

Computation of Essential Molecular Dynamics by Subdivision Techniques

P. Deuffhard^{1,2}, M. Dellnitz³, O. Junge³, and Ch. Schütte^{1,2}

¹ Konrad Zuse Zentrum Berlin, Takustr. 7, 14195 Berlin, Germany

² Freie Universität Berlin, Fachbereich Mathematik, Arnimallee 2-6, 14195 Berlin, Germany

³ Mathematisches Institut, Universität Bayreuth, 95440 Bayreuth

Dedicated to Prof. Dr. Dr. h.c. Roland Bulirsch on the occasion of his 65th birthday.

Abstract. The paper presents basic concepts of a new type of algorithm for the numerical computation of what the authors call the *essential dynamics* of molecular systems. Mathematically speaking, such systems are described by Hamiltonian differential equations. In the bulk of applications, individual trajectories are of no specific interest. Rather, time averages of physical observables or relaxation times of conformational changes need to be actually computed. In the language of dynamical systems, such information is contained in the natural invariant measure (infinite relaxation time) or in almost invariant sets ("large" finite relaxation times). The paper suggests the direct computation of these objects via eigenmodes of the associated Frobenius-Perron operator by means of a multilevel subdivision algorithm. The advocated approach is different from both Monte-Carlo techniques on the one hand and long term trajectory simulation on the other hand: in our setup long term trajectories are replaced by short term sub-trajectories, Monte-Carlo techniques are connected via the underlying Frobenius-Perron structure. Numerical experiments with the suggested algorithm are included to illustrate certain distinguishing properties.

1 Introduction

The classical microscopic description of molecular processes leads to a mathematical model in terms of Hamiltonian differential equations. In principle, the discretization of such systems permits a simulation of the dynamics. However, as will be worked out below in Section 2, both forward and backward numerical analysis restrict such simulations to only short time spans and to comparatively small discretization steps. Fortunately, most questions of chemical relevance just require the computation of *averages* of physical observables, of *stable conformations* or of *conformational changes*. The computation of averages is usually performed on a *statistical physics* basis. In the subsequent Section 3 we advocate a new computational approach on the basis of the mathematical theory of *dynamical systems*: we directly solve a discretized eigenvalue problem for the Frobenius-Perron operator without

any physical a-priori assumptions. In this framework, the computation of averages corresponds to the approximation of *invariant measures* and *invariant sets* associated with eigenvalue $\lambda = 1$ – a fact, which is well-known for quite a while. In a similar way, conformations of molecular systems correspond to *almost invariant sets* related to eigenmodes of the Frobenius–Perron operator for $\lambda \approx 1$ – a fact, which has just recently been discovered [6]. On the basis of this insight, a multilevel box discretization (or subdivision technique) is applied to the Frobenius–Perron eigenvalue problem, which only requires short term subtrajectory computations. Finally, an illustrative numerical example is included in Section 4. This paper is a shortened and improved version of the more elaborate Technical Report [8].

2 Trajectory Simulation

In classical MD (cf. textbook [1]) a molecule is modelled by a Hamiltonian function

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

where q and p are the corresponding positions and momenta of the atoms, M the diagonal mass matrix, and V a differentiable potential. The Hamiltonian H is defined on the phase space $\Gamma \subset \mathbb{R}^{6N}$. The corresponding canonical equations of motion

$$\dot{q} = M^{-1} p, \quad \dot{p} = -\text{grad } V \quad (1)$$

describe the dynamics of the molecule. The formal solution of (1) with initial state $x_0 = (q(0), p(0))$ is given by $x(t) = (q(t), p(t)) = \Phi^t x_0$, where Φ^t denotes the flow. In the process of one-step numerical integration of (1) we replace the flow by a *discrete flow* Ψ^τ , so that

$$x_{k+1} = \Psi^\tau x_k \quad \Rightarrow \quad x_k = (\Psi^\tau)^k x_0,$$

with stepsize τ (assumed to be constant, for the time being). An important feature of molecular processes is that *long term predictions* over periods much longer than the applied time steps are required.

Forward Analysis. In this type of analysis, we are interested in the propagation of initial perturbations δx_0 along the flow Φ^t of (1), i.e., in the growth of the perturbations $\delta x(t; x_0) = \Phi^t(x_0 + \delta x_0) - \Phi^t x_0$. The *condition number* $\kappa(t)$ may be defined as the worst case error propagation factor (cf. textbook [7]), so that, in first order perturbation analysis and with a suitable norm $|\cdot|$:

$$|\delta x(t; x_0)| < \kappa(t) |\delta x_0| \quad \text{for all } x_0.$$

Note that this number $\kappa(t)$ is *independent of any discretization*. From this point of view, numerical integration is reasonable only over time intervals

$[0, T]$ with $\kappa(T)$ sufficiently small compared to expected input errors. Integrable systems (such as the popular Kepler problem) are characterized by $\kappa(T) \sim T$ [13], which allows for quite long term simulations. In real life MD problems, however, κ is exponentially increasing. This fact is illustrated in Fig. 1, where test simulations for the Butane molecule are presented. Note that here we are discussing a property of the *continuous* Hamiltonian system. Therefore, in order to avoid any discretization error effects unusually small time steps ($\tau = 0.005$ fs) have been chosen within the Verlet scheme. As can be seen, global propagation of physically negligible initial perturbations totally spoils any information after a time span, which is significantly shorter than time spans of physical interest.

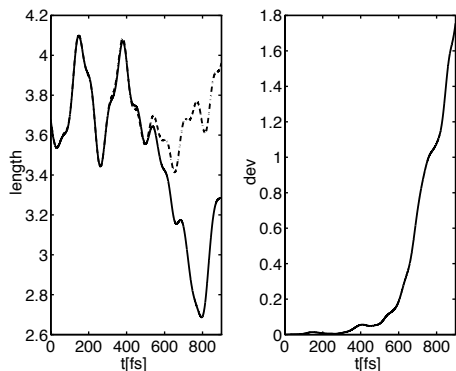


Fig. 1. Comparison of two different dynamical simulations for the Butane molecule: Verlet discretization with stepsize $\tau = 0.005$ fs. Initial spatial deviation: 10^{-4} Å. Left: Evolutions of the total length (=distance between the first and the last carbon atom) of the molecule (in Å). Right: Spatial deviation (in Å) of the two trajectories versus time.

Backward Analysis. In this type of analysis, the *discrete* solution is regarded as an exact solution of a perturbed problem. In particular, backward analysis of *symplectic discretizations* of Hamiltonian systems (such as the popular Verlet scheme) has recently achieved a considerable amount of attention (see [17,12,3]). Such discretizations give rise to the following feature: the discrete solution of a Hamiltonian system is “exponentially close” to the exact solution of a *perturbed* Hamiltonian system, in which, for consistency order p and stepsize τ , the perturbed Hamiltonian has the form [11,3]

$$\tilde{H} = H + \sum_{k=0}^N \tau^{p+k} H_k \quad (2)$$

This means that the discrete solution nearly conserves the Hamiltonian \tilde{H} and, thus, conserves H up to $\mathcal{O}(\tau^p)$. If H is analytic, then the truncation index

N in (2) is arbitrary. In general, however, the above formal series diverges as $N \rightarrow \infty$. The term “exponentially close” may be specified by the following theorem.

Theorem 1 ([12]). *Let H be analytic. There exists some $\tau_* > 0$, so that for all $\tau < \tau_*$ the numerical solution $x_k = (\Psi^\tau)^k x_0$ and the exact solution \tilde{x} of the perturbed system \tilde{H} (the sum being truncated after $N = \mathcal{O}(1/\tau)$ terms) with $\tilde{x}(0) = x_0$ remain exponentially close in the sense that*

$$x_k - \tilde{x}(k\tau) = \mathcal{O}(e^{-c/\tau})$$

with some problem-dependent constant $c > 0$ over a time interval $T = \mathcal{O}(1/\tau)$, i.e., for all $k\tau < T$.

In applications, one is often interested in approximating time averages over a time interval $[0, T]$ via associated mean values of x_k , $k = 1 \dots T/\tau$. For T (or τ) small enough, the above backward analysis may lead to much better error estimates than the worst case estimates of forward analysis.

In fact, numerical observations show that the average of the *total energy* is nearly constant over rather long time spans for large stepsizes, say $\tau \approx 1$ fs. However, this desirable property does not carry over to other averages, where stepsizes much smaller than desirable ($\tau \ll 1$ fs) may be required. This phenomenon is illustrated in Fig. 2. Here the time average of the molecular length of Butane over $T = 200$ ps requires a discretization with $\tau_* \approx 10^{-2}$ fs in comparison with physically interesting stepsizes $\tau \approx 1 \dots 10$ fs. This illustrates, that —even though the discrete system is an only slightly perturbed Hamiltonian system— a successful control of energy is not sufficient for the reliable computation of other observables.

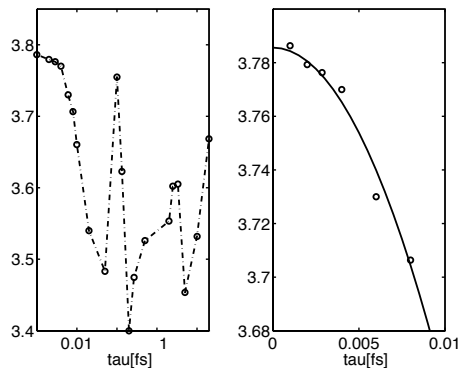


Fig. 2. Left: Time average (over $T = 200$ ps) of the molecular length of Butane versus discretization stepsize τ for the Verlet discretization. Right: Zoom of the asymptotic domain ($\tau < 10^{-2}$ fs) and quadratic fit.

Summarizing, from a mathematical point of view, both forward and backward analysis lead to the insight that long term trajectory simulation should be avoided even with symplectic discretizations. Rather, in the spirit of *multiple* as opposed to *single* shooting (cf. BULIRSCH [4,18]), only *short term* trajectories should be used to obtain reliable information.

Remark. The authors are well aware of the commonly shared belief within the physics MD community that the apparent chaos does not destroy all long term information, but only irrelevant information; in particular, average quantities are supposed to be not sensitive to numerical perturbations. We do not aim at deciding about this fundamental question here.

Essential Dynamics. In most applications details of individual MD trajectories are of only minor interest. An illustrative example due to GRUBMÜLLER [10] is documented in Figure 3. It describes the dynamics of a polymer chain of 100 CH₂ groups. Possible stepsizes for numerical integration are confined by the fast oscillations ($\tau < 10$ fs). Time scales of physical interest range between 10^3 and 10^5 ps, which is a factor $10^5 - 10^7$ larger. The figure presents six different zoom levels, each of which scales up in time by a factor of 10. On the small time scales (upper levels) the dynamical behavior is characterized by nonlinear *oscillations* around certain vague “equilibrium positions”. On larger and larger time scales these oscillations become less and less important. On the largest time scale (lowest level) we observe an “essential” dynamical behavior as a kind of flip–flop between two “conformations”.

As a consequence of this observation, the *essential* dynamics of the molecular process could as well be modelled by *probabilities* describing mean durations of stay within different conformations of the system. This idea is not new, cf. [10]. Even the phrase “essential dynamics” has already been coined in [2]: it has been chosen for the reformulation of molecular motion in terms of its “almost invariant” degrees of freedom. But unlike the former approaches, which aim in the same direction, we herein advocate a different line of method: we suggest to *directly* attack the computation of the conformations and their stability time spans, which means some global approach clearly differing from any kind of statistical analysis based on long term trajectories.

3 Dynamical Systems Approach

We restrict our attention to symplectic one-step discretizations of (1), which leads to discrete dynamical systems of the form

$$x_{j+1} = f(x_j), \quad j = 0, 1, 2, \dots, \quad (3)$$

where m denotes the number of time steps between two updates of the discrete mapping $f = (\Psi^\tau)^m : \Gamma \rightarrow \Gamma$.

The long term behavior of any system (3) is described by so-called *invariant measures*: a probability measure μ is invariant, iff $\mu(f^{-1}(B)) = \mu(B)$

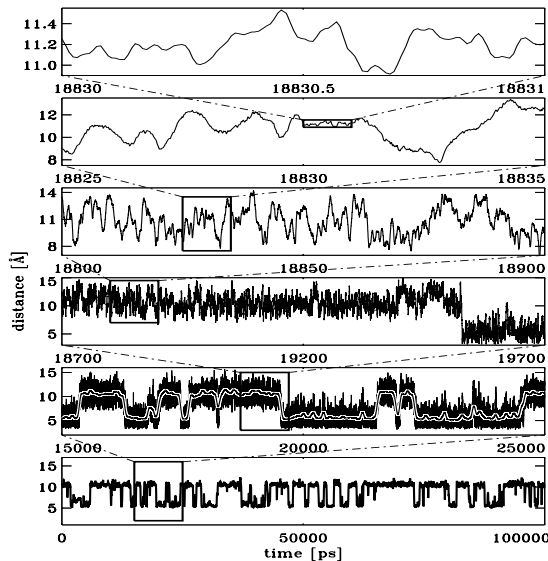


Fig. 3. MD simulation of a polymer chain of 100 CH_2 groups due to [10]. The dynamics of the distance between two CH_2 -groups (# 12 and # 36). The series of plots illustrates the oscillations of the distance at time scales increasing by a zoom factor of 10 at each level.

for all measurable subsets $B \subset \Gamma$. The associated *invariant sets* are defined by the property that $B = f^{-1}(B)$. Throughout the paper we will restrict our attention to so-called SBR-measures (cf. [16]), which are robust with respect to stochastic perturbations. Such measures are the only ones of physical interest. In view of the above considerations about modelling in terms of probabilities, the following interpretation will be crucial: given an invariant measure μ and a measurable set $B \subset \Gamma$, the value $\mu(B)$ may be understood as the probability of finding the system within B .

3.1 Frobenius-Perron Eigenvalue Problem

A key observation for our purposes here is that the numerical computation of invariant measures is equivalent to the solution of an *eigenvalue problem* for the so-called *Frobenius-Perron operator* $P : \mathcal{M} \rightarrow \mathcal{M}$ defined on the set \mathcal{M} of probability measures on Γ by virtue of

$$(P\mu)(B) = \mu(f^{-1}(B)) \quad \text{for all measurable } B \subset \Gamma \text{ and arbitrary } \mu \in \mathcal{M}.$$

Invariant measures correspond to fixed points of P which means that $P\mu = \mu$ iff $\mu \in \mathcal{M}$ is invariant. In what follows, we will advocate to discretize the operator P in such a way that its (matrix) approximation P_d has an eigenvector v_d satisfying $P_d v_d = v_d$, which means that v_d is an approximation of an in-

variant measure. For an invariant measure, any numerical discretization may be interpreted as a stochastic perturbation of the original problem.

Chemical conformations. From a chemical point of view, biomolecular systems are characterized by different “conformations” – a term, which simultaneously describes both distinguishable geometric configurations and the associated chemical “functionality”. In a conformation, the large scale geometric structure of the molecule is understood to be conserved, whereas on smaller scales the system may well rotate, oscillate or fluctuate. For a conformation to be an object of chemical interest, the duration of stay within that conformation should be long enough (*stable* conformation) or, equivalently, it should make a significant contribution to any (statistical) averages. Conformational *changes* are therefore rare events, which will show up only in long-term simulations.

From a mathematical point of view, conformations are special subsets of phase space: a) *invariant sets* of MD systems, which correspond to infinite durations of stay (or relaxation times) and contain all subsets associated with different conformations, b) *almost invariant sets*, which correspond to finite relaxation times and consist of conformational subsets. In order to characterize the dynamics of a system, these subsets are the interesting objects. As already mentioned above, invariant measures are fixed points of the Frobenius-Perron operator or, equivalently, eigenmodes of the Frobenius-Perron operator associated with eigenvalue exactly 1. In view of this property, almost invariant sets will be understood to be connected with eigenmodes associated with (real) eigenvalues close (but not equal) to 1 – an idea recently developed in [6].

Almost Invariant Sets. Due to Frobenius-Perron theory, the eigenmode for $\lambda = 1$ has only positive components, which permits a direct interpretation as an eigenmeasure – in this case the invariant measure. The situation is different for eigenmodes associated with $\lambda \neq 1$, which cannot directly be interpreted as measures. In order to clarify the connection between eigenmodes to eigenvalues $\lambda \approx 1$ but $|\lambda| < 1$ with almost invariant sets, we now perform some “Gedankenexperiment”: the basic idea is that almost invariant sets should allow for an interpretation as being *continuous* perturbations of invariant sets. This interpretation will lead us to an appropriate criterion for the identification of almost invariant sets exploiting the eigenmodes to eigenvalues $\lambda \approx 1$. Suppose, that the system under investigation depends on a suitable parameter γ (e.g. the total energy or a parameter in the potential, cf. example (15) in Section 4). Let $B = B_1 \cup B_2$ with B_1, B_2 subsets to be defined.

In the *unperturbed* case, say $\gamma = \gamma_0$, let the system have two *disjoint invariant* sets B_1 and B_2 associated with two eigenmodes and invariant mea-

asures μ_1 and μ_2 , respectively. In this situation, we have

$$\mu_1(B_2) = \mu_2(B_1) = 0 \quad \text{and} \quad \mu_1(B_1) = \mu_2(B_2) = 1. \quad (4)$$

For $B = B_1 \cup B_2$, both measures are eigenmeasures of P associated with the eigenvalue $\lambda = 1$. Hence, there is no unique invariant measure μ . In fact, any linear combination

$$\mu = \alpha\mu_1 + (1 - \alpha)\mu_2, \quad \alpha \in [0, 1]$$

will be an invariant measure. In order to span the thus arising two-dimensional eigenspace by orthogonal eigenmodes, say μ, ν , we are directly led to define

$$\nu = \alpha\mu_2 - (1 - \alpha)\mu_1.$$

From (4) we then find

$$\nu(B_2) = \alpha, \quad \nu(B_1) = \alpha - 1, \quad (5)$$

and thus

$$\nu(B) = 2\alpha - 1, \quad |\nu|(B) = \mu(B) = 1. \quad (6)$$

In the *perturbed* case, assume now a small change in γ , which induces a small intersection of B_1 and B_2 . Let $B = B_1 \cup B_2$ remain to be invariant. Then, we have a unique eigenmeasure $\tilde{\mu}$ with eigenvalue $\lambda_1 = 1$ and another eigenvector $\tilde{\nu}$ associated with $\lambda_2 \neq 1$. Under some continuity assumption λ_2 should be close to 1 and thus we have $\tilde{\nu}(B) = 0$. In view of (6), continuity for $\gamma = \gamma_0$ then requires $\alpha = 1/2$. Therefore (5) implies that

$$\tilde{\nu}(B_1) = -1/2, \quad \tilde{\nu}(B_2) = 1/2, \quad (7)$$

while $|\tilde{\nu}|$ approximates a probability measure. From this insight, we may infer a *construction principle* for almost invariant sets: decompose B into two almost invariant sets B_1, B_2 such that conditions (7) and (6) hold simultaneously. Given a (spatial) discretization (cf. Section 3.2) this means to collect all positive components within the one and all negative components within the other subset (cf. Section 4) — thus defining a unique identification of almost invariant sets. Note, that the number $1/2$ does *not* arise from any symmetry argument. This simplified treatment only covers the identification of two almost invariant sets. For a generalization along these lines of thought see [9,6].

After these preliminaries we are now ready for a mathematically precise definition of an almost invariant set. Let $\rho \in \mathcal{M}$ be any probability measure. We say that the set B is δ -almost invariant with respect to ρ if

$$\frac{\rho(f^{-1}(B) \cap B)}{\rho(B)} = \delta. \quad (8)$$

In words: δ is the probability that points in B are mapped into B under f . In particular, if B is an invariant set, that is $f^{-1}(B) = B$, then $\delta = 1$ independent of the choice of ρ . Once $\delta = \delta_B$ has been computed for a given set $B \subset \Gamma$ using the stepsize τ in the discrete dynamical system with $f = (\Psi^\tau)^m$, the system's probability of staying within B for time T can be estimated to be

$$p_B(T) = \delta_B^{T/(m\tau)}. \quad (9)$$

This is just the kind of information required from the chemical point of view.

As it turns out, there exists a relationship between those probabilities, by which sets are almost invariant, and associated eigenvalues λ (cf. [6]).

Proposition 2. *Let ν be an eigenmode to P with respect to a real eigenvalue $|\lambda| < 1$. Furthermore, let $B \subset \Gamma$ be a set with $\nu(B) = \frac{1}{2}$. If B is δ_1 -almost invariant and $\Gamma - B$ is δ_2 -almost invariant with respect to $|\nu|$, then*

$$\delta_1 + \delta_2 = \lambda + 1. \quad (10)$$

For more than two almost invariant sets one has to consider all eigenmeasures corresponding to eigenmodes for eigenvalues close to one. In this case, the following lemma will be helpful.

Lemma 3. *Let $\rho \in \mathcal{M}$ be a probability measure and let X and Y be disjoint sets which are δ_X - resp. δ_Y -almost invariant with respect to ρ . Moreover suppose that $f^{-1}(X) \cap Y = \emptyset$ and $f^{-1}(Y) \cap X = \emptyset$. Then $X \cup Y$ is $\delta_{X \cup Y}$ -almost invariant with respect to ρ where*

$$\delta_{X \cup Y} = \frac{\rho(X)\delta_X + \rho(Y)\delta_Y}{\rho(X) + \rho(Y)}. \quad (11)$$

In (10), both δ_1 and δ_2 appear as independent constants. If, in addition, the dynamical system possesses some symmetry, then these numbers may satisfy a further relation. To illustrate this fact, let us consider the simplest case where we have a symmetry transformation κ in the problem with $\kappa^2 = id$. Then one can show (see again [6]):

Corollary 4. *In addition to the assumptions in Proposition 2 suppose that*

- (i) *the set B satisfies $\kappa B = \Gamma - B$, and*
- (ii) *the measure $|\nu|$ is κ -symmetric, that is $\kappa^*|\nu| = |\nu|$.*

Then $\Gamma - B$ is δ -almost invariant with respect to $|\nu|$ if and only if B is δ -almost invariant. In particular

$$\delta = \frac{1}{2}(\lambda + 1). \quad (12)$$

These relations will be exploited in our subsequent Section 4.

The literature on ergodic theory contains an interesting theorem concerning the spectrum of the Frobenius-Perron operator P . In order to state this

result, we have to reformulate P as an operator on the Hilbert space $L^2(\Gamma)$ of all square integrable functions on the phase space Γ . Since Φ^τ and, therefore, f are volume preserving, this operator $P : L^2(\Gamma) \rightarrow L^2(\Gamma)$ is *unitary* (cf. [20], Thm. 1.25). As a consequence, its spectrum lies on the unit circle.

However, we consider the Frobenius-Perron operator acting on measures rather than on $L^2(\Gamma)$. The reason is that we are working on energy cells approximating energy surfaces (see Section 3.2) and not in the entire space Γ – and on an energy surface it may be the case that there is no invariant measure with an L^2 -density. For instance, consider the situation that (part of) the energy surface is given by a homoclinic trajectory connecting an equilibrium p with itself. Then it is easy to see that the only invariant measure supported on this homoclinic orbit is the Dirac measure δ_p supported in the equilibrium p . In particular, there is no invariant measure possessing an L^2 -density. Hence the space of measures is certainly more appropriate than $L^2(\Gamma)$ in our context.

On the other hand, also measure spaces have significant disadvantages. Roughly speaking, the reason is that a measure cannot take into account the dynamical behavior in the neighborhood of its support. Hence there is some need for a new functional analytic setting for the Frobenius-Perron operator which allows to represent correctly the dynamical behavior. Indeed, this is currently under investigation [15]. We would also like to emphasize that our numerical approach seems to reproduce precisely the correct results from the dynamical point of view. In fact, we obtain the correct almost invariant sets together with reasonable corresponding eigenvalues.

However, by constructing a *nested* sequence of successively larger discrete spaces and approximations therein we hope to end up with some approximation of a unique invariant measure, which is then implicitly defined via the constructed sequence of subspaces. An expression of this mathematical consideration is the *multilevel* structure of the suggested algorithm – details see below (Section 3.2). In physical terms, we hope that the perturbations introduced by discretization induce a unique and smooth invariant measure but are so weak that they do *not* destroy the essential *physical* structure of the problem.

3.2 Subdivision Techniques

This section deals with the question of how to approximate the essential features of the flow Φ^τ for given energy E . Recall that the flow ϕ^τ conserves energy, i.e., it maps the *energy surface* $\Gamma_0(E) = \{x \in \Gamma : H(x) = E\}$ onto itself. In the language of statistical physics, we want to approximate the *microcanonical ensemble*. However, even for a symplectic discretization, the discrete flow $f = (\Psi^\tau)^m$ does *not* conserve energy exactly, but only on average. Therefore, rather than discretizing the energy surface, we will have to discretize an *energy cell* defined by

$$\Gamma_{\delta E}(E) = \{x \in \Gamma, |H(x) - E| \leq \delta E\}$$

in terms of some perturbation parameter δE . On the basis of the above considerations, δE must be small enough to approximate $\Gamma_0(E)$, but also large enough to allow for energy perturbations due to the discretization. In the following we use the notation $\delta E(\tau)$ for a suitable choice. In view of subdivision techniques applied to hyperbolic dynamical systems (cf. [5]), the main algorithmic steps for Hamiltonian systems are as follows:

1. Construction of an approximate covering of the energy cell.
2. Setting up the Frobenius-Perron operator with respect to this subset.

We now describe each of these steps in more detail.

Covering of Energy Cells. Assume that the energy cells under consideration are compact sets and the stepsize τ is fixed. We want to construct a collection \mathcal{B} of boxes in phase space such that the union Q of these subsets is a covering of $\Gamma_{\delta E(\tau)}(E)$, the energy cell we focus on. To this end, consider a sequence of energy cells $\Gamma_{\delta E_k}(E)$ that shrink to $\Gamma_{\delta E(\tau)}(E)$, i.e., consider $\delta E_k \geq \delta E_{k+1} \geq \dots \geq \delta E(\tau)$. The collection \mathcal{B} is constructed via a sequence of collections \mathcal{B}_k by the following *recursive subdivision algorithm*: $\hat{\mathcal{B}}_k$ results from \mathcal{B}_{k-1} by subdivision and gives \mathcal{B}_k by the following *selection step*

$$\mathcal{B}_k = \{B \in \hat{\mathcal{B}}_k : B \cap \Gamma_{\delta E_k}(E) \neq \emptyset\}. \quad (13)$$

Thus, this multi-level process produces a finer and finer covering of $\Gamma_{\delta E(\tau)}(E)$. Up to now, the parameters δE_k are adapted to the size of the boxes according to some heuristics. Recall that an approximation of the energy surface $\Gamma_0(E)$ would only be possible in the limit $\tau \rightarrow 0$ which implies $\delta E(\tau) \rightarrow 0$.

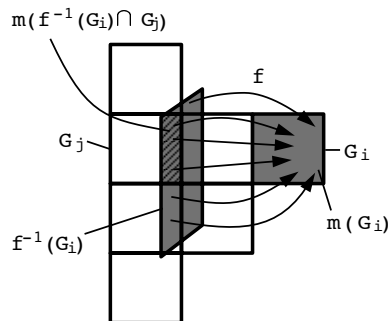


Fig. 4. Computation of the stochastic matrix P_d via mapping of discretization boxes.

Discretization of the Frobenius-Perron Operator The previous step led to a collection $\mathcal{B} = \{B_1, \dots, B_d\}$ covering some energy cell $\Gamma_{\delta E}(E)$. Considering now the dynamics inside this energy cell, we are only interested in

the subsets $G_i = B_i \cap \Gamma_{\delta E}(E)$ of the boxes $B_i \in \mathcal{B}$. We may now use this covering for a discretization of the Frobenius-Perron operator. The discretization is realized via a Galerkin type ansatz as described in [6]. Consider the case of locally constant basis functions

$$\varphi_i = \chi_{G_i}, \quad i = 1, 2, \dots, d.$$

Then, the discretized Frobenius-Perron operator $v = P_d u$ can be written componentwise as

$$v(G_i) = \sum_{j=1}^d p_{ij} u(G_j), \quad p_{ij} = \frac{m(f^{-1}(G_i) \cap G_j)}{m(G_j)}, \quad i = 1, \dots, d, \quad (14)$$

where m denotes the Lebesgue measure (i.e., $m(G_j)$ is the volume of the box G_j). For approximating the “volume”

$$m(f^{-1}(G_i) \cap G_j) = \int_{G_j} \chi_{G_i}(f(x)) dx$$

we use a Monte-Carlo approximation of the integral. That is, we approximate the *transition probabilities* p_{ij} via a Monte-Carlo discretization,

$$p_{ij} = \frac{1}{m(G_j)} \int_{G_j} \chi_{G_i}(f(x)) dx \approx \frac{1}{N} \sum_{n=1}^N \chi_{G_i}(f(x_n)),$$

where the x_n are chosen randomly and uniformly distributed in G_j (cf. Fig. 4). Since the algorithmic control guarantees that each point is mapped to exactly one box G_j , the matrix P_d is certainly singly stochastic (w.r.t. columns). The map f is symplectic and hence volume preserving. Therefore, if the union $Q = \cup_i G_i$ of all subsets were invariant under f , i.e., $f(Q) = Q$, the matrix P_d would also be stochastic with respect to its rows. However, such an effect would be unwanted, since then, we would always end up with an approximate invariant measure being equidistributed on Q (which is not always correct). Fortunately, $f(Q)$ in general deviates from Q , which reflects the fact that Q approximates the energy surfaces of the original problem instead of that of the symplectic discretization Ψ . But $f(Q) \not\subset Q$ implies that there are some points $x \in Q$ with $f(x) \notin Q$. Let $x \in G_j$ be one of these points. We then assign $f(x)$ to the nearest box G_i , i.e., the transition $x \rightarrow f(x)$ is counted for the transition probability p_{ij} . The same is done in the case when the covering Q of the energy cell $\Gamma_{\delta E}(E)$ is eventually incomplete. These perturbations of f are artificial but necessary in order to assure that the matrix approximation P_d is stochastic (w.r.t. columns) thus inheriting the most important property of the operator P .

After the assembling of the stochastic matrix P_d we have to solve the associated *non-selfadjoint* eigenvalue problem. Our present numerical results have been computed using the code `speig` by RADKE AND SØRENSEN in MATLAB, which allow for a simultaneous subspace iteration to compute eigenmodes associated with the eigenvalue cluster around $\lambda = 1$.

The basic scheme of this algorithm is similar to “cell-to-cell mapping” techniques [14] but differs substantially in one important aspect: If applied to larger problems, a direct cell-to-cell approach quickly leads to tremendous computational effort. Only a proper exploitation of the multi-level structure of the subdivision algorithm (also for the eigenvalue problem) may allow for application to molecules of real chemical interest. But even this more sophisticated approach suffers from combinatorial explosion already for moderate size molecules. In a next stage of development [19] this restriction will be circumvented using certain hybrid Monte-Carlo methods.

4 Illustrative Numerical Example

Let us introduce a suitably simple example in order to illustrate the notion of almost invariant sets and the performance of our algorithm for Hamiltonian systems. For $p = (p_1, p_2), q = (q_1, q_2) \in \mathbb{R}^2$ consider the potential

$$V_4(q) = \left(\frac{3}{2}q_1^4 + \frac{1}{4}q_1^3 - 3q_1^2 - \frac{3}{4}q_1 + 3\right) \cdot (2q_2^4 - 4q_2^2 + \gamma) \quad \text{with } \gamma = 3. \quad (15)$$

As illustrated in Fig. 5, this potential comprises four local minima at the points $(\pm 1, \pm 1)$ (named A, B, C, D), which are separated by four saddle-points. The energy barrier between A and B is significantly higher than the other three ones. The dynamical behavior of the system consists of oscillations around the local minima and, if the total energy is large enough for the system to cross the barriers, of motions from one minimum to the other. If the energy is not too large, there will be two kinds of “long term” dynamical behavior:

- (a) oscillations in the neighborhood of the four different minima,
- (b) back and forth oscillations between two different minima: $A \leftrightarrow D, B \leftrightarrow C$, and $C \leftrightarrow D$.

This is observed in simulations of the dynamics. Fig. 5 presents a solution which starts with an oscillation between A and D , followed by an oscillation around C , a long period of oscillations between A and D and so on. The similarity of the trajectories shown in Fig. 5 (right) and Fig. 3 illustrates that we are actually looking at the same kind of phenomena. Thus, for the case presented in Fig. 5, the neighborhoods of the different minima should turn out to be “almost invariant sets” as well as neighborhoods of the pairs of minima (A, D) , (C, D) and (B, C) together with regions around the corresponding saddle-points “between” them.

Inefficiency of Direct Simulation Suppose we want to compute the corresponding invariant measure μ by direct simulation. Direct long term simulation by symplectic discretization of (1) yields the discrete solution $(x_k)_{1, \dots, N}$. For N large enough and a box $B \subset \Gamma$ one takes the relative frequency of $x_j \in B$ as an approximation of the invariant density in B . If the system

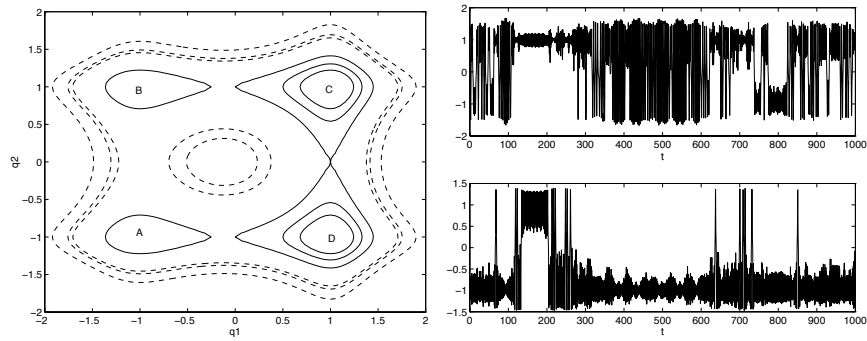


Fig. 5. The left hand side figure shows a contour plot of the potential energy landscape due to V_4 with equipotential lines of the energies $E = 1.5, 2, 3$ (solid lines) and $E = 7, 8, 12$ (dashed lines). There are minima at the four points $(\pm 1, \pm 1)$ (named A to D), a local maximum at $(0, 0)$, and saddle-points in between the minima. The right hand figure illustrates a solution of the corresponding Hamiltonian system with total energy $E = 4.5$ (positions q_1 and q_2 versus time t).

were ergodic, the convergence of this algorithm would be guaranteed. Even in this case the convergence could be arbitrarily slow, when the iteration gets trapped within an almost invariant set of the system.

Our global subdivision approach is not sensitive to such a situation. Over sufficiently long run times of direct simulation both methods eventually yield roughly the same results, see Fig. 6.

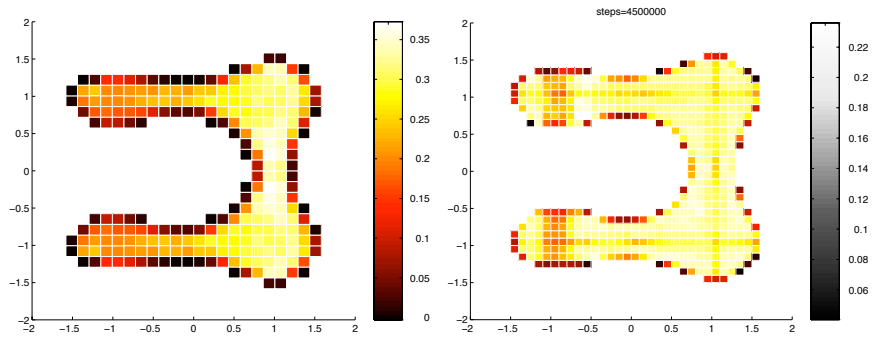


Fig. 6. The density of the invariant measure of the potential V_4 for total energy $E = 4.5$. Results of the subdivision approach (left) and a direct simulation with about 4.5 million steps for stepsize $\tau = 1/30$ (right).

Almost Invariant Sets Recall that the relevant almost invariant sets correspond to eigenvalues $\lambda \approx 1$ with $|\lambda| < 1$ of the associated Frobenius–Perron operator.

Based on observations concerning the dynamical behavior we already conjectured that there exist seven almost invariant sets – a conjecture that we now want to check numerically. We employ the subdivision algorithm for subtrajectories of length $m\tau = 0.1$. The final box-collection corresponding to the total energy $E = 4.5$ after 18 subdivision steps consists of 18963 boxes.

A simultaneous computation of the four largest eigenvalues $\lambda_1, \dots, \lambda_4$ leads to the following table:

Number	Eigenvalue
1	1.0000
2	0.9963
3	0.9891
4	0.9782

The invariant measure ν_1 corresponding to $\lambda_1 = 1$ has already been shown in Fig. 6. Next, we discuss the information provided by the eigenmeasure ν_2 corresponding to λ_2 . The box coverings in the two parts of Fig. 7 approximate two sets B_1 and B_2 , where the discrete density of ν_2 is positive resp. negative. We observe, that for $\gamma > 4.5$ in (15) the energy $E = 4.5$ of the system would not be sufficient to move from B_1 to B_2 or vice versa. That is, in this case B_1 and B_2 would be invariant sets. Thus, we are exactly in the situation illustrated in our Gedankenexperiment in Section 3.1.

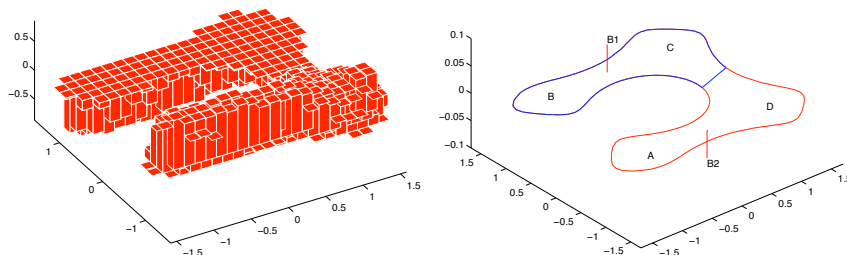


Fig. 7. Eigenmeasure ν_2 of the Frobenius–Perron operator to the second largest eigenvalue $\lambda_2 = 0.9963$ for the test system (15) with $\gamma = 3$. ν_2 was computed via our new subdivision algorithm (cf. Section 4).

Moreover, our Hamiltonian system possesses an additional symmetry — it is equivariant under the transformation $(q_2, p_2) \rightarrow -(q_2, p_2)$. In other words each of these sets is a candidate for a set B mentioned in the assumptions of Corollary 4. Thus, by this result, both of these sets are almost invariant with

probability $\delta = (\lambda_2 + 1)/2 = (0.9963 + 1)/2 = 0.9981$. Observe that these almost invariant sets confirm the observation made above that dynamically there exist “long term” oscillations between the minima $A \leftrightarrow D$ and $B \leftrightarrow C$.

The third eigenmeasure ν_3 corresponding to λ_3 provides information about three additional almost invariant sets: on the left hand side in Fig. 8 we have the set corresponding to the oscillation $C \leftrightarrow D$, whereas on the right hand side the two almost invariant sets around the equilibria A and B are identified. Again the boxes shown in the two parts of Fig. 8 approximate two sets where the discrete density of ν_3 is positive resp. negative. In this case we can use Proposition 2 and the fact that A and B are symmetrically related to conclude that for all these almost invariant sets $\delta \geq \lambda_3 = 0.9891$.

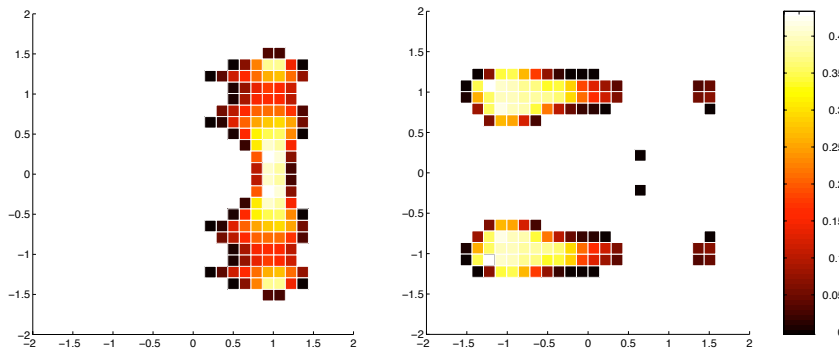


Fig. 8. Illustration of three almost invariant sets with respect to the probability measure $|\nu_3|$. The coloring is done according to the magnitude of the discrete density.

Finally, the information on the remaining almost invariant sets in the neighborhood of the equilibria C and D can be extracted using the eigenvalue λ_4 with the eigenmeasure ν_4 (see Fig. 9). In the two parts of Fig. 9 we show again the boxes, which approximate two sets, where the discrete density of ν_4 is positive resp. negative. Let us denote by Y the union of the boxes around equilibrium B in the first part of the figure and by X the boxes around D . (We ignore the isolated box in the left lower corner, which we regard as a numerical artifact.) We now use Lemma 3 to derive a lower bound for δ_X . Numerically we obtain the values $|\nu_4(X)| = 0.3492$ and $|\nu_4(Y)| = 0.1508$. Note that $|\nu_4(X \cup Y)| = 0.5$ and $\lambda_4 + 1 = 2\delta_{X \cup Y}$ (using again the symmetry and Corollary 4) which leads to the estimate

$$\delta_X = \frac{0.5\delta_{X \cup Y} - |\nu_4(Y)\delta_Y}{|\nu_4(X)|} = \frac{\lambda_4 + 1 - 4|\nu_4(Y)\delta_Y}{4|\nu_4(X)|} \geq \frac{\lambda_4 + 1 - 4|\nu_4(Y)|}{4|\nu_4(X)|} = 0.9844.$$

In all calculations done so far a fixed stepsize $\tau = 0.1$ has been used. Hence an application of formula (9) leads to the following table concerning flip-flop probabilities between different conformations.

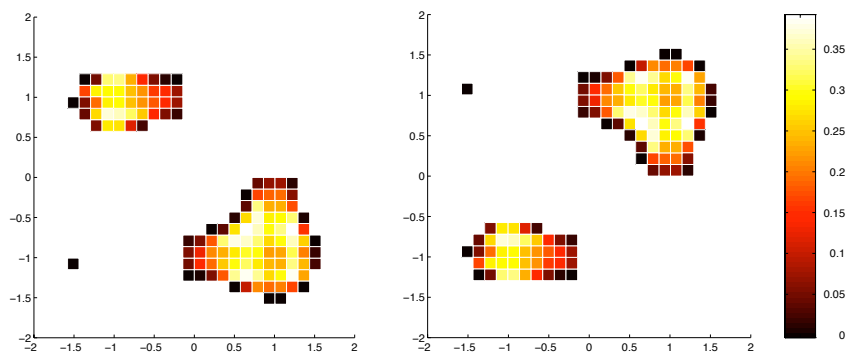


Fig. 9. Illustration of four almost invariant sets with respect to the probability measure $|\nu_4|$. The coloring is done according to the magnitude of the discrete density.

conformation	probability to stay within for			
	0.1 sec.	1 sec.	10 sec.	100 sec.
$A \leftrightarrow D, B \leftrightarrow C$	0.9981	0.9812	0.8268	0.1493
$C \leftrightarrow D, A, B$	0.9891	0.8962	0.3342	< 0.0002
C, D	0.9844	0.8545	0.2076	$< 10^{-6}$

These numbers indicate that it is very unlikely for the system to stay in C and D for more than 100 seconds, whereas for an oscillation $A \leftrightarrow D$ or $B \leftrightarrow C$ this may well be the case. In particular, these results are in nice agreement with Fig. 5 (right): there we observe an oscillation $A \leftrightarrow D$ for about 200 seconds, whereas the longest stay in the neighborhood of the minimum C only lasts about 60 seconds.

5 Conclusion

The paper suggests a novel concept for computing essential features of Hamiltonian systems arising in molecular dynamics. The concept involves the determination of invariant and almost invariant sets via eigenmodes of the associated Frobenius-Perron operator. The numerical findings in an illustrative example are intriguing, but a sound theoretical basis of the approach is still missing. Moreover, the algorithm as it stands now is suitable only for small systems. However, extensions to avoid the "curse of dimension" are already under development. The value of the suggested concept and its range of applicability to MD will prove or disprove in the years to come.

Acknowledgment. We thank Sebastian Reich for helpful discussions.

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