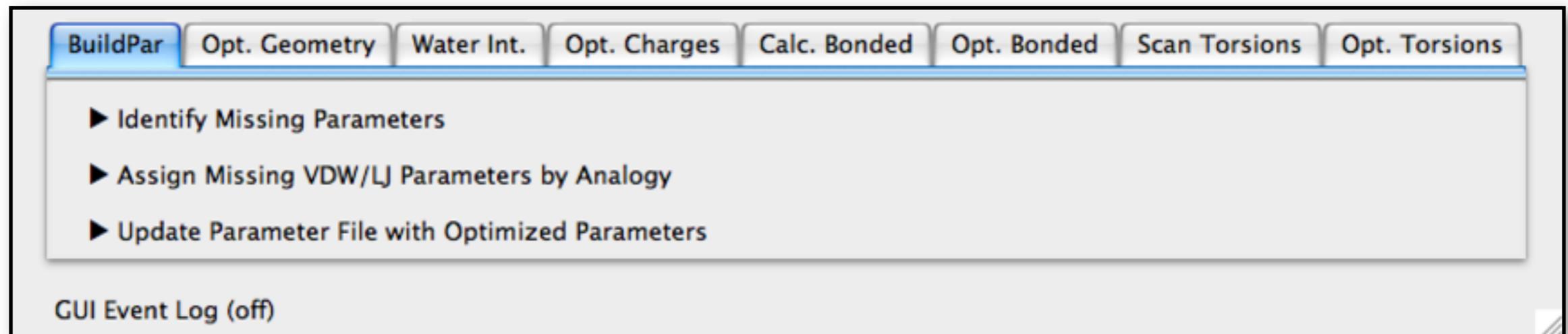


Parameterizing Small Molecules Using: The Force Field Toolkit (ffTK)



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

Klaus Schulten
University of Illinois, Urbana-Champaign

James C. Gumbart, Anna Pavlova
Georgia Institute of Technology

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

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

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

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

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

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

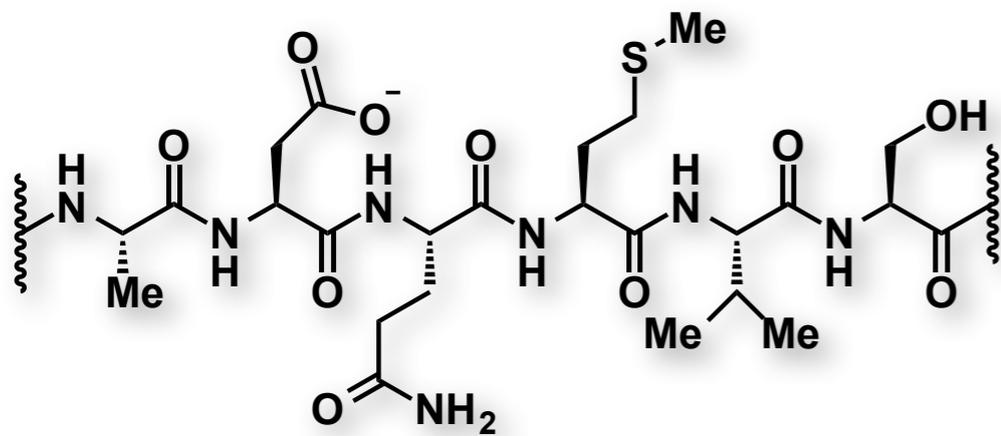
$$\sum_{\text{dihedrals}} k_i^{\text{dihedral}} [1 + \cos(n_i \phi_i + \delta_i)] +$$

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

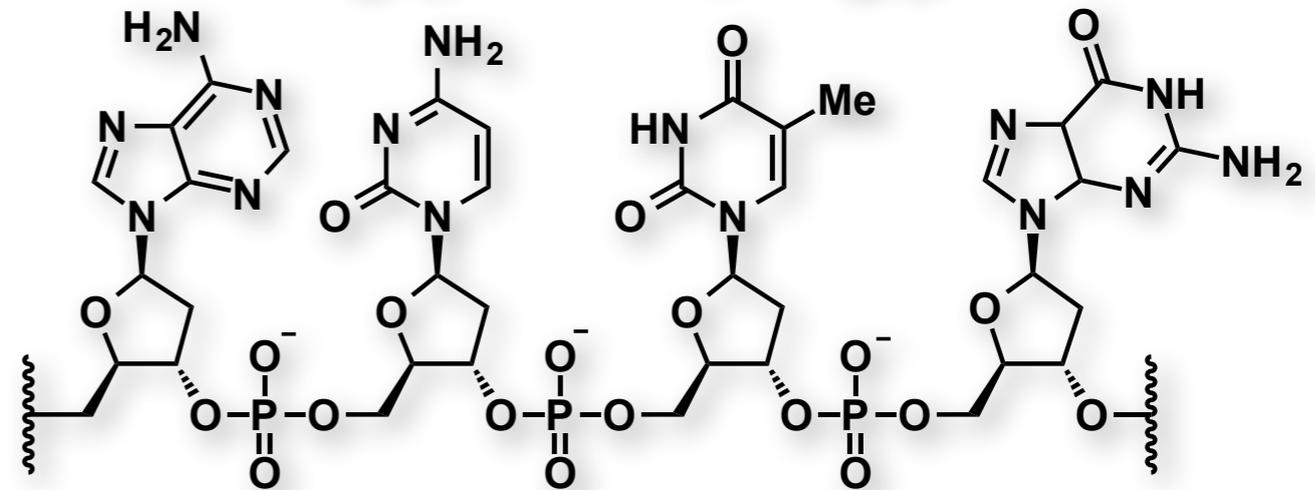
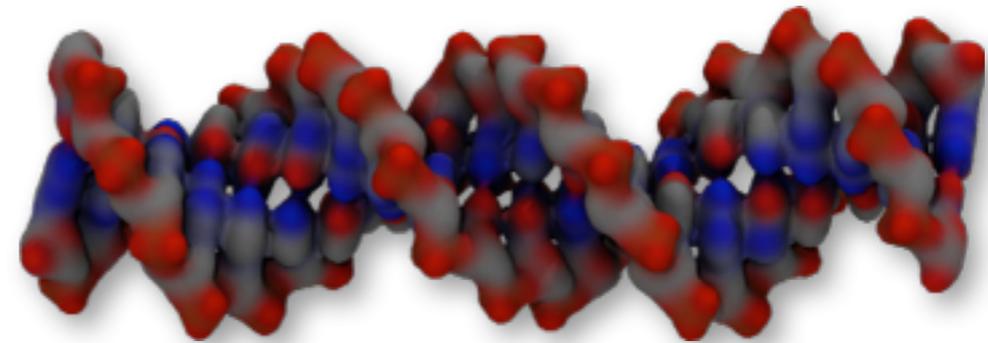
Parameter Transferability In Biopolymers

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

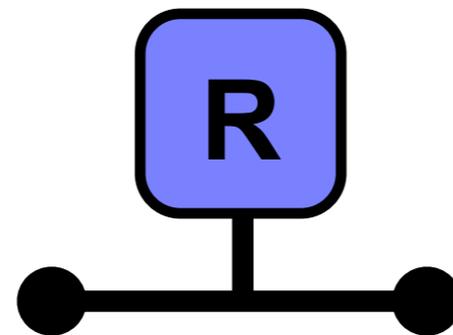
Peptides and Proteins



Nucleic Acids



Key Features:

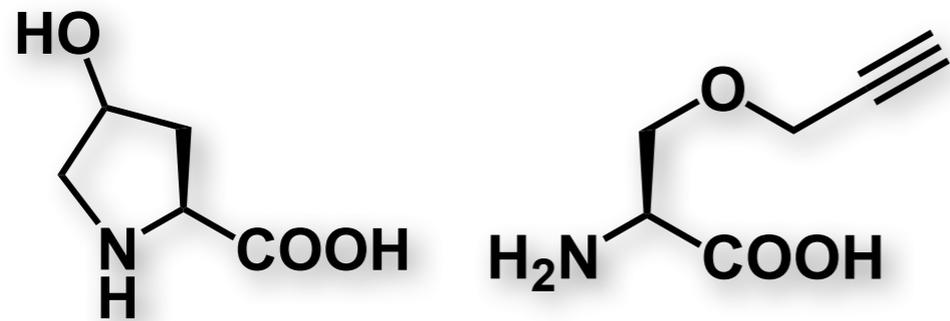


limited set of isolated building blocks

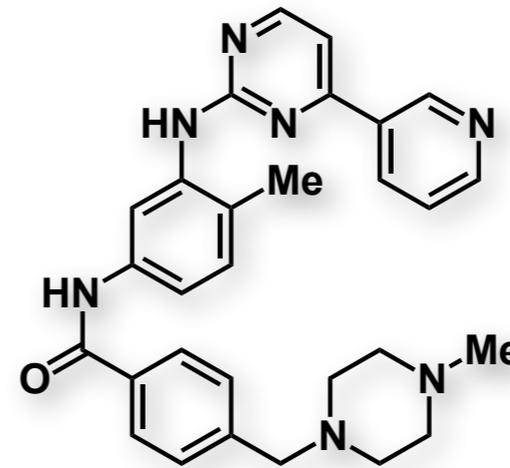
repetitive backbone unit

Parameterization as an Impasse

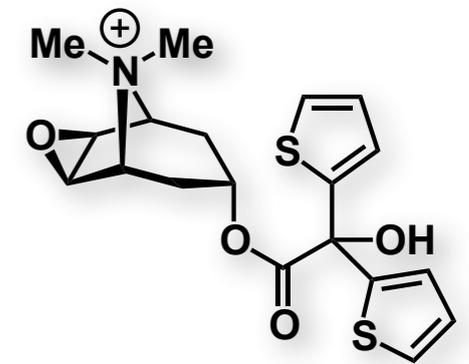
non-standard or
engineered amino acids



small molecule ligands

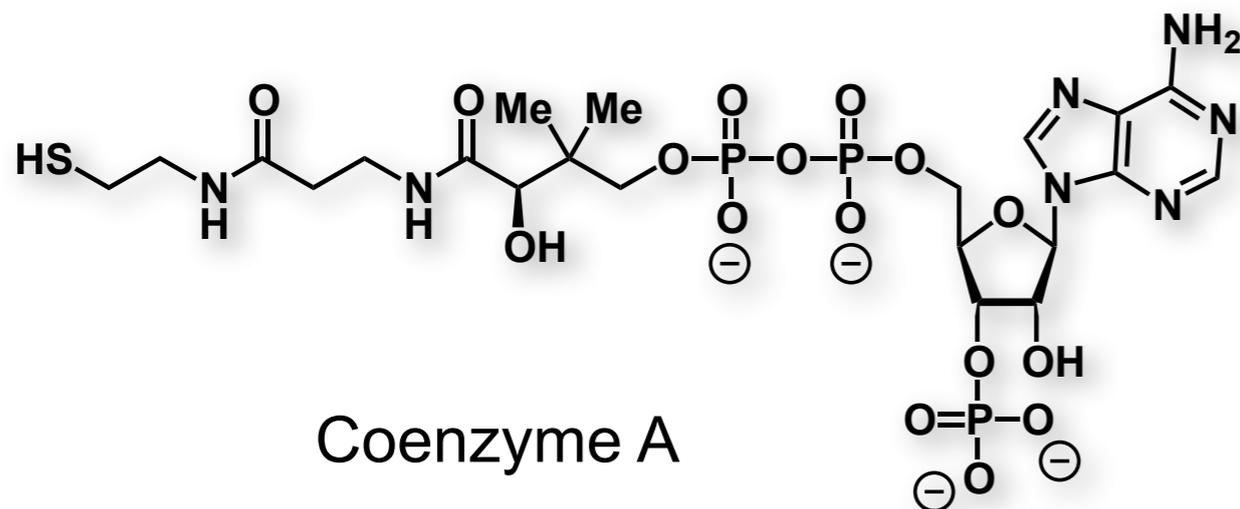


Imatinib (Gleevec)



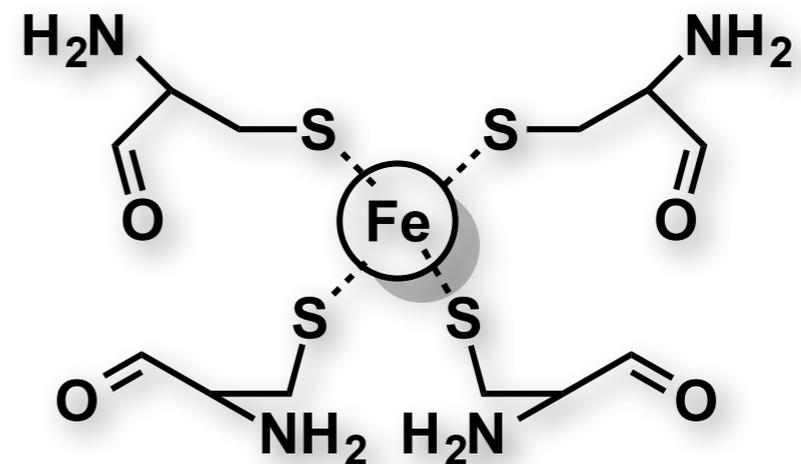
Tiotropium (Spiriva)

cofactors

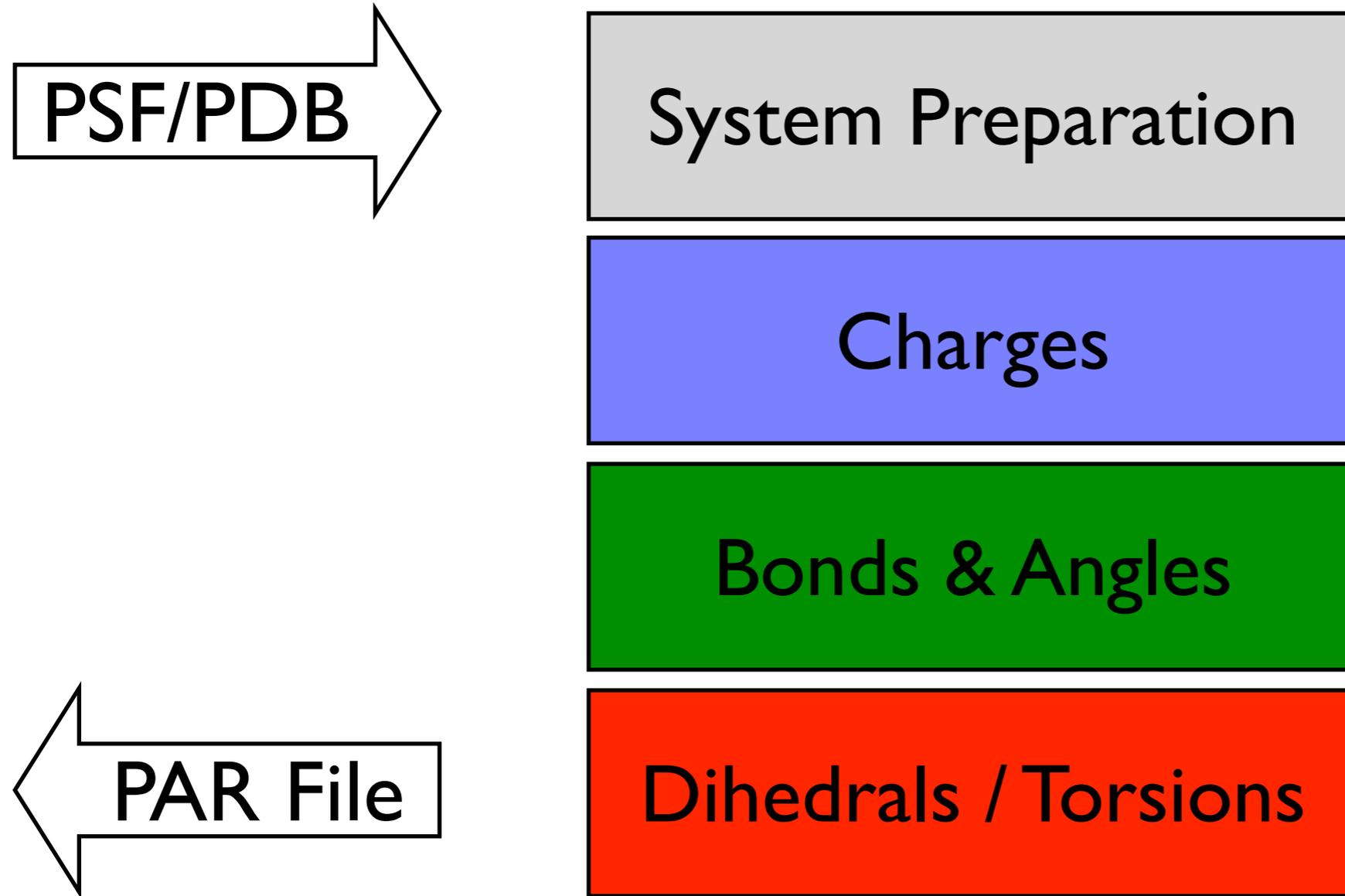


Coenzyme A

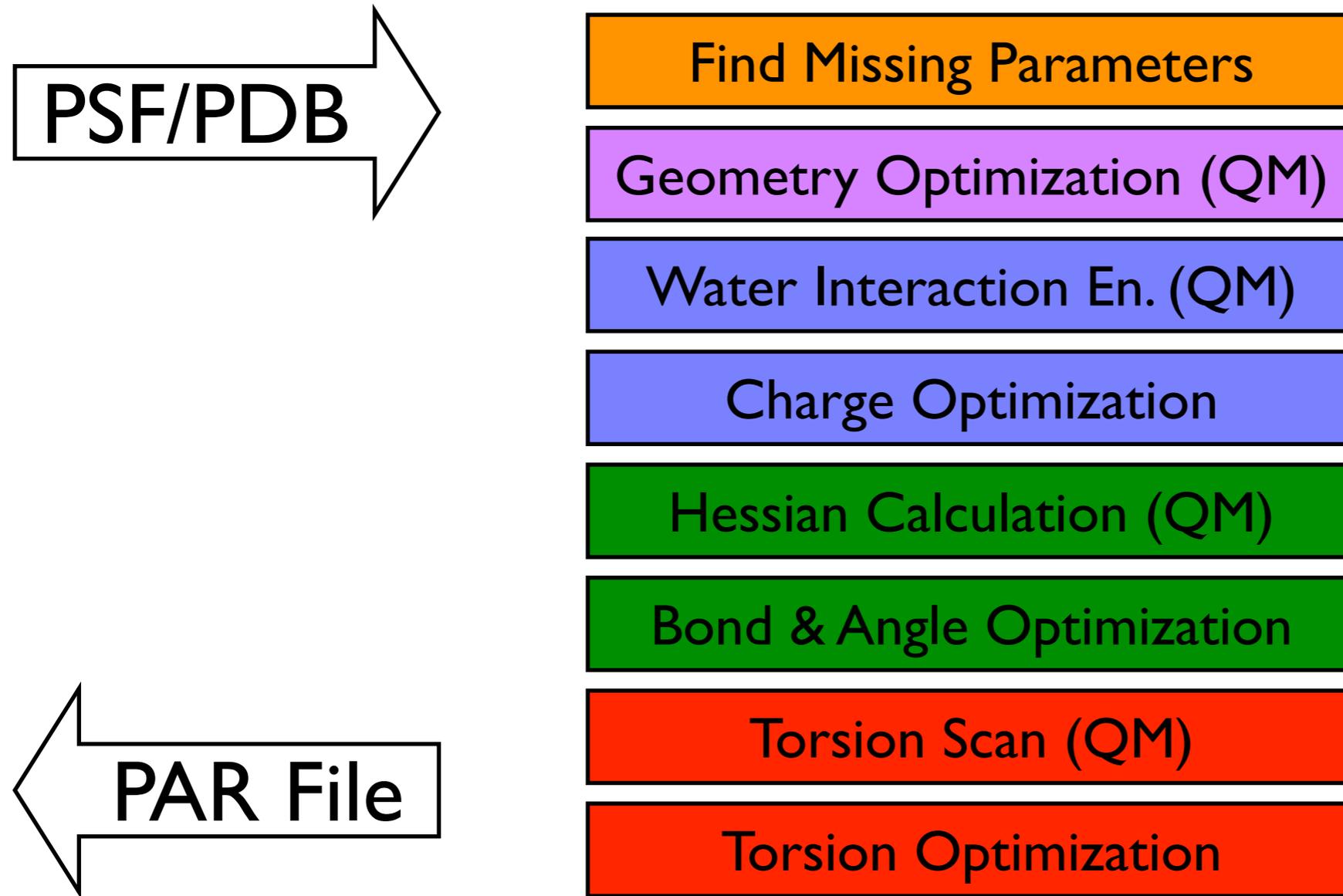
metal centers



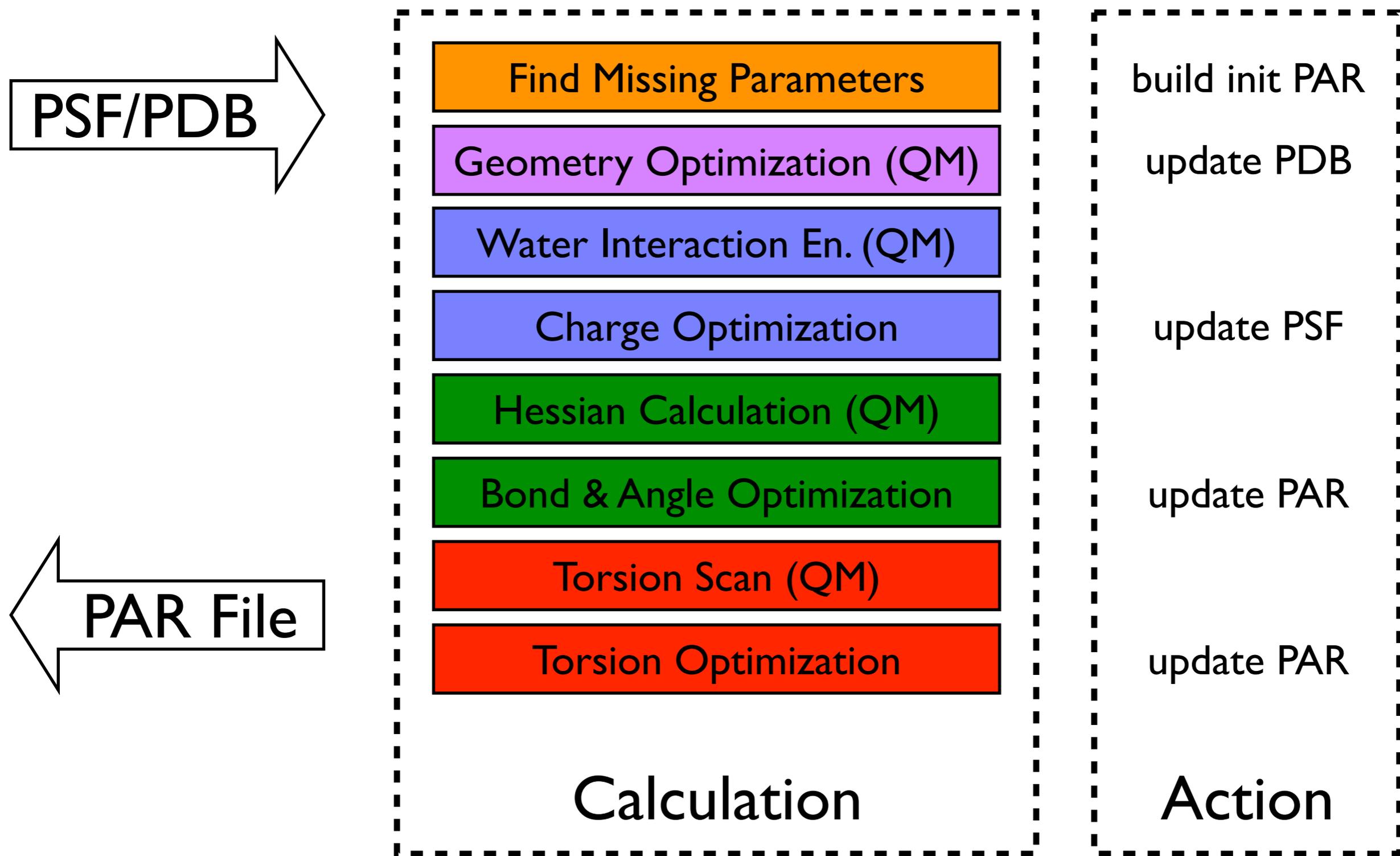
General Parameterization Workflow



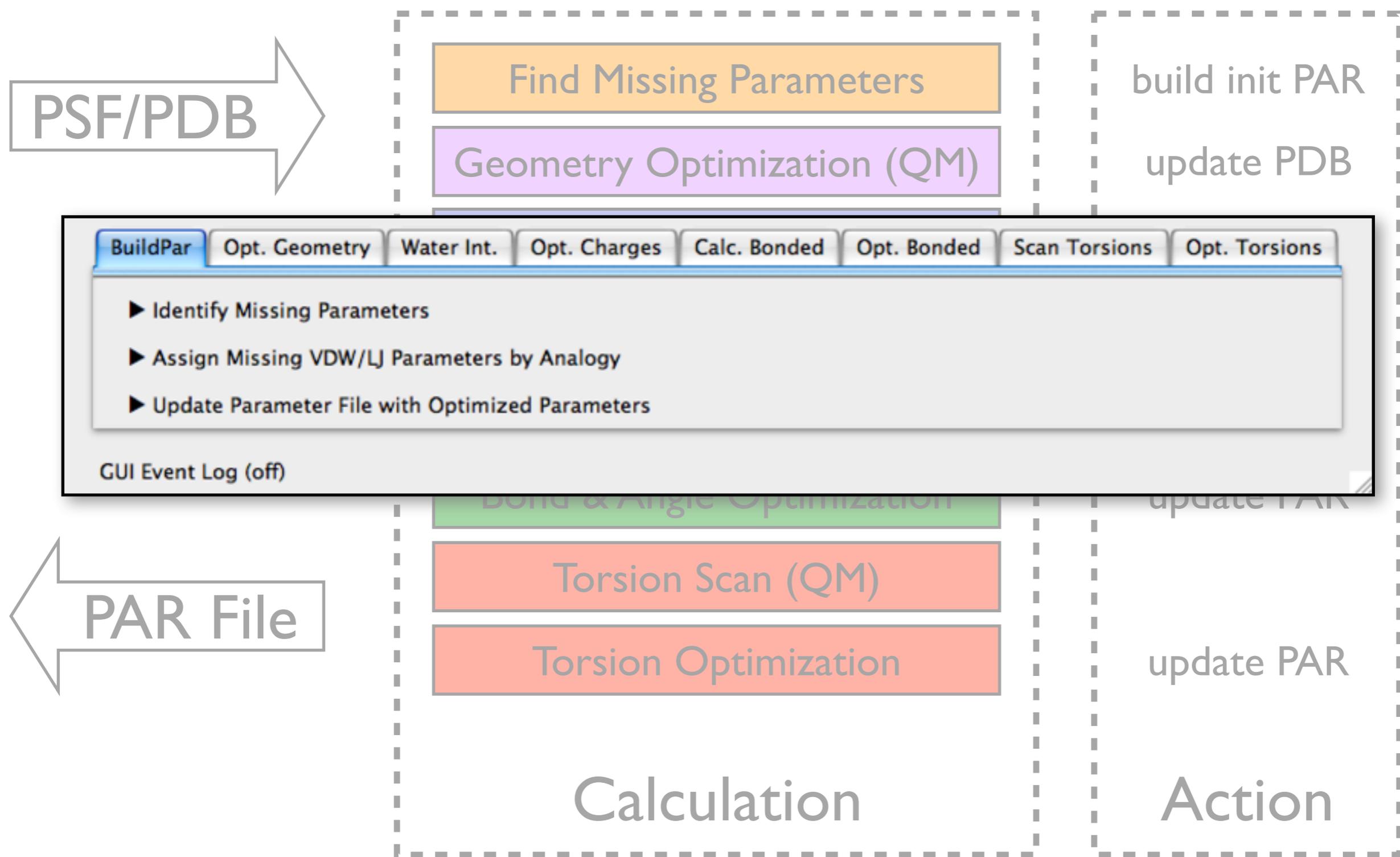
CGenFF Parameterization Workflow



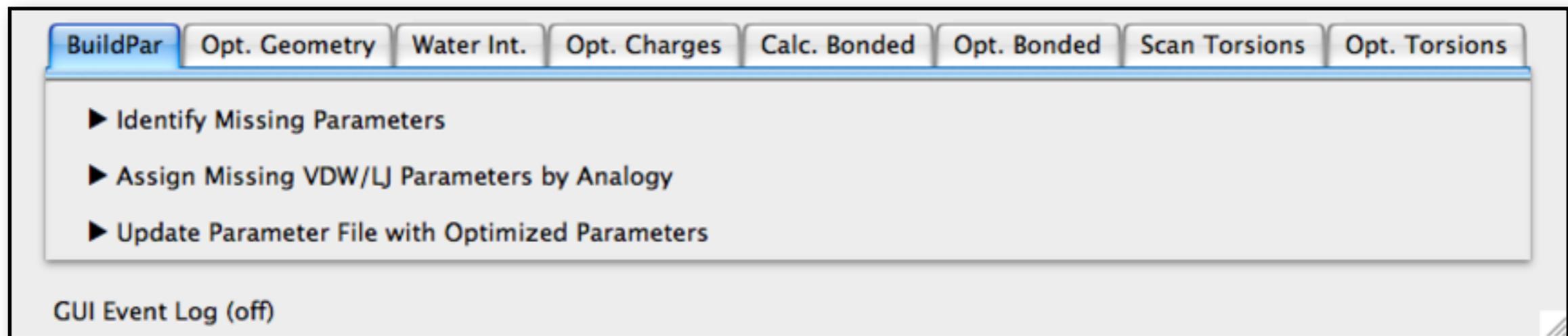
CGenFF Parameterization Workflow



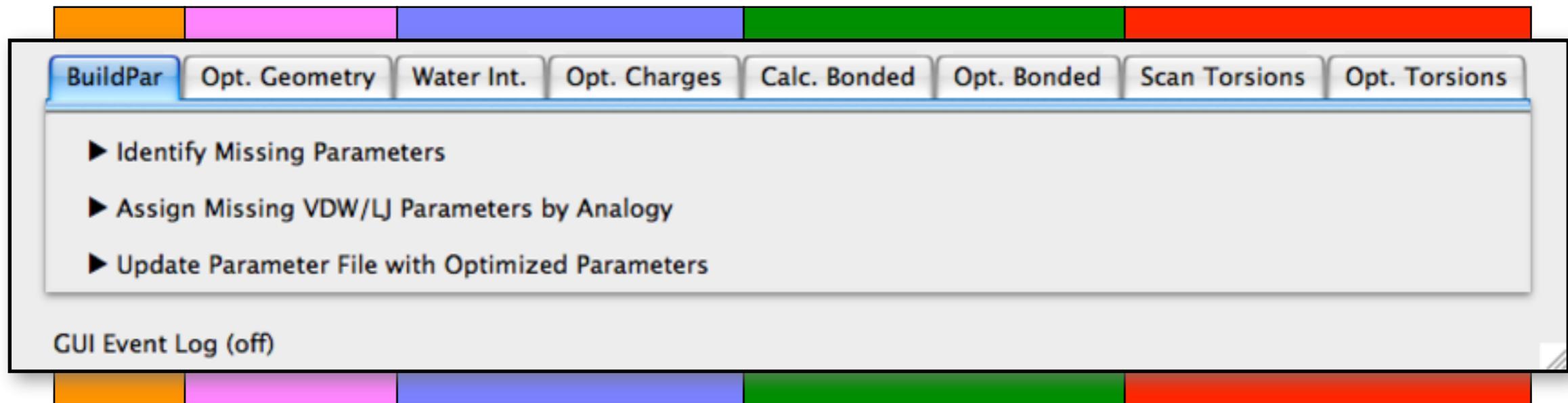
CGenFF Parameterization Workflow



ffTK Interface

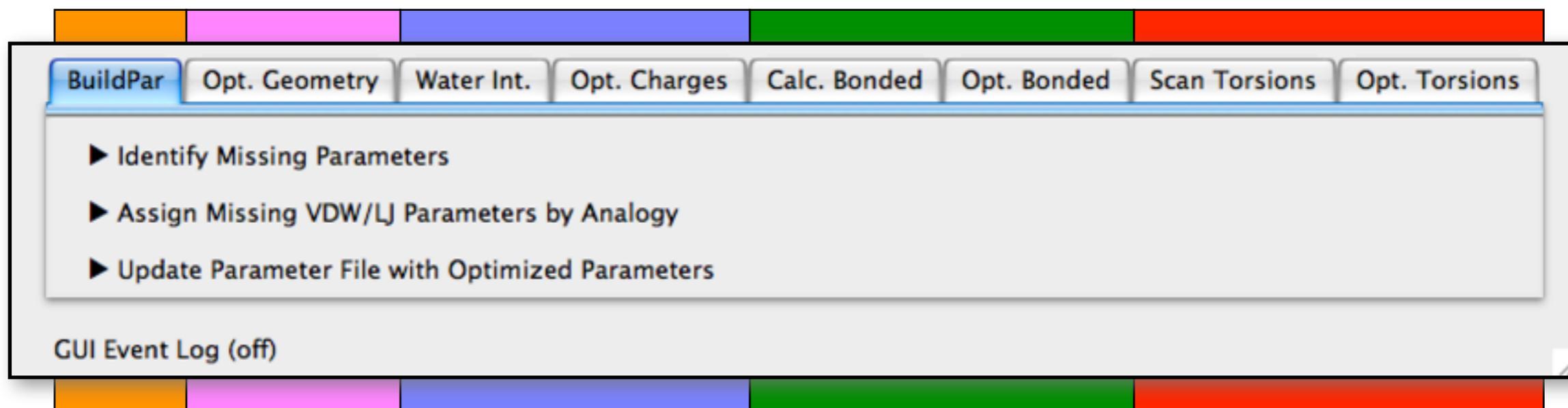


ffTK Interface



ffTK Interface

tasks organized under tabs



ffTK Interface

standard file dialogs ← action buttons

The image shows a screenshot of the ffTK software interface. At the top, there is a horizontal bar with colored segments: orange, pink, blue, green, and red. Below this bar is a menu bar with tabs: BuildPar, Opt. Geometry, Water Int., Opt. Charges (highlighted), Calc. Bonded, Opt. Bonded, Scan Torsions, and Opt. Torsions. The main window is titled "Input" and contains several input fields and buttons. The "PSF File:" field contains "/users/mayne/fftk/PRLD/1-sysprep/prld.psf" with a "Browse" button to its right. The "PDB File:" field contains "/users/mayne/fftk/PRLD/2-geomopt/prld-opt.pdb" with a "Browse" button to its right. The "Residue Name:" field contains "PRLD" with a "Resname From TOP" button to its right. To the right of these fields are buttons for "Load PSF/PDB" and a "Label Atoms" dropdown menu currently set to "None". Below these is a section for "Parameter Files (both pre-defined and in-progress)" with a text area containing "/users/mayne/fftk/PRLD/parfiles/prld-init.par" and buttons for "Add", "Delete", and "Clear". At the bottom, the "Output LOG:" field contains "/users/mayne/fftk/PRLD/3-charges/ChargeOpt.log" with a "SaveAs" button to its right. On the left side, there is a list of expandable sections: "Charge Constraints", "QM Target Data", "Advanced Settings", and "Results".

action buttons

action menus

Functionality Provided by ffTK

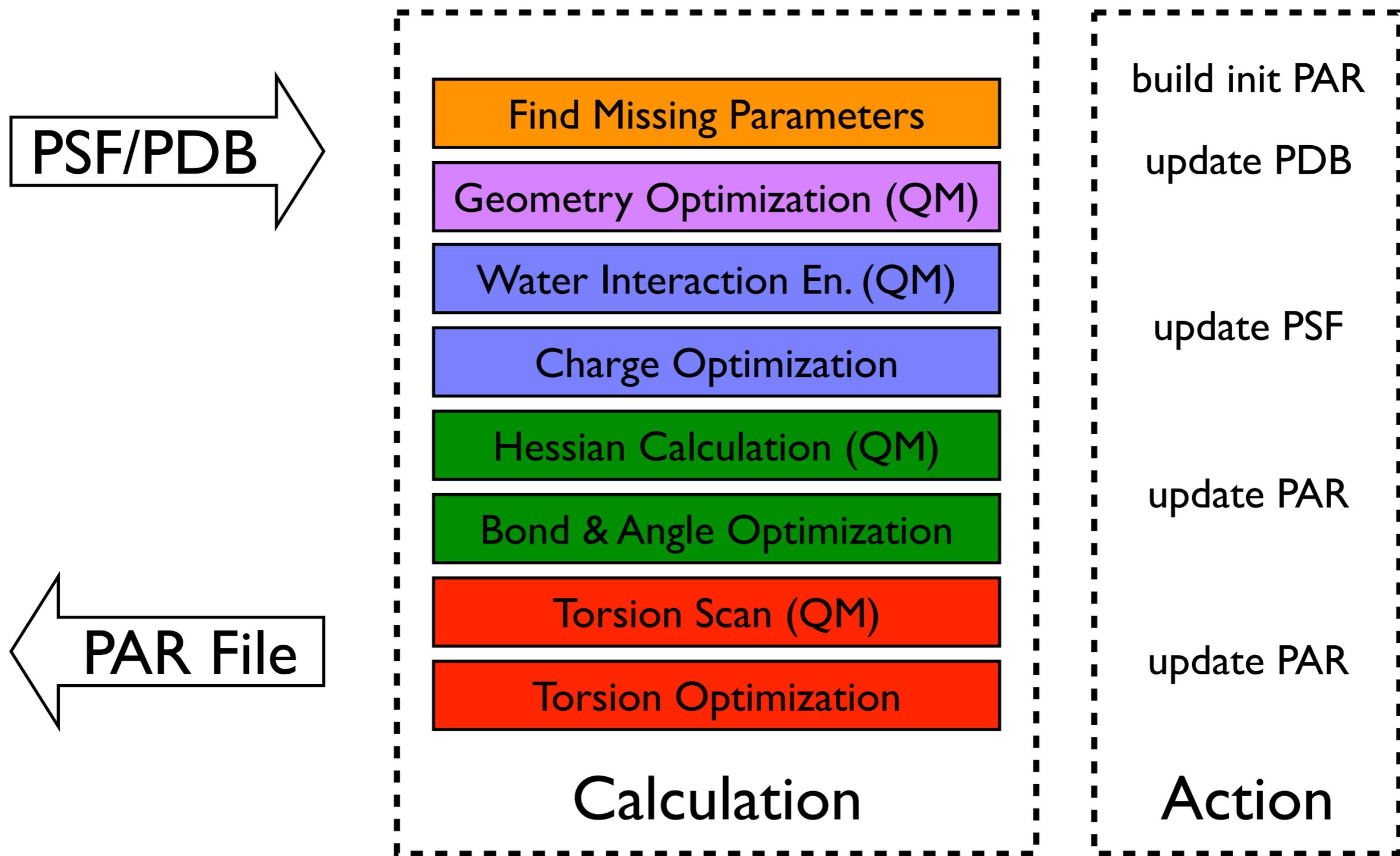
Core Functions

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

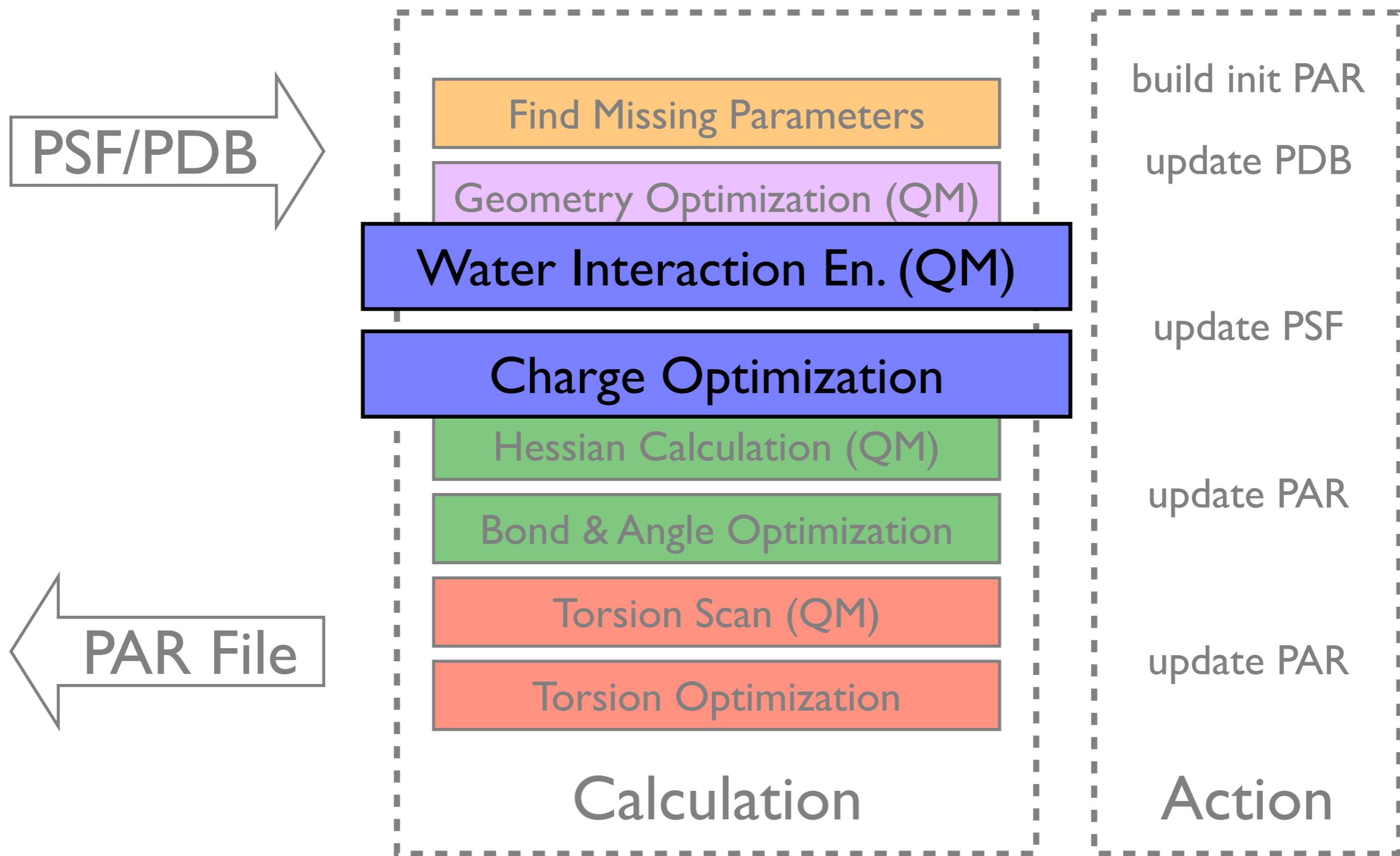
Support Functions

- 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



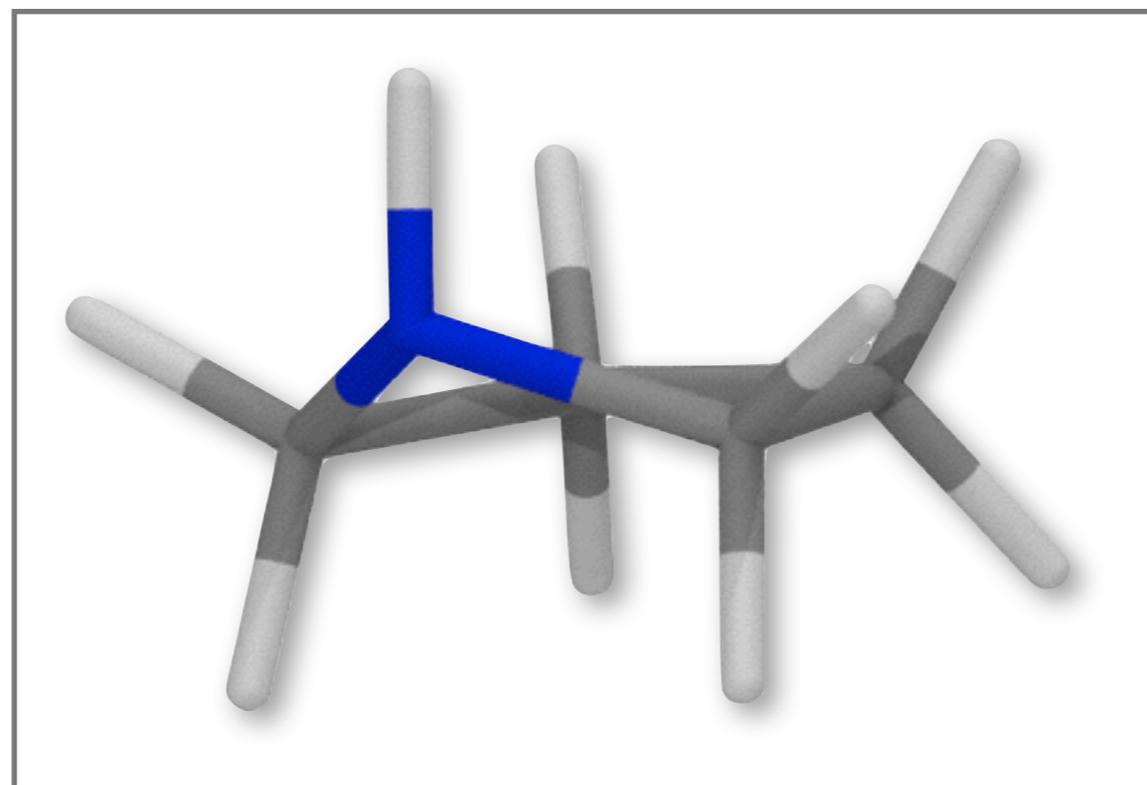
ffTK Exemplified by Charge Optimization



Generating Charge Optimization Target Data

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

pyrrolidine



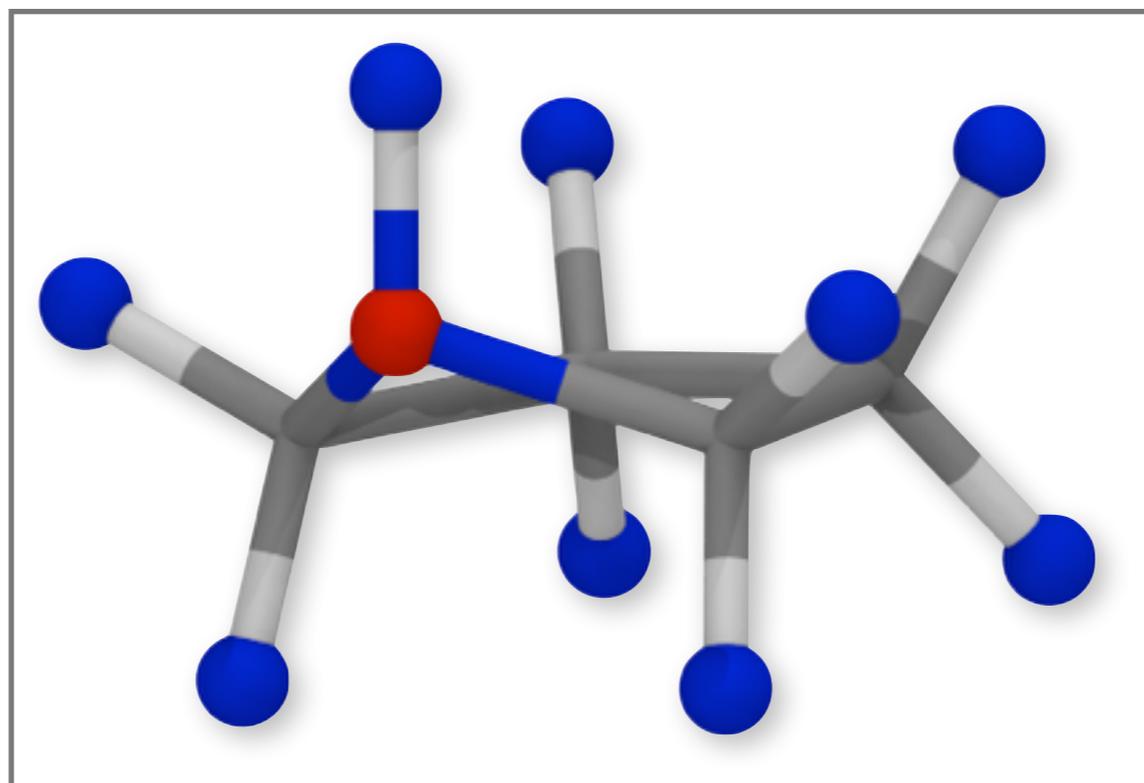
VMD main window

ffTK GUI

Input/Output	
PSF File:	<input type="text" value="/Users/mayne/Desktop/pub_test/PRLD/rnd1/3-charges/prld-charged.psf"/> <input type="button" value="Browse"/>
PDB File:	<input type="text" value="/Users/mayne/Desktop/pub_test/PRLD/rnd1/2-geomopt/prld-opt.pdb"/> <input type="button" value="Browse"/>
Output Path:	<input type="text" value="./output"/> <input type="button" value="Browse"/>
Basename:	<input type="text" value="PRLD"/> <input type="button" value="Basename From TOP"/> <input type="button" value="Load PSF/PDB"/>

Generating Charge Optimization Target Data

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



VMD main window

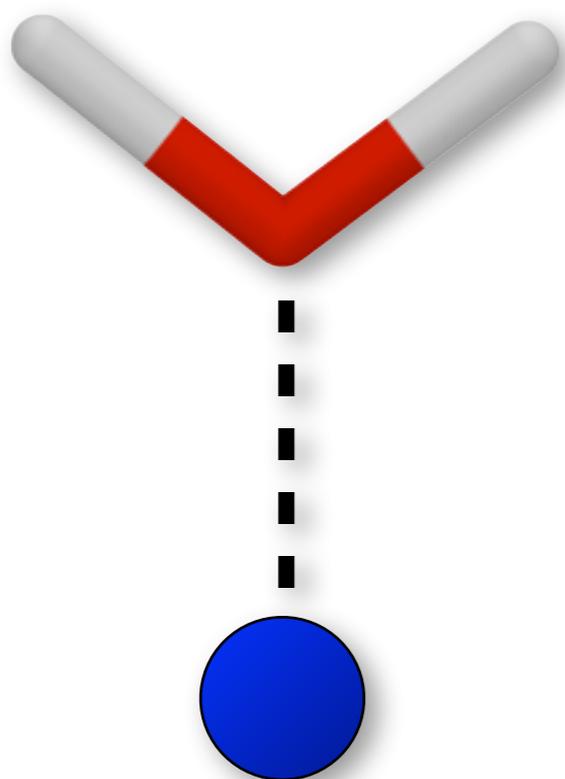
ffTK GUI

Hydrogen Bonding Atoms	
Donor Indices (Interact with oxygen of water)	<input type="button" value="Toggle Atom Labels"/>
<input type="text" value="5 6 7 8 9 10 11 12 13"/>	<input type="button" value="Toggle Sphere Viz."/>
Acceptor Indices (Interact with hydrogen of water)	<input type="button" value="AutoDetect Indices"/>
<input type="text" value="2"/>	<input type="button" value="Clear Lists"/>

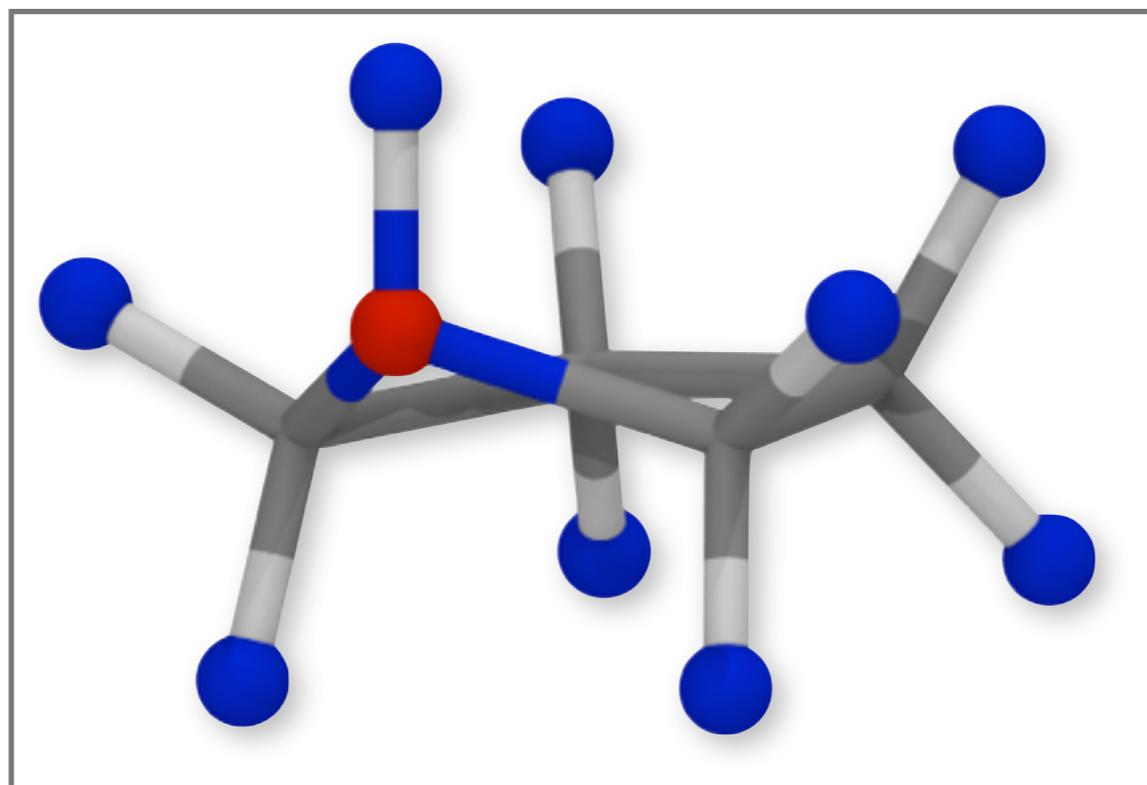
Generating Charge Optimization Target Data



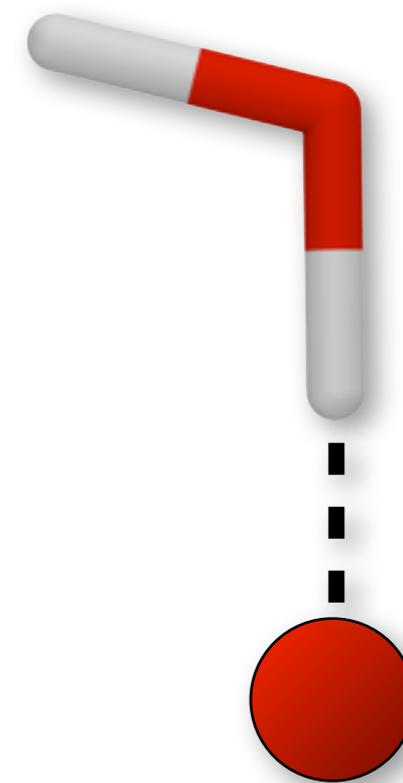
geometry | Auto-detect interaction sites | Generate Gaussian Input Files | Run



Donor



VMD main window



Acceptor

ffTK GUI

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

Toggle Atom Labels

Toggle Sphere Viz.

AutoDetect Indices

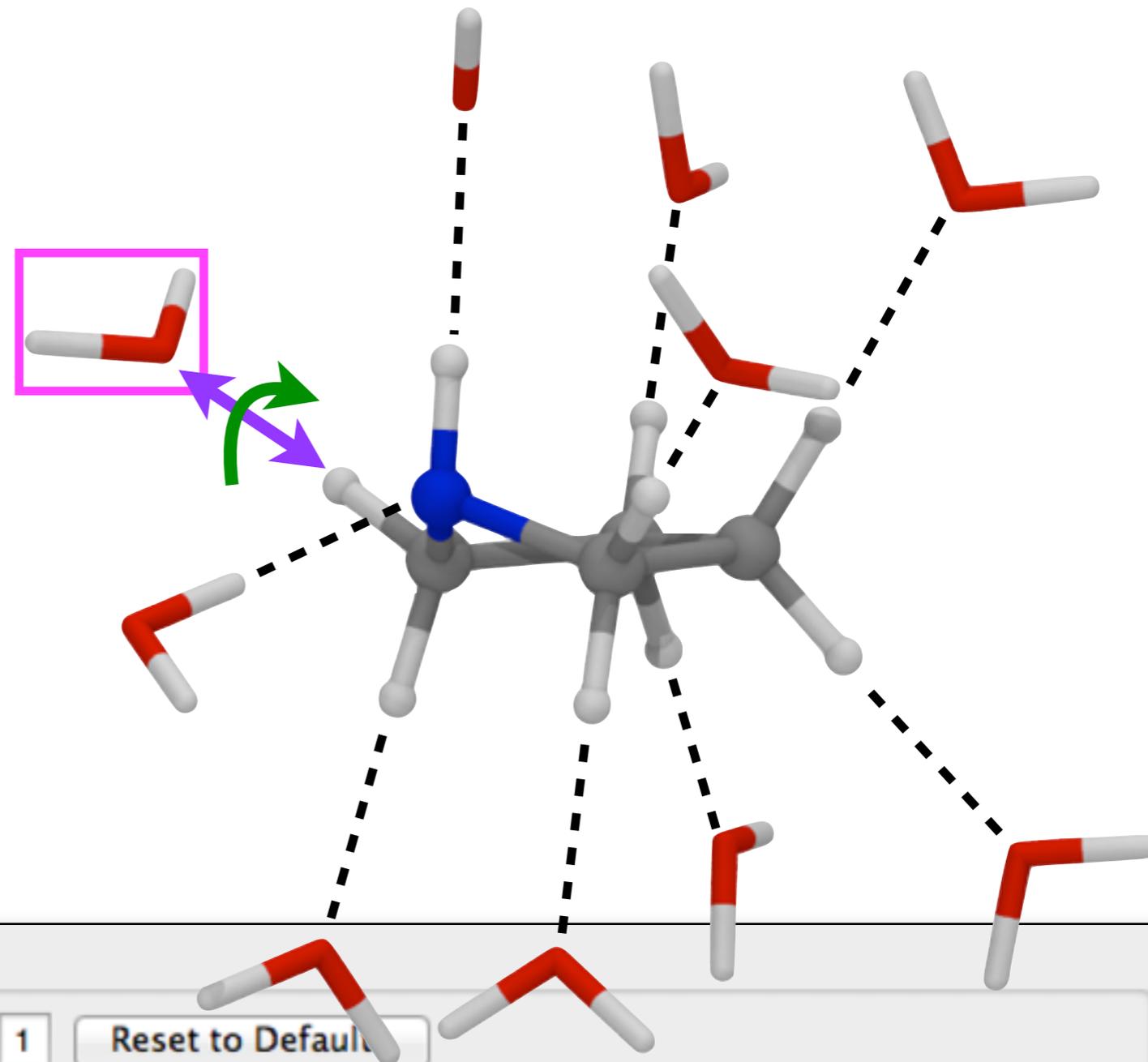
Clear Lists

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

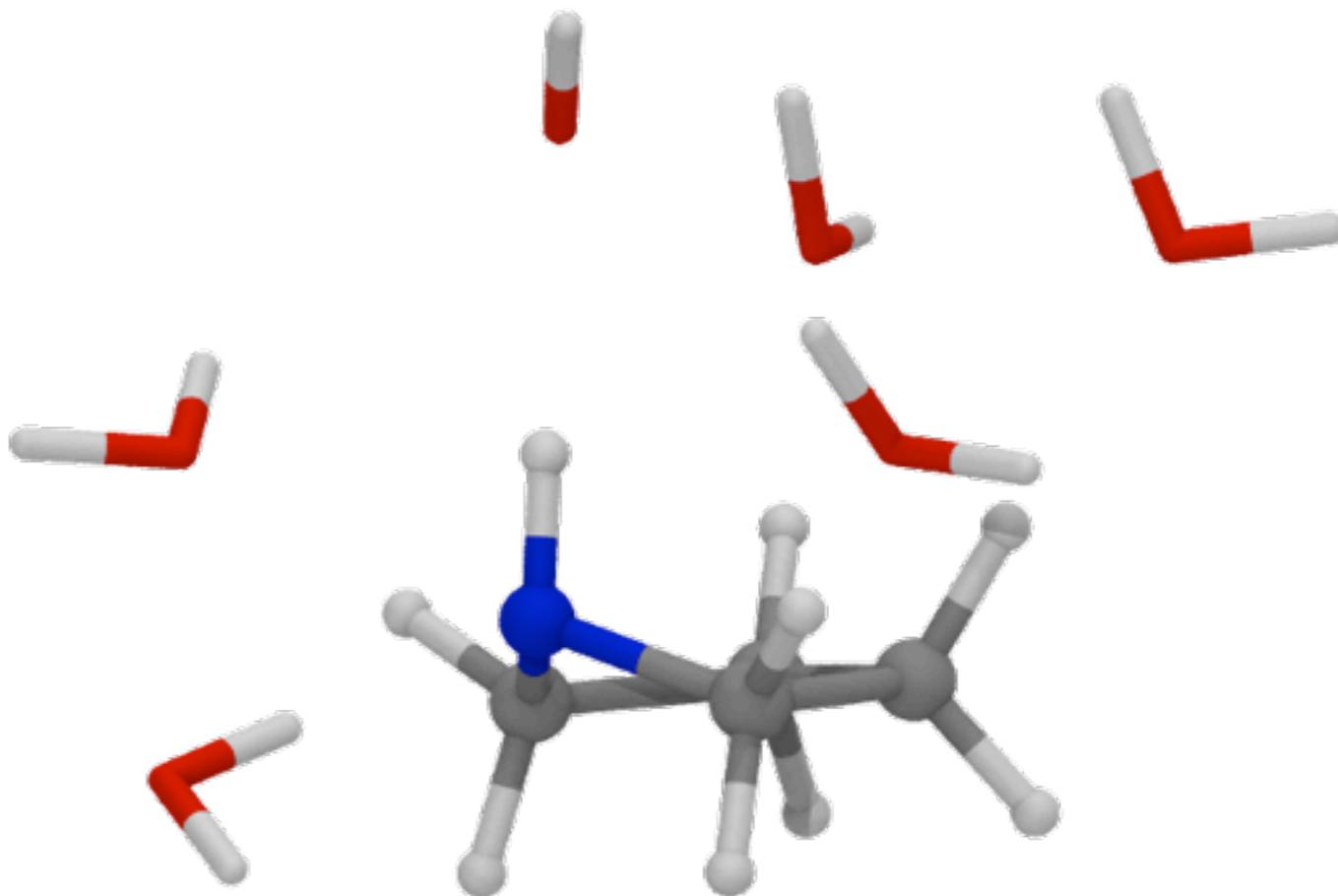
Processors: Memory (GB): Charge: Multiplicity:

Route:

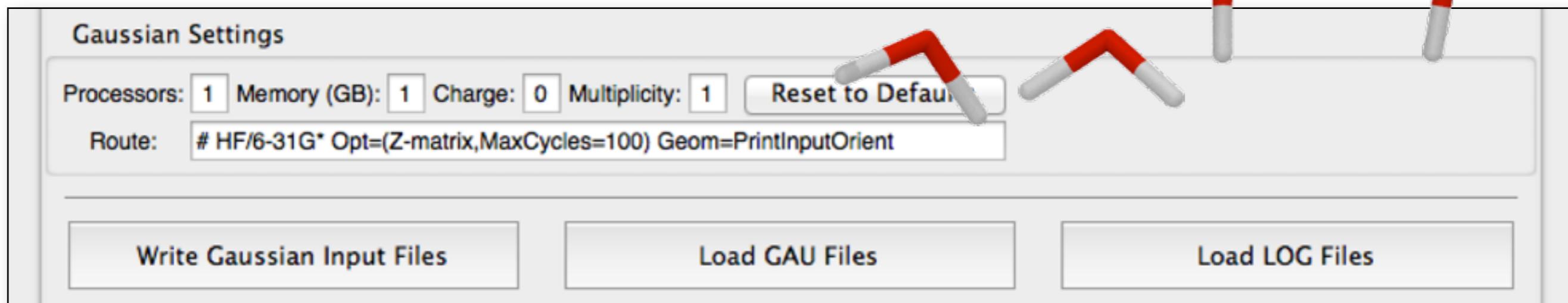
Generating Charge Optimization Target Data

Run QM | **Inspect water optimization**

Visually assess
QM-optimized
water position(s)



ffTK GUI

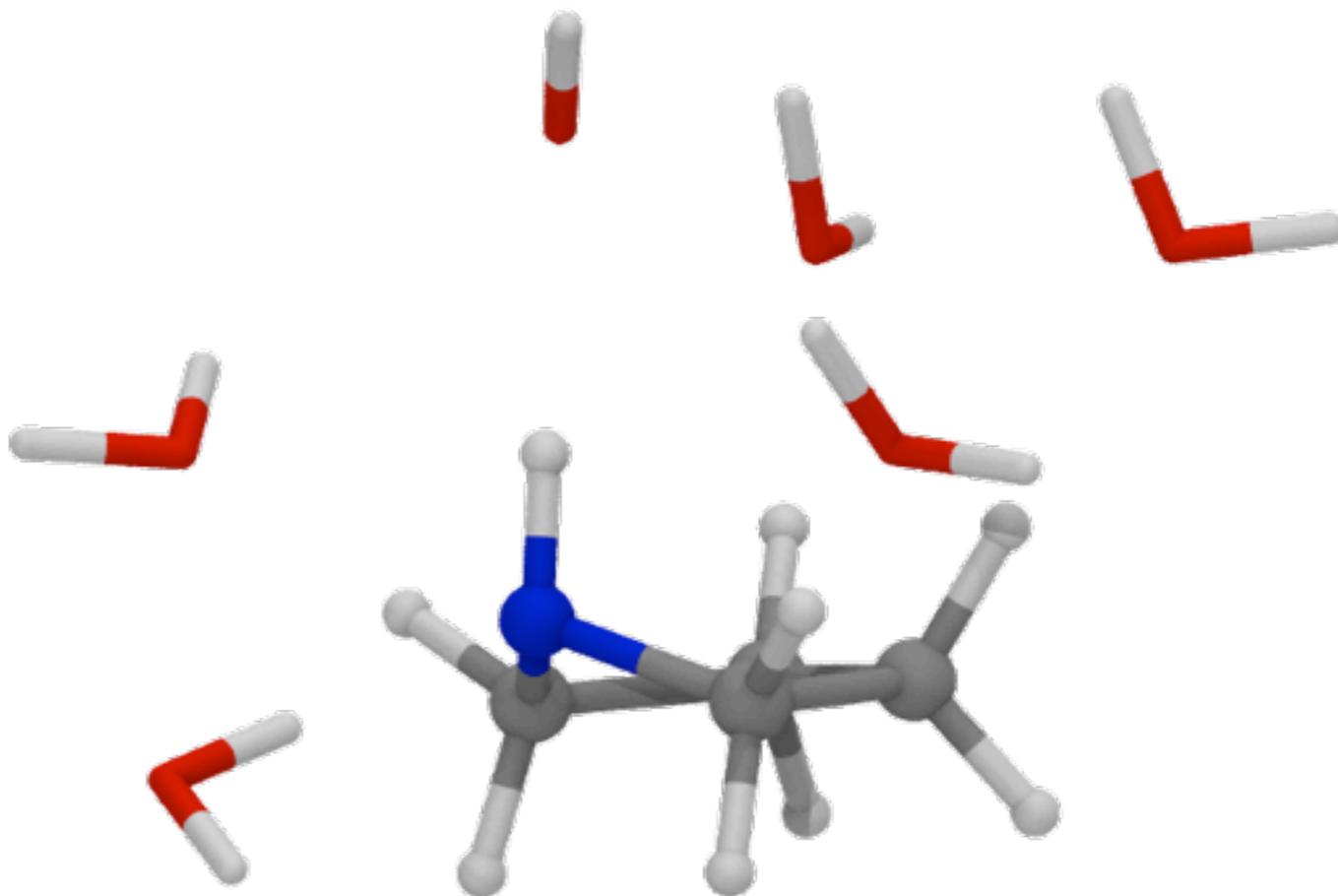


A screenshot of the ffTK GUI interface. The top section is titled "Gaussian Settings" and contains several input fields and a button: "Processors: 1", "Memory (GB): 1", "Charge: 0", "Multiplicity: 1", and a "Reset to Default" button. Below these is a "Route:" field containing the text "# HF/6-31G* Opt=(Z-matrix,MaxCycles=100) Geom=PrintInputOrient". At the bottom of the GUI, there are three large buttons: "Write Gaussian Input Files", "Load GAU Files", and "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

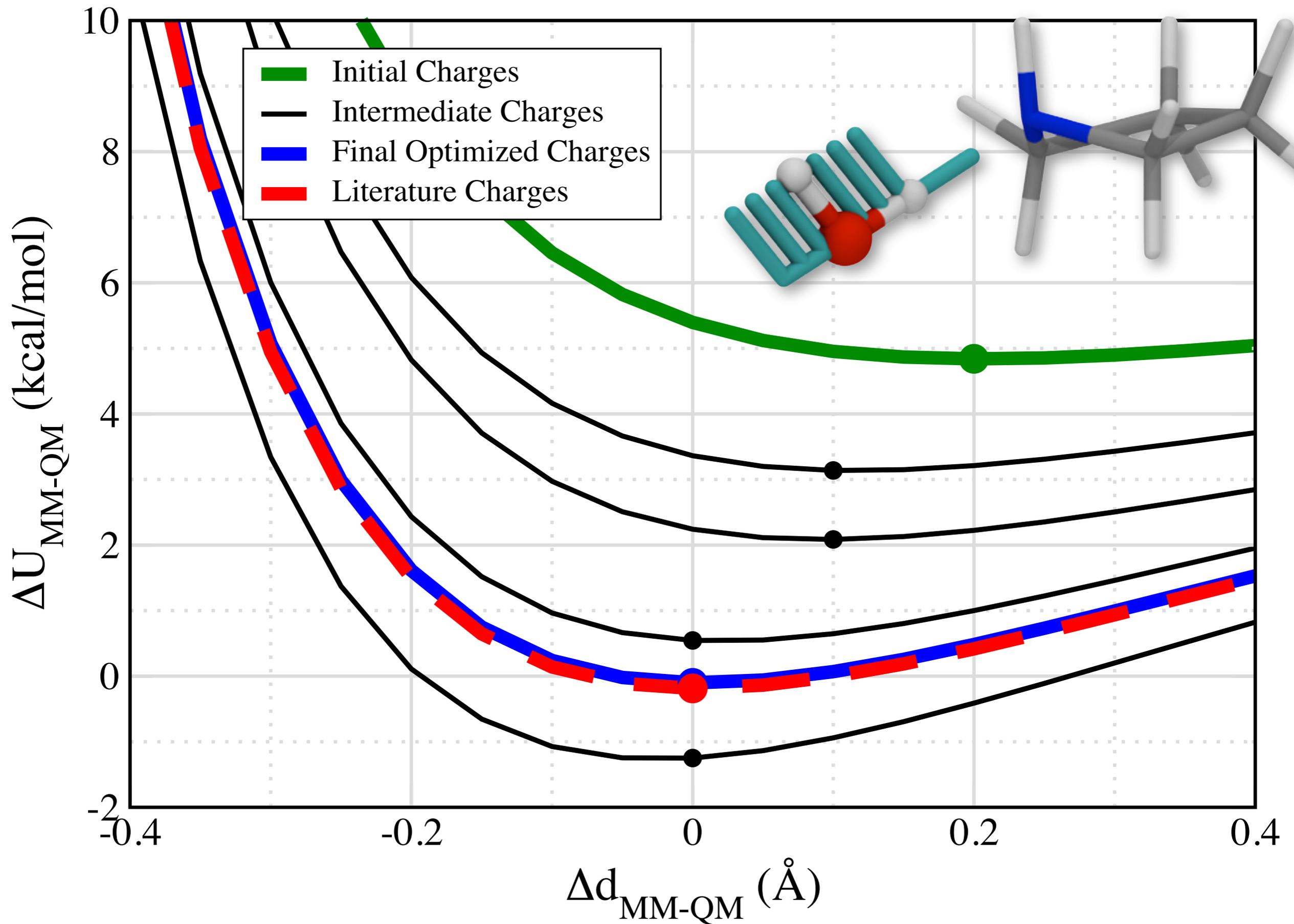
Analyze Performance

Write Charges to PSF

Objective Function

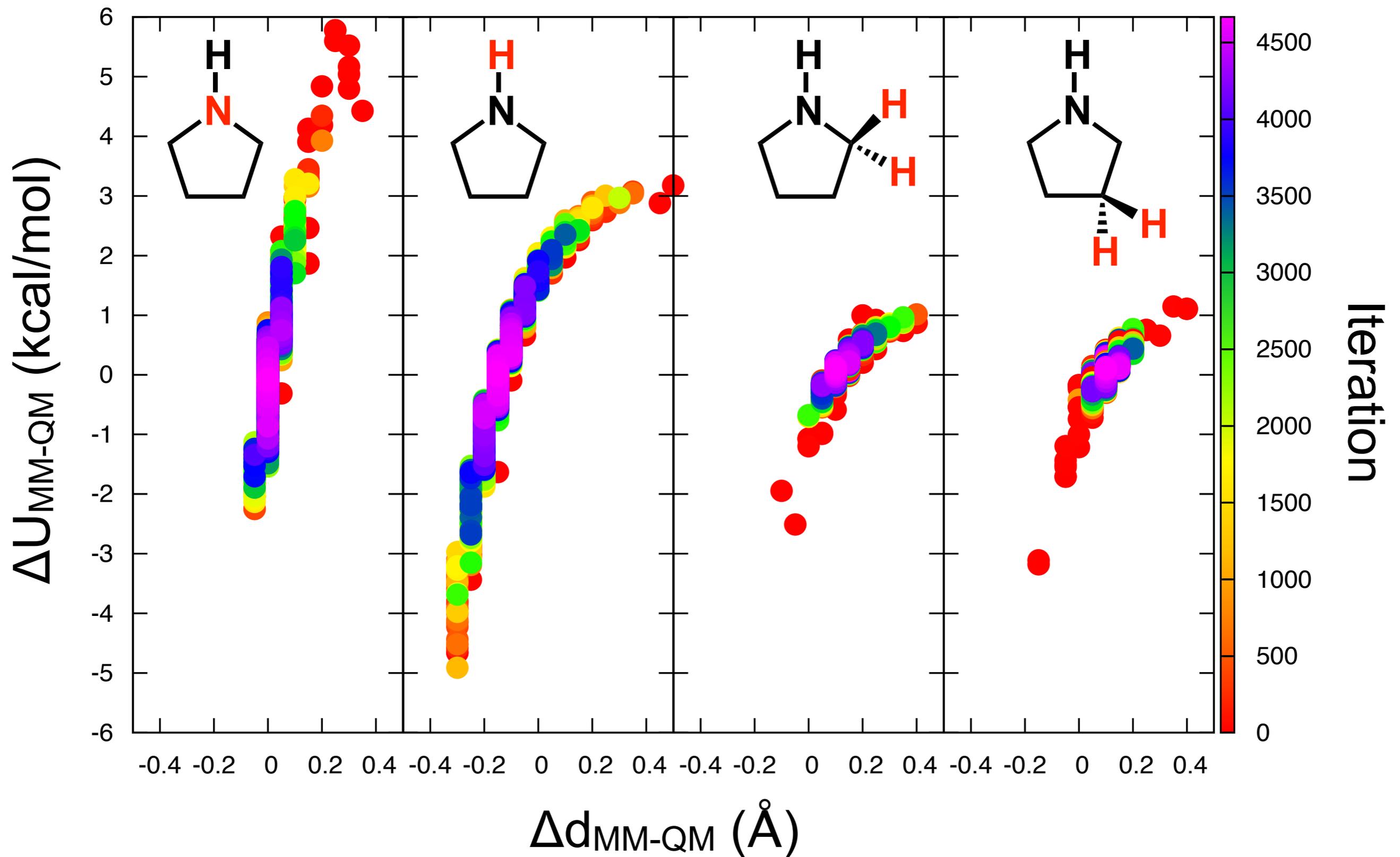
$$\begin{aligned} & \sum_{\text{wat. int.}} f(U_{MM} - U_{QM}) \\ & + \\ & \sum_{\text{wat. int.}} f(d_{MM} - d_{QM}) \\ & + \\ & f(\mu_{MM} - \mu_{QM}) \end{aligned}$$

Assessing MM Water-Interaction Profiles



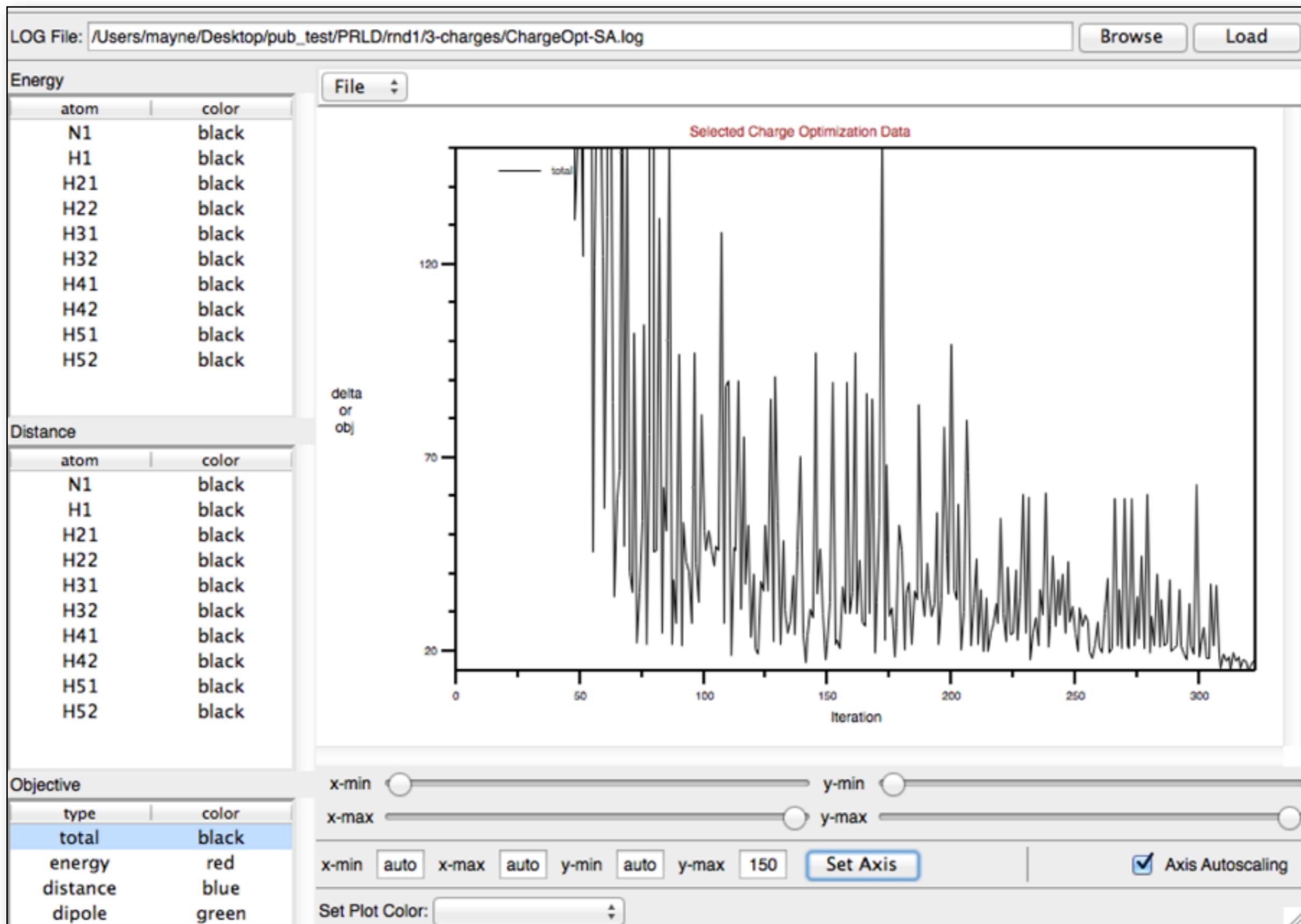
Sampling MM Water-Interaction Profiles

Mode: Simulated Annealing

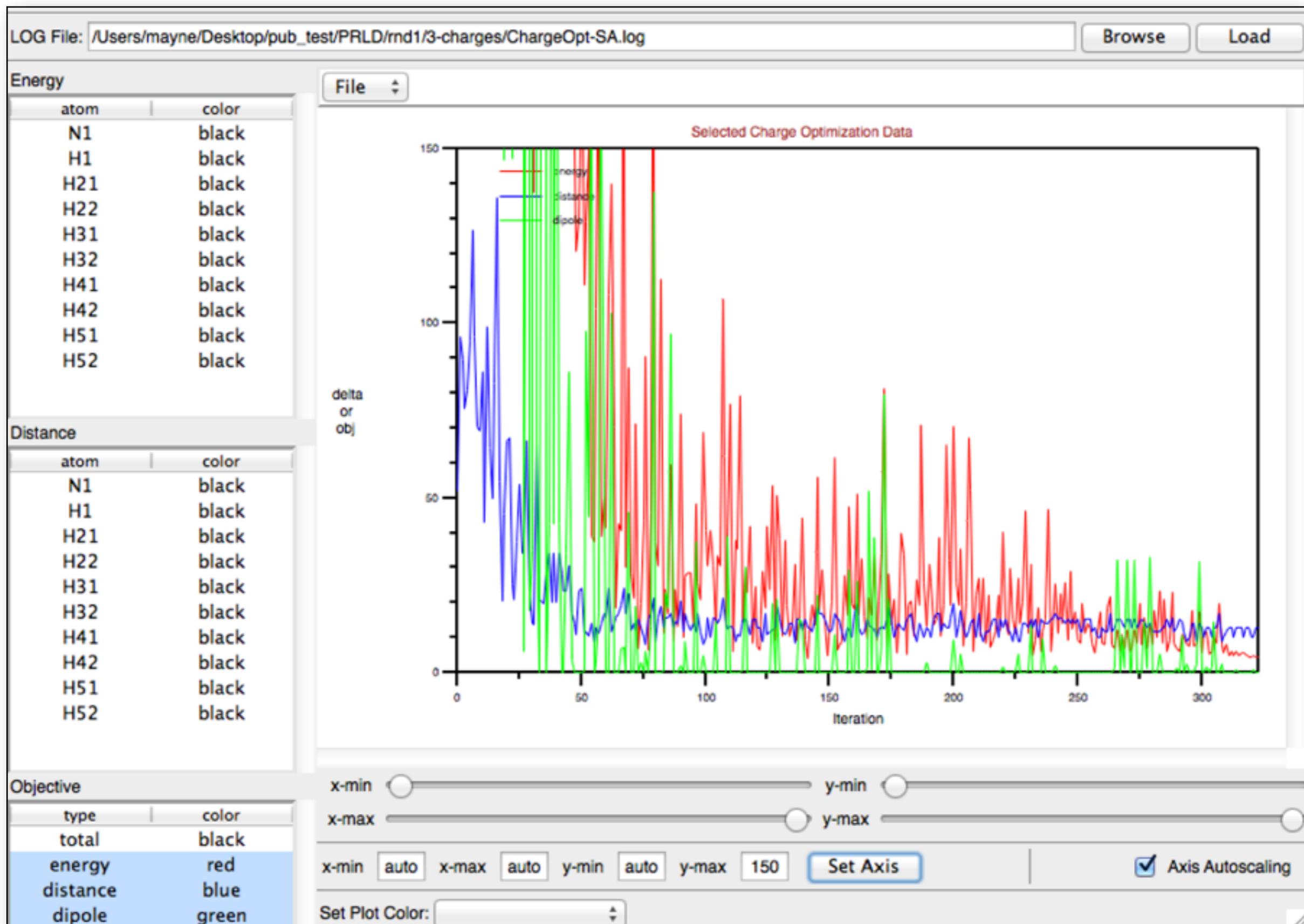


Plotting Charge Optimization Data

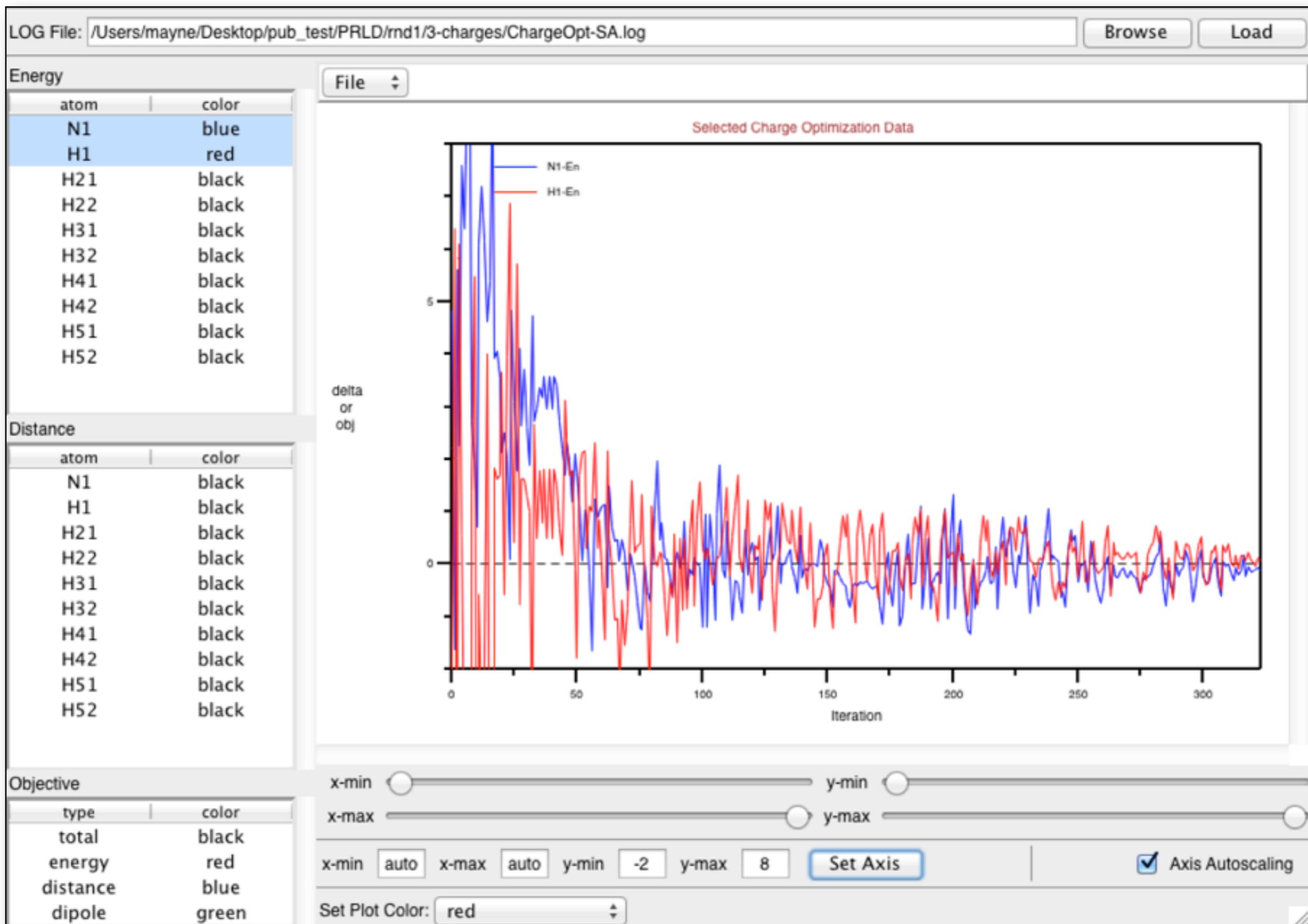
Plotting Charge Optimization Data



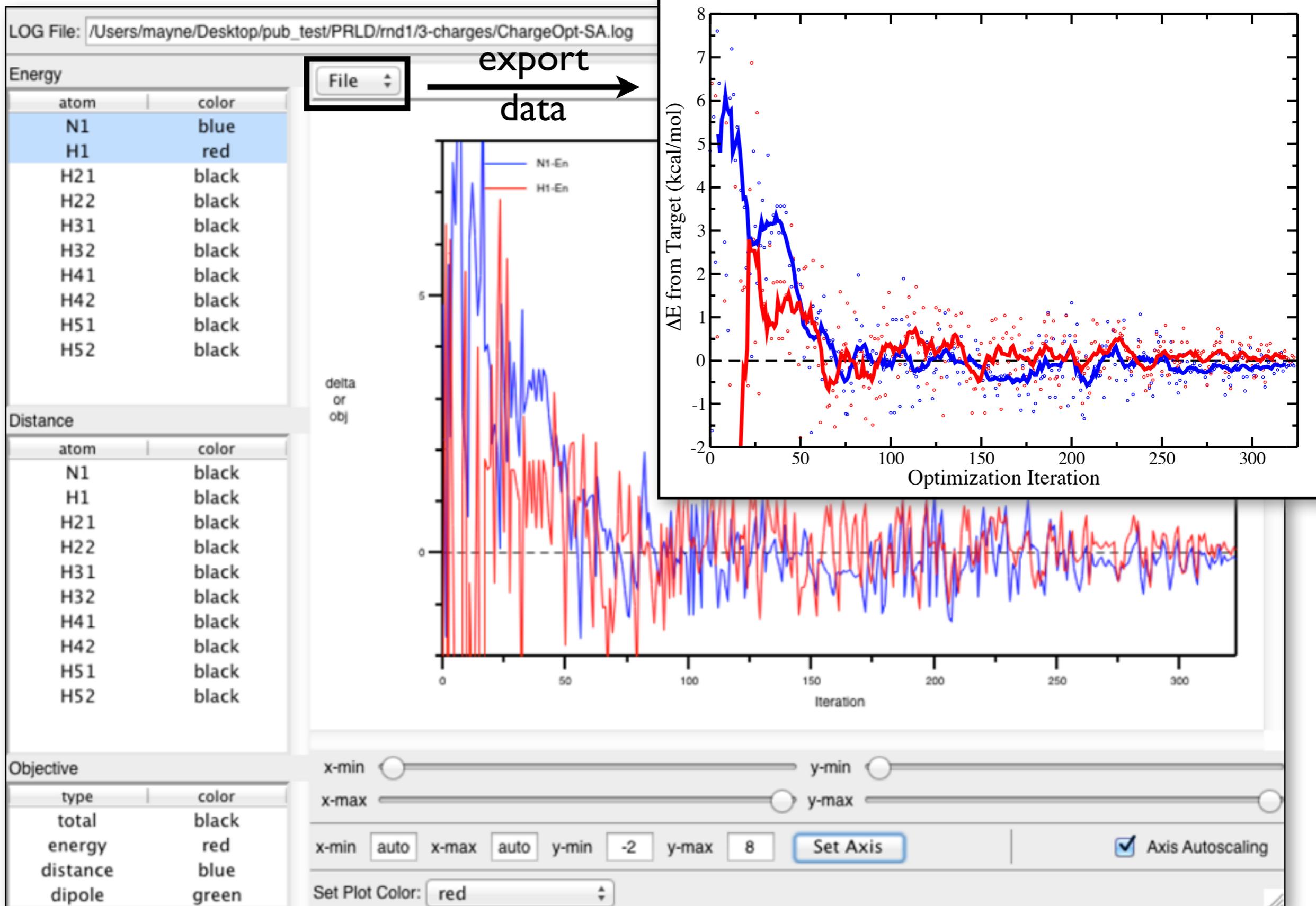
Plotting Charge Optimization Data



Plotting Charge Optimization Data

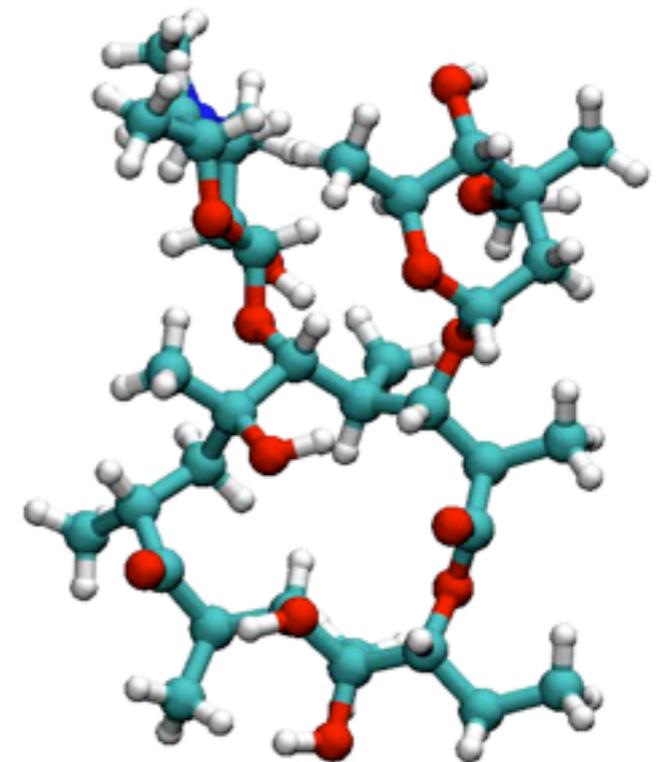
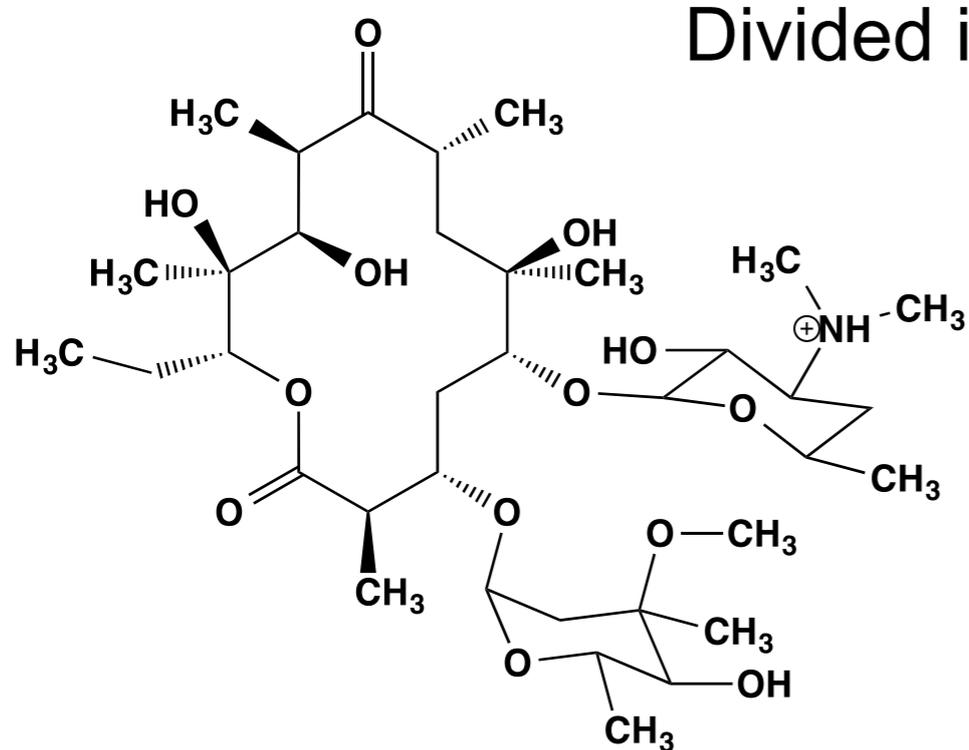
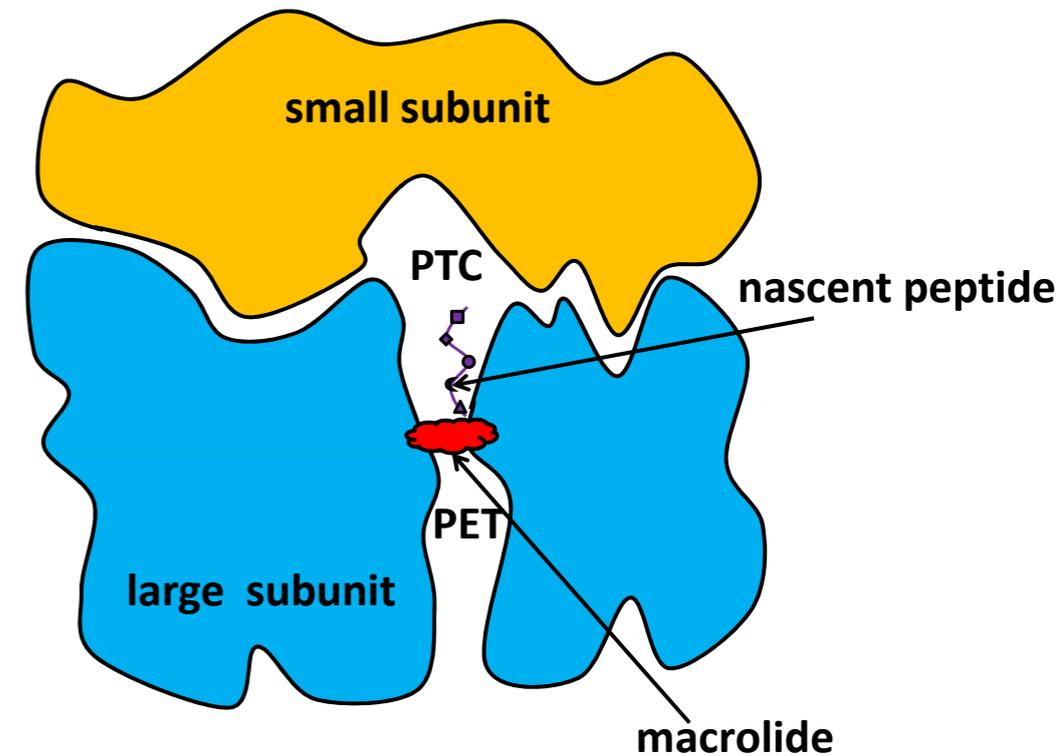


Plotting Charge Optimization Data



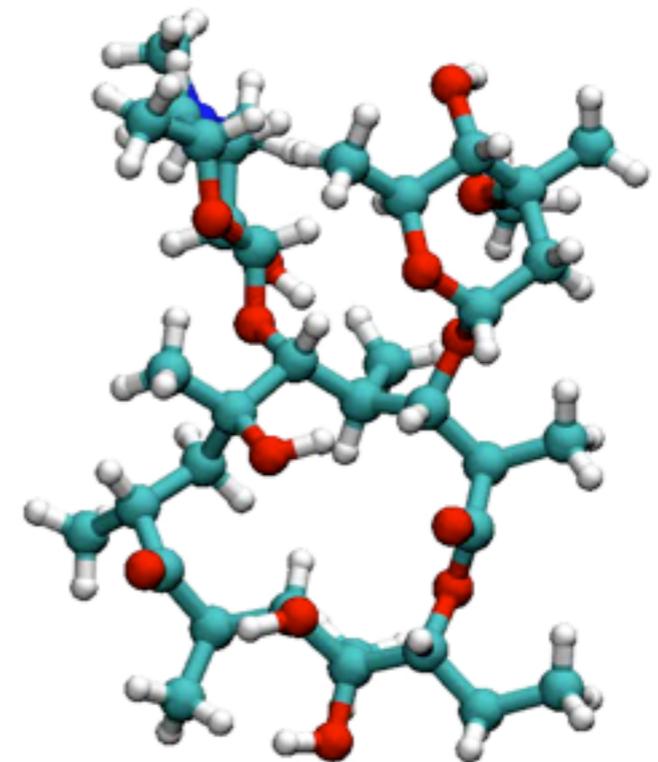
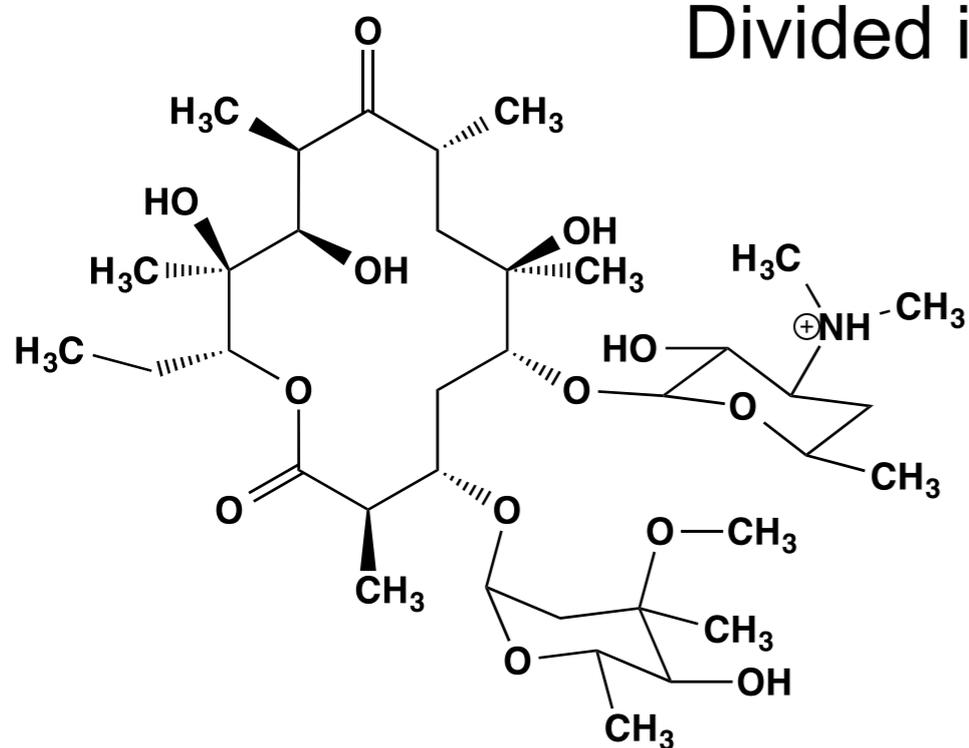
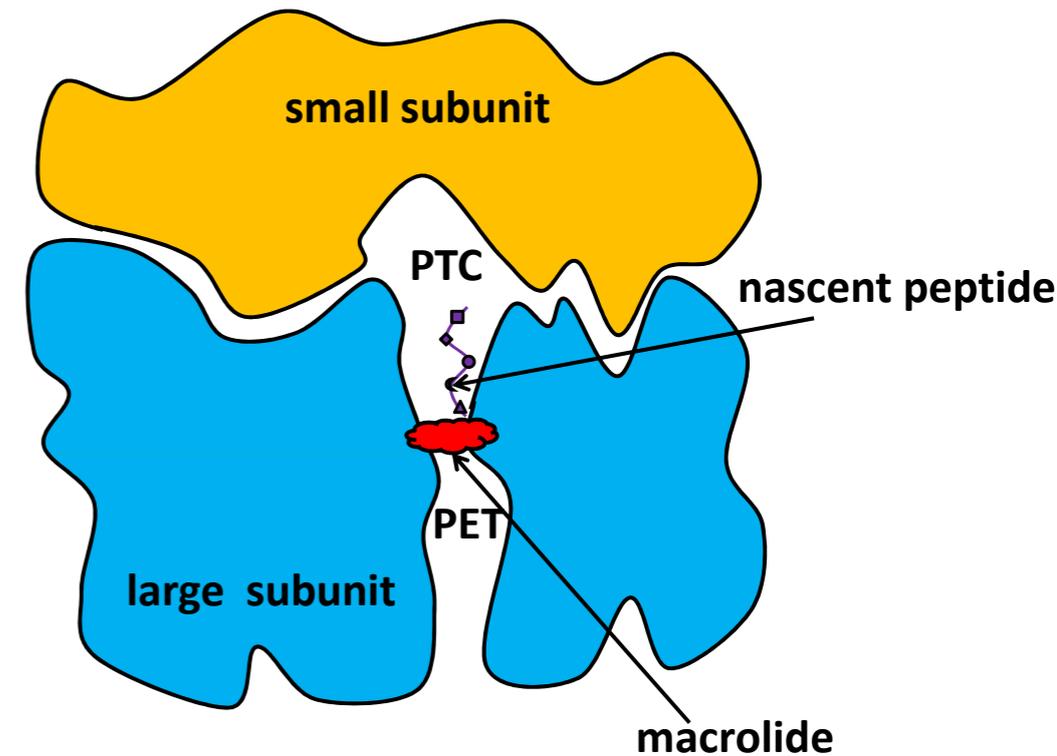
Parameterization of Erythromycin

macrolides - antibiotics that prevent peptide synthesis in bacterial ribosomes



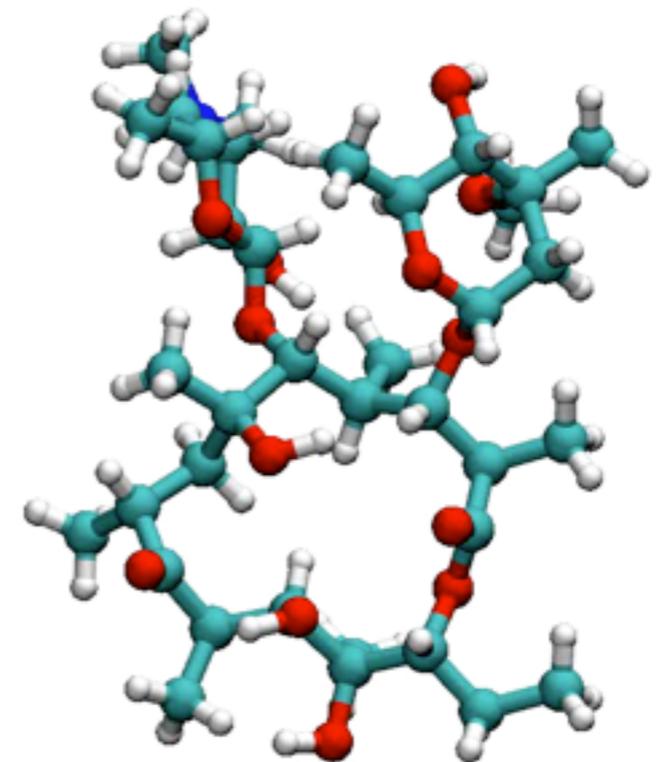
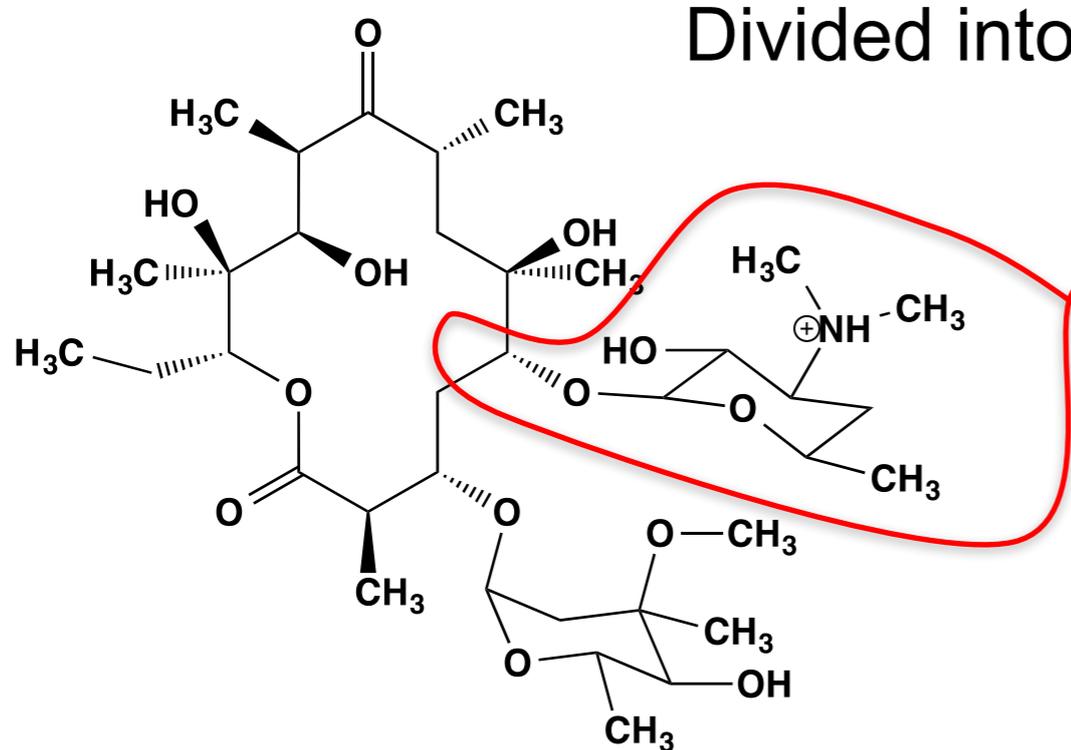
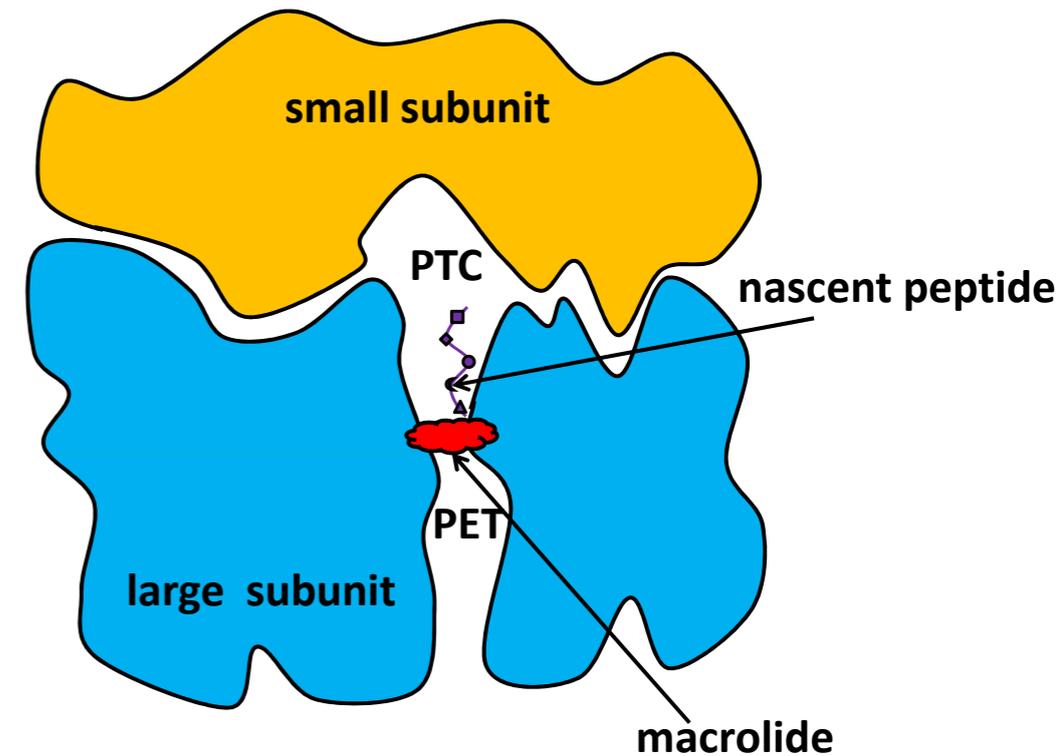
Parameterization of Erythromycin

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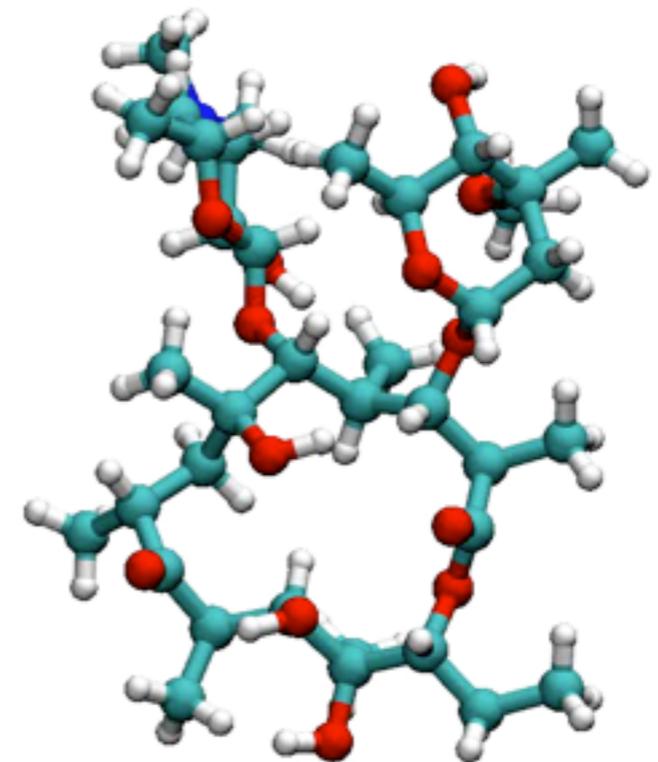
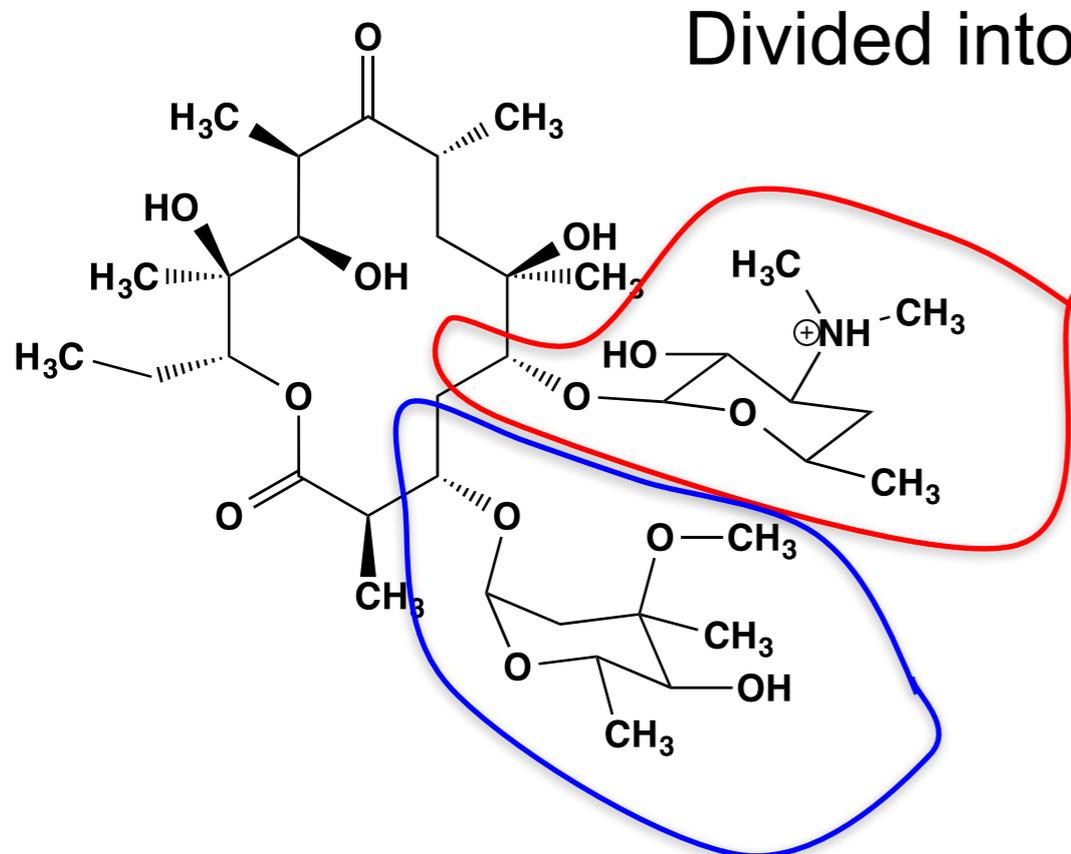
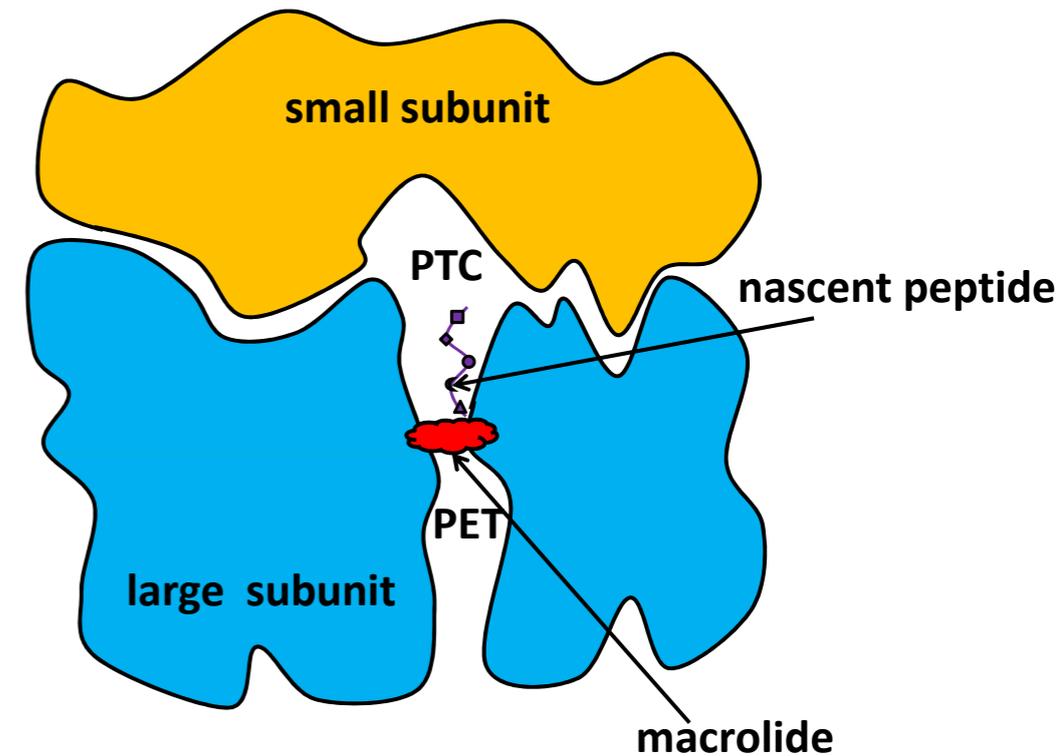
Parameterization of Erythromycin

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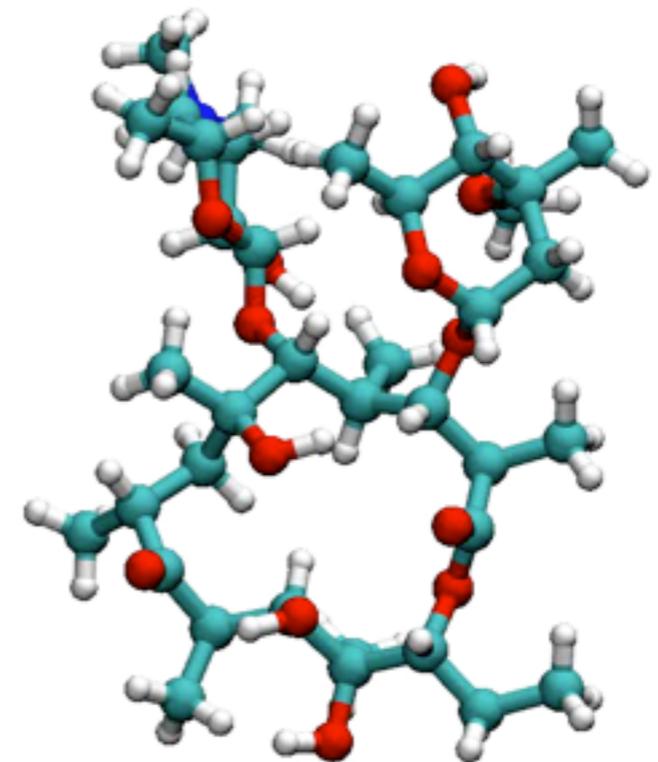
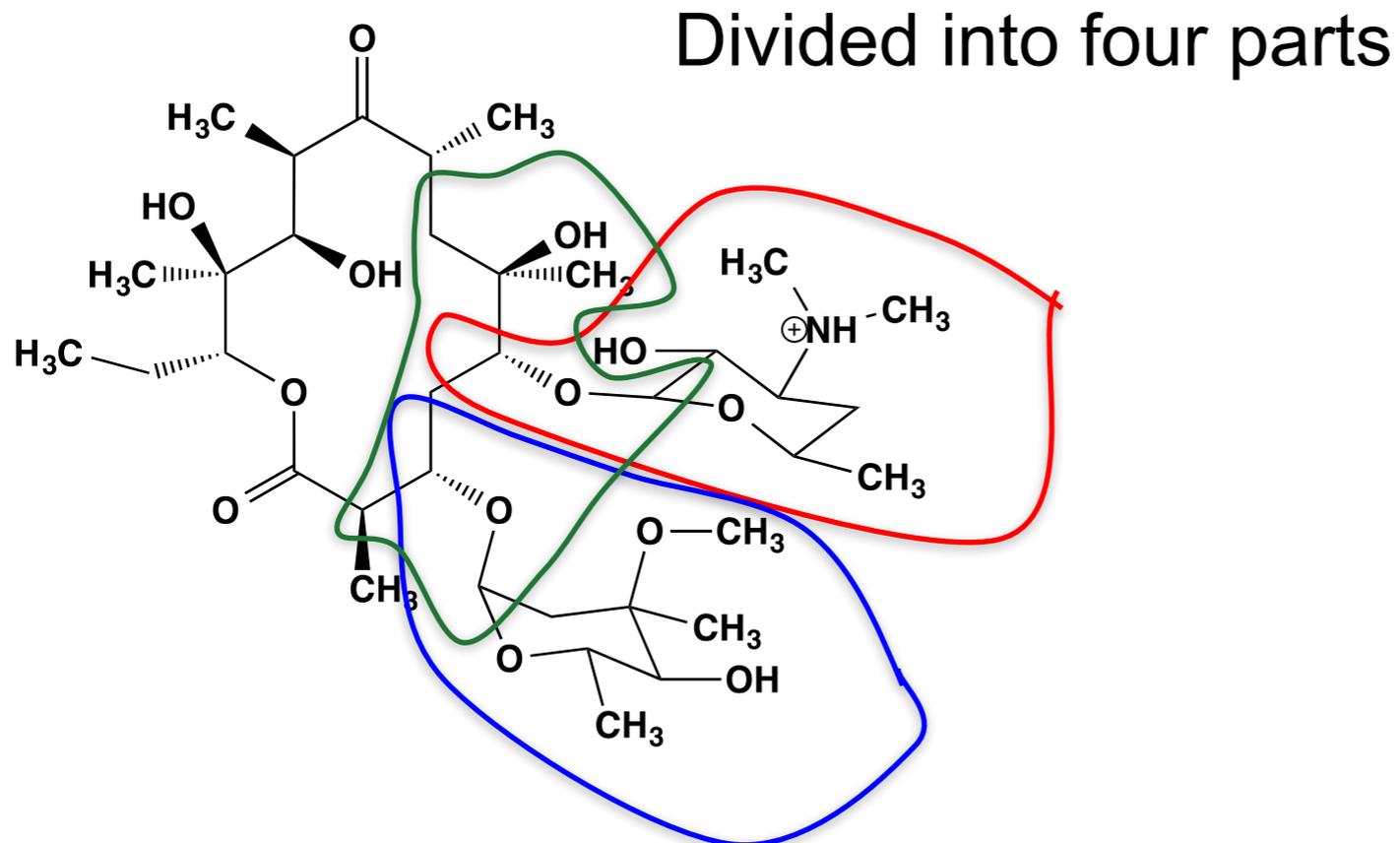
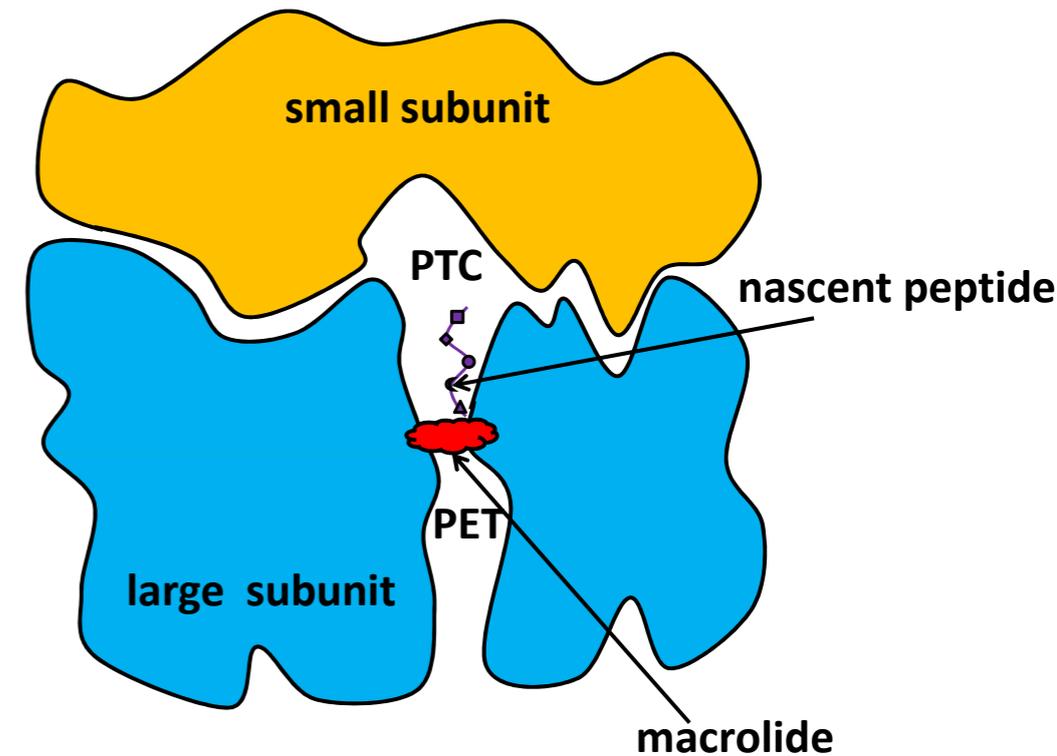
Parameterization of Erythromycin

macrolides - antibiotics that prevent peptide synthesis in bacterial ribosomes



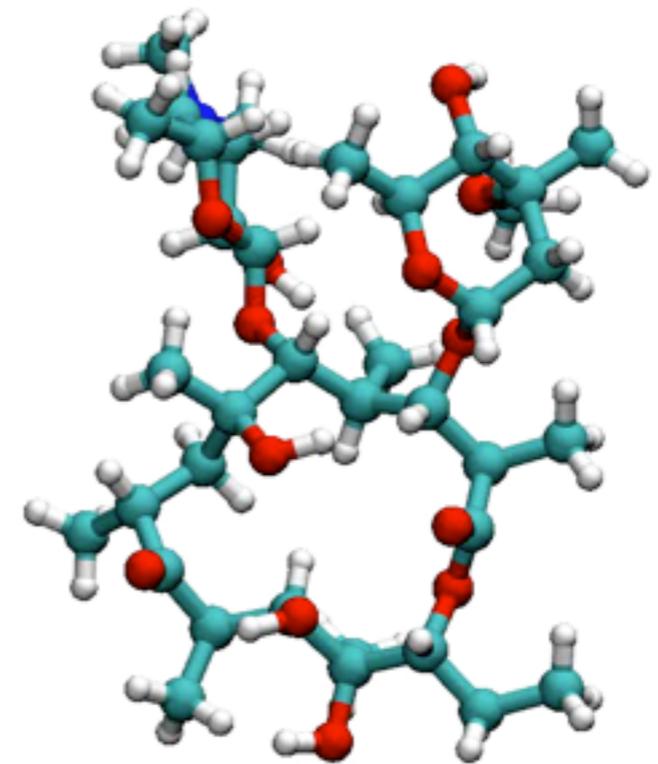
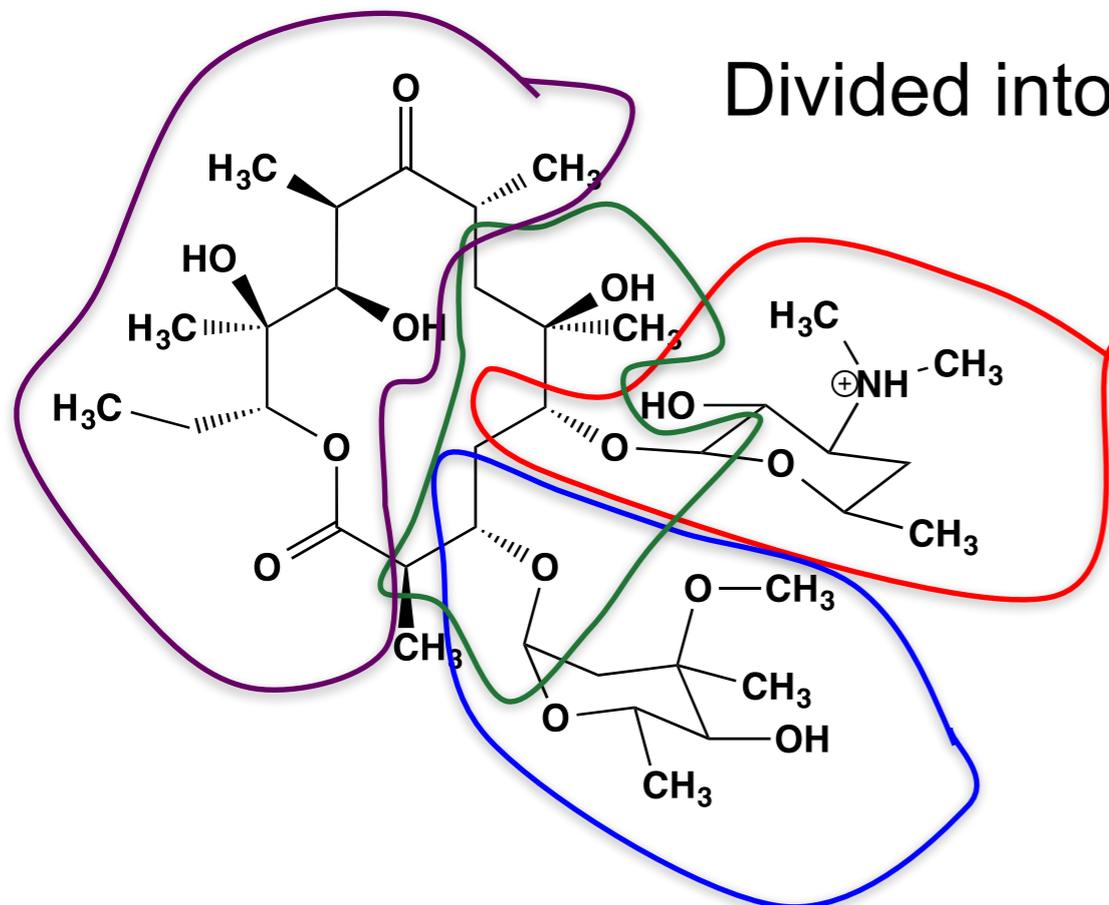
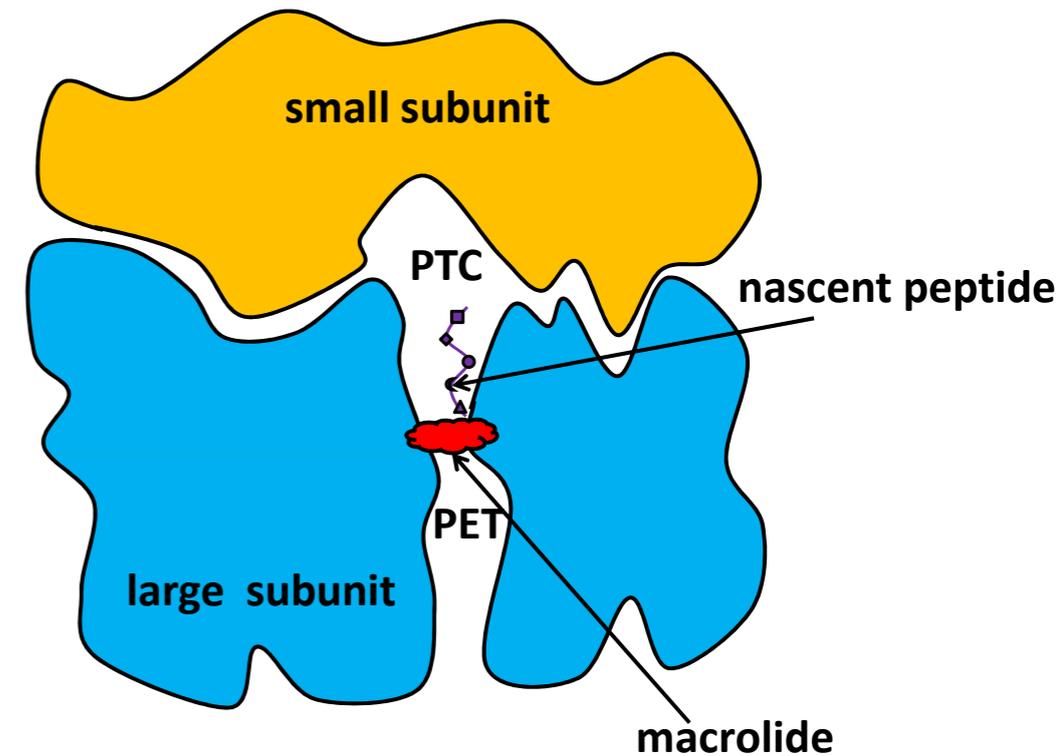
Parameterization of Erythromycin

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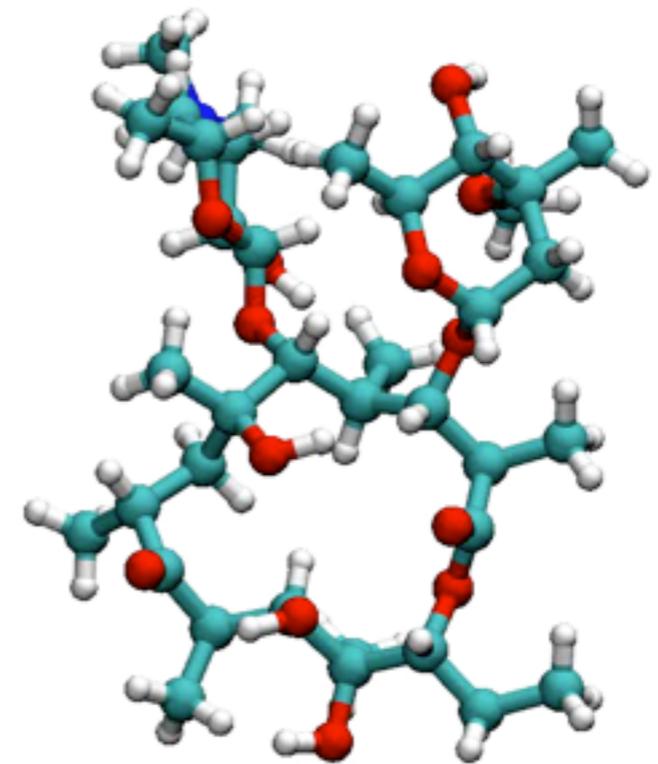
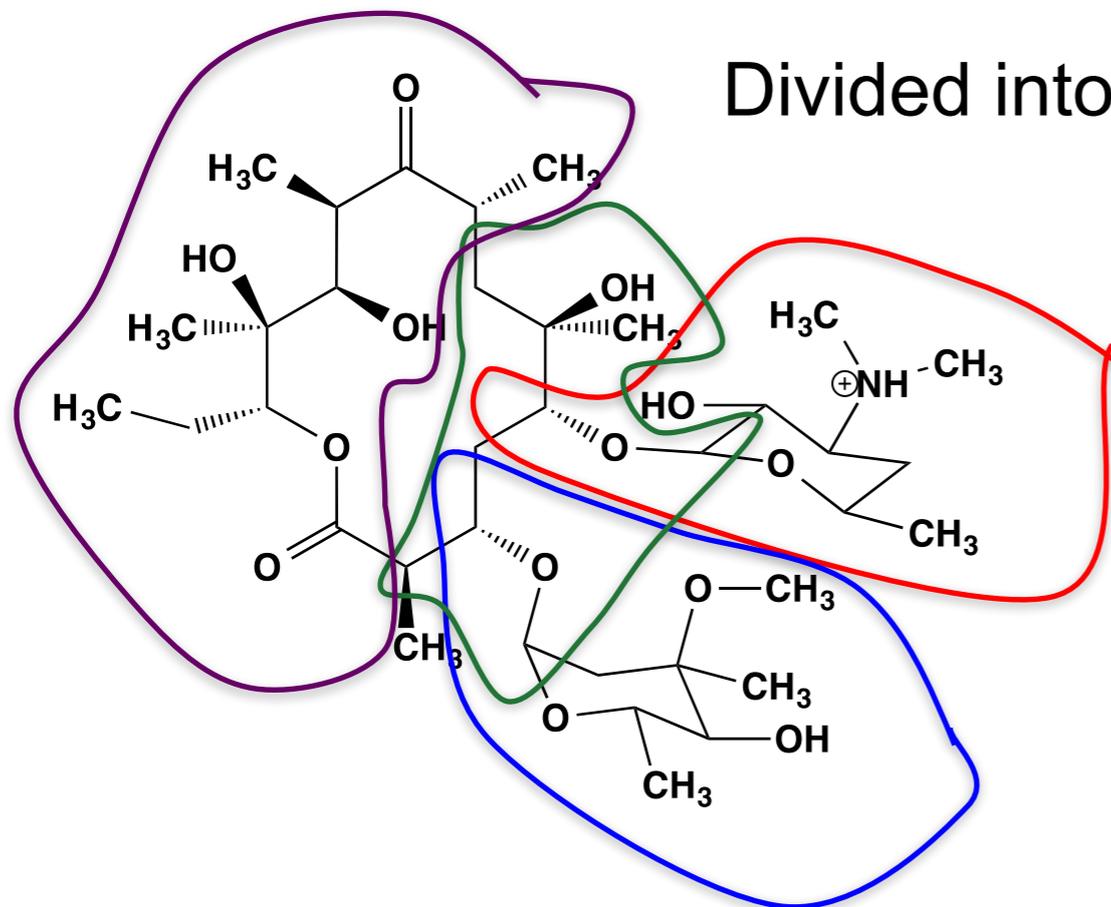
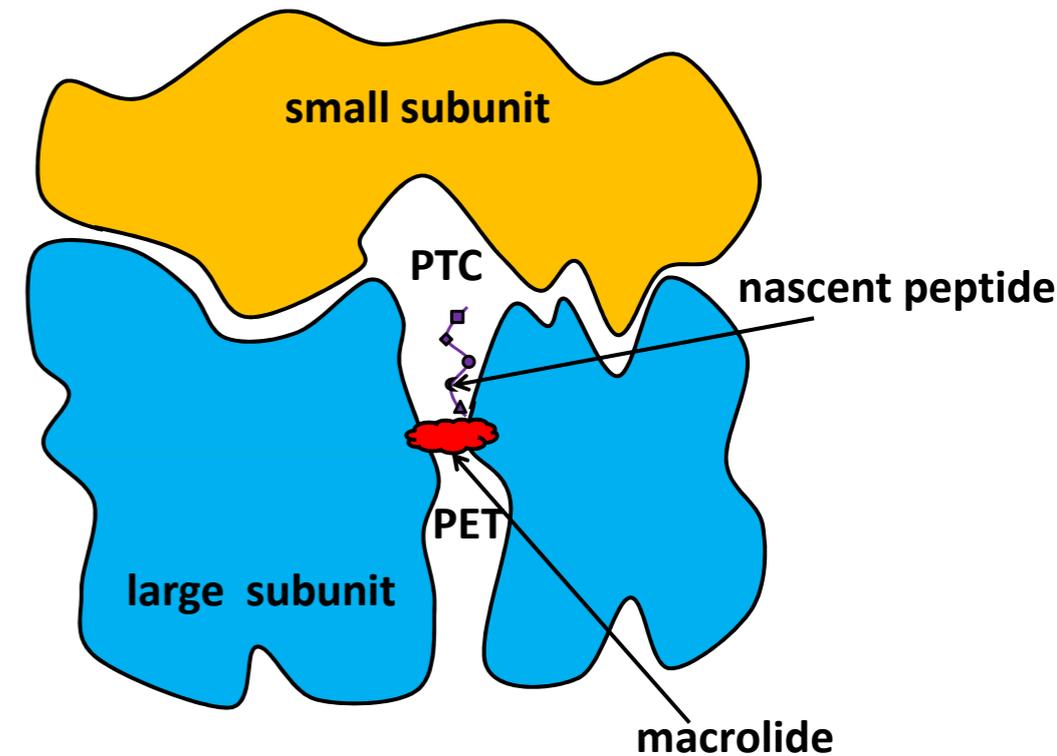
Parameterization of Erythromycin

macrolides - antibiotics that prevent peptide synthesis in bacterial ribosomes



Parameterization of Erythromycin

macrolides - antibiotics that prevent peptide synthesis in bacterial ribosomes



Fitting of Partial Charges

CHARMM partial charges are derived from interactions with water
Calculated for each atom that is fitted

Fitting of Partial Charges

CHARMM partial charges are derived from interactions with water
Calculated for each atom that is fitted

The screenshot displays the Force Field Toolkit (ffTK) GUI, specifically the 'Opt. Charges' tab. The interface is organized into several sections:

- Input**: Contains 'Charge Constraints' and 'QM Target Data'.
- Single Point Energy Data**: Includes three text input fields for 'Cmpd LOG (HF)', 'Cmpd LOG (MP2)', and 'Water LOG', each with a 'Browse' button.
- Water Interaction Energy Data**: Features a table with columns for 'LOG File', 'Atom Name', and 'Weight'. The table lists several entries with atom names like C62, C63, N31, N41, N52, C40, C43, H, and H17, all with a weight of 1.0. To the right of the table are 'Add', 'Delete', and 'Clear' buttons.
- Edit Entry**: A section with a text input field, a 'Browse' button, and two numerical input fields containing the values 'u2713' and 'u2715'.
- Advanced Settings** and **Results**: Collapsible sections.
- Status**: Shows 'Status: IDLE'.
- Run Optimization**: A large button at the bottom.
- GUI Event Log (on)**: A log window at the bottom showing three entries: '004 Dihedral optimization data read from file 11/03/2014 -- 06:05:52 PM', '003 Dihedral optimization data read from file 11/03/2014 -- 06:05:06 PM', and '002 Dihedral optimization data read from file 11/03/2014 -- 06:04:23 PM'. Below the log is a citation: 'To cite ffTK please use: C.G. Mayne, J. Saam, K. Schulten, E. Tajkhorshid, J.C. Gumbart. *J. Comput. Chem.* **2013**, 34, 2757-2770.'

Fitting of Partial Charges

CHARMM partial charges are derived from interactions with water
Calculated for each atom that is fitted

Loaded into FFTK

Force Field Toolkit (ffTK) GUI

BuildPar Opt. Geometry Water Int. Opt. Charges Calc. Bonded Opt. Bonded Scan Torsions Opt. Torsions Calc. ESP

Input
Charge Constraints
GM Target Data

Single Point Energy Data

Cmpd LOG (HF): /localdata/apaviova3/Telthro/WatArm/TEL-sp-HF.log Browse

Cmpd LOG (MP2): /localdata/apaviova3/Telthro/WatArm/TEL-sp-MP2.log Browse

Water LOG: /localdata/apaviova3/Telthro/WatArm/wat-sp.log Browse

Water Interaction Energy Data

LOG File	Atom Name	Weight
/localdata/apaviova3/Telthro/WatArm/TEL-ACC-C62.log	C62	1.0
/localdata/apaviova3/Telthro/WatArm/TEL-ACC-C63.log	C63	1.0
/localdata/apaviova3/Telthro/WatArm/TEL-ACC-N31.log	N31	1.0
/localdata/apaviova3/Telthro/WatArm/TEL-ACC-N41.log	N41	1.0
/localdata/apaviova3/Telthro/WatArm/TEL-ACC-N52.log	N52	1.0
/localdata/apaviova3/Telthro/WatArm/TEL-DON-C40.log	C40	1.0
/localdata/apaviova3/Telthro/WatArm/TEL-DON-C43.log	C43	1.0
/localdata/apaviova3/Telthro/WatArm/TEL-DON-H.log	H	1.0
/localdata/apaviova3/Telthro/WatArm/TEL-DON-H17.log	H17	1.0

Edit Entry

Advanced Settings

Results

Status: IDLE

Run Optimization

GUI Event Log (on)

004 Dihedral optimization data read from file 11/03/2014 -- 06:05:52 PM

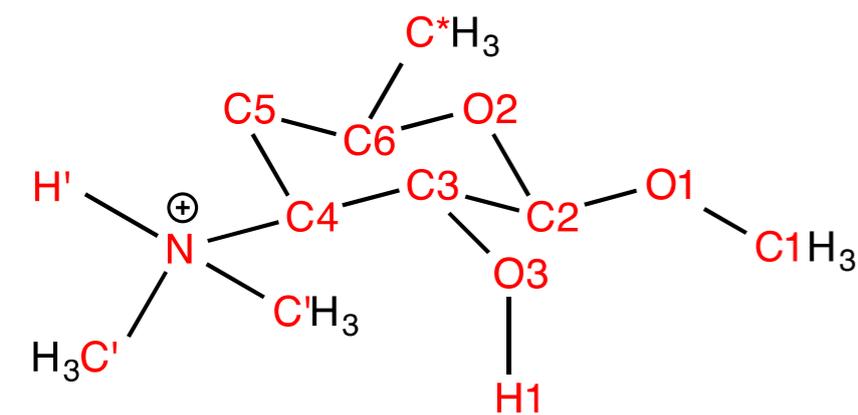
003 Dihedral optimization data read from file 11/03/2014 -- 06:05:06 PM

002 Dihedral optimization data read from file 11/03/2014 -- 06:04:23 PM

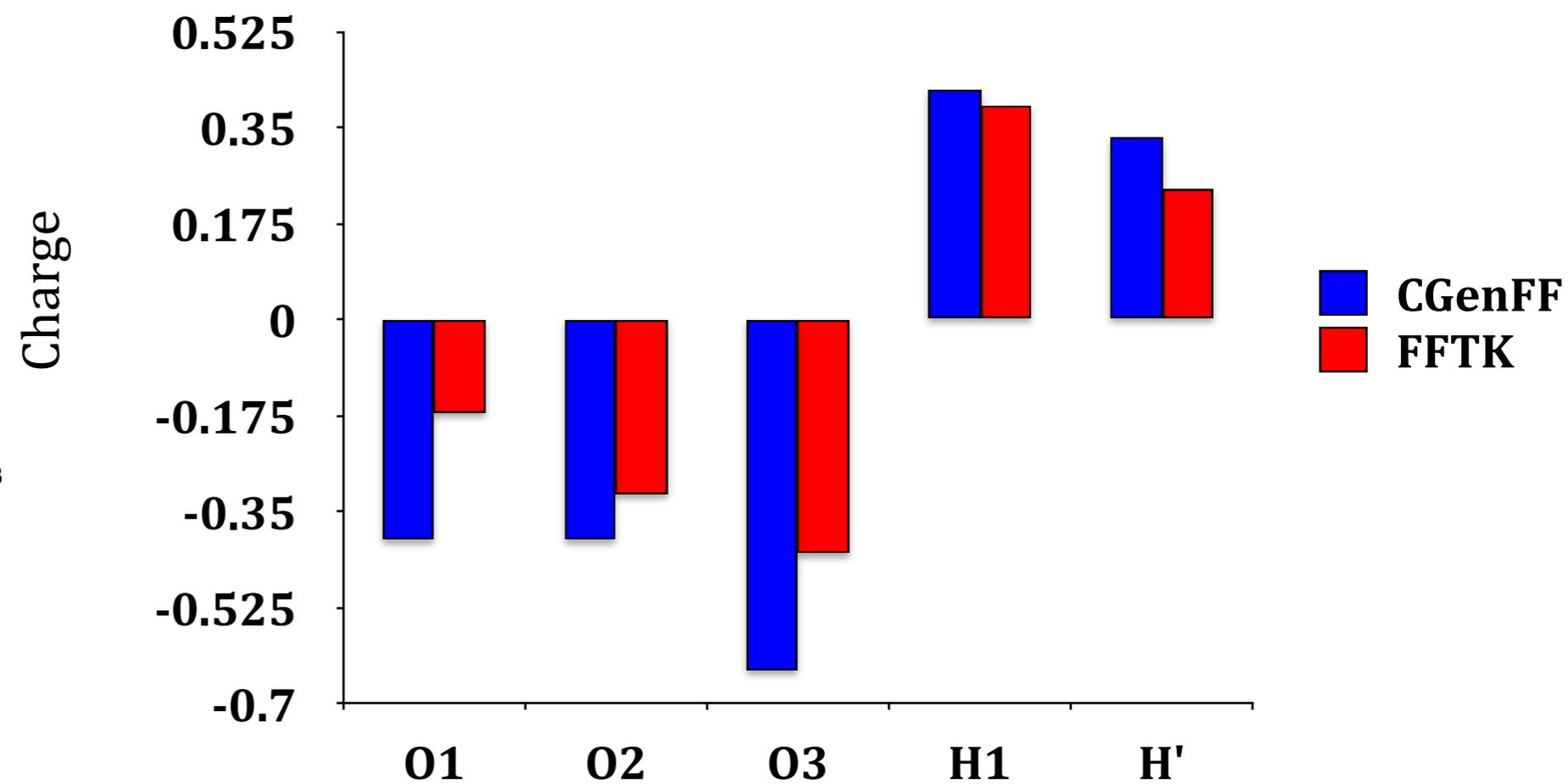
To cite ffTK please use: C.G. Mayne, J. Saam, K. Schulten, E. Tajkhorshid, J.C. Gumbart. *J. Comput. Chem.* **2013**, 34, 2757-2770.

Accuracy of Fitting: Charges

Desosamine
charges fitted for red atoms



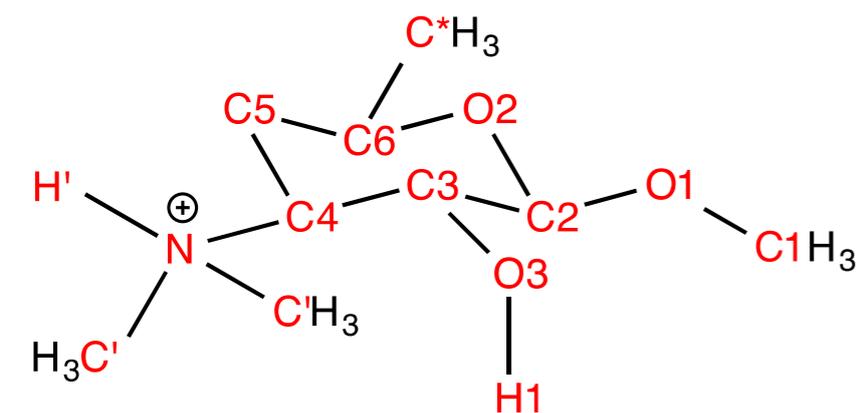
Partial charges for polar atoms



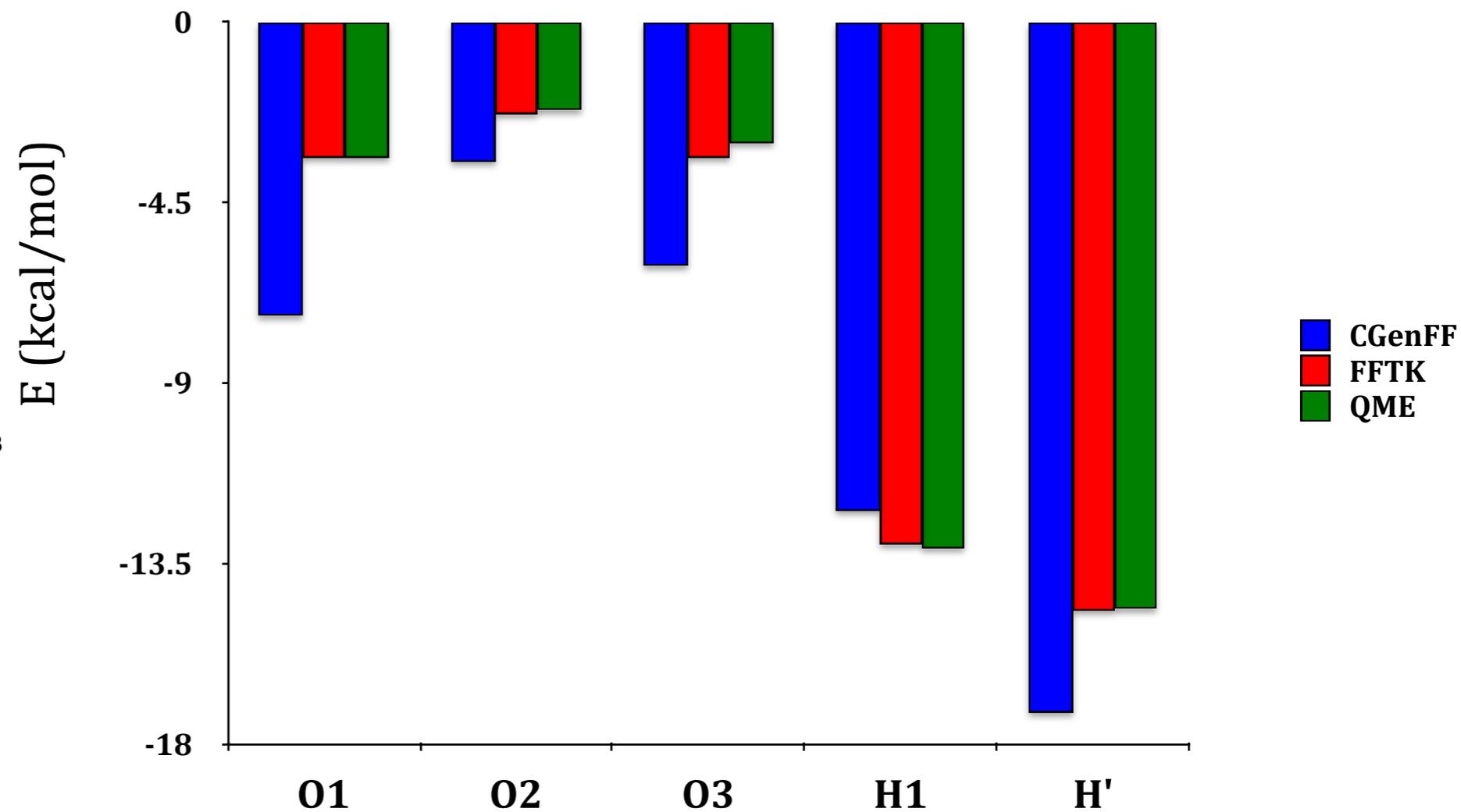
FTK can be used to get better agreement with QM data

Accuracy of Fitting: Charges

Desosamine
charges fitted for red atoms



Interaction energies with water for polar atoms

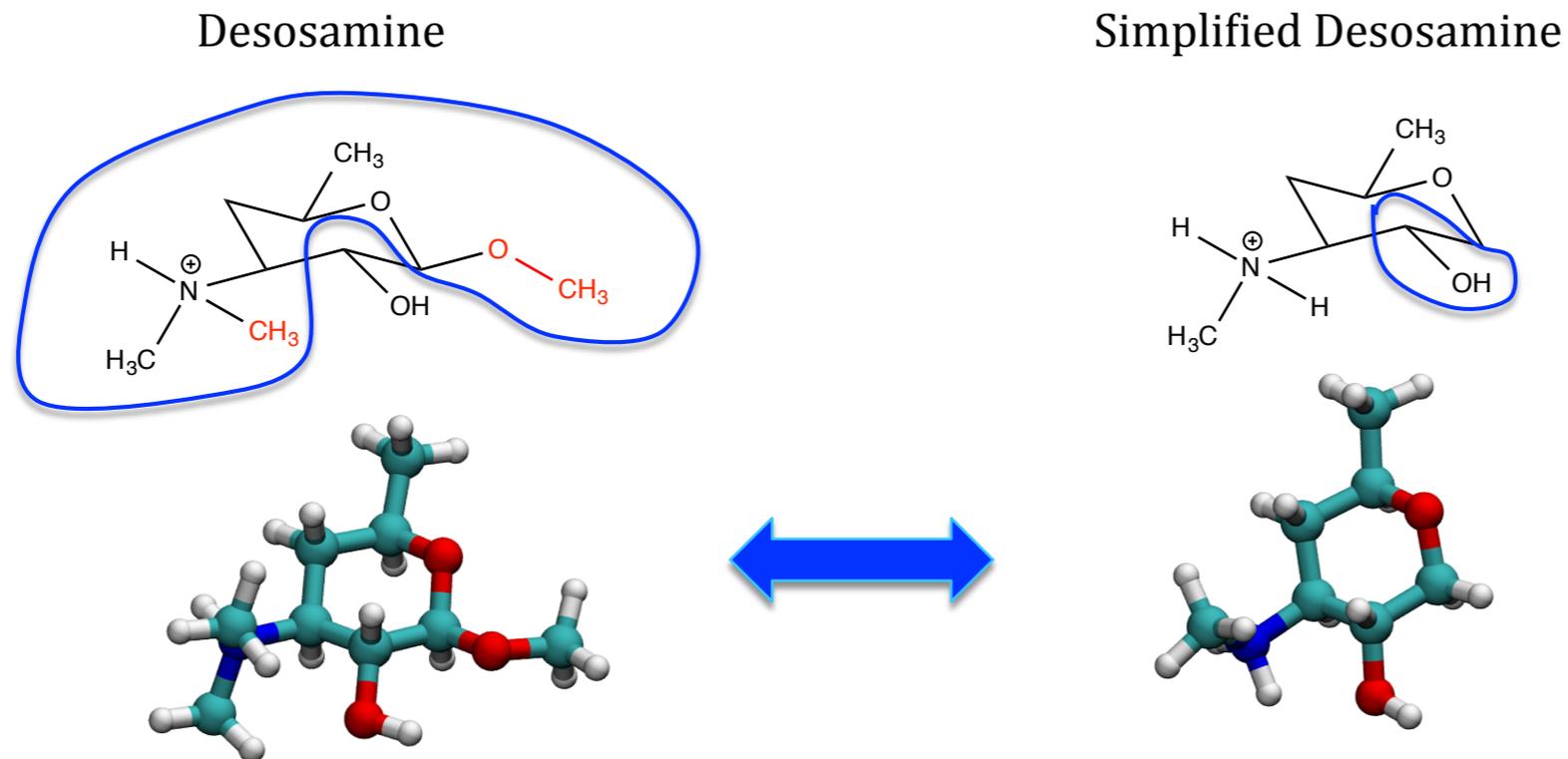


FFTK can be used to get better agreement with QM data

Fitting of Partial Charges

Optimization of water interactions can be difficult for sterically hindered groups

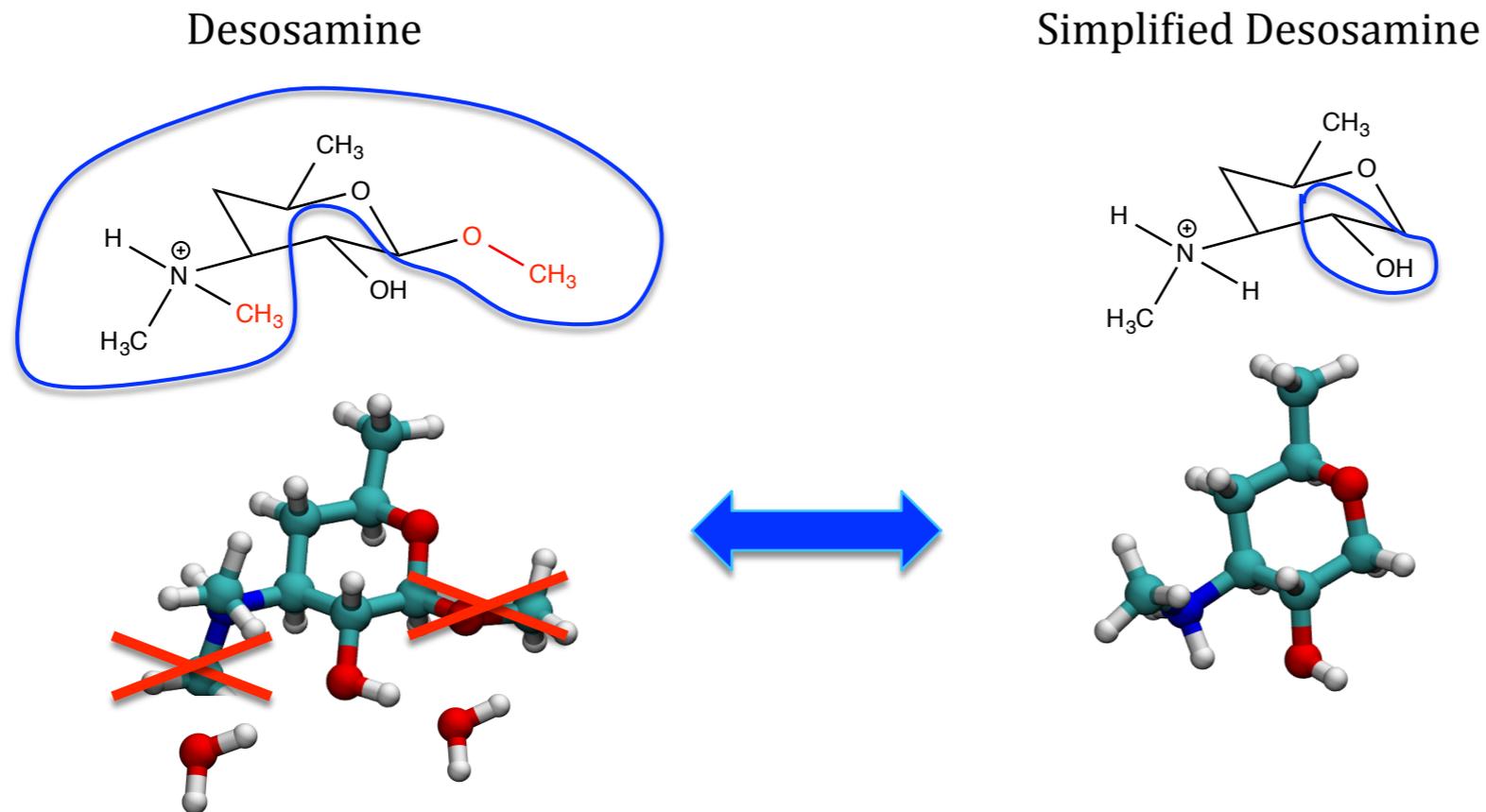
Our self consistent iterative charge optimization scheme



Fitting of Partial Charges

Optimization of water interactions can be difficult for sterically hindered groups

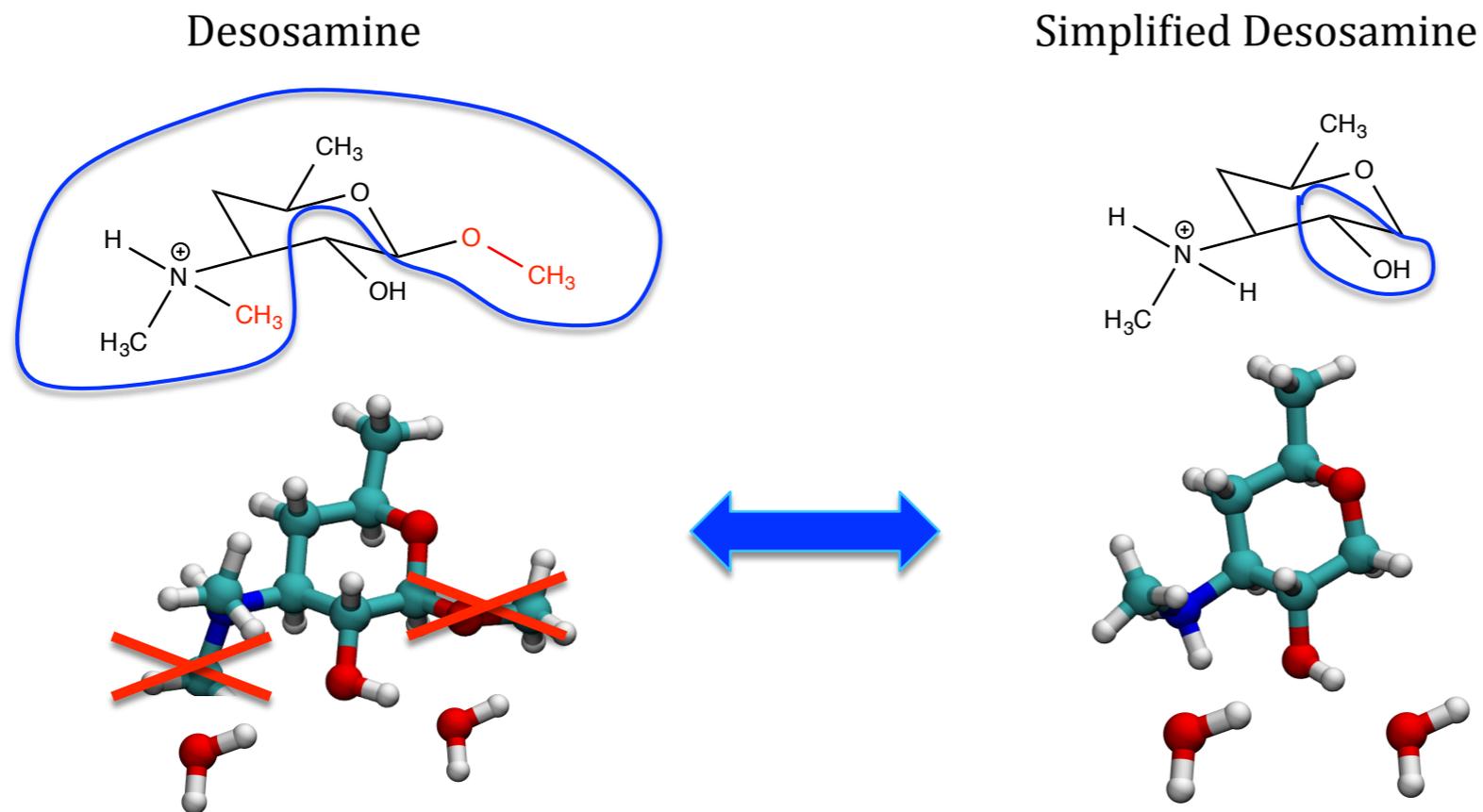
Our self consistent iterative charge optimization scheme



Fitting of Partial Charges

Optimization of water interactions can be difficult for sterically hindered groups

Our self consistent iterative charge optimization scheme



An Alternative to Water Interactions for Charges

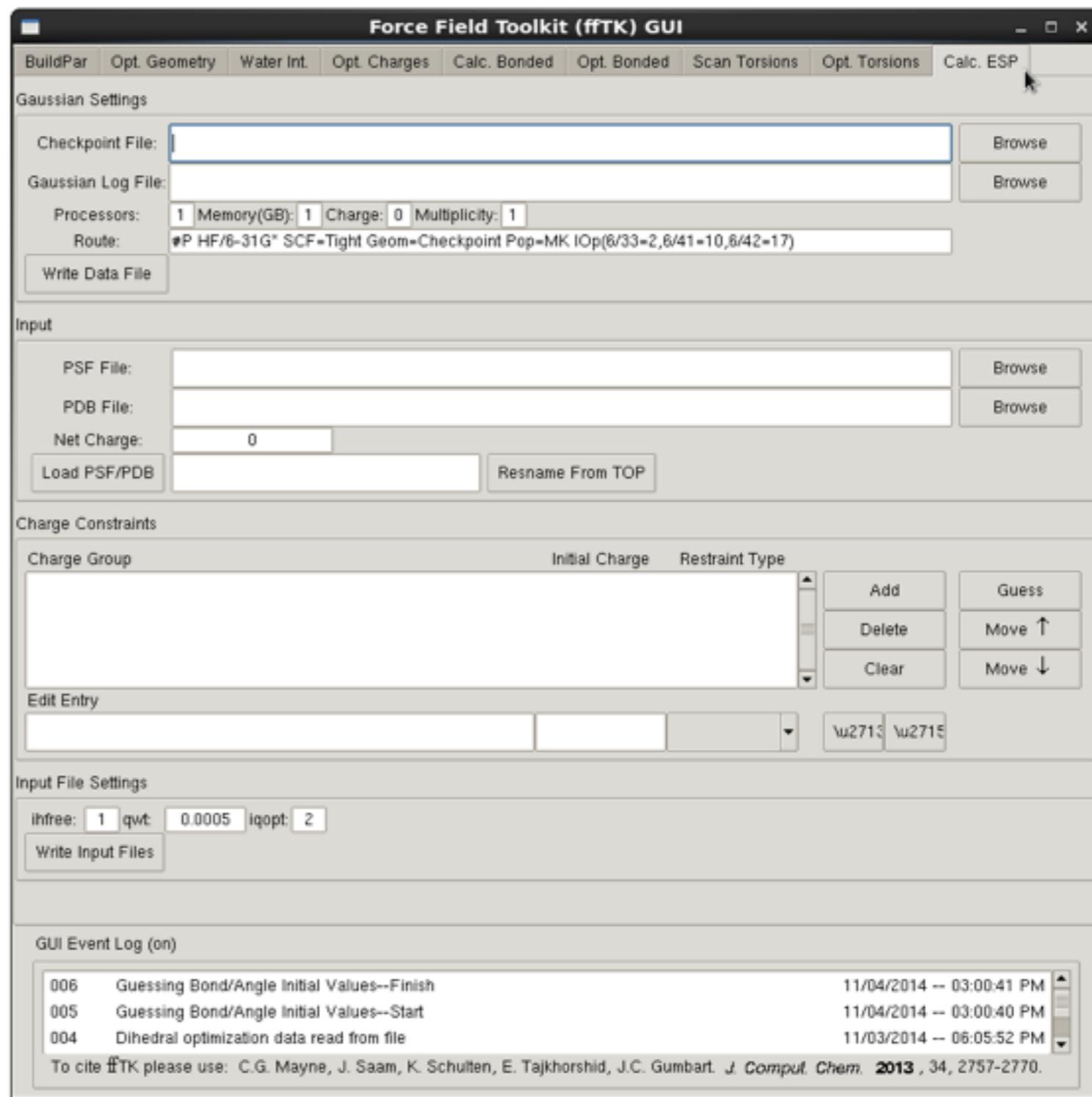
RESP fitting of charges
Based electrostatic potential

Much easier to implement
Tests on compatibility with
CHARMM in progress

An Alternative to Water Interactions for Charges

RESP fitting of charges
Based electrostatic potential

Much easier to implement
Tests on compatibility with
CHARMM in progress



Fitting of Bonds and Angles

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

- Input:** Fields for PSF File, PDB File, Hess LOG File, and In-Progress PAR File, each with a 'Browse' button.
- Additional Associated Parameter Files:** A list box with 'Add', 'Delete', and 'Clear' buttons.
- NAMD Bin:** Field containing 'namd2' with a 'Browse' button.
- Output LOG:** Field containing 'BondedOpt.log' with a 'SaveAs' button.
- Parameters to Optimize:** A table listing bond and angle parameters with their respective force constants and b_0/θ values.
- Advanced Settings:** Includes Tolerance, Geom. Weight, Energy Weight, Mode, and Iter. settings.
- Run Settings:** Checkboxes for 'Write debugging log' and 'Build run script'.
- Results:** A 'Run Optimization' button and a 'Status: IDLE' indicator.
- GUI Event Log (on):** A log window showing recent events and a citation for ffTK.

Bond/Angle	Atom Type Def.	Force Constant	b_0/θ
bond	C2R61M C2R63M	467.7373	1.4050
bond	CC322M HCA2	346.1829	1.1028
bond	C2R53M N2R50M	511.8103	1.3314
bond	C2R62M C2R63M	481.5120	1.4126
bond	HCA3 CC331M	349.9612	1.1028
bond	N2R51M C2R53M	482.8518	1.3735
bond	C2R51M HGR52	381.2354	1.0889
bond	C2R63M N2360M	492.8398	1.3467

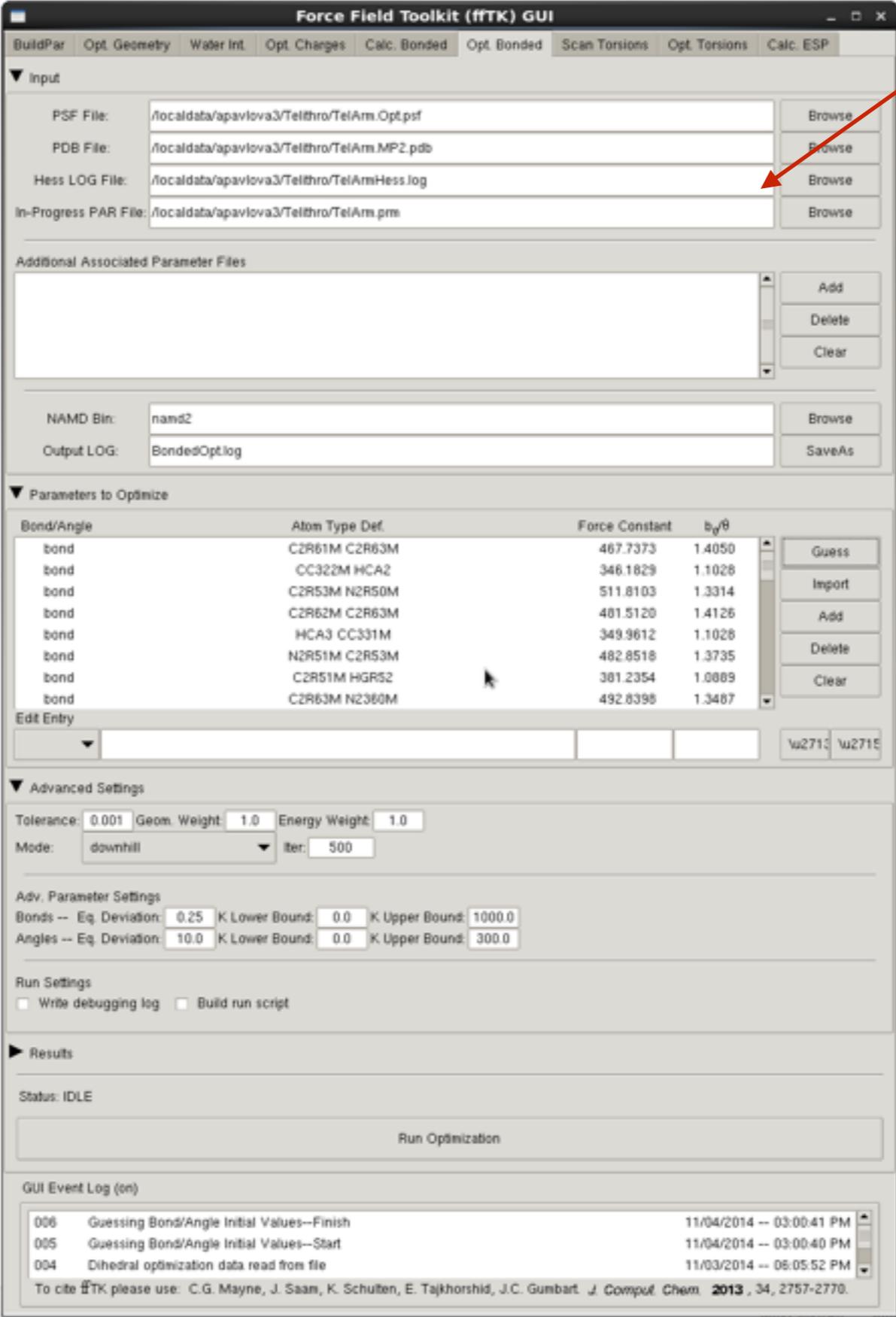
GUI Event Log (on)

```
006 Guessing Bond/Angle Initial Values--Finish 11/04/2014 -- 03:00:41 PM
005 Guessing Bond/Angle Initial Values--Start 11/04/2014 -- 03:00:40 PM
004 Dihedral optimization data read from file 11/03/2014 -- 05:05:52 PM
```

To cite ffTK please use: C.G. Mayne, J. Saam, K. Schulten, E. Tajkhorshid, J.C. Gumbart. *J. Comput. Chem.* **2013**, *34*, 2757-2770.

Fitting of Bonds and Angles

input Hessian file



The screenshot shows the Force Field Toolkit (ffTK) GUI. The 'Input' section is expanded, showing fields for PSF File, PDB File, Hess LOG File, and In-Progress PAR File. A red arrow points to the Hess LOG File field, which is labeled 'input Hessian file' in the text above. Below the input fields is a section for 'Additional Associated Parameter Files' with 'Add', 'Delete', and 'Clear' buttons. Further down are fields for 'NAMD Bin' and 'Output LOG'. The 'Parameters to Optimize' section contains a table with columns for 'Bond/Angle', 'Atom Type Def.', 'Force Constant', and 'b_{ij}^θ'. Below the table are 'Guess', 'Import', 'Add', 'Delete', and 'Clear' buttons. The 'Advanced Settings' section includes 'Tolerance', 'Geom. Weight', 'Energy Weight', 'Mode', and 'Iter' fields. The 'Run Settings' section has checkboxes for 'Write debugging log' and 'Build run script'. The 'Results' section shows 'Status: IDLE' and a 'Run Optimization' button. The 'GUI Event Log (on)' section at the bottom shows a log of events with timestamps.

Bond/Angle	Atom Type Def.	Force Constant	b _{ij} ^θ
bond	C2R61M C2R63M	467.7373	1.4050
bond	CC322M HCA2	346.1829	1.1028
bond	C2R53M N2R50M	511.8103	1.3314
bond	C2R62M C2R63M	481.5120	1.4126
bond	HCA3 CC331M	349.9612	1.1028
bond	N2R51M C2R53M	482.8518	1.3735
bond	C2R51M HGR52	381.2354	1.0889
bond	C2R63M N2360M	492.8398	1.3467

Fitting of Bonds and Angles

input Hessian file

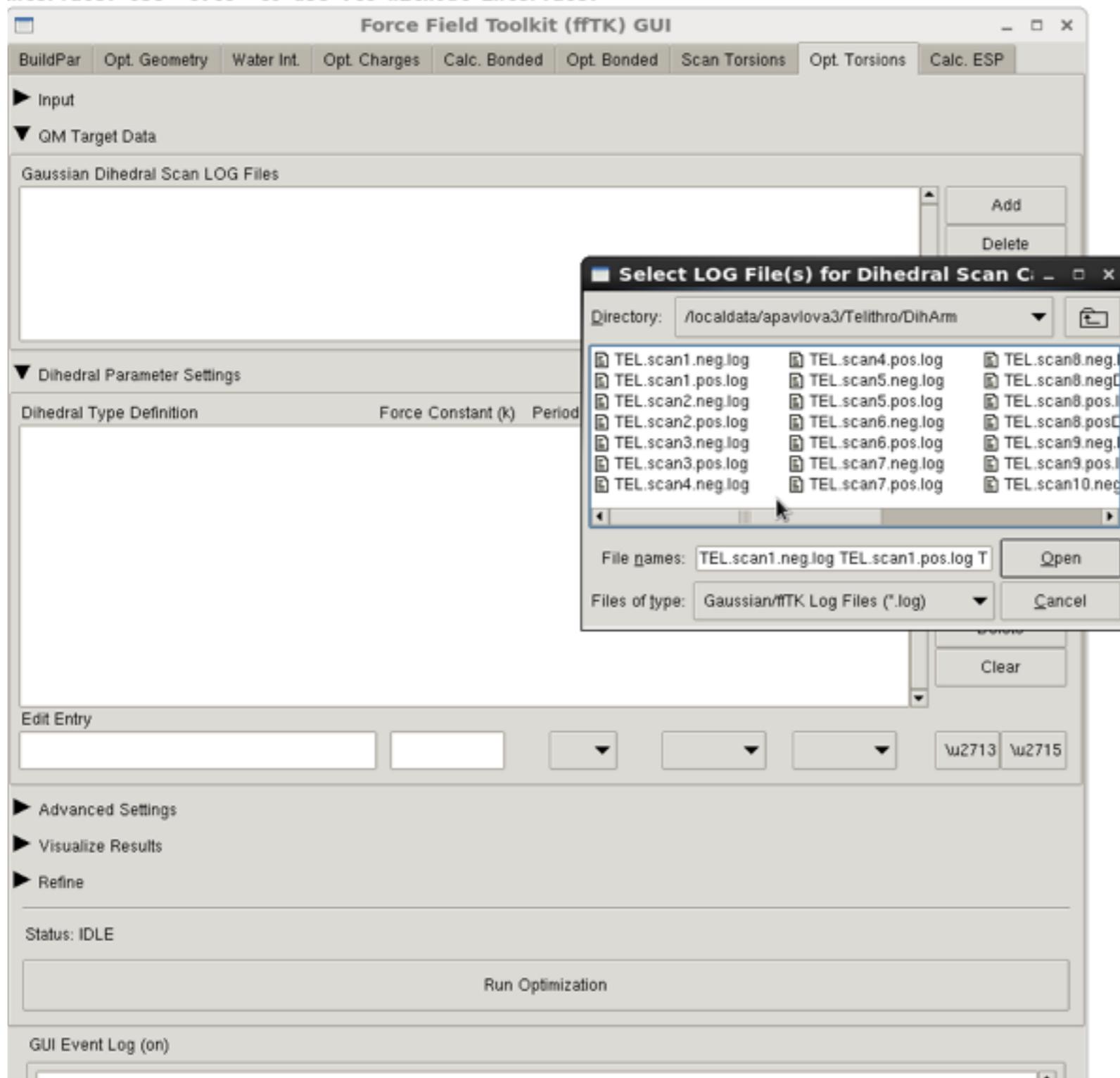
The screenshot shows the Force Field Toolkit (ffTK) GUI. The 'Parameters to Optimize' section contains a table with the following data:

Bond/Angle	Atom Type Def.	Force Constant	b_0/θ	
bond	C2R61M C2R63M	467.7373	1.4050	Guess
bond	CC322M HCA2	346.1829	1.1028	Import
bond	C2R53M N2R50M	511.8103	1.3314	Add
bond	C2R62M C2R63M	481.5120	1.4126	Delete
bond	HCA3 CC331M	349.9612	1.1028	Clear
bond	N2R51M C2R53M	482.8518	1.3735	
bond	C2R51M HGR52	381.2354	1.0889	
bond	C2R63M N2360M	492.8398	1.3467	

Below the table is an 'Edit Entry' section with input fields for 'w2710' and 'w2715'. The 'Advanced Settings' section includes 'Tolerance: 0.001', 'Geom. Weight: 1.0', 'Energy Weight: 1.0', 'Mode: downhill', and 'iter: 500'. The 'Results' section shows 'Status: IDLE' and a 'Run Optimization' button. The 'GUI Event Log (on)' at the bottom shows a log of events including 'Guessing Bond/Angle Initial Values--Finish' and 'Dihedral optimization data read from file'.

Obtained force constants and values

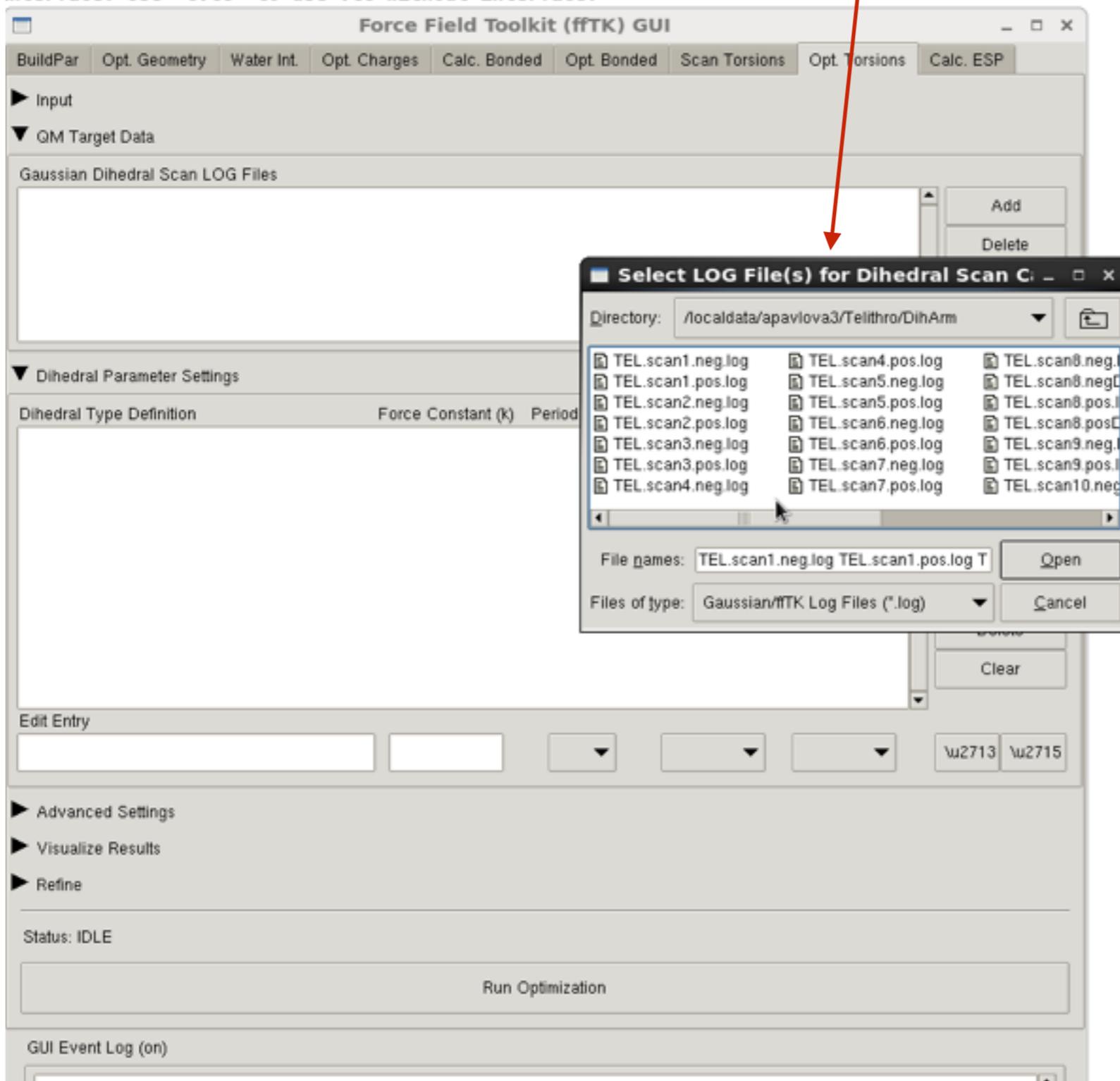
Fitting of Dihedrals



$$K_{\phi}(1 + \cos(n\phi - \delta))$$

Fitting of Dihedrals

Feed in the dihedral scans



$$K_{\phi}(1 + \cos(n\phi - \delta))$$

Fitting of Dihedrals

Select multiplicity and phase settings

The screenshot shows the Force Field Toolkit (ffTK) GUI. The 'Dihedral Parameter Settings' section is active, displaying a table of data sets and their RMSE values. The 'Refine' section is also visible, showing the 'Modify Dihedral Parameters for Refitting/Refinement' table.

Reference Data -- GME: Loaded MMEi: Loaded dihAll: Loaded

Data Set	RMSE	Plot Color
import	2.0496	blue
r00	2.091	blue
r01	0.967	blue
r02	0.989	blue
r03	0.889	blue
r04	0.700	blue
r05	0.599	blue
r06	0.550	blue
r07	0.501	blue

Set Data Color: [Dropdown]
Plot Selected
 Include GME Include MMEi
Delete Clear

Import From LOG Write Selected to LOG Set As Refit Input

Refine

Modify Dihedral Parameters for Refitting/Refinement

Dihedral Type Definition	Force Constant (k)	Periodicity (n)	Phase Shift (ϕ)	Lock Phase?
C2R51M C2R51M C2R62M C2R61M	9.052	1	0.00	no
C2R51M C2R51M C2R62M C2R61M	2.221	2	180.00	no
C2R51M C2R51M C2R62M C2R61M	3.692	3	180.00	no
C2R51M C2R51M C2R62M C2R63M	2.079	1	0.00	no
C2R51M C2R51M C2R62M C2R63M	3.890	2	180.00	no
C2R51M C2R51M C2R62M C2R63M	1.602	3	180.00	no
C2R51M C2R51M N2R50M C2R53M	0.316	1	180.00	no
C2R51M C2R51M N2R50M C2R53M	4.173	2	180.00	no

Edit Entry

C2R51M C2R51M C2R62M C2R61M 9.052 1 0.00 no \u2713 \u2715

Kmax: 15.0 Cutoff: 10.0 Tot: 0.01
Mode: downhill

Run Refitting/Refinement

Status: IDLE

Run Optimization

$$K_{\phi}(1 + \cos(n\phi - \delta))$$

Fitting of Dihedrals

Select multiplicity and phase settings

The screenshot shows the Force Field Toolkit (ffTK) GUI. The 'Refine' section is active, displaying a table of dihedral parameters for refinement. The table has columns for Dihedral Type Definition, Force Constant (k), Periodicity (n), Phase Shift (δ), and Lock Phase?. The first row is selected, showing a Force Constant of 9.052, Periodicity of 1, and Phase Shift of 0.00. Below the table, there are input fields for editing the selected entry, with values 9.052, 1, 0.00, and no. The 'Mode' is set to 'downhill'. Buttons for 'Run Refitting/Refinement' and 'Run Optimization' are visible at the bottom.

Dihedral Type Definition	Force Constant (k)	Periodicity (n)	Phase Shift (δ)	Lock Phase?
C2R51M C2R51M C2R62M C2R61M	9.052	1	0.00	no
C2R51M C2R51M C2R62M C2R61M	2.221	2	180.00	no
C2R51M C2R51M C2R62M C2R61M	3.692	3	180.00	no
C2R51M C2R51M C2R62M C2R63M	2.079	1	0.00	no
C2R51M C2R51M C2R62M C2R63M	3.890	2	180.00	no
C2R51M C2R51M C2R62M C2R63M	1.602	3	180.00	no
C2R51M C2R51M N2R50M C2R53M	0.316	1	180.00	no
C2R51M C2R51M N2R50M C2R53M	4.173	2	180.00	no

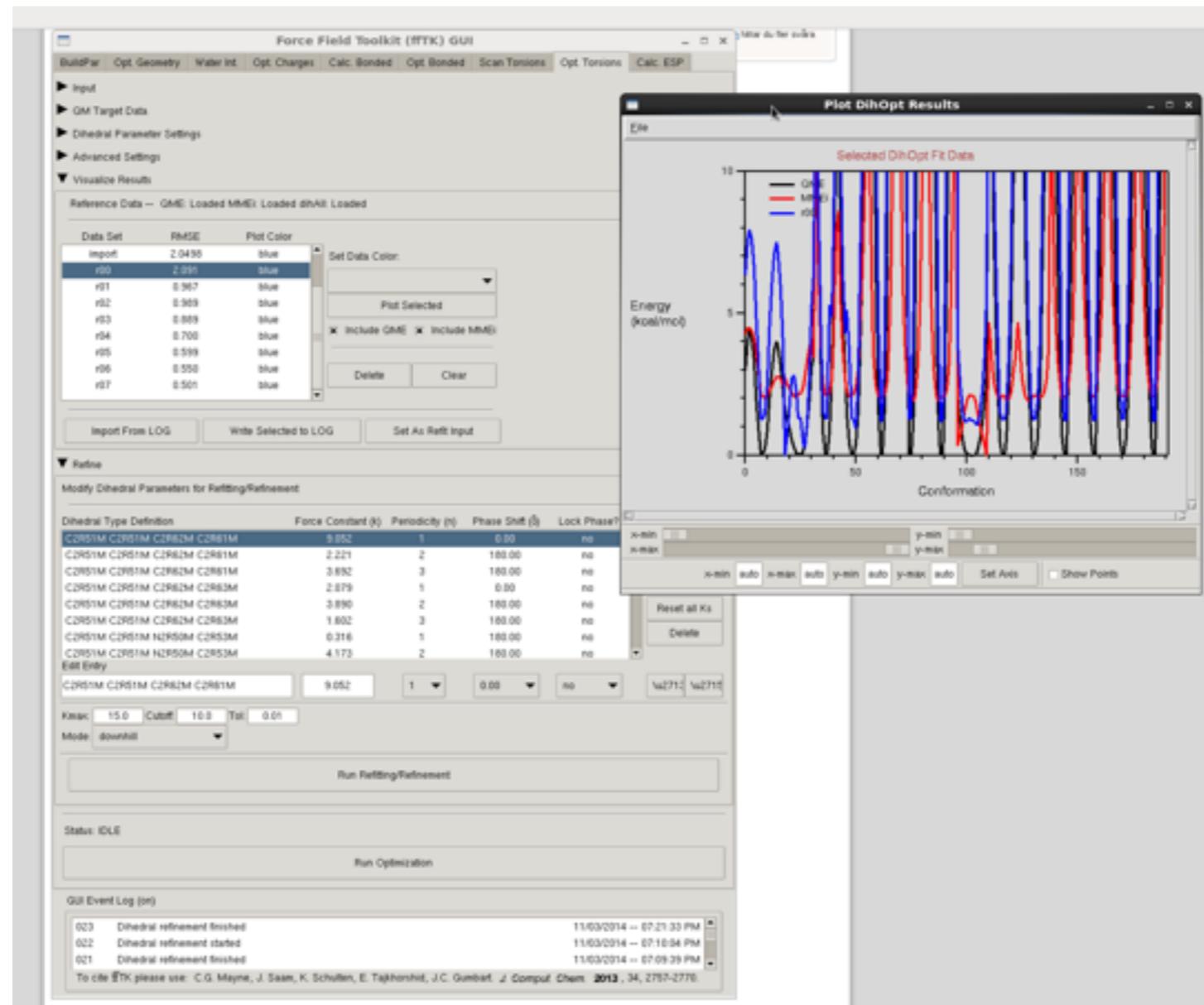
multiplicity **phase**

$$K_{\phi}(1 + \cos(n\phi - \delta))$$

Fitting of Dihedrals

First fit is not great
but better than the starting fit

QM PES: black
First fit: blue
Starting fit: red



Fitting of Dihedrals

After 7 iterations the fit is much better

Force Field Toolkit (ffTK) GUI

BuildPar Opt. Geometry Water Int. Opt. Charges Calc. Bonded Opt. Bonded Scan Torsions

Input
QM Target Data
Dihedral Parameter Settings
Advanced Settings
Visualize Results

Reference Data -- GME: Loaded MME: Loaded dhAll: Loaded

Data Set	RMSE	Plot Color
import	2.0498	blue
r00	2.091	blue
r01	0.967	blue
r02	0.989	blue
r03	0.689	blue
r04	0.700	blue
r05	0.539	blue
r06	0.550	blue
r07	0.501	blue

Set Data Color:
Plot Selected
 Include GME Include MME
Delete Clear

Input From LOG Write Selected to LOG Set As Refit Input

Refine

Modify Dihedral Parameters for Refitting/Refinement

Dihedral Type Definition	Force Constant (k)	Periodicity (n)	Phase Shift (ϕ)	Lock Phaser?
C2R51M C2R51M C2R62M C2R61M	9.052	1	0.00	no
C2R51M C2R51M C2R62M C2R61M	2.221	2	180.00	no
C2R51M C2R51M C2R62M C2R61M	3.692	3	180.00	no
C2R51M C2R51M C2R62M C2R63M	2.079	1	0.00	no
C2R51M C2R51M C2R62M C2R63M	3.890	2	180.00	no
C2R51M C2R51M C2R62M C2R63M	1.802	3	180.00	no
C2R51M C2R51M N2R50M C2R53M	0.316	1	180.00	no
C2R51M C2R51M N2R50M C2R53M	4.173	2	180.00	no

Edit Entry
C2R51M C2R51M C2R62M C2R61M 9.052 1 0.00 no μ 271: μ 271E

Kmax: 15.0 Cutoff: 10.0 Tol: 0.01
Mode: downhill

Run Refitting/Refinement

Status: IDLE

Run Optimization

GUI Event Log (on)

```
023 Dihedral refinement finished 11/03/2014 -- 07:21:33 PM
022 Dihedral refinement started 11/03/2014 -- 07:10:04 PM
021 Dihedral refinement finished 11/03/2014 -- 07:09:39 PM
```

To cite ffTK please use: C.G. Mayne, J. Saam, K. Schulten, E. Tajkhorshid, J.C. Gumbart. *J. Comput. Chem.* **2013**, *34*, 2757-2770.

Plot DihOpt Results

Selected DihOpt Fit Data

Energy (kcal/mol)

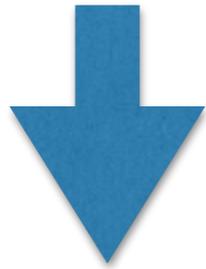
Conformation

Legend: GME (black line), r07 (blue line)

Plot controls: x-min auto x-max auto y-min auto y-max auto Set Axis Show Points

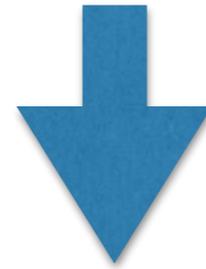
Two Approaches to Fitting the Dihedrals

Several multiplicities
and free phase



Pro: very good fit of QM PES
Cons: possible incorrect behavior
multiple sets of force constants

One multiplicity and
locked phase

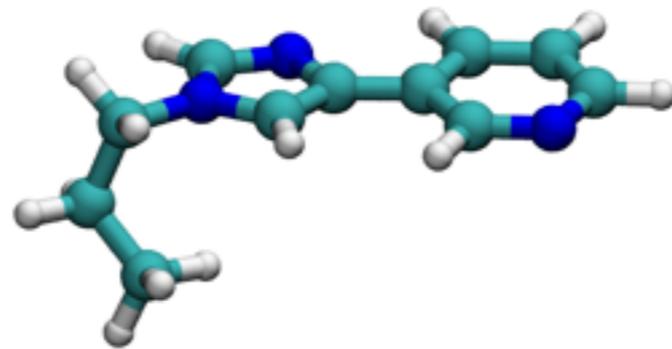


Pros: limits incorrect behavior,
sets of force constants
Con: fit to QM PES not always
possible

In practice a tradeoff is needed!

Example of Overfitting

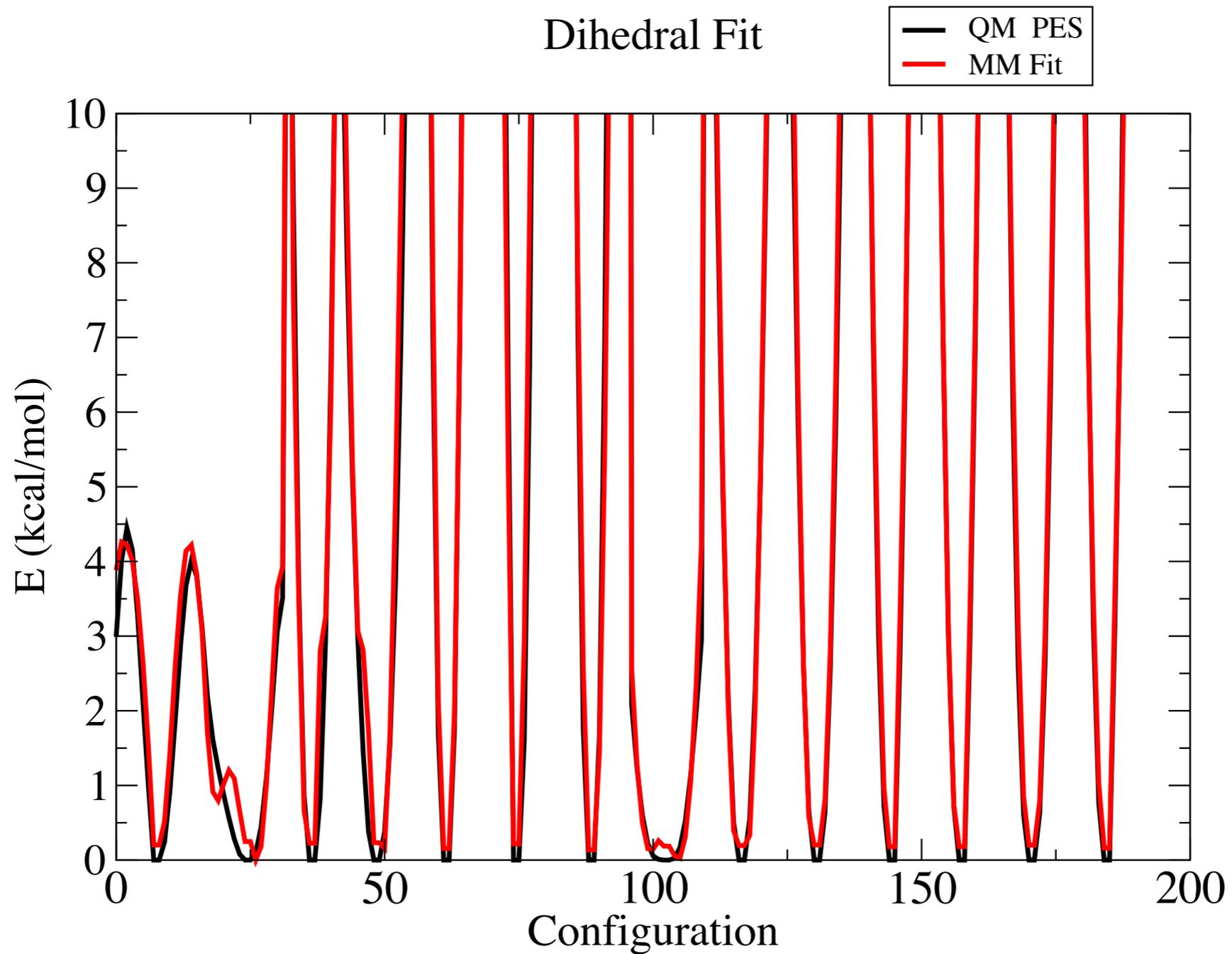
imidazole-pyrridine moiety of antibiotic telithromycin



Example of Overfitting

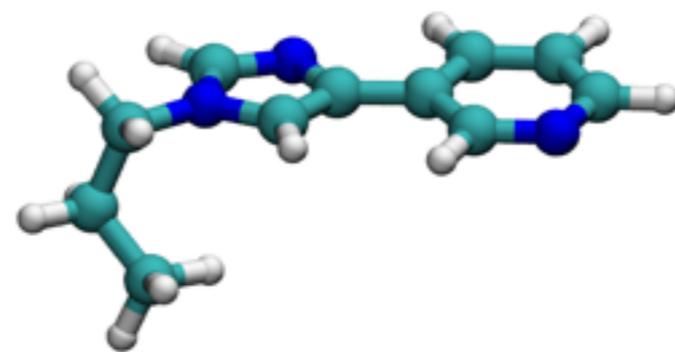
imidazole-pyrridine moiety of antibiotic telithromycin

3 multiplicities, free phase



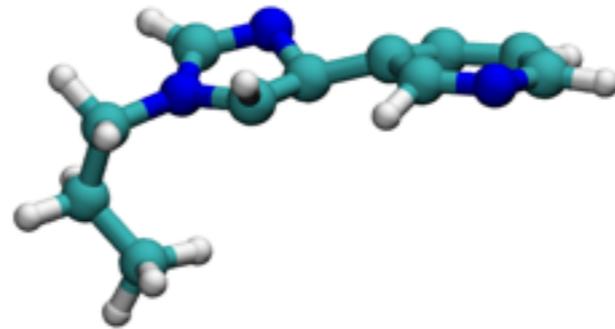
Example of Overfitting

imidazole-pyrridine moiety of antibiotic telithromycin



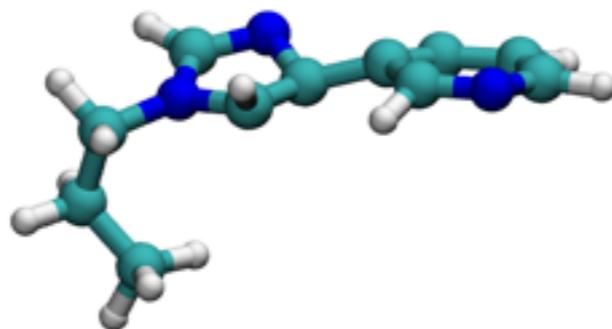
Example of Overfitting

imidazole-pyrridine moiety of antibiotic telithromycin



Example of Overfitting

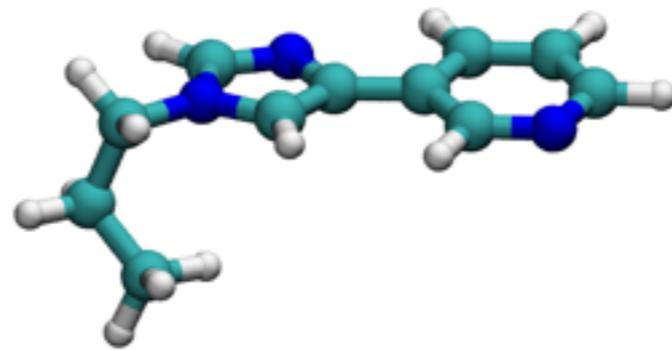
imidazole-pyrridine moiety of antibiotic telithromycin



Using too many dihedral multiplicities
can lead to distortion of a planar molecule!

Example of Overfitting

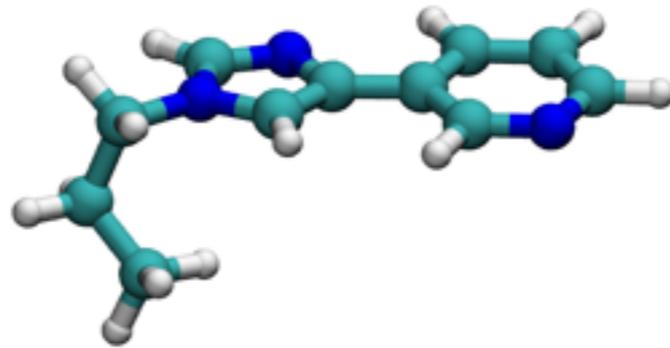
imidazole-pyrridine moiety of antibiotic telithromycin



Example of Overfitting

imidazole-pyrridine moiety of antibiotic telithromycin

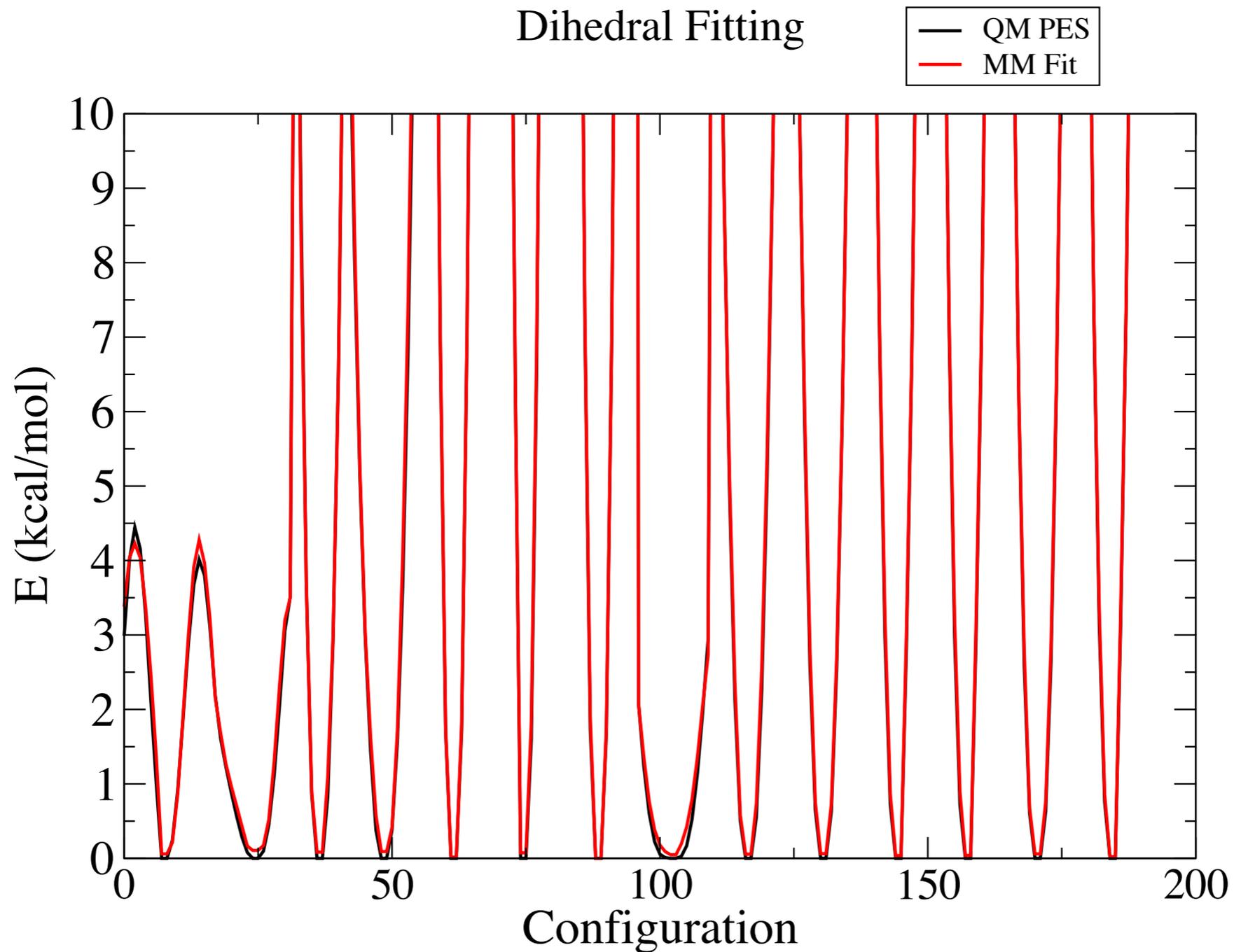
planar dihedrals have multiplicity 2 and phase 180



Example of Overfitting

imidazole-pyrridine moiety of antibiotic telithromycin

planar dihedrals have multiplicity 2 and phase 180

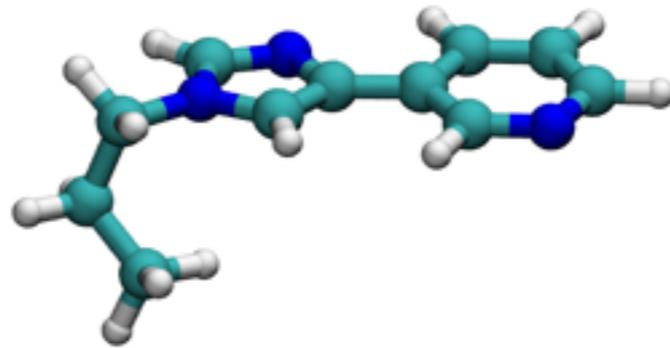


The fit looks even better!

Example of Overfitting

imidazole-pyrridine moiety of antibiotic telithromycin

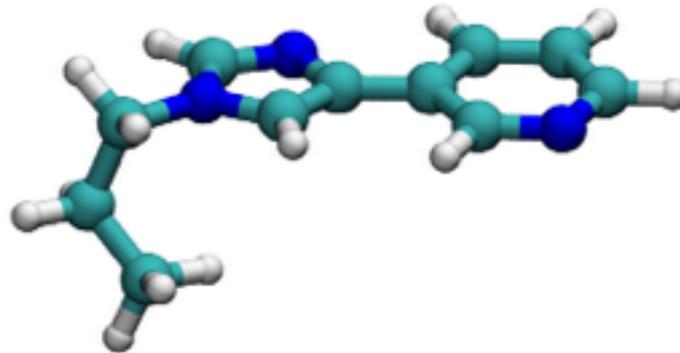
planar dihedrals have multiplicity 2 and phase 180



Example of Overfitting

imidazole-pyrridine moiety of antibiotic telithromycin

planar dihedrals have multiplicity 2 and phase 180

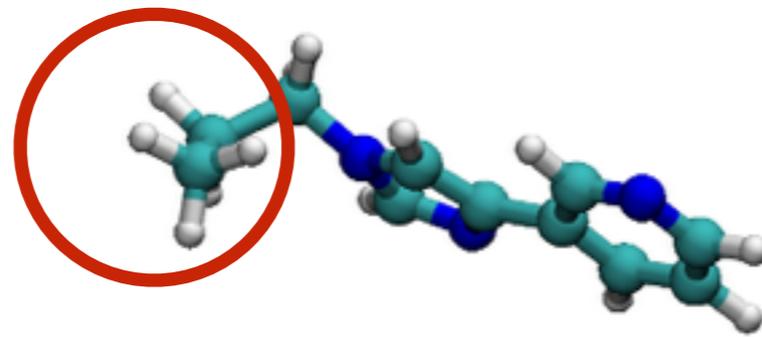


Planarity is maintained!

Example of Overfitting

imidazole-pyrridine moiety of antibiotic telithromycin

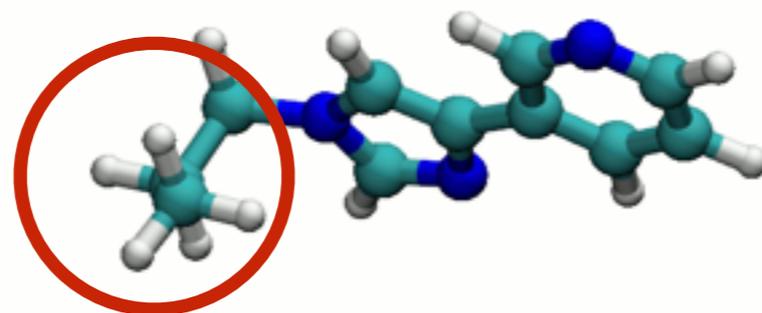
Problems persist
eclipsed conformation of the alkane part



Example of Overfitting

imidazole-pyrridine moiety of antibiotic telithromycin

Problems persist
eclipsed conformation of the alkane part



Restraining phase of CH dihedrals to 0 prevents
eclipsed conformations

How to know what terms to include?

[Back to CGenFF main page](#)

CGenFF Frequently Asked Questions

Contents

- [Technical questions](#)
 - [How do I compile CHARMM with CGenFF support?](#)
 - [What should I do if I get "LEVEL -4 WARNING FROM <RTFRDR> - LIMIT EXCEEDED"?](#)
 - [What should I do if I get "LEVEL -3 WARNING FROM <PARRDR> - Maximum no. of dihedrals reached"?](#)
- [Using CGenFF](#)

How can dihedral contributions cancel out?

Why does a wind turbine or a propeller with 2 or 3 blades not wobble?

There are a number of common cases in which dihedral contributions cancel out:

- If a dihedral involves an sp^2 center as one of the inner atoms, and both substituents on this center are identical or have identical dihedrals, all terms with an odd multiplicity will cancel out.
- If a dihedral involves an sp^3 center as one of the inner atoms, and all three substituents on this center are identical or have identical dihedrals, all terms with a multiplicity that is not a multiple of 3 (ie. all terms other than 3-fold and 6-fold) will cancel out.
- Consequence 1: if both of the above conditions are satisfied (example: methyl rotation in toluene), only the 6-fold term will *not* cancel out.
- Consequence 2: if the substituents are not identical but some of their dihedral terms have the same phase and multiplicity, there may be partial cancellation and some of the terms can be omitted. (In practice, one would typically choose to omit H-X-X-H terms because these are more prone to transferability problems.)

All these observations follow from the expression for the dihedral energy:

<http://mackerell.umaryland.edu/~kenno/cgenff/faq.html>

Conclusions

Find Missing Parameters

Geometry Optimization (QM)

Water Interaction En. (QM)

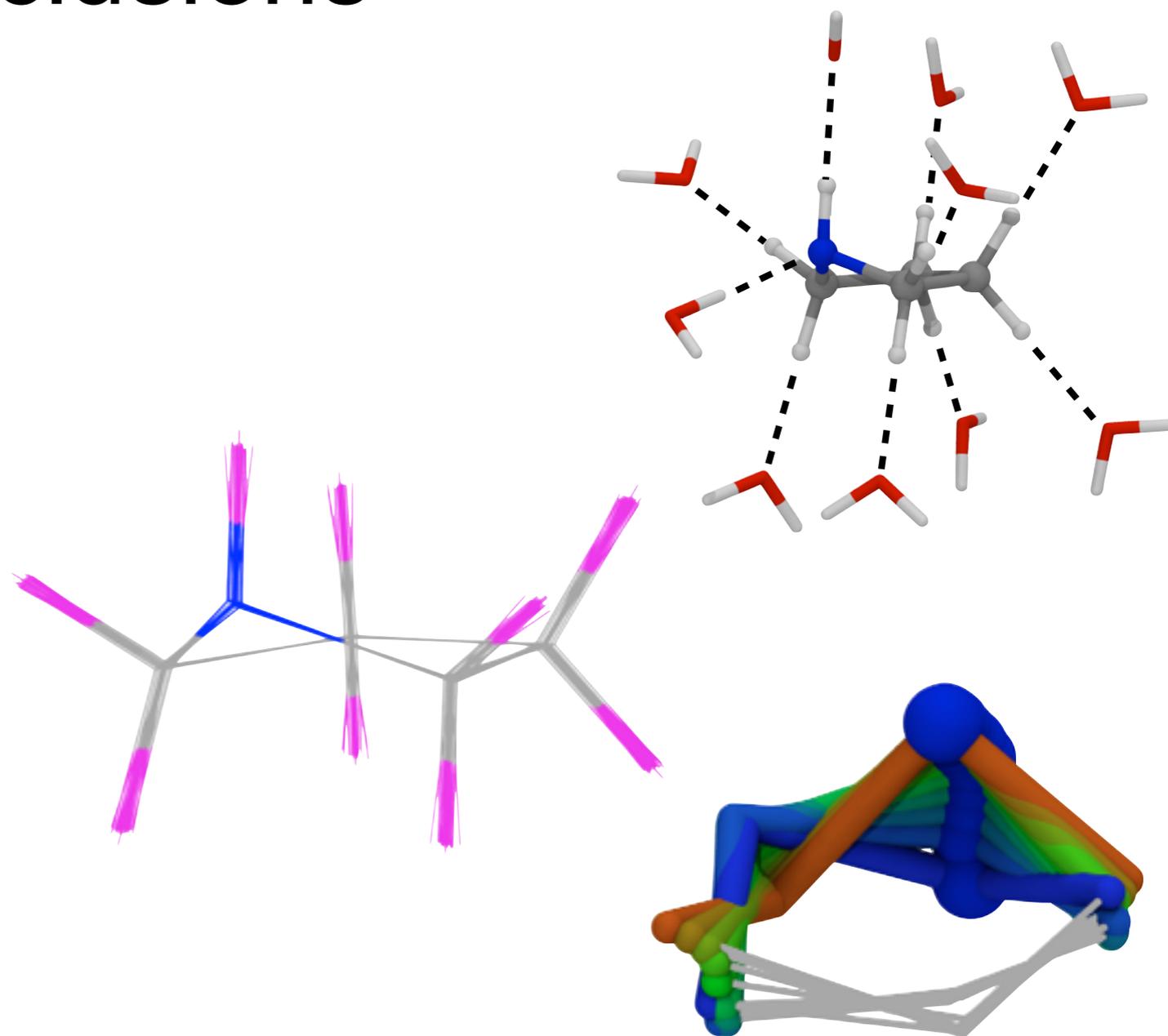
Charge Optimization

Hessian Calculation (QM)

Bond & Angle Optimization

Torsion Scan (QM)

Torsion Optimization



ffTK:

- 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

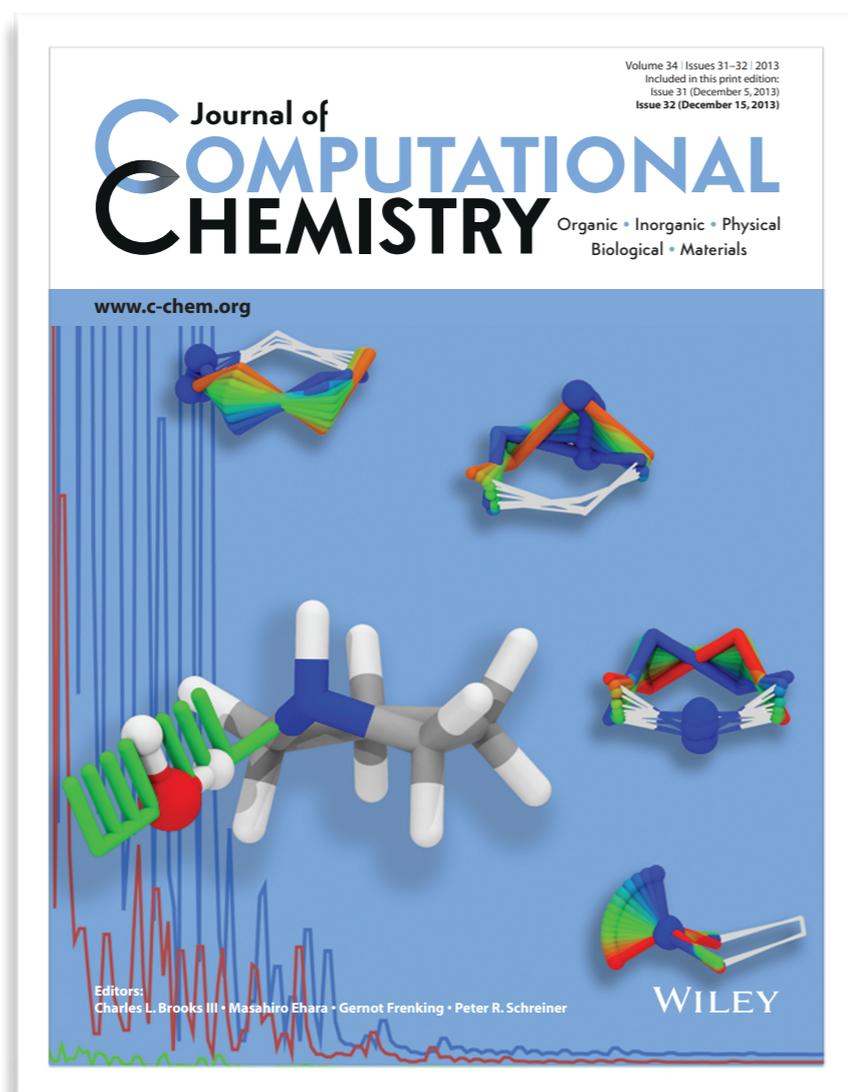
Support multiple QM packages

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?