A Cost-Effective Method for Free-Energy Minimization in Complex Systems with Elaborated Ab Initio Potentials

Carlos Bistafa,^{*a*} *Yukichi Kitamura*,^{*a*} *Marilia T. C. Martins-Costa*,^{*b*} *Masataka Nagaoka*^{*a,c,d**} and *Manuel F. Ruiz-López*^{*b,e**}

^a Department of Complex Systems Science, Graduate School of Informatics, Nagoya University, Chikusa Ku, Furo Cho, Nagoya, Aichi 4648601, Japan

 ^b Laboratoire de Physique et Chimie Théoriques, UMR CNRS 7019, Faculté des Sciences et Technologies, Université de Lorraine, CNRS, BP 70239, 54506 Vandoeuvre-lès-Nancy Cedex, France

^c ESICB, Kyoto University, Kyodai Katsura, Nishikyo-ku, Kyoto 6158520, Japan

^d Core Research for Evolutional Science and Technology, Japan Science and Technology Agency, Honmachi, Kawaguchi 3320012, Japan

^e Future Value Creation Research Center, Graduate School of Informatics, Nagoya University, Chikusa Ku, Furo Cho, Nagoya, Aichi 4648601, Japan

1. Free energy perturbation theory

Free-energy perturbation (FEP) theory was initially introduced by Zwanzig.¹ It represents an efficient and widely used method to estimate the free energy difference between a reference and a target state of a system. It requires calculating the average of a function of the reference and target states energy difference using the sampling for the reference state.

The Helmholtz free energy difference between a system described by the Hamiltonian H_o and a target system described by the Hamiltonian H_1 is given by:^{2,3}

$$\Delta A = A_1 - A_o = -\frac{1}{\beta} \ln Q_1 - \left(-\frac{1}{\beta} \ln Q_0\right) = -\frac{1}{\beta} \ln \frac{Q_1}{Q_0}$$
(S1)

where the constant β is the inverse temperature $(k_B T)^{-1}$ and Q_i are the corresponding canonical partition functions:

$$Q_i = \frac{1}{h^{3N}N!} \iint e^{-\beta H_i(\mathbf{x}, \mathbf{p}_{\mathbf{x}})} \, d\mathbf{x} \, d\mathbf{p}_{\mathbf{x}}$$
(S2)

Here, *N* is the number of particles and \mathbf{x} and $\mathbf{p}_{\mathbf{x}}$ are the Cartesian coordinates and associated momenta.

Substituting (S2) into equation (S1) and using the definition:

$$H_1(\mathbf{x}, \mathbf{p}_{\mathbf{x}}) = H_o(\mathbf{x}, \mathbf{p}_{\mathbf{x}}) + \Delta H(\mathbf{x}, \mathbf{p}_{\mathbf{x}})$$
(S3)

one can write:

$$\Delta A = -\frac{1}{\beta} \ln \frac{\iint e^{-\beta \,\Delta H(\mathbf{x},\mathbf{p}_{\mathbf{x}})} \, e^{-\beta \,H_O(\mathbf{x},\mathbf{p}_{\mathbf{x}})} \, d\mathbf{x} \, d\mathbf{p}_{\mathbf{x}}}{\iint e^{-\beta \,H_O(\mathbf{x},\mathbf{p}_{\mathbf{x}})} \, d\mathbf{x} \, d\mathbf{p}_{\mathbf{x}}} \tag{S4}$$

In this expression, one recognizes the probability $P_o(\mathbf{x}, \mathbf{p}_x)$ of finding the reference system in a state with values $(\mathbf{x}, \mathbf{p}_x)$ for the coordinates and momenta:

$$P_o(\mathbf{x}, \mathbf{p}_{\mathbf{x}}) = \frac{e^{-\beta H_o(\mathbf{x}, \mathbf{p}_{\mathbf{x}})}}{\iint e^{-\beta H_o(\mathbf{x}, \mathbf{p}_{\mathbf{x}})} d\mathbf{x} d\mathbf{p}_{\mathbf{x}}}$$
(S5)

so that one can write:

$$\Delta A = -\frac{1}{\beta} \ln \langle e^{-\beta \,\Delta H(\mathbf{x}, \mathbf{p}_{\mathbf{x}})} \rangle_o \tag{S6}$$

The brackets indicate an ensemble average over configurations sampled in the reference state. If the Hamiltonians H_o and H_1 involve systems with the same masses, as assumed in our case, then equation (S6) simplifies to:

$$\Delta A = -\frac{1}{\beta} \ln \langle e^{-\beta \, \Delta V} \rangle_o \tag{S7}$$

where ΔV represents the potential energy difference between the target and the reference system:

$$\Delta V = V_1 - V_0 \tag{S8}$$

Equation (S7) is the basic equation in FEP theory. It states that the free energy difference can be computed over configurations from the reference state sampling. Though this expression is exact in principle, in practice it can only be successfully used when ΔH represents a perturbation of the system so that the sampling from the reference state does not deviate much from the sampling of the target state. Note that it can be useful to rewrite equation (S7) as:

$$\Delta A = \langle \Delta V \rangle_o - \frac{1}{\beta} \ln \langle e^{-\beta \, \delta \Delta V} \rangle_o \tag{S9}$$

where $\delta \Delta V = \Delta V - \langle \Delta V \rangle_o$ represents the fluctuations of the potential energy difference with respect to its average value $\langle \Delta V \rangle_o$.

In many chemical problems, statistical simulations are carried out in the isothermalisobaric ensemble to parallel standard experimental conditions. In that case, Gibbs free energies are used instead of Helmholtz free energy leading to:⁴

$$\Delta G = -\frac{1}{\beta} \ln \langle e^{-\beta \, \Delta V} \rangle_o \tag{S10}$$

which is equivalent to the so-called potential distribution theorem for calculating the excess chemical potential of a solute in solution.³ It is worth reminding also that the reference and target systems can be reversed. Following the same procedure and keeping the same meaning for ΔG and ΔV one obtains (see page 36 of reference²):

$$\Delta G = \frac{1}{\beta} \ln \langle e^{\beta \, \Delta V} \rangle_1 \tag{S11}$$

where the average is made now over the sampling of the target state.

In the FEG-FEP method, described in our work, the reference and target systems correspond to the same solute-solvent system described by two different QM/MM Hamiltonians at low QM level (LL) and high QM level (HL), respectively.⁵ Hence substituting in equation (S10) above V_0 by V_{LL} and V_1 by V_{HL} , equation (3) of the manuscript is obtained.

	d _{он} (Å)	α_{HOH} (degrees)	Dipole moment (D)
HF/6-31G(d)	0.947	105.5	2.20
B3LYP/6-311+G(d,p)	0.962	105.1	2.16
QCISD/aug-cc-pVTZ	0.959	104.4	1.86
CCSD/aug-cc-pVTZ	0.959	104.4	1.86
experiment	0.957	104.5	1.85

2. Structure of the water molecule in gas phase using different methods

3. Details on FEP-FEG convergence tests

We show below the results of some tests concerning the convergence of the calculated free energy gradients or atom displacements in the FEG-FEP study of the water molecule

in liquid water reported in the paper. We discuss the convergence when the gradients are calculated using the standard equation or the approximated FEG-FEP equation separately.

1) Convergence of the standard FEG calculation

To discuss the convergence of the free energy gradient in the standard FEG calculation, let us consider the reference simulation of the water molecule in liquid water in case study 1, i. e. the QM/MM simulation at the B3LYP/6-311+G(d,p) level. The geometry of the QM water molecule corresponds to the starting structure in that study (i. e. the optimized geometry in gas phase at the HF level, d_{OH} =0.947 Å, α_{HOH} =105.5°). We analyze the data for the 40 ps simulation carried out after equilibration of the system.

Figure S1 illustrates the instantaneous value of the potential energy gradient and of its time average, i. e. the free energy gradient in the standard FEG equation:

$$\frac{\partial G}{\partial q} = \langle \frac{\partial V}{\partial q} \rangle \tag{S12}$$

For the sake of simplicity, we only show the largest component in the Figure, i. e. the oxygen Z-component. As shown, a good convergence of the free energy gradient is obtained in the first few picoseconds because despite the presence of large fluctuations of the potential energy gradient, they occur at a quite short time scale. This fact can also be illustrated with the predicted change in the geometry. For instance, after 10 ps, the predicted change in OH distance is +0.0047±0.0002 Å, very close to the final value (after 40 ps), which amounts +0.0046±0.0001 Å. Note that only half of this change is due to the gradient of the solute internal potential energy (+0.0023). We made another convergence test by comparing the results obtained using the first 20 ps and the last 20 ps. The predicted changes in OH distance are quite similar, specifically, +0.0047±0.0002 Å and +0.0045±0.0001 Å, respectively. The error bars given in these figures correspond

to the differences found for the two OH distances, which as pointed out in the manuscript are smaller than 0.0002 Å on average.



Figure S1. The potential energy gradient (the oxygen Z-component), and its time average, i.e., the free energy gradient, as a function of simulation time. Calculations correspond to the first step of the optimization process in case study 1 using the QM/MM simulation at the B3LYP/6-311+G(d,p) level

2) Convergence of the FEG-FEP calculation

To illustrate the convergence of the FEG-FEP calculation of the free energy gradient, we consider again the computations in case study 1. The free energy gradient components are calculated using the approximate equation:

$$\frac{\partial G_{HL}^{FEG-FEP}(\boldsymbol{q})}{\partial \boldsymbol{q}} = \langle \frac{\partial V_{HL}(\boldsymbol{q};\boldsymbol{s})}{\partial \boldsymbol{q}} W(\boldsymbol{q};\boldsymbol{s}) \rangle_{LL}$$
(S13)

and are compared with calculations using the standard FEG equation:

$$\frac{\partial G_{HL}^{FEG}(q)}{\partial q} = \langle \frac{\partial V_{HL}(q;s)}{\partial q} \rangle_{\rm HL}$$
(S14)

The high-level (HL) is B3LYP/6-311+G(d,p) while the low-level (LL) is HF/6-31G(d). Figure S2 displays the mean squared errors between the approximate and rigorous values of the gradient:

$$MSE = \frac{1}{9} \sum_{i=1}^{9} \left(\frac{\partial G_{HL}^{FEG}(q)}{\partial q_i} - \frac{\partial G_{HL}^{FEG-FEP}(q)}{\partial q_i} \right)^2$$
(S15)

As shown in Figure S2, a suitable agreement between the FEG and FEG-FEP gradients is obtained after 20-25 ps of simulation time. This time is significantly longer than the time required for the FEG to converge. Hence, 25 ps was considered to be the minimum simulation time to ensure that both 1) the FEG gradient is converged, and 2) the approximate FEG-FEP gradient accurately reproduces the FEG gradient. The longer time required for getting a good agreement between the FEG and FEG-FEP gradients, compared to the time required for the FEG gradient to converge, is explained by the fact that FEP calculations use the sampling from the simulation at the low level. It is therefore necessary to explore the configurational space thoroughly in order to include favorable configurations at the high level. The convergence of the FEG-FEP calculations can also be illustrated, as made above, using the predicted change in OH distance. After 25 ps, the predicted change is +0.0046±0.0001 Å, which is exactly the same than the one obtained after 40 ps with either the FEG gradient (see above), or the FEG-FEP gradient.



Figure S2. Mean squared error (MSE) of the free energy gradient components as a function of the simulation time in case study 1; we compare the rigorous FEG calculations with approximate FEG-FEP calculations in the first step of the optimization process.

Finally, we have examined the minimum number of snapshots that are necessary to get accurate averages. This is illustrated in Figure S3 using data from case study 2 for the predicted change in OH distances, at the first step of the optimization process. We use the sampling of the 40 ps simulation, but we take a number of points that varies from 125 to 4000 (by doubling the number of points each time). The snapshots in all cases are uniformly distributed along the simulation. As described in our paper, we decided to use 4000 points, i. e. one snapshot every 10 fs, but as shown in Figure S3, a good convergence is obtained using 1000 snapshots.



Figure S3. Values of the predicted OH_1 and OH_2 distances change as a function of the number of snapshots taken to calculate the average gradients in case study 2 using the FEG-FEP method (QCISD/aug-cc-pVTZ::B3LYP/6-311+G(d,p) dual level). Calculations correspond to the first step of the optimization process. The simulation time was 40 ps and the points are taken uniformly distributed along the simulation. The final converged values are d_{0H1} =0.001006 Å (full circles) and d_{0H2} =0.001010 Å (open circles).

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