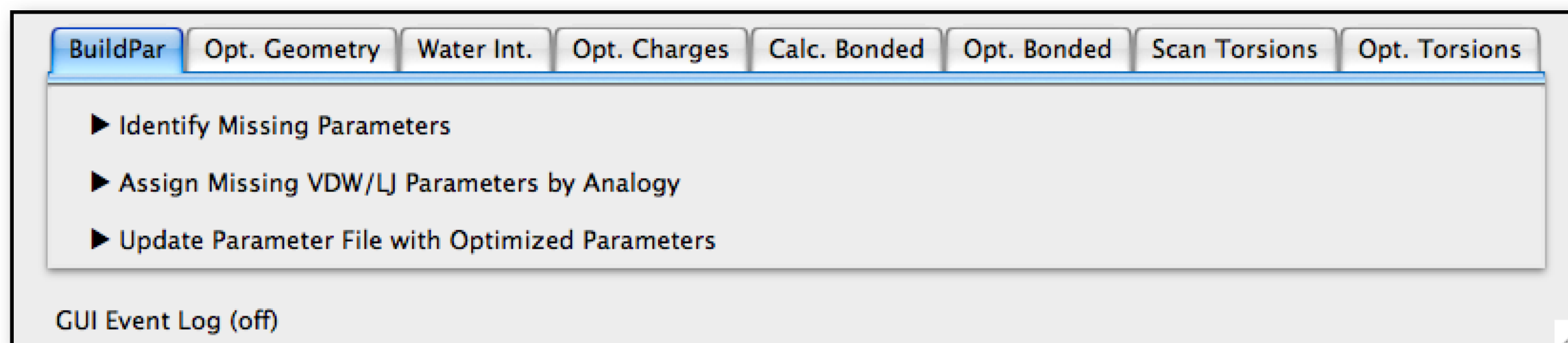


Parameterizing Small Molecules Using: The Force Field Toolkit (*ffTK*)



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MD Simulations of Biological Systems

Molecular Mechanics Force Fields

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

The CHARMM Force Field

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

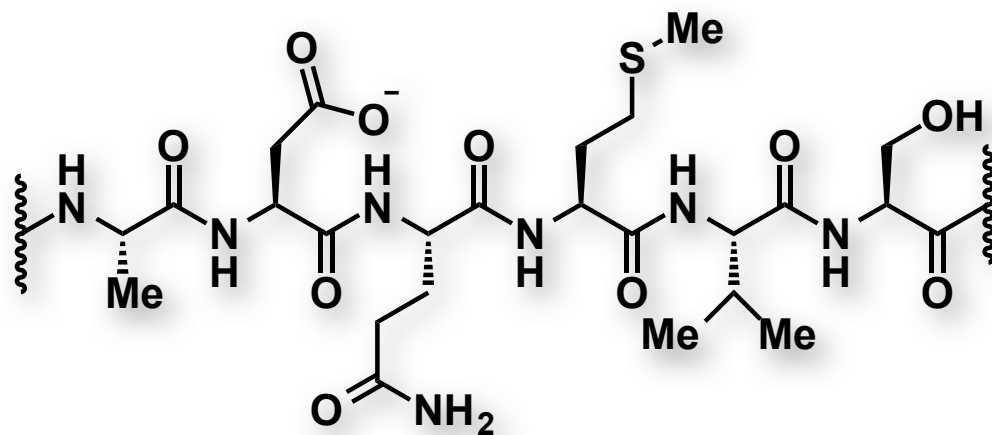
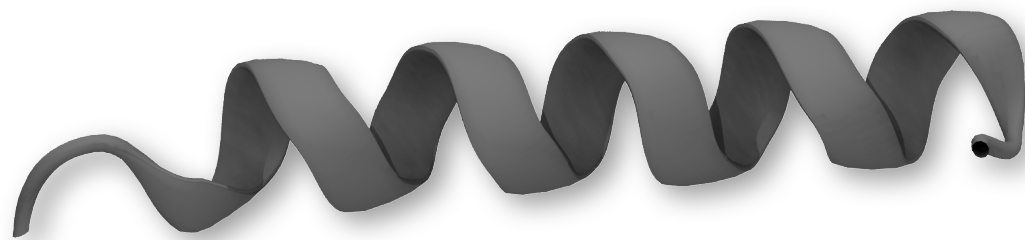
$$\sum_{\text{dihedrals}} k_i^{\text{dihedral}} [1 + \cos(n_i \phi_i + \delta_i)] +$$

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

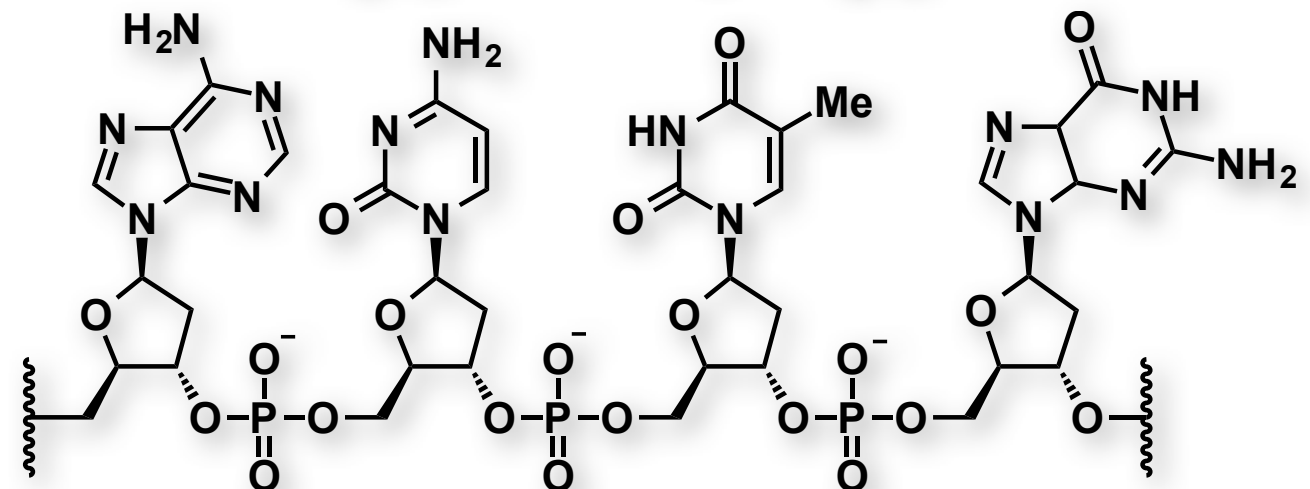
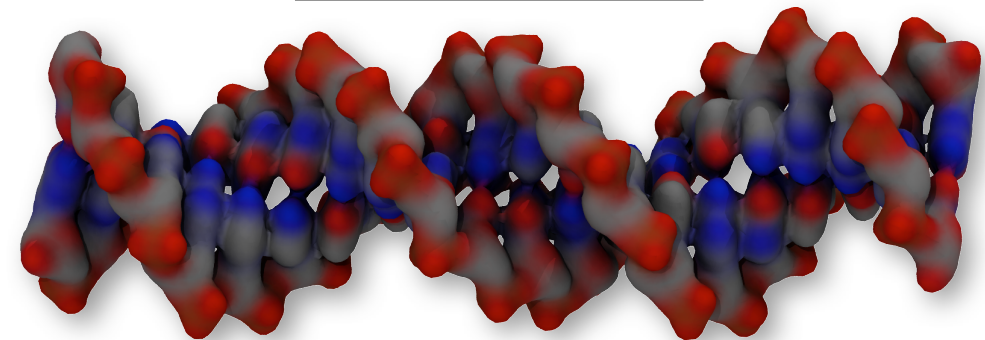
Parameter Transferability In Biopolymers

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

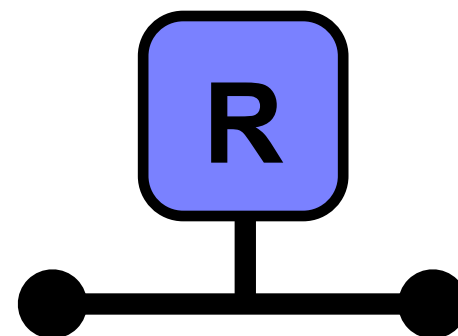
Peptides and Proteins



Nucleic Acids



Key Features:

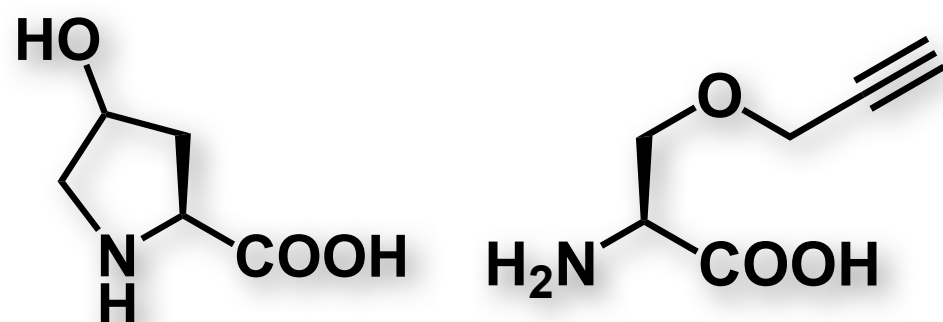


limited set of isolated
building blocks

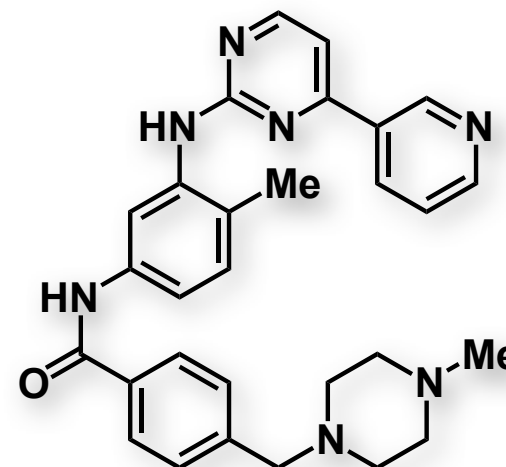
repetitive backbone unit

Parameterization as an Impasse

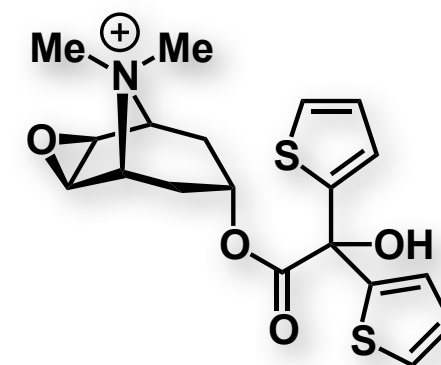
non-standard or
engineered amino acids



small molecule ligands

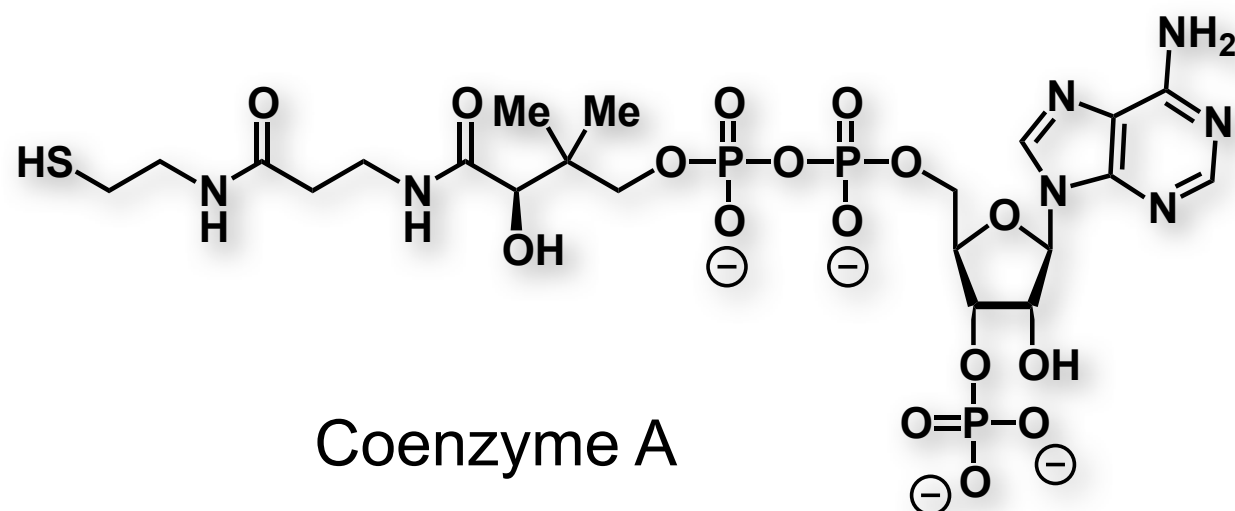


Imatinib (Gleevec)



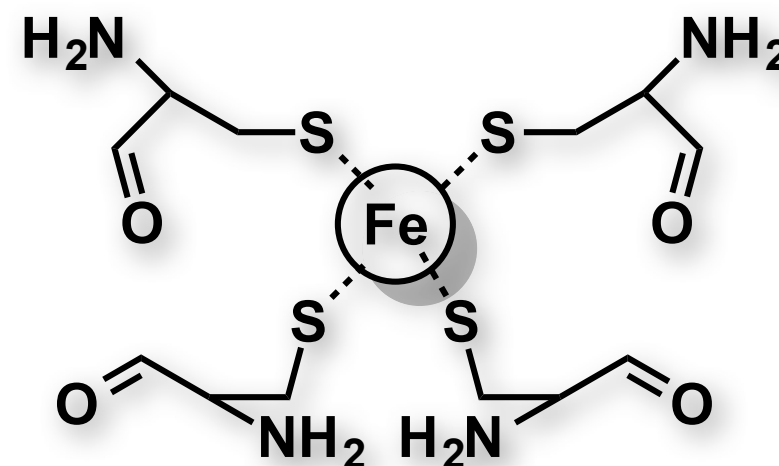
Tiotropium (Spiriva)

cofactors

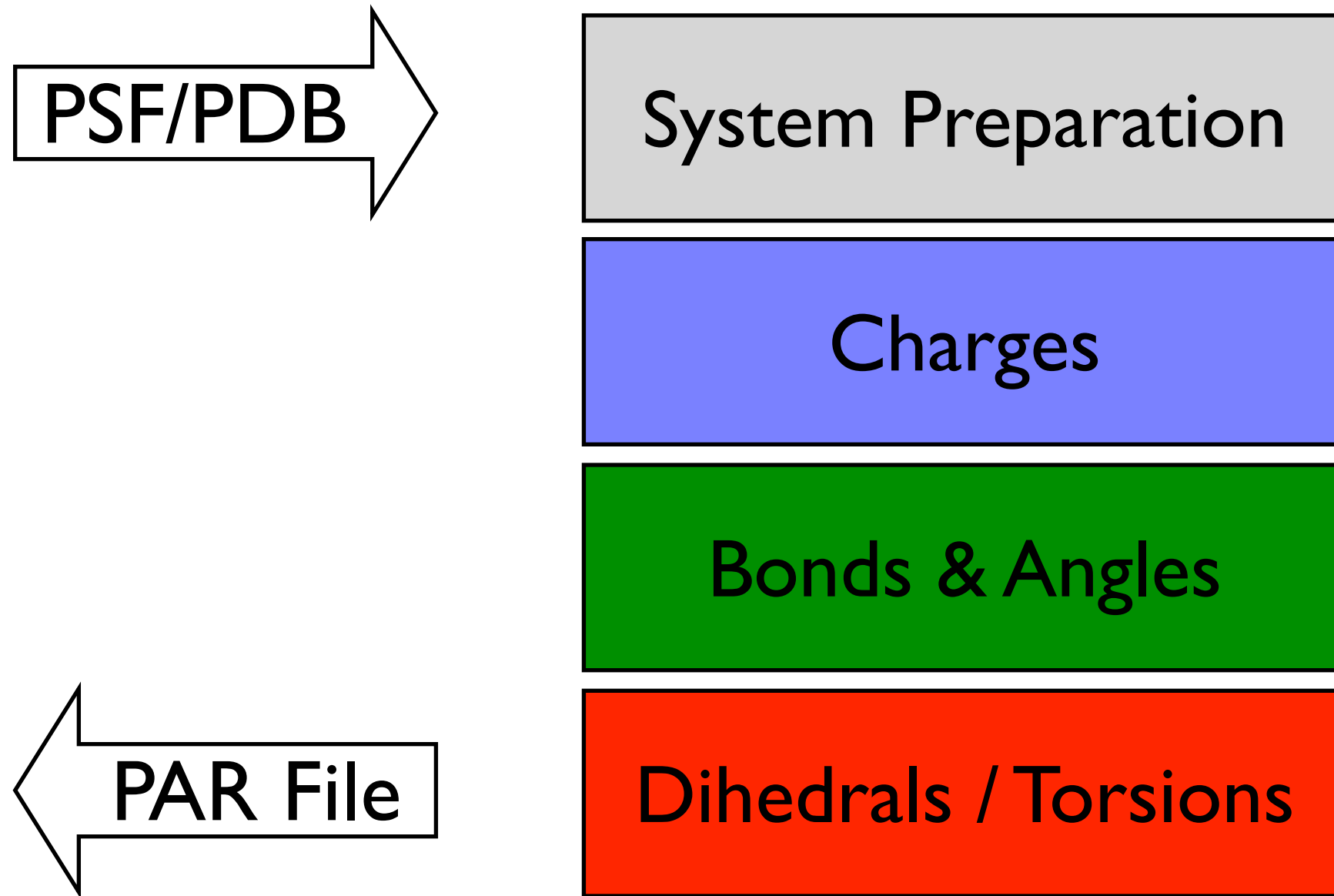


Coenzyme A

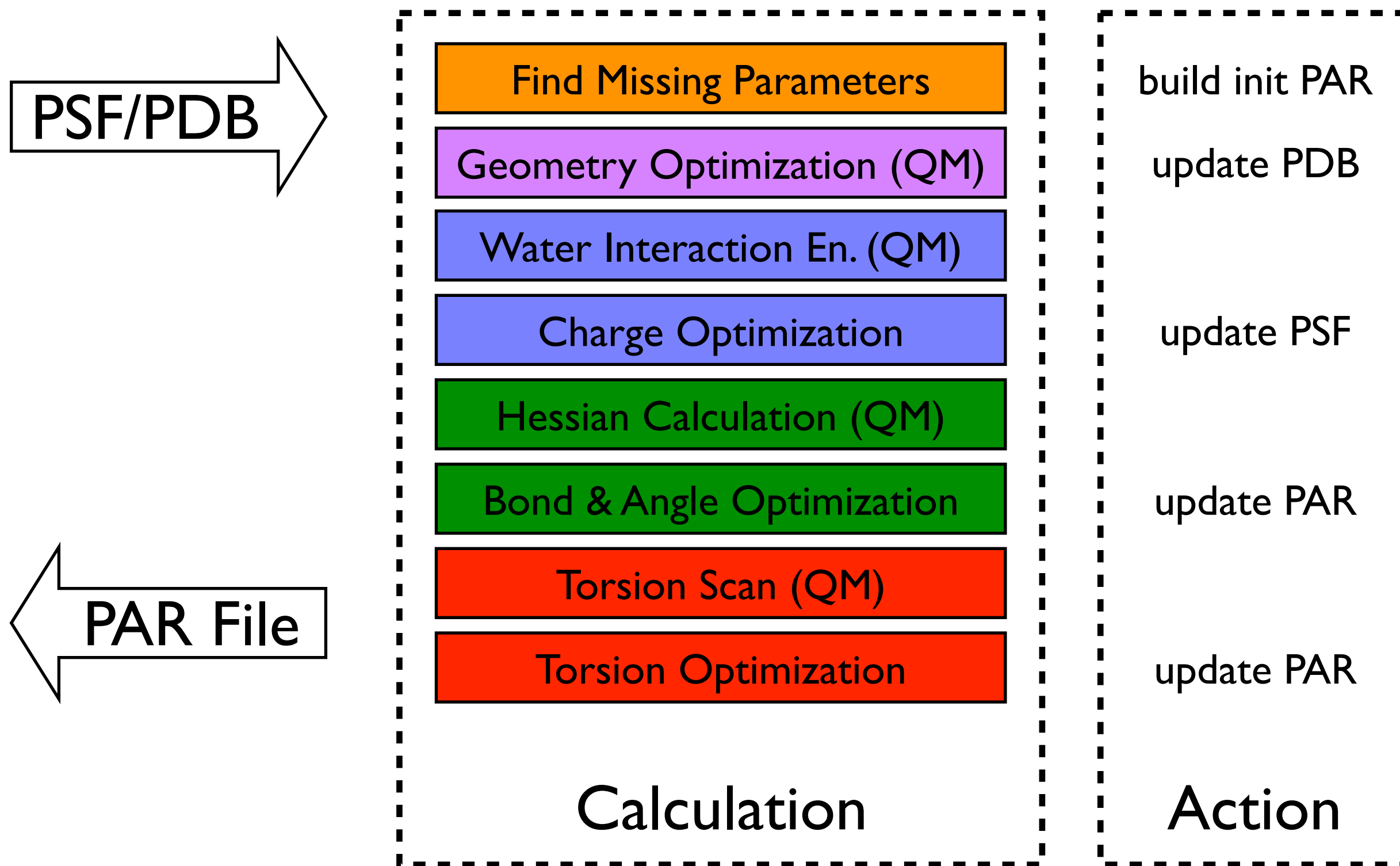
metal centers



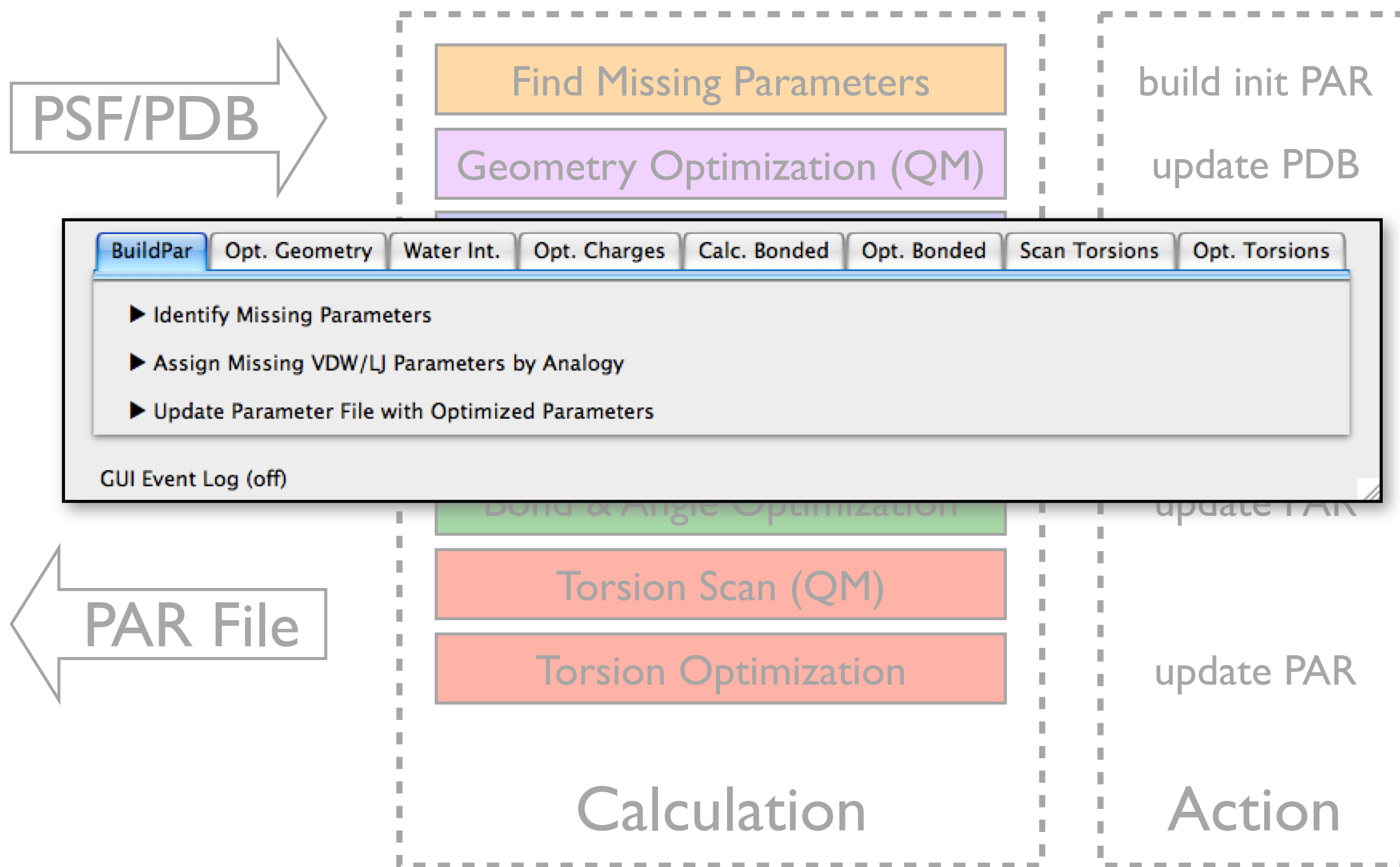
General Parameterization Workflow



CGenFF Parameterization Workflow

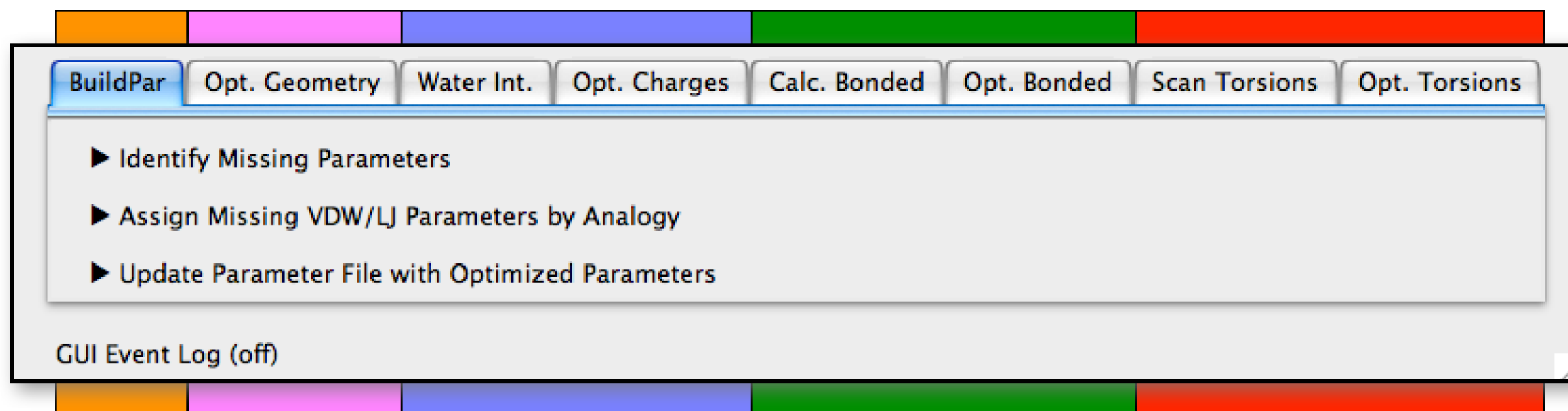


CGenFF Parameterization Workflow



ffTK Interface

tasks organized under tabs



ffTK Interface

standard file dialogs ← action buttons

The screenshot displays the ffTK interface with a multi-colored header bar (orange, pink, blue, green, red) and a tabbed menu at the top. The 'Opt. Charges' tab is selected. The interface is divided into several sections:

- Input Section:** Contains fields for 'PSF File' (set to /users/mayne/fftk/PRLD/1-sysprep/prld.psf), 'PDB File' (set to /users/mayne/fftk/PRLD/2-geomopt/prld-opt.pdb), and 'Residue Name' (set to PRLD). There are 'Browse' buttons for the file fields and a 'Resname From TOP' button. A 'Load PSF/PDB' button is also present.
- Parameter Files Section:** A list box shows '/users/mayne/fftk/PRLD/parfiles/prld-init.par'. To its right are 'Add', 'Delete', and 'Clear' buttons.
- Output LOG Section:** A text field shows '/users/mayne/fftk/PRLD/3-charges/ChargeOpt.log' with a 'SaveAs' button next to it.
- Bottom Section:** A list of expandable items: 'Charge Constraints', 'QM Target Data', 'Advanced Settings', and 'Results'.

Annotations with arrows point to specific UI elements:

- An arrow points from the text 'standard file dialogs' to the 'Browse' buttons in the 'Input' section.
- An arrow points from the text 'action buttons' to the 'Load PSF/PDB' button.
- An arrow points from the text 'action menus' to the 'Add', 'Delete', and 'Clear' buttons.

Functionality Provided by *ff*TK

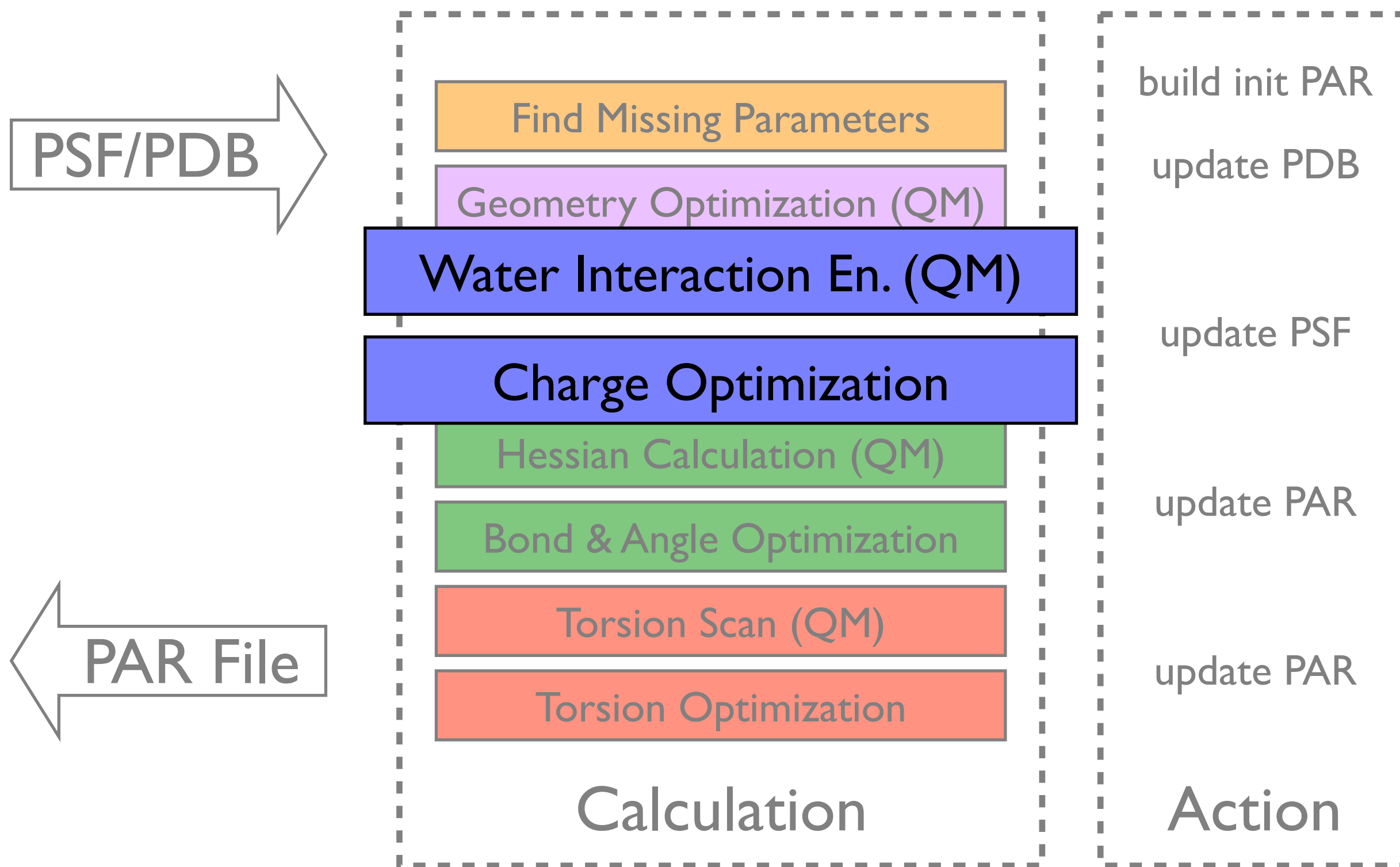
Core Functions

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

Support Functions

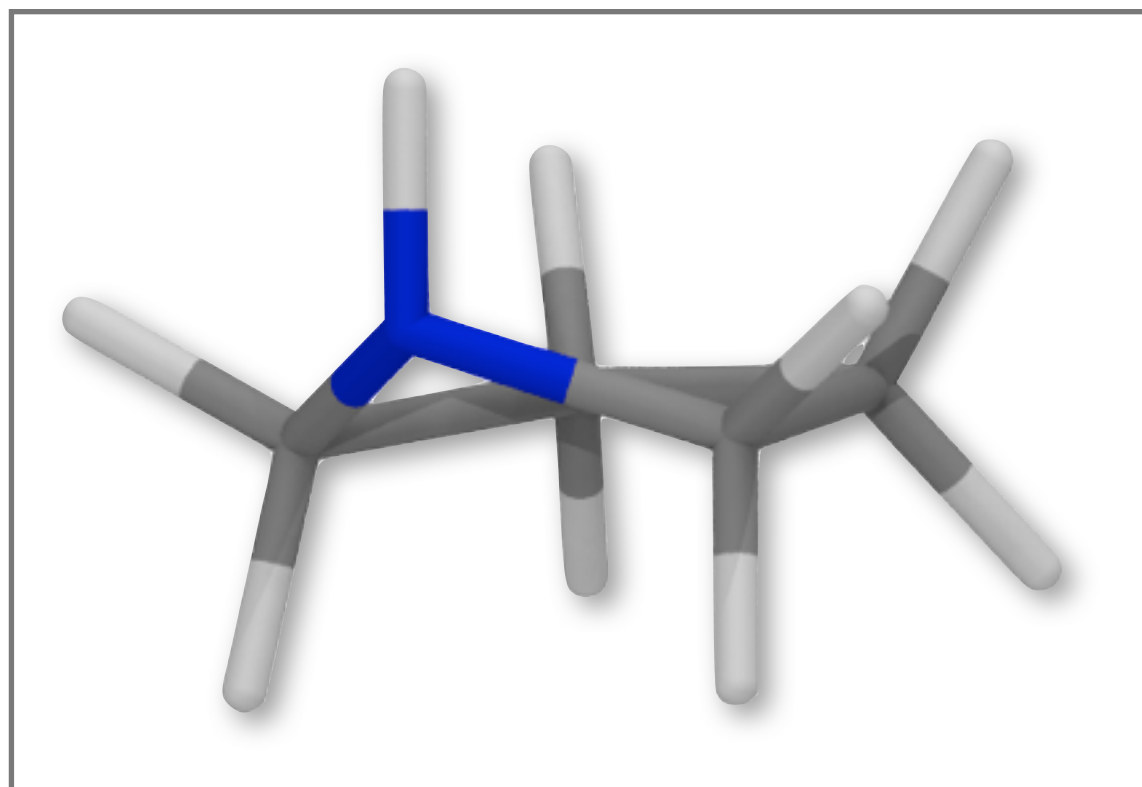
- Auto-detect Water Interaction Sites
- Auto-detect Charge Groups
- Auto-detect Non-redundant Torsions
- Build & Update Parameter Files
- Browse Existing Parameter Sets
- Write Updated Charges to PSF
- Reset Opt. Input from Output
- Visualize Target Data in VMD
- Create Graphic Objects in VMD
- Label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

ffTK Exemplified by Charge Optimization



Generating Charge Optimization Target Data

△
Load QM optimized geometry | Auto-detect interaction sites | Generate



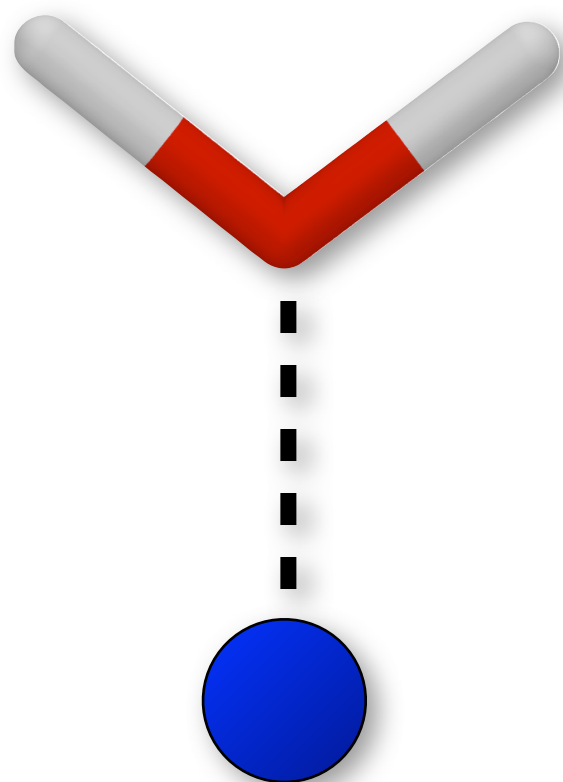
VMD main window

ffTK GUI

Input/Output			
PSF File:	/Users/mayne/Desktop/pub_test/PRLD/rnd1/3-charges/prld-charged.psf	Browse	
PDB File:	/Users/mayne/Desktop/pub_test/PRLD/rnd1/2-geomopt/prld-opt.pdb	Browse	
Output Path:	./output	Browse	
Basename:	PRLD	Basename From TOP	Load PSF/PDB

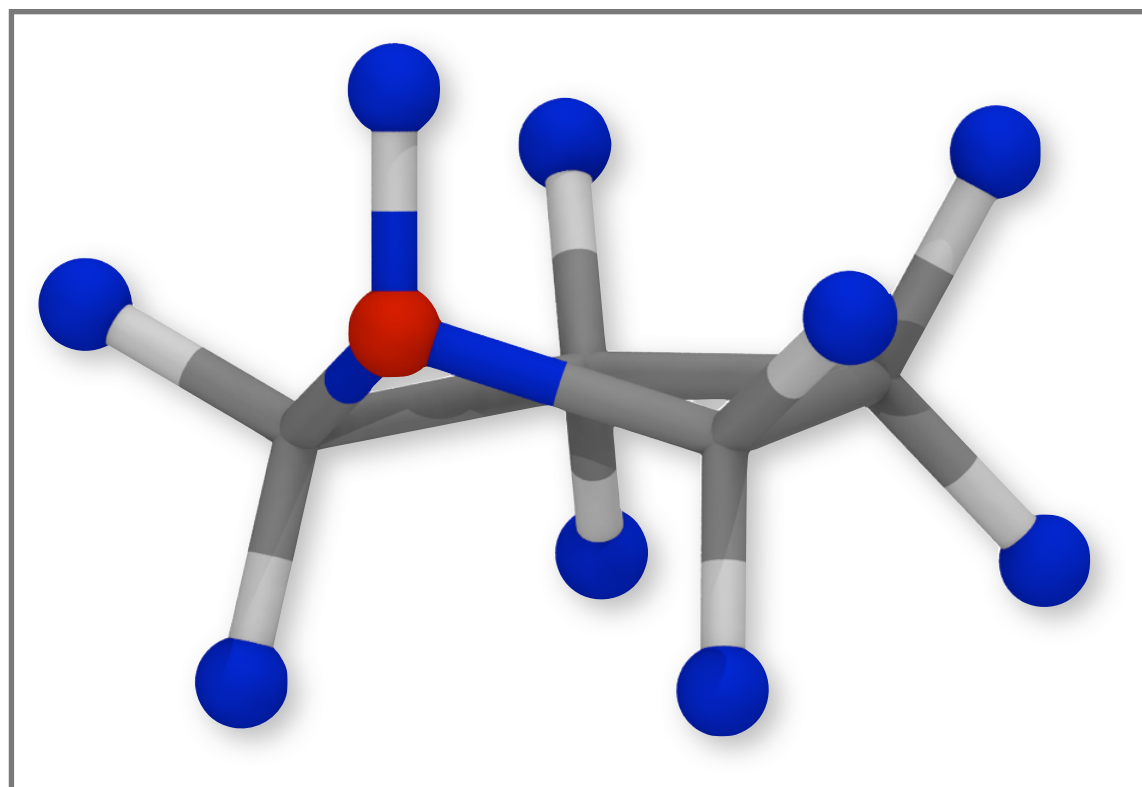
Generating Charge Optimization Target Data

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

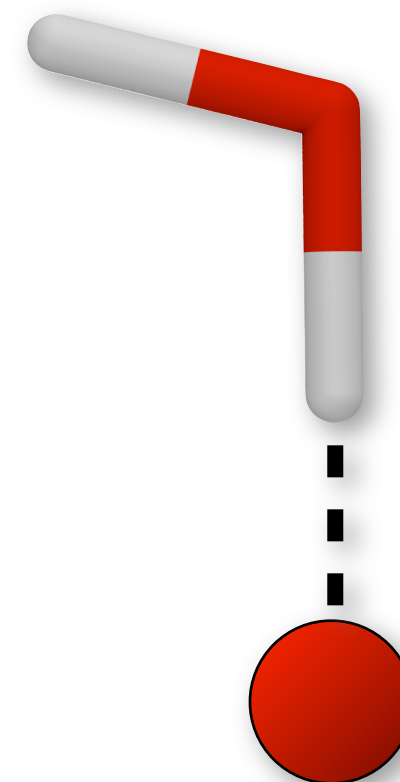


Donor

ffTK GUI



VMD main window



Acceptor

Hydrogen Bonding Atoms

Donor Indices (Interact with oxygen of water)

5 6 7 8 9 10 11 12 13

Acceptor Indices (Interact with hydrogen of water)

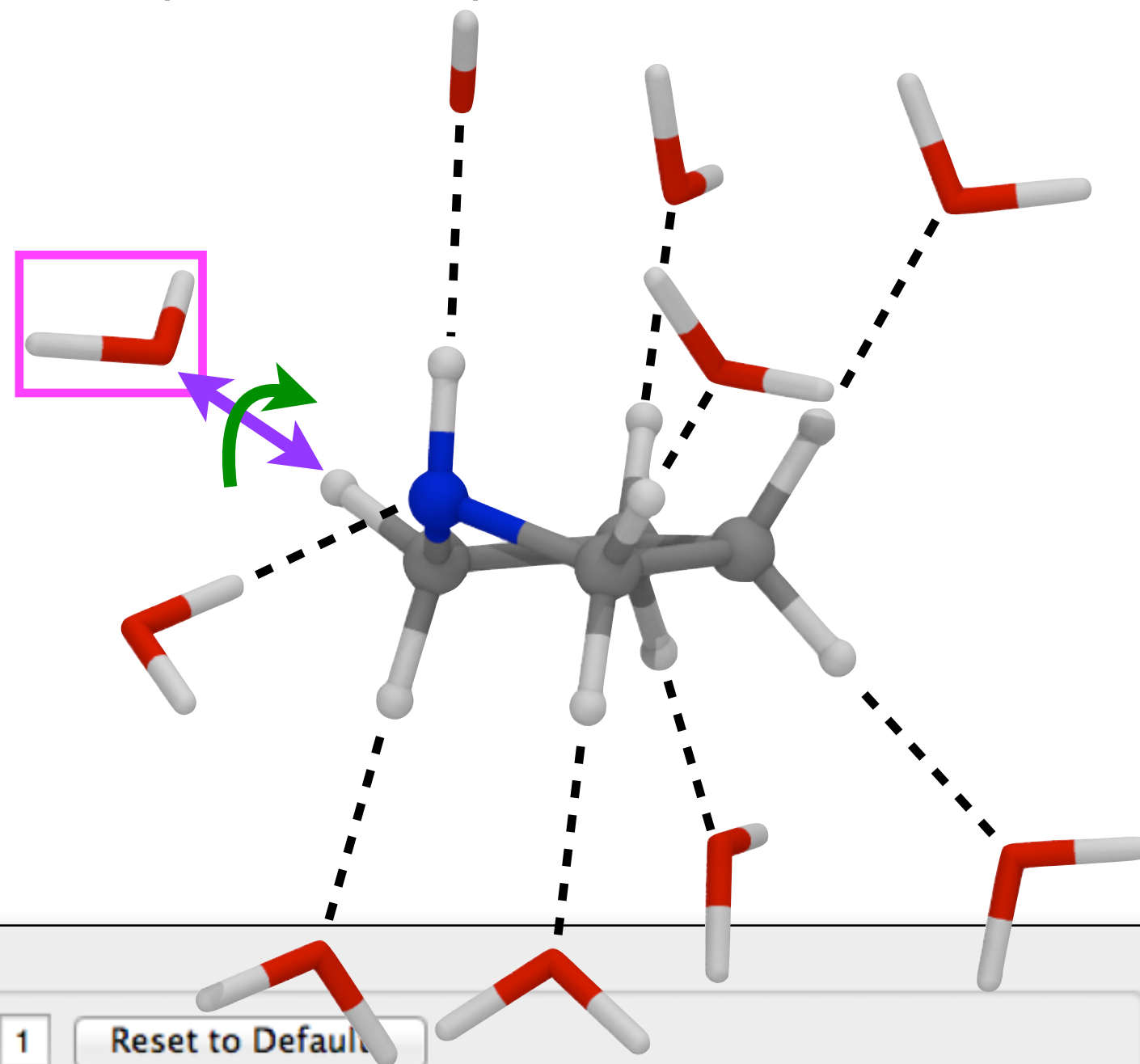
2

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: Memory (GB): Charge: Multiplicity: Reset to Default

Route:

Write Gaussian Input Files

Load GAU Files

Load LOG Files

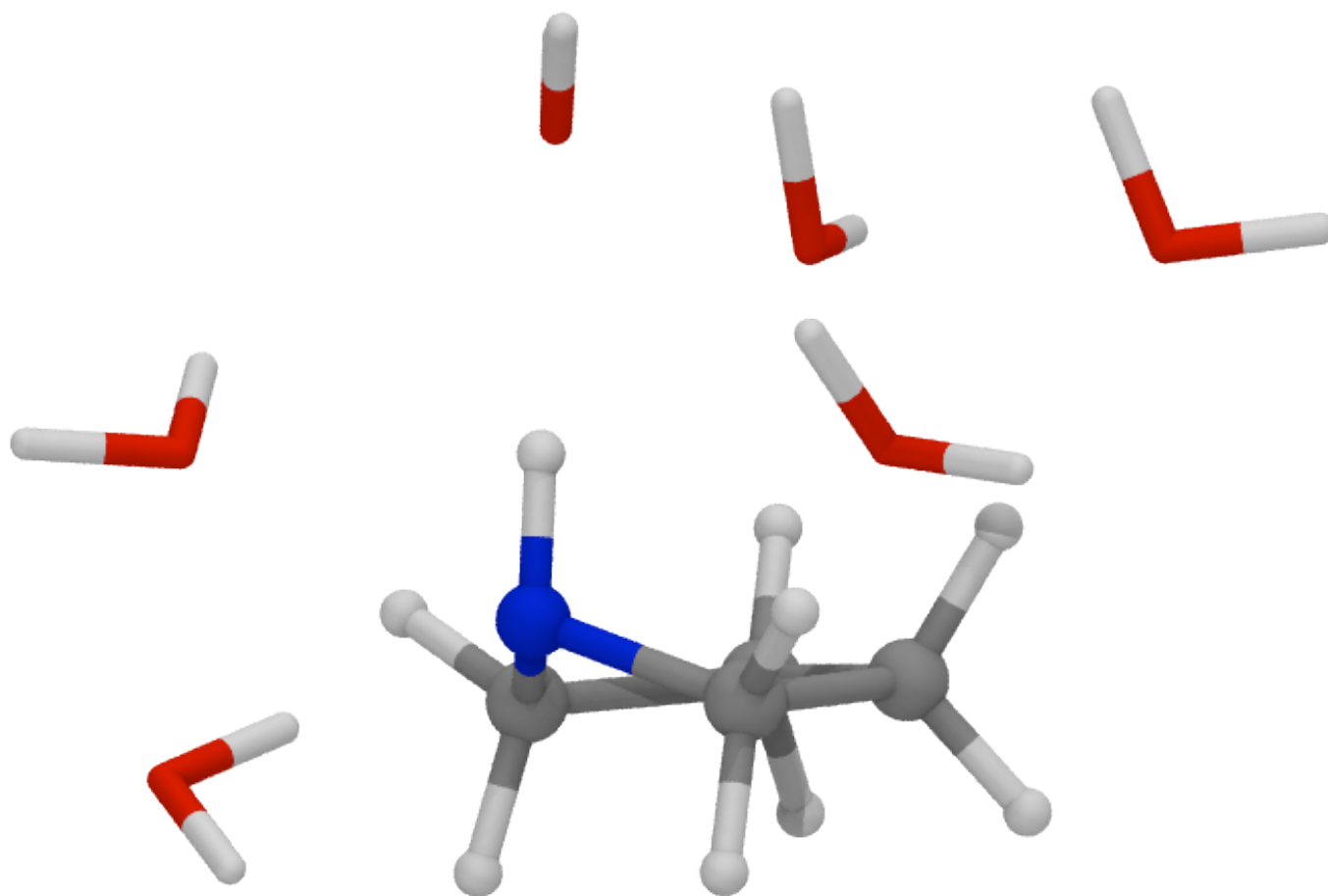
Generating Charge Optimization Target Data



| Run QM |

Inspect water optimization

Visually assess
QM-optimized
water position(s)



ffTK GUI

Gaussian Settings

Processors: Memory (GB): Charge: Multiplicity:

Route:

Charge Optimization



Setup Optimization

Load QM Target Data
Prepare Optimization

Optimizer:

Assign Charges
Compute U_{MM} , d_{MM} , μ_{MM}
Compute Objective Function

Return Optimized Charges

Analyze Performance

Write Charges to PSF

Objective Function

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

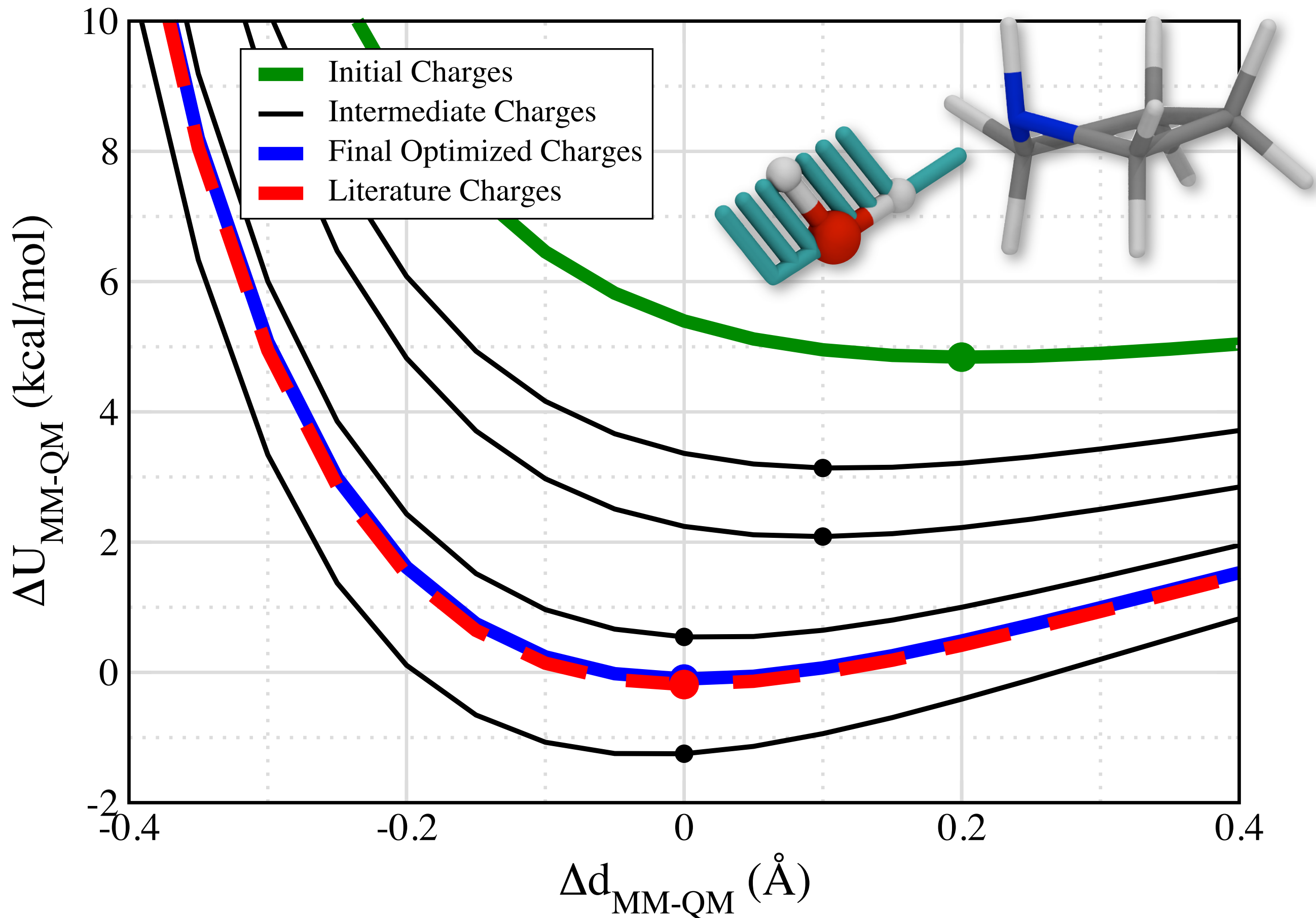
+

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

+

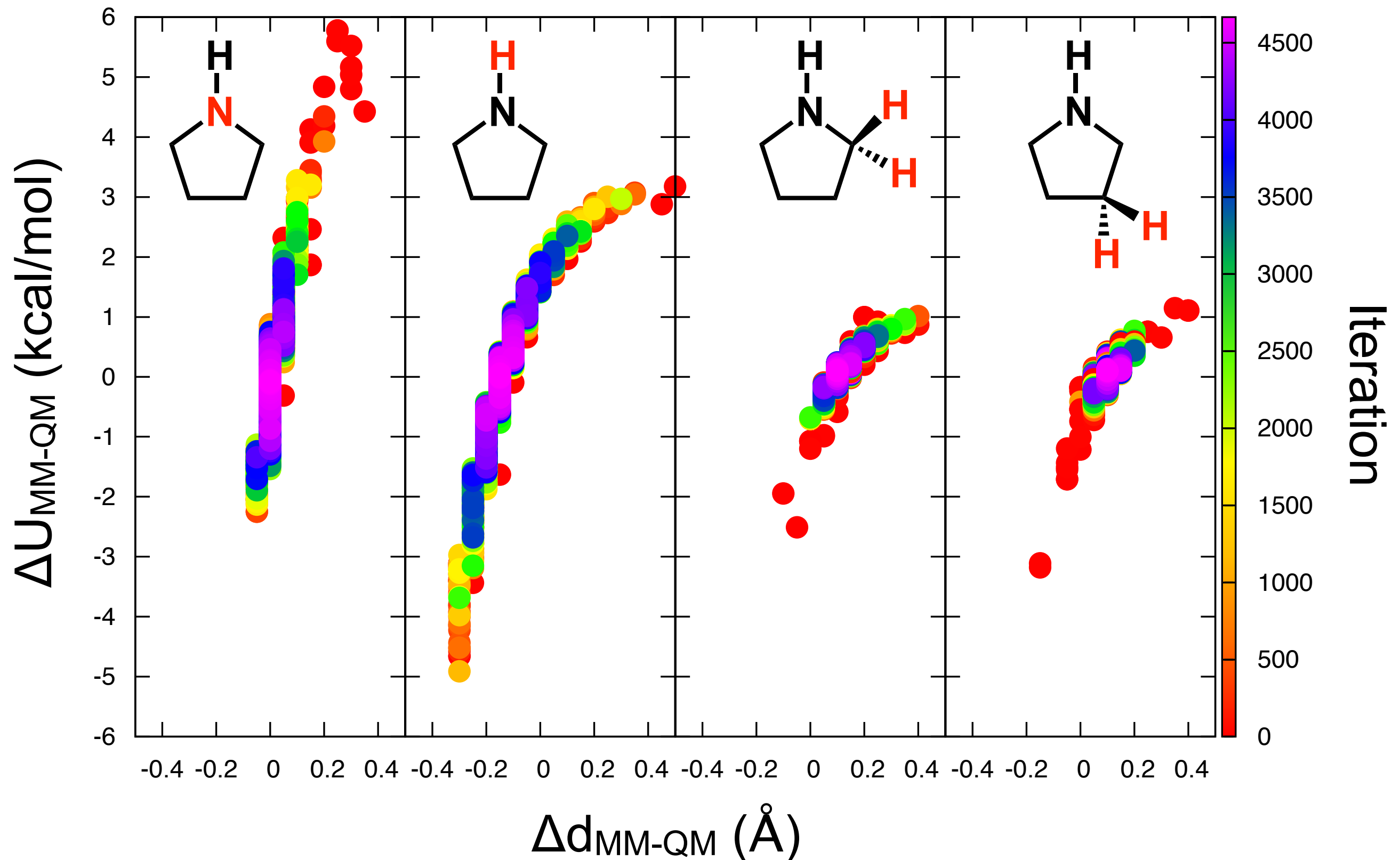
$$f(\mu_{MM} - \mu_{QM})$$

Assessing MM Water-Interaction Profiles

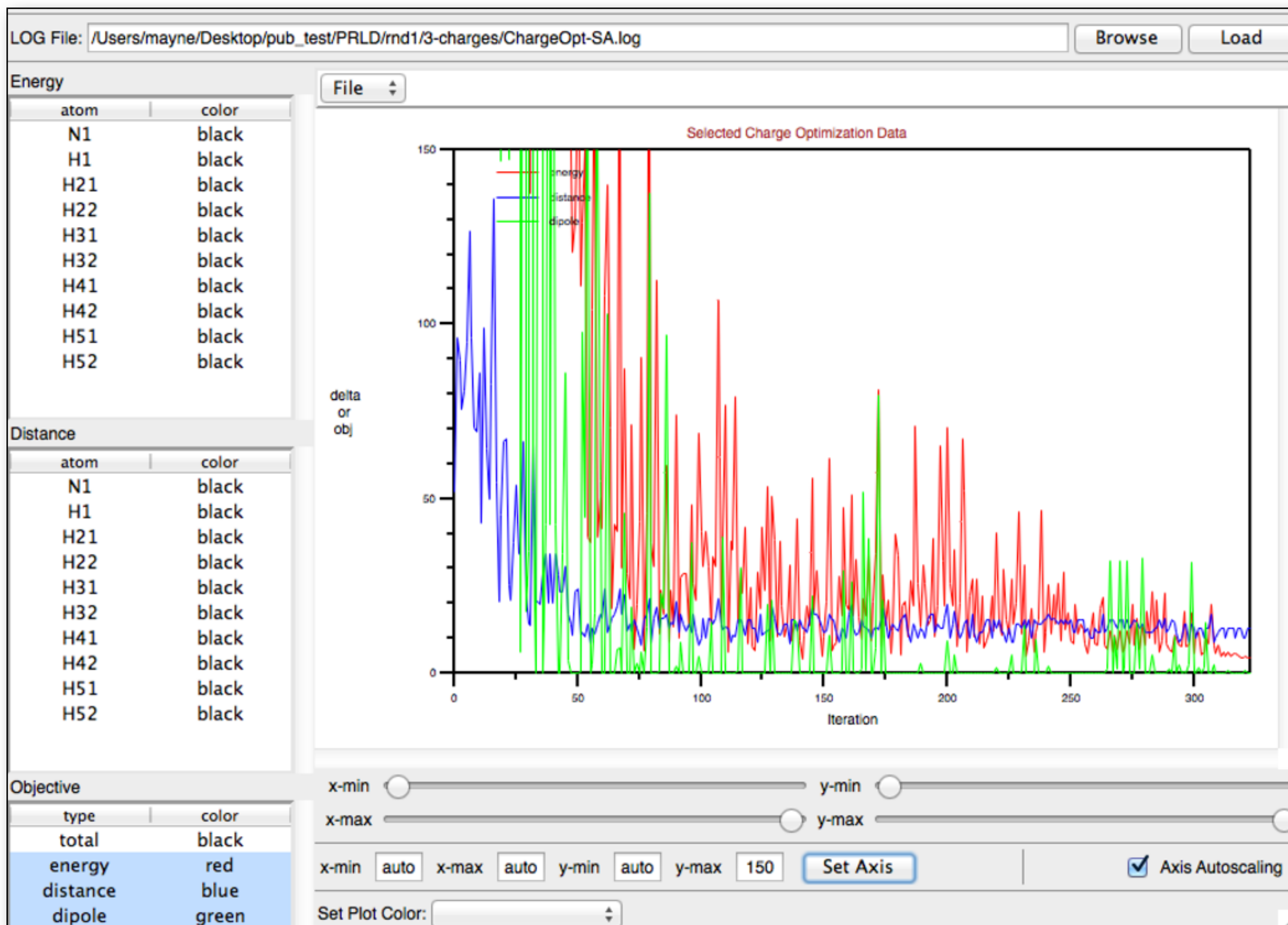


Sampling MM Water-Interaction Profiles

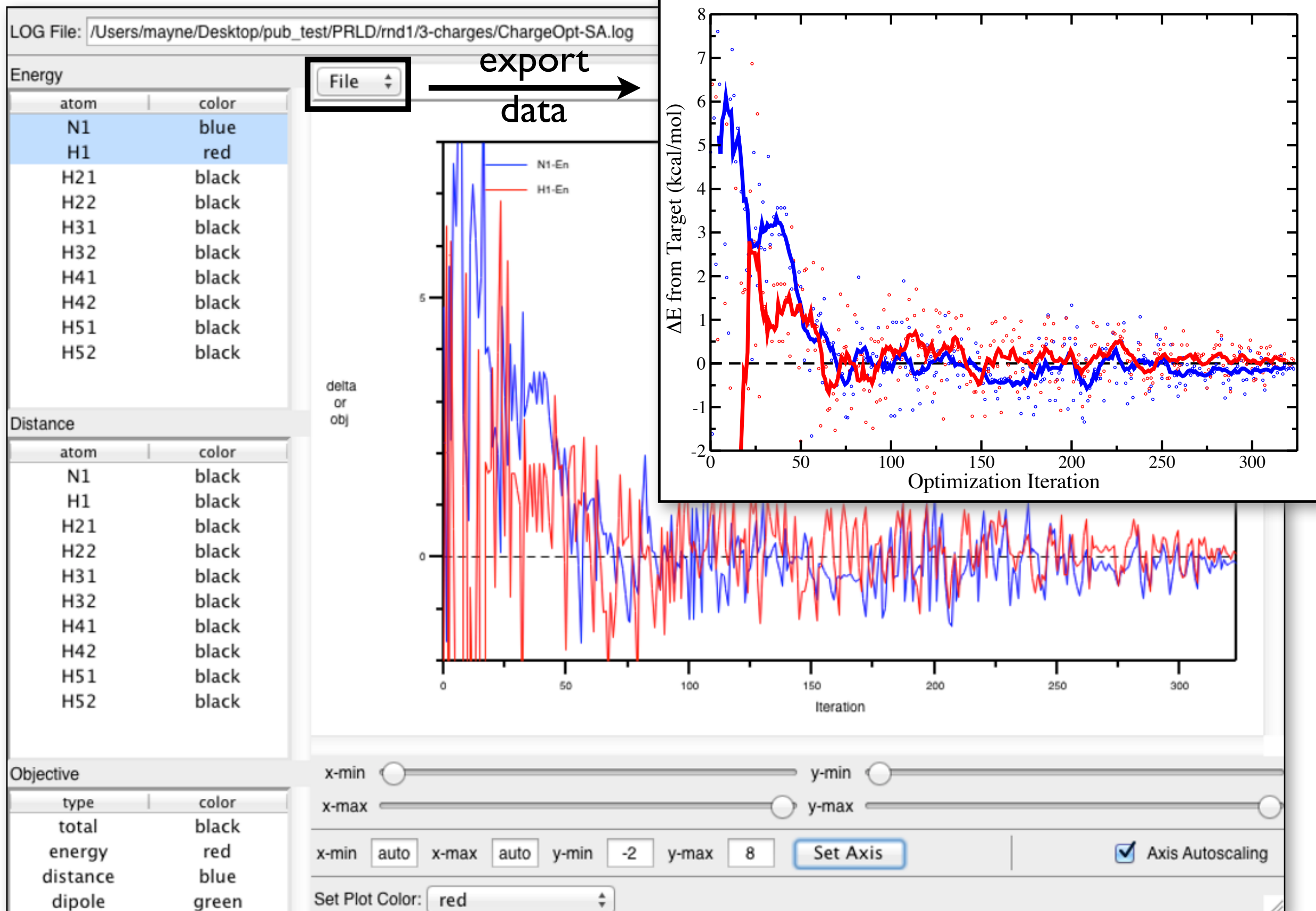
Mode: Simulated Annealing



Plotting Charge Optimization Data



Plotting Charge Optimization Data



Conclusions

Find Missing Parameters

Geometry Optimization (QM)

Water Interaction En. (QM)

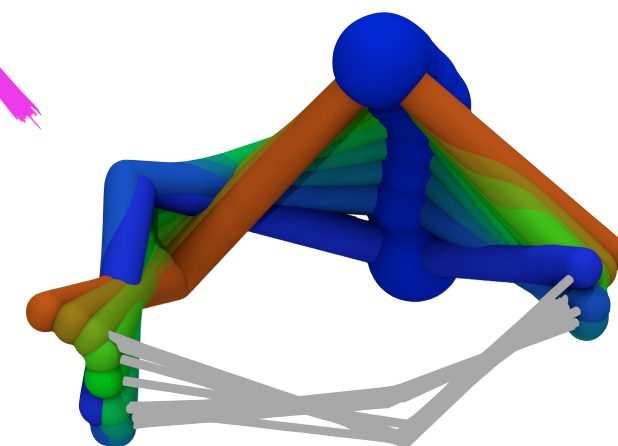
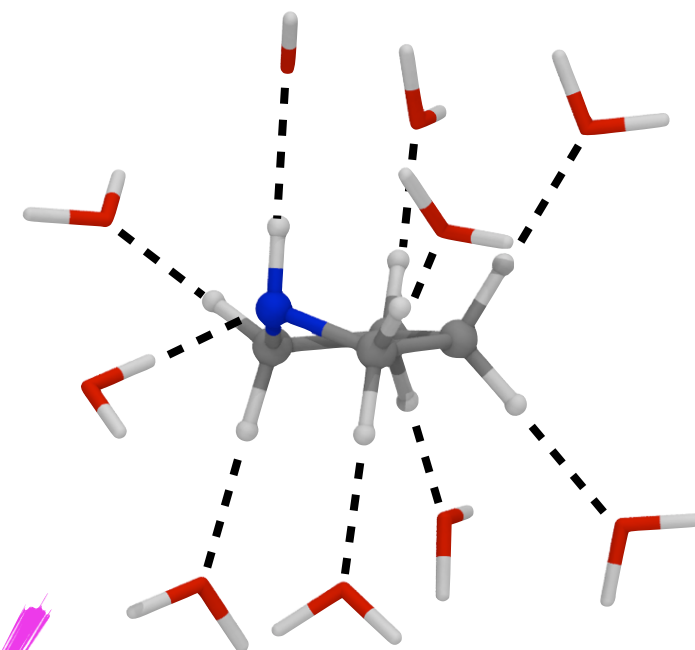
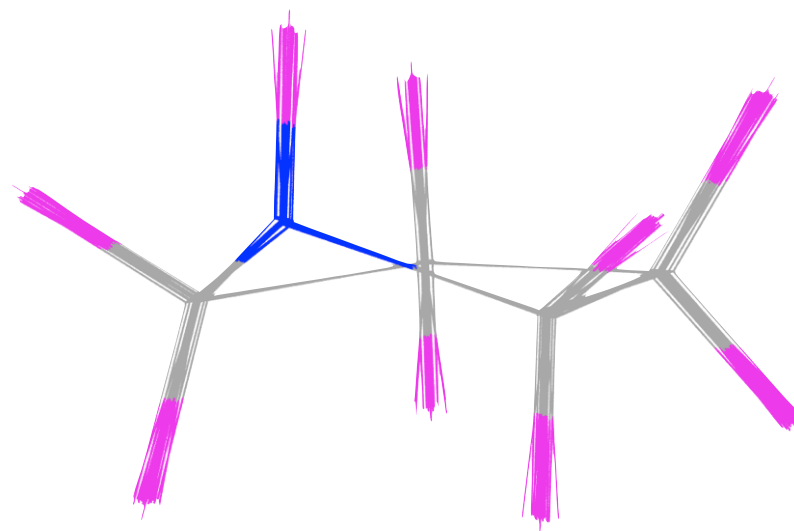
Charge Optimization

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

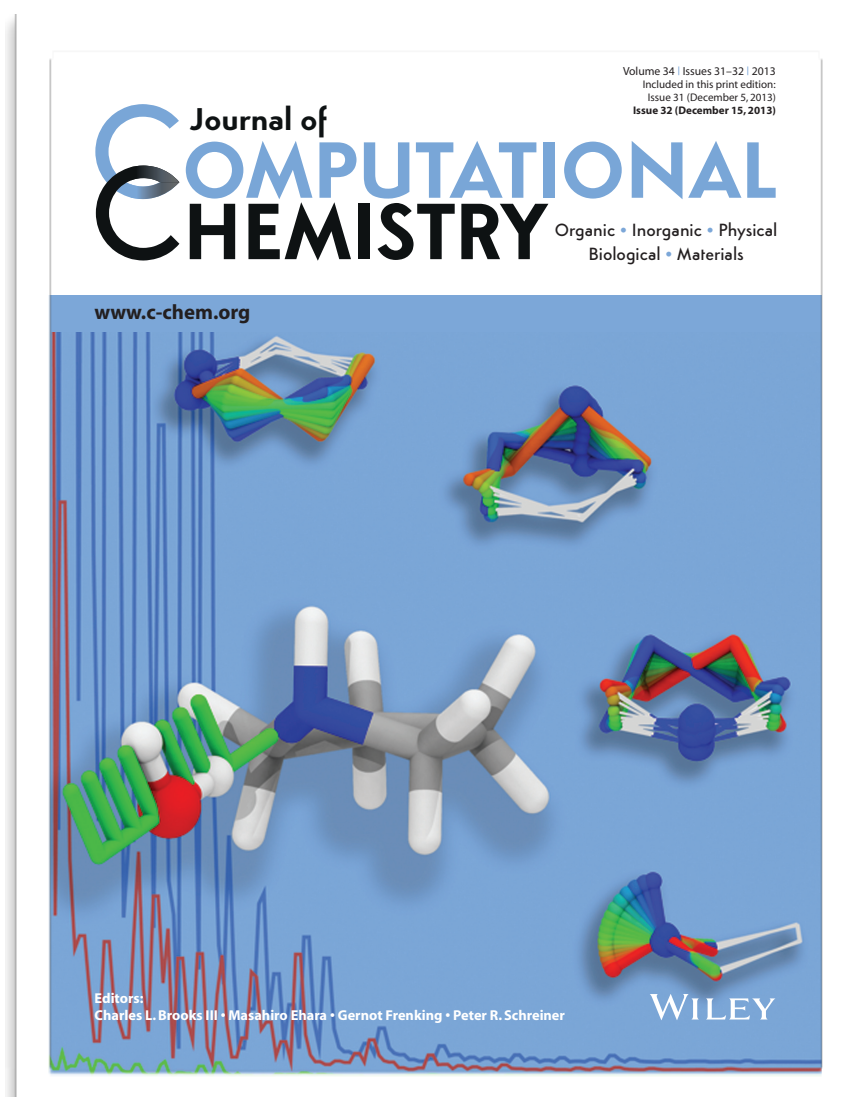
Office: 3011 in Innovation Courtyard II

ffTK

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

ffTK is available as a VMD Plugin (1.9.1 or newer)

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



Questions?