Lecture 7

Escape rate problem and Pontrjagin's theory

CONTENTS

I. INTRODUCTION

The escape rate theory addresses the problem of estimating transition rates of metastable systems, i.e. dynamical systems whose state space is characterised by metastable regions in which the system can remain for a very long time before jumping into another metastable region, and by transition regions in which the system can only remain for a very short time. Several examples of metastable systems can be observed in nature, e.g. chemical reactions for dimerization ($A + B \rightleftharpoons C$), folding-unfolding of proteins, protein-ligand binding processes. These are high-dimensional problems, however they can be represented as one-dimensional problems characterised by a reaction coordinate and a potential energy function formed by wells (representing the metastable states) and barriers (representing the transition regions) as illustrated in fig. 1 Actually, reducing a high-dimensional problem to a one-dimensional problem is anything but simple. Several obstacles are involved, starting with the definition of what a reaction coordinate is. In addition, dynamics in full space is usually Markovian (e.g. when described by a Hamiltonian function), but reduction to one or a few dimensions

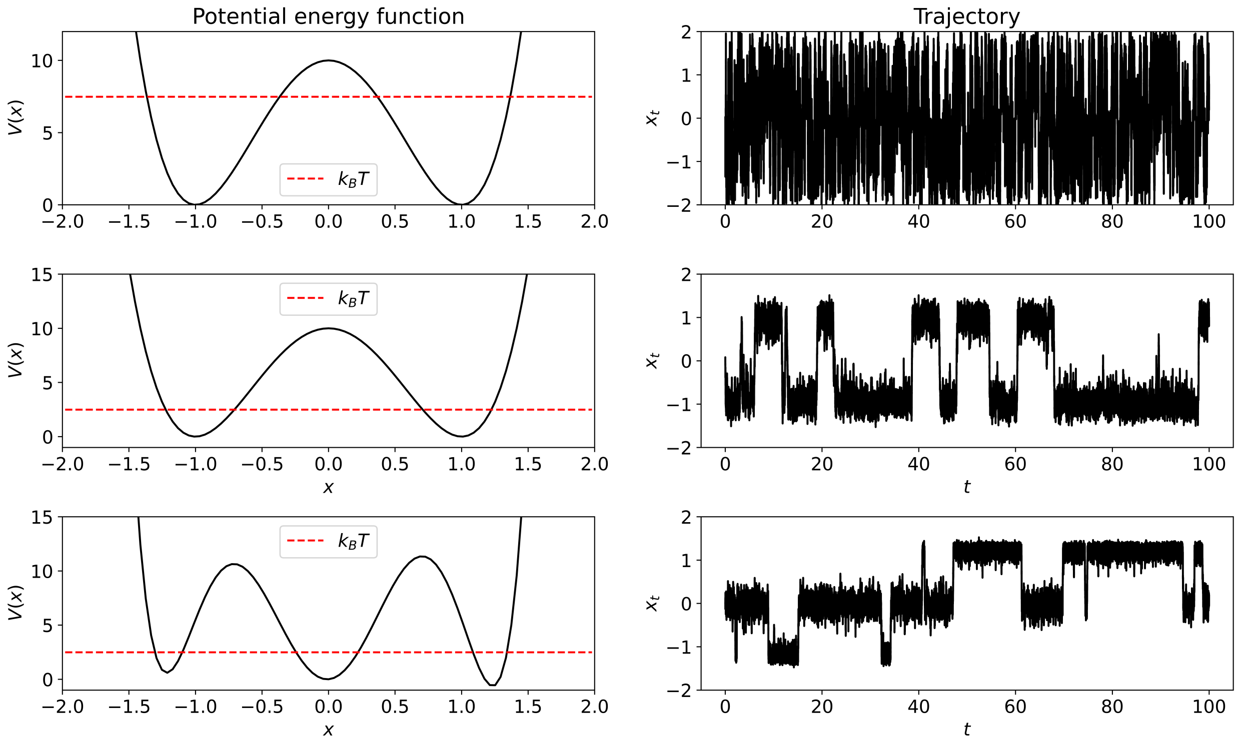

FIG. 1. Double and triple well potential. When the energy barrier $V(x)$ is several units higher than the thermal energy k_BT, the system exhibits metastability.

involves non-Markovian effects that cannot always be neglected. However, in this context, we will not deal with these problems and make the following assumptions.

- The dynamics of a $3N$-dimensional system made of N components (molecules, atoms, particles...), described by Euclidean coordinates $\mathbf{r}_i \in \mathbb{R}^3$, are fully described by a one-dimensional reaction coordinate $x := x(\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_N) : \mathbb{R}^{3N} \to \mathbb{R}$.
- The $3N$-dimensional potential energy function governing the dynamics in full space is reduced to a one-dimensional function $V(x) : \mathbb{R} \to \mathbb{R}$.
- The dynamics along the reaction coordinate is Markovian and can be described by the Langevin dynamics equation

$$\begin{cases} \dot{x}_t = v_t \\ m\dot{v}_t = -\dfrac{d}{dx}V(x_t) - m\gamma v_t + \bar{\sigma}\eta_t \,, \end{cases} \tag{1}$$

where m is the reduced mass of the system, γ is a friction coefficient, η is a Gaussian white noise which satisfies the properties

$$\begin{cases} \langle \eta_t \rangle = 0 \\ \langle \eta_t \eta_s \rangle = \delta(t-s)\,. \end{cases} \tag{2}$$

and the standard deviation

$$\bar{\sigma} = \sqrt{2k_B T m \gamma}\,. \tag{3}$$

The function of the friction and noise term is to simulate the interaction between the system and the surroundings while keeping a constant temperature.

Studying the escape rate problem means studying the dynamics of metastable systems and in particular calculating the rate of transition from one metastable region to another across the barrier. Over the last century and a half, various theories and methods have been developed. Initially, most of the methods fell into the category of model-based methods, as they were developed to study specific problems and were conditioned by the characteristics of the problem. Instead, in recent decades, data-driven techniques, or machine learning techniques, have been developed.

The first formulation of the problem dates back to Svante Arrhenius, who derived in 1884 the famous formula

$$k = Ae^{-\beta E_b}\,, \tag{4}$$

which shows that the transition rate depends exponentially on the inverse of the system temperature and the height of the barrier.

Several more elaborate theories were developed later. Here, we will deal with Pontrjagin's formula, which is valid for overdamped Langevin dynamics, i.e. in the high friction limit. Here, we summarized the Pontrjagin's theory in six steps.

- Definition of the high friction regime for Langevin dynamics.
- Introduction of the forward and backward Kolmogorov equation.
- Definition of Mean First Passage Time $\langle \tau \rangle$
- Definition of a partial differential equation for the MFPT.

- Solution of the partial differential equation for the MFPT.
- Calculation of the transition rate as

$$\langle \tau \rangle = \frac{1}{k} \, . \tag{5}$$

II. THE HIGH FRICTION REGIME OF THE LANGEVIN EQUATION

Let us now consider the Langevin equation defined in eq. 2 and assume to have a trajectory realised with a very fine time discretization in Δt timesteps. If we counted the number of collisions between the molecular system and the solvent molecules, whose action is represented by the friction term and the noise term, we would observe few collisions in the time unit Δt. Imagine now to enlarge the time unit Δt by a unitless factor $g > 1$, we would observe more collisions and the time-averaged acceleration over the timestep $g \cdot \Delta t$ would be zero. In other words, by increasing the number of collisions in the unit time, the velocity reaches a steady-state. Then, by coarse-graining the time, the term $m\dot{v}_t$ on the left-hand side of the Langevin equation can be neglected. Instead of enlarging the time unit, to increase the number of observed collisions in the unit time, we can act on the parameter γ, i.e. the friction coefficient. Increasing $\gamma \to g \cdot \gamma$ is in fact equivalent to increasing the number of collisions in the unit time Δt. This allows us, in a completely equivalent manner, to delete the term on the left-hand side of eq. 2 and write the so-called Langevin equation for the high friction regime:

$$\begin{aligned} \dot{x}_t &= -\frac{1}{m\gamma}\frac{d}{dx}V(x_t) + \frac{\bar{\sigma}}{m\gamma}\,\eta_t \qquad (6) \\ &= -\frac{1}{m\gamma}\frac{d}{dx}V(x_t) + \sigma\,\eta_t \, , \qquad (7) \end{aligned}$$

where the standard deviation $\bar{\sigma}$ has been replaced with

$$\sigma = \sqrt{\frac{2k_BT}{m\gamma}} = \sqrt{\frac{2}{\beta m\gamma}} = \sqrt{2D} \, . \tag{8}$$

III. KOLMOGOROV EQUATIONS

A. Forward Kolmogorov equations or Fokker-Planck equation

Associated to the stochastic differential equation defined in eq. 7, there exists a partial differential equation known as Fokker-Planck equation or forward Kolmogorov equation or Smoluchowski equation

$$\begin{aligned}\frac{\partial P(x,t|x_0.t_0)}{\partial t} &= \left\{\frac{\partial}{\partial x}\left[\frac{1}{m\gamma}\frac{d}{dx}V(x)\right] + D\frac{\partial^2}{\partial x^2}\right\} P(x,t|x_0.t_0) \qquad (9)\\ &= \mathcal{Q}^* P(x,t|x_0.t_0)\,, \qquad (10)\end{aligned}$$

which describes how the probability density $P(x,t;x_0.t_0)$ evolves with time given the initial condition $P(x_0.t_0) = u(x_0,t_0)$. The Fokker-Planck equation can be defined in terms of the operator $\mathcal{Q}^*$, that is the adjoint operator of $\mathcal{Q}$ that defines the backward Kolmogorov equation

$$\begin{aligned}-\frac{\partial P(x,t|x_0,t_0)}{\partial t_0} &= \left\{-\frac{1}{m\gamma}\,\frac{d}{dx}V(x)\bigg|_{x_0}\frac{\partial}{\partial x_0} + D\frac{\partial^2}{\partial x_0^2}\right\} P(x,t|x_0,t_0) \qquad (11)\\ &= \mathcal{Q}P(x,t|x_0,t_0)\,. \qquad (12)\end{aligned}$$

The backward Kolmogorov equation answers the question: how does the system evolve to reach a final distribution $P(x,t) = u(x,t)$ (final condition)? Then, instead of varying the final state x and the time t as in eq. 10, the backward Kolmogorov equation acts on the initial state x_0 and the initial time t_0. Let us now consider the case where potential V and diffusion D do not depend on time. Then, the system is temporally homogeneous and the solutions of eqs. 10 and 12 do not depend on the specific times t_0 and t, but only on their difference:

$$P(x,t|x_0,t_0) = P(x,t-t_0|x_0,0)\,, \qquad (13)$$

It follows that

$$-\frac{\partial P(x,t|x_0,t_0)}{\partial t_0} = -\frac{\partial P(x,t-t_0|x_0,0)}{\partial t_0} = \frac{\partial P(x,t-t_0|x_0,0)}{\partial t} = \frac{\partial P(x,t|x_0,t_0)}{\partial t}\,. \qquad (14)$$

Applying eq. 14 to eq. 12 yields the backward Kolmogorov equation

$$\frac{\partial P(x,t|x_0,t_0)}{\partial t} = \left\{-\frac{1}{m\gamma}\,\frac{d}{dx}V(x)\bigg|_{x_0}\frac{\partial}{\partial x_0} + D\frac{\partial^2}{\partial x_0^2}\right\} P(x,t|x_0,t_0) = L^\dagger P(x,t|x_0,t_0)\,, \qquad (15)$$

whose time-derivative depend on t.

IV. MEAN FIRST PASSAGE TIME

Within the Pontrjagin's theory the transition rate is defined as the inverse of the MFPT $\langle \tau(x_F|x_0,t_0)\rangle$, that is the mean time that the system needs to reach a final state x_F starting at x_0 at time t_0 (see fig. 2). From a mathematical point of view, it is the first moment of the distribution of trajectories that reach the point x_F starting at x_0 at time t_0:

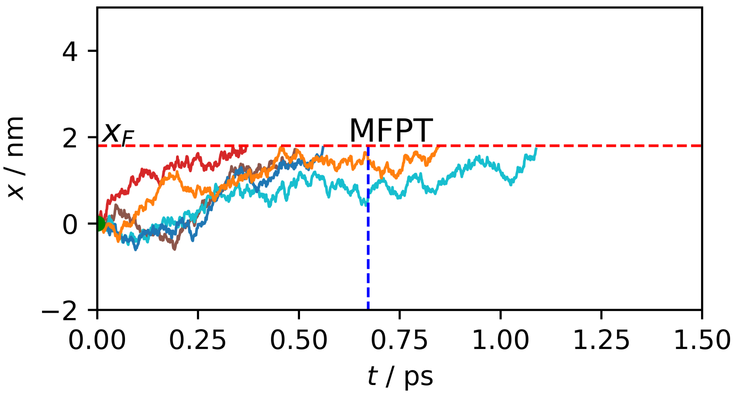

FIG. 2. MFPT.

$$\langle \tau(x_F|x_0,t_0)\rangle = \int_0^\infty d\tau\, \tau \Pi(x,\tau|x_0,t_0)\,, \tag{16}$$

where $\Pi(x_F,t|x_0,t_0)$ is the associated probability density. To define $\Pi(x_F,t|x_0,t_0)$, we first consider the solution $P(x_F,t|x_0,t_0)$ of the Fokker-Planck equation (eq. 10) and impose the absorbing boundary condition

$$P(x_F,t|x_0,t_0) = 0\,. \tag{17}$$

We denote this distribution with $P_a(x,t|x_0,t_0)$, then, we introduce the function

$$\Phi(x_F,t|x_0,t_0) = \int_{-\infty}^{x_F} dx\, P_a(x,t|x_0,t_0)\,, \tag{18}$$

which describes the fraction of trajectories starting at x_0 at time t_0, that did not reach x_F at time time t.

To better illustrate the meaning of these distributions, let us consider the pure Brownian motion (i.e. without drift) described by the Einstein diffusion equation

$$\frac{\partial P(x,t|x_0,t_0)}{\partial t} = D\frac{\partial^2 P(x,t|x_0,t_0)}{\partial x^2}\,. \tag{19}$$

The solution with infinite boundary conditions $P(x \to \pm\infty, t|x_0, t_0) = 0$, is written as

$$P(x, t|x_0, t_0) = \frac{1}{\sqrt{4\pi D(t - t_0)}} \exp\left(-\frac{(x - x_0)^2}{4\pi D(t - t_0)}\right) . \tag{20}$$

Whereas, the solution of eq. 19 applying the absorbing boundary conditions defined in eq. 17 reads

$$P_a(x, t|x_0, t_0) = P(x, t|x_0, t_0) - P(2x_F - x, t|x_0, t_0) . \tag{21}$$

These functions are illustrated in figs. 3-(b,c), and represent the distributions of trajectories in fig. 3-(a). Finally, to build $\Phi(x_F, t|x_0, t_0)$, we integrate $P_a(x, t|x_0, t_0)$ from $-\infty$ to x_F. This function, reported in fig. 3-(d), represents the amount of trajectories that have not yet reached the point x_F at time t as function of time. Then, $\Phi(x_F, t|x_0, t_0) = 1$ at time $t = t_0$ and $\Phi(x_F, t|x_0, t_0) = 0$ as $t \to \infty$. In fact, we expect that after an infinite time all trajectories will have reached the target x_F.

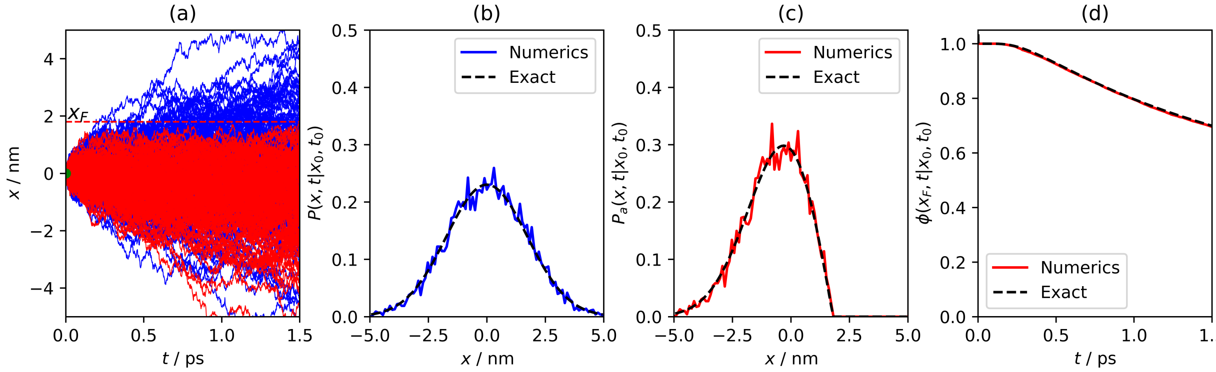

FIG. 3. (a) Ensemble of trajectories that have reached the x_F point (blue), ensemble of trajectories that did not reach the x_F point (red); (b) distribution $P(x, t|x_0, t_0)$ with infinite boundary conditions; (c) distribution $P(x, t|x_0, t_0)$ with absorbing boundary conditions; (d) fraction of trajectories that did not reach the point x_F at time t.

Consider now a small timestep $\Delta t > 0$, then the difference $\Phi(x, t|x_0, t_0) - \Phi(x, t + \Delta t|x_0, t_0) > 0$ represents the percentage of trajectories that crossed x_F between time t and $t + \Delta t$ for the first time. It follows that the quantity

$$\frac{\partial \Phi}{\partial t} = \lim_{\Delta t \to 0^+} \frac{\Phi(x, t|x_0, t_0) - \Phi(x, t + \Delta t|x_0, t_0)}{\Delta t} , \tag{22}$$

represents the probability density of the distribution of trajectories that reached x_F between time t and $t + \Delta t$ for the first time in the unit time Δt; while the opposite is the probability that the system will reach x_F for the first time between t and $t + \Delta t$:

$$\Pi(x, t|x_0, t_0) = -\frac{\partial \Phi}{\partial t} \,. \tag{23}$$

Fig. 4 shows the functions Φ, Π and the MFPT for four different values of x_F.

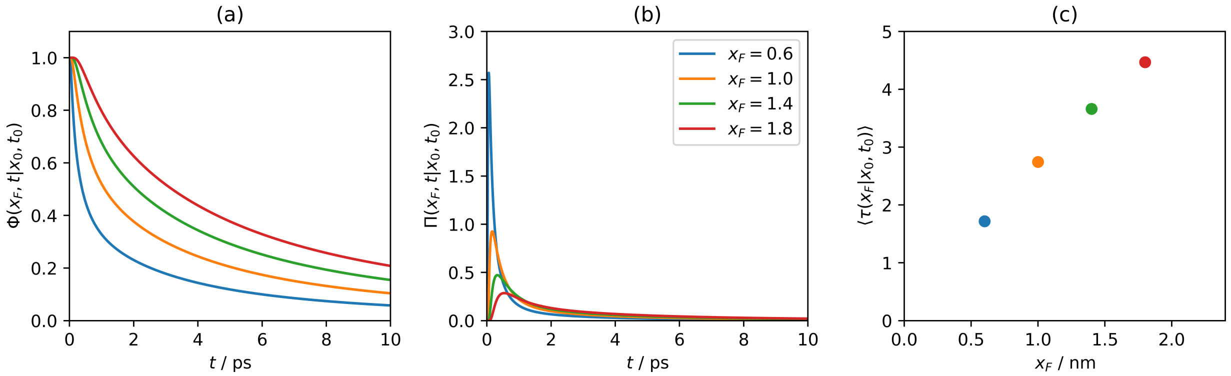

FIG. 4. (a) Function $\Phi(x_F, t|x_0, t_0)$; (b) distribution $\Pi(x_F, t|x_0, t_0)$ with infinite boundary conditions; (c) MFPT $\langle\tau(x_F|x_0, t_0)\rangle$.

Unfortunately, in most of the cases, we cannot analytically determine $\Pi(x, t|x_0, t_0)$. Thus, in order to calculate the MFPT, it is convenient to write a differential equation for $\langle\tau(x_F|x_0, t_0)\rangle$. For this purpose, we use the backward Kolmogorov equation defined in eq. 15, since the MFPT is defined for a fixed end point x_F, whereas we are interested in calculating the MFPT as the initial point x_0 varies. First of all, we rewrite the definition of MFPT (eq. 16):

$$\begin{aligned}
\langle\tau(x_F|x_0, t_0)\rangle &= \int_0^\infty d\tau\, \tau \Pi(x, \tau|x_0, t_0) && (24)\\
&= \int_0^\infty d\tau\, \tau \left(-\frac{\partial \Phi}{\partial t}\right) && (25)\\
&= -\, \tau\Phi|_0^\infty + \int_0^\infty d\tau\, \Phi(x_F, \tau|x_0, t_0) && (26)\\
&= \int_0^\infty d\tau\, \Phi(x_F, \tau|x_0, t_0) && (27)\\
&= \int_0^\infty d\tau \int_{-\infty}^{x_F} dx\, P_a(x, \tau|x_0, t_0)\,, && (28)
\end{aligned}$$

where we integrated by parts and used $\Phi(x_F, \tau|x_0, t_0) \to 0$ as $t \to \infty$. Then, we apply the operator $\mathcal{Q}$ to eq. 16:

$$\mathcal{Q}\langle\tau(x_F|x_0,t_0)\rangle = \int_0^\infty d\tau \int_{-\infty}^{x_F} dx\, \frac{\partial}{\partial\tau} P_a(x,\tau|x_0,t_0) \tag{29}$$

$$= \int_{-\infty}^{x_F} dx\ \ P_a(x,\tau|x_0,t_0)\big|_0^\infty \tag{30}$$

$$= \int_{-\infty}^{x_F} dx\ (0 - P_a(x,t_0|x_0,t_0)) = -1\,, \tag{31}$$

From the equality

$$\mathcal{Q}\langle\tau(x_F|x_0,t_0)\rangle = -1\,, \tag{32}$$

we obtain the differential equation

$$-\frac{1}{m\gamma}\frac{d}{dx}V(x)\frac{d}{dx_0}\langle\tau(x_F|x_0,t_0)\rangle + D\frac{\partial^2}{\partial x_0^2}\langle\tau(x_F|x_0,t_0)\rangle = -1\,. \tag{33}$$

The solution of eq. 33 is the Pontryagin formula:

$$\langle\tau(x_F|x_0,t_0)\rangle = \frac{1}{D}\int_{x_0}^{x_F} dx\, e^{\beta V(x)} \int_{-\infty}^{x} dx'\, e^{-\beta V(x')}\,. \tag{34}$$

A. Harmonic approximation

Assume that the potential energy function $V(x)$ is a double well potential (see fig. 5) whose left well can be approximated by an harmonic potential

$$V(x) \approx V(x_A) + \frac{1}{2}\omega_A^2 m(x-x_A)^2\,, \tag{35}$$

with

$$\omega_A^2 m = \left.\frac{d^2V}{dx^2}\right|_{x_A}\,, \tag{36}$$

around the minimum of the well x_A and by

$$V(x) \approx V(x_B) - \frac{1}{2}\omega_B^2 m(x-x_B)^2\,, \tag{37}$$

close to the barrier x_B. Then eq 34 can be approximated as

$$\langle\tau(x_F|x_0,t_0)\rangle = \frac{2\pi\gamma}{\omega_A\omega_B}\exp\left(\beta E_b\right)\,, \tag{38}$$

with $E_b = V(x_B) - V(x_A)$.

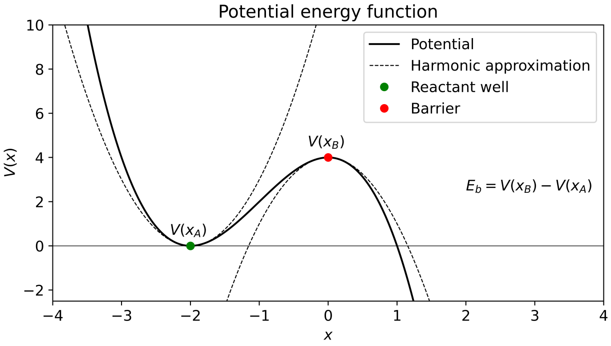

FIG. 5. Double well potential with harmonic approximation