Biomolecular Conformations as Metastable Sets of Markov Chains

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Abstract

The function of many important biomolecules comes from their dynamic properties and their ability to make statistically rare switches between different *conformations*. Recent investigations demonstrated that (a) these conformations can be understood as *metastable* or *almost invariant* sets of certain Markov chains related with the dynamical behavior of the molecular system and that (b) these sets can efficiently be computed via eigenvectors of some associated transfer operators. The article presents in general the idea of computing metastable sets of Markov chains via the dominant eigenmodes of some associated transfer operator, refers its rigorous justification for specific chains, and illustrates the application of the resulting algorithm to problems arising from molecular systems.

1 Introduction

The chemically interesting *function* of many important biomolecules, like proteins or enzymes, results from their *dynamical* properties, particularly from their ability to undergo so-called *conformational transitions* (cf. [22]). 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. Recently, Deuflhard et al. demonstrated that conformations can be understood as *almost invariant* or *meta-stable* sets of the Hamiltonian system governing the molecular dynamics [5]. In 1996, Dellnitz and Junge demonstrated that such almost invariant sets of discrete dynamical systems with small random perturbations can be identified numerically via certain "dominant" eigenvectors of the Markov operator associated with the perturbed system [4].

By transferring this idea to statistical mechanics, Schütte et al. showed that the almost invariant sets of dynamical fluctuations in statistical molecular ensembles can be determined via the "dominant" eigenvectors of a specific class of Markov operators associated with discrete time Markov chains with nonlinear state space [16, 17]. It has been demonstrated that, even for larger (bio)molecules, the eigenvectors of interest can be computed efficiently and allow to identify the desired almost invariant sets [6, 16]. This allows for the first time to identify dynamical conformations of molecular ensembles including their stability life spans and the rate of transitions between them [10].

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The present article summarizes the basic ideas by reformulating it in a rather general framework for a large class of Markov chains. The presentation is tailored to demonstrate how the molecular applications and such of DELLNITZ ET AL. result from the general framework (s. Sec. 5). The article closes with a specific example which illustrates that the suggested approach allows to uncover purely dynamically induced metastabilities which are *not* explained by the common physical beliefs (s. Sec. 6).

2 Markov Chains and Transfer Operators

Consider a probability space $(\mathbf{X}, \mathcal{A}, \mu)$, where $\mathbf{X} \subset \mathbf{R}^m$ for some $m \in \mathbf{N}$ denotes the state space, $\mathcal{A}$ the Borel σ–algebra on $\mathbf{X}$ and μ a probability measure on $\mathcal{A}$. By $t \in \mathbf{T}$ we denote the discrete or continuous time, i.e., $\mathbf{T} = \mathbf{R}_0^+$ or $\mathbf{T} = \mathbf{N}$.

A function $p : \mathbf{T} \times \mathbf{X} \times \mathcal{A} \to [0, 1]$ is called a *stochastic transition kernel* [3, 12], if (i) $p(t, x, \cdot)$ is a probability measure on $\mathcal{A}$ for every $t \in \mathbf{T}$, $x \in \mathbf{X}$ and furthermore, $p(0, x, \mathbf{X} \setminus \{x\}) = 0$ for every $x \in \mathbf{X}$, (ii) $p(t, \cdot, A)$ is measurable for every $t \in \mathbf{T}$, $A \in \mathcal{A}$, and (iii) $p(\cdot, x, A)$ satisfies the Chapman–Kolmogorov equation [7, 12]

$$p(t + s, x, A) \;=\; \int_{\mathbf{X}} p(t, x, \mathrm{d}y)\, p(s, y, A) \tag{1}$$

for all $t, s \in \mathbf{T}$, $x \in \mathbf{X}$ and $A \in \mathcal{A}$. The family $\{X_t\}_{t \in \mathbf{T}}$ is called a homogeneous Markov process, if [3, 12]

$$\mathbf{P}[X_{t+s} \in A \mid X_s = x] \;=\; p(t, x, A) \tag{2}$$

for all $s, t \in \mathbf{T}$, $x \in \mathbf{X}$ and and $A \in \mathcal{A}$. Thus $p(t, x, C)$ is the probability that the Markov process started in x stays in A after the time span t.

In order to determine the essential statistical behavior of the Markov process, we have to be able to analyze the evolution of the process for some given statistical distribution of initial states. This is usually done by considering initial probability distributions rather than initial states for starting the Markov process. Assume that X_0 is distributed according to some probability measure ν, i.e., $\mathbf{P}[X_0 \in C] = \nu(C)$. Then, the evolution of the distribution of X_t is given by

$$\mathbf{P}_\nu[X_t \in C] \;=\; \int_X \nu(\mathrm{d}x) p(t, x, C).$$

Of special interest are probability measures that are invariant w.r.t. X_t, i.e., which satisfy $\mathbf{P}_\mu[X_t \in C] = \mu(C)$ for every $t \in \mathbf{T}$; they are also called stationary probability distributions.

Governed by application to biomolecular systems, we focus our attention to Markov processes that exhibit a unique stationary probability distribution, denoted by μ. Furthermore, we are interested in determine the internal fluctuations within the stationary distribution, which then will enable us to identify metastable subsets of the state space. As we will see in the next section, the description of such internal fluctuation requires to consider only initial probability distribution that are absolutely continuous w.r.t. the stationary distribution μ. The evolution of some ensemble of initial states distributed according to $\nu(\mathrm{d}x) = u(x)\mu(\mathrm{d}x)$ for some density $u \in L^1(\mu)$ may be described by the *propagator* or *forward transfer operator*

$$P_t u(y)\, \mu(\mathrm{d}y) \;=\; \int_{\mathbf{X}} p(t, x, \mathrm{d}y)\, u(x)\, \mu(\mathrm{d}x),$$

which is well–defined on $L^1(\mu)$ [13, Chpt. 4]. Its adjoint operator, the *backward transfer operator* acts on $L^\infty(\mu)$ according to [7]

$$T_t u(x) \;=\; \mathbf{E}_x[u(X_t)] \;=\; \int_{\mathbf{X}} u(y)\, p(t,x,\mathrm{d}y), \tag{3}$$

where $\mathbf{E}_x[u(X_t)]$ denotes the expectation of an observable $u : \mathbf{X} \to \mathbf{C}$ under the condition that the process $\{X_t\}$ has been started at $t = 0$ in x. Hence, in terms of the duality bracket $\langle \cdot, \cdot \rangle_\mu$ between $L^\infty(\mu)$ and $L^1(\mu)$ we have $\langle T_t u, v\rangle_\mu = \langle u, P_t v\rangle_\mu$ for $u \in L^\infty(\mu)$ and $v \in L^1(\mu)$.

Since $p(t,\cdot,\cdot)$ is a transition kernel, the thereby defined operator P_t is a *Markov operator* on $L^1(\mu)$. Furthermore, the semigroup property of the Markov process implies that $\{P_t\}_{t\in\mathbf{T}}$ is a semigroup of Markov operators. Due to the properties of the transition kernel and the definition of the backward transfer operator, we have for every $t \in \mathbf{T}$, $T_t \mathbf{1}_\mathbf{X} = \mathbf{1}_\mathbf{X}$, where $\mathbf{1}_A$ denotes the characteristic function of the subset A. Note, that $\mathbf{1}_X$ represents the stationary probability distribution μ. The above equality does in general not hold for the forward transfer operator, because P_t depends on the probability measure μ. However, if we assume μ to be invariant, we also get $P_t \mathbf{1}_\mathbf{X} = \mathbf{1}_\mathbf{X}$ for all $t \in \mathbf{T}$. In other words, $\mathbf{1}_\mathbf{X}$ is an invariant density of P_t, whenever μ is invariant.

3 Transition Probabilities and Almost Invariant Sets

Assume that the Markov process is initially distributed according to μ. The *transition probability* $p(s, C, D)$ within the stationary distribution from $C \in \mathcal{A}$ to $D \in \mathcal{A}$ within the time span s is defined as the conditional probability

$$p(s,C,D) \;=\; \mathbf{P}_\mu[X_s \in D \;|X_0 \in C]. \tag{4}$$

The similar symbols for both the transition probability $p(s,C,D)$ and for the transition kernel $p(s,x,C)$ corresponding to the process emphasizes the strong relation to (2), which, in addition to the above assumption, allows to rewrite the transition probability as

$$p(s,C,D) \;=\; \frac{1}{\mu(C)} \int_C p(s,x,D)\, \mu(\mathrm{d}x). \tag{5}$$

The transition probabilities quantify the *dynamical fluctuations within the stationary distribution*. Using the duality bracket $\langle \cdot, \cdot \rangle_\mu$, the definitions of the transfer operators T_t and P_t yield

$$p(s,C,D) \;=\; \frac{\langle T_s \mathbf{1}_D, \mathbf{1}_C\rangle_\mu}{\langle \mathbf{1}_C, \mathbf{1}_C\rangle_\mu} \;=\; \frac{\langle \mathbf{1}_D, P_s \mathbf{1}_C\rangle_\mu}{\langle \mathbf{1}_C, \mathbf{1}_C\rangle_\mu}. \tag{6}$$

Following [4], we call some subset $C \in \mathcal{A}$ *almost invariant*, whenever the fraction of systems within the distribution that stay in C after some characteristic time span $s \in \mathbf{T}$ is close to 1:

$$C \text{ almost invariant} \;\iff\; p(s,C,C) \approx 1.$$

Almost invariance may equivalently be characterized by $p(s, C, \mathbf{X} \setminus C) \approx 0$, which allows to relate it to the semigroup of forward transfer operators $\{P_t\}_{t\in\mathbf{T}}$ by the following general identity [21]:

$$\left\| P_s \frac{1}{\mu(C)} \mathbf{1}_C \;-\; \frac{1}{\mu(C)} \mathbf{1}_C \right\|_1 \;=\; 2\, p(s, C, \mathbf{X} \setminus C). \tag{7}$$

4 Identification of Almost Invariant Sets

Since P_s is a Markov operator its $L^1(\mu)$–spectrum is contained in the unit ball $\{\lambda \in \mathbf{C} : |\lambda| \leq 1\}$. Every *invariant* density $u \in L^1(\mu)$ of P_s satisfies $P_s u = u$ and therefore is an eigenvector of P_s corresponding to the eigenvalue $\lambda = 1$, the so–called *Perron root*. Since μ is assumed to be invariant, in particular $u = \mathbf{1}_X$ is an invariant density.

Whenever a proper subset C of $\mathbf{X}$ is invariant under the Markov process, i.e., $p(s, x, \mathbf{X} \setminus C) = 0$ for all $x \in C$, the density $u = \mathbf{1}_C/\mu(C)$ is an eigenvector corresponding to $\lambda = 1$. Due to our above characterization, the set $C \in \mathcal{A}$ is almost invariant if $p(s, C, \mathbf{X} \setminus C) \approx 0$, which via formula (7) implies that $\mathbf{1}_C/\mu(C)$ is an approximate invariant density, i.e., an approximate normalized eigenvector associated with an eigenvalue close to the Perron root $\lambda = 1$. This motivates the following *algorithmic strategy*:

> *Invariant* sets can be identified via eigenvectors of P_s corresponding to the Perron root $\lambda = 1$, while *almost invariant* sets may be identified via eigenvectors corresponding to eigenvalues $|\lambda| < 1$ close to the Perron root $\lambda = 1$.

This strategy has first been proposed by Dellnitz and Junge [4] for discrete dynamical systems with weak random perturbations and has been successfully applied to molecular dynamics in different contexts [16, 17, 18]; it is justified in more detail in [19]. For a detailed description of the resulting *identification algorithm* in the molecular context, cf. [6, 19]; for an illustration of its basic idea see Fig. 1.

We want to emphasize that almost invariance is defined herein with respect to some pre–selected invariant probability measure μ that describes the stationary ensemble under consideration. The above algorithmic strategy requires uniqueness of the invariant measure. For its numerical realization via an eigenvalue problem we moreover need that the remaining spectrum of P_s is strictly bounded away from the Perron root, i.e., $\lambda = 1$ must be an isolated, simple eigenvalue of P_s. Additionally, the physical interpretation of the ensemble excludes other eigenvalues than $\lambda = 1$ *on* the unit circle or, equivalently, we exclude asymptotic periodicity of P_s.

We introduce the following two *fundamental conditions* on the forward transfer operator P_s that are sufficient to guarantee the desired properties:

(C1) P_s is asymptotically stable, i.e., $(P_s)^n u \to \mathbf{1}_\mathbf{X}$ in $L^1(\mu)$ for every density $u \in L^1(\mu)$ as $n \to \infty$.

(C2) The essential spectrum of P_s in $L^1(\mu)$—and sometimes in $L^2(\mu)$—is strictly bounded away from $|\lambda| = 1$.

For details about the essential spectral radius (and its relation to asymptotic properties of transfer operators) see [9].

5 Examples from Molecular Dynamics (MD)

Stochastically perturbed Hamiltonian dynamics. Classical models for molecular motion describe the molecular system via coupled equations of motion for the N atoms

in the system. For a differentiable potential function $V : X \subset \mathbf{R}^d \to \mathbf{R}$, the *Hamiltonian equations of motion* are given by

$$\dot{q} \;=\; M^{-1}p, \qquad \dot{p} \;=\; -\nabla_q V(q) \tag{8}$$

where $d = 3N$, and q and p denote the positions and the momenta of the atoms in the system, respectively and M the diagonal mass matrix [8]. Let $q_t = q_t(q_0, p_0), p_t = p_t(q_0, p_0)$ denote the solution of (8) for the initial data q_0, p_0. It is well–known that the *canonical measure*

$$\mu_{\mathrm{can}}(\mathrm{d}q\,\mathrm{d}p) \;=\; \underbrace{\frac{1}{Z_q}\exp(-\beta V(q))\mathrm{d}q}_{\mu_Q(\mathrm{d}q)} + \underbrace{\frac{1}{Z_p}\exp(-\frac{\beta}{2}p^t M^{-1}p)\mathrm{d}p}_{\mu_P(\mathrm{d}p)}$$

corresponding to the so–called inverse temperature β is invariant w.r.t. the evolution process of (8). Since μ_{can} is known to decribe molecular ensembles with constant temperature, as they appear in biomolecular applications, this is the stationary distribution of interest. In the following, we restrict our attention to potential functions V that allow to normalize μ_{can} to a probability measure.

Aiming at the identification of molecular conformations, we choose some *fixed* observation time span $\tau > 0$ and introduce the *Hamiltonian stochastic system*

$$Q_{n+1} \;=\; q_\tau(Q_n, P_n), \quad n = 1, 2, \dots, \tag{9}$$

where $\{P_n\}_{n\in\mathbf{N}}$ is an i.i.d. sequence of random variables, each distributed according to μ_P, i.e., $\mathbf{P}[P_n \in A] = \mu_P(A)$ [16, 17]. Metastable sets of this Markov chain are *biomolecular conformations* of ensembles of molecular systems with constant temperature [17]. The stochastic transition function corresponding to (9) is given by

$$p(q, A) \;=\; \int_{\mathbf{R}^d} \mathbf{1}_A(q_\tau(q,p))\; \mu_P(\mathrm{d}p)$$

for all $A \in \mathcal{B}(X)$; in [16] it is shown that μ_Q is stationary for the process. Exploiting properties of the Hamiltonian equation of motion, the corresponding propagator $P : L^1(\mu_Q) \to L^1(\mu_Q)$ may be written as

$$Pv(y) \;=\; \int_{\mathbf{R}^d} v\,(q_\tau(q,p))\;\; \mu_P(\mathrm{d}p)$$

for $v \in L^1(\mu_Q)$ [17, 16]. Under additional conditions on the Hamiltonian system, which hold for the most significant application class in molecular dynamics, one can show that the propagator satisfies the conditions (C1) and (C2) of the preceding section [16].

Figure 1 illustrates the basic idea of the identification algorithm: metastable sets are identifiable via almost constant levels or "sign structure" of the dominant eigenvectors.

Langevin dynamics. The most popular model for an *open system* with stochastic interaction with its environment is the so-called Langevin model [14]:

$$\dot{q} \;=\; p, \qquad \dot{p} \;=\; -\nabla_q\, V(q) \;-\; \gamma\, p \;+\; \sigma\, \dot{W} \tag{10}$$

with some friction constant $\gamma > 0$ and an external force given by a $3N$-dimensional Brownian motion W_t. The stochastic force models the influence of the Brownian motion of the

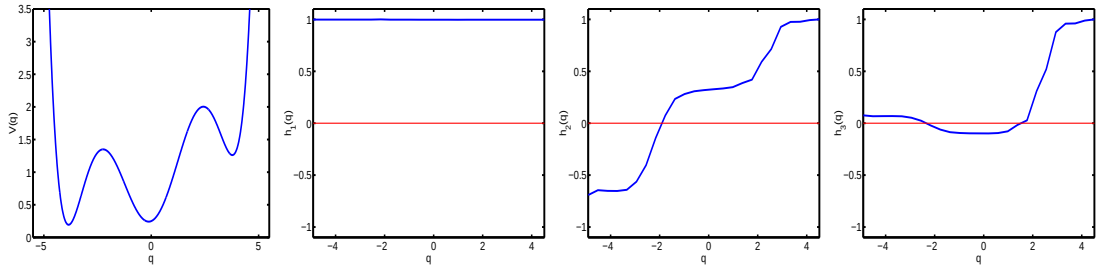

Figure 1: Three well potential and dominant eigenvectors. The choice of β implies the average kinetic energy to be small enough so that the neighborhood around the three potential energy minima are metastable sets of the Markov chain (9). Please observe that the dominant eigenvectors are almost constant on these sets and that the combination of signs of the three eigenvectors—the so–called sign structure—are different on the three sets.

heat bath surrounding the molecular system. The process induced by the Langevin equation (10) leaves the canonical measure μ_{can} corresponding the the inverse temperature β invariant, if the noise and damping constants satisfy $\beta = 2\gamma/\sigma^2$ [14]. The evolution of $u = u(x,t)$ with respect to μ_{can} is governed by the well–known *Fokker–Planck equation* [14]:

$$\partial_t u \;=\; \left(\underbrace{\frac{\sigma^2}{2}\Delta_p \;-\; p\cdot\nabla_q \;+\; \nabla_q V\cdot\nabla_p \;-\; \gamma p\cdot\nabla_p}_{=A} \right) u. \tag{11}$$

As a consequence, the operator A is the infinitesimal generator of the semigroup of forward transition operators $\{P_t\}_{t\in\mathbf{R}_0^+}$ acting on $L^1(\mu_{\text{can}})$ with

$$P_t u \;=\; \exp(tA)u. \tag{12}$$

Since μ_{can} is invariant, we have $P_t\mathbf{1}_{\mathbf{X}} = \mathbf{1}_{\mathbf{X}}$. Moreover, under certain conditions on the potential V, this is the *unique stationary density* and the semigroup $\{P_t\}_{t\in\mathbf{R}_0^+}$ is asymptotically stable [11], i.e., $P_t u \to \mathbf{1}_{\mathbf{X}}$ for $t\to\infty$ and every density $u \in L^1(\mu_{\text{can}})$. Due to this property, the Langevin equation is the most prominent stochastic model for a heat bath driven relaxation of molecular ensembles to the canonical ensemble.

6 Identifying Dynamical Barriers in MD

In order to illustrate the power of the algorithmic idea presented so far, let us return to the stochastically perturbed Hamiltonian dynamics and consider so-called strong constraining potentials of the form

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

for significantly small values of ϵ. The solutions $q^\epsilon = q_t^\epsilon(q_0,p_0)$ of the resulting Hamiltonian system depend on the smallness parameter ϵ. For sufficiently small $\epsilon > 0$ the strong part W/ϵ^2 of the potential may induce unexpected dynamical behavior. We will show that the transfer operator approach allows to detect and characterize this behavior, and that, in addition, this can be understood by studying the transfer operator in the limit $\epsilon \to 0$.

Our illustrative system for this process is the following two-dimensional system: $q = (x, y) \in \Omega = \mathbf{R}^2$, in polar coordinates $x = r(x, y) \cos \phi(x, y)$ and $y = r(x, y) \sin \phi(x, y)$, with potential

$$V_\epsilon(r, \phi) \;=\; U(\cos \phi) \;+\; \frac{1}{\epsilon^2} W(r, \phi), \qquad W(r, \phi) = \frac{1}{2}\, \omega^2(\phi)\, (r - \pi)^2, \tag{13}$$

with $\omega = \omega(\phi)$ smooth and strictly bounded away from zero. Figure 2 illustrates this potential for the specific choices $U(c) = (c^2 - 1)^2/2$ and $\omega(\phi) = 1 + \exp(-(\phi - \pi)^2/\sigma^2)$ mod 2π with $\sigma = 0.05$, which we will herein discuss in detail.

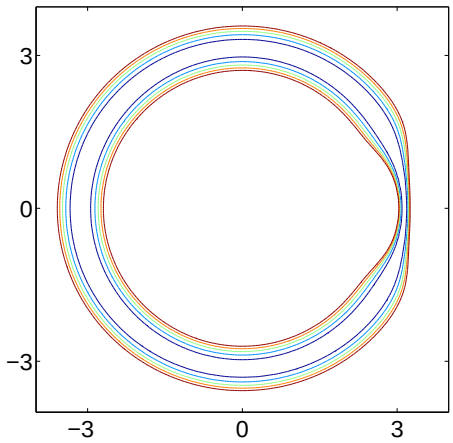

Figure 2: Illustration of the potential V_ϵ for $\epsilon = 0.1$ with U and ω as given in the text above. Contour plot with equipotential curves for $V_\epsilon = 0, 2, 4, \ldots, 10$. Observe that, *on the circle* $r = \pi$, the potential has two saddle points at $\phi = \pi/2, 3\pi/2$, and two global minima, one for $\phi = 0$, the other one in the middle of the narrow pathway at $\phi = \pi$.

In this case the solutions q_t^ϵ display the following feature: the motion is a combination of a slow motion along the circle $r = \pi$ and some significantly faster oscillations in radial direction, normal to the circle, which are induced by the part W/ϵ^2 of the potential. These fast normal oscillations may induce unexpected dynamical behavior. For certain choices of the initial conditions, the amplitude of these normal oscillations is too large to pass the narrow pathway at $\phi = \pi$ (see Fig. 2), *although* the potential V_ϵ has one of its *global minima* at $(r, \phi) = (\pi, \pi)$. One says, that there is a "dynamical barrier" at $\phi = \pi$. Whenever one considers an statistical ensemble of initial states, e.g., the canonical ensemble, the dynamical barrier has the effect that a certain ratio of trajectories will never cross the point $\phi = \pi$ so that it may separate two metastable sets from each other. Whenever, in addition, the average kinetic energy in the ensemble is significantly smaller than the potential energy barrier at the local saddle points at $(r, \phi) = (\pi, \pi/2)$ and $(r, \phi) = (\pi, 3\pi/2)$, these points may also induce separations between metastable sets. Thus, one may expect to find three metastable sets separated by the lines $\phi = \pi/2$, $\phi = \pi$, and $\phi = \pi/2$. We will see below that this eventually is true.

Spectrum of P_ϵ. The largest eigenvalues of the full transfer operator P_ϵ for $\epsilon = 0.1$ and $\tau = 1.5$ in the canonical ensemble with inverse temperature $\beta = 5$ are:

k	1	2	3	4	5	6	...
λ_k	1.0000	0.9938	0.9639	0.9221	0.8441	0.7895	...

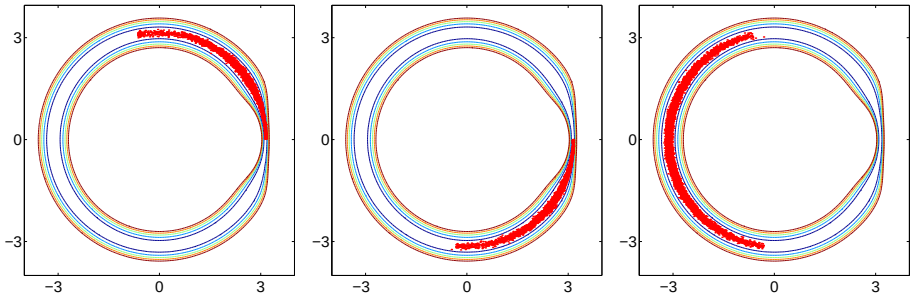

Figure 3: Illustration of the three metastable sets computed via the identification algorithm.

Evaluation of the eigenvectors corresponding to the three dominant eigenvalues yields a decomposition of the inner part of the potential energy well into three metastable sets which are shown in Fig. 3 above. Since it is the common physical belief that metastable sets of molecular motion are separated by saddle points of the potential energy function, our illustrative systems displays an unexpected dynamical behavior.

6.1 Limit dynamics

In order to further understand our observation, we study the motion in the limit $\epsilon \to 0$. Therefore, consider the sequence $q^\epsilon = q_t^\epsilon(q_*^\epsilon, p_*^\epsilon)$ of solutions of (8) with potential V_ϵ given by (13). We also use the alternative notations $q^\epsilon = (x^\epsilon, y^\epsilon) = (r^\epsilon, \phi^\epsilon)$. Let $(q^*, p^*) \in \Omega \times \mathbf{R}^d$ be arbitrary initial values, and $S_\epsilon : \Omega \to \Omega$ the scaling transformation given by $S_\epsilon(x, y) = (R_\epsilon \cos\phi, R_\epsilon \sin\phi)$, with $R_\epsilon = \pi + (r(x, y) - \pi)\,\epsilon$. Consider the family of solutions $q^\epsilon = q_t^\epsilon(S_\epsilon q^*, p^*)$ in a finite time interval $[0, T]$.

In the limit $\epsilon \to 0$, the strong part W/ϵ^2 of the potential will constrain the motion to the minimum of W, i.e., to the manifold $\mathcal{M} = \{q \in \Omega : \quad r(q) = \pi\}$. For every set (q, p) of state variables, we can find the projection q_M of every positions q onto $\mathcal{M}$ via $q_M = \pi\,(\cos\phi(q), \sin\phi(q))$ with normal component $q_N = (r(q) - \pi)\,(\cos\phi(q), \sin\phi(q))$, and decompose the momenta into components tangential and normal to $\mathcal{M}$ at q, i.e.,

$$p = p_M + p_N \quad \text{with} \quad p_N = \frac{p^T q}{q^T q}\, q.$$

According to [15, 2, 1] the limit dynamics q^0 is the strong limit of $q^\epsilon = q_t^\epsilon(S_\epsilon q^*, p^*)$ in $C^1[0, T]$ and is governed by the *limit equation of motion* that—in polar coordinates $q^0 \mapsto (r^0, \phi^0)$—has the form

$$\ddot{\phi}^0 + \frac{1}{\pi^2}\mathrm{grad}_\phi\,(U + \theta\,\omega)\,|_{\phi=\phi^0} = 0, \qquad r^0 = \pi, \tag{14}$$

with initial conditions $\phi^0(0) = \arccos(q_M^*/\pi)$ and $\dot{\phi}^0(0) = (e_\phi(\phi^*)p_M^*)/\pi$, where e_ϕ denotes the unit vector in the direction of ϕ in polar coordinates. The parameter θ is a constant which is uniquely determined by the initial values via the formula $\theta = \frac{1}{\omega(q_M^*)}\left(\frac{1}{2}\,|p_N^*|^2 + W(q^*)\right)$. Obviously, the limit motion on the circle $\mathcal{M}$ sees an additional potential $\theta\omega$ which represents the influence of the energy that is contained in the motion normal to $\mathcal{M}$, although this motion has vanishing amplitude for $\epsilon \to 0$. For details see [2].

Figure 4 clearly indicates that the correcting potential $\theta\omega$ induces an additional potential energy barrier at $\phi = \pi$ to the original potential U on the circle $\mathcal{M}$. This perfectly explains the existence of a dynamical barrier at $\phi = \pi$ for small $\epsilon > 0$.

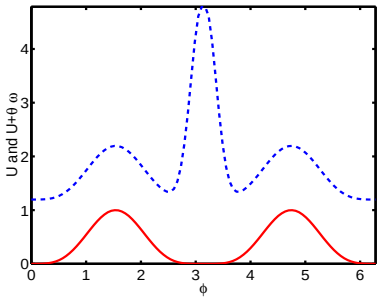

Figure 4: Original potential U on the manifold $\mathcal{M}$ and corrected potential $U + \theta\omega$ for the case shown in Fig. 2 and initial conditions $p^* = (1.5, 1.5)$ and $q^* = (0.1, \sqrt{\pi - 0.1})$.

Limit Transfer Operator T_0. It is shown in [20] that the limit transfer operator in the canonical ensemble is given by

$$T_0 u(q) \;=\; \int_{\mathbf{R}^d} u\left(q_\tau^0(q_M, p)\right) \mu_P(dp). \tag{15}$$

Obviously, P_0 acts on functions defined on the constraining manifold $\mathcal{M}$.

Spectrum of P_0. The six largest eigenvalues of P_0 for $\tau = 1.5$ with $\beta = 5$ are

k	1	2	3	4	5	6	...
λ_k	1.0000	0.9933	0.9633	0.9246	0.8440	0.7945	...

which is in perfect agreement to the results given above. Evaluation of the eigenvectors corresponding to the three dominant eigenvalues yields a decomposition of the circle $r = \pi$ into three metastable sets ($\phi \in [0, \pi/2] \cup [3\pi/2, 2\pi]$, $\phi \in [\pi, 3\pi/2]$, and $\phi \in [\pi/2, \pi]$). This result perfectly corresponds to the sets computed from the full transfer operator P_ϵ for $\epsilon = 0.1$, see Fig. 3.

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