

Blue Moon Sampling, Vectorial Reaction Coordinates, and Unbiased Constrained Dynamics

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We give a new formula expressing the components of the mean force in terms of a conditional expectation which can be computed by Blue Moon sampling. This generalizes to the vectorial case a formula first derived by Ruiz-Montero et al. [Mol. Phys. 1997, 90, 925] for a scalar reaction coordinate. We also discuss how to

compute this conditional average by means of constrained stochastic dynamics which, unlike the usual constrained molecular dynamics, introduces no bias. Finally, we give a new perspective on bias removal by using constrained molecular dynamics.

1. Introduction

Fifteen years ago, the Blue Moon ensemble method was introduced to sample rare events that occur “once in a blue moon”.^[1] By now, Blue Moon has become well-known and widely used as an alternative to umbrella sampling, and it is explained in standard textbooks on molecular dynamics such as ref. [2]. The Blue Moon method uses constrained molecular simulations using holonomic constraints to confine the system to the hypersurface where a prescribed reaction coordinate is constant. This allows one to sample regions in configuration space such as, for example, the transition state region of an activated process which, in absence of constraint, would be rarely visited by the dynamics. In particular, Blue Moon sampling allows one to compute conditional expectations over the equilibrium distribution of the system restricted to the hypersurface where the reaction coordinate is constant. One such conditional expectation gives the gradient of the free energy associated with the reaction coordinate, usually referred to as the mean force. From the mean force, the free energy can be readily obtained by thermodynamic integration.^[2] Other interesting quantities which can be obtained by Blue Moon sampling include the transition state theory rate^[3–5] of the activated process described by this reaction coordinate and (by running unconstrained trajectories initiated from the blue moon ensemble) the transmission coefficient accounting for the dynamical corrections to the transition state theory rate.^[6–8]

The Blue Moon approach was immediately applied to some simple reactive systems (see, e.g., refs. [9–14]), but its more general use was hampered by a major problem. It appeared that the computation of the mean force by the Blue Moon approach was required to define a complete set of new coordinates containing the reaction coordinate as one of the independent variables. Indeed, the original expression for the mean force is a conditional expectation which involves directional derivatives of the force and the full Jacobian of this coordinate transformation.

Shortly thereafter, inspired by an original idea by Müller et al.,^[15] Sprik and Ciccotti^[16] showed how to circumvent this difficulty and avoid any reference to directional derivatives and

Jacobians in the case of a scalar reaction coordinate. This was obtained by expressing the mean force in terms of an expectation involving the Lagrange multiplier (used to enforce the constraint) plus a correction term. This approach was later generalized to the vectorial case by Sergi et al.^[17] and, in the presence of additional molecular constraints, by Coluzza et al.^[18] As a result of these works, more complex applications could be treated (see, e.g., refs. [19–25]). In spite of these developments, it remained conceptually puzzling that the original formula for the mean force required to define a full coordinate transformation and could not be expressed in terms of the reaction coordinate alone. Most likely, a simpler formula should exist. Ruiz-Montero et al.^[26] gave one such formula, but for a scalar reaction coordinate only.

Herein, we give a simple formula for the mean force in the general case of a vectorial reaction coordinate in the presence of additional molecular constraints. We also discuss how to sample the Blue Moon ensemble using overdamped stochastic dynamics instead of constrained molecular dynamics. The use of stochastic dynamics has the advantage that it has no bias, unlike the original Blue Moon formulation which introduced a bias on the momenta which had to be corrected. Finally, we discuss how to remove the bias by using constrained molecular dynamics. This was already explained in the original Blue Moon paper, but we take a slightly different viewpoint here which leads to simpler formulas.

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2. Mean Force and Conditional Expectation

We shall focus on a system in the (N, V, T) ensemble subject to M molecular constraints, $\sigma_j(x) = 0$, $j = 1, \dots, M$, whose equilibrium probability density function on the configuration space \mathbb{R}^n reads,

$$\rho(x) = Z_\sigma^{-1} e^{-\beta V(x)} \prod_{j=1}^M \delta(\sigma_j(x)) \quad (1)$$

where

$$Z_\sigma = \int_{\mathbb{R}^n} e^{-\beta V(x)} \prod_{j=1}^M \delta(\sigma_j(x)) dx \quad (2)$$

is the configuration integral. We shall not dwell on the origin of Equation (1), but we note that Equation (1) is quite general, at least upon appropriate definition of the “potential” $V(x)$. Indeed, any probability density function composed of a smooth part $g(x)$ times $\prod_{j=1}^M \delta(\sigma_j(x))$ can be written as Equation (1) by taking $V(x) = -k_B T \log g(x)$.

Suppose that we introduce N reaction coordinates, $\{q_j(x)\}_{j=1, \dots, N}$, defined on $x \in \mathbb{R}^n$. Assume that they are “nice” reaction coordinates, in the sense that the level sets (or isosurfaces) $q_j(x) = \text{cst}$ are smooth given by connected hypersurfaces. By definition, the free energy associated with the vectorial reaction coordinate $q(x) = (q_1(x), \dots, q_N(x))$ is given by:

$$e^{-\beta F(z)} := Z_\sigma^{-1} \int_{\mathbb{R}^n} e^{-\beta V(x)} \prod_{k=1}^N \delta(q_k(x) - z_k) \prod_{j=1}^M \delta(\sigma_j(x)) dx \quad (3)$$

where $z = (z_1, \dots, z_N)$. Our main claim is that the gradient of $F(z)$ (i.e., the mean force) can be expressed as

$$\frac{\partial F}{\partial z_j} = \langle b_j(x) \cdot \nabla V - k_B T \nabla \cdot b_j(x) \rangle_{q(x)=z, \sigma(x)=0} \quad (4)$$

Here, $\langle \cdot \rangle_{q(x)=z, \sigma(x)=0}$ denotes the conditional average at $q(x) = z$, $\sigma(x) = 0$ fixed, that is, for any $f(x)$,

$$\langle f \rangle_{q(x)=z, \sigma(x)=0} = \frac{\int_{\mathbb{R}^n} f(x) e^{-\beta V(x)} \prod_{k=1}^N \delta(q_k(x) - z_k) \prod_{j=1}^M \delta(\sigma_j(x)) dx}{\int_{\mathbb{R}^n} e^{-\beta V(x)} \prod_{k=1}^N \delta(q_k(x) - z_k) \prod_{j=1}^M \delta(\sigma_j(x)) dx} \quad (5)$$

and the $b_j(x)$, $j = 1, \dots, N$ are vector fields satisfying

$$b_j(x) \cdot \nabla \sigma_k(x) = 0 \quad \forall j = 1, \dots, N, k = 1, \dots, M \quad (6)$$

and

$$b_j(x) \cdot \nabla q_k(x) = \begin{cases} 1 & \text{if } j = k \\ 0 & \text{otherwise} \end{cases} \quad (7)$$

Note that a set of $b_j(x)$ can always be constructed by orthogonalization:

$$b_j(x) = Q^j \nabla q_j(x) / |Q^j \nabla q_j(x)| \quad (8)$$

where Q^j denotes the projector onto the subspace perpendicular to the subspace spanned by $\{\nabla q_k(x) \mid \}_{k \neq j} \cup \{\nabla \sigma_k(x) \mid \}_{k=1, \dots, M}$. Explicitly, Q^j is given by

$$Q^j = 1 - \sum_{k \neq j} \hat{n}_k^j(x) \otimes \hat{n}_k^j(x) \quad (9)$$

where $\{\hat{n}_k^j(x)\}_{k \neq j}$ is an orthonormal basis in the subspace spanned by $\{\nabla q_k(x) \mid \}_{k \neq j} \cup \{\nabla \sigma_k(x) \mid \}_{k=1, \dots, M}$ which can be constructed, for example, by Gram–Schmidt orthogonalization.

To derive Equation (4), differentiate both sides of Equation (3) with respect to z_j to obtain:

$$\begin{aligned} -\beta \frac{\partial F}{\partial z_j} e^{-\beta F(z)} &= Z_\sigma^{-1} \int_{\mathbb{R}^n} e^{-\beta V(x)} \frac{\partial}{\partial z_j} \prod_{k=1}^N \delta(q_k(x) - z_k) \\ &\quad \times \prod_{k=1}^M \delta(\sigma_k(x)) dx \end{aligned} \quad (10)$$

Notice that

$$\begin{aligned} \frac{\partial}{\partial z_j} \prod_{k=1}^N \delta(q_k(x) - z_k) \prod_{k=1}^M \delta(\sigma_k(x)) &= -\delta'(q_j(x) - z_j) \prod_{k \neq j} \delta(q_k(x) - z_k) \prod_{k=1}^M \delta(\sigma_k(x)) \\ &= -(b_j(x) \cdot \nabla \delta(q_j(x) - z_j)) \prod_{k \neq j} \delta(q_k(x) - z_k) \prod_{k=1}^M \delta(\sigma_k(x)) \\ &= -b_j(x) \cdot \nabla \left(\prod_{k=1}^N \delta(q_k(x) - z_k) \prod_{k=1}^M \delta(\sigma_k(x)) \right) \end{aligned} \quad (11)$$

where we used the following chain rule formula:

$$b_j(x) \cdot \nabla \delta(q_k(x) - z_k) = b_j(x) \cdot \nabla q_k(x) \delta'(q_k(x) - z_k) \quad (12)$$

as well as Equations (6) and (7). It follows that Equation (10) can be expressed as

$$\begin{aligned} -\beta \frac{\partial F}{\partial z_j} e^{-\beta F(z)} &= Z_\sigma^{-1} \int_{\mathbb{R}^n} e^{-\beta V(x)} b_j(x) \cdot \nabla \left(\prod_{k=1}^N \delta(q_k(x) - z_k) \prod_{k=1}^M \delta(\sigma_k(x)) \right) dx \\ &= Z_\sigma^{-1} \int_{\mathbb{R}^n} e^{-\beta V(x)} (-\beta b_j(x) \cdot \nabla V(x) + \nabla \cdot b_j(x)) \\ &\quad \times \prod_{k=1}^N \delta(q_k(x) - z_k) \prod_{k=1}^M \delta(\sigma_k(x)) dx \end{aligned} \quad (13)$$

where we integrated by parts. After elementary reorganization, Equation (13) gives Equation (4). Notice that Equation (4) involves the gradient of V , which may contain more than the force if V contains additional factor besides the bare potential

energy. We shall not dwell on this issue here, but we note that it can be handled computationally by a method similar to the one discussed in Section 4.

3. Constrained Dynamics

The next question is how to compute in practice conditional expectations like the one in Equation (4). The standard Blue Moon procedure uses constrained molecular dynamics to do so. Unfortunately, because this procedure introduces additional constraints on the momenta, it introduces a bias which has to be removed. Since using molecular dynamics simulation may be unavoidable in practice, we discuss this issue in Section 4. Here, however, we show how to avoid this issue by using an alternative type of constrained dynamics.

Consider the stochastic differential,

$$\dot{X}(t) = -\nabla V(X(t)) + \sqrt{2k_B T} \eta(t) \quad (14)$$

where $\eta(t)$ is a standard white-noise, that is, a Gaussian process with zero mean and covariance $\mathbf{E} \eta(t)\eta(s) = \mathbf{1} \delta(t-s)$ (here, \mathbf{E} denotes expectation with respect to η and $\mathbf{1}$ is the identity matrix). It is well-known that Equation (14) is ergodic with respect to the unconstrained Gibbs density, that is, for any $f(x)$ and for almost any initial condition $X(0)=x$ have:

$$\lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T f(X(t)) dt = Z^{-1} \int_{\mathbb{R}^n} f(x) e^{-\beta V(x)} dx \quad (15)$$

where $Z = \int_{\mathbb{R}^n} e^{-\beta V(x)} dx$. The question is how to account for the constraints $q(x)=z$ and $\sigma(x)=0$.

Let $\{\hat{e}_j(x)\}_{j=1, \dots, N+M}$ be an orthonormal basis in the space spanned by

$$\{\nabla q_j(x)\}_{j=1, \dots, N} \cup \{\nabla \sigma_j(x)\}_{j=1, \dots, M} \quad (16)$$

and denote by P the projector into the space perpendicular to this subspace

$$P(x) = 1 - \sum_{j=1}^{N+M} \hat{e}_j(x) \otimes \hat{e}_j(x) \quad (17)$$

The basis $\{\hat{e}_j(x)\}_{j=1, \dots, N+M}$ can be constructed at each x , for example, by Gram-Schmidt orthogonalization. We claim that the following Itô stochastic differential equation

$$\dot{X}(t) = -P(X(t)) \nabla V(X(t)) + k_B T \operatorname{div} P(X(t)) + \sqrt{2k_B T} P(X(t)) \eta(t) \quad (18)$$

is ergodic with respect to the conditional measure used in Equation (5), that is,

$$\lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T f(X(t)) dt = \langle f \rangle_{q(x)=z, \sigma(x)=0} \quad (19)$$

In Equation (18), the vector $\operatorname{div} P(x)$ is the divergence of the tensor $P(x)$, given explicitly by (this formula and the next ones are most conveniently derived working componentwise in configuration space).

$$\operatorname{div} P(x) = - \sum_{j=1}^{N+M} (\hat{e}_j(x) (\nabla \cdot \hat{e}_j(x)) + (\hat{e}_j(x) \cdot \nabla) \hat{e}_j(x)) \quad (20)$$

To verify the claim, notice that the equilibrium probability distribution associated with Equation (18), say $\rho(x)$, satisfies the Fokker-Planck equation (for a derivation see, for example, ref. [27] and notice that $P^2(x) = P(x)$ since it is a projector),

$$0 = \nabla \cdot (P(x) \nabla V(x) \rho(x) - k_B T \operatorname{div} P(x) \rho(x)) + k_B T \nabla \nabla : (P(x) \rho(x)) \quad (21)$$

Since $\nabla \nabla : (P(x) \rho(x)) = \nabla \cdot (P(x) \nabla \rho(x)) + \nabla \cdot (\operatorname{div} P(x) \rho(x))$, this equation can also be written as

$$0 = \nabla \cdot (P(x) \nabla V(x) \rho(x) + k_B T P(x) \nabla \rho(x)) \quad (22)$$

This equation is satisfied by

$$\rho(x) = Z_{q,\sigma}^{-1} e^{-\beta V(x)} \prod_{j=1}^N \delta(q_j(x) - z_j) \prod_{k=1}^M \delta(\sigma_k(x)) \quad (23)$$

where the constant $Z_{q,\sigma}$ is a normalization factor [equal to the denominator in the fraction at the right-hand side of Eq. (5)]. Indeed, we have:

$$\begin{aligned} k_B T P(x) \nabla \rho(x) &= -P(x) \nabla V(x) \rho(x) \\ &+ k_B T Z_{q,\sigma}^{-1} e^{-\beta V(x)} P(x) \nabla \left(\prod_{j=1}^N \delta(q_j(x) - z_j) \prod_{k=1}^M \delta(\sigma_k(x)) \right) \\ &= -P(x) \nabla V \rho(x) \end{aligned} \quad (24)$$

where we used $0 = P(x) \nabla q_j(x) = P(x) \nabla \sigma_k(x)$ for any $j=1, \dots, N$ and $k=1, \dots, M$, which follows from the definition of $P(x)$. This shows that $\rho(x)$ is an equilibrium distribution for Equation (22); it is also unique if the level sets $q_j(x)=\text{cst}$ and $\sigma_k(x)=\text{cst}$ are connected.

Finally, notice that Equation (18) can be readily implemented numerically using a split-time scheme. Given X_n , compute first

$$X_* = X_n - P(X_n) \nabla V(X_n) \Delta t + \sqrt{2k_B T \Delta t} P(X_n) \xi_n \quad (25)$$

where $\{\xi_n\}_{n \in \mathbb{N}}$ are independent Gaussian variables with mean zero and variance one. Then use

$$X_{n+1} = X_* - k_B T \Delta t \lambda \operatorname{div} P(X_n) \quad (26)$$

where the scalar λ is chosen so that we have

$$q_j(X_{n+1}) = z, \quad \sigma(X_{n+1}) = 0 \quad (27)$$

for all $j=1, \dots, N$ and $k=1, \dots, M$. It is easy to see that $\lambda=1$ to leading order in Δt , but this scheme allows one to satisfy the

constraint to arbitrary precision by enforcing Equation (27) (much in the spirit of SHAKE^[28]).

4. Unbiasing Constrained Molecular Dynamics

The stochastic differential equation, Equation (18), provides one with a simple way to compute the conditional expectation in Equation (5). Yet, one may prefer using more standard constrained molecular dynamics to compute this average. This amounts to using (assuming we work with mass-weighted coordinates),

$$\ddot{X}(t) = -\nabla V(X(t)) + \sum_{j=1}^{N+M} \lambda_j \nabla c_j(X(t)) \quad (28)$$

where we defined:

$$c(x) = (c_1(x), \dots, c_{N+M}(x)) = (q_1(x), \dots, q_N(x), \sigma_1(x), \dots, \sigma_M(x)) \quad (29)$$

The λ_j are chosen so that $q_j(X(t)) = z$ and $\sigma_k(X(t)) = 0$, or, equivalently, that $\dot{q}_j(X(t)) = \dot{\sigma}_k(X(t)) = 0$. In terms of the $c(x)$ terms defined in Equation (29), this gives

$$0 = -\nabla c_j \cdot \nabla V + \sum_{k=1}^{N+M} \nabla c_j \nabla c_k \lambda_k + v v : \nabla \nabla c_j \quad (30)$$

where v is the phase-space coordinate associated with the momenta $\dot{X}(t)$. Defining

$$C_{jk}(x) = \nabla c_j(x) \cdot \nabla c_k(x), \quad j, k = 1, \dots, N+M \quad (31)$$

the solution of Equation (30) can be expressed as

$$\lambda_j = \sum_{k=1}^{N+M} (C^{-1})_{jk} (\nabla c_k \cdot \nabla V - v v : \nabla \nabla c_k) \quad (32)$$

Unfortunately, there are two problems with Equation (28). First, and most importantly, Equation (28) conserves both $q_j(x) = z$ and $\sigma(x) = 0$, but also the following additional constraints

$$v \cdot \nabla q_j(x) = 0, \quad v \cdot \nabla \sigma_k(x) = 0 \quad (33)$$

for any $j = 1, \dots, N$ and $k = 1, \dots, M$. Second it may only be ergodic with respect to the microcanonical distribution where $H(x, v) = \frac{1}{2}|v|^2 + V(x)$ is conserved as well, $H(x, v) = E$. The second problem is easily fixed by adding a thermal bath term in Equation (28) using for example, Nosé–Hoover thermostat or a Langevin random term.^[2] But it remains true that the equilibrium distribution for Equation (28) properly thermalized is

$$\begin{aligned} \bar{\rho}(x, v) &= Z_H^{-1} e^{-\beta H(x, v)} \prod_{j=1}^N \delta(q_j(x) - z_j) \delta(v \cdot \nabla q_j(x)) \\ &\times \prod_{k=1}^M \delta(\sigma_k(x)) \delta(v \cdot \nabla \sigma_k(x)) A(x) \end{aligned} \quad (34)$$

Here:

$$\begin{aligned} Z_H &= \int_{\mathbb{R}^n \times \mathbb{R}^n} e^{-\beta H(x, v)} \prod_{j=1}^N \delta(q_j(x) - z_j) \delta(v \cdot \nabla q_j(x)) \\ &\times \prod_{k=1}^M \delta(\sigma_k(x)) \delta(v \cdot \nabla \sigma_k(x)) A(x) dx dv \end{aligned} \quad (35)$$

and

$$A(x) = \det C(x) \quad (36)$$

where $C(x)$ is the tensor defined in Equation (31). The factor $A(x)$ must be included because the dynamics in Equation (28) is not volume-preserving.^[29,30]

Taking the expectation with respect to this distribution is not equivalent to taking expectation with the distribution in Equation (5). In other words, an additional density must be introduced, which can be computed exactly. To see this, start from the following expectation of $g(x)$ with respect to $\bar{\rho}(x, v)$, denoted as

$$\begin{aligned} \langle g(x) \rangle_{\substack{v \cdot \nabla q_j(x) = v \cdot \nabla \sigma_k(x) = 0 \\ q_j(x) = z, \sigma_k(x) = 0}} &= Z_H^{-1} \int_{\mathbb{R}^n \times \mathbb{R}^n} g(x) e^{-\beta H(x, v)} \\ &\times \prod_{j=1}^N \delta(q_j(x) - z_j) \delta(v \cdot \nabla q_j(x)) \\ &\times \prod_{k=1}^M \delta(\sigma_k(x)) \delta(v \cdot \nabla \sigma_k(x)) A(x) dx dv \end{aligned} \quad (37)$$

and, for every x fixed, decompose v as

$$v = \sum_{j=1}^{N+M} \hat{e}_j(x) v_j + v_{\perp} \quad (38)$$

where $v_j = v \cdot \hat{e}_j(x)$ and v_{\perp} is the remaining component of v in the subspace perpendicular to the one spanned by the $\hat{e}_j(x)$ —

notice in particular that $|v|^2 = \sum_{j=1}^{N+M} v_j^2 + |v_{\perp}|^2$. In terms of this decomposition, we have

$$\begin{aligned} &\prod_{j=1}^N \delta(v \cdot \nabla q_j(x)) \prod_{k=1}^M \delta(v \cdot \nabla \sigma_k(x)) dv \\ &= \prod_{j=1}^{N+M} \delta\left(\sum_{k=1}^{N+M} K_{jk}(x) v_k\right) dv \\ &= \prod_{j=1}^{N+M} \delta(u_j) |\det K(x)|^{-1} du dv_{\perp} \end{aligned} \quad (39)$$

where $K_{jk}(x)$ is given by

$$K_{jk}(x) = \nabla c_j(x) \cdot \hat{e}_k(x) \quad (40)$$

and for the last step we used $u_j = \sum_{k=1}^{N+M} K_{kj}(x) v_k$, $j = 1, \dots, N+M$ and v_{\perp} as new integration variable. Using Equation (39) in Equation (37) and performing explicitly the integration over the u_j 's, we deduce that:

$$\begin{aligned}
\langle g(x) \rangle_{q(x)=z, \sigma(x)=z, \sigma(x)=0}^{v \cdot \nabla q(x)=v \cdot \nabla \sigma(x)=0} &= Z_H^{-1} \int_{\mathbb{R}^n \times \mathbb{R}^{n-N-M}} g(x) e^{-\beta(\frac{1}{2}v_{\perp}^2 + V(x))} \\
&\times \prod_{j=1}^N \delta(q_j(x) - z_j) \prod_{k=1}^M \delta(\sigma_k(x)) |\det K(x)|^{-1} A(x) dx dv_{\perp} \\
&= Z_H^{-1} (2\pi k_B T)^{(n-N-M)/2} \int_{\mathbb{R}^n} g(x) e^{-\beta V(x)} \\
&\times \prod_{j=1}^N \delta(q_j(x) - z_j) \prod_{k=1}^M \delta(\sigma_k(x)) |\det K(x)|^{-1} A(x) dx
\end{aligned} \quad (41)$$

Choosing $g(x) = f(x) |\det K(x)| / A(x)$, this can be written

$$\begin{aligned}
&\int_{\mathbb{R}^n} f(x) e^{-\beta V(x)} \prod_{j=1}^N \delta(q_j(x) - z_j) \prod_{k=1}^M \delta(\sigma_k(x)) dx \\
&= Z_H (2\pi k_B T)^{-(n-N-M)/2} \langle f(x) |\det K(x)| / A(x) \rangle_{q(x)=z, \sigma(x)=0}^{v \cdot \nabla q(x)=v \cdot \nabla \sigma(x)=0}
\end{aligned} \quad (42)$$

Finally, use this equality for $f(x) = 1$, and use it to divide side by side Equation (42). This gives us the desired expression, Equation (43), which relates the expectation in Equation (5) to the ratio of two expectation with respect to $\bar{\rho}(x, v)$ [Eq. (34)]

$$\langle f(x) \rangle_{q(x)=z, \sigma(x)=0} = \frac{\langle f(x) |\det K(x)| / A(x) \rangle_{q(x)=z, \sigma(x)=0}^{v \cdot \nabla q(x)=v \cdot \nabla \sigma(x)=0}}{\langle |\det K(x)| / A(x) \rangle_{q(x)=z, \sigma(x)=0}^{v \cdot \nabla q(x)=v \cdot \nabla \sigma(x)=0}}} \quad (43)$$

Notice that,

$$|\det K(x)| = \sqrt{|\det K(x) K^T(x)|} = \sqrt{|\det C(x)|} \quad (44)$$

where $C(x)$ is the tensor defined in Equation (31). This allows one to connect Equation (43) to the original formula derived in ref. [1]. But Equation (43) may be more convenient in practice because the basis of $\hat{e}_j(x)$ can always be constructed by the Gram–Schmidt orthogonalization procedure in such a way that

$$\hat{e}_j(x) \cdot \nabla c_k(x) = 0 \quad \text{for all } j > k \quad (45)$$

where the $c_j(x)$'s are defined in Equation (29). In this case, the matrix K is upper triangular and the determinant of K is simply the following product

$$\det K(x) = \prod_{j=1}^{N+M} \hat{e}_j(x) \cdot \nabla c_j(x) \quad (46)$$

5. Concluding Remarks

Herein, we have shown that the identity in Equation (12) can be used to derive the (long-awaited) formula (4) for the mean force. We also showed that the conditional expectation in this formula is most conveniently computed in terms of the stochastic constrained dynamics introduced in Section 3, see Equation (18). In contrast to the standard molecular dynamics simulations with holonomic constraints considered in Section 4, the stochastic dynamics has the advantage that it introduces no bias.

As mentioned before, to obtain the actual free energy from the mean force, Equation (4), requires a thermodynamic integration step which may prove tedious if the number of reaction coordinates is large. However, the mean force, Equation (4), is the only quantity needed to compute the minimum free energy paths (MFEPs) on the free energy surface by using techniques like the nudged elastic band method^[31] or the string method^[32] (see also ref. [35]). Provided that the reaction coordinates are chosen appropriately, the MFEPs may provide some useful information about the mechanisms of reaction and the rates of activated processes. As such the formula given here may provide an interesting alternative to other recent techniques that have been introduced to sample the free energy landscape associated with a prescribed set of reaction coordinates, like, for example, the metadynamics introduced by Parrinello et al.^[33,34]

Acknowledgments

R.K. was supported in part by a grant from the Natural Sciences and Engineering Research Council of Canada. E.V.-E. was supported in part by NSF by grants DMS02-09959 and DMS02-39625.

Keywords: Blue Moon sampling • constrained stochastic dynamics • free energy • mean force • reaction coordinates

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Received: December 31, 2004

Revised: March 30, 2005
