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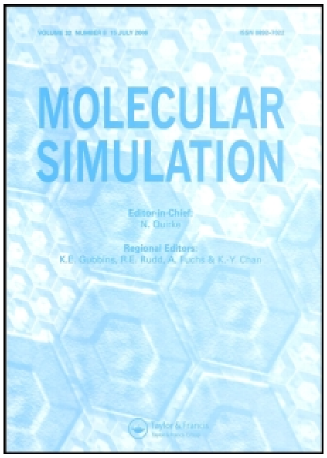

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FREE ENERGY SIMULATIONS OVER CREATION/ANNIHILATION PATHS FOR A FLEXIBLE SOLUTE

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The inclusion of molecular flexibility into free energy simulations over creation/annihilation paths has been analyzed. A new formalism is presented for such simulations with the intramolecular degrees of freedom being active during the simulation and a recently introduced path is reviewed that allows the inclusion of the flexibility using separate simulations.

Keywords: Free energy simulation; Flexible solute; Creation/annihilation path; Scaled constraint method

INTRODUCTION

Most free energy simulations are performed over a path defined by the so-called coupling parameter, that smoothly transforms the initial state into the final state [1]. The shorter this path, the less computational effort is required for the simulation. It has been argued before [1–3] that a creation/annihilation path over a nearly linear [2] path is likely to be a smooth one, allowing for reliable interpolation and, furthermore, polynomial [3] paths provide an additional improvement in this respect (see, *e.g.*, Ref. [4]). While the term ‘creation/annihilation path’ has been deemed potentially misleading, *e.g.*, by Gilson *et al.* [5], the same is true for ‘dual topology’, the frequently used alternative [6, 7] while the latter has the additional drawback of being less informative.

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Creation/annihilation paths, however, raise the problem of the treatment of molecular flexibility. It is clear that applying the creation/annihilation process to the molecular structures would lead to unsurmountable complications: the molecule would fall apart into a mixture of its contributing atoms in a practically irreversible way. With this problem in mind, the following options present themselves:

1. Calculate the free energy difference based on fixed solute conformations and approximate the intramolecular contribution to the free energy difference by the difference in the respective intramolecular energies (*i.e.*, assume that the intramolecular entropies cancel).
2. Include intramolecular degrees of freedom into the calculation of the free energy difference and perform additional simulations in the gas phase. A new formalism for this option is presented below.
3. For the special case of conformational free energy difference, it is possible to calculate the contribution of selected degrees of freedom to the free energy with simulations over a recently introduced path that releases gradually the constraints of these degrees of freedom [8]. This technique will also be reviewed below.

CREATION/ANNIHILATION SIMULATIONS WHILE INTRAMOLECULAR DEGREES OF FREEDOM ARE ACTIVE

When the intramolecular degrees of freedom are active during the simulation, the terms representing intramolecular interactions should not be affected directly by the coupling parameter λ. With this in mind, we define

$$E^i(\text{solvated}) = E^i_{\text{SLT-SLV}} + E^i_{\text{intra}}, \quad \{i = 0, 1\} \tag{1}$$

and

$$\begin{aligned} E^{*i} &= E^i_{\text{SLT-SLV}} + E^i_{\text{intra}} + E^{1-i}_{\text{intra}}, \\ &= E^i(\text{solvated}) + E^{1-i}(\text{vacuum}) \quad \{i = 0, 1\}. \end{aligned} \tag{2}$$

where the subscript ‘SLT-SLV’ refers to interactions between the solute (the species whose solvation free energy is under consideration) and the solvent and the subscript ‘intra’ refers to intramolecular energies. Then we can define a path that creates/annihilates the solute only in terms of its interaction with the solvent:

$$E(\lambda) = (1-\lambda)^k E^0_{\mathrm{SLT-SLV}} + E^0_{\mathrm{intra}} + \lambda^k E^1_{\mathrm{SLT-SLV}} + E^1_{\mathrm{intra}}. \tag{3}$$

At $\lambda = 0$ and 1 (3) returns E^{*0} and E^{*1}, respectively.

Thus, applying the standard formula for thermodynamic integration (see, *e.g.*, Ref. [1]) gives

$$\begin{aligned} \Delta A^* &= \int_0^1 \left\langle \frac{\partial E(\lambda)}{\partial \lambda} \right\rangle_\lambda \\ &= \int_0^1 k(1-\lambda)^{k-1} \langle E^0_{\mathrm{SLT-SLV}} \rangle_\lambda \\ &\quad + k\lambda^{k-1} \langle E^1_{\mathrm{SLT-SLV}} \rangle_\lambda - \Delta A^{\mathrm{vacuum}} \\ &= \Delta A^{\mathrm{solvated}} - \Delta A^{\mathrm{vacuum}}. \end{aligned} \tag{4}$$

This means that the free energy difference between fully solvated, flexible solutes, $\Delta A^{\mathrm{solvated}}$ can be obtained from a free energy simulation following (4) if a separate, vacuum calculation yields the vacuum free energy difference $\Delta A^{\mathrm{vacuum}}$. Note, that (4) includes implicitly the coupling between the intra and intermolecular degrees of freedom since $\Delta A^{\mathrm{solvated}}$ is calculated with sampling the intramolecular degrees of freedom as well.

The significance of this formalism lies in the fact that $\Delta A^{\mathrm{vacuum}}$ is likely to be easier to calculate (*e.g.*, with normal mode analysis [9] or in the quasi-harmonic approximation [10]). This will allow us to take advantage of the benefits of using a creation/annihilation path.

Note also that (4) highlights the rarely emphasized problem of carefully defining conformational free energy differences (see, *e.g.*, Refs. [11, 12]). In principle, a fully flexible solute has a single free energy (*i.e.*, $\Delta A^{\mathrm{vacuum}}$ is meaningless in this case). Thus, in order to be able to talk about conformational free energy one has to either freeze some of the conformational degrees of freedom (*e.g.*, a backbone conformation) or delineate conformational basins defined by (nonoverlapping) limits on some of the degrees of freedom.

SEPARATE CALCULATION OF CONTRIBUTION OF THE INTRAMOLECULAR DEGREES OF FREEDOM TO CONFORMATIONAL FREE ENERGY DIFFERENCES

Recently a new formalism was introduced for the calculation of the contribution of molecular flexibility to conformational free energy differences, called the *Scaled Constraint Method.* The coupling parameter was defined as a scaling factor to the limits of the internal degrees of freedom. For a system with a single internal degree of freedom x limited to a finite interval $[0, X]$ with $x = 0$ being the rigid state and $e(x)$ the intramolecular Hamiltonian with $e(0) = 0$, the (Helmholtz) free energy at coupling parameter value λ is

$$A(\lambda) = -kT \ln \int_0^{\lambda X} \exp[-e(x)/kT] dx. \tag{5}$$

Applying the fundamental law of calculus – the standard technique of the thermodynamic integration (TI) formalism – leads to

$$\Delta A = \int_0^1 \frac{\partial}{\partial\lambda} \left\{ -kT \ln \int_0^{\lambda X} \exp[-e(x)/kT] dx \right\} d\lambda. \tag{6}$$

Application of the chain rule and recognizing that the derivative of an integral with respect to its upper limit is just the integrand we obtain

$$\begin{aligned} \Delta A &= -kT \int_0^1 \frac{(\partial/\partial\lambda) \int_0^{\lambda X} \exp[-e(x)/kT] dx}{\int_0^{\lambda X} \exp[-e(x)/kT] dx} d\lambda \\ &= -kT \int_0^1 \frac{X \exp[-e(\lambda X)/kT]}{\int_0^{\lambda X} \exp[-e(x)/kT] dx} d\lambda \\ &= -kT\, X \int_0^1 \langle \delta(x - \lambda X) \rangle_\lambda \, d\lambda. \end{aligned} \tag{7}$$

Here δ denotes the Dirac δ function (whose integral is just its argument) and the integrand $\langle \delta(x - \lambda X) \rangle_\lambda$ is simply the probability density for the system hitting the limit:

$$P(\lambda X) = \lim_{\Delta x \to 0} \frac{P(x \in [\lambda X - \Delta x, \lambda X])}{\Delta x}. \tag{8}$$

Note, however, that (8) shows a divergent integrand. This divergence reflects the fact that the entropy cost of fully immobilizing a degree of freedom is infinite. Fortunately, it can be shown [8] that the TI integrand for the *difference* between two ΔA's is finite and is obtained as the difference between the P's in the two systems.

Generalizing the problem to N dimensions and to general ranges $(\mathbf{x} \in [\mathbf{X}', \mathbf{X}])$ leads to TI integrands containing term of the type

$$\frac{(\partial/\partial\lambda) \int_{\lambda X_1'}^{\lambda X_1}, \ldots, \int_{\lambda X_n'}^{\lambda X_n} \exp[-e(\mathbf{x})/kT] \, \mathbf{dx}}{\int_{\lambda X_1'}^{\lambda X_1}, \ldots, \int_{\lambda X_n'}^{\lambda X_n} \exp[-e(\mathbf{x})/kT] \, \mathbf{dx}}. \tag{9}$$

By evaluating the limit expression of the partial derivative and following the transformations in (7) it can be shown that this leads to the expression

$$\sum_{\mathrm{i}=1}^{\mathrm{n}} X_{\mathrm{i}}' P(\lambda X_{\mathrm{i}}') + X_{\mathrm{i}} P(\lambda X_{\mathrm{i}}). \tag{10}$$

An attractive feature of (10) is the fact that the increase in the dimensionality only adds additive terms to the TI integrand (*i.e.*, there are no terms directly involving more than one degree of freedom).

In Ref. [8] the Scaled Constraint Method was successfully tested on the harmonic oscillator. Methods for approximating $P(\lambda X_{\mathrm{i}})$, as well as strategies for variable runlength selection and choice of quadrature are also discussed there.

Note, however, that for (10) to be of practical use it has to be also generalized to internal coordinates. In Ref. [5] it has been argued that the formalism remains valid after a transformation to internal coordinates but it has not been tested in actual calculations. Further, its use requires simulations with hard limits on internal coordinates. This would either require the development of molecular dynamics with such hard limits or the use of Monte Carlo methods. While the Monte Carlo methodology is generally thought as inefficient for large solutes, the recently developed techniques moving a limited chain segment only [13] may change this.

CONCLUSION

Two alternatives were presented for the inclusion of intramolecular flexibility into free energy simulations performed over creation/annihilation paths. The potential smoothness of such paths provides a powerful edge over other option for large changes – in one example a 5-point quadrature was found adequate for the calculation of the solvation free-energy difference between extended and turn conformations of a decapeptide.

The formalism described in (1–4) will allow the exploitation of such path with the solute being flexible during the simulation. The recently introduced path [8], while requiring more development, is particularly promising in that it allows the free energy simulations involving the conformational change to be performed with rigid solute. Freezing out intramolecular degrees of freedom during the transformation not only reduces the computational cost of each simulation step but, more importantly, significantly reduces the dimensions of the configuration space that is to be explored by a properly converged simulation.

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