Lecture "Soft matter physics"
(Prof. Dr. R. Seidel)

Lecture 7

Dynamics of reaction processes

- Reaction rates and rate laws
- Kinetics of reaction processes
- Reaction rates and equilibrium
- Transition state model of reaction processes
- Force-dependence of reaction rates

Only for internal use within the lecture

1) Kinetics of reaction processes

So far, we only considered occupancies/concentrations in equilibrium but did not consider any dynamics, i.e. how quick equilibrium is reached. Many systems including every living being are however a non-equilibrium systems. There is a **constant turnover of material** (proteins, RNAs, lipids, other macromolecules, small metabolites) i.e. a **constant production and degradation/decay cycles.**

Example 1: Daily turnover of ATP in an adult human: 40 kg!!!

Example 2: Dynamics of cytoskeleton
Cytoskeletal polymers within living cells are constantly growing and shrinking by addition and loss of protein subunits. One can reconstitute actin polymerization in vitro from purified monomers on a minute time scale. In vivo actin polymerization of aligned filaments pushes forward the leading edge of a crawling cell. Overall actin polymerization is a complex chemical reaction.
Hijacking actin polymerization by infectious bacteria (Listeria monocytogenes) can provide motion by a chemical reaction: nucleation of actin polymerization at its surface provides the production of comet tail made up of actin filaments that pushes the bacterium along at rates ranging between 0.05 and 1.4µm/s (**show slides**)

Understanding the dynamics of such processes are described by rate equations:

$$\frac{d\,c_i(t)}{d\,t} = f\left(\{c_j\};\{k_i\}\right)$$

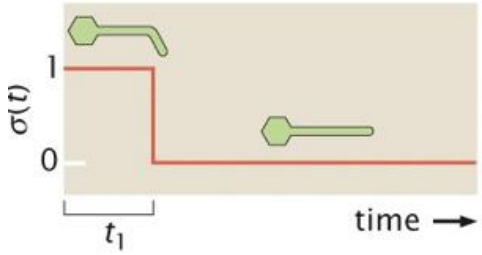
A change in concentration of a given species per time is a function of the concentration of different reactant species in solution and of certain rate constants that provide information about the speed of a given reaction.

A) Simple decay process (simplest example)

The simplest example is a decay process:

$$A \rightarrow B$$

such as a radioactive decay, excited electronic state of an atom/molecule, a molecular transition or molecule isomerization:



Such processes are typically modelled as a **Markov process**, i.e. **a stochastic process without memory (memoryless process)**. The Markov process makes future predictions assuming that the conditional probability distribution of future states of the process depends only upon the present state but not on the sequence of events that preceded it.

If the molecule is in state A then it decays within the interval dt at each time point to state B with the conditional probability:

$$dP_{i|A} = -kdt$$

where k is the **rate constant** (probability change per time) of the process. To consider the absolute (non-conditional) probability to decay within dt, one has to multiply the equation above with the probability to be in state A:

$$dP_A = -kP_A dt$$

Since $P_A + P_B = 1$, we get for P_B

$$dP_B = kP_A dt$$

This equation can be solved by separation of the variables and integration to yield the **probability to be in state A after time t**. At $t = 0$ we assume that the molecule is always in state A, i.e. $P_A(0) = 1$:

By separation of the variables we can easily transform the equation into an integral form:

$$\int_1^{p_A} \frac{dP_A}{P_A} = \int_0^t -k dt$$

from which we get the time dependence of P_A:

$$P_A(t) = e^{-t/\tau}$$

This is also called the **survival probability**, since it gives the probability that molecule A has not decayed yet. Using normalization we get also the time dependence of P_B:

$$P_B(t) = 1 - e^{-t/\tau}$$

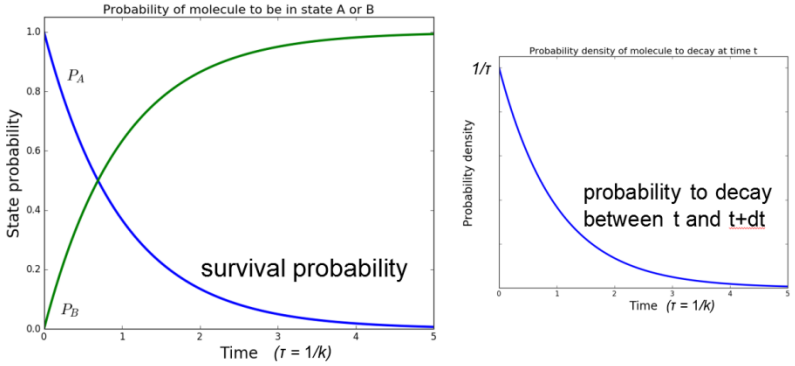
where $\tau = 1/k$ is the **characteristic decay time** when averaging over an ensemble of single decays. When looking at an **ensemble of molecules** at concentration $\boldsymbol{c_0}$ that all where in state A at $t = 0$, we can simply transform our probability into a concentration:

$$c(t) = c_0 P(t)$$

This yields:

$$c_A = c_0 e^{-t/\tau}$$

This is a typical result for a so-called first order reaction.



The survival probability gives the probability that the molecule has not decayed yet. It can be used to calculate the **probability p_A that a molecule decays within $t < t_{\text{decay}} < t + dt$**

from the change in survival probability between t and $t + dt$:

$$p_A(t)dt = |P_A(t + dt) - P_A(t)| \approx \left|P_A(t) + \left|\frac{dP_A}{dt}(t)\right| dt - P_A(t)\right| = \left|\frac{dP_A}{dt}(t)\right| dt = \frac{1}{\tau} e^{-t/\tau}$$

This distribution is normalized, since integration over the derivative of P_A provides P_A that has an initial value of 1. In other words, there must be a 100% chance to make a decay somewhen given enough time. The mean departure time from the original state (or the mean arrival time in the new state) is then given by:

$$\langle t_A \rangle = \int_0^\infty t \cdot p_A(t) dt = \tau = \frac{1}{k}$$

i.e. for an exponential kinetics $\boldsymbol{\tau = 1/k}$ is also **the mean time for a molecule to decay**.

B) General rate laws

Generally, reactions can be more complicated and involve multiple reactants + products in arbitrary stoichiometries, e.g. for example:

$$A + 2B \rightarrow 3C + D$$

In this case the changes in concentrations are linked by the stoichiometry:

$$\frac{d[D]}{dt} = \frac{1}{3}\frac{d[C]}{dt} = -\frac{d[A]}{dt} = -\frac{1}{2}\frac{d[B]}{dt} = v$$

where v provides the number of reactions done per time. This unique **rate of reaction** v can be written in the general form:

$$v = \frac{1}{\nu_j}\frac{d[J]}{dt}$$

where ν_J is the signed stoichiometry factor of a given reactant ($\nu_J < 0$) or product ($\nu_J > 0$). Generally, rate laws of reactions can be formulated in the following form

$$v = k[A]^a[B]^b \ldots$$

where $A, B, \ldots$ are the reactant concentrations. This **reaction is said to be of order a in A** (first, second, third, …) **of order b in B** and **of overall order $a + b + \ldots$** . Often the rate of the reaction can be written in a more simple form where the stoichiometry factors of the reactions equal the exponents in the rate law, i.e. $a = |\nu_A|$, $b = |\nu_B|$, … :

$$v = k[A]^{|\nu_A|}[B]^{|\nu_B|}$$

- **Example 1:** $2A \rightarrow B$

  $$v = \frac{d[B]}{dt} = k[A]^2$$

  which is a second order reaction

- **Example 2:** $A + B \rightarrow C$

  $$v = \frac{d[C]}{dt} = k[A][B]$$

  is a second order reaction. If $[B]_0 \gg [A]_0, [B]_0 \approx [B]$]. Then $k[B]_0$ is roughly constant:

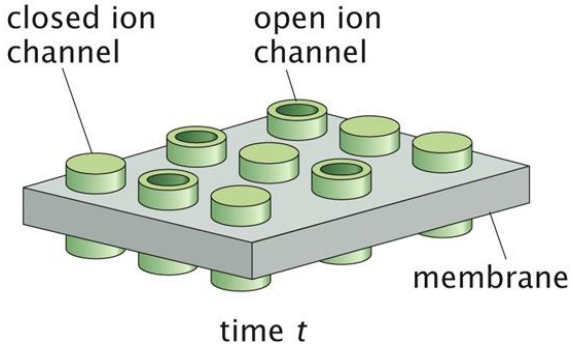
  $$v = k[A][B]_0 = k'[A]$$
  $$k' = k[B]_0$$

  is then a pseudo first-order reaction.

C) Example: Reversible conversion (reactions approaching equilibrium)

Channel gating kinetics, i.e. opening-closing transition of ion channel:

$$O \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C$$



In this case, one has to add the effect of both, the forward and the backward reaction, each providing a reaction rate in opposite direction. With this we can write a rate equation including **two different rate constants** for the change of the open probability per time:

$$\frac{dP_O}{dt} = -k_+ P_O + k_- P_C$$

With $P_O + P_C = 1$ we can transform this equation to:

$$\frac{dP_O}{dt} = -k_+ P_O + k_-(1 - P_O) = k_- - (k_+ + k_-)P_O$$

We next substitute:

$$p = k_- - (k_+ + k_-)P_O \quad and \quad \frac{dp}{dt} = -(k_+ + k_-)\frac{dP_O}{dt}$$

and get:

$$\frac{1}{-(k_+ + k_-)}\frac{dp}{dt} = p$$

Inserting and separation of the variables then gives:

$$\frac{1}{-(k_+ + k_-)}\int_{p_0}^{p}\frac{dp}{p} = \int_0^t dt$$

Solving the integral and inserting $p(t)$ into the relation for P_O then gives

$$P_O(t) = \frac{k_- - p}{k_+ + k_-} = \frac{k_- - p_0 e^{-(k_- + k_+)t}}{k_+ + k_-}$$

The starting conditions define the actual value of p_0. If all channels would be open at t = 0 due to a gating event ($P_O(0) = 1$), then $p_0 = -k_+$ and we arrive at:

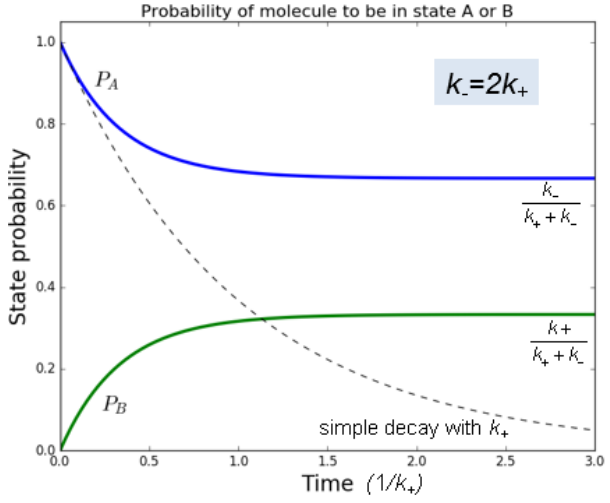
$$P_O = \frac{k_- + k_+ e^{-(k_- + k_+)t}}{k_+ + k_-}$$

The constant term in the equation is the equilibrium concentration:

$$P_O{}^{\mathrm{eq}} = \frac{k_-}{k_+ + k_-}$$

As one sees from the rate sum in the equation, equilibrium is reached faster with a backward reaction! The function can be considered as correlation function of state variable function $\langle\sigma(0)\sigma(t)\rangle$. Using the normalization condition from above we get for the closed-state probability:

$$P_C = \frac{k_+ - k_+ e^{-(k_- + k_+)t}}{k_+ + k_-}$$



D) Example: Two-step reaction

Reaction processes frequently involve multiple consecutive steps, where first intermediate products need to formed before one gets the final product. The simplest example for such a process would be:

$$A \overset{k_1}{\rightarrow} B \overset{k_2}{\rightarrow} C$$

Here we have 3 "concatenated" rate equations:

$$\dot{P}_A = -k_1 P_A$$
$$\dot{P}_B = +k_1 P_A - k_2 P_B$$
$$\dot{P}_C = +k_2 P_B$$

With $P_A = 1$ and $P_B = P_C = 0$ the solution to the first equation is simply our previous solution:

$$P_A(t) = e^{-k_1 t}$$

Using the normalization of the rate constants one can express P_B as:

$$P_B = 1 - e^{-k_1 t} - P_C$$

Inserting in the last equation then provides:

$$\dot{P}_C + k_2 P_C = k_2(1 - e^{-k_1 t})$$

Solving this set of linear differential equations gives for the probability for the arrival time in state C:

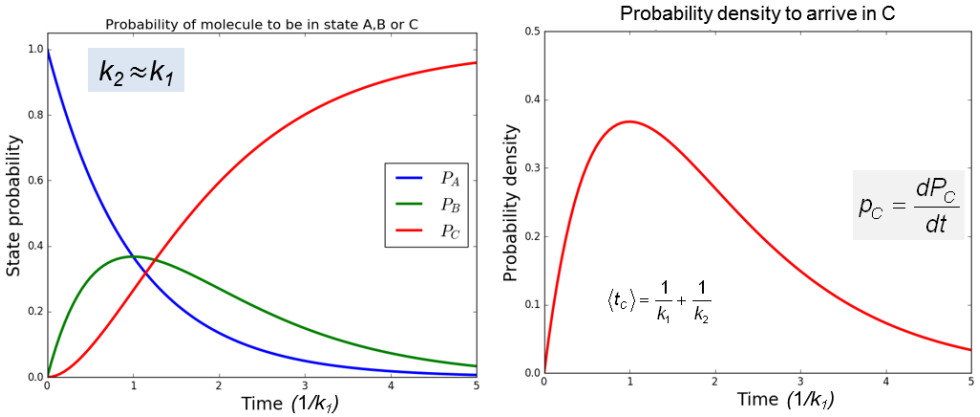
$$p_C = \frac{dP_C}{dt} = \frac{k_2 k_1}{k_2 - k_1}[e^{-k_1 t} - e^{-k_2 t}]$$

One can show that the mean arrival time in state C is given as:

$$\langle t_C \rangle = \frac{1}{k_1} + \frac{1}{k_2}$$

i.e. the mean times of the individual steps add up.

The final solutions for the time-dependence of the different species (left) as well as the probability density for the arrival time in state C is given in the following plot. One sees that the B state is only transiently.

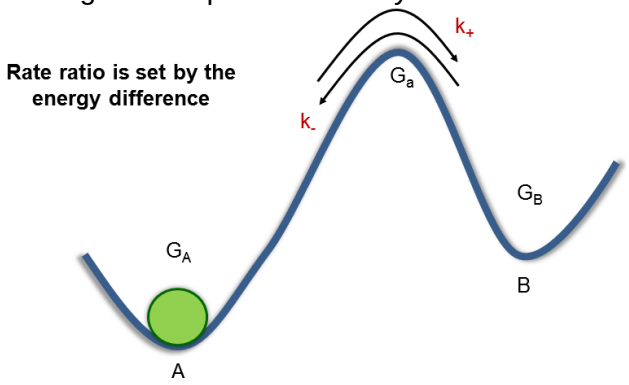


Solutions for the kinetics of reactions or reaction networks easily become very complex. In these cases, numeric integration is often used to solve the kinetics.

2) Rates and equilibrium

As we discussed before, equilibrium does not mean that reaction are not taking place. Rather, we have no net change of product and reaction species, i.e. the forward reaction goes on with the

same rate as the backward reaction. Thus, the **equilibrium is dynamic**. Let us understand the consequences of this by looking at a simple two state system:



According to the considerations above, the change in the B state occupancy is given by:

$$\frac{dP_B}{dt} = k_+ P_A - k_- P_B = 0$$

It is zero in equilibrium, where the state occupancy remains constant in time. This is the **principle of detailed balance** stating that **in equilibrium each elementary process should be equilibrated by its reverse process.**

We can thus write

$$\frac{P_B}{P_A} = \frac{k_+}{k_-} = e^{-\overbrace{(G_B - G_A)}^{\Delta_r G^\circ}/k_\mathrm{B}T} = K_\mathrm{eq}$$

where we **obtain the exponential term on the right hand side of the equation from the Boltzmann distribution which holds for the probability ratio in equilibrium**. For a two-state system this is nothing else than the **equilibrium constant**.

The **equality between the equilibrium constant and the rate ratio of forward and backward rate** can also be shown for more complex reactions e.g. ligand-receptor binding:

$$L + R \rightleftharpoons LR$$

where we can write:

$$\frac{d[LR]}{dt} = -k_\mathrm{off}[LR] + k_\mathrm{on}[L][R]$$

with on-rate k_{on} for association and off-rate k_off for dissociation. In equilibrium $d[LR]/dt = 0$, such that we get after transformation:

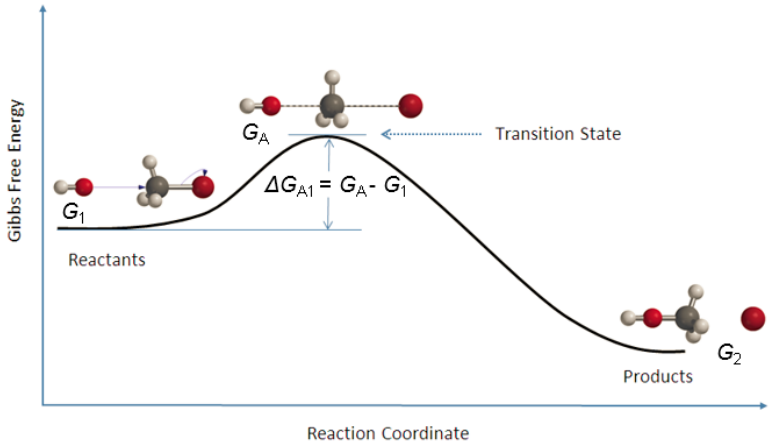
$$K_\mathrm{d} = \frac{[L]_\mathrm{eq}[R]_\mathrm{eq}}{[LR]_\mathrm{eq}} = \frac{k_\mathrm{off}}{k_\mathrm{on}}$$

This is the mass action law with dissociation constant K_d (can also be obtained more generally for complex reactions). **Equilibrium constant, standard free energy of the reaction and the associated kinetic rate constants are thus connected**. However, only rates but not the equilibrium constant reveal the reaction kinetics.

3) Transition state model of chemical reactions

A) Arrhenius equation

Properties of first order chemical reactions can often be understood when assuming that the reaction proceeds via a high-energy **activated/transition state** with free energy G_A above the initial state:



Assumptions for this model are:

(i) The reactant at free energy G_1 is in equilibrium with the activated state G_A

(ii) For the back reaction, the product at G_2 is in equilibrium with the activated state G_A

(iii) The activated state is equally likely to break down to reactant or product

In this case, the population of the activated state is given by Boltzmann distribution:

$$p_A/p_1 = e^{-(G_A - G_1)/k_B T}$$

Thus, the rate constant of the forward reaction is described by:

$$k_1 = A\, e^{-\Delta G_{A1}/k_B T}$$

with $\Delta G_{A1} = G_A - G_1$ being the so-called **transition-state barrier or activation energy**.

This equation is called **Arrhenius equation** and the constant *A* is called the **pre-exponential** or **frequency factor**. It is valid for many thermally activated processes in chemistry, physics and biology and describes their temperature dependence. Strictly speaking, the temperature dependence is just given by the activation enthalpy (or internal energy) since we can write:

$$k_1 = A \cdot e^{-(\Delta H_{A1} - T\Delta S_{A1})/k_B T} = A \cdot e^{\Delta S_{A1}/k_B} e^{-\Delta H_{A1}/k_B T}$$

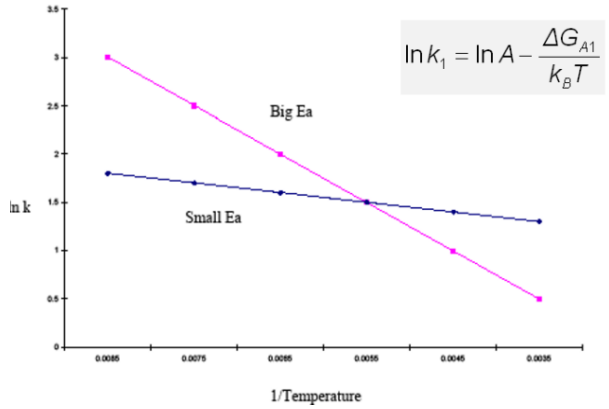
For the **backward reaction**, the Arrhenius law would be given as:

$$k_2 = A \cdot e^{-(G_A - G_2)/k_B T}$$

The Arrhenius law can be used to determine the activation energy by measuring the **temperature-dependent rate constant**. The logarithm of the rate is provided as:

$$\ln\, k_1 = \ln A - \frac{\Delta G_{A1}}{k_B T}$$

i.e. it can be obtained from the slope the rate plotted over $1/T$ in a semilogarithmic plot. **Such a plot is called Arrhenius plot**:



Transition state barriers for biochemical reactions are often in the range of $20-40\ k_B T$. This provides a 2-fold to 4-fold rate increase for a temperature increase by 10K. Therefore, the metabolism of living organisms is highly temperature dependent, which is e.g. used when cooling food to prevent bacterial and fungal growth.

B) Models for preexponential factors

Several models have been formulated to describe the preexponential factor.

Eyring rate theory (Henry Eyring – 1935):

In the Eyring theory, the reaction rate is assumed to correspond to the **breakdown of a single quantum mechanical vibration of the molecule of interest.** In this case, the preexponential factor provides something like the vibration frequency of the loosely bound transition state. The rate equation becomes:

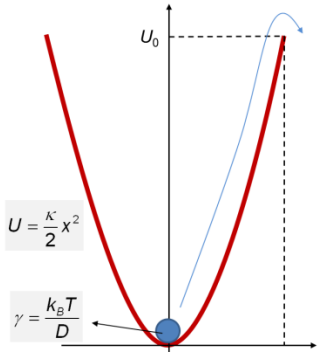
$$k_1 = \frac{k_B T}{h} \cdot e^{-\Delta G_{A1}/k_B T}$$

where *h* is the Planck constant. The preexponential factor corresponds to 6x10^{12} s^{-1}. The Eyring rate theory is suited to describe chemical reactions between small molecules, that can be described by few quantum states. For larger objects, in which multiple bonds have to be broken to form the product (e.g. conformational change of a protein), it is not valid.

Kramers rate theory (Kramers 1940):

Kramers theory applies to systems that are in contact with a viscous medium. Here conformational changes that are required to reach the transition state are thought to be limited by the diffusion within the solvent. The system is assumed to possess a drag coefficient γ at which it diffuses into the transition state.

Kramers calculated the time for an object with drag coefficient $\gamma = k_B T/D$ (D being the diffusion coefficient) to diffuse out of a harmonic potential with spring constant κ and height U_0.



This is known as the Kramers time:

$$t_k = \underbrace{\frac{\gamma}{\kappa}}_{\tau} \frac{\sqrt{\pi}}{2} \sqrt{\frac{k_B T}{U_0}}\, e^{U_0/k_B T}$$

The prefactor $\tau = \gamma/\kappa$ is in this case the relaxation time for a harmonic-oscillator system under conditions of strong overdamping as typically obeyed for microscopic systems.

The Kramers rate for reactions that are fully coupled to the medium viscosity is then given as

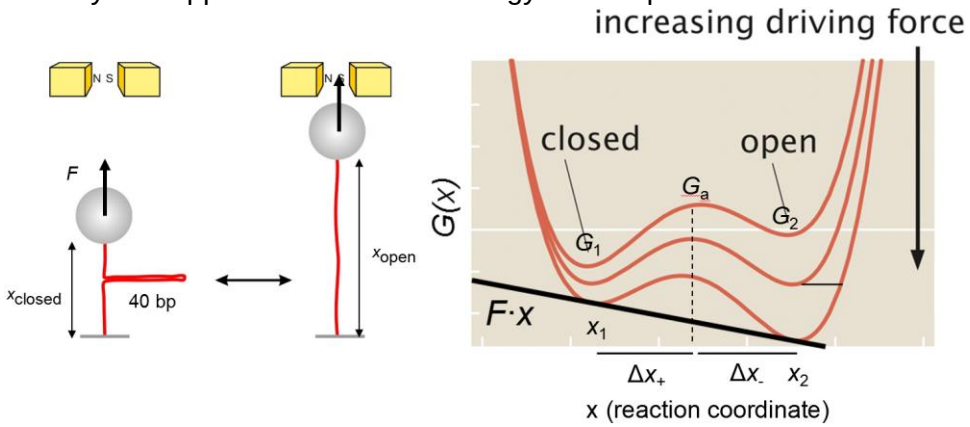
$$k_1 = \frac{\varepsilon_1}{2t_k} = \frac{\varepsilon_1}{\sqrt{\pi}} \frac{\kappa}{\gamma} \sqrt{\frac{\Delta G_{A1}}{k_B T}}\, e^{-\Delta G_{A1}/k_B T}$$

where the additional factor ε_1 denotes the efficiency at which the reaction is done once the potential edge is reached. The additional factor 2 accounts for the fact that only escapes to a single side of the potential are counted. The Kramers rate theory is only valid, if τ is large over the time the solvents needs to relax to follow the conformational changes of the reactants. If τ is too small, so called hydrodynamic memory effects occur.

C) Force dependence of reaction rates

In case of an external driving force and a reaction where the "extension/alignment" of the system changes along the force direction (e.g. a length change under the influence of a force during a conformational change of a molecule), the external force can not only change the equilibrium but also the rates of the reaction.

We saw previously that applied force tilts the energy landscape:



since it reduces the free energy of the system by the work that the force has done on it. This can be expressed as:

$$G(x,F) = G(x,0) - Fx$$

in case of an assisting force acting along the reaction coordinate with x.

The **activation energy for the forward reaction** from the initial state 1 proceeding **along the force direction** is then given as

$$\Delta G_{a1}(F) = G(x_a,F) - G(x_1,F) = \underbrace{\Delta G_{a1}(0)}_{G(x_a,0)-G(x_1,0)} - F\,\underbrace{\Delta x_+}_{x_a-x_1}$$

where Δx_+ is the physical distance of the transition state from the initial state 1. For an assisting (positive) force, the activation energy ΔG_{a1} is lowered, such that the reaction rate increases. Likewise, the **free energy change for the reverse reaction** is given for the distance of the transition state from state 2 $\Delta x_- = x_2 - x_a$ (inserted as positive value) as:

$$\Delta G_{a2}(F) = \Delta G_{a0} + F\Delta x_-$$

Since the free energy of state 2 is reduced more strongly than the transition state, the activation barrier for the reverse reaction increases. Under force, forward and backward rates thus change within the transition state model to:

$$k_+(F) = A \cdot e^{-\beta[\Delta G_{a1} - F\Delta x_+]} = k_+(0)e^{\beta F\Delta x_+}$$
$$k_-(F) = A \cdot e^{-\beta[\Delta G_{a2} + F\Delta x_-]} = k_-(0)e^{-\beta F\Delta x_-}$$

Where $k_+(0)$ and $k_-(0)$ are the forward and backward rates of the reactions in absence of force. Thus, the **forward rate is increasing and the backward rate is decreasing** with an applied force along the reaction coordinate (see **slides** for force regulated binding of the protein RPA to DNA).

We can furthermore determine the equilibrium constant as function of force from the rate ratio:

$$K_{\mathrm{eq}}(F) = \frac{k_+(F)}{k_-(F)} = \frac{k_+(0)e^{F\Delta x_+/k_\mathrm{B}T}}{k_-(0)e^{-F\Delta x_-/k_\mathrm{B}T}} = K_{\mathrm{eq}}(0)e^{F(\Delta x_+ + \Delta x_-)/k_\mathrm{B}T}$$

In the exponent, the total distance between initial state 1 and final state 2 enters, which equals our previous finding for the two-state system under force.