

Optimal intermediates in staged free energy calculations

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We examine the precision of free energy perturbation (FEP) methods of molecular simulation. We develop a quantitative model of the calculation in terms of the so-called f and g distributions that characterize the energies sampled in a FEP calculation. The model is then re-expressed in terms of the entropy difference between the systems of interest, and the variance of the g distribution. We apply the model to analyze the optimization of multistage insertion free energy calculations, and reach a quantitative criterion for minimizing the overall variance. The analysis indicates that the appropriate heuristic for optimizing the choice of intermediates is to select them to equalize the *entropy* differences among all stages of the overall FEP calculation. A more accurate criterion is specified, but in practice it differs little from this simpler one. We illustrate our conclusions by conducting two-stage FEP calculations using Monte Carlo simulations on Lennard-Jones (LJ) systems at several temperatures and two densities. The LJ systems differ in the presence of a single LJ particle, and the intermediate is defined to have a single hard sphere of diameter that can be used to optimize the two-stage FEP calculation. The model provides an excellent description of the precision of the FEP calculations. © 1999 American Institute of Physics.
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I. INTRODUCTION

Free energies play a critical role in modeling of many physical phenomena, including phase and reaction equilibria, solubility, stability, and kinetics. Accordingly, over the years many molecular simulation methods for the calculation of the free energy have been developed. Free energy calculations are computationally intensive. Moreover, they are highly prone to inaccuracies, even when implemented in a way that is technically correct. Simply put, the workings and limitations of free-energy calculation methods are not well understood. Improvement in this understanding can help us to avoid pitfalls when performing free-energy calculations while leading us to their most optimal implementation.

No commonly used molecular simulation method¹⁻⁴ computes the free energy A via direct summation of the partition function; rather free-energy *differences* are calculated. Often these differences are computed with respect to a reference system of known free energy (such as the ideal gas), while at other times the free-energy difference is an end in itself, such as when it is evaluated to determine the relative stability of two systems (a “system” may be defined, e.g., by the Hamiltonian or the thermodynamic state). We will use ‘0’ and ‘1’ to indicate the systems at either end of this difference calculation, defining the difference $\Delta A = A_1 - A_0$. One of the main points to be made in this paper is the importance of the entropy S in guiding the formulation of an effective free-energy calculation scheme. Accordingly, and without loss of generality, we will adopt a convention in which the 0 system is the one with the larger entropy, so that $S_0 > S_1$ and $\Delta S < 0$.

Free-energy difference methods can be (roughly) categorized into free-energy perturbation, expanded ensembles, thermodynamic integration, and histogram/distribution methods.⁵ The first of these, free-energy perturbation (FEP) methods, computes the free-energy difference between two systems while sampling only one of them. We will designate as the *reference* that system which governs the sampling of configurations; the system at the other end of the free-energy difference, and which does not govern the sampling, we designate as the *target*. Note that our definition of the reference and the target are based on how the FEP method is implemented, while our 0 and 1 designations depend only on their states or Hamiltonians. Thus the free-energy perturbation method may be applied such that either the 0 or the 1 system serves as the reference, while the other forms the target.

Single-stage FEP methods yield ΔA via a single ensemble average. In contrast, many free-energy methods require multiple simulations to produce a result, so the ability to complete a ΔA calculation in one simulation makes single-stage FEP methods very appealing. Widom’s insertion technique^{6,7} for computing the chemical potential is a widely used single-stage FEP method. It yields the chemical potential, the free-energy difference between systems differing by a single molecule. Like all single-stage methods it is short on flexibility, which is both a feature and a weakness. Its inflexibility frees the user from the burden of deciding how to best implement it—its implementation neither permits nor requires any tuning for proper use. This is appealing because it minimizes the danger of making a bad implementation decision. On the other hand, when the method fails one is left with little recourse to adjust its operation and thereby improve its performance. Excluded volume map methods⁸ can

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TABLE I. Four approaches to construct two-stage free-energy perturbations. Arrows point from the reference to the target for each calculation scheme. We assume that the entropy decreases from system 0 to system 1, so arrows pointing to the right describe *generalized insertion* perturbation calculations.

Staging approach	Method name
$0 \leftarrow W \rightarrow 1$	Umbrella sampling
$0 \rightarrow W \leftarrow 1$	Bennett's method
$0 \rightarrow W \rightarrow 1$	Staged insertion
$0 \leftarrow W \leftarrow 1$	Staged deletion

help, but they are limited in their ability to extend the basic approach.

With single-stage methods one has only the choice of which of the two systems (0 and 1) forms the reference (and thus governs the sampling) and which is the target. There exist a complement to the Widom insertion method in which the free-energy difference is computed by deletion of an existing molecule rather than insertion of a new one.⁹ Although equally easy to implement, Widom deletion is never used because it is wildly inaccurate.^{5,10–16} This well-known asymmetry in the Widom calculation is symptomatic of an asymmetry in the general FEP calculation. The performance of these calculations depends greatly on which system is selected as the reference and which is the target. We have advocated^{5,16} a heuristic such that the FEP is always performed in what we refer to as the *insertion* direction. With this choice, the reference system selected to have greater entropy, and the target is the system of smaller entropy. An incorrect choice here can lead to inaccuracies, but unlike Widom deletion the inaccuracies may not be so wild as to make the user suspect a problem. A more thorough treatment and demonstration of this effect is planned for a subsequent publication.

Multistage FEP methods arise as the natural generalization of single-stage methods. The basic idea of multistage methods is to construct intermediate system(s) between the reference and target systems, and to evaluate the overall free-energy difference by summing the successive differences associated with the intervening stages. Each intermediate is defined in terms of a phase-space weighting function or modified Hamiltonian. We will use the symbol W to indicate an intermediate system, and we will make the assumption that the entropy of the intermediate lies between the entropies of the 0 and 1 systems: $S_0 > S_W > S_1$. We lose some generality in making this assumption, but it facilitates our analysis and discussion, and in cases where it does not hold one may apply the concepts here with only minor modification.

Introduction of even a single intermediate system presents a great variety of choices for improving (or ruining!) a free-energy calculation. First, one has four possible ways of making the reference/target designation for the two free-energy difference calculations.^{5,17} Two of the choices are commonly known as umbrella sampling^{18,19} and Bennett's method,²⁰ respectively. The other two choices we call staged insertion and staged deletion.^{5,16} Table I summarizes the methods. Of these four methods, only staged insertion

involves no deletion component in the overall free energy calculation. All of the other methods include a reference/target choice that leads to a deletion-perturbation calculation (given our assumption about the relative entropies). In previous work⁵ we examined all these methods for a hard-core system and found that optimally staged insertion is the most efficient and precise multistage scheme. We anticipate that the superiority of staged insertion holds generally, but at present this matter is not definitively resolved.²¹ For the remainder of this article we shall examine only staged-insertion FEP calculations.

Additional choices accompanying the introduction of an intermediate lay in the specification of details that define it. Usually the intermediate interpolates the two states of interest. The degree to which this intermediate is more like one state or the other is available to optimize the calculation. Clearly, the aim should be to use this degree of freedom to minimize the overall variance, computed as the sum of variances for each intermediate stage (assuming sampling for each stage is independent of the others). The issue of optimization of multistage FEP methods has been examined by several researchers. Bennett²⁰ first did this, and was able to make much progress in formulating the optimization conditions because his staging method is such that the intermediate always represents the target, not the reference. Thus the weighting function never affects the sampling, which greatly eases the optimization process. Subsequently Perlman and Kollman,²² Straatsma and McCammon,²³ Radmer and Kollman,¹⁷ and Boulougoris *et al.*²¹ have put forth optimization heuristics for other staging approaches. Most often, *free-energy* differences are treated as the central quantity in specifying the optimum. Recently, we have argued^{5,16} that the entropy difference, rather than free-energy difference, is the quantity needed to be considered for the optimization. This is the primary issue we examine in the present work.

As an expansion of our previous work, the current study presents a quantitative description of the variance involved in the staged insertion method. We develop a model of the simulation to investigate the uncertainty rather than to analyze the simulation results directly. To do so, first we present in the Sec. II a quantitative model to characterize the variance in a single-stage FEP calculation. We analyze this model to ascertain the optimal intermediate for the staged-insertion method, and show that the entropy is indeed much more important than the free energy in prescribing the optimum. Then in Sec. III we describe simulations used to test these conclusions as applied to the computation of the chemical potential in the Lennard-Jones (LJ) model using a single hard sphere to define the intermediate system. In Sec. IV we discuss the results of the comparison, and concluding remarks are presented in Sec. V.

II. BACKGROUND AND THEORY

A. Single-stage free energy perturbation method

In the single-stage FEP method,²⁴ the free-energy difference between two systems 0 and 1 is given as

$$\begin{aligned} \exp[-\Delta(\beta A)] &\equiv \exp\{-[(\beta A)_1 - (\beta A)_0]\} \\ &= \langle \exp\{-[(\beta U)_1 - (\beta U)_0]\} \rangle_0 \\ &\equiv \langle \exp[-\Delta(\beta U)] \rangle_0, \end{aligned} \quad (1)$$

where U is the potential energy (we ignore momentum contributions to the Hamiltonian, assuming they are the same in both systems), $\beta = 1/kT$ with k the Boltzmann's constant, and T the absolute temperature. The subscripted angle brackets $\langle \cdots \rangle_0$ indicate the canonical-ensemble average at system 0, which thus forms the reference while the system 1 is the target. The delta operator (Δ) always describes a difference between the 0 and 1 systems, formed as (system-1 property) minus (system-0 property).

Given our entropy convention for the 0 and 1 systems, Eq. (1) describes what we call an insertion calculation. The deletion counterpart implements the formula

$$\exp[+\Delta(\beta A)] = \langle \exp[+\Delta(\beta U)] \rangle_1. \quad (2)$$

Often the temperatures of the 0 and 1 systems are the same, $\beta_0 = \beta_1$, and to simplify the notation we will henceforth assume that this is the case.

B. Modeling of variance calculation: Example using hard-sphere chemical potential

The variance statistic addresses the question of reproducibility, or precision, of a simulation average. In principle, the variance characterizes the spread observed upon performing an infinite number L of averages, each taken on a finite sample of size that we designate as M . In practice only one average ($L = 1$, or some other very small number) of length M is taken, and the variance, which is used to formulate the confidence limits on the measurement, must be estimated. This estimate may itself be subject to substantial imprecision, or even inaccuracy (systematic error), but we will not be concerned with such complications here. We conduct our analysis considering the true (infinite L) variance of the distribution of outcomes for the measurement process. We are able to do this because we consider models of the simulation, rather than simulation data themselves, to perform our analysis.

In previous work⁵ we set up such a model for chemical-potential measurement of hard-sphere systems via the single-stage (Widom) insertion method. The analysis is very simple, because each insertion attempt has only two possible outcomes, contributing zero or unity, respectively, to the ensemble average. For M independent insertion trials, the probability p_M that exactly m succeed (do not encounter overlap) is given by the binomial distribution

$$p_M(m; p_1) = \binom{M}{m} p_1^m (1-p_1)^{M-m}, \quad (3)$$

where p_1 is the probability that any single insertion attempt is successful. The mean of this distribution is Mp_1 , and its variance is $Mp_1(1-p_1)$. The mean and variance for $\exp(-\beta\Delta A)$ are given simply by dividing these expressions by M or M^2 , respectively; the variance of $\beta\Delta A$ itself is estimated from a straightforward propagation-of-error formula, resulting in

$$\sigma_{\beta\Delta A}^2 = \frac{1-p_1}{Mp_1}. \quad (4)$$

From Eq. (4) we can see the group $M\sigma^2$ is independent of the number of measurements, M . This well-known independence is true for all free-energy measurement methods for M sufficiently large ("sufficiently large" is a condition that is sometimes difficult to meet). Therefore, $M\sigma^2$ is the appropriate quantity to characterize the variance, smaller obviously being better.

The key parameter of this model is the probability p_1 , which can be estimated from the Carnahan–Starling equation of state.²⁵ Model predictions for the variance and extensive simulation data have been compared at several densities, and they agree very well. Clearly, this outcome demonstrates that a properly derived model of the simulation can provide reliable estimates of the simulation performance statistics, in this case the variance of an ensemble average. Complications surface when one confronts more realistic or complicated systems which are not simply characterized in terms of a single probability such as p_1 . But this difficulty does not debase the idea of characterizing the variance via modeling. The point is to identify the proper features that describe the essence of simulation process. Quantifying the behavior of the simulation can be done in terms of simulation parameters and statistical-mechanical properties of the simulated system.

C. f and g distributions

For continuous intermolecular-potential models (unlike hard spheres) potential-energy differences ΔU are sampled (via sampling of phase space) on a continuum. Clearly, the variance in free-energy estimates is closely related to the sampling statistics of the potential-energy difference. These statistics can be extracted from probability distributions that describe the likelihood of the system sampling a configuration in which ΔU has a given value. For chemical-potential calculations these probability distributions were studied by Shing and Gubbins⁹ and are commonly known as the f and g distributions. For the chemical potential calculation, f refers to the system of $N-1$ molecules, while g refers to that containing N molecules. To generalize their notation for application to arbitrary free-energy difference calculations, we define f as the probability density of energy differences ΔU encountered when sampling the system 0 (of larger entropy); correspondingly g is the probability density of energy differences for sampling of system 1.

During ensemble averaging a simulation samples values of ΔU , which for the moment we assume can take on only a discrete set of values, with n the number of such values. The f and g distributions can be measured by making histograms of sampled energies during the simulation. Then the free-energy change is given as^{4,9}

$$\exp(-\beta\Delta A) = \sum_{i=1}^n f(\Delta U_i) \exp(-\beta\Delta U_i), \quad (5)$$

$$\exp(\beta\Delta A) = \sum_{i=1}^n g(\Delta U_i) \exp(\beta\Delta U_i), \quad (6)$$

where the sums run over all n values of ΔU_i . Note that both f and g are normalized to unity, and Eqs. (5) and (6) are identical to Eqs. (1) and (2) in Sec. II A, respectively. It is recognized that f and g can be related as follows:^{4,9}

$$\Delta A = \ln g(\Delta U) - \ln f(\Delta U) + \Delta U, \quad (7)$$

or

$$g(\Delta U) \exp(\Delta U) = f(\Delta U) \exp(\Delta A). \quad (8)$$

D. Modeling of variance calculation

We can model the variance in the calculation of ΔA in terms of f and/or g , basing the analysis on Eqs. (5) or (6). Depending on the choice of target and reference, the probability of observing a particular value ΔU_i is given by $f_i = f(\Delta U_i)$ or $g_i = g(\Delta U_i)$ and each observed value contributes $\exp(-\beta\Delta U_i)$ or $\exp(+\beta\Delta U_i)$ to the ensemble average. To treat both cases, we will designate the probability as p_i and the contribution as y_i .

We perform M independent samples of y in a simulation, and suppose we perform L independent simulations. In the j th simulation we observe the average

$$\langle y \rangle^{(j)} = \sum_{i=1}^n p_i^{(j)} y_i, \quad j=1, \dots, L,$$

with $p_i^{(j)}$ the fraction of time that the energy was in bin i during the j th simulation. The average of y over all simulations is then given by

$$\bar{y} = \frac{1}{L} \sum_{j=1}^L \langle y \rangle^{(j)} = \frac{1}{L} \sum_{j=1}^L \sum_{i=1}^n p_i^{(j)} y_i = \sum_{i=1}^n \bar{p}_i y_i, \quad (9)$$

where

$$\bar{p}_i = \frac{1}{L} \sum_{j=1}^L p_i^{(j)}.$$

The variance of \bar{y} , $\sigma_{\bar{y}}^2$, can be written as

$$\begin{aligned} \sigma_{\bar{y}}^2 &= \frac{1}{L} \sum_{j=1}^L (\langle y \rangle^{(j)} - \bar{y})^2 \\ &= \frac{1}{L} \sum_{j=1}^L \left[\sum_{i=1}^n (y_i p_i^{(j)} - y_i \bar{p}_i) \right]^2 \\ &= \sum_{i=1}^n y_i^2 \overline{(\delta p_i)^2} + \sum_{i=1}^n \sum_{k \neq i}^n y_i y_k \overline{\delta p_i \delta p_k}, \end{aligned} \quad (10)$$

where $\delta p_i^{(j)} = p_i^{(j)} - \bar{p}_i$. The number of times m_i that bin i is sampled during the L independent measurements follows a binomial distribution, and its variance is $M p_i(1-p_i)$. It follows that

$$\overline{(\delta p_i)^2} = \frac{1}{M^2} \overline{(\delta m_i)^2} = \frac{1}{M} p_i(1-p_i) \quad (11)$$

and for the covariance term in Eq. (10), it can be shown that

$$\overline{\delta p_i \delta p_k} = -\frac{1}{M} p_i p_k. \quad (12)$$

Then the variance of \bar{y} becomes

$$\sigma_{\bar{y}}^2 = \frac{1}{M} \left[\sum_{i=1}^n y_i^2 p_i(1-p_i) - \sum_{i=1}^n y_i p_i \sum_{k \neq i}^n y_k p_k \right]. \quad (13)$$

When M is large, Eq. (13) can be approximated as

$$M \sigma_{\bar{y}}^2 \cong \sum_{i=1}^n y_i^2 p_i(1-p_i) - \bar{y}^2. \quad (14)$$

For the free-energy calculation, this analysis yields the variance in $\exp(\pm\beta\Delta A)$, from which we obtain the variance in $\beta\Delta A$ itself. For the case where sampling is performed according to the f distribution (insertion).

$$(M \sigma^2)_{\text{ins}} = \exp(2\beta\Delta A) \sum_{i=1}^n \exp(-2\beta\Delta U_i) f_i(1-f_i) - 1. \quad (15)$$

For large n (the continuum limit), f_i is a small number and f_i^2 can be ignored; also, we can neglect 1 on the right hand side (RHS) of Eq. (15) because it contributes very little to $M \sigma^2$, which is typically on the order of 1000 or more. Then we get

$$(M \sigma^2)_{\text{ins}} = \exp(2\beta\Delta A) \sum_{i=1}^n \exp(-2\beta\Delta U_i) f_i. \quad (16)$$

By noting the relationship between f and g distributions [Eq. (8)], we have

$$(M \sigma^2)_{\text{ins}} = \exp(\beta\Delta A) \sum_{i=1}^n \exp(-\beta\Delta U_i) g_i. \quad (17)$$

Formulas for the deletion calculation are derived in a similar way. We get

$$\begin{aligned} (M \sigma^2)_{\text{del}} &= \exp(-2\beta\Delta A) \sum_{i=1}^n \exp(2\beta\Delta U_i) g_i(1-g_i) - 1 \\ &\cong \exp(-2\beta\Delta A) \sum_{i=1}^n \exp(2\beta\Delta U_i) g_i, \end{aligned} \quad (18)$$

or,

$$(M \sigma^2)_{\text{del}} = \exp(-\beta\Delta A) \sum_{i=1}^n \exp(\beta\Delta U_i) f_i. \quad (19)$$

Continuum versions of these formulas are obtained simply by replacing the sums by integrals over ΔU , and writing $f(\Delta U)d(\Delta U)$ in place of f_i (likewise for g_i). Some of the formulas we derive here have been derived independently, and presented in a different form, by Radmer and Kollman.¹⁷

E. Energy and entropy components

Our aim is to apply Eq. (17) for the purpose of optimizing multistage insertion FEP calculations. A practical weakness in the equations of the preceding section is the general difficulty of knowing the f and g distributions, particularly *a priori*. However we can apply these formulas to develop a very useful heuristic to guide the formulation of a multistage sampling scheme, without detailed knowledge of f and/or g .

Thermodynamics tells us that the free-energy difference can be written in terms of the differences in energy and entropy, that is,

$$\beta\Delta A = \beta\Delta U - \Delta S/k. \quad (20)$$

Substitution of Eq. (20) into Eq. (17) yields

$$(M\sigma^2)_{\text{ins}} = \exp(-\Delta S/k) \sum g_i \exp[-\beta(\Delta U_i - \langle \Delta U \rangle)]. \quad (21)$$

Typically, the g distribution is narrowly peaked near $\langle \Delta U \rangle$, so that $\beta(\Delta U_i - \langle \Delta U \rangle)$ is small where g_i is non-negligible. Application of a Taylor series expansion near $\langle \Delta U \rangle$ for Eq. (21) yields (to second order)

$$(M\sigma^2)_{\text{ins}} = \exp(-\Delta S/k) \sum g_i \left[1 + \frac{1}{2} \beta^2 (\Delta U_i - \langle \Delta U \rangle)^2 \right] \\ = \exp(-\Delta S/k) \left(1 + \frac{1}{2} \beta^2 \hat{\sigma}_{\Delta U}^2 \right), \quad (22)$$

where $\hat{\sigma}_{\Delta U}^2$ indicates the variance of the energy difference between two states (based on distribution g). It should be emphasized that $\hat{\sigma}_{\Delta U}^2$ is an ensemble statistic, and is of a different nature than the variance in the FEP calculation, which is a function of the length of the simulation M . To simplify the notation we define

$$\zeta \equiv 1 + \frac{1}{2} \beta^2 \hat{\sigma}_{\Delta U}^2, \quad (23)$$

then Eq. (22) becomes

$$(M\sigma^2)_{\text{ins}} = \zeta \exp(-\Delta S/k). \quad (24)$$

Because this applies to an insertion FEP calculation, ΔS is negative. As in our previous work,⁵ if we adopt a picture in which the configurations important to the target system form a subset of the configurations important to the reference, then $\exp(+\Delta S/k)$ can be loosely characterized as the probability that a randomly selected configuration of the reference system will lie in the range of configurations important to the target system. For the hard-sphere system discussed above this interpretation is more precise, and in particular we have $p_1 = \exp(+\Delta S/k)$, and Eqs. (4) and (24) agree, assuming p_1 is small. The term $\exp(-\Delta S/k)$ describes the precision with which the entropy difference by itself is measured. In general, the total variance in the free energy contains in addition contributions from the variance in the measurement of the energy (this contribution is zero for hard spheres). Knowledge about the energy difference ΔU is obtained during the simulation *only when the system encounters target-system configurations*. Since the fraction of all configurations in which this happens is given by $\exp(+\Delta S/k)$, the entropy term again plays a role in determining the energy contribution to the variance, as can be seen in Eqs. (22) or (24). Note that the intrinsic variance of the energy in the target state is divided by this fraction, in effect reducing M to an effective value reflecting the actual number of configurations that contributed to the measurement of ΔU .

F. Multistage insertion method

In a multistage insertion method, intermediate states are constructed between the reference and target states. An intermediate is defined by the potential Φ_{U_i} , which in turn is defined via a weight function W_i : $\Phi_{U_i} = U_0 - \ln W_i$. The relationship is schematically shown as

$$(0) \rightarrow (W_1) \rightarrow (W_2) \rightarrow \dots \rightarrow (W_k) \rightarrow (1).$$

For staged insertion, the entropy of state W_i is larger than that of state W_{i+1} . The total free-energy difference is divided into a series of successive and smaller ones. We define the i th stage as the process from state W_i to W_{i+1} ; state $W_0 \equiv 0$, and state $W_{k+1} \equiv 1$, where k is the number of intermediate states. The free-energy difference between states W_i and W_{i+1} is referred to as ΔA_i . Then the overall free-energy difference is given by

$$\Delta A = \sum_{i=0}^k \Delta A_i. \quad (25)$$

The working formula, Eq. (1), becomes

$$\exp(-\beta \Delta A) = \prod_{i=0}^k \langle \exp(-\beta \Delta U_i) \rangle_i, \quad (26)$$

where ΔU_i is the potential energy difference between states W_{i+1} and W_i .

Assuming simulations for the stages are mutually independent, the overall variance of the free energy calculation is the sum of the variance for each stage. The free energy is a state function, and the difference between state 0 and 1 will not be affected by the choice of intermediate states W_i , but it is clear that this choice will affect the corresponding variances and thereby affect the overall variance. Hence, by defining proper intermediate states, it is possible to minimize the overall simulation variance and improve the simulation efficiency. This raises two questions. The first concerns the number of intermediate states to be used. The optimal number will depend on the specific system and thermodynamic state. For calculation of the hard-sphere chemical potential, for example, we found⁵ that the optimal number of intermediates increased from zero at low density to about ten at the highest fluid density; however, the minimum with respect to the number of stages was very shallow, and the greatest gain came with the introduction of the first intermediate state. The second question concerns the choice of the weighting function(s) that defines the intermediate states. This is the main point that we now address.

G. Optimization of multistage insertion method

Samplings on different stages are independent and the overall variance is the sum of those for individual stages. That is

$$(M\sigma^2)_{\text{tot}} = \sum_{i=0}^k (M\sigma^2)_i. \quad (27)$$

With Eq. (24) into the RHS of Eq. (27), we get

$$(M\sigma^2)_{\text{tot}} = \sum_{i=0}^k \zeta_i \exp(-\Delta S_i/k), \quad (28)$$

where $\zeta_i = 1 + \frac{1}{2} \beta^2 \hat{\sigma}_{\Delta U,i}^2$, with $\hat{\sigma}_{\Delta U,i}^2$ the variance of energy change in the i th stage.

The entropy is a state variable. Hence, the overall entropy difference between state 0 and 1 is the sum of those of all individual stages, regardless of how they are defined, i.e.,

$$\Delta S_{\text{tot}} = \sum_{i=0}^k \Delta S_i. \quad (29)$$

We can apply the Lagrange multiplier method to find the minimum of the overall variance with the constraint of Eq. (29). It is easy to show that corresponding to the minimum variance (or the optimization process), the entropy difference between the i th and j th stages is

$$\Delta(\Delta S)_{ij} \equiv \Delta S_j - \Delta S_i = k \ln(\zeta_j / \zeta_i), \quad (30)$$

or

$$\zeta_i \exp(-\Delta S_i / k) = \text{constant}. \quad (31)$$

It is interesting to note that, if there is no contribution from the energy difference to the overall variance, then $\Delta(\Delta S/k)$ corresponding the optimized stages will be 0. That is, optimal staging is obtained by choosing weighting functions that offer *equal entropy differences* for all stages. This criterion differs significantly from the one often used to guide staging calculations, namely a criterion that aims to equalize the free-energy differences of all stages.^{17,22,23} The more general case, for which Eq. (31) describes the uniform quantity for optimal staging, adheres much more closely to the uniform-entropy criterion than to anything else. So, if lacking information about the energy variance, the uniform-entropy criterion provides a simple rule-of-thumb to guide selection of intermediate states.

III. TESTS

A. System definition

To test and demonstrate our analysis, we examine the calculation of the chemical potential of the LJ model at several temperatures and densities, using a single intermediate stage that leads to the insertion of a LJ particle via a hard-sphere (HS) intermediate. We consider optimization of this calculation by adjustment of the diameter of the HS, α . The systems and their relationships are shown schematically in Fig. 1. The system 0 contains $(N-1)$ LJ particles and a single ideal-gas particle (the N th particle) which has no interaction with the LJ particles. In the intermediate system W the N th particle interacts with the other $(N-1)$ LJ particles as a HS of diameter α ; that is, the HS and a LJ particle have infinite interaction energy if separated by a distance less than α , and have zero energy otherwise. The final system 1 has N identical LJ particles, and thus differs from the intermediate by conversion of the N th particle from the HS to a LJ sphere. The difference in free energy between systems 0 and 1 gives the chemical potential. For α not too large (certainly less than the LJ diameter), it is clear that the “insertion” direction is from system 0 to the intermediate, and from the intermediate to system 1: $0 \rightarrow W \rightarrow 1$, as shown in Fig. 1. Consequently this is the staging approach that we will examine.

By our specific definition of the systems, Eqs. (28) and (30) can be simplified. Note in the intermediate W , if the HS is overlapping with any other particle, then the system energy will be infinite and this configuration will be rejected in the Monte Carlo simulation. This means that configurations in W that include the overlap of HS and LJ particles will

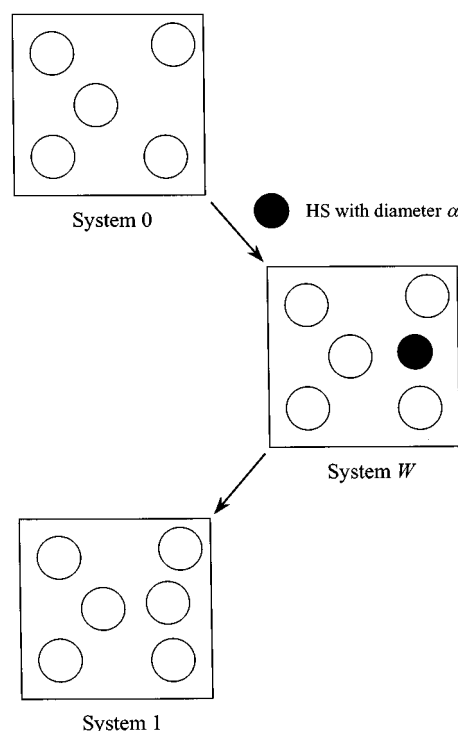


FIG. 1. Depiction of staged-insertion scheme to compute the free-energy change associated with the addition of a LJ molecule to a pure LJ fluid.

never happen. By the definition of the HS potential model, we know $\Delta U_{\text{HS}} = 0$, further, $\hat{\sigma}_{\Delta U, \text{HS}}^2 = 0$ and $\zeta_{\text{HS}} = 1$. Here and in the following context, we use subscript HS to refer to the $0 \rightarrow W$ (HS insertion) stage, and subscript LJ for the $W \rightarrow 1$ (HS converts to LJ particle) stage. Equations (28) and (30) then become

$$(M\sigma^2)_{\text{tot}} = \exp(-\Delta S_{\text{HS}}/k) + \zeta_{\text{LJ}} \exp(-\Delta S_{\text{LJ}}/k), \quad (32)$$

$$\Delta(\Delta S/k) = \ln \zeta_{\text{LJ}}, \quad (33)$$

and

$$\Delta S_{\text{LJ}}/k = \frac{1}{2}[\Delta S_{\text{tot}}/k - \ln(\zeta_{\text{LJ}})]. \quad (34)$$

B. Simulation details

We conducted Monte Carlo (MC) simulations in the canonical (NVT) ensemble, examining different choices of system density ρ , temperature T , and HS diameter α (all quantities are given in units of the LJ size and energy parameters); the states are summarized in Table II. For the sake of

TABLE II. Summary of simulation conditions. Temperature and density are given in units of the Lennard-Jones energy and size parameters.

Series	Particle number, N	Temperature, T	Density, ρ
A	108	0.8	0.9
B	108	1.0	0.9
C	108	1.2	0.9
D	108	1.4	0.9
E	108	2.0	0.9
F	108	4.0	0.9
G	500	1.4	0.9
H	200	1.0	0.8

TABLE III. Average energy per particle (U/N), overall entropy change ($\Delta S_{\text{tot}}/k$) calculated in the simulations, and quantities related to the optimization of stages. The variance of the potential energy change $\sigma_{\Delta U}^2$ and ζ_{LJ} are calculated from the g distribution. Difference in entropy change $\Delta(\Delta S/k)$ and difference in free-energy change $\Delta(\beta\Delta A)$ between the optimal two stages are also presented. All calculation formulas are described in the text. Simulation conditions for each series are given in Table II. The star symbol indicates the optimal staging.

Series	A	B	C	D	E	F	G	H
U/N	-5.771	-5.370	-5.322	-5.121	-4.581	-3.065	-5.121	-5.161
$\Delta S_{\text{tot}}/k$	-13.286	-11.845	-11.443	-10.822	-9.455	-7.288	-10.928	-8.853
$\sigma_{\Delta U}^2$	1.802	2.592	3.519	4.598	8.296	24.256	4.671	5.624
ζ_{LJ}	2.408	2.296	2.222	2.173	2.037	1.758	2.191	3.812
$\Delta(\Delta S/k)^*$	0.879	0.831	0.798	0.776	0.711	0.564	0.784	1.338
$\Delta(\beta\Delta A)^*$	-15.306	-11.571	-9.668	-8.092	-5.292	-2.096	-8.100	-11.66

efficiency, we performed calculations for both free-energy stages in a single simulation. Thus all simulations were conducted using $(N-1)$ LJ molecules and a single hard sphere. In principle this adds to the finite-size effects in the first stage of the free-energy calculation, but we neglect this error as our primary concern is with the precision and not the accuracy of the calculation. The LJ potentials are truncated at a separation of 2.5, and a long-range correction is *not* included.

In each simulation we perform 10 000 cycles, where one cycle comprises one attempted MC trial move per particle, one attempted trial swap of coordinates of the HS with a LJ particle, and one attempt to move the HS to a new position chosen randomly in the simulation box. At the end of each cycle one Widom trial insertion of an additional HS is performed. For each state, up to 50 independent simulations were conducted as described, each beginning from an independently equilibrated configuration (and not from a configuration obtained from one of the other runs). These runs provide us with completely independent free-energy measurements with which to gauge the precision of the calculation.

Most simulations were performed for $N=108$ particles, but in a few cases larger systems ($N=200$ or 500) were examined.

Certain averages are needed to implement our model of the calculation. The entropy difference for either stage is calculated from the simulation data. For the HS insertion stage there is no energy change, so $\Delta S_{\text{HS}}/k = -\beta\Delta A_{\text{HS}}$. The energy change associated with converting the HS to a LJ particle is just twice the average energy per particle for the LJ system, as reported by Parsonage.¹⁵ So $\Delta S_{\text{LJ}}/k = 2\beta(U/N) - \beta\Delta A_{\text{LJ}}$. Values of the average energy per particle for each series are listed in Table III. We also measured the variance in this quantity for evaluation of ζ , and these values are also recorded in Table III.

IV. RESULTS AND DISCUSSION

Simulation results of the overall free-energy difference ΔA , and its components for each stage are presented as a function of the intermediate HS diameter α in Fig. 2. The overall free-energy difference is the sum of those of the two

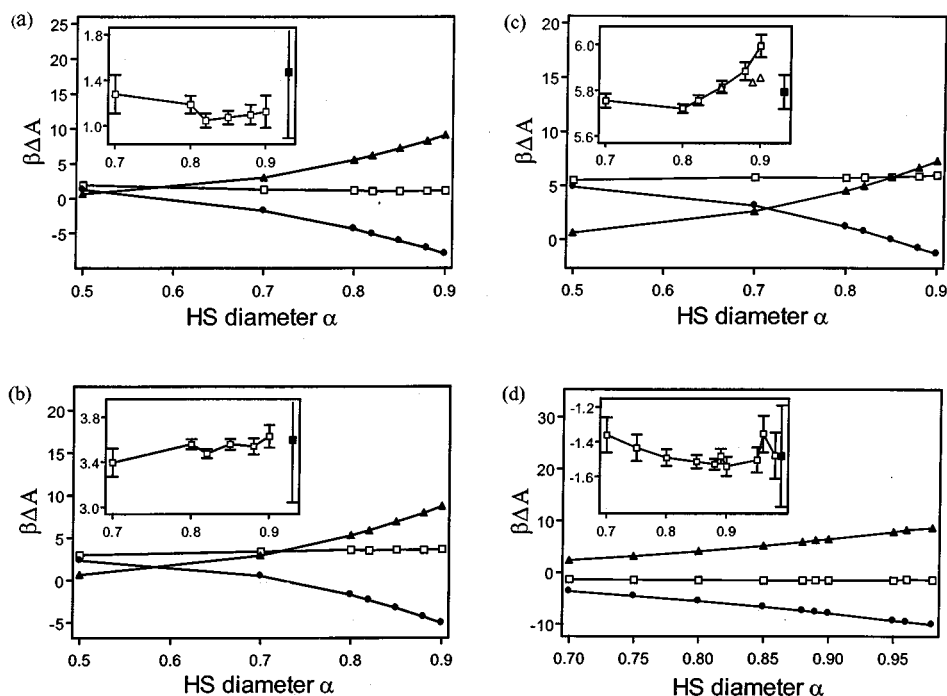


FIG. 2. Simulation results of the overall free-energy difference ΔA (open squares), and its components: HS insertion stage (ΔA_{HS} , filled triangles) and HS \rightarrow LJ stage (ΔA_{LJ} , filled circles) as functions of the intermediate HS diameter α . In the inset box shows an expanded view of the figure, centered on ΔA , with confidence limits (67%) indicated. The average free-energy difference from single-stage Widom insertion calculation and its confidence limits are also given (as the rightmost filled-square datum) in the inset box. For plot (c), the open triangles in the inset represent the corrected free-energy estimates, as described in the text. Simulation conditions: (a) $N=108$, $T=1.0$, $\rho=0.9$; (b) $N=108$, $T=1.4$, $\rho=0.9$; (c) $N=108$, $T=4.0$, $\rho=0.9$; (d) $N=200$, $T=1.0$, $\rho=0.8$.

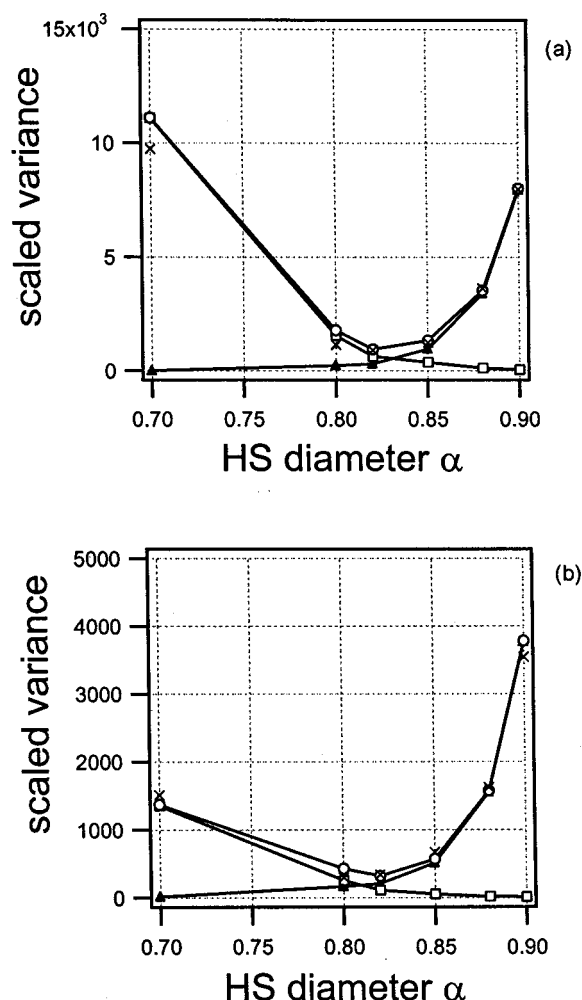


FIG. 3. Scaled variance $M\sigma^2$ as a function of intermediate HS diameter α . The overall variance (open circles) are the sum of those of two stages: HS insertion (filled triangles) and HS \rightarrow LJ (open squares). Values calculated via the variance model are also shown (crosses). Simulation conditions: (a) $N = 108$, $T = 1.2$, $\rho = 0.9$; (b) $N = 108$, $T = 2.0$, $\rho = 0.9$.

individual stages. The free-energy estimates for various α are mutually consistent, considering their confidence limits. A significant exception to this observation occurs at high temperature and large α ; the origin of this discrepancy is discussed below. In Fig. 2 we also present the free-energy difference obtained by using the single-stage Widom insertion method, under the same simulation conditions as the two-stage counterpart. The confidence limits on the single-stage calculation are much greater than those of the two-stage method, reflecting the much poorer reproducibility of the results. If efficiency of the free-energy calculation is the only consideration, it is clear that the multistage approach is preferred.

The variance statistic describing the L free-energy measurements taken for each FEP calculation are given in Fig. 3, again broken into its contributions from the two stages. As one would expect, the variance associated with HS insertion is an increasing function of HS diameter α , while the variance of HS \rightarrow LJ is a decreasing function in the range of interest. The overall variance therefore has a minimum at a certain value of α , which corresponds to the optimal inter-

mediate. We also present in Fig. 3 data calculated by our variance model, which gives an excellent description of the simulation variance.

Figure 4 presents the scaled variance as a function of α for several state conditions. It also shows the difference between the two stages in the values of the entropy and free-energy differences, respectively $\Delta(\Delta S/k)$ and $\Delta(\beta\Delta A)$. Finally, Fig. 4 also indicates the value of α at which Eq. (34) predicts that the variance will be a minimum. Several points are worth noting. First, the model works very well at locating the optimal intermediate. Second, this optimum adheres closely to the simple heuristic $\Delta(\Delta S/k) = 0$. Third, the commonly applied rule of thumb $\Delta(\beta\Delta A) = 0$ corresponds to a variance that is up to two orders of magnitude greater than the optimum, and clearly provides a bad guideline to follow in formulating an intermediate state.

Finally, we note that the optimum diameter decreases slightly with increasing temperature. This can be understood as follows. For fixed α , the entropy change for HS insertion is relatively insensitive to temperature. However the entropy change for the second stage HS \rightarrow LJ decreases with increasing temperature, because as T increases larger energies become viable ($e^{-\beta U}$ is not as small) and the LJ particles explore configurations in which they are closer together. This means that the N -particle LJ system explores more of the configurations that were previously seen only in the HS intermediate. This situation corresponds to a smaller entropy difference between the W and 1 systems. Consequently, the optimal intermediate moves to a smaller diameter to re-equalize the entropy differences for the two stages.

As noted above, there is a consistent, reproducible discrepancy in the calculation for the large- α intermediates when applied at the higher temperatures. This outcome is connected to the considerations just described. It occurs because at these conditions the intermediate system incompletely samples all the relevant configurations of the N -particle LJ system. Because at higher temperature the LJ particles can come closer together, a small but significant fraction of the configurations of the LJ target system have some particles separated by a distance less than α . The problem is exacerbated at higher temperature and larger α . It is easily remedied by using (for example) a soft-sphere instead of a hard-sphere potential as the intermediate. Alternatively a correction may be applied by recording during a simulation the fraction of the total configurations in which a given LJ particle has a nearest neighbor closer than α . If this fraction is denoted ϕ , then the corrected free energy is obtained by adding $kT \ln(1 - \phi)$ to the previous value. The so-corrected values are included in Fig. 2(c). For the range of α used, the correction is measurable only at the highest temperature of the study.

At a single state ($\rho = 0.9$ and $T = 1.4$) we performed simulations of 500-particle systems to examine the finite-size effect in our calculations. Results are listed in Table IV, where data for $N = 108$ systems under the same conditions are also presented for comparison. From Table IV we can see the free-energy estimates from both systems are in good agreement, although the larger-system result is consistently higher by about 3%; presumably this is a finite-size effect.

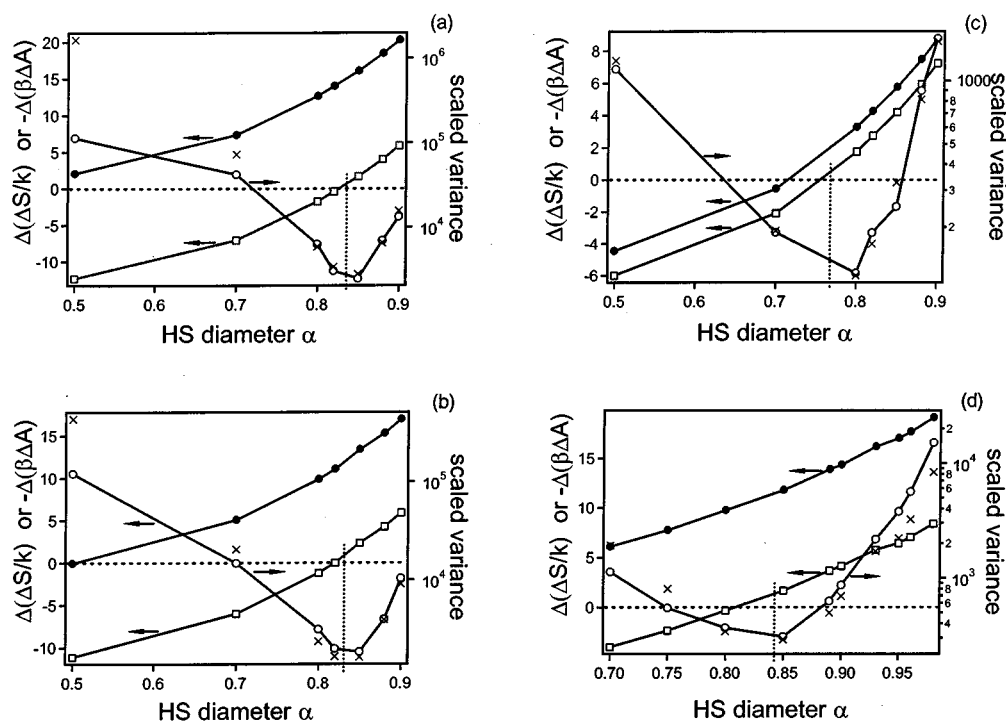


FIG. 4. Difference in entropy change $\Delta(\Delta S/k)$ (open squares) and difference in free-energy change $-\Delta(\beta\Delta A)$ (filled circles) in the two-stage FEP calculations. Scaled variance $M\sigma^2$ is plotted on the right ordinate (open circles). Prediction of scaled variance from the model is presented also (crosses). The vertical dotted line indicates the minimized variance (optimal staging) as given by the model. The horizontal dashed line is simply the zero line for the left ordinate. Simulation conditions: (a) $N=108$, $T=0.8$, $\rho=0.9$; (b) $N=108$, $T=1.0$, $\rho=0.9$; (c) $N=108$, $T=4.0$, $\rho=0.9$; (d) $N=200$, $T=1.0$, $\rho=0.8$.

More importantly, the difference in $\Delta(\beta\Delta A)$ or $\Delta(\Delta S/k)$ between two different sized systems is negligible compared with their variation with HS diameter. This means that the optimal α given by the model is insensitive to system size. Also, these results indicate that the economy of performing both stages in one simulation does not introduce serious error; nevertheless, calculations aiming to determine accurate values for the free-energy difference should not use this approximation.

V. CONCLUSIONS

The variance involved in a simulation is prone to error when obtained by analyzing the statistics of simulation results. However, it can be well predicted by a model based on consideration of the simulation process. In this work we present such a model for the multistage insertion simulation.

TABLE IV. Simulation results for two system sizes. $N=108$ for series D and $N=500$ for series G; $T=1.4$, $\rho=0.9$ for both cases.

Series	HS diameter α	$\beta\Delta A_{\text{tot}}$	$\Delta(\beta\Delta A)$	$\Delta(\Delta S/k)$
D1	0.80	3.545	-6.989	-0.327
G1	0.80	3.667	-6.954	-0.360
D2	0.82	3.586	-8.100	0.784
G2	0.82	3.614	-8.066	0.751
D3	0.85	3.490	-10.130	2.814
G3	0.85	3.512	-9.947	2.632
D4	0.88	3.524	-12.266	4.950
G4	0.88	3.671	-12.025	4.710
D5	0.90	3.548	-13.736	6.420
G5	0.90	3.602	-13.580	6.266

Further, we apply this model to analyze the optimization of the intermediate states and reach a new criterion that improves the precision of the measurement greatly. Our model predictions are confirmed by test simulations of LJ systems via a two-stage insertion method. Our analysis provides a better understanding of the insertion-based FEP process. In a simulation, uncertainty in measurement of the free-energy difference can be separated into contributions from the entropy and the internal energy. However the magnitude of both of these uncertainties depends primarily on the entropy difference between the system, and the consequence is that one should strive to equalize these entropy differences in formulating a multistage FEP technique.

Our analysis is based on a picture of the FEP calculation in which the entropy of the target is smaller than the entropy of the reference, and implicitly assumes that the configurations important to the former constitute a wholly contained subset of the configurations important to the latter. While there are many situations in which this is so, certainly the picture cannot apply to all problems of interest. Specific exceptions can nevertheless be treated with the concepts presented here, but one must have a good understanding of the nature of the overlap of the parts of phase space relevant to the systems of interest. We would venture to say that exceptions to the "whole-subset" picture are less common than one might think.

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