Calculation of the Chemical Potential beyond the First-Order Free-Energy Perturbation: From Deletion to Reinsertion[†]

Georgios C. Boulougouris[*,‡,§]

Department of Chemical Engineering, University of Patras, Caratheodory 1, University Campus, GR-26500 Patras, Greece, and Scienomics SARL, 17, Square Edouard VII, 75009 Paris, France

The estimation of the chemical potential is crucial in a variety of applications involving phase equilibrium. The heart of such calculation lies in the evaluation of a free-energy difference usually in the form of a partition function ratio. In this work, a general formulation is proposed for the calculation of the chemical potential from molecular simulation based on an integrated form of the first-order free-energy perturbation theory, which is able to overcome the main obstacle of the traditional first-order free-energy perturbation theory. The formulation is based on a novel scheme, where the perturbation is performed in an integral over a set of degrees of freedom. Beyond the general formalism, a specific example is presented leading to a reinsertion scheme for the evaluation of the chemical potential. Calculations based on this scheme are in excellent agreement with predictions from an accurate equation of state and equivalent to the test particle insertion scheme (Widom insertion scheme) for the pure Lennard-Jones fluid at high densities from *NVT* Monte Carlo simulations. The proposed method has a straightforward implementation and can be combined with the traditional test particle insertion method (Widom, B. *J. Chem. Phys.* **1982**, *86*, 869.). Furthermore, since test particle insertion estimates the excess chemical potential as a forward difference and the proposed reinsertion scheme as a backward difference, their combination can be used as a consistency check to ensure efficient sampling.

Introduction

The prediction of phase diagrams is one of the main objectives for both chemical engineering and materials science modern research. One of the greatest challenges in such predictions is the evaluation of the chemical potential since it has to be equalized between the different phases at the point of phase equilibrium. Over the years, several methods have been developed for the chemical potential calculation,[1−16] based on: (a) free-energy perturbation,[3,4,7−9,17−21] (b) thermodynamic integration,[14,22] (c) population ratio measurements in ensembles which populate both systems[23] (usually enhanced via an expanded ensemble[24,25] or umbrella sampling[26,27]), or (d) nonequilibrium fluctuation theorems of trajectory ensembles.[15,16,28−35] In all cases, the chemical potential is evaluated as the partial difference of the free energy with respect to the number of molecules. The first attempt proposed a long time ago by B. Widom[17] is, probably, still the first choice in molecular simulation, provided that efficient sampling can be achieved. For many years since the original work by B. Widom, the scientific community considered the chemical potential evaluation via a backward difference as impossible.[12] Over the last ten years, it has been demonstrated that methods based on particle deletion are not only feasible but even more efficient in the case of dense systems,[3−8,13,18] where accessible volume is very small and therefore molecule insertion becomes extremely difficult.

Traditionally, the chemical potential is evaluated based on the logarithm of the ratio between two partition functions. In the free-energy perturbation scheme, one of the two partition functions, namely, the one which corresponds to the reference system, is sampled according to the equilibrium distribution and the other to the perturbed system. In Widom's insertion scheme,[17] the reference system contains N molecules, whereas the perturbed system applies to $N + 1$ molecules. In removal schemes, reference and perturbed systems are interchanged, leading to a reference system containing N molecules and a perturbed system with $N - 1$ molecules. In reality, the "ghost" insertions correspond to a transformation of an "ideal gas" particle to a "real" one by turning on the intermolecular interactions, whereas deletions describe the reverse transformation, due to the erasure of the intermolecular interaction. This procedure conceals the thermodynamic reference state used to calculate the total chemical potential from the excess chemical potential measured through the free-energy perturbation schemes. Although test particle insertion and deletion look similar, in fact they are not. In the removal schemes, the partition function ratio cannot be calculated directly via a traditional first-order free-energy perturbation. In this work, we will prove that this is now possible via an integrated form[19] of the first-order perturbation theory.

Historically, the first attempt to calculate the chemical potential through a molecule's removal was introduced by Shing and Gubbins.[12] However, their calculations concluded in proposing an alternative route implying that chemical potential estimation via particle deletion is not feasible.[1,2] This conclusion was based on the inefficient sampling of the highly positive energies felt by the removed molecule.[1,2] Whereas the inefficient sampling was correctly attributed to the use of importance sampling in the N-particle reference system, i.e., the reference system is not sampling the highly positive energy configurations

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[†] Part of the "Sir John S. Rowlinson Festschrift".
[‡] University of Patras.
[§] Scienomics SARL.
[*] Corresponding author. E-mail: gboul@chemeng.upatras.gr.

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produced if the candidate removal particle comes close to any other particle in the system, due to the excluded volume interactions present in all particle systems, on the other hand, such configurations contribute greatly to the chemical potential since they are quite probable in the system of the $N - 1$ particles with the additional "ideal" molecule, where the ideal particle can come arbitrarily close to the rest. This series of correct observations produced the somehow "misleading" conclusion[2] that the chemical potential cannot be calculated via particle deletion.

Later on, Parsonage[5,6] attributes the "inability" to estimate the chemical potential via particle deletion to the traditional use of an additional hard core interaction within very short distances. This numerical "trick" is often used to prevent numerical overflows from the estimation of energies in trial moves, which place two molecules very close to each other, well within the steep repulsive excluded volume interaction region. Parsonage[5,6] noticed that if one increases the range of the hard core interaction in the region where some of the trial moves would have been accepted otherwise, it is possible to retrieve an accurate value of the chemical potential by adding the free-energy cost of creating a cavity of the size of the additional hard core potential. Indeed, when the hard core interaction used was not large enough, then the addition of the hard sphere was not expected to alter significantly the original system, provided that the repulsive part of the potential does not become important. Parsonage's[5,6] methodology, despite the necessity to slightly alter the intermolecular potential of the system, was the first to overcome the deficiencies related to the deletion methods. On the other hand, although the calculations can be tuned to be accurate enough, no clear physical justification for the alteration of the intermolecular potential is given, other than to avoid numerical overflow. Later on, Kofke and Cummings[3,4] presented a very thorough and extensive analysis of methods for the evaluation of the chemical potential with molecular simulation techniques based on the introduction of an intermediate stage. In their thorough work,[3,4] they proposed an insertion scheme based on the introduction of an intermediate state testing both stage insertion and deletion schemes. In their conclusions, they recommend the use of the insertion techniques based on simulation results in hard-sphere and Lennard-Jones systems. In their work, the hard core potential does not alter the intermolecular interaction, but special attention should be given to the range of the hard core diameter use in the insertion and deletion process as in the case of any free-energy perturbation in liquid theory.[36−40] The diameters used in the insertion schemes have to be smaller than the minimum distance between two molecules under the given conditions, whereas those in the deletion scheme should be larger. Considering the above and the ability of analytical evaluation for the accessible volume, provided by the work of Dodd and Theodorou,[41] a more efficient deletion scheme can be implied.[8]

Finally, Boulougouris and co-workers[8] independently presented a detailed formulation of the inverse Widom method, namely, the "staged particle deletion method", based on particle deletion and leading to an accurate calculation of the chemical potential providing also a theoretical basis for the deletion schemes. The formulation is based on the idea that if one removes a molecule from the N molecule reference system the perturbed system is not "allowed" to relax. This is a direct consequence of the use of a first-order free-energy perturbation for the evaluation of the partition function ratio. Interestingly, in the case of particle deletion, it creates a bias in the sampling of the perturbed system. The perturbed system is not simply a system of $N - 1$ molecules but rather a system of $N - 1$ molecules and a "hole" since the remaining $N - 1$ molecules can never occupy the volume accessed by the Nth molecule, unless the reference system would have been allowed to sample an "impossible" condition, where at least two molecules would have to overlap.[8] So, if one removes a molecule in the way described initially by Shing and Gubbins,[12] he will always sample configurations with a hole, leading to biased results. Boulougouris and co-workers[7,8,19] derived an expression for the evaluation of the excess chemical potential based on statistical mechanics first principles that allow the removal of this bias, by explicitly accounting for the difference between a system with $N - 1$ molecules and one hole and a system with $N - 1$ molecules, that is, the free energy of cavity formation measured from the accessible volume for inserting a hard sphere into the $(N - 1)$ molecule system. It should be noted that beyond the traditional approaches to unbias the sampling by either measuring it or creating a mapping that overcomes it[7,8,19] the bias for the creation of a cavity can now be expressed as a perturbation from the equilibrium distribution based on the recent development of the Eigenvalue Representation of Observables and Probabilities in a HIgh-dimensionaL Euclidean space[42] (EROPHILE). Under this description, a perturbation from equilibrium can now be used to express a bias or the reweight of the reference system distribution, in terms of both a displacement in an ortho-normal space of transformed probabilities or equivalently on an ortho-normal space of observables.[42]

In this work, the proposed methodology is based on a more elaborate idea, that of evaluating the partition function ratio via a comparison between an integral of configurations of the two systems. In traditional first-order free-energy perturbation schemes (based on either deletions or insertions), a molecule is transformed from a "real" to an "ideal" molecule, or vice versa, in a configuration base. However, there is a big difference between adding and removing molecules since in the case of removing molecules the removing particle bounded by the presence of the $N - 1$ molecules is not allowed to access all the positions in the simulation box. It is only allowed to access a small part of that volume, namely, the accessible volume schematically represented in Figure 1. To overcome this difficulty, we follow a novel and more drastic approach where comparison now takes place between the configuration points integral, which the reference and perturbed systems can access, if one integrates over the removed particle degrees of freedom.

As a test system, we choose the pure Lennard-Jones fluid, where the new method results are compared to simulations using the Widom insertion scheme and an accurate equation of state.[43]

The new methodology can be easily applied to both Monte Carlo and molecular dynamics simulations.

Theory

Several years ago, Widom showed that the evaluation of the chemical potential is possible via the comparison of the free energy of a system of N molecules with the free energy of a system of $N + 1$ molecules based on a first-order perturbation with the former being the reference and the latter being the perturbed system. Since then his method is very frequently used in molecular simulation. In an "inverse Widom" scheme, the roles of the reference and perturbed system would have to be interchanged, leading to a reference system of N molecules and to a perturbated system with $N - 1$ molecules. As discussed above, a simple particle deletion scheme cannot be generated by simply deleting a molecule.[8] The additional restriction originates from the nature of the first-order perturbation theory

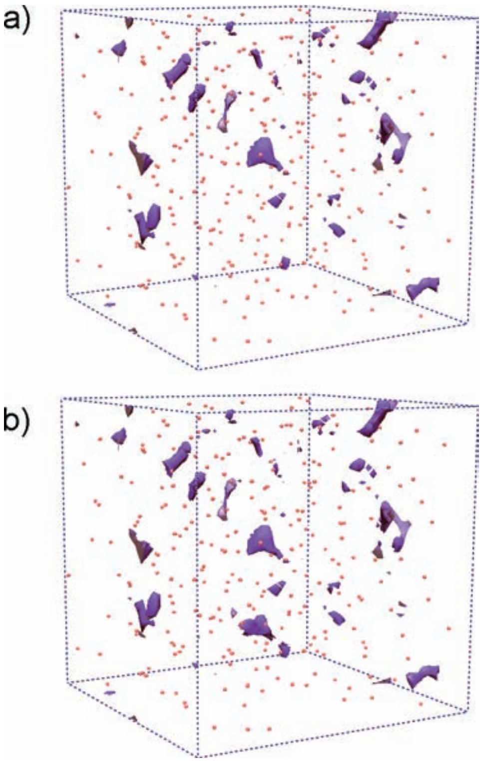

Figure 1. Pockets of accessible volume, for hard sphere diameter $d = 0.9\sigma$: (a) in a representative configuration of a 250 molecule system and (b) in the same system after the removal of one molecule, produced using MAPS[50] 3.1.

itself since the reference system upon perturbation should be able to sample *all parts* of the configurational space for which the final perturbed systems acquire a significant probability to be observed. In the case of a deletion scheme, the perturbed system has additional space inaccessible to the final reference system, generated by the ability of the *N*th removed molecule to sample the complete volume of the system as an ideal molecule. In this work, we propose a new scheme, which overcomes those obstacles and provides a route for the calculation of the chemical potential through reinsertion of a real molecule, and a more general scheme, where an additional function can be used for scheme creation ranging from particle deletion to reinsertion.

The mathematical formulation presented here is in the *NVT* ensemble for a monoatomic molecular system. Whereas it is trivial to extend it in other ensembles, the extension to polyatomic molecules has to take into account the inter- and intramolecular part of the interactions. This can be done following the procedure proposed for the staged particle deletion[7] or the recent work on the direct particle deletion.[13,44] The free energy of *N* molecules at temperature *T* and volume *V* is given by eq 1

$$A(N,V,T) = -\frac{1}{\beta}\ln(Z(N,V,T)) \tag{1}$$

where $Z(N,V,T)$ *describes* its partition function, whereas the estimation of the chemical potential, based on backward difference of the free energy, leads to

$$\beta\mu = \beta\mu^{\mathrm{ig}} - \ln\left(\left(\frac{1}{V}\right)\frac{Z(N,V,T)}{Z(N-1,V,\mathrm{T})}\right) \tag{2}$$

where $\beta\mu^{\mathrm{ig}}$ is the ideal gas chemical potential at temperature *T* and molecular density $<N/V>$.

In the first attempt by Shing and Gubbins,[12] a first-order perturbation was proposed by multiplying and dividing with the potential energy change upon the deletion of the *N*th molecule in the footsteps of Widom's insertion method. Its mathematical interpretation could be expressed by setting the volume of the system appearing in the denominator of eq 2 as

$$V = \int \mathrm{d}^3 r_N = \int \frac{\mathrm{e}^{-\beta U^N(\vec{r}_1,\ldots,\vec{r}_N)}}{\mathrm{e}^{-\beta U^N(\vec{r}_1,\ldots,\vec{r}_N)}}\mathrm{d}^3 r_N \tag{3}$$

where $U^N(\vec{r}_1, ..., \vec{r}_N) \equiv U_N(\vec{r}_1, ..., \vec{r}_N) - U_{N-1}(\vec{r}_1, ..., \vec{r}_{N-1})$ stands for the intermolecular energy felt by the *N*th molecule due to its interactions with the remaining $N - 1$ molecules of the system. As was shown from the development[8] of the "staged particle deletion", this kind of first-order perturbation fails because several configurational portions of the *N*th molecule system lead to indeterminate terms. To resolve this problem, the stage particle deletions scheme proposed the use of an intermediate stage, where a hard sphere is replacing the removed molecule. With the appropriate choice of the hard sphere diameter, one can guarantee the absence of indeterminate terms leading to the apparent "bad sampling". On the other hand, in the direct particle deletion approach,[13,19] instead of using eq 3, one has to multiply and divide by the accessible volume of the hard molecule, replacing the *N*th molecule, instead of using simply the Boltzmann weight. In mathematical terms, this reads as

$$1 = \int \prod_{i}^{N-1} H(\boldsymbol{r}_{i,N})\mathrm{d}^3 r_N / \int \prod_{i}^{N-1} H(\boldsymbol{r}_{i,N})\mathrm{d}^3 r_N \tag{4}$$

where $\prod_i^{N-1} H(\boldsymbol{r}_{i,N})$ is a product of Heaviside functions[8] accounting for the distances between atomic centers of the hard molecule and atomic centers in the $N - 1$ molecules. Each Heaviside function switches from 0 to 1 as its argument distance goes through *d*. $\int\prod_i^{N-1} H(\boldsymbol{r}_{i,N})\mathrm{d}^3 r_N$ is then, by definition, the accessible volume.[8] In this work we will show that by changing this step it is possible to construct a series of valid schemes for the evaluation of the chemical potential, ranging from particle deletion to particle reinsertion.

To derive the proposed reinsertion scheme, one has to perturb the system over the partition integral of the real *N*th molecule, $\int\exp(-\beta U^{(N)})\mathrm{d}^3 r_N$, instead of the accessible volume. By multiplying and dividing by $\int\exp(-\beta U^{(N)})\mathrm{d}^3 r_N$, we get

$$\frac{Z(N,V,T)}{VZ(N-1,V,T)} = \frac{\int \mathrm{e}^{(-\beta U_N(\boldsymbol{r}_1,\ldots,\boldsymbol{r}_N))}\mathrm{d}^3 r_1 \ldots \mathrm{d}^3 r_N}{\int \dfrac{V\exp(-\beta U^{(N)}(\boldsymbol{r}_1, \ldots, \boldsymbol{r}_{N-1}))}{\int \exp(-\beta U^{(N)}(\boldsymbol{r}_1, \ldots, \boldsymbol{r}_{N-1}))\mathrm{d}^3 r_N} \mathrm{e}^{(-\beta U_{N-1}(\boldsymbol{r}_1,\ldots,\boldsymbol{r}_{N-1}))}\mathrm{d}^3 r_1 \ldots \mathrm{d}^3 r_{N-1}\mathrm{d}^3 r_N} \tag{5}$$

where we have applied the simple mathematical equality $\int\mathrm{d}y = \int(\int f(x,y)\mathrm{d}x/\int f(x,y)\mathrm{d}x)\mathrm{d}y = \int\int(f(x,y)/\int f(x,y)\mathrm{d}x)\mathrm{d}x\mathrm{d}y$ instead of the $\int\int\mathrm{d}x\mathrm{d}y = \int\int(f(x,y)/f(x,y))\mathrm{d}x\mathrm{d}y$ used in the classical first-order free-energy perturbation theory, with *y* representing the position vectors of the $N - 1$ molecules and *x* representing the position vector of the *N*th molecule.

Table 1. Different Expressions for the Evaluation of the Excess Chemical Potential Based on Different Choice of the Weighting Function $W(\vec{r}_1, ..., \vec{r}_N)$

$W(\vec{r}_1, ..., \vec{r}_N)$	$\beta\mu^{\mathrm{ex}} = +\ln\left(\left\langle \frac{\int d^3 r_N^{\mathrm{ghost}} W(\vec{r}_1, ..., \vec{r}_N) \mathrm{e}^{\beta U^{(N)}(\vec{r}_1,...,\vec{r}_N)}}{\int W(\vec{r}_1, ..., \vec{r}_N) \mathrm{d}^3 r_N^{\mathrm{ghost}}} \right\rangle_{N,V,T}\right)$	general method
$W(\vec{r}_1, ..., \vec{r}_N) \equiv \prod_i^{N-1} H(\boldsymbol{r}_{i,N}, d)$	$\beta\mu^{\mathrm{ex}} = +\ln\left(\left\langle \frac{V \prod_i^{N-1} H(\boldsymbol{r}_{i,N}, d) \mathrm{e}^{\beta U^{(N)}(\vec{r}_1,...,\vec{r}_N)}}{\int \prod_i^{N-1} H(\boldsymbol{r}_{i,N}, d) \mathrm{d}^3 r_N^{\mathrm{ghost}}} \right\rangle_{N,V,T}\right)$	direct particle deletion
$W(\vec{r}_1, ..., \vec{r}_N) \equiv \mathrm{e}^{-\beta U^{(N)}(\vec{r}_1,...,\vec{r}_N)}$	$\beta\mu^{\mathrm{ex}} = +\ln\left(\left\langle \frac{\int \mathrm{d}^3 r_N^{\mathrm{ghost}}}{\int \exp(-\beta U^{(N)_{\mathrm{ghost}}}) \mathrm{d}^3 r_N^{\mathrm{ghost}}} \right\rangle_{N,V,T}\right)$	reinsertion

By recognizing that $V = \int \mathrm{d}^3 r_N$, eq 5 results to eq 6

$$\frac{Z(N,V,T)}{VZ(N-1,V,T)} = \frac{1}{\left\langle \frac{\int \mathrm{d}^3 r_N}{\int \exp(-\beta U^{(N)}) \mathrm{d}^3 r_N} \right\rangle_{N,V,T}} \tag{6}$$

From eqs 2 and 6, it becomes evident that the excess chemical potential can now be expressed via an ensemble average of reinserted "ghost" molecules as

$$\beta\mu^{\mathrm{ex}} = +\ln\left(\left\langle \frac{\int \mathrm{d}^3 r_N^{\mathrm{ghost}}}{\int \exp(-\beta U^{(N)_{\mathrm{ghost}}}) \mathrm{d}^3 r_N^{\mathrm{ghost}}} \right\rangle_{N,V,T}\right) \tag{9}$$

whereas the direct particle deletion and the original Widom schemes would calculate the excess chemical potential as described in the following equations

$$\beta\mu^{\mathrm{ex}} = + \ln\left(\left\langle \frac{\int \mathrm{d}^3 r_N^{\mathrm{ghost}}}{\int \prod_i^{N-1} H(\boldsymbol{r}_{i,N}, d) \mathrm{d}^3 r_N^{\mathrm{ghost}}} \prod_i^{N-1} H(\boldsymbol{r}_{i,N}, d) \mathrm{e}^{\beta U^{(N)}(\vec{r}_1,...,\vec{r}_N)} \right\rangle_{N,V,T}\right) \tag{10}$$

$$\beta\mu^{\mathrm{ex}} = -\ln\left(\left\langle \frac{\int \mathrm{e}^{-\beta U^{(N)_{\mathrm{ghost}}}(\vec{r}_1,...,\vec{r}_N)} \mathrm{d}^3 r_N^{\mathrm{ghost}}}{\int \mathrm{d}^3 r_N^{\mathrm{ghost}}} \right\rangle_{N,V,T}\right) \tag{11}$$

Note the difference between the $\mathrm{e}^{\beta U^{(N)}(\vec{r}_1,...,\vec{r}_N)}$ term in the nominator of the particle deletion methods and the $\int \mathrm{e}^{-\beta U^{(N)_{\mathrm{ghost}}}(\vec{r}_1,...,\vec{r}_N)} \mathrm{d}^3 r_N$ terms in the Widom insertion and reinsertion scheme. In the former, the position of the *N*th molecule is that of the "real" one, whereas in the insertions and reinsertions the position corresponds to that of the ghost molecule. The analysis presented above for the *NVT* ensemble can be easily applied to other ensembles, such as the *NPT*, grand canonical, or the Gibbs ensemble.[45]

Furthermore, the derivation can be generalized by the introduction of an arbitrary function $W(\vec{r}_1, ..., \vec{r}_N)$ in the following form

$$\beta\mu^{\mathrm{ex}} = + \ln\left(\left\langle \frac{\int \mathrm{d}^3 r_N^{\mathrm{ghost}}}{\int W(\vec{r}_1, ..., \vec{r}_N) \mathrm{d}^3 r_N^{\mathrm{ghost}}} W(\vec{r}_1, ..., \vec{r}_N) \mathrm{e}^{\beta U^{N}(\vec{r}_1,...,\vec{r}_N)} \right\rangle_{N,V,T}\right) \tag{12}$$

Table 1 lists the weighting function $W(\vec{r}_1, ..., \vec{r}_N)$, leading to the different expressions for the evaluation of the excess chemical potential.

Although there is relative freedom in the choice of the weighting function, $W(\vec{r}_1, ..., \vec{r}_N)$, and therefore a variety of schemes can be derived, the weighting function $W(\vec{r}_1, ..., \vec{r}_N)$ has to obey a simple rule. There should be no point $\{\vec{r}_1, ..., \vec{r}_N\}$ in the configurational space for which $W(\vec{r}_1, ..., \vec{r}_N)$ has a nonzero value, whereas $\mathrm{e}^{+\beta U^{(N)}(\vec{r}_1,...,\vec{r}_N)} \rightarrow \infty$. The condition should hold of the configurational space sampled according to the Boltzmann weight of the reference system, whereas the *N*th molecule is the "real" molecule. In mathematical terms, the Kernel of $\mathrm{e}^{-\beta U^{(N)}(\vec{r}_1,...,\vec{r}_N)}$ should be a subset of the Kernel of $W(\vec{r}_1, ..., \vec{r}_N)$, at least at the points of the configurational space for which the equilibrium Boltzmann weights are nonzero. If the above condition is not satisfied, as in the case of the first attempts to evaluate the chemical potential via deletion, a bias will be introduced. Similarly, if the choice of $W(\vec{r}_1, ..., \vec{r}_N)$ does not prevent the $\mathrm{e}^{+\beta U^{(N)}(\vec{r}_1,...,\vec{r}_N)}$ term of the real molecule appearing in the nominator of eq 10 to take large values, significant sampling problems will appear. In the direct particle deletion scheme, this is satisfied through a proper choice of the hard core diameter, which guarantees that the $\mathrm{e}^{+\beta U^{(N)}(\vec{r}_1,...,\vec{r}_N)}$ term will become well bound, at last from the short-range excluded volume highly repulsive contributions. In a more complex potential, one may have to choose between more elaborate functional forms which will allow for efficient sampling for both contributions for the "real" and the "ghost" molecule. As one should expect, there is "no free meal". When the kernel of $W(\vec{r}_1, ..., \vec{r}_N)$ is increased (i.e., the point of the configurational space for which $W(\vec{r}_1, ..., \vec{r}_N)$ is zero), to reduce the sampling requirements posed by the $W(\vec{r}_1, ..., \vec{r}_N)\mathrm{e}^{\beta U^{(N)}(\vec{r}_1,...,\vec{r}_N)}$ of the real molecule, the term of the ghost particle $\int W(\vec{r}_1, ..., \vec{r}_N)\, \mathrm{d}^3 r_N^{\mathrm{ghost}} / \int \mathrm{d}^3 r_N^{\mathrm{ghost}}$ becomes harder to evaluate since it will become more rare to get a nonzero value. The optimal weighting function should balance those errors, and in general it may depend on the way the terms are actually evaluated. For example, in the stage and direct particle deletions, the ghost particle contribution is highly facilitated by the analytical calculation of the accessible volume provided by the work of Dodd and Theodorou.[46] Another promising direction will be an analytical function, for which the proposed condition holds, and at the same time the ghost particle integral may be calculated analytically.

It has to be pointed out that the condition described above is intimately related to the restrictions of the traditional first-order perturbation, as is described by Bennett[20] and analyzed above. Note that the above condition holds even beyond the first-order perturbation, where the mapping may be brilliantly designed to allow the "relaxation" of the environment around the perturbation, as is the case of the "minmap" method of Theodorou.[10]

However, there is a significant difference; in the traditional perturbation procedure the restriction is imposed by the nature of the mapping, whereas in our case the restriction has been moved to the choice of the weighting function used to calibrate each of the mapped points.

In a similar fashion, one can derive a generalized expression for the staged particle deletion

$$\beta\mu^{\mathrm{ex}} = +\ln(\langle W(\vec{r}_1, ..., \vec{r}_N)\mathrm{e}^{\beta U^{(N)}(\vec{r}_1,...,\vec{r}_N)}\rangle) - \ln\langle W(\vec{r}_1, ..., \vec{r}_N)\rangle \quad (13)$$

One can even try to minimize the variance of the calculation based on the work of Bennett[20] by an appropriate choice of the weighting function $W(\vec{r}_1, ..., \vec{r}_N)$, but this goes beyond the scope of this work.

Results and Discussion

A particular application of a generalized scheme proposed for the calculation of the excess chemical potential leading to the reinsertions of ghost molecules was tested for systems of spheres interacting through a Lennard-Jones (L-J) potential. Monte Carlo simulations were performed in the *NVT* ensemble at high density conditions. Provided that sufficient insertions have been allowed, the original Widom and the proposed reinsertion method produce identical results.

A system of 250 molecules in a cubic box with periodic image boundary conditions is chosen for numerical conformation. Monte Carlo simulations with an equilibration period of 0.5 million steps, followed by an average of 5.5 million steps, were used to provide the ensemble of configurations according to the *NVT* statistical ensemble. In this work, the Metropolis acceptance criteria[47] were used, whereas, in general, the efficiency of the proposed scheme can be extended by either introducing a bias[26] that incorporates the $W(\vec{r}_1, ..., \vec{r}_N)$ term in the sampling or by taking into account states, which under standard Metropolis acceptance would have been rejected.[48] The latter is possible via Integration over a Markovian web method,[48] which enables statistical enrichment beyond the importance sampling by incorporation to the ensemble average trial and rejected Monte Carlo moves without introducing a bias.[48,49] Both approaches can potentially increase the overall efficiency since the evaluation of the chemical potential is related to the evaluation of an ensemble average for a quantity with important contributions to the "outskirts" of the important sampling distribution provided by Metropolis sampling.

Results are reported in dimensionless L-J units (σ for length, σ^{-3} for density, ε for energy and chemical potential). The simulation results for the chemical potential (μ^{ex}) of the pure Lennard-Jones fluid are compared to predictions from a very accurate[43] equation of state (EoS). The Monte Carlo simulations have been performed in the *NVT* statistical ensemble, whereas the excess chemical potential μ^{ex} has been evaluated from simulation using the Widom insertion and the proposed reinsertion scheme developed in this work. When a sufficient number of insertions are used, simulation results are in very good agreement with each other, within the statistical uncertainty of the calculations, and with EoS predictions. In Figure 2, the running average of the excess chemical potential is presented for the Widom insertion and the reinsertion methods, exhibiting practical equivalence between the two methods at the specific conditions of molar density $\rho = 0.723$ and temperature $T = 1$ in reduced units. Note that all comparisons between the reinsertion and the Widom insertion method have been done on the basis of equal CPU consumption by keeping the number of total insertions constant. Special attention has been given to the distribution of the reinsertion trials. Usually, when a computationally demanding property is requested, in molecular simulation it is computationally more efficient to perform the evaluation procedure of the ensample average not in every step, but with a fixed period which guarantees decorrelation. The choice of an efficient balancing between computational cost and sampling efficiency is done, most of the times, in an empirical way. In the case of the reinsertion method, one should be more careful. Unlike Widom's method, where a single ensemble average is evaluated at the end of the simulation over all trial ghost insertions, in the reinsertion scheme an ensemble of average is estimated. Each average is taken over trial reinsertions of a given configuration. As a consequence, there should be a sufficient number of ghost insertions for each configuration. Note, that if one uses inefficient sampling, i.e., a small number of insertions, the two methods will deviate from the correct value and from each other, which can be used as a test in the sampling efficiency. From Figure 3 it becomes evident that under the given conditions a reduction in the number of (re)insertions per configuration of the reference system is stronger for the reinsertion method. In Figure 3, the open symbols report the evaluations done every 1000 Monte Carlo (MC) steps, whereas closed symbols represent the evaluation every 500 MC steps. In the case where the evaluation has been done every 500 MC steps and 10 000 trial insertions have been used, the reinsertion method seems to fail, whereas with exactly the same computational cost, if the calculation is performed every 1000 MC steps with 20 000 insertions, the reinsertion method produces correct results. Nevertheless, comparison between insertion and reinsertion, which is now trivial, can be used to secure that an appropriate sampling has been performed, especially now, where the number of necessary ghost insertions is very sensitive to the system and to the conditions under investigation.

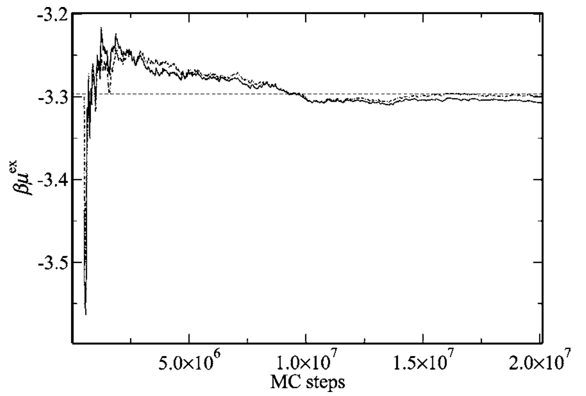

Figure 2. Running average of the excess chemical potential evaluated based on the Widom insertions (long dashed line), the reinsertion methods (solid line), and the equation of state proposed by Johnson and co-workers[43] (short dusted line), showing the equivalence between the two methods at the specific conditions of $\rho = 0.723$ and $T = 1$ (in reduced units).

In opposition to the case of the staged (SPD)[7,8] and direct particle deletion (DPD),[13,18] in the reinsertion method, as in the original Widom insertion method, there is no hard core diameter. On the other hand, in the generalized[19] version proposed by eq 12, the use of a hard core might be an efficient way of satisfying

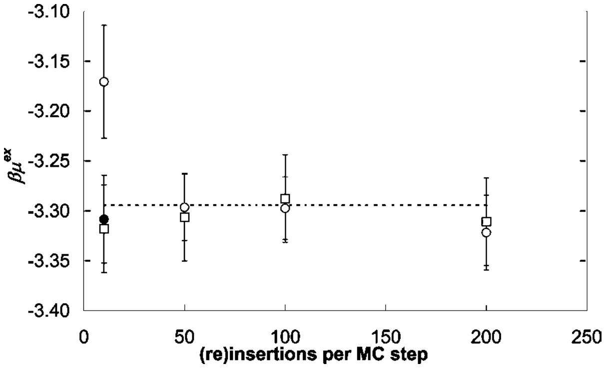

Figure 3. Effect of the number of trial insertions/reinsertions in the estimate of the excess chemical potential. The results arise from identical Markov chains, where the evaluation of the excess chemical potential has been performed based on the Widom insertion scheme (squares) and the proposed reinsertion scheme (circles). The (re)insertions performed every 1000 MC steps are reported with open symbols, whereas a run where reinsertions have been performed every 500 MC steps is reported with closed symbols. All runs have been preformed in an *NVT* statistical ensemble and compared to the equation of state proposed by Johnson and co-workers[43] (dusted line).

the validity of the perturbation scheme, as described above. In that case, as in the case of the DPD and SPD schemes, is quite important to chose an appropriate hard core diameter, not only to satisfy consistency of the calculation but also to optimize in terms of the statistical error and the computational cost. As it has been shown[7,8,13,19] in the cases of the SPD and the DPD, the hard core diameter should not be smaller than the minimum distance between two particles interacting with the full potential. Note that the use of an effective hard core diameter is by no means strange to the perturbation theory of fluids. Moreover, as it has been demonstrated by the pioneered work[37,38] of Sir John S. Rowlinson, the effective hard sphere diameter, used to map the soft repulsive part of the intermolecular interaction onto an effective hard sphere system in the perturbation theory of simple fluids, is a function of the temperature and the actual form of the soft repulsive intermolecular potential, and it plays a critical roll in the theory of simple fluids.[39] Therefore, the optimal use of the hard core diameter used in SPD and DPD is expected to be also a function of the simulation conditions and of the actual functional form of the repulsive part of the interatomic interactions in general, since although the two diameters are not identical they bear a close resemblance to each other.

It goes without saying that the LJ system under study does not represent a great challenge with current computational facilities. Nevertheless, since it is a well-examined system, where the Widom insertion is capable of evaluating with sufficient accuracy the chemical potential, it provides an excellent ground for the demonstration of the validity of the method(s)/theory proposed in the current work. In general, the proposed reinsertion scheme is expected to work well under conditions where the original Widom insertion scheme is applicable, offering a very simple validation scheme since a discrepancy between the two methods is a strong indicator of inefficient sampling. On the other hand, in the study of more complex systems, like polyatomic solutes or molecules with strong electrostatic interactions where the application of the original Widom insertion method becomes inefficient, the use of the generalized scheme is expected to be of great use upon the appropriate choice for the weighting function $W(\vec{r}_1, ..., \vec{r}_N)$. This has been demonstrated by the use of the direct particle deletion scheme (one of many possible implementations of the generalized scheme) recently in the prediction of the CO_2 solubility in atactic polystyrene,[13] benzene in polyethylene,[44] and in the original work on aqueous solutions.[18]

Conclusions

The generalization of the deletion methods for the calculation of the chemical potential in the course of a molecular simulation has been proposed, along with a specific application leading to a reinsertion scheme. The new approach is based on a novel method[13,19] of free-energy perturbation, where we are able to compare systems sampling different parts of phase space, “lifting” one of the stronger restrictions of first-order perturbation theory. In the proposed reinsertion scheme, a molecule is removed and reinserted randomly, performing a perturbation over the “partition integral” of the *N*th molecule degrees of freedom. The computed values for the excess chemical potential, μ^{ex}, from the reinsertion schemes are in good agreement with values obtained using the Widom insertion scheme and an accurate equation scheme.[43]

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