Path-metadynamics: A computational study of conformational transitions in proteins

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In this chapter we present the theoretical background of different molecular dynamics methods developed for the study of rare events in complex systems. We start with the description of the molecular dynamics (MD) method for the direct computation of atomic motions during a molecular transition. We review the concept of rare events and the limitations faced by MD to study long timescale transitions. Starting from key concepts to understand the mechanism of a rare event, such as reaction coordinates, committor probabilities and transition states, we review the well known umbrella sampling and metadynamics methods for the calculation of free energy landscapes. We review briefly the theory on the rate constant calculation using free energy and transition path concepts. Finally, within the framework of transition path theory (TPT), we give an overview of the string method and finite temperature string method developed for the computation of transition pathways in complex and high-dimensional spaces. The aim of this chapter is to provide an overview of the challenges, and the current advanced sampling methods related to the computation of transition paths and free energy landscapes of conformational transitions. This sets the stage for the methodological advances and their applications to activated transitions in proteins that we present in the following chapters of the thesis.
2-1 Molecular dynamics

Molecular Dynamics (MD) is a computational method to calculate the time dependent behaviour of a classical many-body system. MD is routinely used to investigate equilibrium and transport properties of molecules and their complexes. The method computes the atomic motions of molecules by obtaining the trajectory in time of a classical system of $N$ atoms interacting under the action of a potential $U(\mathbf{q}^n)$ \cite{1; 2}. In this approach the positions and the velocities of the atoms are computed by integrating Newton’s equations of motion,

$$\mathbf{F}_i = m_i \ddot{\mathbf{q}}_i : \mathbf{F}_i = -\nabla_i U(\mathbf{q}^n) \quad (2.1)$$

Where $\mathbf{F}_i$, $m_i$ and $\mathbf{q}_i$ are the force, the mass and the position of the particle $i$ in the system, and $\nabla_i$ indicates the gradient of the potential with respect to the position $\mathbf{q}_i$. In MD, the equations of motion are integrated by using a numerical algorithm to iteratively find the trajectory of the system using a time step $\Delta t$.

There are some criteria to decide what is a good algorithm to integrate the equations of motion in MD: 1) the algorithm must follow the law of conservation of energy, 2) it should obey time reversibility and 3) it should conserve the volume of the phase-space. The class of integrators that satisfy these criteria are known as symplectic algorithms and they are designed to find the numerical solution for the evolution of a Hamiltonian system in the phase space, described by the equations of motion in classical mechanics (Eq. 2.1). Additionally, it is desirable to obtain accuracy for large time steps, because the longer the time steps we use, the fewer evaluations of the force required and the higher the efficiency (in computational time) of the numerical integration. Computing the forces is typically the most expensive step of the MD simulation because it involves the calculation of the force contribution of all the neighbour particles acting on every particle. The most common algorithms that fulfil these conditions include the velocity-Verlet algorithm \cite{3} and the Leap-Frog \cite{4} algorithm which are based on the original Verlet method \cite{5}. The Verlet algorithm uses a Taylor expansion to calculate the position of a particle $i$ at a time $t + \Delta t$,

$$\mathbf{q}_i(t + \Delta t) = \mathbf{q}_i(t) + \dot{\mathbf{q}}_i \Delta t + \frac{F_i(t)}{2m} \Delta t^2 + \frac{\Delta t^3}{3!} \ddot{\mathbf{q}}_i + O(\Delta t^4) \quad (2.2)$$

and similarly for time $t - \Delta t$,

$$\mathbf{q}_i(t - \Delta t) = \mathbf{q}_i(t) - \dot{\mathbf{q}}_i \Delta t + \frac{F_i(t)}{2m} \Delta t^2 - \frac{\Delta t^3}{3!} \ddot{\mathbf{q}}_i + O(\Delta t^4) \quad (2.3)$$

By summing up $\mathbf{q}_i(t + \Delta t)$ and $\mathbf{q}_i(t - \Delta t)$ an approximation for the position of the system is obtained,

$$\mathbf{q}_i(t + \Delta t) = 2\mathbf{q}_i(t) - \mathbf{q}_i(t - \Delta t) + \frac{F_i(t)}{m} \Delta t^2 + O(\Delta t^4) \quad (2.4)$$
In the next step of the Verlet algorithm the velocities are calculated to compute the trajectory of the particles,

$$\dot{q}_i(t) = \frac{q_i(t + \Delta t) - q_i(t - \Delta t)}{2\Delta t} + O(\Delta t^2)$$  \hspace{1cm} (2.5)$$

In the Verlet algorithm, only the force $F_i$ at time $t$ is needed to compute the position of the particles at a time $t + \Delta t$ and the error is of the order of $\Delta t^4$. The force $F_i$ is obtained from the potential $U(q^n)$ according to Eq. 2.1. The potential $U(q^n)$ is expressed as a sum of pair potential functions known as forcefields.

Leap-Frog is another algorithm based on Verlet method to compute the trajectory of the system. In this case the velocities are calculated at half time steps

$$\dot{q}_i(t + \frac{1}{2}\Delta t) = \frac{q_i(t + \Delta t) - q_i(t)}{\Delta t}$$  \hspace{1cm} (2.6)$$

$$\dot{q}_i(t - \frac{1}{2}\Delta t) = \frac{q_i(t) - q_i(t - \Delta t)}{\Delta t}$$  \hspace{1cm} (2.7)$$

leading to an expression for the positions,

$$q_i(t + \Delta t) = q_i(t) + \Delta t \dot{q}_i(t + \frac{\Delta t}{2})$$  \hspace{1cm} (2.8)$$

An expression for the velocities at half time steps can be derived from Eq. 2.4 as

$$\dot{q}_i(t + \frac{1}{2}\Delta t) = \dot{q}_i(t - \frac{1}{2}\Delta t) + \Delta t \frac{F_i(t)}{m}$$  \hspace{1cm} (2.9)$$

However in Leap-Frog the velocities and the positions are calculated at different times, so that we can not calculate the kinetic and potential energy at the same time, and hence we can not calculate the total energy directly. It is possible to calculate the velocities and positions at the same time by using the velocity-Verlet algorithm which uses the following Taylor expansion approach to compute the trajectory of the particles:

$$q_i(t + \Delta t) = q_i(t) + \Delta t \dot{q}_i(t) + \frac{F_i(t)}{2m} \Delta t^2$$  \hspace{1cm} (2.10)$$

$$\ddot{q}_i(t + \Delta t) = \ddot{q}_i(t) + \Delta t \frac{F_i(t + \Delta t) + F_i(t)}{2m}$$  \hspace{1cm} (2.11)$$
We would imagine that the aim of these algorithms is to predict accurate trajectories of the particles in the system as a function of time, however it does not exist any integrator algorithm capable of doing this. The reason is that for most of the systems studied with MD, we are in a regime where the trajectory through the phase space (a space of 6-N dimensions of position and momentum) is sensitive to the initial conditions. Any difference in the initial conditions of the system configuration will make two trajectories diverge exponentially from each other with time. This is called the Lyapunov instability [2]. In this case, any integrator with certain small error in the initial steps of the simulation will make the trajectories diverge in time. However, this instability is not dramatic for MD, since the real aim of these simulations is not to predict exact trajectories of the system from an initial condition, but to do statistical predictions of the average behaviour of a molecular system in equilibrium. The averages from computed trajectories are realistic and, based on numerical evidence, the trajectories calculated by MD are believed to be close to the true trajectories.

With the aim of providing information about the properties of a macroscopic system, MD needs to sample the average behaviour of large enough systems. But, what do we mean by large enough? In this case, large enough refers to a number of particles approaching the well-known thermodynamic limit where fluctuations are negligible when calculating thermodynamic properties. Nowadays MD can handle as many degrees of freedom as hundreds to few million. Clearly, such small systems are far away from the thermodynamic limit. In this case, the boundary effects of the system can affect strongly the averages calculated by the simulation. This problem of finite size is strongly reduced by adding periodic boundary conditions (PBC) to the system [1; 2]. PBC consists of adding a copies of the initial box of particles in all directions, filling the space with periodic images. A given particle in the system now will interact with all the other particles in its initial box and in the surrounding periodically copied boxes. This allows us mimic an infinite bulk around the system and reduce the boundary effects. Nevertheless, calculating the forces of all these particles seems inefficient for MD simulations. Fortunately, in practice, we are often dealing with short-range interactions where we can select a cut-off distance to compute forces with the nearest neighbours of each particle.

It is important to point out the fact that the use of PBC limits the use of any shape in the system box since not all the shapes of the periodic images would fill the whole space around the system. The simplest boxes used are cubic, however by using truncated octahedron or dodecahedron shapes we can gain efficiency in the computation since the amount of solvent used in these boxes reduces by approximately 30%, while maintaining a maximum distance between each atom and its periodic image [2; 6].

The average behaviour of a system can be calculated in different statistical ensembles where we average over all the microscopic states of the systems that are consistent with certain desired macroscopic quantities. An ensemble is a collection of all possible microscopic states in the phase space satisfying the conditions of particu-
lar macroscopic or thermodynamics state. Straightforward MD samples by itself the microcanonical ensemble (NVE), which corresponds to an isolated system with a fixed number of particles $N$, a fixed volume $V$ and a fixed energy $E$. By adding a thermostat, such as the Andersen thermostat [7] or the Nosé-Hoover thermostat [8; 9], we are able to sample the canonical ensemble (NVT), where the thermodynamic state is characterized by a fixed number of atoms $N$, a fixed volume $V$ and a constant temperature $T$. Additional implementation of a barostat such as the Parrinello-Rahman barostat [10; 11] allows us to control the pressure of the system and sample, for example, an isothermal-isobaric ensemble (NPT).

2-2 Rare events

Nowadays, the timescale and system size accessible to MD are still relatively small. On modern computer clusters/supercomputers, MD simulations can reach up to a $\mu$s timescale for several tens of thousands of atoms. In principle, this time and size window accessible by MD is appropriate to study various structural and dynamical properties of the molecular system. Nevertheless, there can be other interesting dynamical processes that occur in time scales that are much longer than the molecular motion time scale and can not be studied in this way. When the time scale of a dynamical process is much larger than the molecular motion time scale, we call this process a rare event.

This separation of timescales is normally associated to an energy barrier or entropic bottleneck that separates the dynamical trajectory and the system into different stable states. Fig. 2.1 shows an schematic example of a rare event. Starting from one stable state A (represented by a minimum in the energy landscape), the system remains in state A for a long time before it finds a way to escape, to state B. Once it has found the way, the system relaxes to the second stable state relatively fast. For such a rare event, the transition time from one stable state to another is much shorter than the time the system spends in the initial stable state,

$$\tau_{\text{transition}} \ll \tau_{\text{stable}}$$

In principle, we should be able to extract all information of the dynamical properties of the system using straightforward MD. However the lifetime $\tau_{\text{stable}}$ of the stable states depends exponentially on the height of the barriers and the timescale of the process can become very large ranging from millisecond to even seconds. For the timescales accessible to MD this is impossible to compute. Special rare event methods have to be employed to study these transitions of the system.
2-3 Finding the mechanism of a rare event

As mentioned in sec. 2-1, the systems studied with MD simulations have, in general, a high dimensional phase space. This means that investigating the rare transitions between stable states in the energy landscape represents a challenge not just because of the time scale of the event but also due to the complexity that represents describing a transition in the $6N$-dimensions of positions and momentum of the phase space. Imagine for a second that we could follow the evolution of a complex system with a MD simulation and observe what happens in a movie of the dynamical trajectory. Even if the images can provide insights and some understanding about the process the system follows, important features of the mechanism can be missed or misinterpreted. For such reactive processes, it is important to localize common characteristics to the trajectories that help us to elucidate the real mechanism of a rare event.

Transition state theory (TST) has provided a simple theoretical framework that became the foundation for the development of computational techniques to study barrier-crossing events [12; 13; 14]. The basic idea of TST is that, to overcome a barrier from the reactant to the product state, the system has to visit intermediate configurations called transition states, which are saddle points on the potential energy surfaces. Additionally, it states that the reaction rate can be obtained by calculating the number of trajectories of the system crossing the dividing surface between the stable states (probability flux) where the transition state lies on [15; 16]. According to TST, the essence of the problem of rare events remains in the identification of the important degrees of freedom that characterize the transition mechanism (the so-called reaction coordinates) and what is common to the reactive transitions in a molecular event: the transition states [17; 18].
But, how do we locate the transition states and good reaction coordinates in such complex transitions? Answering these questions requires information from the ensemble of dynamical trajectories that connect stable states and the free energy landscape along the reaction coordinates. In this section we review some key concepts, computational methods and approaches to study rare reactive events.

2-3.1 Reaction coordinates: Defining collective variables to describe a transition

The high dimensionality of large conformational transitions in molecules make it very difficult to analyse the role of all the degrees of freedom in the phase space of the reactive event. One way to reduce the problem is by projecting a very high-dimensional configuration space into a few geometric parameters that are good candidates to describe some transition of interest in a system [19]. We call these parameters collective variables (CVs),

\[ z = (z_1(q^n), z_2(q^n), ..., z_N(q^n)) \] (2.13)

The collective variables are functions of the configurational space \( q^n \) and the dimensionality of the CV space is reduced to a few degrees of freedom \( N \ll n \).

Examples of CVs used in molecular transitions can be either simple parameters, such as bond lengths, angles, torsions, etc., or in the case of more complex transitions, they can be less simple parameters, such as Root Mean Square Deviation (RMSD) from a given reference structure of a protein, coordination numbers, helicity of proteins, dipole moment, etc.

The goal of these parameters is to provide a dynamically meaningful measure of the progress of a rare molecular transition from one state to another. This means that these CVs should not just measure the progress of the transition but also should be useful to provide an understanding of the dynamical process. However, how do we identify good CVs for a rare molecular reaction? Answering this question requires an analysis of reactive trajectories between stable states and the exploration of the free energy landscapes. In the next section, we aim to give an overview on how to identify the relevant order parameters and the attempts to solve the well-known ‘reaction coordinate problem’ to understand complex molecular transitions.

2-3.2 Committor probabilities

Consider a molecular system with deterministic Newtonian or Langevin dynamics (in the diffusive limit) in the configuration space \( q^n \) and evolving under the action of a potential \( U(q^n) \). Let’s assume that the system is stable over two non overlapping regions A and B identified with reactants and products respectively. In this system, the ensemble of transition paths is defined as all the trajectories that exit from region A and reach region B or vice versa [18].
Figure 2.2: Schematic representation of the committor isosurfaces \( p_B(q^n) \) in the phase space for a particular configuration \( q^n \). The committor \( p_B(q^n) \) measures the fraction of trajectories that reach the product state B starting from \( q^n \).

For such a system, the transition state ensemble (TSE) has been widely defined as the intermediate configurations of the transition path ensemble that have an equal probability of reaching reactant and product regions \([20; 21; 22; 23; 24]\). The measure of this chance of proceeding to reactants or products has been quantified by the splitting (or committor) probability introduced by Onsager in Ref. \([25]\). The committor is the probability \( p_B(q^n) \) defined as the fraction of trajectories that reach state B before going through A when started at a given configuration with random Maxwell-Boltzman velocities \( q^n \). Since along the pathways the committor changes continuously from 0 in region A to 1 in region B, the committor takes a value 0.5 at intermediate configurations. Therefore the TSE can be defined as all intermediate configurations lying on the iso-surface \( p_B(q^n) = 0.5 \) \([17]\) (See an esquematic representation of the committor in Fig. 2.2).

In principle, the committor has been stated as a perfect reaction coordinate because it provides a dynamical meaningful measure of the progress of a rare reaction from one state to another \([26]\). Unfortunately, in practice, its definition cannot be measured experimentally. The reason is that multiple initializations with the same initial position, including the water positions would be required, making measurements impossible. However, the properties of the committor surfaces provide a criterion for distinguishing a ‘good’ reaction coordinate from a ‘poor’ one. A good reaction coordinate needs to parametrize the committor in the sense that in all the configurations with constant values of \( z(q^n) \) or at least with values that are highly populated, the reaction coordinates should have the same committor surfaces \( p_B(q^n) \). On the other hand, for a poor reaction coordinate, the configurations with the same value of \( z(q^n) \) show different committor values and poorly measure the progress of the reaction. This parametrization of the committor can be tested by measuring the probability distribution of \( p_B(q^n) \) for equilibrium weighted configurations with a value \( z' \).
2-3. FINDING THE MECHANISM OF A RARE EVENT

\[ P(p_B) = \left\langle \delta[p_B - p_B(q^n)] \right\rangle_{z=z'} \tag{2.14} \]

Where the symbol \( \langle \cdot \rangle_{z=z'} \) represents the equilibrium average on a particular value \( z' \). If the reaction coordinate parametrizes the committor surfaces then for \( z(q^n) = z' \) the distribution \( P(p_B) \) will be peaked at the value of the committor \( p_B \). However, if the committor \( p_B \) shows a broad distribution or \( p_B \) is not unimodal, then there is a poor reaction coordinate. In practice, for computational simulations, the calculation of \( P(p_B) \) can be done by generating equilibrium configurations with \( z(q^n) = z' \) (for instance using the Constrained MD method [2]), followed by starting a number of MD trajectories from these configurations to measure the fraction of trajectories that end up in state B, which would represent the value of \( p_B \).

The committor probability functions as a guide to identify good reaction coordinates. In the study of rare events it is a good idea to perform the committor analysis on the transition state \( z(q^n) = z^* \) where we should find that the distribution \( P(p_B) \) is peaked at value \( p_B = 0.5 \). If the transition state does not show a unimodal distribution peak at \( p_B = 0.5 \), better reaction coordinates are required to describe the transition from A to B.

2-3.3 Free energy landscapes

Until now we have discussed a criterion to define the transition states and localize good reaction coordinates using the concepts of the transition paths and committor distributions, but we have not addressed the question of how to identify in practice the intermediate configurations that represents the transition state \( z^* \). From transition state theory (TST) [12; 13; 14] we know that the transition states are also represented by the maximum of the energy barrier that separate states A and B (of course assuming that a large barrier separates these states). When there is a large barrier separating two stable states, the system will mainly fluctuate in the potential energy wells around the minima and only rarely the system can be driven out of one minimum by a thermal fluctuation and cross the barrier. In this picture, crossing the barrier with the lowest energetic cost can be done just by crossing the potential energy barrier at the lowest point. This point is a first order saddle point where the first derivatives vanish and the curvatures are positive in all the directions except one. This saddle point is well know as the transition state (TS) where the trajectories of low temperature will most likely cross the barrier. Therefore, localizing the TS and the stable states can be done by exploring the energy landscape of systems with low temperature.

This concept of TS can be extended for complex systems with higher temperatures (where entropy effects become important) by exploring instead the free energy landscape. The free energy landscape is defined along the collective variables \( z \) as,
\[ F(z') = \frac{1}{\beta} \ln \left( \int dq^n \exp\left( -\beta U(q^n) \right) \delta(z'_1 - z_1(q^n))...\delta(z'_N - z_N(q^n)) \right) \]

(2.15)

where \( \beta = k_B T \) and the integration is done over all the configurational space \( q^n \). The free energy landscape is related to the canonical probability distribution of the system as a function of collective variables by

\[ P(z') = \frac{\exp(-\beta F(z'))}{\int dz' \exp(-\beta F(z'))} \]

(2.16)

which gives us a description of the statistics of configurations described by the collective variables (or reaction coordinates) \( z \).

This means that localizing the position of the TS in a complex system with finite temperature can be done on the basis of the free energy profile \( F(z') \). Fig. 2.3 shows a representation of the transition state \( z^* \) located at the top of the free energy barrier separating two stable states A and B. The free energy along given collective variables can be calculated using different computational methodologies. In the next section we discuss two methods used in this work which aim to compute the free energy landscape: Umbrella Sampling and Metadynamics.

**Figure 2.3:** Free energy profile along the reaction coordinate \( z \). The transition state \( z^* \) is located at the maximum of \( F(z^*) \) on top of the barrier that divides stable states regions A and B.

### 2-3.4 Rate constants

The reaction rate can be calculated from the flux of reactive trajectories that escape through the dividing hypersurface \( z(q^n) = z^* \) separating states A and B [2; 17; 27].

The instantaneous probability density of finding the system at position \( z(t) \) is given by
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\[ \rho(z, t) = \langle \delta(z - z(t)) \rangle_t \quad (2.17) \]

where \( \langle \cdots \rangle_t \) denotes the average over time \( t \) on a particular value \( z \). The probability current then can be defined by taking the time derivative of the probability density \( \rho \) and using the conservation law,

\[ \frac{\partial \rho(z, t)}{\partial t} = \langle \nabla \delta(z - z(t)) \cdot \dot{z} \rangle = \nabla \cdot J(z, t) \quad (2.18) \]

This equation gives us an expression for the instantaneous probability current

\[ J(z, t) = \langle \delta(z - z(t)) \cdot \dot{z} \rangle_t \quad (2.19) \]

In the ergodicity assumption we know that \( \lim_{t \to \infty} \rho(z, t) = \rho(z) \) and the steady-state current becomes \( \lim_{t \to \infty} J(z, t) = J(z) \) defined by,

\[ J(z, t) = \lim_{t \to \infty} \langle \delta(z - z(t)) \cdot \dot{z} \rangle_t = \langle \delta(z - z(t)) \cdot \dot{z} \rangle \quad (2.20) \]

where the brackets \( \langle \cdots \rangle \) without the subindex \( t \) indicate the equilibrium average on a particular value \( z(t) \). We can see the reaction process \( A \to B \) as an steady state where the current from \( A \) to \( B \) does not vanish and \( J \) is related with the rate of trajectories going out from \( A \) and reaching \( B \).

The current associated with reactive trajectories from \( A \) to \( B \) can be written as,

\[ J_{AB}(z, t) = \langle \delta(z - z(t)) \cdot \dot{z} h_B \rangle \quad (2.21) \]

where \( h_B \) is a function that becomes 1 if, at time \( t \), \( z(t) \) crosses to state \( B \) (or if \( z(q^n) \geq z^* \)) and is 0 otherwise. In this case we are calculating the flow where the source is \( A \) and \( B \) is a sink of reactive trajectories. This expression can help us to compute the reactive rate.

The reactive rate from state \( A \) to \( B \) is the number of reactive trajectories \( N_{AB} \) divided over the total time \( T_A \) that the trajectory has hit state \( A \) in the limit \( t \to \infty \),

\[ k_{AB} = \lim_{t \to \infty} \frac{N_{AB}}{T_A} \quad (2.22) \]

\( k_{AB} \) is in other words the probability flux of trajectories through a dividing surface \( z(q^n) = z^* \) between \( A \) and \( B \) and can be written in connection with the current as [27]
where we assume that at time $t = 0$ the trajectory crosses through the surface $z(q^n) = z^*$ dividing states A and B. $\dot{h}_A$ is in this case a function that become 1 if the trajectory $z(t)$ hits state A (or if $z(q^n) \leq z^*$) and 0 otherwise.

The above equation can be related to the free energy surface if we write it in a more suggestive way [17]

$$k_{AB} = \langle \delta(z^* - z(0)) \cdot \dot{z} \ h_B \rangle \langle \delta(z^* - z(0)) \rangle \langle h_A \rangle$$

$$\Rightarrow k_{AB} = \langle \delta(z^* - z(0)) \cdot \dot{z} \ h_B \rangle_{z = z^*} \frac{e^{-\beta F(z^*)}}{\int_{-\infty}^{z^*} e^{-\beta F(z^*)}}$$

The rate constant $k_{AB}$ depends on the free energy difference between the transition state and the stable state and can be computed with free energy estimation methods. Moreover, to define the dividing surfaces in an optimal way we can use the definition of the isocommittor surfaces in Eq. 2.14 at the transition state $z^*$ where the committor takes a value $p_B = 0.5$. In the next section we describe methods to compute the free energy and the transition paths connecting A and B.

### 2-4 Free energy methods

#### 2-4.1 Umbrella sampling

Umbrella sampling is a method developed by Torrie and Valleau in 1977 [28] to improve sampling along the reaction coordinates of systems whose two free energy minima, A and B, are separated by a large free energy barrier. This is done by adding a bias or an additional Hamiltonian term to flatten the free energy landscape between states A and B and ensure efficient sampling of the regions unfavored to be visited. The bias is then subtracted from the resulting distributions to recover the unbiased free energy differences between states A and B. In this section we discuss briefly the formalism to obtain the free energy from bias simulations using umbrella.

The bias potential $w(z(q^n))$ is an additional energy term,

$$U_{ext} = U(q^n) + w(z(q^n))$$

which depends just on the reaction coordinate $z = z(q^n)$ and provides to the MD simulation a biased distribution given by,
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\[ P_b(z') = \frac{\int \exp \left( -\beta [U(q^n) + w(z(q^n))] \right) \delta(z(q^n) - z') d^v \mathbf{q}}{\int \exp \left( -\beta [U(q^n) + w(z(q^n))] \right) d^v \mathbf{q}} \]  \hspace{1cm} (2.26)

Since the bias potential just depends on \( z \) and we can write Eq. 2.26 as,

\[ P_b(z') = \frac{\int \exp \left( -\beta w(z') \right) \delta(z(q^n) - z') d^v \mathbf{q}}{\int \exp \left( -\beta [U(q^n) + w(z(q^n))] \right) d^v \mathbf{q}} \]  \hspace{1cm} (2.27)

Using the expression for the unbiased equilibrium distribution in Eq. 2.15 and 2.16, we can express \( P(z') \) (unbiased distribution) in terms of the biased distribution \( P_b(z') \),

\[ P(z') = P_b(z') \exp[\beta w(z')] \frac{\int \exp \left( -\beta [U(q^n) + w(z(q^n))] \right) d^v \mathbf{q}}{\int \exp \left( -\beta U(q^n) \right) d^v \mathbf{q}} \]  \hspace{1cm} (2.28)

\[ = P_b(z') \exp[\beta w(z')] \frac{\int \exp \left( -\beta U(q^n) \right) \exp[\beta w(z(q^n))] d^v \mathbf{q}}{\int \exp \left( -\beta U(q^n) \right) d^v \mathbf{q}} \]  \hspace{1cm} (2.29)

From Eq. 2.28 the free energy can be evaluated exactly because \( P_b(z') \) is obtained from an MD simulation of the biased system, \( w(z') \) is given analytically and \( \langle \exp[-\beta w(z)] \rangle \) is independent of \( z' \). This means that the free energy can be written as,

\[ F(z') = -\frac{1}{\beta} \ln[P(z')] = -\frac{1}{\beta} \ln[P_b(z')] - w(z') + F' \]  \hspace{1cm} (2.30)

where \( F' = 1/\beta \ln\langle \exp[-\beta w(z)] \rangle \). This is the idea of the method to recover unbiased free energies from biased simulations.

In principle, it is possible to select an umbrella potential \( w(z) \) in such a way that all the regions from A to B are sampled in a single simulation. However, for reasons of efficiency, the free energy \( F(z') \) is usually calculated in different windows or simulations which distributions \( P(z') \) overlap. Each window has an umbrella sampling potential to improve the sampling around a particular value of \( z' \). By estimating \( F' \) in each window the overlap of the distributions is obtained and the free energy profile can be recovered along the reaction coordinate \( z' \). An efficient method to analyse umbrella sampling simulations is the well-known weighted histogram analysis method [29] which is used to calculate \( F' \) and combine the results of different windows. The fact that the bias potential connects energetically separated regions A an B gave the name of ‘umbrella’ sampling to the method.
Ideally, an optimal selection for the umbrella potential would be the inverse of the free energy \( w(z') = -F(z') \). This would allow us to calculate an exact and uniform distribution \( P_b(z') \). However, we do not know beforehand the free energy landscape and the main aim of the method is to compute it. For this reason, two kind of bias potentials are commonly proposed: (1) harmonic potentials that act along \( z' \) in each window and (2) adaptive bias potentials, which adapt an initial guess of \( w(z') \) to match \(-F(z')\) by iteratively improving the \( w(z') \) in a single window that includes all the range of \( z' \) from A to B.

For simplicity, a harmonic potential is often used. In each window the bias is applied to keep the system nearby a value \( z_i \),

\[
 w_i(z) = \frac{k}{2}(z - z_i)^2 \tag{2.31}
\]

where the subscript \( i \) indicates the window in which we put the umbrella potential. This bias potential is simple because it contains just few parameters to tune such as \( k \), the reference value \( z_i \) and the number of windows. A good estimation of the free energy along \( z \) will depend on the selection of these parameters: we should select \( k \) large enough to drive the system over the barrier between A and B, but the windows on each \( z_i \) should be distributed apart from each other in such a way that sufficient overlapping between \( P_b(z_i) \) is observed. Additionally, if \( k \) is too large we could add high energy to the system resulting in errors in the integration of the equations of motion.

### 2-4.2 Metadynamics

Metadynamics is a method developed by Laio and Parrinello [30; 31] to enhance the sampling of rare events and reconstruct the free energy landscape of a complex systems by means of a coarse grained description of the molecular system defined by a set of collective variables (CVs)[30]. These CVs are assumed to be a finite number of relevant reaction coordinates \( z(q^n) \), that provide a description of a system that evolves under the action of a potential \( U(q^n) \) whose equilibrium distribution is canonical with temperature \( 1/\beta \).

In this algorithm, a modification to the potential \( U(q^n) \) is proposed to eliminate the metastability and reconstruct the free energy \( F(z) \). This modification is done by adding a history-dependent potential term consisting of gaussians centered on the trajectory and deposited during the evolution of the system every time \( \tau_G \),

\[
 U_{\text{ext}} = U(q^n) + H \sum_{t' \leq t, t' = \tau_G} \exp \left( -\frac{[z(q^n) - z(q^n_{G})]^2}{2w^2} \right) \tag{2.32}
\]

with \( H \) and \( w \) the height and the width of the gaussians respectively, and \( z(q^n_{G}) \) denotes the trajectory of the system under the action of the extended potential \( U_{\text{ext}} = \).
Figure 2.4: An schematic representation of the Metadynamics method: The bias potential fills in the first minima along the time $t$ allowing the walker to sample the next minima and eventually, after the potential has filled in the second minima, the complete landscape.

$U + U_{bias}$. Therefore the total force at time $t$ is given by the thermodynamic force plus additional forces added by the gaussian potential,

$$f_{ext} = -\frac{\partial F(z)}{\partial z} - \frac{\partial U_{bias}}{\partial z}$$  \hfill (2.33)

If the system is metastable over two states separated by a large free energy barrier, the motion of $\mathbf{q}^n(t)$ will get trapped in the free energy minima. The bias potential is then deposited to add a repulsive force term that prevents the system of revisiting previous configurations and at the same time drives it away from the minima.

In metadynamics, it is common to see this deposition of $U_{bias}$ as a *walker* travelling through the CVs space and marking the regions of $\mathbf{q}^n$ that have already been visited. The gaussian potential will then gradually fill the minimum forcing the walker to escape to the other minimum. This procedure of deposition allows the computation of the FES. Fig. 2.4 shows a representation to metadynamics potential filling the free energy minima and allowing the system to escape and explore regions not visited.

The ability of metadynamics to reconstruct the free energy landscape $F(z')$ relies on the probability distribution for the system as a function of the CVs,

$$P(z') = \frac{\exp(-\beta F(z'))}{\int dz' \exp(-\beta F(z'))}$$  \hfill (2.34)

with the free energy given by Eq. 2.15.

If the trajectory $\mathbf{q}^n(t)$ could be computed for a very long time, $P(z)$ could be as well computed by taking the histogram of the collective variables along the trajectory,

$$P(z') = 1/t \int_0^t dt' \delta(z(\mathbf{q}^n(t')) - z')$$  \hfill (2.35)
which can be thought as,

\[
P_{\Delta z}(z') = \lim_{\Delta z \to 0} \frac{1}{\Delta z \sqrt{2\pi t}} \int_0^t dt' \exp\left(-\frac{[z' - z(q^n(t'))]^2}{2\Delta z^2}\right)
\]  

(2.36)

where \(\Delta z\) represents the width of the sequence of normal distributions centered on \(z(q^n(t'))\). Notice that in the limit of slow deposition, i.e. large \(\tau_G\), \(U_{bias}\) can be written in a continuous form,

\[
U_{bias} = H' \int_0^t \exp\left(-\frac{[z(q^n) - z(q^n_G(t'))]^2}{2 w^2}\right) dt
\]  

(2.37)

where \(H' = H/\tau_G\). The gaussian potential is then very similar to the probability distribution in Eq. 2.36 with a width \(w = \Delta z\) and hence the function defined as,

\[
F_G(z,t) = -U_{bias} = -H \sum_{t' t' = \tau_G, 2\tau_G, ...}^{t < t'} \exp\left(-\frac{[z(q^n) - z(q^n_G(t'))]^2}{2 w^2}\right)
\]  

(2.38)

is a direct approximation of \(F(z)\) in the region explored by \(z(q^n_G)\). This can also be understood in the limit of slow deposition because then the probability distribution is approximately proportional to \(\exp(-\beta(F - F_G))\). If the free energy landscape has a minimum, the gaussian potential \(U_{bias}\) will be deposited filling the minima until this minimum is flattened and \(F(z) \sim F_G(z,t)\) modulus to an additive constant. Therefore, after filling the minima with \(U_{bias}\), the only corrugations of \(F(z)\) that are not flattened are in the order of the height and width of the gaussians deposed, providing an estimation of the underlying free energy landscape [32],

\[
\lim_{t \to \infty} U_{bias} \approx -F(z)
\]  

(2.39)

2-5 Transition path methods

Most of the time the complex transitions of interest, such as large conformational transitions in proteins, require to take into account a large number of reaction co-ordinates to describe the mechanism. Due to the high dimensionality of the phase space, the energy landscape can be rugged and dense in saddle points and transition states. Unfortunately, most of the free energy methods are limited in the number of collective variables they can handle since they become computationally expensive as the number of degrees of freedom increase. Additionally, even if these methods could handle a lot of degrees of freedom, the interpretation of the landscape would become difficult to analyse. For this reason it is customary to try to explain the mechanism of the reaction by sampling statistically an unbiased ensemble of trajectories connecting two stable states [33] or by localizing one (or few) paths that represent the most likely mechanism of the complex transition in a CVs space [34; 35; 36; 37; 38; 39; 40; 41].
2-5. TRANSITION PATH METHODS

The first approach belongs to the theoretical framework developed in Transition Path Sampling [33; 42; 24] where the central idea is to generate reactive trajectories with a frequency proportional to their probability in the real transition path ensemble. The paths obtained are then analysed to get information about the relevant reaction coordinates and the rate constants. The second approach belongs to the theoretical framework developed in Transition Path Theory (TPT) [27; 26] based on the concept of isocommittor surfaces as the ideal reaction coordinate to study statistical properties of the transition pathways. From the committor probabilities one can determine the distribution of highly probable transition pathways (the reaction tubes) connecting two stable states and the rate constants.

In this work we focus on the second approach and review the efforts made to compute representative pathways of the reaction mechanisms. We discuss two different ways that TPT provides to identify isocommittor surfaces: (1) by solving the backward Kolmogorov equation [43] to identify the minimum free energy path with the string method or (2) by identifying the average path over the distribution of the path ensemble with the finite temperature string method.

2-5.1 The minimum energy path

A well-known definition to represent the most likely mechanism of the transition is the minimum energy path (MEP) [35; 27]. The MEP is the path which connects the heteroclinic orbits in the phase space between two minima A and B that are solution for the dynamics of the system $\dot{q}_i = -\nabla_i U$. The heteroclinic orbits are connected by a saddle point that represents the transition state of the reaction. By definition, the heteroclinic orbits take an infinite time to arrive and go out from the saddle point and for this reason, it is better to see the MFEP as a curve $s(\sigma)$ with $\sigma \in [0,1]$ in the configurational space connecting two minima A and B in order to avoid using the time parameter for its description.

Along the MEP, the gradient $\nabla U$ is parallel to the curve $q^n(\sigma)$ satisfying the boundary conditions $q^n(0) = q_A$ and $q^n(1) = q_B$. This means that the MEP satisfies the condition

$$\frac{dq_k}{d\sigma} \text{ is parallel to } \frac{\partial U}{\partial q_k} \quad (2.40)$$

$$\Rightarrow [\nabla U(q^n)]^\perp = 0 \quad \text{along the MEP}$$

where $\perp$ indicate the perpendicular component of $\nabla U$ to the path $q^n(\sigma)$. Eq. 2.40 indicates that the MEP is a pathway obtained by walking downhill from the saddle point in the steepest descent direction.

Now, suppose we introduce $N$ collective variables in the system which are function of the coordinate $q^n$ and are good candidates to describe a reaction of interest

$$z = (z_1(q^n), z_2(q^n), ..., z_N(q^n)) \quad (2.41)$$
CHAPTER 2. COMPUTER SIMULATIONS OF RARE EVENTS

Assuming for simplicity that \( q^n \rightarrow z \) is a change of coordinates with \( N = n \) and the potential can be written in terms of the CVs descriptors, \( U = U(z(q^n)) \), a similar condition to 2.40 can be derived for the MEP in the space of CVs,

\[
\frac{dz_i(\sigma)}{d\sigma} = \sum_{k=1}^{3n} \frac{\partial z_i(q^n(\sigma))}{\partial q_k} dq_k
\]

and using that \( \frac{dq_k}{d\sigma} \) is parallel to \( \frac{\partial U}{\partial q_k} \) along the MEP

\[
\Rightarrow \frac{dz_i(\sigma)}{d\sigma} = \sum_{k=1}^{3n} \frac{\partial z_i(q^n(\sigma))}{\partial q_k} \frac{dq_k}{d\sigma} \text{ parallel to } \sum_{k=1}^{3n} \frac{\partial z_i(q^n(\sigma))}{\partial q_k} \frac{\partial U}{\partial q_k} \quad (2.42)
\]

\[
\Rightarrow \frac{dz_i(\sigma)}{d\sigma} \text{ parallel to } \sum_{k=1}^{3n} \sum_{j=1}^{3n} \frac{\partial z_i(q^n(\sigma))}{\partial q_k} \frac{\partial z_j(q^n(\sigma))}{\partial q_k} \frac{\partial U}{\partial z_j}
\]

Eq. 2.42 is the definition of the MEP in the space of collective variables \( z \) and can be rewritten as [35],

\[
\frac{dz_i(\sigma)}{d\sigma} \text{ parallel to } M \nabla_z U(z) \quad (2.43)
\]

\[
\Rightarrow [M \nabla_z U(z)]^\perp = 0 \text{ along the MEP}
\]

where \( M \) represents the metric tensor which takes into account the stretch of the space when changing the coordinates,

\[
M_{ij} = \sum_{k=1}^{3n} \frac{\partial z_i(q^n(\sigma))}{\partial q_k} \frac{\partial z_j(q^n(\sigma))}{\partial q_k} \quad (2.44)
\]

When \( N < n \), an extra averaging is required due to the projection from the original cartesian space of \( n \) dimensions (see Ref. [35] for more details on this derivations).

2-5.2 The minimum free energy path

For systems with finite temperatures where entropic effects are relevant, the concept of the MEP can be extended to that of the minimum free energy path (MFEP) between minima \( A \) and \( B \). As we mentioned in section 2-3.3, one reason to explore the free energy landscape \( F(z) \), instead of the energy landscape, is that the free energy has a well defined probabilistic meaning \( e^{-\beta F(z)} \) which gives us the equilibrium probability density function of the CVs. Moreover, the free energy provides dynamical properties of the system, such as the saddle points which are identified as the transition states of a reaction, and the MFEP which describes the most likely reaction path in complex systems [35; 27].
2-5. TRANSITION PATH METHODS

We can follow the same argument as for the MEP in the space of collective variables introduced in Ref. [35] and define the MEFP as the pathway which satisfies the condition,

\[
\frac{dz_i(\sigma)}{d\sigma} \parallel M \nabla_z F(z) \quad (2.45)
\]

\[
\Rightarrow \quad [M \nabla_z F(z)]^\perp = 0 \quad \text{along the MFEP}
\]

where \( \perp \) indicates the component of the gradient perpendicular to the path and \( M \) is the metric tensor which components \( M_{ij} \) are defined by

\[
M_{ij}(z(\alpha)) = Z^{-1} e^{\beta F(z)} \int_0^1 \sum_{j,k} \frac{\partial z_i(q^n(\sigma))}{\partial q_k} \frac{\partial z_j(q^n(\sigma))}{\partial q_k} e^{-\beta U(q^n)} d^n q \quad (2.46)
\]

The form of the expressions 2.46 and 2.45 are justified in Ref. [35] and the appendix 2.A by solving the backward Kolmogorov equation which determines the committor and the MFEP.

2-5.3 String method to determine the MFEP

In this section we describe a computational approach known as the String Method (SM) which aims to solve the equation \([M \nabla_z F(z)]^\perp = 0\) and to find the MFEP in a set of collective variables \( z_i \). [35]

The general idea of the string method is to construct an evolution equation for a parametrized curve (the string) that connects two stable states A and B. By integrating the evolution equation for the path numerically, the SM finds a solution for the MFEP. The pathway between A and B is represented by a parametrized curve \( s(\sigma, \tau) \) where \( \sigma \in [0, 1] \) and \( \tau \) is the time evolution parameter for the string. Starting from an arbitrary path \( s(\sigma, \tau_0) \) connecting the stable states A and B, the string evolves in a steepest descent dynamics

\[
\frac{\partial s_i(\sigma, \tau)}{\partial \tau} = -[M \nabla_z F]^\perp
\]

\[
= - \sum_{j,k=1}^N P_{ij}(\sigma) M_{jk} \frac{\partial F(s(\sigma, \tau))}{\partial z_k}
\]

where \( P_{ij} \) is the projector of \( M \nabla_z F \) into the perpendicular component to the path \( s(\sigma) \) given by \( P_{ij}(\sigma) = \delta_{ij} - t_i(\sigma) t_j(\sigma) \) where \( t_i(\sigma) = \frac{\partial s_i}{\partial \sigma} | \frac{\partial s_i}{\partial \sigma} |^{-1} \). Fig. 2.5 shows an schematic representation of the evolution of an initial string on a landscape stable over two states A and B.

In the string method the boundary conditions \( s(0, \tau) = s_A \) and \( s(1, \tau) = s_B \) do not need to be imposed since the boundary points evolve by steepest descent according to
Eq. 2.47. However the boundary must follow the condition of being inside the basins of attraction of A and B respectively. This is a technical disadvantage of the method when it is applied to complex systems in which we do not have information about the free energy landscape. If the boundary points are in the basins of attraction then the path evolves towards the MFEP satisfying \( s(0, \tau) = s_A \) and \( s(1, \tau) = s_B \).

In practice the SM is applied by discretizing the string into \( M \) images \( s_{\tau_i}^m \) with \( m = 1, ..., M \) and \( \tau_i \) indicating the time index during the evolution of the string. The evolutionary equation of the string is then integrated using any standard ordinary differential equation solver (ODE) like Euler method or Runge-Kutta and the images of the string are updated by

\[
s_{\tau_i+1}^m = s_{\tau_i}^m - \delta \tau [M \nabla_z F]^\perp \tag{2.48}
\]

with \( \delta \tau \) the artificial time step of the string evolution.

Note that Eq. 2.47 has a practical problem because it does not constrain the length of the curve during the evolution. This leads to stability problems in the integration scheme since the points along the discretized string can drift one away from another into the stable states obtaining a wrong estimation of the MFEP. The difficulty can be solved by adding a reparametrization step to redistribute the nodes along the string and avoid possible stability problems.

In this work we will use a linear reparametrization [35]: In each step the nodes are redistributed along linear segments of the string in such a way that each pair of nodes are separated by the same distance. The evolution of the string then becomes,

\[
s_{\tau_i+1}^m = s_{\tau_i}^m - \delta \tau [M \nabla_z F]^\perp + \lambda \hat{\tau} \tag{2.49}
\]

where \( \hat{\tau} \) is a unitary vector tangential to the string and \( \lambda \) is a proportional factor to move the nodes along the string.

**Figure 2.5:** Schematic representation of the string method: An initial discretized pathway connecting two stable states A and B (black line with yellow nodes) evolves using steepest descent dynamics in the direction of the \( -M \nabla_z F \) towards the minimum free energy path (blue line) perpendicular to the iscommittor surfaces \( P(\sigma) \) in the zero temperature limit.
Moreover, the reparametrization step allows a simplification of the algorithm since the perpendicular component of the mean force can be written in terms of \( \nabla_z F \) and the tangential component \( \lambda \hat{\tau} \). In this version of the string method, also known as the simplified string method [44], the projector \( P_{ij}(\sigma) \) is no longer required and the evolution equation of the string can be written as

\[
\frac{\partial s_i(\sigma, \tau)}{\partial \tau} = -M \nabla_z F + \lambda \hat{\tau} \tag{2.50}
\]

### 2-5.4 Calculation of the mean force and the metric tensor using MD

In the SM, the calculation of the mean force is done using an extended potential approach,

\[
U_{\text{ext}}(q^n) = U(q^n) + \frac{k}{2} \sum_{j=1}^{N} (z_j(q^n) - z_j)^2 \tag{2.51}
\]

In the limit \( k \to \infty \) and for a time \( T \) large enough, an expression for the mean force and the metric tensor can be directly obtained from constraint MD simulations

\[
\frac{k}{T} \int_0^T [z_j(q^n) - z_j(q^n)] \, dt \approx \frac{\partial F(z)}{\partial z_j} \tag{2.52}
\]

\[
\frac{k}{T} \sum_{k=1}^{3n} \int_0^T \frac{\partial z_i(q^n)}{\partial q_k} \frac{\partial z_j(q^n)}{\partial q_k} \, dt \approx M_{ij}
\]

The details for the derivations of Eq. 2.52 can be found in [35]. The general idea of this derivation is that the expression

\[
F_k(z) = \frac{1}{\beta} \ln \left( \int dq^n \exp - \beta \left[ U(q^n) + \frac{k}{2} \sum_{j=1}^{N} (z_j(q^n) - z_j)^2 \right] \right) \tag{2.53}
\]

becomes the free energy \( F(z) \) (Eq. 2.15) for \( k \to \infty \) because in this limit the expression \( e^{-\beta \frac{k}{2}(z_j(q^n) - z_j)^2} \propto \delta(z_j(q^n) - z_j) \) is valid. Moreover, for \( T \) large enough the time average of Eq. 2.52 can be written as an ensemble average and the expression Eq. 2.52 becomes an approximation for \( \partial F(z)/\partial z_j \) and \( M_{ij}(z) \). In practice the computation of the local values of the mean force and the metric tensor in each node of the string \( s_i \) is done by constraining the dynamical trajectory of the CVs to visit the region nearby \( s_i \) with large values of \( k \) in the extended potential (Constrained MD). Fig. 2.6 shows an schematic representation of the computation of \( M_{ij} \) and \( \nabla_z F \) with constrained MD.
2.5.5 Finite temperature string method and the principal curves

At finite temperatures, the MEP and MFEP are not in general representative paths of the ensemble of transition paths from A to B since the free energy landscape of complex systems is often rugged and the transition path channels become broad. The MEP and the MFEP have difficulties to represent the most likely mechanism because they give a viewpoint of the reaction that is too local to capture the feature of the free energy landscape. Nevertheless, transition pathways often remain concentrated in one or few regions that we call transition tubes. For these cases, Vanden-Eijden et. al. [45] has suggested to go beyond the concept of the MFEP and localize the transition pathway that maximizes the probability along the iscommittor surfaces using the finite temperature string method. The assumption of this method is that, along a transition tube, the iscommittor surfaces can be approximated as hyperplanes and the probabilistic distribution of transition pathways is identical to the equilibrium distribution on each surface (see Fig. 2.7). The path $s(\sigma)$ perpendicular to iscommittor hyperplanes and connecting the maximum probability points along the surfaces is well known as the principal curve (or average transition pathway). Its main advantage over the MFEP is that it allows to look more globally to the flux of paths going through each surface.

Numerically, the finite temperature string method is an iterative procedure that starts with a discretized path $s(\sigma)$ and a hyperplane attached to each node. Then the
average position of the system is determined by performing constrained simulations on each hyperplane in order to compute the equilibrium distribution. The string is corrected to the new position until converging to the centre of the transition tube.

In this work, we start from the concept of a principal curve or average transition pathway and we build on the development and application of a new algorithm to efficiently compute highly probable pathways along the transition tubes. The next chapters describe a more detailed theoretical framework of the average transition path and the numerical algorithm developed to compute it.
2-6 References


CHAPTER 2. COMPUTER SIMULATIONS OF RARE EVENTS


Appendix 2.A  Variational formulation of the MFEP as a maximum likelihood path

In this section we review the connection between the string method, developed to localize the minimum free energy path (MFEP), and the committor probabilities. The derivations are presented in more detail in Ref. [35; 27].

2.A.1 MFEP and committor probabilities

Suppose that a system is governed by Langevin dynamics under the action of a potential $U(q^n)$

$$\dot{q}_i = v_i(t)$$
$$\dot{v}_i = -m_i^{-1} \frac{\partial U}{\partial q_i} - \gamma m_i^{-1} v_i(t) + \sqrt{2\gamma\beta^{-1}m_i^{-1}} \eta_i(t)$$ (2.54)

Where $\gamma$ is the friction coefficient, $m_i$ is the mass of the particle with position $q_i$ and $\eta_i(t)$ is an stochastic term given by the white noise satisfying which satisfies condition $\langle \eta_i(t) \eta_j(t') \rangle = \delta_{ij} \delta(t-t')$. Langevin dynamics is an approach that uses simplified models and stochastic differential equations to model the dynamics of molecular systems. The dynamics described by Eq. 2.54 attempts to extend molecular dynamics taking into account effects of friction and occasional high velocity collision that perturbs the system. This dynamics is consistent with the Boltzman-Gibbs probability density.

We are interested in understanding the mechanism of the reaction between two stable states A and B. It is known that an ideal coordinate to describe the mechanism of a reaction between A and B is the committor function $p_B(q^n, v^n)$ which measures the probability that the trajectory solution of Eq. 2.54 initiated at the point $(q^n, v^n)$ will reach B before coming back to A. This quantity measures the chance that a trajectory proceeds to the product state B, providing a way to explore the reactive trajectories and, for instance, compute the rate constants of the reaction. In probability theory the committor function is well-known for satisfying the backward Kolmogorov partial differential equation,

$$L p_B = \sum_{i=1}^{3n} v_i \frac{\partial p_B}{\partial q_i} - \frac{\partial U(q^n)}{\partial q_i} \frac{\partial p_B}{\partial v_i} + \gamma \sum_{i=1}^{3n} m_i^{-1} \left( - v_i \frac{\partial p_B}{\partial v_i} + \beta^{-1} \frac{\partial^2 p_B}{\partial v_i^2} \right) = 0$$ (2.55)

with boundary conditions $p_B(q^n, v^n) \in A = 0$ and $p_B(q^n, v^n) \in B = 1$

Where we can define the operator $L$ as

$$L = \sum_{i=1}^{3n} v_i \frac{\partial}{\partial q_i} - \frac{\partial U(q^n)}{\partial q_i} \frac{\partial}{\partial v_i} + \gamma \sum_{i=1}^{3n} m_i^{-1} \left( - v_i \frac{\partial}{\partial v_i} + \beta^{-1} \frac{\partial^2}{\partial v_i^2} \right)$$ (2.56)
CHAPTER 2. COMPUTER SIMULATIONS OF RARE EVENTS

Suppose now that the committor distribution can be written as a function of $N$ collective variables $z$ and that, in the limit of Brownian dynamics, it does not depend on the velocity, i.e., $p_B(q^n, v^n) \approx f(z_1(q^n), ..., z_N(q^n))$. This assumption about the velocity is not always true, however in the limit of no-inertia (commonly described as Brownian dynamics), when no average acceleration takes place during the simulation, this assumption is reasonable.

To derive the trajectory of the collective variables $z_i$ associated to Eq. 2.55, a variational formulation can be used \[35\]

\[
I = \int_{\mathbb{R}^n} e^{-\beta H} |Lp_B|^2 d^nq d^n v
\]

where $H(q^n, v^n) = \frac{m}{2} |v^n|^2 + U(q^n)$. Since $I \geq 0$, the solution $p_B$ of the Kolmogorov equation minimizes $I$ over all functions satisfying $p_B(q^n, v^n) \in A = 0$ and $p_B(q^n, v^n) \in B = 1$. Substituting the committor function $p_B(q^n, v^n)$ with the approximation $f(z_1(q^n), ..., z_N(q^n))$ in 2.57, only the first term in the operator 2.56 survives and we can write

\[
I = C \int_{\mathbb{R}^n} d^nq \ e^{-\beta U} \sum_{i,j=1}^N \frac{\partial f}{\partial z_i} \nabla z_i \cdot \nabla z_j \frac{\partial f}{\partial z_j}
\]

\[
I = C \int_{\mathbb{R}^n} \int_{\mathbb{R}^n} d^nq \ dz \ e^{-\beta U} \sum_{i,j=1}^N \frac{\partial f}{\partial z_i} \nabla z_i \cdot \nabla z_j \frac{\partial f}{\partial z_j} \delta(z_1 - z_1(q^n)) \cdots (z_N - z_N(q^n))
\]

\[\text{I} = CZ \int_{\mathbb{R}^n} dz \ e^{-\beta F} \sum_{i,j=1}^N \frac{\partial f}{\partial z_i} M_{ij}(z) \frac{\partial f}{\partial z_j}\]

Where $C$ is a constant, $F$ is the free energy and $M$ is the tensor defined by:

\[
M_{ij} = Z^{-1} e^{\beta F} \int_{\mathbb{R}^n} d^nq \ e^{-\beta U} \sum_{k=1}^n \frac{\partial z_i}{\partial q_k} \frac{\partial z_j}{\partial q_k} \delta(z_1 - z_1(q^n)) \cdots \delta(z_N - z_N(q^n))
\]

Minimizing Eq. 2.58 with a variational principle $\delta I = 0$ and imposing the boundary conditions $f_{z \in A} = 0$ and $f_{z \in B} = 1$, we get the Euler-Lagrange equation associated

\[
\sum_{i,j=1}^N \frac{\partial}{\partial z_i} \left( e^{-\beta F} M_{ij} \frac{\partial f}{\partial z_j} \right) = 0
\]

From Eq. 2.60 we can determine the committor function $p_B(q^n, v) \approx f(z_1(q^n), ..., z_N(q^n))$. The important point here is that Eq. 2.60 is the backward Kolmogorov equation associated to the dynamics.
2. A. VARIATIONAL FORMULATION OF THE MFEP

\[ \dot{z}(\tau) = -\sum_{j=1}^{N} M_{ij}(z(\tau)) \frac{\partial F(z)}{\partial z_j} - \beta^{-1} \frac{\partial M_{ij}}{\partial z_j} + \sqrt{2\beta^{-1}M_{ij}^{1/2}(z(\tau))} \eta_j(\tau) \quad (2.61) \]

where \( \eta_j \) is a white noise satisfying \( \langle \eta_i(\tau) \eta_j(\tau') \rangle = 0 \). In this case, the parameter \( \tau \) is an artificial time parameter to move the path on the free energy surface.

It is possible to prove that in the zero temperature limit, \( \beta \to \infty \), the most likely trajectory obtained from Eq. 2.61 is the MFEP (see appendix in Ref. [35] to find this proof). This means that the Eq. 2.61 becomes

\[ \dot{z}(\tau) = -\sum_{j=1}^{N} M_{ij}(z(\tau)) \frac{\partial F(z)}{\partial z_j} \quad (2.62) \]

and represents the evolutionary equation of the path that converges to the MFEP. This is evolution equation for the path is identical to the steepest descent dynamics used by the string method to find the MFEP.