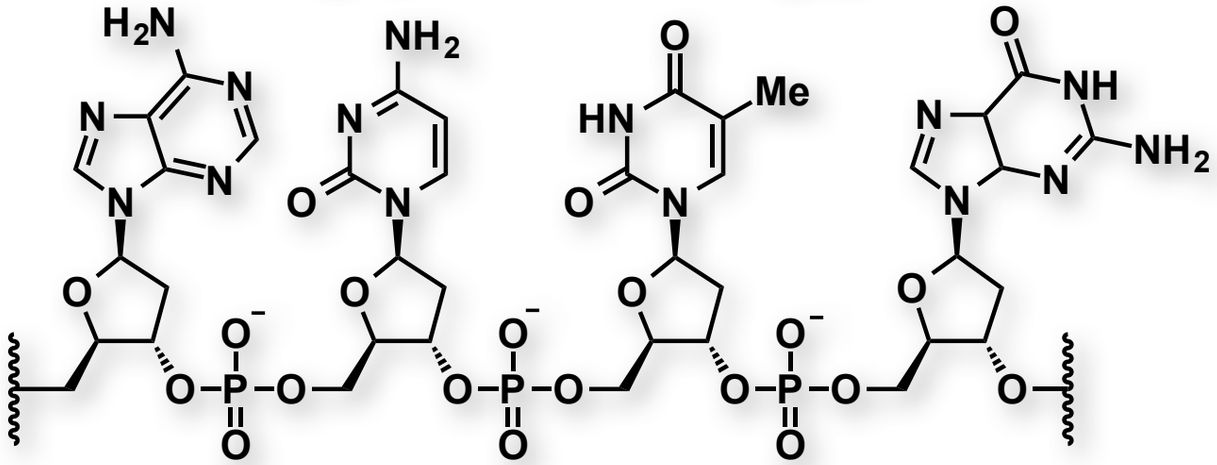
Parameter set describes molecular behavior in varied chemical (connectivity) and spatial (conformation) contexts

Peptides and Proteins

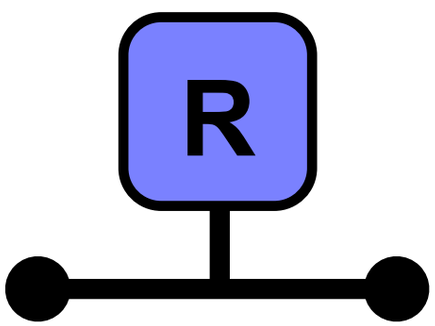


Nucleic Acids





Key Features:

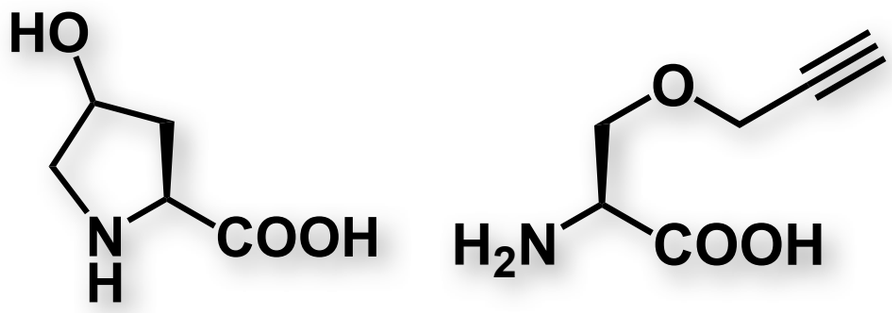


limited set of isolated building blocks

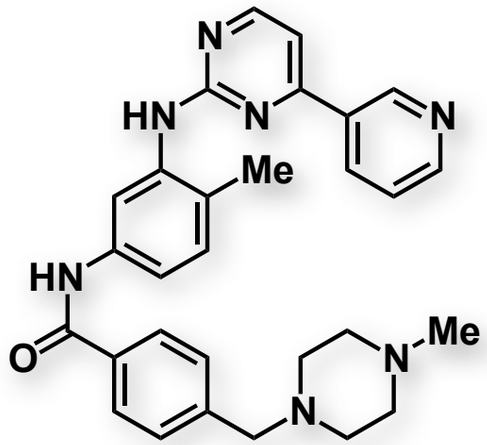
repetitive backbone unit

Parameterization as an Impasse

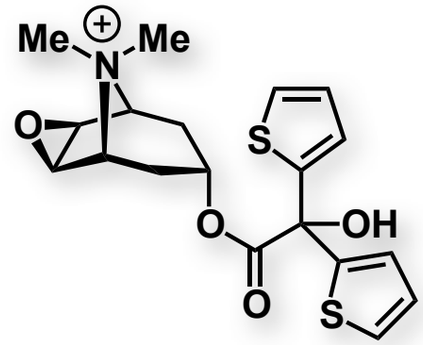
non-standard or engineered amino acids



small molecule ligands

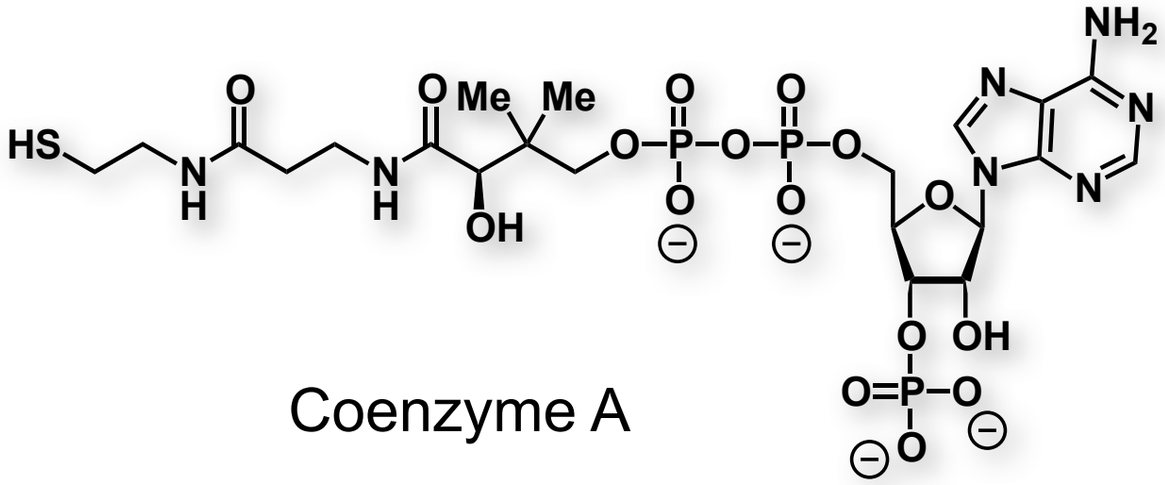


Imatinib (Gleevec)



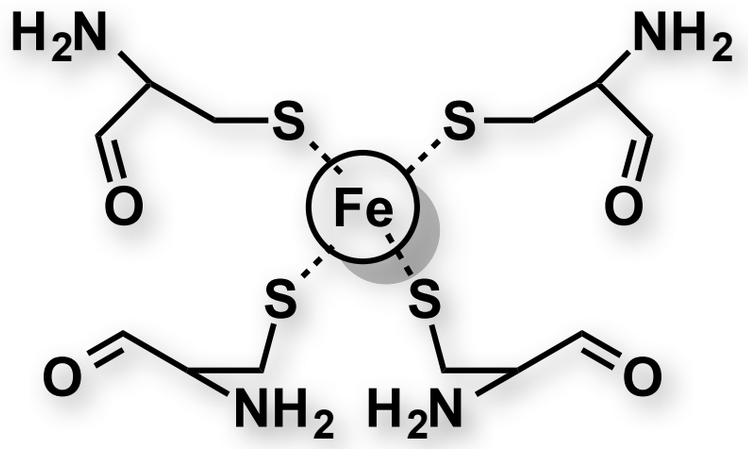
Tiotropium (Spiriva)

cofactors

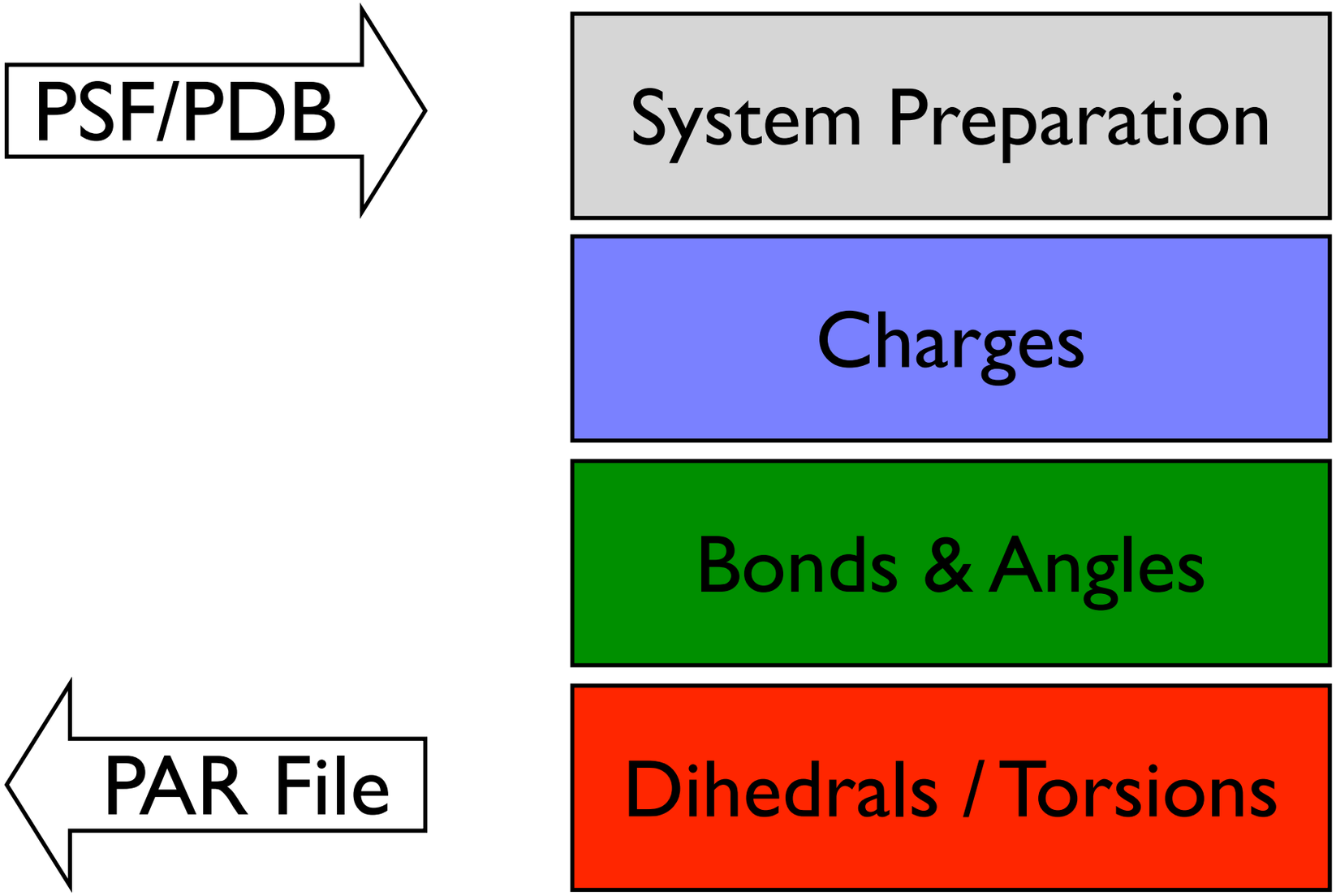


Coenzyme A

metal centers



General Parameterization Workflow



CGenFF Parameterization Workflow

PSF/PDB

Find Missing Parameters

Geometry Optimization (QM)

Water Interaction En. (QM)

Charge Optimization

Hessian Calculation (QM)

Bond & Angle Optimization

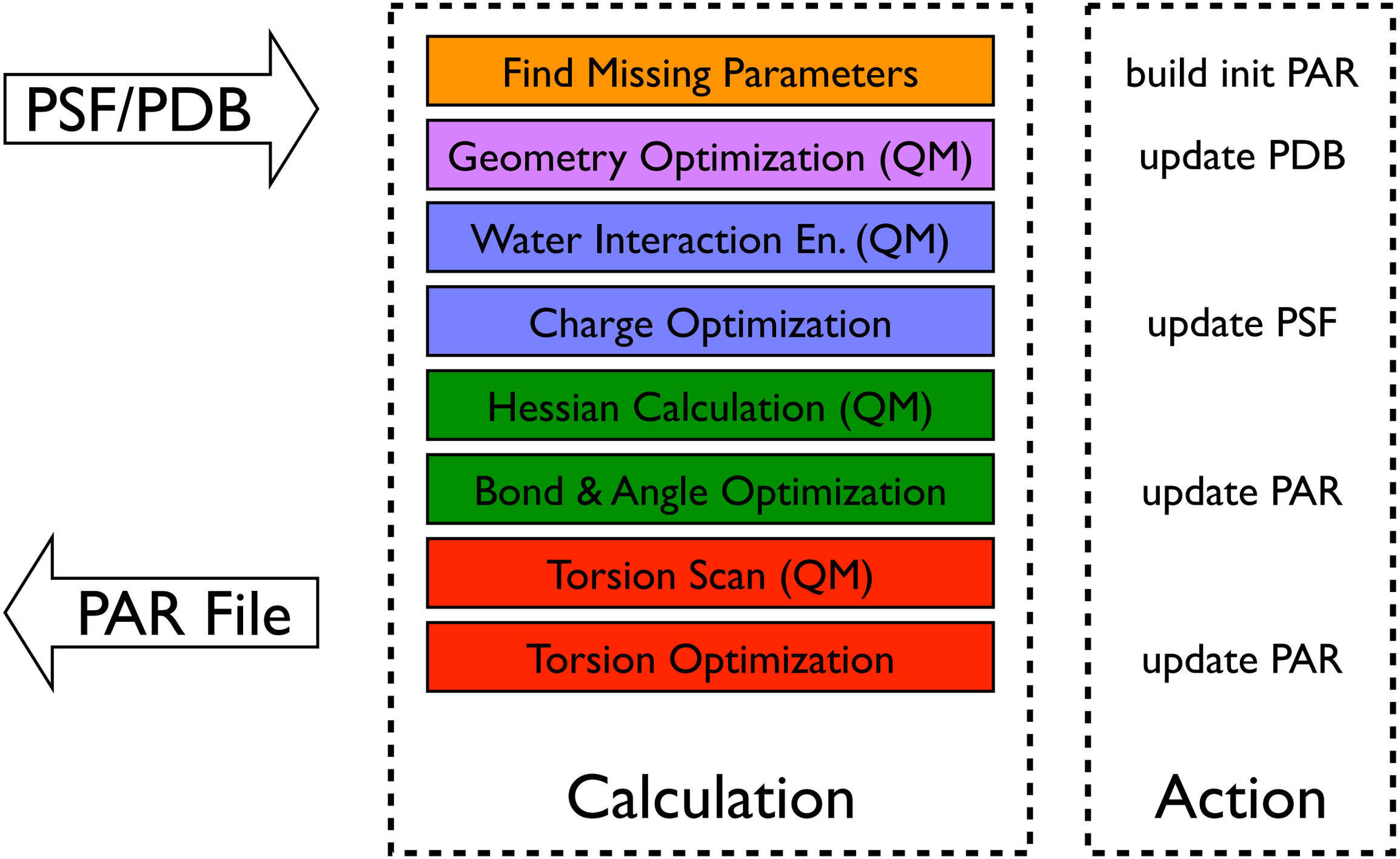
Torsion Scan (QM)

Torsion Optimization

PAR File

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

CGenFF Parameterization Workflow



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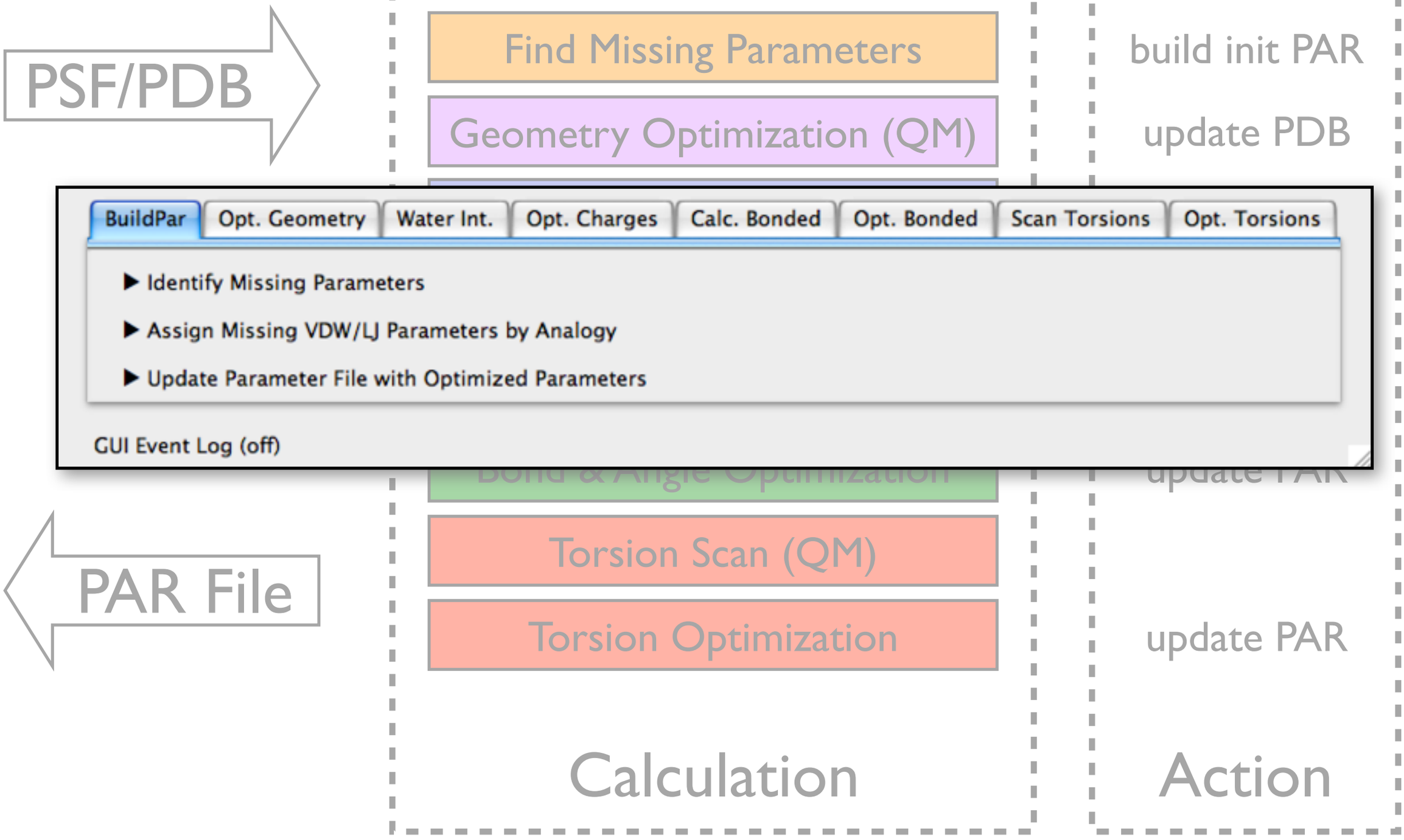
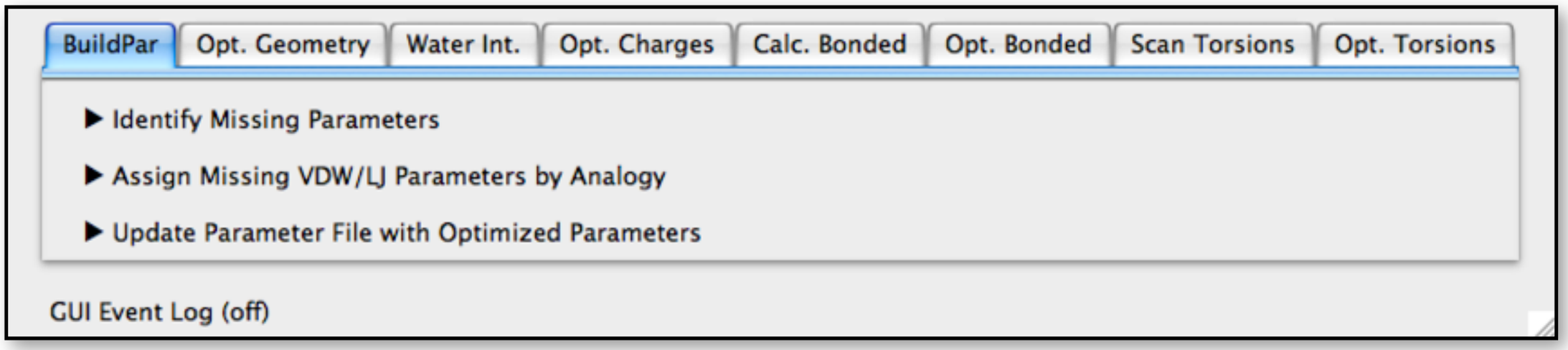
CGenFF Parameterization Workflow



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

*ff*TK Interface



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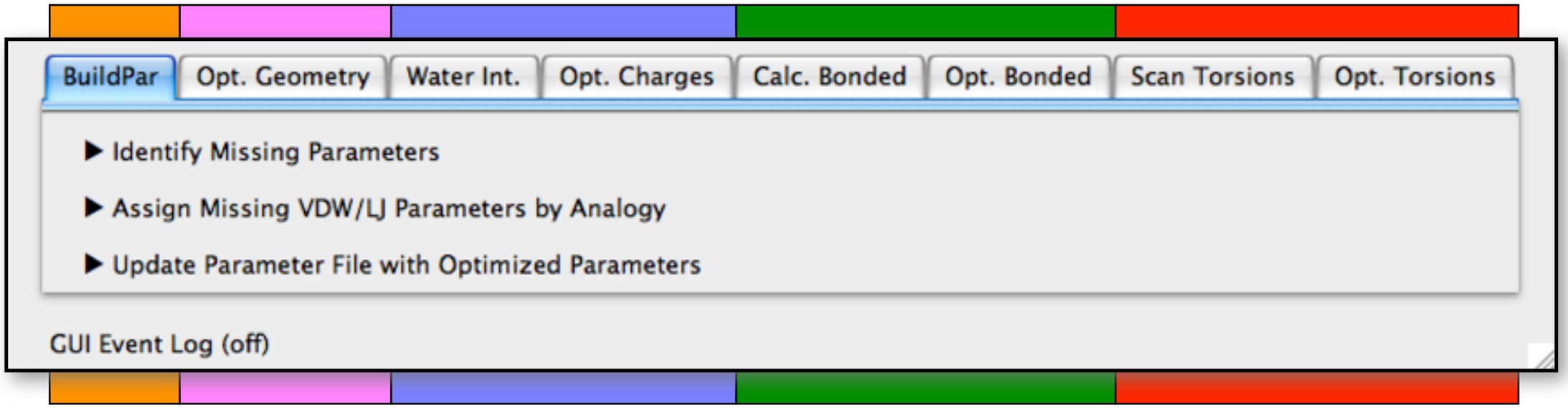
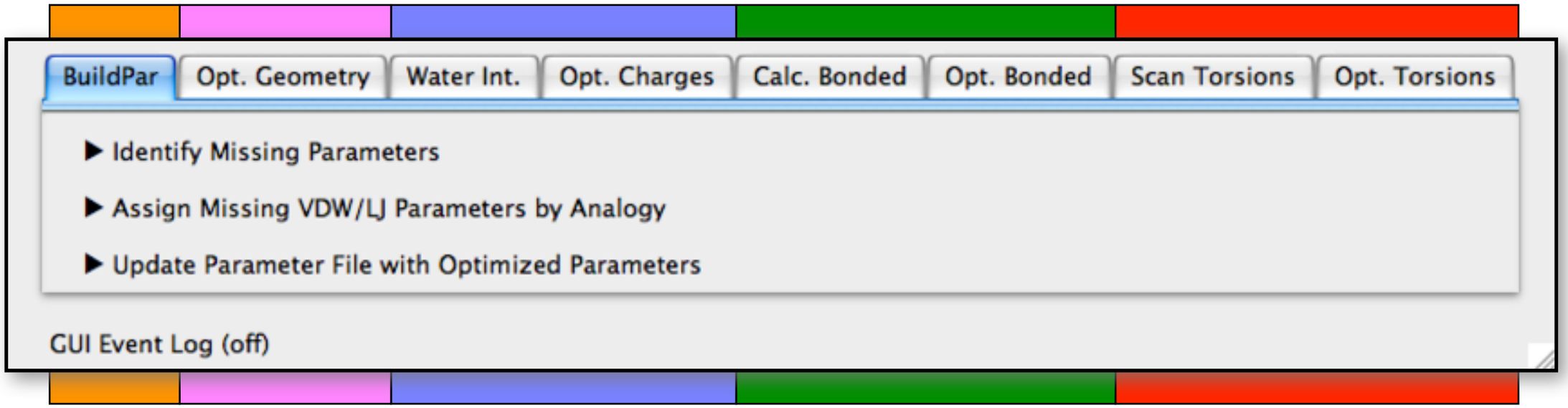


*ff*TK Interface

tasks organized under tabs



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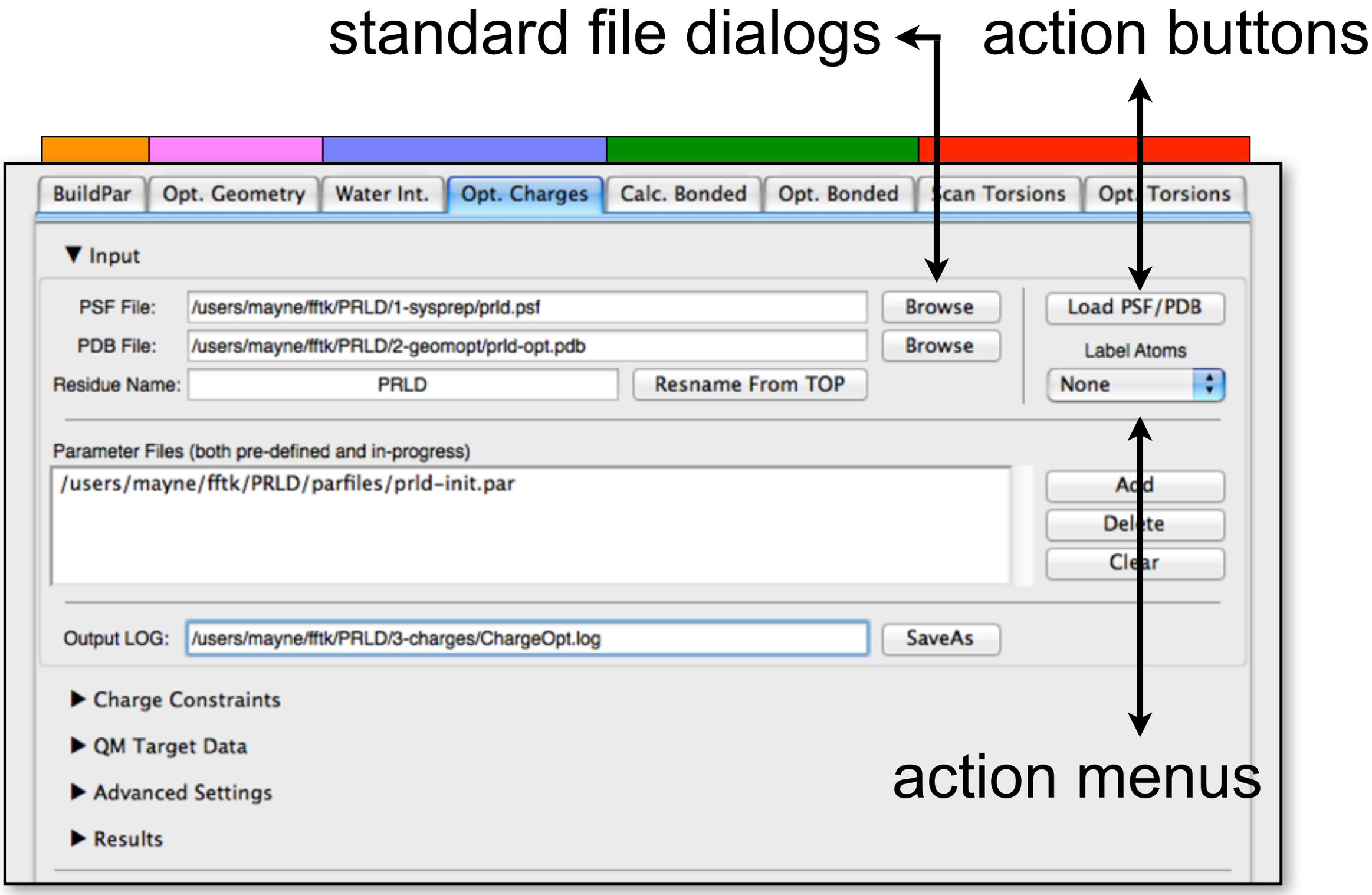


Functionality Provided by *ff*TK

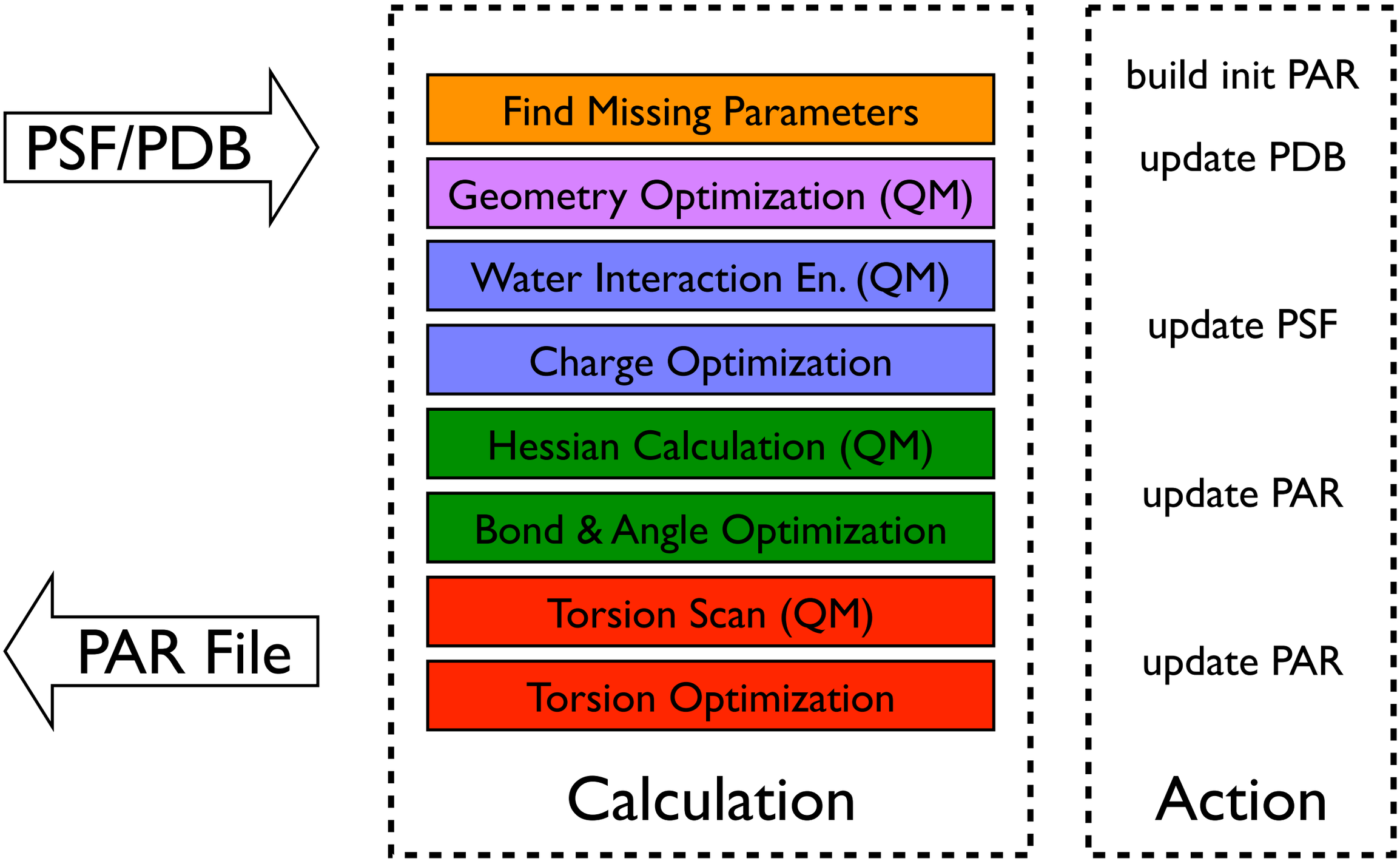
Core Functions

- 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



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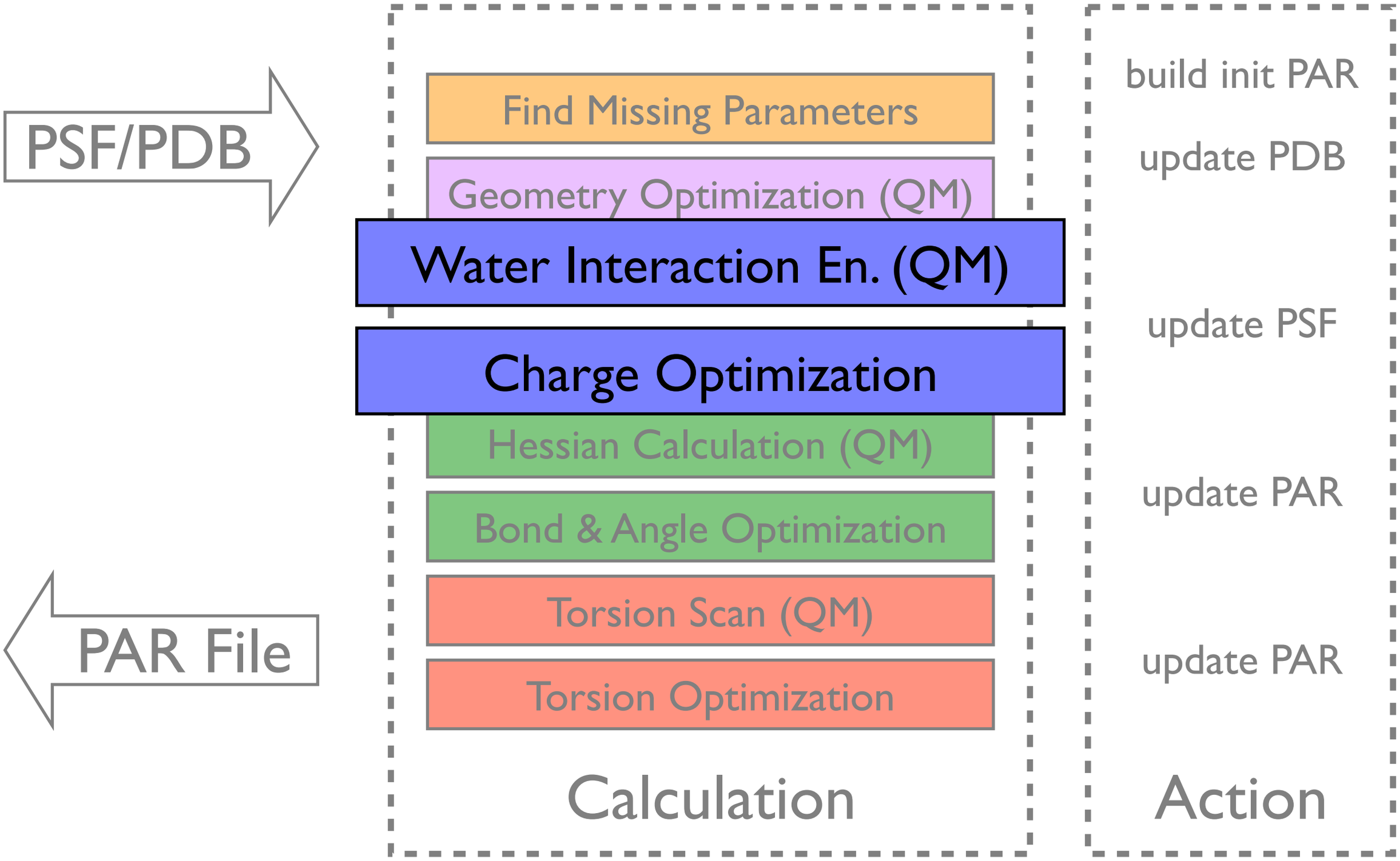
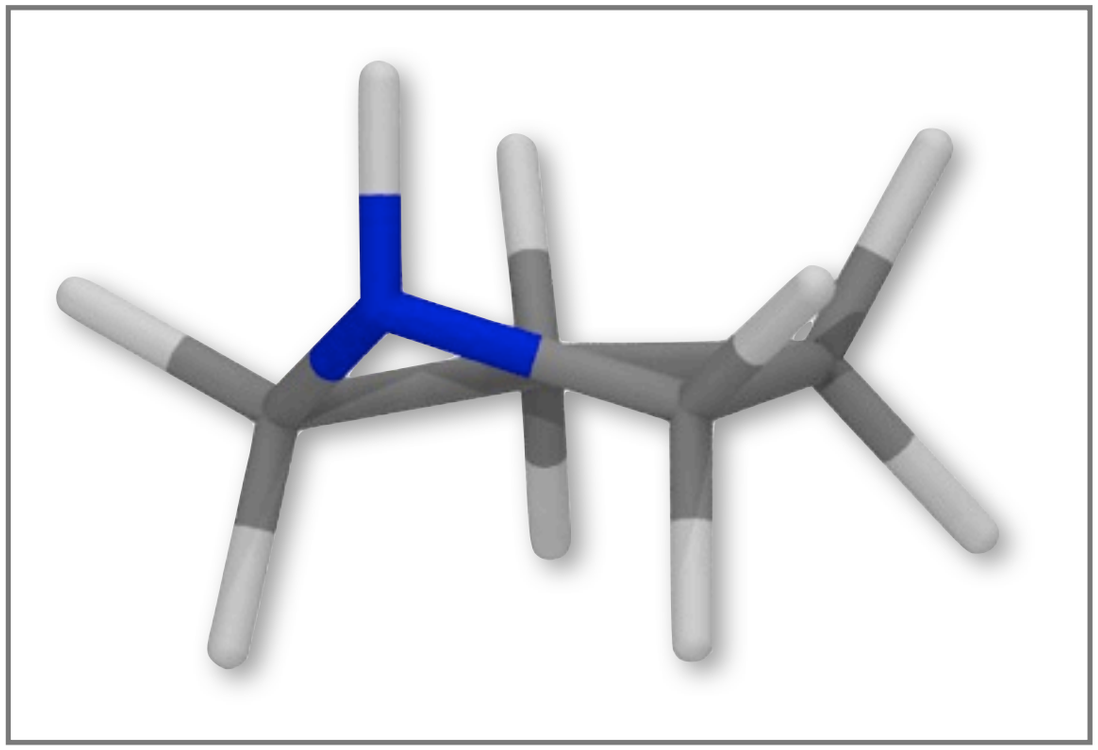


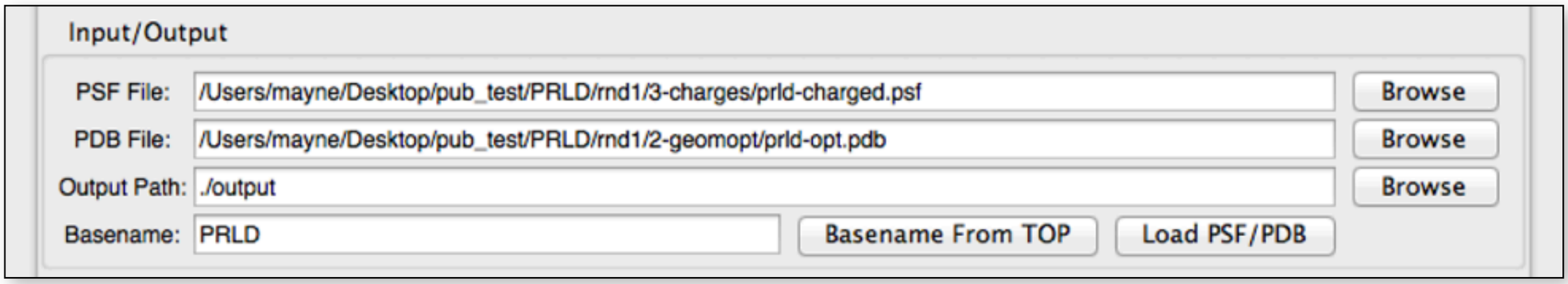
Generating Charge Optimization Target Data

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



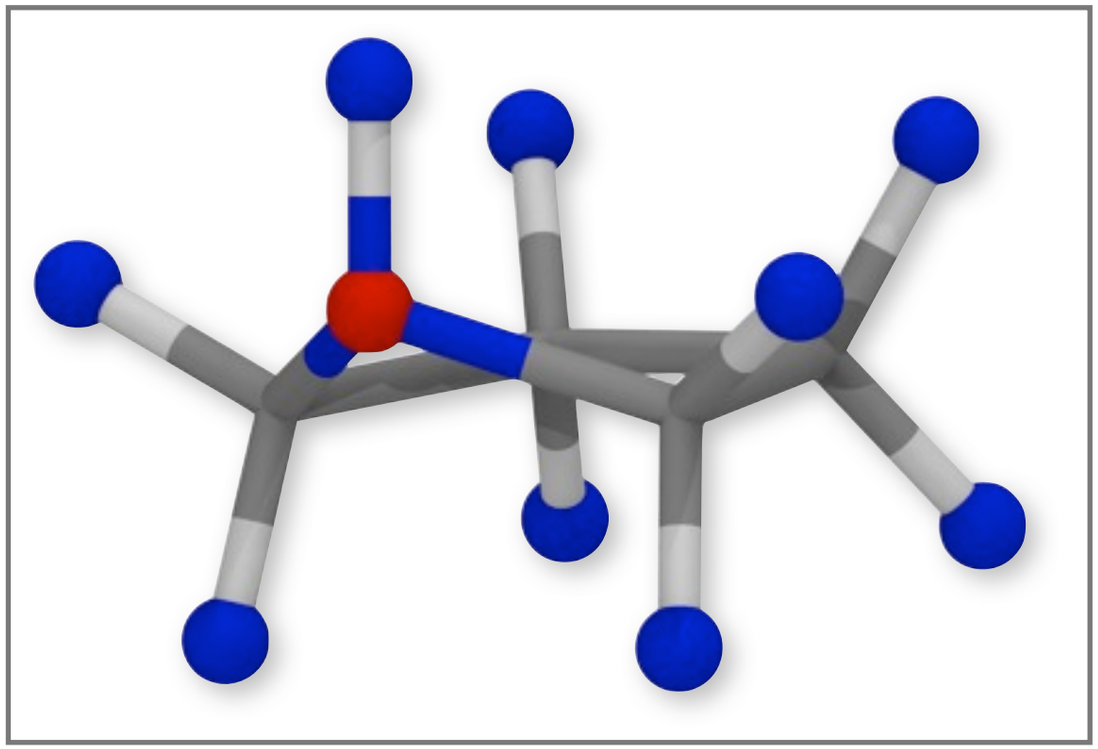
VMD main window

*ff*TK GUI



Generating Charge Optimization Target Data

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



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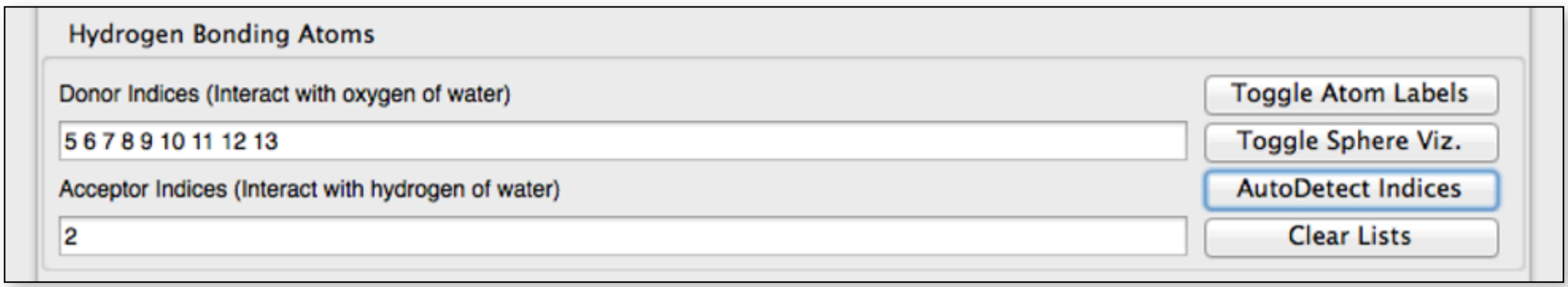

Generating Charge Optimization Target Data

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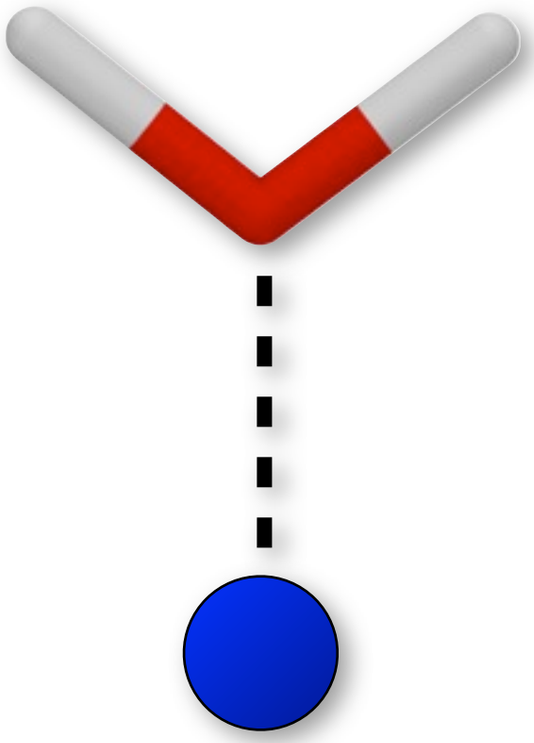
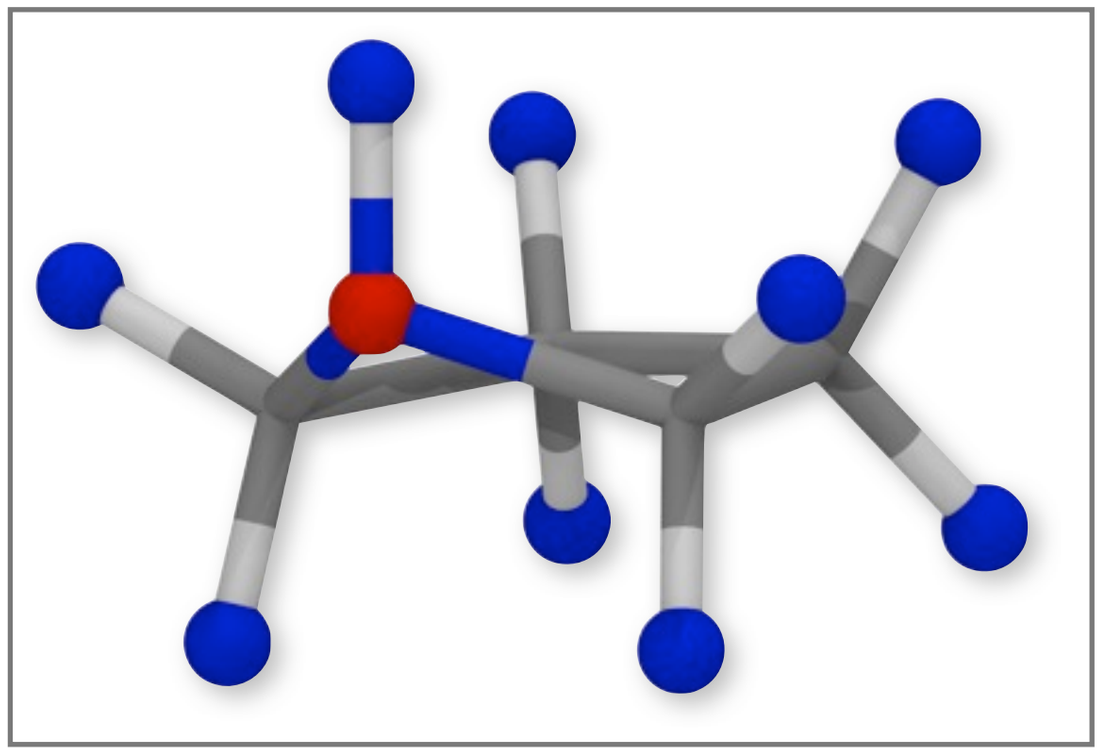
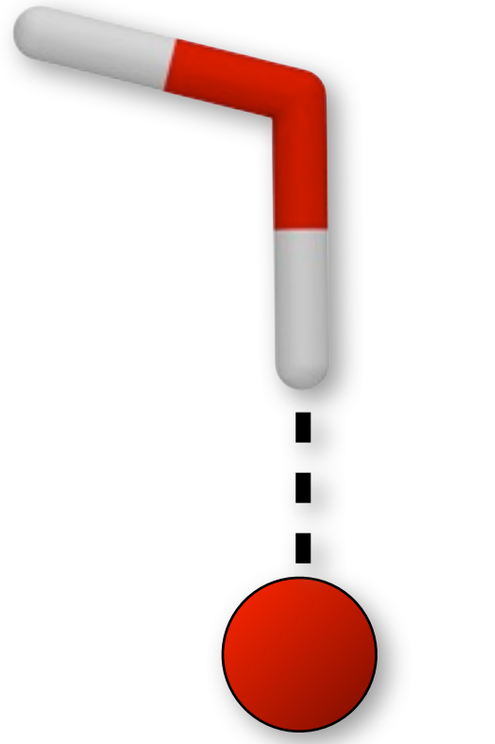


Donor

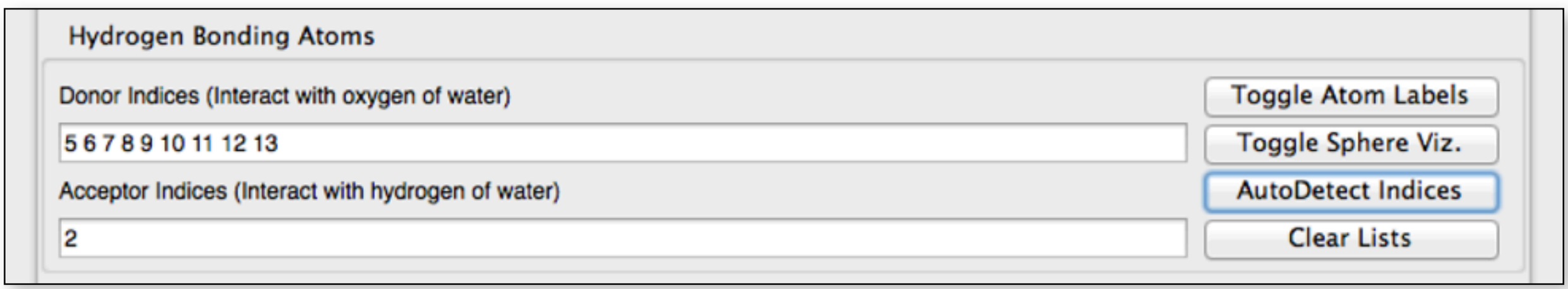


VMD main window



Acceptor

*ff*TK GUI

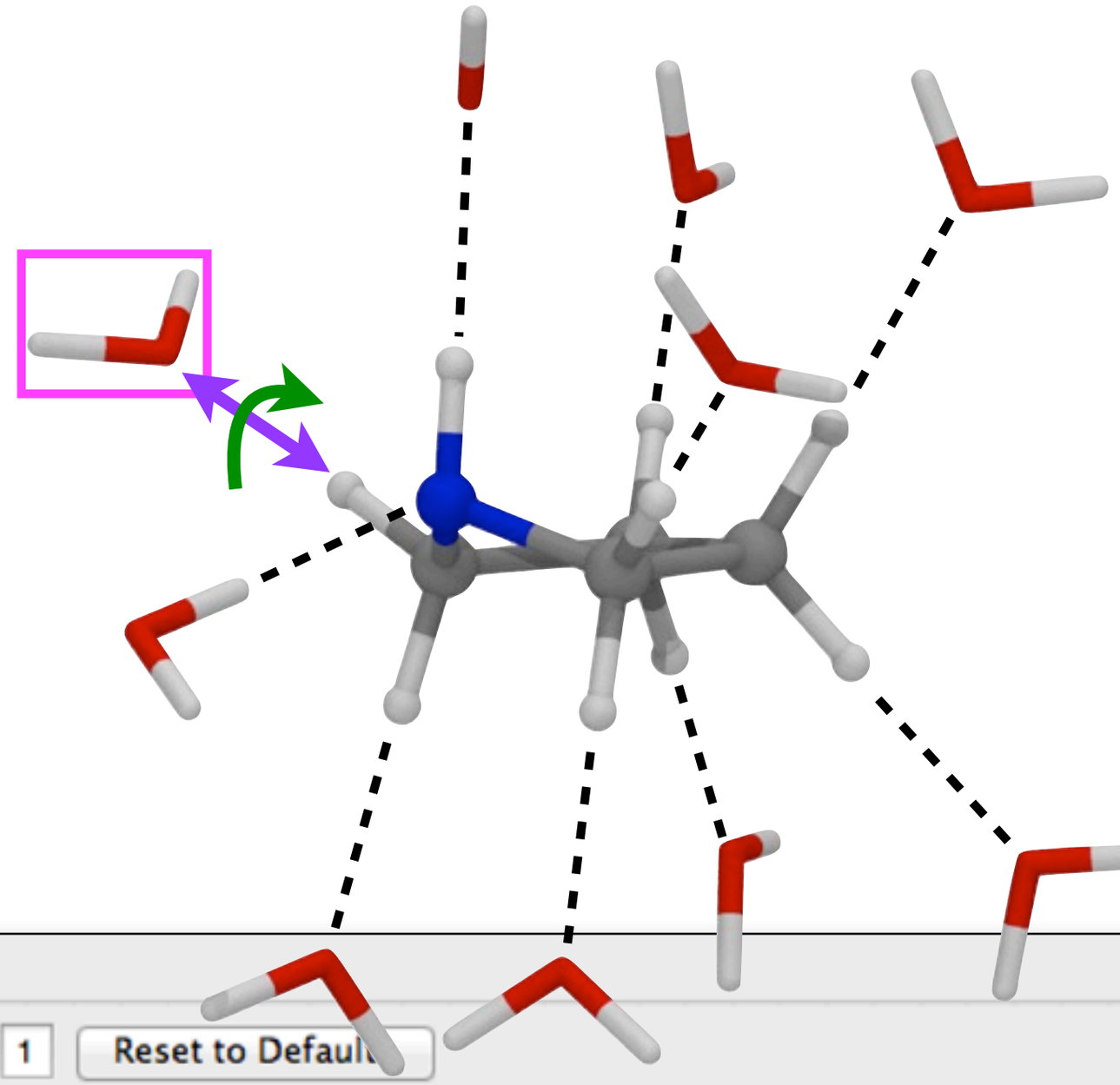


Generating Charge Optimization Target Data

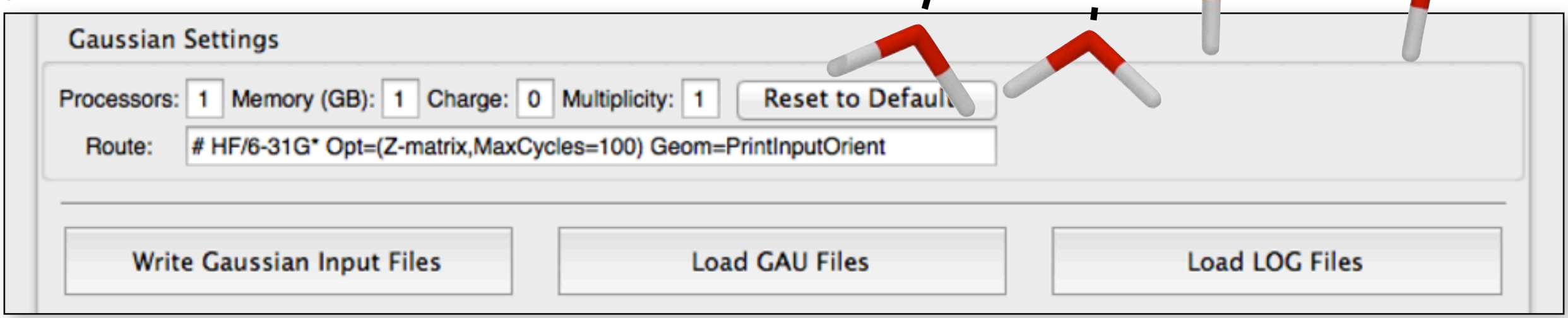
on sites | Generate Gaussian Input Files | Run QM | Inspect water optimization

Compute water position

Optimize
distance & rotation



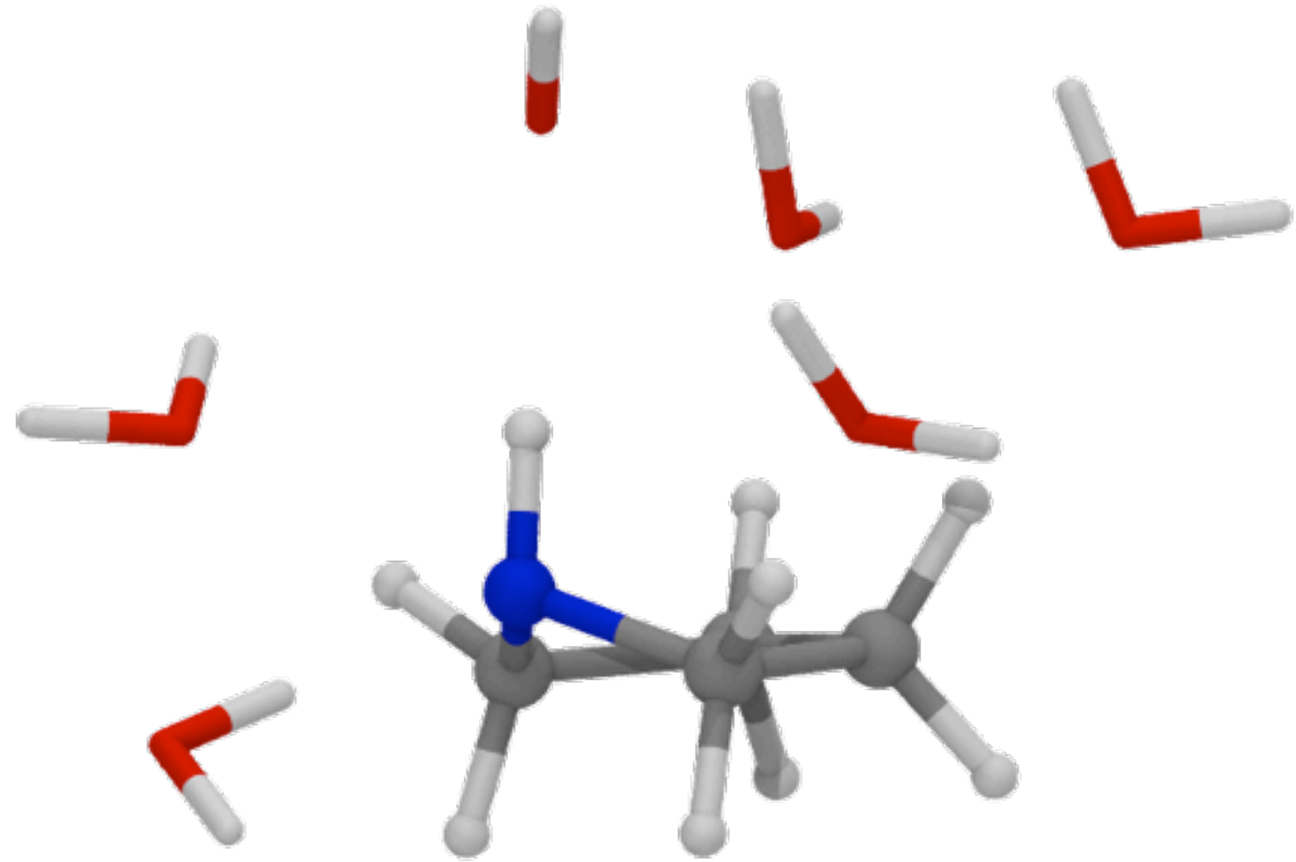
ffTK GUI



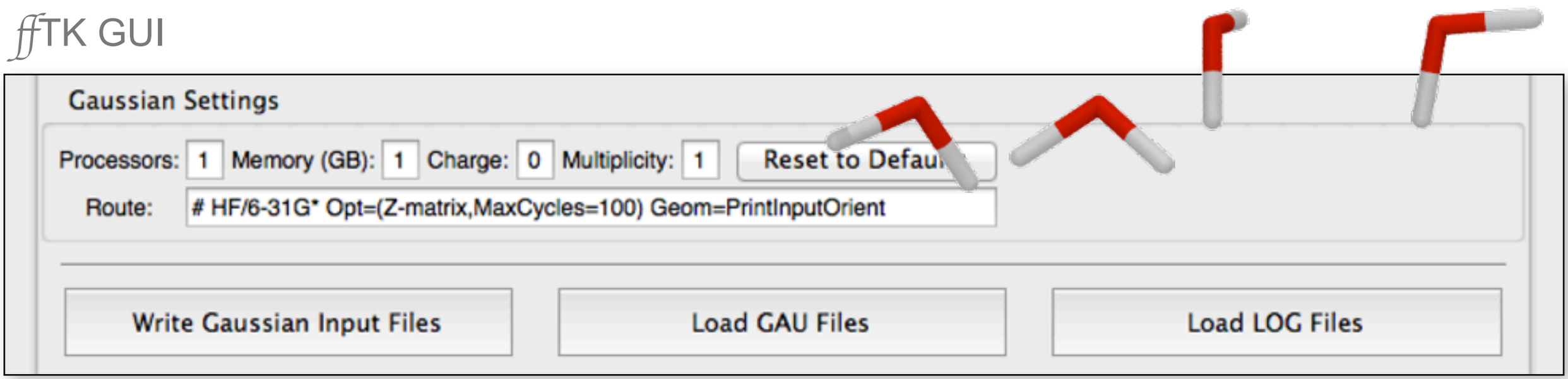
Generating Charge Optimization Target Data

| Run QM | Inspect water optimization

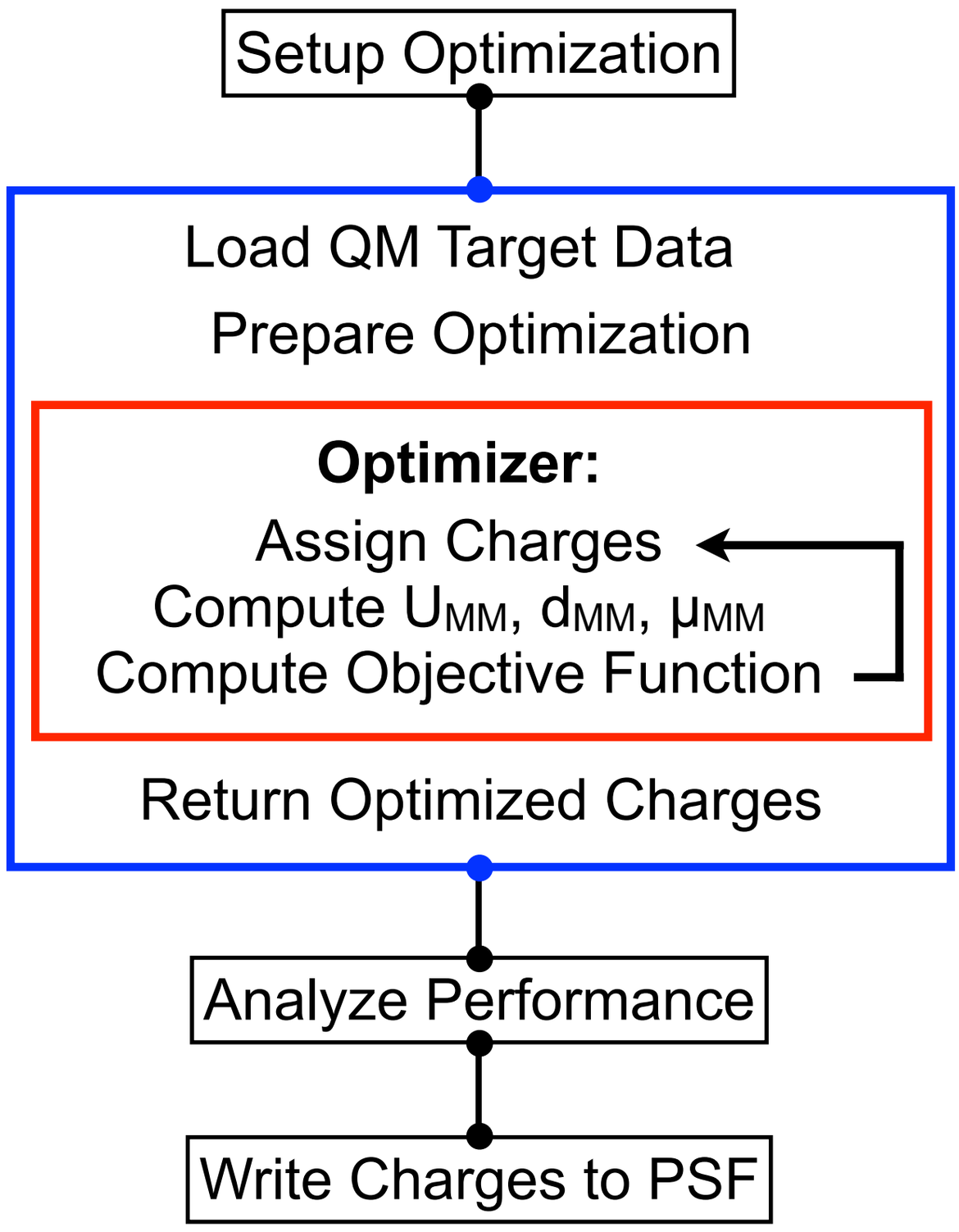
Visually assess QM-optimized water position(s)



*ff*TK GUI



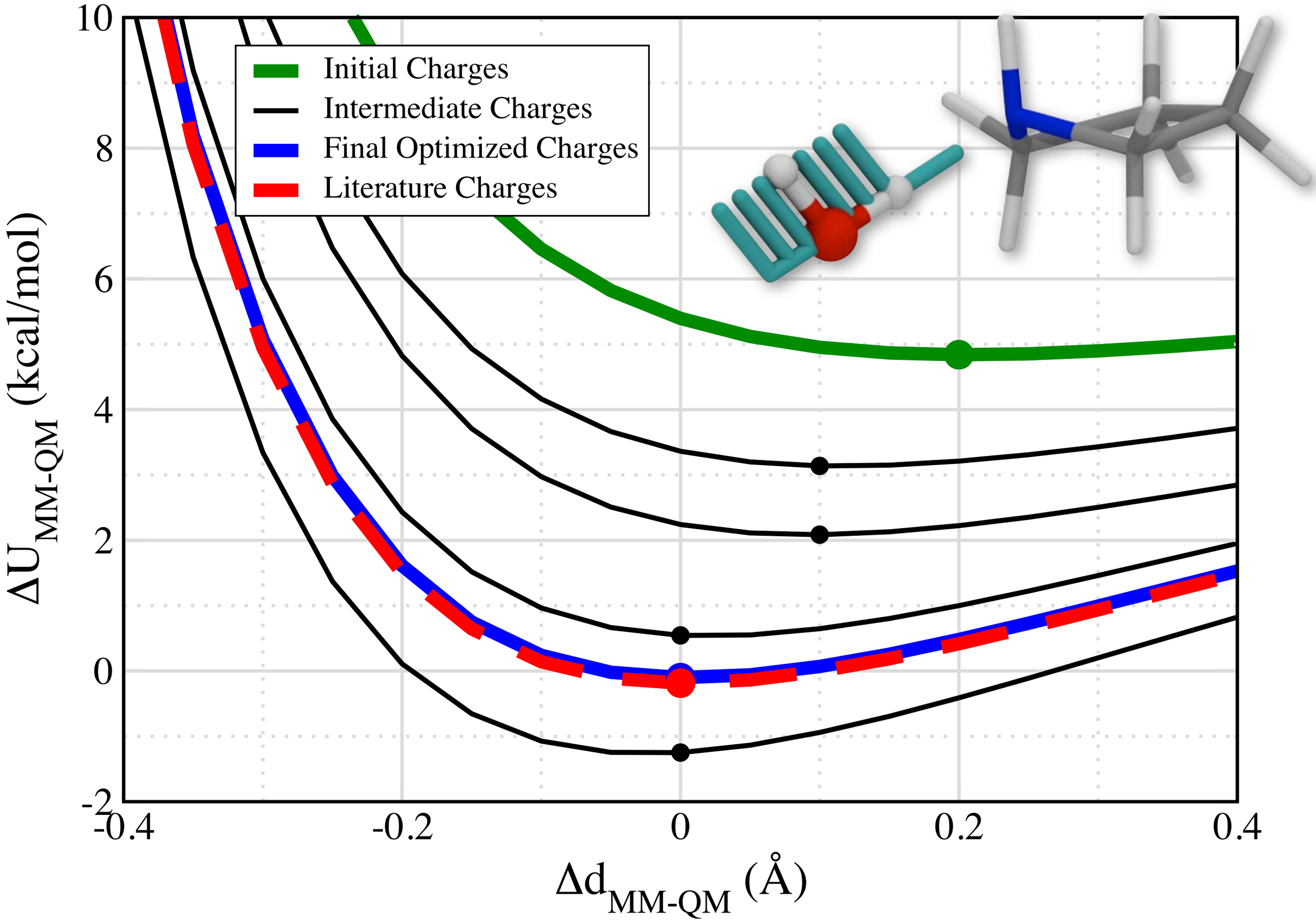
Charge Optimization



Objective Function

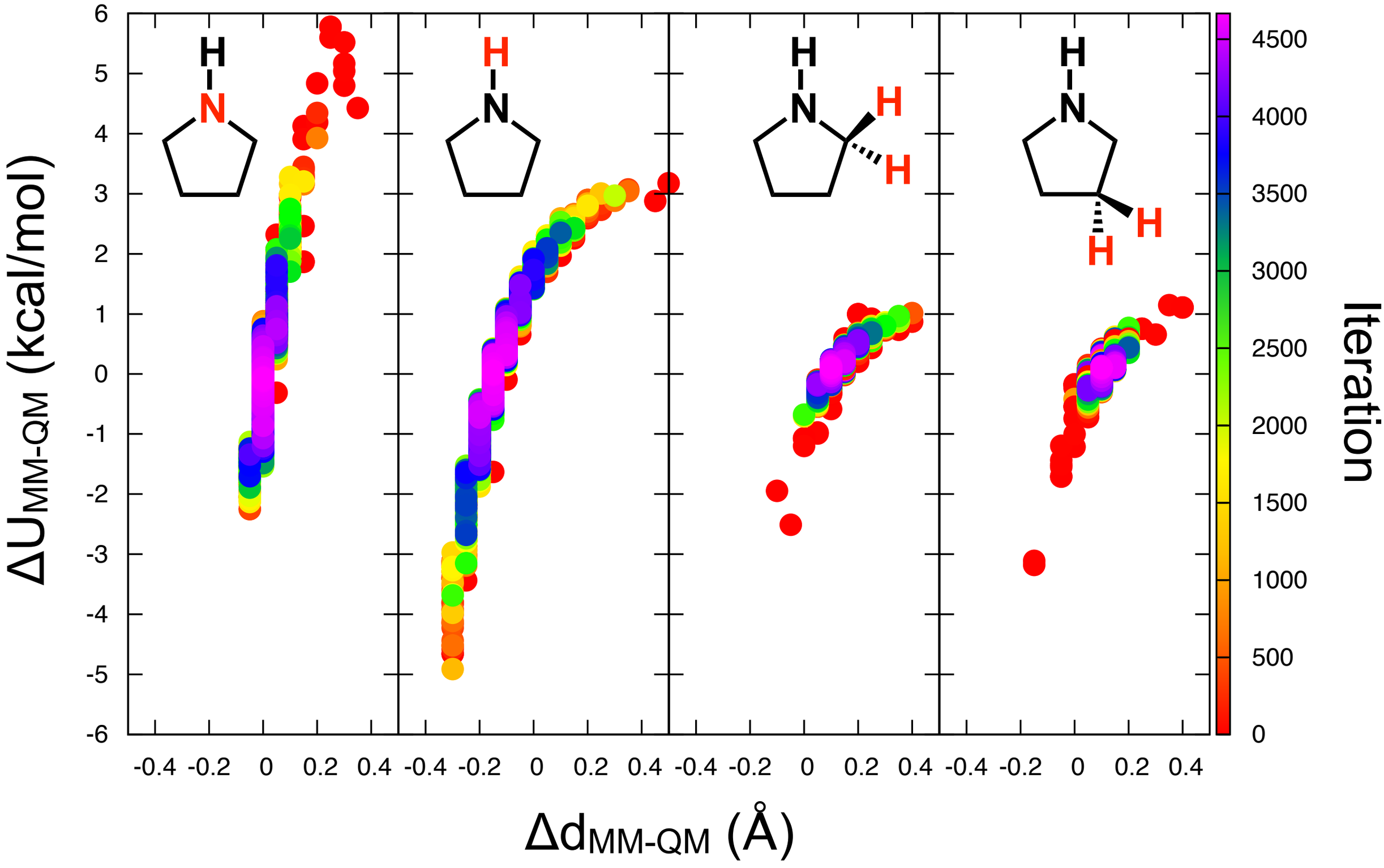
$$\sum_{\text{wat. int.}} f(U_{MM}\text{-}U_{QM}) + \sum_{\text{wat. int.}} f(d_{MM}\text{-}d_{QM}) + f(\mu_{MM}\text{-}\mu_{QM})$$

Assessing MM Water-Interaction Profiles



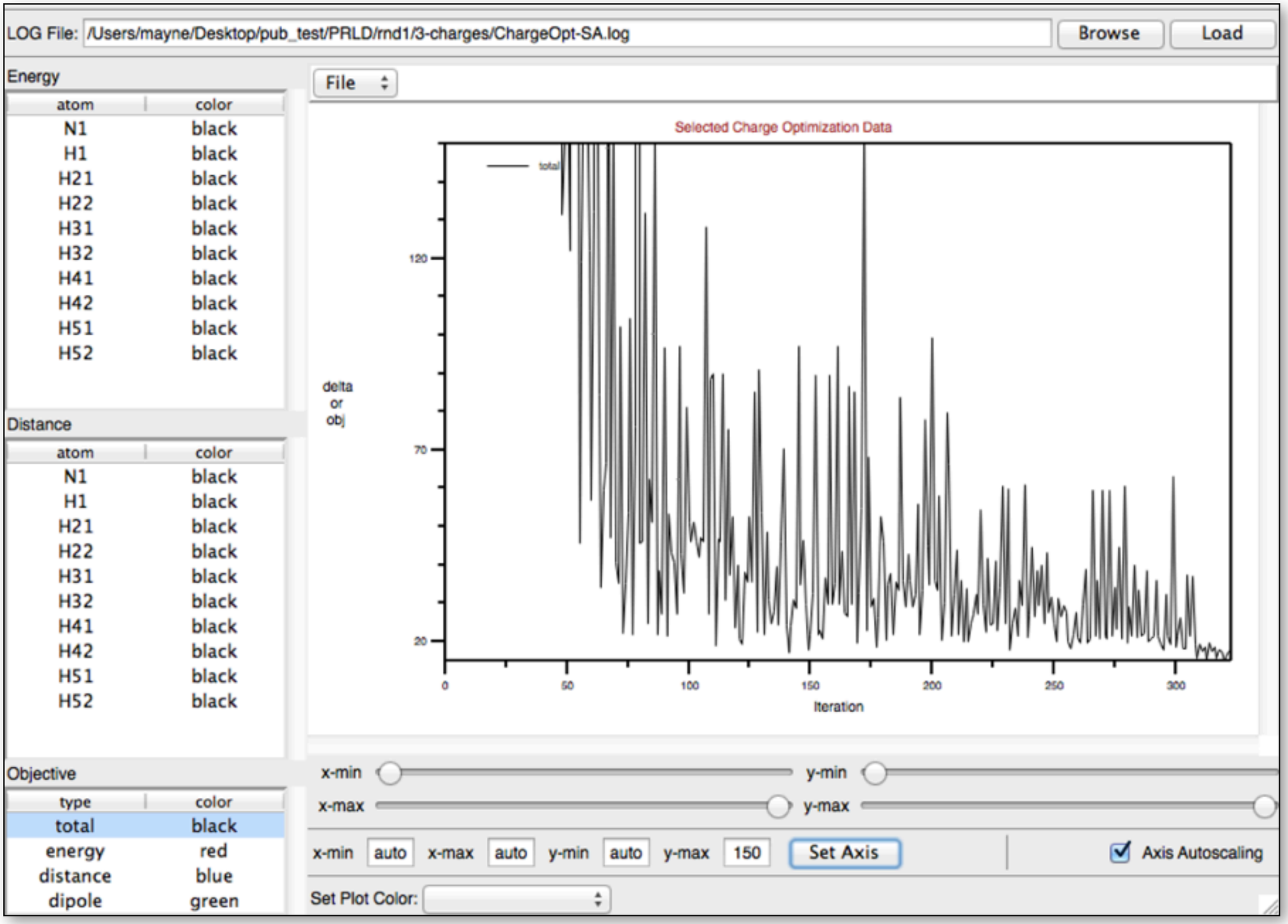
Sampling MM Water-Interaction Profiles

Mode: Simulated Annealing

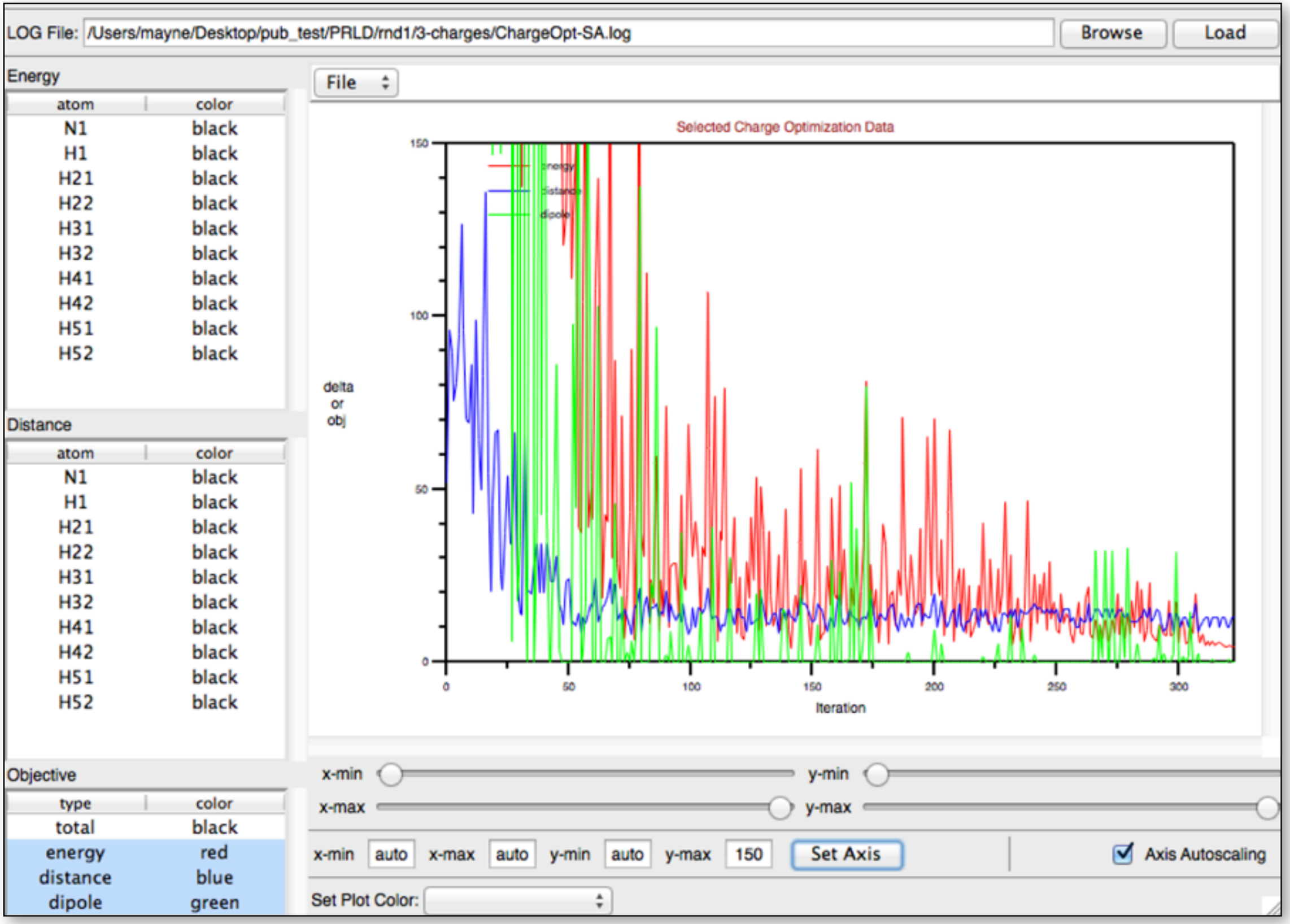


Plotting Charge Optimization Data

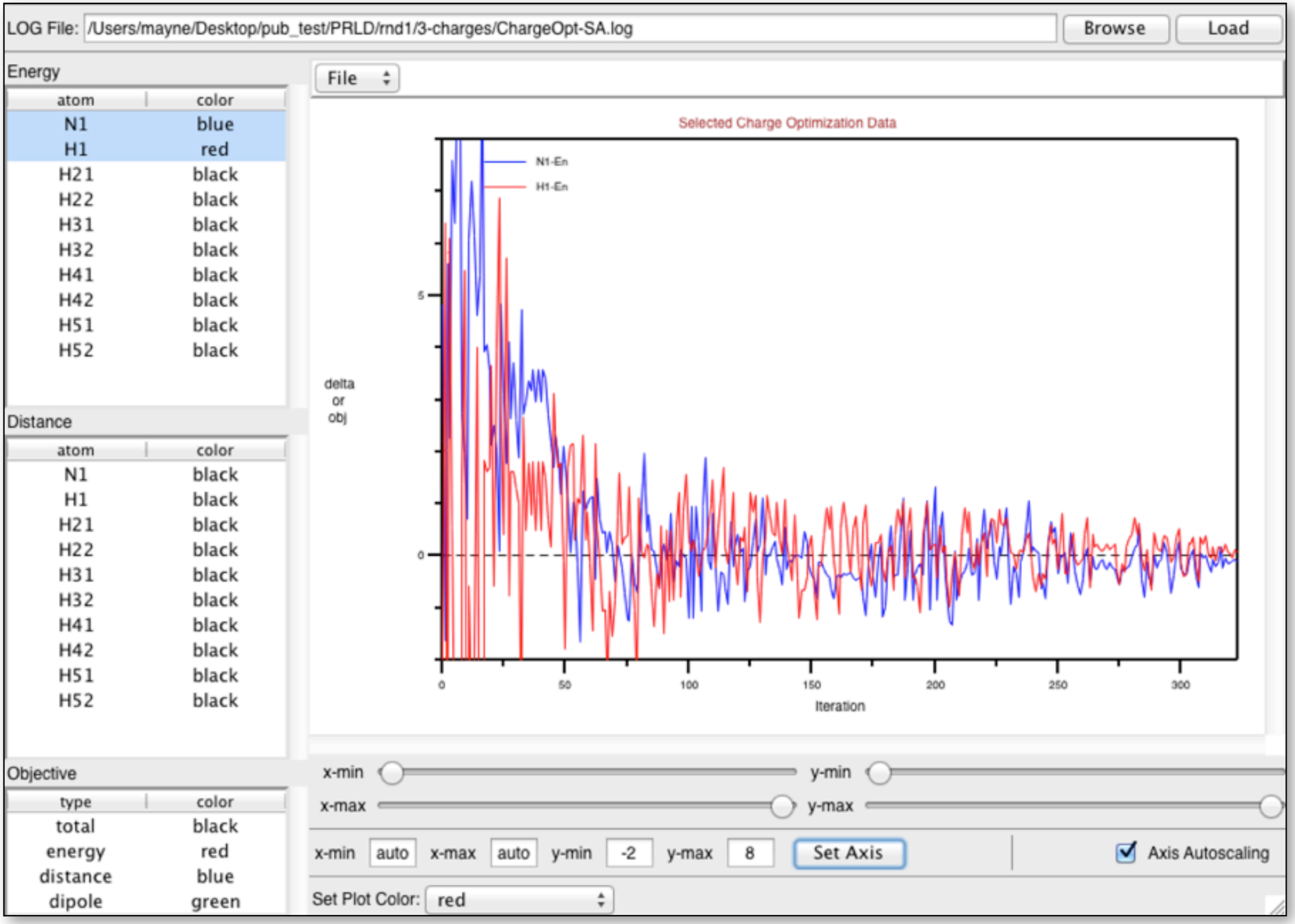
Plotting Charge Optimization Data



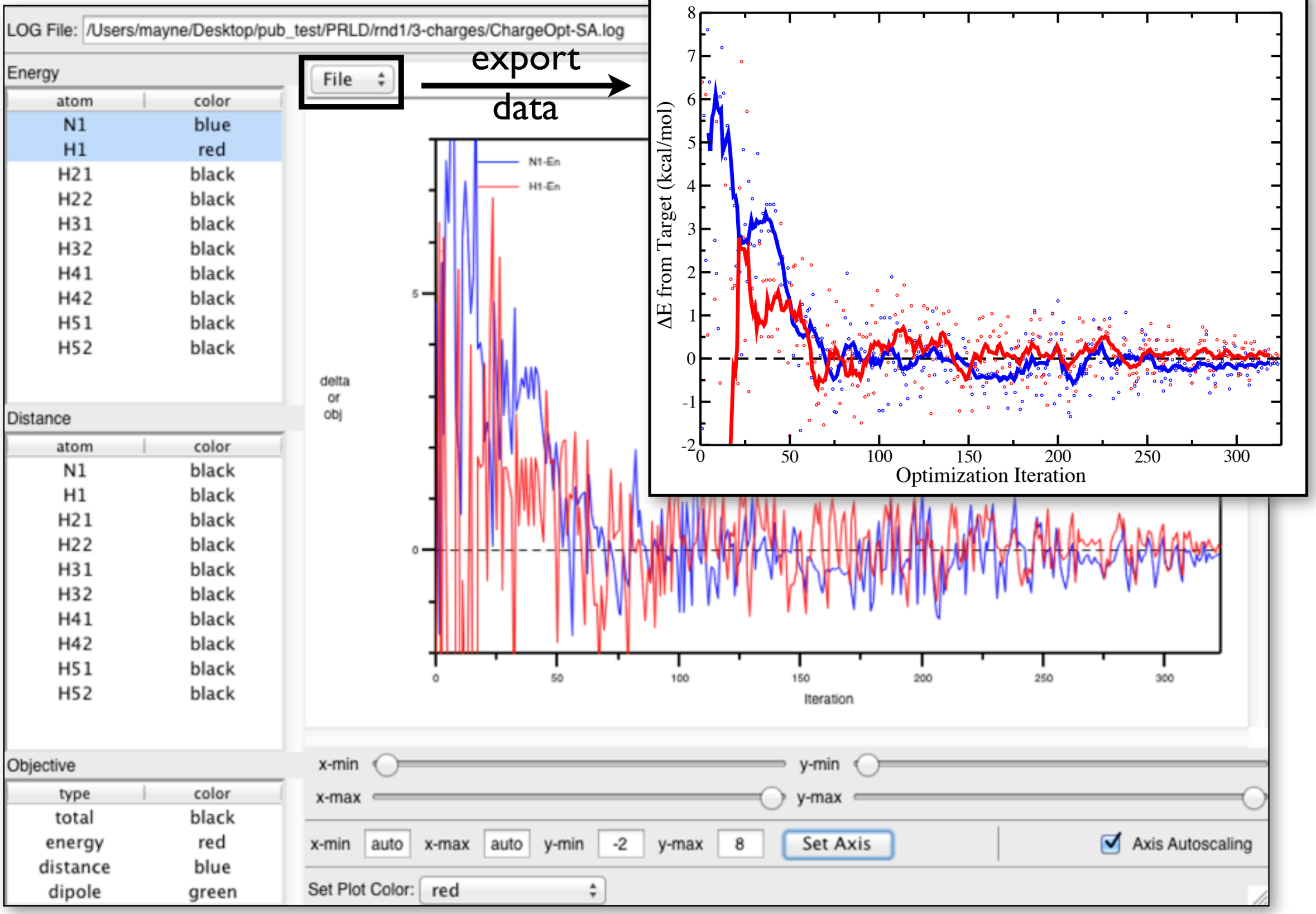
Plotting Charge Optimization Data



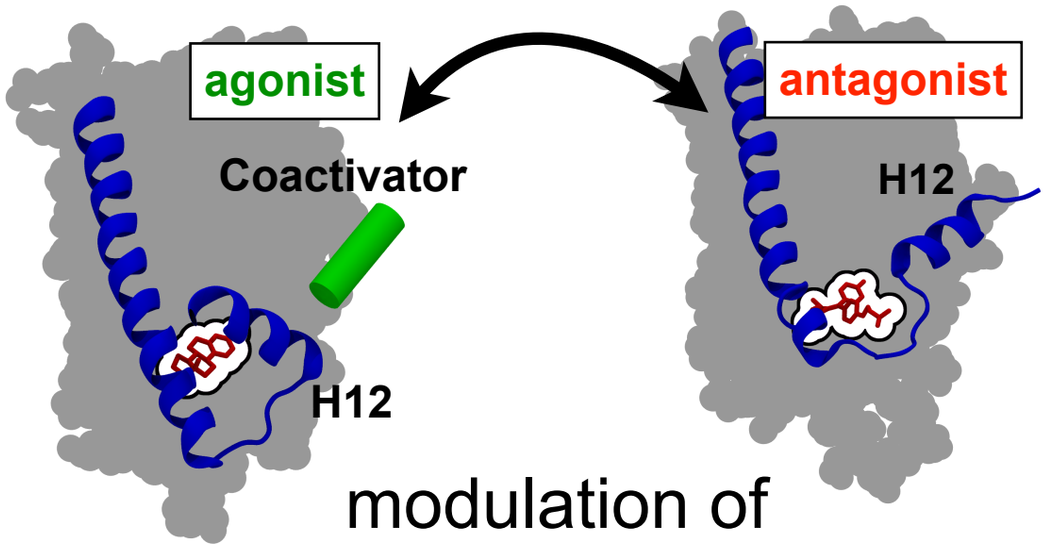
Plotting Charge Optimization Data



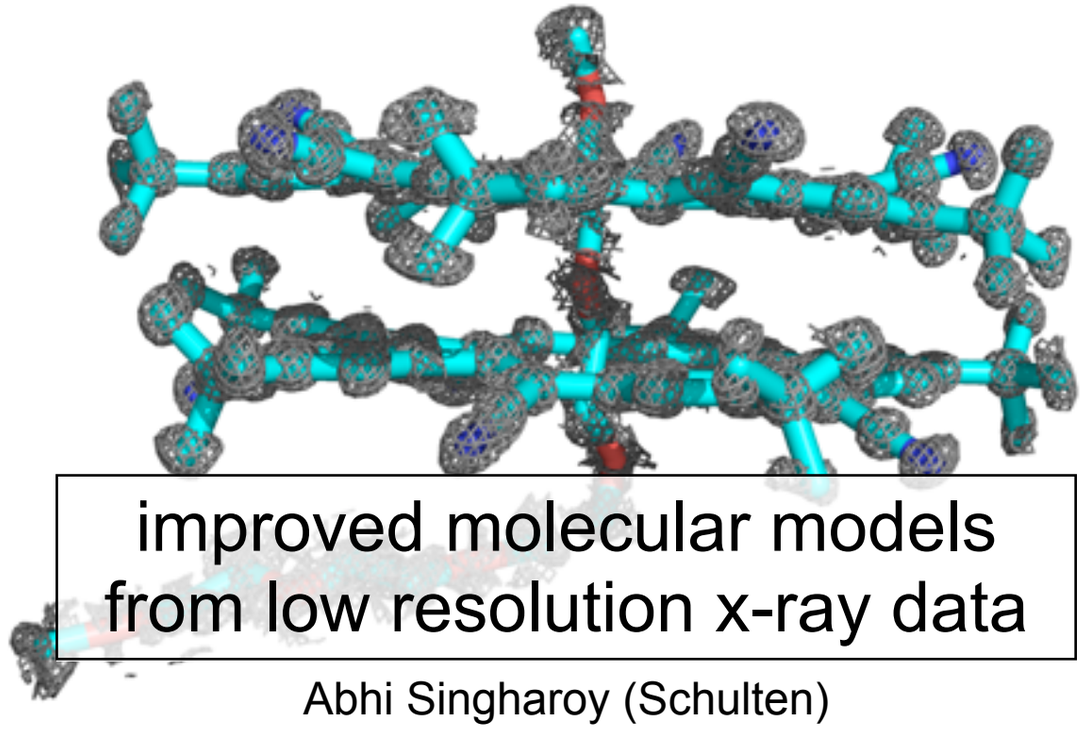
Plotting Charge Optimization Data



*ff*TK Enables Exciting Science

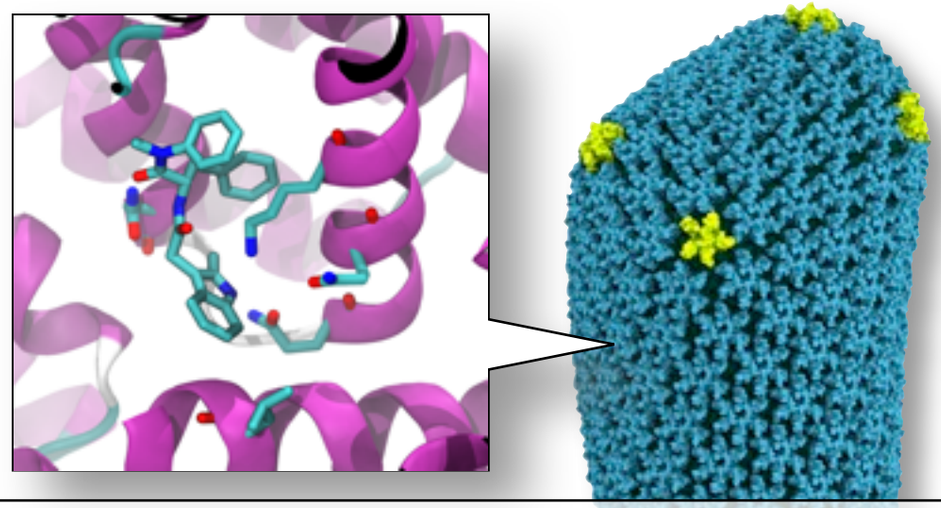


modulation of
nuclear receptor dynamics



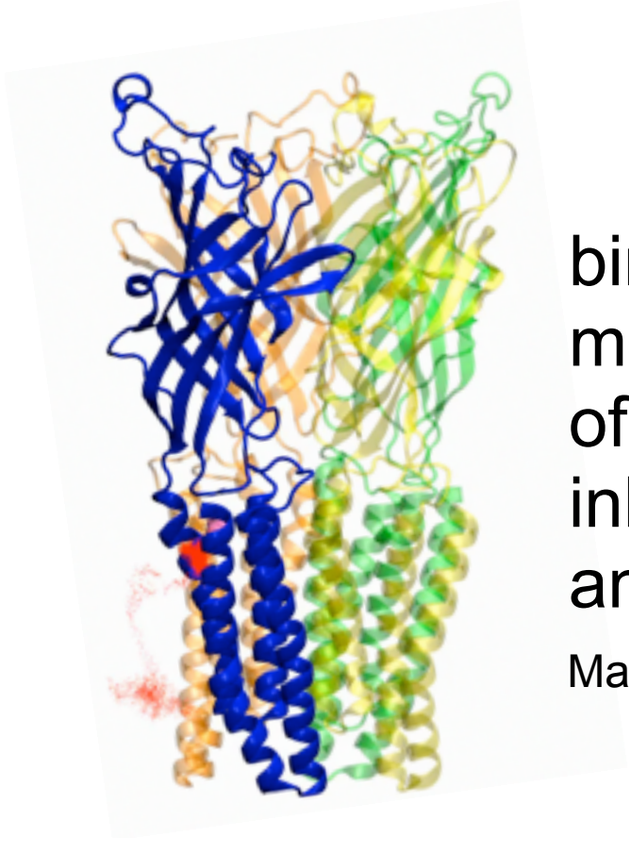
improved molecular models
from low resolution x-ray data

Abhi Singharoy (Schulten)



mechanism of action for anti-retroviral
drugs targeting the HIV capsid

Juan Perilla (Schulten)

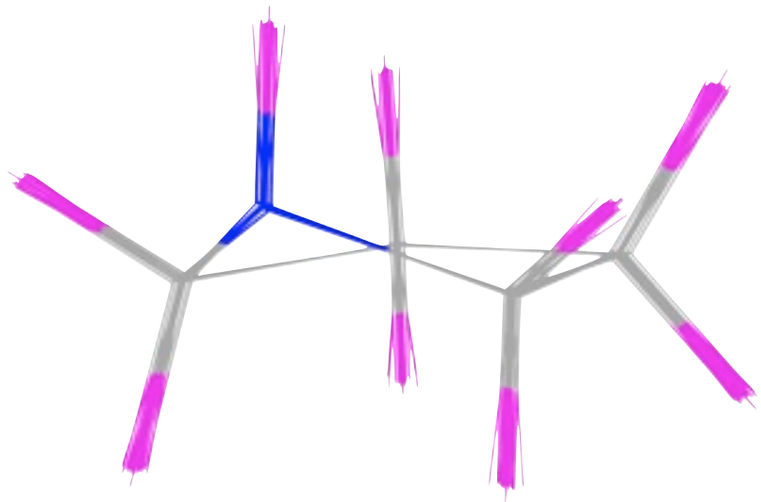


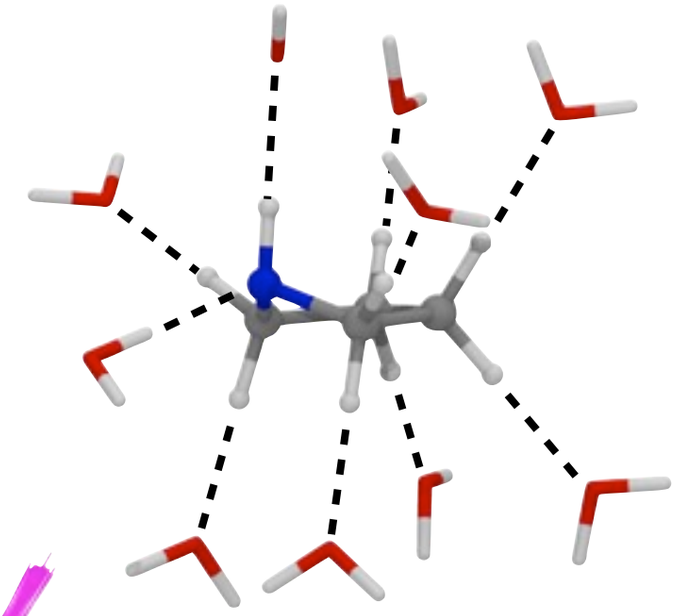
binding
mechanisms
of
inhaled
anesthetics

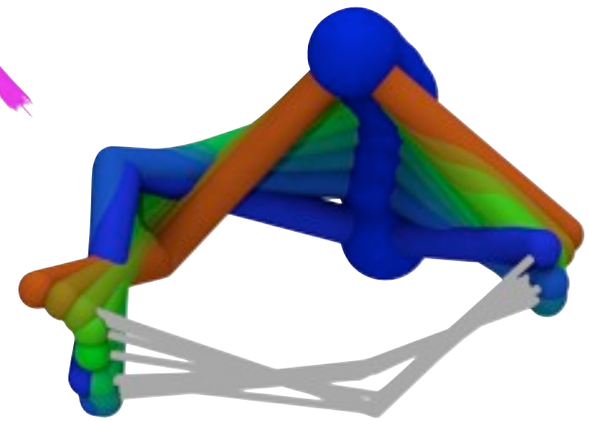
Mark Arcario (Tajkhorshid)

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

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

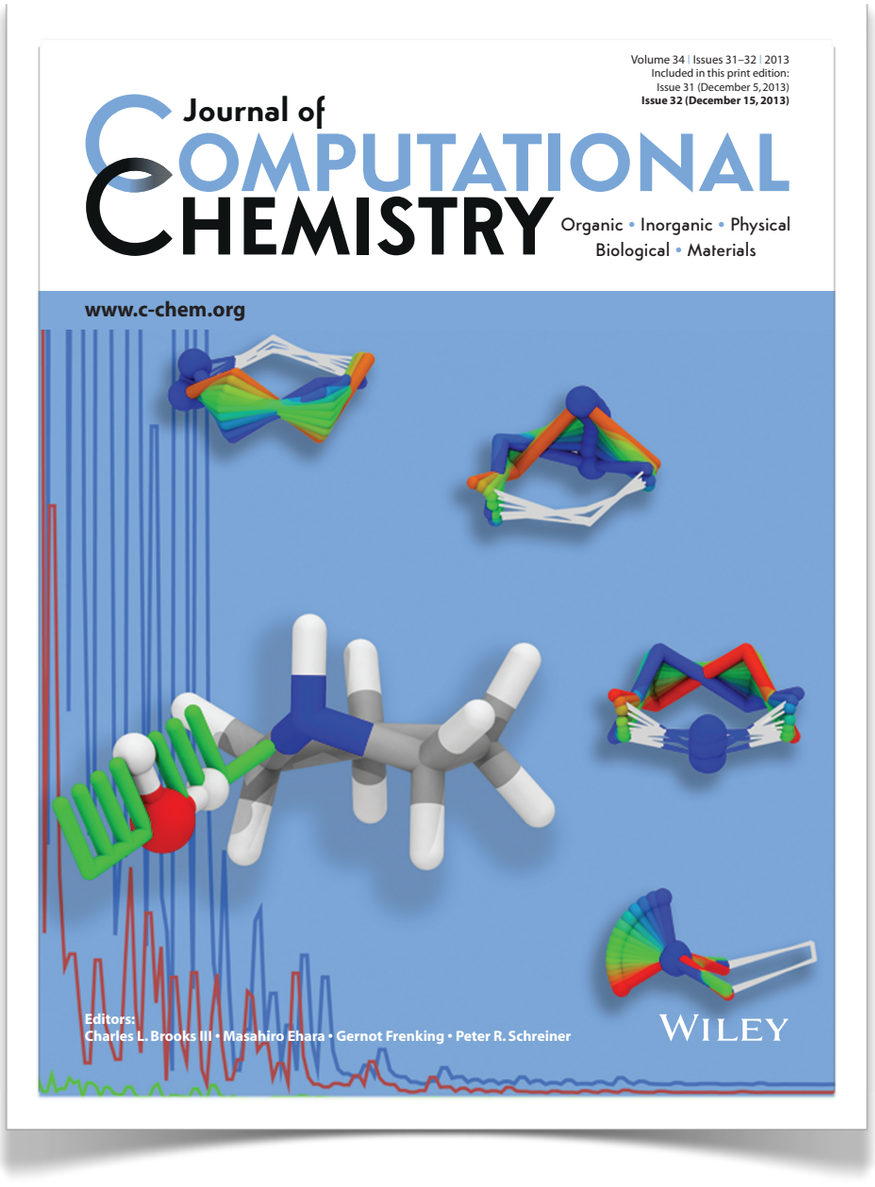
*ff*TK is available as a VMD Plugin (1.9.2)

Full Documentation and Screencast Tutorials

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

May the Force Field Be With You!

http://www.ks.uiuc.edu/Highlights/?section=2013&highlight=2013-09



Questions?