1 Modeling Conformational Dynamics

The chemically interesting function of many important biomolecules, like proteins or enzymes, results from their dynamical properties, particularly from their ability to undergo so–called conformational transitions [86]. The term **conformations** describes metastable global states of the molecule, in which the large scale geometric structure is understood to be conserved. While on the smallest time scale of about femto- to picoseconds molecular dynamics consists of fast oscillations or fluctuations around equilibrium positions, conformational transitions show up only on a nano- or millisecond time scale and are therefore rare events.

The classical description of molecular processes deals with the microscopic configuration of a molecule, i.e., the positions q and momenta p of all atoms, and leads to a mathematical model in terms of coupled equations of motion for all atoms in the systems (see model systems in Section 2). However, most applications of molecular dynamics are in the context of thermodynamic, not only because most experiments measure thermodynamic quantities, but also since most biomolecular processes can only be understood within a thermodynamical context.

1.1 Thermodynamics and Biomolecular Conformations

Most experiments on biomolecular systems are performed under the conditions of constant temperature T and volume. In equilibrium thermodynamics, the corresponding stationary ensemble is known as the canonical ensemble, whose density w.r.t. the Lebesgue measure $\mathrm{d}x$ we denote by f_{can}. To give an explicit formula of f_{can}, we introduce the **Hamiltonian function**

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

which denotes the internal energy of some single molecular system in state $x = (q,p)$. Here $V : \mathbf{R}^d \to \mathbf{R}$ is a differentiable potential energy function describing all interactions between the atoms, and M denotes the mass matrix[1]. The phase space of a single molecular system is given by $\mathbf{X} \subset \mathbf{R}^{6N}$, where N is the number of atoms. In most cases, it has the simpler form $\Gamma = \Omega \times \mathbf{R}^{3N}$, where Γ is called the phase space and $\Omega \subset \mathbf{R}^{3N}$ is called the position space. Within this setting, the **canonical density** f_{can} associated with the Hamiltonian H is defined as

$$f_{\mathrm{can}}(x) \;=\; \frac{1}{Z}\, \exp\left(-\beta\, H(x)\right), \tag{2}$$

where $Z = \int_\Gamma \exp\left(-\beta\, H(x)\right) \mathrm{d}x$ denotes the partition function, $\beta = 1/(k_B T)$ the inverse temperature and k_B Boltzmann's constant. Since H separates

[1] For simplicity, we assume in the following that M is the identity matrix.

into the sum of two parts depending either only on the momenta or only on the positions, the canonical density factorizes into a product of two densities $\mathcal{P}$ and $\mathcal{Q}$ depending on the momenta and the positions, respectively, only:

$$f_{\text{can}}(x) \;=\; \underbrace{\frac{1}{Z_p}\,\exp\left(-\frac{\beta}{2}\,p^T M^{-1} p\right)}_{\mathcal{P}(p)}\;\underbrace{\frac{1}{Z_q}\,\exp\left(-\beta\,V(q)\right)}_{\mathcal{Q}(q)}. \tag{3}$$

For later reference, we denote by μ_{can} and $\mu_{\mathcal{Q}}$ the probability measures induced by the densities f_{can} and $\mathcal{Q}$, respectively.

Typically, metastability w.r.t. the canonical ensemble is measured via the following two–step experiment:

1. Pre–Selection: Select from the canonical ensemble all such systems with states $x \in C$, where the subset C corresponds to some (measurable) physical property. This selection prepares a **sub–ensemble** μ_C. Physically the sub–ensemble is associated with the property C; mathematically it is associated with the subset C of the state space.

2. Transition-Counting: Fix some observation time span $\tau > 0$ and determine the relative frequency of systems within the sub–ensemble μ_C that stay in C after the time τ.

A sub–ensemble μ_C will be called **metastable** (on the timescale τ), if the fraction of systems in the sub–ensemble that stays in C after the time τ is close to 1. Hence, metastability depends on C and τ. Identifying metastable sub–ensembles mathematically necessitates the description of internal fluctuation within the canonical ensemble.

> Since equilibrium thermodynamics states nothing about the microscopic dynamics of single systems within the ensemble, we have to specify some microscopic dynamics. We will see in the next section that there is no "canonical" single system dynamics but several [31].

We will restrict our considerations to the broad class of microscopic dynamics that can be interpreted as Markov processes. This will enable us to describe internal fluctuations within the stationary ensemble by studying transfer operators induced by the Markov process, as we are going to outline in the next sections.

In the introduction we have characterized conformations as metastable large scale geometric structures. Hence, conformations are thought to be objects in the position space. However, both the canonical ensemble as well as the classical models for microscopic dynamics presented below are

defined in the phase space Γ (positions and momenta). Therefore, we have to specify the relation between metastable sub–ensembles defined in Γ and conformations, characterized in terms of the position space Ω only. In [68] the following relation is proposed:

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

In this sense, conformations contain no information on momenta, and are determined within the positions space only. With this characterization of conformations in mind, we could think of reduced microscopic models defined only in the position space Ω. Such simplified models indeed exist and will be presented below. They allow to describe internal fluctuations within the positional canonical density $\mathcal{Q}$. In agreement with the relation above, metastable sub–ensembles of reduced models are called conformations, too.

1.2 Single System Dynamics and Markov Processes

This section gives a brief mathematical description of Markovian systems. For a detailed introduction see, e.g., [18, 52, 55].

Consider the state space $\mathbf{X} \subset \mathbf{R}^m$ for some $m \in \mathbf{Z}_+$ equipped with the Borel σ–algebra $\mathcal{A}$ on $\mathbf{X}$. The evolution of a single microscopic system is supposed to be given by a **homogeneous Markov process** $X_t = \{X_t\}_{t\in\mathbf{T}}$ in continuous or discrete time with $\mathbf{T} = \mathbf{R}_+$ or $\mathbf{T} = \mathbf{Z}_+$, respectively. We write $X_0 \sim \mu$, if the Markov process X_t is initially distributed according to μ, i.e., if $\mathbf{P}[X_0 \in A] = \mu(A)$ for every $A \in \mathcal{A}$, and $X_0 \sim x$ if $\mu = \delta_x$ for the dirac measure at x. The motion of X_t is given in terms of a **stochastic transition function** p according to

$$p(t, x, A) \quad = \quad \mathbf{P}[X_{t+s} \in A \,|X_s = x], \tag{4}$$

for every $t, s \in \mathbf{T}$, $x \in \mathbf{X}$ and $A \in \mathcal{A}$. The map $p : \mathbf{T} \times \mathbf{X} \times \mathcal{B}(\mathbf{X}) \to [0, 1]$ has the following properties

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

(ii) $A \mapsto p(t, x, A)$ is a probability measure for every $t \in \mathbf{T}$ and $x \in \mathbf{X}$.

(iii) $p(0, x, \mathbf{X} \setminus \{x\}) = 0$ for every $x \in \mathbf{X}$.

(iv) the Chapman–Kolmogorov equation

$$p(t + s, x, A) \quad = \quad \int_{\mathbf{X}} p(t, x, \mathrm{d}z)\, p(s, z, A) \tag{5}$$

holds for every $t, s \in \mathbf{T}$, $x \in \mathbf{X}$ and $A \in \mathcal{A}$.

The relation between Markov processes and stochastic transition functions is one–to–one, i.e., every homogeneous Markov process defines a stochastic transition function satisfying properties (i) to (iv), and vice versa [52, Chapter 3]. We say that the Markov process X_t admits an **invariant probability measure** μ, or μ is invariant w.r.t. the Markov process, if

$$\int_{\mathbf{X}} p(t,x,A)\mu(\mathrm{d}x) \quad = \quad \mu(A) \tag{6}$$

for every $t \in \mathbf{T}$ and $A \in \mathcal{A}$ [52, Chapter 10]. Note that the invariant probability measure needs not be unique. A Markov process X_t is called **reversible** w.r.t. an invariant probability measure μ, if

$$\int_A p(t,x,B)\mu(\mathrm{d}x) \quad = \quad \int_B p(t,x,A)\mu(\mathrm{d}x) \tag{7}$$

for every $t \in \mathbf{T}$ and $A, B \in \mathcal{A}$. If μ is unique, X_t is simply called reversible. For the special case of a stochastic transition function being absolutely continuous w.r.t. μ, the Markov process X_t is reversible, if $p(t,x,y) = p(t,y,x)$ for every $t \in \mathbf{T}$ and μ–a.e. $x, y \in \mathbf{X}$.

1.3 Ensemble Dynamics and Transfer Operators

Based on the assumption that the microscopic dynamics is given by a homogeneous Markov process we are now able to introduce a Markov operator that allows to describe internal fluctuations within the stationary ensemble.

The basic idea is the following: Consider all systems within the stationary ensemble μ with states in some subset $C \in \mathcal{A}$ (see pre–selection step in Section 1.1). This sub–ensemble of systems is distributed according to the probability measure

$$\nu_0(A) \quad = \quad \frac{1}{\mu(C)} \int_A \mathbf{1}_C(x)\mu(\mathrm{d}x),$$

where $\mathbf{1}_C$ denotes the characteristic function of the subset C. In other words, the sub–ensemble corresponds to the density $\hat{\mathbf{1}}_C = \mathbf{1}_C/\mu(C)$ w.r.t. to μ. Since every single microscopic system evolves according to the dynamics of the Markov process, the distribution of the sub–ensemble at time $t \in \mathbf{T}$ is given by the probability measure

$$\begin{aligned} \nu_t(A) \quad &= \quad \int_{\mathbf{X}} \mathbf{P}[X_t \in A | X_0 = x] \; \nu_0(\mathrm{d}x) \\ &= \quad \int_{\mathbf{X}} \hat{\mathbf{1}}_C(x) \, p(t,x,A) \; \mu(\mathrm{d}x). \end{aligned} \tag{8}$$

Therefore, the relative frequencies of systems within the sub–ensemble that stay in C after the observation time span τ (see transition counting step in

Section 1.1) is determined by $\nu_\tau(C)$. Note that (8) for the special choice of $C = \mathbf{X}$, and hence $\nu_0 = \mu$ becomes $\nu_t(A) = \int_X p(t,x,A)\mu(\mathrm{d}x)$. Since the canonical ensemble μ is by assumption stationary, we have to require that $\nu_t = \mu$ for every $t \in \mathbf{T}$ and obtain

$$\int_{\mathbf{X}} p(t,x,A)\mu(\mathrm{d}x) \quad = \quad \mu(A) \tag{9}$$

for every $t \in \mathbf{T}$ and $A \in \mathcal{A}$. **Thus, we will henceforth assume that the probability measure μ is invariant w.r.t. the Markov process X_t.**

Our interest is to define an operator P_t that propagates sub–ensembles in time, thus allows to describe the evolution of ν_t. Since invariance of μ implies that $\nu_t \ll \mu$ whenever $\nu_0 \ll \mu$ [60, Chapter 4], we consider the operator on the space of measures that are absolutely continuous w.r.t. μ—or equivalently, on the space of densities w.r.t. μ—rather than on the space of arbitrary probability measures. To do so, we introduce the Banach spaces of equivalence classes of measurable functions

$$L^r(\mu) \quad = \quad \left\{ u : \mathbf{X} \to \mathbf{C} : \int_{\mathbf{X}} |u(x)|^r \mu(\mathrm{d}x) < \infty \right\}. \tag{10}$$

for $1 \leq r < \infty$ and

$$L^\infty(\mu) \quad = \quad \left\{ u : \mathbf{X} \to \mathbf{C} : \mu\text{-}\operatorname*{ess\,sup}_{x \in \mathbf{X}} |u(x)| < \infty \right\}$$

with corresponding norms $\| \cdot \|_r$ and $\| \cdot \|_\infty$, respectively. Due to Hölder's inequality we have $L^r(\mu) \subset L^s(\mu)$ for every $1 \leq s \leq r \leq \infty$. Based on the initially given motivation, we define the **semigroup of propagators** or forward transfer operators $P_t : L^1(\mu) \to L^1(\mu)$ with $t \in \mathbf{T}$ according to

$$\int_A P_t v(y)\ \mu(\mathrm{d}y) \quad = \quad \int_{\mathbf{X}} p(t,x,A) v(x) \mu(\mathrm{d}x) \tag{11}$$

for $A \in \mathcal{A}$. As a consequence of the invariance of μ, the characteristic function $\mathbf{1}_{\mathbf{X}}$ of the entire space is an invariant density of P_t, i.e., $P_t \mathbf{1}_{\mathbf{X}} = \mathbf{1}_{\mathbf{X}}$. Furthermore, P_t is a Markov operator, i.e., P_t conserves norm: $\|P_t v\|_1 = \|v\|_1$ and positivity: $P_t v \geq 0$ if $v \geq 0$, which is a simple consequence of the definition. Using the propagator in the context of the initially given motivation, we see that the sub–ensemble ν_t, originating from ν_0 at time $t = 0$, is distributed according to

$$\nu_t(A) \quad = \quad \int_{\mathbf{X}} P_t \hat{\mathbf{1}}_A(x) \mu(\mathrm{d}x).$$

Consequently, $P_t \hat{\mathbf{1}}_A$ is the density of ν_t w.r.t. μ. The semigroup of propagators mathematically models the physical phenomena of evolution of sub–ensembles in time.

In the theory of Markov processes a different semigroup of operators is considered. We will call it[2] the **semigroup of backward transfer operators** $T_t : L^\infty(\mu) \to L^\infty(\mu)$ with $t \in \mathbf{T}$, defined by

$$T_t u(x) \;=\; \mathbf{E}_x[u(X_t)] \;=\; \int_{\mathbf{X}} u(y) p(t,x,\mathrm{d}y). \tag{12}$$

As a consequence of property (ii) of the stochastic transition function, we have $T_t \mathbf{1}_{\mathbf{X}} = \mathbf{1}_{\mathbf{X}}$ for every $t \in \mathbf{T}$. Both operators are closely related via the duality bracket

$$\langle v, u \rangle_\mu \;=\; \int_{\mathbf{X}} v(x) u(x) \mu(\mathrm{d}x)$$

for $v \in L^1(\mu)$ and $u \in L^\infty(\mu)$, namely $\langle P_t v, u \rangle = \langle v, T_t u \rangle$. Thus, the backward transfer operator is the adjoint of the propagator: ${P_t}^* = T_t$. Since $L^1(\mu)$ is a proper subset of the dual of $L^\infty(\mu)$, we have $P_t \subsetneq T_t^*$, hence P_t is not the adjoint of T_t. As a consequence, it is much easier to relate properties of P_t to T_t than vice versa. If the Markov process corresponds to a deterministic dynamical system, the propagator and the backward transfer operator are known as the Frobenius–Perron and the Koopman operator, respectively [46].

Propagators associated with reversible Markov processes are of particular interest, since they possess additional structure on the Hilbert space $L^2(\mu)$. Such propagators will be called reversible, too. Note that the propagator is well–defined on any Banach space $L^r(\mu)$ for $1 \le r < \infty$ with $\|P\|_r \le 1$, see [62] and cited reference.

Proposition 1.1 *Let $P_t : L^2(\mu) \subset L^1(\mu) \to L^2(\mu)$ denote the propagator corresponding to the Markov process X_t. Then P_t is self–adjoint w.r.t. the scalar product $\langle \cdot, \cdot \rangle_\mu$ in $L^2(\mu)$, i.e.,*

$$\langle u, P_t v \rangle_\mu \;=\; \langle P_t u, v \rangle_\mu; \qquad t \in \mathbf{T}$$

for every $u, v \in L^2(\mu)$, if and only if X_t is reversible.

Proof: For $u, v \in L^2(\mu)$ we have

$$\begin{aligned}
\langle u, P_t v \rangle_\mu &= \int_{\mathbf{X}} u(y) \overline{P_t v(y)} \mu(\mathrm{d}y) \;=\; \int_{\mathbf{X}} \int_{\mathbf{X}} u(y) \overline{v(x) p(t,x,\mathrm{d}y)} \mu(\mathrm{d}x) \\
&= \int_{\mathbf{X}} \int_{\mathbf{X}} u(y) \overline{v(x)} p(t,y,\mathrm{d}x) \mu(\mathrm{d}y) \;=\; \int_{\mathbf{X}} P_t u(x) \overline{v(x)} \mu(\mathrm{d}x) \\
&= \langle P_t u, v \rangle_\mu,
\end{aligned}$$

[2]The nomenclature is motivated by the fact that the forward transfer operator is for some model systems related to a reweighted version of the forward Kolmogorov equation, while the backward transfer operator is related to the backward Kolmogorov equation (see the Langevin and the Smoluchowski equation in Sections 2.3 and 2.4, respectively).

where the first identity in the second line is due to reversibility of the Markov process. The reversed implication is just a rearrangement of the calculation. □

We want to close this section with a remark about the mathematical model used to describe internal fluctuations within the canonical ensemble. Physical experiments on molecular ensembles allow to measure relative frequencies in the canonical ensemble μ. Assuming, as in our case, that μ has the form

$$\mu(\mathrm{d}x) \quad = \quad f(x)\mathrm{d}x,$$

i.e., is absolutely continuous w.r.t. the Lebesgue measure $\mathrm{d}x$, physical experiments correspond to the densities of the form

$$v_{\mathrm{phys}}(x) \quad = \quad \hat{\mathbf{1}}_C(x)f(x)$$

w.r.t. the Lebesgue measure $\mathrm{d}x$. Whenever physicists use the phrase "probability density" they refer to v_{phys} rather than to densities

$$v_{\mathrm{math}}(x) \quad = \quad \hat{\mathbf{1}}_C(x)$$

w.r.t. probability measure μ, as we do. As will become apparent later, it is mathematically advantageous to consider the semigroup of propagators acting on densities v_{math} rather than on v_{phys}. However, it should be clear that results obtained in either of the two pictures can be transformed into the other.