

Corrected Potential Energy Functions for Constrained Molecular Dynamics

Robert D. Skeel^{1,a} and Sebastian Reich²

¹ Department of Computer Science, Purdue University

² Institut für Mathematik, Universität Potsdam

Abstract. Atomic oscillations present in classical molecular dynamics restrict the step size that can be used. Multiple time stepping schemes offer only modest improvements, and implicit integrators are costly and inaccurate. The best approach may be to actually remove the highest frequency oscillations by constraining bond lengths and bond angles, thus permitting perhaps a 4-fold increase in the step size. However, omitting degrees of freedom produces errors in statistical averages, and rigid angles do not bend for strong excluded volume forces. These difficulties can be addressed by an enhanced treatment of holonomic constrained dynamics using ideas from papers of Fixman (1974) and Reich (1995, 1999). In particular, the 1995 paper proposes the use of “flexible” constraints, and the 1999 paper uses a modified potential energy function with rigid constraints to emulate flexible constraints. Presented here is a more direct and rigorous derivation of the latter approach, together with justification for the use of constraints in molecular modeling. With rigor comes limitations, so practical compromises are proposed: simplifications of the equations and their judicious application when assumptions are violated. Included are suggestions for new approaches.

1 Introduction

Classical molecular dynamics is described by a Hamiltonian system of $6n$ first order ordinary differential equations with Hamiltonian

$$H(x, p) = U(x) + \frac{1}{2} p^\top M(x)^{-1} p, \quad (1)$$

where $U(x)$ is potential energy and $M(x)$ is a symmetric positive definite mass matrix. For Cartesian coordinates, $M(x)$ is a constant diagonal matrix, but not for more general coordinates. The integration of the equations of motion is computationally very demanding due to the need to take time steps much smaller than time scales of interest in most applications. Small time steps are due to the need to resolve bond length and bond angle vibrations. A factor of 2 increase in time step is possible by constraining covalent bonds to hydrogen atoms. However, additional constraints

^a e-mail: skeel@cs.purdue.edu

produce significant inaccuracies. The article [12] shows how to avoid such inaccuracies by modifying the potential energy function to compensate for the artifacts introduced by the aggressive use of constraints. This should perhaps provide an additional factor of 2 increase in time step. The present work is an alternative, rigorous derivation of the method of modifying the potential energy. This article also suggests and is suggestive of new approaches.

The potential energy function easily partitions as

$$U(x) = U^{\text{non}}(x) + U^{\text{osc}}(g_1(x), g_2(x), \dots, g_m(x)), \quad (2)$$

where the $g_k(x)$ are deviations of selected pairwise distances and angles from reference values. More specifically, assume the oscillatory part of U is quadratic in $g(x)$,

$$U^{\text{osc}}(\eta) = \frac{1}{2\varepsilon^2} \eta^T W^{-1} \eta, \quad \eta = [\eta_1, \eta_2, \dots, \eta_m]^T,$$

where ε is chosen so that—for typical values of x —the the eigenvalues of the Hessian of $U^{\text{non}}(x)$ do not exceed those of $\varepsilon^2 U^{\text{osc}}(g(x))$. In practice, W is diagonal, which is important only insofar that it expedites computation. In one flexible water model [8], bond stretching terms contribute frequencies of 110 ps^{-1} , angle bending terms 53 ps^{-1} , but nonbonded terms (in U^{non}) have frequencies no higher than 26 ps^{-1} . Thus, in practice, the time scale separation factor ε is not so small, perhaps only $\frac{1}{2}$. This matter is addressed in Sect. 4.

Note that the oscillatory term is highly nonlinear. Transforming to different coordinates (canonically) to make the oscillatory term quadratic would merely transfer the nonlinearity to the kinetic energy term. Additionally, the system occasionally encounters “nontypical” values of x where the assumption of scale separation between eigenvalues of the Hessians of $U^{\text{non}}(x)$ and $U^{\text{osc}}(g(x))$ does not hold.

Approximations must be done with regard to what is to be computed. For molecular dynamics there a couple of important considerations:

1. The dynamics is chaotic: accurate trajectories cannot be calculated for more than 1000 oscillations. For material science applications, short simulations are often of interest, but this is seldom the case for biology, where typical simulations last 1 000 000 oscillations.
2. Initial conditions are drawn at random (from a specified probability distribution). Typically initial values are taken from a Boltzmann distribution corresponding to a prescribed inverse temperature β .

The second of these considerations ameliorates the first in the sense that it restricts what can be calculated to statistical quantities, and such calculations are feasible in the presence of chaos. What can be computed includes time averages

$$\lim_{\tau \rightarrow +\infty} \frac{1}{\tau} \int_0^\tau A(x(t), p(t)) dt,$$

for some “observable” $A(x, p)$, and time correlation functions, which includes many statistical kinetic quantities of interest.

The limitation on the time step happens to be due to stability rather than the need to accurately resolve the vibrational motion. For this reason it is sometime suggested that implicit integrators be used. However, they are not only costly to implement, but they introduce quantitative artifacts. The mechanism by which they overcome the stability limitation is by reducing the highest frequencies so that there is less than one-third of an oscillation per time step [15]. This has the effect of increasing the amplitude of high frequency modes. Also, reduction of high frequencies compresses

their range, which increases coupling among the high frequency modes. A better approach is to impose constraints:

Freezing the values of the $g_k(x)$ to those values $\eta_k = 0$ that minimize $U^{\text{osc}}(\eta_1, \eta_2, \dots, \eta_m)$ results in the constrained Hamiltonian system

$$\frac{d}{dt}x = M(x)^{-1}p, \quad \frac{d}{dt}p = -H_x(x, p)^\top - g_x(x)^\top \lambda, \quad g(x) = 0,$$

where the Lagrange multipliers λ are determined by the constraints $g(x) = 0$. Differentiating the position constraints with respect to time reveals hidden constraints $g_x(x)M(x)^{-1}p = 0$ on the momenta.

Note 1 The use of an independent variable like x as a subscript denotes a Jacobian matrix. Applied to a scalar, it creates is a row vector. A double subscript denotes a Hessian.

Constraints are a type of coarse-graining, since they introduce an uncontrolled approximation of the original model using fewer degrees of freedom, e.g., see [3] in the present volume. It has long been known [6] that constrained dynamics can produce incorrect time averages due to neglect of entropic effects of the missing degrees of freedom. This can be corrected by including a ‘‘Fixman potential’’ in the potential energy function. Not long after, it was discovered [16] that angle constraints can significantly increase the height of energy barriers, because rigid angles do not bend for strong excluded volume forces. Because of this problem (and the inconvenience of including a Fixman potential), only bond lengths and not bond angles are routinely constrained, yielding an increase in the step size by a factor of 2 only. In cases where angles *are* constrained, the excluded volume part of the Lennard-Jones potential is softened to compensate for the rigidity of the angles.

The problem of rigid angles is addressed in a systematic way in the article [11], which proposes flexible constraints (in the form of a modification to the constraints). Conventional constraints simply fix distances, and possibly angles, between selected pairs of atoms. They are obtained by identifying very strong bonded interactions in the force field. Flexible constraints generalize this process by making these distances and angles responsive to other forces—in practice, just to the strongest forces such as excluded volume forces. Analytical results in [11] establish accuracy for time averages and short-time trajectories. An application is given in the article [17]. For recent accounts of flexible constraints, see [4, 13] in the present volume.

However, flexible constraints are complicated and computationally costly, so an alternative is introduced in [12] based on *employing conventional rigid constraints* and, instead, modifying the potential energy function to mimic the flexible constraint dynamics. Figure 1 of that article compares full dynamics to the use of a constraint with a modified potential for the collision of two water molecules. For the purpose of comparison, the coordinates for the modified potential simulation are transformed back to coordinates for the equivalent flexible constraint dynamics. It is seen that the dynamics of a bond angle are visually indistinguishable between the two simulations.

The present article is a direct first-principles derivation of the approach based on modifying the potential energy function. It also offers justification for the introduction of holonomic constraints in molecular modeling. The explicit construction of a corrected potential enables a partial assessment of the quality of a constrained model using an uncorrected potential. The section that follows gives a statement of the theoretical results. Rigorous results have limitations, so practical compromises are proposed: simplifications of the equations and their judicious application when assumptions are violated. These practical issues are discussed for biomolecules in Sect. 3, including a suggested new approach. This is followed by a brief discussion section. The last two sections contain the detailed derivations and arguments.

2 Results

Here for convenient reference is a glossary of those symbols that might easily be confused with each other:

- position variables:
 $x = X(\xi, \eta)$ original, $\xi = b(x)$ slow, $\eta = g(x)$ fast, $Z(x) = [b(x)^\top \ g(x)^\top]^\top$.
- momenta variables:
 $p = P(\xi, \eta, \nu, \pi)$ original, ν slow, $\pi = h(x, p)$ fast.
- Hamiltonians:
 $H(x, p)$ original, $K(\xi, \eta, \nu, \pi)$ transformed,
 $\bar{H}(x, p)$ modified, $\bar{K}(\xi, \eta, \nu, \pi)$ transformed,
 $\bar{H}^+(x, p)$ unconstrained modified, $\bar{K}^+(\xi, \eta, \nu, \pi)$ transformed.
- potential energy functions:
 $U(x)$ original, $V(\xi, \eta)$ transformed,
 $U^{\text{osc}}(g(x))$ oscillatory part, $U^{\text{non}}(x)$ nonoscillatory part,
 $\bar{U}(x)$ modified, $\bar{V}(\xi, \eta)$ transformed,
 $U^*(x; \eta)$ momenta-averaged, $V^*(\xi, \eta)$ transformed,
 $\hat{U}(x; \eta)$ nonoscillatory part of $U^*(x; \eta)$,
 $U^{\text{F}}(x)$ Fixman part of $\hat{U}(x; \eta)$, $V^{\text{F}}(\xi)$ transformed,
 $U^{\text{K}}(x; \eta)$ another part of $\hat{U}(x; \eta)$, $V^{\text{K}}(\xi, \eta)$ transformed.
- superscript 0 denotes setting $\eta = 0$, superscript 00 denotes also setting $\pi = 0$.

2.1 The reduced model

A typical route to coarse-graining begins with the Mori-Zwanzig formalism [1, p. 257], which involves a stochastic noise term and a memory kernel. Equations of this type require parameters that cannot be determined analytically but must be obtained by CPU-intensive numerical calculations. To avoid this, consideration is restricted to a model based on ordinary differential equations. An added virtue of nondissipative deterministic models is that they are sensitive to poor parameter choices and implementation errors.

To get reasonable phase space densities for the dynamics, it seems necessary to use *Hamiltonian* dynamics on the $(3n - m)$ -dimensional configuration manifold \mathcal{M} : $g(x) = 0$. This can be achieved conveniently with holonomic constraints.

Given a Hamiltonian system with Hamiltonian H given by Eq. (1) and initial conditions $x(0) = x_0$, $p(0) = p_0$, the goal is to approximate its dynamics by a constrained Hamiltonian system,

$$\frac{d}{dt}x = M(x)^{-1}p, \quad \frac{d}{dt}p = -\bar{H}_x(x, p)^\top - g_x(x)^\top \lambda, \quad g(x) = 0.$$

with Hamiltonian $\bar{H}(x, p) = \bar{U}(x) + \frac{1}{2}p^\top M(x)^{-1}p$ having a modified potential $\bar{U}(x)$ and with initial conditions $x(0) = x'_0$, $p(0) = p'_0$ on the cotangent bundle $\text{T}\mathcal{M}$: $g(x) = 0$, $g_x(x)M(x)^{-1}p = 0$. To be constructed are

1. a nonlinear projection from phase space onto $\text{T}\mathcal{M}$ (if only to get proper initial conditions) and
2. a corrected potential energy function \bar{U} .

The construction proceeds as follows:

1. Express the constrained Hamiltonian system as an equivalent unconstrained Hamiltonian system with Hamiltonian \bar{H}^+ for which $\text{T}\mathcal{M}$ is an invariant manifold.

2. Compare this to the original system by canonically transforming to new position variables $[\xi^\top, \eta^\top]^\top$ and momenta variables $[\nu^\top, \pi^\top]^\top$ for which the constraint $g(x) = 0$ becomes $\eta = 0$ and the hidden constraint $g_x(x)M(x)^{-1}p = 0$ becomes $\pi = 0$. Let $x = X(\xi, \eta)$, $p = P(\xi, \eta, \nu, \pi)$ denote the transformation. The transformed energy functions are $K = H(X, P)$, $\bar{K} = \bar{H}(X, P)$, $\bar{K}^+ = \bar{H}^+(X, P)$, $V = U(X)$, $\bar{V} = \bar{U}(X)$, and $T = \frac{1}{2}P^\top M(X)P$, where the omitted arguments are either (ξ, η) or (ξ, η, ν, π) .
3. Construct the corrected potential energy \bar{U} so that the dynamics of $\bar{K}^{00}(\xi, \nu) \stackrel{\text{def}}{=} \bar{K}^+(\xi, 0, \nu, 0)$ well approximates that of $K(\xi, \eta, \nu, \pi)$. Use only $U(x)$, $M(x)$, and $g(x)$ and their derivatives to define \bar{U} . In particular, the function $\bar{U}(x)$ must be independent of any parameterization of the manifold \mathcal{M} .

Sect. 5.1 shows that the constrained Hamiltonian system is equivalent to an unconstrained Hamiltonian system with Hamiltonian $\bar{H}^+ = \bar{H} + g^\top \Lambda$ where $\Lambda(x, p)$ is given in Eq. (13).

Sects. 5.2 and 5.3 present a transformation to new variables where $\eta = g(x)$. It follows that the transformed Hamiltonian

$$\bar{K}^+ = T + \bar{V} + \eta^\top \Lambda(X, P) \quad (3)$$

(where innermost arguments have been omitted).

Define $G(x)$ by

$$G = (g_x M^{-1} g_x^\top)^{-1} g_x M^{-1}.$$

Appropriate projected values x' , p' are obtained in Sect. 5.4. In particular, the projected value x' is given by $x' = \Xi(x; -g(x))$ where $\Xi(x; \eta)$ is the solution of the initial value problem

$$\frac{d}{ds} \Xi^s = G(\Xi^s)^\top \eta, \quad \Xi^0 = x.$$

at $s = 1$. Note that $\Xi(x; \eta)$ is independent of the transformation $X(\xi, \eta)$, so it can be computed without specifying transformed position coordinates.

Note 2 When used in the same expression, both x and η are to be regarded as independent variables. (Otherwise, either g or X would be used.)

2.2 A desirable property

The goal is to fit for kinetics as well as thermodynamics. Fitting for kinetics includes reproducing time averages. However, fitting to time averages exhausts all the flexibility that is available with a *deterministic* constrained dynamics (not to mention difficulties that might be encountered in trying to match kinetic quantities). Bond length constraints apparently succeed in retaining coarser features of the kinetics. Limited theoretical and empirical evidence [11] suggests that the use of flexible constraints for bond angles can reproduce kinetic quantities. This gives hope that such might be the case for angle constraints coupled with a modified potential energy function. A known kinetic artifact for bond angle constraints involves excessive energy barrier heights. Fitting to time averages helps to maintain correct energy barrier heights, addressing the problem of the rigid angles reducing the frequency of barrier crossings.

Consider then the question of getting time averages computed with the reduced dynamics of Hamiltonian $\bar{K}^{00}(\xi, \nu)$ to match those computed with the dynamics of Hamiltonian $K(\xi, \eta, \nu, \pi)$. Because only modifications to the potential energy term U are being considered, time averages can be duplicated only for observables $A(x)$

that depend on x alone (which includes most observables of practical interest). And because the dynamics is restricted to the manifold $g(x) = 0$, it will be seen that time averages can be duplicated only for observables $A(x)$ that are “independent” of $g(x)$. The concept of independence depends on a notion of orthogonality. The precise assumption, justified in Sect. 5.3, is $g_x M^{-1} A_x^\top = 0$. For observables of interest, this is satisfied only approximately.

Giving the same time averages is equivalent to \bar{K}^{00} giving the same microcanonical ensemble averages as K (assuming ergodicity). If this is to hold for arbitrary observables $B(\xi)$, it must be that

$$\int \delta(\bar{V}^0(\xi) + T^{00}(\xi, \nu) - E') d\nu = \text{const} \int \int \int \delta(K(\xi, \eta, \nu, \pi) - E) d\eta d\nu d\pi$$

where $\bar{V}^0(\xi) \stackrel{\text{def}}{=} \bar{V}(\xi, 0)$, $T^{00}(\xi, \nu) \stackrel{\text{def}}{=} T(\xi, 0, \nu, 0)$, $E' = H(x'_0, p'_0)$, and $E = H(x_0, p_0)$. Hence, the requirement of giving the same time averages uniquely determines $\bar{V}^0(\xi) = \bar{U}(X(\xi, 0))$ and, thus, uniquely determines $\bar{U}(x)$ for $x \in \mathcal{M}$.

2.3 Simplifying assumption

The choice of a Hamiltonian model is motivated by having a reduced model that requires very little computational preprocessing. To be able to proceed analytically, the microcanonical ensemble is approximated by a canonical ensemble. This is a good approximation for larger systems, since microcanonical ensemble averages are the same as canonical ensemble averages in the thermodynamic limit $n \rightarrow \infty$, with an error is proportional to n^{-1} [1, p. 45]. Hence, seek an equality of probability densities for canonical ensemble averages:

$$\exp(-\beta \bar{V}^0(\xi)) \int \exp(-\beta T^{00}(\xi, \nu)) d\nu = \text{const} \int \int \int \exp(-\beta K(\xi, \eta, \nu, \pi)) d\eta d\nu d\pi. \quad (4)$$

It is shown by Prop. 4 that

$$\exp(-\beta \bar{V}^0(\xi)) = \text{const} \int \exp(-\beta U^*(X(\xi, 0); \eta)) d\eta \quad (5)$$

where

$$U^*(x; \eta) = U(\Xi(x; \eta)) + U^{\text{F}}(x) + U^{\text{K}}(x; \eta) \quad (6)$$

with

$$\beta U^{\text{F}}(x) = \frac{1}{2} \log \det(g_x(x) M(x)^{-1} g_x(x)^\top)$$

and

$$\beta U^{\text{K}}(x; \eta) = \frac{1}{2} \log \det M(x) - \frac{1}{2} \log \det M(\Xi(x; \eta)) + \int_0^1 (\nabla_x^\top G^\top)(\Xi(x; s\eta)) \eta ds. \quad (7)$$

Note that $U^*(x; \eta)$ is constructed in terms of the given functions $M(x)$, $U(x)$, and $g(x)$. The second term $U^{\text{F}}(x)$ is the Fixman potential. For $\eta = 0$, Eq. (6) simplifies to $U^*(x; 0) = U^{\text{non}}(x) + U^{\text{F}}(x)$. Recall from Eq. (2) that $U^{\text{non}}(x)$ is the nonoscillatory part of $U(x)$. Formula (5) for $\bar{V}^0(\xi)$ can be expressed as

$$\exp(-\beta \bar{U}(x)) = \text{const} \int \exp(-\beta U^*(x; \eta)) d\eta, \quad x \in \mathcal{M}. \quad (8)$$

Note 3 It is assumed that all quantities are physically dimensionless. Otherwise, it would be necessary to insert constants into the arguments of logarithms to render them dimensionless.

2.4 An asymptotic expansion

Under the assumption that $U^{\text{non}}(x)$ is bounded below, the term $1/(2\varepsilon^2)\eta^\top W^{-1}\eta$ can be pulled out of $U^*(x; \eta)$ to yield an asymptotic expansion in powers of ε , which can be carried out to any number of terms. The resulting expansion for the corrected potential energy is

$$\bar{U}(x) = U^{\text{non}}(x) + U^{\text{F}}(x) - \frac{\varepsilon^2}{2} f(x)^\top W f(x) + \frac{\varepsilon^2}{2\beta} \text{tr}(WG(x)f_x(x)^\top) + \mathcal{O}(\varepsilon^4) \quad (9)$$

where

$$f(x) = G(x)U_x^{\text{non}}(x)^\top - \frac{1}{2\beta}G(x)(\log \det M(x))_x^\top + \frac{1}{\beta}(\nabla_x^\top G(x)^\top)^\top.$$

3 Application to Biomolecules

We conclude with an illustration of how these ideas might be applied to biomolecules. The implementation is easier than it might seem and the incremental cost in CPU time is modest.

The parameter $1/\beta$ is of modest size compared to energy barriers separating interesting conformations or states of the system. If terms of order ε^2/β are neglected, the expansion given above simplifies to

$$\bar{U} = U^{\text{non}}(x) + U^{\text{F}}(x) - \frac{\varepsilon^2}{2} U_x^{\text{non}}(x)G(x)^\top WG(x)U_x^{\text{non}}(x)^\top + \mathcal{O}(\varepsilon^2/\beta + \varepsilon^4). \quad (10)$$

This is in agreement with that obtained in [12, Eqs. (11)–(13)].

The term $-\frac{1}{2}\varepsilon^2 U_x^{\text{non}}G^\top WG(U_x^{\text{non}})^\top$ can be regarded as a theoretically justified way to soften the excluded volume forces when they encounter restraints. In practice, one can replace $U^{\text{non}}(x)$ in the 3rd term by $U^{\text{hard}}(x)$ where $U^{\text{hard}}(x)$ is the short-range part of the Lennard-Jones potential.

It happens that there may be a flaw in this formula caused by the truncation of an asymptotic expansion, which is illustrated by the following example:

Example 1 Consider unit masses with

$$U(x) = \frac{1}{2\varepsilon^2 W} (x_2 - x_1 - 2)^2 + \frac{1}{2}((2 + x_1)^{-12} + (2 - x_2)^{-12}), \quad -2 < x_1 < x_2 < 2.$$

This describes two particles connected by a harmonic bond of rest length 2, which are between two fixed particles at positions ± 2 (neglecting the less significant $1/r^{12}$ excluded volume terms). Choosing $W^{-1} = 78$ balances the Hessians of the two terms at the energy minimum for $\varepsilon = 1$. Defining $g(x) = x_2 - x_1 - 2$ and applying the preceding formulas gives $G(x) = \begin{bmatrix} -\frac{1}{2} & \frac{1}{2} \end{bmatrix}$ and

$$G(x)U_x^{\text{non}}(x)^\top = 3((2 + x_1)^{-13} + (2 - x_2)^{-13}).$$

For $x \in \mathcal{M}$ we can write $x_1 = \xi - 1$ and $x_2 = \xi + 1$. Formula (10) for the corrected energy on the manifold gives

$$\bar{U} = \frac{1}{2}((1 + \xi)^{-12} + (1 - \xi)^{-12}) - \frac{3}{52}\varepsilon^2((1 + \xi)^{-13} + (1 - \xi)^{-13})^2.$$

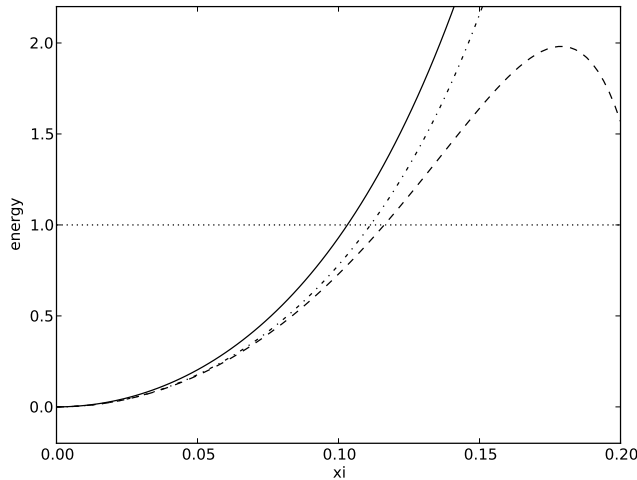


Fig. 1. Plot of energy as a function of ξ for original potential energy (solid), the modified one (dashed), the alternative modified one (dash-dot), and β^{-1} . Here $\varepsilon = \frac{1}{2}$.

Note that, as ξ varies from 0 to ± 1 , the “corrected” energy first increases steeply; but beyond a certain point, it plunges to $-\infty$ as the bonded particles approach the fixed particles at $\xi = \pm 1$. The energy barrier is at the two points $\xi = \pm \xi^*$, $\xi^* = 1 - (\varepsilon/2)^{1/7} + \mathcal{O}(\varepsilon^2)$. The height of this barrier is $\frac{7}{13}(2/\varepsilon)^{12/7} + \mathcal{O}(1)$.

The explanation for this dangerous anomaly is that the approximation derived in Sect. 6.2 is not uniformly good for all $x \in \mathcal{M}$ and becomes quantitatively worthless on some high energy parts of \mathcal{M} . These are low probability parts of configuration space, which contribute little to most (but not all) observable averages. For most observables, it is enough to have an approximation that is merely qualitatively correct in regions of high energy. This can be achieved as follows: The derivation uses an approximation of the form $-\log(1 + \delta_1 - \delta_2) \approx -\delta_1 + \delta_2$ in Eq. (24). One might instead use an approximation $-\log(1 + \delta_1 - \delta_2) \approx (1 + \delta_1)^{-1} - 1 + \delta_2$, in which case the term $-\frac{\varepsilon^2}{2} f(x)^\top W f(x)$ in Eq. (9) becomes

$$\beta^{-1} \left(1 + \frac{1}{2} \beta \varepsilon^2 f(x)^\top W f(x) \right)^{-1} - \beta^{-1}. \quad (11)$$

Figure 1 gives a plot for the original and two modified potential energy functions for $\varepsilon = \frac{1}{2}$ and $\beta^{-1} = 1$. The point at which the alternative modified potential energy function separates from the other modified one can be controlled by scaling β in formula (11).

The article [12] suggests an alternative approach that not only avoids catastrophes but also avoids evaluation of the Hessian of $U^{\text{non}}(x)$ when evaluating the corrected force $-\bar{U}_x(x)^\top$. The idea is to replace the first and third term of the right-hand side of Eq. (10) by $\tilde{U}(x) = U(x - \varepsilon^2 G(x)^\top \omega(x))$ where the m elements of $\omega(x)$ are defined implicitly by the system of m equations

$$G(x) U_x(x - \varepsilon^2 G(x)^\top \omega(x))^\top = 0.$$

It can be verified that $\omega(x) = WG(x)U_x^{\text{non}}(x)^\top + \mathcal{O}(\varepsilon^2)$ and that the calculation of the force $-\tilde{U}_x(x)^\top$ does not require $\omega_x(x)$. The drawback of this approach is the need to iterate, and repeatedly reevaluate forces, to solve for $\omega(x)$.

For application to biomolecules, assume the use of Cartesian coordinates, so that M is constant. Also suppose that bond length and angle constraints are to be imposed.

The computation of the modified potential energy requires matrix–vector products of the Jacobian matrix g_x of constraint functions with other vectors. This Jacobian matrix is needed in any case to solve the constraint equations. Because it is sparse, g_x should not be explicitly assembled; rather each row of g_x should be stored in compact form. To this end, note that each constrained angle θ_{ijk} can be expressed in terms of distances using the identity

$$\cos \theta_{ijk} = \frac{r_{ij}^2 + r_{jk}^2 - r_{ki}^2}{2r_{ij}r_{jk}}$$

where atomic positions $\mathbf{r}_i, \mathbf{r}_j, \mathbf{r}_k$ define θ_{ijk} , $\mathbf{r}_{ij} = \mathbf{r}_j - \mathbf{r}_i$, and $r_{ij} = |\mathbf{r}_{ij}|$. This identity can be used to express each angle constraint as some function $\gamma(r_{ij}, r_{jk}, r_{ki})$ of the 3 distances. For the purpose of evaluating inner products of vectors, it is enough to store $\mathbf{r}_{ij}, \mathbf{r}_{jk}$, and the 3 (constant) partial derivatives of γ evaluated at (r_{ij}, r_{jk}, r_{ki}) . To avoid the explicit inverse of $g_x M^{-1} g_x^\top$, a sparse factorization can be efficiently computed by exploiting the near tree-like graph structure of the pattern of nonzeros in the matrix. By an appropriate ordering of unknowns, disulphide bridges can be accommodated with marginal fill in. (Place the bridging sulphurs last.) The matrix factorization would be needed, anyway, for a rapid solution of the constraint equations. For further information on solving constraint equations, see [5]. Evaluation of the modified force requires products of the Hessians of the constraints $g_{k,xx}$ with vectors. These Hessians can be computed at the same time as the gradients and stored in *unassembled* form in terms of $\mathbf{r}_{ij}, \mathbf{r}_{jk}$, and several (constant) scalars involving the first and (5 of) the second partial derivatives of γ evaluated at (r_{ij}, r_{jk}, r_{ki}) .

For U^{hard} , use the repulsive part of the Lennard-Jones potential, but with a shorter cutoff than the Lennard-Jones potential itself. The computation of $U^{\text{hard}}, U_x^{\text{hard}}$, and U_{xx}^{hard} can be done at the same time as the Lennard-Jones potential with little additional cost. The Hessian U_{xx}^{hard} is required only in the form of a matrix–vector product, and, because it is sparse, it need not be explicitly assembled. Rather, it can be computed as a list of Hessians, one for each active 2-body interaction, and each 2-body Hessian can be stored in unassembled form, e.g., as a displacement \mathbf{r}_{ij} and a pair of scalar values.

For the value of the energy, use Eq. (10) adjusted as in formula (11):

$$\bar{U} = U^{\text{non}} + U^{\text{F}} + \beta^{-1} \left(1 + \frac{1}{2} \beta f^\top W_\varepsilon f \right)^{-1} - \beta^{-1}$$

where

$$f = G(U_x^{\text{non}})^\top \quad \text{and} \quad W_\varepsilon = \varepsilon^2 W.$$

(The somewhat arbitrary extraction of ε from W_ε was for the purpose of making the analysis more transparent.) The exact calculation of the Fixman potential is practical, using a triangular factorization of $g_x M^{-1} g_x^\top$. However, the Fixman force would require an explicit inverse of $g_x M^{-1} g_x^\top$, which is not sparse. See Reich [10, Sect. 5] for how this might be approximated in a practical way.

For evaluation of the force, use

$$\bar{U}_x^\top = (U_x^{\text{non}})^\top + (U_x^{\text{F}})^\top - \left(1 + \frac{1}{2} \beta f^\top W_\varepsilon f \right)^{-2} f_x^\top W_\varepsilon f$$

and

$$f_x^\top W_\varepsilon f = U_{xx}^{\text{hard}} G^\top W_\varepsilon f + \sum_{k=1}^m ((g_x M^{-1} g_x^\top)^{-1} W_\varepsilon f)_k g_{k,xx} M^{-1} ((U_x^{\text{hard}})^\top - g_x^\top G (U_x^{\text{hard}})^\top) - \sum_{k=1}^m (G (U_x^{\text{hard}})^\top)_k g_{k,xx} G^\top W_\varepsilon f$$

where the subscript k denotes the k th element. The derivation of this last expression is fairly intricate. Note that by reusing common subexpressions and exploiting associativity of matrix multiplication, the operation count can be kept quite low.

4 Discussion

The key result is formula (9) and the formulation in Sect. 3 of its practical application.

Yet to be considered is the value of an approximation based on the assumption of a small value for the parameter ε , representing the separation of time scales, in situations where it is not so small, e.g., $\varepsilon \approx \frac{1}{2}$ for a model of flexible water. First, note that the expansion is in powers of ε^2 . Second, an asymptotic expansion has the virtue of giving a well defined result, and, as illustrated, if supplemented by good judgment, it can be adjusted to produce an approximation having good qualities. Also, the success of relatively crude models suggests that although the omission of the fastest scales moderately perturbs the dynamics of the next-to-fastest scales, it has little effect on the slowest scales. Finally, there may exist other applications for which ε is much smaller.

As discussed in Section 2.2, the use of a reduced Hamiltonian model does not provide enough freedom to explicitly match both the thermodynamics and the kinetics. At the same time, this approach does explicitly address an identified weakness of the use of torsion dynamics with an unmodified potential energy function, namely, the increase in energy barrier heights due to the refusal of angles to bend in response to strong excluded volume forces.

Finally, as explained in the preceding section, the extra cost is modest—less than the cost of imposing constraints.

5 Construction of the Projection

5.1 An equivalent unconstrained modified Hamiltonian system

We recall that a Hamiltonian system with holonomic constraints can be formulated as an unconstrained Hamiltonian system for which $\text{T}\mathcal{M}$ is an invariant manifold: Let $x(t)$, $p(t)$ satisfy the constrained Hamiltonian system

$$\frac{d}{dt}x = \bar{H}_p(x, p)^\top, \quad \frac{d}{dt}p = -\bar{H}_x(x, p)^\top - g_x(x)^\top \lambda, \quad g(x) = 0,$$

(with initial conditions that satisfy the constraints). Differentiating $g(x(t)) \equiv 0$ gives the momenta constraints $h(x(t), p(t)) \equiv 0$ where

$$h(x, p) = G(x)p. \tag{12}$$

Differentiating again with respect to t gives

$$h_x \bar{H}_p^\top + h_p (-\bar{H}_x^\top - g_x^\top \lambda) = 0,$$

which can be solved to yield $\lambda = h_x \bar{H}_p^\top - h_p \bar{H}_x^\top$, transforming the given constrained modified Hamiltonian system into an unconstrained Hamiltonian system with Hamiltonian

$$\bar{H}^+ = \frac{1}{2} p^\top M p + \bar{U} + g^\top \Lambda \quad \text{where } \Lambda = h_x \bar{H}_p^\top - h_p \bar{H}_x^\top. \quad (13)$$

5.2 Canonical change of variables

To compare Eq. (13) to the original system, it is convenient to effect a change of coordinates

$$x = X(\xi, \eta), \quad p = P(\xi, \eta, \nu, \pi),$$

for which the invariant manifold $\mathcal{T}\mathcal{M}$ becomes $\eta = 0, \pi = 0$. Hence, we consider a new coordinate system of the form

$$\begin{bmatrix} \xi \\ \eta \end{bmatrix} = Z(x) = \begin{bmatrix} b(x) \\ g(x) \end{bmatrix}, \quad (14)$$

where b is to be determined. Coordinates η might be considered to be fast variables and ξ slow variables. As stated previously, the final results are formulated independently of $b(x)$. In particular, the projection depends only on $g(x)$ and $M(x)$ and their derivatives.

It is convenient to work with Hamiltonian dynamics. To obtain this on the configuration manifold \mathcal{M} , extend $x = X(\xi, \eta)$ to phase space canonically: define momenta ν, π for the new coordinates ξ, η so that the transformation $x = X(\xi, \eta), p = P(\xi, \eta, \nu, \pi)$ is *symplectic* [9, 14, 7]:

$$P(\xi, \eta, \nu, \pi) = [X_\xi \ X_\eta]^{-\top} \begin{bmatrix} \nu \\ \pi \end{bmatrix} = Z_x(X)^\top \begin{bmatrix} \nu \\ \pi \end{bmatrix} = [b_x(X)^\top \ g_x(X)^\top] \begin{bmatrix} \nu \\ \pi \end{bmatrix}. \quad (15)$$

Because the transformation is symplectic, its Jacobian matrix

$$S = \begin{bmatrix} X_\xi & X_\eta & 0 & 0 \\ P_\xi & P_\eta & P_\nu & P_\pi \end{bmatrix} \quad \text{satisfies } S^\top \begin{bmatrix} 0 & I \\ -I & 0 \end{bmatrix} S = \begin{bmatrix} 0 & I \\ -I & 0 \end{bmatrix},$$

whence

$$S^{-1} = \begin{bmatrix} P_\nu^\top & 0 \\ P_\pi^\top & 0 \\ -P_\xi^\top & X_\xi^\top \\ -P_\eta^\top & X_\eta^\top \end{bmatrix}.$$

5.3 Modified Hamiltonian system of reduced dimension

Proposition 1 *To have $\eta = 0, \pi = 0$ as an invariant manifold for the Hamiltonian system with Hamiltonian $\bar{K}^+(\xi, \eta, \nu, \pi)$ given by Eq. (3), it is necessary that $g_x(x)M(x)^{-1}b_x(x)^\top = 0$ on $g(x) = 0$, or, equivalently, that $X_\eta^\top M(X)X_\xi = 0$ for $\eta = 0$.*

Proof It is necessary that $(d/dt)\eta = 0$ whenever $\eta = \pi = 0$. From Eq. (3), it follows that

$$0 = \bar{K}_\pi^+ = P^\top M(X)^{-1} P_\pi \quad \text{for } \eta = \pi = 0.$$

and from Eq. (15) that

$$0 = \nu^\top b_x(X) M(X)^{-1} g_x(X)^\top \quad \text{for } \eta = 0,$$

which establishes the first orthogonality condition. It also follows that

$$\begin{bmatrix} X_\xi^\top \\ X_\eta^\top \end{bmatrix} M(X) \begin{bmatrix} X_\xi \\ X_\eta \end{bmatrix} = \left(\begin{bmatrix} b_x(X) \\ g_x(X) \end{bmatrix} M(X)^{-1} \begin{bmatrix} b_x(X)^\top \\ g_x(X)^\top \end{bmatrix} \right)^{-1},$$

proving the equivalence of the two orthogonality conditions. \square

Proposition 2 *To have $\eta = 0$, $\pi = 0$ as an invariant manifold, it is sufficient that $g_x(x)M(x)^{-1}b_x(x)^\top = 0$ on $g(x) = 0$.*

Proof It is enough to show that $(d/dt)\eta = (d/dt)\pi = 0$ whenever $\eta = \pi = 0$. The first of these is shown in the proof of Proposition 1, so we need only show that $\bar{K}_\eta^+ = 0$ whenever $\eta = \pi = 0$. From Eqs. (3) and (13), it follows that

$$\bar{K}_\eta^+ = \bar{H}_x(X, P)X_\eta + \bar{H}_p(X, P)P_\eta + \Lambda(X, P)^\top \quad \text{for } \eta = \pi = 0$$

where

$$\Lambda(X, P)^\top = \bar{H}_p(X, P)h_x(X, P)^\top - \bar{H}_x(X, P)h_p(X, P)^\top.$$

The relation $X_\eta^\top M(X)X_\xi = 0$ for $\eta = 0$ implies

$$\begin{aligned} [P_\nu \ P_\pi] &= [X_\xi \ X_\eta]^{-\top} \\ &= [M(X)X_\xi(X_\xi^\top M(X)X_\xi)^{-1} M(X)X_\eta(X_\eta^\top M(X)X_\eta)^{-1}] \quad \text{for } \eta = 0. \end{aligned}$$

From $g_x(X) = P_\pi^\top$, it is straightforward to show that

$$G(X) = X_\eta^\top \quad \text{for } \eta = 0. \tag{16}$$

Since $h_p(X, P) = G(X)$, the expression for \bar{K}_η^+ simplifies to

$$\bar{K}_\eta^+ = P^\top M(X)^{-1} (h_x(X, P)^\top + P_\eta) \quad \text{for } \eta = \pi = 0.$$

Using the expression for P_ν , the expression for \bar{K}_η^+ becomes

$$\bar{K}_\eta^+ = \nu^\top (X_\xi^\top M(X)X_\xi)^{-1} X_\xi^\top (h_x(X, P)^\top + P_\eta) \quad \text{for } \eta = \pi = 0.$$

For $\eta = \pi = 0$, $h(X, P) = G(X)b_x(X)^\top \nu = 0$; hence,

$$h_x(X, P)X_\xi + h_p(X, P)P_\xi = 0 \quad \text{for } \eta = \pi = 0$$

and

$$\bar{K}_\eta^+ = \nu^\top (X_\xi^\top M(X)X_\xi)^{-1} (-P_\xi^\top X_\eta + X_\xi^\top P_\eta).$$

The sum in parentheses vanishes as a consequence of the symplectic property of the transformation $x = X$, $p = P$. \square

5.4 Projection mapping

We assume that $b(x)$ is defined so that

$$g_x(x)M(x)^{-1}b_x(x)^\top = 0 \quad \text{for all } x, \quad (17)$$

which means that the ξ -coordinates are required to be $M(x)^{-1}$ -orthogonal to the η -coordinates. Existence of $b(x)$ follows [11, Sec. 2] from Frobenius' theorem [2]. The construction may break down far from the manifold \mathcal{M} , but these parts of configuration space have “low probability,” and the analysis that justifies the proposed approximations can, in principle, be extended to handle this possibility.

Assumption Eq. (17) produces a simplified formula for momenta π : Multiply Eq. (15) by $G(X)$ and use Eq. (17) to obtain $G(X)P = \pi$; whence

$$\pi = h(x, p)$$

where $h(x, p)$ is defined by Eq. (12).

Define mappings $\Xi(x; \eta)$ and $\Pi(x, p; \eta, \pi)$ by the relations

$$\begin{aligned} \Xi(X(\xi', \eta'); \eta) &= X(\xi', \eta' + \eta), \\ \Pi(P(\xi', \eta', \nu', \pi'); \eta, \pi) &= P(\xi', \eta' + \eta, \nu', \pi' + \pi). \end{aligned} \quad (18)$$

The projection onto \mathcal{TM} is given by $x' = \Xi(x; -g(x))$, $p' = \Pi(x, p; -g(x), -h(x, p))$.

We can compute these mappings without knowing the complete transformation $X(\xi, \eta)$. The basic idea is to define them as the solution of a system of ordinary differential equations involving known functions. To do this, we need expressions for X_η , P_η , P_π that use only the values X and P and formulas for $M(x)$ and $g(x)$ and their derivatives w.r.t. x : Forming the Jacobian matrix of $h(X, P) = \pi$ gives $[h_x(X, P) \ h_p(X, P)] S = [0 \ 0 \ 0 \ I]$, whence

$$[h_x(X, P) \ h_p(X, P)] = [-P_\eta^\top \ X_\eta^\top]. \quad (19)$$

Proposition 3 *The mappings Ξ , Π are the solution at $s = 1$ of the ordinary differential equations*

$$\frac{d}{ds} \Xi^s = G(\Xi^s)^\top \eta, \quad \frac{d}{ds} \Pi^s = -h_x(\Xi^s, \Pi^s)^\top \eta + g_x(\Xi^s)^\top \pi$$

with initial values $\Xi^0 = x$, $\Pi^0 = p$.

Proof Define $\Xi^s = \Xi(x; s\eta)$ and $\Pi^s = \Pi(x, p; s\eta, s\pi)$. Write $x = X(\xi', \eta')$, whence $\Xi(x; s\eta) = X(\xi', \eta' + s\eta)$. Then, using Eq. (19),

$$\frac{d}{ds} \Xi^s = X_\eta \eta = G(X)^\top \eta = G(\Xi^s)^\top \eta.$$

The equation for $(d/ds)\Pi^s$ follows in a similar way. \square

6 Construction of the corrected potential energy function

The aim is to construct an approximation for $\bar{V}^0(\xi)$ in Eq. (4) of the form $\bar{V}^0(\xi) = \bar{U}(X(\xi, 0))$. This is done in two stages: (i) averaging over ν , π exactly, and (ii) averaging over η asymptotically.

6.1 Averaging over the momenta

Lemma 1

$$\exp(-\beta\bar{V}^0(\xi)) = \text{const} \int \exp(-\beta V^*(\xi, \eta)) d\eta$$

where $V^* = U(X) + U^F(X^0) + V^K$ with

$$\beta U^F(x) = \frac{1}{2} \log \det(g_x(x)M(x)^{-1}g_x(x)^\top),$$

$$\beta V^K = \frac{1}{2} \log \det M(X) - \frac{1}{2} \log \det M(X^0) - \log \det Z_x(X) + \log \det Z_x(X^0),$$

and $X^0 = X^0(\xi) = X(\xi, 0)$.

Proof We write Eq. (4) as

$$\exp(-\beta\bar{V}^0(\xi)) = \text{const} \int \exp(-\beta V^*(\xi, \eta)) d\eta \quad (20)$$

where

$$\exp(-\beta V^*(\xi, \eta)) = \text{const} \frac{\iint \exp(-\beta T(\xi, \eta, \nu, \pi)) d\nu d\pi}{\int \exp(-\beta T^{00}(\xi, \nu)) d\nu} \exp(-\beta V(\xi, \eta)) \quad (21)$$

where *const* is to be determined. Hence, $V^* = V + V^F + V^K$ where

$$\exp(-\beta V^F(\xi)) = \text{const} \frac{\iint \exp(-\beta T^0(\xi, \nu, \pi)) d\nu d\pi}{\int \exp(-\beta T^{00}(\xi, \nu)) d\nu}$$

and

$$\exp(-\beta V^K(\xi, \eta)) = \frac{\iint \exp(-\beta T(\xi, \eta, \nu, \pi)) d\nu d\pi}{\iint \exp(-\beta T^0(\xi, \nu, \pi)) d\nu d\pi}$$

with $T^0(\xi, \nu, \pi) = T(\xi, 0, \nu, \pi)$. We have

$$T^0(\xi, \nu, \pi) = T^{00}(\xi, \nu) + T(\xi, 0, 0, \pi),$$

and, using Eq. (15),

$$T(\xi, 0, 0, \pi) = \frac{1}{2} \pi^\top g_x(X^0) M(X^0)^{-1} g_x(X^0)^\top \pi,$$

whence

$$\exp(\beta V^F) = \text{const} \int \exp\left(-\frac{\beta}{2} \pi^\top g_x(X^0) M(X^0)^{-1} g_x(X^0)^\top \pi\right) d\pi.$$

Substituting $\pi = (g_x(X^0)M(X^0)^{-1}g_x(X^0)^\top)^{-1/2}\pi'$ and dropping the prime gives

$$\exp(\beta V^F) = \det(g_x(X^0)M(X^0)^{-1}g_x(X^0)^\top)^{-1/2}.$$

With the change of variables

$$\begin{bmatrix} \nu \\ \pi \end{bmatrix} = Z_x(X)^{-\top} p,$$

we have

$$\iint e^{-\beta T} d\nu d\pi = \int \exp\left(-\frac{\beta}{2} p^\top M(X)^{-1} p\right) \det Z_x(X)^{-1} dp = \det Z_x(X)^{-1} \int \exp\left(-\frac{\beta}{2} p^\top p\right) \det M(X)^{1/2} dp,$$

whence

$$\frac{\iint \exp(-\beta T) d\nu d\pi}{\iint \exp(-\beta T^0) d\nu d\pi} = \exp\left(\frac{1}{2} \log \det M(X) - \frac{1}{2} \log \det M(X^0) - \log \det Z_x(X) + \log \det Z_x(X^0)\right).$$

□

Lemma 2 $V^K(\xi, \eta) = U^K(X^0; \eta)$ where

$$\beta U^K(x; \eta) = \frac{1}{2} \log \det M(x) - \frac{1}{2} \log \det M(\Xi(x; \eta)) + \int_0^1 (\nabla_x^\top G^\top)(\Xi(x; s\eta)) \eta ds.$$

Proof Letting X^s denote $X(\xi, s\eta)$,

$$\log \det Z_x^0 - \log \det Z_x = - \int_0^1 \frac{d}{ds} \log \det Z_x(X^s) ds = - \int_0^1 \text{tr} \left(Z_x(X^s)^{-1} \frac{d}{ds} Z_x(X^s) \right) ds.$$

Note that for an arbitrary scalar function $\varphi(x)$,

$$\frac{d}{ds} \varphi_x(X^s) = \eta^\top (X_\eta^s)^\top \varphi_{xx}^s = \eta^\top G^s \varphi_{xx}^s = (\varphi_x G^\top \eta)_x^s - \varphi_x^s (G^\top \eta)_x^s$$

where the superscript s denotes an argument X^s . Hence,

$$\frac{d}{ds} Z_x(X^s) = (Z_x G^\top \eta)_x^s - Z_x^s (G^\top \eta)_x^s = -Z_x^s (G^\top \eta)_x^s,$$

where the last equality holds because of Eq. (17), which implies that $Z_x G^\top$ equals the last m columns of the n by n identity matrix. Hence,

$$- \int_0^1 \text{tr} \left((Z_x^s)^{-1} \frac{d}{ds} Z_x^s \right) ds = \int_0^1 \text{tr} \left((G^\top \eta)_x^s \right) ds = \int_0^1 (\nabla_x^\top G^\top \eta)^s ds.$$

□

Proposition 4

$$\exp(-\beta \bar{V}^0(\xi)) = \text{const} \int \exp(-\beta U^*(X(\xi, 0); \eta)) d\eta \quad (22)$$

with U^* given by Eq. (6).

6.2 Averaging over the fast position variables

To approximate the integral in Eq. (8), we isolate the stiffness by writing $U^*(x; \eta) = U^{\text{osc}}(\eta) + \hat{U}(x; \eta)$ where

$$\hat{U}(x; \eta) = U^{\text{non}}(\Xi(x; \eta)) + U^{\text{F}}(x) + U^K(x; \eta),$$

and expand \hat{U} in powers of η , $\hat{U} = \hat{U}^0 + \hat{U}_\eta^0 \eta + \frac{1}{2} \eta^\top \hat{U}_{\eta\eta}^0 \eta + \dots$, where the superscript 0 denotes evaluation at $\eta = 0$.

Lemma 3

$$\hat{U}^0 = U^F + U^{\text{non}}, \quad \hat{U}_\eta^0 = f^\top, \quad \hat{U}_{\eta\eta}^0 = \frac{1}{2}(f_x G^\top + G f_x^\top),$$

where $f(x) = G(x)U_x^{\text{non}}(x)^\top - \frac{1}{2}\beta^{-1}G(x)(\log \det M(x))_x^\top + \beta^{-1}(\nabla_x^\top G(x))^\top$.

Proof Using Eq. (19), we have that $\Xi(x; s\eta) = X(b(x), g(x) + s\eta)$; whence, using Eq. (18),

$$(\Xi^s)_\eta = sG(\Xi^s)^\top \quad \text{where } \Xi^s = \Xi(x; s\eta).$$

Using this and Eqs. (6) and (7), we have

$$\begin{aligned} \hat{U} &= U^{\text{non}}(\Xi) + U^F + U^K, \\ \hat{U}_\eta &= u(\Xi)^\top + \left(\int_0^1 v(\Xi^s)^\top \eta ds \right)_\eta \end{aligned}$$

where

$$u = G(U_x^{\text{non}})^\top - \frac{1}{2\beta}G(\log \det M)_x^\top \quad \text{and} \quad v = \frac{1}{\beta}(\nabla_x^\top G)^\top.$$

Hence,

$$\hat{U}_\eta = u(\Xi)^\top + \int_0^1 v(\Xi^s) ds + \int_0^1 s\eta^\top v_x(\Xi^s)G(\Xi^s)^\top ds$$

and

$$\hat{U}_{\eta\eta} = u_x(\Xi)G(\Xi)^\top + \int_0^1 s v_x(\Xi^s)G(\Xi^s)^\top ds + \int_0^1 sG(\Xi^s)v_x(\Xi^s)^\top ds + \text{term linear in } \eta.$$

The first term is a Hessian with respect to η and hence symmetric. \square

Proposition 5

$$\bar{U} = U^{\text{non}} + U^F - \frac{\varepsilon^2}{2}f^\top W f + \frac{\varepsilon^2}{2\beta}\text{tr}(W G f_x^\top) + \mathcal{O}(\varepsilon^4).$$

Proof For the duration of this proof, x is fixed, so the notation suppresses dependence on x . Write

$$U^* = \hat{U}^0 + Q + R \quad \text{with } Q(\eta) = \frac{1}{2\varepsilon^2}\eta^\top W^{-1}\eta \quad \text{and } R = \hat{U} - \hat{U}^0.$$

Hence, $R(\eta) = \hat{U}_\eta^0 \eta + \frac{1}{2}\eta^\top \hat{U}_{\eta\eta}^0 \eta + \dots$, and

$$e^{-\beta R} = 1 - \frac{\beta}{2}\eta^\top A \eta + E(\eta)$$

where

$$A = \hat{U}_{\eta\eta}^0 - \beta(\hat{U}_\eta^0)^\top \hat{U}_\eta^0,$$

and

$$E(\eta) = \text{odd powers of } \eta + \mathcal{O}(|\eta|^4).$$

Therefore,

$$\int e^{-\beta(Q+R)} d\eta = \int e^{-\beta Q} q d\eta \left(1 + \frac{\int e^{-\beta Q} E d\eta}{\int e^{-\beta Q} q d\eta} \right) \quad (23)$$

where

$$q(\eta) = 1 - \frac{\beta}{2} \eta^\top A \eta.$$

The first integral on the right of Eq.(23) can be evaluated analytically with the change of variables from η to $\varepsilon W^{1/2} \eta' / \sqrt{\beta}$:

$$\begin{aligned} \int e^{-\beta Q} q d\eta &= \int \exp(-\beta \eta^\top W^{-1} \eta / 2\varepsilon^2) q(\eta) d\eta \\ &= \varepsilon^{-m} (\beta^m \det W)^{1/2} \int e^{-\eta^\top \eta / 2} \left(1 - \frac{\varepsilon^2}{2} \eta^\top W^{1/2} A W^{1/2} \eta \right) d\eta. \end{aligned}$$

Integrating by parts yields

$$\int e^{-\beta Q} q d\eta = \varepsilon^m (\beta^{-m} \det W)^{1/2} \left(1 - \frac{\varepsilon^2}{2} \text{tr}(WA) \right) \int e^{-\eta^\top \eta / 2} d\eta.$$

From Eq. (23)

$$|\text{error term}| \leq \text{const} \frac{\int e^{-\beta Q} |\eta|^4 d\eta}{\int e^{-\beta Q} q d\eta}.$$

With the same change of variables as previously, this becomes

$$|\text{error term}| \leq \text{const} \frac{\varepsilon^4 \int e^{-\eta^\top \eta / 2} |W^{1/2} \eta|^4 d\eta}{\beta^2 \left(1 - \frac{\varepsilon^2}{2} \text{tr}(WA) \right) \int e^{-\eta^\top \eta / 2} d\eta}.$$

Putting it all together,

$$\begin{aligned} \int e^{-\beta Q} P d\eta &= \text{const} \left(1 - \frac{\varepsilon^2}{2} \text{tr}(W \hat{U}_{\eta\eta}^0) - \beta W (\hat{U}_\eta^0)^\top \hat{U}_\eta^0 \right) \\ &= \text{const} \left(1 - \frac{\varepsilon^2}{2} \text{tr}(W \hat{U}_{\eta\eta}^0) + \beta \frac{\varepsilon^2}{2} \hat{U}_\eta^0 W (\hat{U}_\eta^0)^\top \right); \end{aligned}$$

whence

$$\begin{aligned} \bar{U}^0(\xi) &= \text{const} + \hat{U}^0 - \frac{1}{\beta} \log \left(1 - \frac{\varepsilon^2}{2} \text{tr}(W \hat{U}_{\eta\eta}^0) + \beta \frac{\varepsilon^2}{2} \hat{U}_\eta^0 W (\hat{U}_\eta^0)^\top \right) - \frac{1}{\beta} \log(1 + \mathcal{O}(\varepsilon^4)) \\ &= \text{const} + \hat{U}^0 - \frac{1}{2} \varepsilon^2 \hat{U}_\eta^0 W (\hat{U}_\eta^0)^\top + \frac{1}{2\beta} \varepsilon^2 \text{tr}(W \hat{U}_{\eta\eta}^0) + \mathcal{O}(\varepsilon^4). \end{aligned} \quad (24)$$

□

References

1. M. P. Allen and D. J. Tildesley. *Computer Simulation of Liquids*. Clarendon Press, Oxford, New York, 1987. Reprinted in paperback in 1989 with corrections.
2. W. M. Boothby. *An Introduction to Differentiable Manifolds and Riemannian Geometry*. Academic Press, New York, 2nd edition, 1986.
3. J. A. de la Torre, G. Ciccotti, P. Español, and M. Ferrario. Constraints and coarse-graining. *Eur. Phys. J. ST*. This issue.

4. P. Echenique, C. N. Cavasotto, and P. García-Risueño. The canonical equilibrium of constrained molecular models. *Eur. Phys. J. ST*. This issue.
5. R. Elber and B. Hess. Strategies to parallelize SHAKE. *Eur. Phys. J. ST*. This issue.
6. M. Fixman. Classical statistical mechanics of constraints: A theorem and application to polymers. *Proc. Nat. Acad. Sci.*, 71:3050–3053, 1974.
7. E. Hairer, C. Lubich, and G. Wanner. *Geometric Numerical Integration · Structure-Preserving Algorithms for Ordinary Differential Equations*, volume 31 of *Springer Series in Computational Mathematics*. Springer-Verlag, Berlin, 2nd edition, 2006.
8. J. A. Izaguirre, S. Reich, and R. D. Skeel. Longer time steps for molecular dynamics. *J. Chem. Phys.*, 110:9853–9864, 1999.
9. B. Leimkuhler and S. Reich. *Simulating Hamiltonian Dynamics*. Cambridge University Press, 2004.
10. S. Reich. A free energy approach to the torsion dynamics of macromolecules. Technical report, Konrad-Zuse-Zentrum für Informationstechnik Berlin, 1995.
11. S. Reich. Smoothed dynamics of highly oscillatory Hamiltonian systems. *Physica D*, 89:28–42, 1995.
12. S. Reich. Modified potential energy functions for constrained molecular dynamics. *Numer. Algorithms*, 19:213–221, 1998.
13. S. Reich and T. Hundertmark. On the use of constraints in molecular and geophysical fluid dynamics. *Eur. Phys. J. ST*. This issue.
14. J. Sanz-Serna and M. Calvo. *Numerical Hamiltonian Problems*. Chapman and Hall, London, 1994.
15. R. D. Skeel and K. Srinivas. Nonlinear stability analysis of area-preserving integrators. *SIAM J. Numer. Anal.*, 38:129–148, 2000.
16. W. F. van Gunsteren and M. Karplus. Effect of constraints on the dynamics of macromolecules. *Macromolecules*, 15:1528–1544, 1982.
17. J. Zhou, S. Reich, and B. R. Brooks. Elastic molecular dynamics with self-consistent flexible constraints. *J. Chem. Phys.*, 112:7919–7929, 2000.