21.4: Biomolecular Kinetics

Returning to our basic two-state scheme, we define the rate constants k_a and k_d for the association and dissociation reactions:

$$A + B \underset{k_d}{\overset{k_a}{\rightleftharpoons}} C \tag{21.4.1}$$

From detailed balance, which requires that the total flux for the forward and back reactions be equal under equilibrium conditions:

$$K_a = \frac{k_a}{k_d} \tag{21.4.2}$$

The units for K_a are M^{-1}, $M^{-1}s^{-1}$ for k_a, and s^{-1} for k_d.

For the case where we explicitly consider the AB encounter complex:

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (AB) \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C \tag{21.4.3}$$

Schemes of this sort are referred to as reaction–diffusion problems. Note, this corresponds to the scheme used in Michaelis–Menten kinetics for enzyme catalysis, where AB is an enzyme–substrate complex prior to the catalytic step.

The kinetic equations corresponding to this scheme are often solved with the help of a steady-state approximation ($\partial[AB]/\partial t \approx 0$), leading to

$$\frac{d[C]}{dt} = k_a[A][B] - k_d[C] \tag{21.4.4}$$

$$k_a = \frac{k_1 k_2}{(k_{-1} + k_2)} \qquad k_d = \frac{k_{-1} k_{-2}}{k_{-1} + k_2} \tag{21.4.5}$$

Let's look at the limiting scenarios:

1. Diffusion controlled reactions refer to the case when reaction or final association is immediate once A and B diffusively encounter one another, i.e., $k_2 \gg k_{-1}$. Then the observed rate of product formation $k_a \approx k_1$,and we can then equate k_1 with the diffusion-limited association rate we have already discussed.
2. Pre-Equilibrium. When the reaction is limited by the chemical step, an equilibrium is established by which A and B can associate and dissociate many times prior to reaction, and the AB complex establishes a pre-equilibrium with the unbound partners defined by a nonspecific association constant $K'_a = k_1/k_{-1}$. Then the observed association rate is $k_a = k_2 K'_a$.

What if both diffusion and reaction within encounter complex matter? That is the two rates $k_1 \approx k_2$.

$$A + B \underset{}{\overset{k_a}{\rightleftharpoons}} AB \overset{k_{rxn}}{\rightleftharpoons} C \tag{21.4.6}$$

Now all the rates matter. This can be solved in the same manner that we did for diffusion to capture by a sphere, but with boundary conditions that have finite concentration of reactive species at the critical radius. The steady-state solution gives:

$$k_{eff} = \frac{k_a k_{rxn}}{k_a + k_{rxn}}$$
$$k_{eff}^{-1} = k_a^{-1} + k_{rxn}^{-1}$$

k_{eff} is the effective rate of forming the product C. It depends on the association rate k_a (or k_1) and k_{rxn} is an effective forward reaction rate that depends on k_2 and k_{-1}.

Competing Factors in Diffusion–Reaction Processes

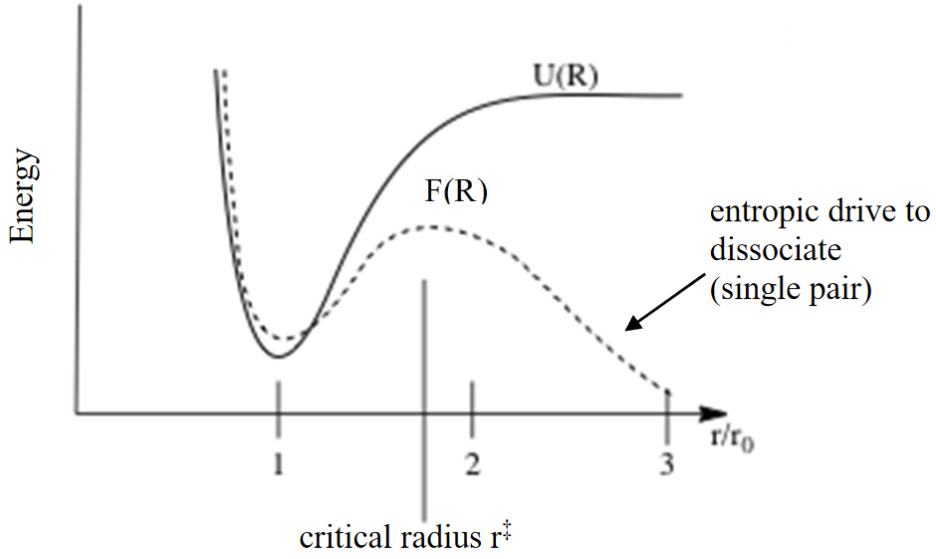
In diffusion–reaction processes, there are two competing factors that govern the outcome of the binding process. These are another manifestation of the familiar enthalpy–entropy compensation effects we have seen before. There is a competition between enthalpically favorable contacts in the bound state and the favorable entropy for the configurational space available to the unbound partners. Overall, there must be some favorable driving force for the interaction, which can be expressed in terms of a binding potential $U_{AB}(R)$ that favors the bound state. On the other hand, for any one molecule A, the translational configuration space available to the partner B will grow as R^2.

We can put these concepts together in a simple model.[1] The probability of finding B at a distance R from A is

$$P(R)dR = Q^{-1}e^{-U(R)/kT}4\pi R^2 dR \tag{21.4.7}$$

where Q is a normalization constant. Then we can define a free energy along the radial coordinate

$$\begin{aligned} F(R) &= -k_B T \ln P(R)dR \\ &= U(R) - k_B T \ln R^2 - \ln Q \end{aligned}$$



Here F(R) applies to a single A-B pair, and therefore the free energy drops continuously as R increases. This corresponds to the infinitely dilute limit, under which circumstance the partners will never bind. However, in practice there is a finite volume and concentration for the two partners. We only need to know the distance to the nearest possible binding partner $\langle R_{AB} \rangle$. We can then put an upper bound on the radii sampled on this free energy surface. In the simplest approximation, we can determine a cut off radius in terms of the volume available to each B, which is the inverse of the B concentration: $\frac{4}{3}\pi r_c^3 = [B]^{-1}$. Then, the probability of finding the partners in the bound state is

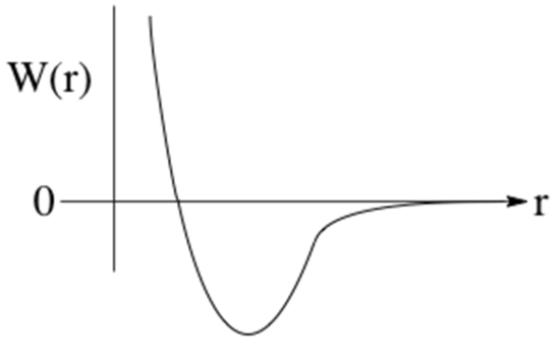
$$P_a = \frac{\int_0^{r^*} e^{-F(r)/k_B T}4\pi r^2 dr}{\int_0^{r_c} e^{-F(r)/k_B T}4\pi r^2 dr} \tag{21.4.8}$$

At a more molecular scale, the rates of molecular association can be related to diffusion on a potential of mean force. g(r) is the radial distribution function that describes the radial variation of B density about A, and is related to the potential of mean force W(r) through $g(r) = exp[-W(r)/k_B T]$. Then the association rate obtained from the flux at a radius defined by the association barrier (r = $r^{\dagger}$) is

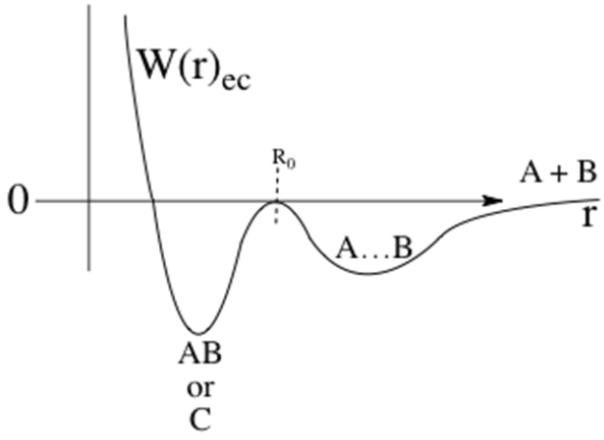
$$k_a^{-1} = \int_{r^{\dagger}}^{\infty} dr[4\pi r^2 D(r) e^{-W(r)/k_B T}]^{-1} \tag{21.4.9}$$

Here D(r) is the radial diffusion coefficient that describes the relative diffusion of A and B. The spatial dependence reflects the fact that at small r the molecules do not really diffuse independently of one another.

For weakly attractive:



or structural/large solutes
or encounter complex



1. D. A. Beard and H. Qian, *Chemical Biophysics*; *Quantitative Analysis of Cellular Systems*. (Cambridge University Press, Cambridge, UK, 2008).