12. Targeted Diffusion

Diffusion to Capture[1]

Consider a diffusion limited chemical reaction: A+B → X. What is the rate at which a diffusing molecule reaches its target? Two classes of these diffusion-to-capture problems:

1) Molecule diffusing to fixed target(s). Binding of ligands to enzymes or receptors. Binding of transcription factors to DNA. Here the target may have varying configurations in space, but it is fixed $\left(D_{\text{molec}} \gg D_{\text{target}}\right)$. The diffusion may occur in 1, 2, and/or 3 dimensions, depending on the problem.

2) Bimolecular Diffusive Encounter. How do two molecules diffuse into proximity and react? Reaction–diffusion equations.

The general strategy to these problems is to determine the flux of molecules incident on the target from the diffusion equation. Rather than using a time-dependent problem, we use a steady state solution with an absorbing boundary condition at the target to account for loss of diffusing molecules once they reach the target. Then the concentration gradient at the target surface can be used to calculate a flux or rate of collisions.

Diffusion to Capture by Sphere

What is the rate of encounter of a diffusing species with a spherical target? We can find a steady-state solution by determining the steady-state radial concentration profile $C(r)$. Assume that reaction is immediate on encounter at a radius b. This sets the boundary condition, $C(b) = 0$. We also know the bulk concentration $C_0 = C(\infty)$. From our earlier discussion, the steady state solution to this problem is

$$C(r) = C_0\left(1 - \frac{b}{r}\right)$$

Next, to calculate the rate of collisions with the sphere, we first calculate the flux density of molecules incident on the surface of the sphere ($r = b$):

$$J(b) = -D\frac{\partial C}{\partial r}\bigg|_{r=b} = \frac{DC_0}{b} \tag{1}$$

1. D. F. Calef and J. M. Deutch, *Diffusion and reversible-reaction in a medium with penetrable sinks*, J. Chem. Phys. **79** (1), 203-212 (1983).

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J is expressed as (molecules area^{-1} sec^{-1}) or [(mol/L) area^{-1} sec^{-1}]. We then calculate the flux, or rate of collisions of molecules with the sphere (molec sec^{-1}), by multiplying the flux density by the surface area of the sphere ($a = 4\pi b^2$):

$$\frac{dN}{dt} = Ja = \left(\frac{DC_0}{b}\right)(4\pi b^2)$$
$$= 4\pi D b C_0$$
$$\equiv k C_0$$

We associate the constant or proportionality between rate of collisions and concentration with the pseudo first-order association rate constant, $k = 4\pi Db$, which is proportional to the rate of diffusion to the target and the size of the target.

Reaction–diffusion

The discussion above describes the rate of collisions of solutes with an absorbing sphere, which are applicable if the absorbing sphere is fixed. For problems involving the encounter between two species that are both diffusing in solution $(A + B \rightarrow X)$, you can extend this treatment to the encounter of two types of particles A and B, which are characterized by two bulk concentrations C_A and C_B, two radii R_A and R_B, and two diffusion constants D_A and D_B.

To describe the rate of reaction, we need to calculate the total rate of collisions between A and B molecules. Rather than describing the diffusion of both A and B molecules, it is simpler to fix the frame of reference on B and recognize that we want to describe the diffusion of A with respect to B. In that case, the effective diffusion constant is

$$D = D_A + D_B$$

Furthermore, we expand our encounter radius to the sum of the radii of the two spheres ($R_{AB} = r_A + r_B$). The flux density of A molecules incident on a single B at an encounter radius of R_{AB} is given by eq. (1)

$$J_{A \rightarrow B} = \frac{DC_A}{R_{AB}}$$

Here J describes the number of molecules of A incident per unit area at a radius R_{AB} from B molecules per unit time, [*molec A*] [*area of B*]$^{-1}$ sec^{-1}. If we treat the motion of B to be uncorrelated with A, then the total rate of collisions between A and B can be obtained
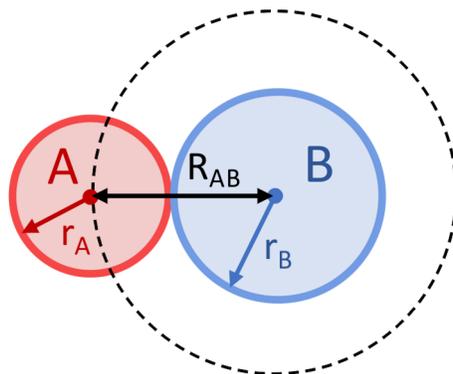
from the product of $J_{A \to B}$ with the area of a sphere of radius R_{AB} and the total concentration of B:

$$\frac{dN_{A \leftrightarrow B}}{dt} = J_{A \to B}(4\pi R_{AB}^2)C_B$$

$$= 4\pi D R_{AB} C_A C_B$$

The same result is obtained if we begin with the flux density of B incident on A, $J_{B \to A}$, using the same encounter radius and diffusion constant. Now comparing this with expected second order rate law for a bimolecular reaction

$$\frac{dN_{A \leftrightarrow B}}{dt} = k_a C_A C_B$$

we see

$$k_a = 4\pi(D_A + D_B)R_{AB}$$

k_a is the rate constant for a diffusion limited reaction (association). It has units of cm^3 s^{-1}, which can be converted to (L mol^{-1} s^{-1}) by multiplying by Avagadro's number.

Reactive Patches

If you modify these expressions so that only part of the sphere is reactive, then similar results ensue, in which one recovers the same diffusion limited association rate ($k_{a,0}$) multiplied by an additional factor that depends on the geometry of the surface area that is active. For instance if we consider a small circular patch on a sphere that subtends a half angle θ, the geometric factor should scale as $sin\theta$. For small θ, $sin\theta \approx \theta$. If you have small patches on two spheres, which must diffusively encounter each other, the slowing of the association rate relative to the case with the fully accessible spherical surface area is

$$k_a / k_{a,0} = \theta_A \theta_B (\theta_A + \theta_B)/8$$

For the association rate of molecules with a sphere of radius R covered with n absorbing spots of radius b:

$$k_a / k_{a,0} = \left(1 + \frac{\pi R}{nb}\right)^{-1}$$

Additional configurations are explored in Berg.
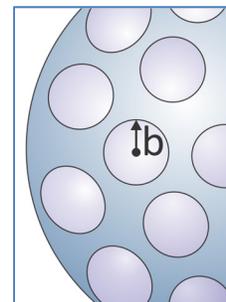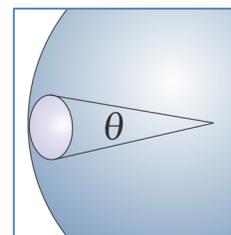
Diffusion to Capture with Interactions

What if the association is influenced by an additional potential for A-B interactions? Following our earlier discussion for diffusion in a potential, the potential U_{AB} results in an additional contribution to the flux:

$$J_U = -\frac{D_A C_A}{k_B T}\frac{\partial U_{AB}}{\partial r}$$

So the total flux of A incident on B from normal diffusion J_{diff} and the interaction potential J_U is

$$J_{A\to B} = -D_A\left[\frac{\partial C_A}{\partial r} + \frac{C_A}{k_B T}\frac{\partial U_{AB}}{\partial r}\right]$$

To solve this we make use of a mathematical manipulation commonly used in solving the Smoluchowski equation in which we rewrite the quantity in brackets as

$$J_{A\to B} = -D_A\left[e^{-U_{AB}/k_B T}\frac{d\left[C_A e^{U_{AB}/k_B T}\right]}{dr}\right] \tag{2}$$

Substitute this into the expression for the rate of collisions of A with B:

$$\frac{dn_{A\to B}}{dt} = 4\pi R_B^2 J_{A\to B}$$

Separate variables and integrate from the surface of the sphere to $r=\infty$ using the boundary conditions: $C(R_B)=0$, $C(\infty)=C_A$:

$$\left(\frac{dn_{A\to B}}{dt}\right)\underbrace{\int_{R_B}^{\infty} e^{U_{AB}/k_B T}\frac{dr}{r^2}}_{(R^*)^{-1}} = 4\pi D_A \underbrace{\int_0^{C_A} d\left[C_A e^{U_{AB}/k_B T}\right]}_{C_A} \tag{3}$$

Note that integral on the right is just the bulk concentration of A. The integral on the right has units of inverse distance, and we can write this in terms of the variable R^*:

$$(R^*)^{-1} = \int_{R_B}^{\infty} e^{U_{AB}/k_B T} r^{-2} dr$$

Note that when no potential is present, then $U_{AB}\to 0$, and $R^* = R_B$. Therefore R^* is an effective encounter distance which accounts for the added influence of the interaction potential, and we can express it in terms of f, a correction factor the normal encounter radius: $R^* = f\,R_B$. For attractive interactions $R^* > R_B$ and $f>1$, and vice versa.[2]

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2. A more general form for the flux, in which the boundary condition at the surface of the sphere $CB(R0)$ is non-zero, for instance when there is an additional chemical reaction on contact is

Returning to eq. (3), we see that the rate of collisions of A with B is

$$\frac{dn_{A \to B}}{dt} = 4\pi D_A R_B^* C_A$$

As before, if we account for the total number of collisions for two diffusing molecules A and B:

$$\frac{dn_{TOT}}{dt} = k_a C_A C_B$$

$$k_a = 4\pi \left(D_A + D_B \right) R_{AB}^*$$

$$R_{AB}^* = R_A^* + R_B^*$$

Example: Electrostatic potential:[3]

Let's calculate the form of the where the interaction is the Coulomb potential:[4]

$$U_{AB}(r) = \frac{z_A z_B e^2}{4\pi\varepsilon r}$$

$$= k_B T \frac{\ell_B}{r}$$

where $\ell_B = z_A z_B e^2 / (4\pi\varepsilon k_B T)$. Then

$$\left(R_{AB}^* \right)^{-1} = \int_{R_{AB}}^{\infty} e^{U_{AB}/k_B T} \frac{dr}{r^2}$$

$$= \ell_B^{-1} \left[\exp\left(\ell_B / R_{AB} \right) - 1 \right]$$

and $R_{AB}^* = \ell_B \left(e^{\ell_B/R_{AB}} - 1 \right)^{-1}$.

$$4\pi r^2 J_{A \to B} = \frac{4\pi D_A \left[C_A(\infty) e^{U_{AB}(\infty)/k_B T} - C_A(R_0) e^{U_{AB}(R_0)/k_B T} \right]}{\int_{R_0}^{\infty} r^{-2} e^{U_{AB}(r)/k_B T} dr}$$

$C_A(\infty)$ is the bulk concentration of A. For the perfectly absorbing sphere, the concentration of A at the boundary with B, $C_A(R_0) = 0$. For a homogeneous solution we also assume that the interaction potential at long range $UAB(\infty) = 0$.

3. See also J. I. Steinfeld, *Chemical Kinetics and Dynamics*, 2nd ed. (Prentice Hall, Upper Saddle River, N.J., 1998), 4.2-4.4.

4. See M. Vijayakumar, K.-Y. Wong, G. Schreiber, A. R. Fersht, A. Szabo and H.-X. Zhou, Electrostatic enhancement of diffusion-controlled protein-protein association: comparison of theory and experiment on barnase and barstar, J. Mol. Biol. **278** (5), 1015-1024 (1998).

Mean First Passage Time[5]

Another way of describing diffusion-to-target rates is in terms of first passage times. The mean first passage time (MFPT), $\langle \tau \rangle$, is the average time it takes for a diffusing particle to reach a target position for the first time. The inverse of $\langle \tau \rangle$ gives the rate of the corresponding diffusion-limited reaction. A first passage time approach is particularly relevant to problems in which a description the time-dependent averages hide intrinsically important behavior of outliers and rare events, particularly in the analysis of single molecule kinetics.

To describe first passage times, we begin by defining the reaction probability R and the survival probability S. R is a conditional probability function that describes the probability that a molecule starting at a point $x_0 = 0$ at time $t_0 = 0$ will reach a reaction boundary at $x = x_f$ <u>for the first time</u> after time t: $R(x_f,t|x_0,t_0)$. S is just the conditional probability that the molecule has *not* reached $x = b$ during that time interval: $S(x_f,t|x_0,t_0)$. Therefore

$$R + S = 1$$

Next, we define $F(\tau,x_f|x_0)$, the first passage probability density. $F(\tau)d\tau$ is the probability that a molecule passes through $x = x_f$ for the first time between times τ and $\tau + d\tau$. R, S, and F are only a function of time for a fixed position of the reaction boundary, i.e. they integrate over any spatial variations. To connect F with the survival probability, we recognize that the reaction probability can be obtained by integrating over all possible first passage times for time intervals $\tau < t$. Dropping space variables, recognizing that $(t-t_0) = \tau$, and setting $x_0 = 0$,

$$R(t) = \int_0^t F(\tau)\,d\tau$$

This relation implies that the first passage time distribution can be obtained by differentiating S

$$F(t) = \frac{\partial}{\partial t} R(t) = -\frac{\partial}{\partial t} S(t) \tag{4}$$

Then the MFPT is obtained from the first moment of the $F(t)$ distribution

$$\langle \tau \rangle = \int_0^\infty \tau F(\tau)\,d\tau \tag{5}$$

To evaluate these quantities for a particular problem, we seek to relate them to the time-dependent probability density, $P(x,t|x_0,t_0)$, which is an explicit function of time and space. The connection between P and F is not immediately obvious because evaluating P at $x = x_f$ without the proper boundary conditions includes trajectories that have passed through $x = x_f$ before returning there again later. The key to relating these is to recognize that the survival probability

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5. S. Iyer-Biswas and A. Zilman, First-Passage Processes in Cellular Biology, Adv. Chem. Phys. **160**, 261-306 (2016).

can be obtained by calculating a diffusion problem with an absorbing boundary condition at $x = x_f$ that does not allow the particle to escape: $P(x_f,t|x_0) = 0$. The resulting probability distribution $P_a(x,t|x_0,t_0)$ is not conserved but gradually loses probability density with time. Hence, we can see that the survival probability is an integral over the remaining probability density that describes particles that have not yet reached the boundary:

$$S(t) = \int_{-\infty}^{x_f} dx\, P_a(x,t) \tag{6}$$

The mean free passage time can be written as

$$\langle \tau \rangle = \int_{-\infty}^{x_f} dx \int_0^{\infty} dt\, P_a(x,t)$$

The next important realization is that the first passage time distribution is related to the flux of diffusing particles through x_f. Combining eq. (4) and (6) shows us

$$F(t) = -\int_{-\infty}^{x_f} dx \frac{\partial}{\partial t} P_a(x,t) \tag{7}$$

Next we make use of the continuity expression for the probability density

$$\frac{\partial P}{\partial t} = -\frac{\partial j}{\partial x}$$

j is a flux, or *probability current*, with units of s^{-1}, not the flux density we used for continuum diffusion J $(m^{-2}\ s^{-1})$. Then eq. (7) becomes

$$F(t) = \int_{-\infty}^{x_f} dx \frac{\partial}{\partial x} j_a(x,t)$$
$$= j_a(x_f,t) \tag{8}$$

So the first passage time distribution is equal to the flux distribution for particles crossing the boundary at time t. Furthermore, from eq. (5), we see that the MFPT is just the inverse of the average flux of particles crossing the absorbing boundary:

$$\langle \tau \rangle = \frac{1}{\langle j_a(x_f) \rangle} \tag{9}$$

In chemical kinetics, $\langle j_a(x_f) \rangle$ is the rate constant from transition state theory.
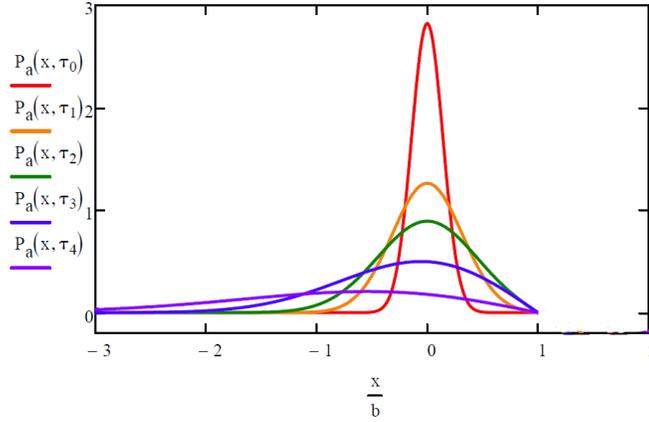
Calculating the First Passage Time Distribution

To calculate F one needs to solve a Fokker–Planck equation for the equivalent diffusion problem with an absorbing boundary condition. As an example, we can write these expressions explicitly for diffusion from a point source. This problem is solved using the Fourier transform method, applying absorbing boundary conditions at x_f to give

$$P_a(x,t) = P(x,t) - P(2x_f - x,t) \qquad\qquad (x \le x_f)$$

which is expressed in terms of the probability distribution in the *absence* of absorbing boundary conditions:

$$P(x,t) = \left(4\pi Dt\right)^{1/2} \exp\left[\frac{-(x-x_0)^2}{4Dt}\right].$$

The corresponding first passage time distribution is:

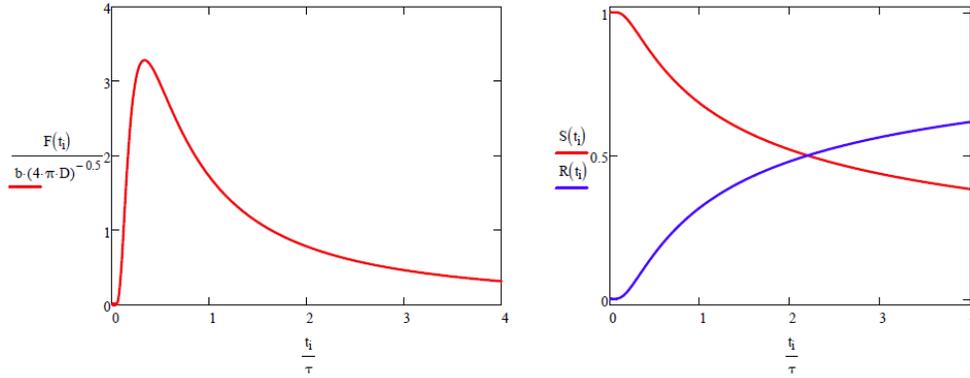$$F(t) = \frac{x_f - x_0}{\left(4\pi Dt^3\right)^{1/2}} \exp\left[-\frac{(x_f - x_0)^2}{4Dt}\right]$$

$F(t)$ decays in time as $t^{-3/2}$, leading to a long tail in the distribution. The MFPT is

$$\langle\tau\rangle = x_f^2 / 2D$$

and the most probable passage time is $x_f^2 / 6D$. Also, we can use eq. (6) to obtain the survival probability

$$S(t) = \mathrm{erf}\left(\frac{x_f}{\sqrt{4Dt}}\right) = \mathrm{erf}\left(\sqrt{\frac{\langle\tau\rangle}{2t}}\right)$$

$S(t)$ depends on the distance of the target and the *rms* diffusion length over time t. At long times $S(t)$ decays as $t^{-1/2}$.

It is interesting to calculate the probability that the diffusing particle will reach x_f at *any* time. From eq. (7), we can see that this probability can be calculated from $\int_0^\infty F(\tau)d\tau$. For the current example, this integral over F gives unity, saying that a random walker in 1D will eventually reach every point on a line. Equivalently, it is guaranteed to return to the origin at some point in time. This observation holds in 1D and 2D, but not 3D.

Calculating the MFPT

From eq. (9) we see that it is also possible to calculate the MFPT by solving for the flux at an absorbing boundary in a steady state calculation. As a simple example, consider the problem of releasing a particle on the left side of a box, $P(x,0) = \delta(x - x_0)$, and placing the reaction boundary at the other side of the box $x = b$. We solve the steady-state diffusion equation $\partial^2 P_a / \partial x^2 = 0$ with an absorbing boundary at $x = b$, i.e., $P(b,t) = 0$. This problem is equivalent to absorbing every diffusing particle that reaches the right side and immediately releasing it again on the left side.
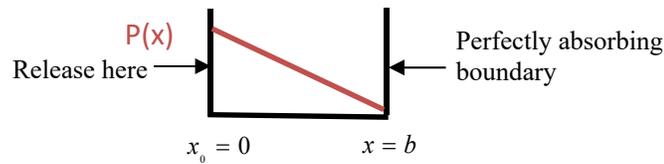
The steady-state solution is
$$P_a(x) = \frac{2}{b}\left(1 - \frac{x}{b}\right)$$

Then, we can calculate the flux of diffusing particles at $x = b$:
$$j(b) = -D\frac{\partial P}{\partial x}\bigg|_{x=b} = \frac{2D}{b^2}$$

and from the inverse we obtain the MFPT:
$$\langle\tau\rangle = \frac{1}{j(b)} = \left(\frac{b^2}{2D}\right)$$

MFPT in a Potential

To extend this further, let's examine a similar 1D problem in which a particle is released at $x_0 = 0$, and diffuses in x toward a reaction boundary at $x = b$, but this time under the influence of a potential $U(x)$. We will calculate the MFPT for arrival at the boundary. Such a problem could be used to calculate the diffusion of an ion through an ion channel under the influence of the transmembrane electrochemical potential.
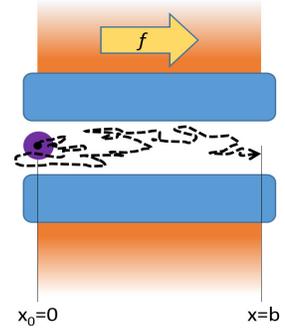
From our earlier discussion of diffusion in a potential, the steady state flux is

$$ j = \frac{-D\left[P(b)e^{U(b)/k_BT} - P(x)e^{U(x)/k_BT} \right]}{\int_x^b e^{U(x')/k_BT} dx'} $$

Applying the absorbing boundary condition, $P(b) = 0$, the steady state probability density is

$$ P_a(x) = \frac{j}{D} e^{-U(x)/k_BT} \int_x^b e^{U(x')/k_BT} dx' \tag{10} $$

Now integrating both sides over the entire box, the left side is unity, so we obtain an expression for the flux

$$ \frac{1}{j} = \frac{1}{D} \int_0^b e^{-U(x)/k_BT} \left[\int_x^b e^{U(x')/k_BT} dx' \right] dx \tag{11} $$

But j^{-1} is just the MFPT, so this expression gives us $\langle \tau \rangle$. Note that if we set U to be a constant in eq. (11), that we recover the expressions for $\langle \tau \rangle, j$, and P_a in the preceding example.

Diffusion in a linear potential

For the case of a linear external potential, we can write the potential in terms of a constant external force $U = -fx$. Solving this with the steady state solution, we substitute U into eq. (11) and obtain

$$ \langle \tau \rangle = \frac{1}{j} = \frac{1}{D\underset{\sim}{f}^2} \left[e^{-\underset{\sim}{f}b} - 1 + \underset{\sim}{f}b \right] \tag{12} $$

where $\underset{\sim}{f} = f/k_BT$ is the force expressed in units of thermal energy. Substituting into eq. (10) gives the steady state probability density

$$ P(x) = \frac{\underset{\sim}{f}\left(1 - e^{-\underset{\sim}{f}(b-x)}\right)}{e^{-\underset{\sim}{f}b} - 1 + \underset{\sim}{f}b} $$

Now let's compare these results from calculations using the first passage time distribution. This requires solving the diffusion equation in the presence of the external potential. In the case of a linear potential, we can solve this by expressing the constant force as a drift velocity

$$v_x = \frac{f}{\zeta} = \frac{fD}{k_B T} = \underset{\sim}{f} D$$

Then the solution is obtained from our earlier example of diffusion with drift:

$$P(x,t) = \frac{1}{\sqrt{4\pi Dt}} \exp\left[-\frac{\left(x - \underset{\sim}{f}Dt\right)^2}{4Dt} \right]$$

The corresponding first passage time distribution is

$$F(t) = \frac{b}{\sqrt{4\pi Dt^3}} \exp\left[-\frac{\left(b - \underset{\sim}{f}Dt\right)^2}{4Dt} \right]$$

and the MFPT is given by eq. (12).

Readings

1. H. C. Berg, *Random Walks in Biology*. (Princeton University Press, Princeton, N.J., 1993).