

On Kinetic Rate Theory Math 6770 Fall 2005

It is common practice when building kinetic models of chemical reactions to invoke the famous Arrhenius formula

$$k_{off} = \kappa_0 \exp\left(-\frac{\Delta G}{k_B T}\right), \quad (1)$$

where ΔG is the free energy of the chemical bond, k_B is Boltzmann's constant, and T is absolute temperature.

When a bond is externally forced, the off-rate is increased. If ΔG is thought of as the height of the potential well out of which the binding molecule must escape, then an applied force can be viewed as "tilting" the potential well. With tilting, the height of the barrier is decreased by the amount FL , where L is an appropriate scale factor. Thus, according to this reasoning, the off rate from the modified potential well should be

$$k_{off} = \kappa_0 \exp\left(-\frac{\Delta G - FL}{k_B T}\right) = k_0 \exp\left(\frac{FL}{k_B T}\right) = k_0 \exp\left(\frac{F}{F_0}\right), \quad (2)$$

where F is the external force. This is referred to as Bell's law.

The purpose of these notes is to examine the off-rate of a forced potential well as a function of the external force F . It is shown, using rigorous estimates, that for $\frac{\Delta G - FL}{k_B T} \gg 1$,

$$k_{off} \approx 2\sqrt{\frac{a}{\pi}} a \left(1 - \frac{f}{2a}\right) \exp\left(-a\left(1 - \frac{f}{2a}\right)^2\right), \quad (3)$$

where $a = \frac{\Delta G}{k_B T}$, $f = \frac{FL}{k_B T}$,

1 Mean First Exit Times

A detailed understanding of off-rates is found by examining the Fokker-Planck equation. We suppose that a molecule is subject to three forces, namely the force from the potential well of a binding site, the applied force F , and Brownian forcing from the environment. The Fokker-Planck equation describes the evolution of the probability $p(x, t)$ that the molecule is at position x at time t and is given by

$$\nu p_\tau = ((U'(x) - F)p)_x + k_B T p_{xx}, \quad (4)$$

where ν is the molecular viscosity, $k_B T$ is the thermal energy. We have ignored molecular inertia. For the problem at hand, we suppose that the binding site is located in the interval $-L < x < L$, and that the boundary at $x = -L$ is reflecting. The off rate is defined as the inverse of the mean first exit time from the binding region at $x = 0$, with x starting at the minimal point of the potential.

According to Gardner, the function $p(x, t)$ is more precisely given as the conditional probability $p(x, t|x', t')$, and the problem at hand is to determine how long the particle remains in the domain. We define

$$G(y, t) = \int_{-L}^L p(x, t|y, 0) dx, \quad (5)$$

as the probability that the particle is in the domain at time t , and observe that, if $T(y)$ is the random variable for the time at which the particle first leaves the domain having started at y , then

$$P(T(y) > t) = G(y, t) = - \int_t^\infty G_t(y, t) dt, \quad (6)$$

and

$$P(T(y) < t) = - \int_0^t G_t(y, t) dt. \quad (7)$$

Thus, $G_t(y, t)$ is the pdf for the random variable $T(y)$. Furthermore, the expected value of the random variable $T(y)$ is

$$E(T(y)) = - \int_0^\infty t G_t(y, t) dt = \int_0^\infty G(y, t) dt. \quad (8)$$

We also observe that, for a time-autonomous process

$$G_t(y, t) = \int_\Omega p_t(x, t|y, 0) dy = \int_\Omega p_t(x, 0|y, -t) dy. \quad (9)$$

Now, $p(x, 0|y, \tau)$ satisfies the backward Fokker-Planck equation

$$-\nu p_\tau = -(U'(y) - F)p_y + k_B T p_{yy}, \quad (10)$$

so that

$$\nu G_t = -(U'(y) - F)G_y + k_B T G_{yy}, \quad (11)$$

Finally, integrate this equation with respect to t to get the ordinary differential equation

$$k_B T \tau_{yy} - (U'(y) - F)\tau_y = -\nu, \quad (12)$$

where $\tau(y) = E(T(y))$, subject to boundary conditions $\tau'(-L) = 0$, and $\tau(L) = 0$.

1.1 A quadratic potential well

We suppose that the potential well is exactly the quadratic polynomial

$$U(y) = \Delta G \left(\frac{y}{L}\right)^2. \quad (13)$$

We introduce nondimensional variables $x = \frac{y}{L}$, $\tau = \frac{\nu L^2}{k_B T} \sigma$, in terms of which (12) becomes

$$\sigma'' - (2ax - f)\sigma' = -1, \quad (14)$$

with $\sigma'(-1) = 0$, $\sigma(1) = 0$, where $a = \frac{\Delta G}{k_B T}$, and $f = \frac{FL}{k_B T}$.

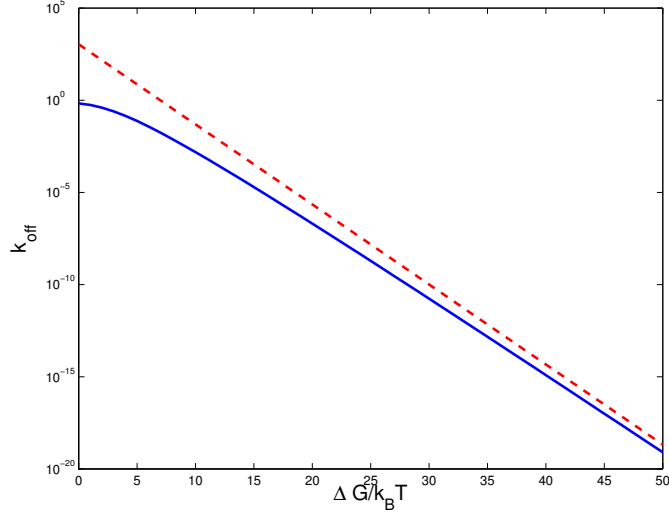


Figure 1: Plot of k_{off} (solid curve) and $\kappa_0 \exp(-\frac{\Delta G}{k_B T})$ (dashed curve), on a logarithmic scale, plotted as functions of $\frac{\Delta G}{k_B T}$.

1.2 The numerical solution

It is easy to find the numerical solution of this boundary value problem. Let $\sigma_0(x)$ be the solution of the differential equation (14) subject to initial data $\sigma_0(-1) = \sigma'_0(-1) = 0$. Then, $\sigma(x) = \sigma_0(x) - \sigma_0(1)$. This is easily found using a standard numerical integrator.

The classic result (1) was derived for a quadratic potential

$$U(x) = \Delta G \left(\frac{x}{L}\right)^2, \quad -L < x < L \quad (15)$$

and is an approximate result that applies only if $\frac{\Delta G}{k_B T}$ is sufficiently large. We can readily verify this by solving (12) numerically. In Fig. 1 are shown the results of this computation. In Fig. 1 is shown the ratio of the computed k_{off} to the asymptotic off rate $\kappa_0 \exp(-\frac{\Delta G}{k_B T})$, plotted on a logarithmic scale as functions of $\frac{\Delta G}{k_B T}$. It is clear from these plots that the asymptotic formula is not valid for small arguments. In fact, with $\frac{\Delta G}{k_B T}$ less than 5, the Arrhenius formula is too large by an order of magnitude.

Given that the Arrhenius formula is not correct for small $\frac{\Delta G}{k_B T}$, it is not surprising that the effect of a constant load is not as stated by (??). In Fig. 2 is shown k_{off} plotted as a function of the unloading force $\frac{FL}{k_B T}$ for several values of $\frac{\Delta G}{k_B T}$. For small F , each of these curves is nearly linear on a log scale (at least for $\frac{\Delta G}{k_B T}$ sufficiently large), indicating that for small enough F , and large enough $\frac{\Delta G}{k_B T}$, the effect of F is approximately exponential, as hypothesized. However, the range of validity of this approximation is quite limited.

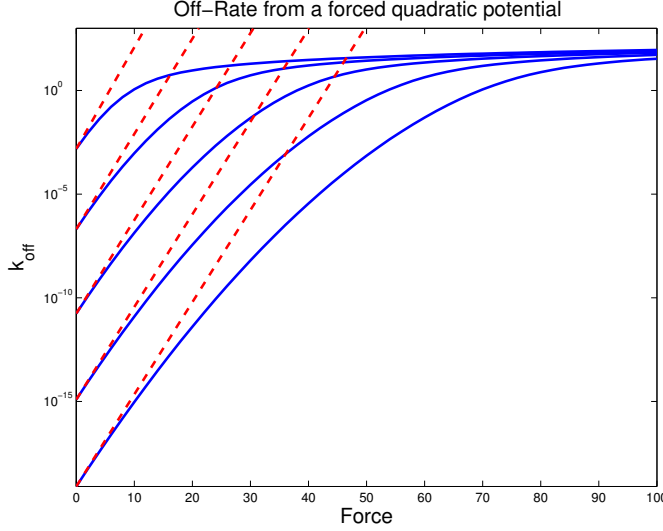


Figure 2: Plot of k_{off} , on a logarithmic scale, as a function of $\frac{FL}{k_B T}$ shown for $\frac{\Delta G}{k_B T} = 1, 11, 21, 31, 41,$ and 51 (top to bottom).

1.2.1 Large $\frac{\Delta G}{k_B T}$ Asymptotics

We begin by examining the unforced problem, $f = 0$. We use an integrating factor, so that (14) becomes

$$(\exp(-ax^2)\sigma')' = -\exp(-ax^2), \quad (16)$$

or

$$\sigma'(x) = -\exp(ax^2) \int_{-\alpha}^x \exp(-a\eta^2) d\eta, \quad (17)$$

so that

$$\sigma(x) = \int_x^1 \exp(ax^2) \int_{-\alpha}^x \exp(-a\eta^2) d\eta dx, \quad (18)$$

and

$$\sigma(0) = \int_0^1 \exp(ax^2) \int_{-\alpha}^x \exp(-a\eta^2) d\eta dx. \quad (19)$$

This is the integral we wish to approximate.

There are several approximations we make. Observe first that

$$\sigma(0) = \int_0^1 \exp(ax^2) \int_{-1}^1 \exp(-a\eta^2) d\eta dx - \int_0^1 \int_x^1 \exp(a(x^2 - \eta^2)) d\eta dx. \quad (20)$$

The second of the integrals in (20) is small. This can be established by introducing the change of variables $z = x - \eta$, $\xi = x + \eta$. It follows that

$$\int_0^1 \int_x^1 \exp(a(x^2 - \eta^2)) d\eta \leq \frac{1}{2} \int_0^2 \int_{-\xi}^0 \exp(a z \xi) dz d\xi \quad (21)$$

$$= \frac{1}{2} \int_0^2 \frac{1 - \exp(-a\xi^2)}{a\xi} d\xi \quad (22)$$

$$= \frac{1}{4a} \left(\int_0^1 \frac{1 - e^{-s}}{s} ds + \ln(4a) - E_1(1) + E_1(4a) \right), \quad (23)$$

where $E_1(x)$ is the exponential integral

$$E_1(x) = \int_x^\infty \frac{e^{-s}}{s} ds = \frac{e^{-x}}{x} + O\left(\frac{e^{-x}}{x^2}\right). \quad (24)$$

Thus,

$$0 < \int_0^1 \int_x^1 \exp(a(x^2 - \eta^2)) d\eta \leq \frac{\ln(a)}{4a} + O\left(\frac{1}{a}\right), \quad (25)$$

for large a .

A useful formula will be that

$$\int_\beta^\infty \exp(-as^2) ds \approx \frac{1}{2a\beta} \exp(-a\beta^2) \left(1 + O\left(\frac{1}{a}\right)\right). \quad (26)$$

Now we make two approximations. First,

$$\begin{aligned} \int_{-1}^1 \exp(-a\eta^2) d\eta &= \int_{-\infty}^\infty \exp(-a\eta^2) d\eta - 2 \int_1^\infty \exp(-a\eta^2) d\eta \\ &= \sqrt{\frac{\pi}{a}} - \frac{1}{a} \exp(-a) \left(1 + O\left(\frac{1}{a}\right)\right). \end{aligned} \quad (27)$$

Second, we use the change of variables $x^2 = 1 - z$ and Watson's Lemma to show that

$$\int_0^1 \exp(ax^2) dx = \exp(a) \int_0^1 \frac{\exp(-az)}{\sqrt{1-z}} dz \quad (28)$$

$$= \frac{\exp(a)}{2} \left(\frac{1}{a} + \frac{1}{2a^2} + O\left(\frac{1}{a^3}\right) \right). \quad (29)$$

Putting all of these together, we find that

$$-\frac{\ln(a)}{4a} + O\left(\frac{1}{a}\right) < \sigma(0) - \frac{\sqrt{\pi} \exp(a)}{2 a^{3/2}} \left(1 + O\left(\frac{1}{a}\right)\right) < 0, \quad (30)$$

so that the leading order approximation is

$$\sigma(0) \approx \frac{\sqrt{\pi} \exp(a)}{2 a^{3/2}} \left(1 + O\left(\frac{1}{a}\right)\right), \quad (31)$$

a well known result.

Now we turn to the forced problem, $f \neq 0$, and use the same method. That is, after multiplying by an integrating factor,

$$(\exp(-ax^2 + fx)\sigma')' = -\exp(-ax^2 + fx), \quad (32)$$

or

$$\sigma'(x) = -\exp(ax^2 - fx) \int_{-1}^x \exp(-a\eta^2 + f\eta) d\eta, \quad (33)$$

so that

$$\sigma(0) = \int_0^1 \int_{-1}^x \exp(a(x^2 - \eta^2) - f(x - \eta)) d\eta dx. \quad (34)$$

This is the integral we wish to approximate.

First we break this expression into two,

$$\sigma(0) = \int_0^1 \int_{-1}^1 \exp(a(x^2 - \eta^2) - f(x - \eta)) d\eta dx - \int_0^1 \int_x^1 \exp(a(x^2 - \eta^2) - f(x - \eta)) d\eta dx. \quad (35)$$

We can show that the second of these is small using the Cauchy-Schwarz inequality. That is,

$$\begin{aligned} \int_0^1 \int_x^1 \exp(a(x^2 - \eta^2) - f(x - \eta)) d\eta dx &\leq \left(\int_0^1 \int_x^1 \exp(2a(x^2 - \eta^2)) d\eta dx \int_0^1 \int_x^1 \exp(-2f(x - \eta)) d\eta dx \right)^{1/2} \\ &\leq \left(\frac{\exp(2F) - 1 - 2F}{4F^2} \left(\frac{\ln(a)}{8a} + O\left(\frac{1}{a}\right) \right) \right)^{1/2}. \end{aligned} \quad (36)$$

Now we approximate two integrals,

$$\begin{aligned} \int_{-1}^1 \exp(-a\eta^2 + f\eta) d\eta &= \exp\left(\frac{f^2}{4a}\right) \int_{-1}^1 \exp\left(-a\left(\eta - \frac{f}{2a}\right)^2\right) d\eta \\ &= \exp\left(\frac{f^2}{4a}\right) \int_{-\infty}^{\infty} \exp\left(-a\left(\eta - \frac{f}{2a}\right)^2\right) d\eta \\ &\quad - \exp\left(\frac{f^2}{4a}\right) \int_{-\infty}^{-1} \exp\left(-a\left(\eta - \frac{f}{2a}\right)^2\right) d\eta \\ &\quad - \exp\left(\frac{f^2}{4a}\right) \int_1^{\infty} \exp\left(-a\left(\eta - \frac{f}{2a}\right)^2\right) d\eta \\ &= \exp\left(\frac{f^2}{4a}\right) \int_{-\infty}^{\infty} \exp(-as^2) ds \\ &\quad - \exp\left(\frac{f^2}{4a}\right) \int_{1+f/2a}^{\infty} \exp(-as^2) ds \\ &\quad - \exp\left(\frac{f^2}{4a}\right) \int_{1-f/2a}^{\infty} \exp(-as^2) ds \\ &\approx \sqrt{\frac{\pi}{a}} \exp\left(\frac{f^2}{4a}\right) - \frac{1}{2a+f} \exp(-(a+f)) - \frac{1}{2a-f} \exp(-a+f), \end{aligned}$$

provided $\frac{f}{2a} < 1$.

To approximate the second, we assume that $\frac{f}{2a} < 1$ to write

$$\int_0^1 \exp(ax^2 - fx) dx = \int_0^{f/2a} \exp(ax^2 - fx) dx + \int_{f/2a}^1 \exp(ax^2 - fx) dx. \quad (37)$$

Now we introduce the change of variables $z = (\frac{f}{2a})^2 - (x - \frac{f}{2a})^2$ in the first of these and $z = (1 - \frac{f}{2a})^2 - (x - \frac{f}{2a})^2$ in the second, so that

$$\int_0^1 \exp(ax^2 - fx) dx = \int_0^{f/2a} \exp(ax^2 - fx) dx + \int_{f/2a}^1 \exp(ax^2 - fx) dx \quad (38)$$

$$= \frac{1}{2} \int_0^{(\frac{f}{2a})^2} \frac{\exp(-az)}{\sqrt{(\frac{f}{2a})^2 - z}} dz \quad (39)$$

$$+ \frac{1}{2} \exp(a - f) \int_0^{(1-\frac{f}{2a})^2} \frac{\exp(-az)}{\sqrt{(1-\frac{f}{2a})^2 - z}} dz. \quad (40)$$

A useful observation is that

$$\int_0^b \frac{\exp(-az)}{\sqrt{b-z}} dz \approx \frac{1}{a\sqrt{b}} \quad (41)$$

It follows that

$$\int_0^1 \exp(ax^2 - fx) dx \approx \frac{1}{f} + \frac{\exp(a-f)}{a-f}. \quad (42)$$

Finally, we obtain the leading order approximation

$$\sigma(0) \approx \frac{1}{2} \sqrt{\frac{\pi}{a}} \frac{\exp(a(1 - \frac{f}{2a})^2)}{a(1 - \frac{f}{2a})}, \quad (43)$$

which holds provided $a \gg 1$ and $f < 2a$.