# ENTROPY IN BIOLOGY

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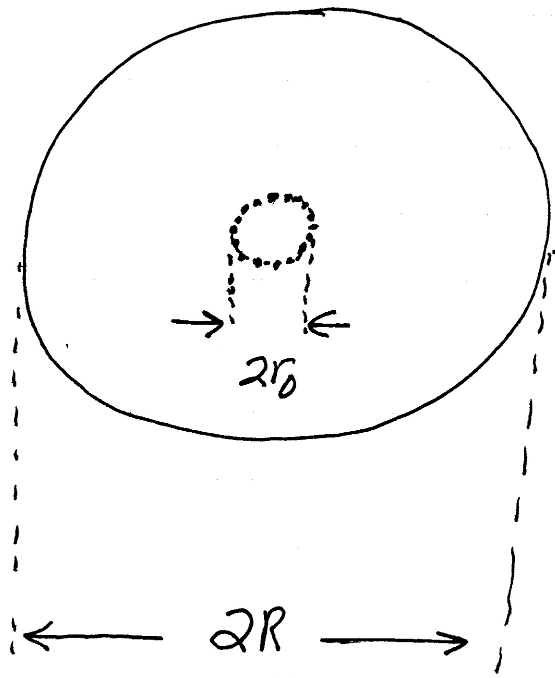
## Lecture 12: Bimolecular Reaction Rates with Diffusion and Detailed Balance

- Implication of detailed balance for a spatial model of binding/unbinding with diffusion.
- Equilibrium constant
- Evaluation of $k_{on}$
- Evaluation of $P_{escape}$ and $k_{off}$
- Project suggestion

# Bimolecular reaction rates with diffusion and detailed balance




Consider a particle that diffuses with diffusion coefficient $D$ within a domain $\Omega$ that is the interior of a sphere of radius $R$, centered on the origin, in $\mathbb{R}^3$.

Let $\Omega_0$ be the interior of a sphere of radius $r_0 \ll R$, also centered on the origin.

The diffusing particle can freely enter and leave $\Omega_0$, and its diffusion coefficient within $\Omega_0$ is also $D$.

When the diffusing particle is within $\Omega_0$, it can <u>bind</u>, with probability per unit time $\lambda$.

When the particle is bound, it can <u>unbind</u> with probability per unit time $\mu$.

The location of a bound particle is undefined. We can think of it, if we like, as wandering within $\Omega_0$, but our model does not provide any description of the bound state.

At the moment that a particle becomes unbound, it is randomly assigned a position with probability density $\sigma_0(\underline{x})$. The function $\sigma_0(\underline{x})$ will be determined by an argument based on detailed balance.

Let

(1) $P(t)$ = probability that the particle is bound at time $t$

(2) $\int_{\Omega'} \rho(\underline{x},t)\, d\underline{x}$ = probability that the particle is unbound at time $t$ and has $x \in \Omega' \subset \Omega$, for any such $\Omega'$.

Since the particle is either bound or unbound, we get

(3) $$P(t) + \int_{\Omega} \rho(\underline{x},t)\, d\underline{x} = 1$$

The dynamics of $P$ and $\rho$ are given by the following equations

$$(4) \quad \frac{\partial \rho}{\partial t}(\underline{x},t) = D(\Delta\rho)(\underline{x},t) - \lambda u_0(\underline{x})\rho(\underline{x},t) + \mu\,\sigma_0(\underline{x})\,P(t)$$

$$(5) \quad \frac{dP}{dt}(t) = \lambda \int_{\Omega_0} \rho(\underline{x},t)\,d\underline{x} - \mu P(t)$$

where

$$(6) \quad u_0(\underline{x}) = \begin{cases} 1 , & x \in \Omega_0 \\ 0 , & x \notin \Omega_0 \end{cases}$$

and where $\rho(\underline{x},t)$ satisfies the boundary condition

$$(7) \quad \hat{\underline{r}} \cdot \nabla\rho = 0 \quad , \quad \|\underline{x}\| = R$$

in which $\hat{\underline{r}}$ is a unit vector in the radial direction.

Note that (4) & (5) are consistent with the normalization (3). For this it is important that

$$\int_\Omega \sigma_0(\underline{x})\, d\underline{x} = 1 \tag{8}$$

and this is valid, since $\sigma_0$ is a probability density function.

At thermodynamic equilibrium, the principle of detailed balance states that there are no net fluxes of any process — in particular no diffusion fluxes. Therefore, at thermodynamic equilibrium

$$\rho = \text{constant} \tag{9}$$

in both space and time, and of course $P$ is independent of time. It then follows from (5) that

(10) $$\lambda V_0 \rho = \mu P$$

Substituting (10) into (4) with $\rho$ = constant yields the conclusion that

(11) $$\sigma_0(x) = \frac{u_0(x)}{V_0}$$

Thus, the principle of detailed balance leaves us with no choice about the assignment of a location to a particle as it becomes unbound; the location must be chosen by sampling from the uniform distribution supported on $\Omega_0$. Note that this conclusion does not depend at all on the shapes or relative sizes of $\Omega$ and $\Omega_0$.

Making use of (11), we can rewrite (4) as follows:

(12) $$\frac{\partial \rho}{\partial t}(\underline{x},t) = D(\Delta\rho)(\underline{x},t) + u_0(\underline{x})\left(-\lambda\rho(\underline{x},t) + \frac{\mu}{V_0}P(t)\right)$$

let

(13) $$K = \frac{\mu}{\lambda V_0}$$

which has units of concentration. Then (10) becomes

(14) $$\rho = KP$$

and by substituting this into (3), we get

(15) $$P = \frac{1}{1 + KV}$$

and then

(16) $$\rho = \frac{K}{1 + KV}$$

(17) $$\rho V = \frac{KV}{1 + KV}$$

We claim that $K$ is the equilibrium constant (dissociation constant) of the reaction

(18) $$A + B \underset{K}{\rightleftharpoons} AB$$

where $A$ denotes the free diffusing particle, $B$ denotes the region $\Omega_0$ with no particle bound, and $AB$ denotes the bound state of the system. To verify this interpretation of $K$, recall the theory of the previous lecture, in which we considered the microscopic equilibrium of the reaction (18). Here we have the special case of that theory in which

(19) $$n_A = n_B = 1$$

and then equation (43) of the previous lecture becomes

(20) $$p_n = \left(\frac{1}{KV}\right)^n \frac{1}{(1-n)!(1-n)!\,n!}\, p_0$$

for $n=0$ or $1$. Setting $n=0$ just gives

$p_0 = p_0$, and setting $n = 1$ gives

(21) $$p_1 = \frac{1}{KV}\, p_0$$

Since $p_0 + p_1 = 1$, this implies

(22) $$p_0 = \frac{KV}{1+KV}$$

(23) $$p_1 = \frac{1}{1+KV}$$

In our present notation $p_0 = \rho V$ and $p_1 = P$, so equation (22) is the same as (17), and equation (23) is the same as (15). This establishes the interpretation of $K$ as the equilibrium constant of the reaction.

An important remark is that the macroscopic formula for $K$ is not valid here because we are dealing with small (indeed, smallest possible!) numbers of molecules. At equilibrium, we have

(24) $$[A]=[B]=\frac{p_0}{V}$$

(25) $$[AB]=\frac{p_1}{V}$$

and therefore

(26) $$\frac{[A][B]}{[AB]}=\frac{p_0^2}{p_1 V}=K\frac{KV}{1+KV}\neq K$$

Now that we have a formula for the equilibrium constant, we would also like to derive formula for the rate constants for binding and unbinding. It would be reasonable to think that $k_{off} = \mu$ and $k_{on} = \lambda V_0$, and indeed

it is hard to see how $k_{off}$ could be anything other than $\mu$, and then $k_{on}$ has to be $\lambda V_0$, given our formula for $K$. This has the right units and seems perfectly reasonable, but in fact it is incorrect!

To determine $k_{ON}$, we imagine that we have an ensemble of systems of the type described above, at equilibrium. We choose a member of the ensemble in which the particle is known to be unbound at $t=0$, and we follow that system until the particle first binds, and we note the time at which this first binding event occurs. We do this repeatedly and build up a distribution of the exit (binding) times.

Since the process we are considering now terminates when the particle binds, it is fully described by

(27) $$\frac{\partial \rho}{\partial t} = D \Delta \rho - \lambda u_0(\underline{x}) \rho$$

with the boundary condition (7).

The initial condition is

(28) $$\rho(\underline{x}, 0) = \frac{1}{V}$$

since we start from the equilibrium distribution conditioned on the particle's state being unbound at $t=0$.

The probability that the particle is still unbound at time $t$ is given by

(29) $$\int_{\Omega} \rho(\underline{x}, t)\, d\underline{x}$$

Let $f(t)$ be the probability density function for the exit time, i.e., the time at which the particle binds. It is given by

$$f(t) = -\frac{d}{dt}\int_{\Omega} \rho(\underline{x},t)\,d\underline{x} \tag{30}$$

$$= \lambda \int_{\Omega_0} \rho(\underline{x},t)\,d\underline{x}$$

In the last step of the foregoing, we integrated both sides of (27) over $\Omega$.

In spherical coordinates and assuming spherical symmetry, we have the following problem:

(31) $$\frac{\partial \rho}{\partial t} = D \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial \rho}{\partial r}\right) - \lambda \rho, \quad 0 < r < r_0$$

(32) $$\frac{\partial \rho}{\partial t} = D \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial \rho}{\partial r}\right), \quad r_0 < r < R$$

with $\rho$ and $\partial\rho/\partial r$ continuous at $r = r_0$, and with

(33) $$\frac{\partial \rho}{\partial r}(0,t) = \frac{\partial \rho}{\partial r}(R,t) = 0$$

(34) $$\rho(r,0) = \frac{1}{V}$$

Note that (34) holds for all $r \in (0,R)$, not merely for $r > r_0$.

This system can be solved by Laplace transform..

Let

(35) $$\tilde{\rho}(r,s) = \int_0^\infty e^{-st} \rho(r,t)\, dt$$

and recall the standard result (derived using integration by parts) that

(36) $$\widetilde{\left(\frac{\partial \rho}{\partial t}\right)}(r,s) = \int_0^\infty e^{-st} \frac{\partial \rho}{\partial t}(r,t)\, dt$$

$$= -\rho(r,0) + s\tilde{\rho}(r,s)$$

In terms of $\tilde{\rho}$, our problem is the following:

(37) $$(\lambda + s)\tilde{\rho}(r,s) = \frac{1}{V} + D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\tilde{\rho}(r,s)\right),$$

$$0 < r < r_0$$

(38) $$s\tilde{\rho}(r,s) = \frac{1}{V} + D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\tilde{\rho}(r,s)\right),$$

$$r_0 < r < R$$

with $\tilde{\rho}$ and $\partial\tilde{\rho}/\partial r$ continuous at $r = r_0$,
and with

(39) $$\frac{\partial \tilde{\rho}}{\partial r}(0,s) = \frac{\partial \tilde{\rho}}{\partial r}(R,s) = 0$$

Now let

(40) $$\tilde{\rho}(r,s) = \frac{1}{r}\,\tilde{\phi}(r,s)$$

Then

(41) $$\frac{\partial \tilde{\rho}}{\partial r} = -\frac{1}{r^2}\,\tilde{\phi} + \frac{1}{r}\,\frac{\partial \tilde{\phi}}{\partial r}$$

(42) $$r^2 \frac{\partial \tilde{\rho}}{\partial r} = -\tilde{\phi} + r\frac{\partial \tilde{\phi}}{\partial r}$$

(43) $$\frac{\partial}{\partial r}\left(r^2 \frac{\partial \tilde{\rho}}{\partial r}\right) = \cancel{-\frac{\partial \tilde{\phi}}{\partial r} + \frac{\partial \tilde{\phi}}{\partial r}} + r\frac{\partial^2 \tilde{\phi}}{\partial r^2}$$

(44) $$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial \tilde{\rho}}{\partial r}\right) = \frac{1}{r}\,\frac{\partial^2 \tilde{\phi}}{\partial r^2}$$

Therefore, when rewritten in terms of $\tilde{\phi}$, our problem is as follows:

$$(\lambda+s)\,\tilde{\phi} = \frac{r}{V} + D\frac{\partial^2\tilde{\phi}}{\partial r^2}\,, \quad 0<r<r_0 \tag{45}$$

$$s\,\tilde{\phi} = \frac{r}{V} + D\frac{\partial^2\tilde{\phi}}{\partial r^2}\,, \quad r_0<r<R \tag{46}$$

with $\tilde{\phi}$ and $\frac{\partial\tilde{\phi}}{\partial r}$ continuous at $r=r_0$,

and with

$$\tilde{\phi}(0,s)=0\,, \quad \tilde{\phi}(R,s) = R\frac{\partial\tilde{\phi}}{\partial r}(R,s) \tag{47}$$

<u>Remark</u>: The condition $\tilde{\phi}(0,s)=0$ is certainly needed to keep $\tilde{\rho}$ bounded as $r\to 0$. It is not obvious that this will ensure $\frac{\partial\tilde{\rho}}{\partial r}(0,s)=0$, but we can check later that this is the case.

The unique solution of (45-47) is:

$$(48)\quad \tilde{\phi} = \frac{r}{(\lambda+s)V} + a \sinh\left(\sqrt{\frac{\lambda+s}{D}}\, r\right), \quad 0<r<r_0$$

$$(49)\quad \tilde{\phi} = \frac{r}{sV} + b\left(R\sqrt{\frac{s}{D}} \cosh\left(\sqrt{\frac{s}{D}}(R-r)\right) - \sinh\left(\sqrt{\frac{s}{D}}(R-r)\right)\right), \quad r_0<r<R$$

where $a$ and $b$ are to be determined by imposing the continuity of $\tilde{\phi}$ and $\partial\tilde{\phi}/\partial r$ at $r=r_0$

Note that $\tilde{\phi}(0,s)=0$, and moreover

$\tilde{\rho}(r,s) = \frac{\tilde{\Phi}(r,s)}{r}$ satisfies $\frac{\partial\tilde{\rho}}{\partial r}(0,s) = 0$

Also,

for $r \in (r_0, R)$, we have

(50) $$\frac{\partial \tilde{\phi}}{\partial r} = \frac{1}{sV} + b\left(-R\frac{s}{D}\sinh\left(\sqrt{\frac{s}{D}}(R-r)\right) + \sqrt{\frac{s}{D}}\cosh\left(\sqrt{\frac{s}{D}}(R-r)\right)\right)$$

and if we evaluate this at $r=R$, we get

(51) $$\frac{\partial \tilde{\phi}}{\partial r}(R,s) = \frac{1}{sV} + b\sqrt{\frac{s}{D}}$$

so

(52) $$R\frac{\partial \tilde{\phi}}{\partial r}(R,s) = \frac{R}{sV} + bR\sqrt{\frac{s}{D}} = \tilde{\phi}(R,s)$$

see (49). Thus $\tilde{\phi}(r,s)$ satisfies the boundary condition at $r=R$ that is equivalent to $\frac{\partial \tilde{\rho}}{\partial r}(R,s) = 0$ .

The equations that determine $a, b$ are as follows:

From continuity of $\tilde{\phi}$ at $r = r_0$:

(53) $$\frac{r_0}{(\lambda+s)V} + a \sinh\left(\sqrt{\frac{\lambda+s}{D}}\, r_0\right) =$$

$$\frac{r_0}{sV} + b\left(R\sqrt{\frac{s}{D}} \cosh\left(\sqrt{\frac{s}{D}}(R-r_0)\right) - \sinh\left(\sqrt{\frac{s}{D}}(R-r_0)\right)\right)$$

and from the continuity of $\partial\tilde{\phi}/\partial r$ at $r = r_0$:

(54) $$\frac{1}{(\lambda+s)V} + a\sqrt{\frac{\lambda+s}{D}} \cosh\left(\sqrt{\frac{\lambda+s}{D}}\, r_0\right) =$$

$$\frac{1}{sV} + b\left(-R\frac{s}{D} \sinh\left(\sqrt{\frac{s}{D}}(R-r_0)\right) + \sqrt{\frac{s}{D}} \cosh\left(\sqrt{\frac{s}{D}}(R-r_0)\right)\right)$$

Let

(55) $$\theta_0 = \sqrt{\frac{\lambda+s}{D}}\, r_0 \,, \quad \psi_0 = \sqrt{\frac{s}{D}}\, r_0 \,, \quad \psi = \sqrt{\frac{s}{D}}\, R$$

Then equations (53-54) become, after multiplication by $r_0$ in (54)

(56) $$a \sinh\theta_0 - b\left(\psi \cosh(\psi-\psi_0) - \sinh(\psi-\psi_0)\right)$$
$$= \frac{r_0}{V}\left(\frac{1}{s} - \frac{1}{\lambda+s}\right)$$

(57) $$a\theta_0 \cosh\theta_0 - b\psi_0\left(\cosh(\psi-\psi_0) - \psi \sinh(\psi-\psi_0)\right)$$
$$= \frac{r_0}{V}\left(\frac{1}{s} - \frac{1}{\lambda+s}\right)$$

Instead of solving this pair of equations, which is easy to do but leads to messy results, we consider a limiting case:

Let $r_0 \to 0$, $\lambda \to \infty$ in such a way that

(58) $$\sqrt{\frac{\lambda}{D}}\, r_0 = \overline{\theta_0}$$

with $\overline{\theta_0}$ constant. In that case, for any fixed $s$,

(59) $$\theta_0 \to \overline{\theta_0}$$

Also, when $r_0 \to 0$,

(60) $$\psi - \psi_0 \to \psi$$

and when $\lambda \to \infty$

(61) $$\frac{1}{s} - \frac{1}{\lambda + s} \to \frac{1}{s}$$

We look for a solution of (56-57) in which $a$ and $b$ are $O(r_0)$, and in that case we can drop the term involving $b$ in (57) since it is $O(r_0^2)$ because it contains $\psi_0 = O(r_0)$ as well as $b$.

After these simplifications, we have

$$a \sinh \bar{\theta}_0 - b\left(\Psi \cosh \Psi - \sinh \Psi\right) = \frac{r_0}{Vs} \tag{62}$$

$$a\,\bar{\theta}_0 \cosh \bar{\theta}_0 = \frac{r_0}{Vs} \tag{63}$$

and therefore

$$a = \frac{1}{\bar{\theta}_0 \cosh \bar{\theta}_0} \; \frac{r_0}{Vs} \tag{64}$$

$$b = -\left(\frac{\bar{\theta}_0 \cosh \bar{\theta}_0 - \sinh \bar{\theta}_0}{\Psi \cosh \Psi - \sinh \Psi}\right) a \tag{65}$$

$$= -\frac{\left(1 - \dfrac{\sinh \bar{\theta}_0}{\bar{\theta}_0 \cosh \bar{\theta}_0}\right)}{\Psi \cosh \Psi - \sinh \Psi} \left(\frac{r_0}{Vs}\right)$$

Note that these are asymptotic results; if we literally take the limit described above we just get $a = b = 0$.

Now we are ready to evaluate the Laplace transform of the probability density function for the time at which the particle binds. Starting from the Laplace transform of equation (30), we have

(66) $$\tilde{f}(s) = \lambda \int_0^{r_0} \tilde{\rho}(r,s)\, 4\pi r^2 \, dr$$

$$= 4\pi\lambda \int_0^{r_0} \tilde{\phi}(r,s)\, r \, dr$$

$$= 4\pi\lambda \int_0^{r_0} \left( \frac{r^2}{(\lambda+s)V} + \operatorname{arsinh}\left( \sqrt{\frac{\lambda+s}{D}}\, r \right) \right) dr$$

The first term of the foregoing is equal to

(67) $$\frac{\lambda}{\lambda+s} \frac{V_0}{V}$$

where $V_0$ is the volume of $\Omega_0$.

To evaluate the second term, we use integration by parts

(68) $$\int_0^{r_0} r \sinh(\gamma r)\, dr = \frac{1}{\gamma} \int_0^{r_0} r \frac{d}{dr} \cosh(\gamma r)\, dr$$

$$= \frac{1}{\gamma}\left( r_0 \cosh(\gamma r_0) - \int_0^{r_0} \cosh(\gamma r)\, dr \right)$$

$$= \frac{1}{\gamma}\left( r_0 \cosh(\gamma r_0) - \frac{1}{\gamma} \sinh(\gamma r_0) \right)$$

$$= \frac{1}{\gamma^2}\left( (\gamma r_0) \cosh(\gamma r_0) - \sinh(\gamma r_0) \right)$$

In our case

(69) $$\gamma = \sqrt{\frac{\lambda + s}{D}}, \qquad \gamma r_0 = \theta_0$$

Therefore, (66) becomes

$$(70) \quad \tilde{f}(s) = \frac{\lambda}{\lambda+s}\frac{V_0}{V} + \frac{4\pi a D\lambda}{\lambda+s}\left(\theta_0 \cosh\theta_0 - \sinh\theta_0\right)$$

In the limit we have been considering, $\frac{\lambda}{\lambda+s} \to 1$, $\theta_0 \to \bar{\theta}_0$ and the coefficient $a$ is given by (64). Therefore

$$(71) \quad \tilde{f}(s) = \frac{V_0}{V} + \frac{4\pi D r_0}{V}\left(1 - \frac{\sinh\bar{\theta}_0}{\bar{\theta}_0 \cosh\bar{\theta}_0}\right)\frac{1}{s}$$

and the corresponding function of time is

$$(72) \quad f(t) = \frac{V_0}{V}\delta(t) + \frac{4\pi D r_0}{V}\left(1 - \frac{\sinh\bar{\theta}_0}{\bar{\theta}_0 \cosh\bar{\theta}_0}\right)$$

Note that $f(t)$ is not a legitimate probability density function, since its integral is infinite. This is an artifact of our limiting process. As mentioned previously, this is an asymptotic result for small $r_0$ and large $\lambda$, given that $\lambda$ and $r_0$ are adjusted so that $\theta$ has the finite limit $\theta_0$.

The interpretation of (72) is that there is essentially instantaneous binding if the particle happens to be within $\Omega_0$ at $t = 0$, the probability of which is $V_0/V$, and if not there is a small but constant probability per unit time of binding given by the second term of (72). Of course this cannot go on forever; certainly not longer than the time $T$ such that

(73) $$\int_0^T f(t)\,dt = 1$$

but that time $T \to \infty$ as $r_0 \to 0$. Thus, we may interpret

(74) $$\frac{4\pi D r_0}{V}\left(1 - \frac{\sinh \overline{\theta_0}}{\overline{\theta_0} \cosh \overline{\theta_0}}\right)$$

as the probability per unit time of binding.

Since the concentration of our particle is $\left(\frac{1}{V}\right)$, this means that the macroscopic rate constant for binding must be given by

$$k_{ON} = 4\pi D r_0 \left(1 - \frac{\sinh \bar{\theta}_0}{\bar{\theta}_0 \cosh \bar{\theta}_0}\right) \tag{75}$$

which has units of volume/time, as it should.

Since the equilibrium constant of the reaction has to be $k_{off}/k_{on}$, we can immediately find $k_{off}$ by combining (13) & (75):

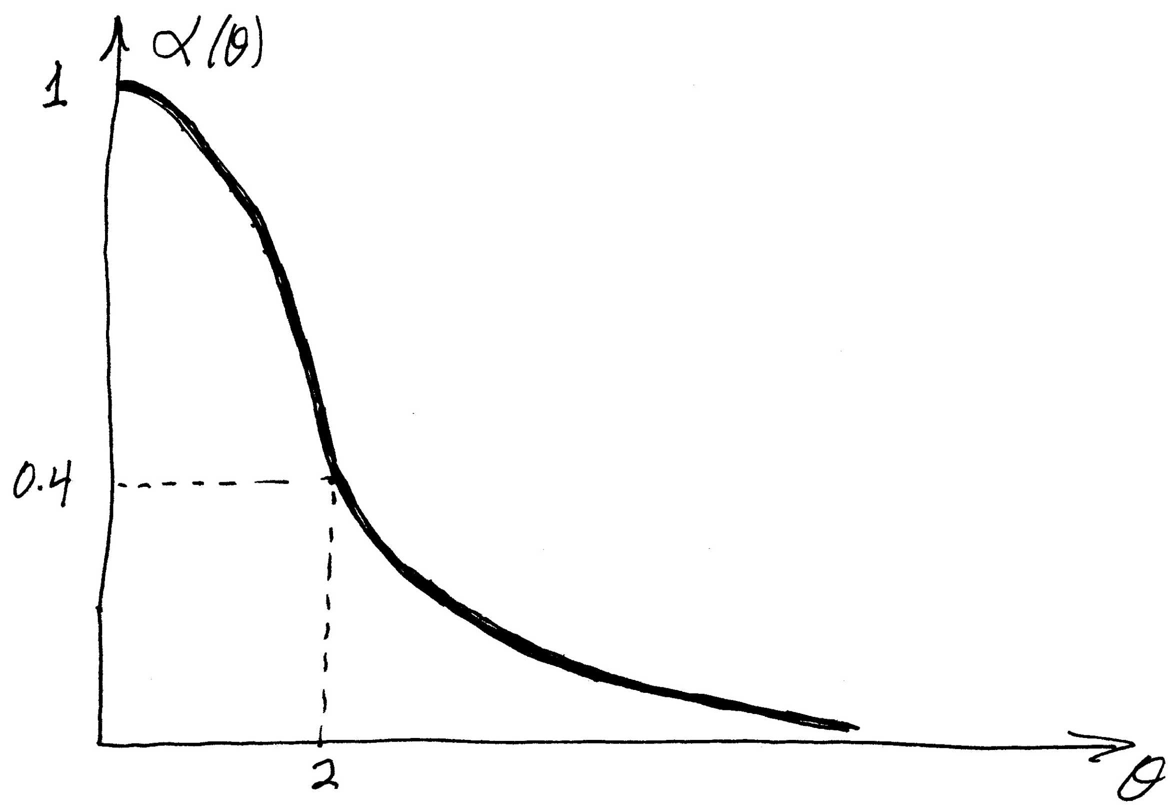
$$\begin{aligned} k_{off} &= K\, k_{on} \\ &= \frac{\mu}{\lambda V_0} 4\pi D r_0 \left(1 - \frac{\sinh \bar{\theta}_0}{\bar{\theta}_0 \cosh \bar{\theta}_0}\right) \\ &= \mu \frac{3}{(\bar{\theta}_0)^2} \left(1 - \frac{\sinh \bar{\theta}_0}{\bar{\theta}_0 \cosh \bar{\theta}_0}\right) \end{aligned} \tag{76}$$

The function

$$\alpha(\theta) = \frac{3}{\theta^2}\left(1 - \frac{\sinh\theta}{\theta\cosh\theta}\right) \tag{77}$$

has a local maximum at $\theta = 0$, where it has the value $\alpha(0) = 1$. This is easy to show by using the Taylor series for sinh and cosh.

A matlab plot reveals that this is actually the global maximum, and that $\alpha'(\theta) < 0$ on $\theta > 0$. (I do not see how to prove these statements.) Here is a sketch:



When $\alpha(\theta) < 1$, $k_{off} < \mu$.

This seems impossible, since $\mu$ by definition is the unbinding probability per unit time in our model.

The only possible explanation is that $k_{off}$ is taking into account the possibility that a recently released molecule can be recaptured almost instantaneously, and indeed this can happen repeatedly before the molecule finally makes its escape.

To analyze this, we ask the following question: If a molecule unbinds at $t=0$, what is the probability that it reaches a sphere of radius $r_1$ before rebinding. Here $r_1 > r_0$, and presumably $r_1 < R$, although $R$ will play no role in the problem.

To answer this question, we consider the same partial differential equation as before

(78) $$\frac{\partial \rho}{\partial t} = D\Delta\rho - \lambda u_0(\underline{x})\rho$$

but with <u>different</u> initial and boundary conditions. The initial condition is now

(79) $$\rho(\underline{x},0) = \frac{1}{V_0}\, u_0(\underline{x})$$

since the position of an unbound particle is chosen at the moment of unbinding from the uniform distribution on $\Omega_0$. Also the boundary condition is

(80) $$\rho(\underline{x},t) = 0 \qquad \|\underline{x}\| = r_1$$

since the process we are considering stops if the particle reaches the distance $r_1$ from the origin before rebinding.

The quantity of interest is the probability that the particle reaches the sphere at distance $r_1$, and this can be evaluated as follows

(81) $$P_{escape}(r_1) = \int_0^\infty D \int_{\|\underline{x}\|=r_1} -\hat{\underline{r}} \cdot \nabla \rho \, dA \, dt$$

Let

(82) $$\bar{\rho}(\underline{x}) = \int_0^\infty \rho(\underline{x}, t) \, dt$$

To get an equation for $\bar{\rho}(\underline{x})$ we integrate over $(0, \infty)$ with respect to $t$ on both sides of (78). On the left-hand side we get

(83) $$\rho(\underline{x}, \infty) - \rho(\underline{x}, 0) = -\rho(\underline{x}, 0)$$

since the particle will eventually rebind or reach the sphere at $r_1$. Thus, equation (78) becomes

(84) $$0 = D\Delta\bar{\rho} + \left(\frac{1}{V_0} - \lambda\bar{\rho}\right) u_0(\underline{x})$$

with the boundary condition

(85) $$\bar{\rho}(\underline{x}) = 0 \quad , \quad \|\underline{x}\| = r_1$$

Once $\bar{\rho}(\underline{x})$ has been found, we can evaluate

(86) $$P_{escape}(r_1) = D\int_{\|\underline{x}\| = r_1} -\hat{\underline{r}}\cdot\nabla\bar{\rho}\, dA$$

Note that the above procedure for removing the time dependence from the problem is actually the same as taking the Laplace transform and evaluating the result at $s=0$.

Now we use spherical coordinates and assume spherical symmetry. Our system becomes

(87) $$0 = D \frac{1}{r^2} \frac{d}{dr}\left(r^2 \frac{d\bar{\rho}}{dr}\right) + \left(\frac{1}{V_0} - \lambda\bar{\rho}\right), \quad 0<r<r_0$$

(88) $$0 = D \frac{1}{r^2} \frac{d}{dr}\left(r^2 \frac{d\bar{\rho}}{dr}\right) \quad , r_0<r<r_1$$

with continuity of $\bar{\rho}$ and $d\bar{\rho}/dr$ at $r=r_0$, and with

(89) $$\frac{d\bar{\rho}}{dr}(0) = 0 \;, \quad \bar{\rho}(r_1)=0$$

(90) $$P_{escape}(r_1) = -4\pi r_1^2 \frac{d\rho}{dr}(r_1) D$$

Here we skip the step of changing variables from $\bar{p}$ to $\bar{\phi}$ and just write the form of $\bar{p}$ that we would get:

(91)
$$\bar{p}(r) = \begin{cases} \dfrac{1}{\lambda V_0} + \dfrac{a}{r} \sinh\left(\sqrt{\dfrac{\lambda}{D}}\, r\right), & 0 < r < r_0 \\[2ex] b\left(\dfrac{1}{r} - \dfrac{1}{r_1}\right), & r_0 < r < r_1 \end{cases}$$

Note that the boundary conditions (89) are satisfied, as well as the equations (87-88). To determine a and b, we enforce continuity of $\bar{p}$ and $d\bar{p}/dr$ at $r = r_0$:

(92)
$$\frac{1}{\lambda V_0} + \frac{a}{r_0} \sinh\left(\sqrt{\frac{\lambda}{D}}\, r_0\right) = b\left(\frac{1}{r_0} - \frac{1}{r_1}\right)$$

(93)
$$-\frac{a}{r_0^2} \sinh\left(\sqrt{\frac{\lambda}{D}}\, r_0\right) + \frac{a}{r_0}\sqrt{\frac{\lambda}{D}} \cosh\left(\sqrt{\frac{\lambda}{D}}\, r_0\right) = -\frac{b}{r_0^2}$$

Now we multiply by $r_0$ in (92) and by $r_0^2$ in (93), and rewrite the results in terms of $\bar{\theta}_0$, see (58):

(94) $$a \sinh \bar{\theta}_0 - b\left(1 - \frac{r_0}{r_1}\right) = -\frac{r_0}{\lambda V_0}$$

(95) $$a\left(\bar{\theta}_0 \cosh \bar{\theta}_0 - \sinh \bar{\theta}_0\right) + b = 0$$

The solution of this pair of equations is

(96) $$a = \frac{-\dfrac{r_0}{\lambda V_0}}{\left(\bar{\theta}_0 \cosh \bar{\theta}_0 - \sinh \bar{\theta}_0\right)\left(1 - \dfrac{r_0}{r_1}\right) + \sinh \bar{\theta}_0}$$

(97) $$b = \frac{\dfrac{r_0}{\lambda V_0}\left(\bar{\theta}_0 \cosh \bar{\theta}_0 - \sinh \bar{\theta}_0\right)}{\left(\bar{\theta}_0 \cosh \bar{\theta}_0 - \sinh \bar{\theta}_0\right)\left(1 - \dfrac{r_0}{r_1}\right) + \sinh \bar{\theta}_0}$$

From (90), (91), and (97)

(98) $$P_{escape}(r_1) = 4\pi b D$$

$$= 4\pi D \frac{\frac{r_0}{\lambda V_0}\left(\bar{\theta}_0 \cosh\bar{\theta}_0 - \sinh\bar{\theta}_0\right)}{\left(\bar{\theta}_0 \cosh\bar{\theta}_0 - \sinh\bar{\theta}_0\right)\left(1-\frac{r_0}{r_1}\right) + \sinh\bar{\theta}_0}$$

This result depends on $r_1$, but it becomes independent of $r_1$ for fixed $\bar{\theta}_0$ if

(99) $$r_0 << r_1$$

which we now assume. In that case

(100) $$P_{escape} = \frac{4\pi r_0 D}{\lambda V_0} \frac{\bar{\theta}_0 \cosh\bar{\theta}_0 - \sinh\bar{\theta}_0}{\bar{\theta}_0 \cosh\bar{\theta}_0}$$

$$= \frac{3}{\bar{\theta}_0^{\,2}}\left(1 - \frac{\sinh\bar{\theta}_0}{\bar{\theta}_0 \cosh\bar{\theta}_0}\right)$$

$$= \alpha(\bar{\theta}_0)$$

Comparison with equation (76) shows that

(101) $$k_{off} = \mu \, P_{escape}$$

where $\mu$ is the probability per unit time of unbinding, and $k_{off}$ is the probability per unit time of effective unbinding.

This is a very sensible result!

In summary the equilibrium constant for our model bimolecular reaction is

(102) $$K = \frac{\mu}{\lambda V_0}$$

where $\mu$ is the probability per unit time of unbinding and $\lambda$ is the probability per unit time of binding when the mobile species is within the region where binding can occur, and where $V_0$ is the volume of that reactive region.

One might expect, then, that the rate constants for the reaction would be $k_{off} = \mu$ and $k_{on} = \lambda V_0$, but this is not correct. Instead, we have found that

(103) $$k_{off} = \mu \, P_{escape}$$

(104) $$k_{on} = \lambda V_0 \, P_{escape}$$

where

(105) $$P_{escape} = \frac{3}{(\bar{\theta}_0)^2}\left(1 - \frac{\sinh \bar{\theta}_0}{\bar{\theta}_0 \cosh \bar{\theta}_0}\right)$$

(106) $$\bar{\theta}_0 = \sqrt{\frac{\lambda}{D}}\, r_0$$

These results are valid whenever $r_0$ is small in comparison to the dimensions of the system, but for the results to be <u>interesting</u> it is necessary that $\bar{\theta}_0$ be substantially different from <u>zero</u> despite the smallness of $r_0$. If $\bar{\theta}_0$ is close to zero, then $P_{escape}$ is nearly 1, and the naive choices $k_{off} = \mu$, $k_{on} = \lambda V_0$ are substantially correct.

Once the equilibrium constant is known and given by (102), equations (103) & (104) imply each other, since it is required that $K = k_{off}/k_{on}$. In these notes, we have derived (103) and (104) separately, but our derivation of (103) required a complicated limiting process and some interpretation of the result that may leave the reader feeling uneasy. The derivation of (104), by contrast, seems much more clear-cut, and the only requirement in it seems to be that $r_0$ is small enough to make $P_{escape}$ have an unambiguous value, see equations (98-100). It is therefore reassuring about the earlier derivation that we get the same result in both cases.

It would be an interesting project to simulate the model described in these notes, to see whether the predictions we have made are confirmed computationally, and also to visualize the process of attempted escape with the possibility of recapture. Note that the simulation has to be 3D for the theory of these notes to be applicable.