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Sampling Boltzmann-Gibbs distributions restricted on a manifold with diffusions: Application to free energy calculations

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Abstract

We consider the problem of sampling a Boltzmann-Gibbs probability distribution when this distribution is restricted (in some suitable sense) on a manifold Σ of $\mathbb{R}^n$ implicitly defined by N constraints $q_1(\boldsymbol{x}) = \cdots = q_N(\boldsymbol{x}) = 0$. This problem arises for example in systems subject to hard constraints or in the context of free energy calculations. We prove that the constrained stochastic differential equations (*i.e.* diffusions) proposed in [W. E and E. Vanden-Eijnden, in: *Multiscale Modelling and Simulation*, eds. S. Attinger and P. Koumoutsakos (LNCSE **39**, Springer, 2004)] and [G. Ciccotti, R. Kapral, and E. Vanden-Eijnden, *ChemPhysChem* **6**, 1809 (2005)] are ergodic with respect to this restricted distribution. We also construct numerical schemes for the integration of the constrained diffusions. Finally, we show how these schemes can be used to compute the gradient of the free energy associated with the constraints.

Contents

1 Introduction

A standard computational issue in statistical mechanics is the calculation of the expectation

$$I(\phi) = \int_{\mathbb{R}^n} \phi(\boldsymbol{x}) d\mu(\boldsymbol{x}) \tag{1.1}$$

of an observable $\phi : \mathbb{R}^n \to \mathbb{R}$ with respect to the Boltzmann-Gibbs distribution μ defined as

$$d\mu(\boldsymbol{x}) = Z^{-1} \exp(-\beta V(\boldsymbol{x}))\, d\boldsymbol{x}. \tag{1.2}$$

Here $Z = \int_{\mathbb{R}^n} \exp(-\beta V(\boldsymbol{x}))\, d\boldsymbol{x}$ is the partition function, $\beta > 0$ is the inverse temperature, and $V : \mathbb{R}^n \to \mathbb{R}$ is the potential. When the dimensionality of space is high, $n \gg 1$, standard numerical techniques based on discretizing the integral in (1.1) become impractical, and various alternative techniques have been developed to evaluate (1.1). By far the most common techniques are the so-called Monte-Carlo sampling techniques, which amount to devising a stochastic process ergodic with respect to (1.2), and replace the ensemble average in (1.1) by a time-average over this process using the ergodic theorem:

$$I(\phi) = \lim_{T\to\infty} I_T(\phi) \qquad \text{where} \qquad I_T(\phi) = \frac{1}{T}\int_0^T \phi(\boldsymbol{X}_t) dt, \tag{1.3}$$

where $\boldsymbol{X}_t$ is a generic sample path of the stochastic process. In the case at hand, one may for instance consider the diffusion:

$$d\boldsymbol{X}_t = -\nabla V(\boldsymbol{X}_t)\, dt + \sqrt{2\beta^{-1}}\, d\boldsymbol{W}_t, \tag{1.4}$$

where $\boldsymbol{W}_t$ is a Brownian motion in $\mathbb{R}^n$. Under mild assumptions on the potential V (see Section 1.3), the process $\boldsymbol{X}_t$ is ergodic with respect to the measure μ. Standard numerical schemes exist to compute $\boldsymbol{X}_t$ and these can be used to calculate $I_T(\phi)$ which, for T sufficiently large, provides an accurate estimate of $I(\phi)$.

Many applications require a more general framework, where the Boltzmann-Gibbs distribution μ is replaced by

$$d\mu_\Sigma(\boldsymbol{x}) = Z_\Sigma^{-1} e^{-\beta V(x)} d\sigma_\Sigma(\boldsymbol{x}) \tag{1.5}$$

where

$$Z_\Sigma = \int_\Sigma e^{-\beta V(x)} d\sigma_\Sigma(\boldsymbol{x}). \tag{1.6}$$

Here Σ is a codimension N submanifold of $\mathbb{R}^n$ and the measure σ_Σ denotes the surface element on Σ (*i.e.* the Lebesgue measure on Σ defined from the Lebesgue measure in the ambient space $\mathbb{R}^n \supset \Sigma$). In practice, the submanifold Σ is typically defined as the zero level-set of a smooth function $\boldsymbol{q}$ with values in $\mathbb{R}^N$.

The distribution μ_Σ may be thought of as the projection (or restriction) of μ into Σ. This distribution arises in applications where the system is subject to hard constraints, these being either of physical origin or artificially imposed for some numerical purposes, or in the context of free energy calculations. In this context, the expectation in (1.1) is replaced by

$$I_\Sigma(\phi) = \int_\Sigma \phi(\boldsymbol{x}) d\mu_\Sigma(\boldsymbol{x}), \tag{1.7}$$

and the questions become how to construct a stochastic process (or, more specifically, a diffusion) ergodic with respect to μ_Σ to sample this distribution and how to design numerical algorithms to compute this diffusion in practice ? In [13], a diffusion ergodic with respect to μ_Σ was proposed and in [6] it was shown how to use it in the context of free energy calculations. In the present paper, we put the results of these two references on firm mathematical grounds. We also design some specific algorithms to compute the diffusion ergodic with respect to μ_Σ and show how to use these in the context of free energy calculations.

1.1 Summary of the main results

In Section 2, we recall the diffusion constrained on Σ introduced in [13, 6], and we prove that this constrained diffusion is ergodic with respect to (1.5) and thereby allows to compute expectations like (1.7). These results are given in Proposition 2.1 in Section 2.1 (for the simpler case when Σ has codimension 1) and Proposition 2.2 in Section 2.2 (for the general case when Σ has codimension $N \geq 1$). In Section 2.3, we also discuss some generalizations when the distribution (1.5) is modified by including some extra weight factor (which is relevant in the context of free energy calculations), and we compare the diffusion constrained on Σ with that arising when (1.4) is constrained to stay close to Σ by means of soft constraints whose strength is taken to infinity.

In Section 3, we derive some numerical algorithms to integrate the constrained diffusion proposed in Section 2: these are given in Proposition 3.1.

In Section 4, we show how to use these results to compute the mean force, *i.e.* the gradient of the free energy associated with the reaction coordinate $\boldsymbol{q}$, which defines a foliation of $\mathbb{R}^n$ by a family of manifolds Σ. In Section 4.1, we first recall the definition of the free energy, then in Section 4.2, we derive several expressions for its gradient, the mean force. These expressions are given in Lemma 4.1 and Proposition 4.2. Finally, in Section 4.3, we show how to compute the mean force in practice and in Section 4.4 we give a variance reduction technique which enhances the efficiency of these calculations. These results are generalized in Appendix D for the situations with molecular constraints.

For the reader convenience, several technical results are deferred to Appendices A, B and C.

1.2 Comparison with other approaches

Traditionally in the molecular dynamics community, the sampling of the Boltzmann-Gibbs distribution (1.2) has been done using Nosé-Hoover, hybrid kinetic Monte-Carlo, or (non-zero-mass) Langevin dynamics rather than the diffusion (1.4). Similarly, the restricted distribution (1.5) is usually sampled by adding holonomic constraints to the Nosé-Hoover, hybrid kinetic Monte-Carlo (HKMC), or Langevin equations of motion (see e.g. [29, 7, 8, 19, 18]). Since these equations of motion involves both the position $\boldsymbol{x}$ of the system and the momentum $\boldsymbol{p}$ associated with this position, adding holonomic constraints not only forces the position of the system to remain on the manifold Σ, but also its momentum to always be tangent to Σ. In turns, this means that the restricted distribution sampled by constrained Nosé-Hoover, HKMC, or Langevin dynamics is a distribution on a submanifold of $\mathbb{R}^n \times \mathbb{R}^n$ whose marginal in position space is precisely (1.5).

In this paper, we give the counterparts of these results by working in configuration space alone and using a constrained version of the diffusion in (1.4). We also give the counterparts of the various results developed in the context of Nosé-Hoover, HKMC, or Langevin equations (see e.g. [5, 30, 11, 10, 9, 19, 18]) to compute the gradient of the free energy (the so-called mean force) as seamlessly as possible.

1.3 Main assumptions and notations

Thorough this paper we assume that the potential V is a $\mathcal{C}^2$-function which grows sufficiently fast at infinity so that the diffusion in (1.4) is ergodic with respect to the Boltzmann-Gibbs distribution (1.2). Most of our results generalize straightforwardly to situations where the distribution (1.2) is supported on some connected region $\Omega \subset \mathbb{R}^n$, but we will not consider these cases for simplicity. We also assume that the manifold Σ is connected and can be defined as the zero level-set of a smooth vector-valued function $\boldsymbol{q} = (q_1, \dots, q_N)$ where $0 < N < n$ and $q_\alpha : \mathbb{R}^n \to \mathbb{R}$ for each $1 \le \alpha \le N$ and we suppose that

$$\text{rank}(\nabla q_1, ..., \nabla q_N) = N \text{ on } \Sigma, \tag{1.8}$$

where $\text{rank}(\nabla q_1, ..., \nabla q_N)$ denotes the rank of the matrix

$$\left(\frac{\partial q_\alpha}{\partial x_j}\right)_{1\le\alpha\le N,\, 1\le j\le n}. \tag{1.9}$$

We also suppose that

$$\infty > M \ge \sup_{1\le\alpha\le N} \Big|\sum_{\zeta=1}^{N} G^{-1}_{\alpha,\zeta}(\boldsymbol{x})\nabla q_\zeta(\boldsymbol{x})\Big|, \qquad \forall \boldsymbol{x} \in \Sigma, \tag{1.10}$$

where

$$G_{\alpha,\zeta}(\boldsymbol{x}) = \nabla q_\alpha(\boldsymbol{x}) \cdot \nabla q_\zeta(\boldsymbol{x}), \qquad 1 \le \alpha, \zeta \le N, \tag{1.11}$$

and $G^{-1}_{\alpha,\zeta}(\boldsymbol{x})$ denotes the (α, ζ)-entry of the inverse matrix $(G(\boldsymbol{x}))^{-1}$. For a scalar constraint ($N = 1$), this amounts to assuming that $|\nabla q|$ is uniformly bounded from below by a positive constant. (1.10) guarantees that the expectation

$$\int_\Sigma \Big|\sum_{\zeta=1}^{N} G^{-1}_{\alpha,\zeta}(\boldsymbol{x})\nabla q_\zeta(\boldsymbol{x})\Big|^2 d\mu_\Sigma(x)$$

is finite, a property that we will use below.

We use Greek indices (varying between 1 and N) to denote the components of quantities related to constraints. Latin indices vary between 1 and n, n being the dimension of the ambient space. For brevity, we use the summation convention on repeated indices for some long formulae: for Greek indices, the sum is over $1 \dots N$ and for Latin indices, the sum is over $1 \dots n$. We denote by $\otimes$ the tensor product, and by

$$\nabla^2 u = \left(\frac{\partial^2 u}{\partial x_i \partial x_j}\right)_{1\le i,j\le n} \tag{1.12}$$

the Hessian matrix of a function $u : \mathbb{R}^n \to \mathbb{R}$. We also denote by $\nabla_i u$ (resp. $\nabla_i \nabla_j u$) its partial derivative $\partial u/\partial x_j$ (resp. $\partial^2 u/\partial x_i \partial x_j$). Finally, the superscript ^{T} denotes the transposition operator.

2 A diffusion ergodic with respect to the distribution μ_Σ

In this section, we give a diffusion that is ergodic with respect to μ_Σ [13, 6]. For clarity, we first consider in Section 2.1 the case when Σ is a manifold of codimension 1. Then we generalize our result in Section 2.2 to the case of a manifold of codimension $N \geq 1$. Section 2.3 is then devoted to some remarks, especially concerning the case when the constraints are softly imposed by a constraining potential. We suppose in this section that $\boldsymbol{q}(\boldsymbol{X}_0) = 0$.

2.1 The codimension 1 situation

Let $\Sigma := \{\boldsymbol{x} : q(\boldsymbol{x}) = 0\}$ be the zero level-set of the scalar valued $\mathcal{C}^2$-function $q : \mathbb{R}^n \to \mathbb{R}$.

Let us introduce the normal $\hat{\boldsymbol{n}}(\boldsymbol{x})$ to Σ at point $\boldsymbol{x}$

$$\hat{\boldsymbol{n}}(\boldsymbol{x}) = \frac{\nabla q(\boldsymbol{x})}{|\nabla q(\boldsymbol{x})|} \tag{2.1}$$

and the orthogonal projector $P(\boldsymbol{x})$ on the tangent space at point $\boldsymbol{x}$ to Σ defined by:

$$P(\boldsymbol{x}) = \mathrm{Id} - \hat{\boldsymbol{n}}(\boldsymbol{x}) \otimes \hat{\boldsymbol{n}}(\boldsymbol{x}). \tag{2.2}$$

Notice that $P^2 = P$ and $P = P^T$, since P is an orthogonal projector. Let

$$\kappa(\boldsymbol{x}) = \mathrm{div}\ \hat{\boldsymbol{n}}(\boldsymbol{x}). \tag{2.3}$$

be the mean curvature of Σ at point $\boldsymbol{x}$. We have:

Proposition 2.1 *The distribution μ_Σ in (1.5) is the unique equilibrium distribution of the diffusion (written in Itô form):*

$$d\boldsymbol{X}_t = P(\boldsymbol{X}_t)\left(-\nabla V(\boldsymbol{X}_t)\,dt + \sqrt{2\beta^{-1}}d\boldsymbol{W}_t\right) - \beta^{-1}\kappa(\boldsymbol{X}_t)\hat{\boldsymbol{n}}(\boldsymbol{X}_t)\,dt. \tag{2.4}$$

Proposition 2.1 implies that if ϕ in $L^p(\mu_\Sigma)$ (with $p > 1$),

$$I_\Sigma(\phi) = \lim_{T\to\infty} I_{\Sigma,T}(\phi) \qquad \text{where} \qquad I_{\Sigma,T}(\phi) = \frac{1}{T}\int_0^T \phi(\boldsymbol{X}_t)dt, \tag{2.5}$$

where $\boldsymbol{X}_t$ is a solution of (2.4) and the convergence is a.s. and in L^p.

PROOF: First let us note that by assumption on Σ and V, V viewed as a function from Σ to $\mathbb{R}^n$ is $\mathcal{C}^2$ and grows sufficiently fast at infinity so that $Z_\Sigma < \infty$. Therefore μ_Σ is well defined. Moreover, the transition probability function is strictly positive so that any invariant measure is equivalent to the Lebesgue measure σ_Σ, which implies the uniqueness of the invariant measure (see Proposition 6.1.9 p. 188 in [12]).

So it suffices to prove that μ_Σ is an invariant measure for (2.4). To this end let $u(t, \boldsymbol{x}) = \mathbf{E}_{\boldsymbol{x}}(f(\boldsymbol{X}_t))$, where $\boldsymbol{X}_t$ satisfies (2.4) and $\mathbf{E}_{\boldsymbol{x}}$ denotes the expectation over this process conditional on $\boldsymbol{X}_0 = \boldsymbol{x}$. Then μ_Σ is an invariant measure for (2.4) if

$$\int_\Sigma u(t, \boldsymbol{x}) d\mu_\Sigma(\boldsymbol{x}) = \int_\Sigma u(0, \boldsymbol{x}) d\mu_\Sigma(\boldsymbol{x}). \tag{2.6}$$

To check (2.6), notice that $u(t, \boldsymbol{x})$ satisfies the backward Kolmogorov equation

$$\frac{\partial u}{\partial t} = -P(\boldsymbol{x})\nabla V(\boldsymbol{x}) \cdot \nabla u + \beta^{-1}\boldsymbol{H}(\boldsymbol{x}) \cdot \nabla u + \beta^{-1} P(\boldsymbol{x}) : \nabla^2 u$$

where

$$P(\boldsymbol{x}) : \nabla^2 u = \sum_{i,j=1}^n P_{i,j}(\boldsymbol{x}) \frac{\partial^2 u}{\partial x_i \partial x_j}$$

and $\boldsymbol{H} = -\kappa \hat{\boldsymbol{n}}$ denotes the mean curvature vector. It follows that

$$\begin{aligned}
&\frac{d}{dt} \int_\Sigma u(t, \boldsymbol{x}) d\mu_\Sigma(\boldsymbol{x}) \\
&= Z_\Sigma^{-1} \int_\Sigma \Big(-P(\boldsymbol{x})\nabla V(\boldsymbol{x}) \cdot \nabla u(t, \boldsymbol{x}) + \beta^{-1} \boldsymbol{H}(\boldsymbol{x}) \cdot \nabla u(t, \boldsymbol{x}) \\
&\qquad\qquad + \beta^{-1} P(\boldsymbol{x}) : \nabla^2 u(t, \boldsymbol{x}) \Big) \exp(-\beta V(\boldsymbol{x}))\, d\sigma_\Sigma(\boldsymbol{x}), \\
&= \beta^{-1} Z_\Sigma^{-1} \int_\Sigma \Big(\mathrm{div}\,_\Sigma (\nabla u(t, \boldsymbol{x}) \exp(-\beta V(\boldsymbol{x}))) \\
&\qquad\qquad + \boldsymbol{H}(\boldsymbol{x}) \cdot \nabla u(t, \boldsymbol{x}) \exp(-\beta V(\boldsymbol{x})) \Big)\, d\sigma_\Sigma(\boldsymbol{x}), \\
&= 0.
\end{aligned}$$

Here $\mathrm{div}\,_\Sigma$ denotes the surface divergence:

$$\mathrm{div}\,_\Sigma(\boldsymbol{\phi}) = \mathrm{tr}(P \nabla \boldsymbol{\phi}) \tag{2.7}$$

and we used the divergence theorem on manifolds (see [2, 3]):

$$\forall \boldsymbol{\phi} \in \mathcal{C}_c^1(\mathbb{R}^n, \mathbb{R}^n) : \quad \int_\Sigma \mathrm{div}\,_\Sigma(\boldsymbol{\phi})\, d\sigma_\Sigma = -\int_\Sigma \boldsymbol{H} \cdot \boldsymbol{\phi}\, d\sigma_\Sigma. \tag{2.8}$$

This shows that (2.6) holds, which concludes the proof. ∎

Componentwise, (2.4) can be written as

$$\begin{aligned} d(\boldsymbol{X}_t)_i = & \left(P(\boldsymbol{X}_t)\left(-\nabla V(\boldsymbol{X}_t)\,dt + \sqrt{2\beta^{-1}}d\boldsymbol{W}_t\right)\right)_i \\ & + \beta^{-1}\sum_{j,k=1}^n P_{j,k}\nabla_j P_{i,k}(\boldsymbol{X}_t)\,dt. \end{aligned} \tag{2.9}$$

where we used the identity $\sum_{j,k=1}^n P_{j,k}\nabla_j P_{i,k} = -\kappa\hat{\boldsymbol{n}}_i$ (see (A.1)). From (2.9), we see that (2.4) can also be written in Stratonovich form as

$$d\boldsymbol{X}_t = -P(\boldsymbol{X}_t)\nabla V(\boldsymbol{X}_t)\,dt + \sqrt{2\beta^{-1}}P(\boldsymbol{X}_t)\circ d\boldsymbol{W}_t, \tag{2.10}$$

which shows that (2.4) essentially amounts to projecting (1.4) onto Σ. In particular, it implies that

$$dq(\boldsymbol{X}_t) = \nabla q(\boldsymbol{X}_t)\cdot\left(-P(\boldsymbol{X}_t)\nabla V(\boldsymbol{X}_t)\,dt + \sqrt{2\beta^{-1}}P(\boldsymbol{X}_t)\circ d\boldsymbol{W}_t\right) = 0,$$

as necessary since we must have $\boldsymbol{X}_t \in \Sigma$.

With a view to the discretization of (2.4) (see Section 3), it is also worth mentioning that (2.4) may be obtained by imposing the constraint that $\boldsymbol{X}_t \in \Sigma$ using Lagrange multipliers. Indeed, let us modify the stochastic differential equation (1.4) in the following way:

$$\begin{cases} d\boldsymbol{X}_t = -\nabla V(\boldsymbol{X}_t)\,dt + \sqrt{2\beta^{-1}}d\boldsymbol{W}_t + d\boldsymbol{Y}_t, \\ \text{with } \boldsymbol{Y}_t \text{ such that } P(\boldsymbol{X}_t)d\boldsymbol{Y}_t = 0 \text{ and } q(\boldsymbol{X}_t) = 0. \end{cases} \tag{2.11}$$

Since we suppose that $q(\boldsymbol{X}_0) = 0$, we set $\boldsymbol{Y}_0 = 0$. We assume moreover that $\boldsymbol{Y}_t$ is adapted with respect to the filtration of the Brownian motion $\boldsymbol{W}_t$. Computing $dq(\boldsymbol{X}_t)$, and decomposing $d\boldsymbol{Y}_t = dA(t) + S(t)d\boldsymbol{W}_t$, where $A(t)$ is a process with finite variation, one obtains:

$$\begin{aligned} dq(\boldsymbol{X}_t) = & \nabla q(\boldsymbol{X}_t)\cdot(-\nabla V(\boldsymbol{X}_t)\,dt + dA(t)) \\ & + \tfrac{1}{2}\nabla^2 q(\boldsymbol{X}_t) : \left(\sqrt{2\beta^{-1}}\mathrm{Id} + S(t)\right)\left(\sqrt{2\beta^{-1}}\mathrm{Id} + S(t)\right)^T dt \\ & + \nabla q(\boldsymbol{X}_t)\cdot\left(\sqrt{2\beta^{-1}}d\boldsymbol{W}_t + S(t)d\boldsymbol{W}_t\right). \end{aligned}$$

Therefore, in order that $d(q(\boldsymbol{X}_t)) = 0$ we must have (using the fact that $d\boldsymbol{Y}_t$, and hence $dA(t)$ and $S(t)d\boldsymbol{W}_t$, are aligned with the normal direction $\nabla q(\boldsymbol{X}_t)$)

$$S(t) = -\sqrt{2\beta^{-1}}\frac{\nabla q\otimes\nabla q}{|\nabla q|^2}(\boldsymbol{X}_t)$$

and thus

$$\begin{aligned} dA(t) &= \frac{\nabla q \cdot \nabla V}{|\nabla q|^2} \nabla q(\boldsymbol{X}_t)\, dt - \beta^{-1} \frac{\nabla q}{|\nabla q|^2} \nabla^2 q : P(\boldsymbol{X}_t)\, dt, \\ &= \frac{\nabla q \cdot \nabla V}{|\nabla q|^2} \nabla q(\boldsymbol{X}_t)\, dt - \beta^{-1} \kappa \hat{\boldsymbol{n}}(\boldsymbol{X}_t)\, dt, \end{aligned}$$

where we used the second equality in (A.1). As a result

$$\begin{aligned} d\boldsymbol{Y}_t = (P(\boldsymbol{X}_t) - \mathrm{Id}) \left(-\nabla V(\boldsymbol{X}_t)\, dt + \sqrt{2\beta^{-1}} d\boldsymbol{W}_t \right) \\ + \beta^{-1} \boldsymbol{H}(\boldsymbol{X}_t)\, dt. \end{aligned} \tag{2.12}$$

Thus, we recover (2.4).

2.2 The codimension N situation

The result in Section 2.1 can be generalized to the case of a codimension N manifold Σ which is the zero level-set of the vector valued function $\boldsymbol{q} = (q_1, ..., q_N)$ with $q_\alpha : \mathbb{R}^n \to \mathbb{R}$ $(1 \le \alpha \le N)$.

One central object we have considered in Section 2.1 is the orthogonal projector P onto Σ. In the case of N constraints, this projector reads (compare (2.2)):

$$P(\boldsymbol{x}) = \mathrm{Id} - \sum_{\alpha,\zeta=1}^{N} G^{-1}_{\alpha,\zeta}(\boldsymbol{x}) \nabla q_\alpha(\boldsymbol{x}) \otimes \nabla q_\zeta(\boldsymbol{x}), \tag{2.13}$$

where we recall the definition in (1.11) for the $N \times N$ matrix G:

$$G_{\alpha,\zeta}(\boldsymbol{x}) = \nabla q_\alpha(\boldsymbol{x}) \cdot \nabla q_\zeta(\boldsymbol{x}), \qquad 1 \le \alpha, \zeta \le N,$$

and $G^{-1}_{\alpha,\zeta}$ denotes the (α, ζ)-entry of the inverse matrix G^{-1}. To check that $P(\boldsymbol{x})$ is the orthogonal projector onto Σ at point $\boldsymbol{x}$, notice that for any $1 \le \gamma \le N$,

$$\begin{aligned} P \nabla q_\gamma &= \nabla q_\gamma - \sum_{\alpha,\zeta=1}^{N} G^{-1}_{\alpha,\zeta} \nabla q_\alpha \nabla q_\zeta \cdot \nabla q_\gamma \\ &= \nabla q_\gamma - \sum_{\alpha,\zeta=1}^{N} G^{-1}_{\alpha,\zeta} G_{\zeta,\gamma} \nabla q_\alpha = 0, \end{aligned}$$

while, for any vector $\boldsymbol{u}$ such that $\forall 1 \le \zeta \le N$, $\boldsymbol{u} \cdot \nabla q_\zeta = 0$, we have

$$P\boldsymbol{u} = \boldsymbol{u} - \sum_{\alpha,\zeta=1}^{N} G^{-1}_{\alpha,\zeta} \nabla q_\alpha \nabla q_\zeta \cdot \boldsymbol{u} = \boldsymbol{u}.$$

Since $P(\boldsymbol{x})$ is an orthogonal projector, it is a symmetric matrix. Notice also that in the special case of orthogonal constraints, namely if $\nabla q_\alpha \cdot \nabla q_\zeta = \delta_{\alpha,\zeta} |\nabla q_\alpha|^2$, (2.13) simplifies into:

$$P(\boldsymbol{x}) = \mathrm{Id} - \sum_{\alpha=1}^{N} \hat{\boldsymbol{n}}_\alpha(\boldsymbol{x}) \otimes \hat{\boldsymbol{n}}_\alpha(\boldsymbol{x}), \tag{2.14}$$

where the normal $\hat{\boldsymbol{n}}_\alpha$ is defined by

$$\hat{\boldsymbol{n}}_\alpha(\boldsymbol{x}) = \frac{\nabla q_\alpha(\boldsymbol{x})}{|\nabla q_\alpha(\boldsymbol{x})|}, \qquad 1 \le \alpha \le N. \tag{2.15}$$

In the case at hand, the equivalent of the curvature κ in (2.3) is

$$\kappa_\alpha = |\nabla q_\alpha| \sum_{\gamma=1}^{N} G^{-1}_{\gamma,\alpha} \Big(\Delta q_\gamma - \nabla^2 q_\gamma : \big(\sum_{\zeta,\delta=1}^{N} G^{-1}_{\delta,\zeta} \nabla q_\delta \otimes \nabla q_\zeta \big) \Big), \tag{2.16}$$

and Proposition 2.1 generalizes as

PROPOSITION 2.2 *The distribution μ_Σ in (1.5) is the unique equilibrium distribution of the diffusion:*

$$\begin{aligned} d\boldsymbol{X}_t = {} & P(\boldsymbol{X}_t) \left(-\nabla V(\boldsymbol{X}_t)\, dt + \sqrt{2\beta^{-1}}\, d\boldsymbol{W}_t \right) \\ & - \beta^{-1} \sum_{\alpha=1}^{N} \kappa_\alpha(\boldsymbol{X}_t) \hat{\boldsymbol{n}}_\alpha(\boldsymbol{X}_t)\, dt. \end{aligned} \tag{2.17}$$

Equation (2.17) is the generalization of (2.4), and the equivalent of (2.5) holds here as well. The proof of Proposition 2.2 is similar to that of Proposition 2.1. It is again based upon the divergence theorem on manifolds, and the fact that the mean curvature vector is

$$\boldsymbol{H} = - \sum_{\alpha=1}^{N} \kappa_\alpha \hat{\boldsymbol{n}}_\alpha \tag{2.18}$$

(see Appendix B below for further details). We skip it for the sake of brevity.

As in the case $N=1$, (2.17) can be seen as the projection of (1.4) using the projection operator P defined by (2.13), and a Stratonovich integration rule. In other words, (2.9) and (2.10) also hold in the codimension N situation, since $\sum_{j,k=1}^{n} P_{j,k}\nabla_j P_{i,k} = -\sum_{\alpha=1}^{N} \kappa_\alpha(\hat{\boldsymbol{n}}_\alpha)_i$ (see (A.3)).

Notice that (2.17) can also be obtained by imposing the constraint through Lagrange multipliers, as in the case $N=1$. For $N>1$, the constraining force $\boldsymbol{Y}_t$ is also defined by (2.11) and similar computations as in the case $N=1$ yield (2.12) (with $\boldsymbol{H}$ defined by (2.18)).

2.3 Remarks and generalizations

Later on in Section 4, we will see that the free energy calculations involve the following distribution which generalizes (1.5):

$$d\mu_{\Sigma,f}(\boldsymbol{x}) = Z_{\Sigma,f}^{-1}\, e^{-\beta V(\boldsymbol{x})} f(\boldsymbol{x}) d\sigma_\Sigma(\boldsymbol{x}), \tag{2.19}$$

where

$$Z_{\Sigma,f} = \int_\Sigma e^{-\beta V(\boldsymbol{x})} f(\boldsymbol{x}) d\sigma_\Sigma(\boldsymbol{x}), \tag{2.20}$$

and $f:\mathbb{R}^n \to (0,\infty)$ is a $\mathcal{C}^2$-function to be defined, with a growth condition at infinity consistent with $Z_{\Sigma,f}<\infty$. Obviously $\mu_\Sigma \equiv \mu_{\Sigma,1}$ and

$$I_{\Sigma,f}(\phi) = \int_\Sigma \phi(\boldsymbol{x}) d\mu_{\Sigma,f}(\boldsymbol{x}) = \frac{I_\Sigma(f\phi)}{I_\Sigma(f)}.$$

On the other hand, sampling with respect to (2.19) can also be straightforwardly performed upon noting that the measure $\mu_{\Sigma,f}$ associated with the potential V is simply the measure μ_Σ associated with the potential

$$V_f = V - \beta^{-1}\ln f. \tag{2.21}$$

In other words, a diffusion allowing to sample $\mu_{\Sigma,f}$ is provided by (2.17) in which V_f is substituted for V, that is

$$\begin{aligned} d\boldsymbol{X}_t = P(\boldsymbol{X}_t)\Big(&-\nabla(V-\beta^{-1}\ln f)(\boldsymbol{X}_t)\,dt + \sqrt{2\beta^{-1}}\,d\boldsymbol{W}_t\Big) \\ &- \beta^{-1}\sum_{\alpha=1}^{N} \kappa_\alpha(\boldsymbol{X}_t)\hat{\boldsymbol{n}}_\alpha(\boldsymbol{X}_t)\,dt. \end{aligned} \tag{2.22}$$

In Section 4, we will see that the measure $\mu_{\Sigma,|\det G|^{-1/2}}$ (corresponding to the specific choice $f=|\det G|^{-1/2}$) naturally arises in the context of free energy calculations.

Let us describe another instance where the stochastic differential equation (2.22) with $f = |\det G|^{-1/2}$ also appears. Consider

$$dX_t^\eta = -\nabla V(X_t^\eta)\,dt - \frac{1}{2\eta}\sum_{\alpha=1}^N \nabla(q_\alpha^2)(X_t^\eta)\,dt + \sqrt{2\beta^{-1}}dW_t, \tag{2.23}$$

where $\eta > 0$ is a parameter. The additional term involving $\nabla(q_\alpha^2)$ in (2.23) is a penalty term which constraints X_t in the vicinity of $\Sigma = \{x : q(x) = 0\}$. Letting $\eta \to 0$ amounts to imposing the constraint that $X_t \in \Sigma$ a.s. In fact, we prove in Appendix C (in the case $N = 1$) that the limit process X_t of X_t^η when $\eta \to 0$ is solution of the stochastic differential equation:

$$\begin{aligned} dX_t = P(X_t)\Big(&-\nabla\left(V + \beta^{-1}\ln|\det G|^{1/2}\right)(X_t)\,dt + \sqrt{2\beta^{-1}}\,dW_t\Big) \\ &- \beta^{-1}\sum_{\alpha=1}^N \kappa_\alpha(X_t)\hat{n}_\alpha(X_t)\,dt. \end{aligned} \tag{2.24}$$

This equation is not (2.17). Rather it is a special case of (2.22) for $f = |\det G|^{-1/2}$, *i.e.* X_t samples the distribution $\mu_{\Sigma,|\det G|^{-1/2}}$.

Notice that the measure μ_Σ depends on q_α only through its zero set (which defines Σ). The values of q_α around Σ are irrelevant. In this sense, μ_Σ is an intrinsic quantity. Accordingly the stochastic differential equation (2.17) (and in particular the mean curvature vector H) can be defined knowing only Σ. In contrast, the measure $\mu_{\Sigma,|\det G|^{-1/2}}$ also depends on the values of q_α around Σ. In this sense, it is a non-intrinsic quantity. Because the constraints are softly imposed in (2.24) (and not rigidly as in (2.4)), in the limit as $\eta \to 0$ the limiting process X_t still "sees" the variation of q_α around Σ, through the term $\ln|\det G|^{-1/2}$ in the modified potential $V_{|\det G|^{-1/2}}$.

REMARK 2.3 (Rigidly and softly constrained dynamics) *The fact that the statistics at equilibrium associated with the rigidly constrained dynamics (2.4) and the softly constrained dynamics (2.24) are not identical is related to an apparent paradox which has been often discussed in the literature, about the different statistics at equilibrium of rigid and stiff bonds in bead spring models: see [27] p. 228, Section 4.6 in [28], [20], [15], [31], or paragraph 3 in [26]. We here exhibit the difference between statistical properties of rigidly and softly constrained dynamics in the framework of over-damped Langevin dynamics, but this question has also been discussed either in the framework of Hamiltonian systems at equilibrium (in the canonical ensemble) or in the non-zero-mass Langevin dynamics framework (see e.g. [30, 9, 19, 18]).*

3 Numerical schemes

In this section, we construct numerical schemes which satisfy exactly the constraint $\boldsymbol{q}(\boldsymbol{x}) = 0$ since we have in mind long-time simulations for computing $I_\Sigma(\phi)$ (defined by (1.7)) by a mean over a sample path. For more general results on the consistency of these schemes, we refer to [24]. We suppose in this section that $\boldsymbol{q}(\boldsymbol{X}_0) = 0$. We have:

PROPOSITION 3.1 *The following two schemes are consistent with (2.17):*

$$\left\{\begin{aligned} &\boldsymbol{X}_{n+1} = \boldsymbol{X}_n - \nabla V(\boldsymbol{X}_n)\,\Delta t + \sqrt{2\beta^{-1}}\Delta \boldsymbol{W}_n \\ &\qquad\qquad + \sum_{\alpha=1}^{N} \lambda_{\alpha,n} \nabla q_\alpha(\boldsymbol{X}_{n+1}), \\ &\textit{where}\ \ \lambda_{\alpha,n}\ \textit{such that}\ \boldsymbol{q}(\boldsymbol{X}_{n+1}) = 0, \end{aligned}\right. \tag{3.1}$$

and

$$\left\{\begin{aligned} &\boldsymbol{X}_{n+1} = \boldsymbol{X}_n - \nabla V(\boldsymbol{X}_n)\,\Delta t + \sqrt{2\beta^{-1}}\Delta \boldsymbol{W}_n \\ &\qquad\qquad + \sum_{\alpha=1}^{N} \lambda_{\alpha,n} \nabla q_\alpha(\boldsymbol{X}_{n}), \\ &\textit{where}\ \ \lambda_{\alpha,n}\ \textit{such that}\ \boldsymbol{q}(\boldsymbol{X}_{n+1}) = 0, \end{aligned}\right. \tag{3.2}$$

where $\Delta \boldsymbol{W}_n = \boldsymbol{W}_{t_{n+1}} - \boldsymbol{W}_{t_n}$ *denotes the Brownian increment.*

The proof of the Proposition is given at the end of this section. The semi-implicit scheme in (3.1) can in fact be rewritten in a variational formulation as follows:

$$\left\{\begin{aligned} &\boldsymbol{X}_\star = \boldsymbol{X}_n - \nabla V(\boldsymbol{X}_n)\,\Delta t + \sqrt{2\beta^{-1}}\Delta \boldsymbol{W}_n, \\ &\boldsymbol{X}_{n+1} = \underset{\boldsymbol{Y}\in\mathbb{R}^n}{\arg\min} \left\{ |\boldsymbol{X}_\star - \boldsymbol{Y}|^2 : \boldsymbol{q}(\boldsymbol{Y}) = 0 \right\}. \end{aligned}\right. \tag{3.3}$$

In this case, the $\lambda_{\alpha,n}$ can be interpreted as scalar Lagrange multipliers associated with the constraint $\boldsymbol{q}(\boldsymbol{X}_{n+1}) = 0$. We expect the scheme (3.1) to exhibit better stability properties than the scheme (3.2) since it admits a variational interpretation.

In practice, in order (3.1), (3.2) and (3.3) to be well-posed, we need Δt to be sufficiently small so that $\boldsymbol{X}_\star$ is not "too far" from the manifold Σ. To solve Problem (3.1), one can use classical methods for optimization problems with constraints. We refer to [16] for a presentation of the classical Uzawa algorithm, and to [4] for more advanced methods. To solve

Problem (3.2), one can use classical methods to solve nonlinear problems (like Newton method, see [4]). We also refer to Chapter 7 of [25] where similar problems are discussed.

In the following, we will admit that the schemes (3.1), (3.2) and (3.3) are well posed and indeed convergent (in the mean square sense for example), namely that the trajectory $(\boldsymbol{X}_0, \dots, \boldsymbol{X}_M)$ where $M = T/\Delta t$ converges when $\Delta t \to 0$ (for a fixed T) to $(\boldsymbol{X}_s)_{0 \le s \le T}$ which satisfies (2.17). Since $(\boldsymbol{X}_t)_{t \ge 0}$ is ergodic with respect to μ_Σ (see Proposition 2.2), the schemes (3.1) and (3.2) can be used to sample μ_Σ and to compute quantities such as (1.7). In Section 4, we more specifically discuss how they allow the computation of free energy differences and mean forces.

REMARK 3.2 (Computation of $\nabla V_{|\det G|^{-1/2}}$) *As mentioned earlier, in the context of free energy calculations (see Section 4), the distribution $\mu_{\Sigma, |\det G|^{-1/2}}$ (corresponding to the specific choice $f = |\det G|^{-1/2}$ in (2.19)) arises naturally and this amount to replacing V by $V_{|\det G|^{-1/2}}$ in (3.1) or (3.2). Since $V_{|\det G|^{-1/2}} = V - \beta^{-1} \ln |\det G|^{-1/2}$, this requires the computation of the following term:*

$$\begin{aligned}
&\beta^{-1} \nabla \ln \left(|\det G|^{-1/2} \right) (\boldsymbol{X}_n) \Delta t \\
&\quad = -\frac{1}{2} \beta^{-1} \sum_{\alpha, \zeta} \left(G^{-1}_{\alpha,\zeta} \nabla G_{\alpha,\zeta} \right) (\boldsymbol{X}_n) \Delta t, \\
&\quad = -\beta^{-1} \sum_{\alpha, \zeta} \left(G^{-1}_{\alpha,\zeta} \nabla^2 q_\alpha \nabla q_\zeta \right) (\boldsymbol{X}_n) \Delta t,
\end{aligned} \tag{3.4}$$

where we used Jacobi's formula: for a given tensor M,

$$\nabla \ln(\det M) = \sum_{\alpha,\zeta} M^{-1}_{\alpha,\zeta} \nabla M_{\zeta,\alpha}. \tag{3.5}$$

In order to avoid the computation of $\nabla^2 q_\alpha(\boldsymbol{X}_n)$ which is cumbersome, one can approximate (3.4) by:

$$\begin{aligned}
&- \beta^{-1} \sum_{\alpha,\zeta} \left(G^{-1}_{\alpha,\zeta} \nabla^2 q_\alpha \nabla q_\zeta \right) (\boldsymbol{X}_n) \Delta t \\
&= -\beta^{-1} \sum_{\alpha,\zeta=1}^{N} G^{-1}_{\alpha,\zeta}(\boldsymbol{X}_n) (\nabla q_\alpha \left(\boldsymbol{X}_n + \Delta t \nabla q_\zeta(\boldsymbol{X}_n) \right) - \nabla q_\alpha(\boldsymbol{X}_n)) + o(\Delta t).
\end{aligned} \tag{3.6}$$

The proof of Proposition 3.1 relies on the following Lemma which gives expansions of the $\lambda_{\alpha,n}$ appearing in (3.1) and (3.2).

LEMMA 3.3 *Let $\boldsymbol{X}_n$ be the solution of (3.1) or (3.2). Then $\lambda_{\alpha,n}$ is such that:*

$$\lambda_{\alpha,n} = \lambda^0_{\alpha,n}\sqrt{\Delta t} + \lambda^1_{\alpha,n}\Delta t + o(\Delta t), \tag{3.7}$$

with

$$\lambda^0_{\alpha,n} = -\sqrt{2\beta^{-1}}\sum_{\zeta=1}^{N} G^{-1}_{\alpha,\zeta}\nabla q_\zeta(\boldsymbol{X}_n)\cdot \boldsymbol{w}_n, \tag{3.8}$$

where $\boldsymbol{w}_n = \Delta \boldsymbol{W}_n/\sqrt{\Delta t}$ are i.i.d. Gaussian variables in $\mathbb{R}^n$ with zero mean and variance Id, and

$$\begin{aligned}\lambda^1_{\alpha,n} &= \sum_{\zeta=1}^{N} G^{-1}_{\alpha,\zeta}\nabla q_\zeta\cdot\nabla V(\boldsymbol{X}_n)\\ &\quad+\beta^{-1}\sum_{\zeta,\delta=1}^{N} G^{-1}_{\alpha,\zeta}G^{-1}_{\gamma,\delta}\nabla^2 q_\zeta : \nabla q_\gamma\otimes\nabla q_\delta(\boldsymbol{X}_n)\\ &\quad-\beta^{-1}\sum_{\zeta=1}^{N} G^{-1}_{\alpha,\zeta}\Delta q_\zeta(\boldsymbol{X}_n).\end{aligned} \tag{3.9}$$

PROOF OF LEMMA 3.3: For the sake of brevity we only present the proof of Lemma 3.3 for the scheme (3.1). The proof for the scheme (3.2) is similar.

The Lagrange multipliers $\lambda_{\alpha,n}$ are obtained by requiring that $q(\boldsymbol{X}_{n+1}) = 0$ if $q(\boldsymbol{X}_n) = 0$. Using (3.1) as well as the *a priori* expansion (3.7) of $\lambda_{\alpha,n}$, this is equivalent to requiring that: for any $1\le\zeta\le N$,

$$\begin{aligned}0 &= q_\zeta(\boldsymbol{X}_{n+1}),\\ &= \nabla q_\zeta(\boldsymbol{X}_n)\cdot\Big(-\nabla V(\boldsymbol{X}_n)\,\Delta t + \sqrt{2\beta^{-1}}\Delta\boldsymbol{W}_n\\ &\qquad\qquad + (\lambda^0_{\alpha,n}\sqrt{\Delta t} + \lambda^1_{\alpha,n}\Delta t)\nabla q_\alpha(\boldsymbol{X}_{n+1})\Big)\\ &\quad+\frac{1}{2}\boldsymbol{K}_n^T\nabla^2 q_\zeta(\boldsymbol{X}_n)\boldsymbol{K}_n + o(\Delta t),\end{aligned} \tag{3.10}$$

where $\boldsymbol{K}_n = \sqrt{2\beta^{-1}}\Delta\boldsymbol{W}_n + \lambda^0_{\alpha,n}\sqrt{\Delta t}\nabla q_\alpha(\boldsymbol{X}_{n+1})$. Since

$$\nabla q_\alpha(\boldsymbol{X}_{n+1}) = \nabla q_\alpha(\boldsymbol{X}_n) + \nabla^2 q_\alpha(\boldsymbol{X}_n)\overline{\boldsymbol{K}}_n + o(\sqrt{\Delta t}),$$

where $\overline{\boldsymbol{K}}_n = \sqrt{2\beta^{-1}}\Delta \boldsymbol{W}_n + \lambda^0_{\alpha,n}\sqrt{\Delta t}\nabla q_\alpha(\boldsymbol{X}_n)$, equating terms of equal order in Δt in (3.10) gives

$$\begin{cases} 0 = \sqrt{2\beta^{-1}}\nabla q_\zeta(\boldsymbol{X}_n)\cdot \Delta \boldsymbol{W}_n + \lambda^0_{\alpha,n}\sqrt{\Delta t}\, G_{\alpha,\zeta}(\boldsymbol{X}_n), \\ 0 = -\nabla q_\zeta(\boldsymbol{X}_n)\cdot \nabla V(\boldsymbol{X}_n)\Delta t + \lambda^1_{\alpha,n} G_{\alpha,\zeta}(\boldsymbol{X}_n)\Delta t \\ \qquad + \sqrt{\Delta t}\lambda^0_{\alpha,n}(\nabla q_\zeta)^T\nabla^2 q_\alpha(\boldsymbol{X}_n)\overline{\boldsymbol{K}}_n + \dfrac{1}{2}\overline{\boldsymbol{K}}_n^T\nabla^2 q_\zeta(\boldsymbol{X}_n)\overline{\boldsymbol{K}}_n. \end{cases}$$

From this, we obtain formula (3.8) for $\lambda^n_{0,\alpha}$ and the following expression for $\lambda^n_{1,\alpha}$:

$$\begin{aligned} \lambda^1_{\alpha,n} = {} & G^{-1}_{\alpha,\zeta}\nabla q_\zeta\cdot\nabla V(\boldsymbol{X}_n) \\ & - G^{-1}_{\alpha,\zeta}\lambda^0_{\gamma,n}\lambda^0_{\delta,n}\nabla^2 q_\gamma : \nabla q_\zeta\otimes\nabla q_\delta(\boldsymbol{X}_n) \\ & - \tfrac{1}{2}G^{-1}_{\alpha,\zeta}\lambda^0_{\gamma,n}\lambda^0_{\delta,n}\nabla^2 q_\zeta : \nabla q_\gamma\otimes\nabla q_\delta(\boldsymbol{X}_n) \\ & - \sqrt{2\beta^{-1}}\, G^{-1}_{\alpha,\zeta}\,\lambda^0_{\gamma,n}\,\nabla^2 q_\gamma(\boldsymbol{X}_n) : \nabla q_\zeta\otimes\boldsymbol{w}_n \\ & - \sqrt{2\beta^{-1}}\, G^{-1}_{\alpha,\zeta}\,\lambda^0_{\gamma,n}\,\nabla^2 q_\zeta(\boldsymbol{X}_n) : \nabla q_\gamma\otimes\boldsymbol{w}_n \\ & - \beta^{-1}\, G^{-1}_{\alpha,\zeta}\nabla^2 q_\zeta(\boldsymbol{X}_n) : \boldsymbol{w}_n\otimes\boldsymbol{w}_n. \end{aligned}$$

We now use (3.8) in this expression together with the fact that in the limit as $\Delta t\to 0$, $\boldsymbol{w}_n\otimes\boldsymbol{w}_n = \mathrm{Id}$ since $\boldsymbol{w}_n$ is always multiplied by $\mathcal{F}_{n\Delta t}$ measurable functions. For example, we have in the limit $\Delta t\to 0$,

$$\begin{aligned} \lambda^0_{\gamma,n}\lambda^0_{\delta,n} &= 2\beta^{-1}\Delta t^{-1}G^{-1}_{\gamma,\gamma'}\nabla q_{\gamma'}(\boldsymbol{X}_n)\cdot\Delta\boldsymbol{W}_n G^{-1}_{\delta,\delta'}\nabla q_{\delta'}(\boldsymbol{X}_n)\cdot\Delta\boldsymbol{W}_n, \\ &= 2\beta^{-1}\, G^{-1}_{\gamma,\gamma'}\, G^{-1}_{\delta,\delta'}\, G_{\gamma',\delta'}(\boldsymbol{X}_n) + o(1) = 2\beta^{-1}\, G^{-1}_{\gamma,\delta}(\boldsymbol{X}_n) + o(1). \end{aligned}$$

We thus obtain the following expression for $\lambda^n_{1,\alpha}$:

$$\begin{aligned} \lambda^1_{\alpha,n} = {} & G^{-1}_{\alpha,\zeta}\nabla q_\zeta\cdot\nabla V(\boldsymbol{X}_n) \\ & - 2\beta^{-1}G^{-1}_{\alpha,\zeta}G^{-1}_{\gamma,\delta}\nabla^2 q_\gamma : \nabla q_\zeta\otimes\nabla q_\delta(\boldsymbol{X}_n) \\ & - \beta^{-1}G^{-1}_{\alpha,\zeta}G^{-1}_{\gamma,\delta}\nabla^2 q_\zeta : \nabla q_\gamma\otimes\nabla q_\delta(\boldsymbol{X}_n) \\ & + 2\beta^{-1}\, G^{-1}_{\alpha,\zeta}G^{-1}_{\gamma,\delta}\,\nabla^2 q_\gamma : \nabla q_\delta\otimes\nabla q_\zeta(\boldsymbol{X}_n) \\ & + 2\beta^{-1}\, G^{-1}_{\alpha,\zeta}\, G^{-1}_{\gamma,\delta}\,\nabla^2 q_\zeta : \nabla q_\delta\otimes\nabla q_\gamma(\boldsymbol{X}_n) \\ & - \beta^{-1}\, G^{-1}_{\alpha,\zeta}\Delta q_\zeta(\boldsymbol{X}_n) + o(1), \end{aligned}$$

from which we deduce (3.9). ∎

We are now in position to prove Proposition 3.1.

Proof of Proposition 3.1: Let us first consider the scheme (3.1) (or, equivalently, (3.3)). To check its consistency with (2.17), we compute the value of the term $\lambda_{\alpha,n}\nabla q_\alpha(\boldsymbol{X}_{n+1})\Delta t$ using the expressions for $\lambda^0_{\alpha,n}$ and $\lambda^1_{\alpha,n}$ given in Lemma 3.3. and the property that $\Delta\boldsymbol{W}_n\otimes\Delta\boldsymbol{W}_n = \mathrm{Id}\,\Delta t$ in the limit as $\Delta t\to 0$, since $\Delta\boldsymbol{W}_n$ is always multiplied by $\mathcal{F}_{n\Delta t}$ measurable functions. This gives

$$
\begin{aligned}
&\lambda_{\alpha,n}\nabla q_\alpha(\boldsymbol{X}_{n+1})\\
&= \left(\lambda^0_{\alpha,n}\sqrt{\Delta t} + \lambda^1_{\alpha,n}\Delta t\right)\nabla q_\alpha(\boldsymbol{X}_n)\\
&\quad + \lambda^0_{\alpha,n}\sqrt{\Delta t}\nabla^2 q_\alpha(\boldsymbol{X}_n)\left(\sqrt{2\beta^{-1}}\Delta\boldsymbol{W}_n + \lambda^0_{\gamma,n}\sqrt{\Delta t}\nabla q_\gamma(\boldsymbol{X}_n)\right) + o(\Delta t),\\
&= -\sqrt{2\beta^{-1}}G^{-1}_{\alpha,\zeta}\nabla q_\alpha\nabla q_\zeta(\boldsymbol{X}_n)\cdot\Delta\boldsymbol{W}_n + G^{-1}_{\alpha,\zeta}\nabla q_\alpha\nabla q_\zeta\cdot\nabla V(\boldsymbol{X}_n)\Delta t\\
&\quad + \beta^{-1}G^{-1}_{\alpha,\zeta}\nabla q_\alpha G^{-1}_{\gamma,\delta}\nabla^2 q_\zeta : \nabla q_\gamma\otimes\nabla q_\delta(\boldsymbol{X}_n)\Delta t\\
&\quad - \beta^{-1}\,G^{-1}_{\alpha,\zeta}\nabla q_\alpha\Delta q_\zeta(\boldsymbol{X}_n)\Delta t - 2\beta^{-1}G^{-1}_{\alpha,\zeta}\nabla^2 q_\alpha\nabla q_\zeta(\boldsymbol{X}_n)\Delta t\\
&\quad + 2\beta^{-1}\,G^{-1}_{\gamma,\alpha}\nabla^2 q_\alpha\nabla q_\gamma(\boldsymbol{X}_n)\Delta t + o(\Delta t),\\
&= (P(\boldsymbol{X}_n)-\mathrm{Id})\left(-\nabla V(\boldsymbol{X}_n)\Delta t + \sqrt{2\beta^{-1}}\Delta\boldsymbol{W}_n\right)\\
&\quad - \beta^{-1}\nabla q_\alpha G^{-1}_{\alpha,\zeta}\left(-G^{-1}_{\gamma,\delta}\nabla^2 q_\zeta : \nabla q_\gamma\otimes\nabla q_\delta(\boldsymbol{X}_n) + \Delta q_\zeta(\boldsymbol{X}_n)\right)\Delta t + o(\Delta t),\\
&= (P(\boldsymbol{X}_n)-\mathrm{Id})\left(-\nabla V(\boldsymbol{X}_n)\Delta t + \sqrt{2\beta^{-1}}\Delta\boldsymbol{W}_n\right)\\
&\quad - \beta^{-1}\kappa_\alpha\hat{\boldsymbol{n}}_\alpha(\boldsymbol{X}_n)\Delta t + o(\Delta t).
\end{aligned}
$$

This shows that (3.1) is equivalent to

$$
\begin{aligned}
\boldsymbol{X}_{n+1} = \boldsymbol{X}_n + P(\boldsymbol{X}_n)&\left(-\nabla V(\boldsymbol{X}_n)\Delta t + \sqrt{2\beta^{-1}}\Delta\boldsymbol{W}_n\right)\\
&- \beta^{-1}\kappa_\alpha\hat{\boldsymbol{n}}_\alpha(\boldsymbol{X}_n)\Delta t + o(\Delta t),
\end{aligned}
\tag{3.11}
$$

which is a consistent discretization of (2.17).

We now consider the scheme (3.2). In this case, using the expressions for $\lambda^0_{\alpha,n}$ and $\lambda^1_{\alpha,n}$ given in Lemma 3.3, we obtain

$$\begin{aligned}
&\lambda_{\alpha,n}\nabla q_\alpha(\boldsymbol{X}_n)\\
&= \left(\lambda^0_{\alpha,n}\sqrt{\Delta t}+\lambda^1_{\alpha,n}\Delta t\right)\nabla q_\alpha(\boldsymbol{X}_n)+o(\Delta t),\\
&= -\sqrt{2\beta^{-1}}G^{-1}_{\alpha,\zeta}\nabla q_\alpha\nabla q_\zeta(\boldsymbol{X}_n)\cdot\Delta\boldsymbol{W}_n+G^{-1}_{\alpha,\zeta}\nabla q_\alpha\nabla q_\zeta\cdot\nabla V(\boldsymbol{X}_n)\Delta t\\
&\quad+\beta^{-1}G^{-1}_{\alpha,\zeta}\nabla q_\alpha G^{-1}_{\gamma,\delta}\nabla^2 q_\zeta:\nabla q_\gamma\otimes\nabla q_\delta(\boldsymbol{X}_n)\Delta t\\
&\quad-\beta^{-1}\,G^{-1}_{\alpha,\zeta}\nabla q_\alpha\Delta q_\zeta(\boldsymbol{X}_n)\Delta t+o(\Delta t),\\
&= (P(\boldsymbol{X}_n)-\mathrm{Id})\left(-\nabla V(\boldsymbol{X}_n)\Delta t+\sqrt{2\beta^{-1}}\Delta\boldsymbol{W}_n\right)\\
&\quad-\beta^{-1}\kappa_\alpha\hat{\boldsymbol{n}}_\alpha(\boldsymbol{X}_n)\Delta t+o(\Delta t),
\end{aligned}$$

which shows that (3.2) is also equivalent to (3.11) and proves that this scheme is consistent with (2.17). ∎

4 Free energy calculations

In this section, we discuss the computation of free energy differences, defined in Section 4.1, and more precisely of the gradient of the free energy, the so-called *mean force*. In Section 4.2, we give an explicit expression for the mean force and exhibit a link between the mean force and the constraining force $\boldsymbol{Y}_t$ defined by (2.11)–(2.12). We then use this link to build a numerical scheme to compute the mean force in Section 4.3. A variance reduction method is proposed in Section 4.4. In this section, we assume that no molecular constraints are present: for completeness, the situation with molecular constraints is discussed in Appendix D.

In this paper, we describe the computation of free energy differences by imposing the reaction coordinate at a fixed value (this is the so-called Thermodynamic Integration, see [22]). Note that it is also possible to compute free energy differences by prescribing an evolution of the reaction coordinate, in the spirit of Jarzinski equality (see [21, 23]).

4.1 Definition

Let $\boldsymbol{X}\in\mathbb{R}^n$ denote the random variable whose distribution is the Boltzmann-Gibbs distribution (1.2). Given $\boldsymbol{q}=(q_1,\ldots,q_N)$ where $q_\alpha:\mathbb{R}^n\to\mathbb{R}$ for each $1\le\alpha\le N$, the quantity

$$\boldsymbol{Z}=\boldsymbol{q}(\boldsymbol{X}) \tag{4.1}$$

is a random variable in $\mathbb{R}^N$. Let us denote by $m(\boldsymbol{z})$ the probability density function (with respect to the Lebesgue measure on $\mathbb{R}^N$) of $\boldsymbol{Z}$. Then, by definition, the quantity

$$F(\boldsymbol{z}) = -\beta^{-1} \ln m(\boldsymbol{z}) \tag{4.2}$$

is called *the free energy* associated with $\boldsymbol{q}$, which is called *the reaction coordinate*. The free energy is directly relevant to compute expectations of observables depending on $\boldsymbol{x}$ only implicitly via $\boldsymbol{q}$, since by construction

$$\int_{\mathbb{R}^n} \phi(\boldsymbol{q}(\boldsymbol{x})) d\mu(\boldsymbol{x}) = \int_{\mathbb{R}^N} \phi(\boldsymbol{z}) e^{-\beta F(\boldsymbol{z})} d\boldsymbol{z}. \tag{4.3}$$

Let us now introduce the following generalization of Fubini's theorem, derived from the co-area formula (see Theorem 2 p. 117 of [14]): if $\boldsymbol{q} : \mathbb{R}^n \to \mathbb{R}^N$ is Lipschitz and $g : \mathbb{R}^n \to \mathbb{R}$ is a function in $L^1(\mathbb{R}^n)$, then

$$\int_{\mathbb{R}^n} g(\boldsymbol{x}) |\det G(\boldsymbol{x})|^{1/2} \, d\boldsymbol{x} = \int_{\mathbb{R}^N} \int_{\Sigma(\boldsymbol{z})} g(\boldsymbol{x}) d\sigma_{\Sigma(\boldsymbol{z})}(\boldsymbol{x}) d\boldsymbol{z}. \tag{4.4}$$

Here $\Sigma(\boldsymbol{z}) = \{\boldsymbol{x} : \boldsymbol{q}(\boldsymbol{x}) = \boldsymbol{z}\}$, $\sigma_{\Sigma(\boldsymbol{z})}$ is the $(n-N)$-dimensional Hausdorff measure, which reduces in our case to the Lebesgue measure on $\Sigma(\boldsymbol{z})$ since $\boldsymbol{q}$ is regular, and G is the matrix defined in (1.11) which we recall for convenience

$$G_{\alpha,\zeta}(\boldsymbol{x}) = \nabla q_\alpha(\boldsymbol{x}) \cdot \nabla q_\zeta(\boldsymbol{x}), \qquad 1 \le \alpha, \zeta \le N.$$

Using (4.4) and the definition (1.2) of μ, we have:

$$\begin{aligned} &\int_{\mathbb{R}^n} \phi(\boldsymbol{q}(\boldsymbol{x})) d\mu(\boldsymbol{x}) \\ &\quad = \int_{\mathbb{R}^N} \phi(\boldsymbol{z}) \Big(Z^{-1} \int_{\Sigma(\boldsymbol{z})} e^{-\beta V(\boldsymbol{x})} |\det G(\boldsymbol{x})|^{-1/2} d\sigma_{\Sigma(\boldsymbol{z})}(\boldsymbol{x}) \Big) d\boldsymbol{z}. \end{aligned} \tag{4.5}$$

Therefore, by comparing (4.3) and (4.5) we deduce that $F(\boldsymbol{z})$ is given by

$$F(\boldsymbol{z}) = -\beta^{-1} \ln \Big(Z^{-1} \int_{\Sigma(\boldsymbol{z})} e^{-\beta V(\boldsymbol{x})} |\det G(\boldsymbol{x})|^{-1/2} d\sigma_{\Sigma(\boldsymbol{z})}(\boldsymbol{x}) \Big). \tag{4.6}$$

Equation (4.6) can also be written as

$$F(\boldsymbol{z}) = -\beta^{-1} \ln \left(Z^{-1} Z_{\Sigma(\boldsymbol{z}), |\det G|^{-1/2}} \right) \tag{4.7}$$

where $Z_{\Sigma(\boldsymbol{z}), |\det G|^{-1/2}}$ is the normalization factor associated with the distribution $\mu_{\Sigma(\boldsymbol{z}), |\det G|^{-1/2}}$ (see (2.19)). In other words, computing the mean force amounts to computing some partition functions.

4.2 The mean force

In practice, a way to compute the free energy F defined by (4.6) (or (4.7)) is to compute first its gradient, since the latter can be expressed as an expectation over the distribution $\mu_{\Sigma(\boldsymbol{z}),|\det G|^{-1/2}}$ (see Lemma 4.1 below). The gradient of F is usually referred to as *the mean force*, and it can be expressed via the following:

LEMMA 4.1 *The gradient of F (namely the mean force) can be expressed as: for any $1 \leq \alpha \leq N$,*

$$\nabla_\alpha F(\boldsymbol{z})$$

$$= \sum_{\gamma=1}^{N} \int_{\Sigma(\boldsymbol{z})} \Big(\nabla V \cdot G^{-1}_{\alpha,\gamma} \nabla q_\gamma - \beta^{-1} \nabla \cdot (G^{-1}_{\alpha,\gamma} \nabla q_\gamma) \Big) \, d\mu_{\Sigma(\boldsymbol{z}),|\det G|^{-1/2}}, \tag{4.8}$$

$$= \sum_{\gamma=1}^{N} \int_{\Sigma(\boldsymbol{z})} G^{-1}_{\alpha,\gamma} \nabla q_\gamma \cdot \Big(\nabla V_{|\det G|^{-1/2}} + \beta^{-1} \boldsymbol{H} \Big) \, d\mu_{\Sigma(\boldsymbol{z}),|\det G|^{-1/2}}. \tag{4.9}$$

The proof of this Lemma is given below. From these two expressions of the mean force, one may use two different methods to compute the mean force. The expression (4.8) of $\nabla_\alpha F$ is rather complicated since it involves the divergence of the inverse of G. However, remarkably enough, we shall show in Section 4.3 that we do not have to compute explicitly this divergence to evaluate $\nabla_\alpha F(\boldsymbol{z})$. This can be done by suitable numerical approximation of (4.8) (together with the approximation (3.6) of $\nabla V_{|\det G|^{-1/2}}$).

On the other hand, the expression (4.9) of $\nabla_\alpha F$ can be used to derive an alternative and even simpler procedure. It is based on the following proposition where $\nabla_\alpha F(\boldsymbol{z})$ is expressed as a mean over the component along ∇q_α (taking $(\nabla q_1, \ldots, \nabla q_N)$ as a basis of the normal space to $\Sigma_{\boldsymbol{z}}$) of the constraining force $\boldsymbol{Y}_t$ (defined by (2.12)), using the corrected potential $V_{|\det G|^{-1/2}}$ (defined by (2.21)) instead of V. This has also been observed in the framework of Hamiltonian dynamics (see [30, 9, 19, 18]).

PROPOSITION 4.2 *Consider the processes $\boldsymbol{X}_t$ and $\boldsymbol{Y}_t$ defined by (2.11) and (2.12), with V replaced by $V_{|\det G|^{-1/2}}$. Then for $1 \leq \alpha \leq N$,*

$$\lim_{T\to\infty} \frac{1}{T} \int_0^T \sum_{\zeta=1}^{N} G^{-1}_{\alpha,\zeta} \nabla q_\zeta(\boldsymbol{X}_t) \cdot d\boldsymbol{Y}_t = \nabla_\alpha F(0), \tag{4.10}$$

a.s. and in L^p*,* $p \geq 1$*.*

PROOF OF LEMMA 4.1: Let Φ by a $\mathcal{C}_c^\infty(\mathbb{R})$ function and $\phi = \Phi'$. Let us consider, for a fixed $1 \leq \alpha \leq N$,

$$\int_{\mathbb{R}^N} \phi(z_\alpha) \exp(-\beta F(\boldsymbol{z}))\, d\boldsymbol{z} = Z^{-1} \int_{\mathbb{R}^n} \phi(q_\alpha(\boldsymbol{x})) e^{-\beta V(\boldsymbol{x})} d\boldsymbol{x},$$

where we have used (4.3) and (1.2). The left-hand side can be expressed as follows (using (4.7)):

$$\begin{aligned}
&\int_{\mathbb{R}^N} \phi(z_\alpha) \exp(-\beta F(\boldsymbol{z}))\, d\boldsymbol{z} \\
&\quad = \int_{\mathbb{R}^N} \Phi'(z_\alpha) \exp(-\beta F(\boldsymbol{z}))\, d\boldsymbol{z}, \\
&\quad = \beta \int_{\mathbb{R}^N} \Phi(z_\alpha) \nabla_\alpha F(\boldsymbol{z}) \exp(-\beta F(\boldsymbol{z}))\, d\boldsymbol{z}, \\
&\quad = \beta Z^{-1} \int_{\mathbb{R}^N} \Phi(z_\alpha) Z_{\Sigma(\boldsymbol{z}), |\det G|^{-1/2}} \nabla_\alpha F(\boldsymbol{z})\, d\boldsymbol{z}.
\end{aligned} \tag{4.11}$$

The right-hand side can be expressed as follows:

$$\begin{aligned}
&Z^{-1} \int_{\mathbb{R}^n} \phi(q_\alpha(\boldsymbol{x})) e^{-\beta V(\boldsymbol{x})} d\boldsymbol{x} \\
&\quad = Z^{-1} \int_{\mathbb{R}^n} \Phi'(q_\alpha(\boldsymbol{x})) e^{-\beta V(\boldsymbol{x})} d\boldsymbol{x}, \\
&\quad = Z^{-1} \int_{\mathbb{R}^n} G^{-1}_{\alpha,\gamma} \nabla q_\gamma \cdot \nabla \left(\Phi \circ q_\alpha\right) (\boldsymbol{x}) e^{-\beta V(\boldsymbol{x})} d\boldsymbol{x}, \\
&\quad = -Z^{-1} \int_{\mathbb{R}^n} \nabla \cdot \left(G^{-1}_{\alpha,\gamma} \nabla q_\gamma e^{-\beta V} \right) (\boldsymbol{x}) \Phi \circ q_\alpha(\boldsymbol{x}) d\boldsymbol{x}, \\
&\quad = Z^{-1} \int_{\mathbb{R}^n} \left(\beta \nabla V \cdot G^{-1}_{\alpha,\gamma} \nabla q_\gamma - \nabla \cdot \left(G^{-1}_{\alpha,\gamma} \nabla q_\gamma \right) \right) (\boldsymbol{x}) e^{-\beta V(\boldsymbol{x})} \Phi(q_\alpha(\boldsymbol{x})) d\boldsymbol{x}, \\
&\quad = Z^{-1} \int_{\mathbb{R}^N} \Phi(z_\alpha) Z_{\Sigma(\boldsymbol{z}), |\det G|^{-1/2}} \\
&\qquad \times \left(\int_{\Sigma(\boldsymbol{z})} \left(\beta \nabla V \cdot G^{-1}_{\alpha,\gamma} \nabla q_\gamma - \nabla \cdot \left(G^{-1}_{\alpha,\gamma} \nabla q_\gamma \right) \right) d\mu_{\Sigma(\boldsymbol{z}), |\det G|^{-1/2}} \right) d\boldsymbol{z},
\end{aligned} \tag{4.12}$$

where we have used (4.4) and (2.19) for the last equality. The fact that (4.11) is equal to (4.12) for all functions Φ completes the proof of (4.8).

To prove (4.9), it remains to show that

$$\begin{aligned}
&\nabla V \cdot G^{-1}_{\alpha,\gamma} \nabla q_\gamma - \beta^{-1} \nabla \cdot (G^{-1}_{\alpha,\gamma} \nabla q_\gamma) \\
&\quad = \nabla V_{|\det G|^{-1/2}} \cdot G^{-1}_{\alpha,\gamma} \nabla q_\gamma + \beta^{-1} G^{-1}_{\alpha,\gamma} \nabla q_\gamma \cdot \boldsymbol{H}.
\end{aligned}$$

Using (2.18) and $V_{|\det G|^{-1/2}} = V + \beta^{-1}\ln\Big(|\det G|^{1/2}\Big)$, this is equivalent to show that:

$$\begin{aligned}
&-\beta^{-1}\nabla\cdot(G^{-1}_{\alpha,\gamma}\nabla q_\gamma)\\
&\quad=\beta^{-1}G^{-1}_{\alpha,\gamma}\nabla q_\gamma\cdot\nabla\ln|\det G|^{1/2}-\beta^{-1}|\nabla q_\alpha|^{-1}\kappa_\alpha,
\end{aligned}$$

which is a direct consequence of the expression (A.5) of κ_α given in Appendix A. ∎

We are now in position to prove Proposition 4.2.

Proof of Proposition 4.2: By replacing V by $V_{|\det G|^{-1/2}}$, the measure sampled by $\boldsymbol{X}_t$ is $\mu_{\Sigma,|\det G|^{-1/2}}$. Moreover, the process $\boldsymbol{Y}_t$ is then defined by

$$\begin{aligned}
d\boldsymbol{Y}_t &= (P(\boldsymbol{X}_t)-\mathrm{Id})\Big(-\nabla V_{|\det G|^{-1/2}}(\boldsymbol{X}_t)\,dt+\sqrt{2\beta^{-1}}d\boldsymbol{W}_t\Big)\\
&\quad+\beta^{-1}\boldsymbol{H}(\boldsymbol{X}_t)\,dt,\qquad \boldsymbol{Y}_0=0.
\end{aligned}$$

Hence, since $(P(\boldsymbol{X})-I)\,G^{-1}_{\alpha,\zeta}\nabla q_\zeta(\boldsymbol{X})=-G^{-1}_{\alpha,\zeta}\nabla q_\zeta(\boldsymbol{X})$, we obtain

$$\begin{aligned}
G^{-1}_{\alpha,\zeta}\nabla q_\zeta(\boldsymbol{X}_t)\cdot d\boldsymbol{Y}_t &= \sum_{\gamma=1}^N G^{-1}_{\alpha,\gamma}\nabla q_\gamma\cdot\Big(\nabla V_{|\det G|^{-1/2}}+\beta^{-1}\boldsymbol{H}\Big)(\boldsymbol{X}_t)\,dt\\
&\quad-\sqrt{2\beta^{-1}}\sum_{\zeta=1}^N G^{-1}_{\alpha,\zeta}\nabla q_\zeta(\boldsymbol{X}_t)\cdot d\boldsymbol{W}_t.
\end{aligned}$$

In the bounded variation part, we recover the expression (4.9) of the mean force. Now, (4.10) follows from the ergodicity of $\boldsymbol{X}_t$ (see (2.5)) and the fact that

$$\lim_{T\to\infty}\frac{1}{T}\int_0^T\sum_{\zeta=1}^N G^{-1}_{\alpha,\zeta}\nabla q_\zeta(\boldsymbol{X}_t)\cdot d\boldsymbol{W}_t=0,$$

by (1.10). ∎

4.3 Computational aspects

We now discuss the computation of the mean force defined by (4.6), using the expressions (4.8) or (4.9). In the following, we suppose that $\boldsymbol{z}=0$, without loss of generality.

The first method we propose is based on (4.8). The first term at the right hand side of (4.8) can be obtained from

$$
\begin{aligned}
&\lim_{T\to\infty}\lim_{\Delta t\to 0}\frac{1}{M}\sum_{m=1}^{M}\sum_{\gamma=1}^{N}\left(\nabla V\cdot G^{-1}_{\alpha,\gamma}\nabla q_\gamma\right)(\boldsymbol{X}_n)\\
&\qquad=\sum_{\gamma=1}^{N}\int_\Sigma \nabla V\cdot G^{-1}_{\alpha,\gamma}\nabla q_\gamma d\mu_{\Sigma,|\det G|^{-1/2}},
\end{aligned}
\tag{4.13}
$$

where $M = T/\Delta t$ and $\boldsymbol{X}_n$ is the solution to (3.1) or to (3.2), with V replaced by $V_{|\det G|^{-1/2}} = V + \beta^{-1}\ln|\det G|^{1/2}$. As for the second term, we have

$$
\begin{aligned}
&-\beta^{-1}\lim_{T\to\infty}\lim_{\Delta t\to 0}\frac{1}{M\Delta t}\sum_{m=1}^{M}\sum_{\gamma=1}^{N}\Big((G^{-1}_{\alpha,\gamma}\nabla q_\gamma)(\boldsymbol{X}_n+\Delta\boldsymbol{W}_n)\\
&\qquad\qquad\qquad\qquad\qquad\qquad-(G^{-1}_{\alpha,\gamma}\nabla q_\gamma)(\boldsymbol{X}_n)\Big)\cdot\Delta\boldsymbol{W}_n\\
&\qquad=-\beta^{-1}\sum_{\gamma=1}^{N}\int_\Sigma\nabla\cdot(G^{-1}_{\alpha,\gamma}\nabla q_\gamma)d\mu_{\Sigma,|\det G|^{-1/2}},
\end{aligned}
\tag{4.14}
$$

where we used the fact that $\Delta\boldsymbol{W}_n\otimes\Delta\boldsymbol{W}_n = \mathrm{Id}\,\Delta t$ in the limit as $\Delta t\to 0$. Equations (4.13) and (4.14) (together with the approximation (3.6)) allow to estimate $\nabla_\alpha F(0)$ without having to compute $\nabla^2 q_\alpha$.

The second method is based on (4.9), and more precisely, on Proposition 4.2. As in the continuous in time case (see (4.10)), the mean force $\nabla_\alpha F(0)$ may be computed by averaging the Lagrange multipliers $\lambda_{\alpha,n}$ entering the algorithms (3.1) or (3.2).

PROPOSITION 4.3 *Let $\boldsymbol{X}_n$ be the solution to (3.1) or to (3.2), with V replaced by $V_{|\det G|^{-1/2}} = V + \beta^{-1}\ln|\det G|^{1/2}$. Then,*

$$
\lim_{T\to\infty}\lim_{\Delta t\to 0}\frac{1}{M\Delta t}\sum_{m=1}^{M}\lambda_{\alpha,m} = \nabla_\alpha F(0),
\tag{4.15}
$$

where $M = T/\Delta t$.

We recall that in practice, in order to compute $\nabla V_{|\det G|^{-1/2}}$, one can resort to a suitable finite difference scheme (see the approximation (3.6)). This proposition is a direct consequence of Proposition 4.2 and the following lemma.

LEMMA 4.4 *Let $\boldsymbol{X}_n$ be the solution to (3.1) or to (3.2). Assume moreover (1.10). Then, for $1 \leq \alpha \leq N$, $\lambda_{\alpha,n}$ is such that*

$$\lim_{\Delta t \to 0} \frac{1}{M\Delta t} \sum_{m=1}^{M} \lambda_{\alpha,m} = \frac{1}{T} \int_0^T \sum_{\zeta=1}^{N} G^{-1}_{\alpha,\zeta} \nabla q_\zeta(\boldsymbol{X}_t) \cdot d\boldsymbol{Y}_t \tag{4.16}$$

with $\boldsymbol{Y}_t$ defined by (2.12) and where $T = M\Delta t$ is fixed, and therefore $M \to \infty$.

REMARK 4.5 (Computation of other energies) *All the preceding computations may be generalized to the following energy:*

$$F_f(\boldsymbol{z}) = -\beta^{-1} \ln \int \exp(-\beta V(\boldsymbol{x}))\, f(\boldsymbol{x})\, d\sigma_{\Sigma(\boldsymbol{z})}(\boldsymbol{x}), \tag{4.17}$$

where f is a given positive function[1] *such that $Z_{\Sigma(\boldsymbol{z}),f} < \infty$. Indeed, in this case, the expression of the gradient of F_f is given by the following formula (which is a generalization of (4.9))*

$$\nabla_\alpha F_f(\boldsymbol{z}) = \int_{\Sigma(\boldsymbol{z})} \sum_{\gamma=1}^{N} G^{-1}_{\alpha,\gamma} \nabla q_\gamma \cdot \left(\nabla V_f + \beta^{-1} \boldsymbol{H} \right) d\mu_{\Sigma(\boldsymbol{z}),f}, \tag{4.18}$$

where the modified potential V_f is defined by (2.21).

Suppose now that we use in our numerical schemes (3.1) or (3.2) the potential V_f instead of V. Then, following the arguments of Section 4.3 we obtain that the mean of the Lagrange multipliers converges to the mean force (written here for $\boldsymbol{z} = 0$): for $1 \leq \alpha \leq N$,

$$\lim_{T \to \infty} \lim_{\Delta t \to 0} \frac{1}{M\Delta t} \sum_{m=1}^{M} \lambda_{\alpha,m} = \nabla_\alpha F_f(0), \tag{4.19}$$

where $M = T/\Delta t$.

PROOF OF LEMMA 4.4: Using Lemma 3.3, we have

$$\begin{aligned}
&\lim_{\Delta t \to 0} \frac{1}{M\Delta t} \sum_{m=1}^{M} \lambda_{\alpha,m} \\
&= \frac{1}{T}\int_0^T G^{-1}_{\alpha,\zeta} \left(\nabla q_\zeta \cdot \nabla V + \beta^{-1} G^{-1}_{\gamma,\delta} \nabla^2 q_\zeta : \nabla q_\gamma \otimes \nabla q_\delta - \beta^{-1} \Delta q_\zeta \right) (\boldsymbol{X}_t)\, dt \\
&\qquad - \sqrt{2\beta^{-1}} \frac{1}{T} \int_0^T G^{-1}_{\alpha,\zeta} \nabla q_\zeta(\boldsymbol{X}_t) \cdot d\boldsymbol{W}_t.
\end{aligned}$$

[1] With this notation, the free energy defined by (4.6) is $F_{|\det G|^{-1/2}}$, up to an additive constant. Notice that this constant does not intervene in the mean force.

Using the fact that $(P(\boldsymbol{X}) - I)\, G^{-1}_{\alpha,\zeta} \nabla q_\zeta(\boldsymbol{X}) = -G^{-1}_{\alpha,\zeta} \nabla q_\zeta(\boldsymbol{X})$ and

$$G^{-1}_{\alpha,\gamma} \nabla q_\gamma \cdot \boldsymbol{H} = G^{-1}_{\alpha,\zeta} G^{-1}_{\gamma,\delta} \nabla^2 q_\zeta : \nabla q_\gamma \otimes \nabla q_\delta - \, G^{-1}_{\alpha,\zeta} \Delta q_\zeta = \kappa_\alpha$$

one easily obtains (4.16). ∎

4.4 A variance reduction method

In the numerical scheme we have described to compute the mean force (see formula (4.15)), there are three sources of errors: the time discretization error ($\Delta t \to 0$), the longtime limit error ($T \to \infty$) and the statistical error due to the fact that we use a stochastic process. In this section, we focus on the statistical error. It is linked to the the variance of the result. Let us consider the case $N = 1$. We have:

$$\frac{1}{M\Delta t} \sum_{m=1}^{M} \lambda_m = -\sqrt{2\beta^{-1}} \frac{1}{T} \sum_{m=1}^{M} |\nabla q|^{-2} \nabla q(\boldsymbol{X}_n) \cdot \Delta \boldsymbol{W}_n + \frac{1}{T} \sum_{m=1}^{M} \lambda^1_m \Delta t + o(1).$$

In the limit Δt goes to zero, the first term in the right-hand side converges to the martingale part

$$-\sqrt{2\beta^{-1}} \frac{1}{T} \int_0^T |\nabla q|^{-2} \nabla q(\boldsymbol{X}_s) \cdot d\boldsymbol{W}_s$$

of the constraining force $\boldsymbol{Y}_t$, while the second part converges to the bounded variation part of $\boldsymbol{Y}_t$ (see Equation (2.12)). It is the limit, when T goes to infinity, of the second term which yields the mean force $F'(0)$. The first term goes to 0 in the limit $T \to \infty$ but this term is responsible for a large variance of the result.

Therefore, a natural idea to reduce the variance is to eliminate the first term. It is possible to directly compute this term (which is the projection of the Brownian increment) and to subtract it from the Lagrange multiplier. Alternatively, the following scheme, which is very easy to implement, may be used. We consider that $t = t_n$ and we denote by $\lambda(\Delta \boldsymbol{W}_n)$ the Lagrange multiplier obtained from (3.1) or (3.2) with a Brownian increment $\Delta \boldsymbol{W}_n$. The next position $\boldsymbol{X}_{n+1}$ is defined by (3.1) or (3.2), but the Lagrange multiplier used in formula (4.15) is now defined as:

$$\lambda_n = \frac{1}{2} \left(\lambda(\Delta \boldsymbol{W}_n) + \lambda(-\Delta \boldsymbol{W}_n) \right).$$

One can check that this does not change the value of the bounded variation part λ_n^1 of λ_n, but "eliminates" the martingale part λ_n^0. This method reminds us of the antithetic variables variance reduction method classically used in Monte Carlo methods. In practice, this method seems to be very efficient (see [23]). This idea can be straightforwardly generalized to the case $N > 1$.

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A Some useful identities

Here we give some useful identities that were used in text.

LEMMA A.1 (Scalar constraint case, $N = 1$) *We define by (2.2) the orthogonal projection $P(\boldsymbol{x})$ on the tangent space of $\Sigma = \{\boldsymbol{x}, q(\boldsymbol{x}) = 0\}$ at point $\boldsymbol{x}$ (where $q : \mathbb{R}^n \to \mathbb{R}$). The normal $\hat{\boldsymbol{n}}(\boldsymbol{x})$ and the curvature $\kappa(\boldsymbol{x})$ at point $\boldsymbol{x} \in \Sigma$ are defined by formulas (2.1) and (2.3). The mean curvature vector is defined by $\boldsymbol{H} = -\kappa\hat{\boldsymbol{n}}$. The following equalities hold: for $1 \leq i \leq n$,*

$$\begin{aligned} \sum_{j,k=1}^{n} P_{j,k} \nabla_j P_{i,k} &= |\nabla q|^{-1} \sum_{j=1}^{n} \nabla_j (|\nabla q| P_{i,j}), \\ &= -|\nabla q|^{-2} \nabla_i q \sum_{j,k=1}^{n} \nabla_j \nabla_k q P_{j,k}, \\ &= -\kappa \hat{\boldsymbol{n}}_i = \boldsymbol{H}_i. \end{aligned} \tag{A.1}$$

Moreover, we have: for $1 \leq i \leq n$,

$$\sum_{j=1}^{n} \nabla_j P_{i,j} = -\sum_{j=1}^{n} P_{i,j} \nabla_j \ln |\nabla q| + \boldsymbol{H}_i. \tag{A.2}$$

LEMMA A.2 (Vectorial constraint case, $N \geq 1$) *We define the orthogonal projection $P(\boldsymbol{x})$ on the tangent space of $\Sigma = \{\boldsymbol{x}, q_\alpha(\boldsymbol{x}) = 0, 1 \leq \alpha \leq N\}$ (where $q_\alpha : \mathbb{R}^n \to \mathbb{R}$) at point $\boldsymbol{x}$ by (2.13). The normal $\hat{\boldsymbol{n}}_\alpha$ and the curvature κ_α are defined by (2.15) and (2.16). The mean curvature vector is defined by $\boldsymbol{H} = -\sum_{\alpha=1}^{N} \kappa_\alpha \hat{\boldsymbol{n}}_\alpha$ (see (2.18)). Then, we have: for $1 \leq i \leq n$,*

$$\begin{aligned} \sum_{j,k=1}^{n} P_{j,k} \nabla_j P_{i,k} &= (\det G)^{-1/2} \sum_{j=1}^{n} \nabla_j ((\det G)^{1/2} P_{i,j}), \\ &= -\sum_{\alpha=1}^{N} \kappa_\alpha (\hat{\boldsymbol{n}}_\alpha)_i = \boldsymbol{H}_i. \end{aligned} \tag{A.3}$$

Moreover, we have: for $1 \leq i \leq n$,

$$\sum_{j=1}^{n} \nabla_j P_{i,j} = -\sum_{j=1}^{n} P_{i,j} \nabla_j \ln((\det G)^{1/2}) + \boldsymbol{H}_i. \tag{A.4}$$

For brevity, we only provide the proof of Lemma A.2 below.

The following lemma giving another expression for the curvature κ_α defined in (2.16) is also useful.

LEMMA A.3 *Let $1 \leq \alpha \leq N$. The curvature κ_α defined by (2.16) can be written in the following form:*

$$\kappa_\alpha = |\nabla q_\alpha| (\det G)^{-1/2} \mathrm{div} \left((\det G)^{1/2} \sum_{\gamma=1}^{N} G^{-1}_{\alpha,\gamma} \nabla q_\gamma \right). \tag{A.5}$$

PROOF OF LEMMA A.2: Let us start with $P_{j,k}\nabla_j P_{i,k}$. We have:

$$\begin{aligned}
P_{j,k}\nabla_j P_{i,k} &= \nabla_j (P_{j,k}P_{i,k}) - P_{i,k}\nabla_j (P_{j,k}),\\
&= \nabla_j (P_{i,j}) - P_{i,k}\nabla_j (P_{j,k}),\\
&= (\delta_{i,k} - P_{i,k})\nabla_j (P_{j,k}),\\
&= -G^{-1}_{\alpha,\zeta}\nabla_i q_\alpha \nabla_k q_\zeta \nabla_j (G^{-1}_{\gamma,\delta}\nabla_j q_\gamma \nabla_k q_\delta),\\
&= -G^{-1}_{\alpha,\zeta}\nabla_i q_\alpha \nabla_k q_\zeta \Big(\nabla_j G^{-1}_{\gamma,\delta}\nabla_j q_\gamma \nabla_k q_\delta + G^{-1}_{\gamma,\delta}\Delta q_\gamma \nabla_k q_\delta\\
&\quad + G^{-1}_{\gamma,\delta}\nabla_j q_\gamma \nabla_j \nabla_k q_\delta\Big),\\
&= -\nabla_i q_\delta \nabla_j G^{-1}_{\gamma,\delta}\nabla_j q_\gamma - \nabla_i q_\delta G^{-1}_{\gamma,\delta}\Delta q_\gamma\\
&\quad - G^{-1}_{\alpha,\zeta}\nabla_i q_\alpha \nabla_k q_\zeta G^{-1}_{\gamma,\delta}\nabla_j q_\gamma \nabla_j \nabla_k q_\delta,
\end{aligned} \tag{A.6}$$

where the summation convention is from 1 to n for Latin indices and from 1 to N for Greek indices. Let us now compute $\nabla_j(G^{-1}_{\gamma,\delta})$. We have

$$0 = \nabla_j (G_{\alpha,\zeta}G^{-1}_{\zeta,\delta}) = \nabla_j (G_{\alpha,\zeta})G^{-1}_{\zeta,\delta} + G_{\alpha,\zeta}\nabla_j (G^{-1}_{\zeta,\delta}),$$

so that

$$\begin{aligned}
\nabla_j (G^{-1}_{\gamma,\delta}) &= -G^{-1}_{\gamma,\alpha}\nabla_j (G_{\alpha,\zeta})G^{-1}_{\zeta,\delta},\\
&= -G^{-1}_{\gamma,\alpha}G^{-1}_{\zeta,\delta}\left(\nabla_j \nabla_k q_\alpha \nabla_k q_\zeta + \nabla_j \nabla_k q_\zeta \nabla_k q_\alpha\right)
\end{aligned} \tag{A.7}$$

Therefore, the first term in (A.6) is

$$\begin{aligned}
&- \nabla_i q_\delta \nabla_j G^{-1}_{\gamma,\delta}\nabla_j q_\gamma\\
&= \nabla_i q_\delta \nabla_j q_\gamma G^{-1}_{\gamma,\alpha}G^{-1}_{\zeta,\delta}\left(\nabla_j \nabla_k q_\alpha \nabla_k q_\zeta + \nabla_j \nabla_k q_\zeta \nabla_k q_\alpha\right),\\
&= \nabla_i q_\delta \nabla_j q_\gamma G^{-1}_{\gamma,\alpha}G^{-1}_{\zeta,\delta}\nabla_j \nabla_k q_\alpha \nabla_k q_\zeta + \nabla_i q_\delta \nabla_j q_\gamma G^{-1}_{\gamma,\alpha}G^{-1}_{\zeta,\delta}\nabla_j \nabla_k q_\zeta \nabla_k q_\alpha\\
&= \nabla_i q_\alpha \nabla_j q_\gamma G^{-1}_{\gamma,\delta}G^{-1}_{\zeta,\alpha}\nabla_j \nabla_k q_\delta \nabla_k q_\zeta + \nabla_i q_\delta \nabla_j q_\zeta G^{-1}_{\zeta,\alpha}G^{-1}_{\gamma,\delta}\nabla_j \nabla_k q_\gamma \nabla_k q_\alpha,
\end{aligned}$$

where, in the last line, we have swapped α and δ in the first term and we have swapped ζ and γ in the second term. Notice now that the first term in the last line and the last term in (A.6) cancel, so that:

$$\begin{aligned} P_{j,k}\nabla_j P_{i,k} &= \nabla_i q_\delta\, G^{-1}_{\gamma,\delta}\left(-\Delta q_\gamma + G^{-1}_{\zeta,\alpha}\nabla_j q_\zeta \nabla_j\nabla_k q_\gamma \nabla_k q_\alpha\right), \\ &= \nabla_i q_\delta\, G^{-1}_{\gamma,\delta}\left(-\Delta q_\gamma + \nabla^2 q_\gamma : (G^{-1}_{\alpha,\zeta}\nabla q_\alpha \otimes \nabla q_\zeta)\right), \\ &= -\kappa_\delta \nabla_i q_\delta |\nabla q_\delta|^{-1}, \end{aligned}$$

which proves one equality in (A.3).

Let us now consider $(\det G)^{-1/2}\nabla_j((\det G)^{1/2}P_{i,j})$. Using (3.5), we have:

$$\begin{aligned} &(\det G)^{-1/2}\nabla_j((\det G)^{1/2}P_{i,j}) \\ &= (\det G)^{-1/2}\nabla_j((\det G)^{1/2})P_{i,j} + \nabla_j P_{i,j}, \\ &= \frac{1}{2}\nabla_j \ln(\det G)P_{i,j} - \nabla_j(G^{-1}_{\gamma,\delta}\nabla_i q_\gamma \nabla_j q_\delta), \\ &= \frac{1}{2}G^{-1}_{\alpha,\zeta}\nabla_j G_{\alpha,\zeta}P_{i,j} - \nabla_j G^{-1}_{\gamma,\delta}\nabla_i q_\gamma \nabla_j q_\delta \\ &\quad - G^{-1}_{\gamma,\delta}\nabla_j\nabla_i q_\gamma \nabla_j q_\delta - G^{-1}_{\gamma,\delta}\nabla_i q_\gamma \Delta q_\delta, \\ &= \frac{1}{2}G^{-1}_{\alpha,\zeta}\nabla_i G_{\alpha,\zeta} - \frac{1}{2}G^{-1}_{\alpha,\zeta}\nabla_j G_{\alpha,\zeta}G^{-1}_{\gamma,\delta}\nabla_i q_\gamma \nabla_j q_\delta \\ &\quad + G^{-1}_{\gamma,\alpha}G^{-1}_{\zeta,\delta}\left(\nabla_j\nabla_k q_\alpha \nabla_k q_\zeta + \nabla_j\nabla_k q_\zeta \nabla_k q_\alpha\right)\nabla_i q_\gamma \nabla_j q_\delta \\ &\quad - G^{-1}_{\gamma,\delta}\nabla_j\nabla_i q_\gamma \nabla_j q_\delta - G^{-1}_{\gamma,\delta}\nabla_i q_\gamma \Delta q_\delta, \\ &= G^{-1}_{\alpha,\zeta}\nabla_i\nabla_j q_\alpha \nabla_j q_\zeta - G^{-1}_{\alpha,\zeta}\nabla_j\nabla_k q_\alpha \nabla_k q_\zeta G^{-1}_{\gamma,\delta}\nabla_i q_\gamma \nabla_j q_\delta \\ &\quad + G^{-1}_{\gamma,\alpha}G^{-1}_{\zeta,\delta}\nabla_j\nabla_k q_\alpha \nabla_k q_\zeta \nabla_i q_\gamma \nabla_j q_\delta + G^{-1}_{\gamma,\alpha}G^{-1}_{\zeta,\delta}\nabla_j\nabla_k q_\zeta \nabla_k q_\alpha \nabla_i q_\gamma \nabla_j q_\delta \\ &\quad - G^{-1}_{\gamma,\delta}\nabla_j\nabla_i q_\gamma \nabla_j q_\delta - G^{-1}_{\gamma,\delta}\nabla_i q_\gamma \Delta q_\delta \\ &= -G^{-1}_{\zeta,\alpha}\nabla_j\nabla_k q_\zeta \nabla_k q_\alpha G^{-1}_{\gamma,\delta}\nabla_i q_\gamma \nabla_j q_\delta \\ &\quad + G^{-1}_{\gamma,\delta}G^{-1}_{\zeta,\alpha}\nabla_j\nabla_k q_\delta \nabla_k q_\zeta \nabla_i q_\gamma \nabla_j q_\alpha + G^{-1}_{\gamma,\delta}G^{-1}_{\zeta,\alpha}\nabla_j\nabla_k q_\zeta \nabla_k q_\delta \nabla_i q_\gamma \nabla_j q_\alpha \\ &\quad - G^{-1}_{\gamma,\delta}\nabla_i q_\gamma \Delta q_\delta, \end{aligned}$$

where, in the last expression we have swapped α and ζ in the first term and α and δ in the third term. Now notice that the third term cancels with the first term so that we obtain:

$$\begin{aligned} &(\det G)^{-1/2}\nabla_j((\det G)^{1/2}P_{i,j}) \\ &\qquad = \nabla_i q_\gamma G^{-1}_{\gamma,\delta}\left(G^{-1}_{\zeta,\alpha}\nabla_j\nabla_k q_\delta \nabla_k q_\zeta \nabla_j q_\alpha - \Delta q_\delta\right), \\ &\qquad = -\kappa_\gamma \nabla_i q_\gamma |\nabla q_\gamma|^{-1}, \end{aligned}$$

which completes the proof of (A.3).

Let us finally consider (A.4). We have:

$$\begin{aligned}\nabla_j P_{i,j} &= (\det G)^{-1/2}\nabla_j((\det G)^{1/2}P_{i,j}) - (\det G)^{-1/2}P_{i,j}\nabla_j((\det G)^{1/2})\\ &= -\sum_{\alpha=1}^{N}\kappa_\alpha(\hat{\boldsymbol{n}}_\alpha)_i - P_{i,j}\nabla_j(\ln(\det G)^{1/2}),\end{aligned}$$

which is exactly (A.4). ∎

Proof of Lemma A.3: For a fixed $1 \le \alpha \le N$, we have

$$\begin{aligned}&(\det G)^{-1/2}\mathrm{div}\,\left((\det G)^{1/2}G^{-1}_{\alpha,\gamma}\nabla q_\gamma\right)\\ &\quad= G^{-1}_{\alpha,\gamma}\nabla q_\gamma\cdot\nabla\ln\left((\det G)^{1/2}\right) + \nabla G^{-1}_{\alpha,\gamma}\cdot\nabla q_\gamma + G^{-1}_{\alpha,\gamma}\Delta q_\gamma.\end{aligned} \tag{A.8}$$

Using (3.5), the first term in (A.8) is:

$$\begin{aligned}G^{-1}_{\alpha,\gamma}\nabla q_\gamma\cdot\nabla\ln(\det G)^{1/2} &= \frac{1}{2}G^{-1}_{\alpha,\gamma}\nabla q_\gamma\cdot G^{-1}_{\zeta,\delta}\nabla G_{\delta,\zeta},\\ &= \frac{1}{2}G^{-1}_{\alpha,\gamma}\nabla q_\gamma\cdot G^{-1}_{\zeta,\delta}\left(\nabla^2 q_\delta\nabla q_\zeta + \nabla^2 q_\zeta\nabla q_\delta\right),\\ &= G^{-1}_{\alpha,\gamma}G^{-1}_{\zeta,\delta}\nabla^2 q_\delta : \nabla q_\zeta\otimes\nabla q_\gamma.\end{aligned}$$

Using (A.7) the second term in (A.8) is

$$\begin{aligned}\nabla G^{-1}_{\alpha,\gamma}\cdot\nabla q_\gamma &= -G^{-1}_{\gamma,\delta}G^{-1}_{\zeta,\alpha}\left(\nabla^2 q_\delta\nabla q_\zeta + \nabla^2 q_\zeta\nabla q_\delta\right)\cdot\nabla q_\gamma,\\ &= -G^{-1}_{\gamma,\delta}G^{-1}_{\zeta,\alpha}\left(\nabla^2 q_\delta : \nabla q_\zeta\otimes\nabla q_\gamma + \nabla^2 q_\zeta : \nabla q_\delta\otimes\nabla q_\gamma\right).\end{aligned}$$

Therefore, we have:

$$\begin{aligned}&(\det G)^{-1/2}\mathrm{div}\,\left((\det G)^{1/2}G^{-1}_{\alpha,\gamma}\nabla q_\gamma\right)\\ &\qquad= -G^{-1}_{\zeta,\alpha}\nabla^2 q_\zeta : \left(G^{-1}_{\gamma,\delta}\nabla q_\delta\otimes\nabla q_\gamma\right) + G^{-1}_{\alpha,\gamma}\Delta q_\gamma,\end{aligned}$$

which yields (A.5), using the definition (2.16) of κ_α. ∎

B The mean curvature vector $\boldsymbol{H}$

Here we show that the vector $-\sum_{\alpha=1}^N \kappa_\alpha\hat{\boldsymbol{n}}_\alpha$ is the so-called mean curvature vector $\boldsymbol{H}$ defined as [2][2]

$$\boldsymbol{H} = -\sum_{\alpha=1}^{N}\mathrm{div}_{\,\Sigma}(\boldsymbol{\nu}_\alpha)\boldsymbol{\nu}_\alpha, \tag{B.1}$$

[2] Depending on the textbooks, the mean curvature vector is defined as $\pm\sum_{\alpha=1}^N \kappa_\alpha\hat{\boldsymbol{n}}_\alpha$, or as $N^{-1}\sum_{\alpha=1}^N \kappa_\alpha\hat{\boldsymbol{n}}_\alpha$. The vector $\boldsymbol{H}$ defined by (B.1) is also sometimes called the additive curvature vector.

where div_{Σ} is the tangential divergence and $(\boldsymbol{\nu}_1, ..., \boldsymbol{\nu}_N)(\boldsymbol{x})$ denotes a smooth orthonormal vector field generating the space normal to Σ at point $\boldsymbol{x}$. Geometrically, $\boldsymbol{H}$ points in the direction where the area of Σ decreases most, and intervenes in mean curvature flows or in the divergence theorem on manifolds (2.8) (see [2, 3]). This vector only depends on the geometry of the surface Σ as a submanifold of $\mathbb{R}^n$. In other words, the dynamics (2.17) is intrinsic, like the measure μ_Σ it samples.

To derive the expression $\boldsymbol{H} = -\sum_{\alpha=1}^N \kappa_\alpha \hat{\boldsymbol{n}}_\alpha$ from (B.1), notice first that this definition does not depend on the choice of the vector field $(\boldsymbol{\nu}_1, ..., \boldsymbol{\nu}_N)$. Thus, the mean curvature vector is characterized by the fact that, for any vector $\boldsymbol{\nu}$ in the normal space to Σ at point $\boldsymbol{x}$, $\boldsymbol{H} \cdot \boldsymbol{\nu} = -\mathrm{div}_{\Sigma}(\boldsymbol{\nu})$. Let us then compute: for $1 \le \alpha_0 \le N$,

$$\begin{aligned}
&-\kappa_\alpha \hat{\boldsymbol{n}}_\alpha \cdot \hat{\boldsymbol{n}}_{\alpha_0} \\
&\quad = - |\nabla q_\alpha| G^{-1}_{\gamma,\alpha} \left(\Delta q_\gamma - \nabla^2 q_\gamma : (G^{-1}_{\delta,\zeta} \nabla q_\delta \otimes \nabla q_\zeta) \right) \\
&\qquad\qquad \times \nabla q_\alpha |\nabla q_\alpha|^{-1} \cdot \nabla q_{\alpha_0} |\nabla q_{\alpha_0}|^{-1}, \\
&\quad = - G^{-1}_{\gamma,\alpha} \left(\Delta q_\gamma - \nabla^2 q_\gamma : (G^{-1}_{\delta,\zeta} \nabla q_\delta \otimes \nabla q_\zeta) \right) G_{\alpha,\alpha_0} |\nabla q_{\alpha_0}|^{-1}, \\
&\quad = - \left(\Delta q_{\alpha_0} - \nabla^2 q_{\alpha_0} : (G^{-1}_{\delta,\zeta} \nabla q_\delta \otimes \nabla q_\zeta) \right) |\nabla q_{\alpha_0}|^{-1}.
\end{aligned}$$

But we also have: for $1 \le \delta \le N$,

$$\begin{aligned}
&\mathrm{div}_{\Sigma}(\hat{\boldsymbol{n}}_\delta) = \mathrm{Id} : (P \nabla (\nabla q_\delta / |\nabla q_\delta|)), \\
&= \delta_{i,j} \left(\delta_{i,k} - G^{-1}_{\alpha,\zeta} \nabla_i q_\alpha \nabla_k q_\zeta \right) \nabla_k \left(\nabla_j q_\delta |\nabla q_\delta|^{-1} \right), \\
&= \left(\delta_{i,k} - G^{-1}_{\alpha,\zeta} \nabla_i q_\alpha \nabla_k q_\zeta \right) \left(\nabla_k \nabla_i q_\delta |\nabla q_\delta|^{-1} - \nabla_i q_\delta \nabla_k q_\delta |\nabla q_\delta|^{-2} \right), \\
&= \Delta q_\delta |\nabla q_\delta|^{-1} - G^{-1}_{\alpha,\zeta} \nabla_i q_\alpha \nabla_k q_\zeta \nabla_k \nabla_i q_\delta |\nabla q_\delta|^{-1} - 1 \\
&\quad + G^{-1}_{\alpha,\zeta} \nabla_i q_\alpha \nabla_k q_\zeta \nabla_i q_\delta \nabla_k q_\delta |\nabla q_\delta|^{-2}, \\
&= \Delta q_\delta |\nabla q_\delta|^{-1} - \nabla^2 q_\delta : (G^{-1}_{\alpha,\zeta} \nabla q_\alpha \otimes \nabla q_\zeta) |\nabla q_\delta|^{-1}.
\end{aligned}$$

Therefore, for any $1 \le \alpha_0 \le N$,

$$-\sum_{\alpha=1}^N \kappa_\alpha \hat{\boldsymbol{n}}_\alpha \cdot \hat{\boldsymbol{n}}_{\alpha_0} = -\mathrm{div}_{\Sigma}(\hat{\boldsymbol{n}}_{\alpha_0}).$$

Since $(\hat{\boldsymbol{n}}_1, ..., \hat{\boldsymbol{n}}_N)(\boldsymbol{x})$ generates the space normal to Σ at point $\boldsymbol{x}$, this proves that $\boldsymbol{H} = -\sum_{\alpha=1}^N \kappa_\alpha \hat{\boldsymbol{n}}_\alpha$.

C The proof of $\lim_{\eta\to 0} \boldsymbol{X}_t^\eta = \boldsymbol{X}_t$

This appendix is devoted to the proof of

$$\lim_{\eta\to 0} \boldsymbol{X}_t^\eta = \boldsymbol{X}_t,$$

where $\boldsymbol{X}_t^\eta$ and $\boldsymbol{X}_t$ are such that $\boldsymbol{X}_0^\eta = \boldsymbol{X}_0$ and respectively satisfy (2.23) and (2.24). For simplicity, we restrict ourselves to the scalar constraint case, $N = 1$. Moreover, we suppose in this section that

$$0 < m \le |\nabla q| \le M \text{ and } |\Delta q| \le M. \tag{C.1}$$

LEMMA C.1 *Let $\boldsymbol{X}_t^\eta$ be the solution of the stochastic differential equation (2.23) with initial condition $\boldsymbol{X}_0^\eta = \boldsymbol{X}_0$. Let us suppose (C.1) and that:*

$$q(\boldsymbol{X}_0) = 0, \tag{C.2}$$

and

$$|\nabla V| \le M. \tag{C.3}$$

Then we have:

$$\mathbf{E}\left(\sup_{t\le T} |q(\boldsymbol{X}_t^\eta)|\right) \le C_2\sqrt{2\beta^{-1}\eta}\,\ln(1+M^2T/\eta) + \frac{\beta^{-1}M + M^2}{m^2}\eta, \tag{C.4}$$

$$\sup_{t\ge 0} \mathbf{E}\left(|q(\boldsymbol{X}_t^\eta)|^2\right) \le 2\beta^{-1}\eta + 2\left(\frac{\beta^{-1}M + M^2}{m^2}\right)^2 \eta^2. \tag{C.5}$$

PROOF: We have:

$$\begin{aligned} q(\boldsymbol{X}_t^\eta) = &-\frac{1}{\eta}\int_0^t |\nabla q|^2(\boldsymbol{X}_s^\eta) q(\boldsymbol{X}_s^\eta)\, ds - \int_0^t \nabla q(\boldsymbol{X}_s^\eta)\cdot \nabla V(\boldsymbol{X}_s^\eta)\, ds \\ &+ \sqrt{2\beta^{-1}}\int_0^t \nabla q(\boldsymbol{X}_s^\eta)\cdot d\boldsymbol{W}_s + \beta^{-1}\int_0^t \Delta q(\boldsymbol{X}_s^\eta)\, ds. \end{aligned}$$

Let us first perform a change of time. The local martingale $M_t = \int_0^t \nabla q(\boldsymbol{X}_s^\eta)\cdot d\boldsymbol{W}_s$ is such that $\langle M\rangle_t = \int_0^t |\nabla q|^2(\boldsymbol{X}_s^\eta) ds \ge m^2 t$ (by (C.1)). Therefore, $\langle M\rangle_\infty = \infty$ almost surely and thus, by the Dubins-Schwartz Theorem, there exists a Brownian motion B such that $M_t = B_{\langle M\rangle_t}$. Let us set

$\tau(t) = \inf\{s, \langle M\rangle_s > t\}$ and $Z_t = q(\boldsymbol{X}^\eta_{\tau(t)})$. By a change of variable, we obtain:

$$Z_t = -\frac{1}{\eta}\int_0^t Z_s\,ds + \sqrt{2\beta^{-1}}B_t + \int_0^t \frac{(\beta^{-1}\Delta q - \nabla V\cdot\nabla q)}{|\nabla q|^2}(\boldsymbol{X}^\eta_{\tau(s)})\,ds.$$

Therefore, we have:

$$\begin{aligned}Z_t =&\sqrt{2\beta^{-1}}\int_0^t e^{-(t-s)/\eta}dB_s + \int_0^t e^{-(t-s)/\eta}\frac{(\beta^{-1}\Delta q - \nabla V\cdot\nabla q)}{|\nabla q|^2}(\boldsymbol{X}^\eta_{\tau(s)})\,ds,\\ \le&\sqrt{2\beta^{-1}}\int_0^t e^{-(t-s)/\eta}dB_s + \frac{\beta^{-1}M + M^2}{m^2}\eta.\end{aligned}$$

Therefore,

$$\mathbf{E}\left(\sup_{t\le T}|Z_t|\right) \le \sqrt{2\beta^{-1}}\mathbf{E}\left(\sup_{t\le T}\left|\int_0^t e^{-(t-s)/\eta}dB_s\right|\right) + \frac{\beta^{-1}M + M^2}{m^2}\eta.$$

The process $g_t = \displaystyle\int_0^t e^{-(t-s)/\eta}dB_s$ is an Ornstein-Uhlenbeck process so that, by [17], there exist $C_1, C_2 > 0$ such that

$$C_1\sqrt{\eta}\ln(1+T/\eta) \le \mathbf{E}\sup_{t\le T}|g_t| \le C_2\sqrt{\eta}\ln(1+T/\eta).$$

Thus, we have:

$$\mathbf{E}\left(\sup_{t\le T}|Z_t|\right) \le C_2\sqrt{2\beta^{-1}\eta}\ln(1+T/\eta) + \frac{\beta^{-1}M + M^2}{m^2}\eta.$$

This means that

$$\mathbf{E}\left(\sup_{t\le\tau(T)}|q(\boldsymbol{X}^\eta_t)|\right) \le C_2\sqrt{2\beta^{-1}\eta}\ln(1+T/\eta) + \frac{\beta^{-1}M + M^2}{m^2}\eta.$$

Using the fact that $\tau(t) \ge \frac{t}{M^2}$, we then obtain (C.4).

If we consider another norm, we have:

$$\begin{aligned}\mathbf{E}|Z_t|^2 &\le 4\beta^{-1}\mathbf{E}\left|\int_0^t e^{-(t-s)/\eta}dB_s\right|^2 + 2\left(\frac{\beta^{-1}M + M^2}{m^2}\right)^2\eta^2.\\ &\le 2\beta^{-1}\eta + 2\left(\frac{\beta^{-1}M + M^2}{m^2}\right)^2\eta^2.\end{aligned}$$

This yields (C.5). ∎

We now introduce the following change of coordinates:

$$\Phi : \left\{ \begin{array}{ccc} \mathbb{R}^n & \to & \mathbb{R}^n \\ \boldsymbol{x} & \mapsto & \begin{pmatrix} \boldsymbol{p}(\boldsymbol{x}) \\ q(\boldsymbol{x}) \end{pmatrix} \end{array} \right. \tag{C.6}$$

where $\boldsymbol{p} = (p_1, \dots, p_{n-1}) : \mathbb{R}^n \to \mathbb{R}^{n-1}$ is such that $\nabla p_i \cdot \nabla q = 0$ for all $1 \leq i \leq n-1$ and for all $\boldsymbol{x} \in \Sigma$. In other words, $\Phi_n = q$, while $\Phi_i = p_i$, for $1 \leq i \leq n-1$. We suppose that Φ is invertible, and thus, $Range(\nabla p_1, ..., \nabla p_{n-1}) = n-1$. It is always possible to build such a function Φ, at least locally, by considering a parametrization of Σ.

For the statement of the next proposition, we suppose that:

(C.7) $\quad 0 < m \leq |\nabla \Phi| \leq M$, and $\nabla \Phi$ and $\Delta \Phi$ are Lipschitz functions.

Notice that the assumptions on Φ are actually some assumptions related to the regularity of the surface Σ, and therefore, some assumptions related to the regularity of q. If Σ is sufficiently smooth, it is possible to define the parametrization Φ at least in a neighborhood of $\boldsymbol{X}_0$, so that the arguments given below still hold, by a localization procedure on the processes $\boldsymbol{X}_t$ and $\boldsymbol{X}^\eta_t$.

Proposition C.2 *Let $\boldsymbol{X}^\eta_t$ be the solution of the stochastic differential equation (2.23) with initial condition $\boldsymbol{X}^\eta_0 = \boldsymbol{X}_0$. Let $\boldsymbol{X}_t$ be the solution of the following stochastic differential equation:*

$$\begin{aligned} \boldsymbol{X}_t = \boldsymbol{X}_0 - \int_0^t P(\boldsymbol{X}_s) \nabla V(\boldsymbol{X}_s)\, ds + \sqrt{2\beta^{-1}} \int_0^t P(\boldsymbol{X}_s)\, d\boldsymbol{W}_s \\ + \beta^{-1} \int_0^t \nabla \cdot P(\boldsymbol{X}_s)\, ds. \end{aligned} \tag{C.8}$$

We suppose that (C.2), (C.1) , (C.3) and (C.7) hold. In addition, we suppose that:

$$\nabla V \text{ is a Lipschitz function.} \tag{C.9}$$

Then, for small η,

$$\sup_{t \leq T} \mathbf{E} \left| \boldsymbol{X}^\eta_t - \boldsymbol{X}_t \right|^2 \leq C\eta, \tag{C.10}$$

where C is a constant depending on the data, and on T.

Notice that $\boldsymbol{X}_t$ solution to (C.8) satisfies (2.24) since $\nabla\cdot P = -P\nabla \ln|\nabla q| - \kappa\hat{\boldsymbol{n}}$ (see (A.2)). All this can be generalized to the case $N > 1$.

PROOF: By rewriting the stochastic differential equations in the coordinates $(\boldsymbol{p}, q)$, we have, for $\boldsymbol{X}_t^\eta$,

$$\begin{cases} \text{for all } 1 \le i \le n-1, \\ d\Phi_i(\boldsymbol{X}_t^\eta) = \nabla_j \Phi_i(\boldsymbol{X}_t^\eta)(-\nabla_j V(\boldsymbol{X}_t^\eta)\,dt + \sqrt{2\beta^{-1}}d\boldsymbol{W}_j(t)) + \beta^{-1}\Delta\Phi_i(\boldsymbol{X}_t^\eta)\,dt, \\ dq(\boldsymbol{X}_t^\eta) = -\frac{1}{\eta}|\nabla q|^2(\boldsymbol{X}_t^\eta)q(\boldsymbol{X}_t^\eta)\,dt + \nabla q(\boldsymbol{X}_t^\eta)\cdot(-\nabla V(\boldsymbol{X}_t^\eta)\,dt + \sqrt{2\beta^{-1}}d\boldsymbol{W}_t) \\ \qquad\qquad + \beta^{-1}\Delta q(\boldsymbol{X}_t^\eta)\,dt, \end{cases}$$

and for $\boldsymbol{X}_t$,

(C.11)

$$\begin{cases} \text{for all } 1 \le i \le n-1, \\ d\Phi_i(\boldsymbol{X}_t) = \nabla_j \Phi_i(\boldsymbol{X}_t)(-\nabla_j V(\boldsymbol{X}_t)\,dt + \sqrt{2\beta^{-1}}d\boldsymbol{W}_j(t)) + \beta^{-1}\Delta\Phi_i(\boldsymbol{X}_t)\,dt, \\ dq(\boldsymbol{X}_t) = 0. \end{cases}$$

Let us prove (C.11). By Itô Formula, we have,

$$\begin{aligned} d\Phi_i(\boldsymbol{X}_t) =& \nabla\Phi_i \cdot (P\nabla V + \beta^{-1}\nabla\cdot P)(\boldsymbol{X}_t)\,dt \\ &+ \sqrt{2\beta^{-1}}\nabla\Phi_i\cdot(P(\boldsymbol{X}_t)d\boldsymbol{W}_t) + \beta^{-1}P : \nabla^2\Phi_i(\boldsymbol{X}_t)\,dt \end{aligned}$$

Equation (C.11) can be straightforwardly obtained from this equation using the fact that: on Σ,

$$P\nabla\Phi_i = \begin{cases} \nabla\Phi_i & \text{if } 1 \le i \le n-1, \\ 0 & \text{if } i = n, \end{cases} \quad \text{and } \nabla\cdot(P\nabla\Phi_i) = \begin{cases} \Delta\Phi_i & \text{if } 1 \le i \le n-1, \\ 0 & \text{if } i = n. \end{cases}$$

Now, by (C.5), we know that, for small η, $\sup_{t\ge 0} \mathbf{E}\left(\left|q(\boldsymbol{X}_t^\eta) - q(\boldsymbol{X}_t)\right|^2\right) \le C\eta$. For the other components of $\Phi(\boldsymbol{X}_t)$, we have, by using (C.3), (C.9), (C.7): $\forall 0 \le t \le T$,

$$\mathbf{E}\left(\sum_{i=1}^{n-1}\left|\Phi_i(\boldsymbol{X}_t^\eta) - \Phi_i(\boldsymbol{X}_t)\right|^2\right) \le C(T)\int_0^t \mathbf{E}|\boldsymbol{X}_s^\eta - \boldsymbol{X}_s|^2\,ds.$$

Therefore, by using (C.7) and (C.5), we obtain: $\forall 0 \le t \le T$,

$$\mathbf{E}\left|\Phi(\boldsymbol{X}_t^\eta) - \Phi(\boldsymbol{X}_t)\right|^2 \le C(T)\int_0^t \mathbf{E}|\boldsymbol{X}_s^\eta - \boldsymbol{X}_s|^2\,ds + C\eta,$$

and thus

$$\mathbf{E}\left|\boldsymbol{X}_t^\eta - \boldsymbol{X}_t\right|^2 \le C(T)\int_0^t \mathbf{E}|\boldsymbol{X}_s^\eta - \boldsymbol{X}_s|^2\,ds + C\eta,$$

which yields (C.10). ∎

D The situation with molecular constraints

In many applications, in addition to the constraints associated with the reaction coordinates $\boldsymbol{q}(\boldsymbol{x})$ whose free energy is of interest, some molecular constraints $\boldsymbol{c}(\boldsymbol{x}) = (c_1(\boldsymbol{x}), \ldots, c_M(\boldsymbol{x})) = 0$ $(M < n)$ are needed. These correspond to physical constraints on the system, such as fixed bond lengths for example. For completeness, we discuss this case here. We suppose in the following that $\mathrm{rank}(\nabla c_1, ..., \nabla c_M) = M$ and

$$\mathrm{rank}(\nabla q_1, ..., \nabla q_N, \nabla c_1, ..., \nabla c_M) = N + M.$$

In this section, Latin indices go from 1 to M or from 1 to $N + M$.

When molecular constraints are present, the original Boltzmann-Gibbs distribution (replacing (1.2)) is

$$d\mu_\Gamma(\boldsymbol{x}) = Z_\Gamma^{-1} e^{-\beta V(\boldsymbol{x})} d\sigma_\Gamma(\boldsymbol{x}) \tag{D.1}$$

where $\Gamma = \{\boldsymbol{x} : \boldsymbol{c}(\boldsymbol{x}) = 0\}$ is the codimension M manifold on which the system is constrained due to the presence of the molecular constraints, σ_Γ is the Lebesgue measure on this manifold, and

$$Z_\Gamma = \int_\Gamma e^{-\beta V(\boldsymbol{x})} d\sigma_\Gamma(\boldsymbol{x}). \tag{D.2}$$

D.1 Definition of the free energy

As in in the case without molecular constraints (see Section 4.1), the free energy F_Γ associated with $\boldsymbol{q}(\boldsymbol{x})$ is such that $e^{-\beta F_\Gamma(\boldsymbol{z})}$ is the probability density function of the variable $\boldsymbol{Z} = \boldsymbol{q}(\boldsymbol{X})$ when $\boldsymbol{X}$ is distributed according to μ_Γ. Thus, the free energy F_Γ is defined by: for all function $\phi : \mathbb{R}^N \to \mathbb{R}$,

$$\int_\Gamma \phi(\boldsymbol{q}(\boldsymbol{x})) Z_\Gamma^{-1} e^{-\beta V(\boldsymbol{x})} d\sigma_\Gamma(\boldsymbol{x}) = \int_{\mathbb{R}^N} \phi(\boldsymbol{z}) e^{-\beta F_\Gamma(\boldsymbol{z})}\, d\boldsymbol{z}. \tag{D.3}$$

To obtain an explicit expression of F_Γ, we need the following generalization of the co-area formula (see Theorem 2.93 p. 101 in [1]): for any function $g : \mathbb{R}^n \to \mathbb{R}$ (possibly defined only on Γ) and a smooth function $\boldsymbol{q} : \mathbb{R}^n \to \mathbb{R}^N$,

$$\int_\Gamma g(\boldsymbol{x}) |\det G_\Gamma(\boldsymbol{x})|^{1/2} d\sigma_\Gamma(\boldsymbol{x}) = \int_{\mathbb{R}^N} \int_{\Gamma \cap \Sigma(\boldsymbol{z})} g(\boldsymbol{x}) d\sigma_{\Gamma \cap \Sigma(\boldsymbol{z})}(\boldsymbol{x}) d\boldsymbol{z}, \tag{D.4}$$

where the matrix G_Γ is defined by: for $1 \leq \alpha, \zeta \leq N$,

$$(G_\Gamma)_{\alpha,\zeta} = \nabla_\Gamma q_\alpha \cdot \nabla_\Gamma q_\zeta. \tag{D.5}$$

In (D.5), ∇_Γ denotes the surface gradient. More explicitly, let us introduce the orthogonal projector $Q(\boldsymbol{x})$ on the tangent space to Γ at point $\boldsymbol{x}$:

$$Q(\boldsymbol{x}) = \mathrm{Id} - \sum_{i,j=1}^{M} K_{i,j}^{-1}(\boldsymbol{x}) \nabla c_i(\boldsymbol{x}) \otimes \nabla c_j(\boldsymbol{x}), \tag{D.6}$$

where, $\forall 1 \leq i, j \leq M$,

$$K_{i,j} = \nabla c_i \cdot \nabla c_j. \tag{D.7}$$

Since q_α is also defined in the vicinity of Γ, we can thus express the surface gradient of q_α as:

$$\nabla_\Gamma q_\alpha(\boldsymbol{x}) = Q(\boldsymbol{x}) \nabla q_\alpha(\boldsymbol{x}). \tag{D.8}$$

We also recall that the surface divergence on Γ is the trace of the surface gradient on Γ (see (2.7) with Σ replaced by Γ and P by Q),

Now, using (D.4), by similar computations as those made in Section 4.1 to obtain (4.6), we have the following expression for the free energy:

$$F_\Gamma(\boldsymbol{z}) = -\beta^{-1} \ln\Big(Z_\Gamma^{-1} \int_{\Gamma \cap \Sigma(\boldsymbol{z})} e^{-\beta V(\boldsymbol{x})} |\det G_\Gamma(\boldsymbol{x})|^{-1/2} d\sigma_{\Gamma \cap \Sigma(\boldsymbol{z})}(\boldsymbol{x}) \Big), \tag{D.9}$$

or equivalently

$$F_\Gamma(\boldsymbol{z}) = -\beta^{-1} \ln\Big(Z_\Gamma^{-1} Z_{\Gamma \cap \Sigma(\boldsymbol{z}), |\det G_\Gamma|^{-1/2}} \Big). \tag{D.10}$$

This means that, similarly to the case without constraints, we need to replace the potential V by $V_{|\det G_\Gamma|^{-1/2}}$ in order to sample the right measure. Thus, the numerical schemes to consider are (written here for $\boldsymbol{z} = 0$):

$$\begin{cases} \boldsymbol{X}_{n+1} = \boldsymbol{X}_n - \nabla(V_{|\det G_\Gamma|^{-1/2}})(\boldsymbol{X}_n)\, \Delta t + \sqrt{2\beta^{-1}} \Delta \boldsymbol{W}_n \\ \qquad\qquad + \sum_{\alpha=1}^N \lambda_{\alpha,n} \nabla q_\alpha(\boldsymbol{X}_{n+1}) + \sum_{i=1}^M \mu_{i,n} \nabla c_i(\boldsymbol{X}_{n+1}), \\ \text{where } \lambda_{\alpha,n} \text{ and } \mu_{i,n} \text{ such that } \boldsymbol{q}(\boldsymbol{X}_{n+1}) = \boldsymbol{c}(\boldsymbol{X}_{n+1}) = 0, \end{cases} \tag{D.11}$$

and

$$\begin{cases} \boldsymbol{X}_{n+1} = \boldsymbol{X}_n - \nabla(V_{|\det G_\Gamma|^{-1/2}})(\boldsymbol{X}_n)\, \Delta t + \sqrt{2\beta^{-1}} \Delta \boldsymbol{W}_n \\ \qquad\qquad + \sum_{\alpha=1}^N \lambda_{\alpha,n} \nabla q_\alpha(\boldsymbol{X}_n) + \sum_{i=1}^M \mu_{i,n} \nabla c_i(\boldsymbol{X}_{n+1}), \\ \text{where } \lambda_{\alpha,n} \text{ and } \mu_{i,n} \text{ such that } \boldsymbol{q}(\boldsymbol{X}_{n+1}) = \boldsymbol{c}(\boldsymbol{X}_{n+1}) = 0. \end{cases} \tag{D.12}$$

Notice that $\nabla V_{|\det G_\Gamma|^{-1/2}})$ involves the Hessian $\nabla_\Gamma^2 q_\alpha$, but the computation of this quantity can be avoided in practice by using an approximation similar to (3.6).

D.2 Expression for the mean force

We now turn to the question of the computation of the mean force. As in the case without molecular constraints, we obtain the following generalization of Lemma 4.1:

LEMMA D.1 *The gradient of F_Γ (namely the mean force) can be expressed as: for any $1 \le \alpha \le N$,*

$$\begin{aligned}\nabla_\alpha F_\Gamma(\boldsymbol{z}) = \sum_{\gamma=1}^{N} \int_{\Gamma\cap\Sigma(\boldsymbol{z})} \Big(&\nabla_\Gamma V \cdot (G_\Gamma^{-1})_{\alpha,\gamma} \nabla_\Gamma q_\gamma \\ &- \beta^{-1} \mathrm{div}\,_\Gamma\big((G_\Gamma^{-1})_{\alpha,\gamma}\nabla_\Gamma q_\gamma\big)\Big) d\mu_{\Gamma\cap\Sigma(\boldsymbol{z}),|\det G_\Gamma|^{-1/2}}.\end{aligned} \tag{D.13}$$

As in the case without molecular constraints, this formula can be used directly to evaluate $\nabla_\alpha F_\Gamma(\boldsymbol{z})$. Let $\boldsymbol{X}_n$ be the solution to (D.11) or (D.12). Then, the first term at the right hand side of (D.13) can be obtained from

$$\begin{aligned}&\lim_{T\to\infty}\lim_{\Delta t\to 0}\frac{1}{M}\sum_{m=1}^{M}\sum_{\gamma=1}^{N}\Big(\nabla_\Gamma V \cdot (G_\Gamma^{-1})_{\alpha,\gamma}\nabla_\Gamma q_\gamma\Big)(\boldsymbol{X}_n) \\ &\quad = \sum_{\gamma=1}^{N}\int_{\Gamma\cap\Sigma(\boldsymbol{z})} \nabla_\Gamma V \cdot (G_\Gamma^{-1})_{\alpha,\gamma}\nabla_\Gamma q_\gamma \, d\mu_{\Gamma\cap\Sigma(\boldsymbol{z}),|\det G_\Gamma|^{-1/2}},\end{aligned} \tag{D.14}$$

where $M = T/\Delta t$. As for the second term, we have

$$\begin{aligned}&-\beta^{-1}\lim_{T\to\infty}\lim_{\Delta t\to 0}\frac{1}{M\Delta t}\sum_{m=1}^{M}\sum_{\gamma=1}^{N}\Big(((G_\Gamma)^{-1}_{\alpha,\gamma}\nabla_\Gamma q_\gamma)(\boldsymbol{X}_n + \Delta\boldsymbol{W}_n) \\ &\qquad\qquad - ((G_\Gamma)^{-1}_{\alpha,\gamma}\nabla_\Gamma q_\gamma)(\boldsymbol{X}_n)\Big)\cdot Q(\boldsymbol{X}_n)\Delta\boldsymbol{W}_n \\ &= -\beta^{-1}\sum_{\gamma=1}^{N}\int_{\Gamma\cap\Sigma(\boldsymbol{z})} \mathrm{div}\,_\Gamma((G_\Gamma^{-1})_{\alpha,\gamma}\nabla_\Gamma q_\gamma) d\mu_{\Gamma\cap\Sigma(\boldsymbol{z}),|\det G_\Gamma|^{-1/2}}.\end{aligned} \tag{D.15}$$

PROOF OF LEMMA D.1: Let Φ by a $\mathcal{C}_c^\infty(\mathbb{R})$ function and $\phi = \Phi'$. Then for a fixed $1 \le \alpha \le N$,

$$\begin{aligned}&\int_{\mathbb{R}^N}\phi(z_\alpha)\exp(-\beta F_\Gamma(\boldsymbol{z}))\,d\boldsymbol{z} \\ &\quad = \int_{\mathbb{R}^N}\Phi'(z_\alpha)\exp(-\beta F_\Gamma(\boldsymbol{z}))\,d\boldsymbol{z}, \\ &\quad = \beta\int_{\mathbb{R}^N}\Phi(z_\alpha)\nabla_\alpha F_\Gamma(\boldsymbol{z})\exp(-\beta F_\Gamma(\boldsymbol{z}))\,d\boldsymbol{z} \\ &\quad = \beta Z_\Gamma^{-1}\int_{\mathbb{R}^N}\Phi(z_\alpha) Z_{\Gamma\cap\Sigma(\boldsymbol{z}),|\det G_\Gamma|^{-1/2}}\nabla_\alpha F_\Gamma(\boldsymbol{z})\,d\boldsymbol{z}.\end{aligned} \tag{D.16}$$

On the other hand, using successively (D.4), (2.8), and the fact that the mean curvature vector of Γ is orthogonal to $\nabla_\Gamma q_\gamma$, for any $1 \leq \gamma \leq N$ we have

(D.17)
$$
\begin{aligned}
&\int_{\mathbb{R}^N} \phi(z_\alpha) \exp(-\beta F_\Gamma(\boldsymbol{z}))\, d\boldsymbol{z} \\
&\quad = Z^{-1} \int_{\mathbb{R}^N} \int_{\Gamma\cap\Sigma(\boldsymbol{z})} \phi(q_\alpha(\boldsymbol{x})) e^{-\beta V(\boldsymbol{x})} |\det G_\Gamma(\boldsymbol{x})|^{-1/2} d\sigma_{\Gamma\cap\Sigma(\boldsymbol{z})}(\boldsymbol{x}) d\boldsymbol{z} \\
&\quad = Z^{-1} \int_\Gamma \Phi'(q_\alpha(\boldsymbol{x})) e^{-\beta V(\boldsymbol{x})} d\sigma_\Gamma(\boldsymbol{x}), \\
&\quad = Z^{-1} \int_\Gamma (G_\Gamma^{-1})_{\alpha,\gamma} \nabla_\Gamma q_\gamma \cdot \nabla_\Gamma \left(\Phi \circ q_\alpha\right)(\boldsymbol{x}) e^{-\beta V(\boldsymbol{x})} d\sigma_\Gamma(\boldsymbol{x}), \\
&\quad = -Z^{-1} \int_\Gamma \mathrm{div}_\Gamma \left((G_\Gamma^{-1})_{\alpha,\gamma} \nabla_\Gamma q_\gamma e^{-\beta V} \right) (\boldsymbol{x}) \Phi \circ q_\alpha(\boldsymbol{x}) d\sigma_\Gamma(\boldsymbol{x}), \\
&\quad = Z^{-1} \int_\Gamma \left(\beta \nabla_\Gamma V \cdot (G_\Gamma^{-1})_{\alpha,\gamma} \nabla_\Gamma q_\gamma - \mathrm{div}_\Gamma \left((G_\Gamma^{-1})_{\alpha,\gamma} \nabla_\Gamma q_\gamma \right) \right)(\boldsymbol{x}) \\
&\qquad\qquad \times e^{-\beta V(\boldsymbol{x})} \Phi(q_\alpha(\boldsymbol{x})) d\sigma_\Gamma(\boldsymbol{x}), \\
&\quad = Z^{-1} \int_{\mathbb{R}^N} \Phi(z_\alpha) Z_{\Gamma\cap\Sigma(\boldsymbol{z}), |\det G_\Gamma|^{-1/2}} \\
&\qquad \times \int_{\Gamma\cap\Sigma(\boldsymbol{z})} \left(\beta \nabla_\Gamma V \cdot (G_\Gamma^{-1})_{\alpha,\gamma} \nabla_\Gamma q_\gamma - \mathrm{div}_\Gamma \left((G_\Gamma^{-1})_{\alpha,\gamma} \nabla_\Gamma q_\gamma \right) \right) \\
&\qquad\qquad \times d\mu_{\Gamma\cap\Sigma(\boldsymbol{z}), |\det G_\Gamma|^{-1/2}}\, d\boldsymbol{z}.
\end{aligned}
$$

The fact that (D.16) is equal to (D.17) for all functions Φ completes the proof of (D.13). ∎

Notice that, as a generalization of (4.9), $\nabla_\alpha F_\Gamma(\boldsymbol{z})$ can also be expressed as

$$
\begin{aligned}
&\nabla_\alpha F_\Gamma(\boldsymbol{z}) \\
&\quad = \int_{\Gamma\cap\Sigma(\boldsymbol{z})} \sum_{\gamma=1}^{N} (G_\Gamma^{-1})_{\alpha,\gamma} \nabla_\Gamma q_\gamma \cdot \left(\nabla_\Gamma V_{|\det G_\Gamma|^{-1/2}} + \beta^{-1} \boldsymbol{H}_\Gamma \right) \\
&\qquad\qquad \times d\mu_{\Gamma\cap\Sigma(\boldsymbol{z}), |\det G_\Gamma|^{-1/2}},
\end{aligned}
\tag{D.18}
$$

where $\boldsymbol{H}_\Gamma$ is defined by:

$$
\boldsymbol{H}_\Gamma = -\sum_{\alpha=1}^{N} (\kappa_\Gamma)_\alpha (\hat{\boldsymbol{n}}_\Gamma)_\alpha, \tag{D.19}
$$

with
(D.20)

$$(\kappa_\Gamma)_\alpha = |\nabla_\Gamma q_\alpha| |\det G_\Gamma|^{-1/2} \mathrm{div}_{\,\Gamma} \left(|\det G_\Gamma|^{1/2} \sum_{\gamma=1}^{N} (G_\Gamma^{-1})_{\alpha,\gamma} \nabla_\Gamma q_\gamma \right),$$

and

$$(\hat{\boldsymbol{n}}_\Gamma)_\alpha(\boldsymbol{x}) = \frac{\nabla_\Gamma q_\alpha(\boldsymbol{x})}{|\nabla_\Gamma q_\alpha(\boldsymbol{x})|}. \tag{D.21}$$

D.3 The orthogonal case

By Proposition 4.3, we know that for $1 \le \alpha \le N$,
(D.22)

$$\begin{aligned}&\lim_{T\to\infty} \lim_{\Delta t\to 0} \frac{1}{T} \sum_{m=1}^{T/\Delta t} \lambda_{\alpha,m} \\ &= \int_{\Gamma\cap\Sigma} \sum_{i=1}^{N+M} L^{-1}_{\alpha,i} \nabla r_i \cdot \left(\nabla V_{|\det G_\Gamma|^{-1/2}} + \beta^{-1} \boldsymbol{H} \right) d\mu_{\Gamma\cap\Sigma, |\det G_\Gamma|^{-1/2}},\end{aligned}$$

where we have used the $(N+M)$ dimensional constraints vector

$$\boldsymbol{r} = (q_1, \dots, q_N, c_1, \dots, c_M)$$

and the $(N+M) \times (N+M)$ matrix L:

$$L_{i,j}(\boldsymbol{x}) = \nabla r_i(\boldsymbol{x}) \cdot \nabla r_j(\boldsymbol{x}). \tag{D.23}$$

Notice that in (D.22), $\boldsymbol{H}$ is the mean curvature vector of the surface $\Gamma\cap\Sigma$:

$$\boldsymbol{H} = -\sum_{i=1}^{N+M} \kappa_i \hat{\boldsymbol{n}}_i$$

with $\hat{\boldsymbol{n}}_i = \frac{\nabla r_i}{|\nabla r_i|}$ and (see (A.5))

$$\kappa_i = |\nabla r_i| |\det L|^{-1/2} \mathrm{div} \left(|\det L|^{1/2} \sum_{j=1}^{N+M} L^{-1}_{i,j} \nabla r_j \right).$$

In the case the molecular constraints and the constraints related to the reaction coordinates are orthogonal in the sense that: $\forall 1 \le i \le M$ and $\forall 1 \le \alpha \le N$, $\nabla c_i(\boldsymbol{x}) \cdot \nabla q_\alpha(\boldsymbol{x}) = 0$ for $\boldsymbol{x} \in \Gamma \cap \Sigma$, (D.22) indeed gives the correct expression of the mean force $\nabla F_\Gamma(0)$. This is because in this case, $\forall 1 \le \alpha \le N$, $\nabla_\Gamma q_\alpha = \nabla q_\alpha$, $\forall 1 \le \alpha, \beta \le N$, $L_{\alpha,\beta} = (G_\Gamma)_{\alpha,\beta}$, $\forall 1 \le \alpha \le N$ and $\forall N+1 \le i \le M$, $L_{\alpha,i} = 0$, so that $\forall 1 \le \alpha, \beta \le N$, $L^{-1}_{\alpha,\beta} = (G_\Gamma^{-1})_{\alpha,\beta}$ and $\forall 1 \le \alpha \le N$ and $\forall N+1 \le i \le M$, $L^{-1}_{\alpha,i} = 0$. Thus, one easily obtains that:

$$\begin{aligned}
&\sum_{i=1}^{N+M} L^{-1}_{\alpha,i} \nabla r_i \cdot \left(\nabla V_{|\det G_\Gamma|^{-1/2}} + \beta^{-1} \boldsymbol{H} \right) \\
&\quad = \sum_{\gamma=1}^{N} (G_\Gamma^{-1})_{\alpha,\gamma} \nabla_\Gamma q_i \cdot \left(\nabla V_{|\det G_\Gamma|^{-1/2}} + \beta^{-1} \boldsymbol{H} \right), \\
&\quad = \sum_{\gamma=1}^{N} (G_\Gamma^{-1})_{\alpha,\gamma} \nabla_\Gamma q_\gamma \cdot \left(\nabla_\Gamma V_{|\det G_\Gamma|^{-1/2}} - \beta^{-1} \sum_{\delta=1}^{N} \kappa_\delta (\hat{\boldsymbol{n}}_\Gamma)_\delta \right).
\end{aligned}$$

Thus, it remains only to check that $\kappa_\alpha = (\kappa_\Gamma)_\alpha$, which amounts to prove that

$$\begin{aligned}
|\det K|^{-1/2} \mathrm{div} &\left(|\det K|^{1/2} (\det G_\Gamma)^{1/2} \sum_{\gamma=1}^{N} (G_\Gamma^{-1})^{-1}_{\alpha,\gamma} \nabla_\Gamma q_\gamma \right) \\
&= \mathrm{div}_\Gamma \left(|\det G_\Gamma|^{1/2} \sum_{\gamma=1}^{N} (G_\Gamma^{-1})_{\alpha,\gamma} \nabla_\Gamma q_\gamma \right),
\end{aligned}$$

using the fact that $\det L = (\det K)(\det G_\Gamma)$. This holds since for any smooth function $\boldsymbol{\phi}$ such that, $\forall \boldsymbol{x} \in \Gamma$, $Q(\boldsymbol{x})\boldsymbol{\phi}(\boldsymbol{x}) = 0$, we have:

$$\begin{aligned}
&|\det K|^{-1/2} \mathrm{div} \left(|\det K|^{1/2} \boldsymbol{\phi} \right) \\
&\quad = |\det K|^{-1/2} \mathrm{div} \left(|\det K|^{1/2} Q \boldsymbol{\phi} \right), \\
&\quad = |\det K|^{-1/2} \mathrm{div} \left(|\det K|^{1/2} Q \right) \cdot \boldsymbol{\phi} + \mathrm{div}_\Gamma(\boldsymbol{\phi}), \\
&\quad = \mathrm{div}_\Gamma(\boldsymbol{\phi}),
\end{aligned}$$

since $|\det K|^{-1/2} \mathrm{div} \left(|\det K|^{1/2} Q \right)$ is the mean curvature vector to Γ (see (A.3)) and is therefore orthogonal to $\boldsymbol{\phi}$.