

A Free Energy Approach to the Torsion Dynamics of Macromolecules

Sebastian Reich
Konrad-Zuse Zentrum Berlin
Heilbronner Str. 10
D-10711 Berlin

June 13, 1995

Abstract

Based on the concept of free energy, we give a Hamiltonian formulation for the torsion dynamics of macromolecules. The appropriate reaction coordinates for the free energy calculations are defined in terms of soft constraints as introduced in [3] and [14]. We consider a few simplifications that allow one to calculate the free energy analytically and to write the corresponding equations of motion as a constrained Hamiltonian system. We also discuss a possible stochastic embedding of the reduced dynamics by means of a generalized Langevin approach.

1 Introduction

For classical molecular dynamics (MD) of macromolecules such as nucleic acids, proteins, and polymers, atomic trajectories obey the Hamiltonian equation of motion

$$\begin{aligned}\frac{d}{dt}q &= M^{-1}p \\ \frac{d}{dt}p &= -\nabla V(q)\end{aligned}\tag{1}$$

where q is the vector containing all positions (in cartesian coordinates), p is the vector containing all conjugate momenta, M is a diagonal matrix of atomic masses replicated thrice, and $V(q)$ is the (empirical) potential energy function [10],

[4]. Standard numerical schemes for simulating the dynamical behavior of a macromolecule are based on discrete timestepping. Such numerical simulations are complicated by the presence of *multiple time scales* [9]. Standard integrators, such as Verlet [19], have to use timesteps which are small compared to the fastest time scales. In most cases, those time scales come from bonded interactions. The interesting dynamical phenomena of a macromolecule, however, happen on much slower time scales and are primarily related to motions in the dihedral angles [4]. Thus it seems reasonable to average over the fastest degrees of motion and then to solve the reduced equations numerically. This allows one to use larger timesteps and the computation of the long-term dynamics of macromolecules could become feasible. Several methods for the removal of the bonded interactions have been suggested [15], [13], [5], [18], [14]. In this paper we derive the reduced equations of motion by calculating the free energy in terms of appropriately chosen reaction coordinates. We also give a stochastic embedding of the reduced dynamics by using a generalized Langevin approach [11], [1].

2 The Equations of Motion

Let us rewrite the equations of motions (1) as

$$\begin{aligned}\frac{d}{dt}q &= M^{-1}p \\ \frac{d}{dt}p &= -\nabla\tilde{U}(q) - \tilde{G}(q)^T K \tilde{g}(q)\end{aligned}$$

where $\tilde{G} = \tilde{g}_q$ and \tilde{g} is the collection of functions $\tilde{g}_i : R^n \rightarrow R$, $i = 1, \dots, m$, with corresponding force constant K_{ii} , i.e.

$$\frac{\tilde{g}(q)^T K \tilde{g}(q)}{2} = \frac{1}{2} \sum_i K_{ii} (\tilde{g}_i(q))^2,$$

and K the m -dimensional diagonal matrix with entries K_{ii} . The potential $\tilde{U} : R^n \rightarrow R$ is defined by

$$\tilde{U}(q) = V(q) - \frac{\tilde{g}(q)^T K \tilde{g}(q)}{2}.$$

The potential $\tilde{g}(q)^T K \tilde{g}(q)/2$ stands for covalent bond stretching, i.e. $\tilde{g}_i(q) = r - r_0$, bond-angle bending, i.e. $\tilde{g}_i(q) = \phi - \phi_0$, improper dihedral angles, i.e. $\tilde{g}_i(q) = \psi - \psi_0$, and bonded Lennard-Jones interactions, i.e.

$$\tilde{g}_i(q) = 2 \left(\frac{\sigma}{r} \right)^6 - 1.$$

Here we have used the fact that the Lennard-Jones potentials

$$V_{LJ}(q) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$$

can, up to a constant, be rewritten as

$$V_{LJ}(q) = \epsilon \left[2 \left(\frac{\sigma}{r} \right)^6 - 1 \right]^2.$$

A Lennard-Jones interaction can be considered as bonded (at least temporarily) if $2\epsilon > k_B T$ and the corresponding function $\tilde{g}_i(q)$ is close to zero.

The potential $\tilde{g}(q)^T K \tilde{g}(q)/2$ represents the fastest degrees of motion of a macromolecule. To remove those degrees of freedom, we have to calculate the free energy of our system in terms of properly chosen reaction coordinates. In contrast to simply defining reaction coordinates through the (hard) constraints

$$\tilde{g}(q) = 0,$$

we use soft constraints as introduced in [3] and [14], i.e.

$$0 = \tilde{g}(q) + K^{-1} [\tilde{G}(q) M^{-1} \tilde{G}(q)^T]^{-1} \tilde{G}(q) M^{-1} \nabla \tilde{U}(q) \quad (2)$$

where we have assumed that

$$\tilde{G}(q) M^{-1} \tilde{G}(q)^T \quad (3)$$

is invertible. See Section 7 for a brief discussion of the case when (3) is not invertible. However, in this and the following sections, we will assume that (3) is invertible. Then we define the new function $g : R^n \rightarrow R$ by

$$g(q) := \tilde{g}(q) + K^{-1} [\tilde{G}(q) M^{-1} \tilde{G}(q)^T]^{-1} \tilde{G}(q) M^{-1} \nabla \tilde{U}(q).$$

The reduced dynamics of (1) will now be defined by the free energy of (1) on the constraint manifold

$$\mathcal{M} = \{(q, p) \in R^{2n} : g(q) = 0, G(q) M^{-1} p = 0\}.$$

The manifold can be parameterized by the unconstrained dihedral angles, the external degrees of freedom, and their corresponding conjugate momenta. For simplicity, we refer to the reduced dynamics on \mathcal{M} as the torsion dynamics of (1).

The corresponding free energy will be derived in Section 4. We finally rewrite (1) as

$$\begin{aligned}\frac{d}{dt}q &= M^{-1}p \\ \frac{d}{dt}p &= -\nabla U(q) - G(q)^T K g(q)\end{aligned}\tag{4}$$

with

$$U(q) = V(q) - \frac{g(q)^T K g(q)}{2}.$$

Remark. Typical constraint methods for molecular dynamics use the (hard) constraints $\tilde{g}(q) = 0$ [16], [17]. However, when applied to the bond-angle bending, the resulting molecule becomes too rigid and transition rates are no longer reproduced correctly [17]. For that reason we introduced in [14] the soft constraints (2) which maintain the flexibility of a molecule in terms of its bonds and bond-angles.

3 Mathematical Background

First we rewrite (4) in local coordinates (q_1, q_2) defined by

$$\begin{aligned}q_1 &= g(q) \\ q_2 &= b(q)\end{aligned}$$

where $b(q)$ is a vector valued function such that $B(q)M^{-1}G(q)^T = 0$, $B(q) = b_q(q)$, and the composed matrix $[G(q)^T B(q)^T]$ is invertible and well conditioned. The existence of such a coordinate system follows, at least locally, from the Frobenius Theorem [2]. The corresponding conjugate momenta are given by

$$[G(q)^T B(q)^T] \begin{bmatrix} p_1 \\ p_2 \end{bmatrix} = p$$

which results in the Hamiltonian

$$H(q, p) = \frac{p_1^T G M^{-1} G^T p_1}{2} + \frac{p_2^T B M^{-1} B^T p_2}{2} + U + \frac{q_1^T K q_1}{2}.\tag{5}$$

The equations of motion are now given by

$$\begin{aligned}\frac{d}{dt}q_1 &= G M^{-1} G^T p_1 \\ \frac{d}{dt}p_1 &= -\nabla_{q_1} U - K q_1 - \nabla_{q_1} \frac{p_1^T G M^{-1} G^T p_1 + p_2^T B M^{-1} B^T p_2}{2}\end{aligned}\tag{6}$$

and

$$\begin{aligned}\frac{d}{dt}q_2 &= BM^{-1}B^T p_2 \\ \frac{d}{dt}p_2 &= -\nabla_{q_2}U - \nabla_{q_2}\frac{p_1^T GM^{-1}G^T p_1 + p_2^T BM^{-1}B^T p_2}{2}\end{aligned}\quad (7)$$

where, for notational convenience, we suppressed the arguments in the mappings $V(q_1, q_2)$, $G(q_1, q_2)$, and $B(q_1, q_2)$.

Let us now review a few results from statistical mechanics. A Hamiltonian system with Hamiltonian H is called ergodic [12] if the time average

$$\langle \mathcal{A} \rangle := \lim_{T \rightarrow \infty} \frac{1}{2T} \int_{-T}^T \mathcal{A}(q(t), p(t)) dt \quad (8)$$

of an observable $\mathcal{A}(q, p)$ along a solution of (1) is equal to the microcanonical (constant energy $E = H(q, p)$) ensemble average [12]

$$\langle \mathcal{A} \rangle_{\text{ens}} := \int \int \rho_{\text{ens}}(q, p) \mathcal{A}(q, p) dq dp \quad (9)$$

with the microcanonical density function

$$\rho_{\text{ens}}(q, p) := \frac{\delta(H(q, p) - E)}{\int \int \delta(H(q, p) - E) dq dp}$$

where $\delta(x)$ denotes Dirac's delta function.

Remark. (i) If the Hamiltonian H possesses first integrals, ergodicity is always understood as ergodicity on the level sets of these first integrals.

(ii) Throughout this paper we will assume that, along solutions of (1), we have

$$\frac{p^T M^{-1} p}{2} \approx \frac{n k_B T}{2}$$

n the number of degrees of freedom. Thus the microcanonical ensemble average of (1) is almost identical to the macrocanonical (constant temperature) ensemble average with density function

$$\rho_{\text{ens}}(q, p) := \frac{\exp(-\beta H(q, p))}{\int \int \exp(-\beta H(q, p)) dq dp}$$

where $\beta = 1/k_B T$. This is always true for systems with n large enough [1].

Let $H(q_1, p_1, q_2, p_2)$ be an arbitrary Hamiltonian in the variable (q_1, p_1, q_2, p_2) . We consider the ensemble average over the variable (q_1, p_1) , i.e.

$$\langle \mathcal{A} \rangle_{\text{ens}}^{(1)}(q_2, p_2) = \int \int \mathcal{A}(q_1, p_1, q_2, p_2) \rho_{\text{ens}}^{(1)}(q_1, p_1, q_2, p_2) dq_1 dp_1.$$

with

$$\rho_{\text{ens}}^{(1)} := \frac{\exp(-\beta H)}{\int \int \exp(-\beta H) dq_1 dp_1}$$

The free energy $\mathcal{H}(q_2, p_2)$ of the remaining variable (q_2, p_2) is a function that satisfies

$$\nabla_{q_2} \mathcal{H}(q_2, p_2) = \langle \nabla_{q_2} H \rangle_{\text{ens}}^{(1)}(q_2, p_2)$$

and

$$\nabla_{p_2} \mathcal{H}(q_2, p_2) = \langle \nabla_{p_2} H \rangle_{\text{ens}}^{(1)}(q_2, p_2)$$

[8]. Furthermore, let $\rho_{\text{ens}}^{(2)}(q_2, p_2)$ denote the density function corresponding to the (Hamiltonian) free energy $\mathcal{H}(q_2, p_2)$, then the total ensemble average

$$\langle \mathcal{A} \rangle_{\text{ens}} := \int \int \int \int \mathcal{A}(q_1, p_1, q_2, p_2) \rho_{\text{ens}}(q_1, p_1, q_2, p_2) dq_1 dp_1 dq_2 dp_2$$

satisfies

$$\langle \mathcal{A} \rangle_{\text{ens}} = \langle \langle \mathcal{A} \rangle_{\text{ens}}^{(1)} \rangle_{\text{ens}}^{(2)}$$

with

$$\langle \langle \mathcal{A} \rangle_{\text{ens}}^{(1)} \rangle_{\text{ens}}^{(2)} := \int \int \langle \mathcal{A} \rangle_{\text{ens}}^{(1)}(q_2, p_2) \rho_{\text{ens}}^{(2)}(q_2, p_2) dq_2 dp_2$$

[8].

In general, the evaluation of ensemble averages is fairly expensive. However, there are a few ensemble averages that are easy to obtain. For example, equipartition of energy [12] implies that

$$\langle p^i \frac{\partial H}{\partial p^i} \rangle_{\text{ens}} = k_B T \quad (10)$$

and

$$\langle q^i \frac{\partial H}{\partial q^i} \rangle_{\text{ens}} = k_B T \quad (11)$$

where q^i and p^i , $i = 1, \dots, n$, denote the i th component of the vector q, p respectively.

4 Free Energy of the Slow Dynamics

In this Section we want to derive an approximation to the free energy of (5) in the variable (q_2, p_2) .

In a first step we derive an approximation to the density function

$$\rho_{\text{ens}}^{(1)}(q_1, q_2, p_1, p_2) = \frac{\exp(-\beta H(q_1, q_2, p_1, p_2))}{\int \int \exp(-\beta H(q_1, q_2, p_1, p_2)) dq_1 dp_1} \quad (12)$$

with $H = H(q_1, q_2, p_1, p_2)$ the Hamiltonian (5). Note that

$$\begin{aligned} \exp(-\beta H) &= \exp\left(-\beta \frac{p_1^T G M^{-1} G^T p_1}{2}\right) \cdot \exp\left(-\beta \frac{p_2^T B M^{-1} B^T p_2}{2}\right) \\ &\quad \cdot \exp(-\beta U(q_1, q_2)) \cdot \exp\left(-\beta \frac{q_1^T K q_1}{2}\right). \end{aligned}$$

The characteristic length of the potential U , which will be called α , is the distance over which the potential changes by $k_B T$. We assume that the characteristic length of the potential U is larger than the characteristic length of $q_1^T K q_1/2$ which is $\sqrt{2 \|K^{-1}\| k_B T}$. (This is just another way of saying that (q_1, p_1) is the fast variable and (q_2, p_2) is the slow variable.) Provided that we scale the Hamiltonian H such that $\alpha \approx 1$, we have

$$\exp\left(-\beta \frac{q_1^T K q_1}{2}\right) \approx \delta(q_1^T q_1)$$

where $\delta(x)$ is Dirac's delta function. Then, in the computation of

$$\langle \mathcal{A} \rangle_{\text{ens}}^{(1)}(q_2, p_2) = \int \int \mathcal{A}(q_1, q_2, p_1, p_2) \rho_{\text{ens}}^{(1)}(q_1, q_2, p_1, p_2) dq_1 dp_1$$

integration over q_1 becomes trivial. In fact, integration over p_1 is not much harder either. The expression

$$\exp\left(-\beta \frac{p_1^T G M^{-1} G^T p_1}{2}\right)$$

describes a Gaussian distribution and, for the particular

$$\mathcal{A}(q_1, q_2, p_1) = \nabla_{q_2} \frac{p_1^T G M^{-1} G^T p_1}{2},$$

equipartitioning of energy can be used to evaluate the integral over p_1 . This will be shown below.

We summarize our discussion so far by replacing the correct reduced density function $\rho_{\text{ens}}^{(1)}$ by our approximation $\tilde{\rho}_{\text{ens}}^{(1)}$ defined by

$$\tilde{\rho}_{\text{ens}}^{(1)}(q_2, p_2) := \frac{\exp\left(-\beta \frac{p_1^T G(q_2) M^{-1} G(q_2)^T p_1}{2}\right) \cdot \delta(q_1^T q_1)}{\int \int \exp\left(-\beta \frac{p_1^T G(q_2) M^{-1} G(q_2)^T p_1}{2}\right) \cdot \delta(q_1^T q_1) dq_1 dp_1}.$$

Remark. In local coordinates (q_1, q_2) , the definition of the soft constraint $g(q) = 0$ and $q_1 := g(q)$ imply that

$$\nabla_{q_1} U(q_1, q_2) + K q_1 \approx 0 \quad (13)$$

for $q_1 = 0$. Now the potential $U(q_1, q_2)$ can be formally expanded in a Taylor series w.r.t. the variable q_1 , i.e.

$$U(q_1, q_2) = U(q_2) + R(q_2)^T q_1 + q_1^T S(q_2) q_1 + \dots$$

Because of (13), we have $R(q_2) \approx 0$. Furthermore, $\|S(q_2)\| \ll \|K^{-1}\|^{-1}$ and

$$\exp\left(-\beta\left(U(q_1, q_2) + \frac{q_1^T K q_1}{2}\right)\right)$$

is well approximated by

$$\exp(-\beta U(q_2)) \cdot \delta(q_1^T q_1). \quad (14)$$

Note that, for the hard constraints $\tilde{g}(q) = 0$ and $q_1 := \tilde{g}(q)$, we do not have $R(q_2) \approx 0$ and the approximation (14) would be questionable unless $\|K^{-1}\| \ll 1$.

The free energy $\mathcal{H}(q_2, p_2)$ in the slow variable (q_2, p_2) is now a function that satisfies

$$\nabla_{q_2} \mathcal{H}(q_2, p_2) = \langle \nabla_{q_2} H \rangle_{\text{ens}}^{(1)}(q_2, p_2)$$

and

$$\nabla_{p_2} \mathcal{H}(q_2, p_2) = \langle \nabla_{p_2} H \rangle_{\text{ens}}^{(1)}(q_2, p_2)$$

where

$$\langle \mathcal{A} \rangle_{\text{ens}}^{(1)}(q_2, p_2) = \int \int \mathcal{A}(q_1, q_2) \tilde{\rho}_{\text{ens}}^{(1)}(q_1, p_1, q_2, p_2) dq_1 dp_1.$$

For the expressions $\nabla_{q_2} U$, $BM^{-1}B^T p_2$, and

$$\nabla_{q_2} \frac{p_2^T B M^{-1} B^T p_2}{2},$$

the corresponding entries in the free energy \mathcal{H} are simply given by $V(\boldsymbol{q}) = V(0, q_2)$ and

$$\frac{p_2^T B(q_2) M^{-1} B(q_2)^T p_2}{2}.$$

Things are a bit more tricky for

$$\nabla_{q_2} \frac{p_1^T G M^{-1} G^T p_1}{2}.$$

We note first that equipartitioning of energy implies that

$$\begin{aligned} \langle p_1^T G(q) M^{-1} G(q)^T p_1 \rangle_{\text{ens}}^{(1)} &= \langle p_1^T \frac{\partial H}{\partial p_1}(q, p) \rangle_{\text{ens}}^{(1)} \\ &= m k_B T \end{aligned}$$

with m the dimension of p_1 . Now let $W(q)$ be an orthogonal matrix such that $W(q)^T G(q) M^{-1} G(q)^T W(q)$ is a diagonal matrix $D(q)$ with entries $d_{ii}(q)$ and define $\tilde{p}_1 := W(q)^T p_1$. Then

$$\begin{aligned} \langle \tilde{p}_1^T D(q) \tilde{p}_1 \rangle_{\text{ens}}^{(1)} &= \langle p_1^T G(q) M^{-1} G(q)^T p_1 \rangle_{\text{ens}}^{(1)} \\ &= m k_B T \end{aligned}$$

and equipartitioning of energy between the m degrees of freedom \tilde{p}_1^i yields

$$\langle (\tilde{p}_1^i)^2 d_{ii}(q) \rangle_{\text{ens}}^{(1)} = k_B T$$

$i = 1, \dots, m$. Now

$$\langle (\tilde{p}_1^i)^2 d_{ii}(q) \rangle_{\text{ens}}^{(1)} = \langle (\tilde{p}_1^i)^2 \rangle_{\text{ens}}^{(1)} d_{ii}(q_2)$$

and, therefore,

$$\langle (\tilde{p}_1^i)^2 \rangle_{\text{ens}}^{(1)} = \frac{k_B T}{d_{ii}(q_2)}.$$

With

$$\langle \nabla_{q_2} \frac{p_1^T G(q) M^{-1} G(q)^T p_1}{2} \rangle_{\text{ens}}^{(1)} = \sum_i \frac{\langle (\tilde{p}_1^i)^2 \rangle_{\text{ens}}^{(1)}}{2} \nabla_{q_2} d_{ii}(q_2),$$

we finally obtain

$$\langle \nabla_{q_2} \frac{p_1^T G(q) M^{-1} G(q)^T p_1}{2} \rangle_{\text{ens}}^{(1)} = \frac{k_B T}{2} \nabla_{q_2} \ln [\det D(q_2)]$$

which, in terms of the original matrix $G(q)M^{-1}G(q)^T$, leads to the potential

$$U_F(q_2) = \frac{k_B T}{2} \ln \det [G(q_2)M^{-1}G(q_2)^T] \quad (15)$$

where we used that

$$\det D(q) = \det [W(q)D(q)W(q)^T].$$

Remark. The potential (15) has been introduced before by Fixman [5] in the context of statistical mechanics. He showed that (15) has to be included into the constrained formulation, defined in local coordinates by $q_1 = p_1 = 0$, to make sure that, in the limit $\|K^{-1}\| \rightarrow 0$, the unconstrained system (4) and the corresponding constrained system possess the same reduced density function $\rho_{\text{ens}}^{(2)}(q_2, p_2)$. Similar results can be found in [18] and [13].

The free energy in the variable (q_2, p_2) is thus (approximately) given by

$$\mathcal{H}(q_2, p_2) = \frac{p_2^T B(q_2)M^{-1}B(q_2)^T p_2}{2} + U(q_2) + U_F(q_2) \quad (16)$$

or, in terms of the cartesian coordinates $(q, p) \in \mathbb{R}^{2n}$, by the Hamiltonian

$$\mathcal{H}(q, p) = \frac{p^T M^{-1}p}{2} + U(q) + U_F(q) + g(q)^T \lambda$$

together with the constraint

$$g(q) = 0.$$

The corresponding equations of motion are

$$\begin{aligned} \frac{d}{dt}q &= M^{-1}p \\ \frac{d}{dt}p &= -\nabla U(q) - \nabla U_F(q) - G(q)^T \lambda \\ 0 &= g(q) \end{aligned} \quad (17)$$

which are identical to the equations derived in [14] by smoothing of (4) w.r.t. time.

Remark. The approximation (16) can be improved by using

$$U(q_2) := \frac{\int U(q_1, q_2) \exp(-\beta q_1^T K q_1 / 2) dq_1}{\int \exp(-\beta q_1^T K q_1 / 2) dq_1}$$

instead of

$$U(q_2) := U(0, q_2).$$

However, in terms of the cartesian coordinates (q, p) , the evaluation of the corresponding integral is far from trivial and we will use from now on the simpler $U(q_2) := U(0, q_2)$.

5 A Simplification

For large systems, the computation of the potential

$$U_F(q) = \frac{k_B T}{2} \ln \det [G(q)M^{-1}G(q)^T]$$

becomes rather expensive. To avoid this, we first simplify U_F to

$$U_F(q) \approx \frac{k_B T}{2} \ln \det [\tilde{G}(q)M^{-1}\tilde{G}(q)^T]$$

where $\tilde{G} = \tilde{g}_q$ and \tilde{g} as defined in Section 2. This approximation introduces an error of order $k_B T \|K^{-1}\|$.

The evaluation of this U_F is still too expensive for large molecules. Therefore, Fixman suggested in [6] to simplify U_F further by

$$U_F(q) \approx \frac{k_B T}{2} [\ln \det D - \sum_k \sum_i D_{kk}^{-1} D_{ii}^{-1} (E_{ki}(q))^2] \quad (18)$$

where D denotes the diagonal part of $\tilde{G}M^{-1}\tilde{G}^T$ and E the off diagonal part of $\tilde{G}M^{-1}\tilde{G}^T$. It turns out (see the example below) that this approximation is rather poor and we do not recommend using it.

Instead we note that, with all the bond-lengths and bond-angles constrained, U_F will depend only on the dihedral angles ψ . Our approximation is based on the idea that the potential U_F introduces only a weak or no coupling at all between the dihedral angles ψ^j , $j = 1, \dots$, i.e.

$$\frac{\partial^2}{\partial \psi^i \partial \psi^j} U_F(\psi) \approx 0$$

for $i \neq j$. Our assumption implies that U_F can be written as

$$U_F(\psi) \approx \sum_j U_F^j(\psi^j). \quad (19)$$

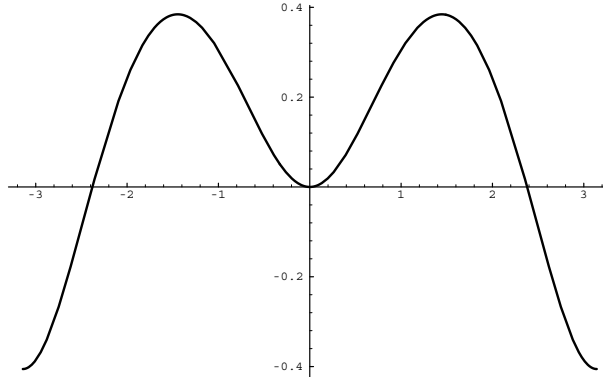


Figure 1: Fixman potential in $k_B T$ as a function of the torsion angle ψ .

Here U_F^j is defined by the submatrix of $\tilde{G}M^{-1}\tilde{G}^T$ that contains only those bond-length and bond-angle constraints that are involved in the definition of the dihedral angle ψ^j . For a simple polymer chain, this submatrix will be a 5×5 matrix $\tilde{G}M^{-1}\tilde{G}^T$ with \hat{g} the vector-valued function containing the three bond-length and two bond-angle constraints defining the torsion angle ψ^j .

Example. We compute the Fixman potential for a polymer with three, four respectively, bars. We assume that the particles have equal mass $m = 1$ and that the bond-lengths and bond-angles are rigidly fixed at $r = 1$, $\phi = \pi/2$ respectively. In case of three bars, there is one torsion angle ψ and the corresponding potential U_F (in $k_B T$) as a function of ψ can be found in Figure 1. In Figure 2, we plotted the approximation obtained by using (18). Obviously, the approximation is rather poor. Next we computed the exact potential U_F for the chain with four bars. The result as a function of the two torsion angles ψ^1 and ψ^2 can be found in Figure 3. The resulting approximate potential using (19) is plotted in Figure 4.

6 Stochastic Embedding of the Slow Dynamics

We first rewrite the slow dynamics in the variable (q_2, p_2) in terms of the torsion angles ψ and their conjugate momenta ψ_p . Let the torsion angles be uniquely defined by q_2 (and $q_1 = 0$) through the function

$$\psi = \psi(q_2).$$

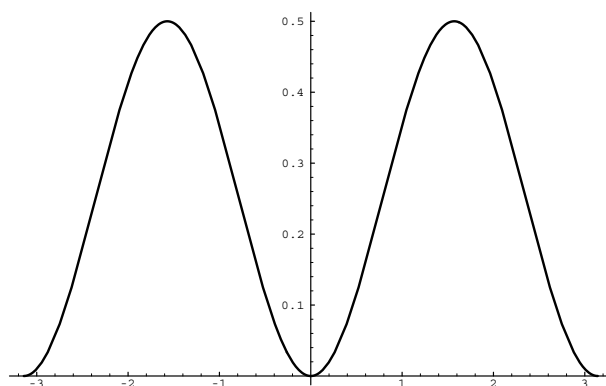


Figure 2: Approximate Fixman potential as a function of ψ .

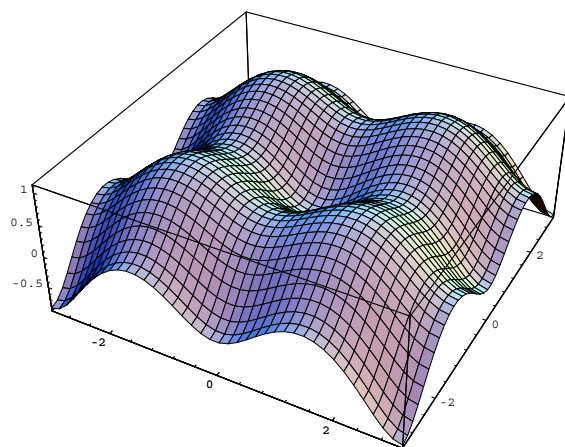


Figure 3: Fixman potential for the polymer chain with four bars as a function of the two torsion angles ψ^1 and ψ^2 .

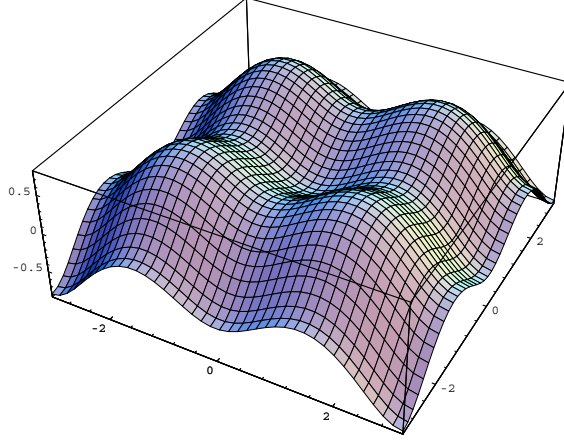


Figure 4: Approximate Fixman potential for the polymer chain with four bars.

Then the momenta ψ_p are given by

$$p_2 = \Psi(q_2)^T \psi_p$$

where Ψ denotes the derivative of ψ w.r.t. q_2 , i.e. $\Psi = \psi_{q_2}$. Upon neglecting the three translational and three rotational degrees of freedom, the free energy \mathcal{H} can now be rewritten as

$$\mathcal{H} = \frac{\psi_p^T \Psi B M^{-1} B^T \Psi^T \psi_p}{2} + U(\psi) + \sum_j U_F^j(\psi^j). \quad (20)$$

Let us also write U_F^j as

$$U_F^j(\psi^j) = \frac{k_B T}{2} \ln w^j(\psi^j).$$

With each torsion angle ψ^j , we associate the fictitious degree of freedom $(Q^j, P^j) \in R^2$ with corresponding equations of motion

$$\begin{aligned} \frac{d}{dt} Q^j &= w^j(\psi^j) P^j \\ \frac{d}{dt} P^j &= -\frac{1}{\epsilon} Q^j \end{aligned} \quad (21)$$

where $0 < \epsilon \ll 1$. This can be considered as a simplified model for the (fast) subsystem (6). The slow system (7) is now given by

$$\begin{aligned} \frac{d}{dt}\psi &= \Psi B M^{-1} B^T \Psi^T \psi_p \\ \frac{d}{dt}\psi_p &= -\nabla_\psi U - \sum_j \frac{(P^j)^2}{2} \nabla_\psi w^j - \nabla_\psi \frac{\psi_p^T \Psi B M^{-1} B^T \Psi^T \psi_p}{2} \end{aligned} \quad (22)$$

Upon computing the free energy of this combined system in terms of (ψ, ψ_p) , one would obtain again (20). Thus, the transition from (6) and (7) to the new system (21) and (22) does not change anything w.r.t. the mean force field, free energy respectively. However, (21) allows for a stochastic embedding of our mean force field via a nonlinear extension [7] of Mori's projection operator calculus [11].

Remark. Note that

$$\begin{aligned} \nabla_\psi \frac{p_1^T G M^{-1} G^T p_1}{2} + \nabla_\psi \frac{\psi_p^T \Psi B M^{-1} B^T \Psi^T \psi_p}{2} &= \nabla_\psi \frac{p^T M^{-1} p}{2} \\ &= 0 \end{aligned}$$

which implies that

$$\frac{k_B T}{2} \nabla_\psi \ln \det [G M^{-1} G^T] = -\frac{k_B T}{2} \nabla_\psi \ln \det [\Psi B M^{-1} B^T \Psi^T]. \quad (23)$$

Now, as discussed in the previous section, U_F can be approximated by

$$U_F(\psi) \approx \sum_j \frac{k_B T}{2} \ln w^j(\psi^j).$$

This and (23) yield that the matrix $\Psi B M^{-1} B^T \Psi^T$ is almost diagonal, i.e.

$$\psi_p^T \Psi B M^{-1} B^T \Psi^T \psi_p \approx \sum_j (\psi_p^j)^2 v^j(\psi^j).$$

Of course, $\Psi B M^{-1} B^T \Psi^T$ could contain off-diagonal elements which are constant. In the following we will assume that those elements are small compared to $v^j(\psi^j)$, $j = 1, \dots$

The functions v^j , $j = 1, \dots$, satisfy

$$v^j(\psi^j) w^j(\psi^j) \approx \text{const.}$$

This follows from (23) and

$$\begin{aligned} 0 &= \sum_j k_B T \nabla_\psi \ln w^j(\psi^j) + \sum_j k_B T \nabla_\psi \ln v^j(\psi^j) \\ &= \sum_j k_B T \nabla_\psi \ln [w^j(\psi^j) v^j(\psi^j)]. \end{aligned}$$

Since each variable $(Q^j, P^j, \psi^j, \psi_p^j)$ can be treated separately, we will simply drop superscript j from now on. Following [7] and putting $U \equiv 0$ for now, the nonlinear Langevin equation for $d\psi_p/dt$ ($d\psi_p^j/dt$, to be more precise) is

$$\begin{aligned} \frac{d}{dt}\psi_p &= -\nabla_\psi \frac{(\psi_p)^2 v(\psi)}{2} - \frac{k_B T}{2} \nabla_\psi \ln w(\psi) - F(t) - \\ &\quad - \frac{v(\psi)}{k_B T} \int_{t'}^t \langle F(\tau) F(t') \rangle \psi_p(t + t' - \tau) d\tau \end{aligned} \quad (24)$$

with $t' < t$, $F(t)$ given by

$$F(t) = \left[\frac{(P(t))^2}{2} - \frac{k_B T}{2w(\psi(t'))} \right] \nabla_\psi w(\psi(t')),$$

and $P(t)$ the solution of (21) with $\psi = \psi(t')$ and the initial value $(P(t'), Q(t'))$ satisfies $(P(t'))^2 w^j(\psi)/2 + (Q(t'))^2/(2\epsilon) = k_B T$.

The next step is now to replace $F(t)$ by a random force with first moment $\langle F(t) \rangle = 0$ and second moment

$$\langle F(t_1) F(t_2) \rangle = 4\gamma \left[\frac{k_B T}{2} \nabla_\psi \ln w(\psi) \right]^2 \delta(t_1 - t_2)$$

with $\gamma > 0$ the characteristic correlation time of $F(t)$. We also formally set $t = t$ in (24). Then the frictional force becomes

$$-2\gamma \frac{v(\psi)}{k_B T} \left[\frac{k_B T}{2} \nabla_\psi \ln w(\psi) \right]^2 \psi_p$$

which we write as

$$- \Gamma(\psi) \frac{d}{dt} \psi \quad (25)$$

where

$$\Gamma(\psi) := \gamma \frac{k_B T}{2} [\nabla_\psi \ln w(\psi)]^2$$

and $d\psi/dt = v(\psi)\psi_p$. With this notation we obtain

$$\langle F(t_1)F(t_2) \rangle = 2k_B T \Gamma(\psi) \delta(t_1 - t_2)$$

which, together with (25), can be considered as generalized dissipation-fluctuation. Note that the function Γ is different for each torsion angle ψ^j . Thus, going back to the vector valued ψ , we have in fact

$$\Gamma^j(\psi^j) := \gamma^j \frac{k_B T}{4} [\nabla_{\psi^j} \ln w^j(\psi^j)]^2$$

with corresponding random and friction forces acting on each torsion angle ψ^j .

Finally, we have to reformulate everything in terms of the original cartesian coordinates $(q, p) \in R^{2n}$. We obtain

$$\begin{aligned} \frac{d}{dt}q &= M^{-1}p \\ \frac{d}{dt}p &= -\nabla U(q) - \sum_j \nabla U_F^j(\psi^j(q)) - G(q)^T \lambda - \\ &\quad - \sum_j [F^j(t) + \Gamma^j(\psi^j(q)) \Psi^j(q) M^{-1}p] \nabla \psi^j(q) \\ 0 &= g(q) \end{aligned}$$

with

$$\langle F^j(t_1)F^j(t_2) \rangle = 2k_B T \Gamma^j(\psi^j(q)) \delta(t_1 - t_2)$$

and $\Psi^j(q) = \psi_q^j(q)$. Here we used that

$$\begin{aligned} \frac{d}{dt}\psi^j &= \Psi^j(q) \frac{d}{dt}q \\ &= \Psi^j(q) M^{-1}p \end{aligned}$$

and

$$p = \sum_j \psi_p^j \nabla \psi^j(q).$$

7 Towards the Essential Dynamics of Macromolecules

The approach described in this paper allows one also to constrain Lennard-Jones interactions. The problem with this is that it might lead to an overdetermined system of constraints and that it is very likely that, if at all, Lennard-Jones interactions can be considered as bonded only temporarily. Thus we need an adaptive

approach to the selection of the proper constraint functions \tilde{g} , g respectively. In principle, this problem can be solved by first writing all the bond stretching, bond-angle bending, and Lennard-Jones potentials in the form

$$\frac{\tilde{g}(q)^T K \tilde{g}(q)}{2} = \frac{1}{2} \sum_i K_{ii} (\tilde{g}_i(q))^2.$$

Then we compute a projector $P(q)$ onto the eigenspace of the m (with m chosen properly) largest eigenvalues of

$$\tilde{G}(q)^T K \tilde{G}(q).$$

and let $S(q)$ be a projector that satisfies

$$P(q)^T \tilde{G}(q)^T K \tilde{G}(q) P(q) = \tilde{G}(q)^T S(q)^T K S(q) \tilde{G}(q).$$

Now, assuming that $S(q)$ can be kept constant over a certain time interval, $S \tilde{g}(q)$ yields the proper (hard) constraint function from which we can also derive the appropriate soft constraints (2) as needed in Section 4 to formulate the corresponding slow dynamics on the constraint manifold \mathcal{M} . We will report about the numerical aspects of this approach to the slow (or essential) dynamics of macromolecules in a forthcoming publication.

References

- [1] Allen, M.P. and Tildesley, D.J., *Computer simulations of liquids*, Oxford University Press, New York, 1987.
- [2] Boothby, W.M., *An introduction to differentiable manifolds and Riemannian geometry*, 2nd edition, Academic Press, 1986.
- [3] Brooks, B.R., Zhou, J., and Reich, S., Elastic molecular dynamics with flexible constraints, in preparation.
- [4] Brooks III, C.L., Karplus, M., and Pettitt, B.M., *Proteins: A theoretical perspective of dynamics, structure, and thermodynamics*, John Wiley & Sons, New York, 1988.
- [5] Fixman, M., Classical statistical mechanics of constraints: A theorem and applications to polymers, *Proc. Nat. Acad. Sci.*, **71**, 3050–53, 1974.
- [6] Fixman, M., Simulation of polymer dynamics. I. General theory, *J. Chem. Phys.*, **69**, 1527–1537, 1978.

- [7] Helfand, E., Flexible vs. rigid constraints in statistical mechanics, *J. Chem. Phys.*, **71**, 5000–07, 1979.
- [8] Kuczera, K., Conformational free energy from thermodynamic integration simulations, Techn. Report, University of Kansas, Lawrence, 1995.
- [9] Leimkuhler, B., Reich, S., and Skeel, R.D., Integration methods for molecular dynamics, to appear in *IMA Volumes in Mathematics and its Applications*, Mesirov, J. and Schulten, K., editors, Springer Verlag, 1995.
- [10] McCammon, J.A. and Harvey, S.C., *Dynamics of proteins and nucleic acids*, Cambridge University Press, 1987.
- [11] Mori, H., Fujisaka, H., and Shigermatsu, Y., *Prog. Theor. Phys.*, **51**, 109, 1974.
- [12] Pathria, P.K., *Statistical mechanics*, Pergamon Press, Oxford, 1972.
- [13] Pear, M.R. and Weiner, J.H., Brownian dynamics study of a polymer chain of linked rigid bodies, *J. Chem. Phys.*, **71**, 212–224, 1979.
- [14] Reich, S., Smoothed Dynamics of Highly Oscillatory Hamiltonian Systems, *Physica D*, to appear, 1995.
- [15] Rubin, H. and Ungar, P., Motion under a strong constraining force, *Comm. Pure Appl. Math.*, **10**, 65–87, 1957.
- [16] Ryckaert, J.P., Ciccotti, G., and Berendsen, H.J.C., Numerical integration of the Cartesian equations of motion of a system with constraints: Molecular dynamics of n-alkanes, *J. Comput. Phys.*, **23**, 327–342, 1977.
- [17] van Gunsteren, W.F. and Karplus, M., Effects of constraints on the dynamics of macromolecules, *Macromolecules*, **15**, 1528–44, 1982.
- [18] van Kampen, N.G. and Lodder, J.J., Constraints, *Am. J. Phys.*, **52**, 419–424, 1984.
- [19] Verlet, L., Computer experiments on classical fluids, Part I, *Phys. Rev.*, **159**, 98–103, 1967.