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A Mathematical Approach to Smoothed Molecular Dynamics: Correcting Potentials for Freezing Bond Angles

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Abstract

The interaction potential of molecular systems which are typically used in molecular dynamics can be split into two parts of essentially different stiffness. The strong part of the potential forces the solution of the equations of motion to oscillate on a very small time scale. There is a strong need for eliminating the smallest time scales because they are a severe restriction for numerical long-term simulations of macromolecules. This leads to the idea of just freezing the high frequency degrees of freedom (bond stretching and bond angles). However, the naive way of doing this via holonomic constraints is bound to produce incorrect results. The paper presents a mathematically rigorous discussion of the limit situation in which the stiffness of the strong part of the potential is increased to infinity. It is demonstrated that the average of the limit solution indeed obeys a constrained Hamiltonian system but with a *corrected soft potential.* An explicit formula for the additive potential correction is given and its significant contribution is demonstrated in an illustrative example. It appears that this correcting potential is definitely not identical with the Fixman-potential as was repeatedly assumed in the literature.

Keywords: Smoothed dynamics, running average, molecular systems, Hamiltonian systems, strong constraining potential, high frequency degrees of freedom, weak convergence, Virial Theorem, correcting potential, Fixman potential, bond angle potential, bond stretching potential.

AMS classification: 70B05, 70F20, 70J99, 92C40

Introduction

In classical molecular dynamics (MD) one is interested in a description of the dynamical behavior of a (macro)molecular system in the scope of classical mechanics. The description is fully microscopic, i.e., the unknowns are the positions $q_i \in \mathbb{R}^3$ and momenta $p_i \in \mathbb{R}^3$ of all atoms in the system. The atomic trajectories are assumed to obey classical Hamiltonian equations of motion connected to the Hamiltonian:

$$H(q,p) \;=\; \frac{1}{2}p^T M^{-1} p \,+\, \mathcal{V}(q) \tag{1}$$

with $q^T = (q_1^T, \ldots, q_d^T) \in \mathbb{R}^{3d}$, $p^T = (p_1^T, \ldots, p_d^T) \in \mathbb{R}^{3d}$, and M the diagonal mass matrix. In classical MD, quantum theory is only used in order to construct the interaction potential $\mathcal{V}$ in the context of Born-Oppenheimer approximation. In most systems — in particular in biomolecular ones like nucleic acids, proteins, or polymers — this potential is of special structure. It consists of a sum of atom-to-atom potentials representing the contribution of different types of interaction between the atoms: non- or weak-binding long distance interactions (e.g. electrostatic or van der Waals), or binding interactions representing the bond-structure of the molecule. The motions effected by the bond-interactions are nonlinear vibrations around an equilibrium position: dihedral-angle, bond-angle, and bond-stretching oscillations. Therefore, typical MD-simulations show *nonlinear highly-oscillatory behavior on multiple time scales* in which the fastest vibrations have periods of about a few femtoseconds (fs).

Up to now, this highly oscillatory behavior is one main bottleneck of classical MD: Using standard techniques, the numerical integration of the equations of motion in a typical MD-simulations requires a stepsize τ which is small compared to the shortest period of oscillation [13], i.e., $\tau \approx 1\,\mathrm{fs}$ in a typical case. Indeed, this stepsize restriction is a *necessary* condition for stability and accuracy of *any* explicit discretization like, e.g., the commonly used Verlet-method, cf. [6]. For that reason, the maximal time span of a MD-simulation is restricted to at most a few nanoseconds, thus precluding the simulation of the important long-term dynamics of macromolecules.

The fastest of the molecular vibrations are caused by the bond-angle and bond-stretching interactions, because mostly the forces effected by these both types of potentials are two orders of magnitude stronger than all other forces. Thus, the potential $\mathcal{V}$ can be divided into *strong* and *soft* contributions. In order to indicate this separation we rewrite the potential as the sum

$$\mathcal{V}(q) \;=\; V(q) + \frac{1}{\epsilon^2}\, U(q),$$

where U represents the strong parts (e.g. sum of all bond-angle and bond-stretching potentials) and V the collection of all soft contributions. The number $\epsilon > 0$ is small ($\epsilon \ll 1$) and $1/\epsilon^2$ gives the scale ratio of the different kinds of oscillations (i.e., the spectral norms of the Hessian matrices of U and V are comparably to each other). Thus, we are concerned with the following Hamiltonian equations of motion:

$$\left.\begin{array}{rcl} \dot{q} &=& M^{-1}p \\ \dot{p} &=& -DV^T \,-\, \epsilon^{-2}\, DU^T \end{array}\right\} \Rightarrow M\,\ddot{q} + DV^T(q) + \frac{1}{\epsilon^2}\, DU^T(q) \;=\; 0, \quad (2)$$

in which D denotes derivation with respect to $q \in \mathbb{R}^{3d}$. The U-part of the potential effects oscillations on time scale $\mathcal{O}(\epsilon)$, the soft V-part those on scale $\mathcal{O}(1)$.

Mostly, we do not want to compute all the "unessential" oscillatory details on scale $\mathcal{O}(\epsilon)$. But we want to get *correct* information about the physically relevant dynamical behavior of the considered system, i.e., we cannot simply ignore or eliminate the bond dynamics. The idea of *smoothed MD* is to compute the "running average" of the exact solution q of (2) only. In the simplest case we have $q(t) = q^0(t) + a\sin(2\pi t/T)$ with q^0 oscillating on scale $\mathcal{O}(1)$ and $T = \mathcal{O}(\epsilon)$. Its running average is defined by

$$\bar{q}(t) \;=\; \frac{1}{T} \int\limits_{t-T/2}^{t+T/2} q(s)\, ds \;=\; q^0(t), \qquad (3)$$

which is not any longer affected by the small time scale T. Thus, a direct numerical computation of $\bar{q}$ would allow larger timesteps and, in turn, larger maximal time spans for MD-simulations.

In many previous approaches the computation of the fastest oscillations has been avoided using the following physical argument: If ϵ is small enough, i.e., the bonds stiff enough, the strong binding force nearly *fixes* the corresponding bonds to their equilibrium position; only small deviations are possible. Thus, the U-part of the potential can be considered as a static constraint, which forces the atomic trajectories on the manifold $\mathcal{M}$ of the equilibrium positions of the fastest vibrations:

$$\mathcal{M} \;=\; \{q : DU(q) = 0\}.$$

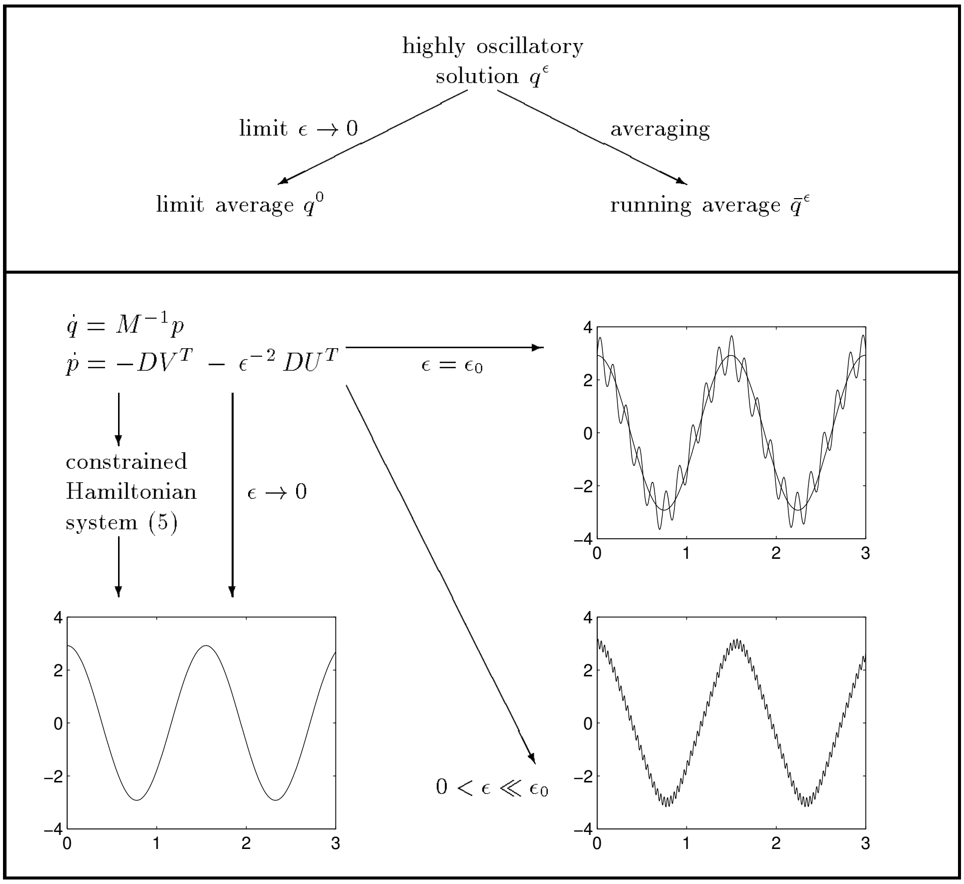

Figure 1: Illustration of running average and limit average. The subfigures on the right hand side show the oscillating solutions of a system with strong binding potential for two different sizes of the strength parameter ϵ. The "original" strength in the molecular system under consideration may be associated with $\epsilon = \epsilon_0$. The corresponding solution q^ϵ is shown on top together with its running average $\bar{q}^\epsilon$. The picture below shows the solution for a typical case $0 < \epsilon \ll \epsilon_0$ which intermediately will appear in the limit process $\epsilon \to 0$. Note, that its running average is about identical with the running average on top. For $\epsilon \to 0$ it converges to a *slowly oscillating limit average* q^0 shown on the left hand side. This limit average gives us a good approximation of the running average $\bar{q}^\epsilon$ for the case of interest $\epsilon = \epsilon_0$. Compare Figures 2 and 3 in addition.

Hence, one switches from system (2) to the *constrained Hamiltonian system*

$$\begin{aligned} M\,\ddot{q} + DV^T(q) + D^2U(q)\cdot\lambda &= 0 \\ DU(q) &= 0, \end{aligned} \tag{4}$$

the solution of which is slowly varying. This approach can only be justified if the potential U fulfills some quite restrictive conditions. Interestingly enough, the bond-stretching potentials are of the required type, which explains the success of this approach applied to them. However, in general equation (4) leads to completely wrong results. It fails, for example, if U contains bond-angle potentials; this will be extensively demonstrated in Section 3. The concern of our paper is a correction of this approach for such cases.

To this end, we look at a *limit average*: We *mathematically* study the dynamical behavior of a molecular system in the *limit situation* in which the period of the fastest oscillation is artificially decreased to zero, i.e., the limit $\epsilon \to 0$ (see Fig. 1). In other words, we rigorously investigate the motion of a molecular system in which the strong parts of the potential are infinitely stiff. This somewhat artificial limit should give a good resemblance of the situation for very strong potentials. Now, the question is posed whether one can derive a differential equation governing this limit solution. This question has been addressed — within a wide ranging gradation of mathematical rigor — in many previous works in various different contexts: For example, in the discussion of the realization of holonomic constraints in mechanics [3][4][10][11][18][20][22] or in connection to problems of plasma physics [19][15] and, indeed, for motivating smoothed numerical solution for oscillatory mechanical systems [14]. In this paper, we will mainly refer to our paper [5] which reviews this work in a generalized mathematical setting. Moreover the question was addressed in classical statistical mechanics [7], particularly concerning the free energy contribution of stiff potentials in thermal equilibrium [12][17], and in the context of smoothed MD [16].

Using the theorems of our paper [5] we will present a *rigorous* statement of the correct limit equation for the case that the total energy is bounded in the limit $\epsilon \to 0$. It should be emphasized that — in contrast to the previous approach [16] — no additional assumptions are involved in this derivation. We will demonstrate that, for bounded energy:

- The limit equation can in fact be written as a *constrained Hamiltonian system*, whose constraints are indeed given by the manifold $\mathcal{M}$.
- The *limit average* is *slowly varying* in the above sense, i.e., the infinitely fast oscillations normal to $\mathcal{M}$ need not be computed.

- However, the energy stored in these oscillations have to be considered correctly. This energy can explicitly be computed and leads to a *correction W of the soft potential V.*

The limit equation finally reads as:

$$\begin{aligned} M\,\ddot{q} + D(V+W)^T(q) + D^2U(q)\cdot\lambda &= 0 \\ DU(q) &= 0. \end{aligned} \tag{5}$$

An explicit formula for the correcting potential W will be given in Section 2.2. The final results show that it is *not* the so called Fixman-potential. This should be contrasted with results in the approaches which use statistical physics, e.g., [7][16][17].

For means of clear distinction in the following let us call equation (5) the *corrected constrained system* and (4) the *naively constrained system.*

Acknowledgements: It is a pleasure to thank P. Deuflhard whose steady support for the concept of a smoothed MD initiated this work. We also thank S. Reich for many controversial discussions on the subject and for pointing out references [18][20] which were an important key for the explicit construction of the correcting potential.

1 Different Types of Convergence for $\epsilon \to 0$

We now consider the sequence $q^\epsilon : [0,T] \to \mathbb{R}^{3d}$ of solutions of the equation (2) of motion *parametrized* by ϵ. That is, we do not fix ϵ to the small specific value which corresponds to the bond-potential in question, but rather approximate this case by the limit situation $\epsilon \to 0$. To that end we have to investigate in which sense and under which conditions our sequence q^ϵ converges to a limit q^0. Since the main goal is the derivation of a differential equation for q^0, we rewrite the equation of motion as the second order equation

$$\ddot{q}^\epsilon + F(q^\epsilon) + \frac{1}{\epsilon^2}G(q^\epsilon) = 0, \tag{6}$$

with forces $F(q) = M^{-1}DV^T(q)$ and $G(q) = M^{-1}DU^T(q)$. For the sake of notational simplicity we set $M = I$ throughout, which corresponds to a simple redefinition of the potentials V and U.

In order to give an answer to the question posed we have to introduce a concept of averaging

- which is independent from the special form of the oscillations (which in general are not harmonic) and

- which is connected to the limit $\epsilon \to 0$ allowing a rigorous analysis of the type of convergence of $q^\epsilon \to q^0$.

1.1 Weak Convergence as a Concept for Averaging

These requirements on a concept of averaging in the limit are met by the notion of *weak convergence*. Here, one only requires that the averages with respect to a certain class of *test functions* converge to the corresponding averages of the limit function. A particular important type of weak convergence is given by the weak*-convergence in $L^\infty[0,T]$: We have $q^\epsilon \overset{*}{\rightharpoonup} q^0$ if and only if

1. q^ϵ is uniformly bounded in $L^\infty[0,T]$, i.e., there exists a $C > 0$ with $\|q^\epsilon\| < C$ for all $\epsilon > 0$.
2. For each compact subinterval $I \subseteq [0,T]$ the averages converge:

$$\int_I q^\epsilon(t)\,dt \;\to\; \int_I q^0(t)\,dt \qquad \text{for } \epsilon \to 0.$$

Condition 2 links the weak*-limit with the running average of the introduction. It may be illustrated for the easiest situation, i.e., for sequences of harmonic oscillations:

- In the case of constant amplitude with period ϵ, i.e.,

$$q^\epsilon(t) \;=\; q^0(t) \;+\; a\,\sin(t/\epsilon) \tag{7}$$

  we have $q^\epsilon \overset{*}{\rightharpoonup} q^0$ (Riemann-Lebesgue-Lemma) but no strong convergence.

- If the amplitude a is of order $\mathcal{O}(\epsilon)$ also, e.g.,

$$q^\epsilon(t) \;=\; q^0(t) \;+\; \epsilon\,\sin(t/\epsilon), \tag{8}$$

  we get strong convergence $q^\epsilon \to q^0$.

Furthermore, it is easy to understand the central problem of averaging: The strong (pointwise) convergence $q^\epsilon \to q^0$ of functions implies the strong convergence $f(q^\epsilon) \to f(q^0)$, where f is a function continuous in the point argument q. However, $q^\epsilon \overset{*}{\rightharpoonup} q^0$ does *not* imply $f(q^\epsilon) \overset{*}{\rightharpoonup} f(q^0)$. For example, we get

$$\sin^2(t/\epsilon) \overset{*}{\rightharpoonup} \frac{1}{2} \neq 0.$$

This fact — continuous functions do not in general constitute weak*-continuous operators — appears to be the reason for the necessity of the potential correction W mentioned above.

An equivalent formulation of weak*-convergence $q^\epsilon \overset{*}{\rightharpoonup} q^0$ for a sequence $q^\epsilon \in L^\infty$ is given by the convergences of the averages

$$\int q^\epsilon(t)\,\phi(t)\,dt \;\to\; \int q^0(t)\,\phi(t)\,dt$$

for all $\phi \in L^1$. Here we can avoid the assumption of uniform boundedness. An even "weaker" notion of weak convergence is given, if we restrict these test functions ϕ to the space of infinitely continuous functions with compact support, which gives us the notion of weak convergence in the space of distributions $\mathscr{D}'$, $q^\epsilon \overset{\mathscr{D}'}{\rightharpoonup} q^0$. The following important implications hold

$$q^\epsilon \overset{*}{\rightharpoonup} q^0 \;\;\Rightarrow\;\; q^\epsilon \overset{\mathscr{D}'}{\rightharpoonup} q^0 \;\;\Rightarrow\;\; \dot q^\epsilon \overset{\mathscr{D}'}{\rightharpoonup} \dot q^0,$$

which we will use later on. One should however note, that the notion of weak*-convergence has the advantage of offering compactness results which are not supplied by the space of distributions $\mathscr{D}'$. This is used in the proofs of Theorem 1.1, 2.1, and 2.3.

1.2 Type of Convergence — Bounded and Unbounded Energy

Let us now turn back to the sequence of solutions of (6) and ask whether they converge strongly or weakly. It appears that the answer to this question essentially depends on the choice of the sequence of initial values for position and velocity:

$$q^\epsilon(0) = q_0^\epsilon \quad \text{and} \quad \dot q^\epsilon(0) = \dot q_0^\epsilon,$$

and on the corresponding sequence of total energies given by these initial values:

$$E^\epsilon \;=\; \frac{1}{2}\,|\dot q_0^\epsilon|^2 \,+\, V(q_0^\epsilon) \,+\, \frac{1}{\epsilon^2}\,U(q_0^\epsilon).$$

If we again inspect the simple harmonic case $U(q) = |q|^2/2$ we immediately observe that E^ϵ can only be bounded if q_0^ϵ and q^ϵ behave like $\mathcal{O}(\epsilon)$ (and $\dot q_0^\epsilon$ and $\dot q^\epsilon$ like $\mathcal{O}(1)$). That is, for bounded E^ϵ, the positions q^ϵ converge strongly and the velocities $\dot q^\epsilon$ converge in general only weakly (cf. Fig. 2).

The demand for bounded energy seems to be *natural* in this situation. But we should keep in mind that the whole limit $\epsilon \to 0$ is a mathematical "trick" without specific physical reality. To the opinion of the authors the following two different scenarios should be considered:

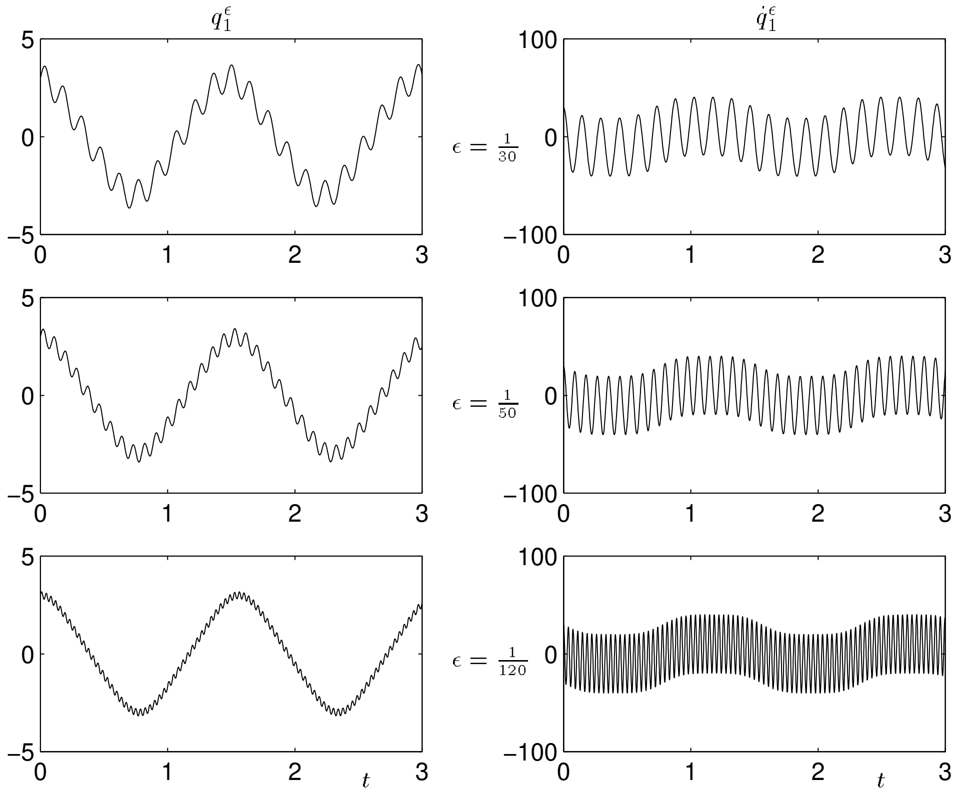

Figure 2: Illustration of Scenario 1 for the system (6) in the two-dimensional collinear case with $V(q) = q_1^4$ and $U(q) = (q_2 - q_1)^2/2$: on the left hand side the first component q_1^ϵ of the solution versus time for ϵ decreasing from top to bottom ($\epsilon = 1/30, 1/50, 1/120$), on the right hand side the corresponding derivatives $\dot q_1^\epsilon$ in the corresponding order. The total energy is identical in all three cases. Note that q_1^ϵ converges strongly to its running average while $\dot q_1^\epsilon$ converges only weakly.

Scenario 1: E^ϵ is a bounded sequence.

Scenario 2: E^ϵ is unbounded, i.e., $E^\epsilon \to \infty$ for $\epsilon \to 0$.

Indeed, these two scenarios characterize the type of convergence of q^ϵ, $\dot q^\epsilon$, and $\ddot q^\epsilon$. Firstly, our observation from above can be put to a rigorous statement, which is proved in our paper [5].

Theorem 1.1 *The sequence (E^ϵ) of total energies is bounded, i.e., there is a bound $C > 0$ such that $|E^\epsilon| < C$ for all $\epsilon > 0$, if and only if the following three conditions hold (up to a possible extraction of subsequences):*

1. q^ϵ converges strongly in C^0: $q^\epsilon \to q^0$.

2. $\dot{q}^\epsilon$ converges weakly in L^∞: $\dot{q}^\epsilon \overset{*}{\rightharpoonup} \dot{q}^0$.

3. $\ddot{q}^\epsilon = \mathcal{O}(\epsilon^{-1})$ converges in the sense of distributions: $\ddot{q}^\epsilon \overset{\mathcal{D}'}{\rightharpoonup} \ddot{q}^0$.

As a consequence of this theorem, a lack of strong convergence of q^ϵ to q^0 implies that E^ϵ is unbounded, i.e., the case that $q^\epsilon \overset{*}{\rightharpoonup} q^0$ weakly but not strongly corresponds to Scenario 2 (cf. Fig. 3).

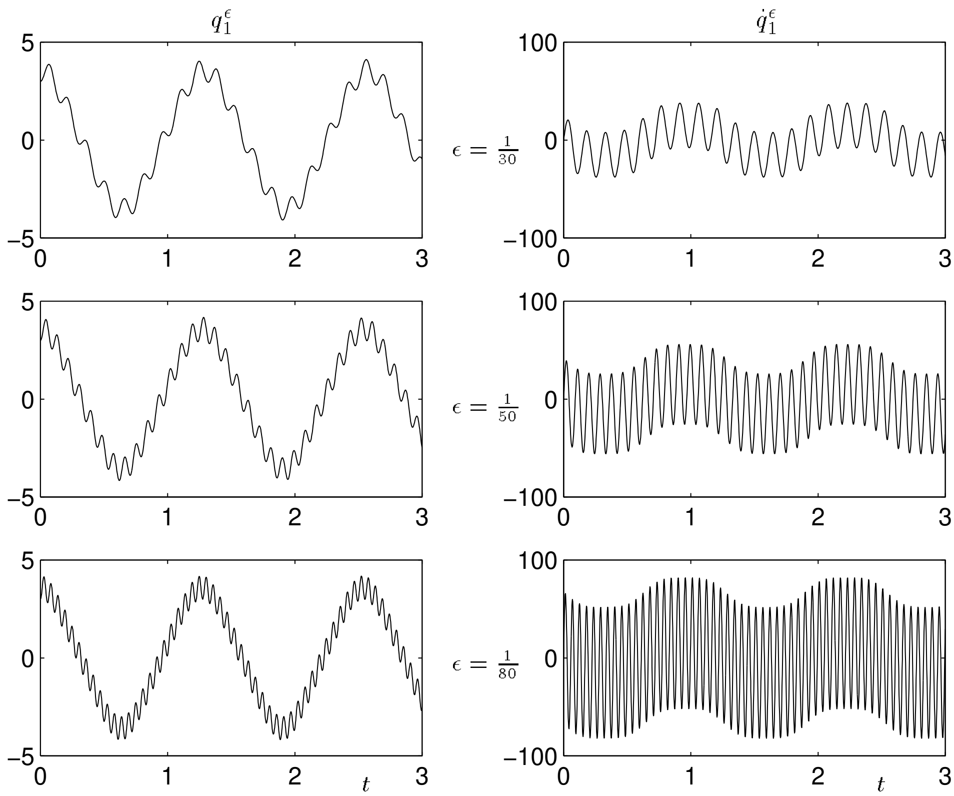

Figure 3: Illustration of Scenario 2 for the same system as in Fig. 2: on the left hand side the first component q_1^ϵ of the solution versus time for ϵ decreasing from top to bottom ($\epsilon = 1/30, 1/50, 1/80$), on the right hand side the corresponding derivatives $\dot{q}_1^\epsilon$ in the corresponding order. The initial values are identical in all cases, i.e., the total energy is increasing from top to bottom. Note that q_1^ϵ converges only weakly to its running average while the amplitude of $\dot{q}_1^\epsilon$ increases like $1/\epsilon$.

In the next section we will derive the limit equation for Scenario 1. As has already been said the limit equation will be a constrained Hamiltonian system with constraining manifold $\mathcal{M} = \{q : DU(q) = 0\}$. This is *definitely not* the case in Scenario 2 as the following simple example shows:

We investigate the simple 1-dimensional case with a vanishing soft potential $V \equiv 0$ and a nonlinear, differentiable strong potential U:

$$U(q) \;=\; \begin{cases} \frac{1}{2}\, q^2 & : \quad x \leq 0 \\ 2\, q^2 & : \quad x > 0 \end{cases} .$$

Furthermore, we fix the initial values $q_0^\epsilon = 1$ and $\dot{q}_0^\epsilon = 0$ leading to an unbounded sequence $E^\epsilon = 2/\epsilon^2$ of energies. The sequence of solutions is given by $q^\epsilon(t) = q^1(t/\epsilon)$ with a $3\pi/2$-periodic function q^1 with

$$q^1(t) \;=\; \begin{cases} \cos(2t) & : \quad 0 \leq t \leq \pi/4 \\ -2\,\sin\,(t - \pi/4) & : \quad \pi/4 \leq t \leq 5\pi/4 \\ \sin\,(2t - 5\pi/2) & : \quad 5\pi/4 \leq t \leq 3\pi/2 \end{cases} .$$

Thus, we have

$$q^\epsilon \stackrel{*}{\rightharpoonup} \frac{2}{3\pi} \int_0^{3\pi/2} q^1(s)\, ds \;=\; -2/\pi = q^0,$$

for which we get $DU(q^0) = -2/\pi \neq 0$. This shows that the limit average q^0 is *not* constrained to $\mathcal{M}$. Conclusively, we find the characterization of the situation as illustrated in Fig. 4.

Scenario 1: Energies (E_ϵ) bounded	$\Longleftrightarrow$	$q^\epsilon \to q^0$ $\dot{q}^\epsilon \stackrel{*}{\rightharpoonup} \dot{q}^0$ $\ddot{q}^\epsilon = \mathcal{O}(\epsilon^{-1})$	$\Longrightarrow$	Evolution on $\mathcal{M} = \{q : DU(q) = 0\}$
Scenario 2: Energies (E_ϵ) unbounded	$\Longleftarrow$	$q^\epsilon \stackrel{*}{\rightharpoonup} q^0$, $q^\epsilon \not\to q^0$ $\dot{q}^\epsilon \stackrel{\mathscr{D}'}{\rightharpoonup} \dot{q}^0$ $\ddot{q}^\epsilon = \mathcal{O}(\epsilon^{-2})$	$\Longrightarrow$	Evolution *not* necessarily on $\mathcal{M}$

Figure 4: Characterization of the different types of convergence and their implications.

The importance of this unbounded energy scenario can be illustrated if we take a look at a potential U with several minima, i.e., points of equilibrium. As an example let us consider $M = 1$, $V = 0$, the 1-dimensional double well potential

$$U(q) \;=\; \left(q^2 - 1\right)^2,$$

and initial values $q_0 > 1$ on the right hand side of the minimum $q = 0$. For realization of bounded energy, one has to take $q_0^\epsilon = 1 + \mathcal{O}(\epsilon)$, and for example, $\dot{q}_0^\epsilon = 0$. But then, q^ϵ converges strongly to $q^0 = 1$, i.e., the motion gets trapped in the minimum $q = 1$ for increasing stiffness. Hence, the essential property of the potential, the existence of two connected minima, is lost and this kind of artificial limit is not appropriate for such potentials. Instead of it, the limit which increases the stiffness of U should conserve the form of the potential, i.e., we should

$$\text{replace the model } \mathcal{V}(q) \;=\; \frac{1}{\epsilon^2}\, U(q) \quad \text{ by } \quad \mathcal{V}(q) \;=\; U(q/\epsilon).$$

Now, the equation of motion reads

$$\ddot{q}^\epsilon \;+\; \frac{1}{\epsilon}\, DU^T(q^\epsilon/\epsilon) \;=\; 0,$$

and useful initial values are, e.g., $q_0^\epsilon = 2\epsilon$ and $\dot{q}_0^\epsilon = 0$ which again lead to bounded energy. By the substitution $x^\epsilon = q^\epsilon/\epsilon$ this transforms to

$$\ddot{x}^\epsilon \;+\; \frac{1}{\epsilon^2}\, DU^T(x^\epsilon) \;=\; 0, \tag{9}$$

with initial values $x_0^\epsilon = 2$ and $\dot{x}_0^\epsilon = 0$. Now, the new system (9) may be associated with the U/ϵ^2 model but with unbounded energy $E^\epsilon = 9/\epsilon^2$! Hence, x^ϵ converges only weakly. Since all energies E^ϵ are large enough, all x^ϵ visit both minima with the same rate and, because of symmetry, the limit is $x^\epsilon \stackrel{*}{\rightharpoonup} 0$. Thus, we have $q^\epsilon \to 0$ which definitely is a better representation of the geometry of the potential. Conclusively, this example shows that the case of unbounded energy is important because it is deeply connected to scenarios in which one wants to conserve the geometry of the potential in the limit $\epsilon \to 0$. Thus, the U/ϵ^2 model is limited to those potentials U which are strictly convex in directions orthogonal to the manifold $\mathcal{M}$ of its equilibrium positions with

$$U|_{\mathcal{M}} = 0 \quad \text{ and } \quad DU|_{\mathcal{M}} = 0.$$

This is the typical case for bond potentials.

2 Limit Equation and Correcting Potential

We now restrict our investigation to Scenario 1, i.e., to the case of bounded energies (E^ϵ) yielding $q^\epsilon \to q^0$. We ask whether the limit average q^0 is given by the *naively constrained system* (4), i.e., by

$$\begin{aligned} \ddot{q}^0 + F(q^0) + DG(q^0)\cdot\lambda &= 0 \\ G(q^0) &= 0, \end{aligned} \tag{10}$$

or whether some kind of correction will appear.

This is the point to introduce a notation which will be useful in the following: The orthogonal projection of a position q on $\mathcal{M} = \{q : G(q) = 0\}$ will be denoted with q_M. Each position q in a sufficiently small neighborhood of $\mathcal{M}$ can uniquely be written as the sum of its projection and the distance vector q_N normal to the manifold: $q = q_M + q_N$. We herein may always assume that q^ϵ is in such a neighborhood, because its distance to $\mathcal{M}$ is of order $\mathcal{O}(\epsilon)$.

2.1 Limit Equation

To this end, let us note two relatively simple implications from Theorem 1.1:

First implication: The strong convergence of q^ϵ implies $F(q^\epsilon) \to F(q^0)$ and $G(q^\epsilon) \to G(q^0)$. Moreover, it is $\ddot{q}^\epsilon = \mathcal{O}(1/\epsilon)$. We multiply equation (6) with ϵ^2 and use these facts to get

$$\underbrace{\epsilon^2\,\ddot{q}^\epsilon}_{\to 0} + \underbrace{\epsilon^2\,F(q^\epsilon)}_{\to 0} + \underbrace{G(q^\epsilon)}_{\to G(q^0)} = 0.$$

Thus, we observe that the limit average q^0 fulfills $G(q^0) = 0$, i.e., q^0 indeed lives on the constraints manifold $\mathcal{M}$.

Second implication: By the same means we directly get from (6):

$$\underbrace{\ddot{q}^\epsilon}_{\stackrel{\mathscr{D}'}{\rightharpoonup}\ddot{q}^0} + \underbrace{F(q^\epsilon)}_{\to F(q^0)} + \underbrace{\frac{1}{\epsilon^2}G(q^\epsilon)}_{\stackrel{\mathscr{D}'}{\rightharpoonup}\mathscr{D}'\text{-}\lim\limits_{\epsilon\to 0} G(q^\epsilon)/\epsilon^2} = 0. \tag{11}$$

Herein, $G(q^\epsilon)/\epsilon^2 = \mathcal{O}(1/\epsilon)$ only converges in the sense of distributions. In order to compute the desired $\mathscr{D}'$-limit one can use Taylor expansion of $G(q^\epsilon)$ around the projection q^ϵ_M of q^ϵ on $\mathcal{M}$. A careful treatment of the different convergences (strong, weak*, weak in $\mathscr{D}'$) in this expansion leads to the following theorem, which is proved in our paper [5].

Theorem 2.1 *For the case of bounded energy the limit average q^0 fulfills*

$$\begin{aligned} \ddot{q}^0 \,+\, F(q^0) \,+\, DG(q^0)\cdot\lambda \,+\, \tfrac{1}{2}\, D^2G(q^0) : \Sigma &= 0 \\ G(q^0) &= 0, \end{aligned} \tag{12}$$

where $\eta^\epsilon/\epsilon \overset{\mathscr{D}'}{\rightharpoonup} \lambda$ and $\eta^\epsilon \otimes \eta^\epsilon \overset{*}{\rightharpoonup} \Sigma$ with the quantity $\eta^\epsilon = (q^\epsilon - q^\epsilon_M)/\epsilon \overset{*}{\rightharpoonup} 0$.

Thus, we indeed arrive at a limit equation with constraints on $\mathcal{M}$. Unfortunately, λ and Σ are not directly known. Note, that although we have $\eta^\epsilon \overset{*}{\rightharpoonup} 0$ in general

$$\Sigma \neq 0$$

holds because squaring a function is *not* a weak*-continuous operation as we have already observed above.

Hence, we found an additional term $D^2G : \Sigma/2$ which does not appear in the simple approach (10). In certain situations this term vanishes or gives only a correction of the Lagrange parameter λ, e.g., if G is linear or for pure bond-stretching potentials, as we will see later on. In general however, it is an important contribution, in particular for bond angle potentials. But Theorem 2.1 does not give us an explicit possibility for computing the correction; this gap must be bridged.

2.2 Correcting Potential for Codimension 1

Many previous approaches demonstrated, that the energy stored in the oscillations of q^ϵ *normal* to the manifold $\mathcal{M}$ is responsible for correcting the soft potential V in the limit $\epsilon \to 0$, cf. [5]. We will now explain that there is a connection between the correction $D^2G : \Sigma/2$ from above and this normal energy. For the sake of simplicity the discussion will herein be restricted to the case in which $\mathcal{M}$ is of codimension one. This will be sufficient in order to discuss that the bond-angle potentials cause a nonvanishing correction of the soft potential and how this corrections may correctly be computed.

In a neighborhood of q^ϵ_M the strong potential U is harmonic with "spring constant"

$$\omega^2(q) \;=\; D_N^2 U(q), \qquad q \in \mathcal{M}, \tag{13}$$

where D_N denotes the derivation normal to $\mathcal{M}$. $D_N^2 U$ is a positive scalar value because $\mathcal{M}$ is of codimension 1 and U is assumed to be strictly convex in normal direction to $\mathcal{M}$. Thus, ω is a positive scalar function on $\mathcal{M}$. Since $q^\epsilon - q^\epsilon_M = \mathcal{O}(\epsilon)$, one intuitively assumes that the normal oscillation of q^ϵ is nearly harmonic with this frequency $\omega(q^\epsilon_M)$.

The *normal energy* corresponding to a state $(q, \dot{q})$ may be defined as

$$E_N(q,\dot{q}) \;=\; \underbrace{\frac{1}{2}\,|\dot{q}_N|^2}_{=T_N} + \underbrace{\frac{1}{2}\,\omega^2\,(q_M(t))\;\; q_N^2}_{=U_N}. \tag{14}$$

It turns out that, in the limit $\epsilon \to 0$, the normal energy $E_N^\epsilon = E_N(q^\epsilon, \dot{q}^\epsilon)$ is *equipartioned* into its kinetic part T_N^ϵ and its potential part U_N^ϵ, i.e., $T_N^0 = U_N^0 = E_N^0/2$. This equipartition is a well known fact for the *time averages* of these energy parts for harmonic oscillations and is connected to the so called *Virial Theorem* of Statistical Mechanics, a *mathematical* result which has the appearance of an ergodic theorem, but no ergodicity is assumed, cf. [1][9][21]. The observation of equipartition in the limit leads to the following theorem, which is proved in our paper [5].

Theorem 2.2 *The sequence $E_N^\epsilon = E_N(q^\epsilon, \dot{q}^\epsilon)$ converges strongly, $E_N^\epsilon \to E_N^0$. The magnitude $E_N^0/\omega(q^0)$ is an* adiabatic invariant *of the motion in the limit $\epsilon \to 0$, i.e., it exists a constant $\Theta \in \mathbb{R}$ such that*

$$E_N^0 \;=\; \Theta\,\omega(q^0), \qquad \Sigma_{NN} \;=\; \frac{\Theta}{\omega(q^0)}, \tag{15}$$

where Σ_{NN} denotes the normal part of the matrix Σ. This constant Θ can uniquely be determined via the initial positions $q_0^0 = \lim_{\epsilon\to 0} q_0^\epsilon$ of the limit average q^0 in $t = 0$,

$$\Theta \;=\; E_N^0(0)/\omega(q_0^0). \tag{16}$$

Since $q_N^\epsilon = \mathcal{O}(\epsilon)$, the total energy splits as

$$E^\epsilon \;=\; \frac{1}{2}|\dot{q}^\epsilon|^2 \,+\, V(q_M^\epsilon) + E_N^\epsilon + \mathcal{O}(\epsilon).$$

Hence, in the limit we have

$$E^0 \;=\; \frac{1}{2}|\dot{q}^0|^2 \,+\, V(q_M^0) \,+\, E_N^0$$

i.e., the limit of the normal energy occurs as a correction of the soft potential V in the limit of total energy. Indeed, E^0 turns out to be the corresponding Hamiltonian of the limit equation, as is proved in [5].

Theorem 2.3 *The limit average q^0 obeys the following* constrained Hamiltonian system

$$\begin{aligned} \ddot{q}^0 \,+\, D(V+W)^T(q^0) \,+\, D^2U(q^0)\cdot\lambda \;&=\; 0 \\ DU(q^0) \;&=\; 0, \end{aligned} \tag{17}$$

in which the correcting potential W is given by the limit of the normal energy

$$W(q) \;=\; \Theta\,\omega(q)$$

for $q \in \mathcal{M}$.

Herein, Θ denotes the constant of Theorem 2.2, i.e., W can *explicitly* be computed. Thus, for the case of codimension 1, the general correction $D^2G : \Sigma/2$ can be computed via the second normal derivative of U and the limit of the initial conditions. These results can be extended to general codimension if certain resonances and singularities can be excluded beforehand, cf. [5].

Before we go into the details of an illustrative example, in which W is an important correction, let us state some situations in which the corrected constrained system (17) may indeed be reduced to the naively constrained system (10).

2.3 Vanishing Potential Corrections

In specific situations the correction potential W vanishes or gives only a correction of the Lagrange parameter λ. For the case of codimension 1 we can easily determine these situations by the condition that the gradient DW vanishes. There are two possibilities: the initial conditions lead to a constant $\Theta = 0$ (vanishing normal energy), or ω is constant on $\mathcal{M}$ (constant gully width). In fact, using the general result of Theorem 2.1, we have shown in [5] that the correction does not contribute in *precisely* these two cases — *independently* of the codimension of $\mathcal{M}$.

1. *Vanishing normal energy.* The correction W is zero if $E_N^\epsilon(0) \to 0$. The corresponding implication is well-known: The simple approach (10) is correct if the initial velocity has no component normal to $\mathcal{M}$. This can already be proved by standard perturbation theory, cf. [14]. For this case it can be shown that $q_N^\epsilon = \mathcal{O}(\epsilon^2)$ which implies the *strong* convergence $\eta^\epsilon \to 0$ and therefore $\Sigma = \eta^\epsilon \otimes \eta^\epsilon \to 0$.

2. *Constant gully width.* The correction does only change the Lagrange parameter λ if the second normal derivative of U is constant along $\mathcal{M}$:

$$D_N^2 U\big|_{\mathcal{M}} \;=\; \text{const.} \tag{18}$$

   This is the so called Arnold-theorem [2][5][8]. It is of particular interest for MD, because condition (18) is fulfilled *if U is a collection of bond-stretching potentials only.*

3 Illustrative Example

In this section the necessity of the correction of the soft potential for the direct computation of the correct limit average is illustrated. Moreover, the explicit evaluation of the correction is demonstrated for an bond-angle potential with codimension 1 and the resulting potential is compared with the Fixman-potential in this case.

3.1 The Test System

For simplicity we choose a test system with 2-dimensional position space (cf. Fig. 5):

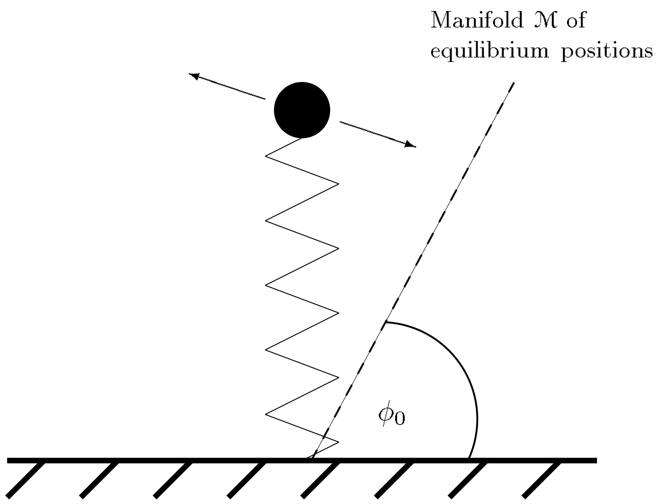

Figure 5: Illustration of the test system. In addition to a soft spring the motions of the mass point are effected by a stiff potential with equilibrium positions for angles $\phi = \phi_0$.

A mass point with mass $m = 1$ and position $q \in \mathbb{R}^2$ is subjected to the potential $V(q) = (|q| - 1)^2/2$ of a soft spring and an angle-dependent stiff potential

$$U(q) \;=\; \frac{1}{2}\,(\cos\phi(q) \;-\; \cos\phi_0)^2, \qquad \cos\phi(q) \;=\; \frac{q_1}{|q|}, \tag{19}$$

with equilibrium angle $\phi_0 = \pi/4$. Clearly, this system reflects the situation of a stiff bond-angle potential and an additional soft one. The manifold of constraints is $\mathcal{M} = \{\mu\, e_M,\, \mu \in \mathbb{R}\}$ with $e_M = (1,1)^T/\sqrt{2}$ being the tangential unit vector. The corresponding unit vector normal to $\mathcal{M}$ is $e_N = (1,-1)^T/\sqrt{2}$. Obviously, $\mathcal{M}$ is of codimension 1. The initial values are fixed to

$$q_0^\epsilon \;=\; e_M \qquad \text{and} \qquad \dot{q}_0^\epsilon \;=\; (3,-2)^T,$$

which corresponds to Scenario 1 (bounded total energy), but leads to a *nonvanishing normal component* of the initial velocities:

$$\dot{q}_{0\,N}^\epsilon \;=\; \frac{1}{2}\,(5,-5)^T.$$

Thus, according to (14) the initial normal energy is:

$$E_N^0(0) \;=\; \frac{1}{2}\,|\dot{q}_{0\,N}^0|^2 \;=\; \frac{25}{8}.$$

The initial values for the limit average q^0 are obtained as limits of the projection of q_0^ϵ and $\dot{q}_0^\epsilon$ onto $\mathcal{M}$:

$$q_0 \;=\; e_M \qquad \text{and} \qquad \dot{q}_0 \;=\; \frac{1}{2}\,(1,1)^T.$$

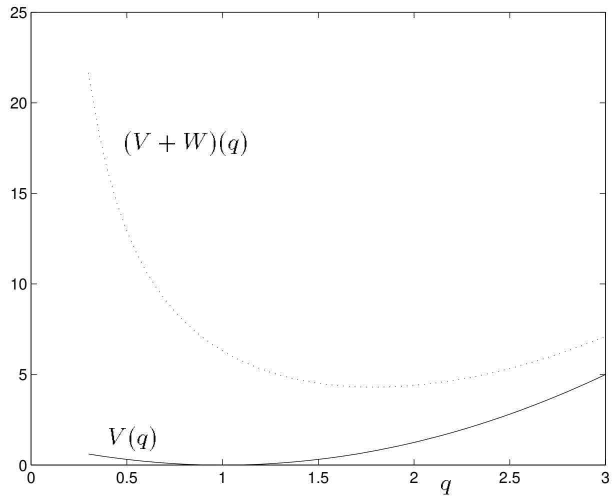

Figure 6: Comparison between the original soft potential V (solid line) and the corrected one $V+W$ (dotted line).

3.2 Correction of Soft Potential

For computing the correcting potential W we have to find the second derivative of U normal to $\mathcal{M}$ which implies the position dependent frequency ω of the normal oscillations. It is given by

$$D_N^2 U(q) \;=\; D^2 U(q) : e_N \otimes e_N \;=\; \frac{1}{2\,|q|^2} \quad\Longrightarrow\quad \omega(q) \;=\; \frac{1}{\sqrt{2}\,|q|}$$

for $q \in \mathcal{M}$. Thus, the constant Θ of Theorem 2.2 results from (16) to be

$$\Theta \;=\; \frac{25}{4}\sqrt{2},$$

which gives us the explicit form of the potential- and force-correction for $q \in \mathcal{M}$:

$$W(q) \;=\; \frac{25}{4}\,\frac{1}{|q|} \quad\Longrightarrow\quad DW(q) \;=\; -\,\frac{25}{4}\,\frac{q}{|q|^3}. \tag{20}$$

Fig. 6 illustrates that the effect of this correction is essential.

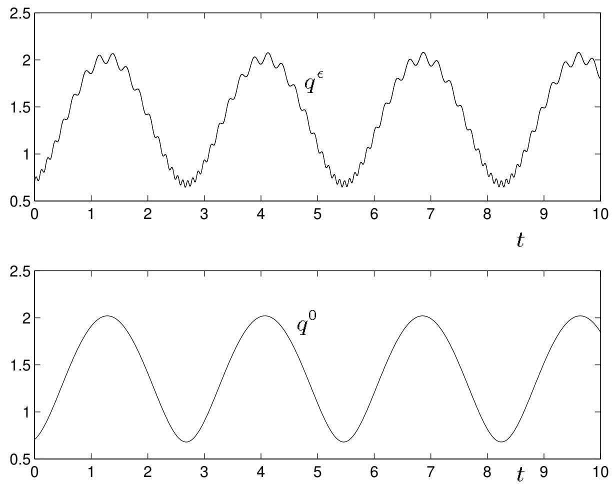

Figure 7: Comparison of the highly oscillatory solution q^ϵ of (6) for $\epsilon = 1/100$ (on top) with the smooth limit average q^0, which is the solution of the limit equation with corrected soft potential. The running average of the trajectory on top and the limit average would be indistinguishable in "picture-norm".

Now, we can compute the limit average q^0 directly from our limit equation (17) with the potential correction W due to (20). Moreover, we are interested in the solution $\tilde{q}^0$ of the naively constrained system (10) without potential correction. We find what we have expected: q^0 is nearly identical with the running average of q^ϵ for small $\epsilon > 0$ (see Fig. 7) and $\tilde{q}^0$ essentially deviates from q^0 (see Fig. 8).

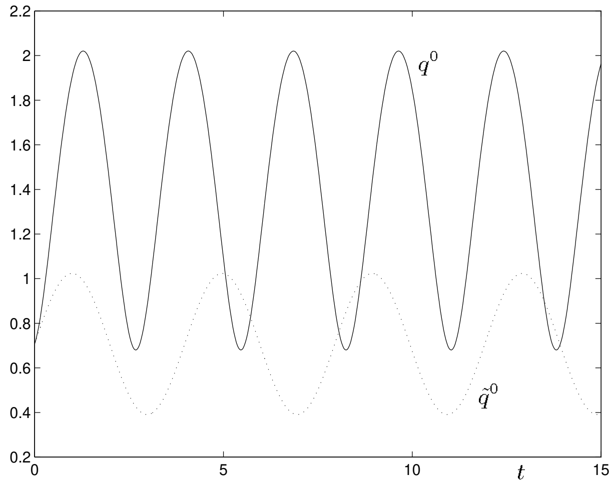

Figure 8: Comparison of the solution $\tilde{q}^0$ of the naively constrained system (10) without correction (dotted line) with the smooth correct limit average q^0 (solid line).

3.3 Comparison with Fixman-Potential

As already stated before, some previous approaches [16][8] argued mistakenly that the potential correction must be given by the so called Fixman-potential, which is for $U(q) = g(q)^2/2$ defined as follows:

$$V_{\mathrm{Fix}}(q) \;=\; \frac{\delta}{2} \log\det\left(Dg(q) \cdot Dg^T(q)\right),$$

with a constant parameter δ which is statistically interpreted via the "temperature" of the system (see [16]). For the herein considered test system we compute for $q \in \mathcal{M}$:

$$V_{\mathrm{Fix}}(q) \;=\; \frac{\delta}{2}\,\log\left(\frac{1}{2|q|^2}\right) \quad\Longrightarrow\quad DV_{\mathrm{Fix}}(q) \;=\; -\,\delta\,\frac{q}{|q|^2}, \tag{21}$$

which is definitely different from the correct result (20). In comparison with (20) the best choice of the free parameter seems to be

$$\delta = \frac{25}{4}\frac{1}{|q_0|} \quad \Longrightarrow \quad DV_{\mathrm{Fix}}(q) \;=\; -\;\frac{25}{4}\frac{1}{|q_0|}\frac{q}{|q|^2}.$$

A comparison of the resulting solution q_{Fix} (limit equation with Fixman-correction $W = V_{\mathrm{Fix}}$) with the correct limit average q^0 is given in Fig. 9. It demonstrates that q_{Fix} is wrong in amplitude *and* frequency.

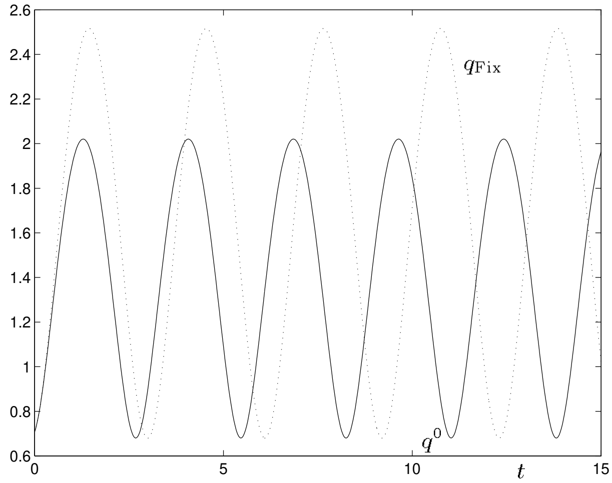

Figure 9: Comparison of the correct limit average q^0 computed via the exact potential-correction W with the limit average q_{Fix} computed via the fitted Fixman-potential V_{Fix} due to (21). Note that the Fixman-limit average is wrong in amplitude *and* frequency.

Remark. This discussion proves that the Fixman potential is *not* the right potential correction in order to establish a limit equation for q^0 — although the statements of [16] are often interpreted in this way. However, the Fixman potential has been suggested in [16] on the base of additional physical assumptions, which considerably change the problem: embedding of the molecular system in a heat bath of constant temperature. Thus, the paper [16] does not deal as claimed with the limit situation for the Hamiltonian system (2), which describes a *single* molecular system. Rather it deals with a statistical *ensemble* of those systems and applies standard modeling techniques of statistical physics to it, e.g., thermalization. In this context the Fixman potential could be a good model, however, a justification of this model is still missing and can in practice only be given on the basis of comparisons with reliable simulations of ensembles or with experiments.

3.4 Deviations for $\epsilon > 0$

Our starting point has been the search for a rigorous approach to smoothed MD. We have learned, that we can compute a slowly varying solution q^0 which is the correct *limit* average of the sequence q^ϵ of solutions of the original equations of motion for $\epsilon \to 0$. Naturally, the potentials are fixed for a given particular molecular system, leading to a fixed specific value

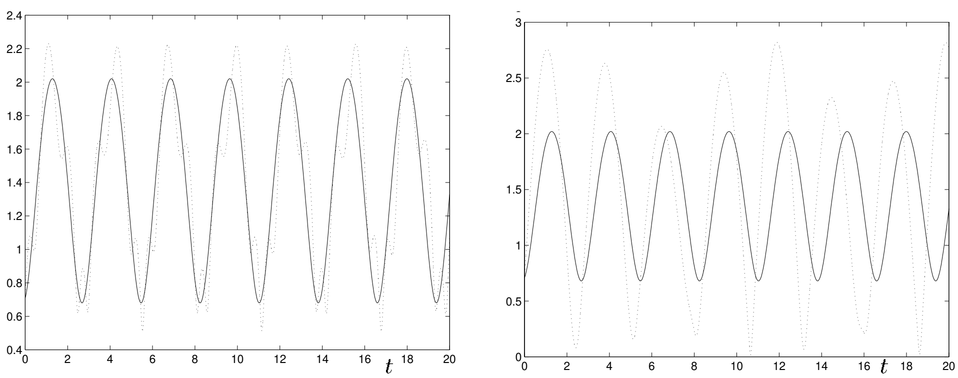

Figure 10: Deviations between correct limit average q^0 and oscillatory solutions q^ϵ for values of ϵ significantly larger than 0. q^0 still is a good approximation of the running average q^ϵ for $\epsilon = 1/20$ (right hand side) but there are significant deviations for $\epsilon = 1/5$ (left hand side).

$\epsilon_0 > 0$ of the parameter ϵ. The question remains, for which ϵ_0 the limit average q^0 constitutes still a good approximation of the running average $\bar{q}^\epsilon$ of q^ϵ. The spectral gap between frequencies resulting from U/ϵ^2 and those effected by V is steadily increased in the limit $\epsilon \to 0$, which, in turn, leads to a decoupling of possibly resonant scenarios. Thus, we expect essential deviations between the running average $\bar{q}^\epsilon$ and q^0 if ϵ is too large. We will not address this question in more detail; as an illustration of the situation, a direct comparison of some q^ϵ with q^0 may be found in Fig. 10.

4 Concluding Remarks

The interaction potential $\mathcal{V}$ of molecular systems can be split into two parts

$$\mathcal{V}(q) \;=\; V(q) + \frac{1}{\epsilon^2} U(q)$$

according to the essentially different time scales of the involved potentials. The aim of long term MD-simulations for macromolecules requires a "smooth" solution, i.e., a solution in which the fast oscillations effected by the stiff U-part are correctly averaged.

In this paper we have studied the kind of motion which appears if this stiffness is increased to infinity, i.e., we studied the limit $\epsilon \to 0$ and asked for an initial value problem, which is obeyed by the limit q^0 of the sequence of solutions q^ϵ. Let us once more collect the essential results:

The type of convergence of q^ϵ crucially depends on the sequence E^ϵ of total energies. The sequence q^ϵ of positions converges strongly to a q^0 if E^ϵ is bounded; this is the interesting case for potentials U representing molecular bond-stretching and bond-angle interactions. The convergence of the positions is only weak, if E^ϵ is unbounded; this case appeared to be connected to the potentials with several minima, e.g., dihedral angle potentials. However, besides very special situations the sequence $p^\epsilon = M\dot{q}^\epsilon$ of momenta converges only *weakly* in either case.

We discussed the case of bounded energy in detail: The strong potential forces the motion on the manifold $\mathcal{M}$ of equilibrium points. The limit average q^0 can be computed as the unique solution of a certain constrained Hamiltonian system with corrected soft potentials $V + W$. The limit function q^0 is "smooth" in the required sense, i.e., the fast oscillations normal to $\mathcal{M}$ need not be computed. But the energy E_N^ϵ stored in these oscillations must be considered correctly. Its limit E_N^0 can be evaluated and allows the construction of an explicit formula for the correcting potential W which depends on the initial normal energy and on the second normal derivative of the strong potential U.

It appears that this correcting potential W is definitely not the Fixman potential as repeatedly assumed in the literature. Moreover, we observed that W does not contribute if U includes bond stretching potentials only, while it is of essential importance for bond angle potentials. Consequently, this paper shows how to evaluate the correct limit solution for molecular systems with strong bond angle interactions. A realistic application including a comparison with the average of MD-trajectories is the subject of a forthcoming paper.

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