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Letter

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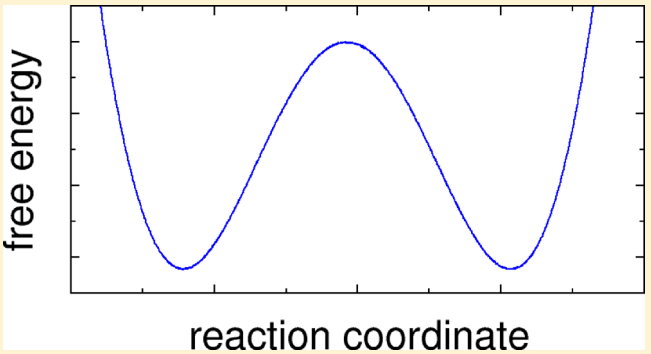
Revisiting the Exact Relation between Potential of Mean Force and Free-Energy Profile

Wouter K. den Otter*

Multi Scale Mechanics, Faculty of Engineering Technology, and Computational BioPhysics, Faculty of Science and Technology, and MESA+ Institute for Nanotechnology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

Supporting Information

ABSTRACT: Constraints are convenient in the calculation of free energy profiles via molecular dynamics simulations, but they subtly alter the phase space distribution. In a recent letter of a related title in this journal, Wong and York [*J. Chem. Theory Comput.* **2012**, *8*, 3998−4003] suggest replacing Fixman's mass-metric correction with its inverse and adding a Jacobian contribution to the potential of mean constraint force. This letter refutes both suggestions, discusses the underlying interpretation problems, and provides supporting numerical simulations.



1. INTRODUCTION

Constraints on generalized coordinates are readily introduced in Molecular Dynamics (MD) simulations in Cartesian coordinates by the expedient of Lagrange multipliers.[1] Constraining bond lengths is a common practice in molecular dynamics simulations to eliminate high frequency vibrations and thereby to allow larger time steps.[2,3] Constraints are also employed in the calculation of free energy profiles, to enforce sampling of the regions of phase space that are rarely sampled in nonconstrained equilibrium simulations, such as the activation barrier of a reaction.[3−12] Constraints are well-known to alter the sampling of phase space: they obviously restrict the available coordinate space to the hyperplane defined by the constrained coordinate(s). More subtly, the eliminated velocities along the constrained coordinate(s) turn the integral over momentum space into a configuration-dependent function—this effect would not have occurred if these motions had been suppressed by (infinitely) stiff springs rather than by rigid constraints. The textbook correction[2,3] for this effect is to weight the configurations sampled in a constrained MD simulation with the Fixman mass-metric tensor correction.[13]

In a recent article in this journal, Wong and York[14] suggested that the proper correction should have been the inverse of the traditional Fixman mass-metric correction. They presented accordingly modified expressions to calculate free energy profiles from constrained MD simulations, and also appended a "mass-scaled Jacobian scale factor" to the Potential of Mean Constraint Force (PMCF).[5,6,10] Their numerical example appears to confirm the validity of the modified expressions. Our objectives here are to show that the original expressions are exact. We will elucidate the theoretical steps that led Wong and York to conclude otherwise and re-examine their numerical example.

2. CONSTRAINED AND UNCONSTRAINED ENSEMBLES

Consider a system of N particles with Cartesian coordinates $\mathbf{x}_i$ and masses m_i. For notational convenience, a column vector $\mathbf{x}$ will be used to collect all coordinates, $\mathbf{x} = (\mathbf{x}_1^T, \mathbf{x}_2^T, ..., \mathbf{x}_N^T)^T$ with the superscript T denoting transposed. The free energy as a function of a reaction coordinate $\xi = \xi(\mathbf{x})$ for an unconstrained system is defined as

$$A_\xi^u(\xi^*) \equiv -k_B T \ln[\delta(\xi(\mathbf{x}) - \xi^*)]^u \quad (1)$$

with Boltzmann constant k_B, temperature T, and Dirac delta function δ. To compress the notation, we introduce square brackets with a superscript u to denote the phase space integral of an arbitrary function $f(\mathbf{x})$ over the canonical ensemble generated by the unconstrained Hamiltonian $\mathcal{H}_x^u(\mathbf{x}, \mathbf{p}_x)$

$$[f(\mathbf{x})]^u \equiv \frac{1}{h^{3N}} \iint f(\mathbf{x})\, e^{-\beta \mathcal{H}_x^u(\mathbf{x},\mathbf{p}_x)}\, d\mathbf{x}\, d\mathbf{p}_x \quad (2)$$

where h denotes Planck's constant, $\beta = 1/(k_a T)$, and $\mathbf{p}_x$ is the column vector of Cartesian momenta. When sampling the phase space integral of eq 1 via molecular dynamics simulations, it proves highly advantageous to restrict the value of ξ to ξ^* by a mechanical constraint on ξ. This is readily achieved by the method of Lagrange multipliers, resulting in the constrained Hamiltonian $\mathcal{H}_x^c = \mathcal{H}_x^u - \lambda_\xi(\xi - \xi^*)$ where $\lambda_\xi(t)$ is solved from the condition $\xi(\mathbf{x}(t)) = \xi^*$.[2,3,15,16] In constraint

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algorithms like SHAKE,[1] the displacements due to the constraint term are superimposed on the displacements due to the unconstrained MD step, and the Lagrange multiplier is solved iteratively in every step. Since the presence of a Lagrange multiplier complicates the analytical analysis of the probability distribution sampled by constrained simulations, it is more convenient for the current discussion to switch to a full set of generalized coordinates $\mathbf{u} = (\mathbf{q}^T,\xi)^T$, including the reaction coordinate as one of the coordinates. The Hamiltonian of the constraint system expressed in terms of its $3N - 1$ free coordinates $\mathbf{q}$ and their conjugate momenta $\mathbf{p}_q$ will be called $\mathcal{H}^c_q = (\mathbf{q}, \mathbf{p}_q; \xi^*)$.[15,16] Of course, both Hamiltonians of the constrained system, $\mathcal{H}^c_x$ and $\mathcal{H}^c_q$, describe the exact same constrained motion. Their detailed expressions are derived from the Hamiltonian of the unconstrained system in the Supporting Information (SI). Integrating the right-hand side of eq 2 over the reaction coordinate ξ and its velocity $\dot{\xi}$ then yields (see SI)

$$[f(\mathbf{x})]^u_{\xi^*} \equiv [f(\mathbf{x})\ \delta(\xi(\mathbf{x}) - \xi^*)]^u = \sqrt{\frac{2\pi k_B T}{h^2}}\,[f(\mathbf{u})\ Z_\xi^{-1/2}(\mathbf{u})]^c_{\xi^*\dot{\xi}} \tag{3}$$

where in the last line we introduced the phase space integral over the canonical ensemble generated by the constrained Hamiltonian:

$$[f(\mathbf{u})]^c_{\xi^*\dot{\xi}} \equiv \frac{1}{h^{3N-1}} \iint f(\mathbf{q}, \xi^*)\ e^{-\beta\mathcal{H}^c_q(\mathbf{q},\mathbf{p}_q;\xi^*)}\,d\mathbf{q}\,d\mathbf{p}_q \tag{4}$$

and where

$$Z_\xi = \sum_{i=1}^{N} \frac{1}{m_i}\frac{\partial\xi}{\partial\mathbf{x}_i}\cdot\frac{\partial\xi}{\partial\mathbf{x}_i} \tag{5}$$

is an element of the mass-metric tensor (see SI).

A comment on the short-hand notation of phase space integrals: the superscripts u and c to the square brackets refer to integrals over unconstrained and constrained Hamiltonians, respectively, while the subscripts highlight the constant parameters in the phase space integral, namely ξ^* denoting $\xi = \xi^*$ and $\dot{\xi}$ for $\dot{\xi} = 0$. Note the subtle but crucial difference between $[f]^u_{\xi^*\dot{\xi}} = [f\delta(\xi - \xi^*)\delta(\dot{\xi})]^u$ and $[f]^c_{\xi^*\dot{\xi}}$: the former denotes a $6N$-dimensional phase space integral of the unconstrained system, where the set of sampled states is restricted by the delta functions to the subset of states with $\xi = \xi^*$ and a vanishing velocity $\dot{\xi} = 0$, while the latter denotes the $(6N-2)$-dimensional phase space integral of the constrained system, with the constrained Hamiltonian dictating that all states of the system obey $\xi = \xi^*$ and $\dot{\xi} = 0$.

Since constraining ξ to the fixed value ξ^* reduces its velocity to zero, $\dot{\xi} = 0$, Wong and York[14] focused on phase space integrals of the form

$$[f(\mathbf{x})]^u_{\xi^*\dot{\xi}} \equiv [f(\mathbf{x})\ \delta(\xi(\mathbf{x}) - \xi^*)\ \delta(\dot{\xi}(\dot{\mathbf{x}}))]^u = \frac{1}{h}[f(\mathbf{u})\ Z_\xi^{-1}(\mathbf{u})]^c_{\xi^*\dot{\xi}} \tag{6}$$

where the last line follows by integration of the right-hand side of eq 2 over ξ and $\dot{\xi}$ (see SI). By multiplying the above integration arguments with $Z_\xi^{1/2}$, to match the integral on the second line with that on the second line of eq 3, it follows that

$$[f(\mathbf{x})]^u_{\xi^*} = \sqrt{2\pi k_B T}\,[f(\mathbf{x})\ Z_\xi^{1/2}(\mathbf{x})]^u_{\xi^*\dot{\xi}} \tag{7}$$

The ensemble average of the unconstrained system subject to the condition $\xi = \xi^*$, but without a restriction on the velocity $\dot{\xi}$, can then be expressed as

$$\langle f(\mathbf{x})\rangle^u_{\xi^*} \equiv \frac{[f(\mathbf{x})\ \delta(\xi(\mathbf{x}) - \xi^*)]^u}{[\delta(\xi(\mathbf{x}) - \xi^*)]^u} \tag{8}$$

$$= \frac{[f(\mathbf{x})\ Z_\xi^{1/2}(\mathbf{x})]^u_{\xi^*\dot{\xi}}}{[Z_\xi^{1/2}(\mathbf{x})]^u_{\xi^*\dot{\xi}}} \tag{9}$$

where the indices to the broken brackets denoting an average follow the convention outlined above. Wong and York[14] *interpreted* this result as a recipe to calculate $\langle f(\mathbf{x})\rangle^u_{\xi^*}$, i.e., the conditional average in an unconstrained system, from weighted phase space integrals over $\xi = \xi^*$ constrained MD simulations. Noting that the correction term $Z_\xi^{1/2}$ is the inverse of the Fixman term $Z_\xi^{-1/2}$ reported in the preceding literature on free energy calculations,[5,6,8−10,17] Wong and York presented several modified "exact relations" for calculating free energy profiles from constrained MD simulations. Since metric tensor corrections appear in many constrained MD simulations, the potential ramifications of this revised correction term are not limited to free energy calculations alone.

A textbook example to illustrate metric tensor corrections is the triatomic molecule ABC.[3] For a force field limited to merely two harmonic springs, connecting A to B and B to C, respectively, one readily derives that the probability distribution of the ABC bending angle θ follows $P_\theta(\theta) = 1/2\ \sin(\theta)$, and hence that the probability distribution of the cosine of the bending angle has the constant value $P'_\theta(\cos\theta) = 1/2$. Our simulations of this system, as detailed in the Supporting Information, confirm this flat distribution. The distribution is no longer flat upon constraining the two bond lengths, σ_{AB} and σ_{BC}, which was realized by means of the SHAKE algorithm.[1] Figure 1 clearly illustrates that the correct flat distribution is recovered by weighting the configurations sampled in the constrained simulation by the traditional Fixman term, $\det(\mathbf{Z}_\sigma)^{-1/2}$. Weighting the configurations sampled in a constrained MD simulation by the correction term obtained

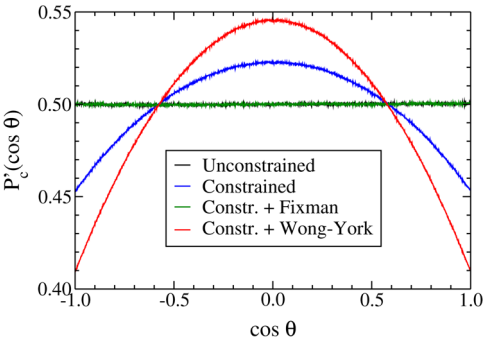

Figure 1. Probability distribution of the bending angle θ in a triatomic ABC molecule without AC interactions. The blue line was sampled in an MD simulation with both bond lengths σ constrained to σ^*. Weighting this distribution with Fixman's mass-metric correction $\det(\mathbf{Z}_\sigma)^{-1/2}$ yields the green line, which is in perfect agreement with the distribution sampled in an unconstrained simulation (black line, coinciding with the green line) and the theoretical result $P'_\theta = 1/2$. Applying the inverse mass-metric $\det(\mathbf{Z}_\sigma)^{1/2}$, as proposed by Wong and York,[14] does not recover the desired result (red line).

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along the line of thought of Wong and York, i.e. $\det(\mathbf{Z}_\sigma)^{(1/2)}$, is seen to exacerbate the deviation from flatness and thereby fails the test.

Returning to the derivation presented by Wong and York, one readily verifies that it is mathematically correct. As illustrated by the above example, the problematic step is the *assumption* that the constrained ensemble is identical to the $\xi = \xi^*$ and $\dot{\xi} = 0$ cross-section of the unconstrained ensemble. Since the equations of motion of the constrained system differ from those of the unconstrained system—recall that they result from the distinct Hamiltonians $\mathcal{H}^{\mathrm{c}}_x$ and $\mathcal{H}^{\mathrm{u}}_x$, respectively—the two systems will in general *not* sample the $\xi = \xi^*$ and $\dot{\xi} = 0$ hyperplane with the same probability distribution. The phase space integral sampled by a ξ-constrained system is given by eq 4. It then follows that the correction to recover the conditional unconstrained phase space integral from a constrained phase space integral has already been derived in eq 3, namely the traditional Fixman term $Z_\xi^{-(1/2)}$, resulting in

$$\langle f(\mathbf{x})\rangle^{\mathrm{u}}_{\xi^*} = \frac{[f(\mathbf{u})\, Z_\xi^{-1/2}(\mathbf{u})]^{\mathrm{c}}_{\xi^*\dot{\xi}}}{[Z_\xi^{-1/2}(\mathbf{u})]^{\mathrm{c}}_{\xi^*\dot{\xi}}} = \frac{\langle f(\mathbf{u})\, Z_\xi^{-1/2}(\mathbf{u})\rangle^{\mathrm{c}}_{\xi^*\dot{\xi}}}{\langle Z_\xi^{-1/2}(\mathbf{u})\rangle^{\mathrm{c}}_{\xi^*\dot{\xi}}} \tag{10}$$

In the last step, we have introduced the phase space average over the constrained ensemble, $\langle f\rangle^{\mathrm{c}}_{\xi^*\dot{\xi}} = [f]^{\mathrm{c}}_{\xi^*\dot{\xi}}/[1]^{\mathrm{c}}_{\xi^*\dot{\xi}}$. Since this ensemble is being sampled in constrained MD simulations, the ergodicity hypothesis[2,3] allows us to calculate the phase space averages on the right-hand side of eq 10 as time averages over constrained MD simulations (see SI). We recall that the generalized coordinates $\mathbf{u}$ were introduced merely to simplify the derivation of the above expression. The constrained MD simulations are best performed in Cartesian coordinates, with Z_ξ readily obtained from eq 5. As the simulations on the triatomic molecule show, see Figure 1, weighting the time average over the σ-constrained simulation of the triatomic molecule with the conventional Fixman term $\det(\mathbf{Z}_\sigma)^{-1/2}$ does indeed recover the angular distribution expected of the unconstrained system.

3. THERMODYNAMIC INTEGRATION

The main objective of Wong and York was to derive exact expressions for the calculation of free energy profiles, as defined in eq 1, with the constraint as a convenient expedient to efficiently sample the elevated free-energy regions of phase space that are rarely sampled by brute force simulations, e.g., the activation barrier of a reaction. In eq 10 of ref 14, these authors arrive at the expression

$$A^{\mathrm{u}}_\xi(\xi^*) = A^{\mathrm{u}}_{\xi\dot{\xi}}(\xi^*) - k_{\mathrm{B}}T\,\ln\langle Z_\xi^{1/2}\rangle^{\mathrm{u}}_{\xi^*\dot{\xi}} - k_{\mathrm{B}}T\,\ln\sqrt{2\pi k_{\mathrm{B}}T} \tag{11}$$

This result is analytically correct, as shown in the SI, but of limited practical value since neither $A^{\mathrm{u}}_{\xi\dot{\xi}}(\xi^*) = -k_{\mathrm{B}}T\,\ln\,[1]^{\mathrm{u}}_{\xi^*\dot{\xi}}$ nor $\langle Z_\xi^{(1/2)}\rangle^{\mathrm{u}}_{\xi^*\dot{\xi}}$ can be retrieved from constrained MD simulations—both terms require unconstrained simulations. A similar expression based on phase space integrals of the constrained system, to efficiently sample the elevated free-energy regions, was presented by Schlitter and Klähn[10] and is discussed in the Supporting Information.

Since absolute free energies are not easily accessible, in the Thermodynamic Integration (TI) approach, the free energy difference is obtained by integrating the readily available free energy derivative from an initial value ξ_i to a final vaule ξ_f of the reaction coordinate. Equation 1 can be differentiated analytically when using the full set of generalized coordinates $\mathbf{u}$, as detailed in the Supporting Information. This yields the familiar expressions[3] for unconstrained simulations

$$\frac{dA^{\mathrm{u}}_\xi(\xi^*)}{d\xi^*} = \left\langle \left(\frac{\partial\Phi}{\partial\xi} - k_{\mathrm{B}}T\frac{1}{J}\frac{\partial J}{\partial\xi}\right)_{\mathbf{q}} \right\rangle^{\mathrm{u}}_{\xi^*} \tag{12}$$

and, by eq 10, for constrained simulations

$$\frac{dA^{\mathrm{u}}_\xi(\xi^*)}{d\xi^*} = \frac{\left\langle \left(\frac{\partial\Phi}{\partial\xi} - k_{\mathrm{B}}T\frac{1}{J}\frac{\partial J}{\partial\xi}\right)_{\mathbf{q}} Z_\xi^{-1/2} \right\rangle^{\mathrm{c}}_{\xi^*\dot{\xi}}}{\langle Z_\xi^{-1/2}\rangle^{\mathrm{c}}_{\xi^*\dot{\xi}}} \tag{13}$$

where the partial derivatives with respect to ξ are evaluated at constant $\mathbf{q}$. In ref 8, we showed that this equation belongs to a family of projection formulas. For a vector field $\mathbf{v}(\mathbf{x}) = (\mathbf{v}_1^{\mathrm{T}}, \mathbf{v}_2^{\mathrm{T}}, ..., \mathbf{v}_N^{\mathrm{T}})^{\mathrm{T}}$ that smoothly projects, in a one-to-one correspondence, all elements $\mathbf{x}$ of the $\xi = \xi^*$ hypersurface onto elements $\mathbf{x} + \Delta\xi^*\mathbf{v}(\mathbf{x})$ of the $\xi = \xi^* + \Delta\xi^*$ hypersurface, the generalized expression for the free energy derivative reads as

$$\frac{dA^{\mathrm{u}}_\xi(\xi^*)}{d\xi^*} = \langle \mathbf{v}\cdot\nabla_x\Phi - k_{\mathrm{B}}T\nabla_x\cdot\mathbf{v}\rangle^{\mathrm{u}}_{\xi^*} \tag{14}$$

A particularly interesting member of this family is obtained for $\mathbf{v} = \nabla_x\xi/(\nabla_x\xi)^2$, in which case[8,17]

$$\frac{dA^{\mathrm{u}}_\xi(\xi^*)}{d\xi^*} = \frac{\left\langle \left(\frac{\nabla_x\xi\cdot\nabla_x\Phi}{(\nabla_x\xi)^2} - k_{\mathrm{B}}T\nabla_x\cdot\frac{\nabla_x\xi}{(\nabla_x\xi)^2}\right) Z_\xi^{-1/2} \right\rangle^{\mathrm{c}}_{\xi^*\dot{\xi}}}{\langle Z_\xi^{-1/2}\rangle^{\mathrm{c}}_{\xi^*\dot{\xi}}} \tag{15}$$

This vector field alleviates the troublesome need, demanded by the partial derivatives and Jacobian in eqs 12 and 13, of extending ξ into a full set of $3N$ generalized coordinates $\mathbf{u} = (\mathbf{q}^{\mathrm{T}},\xi)^{\mathrm{T}}$. Motivated by their rederivation of this result in "the orthogonal contravariant space to ξ," Wong and York comment on "the orthogonality requirement that is ignored in ref 8." The argumentation followed in the latter reference, however, avoids this premise and thereby indicates that the validity of eq 14 is restricted neither to orthogonalized generalized coordinates $\mathbf{q}$ parametrizing the $\xi = \xi^*$hyperplane nor to vector fields that are orthogonal to this hyperplane. The suggestion by Wong and York that the potential and Jacobian terms of eq 12 yield numerically different values from their respective counterparts in eq 14 is curious, considering that these terms measure the energetic and entropic contributions to the free energy, respectively.

Wong and York applied eqs 13 and 15 to calculate the free energy curve of a simple two-dimensional benchmark system in standard elliptic coordinates μ and ν, as described in detail in the Supporting Information. They reported substantial deviations, of up to 35% underestimation, between the free energies calculated by the standard constrained MD expressions and the exact free energy profile along the reaction coordinate ν and only recovered the correct free energy function upon replacing the traditional Fixman term $Z_\nu^{-1/2}$ by its inverse $Z_\nu^{1/2}$, as in eq 9. Our constrained MD simulations of the same model system, however, indicate that eqs 13 and 15—with the conventional Fixman term—reproduce the exact free energy profile, as shown in Figure 2. The exact free energy profile was calculated from the probability distribution $P(\xi)$ in a long unconstrained MD simulation and confirmed by unconstrained

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Monte Carlo simulations. An identical curve was also obtained by analyzing the unconstrained MD simulation by the conditional average TI approach of eq 12, using a binning approach to measure the profile along ν (clearly, an unconstrained simulation does not require a bias correction). Constrained MD simulations were run in Cartesian coordinates, using the SHAKE routine[1] to iteratively calculate and apply the constraint force, $\mathbf{f}^c = \lambda_\nu \partial\nu/\partial\mathbf{x}$. Constrained MD simulations were also run in generalized coordinates, using the analytically derived equation of motion for the sole unconstrained coordinate of the system, i.e., μ (see Supporting Information). The runs were executed at intervals of $\Delta\nu^* = 0.02$; the calculated free energy derivatives were integrated using the trapezium rule. As Figure 2 shows, the free energy

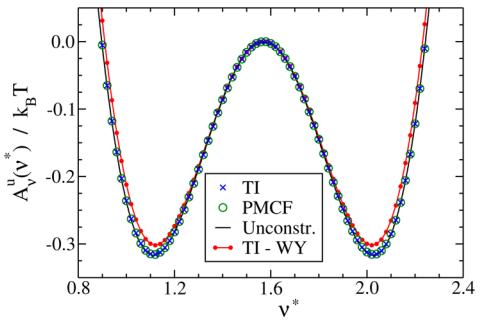

Figure 2. Free energy profile of a simple 2D system in elliptic coordinates, plotted as a function of the reaction coordinate ν. Details of the system are provided in the Supporting Information. The markers were calculated from constrained MD simulations: the blue crosses (×) denote the identical results of eqs 13 and 15; the green circles (○) are obtained with eq 16. The solid black line is the probability distribution of ν in an unconstrained simulation. The red dots and line were calculated by using the inverse Fixman correction, as suggested by Wong and York, in eqs 13 and 15. Note also the marked differences with the numerical results reported by Wong and York for this system, see Figure 3 of ref 14.

profiles derived by eqs 13 and 15—using the conventional Fixman term—reproduce the profile obtained in the unconstrained simulations. Replacing the Fixman term by its inverse, as proposed by Wong and York, results in a slight shift of the TI free energy profile, also shown in Figure 2. We note, and prove in the SI, that in this simple example the two partial derivatives in eqs 12 and 13 are identical, for any configuration, to the two corresponding terms in eq 15.

4. POTENTIAL OF MEAN CONSTRAINT FORCE

Since the constraint force is opposing the system's propensity to drift to lower free energies, one intuitively suspects that the constraint force and the free energy are related. The exact relation, including mass-metric corrections, was established some 15 years ago by den Otter and Briels[5] and independently by Sprik and Ciccotti.[6] In its most concise form, the Potential of Mean Constraint Force (PMCF) reads[10]

$$A^u_\xi(\xi_f) = \int_{\xi_i}^{\xi_f} \langle \lambda_\xi \rangle^c_{\xi^*\xi}\, d\xi^* - k_B T \ln \langle Z_\xi^{-1/2} \rangle^c_{\xi^*\xi} + A(\xi_i) \tag{16}$$

Note that the various contributions to this free energy profile can be obtained by differentiating ξ only once, whereas eqs 13 and 15 require second derivatives, making this an attractive approach for free energy calculations.

Wong and York commented on the PMCF relation that "the Jacobian contribution is not discussed (or assumed to vanish), and the Fixman term is the inverse" of their mass-metric correction. The explicit Jacobian contribution in eq 12 reflects the particular route followed in deriving this expression. One starts from eq 2, with $f = \delta(\xi - \xi^*)$, by integrating over the $3N$ Cartesian momenta, followed by a transformation to generalized coordinates $\mathbf{u} = (\mathbf{q}^T, \xi)^T$, a differentiation with respect to ξ, a transformation back to Cartesian coordinates, and, finally, the reinstatement of the $3N$ Cartesian momenta.[3] The back and forth coordinate transformations give rise to the Jacobian contribution. It is, however, also possible to first differentiate with respect to ξ^*, obtaining the conditional average of the Hamiltonian derivative $\langle (\partial \mathcal{H}^u_u/\partial\xi)_\mathbf{q} \rangle^u_{\xi^*}$, followed by an analytical integration over the generalized momenta. The final result is again eq 12, as shown in the Supporting Information, but the "Jacobian" contribution now emerges as the ξ-dependence of the kinetic energy (at constant generalized momenta). Mülders et al.[18] noted that the closely related average of the constrained Hamiltonian derivative $\langle (\partial \mathcal{H}^c_q/\partial\xi)_\mathbf{q} \rangle^c_{\xi^*\xi}$ is equal to the average Lagrange multiplier $\langle \lambda_\xi \rangle^c_{\xi^*\xi}$ of the constraint force and thereby paved the way for derivations of the exact potential of mean constraint force,[5,6,10] implicitly *including* the entropic—"Jacobian" or "kinetic"—contribution. It has also been shown that PMCF, after averaging the Lagrange multiplier over the momenta, recovers an expression of the generalized form of eq 14, with a mass-weighted vector field,[8] thus showing once more that the entropic Jacobian contribution is properly accounted for. It is interesting to note that the Jacobian term featured in eq 15 can also be envisaged as a measure of the local curvature of the $\xi = \xi^*$ hyperplane.[19] The PMCF method has been extended to systems with multiple constraints, with the additional constraints serving either to map a multidimensional free energy landscape or to speed up the sampling of phase space by eliminating the high frequency vibrations.[7]

Wong and York proceeded to show that the PMCF equation fails for the aforementioned 2D numerical example, yielding an overestimate of 10%, and they proposed corrections to recover the correct free energy profile by adding an explicit Jacobian contribution and reverting the Fixman correction.[14] By repeating these calculations, however, we find that eq 16 accurately recovers the correct free energy profile from constrained MD simulations, as illustrated in Figure 2. Other tests of the PMCF method confirming the correctness of eq 16 were reported in refs 5, 7, and 8, by calculating free energy profiles along the bending or dihedral angles of simple molecules.

It is unclear why Wong and York did not retrieve the correct free energy profile by employing the correct TI and PMCF equations. In view of the significant differences between the profiles in Figure 2 and those in Figure 3 of Wong and York,[14] it appears unlikely that these authors have actually calculated their profiles from standard constrained MD simulations. Instead, they may have numerically integrated the configuration and phase space integrals. Since the integrals over the momenta are trivially dealt with in Cartesian coordinates, it is clear that there is no real need for mass-dependent correction terms in this approach. For the 2D sample discussed above, which is small enough to be amenable to brute force integration, Wong and York present in their Supporting Information three integrals that recover the free energy profile *without* metric

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tensor corrections. They also suggest a fourth method that does include a Fixman-like correction, namely $A^{u}_{\xi}(\xi^*) = -k_BT \ln[Z^{1/2}_{\xi}]^{u}_{\xi^*\xi}$, but this expression is *not* generally valid and does *not* hold true for the numerical example discussed by these authors (see SI). Note that the similarly structured expression $A^{u}_{\xi}(\xi^*) = -k_BT \ln[Z^{-1/2}_{\xi}]^{c}_{\xi^*\xi}$ holds generally true for constrained MD simulations, as was proven in eq 3.

5. CONCLUSIONS

It has recently been suggested in this journal by Wong and York[14] that the Fixman mass-metric correction to undo the bias of constraints in MD simulations has hitherto been implemented the wrong way round, and that various expressions to calculate free energy profiles from constrained simulations are incomplete and require corrections to recover the exact free energy profile. By a careful study of the original expressions and their proposed amendments, both theoretically and by a numerical example, we established that the suggested modifications do not apply to constrained MD simulations, and that the original expressions are correct.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

An elaborate discussion of the mathematical steps, and details on both simulation models, are provided in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: w.k.denotter@utwente.nl.

Notes

The authors declare no competing financial interest.

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