5.1 First passage time on an interval

So far we have assumed particles diffuse in an unbounded domain. Now consider 1D diffusion on the finite interval $x \in [0, L]$. The two most common types of boundary condition at the ends $x = 0, L$ are the Dirichlet and Neumann boundary conditions. For example, at $x = 0$

$$p(0, t) = f(t) \text{ (Dirichlet)} \quad \text{or} \quad J(0, t) = g(t) \text{ (Neumann)},$$

where $J(x, t)$ is the probability flux (3.15), and $f, g$ are prescribed functions of time $t$, which could be time-independent. A homogeneous Dirichlet boundary condition ($f \equiv 0$) is often called an absorbing boundary condition, whereas a homogeneous Neumann boundary condition ($g \equiv 0$) is often called a no-flux or reflecting boundary condition. In the latter case, integrating both sides of equation (3.14) with respect to $x$ shows that

$$\int_0^L \frac{\partial p(x, t)}{\partial t} \, dx = - \int_0^L \frac{\partial J(x, t)}{\partial x} \, dx = J(0, t) - J(L, t) = 0,$$

which means that $\int_0^L p(x, t) \, dx = 1$ for all $t > 0$ (conservation of probability).

Suppose that the corresponding FP equation (3.13) has a reflecting boundary condition at $x = 0$ and an absorbing boundary condition at $x = L$, see Fig. 6:

$$J(0, t) = 0, \quad p(L, t) = 0.$$

We would like to determine the stochastic time $T(y)$ for the particle to exit the right hand boundary at time $t$ given that it starts at location $y \in [0, L]$. As a first step, we introduce the survival probability $S(y, t)$ that the particle has not yet exited the interval at time $t$:

$$S(y, t) = \int_0^L p(x, t | y, 0) \, dx.$$

It follows that

$$\mathbb{P}[T(y) \leq t] = \text{probability that particle has exited before time } t = 1 - S(y, t),$$

Figure 6: First passage time problem on an interval
Now define the first passage time (FPT) density according to
\[ f(y, t) \Delta t = \mathbb{P}[t < T(y) < t + \Delta t] = \mathbb{P}[T(y) \leq t + \Delta t] - \mathbb{P}[T(y) \leq t] \]
\[ 1 - S(y, t + \Delta t) - (1 - S(y, t)) = S(y, t) - S(y, t + \Delta t). \]
in the limit \( \Delta t \to 0 \). That is,
\[ f(y, t) = -\frac{\partial S(y, t)}{\partial t} = -\int_0^L \frac{\partial}{\partial t} p(x, t|y, 0) dx \]
\[ = \int_0^L \frac{\partial J(x, t|y, 0)}{\partial x} dx = J(L, t|y, 0) - J(0, t|y, 0) \tag{5.4} \]
where we have used the FP equation written in conservation form (3.14). The reflecting boundary condition at \( x = 0 \) thus implies that the FPT density is equal to the flux through the absorbing boundary at \( x = L \),
\[ f(y, t) = J(L, t|y, 0). \tag{5.5} \]
In certain simple cases, the flux can be calculated explicitly. However, for more general cases, it is useful to derive explicit differential equations for moments of the FPT density, in particular, the first moment or mean first passage time (MFPT).

5.2 The backward FP equation

An important property of the solution \( p(x, t) = p(x, t|x_0, t_0) \) to the FP equation on some interval \([0, L]\) is that it satisfies the so-called Chapman-Kolmogorov equation
\[ p(x, t|x_0, t_0) = \int_0^L p(x, t|y, \tau)p(y, \tau|x_0, t_0)dy. \tag{5.6} \]
This essentially states that the probability of \( x \) given \( x_0 \) is the sum of the probabilities of each possible path via which one can get from \( x_0 \) to \( x \). It is a reflection of the fact that Brownian motion is a Markov process (memoryless)

The Chapman-Kolmogorov equation can be used to derive a corresponding backward FP equation for \( q(y, t) = p(x, t|y, \tau) \):
\[ \frac{\partial q}{\partial t} = A(y) \frac{\partial q}{\partial y} + D \frac{\partial^2 q}{\partial y^2}. \tag{5.7} \]
This plays an important role in studying first passage time or escape problems.

First, differentiate both sides of equation (5.6) with respect to the intermediate time \( \tau \) gives
\[ 0 = \int_0^L \partial_\tau p(x, t|y, \tau)p(y, \tau|x_0, t_0) dy + \int_0^L p(x, t|y, \tau) \partial_\tau p(y, \tau|x_0, t_0) dy \]
Using the fact that \( p(y, \tau|x_0, t_0) \) satisfies the forward FP equation, \( \partial_\tau [p(y, \tau|x_0, t_0)] \) can be replaced by terms involving derivatives with respect to \( y \). Integrating by parts with respect to \( y \) then leads to the result
\[ 0 = \int_0^L [\partial_y q(y, \tau) + A(y) \partial_y q(y, \tau) + D \partial^2_{yy} q(y, \tau)] p(y, \tau) dy \]
\[ + [-A(y)q(y, \tau)p(y, \tau) + Dq(y, \tau) \partial_\tau p(y, \tau) - D \partial_y q(y, \tau)p(y, \tau)]|_{y=0}^{y=L}, \]
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where \( p(y, \tau) = p(y, \tau|x_0, t_0) \).

Choose (adjoint) boundary conditions for \( q \) so that the boundary terms vanish. If \( p = 0 \) on one of the boundaries then we require \( q = 0 \) on the same boundary. On the other hand, if \(-Ap + \partial_y p = 0\) then we require \( q' = 0 \). Finally taking \( \tau = t_0 \) with \( p(y, \tau|x_0, \tau) \) arbitrary, it follows that

\[
\partial_{\tau}q(y, \tau) + A(y)\partial_y q(y, \tau) + D\partial^2_{yy}q(y, \tau) = 0.
\]

Using time translation invariance,

\[
\partial_{\tau}p(x, t|y, \tau) = \partial_{\tau}p(x, 0|y, \tau - t) = -\partial_t p(x, 0|y, \tau - t) = -\partial_t p(x, t|y, \tau),
\]

then yields the backward FP equation for \( q \).

### 5.3 Mean first passage time

The MFPT \( \tau(y) \) is defined according to

\[
\tau(y) := \mathbb{E}[T(y)] = \int_0^\infty f(y, t)tdt.
\]

We then have two alternative formulae for \( \tau(y) \), depending on whether we use equation (5.4a) or (5.4b) for the FPT density:

\[
\tau(y) = -\int_0^\infty t\frac{\partial S(y, t)}{\partial t}dt = \int_0^\infty S(y, t)dt,
\]

(5.9a)

after integration by parts, or

\[
\tau(y) = \int_0^\infty tJ(L, t|y, 0) = -\frac{\partial}{\partial s} \hat{J}(s, y) \bigg|_{s=0},
\]

(5.9b)

where \( \hat{J}(s, y) \) is the Laplace transform of \( J(L, t|y, 0) \) with respect to \( t \). Equation (5.9b) suggests that one method for determining \( \tau(y) \) is to solve the FP equation (3.13) in Laplace space. However, it is often easier to use equation (5.9a) and the fact that the survival probability satisfies a backward FP equation. In particular, setting \( q(y, t|x) = p(x, t|y, 0) \), we have

\[
\frac{\partial q(y, t|x)}{\partial t} = A(y)\frac{\partial[q(y, t|x)]}{\partial y} + D\frac{\partial^2 q(y, t|x)}{\partial y^2},
\]

(5.10)

with \( A(y) = F(y)/\gamma \). Integrating with respect to \( x \) implies that \( S(y, t) \) also satisfies a backward FP equation:

\[
\frac{\partial S(y, t)}{\partial t} = A(y)\frac{\partial S(y, t)}{\partial y} + D\frac{\partial^2 S(y, t)}{\partial y^2}.
\]

(5.11)

Integrating both sides of equation (5.11) with respect to time \( t \) and using equation (5.9a) generates a differential equation for \( \tau(y) \): The MFPT \( \tau(y) \) for a particle to escape the interval \([0, L]\) at the end \( x = L \) with a reflecting boundary at \( x = 0 \) satisfies the differential equation

\[
A(y)\frac{d\tau(y)}{dy} + D\frac{d^2\tau(y)}{dy^2} = -1.
\]

(5.12)
with the reflecting and absorbing boundary conditions
\[ \tau'(0) = 0, \quad \tau(L) = 0. \]

It is straightforward to solve equation (5.12) by direct integration First, introduce the integration
factor
\[ \psi(y) = \exp \left( \frac{1}{D} \int_0^y A(y')dy' \right) = \exp \left( -\frac{U(y)}{k_B T} \right), \]
where we have set \( F(y) = -U'(y) \) with \( U(y) \) a potential energy, used the Einstein relation, and
integrated with respect to \( y \). Equation (5.12) becomes
\[ \frac{d}{dy} \left[ \psi(y)\tau'(y) \right] = -\frac{\psi(y)}{D} \]
so that
\[ \psi(y)\tau'(y) = -\frac{1}{D} \int_0^y \psi(y')dy', \]
where the boundary condition \( \tau'(0) = 0 \) has been used. Integrating once more with respect to \( y \)
and using \( \tau(L) = 0 \) then gives
\[ \tau(y) = \int_y^L \frac{dy'}{\psi(y')} \int_0^{y'} \frac{\psi(y'')}{D} dy''. \] (5.13)

In the case of pure diffusion \( (A(x) = 0) \), we have \( \psi(y) = 1 \) and
\[ \tau(y) = \frac{L^2 - y^2}{2D}. \] (5.14)

In particular, suppose the particle starts at the left–hand boundary. The corresponding MFPT is
then \( \tau(0) = L^2/2D \).

**Diffusion in the cytosol.** Within the cytosol of cells, macromolecules such as proteins tend to
have diffusivities \( D < 1 \mu m^2 s^{-1} \), which is due to effects such as molecular crowding. This implies
that the mean time for a diffusing particle to travel a distance \( 100 \mu m \) is at least \( 10^4 s \) (a few hours),
whereas to travel a distance \( 1 mm \) is at least \( 10^6 s \) (10 days). Since neurons, for example, which
are the largest cells in humans, have axonal and dendritic protrusions that can extend from \( 1 mm \)
up to \( 1 m \), the mean travel time due to passive diffusion becomes prohibitively large, and an active
form of transport becomes essential.

### 5.4 Splitting probabilities.

It is also possible to extend the above 1D analysis to the case where the particle can exit from either
end. It is often of interest to keep track of which end the particle exits, which leads to the concept
of a splitting probability. Equation (5.4) shows that the survival probability can be written as
\[ S(y, t) = \int_t^\infty J(L, t'|y, 0)dt' - \int_t^\infty J(0, t'|y, 0)dt' \equiv S_L(y, t) + S_0(y, t). \] (5.15)
where \( S_0(y, t) \) \( (S_L(y, t)) \) denotes the probability that the particle exits at \( x = 0 \) \((x = L)\) after time \( t \), having started at the point \( y \). Differentiating with respect to \( t \) and using the backward FP equation (5.7) we see that

\[
\frac{\partial S_0(y, t)}{\partial t} = J(0, t|y, 0) = - \int_t^\infty \frac{\partial J(0, t'|y, 0)}{\partial t'} dt'
\]

\[
= A(y) \frac{\partial S_0(y, t)}{\partial x} + D \frac{\partial^2 S_0(y, t)}{\partial x^2}.
\]

(5.16)

The hitting or splitting probability that the particle exits at \( x = 0 \) (rather than \( x = L \)) is \( \Pi_0(y) = S_0(y, 0) \). Moreover, the probability that the particle exits after time \( t \), conditioned on definitely exiting through \( x = 0 \), is \( \text{Prob}(T_0(y) > t) = S_0(y, t)/S_0(y, 0) \), where \( T_0(y) \) is the corresponding conditional FPT. Since the conditional MFPT satisfies

\[
\tau_0(y) = - \int_0^\infty t \frac{\partial \text{Prob}(T_0(y) > t)}{\partial t} dt = \int_0^\infty \frac{S_0(y, t)}{\Pi_0(y)} dt,
\]

Equation (5.16) is integrated with respect to \( t \) to give

\[
A(y) \frac{\partial \Pi_0(y) \tau_0(y)}{\partial y} + D \frac{\partial^2 \Pi_0(y) \tau_0(y)}{\partial y^2} = -\Pi_0(y),
\]

(5.17)

with boundary conditions \( \Pi_0(0) \tau_0(0) = \Pi_0(L) \tau_0(L) = 0 \). Finally, taking the limit \( t \to 0 \) in equation (5.16) and noting that \( J(0, 0|y, 0) = 0 \) for \( y \neq 0 \),

\[
A(y) \frac{\partial \Pi_0(y)}{\partial y} + D \frac{\partial^2 \Pi_0(y)}{\partial y^2} = 0,
\]

(5.18)

with boundary conditions \( \Pi_0(0) = 1, \Pi_0(L) = 0 \). A similar analysis can be carried out for exit through the other end \( x = L \) such that \( \Pi_0(y) + \Pi_L(y) = 1 \).

### 5.5 Higher spatial dimensions.

The construction of the FPT density can also be extended to higher spatial dimensions. Suppose that a particle evolves according to the Langevin equation (3.21) in a compact domain \( \Omega \) with boundary \( \partial \Omega \). Suppose that at time \( t = 0 \) the particle is at the point \( y \in \Omega \) and let \( T(y) \) denote the first passage time to reach any point on the boundary \( \partial \Omega \). The probability that the particle has not yet reached the boundary at time \( t \) is then

\[
\mathbb{P}(y, t) = \int_\Omega p(x, t|y, 0) dx,
\]

where \( p(x, t|y, 0) \) is the solution to the multivariate FP equation (3.24) with an absorbing boundary condition on \( \partial \Omega \). The FPT density is again \( f(y, t) = -d\mathbb{P}(y, t)/dt \) which, on using equation (3.24) and the divergence theorem, can be expressed as

\[
f(y, t) = - \int_{\partial \Omega} [-A(x)p(x, t|y, 0) + D \nabla p(x, t|y, 0)] \cdot d\sigma
\]

with \( A = F/\gamma \). Similarly, by constructing the corresponding backward FP equation, it can be shown that the MFPT satisfies the equation

\[
A(y) \cdot \nabla \tau(y) + D \nabla^2 \tau(y) = -1
\]

(5.19)

with \( \tau(y) = 0 \) for \( y \in \partial \Omega \).