Chapter 8

The Kramers problem and first passage times.

The Kramers problem is to find the rate at which a Brownian particle escapes from a potential well over a potential barrier. One method of attack is based on the theory of first passage times.

There are a variety of problems in chemical physics and biophysics where one wishes to calculate the average time τ required for a particle, generated at some point and diffusing under the influence of a potential, to reach and be bound to a certain target. Examples are diffusion controlled interchain reactions in polymers, diffusion ligand binding to receptor molecules and protein folding.

8.1 First passage times

Suppose that the motion of the set of variables $\boldsymbol{a} = (a_1, a_2, \ldots, a_n)$ is governed by a Langevin equation. In any single experiment it follows a specific path $\boldsymbol{a}(t)$ which wonders through $\boldsymbol{a}$-space. The initial point $\boldsymbol{a}_0$ starts out somewhere in a volume Ω in this space bounded by a surface $\partial\Omega$. The first passage time is the first time that the point leaves Ω. Because of the noise repeated experiments, even with the same initial position lead to different paths, and hence different first passage times. Our problem is to find the distribution of first passage times and in particular the mean first passage time.

From the Langevin equation

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{a}(t) = \boldsymbol{V}(\boldsymbol{a}) + \Xi(t)$$

with the streaming term $\boldsymbol{V}$ and noise $\Xi(t)$, we obtain the Fokker-Planck equation

$$\frac{\partial}{\partial t}P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) = -\frac{\partial}{\partial \boldsymbol{a}} \cdot [\boldsymbol{V}(\boldsymbol{a})P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0)] + \frac{\partial}{\partial \boldsymbol{a}} \cdot \boldsymbol{D} \cdot \frac{\partial}{\partial \boldsymbol{a}}P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) \tag{8.1}$$

Here $\langle \Xi(t_2)\Xi(t_1)\rangle = 2\boldsymbol{D}\delta(t_2 - t_1)$ and $\boldsymbol{D}$ is a diffusion tensor.

If we focus on those paths that have not left Ω by time t, we must remove all paths that have crossed the boundary of Ω before time t. This can be done by imposing an

absorbibg boundary condition on $\partial\Omega$. Then

$$\begin{aligned} P(\boldsymbol{a}, t_0|\boldsymbol{a}_0, t_0) &= \delta(\boldsymbol{a}-\boldsymbol{a}_0) \\ P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) &= 0 \quad \text{on} \quad \partial\Omega \end{aligned}$$

We can call the Fokker-Planck operator L_{FP} i.e.

$$\frac{\partial}{\partial t}P = -L_{FP}P$$

with

$$L_{FP} = \frac{\partial}{\partial \boldsymbol{a}} \cdot \boldsymbol{V}(\boldsymbol{a}) - \frac{\partial}{\partial \boldsymbol{a}} \cdot \boldsymbol{D} \cdot \frac{\partial}{\partial \boldsymbol{a}}$$

and the formal solution

$$P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) = \mathrm{e}^{-L_{FP}(t-t_0)}\delta(\boldsymbol{a}-\boldsymbol{a}_0)$$

Due to the absorbing boundary condition on $\partial\Omega$ we have

$$P(\boldsymbol{a}, t \to \infty|\boldsymbol{a}_0, t_0) = 0$$

The probability that the Brownian particle is still in Ω at time t can be written as

$$G(t|\boldsymbol{a}_0, t_0) = \int_\Omega \mathrm{d}\boldsymbol{a} P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0)$$

This is also the probability that the first passage time from $\boldsymbol{a}_0$ to $\partial\Omega$ is larger than t

$$G(t|\boldsymbol{a}_0, 0) = \Pr\{\tau > t\} = \int_t^\infty \varrho(\tau|\boldsymbol{a}_0)\mathrm{d}\tau$$

where $\varrho(\tau)$ is the probability density for the first passage time. This gives

$$\varrho(\tau|\boldsymbol{a}_0) = -\frac{\partial}{\partial\tau}G(\tau|\boldsymbol{a}_0, 0) \tag{8.2}$$

The mean first passage time is the first moment of τ

$$\langle\tau(\boldsymbol{a}_0)\rangle = \int_0^\infty \mathrm{d}\tau\, \tau\varrho(\tau|\boldsymbol{a}_0)$$

Then using (8.2) we find

$$\langle\tau(\boldsymbol{a}_0)\rangle = -\int_0^\infty \mathrm{d}\tau\, \tau\frac{\partial}{\partial\tau}G(\tau|\boldsymbol{a}_0, 0) = \int_0^\infty \mathrm{d}\tau\, G(\tau|\boldsymbol{a}_0, 0) = \int_0^\infty \mathrm{d}\tau \int_\Omega \mathrm{d}\boldsymbol{a} P(\boldsymbol{a}, \tau|\boldsymbol{a}_0, 0) \tag{8.3}$$

From the Chapman-Kolmogorov equation

$$P(\boldsymbol{a}_1, t_1|\boldsymbol{a}_0, t_0) = \int \mathrm{d}\boldsymbol{a} P(\boldsymbol{a}_1, t_1|\boldsymbol{a}, t)P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0)$$

where $t_0 < t < t_1$ we find by taking the derivative with repsect to t

$$\int \mathrm{d}\boldsymbol{a}\frac{\partial}{\partial t}P(\boldsymbol{a}_1, t_1|\boldsymbol{a}, t)P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) + \int \mathrm{d}\boldsymbol{a} P(\boldsymbol{a}_1, t_1|\boldsymbol{a}, t)\frac{\partial}{\partial t}P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) = 0$$

or

$$\begin{aligned} & \int \mathrm{d}\boldsymbol{a} \frac{\partial}{\partial t} P(\boldsymbol{a}_1, t_1|\boldsymbol{a}, t) P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) - \int \mathrm{d}\boldsymbol{a} P(\boldsymbol{a}_1, t_1|\boldsymbol{a}, t) L_{FP} P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) \\ = & \int \mathrm{d}\boldsymbol{a} \left[\frac{\partial}{\partial t} P(\boldsymbol{a}_1, t_1|\boldsymbol{a}, t) - L_{FP}^{\dagger} P(\boldsymbol{a}_1, t_1|\boldsymbol{a}, t) \right] P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) \end{aligned}$$

i.e we have the adjoint equation

$$\frac{\partial}{\partial t} P(\boldsymbol{a}_1, t_1|\boldsymbol{a}, t) - L_{FP}^{\dagger} P(\boldsymbol{a}_1, t_1|\boldsymbol{a}, t) = 0$$

where the adjoint operator is

$$L^{\dagger} = -\boldsymbol{V}(\boldsymbol{a}) \cdot \frac{\partial}{\partial \boldsymbol{a}} - \frac{\partial}{\partial \boldsymbol{a}} \cdot \boldsymbol{D} \cdot \frac{\partial}{\partial \boldsymbol{a}}$$

and operates on the variable $\boldsymbol{a}$.

We can now find a differential equation for the mean first passage time. If we operate with the adjoint operator in (8.3) we find

$$\begin{aligned} L_{FP}^{\dagger} \langle \tau(\boldsymbol{a}_0) \rangle &= \int_0^{\infty} \mathrm{d}\tau \int_{\Omega} \mathrm{d}\boldsymbol{a} L_{FP}^{\dagger} P(\boldsymbol{a}, \tau|\boldsymbol{a}_0, 0) = \int_0^{\infty} \mathrm{d}\tau \int_{\Omega} \mathrm{d}\boldsymbol{a} \left(\frac{\partial}{\partial t_0} P(\boldsymbol{a}, \tau|\boldsymbol{a}_0, t_0) \right)_{t_0=0} \\ &= -\int_0^{\infty} \mathrm{d}\tau \int_{\Omega} \mathrm{d}\boldsymbol{a} \frac{\partial}{\partial \tau} P(\boldsymbol{a}, \tau|\boldsymbol{a}_0, 0) = 1 \end{aligned}$$

where we used the stationary condition $P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) = P(\boldsymbol{a}, t - t_0|\boldsymbol{a}_0, 0)$. Therefore, the differential equation for the mean first passage time is

$$\boldsymbol{V}(\boldsymbol{a}) \cdot \frac{\partial}{\partial \boldsymbol{a}} \langle \tau(\boldsymbol{a}) \rangle + \frac{\partial}{\partial \boldsymbol{a}} \cdot \boldsymbol{D} \cdot \frac{\partial}{\partial \boldsymbol{a}} \langle \tau(\boldsymbol{a}) \rangle = -1 \tag{8.4}$$

This must be solved with the boundary condition

$$\langle \tau(\boldsymbol{a}) \rangle = 0 \quad \text{on} \quad \partial\Omega$$

Similarly we can find a differential equation for the function $G(t|\boldsymbol{a}_0, t_0)$ by using the adjoint equation

$$\begin{aligned} \frac{\partial}{\partial t} G(t|\boldsymbol{a}_0, t_0) &= \int_{\Omega} \mathrm{d}\boldsymbol{a} \frac{\partial}{\partial t} P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) = -\int_{\Omega} \mathrm{d}\boldsymbol{a} \frac{\partial}{\partial t_0} P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) \\ &= -\int_{\Omega} \mathrm{d}\boldsymbol{a} L_{FP}^{\dagger} P(\boldsymbol{a}, t|\boldsymbol{a}_0, t_0) = -L_{FP}^{\dagger} G(t|\boldsymbol{a}_0, t_0) \end{aligned}$$

or

$$\frac{\partial}{\partial t} G(t|\boldsymbol{a}, 0) = \boldsymbol{V}(\boldsymbol{a}) \cdot \frac{\partial}{\partial \boldsymbol{a}} G(t|\boldsymbol{a}, 0) + \frac{\partial}{\partial \boldsymbol{a}} \cdot \boldsymbol{D} \cdot \frac{\partial}{\partial \boldsymbol{a}} G(t|\boldsymbol{a}, 0)$$

From here we immediately get an equation for the first passage time probability density $\varrho(\tau|\boldsymbol{a}_0)$.

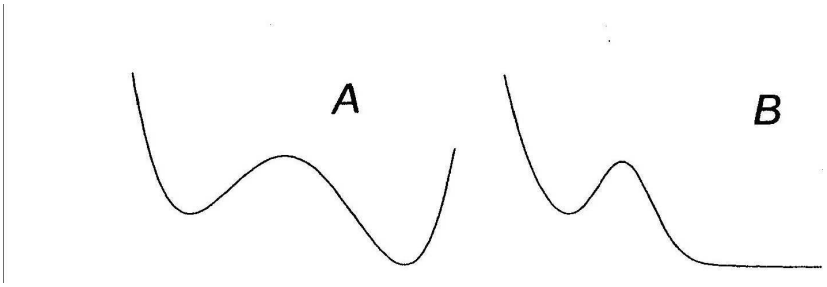

Figure 8.1: *Potential energy as a function of reaction coordinate in two typical cases,* A *is a potential with two minima, and* B *is a potential that allows escape from sa single minimum.*

8.2 The Kramers problem

The Kramers problem is to determine the rate at which a Brownian particle escapes from a potential well. Two typical situations are shown in fig. 8.1. In case A the system can be either in an equilibrium state of lowest energy or in a metastable state which is a local minimum in energy as a function of some coordinate x, but not the absolute minimum in energy. When the temperature is low (compared to the barrier height), the particle will spend a lot of time near the potential minimum where it started, and only rarely will Brownian motion take it to the top of the barrier. Once there the particle is equally likely to fall to either side of the barrier. If it goes to the right-hand side in fig. 8.1 it will fall rapidly to the other minimum stay there for a while and then perhaps cross back to the original minimum. In case B it will not return.

An example of these situations is the description of a chemical reaction. State A in fig. 8.2 corresponds to the unreacted products and state C to the reacted products. For this reason it is common to call x a generalized reaction coordinate. In order for the reaction to cross a barrier at x_B with energy difference $E_b^+ = U_B - U_A$ compared to the unstable state A and $E_b^- = U_B - U_C$ compared to the stable state C. Since $E_b^+ < E_b^-$ we expect the rate k^- with which the system crosses the barrier from A to C to be larger than the rate k^+ for the reverse process.

Kramers modeled this problem using the one dimensional model

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= v \\ m\frac{\mathrm{d}x}{\mathrm{d}t} &= -\gamma v + F(x) + \xi(t) \end{aligned} \tag{8.5}$$

where $F(x) = -U'(x)$ is the force excerted on the Brownian particle in the external potential $U(x)$. The time development of the reaction coordinate is therefore modeled as the Brownian motion of a particle in an external potential.

Contrary to the free Brownian motion problem the Kramers problem has more than one inherent time-scale:

i) the equilibration time τ_T within one of the minima: this is the time after which an ensemble of systems started for instance at x_A, has assumed the Maxwell-Boltzmann equilibrium distribution corresponding to an infinite barrier at x_B.

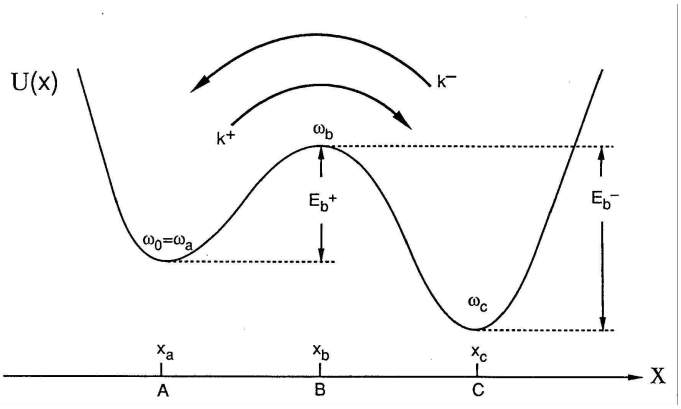

Figure 8.2: *Schematic representation of a bistable potential governing diffusive barrier crossing.*

ii) the escape time τ_e: this is the mean time a Brownian particle will need to go from A to C. There is a corresponding time for going from C to A.

When τ_s is a typical scale for the fast degrees of freedom, we require the following inequalities

$$\tau_s \ll \tau_T \ll \tau_e$$

The second inequality is the basis for calling the barrier crossing thermally activated. On a timescale τ_T the reaction coordinate has reached thermal equilibrium with the bath variables, and it is the thermal fluctuations of these variables that create the stochastic forces which finally drive the system over the barrier.

To be consistent with the last inequality of the time scales, we have to assume that

$$k_{\mathrm{B}}T \ll E_b^+ < E_b^-$$

which means that the mean thermal energy of the Brownian particle has to be much smaller than the barrier height. If it were larger than the barrier height the Brownian particle would diffuse more or less freely from A to C and back, and if it were of comparable height the timescales for equilibration and escape would not be clearly separated.

There is one more set of competing time scales contained in (8.5). The time-scale for the coupling to the bath coordinates is set by the kinematic friction γ/m. Without the coupling to the bath the particle would perform a Newtonian motion in the external potential U. When the particle has a total energy smaller than the barrier, it performs oscillations around either A or B with typical frequencies

$$\omega_a = \sqrt{\frac{U''(x_a)}{m}}, \quad \omega_c = \sqrt{\frac{U''(x_c)}{m}}$$

When the particle has a total energy larger than the barrier, however, there is a time scale for the exchange between kinetic and potential energy during the barrier crossing. This time scale is given by

$$\omega_b = \sqrt{\frac{U''(x_b)}{m}}$$

We can now distinguish two different regimes

i) strong friction $\frac{\gamma}{m} \gg \omega_b$

ii) weak friction $\frac{\gamma}{m} \ll \omega_b$

In the strong friction region $m/\gamma \to 0$ we can neglect the inertial term in (8.5) and obtain

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{1}{\gamma}F(x) + \frac{1}{\gamma}\xi(t)$$

Then for this case

$$V(x) = \frac{1}{\gamma}F(x), \quad D = \frac{k_\mathrm{B}T}{\gamma}.$$

The corresponding Fokker-Planck equation is the Smoluchovski equation

$$\frac{\partial}{\partial t}P(x,t|x_0,0) = -\frac{\partial}{\partial x}\left(\frac{1}{\gamma}F(x)P(x,t|x_0,0)\right) + D\frac{\partial^2}{\partial x^2}P(x,t|x_0,0) \tag{8.6}$$

The average first passage time satisfies the equation

$$\frac{1}{\gamma}F(x)\frac{\mathrm{d}}{\mathrm{d}x}\langle\tau(x)\rangle + D\frac{\mathrm{d}^2}{\mathrm{d}x^2}\langle\tau(x)\rangle = -1$$

Using $F(x) = -U'(x)$ and multiply with the integrating factor $\exp(-\beta U)$, where $\beta = 1/k_\mathrm{B}T$ we have

$$\left(\frac{\mathrm{d}}{\mathrm{d}x}\mathrm{e}^{-\beta U(x)}\right)\frac{\mathrm{d}}{\mathrm{d}x}\langle\tau(x)\rangle + \mathrm{e}^{-\beta U(x)}\frac{\mathrm{d}^2}{\mathrm{d}x^2}\langle\tau(x)\rangle = -\frac{1}{D}\mathrm{e}^{-\beta U(x)}$$

or

$$\frac{\mathrm{d}}{\mathrm{d}x}\left[\mathrm{e}^{-\beta U(x)}\frac{\mathrm{d}}{\mathrm{d}x}\langle\tau(x)\rangle\right] = -\frac{1}{D}\mathrm{e}^{-\beta U(x)}$$

Integrating from $-\infty$ to x this gives

$$\frac{\mathrm{d}}{\mathrm{d}x}\langle\tau(x)\rangle = -\frac{1}{D}\mathrm{e}^{\beta U(x)}\int_{-\infty}^{x}\mathrm{d}z\mathrm{e}^{-\beta U(z)}$$

Finally integrating from x_a to x using $\langle\tau(x_a)\rangle = 0$ we find

$$\langle\tau(x)\rangle = \frac{1}{D}\int_{x_a}^{x}\mathrm{d}y\,\mathrm{e}^{\beta U(y)}\int_{-\infty}^{y}\mathrm{d}z\mathrm{e}^{-\beta U(z)}$$

In the first integral the integrand is largest around x_b and we expand the external potential around this point

$$U(y) = U_b - \frac{1}{2}m\omega_b^2(y - x_b)^2$$

In the second integral the integrand is largest around x_a and

$$U(z) = U_a + \frac{1}{2}m\omega_a^2(z - x_a)^2$$

Since the integrands decays rapidly with y and z we can replace the lower limit of integration in the first integral with $-\infty$, and the upper limit in both integrals with ∞. Then

$$\langle \tau_{A\to C}\rangle = \frac{1}{D}\int_{-\infty}^{\infty} \mathrm{d}y\, \mathrm{e}^{\beta U_b}\mathrm{e}^{-\frac{\beta}{2}m\omega_b^2(y-x_b)^2}\int_{-\infty}^{\infty}\mathrm{d}z\mathrm{e}^{-\beta U_a}\mathrm{e}^{-\frac{\beta}{2}m\omega_a^2(z-x_a)^2} = \frac{1}{D}\frac{2\pi k_\mathrm{B}T}{m\omega_a\omega_b}\mathrm{e}^{\beta E_b^+}$$

For the traqnsition rate from A to B we obtain

$$k_{CA} = \frac{1}{\langle \tau_{A\to C}\rangle} = \frac{m\omega_a\omega_b}{2\pi\gamma}\mathrm{e}^{-E_b^+/k_\mathrm{B}T} \tag{8.7}$$

This is Kramers result for the reaction rate. The reaction rate from C to A folow similarly.

8.3 Intrachain reaction of polymers

Consider the diffusion controlled interchain reaction of a polymer with two reactive groups attached at the ends. The simplest description of the dynamics of the end-to-end distance of the polymer is to liken its time development to a diffusion under the influence of a potential.

Assuming that the reaction occurs with a certain rate whenever the ends are sufficiently close, one would typically like to know the fraction of unreacted molecules at time t and the average time needed for the ends to collide for the first time.

The quantity of interest is $G(t)$ the fraction of polymers yet unreacted at time t. Here

$$G(t) = \int \mathrm{d}\boldsymbol{r}_0 G(t|\boldsymbol{r}_0)P_\mathrm{eq}(\boldsymbol{r}_0)$$

where $P_\mathrm{eq}(\boldsymbol{r}_0)$ is the equilibrium distribution for the intial ened-to-end distance, i.e. we assume that we nitially have a distribution of end-to-end distances given by P_eq. We assume that the dynamics of the end-to-end distance r is described by a Smoluchowski type equation. In the harmonic spring model for a d-dimensional polymer the potential is

$$U(r) = \frac{dr^2}{2\beta b^2}$$

where b is the mean distance between the polymer ends, i.e. $b^2 = \langle r^2\rangle$. The corresponding equilibrium end-to-end distribution is

$$P_\mathrm{eq}(r) = Cr^{d-1}\mathrm{e}^{-dr^2/2b^2}$$

representing a Gaussian chain.

Let's for simplicity consider a one-dimensional chain. The Smoluchowski equation for this problem is

$$\frac{\partial}{\partial t}P(x,t|x_0 0) = D\left[\frac{\partial^2}{\partial x^2} + \frac{1}{b^2}\frac{\partial}{\partial x}x\right]P(x,t|x_0,0) \tag{8.8}$$

We assume that the reaction takes place when the ends touch for $x = 0$ where

$$P(0,t|x_0,0) = 0$$

The normalized equilibrium distribution for the chain without reaction is

$$P_{\rm eq}(x) = \left(\frac{2}{\pi b^2}\right)^{1/2} {\rm e}^{-x^2/2b^2}, \quad x > 0$$

The solution to (8.8) in the absence of any reaction is

$$P_0(x,t|x_0 0) = \left(\frac{1}{2\pi b^2 \sigma^2(t)}\right)^{1/2} \exp\left(-\frac{(x - x_0 {\rm e}^{-Dt/b^2})^2}{2b^2\sigma^2(t)}\right)$$

where

$$\sigma^2(t) = 1 - {\rm e}^{-2Dt/b^2}$$

The Green function satisfying the boundary condition at $x = 0$ can be obtained by the method of images

$$P(x,t|x_0 0) = P_0(x,t|x_0 0) - P_0(x,t|-x_0 0)$$

The reaction rate is then

$$\begin{aligned} -\frac{\partial}{\partial t}G(t|x_0) &= -\int_0^\infty {\rm d}x \frac{\partial}{\partial t} P(x,t|x_0 0) = D\left[\frac{\partial}{\partial x}P(x,t|x_0,0)\right]_{x=0} \\ &= \frac{2Dx_0 {\rm e}^{-Dt/b^2}}{b^2\sigma^2(t)(2\pi b^2\sigma^2(t))^{1/2}} \exp\left(-\frac{x_0^2 {\rm e}^{-2Dt/b^2}}{2b^2\sigma^2(t)}\right) \end{aligned}$$

Averaging over $P_{\rm eq}(x), x > 0$ yields

$$-\frac{\partial}{\partial t}G(t|x_0) = -\frac{2D{\rm e}^{-Dt/b^2}}{\pi\left[1 - {\rm e}^{-2Dt/b^2}\right]^{1/2}}$$

Integrating this expression with initial condition $G(0) = 1$ gives finally

$$G(t) = \frac{2}{\pi} \arcsin {\rm e}^{-Dt/b^2}$$

From this expression we can calculate the mean first passage time.