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On Conformational Dynamics induced by Langevin Processes

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Abstract

The function of many important biomolecules is related to their dynamic properties and their ability to switch between different *conformations*, which are understood as *almost invariant* or *metastable* subsets of the positional state space of the system. Recently, the present authors and their coworkers presented a novel algorithmic scheme for the direct numerical determination of such metastable subsets and the transition probability between them [24]. Although being different in most aspects, this method exploits the same basic idea as Dellnitz and Junge [5] in their approach to almost invariance in discrete dynamical systems: the almost invariant sets are computed via certain eigenvectors of the Markov operators associated with the dynamical behavior.

In the present article we analyze the application of this approach to (high–friction) Langevin models describing the dynamical behavior of molecular systems coupled to a heat bath. We will see that this can be related to theoretical results for (symmetric) semigroups of Markov operators going back to Davies [3, 4]. We concentrate on a comparison of our approach in respect to random perturbations of dynamical systems.

Keywords. Smoluchowski equation, Fokker–Planck equation, semigroup of Markov operators, canonical ensemble, small noise, first exit time, half time period.

Mathematics subject classification. 65U05, 60J25, 60J60, 15A18

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. [27]). In a conformation, the large scale geometric structure of the molecule is understood to be conserved, whereas on smaller scales, the system may as well rotate, oscillate or fluctuate. Recently, DEUFLHARD et al. demonstrated that conformations can be understood as *metastable* or *almost invariant* sets of the Hamiltonian system governing the molecular dynamics [6].

DELLNITZ and JUNGE demonstrated that such metastable or 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 [5].

By transferring this idea to statistical mechanics, SCHÜTTE et al.[24] 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 continuous space Markov chains [24, 23]. It has been demonstrated that, even for larger biomolecules, the eigenvectors of interest can be computed efficiently and allow to identify the desired almost invariant sets [23, 7]. 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 [12].

Although being different in most algorithmic aspects, the two approaches are both based on the same three fundamental concepts first introduced in [5]: (1) some set B is called almost invariant if it is almost certain (with respect to the invariant probability measure of the system) to find the system in B initially *and* again after a discrete observation time step; (2) the presence of m almost invariant sets results in a cluster of m eigenvalues λ_k (of a specific Markov operator) with absolute value close to one, while the remaining part of the spectrum is contained in some disc with radius significantly smaller than one. The almost invariant sets can be determined via the eigenvectors corresponding to these eigenvalues λ_k; (3) these eigenvectors are computed via a Galerkin discretization of the Markov operator; the entries of the resulting discretization matrix are evaluated via appropriately chosen short–term trajectories of the (randomly perturbed) dynamical system under investigation.

In this contribution we consider (high–friction) Langevin models of molecular motion under the influence of a heat bath and apply the first two concepts mentioned above to this type of dynamics. In this case, the Markov operators that describe the dynamical fluctuations, are given by the evolution semigroup of a Fokker–Planck equation associated with the Langevin equation. This will allow us to compute the dominant eigenvectors of these Markov operators via the Fokker–Planck operator generating the semigroup and, thus, entirely without any trajectory simulation. Moreover, we will show that this new approach leads exactly to the situation already discussed by DAVIES [3, 4] in the early 80's.

We will concentrate on the comparison of this approach with some related aspects on random perturbations of dynamical systems as originating from the work of FREIDLIN and WENTZELL [9]. For example, we will discuss the relation between the first exit time from some domain (Sec. 4) and its characterization as almost invariant in the above sense (Sec. 5).

2 Classical Molecular Dynamics

In classical molecular dynamics (cf. textbook [1]), a molecule is modelled by a separable total energy or Hamilton function

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

where q and p are the corresponding positions and momenta of the atoms, M the diagonal mass matrix, and V a differentiable potential. The Hamilton function $\mathcal{H}$ is defined on the phase space $\Gamma \subset \mathbb{R}^{2d}$. Realistic MD–simulations typically include a large number N of atoms resulting in $d = 3N$ spatial coordinates. Thus, the dimension of Γ is $2d = 6N$. The corresponding canonical equations of motion

$$\dot{q} \;=\; M^{-1}p, \qquad \dot{p} \;=\; -\mathrm{grad}\, V(q) \tag{2}$$

describe the dynamics of the molecule. In the following we set $M = \mathrm{Id}$ for brevity. In most cases, the phase space is simply given by $\Gamma = \Omega \times \mathbb{R}^d$. We will call $\Omega \subset \mathbb{R}^d$ the position space of the system.

Statistical Mechanics

Due to measurement uncertainties it is *in principle* impossible to determining the precise initial state—all the positions and momenta— of the entire molecule. Thus, when modelling physical reality, we are forced to propagate a *collection* of trajectories which "samples" the distribution of possible initial states. In this sense, we always have to simulate an *ensemble* of molecular systems which represents the *distribution of possible initial states determined via the initial measurement.* Then, every comparison of later measurements with simulation results will concern *mean* or *expectation values* and *not* any single system in the ensemble. Hence, we now consider an ensemble of systems described by a *time dependent probability density* $f = f(x,t)$ in the phase space.

Most experiments on molecular systems are performed under the equilibrium conditions of constant temperature, particle number, and volume. The corresponding stationary density is the *canonical density* associated with the Hamilton function $\mathcal{H}$

$$f_{\text{can}}(x) \;=\; \frac{1}{\mathcal{Z}}\exp\left(-\beta\,\mathcal{H}(x)\right), \quad \text{with} \quad \mathcal{Z} = \int_\Gamma \exp\left(-\beta\,\mathcal{H}(x)\right) dx,$$

where $\beta = 1/k_B\mathcal{T}$, with $\mathcal{T}$ being the system's temperature and k_B the Boltzmann's constant. Since $\mathcal{H}$ was assumed to be separable, $f_{\rm can}$ is a product

$$f_{\rm can}(x) = \underbrace{\frac{1}{\mathcal{Z}_p}\exp\left(-\frac{\beta}{2}p^T M^{-1} p\right)}_{=\mathcal{P}(p)} \underbrace{\frac{1}{\mathcal{Z}_q}\exp\left(-\beta V(q)\right)}_{=\mathcal{Q}(q)}, \tag{3}$$

where we normalize $\mathcal{P}$ and $\mathcal{Q}$ so that

$$\int \mathcal{P}(p)dp = \int \mathcal{Q}(q)dq = 1. \tag{4}$$

3 Langevin Dynamics

The canonical ensemble cannot be simulated via time averages over long–term simulations of the pure Hamiltonian dynamics (2) of any *single* molecular system from the ensemble, since for every single system the energy is conserved. In order to get the dynamical behavior of a *typical system* within the ensemble one has to *remodel* the equation of motion under the restriction that the canonical density is the *unique* invariant density of the remodelled dynamics.

One approach involves a thermal embedding of the molecular system into the dynamical description. Most commonly one assumes that the thermal embedding is due to a *heat bath* surrounding the molecule and that the influence of the heat bath can be modelled by an additional random force acting on the molecular system. The corresponding equation of motion is the *Langevin equation*

$$\dot{q} = p, \qquad \dot{p} = -\mathrm{grad}\, V(q) - \gamma p + \sigma \dot{W}, \tag{5}$$

which describes the dynamics of the molecule under influence of the Brownian motion of the heat bath and an additional damping that equilibrates the energy. Here, $W = W(t, \omega)$ denotes a $3N$–dimensional Wiener process with mean zero and correlation $\langle W(t)W(s)\rangle = \delta(t-s)\mathrm{Id}$. In order to force the canonical density with inverse temperature β to be the invariant density we have to choose the damping constant γ relative to the noise amplitude σ according to

$$\beta = \frac{2\gamma}{\sigma^2}. \tag{6}$$

See [1] for details of the remodelling step.

3.1 High Friction Limit

For many practical investigations, this Langevin model is simplified by the *high friction limit* [1, 22] which results in the *Smoluchowski equation* or *high* *friction Langevin equation*:

$$\gamma \dot{q} \,+\, \mathrm{grad}\, V(q) \;=\; \sigma \dot{W}. \tag{7}$$

Every family of solution processes $\{Q_t^{q_0}\}_{t\geq 0}$ of (7) for given initial positions q_0 constitutes a Markov process P_t. The evolution of an ensemble of systems $u(q,t)$ induced by (7) is determined by the Cauchy problem given by the well–known *Fokker–Planck* or *Kolmogorov–forward equation*:

$$\gamma^2 \partial_t u \;=\; \Bigg(\underbrace{\frac{\sigma^2}{2} \Delta_q \,+\, \gamma\, \nabla_q V \cdot \nabla_q \,+\, \gamma\, \Delta_q V}_{=A_f} \Bigg)\; u \tag{8}$$

with initial distribution $u(q, t = 0) \;=\; f(q)$. Thus, the semigroup P_t is generated by the Fokker–Planck operator A_f, i.e.,

$$P_t \;=\; \exp(tA_f)$$

and $u(q,t) = P_t f(q)$. The stationary density of the Fokker-Planck equation (8) is the canonical position density $\mathcal{Q}$:

$$\beta = \frac{2\gamma}{\sigma^2}, \quad \mathcal{Q} \;=\; \frac{1}{Z} \exp\left(-\beta V\right) \quad \Rightarrow \quad A_f \mathcal{Q} \;=\; 0 \text{ and } P_t \mathcal{Q} = \mathcal{Q},$$

and, again under certain conditions on the potential, this is the unique normalized stationary density and the semigroup P_t is asymptotically stable, i.e., $P_t f \to \mathcal{Q}$ for $t \to \infty$ and for every normalized position densities $f \in L^1(\Omega)$ [11, 15, 25]. In fact, in many situations the convergence $P_t f \to \mathcal{Q}$ is even exponentially fast [2]. Due to this properties, the Langevin equation is the most prominent stochastic model for the heat–bath–driven relaxation of molecular ensembles to the canonical ensemble.

3.2 Metastability

The most popular example for the existence of almost invariant sets in the dynamical behavior of Smoluchowski processes is the *double-well potential*

$$V_{\mathrm{dw}}(q) \;=\; \frac{1}{2}\,(q^2 - 1)^2 \tag{9}$$

with one–dimensional position space $\Omega = \mathbb{R}$. Fig. 1 illustrates the typical dynamical behavior of the process which is connected to the existence of the two almost invariant sets $B_1 = (-\infty, 0)$ and $B_2 = (-\infty, 0)$.

For applications to complex systems, the **main computational problem** is the following:

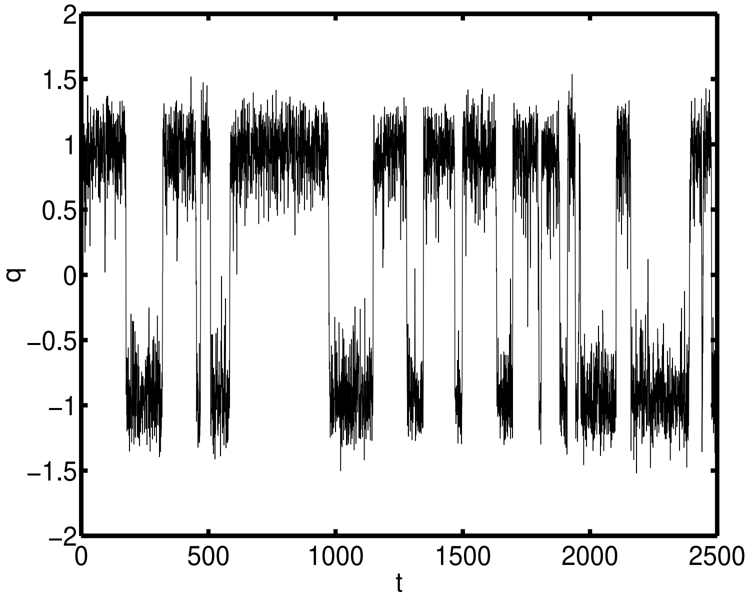

Figure 1: Illustration of a typical trajectory of the Smoluchowski equation for the double-well potential $V_{\rm dw}$ with white noise amplitude $\sigma = 0.5$ and friction constant $\gamma = 1$. The dynamics is characterized by certain sudden jumps between the two potential wells (around $q = \pm 1$). (Results of numerical experiments using discretizations of (7) due to [14, 19]).

> In most realistic applications, the almost invariant sets are *unknown* and it is impossible to efficiently determine them via analyzing the structure of the potential energy function. The algorithmic problem discussed herein is how to identify the most significant almost invariant sets in this situations.

But even if we assumed that the almost invariant sets have already been determined, the question remains how to compute the rate of transitions between them. Before we explain how the "main computational problem" can be attacked (see Sec. 5), we summarize some results concerning the probability to leave the neighborhood of some local minimum of the potential energy function V, which is a almost invariant set whenever the noise amplitude σ is small enough.

4 Small Noise Asymptotics

Let us consider the behavior of the solution process of the Smoluchowski equation (7) for the case of small noise amplitudes $\sigma = \epsilon$. Since the inverse temperature is then given by $\beta_\epsilon = 2\gamma/\epsilon$, its limit corrresponds to the limit of zero temperature. Suppose that $\{Q_t^{q,\epsilon}\}_{t \geq 0}$ denotes the corresponding family of Smoluchowski Markov processes started in q at time $t = 0$.

Let our potential V be twice continuously differentiable, let $q_0 \in \Omega$ be one of its local minima, and D some domain with sufficiently smooth boundary ∂D containing q_0 in its interior but no other minimum of V (no other minimum in $D \cup \partial D$). Without loss of generality we may assume that $V(q_0) = 0$.

Whenever ϵ is sufficiently small, the invariant density $\mathcal{Q}$ of the process will be exponentially close to zero in D excluding a small neighborhood of q_0, i.e., the system will be with overwhelming probability near q_0 and far from ∂D. Nevertheless, the trajectories of the process $Q_t^{q,\epsilon}$ leave D with probability one. We are interested in the asymptotic behavior of the exit time from D. Such questions have been discussed in detail, e.g., by FREIDLIN and WENTZELL, see [9], to which we will refer in the following.

In order to present their results for the Smoluchowski equation, let τ_q^ϵ denote the *first exit time* of the process $Q_t^{q,\epsilon}$ from D,

$$\tau_q^\epsilon \;=\; \inf\{t : Q_t^{q,\epsilon} \in \partial D\}, \qquad \text{for } q \in D.$$

It can be shown that the exit of the process happens with probability close to one near the point of minimal potential energy along ∂D. That is, suppose that $q_{\min}$ is the unique point on the boundary ∂D with

$$V_{\text{barrier}} \;=\; V(q_{\min}) \;=\; \min_{q \in \partial D} V(q).$$

Then, the following theorem holds:

THEOREM 4.1 *[9, Thms. 2.1, 3.1., 4.1., and 4.2 of Chap. 4] Let the above assumptions on V, D, and ∂D hold. In addition, let the boundary be chosen such that its exterior normal $n = n(q)$ satisfies $n(q) \cdot \nabla V(q) > 0$. Then, the exit time asymptotically scales like*

$$\lim_{\epsilon \to 0} \text{prob}\left(e^{\beta_\epsilon (V_{\text{barrier}} - \alpha)} \;<\; \tau_q^\epsilon \;<\; e^{\beta_\epsilon (V_{\text{barrier}} + \alpha)}\right) \;=\; 1, \quad \beta_\epsilon \;=\; \frac{2\gamma}{\epsilon^2}, \tag{10}$$

for arbitrary $\alpha > 0$ and $q \in D$. The mean exit time *$\overline{\tau_q^\epsilon}$ over the process $Q^{q,\epsilon}$ then satisfies*

$$\lim_{\epsilon \to 0} \epsilon^2 \log \overline{\tau_q^\epsilon} \;=\; 2\gamma\, V_{\text{barrier}}.$$

Moreover, the process leaves D near $q_{\min}$ in the sense that, for every $\delta > 0$, we have

$$\lim_{\epsilon \to 0} \text{prob}\left(|Q_{\tau_q^\epsilon}^{q,\epsilon} \;-\; q_{\min}| \;<\; \delta\right) \;=\; 1. \tag{11}$$

The condition $\langle n(q), \nabla V(q) \rangle > 0$ guarantees that the trajectories of the (unperturbed) dynamical system $\gamma \dot{q} + \nabla V = 0$ converge to the potential energy minimum at q_0 whenever started on ∂D. Thus, the condition excludes limit cycles of the dynamical system.

In addition to these results for the limit $\epsilon \to 0$, full asymptotic expansions up to arbitrary orders in ϵ have been constructed, cf. Fleming and James [8].

If $q_{\min}$ is not the unique minimum on ∂D, the exit takes place at all minima at ∂D, and the probability of exit near each minimum can be estimated asymptotically [9, Chap. IV, Sec. 3], .

4.1 Connection to Eigenvalue Problems

There are also results concerning the *distribution of exit times* of the process in some bounded domain $D \subset \Omega$ (which should have sufficiently smooth boundary ∂D but can be arbitrary otherwise). The following results are of particular interest: The weighted probability to find the process in D at time t (after starting it at $q \in D$ at $t = 0$) is denoted by

$$u_\epsilon(q,t) \;=\; \mathcal{Q}_\epsilon(q)\ \mathrm{prob}\,(Q_t^{q,\epsilon} \in D)\,,$$

while we denote the weighted probability for the process to leave D *later* than time t by

$$v_\epsilon(q,t) \;=\; \mathcal{Q}_\epsilon(q)\ \mathrm{prob}\left(\tau_q^\epsilon > t\right).$$

Let A_ϵ denote the Fokker–Planck operator A_f from (8) for $\sigma = \epsilon$. According to [9, 8], the two weighted probabilities u_ϵ and v_ϵ can be computed via PDEs generated by A_ϵ:

$$\gamma^2 \partial_t u_\epsilon \;=\; A_\epsilon u_\epsilon \ \text{ in } \Omega, \qquad u_\epsilon(\cdot, t=0) \;=\; \mathcal{Q}_\epsilon \cdot \chi_D, \tag{12}$$

$$\begin{aligned} \gamma^2 \partial_t v_\epsilon \;=\; A_\epsilon v_\epsilon \ \text{ in } D, \qquad v_\epsilon(\cdot, t=0) \;&=\; \mathcal{Q}_\epsilon \ \text{ in } D, \\ v_\epsilon(\cdot, t) \;&=\; 0, \ \text{ on } \partial D \text{ for all } t \geq 0 \end{aligned} \tag{13}$$

in appropriate function spaces.

In [9] the problem for v is solved asymptotically via a certain *variational problem*; the statements of Thm. 4.1 result from this approach. We observe that v_ϵ is governed by nearly the same PDE as u_ϵ merely with Dirichlet boundary conditions instead of transparent ones.

For every initial position q, the function $v_\epsilon(q, T)$ decays exponentially with t, i.e.,

$$v_\epsilon(q,t) \;=\; \mathcal{Q}_\epsilon(q)\ \mathrm{prob}\left(\tau_q^\epsilon > t\right) \;\propto\; \exp(-\lambda_\epsilon\, t),$$

where λ_ϵ is given by the bottom of the spectrum of the operator $-A_\epsilon^D$, with A_ϵ^D denoting the Fokker-Planck operator associated with the Dirichlet boundary conditions in (13).

Whenever the domain D satisfies the assumption of Thm 4.1, the bottom of $-A_\epsilon^D$ is asymptotically given by

$$\lim_{\epsilon \to 0} \epsilon^2 \,\log \lambda_\epsilon \;=\; 2\,\gamma\, V_{\mathrm{barrier}}, \tag{14}$$

where V_{barrier} is the same as in Thm 4.1, cf. [9, Thm. 7.4 in Chap. 6].

5 Identification of Almost Invariant Sets

We are herein only interested in considering transition probabilities which are suitable for an *experimental* determination. In most experiments on biomolecular systems, one has only access to an ensemble of molecules—in contrast to a single molecule—and can measure only at discrete points in time—in contrast to a permanent measurement. Therefore, we do not characterize the metastability of a subset $B \subset \Omega$ in terms of the mean exit time $\overline{\tau_q^\epsilon}$ from B but proceed in a different way.

5.1 Measurable Transition Probabilities

The typical (experimental) measurement process for any kind of transition probabilities is the following two–step experiment for given subsets $B, C \subset \Omega$:

1. *Pre-Selection:* Select from the canonical ensemble $\mathcal{Q}$ at $t = 0$ all systems with $q \in B$. This selection prepares a new ensemble with density

$$f_B(q) \;=\; \left(\int_B \mathcal{Q}(q)\,dq\right)^{-1} \chi_B(q)\,\mathcal{Q}(q).$$

2. *Transition-Counting:* After an observation time span τ, determine the relative frequency of systems in the ensemble f_B that are located in C. Since we assume that all systems evolve due to the Smoluchowski equation (7), this relative frequency is equal to

$$\int_B f_B(q)\,\mathrm{prob}\left(Q_t^q \in C\right)\,dq$$

Thus, the transition probabilities induced by the Smoluchowski dynamics in the canonical ensemble have to be defined by

$$w(B,C,t) \;=\; \left(\int_B \mathcal{Q}\,dq\right)^{-1} \int_B \mathcal{Q}(q)\,\mathrm{prob}\left(Q_t^q \in C\right)\,dq,$$

which by means of the semigroup P_t associated with the Smoluchowski processes can be rewritten as

$$w(B,C,t) \;=\; \left(\int_B \mathcal{Q}\,dq\right)^{-1} \int_C P_t(\chi_B \mathcal{Q})\,dq. \tag{15}$$

Thus, we may try to apply the basic algorithmic scheme explained in the introduction: Determine the almost invariant sets of the Smoluchowski dynamics in the canonical ensemble via the dominant eigenfunctions of the semigroup P_t. Since P_t is generated by the Fokker–Planck operator A_f due to (8), we may reduce this problem to the eigenfunctions associated with the lowest eigenvalues of A_f.

5.2 Transformation into a Schrödinger Problem

For convenience, we set $\gamma = 1$ and assume that the potential V is scaled appropriately. Thus, there is only one parameter (σ) left, since the inverse temperature is given by $\beta = 2/\sigma^2$.

Associated with the Smoluchowski equation (7), there is another semigroup of Markov operators $\{\exp(tA_b)\}_{t\geq 0}$ defined by the *Kolmogorov–backward–equation*

$$\gamma^2 \partial_t u \;=\; \left(\underbrace{\frac{\sigma^2}{2}\Delta_q \;-\; \gamma\, \nabla_q V \cdot \nabla_q}_{=A_b} \right) u, \quad u(\cdot, t=0) \;=\; f.$$

The "backward" Fokker–Planck operator A_b is related to the "forward" operator A_f by conjugacy, i.e.,

$$A_f\, \mathcal{Q} = \mathcal{Q}\, A_b. \tag{16}$$

Using (16), it is easy to prove that A_b is self–adjoint with respect to the weighted scalar product

$$\langle u, v \rangle_{\mathcal{Q}} = \int u(q)^* v(q) \mathcal{Q}(q) dq$$

for $u, v \in L^2_{\mathcal{Q}}(\Omega) = \{f : \int |f|^2 \mathcal{Q} dq < \infty\}$. In a similar way, one proves that A_f is self–adjoint in $L^2_{\mathcal{Q}^{-1}}$. In order to identify almost invariant sets, we could apply results for metastable states of symmetric Markov semigroups due to Davies [3, 4]. However, here we proceed in a different way and exploit the fact, that the Fokker–Planck operators can be related to the well–established theory of Schrödinger operators.

Define $\sqrt{\mathcal{Q}} = \frac{1}{Z}\exp(-\frac{\beta}{2}V)$ and $A_s = \sqrt{\mathcal{Q}}^{-1} A_f \sqrt{\mathcal{Q}} = \sqrt{\mathcal{Q}} A_b \sqrt{\mathcal{Q}}^{-1}$, thus

$$A_s \;=\; \frac{\sigma^2}{2}\Delta_q \;-\; \frac{1}{2\sigma^2}\left(\nabla_q V\right)^2 \;+\frac{1}{2}\Delta_q V.$$

Formally, the operator $-A_s$ is of the form of a Schrödinger operator for a certain potential U:

$$H \;=\; -A_s \;=\; -\frac{\sigma^2}{2}\Delta_q \;+\; U(q); \qquad U(q) \;=\; \frac{1}{2\sigma^2}\left(\nabla_q V\right)^2 \;-\frac{1}{2}\Delta_q V \tag{17}$$

and it is well–known that H is self–adjoint in $L^2(\Omega)$ for a large class of potentials [21].

Since all operators from above are conjugate to each other, we may investigate the spectrum of any one operator to get spectral information for the remaining two. In the following, we will concentrate on the Schrödinger operator.

For the Hamiltonian operator H defined in (17) we have the following characterization of its spectrum in $L^2(\Omega)$:

THEOREM 5.1 *([21, Thm. XIII.67], [20, Thm. VII.1]) Let* $U \in L^1_{\text{loc}}(\mathbb{R}^d)$ *be bounded from below and suppose that* $V \to \infty$ *for* $|q| \to \infty$*. Moreover, set* $\Omega = \mathbb{R}^d$*. Then,* H *has purely discrete spectrum and a complete set of eigenfunctions. Moreover, the semigroup* $\exp(-tH)$ *associated with* $A_s = -H$ *also has purely discrete spectrum in* $L^2(\Omega)$ *which is given by*

$$\sigma(\exp(-tH)) \subset \{\exp(-\lambda t) : \lambda \in \sigma(H)\} \cup \{0\}.$$

Illustrating Example For the double-well potential V_{dw} we have

$$U(q) = \left(\frac{4}{\sigma^2}V(q) - 3\right) q^2 + 1$$

Fig. 2 presents the dependence of U on the value of σ.

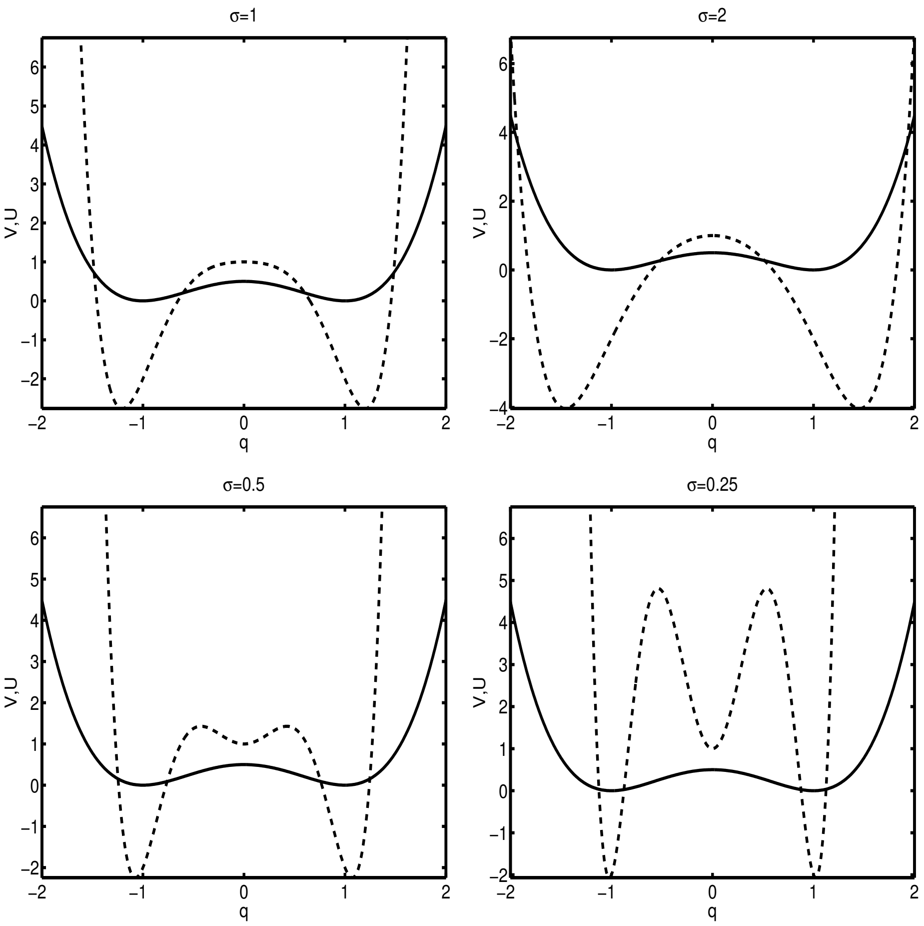

Figure 2: Illustration of the transformed potential U (dashed line) for V_{dw} (solid line) and different values of σ.

Figure 3 and the following table show highly accurate numerical computations of the lowest eigenvalues $0 = \lambda_0 < \lambda_1 < \ldots$ and the corresponding eigenvectors of the Hamiltonian H for different values of σ.

σ	λ_0	λ_1	λ_2	λ_3	λ_4	$\langle E \rangle$
0.25	0	$< 10^{-7}$	1.894	3.460	3.532	0.0473
0.50	0	0.015	1.655	2.756	3.956	0.197
1.00	0	0.374	3.002	5.830	9.322	0.709
2.00	0	1.584	7.098	13.687	21.654	2.426

REMARK 5.2 All the numerical results presented herein are based on highly accurate finite difference discretizations of the eigenvalue problem for the corresponding self–adjoint operator H. The resulting discrete eigenvalue problem is solved via subspace–oriented iterative eigenproblem solvers, cf. [16]. In this article, we will restrict our attention to low–dimensional examples in order to illustrate some fundamental aspects and problems of computational characterization of metastability. Whenever one is really interested in computing the lowest eigenvalues of the operator H for highly dimensional (molecular) systems, one has to apply other discretization techniques. Most popular Schrödinger eigenproblem solvers (like DVR techniques [18] or variational basis set expansions [26]) are restricted to at most seven degrees of freedom, i.e., to relatively small systems. However, *Quantum Monte Carlo* techniques seem to be applicable to really large systems [10, 17].

5.3 Decay of Transition Probabilities

The weighted scalar products allows to rewrite our definition (15) of the transition probabilities between $B \subset \Omega$ and $C \subset \Omega$ in a symmetric form:

$$w(B,C,t) \;=\; \frac{\langle \chi_C \mathcal{Q}\,,\, e^{tA_f}(\chi_B \mathcal{Q})\,\rangle_{\mathcal{Q}^{-1}}}{\langle \chi_B \mathcal{Q}, \chi_B \mathcal{Q}\rangle_{\mathcal{Q}^{-1}}} \;=\; \frac{\langle \chi_C,\, e^{tA_b}\chi_B\,\rangle_{\mathcal{Q}}}{\langle \chi_B, \chi_B\rangle_{\mathcal{Q}}}.$$

Exploiting

$$\exp(tA_s) \;=\; \sqrt{\mathcal{Q}}^{-1}\exp(tA_f)\sqrt{\mathcal{Q}},$$

we find that, in terms of the usual L^2-scalar product $\langle \cdot, \cdot \rangle$,

$$w(B,C,t) \;=\; \frac{\langle \chi_C\sqrt{Q},\; e^{-tH}(\chi_B\sqrt{Q})\rangle}{\langle \chi_B\sqrt{Q}, \chi_B\sqrt{Q}\rangle}.$$

Let V be such that U satisfies the assumptions of Thm. 5.1. Then H has a purely discrete spectrum which is bounded from below. The lowest eigenvalue $\lambda = 0$ corresponds to the eigenvector $\sqrt{Q}$. Let λ_k be its eigenvalues in increasing order and let Φ_k be the associated eigenvectors such that

$$H\Phi_k \;=\; \lambda_k \Phi_k, \qquad k = 0, 1, 2, \ldots$$

where the λ_k may be repeated according to their multiplicity. Moreover, assume that we can compute the coefficients b_k and c_k, $k = 0, 1, \ldots$, of the expansions

$$\chi_B \sqrt{Q} = \sum_{k=0}^{\infty} b_k \Phi_k, \quad \text{and} \quad \chi_C \sqrt{Q} = \sum_{k=0}^{\infty} c_k \Phi_k.$$

Then, the transition probabilities may be computed due to:

$$w(B, C, t) = \frac{\sum_{k=0}^{\infty} c_k^* b_k \, e^{-t\lambda_k}}{\sum_{k=0}^{\infty} |b_k|^2}. \tag{18}$$

Half-Time Periods. According to our definitions, the *probability to stay within* some set $B \subset \Omega$ is given by $w(B, B, t)$. Due to (18), this probability to stay within decays from its initial value $w(B, B, 0) = 1$ exponentially to the asymptotic value

$$w_\infty(B) = \lim_{t \to \infty} w(B, B, t) = \frac{|b_0|^2}{\sum_{k=0}^{\infty} |b_k|^2}.$$

For classifying the rate of convergence, we define the *half-time period* τ_B associated with B via

$$w(B, B, \tau_B) - w_\infty(B) = \frac{1}{e} \left(\underbrace{w(B, B, 0)}_{=1} - w_\infty(B) \right), \tag{19}$$

with e denoting Euler's constant. Since $w(B, B, t) - w_\infty(B)$ decays strictly monotonic in t, τ_B is uniquely defined. Simple algebraic calculations using (18) show that τ_B satisfies

$$\sum_{k=1}^{\infty} |b_k|^2 \, [1 - \exp(1 - \lambda_k \tau_B)] = 0. \tag{20}$$

5.4 Almost Invariant Sets

We are interested in *almost invariant sets* of the stochastic motion, i.e., sets $B \subset \Omega$ for which the decay $w(B, B, t) \to w_\infty(B)$ is as slow as possible.

Let us first consider the case where the second–lowest eigenvalue λ_1 is significantly close to $\lambda_0 = 0$ and well separated from the remaining part of the spectrum by a spectral gap, i.e., $\lambda_k \gg \lambda_1$ for all $k > 1$. Since for every subsets B with $b_1 \neq 0$ the decay is asymptotically governed by $\exp(-\lambda_1 t)$, the main difference is connected to the magnitude of $|b_1|^2 = |\langle \chi_B, \Phi_1 \rangle|^2$. Since $\langle \sqrt{\mathcal{Q}}, \Phi_1 \rangle = 0$, the eigenvector Φ_1 must take positive and negative values and the subset $B \subset \Omega$, for which $|b_1|^2$ is *maximal*, is given by the sign of Φ_1:

$$\text{either} \quad B = \Phi_1^{-1}(\mathbb{R}^+) \quad \text{or} \quad B = \Phi_1^{-1}(\mathbb{R}^-).$$

This motivates the decomposition of Ω into two almost invariant sets, $B, C \subset \Omega$ with $C = \Omega \setminus B$, being separated by the zeros of the eigenvector Φ_1 associated with λ_1. Moreover, these sets have the property that only the leading two coefficients, b_0 and b_1, or c_0 and c_1, respectively, are significantly larger than zero while all other coefficients almost vanish. Together with (20), this property gives us that the half-time period is approximately given by the inverse of the second eigenvalue:

$$\tau_B \approx \lambda_1^{-1} \quad \text{as well as} \quad \tau_C \approx \lambda_1^{-1}.$$

For example, we may again consider the double–well potential $V_{\rm dw}$ from above. For $\sigma = 0.5$, we find $\lambda_1 = 0.015 \ll \lambda_2$, and the coefficient of the two almost invariant sets $B = (0, \infty)$ and $B = (-\infty, 0)$ satisfy

$$|b_0|^2 = 0.2500, \quad |b_1|^2 = 0.2485, \quad \text{and} \quad |b_k|^2 < 5 \cdot 10^{-4}, \quad \forall k > 1.$$

Thus, the half–time period can be estimated by $\tau_{(0,\infty)} \approx 1/\lambda_1 \approx 67$.

The general case. Let us consider the case where m eigenvalues $\lambda_1, \dots, \lambda_m$ are significantly close to $\lambda_0 = 0$ and $\lambda_k \gg \lambda_1$ for all $k > m$. If the potential U is smooth, the eigenfunctions Φ_k associated with the λ_k, $k = 1, \dots, m$, are smooth functions of q. The problem of identifying almost invariant sets from these eigenvectors Φ_k, $k = 1, \dots, m$, has been studied in different settings, for example in [3, 7]. We will herein shortly explain and illustrate the algorithm proposed in [7]: Therefore, we consider the Hilbert space $L^2_{\mathcal{Q}}(\Omega)$ where the Fokker–Planck operator A_b and the associated semigroup of Markov operators are self–adjoint. The analytical investigation in [7] reveals that —whenever the noise amplitude σ is small enough— the eigenvectors $u_k = \sqrt{\mathcal{Q}}^{-1}\Phi_k$ of A_b are just "perturbed step functions"

$$u_k \approx \sum_{j=0}^{m} \alpha_{kj}\, \chi_{B_j}, \tag{21}$$

where the $B_j \subset \Omega$ are the desired almost invariant sets (see [7] for details and Fig. 3 for illustration). If (21) were an identity, the B_j could be identified uniquely via the *sign structure* $s : \Omega \to \{+1, -1, 0\}^m$ given by

$$s(q) = (s_k(q))_{k=1,\dots,m}, \quad s_k(q) = \mathrm{sign}\,(u_k(q)).$$

Up to sets of measure zero, the B_j would be the sets on which the sign structure s is constant (since the eigenvectors have to be orthogonal!). Since (21) holds only approximately, the algorithmic strategy is to identify the "core" sets of the B_j via sign structures and assign the remaining positions to these cores in order to construct a decomposition of Ω into almost invariant subsets. The details of this *identification algorithm* (including an error estimation scheme) can be found in [7].

Illustration for Three–Well Potential. Consider the three-well potential V_{3w} given by

$$V_{3\mathrm{w}}(q) \;=\; \left((q^2-1)^2 \;-\; 1 \;+\; cq\right)^2, \tag{22}$$

with $c = 0.1$, for example. Fig. 4 shows V and the associated potential U for $\sigma = 0.75$ and $\gamma = 1$.

The following table presents the lowest eigenvalues of the Hamiltonian H for the three–well potential with $\sigma = 0.75$ and $\gamma = 1$:

λ_0	λ_1	λ_2	λ_3	λ_4
0.000	0.072	0.234	2.450	6.768

There are three eigenvalues $\lambda_0, \lambda_1, \lambda_2$ near and at $\lambda = 0$ and we observe a significant gap to the remaining eigenvalues. The eigenvectors Φ_1 and Φ_2 associated with λ_1 and λ_2 are shown in Fig. 5. The associated eigenvectors of A_b, i.e., the reweighted eigenvectors $u_k = \sqrt{\mathcal{Q}}^{-1} u_k$, may in fact be interpreted as perturbed step functions and we find that

$$\begin{aligned} q < -1.066 \quad &\Rightarrow \quad u_1 > 0 \text{ and } u_2 > 0, \\ -0.779 < q < 0.760 \quad &\Rightarrow \quad u_1 < 0 \text{ and } u_2 < 0, \\ 0.760 < q \quad &\Rightarrow \quad u_1 < 0 \text{ and } u_2 > 0. \end{aligned}$$

The corresponding behavior of the sign structure map s is indicated in Fig. 5. Obviously, the subset $C = (-1.066, -0.779)$ with sign structure $s = (+1, -1)$, a region with steep gradients between almost constant levels, is problematic. The identification algorithm mentioned above assigns the positions from C to the other sets and results in approximate almost invariant sets $B_1 = \{q < -1.05\}$, $B_2 = \{-1.05 < q < 0.76\}$, and $B_3 = \{q > 0.76\}$.

Let $\{u_k\}$ denote the entire system of eigenvectors of H (in the same order as the eigenvalues). The corresponding expansion coefficients $|b_k|^2 = |\langle \Phi_k, \chi_B \sqrt{\mathcal{Q}} \rangle|^2$ for the three almost invariant sets come out as:

B_j	$\lvert b_0\rvert^2$	$\lvert b_1\rvert^2$	$\lvert b_2\rvert^2$	$\lvert b_3\rvert^2$	$\lvert b_k\rvert^2, k > 3$	$\sum_{k=0}^{\infty} \lvert b_k\rvert^2$
$(-\infty, -1.05)$	0.014	0.104	0.001	$< 10^{-4}$	$< 10^{-4}$	0.120
$(-1.05, 0.76)$	0.523	0.054	0.138	$< 10^{-3}$	$< 10^{-4}$	0.727
$(0.76, \infty)$	0.025	0.008	0.117	0.001	$< 10^{-4}$	0.153

We observe that the half–time period of $B = (-\infty, -1.05)$ is approximately given by $\tau_B = 1/\lambda_1 \approx 13.9$ while that of $C = (0.76, \infty)$ is given by $\tau_C = 1/\lambda_2 \approx 4.3$.

5.5 Half–Time Periods versus Mean Exit Times

It is clear from the definition, that the half–time period of the probability to stay in some set B as introduced above will in general be larger than the mean exit time from the B. We saw in Sec. 4.1 that (for every B with appropriate boundary) the latter one is connected to the lowest eigenvalue of the Fokker–Planck operator A^B restricted to B with Dirichlet boundary conditions on ∂B while the former one is connected to the lowest eigenvalues $\lambda > 0$ of A_f in $L^2_{Q^{-1}}(\Omega)$.

For a specific B, the lowest eigenvalue of A^B can be related intrinsically to the structure of the potential energy function (cf. [9]). Under the assumption of Thm. 4.1, we even have the explicit formula (14) for small noise amplitudes $\sigma = \epsilon$.

A comparable formula for the second–lowest eigenvalue λ_1 of A_f in $L^2_{Q^{-1}}(\Omega)$ seems to be not available in general. One knows that, asymptotically for $\sigma = \epsilon$, the eigenvalue $\lambda_1 = \lambda_1(\epsilon)$ scales like

$$\lim_{\epsilon \to 0} \epsilon^2 \, \log \lambda_1(\epsilon) \; = \; \Lambda,$$

with some constant $\Lambda < 0$, whose intrinsical dependency on the potential V seems to be unknown [13]. However, in specific situations, the value of Λ can be constructed: for example, the symmetry of double-well potential implies that $\Lambda = 2V_{\mathrm{barrier}} = 1$ in this case.

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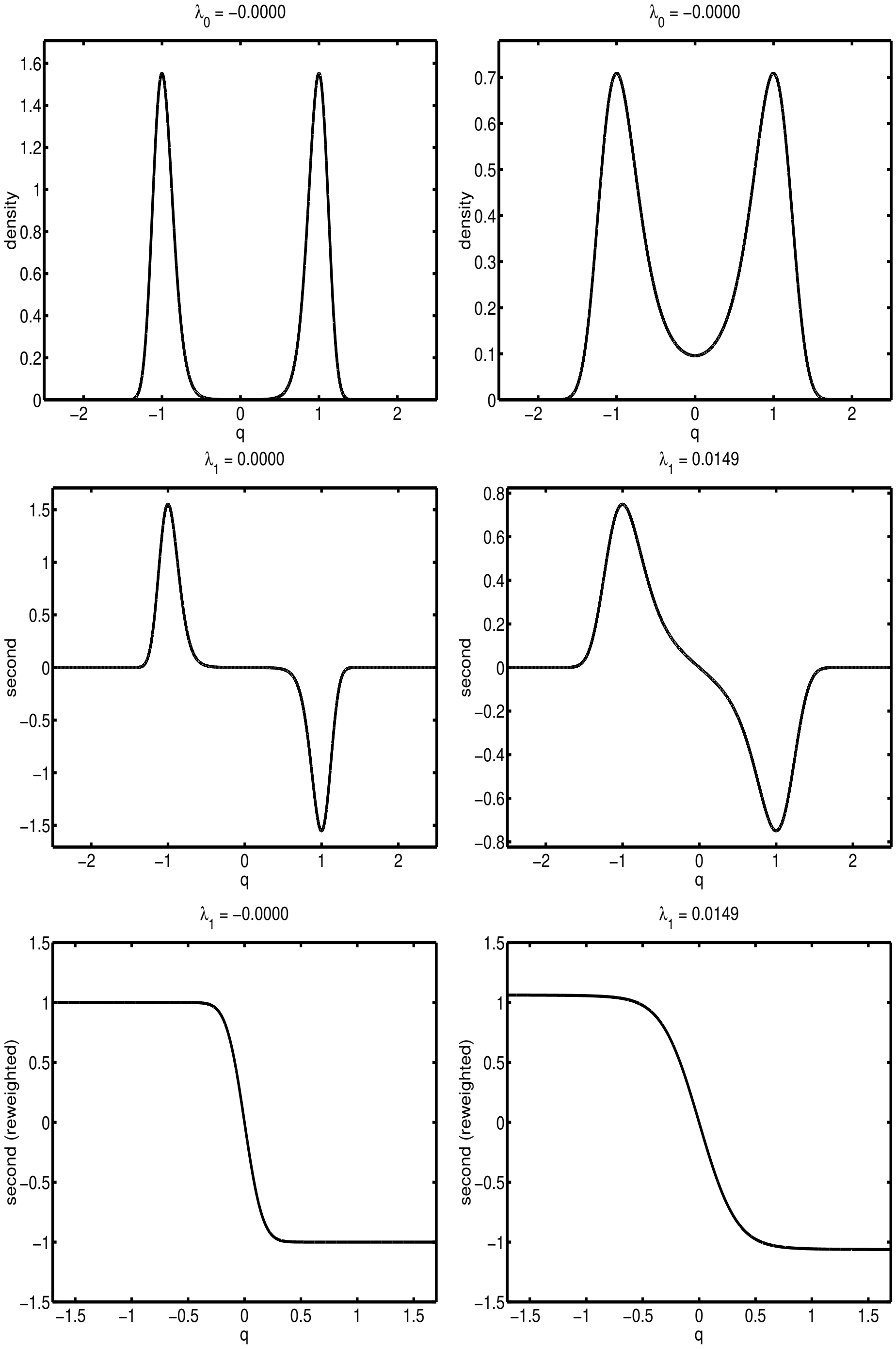

Figure 3: Eigenvectors $\Phi_0 = \sqrt{\mathcal{Q}}$ and Φ_1 to the lowest (top row) and second lowest (middle row) eigenvalues of the Hamiltonian H for the double–well potential V_{dw} and different values of σ (left = 0.25 and right = 0.5). The pictures in the bottom row show the "reweighted" second eigenvectors $\sqrt{\mathcal{Q}}^{-1}\Phi_1$ which converge to a step function for $\sigma \to 0$ (see Sec. 5.4 for interpretation).

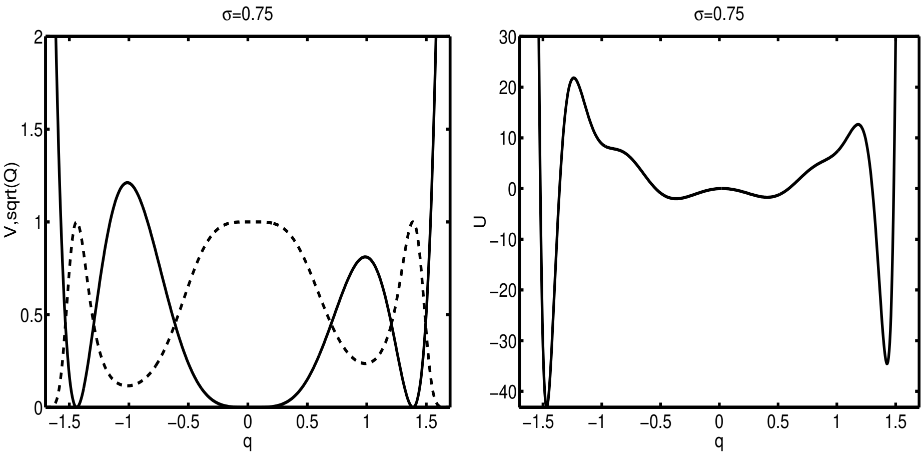

Figure 4: Left: Three–well potential $V_{3\mathrm{w}}$ due to (22) with $c = 0.1$ and corresponding ground state $\sqrt{Q}$ for $\sigma = 0.75$ and $\gamma = 1$. Right: Associated potential U.

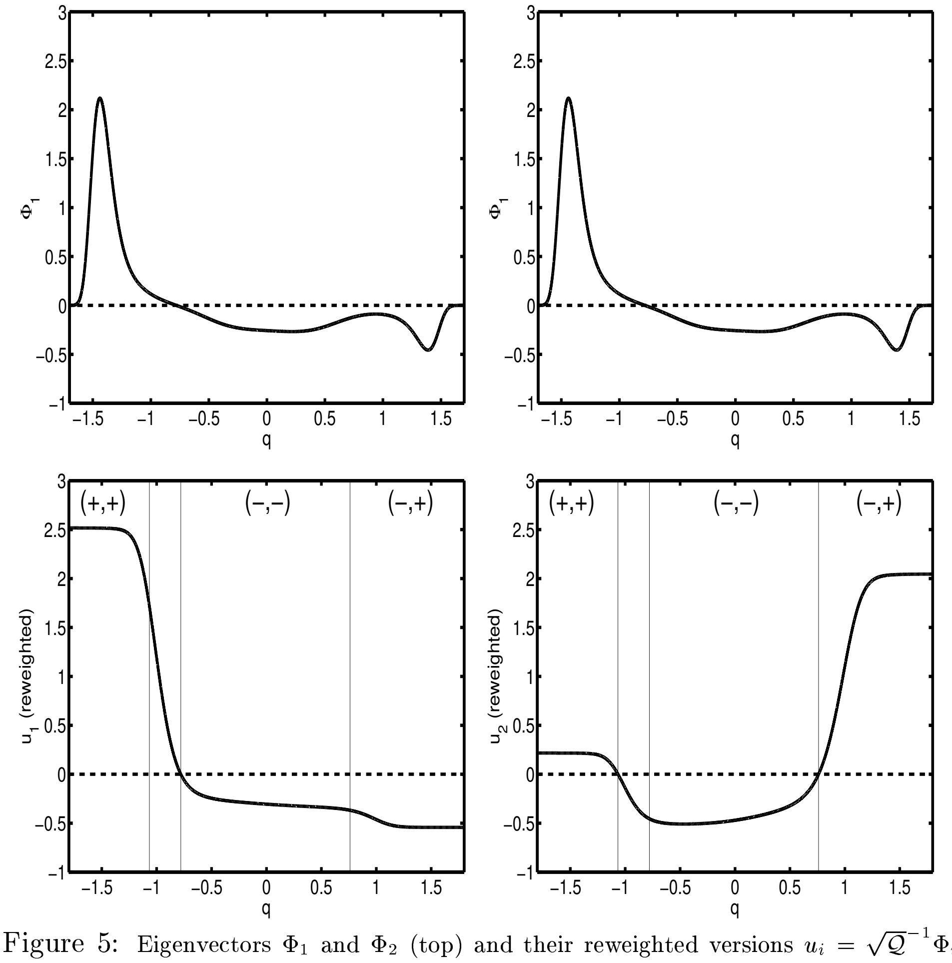

Figure 5: Eigenvectors Φ_1 and Φ_2 (top) and their reweighted versions $u_i = \sqrt{Q}^{-1}\Phi_i$ (bottom) for the eigenvalues λ_1 and λ_2 of the Hamiltonian H for the three well potential $V_{3\mathrm{w}}$. (The eigenvector corresponding to $\lambda = 0$ can be found in Fig. 4).