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The generating structure of spatial conformation dynamics

Andreas Bittracher

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Vorsitzender:		Prof. Dr. Christian Liedtke
Prüfer der Dissertation:	1.	Prof. Dr. Oliver Junge
	2.	Prof. Dr. Carsten Hartmann

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Contents

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Abstract

This thesis develops a new approximation method for the transfer operator of a momentum–averaged Langevin equation. This transfer operator can be used to detect metastable sets and thus occurs in classical molecular conformation dynamics. It is shown to possess a generator-like analytic structure despite not forming a time–semigroup. This is exploited to discretize the operator without the computationally expensive time–integration and momentum–averaging steps of established methods. The performance of the new method is evaluated both analytically and by numerical examples.

Zusammenfassung

Diese Arbeit entwickelt ein neues Approximationsverfahren für den Transferoperator einer impulsgemittelten Langevin–Gleichung. Dieser Transferoperator kann zum Auffinden metastabilier Mengen verwendet werden, weshalb er in der klassischen molekularen Konformationsdynamik vorkommt. Ihm wird eine generator–artige analytische Struktur nachgewiesen, obwohl er keine Zeit-Halbgruppe bildet. Dies wird benutzt um den Operator ohne die rechnerisch aufwendigen Zeitintegrations- und Impulsmittelungsschritte etablierter Methoden zu diskretisieren. Die Leistung der neuen Methode wird analytisch und anhand von numerischen Beispielen bewertet.

Introduction

Motivation. Transitions between metastable states of dynamical processes are an often–observed and important phenomenon in a great number of chemical disciplines, most prominently in the field of molecular conformation dynamics. While the microscopic state of a bonded molecule is described by its *configuration*, i.e. the atoms' positions relative to each other, a *conformation* is the molecule's *global* state or shape that is largely conserved under small-scale atom vibrations.

The macroscopic properties that a molecular system exhibits are often greatly influenced by the conformation it currently resides in. An example for a small molecule is 1,2-dichloroethylene, whose boiling point changes from 333.5 °K for the cis isomer to 320.7 °K for the trans isomer [32]. This phenomenon can be explained by the differing polarity of the two isomers, resulting from the conformational alignment of the two chlorine atoms. In molecular biochemistry, the most prominent example for a system undergoing conformational transitions is the multi–step folding process of polypeptide chains into their biologically functional protein form. The knowledge about the intermediate steps (the *folding pathway*), the transition rates between them and the stability of the end product is of use in countless applications in the biological, chemical and pharmaceutical sciences [18, 83, 23, 52, 49], and motivates the development of efficient and robust computational methods for analyzing metastable processes.

Rare event dynamics. Classical molecular dynamics can be modeled as a Hamiltonian mechanical system, i.e. an ordinary differential equation describing the change of the molecule's configuration and of its momenta. However, it is physically sound[1] (and computationally useful) to consider a *stochastically perturbed* Hamiltonian model. A common model is the *Langevin dynamics*, modeled by a *stochastic* differential equation. The evolution of the configuration can then be viewed as a randomly perturbed path on the *potential energy surface* (PES). Metastable conformations then correspond to the (main) minima of the PES, and conformational changes correspond to the overcoming of potential energy barriers.

To illustrate this, consider a butane molecule, whose three conformations can be described by the dihedral angle around the central carbon-carbon bond (Figure 0.1). For

[1] Stochastic perturbations can mimic collisions of the molecule of interest with solvent particles without having to explicitly model them. This can serve to equilibrate the system's internal energy around a given target temperature. This procedure is known as *thermostated molecular dynamics*.

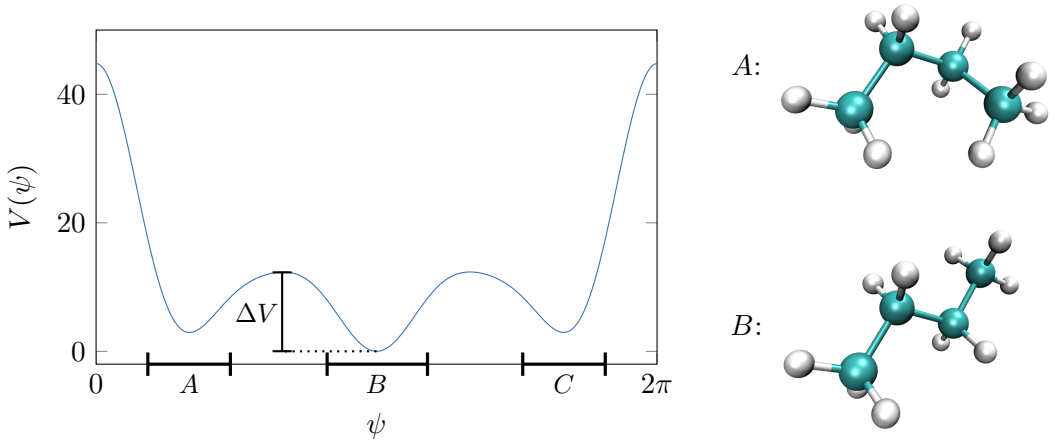

Figure 0.1.: Left: The potential energy landscape of n-butane, projected onto the central dihedral angle. The metastable conformations can be seen as the subsets of the configuration space around the minima. Right: The molecular configuration at the minima of the conformations A and B, distinguished by the central dihedral angle. The molecular data was obtained from [27, Chapter 5.2], [4].

a transition from the central *trans* conformation B to the *gauche* transformation A, an energy barrier $\Delta V \approx 12.35\text{mJ/mol}$ has to be overcome. As a first quantifier of the overall metastability of a conformation, the *escape rate* k can be calculated by the Van't Hoff-Arrehius law [29] to

$$k = \nu \exp(-\beta \Delta V) \ ,$$

where $\beta = 1/(k_B T)$ is the inverse temperature, with k_B Boltzmann's constant, and ν is a constant prefactor. The escape rate decays exponentially in the height of the energy barrier ΔV.

Conformational changes across high energy barriers can therefore be considered as rare events. In big molecules like proteins, the major transitions take place on time scales typically ranging from micro- to milliseconds, while the basic frequencies, such as bond vibrations, are in the order of femtoseconds. A direct numerical simulation of these events by integrating the Langevin equations of motion would thus have to span 9 to 12 orders of magnitude relative to the basic time scale, a task infeasible for all but the most specialized [68] of today's high-performance computers.

It is therefore highly desirable to avoid microscopic simulations, and still obtain an adequate insight into a system's large–scale and long–time behavior. Thus, beyond established model–reduction techniques[2], much effort has recently been put into build-

[2]For example, using averaging techniques from the Mori–Zwanzig formalism to eliminate the fastest

ing reduced-order models on the level of the conformations [7, 8, 33, 53, 58, 63, 78]. However, to effectively build those *Markov state models*, the conformations and their transition rates have to be known beforehand. As identifying them by analyzing a long-time microscopic numerical simulation would run counter to the reduced–order modeling idea, alternative methods have to be used.

Transfer operator–based metastability analysis. In their seminal works, Deuflhard, Dellnitz and coworkers [13, 62, 12] exploited that metastable structures in dynamical systems can be identified via the eigenfunctions of the system's *transfer operator* P^t. This time-parametrized family of linear operators is the push–forward for densities under the dynamics.

To compute its eigenfunctions, P^t is commonly discretized by a stochastic matrix, whose elements contain the transition probabilities from some subset of state space to another. The transition probabilities in turn are computed using many relatively short numerical trajectories that were sampled over the domain of the flow. While it seems that we have only replaced the long–time simulation by multiple short–time simulations, the transfer operator approach is advantageous. It offers a systematic and robust way to map the flow on the whole state space, as opposed to only the high–probability regions visited by a single long trajectory. Moreover, the number of sampling points can be often kept low [77, 39], and their numerical integration is easy to parallelize.

For molecular Langevin systems, a state consists of both position and momentum parts. Yet, metastable conformations are a feature of position space only. One way to model molecular dynamics on position space only is via the *Smoluchowski dynamics*[3] [69, 40]. It is comparable to the Langevin dynamics only in a high–friction and time–rescaled limit (the *Kramers–Smoluchowski limit*), which makes it initially unclear whether it accurately models conformation dynamics, in particular the transition rates. Schütte [61] thus introduced the *spatial dynamics* (or *Langevin dynamics with randomized momenta*), and with it the *spatial transfer operator* S^t which propagates positional densities in a physically justifiable manner. It can be seen as a *momentum-averaged* version of the full transfer operator. Unfortunately, when computing the spatial transition probabilities in order to discretize S^t, the momentum averaging has to be performed explicitly, which increases computational cost.

Simulation-free and generator-based methods. Analyzing the transfer operator instead of long–time trajectories can be seen as stepping away from single–system dynamics and towards solving the underlying density transport equations. Lately, techniques have been proposed that complete this step, by working directly with the

degrees of freedom [19] or considering course-grained molecular models [51].

[3] It is also known as *overdamped Langevin dynamics*, *Brownian dynamics* or *Kramer's equation*.

transport equations [25, 39, 78], albeit only for a special class of dynamical systems. If the system exhibits the *Markov property* and other regularity conditions, the system's density transport can be described by an abstract Cauchy problem of the form $\partial_t f = Lf$. The operator L is called the *infinitesimal generator*, and is a linear partial differential operator. L is deeply connected to the transfer operator (it can be seen as the formal time derivative of P^t), and their eigenfunctions coincide.

This last property can again be exploited for metastability analysis. Analyzing the generator is advantageous, as its discretization requires no numerical trajectory integration. Also, spectral collocation methods can be used for the discretization, which converge with spectral accuracy under further regularity assumptions.

Unfortunately, Schütte's spatially projected dynamics does not exhibit the Markov property; its transport equations cannot even be set up in a momentum–free form. Clearly, the generator approach is not applicable here.

This thesis. The main goal of this thesis is to extend the efficient generator-based methods to spatial dynamics in order to

1. avoid numerical trajectory integration,
2. eliminate explicit momentum averaging.

The central idea is that, formally, (higher) time-derivatives of the spatial transfer operator can still be defined. We hypothesized that these *pseudogenerators* contain the relevant information about the density transport to perform metastability analysis.

In the present work, this hypothesis is thoroughly tested and both analytically and numerically confirmed. We develop a Taylor–like approximation scheme that accurately restores the eigenfunctions and the spectrum of the spatial transfer operator S^t for small lag times t. We give asymptotic error estimates and validate them numerically.

We show that the pseudogenerators up to order 3 exhibit a very simple and regular structure that is accessible for collocation methods. This structure is largely retained under the projection onto one–dimensional *reaction coordinates*. This represents a potential tool for further model reduction and is an important step towards the application to chemically relevant high–dimensional systems.

Moreover, we found a surprising and previously unknown connection to the generator of the aforementioned Smoluchowski dynamics. This connection is independent of the damping. This provides new insights into the approximation quality of Smoluchowski dynamics to spatially projected Langevin dynamics in the low–damping setting.

While we demonstrate the efficacy of pseudogenerator–based methods for identifying spatial metastable sets and their short–time degree of metastability, the conformationally important long–time transition rates could not yet be reconstructed. There are, however, advancements in that regard: for increasing lag times spatial dynamics is

observed to converge to a Markov process. We discuss first results on the analysis of this limiting process.

Outline. This thesis is organized as follows:

Chapter 1 introduces the dynamical systems used for modeling molecular dynamics, with a special focus on different coordinate descriptions for molecular degrees of freedom.

Chapter 2 provides the operator theoretical framework of density dynamics. The (spatial) transfer operators are introduced, as well as the density transport equations and infinitesimal generators. Finally, we describe established numerical discretization schemes, including the collocation method.

Chapter 3 introduces the concept of pseudogenerators of spatial transfer operators. After the definition and the derivation of some basic properties, we derive an explicit coordinate expression for the first three pseudogenerators. We draw the connection to Smoluchowski dynamics and interpret our findings. Also the projection of pseudogenerators onto one-dimensional reaction coordinates is presented.

Chapter 4 presents the development of pseudogenerator-based approximation schemes for the spatial transfer operator and discusses their asymptotic error estimates. The chapter concludes with numerical examples that demonstrate the usefulness of the approximation schemes for short–time metastability analysis.

Chapter 5 evaluates the approximation quality for the reconstruction methods for extended time scales. Also, the long–term limit of the spatial dynamics is explored.

Chapter 6 contains the conclusions and discusses possible future work.

Two appendices are given:

Appendix A presents the proof of self–adjointness of the spatial transfer operator, as well as a formal derivation of Smoluchowski dynamics from high–friction Langevin dynamics.

Appendix B contains technical vector–analytic proofs regarding the coordinate expression of pseudogenerators. Also, for the special case of a one–dimensional position space, we present code for a computer–assisted automated derivation of the first three pseudogenerators.

Contributions. A large part of the work presented in this thesis has been developed in cooperation with coworkers, and is already published [6, 5]. Of the main Chapters 3, 4 and 5, the results from Sections 3.1, 3.2 (and the attached Appendix B), 4.1, 4.2 and 5.2 can be attributed primarily to the author.

1. Classical molecular dynamics

1.1. Representation of molecules

When speaking of a *molecule*, we mean a collection of n atomic particles in $\mathbb{R}^3$, whose movement is governed by laws derived from classical Hamiltonian mechanics. The particles may be individual atoms, atomic groups according to a united-atom model [43] or even whole chemical functional groups that stem from coarse-grained molecular mechanics [51]. In any case we see these particles as zero-dimensional point masses and simply call them *atoms* from now on. The mass of the i-th atom is denoted by m_i.

Cartesian coordinates. The most straight-forward description of a molecular configuration is as a point $\mathbf{q} = (\mathbf{q}_1, \ldots, \mathbf{q}_n)^\intercal \in \mathbf{Q} = \mathbb{R}^{3n}$, with $\mathbf{q}_i \in \mathbf{Q}_i = \mathbb{R}^3$ the position of the i-th atom. Note that we do not impose any explicit bounds on the positions. We refer to $\mathbf{Q}$ as the *Cartesian position space*.

Generalized coordinates. We will, however, define our various dynamical systems on more general coordinate spaces. They are motivated by internal coordinate representation, which is frequently used in computational chemistry. A more comprehensive description can be found in molecular simulation and computational chemistry literature, for example [27, 11].

In *internal*, *intrinsic* or *inner coordinates*, the atoms' positions are described relative to one another via the use of bond lengths, valence angles and torsion angles, accordingly also called the BAT-representation.

- The bond lengths $r_{ij} \in \mathbb{R}^+$ are the euclidean distances between two bonded atoms $\mathbf{q}_i$ and $\mathbf{q}_j$.
- Given three atoms $\mathbf{q}_i, \mathbf{q}_j, \mathbf{q}_k$ bonded in sequence, the valence angle $\varphi_{ijk} \in [0, \pi)$ describes the angle between the two bond vectors $(\mathbf{q}_i - \mathbf{q}_j)$ and $(\mathbf{q}_k - \mathbf{q}_j)$.
- Given four atoms $\mathbf{q}_i, \mathbf{q}_j, \mathbf{q}_k, \mathbf{q}_l$ bonded in sequence, the torsion (or dihedral) angle $\psi_{ijkl} \in [0, 2\pi)$ is the angle between the two bond vectors $(\mathbf{q}_i - \mathbf{q}_j)$ and $(\mathbf{q}_l - \mathbf{q}_k)$ projected into the plane orthogonal to $(\mathbf{q}_k - \mathbf{q}_j)$.

A geometric illustration of the internal coordinates can be seen in Figure 1.1.

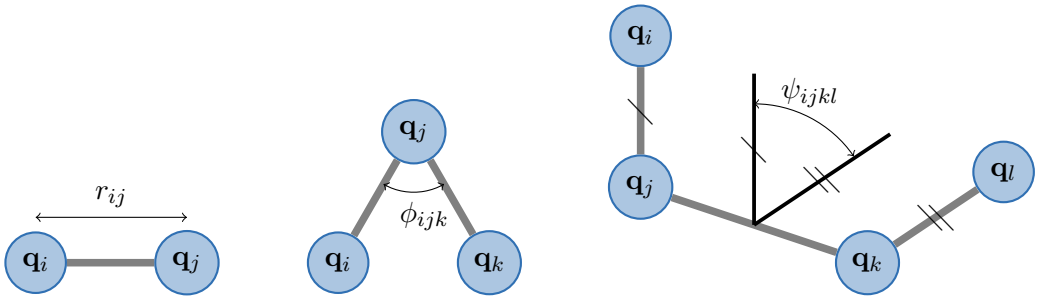

Figure 1.1.: Illustration of the degrees of freedom of inner coordinates: bond lengths, valence angles and torsion angles.

It can easily be seen that at most $3n - 6$ internal coordinates are necessary to provide a complete description of a molecule's internal configuration. Also, it is clear that from a given set of Cartesian coordinates, the BAT-representation can be computed[1] and the conversion is smooth, i.e. a $\mathcal{C}^\infty$ map. However the reverse is not true; there is no single set of Cartesian coordinates corresponding to a set of internal coordinates, as the latter retains no information about the absolute position and orientation of the overall molecule in three-dimensional space.

Meaningful molecular dynamics in internal coordinates still can be performed, albeit due to the "lack of information", certain restrictions have to be imposed on the original Cartesian molecular system. For example, Koltai in [39] worked with molecular systems in inner coordinates with zero translational and rotational momentum, and encoded this restriction in a transformed mass matrix. A systematic approach would lead to discussing molecular dynamics under holomorphic constraints [2], thus leading into the field of classical mechanics on Riemannian manifolds [1].

Alternatively, one could to complement the internal coordinates with information about the overall position and orientation, in such a way that the conversion to Cartesian coordinates is possible and smooth, for example by means of the center of mass and the mass variance, or with the global positions of certain "reference atoms".

Thus, with internal coordinates in mind, but not restricted to them, we broaden our notion of what a valid representation of a molecule looks like. For $d \in \mathbb{N}^+$ let $\mathcal{Q} \subset \mathbb{R}^d$ be a Lipschitz domain with respect to the Euclidean norm. We call $\mathcal{Q}$ the *generalized position space*, and any point $q \in \mathcal{Q}$ a *(generalized) position coordinate*.

Remark. We still work under the assumption that the generalized coordinates are somehow derived from Cartesian coordinates, and thus still speak of a "molecular system". Also, for the important special case of $\mathcal{Q}$ being the pre–image of $\mathbf{Q}$ under a diffeomorphism Φ, i.e. $\mathbf{Q} = \Phi(\mathcal{Q})$, we will see in Section 1.2.3 how to explicitly derive

[1] For the specific maps to convert Cartesian to inner coordinates, see [11].

the coordinate expressions for our dynamical models in generalized coordinates.

1.2. Dynamical models

So far, we only had a static description of the molecular system. In order to make the molecule move, we need to introduce time-dependency of the positions, and with it the useful concepts of velocity, momentum and generally what is known as *molecular dynamics*.

1.2.1. General Itô dynamics

Broadly speaking, we will be studying continuous time stochastic dynamical systems on a phase space $\mathcal{X} \subset \mathbb{R}^d$. They are described by time–parametrized random variables x_t , $t \geq 0$ that take values in $\mathcal{X}$. For most of the systems relevant for us, the evolution of x_t over time is governed by a stochastic differential equation (SDE) of the form

$$\frac{dx_t}{dt} = b(x_t) + \sigma(x_t)w_t \ , \tag{1.1}$$

Here $b : \mathcal{X} \to \mathbb{R}^d$ will be called the *drift coefficient* and $\sigma : \mathcal{X} \to \mathbb{R}^{d\times d}$ the *diffusion coefficient* or *-matrix*, and we assume b and σ to be Lipschitz-continuous. The symbol w_t denotes a $\mathbb{R}^d$-valued, zero-mean uncorrelated Gaussian "white noise" process, that can be formally seen as the (generalized) derivative of the standard Brownian motion B_s. Under these conditions, the SDE is called *Itô diffusion equation*.

As a *stochastic* differential equation, (1.1) has to be interpreted in the context of Itô integrals, which are thoroughly covered in [50]. As a short primer, the solution of (1.1) is the stochastic process

$$x_t = x_0 + \int_0^t b(x_s)\ ds + \underline{\int_0^t \sigma(x_s)\ dB_s} \ ,$$

where the stochastic part is induced by the underlined Itô integral with respect to the Brownian motion process B_s.

We will begin to discuss molecular dynamics in a purely stochastic context very soon, but still briefly require the notion of a *deterministic* dynamical system. It arises as a special case from (1.1), when setting

$$\frac{dx_t}{dt} = b(x_t) \ , \tag{1.2}$$

and the solving stochastic process $\{x_t\}_{t\geq 0}$ can be interpreted as a deterministic trajectory in $\mathcal{X}$. We will use this "overloaded" notation in the following without further comment.

1.2.2. Hamilton dynamics

Potential energy. Molecular dynamics is now induced by quantum-mechanical interactions between the atoms. These position-dependent forces are combined into the *force field* $F : \mathcal{Q} \to \mathbb{R}^d$, which in our case is the negative gradient of a *potential* $V : \mathcal{Q} \to \mathbb{R}$:

$$F(q) = -\nabla V(q) \ .$$

The potential energy terms often can be expressed as functions in internal coordinates or in the atoms' distances [11, Section 2.2]. However, as we work in generalized and not necessarily internal coordinates, we do not want to dictate the specific shape of V, but only demand that V is at least twice continuously differentiable, polynomially growing at infinity and bounded from below. We will impose further restrictions on V if the need arises.

Equations of motion. The most basic law to describe the movement of the dynamical system is now given by the (deterministic) ordinary differential equation

$$M(q_t) \cdot \frac{d^2}{dt^2} q_t = F(q_t) \ , \tag{1.3}$$

where $M : \mathcal{Q} \to \mathbb{R}^{d \times d}$ is the *mass matrix*, from now on assumed to be symmetric and positive-definite. Introducing $p_t := M(q_t)\dot{q}_t \in \mathbb{R}^d$ as the system's momenta, and the *Hamiltonian*

$$H(q, p) := V(q) + \frac{1}{2} p^\intercal M^{-1}(q) p \ , \tag{1.4}$$

equation (1.3) can be written as

$$\begin{aligned} \frac{dq_t}{dt} &= \nabla_p H(q_t, p_t) \ , \\ \frac{dp_t}{dt} &= -\nabla_q H(q_t, p_t) \ . \end{aligned} \tag{1.5}$$

This defines a dynamical system on $\Omega := \mathcal{Q} \times \mathcal{P}$ (called the *(generalized) phase space*), with $\mathcal{P} := \mathbb{R}^d$ the *(generalized) momentum space*. In (1.4), V is also called *potential energy* and $E_{\text{kin}}(q, p) := \frac{1}{2} p^\intercal M^{-1}(q) p$ is called *kinetic energy*, giving the Hamiltonian $H(q, p)$ the interpretation of the *total energy*.

Coordinate transformations. We now discuss the special case where generalized coordinates are the result of a coordinate transformation from Cartesian coordinates: $q := \Phi^{-1}\mathbf{q}$, with $\Phi : \mathcal{Q} \to \mathbf{Q}$ a $\mathcal{C}^3$-diffeomorphism. The purpose of these detailed formulations is to retain the connection to the original atomic description, which in

particular provides the atoms' masses, while the potential energy is often given as a function in generalized coordinates.

To write the Hamilton ODE (1.3) in the new generalized coordinate system, the Cartesian potential $\mathbf{V}$ and mass matrix $\mathbf{M}$ have to be converted accordingly. By the principle of objectivity, we demand the potential and kinetic energy to be independent under coordinate transformation. The new potential $V(q) := \mathbf{V}\big(\Phi(q)\big)$ obviously fulfills that requirement.

The mass matrix in Cartesian coordinates consists of the physical masses of the atoms,

$$\mathbf{M} := \begin{pmatrix} \mathbf{M}_1 & & \\ & \ddots & \\ & & \mathbf{M}_n \end{pmatrix}, \quad \text{where } \mathbf{M}_i := \begin{pmatrix} m_i & & \\ & m_i & \\ & & m_i \end{pmatrix} .$$

For E_{kin} to be independent under coordinate transformation, we demand

$$p_t^\intercal M^{-1}(q_t) p_t \overset{!}{=} \mathbf{p}_t^\intercal \mathbf{M}^{-1} \mathbf{p}_t \, . \tag{1.6}$$

We have $\dot{\mathbf{q}}_t = \frac{d}{dt}\Phi(q_t) = \nabla\Phi(q_t) \cdot \dot{q}_t$, and thus the right hand side of (1.6) can be written as

$$= p_t^\intercal M^{-1}(q_t) \Big(\nabla\Phi(q_t)^\intercal \mathbf{M} \nabla\Phi(q_t) \Big) M^{-1}(q_t) p_t \, .$$

By setting $M(q) := \nabla\Phi(q)^\intercal \mathbf{M} \nabla\Phi(q)$, the two sides coincide and we have an expression for the generalized mass matrix. Clearly $M(q)$ is symmetric and positive definite, if $m_i > 0$ for all i.

In addition, this defines a momentum conversion map, analogous to the position conversion map Φ^{-1}:

$$\begin{aligned} \mathbf{p}_t = \mathbf{M}\dot{\mathbf{q}}_t &= \mathbf{M} \cdot \frac{d}{dt}\Phi(q_t) \\ &= \mathbf{M} \nabla\Phi\big(\Phi^{-1}(\mathbf{q}_t)\big) M^{-1}\big(\Phi^{-1}(\mathbf{q}_t)\big) p_t \, . \end{aligned}$$

Multiplying from left by $\nabla\Phi\big(\Phi^{-1}(\mathbf{q}_t)\big)^\intercal$ gives

$$\begin{aligned} \nabla\Phi\big(\Phi^{-1}(\mathbf{q}_t)\big)^\intercal \mathbf{p}_t &= \underbrace{\nabla\Phi\big(\Phi^{-1}(\mathbf{q}_t)\big)^\intercal \mathbf{M} \nabla\Phi\big(\Phi^{-1}(\mathbf{q}_t)\big)}_{= M\left(\Phi^{-1}(\mathbf{q}_t)\right)} M^{-1}\big(\Phi^{-1}(\mathbf{q}_t)\big) p_t \\ &= p_t \, . \end{aligned}$$

Thus, a given set $(\mathbf{q}, \mathbf{p})$ of Cartesian coordinates can be converted to generalized coordinates via

$$\Psi : (\mathbf{q}, \mathbf{p}) \mapsto \big(\Phi^{-1}(\mathbf{q}), \nabla\Phi\big(\Phi^{-1}(\mathbf{q})\big)^\intercal \mathbf{p}\big) =: (q, p) \, . \tag{1.7}$$

In a differential geometric interpretation, this is the pullback between $\mathcal{Q}$ and $\mathbf{Q}$ (interpreted as manifolds). Note that as Φ is a $\mathcal{C}^3$-diffeomorphism, $\Psi \in \mathcal{C}^2(\mathbf{\Omega}, \Omega)$.

1.2.3. Langevin dynamics

Hamiltonian dynamics describe the motion of a molecule in vacuum, without any external influence. Of more physical interest, however, are systems which are stochastically coupled to their surroundings, physically motivated by the presence of a heat bath or implicit solvent not modeled explicitly. A prominent way of doing this is via a stochastic perturbation of (1.5), known as the *Langevin equations of motion* [41, 66, 74]. In generalized coordinates, the system is described by the following SDE:

$$\begin{aligned} \frac{d}{dt}q_t &= \nabla_p H(q_t, p_t) \\ \frac{d}{dt}p_t &= -\nabla_q H(q_t, p_t) - \gamma(q_t)\nabla_p H(q_t, p_t) + \sigma(q_t)w_t \ . \end{aligned} \tag{1.8}$$

Here, $\gamma : \mathcal{Q} \to \mathbb{R}^{d\times d}$ is called the *friction* or *damping matrix*, $\sigma : \mathcal{Q} \to \mathbb{R}^{d\times d}$ is called the *noise matrix*, and w_t is a white noise process on $\mathcal{P}$. We demand γ and σ to be symmetric positive definite with uniformly bounded inverse.

In (1.8), γ mimics the drag of (not explicitly modeled) solvent atoms on the molecule's degrees of freedom q, thus decreasing its acceleration. Likewise, the term σw_t stands for random collisions with said solvent, causing random Brownian fluctuations in the momentum variable p.

The interplay of γ and σ is what determines the stochastic system's average internal energy. Setting $\beta := 1/(k_B T)$, with k_B the Boltzmann constant, in order for the system to remain at constant temperature T, γ and σ have to fulfill

$$2\gamma(q) = \beta\sigma(q)\sigma(q)^\intercal \quad \text{for all } q \in \mathcal{Q} \ . \tag{1.9}$$

Equation (1.9) is called the *fluctuation-dissipation relation*, and we demand γ and σ to fulfill it for all our systems.

Equation (1.8) is an Itô SDE on Ω and can be brought to the general form (1.1) by setting $x_t := (q_t, p_t)$ and

$$b(q_t, p_t) = \begin{pmatrix} \nabla_p H(q_t, q_t) \\ -\nabla_q H(q_t, p_t) - \gamma(q_t)\nabla_p H(q_t, p_t) \end{pmatrix} \ , \quad \Sigma(q_t, p_t) = \begin{pmatrix} 0 & 0 \\ 0 & \sigma(q_t) \end{pmatrix} \ , \tag{1.10}$$

where 0 in Σ is the d-dimensional zero matrix.

As mentioned in the introduction, the Langevin system can be formally derived from a larger deterministic Hamiltonian system that explicitly models the solvent degrees of freedom. This is done via averaging and homogenization techniques, also known as the Mori-Zwanzig formalism (see e.g. [55]). However, we omit a rigorous derivation of (1.8) and settle for the intuitive friction/noise interpretation instead.

Coordinate transformation. In Cartesian coordinates, the Langevin SDE reads

$$\begin{aligned} \frac{d}{dt}\mathbf{q}_t &= \mathbf{M}^{-1}\mathbf{p}_t \\ \frac{d}{dt}\mathbf{p}_t &= -\nabla_{\mathbf{q}}\mathbf{V}(\mathbf{q}_t) - \boldsymbol{\gamma}\mathbf{M}^{-1}\mathbf{p}_t + \boldsymbol{\sigma}\mathbf{w}_t \,, \end{aligned} \tag{1.11}$$

where now $\boldsymbol{\gamma}, \boldsymbol{\sigma} > 0$ are real numbers fulfilling $2\boldsymbol{\gamma} = \beta\sigma^2$, and $\mathbf{w}_t$ is a white noise process on $\mathbb{R}^{3n}$.

Applying the coordinate transformation Ψ from (1.7) to (1.11) by setting $(q_t, p_t) := \Psi(\mathbf{q}_t, \mathbf{p}_t)$, one then gets the following SDE for (q_t, p_t):

$$\begin{aligned} \frac{d}{dt}q_t &= M^{-1}(q_t)p_t \\ \frac{d}{dt}p_t &= -\nabla_q\Big(\frac{1}{2}p_t^{\intercal}M^{-1}(q_t)p_t\Big) - \nabla_q V(q_t) \\ &\quad - \nabla\Phi(q_t)^{\intercal}\boldsymbol{\gamma}\nabla\Phi(q_t)M(q)p_t + \nabla\Phi(q_t)\boldsymbol{\sigma}w_t \,, \end{aligned} \tag{1.12}$$

were we already inserted the transformed potential $V = \mathbf{V} \circ \Phi$ and mass matrix $M = \nabla\Phi^{\intercal}\mathbf{M}\nabla\Phi$.

With the Hamiltonian in generalized coordinates,

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

and the new friction and noise coefficients

$$\gamma(q) := \nabla\Phi(q_t)^{\intercal}\boldsymbol{\gamma}\nabla\Phi(q_t), \quad \sigma(q) := \nabla\Phi(q_t)\boldsymbol{\sigma} \,,$$

(1.12) takes exactly the form of (1.8).

Due to Itôs formula [50, Theorem 4.2.1], the transformed Langevin equation again is an Itô diffusion. Also, the new drag and noise coefficients γ, σ again satisfy the fluctuation-dissipation relation.

Remark. An analogue of equation (1.8) for dynamics on Riemannian manifolds has been derived by Hartmann in [5].

1.2.4. Smoluchowski dynamics

Smoluchowski dynamics, also called *Brownian dynamics* or *overdamped Langevin dynamics*, is another Itô process that will play an important role throughout this thesis. It is described by an SDE on $\mathcal{Q}$ only:

$$\gamma(q_t)\frac{d}{dt}q_t = -\nabla V(q_t) + \sigma(q_t)w_t \,, \tag{1.13}$$

with γ, σ and w_t having the same interpretations and properties as in (1.8).

Conceptually, the equation can be derived by rescaling the friction parameter $\gamma \mapsto \varepsilon^{-1}\gamma$ for small ε, and simultaneously rescaling the time frame to compensate for the now increasingly slow dynamics: $t \mapsto \varepsilon t$. The limit $\varepsilon \to 0$, called the *Smoluchowski-Kramers* or shortly *Smoluchowski limit*, then yields (1.13).

For a precise derivation of (1.13) on the SDE level, see [48]. We will come back to discussing (and then interpreting) the Smoluchowski limit in Section 2.1.2 and Appendix A.2 in the context of density transport equations.

2. Statistical mechanics and metastability

2.1. Density transport under Itô dynamics

As pointed out in the introduction, our task is metastability analysis. A rigorous definition of metastability will follow soon, but for now, have in mind the following intuition: for the general Itô process (1.1), a set $A \subset \mathcal{X}$ can be called metastable, if all paths of the process x_t starting in $x_0 \in A$ remain in A with high probability. We thus have to track the time evolution of this uncountable number of systems (also called an *ensemble*). This shift from single system dynamics to *ensemble dynamics* is what is generally known as statistical mechanics, and will lead to the definition of our central objects of interest, the transfer operators.

2.1.1. Transfer operators

Let $f \in \mathcal{L}^1(\mathcal{X})$[1] be a probability density function with respect to the Lebesgue measure m. We are now interested in the time evolution of f under the dynamics, or rather that of an ensemble distributed according to f: Given that $x_0 \sim f_0 := f$, what is f_t such that $x_t \sim f_t$, assuming that x_0 evolves under (1.1)?

For this, consider the *stochastic transition function* $p : \mathbb{R}_{\geq 0} \times \mathcal{X} \times \mathcal{B}(\mathcal{X}) \to [0, 1]$,

$$p(t, x, B) = \text{Prob}\left[x_t \in B \,|\, x_0 = x\right]. \tag{2.1}$$

We then have that $x_t \sim f_t$ with

$$\int_B f_t(x)\, dm(x) = \int_{\mathcal{X}} f_0(x) p(t, x, B)\, dm(x), \qquad \forall\, B \in \mathcal{B}(\mathcal{X}). \tag{2.2}$$

Under mild conditions[2], satisfied by the Langevin and the Smoluchowski equation, f_t is uniquely defined by (2.2). This in turn defines the *transfer operator with respect to m* with lag time t via

$$\bar{P}^t f(x) := f_t(x) \tag{2.3}$$

[1] In the literature, $\mathcal{L}^p$ sometimes denotes the "pre-Lebesgue space", i.e. the Lebesgue space before equivalence class formation, and L^p usually denotes the actual Lebesgue space. Due to clash of notation, however, we call the actual Lebesgue space $\mathcal{L}^p$ and use $\|\cdot\|_p$ to denote the standard p-norm.

[2] See the discussion about existence and uniqueness of solutions of the associated Fokker–Planck equation in Section 2.1.2.

where $\bar{P}^t : \mathcal{L}^1(\mathcal{X}) \to \mathcal{L}^1(\mathcal{X})$ and we extend the definition of $\bar{P}^t$ from densities to arbitrary $\mathcal{L}^1(\mathcal{X})$-integrable functions using the linearity of (2.2) in f_0.

In the deterministic case (1.2) with solution $x_t = \Xi^t(x_0)$, $\Xi^t : \mathcal{X} \to \mathcal{X}$ the flow of the ODE, $\bar{P}^t$ is the well-known *Perron–Frobenius operator* [41]:

$$\bar{P}^t f(x) = f\big(\Xi^{-t}(x)\big) \cdot \left|\nabla_x \Xi^{-t}(x)\right| .$$

Invariant densities and the weighted transfer operator. Invariant densities will play an important role, primarily as reference for other "sub-densities". Let $f_\mathcal{X} \in \mathcal{L}^1(\mathcal{X})$ be such that $\bar{P}^t f_\mathcal{X} = f_\mathcal{X}$ for all $t \geq 0$, and let $u : \mathcal{X} \to \mathbb{R}$ be such that $u \cdot f_\mathcal{X} \in \mathcal{L}^1(\mathcal{X})$. With the measure $\mu_\mathcal{X}$ defined via $d\mu_\mathcal{X} = f_\mathcal{X} dm$, this means $u \in \mathcal{L}^1_{\mu_\mathcal{X}}(\mathcal{X})$. The function u can be considered a "portion" of the invariant density $f_\mathcal{X}$.

The transport of u can again be expressed via a transfer operator. Applying (2.2) to $f_0 := u_0 f_\mathcal{X}$ allows us to track the evolution of u_t:

$$\begin{aligned} \int_B u_t(x)\, d\mu_\mathcal{X}(x) &= \int_B u_t(x) f_\mathcal{X}(x)\, dm(x) \\ &\overset{(*)}{=} \int_\mathcal{X} u_0(x) f_\mathcal{X}(x) p(t,x,B)\, dm(x) \\ &= \int_\mathcal{X} u_0(x) p(t,x,B)\, d\mu_\mathcal{X}(x), \end{aligned} \tag{2.4}$$

where for $(*)$ the invariance of $f_\mathcal{X}$ and (2.2) was used. Again, under suitable conditions, including the non-singularity of $\mu_\mathcal{X}$, this uniquely defines u_t. Written in operator form,

$$P^t u_0 := u_t, \tag{2.5}$$

where $P^t : \mathcal{L}^1_{\mu_\mathcal{X}}(\mathcal{X}) \to \mathcal{L}^1_{\mu_\mathcal{X}}(\mathcal{X})$ is called the *transfer operator with respect to* $\mu_\mathcal{X}$ or the *$\mu_\mathcal{X}$-weighted transfer operator*. However, in the following we will more often use P^t instead of $\bar{P}^t$, and thus usually omit the reference to $\mu_\mathcal{X}$. The definition of P^t of course depends on the specific choice of $f_\mathcal{X}$, but the relevant systems possess exactly one invariant density.

The conversion between $\bar{P}^t$ and P^t is a simple reweighting:

$$P^t u = \frac{\bar{P}^t(u f_\mathcal{X})}{f_\mathcal{X}}, \qquad \bar{P}^t f = P^t\big(f/f_\mathcal{X}\big) f_\mathcal{X} . \tag{2.6}$$

Properties

We state some useful and defining properties of P^t. Because of (2.6), all of them hold for $\bar{P}^t$ as well, as has been show in [6]. Thus, working with P^t instead of $\bar{P}^t$ is only a matter of convenience, as this will simplify some calculations in Section 3.2.

Additionally, "transporting portions of the invariant density" will fit our intuition in metastability analysis.

It will however be necessary to distinguish between the transfer operators of the general Itô diffusion, and the special cases of the Langevin and Smoluchowski dynamics. They will be referred to as P^t, P^t_{Lan} and P^t_{Smol}, respectively. The corresponding transition functions are denoted p, p_{Lan} and p_{Smol}. Of course, statements concerning P^t will hold for P^t_{Lan} and P^t_{Smol} as well.

Domain and spectrum. While a stochastic interpretation makes sense only in the preceding setting (i.e. on $\mathcal{L}^1_{\mu_\mathcal{X}}(\mathcal{X})$), the formal extension of P^t to the spaces $\mathcal{L}^k_{\mu_\mathcal{X}}(\mathcal{X})$, $1 \leq k \leq \infty$, is well defined for proper choices of $\mu_\mathcal{X}$:

Corollary 2.1.1 ([3, Corollary to Lemma 1])**.** *Let T^t be a transfer operator associated with a transition function having an invariant measure μ. Then T^t is a well-defined contraction on $\mathcal{L}^k_\mu$ for every $1 \leq k \leq \infty$.*

We will see in Section 2.1.2 that for P^t_{Lan} and P^t_{Smol} the existence of a unique invariant measure is always ensured.

Due to being a contraction, P^t possesses a spectrum inside the complex unit circle, on every $\mathcal{L}^k_{\mu_\mathcal{X}}(\mathcal{X})$. Moreover, on the subspace $\{u \in \mathcal{L}^1_{\mu_\mathcal{X}}(\mathcal{X}) \mid u > 0\}$, P^t is norm-preserving, i.e. P^t maps densities onto densities.

Semigroup properties. One of the most characteristic features of P^t is the *semigroup property* (also called the *Chapman-Kolmogorov property*) [41, Corollary 11.8.1]:

(i) $P^t\big|_{t=0} f = f$,

(ii) $P^{t+s} f = P^s\big(P^t f\big)$ for all $s, t \geq 0$.

The second point follows from the identity

$$p(t+s, x, B) = \int_\Omega p(t, x, y) p(s, y, B)\, dy, \tag{2.7}$$

where $p(t, x, y)$ is the Radon-Nikodym derivative [41, Definition 3.1.4] of $p(t, y, B)$, i.e. for $y \in \mathcal{X}$, $B \subset \mathcal{X}$,

$$p(t, y, B) = \int_B p(s, y, x)\, dx\ .$$

Equation (2.7) is known as the *Markov property*, which holds for any autonomous Itô diffusion process [50, Theorem 7.1.2]. Stochastic processes which satisfy (2.7) are called *Markov processes*. In the deterministic case this simply reads $\Xi^{t+s}(x) = \Xi^s\big(\Xi^t(x)\big)$.

Under the right regularity conditions[3] on b, σ in (1.1), the transfer operator P^t satisfies the stronger C^0–semigroup[4] property

(i') $\lim_{t\to 0} P^t f = f$,

(ii) $P^{t+s} f = P^s\big(P^t f\big)$ for all $s, t \geq 0$.

We assume from now on that for Langevin and Smoluchowski dynamics b and σ, i.e. V, γ and σ in (1.8) and (1.13), satisfy these conditions.

Reversibility and self-adjointness. In general, the transfer operator of a general Itô diffusion process is *not* self-adjoint on $\mathcal{L}^2_{\mu_\mathcal{X}}(\mathcal{X})$ [84, p. 41], i.e.

$$\langle P^t f, g\rangle_{\mu_\mathcal{X}} \neq \langle f, P^t g\rangle_{\mu_\mathcal{X}} \quad \text{with} \quad \langle f, g\rangle_{\mu_\mathcal{X}} = \int_\mathcal{X} fg \, d\mu_\mathcal{X}.$$

In particular, the Langevin transfer operator P^t_{Lan} is not self-adjoint on $\mathcal{L}^2_{\mu_\Omega}(\Omega)$, thus its spectrum is not necessarily real. As we will see in Section 2.1.4, this makes interpreting eigenvalues of P^t in the context of metastability analysis difficult. However, it has been shown by Schütte and Sarich [64, Theorem 4.12] that the restriction of P^t_{Lan} to the space spanned by its dominant eigenfunctions is self-adjoint, thus at least the dominant eigenvalues of P^t_{Lan} are real.

The Smoluchowski transfer operator on the other hand *is* self adjoint on $\mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q})$, as has been shown in [34, Proposition 2.2].

Geometric ergodicity. The notion of geometric ergodicity helps to understand the long-time ensemble dynamics, to be precise the convergence of the stochastic transition function towards the invariant measure:

Definition 2.1.2. Let x_t, where t denotes either discrete or continuous time, be a Markov process with transition function $p(t, \cdot, \cdot)$ and unique invariant measure $\mu_\mathcal{X}$. Then x_t is called *geometrically ergodic* if for every state $x \in \mathcal{X}$ and time t

$$\|p(t, x, \cdot) - \mu_\mathcal{X}\|_{\text{TV}} \leq M(x)\rho^t$$

holds for some $M \in \mathcal{L}^1_{\mu_\mathcal{X}}(\mathcal{X})$ and $\rho < 1$. Here, $\|\cdot\|_{\text{TV}}$ denotes the total variation norm for signed measures.

Geometric ergodicity has been shown in [34, Proposition 6.3] for Langevin dynamics in Cartesian coordinates. As its proof is a direct consequence of [45, Theorem 3.2] (see also [46]), which can also be applied to Langevin dynamics in generalized coordinates, we have

[3] The conditions have to ensure that the associated Fokker–Planck equation (2.12) with initial value f_0 possesses a classical solution f_t for which holds $f_t \to f_0$ $(t \to 0)$. P^t is then the solution operator of the equation and thus satisfies (i'). Also see [41, Definition 11.7.2].

[4] read: "continuous semigroup"

Proposition 2.1.3. *Let x_t denote the Langevin process in generalized coordinates. Fix some lag time $t > 0$, and let $z_n := x_{nt}$ be the sampled time process. In either of the following cases, z_n has the unique invariant measure μ_Ω and is geometrically ergodic.*

(i) The state space $\mathcal{Q}$ is periodic and the potential $V : \mathcal{Q} \to \mathbb{R}$ is smooth.

(ii) The state space $\mathcal{Q} = \mathbb{R}^d$, the potential $V : \mathcal{Q} \to \mathbb{R}_{\geq 0}$ is smooth and $V(q)$ is growing at infinity as $\|q\|^{2l}$ for some positive integer l.

We assume from now on that either condition (i) or (ii) of Proposition 2.1.3 is satisfied. This means, in particular, that for a fixed $t > 0$ there is a function $M \in \mathcal{L}^1_{\mu_\Omega}(\Omega)$ and a constant $\rho < 1$ such that for every $q \in \mathcal{Q}$ and $p \in \mathcal{P}$ holds

$$\|p_{\mathrm{Lan}}(nt, (q,p), \cdot) - \mu_\Omega\|_{\mathrm{TV}} \leq M(q,p)\rho^n \,. \tag{2.8}$$

2.1.2. Infinitesimal generators and the Fokker–Planck equation

The $\mathcal{C}^0$–semigroup property can be interpreted as "memorylessness" of $\bar{P}^t$. The crucial identity $\bar{P}^t = \left(\bar{P}^{t/n}\right)^n$ suggests that all information about the density transport is contained in $\bar{P}^\tau$ for *arbitrarily small* τ.

This suggests to study the operator $\bar{L} : \mathcal{D}(\bar{L}) \to \mathcal{L}^k(\mathcal{X})$ given by

$$\bar{L}f := \lim_{\tau \to 0} \frac{\bar{P}^\tau f - f}{\tau}, \tag{2.9}$$

where $\mathcal{D}(\bar{L}) \subset \mathcal{L}^k(\mathcal{X})$ is the linear subspace of $\mathcal{L}^k(\mathcal{X})$ where the above limit exists. $\bar{L}$ is called the *infinitesimal generator* (or short *generator*) of the semigroup $\bar{P}^t$. The power of the generator lies in the fact that all the relevant information about $\bar{P}^t$ for *all times* $t \geq 0$ is already encoded in $\bar{L}$. This will be formalized below.

Definition (2.9) also appears when constructing a differential equation for the transport of some density f_t under the dynamics:

$$\partial_t f_t(x) = \lim_{\tau \to 0} \frac{f_{t+\tau}(x) - f_t(x)}{\tau} = \lim_{\tau \to 0} \frac{\bar{P}^\tau f_t(x) - f_t(x)}{\tau} = \bar{L} f_t(x). \tag{2.10}$$

Thus, $\bar{L}$ can be understood as the differential operator of the Cauchy problem

$$\partial_t f_t = \bar{L} f_t, \qquad f_t\big|_{t=0} = f_0 \,. \tag{2.11}$$

Under the right conditions on b, σ, (2.11) possesses a classical solution and P^t is its solution operator [56, Theorem 4.1.4]. Further discussion on existence and uniqueness of solutions for the general Itô case can also be found in literature on Brownian motion and diffusion processes, see for example [48, 38].

Equation (2.11) is called the *Fokker–Planck equation* or *Kolmogorov forward equation* of the diffusion process 1.1 and is a linear homogeneous partial differential equation. In coordinates, it reads [41, Theorem 11.6.1]

$$\partial_t f_t(x) = \underbrace{\frac{1}{2}\sum_{i,j}\frac{\partial^2}{\partial x_i \partial x_j}\big(\Sigma_{ij}(x) f_t(x)\big) - \sum_i \frac{\partial}{\partial x_i}\big(b_i(x) f_t(x)\big)}_{=Lf_t(x)} . \tag{2.12}$$

Langevin Fokker–Planck equation. We are mostly interested in the Langevin version of this equation, i.e.

$$\partial_t f_t(q,p) = \bar{L}_{\mathrm{Lan}} f_t(q,p) \qquad f_t\big|_{t=0} = f_0 . \tag{2.13}$$

Grouping the terms on the right hand side of (1.8) according to

$$b(q,p) = \begin{pmatrix} \nabla_p H(q,p) \\ -\nabla_q H(q,p) - \gamma(q)\nabla_p H(q,p) \end{pmatrix}, \qquad \Sigma(q,p) = \begin{pmatrix} 0 & 0 \\ 0 & \sigma(q)\sigma(q)^\intercal \end{pmatrix}$$

and inserting them into (2.12), one can write

$$\bar{L}_{\mathrm{Lan}} = \bar{L}_{\mathrm{Ham}} + \bar{L}_{\mathrm{OU}} \tag{2.14}$$

with

$$\begin{aligned} \bar{L}_{\mathrm{Ham}} f &:= \nabla_q H^\intercal \nabla_p f - \nabla_p H^\intercal \nabla_q f , \\ \bar{L}_{\mathrm{OU}} f &:= \frac{1}{2}\sigma\sigma^\intercal : \nabla_p^2 f + (\gamma M^{-1} p)^\intercal \nabla_p f + (\gamma : M^{-1}) f . \end{aligned} \tag{2.15}$$

Here, ∇f denotes the gradient of f, assumed to be a column vector, and $\nabla^2 f$ is the Hessian of f. Moreover, we denote by $\nabla^\intercal f$ the divergence of f.

To express the results as compactly as possible, we also make use of the generalized *Frobenius product* for tensors (also known as *tensor contraction*). Define for tensors $A \in \mathbb{R}^{n_1 \times \ldots \times n_{d_1}}$, $B \in \mathbb{R}^{n_1 \times \ldots \times n_{d_2}}$ and $d_1 \leq d_2$

$$(A : B) := \sum_{j_1=1}^{n_1} \ldots \sum_{j_{d_1}=1}^{n_{d_1}} A(j_1, \ldots, j_{d_1}) \cdot B(j_1, \ldots, j_{d_1}, :, \ldots, :) \tag{2.16}$$

where arguments in A and B represent indices and a colon in the argument means all values in the respective dimension. The result is a $(d_2 - d_1)$-tensor. For $d_2 \leq d_1$, the definition is analogous.

Equation (2.14) can be seen as application of the Lie-Trotter splitting method for evolution equations [73]. The two components then have individual interpretations:

- $\bar{L}_{\mathrm{Ham}}$ is the generator of the deterministic Hamilton process

$$\partial_t q_t = \nabla_p H(q_t, p_t), \quad \partial_t p_t = -\nabla_q H(q_t, p_t)\ ,$$

  whose associated Fokker–Planck equation is known as the *Liouville equation*.

- $\bar{L}_{\mathrm{OU}}$ is the generator of an *Ornstein-Uhlenbeck process* [38] in p:

$$\partial_t p_t = -\gamma(q)M^{-1}(q)p_t + \sigma(q)w_t\ , \tag{2.17}$$

  in which q appears only as a parameter.

Weighted Langevin Fokker–Planck equation. As P^t, the transfer operator with respect to the invariant measure $\mu_{\mathcal{X}}$, is also a $\mathcal{C}^0$-semigroup, all the statements about $\bar{P}^t$ from the beginning of this section hold for P^t as well. Thus, for the density transport with respect to the invariant measure $\mu_{\mathcal{X}}$, i.e. $u_t = P^t u_0,\ u_0 \in \mathcal{L}^k_{\mu_{\mathcal{X}}}(\mathcal{X})$, the definition of an infinitesimal generator $L : \mathcal{D}(L) \to \mathcal{L}^k_{\mu_{\mathcal{X}}}(\mathcal{X}),\ \mathcal{D}(L) \subset \mathcal{L}^k_{\mu_{\mathcal{X}}}(\mathcal{X})$ is completely analogous. Define

$$Lu := \lim_{\tau \to 0} \frac{P^\tau u - u}{\tau}, \tag{2.18}$$

which again induces a Cauchy problem:

$$\partial_t u_t = L u_t, \qquad u_t\big|_{t=0} = u_0. \tag{2.19}$$

We want to derive a coordinate expression for L for Langevin dynamics, analogous to (2.15). For that, we will need to specify the invariant densities on the basis of which the weighted transfer operator P^t is defined. Set

$$f_\Omega(q,p) := f_{\mathcal{Q}}(q) \cdot f_{\mathcal{P}}(q,p), \tag{2.20}$$

where

$$f_{\mathcal{Q}}(q) := \frac{1}{Z_{\mathcal{Q}}} \exp\big(-\beta V(q)\big), \qquad f_{\mathcal{P}}(q,p) := \frac{1}{Z_{\mathcal{P}}(q)} \exp\big(-\frac{\beta}{2} p^\intercal M^{-1}(q) p\big),$$

with the normalizing factors

$$Z_{\mathcal{P}}(q) := \int_{\mathcal{P}} \exp\big(-\frac{\beta}{2} p^\intercal M(q)^{-1} p\big) dp\ , \quad Z_{\mathcal{Q}} := \int_{\mathcal{Q}} \exp\big(-\beta V(q)\big) dq\ .$$

The existence of $f_{\mathcal{Q}}$ and f_Ω requires the integrability of $\exp(-\beta V)$, which follows from the assumption that V is at most polynomially growing at infinity, see Section 1.2.2.

The densities f_Ω and $f_{\mathcal{Q}}$, are then the unique invariant densities for the Langevin- and Smoluchowski processes, respectively:

$$\bar{P}^t_{\mathrm{Lan}} f_\Omega = f_\Omega\ , \qquad \bar{P}^t_{\mathrm{Smol}} f_{\mathcal{Q}} = f_{\mathcal{Q}}\ ,$$

and describe the *Boltzmann* (or *Gibbs*) *distribution* of the respective dynamics.

An explicit expression for L_{Lan} can now be derived by applying $\bar{L}_{\text{Lan}}$ to $u_t f_\Omega$:

$$\partial_t(u_t f_\Omega) = \bar{L}_{\text{Lan}}(u_t f_\Omega) = \bar{L}_{\text{Ham}}(u_t f_\Omega) + \bar{L}_{\text{OU}}(u_t f_\Omega)\ . \tag{2.21}$$

Expanding the two summands and applying the product rule for gradients yields

$$\begin{aligned}\bar{L}_{\text{Ham}}(u_t f_\Omega) &= \nabla_q H \cdot \nabla_p(u_t f_\Omega) - \nabla_p H \cdot \nabla_q(u_t f_\Omega)\\ &= \nabla_q H \cdot \big(\nabla_p u_t f_\Omega + u_t f_\Omega(-\beta\nabla_p H)\big) - \nabla_p H \cdot \big(\nabla_q u_t f_\Omega + u_t f_\Omega(-\beta\nabla_q H)\big)\\ &= \big(\nabla_q H \cdot \nabla_p u_t - \nabla_p H \cdot \nabla_q u_t\big) f_\Omega,\end{aligned} \tag{2.22}$$

and

$$\begin{aligned}\bar{L}_{\text{OU}}(u_t f_\Omega) &= \frac{1}{2}\sigma\sigma^\intercal : \nabla_p^2(u_t f_\Omega) + (\gamma M^{-1}p)^\intercal \nabla_p(u_t f_\Omega) + (\gamma : M^{-1})(u_t f_\Omega)\\ &= \frac{1}{2}\sigma\sigma^\intercal : \Big[\big(\nabla_p^2 u_t\big) f_\Omega + 2\nabla_p u_t(-\beta M^{-1}p)^\intercal f_\Omega\\ &\qquad + u_t(-\beta M^{-1}) f_\Omega + u_t\beta^2(M^{-1}p)(M^{-1}p)^\intercal f_\Omega\Big]\\ &\qquad + (\gamma M^{-1}p)^\intercal\big(\nabla_p u_t f_\Omega + u_t(-\beta M^{-1}p) f_\Omega\big) + (\gamma : M^{-1}) u_t f_\Omega\ ,\end{aligned}$$

where we used the identities $\nabla_p f_\Omega = (-\beta M^{-1}p) f_\Omega$ and $\nabla_p^2 f_\Omega = (-\beta M^{-1}) f_\Omega + \beta^2(M^{-1}p)(M^{-1}p)^\intercal f_\Omega$. With $2\gamma = \beta\sigma\sigma^\intercal$, this reduces to

$$\bar{L}_{\text{OU}}(u_t f_\Omega) = \Big(\frac{1}{2}\sigma\sigma^\intercal : \nabla_p^2 u_t - (\gamma M^{-1}p)^\intercal \nabla_p u_t\Big) f_\Omega. \tag{2.23}$$

As f_Ω is independent of t, the left hand side of (2.21) reads

$$\partial_t(u_t f_\Omega) = (\partial_t u_t) f_\Omega. \tag{2.24}$$

Combining (2.22)-(2.24) finally gives the μ_Ω-weighted Fokker–Planck equation for Langevin dynamics:

$$\partial_t u_t = L_{\text{Lan}} u_t = L_{\text{Ham}} u_t + L_{\text{OU}} u_t \tag{2.25}$$

with

$$L_{\text{Ham}} := \nabla_q H \cdot \nabla_p - \nabla_p H \cdot \nabla_q\ , \qquad L_{\text{OU}} := \frac{1}{2}\sigma\sigma^\intercal : \nabla_p^2 - (\gamma M^{-1}p)\nabla_p\ . \tag{2.26}$$

Remark. The expression of the weighted Fokker–Planck equation strongly resembles another type of transport equation; for $\varphi_t : \Omega \to \mathbb{R}$, the *Kolmogorov backward equation* reads

$$\partial_t \varphi_t = A_{\text{Lan}} \varphi_t = A_{\text{Ham}} \varphi_t + A_{\text{OU}} \varphi_t \tag{2.27}$$

with

$$A_{\text{Ham}} := \nabla_p H \cdot \nabla_q - \nabla_q H \cdot \nabla_p\ , \qquad A_{\text{OU}} := \frac{1}{2}\sigma\sigma^\intercal : \nabla_p^2 - (\gamma M^{-1}p)\nabla_p\ , \tag{2.28}$$

i.e. it only differs from the forward equation in the sign of the Hamilton generator. It can be derived from its general Itô process form [59, p. 83]

$$\partial_t \varphi_t(x) = \underbrace{\frac{1}{2}\sum_{i,j}\Sigma_{ij}(x)\frac{\partial^2}{\partial x_i \partial x_j}\varphi_t(x) + \sum_i b_i(x)\frac{\partial}{\partial x_i} f_t(x)}_{=:A}\,.$$

Equation (2.27) governs the evolution of *observables*. For any $\varphi_0 : \Omega \to \mathbb{R}$ and $x_t = (q_t, p_t)$ the solution of the SDE (1.8), for the solution φ_t of (2.27) holds

$$\varphi_t(x) = \mathbb{E}\big[\varphi_0(x_t) \;\big|\; x_0 = x\big]\;.$$

The solution operator of (2.27), the *Koopman operator*, can be interpreted as the dual of the transfer operator [50, Section 7.3].

Weighted Smoluchowski Fokker–Planck equation. For Smoluchowski dynamics, the associated Fokker–Planck equations can be compiled the same way as for Langevin dynamics: Identify the Itô parameters $b = b(q)$ and $\Sigma = \Sigma(q)$ in (1.13) and insert them in (2.12). The μ_Q-weighted Smoluchowski generator can then be cast as

$$L_{\text{Smol}} = \beta^{-1}\tilde{\Delta} - \nabla V \cdot \tilde{\nabla}\,, \tag{2.29}$$

where

$$\tilde{\nabla} u = \gamma^{-1}\nabla u \quad \text{and} \quad \tilde{\Delta} = \frac{1}{\sqrt{\det\gamma}}\nabla\cdot\Big(\sqrt{\det\gamma}\,\gamma^{-1}\nabla u\Big)\;. \tag{2.30}$$

The operator $\tilde{\Delta}$ is known as the *Laplace-Beltrami operator*.

Equation (2.31) can also be derived by taking the high-friction limit in the Langevin Fokker–Planck equation (2.25). To help the interested reader understand the deeper connection the between density transport under Langevin and Smoluchowski dynamics, we have formulated the derivation in Appendix A.2. The connection can be summarized as follows:

Lemma 2.1.4. *Let w be the solution of the μ_Q–weighted Smoluchowski transport equation*

$$\partial_t w(\cdot, t) = L_{\text{Smol}} w(\cdot, t)\;, \tag{2.31}$$

and u^ε be the solution of the μ_Q–weighted Langevin transport equation (2.25) with damping matrix γ/ε. Then

$$\big\|u^\varepsilon\big(\cdot, t/\varepsilon\big) - w(\cdot, t)\big\|_{2,\mu_\Omega} \to 0, \quad (\varepsilon \to 0). \tag{2.32}$$

Note that the solutions u^ε and w are compared to each other on different time scales. We have thus no reason to expect that transition rates from the Smoluchowski process approximate in any way the rates of the non–rescaled Langevin process. This will be confirmed later in numerical experiments.

2.1.3. The spectral mapping theorem

General semigroup theory provides more insight into the relationship between transfer operators and their generators. Let $\mathcal{M}$ be a Banach space, $T^t : \mathcal{M} \to \mathcal{M}$ be a C_0–semigroup of operators and A be its infinitesimal generator.

Under additional assumptions, T^t can easily be computed from A:

Theorem 2.1.5 ([56], Corollary 1.4)**.** *Let A, T^t be as above, and A additionally be bounded. Then*

$$T^t = e^{tA} = \sum_{k=0}^{\infty} \frac{(tA)^k}{k!}.$$

The boundedness of A ensures the global existence of the right–hand series. It is in this case equivalent to T^t being a *uniformly continuous* semigroup of bounded linear operators, i.e. $\lim_{t\to 0} \| T^t - \mathrm{Id} \| = 0$.

Unfortunately, the Itô transfer operators P^t and $\bar{P}^t$ are not uniformly continuous semigroups in general. Thus, for our intents and purposes, the principal connection between a semigroup of operators and their generator is given by the following, slightly weaker, spectral mapping theorem:

Theorem 2.1.6 (Spectral mapping theorem [56])**.** *Let $\mathcal{M}$ be a Banach space, $T^t : \mathcal{M} \to \mathcal{M}$, $t \geq 0$, a C_0 semigroup of bounded linear operators and let A be its infinitesimal generator. Then*

$$e^{t\sigma_p(A)} \subset \sigma_p(T^t) \subset e^{t\sigma_p(A)} \cup \{0\},$$

with σ_p denoting the point spectrum. The corresponding eigenfunctions are identical.

We can immediately deduce the following assertions.

Corollary 2.1.7. *A function u is an invariant density of P^t for all $t \geq 0$, if and only if $Lu = 0$.*

Corollary 2.1.8. *Since P^t is a contraction in $\mathcal{L}^k_{\mu_\Omega}(\Omega)$, the eigenvalues of L lie in the left complex half-plane.*

While the intuition "$P^t = \sum_{k=0}^{\infty} \frac{t^k}{k!} L^k$" is false in general, P^t can be approximated by a truncated "Taylor series", at least pointwise, in the space

$$\mathcal{V}^N(\Omega) := \left\{ u \in \mathcal{C}^{2N}(\Omega) \;\middle|\; L^n u \in \mathcal{L}^2_{\mu_\Omega}(\Omega) \;\; \forall n = 0, \ldots, N \right\}. \tag{2.33}$$

Think of $\mathcal{V}^N(\Omega)$ as an analog to the Sobolev space $\mathcal{W}^{2,2N}(\Omega)$, with L^n taking the role of the differential operator D^α, $|\alpha| = n$. We require u to be $2N$-times continuously differentiable, as this is the highest derivative occurring in L^N, see (2.12).

The following convergence result also holds true if choosing $\mathcal{L}^k_{\mu_\Omega}(\Omega)$ instead of $\mathcal{L}^2_{\mu_\Omega}(\Omega)$ in the definition of $\mathcal{V}^N(\Omega)$, and correspondingly regarding the norm $\| \cdot \|_{k,\mu_\Omega}$. However, we state it for $\mathcal{L}^2_{\mu_\Omega}(\Omega)$ only, as this is the space we are ultimately operating in.

Proposition 2.1.9 ([6, Proposition 2.5]). *Let $u \in \mathcal{V}^{N+1}(\Omega)$. Then*

$$\Big\| P^t u - \sum_{n=0}^{N} \frac{t^n}{n!} L^n u \Big\|_{2,\mu_\Omega} = \mathcal{O}(t^{N+1}) \text{ for } t \to 0.$$

Proof. Let $u \in \mathcal{V}^{N+1}(\Omega)$. Then, $P^t u : t \mapsto \mathcal{L}^1_{\mu_\Omega}(\Omega)$ is $N+1$ times differentiable in t because $\partial^k P^t\big|_{t=0} u = L^k f$, $k \leq N+1$ exist as per choice of u. A Taylor series expansion for Banach space valued functions can for example be found in [82, Section 4.5]. Application to $P^t u$ as a function in t yields

$$P^t u = \sum_{n=0}^{N} \frac{t^n}{n!} L^n u + \Big(\int_0^1 \frac{1}{N!} (1-s)^N \partial_s^{N+1} P^{st} u \, ds \Big) t^{N+1}.$$

We estimate the remainder:

$$\Big\| P^t u - \sum_{n=0}^{N} \frac{t^n}{n!} L^n u \Big\|_{2,\mu_\Omega} = \Big\| \int_0^1 \frac{1}{N!} (1-s)^N \partial_s^{N+1} P^{st} u \, ds \Big\|_{2,\mu_\Omega} t^{N+1}.$$

As we are interested in the limit $t \to 0$ we can assume $t < 1$. In that case, $st < s$, and therefore

$$\leq \frac{t^{N+1}}{N!} \sup_{s\in[0,1]} \big\| \partial_s^{N+1} P^s f \big\|_{2,\mu_\Omega}.$$

$P^t u$ is the solution of the Fokker–Planck equation (2.19), and thus $\partial_s P^s u = L P^s u$ and, by extension, $\partial_s^{N+1} P^s u = L^{N+1} P^s u$. It is easy to see from the definition of the generator (2.18) that the transfer operator and its generator commute, thus $L P^s u = P^s L u$. Therefore,

$$\begin{aligned} \frac{t^{N+1}}{N!} \sup_{s\in[0,1]} \big\| \partial_s^{N+1} P^s u \big\|_{2,\mu_\Omega} &= \frac{t^{N+1}}{N!} \sup_{s\in[0,1]} \big\| P^s L^{N+1} u \big\|_{2,\mu_\Omega} \\ &\leq \frac{t^{N+1}}{N!} \sup_{s\in[0,1]} \underbrace{\big\| P^s \big\|_{2,\mu_\Omega}}_{\leq 1} \big\| L^{N+1} u \big\|_{2,\mu_\Omega}. \end{aligned}$$

In the last line, $\big\| P^s \big\|_{2,\mu_\Omega} \leq 1$ holds because P^t is a contraction (Corollary 2.1.1). As $L^{N+1} u \in \mathcal{L}^2_{\mu_\Omega}(\Omega)$ by the choice of $u \in \mathcal{V}^{N+1}(\Omega)$, $\|L^{N+1} u\|$ is finite and independent of t. This completes the proof. □

2.1.4. Metastability

Based on the stochastic transition function 2.1, we define by

$$p_{\mu_\mathcal{X}}(t, A, B) := \mathrm{Prob}_{\mu_\mathcal{X}} [x_t \in B \,|\, x_0 \in A] \tag{2.34}$$

the *transition probability* between two $\mu_{\mathcal{X}}$-measurable sets $A, B \subset \mathcal{X}$, where $\text{Prob}_{\mu_{\mathcal{X}}}$ indicates that $x_0 \sim \mu_{\mathcal{X}}$; i.e. the initial condition is distributed according to $\mu_{\mathcal{X}}$. In the case of our physically motivated systems, i.e. assuming the existence of a unique invariant measure $\mu_{\mathcal{X}}$ with density $f_{\mathcal{X}}$, the transition probabilities can then be expressed via the transfer operator P^t:

$$p_{\mu_{\mathcal{X}}}(t, A, B) = \frac{1}{\mu_{\mathcal{X}}(A)} \int_B P^t \chi_A \, d\mu_{\mathcal{X}} = \frac{1}{\mu_{\mathcal{X}}(A)} \int_{\mathcal{X}} P^t \chi_A \chi_B \, d\mu_{\mathcal{X}} = \frac{\langle P^t \chi_A, \chi_B \rangle_{\mu_{\mathcal{X}}}}{\langle \chi_A, \chi_A \rangle_{\mu_{\mathcal{X}}}} \ . \quad (2.35)$$

Here, $\langle \cdot, \cdot \rangle_{\mu_{\mathcal{X}}}$ is the standard scalar product on $\mathcal{L}^2_{\mu_{\mathcal{X}}}(\Omega)$ and χ is the indicator function. A set $A \subset \mathcal{X}$ is now called *metastable*[5], if $p_{\mu_{\mathcal{X}}}(t, A, A) \approx 1$. The value $p_{\mu_{\mathcal{X}}}(t, A, A)$ is called the *degree of metastability* of A.

Equation (2.35) hints at the role of dominant eigenfunctions of P^t for metastability analysis: If χ_A were an eigenfunction at eigenvalue $\lambda \approx 1$, then

$$p_{\mu_{\mathcal{X}}}(t, A, A) = \frac{\langle P^t \chi_A, \chi_A \rangle_{2,\mu_{\mathcal{X}}}}{\langle \chi_A, \chi_A \rangle_{\mu_{\mathcal{X}}}} = \frac{\lambda \langle \chi_A, \chi_A \rangle_{\mu_{\mathcal{X}}}}{\langle \chi_A, \chi_A \rangle_{\mu_{\mathcal{X}}}} = \lambda \approx 1 \ ,$$

so the degree of metastability of A would be high.

The precise connection is a little more subtle, however, as P^t is integral-preserving on $\mathcal{L}^1_{\mu_{\mathcal{X}}}(\mathcal{X})$ for $u \geq 0$, and so for all eigenfunctions v at eigenvalues $\lambda \neq 1$ must hold $\int_{\mathcal{X}} v \, d\mu_{\mathcal{X}} = 0$. The result was first formalized in [13], and a reformulation for our setting reads:

Proposition 2.1.10 ([13, Proposition 5.7])**.** *Let $v \in \mathcal{L}^1_{\mu_{\mathcal{X}}}(\mathcal{X})$ be an eigenfunction of P^t at eigenvalue λ, and let v be normed so that $\int_{\mathcal{X}} |v| \, d\mu_{\mathcal{X}} = 1$. Let $A \subset \mathcal{X}$ be a set with $\int_A v \, d\mu_{\mathcal{X}} = \frac{1}{2}$, and let $B = \mathcal{X} \setminus A$. Then*

$$p_{\mu_{\mathcal{X}}}(t, A, A) + p_{\mu_{\mathcal{X}}}(t, B, B) = 1 + \lambda.$$

We call

$$s_{\mu_{\mathcal{X}}}(t, A, B) := p_{\mu_{\mathcal{X}}}(t, A, A) + p_{\mu_{\mathcal{X}}}(t, B, B) \quad (2.36)$$

the *combined degree of metastability* of the decomposition $A \cup B = \mathcal{X}$, which is bounded from above by 2 (indicating invariance of A and B).

2.2. Spatial dynamics

In order to analyze the behavior of molecular systems in regard of configurational stability, we have to restrict our view to the dynamics on position space $\mathcal{Q}$. For this

[5] In other works concerning conformational metastability analysis, such a set is be called *almost invariant*, while the corresponding chemical conformation is called *metastable*. We do not make this distinction and call both the set and structure *metastable*.

purpose, Schütte in [61] proposed a reduction of the classical Hamiltonian dynamics, called *Hamiltonian dynamics with randomized momenta*, while Weber [78] proposed the corresponding generalized version for a stochastic evolution. Following Schütte and Weber, we formulate the extension to Langevin dynamics in generalized coordinates and state the appropriate definition of metastability.

We will find that the dynamics can no longer be described by an Itô diffusion equation of form (1.1). Thus, many of the properties and regularities derived in the preceding sections no longer apply, as we will see shortly. Still, there are good reasons for the introduction of this new dynamics, as the extraction of the relevant metastability information from the full Langevin dynamics is neither fully possible nor practical:

1. The original and most evident justification for spatial dynamics came from its creator Schütte [61], but is only partially applicable to our extended case.

   The transfer operator for the *deterministic* Hamiltonian dynamics has uncountably many invariant densities, corresponding to individual level sets of the Hamiltonian H. As a result, the spectrum of the operator lies *on* the unit circle, and thus identification of metastable sets via subdominant eigenvalues in the style of Proposition 2.1.10 is not possible.

   However, this argumentation doesn't (fully) hold for the stochastically perturbed Langevin dynamics. While the spectrum of its transfer operator in general still isn't purely real, Schütte and Sarich show in [64, Theorem 4.12] that, at least for small temperatures, P^t_{Lan} has a real dominant spectrum.
   Theorem 2.2.1 ([64, Theorem 4.12])**.** *Define on* $\mathcal{L}^2_{\mu_\Omega}(\Omega)$ *the bilinear form*

   $$\langle u, v\rangle_R := \langle Ru, v\rangle_{\mu_\Omega},$$

   where R is the momentum reversion map $R(q,p) = (q,-p)$. Let $\mathcal{E}_n$ be the subspace of $\mathcal{L}^2_{\mu_\Omega}(\Omega)$ *spanned by the n dominant eigenfunctions of P^t_{Lan}.*
   Then, for small enough temperature, P^t_{Lan} is self-adjoint with respect to $\langle u, v\rangle_R$, which is a scalar product on $\mathcal{E}_n$. Consequently, the dominant n eigenvalues of P^t_{Lan} must be real-valued.

   For the example systems considered in Section 4.2, P^t_{Lan} had a real dominant spectrum whenever metastability in $\mathcal{Q}$ could be observed. This suggests that the constraint to "small temperatures" is rather mild. Still, in other systems it might pose a practical hurdle. Furthermore, the question of how to interpret the non-dominant, potentially imaginary spectrum remains.

2. Conformations in the chemical sense are understood to correspond to the regions of minima on the potential energy surface, i.e. are metastable sets in *position* space $\mathcal{Q}$ only. However, the eigenfunctions of P^t_{Lan} reveal metastable sets on the whole phase space Ω, whether they correspond to minima of V or not.

As an example, consider the Cartesian Langevin system on $\mathcal{Q} = \mathbb{T}^1$ (the one-dimensional unit circle), $\mathcal{P} = \mathbb{R}^1$, with zero potential $V \equiv 0$ and identity mass matrix, i.e.

$$\frac{d^2}{dt^2} q_t = -\gamma \frac{d}{dt} q_t + \sigma w_t.$$

The associated Fokker–Planck equation (with respect to the Lebesgue measure) reads

$$\partial_t f_t(q,p) = \Big(\frac{\gamma}{\beta} \Delta_p - p \cdot \nabla_q + \gamma p \cdot \nabla_p + \gamma \Big) f_t(q,p), \tag{2.37}$$

from which it can easily be seen that its infinitesimal generator has the eigenvalue $-\gamma$ with eigenfunction $g(q,p) = p \cdot f_\Omega(q,p)$. For γ small enough, this eigenpair is subdominant.

Now, sign analysis of g on $\Omega = \mathcal{Q} \times \mathcal{P}$ reveals the two sets

$$A = \big\{ (q,p) \in \Omega \mid p > 0 \big\}, \quad B = \big\{ (q,p) \in \Omega \mid p < 0 \big\},$$

with degrees of metastability

$$p_m(t, A, A) = p_m(t, B, B) = e^{-\gamma t},$$

which are high if γ is small. Numerical investigation even reveals a spectral gap after the fifth eigenvalue (see Figure 2.1).

However, the system does not contain metastable configurations in the chemical (and thus our) sense, as the potential energy surface is completely flat. Thus deducing the existence of spatial metastable sets from the existence of a dominant spectrum of the Langevin transfer operator is, in general, not possible.

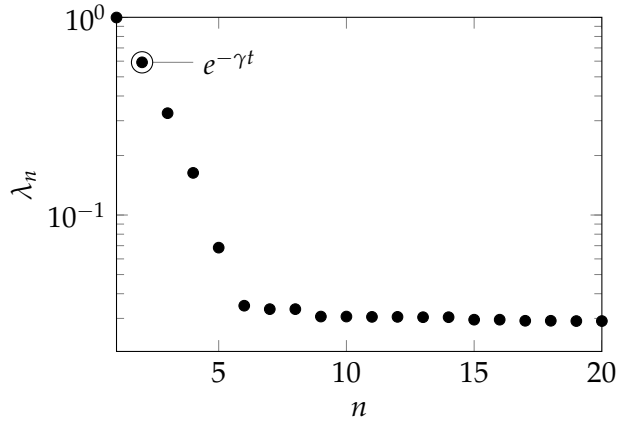

Figure 2.1.: Dominant eigenvalues of a discretization of P^t_{Lan} for the zero potential system for small γ. The first five eigenvalues appear to be isolated.

3. Finally, having to deal with the dynamics only on $\mathcal{Q}$ vastly reduces the numerical effort. As we will see in Section 2.3, the classical numerical analysis methods require a discretization of the respective phase space. As $\dim(\mathcal{Q}) = \dim(\mathcal{P}) = d$, and for simplicity assuming a resolution of N in each (position and momentum) dimension, the number of required discretization elements reduces from N^{2d} to N^d.

2.2.1. The spatial transfer operator

Consider an ensemble of molecules, modeled by (1.8) in thermodynamic equilibrium, i.e. identically and independently distributed according to f_Ω. To determine which portion of the ensemble undergoes a certain configurational change, e.g. leaves some set $A \subset \mathcal{Q}$, we have to track the evolution of all paths (q_t, p_t) under Langevin dynamics with position coordinate q_t starting in $q_0 \in A$. We therefore have $q_0 \sim \tilde{\chi}_A f_\mathcal{Q}$, where $\tilde{\chi}_A = \chi_A / \mu_\mathcal{Q}(A)$ is the $\mu_\mathcal{Q}$–normed indicator function.

Due to the product structure (2.20) of f_Ω, the initial momenta p_0 are distributed according to $f_\mathcal{P}$ and so $(q_0, p_0) \sim \tilde{\chi}_A f_\Omega$. This full phase space density now evolves under the action of the Langevin transfer operator P^t_{Lan}, but as we are only interested in the positional portion of the evolving density, we form the marginal distribution of $P^t_{\text{Lan}} \tilde{\chi}_A f_\Omega$ with respect to q.

The evolution of $\tilde{\chi}$ can again be expressed in transfer operator form, defining the *spatial transfer operator*

$$S^t \tilde{\chi}_A(q) := \frac{1}{f_\mathcal{Q}(q)} \int_\mathcal{P} \bar{P}^t_{\text{Lan}}\big(\tilde{\chi}_A(q) f_\Omega(q,p)\big)\, dp \tag{2.38}$$

which can be recast in terms of the $\mu_\mathcal{Q}$-weighted transfer operator, using (2.6):

$$S^t \tilde{\chi}_A(q) = \int_\mathcal{P} P^t_{\text{Lan}}(\tilde{\chi}_A)(q,p)\, d\mu_\mathcal{P} \,. \tag{2.39}$$

Note that the position q appears in $\mu_\mathcal{P}$ as a parameter, as $d\mu_\mathcal{P}(p) = f_\mathcal{P}(q,p) dm(p)$.

Due to Corollary 2.1.1 applied to the operator P^t_{Lan} and the invariant measure μ_Ω, the spatial transfer operator S^t can formally be extended to $\mathcal{L}^k_{\mu_\mathcal{Q}}(\mathcal{Q})$ with $\mu_\mathcal{Q}$ defined by $d\mu_\mathcal{Q} := f_\mathcal{Q} dm$. Intuitively, one can think of $S^t u$ with $u \in \mathcal{L}^k_{\mu_\mathcal{Q}}(\mathcal{Q})$ as transporting a positional portion of the canonical density under the full phase space dynamics.

S^t induces a new stochastic dynamical process, called *spatial dynamics* or *Langevin dynamics with randomized momenta* [61]. We will see below that this is no longer an Itô process, and thus cannot be described by an SDE of form (1.1). Instead, we characterize it purely by its stochastic transition function, which reads for measurable sets $B \subset \mathcal{Q}$

$$p_S(t, q, B) := \frac{1}{f_\mathcal{Q}(q)} \int_\mathcal{P} p_{\text{Lan}}(t, (q,p), B \times \mathcal{P}) f_\Omega(q,p)\, dp \,. \tag{2.40}$$

The *spatial transition probability* then is for $\mu_{\mathcal{Q}}$–measurable $A, B \subset \mathcal{Q}$ defined by

$$p_{\mathrm{S},\mu_{\mathcal{Q}}}(t, A, B) := \frac{1}{\mu_{\mathcal{Q}}(A)} \int_A p_{\mathrm{S}}(t, q, B)\, d\mu_{\mathcal{Q}}(q). \tag{2.41}$$

Properties

In the following we state some important properties of the spatial transfer operator. The central properties regarding self–adjointness, geometric ergodicity and the spectrum of S^t have been shown by Koltai in [6].

Semigroup property. The spatial transfer operator lacks the semi-group property that fundamentally characterizes the Itô transfer operators: $S^{t+s} \neq S^s \circ S^t$. With the projection and extension operators

$$\begin{aligned} \Pi_{\mathcal{Q}} &: \mathcal{L}^1(\Omega) \to \mathcal{L}^1_{\mu_{\mathcal{Q}}}(\mathcal{Q}) \ , \qquad (\Pi_{\mathcal{Q}} f)(q) := \frac{1}{f_{\mathcal{Q}}(q)} \int_{\mathcal{P}} f(q,p)\, dp \\ \Gamma_{\Omega} &: \mathcal{L}^1_{\mu_{\mathcal{Q}}}(\mathcal{Q}) \to \mathcal{L}^1(\Omega) \ , \qquad (\Gamma_{\Omega} u)(q,p) := u(q) f_{\Omega}(q,p) \end{aligned}$$

this can be seen easily, as

$$\begin{aligned} S^{t+s} &= \Pi_{\mathcal{Q}} \bar{P}^{t+s}_{\mathrm{Lan}} \Gamma_{\Omega} = \Pi_{\mathcal{Q}} \bar{P}^{s}_{\mathrm{Lan}} \bar{P}^{t}_{\mathrm{Lan}} \Gamma_{\Omega} \\ S^s \circ S^t &= \Pi_{\mathcal{Q}} \bar{P}^{s}_{\mathrm{Lan}} \Gamma_{\Omega} \Pi_{\mathcal{Q}} \bar{P}^{t}_{\mathrm{Lan}} \Gamma_{\Omega} \end{aligned}$$

and as $\Gamma_{\Omega}\Pi_{\mathcal{Q}} \neq \mathrm{id}$, the two expressions differ.

As a consequence, S^t cannot be the solution operator of an autonomous PDE, such as the Fokker–Planck equation. This is equivalent to spatial dynamics not being induced by an Itô diffusion process, and it thus has no infinitesimal generator in the sense of (2.19).

Reversibility and self-adjointness. S^t is a self-adjoint operator on $\mathcal{L}^2_{\mu_{\mathcal{Q}}}(\mathcal{Q})$, i.e.

$$\langle S^t u, v \rangle_{\mu_{\mathcal{Q}}} = \langle u, S^t v \rangle_{\mu_{\mathcal{Q}}} \tag{2.42}$$

for $u, v \in \mathcal{L}^2_{\mu_{\mathcal{Q}}}(\mathcal{Q})$. This has been shown in [6] for the special case of Cartesian coordinates with mass matrix $M = I$, but the proof has to be adapted only slightly to suit our more general setting. It can be found in Appendix A.1.

Equivalent to the self-adjointness of S^t is the notion that the underlying dynamical process is *reversible*. While for deterministic dynamics, this corresponds to the invertibility of the flow Ξ^t, for stochastic spatial dynamics with transition probability $p_{S,\mu_{\mathcal{Q}}}(t, \cdot, \cdot)$ (compare (2.34)), reversibility can be defined as

$$p_{S,\mu_{\mathcal{Q}}}(t, A, B) = p_{S,\mu_{\mathcal{Q}}}(t, B, A)\ .$$

Geometric ergodicity. Geometric ergodicity of the spatial dynamics can easily be reduced to geometric ergodicity of the Langevin dynamics. We repeat the short argument that was first stated in [6].

Proposition 2.2.2 ([6, Appendix B])**.** *Under the prerequisites of Proposition 2.1.3 on the configuration space $\mathcal{Q}$ and the potential V, spatial dynamics has the unique invariant measure $\mu_{\mathcal{Q}}$ and is geometrically ergodic.*

Proof. Note that $\mu_{\mathcal{Q}} = \mu_\Omega(\cdot \times \mathcal{P})$. With the description (2.40) for the spatial transition function p_S, we have

$$\begin{aligned}
\left\|p_S(nt,q,\cdot) - \mu_{\mathcal{Q}}\right\|_{\mathrm{TV}} &= \left\| \frac{1}{f_{\mathcal{Q}}(q)} \int_{\mathcal{P}} p_{\mathrm{Lan}}\big(nt,(q,p),\cdot \times \mathcal{P}\big) f_\Omega(q,p)\, dp - \mu_\Omega(\cdot \times \mathcal{P}) \right\|_{\mathrm{TV}} \\
&= \left\| \frac{1}{f_{\mathcal{Q}}(q)} \int_{\mathcal{P}} \left[p_{\mathrm{Lan}}\big(nt,(q,p),\cdot \times \mathcal{P}\big) - \mu_\Omega(\cdot \times \mathcal{P}) \right] f_\Omega(q,p)\, dp \right\|_{\mathrm{TV}} \\
&\leq \int_{\mathcal{P}} \tfrac{f_\Omega(q,p)}{f_{\mathcal{Q}}(q)} \left\| p_{\mathrm{Lan}}\big(nt,(q,p),\cdot \times \mathcal{P}\big) - \mu_\Omega(\cdot \times \mathcal{P}) \right\|_{\mathrm{TV}} dp \\
&= (*)\ .
\end{aligned}$$

By the supremum definition of the total variation norm, one sees that the norm of a measure projected onto a subspace of the original phase space is not greater then the norm of the unprojected measure:

$$\|\mu\|_{\mathrm{TV}} = \sup_{\substack{\pi \text{ partition} \\ \text{of } \Omega}} \sum_{A \in \pi} |\mu(A)| \geq \sup_{\substack{\pi \text{ partition} \\ \text{of } \mathcal{Q}}} \sum_{A \in \pi} |\mu(A \times \mathcal{P})| = \|\mu(\cdot \times \mathcal{P})\|_{\mathrm{TV}}\ ,$$

as for all $A \subset \mathcal{Q}$ the sets $A \times \mathcal{P}$ are contained in partitions of Ω. Thus we continue

$$\begin{aligned}
(*) &\leq \int_{\mathcal{P}} \tfrac{f_\Omega(q,p)}{f_{\mathcal{Q}}(q)} \left\| p_{\mathrm{Lan}}\big(nt,(q,p),\cdot\big) - \mu_\Omega(\cdot) \right\|_{\mathrm{TV}} dp \\
&\leq \rho^n \underbrace{\int_{\mathcal{P}} \tfrac{f_\Omega(q,p)}{f_{\mathcal{Q}}(q)} M(q,p)\, dp}_{=:\tilde{M}(q)}\ .
\end{aligned}$$

In the last line $M(q,p)$ and ρ are the ergodicity factor and constant for Langevin dynamics, which exist due to Proposition (2.1.3), and $M \in \mathcal{L}^1_{\mu_\Omega}(\mathcal{Q} \times \mathcal{P})$ implies $\tilde{M} \in \mathcal{L}^1_{\mu_{\mathcal{Q}}}(\mathcal{Q})$. Thus spatial dynamics is geometrically ergodic, with prefactor $\tilde{M}$ and ergodicity constant ρ □

Spectrum. Using the *dynamical* properties of reversibility and geometric ergodicity of spatial dynamics, Koltai in [6] has shown some desirable *spectral* properties of the associated spatial transfer operator.

Consider the following assumption for some transfer operator P^t:

Assumption 2.2.3 ([35], Assumption S)**.** The operator $P^t : \mathcal{L}^2_\mu(\mathcal{X}) \to \mathcal{L}^2_\mu(\mathcal{X})$ is self-adjoint and exhibits n eigenvalues

$$\lambda_n \leq \ldots \leq \lambda_2 < \lambda_1 = 1,$$

counted according to their multiplicity. Furthermore, the spectrum $\sigma(T)$ satisfies

$$\sigma(P^t) \subset [a, b] \cup \{\lambda_n, \ldots, \lambda_1\}$$

for some constants $a, b \in (-1, 1)$ satisfying $a \leq b < \lambda_n$.

[34, Theorem 4.31], re-stated for our purposes gives

Theorem 2.2.4. *Let $P : \mathcal{L}^2_\mu(\mathcal{X}) \to \mathcal{L}^2_\mu(\mathcal{X})$ be a transfer operator associated with the reversible stochastic transition function p. Then P satisfies Assumption 2.2.3 if and only if p is μ-irreducible and (μ-a.e.) geometrically ergodic. The latter two conditions on p are satisfied, in particular, if p is geometrically ergodic.*

Thus, we have

Corollary 2.2.5 ([6, Corollary B.7])**.** *If the potential V satisfies either conditions in Proposition 2.1.3, then the spatial transfer operator $S^t : \mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q}) \to \mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q})$ is self-adjoint and satisfies Assumption 2.2.3.*

2.2.2. Spatial metastability

Considering S^t as an operator on $\mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q})$ and using the standard associated scalar product $\langle u, v\rangle_{\mu_\mathcal{Q}}$ gives us access to the spatial transition probabilities on $\mathcal{Q}$. For $A \subset \mathcal{Q}$ we call

$$\Gamma(A) := \big\{(q, p) \in \Omega \mid q \in A\big\} \tag{2.43}$$

the *slice* of phase space corresponding to A. It is easy to see that for the spatial transition probability holds

$$p_{\mathrm{S},\mu_\mathcal{Q}}(t, A, B) = p_{\mathrm{Lan},\mu_\Omega}\big(t, \Gamma(A), \Gamma(B)\big)\ .$$

The spatial transition probabilities between slices A and B can now again be expressed

in terms of S^t:

$$\begin{aligned}
p_{\mathrm{S},\mu_{\mathcal{Q}}}(t,A,B) &= p_{\mathrm{Lan},\mu_\Omega}\left(t,\Gamma(A),\Gamma(B)\right) \\
&\overset{(2.35)}{=} \frac{\left\langle P^t_{\mathrm{Lan}}\chi_{\Gamma(A)},\chi_{\Gamma(B)}\right\rangle_{\mu_{\mathcal{Q}}}}{\left\langle \chi_{\Gamma(A)},\chi_{\Gamma(A)}\right\rangle_{\mu_{\mathcal{Q}}}} \\
&= \frac{1}{\mu_\Omega(\Gamma(A))}\int_{\Gamma(B)}\left(P^t_{\mathrm{Lan}}\chi_{\Gamma(A)}\right)(q,p)\,d\mu_\Omega \\
&= \frac{1}{\mu_{\mathcal{Q}}(A)}\int_B\int_{\mathcal{P}}\left(P^t_{\mathrm{Lan}}(\chi_A\chi_{\mathcal{P}})\right)(q,p)f_\Omega(q,p)\,dp\,dq \\
&= \frac{1}{\mu_{\mathcal{Q}}(A)}\int_B\left(S^t\chi_A\right)(q)\,d\mu_{\mathcal{Q}} \\
&= \frac{\left\langle S^t\chi_A,\chi_B\right\rangle_{\mu_{\mathcal{Q}}}}{\left\langle \chi_A,\chi_A\right\rangle_{\mu_{\mathcal{Q}}}}\,.
\end{aligned}$$

This defines our task for metastability analysis motivated by spatial conformation dynamics: find a disjoint decomposition $\{A_1,\ldots,A_n\}$ of position space $\mathcal{Q}$, so that

$$p_{\mathrm{S},\mu_\Omega}\left(t,A_j,A_j\right)\approx 1,\ j=1,\ldots,n.$$

Connection to the spectrum of S^t. The connection between eigenvalues close to one of arbitrary transfer operators and metastable sets was first formalized in [13] (see Proposition 2.1.10) and applied to conformation dynamics in [14]. However, we will primarily use a result from Huisinga and Schmidt [35], developed for the special class of transfer operators satisfying Assumption 2.2.3.

For the n dominant eigenvalues $\lambda_1,\ldots,\lambda_n$ of S^t let the corresponding set of $\mu_{\mathcal{Q}}$-orthonormal eigenfunctions be denoted by $\{v_1,\ldots,v_n\}$. We then have

Theorem 2.2.6 (Application of [35, Theorem 2])**.** *Let $\{A_1,\ldots,A_n\}$ be a measurable decomposition of $\mathcal{Q}$ and $\Pi:\mathcal{L}^2_{\mu_{\mathcal{Q}}}(\mathcal{Q})\to\mathcal{L}^2_{\mu_{\mathcal{Q}}}(\mathcal{Q})$ be the orthogonal projection onto* $\mathrm{span}(\chi_{A_1},\ldots,\chi_{A_n})$*, i.e.*

$$\Pi v=\sum_{j=1}^n\frac{\left\langle v,\chi_{A_j}\right\rangle_{\mu_{\mathcal{Q}}}}{\left\langle \chi_{A_j},\chi_{A_j}\right\rangle_{\mu_{\mathcal{Q}}}}\chi_{A_j}\,.$$

The combined degree of metastability of the decomposition can then be bounded from above by

$$p_{\mathrm{S},\mu_{\mathcal{Q}}}\left(t,A_1,A_1\right)+\ldots+p_{\mathrm{S},\mu_{\mathcal{Q}}}\left(t,A_n,A_n\right)\leq 1+\lambda_2+\ldots+\lambda_n,$$

while it is bounded from below by

$$1+\rho_2\lambda_2+\ldots+\rho_n\lambda_n+c\leq p_{\mathrm{S},\mu_{\mathcal{Q}}}\left(t,A_1,A_1\right)+\ldots+p_{\mathrm{S},\mu_{\mathcal{Q}}}\left(t,A_n,A_n\right).$$

Here, $\rho_j=\|\Pi v_j\|_{2,\mu_{\mathcal{Q}}}\in[0,1]$ and $c=a(1-\rho_2+\ldots+1-\rho_n)$ (a the left interval bound in Assumption 2.2.3).

We see that, the lower the projection error of Πv_j, i.e. the more the eigenfunctions resemble step functions over the sets $A_1, \ldots, A_n$, the better the bounds coincide. As a first heuristics when aiming to construct a metastable decomposition, one can choose $A_1, \ldots, A_n$ in accordance to the the sign structure of $v_1, \ldots, v_n$ (i.e. we treat the eigenfunctions as approximate one-step functions of the form $\chi_A - \chi_B$).

Note that the focus of this work is the approximation and computation of the eigenfunctions and the spectrum of S^t, and *not* the extraction of the individual metastable sets from the eigenfunctions. Sophisticated schemes, such as the spectral clustering-based PCCA algorithm [15, 60], have been developed for this purpose, and they can in principle be applied as a post-processing step to the eigenfunctions computed by our methods.

2.3. Operator discretization methods

We have seen the connection between metastable sets and eigenfunctions of the transfer operator and generator , for our purposes formalized by Theorem 2.2.6 and Theorem 2.1.5. For numerical metastability analysis, the operators have to be discretized in order to compute their eigenvectors. We present two established discretization strategies, one for the transfer operator and one for the generator.

2.3.1. Transfer operator-based analysis

Assume $\mathcal{Q}$ satisfies the conditions in Proposition 2.1.3 and let, for this section only, P^t denote

(i) either the transfer operator of some Itô diffusion of form (1.1) on $\mathcal{Q}$ (for example Smoluchowski dynamics)

(ii) or the spatial transfer operator S^t.

In accordance with the notation from section 2.1.1, P^t denotes the *weighted* transfer operator with respect to the unique invariant density $f_{\mathcal{Q}}$ and the according invariant measure $\mu_{\mathcal{Q}}$, which we assume to exist in case (i) above.

Ulam's method. Let $\mathcal{U}_n$ denote some n-dimensional subspace of $\mathcal{L}^2_{\mu_{\mathcal{Q}}}(\mathcal{Q})$, with orthogonal basis $\{\varphi_1, \ldots, \varphi_n\}$. The orthogonal projection onto $\mathcal{U}_n$ is called the *Galerkin projection*, denoted by $\Pi_n : \mathcal{L}^2_{\mu_{\mathcal{Q}}}(\mathcal{Q}) \to \mathcal{U}_n$, and given by

$$\Pi_n u := \sum_{i=1}^{n} c_i \varphi_i \,, \quad \text{with} \quad c_i = \frac{\langle u, \varphi_i \rangle_{\mu_{\mathcal{Q}}}}{\langle \varphi_i, \varphi_i \rangle_{\mu_{\mathcal{Q}}}} \,. \tag{2.44}$$

This lets us define the *projected transfer operator* $P_n^t := \Pi_n P^t$. Restricted to $\mathcal{U}_n$, P_n^t can be represented by a matrix[6], with entries

$$\left(P_n^t\right)_{i,j} = \frac{\langle P^t \varphi_i, \varphi_j \rangle_{\mu_\mathcal{Q}}}{\langle \varphi_i, \varphi_i \rangle_{\mu_\mathcal{Q}}} \,. \tag{2.45}$$

Ulam [75] suggested to use indicator functions over a partition of $\mathcal{Q}$ as basis for $\mathcal{U}_n$. This was also the first approach used in numerical transfer operator based metastability analysis [13, 15], as the resulting propagator matrix (2.45) has a nice stochastic interpretation. Let $\mathcal{D} = \{\mathcal{D}_1, \ldots, \mathcal{D}_n\}$ denote a disjoint decomposition of $\mathcal{Q}$ into $\mu_\mathcal{Q}$-measurable sets with positive finite measure and $\mathcal{U}_n := \operatorname{span}\left(\chi_{\mathcal{D}_1}, \ldots, \chi_{\mathcal{D}_n}\right)$. The matrix representation of P_n^t then has entries

$$\left(P_n^t\right)_{i,j} = \frac{\langle P^t \chi_{\mathcal{D}_i}, \chi_{\mathcal{D}_j} \rangle_{\mu_\mathcal{Q}}}{\langle \chi_{\mathcal{D}_i}, \chi_{\mathcal{D}_i} \rangle_{\mu_\mathcal{Q}}} = \frac{1}{\mu_\mathcal{Q}(\mathcal{D}_i)} \int_{\mathcal{D}_j} P^t \chi_{\mathcal{D}_i} \, d\mu_\mathcal{Q} \,,$$

which can be seen as the *transition probabilities* of the underlying system,

$$= p_{\mu_\mathcal{Q}}(t, \mathcal{D}_i, \mathcal{D}_j) = \operatorname{Prob}_{\mu_\mathcal{Q}}\left[x_t \in \mathcal{D}_j \;\middle|\; x_0 \in \mathcal{D}_i\right] . \tag{2.46}$$

P_n^t is a (row) stochastic matrix [24], i.e.

$$1. \quad \left(P_n^t\right)_{i,j} \geq 0 \,, \qquad 2. \quad \sum_j \left(P_n^t\right)_{i,j} = 1 \,,$$

which by the Perron–Frobenius Theorem implies that all its eigenvalues satisfy $|\lambda| \leq 1$ and $\lambda = 1$ is a single eigenvalue of P_n^t with eigenvector $v = (1, \ldots, 1)^\intercal$.

We now solve the projected eigenvalue problem on $\mathcal{U}_n$ instead of $\mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q})$, i.e. solve $P_n^t u = \lambda u$ for $u \in \mathcal{U}_n$. Under which conditions (λ, u) then converges to an eigenpair of P^t has been investigated for example in [61].

Monte Carlo integration. The interpretation of the entries of P_n^t as transition probabilities is key to the algorithmic strategy for numerically computing them. Equation (2.46) can be interpreted as the portion of the canonical ensemble which, after time t, ends up in $\mathcal{D}_j$ after starting from $\mathcal{D}_i$. Thus sampling the canonical ensemble on $\mathcal{D}_i$ and counting the transitions to $\mathcal{D}_j$ should give an approximation to $(P_n^t)_{i,j}$, with an error depending on the number of sampling points.

This intuitive strategy can be made precise under the notion of Monte Carlo quadrature, for a thorough introduction see [36]. With the density $f_{\mathcal{D}_i} := \frac{\chi_{\mathcal{D}_i}}{\mu_\mathcal{Q}(\mathcal{D}_i)} f_\mathcal{Q}$, i.e. the restriction of the canonical density $f_\mathcal{Q}$ to $\mathcal{D}_i$, we can write

$$(2.46) = \mathbb{E}\left[\chi_{\mathcal{D}_j}(q_t) \mid q_0 \sim f_{\mathcal{D}_i}\right] =: J_M \,.$$

[6] For the sake of notational simplicity, we denote both the operator on $\mathcal{U}_n$ and the matrix in $\mathbb{R}^{n \times n}$ by P_n^t.

By the law of large numbers, this conditional expectation can be approximated by

$$\approx \frac{1}{M} \sum_{m=1}^{M} \chi_{\mathcal{D}_j}\big(q_t(q_0^{(m)})\big) =: \hat{J}_M, \tag{2.47}$$

where the $q_t(q_0^{(m)})$ are independent realizations of the underlying stochastic process at time t, starting at different $q_0^{(m)} \sim f_{\mathcal{D}_i}$. The approximation error is typically given in terms of the standard deviation $\mathbb{E}\big[(J_M - \hat{J}_M)^2\big]^{1/2}$ which can be shown to be of order $\mathcal{O}(1/\sqrt{M})$, independent of the system's dimension [22].

Stochastic trajectories. For Itô processes on $\mathcal{Q}$, the realizations $q_t^{(m)}$ can be computed by numerically integrating the associated SDE (1.1), using stochastic symplectic integrators such as the Störmer-Verlet method with Langevin thermostat [28].

For spatial dynamics, however, a small intermediate step is necessary, as it is not described by an SDE but we rather rely on the momentum-averaged Langevin transition function (2.34) to describe it. We have

$$p_{S,\mu_{\mathcal{Q}}}(t, \mathcal{D}_i, \mathcal{D}_j) = p_{\mathrm{Lan},\mu_{\mathcal{Q}}}(t, \mathcal{D}_i \times \mathcal{P}, \mathcal{D}_j \times \mathcal{P})$$

which can be approximated as in (2.47) by

$$\approx \frac{1}{M} \sum_{m=1}^{M} \chi_{\mathcal{D}_j}\Big(\pi_q x_t(x_0^{(m)})\Big),$$

where π_q is the restriction to the q-component and

$$x_t(x_0^{(m)})) = \Big(q_t(q_0^{(m)}, p_0^{(m)}), p_t(q_0^{(m)}, p_0^{(m)})\Big)$$

are independent realizations of the full phase space *Langevin* process at time t, starting at randomly drawn $q_0^{(m)} \sim f_{\mathcal{D}_i}$, $p_0^{(m)} \sim f_{\mathcal{P}}(q_0^{(m)}, \cdot)$. It is helpful to split the above sum into individual Monte Carlo quadrature sums over $\mathcal{D}_i$ and $\mathcal{P}$:

$$p_{S,\mu_{\mathcal{Q}}}(t, \mathcal{D}_i, \mathcal{D}_j) = \frac{1}{M_1} \sum_{m_1=1}^{M_1} \frac{1}{M_2} \sum_{m_2=1}^{M_2} \chi_{\mathcal{D}_j}\Big(\pi_q x_t(q_0^{(m_1)}, p_0^{(m_1,m_2)})\Big),$$

so for every sample $q_0^{(m_1)} \sim f_{\mathcal{D}_i}$ we draw M_2 samples $p_0^{(m_1,m_2)} \sim f_{\mathcal{P}}(q_0^{(m_1)}, \cdot)$. Thus, although spatial density dynamics takes place in position space $\mathcal{Q}$, the momentum averaging requires the sampling of $\mathcal{P}$ as well.

The curse of dimensionality. In the case where $\mathcal{Q}$ is bounded or periodic, a straightforward choice for the decomposition of $\mathcal{Q}$ is a regular rectangular grid. Consider for

simplicity $\mathcal{Q} = [0,1]^d$, the d-dimensional unit cube, and some dynamical system on it with periodic boundary conditions. Dividing each edge of $\mathcal{Q}$ into n intervals of the same length $1/n$ yields a decomposition of $\mathcal{Q}$ into a total of n^d congruent hypercubes ("boxes"), denoted by $\mathcal{D}_i$, $i = 1, \ldots, n^d$.

Using the approximation space $\mathcal{U}_{n^d} = \{\mathcal{D}_1, \ldots, \mathcal{D}_{n^d}\}$, it is a standard result from Finite elements theory that the approximation error for $\mathcal{L}^1$-integrable Lipschitz-continuous functions $f : \mathcal{Q} \to \mathbb{R}$ can be estimated by $\|f - \Pi_{n^d} f\| = \mathcal{O}(n^{-1})$. Thus, to achieve a given approximation error ε, in the order of ε^{-d} boxes are needed.

This exponential growth in the number of ansatz functions, known as the *curse of dimensionality*, quickly represents prohibitive computational costs, and makes this box-based Galerkin discretization infeasible in dimensions as low as $d = 4$.

Related approaches

There are of course other options in choosing the ansatz space $\mathcal{U}_n$, and standard approximation spaces as well as specifically tailored ansatz functions have been considered in transfer operator analysis, some of which are presented below.

- In [37], Junge and Koltai used a hierarchical *Haar basis* to combat the curse of dimensionality. They reduced the number of basis functions required to achieve a given Galerkin discretization error ε from $\mathcal{O}(\varepsilon^{-d})$ for basis functions based on a regular grid of boxes, to $\mathcal{O}\big((\log_2 \varepsilon^{-1})^{2d-2}\varepsilon^{-1}\big)$ for their sparse-grid basis.
- Weber [77] diverted from the point of view of each point in configuration space lying inside of exactly one metastable set, and instead characterized their affiliation to conformations by *membership functions*, one for each conformation. The Galerkin projection onto the space spanned by these membership functions leads to a meshfree algorithm, which also aims to break the curse of dimensionality.
- In the *core set approach*, Schütte and coworkers [63, 65] use a Galerkin projection onto so-called *commitor functions*. For sets $\mathcal{D}_1, \ldots, \mathcal{D}_n \subset \mathcal{Q}$, the commitor function c_i is defined by the probability of hitting $\mathcal{D}_i$ next if starting in q, i.e. with the *hitting time* $\tau_q(\mathcal{D}_i) = \inf\{t \geq 0 \mid q_0 = q \wedge q_t \in \mathcal{D}_i\}$,

  $$c_i(q) = \mathrm{Prob}\big[\tau_q(\mathcal{D}_i) < \tau_q(\mathcal{D}_1) \wedge \ldots \wedge \tau_q(\mathcal{D}_i) < \tau_q(\mathcal{D}_n)\big] \ .$$

  In case of a full partition $\mathcal{Q} = \bigcup_i \mathcal{D}_i$, we again have $c_i = \chi_{\mathcal{D}_i}$. However the idea is to choose the $\mathcal{D}_i$ to cover only regions in phase space of high interest for conformation dynamics[7]. The resulting transition matrix can be interpreted

[7] Typical choices for the $\mathcal{D}_i$ are the (assumed) metastable sets themselves or "milestones" along the transition paths. The information about the location of these sets has to be supplied, for example by preceding computations or chemical intuition.

as a Markov jump process on n states which approximates the original high-dimensional (spatial) molecular dynamics. This model reduction technique has been implemented in form of the software package EMMA [67].

All these transfer operator-based discretization methods have in common that they implement the underlying dynamical system by computing *numerical trajectories* to approximate transition probabilities between certain subsets of phase space. While by meshfree approaches, the number of these sets may be kept low, the cost for accurately approximating the individual transition probabilities is still dependent on the system dimension.

Thus, the integration of these trajectories typically is the computationally most expensive step in operator-based Ulam-like methods. It is this step we are aiming to avoid by looking directly at the infinitesimal generator instead.

2.3.2. Generator-based analysis

According to the spectral mapping theorem 2.1.5, the spectra of transfer operator semigroups P^t and their corresponding infinitesimal generator L are equivalent in the context of metastability analysis: given the dominant eigenvalues $\{\lambda_1, \ldots, \lambda_n\}$ of L_{Lan}, the dominant eigenvalues of P^t can be computed to $\{e^{t\lambda_1}, \ldots, e^{t\lambda_n}\}$. The respective eigenvectors are the same.

Froyland et. al. [25] used this equivalence to perform metastability analysis completely without the costly numerical simulations that the Galerkin discretization for the transfer operator is based on. They did so by discretizing the generator instead, using spectral collocation methods.

Spectral collocation

Collocation is a well-known interpolation-based technique for the numerical solution of ordinary and partial differential equations. For our abridged notion of this method, we refer directly to [25]; for a more general introduction, see, for example, [71].

Consider a set of—not necessarily orthogonal—basis functions $\{\varphi_1, \ldots, \varphi_n\}$ on $\mathcal{Q}$, spanning the approximation space $\mathcal{U}_n$, and call some $\mathcal{Q}_n := \{q_1, \ldots, q_n\} \subset \mathcal{Q}$ the set of *collocation nodes*. Now let $\mathcal{U}$ be some function space and $\mathcal{I}_n : \mathcal{U} \to \mathcal{U}_n$ be the interpolation operator corresponding to $\mathcal{U}_n$. For $f \in \mathcal{U}$, $\mathcal{I}_n f$ thus denotes the function in $\mathcal{U}_n$ for which holds

$$\mathcal{I}_n f(q_i) = f(q_i), \quad i = 1, \ldots, n \, .$$

In order to guarantee existence and uniqueness of the interpolant $\mathcal{I}_n f$, the collocation nodes have to be chosen in accordance with the basis functions. We present two

popular choices of pairs $(\mathcal{U}_n, \mathcal{Q}_n)$, suitable for the two different assumptions on our phase space $\mathcal{Q}$ from Proposition 2.1.3:

1. For $\mathcal{Q}$ periodic, first consider $\mathcal{Q} = \mathbb{T}^1$, the one-dimensional unit circle. Define for n odd the finite dimensional approximation space $\mathcal{U}_n$ of trigonometric polynomials with basis of Fourier modes

$$\left\{\varphi_k\right\}_{-\frac{n-1}{2} \leq k \leq \frac{n-1}{2}}, \quad \varphi_k(q) = e^{2i\pi kq}, \tag{2.48}$$

   as well as the corresponding collocation nodes $\mathcal{Q}_n := \{0, 1/n, \ldots, (n-1)/n\}$. These basis functions possess inherent periodic boundary conditions.

   For systems on differing periodic intervals $[a, b]$, a shifted-and-stretched Fourier basis can be used, together with correspondingly shifted nodes. Multidimensional periodic phase spaces then can be discretized using a corresponding product basis.

2. For the unbounded state space $\mathcal{Q} = \mathbb{R}^d$, a grid-based ansatz space does not seem appropriate at first. However, as the potential V grows at least quadratic at infinity (due to the requirement in Proposition 2.1.3), the canonical density $f_{\mathcal{Q}}$ decreases as $\mathcal{O}(e^{-\beta\|q\|^2})$ for $\|q\| \to \infty$. Thus, we can always find a bounded region $\hat{\mathcal{Q}} \subset \mathcal{Q}$ that the canonical ensemble concentrates in, i.e. $\mu_{\mathcal{Q}}(\hat{\mathcal{Q}}) \approx 1$. Placing the collocation nodes on a grid that covers $\hat{\mathcal{Q}}$ then captures the essential dynamics.

   Again we start with a one-dimensional case. For $\hat{\mathcal{Q}} = [-1, 1]$ we place the collocation nodes on the Chebyshev grid $\mathcal{Q}_n := \left\{ -\cos\left(2\pi k/(n-1)\right),\ k = 0, \ldots, n-1 \right\}$ and use Chebyshev polynomials as basis functions:

$$\left\{\varphi_k\right\}_{0 \leq k \leq n-1}, \quad \varphi_k(q) = \cos\left(k \arccos(q)\right). \tag{2.49}$$

   For any other interval $[a, b]$, grid and basis functions can be shifted and stretched as in the periodic case. Multidimensional $\hat{\mathcal{Q}}$ are covered by tensor products of polynomials.

We can then write the interpolant $\mathcal{I}_n f$ as a linear combination of the φ_i:

$$\mathcal{I}_n f(q) = \sum_{i=1}^{n} c_i \varphi_i(q),$$

where the c_i solve the linear system

$$f(q_j) = \sum_{i=1}^{n} c_i \varphi_i(q_j), \quad j = 1, \ldots, n.$$

Operator approximation For an operator $A : \mathcal{U} \to \mathcal{U}$, we define the discretized operator $A_n : \mathcal{U}_n \to \mathcal{U}_n$ by

$$A_n : \mathcal{U}_n \to \mathcal{U}_n, \quad A_n f := \mathcal{I}_n A f. \tag{2.50}$$

The operator A_n has a matrix representation (which again is also denoted by A_n):

$$A_n = \left(A\varphi_i(q_j)\right)_{ij},$$

Suppose now that $\mathcal{U} = \mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q})$ and $A = L$, the generator of some Itô diffusion, i.e. a second-order differential operator. The entries $\left(L\varphi_i(q_j)\right)_{ij}$ are now computed by analytically applying the differential operator to the basis functions and evaluating at the collocation nodes.

We are interested in parts of the spectrum and the associated eigenspaces of L. So instead of solving $Lv = \lambda v$ on $\mathcal{L}^2_\mu(\mathcal{Q})$, we solve $L_n v = \lambda v$ on $\mathcal{U}_n$. In matrix form, using the weight matrix[8] $W_n = \left(\varphi_i(q_j)\right)_{ij}$, this becomes a generalized eigenvalue problem on $\mathbb{C}^n$:

$$A_n c = \lambda W_n c \quad \text{or} \quad (L_n - \lambda W_n)c = 0, \tag{2.51}$$

where $\sum_{k=1}^n c_k \varphi_k$ then is the approximated eigenfunction of L at eigenvalue λ in Laplace space.

Convergence of the spectrum. [25, Theorem 4.9] states that the eigenvalues λ and eigenfunctions v of L can be approximated by the corresponding eigenfunctions and eigenvalues of $\mathcal{I}_n L$ with spectral accuracy, provided that the v are $\mathcal{C}^\infty$ smooth.

In Cartesian coordinates, the eigenfunctions of the transfer operator of the Smoluchowski and spatial dynamics P^t_{Smol} and S^t have been shown to be $\mathcal{C}^\infty$ under the assumption that the potential $V : \mathbb{R}^d \to \mathbb{R}$ is $\mathcal{C}^\infty$ and all its derivatives of order greater or equal two are bounded.

The proof was first performed by Koltai in [6], and the author suspects that it can be directly transferred to generalized coordinates. However, since the proof was not performed rigorously, we restrain from claiming spectral convergence.

Applicability to spatial dynamics. Of course, this discretization method relies on the existence of an infinitesimal generator for the respective dynamics. Unfortunately, spatial dynamics does *not* possess a generator in the sense that its density flow can be described by a PDE. Spectral collocation for the generator is thus not applicable to spatial dynamics.

[8] In the literature, this matrix is commonly called *mass matrix*. To not confuse it with the system mass matrix, we adapt our notation.

An alternative generator discretization. Weber [78] argued that under certain conditions[9], the spatial transfer operator S^t "almost" behaves like a semigroup of operators, so the existence of a generator-like object L_S can be assumed. Weber went on and constructed a Galerkin-like discretization of L_S.

Let $\hat{P}^t$ be the Ulam discretization of P^t on the disjoint decomposition $\mathcal{D} = \{\mathcal{D}_1, \ldots, \mathcal{D}_n\}$ of $\mathcal{Q}$, and define

$$\hat{L}_{i,j} := \frac{d}{dt}\left(\hat{P}^t\right)_{i,j} .$$

Using Gauß' theorem, one sees that the entries of $\hat{L}$ can be computed by a surface integral of the form

$$\hat{L}_{i,j} = \oint_{\partial \mathcal{D}_i \mathcal{D}_j} z(q) f_{\mathcal{D}_i}(q) \, dS \tag{2.52}$$

where $\partial \mathcal{D}_i \mathcal{D}_j$ is the common edge between $\mathcal{D}_i$ and $\mathcal{D}_j$ (if it exists), and $z(q)$ can be interpreted as the average (with respect to the momenta) flow rate of the system. (2.52) can be approximated by Monte Carlo quadrature, effectively counting transitions of sampled trajectories over the respective edges.

By using a (meshfree) Voronoi tessellation for the the decomposition $\mathcal{D}$, Weber developed an adaptive algorithm, whose complexity depends the number of metastable sets instead of the system dimension. However, again numerical trajectory simulation lies at the heart of this method, which is what we are aiming to avoid.

[9] These conditions will be explored in Section 5.2.

3. The generating structure of spatial dynamics

3.1. Pseudogenerators: definition and properties

We have seen in the previous section that the generator approach offers great benefits in form of numerical complexity reduction, but that it is unfortunately not applicable to spatial dynamics. Thus, in this chapter, we describe the discovery of a generator-like object for spatial dynamics and its numerical exploitation. The main idea is that formally, the time-derivatives of the spatial transfer operator S^t can still be defined, in analogy to (2.9). We will see in Chapter 4) how the resulting operators can play roles similar to the infinitesimal generator in the context of metastability analysis.

We first define time derivatives for general time-parametrized operators:

Definition 3.1.1. Let $\mathcal{X}$ be a Banach space, $T^t : \mathcal{X} \to \mathcal{X},\ t > 0$ be a time-parametrized family of bounded linear operators. We define the operator $\partial_t T^t : \mathcal{D}\left(\partial_t T^t\right) \to \mathcal{X}$

$$\partial_t T^t u = \lim_{h \to 0} \frac{T^{t+h}u - T^t u}{h}$$

and refer to it as the *time-derivative* of T^t. $\mathcal{D}\left(\partial_t T^t\right)$ here is the subspace of $\mathcal{X}$ where the above limit exists. Iteratively, we define by $\partial_t^n T^t := \partial_t\left(\partial_t^{n-1} T^t\right)$ the n-th time-derivative on $\mathcal{D}\left(\partial_t^n T^t\right)$. Finally,

$$G_n := \partial_t^n T^t\big|_{t=0}$$

is called the n-th *pseudogenerator* of T^t.

As explained in Section 2.1.2, the generator of a semigroup induces the associated Fokker–Planck equation (2.19). As T^t does not necessarily have a Fokker–Planck equation (it is not necessarily a semigroup), we refer to the G_n as *pseudo*generators instead.

For $T^t = P^t$, the transfer operator of an Itô process, the pseudogenerators are simply powers of the infinitesimal generator:

Lemma 3.1.2. *On $\mathcal{D}(L^n)$, the n-th pseudogenerator G_n of P^t takes the form*

$$G_n = L^n,$$

with L the infinitesimal generator of the respective dynamics.

Proof. $G_1 = L$ follows directly from the definition of the generator (2.9).

By repeated application of the Fokker–Planck equation (2.19) and using the commutativity of P^t and L, we have

$$\partial_t^n P^t u = L^n P^t u \ .$$

Evaluating at $t = 0$ now gives the result. □

To investigate pseudogenerators for the spatial transfer operator, we will first specify its domain. Let

$$\mathcal{W}^{k,n}(\mathcal{Q}) := \left\{ u \in \mathcal{C}^{2n}(\mathcal{Q}) \mid L_{\text{Lan}}^m u \in \mathcal{L}^1_{\mu_\Omega}(\Omega) \wedge L_{\text{Lan}}^m u \in \mathcal{L}^k_{\mu_\Omega}(\Omega) \ \ \forall\, 0 \le m \le n \right\} . \quad (3.1)$$

Note that, while similar in notation, $\mathcal{W}^{k,n}(\mathcal{Q})$ is not the usual Sobolev space. Also note that u is defined on $\mathcal{Q}$, but $L_{\text{Lan}}^n u$ is defined on Ω, and thus integrability over Ω is required. The requirement is motivated in the following Proposition :

Proposition 3.1.3. *On $\mathcal{W}^{k,n}(\mathcal{Q})$, the n-th pseudogenerator G_n of the spatial transfer operator S^t takes the form*

$$G_n u = \int_{\mathcal{P}} (L_{\text{Lan}})^n u \ d\mu_{\mathcal{P}}.$$

Proof. For this proof, let u_t denote the time-evolution of an $\mathcal{L}^1_{\mu_\mathcal{Q}}(\mathcal{Q})$-function under the *full* Langevin dynamics starting at $u_0 := u$, i.e. $u_t = P^t_{\text{Lan}} u$ and $\partial_t u_t = L_{\text{Lan}} u_t$. Then

$$\partial_t S^t u = \partial_t \int_{\mathcal{P}} P^t_{\text{Lan}} u \ d\mu_{\mathcal{P}} \ .$$

As $u \in \mathcal{L}^1_{\mu_\Omega}(\Omega)$, and P^t_{Lan} is a contraction, $P^t_{\text{Lan}} u$ is absolutely integrable. So

$$\partial_t S^t u = \int_{\mathcal{P}} \partial_t P^t_{\text{Lan}} u \ d\mu_{\mathcal{P}} = \int_{\mathcal{P}} L_{\text{Lan}} u_t \ d\mu_{\mathcal{P}} = \int_{\mathcal{P}} L_{\text{Lan}} P^t_{\text{Lan}} u \ d\mu_{\mathcal{P}} \ .$$

As L_{Lan} and P^t_{Lan} commute and $L_{\text{Lan}} u \in \mathcal{L}^1_{\mu_\Omega}(\Omega)$, the iteration of this argument yields

$$\partial_t^n S^t u\big|_{t=0} = \Big(\int_{\mathcal{P}} (L_{\text{Lan}})^n u_t \ d\mu_{\mathcal{P}} \Big)\Big|_{t=0} \ .$$

By the same argument as above, $L^n_{\text{Lan}} u_t$ is absolutely integrable, and limit and integration can be swapped:

$$\partial_t^n S^t u\big|_{t=0} = \int_{\mathcal{P}} \left((L_{\text{Lan}})^n u_t \right)\big|_{t=0} \ d\mu_{\mathcal{P}} = \int_{\mathcal{P}} (L_{\text{Lan}})^n u \ d\mu_{\mathcal{P}} \ .$$ □

From now on, when speaking of pseudogenerators, we always mean pseudogenerators of S^t. Note that, in general, G_n is not simply a power of G_1, as

$$\int_{\mathcal{P}} (L_{\text{Lan}})^n u \ d\mu_{\mathcal{P}} \neq \Big(\int_{\mathcal{P}} L_{\text{Lan}} \ d\mu_{\mathcal{P}} \Big)^n u \ .$$

3.2. A coordinate expression for pseudogenerators

In this section, we derive explicit expressions for the first couple of pseudogenerators. The derivation will be based on the representation from Proposition 3.1.3, and performing the rigorous vector-analytic calculations therein. Due to the length of said calculations, most proofs of this section are relegated to Appendix B, Section B.1.

We begin with the main result, which expresses G_2 as a partial differential operator:

Theorem 3.2.1. *Let S^t be the spatial transfer operator for the Langevin dynamical process in generalized coordinates on $\mathcal{W}^{k,2}(\mathcal{Q})$. The first three pseudogenerators of S^t take the form*

0. $G_0 = I$,
1. $G_1 = 0$,
2. $G_2 u = \dfrac{1}{\beta}\dfrac{1}{\sqrt{\det M}}\nabla_q^\intercal\Big(\sqrt{\det M}M^{-1}\nabla_q u\Big) - \nabla_q V^\intercal M^{-1}\nabla_q u$.

Proof. See Appendix B.1. □

Remark. The proof of the one-dimensional formulation of Theorem 3.2.1 is easily automatable using a computer algebra system such as Wolfram Mathematica [81]. Program code is provided in Appendix B, Section B.2.

In the important special case of Cartesian coordinates, the term $\nabla_q M^{-1}(q)$ vanishes, and we can slightly extend the technique of this proof to derive G_3:

Corollary 3.2.2. *Consider the spatial transfer operator for the Langevin dynamical process in Cartesian coordinates on $\mathcal{W}^{k,3}(\mathcal{Q})$. Its first pseudogenerators take the form*

0. $G_0 = I$
1. $G_1 = 0$
2. $G_2 u = \dfrac{1}{\beta}\nabla_q^\intercal\big(M^{-1}\nabla_q u\big) - \nabla_q V^\intercal M^{-1}\nabla_q u$
3. $G_3 u = -\gamma\Big[\dfrac{1}{\beta}\nabla_q^\intercal\big(\big(M^{-1}\big)^2\nabla_q u\big) - \nabla_q V^\intercal\big(M^{-1}\big)^2\nabla_q u\Big]$

Proof. See Appendix B, Section B.1. □

Remarks.

1. For the special case $M = I$, Corollary 3.2.2 has been proven in [6, Proposition 4.4].
2. The subsequent pseudogenerators ($G_4, G_5, \ldots$) do, in general, *not* display an analogous structure. This can be seen by an automated derivation of G_4 for the one-dimensional case (see Appendix B, Section B.2).

Connection to Smoluchowski dynamics. Upon inspecting G_2 in Theorem 3.2.1, one discovers an interesting connection:

Corollary 3.2.3. *In the setting of Theorem 3.2.1,*

$$G_2 = L_{\mathrm{Smol}}(M)\,,$$

where $L_{\mathrm{Smol}}(M)$ is the infinitesimal generator of Smoluchowski dynamics with damping matrix M (i.e. the former mass matrix).

Proof. As stated in section A.2, the Smoluchowski infinitesimal generator reads

$$\begin{aligned} L_{\mathrm{Smol}}u &= \beta^{-1}\tilde{\Delta}u - \nabla V \cdot \tilde{\nabla} \\ &= \beta^{-1}\frac{1}{\sqrt{\det\gamma}}\nabla\cdot\left(\sqrt{\det\gamma}\gamma^{-1}\nabla u\right) - \nabla V\cdot\gamma^{-1}\nabla u. \end{aligned}$$

Replacing γ by the mass matrix M gives the result. □

For Cartesian coordinates we additionally have

Corollary 3.2.4. *In the setting of Corollary 3.2.2,*

$$G_3 = -\gamma L_{\mathrm{Smol}}\left(M^2\right)$$

where $L_{\mathrm{Smol}}\left(M^2\right)$ is the infinitesimal generators of Smoluchowski dynamics with damping matrix M^2.

The emergence of Smoluchowski dynamics in the second time derivative of spatial dynamics came as a surprise, and, to the best knowledge of the author, cannot be explained fully by established theory. Recall that Smoluchowski dynamics normally arises from the limit of infinite damping and subsequent time rescaling (see Lemma 2.1.4 and Appendix A.2), and no such procedure is applied for deriving spatial dynamics. Moreover, in the emerging Smoluchowski generator, the original mass matrix takes the place of a damping matrix, which so far has not been interpreted yet.

To the author's knowledge, the connection between spatial dynamics and Smoluchowski dynamics was previously unknown.

3.3. Application of Dyson's formula

We derived the connection between pseudogenerators and the Smoluchowski dynamics by technical, purely vector-analytical calculations. A dynamical and physical understanding of this connection is thus still lacking. Further, expressing the pseudogenerators in a closed form without having to manually conduct the complicated vector-arithmetical calculations would be highly desirable.

While, until now, a closed form for the pseudogenerators could not be derived yet, the most successful approach to explaining the generating structure of S^t and the role of G_2 was the application of the Mori-Zwanzig theory to our problem. The idea was first presented by Koltai in [5], and is expanded in the following.

Central to this approach is the concept of spatial density dynamics as a projection of the phase space density dynamics. Define the projection operator $\Pi : \mathcal{L}^k_{\mu_\Omega}(\Omega) \to \mathcal{L}^k_{\mu_\mathcal{Q}}(\mathcal{Q})$ as

$$\Pi u(q,p) := \mathbb{E}\big[u(q,p) \mid q\,\big] = \frac{\int_\mathcal{P} u(q,p)\, d\mu_\mathcal{P}}{\int_\mathcal{P} d\mu_\mathcal{P}} = \int_\mathcal{P} u(q,p)\, d\mu_\mathcal{P}\,. \tag{3.2}$$

Moreover, let $\Pi^\perp = \mathrm{Id} - \Pi$ denote the complimentary projection on $\mathcal{L}^k_{\mu_\mathcal{Q}}(\mathcal{Q})$. The spatial transfer operator and its pseudogenerators can then be expressed as

$$S^t = \Pi P^t_{\mathrm{Lan}}\,, \qquad G_k = \Pi L^k_{\mathrm{Lan}}\,. \tag{3.3}$$

Combined with Theorem 3.2.1, this leads to

Lemma 3.3.1. *Let $u \in \mathcal{W}^{k,2}(\mathcal{Q})$ (i.e. u is a function independent of p). Then the following holds:*

(a) $\Pi\big(u\cdot\chi(p)\big) = u$, *and* $\Pi^\perp\big(u\cdot\chi(p)\big) = 0$,

(b) $\Pi L_{\mathrm{Lan}} = 0$,

(c) $\Pi L_{\mathrm{Lan}}\Pi^\perp L_{\mathrm{Lan}} = L_{\mathrm{Smol}}(M)$,
where $L_{\mathrm{Smol}}(M)$ is the Smoluchowski generator with damping matrix M.

Proof. (a) As $\int_\mathcal{P} d\mu_\mathcal{P} = 1$, the identities follow directly from the definition of Π.

(b) By Proposition 3.1.3, $\Pi L_{\mathrm{Lan}} = G_1$, which is 0 by Theorem 3.2.1.

(c) The left hand side reads

$$\Pi L_{\mathrm{Lan}}\Pi^\perp L_{\mathrm{Lan}} u = \Pi L^2_{\mathrm{Lan}} u - \Pi L_{\mathrm{Lan}}\Pi L_{\mathrm{Lan}} u \overset{(b)}{=} \Pi L^2_{\mathrm{Lan}} u.$$

By Proposition 3.1.3, this is the second pseudogenerator G_2, which equals $L_{\mathrm{Smol}}(M)$ due to Corollary 3.2.3. □

Let A and B be arbitrary operators for which the operator exponentials e^{tA}, e^{tB} exist in a sensible way[1]. Then $e^{t(A+B)}$ exists, and

$$e^{t(A+B)} = e^{tA} + \int_0^t e^{\tau A} B e^{(t-\tau)(A+B)}\, d\tau. \tag{3.4}$$

[1]For unbounded operators A, $\exp(A)$ can be defined by the so-called *Yosida-approximation*, which we will introduce in Section 4.1.2.

This equation is called *Dyson's formula*, in a formulation following [19].

We can formally write $S^t = \Pi e^{tL_{\text{Lan}}}$, and thus

$$\frac{d}{dt}S^t = \frac{d}{dt}\Pi e^{tL_{\text{Lan}}} = \Pi L_{\text{Lan}} e^{tL_{\text{Lan}}} .$$

Now, setting $A := \Pi L_{\text{Lan}}$, $B := \Pi^\perp L_{\text{Lan}}$, thus $A + B = L_{\text{Lan}}$, and applying (3.4) to $e^{tL_{\text{Lan}}}$, we obtain

$$\frac{d}{dt}S^t = \Pi L_{\text{Lan}}\Big[e^{t\Pi L_{\text{Lan}}} + \int_0^t e^{\tau\Pi L_{\text{Lan}}}\Pi^\perp L_{\text{Lan}} e^{(t-\tau)L_{\text{Lan}}}\, d\tau\Big].$$

Note that for $e^{t\Pi^\perp L_{\text{Lan}}}$ to exist, we have to assume that the orthogonal dynamics is well-defined, i.e. that $\Pi^\perp L_{\text{Lan}}$ again generates a semigroup of propagators, see [26] for details. When applied to a function $u = u(q)$, together with Lemma 3.3.1, one gets

$$\frac{d}{dt}S^t u = \Pi L_{\text{Lan}} \int_0^t e^{\tau\Pi L_{\text{Lan}}}\Pi^\perp L_{\text{Lan}} S^{t-\tau} u\, d\tau.$$

This integral can be approximated via $\int_0^t h(\tau)\, d\tau = th(0) + \mathcal{O}(t^2)$ $(t \to 0)$:

$$\frac{d}{dt}S^t u = t\Pi L_{\text{Lan}}\Pi^\perp L_{\text{Lan}} S^t u + \mathcal{O}(t^2) ,$$

which is by Lemma 3.3.1

$$= tL_{\text{Smol}} S^t u + \mathcal{O}(t^2).$$

We have thus derived an approximate differential equation for the density transport under spatial dynamics in the sense of the Fokker–Planck equation:

Proposition 3.3.2. *Let $u_0 \in \mathcal{W}^{k,2}(\mathcal{Q})$, and consider the transport of u_0 under spatial dynamics, i.e. $u_t = S^t u_0$. Then, with error $\mathcal{O}(t^2)$ $(t \to 0)$, u_t follows the differential equation*

$$\partial_t u_t = tL_{\text{Smol}} u_t . \tag{3.5}$$

Remark. In [26], an alternative formulation of Dyson's formula (3.4) was used:

$$e^{t(A+B)} = e^{tB} + \int_0^t e^{(t-\tau)(A+B)} A e^{\tau B}\, d\tau. \tag{3.6}$$

With this, in the same setting and definitions for A, B as above,

$$e^{tL_{\text{Lan}}} = e^{t\Pi^\perp L_{\text{Lan}}} + \int_0^t e^{(t-\tau)L_{\text{Lan}}}\Pi L_{\text{Lan}} e^{\tau\Pi^\perp L_{\text{Lan}}}\, d\tau . \tag{3.7}$$

and so now we get

$$\frac{d}{dt}\Pi e^{tL_{\text{Lan}}} = \Pi L_{\text{Lan}}\Big[e^{t\Pi^\perp L_{\text{Lan}}} + \int_0^t e^{(t-\tau)L_{\text{Lan}}}\Pi L_{\text{Lan}} e^{\tau\Pi^\perp L_{\text{Lan}}}\, d\tau\Big],$$

Applying this to $u = u(q)$ yields, due to Lemma 3.3.1,

$$\frac{d}{dt} S^t u = \Pi L_{\mathrm{Lan}} \int_0^t e^{(t-\tau)L_{\mathrm{Lan}}} \Pi L_{\mathrm{Lan}} u \, d\tau.$$

Again we approximate the integral, this time by the integrand's end point: $\int_0^t h(\tau)\, d\tau = th(t) + \mathcal{O}(t^2)$ $(t \to 0)$. This gives

$$\begin{aligned} \frac{d}{dt} S^t &= t \Pi L_{\mathrm{Lan}} \Pi L_{\mathrm{Lan}} u + \mathcal{O}(t^2) \\ &= t L_{\mathrm{Smol}} u + \mathcal{O}(t^2). \end{aligned}$$

Note that $S^t u$ no longer appears on the right hand side. We can thus integrate over t and get

$$S^t u = u + \frac{t^2}{2} L_{\mathrm{Smol}} u + \mathcal{O}(t^3). \tag{3.8}$$

We will re-encounter this approximation for S^t in Section 4.1.

3.4. Pseudogenerators in reaction coordinates

We introduced spatial dynamics as a projection onto a specific part of the Langevin phase space, namely the position space. This procedure can be extended by averaging over additional positional degrees of freedom, thus ultimately projecting onto a subset of position space. We will see that the previously found generating structure will be largely retained.

This approach is of particular interest in the molecular dynamical context. Given some molecule in internal coordinates, i.e. bond lengths, valence- and dihedral angles, the conformational behavior is often determined by only a few of these coordinates[2], for example certain collections of dihedral angles, acting as hinges in a protein backbone. Physically relevant observables, even one-dimensional, are also used as reaction coordinates, see for example [79], where the root mean square distance between the functional groups of a receptor and its ligand described the relevant conformational dynamics. We will discuss solely this case of one-dimensional reaction coordinates, but the concept seems transferable to higher dimensions as well (see the remarks at the end of this section). The results have been published in [5].

Let $\xi \colon \mathcal{Q} \to \mathcal{Z} \subset \mathbb{R}$ be a smooth map with the property that for every $z \in \mathcal{Z}$ the level sets

$$\mathcal{M}_z = \{q \in \mathcal{Q} \colon \xi(q) = z\} \subset \mathcal{Q}$$

[2]The existence of these so-called *essential degrees of freedom* requires of course prior knowledge.

are smooth submanifolds of $\mathcal{Q}$ with codimension 1, i.e. hypersurfaces. ξ is then called the *essential* or *reaction coordinate*. Assume that ξ is smooth enough for $\mathcal{M}_z$ to form a foliation of $\mathcal{Q}$. The $\mathcal{M}_z$ take the role of the slices $\Gamma(q)$ (see (2.43)). The unessential coordinates now are given implicitly, in that they parametrize the leaves $\mathcal{M}_z$ for every value z of ξ.

We now want to compute, for a given z, the average value of some quantity $u \in \mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q})$ over the leaf $\mathcal{M}_z$, i.e. the expected value (with respect to $\mu_\mathcal{Q}$) of u conditional on $\xi(q) = z$:

$$\mathbb{E}_{\mu_\mathcal{Q}}\big[u(q) \mid \xi(q) = z\big] = \int_{\mathcal{M}_z} u(q)\, d\mu_z \,. \tag{3.9}$$

To derive an expression for the probability measure μ_z on the leaf $\mathcal{M}_z$, consider

$$\int_\mathcal{Q} u(q)\, d\mu_\mathcal{Q}(q) = \int_\mathcal{Q} u(q) f_\mathcal{Q}(q)\, dq \overset{(*)}{=} \int_\mathcal{Z} \Big(\int_{\mathcal{M}_z} u f_\mathcal{Q} |\nabla\xi|^{-1}\, d\sigma_z \Big)\, dz \,. \tag{3.10}$$

$(*)$ is the *coarea formula* [21, Sect. 3.2] and σ_z is the Riemannian volume element on $\mathcal{M}_z$. With the law of total expectation, one gets

$$\begin{aligned}
\int_\mathcal{Z} \Big(\int_{\mathcal{M}_z} u\, d\mu_z \Big)\, dz &= \mathbb{E}\big[\mathbb{E}_{\mu_z}\big[u(q) \mid \xi(q) = z\big]\big] \\
&= \mathbb{E}_{\mu_\mathcal{Q}}\big[u(q)\big] \\
&= \int_\mathcal{Q} u\, d\mu_\mathcal{Q} \\
&= \int_\mathcal{Z} \Big(\int_{\mathcal{M}_z} u f_\mathcal{Q} |\nabla\xi|^{-1}\, d\sigma_z \Big)\, dz \,.
\end{aligned}$$

Thus we have

$$d\mu_z = \frac{1}{N_\mathcal{Q}(z)} f_\mathcal{Q} |\nabla\xi|^{-1}\, d\sigma_z \,, \quad \text{with} \quad N_\mathcal{Q}(z) = \int_{\mathcal{M}_z} f_\mathcal{Q} |\nabla\xi|^{-1}\, d\sigma_z \,, \tag{3.11}$$

where $N_\mathcal{Q}(z)$ is a normalization factor. This now allows us to define a projection operator $\Pi_z : \mathcal{L}^k_{\mu_\mathcal{Q}}(\mathcal{Q}) \to \mathcal{L}^k(\mathcal{Z})$:

$$\big(\Pi_z u\big)(z) = \frac{1}{N_\mathcal{Q}(z)} \int_{\mathcal{M}_z} u\, d\mu_z \,, \tag{3.12}$$

with which we can define the *essential spatial transfer operator* S^t_{ess}:

$$S^t_{\text{ess}} w(z) := \big(\Pi_z S^t (w \circ \xi)\big)(z) = \int_{\mathcal{M}_z} \int_\mathcal{P} P^t_{\text{Lan}}\big(w \circ \xi\big)(q,p)\, d\mu_\mathcal{P}\, d\mu_z \,. \tag{3.13}$$

Projected pseudogenerators

The according *essential pseudogenerators* are now defined analogous to Definition 3.1.1,

$$G_n^{\mathrm{ess}} := \partial_t^n S_{\mathrm{ess}}^t\big|_{t=0} \,. \tag{3.14}$$

From (3.13) in conjunction with Proposition 3.1.3, it follows directly that, for $w = w(z)$ and $w \circ \xi$ sufficiently smooth,

$$G_n^{\mathrm{ess}} w(z) = \big(\Pi_z G_n (w \circ \xi)\big)(z) \,, \tag{3.15}$$

thus $G_0^{\mathrm{ess}} = I$, $G_1^{\mathrm{ess}} = 0$. Moreover, it has been shown by Hartmann in [5], that for Cartesian coordinates, G_2^{ess} again admits the form of an infinitesimal generator for an Itô diffusion. We extend this result to generalized coordinates in the following

Lemma 3.4.1. *For sufficiently smooth functions $w = w(z)$, the second essential pseudogenerator reads*

$$G_2^{\mathrm{ess}} = \beta^{-1} a(z) \frac{\partial^2}{\partial z^2} + b(z) \frac{\partial}{\partial z} \,,$$

with the noise and drift coefficients

$$a(z) = \Pi_z \Big[\nabla^\intercal \xi M^{-1} \nabla \xi \Big] \,,$$
$$b(z) = \Pi_z \Big[\frac{1}{\sqrt{\det M}} \beta^{-1} \operatorname{tr} \Big(\nabla \xi : \nabla \big(\sqrt{\det M} M^{-1} \big) + \sqrt{\det M} (\nabla^2 \xi) M^{-1} \Big) - \nabla^\intercal V M^{-1} \nabla \xi \Big] \,.$$

Proof. By Corollary 3.2.3, the second pseudogenerator is given by $G_2 = \beta^{-1} \tilde{\Delta} - \nabla V \cdot \tilde{\nabla}$, with $\tilde{\Delta}$ and $\tilde{\nabla}$ defined in (2.30) with γ replaced by the mass matrix M. Applied to $w \circ \xi$, using the matrix calculus version of the chain rule, give

$$\begin{aligned}
\tilde{\Delta}\big(w \circ \xi\big)(q) &= \frac{1}{\sqrt{\det M}} \nabla \cdot \Big(\sqrt{\det M} M^{-1} \nabla w(\xi(q)) \Big) \\
&= \frac{1}{\sqrt{\det M}} \operatorname{tr} \Big[\sqrt{\det M} \nabla^\intercal \xi(q) M^{-1} \nabla \xi(q) w''(\xi(q)) \\
&\quad + \Big(\nabla \xi(q) : \nabla \big(\sqrt{\det M} M^{-1} \big) + \big(\sqrt{\det M} (\nabla^2 \xi(q)) M^{-1} \big) \Big) w'(\xi(q)) \Big] \,,
\end{aligned}$$

$$\tilde{\nabla}\big(w \circ \xi\big)(q) = M^{-1} \nabla w(\xi(q)) = M^{-1} \nabla \xi(q) w'(\xi(q)) \,.$$

Application of Π_z with $\Pi_z w'(\xi(q)) = w'(z)$ and $\Pi_z w''(\xi(q)) = w''(z)$ yields the assertion. □

Remarks.

1. The second essential pseudogenerator G_2^{ess} can be interpreted as the infinitesimal generator of the diffusion

$$\frac{dz}{dt} = b(z) + \sqrt{2\beta^{-1}}\sigma(z)w_t\,, \tag{3.16}$$

   with $\sigma(z) = \sqrt{a(z)}$ and w_t being a one-dimensional uncorrelated Gaussian white noise process. For Cartesian coordinates and mass matrix $M = I$, equation (3.16) has been derived by Legoll and Lelièvre [42] using first-order (Markovian) optimal prediction.

2. In order to use G_2^{ess} in metastability analysis, it has to be discretized. Collocation methods require the evaluation of $G_2^{\mathrm{ess}}\varphi_i(z_j)$ for ansatz functions φ_i at collocations points z_j (see Section 2.3.2), which in turn requires the evaluation of the noise and drift-coefficients $a(z_j)$, $b(z_j)$ in Lemma 3.4.1. As this involves (potentially high-dimensional) integrals that represent averages over the non-essential degrees of freedom, this could be challenging.

3. Though we suspect Lemma 3.4.1 to be generalizable to reaction coordinates of higher dimension, it is unclear whether the resulting projected second pseudogenerator can again be interpreted as the infinitesimal generator of a diffusion of form (3.16).

4. Pseudogenerator–based metastability analysis

4.1. Restoration of the spatial transfer operator

In this section we aim to reconstruct the spatial transfer operator S^t from its pseudogenerators, with the final goal to numerically discretize this reconstruction instead of S^t. For Cartesian coordinates, these reconstruction schemes have first been derived in [6].

The premise for this approach to yield an efficient numerical strategy is of course that the pseudogenerators (more precise: their discretization via collocation methods) can be computed with reasonable numerical effort. If the system at hand is given in Cartesian coordinates, this is indeed the case for its first three pseudogenerators (see Corollary 3.2.2):

- The potential and force field V and ∇V have to be evaluable even for a simple trajectory-based analysis. Thus, we assume that they are readily available and can be evaluated at the collocation points with little numerical effort.
- As we aim for a collocation-like discretization, the complexity of computing the derivatives ∇u and $\nabla^2 u$ depends on the ansatz space we operate on. If chosen sensibly, both derivatives can be compiled analytically and evaluated cheaply. Both Fourier– and Chebyshev ansatz functions—and the ansatz functions of the corresponding product spaces—can be differentiated analytically.

Unfortunately, in generalized coordinates, the additional term ∇M^{-1} in G_2 (see Theorem 3.2.1) poses some challenges:

- Its computation represents real additional cost over simulation-based methods, as it is not needed there.
- $\nabla M^{-1}(q)$ is a tensor of order 3, which, when compiled naively, takes up significant storage space in higher dimensions.
- In the case where the generalized Langevin dynamics is constructed from atom-based Langevin dynamics via a diffeomorphism Φ (see Section 1.2.2), we have $M(q) = \nabla\Phi(q)^\intercal \mathbf{M} \nabla\Phi(q)$. Thus, for the evaluation of $\nabla_q M^{-1}(q)$, the first and second derivatives of Φ are required. As we assume Φ to be known analytically

and consist only of simple geometric transformations[1], this could be automated using a symbolic computer algebra system or automated differentiation, but it is unclear how this scales to higher dimensions. Again, $\nabla^2\Phi$ is a 3-tensor, and can become unwieldy when stored explicitly.

Thus we expect that in generalized coordinates, the discretization of G_2 can be computed only for low-dimensional systems. However, as $G_2 = L_{\text{Smol}}$, the following pseudogenerator based restoration methods are applicable whenever generator-based collocation methods for the Smoluchowski dynamics are.

4.1.1. Taylor reconstruction

As the G_k correspond to time-derivatives of S^t for $t = 0$, a straight-forward idea for approximating S^t is via an operator-valued Taylor-like sum.

We first prove the spatial analogue to Proposition 2.1.9:

Proposition 4.1.1. *Let $u \in \mathcal{W}^{k,n}(\mathcal{Q})$. Then,*

$$\left\| S^t u - \sum_{l=0}^{n} \frac{t^l}{l!} G_l u \right\|_{k,\mu_{\mathcal{Q}}} = \mathcal{O}(t^{n+1}), \quad (t \to 0).$$

Proof. By definition of S^t and Lemma 3.1.3, we can write

$$\begin{aligned}
&\left\| S^t u - \sum_{l=0}^{n} \frac{t^l}{l!} G_l u \right\|_{k,\mu_{\mathcal{Q}}} \\
&\quad = \left\| \frac{1}{f_{\mathcal{Q}}} \int_{\mathcal{P}} P^t_{\text{Lan}}(u)\, d\mu_{\mathcal{P}} - \sum_{l=0}^{n} \left(\frac{t^l}{l!} \frac{1}{f_{\mathcal{Q}}} \int_{\mathcal{P}} L^l(u)\, d\mu_{\mathcal{P}} \right) \right\|_{k,\mu_{\mathcal{Q}}} \\
&\quad \leq \frac{1}{f_{\mathcal{Q}}} \int_{\mathcal{P}} \left\| P^t_{\text{Lan}}(u) - \sum_{l=0}^{n} \frac{t^l}{l!} L^l(u) \right\|_{k,\mu_{\mathcal{Q}}} d\mu_{\mathcal{P}}.
\end{aligned}$$

However, the integrand is of order $\mathcal{O}(t^{K+1})$ by Proposition 2.1.9. □

We define on $\mathcal{W}^{k,n}(\mathcal{Q})$ the n-th *Taylor reconstruction* of S^t:

$$T^t_n u := \sum_{l=0}^{n} \frac{t^l}{l!} G_l u \,. \tag{4.1}$$

As described in the last section, the G_n for $n > 3$ are not readily available, and G_3 only is available in the Cartesian case. Thus T^t_3 and T^t_2 respectively will be used primarily. We then get quartic and cubic convergence for the density propagation:

[1] Remember that the generalized coordinates were originally motivated by internal coordinates, so imagine Φ to describe the computation of bond lengths, valence– and dihedral angles from the atoms' positions.

Corollary 4.1.2. *Let $u \in \mathcal{W}^{k,3}(\mathbf{Q})$, S^t the spatial transfer operator for Langevin dynamics in Cartesian coordinates and T_3^t its third Taylor reconstruction. Then*

$$\left\| S^t u - T_3^t u \right\|_{k,\mu_{\mathbf{Q}}} = \mathcal{O}(t^4), \quad (t \to 0).$$

Let $u \in \mathcal{W}^{k,2}(\mathcal{Q})$, S^t the spatial transfer operator for Langevin dynamics in generalized coordinates, T_2^t its second Taylor reconstruction. Then

$$\left\| S^t u - T_2^t u \right\|_{k,\mu_{\mathbf{Q}}} = \mathcal{O}(t^3), \quad (t \to 0).$$

In the special case of Cartesian coordinates with identity mass matrix, T_3^t assumes a particularly simple form:

Corollary 4.1.3. *Let T_3^t be the Taylor reconstruction for Langevin dynamics in Cartesian coordinates with $M = I$. Then T_3^t is defined on $\mathcal{W}^{k,2}(\mathcal{Q})$ and for $u \in \mathcal{W}^{k,2}(\mathcal{Q})$,*

$$T_3^t = \mathrm{id} + \left(\frac{t^2}{2} - \gamma \frac{t^3}{6} \right) \left(\frac{1}{\beta} \Delta - \nabla V \cdot \nabla \right) .$$

Proof. Using $M = I$ in the equation for G_2 and G_3 in Corollary 3.2.2 gives $G_3 = -\gamma G_2$. As for Cartesian coordinates the Smoluchowski generator takes the form $L_{\mathrm{Smol}} = \frac{1}{\beta}\Delta - \nabla V \cdot \nabla$, and $G_2 = L_{\mathrm{Smol}}$, the Taylor reconstruction T_3^t takes the asserted form. □

We expect that T_2^t and T_3^t approximate S^t well (for $t \to 0$) and can be computed cheaply, under the assumptions described at the beginning of this section. However, unlike S^t, T_n^t is neither norm-preserving nor positive for densities with respect to f_Ω, i.e.

$$\|T_n^t u\|_{1,\mu_{\mathcal{Q}}} \neq \|u\|_{1,\mu_{\mathcal{Q}}} \quad \text{for } u \geq 0 .$$

Therefore, when transporting u, we lose the interpretation of $\left(T_n^t u\right) f_\Omega$ as a physical density[2].

Moreover, for t sufficiently large, $T_n^t u$ is not even a contraction on $\mathcal{W}^{1,2}(\mathcal{Q})$, as can be seen easily for the Cartesian coordinate case. Here, with $\lambda \in \sigma(G_2),\ \lambda \neq 0$,

$$\Big| \underbrace{1 + \frac{t^2}{2}\lambda - \frac{\gamma t^3}{6}\lambda}_{\in \sigma(T^t)} \Big| \ \to \ \infty, \quad (t \to \infty),$$

and so $\|T_n^t\|_{2,\mu_{\mathcal{Q}}} \to \infty, \quad (t \to \infty)$. We will see in the numerical experiments that this quickly (i.e. already for small to moderate t) destroys the interpretation of the eigenvalues of T_n^t as metastability quantifiers.

[2] While this limits the usefulness of T_n^t for pure density transport, it is actually irrelevant for the detection of metastable sets, as the eigenfunctions of T_n^t are constant in t.

Remark. In equation (3.8), a third–order approximation for the density transport under S^t was given:

$$S^t u = \underbrace{u + \frac{t^2}{2} L_{\text{Smol}} u}_{T_2^t u} + \mathcal{O}(t^3).$$

As the operator on the right hand side is the second Taylor reconstruction T_2^t, this can be seen as an alternative proof of its third–order approximation quality.

4.1.2. Exponential reconstruction

To avoid the structural disadvantages of T_n^t, an alternative approximation to S^t can be defined, which we will call the *exponential reconstruction* E^t. It will indeed be norm-preserving and positive for densities, further contractive on $\mathcal{W}^{1,2}(\mathcal{Q})$. Let

$$E^t u := \exp\left(\frac{t^2}{2} G_2\right) u \,. \tag{4.2}$$

One has to be careful with notation, however. As a differential operator, G_2 is unbounded on $\mathcal{W}^{k,2}(\mathcal{Q})$, and thus the above operator exponential cannot be defined by an infinite series. However, considerations of e.g. Pazy [56] allow us to define E^t over a bounded operator approximating G_2, the so-called *Yosida approximation*:

$$G_2^\lambda := \lambda G_2 (\lambda I - G_2)^{-1} \quad \text{for } \lambda \in \mathbb{R}_{\geq 0} \,.$$

Lemma 4.1.4. *G_2^λ is a bounded linear operator on $\mathcal{W}^{1,2}(\mathcal{Q})$, and*

$$\lim_{\lambda \to \infty} G_2^\lambda = G_2.$$

Proof. As G_2 is the infinitesimal generator of the Smoluchowski dynamics, it fulfills the assumptions of [56, Chapter 1, Theorem 3.1]. Thus, the convergence holds due to [56, Chapter 1, Lemma 3.3]. □

The operator exponential in (4.2) is now defined as

$$\exp\left(\frac{t^2}{2} G_2\right) u := \lim_{\lambda \to \infty} \exp\left(\frac{t^2}{2} G_2^\lambda\right) u.$$

The operator family E^t now indeed maps densities (with respect to $\mu_{\mathcal{Q}}$) onto densities:

Proposition 4.1.5. *Let $u \in \mathcal{L}^1_{\mu_{\mathcal{Q}}}(\mathcal{Q})$, $u \geq 0$. Then*

$$E^t u \geq 0 \quad \textit{and} \quad \|E^t u\|_{1,\mu_{\mathcal{Q}}} = \|u\|_{1,\mu_{\mathcal{Q}}} \quad \textit{for all } t \geq 0.$$

Moreover, for each t, E^t is a contraction on $\mathcal{L}^k_{\mu_{\mathcal{Q}}}(\mathcal{Q})$.

Proof. The Smoluchowski transfer operator P^t_{Smol} possesses all of the described properties due to being the solution operator to the Smoluchowski Fokker–Planck equation (2.31).

Due to Corollary 3.2.3 and Lemma 4.1.4, E^t simply is a time-scaled version of the transfer operator of the Smoluchowski dynamics:

$$E^t = P^{t^2/2}_{\text{Smol}}.$$

As such, it inherits the desired properties from P^t_{Smol}. □

The following statements describe the approximation quality of E^t in the limit $t \to 0$, analogously to the Taylor reconstruction:

Lemma 4.1.6. *Let $u \in \mathcal{W}^{k,N}(\mathcal{Q})$. Then for $t \to 0$,*

$$\varepsilon(t) := \left\| E^t u - \sum_{n=0}^{N} \frac{\left(\frac{t^2}{2} G_2\right)^n}{n!} u \right\|_{k,\mu_{\mathcal{Q}}} = \mathcal{O}(t^{2N+1}).$$

Proof. $E^t u$, as the smoothly time-rescaled Smoluchowski transfer operator, is $N+1$ times differentiable in t. Thus we can apply the Taylor expansion for Banach space valued functions to E^t (see [82, Section 4.5]):

$$E^t u = \sum_{n=0}^{2N} \frac{t^n}{n!} (\partial_s^n E^s\big|_{s=0}) u + \Big(\int_0^1 \frac{1}{(2N)!} (1-s)^{2N} \partial_s^{2N+1} E^{st} u \, ds \Big) t^{2N+1}. \tag{4.3}$$

It can be shown iteratively that the n-th derivative of E^s is

$$\partial_s^n E^s = E^s \sum_{j=0}^{\lfloor \frac{n}{2} \rfloor} \frac{n!\, s^{n-2j}}{2^j\, j!\, (n-2j)!} G_2^{n-j}\,,$$

so with the operator $A_n := \sum_{j=0}^{\lfloor \frac{n}{2} \rfloor} \frac{n!\, s^{n-2j}}{2^j\, j!\, (n-2j)!} G_2^{n-j}$, we have $\partial_s^n E^s = E^s A_n$.

Evaluation at $s = 0$ yields

$$\partial_s^n E^s\big|_{s=0} = \begin{cases} 0\,, & n \text{ odd}\,, \\ \frac{n!}{2^{\frac{n}{2}} (\frac{n}{2})!} G_2^{\frac{n}{2}}\,, & n \text{ even}\,, \end{cases}$$

and so

$$\sum_{n=0}^{2N} \frac{t^n}{n!} (\partial_s^n E^s\big|_{s=0}) u = \sum_{n=0}^{N} \frac{t^{2n}}{(2n)!} \Big(\frac{(2n)!}{2^n n!} G_2^n \Big) u = \sum_{n=0}^{N} \frac{t^{2n}}{2^n n!} G_2^n u\,.$$

Thus, the remainder is only the integral in (4.3):

$$\begin{aligned}\left\| E^t u - \sum_{n=0}^{N} \frac{\left(\frac{t^2}{2} G_2\right)^n}{n!} u \right\|_{2,\mu_{\mathcal{Q}}} &= \left\| t^{2N+1} \int_0^1 \frac{1}{(2N)!} (1-s)^{2N} \partial^{2N+1} E^{st} u \, ds \right\|_{2,\mu_{\mathcal{Q}}} \\ &\leq \frac{t^{2N+1}}{(2N)!} \sup_{s\in[0,1]} \left\| \partial^{2N+1} E^s u \right\|_{2,\mu_{\mathcal{Q}}} \\ &= \frac{t^{2N+1}}{(2N)!} \sup_{s\in[0,1]} \left\| (E^s A_{2N+1}) u \right\|_{2,\mu_{\mathcal{Q}}} \\ &\leq \frac{t^{2N+1}}{(2N)!} \sup_{s\in[0,1]} \underbrace{\left\| E^s \right\|_{2,\mu_{\mathcal{Q}}}}_{\leq 1} \left\| A_{2N+1} u \right\|_{2,\mu_{\mathcal{Q}}} .\end{aligned}$$

As $u \in \mathcal{W}^{k,N}(\mathcal{Q})$, we have $\|A_{2N+1}u\|_{2,\mu_{\mathcal{Q}}} < \infty$. This completes the proof. □

Corollary 4.1.7. *Let $u \in \mathcal{W}^{1,2}(\mathcal{Q})$. Then*

$$\left\| E^t u - S^t u \right\|_{2,\mu_{\mathcal{Q}}} = \mathcal{O}(t^3) \quad \text{for } t \to 0.$$

Proof.

$$\begin{aligned}\left\| E^t u - S^t u \right\|_{2,\mu_{\mathcal{Q}}} &\leq \left\| E^t u - \Big(\sum_{n=0}^{2} \frac{t^n}{n!} G_n \Big) u \right\|_{2,\mu_{\mathcal{Q}}} + \left\| \Big(\sum_{n=0}^{2} \frac{t^n}{n!} G_n \Big) u - S^t u \right\|_{2,\mu_{\mathcal{Q}}} \\ &= \left\| E^t u - \sum_{n=0}^{1} \frac{\left(\frac{t^2}{2} G_2\right)^n}{n!} u \right\|_{2,\mu_{\mathcal{Q}}} + \left\| \Big(\sum_{n=0}^{2} \frac{t^n}{n!} G_n \Big) u - S^t u \right\|_{2,\mu_{\mathcal{Q}}}.\end{aligned}$$

Both summands decline like $\mathcal{O}(t^3)$ $(t \to 0)$, the first due to Lemma 4.1.6, the second due to Theorem 4.1.1. □

Remarks.

1. E^t is exactly the solution operator of the (approximate) differential equation for the spatial dynamics which we derived in Proposition 3.3.2: For $u \in \mathcal{W}^{k,2}(\Omega)$,

$$\partial_t \Big(\exp\Big(\frac{t^2}{2} G_2\Big) u \Big) = t G_2 \exp\Big(\frac{t^2}{2} G_2\Big) u,$$

   so $E^t u$ solves (3.5).

2. In the Cartesian setting, where G_3 takes a simple form similar to G_2, an approximation order of $\mathcal{O}(t^4)$ can be achieved by including G_3 into E^t, i.e. setting

$$E_3^t := \exp\left(\frac{t^2}{2} G_2 + \frac{t^3}{6} G_3\right) .$$

E_3^t again is a time-rescaled transfer operator of the Smoluchowski dynamics. However, it is not contractive for all t, as $\sigma(G_3) \subset [0, \infty)$. This follows from $\sigma(L_{\text{Smol}}) \subset (-\infty, 0]$ and $G_3 = -\gamma L_{\text{Smol}}$. We thus stick to the lower-order approximation to retain the correct qualitative behavior for larger t.

3. In contrast to the operator T^t, which is only defined on the domain of the associated pseudogenerators, the operator E^t can be defined for every $u \in \mathcal{L}^k_{\mu_\mathcal{Q}}(\mathcal{Q})$. We conjecture that Corollary 4.1.7 holds also for this class of functions, although our proof is not extendable to this case—it uses the Taylor reconstruction to estimate the error. More advanced techniques from semigroup theory are needed, hence this will be subject of future studies.

4.1.3. Reconstruction of the spectrum

The previous section deals with the pointwise convergence of T_n^t and E^t to S^t. For conformation analysis, however, the approximation to the spectrum of S^t has to be examined. We perform the following analysis exemplarily for E^t, but it holds for T_2^t analogously.

For some operator A, the set

$$\sigma_\varepsilon(A) = \left\{\lambda \in \mathbb{C} \mid \left\|Au - \lambda u\right\| \leq \varepsilon \text{ for some } u \in \mathcal{D}(A)\right\} \tag{4.4}$$

is called the *ε-pseudospectrum* of A, the theory of which is covered extensively in [72].

From Corollary 4.1.7 (respectively Proposition 4.1.1 for T_2^t) it follows that if u is an eigenfunction of E^t at eigenvalue λ_E, then

$$\left\|S^t u - \lambda_E u\right\|_{2,\mu_\mathcal{Q}} = \left\|S^t u - E^t u\right\|_{2,\mu_\mathcal{Q}} = \mathcal{O}(t^3).$$

Likewise, for u an eigenfunction of S^t at eigenvalue λ,

$$\left\|E^t u - \lambda u\right\|_{2,\mu_\mathcal{Q}} = \left\|E^t u - S^t u\right\|_{2,\mu_\mathcal{Q}} = \mathcal{O}(t^3)\ .$$

Thus we can always find a small $\varepsilon(t) > 0$ with $\varepsilon(t) = \mathcal{O}(t^3)$ so that

$$\sigma_p(S^t) \subset \sigma_{\varepsilon(t)}(E^t) \quad \text{and} \quad \sigma_p(E^t) \subset \sigma_{\varepsilon(t)}(S^t)\ .$$

Since S^t is self-adjoint, thus normal, for each $\tilde{\lambda} \in \sigma_{\varepsilon(t)}(S^t)$ there exists an eigenvalue $\lambda \in \sigma_p(S^t)$ with $|\lambda - \tilde{\lambda}| \leq \varepsilon(t)$. Likewise, E^t is self-adjoint as a time–rescaled Smoluchowski transfer operator, so for each $\tilde{\lambda}_E \in \sigma_{\varepsilon(t)}(E^t)$ there exists $\lambda_E \in \sigma_p(T^t)$ with $|\lambda_E - \tilde{\lambda}_E| \leq \varepsilon(t)$.

Together we have

Proposition 4.1.8. *Let $B_\varepsilon(A)$ denote the ε-neighborhood of a set $A \subset \mathbb{R}$ and $\sigma_p(S^t)$, $\sigma_p(E^t)$ denote the point spectra of the spatial transfer operator S^t and its exponential restoration E^t. Then*

$$\sigma_p(S^t) \subset B_{\varepsilon(t)}\big(\sigma_p(E^t)\big) \ ,$$

with $\varepsilon(t) = \mathcal{O}(t^3)$.

Remarks.

1. In Corollary 4.1.8, it suffices to consider the absolute approximation error as

$$\lambda(t), \lambda_T(t), \lambda_E(t) \to 1 \ (t \to 0) \ .$$

2. The result can be extended to the n–th Taylor restoration T_n^t, thus giving an approximation error of $\mathcal{O}(t^{n+1})$ for the spectrum, provided T_n^t is self-adjoint (or at least normal). For Cartesian coordinates and $n = 3$, that is the case.

4.2. Numerical experiments

In this section we numerically demonstrate the pseudogenerator– and collocation–based restoration methods from Section 4.1 by means of two academic examples. As the theoretical results concerning pseudogenerators for Langevin dynamics in generalized coordinates are relatively new, only Langevin systems in Cartesian coordinates are considered. The experiments were first published in [6].

4.2.1. One-dimensional double-well potential

To accurately test the approximation quality of the third order Taylor approximation T_3^t and the exponential approximation E^t to S^t, we first analyze a simple one-dimensional Cartesian Langevin system on the unit circle, which can be discretized to high resolution by the classical Ulam method. It has the 1–periodic double-well potential

$$V(q) = 1 + 3\cos(2\pi q) + 3\cos^2(2\pi q) - \cos^3(2\pi q).$$

We consider the system with constant mass matrix $M = 1$, inverse temperature $\beta = 1$, Langevin damping constant $\gamma = 1$ and corresponding noise constant $\sigma = \sqrt{2}$. As even for this simple system neither eigenvalues nor -vectors can be computed analytically, we first compute a classic Ulam discretization (see Section 2.3.1) to S^t with a large number of discretization boxes and sampling points, denoted by $\tilde{S}^t$. Spectra and eigenvectors of $\tilde{S}^t$ then serve as a reference point for the error analysis. A resolution of 2^{10} boxes and 10^4 sampling points produce sufficiently accurate spectral data, as a further increase does not alter the results considerably.

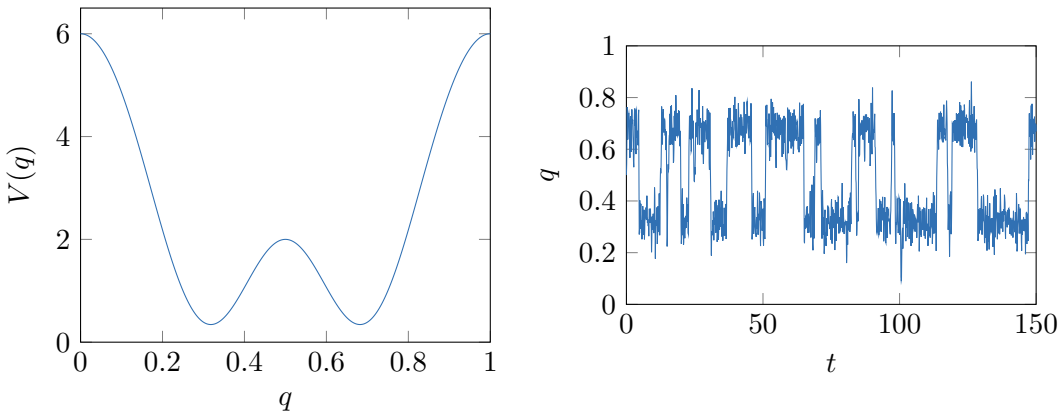

Figure 4.1.: The two wells of the periodic double well potential indicate two metastable regions in configuration space. A trajectory q_t of the according Langevin dynamics with appropriate temperature shows the characteristic jumping pattern between the wells.

As our goal is metastability analysis, we analyze the error in the portion of the subdominant spectrum and the associated eigenvectors. Table 4.2 shows a distinct *spectral gap* after the second eigenvalue of $\tilde{S}^t$, so analyzing λ_1, λ_2 and v_1, v_2 should reveal the main metastable sets.

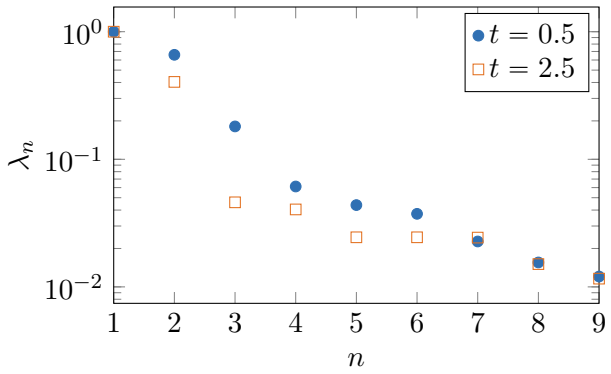

Figure 4.2.: The dominant eigenvalues of $\tilde{S}^t$ for different lag times t. A spectral gap after λ_2 is observable (more noticeable for larger lag times).

For the discretization $\tilde{G}_2$ of the pseudogenerator G_2, we use 33 Fourier ansatz functions of form (2.48) and the same number of collocation points on a equidistant grid. The Fourier modes possess inherent periodic boundary conditions that match the periodic domain.

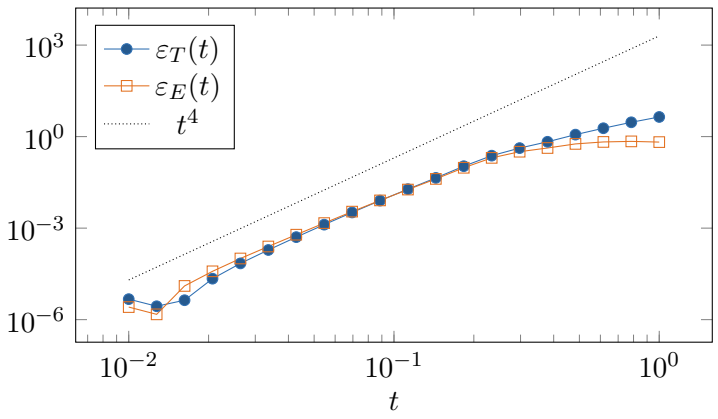

Figure 4.3.: Eigenvalue errors for the Taylor and Exponential approximation for small t. The error "bottoming out" on the left side of the plot is due to the fact that computing the Ulam discretization $\tilde{S}^t$ to high accuracy for very small values of t requires increasingly large numbers of sampling points, as the box transitions get very rare.

Eigenvalue comparison

The absolute error in the subdominant eigenvalues is now measured by

$$\varepsilon_T(t) := \left|\lambda_2(\tilde{S}^t) - \lambda_2(\tilde{T}_3^t)\right| , \qquad \varepsilon_E(t) := \left|\lambda_2(\tilde{S}^t) - \lambda_2(\tilde{E}^t)\right|$$

where $\lambda_2(\tilde{S}^t), \lambda_2(\tilde{T}_3^t), \lambda_2(\tilde{E}^t)$ is the subdominant eigenvalue of $\tilde{S}^t, \tilde{T}_3^t$ and $\tilde{E}^t$, respectively.

Figure 4.3 shows $\varepsilon_T(t)$ and $\varepsilon_E(t)$ for small lag times. The suspected convergence rate $\varepsilon_T(t) = \mathcal{O}(t^4)$ for $t \to 0$ for the Taylor approximation is confirmed. Also, while Corollary 4.1.8 depicted a rate of convergence of only $\mathcal{O}(t^3)$ for $\varepsilon_E(t)$, this rate seems to be exceeded for this particular example system.

In Figure 4.4 the 8 largest eigenvalues for increasing lag times are shown. We see that for small t (up to $t \approx 0.1$), a qualitative agreement of the eigenvalues of $\tilde{S}^t$, $\tilde{E}^t$ and $\tilde{T}_3^t$ can be observed. However, for increasing t, the spectrum of $\tilde{T}_3^t$ becomes negative, while the spectrum of $\tilde{E}^t$ at least shows the right qualitative behavior

$$\sup\{\lambda \in \sigma_p(\tilde{E}^t),\ \lambda \neq 1\} \to 0 , \quad (t \to \infty) .$$

Added for comparison, the spectrum of the discretized Smoluchowski transfer operator $\tilde{P}^t_{\text{Smol}}$, representing dynamics on a completely different time scale, inadequately approximates the spectrum of $\tilde{S}^t$.

Eigenvector comparison. Before considering the eigenvectors of T_3^t and E^t, note that all but the first eigenvector of S^t (and $\tilde{S}^t$) are in general time-dependent. In

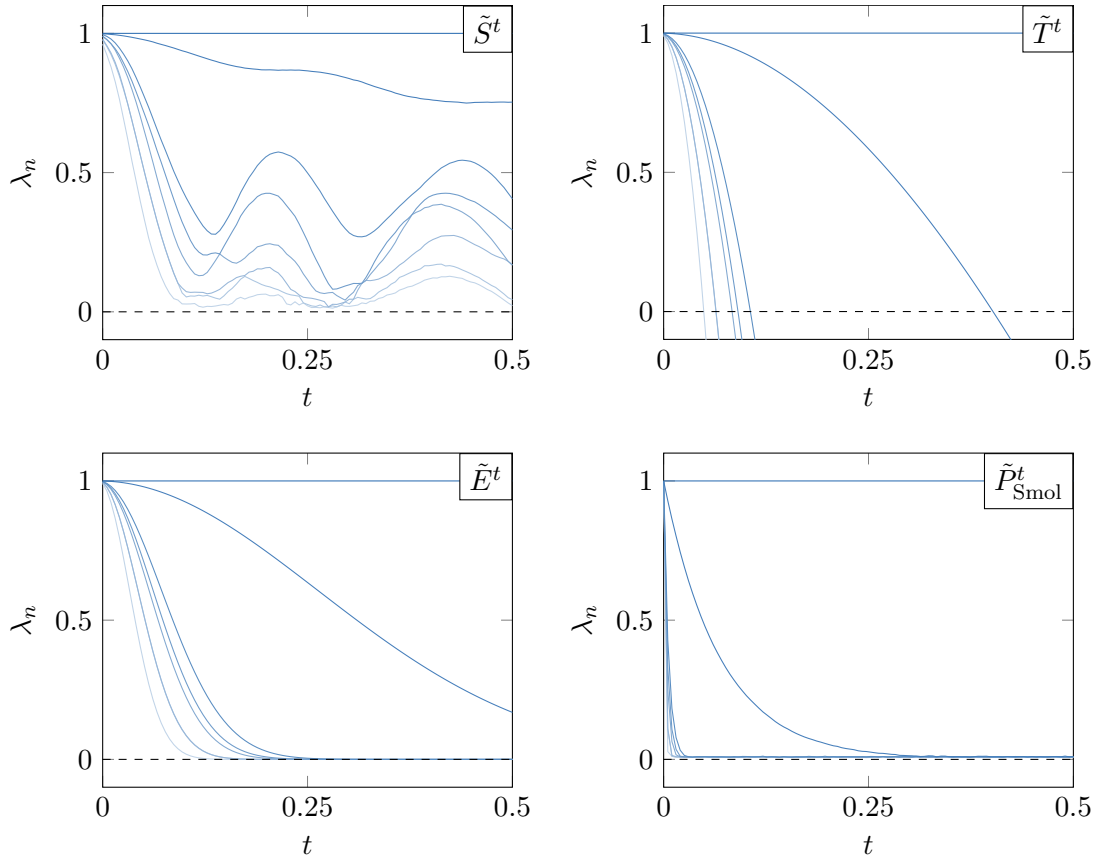

Figure 4.4.: The 8 dominant eigenvalues of the various discretized operators in dependence of the lag time t.

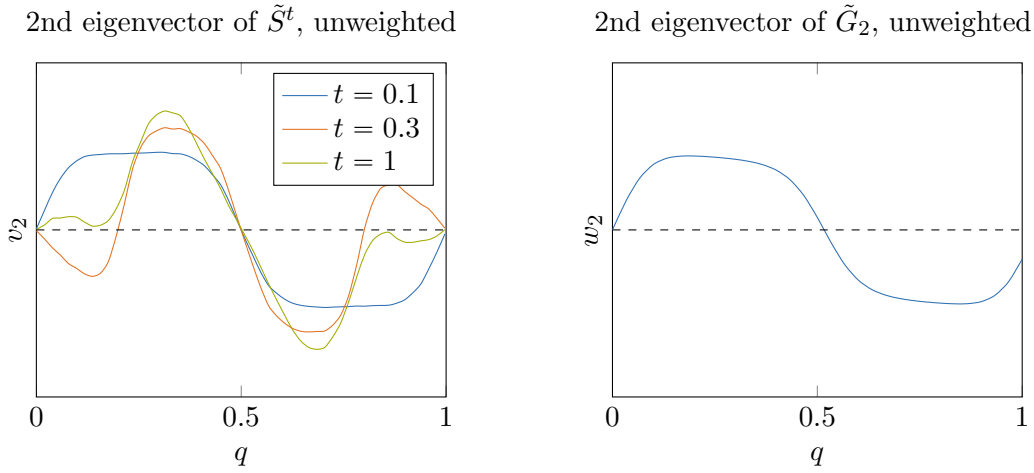

Figure 4.5.: Comparison of the second largest eigenvectors of $\tilde{S}^t$ and $\tilde{G}_2$. We see that for $\tilde{S}^t$, the eigenvector is strongly time-dependent in the unweighted case.

contrast, the eigenvectors of any semi-group transfer operator coincide with those of its infinitesimal generator for all times, see Theorem 2.1.5.

In our example, while the first eigenvector of $\tilde{S}^t$ remains constant ($v_1 \equiv 1$), the second eigenvector starts out as almost a step function, but gets more and more concentrated in the potential wells for increased lag times and even repeatedly changes signs at some positions (Figure 4.5 left). The eigenvectors of $\tilde{T}_3^t$ and $\tilde{E}^t$ (see Figure, however, are time-invariant, and coincide with those of G_2, by construction. For small lag times, the second eigenvector w_2 of $\tilde{G}_2$ compares well to the second eigenvector v_2 of $\tilde{S}^t$ (Figure 4.5). For larger t, there is a clear difference.

As we understand S^t, E^t and T_3^t to be defined on $\mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q})$, their physical interpretation is to transport functions *with respect to* $f_\mathcal{Q}$. It is therefore appropriate to weight their eigenvectors with $f_\mathcal{Q}$, as this gives their representation with respect to the Lebesgue measure. Weighted with $f_\mathcal{Q}$, the time-dependence of v_2 becomes insignificant, as the parts of $\mathcal{Q}$ where v_2 and w_2 differ are sets of small $\mu_\mathcal{Q}$-measure. Consequently, our restoration provides a very good approximation of the $f_\mathcal{Q}$-weighted eigenvectors (see Figures 4.6). It has to be investigated whether this phenomenon hints at some underlying regularity or is just a singular fluke.

The sign structure of w_2 can now be used (see the comment after Theorem 2.2.6) to identifies the following pair of presumably metastable sets:

$$A_1 = \{w_2 \geq 0\} = (0, 0.5], \quad A_2 = \{w_2 < 0\} = (0.5, 1].$$

It can be easily verified that A_1, A_2 form the maximally metastable decomposition of the system, as they correspond to the areas between the two energy barriers of the potential.

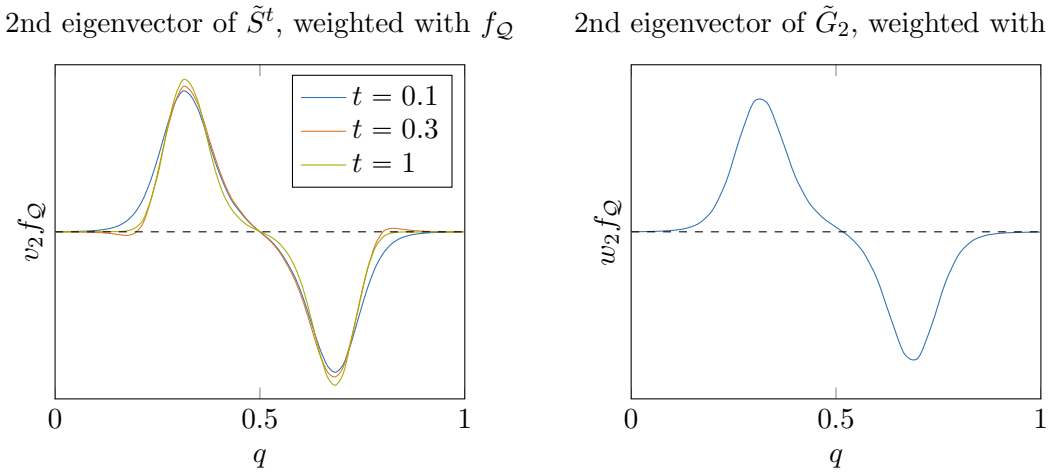

Figure 4.6.: Comparison of the second largest eigenvectors of $\tilde{S}^t$ and $\tilde{G}_2$, weighted with f_Q. The time-dependency for $\tilde{S}^t$ decreases significantly.

Transition probabilities. Theorem 2.2.6 now provides bounds for the transition probabilities between those metastable sets. Recall that the combined degree of metastability

$$s(t, A_1, A_2) = p(t, A_1, A_1) + p(t, A_2, A_2)$$

can be bounded from above and below by

$$1 + \rho_2(S^t)\lambda_2(S^t) + c(S^t) \leq s(t, A_1, A_2) \leq 1 + \lambda_2(S^t) \,,$$

where

- $\lambda_2(S^t)$ is the subdominant eigenvalue of S^t ,
- $\rho_2(S^t) = \langle v_2(S^t), \chi_{A_1} - \chi_{A_2} \rangle$, with $v_2(S^t)$ the subdominant eigenvector of S^t ,
- $c(S^t) = a(S^t)\big(1 - \rho_2(S^t)\big)$ with $a(S^t)$ the lower bound of the spectrum of S^t.

We want to verify these bounds numerically and examine whether they can be approximated by the restored operator E^t, i.e. whether the respective bounds based on E^t hold:

$$1 + \rho_2(E^t)\lambda_2(E^t) + c(E^t) \overset{?}{\leq} s(t, A_1, A_2) \overset{?}{\leq} 1 + \lambda_2(E^t) \,,$$

We first compute an estimate for $s(t, A_1, A_2)$ by a simple Monte Carlo algorithm:

1. Randomly draw two sets of starting points, with density $\chi_{A_1} f_Q / \mu_Q(A_1)$ and $\chi_{A_2} f_Q / \mu_Q(A_2)$ (i.e. sample f_Q in A_1 and A_2).
2. Numerically integrate those samples to time t.
3. Count the portion of the endpoints that are located in A_1 and A_2, respectively.

For sufficiently many samples, this provides an accurate estimate for $p(t, A_1, A_1)$ and $p(t, A_2, A_2)$.

The left portion of Figure 4.8 confirms that the bounds hold when based on $\lambda_2(\tilde{S}^t)$ and $v_2(\tilde{S}^t)$. They do, however, provide a significant margin of error, and diverge for increasing lag time. The right portion of Figure 4.8 shows that *only for small lag times* (again up to about $t \approx 0.1$, $s(t, A_1, A_2)$ is contained within the bounds based on the restored eigenvalue $\lambda_2(E^t)$ and its eigenvector $v_2(E^t)$.

We can thus conclude that, while the sign structure of the eigenfunctions w_2 of G_2 correctly identifies the maximally metastable decomposition A_1, A_2, the eigenvalue $\lambda_2(E^t)$ of the exponential reconstruction contains information about the combined degree of metastability (hence indirectly the transition rates between A_1 and A_2) only for small t. The same conclusions can be drawn for the Taylor reconstruction T_3^t.

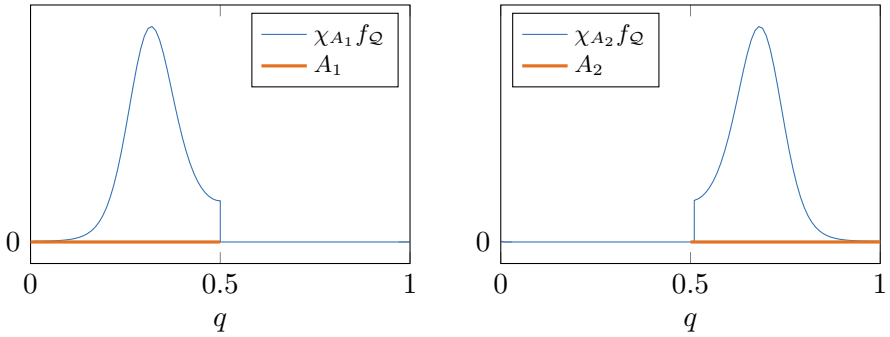

Figure 4.7.: The metastable sets with the corresponding portion of the canonical density $f_{\mathcal{Q}}$.

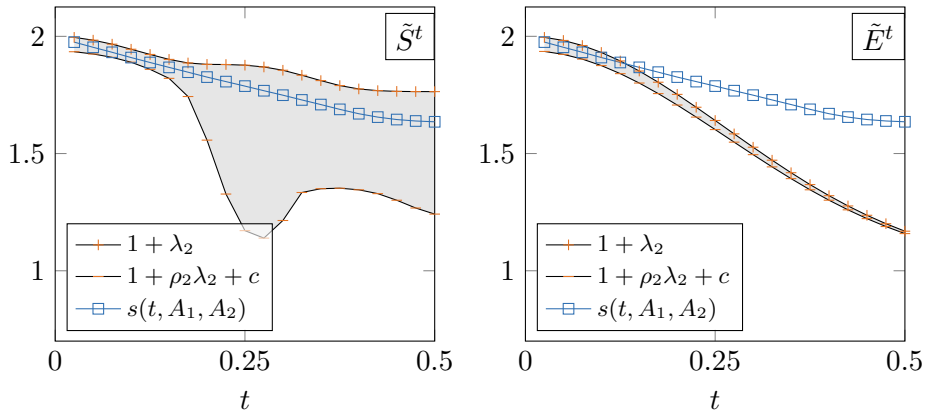

Figure 4.8.: Metastability of the partition A_1, A_2 and comparison to the bounds of Theorem 2.2.6, calculated based on the spectral information of $\tilde{S}^t$ (left) and $\tilde{E}^t$ (right).

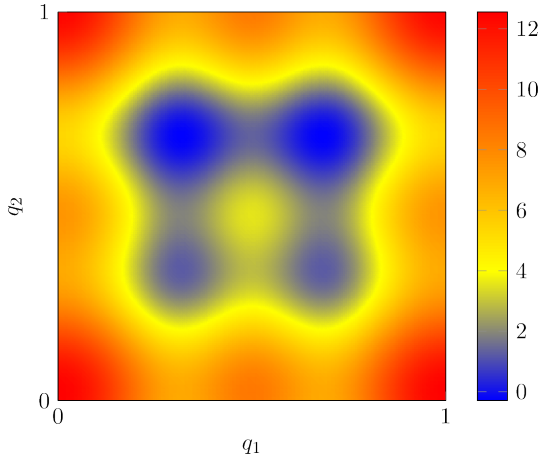

Figure 4.9.: The quad-well potential in the region $[0,1]^2$.

4.2.2. Two-dimensional quad-well potential

The discretization and restoration methods perform similarly on higher-dimensional domains. Again using grid-based spectral collocation, we will demonstrate how to reconstruct the spatial transfer operator for a periodic two-dimensional quad-well potential of the form

$$\begin{aligned} V(q_1,q_2) = {} & 1+3\cos(2\pi q_1)+3\cos^2(2\pi q_1)-\cos^3(2\pi q_1) \\ & +1+3\cos(2\pi q_2)+3\cos^2(2\pi q_2)-\cos^3(2\pi q_2)+\cos(2\pi q_2-\frac{\pi}{3}), \end{aligned} \tag{4.5}$$

visualized in Figure 4.9.

This potential is of interest, as the four local minima of different depth form multiple hierarchies of metastable sets. A similar (albeit non-periodic) potential was considered in [14]. The potential is periodic on the torus $\mathbb{T}^2$, so for discretization we use (products of) Fourier modes. As for this example we do not perform rigorous error analysis, a resolution of 31 per dimension is sufficient for both the Ulam and collocation discretizations, resulting in a total of 961 boxes and ansatz functions, respectively. We use heat and damping parameters $\beta = 1,\ \gamma = 1$ and mass matrix $M = \left(\begin{smallmatrix} 1 & 0 \\ 0 & 1 \end{smallmatrix}\right)$

The spectrum of the (Ulam-approximated) spatial transfer operator shows a gap after the fourth eigenvalue (Figure 4.10). We thus expect to identify three pairs of metastable decompositions of $\mathcal{Q}$, ultimately separating the four potential wells.

For the subdominant eigenvectors v_2, v_3, v_4 of $\tilde{S}^t$, we observe a similar behavior as in the one-dimensional case: For longer lag times, the relevant eigenvectors become more concentrated in the regions of the potential wells (Figure 4.11). Also, in regions where $f_{\mathcal{Q}}$ is small, sign structure fluctuations occur for larger lag times. While again the subdominant eigenvectors $w_2,\ w_3,\ w_4$ of $\tilde{G}_2$ provide a good approximation for

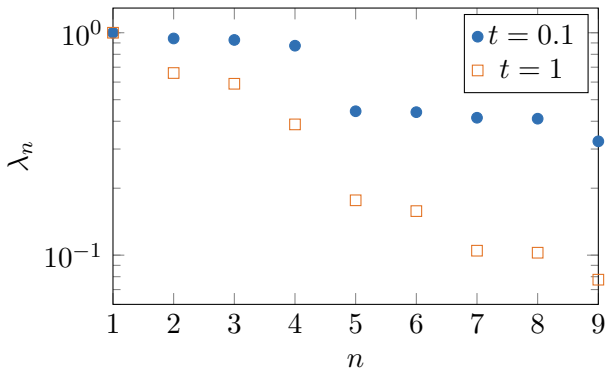

Figure 4.10.: The dominant eigenvalues of $\tilde{S}^t$ for short and intermediate lag times t. There is a spectral gap after λ_4.

small lag times, the dynamic behavior of v_2, v_3, v_4 for larger lag times cannot be reconstructed.

Transition probabilities. The sign structure of the eigenvectors w_2, w_3, w_4 of $\tilde{G}_2$ decomposes $\mathcal{Q}$ into three pairs of metastable sets, each with a different combined degree of metastability (Figure 4.12). Clearly the decompositions correspond to the potential wells, and are thus metastable in an intuitive sense.

The portion of $f_{\mathcal{Q}}$ on the respective metastable sets now is

$$f_{A_i} = \frac{\chi_{A_i} f_{\mathcal{Q}}}{\mu_{\mathcal{Q}}(A_i)}, \qquad f_{B_i} = \frac{\chi_{B_i} f_{\mathcal{Q}}}{\mu_{\mathcal{Q}}(B_i)}, \qquad f_{C_i} = \frac{\chi_{C_i} f_{\mathcal{Q}}}{\mu_{\mathcal{Q}}(C_i)}, \qquad i = 1, 2.$$

We again deploy the sampling–based algorithm from Section 4.2.1 to estimate the combined degrees of metastability $s(t, A_1, A_2)$, $s(t, B_1, B_2)$, $s(t, C_1, C_2)$ and demonstrate the bounds from Theorem 4.13. Again $\tilde{E}^t$ provides accurate bounds only for short lag times (Figure 4.13).

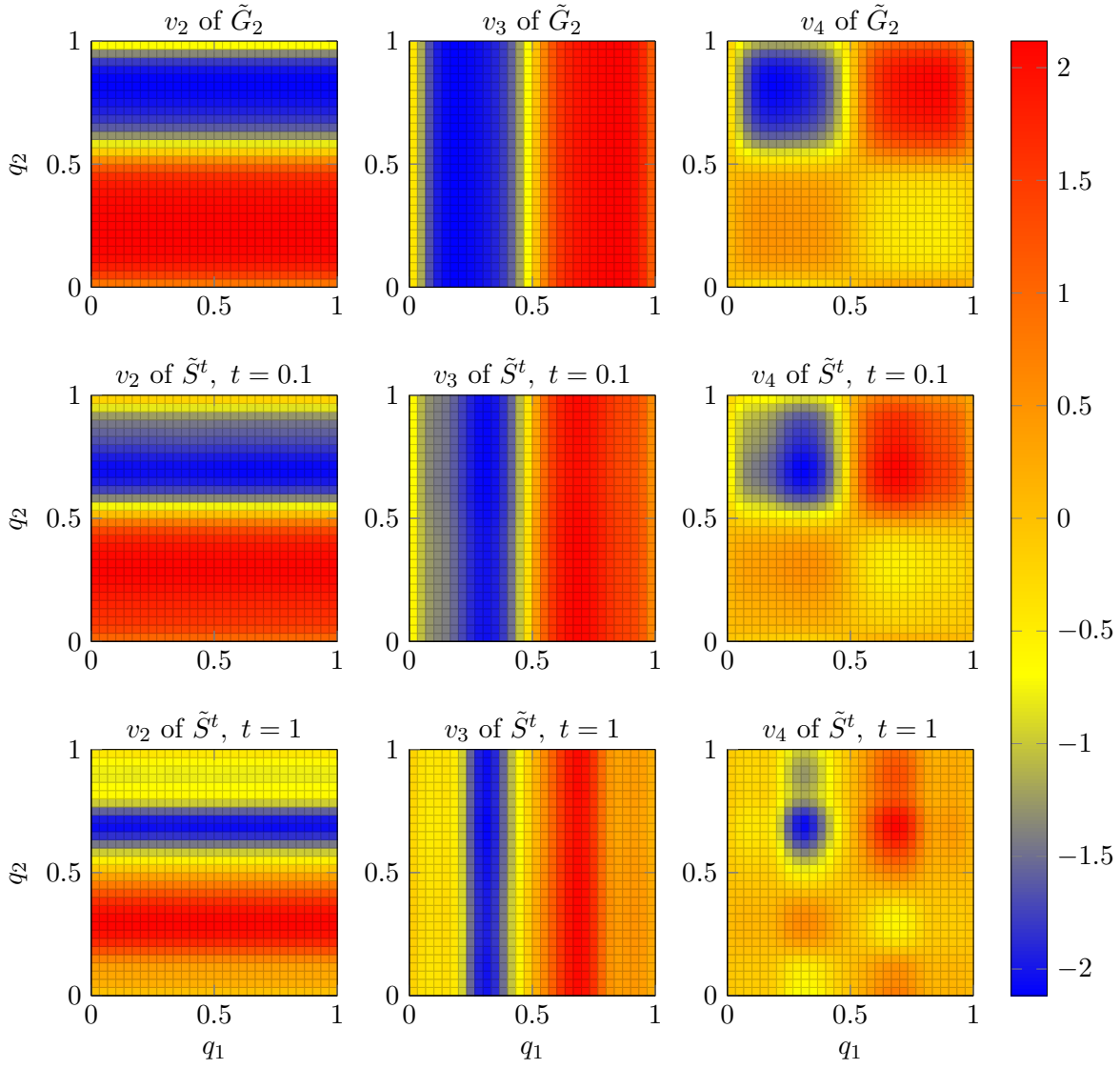

Figure 4.11.: The three most significant eigenvectors of $\tilde{G}_2$ (top row) and $\tilde{S}^t$ for different lag times (second and third row), unweighted.

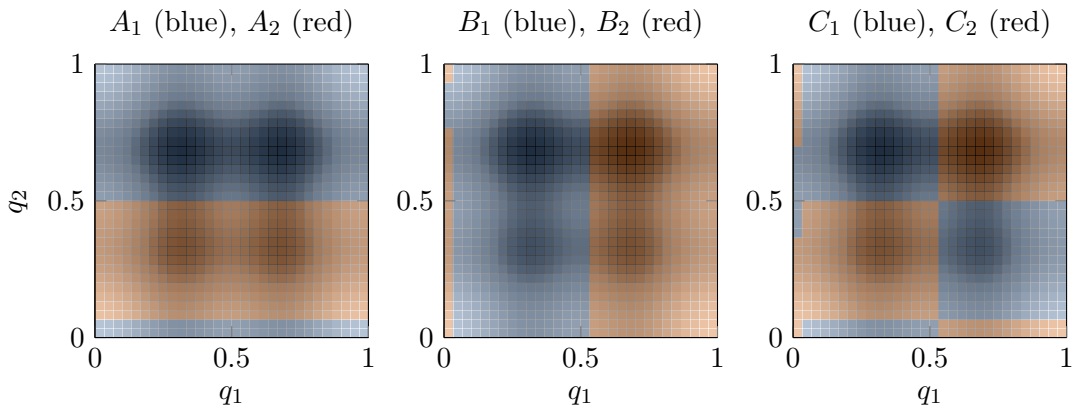

Figure 4.12.: The three tiers of invariant sets, identified via $\tilde{G}_2$. The artifacts on the left border of $B_{1/2}, C_{1/2}$ can be attributed to the ill-conditioned sign structure analysis.

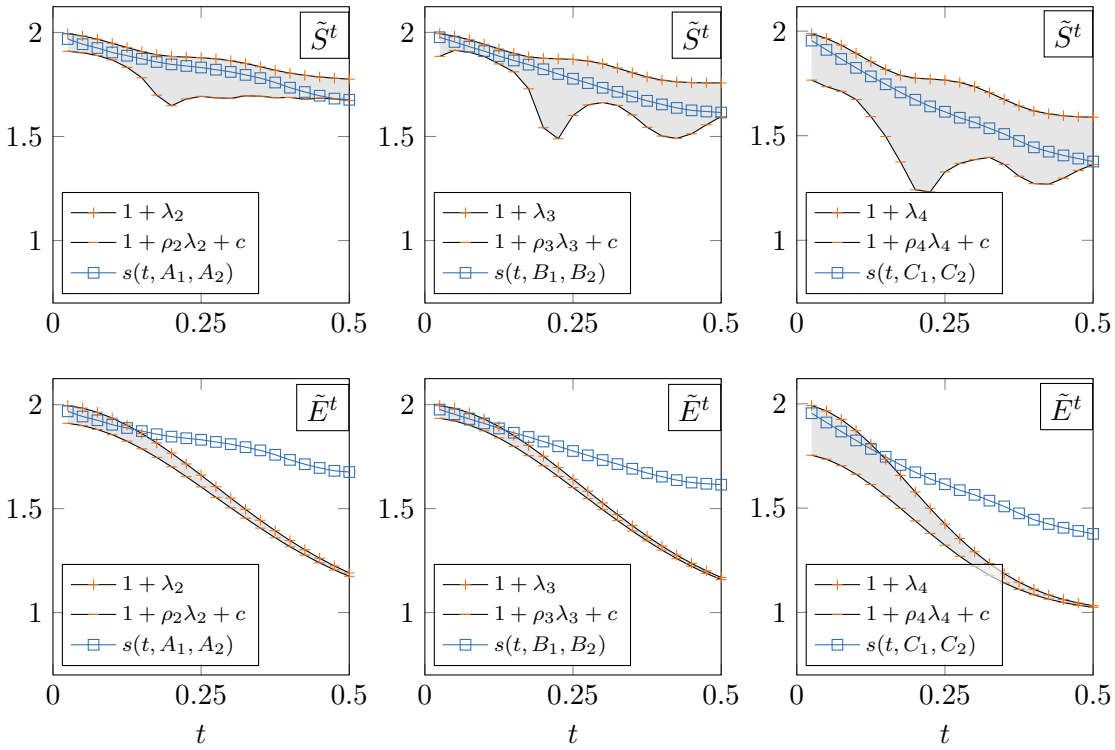

Figure 4.13.: Combined degrees of metastability of the identified pairs of sets and comparison to the bounds of Theorem 2.2.6 based on both S^t and E^t.

5. Long-time spatial dynamics

5.1. Extended pseudogenerator approximation

In Section 4.1 we discussed strategies for restoring the spatial transfer operator S^t for small lag times and showed convergence results for $t \to 0$. The numerical experiments in Section 4.2 confirmed that there is indeed a limit to how long the spectrum and eigenfunctions of T_n^t and E^t provide a reasonable approximation to S^t.

The damping constant γ seems to somewhat influence this limit. Figure 5.1 suggests that the higher the damping constant, the closer the dominant eigenfunctions of P_{Smol}^t and G_2 match for a fixed lag time t. In this section, we repeat the ideas of Koltai from [5] to explain this phenomenon.

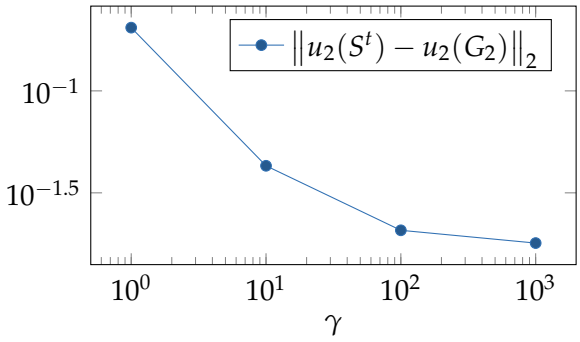

Figure 5.1.: L^2-distance between approximations of the subdominant eigenfunctions of S^t and G_2 in the double-well system for fixed $t = 0.5$ and variable γ. Note that we do not wish to imply any convergence rate yet.

Perturbation expansion For simplicity, assume that the system at hand is given in Cartesian coordinates with identity mass matrix at inverse temperature $\beta = 1$. Similar to the perturbation expansion used to derive Smoluchowski dynamics (see Appendix A.2), we begin by looking at the Langevin dynamics with rescaled friction and noise-coefficients. However, we do not use the scaling $\gamma \mapsto \gamma/\varepsilon$, but set $\gamma := \varepsilon^{-1}$ instead. The according infinitesimal generator can then be written as $L_{\text{Lan}} = L_{\text{Ham}} + \frac{1}{\varepsilon} L_{\text{OU}}$ with

$$L_{\text{Ham}} = \nabla_q H \cdot \nabla_p - \nabla_p H \cdot \nabla_q \,, \qquad L_{\text{OU}} = \Delta_p - p \cdot \nabla_p \,,$$

and the associated Smoluchowski generator reads $L_{\text{Smol}} = \Delta_q - \nabla_q V \cdot \nabla_q$.
To counter the increasingly slow dynamics, we re-scale time $t \mapsto \varepsilon t =: \tau$. Via

$$L_{\text{Lan}} u(\varepsilon t, \cdot) = \frac{d}{dt} u(\varepsilon t, \cdot) = \varepsilon \dot{u}(\varepsilon t, \cdot)$$

we see that density transport on the new time scale is governed by the new generator $L^{\varepsilon}_{\text{Lan}} := \varepsilon^{-1} L_{\text{Lan}}$.
The connection between the eigenfunctions of L_{Smol} and $L^{\varepsilon}_{\text{Lan}}$ is then given by

Theorem 5.1.1 ([64, Theorem 4.13]). *Assume there is an isolated eigenvalue λ_ε of $L^{\varepsilon}_{\text{Lan}}$ with associated eigenfunction u_ε and assume that the asymptotic expansions*

$$u_\varepsilon = u_0 + \varepsilon u_1 + \varepsilon^2 u_2 + \dots$$
$$\lambda_\varepsilon = \lambda_0 + \varepsilon \lambda_1 + \varepsilon^2 \lambda_2 + \dots$$

hold. Then the eigenvalues and eigenfunctions of $L^{\varepsilon}_{\text{Lan}}$ can be approximated up to $\mathcal{O}(\varepsilon)$ by the eigenvalues and eigenfunctions of L_{Smol}: we have

$$\begin{aligned} L_{\text{Smol}} u_0 &= \lambda_0 u_0 \\ u_\varepsilon &= u_0 + \varepsilon \underbrace{p \nabla_q u_0}_{=u_1} + \mathcal{O}(\varepsilon^2) \,. \end{aligned}$$

This explains the convergence of the rescaled Langevin- to the Smoluchowski eigenfunctions in the high friction limit. However, remember that we are interested in u_0 as an approximative eigenfunction of the *spatial* transfer operator S^t on the original time scale. For this, we have to take a look at the system's decay rates.

Decay rates. As metastability information is encoded in the dominant eigenfunctions to non-zero eigenvalues, we restrict ourselves to that case, i.e. assume that $\lambda_\varepsilon \neq 0 \neq \lambda_0$ and $\lambda_\varepsilon, \lambda_0$ are dominant. L_{Smol} is self-adjoint on $\mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q})$, and thus its eigenfunctions are orthogonal. As $\chi_\mathcal{Q}$ is an eigenfunction of L_{Smol} at eigenvalue 0, we have

$$\begin{aligned} \langle \chi_\Omega, u_0 \rangle_{\mu_\Omega} &= \int_\Omega \chi_\Omega(q,p) u_0(q) \, d\mu_\Omega \\ &= \int_\mathcal{Q} \chi_\mathcal{Q}(q) u_0(q) \, d\mu_\mathcal{Q} = \langle \chi_\mathcal{Q}, u_0 \rangle_{\mu_\mathcal{Q}} = 0 \,. \end{aligned}$$

Moreover, u_ε is also the eigenfunction of the Langevin transfer operator P^t_{Lan} (at eigenvalue $e^{\varepsilon \lambda_\varepsilon t}$). P^t_{Lan} is self-adjoint in the space spanned by the dominant eigenfunctions (see the properties part in Section 2.1.1) and possesses the eigenfunction χ_Ω (at eigenvalue 1). Thus we also have $\langle \chi_\Omega, u_\varepsilon \rangle_{\mu_\Omega} = 0$.

Define the *decay rate* of $L^\varepsilon_{\mathrm{Lan}}$ by

$$\eta_\varepsilon := \max\left\{ \operatorname{Re}\lambda_\varepsilon \mid 0 \neq \lambda_\varepsilon \in \sigma(L^\varepsilon_{\mathrm{Lan}}) \right\} .$$

Under the assumption that $L^\varepsilon_{\mathrm{Lan}}$ has a (real) dominant spectrum, η_ε is simply its second-largest eigenvalue. Both u_0 and u_ε lie in the space orthogonal to χ_Ω, and thus decay exponentially under the action of P^t_{Lan}. Let $u \perp \chi_\Omega$. Then

$$\begin{aligned}\left\|P^t_{\mathrm{Lan}}u\right\| &= \left\|\exp(tL_{\mathrm{Lan}})u\right\| = \left\|\exp(t\varepsilon L^\varepsilon_{\mathrm{Lan}})u\right\| \\ &\leq \exp(t\varepsilon\eta_\varepsilon)\|u\| = \mathcal{O}(e^{t\varepsilon\eta_\varepsilon}) \quad \text{for } t \to 0 .\end{aligned}$$

With this, we can now analyze the action of the spatial propagator S^t on the Smoluchowski eigenfunction u_0:

$$\begin{aligned}S^t u_0(q) &= \int_{\mathcal{P}} \left(P^t_{\mathrm{Lan}}u_0\right)(q,p)\, d\mu_{\mathcal{P}} \\ &= \int_{\mathcal{P}} \left(P^t_{\mathrm{Lan}}(u_\varepsilon - (u_\varepsilon - u_0))\right)(q,p)\, d\mu_{\mathcal{P}}\end{aligned}$$

u_ε is an eigenfunction of P^t_{Lan} and $u_\varepsilon - u_0$ is orthogonal to χ_Ω. Moreover, $u_\varepsilon - u_0 = \varepsilon u_1 + \varepsilon^2 u_2 + \dots$, and so $P^t_{\mathrm{Lan}}(u_\varepsilon - u_0)$ decays with rate $\mathcal{O}(\varepsilon e^{t\varepsilon\eta_\varepsilon})$.

$$\begin{aligned}&= e^{t\varepsilon\lambda_\varepsilon} \int_{\mathcal{P}} u_\varepsilon(q,p)\, d\mu_{\mathcal{P}} + \mathcal{O}(\varepsilon e^{t\varepsilon\eta_\varepsilon}) \\ &= e^{t\varepsilon\lambda_\varepsilon} \int_{\mathcal{P}} \left(u_0(q) + \varepsilon u_1(q,p) + \mathcal{O}(\varepsilon^2)\right) d\mu_{\mathcal{P}} + \mathcal{O}(\varepsilon e^{t\varepsilon\eta_\varepsilon})\end{aligned}$$

Using that u_1 is antisymmetric with respect to p (see Theorem 5.1.1) finally yields

$$\begin{aligned}&= e^{t\varepsilon\lambda_\varepsilon}u_0(q) + \mathcal{O}(\varepsilon^2 e^{t\varepsilon\lambda_\varepsilon}) + \mathcal{O}(\varepsilon e^{t\varepsilon\eta_\varepsilon}) \quad \text{for } \varepsilon \to 0 \\ &= e^{t\varepsilon(\lambda_0+\mathcal{O}(\varepsilon))}u_0(q) + \mathcal{O}(\varepsilon^2 e^{t\varepsilon(\lambda_0+\mathcal{O}(\varepsilon))}) + \mathcal{O}(\varepsilon e^{t\varepsilon\eta_\varepsilon}) \quad \text{for } \varepsilon \to 0 .\end{aligned}$$

In order for u_0 to represent a good approximative eigenfunction[1] of S^t, the last two summands must be small in comparison to the first one, i.e.[2]

$$|e^{t\varepsilon\lambda_0}| \gg |\varepsilon^2 e^{t\varepsilon\lambda_0}| , \qquad |e^{t\varepsilon\lambda_0}| \gg |\varepsilon e^{t\varepsilon\eta_\varepsilon}| .$$

The first condition is always fulfilled whenever ε is small. The second condition can be recast as

$$t \lesssim \frac{1}{|\lambda_0 - \eta_\varepsilon|}\varepsilon^{-1}|\log\varepsilon| . \tag{5.1}$$

This allows for the following interpretation:

[1] See the pseudospectrum discussion in Section 4.1.3.

[2] $x \gtrsim y$ here means "greater than up to some additive constant".

1. Lemma 2.1.4 allows the (positional) density transport under Langevin dynamics to be approximated by Smoluchowski dynamics on a time scale $t = \varepsilon^{-1}\tau = \mathcal{O}(\varepsilon^{-1})$ ($\varepsilon \to 0$). Our analysis suggests that with respect to metastability analysis, this time scale can be stretched by a factor $|\log \varepsilon|$.

2. The more dominant an eigenvalue, i.e. the smaller $|\lambda_0 - \eta_\varepsilon|$, the longer the time scale is on which the Smoluchowski eigenfunction, and thus the eigenfunction of the restored operators E^t and T_3^t, approximates the corresponding eigenfunction of the spatial transfer operator well. For the first subdominant eigenfunction, where $\lambda_\varepsilon = \eta_\varepsilon$, and hence $\lambda_0 - \eta_\varepsilon = \mathcal{O}(\varepsilon)$, the estimate reads $t \lesssim \varepsilon^{-2}|\log \varepsilon|$.

Numerical validation. In order to validate the estimate (5.1) numerically, we perform the following experiment: Consider the Langevin system induced by the one-dimensional periodic potential discussed in Section 4.2.1, with constant mass matrix $M = 1$ at temperature $\beta = 1$.

For varying $\varepsilon = \gamma^{-1}$, we compute the largest lag time $t = t_\nu(\varepsilon)$ such that the eigenfunctions $u_\varepsilon = u_\varepsilon^2$ at the subdominant eigenvalue $\lambda_\varepsilon = \lambda_\varepsilon^2$ of S^t and P_{Smol}^t differ by less than a given threshold ν, i.e. we compute

$$t_\nu(\varepsilon) := \inf\left\{t > 0 : \|u_\varepsilon^2(S^t) - u_\varepsilon^2(P_{\text{Smol}}^t)\|_{\mu_\mathcal{Q}} > \nu\right\}.$$

Figure 5.2 shows $\varepsilon \mapsto t_\nu(\varepsilon)$ for $\nu = 0.05$, and for comparison, the graph of $\varepsilon \mapsto c_1 \log(\varepsilon)\varepsilon^{-2} + c_2$ (where we obtained the constants c_1 and c_2 by a least squares fit on the given data). Clearly, on the chosen domain for t_ν, there is an excellent agreement with the estimate.

Although these first estimates allow merely a slight quantitative extension of the time scale on which the Smoluchowski dynamics approximates the spatial component of the Langevin dynamics well, it suggests that the consideration of further structural information from the perturbation expansion may allow for an extension of approximation time scales beyond the current, or inspire corrections terms to do so.

5.2. Almost Markovian behavior

For small t, the non-Markovianity of spatial dynamics is an important feature which characterizes the density transport and thus the metastable behavior. We have seen that an eigenvalue λ of S^t satisfies $\lambda \to 1$ as $t \to 0$ with a rate of $\mathcal{O}(\exp(-\kappa t^2/2))$ (for some $\kappa > 0$), in contrast to the rate for semigroups of operators, which is $\mathcal{O}(\exp(-\kappa t))$.

However, for *increasing* t, S^t exhibits a more regular, almost Markovian behavior [9,

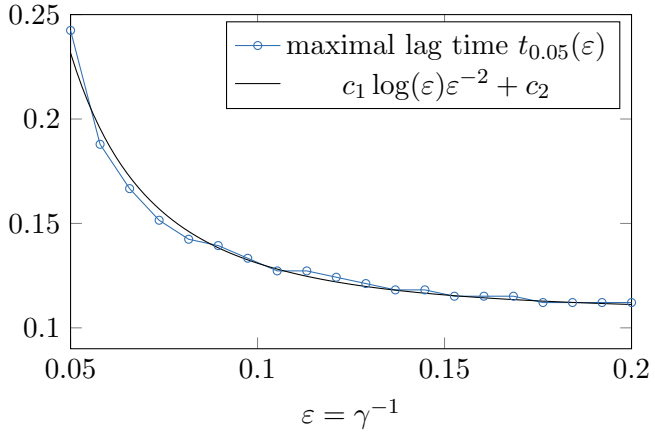

Figure 5.2.: ε-dependence of the maximal lag time. The blue graph shows the largest lag time such that $\|u_\varepsilon^1(S^t) - u_\varepsilon^1(P_{\text{Smol}}^t)\|_{L^2_{f_\Omega}} < 0.05$. The black graph is the prediction $c_1 \log(\varepsilon)\varepsilon^{-2} + c_2$ with $c_1 \approx -1.04 \cdot 10^{-4}$, $c_2 \approx 1.07 \cdot 10^{-1}$ obtained from least-squares fitting. The eigenfunctions were computed by an Ulam discretization of S^t and P_{Smol}^t with resolution 256.

70]. We explore how this could be exploited for efficient, trajectory-free metastability analysis in this time region.

In this section, we will settle for less precise arguments than for the rest of the thesis, and the justifications will mainly aim at the reader's intuition. It can be seen as a collection of ideas (partially published in [5]) justified by numerical experiments and will conclude with some conjectures from current work in progress.

5.2.1. An extrapolation algorithm

Langevin dynamics, the underlying model of S^t, is a time-continuous ergodic Markov process [45]. Due to ergodicity, we observe the convergence of any density to the canonical density f_Ω. Moreover, for sufficiently large damping, the relaxation of the momentum coordinates is significantly faster than that of the position coordinates, which can be seen by considering the associated Fokker–Planck equation (with respect to the Lebesgue measure). For simplicity and a compact presentation, we consider a system in Cartesian coordinates.

$$\frac{d}{dt} f_t = (\bar{L}_{\text{Ham}} + \gamma \bar{L}_{\text{OU}}) f\,, \quad \text{with} \quad \bar{L}_{\text{OU}} g = \frac{1}{\beta} \Delta_p g + \nabla_p \cdot \left(g M^{-1} p \right).$$

Thus, higher friction γ implies that the Ornstein–Uhlenbeck-part dominates the time evolution. The solution of the Ornstein–Uhlenbeck Fokker–Planck equation is

$$g(p,t) = \int_{\mathcal{P}} K(t,p,r) g(r,0) dr, \tag{5.2}$$

with the Green's function

$$K(t,p,r) = \left(\det(2\pi\beta^{-1}C(t))\right)^{-1/2} \exp\left(-\frac{\beta}{2}\left(p - re^{-\gamma t}\right)^{\mathsf{T}} C(t)^{-1}\left(p - re^{-\gamma t}\right)\right).$$

and the covariance matrix

$$C(t) = M\left(\mathrm{id} - e^{-2\gamma M^{-1}t}\right).$$

Observe that the time variable t appears in K always multiplied by γ. Thus, the larger the damping γ, the more rapidly $g(t,\cdot)$ tends towards the stationary solution[3]:

$$\lim_{t\to\infty} K(t,p,r) = f_{\mathcal{P}}(p).$$

This suggests that we can find a *relaxation lag time* τ_r, such that for all $t \geq \tau_r$ and for all $f : \mathcal{X} \to \mathbb{R}$

$$P^t_{\mathrm{Lan}} f(q,p) \approx h_t(q) f_\Omega(q,p)$$

for some $h_t : \mathcal{Q} \to \mathbb{R}$.

We use this to argue in favor of "almost-Markovianity" of S^t. In the following let $t \geq \tau_r$. For $u : \mathcal{Q} \to \mathbb{R}$ there is an $u_t : \mathcal{Q} \to \mathbb{R}$ such that

$$\bar{P}^t_{\mathrm{Lan}}\big(u(q) f_\Omega(q,p)\big) \approx u_t(q) f_\Omega(q,p).$$

Using this and the semi-group property of $\bar{P}^t_{\mathrm{Lan}}$, we get

$$\begin{aligned}
S^{2t}u(q) &= \frac{1}{f_{\mathcal{Q}}(q)} \int_{\mathcal{P}} \bar{P}^{2t}_{\mathrm{Lan}}\big(u(q) f_\Omega(q,p)\big) dp \\
&\approx \frac{1}{f_{\mathcal{Q}}(q)} \int_{\mathcal{P}} \bar{P}^{t}_{\mathrm{Lan}}\big(u_t(q) f_\Omega(q,p)\big) dp \\
&= S^t u_t(q) \\
&= S^t\Big(\frac{1}{f_{\mathcal{Q}}(q)} \int_{\mathcal{P}} u_t(q) f_\Omega(q,p) dp\Big) \\
&\approx S^t\Big(\frac{1}{f_{\mathcal{Q}}(q)} \int_{\mathcal{P}} \bar{P}^{t}_{\mathrm{Lan}}\big(u(q) f_\Omega(q,p)\big) dp\Big) \\
&= (S^t)^2 u(q).
\end{aligned}$$

[3]Remember that in Cartesian coordinates, $f_{\mathcal{P}}$ does not depend on q.

Inductively, it follows that $S^{nt} \approx (S^t)^n$ for $t \geq \tau_r$, so in this sense, S^t is almost a semigroup for big enough t. As the relaxation rate in (5.2) scales with $1/\gamma$, we expect the relaxation lag time to do the same.

Now assume that the relaxation lag time τ_r is small enough so that the pseudogenerator-restored operators $T_n^{\tau_r}$ or E^{τ_r} are a reasonable approximation to S^{τ_r}. Then we have, exemplary for E^t,

$$S^{(k\tau_r)} \approx (S^{\tau_r})^k \approx (E^{\tau_r})^k.$$

We investigate this with a simple numerical experiment. Using the one-dimensional periodic double-well potential (see Section 4.2.1) with $M = 1$, $\beta = 1$ and $\gamma = 5$, we want to compute the second largest eigenvalue $\lambda_2(S^t) < \lambda_1(S^t) = 1$.

With damping $\gamma = 5$, a choice of $\tau_r = 1/\gamma = 0.2$ seems reasonable, as by visual inspection, $\lambda_2(S^t)$ in this region begins to show exponential decay. Note that $\lambda_2(E^t)$ does *not* provide a good approximation for t significantly larger than τ_r, as the error asymptotics of Proposition 4.1.8 only hold for $t \to 0$. However, $T_2^{\tau_r}$ and E^{τ_r} still approximate S^{τ_r} well enough:

$$|\lambda_2(S^{\tau_r}) - \lambda_2(T_2^{\tau_r})| \approx 0.15\,, \quad |\lambda_2(S^{\tau_r}) - \lambda_2(E^{\tau_r})| \approx 0.12\,.$$

Figure 5.3 compares $\lambda_2(S^t)$ with $\lambda_2\big(S^{\tau_r}\big)^n$, $\lambda_2\big(T_2^{\tau_r}\big)^n$ and $\lambda_2\big(E^{\tau_r}\big)^n$ for $n = 1, \ldots, 10$.

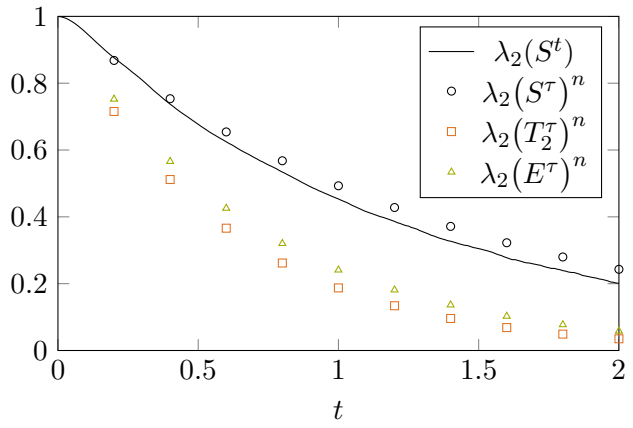

Figure 5.3.: The subdominant eigenvalue of S^t and its approximations via extrapolation.

As an error estimate for the eigenvalues, we get, again exemplary for E^t,

$$\begin{aligned}\big|\lambda\big(S^{n\tau_r}\big) - \lambda\big((E^{\tau_r})^n\big)\big| &\leq \big|\lambda\big(S^{n\tau_r}\big) - \lambda\big((S^{\tau_r})^n\big)\big| + \big|\lambda\big((S^{\tau_r})^n\big) - \lambda\big((E^{\tau_r})^n\big)\big| \\ &\leq \big|\lambda\big(S^{n\tau_r}\big) - \lambda\big(S^{\tau_r}\big)^n\big| + \big|\lambda\big(S^{\tau_r}\big) - \lambda\big(E^{\tau_r}\big)\big|^n,\end{aligned}$$

with using the binomial formula to obtain the second inequality. The first term on the right hand side depends on the relaxation of the underlying process after lag time

τ_r, and (for fixed n) decreases with increasing τ_r. The second term depends on the approximation error of E^{τ_r} on S^{τ_r} and increases with increasing τ_r. A balance between these two error sources must thus be found. Typically, the relaxed lag time lies in the approximation region of E^t and T_3^t only for high damping γ. This may or may not correspond to the physical model at hand.

5.2.2. Towards a spatial Itô process.

For lag times $t > \tau_r$, the almost-Markovianity described in Section 5.2, along with the geometric ergodicity of the spatial process (Theorem 2.2.2) implies an exponential decay of the subdominant eigenfunctions in time. This suggests that for $t > \tau_r$, statistical mechanics under spatial dynamics is approximately governed by an Itô process on $\mathcal{Q}$, at least on the subspace of $\mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q})$ spanned by the dominant eigenvalues.

Conjecture 5.2.1. *Let $\mathcal{E}_n$ be the space spanned by the n dominant eigenfunctions of S^t. Then there exists an Itô diffusion process on $\mathcal{Q}$ that is the long time limit of spatial dynamics on $\mathcal{E}_n$, in the following sense: let L_{LT} be the generator of this dynamics, and $P^t_{\mathrm{LT}} := \exp(-tL_{\mathrm{LT}})$. Then, for $u \in \mathcal{E}_n$,*

$$\frac{\left\|S^t u - P^t_{\mathrm{LT}} u\right\|}{\left\|S^t u\right\|} \to 0 \quad (t \to \infty)$$

in some suitable norm.

On $\mathcal{E}_n$, the transport under this hypothetical transfer operator P^t_{LT} is determined by the decay rates of the dominant eigenfunctions spanning $\mathcal{E}_n$, i.e. the corresponding eigenvalues of L_{LT}. As these decay rates correspond to the decay rates of the dominant eigenfunctions of S^t for large t, they can be found experimentally by least squares fitting a μ-parametrized function $e^{-t\mu}$ to the individual eigenvalues of S^t (or intuitively by reading their slope in a logarithmic plot). This process is demonstrated in Figure 5.4 for the three subdominant eigenvalues of the two-dimensional quad-well potential from Section 4.2.2.

The rate apparently depends on the friction parameter γ, and for $\gamma \gg 1$ can be explained by the Kramers–Smoluchowski limit. However, this relaxation is observed across the whole friction regime. For small to moderate γ, the rate could not be connected to a known diffusion process yet.

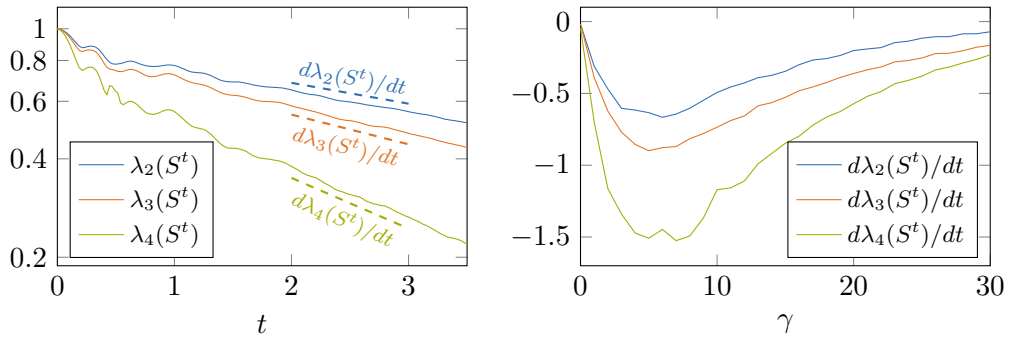

Figure 5.4.: Left: the three subdominant eigenvalues of the quad–well system (for small γ). The slope of the dotted lines illustrates the decay rate on the respective eigenspace. Right: the decay rates in dependence of the friction parameter γ.

6. Conclusion and outlook

We investigated the transport of momentum–averaged probability densities under the Langevin equation with the goal of metastability analysis. Even though this transport cannot be expressed without explicit momentum averaging, we could show that the associated transfer operator can (for $t \to 0$) be approximated up to third order by a $t \mapsto \frac{t^2}{2}$ scaled Smoluchowski transfer operator that involves no momentum averaging.

We have seen that this approximation to the spatial transfer operator can be discretized efficiently by collocation methods. As the information about the underlying flow is obtained directly from the transport equation, the discretization requires no numerical trajectory integration of any kind. This represents a major conceptual advantage over established Ulam–type discretization methods. We have proven error estimates for the asymptotic regime $t \to 0$ for both the transport of densities and for the spectrum of the spatial transfer operator. These estimates could be confirmed numerically.

Our goal of a simulation–free approach to conformation analysis could therefore be partially accomplished. The numerical experiments confirm that the eigenfunctions of the restored spatial transfer operator can be used to identify metastable sets. However, the chemically important long–time transition rates could not be restored yet, as they lie beyond the regime of our convergence results. Still, we have shown that this regime can be slightly expanded with respect to what classical results predict.

Future work. The main goal of future studies should be to show the applicability of the pseudogenerator–based methods to biochemically relevant, possibly high–dimensional systems.

This thesis already represents progress in that regard, as it expands the applicability from systems in Cartesian coordinates (as considered in the original publication [6]) to systems in generalized coordinates. However, there still are multiple issues that have to be addressed:

- In order to build meaningful Markov State Models based on the metastable sets discovered by transfer operator analysis, these sets' long–time stable behavior has to be estimated.

  In Section 5.2, we argued in favor for the existence of a *relaxation lag time* τ_r, after which the spatial dynamics exhibits almost Markovian behavior. This is indicated by exponentially decaying subdominant eigenvalues. We thus hope

to discover a closed (i.e. momentum–independent) stochastic Itô process on position space that describes the long–time density transport of spatial dynamics. Provided the generator of this process can be applied to the collocation basis functions from Section 2.3.2 with reasonable numerical effort, this would again allow the simulation–free treatment of long–time spatial dynamics.

- The Fourier mode and Chebyshev polynomial collocation bases considered in this thesis both require a grid covering of configuration space, which is susceptible for the curse of dimensionality. For higher dimensions, we intend to employ meshfree methods based on radial basis function [80, 20]. Recent results from transition path theory [16, 17, 76] raise the hope that the essential density dynamics can be captured by placing collocation nodes along so–called *transition pathways*, low–dimensional structures in configuration space along which the majority of transitions occur.
- While the collocation basis is typically chosen to allow the analytical differentiation of the basis elements[1], the evaluation of the potential, the mass matrix and the friction and noise matrices at the collocation points may prove costly in more complex systems (see the discussion at the beginning of Section 2.2).

  This problem intensifies when the projected pseudogenerator G_2^{ess} in essential coordinates is considered (see Lemma 3.4.1). The projected drift– and diffusion–coefficients $a(z), b(z)$ involve averaging over non–essential degrees of freedom, which, unlike the well–structured momentum averaging, appears infeasible to be carried out analytically; sampling–based quadrature methods [10, 30, 44] seem to be a natural choice here.
- It is still unclear how the emergence of the Smoluchowski generator in the second derivative of the spatial transfer operator can be interpreted physically. Also, the structure of pseudogenerators higher than three has not yet been examined. To avoid intransparent technical vector–analytic calculations, the analysis should be performed in a coordinate–free manner. Understanding the structure of higher pseudogenerators would by Proposition 4.1.1 allow Taylor–based restoration schemes of higher order. Ideally the higher pseudogenerators would involve the friction parameter γ, to provide precise quantitative estimates of the quantities of interest. For the interpretation, a continuation of the techniques from the Mori–Zwanzig formalism (as initialized by using Dyson's formula in Section 3.3) seems promising.

[1] This also holds for typical choices of radial basis functions, such as Gaussians or Wendland functions.

A. Auxiliary statements

A.1. Reversibility and self-adjointness of the spatial transfer operator

Koltai in [6] showed that S^t is self-adjoint on $\mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q})$, for the Cartesian coordinate space $\mathcal{Q}$. While the procedure is largely analogous, we will adapt the proof to generalized coordinates for completeness' sake.

Self-adjointness of the transfer operator is equivalent with reversibility of the corresponding dynamical process: the following result is from [34, Proposition 1.1], restated for our purposes.

Proposition A.1.1. *Fix $t > 0$. Let $S^t : \mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q}) \subset \mathcal{L}^1_{\mu_\mathcal{Q}}(\mathcal{Q}) \to \mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q})$ denote the transfer operator of the spatial dynamics for lag time t. Let the associated (discrete time) Markov process be denoted by q_n, $n \in \mathbb{N}$. Then S^t is self-adjoint with respect to the scalar product $\langle \cdot, \cdot \rangle_{\mu_\mathcal{Q}}$, i.e. $\langle S^t u, v \rangle_{\mu_\mathcal{Q}} = \langle u, S^t v \rangle_{\mu_\mathcal{Q}}$ for all $u, v \in \mathcal{L}^2_{\mu_\mathcal{Q}}(\mathcal{Q})$, if and only if q_n is reversible.*

Reversibility in this case is equivalent with $p_{S,\mu_\mathcal{Q}}(t, A, B) = p_{S,\mu_\mathcal{Q}}(t, B, A)$ for any measurable $A, B \subset \mathcal{Q}$. Here, $p_{S,\mu_\mathcal{Q}}(t, A, B)$ describes the transition probability of the spatial process, with $p_S(t, q, B)$ its transition function (see (2.40). Indeed, one way to define the reversed process is by setting $p_{S,rev,\mu_\mathcal{Q}}(t, A, B) := p_{S,\mu_\mathcal{Q}}(t, B, A)$ for any measurable $A, B \subset \mathcal{Q}$. In order to show reversibility let us start with a property of the Langevin process.[1]

Lemma A.1.2. *Let $p_{Lan,rev}$ denote the transition function of the reversed Langevin process, and let $A \subset \mathcal{Q} \times \mathcal{P}$ be a measurable set which is symmetric in the momentum coordinate, i.e.*

$$A = \{(q, -p) \,|\, (q, p) \in A\}.$$

Then $p_{Lan}\big(t, (q, p), A\big) = p_{Lan,rev}\big(t, (q, -p), A\big)$ for any $q \in \mathcal{Q}$, $p \in \mathcal{P}$.

Proof. Let $x_t \subset \mathcal{X}$ be an Itô process described by (1.1), and $\bar{x}_t := x_{-t}$ its time-reversed process. According to [31] (see also [47]), $\bar{x}_t$ is again an Itô process and described by

$$\partial_t \bar{x}_t = \bar{b}(\bar{x}_t) + \sigma(\bar{x}_t) w_t,$$

[1] The property described in Lemma A.1.2 is also known as *extended detailed balance condition*, see [64, Lemma 4.10].

with $\bar{b}$ taking the form

$$\bar{b}(x) = -b(x) + \frac{2}{f_{\mathcal{X}}(x)} \operatorname{div}\left(\Sigma(x) f_{\mathcal{X}}(x)\right) ,$$

where $\Sigma = \frac{1}{2}\sigma\sigma^{\intercal}$, $f_{\mathcal{X}}$ is the unique canonical density (which we assume to exist), and div is applied row wise.

Applied to the Langevin process in generalized coordinates (1.8), we get

$$\bar{b}(q,p) = \begin{pmatrix} -\nabla_p H(q,p) \\ \nabla_q H(q,p) + \gamma(q)\nabla_p H(q,p) \end{pmatrix} + \frac{2}{f_\Omega(q,p)} \begin{pmatrix} 0 \\ -\frac{1}{2\beta}\sigma(q)\sigma(q)^{\intercal} M^{-1}(q) p f_\Omega(q,p) \end{pmatrix} ,$$

which becomes, using the fluctuation-dissipation relation,

$$= \begin{pmatrix} -\nabla_p H(q,p) \\ \nabla_q H(q,p) - \gamma(q)\nabla_p H(q,p) \end{pmatrix} .$$

The reversed Langevin process thus follows

$$\begin{aligned} \partial_t \bar{q}_t &= -\nabla_p H(\bar{q}_t, \bar{p}_t) \\ \partial_t \bar{p}_t &= \nabla_q H(\bar{q}_t, \bar{p}_t) - \gamma(\bar{q}_t)\nabla_p H(\bar{q}_t, \bar{p}_t) + \sigma(\bar{q}_t) w_t . \end{aligned}$$

On the other hand, applying the substitution $\tilde{p} = -p$ for the original Langevin process in forward time, and using that w_t and $-w_t$ are stochastically equivalent in the sense that their distributions coincide, we obtain

$$\begin{aligned} \partial_t q_t &= -\nabla_p H(q_t, \tilde{p}_t) \\ \partial_t \tilde{p}_t &= \nabla_q H(q_t, \tilde{p}_t) - \gamma(q_t)\nabla_p H(q_t, \tilde{p}_t) + \sigma(q_t) w_t . \end{aligned}$$

Note that this is the same SDE as for the reversed process. Thus, the reversed process starting at $(q, -p)$ has the same distribution as $(q_t, -p_t)$, where (q_t, p_t) is the forward time process starting at (q, p).

□

In [6, Lemma B.3], a formula for the transition probabilities of the reversed spatial process has been derived. Its derivation holds for generalized coordinates as well, so it will not be restated.

Lemma A.1.3 ([6]Lemma B.3)**.** *It holds*

$$p_{S,rev,\mu_{\mathcal{Q}}}(t, A, B) = \frac{1}{\mu_{\mathcal{Q}}(A)} \int_{A\times\mathcal{P}} f_{\mathcal{Q}}(q) f_{\mathcal{P}}(q,p) p^t_{Lan,rev}\big((q,p), B\times\mathcal{P}\big)\, d(q,p)$$

for any measurable $A, B \subset \mathcal{Q}$.

To complete the proof of the self–adjointness of S^t, we transform $p_{S,\mu_\mathcal{Q}}(t, A, B)$:

$$\begin{aligned} p_{S,\mu_\mathcal{Q}}(t, A, B) &= \frac{1}{\mu_\mathcal{Q}(A)} \int_{A\times\mathcal{P}} f_\mathcal{Q}(q) f_\mathcal{P}(q,p) p^t_{Lan}\big((q,p), B\times\mathcal{P}\big)\, d(q,p) \\ &= \frac{(-1)^d}{\mu_\mathcal{Q}(A)} \int_{A\times -\mathcal{P}} f_\mathcal{Q}(q) f_\mathcal{P}(q,-\tilde{p}) p^t_{Lan}\big((q,-\tilde{p}), B\times\mathcal{P}\big)\, d(q,\tilde{p}) \\ &= \frac{1}{\mu_\mathcal{Q}(A)} \int_{A\times\mathcal{P}} f_\mathcal{Q}(q) f_\mathcal{P}(q,-\tilde{p}) p^t_{Lan}\big((q,-\tilde{p}), B\times\mathcal{P}\big)\, d(q,\tilde{p})\,, \end{aligned}$$

where in the first line we used the integral substitution $\tilde{p} = -p$, and in the second line the symmetry of $\mathcal{P}$, such that flipping the integration bounds only introduces change of sign. From this and Lemma A.1.2, applied to the p-symmetric set $B \times \mathcal{P}$, we obtain

$$p_{S,\mu_\mathcal{Q}}(t, A, B) = \frac{1}{\mu_\mathcal{Q}(A)} \int_{A\times\mathcal{P}} f_\mathcal{Q}(q) f_\mathcal{P}(q,\tilde{p}) p_{Lan,rev}\big(t,(q,\tilde{p}), B\times\mathcal{P}\big)\, d(q,\tilde{p})\,, \qquad \text{(A.1)}$$

by exploiting that $f_\mathcal{P}(q,-\tilde{p}) = f_\mathcal{P}(q,\tilde{p})$. (A.1) coincides with the right hand side of Lemma A.1.3, which shows reversibility of the spatial process and thus self–adjointness of the spatial transfer operator.

A.2. Derivation of the Smoluchowski transport equation

In this section we show how to derive the density transport equation for Smoluchowski dynamics in generalized coordinates. We expand the main idea of Hartmann in [5]. The purpose of the detailed derivation of this standard result (see for example [48]) is for the reader to become familiar with the connection between Langevin- and Smoluchowski dynamics, especially in which way the solution of the Smoluchowski Fokker–Planck equation is a good approximation to the solution of the Langevin Fokker–Planck equation. Also, we will re-encounter the technique used herein in Section 5.1.

The approach is also described in [54, 55] and is based on a technique known as *perturbation expansion*: Given a small problem parameter ε (in our case the inverse damping constant), formally expand the property of interest (in our case the solution of the Langevin Fokker–Planck equation), and use the expansion to find a law for the limit $\varepsilon \to 0$.

To begin, let us scale the original (in general position-dependent) drag and noise coefficients according to

$$\gamma \mapsto \gamma/\varepsilon\,, \quad \sigma \mapsto \sigma/\sqrt{\varepsilon}$$

where $\varepsilon > 0$ is assumed to be small. Clearly, the scaling preserves the fluctuation-

dissipation relation. Then the re-scaled Langevin equation reads

$$\begin{aligned} \frac{d}{dt}q_t &= \nabla_p H(q_t, p_t) \\ \frac{d}{dt}p_t &= -\nabla_q H(q_t, p_t) - \frac{\gamma(q_t)}{\varepsilon}\nabla_p H(q_t, p_t) + \frac{\sigma(q_t)}{\sqrt{\varepsilon}}w_t \,. \end{aligned} \tag{A.2}$$

Let the associated μ_Ω-weighted Fokker–Planck equation be denoted by

$$\partial_t u^\varepsilon(q,p,t) = L^\varepsilon_{\mathrm{Lan}} u^\varepsilon(q,p,t) \,, \quad u^\varepsilon(q,p,0) = u_0(q,p) \,. \tag{A.3}$$

where, for this section only, we write the solution as $u^\varepsilon(\cdot,\cdot,t)$ instead of u^ε_t. Assume that for this solution, there exists an asymptotic expansion in ε of the form

$$u^\varepsilon(q,p,\tau+t) \;=\; u_0^\tau(q,p,t) + \varepsilon u_1^\tau(q,p,t) + \varepsilon^2 u_2^\tau(q,p,t) + \dots \,. \tag{A.4}$$

Applying to $L^\varepsilon_{\mathrm{Lan}}$ the same decomposition as in (2.26) yields

$$L^\varepsilon_{\mathrm{Lan}} = L_{\mathrm{Ham}} + \frac{1}{\varepsilon}L_{\mathrm{OU}} \,,$$

where

$$L_{\mathrm{Ham}} = \nabla_q H \cdot \nabla_p - \nabla_p H \cdot \nabla_q \,, \qquad L_{\mathrm{OU}} = \frac{1}{2}\sigma\sigma^\intercal \colon \nabla_p^2 - (\gamma M^{-1} p)\cdot\nabla_p \,.$$

Inserting the expansion (A.4) into the backward equation and equating powers of ε, we obtain a hierarchy of equations, the first three of which read

$$L_{\mathrm{OU}} u_0^\tau = 0 \tag{A.5}$$

$$L_{\mathrm{OU}} u_1^\tau = \partial_t u_0^\tau - L_{\mathrm{Ham}} u_0^\tau \tag{A.6}$$

$$L_{\mathrm{OU}} u_2^\tau = \partial_t u_1^\tau - L_{\mathrm{Ham}} u_1^\tau \,. \tag{A.7}$$

Note that L_{OU} is a second-order differential operator in p with q appearing only as a parameter. By the assumption that γ is symmetric positive definite with uniformly bounded inverse, (A.5) implies that u_0^τ is constant in p. Using a closure argument known as the *centering condition*, it follows that $\partial_t u_0^\tau = 0$.

Equation (A.7) reads

$$\partial_t u_1^\tau = L_{\mathrm{Ham}} u_1^\tau + L_{\mathrm{OU}} u_2^\tau .$$

Combined with (A.6) and $\partial_t u_0^\tau = 0$, we get

$$\partial_t u_1^\tau = -L_{\mathrm{Ham}} {L_{\mathrm{OU}}}^{-1} L_{\mathrm{Ham}} u_0^\tau + L_{\mathrm{OU}} u_2^\tau . \tag{A.8}$$

Let ϱ_q be the solution to $L_{\mathrm{OU}}^* \varrho_q = 0$, with L_{OU}^* being the formal $\mathcal{L}^2$ adjoint of L_{OU}. Multiplying (A.8) by ϱ_q and integrating gets us

$$\int_{\mathcal{P}} \partial_t u_1^\tau \varrho_q \, dp = -\int_{\mathcal{P}} \left(L_{\mathrm{Ham}} {L_{\mathrm{OU}}}^{-1} L_{\mathrm{Ham}} u_0^\tau \right) \varrho_q \, dp. \tag{A.9}$$

Now, taking the time-derivative of (A.6) and using $\partial_t u_0^\tau = 0$, we see that $\partial_t u_1^\tau \in \ker L_{\mathrm{OU}}$:

$$L_{\mathrm{OU}} \partial_t u_1^\tau = -L_{\mathrm{Ham}} \partial_t u_0^\tau = 0.$$

As $\gamma(\cdot)$ is symmetric positive definite with uniformly bounded inverse, $\ker L_{\mathrm{OU}}$ consists only of constant functions (in p). Thus $\partial_t u_1^\tau$ is independent of p, and (A.9) becomes

$$\partial_t u_1^\tau = -\int_{\mathcal{P}} \left(L_{\mathrm{Ham}} {L_{\mathrm{OU}}}^{-1} L_{\mathrm{Ham}} u_0^\tau \right) \varrho_q(p) dp. \tag{A.10}$$

We will see later that the right hand side, seen as an operator applied to u_0^τ, is the familiar Smoluchowski generator, shortly denoted by L_{Smol}. Thus

$$\partial_t u_1^\tau = L_{\mathrm{Smol}} u_0^\tau$$

The evolution of the full density u^ε can then be described by

$$\begin{aligned} \partial_t u^\varepsilon(q,p,\tau+t) &= \underbrace{\partial_t u_0^\tau(q)}_{=0} + \varepsilon \underbrace{\partial_t u_1^\tau(q,p,t)}_{=L_{\mathrm{Smol}} u_0^\tau} + \varepsilon^2 \partial_t u_2^\tau(q,p,t) + \dots \\ &= \varepsilon L_{\mathrm{Smol}} u_0^\tau(q) + \varepsilon^2 \partial_t u_2^\tau(q,p,t) + \dots . \end{aligned}$$

We observe that for $\varepsilon \to 0$, the dynamic is increasingly slow-moving, and thus switch to a faster time scale: $\tau + t \to (\tau+t)/\varepsilon$. The evolution of $u^\varepsilon(q,p,(\tau+t)/\varepsilon)$ for $t \in \mathcal{O}(\varepsilon)$ is then described by the following approximative PDE:

$$\begin{aligned} \frac{d}{dt} u^\varepsilon\big(q,p,(\tau+t)/\varepsilon\big) &= \partial_\sigma u^\varepsilon(q,p,\sigma)\Big|_{\sigma=(\tau+t)/\varepsilon} \cdot \frac{1}{\varepsilon} \\ &= L_{\mathrm{Smol}} u_0^{\tau/\varepsilon}(q) + \varepsilon \partial_t u_2^{\tau/\varepsilon}\big(q,p,t/\varepsilon\big) + \dots && \text{(A.11)} \\ &= L_{\mathrm{Smol}} \Big(u_0^{\tau/\varepsilon}(q) + \varepsilon u_1^{\tau/\varepsilon}\big(q,p,t/\varepsilon\big) + \varepsilon^2 u_2^{\tau/\varepsilon}\big(q,p,t/\varepsilon\big) + \dots \Big) + \mathcal{O}(\varepsilon) && \text{(A.12)} \\ &= L_{\mathrm{Smol}} u^\varepsilon\big(q,p,(\tau+t)/\varepsilon\big) + \mathcal{O}(\varepsilon). && \text{(A.13)} \end{aligned}$$

The step from (A.11) to (A.12) only holds for $t \in \mathcal{O}(\varepsilon)$, as $u_i^{\tau/\varepsilon}(\cdot, t/\varepsilon) \in \mathcal{O}\big((t/\varepsilon)^i\big)$ (this can be shown by Taylor expansion of $u^\varepsilon\big(u,v,(\tau+t)/\varepsilon\big)$). Thus in the limit $(\varepsilon \to 0)$, (A.13) only holds for $t = 0$, and we get an assertion about the evolution of $u^\varepsilon(\cdot,(\tau+t)/\varepsilon)\big|_{t=0} = u^\varepsilon(\cdot,\tau/\varepsilon)$:

Lemma A.2.1. *Let w be the solution of the Smoluchowski transport equation*

$$\partial_\tau w(\cdot,\tau) = L_{\mathrm{Smol}} w(\cdot,\tau)\,,$$

and u^ε be the solution of the ε-rescaled Langevin transport equation (A.3). Then

$$\left\| u^\varepsilon\big(\cdot,\tau/\varepsilon\big) - w(\cdot,\tau)\right\|_{2,\mu_\Omega} \to 0, \quad (\varepsilon \to 0). \tag{A.14}$$

A coordinate expression for the *backward* Smoluchowski equation[2] has been derived in [5], where the same considerations were performed regarding the transport of observables instead of densities. However, as already pointed out (see 2.27), the weighted Fokker–Planck equation and the Kolmogorov backward equation for Langevin dynamics are strongly connected[3], and thus ultimately the expressions for the forward Smoluchowski generator L_{Smol} and backward Smoluchowski generator A_{Smol} coincide. It has been formally shown by Hartmann in [5], that

$$A_{\mathrm{Smol}} = \beta^{-1}\tilde{\Delta} - \nabla V \cdot \tilde{\nabla}\,, \tag{A.15}$$

where

$$\tilde{\nabla} = \gamma^{-1}\nabla \quad \text{and} \quad \tilde{\Delta} = \frac{1}{\sqrt{\det\gamma}}\nabla\cdot\left(\sqrt{\det\gamma}\,\gamma^{-1}\nabla\right),$$

denote gradient and Laplace-Beltrami operator with respect to γ. Hence we have

$$L_{\mathrm{Smol}} = \beta^{-1}\tilde{\Delta} - \nabla V \cdot \tilde{\nabla}\,, \tag{A.16}$$

Note that L_{Smol} no longer depends on the mass matrix M.

[2] i.e. the backward Kolmogorov equation associated with the Smoluchowski dynamics.
[3] They differ only by a sign in front of L_{Ham}, which cancels out in (A.10).

B. Pseudogenerators: technical proofs

B.1. Vector analytic proofs

In this section the various results from Section 3.2 will be proven by vector-arithmetic calculations.

To prove the main Theorem 3.2.1, the following lemma is needed:

Lemma B.1.1. *Let $A \in \mathbb{R}^{n,n}$ be a symmetric, positive definite matrix. Then*

(i) $\int_{\mathbb{R}^n} \exp\Big(-\frac{1}{2}x^\intercal Ax\Big)\,dx = \sqrt{\frac{(2\pi)^n}{\det A}}$,

(ii) $\int_{\mathbb{R}^n} x_i \exp\Big(-\frac{1}{2}x^\intercal Ax\Big)\,dx = 0$,

(iii) $\int_{\mathbb{R}^n} x_i x_j \exp\Big(-\frac{1}{2}x^\intercal Ax\Big)\,dx = \sqrt{\frac{(2\pi)^n}{\det A}} A^{-1}_{ij}$,

(iv) $\int_{\mathbb{R}^n} x_i x_j x_k \exp\Big(-\frac{1}{2}x^\intercal Ax\Big)\,dx = 0$.

Proof. (i) The formula for this standard Gaussian integral can for example be found in [57].

(ii) It can easily be seen that the integrand is antisymmetrical with respect to x_i, thus the integral vanishes.

(iii) First note that we can write $x_i x_j = x^\intercal Bx$, with $B \in \mathbb{R}^{n,n}$, $B_{kl} = \begin{cases} 1 & \text{if } k = i \ \wedge \ l = j \\ 0 & \text{otherwise} \end{cases}$.

As A is s.p.d., there exists a factorization $A = Q^\intercal \Lambda Q$, $Q \in \mathbb{R}^{n\times n}$ orthogonal and $\Lambda \in \mathbb{R}^{n\times n}$ diagonal. With the transformation

$$y := \Lambda^{\frac{1}{2}} Qx, \quad \text{thus} \quad x = Q^\intercal \Lambda^{-\frac{1}{2}} y,$$

we get

$$\begin{aligned}\int_{\mathbb{R}^n} x_i x_j \exp\Big(-\frac{1}{2}x^\intercal Ax\Big)\,dx &= \int_{\mathbb{R}^n} x^\intercal Bx \exp\Big(-\frac{1}{2}x^\intercal Ax\Big)\,dx \\ &= \int_{\mathbb{R}^n} \big(Q^\intercal \Lambda^{-\frac{1}{2}} y\big)^\intercal B\big(Q^\intercal \Lambda^{-\frac{1}{2}} y\big) \exp\Big(-\frac{1}{2}y^\intercal y\Big)\cdot\big|\det\big(\Lambda^{-\frac{1}{2}}Q\big)\big|\,dy \\ &= \int_{\mathbb{R}^n} y^\intercal \underbrace{\Big(\Lambda^{-\frac{1}{2}} q_i q_j^\intercal \Lambda^{-\frac{1}{2}}\Big)}_{=:R} y \exp\Big(-\frac{1}{2}y^\intercal y\Big)\,dy\cdot\sqrt{\det A^{-1}},\end{aligned}$$

where q_k is the k-th column of Q. Also it was used that $\det\big(\Lambda^{-\frac{1}{2}}Q\big) = \sqrt{\det A^{-1}}$ and that it is positive due to A being s.p.d.. Writing out the matrix–vector multiplication $y^\intercal Ry$, the integral reduces to

$$\begin{aligned}\int_{\mathbb{R}^n} x_i x_j \exp\Big(-\frac{1}{2}x^\intercal Ax\Big)\,dx &= \sum_{k,l=1}^n R_{kl}\int_{\mathbb{R}^n} y_k y_l \exp\big(-\frac{1}{2}y^\intercal y\big)\,dy\cdot\sqrt{\det A^{-1}} \\ &= \sum_{k=1}^n R_{kk}\int_{\mathbb{R}^n} y_k^2 \exp\big(-\frac{1}{2}y^\intercal y\big)\,dy\cdot\sqrt{\det A^{-1}},\end{aligned}$$

as the mixed integrals $\int y_k y_l \exp\big(-\frac{1}{2}y^\intercal y\big)\,dy$ vanish due to antisymmetry. With the one-dimensional integrals

$$\int_{-\infty}^{\infty}\exp\big(-\frac{1}{2}z^2\big)\,dz = \sqrt{2\pi} = \int_{-\infty}^{\infty} z^2\exp\big(-\frac{1}{2}z^2\big)\,dz\,,$$

we finally get

$$\int_{\mathbb{R}^n} x_i x_j \exp\Big(-\frac{1}{2}x^\intercal Ax\Big)\,dx = \Big(\sum_{k=1}^n R_{kk}\Big)\sqrt{\frac{(2\pi)^n}{\det A}} = A_{ij}^{-1}\sqrt{\frac{(2\pi)^n}{\det A}},$$

as

$$\sum_{k=1}^n R_{kk} = \sum_{k=1}^n \Lambda_k^{-1} q_{ik} q_{jk} = \Big(Q^\intercal \Lambda^{-1} Q\Big)_{ij} = (A^{-1})_{ij}\,.$$

(iv) It can easily be seen that the integrand is antisymmetrical with respect to at least one of the integration variables x_i, x_j, x_k.

□

Proof of Theorem 3.2.1.

Proof. Let $u \in \mathcal{W}^{k,2}(\mathcal{Q})$. By Proposition 3.1.3,

$$G_n u = \int_{\mathcal{P}} (L_{\text{Lan}})^n u \, d\mu_{\mathcal{P}}.$$

We can calculate G_n by calculating $L_{\text{Lan}}^k u$, $n \in \{1, 2\}$ and taking the momentum integral afterwards. These two steps are done by hand in the following, i.e. by multivariate vector– and matrix calculus.

By element-wise inspection, it can be seen that for vectors v, w and matrices A of matching dimensions holds

$$v^\intercal A w = v w^\intercal : A \ ,$$

with : the generalized Frobenius product defined in (2.16).

The following derivatives of H will also prove helpful for compiling the L_{Lan}^k:

- $\nabla_p H(q,p) = M^{-1}(q) p$,
- $\nabla_q H(q,p) = \frac{1}{2} p p^\intercal : \nabla_q M^{-1}(q) + \nabla_q V(q)$,
  with the tensor $\nabla_q M^{-1}(q) = \left(\partial_{q_k} \left(M^{-1}(q) \right)_{ij} \right)_{ijk}$,
- $\nabla_p^2 H(q,p) = M^{-1}(q)$,
- $\nabla_p \nabla_q H(q,p) = \nabla_q \nabla_p H(q,p) = p : \nabla_q M^{-1}(q)$.

Here it was already used that M is symmetric.

We now show the three statements from Theorem 3.2.1:

0. $G_0 = I$ follows directly from $L_{\text{Lan}}^0 = I$.
1. We again use the operator splitting $L_{\text{Lan}} = L_{\text{Ham}} + L_{\text{OU}}$ (see (2.14)) with

   $$L_{\text{Ham}} = \nabla_q H^\intercal \nabla_p - \nabla_p H^\intercal \nabla_q \ , \qquad L_{\text{OU}} = \frac{1}{2} \sigma \sigma^\intercal : \nabla_p^2 - \left(\gamma p^\intercal M^{-1} \right) \nabla_p$$

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

   As u is a function of q only, we have $L_{\text{OU}} u = 0$ and $\nabla_p u = 0$, and thus

   $$\begin{aligned} G_1 u(q) &= \int_{\mathcal{P}} \left(L_{\text{Lan}} u \right)(q,p) \, d\mu_{\mathcal{P}} = \int_{\mathcal{P}} \left(L_{\text{Ham}} u \right)(q,p) f_{\mathcal{P}}(q,p) \, dp \\ &= \int_{\mathcal{P}} -\nabla_p H(q,p)^\intercal \nabla_q u(q) f_{\mathcal{P}}(q,p) \, dp \\ &= -\int_{\mathcal{P}} p^\intercal M^{-1}(q) \nabla_q u(q) f_{\mathcal{P}}(q,p) \, dp \ . \end{aligned}$$

   This integral is simply a linear combination of the integrals $\int_{\mathcal{P}} p_i f_{\mathcal{P}}(q,p) \, dp$. As $f_{\mathcal{P}}(q,p) = \frac{1}{Z_{\mathcal{P}}(q)} \exp\left(-\frac{\beta}{2} p^\intercal M^{-1}(q) p \right)$, those integrals vanish due to Lemma B.1.1 and we get $G_1 = 0$.

2. For G_2, we first calculate

$$\begin{aligned} L_{\mathrm{Lan}}^2 u &= (L_{\mathrm{Ham}} + L_{\mathrm{OU}})^2 u \\ &= L_{\mathrm{Ham}}^2 u + L_{\mathrm{Ham}} \underbrace{L_{\mathrm{OU}} u}_{=0} + L_{\mathrm{OU}} \underbrace{L_{\mathrm{OU}} u}_{=0} + L_{\mathrm{OU}} L_{\mathrm{Ham}} u \\ &= L_{\mathrm{OU}} L_{\mathrm{Ham}} u + L_{\mathrm{Ham}}^2 u \ . \end{aligned}$$

The first summand is

$$\begin{aligned} \big(L_{\mathrm{OU}} L_{\mathrm{Ham}} u\big)(q,p) &= L_{\mathrm{OU}}\big(- \nabla_p H(q,p)^\intercal \nabla_q u(q)\big) = L_{\mathrm{OU}}\big(- p^\intercal M^{-1}(q) \nabla_q u(q)\big) \\ &= -\frac{1}{2}\sigma\sigma^\intercal : \nabla_p^2 \Big(p^\intercal M^{-1}(q) \nabla_q u(q)\Big) \\ &\quad + \gamma \Big(M(q)^{-1} p\Big)^\intercal \nabla_p \Big(p^\intercal M^{-1}(q)^\intercal \nabla_q u(q)\Big). \end{aligned}$$

The second p-derivative of the linear term vanishes, so all that remains is

$$= \gamma p^\intercal \Big(M^{-1}(q)\Big)^2 \nabla_q u(q).$$

The integral of this term with respect to $\mu_{\mathcal{P}}$ will again vanish due to Lemma B.1.1.

The second summand of $L_{\mathrm{Lan}}^2 u(q)$ is

$$\begin{aligned} \big(L_{\mathrm{Ham}}^2 u\big)(q,p) &= L_{\mathrm{Ham}}\big(- p^\intercal M^{-1}(q) \nabla_q u(q)\big) \\ &= \nabla_q H(q,p)^\intercal \ \nabla_p \Big[- p^\intercal M^{-1}(q) \ \nabla_q u(q)\Big] \\ &\quad - \nabla_p H(q,p)^\intercal \ \nabla_q \Big[- p^\intercal M^{-1}(q) \ \nabla_q u(q)\Big]. \end{aligned}$$

Using $\nabla_q\big(p^\intercal M^{-1}(q)\big) = \big(p : \nabla_q M^{-1}(q)\big)^\intercal$ and $\nabla_q\big(v^\intercal \nabla_q u(q)\big) = \nabla_q^2 u(q) v$ for some $v \in \mathbb{R}^n$, this becomes

$$\begin{aligned} \big(L_{\mathrm{Ham}}^2 u\big)(q,p) = &\Big(M^{-1}(q)p\Big)^\intercal \ \Big[\big(p : \nabla_q M^{-1}(q)\big)^\intercal \nabla_q u(q) + \nabla_q^2 u(q) M^{-1}(q) p\Big] \\ &- \Big(\frac{1}{2} pp^\intercal : \nabla_q M^{-1}(q) + \nabla_q V(q)\Big)^\intercal \ \Big[M^{-1}(q) \ \nabla_q u(q)\Big] \\ = \ & p^\intercal M^{-1}(q) \ \Big(p : \nabla_q M^{-1}(q)\Big)^\intercal \nabla_q u(q) \\ &+ \ p^\intercal M^{-1}(q) \ \nabla_q^2 u(q) M^{-1}(q) p \\ &- \ \frac{1}{2}\Big(pp^\intercal : \nabla_q M^{-1}(q)\Big)^\intercal M^{-1}(q) \nabla_q u(q) \\ &- \ \nabla_q V(q)^\intercal \ M^{-1}(q) \nabla_q u(q) \ . \end{aligned}$$

To simplify the notation, define the 3-tensor N with $N_{ijk}(q) := \partial_{q_j} M^{-1}_{i,k}(q)$. It can be seen as the gradient of the mass matrix M, transposed with respect to the second and third tensor index. Note the identities

- $p^\intercal M^{-1}(q)\,\Big(p : \nabla_q M^{-1}(q)\Big)^\intercal \nabla_q u(q) = \Big[\big(pp^\intercal M^{-1}(q)\big) : N(q)\Big]^\intercal \nabla_q u(q)$,
  which follows from $\Big(p : \nabla_q M^{-1}(q)\Big)^\intercal = \Big(p : N(q)\Big)$ and $w^\intercal(v : B) = (vw^\intercal) : B$ for $v, w \in \mathbb{R}^n$ and $B \in \mathbb{R}^{n\times n\times n}$.
- $p^\intercal M^{-1}(q)\nabla_q^2 u(q) M^{-1}(q) p = M^{-1}(q) : \big(pp^\intercal M^{-1}(q)\nabla_q^2 u(q)\big)$,
  which follows from $v^\intercal ABv = A : \big(v(Bv)^\intercal\big) = A : (vv^\intercal B)$ for $v \in \mathbb{R}^n$ and $A, B \in \mathbb{R}^{n\times n}$.

With this, $L^2_{\text{Ham}} u$ transforms to

$$L^2_{\text{Ham}} u = \left[\Big[\big(pp^\intercal M^{-1}(q)\big) : N(q)\Big]^\intercal - \frac{1}{2}\Big(pp^\intercal : \nabla_q M^{-1}(q)\Big)^\intercal M^{-1}(q)\right]\nabla_q u(q) + M^{-1}(q) : \Big(pp^\intercal M^{-1}(q)\nabla_q^2 u(q) - \nabla_q V(q)\nabla_q u(q)^\intercal\Big).$$

Now, integrating $L^2_{\text{Lan}} u$ with respect to $\mu_{\mathcal{P}}$ gives

$$\begin{aligned} G_2 u(q) &= \int_{\mathcal{P}} \big(L^2_{\text{Lan}} u\big)(q,p)\, d\mu_{\mathcal{P}} = \int_{\mathcal{P}} \big(L^2_{\text{Ham}} u\big)(q,p)\, d\mu_{\mathcal{P}} + \underbrace{\int_{\mathcal{P}} \big(L_{\text{OU}} L_{\text{Ham}} u\big)(q,p)\, d\mu_{\mathcal{P}}}_{=0} \\ &= \underbrace{\int_{\mathcal{P}} \left[\Big[\big(pp^\intercal M^{-1}(q)\big) : N(q)\Big]^\intercal - \frac{1}{2}\Big(pp^\intercal : \nabla_q M^{-1}(q)\Big)^\intercal M^{-1}(q)\right]\nabla_q u(q) f_{\mathcal{P}}(q,p)\, dp}_{:=(1)} \\ &\quad + \underbrace{\int_{\mathcal{P}} \Big(M^{-1}(q) : \Big(pp^\intercal M^{-1}(q)\nabla_q^2 u(q) - \nabla_q V(q)\nabla_q u(q)^\intercal\Big)\Big) f_{\mathcal{P}}(q,p)\, dp}_{:=(2)}. \end{aligned}$$

For the two integrals we will use that, with v a vector, A a matrix and B a 3-tensor with matching dimensions,

$$\int (Avv^\intercal) : B\, dv = \Big(\int Avv^\intercal\, dv\Big) : B = \Big(A \int vv^\intercal\, dv\Big) : B\,,$$

i.e. the integrals of a linear combination of $v_i v_j$ is the linear combination of integrals $\int v_i v_j\, dv$. Here, $\int vv^\intercal\, dv$ is a matrix containing the component-wise integrals.

The two integrals then finally calculate to

$$\begin{aligned}(1) &= \Bigg(\Big(\int_{\mathcal{P}} pp^\intercal f_{\mathcal{P}}(q,p)\, dp M^{-1}(q) \Big) : N(q) \\ &\qquad - \frac{1}{2}\Big[\Big(\int_{\mathcal{P}} pp^\intercal f_{\mathcal{P}}(q,p)\, dp \Big) : \nabla_q M^{-1}(q) \Big] M^{-1}(q) \Bigg)^\intercal \nabla_q u(q) \\ &\overset{(*)}{=} \frac{1}{\beta}\Big[I : N(q) - \frac{1}{2}\Big(M(q) : \nabla_q M^{-1}(q) \Big) M^{-1}(q) \Big]^\intercal \nabla_q u(q)\end{aligned}$$

$$\begin{aligned}(2) &= M^{-1}(q) : \Big[\Big(\int_{\mathcal{P}} pp^\intercal f_{\mathcal{P}}(q,p)\, dp \Big) M^{-1}(q) \nabla_q^2 u(q) - \nabla_q V(q) \nabla_q u(q)^\intercal \Big] \\ &\overset{(*)}{=} M^{-1}(q) : \Big[\Big(\frac{1}{\beta} M(q) \Big) M^{-1}(q) \nabla_q^2 u(q) - \nabla_q V(q) \nabla_q u(q)^\intercal \Big] \\ &= M^{-1}(q) : \Big[\frac{1}{\beta} \nabla_q^2 u(q) - \nabla_q V(q) \nabla_q u(q)^\intercal \Big]\end{aligned}$$

For $(*)$ it was used that the matrix-valued integral $\int_{\mathcal{P}} pp^\intercal f_{\mathcal{P}}(q,p)\, dp$ computes to $\frac{1}{\beta} M(q)$, due to Lemma B.1.1. The sum of (1) and (2) then yields the fully expanded form of G_2:

$$\begin{aligned}G_2 u(q) = M^{-1}(q) &: \Big[\frac{1}{\beta} \nabla_q^2 u(q) - \nabla_q V(q) \nabla_q u(q)^\intercal \Big] \\ &+ \frac{1}{\beta}\Big[I : N(q) - \frac{1}{2}\Big(M(q) : \nabla_q M^{-1}(q) \Big) M^{-1}(q) \Big]^\intercal \nabla_q u(q)\end{aligned} \tag{B.1}$$

In a last step, we apply Jacobi's formula to show that (B.1) matches the proclaimed form of G_2 in Theorem 3.2.1. As there is no more p-dependence in (B.1), we simplify the remaining expressions by omitting the q-arguments. With the chain- and product rule for the divergence,

$$\begin{aligned}&\frac{1}{\beta} \frac{1}{\sqrt{\det M}} \nabla_q^\intercal \Big(\sqrt{\det M} M^{-1} \nabla_q u \Big) \\ &\qquad = \frac{1}{\beta} \frac{1}{\sqrt{\det M}} \Big[\frac{1}{2\sqrt{\det M}} (\nabla_q \det M)^\intercal M^{-1} \nabla_q u + \sqrt{\det M} \nabla_q^\intercal \big(M^{-1} \nabla_q u \big) \Big] \\ &\qquad = \frac{1}{2\beta} (\nabla_q \det M)^\intercal M^{-1} \nabla_q u + \frac{1}{\beta} \nabla_q^\intercal \big(M^{-1} \nabla_q u \big)\ . \qquad (*)\end{aligned}$$

With Jacobi's formula (A some t-dependent matrix, $t \in \mathbb{R}$)

$$\partial_t \det A(t) = \det A(t)\ \mathrm{tr}\left(A^{-1}(t) \partial_t A(t) \right)\ ,$$

applied to $\partial_{q_i} M$, we get for the first summand of $(*)$

$$\begin{aligned}\frac{1}{2\beta}(\nabla_q \det M)^\intercal M^{-1}\nabla_q u &= \frac{1}{2\beta}\sum_{i=1}^{n} \operatorname{tr}\left(M^{-1}\partial_{q_i} M\right)(M^{-1}\nabla_q u)_i \\ &= -\frac{1}{2\beta}\Big(\big(M : \nabla_q M^{-1}\big)M^{-1}\Big)^\intercal \nabla_q u \ .\end{aligned}$$

For the last equation the identity $A(t)\partial_t A(t) = -\partial_t A(t) A^{-1}(t)$ and the symmetry of M were used.

By element–wise inspection, the second summand of $(*)$ can be written as

$$\frac{1}{\beta}\nabla_q^\intercal\big(M^{-1}\nabla_q u\big) = \frac{1}{\beta}\Big((I : N)^\intercal \nabla_q u + M^{-1} : \nabla_q^2 u\Big) \ .$$

Thus, together we have

$$\begin{aligned}&\frac{1}{\beta}\frac{1}{\sqrt{\det M}}\nabla_q^\intercal\Big(\sqrt{\det M}M^{-1}\nabla_q u\Big) \\ &\qquad = -\frac{1}{2\beta}\Big(\big(M : \nabla_q M^{-1}\big)M^{-1}\Big)^\intercal \nabla_q u + \frac{1}{\beta}\Big((I : N)^\intercal \nabla_q u + M^{-1} : \nabla_q^2 u\Big) \ .\end{aligned}$$

This matches (B.1) up to the summand

$$M^{-1} : (\nabla_q V \nabla_q u^\intercal) = \nabla_q V^\intercal M^{-1}\nabla_q u \ .$$

We thus obtain

$$G_2 u = \frac{1}{\beta}\frac{1}{\sqrt{\det M}}\nabla_q^\intercal\Big(\sqrt{\det M}M^{-1}\nabla_q u\Big) - \nabla_q V^\intercal M^{-1}\nabla_q u \ .$$

□

Proof of Corollary 3.2.2.

Proof. In Cartesian coordinates, M^{-1} is a constant diagonal matrix, and γ and σ are constant scalars. The two parts of L_{Lan} in the decomposition $L_{\text{Lan}} = L_{\text{Ham}} + L_{\text{OU}}$ read

$$L_{\text{Ham}} = p^\intercal M^{-1}\nabla_q - \nabla_q V(q)^\intercal \nabla_p \ , \qquad L_{\text{OU}} = \frac{\sigma^2}{2}\Delta_p - \big(\gamma p^\intercal M^{-1}\big)\nabla_p \ .$$

0. & 1. follow directly from Theorem 3.2.1.
2. Using $\nabla_q M^{-1}(q) = 0$ in Theorem 3.2.1, one sees that G_2 takes the stated form.

3. For G_3, consider $L^3_{\text{Lan}}u$. From the proof of Theorem 3.2.1, we have $L^2_{\text{Lan}} = L^2_{\text{Ham}} + L_{\text{OU}}L_{\text{Ham}}$, thus

$$L^3_{\text{Lan}} = L^3_{\text{Ham}} + L_{\text{Ham}}L_{\text{OU}}L_{\text{Ham}} + L_{\text{OU}}L^2_{\text{Ham}} + L^2_{\text{OU}}L_{\text{Ham}}. \qquad (*)$$

Again from the proof of Theorem 3.2.1, we use that with $\nabla_q M^{-1}(q) = 0$,

$$\begin{aligned} L^2_{\text{Ham}}u &= p^\intercal M^{-1}\nabla_q^2 u(q)M^{-1}p - \nabla_q V(q)^\intercal M^{-1}\nabla_q u(q) \\ L_{\text{OU}}L_{\text{Ham}}u &= \gamma p^\intercal (M^{-1})^2 \nabla_q u(q). \end{aligned}$$

The first summand in $(*)$ extends to

$$\begin{aligned} L^3_{\text{Ham}}u(q) &= \nabla_q H(q,p)^\intercal \nabla_p L^2_{\text{Ham}}u(q) - \nabla_p H(q,p)^\intercal \nabla_q L^2_{\text{Ham}}u(q) \\ &= \nabla_q V(q)^\intercal \Big[2M^{-1}\nabla_q^2 u(q)M^{-1}p\Big] \\ &\quad - p^\intercal M^{-1}\nabla_q \Big[p^\intercal M^{-1}\nabla_q^2 u(q)M^{-1}p - \nabla_q V(q)^\intercal M^{-1}\nabla_q u(q)\Big] \end{aligned}$$

This expression is antisymmetrical in p and will vanish after integration with respect to $\mu_{\mathcal{P}}$, due to Lemma B.1.1.

Likewise, the fourth summand in $(*)$

$$L^2_{\text{OU}}L_{\text{Ham}}u(q) = \gamma p^\intercal M^{-1}\gamma \big(M^{-1}\big)^2 \nabla_q u(q)$$

is antisymmetrical in p and will vanish after integration.

The second summand in $(*)$ is

$$\begin{aligned} L_{\text{Ham}}L_{\text{OU}}L_{\text{Ham}}u(q) &= \nabla_q H(q,p)^\intercal \nabla_p \Big[\gamma p \big(M^{-1}\big)^2 \nabla_q u(q)\Big] \\ &\quad - \nabla_p H(q,p)^\intercal \nabla_q \Big[\gamma p \big(M^{-1}\big)^2 \nabla_q u(q)\Big] \\ &= \gamma \nabla_q V(q)^\intercal \big(M^{-1}\big)^2 \nabla_q u(q) - \gamma p^\intercal M^{-1}\nabla_q^2 u(q)\big(M^{-1}\big)^2 p \\ &= \gamma\Big(\nabla_q V(q)^\intercal \big(M^{-1}\big)^2 \nabla_q u(q) - p^\intercal \big(M^{-1}\big)^2 \nabla_q^2 u(q) M^{-1}p\Big)\,. \end{aligned}$$

In the last line we used $p^\intercal ABp = p^\intercal BAp$ for symmetrical matrices A, B.

Finally, the third summand in $(*)$ is

$$\begin{aligned} L_{\text{OU}}L^2_{\text{Ham}}u(q) &= \frac{\sigma^2}{2}\Delta_p \Big[p^\intercal M^{-1}\nabla_q^2 u(q)M^{-1}p\Big] - \gamma p^\intercal M^{-1}\nabla_p \Big[p^\intercal M^{-1}\nabla_q^2 u(q)M^{-1}p\Big] \\ &= \sigma^2\Big(\nabla_q^\intercal \big[\big(M^{-1}\big)^2 \nabla_q u(q)\big]\Big) - 2\gamma p^\intercal \big(M^{-1}\big)^2 \nabla_q^2 u(q)M^{-1}p \\ &= 2\gamma\Big[\frac{1}{\beta}\nabla_q^\intercal \big[\big(M^{-1}\big)^2 \nabla_q u(q)\big] - p^\intercal \big(M^{-1}\big)^2 \nabla_q^2 u(q)M^{-1}p\Big]\,. \end{aligned}$$

Summing up the non-vanishing terms gives

$$\Big(L_{\mathrm{Ham}}L_{\mathrm{OU}}L_{\mathrm{Ham}} + L_{\mathrm{OU}}L_{\mathrm{Ham}}^2\Big)u(q) = \gamma\Big(\frac{2}{\beta}\nabla_q^\intercal\big[\big(M^{-1}\big)^2\nabla_q u(q)\big] - 3p^\intercal\big(M^{-1}\big)^2\nabla_q^2 u(q)M^{-1}p \\ + \nabla_q V(q)^\intercal\big(M^{-1}\big)^2\nabla_q u(q)\Big),$$

in which p only occurs in the second summand. The third pseudogenerator thus is

$$\begin{aligned} G_3u(q) &= \int_{\mathcal{P}} \big(L_{\mathrm{Lan}}^3 u\big)(q,p)\, d\mu_{\mathcal{P}} \\ &= \gamma\Big(\frac{2}{\beta}\nabla_q^\intercal\big[\big(M^{-1}\big)^2\nabla_q u(q)\big] - 3\underbrace{\int_{\mathcal{P}} p^\intercal\big(M^{-1}\big)^2\nabla_q^2 u(q)M^{-1}p\, d\mu_{\mathcal{P}}}_{(1)} \\ &\qquad + \nabla_q V(q)^\intercal\big(M^{-1}\big)^2\nabla_q u(q)\Big)\,, \end{aligned}$$

The integral calculates to, with Lemma B.1.1,

$$\begin{aligned} (1) &= \big[\big(M^{-1}\big)^2\nabla_q^2 u(q)M^{-1}\big] : \int_{\mathcal{P}} pp^\intercal\, d\mu_{\mathcal{P}} \\ &= \big[\big(M^{-1}\big)^2\nabla_q^2 u(q)M^{-1}\big] : \frac{1}{\beta}M \end{aligned}$$

which is, as $M,\ M^{-1}$ are diagonal matrices,

$$= \frac{1}{\beta}\nabla_q^\intercal\Big(\big(M^{-1}\big)^2\nabla_q u(q)\Big)\,.$$

Overall, we have

$$G_3u = -\gamma\Big[\frac{1}{\beta}\nabla_q^\intercal\big(\big(M^{-1}\big)^2\nabla_q u\big) - \nabla_q V^\intercal\big(M^{-1}\big)^2\nabla_q u\Big].$$

□

B.2. Computer–assisted proofs

For one-dimensional systems, the vector-analytic proofs of the statements in Section 3.2 can be automated. The computer algebra system Wolfram Mathematica [81] allows the declaration of a wide class of differential operators (for functions on $\mathbb{R}$) and the computation of improper integrals, which together allows the automated computation of the pseudogenerators G_k by Proposition 3.1.3.

Computation of the first and second pseudogenerator. First define the Boltzmann density $f_{\mathcal{P}}$, the Hamiltonian H and declare the fluctuation-dissipation relation. V, M, γ and β are hereby regarded as parameters of the system. The normalizing factor $Z_{\mathcal{P}}(q)$ has to be applied to $f_{\mathcal{P}}$ separately (due to technical reasons).

```
fP[q_, p_] := Exp[-beta*(1/2*p*M[q]^-1*p)]
ZP[q_] := Integrate[fP[q, p], {p, -Infinity, Infinity},
                    Assumptions -> Re[beta*M[q]^-1] > 0]
H[q_, p_] := 1/2*p*M[q]^-1*p + V[q]
sigma[q_] := Sqrt[2*gamma[q]/beta]
```

The Hamilton-, Ornstein–Uhlenbeck and Langevin generator can then be defined as follows:

```
Lham[q_, p_] := (D[H[q,p], q]*D[#, p] -
                 D[H[q,p], p]*D[#, q]) &
Lou[q_, p_] := (1/2*sigma[q]^2*D[#, {p, 2}] -
                gamma[q]*p*M[q]^-1*D[#, p]) &
Llan[q_, p_] := (Lham[q,p][#] + Lou[q,p][#]) &
```

Applying L_{Lan} to some density u and integrating with respect to $f_{\mathcal{P}}$ then gives G_1:

```
G1[q_] := Integrate[Simplify[Llan[q,p][u[q]]]*fP[q,p],
            {p, -Infinity, Infinity},
            Assumptions -> Re[beta*M[q]^-1] > 0
          ] / ZP[q]
```

As expected, this computes to 0.

Applying L_{Lan} twice and integrating with respect to $f_{\mathcal{P}}$ yields G_2:

```
G2[q_] := FullSimplify[
            Integrate[Simplify[Llan[q,p][Llan[q,p][u[q]]]*fP[q,p]],
              {p, -Infinity, Infinity},
              Assumptions -> Re[beta*M[q]^-1] > 0
            ] / ZP[q] ]
```

The output

$$\textbf{Out} = \frac{-u'[q](M'[q]+2\textbf{beta } M[q]V'[q])+2M[q]u''[q]}{2\textbf{beta } M^2}$$

matches Theorem 3.2.1 from the main text.

Comparison to the Smoluchowski generator. Definition of the Laplace-Beltrami operator $\tilde{\Delta}$ and the associated gradient $\tilde{\nabla}$:

```
LapBel[q_] := (1/Sqrt[M[q]^-1]*D[Sqrt[M[q]^-1]*M[q]*D[#, q], q]) &
GradBel[q_] := D[#, q]*M[q] &
```

As of Equation 2.31, the Smoluchowski generator reads

```
Lsmol[q_] := (LapBel[q][#]/beta - V'[q]*GradBel[q][#]) &
FullSimplify[Lsmol[q][u[q]]]
```

The output reads

$$\mathbf{Out} = \frac{-u'[q](M'[q]+2\mathbf{beta}\ M[q]V'[q])+2M[q]u''[q]}{2\mathbf{beta}\ M^2}$$

which matches **G2** above.

Special case: Cartesian coordinates. For Cartesian coordinates, i.e. constant M, γ, σ, define

```
fP[q_, p_] := Exp[-beta*(1/2*p*M^-1*p)]
ZP[q_] := Integrate[fP[q, p], {p, -Infinity, Infinity},
                   Assumptions -> Re[beta*M^-1] > 0]
H[q_, p_] := 1/2*p*M^-1*p + V[q]
sigma := Sqrt[2*gamma/beta]
```

and **Lham**, **Lou**, **Llan** as above. For the third pseudogenerator, we then get

```
G3[q_] := FullSimplify[
            Integrate[Simplify[
              Llan[q,p][Llan[q,p][Llan[q,p][u[q]]]]*fP[q,p]],
                {p, -Infinity, Infinity},
                Assumptions -> Re[beta*M^-1] > 0
              ] / ZP[q] ]
```

and receive

$$\mathbf{Out} = \frac{\mathbf{gamma}(\mathbf{beta}\ u'[q]V'[q]-u''[q])}{\mathbf{beta}\ M^2}$$

which matches Corollary 3.2.2.

Higher pseudogenerators do not retain this simple structure. For Cartesian coordinates, G_4 is computed by

```
G4[q_] := FullSimplify[
            Integrate[Simplify[
              Llan[q,p][Llan[q,p][Llan[q,p][Llan[q,p][u[q]]]]]*fP[q,p]],
                {p, -Infinity, Infinity},
                Assumptions -> Re[beta*M^-1] > 0
              ] / ZP[q] ]
```

The output does not show any obvious structure:

$$\begin{aligned}\mathbf{Out} = (\mathbf{beta}^2\mathbf{M}^3)^{-1}(&\mathbf{beta}\ u''[q](\mathbf{gamma}^2+3\mathbf{beta}\ \mathbf{M}\ \mathbf{V}'[q]^2-4\mathbf{M}\ \mathbf{V}''[q])\\ &-\mathbf{beta}\ u'[q](\mathbf{beta}\ \mathbf{V}'[q](\mathbf{gamma}^2-\mathbf{M}\ \mathbf{V}''[q])+\mathbf{M}\ \mathbf{V}^{(3)}[q])\\ &+3\mathbf{M}(-2\mathbf{beta}\ \mathbf{V}'[q]u^{(3)}[q]+u^{(4)}[q])\end{aligned}$$

Bibliography

[1] R. Abraham, J. E. Marsden, and J. E. Marsden. *Foundations of Mechanics*. AMS Chelsea Publishing, Providence, 1978.

[2] V. I. Arnold. *Mathematical Methods of Classical Mechanics*. Springer, New York, 2013.

[3] J. R. Baxter and J. S. Rosenthal. Rates of convergence for everywhere-positive Markov chains. *Statistics & probability letters*, 22(4):333–338, 1995.

[4] H. M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T. Bhat, H. Weissig, I. N. Shindyalov, and P. E. Bourne. The protein data bank. *Nucleic acids research*, 28(1):235–242, 2000.

[5] A. Bittracher, C. Hartmann, O. Junge, and P. Koltai. Pseudo generators for under-resolved molecular dynamics. *The European Physical Journal Special Topics*, 224(12):2463–2490, 2015.

[6] A. Bittracher, P. Koltai, and O. Junge. Pseudogenerators of Spatial Transfer Operators. *SIAM Journal on Applied Dynamical Systems*, 14(3):1478–1517, 2015.

[7] G. R. Bowman, X. Huang, and V. S. Pande. Using generalized ensemble simulations and Markov state models to identify conformational states. *Methods*, 49(2):197–201, 2009.

[8] J. D. Chodera, N. Singhal, V. S. Pande, K. A. Dill, and W. C. Swope. Automatic discovery of metastable states for the construction of Markov models of macromolecular conformational dynamics. *The Journal of chemical physics*, 126(15):155101, 2007.

[9] J. D. Chodera, W. C. Swope, J. W. Pitera, and K. A. Dill. Long-time protein folding dynamics from short-time molecular dynamics simulations. *Multiscale Modeling & Simulation*, 5(4):1214–1226, 2006.

[10] G. Ciccotti, T. Lelièvre, and E. Vanden-Eijnden. Projection of diffusions on submanifolds: Application to mean force computation. *Comm. Pure Appl. Math.*, 61(3):371–408, 2008.

[11] C. Cramer. *Essentials of Computational Chemistry*. Wiley, Hoboken, 2004.

[12] M. Dellnitz and A. Hohmann. A subdivision algorithm for the computation of unstable manifolds and global attractors. *Numerische Mathematik*, 75(3):293–317, 1997.

[13] M. Dellnitz and O. Junge. On the approximation of complicated dynamical behaviour. *SIAM J. Num. Anal.*, 36(2):491–515, 1999.

[14] P. Deuflhard, M. Dellnitz, O. Junge, and C. Schütte. Computation of essential molecular dynamics by subdivision techniques. In *Computational molecular dynamics: challenges, methods, ideas*, pages 98–115. Springer, 1999.

[15] P. Deuflhard, W. Huisinga, A. Fischer, and C. Schütte. Identification of almost invariant aggregates in reversible nearly uncoupled Markov chains. *Linear Algebra and its Applications*, 315(1):39–59, 2000.

[16] W. E and E. Vanden-Eijnden. Metastability, conformation dynamics, and transition pathways in complex systems. In *Multiscale modelling and simulation*, pages 35–68. Springer, 2004.

[17] W. E and E. Vanden-Eijnden. Towards a theory of transition paths. *Journal of statistical physics*, 123(3):503–523, 2006.

[18] R. Elber and M. Karplus. Multiple conformational states of proteins: a molecular dynamics analysis of myoglobin. *Science*, 235(4786):318–321, 1987.

[19] D. J. Evans and G. P. Morriss. *Statistical Mechanics of Nonequilibrium Liquids*. Cambridge University Press, 2008.

[20] G. E. Fasshauer. *Meshfree Approximation Methods with MATLAB*. World Scientific, Singapore, 2007.

[21] H. Federer. *Geometric Measure Theory*. Springer, New York, 1969.

[22] W. Feller. *An Introduction to Probability Theory and Its Applications*. Wiley, Hoboken, 2008.

[23] H. Frauenfelder and B. McMahon. Energy landscape and fluctuations in proteins. *Annalen der Physik*, 9(9-10):655–667, 2000.

[24] G. Froyland. *Estimating Physical Invariant Measures and Space Averages of Dynamical Systems Indicators*. PhD thesis, University of Western Australia, 1996.

[25] G. Froyland, O. Junge, and P. Koltai. Estimating long-term behavior of flows without trajectory integration: the infinitesimal generator approach. *SIAM Journal on Numerical Analysis*, 51(1):223–247, 2013.

[26] D. Givon, R. Kupferman, and O. H. Hald. Existence proof for orthogonal dynamics and the Mori–Zwanzig formalism. *Israel Journal of Mathematics*, 145:221–241, 2004.

[27] M. Griebel, S. Knapek, and G. Zumbusch. *Numerical Simulation in Molecular Dynamics: Numerics, Algorithms, Parallelization, Applications*. Springer, Berlin Heidelberg, 2007.

[28] E. Hairer, C. Lubich, and G. Wanner. *Geometric Numerical Integration: Structure-*

preserving Algorithms for Ordinary Differential Equations. Springer, Berlin Heidelberg, 2006.

[29] P. Hänggi, P. Talkner, and M. Borkovec. Reaction-rate theory: fifty years after Kramers. *Rev. Mod. Phys.*, 62:251–341, 1990.

[30] C. Hartmann. An ergodic sampling scheme for constrained Hamiltonian systems with applications to molecular dynamics. *J. Stat. Phys.*, 130(4):687–711, 2008.

[31] U. G. Haussmann and E. Pardoux. Time reversal of diffusions. *The Annals of Probability*, 14:1188–1205, 1986.

[32] W. M. Haynes. *CRC Handbook of Chemistry and Physics*. CRC press, Boca Raton, 2014.

[33] X. Huang, Y. Yao, G. R. Bowman, J. Sun, L. J. Guibas, G. E. Carlsson, and V. S. Pande. Constructing multi-resolution Markov State Models (MSMs) to elucidate RNA hairpin folding mechanisms. In *Pacific Symposium on Biocomputing*, volume 15, pages 228–239. World Scientific, 2010.

[34] W. Huisinga. *Metastability of Markovian systems*. PhD thesis, Freie Universität Berlin, 2001.

[35] W. Huisinga and B. Schmidt. Metastability and dominant eigenvalues of transfer operators. In B. Leimkuhler, C. Chipot, R. Elber, A. Laaksonen, A. Mark, T. Schlick, C. Schütte, and R. Skeel, editors, *New Algorithms for Macromolecular Simulation*, volume 49 of *Lecture Notes in Computational Science and Engineering*, pages 167–182. Springer, 2006.

[36] F. Y. Hunt. Monte Carlo approach to the approximation of invariant measures. *Random Comput. Dynam.*, 2(1):111–133, 1994.

[37] O. Junge and P. Koltai. Discretization of the Frobenius-Perron operator using a sparse Haar tensor basis: the sparse Ulam method. *SIAM Journal on Numerical Analysis*, 47(5):3464–3485, 2009.

[38] I. Karatzas. *Brownian Motion and Stochastic Calculus*, volume 113. Springer, New York, 1991.

[39] P. Koltai. *Efficient approximation methods for the global long-term behavior of dynamical systems: theory, algorithms and examples*. PhD thesis, Technische Universität München, 2010.

[40] H. A. Kramers. Brownian motion in a field of force and the diffusion model of chemical reactions. *Physica*, 7(4):284–304, 1940.

[41] A. Lasota and M. C. Mackey. *Chaos, Fractals, and Noise: Stochastic Aspects of Dynamics*. Springer, New York, 1994.

[42] F. Legoll and T. Lelièvre. Effective dynamics using conditional expectations. *Nonlinearity*, 23(9):2131, 2010.

[43] B. Leimkuhler, C. Chipot, R. Elber, A. Laaksonen, A. Mark, T. Schlick, C. Schütte, and R. Skeel. *New Algorithms for Macromolecular Simulation*. Springer, Berlin Heidelberg, 2006.

[44] T. Lelièvre, M. Rousset, and G. Stoltz. *Free Energy Computations: A Mathematical Perspective*. Imperial College Press, 2010.

[45] J. C. Mattingly and A. M. Stuart. Geometric ergodicity of some hypo-elliptic diffusions for particle motions. *Markov Process. Related Fields*, 8(2):199–214, 2002.

[46] J. C. Mattingly, A. M. Stuart, and D. J. Higham. Ergodicity for SDEs and approximations: locally Lipschitz vector fields and degenerate noise. *Stochastic processes and their applications*, 101(2):185–232, 2002.

[47] P. Metzner. *Transition path theory for Markov processes*. PhD thesis, Freie Universität Berlin, 2008.

[48] E. Nelson. *Dynamical Theories of Brownian Motion*. Princeton University Press, 1967.

[49] F. Noé, D. Krachtus, J. C. Smith, and S. Fischer. Transition networks for the comprehensive characterization of complex conformational change in proteins. *Journal of Chemical Theory and Computation*, 2(3):840–857, 2006.

[50] B. Øksendal. *Stochastic differential equations*. Springer, New York, 2003.

[51] W. K. Olson and V. B. Zhurkin. Modeling DNA deformations. *Current opinion in structural biology*, 10(3):286–297, 2000.

[52] A. Ostermann, R. Waschipky, F. G. Parak, and G. U. Nienhaus. Ligand binding and conformational motions in myoglobin. *Nature*, 404(6774):205–208, 2000.

[53] V. S. Pande, K. Beauchamp, and G. R. Bowman. Everything you wanted to know about Markov State Models but were afraid to ask. *Methods*, 52(1):99–105, 2010.

[54] G. Papanicolaou. Some probabilistic problems and methods in singular perturbations. *Rocky Mountain J. Math.*, 6(4):653–674, 1976.

[55] G. Pavliotis and A. Stuart. *Multiscale Methods: Averaging and Homogenization*. Springer, New York, 2008.

[56] A. Pazy. *Semigroups of Linear Operators and Applications to Partial Differential Equations*. Springer, New York, 1983.

[57] K. B. Petersen and M. S. Pedersen. The matrix cookbook, nov 2012. Version 20121115.

[58] J.-H. Prinz, H. Wu, M. Sarich, B. Keller, M. Senne, M. Held, J. D. Chodera, C. Schütte, and F. Noé. Markov models of molecular kinetics: Generation and validation. *The Journal of chemical physics*, 134(17):174105, 2011.

[59] H. Risken and T. Frank. *The Fokker–Planck Equation: Methods of Solution and Appli-*

cations. Springer, Berlin Heidelberg, 1996.

[60] S. Röblitz and M. Weber. Fuzzy spectral clustering by PCCA+: application to Markov state models and data classification. *Advances in Data Analysis and Classification*, 7(2):147–179, 2013.

[61] C. Schütte. *Conformational Dynamics: Modelling, Theory, Algorithm, and Application to Biomolecules*. Habilitation thesis, Freie Universität Berlin, 1999.

[62] C. Schütte, W. Huisinga, and P. Deuflhard. Transfer operator approach to conformational dynamics in biomolecular systems. In B. Fiedler, editor, *Ergodic Theory, Analysis, and Efficient Simulation of Dynamical Systems*, pages 191–223. Springer Berlin Heidelberg, 2001.

[63] C. Schütte, F. Noé, J. Lu, M. Sarich, and E. Vanden-Eijnden. Markov state models based on milestoning. *The Journal of chemical physics*, 134(20):204105, 2011.

[64] C. Schütte and M. Sarich. *Metastability and Markov State Models in Molecular Dynamics.* Courant Lecture Notes in Mathematics, New York, 2013.

[65] C. Schütte and M. Sarich. A critical appraisal of Markov State Models. *The European Physical Journal Special Topics*, 224(12):2445 – 2462, 2015.

[66] F. Schwabl. *Statistical Mechanics*. Springer, Berlin Heidelberg, 2000.

[67] M. Senne, B. Trendelkamp-Schroer, A. Mey, C. Schütte, and F. Noé. EMMA—a software package for Markov model building and analysis. *Journal of Chemical Theory and Computation*, 8:2223 – 2238, 2012.

[68] D. E. Shaw, M. M. Deneroff, R. O. Dror, J. S. Kuskin, R. H. Larson, J. K. Salmon, C. Young, B. Batson, K. J. Bowers, J. C. Chao, et al. Anton, a special-purpose machine for molecular dynamics simulation. *Communications of the ACM*, 51(7):91–97, 2008.

[69] M. V. Smoluchowski. Drei Vorträge uber Diffusion, Brownsche Bewegung und Koagulation von Kolloidteilchen. *Zeitschrift fur Physik*, 17:557–585, 1916.

[70] W. C. Swope, J. W. Pitera, and F. Suits. Describing protein folding kinetics by molecular dynamics simulations. 1. Theory. *The Journal of Physical Chemistry B*, 108(21):6571–6581, 2004.

[71] L. N. Trefethen. *Spectral Methods in MATLAB*. SIAM, 2000.

[72] L. N. Trefethen and M. Embree. *Spectra and Pseudospectra: The Behavior of Nonnormal Matrices and Operators*. Princeton University Press, 2005.

[73] H. F. Trotter. On the product of semi-groups of operators. *Proceedings of the American Mathematical Society*, 10(4):545–551, 1959.

[74] G. E. Uhlenbeck and L. S. Ornstein. On the theory of the Brownian Motion. *Phys. Rev.*, 36:823–841, Sep 1930.

[75] S. M. Ulam. *A Collection of Mathematical Problems*. Interscience Publishers, New York, 1960.

[76] E. Vanden-Eijnden. Transition-path theory and path-finding algorithms for the study of rare events. *Annual review of physical chemistry*, 61:391–420, 2010.

[77] M. Weber. *Meshless Methods in Conformation Dynamics*. PhD thesis, FU Berlin, 2006.

[78] M. Weber. *A subspace approach to molecular Markov Sstate Models via a new infinitesimal generator*. Habilitation thesis, Freie Universität Berlin, 2012.

[79] M. Weber, A. Bujotzek, and R. Haag. Quantifying the rebinding effect in multivalent chemical ligand-receptor systems. *The Journal of Chemical Physics*, 137(5), 2012.

[80] H. Wendland. *Scattered Data Approximation*. Cambridge University Press, 2004.

[81] Wolfram Research, Inc. *Mathematica*. Wolfram Research Inc., Champaign, Illinios, 10.4 edition, 2016.

[82] E. Zeidler. *Applied Functional Analysis*. Springer, New York, 1995.

[83] H.-X. Zhou, S. T. Wlodek, and J. A. McCammon. Conformation gating as a mechanism for enzyme specificity. *Proceedings of the National Academy of Sciences*, 95(16):9280–9283, 1998.

[84] R. Zwanzig. *Nonequilibrium Statistical Mechanics*. Oxford University Press, 2001.