

# Lecture 1

## Reaction rate theory and Kramers theory

### CONTENTS

I. Introduction to Reaction Rate Theory	1
A. Rate constant	2
B. Metastability and rare events	2
II. Kramers theory	4
A. Moderate and high friction regime	6
III. Low friction regime	10
A. Harmonic approximation	12
B. Action of the harmonic oscillator	13
References	14

### I. INTRODUCTION TO REACTION RATE THEORY

Reaction Rate Theory (RRT) provides a framework of sophisticated mathematical and computational techniques, such as Monte Carlo simulations, molecular dynamics simulations, and stochastic modeling approaches, for understanding the factors that influence chemical reactions characterized by transitions between two or more states. For examples, dimerization processes ( $A + B \rightleftharpoons C$ ), folding-unfolding of proteins, protein-ligand binding processes, and nucleation processes (see fig. 1). This is crucial for numerous applications, including the design of industrial processes, the development of new materials, and the study of biochemical reactions.

### A. Rate constant

The key concept in RRT is the rate constant (or transition rate), often denoted as  $k$ , which represents the speed at which a chemical reaction occurs. More precisely, if we describe a chemical reaction as a stochastic process defined on the state space  $\Omega$ , the rate is the probability per unit time for a specific transition between states  $x, y \in \Omega$ . The rate constant depends on various factors, including temperature, concentration of reactants/products, and the presence of catalysts. The first attempt to describe how these environmental factors influence the rate of a chemical reaction was due to Svante Arrhenius, who in 1899 derived the famous formula

$$k = Ae^{-\beta E_b}, \quad (1)$$

where  $k$  is the rate constant,  $A$  is a pre-exponential factor which represents the frequency of collisions between molecules in a reaction,  $E_b$  is the activation energy, i.e. the minimum energy required for a reaction to occur,  $\beta = 1/k_B T$  is a constant that depend on the Boltzmann constant  $k_B$  and the temperature  $T$  of the environment.

Over the last century and a half, more 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, researchers have developed data-driven (or machine learning) techniques that analyze and interpret large datasets produced by laboratory experiments or computer simulations to derive insights. In this seminar we will examine some of the methodologies belonging to these categories, comparing them and pointing out benefits and disadvantages.

### B. Metastability and rare events

The dynamical processes underlying chemical reactions are highly dimensional, since they are functions of a large number of atoms and molecules. However, it is convenient to represent them by means of low-dimensional potential energy functions (usually 1 or 2 dimensions) characterized by minima and maxima. The minima represent the initial and final states of a reaction, e.g. the reactants and products in a dimerization process, the bound and unbound state of a ligand-receptor system or the folded and unfolded state of

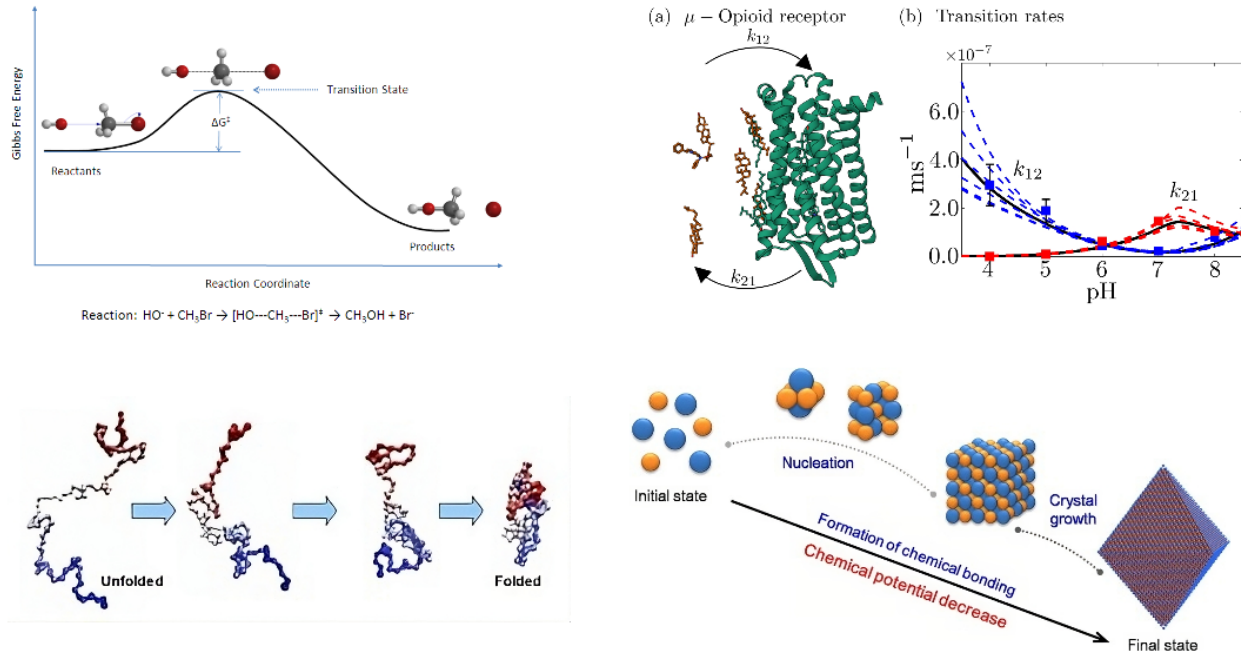


FIG. 1. Examples of phenomena studied by Reaction Rate Theory.

a protein. Instead, the maxima of the potential correspond to the activation energy of the reaction.

Typically, transitions between minima are rare events, i.e. they occur infrequently compared to more common or typical events in a system. For example, the folding of a protein (see fig. 2) is a complex process that requires several milliseconds to occur and that involves several sub-processes such as the oscillation of chemical bonds (timescale of femtoseconds) and the formation of structures such as  $\alpha$ -Helix and  $\beta$ -Hairpin (timescale of microseconds).

These processes are rare because require energy to overcome the potential barrier. If the system is not isolated, but closed, it can take energy from the environment in the form of thermal energy  $k_B T$ . It follows that the higher the temperature  $T$ , the greater the thermal energy, and thus the probability of the reaction to occur. However, the reactions can also be promoted by external perturbations, e.g., catalysis.

The reactions mentioned, are thus referred to as metastable, i.e. are dynamical processes whose state space is characterised by metastable regions (or states) in which the system can remain for a very long time before jumping into another metastable region, and by transition

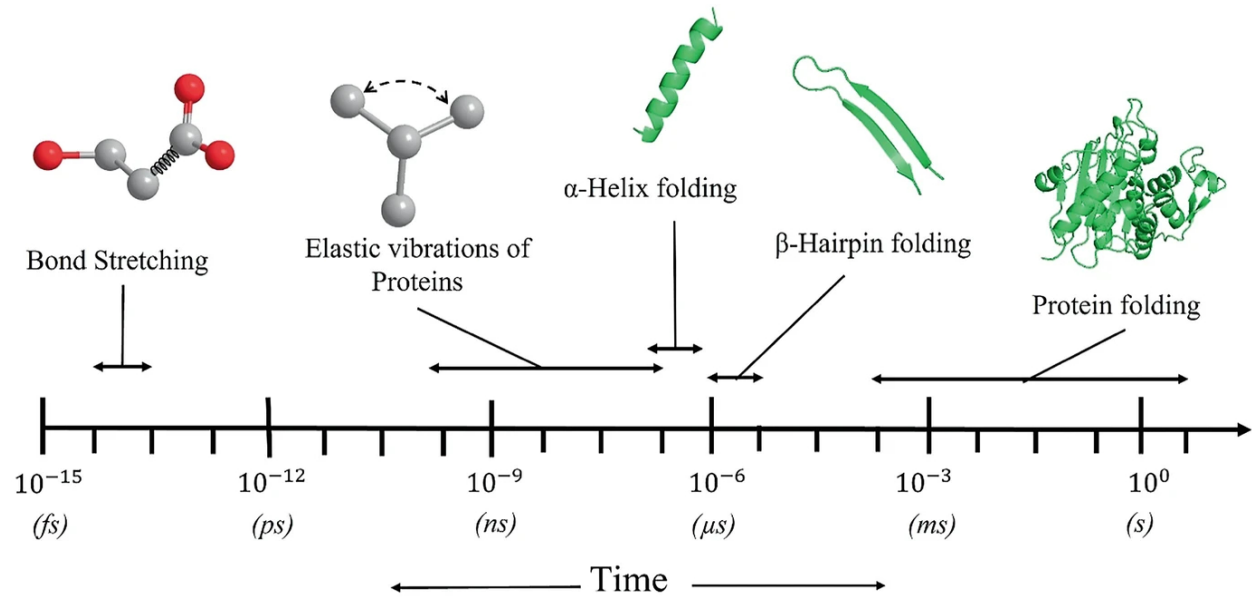


FIG. 2. Protein dynamics.

regions in which the system can only remain for a very short time (see fig. 3).

## II. KRAMERS THEORY

Hendrik A. Kramers, in 1940 [1], studied chemical reactions that can be represented as one-dimensional processes governed by the Langevin equation. In this equation, dynamics is represented by a potential energy function representing the deterministic forces acting on the system (e.g. electric interactions), and by a friction term and a stochastic force, which in pairs represent the interaction between the system and the external surroundings. In particular, Kramers derived three formulas that allow calculation of the transition rate as a function of friction between the system and the surroundings.

Before proceeding, we remark that 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 dynamics), but reduction to one or a few dimensions 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  $3N$ -dimensional system made of  $N$  components (molecules, atoms, particles...)

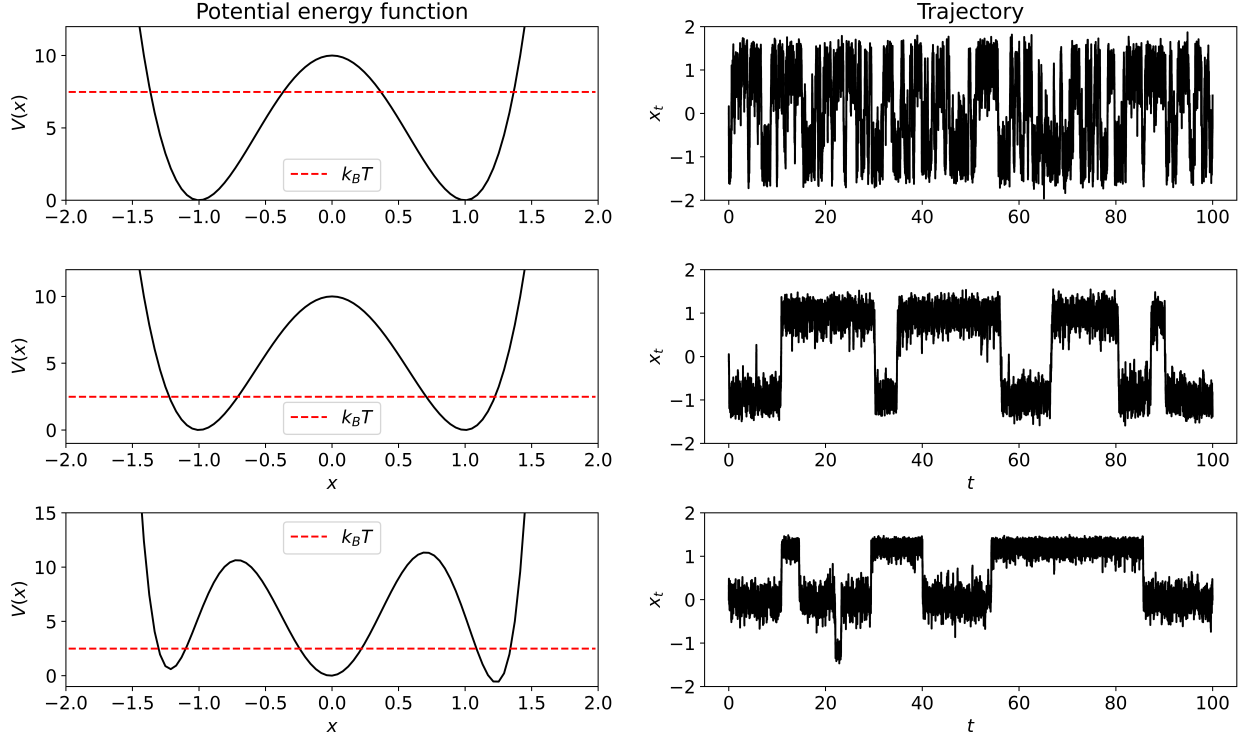


FIG. 3. Metastability. (left) Double and triple well potentials; (right) Trajectories exploring the state space at different temperatures. When the energy barrier  $V(x)$  is several units higher than the thermal energy  $k_B T$ , the system exhibits metastability, i.e. the transitions between minima are rare events.

and described by Cartesian coordinates  $\mathbf{r}_i \in \mathbb{R}^3$ , is fully described by a one-dimensional reaction coordinate  $x := x(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N) : \Omega_x \subset \mathbb{R}^{3N} \rightarrow \mathbb{R}$ . The space  $\Omega_x$  denotes the position space along the reaction coordinate.

- Correspondingly, the velocity of the system along the reaction coordinate  $x$  is described by the one-dimensional variable  $v \in \Omega_v \subset \mathbb{R}$ ;
- The phase space  $\Omega = \Omega_x \times \Omega_v$  represents all possible states of the system.
- The dynamics along the reaction coordinate is Markovian and is described by the Langevin dynamics equation

$$\begin{cases} \dot{x} = v_t \\ m\dot{v} = -\nabla V(x_t) - \gamma m v_t + \sigma \eta_t, \end{cases} \quad (2)$$

where

- $m$  is the effective mass (or reduced mass) of the system. It represents how much inertia the system has along the reaction coordinate.
- $V(x)$  is the potential energy function along the reaction coordinate. This potential is often called free energy profile.
- $-\nabla V(x_t)$  is the deterministic force acting on the system at time  $t$ . Note that here we are assuming the case where  $V(x_t)$  depends only on the position of the system at time  $t$ , but the potential itself does not depend on time;
- $-\gamma m v_t$  is a frictional force, opposite to the speed  $v_t$ , due to the environment that dissipates the energy of the system.  $\gamma$  is a friction coefficient with units  $[\text{time}]^{-1}$ .
- $\eta_t$  is a white noise process that simulates the random collisions between the system and the particles of the environment (e.g. the water molecules of a solvent or the molecules of a gas). It satisfies:

$$\begin{cases} \langle \eta_t \rangle = 0, \\ \langle \eta_t, \eta_{t'} \rangle = \delta(t - t'), \end{cases} \quad (3)$$

with  $\delta$  is the Dirac function.

- $\sigma$  connects the random force  $\eta_t$ , which is a scalar number, to the physical parameters of the system, the mass, the temperature and the friction coefficient:

$$\sigma = \sqrt{2k_B T \gamma m} \quad (4)$$

$$= \sqrt{\frac{2\gamma m}{\beta}}. \quad (5)$$

### A. Moderate and high friction regime

The starting point of Kramers theory is the Klein-Kramers partial differential equation, i.e. the Fokker-Planck equation associated to the stochastic differential equation defined in eq. 2. The Klein-Kramers equation describes the time evolution of the probability density  $\rho := \rho(x, v; t) \in \Omega$  as function of state  $(x, v)$  and the time  $t$ :

$$\frac{\partial \rho}{\partial t} = -v \frac{\partial \rho}{\partial x} + \gamma \frac{\partial}{\partial v} (v \rho) + \gamma \frac{k_B T}{m} \frac{\partial^2 \rho}{\partial v^2} + \frac{1}{m} \frac{dV}{dx} \frac{\partial \rho}{\partial v}. \quad (6)$$

Kramers derived the transition rate by solving this equation. However, the solution is quite elaborate, so we focus on the relevant assumptions:

- The potential includes a well (representing the products of a reaction) and a barrier (corresponding to the transition region) that can be respectively approximated by a harmonic potential in the minimum  $x_A$  and in the maximum  $x_B$ , as in fig. 4. Kramer's theory assumes nothing about the product state, so we leave the well to the right of the barrier undefined.
- The temperature  $T$  of the system is such that  $k_B T \ll E_b = V(x_B) - V(x_A)$ . This ensures the metastability of the system, i.e., that transitions are a rare event.
- Consider the scenario where a trajectory arising in the reactant state, after having crossed the barrier, is absorbed by the product state and replaced with a new trajectory in the reactant state (see fig. 5-left). This process generates a current that is described by a non-equilibrium steady-state probability density  $\rho_{SS}(x, v)$  solution of the Klein-Kramers equation. Steady-state means that  $\rho_{SS}(x, v)$  does not change with respect to time:

$$\frac{\partial \rho_{SS}(x, v)}{\partial t} = 0, \quad (7)$$

However, this is not an equilibrium distribution, as there is a constant flux  $j$  over the barrier.

- Boundary condition of  $\rho_{SS}(x, v)$ :

$$\begin{cases} \lim_{x \rightarrow -\infty} \rho_{SS}(x, v; t) = \pi(x, v) \\ \lim_{x \rightarrow +\infty} \rho_{SS}(x, v; t) = 0 \end{cases}, \quad (8)$$

where  $\pi(x, v)$  is the equilibrium distribution:

$$\pi(x, v) = \frac{1}{Z} \exp \left[ \frac{1}{k_B T} \left( \frac{1}{2} m v^2 + V(x) \right) \right], \quad (9)$$

with  $Z$  normalization constant. With this boundary condition we ask that the trajectories starting in the well are in thermal equilibrium and that are removed when they reach the right side of the barrier (see fig. 5-center).  $\pi(x, v)$  is also known as Boltzmann distribution, it is represented in fig. 5-right.

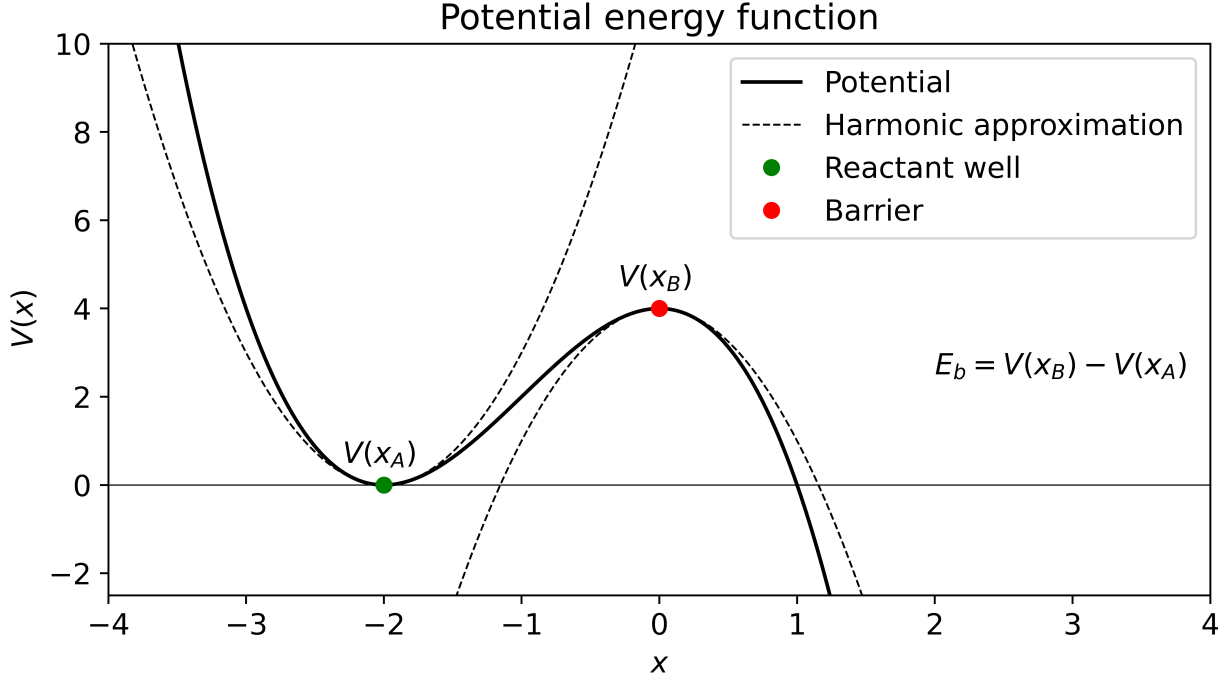


FIG. 4. Potential energy function of the Kramers problem:  $V(x) = -(x+1)^3 + 3(x+1) + 2$ .

Applying these assumptions, it is possible to find an analytical expression for  $\rho_{SS}(x, v)$ . Then, the steady-state distribution is used to calculate the flux of trajectories crossing the potential barrier

$$j_B = \int_{\Omega_v} v \rho_{SS}(x_B, v) dv. \quad (10)$$

where the subscript  $B$  remarks that we are estimating the flux at  $x_B$ . The flux is proportional to the number of trajectories that cross the barrier per unit time. Similarly, the quantity

$$n_A = \int_{\Omega_v} \int_{well} \pi(x, v) dx dv, \quad (11)$$

is proportional to the number of starting trajectories in the well. We calculate  $n_A$  using the Boltzmann distribution as we required that the starting trajectories are in thermal equilibrium (boundary condition of  $\rho_{SS}(x, v)$ ).

Finally, the ratio of  $j_B$  on the total number of trajectories initiated in the well  $n_A$  gives the rate constant as

$$k = \frac{j}{n_A} \quad (12)$$

$$= \frac{\gamma}{\omega_B} \left( \sqrt{\frac{1}{4} + \frac{\omega_B^2}{\gamma^2}} - \frac{1}{2} \right) \cdot \frac{\omega_A}{2\pi} \exp(-\beta E_b), \quad (13)$$



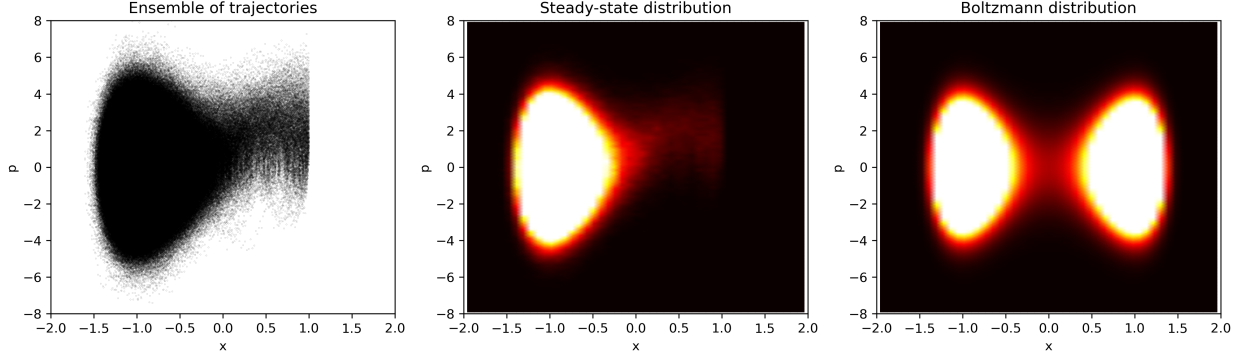


FIG. 5. (Left) Ensemble of trajectories starting in the neighborhood of  $x_A$  and removed at  $x_C = 1$ . (Center) Steady-state distribution  $\rho_{SS}(x, v)$  obtained as two-dimensional histogram using the trajectories in the left figure. (Right) Equilibrium distribution  $\pi(x, v)$ . The color-map denotes the values of the distributions: dark colors are used for regions where  $\rho_{SS}(x, v)$  and  $\pi(x, v)$  are almost zero, light colors denote high positive values.

where

$$\omega_A = \sqrt{\frac{1}{m} \left. \frac{d^2V}{dx^2} \right|_{x=x_A}}, \quad (14)$$

and

$$\omega_B = \sqrt{\frac{1}{m} \left. \frac{d^2V}{dx^2} \right|_{x=x_B}} \quad (15)$$

depend on the curvature of the potential at  $x_A$  and  $x_B$ , respectively (see appendix A for the derivation).

In the limit of high friction  $\gamma \gg \omega_B$ , eq. 13 is approximated as

$$k = \frac{\omega_A \omega_B}{2\pi\gamma} \exp(-\beta E_b). \quad (16)$$

This result agrees with the Pontryagin formula:

$$k = \left( \frac{1}{D} \int_{x_A}^{x_B} dx e^{\beta V(x)} \int_{-\infty}^x dx' e^{-\beta V(x')} \right)^{-1}. \quad (17)$$

On the other side, in the limit of small friction  $\gamma \ll \omega_B$ , eq. 13 converges to

$$k_{TST} = \frac{\omega_A}{2\pi} \exp(-\beta E_b). \quad (18)$$

Eq. 18, also known as transition-state-theory rate. It represents a constant function (yellow dashed line in fig. 6-b), however it overestimates the transition rates estimated by numerical experiments (black squares). We therefore conclude that eq. 13 cannot be used in the

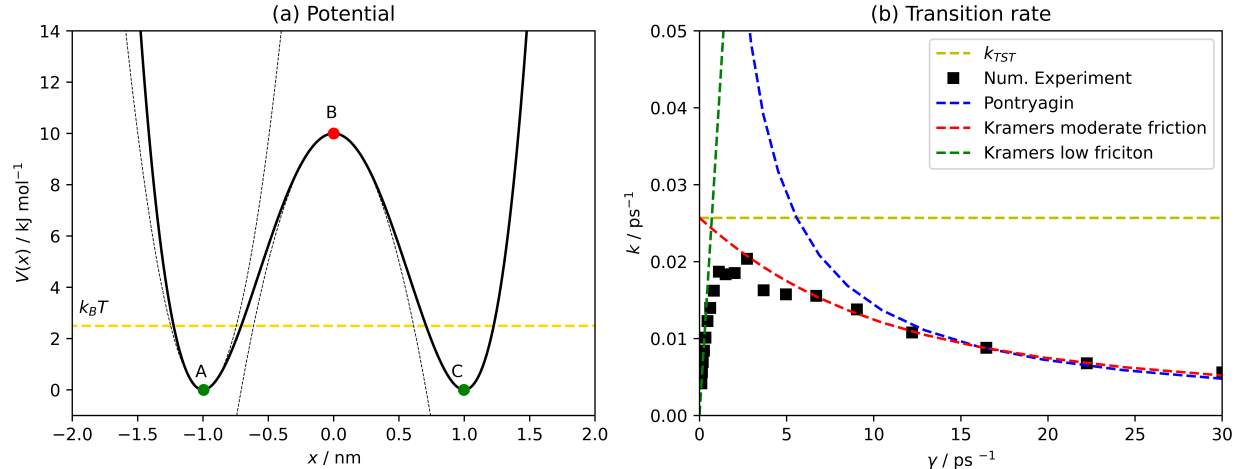


FIG. 6. (a) Potential energy function; (b) Transition rate as function of the  $\gamma$  coefficient.

low-friction regime. The reason is that at low friction, the boundary condition that the trajectories are thermalized in the well does not hold. In the low-friction regime, the dynamics are in fact quasi-Hamiltonian, that is, the trajectories are almost deterministic because the energy exchanges with the environment become rarefied.

### III. LOW FRICTION REGIME

Consider again the Langevin dynamics equation defined in eq. 2 and a potential energy function with a deep well and a barrier as in fig. 7 (left). In the central graph of fig. 7, we show the trajectory  $(x_t, v_t)$  on phase space and, on the right-hand side, the total energy as a function of time:

$$E_t = \frac{1}{2}mv_t^2 + V(x_t). \quad (19)$$

We observe that the trajectory is characterized by rapid and regular oscillations. The friction coefficient is indeed very low and the Langevin dynamics approaches the Hamiltonian dynamics, which is fully deterministic. On the other hand, the total energy, which appears stochastic and diffusive, is a slow variable compared to position and velocity. From this observation, we decide to study the problem in the energy space, instead of the phase space.

The first step to derive the rate formula for the low friction regime is therefore to transform the Langevin equation, defined in phase space, into a stochastic equation for the energy

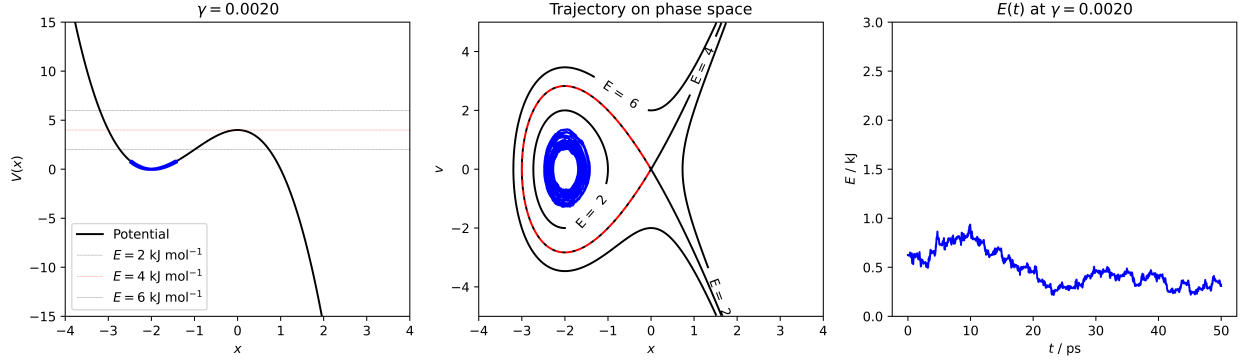


FIG. 7. (left) Potential energy function  $V(x)$ ; (middle) trajectory  $(x_t, v_t)$  on the phase space; (right) total energy  $E_t$  as function of time.

variable. We multiply both sides of the second equation in eq. 2 by the velocity  $v_t$  and obtain

$$mv_t\dot{v} = -v_t\frac{dV}{dx} - m\gamma v_t^2 + \sigma v_t\eta_t. \quad (20)$$

The derivative of the total energy defined in eq. 19 is

$$\dot{E} = -mv_t\dot{v}_t + \dot{x}_t\frac{\partial V}{\partial x} \quad (21)$$

$$= -mv_t\dot{v}_t + v_t\frac{dV}{dx}, \quad (22)$$

then we rewrite eq. 20 as

$$mv_t\dot{v} + v_t\frac{dV}{dx} = -m\gamma v_t^2 + \sigma v_t\eta_t \quad (23)$$

$$\dot{E} = -m\gamma v_t^2 + \sigma v_t\eta_t. \quad (24)$$

From here the derivation requires the use of the action-angle variables (see appendix B for details). Since oscillations in phase space are rapid and regular, we average eq. 24 over an oscillation period. Using the the mean square velocity

$$\langle v^2 \rangle = \frac{E}{m}, \quad (25)$$

and introducing the colored noise

$$\langle v_t\sqrt{2k_B T\gamma m}\eta_t \rangle = \sqrt{\frac{2k_B T\gamma m}{\omega(E_t)}}\eta_t \quad (26)$$

$$v_t\sigma\eta_t = \bar{\sigma}_t\eta_t, \quad (27)$$

yields the new stochastic differential equation for the energy

$$\dot{E} = -\gamma E_t + \bar{\sigma}_t \eta_t. \quad (28)$$

Note that in eq. 27,  $\omega(E_t)$  is the frequency that a harmonic oscillator, driven by Hamiltonian dynamics, would have if it were located at  $(x_t, v_t)$  in phase space and possessed energy  $E_t$ :

$$\omega(E_t) = \sqrt{\frac{1}{x_t^2} \left( \frac{2E_t}{m} - v_t^2 \right)}. \quad (29)$$

The associated Fokker-Planck equation is written as

$$\frac{\partial \rho}{\partial t} = \frac{\partial}{\partial E} \left[ \gamma I(E) \left( 1 + k_B T \frac{\partial}{\partial E} \omega(E) \rho(E; t) \right) \right], \quad (30)$$

where  $\rho(E; t)$  is the time-dependent probability density of the energy and the action  $I(E)$  is the action of a harmonic oscillator with energy  $E$ :

$$I(E) = \oint_E m v(x) dx \quad (31)$$

From the solution  $\rho(E; t)$  of eq. 30, which can be determined analytically, one calculates the energy flux  $j_E$  over the barrier and the density  $n_A$  in the well, similar to what was done in the case of moderate friction. Finally, the rate is written as

$$k = \frac{j_E}{n_A} \quad (32)$$

$$= \beta \gamma I(E_b) \frac{\omega_A}{2\pi} \exp[-\beta E_b] \quad (33)$$

$$= \beta \gamma \exp[-\beta E_b], \quad (34)$$

where we used the action of a harmonic oscillator with energy  $E_b$ :

$$I(E_b) = \oint_{E_b} m v(x) dx = \frac{2\pi E_b}{\omega_A}. \quad (35)$$

### Appendix A: Harmonic approximation

The potential around  $x_A$  is approximated by Taylor expansion as

$$V(x) = V(x_A) + \left. \frac{dV}{dx} \right|_{x=x_A} (x - x_A) + \frac{1}{2} \left. \frac{d^2V}{dx^2} \right|_{x=x_A} (x - x_A)^2 + \dots \quad (A1)$$

Then, using

$$\left. \frac{dV}{dx} \right|_{x=x_A} = 0, \quad (A2)$$

and truncating the sum at the second order, we obtain

$$V(x) \approx V(x_A) + \frac{1}{2} \left. \frac{d^2V}{dx^2} \right|_{x=x_B} (x - x_A)^2. \quad (\text{A3})$$

This is a harmonic potential, where the spring constant is given by the second derivative of  $V(x)$ :

$$k_{spring} = \left. \frac{d^2V}{dx^2} \right|_{x=x_A}, \quad (\text{A4})$$

then, a particle with mass  $m$  oscillates in the well around  $x_A$  with angular frequency

$$\omega_A = \sqrt{\frac{k_{spring}}{m}} = \sqrt{\left. \frac{1}{m} \frac{d^2V}{dx^2} \right|_{x=x_A}}, \quad (\text{A5})$$

which has units  $[\text{time}]^{-1}$ . Likewise, the potential can be approximated by a parabola in  $x_B$ , and we can define the angular frequency

$$\omega_B = \sqrt{\left. \frac{1}{m} \frac{d^2V}{dx^2} \right|_{x=x_B}} \quad (\text{A6})$$

### Appendix B: Action of the harmonic oscillator

Consider the Hamiltonian of the one-dimensional harmonic oscillator

$$H(x, p) = \frac{p^2}{2m} + \frac{1}{2}m\omega^2x^2, \quad (\text{B1})$$

where  $p = mv$  denotes the momentum. The equations of motion are

$$\begin{cases} \dot{x} = \frac{\partial H}{\partial p} = \frac{p}{m} \\ \dot{p} = -\frac{\partial H}{\partial x} = -m\omega^2x \end{cases} \quad (\text{B2})$$

with exact solution

$$\begin{cases} x_t = x_0 \cos(\omega t) + \frac{p_0}{m\omega} \sin(\omega t) \\ p_t = -m\omega x_0 \sin(\omega t) + p_0 \cos(\omega t) \end{cases}, \quad (\text{B3})$$

The total energy is constant and the corresponding solution in phase space is a closed orbit.

We now introduce the action-angles variable, where the action  $I$  is the area of the closed orbit for a specific energy level  $E$ :

$$I = \oint_E p dx, \quad (\text{B4})$$

while the angle variable  $\varphi$  represents an angle on the phase space.

The solution in terms of the action  $I$  and the angle  $\varphi$  is rewritten as

$$\begin{cases} x = \sqrt{\frac{2I}{m\omega}} \sin \varphi \\ p = \sqrt{2Im\omega} \cos \varphi \end{cases} \quad (\text{B5})$$

Then, inserting eq. B5 into the Hamiltonian  $H(x, p)$ , one obtains the Hamiltonian in action-angle variables

$$H(I, \varphi) = \omega I \quad (\text{B6})$$

$$\begin{cases} \dot{\varphi} = \frac{\partial H}{\partial I} \\ \dot{I} = -\frac{\partial H}{\partial \varphi} \end{cases}, \quad (\text{B7})$$

$$\begin{cases} \varphi(t) = \omega t \\ I(t) = \frac{E}{\omega} \end{cases}. \quad (\text{B8})$$

To derive the average of the square velocity in eq. 24, we calculate

$$\langle v^2 \rangle = \frac{1}{2\pi} \int_0^{2\pi} \frac{2I\omega}{m} \cos^2 \varphi d\varphi = \frac{I\omega}{m} = \frac{E}{m}, \quad (\text{B9})$$

where we used eq. B5 and eq. B8.

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- [1] H. Kramers, Brownian motion in a field of force and the diffusion model of chemical reactions, *Physica* **7**, 284 (1940).