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Calculating free energies using average force

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A new, general formula that connects the derivatives of the free energy along the selected, generalized coordinates of the system with the instantaneous force acting on these coordinates is derived. The instantaneous force is defined as the force acting on the coordinate of interest so that when it is subtracted from the equations of motion the acceleration along this coordinate is zero. The formula applies to simulations in which the selected coordinates are either unconstrained or constrained to fixed values. It is shown that in the latter case the formula reduces to the expression previously derived by den Otter and Briels [Mol. Phys. **98**, 773 (2000)]. If simulations are carried out without constraining the coordinates of interest, the formula leads to a new method for calculating the free energy changes along these coordinates. This method is tested in two examples — rotation around the C–C bond of 1,2-dichloroethane immersed in water and transfer of fluoromethane across the water-hexane interface. The calculated free energies are compared with those obtained by two commonly used methods. One of them relies on determining the probability density function of finding the system at different values of the selected coordinate and the other requires calculating the average force at discrete locations along this coordinate in a series of constrained simulations. The free energies calculated by these three methods are in excellent agreement. The relative advantages of each method are discussed. [DOI: 10.1063/1.1410978]

I. INTRODUCTION

Many molecular dynamics computer simulations of chemically and biologically interesting systems are devoted to calculating free energy changes along selected degrees of freedom. In some instances, the full free energy profile is of interest. For example, nonmonotonic changes in the free energy of two small, hydrophobic species in water as a function of their separation, observed in computer simulations,[1,2] reflect the changing patterns of hydrophobic hydration and provide important tests of analytical theories of hydrophobic interactions.[3] Free energy maps of small peptide units in vacuum and in water shed light on conformational preferences of the protein backbone.[4,5] The free energy profiles associated with the transfer of solutes through water-membrane systems yield solute distributions and permeation rates across membranes.[6–8] In other instances, calculations of free energy profiles provide a means of estimating the free energy difference between the end-points which, in turn, yields the relative stabilities of the corresponding states of the system. Determinations of conformational equilibria in flexible molecules and association constants between molecular species are among important applications of such calculations.[9–12]

The free energy changes along the chosen generalized coordinates can be calculated from molecular simulations by a variety of techniques.[13–15] Most (but not all[16,17]) of them require that a sufficient, thermally representative sample of states of the system is generated at different values of these coordinates. This leads to the interpretation of the free energy changes along the chosen coordinates as the potential of mean force exerted by other coordinates. Only a few methods for calculating this potential can be conveniently, efficiently and generally combined with computer simulations. One such class of methods relies on obtaining the probability density function, $P(\xi_1,\ldots,\xi_p)$, of finding the system at values $\xi_1,\ldots,\xi_p$ of the p selected generalized coordinates. Once this probability density function is estimated with satisfactory accuracy the potential of mean force, $A(\xi_1,\ldots,\xi_p)$, can be readily calculated as

$$A(\xi_1,\ldots,\xi_p)=-k_BT\log P(\xi_1,\ldots,\xi_p), \tag{1}$$

where T is temperature and k_B is the Boltzmann constant.

Several extensions to this generic method can markedly improve its efficiency and accuracy. In particular, the Hamiltonian of the system can be augmented by a biasing potential, $U(\xi_1,\ldots,\xi_p)$, chosen such that sampling of phase space in the p selected dimensions becomes more uniform.[18] The efficiency can be further improved by dividing the hypersurface defined by the p selected coordinates into a set of overlapping windows and performing separate simulation in each window. This technique is advantageous even if there is no need to apply a biasing potential.[19] The probability density functions obtained for different windows and different biasing potentials can be self-consistently converted into the unbiased potential of mean force for the full range of $\xi_1,\ldots,\xi_p$.[20,21]

Another, general method for calculating the potential of mean force requires calculating the derivatives $\partial A/\partial \xi$ in a series of calculations, in which ξ_i is kept constrained to fixed values distributed along $[\xi_i^{\min},\xi_i^{\max}]$ in the range of interest. Then, the potential of mean force is recovered by numerical integration. The derivative of the free energy is related to the constraint force needed to keep the system at the fixed value of ξ_i. The exact nature of this relationship was a subject of some debate.[22–26] Several initial suggestions were found to be valid only under special circumstances.[22–24] Only recently, the generally valid and practical to use formula was derived for one-dimensional[25,27,28] and multi-dimensional[26] cases. In this paper, this formula is derived in the general context of multi-dimensional reaction coordinates for constrained and unconstrained simulations. All previous derivations were done in the case of constrained simulations only. This formula requires that the constraint force is corrected by geometric factors that depend on $\xi_1,\ldots,\xi_p$ but not on other (usually difficult to define) generalized coordinates. Since the constraint force can be readily calculated in computer simulations (e.g., using the SHAKE[29] or RATTLE[30] algorithms) practical applications of this method are quite feasible.

Compared to the probability density method, the method of the constraint force has several advantages. In particular, it does not require a good guess of the biasing potential to achieve efficient sampling of $\xi_1,\ldots,\xi_p$. Providing such a guess could be a difficult task, especially for qualitatively new problems. Further, data analysis is markedly simpler; no procedure for matching results obtained for overlapping windows is required. However, the constraint force method also suffers from several disadvantages. It may be inaccurate or inefficient if the potential of mean force is a quickly changing function of $\xi_1,\ldots,\xi_p$. In complex cases, involving for example insertion of a peptide into a membrane or induced fit of an inhibitor into an enzyme, preparation of the system at consecutive, fixed values of the selected degrees of freedom may be difficult, and subsequent equilibration of the system may be slow. In some instances, application of the constraint force method may lead to quasi nonergodic behavior. Finally, information about the dynamic behavior of the system, which also may be of interest in a simulation, is not available in this approach.

In this paper, we propose an alternative and equally general approach to calculating the potential of mean force, which combines several desired features of both methods. As in the constraint force method, the potential of mean force is obtained by integrating its derivative. This derivative, however, is calculated from unconstrained rather than constrained simulations. The centerpiece of our method is a new, general formula that connects $\partial A/\partial \xi_i$ with the instantaneous force acting on ξ_i. This force is acting along the gradient of ξ_i such that if subtracted from the equations of motion the acceleration of ξ_i is zero. This instantaneous force can be also related to the forces of constraint in a constrained simulation. Then, the forces of constraint are applied to maintain ξ_i at a constant value and the force acting on ξ_i is exactly equal to the opposite of these forces of constraint.

The formula that relates $\partial A/\partial \xi_i$ to the instantaneous force acting on ξ_i is different for unconstrained simulations than for constrained simulations. However, as will be shown below, it converges to the den Otter–Briels formula at the appropriate limits. The value of the new formula is not only in providing another route to calculating the potential of mean force but also in clarifying the relationship between the thermodynamic force and the force of constraint. By doing so it forms the theoretical basis for highly efficient methods to calculate the potential of mean force and to investigate rare events.[31]

In the next section we derive the formula for $\partial A/\partial \xi_i$. This is done in two steps. First, the expression for $\partial A/\partial \xi_i$ in unconstrained simulations of a Hamiltonian system is obtained. Then, this expression is generalized so that it applies when the system is only approximately Hamiltonian, as is the case in adiabatic approximation. Then we consider two numerical examples — rotation around the C–C bond of 1,2-dichloroethane immersed in water and transfer of fluoromethane across the water-hexane interface. These examples involve only a single reaction coordinate. Applications to multidimensional cases will be considered separately. We close the paper with discussion of the new method in comparison to its alternatives. The details of how the method is applied in practice are given in one of the Appendices.

II. THEORY

A. Generalized coordinates

We assume that we have a set of M particles and we denote by N the total number of degrees of freedom of our system ($N=3M$). We further assume that there exists a Hamiltonian, H, for this system:

$$H(x_1,\ldots,x_N,p_1,\ldots,p_N)=\frac{1}{2}\sum_i \frac{p_i^2}{m_i}+\Phi(x_1,\ldots,x_N),$$

$$\frac{dx_i}{dt}=\frac{\partial H}{\partial p_i},$$

$$\frac{dp_i}{dt}=-\frac{\partial H}{\partial x_i},$$

where $(x_1,\ldots,x_n)$ are Cartesian coordinates, $(p_1,\ldots,p_n)$ are the conjugated momenta, Φ is the potential and t is time.

We suppose that a set of $N-p$ functions $(q_1,\ldots,q_{N-p})$ can be defined such that $(\xi_1,\ldots,\xi_p,q_1,\ldots,q_{N-p})$ forms a complete set of generalized coordinates. By definition, the Cartesian coordinates $(x_1,\ldots,x_N)$ can be written as functions of ξ_i,q_j:

$$x_1(\xi_1,\ldots,\xi_p,q_1,\ldots,q_{N-p})$$

$$\ldots$$

$$x_N(\xi_1,\ldots,\xi_p,q_1,\ldots,q_{N-p}).$$

We will often denote by x the vector $(x_1,\ldots,x_N)$ and similarly for ξ, q, p_ξ and p_q.

The derivative with respect to ξ_i is defined as the derivative computed with ξ_j, $j\neq i$ and q_k, $k=1,\ldots,N-p$ constant. Using Definition in Eq. (1) of A we can write

$$\frac{\partial A}{\partial \xi_i} = -k_B T \frac{\frac{\partial P}{\partial \xi_i}}{P}. \tag{2}$$

The probability density P for a canonical ensemble can be written as a function of the Hamiltonian H of the system:

$$P(\xi_1^*,\dots,\xi_p^*) = \frac{1}{\mathcal{N}} \int dx_1 \dots dx_N \, dp_1 \dots dp_N \, \delta(\xi_1 - \xi_1^*) \dots \delta(\xi_p - \xi_p^*) \exp\left(-\frac{H}{k_B T}\right), \tag{3}$$

where $\mathcal{N}$ is a normalization factor.

We introduce additional notations to express the Hamiltonian H as a function of the generalized coordinates.

The Jacobian, J, of the transformation from Cartesian to generalized coordinates is defined as

$$J \overset{\text{def}}{=} \begin{pmatrix} \frac{\partial \xi_1}{\partial x_1} & \dots & \frac{\partial \xi_1}{\partial x_N} \\ \dots & \dots & \dots \\ \frac{\partial \xi_p}{\partial x_1} & \dots & \frac{\partial \xi_p}{\partial x_N} \\ \frac{\partial q_1}{\partial x_1} & \dots & \frac{\partial q_1}{\partial x_N} \\ \dots & \dots & \dots \\ \frac{\partial q_{N-p}}{\partial x_1} & \dots & \frac{\partial q_{N-p}}{\partial x_N} \end{pmatrix} = \begin{pmatrix} J_\xi \\ J_q \end{pmatrix}, \tag{4}$$

where J_ξ are the first p lines and J_q are the remaining lines. The inverse of J is denoted by J^{-1}. We define matrix Z as

$$Z \overset{\text{def}}{=} J M^{-1} J^t,$$

where J^t is the transpose of matrix J and M is the mass matrix:

$$M = \begin{pmatrix} m_1 & 0 & \dots & 0 \\ 0 & m_2 & \dots & 0 \\ \dots & \dots & \dots & \dots \\ \dots & \dots & \dots & m_N \end{pmatrix}.$$

Matrix Z can be written as

$$Z = \begin{pmatrix} Z_\xi & Z_{\xi q} \\ Z_{q\xi} & Z_q \end{pmatrix},$$

where Z_ξ is a $p \times p$ matrix defined by

$$[Z_\xi]_{ij} \overset{\text{def}}{=} \sum_{k=1}^{N} \frac{1}{m_k} \frac{\partial \xi_i}{\partial x_k} \frac{\partial \xi_j}{\partial x_k}, \tag{5}$$

$Z_{\xi q}$ is a $p \times (N-p)$ matrix, $Z_{q\xi} = Z_{\xi q}^t$ and Z_q is a $(N-p) \times (N-p)$ matrix.

The inverse of Z is denoted by A:

$$A = \begin{pmatrix} A_\xi & A_{\xi q} \\ A_{q\xi} & A_q \end{pmatrix}.$$

Using generalized coordinates, the Hamiltonian of the system takes the form

$$H(\xi, q, p_\xi, p_q) = \tfrac{1}{2} p_\xi^t Z_\xi p_\xi + \tfrac{1}{2} p_q^t Z_q p_q + p_\xi^t Z_{\xi q} p_q + \Phi(\xi, q), \tag{6}$$

where p_ξ^t and p_q^t are the transpose of vectors p_ξ and p_q.

Inserting the expression for P from Eq. (3) into (2), we obtain:

$$\frac{\partial A}{\partial \xi_i} = \frac{\int dq \; dp_q \; dp_\xi \frac{\partial H}{\partial \xi_i} \exp\left(-\frac{H}{k_B T}\right)}{\int dq \; dp_q \; dp_\xi \exp\left(-\frac{H}{k_B T}\right)} \tag{7}$$

with a change of variables from Cartesian coordinates to generalized coordinates. For all function F, we define the statistical average of F at fixed $\xi^* = (\xi_1^*, \dots, \xi_p^*)$ as

$$\langle F \rangle_{\xi^*} = \frac{\int dx_1 \dots dx_N \; dp_1 \dots dp_N \delta(\xi_1 - \xi_1^*) \dots \delta(\xi_p - \xi_p^*) \exp\left(-\frac{H}{k_B T}\right) F(x_1, \dots, x_N)}{\int dx_1 \dots dx_N \; dp_1 \dots dp_N \delta(\xi_1 - \xi_1^*) \dots \delta(\xi_p - \xi_p^*) \exp\left(-\frac{H}{k_B T}\right)} = \frac{\int dq \; dp_q \; dp_\xi F(x_1, \dots, x_N)}{\int dq \; dp_q \; dp_\xi \exp\left(-\frac{H}{k_B T}\right)},$$

where in the last equation $\xi = \xi^*$. We these notations we can rewrite Eq. (7) as

$$\frac{\partial A}{\partial \xi_i} = \left\langle \frac{\partial H}{\partial \xi_i} \right\rangle_\xi. \tag{8}$$

By differentiating both sides of Eq. (6) we obtain

$$\frac{\partial H}{\partial \xi_i} = \frac{1}{2} p_\xi^t \frac{\partial Z_\xi}{\partial \xi_i} p_\xi + \frac{1}{2} p_q^t \frac{\partial Z_q}{\partial \xi_i} p_q + p_\xi^t \frac{\partial Z_{\xi q}}{\partial \xi_i} p_q + \frac{\partial \Phi}{\partial \xi_i}. \tag{9}$$

After substituting Eq. (9) in Eq. (8), we need to compute

$$\int dp_q\, dp_\xi \exp\left(-\frac{H}{k_BT}\right)$$

$$\times\left(\frac{1}{2}p_\xi^t\frac{\partial Z_\xi}{\partial \xi_i}p_\xi+\frac{1}{2}p_q^t\frac{\partial Z_q}{\partial \xi_i}p_q+p_\xi^t\frac{\partial Z_{\xi q}}{\partial \xi_i}p_q\right).$$

We show in Appendix E that for a given ξ^*, it is possible to choose the basis q such that

$$Z_{q\xi}(\xi^*,q)=0, \quad \forall q. \tag{10}$$

With this choice of q, for $\xi=\xi^*$, the function $\exp(-H/k_BT)$ is an even function of p_ξ and p_q and thus

$$\int dp_q\, dp_\xi \exp\left(-\frac{H}{k_BT}\right)p_\xi^t\frac{\partial Z_{\xi q}}{\partial \xi_i}p_q=0.$$

Using the result from Appendix A, we obtain for the following integral:

$$\int dp_q\, dp_\xi \exp\left(-\frac{H}{k_BT}\right)\left(\frac{1}{2}p_\xi^t\frac{\partial Z_\xi}{\partial \xi_i}p_\xi+\frac{1}{2}p_q^t\frac{\partial Z_q}{\partial \xi_i}p_q\right)$$

$$=\frac{k_BT}{2}\mathrm{Tr}\left(Z^{-1}\frac{\partial Z}{\partial \xi_i}\right)\int dp_q\, dp_\xi \exp\left(-\frac{H}{k_BT}\right).$$

The trace of $Z^{-1}(\partial Z/\partial \xi_i)$ can be computed using the result from Appendix B:

$$\frac{k_BT}{2}\mathrm{Tr}\left(Z^{-1}\frac{\partial Z}{\partial \xi_i}\right)=k_BT\frac{\partial \log|J|}{\partial \xi_i}$$

and thus

$$\nabla_\xi A=\langle \nabla_\xi \Phi+k_BT\nabla_\xi \log|J|\rangle_\xi. \tag{11}$$

The notation $\nabla_\xi A$ denotes a vector with p coordinates:

$$\nabla_\xi A=\begin{pmatrix}\dfrac{\partial A}{\partial \xi_1}\\ \vdots\\ \dfrac{\partial A}{\partial \xi_p}\end{pmatrix}.$$

The derivative of the free energy can be seen as resulting from two contributions: the mechanical forces acting along ξ and the variations of the volume element associated with the generalized coordinates. This formula has been previously derived in many papers,[28,32] and is also given by Smit and Frenkel.[33]

B. Thermodynamics force

Equation (8) explicitly depends on the choice of all generalized coordinates, including q. As this is not practical from a computational point of view, we now modify this equation to obtain an expression independent of the choice of q. This is done by integrating analytically as many terms as possible in Eq. (8).

We start by simplifying the notations. We will now denote

$$x_i' \overset{\text{def}}{=} \sqrt{m_i}x_i, \tag{12}$$

$$\nabla_i' \overset{\text{def}}{=} \frac{\partial}{\partial x_i'}, \tag{13}$$

$$p_{x_i}' \overset{\text{def}}{=} \frac{p_i}{\sqrt{m_i}}, \tag{14}$$

$$\mathcal{H}_r \overset{\text{def}}{=} \left(\frac{\partial^2 \xi_r}{\partial x_i'\,\partial x_j'}\right)=\left(\frac{1}{\sqrt{m_i m_j}}\frac{\partial^2 \xi_r}{\partial x_i\,\partial x_j}\right), \tag{15}$$

where $\mathcal{H}_r$ represents the modified Hessian of ξ_r.

The symbol $\cdot$ denotes a dot product or a matrix-vector product, depending on the context.

We start from the equation for the time evolution of p_{ξ_i}:

$$\frac{dp_{\xi_i}}{dt}=-\frac{\partial H}{\partial \xi_i}. \tag{16}$$

The momentum vector p_ξ is defined as the derivative of the Lagrangian $\mathcal{L}$ with respect to $\dot{\xi}$. Since the Lagrangian $\mathcal{L}$ is defined as

$$\mathcal{L}=\frac{1}{2}\begin{pmatrix}\dot{\xi}\\ \dfrac{dq}{dt}\end{pmatrix}^t\cdot A\cdot\begin{pmatrix}\dot{\xi}\\ \dfrac{dq}{dt}\end{pmatrix}-\Phi(\xi,q)$$

the momentum p_ξ is equal to

$$p_\xi \overset{\text{def}}{=} \frac{\partial \mathcal{L}}{\partial \dot{\xi}}=A_\xi\frac{d\xi}{dt}+A_{\xi q}\frac{dq}{dt}. \tag{17}$$

In Eq. (17), p_ξ is a vector. Considering one coordinate p_{ξ_i} we obtain

$$p_{\xi_i}=\sum_j [A_\xi]_{ij}\frac{d\xi_j}{dt}+\sum_k [A_{\xi q}]_{ik}\frac{dq_k}{dt}. \tag{18}$$

We can differentiate both sides of Eq. (18) with respect to t and use Eq. (16) to obtain an expression for $\partial H/\partial \xi_i$. As the right-hand side of Eq. (18) is the sum of two products, its derivative contains four terms:

$$\frac{\partial H}{\partial \xi_i}=-\frac{dp_{\xi_i}}{dt}=-\sum_j \frac{d[A_\xi]_{ij}}{dt}\frac{d\xi_j}{dt}-\sum_j [A_\xi]_{ij}\frac{d^2\xi_j}{dt^2}$$

$$-\sum_k \frac{d[A_{\xi q}]_{ik}}{dt}\frac{dq_k}{dt}-\sum_k [A_{\xi q}]_{ik}\frac{d^2 q_k}{dt^2}. \tag{19}$$

Since $AZ=I$ by definition, we have

$$A_\xi Z_\xi+A_{\xi q}Z_{q\xi}=I, \tag{20}$$

$$A_\xi Z_{\xi q}+A_{\xi q}Z_q=0. \tag{21}$$

Equations (20) and (21) simplify as $Z_{q\xi}$ satisfies Eq. (10):

$$A_\xi Z_\xi=I, \tag{22}$$

$$A_{\xi q}Z_q=0. \tag{23}$$

The matrices Z_ξ and Z_q are invertible. Therefore,

$$A_\xi=Z_\xi^{-1}, \tag{24}$$

$$A_{\xi q}=0. \tag{25}$$

The last term in Eq. (19) is thus equal to zero.

The derivative of A_ξ can be calculated by differentiating Eq. (20):

$$0=A_\xi\frac{dZ_\xi}{dt}+\frac{dA_\xi}{dt}Z_\xi+A_{\xi q}\frac{dZ_{q\xi}}{dt}+\frac{dA_{\xi q}}{dt}Z_{q\xi}.$$

It leads to

$$\frac{dA_\xi}{dt}=-Z_\xi^{-1}\frac{dZ_\xi}{dt}Z_\xi^{-1}, \tag{26}$$

where A_ξ has been replaced by Z_ξ^{-1} thanks to Eq. (24).

We now compute dZ_ξ/dt using the chain rule of derivation:

$$\frac{dZ_\xi}{dt}=\sum_i\frac{\partial Z_\xi}{\partial x_i}\frac{dx_i}{dt}=\frac{\partial Z_\xi}{\partial x'}\cdot p'_x. \tag{27}$$

We insert Eq. 27 into Eq. 26:

$$\frac{dA_\xi}{dt}=-Z_\xi^{-1}\left(\frac{\partial Z_\xi}{\partial x'}\cdot p'_x\right)Z_\xi^{-1}.$$

Next, we insert the last equation into Eq. 19:

$$\frac{\partial H}{\partial \xi_i}=-\sum_j [Z_\xi^{-1}]_{ij}\frac{d^2\xi_j}{dt^2}+\sum_{jk}[Z_\xi^{-1}]_{ij}\left[\frac{\partial Z_\xi}{\partial x'}\cdot p'_x\right]_{jk}p_{\xi_k} -\sum_k\frac{d[A_{\xi q}]_{ik}}{dt}\frac{dq_k}{dt}. \tag{28}$$

We now focus on the second term on the right-hand side of this equation. Using the definition of p_ξ and p_q as derivatives of the Lagrangian with respect to $\dot{\xi}$ and $\dot{q}$, p'_x can be expressed in terms of p_ξ and p_q:

$$p'_x=(J')^t\begin{pmatrix}p_\xi\\ p_q\end{pmatrix}, \tag{29}$$

where J' is analogous to J in Eq. (4) but the derivatives are taken with respect to x'_i rather than x_i.

We multiply the previous equation by $\partial Z_\xi/\partial x'$:

$$\frac{\partial Z_\xi}{\partial x'}\cdot p'_x=\frac{\partial Z_\xi}{\partial x'}(J')^t\begin{pmatrix}p_\xi\\ p_q\end{pmatrix}. \tag{30}$$

We obtain a new expression for the second term on the right-hand side of Eq. (28):

$$\sum_{jk}[Z_\xi^{-1}]_{ij}\left[\frac{\partial Z_\xi}{\partial x'}\cdot p'_x\right]_{jk}p_{\xi_k} =\sum_{jklr}[Z_\xi^{-1}]_{ij}\frac{\partial[Z_\xi]_{jk}}{\partial x'_l}[J'_\xi]_{rl}p_{\xi_r}p_{\xi_k} +\sum_{jklr}[Z_\xi^{-1}]_{ij}\frac{\partial[Z_\xi]_{jk}}{\partial x'_l}[J'_\xi]_{r+p,l}p_{q_r}p_{\xi_k}. \tag{31}$$

In the last equation, we have split the right-hand side into odd and even functions of p_ξ and p_q. We want to compute

$$\int dp_q\,dp_\xi\,\exp\left(-\frac{H}{k_BT}\right)\frac{\partial H}{\partial \xi_i}.$$

Because we chose a basis q such that Eq. (10) is true, the function $\exp(-H/k_BT)$ is even in p_ξ and p_q. Therefore in Eq. (31), all odd terms in p_ξ and p_q cancel whereas even terms contribute. The only contribution comes from quadratic terms in p_ξ:

$$\sum_{jklr}[Z_\xi^{-1}]_{ij}\frac{\partial[Z_\xi]_{jk}}{\partial x'_l}[J'_\xi]_{rl}p_{\xi_r}p_{\xi_k}.$$

Using Eq. (A1) from Appendix A, we compute the integral over p_ξ and p_q:

$$\int dp_q\,dp_\xi\,\exp\left(-\frac{\frac{1}{2}p_\xi^tZ_\xi p_\xi}{k_BT}\right)\left(\sum_{kr}\frac{\partial[Z_\xi]_{jk}}{\partial x'_l}[J'_\xi]_{rl}p_{\xi_r}p_{\xi_k}\right) =k_BT\sum_{kr}\frac{\partial[Z_\xi]_{jk}}{\partial x'_l}[J'_\xi]_{rl}[Z_\xi^{-1}]_{kr}\int dp_q\,dp_\xi \times\exp\frac{\frac{1}{2}\,p_\xi^tZ_\xi p_\xi}{k_BT}.$$

We multiply the previous equation by Z_ξ^{-1} to obtain

$$\left\langle\sum_{jk}[Z_\xi^{-1}]_{ij}\left[\frac{\partial Z_\xi}{\partial x'}\cdot p'_x\right]_{jk}p_{\xi_k}\right\rangle_\xi =k_BT\left\langle\sum_{jkrl}[Z_\xi^{-1}]_{ij}\frac{\partial[Z_\xi]_{jk}}{\partial x'_l}[Z_\xi^{-1}]_{kr}\frac{\partial\xi_r}{\partial x'_l}\right\rangle_\xi. \tag{32}$$

We now prove that the third term on the right-hand side of Eq. (28) does not contribute to $\langle\nabla_\xi H\rangle_\xi$. Transformations similar to the ones done for the second term are performed.

The derivative with respect to t is written as a scalar product with p'_x:

$$\frac{d[A_{\xi q}]_{ik}}{dt}=\frac{\partial[A_{\xi q}]_{ik}}{\partial x'}\cdot p'_x.$$

Inserting Eq. (29) into the previous equation,

$$\frac{d[A_{\xi q}]_{ik}}{dt}=\frac{\partial[A_{\xi q}]_{ik}}{\partial x'}\cdot(J')^t\cdot\begin{pmatrix}p_\xi\\ p_q\end{pmatrix}.$$

The derivative of q_k can be expressed in terms of p_q only since the basis q satisfies Eq. (10):

$$\frac{dq_k}{dt}=\sum_l[Z_q]_{kl}p_{q_l}.$$

As before when integrating over p_ξ and p_q, the odd terms in p_ξ and p_q cancel and we obtain

$$\int dp_q\, dp_\xi \exp\left(-\frac{H}{k_BT}\right)\frac{d[A_{\xi q}]_{ik}}{dt}\frac{dq_k}{dt}$$

$$=\sum_{lsr}\int dp_q\, dp_\xi \exp\left(-\frac{H}{k_BT}\right)$$

$$\times\frac{\partial[A_{\xi q}]_{ik}}{\partial x'_s}[J']_{r+p,s}[Z_q]_{kl}p_{q_l}p_{q_r}$$

$$=\sum_{lsr}\int dp_q\, dp_\xi \exp\left(-\frac{H}{k_BT}\right)$$

$$\times\frac{\partial[A_{\xi q}]_{ik}}{\partial x'_s}\frac{\partial q_r}{\partial x'_s}[Z_q]_{kl}p_{q_l}p_{q_r}.$$

We now prove that

$$\sum_s \frac{\partial[A_{\xi q}]_{ik}}{\partial x'_s}\frac{\partial q_r}{\partial x'_s}=\sum_s \frac{1}{m_s}\frac{\partial[A_{\xi q}]_{ik}}{\partial x_s}\frac{\partial q_r}{\partial x_s}=0.$$

The vectors $(1/m_s)(\partial q_r/\partial x_s$, are tangent to the surface $\xi=\xi^*$ since they satisfy Eq. (10) and therefore are orthogonal to $\nabla\xi_1,\ldots,\nabla\xi_p$. The function $[A_{\xi q}]_{ik}$ is equal to zero everywhere on the surface $\xi=\xi^*$. As a consequence, its derivative along any tangent to the surface $\xi=\xi^*$, is zero. In particular,

$$\sum_s \frac{\partial[A_{\xi q}]_{ik}}{\partial x_s}\frac{1}{m_s}\frac{\partial q_r}{\partial x_s}=0.$$

We have proved that only the first two terms in Eq. (28) contribute. In matrix notation, inserting Eq. (32) in Eq. (28) we have

$$\langle\nabla_\xi H\rangle_\xi=k_BT\left\langle\sum_l\frac{1}{m_l}Z_\xi^{-1}\cdot\partial_l Z_\xi\cdot Z_\xi^{-1}\cdot\nabla\xi\right\rangle_\xi$$

$$-\left\langle Z_\xi^{-1}\frac{d^2\xi}{dt^2}\right\rangle_\xi, \tag{33}$$

where we denote $\partial_l Z_\xi=\partial Z_\xi/\partial x_l$.

If we denote by λ the vector of RATTLE Lagrange multipliers they are by definition such that

$$Z_\xi\lambda\overset{\text{def}}{=}-\frac{d^2\xi}{dt^2}. \tag{34}$$

We now summarize what we have obtained so far. We have started our derivation from Eq. (8) which relates the derivative of A with respect to ξ_i to the average of $\partial H/\partial\xi_i$. We observed that this expression is not very useful as it depends on a particular choice of generalized coordinates. We transformed this expression by analytically integrating some terms and we obtained Eq. (33). This new expression is much more useful than the initial one [Eq. (8)] as it can be computed numerically without any explicit reference to a particular choice of generalized coordinates. Finally, by inserting Eq. (34) in the last term of Eq. (33), we obtain

$$\nabla_\xi A=\left\langle\lambda+k_BT\sum_l\frac{1}{m_l}Z_\xi^{-1}\cdot\partial_l Z_\xi\cdot Z_\xi^{-1}\cdot\partial_l\xi\right\rangle_\xi\overset{\text{def}}{=}\langle F_\xi^{(1)}\rangle_\xi. \tag{35}$$

The following equality can be used to simplify the previous equation:

$$\partial_l Z_\xi^{-1}=-Z_\xi^{-1}\cdot\partial_l Z_\xi\cdot Z_\xi^{-1}.$$

We insert the last equation into Eq. (35)

$$\nabla_\xi A=\left\langle\lambda-k_BT\sum_l\frac{1}{m_l}\partial_l Z_\xi^{-1}\cdot\partial_l\xi\right\rangle_\xi. \tag{36}$$

However, the last equation is not as convenient as Eq. (35) from a computational point of view because $\partial_l Z_\xi^{-1}$ is not readily available.

Equation (35) has a similar interpretation to Eq. (11) although the terms are now different. The first term λ is related to the force acting along ξ, which is the opposite of the constraint force. The second term $\Sigma_l(1/m_l)\partial_l Z_\xi^{-1}\cdot\partial_l\xi$ is a correction term which accounts for the variation of an infinitesimal volume element in generalized coordinates.

C. Decoupled degrees of freedom

It is often desirable to consider a situation where ξ is decoupled from the other degrees of freedom. By decoupling we mean that $d^2\xi/dt^2$ is not a function of the coordinates q but instead is governed by some other equation of motion. In the previous paper,[31] we derived the formula for $\partial A/\partial\xi$ that applies to a single reaction coordinate. In this paper, this formula is generalized to a multi dimensional case.

One example of decoupling is a constrained simulation in which ξ is constant. In this case $\dot{\xi}=0$ and $d^2\xi/dt^2=0$. We will see that using Eq. (35) we will recover the result from den Otter and Briels.[26] Our derivation can thus be seen as a generalization of their result.

Another choice, which was previously discussed,[31] is a diffusion equation such that the motion of ξ is random and approximately adiabatic. The choice of a Langevin equation is a convenient one because adiabatic approximation can be achieved simply by varying the diffusion constant.

Deriving the relation for $\nabla_\xi A$ in the decoupled case requires modifying the probability density of p_ξ. Previously this density was given by

$$f_\xi=\exp\left(\frac{-\frac{1}{2}p_\xi^t Z_\xi p_\xi}{k_BT}\right). \tag{37}$$

For a constraint simulation, f_ξ becomes a Dirac delta function at the location of the constraint whereas for the other decoupled case, f_ξ is a constant function. Thus if we calculate analytically the integral over p_ξ in Eq. (35) with f_ξ given by Eq. (37), we will obtain the correction for the decoupled case.

Since the equation for the decoupled case can be used for an arbitrary f_ξ, it can be seen as a generalization of Eq. (36). In particular, we will show that in the case of f_ξ satisfying Eq. (37) (ξ coupled to q), the correction to Eq. (36) is equal to zero. Thus, one can implement the equation for the decoupled case [Eq. (46)] and use it in all situations.

By f_q we denote

$$f_q = \exp\left(- \frac{\frac{1}{2} p_q^t Z_q p_q}{k_B T} \right).$$

We start by calculating $d^2\xi_j/dt^2$. The first derivative is

$$\frac{d\xi_j}{dt} = \sum_k \nabla_k \xi_j \frac{dx_k}{dt}.$$

If we differentiate again with respect to t,

$$\frac{d^2\xi_j}{dt^2} = -\sum_k \frac{1}{m_k} \nabla_k \xi_j \nabla_k \Phi + \sum_k \frac{dx_k}{dt} \frac{d\,\nabla_k \xi_j}{dt}, \tag{38}$$

$$= -\sum_k \frac{1}{m_k} \nabla_k \Phi \nabla_k \xi_j + p_x'^{\,t} \cdot \mathcal{H}_j \cdot p_x', \tag{39}$$

using the definition in Eq. (15) of $\mathcal{H}_j$.

In Eq. 35, the only term that depends on p_ξ is λ. As λ is related to $d^2\xi_j/dt^2$ through Eq. (34), we need to compute

$$-Z_\xi^{-1} \int dp_q \, dp_\xi f_q f_\xi \frac{d^2\xi}{dt^2}.$$

Insertion of Eq. (39) leads to the computation of a simpler quantity:

$$-Z_\xi^{-1} \int dp_q \, dp_\xi \, f_q f_\xi (p_x')^t \cdot \mathcal{H}_j \cdot p_x'.$$

Again we insert Eq. (29) to obtain an expression explicitly depending on p_ξ and p_q:

$$\int dp_q \, dp_\xi \, f_q \, f_\xi (p_x')^t \cdot \mathcal{H}_j \cdot p_x'$$

$$= \int dp_q \, dp_\xi f_q f_\xi \begin{pmatrix} p_\xi \\ p_q \end{pmatrix}^t \cdot J' \mathcal{H}_j (J')^t \cdot \begin{pmatrix} p_\xi \\ p_q \end{pmatrix}.$$

The odd contributions in p_ξ and p_q cancel and we obtain

$$\int dp_q \, dp_\xi f_q f_\xi (p_x')^t \cdot \mathcal{H}_j \cdot p_x'$$

$$= \int dp_\xi f_\xi p_\xi \cdot J_\xi' \mathcal{H}_j (J_\xi')^t \cdot p_\xi \int dp_q f_q$$

$$+ \int dp_q f_q p_q \cdot J_q' \mathcal{H}_j (J_q')^t \cdot p_q \int dp_\xi f_\xi. \tag{40}$$

By performing a change of variables with $\tilde{p} = Z_\xi^{1/2} p_\xi$ we can show that

$$\int dp_\xi \, f_\xi = \int dp_\xi \, \exp\left(- \frac{\frac{1}{2} p_\xi^t Z_\xi p_\xi}{k_B T} \right) \propto \frac{1}{|Z_\xi|^{1/2}}, \tag{41}$$

where $|Z_\xi|$ is the determinant of Z_ξ.

The first term on the right-hand side of Eq. (40) can be computed using Eq. (A1) given in the Appendix:

$$\int dp_\xi \, f_\xi \, p_\xi \cdot J_\xi' \mathcal{H}_j (J_\xi')^t \cdot p_\xi$$

$$= k_B T \sum_{krls} [Z_\xi^{-1}]_{kr} \frac{\partial \xi_r}{\partial x_l'} \frac{\partial \xi_k}{\partial x_s'} \frac{\partial^2 \xi_j}{\partial x_l' \, \partial x_s'} \int dp_\xi \, f_\xi. \tag{42}$$

For the unperturbed Hamiltonian system, p_ξ is sampled according to

$$\exp\left(\frac{-k_B T}{2} p_\xi^t Z_\xi p_\xi \right).$$

To account for a different sampling in the decoupled case, we need to subtract all the contributions of p_ξ to $F_\xi^{(1)}$ [see Eq. (35)] and replace them with the correct contribution computed for the unperturbed Hamiltonian system. The incorrect contribution of p_ξ to $F_\xi^{(1)}$ is equal to

$$-\sum_j [Z_\xi^{-1}]_{ij} \sum_{krls} p_{\xi_k} p_{\xi_r} \frac{\partial \xi_r}{\partial x_l'} \frac{\partial \xi_k}{\partial x_s'} \frac{\partial^2 \xi_j}{\partial x_l' \, \partial x_s'}. \tag{43}$$

This is the term that we need to subtract.

The correct contribution is equal to the right hand side of Eq. (42) multiplied by $-Z_\xi^{-1}$:

$$-k_B T \sum_j [Z_\xi^{-1}]_{ij} \sum_{krls} [Z_\xi^{-1}]_{kr} \frac{\partial \xi_r}{\partial x_l'} \frac{\partial \xi_k}{\partial x_s'} \frac{\partial^2 \xi_j}{\partial x_l' \, \partial x_s'}. \tag{44}$$

Equation (42) shows that the last two terms [Eq. (43) and (44)] are equal in the case of ξ coupled to q (unperturbed Hamiltonian). Thus the final equation that we obtain, Eq. (46), is applicable even when ξ is coupled to q and it is equal to Eq. (36) in this particular case.

Adding Eq. (44) and subtracting Eq. (43) we have proved that the correction term is

$$\sum_j [Z_\xi^{-1}]_{ij} \sum_{krls} (p_{\xi_k} p_{\xi_r} - k_B T [Z_\xi^{-1}]_{kr}) \frac{\partial \xi_r}{\partial x_l'} \frac{\partial \xi_k}{\partial x_s'} \frac{\partial^2 \xi_j}{\partial x_l' \, \partial x_s'}. \tag{45}$$

There is a multiplicative factor which is equal to $1/|Z_\xi|^{1/2}$ [see Eq. (41)].

Adding the correction term from Eq. (45) to Eq. (35) and multiplying by $1/|Z_\xi|^{1/2}$ we have

$$\nabla_\xi A = \frac{\left\langle \frac{1}{|Z_\xi|^{1/2}} (\lambda + k_B T \mathcal{D}) \right\rangle_\xi}{\left\langle \frac{1}{|Z_\xi|^{1/2}} \right\rangle_\xi} \overset{\text{def}}{=} \frac{\left\langle \frac{1}{|Z_\xi|^{1/2}} F_\xi^{(2)} \right\rangle_\xi}{\left\langle \frac{1}{|Z_\xi|^{1/2}} \right\rangle_\xi}, \tag{46}$$

where $\mathcal{D}$ is a vector defined by

$$\mathcal{D}_i = -\sum_{rl} \frac{\partial [Z_\xi^{-1}]_{ir}}{\partial x_l'} \frac{\partial \xi_r}{\partial x_l'} + \sum_j [Z_\xi^{-1}]_{ij} \sum_{krls}$$

$$\times \left(\frac{p_{\xi_k} p_{\xi_r}}{k_B T} - [Z_\xi^{-1}]_{kr} \right) \frac{\partial \xi_r}{\partial x_l'} \frac{\partial \xi_k}{\partial x_s'} \frac{\partial^2 \xi_j}{\partial x_l' \, \partial x_s'}. \tag{47}$$

The first term is the original term from Eq. (36). The other terms are the correction from Eq. (45).

We now introduce a new notation:

$$\widetilde{\mathcal{H}}_j = Z_\xi^{-1} J'_\xi \mathcal{H}_j (J'_\xi)^t Z_\xi^{-1}. \tag{48}$$

See Eqs. (4), (5) and (15) for the definition of J_ξ, Z_ξ and $\mathcal{H}_j$. Note that $\widetilde{\mathcal{H}}_j$ is only a function of the first and second derivatives of ξ with respect to Cartesian coordinates and can thus be easily computed numerically.

In Appendix C, we prove that $\mathcal{D}_i$ is equal to

$$\mathcal{D}_i = \sum_j \; [Z_\xi^{-1}]_{ij} \left(\frac{1}{k_B T} \left(\frac{d\xi}{dt} \right)^t \cdot \widetilde{\mathcal{H}}_j \cdot \left(\frac{d\xi}{dt} \right) + \frac{1}{2} \nabla' \xi_j \cdot \nabla' \log |Z_\xi| \right) \tag{49}$$

[see Eq. (A7)].

Inserting the previous equation in Eq. (46), the derivative of the energy can be expressed as

$$\frac{\partial A}{\partial \xi_i} = \frac{\left\langle \dfrac{1}{|Z_\xi|^{1/2}} \left(\lambda + \sum_j \; [Z_\xi^{-1}]_{ij} \left(\left(\dfrac{d\xi}{dt} \right)^t \cdot \widetilde{\mathcal{H}}_j \cdot \left(\dfrac{d\xi}{dt} \right) + \dfrac{k_B T}{2} \nabla' \xi_j \cdot \nabla' \log |Z_\xi| \right) \right) \right\rangle_\xi}{\left\langle \dfrac{1}{|Z_\xi|^{1/2}} \right\rangle_\xi}. \tag{50}$$

From a practical point of view, it is more convenient to write the second term as

$$\nabla' \log |Z_\xi| = \mathrm{Tr}(Z_\xi^{-1} \nabla' Z_\xi)$$

because the derivative of $|Z_\xi|$ is not readily available. See Eq. (13) for the definition of ∇'.

In most cases the degrees of freedom $\{\xi_i\}$ are not functions of all the Cartesian coordinates but rather a subset of them. For example, a bond angle depends only on the three atoms forming the bond and a torsion angle on four atoms. If we denote $\mathcal{C}$ the minimal number of Cartesian coordinates needed to compute ξ_i then the number of floating operations required to compute $F_\xi^{(1)}$ and $F_\xi^{(2)}$ is on the order of $\mathcal{C}^3$ for each coordinate ξ_i. In Appendix D, we describe step by step the implementation of our method.

D. Constrained simulation

In the particular case of a constraint simulation $\dot{\xi} = 0$. Then the first term in the equation for $\mathcal{D}_i$ [see Eq. (49)] vanishes and we are left with

$$\mathcal{D}_i = \frac{1}{2} \sum_j \; [Z_\xi^{-1}]_{ij} (\nabla' \xi_j \cdot \nabla' \log |Z_\xi|).$$

The complete formula for $\nabla_\xi A$ then reads

$$\frac{\partial A}{\partial \xi_i} = \frac{\left\langle \dfrac{1}{|Z_\xi|^{1/2}} \left(\lambda + \dfrac{k_B T}{2} \sum_j \; [Z_\xi^{-1}]_{ij} (\nabla' \xi_j \cdot \nabla' \log |Z_\xi|) \right) \right\rangle_\xi}{\left\langle \dfrac{1}{|Z_\xi|^{1/2}} \right\rangle_\xi}. \tag{51}$$

This is the formula obtained by den Otter and Briels.[26] Note that this formula is applicable to the case of several degrees of freedom. Several authors derived a similar equation for a single reaction coordinate.[25,27] Note that in Eq. (51), Z_ξ is a matrix, $|Z_\xi|$ denotes its determinant and λ is a vector. This contrasts with the single reaction coordinate case.[25,27]

III. NUMERICAL RESULTS

To examine the performance of the method based on Eq. (46), we studied two test cases. One example involved calculating the potential of mean force for the rotation of the C–C bond in 1,2-dichloroethane (DCE) dissolved in water. In the second example, the potential of mean force for the transfer of fluoromethane (FMet) across the water-hexane interface was obtained.

The first system consisted of a DCE molecule surrounded by 343 water molecules, all placed in a cubic box whose edge length was 21.73 Å. This yielded a water density approximately equal to 1 g/cm^3. The second system contained one FMet molecule and a lamella of 486 water molecules in contact with a lamella of 83 hexane molecules. This system was enclosed in a box, whose x,y-dimensions were 24×24 Å^2 and the z-dimension, perpendicular to the water-hexane interface, was equal to 150 Å. Thus, the system contained one liquid–liquid interface and two liquid-vapor interfaces. The same geometry was used in a series of previous studies on the transfer of different solutes across the water-hexane interface.[31] In both cases, periodic boundary conditions were applied in the three spatial directions.

Water-water interactions were described by the TIP4P model.[34] The models of DCE and FMet were described in detail previously.[35,36] Water-DCE interactions were defined from the standard combination rules.[37] All intermolecular interactions were truncated smoothly with a cubic spline function between 8.0 and 8.5 Å. Cutoff distances were measured between molecules or neutral groups (in DCE oxygen atoms of water and carbon atoms of the solutes and hexane served as molecular or group centers.

The equations of motion were integrated using the velocity Verlet algorithm with a 1 fs time step for DCE and 2 fs time step for FMet. The temperature was kept constant at 300 K using the Martyna *et al.* implementation[38] of the Nosé–Hoover algorithm. This algorithm allows for generating configurations from a canonical ensemble. Bond lengths and bond angles of water molecules were kept fixed using RATTLE.[30]

For DCE in water, the potential of mean force was calculated along ξ, defined as the Cl–C–C–Cl torsional angle. For the transfer of FMet across the water-hexane interface, ξ was defined as the z component of the distance between the centers of mass of the solute and the hexane lamella (since both cases involved only one-dimensional potentials of mean force we drop the subscript i following ξ). For each system, three sets of calculations were performed. They yielded $A(\xi)$ using the probability density method and the methods of the constraint force from unconstrained and constrained simulations.

To obtain $A(\xi)$ from the probability density method, a series of simulations was performed. For DCE, we used a single window and a biasing potential obtained previously.[31] The trajectory was 2 ns long. For FMet, ξ was constrained by a harmonic potential in five overlapping windows. No biasing potential was applied. For each window, a molecular dynamics trajectory 2.4 ns long was obtained. From this trajectory the probability density, $P(\xi)$, was calculated. The probability density in the full range of ξ was constructed by matching $P(\xi)$ in the overlapping regions of consecutive windows.[20] $A(\xi)$ was calculated from the complete $P(\xi)$ using Eq. (1).

Calculations of $\partial A/\partial\xi$ from unconstrained simulations were very similar. For DCE, we used a biasing potential and one window. For FMet we did not use a biasing potential and divided the full range of ξ into five windows. In these simulations, however, there was no need for windows to overlap. The molecular dynamics trajectory in each window was 1.5 ns long. In each molecular dynamics step, the force of constraint was calculated using RATTLE. The appropriate geometric corrections required for the calculation of $\partial A/\partial\xi$ in Eq. (36) were obtained using the algorithm described in the Appendix. Since no biasing force was applied the average force in each bin along ξ was simply the arithmetic average of the instantaneous forces.

$\partial A/\partial\xi$ was obtained from constrained simulations by generating a series of trajectories, in which ξ was fixed at several values uniformly spanning the full range of interest. For DCE, simulations were carried out at 37 values of ξ in the range between 0 and 180 deg. This corresponds to 5 deg separation between two values of ξ. For FMet, ξ was fixed at 102 values between -10.1 Å and 10.1 Å (0.2 Å separation between two values). The constraints on ξ were enforced using RATTLE. The average thermodynamic force was obtained by correcting the calculated constraint force according to Eq. (51). Once calculations of $\partial A/\partial\xi$ were completed for all discrete values of ξ, $A(\xi)$ was obtained by numerical integration.

The potentials of mean force for rotation of DCE in water and transfer of FMet across the water-hexane interface, obtained from all three methods, are shown in Figs. 1 and 2, respectively. For DCE, gauche and trans conformations were found to have nearly the same free energy, and were separated by a barrier 4.2 kcal/mol high. These results are in close agreement with the results obtained previously using the same potential functions.[35,39] For FMet, the free energy between dissolving this molecule in water and in hexane was found to be 0.6 kcal mol^{-1}. An appreciable minimum in the potential of mean force, approximately 1.4 kcal mol^{-1} deep, was observed near the interface. A very similar profile of $A(\xi)$ was obtained using the particle insertion method.[40]

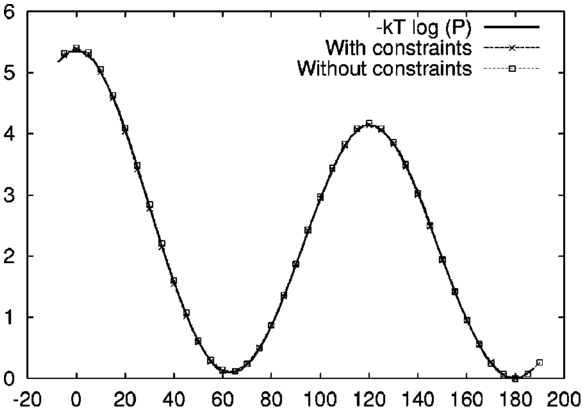

FIG. 1. The free energy of rotating DCE around the C–C bond computed using the probability density method and the methods of the constraint force from unconstrained and constrained simulations. On the *x*-axis is the value of the Cl–C–C–Cl torsional angle (in deg). On the *y*-axis is the free energy (in kcal mol^{-1}).

IV. DISCUSSION

In both numerical examples presented in the previous section, the method based on calculating the probability density along ξ and both methods relying on calculating $\partial A/\partial\xi$ yield the potentials of mean force that are identical to within

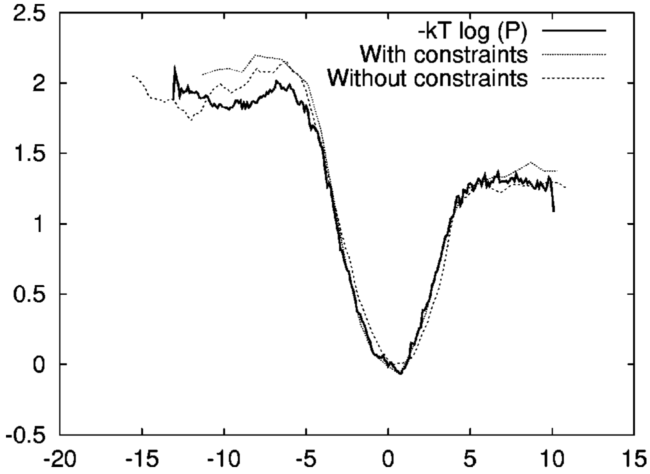

FIG. 2. The free energy of transferring FMet across the water-hexane interface computed using the probability density method and the methods of the constraint force from unconstrained and constrained simulations. On the *x*-axis is the value of the reaction coordinate ξ (in Å). On the *y*-axis is the free energy (in kcal mol^{-1}).

statistical error. This confirms applicability of Eq. (35) to the calculation of the potential of mean force in unconstrained simulations.

From the practical point of view the new method is quite similar to the probability density method. During the course of a simulation there are only two additional steps involved 1— calculation of instantaneous forces of constraints and evaluation of the geometric corrections to these forces, given by Eq. (35). Finally, once the simulation is completed $\partial A/\partial \xi$ needs to be integrated numerically. Since $\partial A/\partial \xi$ is calculated as a continuous function of ξ this can be done without appreciable loss of accuracy. In general, neither method is expected to be efficient unless a good guess for the biasing potential is available. However, in the method based on calculating the force, the derivative of this potential rather than the potential itself is directly used.

The method based on Eq. (35) has one important advantage over the probability density method. No post-processing of the data obtained from different windows, such as WHAM,[20,21] is needed. The average force in a given bin along ξ is simply the arithmetic average of instantaneous forces recorded in this bin in all windows (if different biasing forces were used in different windows they have to be subtracted before the average is calculated). In fact, no overlapping between consecutive windows is needed if sufficiently good estimate of the average force is obtained from one window.

The new approach does not suffer from the same disadvantages as the method based on calculating the force in constrained simulations. These disadvantages were discussed in the introduction. In addition, calculating the forces of constraints becomes less demanding. In constrained simulations analytical formulas for calculating forces of constraints cannot be used. Instead iterative procedures with very low tolerance, sometimes requiring double precision arithmetic, have to be applied. This is needed to prevent drift of the constraint from the preset value due to the accumulation of numerical errors. This problem, however, does not exist in unconstrained simulations. Accuracy in calculating the forces of constraints does not influence motion of the system. This calculation is just a measurement performed on the system and should be done sufficiently accurately that numerical errors associated with this measurement have only negligible contribution to the statistical error of the average force. This is not a very stringent requirement.

Ultimately, both methods measure the same quantity — the thermodynamic force. Thus, they can be seamlessly combined. One might wish to perform unconstrained simulations in some range of ξ and a series of constrained simulations in another range of ξ if this might lead to improved efficiency or accuracy of calculating the potential of mean force.

Calculating the thermodynamic force from unconstrained simulations has one considerable disadvantage compared to calculating the same quantity from constrained simulations. In most cases, to make the method efficient it is necessary to apply a suitable biasing force. However, it is possible to modify unconstrained simulations such that a good estimate of the optimal biasing force, equal to $-\partial A/\partial \xi$, is rapidly constructed without any initial guess. Once this estimate becomes available sampling along ξ becomes nearly uniform, which minimizes statistical error for a fixed length of the simulation. We call this approach the Adaptive Force Method. So far, this method has been applied to study internal rotation of DCE in water, and has proven to be very successful.[31] Other applications will follow.

ACKNOWLEDGMENTS

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APPENDIX A. MULTIDIMENSIONAL INTEGRAL WITH GAUSSIAN FUNCTIONS

We consider the following integral:

$$\int u^t \cdot B \cdot u \, \exp(-u^t \cdot A \cdot u) du,$$

where A and B are square matrices and u is a vector.

We suppose that A is a symmetric, positive definite matrix. Then, it is possible to define a matrix M such that $M^2 = A$. We have

$$\exp(-u^t \cdot A \cdot u) = \exp(-(Mu)^t (Mu)).$$

By changing variables, $\tilde{u} = Mu$, we obtain

$$\int u^t \cdot B \cdot u \, \exp(-u^t \cdot A \cdot u) du$$

$$= \frac{1}{|M|} \int \tilde{u}^t \cdot (M^{-1} B M^{-1}) \cdot \tilde{u} \, \exp(-|\tilde{u}|^2) d\tilde{u}$$

$$= \frac{1}{|M|} \mathrm{Tr}(M^{-1} B M^{-1}) \frac{1}{2} \int \exp(-|\tilde{u}|^2) d\tilde{u}.$$

After rearranging the terms we have

$$\int u^t \cdot B \cdot u \, \exp(-u^t \cdot A \cdot u) du$$

$$= \frac{\mathrm{Tr}(A^{-1} B)}{2} \int \exp(-u^t \cdot A \cdot u) du. \tag{A1}$$

For example, if we insert Eq. (9) into Eq. (8) one of the terms is

$$\int p_\xi^t \frac{\partial Z_\xi}{\partial \xi_i} p_\xi \exp\left(-\frac{H}{k_B T}\right) dp_q \, dp_\xi .$$

With a choice of q such that Eq. (10) is satisfied,

$$H = \tfrac{1}{2} p_\xi^t Z_\xi p_\xi + \tfrac{1}{2} p_q^t Z_q p_q + \Phi(\xi, q)$$

and thus, using the result from Eq. (A1) we have

$$\int p_\xi^t \frac{\partial Z_\xi}{\partial \xi_i} p_\xi \exp\left(-\frac{H}{k_B T}\right) dp_q \, dp_\xi$$

$$= k_B T \, \mathrm{Tr}\left(Z_\xi^{-1} \frac{\partial Z}{\partial \xi_i}\right) \int \exp\left(-\frac{H}{k_B T}\right) dp_q \, dp_\xi .$$

APPENDIX B. DERIVATIVE OF THE DETERMINANT OF A MATRIX

We consider a $N\times N$ matrix $A(t)$ and denote its determinant by $|A(t)|$. The following identity is true:

$$\frac{d|A(t)|}{dt}=\sum_i |A_i|,$$

where A_i is the matrix:

$$A_i=\begin{pmatrix} A_{11} & \dots & A_{1N} \\ \dots & \dots & \dots \\ A_{i-1,1} & \dots & A_{i-1,N} \\ \dfrac{dA_{i1}}{dt} & \dots & \dfrac{dA_{iN}}{dt} \\ A_{i+1,1} & \dots & A_{i+1,N} \\ \dots & \dots & \dots \\ A_{N1} & \dots & A_{NN} \end{pmatrix}.$$

Since $|A_i|$ is equal to

$$|A_i|=|A|\sum_j \frac{dA_{ij}}{dt}A^{-1}_{ij},$$

we obtain

$$\frac{d|A|}{dt}=|A|\sum_{ij} \frac{dA_{ij}}{dt}A^{-1}_{ij}.$$

Using a more condensed notation, this can be written as

$$\frac{d}{dt}\log|A|=\mathrm{Tr}\left(A^{-1}\frac{dA}{dt}\right). \tag{A2}$$

APPENDIX C. FREE ENERGY FOR THE DECOUPLED CASE

Recall Eqs. (46) and (47):

$$\nabla_\xi A=\frac{\left\langle \dfrac{1}{|Z_\xi|^{-1/2}}(\lambda+k_BT\mathcal{D})\right\rangle_\xi}{\left\langle \dfrac{1}{|Z_\xi|^{-1/2}}\right\rangle_\xi},$$

where $\mathcal{D}$ is a vector defined by

$$\mathcal{D}_i=-\sum_{rl} \frac{\partial[Z_\xi^{-1}]_{ir}}{\partial x'_l}\frac{\partial \xi_r}{\partial x'_l}+\sum_j [Z_\xi^{-1}]_{ij}\sum_{krls}\left(\frac{p_{\xi_k}p_{\xi_r}}{k_BT}\right.$$
$$\left.-[Z_\xi^{-1}]_{kr}\right)\frac{\partial \xi_r}{\partial x'_l}\frac{\partial \xi_k}{\partial x'_s}\frac{\partial^2 \xi_j}{\partial x'_l\,\partial x'_s}. \tag{A3}$$

We simplify this equation by rearranging the terms.

Expanding the first term of Eq. (A3) and using definition of Z_ξ from Eq. (5) we obtain

$$-\sum_{rl} \frac{\partial[Z_\xi^{-1}]_{ir}}{\partial x'_l}\frac{\partial \xi_r}{\partial x'_l}=\sum_{jkrl} [Z_\xi^{-1}]_{ij}\frac{\partial[Z_\xi]_{jk}}{\partial x'_l}[Z_\xi^{-1}]_{kr}\frac{\partial \xi_r}{\partial x'_l}$$
$$=\sum_{jkrls} [Z_\xi^{-1}]_{ij}\left(\frac{\partial \xi_j}{\partial x'_s}\frac{\partial^2 \xi_k}{\partial x'_s\,\partial x'_l}\right.$$
$$\left.+\frac{\partial^2 \xi_j}{\partial x'_s\,\partial x'_l}\frac{\partial \xi_k}{\partial x'_s}\right)[Z_\xi^{-1}]_{kr}\frac{\partial \xi_r}{\partial x'_l}.$$

A simplification follows:

$$\mathcal{D}_i=\sum_j [Z_\xi^{-1}]_{ij}\sum_{krls}\left(\frac{p_{\xi_k}p_{\xi_r}}{k_BT}\frac{\partial \xi_r}{\partial x'_l}\frac{\partial \xi_k}{\partial x'_s}\frac{\partial^2 \xi_j}{\partial x'_l\partial x'_s}\right.$$
$$-[Z_\xi^{-1}]_{kr}\left(\frac{\partial \xi_r}{\partial x'_l}\frac{\partial \xi_k}{\partial x'_s}\frac{\partial^2 \xi_j}{\partial x'_l\,\partial x'_s}-\frac{\partial \xi_j}{\partial x'_s}\frac{\partial^2 \xi_k}{\partial x'_s\,\partial x'_l}\frac{\partial \xi_r}{\partial x'_l}\right.$$
$$\left.\left.-\frac{\partial^2 \xi_j}{\partial x'_s\,\partial x'_l}\frac{\partial \xi_k}{\partial x'_s}\frac{\partial \xi_r}{\partial x'_l}\right)\right),$$

and this leads to

$$\mathcal{D}_i=\sum_j [Z_\xi^{-1}]_{ij}\sum_{krls}\left(\frac{p_{\xi_k}p_{\xi_r}}{k_BT}\frac{\partial \xi_r}{\partial x'_l}\frac{\partial \xi_k}{\partial x'_s}\frac{\partial^2 \xi_j}{\partial x'_l\,\partial x'_s}\right.$$
$$\left.+[Z_\xi^{-1}]_{kr}\frac{\partial \xi_j}{\partial x'_s}\frac{\partial^2 \xi_k}{\partial x'_s\,\partial x'_l}\frac{\partial \xi_r}{\partial x'_l}\right). \tag{A4}$$

The first term of Eq. (A4) can be written in a more compact form using matrix notation. We denote by $\tilde{\mathcal{H}}_j$,

$$\tilde{\mathcal{H}}_j=Z_\xi^{-1}J'_\xi\mathcal{H}_j(J'_\xi)^tZ_\xi^{-1}$$

[see Eq. (48)].

Then

$$\sum_j [Z_\xi^{-1}]_{ij}\sum_{krls}\left(p_{\xi_k}p_{\xi_r}\frac{\partial \xi_r}{\partial x'_l}\frac{\partial \xi_k}{\partial x'_s}\frac{\partial^2 \xi_j}{\partial x'_l\,\partial x'_s}\right)$$
$$=\sum_j [Z_\xi^{-1}]_{ij}\left(\left(\frac{d\xi}{dt}\right)^t\cdot\tilde{\mathcal{H}}_j\cdot\left(\frac{d\xi}{dt}\right)\right). \tag{A5}$$

The second term of Eq. A4 is

$$\sum_j [Z_\xi^{-1}]_{ij}\sum_{krls} [Z_\xi^{-1}]_{kr}\frac{\partial \xi_j}{\partial x'_s}\frac{\partial^2 \xi_k}{\partial x'_s\,\partial x'_l}\frac{\partial \xi_r}{\partial x'_l}$$
$$=\sum_j [Z_\xi^{-1}]_{ij}\sum_s \frac{\partial \xi_j}{\partial x'_s}\sum_{kr} [Z_\xi^{-1}]_{kr}\sum_l \frac{\partial \xi_r}{\partial x'_l}\frac{\partial^2 \xi_k}{\partial x'_s\,\partial x'_l}.$$

Due to symmetry properties,

$$\begin{aligned}\sum_{kr}\,[Z_\xi^{-1}]_{kr}\sum_l\,\frac{\partial\xi_r}{\partial x'_l}\,\frac{\partial^2\xi_k}{\partial x'_s\,\partial x'_l}\\
&=\frac{1}{2}\sum_{kr}\,[Z_\xi^{-1}]_{kr}\sum_l\,\left(\frac{\partial\xi_r}{\partial x'_l}\,\frac{\partial^2\xi_k}{\partial x'_s\,\partial x'_l}+\frac{\partial^2\xi_r}{\partial x'_s\partial x'_l}\,\frac{\partial\xi_k}{\partial x'_l}\right)\\
&=\frac{1}{2}\sum_{kr}\,[Z_\xi^{-1}]_{kr}\partial'_s\sum_l\,\frac{\partial\xi_r}{\partial x'_l}\,\frac{\partial\xi_k}{\partial x'_l}\\
&=\frac{1}{2}\sum_{kr}\,[Z_\xi^{-1}]_{kr}\partial'_s[Z_\xi]_{kr}\\
&=\frac{1}{2}\mathrm{Tr}(Z_\xi^{-1}\partial'_s Z_\xi)=\frac{1}{2}\;\partial'_s\log|Z_\xi|,\end{aligned}$$

where ∂'_s is a short notation for $\partial/\partial x'_s$.

Thus the second term of Eq. (A4) is equal to

$$\frac{1}{2}\sum_j\,[Z_\xi^{-1}]_{ij}(\nabla'\xi_j\cdot\nabla'\;\log|Z_\xi|) \tag{A6}$$

[see Eq. (13) for the notation ∇'].

We insert Eqs. (A5) and (A6) into Eq. (A4) to obtain our final result:

$$\begin{aligned}\mathcal{D}_i=\sum_j\,[Z_\xi^{-1}]_{ij}\Bigg(&\frac{1}{k_BT}\left(\frac{d\xi}{dt}\right)^t\cdot\tilde{\mathcal{H}}_j\cdot\left(\frac{d\xi}{dt}\right)\\
&+\frac{1}{2}\nabla'\xi_j\cdot\nabla'\;\log|Z_\xi|\Bigg).\end{aligned} \tag{A7}$$

APPENDIX D. IMPLEMENTATION DETAILS FOR CALCULATING $\partial A/\partial\xi_i$

In this section we describe the steps required to compute $\partial A/\partial\xi_i$ using Eq. (50). We will describe the implementation of the method using Eq. (50) because this is the most general formula. Eq. (51) for a constrained simulation is a particular case of Eq. (50) where $\dot{\xi}=0$ and Eq. (50) is equivalent to Eq. (35) in the case of an unconstrained simulation.

Recall that using Eq. (50), $\partial A/\partial\xi_i$ is obtained by computing the average of

$$\begin{aligned}\frac{1}{|Z_\xi|^{1/2}}\Bigg(\lambda+\sum_j\,[Z_\xi^{-1}]_{ij}&\left(\frac{d\xi}{dt}\right)^t\cdot\tilde{\mathcal{H}}_j\cdot\left(\frac{d\xi}{dt}\right)+\frac{k_BT}{2}\nabla'\xi_j\\
&\cdot\mathrm{Tr}(Z_\xi^{-1}\nabla' Z_\xi)\Bigg)\end{aligned}$$

divided by the average of $1/|Z_\xi|^{1/2}$. These terms can be computed in the following way.

- Compute all nonzero first and second derivatives:
  $$d(i,j)=\frac{\partial\xi_i}{\partial x_j},$$
  $$d_2(i,j,k)=\frac{\partial^2\xi_i}{\partial x_j\,\partial x_k}.$$
- Compute $|Z_\xi|$ where $[Z_\xi]_{ij}$ is defined by
  $$[Z_\xi]_{ij}=\sum_{k=1}^N\frac{1}{m_k}d(i,k)\,d(j,k).$$
  We denote $z=|Z_\xi|$.
- The term $\nabla'\xi_j\cdot\mathrm{Tr}(Z_\xi^{-1}\nabla' Z_\xi)$ can be expanded as
  $$\sum_{klm}\frac{1}{m_k}\frac{\partial\xi_j}{\partial x_k}[Z_\xi^{-1}]_{lm}\frac{\partial[Z_\xi]_{lm}}{\partial x_k}.$$
  The most efficient way to compute this term is as follows.
- Compute ($p^2\,\mathcal{C}$ operations)
  $$v_1(j,l,r)=\sum_{k=1}^N\frac{1}{m_k}d(j,k)\,d_2(l,r,k).$$
  Recall that p is the number of coordinates ξ_i while $\mathcal{C}$ is the minimal number of Cartesian coordinates required to define the ξ_i.
- Compute ($p^2\,\mathcal{C}$ operations)
  $$v_2(j,l,m)=\sum_{r=1}^N\frac{1}{m_r}[v_1(j,l,r)\,d(m,r)+v_1(j,m,r)\,d(l,r)].$$
- Compute (p^2 operations)
  $$v_3(j)=\sum_{lm}\,[Z_\xi^{-1}]_{lm}\,v_2(j,l,m)=\nabla'\xi_j\cdot\mathrm{Tr}(Z_\xi^{-1}\nabla' Z_\xi).$$
- The term $(d\xi/dt)^t\cdot\tilde{\mathcal{H}}_j\cdot(d\xi/dt)$ can be efficiently computed in the following manner.
- Compute ($p\,\mathcal{C}$ operations)
  $$w_1(i)=\sum_{k=1}^N d(i,k)\frac{dx_k}{dt}.$$
- Compute (p^2 operations)
  $$w_2(i)=\sum_l\,[Z_\xi^{-1}]_{il}\,w_1(l).$$
- Compute ($p\,\mathcal{C}$ operations)
  $$w_3(i)=\sum_l\,w_2(l)\,d(l,i).$$
- Compute ($\mathcal{C}^2$ operations)
  $$w_4(j)=\sum_{rs}\frac{1}{m_r\,m_s}w_3(r)\,w_3(s)\,d_2(j,r,s)=\left(\frac{d\xi}{dt}\right)^t\cdot\tilde{\mathcal{H}}_j\cdot\left(\frac{d\xi}{dt}\right).$$
- The coefficient λ can be computed by traditional means, for example using RATTLE.
- The final expression for $\partial A/\partial\xi_i$ now reads
  $$\frac{\partial > A}{\partial\xi_i}=\frac{\left\langle\frac{1}{\sqrt{z}}\left(\lambda+\sum_j\,[Z_\xi^{-1}]_{ij}\left(w_4(j)+\frac{k_BT}{2}v_3(j)\right)\right)\right\rangle_\xi}{\left\langle\frac{1}{\sqrt{z}}\right\rangle_\xi}.$$

APPENDIX E. CONSTRUCTION OF THE BASIS *q*

In this section we discuss the construction of a basis q such that Eq. (10) is satisfied.

Let us consider a vector $\xi^*=(\xi_1^*,\ldots,\xi_p^*)$. The surface $\xi_1(x)=\xi_1^*,\;\ldots,\;\xi_p(x)=\xi_p^*$ is denoted by S^*. Let a be a point on S^*. We start by proving that there exists a set of functions $r_1,\ldots,r_{N-p}$ such that $\xi_1,\ldots,\xi_p,r_1,\ldots,r_{N-p}$ is a local coordinate chart around a. Consider the natural basis $x_1,\ldots,x_N$ of $\mathbb{R}^N$, the set of all ordered N-tuples of real numbers. We make the assumption that the matrix Z_ξ is invertible. This means in particular that $\nabla\xi_1,\ldots,\nabla\xi_p$ spans a p-dimensional subspace of $\mathbb{R}^N$. At point a, there exists $N-p$ vectors among $\nabla x_1,\ldots,\nabla x_N$ such that together with $\nabla\xi_1,\ldots,\nabla\xi_p$ they form a basis of $\mathbb{R}^N$. Suppose that these $N-p$ vectors are $\nabla x_1,\ldots,\nabla x_{N-p}$. Now consider the following map:

$$F:(x_1,\ldots,x_N)\to(\xi_1,\ldots,\xi_p,x_1,\ldots,x_{N-p}).$$

We recall the inverse function theorem:

Theorem 1 (Inverse function theorem): *Suppose that M and N are both n-dimensional smooth manifolds, and $f:M\to N$ is a smooth map. If at point $a\in M$, the tangent map $f_*:T_a(M)\to T_{f(a)}(N)$ is an isomorphism, then there exists a neighborhood U of a in M such that $V=f(U)$ is a neighborhood of f(a) in N and $f|_U:U\to V$ is a diffeomorphism.* (See Ref. 41 page 18 for example.)

Since $\det(\partial F_i/\partial x_j)|_x\neq 0$, the functions $(\xi_1,\ldots,\xi_p,x_1,\ldots,x_{N-p})$ form a local coordinate chart by the inverse function theorem.

We now construct the functions q in a neighborhood of a. We consider the following modification of x_i:

$$q_i=x_i+\sum_j \lambda_{ij}(\xi_j-\xi_j^*).$$

Then

$$\nabla q_i=\nabla x_i+\sum_j \lambda_{ij}\nabla\xi_j \tag{A8}$$

on the surface S^*. After multiplying by $(1/m_k)(\partial\xi_l/\partial x_k)$, we have

$$\sum_k \frac{1}{m_k}\frac{\partial q_i}{\partial x_k}\frac{\partial\xi_l}{\partial x_k}=\frac{1}{m_i}\frac{\partial\xi_l}{\partial x_i}+\sum_j \lambda_{ij}\sum_k \frac{1}{m_k}\frac{\partial\xi_l}{\partial x_k}\frac{\partial\xi_j}{\partial x_k}.$$

Denoting by $\mathcal{V}_q$ and $\mathcal{V}_x$ the matrices

$$[\mathcal{V}_q]_{il}=\sum_k \frac{1}{m_k}\frac{\partial q_i}{\partial x_k}\frac{\partial\xi_l}{\partial x_k}\qquad [\mathcal{V}_x]_{il}=\frac{1}{m_i}\frac{\partial\xi_l}{\partial x_i}$$

and given the definition Eq. (5) of Z_ξ we obtain

$$\mathcal{V}_q=\mathcal{V}_x+\lambda\cdot Z_\xi,$$

where $\cdot$ denotes a matrix product.

Therefore if we choose

$$\lambda=-\mathcal{V}_x\cdot Z_\xi^{-1},$$

which is always possible as Z_ξ is invertible, we have

$$[\mathcal{V}_q]_{il}=\sum_k \frac{1}{m_k}\frac{\partial q_i}{\partial x_k}\frac{\partial\xi_l}{\partial x_k}=0$$

for all i and l. The functions q satisfy Eq. (10). Moreover, since $\det(\partial F_i/\partial x_j)|_x\neq 0$, we also have that

$$G:(x_1,\ldots,x_N)\to(\xi_1,\ldots,\xi_p,q_1,\ldots,q_{N-p})$$

satisfies $\det(\partial G_i/\partial x_j)|_x\neq 0$ since ∇q_i satisfies Eq. (A8). By the inverse function theorem, $(\xi_1,\ldots,\xi_p,q_1,\ldots,q_{N-p})$ is a local coordinate chart around a.

The reader may be interested to know under which condition the previous result can be extended to the existence of functions q such that

- $(\xi_1,\ldots,\xi_p,q_1,\ldots,q_{N-p})$ is a local coordinate chart around a.
- $Z_{q\xi}(\xi,q)=0$ in a neighborhood of a.

Previously we required that $Z_{q\xi}(\xi,q)=0$ is true only on surface S^* while now we want $Z_{q\xi}(\xi,q)$ to be equal to 0 in a neighborhood of a. This problem has an elegant solution by means of the Frobenius theorem. To state this theorem we need to introduce some new definitions. Let M be a manifold. We denote T_a the tangent vector space of M at point a. We denote C_a^∞ the set of all functions for which partial derivatives of arbitrary order exist in a neighborhood of a. For $X\in T_a$ and $f\in C_a^\infty$ we denote Xf the directional derivative of f along the vector X. See Ref. 41 page 16 for a more complete definition. Given a tangent vector field X on M and a function $f\in C^\infty(M)$ we can define a real-valued function on M by

$$(Xf)_a\overset{\text{def}}{=}X_a f,$$

where X_a denotes the value of X at point a. We are now ready to define the Poisson bracket product of two tangent vector fields X and Y:

$$[X,Y]\overset{\text{def}}{=}XY-YX,$$

that is

$$[X,Y](f)=X(Yf)-Y(Xf).$$

See Ref. 41 page 31 for details.

Suppose that we have h smooth tangent vector fields $X_1,\ldots,X_h$. We define an h-dimensional smooth distribution on M, L^h, by assigning at each point a the h-dimensional subspace of T_a spanned by $X_1(a),\ \ldots,\ X_h(a)$. We denote

$$L^h=\{X_1,\ldots,X_h\}.$$

The Frobenius theorem can be stated as:

Theorem 2 (Frobenius theorem): *Suppose $L^h=\{X_1,\ldots,X_h\}$ is an h-dimensional distribution in an open set U containing point a. A necessary and sufficient condition for the existence of a local coordinate system $(W;w^i)$, such that $W\subset U$ is a neighborhood of a and*

$$L^h=\left\{\frac{\partial}{\partial w^1},\ldots,\frac{\partial}{\partial w^h}\right\}$$

is that $[X_i,X_j]$ is a linear combination of X_k, $k=1,\ldots,h$ for all i and j, inside some neighborhood $V\subset U$ of a. This condition is also known as Frobenius condition. (See Ref. 41 page 35).

Our result is a corollary of this theorem. First suppose that there exists q such that

$$Z_{q\xi}(\xi,q)=0$$

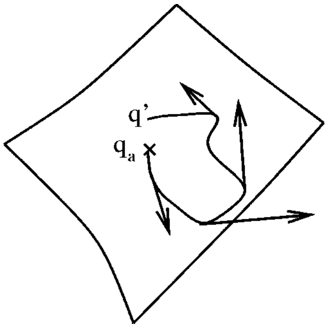

FIG. 3. Illustration of the Frobenius theorem for the construction of functions q satisfying $Z_{\xi q}=0$ in a neighborhood of a given point a.

in a neighborhood of a. For basis (ξ,q), we have that $\partial/\partial\xi_i$ is orthogonal to ∇q_j. On one hand, the p tangent vectors $\partial/\partial\xi_i$ form an independent set and are orthogonal to ∇q_j for all j. On the other hand, the p vectors $1/m_i\nabla\xi_i$ are necessarily independent as Z_ξ is invertible. They are also orthogonal to ∇q_j for all j. Therefore, the subspace spanned by $\partial/\partial\xi_1,\ldots,\partial/\partial\xi_p$ is equal to the subspace spanned by $(1/m_1)\nabla\xi_1,\ldots,(1/m_p)\nabla\xi_p$. As a consequence of the Frobenius theorem, the vectors $(1/m_1)\nabla\xi_1,\ \ldots,\ (1/m_p)\nabla\xi_p$ must satisfy the Frobenius condition. In this particular case, this condition is that $\mathcal{H}_i\nabla'\xi_j-\mathcal{H}_j\nabla'\xi_i$ is a linear combination of $\nabla'\xi_1,\ldots,\nabla'\xi_p$, where $\mathcal{H}_i$ is the modified Hessian matrix from Eq. (15).

On the other hand, suppose that $\mathcal{H}_i\nabla'\xi_j-\mathcal{H}_j\nabla'\xi_i$ is a linear combination of

$$\nabla'\xi_1,\ldots,\nabla'\xi_p$$

in a neighborhood of a. The distribution

$$L^p=\left\{\frac{1}{m_1}\nabla\xi_1,\ldots,\frac{1}{m_p}\nabla\xi_p\right\}$$

satisfies the Frobenius condition. Thanks to the Frobenius theorem, there exists a local coordinate system w^i such that

$$L^p=\left\{\frac{\partial}{\partial w^1},\ldots,\frac{\partial}{\partial w^p}\right\}.$$

The gradient of w^i, $i\geqslant p+1$, is necessarily orthogonal to each $\partial/\partial w^j$, $j\leqslant p$. Therefore it is orthogonal to $(1/m_j)\nabla\xi_j$ for all $1\leqslant j\leqslant p$, which proves that

$$q_1=w^{p+1},\ldots,q_{N-p}=w^N$$

is such that $Z_{q\xi}=0$ in a neighborhood of a. There remains to prove that (ξ,q) is a local coordinate chart. As Z_ξ is invertible the vectors $\nabla\xi_i$ are linearly independent. Suppose that that there exists i such that $\nabla\xi_i$ is a linear combination of ∇q_j, $j=1,\ldots,N-p$. We can assume that $i=1$ and then there exist λ_j such that

$$\nabla\xi_1=\sum_j\lambda_j\nabla q_j.$$

Therefore the first line and column of Z_ξ is equal to 0 which is a contradiction since Z_ξ was assumed to be invertible. Considering

$$G:(x_1,\ldots,x_N)\rightarrow(\xi_1,\ldots,\xi_p,q_1,\ldots,q_{N-p})$$

we have proved that $\det(\partial G_i/\partial x_j)|_x\neq 0$ and thus (ξ,q) is a local coordinate chart by the inverse function theorem.

We have proved that the existence of q such that (ξ,q) is a local coordinate chart and $Z_{q\xi}=0$ in a neighborhood of a is equivalent to the Frobenius condition:

$$\mathcal{H}_i\nabla'\xi_j-\mathcal{H}_j\nabla'\xi_i$$

is a linear combination of

$$\nabla'\xi_1,\ldots,\nabla'\xi_p$$

for all i and j.

The Frobenius condition may appear a little special. We illustrate its necessity in a more intuitive manner. Suppose that ξ does not satisfy the Frobenius condition at point a and that there exists a set of functions q such that $Z_{\xi q}=0$ and (ξ,q) is a local coordinate chart. We show that this leads to a contradiction. It can be proved that if ξ does not satisfy the Frobenius condition at point $a=(\xi^*,q^a)$, then there exists a path γ such that

$$\gamma(0)=(\xi^*,q^a),$$

$$\gamma(1)=(\xi^*,q')\quad\text{with}\quad q'\neq q^a,$$

$$\frac{d\gamma}{dt}\in\left\{\frac{1}{m_1}\nabla\xi_1,\ldots,\frac{1}{m_p}\nabla\xi_p\right\}.$$

As $q'\neq q^a$ there exists i such that $q_i'\neq q_i^a$. Consider $q_i(\gamma(t))$. Since

$$\frac{d\gamma}{dt}\in\left\{\frac{1}{m_1}\nabla\xi_1,\ldots,\frac{1}{m_p}\nabla\xi_p\right\}$$

the function

$$\frac{dq_i(\gamma(t))}{dt}=\nabla q_i\cdot\frac{d\gamma}{dt}$$

must be equal to zero as $Z_{\xi q}=0$. Therefore

$$q_i(\gamma(t))=q_i(\gamma(0))=q_i^a$$

must be equal to $q_i(\gamma(1))=q_i'$ which is a contradiction. This is illustrated by Fig. 3.

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