Master thesis

Computing the minimal rebinding effect for nonreversible processes

Zur Erlangung des akademischen Grades
Master of Science

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Berlin, den 14. Februar 2017

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1 Markov State Models

Stochastic processes, especially Markov processes, are used in a lot of applications in different areas, like biotechnology or ... . Simulations of biomolecular systems (in atomic representation) require often timescales that are far beyond the capacity of computer power currently available (for more detailed example see Anton). To get a a simulation result in a reasonable time, it makes sense to consider a reduced model of that stochastic process which maintains the relevant dynamical properties while at the same time being less complex. Such reduced models are called Markov State Models. There has been a lot of investigations/ recent research activity during the last years, see ...

In order to define/create a Markov State Model, we need at first some basic definitions of stochastic processes, especially Markov processes and how their evolution can be described using the transfer operator. The actual dimension direction of the process happens by applying a Galerkin projection onto the transfer operator. By that action, states of the original process are clustered/ grouped conveniently, such that .. properties/ transition rates?.. are preserved..

1.1 Markov Process

A Markov process is a certain/particular stochastic process with some nice properties which makes it easy to compute with. They are defined on possibly continuous state space and time, in opposite to a Markov chain where both these properties are discrete (finite state space?, transition matrix = stochastic matrix).

Transition function

From now on we will denote by $\mathbb{X} := (\mathbb{X}, \Sigma)$ a measurable space, i.e. a set $\mathbb{X}$ with some σ-algebra Σ defined on it. And $\Omega := (\Omega, \mathcal{A}, \mathbb{P})$ will be a probability space, i.e. a measurable space with a probability measure $\mathbb{P}$ defined on it; for detailed information about these basic notions see ... .

X with Borel-sigma-alg.?

A random variable $X : \Omega \to \mathbb{X}$ is a measurable function from a probability space Ω into a measurable space $\mathbb{X}$, i.e. preimages of measurable sets in $\mathbb{X}$ 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 $\mathbb{X}$, also denoted by $\mathbb{P}$, by $\mathbb{P}(A) := \mathbb{P}(X \in A) := \mathbb{P}(X^{-1}(A))$ for all $A \in \Sigma$, see (...).

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

einschränkung $\mathbb{R}^n$ + Borel?

In order to introduce Markov processes as a special case of stochastic processes, we need a tool to describe the time evolution or propagation of the 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 $p : \mathbb{T} \times \mathbb{X} \times \mathcal{B}(\mathbb{X}) \to [0, 1]$ is a transition function if it fullfills the following properties:*

assigned to a process?

i) $x \mapsto p(t, x, A)$ *is measurable for all* $t \in \mathbb{T}$ *and* $A \in \mathcal{B}(\mathbb{X})$

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

iii) $p(0, x, \mathbb{X} \setminus x) = 0$ *for all* $x \in \mathbb{X}$

iv) the Chapman-Kolmogorov equation ?

$$p(t + s, x, A) = \int_{\mathbb{X}} p(t, x, dz)p(s, z, A). \tag{1.1}$$

holds for all $t, s \in \mathbb{T}, x \in \mathbb{X}$ *and* $A \subset \mathbb{X}$.

Here the first three properties just ensure that we get reasonable (measurable) results and that that the process can only be in one state at a certain time and not make a jump (a transition in 0-time).

So 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 follows from the Chapman-Kolmogorov equation, see (...). 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 (time discrete, finite state space) is a special case of the transition function since it fullfills the above properties.

why? how?

Markov Process

Now we can define Markov processes as a special case of stochastic processes.

Definition 1.3 (Markov Process)**.** *A stochastic process $(X_t)_{t\in\mathbb{T}}$ on a state space $\mathbb{X}$ 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 $s, t \in T$, $x \in \mathbb{X}$ and $A \subset \mathbb{X}$. If that probability is independent from s, then the Markov process is called (time-)homogeneous.

We will be interested only in homogeneous processes. As we can see from the definition the time evolution of a Markov process is described by its transition function. It is a process that has "no memory" in the sense that only the last known state of the process has an influence of the future of the process; as we can see on the right side of the equation.

?

Indeed, there is a one-to-one relation between transition functions and (time-homogeneous) Markov processes, i.e. every homogeneous Markov process defines a transition function and vice versa, see Meyn and Tweedie[7, chapter 3].

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 of a Markov chain. Having introduced the notion of Markov Processes, we can now define some important properties and give some examples.

time homogeneity?

Invariant Measure

stat. distr., stat. measure

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

$$\int_{\mathbb{X}} p(t, x, A)\mu(dx) = \mu(A). \tag{1.3}$$

In other words, a measure is invariant wrt 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.

difference μ, $\mathbb{P}$?

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 w.r.t. μ if for all functions $u : \mathbb{X} \to \mathbb{R}$ with $\int_{\mathbb{X}} |u|\mu(dx) < \infty$ we have*

$$\lim_{T\to\infty} \frac{1}{T} \int_0^T u(X_t)dt = \int_{\mathbb{X}} u(x)\mu(dx). \tag{1.4}$$

for almost all initial values $X_0 = x_0$.

So a Markov process is ergodic if its time average (left side) is the same as its average over the probability space (right side), known in the field of thermodynamics as its ensemble average. In an ergodic process, the state of the process after a long time is nearly independent of its initial state.

Reversibility

A very nice property of Markov processes is reversibility. A process is reversible if it fulfills the detailed balance equation...; it means that they keep the same probability law even if their movement is considered backwards in time.

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 w.r.t. μ if*

$$\int_A p(t,x,B)\mu(dx) = \int_B p(t,x,A)\mu(dx) \tag{1.5}$$

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

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.

L^r-Spaces

As probability densities are defined about their integral properties, we need some convenient integrable spaces on which the transfer operator can act. We are going to define an operator which acts just on general L^r-spaces, i.e. r-integrable spaces.

Definition 1.7 (L^r-Spaces)**.**

$$L^r_\mu(\mathbb{X}) = \{u : \mathbb{X} \to \mathbb{R} \mid \int_{\mathbb{X}} |u(x)|^r \mu(dx) < \infty\} \tag{1.6}$$

for $1 \leq r < \infty$ and

$$L^\infty_\mu(\mathbb{X}) = \{u : \mathbb{X} \to \mathbb{R} \mid \operatorname*{ess\,sup}_{x\in\mathbb{X}} |u(x)|^r \mu(dx) < \infty\}. \tag{1.7}$$

The space L^2 is the only of the L^r-spaces which can be equipped with a canonical scalar product and thus becomes a Hilbert space (see..). For $u, v \in L^2$ we define

$$\langle u, v\rangle_\mu := \int_{\mathbb{X}} u(x)v(x)\mu(dx). \tag{1.8}$$

Now let ν_0 be the density function corresponding to the given start distribution (function). Then the density function of a subset $A \subset \mathbb{X}$ at time t is given by

$$\nu_t(A) = \int_{\mathbb{X}} \nu_0 p(t, x, A)\mu(dx). \tag{1.9}$$

On the other hand, the density ν_t is given by

$$\nu_t(A) = \int_A \nu_t(x)\mu(dx). \tag{1.10}$$

Transfer Operator and spectral properties

The two equations above yield 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.

propagates subensembles?

Definition 1.8 (Transfer Operator)**.** *Let $p : \mathbb{T} \times \mathbb{X} \times \mathcal{B}(\mathbb{X}) \to [0, 1]$ 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 $\mathcal{P}^t : L^r_\mu(\mathbb{X}) \to L^r_\mu(\mathbb{X})$ with $t \in T$ and $1 \leq r \leq \infty$ is defined via*

$$\int_A \mathcal{P}^t\nu(y)\mu(dy) = \int_{\mathbb{X}} \nu(x)p(t, x, A)\mu(dx) \tag{1.11}$$

for measurable $A \subset \mathbb{X}$.

backwards operator important?

The transfer operator is well-defined, see [4]. We will announce here already some properties of the transfer operator which will be useful in the following chapter(s). $\mathcal{P}^t$ is a Markov operator; i.e. it conserves the norm, $\|\mathcal{P}^t\nu\|_1 = \|\nu\|_1$, and is positive, $\mathcal{P}^t\nu \geq 0$ for $\nu \geq 0$. $\mathcal{P}^t\nu_0$ 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:

Markov operator?

$$\nu_0 \mapsto \nu_t = \mathcal{P}^t\nu_0. \tag{1.12}$$

Since μ is invariant(?), we have that the characteristic function of the state space is invariant under the action of $\mathcal{P}^t$, i.e.

$$\mathcal{P}^t\mathbb{1}_{\mathbb{X}} = \mathbb{1}_{\mathbb{X}} \tag{1.13}$$

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

Furthermore $\mathcal{P}$ is a bounded operator with operator norm $\|\mathcal{P}\|_2 = 1$ and $\mathcal{P}\mathbb{1}_{\mathbb{X}} = \mathbb{1}_{\mathbb{X}}$. This implies that the spectrum $\sigma(\mathcal{P})$ of $\mathcal{P}$ is contained in the unit circle of the complex plane; i.e. we have $|\lambda| \leq 1$ for all $\lambda \in \sigma(\mathcal{P}) \subset \mathbb{C}$.

why only in L2?

Transfer operator of reversible processes

The following two theorems give us an important insight about the spectrum of the transfer operator. Since self-adjointness of the transfer operator is equivalent to reversibility of the process, we know that only reversible processes guarantees a real spectrum!

Theorem 1.9. *Let $\mathcal{P}^t : L^2_\mu(\mathbb{X}) \subset L^1_\mu(\mathbb{X}) \to L^2_\mu(\mathbb{X})$ denote the propagator corresponding to the Markov process X_t. Then $\mathcal{P}^t$ is self-adjoint with repect to the scalar product $\langle \cdot, \cdot \rangle_\mu$ in $L^2_\mu(\mathbb{X})$, i.e.*

$$\langle u, \mathcal{P}^t v \rangle_\mu = \langle \mathcal{P}^t u, v \rangle_\mu \quad \text{for all } u, v \in L^2_\mu(\mathbb{X}),$$

if and only if X_t is reversible.

Proof. Huisinga[4] □

Theorem 1.10. *A self-adjoint operator has only real eigenvalues; $\sigma(\mathcal{P}) \subset \mathbb{R}$.*

Proof. □

Since the spectral radius of any transfer operator is 1, it follows for a reversible process that $\sigma(\mathcal{P}) \subset [-1, 1]$.

Later in this thesis, we are going to be very interested in examining the spectrum of the transfer operator of a given Markov process. Unfortunately we also have to consider nonreversible processes, so with a nonreal (complex) spectrum which will be a bit harder to compute with.

Infinitesimal Generator

For $\mathbb{T} = \mathbb{R}$ the Chapman-Kolmogorov property of the transition functions makes the family $\{\mathcal{P}^t\}_{t \in \mathbb{R}}$ a continuous semigroup due to def sem. grp.

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

This leads to the following definition of the the infinitesimal generator. time-indep.?

Definition 1.11 (Infinitesimal Generator)**.** *For the semigroup of propagators or forward transfer operators $\mathcal{P}^t : L^r_\mu(\mathbb{X}) \to L^r_\mu(\mathbb{X})$ with $t \in T$ and $1 \leq r \leq \infty$ we define $\mathcal{D}(L)$ as the set of all $\nu \in L^r_\mu(\mathbb{X})$ s.t. the strong limit*

$$L\nu = \lim_{t \to \infty} \frac{\mathcal{P}^t \nu - \nu}{t}.$$

exists. Then the operator $L : \mathcal{D}(L) \to L^r_\mu(\mathbb{X})$ is called the infinitesimal generator corresponding to the semigroup $\mathcal{P}^t$.

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

So the eigenvalues $\lambda_1, \ldots, \lambda_m$ of the propagator $\mathcal{P}^t$ are related to the eigenvalues $\Lambda_1, \ldots, \Lambda_m$ of the propagator L in the following way:

not yet discrete?

$$\lambda_k = \exp(t\Lambda_k) \tag{1.14}$$

for all $1 \leq k \leq m$. Their corresponding (associated) eigenfunctions are identical. So the spectrum of the infinitesimal generator is $\Lambda_1 = 0, \ldots$.

The stationary distribution of $\mathcal{P}^t$ is the solution of $Q\pi = 0$.

Further properties of infinitesimal generator/ samband med transfer operator/ spectrum p.70

1.3 Galerkin Projection

Until now we have a process on a (possibly) continuous state space. Since we are interested in computations with our process, we are now creating a smaller (namely finite) state space which shall inherit (important) properties of our original process. This can be done by a Galerkin projection/ discretization.

At first, we need to chose an appropriate/ desired/ favoured ansatz space $\chi = \{\chi_1, \ldots, \chi_n\} \subset L^2(\mu)$.

need(?) to get a discrete/finite state space

Partition of Unity

MA Jo p. 15 - 16

Now we are going to change from the original state space $\mathbb{X}$ of our process to a finite (dimensional?) subspace $D \subset \mathbb{X}$. By a projection of the transfer operator onto a finite subspace we get a stochastic process defined on this subset which preserves/ has still many properties of the original process. But in general it doesn't preserve the Markov property. But the projected process is still a good approximation of the original process.

We project our process with a Galerkin projection on a subspace with the aid of a suitable/convenient basis of the subspace.

Definition 1.12 (Partition of Unity)**.** *A family of measurable functions* $\{\chi_1, \ldots, \chi_n\} \subset L^2(\mu)$ *is called a partition of unity if the following two conditions are fullfilled:*

why L2?

i) The χ_i *are non-negative and (pairwise?) linear independent*

ii) $\sum_{i=1}^{n} \chi_i(q) = 1$ *for all* $q \in \mathbb{X}$

bei jo anders; a.e.??

Definition 1.13 (Galerkin Projection)**.** *Let $\{\chi_1, \dots, \chi_n\}$ be a partition of unity and $D = \operatorname{span}\{\chi_1, \dots, \chi_n\}$ the associated finite-dimensional ansatz space. Then the Galerkin projection onto D is defined by $Q : L^2(\mu) \to D$ by*

$$Q\nu = \sum_{k,j=1}^{n} (\langle \chi_k, \chi_j \rangle_\mu)^{-1} \langle \chi_k, \nu \rangle_\mu \chi_j. \tag{1.15}$$

A Galerkin projection can be applied on the transfer operator of a Markov process.

orthogonal projection?

Definition 1.14 (Projected Transfer Operator)**.** *Let $\mathcal{P} := \mathcal{P}^t$ be the transfer operator of a Markov process on a state space $\mathbb{X}$ with unique invariant measure μ, $\{\chi_1, \dots, \chi_n\}$ be a partition of unity and Q the Galerkin projection onto the associated subspace D. Then an operator of the form*

$$Q\mathcal{P}Q : L^2_\mu(\mathbb{X}) \to D \tag{1.16}$$

is called projected transfer operator.

The projected transfer operator can be written in an interesting way.

Theorem 1.15. *Let $\mathcal{P}$ be the transfer operator of a Markov process, $\{\chi_1, \dots, \chi_n\}$ a partition of unity and $Q\mathcal{P}Q$ the Galerkin projection of the transfer operator onto the associated subspace. Then the projected transfer operator $Q\mathcal{P}Q$ has a matrix representation*

ansatz space vs subspace

$$P = S^{-1}T, \tag{1.17}$$

where

$$S_{kj} = \frac{\langle \chi_k, \chi_j \rangle_\mu}{\langle \chi_k, \mathbb{1} \rangle_\mu} \tag{1.18}$$

and

$$T_{kj} = \frac{\langle \chi_k, \mathcal{P}\chi_j \rangle_\mu}{\langle \chi_k, \mathbb{1} \rangle_\mu}. \tag{1.19}$$

Both S and T are $n \times n$-matrices. Furthermore, they are stochastic matrices.

$\mathbb{1}_{\mathbb{X}}$?

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 property $\mathcal{P}\mathbb{1} = \mathbb{1}$ of a transfer operator:

$$\sum_{j=1}^{n} S_{kj} = \frac{\langle \chi_k, \sum_j \chi_j \rangle_\mu}{\langle \chi_k, \mathbb{1} \rangle_\mu} = \frac{\langle \chi_k, \mathbb{1} \rangle_\mu}{\langle \chi_k, \mathbb{1} \rangle_\mu} = 1, \tag{1.20}$$

$$\sum_{j=1}^{n} T_{kj} = \frac{\langle \chi_k, \mathcal{P} \sum_j \chi_j \rangle_\mu}{\langle \chi_k, \mathbb{1} \rangle_\mu} = \frac{\langle \chi_k, \mathcal{P}\mathbb{1} \rangle_\mu}{\langle \chi_k, \mathbb{1} \rangle_\mu} = 1. \tag{1.21}$$

□

Since S and T are both stochastic matrices, they have $\mathbb{1}_D$ as right eigenvectors to the eigenvalue 1. It implies that the same holds for P, i.e. the product $S^{-1}T$ is at least pseudostochastic, i.e. its rows sum up to 1. But nonnegativity is not assured since inverting S can provoke/evoke/produce/cause negative entries. The non-negativity depends on the choice of the partition of unity. There are examples s.t. $S^{-1}T$ is a stochastic matrix.

Now what is the stochastic interpretation of the previous theorem? Can we get some insight into the nature of $Q\mathcal{P}Q$? T is a transition matrix? Its Markovianity is spoiled by S? The closer S is to the unit matrix, the smaller the Recrossing effect? It will be examined later in section 2.4 after we examined the so called Recrossing effect which describes the loss of Markovianity by projecting the process/ transfer operator. By S and T, the recrossing effect can be measured.

Theorem 1.16 (Full Partition Discretization)**.** *Let $\{\chi_1, \dots, \chi_n\}$ be a partition of unity that is induced by a full partition, i.e. the χ_i are the characteristic functions of pairwise disjoint sets A_i s.t. $\cup A_i = \mathbb{X}$. Then the matrix representation P of $Q\mathcal{P}Q$ is a stochastic matrix consisting of the transition probabilities between the partition sets, i.e.*

$$P(k,l) = \mathbb{P}(X_t \in A_l \mid X_0 \in X_k). \tag{1.22}$$

Example 1.17 (Full Partition Discretization)**.** *Example: if we choose a partition as the basis of the subspace on which we want to project. Then we get a Markov chain whose states are just the partition sets. Such a Markov chain keeps/ maintains some important properties of the process on $\mathbb{X}$; the stationary distribution of the so defined Markov chain P_Q is just the projection of the invariant measure μ onto D.*

know this only after definition of galerkin proj.

There are obiously many possibilities to make a Galerkin discretization/ projection because we can define it on any arbitrary partition of unity $\chi_1, \dots, \chi_n$. In chapter 2 we are going to show how the number of clusters (= metastable sets) can be determined using the spectrum of the transfer operator (eigenvalues). Furthermore we will show how to construct functions $\chi_1, \dots, \chi_n$ (=membership functions) that give us a decomposition which is as good as possible (linear combination of eigenfunctions).

1.4 Recrossing Effect

Loss of Markov Property

By projection onto a (finite?) subspace we lose an important property of the transfer operator bzw generator; namely its Markov property. Hence, in general we have

nicht immer?

$$(P_Q)^k \neq (P^k)_Q.$$

Dieses Beispiel, in welchem das überschreiten der Barriere für den nächsten Zeitraum eine höhere Wahrscheinlichkeit einer erneuten Uberschreitung der Barriere bedeutet, wird auch als Recrossing Problem bezeichnet und ist in...

-¿ spoling Markov property???

An important question when it comes to projections of stochastic processes onto lower-dimensional state spaces is shown in the following diagram. Does it make a difference if we first project the process and then propagate it and vice versa?

$$\begin{array}{ccc} P(\tau) & \xrightarrow{\tau \to \tau k} & (P(\tau))^k \\ \Big\downarrow{\scriptstyle projection} & & \Big\downarrow{\scriptstyle projection} \\ P_C(\tau) & \xrightarrow{\tau \to \tau k} & (P_C(\tau))^k \end{array}$$

Weber shows in habilitation that under a certain Galerkin Projection using membership functions (not set-based family) leads to a commuting diagram of projection and propagation. + Markov Property is preserved? non-reversible?

Recrossing Effect

If we consider a (continuous) Markov process (X_t) and project it onto a finite-dimensional state space via a Galerkin projection, then the process can lose his Markov property; that phenomena is called the recrossing effect.

It depends on the chosen partition of unity (the new finite-dim. state space) if the recrossing effect occurs. If we chose a full partition for that ansatz space, then our projected process will maintain its Markovianity.

Error

We will present here shortly how the discretization error can be estimated in general. For our purposes that will not play an important role, since we can zurückgreifen on a transfer operator by Weber which allows a projection without(?) error.

The maximal possible error between the distributions of X_k and $._k$ (same initial distribution) is given by

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

Error can somehow be bounded by λ_1^k. Furthermore, there is a relation between smallness of the projection error and the metastability of a subdivision of the state space.

2 Metastability and Dominant Structures

In section 2.4, we already mentioned that under certain conditions (high complexity/ long-time simulations) a reduction of dimension of our process is needed. In order to be able to apply a reasonable Galerkin Projection, we are now going to introduce the concept of metastability which is a certain behaviour of the trajectory of stochastic processes that occurs in many molecular dynamic systems and describes the characteristics of rare transitions between specific subsets after a long duration of stay inside. We will see why it makes sense to choose these *metastable sets* as clustering sets in the aforementioned Galerkin Projection and how they can be detected using the spectrum of the corresponding transfer operator. We will also see that the optimal metastable decomposition is not shark/crisp but soft/fuzzy. see ..

Unfortunately, metastability of nonreversible processes is much harder to detect, since we are not guaranteed a real spectrum of the transfer operator. So we need the concept of dominant cycles instead of dominant sets. We will give a short outlook how that case could be handled.

2.1 Concept of metastability applied to MD

There exist several different definitions of metastability. Shortly said, metastability is the property of a Markov process which consists of (a decomposition into?) subsets s.t. transitions between these subsets are rare events while the duration of stay inside of each of these subsets is long. Some possible characterizations of that behaviour are based on large hitting times (see...) or small exit rates (...).

Mathematical concept of metastability

To describe the concept of metastability, it is a good way to start with so called *stable* or *invariant subsets*. A subset of the state space of a Markov process 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; i.e. $\mathbb{P}(X_{t_f} \in A \mid X_0 \in A) \approx 1$ for a convenient timescale t_f.

Obviously, being "close to 1" is a rather vague statement. But that lack of concreteness will be eliminated later, since we will only be interested in the "best" metastable decomposition, so for each metastable set we try do get that probability as close to 1 as possible. Instead, we will have to determine the number of subsets we are looking for.

Let $A_1, \ldots, A_m$ be a full partition of the state space $\mathbb{X}$. Then this partition and each of its partition sets are called *metastable* if

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

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.

Importance of metastability to MD systems

Metastability is a concept which is very important for stochastic processes describing molecular dynamic systems. Such systems/processes often have the characteristic behaviour that their trajectory stays inside of a certain conformation/region/subset for a very long time before switching/changing/exiting to another region. Furthermore, transitions between these conformations are rare. So these regions correpond to our above definition of metastable sets if we choose a convenient timescale.

Problem of long-time simulations of MD systems

As transitions between metastable sets are a rather rare event, we need to make long-time simulations of our process in order to get reasonable results about these changes of conformations. But, as mentioned in Chapter 2, long-time simulations of such complex systems are not feasible even with the best computers nowaday, see (...).

So, in order to be able to compute some long-time simulations of a given MD system, a reduction of complexity like described in section 2.4 is needed/ required. This can be achieved by a clustering of a state space. Different states of the state space will be clustered appropriately s.t. we get a process on a smaller state space.

Clustering into metastable sets

So far, we didn't mention how we should choose the clusters for the Galerkin projection, i.e. wich states of the original states should be grouped together for the reduced/projected model.

Galerkin = clustering???

As we are mainly interested (for the moment) in the long-time behaviour of our process, we are not interested in short-time transitions, i.e. transitions inside of a conformation/ metastable set. So knowing now the concept of metastability, it seems directly/intuitively appropriate/reasonable to group/cluster states of a metastable together and create a new process where each state corresponds to one of the metastable sets.

Since we want to maintain/keep the long-time-behaviour/properties of the original space/system/process, the transition probabilities of the clustered/reduced process/model should correspond to the transition rates of the original process between its metastable sets. In doing to, we get a new process which possesses the long-time-behaviour of the original process, but "forgets" its short-time-behaviour, i.e. transitions inside of a conformation.

Advantages / Disadvantages

First of all, our newly created process will have the desired property of a reduced dimension/complexity since the model acts on a (much) smaller state space while maintaining its crucial property (transitions between metastable sets = long-time behavious). So the computation effort for (long-time) simulations is definitely decreased. Furthermore, we get a better overview of our process, 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. Since fast/ short-time transitions (transitions inside conformation/ metastable set) are not our research goal, we just omit this (at least for our case!) superfluous informations. So our advantages in clustering are

i) reduction of dimension (main reason b/c otherwise computation are just not possible)

ii) better overview of the crucial behaviour of the process (rare transitions)

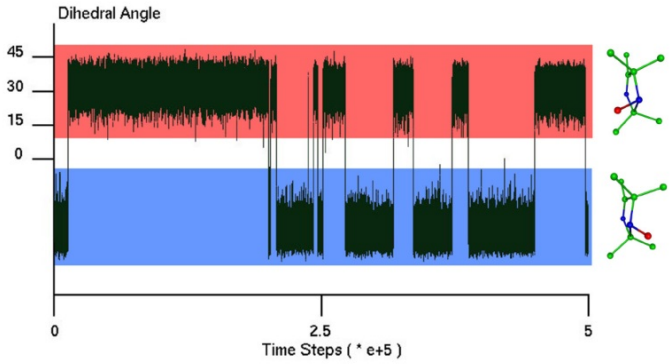
But there is also a disadvantage, as we mentioned in 2.4, by projecting a process it can lose its Markov property.

under certain/ which conditions not?

Example

To explain metastability in Molecular Dynamics, consider the following easy example, figure ... . Our system consists of ..? molecule and can take ...? values. As we can see from figure ..., showing a long-time-simulation of that process,

Disadv: no good metastability -¿ no good model?



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. Namely, the number of metastable sets can be determined by the number of eigenvalues close to 1. And the corresponding eigenfunctions allow a metastable decomposition. partition?

Existence of dominant eigenvalues

For further informations, see Kato[6]. We are interested in large eigenvalues which are close to 1 and separated from the rest of the spectrum. The *discrete spectrum* $\sigma_{\text{discr}}(\mathcal{P})$ is the set consisting of all eigenvalues $\lambda \in \sigma(\mathcal{P})$ that are isolated and of finite multiplicity. The *essential spectral radius* $r_{\text{ess}}(\mathcal{P})$ is defined as follows

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

The existence of dominant eigenvalues requires that the essential/ continuous part of the spectrum is bounded away from the dominant elements of the discrete spectrum. Let us now consider the transfer operator $\mathcal{P} = \mathcal{P}^t$ for some fixed t in the Hilbert space $L^2_\mu(\mathbb{X})$. L^1 Huisinga diss; why L^2, L^1 enough?

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. $r_{\text{ess}} < 1$.

C2 The eigenvalue $\lambda = 1$ pf $\mathcal{P}$ is simple and dominant; i.e. $\eta \in \sigma(\mathcal{P})$ with $|\eta| = 1$ implies $\eta = 1$.

We will not go into further details for which processes the two above conditions are fulfilled; some criteria about it can be found in Huisinga[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 durchmischt than having any metastable sets. Condition **C2** however is important because a transfer operator with more than one eigenvalue of absolut value 1 can be decomposed into stable/invariant sets, i.e. subsets which cannot be left. In that case we could just consider the different stable sets as independent processes. But that is not interesting for us. Instead, we want to know more about almost invariant sets and their critical/transition regions.

has periodic structures? excludes modeling and interpretation problems C2 = ergodic?

Theorem 2.1 (Schuette[12])**.** *The transfer operator $\mathcal{P} : L^2 \to L^2$ of a reversible process with properties* **C1** *and* **C2** *has the following spectrum:*

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

with $-1 < a \leq b < \lambda_n \leq \cdots \leq \lambda_1 = 1$.

why discr. rechts?

This theorem assures us the existence of a discrete set of dominant eigenvalues. In the following we will see that this property results in metastability.

Relation of dominant eigenvalues to metastable sets

The number of metastable sets can be determined by counting the dominant eigenvalues.

Relation of dominant eigenfunctions to metastable decomposition

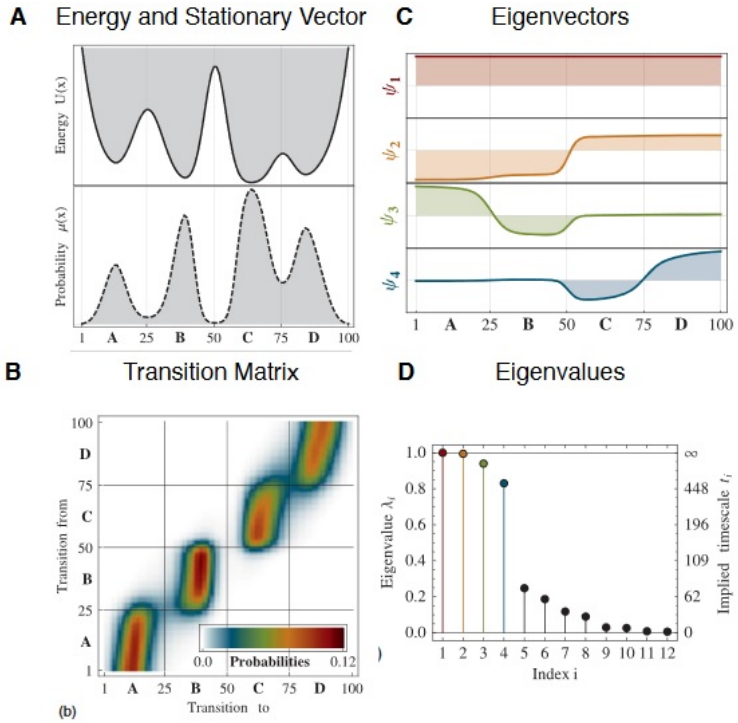
Theorem 2.2. *Each single eigenfunction induces a metastable decomposition*

Proof. □

The zeros of an eigenfunction (bzw. Vorzeichenwechsel) induce a metastable decomposition of the state space.

Different eigenfunction results in a different decomposition. (partition into sets??)

eigenfunctions vs committor functions



Disadvantages

So the spectral approach is suitable/ convenient to characterize metastability of Markov processes. But: there are two disadvantages. 1: the result is only appliable on reversible processes, because a self-adjoint transfer operator is needed in order to get real eigenvalues. 2: eigenvector(?) problem of the transfer operator has only global solutions.

2.3 Fuzzy Clustering via Membership Functions

The above considerations (metastable decomposition induced by zeros of eigenfunctions) result in a metastable full decomposition of the state space, i.e. each state is assigned to exactly one of the partition sets. We will see now, that there exist better solutions, considering/ including the fact that transition regions can belong to several metastable sets. So for this new approach (even though already examined/investigated/analyzed in recent research, see ...), there may be some overlap in the assignment of states to metastable sets.

Set-based vs. Function-based Approach

An easy intuitive approach to decompose the state space would be to determine a certain number of metastable sets which form a full partition of the state space, such that each state is assigned to exactly one of the metastable sets. The problem with that approach is that also the transition regions of the process would have to be assigned to one of these partition sets. But why would you assign a state in a transition region to one adjacent metastable set and not to the/one other? So such an assignment is not a rigoruous description of actual behaviour of the process.

So this *set-based approach* of decomposing the process has been replaced by the *function-based approach*. That means that each state of the process is assigned with a certain probability to each metastable set. That makes sense, because a state in a transition region can go with certain probabilities to different conformations.

Membership functions (=almost characteristic function)

Assuming we have already determined that our process consists of n metastable sets (by knowing its n dominant eigenvalues). We will follow the approach of [14] by defining macro states as *overlapping partial densities*. They can be identified by membership functions $\chi_1, \ldots, \chi_n : \mathbb{X} \to [0, 1]$. Each state of the original state space shall be assigned to the different macro states with a certain *degree of membership*.

Definition 2.3. *membership function χ_i = partition of unity (see 2.4) and non-negative*

Membership functions can be used to decompose the space into metastable sets. In this case, the assignment of a state to a metastable set must not be unique, but a state can belong to different metastable sets with certain probabilities(?). That model takes into consideration the existence of transitions regions which cannot be uniquely assigned to one macro state/ metastable set.

Since membership functions form a partition of unity, we can apply the Galerkin projection as defined in chapter 1. That gives us a Markov State Model where each (macro) state is a metastable set of the original process.

so far: membership fct indep. of metastable set

Example 2.4. *A characteristic function is a membership function. It induces a full partition as metastable decomposition.*

Individual eigenfunctions $\mathcal{X}$ do not overlap since they are orthogonal. But the membership functions χ_i as linear combinations of the dominant eigenfunctions might have an overlap.

Statistical Weights

For each macrostate we can define a statistical weight

$$w_i = \int_\Omega \chi_i(q)\pi_q(q)dq,$$

i.e. ....

$D = \mathrm{diag}(w_1, \ldots, w_n)$ is the diagonal matrix of the statistical weights of the membership functions

Perron Cluster Analysis

The whole approach is called Perron cluster analysis, its agorithmic realization is abbreviated as PCCA (from Perron Custer Custer Analysis).

PCCA+: robust

So now we need to choose/determine convenient/suitable membership functions s.t. the metastable decomposition becomes as good as possible. Normed eigenfunctions are one possibility (no overlap). But better: linear combinations of eigenfunctions.

only for finite matrices? or also cont. operator w/ eigenfct.?

Perron Cluster Analysis has been developed by Deuflhard et al[1] which used the sign structure of the dominant eigenvalues of the stochastic matrix. That approach has been approved by Deuflhard and Weber[2] who transformed the system of eigenvectors into a system of membership functions which results in a soft/fuzzy clustering of the state space of the original process; their algorithm is called PCCA+ (Perron Cluster Cluster Analysis).

set-based approach?

The required membership functions can be built as a linear combination $A\mathcal{X}$ of the dominant eigenfunctions (convex problem?). The algorithm PCCA+ computes the matrix A which results in the best metastable decomposition.

oder Weber und Galliat?

We are considering the set of dominant eigenvalues $\{\lambda_1, \ldots, \lambda_n\}$ with the correponding 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 $\Lambda = \mathrm{diag}(\lambda_1, \ldots, \lambda_n)$.

Let $\mathcal{X}$ be the eigenvector matrix, i.e. the i-th column of $\mathcal{X}$ is an eigenvector corresponding to the eigenvalue λ_i. Weber showed in [15] that the choice $\chi = \mathcal{X}A$ (linear combination of the eigenfunctions $\mathcal{X}$) preserves the Markov property, i.e.

why not eigenfct.?

only dom. spec.

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

jede konvexe lin.komb.?

where $A = \{A_{ij}\}_{i,j=1,\ldots,n} \in \mathbb{R}^{n\times n}$ is the solution of a convex maximization problem (PCCA+), see Weber[14]. In order to fulfill the partition of unity of each χ_i, the matrix A has to be choosen s.t. χ is row-stochastic.

bzw even: discretization error vanishes

Optimal decomposition (PCCA+)

Since there are so many possibilities membership functions (all convex combinations of dominant eigenfunctions), we want to find the solution which gives us the best decomposition into metastable sets; i.e. ...

PCCA+

Finding membership functions which result in optimal solution for metastable decomposition (but PCCA+ works only on finite state spaces(?).

There are infinitely many transformations A of the eigenvectors resulting in a soft membership matrix χ satisfying the positivity and partition of unity constraints. Consequently, we have to determine the transformation A that satisfies some optimality condition.

Do we need PCCA+ to find the best(?) membership functions. And with the help of these membership functions we can apply a Galerkin Projection?

2.4 Dominant cycles (non reversible NESS process)

Approaches for nonreversible processes

What is the dominant structure of a nonreversible process? cycle? What is egentligen the problem with nonreversible processes? non-real eigenvalues

How can the computation of dominant cycles help to detect metastable sets/ metastables cycles?

What is a metastable cycle?

Definition dominant cycle

Schur Decomposition

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 Schur vectors.

3 Rebinding Effect in a Given Kinetics

In which model are we working??? Hamiltonian (Gamma)? Hamiltonian w/ randomized momentum (Omega w/ any momentum)? Langevin? Diffusion Dynamics? ..

In this chapter we are going to examine a special type of a molecular (kinetics?) system, namely receptor-ligand systems. To describe these systems we can use all the previously defined mathematical objects.

To give a short overview about what is going to happen here. A molecular system can be described via a differential equation. The solution of this differential equation is a (Markov?) process which can be described via a transfer operator (chapter 2). This operator will be projected onto a finite-dimensional state space (Galerkin projection, chapter 2) which (maybe?) spoils the Markov Property of the process.
Here we will try to tackle this subject for nonreversible (NESS) processes also.
This chapter is mathematically based on Weber (Quantifying Rebinding Effect)..

3.1 Receptor-Ligand System

Ligand (L) can bind to a receptor (R) and form a receptor-ligand complex (LR)

together with reb. eff.

What is a molecular system? State space, Phase Space, Ensemble, Configurational Space, Conformation Space, reduced density

3.2 Rebinding Effect

The rebinding effect has been characterized as a memory effect which leads to an additional thermodynamic weight of the bound state.
In fact, a stochastic process describing a receptor-ligand molecular system IS NOT necesarrily Markovian. The Markovianity can be spoiled by the Rebinding

impact of multivalency on the rebinding effect (Weber, Chem.)

Effect. If a Receptor-Ligand system dissolves, due to the favorable spatial situation (?) it is more likely to rebing again thain to stay dissolved.

Zusammenhang zum Absatz davor?

There are several papers (...) describing the rebinding effect on a chemical and a mathematical view. In chemistry, there are several reasons/ factors for the rebinding effect discussed.

An important application of receptor-ligand processes is drug design. In short: A drug consists of ligands which should bind to the receptors of the virus. If the drug creates many bindings, the virus is "bound" and cannot attack the human (cell?) anymore. So many bindings are a favorable thing. So a high rebinding effect enhances the (overall?) binding affinity of the process/ system which is good for the efficiency of a drug. We want a high rebinding effect. So in this chapter, we examine the minimal rebinding effect for a given Kinetics. This task has been solved by Weber... for reversible processes.

How: bound -¿ unbound

3.3 Molecular Kinetics as a Projection

Mathematical description of molecular kinetics

In general, to describe molecular systems we can distinguish between two point of views: considering micro states or macro states of the system. Here, we will basically embed the theoretical concepts of chapter 1 and 2 in the physical/ chemical framework (phase space etc.).

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 configurational space $\Omega = \mathbb{R}^{3N}$ and the momentum space $\mathbb{R}^{3N}$.

The Boltzmann distribution is expressed in the form

$$\bar{\rho}(q,p) \propto \exp\left(-\beta H(q,p)\right), \tag{3.1}$$

where $\beta = 1/(k_B T)$ is the inverse of the temperature T multiplied with the Boltzmann constant k_B. The Hamilton function denoted by H is given by $H(q,p) = K(p) + V(q)$, so by the sum of the kinetic energy $K(p)$ and the potential energy $V(q)$. The Boltzmann distribution π can be decomposed as $\pi = \pi_p \pi_q$, where $\pi_p : \mathbb{R}^{3N} \to \mathbb{R}$ is the probability function of the kinetic part in the momentum space and $\pi_q : \Omega \to \mathbb{R}$ is the probability function of the potential part in the spatial/configurational space Ω. Later, we will project our dynamics onto Ω (need a *reduced density*).

see ..

Macro States

Group/cluster a collection of the micro states having the same or similar values in one observable (e.g. bound, unbound state of receptor-ligand system). By grouping micro states, the (corresponding?) macro states yield **TODO: s**tatistical weights and entropic information (?). Macro states need not be distinct sets. Approach here: overlapping partial densities, which can be identified as membership functions $\chi_1, \dots, \chi_n$.

General Approach here

In this section, we are going to describe the mathematical model which we will use to describe a molecular system and its propagation/ evolution/ time changes? As it is a stochastic process (on molecular level small arbitrary changes that cannot be described deterministically), we will get a transfer operator which describes the propagation of EACH state (=micro state) of the process. I.e. we have a state space which is enormous large.

Since we want to make computations on that process, we need to make it smaller. This can be done using the Galerkin Projection as describes in chapter 2. So we get a process on a finite state space which shold maintain the most important properties of the continuous process. (Markovianity?)

This discretization can be achieved by using membership functions (linear combinations of eigenfunctions of the transfer operator corresponding to the dominant eigenvalues). These membership functions can be computes using PCCA+. BUT: PCCA+ works only for reversible processes.

So we will at first handle only the reversible case, since it is much easier to deal with.

At the end, we get our (finite) transition matrix and/or the infinetismal generator of the process. This important tool will help us to maximize/minimize our optimization problem at the end.

Membership functions

There exists different approaches for ... set-based vs function based. Here we use membership functions which can have certain overlap.

here overlap is good?

Membership functions $\chi_1, \dots, \chi_n : \Omega \to [0, 1]$ which form a partition of unity, i.e.

$$\sum_{i=1}^{n} \chi_i(q) = 1. \tag{3.2}$$

membership functions, overlapping partial densities, partition of unity

define macro states as overlapping partial densities, which can be identified as membership functions.

Statistical Weights

We can assign a statistical weight to each macro state (= membership function χ_i): and entropic information?

$$w_i = \int_\Omega \chi_i(q)\pi_q(q)dq \tag{3.3}$$

what is that good for?

Statistical weight w_i = probability to be in conformation/ (metastable) macro state i

Transfer Operator

For reversible(!) processes Weber [15] defines a transfer operator which is self-adjoint! due to the detailed balance condition. trivial?

In his thesis, Weber defined the transfer operator as follows:

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

So for the nonreversible approach we cannot use this operator? Or: we can use this operator but it is not self-adjoint anymore? (so complex eigenvalues)..

We assume that the discrete spectrum of the transfer operator 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 (see Schuette?). The corresponding eigenfunctions are denoted by $\mathcal{X} = \{\mathcal{X}_1, \ldots, \mathcal{X}_n\}$?

Relation between Transfer Operator and Markov Operator

A transfer operator $\mathcal{P}(\tau)$ also defines a (corresponding) projected Markov operator $\mathcal{P}(\bar{\tau})$ acting in configurational space Ω, see [15];

$$\bar{\mathcal{P}}(\tau) = \pi_q \circ \mathcal{P}(\tau) \circ (\pi_q)^{-1}.$$

Discrete Markov State Model

Now we want to create a discrete Markov State Model of our process. We want the states of this dicrete model to correspont to the metastable conformations/sets of the process.

Since each of the n dominant eigenvalues of the transfer operator corresponds to a metastable set (no? because membership fct instead of set?)...

Using the dominant spectrum of the transfer operator, we want to create a discrete Markov State Model on n states. The state space of this Model should

consist of the macro states of our Molecular System and its transition behaviour should be described via a $n \times n$-transition matrix $P(\tau)$ (i.e. row-stochastic matrix).

So somehow we need to get from our continuous operator $\mathcal{P}(\tau)$ to a discrete matrix $P(\tau)$, while we want to preserve the most important properties of the process. (Markovianity?)

For doing this, we have at first to determine the size and shape of the membership function χ_i.

$$\chi_j(q) = \sum_{i=1}^{N} A_{ij} \mathcal{X}_i(q), \ j = 1, \ldots, n, \tag{3.5}$$

where $A = \{A_{ij}\}_{i,j=1,\ldots,n}$ is the solution of PCCA+ (convex maximization problem). This choice of membership functions preserves Markovianity of the process when projecting. As a linear combination of eigenfunctions, the membership functions might have an overlap!

PCCA+ can be applied only for clustering processes on finite/ discrete state spaces Ref?

Galerkin Projection

We can reduce our continuous stochastic process to a discrete process by the Galerkin projection

$$P(\tau) = (\langle \chi, \chi \rangle_\pi)^{-1} (\langle \chi, \mathcal{P}(\tau)\chi \rangle_\pi). \tag{3.6}$$

compare Theorem 1.15

In this case, we have NO discretization error. It means that $(\mathcal{P}(\tau))^k = (P(\tau))^k$. In particular, the Galerkin projection of this particular transfer operator preserves Markovianity!

Infinitesimal Generator

Using the transfer operator $\mathcal{P}(\tau)$ we can define a time-independent operator $\mathcal{Q}$ via

$$\mathcal{Q} = \lim_{\tau \to 0} \frac{\mathcal{P}(\tau) - \mathcal{I}}{\tau}. \tag{3.7}$$

,... then $\mathcal{Q}$ is the infinitesimal generator of $\mathcal{P}$:

$$\mathcal{P}(\tau) = \exp(\tau \mathcal{Q}). \tag{3.8}$$

Weber shows in [15] that such an infinitesimal generator exists for a discretization in terms of membership functions.

Since the eigenfunctions of the infinitesimal generator are the same as for the transfer operator and their eigenvalues are in the relation $\exp(\chi_i) = \lambda_i$, we can

now apply the same Galerkin Projection for the infinitesimal generator as for the transfer operator in (3.6). We get a $n \times n$-rate matrix

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

3.4 Minimizing the Rebinding Effect

For reversible processes, this problem is solved by Weber and Fackeldey [17] with the spectral approach.

With the tools from chapter 2 (Schur Decomposition) we give an approach how this problem can be solved for nonreversible processes (NESS processes) using Schur Decomposition to get rid of the possibly nonreal eigenvalues, see Djurdevac et al[3](2016).

3.5 Approach for nonreversible processes

detecting dominant cycles of the process?

Galerkin Projection

with the help of a Schur decomposition we can make the eigenvalues real???

4 Illustrative Examples

4.1 An 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.

(especialle bivalent or polyvalent case often observed in nature) These systems are of significant interest for pharmaceutical and technical applications. If the ligands are 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.

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