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# profilerTools

## User Manual

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*Corresponding to Version 1.0*

MSSM Group  
Maintained by Yan M. H. Gonçalves



## Citation Information

In the absence of a scientific publication, we kindly ask you to cite this manual if the `profilerTools` suite was helpful in achieving your results, referring to it as

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## Contact

For bug reports or other software-related questions, send an e-mail to [yanmarques@gmail.com](mailto:yanmarques@gmail.com). More information about our research group can be found on the webpage <https://labmmol.iq.ufrj.br/mssm>.

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# Chapter 1

## Molecular Mechanics and Energy Minimization

In `profilerTools`, molecular-mechanics energies and forces are calculated using custom code which depends only on standard Python libraries and `numpy`. In this chapter, we give details about the computation of all quantities which directly involve these calculations. First, we report all force-field functional forms available in the suite. After that, we give the expressions for the calculation of forces. We then describe the energy minimization algorithms implemented in the programs. Finally, we define the central object of the molecular-mechanics calculations of `profilerTools`, namely, the torsional scan and its corresponding energy profile.

Considering a system of  $N$  particles, the following notation and definitions will be used for mathematical and physical quantities whenever convenient:

- $\mathbf{u} \cdot \mathbf{v}$   
Dot product of vectors  $\mathbf{u}$  and  $\mathbf{v}$ .
- $\mathbf{u} \times \mathbf{v}$   
Cross product of vectors  $\mathbf{u}$  and  $\mathbf{v}$ .
- $\mathbf{r}_i$   
Position of particle  $i$ .
- $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$   
Displacement from particle  $j$  to particle  $i$ .
- $r_{ij} = \sqrt{\mathbf{r}_{ij} \cdot \mathbf{r}_{ij}}$   
Distance between particle  $i$  and particle  $j$ .
- $\theta_{ijk} = \arccos \frac{\mathbf{r}_{ij} \cdot \mathbf{r}_{kj}}{r_{ij} r_{kj}}$   
Angle involving particles  $i$ ,  $j$  and  $k$ .
- $\phi_{ijkl} = \text{sign}(\mathbf{r}_{ij} \cdot \mathbf{r}_{nk}) \arccos \left( \frac{\mathbf{r}_{mj} \cdot \mathbf{r}_{nk}}{r_{mj} r_{nk}} \right)$ , with  $\mathbf{r}_{mj} = \mathbf{r}_{ij} \times \mathbf{r}_{kj}$  and  $\mathbf{r}_{nk} = \mathbf{r}_{kj} \times \mathbf{r}_{kl}$   
Dihedral angle involving particles  $i$ ,  $j$ ,  $k$  and  $l$ .
- $\mathbf{r}(t_n) = (\mathbf{r}_1(t_n), \mathbf{r}_2(t_n) \dots \mathbf{r}_N(t_n))$   
Configuration at the  $n$ -th step of the energy-minimization algorithm.
- $\mathbf{f}(t_n) = (\mathbf{f}_1(t_n), \mathbf{f}_2(t_n) \dots \mathbf{f}_N(t_n))$   
Configuration of the forces at the  $n$ -th step of the energy-minimization algorithm.

### 1.1 Force-field Functional Forms

#### 1.1.1 Bond stretching

The following functional forms are supported for the calculation of the energies and forces associated with a bond-stretching degree of freedom:<sup>1,2</sup>

- *Harmonic*  
Potential energy form:

$$\begin{aligned} V(r_{ij}; k_b^h, b_0) &= \frac{1}{2} k_b^h (r_{ij} - b_0)^2 \quad , \\ \frac{\partial V(r_{ij}; k_b^h, b_0)}{\partial r_{ij}} &= k_b^h (r_{ij} - b_0) \quad , \end{aligned} \tag{1.1.1}$$

— *Quartic*

Potential energy form:

$$\begin{aligned}
V(r_{ij}; k_b^q, b_0) &= \frac{1}{4} k_b^q (r_{ij}^2 - b_0^2)^2 \quad , \\
\frac{\partial V(r_{ij}; k_b^q, b_0)}{\partial r_{ij}} &= r_{ij} k_b^q (r_{ij}^2 - b_0^2) \quad ,
\end{aligned}
\tag{1.1.2}$$

where  $V(r_{ij})$  is the potential energy term for the bond between particles  $i$  and  $j$ .

**1.1.2 Bond-angle stretching**

The following functional forms are supported for the calculation of the energies and forces associated with a bond-angle stretching degree of freedom:<sup>1,2</sup>

— *Harmonic*

Potential energy form:

$$\begin{aligned}
V(\theta_{ijk}; k_a^h, \theta_0) &= \frac{1}{2} k_a^h (\theta_{ijk} - \theta_0)^2 \quad , \\
\frac{\partial V(\theta_{ijk}; k_a^h, \theta_0)}{\partial \theta_{ijk}} &= k_a^h (\theta_{ijk} - \theta_0) \quad ,
\end{aligned}
\tag{1.1.3}$$

— *Cosine-harmonic*

Potential energy form:

$$\begin{aligned}
V(\theta_{ijk}; k_a^c, \theta_0) &= \frac{1}{2} k_a^c (\cos \theta_{ijk} - \cos \theta_0)^2 \quad , \\
\frac{\partial V(\theta_{ijk}; k_a^c, \theta_0)}{\partial \theta_{ijk}} &= -k_a^c \sin \theta_{ijk} (\cos \theta_{ijk} - \cos \theta_0) \quad ,
\end{aligned}
\tag{1.1.4}$$

— *Urey-Bradley*

Potential energy form:

$$\begin{aligned}
V(\theta_{ijk}, r_{ik}; k_a^{ub}, \theta_0, k_{13}^{ub}, b_{13}^{ub}) &= \frac{1}{2} k_a^{ub} (\theta_{ijk} - \theta_0)^2 + \frac{1}{2} k_{13}^{ub} (r_{ik} - b_{13}^{ub})^2 \quad , \\
\frac{\partial V(\theta_{ijk}, r_{ik}; k_a^{ub}, \theta_0, k_{13}^{ub}, b_{13}^{ub})}{\partial \theta_{ijk}} &= k_a^{ub} (\theta_{ijk} - \theta_0) \quad , \\
\frac{\partial V(\theta_{ijk}, r_{ik}; k_a^{ub}, \theta_0, k_{13}^{ub}, b_{13}^{ub})}{\partial r_{ik}} &= k_{13}^{ub} (r_{ik} - b_{13}^{ub}) \quad ,
\end{aligned}
\tag{1.1.5}$$

where  $V(\theta_{ijk}, [r_{ik}])$  is the potential energy term for the angle involving particles  $i$ ,  $j$  and  $k$ . Note that the Urey-Bradley form introduces dependence on an additional degree of freedom, the distance  $r_{ik}$ , which is treated as a harmonic bond between particles  $i$  and  $k$ .

**1.1.3 Proper dihedral-angle torsion**

The following functional forms are supported for the calculation of the energies and forces associated with a proper dihedral-angle torsion degree of freedom:<sup>1,2</sup>

— *Standard periodic*

Potential energy form:

$$\begin{aligned}
V(\phi_{ijkl}; \{k_{d,m}^s, \phi_{0,m}\}_{m=1..6}) &= \sum_{m=1}^6 k_{d,m}^s (1 + \cos \phi_{0,m} \cos m\phi_{ijkl}) \quad , \\
\frac{\partial V(\phi_{ijkl}; \{k_{d,m}^s, \phi_{0,m}\}_{m=1..6})}{\partial \phi_{ijkl}} &= - \sum_{m=1}^6 m k_{d,m}^s \cos \phi_{0,m} \sin m\phi_{ijkl} \quad ,
\end{aligned}
\tag{1.1.6}$$

with  $\phi_{0,m} = 0, \pi$ .

— *Ryckaert-Bellemans*

Potential energy form:

$$V(\phi_{ijkl}; \{c_m\}_{m=0..5}) = \sum_{m=0}^5 c_m \cos^m(\phi_{ijkl} - \pi) \quad , \quad (1.1.7)$$

$$\frac{\partial V(\phi_{ijkl}; \{c_m\}_{m=0..5})}{\partial \phi_{ijkl}} = \sum_{m=1}^5 m c_m \sin \phi_{ijkl} \cos^{m-1}(\phi_{ijkl} - \pi) \quad ,$$

— *Fourier*

Potential energy form:

$$V(\phi_{ijkl}; \{f_m\}_{m=1..4}) = \frac{1}{2} \sum_{m=1}^4 f_m [1 + (-1)^{m+1} \cos m\phi_{ijkl}] \quad , \quad (1.1.8)$$

$$\frac{\partial V(\phi_{ijkl}; \{f_m\}_{m=1..4})}{\partial \phi_{ijkl}} = \frac{1}{2} \sum_{m=1}^4 m f_m (-1)^m \sin m\phi_{ijkl} \quad ,$$

Internally, this potential is computed as a Ryckaert-Bellemans potential with

$$\begin{aligned} c_0 &= f_2 + \frac{1}{2}(f_1 + f_3) \\ c_1 &= \frac{1}{2}(-f_1 + 3f_3) \\ c_2 &= -f_2 + 4f_4 \\ c_3 &= -2f_3 \\ c_4 &= -4f_4 \\ c_5 &= 0 \end{aligned}$$

— *Harmonic restraint*

Potential energy form:

$$V(\phi_{ijkl}; k_d^r, \phi_0) = \frac{1}{2} k_d^r (\phi_{ijkl} - \phi_0)^2 \quad , \quad (1.1.9)$$

$$\frac{\partial V(\phi_{ijkl}; k_d^r, \phi_0)}{\partial \phi_{ijkl}} = k_d^r (\phi_{ijkl} - \phi_0) \quad ,$$

where  $V(\phi_{ijkl})$  is the potential energy term for the proper dihedral angle involving particles  $i, j, k$  and  $l$ .

#### 1.1.4 Improper dihedral-angle bending

The following functional forms are supported for the calculation of the energies and forces associated with an improper dihedral-angle bending degree of freedom:<sup>1,2</sup>

— *Harmonic*

Potential energy form:

$$V(\phi_{ijkl}; k_i^h, \phi_0) = \frac{1}{2} k_i^h (\phi_{ijkl} - \phi_0)^2 \quad , \quad (1.1.10)$$

$$\frac{\partial V(\phi_{ijkl}; k_i^h, \phi_0)}{\partial \phi_{ijkl}} = k_i^h (\phi_{ijkl} - \phi_0) \quad ,$$

— *Periodic*

Potential energy form:

$$V(\phi_{ijkl}; k_i^p, \phi_0, m) = k_i^p (1 + \cos \phi_0 \cos m\phi_{ijkl}) \quad , \quad (1.1.11)$$

$$\frac{\partial V(\phi_{ijkl}; k_i^p, \phi_0, m)}{\partial \phi_{ijkl}} = -m k_i^p \cos \phi_0 \sin m\phi_{ijkl} \quad ,$$

with  $\phi_0 = 0, \pi$ .

where  $V(\phi_{ijkl})$  is the potential energy term for the improper dihedral angle involving particles  $i, j, k$  and  $l$ .

### 1.1.5 Nonbonded interactions

#### Standard interactions

The nonbonded interactions are calculated for every pair of non-excluded particles, without applying any type of cutoff-based truncation. The electrostatic and van der Waals interactions are calculated based on the following functional forms, respectively:<sup>1,2</sup>

— *Coulomb*

$$V(r_{ij}; q_i, q_j) = \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \quad , \quad (1.1.12)$$

$$\frac{\partial V(r_{ij}; q_i, q_j)}{\partial r_{ij}} = -\frac{q_i q_j}{4\pi\epsilon_0 r_{ij}^2} \quad ,$$

— *Lennard-Jones*

$$V(r_{ij}; C_{6,ij}, C_{12,ij}) = \frac{C_{12,ij}}{r_{ij}^{12}} - \frac{C_{6,ij}}{r_{ij}^6} \quad , \quad (1.1.13)$$

$$\frac{\partial V(r_{ij}; C_{6,ij}, C_{12,ij})}{\partial r_{ij}} = -\frac{6}{r_{ij}^8} \left( \frac{2C_{12,ij}}{r_{ij}^6} - C_{6,ij} \right) \quad ,$$

where the interaction between particles  $i$  and  $j$  is considered.

When the pair-specific  $C_{12,ij}$  and  $C_{6,ij}$  Lennard-Jones parameters are not explicitly defined in the topology they are obtained from atomic counterparts, using one of the following mixing rules:

— *Geometric*

$$C_{6,ij} = \sqrt{C_{6,i} C_{6,j}} \quad , \quad C_{12,ij} = \sqrt{C_{12,i} C_{12,j}} \quad (1.1.14)$$

— *Lorentz-Berthelot*

$$C_{6,ij} = \frac{C_{6,i} C_{6,j}}{2^6 \sqrt{C_{12,i} C_{12,j}}} \left[ \left( \frac{C_{12,i}}{C_{6,i}} \right)^{1/6} + \left( \frac{C_{12,j}}{C_{6,j}} \right)^{1/6} \right]^6 \quad (1.1.15)$$

$$C_{12,ij} = \frac{C_{6,i} C_{6,j}}{2^{12} \sqrt{C_{12,i} C_{12,j}}} \left[ \left( \frac{C_{12,i}}{C_{6,i}} \right)^{1/6} + \left( \frac{C_{12,j}}{C_{6,j}} \right)^{1/6} \right]^{12} \quad .$$

Some force fields are specified in terms of the  $\sigma$ - $\epsilon$  representation of the Lennard-Jones potential:

— *Lennard-Jones ( $\sigma$ - $\epsilon$ )*

$$V(r_{ij}; \sigma_{ij}, \epsilon_{ij}) = 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] \quad , \quad \sigma_{ij} = (C_{12,ij}/C_{6,ij})^{1/6} \quad , \quad \epsilon_{ij} = C_{6,ij}^2/4C_{12,ij} \quad (1.1.16)$$

with corresponding mixing rules

— *Geometric*

$$\sigma_{ij} = \sqrt{\sigma_i \sigma_j} \quad , \quad \epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j} \quad (1.1.17)$$

— *Lorentz-Berthelot*

$$\sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j) \quad , \quad \epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j} \quad . \quad (1.1.18)$$

When this is the case, the nonbonded parameters are internally converted to the  $C_6$ - $C_{12}$  representation, with which all molecular-mechanics calculations are performed.

#### 1–4 interactions

The interactions of pairs of particles that are identified as sharing a third-neighbor relationship (1–4 interactions) are treated in a different manner. First, all 1–4 Coulomb interactions are scaled down from their standard values by a common factor  $f_{QQ}$  as

$$V(r_{ij}; q_i, q_j) = f_{QQ} \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \quad , \quad 0 \leq f_{QQ} \leq 1 \quad . \quad (1.1.19)$$



For the 1–4 Lennard-Jones interactions, the same Lennard-Jones potential form is used, but with a special set of parameters  $CS_{6,ij}$ ,  $CS_{12,ij}$ :

$$V(r_{ij}; CS_{6,ij}, CS_{12,ij}) = \frac{CS_{12,ij}}{r_{ij}^{12}} - \frac{CS_{6,ij}}{r_{ij}^6} \quad (1.1.20)$$

For the  $\sigma$ - $\epsilon$  representation, the same observations as the standard interactions apply.

When the 1–4 pair-specific nonbonded parameters  $CS_{6,ij}$ ,  $CS_{12,ij}$  (or their  $\sigma_{S,ij}$ ,  $\epsilon_{S,ij}$  equivalents) are not explicitly defined in the topology they are obtained from atomic parameters in one of two ways. The first is more common and establishes a simple mathematical rule for computing them. The second is more uncommon (but is used *e.g.* in GROMOS force fields) and relies on defining additional atomic Lennard-Jones parameters to use exclusively with 1–4 interactions.

- First strategy (*fudge*): Scale down the standard atomic parameters  $C_{6,\alpha}$ ,  $C_{12,\alpha}$  ( $\alpha = i, j$ ) by a common factor  $f_{LJ}$ , obtaining 1–4 atomic parameters  $CS_{6,\alpha} = f_{LJ}C_{6,\alpha}$  and  $CS_{12,\alpha} = f_{LJ}C_{12,\alpha}$  ( $\alpha = i, j$ ). After that, proceed as usual, obtaining the 1–4 pair parameters  $CS_{12,ij}$  and  $CS_{6,ij}$  *via* mixing rule from  $CS_{6,\alpha}$ ,  $CS_{12,\alpha}$  ( $\alpha = i, j$ ) and computing the scaled-down potential energy:

$$V(r_{ij}; C_{6,ij}, C_{12,ij}) = \frac{CS_{12,ij}}{r_{ij}^{12}} - \frac{CS_{6,ij}}{r_{ij}^6} = f_{LJ} \left( \frac{C_{12,ij}}{r_{ij}^{12}} - \frac{C_{6,ij}}{r_{ij}^6} \right) \quad , \quad 0 \leq f_{LJ} \leq 1 \quad (1.1.21)$$

- Second strategy (*atomic*): Instead of using a fixed factor  $f_{LJ}$  to modify the atomic parameters, specify an independent additional set of atomic parameters  $CS_{6,\alpha}$  and  $CS_{12,\alpha}$  ( $\alpha = i, j$ ) which are exclusive to 1–4 interactions. The 1–4 pair parameters  $CS_{12,ij}$  and  $CS_{6,ij}$  are then obtained *via* mixing rule from  $CS_{6,\alpha}$ ,  $CS_{12,\alpha}$  ( $\alpha = i, j$ ), resulting in a pair-specific scaled-down potential energy.

### 1.1.6 Choice of Functional Forms

The functional forms used for each interaction term are selected in the input STP file via type codes. Likewise, the Lennard-Jones potential representation, mixing rule and 1–4 details are specified in this same file. For more information, read about the STP file format in Section 3.3.1.

## 1.2 Calculation of Forces

The atomic forces due to the potential energy terms reported above are obtained by computing the analytical derivatives of the corresponding expressions with respect to the atomic positions involved in the degree of freedom. They are:

- *Bond terms and nonbonded terms*

$$\mathbf{f}_\alpha = -\frac{\partial V(r_{ij})}{\partial r_{ij}} \nabla_{\mathbf{r}_\alpha} r_{ij} \quad , \quad \alpha = i, j \quad , \quad (1.2.1)$$

- *Angle terms*

$$\mathbf{f}_\alpha = -\frac{\partial V(\theta_{ijk})}{\partial \theta_{ijk}} \nabla_{\mathbf{r}_\alpha} \theta_{ijk} \quad , \quad \alpha = i, j, k \quad , \quad (1.2.2)$$

- *Dihedral terms*

$$\mathbf{f}_\alpha = -\frac{\partial V(\phi_{ijkl})}{\partial \phi_{ijkl}} \nabla_{\mathbf{r}_\alpha} \phi_{ijkl} \quad , \quad \alpha = i, j, k, l \quad , \quad (1.2.3)$$

where  $\mathbf{f}_\alpha$  is the force acting on particle  $\alpha$  and  $\nabla_{\mathbf{r}_\alpha}$  denotes the gradient with respect to the position of particle  $\alpha$ . Each expression above is the product of a straightforward uni-dimensional derivative involving the potential expression with a more complicated “geometrical” derivative. The former terms are reported in the Sections above for each functional form. The latter terms are listed below:<sup>1</sup>

- *Bond terms and nonbonded terms*

$$\begin{aligned} \nabla_{\mathbf{r}_i} r_{ij} &= +\frac{\mathbf{r}_{ij}}{r_{ij}} \\ \nabla_{\mathbf{r}_j} r_{ij} &= -\frac{\mathbf{r}_{ij}}{r_{ij}} \end{aligned} \quad (1.2.4)$$

— *Angle terms*

$$\begin{aligned}\nabla_{\mathbf{r}_i} \theta_{ijk} &= + \frac{1}{r_{ij}} \left( \frac{\mathbf{r}_{kj}}{r_{kj}} - \frac{\mathbf{r}_{ij}}{r_{ij}} \cos \theta_{ijk} \right) \\ \nabla_{\mathbf{r}_j} \theta_{ijk} &= -\nabla_{\mathbf{r}_i} \theta_{ijk} - \nabla_{\mathbf{r}_k} \theta_{ijk} \\ \nabla_{\mathbf{r}_k} \theta_{ijk} &= + \frac{1}{r_{kj}} \left( \frac{\mathbf{r}_{ij}}{r_{ij}} - \frac{\mathbf{r}_{kj}}{r_{kj}} \cos \theta_{ijk} \right)\end{aligned}\tag{1.2.5}$$

— *Dihedral terms*

$$\begin{aligned}\nabla_{\mathbf{r}_i} \phi_{ijkl} &= + \frac{r_{kj}}{r_{mj}^2} \mathbf{r}_{mj} \\ \nabla_{\mathbf{r}_j} \phi_{ijkl} &= + \left[ \frac{\mathbf{r}_{ij} \cdot \mathbf{r}_{kj}}{r_{kj}^2} - 1 \right] \nabla_{\mathbf{r}_i} \phi_{ijkl} - \frac{\mathbf{r}_{kl} \cdot \mathbf{r}_{kj}}{r_{kj}^2} \nabla_{\mathbf{r}_l} \phi_{ijkl} \\ \nabla_{\mathbf{r}_k} \phi_{ijkl} &= -\nabla_{\mathbf{r}_i} \phi_{ijkl} - \nabla_{\mathbf{r}_j} \phi_{ijkl} - \nabla_{\mathbf{r}_l} \phi_{ijkl} \\ \nabla_{\mathbf{r}_l} \phi_{ijkl} &= + \frac{r_{kj}}{r_{nk}^2} \mathbf{r}_{nk} \quad ,\end{aligned}\tag{1.2.6}$$

where

$$\mathbf{r}_{mj} = \mathbf{r}_{ij} \times \mathbf{r}_{kj} \quad , \quad \mathbf{r}_{nk} = \mathbf{r}_{kj} \times \mathbf{r}_{kl} \quad .$$

### 1.3 Energy Minimization

In this section, we briefly describe the energy minimization algorithms implemented in **profilerTools**, namely *steepest-descents* and *conjugate-gradients*. Both implementations are based on the descriptions supplied in the GROMOS user manual.<sup>1</sup>

#### 1.3.1 Steepest-descents

In the steepest-descents energy minimization algorithm, one successively updates the configuration by moving along the direction of the gradient of the potential energy over the configurational space. The  $n$ -th step of the steepest-descents energy minimization algorithm is as follows:

1. Calculate  $\mathbf{f}(t_n)$  from the configuration  $\mathbf{r}(t_n)$ .
2. Compute the next configuration from

$$\mathbf{r}(t_{n+1}) = \mathbf{r}(t_n) + \frac{\Delta x(t_n)}{\sqrt{\sum_{i=1}^N \mathbf{f}_i(t_n) \cdot \mathbf{f}_i(t_n)}} \mathbf{f}(t_n) \quad .\tag{1.3.1}$$

The initial value of the step size  $\Delta x(t_n)$  is specified in the input variable DX0. If the energy decreases in a given step  $n$ ,  $\Delta x(t_{n+1}) = \min \{1.2 \cdot \Delta x(t_n), \text{DXM}\}$ , where DXM is an input variable. If the energy increases,  $\Delta x(t_{n+1}) = 0.5 \cdot \Delta x(t_n)$ . The algorithm is terminated if the number of steps reaches the value specified in the input variable NMAX or if the (absolute) energy difference between successive steps is less than the one specified in the input variable DELE.

#### 1.3.2 Conjugate-gradients

In the conjugate-gradients energy minimization algorithm, one does not move strictly along the gradient of the potential energy over the configurational space. Instead, a search direction

$$\mathbf{s}(t_n) = \mathbf{f}(t_n) + \mathbf{s}(t_{n-1}) \frac{\sum_{i=1}^N \mathbf{f}_i(t_n) \cdot \mathbf{f}_i(t_{n-1})}{\sum_{i=1}^N \mathbf{f}_i(t_{n-1}) \cdot \mathbf{f}_i(t_{n-1})}\tag{1.3.2}$$

is defined for each step, with  $\mathbf{s}(t_0) = \mathbf{f}(t_0)$ . Let  $V|_s(s; t_n) = V(\mathbf{r}(t_n) + s \cdot \mathbf{s}(t_n))$  be the restriction of the potential energy hypersurface to this search direction and

$$v(s; t_n) = - \sum_{i=1}^N \mathbf{f}_i(\mathbf{r}(t_n) + s \cdot \mathbf{s}(t_n)) \cdot \mathbf{s}_i(t_n) \quad , \quad \mathbf{s}(t_n) = (\mathbf{s}_1(t_n), \mathbf{s}_2(t_n) \dots \mathbf{s}_N(t_n))$$

its derivative, where  $\mathbf{f}_i(\mathbf{r}(t_n) + s \cdot \mathbf{s}(t_n))$  represents the forces on particle  $i$  calculated for the configuration  $\mathbf{r}(t_n) + s \cdot \mathbf{s}(t_n)$ . In terms of these real functions, the  $n$ -th step of the algorithm involves two substeps:

1. Find a small interval  $I(t_n) = (a(t_n), b(t_n)]$  which is guaranteed to contain a local minimum of  $V|_s(s; t_n)$ .

The existence of a minimum in  $I(t_n)$  is ensured by any of the following pairs of conditions:

$$\begin{cases} v(a(t_n)) < 0 \\ V|_s(b(t_n)) \geq V|_s(a(t_n)) \end{cases} \quad \text{or} \quad \begin{cases} v(a(t_n)) < 0 \\ v(b(t_n)) \geq 0 \end{cases}$$

The loop below is used to select adequate values for  $a(t_n)$  and  $b(t_n)$ .

Starting with  $a_1(t_n) = 0$  and  $b_1(t_n) = \Delta x (\sum_{i=1}^N \mathbf{s}_i(t_n) \cdot \mathbf{s}_i(t_n))^{-1/2}$ , the  $k$ -th step is:

- a) Compute the energies and forces for the configurations  $\mathbf{r}(t_n) + a_k(t_n) \cdot \mathbf{s}(t_n)$  and  $\mathbf{r}(t_n) + b_k(t_n) \cdot \mathbf{s}(t_n)$ .
- b) Verify the terminating conditions above. If none of them are satisfied, proceed with  $a_{k+1}(t_n) = b_k(t_n)$  and  $b_{k+1}(t_n) = 2b_k(t_n)$ . Otherwise,  $a(t_n) = a_k(t_n)$  and  $b(t_n) = b_k(t_n)$ .

The step size  $\Delta x$  is obtained from the input variable DX0. The loop is terminated with an error if, at any step,  $b_{k+1}(t_n) \geq \text{DXM}$ , where DXM is an input variable.

2. Obtain an estimate  $s_m$  of the local minimum in  $I(t_n)$  based on a cubic interpolation:

$$\begin{aligned} s_m &= b - \frac{(b(t_n) - a(t_n))[W - Z + v(b(t_n))]}{v(b(t_n)) - v(a(t_n)) + 2W} \quad , \\ W &= \sqrt{Z^2 - v(a(t_n))v(b(t_n))} \quad , \\ Z &= \frac{3[V|_s(a(t_n)) - V|_s(b(t_n))]}{b(t_n) - a(t_n)} + v(a(t_n)) + v(b(t_n)) \quad . \end{aligned} \quad (1.3.3)$$

If  $V|_s(s_m) < V|_s(a(t_n))$  and  $V|_s(s_m) < V|_s(b(t_n))$ , accept the estimate as the local minimum and proceed with

$$\mathbf{r}(t_{n+1}) = \mathbf{r}(t_n) + s_m \cdot \mathbf{s}(t_n) \quad , \quad (1.3.4)$$

updating the search direction with Equation 1.3.2. Otherwise, repeat the interpolation setting  $b(t_n) = s_m$  (if  $v(s_m) \geq 0$ ) or  $a(t_n) = s_m$  (if  $v(s_m) < 0$ ).

The algorithm is terminated if the number of steps reaches the value specified in the input variable NMAX or if the energy difference between successive steps is less than the value of the input variable DELE.

## 1.4 Torsional-scan Energy Profiles

The central objects of all molecular-mechanics calculations of **profilerTools** are the torsional scan and the corresponding energy profile. We define a *torsional scan* as a sequence of concatenated molecular configurations (*i.e.* a trajectory) in which a single dihedral angle [the *reference dihedral* (RD)] is successively restrained to pre-defined values (the *torsional-scan angles*), while all other internal degrees of freedom are relaxed. In many cases, *torsional scan* may also refer to the process of obtaining these configurations. The sequence of the unrestrained potential energies of the configurations of the torsional scan is the *torsional-scan energy profile* (or simply *energy profile*). All energy profiles in **profilerTools** are shifted (*i.e.* each energy of the sequence is subtracted by the same value) so that their minimum values are equal to 0.

The torsional-scan angles  $\phi_k$  are configured in the INP file for **profilerOpt** (see Section 3.3.2) and in the command-line options for **profilerGen** (see Section 3.1.1). In practice, the torsional-scan energy profile  $\mathcal{V}_s$  for a given system  $s$  is obtained with the following scheme:

1. For each  $\phi_k$ :
  - a. Apply a dihedral restraint with a reference angle of  $\phi_k$  to the RD;
  - b. Perform a restrained energy minimization;
  - c. Compute the value of the total potential energy subtracted by the dihedral-restraint energy (*i.e.* the unrestrained potential energy), referred to as  $\mathcal{V}_{sk}$ ;
2. Subtract the unrestrained potential energies  $\mathcal{V}_{sk}$  by their minimum over the torsional scan:

$$\mathcal{V}_s = \{\mathcal{V}_{sk} - \min_k \mathcal{V}_{sk}, \quad k = 1 \dots N_K\} \quad , \quad (1.4.1)$$

where  $N_K$  is the number of torsional-scan angles.

## 1.5 Limitations

- Periodic boundary conditions are currently not taken into account. Please make sure your systems fit entirely within the central simulation box to avoid any problems.
- The nonbonded interactions are computed explicitly regardless of the distance between the interacting particles. No other scheme for computing the nonbonded interactions is currently supported.
- For a given system, only one functional form is accepted for each type of bonded interaction. For example, if one bond-stretching degree of freedom of the system is described by the harmonic form, then all of them also must be. The only exception is for proper dihedral restraints, which can be defined along with any other form of proper dihedral.

## Chapter 2

# Parameter Optimization

In this chapter, we describe the structure of the parameter optimization and how it is carried out in the context of a simple genetic algorithm (GA) method implemented in the `profilerOpt` program. It is instructive to think of the optimization in terms of three main parts:

1. The definition of the boundary conditions of the generation of trial parameters, *i.e.* setting the functional form of the torsional and Lennard-Jones terms involved in the GA (Section 2.1).
2. The application of these trial parameters in the modelling of the molecular systems of interest, whereby they acquire physical meaning as force-field parameters and their fitness can be assessed and used in the GA as feedback for the evolutionary process (Section 2.2, Section 2.4).
3. The generation and evolution of trial parameters, controlled by the details of the GA (*e.g.* crossover and mutation operators) and carried out in conformity with the items above (Section 2.5).

### 2.1 Boundary Conditions

`profilerOpt` admits a fairly flexible setup of boundary conditions for the optimized parameters. In terms of the torsional parameters, the user can select either a standard periodic or Ryckaert-Bellemans functional form, with customized summands. It is also possible to not optimize torsional parameters at all. In terms of the Lennard-Jones parameters, the user can opt on optimizing both attractive and repulsive parameters, only one of them or none of them. For example, it is possible to carry out a `profilerOpt` run where only  $CS_{12}$  and odd-multiplicity terms of a standard proper dihedral form are taken into account. The configuration of these boundary conditions is performed in the INP input file, as described in Section 3.3.2.

### 2.2 From Trial Parameters to Force-field Terms

In general, each molecular system contains several torsional and Lennard-Jones degrees of freedom, and not all of them should be modelled by the optimized parameters. In fact, for each system there is a specific list of *Optimized Dihedrals* (ODs) and *Optimized Pairs* (OPs) that convey the information of the dihedral-angle terms and 1–4 nonbonded pairs involved in the parameter optimization, *i.e.* whose force-field parameters should be replaced by the GA parameters. The specification of the OPs and ODs is performed in the STP file of each system, as described in Section 3.3.1.

### 2.3 Torsional-scan Performance Issues

The number of energy and force evaluations performed during one generation of the GA increase approximately linearly with the number of energy-minimization steps carried out in the torsional scans. For this reason, it is important to try to reduce as much as possible the duration of the energy minimizations without significantly affecting the accuracy of the optimal torsional-scan energy profile.

For `profilerOpt`, two settings of energy minimization can be configured in the INP file for carrying out the torsional scans (see Section 3.3.2). The first is the one used during the execution of the GA for every individual and every generation and is critical to performance. The second is used only once after the GA has finished to refine the torsional-scan energy profiles of the optimal individual and barely affects performance. By comparing the energy profiles obtained with these two settings, one should be able to at least estimate the errors introduced by using time-saving configurations in the first. For `profilerGen`, only one energy-minimization setting is available, configured in the command-line options (see Section 3.1.1).

## 2.4 Reference Data and Weights

The reference data used in the optimization (usually from QM torsional scans) will be referred to by the notation  $r_{sk}$ , where  $s$  identifies the system and  $k$  identifies the step of the torsional scan. They are supplied in single-column files, one for each system considered, as described in Section 3.1.2.

The relative weights  $w_{sk}$  attributed to each reference data point  $r_{sk}$  in the optimization can be customized by the user. These weights affect the optimization in the manner shown in Section 2.5.4. Full control of these values can be achieved by supplying files containing the desired weights, as described in Section 3.1.2. If these files are not supplied, the values of the weights are derived from the settings in the INP file, as described in Section 3.3.2. There are two options: uniform weights ( $w_{sk} = 1$  for all  $s, k$ ) or Boltzmann weights

$$w_{sk} = \exp(-r_{sk}/RT) \quad ,$$

where  $R$  is the universal gas constant and  $T$  is a customizable temperature. Note that it is implicitly assumed that the minimum of the reference data lies at zero for each system, *i.e.*  $\min_k r_{sk} = 0$  for all  $s$ .

## 2.5 Genetic Algorithm

In this section, we describe the main aspects of the implementation of the genetic algorithm (GA) used in the parameter optimization. In particular, we discuss the population and individual representation (Section 2.5.2), the random initialization of parameters (Section 2.5.3), the calculation of the fitness function (Section 2.5.4) and the selection of mating individuals (Section 2.5.5) and their reproduction (Section 2.5.6), with focus on the available crossover (Section 2.5.6) and mutation (Section 2.5.6) operators.

### 2.5.1 General Scheme

The computational scheme for the  $n$ -th generation of the GA reads,

1. Compute the torsional-scan energy profiles of the necessary individuals (Section 1.4).

Since this is most time-consuming task of the GA, the computation of the profiles for each individual can optionally be parallelized across several processes, as described in Section 3.1.2. Also, the profiles are stored in memory together with each individual, so those copied from the previous generation with no change in their parameters (*i.e.* elite individuals or parents that suffered no crossover or mutation) will not have their profiles re-calculated from the input trajectories.

2. Compute the weighted RMSD and fitness of each individual (Equation 2.5.2 and Equation 2.5.3).
3. If requested in this step,
  - a. Write the parameters of each individual in the TRP output file.
  - b. Write the torsional-scan energy profiles of each individual in the TRE output file.
  - c. Write the average and lowest weighted RMSD in the TRR output file.
4. If elitism is set up, copy the corresponding number  $N_{EL}$  of individuals with the largest fitnesses into the population of the  $(n + 1)$ -th generation.
5. Select the pairs of individuals for reproduction (Section 2.5.5).
6. Carry out the reproduction of each pair of parents selected above (Section 2.5.6):
  - a. Test the occurrence of crossover and, if positive, apply the crossover operator.
  - b. Test the occurrence of mutation and, if positive, apply the mutation operator.
  - c. Carry the children into the population of the  $(n + 1)$ -th generation.

The initial population is obtained randomly, as described in Section 2.5.3. The algorithm stops when the number of generations reaches the maximal value specified in the INP file (Section 3.3.2). At this point, the parameters of the best individual are written in the IFP output file, and its torsional-scan energy profiles are refined with enhanced energy minimization settings if so requested (Section 2.3).

### 2.5.2 Population

In the GA population, each  $i$ -th individual can most generally be visualized as an array of floating-point values

$$I_i = (CS_6(i), CS_{12}(i), \{k_m(i)\}_{m=1\dots 6}) \quad , \quad i = 1 \dots N_P \quad (2.5.1)$$

where  $N_P$  is the size of the population,  $CS_6, CS_{12}$  are Lennard-Jones parameters and  $\{k_m\}_{m=1\dots 6}$  are torsional parameters. If the standard dihedral representation is used, these values are the force constants  $k_{d,m}^s$  for each multiplicity  $m$  in Equation 1.1.6. If the Ryckaert-Bellemans representation is used, these values are the constants  $c_m$  for each  $(m-1)$ -th order term in Equation 1.1.7. The values of all parameters are either obtained randomly (Section 2.5.3) or result from the application of the crossover (Section 2.5.6) or mutation (Section 2.5.6) operators.

At a first glance, one might be confused by the absence of the phase-shift terms  $\phi_{0,m}^s$  of Equation 1.1.6 in the individual representation above (for the case of the standard dihedral representation). However, note that the potential energy function in Equation 1.1.6 satisfies

$$V(\phi_{ijkl}; \dots, k_{d,m'}^s, 0, \dots) = V(\phi_{ijkl}; \dots, -k_{d,m'}^s, \pi, \dots) + 2k_{d,m'}^s \quad ,$$

which implies that a phase-shift alteration in the  $m'$ -th term is physically equivalent to a change of sign in the corresponding force constant. In fact, the last term in the expression above is configuration-independent and does not affect the torsional potential energy curves. Therefore, as long as there is no restriction on the sign of the force constants, the optimization of the phase shifts is redundant and we can take  $\phi_{0,m} = 0$  deg for all individuals.\*

### 2.5.3 Parameter Randomization

Whenever random parameters for the individuals are requested (initialization/mutation), they are obtained from three individual random distributions: one for the torsional parameters, one for  $CS_6$  and one for  $CS_{12}$ . The types of distributions, the ranges of acceptable values and their mean and standard deviation are configured in the INP file, as described in Section 3.3.2. Four types of distributions are available for each of them: Uniform, LogNormal, Normal and LogUniform. In the case of the torsional parameters, after a sample within the acceptable range of values is drawn from the distribution, its sign can be reversed with a fixed probability specified in the INP file, as described in Section 3.3.2. For reasons discussed above, this probability must necessarily be non-zero.

### 2.5.4 Fitness

The *fitness* is the quantity which reflects the chance of reproduction of a given individual of the GA population. Here, it is calculated by considering the differences between the torsional-scan energy profiles of the individual and the reference-data profiles, encoding them into a real number  $\mathcal{R}$  *via* a suitable metric and finally converting this distance-like value into a fitness  $\mathcal{F}$ .

First, each individual  $I_i$  of the population is evaluated in terms of the weighted root-mean-square deviation

$$\mathcal{R}(I_i; \{w_{sk}, r_{sk}\}_k^s) = \sqrt{\frac{\sum_{s=1}^{N_S} \sum_{k=1}^{N_K} w_{sk} (\mathcal{V}_{sk}(I_i) - r_{sk})^2}{N_S \sum_{k=1}^{N_R} w_{sk}}} \quad , \quad (2.5.2)$$

where the  $w_{sk}, r_{sk}$  are the weights and reference data described in Section 2.4 and each  $\mathcal{V}_{sk}(I_i)$  is the  $k$ -th step of the energy profile  $\mathcal{V}_s(I_i)$  described in Section 1.4. This distance-like quantity is converted into a fitness value *via*

$$\mathcal{F}(I_i) = \frac{[\mathcal{R}(I_i)]^{-1}}{\sum_{j=1}^{N_P} [\mathcal{R}(I_j)]^{-1}} \quad . \quad (2.5.3)$$

The  $\mathcal{R}$  and  $\mathcal{F}$  quantities differ in terms of normalization, ordering and interpretability. The latter is normalized over the population and should be maximized in the optimization, but has no clear physical interpretation. The former is (at least *a priori*) not normalized and should be minimized, but has a very clear physical interpretation. For these reasons,  $\mathcal{F}$  is used internally in the GA as the metric of fitness, while  $\mathcal{R}$  is reported in the output files.

### 2.5.5 Selection

The selection operator  $\mathcal{S}$  is responsible for obtaining a list of  $N_S$  pairs of parents  $((s_{11}, s_{12}) \dots (s_{N_S1}, s_{N_S2}))$  from the current population  $P = (I_1 \dots I_{N_P})$ , where

$$N_S = \begin{cases} (N_P - N_{EL})/2 & \text{if } N_P - N_{EL} \text{ is even} \\ (N_P - N_{EL} + 1)/2 & \text{otherwise} \end{cases} \quad (2.5.4)$$

---

\*For a Ryckaert-Bellemans representation, a similar argument could be applied to motivate setting  $k_1 = 0$  in Equation 2.5.1 (or, equivalently,  $c_0 = 0$  in Equation 1.1.7). We do not enforce this in our code, but this behavior can be achieved by setting the input variable TORSNT[1] = 0 together with FTORS = 2 if desired.

and  $s_{ij} \in P$ . Repetition of individuals in this list (*i.e.*  $s_{ij} = s_{(ij)'}$  for  $ij \neq (ij)'$ ) is expected and, in fact, is the practical way by which the ones with large fitness are favoured in reproduction.

The selection operator is chosen *via* the INP file, as described in Section 3.3.2, and three options are available: roulette selection, rank selection and tournament selection. In all selection operators,  $2N_S$  individuals  $(s_1 \dots s_{2N_S})$ ,  $s_i \in P$  are selected from the population and then organized naturally into the pairs  $((s_{11}, s_{12}) \dots (s_{N_S1}, s_{N_S2}))$  with  $s_{11} = s_1$ ,  $s_{12} = s_2$ ,  $s_{21} = s_3$  and so on. The operators differ in how each individual  $s_i$  is selected.

### Roulette Selection

In the roulette operator, the probability that the  $j$ -th individual of the population is chosen at each selection  $s_i$ ,  $i = 1 \dots 2N_S$  is proportional to its fitness, *i.e.*

$$p_j = \frac{\mathcal{F}(I_j)}{\sum_{k=1}^{N_P} \mathcal{F}(I_k)} \quad . \quad (2.5.5)$$

### Rank Selection

In the rank operator, the probability that the  $j$ -th individual of the *sorted* population is chosen at each selection  $s_i$ ,  $i = 1 \dots 2N_S$  is inversely proportional to its position  $j$ . More specifically, assuming that the population is sorted from the individual with largest fitness to the individual with smallest fitness,

$$p_j = \frac{1}{j \sum_{k=1}^{N_P} k^{-1}} \quad . \quad (2.5.6)$$

This means that the first individual (best fitness) is two times more likely to be selected than the second individual (second-best fitness), three times more likely than the third (third-best fitness), and so on.

### Tournament Selection

In the tournament operator, each selection  $s_i$ ,  $i = 1 \dots 2N_S$  is done in two stages. First, two individuals are selected randomly from the population, with no fitness-based bias. Then, the individual with the largest fitness between the two is selected as  $s_i$ . This is equivalent to selecting an individual from the *sorted* population (as in the rank operator) with the probability that the  $j$ -th individual be selected set to

$$p_j = \frac{2N_P + 1 - 2j}{N_P^2} \quad . \quad (2.5.7)$$

## 2.5.6 Reproduction

In the reproduction stage, the  $2N_S$  parents obtained with the selection operator reproduce to generate  $2N_S$  children, out of which  $N_P - N_{EL}$  are carried over to the population of the next generation. The children are generated by (possibly) applying the crossover operator on each pair of parents and then (possibly) applying the mutation operator on each child. If  $N_P - N_{EL}$  is even, then  $2N_S = N_P - N_{EL}$  and all children are carried over to the population of the next generation. If  $N_P - N_{EL}$  is odd, then  $2N_S = N_P - N_{EL} + 1$ , and the last child generated is discarded so as to keep the population size at  $N_P$ . The following sections discuss the crossover and mutation operators in details.

### Crossover

The crossover between two parents occurs with a fixed probability specified in the INP file (Section 3.3.2). In general, the crossover operator  $\mathcal{C}$  specifies a rule to obtain the parameters of two child individuals  $I_{a,b}$  from a mix of the parameters of the two parents  $I_{1,2}$ ,

$$\begin{cases} I_1 = (CS_6^{(1)}, CS_{12}^{(1)}, \{k_m^{(1)}\}_{m=1\dots 6}) \\ I_2 = (CS_6^{(2)}, CS_{12}^{(2)}, \{k_m^{(2)}\}_{m=1\dots 6}) \end{cases} \xrightarrow{\mathcal{C}} \begin{cases} I_a = (CS_6^{(a)}, CS_{12}^{(a)}, \{k_m^{(a)}\}_{m=1\dots 6}) \\ I_b = (CS_6^{(b)}, CS_{12}^{(b)}, \{k_m^{(b)}\}_{m=1\dots 6}) \end{cases} \quad (2.5.8)$$

where each child parameter  $p^{(\alpha)}$  is obtained *via* a mixing function  $f_{p\alpha}$

$$p^{(\alpha)} = f_{p\alpha}(I_1, I_2), \quad \alpha = a, b, \quad p = CS_6^{(\alpha)}, CS_{12}^{(\alpha)}, \{k_m^{(\alpha)}\}_{m=1\dots 6} \quad .$$

The crossover operator is chosen in the INP file (Section 3.3.2), and two options are available: the arithmetic crossover and the heuristic crossover.



In the arithmetic crossover, each child parameter is obtained as the following weighted average of the parent parameters:

$$\begin{aligned} f_{pa} &= rp^{(1)} + (1-r)p^{(2)} \\ f_{pb} &= (1-r)p^{(1)} + rp^{(2)} \end{aligned} \quad (2.5.9)$$

where  $r \in [0, 1]$  is a random number obtained from a uniform distribution at the start of the crossover procedure. It is important to note from the expressions above that the child parameters are bounded by the parent parameters, since

$$\min \{p^{(1)}, p^{(2)}\} \leq p^{(a)}, p^{(b)} \leq \max \{p^{(1)}, p^{(2)}\} \quad .$$

As a consequence, the range of parameter values accessible *via* this crossover operator is bounded by the range of values defined in the randomization scheme (Section 2.5.3).

In the heuristic crossover, one child is obtained as in the arithmetic crossover, but the other child is allowed to explore the parameter space in the direction of largest fitness. More specifically, assuming  $\mathcal{F}(I_1) \geq \mathcal{F}(I_2)$ :

$$\begin{aligned} f_{pa} &= rp^{(1)} + (1-r)p^{(2)} \\ f_{pb} &= p^{(1)} + r(p^{(1)} - p^{(2)}) \end{aligned} \quad (2.5.10)$$

where  $r$  is defined as above. In this case, child  $a$  is bounded by the parents as in the arithmetic crossover, but child  $b$  is not, since

$$\begin{aligned} p^{(2)} \leq p^{(1)} \leq p^{(b)} & \text{ if } p^{(1)} \geq p^{(2)} \\ p^{(b)} \leq p^{(1)} < p^{(2)} & \text{ if } p^{(1)} < p^{(2)} \end{aligned} \quad .$$

## Mutation

The mutation of an individual occurs with the fixed probability specified in the INP file (Section 3.3.2). The mutation operator consists of three steps:

1. Choose which type of interaction is affected by the mutation. When both torsional and Lennard-Jones interactions are under optimization, either can be chosen with 50% chance. When this is not the case, the one under optimization is chosen.
2.
  - a. If torsional interactions are selected above, choose which force constant  $k_m$  (see Equation 2.5.1) is affected by the mutation. Any optimizable term (with TORSNT[I] set to 1; see Section 3.3.2) can be chosen with equal chance, while non-optimizable terms (with TORSNT[I] set to 0) cannot be chosen.
  - b. If Lennard-Jones interactions are selected above, choose whether  $CS_6$  or  $CS_{12}$  is affected by the mutation. When both terms are under optimization, either can be chosen with 50% chance. When this is not the case, the one under optimization is chosen.
3. Replace the term selected in the previous step by a random value generated according to the randomization scheme described in Section 2.5.3.

## Chapter 3

# Program Usage, Input Variables and File Formats

In this chapter, we first describe the usage of the two programs of the **profilerTools** package: **profilerGen**, used to perform torsional scans and calculate the corresponding energy profiles, and **profilerOpt**, used to optimize torsional and/or 1–4 Lennard-Jones parameters based on the reproduction of reference data of torsional-scan energy profiles. The execution of **profilerOpt** and **profilerGen** depends on several input variables and input data supplied either as command-line options or in input files with specified formats. The output data is also written to files with specified formats. In this chapter, we also describe the configuration of these input variables and the format of the input and output files.

### 3.1 Program Usage

#### 3.1.1 Performing Torsional Scans: **profilerGen**

To perform a torsional scan using **profilerGen**, the user must supply the coordinates of the system of interest, an STP file with its topology and the specification of the reference dihedral (see Section 3.3.1), and the definition of the torsional-scan angles. The coordinates can be of a single arbitrary conformation or of a trajectory corresponding to the desired torsional scan (if, for example, the user wants to refine a previously obtained scan trajectory). The user can also optionally control the settings of the energy minimization algorithm involved in the calculation of the energy profiles.

The usage of **profilerGen** is as follows (optional arguments are enclosed in square brackets):

```
/path/to/profilerGen.py
-c <COORDS>      Torsional-scan trajectory or single molecular conformation (.xyz/.gro/.g96).
-t <STP>         Special topology (STP) file.
-op PREFIX       Prefix for output files.
-dr RFRST RSTEP RLST Torsional-scan angles (deg): from RFRST to RLST with a RSTEP step.
[-dk RFCT]      Force constant for dihedral restraint (default = 5000 kJ/(mol.rad^2)).
[-min MALG]     Minimization algorithm: steepest descents (1: default) or conjugate-gradients (2).
[-dx0 DX0]     Initial step size DX0 in minimization algorithm (default = 0.05 nm).
[-dxm DXM]     Maximal step size DXM in minimization algorithm (default = 0.20 nm).
[-dele DELE]    If |En+1 - En| <= DELE, minimization stops (default = 1.0e-09).
[-nsteps NMAX]  Maximal number of steps in minimization (default = 50000).
```

The program will write the following files to disk:

- PREFIX.dat: The requested torsional-scan energy profile;
- PREFIX.xyz: Torsional-scan trajectory;
- PREFIX.full.dat: Torsional-scan energy profile split into components\* (Xmgrace-compatible);
- PREFIX\_1.dat...PREFIX\_K.dat: Energy trajectory of the minimization of each step of the torsional scan;
- PREFIX\_1.xyz...PREFIX\_K.xyz: Coordinates trajectory of the minimization of each step of the torsional scan,

where *K* is the length of the torsional scan.

For more details on the calculation of the energy profiles, see Section 1.4 and Section 1.3.

---

\*Components: total, bonds, angles, proper dihedrals, improper dihedrals, proper dihedral restraints, Lennard-Jones, Coulomb. The total potential energies are not shifted to zero.

### 3.1.2 Optimizing Parameters: profilerOpt

To perform parameter optimization using **profilerOpt**, the user has to supply starting torsional-scan trajectories of the systems of interest, the STP files containing their topologies and the specification of the reference dihedrals and optimized terms (see Section 3.3.1), the reference data to use as targets in the optimization and the input parameters file INP (Section 3.3.2).

The usage of **profilerOpt** is as follows (optional arguments are enclosed in square brackets):

```
/path/to/profilerOpt.py
-np NPROCS           Number of subprocesses spawned in parallelization.
-r <REF_1> ... <REF_S> Reference data files.
-c <COORDS_1> ... <COORDS_S> Torsional-scan trajectory files (.g96/.xyz/.gro).
-t <STP_1> ... <STP_S> Special topology files (.stp).
-i <INP>             Input file containing profilerOpt parameters (.inp).
-op PREFIX           Prefix for output files.
[-w <WEI_1> ... <WEI_S>] Weight files (default = derive weights from <INP> file).
```

where  $S$  is the number of systems. The reference (mandatory) and weight (optional) files of each system contain a single column of values where the  $k$ -th row corresponds to the  $k$ -th step of the torsional scan.

The program will write the following files to disk:

- PREFIX.ifp: Parameters and weighted RMSD of the optimal individual;
- PREFIX\_minim\_1.dat...PREFIX\_minim\_S.dat:  
Refined energy profile of each system for the optimal individual;
- PREFIX\_minim\_1.xyz...PREFIX\_minim\_S.xyz:  
Refined torsional-scan trajectory of each system for the optimal individual;
- PREFIX\_1.dat...PREFIX\_S.dat: Energy profile of each system for the optimal individual;
- PREFIX\_1.xyz...PREFIX\_S.xyz: Torsional-scan trajectory of each system for the optimal individual;
- PREFIX\_1.tre...PREFIX\_S.tre: Energy profile of each system for all individuals and generations;
- PREFIX.trp: Parameters of all individuals for all generations;
- PREFIX.trr: Average and best weighted RMSD values for all generations,

where  $S$  is the number of systems.

The refined quantities mentioned above are obtained based on enhanced energy minimization settings, as described in Section 2.3. The IFP, TRP, TRE and TRR output file formats are described in Section 3.3.

## 3.2 Input Variables

The input variables control the details of execution of the programs and are of two major types: numeric values (integer or float) and arrays of numeric values. They can be supplied either as command-line options or in an appropriate input file, depending on its kind. For example, the input variable NPROCS (number of processes for parallelization) is an integer specified in the command-line option **-np** of **profilerOpt**; the input variable LJNT (controls the optimization of Lennard-Jones terms) is an array of two integers specified in the INP input file. A complete list of input variables and their types is given in Table 3.3 (at the end of the chapter) for reference.

## 3.3 File Formats

### 3.3.1 Special Topology File (STP)

The special topology (STP) file combines the topology with the specification of the RD (Section 1.4), the ODs and the OPs (Section 2.2). Comments can be inserted after a “;” character. This file is organized into blocks, each starting with a line consisting of [ **blockname** ] (where **blockname** is the name of the block) and ending with an empty line. The structure of the STP file is based on three parts, composed by the following blocks:

1. Topology and interaction parameters:  
[ **defaults** ]; [ **atoms** ]; [ **nbpairs** ]; [ **bonds** ]; [ **angles** ]; [ **dihedrals** ].
2. Reference dihedral (RD):  
[ **refdihedral** ].
3. Optimization targets (ODs and OPs):  
[ **optdihedrals** ]; [ **optpairs** ] or [ **optatoms** ].

Table 3.1: Representation of the Lennard-Jones parameters expected in the STP file along with the corresponding mixing rule for each allowed value of `comb-rule` in the [ `defaults` ] block. See Section 1.1.5 for more details.

<code>comb-rule</code>	Representation	Mixing Rule
1	$C_6$ - $C_{12}$	Geometric
2	$\sigma$ - $\epsilon$	Lorentz-Berthelot
3	$\sigma$ - $\epsilon$	Geometric

## Topology and Interaction Parameters

Users who are familiar with the GROMACS package<sup>†</sup> will notice that the format of the STP file looks very similar to that of the GROMACS ITP file, specially in the nomenclature of the blocks of the topology part. However, the correspondence between these two file formats is not perfect. In the following, we discuss in details each of the topology blocks.

[ `defaults` ] The format of this block is similar to its correspondent in the ITP file format<sup>‡</sup>. The following variables are specified in order:

- `nbfunc`: (**Integer**) the non-bonded function type. Only the value 1 (Lennard-Jones) is supported;
- `comb-rule`: (**Integer**) the number of the combination/mixing rule and Lennard-Jones potential representation (see Table 3.1). Note that all molecular-mechanics calculations are ultimately performed in the  $C_6$ - $C_{12}$  representation, regardless of the representation expected in the STP file.
- `gen-pairs`: (**String**) the strategy of automatic obtention of 1–4 Lennard-Jones pair parameters based on the mixing rule. The allowed values are:
  - `no`: do not generate pair parameters. This requires explicitly setting the interaction parameters for all 1–4 nonbonded pairs in the [ `nbpairs` ] block;
  - `fudge`: compute the pair parameters by applying the mixing rule on the standard atomic parameters ( $C_6$ ,  $C_{12}$ ) and then scaling the results by `fudgeLJ` ( $f_{LJ}$ );
  - `atomic`: compute the pair parameters by applying the mixing rule on the 1–4 atomic parameters ( $CS_6$ ,  $CS_{12}$ ). This requires setting  $CS_6$  and  $CS_{12}$  for all atoms in the [ `atoms` ] block.
- `fudgeLJ`: (**Float**) scaling factor  $f_{LJ}$  used to obtain 1–4 Lennard-Jones pair parameters from the standard atomic parameters when `gen-pairs` is `fudge`.
- `fudgeQQ`: (**Float**) scaling factor  $f_{QQ}$  used to obtain 1–4 electrostatic pair parameters from the atomic partial charges.

For more details about the calculation of the pair parameters using the mixing rule and about the scaling factors  $f_{LJ}$  and  $f_{QQ}$ , see Section 1.1.5.

[ `atoms` ] The format of this block depends on the `gen-pairs` strategy and on `comb-rule`. If `gen-pairs` is `atomic`, each line must contain, in sequence and separated by spaces:

- Atom type (**String**)
- Lennard-Jones parameter  $C_6$  or  $\sigma$  (**Float**); see Table 3.1.
- Lennard-Jones parameter  $C_{12}$  or  $\epsilon$  (**Float**); see Table 3.1.
- 1–4 Lennard-Jones parameter  $CS_6$  or  $\sigma_S$  (**Float**); see Table 3.1.
- 1–4 Lennard-Jones parameter  $CS_{12}$  or  $\epsilon_S$  (**Float**); see Table 3.1.
- Atomic partial charge  $q$  (**Float**)

For other values of `gen-pairs`,  $CS_6$  and  $CS_{12}$  are not used and may be omitted. If they are supplied, their values are skipped when parsing the file.

<sup>†</sup>See <http://www.gromacs.org>

<sup>‡</sup>Strictly speaking, this block is in most cases imported into the ITP file from the force-field file, so it is not directly a part of the ITP file.

Table 3.2: Interaction types, interaction type codes and list of corresponding parameters for use in the topology part of the STP file.

Interaction type	Block	Code	List of parameters	Cross-reference
Nonbonded				
Standard pair	<b>nbpairs</b>	1	$C_6$ (kJ mol <sup>-1</sup> nm <sup>-6</sup> ); $C_{12}$ (kJ mol <sup>-1</sup> nm <sup>-12</sup> ) <sup>(a)</sup> $\sigma$ (nm); $\epsilon$ (kJ mol <sup>-1</sup> ) <sup>(b)</sup>	Equation 1.1.13
1-4 pair	<b>nbpairs</b>	2	$CS_6$ (kJ mol <sup>-1</sup> nm <sup>-6</sup> ); $CS_{12}$ (kJ mol <sup>-1</sup> nm <sup>-12</sup> ) <sup>(a)</sup> $\sigma_S$ (nm); $\epsilon_S$ (kJ mol <sup>-1</sup> ) <sup>(b)</sup>	Equation 1.1.20
Bonds				
Harmonic	<b>bonds</b>	1	$b_0$ (nm); $k_b^h$ (kJ mol <sup>-1</sup> nm <sup>-2</sup> )	Equation 1.1.1
Quartic	<b>bonds</b>	2	$b_0$ (nm); $k_b^q$ (kJ mol <sup>-1</sup> nm <sup>-4</sup> )	Equation 1.1.2
Angles				
Harmonic	<b>angles</b>	1	$\theta_0$ (deg); $k_a^h$ (kJ mol <sup>-1</sup> rad <sup>-2</sup> )	Equation 1.1.3
Cosine-harmonic	<b>angles</b>	2	$\theta_0$ (deg); $k_a^c$ (kJ mol <sup>-1</sup> )	Equation 1.1.4
Urey-Bradley	<b>angles</b>	5	$\theta_0$ (deg); $k_a^{ub}$ (kJ mol <sup>-1</sup> rad <sup>-2</sup> ); $b_{13}^{ub}$ (nm); $k_{13}^{ub}$ (kJ mol <sup>-1</sup> nm <sup>-2</sup> )	Equation 1.1.5
Proper dihedrals				
Standard periodic <sup>(c)</sup>	<b>dihedrals</b>	1	$\phi_{0,m}$ (deg); $k_{d,m}^s$ (kJ mol <sup>-1</sup> ); $m$	Equation 1.1.6
Ryckaert-Bellemans	<b>dihedrals</b>	3	$c_0$ ; $c_1$ ; $c_2$ ; $c_3$ ; $c_4$ ; $c_5$ (kJ mol <sup>-1</sup> )	Equation 1.1.7
Fourier	<b>dihedrals</b>	5	$f_1$ ; $f_2$ ; $f_3$ ; $f_4$ (kJ mol <sup>-1</sup> )	Equation 1.1.8
Standard periodic <sup>(d)</sup>	<b>dihedrals</b>	9	$\phi_{0,m}$ (deg); $k_{d,m}^s$ (kJ mol <sup>-1</sup> ); $m$	Equation 1.1.6
Harmonic restraint	<b>dihedrals</b>	-1	$\phi_0$ (deg); $k_d^r$ (kJ mol <sup>-1</sup> rad <sup>-2</sup> )	Equation 1.1.9
Improper dihedrals				
Harmonic	<b>dihedrals</b>	2	$\phi_0$ (deg); $k_i^h$ (kJ mol <sup>-1</sup> rad <sup>-2</sup> )	Equation 1.1.10
Periodic	<b>dihedrals</b>	4	$\phi_0$ (deg); $k_i^p$ (kJ mol <sup>-1</sup> ); $m$	Equation 1.1.11

(a): For a  $C_6$ - $C_{12}$  representation; see Table 3.1.(b): For a  $\sigma$ - $\epsilon$  representation; see Table 3.1.

(c): Using only one summand of Equation 1.1.6.

(d): Using one or more summands of Equation 1.1.6.

[ **nbpairs** ] In this block, each line describes a nonbonded pair  $a_i$ — $a_j$  and must contain, in sequence and separated by spaces, the indexes  $a_i$  (**Integer**) and  $a_j$  (**Integer**), the corresponding interaction type code (**Integer**) and, in some cases, the values of the Lennard-Jones interaction parameters listed in a specific order (see Table 3.2). The interaction parameters are only required when they cannot be inferred from the atomic parameters, *i.e.* for 1-4 nonbonded pairs when **gen-pairs** is **no**. When they are not required but nonetheless supplied, they *override* the default values derived using the mixing rule. In divergence with the ITP file format, note that *all* nonbonded pairs must be listed in this block, regardless if the atoms involved are third-neighbors or not.

[ **bonds** ] In this block, each line describes a bond  $a_i$ — $a_j$  and must contain, in sequence and separated by spaces, the indexes  $a_i$  (**Integer**) and  $a_j$  (**Integer**), the corresponding interaction type code (**Integer**) and the values of the interaction parameters listed in a specific order (see Table 3.2). Note that the format of this block is the same as its correspondent in the ITP file format, with the caveat that the interaction parameters must always be listed explicitly.

[ **angles** ] In this block, each line describes an angle  $a_i$ — $a_j$ — $a_k$  and must contain, in sequence and separated by spaces, the indexes  $a_i$  (**Integer**),  $a_j$  (**Integer**) and  $a_k$  (**Integer**), the corresponding interaction type code (**Integer**) and the values of the interaction parameters listed in a specific order (see Table 3.2). Note that the format of this block is the same as its correspondent in the ITP file format, with the caveat that the interaction parameters must always be listed explicitly.

[ **dihedrals** ] In this block, each line describes a dihedral angle  $a_i$ — $a_j$ — $a_k$ — $a_l$  and must contain, in sequence and separated by spaces, the indexes  $a_i$  (**Integer**),  $a_j$  (**Integer**),  $a_k$  (**Integer**) and  $a_l$  (**Integer**), the corresponding interaction type code (**Integer**) and the values of the interaction parameters listed in a specific order (see Table 3.2). Note that the format of this block is the same as its correspondent in the ITP file format, except that: (i) the interaction parameters must always be listed explicitly and (ii) this block also accommodates dihedral restraints. However, bear in mind that the dihedral restraints specified in this manner have no connection with the dihedral restraints used to perform the torsional scans in **profilerGen** and **profilerOpt** (except for the common functional form).

## Reference Dihedral

The reference dihedral along which to perform the torsional scans is set in the [ **refdihedral** ] block of the STP file. This block is formed by a single line containing the indexes of the four atoms of the desired dihedral angle separated by spaces. For consistency, it is required that the reference dihedral match one of the dihedral angles listed in a [ **dihedrals** ] block.

## Optimization Targets

**Dihedrals** The dihedral-angle terms affected by the optimization are specified in the [ **optdihedrals** ] block. In this block, each line describes a dihedral angle and contains the indexes of its four atoms separated by spaces. For consistency, every dihedral angle listed in this block must match one of the dihedral angles listed in a [ **dihedrals** ] block.

**1–4 Pairs** The third-neighbor nonbonded pairs affected by the optimization can be specified in two mutually exclusive ways. When optimization of specific nonbonded pairs is intended, the most effective strategy is to use the [ **optpairs** ] block, wherein each line describes a 1–4 nonbonded pair and contains the indexes of its two atoms separated by spaces. When the molecular-mechanics calculations are performed, the GA parameters override the pair parameters of all pairs listed in this block. For consistency, it is required that every listed pair must match one of the 1–4 pairs in the [ **nbpairs** ] block.

When optimization of the 1–4 Lennard-Jones parameters of an *atomtype* is intended instead (which only makes sense if **gen-pairs** is **atomic**, which is not the case for most force fields<sup>§</sup>), the [ **optatoms** ] block can be used. In this case, the indexes of the atoms of the desired atomtype are listed, separated by spaces or line breaks. When the molecular-mechanics calculations are performed, the GA parameters override the atomic parameters of all atoms listed in this block. This in turn affects (*via* mixing rule) *all* 1–4 nonbonded pair interactions involving at least one of these atoms.

### 3.3.2 Input Parameters File (INP)

The input parameters (INP) file contains the definition of the majority of the input variables of **profilerOpt**. Like the STP file, the INP file is organized into blocks, wherein input variables of similar nature are defined according to their position. Successive positions in a block are separated by spaces or by a line break, with no syntactic distinction between the two. However, the use of line breaks is recommended to separate clusters of closely related variables within each block. In the following, we go through each block in succession, giving the position, description and allowed values of the input variables. Note that a complete list of the input variables and their corresponding blocks is also given in Table 3.3.

#### [ **parameter.optimization** ]

Positions of the variables:

NTORS	NLJ	FTORS			
TORSNT[1]	TORSNT[2]	TORSNT[3]	TORSNT[4]	TORSNT[5]	TORSNT[6]
LJNT[1]	LJNT[2]				
WTEMP					

Details of the variables:

**NTORS : (Integer)** Controls optimization of torsional parameters.

Allowed values:

- 0 : do not optimize (use values from topology)
- 1 : optimize

**NLJ : (Integer)** Controls optimization of Lennard-Jones parameters.

Allowed values:

- 0 : do not optimize (use values from topology)
- 1 : optimize

**FTORS : (Integer)** Controls functional form of torsional terms.

Allowed values:

- 1 : Standard periodic dihedral
- 2 : Ryckaert-Bellemans dihedral

<sup>§</sup>To our knowledge, only GROMOS-type force fields are compatible with setting **gen-pairs** to **atomic**.

TORSNT[I] : **(Array of Integers)** Fine control of the functional form of torsional terms.

Allowed values:

- 0 : set I-th term to zero
- 1 : optimize I-th term

Array index targets:

- 1 : first summand of Equation 1.1.6 or Equation 1.1.7
- 2 : second summand of Equation 1.1.6 or Equation 1.1.7
- 3 : third summand of Equation 1.1.6 or Equation 1.1.7
- 4 : fourth summand of Equation 1.1.6 or Equation 1.1.7
- 5 : fifth summand of Equation 1.1.6 or Equation 1.1.7
- 6 : sixth summand of Equation 1.1.6 or Equation 1.1.7

LJNT[I] : **(Array of Integers)** Controls which Lennard-Jones components are optimized.

Allowed values:

- 0 : use I-th value derived from STP file
- 1 : optimize I-th term

Array index targets:

- 1 :  $CS_6$
- 2 :  $CS_{12}$

WTEMP : **(Float)** Controls weights given to reference data points when weight files are not supplied.

Allowed values:

- 0 : uniform weights
- > 0 : Boltzmann weights with temperature WTEMP (see Section 2.4)

#### [ parameter\_randomization ]

Positions of the variables:

PINV					
DIST[1]	MIN[1]	MAX[1]	MEAN[1]	STDDEV[1]	
DIST[2]	MIN[2]	MAX[2]	MEAN[2]	STDDEV[2]	
DIST[3]	MIN[3]	MAX[3]	MEAN[3]	STDDEV[3]	

Details of the variables:

PINV : **(Integer)** Probability of inverting sign of random torsional parameters.

Allowed values:

0...100 : set probability to PINV/100

DIST[I] : **(Array of Integers)** Controls types of probability distributions of random parameters.

Allowed values:

- 1 : uniform distribution
- 2 : LogNormal distribution
- 3 : normal distribution
- 4 : LogUniform distribution

Array index targets:

- 1 : torsional terms
- 2 :  $CS_6$
- 3 :  $CS_{12}$

MIN[I] : **(Array of Float)** Minimum values of random parameters.

Allowed values:

$\in \mathbb{R}$  : only accept random values larger than MIN[I]

Array index targets:

- 1 : torsional terms
- 2 :  $CS_6$
- 3 :  $CS_{12}$

MAX[I] : **(Array of Float)** Maximum values of random parameters.

Allowed values:

$\in \mathbb{R}$  : only accept random values smaller than MAX[I]

Array index targets:

- 1 : torsional terms
- 2 :  $CS_6$
- 3 :  $CS_{12}$

MEAN[I] : (**Array of Float**) Mean values of the probability distributions.

Allowed values:

$\in \mathbb{R}$  : set mean of DIST[I] to MEAN[I]; ignored for uniform and LogUniform distributions

Array index targets:

1 : torsional terms

2 :  $CS_6$

3 :  $CS_{12}$

STDDEV[I] : (**Array of Float**) Std. dev. of the probability distributions.

Allowed values:

$\in \mathbb{R}$  : set std. dev. of DIST[I] to STDDEV[I]; ignored for uniform and LogUniform distributions

Array index targets:

1 : torsional terms

2 :  $CS_6$

3 :  $CS_{12}$

Note that the uniform and LogUniform distributions are well defined by the values of MIN and MAX. For this reason, the MEAN and STDDEV values are ignored for these types of distributions.

#### [ seed ]

Positions of the variables:

SEED

Details of the variables:

SEED : (**Integer**) Random number generator seed.

Allowed values:

-1 : set random number generator seed to Python default

> 0 : set random number generator seed to SEED

#### [ genetic.algorithm ]

Positions of the variables:

POPSIZE	NGENS	
SELTTYPE	NTEL	
CRTYPE	CRRATE	MUTRATE

Details of the variables:

POPSIZE : (**Integer**) Size of the GA population.

Allowed values:

> 0 : set population size to POPSIZE

NGENS : (**Integer**) Number of generations of the GA.

Allowed values:

> 0 : set number of generations to NGENS

SELTTYPE : (**Integer**) Selection operator of the GA.

Allowed values:

1 : Roulette operator

2 : Rank operator

3 : Tournament operator

NTEL : (**Integer**) Number of elite individuals of the GA.

Allowed values:

0 : no elitism

> 0 : set number of elite individuals to NTEL

CRTYPE : (**Integer**) Crossover operator of the GA.

Allowed values:

1 : Arithmetic operator

2 : Heuristic operator

CRRATE : (**Integer**) Probability of crossover.

Allowed values:

0...100 : set probability of crossover to CRRATE/100



MUTRATE : (**Integer**) Probability of mutation.

Allowed values:

0...100 : set probability of mutation to MUTRATE/100

#### [ writetraj ]

Positions of the variables:

NSTE NSTP

Details of the variables:

NSTE : (**Integer**) Frequency of writing population energies to the TRE file.

Allowed values:

0 : do not write population energies to the TRE file

> 0 : write population energies to the TRE file every NSTE-th generation

NSTP : (**Integer**) Frequency of writing population parameters to the TRP file.

Allowed values:

0 : do not write population parameters to the TRP file

> 0 : write population parameters to the TRP file every NSTP-th generation

#### [ torsional\_scan ]

Positions of the variables:

RFRST RSTEP RLST RFCT

Details of the variables:

RFRST : (**Float**) First angle of the torsional scans.

Allowed values:

$\in \mathbb{R}$  : set first angle to RFRST degrees

RSTEP : (**Float**) Step angle of the torsional scans.

Allowed values:

$\in \mathbb{R}$  : set step angle to RSTEP degrees

RLST : (**Float**) Last angle of the torsional scans (inclusive).

Allowed values:

$\in \mathbb{R}$  : set last angle to RLST degrees

RFCT : (**Float**) Force constant of the dihedral restraint used the torsional scans.

Allowed values:

> 0 : set force constant of the harmonic dihedral restraint to RFCT ( $\text{kJ mol}^{-1}\text{rad}^{-2}$ )

#### [ minimization ]

Positions of the variables:

MALG[1]	DX0[1]	DXM[1]	NMAX[1]	DELE[1]
MALG[2]	DX0[2]	DXM[2]	NMAX[2]	DELE[2]

Details of the variables:

MALG[I] : (**Array of Integers**) Controls types of the minimization algorithms.

Allowed values:

1 : steepest-descents (more robust, less prone to errors)

2 : conjugate-gradients (less robust, more prone to errors)

Array index targets:

1 : minimization settings for all individuals and all generations

2 : enhanced minimization settings for optimal individual at the end of the run

DX0[I] : (**Array of Floats**) Initial step sizes DX0 in the minimization algorithms.

Allowed values:

> 0 : set DX0 of MALG[I] to DX0[I]

Array index targets:

1 : minimization settings for all individuals and all generations

2 : enhanced minimization settings for optimal individual at the end of the run

**DXM[I] : (Array of Floats)** Maximum step sizes DXM in the minimization algorithms.

Allowed values:

> 0 : set DXM of MALG[I] to DX0[I]

Array index targets:

1 : minimization settings for all individuals and all generations

2 : enhanced minimization settings for optimal individual at the end of the run

**NMAX[I] : (Array of Integers)** Maximum number of steps in the minimization algorithms.

Allowed values:

> 0 : set the maximum number of steps of MALG[I] to NMAX[I]

Array index targets:

1 : minimization settings for all individuals and all generations

2 : enhanced minimization settings for optimal individual at the end of the run

**DELE[I] : (Array of Floats)** Energy-convergence criteria of the minimization algorithms.

Allowed values:

> 0 : set DELE of MALG[I] to DELE[I]

Array index targets:

1 : minimization settings for all individuals and all generations

2 : enhanced minimization settings for optimal individual at the end of the run

For more details about the algorithmic meaning of these variables, see Section 1.3.

### 3.3.3 Interaction Function Parameters File (IFP)

The interaction function parameters file (IFP) contains the final values of the optimized parameters, *i.e.* those of the best individual of the GA population, along with the corresponding value of the weighted RMSD. These quantities are listed below identifying comment lines that are compatible with the notation in Section 2.5.2.

### 3.3.4 Parameters Trajectory File (TRP)

The parameters trajectory file (TRP) contains the parameters of all GA individuals for every NSTP-th generation. The data corresponding to each generation is lead by a line containing the generation number, followed by a comment line labelling the parameters in accordance with the notation in Section 2.5.2 and then one line per individual in which its parameters are listed. Individuals are ranked from best to worst (increasing order on weighted RMSD). This file is intended to allow the user to check on the diversity of the parameters accross the population and their convergence over the generations.

### 3.3.5 Energy Trajectory File (TRE)

The energy trajectory file (TRE) contains the energy profiles of all GA individuals for every NSTE-th generation. The data corresponding to each generation is lead by a line containing the generation number, followed by a comment line labelling the columns and then one line per torsional-scan angle where the energies of each individual at the corresponding torsional-scan step are listed along with the value of the angle itself. This file is intended to allow the user to check on the diversity of the energy profiles accross the population and their convergence over generations.

### 3.3.6 Weighted RMSD Trajectory File (TRR)

The weighted RMSD trajectory file (TRR) contains the average and best values of the weighted RMSD accross the population for every generation. This file is useful to inspect the diversity of the population and its convergence over the generations. If the average value converges too fastly, or if its limiting value is too close to the best value, then more diversity may benefit the optimization. This can be achieved, for example, by raising the value of the mutation probability, using a less-conservative crossover operator (*e.g.* the heuristic operator) or adjusting the parameters of the probability distribution functions involved in parameter randomization.

Table 3.3: Input variables, their types, where they are set and links to more detailed descriptions of their allowed values.

Variable	Type	Description	Set in	Block/Option	Cross-reference
<b>profilerOpt</b>					
NPROCS	Integer	Number of forked subprocesses.	Cmd-line	-np	Section 3.1.2
NTORS	Integer	Controls optimization of torsional parameters.	INP file	parameter_optimization	p. 18
NLJ	Integer	Controls optimization of Lennard-Jones parameters.	INP file	parameter_optimization	p. 18
FTORS	Integer	Controls functional form of torsional terms.	INP file	parameter_optimization	p. 18
TORSNT	Array of Integers	Fine control of the functional form of torsional terms.	INP file	parameter_optimization	p. 19
LJNT	Array of Integers	Controls which Lennard-Jones components are optimized.	INP file	parameter_optimization	p. 19
WTEMP	Float	Controls weights given to reference data points.	INP file	parameter_optimization	p. 19
PINV	Integer	Probability of inverting sign of random torsional parameters.	INP file	parameter_randomization	p. 19
DIST	Array of Integers	Controls types of probability distributions of random parameters.	INP file	parameter_randomization	p. 19
MIN	Array of Float	Minimum values of random parameters.	INP file	parameter_randomization	p. 19
MAX	Array of Float	Maximum values of random parameters.	INP file	parameter_randomization	p. 19
MEAN	Array of Float	Mean values of the probability distributions.	INP file	parameter_randomization	p. 20
STDDEV	Array of Float	Std. dev. of the probability distributions.	INP file	parameter_randomization	p. 20
SEED	Integer	Seed of random number generator.	INP file	seed	p. 20
POPSIZE	Integer	Size of the GA population.	INP file	genetic_algorithm	p. 20
NGENS	Integer	Number of generations of the GA.	INP file	genetic_algorithm	p. 20
SELTYPE	Integer	Selection operator of the GA.	INP file	genetic_algorithm	p. 20
NTEL	Integer	Number of elite individuals of the GA.	INP file	genetic_algorithm	p. 20
CRTYPE	Integer	Crossover operator of the GA.	INP file	genetic_algorithm	p. 20
CRRATE	Integer	Probability of crossover.	INP file	genetic_algorithm	p. 20
MUTRATE	Integer	Probability of mutation.	INP file	genetic_algorithm	p. 21
NSTE	Integer	Frequency of writing population energies to the TRE file.	INP file	writetraj	p. 21
NSTP	Integer	Frequency of writing population parameters to the TRP file.	INP file	writetraj	p. 21
RFRST	Float	First angle of the torsional scans.	INP file	torsional_scan	p. 21
RSTEP	Float	Step angle of the torsional scans.	INP file	torsional_scan	p. 21
RLST	Float	Last angle of the torsional scans.	INP file	torsional_scan	p. 21
RFCT	Float	Force constant of the dihedral restraint used in the torsional scans.	INP file	torsional_scan	p. 21
MALG	Array of Integers	Controls types of the minimization algorithms.	INP file	minimization	p. 21
DX0	Array of Floats	Initial step sizes of the minimization algorithms.	INP file	minimization	p. 21
DXM	Array of Floats	Maximum step sizes of the minimization algorithms.	INP file	minimization	p. 22
NMAX	Array of Integers	Maximum number of steps of the minimization algorithms.	INP file	minimization	p. 22
DELE	Array of Floats	Energy-convergence criteria of the minimization algorithms.	INP file	minimization	p. 22
<b>profilerGen</b>					
RFRST	Float	First angle of the torsional scan.	Cmd-line	-dr	Section 3.1.1

Table 3.3: Input variables, their types, where they are set and links to more detailed descriptions of their allowed values.

Variable	Type	Description	Set in	Block/Option	Cross-reference
RSTEP	Float	Step angle of the torsional scan.	Cmd-line	<b>-dr</b>	Section 3.1.1
RLST	Float	Last angle of the torsional scan.	Cmd-line	<b>-dr</b>	Section 3.1.1
RFACT	Float	Force constant of the dihedral restraint used in the torsional scan.	Cmd-line	<b>-dk</b>	Section 3.1.1
MALG	Integer	Controls type of the minimization algorithm.	Cmd-line	<b>-min</b>	Section 3.1.1
DX0	Float	Initial step size of the minimization algorithm.	Cmd-line	<b>-dx0</b>	Section 3.1.1
DXM	Float	Maximum step size of the minimization algorithm.	Cmd-line	<b>-dxm</b>	Section 3.1.1
NMAX	Integer	Maximum number of steps of the minimization algorithm.	Cmd-line	<b>-dele</b>	Section 3.1.1
DELE	Float	Energy-convergence criterium of the minimization algorithm.	Cmd-line	<b>-nsteps</b>	Section 3.1.1

## Chapter 4

# Tutorial

In this chapter, the use of **profilerTools** is illustrated in a more didactic way. To do this, we consider the problem of optimizing the description of torsions of the form  $\text{CH}_3\text{-CH}_m\text{-CH}_n\text{-CH}_3$  in a united-atoms representation. This involves optimizing the corresponding torsional parameters together with the 1–4 Lennard-Jones parameters that describe the  $\text{CH}_3\text{-CH}_3$  interactions. As reference data, quantum-mechanical torsional-scan energy profiles of two alkane molecules containing this dihedral type are considered: butane (**bu**) and 2-methylbutane (**2mb**); see Figure 4.1. To explore the capabilities of **profilerOpt** and exemplify its usage, we propose several optimization strategies. Two program features are explored in them: the customization of the weights attributed to the reference data (comparing user-specified weights with uniform weights) and the fine control of torsional functional form (comparing a standard periodic dihedral potential with terms of all multiplicities with one with a single term of a chosen multiplicity). Also, the Lennard-Jones part of the optimization problem is formulated in two alternative (and, for these molecules, equivalent) ways. The first considers the direct optimization of the  $\text{CH}_3\text{-CH}_3$  nonbonded pairtype. The other considers the optimization of the  $CS_6$ ,  $CS_{12}$  atomic parameters of the  $\text{CH}_3$  atomtype. This leads to a total of eight scenarios, out of which we consider the following four:

1. Uniform weights; All multiplicities; Pairtype optimization; (Section 4.3.1)
2. User-specified weights; All multiplicities; Pairtype optimization; (Section 4.3.2)
3. Uniform weights; Single multiplicity; Pairtype optimization; (Section 4.3.3)
4. Uniform weights; All multiplicities; Atomtype optimization; (Section 4.3.4)

Before discussing these examples, we describe the organization of the tutorial files in Section 4.1. After that, in Section 4.2, we explain how to obtain torsional-scan trajectories for **bu** and **2mb** using **profilerGen**. Finally, in Section 4.3, we show how to optimize the parameters in the four different scenarios above, using **profilerOpt**.

Throughout this chapter, we assume the reader has access to a Linux terminal emulator and is familiarized with some type of shell. In particular, the terminal snippets in this chapter were written considering the Bash shell. If this is not your case, please adapt the commands to match your terminal configuration.

### 4.1 File Structure

The tutorial files can be found inside the `doc/tutorial/examples` directory, which is organized as follows:

```
|--- coords
| |--- 2mb.g96
| |--- bu.g96
|--- inp
| |--- all-terms.inp
| |--- custom-terms.inp
|--- qm
| |--- 2mb.dat
| |--- bu.dat
```

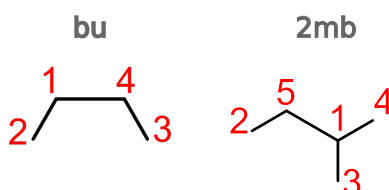


Figure 4.1: Structures and atom indexing of the butane (**bu**) and 2-methylbutane (**2mb**) molecules.

```

|--- stp
|   |--- 2mb_atomic.stp
|   |--- 2mb_pairs.stp
|   |--- bu_atomic.stp
|   |--- bu_pairs.stp
|--- wei
|   |--- 2mb.dat
|   |--- bu.dat

```

The contents of the directories above are:

- **coords**: Initial coordinates of the systems (a single conformation each).
- **inp**: INP files with the input variables for the **profilerOpt** runs.
- **qm**: Quantum-mechanical reference data of the systems.
- **stp**: STP files with topology, reference dihedral and optimization targets of each system.
- **wei**: User-specified weight files.

Note that there are two INP files in the **inp** directory: one for the optimization involving dihedral terms of all multiplicities (**all-terms.inp**) and one for a single multiplicity (**custom-terms.inp**). There are also two STP files for each system in the **stp** directory: one for the optimization of the CH3-CH3 pairtype (**\*\_pairs.stp**) and one for the CH3 atomtype (**\*\_atomic.stp**). These files, and also the weight files in the **wei** directory, will be discussed in more details in the following sections. For conciseness, file names will be referred to with omission of the **doc/tutorial/examples** prefix.

## 4.2 Generating Torsional-Scan Trajectories

The first step in this tutorial is to generate torsional-scan trajectories for the two systems. These will serve as input trajectories to **profilerOpt** later on in the parameter optimization step. To perform the torsional scans, only the coordinate and STP files of each system are necessary. The latter must contain the topology part and the **[ refdihedral ]** block specifying the reference dihedral of the scan (see Section 3.3.1). For this tutorial, it is irrelevant which of the two STP files of each system are chosen for performing its scan, since they are equivalent in terms of their force-field parameters. For example, the **stp/bu\_pairs.stp** file reads

```

[ defaults ]
; nbfunc comb-rule gen-pairs fudgeLJ fudgeQQ
1      1      atomic   1.0    1.0

[ atoms ]
; type c6          c12          cs6          cs12          q
CH2    7.4684160e-03  3.3965580e-05  4.7238130e-03  4.7419260e-06  0.0000
CH3    9.6138020e-03  2.6646240e-05  6.8525280e-03  6.0308650e-06  0.0000
CH3    9.6138020e-03  2.6646240e-05  6.8525280e-03  6.0308650e-06  0.0000
CH2    7.4684160e-03  3.3965580e-05  4.7238130e-03  4.7419260e-06  0.0000

[ nbpairs ]
; ai  aj  type
  2   3   2

[ bonds ]
; ai  aj  type      l0      kb
  1   3   2      0.1530  7.1500e+06
  1   4   2      0.1530  7.1500e+06
  2   4   2      0.1530  7.1500e+06

[ angles ]
; ai  aj  ak  type  theta0    ka
  3   1   4   2    111.00    530.00
  1   4   2   2    111.00    530.00

[ dihedrals ]
; ai  aj  ak  al  type    phi      k      mult
  3   1   4   2   1      0.0000    5.9200    3

[ dihedrals ]
; improper dihedrals
; ai  aj  ak  al  type    phi      k

[ optpairs ]
; idxs
2   3

```

```
[ optdihedrals ]
; idxs
3 1 4 2

[ refdihedral ]
; idx
3 1 4 2
```

and specifies that the torsional scan will be performed along the CH<sub>3</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub> dihedral angle. The optimization blocks [ **opt\*** ] are not necessary to run **profilerGen** and will be ignored in this step.

We now proceed to performing the torsional scans. First, it is convenient to create new directories to receive the **profilerGen** output files. Go inside the **examples** directory and run the command:

```
mkdir scans scans/bu scans/2mb
```

to create them for each system. Now, it is time to run **profilerGen**. For butane, this can be done by running the command:\*

```
../../../../profilerGen.py \
-c coords/bu.g96 \
-t stp/bu_pairs.stp \
-dr 0 10 360 \
-dk 5000 \
-min 1 \
-dx0 0.02 \
-dxm 0.20 \
-dele 1.0e-09 \
-nsteps 500000 \
-op scans/bu/bu
```

To consult the meaning of each command-line option, see Section 3.1.1. The command above performs a torsional scan of which the steps are 0, 10, 20 ... 360 deg. At each step of the scan, the energy minimization is performed with a steepest-descent algorithm until the (absolute) energy difference between successive steps is less than  $1.0 \times 10^{-9}$  kJ mol<sup>-1</sup> or until 500000 steps are carried out. The resulting energy profile is reported in **scans/bu/bu.dat** and is also plotted in Figure 4.3. The torsional-scan trajectory is stored in **scans/bu/bu.xyz**. For 2-methylbutane, we proceed in a similar way, replacing **bu** with **2mb**:

```
../../../../profilerGen.py \
-c coords/2mb.g96 \
-t stp/2mb_pairs.stp \
-dr 0 10 360 \
-dk 5000 \
-min 1 \
-dx0 0.02 \
-dxm 0.20 \
-dele 1.0e-09 \
-nsteps 500000 \
-op scans/2mb/2mb
```

Once again, the resulting energy profile is reported in **scans/2mb/2mb.dat** and plotted in Figure 4.3. The torsional-scan trajectory is stored in **scans/2mb/2mb.xyz**.

### 4.3 Optimizing the Parameters

In the beginning of the chapter, four scenarios of parameter optimization were listed. Any given scenario differs from the other three only in the choice of the STP and/or INP files and/or in the command-line options given to **profilerOpt**. For this reason, we will discuss in details only the first of these scenarios. For the remaining ones, we will only point out the differences in the corresponding input files or command-line options.

Bear in mind that, as the **profilerOpt** code currently stands, each run may take a couple of hours, even for the rather simple examples in this tutorial. For the sake of speed, you might want to consider parallelizing each run, which can be done with the **-np** command-line option (see Section 3.1.2). However, this leads to loss of reproducibility, which originates in technical issues regarding random number generation when the **multiprocessing** library is used for parallelization (as is our case). This is a limitation that we intend to address in future versions of the program. For this tutorial, we prioritize reproducibility instead of speed so we report the commands without requesting parallelization. Also, we supply the output files of the runs of each scenario in the **doc/tutorial/examples\_results** directory.

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\*Backslashes are used to escape the newline character throughout the entire chapter.

### 4.3.1 Scenario 1

This scenario is defined by uniform weights, torsional terms of all six multiplicities and pairtype optimization. These settings are configured in the STP files `stp/*_pairs.stp` and the in the INP file `inp/all-terms.inp`. In the STP files, pairtype optimization is achieved by specifying the Lennard-Jones optimization targets using the block `[ optpairs ]`. For example, in the STP file of 2-methylbutane (`stp/2mb.pairs.stp`), the fragment that reads

```
[ optpairs ]
; idxs
2 3
2 4
```

indicates that the two CH<sub>3</sub>-CH<sub>3</sub> nonbonded pairs of which the involved atoms are 2, 3 and 2, 4 are the targets of the Lennard-Jones optimization. It is followed by the fragment

```
[ optdihedrals ]
; idxs
4 1 5 2
```

that sets the dihedral angle CH<sub>3</sub>-CH<sub>1</sub>-CH<sub>2</sub>-CH<sub>3</sub> formed by the atoms 4, 1, 5 and 2 as the target of the torsional optimization.

The uniform weights and the functional form of the torsional terms are set in the INP file type. The descriptions of all variables specified in this file are given in Table 3.3, in which cross-references to the meaning of their allowed values are also found. For the sake of thoroughness, we will briefly comment the file that corresponds to this scenario (`inp/all-terms.inp`), proceeding block by block.

First, in

```
[ parameter_optimization ]
; NTORS  NLJ  FTORS
   1      1      1
; TORSNT[I]
; I=  1  2  3  4  5  6
     1  1  1  1  1  1
; LJNT[I]
; I=  1  2
;   CS6  CS12
     1    1
; WTEMP
   0
```

the optimization of both torsional (NTORS) and Lennard-Jones (NLJ) terms is set up. For the former, a standard proper dihedral functional form (FTORS) with terms of all six multiplicities (TORSNT) is used. For the latter, both the attractive and the repulsive components are optimized (LJNT). Finally, if weight files are not supplied when `profilerOpt` is called (as is the case in this scenario), the fallback behavior is set to using uniform weights (WTEMP).

In

```
[ seed ]
; SEED
19804
```

the random number generator seed is set to 19804. Control of the seed is useful for reproducibility purposes. As long as parallelization is not requested, two `profilerOpt` runs with the same seed will yield the same results.

In

```
[ parameter_randomization ]
; PINV
   50
; DIST[I]  MIN[I]  MAX[I]  MEAN[I]  STDDEV[I]
; Torsional
   2      0      30      10.0      5.0
; CS6
   2      0      1      8e-3      24e-3
; CS12
   2      0      1      8e-6      24e-6
```

the details of the obtention of random parameters are set up. The distributions (DIST) from which torsional,  $CS_6$  and  $CS_{12}$  values are drawn, respectively, are specified along with their mean (MEAN), standard deviation (STDDEV) and minimum (MIN) and maximum allowed (MAX) values. All of these distributions are LogNormal. In the case of torsional parameters, after randomly obtained, they may have their sign reversed with a probability of 0.50 (PINV).



In

```
[ genetic_algorithm ]
; POPSIZE  NGENS
   128      50
; SELTYPE  NTEL
   3        2
; CRTYPE  CRRATE MUTRATE
   2       100   40
```

the details of the genetic algorithm are set up. The population size (POPSIZE) is set to 128, out of which 2 are elite individuals (NTEL). The tournament selection operator is chosen (SELTYPE), along with the heuristic crossover operator (CRTYPE). The crossover probability (CRRATE) is set to 1, *i.e.* every time two parents reproduce, there is crossover, while the mutation probability (MUTRATE) is set to 0.4. The genetic algorithm is configured to run for 50 generations (NGENS).

In

```
[ writetraj ]
; NSTE  NSTP
   5     5
```

the frequencies of writing individual energy profiles (NSTE) and individual parameters (NSTP) to the TRE and TRP files are specified. In this case, these values are written to disk every 5 generations.

In

```
[ minimization ]
; MALG[I]  DXO[I]  DXM[I]  NMAX[I]  DELE[I]
   1       0.02   0.2     20       1e-2
   1       0.02   0.2    500000    1e-9
```

the minimization algorithm settings are specified. They correspond to two steepest-descents algorithms (MALG) of different precision (DELE) and duration (NMAX). The first one refers to the routine minimization performed for every individual; it runs for at most 20 steps or until the energy difference between successive steps is less than 0.01 kJ mol<sup>-1</sup>. The second one refers to the final minimization performed only for the optimal individual; it runs for at most 500000 steps or until the energy difference between successive steps is less than 10<sup>-9</sup> kJ mol<sup>-1</sup>. The steepest-descents algorithm was chosen instead of the conjugate-gradients one because it is more robust. The conjugate-gradients algorithm may fail when the minimization is performed on individuals with “unbalanced” parameter values, which typically occur on the first generations or after a mutation.

In

```
[ torsional_scan ]
; RFRST RSTEP RLST RFCT
   0     10   360  5000
```

the torsional-scan details are specified. The scan dihedral angles are set to 0, 10, 20...360 deg and maintained with a dihedral restraint of which the force constant is 5000 kJ mol<sup>-1</sup> rad<sup>-2</sup>. It is important that these settings (except for the force constant) match those of the input torsional-scan trajectories. By comparing the contents of this block with the command-line options of the **profilerGen** runs of Section 4.2, one can easily see that this is the case.

With the input files explained, we proceed to the parameter optimization. First, it is once again convenient to create a directory for the output files of **profilerOpt**:

```
mkdir scenario_1
```

To perform the optimization, run the following command:

```
../../../../profilerOpt.py \
-r qm/bu.dat qm/2mb.dat \
-c scans/bu/bu.xyz scans/2mb/2mb.xyz \
-t stp/bu_pairs.stp stp/2mb_pairs.stp \
-i inp/all-terms.inp \
-op scenario_1/opt
```

A complete description of the command-line options can be found in Section 3.1.2. In the above, note that (i) the input trajectories of **profilerOpt** are the output trajectories of **profilerGen** (Section 4.2); (ii) the input STP files are those for pairtype optimization and (iii) the input INP file is the one where a periodic dihedral with all six multiplicities is specified. During execution, **profilerOpt** will notify in **stdout** the start and completion of each generation. It will also notify each time a new best individual is found, informing the value of its weighted RMSD.

As indicated in Section 3.1.2, a successful run of `profilerOpt` will create several output files of which the formats are described in Section 3.3. For the sake of thoroughness, we will comment on each of these output files and the interpretation of their contents. The TRR output file (`scenario_1/opt.trr`) reads

```
# GEN          AVG          BEST
  0      2.9678611e+02      1.4876041e+01
  1      9.2343584e+01      1.2555096e+01
...
 49      7.1041770e+01      2.3566693e+00
 50      2.4350660e+01      2.3566693e+00
```

where the ellipsis ... indicates the omission of lines. As indicated by the comments, the first column refers to the generation (0 stands for the initial population), while the second and last columns refer to the average and best (lowest) value of the weighted RMSD, respectively, at the given generation. This file is useful to inspect the diversity of individuals in the GA and also their convergence along the generations.

The TRP output file (`scenario_1/opt.trp`) reads

```
1
# PHI1          K1  M1 ... PHI6          K6  M6          CS6          CS12          WRMSD
  0.00  -13.6573644  1 ... 0.00      7.8184962  6      1.1244283e-03  4.2265186e-06  1.2555096e+01
  0.00  -9.6352254  1 ... 0.00     -3.1527857  6      4.2770074e-03  2.4808228e-06  1.3642115e+01
...
  0.00  13.4845343  1 ... 0.00      6.4649437  6      7.1490046e-03  6.3541647e-09  1.7612964e+03
  0.00  12.2490638  1 ... 0.00      6.3990019  6      2.1167276e-02  2.1299433e-08  3.9020127e+03
6
# PHI1          K1  M1 ... PHI6          K6  M6          CS6          CS12          WRMSD
```

where the ellipsis ... indicates the omission of lines and columns. The fragment reproduced above reports the parameters of each GA individual (one individual per line) and the corresponding weighted RMSD of the first generation, as indicated by the top number. The meaning of each column is explained by the comments below the generation number. As indicated by the last lines, the data for the first generation is followed by similarly structured data for the sixth generation (since the frequency of writing to this file was set to five generations in the input variable NSTP).

The TRE output files (`scenario_1/opt.1.tre` and `scenario_1/opt.2.tre`) report the energy profiles of all individuals for all generations. There is one such file for each system, and they are numbered in the same order in which the system files are supplied to `profilerOpt` (in this case, 1 refers to butane and 2 refers to 2-methylbutane). For example, the butane TRE file reads

```
1
# ANG          IND1 ...          IND128
  0.00      2.2426570e+01 ... 1.5073598e-01
 10.00     1.7133472e+01 ... 1.4272572e+01
...
 350.00    1.7133447e+01 ... 1.4374804e+01
 360.00    2.2428204e+01 ... 0.0000000e+00
6
# ANG          IND1 ...          IND128
```

where the ellipsis ... indicates the omission of lines and columns. The fragment reproduced above corresponds to the first generation of the GA, as indicated by the top number. The first column lists the angles of the torsional scan. From the second column to the last, the corresponding energy profiles of each individual are given, one per column. As indicated by the last lines, the data for the first generation is followed by similarly structured data for the sixth generation (since the frequency of writing to this file was set to five generations in the input variable NSTE).

The IFP output file (`scenario_1/opt.ifp`) reads

```
#          CS6          CS12
  2.2379720e-03  3.4437180e-06
#          PHI          K          M
  0.00          0.6443053  1
  0.00          0.8438238  2
  0.00          6.7092465  3
  0.00         -0.7038652  4
  0.00          0.4910962  5
  0.00          0.5522696  6
#          WRMSD
  2.3566693e+00
```

and reports the results of the parameter optimization: the parameters of the optimal individual and the corresponding weighted RMSD. The data is clearly explained by the accompanying comments.

The torsional-scan trajectories of the optimal individual and the corresponding energy profiles are written to the output files with XYZ and DAT extensions, respectively. These files are:

```

scenario_1/opt_1.dat
scenario_1/opt_1.xyz
scenario_1/opt_2.dat
scenario_1/opt_2.xyz
scenario_1/opt_minim_1.dat
scenario_1/opt_minim_1.xyz
scenario_1/opt_minim_2.dat
scenario_1/opt_minim_2.xyz

```

Each file is identified with the number of the system and with a string indicating the minimization algorithm used in its obtention. The number of the system is defined by the order in which the system files were given as input to `profilerOpt`, like in the TRE files. The minimization algorithm is identified with the “minim” string: its presence indicates that the file corresponds to the enhanced minimization algorithm settings, while its absence indicates the less-precise minimization settings involved in every generation of the GA. The optimal energy profiles of `scenario_1/opt_minim_1.dat` and `scenario_1/opt_minim_2.dat` are plotted in Figure 4.3.

### 4.3.2 Scenario 2

This scenario differs from Scenario 1 in the weights given to the reference data. Instead of using uniform weights, custom weights are supplied *via* the files `wei/bu.dat` and `wei/2mb.dat`. In these files, data points that are close to peaks and valleys are given weight 1, and the remaining ones are given weight 0, *i.e.*, they are irrelevant in the optimization (see Figure 4.2). To perform the optimization, the most important change necessary is to include the weight files in the call to `profilerOpt`, *i.e.*,

```

../../../../profilerOpt.py \
-r qm/bu.dat qm/2mb.dat \
-c scans/bu/bu.xyz scans/2mb/2mb.xyz \
-t stp/bu_pairs.stp stp/2mb_pairs.stp \
-i inp/all-terms.inp \
-op scenario_2/opt \
-w wei/bu.dat wei/2mb.dat

```

where the last line contains the weight files. In the above, it is assumed that a directory `scenario_2` has been previously created to store the output files. After the run is finished, the optimal parameters reported in the IFP file are

```

#          CS6          CS12
2.9068136e-03  2.9907985e-06
#          PHI          K          M
0.00          -0.2056776  1
0.00          0.1713483  2
0.00          6.6991703  3
0.00          -0.0621579  4
0.00          1.5542293  5
0.00          1.3870725  6
#          WRMSD
1.1921891e+00

```

The corresponding energy profiles of `scenario_2/opt_minim_1.dat` and `scenario_2/opt_minim_2.dat` are plotted in Figure 4.3.

### 4.3.3 Scenario 3

This scenario differs from Scenario 1 in the functional form of the torsional terms. Instead of all summands in Equation 1.1.6, only the term with multiplicity equal to 3 is optimized, while the others are set to zero. This can be achieved by altering the value of the input variable `TORSNT` in the block [ `parameter_optimization` ] of the INP file. This is done in the `inp/custom-terms.inp` file, where this block reads:

```

[ parameter_optimization ]
; NTORS  NLJ  FTORS
1      1      1
; TORSNT[I]
; I=  1      2      3      4      5      6
0      0      1      0      0      0
; LJNT[I]
; I=  1      2
; CS6  CS12
1      1
; WTEMP
0

```

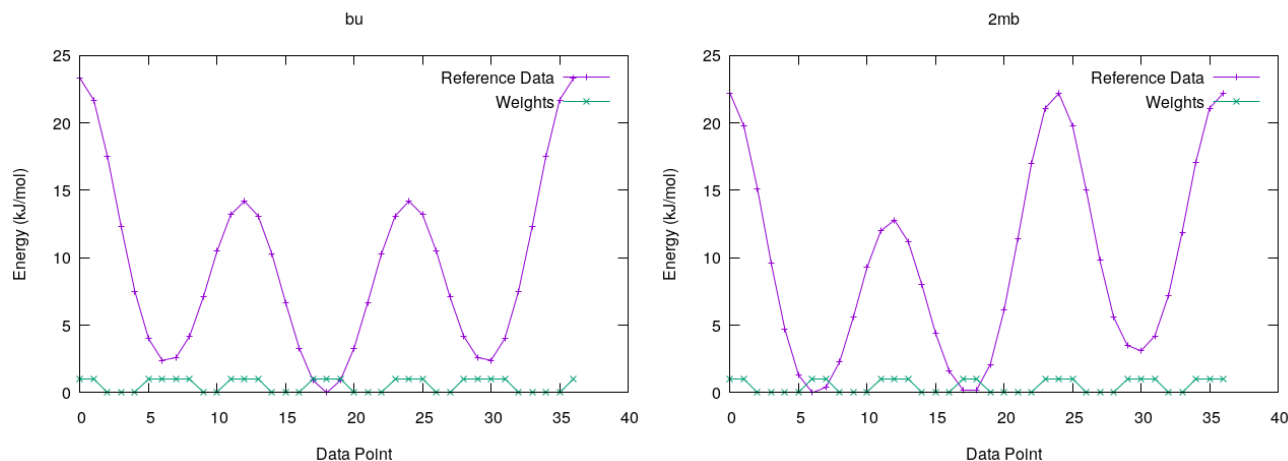


Figure 4.2: Reference data of the optimization and custom weights for each system. The  $y$ -axis labels refer only to the reference data; the weights are dimensionless.

To perform the optimization, the most important change necessary is to use the appropriate INP file in the call to `profilerOpt`, *i.e.*,

```
../../../../profilerOpt.py \
-r qm/bu.dat qm/2mb.dat \
-c scans/bu/bu.xyz scans/2mb/2mb.xyz \
-t stp/bu_pairs.stp stp/2mb_pairs.stp \
-i inp/custom-terms.inp \
-op scenario_3/opt
```

In the above, it is assumed that a directory `scenario_3` has been previously created to store the output files. After the run is finished, the optimal parameters reported in the IFP file are

```
#          CS6          CS12
2.9293877e-03  2.9476463e-06
#          PHI          K          M
0.00          0.0000000  1
0.00          0.0000000  2
0.00          7.2805242  3
0.00          0.0000000  4
0.00          0.0000000  5
0.00          0.0000000  6
#          WRMSD
6.5948745e-01
```

The corresponding energy profiles of `scenario_3/opt_minim_1.dat` and `scenario_3/opt_minim_2.dat` are plotted in Figure 4.3.

#### 4.3.4 Scenario 4

This scenario differs from Scenario 1 in the way that the target of the Lennard-Jones optimization is specified. Instead of the CH3-CH3 pairtype, the CH3 atomtype is targeted in the optimization. Note that these approaches are equivalent for the two molecules considered in this tutorial, since the only 1-4 nonbonded pairtype that they contain is the CH3-CH3 one. If there were any other 1-4 nonbonded pairs involving CH3, this would not be the case, because the atomtype optimization would also affect them, while the pairtype optimization would not.

Atomtype optimization can be achieved by listing the target atoms in the `[ optatoms ]` block of the STP files, which replaces the `[ optpairs ]` block of the previous scenarios. This is done in the STP files `stp/bu_atomic.stp` and `stp/2mb_atomic.stp`. For example, in the 2-methylbutane STP file,

```
[ optatoms ]
; idxs
2 3 4
```

indicates that the atoms 2, 3 and 4 receive the Lennard-Jones parameters of the optimal GA individual. To perform the optimization, the most important change necessary is to use the appropriate STP files in the call to `profilerOpt`, *i.e.*,

```
../../../../profilerOpt.py \
-r qm/bu.dat qm/2mb.dat \
```

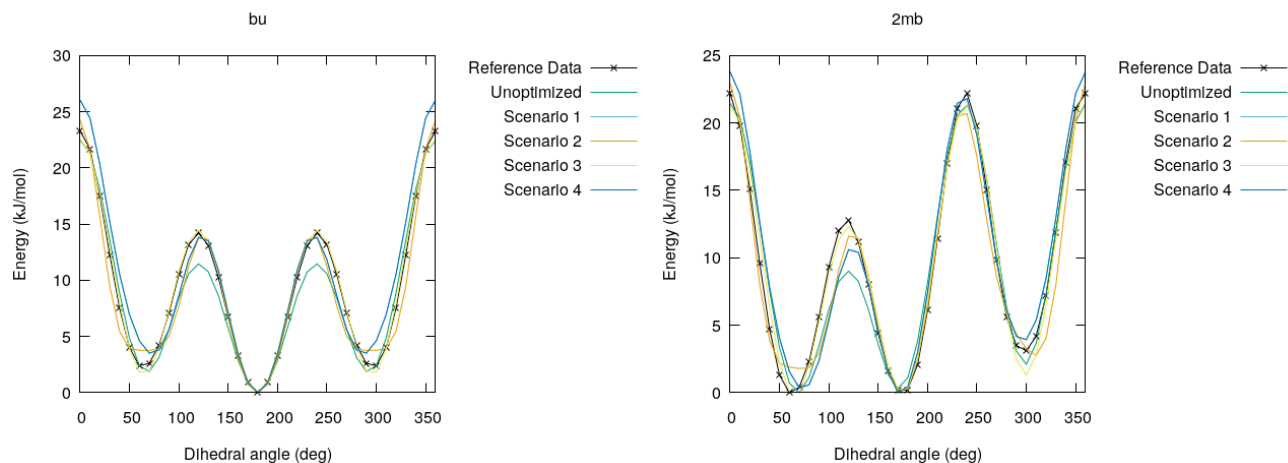


Figure 4.3: Optimal energy profiles of the four scenarios studied in this tutorial, along with the reference and unoptimized data for each system. Note that the lines of Scenario 1 and Scenario 4 superimpose over each other. The unoptimized data is from the energy profiles obtained with `profilerGen` in Section 4.2, using the original parameters of the STP files.

```
-c scans/bu/bu.xyz scans/2mb/2mb.xyz \
-t stp/bu_atomic.stp stp/2mb_atomic.stp \
-i inp/all-terms.inp \
-op scenario_4/opt
```

In the above, it is assumed that a directory `scenario_4` has been previously created to store the output files. After the run is finished, the optimal parameters reported in the IFP file are:

```
#          CS6          CS12
2.2379720e-03  3.4437180e-06
#          PHI          K          M
0.00          0.6443053    1
0.00          0.8438238    2
0.00          6.7092465    3
0.00          -0.7038652   4
0.00          0.4910962    5
0.00          0.5522696    6
#          WRMSD
2.3566693e+00
```

Note that they are identical to the ones obtained in Scenario 1 (Section 4.3.1), as anticipated above. The corresponding energy profiles of `scenario_4/opt_minim.1.dat` and `scenario_4/opt_minim.2.dat` are plotted in Figure 4.3.

# Bibliography

- [1] van Gunsteren, W. F., Billeter, S. R., Eising, A. A., Hünenberger, P. H., Krüger, P., Mark, A. E., Scott, W. R. P. and Tironi, I. G. Biomolecular Simulation: The GROMOS96 Manual and User Guide. Volume 2: Algorithms and Formulae for Modelling of Molecular Systems, Vdf Hochschulverlag AG an der ETH Zürich, Zürich, Switzerland, 1996.
- [2] Abraham, M. J., van der Spoel, D., Lindahl, E., Hess, B. and the GROMACS development team. GROMACS User Manual version 2019. <http://www.gromacs.org>.

# Appendix A

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