Freie Universität Berlin

Masterarbeit am Institut für Mathematik der Freien Universität Berlin

Computing the minimal rebinding effect for nonreversible processes

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Berlin, 07.07.2017

Contents

Introduction

Thesis Structure

Chapter 1 - Markov State Models

We give a short overview of relevant tools from measure theory and Markov processes on measurable state spaces, in order to introduce two different, but strongly related, transfer operators. We show that they propagate probability densities respectively sets(?) of a given Markov process. Then we show how this continuous operator can be projected onto a finite-dimensional space with the aid of a Galerkin discretization. Finally, we analyze the discretization error the possible loss of the Markov property which can occur by this projection.

Chapter 2 - Dominant Structures

We introduce the important concept of metastability as dominant structures of Markov processes. We define metastable sets mathematically and show their relevance for molecular dynamic systems. Furthermore, we reveal their relation to the spectrum of the transfer operator and see how the "best" metastable decomposition can be achieved. At the end of the chapter, we introduce the Schur decomposition. It is a more general method than the spectral decomposition and can help us to cluster metastable sets even in nonreversible processes.

Chapter 3 - Rebinding Effect

In this chapter, we introduce the crucial point of this thesis, the Rebinding Effect. We describe this effect in the context of a receptor-ligand-system, a special case of a molecular system, and set this effect in relation to the Recrossing Effect from chapter 1. We apply the methods from chapter 1 and 2 in order to rigorously describe a molecular system respectively its projection onto a finite subspace. Finally, we compute a minimal bound for the rebinding effect as the solution of an optimization problem.

Chapter 4 - Illustrative Examples

1 Markov State Models

In order to be able to describe dynamical systems having a nondeterministic behaviour, we introduce Markov processes. They are basically memoryless stochastic processes which are commonly used to model different kinds of real-world processes. Recently they have been applied a lot in the research area of modelling biomolecular systems. As those systems are enormous large, it is very difficult to perform simulations on feasible time scales. That is why a reduction of complexity is needed. The originally large process is projected onto a suitable subspace, while maintaining the most relevant dynamical properties of the process. Such a reduced model is called a "Markov State Model".

In order to adequately define a Markov State Model, we need at first some basic definitions and properties of stochastic processes, especially Markov processes, and how their evolution in time can be described using the transfer operator. The actual dimension reduction of the process is realized by a Galerkin projection applied to the transfer operator. By that action, states of the original process are clustered conveniently.

1.1 Markov Process

We introduce Markov processes, which are a special type of stochastic processes and a generalization of the well-known Markov chains. Markov chains were defined as a memoryless process acting on a finite state space and evolving in discrete time, a behaviour that can be described by a stochastic matrix. For general Markov processes, both these properties can be continuous and thus, we need some more extensive formulations and tools in order to describe such processes respectively their time-evolution rigorously.

Transition function

We will denote by $E := (E, \Sigma)$ a *measurable space*, that is a set E with some σ-algebra Σ defined on it. The triple $\Omega := (\Omega, \mathcal{A}, \mathbb{P})$ will be a *probability space*, that is a measurable space with a probability measure $\mathbb{P}$ defined on it; for detailed information about these basic measure theoretic notations, see Bogachev[2, chapter 1].

A *random variable* $X : \Omega \to E$ is a *measurable function* from a probability space Ω into a measurable space E, meaning that preimages of measurable sets in E are measurable in Ω:

$$A \in \Sigma \Rightarrow X^{-1}(A) \in \mathcal{A}.$$

Then the probability measure $\mathbb{P}$ of Ω induces a canonical probability measure on E, by

$$\mu(A) := \mathbb{P}(X \in A) := \mathbb{P}(X^{-1}(A))$$

for all $A \in \Sigma$, called the *distribution* of X, see Øksendal[25, Section 2.1].

Definition 1.1. (Stochastic Process)
A family $(X_t)_{t \in \mathbb{T}}$ of random variables $X_t : \Omega \to E$ on some index set $\mathbb{T}$ is called a *stochastic process* on a state space E.

In the following, we consider stochastic process on real state spaces $E \subset \mathbb{R}^d, d \in \mathbb{N}$, equipped with the Borel-σ-algebra $\Sigma = \mathcal{B}(E)$. In order to introduce Markov processes as a special type of stochastic processes, we need a tool to describe the time evolution or propagation of a process. This can be done using the transition function which describes the propagation of the distribution functions of a stochastic process.

Definition 1.2. (Transition function)
A function $p : \mathbb{T} \times E \times \Sigma \to [0, 1]$ is a *transition function* if it fulfills the following properties:

   i) $x \mapsto p(t, x, A)$ is measurable on E for all $t \in \mathbb{T}$ and $A \in \Sigma$,

   ii) $A \mapsto p(t, x, A)$ is a probability measure for all $t \in \mathbb{T}$ and $x \in E$,

   iii) $p(0, x, E \setminus x) = 0$ for all $x \in E$,

   iv) the Chapman-Kolmogorov equation

$$p(t + s, x, A) = \int_E p(t, x, \mathrm{d}z) p(s, z, A). \tag{1.1}$$

     holds for all $t, s \in \mathbb{T}, x \in E$ and $A \in \Sigma$.

In this definition, the first three properties ensure that we get reasonable results and that that the process can only be in one state at the same time. From the Chapman-Kolmogorov equation (1.1), it follows that the transition function $p(t, x, A)$ can be considered as the probability to get into a certain subset A in a time interval t starting from a point x. That means that we can describe the time evolution of a stochastic process by a transition function. In particular, the transition matrix of a Markov chain is a special case of the transition function since it fulfills the above properties.

Markov Process

With the aid of a transition function, we can define Markov processes.

Definition 1.3. (Markov Process)
A stochastic process $(X_t)_{t \in \mathbb{T}}$ on a state space E is a *Markov process* if its transition function fulfills the equation

$$p(t, x, A) = \mathbb{P}(X_{t+s} \in A \mid X_s = x). \tag{1.2}$$

for all $s, t \in \mathbb{T}$, $x \in E$ and $A \in \Sigma$. If that probability is independent from s, then the Markov process is called *time-homogeneous*.

We are especially interested in time-homogeneous processes, which will be presumed from now on. As we can see from the definition, all possible transition probabilities are given and hence, the time evolution of a Markov process is completely described by its transition function. Thus a Markov process is uniquely determined by its transition function and an initial distribution μ. It is a process that has "no memory" in the sense that only the last known state of the process has an influence on the future of the process, as we can see on the right side of (1.2).

Indeed, there is a one-to-one relation between transition functions and Markov processes, i.e. every homogeneous Markov process defines a transition function and vice versa, see Meyn and Tweedie[23, Section 3.4]. The beginning of a Markov process X_t with the transition function p fulfills

$$\mathbb{P}_\mu(X_0 \in A, X_t \in B) = \int_A p(t, x, B)\mu(\mathrm{d}x) \tag{1.3}$$

for any $A, B \in \Sigma$, where $\mathbb{P}_\mu$ indicates that $X_0 \sim \mu$, or equivalently $\mu(A) = \mathbb{P}(X_0 \in A)$.

The transition function for a Markov process plays the same role as the transition matrix for a Markov chain; it propagates its distributions. If for the transition function   ? we choose $t = 1$ and transitions into one-elementic subsets, then the transition function corresponds to the 1-step transition matrix $[p_{ij}] = P \in \mathbb{R}^{n \times n}$ of a Markov chain. Having introduced the notion of Markov processes, we can define some important properties and give some examples.

Invariant Measure

Definition 1.4. (Invariant measure)
Let $(X_t)_{t \in \mathbb{T}}$ be a Markov process. The probability measure μ is *invariant* with respect to $(X_t)_{t \in \mathbb{T}}$ if for all $t \in \mathbb{T}$ and $A \in \Sigma$ we have

$$\int_E p(t, x, A)\mu(\mathrm{d}x) = \mu(A).$$

In other words, a measure is invariant with respect to a Markov process if the probability to **be** in any subset of the state space is the same as the probability to **get** into that subset by the evolution of the Markov process for any fixed transition time.

Ergodicity

The long-time behaviour of stochastic processes can be described using ergodicity.

Definition 1.5. (ergodic process)
Let $(X_t)_{t \in \mathbb{T}}$ be a Markov process with invariant probability measure μ. Then $(X_t)_{t \in \mathbb{T}}$ is *ergodic* with respect to μ if for all functions $u : E \to \mathbb{R}$ with $\int_E |u|\mu(\mathrm{d}x) < \infty$ we have

$$\lim_{T \to \infty} \frac{1}{T} \int_0^T u(X_t)\,\mathrm{d}t = \int_E u(x)\mu(\mathrm{d}x).$$

for almost all initial values $X_0 = x_0$.

In that sense, a Markov process is ergodic if its time average is the same as its average over the probability space. In an ergodic process, the state of the process after a long time is nearly independent of its initial state.

Reversibility

Reversibility describes the invariance of a process with respect to time-reversal. In the next section, we will see that an operator describing a reversible process yields some very favorable properties, which makes it easy to analyze such a process.

Definition 1.6.   (reversible process)
Let $(X_t)_{t \in \mathbb{T}}$ be a Markov process with invariant probability measure μ. Then $(X_t)_{t \in \mathbb{T}}$ is *reversible* with respect to μ if

$$\int_A p(t, x, B)\mu(\mathrm{d}x) = \int_B p(t, x, A)\mu(\mathrm{d}x)$$

for all $t \in \mathbb{T}$ and $A, B \in \Sigma$. If μ is unique, then X_t is simply called *reversible*.

For a reversible process, the probability to get from any subset A to another subset B in a fixed time is the same as the probability for the reverse transition in the same time span. Thus this definition implies that the process keeps the same probability law even if its movement is considered backwards in time.

If the stochastic transition function is absolutely continuous with respect to μ, then reversibility corresponds to $p(t, x, y) = p(t, y, x)$ for all $t \in \mathbb{T}$ and μ-almost all $x, y \in E$.

Example: Markov Chain

Let $(X_t)_{t \in \mathbb{T}}$ be a Markov chain on discrete time $\mathbb{T} = \mathbb{N}$ and finite state space $E = \{1, \ldots, n\}$. Since we consider 1-step transitions, the associated transition function is given by $p(x, y) := p(1, x, y)$ and corresponds to the entries of the *transition matrix* $P \in \mathbb{R}^{n \times n}$, that is

$$P_{xy} = p(x, y) = \mathbb{P}(X_1 = y \mid X_0 = x).$$

The propagation of a probability distribution $v_0 \in \mathbb{R}^n$ in the state space can be written as $v_1^T = v_0^T P$, where v_0^T denotes the transposed vector of v_0. The invariant measure is given by the stationary distribution $\pi \in \mathbb{R}^n$, a normalized positive vector satisfying $\pi^T = \pi^T P$. If P is irreducible, such an eigenvector exists due to Perron-Frobenius theorem[15, P7.3.5] and in this case, the corresponding eigenvalue 1 is simple.

Reversibility of a Markov chain can be characterized by the *detailed balance condition*

$$\pi_i \cdot \mathbb{P}(X_1 = j \mid X_0 = i) = \pi_j \cdot \mathbb{P}(X_1 = i \mid X_0 = j) \quad \forall i, j \in E.$$

A more compact way to write this equation uses the diagonal matrix $D = \mathrm{diag}(\pi_1, \ldots, \pi_n)$. Then a Markov chain is reversible if and only if its transition matrix P fulfills

$$DP = P^T D. \tag{1.4}$$

This notation will be useful later in order to measure the degree of nonreversibility of a process.

1.2 Transfer Operator

With the previously defined transition function, we have a tool to describe the propagation of **distributions** of stochastic processes. Now we are going to introduce an operator that propagates **probability densities** of Markov processes. Before defining such an operator, we have to specify the space of functions the operator is acting on.

= trans. matr. of M
resp. sets?

L^r-**Spaces**

It seems natural to define such a density propagating operator as acting on $L^1(\mu)$, the Banach space that includes all probability densities with respect to μ. However it is sometimes advantageous to restrict the analysis to $L^2(\mu)$, since this can lead to a self-adjoint operator. As there are different motivations for the choice of a suitable space, we define an operator which acts on $L^r(\mu)$-spaces, i.e. spaces of r-integrable functions.

Definition 1.7. (L^r-**Spaces**)
Let (E, Σ, μ) a measure space. Then we define the corresponding L^r-spaces as equivalence classes of measurable functions

$\mathbb{C}$?

$$L^r(E, \Sigma, \mu) = \{f : E \to \mathbb{R} \mid \int_E |f(x)|^r \mu(\mathrm{d}x) < \infty\}$$

for $1 \le r < \infty$ and

$$L^\infty(E, \Sigma, \mu) = \{f : E \to \mathbb{R} \mid \operatorname*{ess\,sup}_{x \in E} |f(x)|^r \mu(\mathrm{d}x) < \infty\},$$

with the corresponding norms $\|\cdot\|_r$ and $\|\cdot\|_\infty$.

In these equivalence classes, two functions f, g are the identified if $f = g$ μ-almost everywhere, see Werner[46, section I.1]. If it is clear from the context, which measure space (E, Σ, μ) is in consideration, we just write shortly $L^r(\mu) := L^r(E, \Sigma, \mu)$. Due to Hölders inequality, we have $L^r(\mu) \subset L^s(\mu)$ for all $1 \le s \le r \le \infty$. All L^r-spaces are Banach spaces, though $L^2(\mu)$ is the only one which can be equipped with a canonical scalar product and thereby becomes a Hilbert space, see Werner[46, section V.1]. For $f, g \in L^2(\mu)$, the scalar product is defined as

$\mathbb{C}$?

$$\langle f, g \rangle_\mu := \int_E f(x)\overline{g(x)}\mu(\mathrm{d}x).$$

Now let ν_0 be the density function of a given start distribution. Then the density function of a subset $A \in \Sigma$ at time t is given in terms of the transition function by

$$\nu_t(A) = \int_E \nu_0 p(t, x, A)\mu(\mathrm{d}x).$$

On the other hand, the density ν_t is given by

$$\nu_t(A) = \int_A \nu_t(x)\mu(\mathrm{d}x).$$

Forward and Backward Transfer Operator

The two above equations result in the following intuitive definition of a transfer operator which should "propagate" probability densities according to a given Markov process. But instead of limiting us to density functions, we define the transfer operator as acting on any r-integrable function.

Definition 1.8. (Propagator or Forward Transfer Operator)
Let $p : \mathbb{T} \times E \times \Sigma \to [0, 1]$ be the transition function of a Markov Process $(X_t)_{t \in \mathbb{T}}$ and μ be an invariant measure of $(X_t)_{t \in \mathbb{T}}$. The semigroup of *propagators* or *forward transfer operators* $\mathcal{T}^t : L^r(\mu) \to L^r(\mu)$ with $t \in \mathbb{T}$ and $1 \le r \le \infty$ is defined via

$$\int_A \mathcal{T}^t \nu(y)\mu(\mathrm{d}y) = \int_E \nu(x)p(t, x, A)\mu(\mathrm{d}x) \tag{1.5}$$

for all $A \in \Sigma$ and $\nu \in L^r(\mu)$.

The propagator is well-defined on the Banach spaces $L^r(\mu)$, $1 \le r \le \infty$, see [16]. We will list already some properties of this operator which will be useful in the following chapters. $\mathcal{T}^t$ is a *Markov operator*, i.e. it conserves the norm, $\|\mathcal{T}^t\nu\|_1 = \|\nu\|_1$, and is positive, $\mathcal{T}^t\nu \ge 0$ for $\nu \ge 0$. $\mathcal{T}^t\nu_0$ describes the transport of the function ν_0 in time t by the underlying dynamics given by the process X_t and weighted with respect to μ via

$$\nu_0 \mapsto \nu_t = \mathcal{T}^t\nu_0.$$

Since μ is invariant, we see immediately that the characteristic function $\mathbb{1} := \mathbb{1}_E$ of the entire state space is invariant under the action of $\mathcal{T}^t$, that is

$$\mathcal{T}^t\mathbb{1} = \mathbb{1}.$$

It means that $\mathcal{T}^t$ has the eigenvalue 1 which corresponds to its eigenfunction $\mathbb{1}$.

Definition 1.9. (Backwards Transfer Operator[1])
The *backwards transfer operator* $\mathcal{U}^t : L^r(\mu) \to L^r(\mu)$ with $t \in \mathbb{T}$ and $1 \le r \le \infty$ is defined by

$$\mathcal{U}^t f(x) = \int_E f(y)p(t, x, \mathrm{d}y). \tag{1.6}$$

We have again 1 as eigenvalue to the eigenfunction $\mathbb{1}$, that is for all $t \in \mathbb{T}$ we have

$$\mathcal{U}^t\mathbb{1} = \mathbb{1}.$$

The operator $\mathcal{U}^t$ is *adjoint* to $\mathcal{T}^t$, denoted by $(\mathcal{T}^t)^* = \mathcal{U}^t$, that is they are related via the duality bracket, namely for all $f \in L^p(\mu), g \in L^q(\mu)$ with $\frac{1}{p} + \frac{1}{q}$, we have

$$\langle \mathcal{T}^t f, g \rangle_\mu = \langle f, \mathcal{U}^t g \rangle_\mu.$$

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[1]This nomenclature is motivated by the fact that for some models the forward transfer operator is related to the forward Kolmogorov relation, while the backward transfer operator is is related to the backward Kolmogorov relation.

We again remark that both forward as well as backward operator can be defined on arbitrary $L^r(\mu)$-spaces. But the previous equation shows us that either the choice $p = q = 2$ or the choice $p = 1, q = \infty$ or conversely, make sense, in order that we obtain this useful adjointness/duality-relation of the two operators.

If we compare the equations (1.5) and (1.6), the notion of "forward" and "backwards" becomes clear. For the forward case, the state average with respect to f is taken over all initial states x which are propagated forward in time. In the backward case, we take the state average over all final states y.

If the state space is finite and the corresponding process reversible, then we can see the relation of the forward and backward operator still better. Then the forward operator   ? corresponds to the transition matrix, propagating probability distributions, while the backward operator corresponds to the *transposed* transition matrix, propagating subsets.

Spectrum of Transfer operator

Later in this thesis, we will be interested in examining the spectrum of the transfer operator of a given Markov process. The following theorems give us an important insight about the spectrum and its relation to the reversibility of the process.

Definition 1.10. (Self-adjoint Operator)
An operator $\mathcal{T}$ on $L^2(\mu)$ is called *self-adjoint* if for all $f, g \in L^2(\mu)$ we have

$$\langle f, \mathcal{T}g \rangle_\mu = \langle \mathcal{T}f, g \rangle_\mu.$$

Theorem 1.11. (Werner[46, theorem VI.1.2, theorem VI.1.3, lemma VI.3.1])
Let X be a Banach space and $\mathcal{T} : X \to X$ a linear continuous operator. Then we have

$$|\lambda| \leq \|\mathcal{T}\| \quad \text{for all} \quad \lambda \in \sigma(\mathcal{T}).$$

If X is a Hilbert space, then

i) $\sigma(\mathcal{T}^*) = \{\bar{\lambda} \mid \lambda \in \sigma(\mathcal{T})\}$,

ii) if $\mathcal{T}$ is self-adjoint, i.e. if $\mathcal{T}^* = \mathcal{T}$, then $\sigma(\mathcal{T}) \subset \mathbb{R}$,

iii) if $\mathcal{T}$ is self-adjoint, then each two eigenfunctions corresponding to different eigenvalues are orthogonal.

Since we know that the operator norm of any transfer operator $\mathcal{T}$ is 1, it follows immediately from theorem 1.11 that its spectrum $\sigma(\mathcal{T})$ is contained in the unit circle of the complex plane, that is we have $|\lambda| \leq 1$ for all $\lambda \in \sigma(\mathcal{T}) \subset \mathbb{C}$.

Theorem 1.12. (Huisinga[16, proposition 1.1])
Let $\mathcal{T}^t : L^2(\mu) \subset L^1(\mu) \to L^2(\mu)$ be the propagator corresponding to the Markov process $(X_t)_{t\in\mathbb{T}}$. Then $\mathcal{T}^t$ is self-adjoint with repect to the scalar product $\langle \cdot, \cdot \rangle_\mu$ in $L^2(\mu)$ if and only if $(X_t)_{t\in\mathbb{T}}$ is reversible.

Thus, the transfer operator of a reversible process has a spectrum $\sigma(\mathcal{T}) \subset [-1, 1]$. Furthermore, theorem 1.11 guarantees us that the spectrum of a self-adjoint operator is equal to the spectrum of its adjoint. Thus, if we are given a reversible process, it doesn't matter if we examine the spectrum of the forward or the backward transfer operator.

Infinitesimal Generator

For $\mathbb{T} = \mathbb{R}$ the Chapman-Kolmogorov property (1.1) of the transition functions makes the family $\{\mathcal{T}^t\}_{t \in \mathbb{R}}$ of transfer operators a continuous *semigroup* due to

$$\mathcal{T}^{t+s} = \mathcal{T}^t \mathcal{T}^s.$$

This leads to the following definition of the the infinitesimal generator.

Definition 1.13. (Infinitesimal Generator)
For the semigroup of propagators or forward transfer operators $\mathcal{T}^t : L^r(\mu) \to L^r(\mu)$ with $t \in \mathbb{T}$ and $1 \leq r \leq \infty$ we define $\mathcal{D}(L)$ as the set of all $f \in L^r(\mu)$ s.t. the strong limit

$$\mathcal{Q}f = \lim_{t \to 0} \frac{\mathcal{T}^t f - f}{t}$$

exists. Then the operator $\mathcal{Q} : \mathcal{D}(L) \to L^r(\mu)$ is called the *infinitesimal generator* corresponding to the semigroup $\mathcal{T}^t$.

The infinitesimal generator is an operator which describes the behaviour of a Markov process in infinitesimal time. That becomes clear by the relation $\mathcal{T}^t = \exp(t\mathcal{Q})$ in $L^2(\mu)$. We say that $\mathcal{Q}$ "generates" the semigroup of transfer operators $\{\mathcal{T}_t\}_{t \in \mathbb{R}}$ since the whole semi-group of transfer operators can be derived from it.

If the corresponding Markov process is reversible, then $\mathcal{Q}$ is self-adjoint in $L^2(\mu)$ and consequentially the spectrum is contained in $(-\infty, 0]$. Therefore the dominant eigenvalues $1 = \lambda_1, \ldots, \lambda_n$ of the propagator $\mathcal{T}^t$ are related to the dominant eigenvalues $0 = \Lambda_1, \ldots, \Lambda_n$ of the generator $\mathcal{Q}$ via

$$\lambda_k = \exp(t\Lambda_k)$$

for all $1 \leq k \leq n$ and the associated (dominant) eigenfunctions are identical. Thus the invariant measure $\mathbb{1}$ of $\mathcal{T}^t$ satisfies

$$\mathcal{Q}\mathbb{1} = 0.$$

1.3 Galerkin Projection

So far we considered Markov processes on very large, possibly continuous, state spaces. For many applications, simulations of a given process are needed in order to obtain informations about the corresponding system. But computations on **large** state spaces require an enormous amount of computation power and time. On larger state spaces, the computation effort increases exponentially fast, see "curse of dimension". Therefore we are interested in reducing the number of states in order to make computations more feasible. Such a reducing can for instance be done by "grouping similar states together". In this section, we develop a mathematical concept which enables us to create such a reduced model.

Galerkin Projection

The first step in order to create a finite process is to determine a convenient finite state space $D \subset L^2(\mu)$. For this purpose, we choose a partition of unity as a basis, which is a generalization of a set of characteristic functions. That more general idea gives us more flexibility for later applications. The relevance of the choice of a partition of unity for the projection will be clarified in section 2.3.

Definition 1.14. (Partition of Unity)
A family of measurable functions $\{\chi_1, \ldots, \chi_n\} : E \to [0, 1]$ in $L^2(\mu)$ is called a *partition of unity* if the following two conditions are fulfilled:

   i) The χ_i are non-negative and linear independent.

   ii) $\sum_{i=1}^n \chi_i(x) = 1$ for all $x \in E$.

Definition 1.15. (Galerkin Projection)
Let $\{\chi_1, \ldots, \chi_n\}$ be a partition of unity, $D = \text{span}\{\chi_1, \ldots, \chi_n\}$ the associated finite-dimensional ansatz space and $\hat{S} \in \mathbb{R}^{n \times n}$ with $\hat{S}_{kj} = \langle \chi_k, \chi_j \rangle_\mu$. The *Galerkin projection* onto D is defined by $G : L^2(\mu) \to D$ via

$$Gf = \sum_{k,j=1}^n \hat{S}^{-1}(k,j)\langle \chi_k, f \rangle_\mu \chi_j. \tag{1.7}$$

The matrix $\hat{S}$ is invertible since it is the Gramian matrix of linear independent functions. In the easy case that the $\{\chi_1, \ldots, \chi_n\}$ are the characteristic functions $\{\mathbb{1}_{A_1}, \ldots, \mathbb{1}_{A_n}\}$ belonging to a full partition $\{A_1, \ldots, A_n\}$, equation (1.7) becomes

$$Gf = \sum_{k=1}^n \frac{1}{\mu(A_k)}\langle \chi_k, f \rangle_\mu \chi_k,$$

since the χ_i are orthogonal which means that $\chi_k \chi_j = 1$ if $j = k$ and 0 otherwise. A Galerkin projection can be applied on the transfer operator of a Markov process as well.

Definition 1.16. (Projected Transfer Operator)
Let $\mathcal{P} := \mathcal{P}^t$ be the transfer operator of a Markov process on a state space E with unique invariant measure μ, $\{\chi_1, \ldots, \chi_n\}$ be a partition of unity and G the Galerkin projection onto the associated subspace D. Then an operator of the form

$$G\mathcal{P}G : L^2(\mu) \to D$$

is called *projected transfer operator* and we abbreviate it by $G(\mathcal{P})$.

Matrix Representation

Since we are interested in transitions inside of the projected space, we want to propagate n-dimensional vectors by the projected transfer operator. For this reason, we consider the projection of the restricted transfer operator $G\mathcal{P}_{|D} : D \to D$, which will be denoted by $G(\mathcal{P})$ as well.

We recall that every linear map between finite-dimensional vector spaces can be represented by a matrix which is determined by chosen bases. Thus, we can write the projected transfer operator as a $n \times n$-matrix in the following useful way.

Theorem 1.17. (Sarich [29])
Let $\mathcal{P}$ be the transfer operator of a Markov process, $\{\chi_1, \ldots, \chi_n\}$ a partition of unity and $G(\mathcal{P})$ the Galerkin projection of the transfer operator onto the associated subspace. Then $G(\mathcal{P})$ has a matrix representation

$$P_c = TS^{-1},$$

where

$$S_{kj} = \frac{\hat{S}(k,j)}{\langle \chi_k, \mathbb{1} \rangle_\mu} = \frac{\langle \chi_k, \chi_j \rangle_\mu}{\langle \chi_k, \mathbb{1} \rangle_\mu} \tag{1.8}$$

and

$$T_{kj} = \frac{\langle \chi_j, \mathcal{P}\chi_k \rangle_\mu}{\langle \chi_k, \mathbb{1} \rangle_\mu}.$$

Proof. Remember that P_c is a (left) matrix representation of $G(\mathcal{P})$ with respect to a basis $\{\psi_1, \ldots, \psi_n\}$ of D if for any function $f : D \to D$ with

$$f = \sum_{i=1}^{n} \alpha_i \psi_i \quad \text{and} \quad G(\mathcal{P})f = \sum_{i=1}^{n} \beta_i \psi_i \tag{1.9}$$

it holds that

$$(\alpha_1, \ldots, \alpha_n)P_c = (\beta_1, \ldots, \beta_n). \tag{1.10}$$

We assume that (1.9) is true and we aim to show (1.10). For that purpose, we choose a basis $\{\psi_1, \ldots, \psi_n\}$ of D with

$$\psi_k = \frac{\chi_k}{\langle \chi_k, \mathbb{1} \rangle_\mu}. \tag{1.11}$$

As $G(\mathcal{P})$ is a linear map, we have $G(\mathcal{P})f = \sum \alpha_i G(\mathcal{P})\psi_i$. We exploit this fact, as well as the definitions of the Galerkin projection and the basis to compute

$$
\begin{aligned}
G(\mathcal{P})f \ &= \sum_{k=1}^{n} \alpha_k G(\mathcal{P})\psi_k \\
&\overset{(1.7)}{=} \sum_{k,l,j=1}^{n} \alpha_k \hat{S}^{-1}(j,l)\langle \chi_j, \mathcal{P}\psi_k \rangle_\mu \chi_l \\
&\overset{(1.11)}{=} \sum_{k,l,j=1}^{n} \alpha_k \hat{S}^{-1}(j,l)\langle \chi_j, \mathcal{P}\psi_k \rangle_\mu \langle \chi_l, \mathbb{1} \rangle_\mu \psi_l \\
&\overset{(1.9)}{=} \sum_{l=1}^{n} \beta_l \psi_l.
\end{aligned}
$$

Comparing the coefficients of the last two equations, we can express β_l as

$$\beta_l = \sum_{k,j=1}^{n} \alpha_k \hat{S}^{-1}(j,l)\langle \chi_l, \mathbb{1}\rangle_\mu \langle \chi_j, \mathcal{P}\psi_k\rangle_\mu$$

$$= \sum_{k=1}^{n} \alpha_k \underbrace{\sum_{j=1}^{n} \hat{S}^{-1}(j,l)\langle \chi_l, \mathbb{1}\rangle_\mu \frac{\langle \chi_j, \mathcal{P}\chi_k\rangle_\mu}{\langle \chi_k, \mathbb{1}\rangle_\mu}}_{\overset{!}{=}(P_c)_{kl}}. \tag{1.12}$$

The underbraced term **should** be equal to $(P_c)_{kl}$ because we wish that (1.10) is fulfilled. Thus, we compute the (k,l)-th entry of $P_c = TS^{-1}$, employing the fact that $(S^{-1})_{jl} = (\hat{S}^{-1})_{jl}\langle \chi_l, \mathbb{1}\rangle$, as   notation!

$$(TS^{-1})_{kl} = \sum_{j=1}^{n} T_{kj}(S^{-1})_{jl}$$

$$= \sum_{j=1}^{n} \frac{\langle \chi_j, \mathcal{P}\chi_k\rangle}{\langle \chi_k, \mathbb{1}\rangle}(\hat{S}^{-1})_{jl}\langle \chi_l, \mathbb{1}\rangle$$

and discover that it is equal to the underbraced term in (1.12). Hence, (1.10) is true and therefore P_c is the requested matrix representation of $G(\mathcal{P})$. $\qquad\square$

Theorem 1.18. *The matrices S and T from theorem 1.17 are stochastic.*

Proof. In order to be stochastic, each row must sum up to 1. We exploit the partition of unity property $\sum_j \chi_j = 1$ for all j and the aforementioned properties $\mathcal{P}\mathbb{1} = \mathbb{1}$ and $\mathcal{P}^*\mathbb{1} = \mathbb{1}$ of a transfer operator respectively its adjoint:

$$\sum_{j=1}^{n} S_{kj} = \frac{\langle \chi_k, \sum_j \chi_j\rangle_\mu}{\langle \chi_k, \mathbb{1}\rangle_\mu} = \frac{\langle \chi_k, \mathbb{1}\rangle_\mu}{\langle \chi_k, \mathbb{1}\rangle_\mu} = 1,$$

$$\sum_{j=1}^{n} T_{kj} = \frac{\langle \sum_j \chi_j, \mathcal{P}\chi_k\rangle_\mu}{\langle \chi_k, \mathbb{1}\rangle_\mu} = \frac{\langle \mathbb{1}, \mathcal{P}\chi_k\rangle_\mu}{\langle \chi_k, \mathbb{1}\rangle_\mu} = \frac{\langle \mathcal{P}^*\mathbb{1}, \chi_k\rangle_\mu}{\langle \chi_k, \mathbb{1}\rangle_\mu} = 1.$$

Non-negativity follows from the non-negativity of the $\{\chi_1, \ldots, \chi_n\}$. $\qquad\square$

Since S and T are both stochastic matrices, they have the constant vector $\mathbb{1}_D$ as right eigenvector to the eigenvalue 1. It implies that the same holds for P_c, that is its rows sum up to 1 and thus the product TS^{-1} is **at least pseudostochastic**. But nonnegativity is not assured since inverting S can provoke negative entries. The non-negativity depends on the choice of the partition of unity. As we will see, there are examples such that TS^{-1} is a stochastic matrix.

Theorem 1.19. *The matrix representation P_c from theorem 1.17 has the left eigenvector $\hat{\mu} \in D$ with the entries*

$$\hat{\mu}_j = \langle \mathbb{1}, \chi_j\rangle_\mu = \int_E \chi_j(x)\mu(\mathrm{d}x).$$

Proof. We observe that $\hat{\mu}^T S = \hat{\mu}^T$ and $\hat{\mu}^T T = \hat{\mu}^T$ since

$$(\hat{\mu}^T S)_j = \sum_{k=1}^{n} \langle \mathbb{1}, \chi_k \rangle_\mu \frac{\langle \chi_k, \chi_j \rangle_\mu}{\langle \chi_k, \mathbb{1} \rangle_\mu} = \langle \mathbb{1}, \chi_j \rangle_\mu = \hat{\mu}_j$$

and

$$(\hat{\mu}^T T)_j = \sum_{k=1}^{n} \langle \chi_j, \mathcal{P} \chi_k \rangle_\mu = \langle \chi_j, \mathcal{P} \mathbb{1} \rangle_\mu = \langle \chi_j, \mathbb{1} \rangle_\mu = \hat{\mu}_j.$$

We can deduce that $\hat{\mu}^T P_c = \hat{\mu}^T T S^{-1} = \hat{\mu}^T S^{-1} = \hat{\mu}^T S S^{-1} = \hat{\mu}^T$. $\qquad\square$

Remark 1.20. We remark that in theorem 1.17 we stated the matrix representation of the projection of a **forward** transfer operator. For a backward operator, the proof works almost simultaneously and yields the matrix representation $P_c = S^{-1} T$, where $T = \frac{\langle \chi, \mathcal{P} \chi \rangle_\mu}{\langle \chi, \mathbb{1} \rangle_\mu}$. In that case, P_c is a right matrix representation and propagates sets instead of probability distributions.

Example: Full Partition Discretization

Let $A_1, \ldots, A_n$ be a partition of the state space E, i.e. they are pairwise disjoint sets such that $\cup A_i = E$. We consider the family of the corresponding characteristic functions

$$\chi_i(x) = \mathbb{1}_{A_i}(x).$$

Since they are orthogonal, the matrix S is the identity matrix and therefore, the matrix representation of the Galerkin projection is $P_c = T$. We can compute it by combining

$$\langle \mathcal{P} \mathbb{1}_{A_i}, \mathbb{1}_{A_j} \rangle_\mu = \int_{A_j} (\mathcal{P} \mathbb{1}_{A_i})(x) \mu(\mathrm{d}x) \overset{(1.5)}{=} \int_{A_i} p(t, x, A_j) \mu(\mathrm{d}x) \overset{(1.3)}{=} \mathbb{P}_\mu(X_t \in A_j, X_0 \in A_i)$$

and

$$\langle \mathbb{1}_{A_i}, \mathbb{1} \rangle_\mu = \int_E \mathbb{1}_{A_i}(x) \mu(\mathrm{d}x) = \mu(A_i) = \mathbb{P}_\mu(X_0 \in A_i).$$

The entries of the resulting matrix representation are given by

$$T_{ij} = \frac{\langle \mathcal{P} \mathbb{1}_{A_i}, \mathbb{1}_{A_j} \rangle_\mu}{\langle \mathbb{1}_{A_i}, \mathbb{1} \rangle_\mu} = \mathbb{P}_\mu(X_t \in A_j \mid X_0 \in A_i).$$

Thus, P_c represents a Markov chain whose state space consists of the partition sets A_i, e.g. each A_i is a "macro state" of the projected process. The stationary distribution of this Markov chain P_c is just the projection of the invariant measure μ onto D.

For a full partition discretization, the matrix S is a diagonal matrix. If we choose a partition of unity that is *close* to a full partition, i.e. we choose *almost characteristic functions*, then the matrix S is not diagonal, but close to that. We will later see the consequences of that fact regarding to the examination of the *rebinding effect*.

Properties of Galerkin Projection

As the matrix representation of a projected transfer operator is in general **not** a stochastic matrix, and stochastic matrices are in a one-to-one relation with Markov chains, we can immediately deduce that the process can lose its Markovianity by projecting it onto a subspace. This possible loss of Markovianity is certainly a really undesirable effect. But before examining that later in section 1.4, let us now first analyze further, hopefully **nice**, properties of the matrix representation P_c.

We already know that the matrices S and T from Theorem 1.17 are stochastic matrices. This leads to some good properties of P_c:

- The eigenvalue $\lambda = 1$ of P_c has the associated right-eigenvector $e = (1, \ldots, 1)^T$ and left-eigenvector $\hat{\mu}^T$ from theorem 1.19.

- If $\mathcal{P}$ is self-adjoint in $L^2(\mu)$, then $G(\mathcal{P})$ as well. Then the matrices S and T are self-adjoint with respect to the discrete scalar product $\qquad$ P_c self-adj.?
$\langle Av, w \rangle = \langle v, Aw \rangle$

$$\langle u, v \rangle_{\hat{\mu}} = \sum_{i=1}^{n} u_i v_i \hat{\mu}_i.$$

  Since self-adjointness of the operator is equivalent to reversibility of the corre- eigenv. of S, T real sponding process, see theorem 1.12, detailed balance equation (e.g. $\hat{\mu}_k T_{kl} = \hat{\mu}_l T_{lk}$ for all $k, l = 1, \ldots, n$) is fulfilled for both S and T.

- If the transfer operator has a simple and dominant eigenvalue 1 and the continuous part of the spectrum is bounded away from the discrete part, then the process is irreducible and aperiodic which is inherited by the matrix T. In particular T has the simple and dominant eigenvalue $\lambda = 1$ which is the only eigenvalue with $|\lambda| = 1$ and the discrete invariant density $\hat{\mu}$ is the unique invariant density of T.

- As seen in the last example, a full-partition projection yields the transition matrix $P_c = T$ of a Markov chain describing transitions between the partition sets.

Conclusion, Interpretation

The discretization maintains/inherits many important properties of the original process. Interpretation of S as a "stochastic mass matrix" and T as a "coupling matrix" (transition ? matrix).

Projected infinitesimal generator

The Galerkin projection of an infinitesimal generator yields a similar matrix representation as the transfer operator. It can also be written as the product of two stochastic matrices, one of them being the inverted mass matrix of the partition of unity functions.

Theorem 1.21. *Let $\mathcal{Q} : L^2(\mu) \to L^2(\mu)$ be a generator of a semigroup of transfer operators with unique invariant measure μ and satisfying $\mathcal{Q}\mathbb{1} = 0$. Let χ be a partition of unity with a projection G onto the associated subspace spanned by χ. Then the projected*

generator $G(\mathcal{Q})$ has the matrix representation $Q = RS^{-1}$ with the stochastic mass matrix S from (1.8) and

$$R(k,j) = \frac{\langle \mathcal{Q}\chi_k, \chi_j \rangle_\mu}{\langle \chi_k, \mathbb{1} \rangle_\mu}$$

The eigenvalue problem of Q is equivalent to the generalized eigenvalue problem $Ru = \Lambda Su$. For both Q and R the largest eigenvalue is $\lambda = 0$. The associated right eigenvector is $e = (1, \ldots, 1)^T$, the associated left eigenvector is $\hat{\mu}^T$ from theorem 1.19.

Proof. Similar to theorem 1.17. $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\square$

There are obviously many possibilities for the Galerkin projection of a given transfer operator. So far, we gave the example of a full-partition discretization, which results in a very easy matrix representation. But as arbitrary partitions of unity $\chi_1, \ldots, \chi_n$ are allowed for a Galerkin projection, there will be more interesting results. In chapter 2 we are going to see which choice of χ results in a good discretization of the process in the sense that it maintains certain desired properties; in our case the long-time behaviour of the process in terms of so called *metastability*.

1.4 Recrossing Effect

In this section, we are going to examine the so called *Recrossing Effect* which is one of the main topics of this thesis. This effect, occuring when projecting a process onto a smaller state space, may spoil the Markov Property of the process.

We are going to analyze it by means of an easy example. Additionally, we have to face the problem that a projected process/transfer operator does not necessarily behaves/propagates as the original process. We will explain the relevance of this *iteration error* without going into further details, since in the following chapters we will be able to apply a projection where this error/deviation vanishes.

Initial Situation

Assume we are given a Markov process $(X_t)_{t \in \mathbb{T}}$ on a continuous or very large state space E, described by the transfer operator $\mathcal{P} := \mathcal{P}(\tau)$. In order to get a discrete process out of it, we are going to project the time onto $\mathbb{N}$ and the state space onto a finite set $\{1, \ldots, n\}$. Discretizing the time can be done naturally without problems since for every lag-time $\tau > 0$, the process $(X_{k\tau})_{k \in \mathbb{N}}$ is again Markovian.

However, the state-space discretization has to be observed a bit more elaborated. Let's do this on the example of a full partition discretization. We consider the operator $G(\mathcal{P}^k) := G\mathcal{P}^k G$, that is we first propagate the process and project it afterwards. Then for all k-multiples of τ, we assign the current state of the original process X_t to the projected process $\widetilde{X}_k$:

$$\widetilde{X}_k = i \Leftrightarrow X_{k\tau} \in A_i.$$

The process $\widetilde{X}_k$ describes the *snapshot dynamics* of X_t with lag time τ between the partition sets $A_1, \ldots, A_n$. The so defined process is not necessarily Markovian, since $(G(\mathcal{P}^k))_k$ is in general **not** a semigroup.

Rebinding in a Double Well Potential

Let X_t be the Markov process corresponding to the double-well potential $V(x) = (x^2 - 1)^2$. We consider a full-partition of the state space into two sets A and B around the local minima of the energy landscape, as shown in figure 1.1. We are interested if the induced
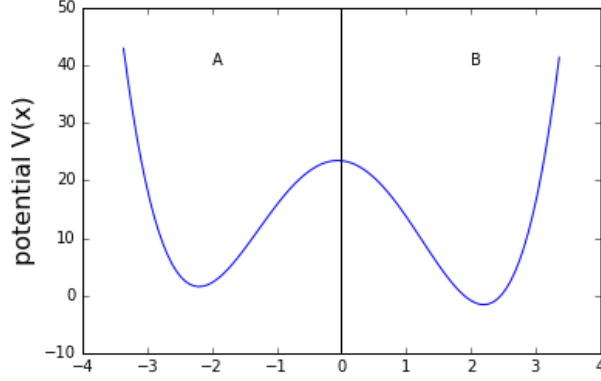

Figure 1.1: Full-partition of a double-well potential

process $\widetilde{X}_k$ inherits the Markovianity of X_t or if it contains any memory effects.

For a small lag-time $\tau = 0.1$ we compute the probability of $\widetilde{X}_k$ to make a transition from B to A in one time-step. We compare it to the probability of the same transition with the **additional** information of having been in B one time-step before/earlier. If the process was Markovian, then this additional information about the past should make no difference and thus, both probabilities should be equal. We compute them in terms of the original process X_t by

$$\mathbb{P}_\mu[X_{(k+1)\tau} \in A \mid X_{k\tau} \in B] \text{ and } \mathbb{P}_\mu[X_{(k+1)\tau} \in A \mid X_{k\tau} \in B, X_{(k-1)\tau} \in A].$$

Using the density functions v_B and v_{BA}, we get $\hfill v$ densities?

$$\mathbb{P}_\mu[X_{(k+1)\tau} \in A \mid X_{k\tau} \in B] = \int_A v_B^\tau(x)\, \mathrm{d}x = ..., \tag{1.13}$$

$$\mathbb{P}_\mu[X_{(k+1)\tau} \in A \mid X_{k\tau} \in B, X_{(k-1)\tau} \in A] = \int_A v_{BA}^\tau(x)\, \mathrm{d}x = ... \tag{1.14}$$

So we see that for such a short lag-time τ, the process $\widetilde{X}_k$ is **not** independent of the past and hence **not** a Markov process. Equation (1.13) describes the probability to get from B to A, where "being in B" could mean everything from "close to the transition region" to "far away from the transition region". So this probability is averaged over **all** possible starting points in B. We compare it to (1.14), where being in A shortly before $\hfill$? being in B increases the probability to return/recross to A again. This behaviour can be interpreted such that for a short time after a **transition**, the process is likely to be still inside ot the **transition region**. In our example, the transition region is the area/region

close to the maximum of potential energy. Thus, there is still an increased probability to return to the previous state.

This issue is called the *recrossing effect*, since additional memory leads to an increased probability to "recross" shortly after a transition. On the other hand, if we choose a large lag-time $\tau = 100$, then the past transition from A to B in (1.14) took place a long time ago. So we cannot certainly know if the process is still in the critical transition region; during that long lag-time it could also have been gone anywhere else. That means that the memory effect included in $\widetilde{X}_k$ becomes smaller for larger lag-times and thus can be considered as a *short-time memory*.

Comparison to Markov State Model

After having observed the *recrossing effect* as a memory effect when projecting the time-series(?) of a given continuous process onto a finite subspace, we want to compare that result to the corresponding *Markov State Model*.

So far, we considered the process $\widetilde{X}_k$ belonging to the operator $G(\mathcal{P}^k)$. Now, let $(\widehat{X}_k)_{k \in \mathbb{N}}$ be the Markov chain that is described by the transition matrix P_c, i.e. the matrix representation of the discretized transfer operator $G(\mathcal{P}) := G\mathcal{P}G$.

A desirable behaviour of this model would be that $\widehat{X}_k$ and $\widetilde{X}_k$ have the same trajectory when started on the same initial distributions $\widehat{X}_0$ and $\widetilde{X}_0$. It will turn out that this is normally not the case. This question is visualized in diagram 1.2. Does it make a difference if we first project the process and then propagate it and vice versa?

$$
\begin{array}{ccc}
 & \mathcal{P}(\tau) \xrightarrow{\ \tau \to \tau k\ } (\mathcal{P}(\tau))^k \\
 & \downarrow{\scriptstyle proj.} \qquad\qquad \downarrow{\scriptstyle proj.} \\
G(\mathcal{P}(\tau)) \widehat{=} & P_c(\tau) \xrightarrow{\ \tau \to \tau k\ } (P_c(\tau))^k
\end{array}
$$

Figure 1.2: Projecting/propagating a transfer operator (non-commutative)

In general, this diagram is **not** commuting and hence, in general we have

$$(P_c)^k \neq (P^k)_c.$$

For the example of a full-partition discretization, we know from section 1.3 that the resulting Markov State Model is a Markov chain. Thus, we have a Markov chain $\widehat{X}_k$ as a model for the non-Markovian process $\widetilde{X}_k$, so it is clear that there is a discretization/iteration error.

That is also where the term *Markov State Model* comes from. We are describing the non-Markovian process $\widetilde{X}_k$ by a Markov chain $\widehat{X}_k$. Originally, processes have been clustered *set-based*, i.e. based on a full partition and thus always resulting in a Markov chain. In chapter 2, we will see that the *function-based* approach yields better results and hence is the current state of the art. Then, the Markov State Model is not necessarily Markovian, as we already know from $P_c = TS^{-1}$ in theorem 1.17.

Discretization Error (Density Propagating Error/Iteration Error)

We will describe here shortly how the discretization error can be estimated. For our purposes that will not play an important role, since later we will be able to perform a projection (with convenient membership functions) s.t. this error vanishes.

The maximal possible error between the distributions of $\widetilde{X}_k$ and $\widehat{X}_k$ after k time-steps is (independently of initial distribution) given by

$$E(k) = \|G(\mathcal{P}^k) - (G(\mathcal{P}))^k\|.$$

Theorem 1.22. *Assume the discrete/dominant spectrum of a transfer operator $\mathcal{P}$ is given/denoted/ordered by $1 = \lambda_0 > \lambda_1 \geq \cdots \geq \lambda_n$. Then the projection error can be bounded from above in terms of the second-largest eigenvalue by*

$$\|(G(\mathcal{P}))^k - \Pi_0\| \leq \lambda_1^k,$$

where Π_0 is the orthogonal projection of ... .

For a proof, see Schütte and Sarich[34, p.72]. In the next chapter we will see further/deeper relations between the spectrum of the transfer operator and the long-time behaviour of the process. We will see how to choose partition for a MSM s.t. the approximation error becomes small/vanishes.

Conclusion

We have to distinguish between two kind of "errors" that can occur:

- Rebinding Events: Projection can include some kind of memory effect
- Iteration Error: Deviation of $G(\mathcal{P}^k)$ and $(G(\mathcal{P}))^k$

what about eig err.?

membership fct = p of unity for clusteri

which norm?

def MSM, P_c ?

2 Dominant Structures

With the Galerkin discretization, we introduced a method to reduce the dimension of a Markov process by projecting it onto a smaller state space. However we don't know yet how to choose a partition of unity such that this projection yields a reasonable Markov State Model, in the sense that important properties of the original process are maintained. Usually, the long-time behaviour of a process is of particular interest. It is often determined by a so called metastable behaviour. We will see why it makes sense to project a process onto its metastable sets and, in order to detect them, analyze their relation to the dominant spectrum of the transfer operator. We will also see that the optimal metastable decomposition is not sharp/crisp but soft/fuzzy.

Additionally, with the Schur decomposition we introduce a rather new approach to decompose the state space. It includes nonreversible processes and is able to cluster a broader class of processes.

2.1 Metastability

There exist several different definitions of metastability. Shortly said, metastability is the property of a process that its state space consists of subsets/regions such that transitions between these subsets are rare events while the duration of stay inside of each of them is rather long. Some possible characterizations of that behaviour are based on large hitting times or small exit rates, see Schütte and Sarich[34, chapter 3], where a good overview of the most common definitions can be found.

Mathematical concept of metastability

In order to describe the concept of metastability, it is a good way to start with so called *stable* or *invariant subsets*. A measurable subset $A \subset E$ of the state space of a Markov process X_t is called stable or invariant if it cannot be left, i.e. if $\mathbb{P}(X_t \in A \mid X_0 \in A) = 1$ for all t. Analoguously, we can define a *metastable* or *almost invariant subset* as a subset in which the process will stay for a very long time before exiting it into any other subset, that is $\mathbb{P}(X_{t_f} \in A \mid X_0 \in A) \approx 1$ for a convenient timescale t_f. Thus, a full partition $A_1, \ldots, A_m$ of the state space E is called *metastable* if

$$\sum_{k=1}^{m} \mathbb{P}_\mu(X_{t_f} \in A_k \mid X_0 \in A_k) \approx m. \tag{2.1}$$

Then each of the sets A_k is almost invariant with respect to timescale t_f; the probability to stay in one of the partition sets being started there is almost 1, while the probability to change between any two different partition sets is almost 0. Such a partition is also called a *metastable decomposition*.

Obviously, being "close to 1" or "close to m" are rather vague statements. But that lack of concreteness will be eliminated later, since we will only be interested in the "best" metastable decomposition. That means that we want to obtain a decomposition where the sum (2.1) is as close as possible to m, or equivalently the probability to stay inside of a metastable set is as close as possible to 1. Also the choice of the timescale t_f is not specified in general and will depend on the particular system in consideration. Hence, the only parameter in (2.1) that has to be determined is the number m of subsets we are looking for.

Metastability in molecular systems

Metastability is a very important concept for stochastic processes corresponding to molecular systems. Such processes describe the movement of atoms or molecules in space and have the characteristic behaviour to oscillate or fluctuate around equilibrium positions on the smallest time scales (about one femtosecond). In contrast to these fast oscillations, the process often stays inside of a certain region, called *conformation*, for a long time before switching to another region (nano- or millisecond time scale). Since transitions between conformations are relatively rare events, they can be identified as metastable sets if we choose a convenient timescale. Such a behaviour is depicted in figure 2.1 on the example of the dihedral angle of a molecule, taken from Weber[42].
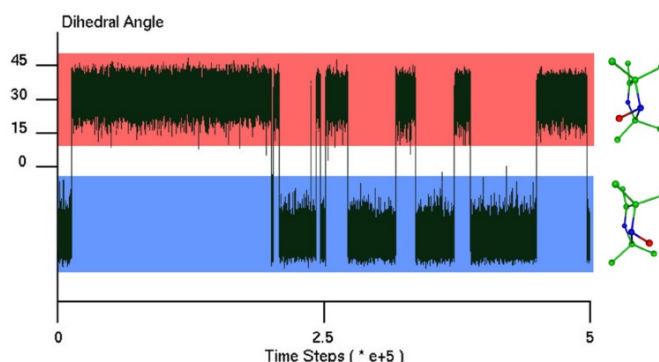

Figure 2.1: Example of a molecule with two (metastable) conformations. The dihedral angle of the molecule can take values between $+45°$ and $-45°$. There are two regions, highlighted red and blue, where the process stays for a rather long time and oscillates **inside**. Transition between these regions don't occur often. Thus, these two conformations can be identified as metastable sets.

As transitions between metastable sets are rare events, long-time simulations of a process are required in order to get informations about conformational changes. However long-time simulations of such large systems are not feasible in reasonable time even with the best computers nowaday, see Anton[35] or its successor Anton2[36].

Hence, in order to be able to compute some long-time simulations of a given molecular system, a reduction of complexity is needed. This can be achieved by a clustering of the state space via a Galerkin projection as depicted in section 1.3. Different states will be

24

wnian motion?

clustered appropriately such that we get a process on a smaller state space.

This point of view also motivates the following terminology. A state in the original state space is called a *micro state*, as it is a state considered on the microscopic or atomistic level. In order to get a smaller state space, micro states are grouped together and such a cluster is called a *macro state*, since we are now considering the process on a macroscopic level (cannot distinguish between smaller states/atoms anymore).

For instance, the spatial coordinates of a single atom could be considered as a micro state, while the corresponding macro state is a cluster of several atoms. If we are working on this smaller state space, we cannot distinguish anymore between the single atoms of the cluster (forget information).

Clustering into metastable sets

The question **how** to cluster a given process such that it maintains the long-time behaviour of the original process can be answered easily with the following intuitive approach: As the long-time behaviour of a process is described by the metastability of the system, we choose the metastable sets as clustering sets. More clearly, we create a new process where each macro state corresponds to one of the metastable sets. In order to represent the correct long-time behaviour of the process, the transition probabilities of the clustered process/reduces model should correspond to the transition rates between the metastable sets of the original process.

As metastability is determined on long timescales, the reduced/projected process should maintain the long-time behaviour of the original process, but forget about its short-time transitions, i.e. transitions inside of a conformation/metastable set.

Since there is not one unique metastable decomposition of the state space, we need to find a decomposition which is in some sense "the best"; then we can use it to create a reduced model. In the next sections we will see how to find such a decomposition.

Most importantly, the clustered process will have the desired property of a reduced dimension/complexity since the model acts on a smaller state space while maintaining the crucial property of the original process (transitions between metastable sets = long-time behaviour). So the computation effort for (long-time) simulations is definitely decreased. Furthermore, we get a better overview of the system, since it is always easier to consider a process on a few states in comparison to a process on a very large or even continuous state space. But there is also a disadvantage, as already mentioned in section 1.4, by projecting a process it can lose its Markov property.   ?

2.2 Spectral Approach

In this section we will see that the spectrum of the transfer operator is highly connected to the metastability of the corresponding Markov process. More precisely, the existence of metastable sets implies the existence of dominant eigenvalues of the associated transfer operator and vice versa. The idea to detect metastable sets via dominant eigenvalues has been first proposed by Dellnitz and Junge[9] and transferred to molecular dynamics by Schütte et al[31, 32].

Existence of dominant eigenvalues

We consider the transfer operator $\mathcal{P} := \mathcal{P}^t$ of a Markov process for some fixed t in the Hilbert space $L^2(\mu)$. We are interested in *dominant eigenvalues* of $\mathcal{P}$, that is large eigenvalues which are close to 1 and separated from the rest of the spectrum. The *discrete spectrum* $\sigma_{\mathrm{discr}}(\mathcal{P})$ is the set consisting of all eigenvalues $\lambda \in \sigma(\mathcal{P})$ that are isolated and of finite multiplicity. The *essential spectral radius* $r_{\mathrm{ess}}(\mathcal{P})$ is defined as

$$r_{\mathrm{ess}}(\mathcal{P}) = \inf\{r \geq 0 \mid \lambda \in \sigma(\mathcal{P}) \text{ with } |\lambda| > r \text{ implies } \lambda \in \sigma_{\mathrm{discr}}(\mathcal{P})\}.$$

The existence of dominant eigenvalues requires that the continuous part of the spectrum is bounded away from the dominant elements of the discrete spectrum. To ensure that the process we are considering actually possesses metastable sets, we need to pose some conditions on the spectrum of the transfer operator:

C1 The essential spectral radius of $\mathcal{P}$ is less than one, i.e. $r_{\mathrm{ess}} < 1$.

C2 The eigenvalue $\lambda = 1$ of $\mathcal{P}$ is simple and dominant, i.e.

$$\eta \in \sigma(\mathcal{P}) \text{ with } |\eta| = 1 \text{ implies } \eta = 1.$$

We will not go into further details for which processes the two above conditions are fulfilled; some criteria can be found in Huisinga[16, chapter 4]. Since these conditions are required for the later investigations, we will just assume that they are true. We need condition **C1** to ensure that the continuous part of the spectrum is bounded away from the discrete eigenvalues. Otherwise they would not be dominant anymore and the process would be rather rapidly mixing than having any metastable sets. Condition **C2** however is important because the state space of a transfer operator with more than one eigenvalue of absolute value 1 can be decomposed into invariant sets, that is subsets which cannot be left. But that case is not interesting for us. Instead, we want to know more about **almost** invariant sets and their critical transition regions.

The transfer operator $\mathcal{P} : L^2(\mu) \to L^2(\mu)$ of a reversible process satisfying the properties **C1** and **C2** is self-adjoint and has the following spectrum:

$$\sigma(\mathcal{P}) \subset [a, b] \cup \{\lambda_n\} \cup \cdots \cup \{\lambda_2\} \cup \{1\}$$

with $-1 < a \leq b < \lambda_n \leq \cdots \leq \lambda_1 = 1$ and isolated, not necessarily simple eigenvalues of finite multiplicity that are counted according to multiplicity.

Relation of dominant spectrum and metastability

In order to find out about the quality of an arbitrary decomposition, we present some upper and lower bounds for the metastability of the decomposition in terms of dominant eigenvalues and eigenvectors of the transfer operator. We will denote by *metastability of a decomposition $\mathcal{D}$* the sum of the metastability of its subsets.

Theorem 2.1.   (Huisinga and Schmidt[17, Theorem 2.4])
Let $\mathcal{P}$ be the transfer operator of a reversible process satisfying **C1** *and* **C2**. *Let $\lambda_1, \ldots, \lambda_n$ denote its isolated eigenvalues and $v_1, \ldots, v_n$ the corresponding eigenfunctions, normalized to $\|v_i\|_2 = 1$. Let Q be the orthogonal projection of $L^2(\mu)$ onto $\operatorname{span}\{\mathbb{1}_{A_1}, \ldots, \mathbb{1}_{A_n}\}$. The metastability of an arbitrary decomposition $\mathcal{D} = \{A_1, \ldots, A_n\}$ of the state space E can be bounded from above by*

$$p(A_1, A_1), + \cdots + p(A_n, A_n) \leq 1 + \lambda_2 + \cdots + \lambda_n,$$

while it is bounded from below by

$$1 + \rho_2 \lambda_2 + \cdots + \rho_n \lambda_n + c \leq p(A_1, A_1), + \cdots + p(A_n, A_n),$$

where $\rho_j = \|Qv_j\|_{L^2(\mu)}^2 = \langle Qv_j, Qv_j \rangle \in [0,1]$ and $c = a(1 - \rho_1) \ldots (1 - \rho_n)$.

Theorem 2.1 reveals the strong relation between metastable sets and the dominant eigenvalues of the transfer operator. It allows us to evaluate the quality of a decomposition by comparing the lower and the upper bound of metastability. The upper bound shows that eigenvalues far away from 1 worsen the metastability of a decomposition. The lower bound is close to the upper bound if the dominant eigenfunctions $v_2, \ldots, v_n$ are almost constant on the metastable subsets $A_1, \ldots, A_n$, implying $\rho_j \approx 1$ and $c \approx 0$. Moreover, Huisinga and Schmidt[17] show that the lower and upper bounds from theorem 2.1 are sharp and asymptotically exact.

That provokes the question if there exists an *optimal* decomposition with the highest possible metastability. By all means, this theorem indicates that the number of metastable sets should be determined by the number of dominant eigenvalues.

maybe ill-conditione

Theorem 2.2.   (Schütte[34])
*Each single eigenfunction induces a metastable decomposition*

Proof. □

The zeros of an eigenfunction (respectively change of sign) induce a metastable decomposition of the state space. Different eigenfunctions result in different decompositions.

eigenfcts vs commi
functions

In figure 2.2, we get a good overview of the relation between the eigenfunctions of the transfer operator and the metastable sets of the corresponding process. We have a potential/energy landscape with 4 energy minima, that is 4 regions where the process could be *trapped* such that it is hard to get outside again. The transition matrix shows this metastable behaviour since we can see 4 regions which large probabilities to stay inside and very small probabilities to go to a different region. Furthermore we see that the process has 4 dominant eigenvalues. Three of them have a change of sign, which induces the metastable decomposition.
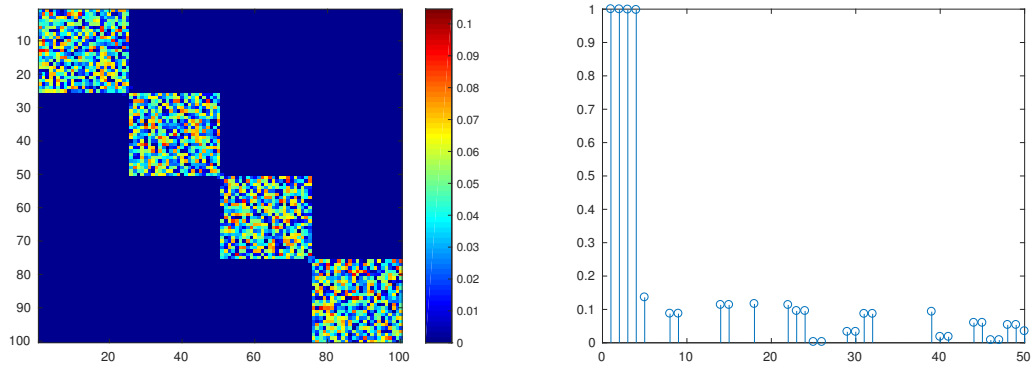
(a) Transition matrix P on 100 states with 4 visible metastable sets

(b) Eigenvalues of P with 4 dominant eigenvalues
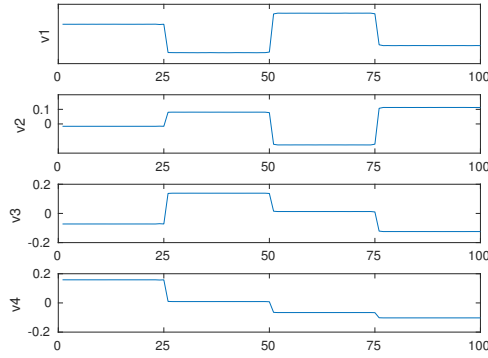
(c) Dominant eigenvectors of P with change of signs corresponding to the transition regions

Figure 2.2: Relation of the transition matrix to its spectrum with regard to metastability

Disadvantages

So the spectral approach is convenient to cluster a process with respect to metastability. However this approach has some disadvantages. The result is only appliable on reversible processes, because real eigenvalues are only guaranteed if the transfer operator is self-adjoint. Moreover, the eigenvector problem of the transfer operator has only global solutions.

Most of all, the previous procedure in computing a metastable decomposition doesn't take into consideration the existence of transition regions, so we need to refine it.

The previous theorems and this entire section have been presented merely with the aim to **point out** the strong relation of the spectrum of the transfer operator to the metastability of the system. However, this approach results in a full partition decomposition. In the next section, we will deduce a related, but improved, method. It also includes the eigenvalues and eigenfunctions of the transfer operator, but will be soft instead of crisp.

2.3 Fuzzy Clustering

The above considerations result in a metastable full decomposition of the state space, where each state is assigned to exactly one of the partition sets. We will see now that there exist better solutions, considering the fact that transition regions can have several adjacent conformations and therefore cannot be uniquely assigned to one of them. We introduce a more general method, allowing some "overlap" of the conformations.

Set-based vs. Function-based Approach

An intuitive approach to decompose the state space of a process is to determine a certain number of metastable sets which form a full partition, such that each state belongs to exactly one of the metastable sets. The problem with that approach is that likewise each state in a transition region has to be assigned to one of these partition sets. Though why would you assign a state in a transition region to one particular adjacent metastable set and not to another one? Such a strict assignment is obviously not an accurate description of the actual behaviour of the process.

Therefore this *set-based* clustering method has been replaced by a *function-based* method. That means that the states of the process are assigned with certain "degrees" to the conformations. This approach is justified by the existence of transition regions. A state inside of a transition region (around local energy maximum) can enter into different adjacent conformations with similar probabilities. Therefore, instead of assigning it to a single conformation, we define that it should belong to these adjacent conformations with a certain degree. In that sense, the conformations may be "overlapping".

Membership functions

Assume we are given a transfer operator having n dominant eigenvalues. Hence we want to create a Markov State Model on n states, corresponding to the metastable sets of the process. We follow the approach of Weber[41] to define macro states as *overlapping partial densities*. They can be identified by membership functions that assign degrees of membership to the micro states.

Definition 2.3.   (Membership Function)
The functions $\chi_1, \ldots, \chi_n : E \to [0, 1]$ are called *membership functions* if they fulfill

- $\chi_j(x) \geq 0 \ \forall i \in E$ and $\forall j \in \{1, \ldots, n\}$ (positivity),

- $\sum_{j=1}^{n} \chi_j(x) = 1 \ \forall x \in E$ (partition of unity).

The value $\chi_j(x)$ is the *degree of membership* of state x to macro state χ_j.

The example of a full-partition discretization corresponds to the choice of characteristic functions $\{\mathbb{1}_{A_1}, \ldots, \mathbb{1}_{A_n}\}$ as membership functions. Each micro state is uniquely assigned to one of the partition sets, without any overlap. Therefore such a clustering is called *crisp* or *hard*, whereas the general, possibly overlapping, membership functions result in a *fuzzy* or *soft* clustering. As there are many possible membership functions, we need to find a choice that yields a reasonable metastable decomposition.

Usually they are chosen to be **close** to a characteristic function, also called *almost characteristic function*, as depicted in 2.3. This choice makes sense, since it puts the emphasis of a conformation on a certain region by assigning a high degree of membership, but also includes the adjacent transition regions by a low degree of membership. Thus they fulfill the following two desired conditions:

- There should be a **soft** assignment inside of a transition region, in order to respect the ambiguous membership of transition states.

- The clustering should be **crisp** enough to distinguish the conformations.
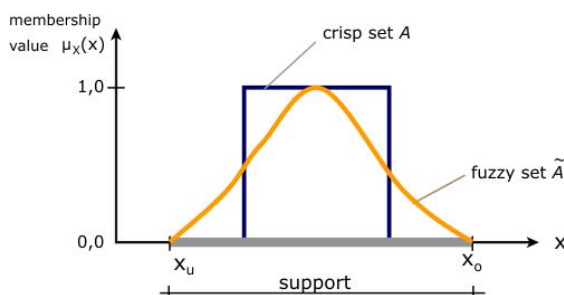

Figure 2.3: Blue: crisp set represented by a characteristic function. Orange: fuzzy set represented by an "almost characteristic function"

These requirements are clarified in figure 2.4 at the recurring example of a double-well potential, i.e. a system consisting of two conformations with one transition region between them. A crisp clustering does not consider the transition region, while a "very fuzzy" choice of membership functions does not represent the conformations.

The degrees of membership are no actual probabilities, yet they can be interpreted as such. Consider for instance the energy maximum of a symmetric double well potential. This transition state tends with the same probability to the left and to the right well. Therefore it seems plausible to assign it with the same degree of membership to both
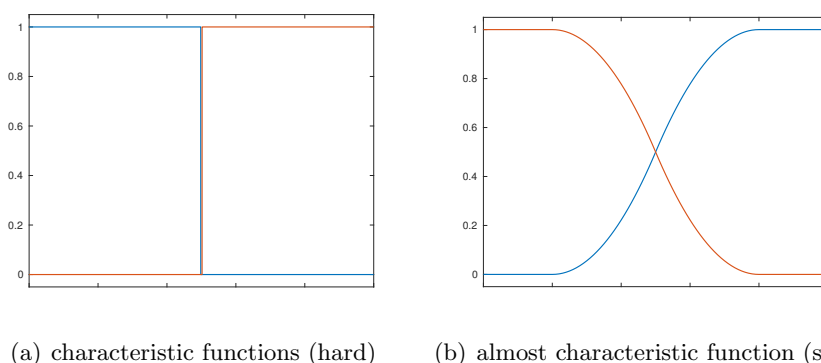

(a) characteristic functions (hard)   (b) almost characteristic function (soft)

Figure 2.4: Possible membership functions: From hard to fuzzy clustering.

30

conformations. On the other hand, a state in the middle of a well cannot immediately jump into the other well, therefore this transition probability is 0 and the state can be assigned with degree of membership 1 to the conformation corresponding to its well.

For each conformation $j \in \{1, \ldots, n\}$, there is a membership function χ_j which determines the portion of the partial density with respect to the total density function. They form a partition of unity, in order to sum up to the total density. Sometimes the χ_j will also be called conformation.

?

In order to represent the conformations as almost invariant sets, almost characteristic functions should be almost eigenfunctions of the transfer operator:

$$\mathcal{P}\chi_j \approx \chi_j \ \forall j = 1, \ldots, n.$$

Galerkin

Since they are a partition of unity, we can apply the Galerkin projection as defined in section 1.3. If we choose the membership functions as almost characteristic functions representing the (fuzzy) conformations, then the resulting Markov State Model consists of the metastable sets of the original process. We remember the matrix representation $P_c = S^{-1}T$. Then the trace of the coupling matrix T is referred to as *metastability* of the conformations $\{\chi_1, \ldots, \chi_n\}$.

Statistical Weights

For each macro state we can assign a statistical weight

$$w_j = \langle \chi_j, \mathbb{1} \rangle_\mu = \int_E \chi_j(x)\mu(\mathrm{d}x),$$

which describes the *portion* of a membership function to the total density function. We remark that the statistical weight vector $w = (w_1, \ldots, w_n)$ coincides with the left eigenvector of the matrix representation P_c of the clustered process, see theorem 1.19. The diagonal matrix $D = \mathrm{diag}(w_1, \ldots, w_n)$ consists of the statistical weights of the membership functions. Then $S = D^{-1}\langle \chi, \chi \rangle_\mu$ and $T = D^{-1}\langle \chi, \mathcal{P}(\tau)\chi \rangle_\mu$, compare theorem 1.17.

?

TS^{-1} vs $S^{-1}T$

The *crispness* of a clustering can be measured by the matrix S. Nonoverlapping membership functions yield an overlap matrix S equal to the unit matrix. Overlapping membership functions result in a matrix with non-zero outer diagonal elements. The higher the outer diagonal elements, the higher the overlap. Therefore the diagonal of S can be seen as a "measure of crispness" of the conformations $\chi_1, \ldots, \chi_n$.

Perron Cluster Analysis

finite/cont. vec./fct

The term *Perron Cluster Analysis* denotes the objective of clustering a Markov process into metastable sets using the *Perron eigenvalues* respective *Perron eigenfunctions*, which means eigenvalues close to 1 and the corresponding eigenfunctions. Perron Cluster

Analysis respectively its algorithmic implementation PCCA (*Perron Cluster Cluster Analysis*) has been developed by Deuflhard et al[10] which used the sign structure of the dominant eigenvalues of the transition matrix. That approach has been improved by Deuflhard and Weber[11] who transformed the system of eigenvectors into a system of membership functions which results in a fuzzy clustering of the state space of the original process; their algorithm is called PCCA+ (*Robust Perron Cluster Analysis*). Originally, PCCA+ was formulated only for discrete Markov chains, but Weber[42] extended it even on continuous processes.

Let $\mathcal{P}$ on $L^2(\mu)$ be the transfer operator of a **reversible** process, that is $\mathcal{P}$ is μ-self-adjoint, see theorem 1.12. We consider the set of dominant eigenvalues $\{\lambda_1, \ldots, \lambda_n\}$ with the corresponding set of eigenfunctions $\mathcal{X} = \{\mathcal{X}_1, \ldots, \mathcal{X}_n\}$. They fulfill the eigenvalue problem $\mathcal{P}(\tau)\mathcal{X} = \mathcal{X}\Lambda$ of the transfer operator $\mathcal{P}(\tau)$, where $\Lambda = \mathrm{diag}(\lambda_1, \ldots, \lambda_n)$. The set of membership functions $\chi = \{\chi_1, \ldots, \chi_n\}$ can be built as a linear combination $\mathcal{X}\mathcal{A}$ of the dominant eigenfunctions, that is

$$\chi_j(x) = \sum_{i=1}^{n} \mathcal{A}_{ij}\mathcal{X}_i(x), \ j = 1, \ldots, n. \tag{2.2}$$

Here, $\mathcal{A} = \{\mathcal{A}_{ij}\}_{i,j=1,\ldots,n} \in \mathbb{R}^{n \times n}$ is a real matrix which has to be chosen in such a way that the resulting membership functions χ fulfill the positivity and partition of unity constraints. As there are infinitely many such transformations $\mathcal{A}$ of the eigenfunctions, we have to determine one that satisfies some optimality condition. The algorithm PCCA+ computes the transformation matrix $\mathcal{A}$ as the solution of a convex maximization problem, see Weber[41].

Having computed the membership functions, we can compute the Galerkin projection by (see chapter 1)

$$P_c(\tau) = G(\mathcal{P}(\tau)) = (\langle \chi, \chi \rangle_\mu)^{-1}(\langle \chi, \mathcal{P}(\tau)\chi \rangle_\mu). \tag{2.3}$$

Weber[42] shows in that for any linear combination of the eigenfunctions $\chi = \mathcal{X}\mathcal{A}$, the discretization error of the Galerkin projection vanishes. Hence diagram 1.2 commutes, implying that propagating and projecting of a transfer operator are commutative actions. In particular, such membership functions preserve the Markov property.

Theorem 2.4.   (Weber [42, Theorem 2])
Let $\mathcal{P}(\tau)$ be a μ-self-adjoint transfer operator with a set $\mathcal{X} = \{\mathcal{X}_1, \ldots, \mathcal{X}_n\}$ of normalized eigenfunctions s.t. $\mathcal{P}(\tau)\mathcal{X} = \mathcal{X}\Lambda$, where $\Lambda = \mathrm{diag}(\lambda_1, \ldots, \lambda_n)$ is the eigenvalue matrix. Let $\chi = \mathcal{X}A$ be a set of functions that is a linear combination of the eigenfunctions $\mathcal{X}$ with a regular $n \times n$-transformation matrix A from (2.2). Then the iteration error for the Galerkin discretization $P_c(\tau) = G(\mathcal{P}(\tau))$ in (2.3) vanishes.

Proof. We compute the Galerkin projection on the propagated transfer operator $(\mathcal{P}(\tau))^k$:

$$
\begin{aligned}
G((\mathcal{P}(\tau))^k) &\overset{(3.7)}{=} (\langle \chi, \chi \rangle_\mu)^{-1}(\langle \chi, (\mathcal{P}(\tau))^k \chi \rangle_\mu) \\
&\overset{(3.6)}{=} (A^T \langle \mathcal{X}, \mathcal{X} \rangle_\mu A)^{-1}(A^T \langle \mathcal{X}, (\mathcal{P}(\tau))^k \mathcal{X} \rangle_\mu A) \\
&= (A^T A)^{-1}(A^T \langle \mathcal{X}, \mathcal{X} \rangle_\mu \Lambda^k A) \\
&= A^{-1} \Lambda^k A.
\end{aligned}
$$

The last two lines are obtained by simply inserting the eigenvalue problem $\mathcal{P}\mathcal{X} = \mathcal{X}\Lambda$ semigroup prop.?
and employing the fact that the eigenfunctions are orthogonal, by theorem 1.11 and
therefore $\langle \mathcal{X}, \mathcal{X} \rangle_\mu = \mathcal{I}$, being the identity operator. ... $\square$

In this proof, it is essential that the process is reversible. If the process is non-
reversible, and thereby the transfer operator is not self-adjoint, then the orthogonality of
the dominant eigenfunctions is not given anymore. Thus, in order to tackle non-reversible
processes as well, it is necessary to introduce a different concept (section 2.4).   why real eigenvect
If we project a finite process, then the above formulation results in a *membership vector*   needed?
matrix χ, which is the result of a linear combination of the *eigenvector matrix*.

Crispness of membership functions

Originally, the objective was to maximize metastability by maximizing $\text{trace}(T)$.
The *crispness* of a clustering can be measured by the matrix S.
The metastability of a process is defined via the trace of T, but can also be measured
via its determinant. If the metastability is high, then $\det(T)$ is close to 1. More clearly, see ...
by multiplication of the determinant we have

$$
\begin{aligned}
\det(T) &= \det(S)\det(A^{-1}\Lambda A) \\
&= \det(S)\det(\Lambda) \\
&= \det(S)\Pi_{i=1}^n \lambda_i.
\end{aligned}
$$

Thus, in order to increase the metastability of a system, both determinants need to be
high. The term $\det(\Lambda)$ is high if the dominant eigenvalues are as close as possible to 1,
whereas $\det(S)$ is maximized if the linear combination $\chi = \mathcal{X}A$ is as *crisp* as possible.
Thus the choice of $\max(\text{trace}(S))$ as objective function for PCCA+ is plausible, since
it provides a clustering with high metastability and furthermore the metastable sets are
well distinguishable because of the crispness.

Different objective functions are possible. The intuitive optimization criterion would
be to maximize the metastability of the membership vectors such that the resulting
clustering is "optimal" wrt metastability. However, a different optimization criterion is
to make the membership vectors as "crisp" as possible by maximizing the trace of the
matrix S. That means that they should be as orthogonal as possible. This was proposed
by Röblitz[27]. Thus the objective function used in PCCA+ is given by

$$
\max_{A \in \mathbb{R}^{n \times n}} \text{trace}(S(XA)) \text{ such that } \chi = XA \geq 0 \text{ and } \sum_j \chi_{ij} = 1. \qquad (2.4)
$$

2.4 Schur Decomposition

All previous decompositions of state spaces into metastable sets were based on the assumption of a reversible process. Unfortunately, many real-world processes are **not** reversible. In that case the corresponding transfer operator is not self-adjoint, see theorem 1.12, and therefore we have to deal with possibly complex eigenvalues and eigenfunctions/eigenvectors, which is not compatible with PCCA+. This problem can be circumvented by considering the real Schur decomposition of the transition matrix instead of its spectral decomposition. This yields an invariant subspace of real Schur vectors on which we can apply PCCA+. This approach is feasible, since the real Schur vectors span the same subspace as the corresponding complex Schur vectors and those span the same subspace as the corresponding eigenvectors.

NESS processes

In this section, we present a method which is only possible for finite processes. Therefore we consider in the following an irreducible and aperiodic (i.e. ergodic) Markov chain on the finite state space $E = \{1, \ldots, N\}$ given by the transition matrix P. Since this Markov chain is irreducible and aperiodic, it possesses a unique invariant measure π that is positive everywhere. Then π is the normalized eigenvector of P for the unique eigenvalue $\lambda = 1$.

Definition 2.5. (NESS process)
A Markov process is called *nonequilibrium steady state (NESS)* process if it is nonreversible, but still has a steady state, given by an invariant measure π w.r.t. which the process is ergodic.

$$p_\tau(A, B) = p(\tau, A, B) = \mathbb{P}(X_\tau = B \mid X_0 = A)$$

As a NESS process is nonreversible, there are regions where the detailed balance equation is not fulfilled, i.e. there is an effective probability flow $p(\tau, A, B) - p(\tau, B, A) \neq 0$ between some subsets $A, B \subset S$ of the state space.

Definition 2.6. (Flow Matrix)
The probability flow associated to a Markov process is given by the flow matrix

$$F = DP,$$

where P is the transition matrix of the process and D the diagonal matrix $D = \mathrm{diag}(\pi_1, \ldots, \pi_N)$ with the entries of the invariant measure π.

So the (steady state) probability flow from state i to j is given by $F_{ij} = \mu_i P_{ij}$. If the process is reversible, the flow matrix F is symmetric due to the detailed balance equation. For a NESS process, F is not symmetric since there are states $i, j \in S$ with $F_{ij} \neq F_{ji}$.

Dominant structures will be defined utilizing the dominant Schur vectors of the transition matrix instead of its eigenvectors. A membership matrix can be defined as a linear combination of these leading Schur vectors (spectral clustering with PCCA+).

34

Schur Decomposition

We have the same aim as in the previous sections: we are given a Markov process acting on a large state space E and want to project it onto a smaller state space $\{1, \ldots, n\}$, where each cluster represents one metastable set of the process. For this purpose, we introduce a matrix decomposition generalizing the spectral approach.

Definition 2.7. (Schur Decomposition)
Let $P \in \mathbb{R}^{N \times N}$ be a transition matrix. Then it can be written as

$$X^{-1}PX = \Lambda, \tag{2.5}$$

where X is a unitary matrix and Λ is an upper triangular matrix, having $\lambda_1, \ldots, \lambda_N$ as diagonal entries, which is called a *Schur decomposition* of P. If $X = [v_1 \mid \cdots \mid v_N]$ is a column partitioning of X, then the v_i are referred to as *Schur vectors*.

The existence of such a matrix X is shown in Golub and van Loan[15, Theorem 7.1.3]. Since Λ is similar to P, both matrices have the same eigenvalues. Since Λ is triangular, they correspond to the diagonal entries $\lambda_1, \ldots, \lambda_N$ of Λ. The Schur vectors v_k satisfy

$$Pv_k = \lambda_k v_k + \sum_{i=1}^{k-1} n_{ik} v_i, \quad k = 1, \ldots, N,$$

and therefore span an invariant subspace given by

$$S_k = \operatorname{span}\{v_1, \ldots, v_k\}.$$

Moreover, if we choose a matrix $X_k = [v_1 \mid \cdots \mid v_k]$, then $\sigma(X_k^{-1} P X_k) = \{\lambda_1, \ldots, \lambda_k\}$. The eigenvalues λ_i in (2.5) can be arbitrarily ordered by an appropriate choice of X. Thus each subset of k eigenvalues induces at least one k-dimensional invariant subspace.

For our purpose, decomposition (2.5) is not sufficient, since it can include complex Schur vectors. As P is a real matrix, its non-real eigenvalues come in complex conjugate pairs. This fact can be used to build a *real Schur decomposition*, where X and Λ are both real matrices. Though this alternative decomposition doesn't result in a triangular matrix, but in a *quasi-triangular* one, allowing 2×2-blocks on its diagonal.

Theorem 2.8. (Real Schur Decomposition)
If $P \in \mathbb{R}^{N \times N}$, then there exists an orthogonal matrix $X_s \in \mathbb{R}^{N \times N}$ such that

$$X_s^{-1} P X_s = \Lambda_s,$$

where Λ_s is block-triangular with 1×1 and 2×2-blocks on its diagonal. The 1×1-blocks contain the real eigenvalues of P and the eigenvalues of the 2×2-blocks are the complex eigenvalues of P.

A proof can be found in Golub and van Loan[15, Theorem 7.4.1]. Each real matrix can be decomposed into such an upper quasi-triangular matrix. Thus the real Schur decomposition can be called an "eigenvalue-revealing" decomposition; the real and the imaginary part of the complex eigenvalues are easily obtained from the 2×2-blocks.

Meaning of the block-diagonal structure

We want to make use of the real Schur decomposition to analyze transition matrices. Depending on the shape of the quasi-triangular matrix Λ_s, we can not only find out informations about the eigenvalues of P, but also on the reversibility of the corresponding process. A case study is presented in Weber[43] and shortly summarized in the following.

By definition, the reversibility of a process is determined by the flow matrix $F = DP$. According to detailed balance, a process is reversible if and only if this matrix is symmetric. We show that nonreversibility of P can also be identified by its Schur decomposition Λ_s.

A Schur decomposition is block-diagonal with eigenvalues and 2×2-blocks on its diagonal. The meaning of an eigenvalue is clear, so we are just going to analyze the shape of such an 2×2-block and its influence on reversibility and eigenvalues of P. Assume we are given the Schur decomposition

$$
\Lambda_s = \left(\begin{array}{c|cc} 1 & 0 & 0 \\ 0 & \lambda_2 & \epsilon \\ 0 & -\delta & \lambda_3 \end{array} \right) \tag{2.6}
$$

with $\epsilon, \delta \geq 0$. We examine the properties of this matrix (eigenvalues, reversibility) by inserting different values for ϵ and δ in the 2×2-block.

Reversible If $\epsilon = \delta = 0$ and furthermore $\lambda_2 \neq \lambda_3$, then Λ_s is a diagonal matrix and P is reversible. In this case, the eigenvalues are identical to the Schur values, $\Lambda_e = \Lambda_s$, and the eigenvectors are identical to the Schur vectors, $X_e = X_s$.

Reversibility of P is equivalent to the symmetry of Λ_s (+ geometric and algebraic multiplicities should correspond; no double eigenvalues).

Nonreversible with real eigenvalues If we add an additional upper diagonal element $\epsilon > 0$, then we make Λ_s asymmetric. The eigenvalues of P correspond to the entries $\lambda_1, \ldots, \lambda_n$ on the diagonal of Λ_s. The eigenvectors of P are real, but **not π-orthogonal** anymore. In contrast to that, the Schur decomposition still leads to π-orthogonal Schur vectors X_s.

Non-reversibility of P can be seen by the fact that the Schur matrix Λ_s is not symmetric.

Nonreversible and not diagonalizable If $\lambda_2 = \lambda_3$ with $\epsilon > 0$ and $\delta = 0$, then P has an "incomplete" 2×2-block, meaning that it has an eigenvalue whose geometrical multiplicity does not correspond to its algebraic multiplicity. Therefore, P does not have an eigendecomposition and is not diagonalizable.

Since P is not diagonalizable, it is non-reversible.

While the eigendecomposition does not exist, the Schur decomposition still exists.

Nonreversible with complex eigenvalues If $\lambda_2 = \lambda_3$ and additionally $\epsilon, \gamma > 0$, then we have a "complete" 2×2-block, encoding the existence of two **complex eigenvalues**.

The complex-valued spectrum implies the non-reversibility of P. However, the Schur decomposition still yields real Schur vectors.

In a summary, there are several problems that can occur when considering the eigendecomposition of non-reversible processes. The existence of an eigendecomposition is not always given (not diagonalizable matrix). Furthermore it can happen that the eigenvectors are be not π-orthogonal or contain complex entries. All these issues are problematic for the use of PCCA+. However, all of that can be circumvented by using the real Schur decomposition instead, since it always exists and provides real and π-orthogonal Schur vectors. Good premises for applying PCCA+!

Clustering wrt metastable sets (GenPCCA)

We have the same aim as in section 2.3 to cluster a given process into metastable sets. However we have seen that it is not possible to insert eigenvectors of a nonreversible process into PCCA+ (do not fulfill the required conditions). A solution replacing eigenvectors by Schur vectors has been proposed by Fackeldey and Weber[13]. Their approach is a generalization of PCCA+ and therefore called Gen-PCCA (Generalized-Perron Cluster Cluster Analysis).

In order to apply PCCA+ to a set of real vectors $X \in \mathbb{R}^{N \times n}$, it has to fulfill the invariant subspace condition

$$PX = X\Lambda \tag{2.7}$$

and the orthogonality relation

$$X^T D_\eta X = I, \tag{2.8}$$

why η enough?

with respect to some initial distribution η. They are not fulfilled for the eigendecomposition of a nonreversible process, as we can see from a comparison with the previous case study. The eigenvectors of a nonreversible process having real eigenvalues are **not** orthogonal (because of non-symmetry of DP or Λ_s?). The eigenvectors of a nonreversible process having complex eigenvalues are complex and therefore not suitable for PCCA+.

In contrast, the real Schur vectors fulfill both conditions. They span an invariant subspace, are orthogonal with respect to any(?) initial distribution and are real. Since we assume NESS processes, thus having a stationary distribution π, we will just employ orthogonality with respect to π.

Gen-PCCA can be summarized as follows:

i) Compute a real Schur decomposition $(\widetilde{X}, \Lambda_s)$ of $\widetilde{P} = D^{0.5} P D^{-0.5}$. Then $X = D^{-0.5}\widetilde{X}$ fulfills the requirements (2.7) and (2.8).

ii) Sort the Schur values and the 2×2-blocks by using SRSchur by Brandts[4] such that they are in a descending order of their absolute value. Pick the dominant Schur values.

iii) Determine the submatrix $\widehat{X}$ (of dominant Schur vectors) and apply PCCA+ (solve optimization problem (2.4)) in order to determine the membership functions χ.

Metastable Cycles

Besides metastable sets, nonreversible processes can also contain metastable cycles. They are different dominant structures representing a cyclic behaviour of the process. Kalpazidou[18], Djurdevac Conrad et al[12].
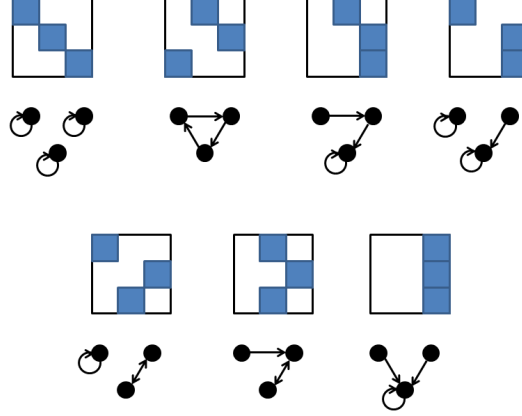

Figure 2.5: Possible structures that can be revealed by GenPCCA.

GenPCCA+ is not only able to identify metastable sets, but also cycles or mixtures of both structures, as depicted in figure 2.5.

Conclusion

The approach to determine metastable sets via a Schur decomposition is relatively new. There is a huge amount of scientific papers using eigenfunctions or eigenvectors to cluster a process into metastable sets. The entire framework of Markov State Models is built on the spectral analysis of the transfer operator/transition matrix; at the beginning in terms of hard sets, nowadays in terms of fuzzy sets. Since the Schur decomposition is a generalization of the Eigen decomposition (for reversible: same, nonreversible: only possible on Schur), it seems to be an appropriate method.

The main advantage of the Schur decomposition is that we can examine reversible as well as nonreversible processes with it. But it also has other benefits in comparison to the Eigen decomposition.

Advantages: Schur decomposition always exists. In contrast to the eigenvalue problem (bad conditioned [15, Subsection 7.2.2]), the Schur decomposition is well-conditioned. Disadvantages: Schur decomposition is not unique. Does not exist for a continuous transfer operator.

Additionally, there is a broader class/set of matrices that can be analyzed by Gen-PCCA/Schur Decomposition. This new approach did not only extend PCCA+ to nonreversible processes (huge progress/advance), but also made it possible to detect further dominant structures; not only metastable sets but also cyclic structures!

3 Rebinding Effect in a Given Kinetics

In this chapter, we will examine a particular type of molecular systems, namely receptor-ligand systems, consisting of special molecules, so called receptors and ligands. These molecules can interact in such a way that under certain conditions they can *bind* to each other and afterwards *dissociate* again. Such a system is originally Markovian and can be described by a transfer operator. However, by projecting this operator onto a finite-dimensional state space, the Markov property of the process may be spoiled.

We explain this memory effect, the so called *rebinding effect*, and examine its influence on the quantity of binding events of a receptor-ligand-system. We show how this effect can be measured with tools we know from chapter 1. We are particularly interested in analyzing an optimization problem to find a lower bound for the rebinding effect.

This chapter highly complies with Weber and Fackeldey[45]. Additionally, we introduce some fundamental definitions and notations from biochemistry, which are necessary for the understanding of receptor-ligand-systems. The importance of such systems becomes clear by a description of its application for drug design.

3.1 Receptor-Ligand System

We present a special molecular system, the *receptor-ligand-system*, and model it mathematically using a differential equation. We discuss the so called *rebinding effect*, a memory effect occuring in this model, and set in in relation to the recrossing effect known from section 1.4. We explain its relevance in the application of *drug design*.

Molecular Dynamics vs Molecular Kinetics

A *molecular system* consists of atoms that are connected by *covalent bonds*. bla bla. The potential energy function, or *energy landscape*, of a molecular system results in a dynamical behaviour on different timescales. The fastest timescales (vibrations of covalent bonds) are around 10^{-15} seconds. bla. up to nanoseconds or, for protein folding, up to microseconds or seconds or even longer..

see ..

Receptors and Ligands

references

In biochemistry, a *receptor* is a molecule, often a protein, that is usually located on the surface of a cell and can receive signals from outside the cell. A molecule that has the ability to *bind* or *associate* to a receptor is called a *ligand*. Each receptor will only bind with ligands of a particular structure, which is often referred to as the "key-lock principle". Both receptor and ligand need to have specific complementary geometric shapes that fit exactly into one another, as exemplarily depicted in figure 3.1.
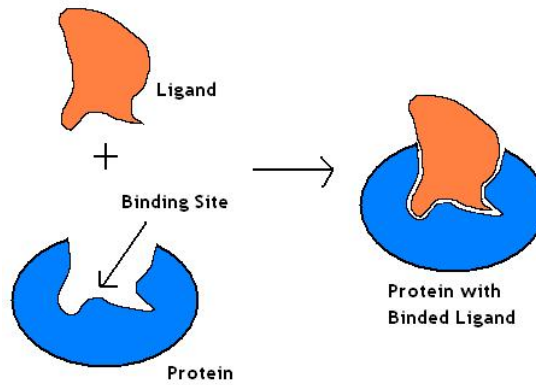
binding site

Figure 3.1: Ligand ("key") binds to a receptor ("lock"). Their shapes fit together.

Such a binding between a receptor and a ligand can *activate* ("unlock") the receptor by producing some kind of a chemical signal and thereby provoke a physiological response. For instance, that could be a conformational change in a protein, caused by a hormone binding to it. However, instead of engaging in the actual physiological consequences of a binding, we focus on the **act** of binding events.

The action of binding is typically reversible[1] through *dissociation* of the involved receptor and ligand. Ligand binding is a *chemical equilibrium* process, which means that the reaction rates of the binding and dissociating events are equal, once this equilibrium is reached. From then on, the concentrations of the reactants (ligands) and the products (complexes) are constant. It is a *dynamic equilibrium*, since reactions take place, even though no net change in the concentrations can be observed.

The binding behaviour of a simple receptor-ligand system is formalized as follows. A ligands (L) can bind to a receptor (R) and form a receptor-ligand complex (LR) which can dissociate again into its original components. This process can be represented by a reaction equation

$$L + R \rightleftharpoons LR. \tag{3.1}$$

Being a process in chemical equilibrium, the law of mass action states that the ratio between the concentration of reactants and products is constant. The corresponding *dissociation constant* k_d is given by

$$k_d = \frac{[L] \cdot [R]}{[LR]},$$

where [L] is the concentration of free/unbound ligands, [R] is the concentration of unoccupied receptors and [LR] is the concentration of receptor-ligand complexes. This constant is used to describe the *binding affinity* between a ligand and a receptor, that is how strongly/tightly the ligand can bind to his particular receptor. If the dissociation constant is small, then there are relatively many complexes in comparison to unbound

---

[1]We remark that in this context, *reversible* means that a ligand can bind and unbind to a receptor, that is the reaction can run forward and backward. In contrary to the mathematical reversible, which means that a process behaves **equally** when running backwards in time.

molecules, and for this reason, the binding affinity between the ligand and the receptor is high. The *association constant* k_a is just the inverse of the dissociation constant

$$k_a = \frac{[\text{LR}]}{[\text{L}] \cdot [\text{R}]}.$$

There are different factors which can influence the binding affinity of a process. It depends on the nature of the constituent molecules, like their shape, size and possible charge. The binding affinity of a particular ligand-protein interaction can also change significantly with solution conditions (e.g., temperature, pH and salt concentration).

In general, high-affinity binding results in a higher degree of occupancy for the ligand at its receptor binding site than is the case for low-affinity binding; the residence time (lifetime of the receptor-ligand complex) does not correlate.

Mathematical Model of Receptor-Ligand-System

Starting from the reaction equation (3.1), we can deduce that the ligand can be found in two different (macro) states: "unbound" (L) or "bound" (LR). Then the probabilities of the ligand to be in one of these states can be described by the probability vector $x^T = \frac{1}{s}(([\text{L}], [\text{LR}]))$, where $s = [\text{L}] + [\text{LR}] = \text{const.}$ is the normalization constant. This leads to an ordinary differential equation

$$\dot{x}^T = x^T Q_c.$$

The matrix Q_c consists of the rates of reaction,

$$Q_c = \begin{pmatrix} -k_a[R] & k_a[R] \\ k_d & -k_d \end{pmatrix},$$

where k_a and k_d are the association and dissociation constants. It corresponds to the transition rate matrix of a Markov chain, that means it describes a **memoryless** process. We will later see that this mathematical description of a receptor-ligand-system is not accurate, since in fact, such a process **will** have some kind of memory.

Figure 3.2: Two possible states (unbound, bound) of a ligand-binding-system.

The two possible states for the easiest case of a ligand-binding-system consisting of one receptor and one ligand are depicted in figure 3.2. We notice that the spatial arrangement of the receptor and the ligand in the unbound case is **not** included in the above model. Therefore, we cannot distinguish if, at a given time, the receptor and the ligand are close to each other or not.

Rebinding Effect

In fact, a stochastic process describing a receptor-ligand system is **not** necessarily Marko-vian. That is due to the spatial arrangement of the system after the dissociating of a receptor-ligand-complex took place. Shortly after such a dissociating, it is more likely that the corresponding receptor and ligand will bind again, since they are still close to each other. Such a binding shortly after being dissociated is called a **rebinding**. The memory effect which thereby occurs is called **rebinding effect**. On large timescales, this effect will vanish since the favorable spatial situation is not necessarily given anymore and the system will be rather mixed again. Thus, Markovianity can be spoiled by the rebinding effect. It is depicted in figure 3.3.

The rebinding effect and its occurence in natural science has been described and analyzed by several authors[14, 40]. In chemistry, it has been discussed in the context of clustered receptors and clustered ligands[6]. Recently, there has been efforts to describe the rebinding effect mathematically, see Weber et al[44, 45].

The rebinding effect has been discussed to increase the binding affinity of a process.
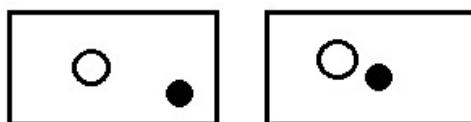

Figure 3.3: Rebinding Effect. Two configurations of a system consisting of one receptor (white) and one ligand (black), represented by the same state ("unbound"). Left: an arbitrary spatial arrangement of the receptor and the ligand in the unbound state. Right: spatial constellation of receptor and ligand shortly after their dissociation. The ligand is still **close** to the receptor, increasing the probability of a fast **rebinding**.

Rebinding Effect vs Recrossing Effect

The characterization of the rebinding effect reminds us of the recrossing effect, as de-scribed in section 1.4. There, we considered the projection of a process onto a finite state space. This projected process (MSM) was described by a transition matrix, thus being a Markov chain, even though the process actually contained a (short-time) memory. The same phenomena occurs with the rebinding effect. We have a process which is modelled by a Markov chain, even though the process actually has a memory. We can interpret the two states of the ligand-binding-system as macro states resulting from the projection of a process on a larger state space (for instance, including more informations about the spatial situation of the receptor and the ligand). In this case, the rebinding effect originates from the loss of information caused by the projection and therefore, qualitatively corresponds to the recrossing effect.

Thus, the rebinding effect is just a special case of the recrossing effect. The different nomenclatures are justified by the use in their original context. While the term recrossing effect denotes the act of **recrossing** a energy barrier, the term rebinding effect denotes the **rebinding** of a receptor-ligand-system. Such a system can also be represented by a potential energy function, having energy minima around the bound (closest possible distance) and unbound state (farthest possible distance).

In chapter 2, we learned that a crisp clustering leads not to the best result and that we should chose a fuzzy clustering instead. Therefore, we are going to include the spatial situation of the system by introducing degrees of membership, which can be interpreted as "intermediate" states such as "almost bound". In this case, an unbound state with a high degree of membership to the bound state could correspond to a ligand which is close to a receptor, e.g. shortly after dissociating.

In the next sections, we are going to quantify this effect by embedding the whole molecular system into the mathematical framework established in the first two chapters.

Application: Drug Design

The term *drug design* denotes the development of new medications based on the knowledge of a biological target, playing the role of the receptor. Drug design is basically about designing a molecule which is complementary in shape and charge to the biomolecular target and therefore will bind to it, see Strømgaard et al[38]. More precisely, drug design describes the design of ligands, that is molecules that will bind tightly to the given target, see Tollenaere[39]. In general, we can distinguish between following two most common functionalities of drugs.

- **Activators** are able to activate, or even deactivate, a receptor and result in a strong biological response. An example for such a drug is morphine, which acts directly to the central nervous system, mimics the actions of endorphins and thereby reduces pain.

- **Inhibitors** bind to a receptor without activating it. Though, as they "block" the binding sites of receptors, they prevent possibly disease causing ... objects .. to bind. A well-known example are protease inhibitors, a class of antiviral drugs that are widely used to treat HIV and hepatitis C.

Independently of the fact whether a drug activates or inhibits receptors, a high binding affinity is required in order to be an efficient drug. The central dogma of receptor pharmacology ("occupation theory") is that a drug effect is directly proportional to the number of receptors that are occupied. Furthermore, a drug effect ceases as a drug-receptor complex dissociates. Thus, a low binding affinity needs to be compensated by a higher concentration of ligands. Though, high concentrations should be avoided, because of possible side effects. Accordingly, the most fundamental goal in drug design is to predict whether a given molecule will bind to a target and if so how strongly.

3.2 Molecular Kinetics as a Projection

We will deduce a rigorous description of molecular systems, in particular receptor-ligand-systems, basically by embedding the mathematical concepts from chapter 1 into a physical context. When considering such systems, we can distinguish between two points of view: we will see how we can get from the *microsopic* or *atomistic* to a *macroscopic* scale by a projection.

Micro States

A micro state of a molecular system with N atoms can be represented in a $6N$-dimensional *phase space* $\Gamma = \Omega \times \mathbb{R}^{3N}$, consisting of the *configuration space* $\Omega = \mathbb{R}^{3N}$ and the *momentum space* $\mathbb{R}^{3N}$. In the following, we consider systems in *thermodynamical equilibrium*. One possible model is given by the *Boltzmann distribution* $\pi : \Omega \times \mathbb{R}^{3N} \to \mathbb{R}$, a probability distribution assigning to each micro state a probability depending on its energy and temperature, see McQuarrie[22]. It can be expressed as

$$\pi(q, p) = \frac{1}{Z} \exp\left(-\beta H(q, p)\right), \tag{3.2}$$

where $\beta = 1/(k_B T)$ is the inverse of the temperature T multiplied with the Boltzmann constant k_B and $Z = \int_\Gamma \exp -\beta H(q, p) \, \mathrm{d}(q, p)$ is the normalization factor. The Hamilton function denoted by H is given by $H(q, p) = K(p) + V(q)$, the sum of the kinetic energy $K(p)$ and the potential energy $V(q)$. Thus, the Boltzmann distribution π can be decomposed into $\pi = \pi_p \pi_q$,

$$\pi(q, p) = \underbrace{\frac{1}{Z_p} \exp\left(-\beta K(p)\right)}_{\pi_p} \cdot \underbrace{\frac{1}{Z_q} \exp\left(-\beta V(q)\right)}_{\pi_q},$$

where $\pi_p : \mathbb{R}^{3N} \to \mathbb{R}$ is the probability density function of the kinetic part in the momentum space $\mathbb{R}^{3N}$ and $\pi_q : \Omega \to \mathbb{R}$ is the probability density function of the potential part in the configuration space Ω. As we are interested in examining conformations, that are objects in configuration space, we will restrict ourselves to Ω, see Huisinga[16]:

> "A conformation $C \subset \Omega$ will be identified with the particular metastable sub-ensemble $\mu_{C \times \mathbb{R}^{3N}}$ corresponding to the particular subset $C \times \mathbb{R}^{3N} \subset \Gamma$. Hence, for every position $q \in C$, the conformation contains all states with $q \in \Omega$ and arbitrary $p \in \mathbb{R}^{3N}$."

In this sense, conformations contain no information on momenta and are determined in configuration space only. We consider a reduced model with the *reduced density* $\pi_q = \int_{\mathbb{R}^{3N}} \pi(q, p) \, \mathrm{d}p$.

Macro States via Membership Functions

As the configuration space of an average molecular system is very large, we aim to reveal the underlying discrete Markov State Model by clustering a collection of the micro states having the same or similar values in one observable. Such a collection of micro states

will be called a *macro state*. For instance, that could be the states/observables "bound" or "unbound" for a simple receptor-ligand system.

We apply the function-based fuzzy clustering method presented in section 2.3. We define macro states as **overlapping** partial densities, which can be identified as membership functions $\chi_1, \ldots, \chi_n : \Omega \to [0, 1]$. They form a partition of unity, that is

$$\sum_{i=1}^{n} \chi_i(q) = 1.$$

By grouping micro states, the corresponding macro states yield *statistical weights*

$$w_i = \langle \chi_i, \mathbb{1} \rangle_\pi := \int_\Omega \chi_i(q) \pi_q(q) \, dq. \tag{3.3}$$

The statistical weight w_i corresponds to the "probability to be in conformation χ_i". ?

Transfer Operator

Each micro state $(q, p) \in \Gamma$ determines a *probability density function* $\Psi^{-\tau}(\cdot \mid (q, p))$ describing the possible evolutions of the system in configuration space Ω in time τ, having started at the initial state (q, p). Weber[42] defines a transfer operator $\mathcal{P}(\tau) : L_{\pi_q}^{1,2}(\Omega) \to L_{\pi_q}^{1,2}(\Omega)$ for the propagation of (membership) functions via $\qquad$ why not densities?

$$\mathcal{P}(\tau) f(q) = \int_{\mathbb{R}^{3N}} \left(\int_\Omega f(\tilde{q}) \Psi^{-r}(\tilde{q} \mid (q, p)) \, d\tilde{q} \right) \pi_p(p) \, dp. \tag{3.4}$$

In this definition, the density function $\Psi^{-\tau}(\cdot \mid (q, p))$ can be interpreted as a transition function as defined in section 1.1. We have to notice that this operator corresponds to the **backward** transfer operator introduced in section 1.2. $\qquad$?

It is a *generalized* transfer operator in the sense that it includes deterministic as well as stochastic dynamical models. In order to describe deterministic dynamics, the density function $\Psi^{-\tau}$ has to be chosen as a Dirac delta function, since an initial state $(q(0), p(0))$ determines exactly the future states in configuration space.

It is important to remark that the transfer operator $\mathcal{P}(\tau)$ also defines a projected Markov operator $\overline{\mathcal{P}}(\tau)$ acting in configuration space Ω, see Weber[42], by

$$\overline{\mathcal{P}}(\tau) = \pi_q \circ \mathcal{P}(\tau) \circ (\pi_q)^{-1}, \tag{3.5}$$

which propagates density functions and thus corresponds to a **forward** transfer operator. The previous equation shows that the space of membership functions is connected to the space of density functions by multiplication with π_q. We will keep that relation in mind, though just use $\mathcal{P}$ in the following.

As $\mathcal{P}(\tau)$ in (3.4) propagates **membership functions**, stationarity is characterized by the equation $e = \mathcal{P}(\tau) e$ for the constant function $e = 1$ in Ω. For the Markov operator $\overline{\mathcal{P}}(\tau)$ in (3.5) propagating **densities**, stationarity can be characterized by $\pi = \overline{\mathcal{P}}(\tau) \pi$, where π is the Boltzmann density. These two operators are adjoint operators. This can also be seen by the fact that a discretization of $\mathcal{P}(\tau)$ results in a matrix P_c, while a discretization of $\overline{\mathcal{P}}(\tau)$ will result in the transposed matrix P_c^T.

Markov State Model for reversible Processes

For now, we consider a reversible process. In that case, the corresponding transfer operator $\mathcal{P}$ is **self-adjoint** with respect to π_q and thus has a real spectrum with $\sigma(\mathcal{P}) \subset [-1, 1]$. The reason for that can be understood by theorem 1.12, but we additionally need to consider the projection onto the configuration space. A rigorous proof is found in Weber[42, theorem 1]. In order to apply the spectral approach from section 2.2, we assume that the **discrete spectrum** of the transfer operator $\mathcal{P}$ has n **dominant eigenvalues** $1 = \lambda_1 \geq \lambda_2 \geq \cdots \geq \lambda_n$ which are all close to 1 and bounded away from the essential spectrum. The corresponding dominant eigenfunctions are denoted by $\mathcal{X} = \{\mathcal{X}_1, \ldots, \mathcal{X}_n\}$ and therefore the eigenvalue problem is given by $\mathcal{P}(\tau)\mathcal{X} = \mathcal{X}\Lambda$, with the eigenvalue matrix $\Lambda = \text{diag}(\lambda_1, \ldots, \lambda_n)$.

As we know from chapter 2, the number of metastable sets of a Markov process is determined by the number of dominant eigenvalues; thus we are going to create a Markov State Model on n states. The state space of this model should consist of the conformations of the molecular system in consideration and its transition behaviour should be described by a $n \times n$-transition matrix $P(\tau)$. In order to obtain this discrete matrix from the continuous operator $\mathcal{P}(\tau)$, we need at first to determine the size and shape of the membership functions χ_i. As described in section 2.3, this can be done by computing a linear combination of the dominant eigenfunctions via

$$\chi_j(q) = \sum_{i=1}^{N} A_{ij}\mathcal{X}_i(q), \ j = 1, \ldots, n, \tag{3.6}$$

where $A = \{A_{ij}\}_{i,j=1,\ldots,n}$ is the solution of PCCA+ (convex maximization problem). As a linear combination of eigenfunctions, the membership functions χ_i might have an overlap; they are not orthogonal.

Galerkin Projection

Having computed the membership functions χ_i, we can project $\mathcal{P}(\tau)$ onto a finite Markov State Model $P_c(\tau)$ by applying the Galerkin discretization

$$P_c(\tau) = G(\mathcal{P}(\tau)) = (\langle \chi, \chi \rangle_\pi)^{-1}(\langle \chi, \mathcal{P}(\tau)\chi \rangle_\pi). \tag{3.7}$$

In order to know about the quality of this model, we are interested in the iteration error under this projection. As mentioned in section 1.4, this error is zero if the Galerkin discretization of $(\mathcal{P}(\tau))^k$ is equal to the iteration $(P_c(\tau))^k$. In that case, the diagram 1.2 commutes. The following theorem shows that there is no discretization error under the projection (3.7), that is we have $(\mathcal{P}(\tau))^k = (P(\tau))^k$, which in particular implies that Markovianity is preserved.

Theorem 3.1. (Weber [42, Theorem 2])
Let $\mathcal{P}(\tau)$ be the π_q-self-adjoint transfer operator as defined in (3.4) with a set $\mathcal{X} = \{\mathcal{X}_1, \ldots, \mathcal{X}_n\}$ of normalized eigenfunctions s.t. $\mathcal{P}(\tau)\mathcal{X} = \mathcal{X}\Lambda$, where $\Lambda = \text{diag}(\lambda_1, \ldots, \lambda_n)$ is the eigenvalue matrix. Let $\chi = \mathcal{X}A$ be a set of functions that is a linear combination of the eigenfunctions $\mathcal{X}$ with a regular $n \times n$-transformation matrix A from (3.6). Then the iteration error for the Galerkin discretization $P_c(\tau) = G(\mathcal{P}(\tau))$ in (3.7) vanishes.

Proof. We compute the Galerkin projection on the propagated transfer operator $(\mathcal{P}(\tau))^k$:

$$\begin{aligned}
G((\mathcal{P}(\tau))^k) &\overset{(3.7)}{=} (\langle \chi, \chi \rangle_\pi)^{-1} (\langle \chi, (\mathcal{P}(\tau))^k \chi \rangle_\pi) \\
&\overset{(3.6)}{=} (A^T \langle \mathcal{X}, \mathcal{X} \rangle_\pi A)^{-1} (A^T \langle \mathcal{X}, (\mathcal{P}(\tau))^k \mathcal{X} \rangle_\pi A) \\
&= (A^T A)^{-1} (A^T \langle \mathcal{X}, \mathcal{X} \rangle_\pi \Lambda^k A) \\
&= A^{-1} \Lambda^k A.
\end{aligned}$$

The last two lines are obtained by simply inserting the eigenvalue problem $\mathcal{P}\mathcal{X} = \mathcal{X}\Lambda$ and employing the fact that the eigenfunctions are orthogonal, by theorem 1.11 and therefore $\langle \mathcal{X}, \mathcal{X} \rangle_\pi = \mathcal{I}$, being the identity operator. ... $\qquad\square$

Theorem 3.1 is true for arbitrary regular transformations A of $\mathcal{X}$, so in particular it holds for the solution computed by PCCA+, which will be used from now on. Since the above projection represents the correct dynamical long-time behaviour of the process, the matrix $P_c(\tau)$ is the correct Markov State Model. We can use the matrix representation $P_c(\tau) = S^{-1}T$ from theorem 1.17. Then S and T are stochastic matrices with

$$\begin{aligned}
T &= D^{-1}\langle \chi, \mathcal{P}(\tau)\chi \rangle_\pi = D^{-1}A^T \Lambda A \quad \text{and} \\
S &= D^{-1}\langle \chi, \chi \rangle_\pi = D^{-1}A^T A,
\end{aligned} \qquad (3.8)$$

where $D = \text{diag}(w_1, \ldots, w_n)$ is the diagonal matrix of statistical weights from (3.3).

Measuring the Rebinding Effect

Even though $P_c(\tau) := P(\tau)$ is the correct Markov State Model, it cannot be interpreted as a transition matrix, since the inverse matrix of S is not necessarily stochastic. The matrix $T = D^{-1}\langle \chi, \mathcal{P}\chi \rangle$ however can be interpreted as a transition matrix. The difference between $P_c(\tau)$ and T is given by

$$SP_c(\tau) = T.$$

Thus, the "disturbance" of stochasticity of $P_c(\tau)$ can be measured by the matrix S. If S is equal to the identity matrix, then the Markov State Model is Markovian. If S is close to the identity matrix, then $P_c(\tau)$ is close to being a stochastic matrix. The more the matrix S differs from the identity matrix, the more the Markov State Model $P_c(\tau)$ differs from the transition matrix T. Since for a matrix, being stochastic is equivalent to being the transition matrix of a Markov chain, the deviation of $P_c(\tau)$ from being stochastic can be interpreted as a violation of Markovianity and thus, of including some kind of memory. The larger this deviation, the larger the occuring memory effects. Thus, the rebinding effect, introduced in section 3.1 as a **memory effect** evoked by a projection, can be measured by the matrix S.

These observations correspond to our previous results from the examinination of the recrossing effect in section 1.4 and the qualitative description of the rebinding effect in section 3.1. There, we found out that a crisp clustering, i.e. a set based-clustering, leads to a model $P_c(\tau)$ which is Markovian, caused by the orthogonality of membership functions characteristic functions and thus S being the identity matrix. The more **overlap** occured

in the membership functions, the more the matrix S deviates from being the identity matrix (has higher outer diagonal elements) and thereby includes more memory effects.

Thus, the rebinding effect can be measured by considering the trace of the matrix S, being the sum of its diagonal elements. It can lie between 0 (very much overlap) and n (diagonal matrix). This approach has been introduced by Weber and Fackeldey[45] and will be used in the next chapter to detect the minimal rebinding effect.

The trace of S is at most n. Optimizing trace(S) is equivalent to optimizing the *crispness* of the conformations χ (Röblitz).

Infinitesimal Generator to transition rate matrix

Often it is more convenient to consider transition rate matrices instead of transition matrices. In order to get a discrete transition rate matrix, we apply the Galerkin projection to the infinitesimal generator induced by a given transfer operator.

The transfer operator $\mathcal{P}(\tau)$ defines a time-independent operator $\mathcal{Q}$ via

$$\mathcal{Q} = \lim_{\tau \to 0} \frac{\mathcal{P}(\tau) - \mathcal{I}}{\tau},$$

which is the infinitesimal generator of $\mathcal{P}$. They are related by

$$\mathcal{P}(\tau) = \exp(\tau \mathcal{Q}).$$

Weber[42] shows that such an infinitesimal generator exists for a discretization in terms of membership functions.

Since the eigenfunctions of $\mathcal{Q}$ and $\mathcal{P}$ are the same and their eigenvalues are related via $\exp(\xi_i) = \lambda_i$, we can apply the same Galerkin Projection for the infinitesimal generator as for the transfer operator in (3.7). We get a $n \times n$-rate matrix

$$Q_c = A^{-1} \Xi A = (\langle \chi, \chi \rangle_\pi)^{-1} (\langle \chi, \mathcal{Q} \chi \rangle_\pi), \tag{3.9}$$

where Ξ is the diagonal matrix consisting of the n leading eigenvalues $0 = \xi_1 > \xi_2 \geq \cdots \geq \xi_n$ of $\mathcal{Q}$ and A is the transformation matrix of (3.6), which analoguously transforms the eigenfunctions of $\mathcal{Q}$ into membership functions of the macro states.

The matrix Q_c can be interpreted as a transition rate matrix.

3.3 Minimizing the Rebinding Effect

Everything we did so far, was to describe molecular systems and the procedure of their projection onto a finite state space. And, of particular interest, how such a projection introduces memory effects in the clustered process. However, in most of the cases, we will not be given the continuous transfer operator describing a system. Instead, we will often be given a finite matrix, for instance stemming from experimental data. In either case, such a discrete/finite matrix can be **interpreted** as a projection, since it is just a model for an originally continuous process (molecules in $\mathbb{R}^3$). Thus, even if we don't know the original process and the clustering, we can deduce that there has to be some

rebinding included, originating from the projection. Therefore, we try to estimate how much rebinding is included **at least** in a given system, without knowing the clustering (membership functions) or the matrix S.

So far, we know that the overlap matrix S from (3.8) provides a measure for the quantity of the rebinding effect. In particular being close to the identity matrix implies a low rebinding, while high outer diagonal elements of S result in a high rebinding effect. However we don't know yet the actual influence of this effect on the system. From its qualitative description, we assume that it slows down the process, in the sense that conformational changes occur less frequently. In order to verify that, we set the rebinding effect in relation to the stability of the system. Afterwards we formulate an optimization problem in order to deduce a lower bound for the rebinding effect.

As the computation of eigenfunctions of a continuous operator $\mathcal{Q}$ is an extensive task, we assume in the further course that the transition rates can be measured experimentally. Accordingly we examine a given transition rate matrix Q_c of a process.

Stability of a system in terms of determinants

If the eigenvalues ξ_i of Q_c are close to 0, then the macro states are very stable in the sense that the probability to stay inside of such a state is close to 1. The trace of Q_c corresponds to the sum of the dominant eigenvalues of $\mathcal{Q}$. Thus we can measure the *stability* of the molecular system by considering the quantity $F := -\text{trace}(Q_c)$. If F is high, then the process is fast and the system less stable. If F is close to 0, then the process is slow and the system is very stable. We want to set the indicator for stability F in relation to the matrices S and T from theorem 1.17.

trace indep. of A?

Lemma 3.2. *Let Q_c is the projected infinitesimal generator of a process and $P_c(\tau)$ the corresponding projected transfer operator with the matrix representation $P_c(\tau) = S^{-1}T$ from theorem 1.17, then the quantity $F := -\text{trace}(Q_c)$ can be measured by*

$$F = \tau^{-1}(\log(\det(S)) - \log(\det(T))),$$

if we assume that S and T are diagonal dominant matrices.

Proof. We use the trace formula[1, p. 208] for matrices $\exp(\text{trace}(A)) = \det(\exp(A))$, the fact that Q_c "generates" $P_c(\tau)$, theorem 1.17 and multiplicativity of determinants to obtain

why $\exp(\tau Q_c) = P_c($

$$
\begin{aligned}
F &= -\text{trace}(Q_c) \\
&= -\tau^{-1} \log(\exp(\text{trace}(\tau Q_c))) \\
&= -\tau^{-1} \log(\det(\exp(\tau Q_c))) \\
&= -\tau^{-1} \log(\det(P_c(\tau))) \\
&= \tau^{-1}(\log(\det(S)) - \log(\det(T))).
\end{aligned}
$$

The diagonal dominance of S and T is a natural property for a process clustered with respect to metastability and ensures us a determinant of Q_c in $[0, 1]$. □

Thus, both determinants of the stochastic matrices S and T influence the stability of the system, but in converse directions. If $\det(T)$ is close to 1, then F is low and consequently the process is stable/slow. If $\det(T)$ is close to 0, then the process is unstable/fast, since F is high. That makes sense because a high determinant of T can be interpreted as "good" metastability and thus corresponds to a slower/stable process, while a low determinant of T ("bad" metastability) makes the process faster/unstable.

On the other hand, if $\det(S)$ is close to 1 (almost unit matrix), then F is high, i.e. the process is unstable/fast. If $\det(S)$ is close to 0 (much overlap), then F is low, i.e. the process is stable/slow. This means that a higher overlap in S leads to a slower process. That is a relation which is not obvious at first sight.

As we figured out in section 3.2, the rebinding effect can be measured by the matrix S. If that matrix is close to the identity matrix, i.e. having a determinant close to 1, yields a low rebinding. Large deviation from the identity matrix, i.e. having higher outer diagonal elements, i.e. having a smaller determinant, results in high rebinding.

Combining these two properties of S, we can deduce that a high rebinding effect corresponds to a high stability of the system. This can be achieved by high outer diagonal elements/deviation from identity, i.e. by a high overlap of the membership functions(?).

Finding a lower bound for the rebinding effect

What is the meaning of the previous results/relation of S to stability of the system? On the one hand, the rebinding effect increases bindings(?). On the other hand, it increases the stability of a system. Thus, we we are interested in a high/increased rebinding effect. We are going to compute a lower bound for it, in order to know how much rebinding there will be at least.

In order to do so, let us first of all remember how S is determined. We were given a transfer operator $\mathcal{P}$ which was projected onto a finite-dimensional state space via membership functions χ_i. These membership functions have been computed as a linear combination of the eigenfunctions with a regular matrix A. Thus, the choice of the matrix A determines S respectively the size of its determinant.

So far, A was assumed to be computed via PCCA+, i.e. such that the result is an optimal metastable decomposition/clustering. Now, we want to take into consideration the set of all possible, *feasible*, matrices A, to see if different choices result in a better/higher or worse/less rebinding.

Thus, we are going to formulate an optimization problem to find out which choice of A results in the lowest rebinding effect, measured by an *optimal matrix* S_{opt}, in order to know how much rebinding we are guaranteed **at least** for a given process. This problem is equivalent to finding the largest possible determinant of S.

Optimization Problem (Maximizing determinant of S)

Since Q_c has the same eigenvalues as $\mathcal{Q}$, the eigenvalue problem of Q_c is given by

$$Q_c X = X \Xi,$$

where the first column of X corresponds to the first eigenvector $X_1 := (1, \ldots, 1)^T$. By (3.9), we see that A^{-1} is an eigenvector matrix of Q_c as well. Therefore the columns of

A^{-1} consist of multiples of the eigenvectors X_i, yielding

$$A^{-1} = \begin{pmatrix} 1 & & & \\ \vdots & \alpha_2 X_2 & \cdots & \alpha_3 X_3 \\ 1 & & & \end{pmatrix}$$

with $\alpha_2, \ldots, \alpha_n \in \mathbb{R}$. We know from theorem 3.2 that a $\det(S)$ close to 1 results in a low rebinding effect. Thus, in order to find a lower bound for the rebinding effect, we try to maximize $\det(S)$, or equivalently minimize $|\det(S) - 1|$, since S is a stochastic matrix having 1 as largest possible determinant. The *objective function* of the optimization problem is then given by

$$\boxed{\min_{\alpha_1, \ldots, \alpha_n \in \mathbb{R}} |\det(S) - 1|}, \qquad (3.10)$$

where we have to include several *side constraints*. As the inverse matrix A^{-1} consists of linear combinations of eigenvectors X_i, we have to consider

$$\boxed{\alpha_1 = 1 \quad \text{and} \quad A_{ij}^{-1} = \alpha_j X_{ij} \quad \forall i, j}.$$

Furthermore, S is a stochastic matrix, see theorem 1.17, and its structure is given in terms of the linear transformation matrix A, so we have two further constraints

row-sum 1 included formula?

$$\boxed{S = D^{-1} A^T A \quad \text{and} \quad S_{ij} \geq 0 \quad \forall i, j}.$$

A *feasible solution* of this optimization problem is a matrix S fullfilling all side contraints, but not necessarily being an optimum.

Interpretation

explain overlap

In the last section, we mentioned how the matrix S describes the *overlap* of the membership functions. For this reason, any feasible solution of the optimization problem (3.10) will be called a *real overlap matrix* S_{real}, while an actual optimum will be called an *optimal overlap matrix* S_{opt}. Clearly, we get $\det(S_{\text{real}}) \leq \det(S_{\text{opt}}) \leq 1$.

???

The real ocurring rebinding effect is high if the determinant of S_{real} is low. Thus, a small determinant of S_{opt} increases the rebinding effect, while a large determinant of S_{opt} gives us only few information about the quantity(?) of the rebinding effect, it could be large or small.

Unfortunately, for a reversible Q_c, the solution of optimization problem (3.10) gives us no information, as the following theorem shows.

Theorem 3.3. (Weber and Fackeldey[45, Theorem 1])
Let $Q_c \in \mathbb{R}^{n \times n}$ be a reversible matrix that stems from a clustering with positive definite overlap matrix S. Then there exists a matrix $A \in \mathbb{R}^{n \times n}$ in optimization problem (3.10) such that $\det(S_{\text{opt}}) = 1$.

Proof. It is enough to show that for a given reversible Q_c, we can find a matrix A fulfilling all constraints such that $S = D^{-1} A^T A$ is equal to the identity matrix I.

Assume that there is a regular matrix B, such that $Q_c = B^{-1} \Xi B$.

Since Q_c is reversible, we have $D Q_c = Q_c^T D$, see section 1.3, and thus

$$D B^{-1} \Xi B = B^T \Xi^T B^{-T} D.$$

Now let $C := B^{-T} D$, then we get

$$Q_c = \cdots = C^{-1} \Xi C.$$

. . .

Have a real positive matrix $M = \mathrm{diag}(m_1, \ldots, m_n)$ and therefore a real positive diagonal matrix $\widetilde{M} = \mathrm{diag}(\sqrt{m_1}, \ldots, \sqrt{m_n})$.

. . .

Let $A := \widetilde{M}^{-1} B$. Show: A fulfills the constraints of (3.10), in order that S is a feasible matrix. Then

$$
\begin{aligned}
S = D^{-1} A^T A = D^{-1} B^T \widetilde{M}^{-1} \widetilde{M}^{-1} B \\
= D^{-1} B^T M^{-1} B \\
= C^{-1} M^{-1} B \\
= B^{-1} M M^{-1} B = I.
\end{aligned}
$$

Since all contraints of (3.10) are fulfilled, S is a feasible matrix with $\det(S) = 1$. $\qquad \square$

This theorem does **not** mean that a reversible process has no rebinding effect. It just means that for **every** reversible process, it is possible to find a clustering with no rebinding.

For instance, if we computed a clustering of a reversible process via PCCA+, then it could be the case that we have a low determinant of S, i.e. a high rebinding. But the optimization problem (3.10) gave us the lower bound of no rebinding, so it gave us no information about the rebinding of a particular/concrete clustering.

Linear Optimization Problem (Maximizing trace of S)

Now we present a different formulation of the above optimization problem (3.10). We will slightly change the objective function and turn the problem into a *linear optimization problem*. As a special case of the class of convex optimization problems, they have the nice property that any local optimum is also a global optimum.

easier to solve?

We want to *minimize* the rebinding effect, i.e. we want to give a bound for how large the rebinding effect is *at least* (lower bound for rebinding effect). The closer the matrix S is to the identity matrix, the smaller is the rebinding effect. A matrix is close to the identity matrix, if its determinant is close to 1 or (equivalently) if its trace is close to n. So in order to compute the minimal rebinding effect, we can either maximize the determinant (get it as close as possible to 1) or maximize the trace of S (get it as close as possible to n), as the following theorem shows.

Theorem 3.4. *In optimization problem (3.10), we have $\det(S) \leq 1$ and $\mathrm{trace}(S) \leq n$ with equality if and only if S is the identity/unit matrix.*

Proof. □

So instead of maximizing $\det(S)$, we can also maximize $\text{trace}(S)$. In order to do so, let us first make some further observations about the eigenvectors of Q_c. We already found out that A^{-1} is a right eigenvector matrix of Q_c, with vectors being linear combinations of the eigenvectors X_i. Similarly, the matrix A is a *left* eigenvector matrix of Q_c, with row vectors being linear combinations of the eigenvectors Y_i. That fact can be expressed as

$$A = \tilde{U}Y^T = \begin{pmatrix} \tilde{\alpha}_1 Y_1 \\ \vdots \\ \tilde{\alpha}_n Y_n \end{pmatrix},$$

where each Y_i is a left eigenvector of Q_c (row vector) and the $\tilde{\alpha}_i \in \mathbb{R}$ are again some optimization parameters. The first eigenvector Y_i corresponds to the leading eigenvalue $\xi_1 = 0$ and is thus the stationary density of the process. The first row of A consists of the statistical weights of the clusters and therefore we have again $\tilde{\alpha}_i = 1$. With these   ? notations we can write the new objective function as

$$\begin{aligned} \text{trace}(S) &= \text{trace}(D^{-1}A^T A) \\ &= \text{trace}(D^{-1}Y\tilde{U}^2 Y^T) \\ &= \sum_{i=1}^{n}\sum_{k=1}^{n}\tilde{\alpha}_k^2 \frac{y_{ik}^2}{y_{k1}}. \end{aligned}$$

The side constraints remain the same, i.e. $S_{ij} = \cdots \geq 0$. Let $\beta = (\beta_1, \ldots, \beta_n)$ with   why $i \neq j$? $\beta_i = \tilde{\alpha}_i^2$. Then the linear optimization problem of maximizing $\text{trace}(S)$ is given by

$$\boxed{\max_{\beta} \sum_{k=1}^{n} \beta_k \left(\sum_{i=1}^{n} \frac{y_{ik}^2}{y_{k1}} \right)}, \tag{3.11}$$

fullfilling the side contraints

$$\boxed{\beta_i \geq 0, \ \beta_1 = 1}$$

and

$$\boxed{\sum_{k=1}^{n} \beta_k y_{ik} y_{jk} \geq 0}.$$

At first sight, this second formulation of the optimization problem might seem a bit more complex/confusing since we introduced several new matrices and variables. But in fact, the only change is that we maximize now the trace instead of the determinant (trace is easier to compute as it is just a sum). This formulation is better since, we have a *linear* program, which makes it easier to solve. And we have fewer contraints than before, because we merged some of the contraints into the objective function.

Let $B = \text{diag}(\beta_1, \ldots, \beta_n)$. Then a solution β of (3.11) gives an optimal matrix $S_{\text{opt}} = D^{-1}YBY^T$ resulting in the smallest possible rebinding effect.

53

Conclusion

A nontrivial rebinding effect can be estimated only if the kinetics Q_c of a system is nonreversible.

3.4 Approach for nonreversible processes

With the tools from section 2.4 (Schur Decomposition and Gen-PCCA) we give an approach how the problem of computing the minimal rebinding effect can be solved for non-reversible processes (NESS processes).

Transfer Operator

We are given the transfer operator $\mathcal{P}$ from (3.4), but from theorem 1.12 we know that the transfer operator of a nonreversible process is not self-adjoint. Thus, some problems can occur, as presented in section 2.4, like complex eigenvalues.

Schur Decomposition

In order to obtain a set of vectors fulfilling the required conditions (invariant subset + orthogonality), we compute the Schur decomposition instead of the eigendecomposition.

In contrast to the previous section, where we computed the eigenfunctions of a reversible transfer operator, we cannot compute a real Schur decomposition for a continuous operator. That's why we need to discretize the transfer operator $\mathcal{P}$ before we can continue.

Having computed a discretized matrix $P \in \mathbb{R}^{N \times N}$ out of $\mathcal{P}$, we can compute its Schur decomposition in order to get membership functions as a linear combination from the real Schur vectors.

The dominant Schur vectors are real and orthogonal and thus can be used in the algorithm Gen-PCCA.

Galerkin Projection

Now that we have computed the membership vectors with the help of Gen-PCCA+, we can compute the corresponding clustered transition matrix $P_c(\tau)$ respectively its matrix decomposition $S^{-1}T$.

$$P_c(\tau) = \langle \chi, \chi \rangle_\mu^{-1} \langle \chi, \mathcal{P}\chi \rangle_\mu \tag{3.12}$$

Rebinding Effect

As we did it in the previous section, we assume that we are given the transition rate matrix of a process, which could either have been measured or computed from a larger process by applying Gen-PCCA.

As before, the rebinding effect is encoded in the overlap matrix S.

4 Illustrative Examples

In order to verify the results from chapter 3, we apply them on some easy examples. On the first example, we demonstrate the relation of the minimal rebinding effect to the nonreversibility of the system. Then we present an artificial example including ligands and receptors (concentrations). Finally we analyze a matrix stemming from Raman spectroscopy. This matrix is originally not a transition matrix, but can be interpreted as such. So that is an application of the rebinding effect to a completely different area.

4.1 Rebinding Effect in terms of nonreversibility

We know that for a reversible process, $\det(S_{\mathrm{opt}}) = 1$ and thus, there exists a clustering (hard) without occuring rebinding effect.

In order to find out the role of nonreversibility to S_{opt}, we follow the approach of Weber[43] to classify the nonreversibility of a process by the real(!) Schur decomposition of the transition matrix. It can be written as $P = X_s \Lambda_s X_s^{-1}$, where the matrix X_s consist of the Schur vectors and the matrix Λ_s is an upper triangular matrix with possible 2×2-blocks on its diagonal.

For this aim, we examine the given Schur decomposition from Weber[43], but compute the corresponding transition rate matrices, instead of transition matrices.

$$\Lambda_s = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 0.99 & \epsilon & 0 & 0 \\ 0 & -\gamma & 0.98 + \delta & 0 & 0 \\ 0 & 0 & 0 & 0.005 & 0 \\ 0 & 0 & 0 & 0 & 0.001 \end{pmatrix} \tag{4.1}$$

Thus we are given a system which acts on five states. Since the Schur decomposition/eigenvalue decomposition has three dominant eigenvalues/Schur values, the process consists of three metastable sets.

Accordingly, we are interested in the minimal occurring rebinding effect, when projecting the process onto a three-dimensional subspace.

P is reversible

P is reversible if $\epsilon = \gamma = \delta = 0$ in the Schur decomposition (4.1). In that case, the Schur vectors are also eigenvectos of P.

From section 3.3, we know that the minimal rebinding effect is given by $\det(S_{\mathrm{opt}}) = 1$. However the application of PCCA+ yields an overlap matrix

$$S_{\mathrm{real}} = \begin{pmatrix} 0.8677 & 0.0061 & 0.1262 \\ 0.0058 & 0.9101 & 0.0841 \\ 0.1144 & 0.0803 & 0.8053 \end{pmatrix},$$

which results in the "real" rebinding effect $\det(S_{\text{real}}) = 0.6171$.

P is nonreversible with real eigenvalues

If we set $\epsilon = 0.004$, the matrix P becomes nonreversible, but still has real eigenvalues, since ϵ is on the upper triangle of Λ_s, while all eigenvalues are distinct (same algebraic and geometric dimension).

P is non-diagonalizable

The Schur decomposition has an upper diagonal element, while the eigenvalue 0.99 occurs algebraically twice.

P is non-reversible with complex eigenvalues

Complex eigenvalues always occur in pairs and are indicated by a complete 2×2-block in the Schur decomposition. For $\epsilon = 0.004$, $\delta = 0.01$ and $\gamma = 10^{-15}$, we get two complex eigenvalues $0.99 + 2.3 \cdot 10^{-9}i$ and $0.99 - 2.3 \cdot 10^{-9}i$.

Q has real eigenvalues

In order to find out the role of nonreversibility to S_{opt}, we begin to examine a reversible transition rate matrix Q_ϵ. It contains a parameter $\epsilon = 0$, guaranteeing its reversibility. In small time steps, we increase ϵ and thereby increase the nonreversibility of the process, measured by $\|DQ - Q^T D\|$, where $D = \text{diag}(\mu_1, \ldots, \mu_n)$ is the diagonal matrix consisting of the entries of the stationary distribution, compare characterization (1.4) of reversibility.

$$(Q_\epsilon)_{\epsilon=0,\ldots,100} = \begin{pmatrix} bla & \epsilon & 0 \\ 0 & bla & 0 \\ 0 & 0 & bla \end{pmatrix}$$

Conclusion

Correlation between the nonreversibility of a process and the minimal rebinding effect included in the system.

4.2 Artificial (bivalent) binding process

One can distinguish between a monovalent binding process and a multivalent binding process (see ...), where multivalent processes are often considered as having a better binding affinity (see..).

For the monovalent case, the mathematical modeling of its kinetics is well understood. ....

Whenever the receptor molecules are spatially preorganized, the corresponding binding process is denoted as multivalent.

(especially bivalent or polyvalent case often observed in nature) These systems are of significant interest for pharmaceutical and technical applications. If the ligands are
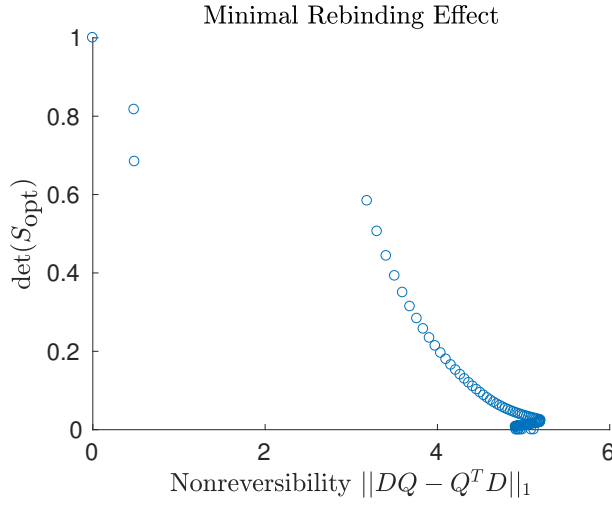
Figure 4.1: The minimal rebinding effect $\det(S_{\mathrm{opt}})$ depending on the degree of nonreversibility $\|DQ - Q^T D\|_1$ of the process/system.

linked to each other in an appropriate way to match the preorganized receptor molecules and, thus, are also presented multivalently, then extremely high binding affinities are often observed.

So we consider here a bivalent process, as the the easiest multivalent case.

4.3 Transition Rate Matrix from Raman Data

We are given the transition matrix

$$P_c = \begin{pmatrix} 8.0832573e-001 & 2.4773678e-001 & -5.6062515e-002 \\ 2.9917361e-002 & 9.7916849e-001 & -9.0858553e-003 \\ 1.8024711e-002 & -5.3149044e-003 & 9.8729019e-001 \end{pmatrix}.$$

Theoretically, the corresponding transition rate matrix Q_c should be independent of time. But for our computations, it is impossible to make the time infinitesimal small. That's why we have to choose a certain (small) lag-time, on which the transition rate matrix will be defined. For a lag-time $t = 0.05(?)$, we compute Q_c in order to solve the optimization problem (3.10) for the rebinding effect.

Conclusion

Summary   In this thesis, we have seen how we can get from a continuous stochastic process to a finite process defined on its metastable sets. The relevance of metastability and the differences between reversible and nonreversible processes have been highlighted, in order to solve an optimization problem for both kind of processes in a given molecular system.

The rebinding effect included in a receptor-ligand system stems from the projection onto a finite state space. Its relevance is based on its influence on the stability of a system. That means that a high rebinding effect increases the binding affinity of a process, which is relevant for applications like (computational) drug design where it is important to predict the exact binding affinity of ligands.

Role of overlap matrix   We want to highlight the role of the matrix S, from theorem 1.17, which is used to measure the rebinding effect. In chapter 1, it has been introduced mathematically as a part of the matrix representation of a clustered Markov process. It basically consists of the statistical weights corresponding to the macro states. In chapter 2, we have seen its relation to the overlap of the membership functions, that is S can be interpreted as an "overlap matrix", containing information about the degree of fuzzyness of the clustering. In chapter 3, we stated a lower bound for the rebinding effect in terms of the matrix S. We have seen that a high rebinding effect, and thus strongly overlapping membership functions (information encoded in S), result in a more stable system. Thus, S influences the metastability of a given system.

> Rebinding Effect $\leftrightarrow$ Overlap of Membership Functions (=Degree of fuzzyness) $\leftrightarrow$ Stability of System $\leftrightarrow$ Degree of Nonreversibility?

Role of Nonreversibility   In a reversible system, the minimal rebinding effect is always given by $\det(S_{\text{opt}}) = 1$, meaning that there is no rebinding. Such a clustering in metastable sets is hard and not fuzzy and therefore not recommended. As described in chapter 2, some overlap in the clustering is good.

In a nonreversible system however, the minimal rebinding effect is higher, meaning that the clustering includes some overlap. The higher the nonreversibility of a system, the higher the minimal rebinding effect and thus, the higher the overlap of the membership functions.

Outlook

This thesis combines two research topics that are highly discussed recently. The general field of molecular design, in particular applications in drug design like the rebinding effect, as well as the analysis of nonreversible processes are ongoing research topics with

Molecular Design Recently: reduction of dimension using metastable decompositions (PCCA+) helped to perform simulations which would have been impossible on the larger (cont.) state space.

Outlook: But still it is only possible to simulate on ...timescales.. longer timescales like several seconds, like needed for protein folding etc, are still infeasible, but with increasing computing power of supercomputers become more and more realistic.

(Noe Weber..)

Rebinding Effect In order to design drug molecules, it is important to know the exact binding affinity of a given system (set of ligands). Therefore the knowledge of the occuring rebinding effect can help to improve this design process/..

Multivalence The kinetics and design of multivalent processes is a current research project of the "Computational Molecular Design" group at ZIB.

Nonreversible Processes The study/analysis of reversible processes is very advanced, using eigendecomposition.

The approach to apply a Schur Decomposition instead has been proposed by Röblitz and further promoted by Weber. This generalized approach includes the special case of reversible processes and thus could become the generalized/improved approach to analyse stochastic processes.

Like it has been the case for reversible processes, the Schurdecomposition approach could be stretched out to continuous processes, also including nonreversible transfer operators.

In general, the study of nonreversible processes is very much at the beginning. Using Schur Decomposition could yield many results for those processes.

Many processes occuring in real life are nonreversible (which ones?).

"Rebinding Effect" for other processes The Rebinding Effect, or Recrossing Effect, can occur if we project a process. Thus, rebinding or recrossing events can happen in all other kind of processes. What is the role of it for these processes? For this reason, we   examples brought up the topic of Raman spectroscopy.

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