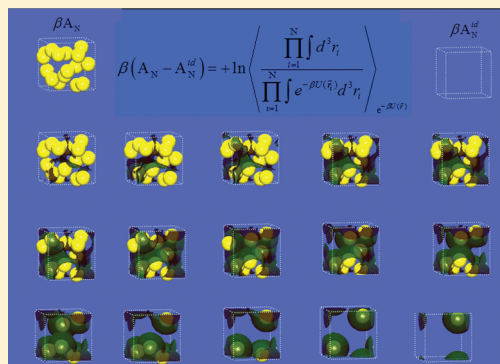


# On the Estimation of the Free Energy, From a Single Equilibrium Statistical Ensemble, via Particle Reinsertion

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**ABSTRACT:** In this work, we propose the evaluation of the free energy in molecular systems, in a “single” step, by “deleting” all the molecules in the system. The approach can be considered as the statistical mechanics analogue of the evaluation of the potential energy in classical mechanics by accounting for the necessary work to transfer all particles one by one to infinite distance. As a result, the free energy of an atomistic system can now be expressed as an ensemble average over a configurational function that corresponds to the contribution of each microstate to the free energy of the ensemble. Moreover, the proposed method is capable of evaluating the free energy as a function of the density, from the simulated density down to zero. Finally, the proposed method is related to the Rosenbluth sampling of the inverse process, that of inserting (instead of deleting) and provide the analogous theorems to Bennett’s and Crooks’ work (Bennett, C. H. J. Comput. Phys. 1976, 22, 245; Crooks, G. E. Phys. Rev. E 1999, 60, 2721). When the proposed process is envisioned as the transformation of an interacting to a noninteracting system, the proposed scheme reduces to the Jarzynski identity linking the free energy of the system to the chemical work related to this transformation.



## INTRODUCTION

In statistical mechanics, apart from some very simple systems, the direct estimate of thermodynamic potentials is by far not trivial, and in most cases is achieved via a thermodynamic integration<sup>1</sup> or perturbation theory<sup>2–15</sup> or the use of expanded ensembles.<sup>16</sup> In all of those cases, one should use a number of calculations in order to link the state of interest with a reference state. In this work, we propose the evaluation of the Helmholtz free energy in a single calculation by removing all the particles of the system.

## THEORY

In the proposed scheme the key concept is the framework behind the evaluation of the chemical potential. The chemical potential is essential in the evaluation of any thermodynamic potential that includes an entropic contribution. Several methods have been developed for its estimation<sup>2,4–6,12–19</sup> based on the following: free energy perturbation,<sup>2,3,5,7–15</sup> thermodynamic integration,<sup>1</sup> expanded ensemble,<sup>16</sup> umbrella sampling,<sup>17</sup> and recently nonequilibrium fluctuation theorems of trajectory ensembles.<sup>18–24</sup> The first and probably one of the most successful approaches has been based on free energy perturbation theory and was proposed by Widom.<sup>7</sup> Widom’s test particle insertion scheme<sup>7</sup> expresses the chemical potential as the forward numerical derivative of the free energy. In Widom’s method a simulation is performed in the reference state of a system with  $N$  particles. Sampling of the reference system can be achieved by means of either Monte Carlo or molecular dynamics.<sup>25</sup> In both cases, a trial attempt to add a molecule is performed and the energy difference

caused by the interaction of the additional particle with the rest of the  $N$  particles is recorded. What the reader should keep in mind is that the configurations of the reference system are not disrupted by the insertion of the  $(N + 1)$ th particle. One has to rely on the sampling of the reference system in order to sample the important states of the perturbed system too. The inability to do so is realized as sampling inefficiency, so severe in some cases that, no matter how long simulations are performed, the correct result may never be achieved. This is the case when trying to evaluate the chemical potential as a backward numerical derivative of the free energy via the test removal of a molecule since the removal leaves a cavity in the system due to the excluded volume interactions. As a consequence, all resulting configurations in the perturbed system will have an additional cavity resulting in a bias sampling. In the stage particle deletion,<sup>10–12</sup> this bias is removed, via the introduction of an intermediate state where the intermolecular interactions of the removed molecule are replaced by a hard-core interaction of a certain range  $d$ . This enabled the exact evaluation of the free energy difference by first transforming the removing molecule into a collection of hard spheres (typically one hard sphere for each atom in the molecule), and then adding the free energy cost to create such a cavity in a system of  $(N - 1)$  particles that can be performed analytically,<sup>10,11,26,27</sup> even in complex or dense systems. On the other hand, there is a more drastic approach of the single-stage

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direct particle deletion<sup>12</sup> and reinsertion<sup>28</sup> scheme where comparison of the reference and perturbed system is not performed by comparing individual configurations in one-to-one manner but rather comparing configurations sets of the two systems. In this work, it will be shown that the particle deletion approach enables the perturbation of a reference system of  $N$  interacting particles to a system of  $N$  ideal molecules and therefore it is possible to estimate the free energy of the system in a single step, by removing and reinserting each of the particle in the system.

For a molecular system consisting of  $N$  monatomic molecules interacting via a pair additive interaction potential  $U(\vec{r})$ , where  $\vec{r}$  is the positions vector of the atoms, the free energy at temperature  $T$  and volume  $V$  is given as  $\beta A_N = -\ln(Z(N,V,T)/[N!\Lambda^{3N}])$ , where  $Z(N,V,T) = \int e^{-\beta U(\vec{r})} d^3r_1 \dots d^3r_N$  is the partition function,  $\Lambda$  is the de Broglie length, and  $\beta = 1/k_b T$ , where  $k_b$  is the Boltzmann constant. For an ideal gas the partition function is simply  $V^N$ . As a result, the free energy of an ideal gas system at the same number density is given as  $\beta A_N^{\text{id}} = -\ln(V^N/[N!\Lambda^{3N}])$ . The absolute value of the free energy can be estimated with respect to a reference state of an ideal gas at the same number density, provided that the excess free energy  $A_N^{\text{ex}} = A_N - A_N^{\text{id}}$  can be estimated.

In this work, we propose an expression for the evaluation of the excess free energy in a statistical ensemble, based on reinsertions of all the particles in the system, in the form of eq 1:

$$\begin{aligned} \beta(A_N - A_N^{\text{id}}) &= -\ln \int e^{-\beta U(\vec{r})} d^3r_1 \dots d^3r_N + N \ln(V) \\ &= +\ln \frac{\int \int \frac{V^N}{\prod_{i=1}^N \int e^{-\beta U(\vec{r}_i)} d^3r_i} e^{-\beta U(\vec{r})} d^3r_1 \dots d^3r_N}{\int e^{-\beta U(\vec{r})} d^3r_1 \dots d^3r_N} \end{aligned} \quad (1)$$

where  $U(\vec{r}_i)$  is the interaction potential energy of the system containing the  $(i-1)$  particles at their sampled position with an  $i$ th "test" particle that is being reinserted on to the system.

The derivation of eq 1, as in the case of the direct particle deletion and reinsertion methods, lies on the simple integral identity  $\int dy / \int \int [(f(x,y)/(f(x,y) dx))] dx dy = 1$  true for any function  $f(x,y)$  (provided  $\int f(x,y) dx \neq 0$ ). In order to build up eq 1, one has to start from the definition of the partition function in the canonical ensemble, multiply and then divide by the integral of all possible placements  $r_1 \equiv \{x_1, y_1, z_1\}$  of the first particle, taking into account that the rest of the particles are treated in this stage as ideal gas with no intermolecular interactions. The partition function will then be equal to  $Z(N,V,T) = (Z(N,V,T) \int d^3r_1 / \int d^3r_1) = \int e^{-\beta U(\vec{r})} d^3r_1 \dots d^3r_N / \int [1 / \int d^3r_1] d^3r_1$ . In the case of polyatomic molecules, the placement of the first particle corresponds to the integration of the translational and internal degrees of freedom.<sup>10,12,29,30</sup> Proceeding to the next particle, one has to keep in mind that, from the second particle on, there will be an additional interaction energy with the particles already added. As a consequence, the integral over all placements of the "reinserted" particle has to be weighted by the Boltzmann weight of the interaction  $U^{(1-2)}(\vec{r}_1, \vec{r}_2)$  between the two particles  $e^{-\beta U^{(1-2)}(\vec{r}_1, \vec{r}_2)}$ . The partition function can then be

written as

$$Z(N,V,T) = \int e^{-\beta U(\vec{r})} d^3r_1 \dots d^3r_N \Bigg/ \int \frac{1}{\int d^3r_1} \int \frac{1}{\int e^{-\beta U^{(1-2)}(\vec{r}_1, \vec{r}_2)} d^3r_2} e^{-\beta U^{(1-2)}(\vec{r}_1, \vec{r}_2)} d^3r_2 d^3r_1$$

By continuing the same procedure for all particles in the system, we can build up the denominator of eq 1. In each step, the weighting function is simply  $e^{-\beta U(\vec{r}_i)}$ , where  $U(\vec{r}_i)$  is the interaction potential energy of the system containing the  $(i-1)$  particle built in the denominator and the  $i$ th particle of the  $i$ th step. In the case of non-pair-additive potentials,  $U(\vec{r}_i)$  has to be calculated from the potential energy difference, caused by the addition of the  $i$ th test particle in the system of the  $(i-1)$  particle. A physical interpretation of this process can be "viewed" as the "transformation" of interacting particles one by one into ideal gas particles until no more interacting particles are left in the system. To understand this, one has to start from the final result and consider the reverse order of the procedure. In the last step (step  $N$ ), the integral includes interactions between all  $N$  particles in the system, i.e., the complete partition function of the sampled system. In  $m$  previous steps, the integral includes interactions between the  $(N-m)$  interacting and  $m$  ideal gas particles.

As in the case of the deletion and reinsertion<sup>28</sup> schemes, this is not the only way of deleting a particle. One can choose another weighting function different from the Boltzmann weight  $e^{-\beta U(\vec{r}_i)}$  used for the derivation of the proposed expression, and produce several similar schemes. For example, an expression based on the direct particle deletion will introduce a hard-core interaction of a specific diameter  $d$  as the weighting function used in the building of the denominator of eq 1 and at the end of the procedure the hard-core particles interactions will be transformed to the "real" interactions via traditional free energy perturbation. As in the case of the particle deletion schemes, the choice of the weighting function has to fulfill several requirements that ensure that no bias is introduced during the perturbation.<sup>28</sup> Once all particles have been reinserted, we have built an estimator (eq 2) for the partition function itself and therefore derived the proposed scheme for the evaluation of the excess free energy based on eq 1.

$$Z(N,V,T) = \frac{\int e^{-\beta U(\vec{r})} d^3r_1 \dots d^3r_N}{\int \int \frac{1}{\prod_{i=1}^N \int e^{-\beta U(\vec{r}_i)} d^3r_i} e^{-\beta U(\vec{r})} d^3r_1 \dots d^3r_N} \quad (2)$$

Note that in general at each step an arbitrary number of particles can be added to the denominator (i.e., reinserted). In eq 2, in each step the integration is performed over the degrees of freedom of a single particle that interacts with the particle that have not been "deleted" up to that point via the interaction  $U(\vec{r}_i)$ . Therefore, the derivation requires the multiplication and division of the term  $\int e^{-\beta U(\vec{r}_i)} d^3r_i$  at each step. If one would prefer to perform the integration over two particles in one step, one would have to multiply and then divide by the corresponding integral over the degrees of freedom of both particles, i.e.  $\int \int e^{-\beta U(\vec{r}_i)} d^3r_i e^{-\beta U(\vec{r}_j)} d^3r_j$ , where  $i = j+1$ . In this case, during the reinsertion of the  $i$  and  $j$  particles the evaluation of the interaction between them has to be done at their trial positions. On the contrary, in the case of the single particle deletion at each step, the  $i$  "trial" particle would interact with the  $j$  particle at the position in

the sampled configuration. Similarly, one could decide to delete an arbitrary number of particles at each step. Even better one can decide to use a bias scheme like Rosenbluth<sup>31</sup> or volume bias sampling in order to reinsert a set of particles. The optimal choice of reinserted particles per step is expected to depend on both system and conditions.

Equation 1 is the main result of this work, but one can do even better: one can calculate not only the difference between a system of  $N$  interacting particles and that of a system with  $N$  ideal particles as described by eq 1, but also can evaluate the free energy difference of the reference system to any system that consists of any partition of  $m$  interacting and  $(N - m)$  ideal molecules and in this way calculate the free energy difference along an isotherm for all intermediate densities with  $m \in [0, N]$ . In order to do so, one simply has to change the starting point in the derivation and instead of starting building the partition function on the denominator from scratch, one will have to start by the partition function of a system with  $m$  interacting particles and then start to build the rest of the partition function as described. Since we can do this for all possible  $m < N$  particles, we can evaluate the free energy along the isotherm in a series of discrete points. Provided that the number of particles is sufficiently large, numerical differentiation of the free energy along those points will result in the chemical potential and the pressure along the isotherm in a single run.

Starting from the partition function of the  $m$  interacting molecule system and following the same procedure, the excess free energy difference as a function of the number of interacting particles in the system reads as follows:

$$\beta(A_N^{\text{ex}} - A_{N_i}^{\text{ex}}) = + \ln \left\langle \frac{\prod_{j=N_i+1}^N \int d^3 r_j}{\prod_{j=N_i+1}^N \int e^{-\beta U(\vec{r}_j)} d^3 r_j} \right\rangle_{e^{-\beta U(\vec{r})}} \quad (3)$$

where  $\langle \rangle_{e^{-\beta U(\vec{r})}}$  represents the ensemble average of the reference system.

The chemical potential can then be derived at each density point by a numerical differentiation scheme (e.g., backward differences). Once the chemical potential is known, the pressure can also be calculated at each intermediate density.

Up to now, we have not defined the deletion order. In principle, one should sum (or average) eq 1 over all possible deletion orders. In the simplest approach, the summation can be replaced by an average over  $n_{\text{trial}}$  randomly selected deletion orders. Unfortunately, as the system becomes larger in size and/or denser, the product of the accessible volumes becomes progressively wider and wider distributed. Eventually, the random sampling is no longer sufficient and a more elaborate scheme has to be used in the estimation of the ensemble average over the permutation of the deletion order in each of the configuration sampled (e.g., in the concept of the configurational bias<sup>32,33</sup> or in the concept of the recoil growth<sup>34,35</sup> developed for polymeric systems). Note that the permutations over the order of removal of the particles is related to the indistinguishable nature of the particles in classical statistical mechanics.

The proposed approach deals with the indistinguishable nature of the particles by treating them as distinguishable, summing over all possible permutations of distinguished particles and divided by the number of the permutations as in the derivation of the partition function of classical particles. In the simplest approach, this summation has been replaced by an average over  $n_{\text{trial}}$  randomly selected deletion orders, since the

complete evaluation of all possible permutations in the deletion order will be for most systems impossible. On the other hand, if the number of permutations is a strong function of the size of the system and under conditions where a broad distribution in the weights ensemble exists, it will be necessary to replace the random selection with a more efficient sampling scheme. Even for a small system size or a hard-sphere system, as the density increases it becomes extremely difficult to evaluate the average contribution in eq 1 over all possible permutations via random sampling of the deletion order. In theory, one can, equivalently, rely on ergodicity in order to sample all possible distinguishable contributions. On the other hand, this is not practical, since it will require prohibitively long runs. As will be shown in the Results and Discussion section, the inability to sample the distribution in the contributions over the different deletion orders by random selection results in an underestimation of the free energy of the hard-sphere fluid at high densities. It turns out that, in order to overcome this, one can perform a biased sampling in the deletion order. Although this can be achieved in a number of ways, the umbrella sampling is probably the best way to implement such biased sampling. The difference with the random selection of the deletion order can be realized as the difference of (a) performing a static Monte Carlo of equal weight ( $W_{\text{del,order}} = 1$  for all possible deletion orders) and averaging the contribution  $\prod_{i=1}^N \int d^3 r_i / \prod_{i=1}^N \int e^{-\beta U(\vec{r}_i)} d^3 r_i$  and (b) performing a dynamical Monte Carlo where each deletion order is weighted according to a predefined function  $W_{\text{del,order}}$ . In terms of the umbrella sampling, this will transform eq 1 into eq 4, where for clarity reasons we have introduced the following symbolism

$$\begin{aligned} \langle C \rangle_{W_{\text{del,order}}} &= \left\langle \frac{\prod_{i=1}^N \int d^3 r_i}{\prod_{i=1}^N \int e^{-\beta U(\vec{r}_i)} d^3 r_i} \frac{1}{W_{\text{del,order}}} \right\rangle_{W_{\text{del,order}}} \\ \langle D \rangle_{W_{\text{del,order}}} &= \left\langle \frac{1}{W_{\text{del,order}}} \right\rangle_{W_{\text{del,order}}} \\ \beta(A_N - A_N^{\text{id}}) &= + \ln \left\langle \langle C \rangle_{W_{\text{del,order}}} / \langle D \rangle_{W_{\text{del,order}}} \right\rangle_{e^{-\beta U(\vec{r}_{[N]}}} \quad (4) \end{aligned}$$

where  $\langle \rangle_{W_{\text{del,order}}}$  indicates a sampling on the deletion order according to the weighting function  $W_{\text{del,order}}$ .

A very simple way to achieve such a sampling will be to randomly select two particles in the deletion list and exchange their order, based on a Metropolis acceptance criterion (as performed in this work). In this work, we examine  $W_{\text{del,order}} = \prod_{i=1}^N \int d^3 r_i / \prod_{i=1}^N \int e^{-\beta U(\vec{r}_i)} d^3 r_i$  and turns out to be a proper choice up to a reduced density  $\rho^* = \rho\sigma^3$  of 0.66. In general, the  $W_{\text{del,order}}$  can include terms that target to a range of free energy differences. For example, we are able to achieve sufficient sampling in the density  $\rho^*$  of 0.72 by choosing a weighted function given in eq 5 that includes a sum over all the free energy differences:

$$\begin{aligned} \ln[W_{\text{del,order}}] &= \ln \left( \prod_{i=1}^N \int d^3 r_i / \prod_{i=1}^N \int e^{-\beta U(\vec{r}_i)} d^3 r_i \right) \\ &+ \sum_{j=1}^N \left[ (N - j + 1) \ln \left( \prod_{i=1}^j \int d^3 r_i / \prod_{i=1}^j \int e^{-\beta U(\vec{r}_i)} d^3 r_i \right) \right] \quad (5) \end{aligned}$$

## ■ RELATION TO OTHER METHODS

The ensemble average of eq 1 can be further enriched via the integration over a Markovian scheme.<sup>36</sup> As in most of the cases of calculating quantities related to free energy, one has to sample



contributions to the ensemble average that come from the tail of the importance sampled reference system. Such contributions, although rare to encounter in the sample of the reference system, once encountered, their contribution to the ensemble average is essential and cannot be neglected. This leads to what is known as sampling inefficiency. One way to overcome these sampling problems is to extend the range of importance sampling. Markovian web is able to do so by incorporating in the ensemble average with the appropriate weight, contributions from the rejected moves or in the most general case by incorporating all outcomes of any trial ghost move. The advantage in the case of free energy calculations comes from the fact that within the Markovian web integration scheme the contribution to the ensemble average of the trial move is evaluated from the product of the acceptance probability in the reference system, times the contribution to the ensemble average. In traditional calculations of the ensemble average, when the acceptance probability is low there is a vanishing low probability of including the appropriate value to the ensemble average, no matter how big the contribution of its product with the average quantity is. On the other hand, Markovian web integration evaluates directly the product of the two terms and in this way includes contributions that have low probability of being accepted in the reference system but at the same time contribute significantly to the ensemble average.

The Markovian web method has shown<sup>36</sup> that any ensemble average  $\langle A \rangle$  of a quantity  $A$  can be evaluated as  $\langle A \rangle = \sum_i \rho_i A_i / \sum_i \rho_i = \sum_i \rho_i \sum_j \pi_{ij} A_j / \sum_i \rho_i = \sum_i \rho_i \sum_j a_{ij} (\text{acc}_{ij} A_j + (1 - \text{acc}_{ij}) A_i) / \sum_i \rho_i$ , where  $\rho_i$  is the Boltzmann weight of the microstate  $i$  and  $\pi_{ij}$  is the element of any transition matrix (real or “ghost”<sup>36</sup>) connecting microstates  $i$  and  $j$ . In most cases this breaks to a trial probability  $a_{ij}$  of an attempt to move from microstate  $i$  to microstate  $j$  and the acceptance probability  $\text{acc}_{ij}$ . In the cases where  $A$  is related to a free energy difference, Markovian web will account for contributions where  $\rho_i a_{ij} \text{acc}_{ij} A_j$  is significant, even if  $\rho_i a_{ij} \text{acc}_{ij}$  is vanishing small (and therefore it would require prohibited long simulations in order to include the proper contributions to the ensemble average). Furthermore, since the transition matrix can be of any “ghost” stochastic move, one can design a trial move that samples the tail of the importance sampling distribution relative to the desired free energy calculation.

Another way of looking at the proposed free energy scheme is in relation to the Rosenbluth sampling.<sup>31</sup> Rosenbluth sampling was derived<sup>31</sup> in order to achieve insertion of a chain molecule by breaking the insertion process into steps of incremental insertion. At each of those steps, a set of trial alternatives for the segmental insertion is examined and the selection is based on this trial set. When Rosenbluth sampling is used in a dynamic Monte Carlo scheme widely known as “configurational bias”,<sup>32,33</sup> the reverse-move chains have to be able to be deleted too. In this case, two Rosenbluth weights have to be calculated, one during the insertion and one during the deletion, where the probability of creating a specific discrete set of trial incremental “branches” during insertion and deletion process usually cancel out and do not appear in the acceptance criterion. In terms of free energy calculations, Rosenbluth sampling has also been used in order to calculate chemical potential based on the insertion scheme, but to our knowledge never for the deletion scheme. Note that any insertion scheme corresponds in performing a static Monte Carlo integration over the translational and internal degrees of freedom of the additional molecule and unlike the case of the dynamic Monte Carlo scheme (e.g., Metropolis sampling), where the biased trial probability of a forward and a reverse move has to be calculated in the static scheme, this weight has to

be included in the ensemble average in order to reduce the average to the unbiased Boltzmann statistics. Nevertheless, the extension from building a chain molecule to build the complete system is straightforward, but it is highly unlikely that this process will be able to sample all relevant configurations in order to accurately evaluate the unbiased Boltzmann statistics. In the following, we will provide a proof that relates the proposed scheme for the evaluation of the free energy of the system, with the inverse Rosenbluth insertion procedure, i.e., a deletion scheme where the Rosenbluth weights of deleting all particles in the system are used in order to evaluate the unbiased Boltzmann ensemble average of the free energy.

To be more precise, the Boltzmann ensemble average of a quantity  $Q$  can be evaluated<sup>37</sup> from the Rosenbluth distribution average of a static Monte Carlo scheme as  $\langle Q \rangle_B = (\langle WQ \rangle_R) / \langle W \rangle_R$ , where  $\langle \rangle_R$  represents a distribution average where the configurations have been created according to Rosenbluth bias, and  $\langle \rangle_B$  represents the Boltzmann ensemble average, where the definitions for a Rosenbluth distribution average  $\langle \rangle_R$  differ from those of what sometimes is referred<sup>37</sup> to as the Rosenbluth ensemble average  $\langle \rangle_{R,W}$ , being the  $W$  weighted average over the Rosenbluth distribution  $\langle Q \rangle_B = \langle WQ \rangle_R / \langle W \rangle_R = \langle Q \rangle_{R,W}$ . It turns out<sup>31,37</sup> that the probability of creating a configuration in the Rosenbluth sampled distribution  $\rho_i^{(R)}$  observed during the Rosenbluth sampling is related to the Boltzmann sampling weight  $\rho_i^{(B)}$  ( $\rho_i^{(B)} \propto e^{-\beta U}$  in a canonical ensemble) of a configuration  $i$  via the following relation  $\rho_i^{(R)} = (\rho_i^{(B)}) / (W_i)$ . Having stressed that Rosenbluth sampling can be performed in a number of different ways, and the reader can find a lot of information in several textbooks, we will briefly give a simple example for clarity reasons. In the case of chain segmental insertions the bias function  $W_i$  is built up as a product of contributions from the insertion of each segment  $i$ seg. For each of the segments  $i$ seg, out of  $k$  trail configurations generated, one is selected based on the probability  $e^{-\beta U^{(i\text{seg},t)}} / \sum_{t=1}^k e^{-\beta U^{(i\text{seg},t)}}$ , where  $U^{(i\text{seg},t)}$  is the interaction energy of the  $i$ seg segment at the  $t$  trial configuration with the rest of the system. Then the probability of creating a chain, and therefore the probability of observing this chain of  $n$ seg segments in the Rosenbluth distribution  $\rho_i^{(R)}$ , will be proportional to the product of “creating” each segment. Whereas the nominator of this product creates the Boltzmann sampling weight  $\rho_i^{(B)}$ , the denominator results in the biasing function  $W = \prod_{i\text{seg}=1}^{n\text{seg}} W_{i\text{seg}} = \prod_{i\text{seg}=1}^{n\text{seg}} \sum_{t=1}^k e^{-\beta U^{(i\text{seg},t)}}$ . Note that in the insertion process usually only a discrete set of trials are included in the trial move, which does not affect these results since the Rosenbluth sampling can be written as  $\rho^{(R)} = \sum_K (\rho_i^{(B)}) / (W_K^*) - (W_K^*) / (W) = (\rho^{(B)}) / (W)$ , where  $(W_K^*) / (W)$  is the probability of selecting a specific discrete set of trials.

To see the connection between the Rosenbluth sampling and the proposed scheme, one can start from the proposed ensemble average for the free energy in the Boltzmann weight sample  $\langle \rangle_B$  and transform it to an average in a Rosenbluth distribution. To do so, we will introduce the probability of observing a configuration in the Rosenbluth distribution by multiplying and dividing by  $W$  the Boltzmann weight as shown in eq 6.

$$\left\langle \frac{1}{\prod_{i=1}^N \int e^{-\beta U(\mathbf{r}_i)} d^3 \mathbf{r}_i} \right\rangle_B = \frac{\sum_l^m \frac{W_l}{\prod_{i=1}^N \int e^{-\beta U(\mathbf{r}_i)} d^3 \mathbf{r}_i} \frac{\rho_l^{(B)}}{W_l}}{\sum_l^m W_l \frac{\rho_l^{(B)}}{W_l}} \quad (6)$$

For simplicity reasons, we have replaced the position vector  $\vec{r}$  with the scaled positions  $\vec{s} = \vec{r}/L$ , where  $L$  is the box length.

If we now envision a process where each particle in the system is attempted to be placed randomly in the system, the Rosenbluth weight will be  $W_i = \prod_{i=1}^N w_i^I = \prod_{i=1}^N \int e^{-\beta U(\vec{s}_i)} d^3 s_i$ . By simply changing the reference system from the Boltzmann to the Rosenbluth distribution, eq 6 results in eq 7 and therefore the proposed scheme for the evaluation of the free energy in the Boltzmann ensemble results in the free energy estimation based on a Rosenbluth insertion sampling.

$$\begin{aligned} \left\langle \frac{1}{\prod_{i=1}^N \int e^{-\beta U(\vec{s}_i)} d^3 s_i} \right\rangle_B &= \frac{\sum_I \frac{\rho_I^{(B)}}{W_I}}{\sum_I \prod_{i=1}^N \int e^{-\beta U(\vec{s}_i)} d^3 s_i \frac{\rho_I^{(B)}}{W_I}} \\ &= \frac{1}{\sum_I \prod_{i=1}^N \int e^{-\beta U(\vec{s}_i)} d^3 s_i \frac{\rho_I^{(B)}}{W_I}} \\ &= \frac{\sum_I \frac{\rho_I^{(B)}}{W_I}}{\sum_I \prod_{i=1}^N \int e^{-\beta U(\vec{s}_i)} d^3 s_i} \quad (7) \\ &= \frac{1}{\left\langle \prod_{i=1}^N \int e^{-\beta U(\vec{s}_i)} d^3 s_i \right\rangle_R} \end{aligned}$$

Note that in the Boltzmann ensemble average  $\langle \rangle_B$  the configurations are sampled based on their Boltzmann weight. On the contrary, the resulting  $\langle \prod_{i=1}^N \int e^{-\beta U(\vec{s}_i)} d^3 s_i \rangle_R$  requires that the configurations are created (inserted) based on the Rosenbluth distribution. One way to create such a Rosenbluth sampling will be to insert particles using as Rosenbluth weight  $W_I = \prod_{i=1}^N w_i^I = \prod_{i=1}^N \int e^{-\beta U(\vec{s}_i)} d^3 s_i$ , leading to an insertion scheme based on Rosenbluth weight that indeed would result in a sampled property of the same free energy difference but in the reverse direction to that of the insertion.

Therefore, we have proved that free energy calculations based on an inserting Rosenbluth sample scheme are, in theory, equivalent to a deletion scheme, where the system is sampled according to the Boltzmann distribution and the “Rosenbluth weight” for the “trial” removal is averaged. The two processes of insertion and deletion are in theory equivalent but not in practice. In the case of insertions, although Rosenbluth sampling has increased significantly our ability to construct even complex polymeric systems and it has a lot of applications in the creation of initial configurations for dynamical Monte Carlo sampling, it is improbable to expect that it can resolve in an accurate distribution of configurations needed for the evaluation of averages related to free energy differences of complex systems. On the other hand, deletion is quite more promising. An oversimplifying statement of saying this is true is that the insertion schemes have to search over a vast variety of possible trials in order to find an ensemble of trials that are able to result in an importance sampled state. The probability of actually succeeding in this is exponentially small, since it is related to the exponential of the free energy difference. On the other hand, one has the “path” sampled but now one has to evaluate the probability of that path relevant to all other paths. Nevertheless, this does not come for free. One should be able to count correctly this probability and ensure that no bias has been introduced from the deletion process.

The “quarrel” between sampling efficiency of the insertion relative to the deletion process is quite old. It probably begins with the first attempts to calculate the chemical potential via deletion. Sing and Gubbiss concluded that the deletion process results in poor sampling of the energy difference distribution in a first-order free energy calculation and therefore results in the development of an alternative method<sup>38</sup> based on Bennett’s theory.<sup>13</sup> Although this statement is formally correct, the underlying reason for this sampling inefficiency lies in the nature of the free energy perturbation performed in a deletion scheme in relation to the excluded volume of the intermolecular interactions of molecular systems. The reason for the sampling problems is the fact that the switching off of intermolecular interaction performed in a deletion scheme results in a biased representation of the  $(N - 1)$  perturbed system. Only sampling the extremely rare events, where particles come very close to each other in the reference system, will result in sampling contributions that are essential to the ensemble average of the free energy difference. This has been solved in three ways: (a) via stage particle deletion, (b) via direct particle deletion, and (c) via the reinsertion scheme. In the first of the two solutions, one has to introduce a hard-core interaction between the deleted molecule and the rest of the system and then account for the free energy of creating (or deleting) a cavity that remains after the intermolecular interaction has been switched off. In staged deletion schemes, this typically has to be done in separate calculations, while in the direct particle deletion schemes all calculations have to be done in the same run. In relation to the staged deletion scheme, Kofke et al. have devised<sup>4–6</sup> an alternative staged insertion scheme where first the cavity is inserted into the system and then the cavity is “transformed” into an interacting particle. Comparing the two staged schemes in a Lennard-Jones system, Kofke concluded that the staged insertion scheme is computationally superior to the staged deletion scheme. On the other hand, Boulouguris, Economou, and Theodorou have shown that, with an appropriate choice of the diameter of the hard-core interaction, staged deletion can become much more efficient especially if an analytical calculation for the accessible volume of the hard-core interaction is used. Although the staged insertions and deletions are valid for a variety of hard-core diameters, the statistical uncertainty is a very strong function of the actual choice. Furthermore, the staged particle insertion schemes have to use diameters that are smaller than the smallest distance of the two particles reached in the sample. In the staged and direct particle deletion scheme, the diameters should be always higher than this distance, so the comparison cannot be made at the same values of the hard-core diameter but at the conditions where each method has its optimum, that can be a strong function of the way that the excluded volume is calculated. The reader can find a nice comparison on the staged insertion and deletion scheme in the work of Prof. Kofke<sup>39</sup> where the ability to sample the states of the perturbed system whose contribution is essential to the free energy is nicely illustrated and expressed as “This means that the configurations important to the target or destination system (B) must be a wholly contained subset of the configurations important to the reference or initiation system (A)”.

On the other hand, the direct particle deletion and reinsertion method is quite different in that respect. The reason is that in the staged insertions or deletions one is trying to find an intermediate state that will be a “wholly contained subset of the reference system” in the deletion process. In the direct methods, this restriction has been lifted. In the direct particle deletion and

reinsertion methods the set of accessible microstates is not being compared one by one. On the contrary, the proposed perturbation scheme allows to extend the set of the perturbed system to that of the reference system by integrating the additional degrees of freedom and by evaluating the difference of that integral instead of the individual contributions from each microstate of the reference system. Due to this we are now able to perform a perturbation far more drastic, i.e., deleting all the particles in our system.

In the particular application of the hard-sphere free energy calculation, one can have a pretty good estimate of the inability of the random or the Rosenbluth insertion sampling, based on the known result in the form of an EoS. First, let us examine the simple case of random insertions. Since in the hard-sphere system there are only excluded volume interactions, we know that the probability of actually getting a configuration with no overlap is, by definition, equal to  $e^{-\beta A^{\text{ex}}}$ . Since the exponent is an extensive property, one can easily realize that this will rapidly tend to zero even for very small system sizes. For the case examined in this work at the reduced density of 0.72 of 108 particles, based on the prediction of excess free energy from the Carnahan–Starling equation of state, the probability of finding one configuration with no overlapping will be of the order of  $10^{-130}$ . So, random insertion is out of the question, but what about Rosenbluth insertion sampling? It turns out that it is also possible to have a fair estimate of the probability of creating a configuration based on a simple Rosenbluth insertion. For simplicity, let us choose the same number of  $K$  trial insertions for each particle in the system. We can then approximate the probability  $p_i = e^{-\beta \mu_i^{\text{ex}}}$  of an accepted insertion (the average number of insertions that did not result in an overlap) from the excess chemical potential  $\mu_i^{\text{ex}}$  of the density that corresponds to the previous stage of insertion  $\rho_i = ((i-1)/N)\rho$ ,  $i \in [1, N]$ . But if we know the probability of an accepted trial insertion  $p_i$ , we can evaluate the probability of having  $\kappa$  acceptances in the set of our  $K$  trials that is given from the binomial distribution  $P(\kappa, K, p) = K! / (\kappa!(K-\kappa)!) p^\kappa (1-p)^{K-\kappa}$  of  $K$  Bernoulli experiments where a success is the acceptance of an insertion and failure is the result of an overlap. We can then evaluate for each density  $\rho_i$  the probability  $p_i$  of having no accepted trials in the set of the  $K$  trials ( $\kappa = 0$ :  $P(0, K, p_i) = (1-p_i)^K$ ), the average contribution to the Rosenbluth weights equal to the average number of accepted trials  $\langle w_i \rangle = K p_i$ , and the variance of the contribution to the Rosenbluth weights  $\langle (w_i - \langle w_i \rangle)^2 \rangle = K p_i (1-p_i)$ . Finally, we can evaluate the probability of building up a configuration of  $N$  particles by accounting for the probability of having at least one accepted insertion in all of the insertion steps. To do so, we can think of another Bernoulli experiment where the “success” is finding NONE accepted trial insertion whereas failure is finding at least one acceptance. Since we now investigate the different densities, the probabilities of success are not equal in those experiments but are equal to  $P(0, K, p_i) = (1-p_i)^K$ . The result of the  $N$  new Bernoulli experiments is the Poisson binomial distribution, from which we can now calculate the probability of zero success as  $P_{\text{insert}} = \prod_{i=1}^N [1 - (1-p_i)^K]$  that is the probability of building up a configuration. Now we can examine the efficiency of the Rosenbluth insertion scheme in our system of 108 particles at the reduced density of 0.72 as a function of the number of  $K$  trials. When  $K = 1$  then the scheme corresponds to the random insertions mentioned above. If we now increase the value of  $K$  we will observe two opposing effects. First, we will succeed in increasing the probability  $P_{\text{insert}}$  of building up our

system since the more trials we make in each step the more probable it is to find at least one to be accepted but we will significantly increase the variance of our Rosenbluth weights. Although it is possible to evaluate the variance of the Rosenbluth weight  $W_I = \prod_{i=1}^N w_i$  based on the variance of its contributions  $w_i$ , assuming independency, for simplicity reasons we will only report the product of the variances that is trivial to evaluate based on the above consideration.  $\delta W_I > \prod_{i=1}^N \delta w_i = K^N \prod_{i=1}^N [p_i(1-p_i)]$  that is sufficient to show that increasing  $K$  results in dramatic increase of the variance. A typical value for  $K$  used in Rosenbluth segmental insertion of chain like molecules is of the order of 10. If we were to use  $K = 10$  in our application at the highest examined density, that of 0.72, the probability of sampling a configuration with no overlap would be of the order of  $10^{-87}$  and therefore prohibited small. By the choice of  $K = 1000$ ,  $P_{\text{insert}}$  significantly increased to  $10^{-3}$  but the variance  $\prod_{i=1}^N \delta w_i$  has an astronomical value of  $10^{+160}$ . The underlying reason for this exponential large variance is that  $W_I = \prod_{i=1}^N w_i$  is an extensive property and it is the logarithm of the Rosenbluth weights that one could deal with even in terms of numerical evaluations. Unfortunately, or maybe inevitably, the Rosenbluth insertion scheme requires sampling of the average of this exponentially deviating quantity from averaging of the Rosenbluth distribution and as a result it is impossible to result in absolute free energy calculations for most of the system of interest. On the contrary, the creation of a small number of configurations based on a Rosenbluth distribution has been known for a long time,<sup>40</sup> and has been used with great success in building initial amorphous configurations that can then be equilibrated in the desired (e.g., Boltzmann) ensemble. Although the generation of a Rosenbluth ensemble from such distribution is not currently feasible, the creation of reasonable initial configurations is possible even for complex systems of industrial interest<sup>35</sup> from commercially available software.<sup>41</sup> But then why does the deletion work? There are at least two reasons that a deletion process is superior to the examined Rosenbluth insertion process: if for a moment one forgets about the deletion order, the deletion methods do not have to sample based on a function with an extensive variance. It has to accumulate the average in a predefined sample. As for the deletion order that actually requires the sampling for such an extensive distribution, the proposed umbrella sampling scheme in the deletion order provides an excellent solution of creating an importance sampling in the deletion orders that contributes mostly to the required ensemble average without having to bias our Boltzmann sample of configurations.

Nevertheless, the “quarrel” will probably continue especially since the efficiency of each method will vary a lot from one application to another and one can always invent new insertion schemes that will overcome the above limitations.

A possible point of reconciliation between insertions and deletions is the Bennett<sup>13</sup> approach that compares the distributions of the intermolecular interaction difference between reference and perturbed system in the insertion and the deletion process. An extension of this comparison is the Crooks fluctuation theorem.<sup>20,42,43</sup> Crooks’ fluctuation theorem relates the distribution of entropy production (or work upon the condition that the entropy production is equal to the work performed in the system minus the equilibrium free energy of the system) in the forward and reverse direction of a stochastic non equilibrium dynamical system that has to obey a microscopic reversibility condition. In both Bennett’s and Crooks’ theorems, the reference system has to be sampled according to equilibrium. Most importantly, in



both theorems the accessible phase space (*in microstates*) in both reference (starting) and perturbed (ending) systems has to be the same before and after the transition has taken place in both directions. This means that each perturbation needs to be able to sample, via the transformation, the importance sampled phase space of the other, i.e., all the microstates that contribute significantly to the partition function of the importance sampling of the state.

This necessity is of the same nature as in the free energy perturbation schemes described above, but now it comes in both ways since the comparisons have two directions. At first, this looks like a handicap, but in reality it is not, since although this restriction is necessary for all microstates considered, one can limit the examined macrostates in a set that possesses such properties for all set of microstates consistent with the condition that defines this macrostate. In Bennett's theory, one has to evaluate the product of the probability of being in each microstate of the system A times the weight from the exponential of the energy difference related with the transformation of that microstate of system A to a microstate of the system B and create a histogram of its distribution. In Crooks' theorem the transformation is required to obey the so-called microreversibility condition and the transition probability of the forward and the reverse move are related via a "detailed balance" condition where the probability flux of the forward relative to the reverse transition is given to the amount of heat exchanged with the environment. In what has been described above, in both schemes one microstate of the one system is associated with another of the other system via a first-order (microstate to microstate) perturbation in Bennett's scheme and via stochastic dynamical trajectories in Crooks' theorem (linking one microstate to many stochastically). From a mathematical perspective, a constraint is embedded when the integration over all microstates of the one ensemble is transformed in an integral of the other by relating the weight of the two microstates upon the transformation.

As it has been argued in the case of the free energy perturbations, the problem arises for the cases where the equilibrium probability of starting in one system tends to zero but its product with the appropriate weight is not. Since in both Bennett's and Crooks' theories one does not have to evaluate such contributions for all microstates but only for the ones that are involved in each of the bins of a histogram, it is sufficient that one finds bins of the histogram that satisfies the condition. For the rest it is sufficient that in theory the product would result in the probability of observing this microstate in an equilibrium ensemble of the system B even if it would require to correctly account (in theory) for products of the form zero times infinity. That is why in Bennett's theory one only has to find a set of intermolecular interaction difference of a specific value and calculate the correct free energy difference between two states even in cases where the first-order free energy perturbation schemes fail. For example, Bennett's method has been applied successfully in the calculation of the chemical potential by switching off the interactions of one molecule with the rest of the system. The reason for that is that the microstates that are causing the bias in the deletion process will contribute only to height energy difference and therefore if there is a range of energy differences that both systems can sample (away from the high energy range) the existence of bad sampling at high energy differences will not affect the calculation of the free energy for the subset of energy differences that can be sampled properly.

Although the proposed method via the integral nature of its perturbation has overcome the original constraint of the

perturbation scheme, we will also present the derivation for an analogous theorem for the proposed free energy calculation scheme. As we have shown above, the insertion process that corresponds to the inverse of the proposed deletion scheme is a Rosenbluth-sampled insertion scheme. As a consequence, we will start by expressing the probability density of observing the logarithm of the inverse of the product of the partition functions  $-\ln(\prod_{i=1}^N \int e^{-\beta U(\vec{s}_i)} d^3 s_i) = -\ln(\mathbb{W}) \equiv \mathcal{W}$  in a specific value between  $\mathcal{W}$  and  $\mathcal{W} + d\mathcal{W}$  in the Rosenbluth sampling distribution ( $P_R(-\ln(\mathbb{W})) \equiv P_R(\mathcal{W})$ ) and relate it to the probability density of observing the same quantity in terms of the Boltzmann ensemble  $P_B(\mathcal{W}) \equiv P_B(-\ln(\mathbb{W}))$ .

$$P_R(\mathcal{W}) = \frac{\sum_l^m \delta(\mathcal{W}_l - \mathcal{W}) \rho_l^{(R)}}{\sum_l^m \rho_l^{(R)}} = \frac{\sum_l^m \delta(\mathcal{W}_l - \mathcal{W}) \frac{\rho_l^{(B)}}{\mathbb{W}_l}}{\sum_l^m \frac{\rho_l^{(R)}}{\mathbb{W}_l}} = \frac{\sum_l^m \delta(\mathcal{W}_l - \mathcal{W}) \frac{\rho_l^{(B)}}{\mathbb{W}_l} / \sum_l^m \rho_l^{(B)}}{\sum_l^m \frac{\rho_l^{(B)}}{\mathbb{W}_l} / \sum_l^m \rho_l^{(B)}} = \frac{1}{\mathbb{W}} \frac{p_B(\mathcal{W})}{\langle \frac{1}{\mathbb{W}} \rangle_B} \quad (8)$$

As we have shown above, if we choose  $\mathbb{W}_l = \prod_{i=1}^N w_i^l = \prod_{i=1}^N \int e^{-\beta U(\vec{s}_i)} d^3 s_i$ , the Boltzmann average on the denominator of eq 8 can be replaced by the result of eq 1 (i.e.,  $e^{\beta \Delta A} = \langle 1/\mathbb{W} \rangle_B$ ), resulting in eq 9

$$e^{\beta(\Delta A) - \mathcal{W}} P_R(\mathcal{W}) = P_B(\mathcal{W}) \quad (9)$$

where  $\mathcal{W} \equiv \ln(1/\mathbb{W})$  can be understood as the "chemical work" in  $k_b T$  units, done on the system during the "insertion process" or done from the system at the "environment" during the "deletion process".

Bennett's theorem relates the probability of measuring a certain value of energy difference  $\Delta U = U_1 - U_0$  between two ensembles that only differ in the weight of their common set of microstates to the free energy difference  $\Delta A = A_1 - A_0$  as  $e^{\beta(\Delta A - \Delta U)} P_0(\Delta U) = P_1(\Delta U)$  whereas eq 9 relates the probability of observing a specific contribution to the free energy estimator in the deletion scheme relevant to an insertion. In the case of total free energy calculation  $\langle 1/\mathbb{W} \rangle_B$  is simply  $\langle (\prod_{i=1}^N \int d^3 r_i) / \int (\prod_{i=1}^N e^{-\beta U(\vec{r}_i)} d^3 r_i) \rangle_{e^{-\beta U(\vec{r})}}$  and  $e^{\beta \Delta A}$  is  $e^{\beta A^\infty}$ .

Once the equivalent of the Bennett theorem has been proven, one can further extend it by implementing the analogues of the acceptance ratio method in order to find the optimum overlap between the Rosenbluth and Boltzmann distributions for the  $\mathbb{W}$ 's. Note that deletion has never been used (to our knowledge) for any free energy calculation based on an "inverse Rosenbluth" sampling. Bennett's theorem has been derived for Rosenbluth sampling of a single-chain molecule, and it has been used for the calculation of the chemical potential of hard-sphere chains.<sup>37</sup>

Finally, the ability to cast eq 9 emplaces the existence of an underlying "density of states" for  $\mathbb{W}$ 's that is commonly shared by Rosenbluth and Boltzmann sampling and can be used in developing histogram weighting techniques that can build up the distribution from several independent simulations.

When  $\mathcal{W} \equiv \ln(1/\mathbb{W})$  is interpreted as the equilibrium chemical work in  $k_b T$  units, done on the system during the "insertion process" or done from the system to the "environment"

during the “deletion process”, eq 9 is the Crooks fluctuation theorem. Although Crooks’ fluctuation theorem has been derived for dynamical evolving systems, and as discussed above in the basis of a “microdetail balance” condition, our approach to relate Rosenbluth insertion sampling and the proposed “integral” deletion scheme resulted in the same fluctuation theorem for the chemical work related to the construction of the system due to the underlying flow balance in the Rosenbluth sampling.

In Crooks’ work the probability of observing a specific value for the work  $\mathcal{W} = \mathcal{W}_{\text{Forw}} = -\mathcal{W}_{\text{Back}}$  done on the system in forward  $P_{\text{Forw}}(\mathcal{W}_{\text{Forw}})$  and reverse direction  $P_{\text{Back}}(-\mathcal{W}_{\text{Back}})$  is related to the free energy between two equilibrium states, resulting in Crooks’ fluctuation theorem  $e^{\beta(\Delta A - \mathcal{W})} P_{\text{Forw}}(\mathcal{W}_{\text{Forw}}) = P_{\text{Back}}(-\mathcal{W}_{\text{Back}})$ . The sign has to be changed due to the time reversal symmetry condition, indicating that the work is either done on the system or from the system on the environment change “direction” upon time reversal.

Once the relation with Crooks’ theorem has been established, the obvious question is the relation to Jarzynski equality. Following the same steps used to derive the Jarzynski equality from Crooks’ fluctuation theorem, it is easy to see that the proposed evaluation of the free energy reduces to the Jarzynski equality where the work is the chemical work done in the system during the switching on of the interactions. Therefore, in analogy to the evaluation of the potential in classical mechanics, we have proposed a scheme that evaluates the free energy from the work related to turning off the interactions between the particles. (Note that  $\Delta A$  and  $\mathcal{W}$  have the opposite sign compared to the usual representation of the Jarzynski equality, simply due to the definitions of starting and ending states.)

$$\begin{aligned} e^{\beta(\Delta A) - \mathcal{W}} P_{\text{R}}(\mathcal{W}) \\ &= P_{\text{B}}(\mathcal{W}) \rightarrow \int_{-\infty}^{\infty} e^{\beta \Delta A} P_{\text{R}}(\mathcal{W}) d\mathcal{W} \\ &= \int_{-\infty}^{\infty} e^{\mathcal{W}} P_{\text{B}}(\mathcal{W}) d\mathcal{W} \rightarrow e^{\beta \Delta A} \int_{-\infty}^{\infty} P_{\text{R}}(\mathcal{W}) d\mathcal{W} \\ &= \langle e^{\mathcal{W}} \rangle_{\text{B}} \rightarrow e^{\beta \Delta A} = \langle e^{\mathcal{W}} \rangle_{\text{B}} = \left\langle \frac{1}{\mathcal{W}} \right\rangle_{\text{B}} \quad (10) \end{aligned}$$

Note that eq 10 can also be solved by keeping the  $e^{\beta(\Delta A) - \mathcal{W}}$  in the left-hand side, a Jarzynski equality resulting in the free energy estimation based on the Rosenbluth sampling insertion scheme. Furthermore, a number of intermediate schemes can be derived with most promising the application of the acceptance ratio method proposed by Bennett.

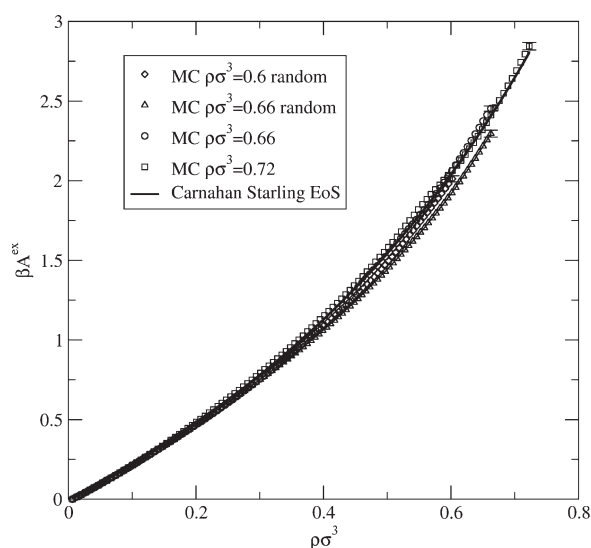
The underlying reason for the connection of the proposed method with the more general theories of Bennett, Crooks, and Jarzynski is the existence of a flow balance in our perturbation scheme that takes the “place” of the “microscopic reversibility condition” in Crooks’ theorem. In general, one can envision perturbation schemes that are invertible, as a stochastic mapping connecting the reference and the perturbed system, that obey detail balance, i.e., a flow balance, condition. As in the case of the dynamic Monte Carlo sampling, this flow balance is not necessary but rather a sufficient condition. Although very similar to the dynamical Monte Carlo sampling, such a static mapping has some unique characteristics. First, the normalizing factor of the stationary probability (i.e., the partition functions) of the two ensembles are different and their ratio is in fact the outcome of the perturbation scheme. But, most important, the mapping itself in perturbation schemes have to be “ergodic” as described above.

On the contrary, in the construction of a dynamic Monte Carlo move that maps states on the same ensemble, the ergodicity of the mapping need not be satisfied in each of the moves designed to obey the detail balance condition. What is required is that the combination of the proposed moves is ergodic. A characteristic example of such difference between static and dynamic Monte Carlo flow balance is the particle insertion and deletion. Whereas in a dynamical Monte Carlo scheme insertions and deletions have been easily constructed in the content of grand canonical or the Gibbs ensemble, and in the form of the Rosenbluth sampling, the static equivalent of inserting and deleting took considerably more consideration and required the development of the particle deletion schemes.<sup>10–12,28–30</sup> As it has been shown in the development of the particle deletion schemes, the insertion and deletion of a molecule are not ergodic on their own, since the deletion of a molecule always results in a cavity. Similarly, no molecule can be inserted if there is no sufficiently large cavity in the system prior to the attempt. On the other hand, in the case of the dynamical sampling, this lack of ergodic sampling is counterbalanced by the existence of other Monte Carlo moves in the system. In the case of the static Monte Carlo, one has to either invent an ergodic mapping or account for the introduced bias, as in the case of particle deletion methods. Note that in the examined cases the flow balance introduced by the forward and reverse perturbation process does not include an irreversible source as in the case of the entropy production<sup>20,42,43</sup> in the Crooks fluctuation theorem (in the form of the heat exchange), and therefore represents a reversible process.

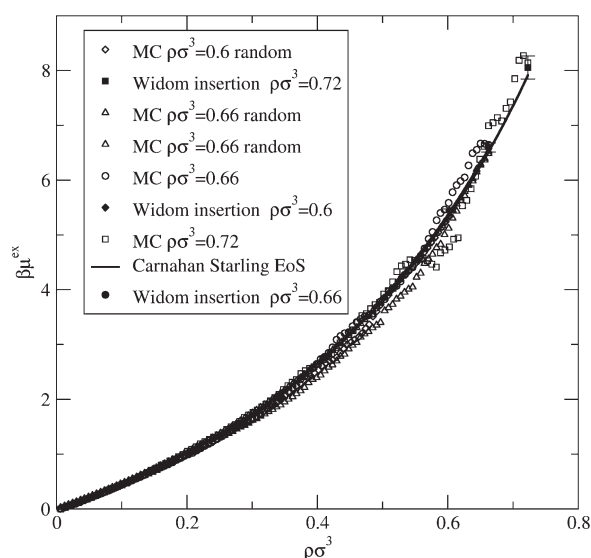
## RESULTS AND DISCUSSION

The proposed method of evaluating the free energy along an isotherm has been tested in a system of hard-sphere fluid for a range of densities. The estimate of the free energy, chemical potential, and pressure is compared with the Carnahan–Starling equation of state (EoS). All results are reported in reduced units<sup>37</sup> whereas the error bars have been calculated based on block averaging over five blocks. In Figure 2 results from the use of the Widom insertion method are reported for comparison at the three simulated densities. Once the extensive excess free energy is known (e.g., using eq 5 or the one that results from the introduction of the umbrella sampling), the chemical potential can be calculated from numerical differentiation at each density. Knowing Helmholtz free energy and Gibbs free energy, the pressure  $P$  can also be calculated at each density point. In Figures 1, 2, and 3 the excess free energy, the chemical potential, and the pressure as a function of density are plotted for a system of 108 particles and the reduced densities  $\rho\sigma^3 = 0.6, 0.66$ , and  $0.72$ . For the denser systems of  $\rho\sigma^3 = 0.72$  and  $0.66$  where the random selection of the deletion order fails to sample efficiently the deletion order, as can be seen from the underestimation of the free energy in Figure 1, we provide the results from the use of the umbrella sampling scheme where we have used the weighting function defined in eq 5 of the  $\rho\sigma^3 = 0.72$  simulation whereas for the  $\rho\sigma^3 = 0.66$  a simpler weighting function  $W_{\text{del,order}} = \prod_{i=1}^N \int d^3r_i / \prod_{i=1}^N \int d^3r_i e^{-\beta U^{(i)}(\vec{r}_i)}$  was sufficient. The difference between the two is that the first tends to increase the accuracy in both the free energy and the chemical potential calculation at the highest densities whereas the latter one tends to increase the accuracy of the free energy calculation but results in poorer sampling of the chemical potential in the denser part of the isotherm, where the random selection is superior. In order to





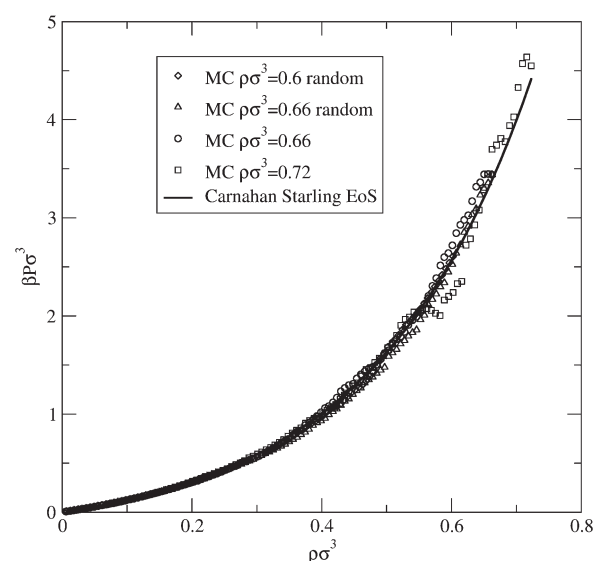
**Figure 1.** Excess Helmholtz free energy calculation of a hard-sphere fluid of 108 particles, at the reduced density  $\rho^*$  of 0.6, 0.66, and 0.72. Solid line, Carnahan–Starling EoS. Free energy calculations from a single simulation at reduced density  $\rho^* = 0.6$  using random deletion are represented by diamonds, at  $\rho^* = 0.66$  using random deletion are represented by triangles, whereas using  $W_{\text{del,order}} = \prod_{i=1}^N \int d^3 r_i / \prod_{i=1}^N \int d^3 r_i e^{-\beta U^{(i)}(r_i)}$  are represented by squares. Open circles correspond to the free energy calculation from a single simulation at  $\rho^* = 0.72$  using the weighting function defined in eq 5.



**Figure 2.** Excess chemical potential, in reduced units along the isotherm based on numerical differentiation of the Helmholtz free energy of a hard-sphere fluid. Symbols and lines as in Figure 1. Results from the use of the Widom insertion method are reported for comparison at the three simulated densities with the symbols in the legend.

evaluate the average free energy (eq 5), 100 Monte Carlo moves in the deletion order have been performed.

From Figures 1–3 one can see that for the modest density of 0.6 it is possible to evaluate in a single run the free energy, the chemical potential, and the pressure as a function of density down to zero. Unfortunately, for the higher density it is evident that a small but systematic error appears in the evaluation of the



**Figure 3.** Pressure along the isotherm based on numerical differentiation of the Helmholtz free energy of a hard-sphere fluid of 108 particles. Symbols and lines as in Figure 1.

free energy. The reason for this small but systematic error in the free energy is due to the bold approximation over the estimation of the possible different orders where the particles can be removed. In a dense system (if there are strong interactions also present this effect is expected to be stronger), the distribution of weights from the different orders of deletions becomes extremely broad. The introduction of the umbrella sampling scheme in the sampling of the deletion order shows that it is capable of improving the sampling and recovering the correct density dependence in the free energy calculation. Note that for most practical reasons in the numerical implementation of the scheme it is more convenient to work with the logarithm of the products rather than the product itself since it is an extensive quantity. As for the computational efficiency, in pair-additive potentials, the cost of the method is comparable to the cost of calculating the chemical potential in the temperature and density of the simulation using Widom's method. This can be achieved by storing in memory the interaction of each of the ghost insertion particles with the rest of the system. Then the insertions have to be performed only once for any deletion order, giving a tremendous advantage over an insertion scheme.

## SUMMARY

In this work, the free energy can be expressed as an ensemble average over a configurational function that corresponds to the contribution of each microstate to the free energy of the ensemble, provided that the microstates are sampled according to the equilibrium. As a result, in the proposed method, entropy and free energy can now be expressed as an equilibrium ensemble over the configurational space. Furthermore, the density dependence of the free energy along the isotherm from the simulated density down to zero is feasible in a single run. In this work, the direct free energy calculation is proposed based on the reinsertion and direct particle deletion scheme; in general, it may be combined with other methods that evaluate accurately the chemical potential, opening new perspectives in perturbation theory (both in theory and in simulation). Finally, the ability

to assign the contribution of individual configurations to the equilibrium free energy opens new perspectives in nonequilibrium statistical mechanics (e.g., in glassy systems<sup>44–48</sup>).

Last, but not least, we relate the proposed method to the Rosenbluth sampling of the inverse process of inserting (instead of deleting) and provide analogous theorems to Bennett's and Crooks' work showing that when the proposed process is envisioned as the transformation of an interacting to a non-interacting system the proposed scheme reduces to the Jarzynski identity.

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