16.3: Mean First Passage Time

Another way of describing diffusion-to-target rates is in terms of first passage times. The mean first passage time (MFPT), ⟨τ⟩, is the average time it takes for a diffusing particle to reach a target position for the first time. The inverse of ⟨τ⟩ 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 will reach a reaction boundary at $x = x_f$ for the first time 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 τand τ+dτ. 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 τ < 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

$$F(t) = \frac{\partial}{\partial t} R(t) = -\frac{\partial}{\partial t} S(t) \tag{16.3.1}$$

Then the MFPT is obtained by averaging over F(t)

$$\langle \tau \rangle = \int_0^\infty \tau F(\tau) d\tau \tag{16.3.2}$$

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 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:

$$S(t) = \int_{-\infty}^{x_f} dx P_a(x,t) \tag{16.3.3}$$

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. (16.3.1) and (16.3.3) shows us

$$F(t) = -\int_{-\infty}^{x_f} dx \frac{\partial}{\partial t} P_a(x,t) \tag{16.3.4}$$

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. (16.3.4) becomes

$$\begin{aligned} F(t) &= \int_{-\infty}^{x_f} dx \frac{\partial}{\partial x} j_a(x,t) \\ &= j_a(x_f,t) \end{aligned} \tag{16.3.5}$$

So the first passage time distribution is equal to the flux distribution for particles crossing the boundary at time t. Furthermore, from eq. (16.3.2), we see that the MFPT is just the inverse of the average flux of particles crossing the absorbing boundary:

$$\langle \tau \rangle = \frac{1}{\langle j_a(x_f) \rangle} \tag{16.3.6}$$

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

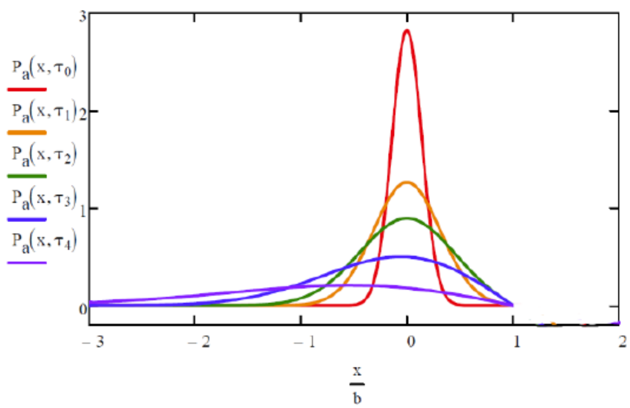
Calculating the First Passage Time Distribution

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

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

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

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



The corresponding first passage time distribution is:

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

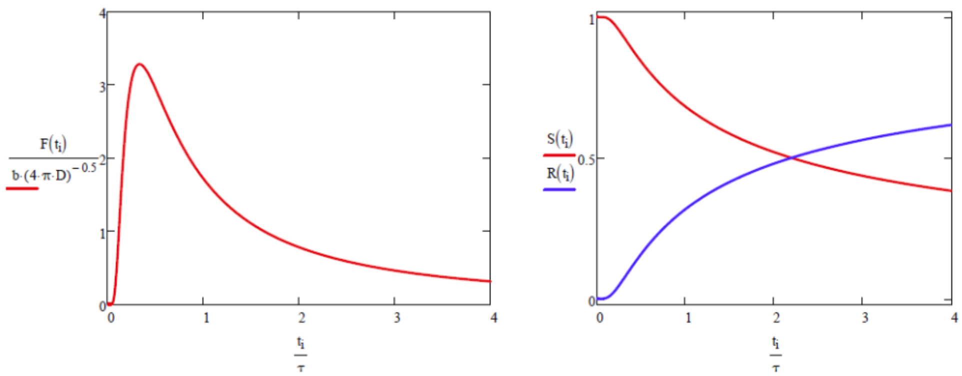
F(t) decays in time as $t^{-3/2}$, leading to a long tail in the distribution. The mean of this distribution gives the MFPT

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

and the most probable passage time is $x_f^2/6D$. Also, we can use eq. (16.3.3) to obtain the survival probability

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

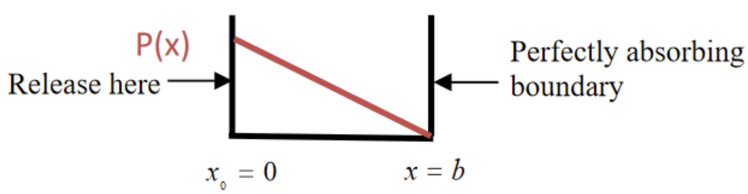
S(t) depends on the distance of the target and the rms diffusion length over time t. At long times S(t) decays as $t^{-1/2}$.



It is interesting to calculate the probability that the diffusing particle will reach xf at any time. From eq. (16.3.4), 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 Steady-State Flux

From eq. (16.3.6) 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

$$P_a(x)=\frac{2}{b}\left(1-\frac{x}{b}\right)$$

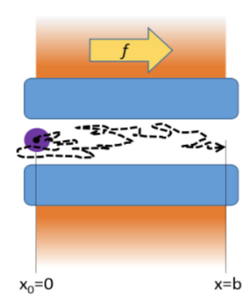
Then, we can calculate the flux of diffusing particles at x=b:

$$j(b)=-D\left.\frac{\partial P}{\partial x}\right|_{x=b}=\frac{2D}{b^2}$$

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

$$P_a(x) = \frac{j}{D}e^{-U(x)/k_BT}\int_x^b e^{U(x')/k_BT}dx' \tag{16.3.7}$$

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

$$\frac{1}{j} = \frac{1}{D}\int_0^b e^{-U(x)/k_BT}\left[\int_x^b e^{U(x')/k_BT}/k_BT dx'\right]dx \tag{16.3.8}$$

But j^{-1} is just the MFPT, so this expression gives us ⟨τ⟩. Note that if we set U to be a constant in eq. (16.3.8), that we recover the expressions for ⟨τ⟩, 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. (16.3.8) and obtain

$$\langle\tau\rangle = \frac{1}{j} = \frac{1}{D\underset{\sim}{f}^2}\left[e^{-\underset{\sim}{f}b} - 1 + \underset{\sim}{f}b\right] \tag{16.3.9}$$

where $\underset{\sim}{f} = f/k_BT$ is the force expressed in units of thermal energy. Substituting into eq. (16.3.7) 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

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

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

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

The corresponding first passage time distribution is

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

and the MFPT is given by eq. (16.3.9).

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1. A. Nitzan, Chemical Dynamics in Condensed Phases: Relaxation, Transfer and Reactions in Condensed Molecular Systems. (Oxford University Press, New York, 2006); S. Iyer-Biswas and A. Zilman, First-Passage Processes in Cellular Biology, Adv. Chem. Phys. 160, 261–306 (2016).
2. H. C. Berg, Random Walks in Biology. (Princeton University Press, Princeton, N.J., 1993).