Stochastic Processes in Cell Biology I: Supplementary material

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Chapter 6
Diffusive transport

A. Encounter-based models of absorption

In the case of the Fokker-Planck equation for single-particle diffusion in a bounded domain Ω (see Sect. 2.4), the most general classical boundary condition is the Robin condition $D\nabla p(\mathbf{x},t)\cdot\mathbf{n}+\kappa_0 p(\mathbf{x},t)=0$ for all $\mathbf{x}\in\partial\Omega$, where κ_0 is a positive reactivity constant, and $\mathbf{n}$ is the outward unit normal at a point on the boundary $\partial\Omega$. The Dirichlet and Neumann boundary conditions are recovered in the limits $\kappa_0\rightarrow\infty$ and $\kappa_0=0$, respectively. However, implementing these boundary conditions at the level of the SDE is non-trivial. In the case of a totally reflecting boundary, the underlying SDE is modified by including an impulsive kick term that keeps the particle within Ω. This term can be written as the differential of the boundary local time, which is a Brownian functional that determines the amount of contact time between particle and boundary [53, 43, 44, 58, 36, 57]. The modified SDE is known as the Skorokhod equation. Probabilistic versions of the Robin boundary condition can also be constructed using the local time [39]. One of the assumptions of the Robin boundary condition is that the surface reactivity is a constant. However, various surface-based reactions are better modeled in terms of a reactivity that is a function of the local time [4, 35]. That is, the surface may need to be progressively activated by repeated encounters with a diffusing particle, or an initially highly reactive surface may become less active due to multiple interactions with the particle (passivation). Recently, a theoretical framework for analyzing a more general class of partially absorbing boundary conditions for diffusion processes has been developed using a so-called encounter-based approach [40, 41, 11, 13]. The latter can also be applied to diffusion with stochastic resetting [14, 15, 5], anomalous diffusion [18, 19], and active particles [16, 17, 20]

A.1 Totally reflecting boundary at $x = 0$

In order to introduce the encounter-based approach we consider the example of a single Brownian particle on the half-line $[0,\infty)$ with a partially absorbing boundary at $x = 0$. First suppose that the boundary is totally reflecting. Let $L(t)$ be the boundary local time, which is a Brownian functional of the form (see Sect. 8.6)

$$L(t) = \lim_{\varepsilon\to 0^+} \frac{D}{\varepsilon}\int_0^t \mathbf{1}_{(0,\varepsilon)}(X(s))ds, \tag{A.1}$$

where $\mathbf{1}$ is the indicator function. (The factor of D means that $Lj(t)$ has units of length.) It can be proven that $j(t)$ exists and is a nondecreasing, continuous function of t [43, 44]. The SDE for $X(t) \in [0,\infty)$ is given by the so-called Skorokhod equation for reflecting Brownian motion,

$$dX(t) = \sqrt{2D}dW(t) + dL(t), \quad dL(t) = D\delta(X(t))dt, \tag{A.2}$$

with $W(t)$ a Brownian motion. The differential $dL(t)$ represents an impulsive kick applied to the particle whenever it hits $x = 0$. We now show that the correspondingh FP equation satisfies the standard Neumann boundary condition at $x = 0$. First, we introducethe stochastic density (empirical measure)

$$\rho(x,t) = \delta(X(t)-x). \tag{A.3}$$

Consider an arbitrary smooth test function $f(x)$, and set

$$F(t) = f(X(t)) = \int_0^\infty \rho(x,t)f(x)dx. \tag{A.4}$$

Using Ito's lemma to determine the differential $dF(t)$, we have

$$\begin{aligned}\left[\int_0^\infty f(x)\frac{\partial\rho(x,t)}{\partial t}dx\right]dt &= \left[f'(X(t))dL_j(t) + Df''(X(t)dt + \sqrt{2D}f'(X(t))dW(t)\right]\\ &\equiv dF(t).\end{aligned} \tag{A.5}$$

Since $dL(t) = D\delta(X(t))dt$, it follows that

$$\int_0^\infty f(x)\frac{\partial\rho(x,t)}{\partial t} = \int_0^\infty \rho(x,t)\left[D\delta(x)f'(0) + Df''(x) + \sqrt{2D}f'(x)\xi(t)\right]dx. \tag{A.6}$$

We have formally set $dW(t) = \xi(t)dt$ where ξ is a white noise term such that

$$\langle\xi(t)\rangle = 0, \quad \langle\xi(t)\xi(t')\rangle = \delta(t-t'). \tag{A.7}$$

Integrating by parts the terms on the right-hand of equation (A.6) and noting that the terms involving $f'(0)$ cancel, we have

$$\int_0^\infty f(x)\frac{\partial \rho(x,t)}{\partial t}dx = \int_0^\infty f(x)\left(-\sqrt{2D}\partial_x \rho(x,t)\xi(t) + D\partial_{xx}\rho(x,t)\right)dx \\ - f(0)\left(\sqrt{2D}\rho(0,t)\xi(t) - D\partial_x\rho(0,t)\right). \tag{A.8}$$

Since $f(x)$ is arbitrary, we obtain the following SPDE (in the weak sense):

$$\frac{\partial \rho(x,t)}{\partial t} = -\sqrt{2D}\frac{\partial \rho(x,t)}{\partial x}\xi(t) + D\frac{\partial^2 \rho(x,t)}{\partial x^2} - \delta(x)\mathcal{J}(0,t), \tag{A.9a}$$

with

$$\mathcal{J}(x,t) \equiv \sqrt{2D}\rho(x,t)\xi(t) - D\frac{\partial \rho(x,t)}{\partial x}. \tag{A.9b}$$

Finally, averaging with respect to the white noise and setting $p(x,t) = \langle \rho(x,t)\rangle$ yields the diffusion equation on the half-line with a totally reflecting boundary at $x = 0$:

$$\frac{\partial p(x,t)}{\partial t} = D\frac{\partial^2 \rho(x,t)}{\partial x^2}, \quad D\frac{\partial \rho(0,t)}{\partial x} = 0. \tag{A.10}$$

A.2 Partially absorbing boundary at $x = 0$

So far we have focused on totally reflecting boundary conditions, which can be handled using Skorokhod SDEs and the differential of the local time. However, the introduction of the local time also allows us to incorporate a much more general class of boundary condition via the encounter-based approach to diffusion-mediated surface absorption [40, 41, 11, 13]. The encounter-based approach assumes that a diffusion process is killed when its local time $L(t)$ at $x = 0$, as defined in equation (A.1), exceeds a randomly distributed threshold $\widehat{\ell}$. In other words, the particle is absorbed at $x = 0$ at the stopping time

$$\mathcal{T} = \inf\{t > 0: \ L(t) > \widehat{\ell}\}, \quad \mathbb{P}[\widehat{\ell} > \ell] \equiv \Psi(\ell). \tag{A.11}$$

Since $L(t)$ is a nondecreasing process, the condition $t < \mathcal{T}$ is equivalent to the condition $L(t) < \widehat{\ell}$. Hence, the corresponding single-particle SDE is

$$dX(t) = [\sqrt{2D}dW(t) + dL(t)]\mathbf{1}_{L(t)<\widehat{\ell}}, \tag{A.12}$$

where $\mathbf{1}_{L(t)<\widehat{\ell}} \equiv \Theta(\widehat{\ell} - L(t))$ with $\Theta(x)$ a Heaviside function. Following along similar lines to a reflecting boundary, we introduce the single-particle empirical measure

$$\mu(x,\widehat{\ell},t) = \delta(x - X(t))\mathbf{1}_{L(t)<\widehat{\ell}}. \tag{A.13}$$

Let $f(x)$ be a bounded smooth test function and set

$$F(\widehat{\ell},t) = f(X(t))\mathbf{1}_{L(t)<\widehat{\ell}}. \tag{A.14}$$

Using Ito's lemma and the definition of the local time, we have

$$\begin{aligned} dF(\widehat{\ell},t) &= \left[Df''(X(t))dt + \sqrt{2D}f'(X(t))dW(t) + Df'(X(t))\delta(X(t))dt\right]\mathbf{1}_{L(t)<\widehat{\ell}} \\ &\quad - Df(0)\delta(X(t))\delta(L(t)-\widehat{\ell}). \end{aligned} \tag{A.15}$$

It follows that

$$\begin{aligned} &\left[\int_0^\infty f(x)\frac{\partial \mu(x,\widehat{\ell},t)}{\partial t}dx\right]dt \\ &= \int_0^\infty \mu(x,\widehat{\ell},t)\left[Df''(x)dt + \sqrt{2D}f'(x)dW(t) + D\delta(x)f'(0)\right]dx \\ &\quad - Df(0)\delta(X(t))\delta(L(t)-\widehat{\ell}). \end{aligned} \tag{A.16}$$

Integrating by parts and using the arbitrariness of f yields an SPDE for μ:

$$\frac{\partial \mu(x,\widehat{\ell},t)}{\partial t} = D\frac{\partial^2 \mu(x,\widehat{\ell},t)}{\partial x^2} + \sqrt{2D}\frac{\partial \mu(x,\widehat{\ell},t)}{\partial x}\xi(t), \qquad x>0 \tag{A.17a}$$

and

$$D\frac{\partial \mu(0,\widehat{\ell},t)}{\partial x} = \sqrt{2D}\xi(t)\mu(0,\widehat{\ell},t) + D\delta(X(t))\delta(L(t)-\widehat{\ell}) \tag{A.17b}$$

The latter equation follows from equating the sum of terms multiplying $f(0)$ to zero.

In order to derive a generalized FP equation we need to take expectations with respect to both the white noise process and the random threshold. Recall that these are denoted by $\langle\cdot\rangle$ and $\mathbb{E}[\cdot]$, respectively. Note, in particular, that

$$\mathbb{E}\left[\mathbf{1}_{L(t)<\widehat{\ell}}\right] = \Psi(L(t)), \qquad E\left[\delta(L(t)-\widehat{\ell})\right] = \psi(L(t)) := -\Psi'(L(t)). \tag{A.18}$$

Introducing the pair of densities

$$p^\Psi(x,t) = \mathbb{E}[\langle \mu(x,\widehat{\ell},t)\rangle] = \left\langle \delta(x-X(t))\mathbb{E}[\mathbf{1}_{L(t)<\widehat{\ell}}]\right\rangle = \left\langle \delta(x-X(t)\Psi(L(t))\right\rangle, \tag{A.19a}$$

$$\nu^\psi(x,t) = \left\langle \delta(x-X(t))\mathbb{E}[\delta(L(t)-\widehat{\ell})]\right\rangle = \left\langle \delta(x-X(t)\psi(L(t))\right\rangle, \tag{A.19b}$$

and taking expectations of equations (A.17) gives

$$\frac{\partial p^{\Psi}(x,t)}{\partial t} = D\frac{\partial^2 p^{\Psi}(x,t)}{\partial x^2},\ x>0, \quad D\frac{\partial p^{\Psi}(x,t)}{\partial x}\Big|_{x=0} = D\nu^{\Psi}(0,t). \tag{A.20}$$

For a general local time threshold distribution Ψ, we do not have a closed equation for the marginal density $p^{\Psi}(x,t)$. However, in the particular case of the exponential distribution $\Psi(\ell) = \mathrm{e}^{-\kappa_0\ell/D}$, we have $\psi(\ell) = \kappa_0\Psi(\ell)/D$ and equations (A.20) reduce to the classical Robin BVP with reactivity κ_0:

$$\frac{\partial p(x,t)}{\partial t} = D\frac{\partial^2 p(x,t)}{\partial x^2}, \quad x>0, \tag{A.21a}$$

$$D\frac{\partial p(0,t)}{\partial x}\Big|_{x=0} = \kappa_0 p(0,t). \tag{A.21b}$$

(We have set $p^{\Psi} = p$ for $\Psi(\ell) = \mathrm{e}^{-\kappa_0\ell/D}$.) Within the context of the encounter-based formalism, we now make the crucial observation that the solution of the Robin BVP is equivalent to the Laplace transform of the so-called local time propagator with respect to ℓ:

$$p(x,t) = \int_0^{\infty} \mathrm{e}^{-z\ell} P(x,\ell,t)d\ell = \mathcal{P}(x,z,t), \quad z = \kappa_0/D, \tag{A.22}$$

where $P(x,\ell,t)$ is known as the local time propagator and can be defined according to [40, 41, 11, 13]

$$P(x,\ell,t) := \left\langle \delta(X(t)-x)\delta(L(t)-\ell)\right\rangle, \tag{A.23}$$

Assuming that the Laplace transform $\mathcal{P}(x,z,t)$, can be inverted with respect to z, the solution of equation (A.20) is obtained from equation (A.20a):

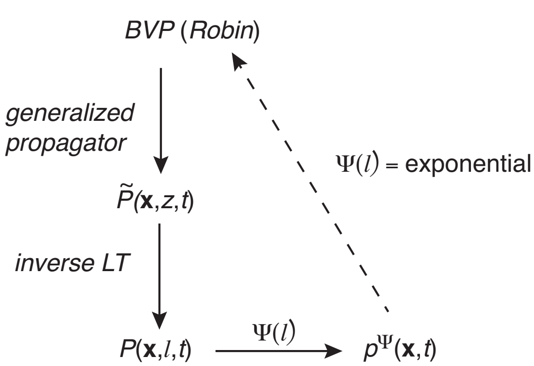

Fig. 6.1: Diagram illustrating the encounter-based framework for diffusion in a domain with a partially absorbing target. The solution of the BVP in the case of a constant absorption rate κ_0 generates the Laplace transform $\widetilde{P}(x,z,t)$ of the local time propagator $P(x,\ell,t)$. The inverse LT determines the marginal probability density $p^{\Psi}(x,t)$ according to equation (A.24).

$$p^{\Psi}(x,t) = \int_0^\infty \Psi(\ell)P(x,\ell,t)d\ell = \int_0^\infty \Psi(\ell)\mathrm{LT}^{-1}\widetilde{P}(x,z,t)d\ell. \tag{A.24}$$

One way to implement a non-exponential law is to consider an ℓ-dependent reactivity $\kappa(\ell)$ such that

$$\Psi(\ell) = \exp(-D^{-1}\int_0^\ell \kappa(\ell')d\ell'). \tag{A.25}$$

Since the probability of absorption now depends on how much time the particle spends in a neighborhood of the boundary, as specified by the local time, it follows that the stochastic process has memory. That is, absorption process itself is non-Markovian. The general probabilistic framework is summarized in Fig. 6.1. One of the challenges in implementing the encounter-based method in higher spatial dimensions is that the solutions of the classical Robin tends to have a non-trivial parametric dependence on the Laplace variable z, which makes it difficult to calculate the inverse transform analytically.

A.3 Partially absorbing traps

The encounter-based approach to single particle absorption has also been developed within the context of heterogeneous media, where one or more subregions of a domain act as partially absorbing traps [11, 13]. A classical example occurs in models of axonal transport of cargo to synaptic targets, see Sect. 7.1. A simpler example is shown in Fig. 6.2 for a single absorbing trap in the interval $[-R,R]$. A Brownian particle can freely enter and exit the trap but is only absorbed within the trap when its occupation time exceeds some random threshold. The occupation time is a Brownian functional defined according to [57]

$$A(t) = \int_0^t \mathbf{1}_{(-R,R)}(X(\tau))d\tau = \int_0^t \left(\int_{-R}^R \delta(x-X(\tau))dx\right)d\tau. \tag{A.26}$$

$A(t)$ specifies the amount of time the particle spends within $[-R,R]$ over the time interval $[0,t]$. The stopping time condition for absorption is

$$\mathcal{T} = \inf\{t>0:\ A(t) > \widehat{a}\}, \tag{A.27}$$

where $\widehat{a}$ is a random variable with probability distribution $\Psi(a) = \mathbb{P}[\widehat{a} > a]$. Hence, the corresponding single-particle SDE is

$$dX(t) = \sqrt{2D}dW(t)\mathbf{1}_{A(t)<\widehat{a}}. \tag{A.28}$$

Following along analogous lines to an absorbing boundary, we introduce the single-particle empirical measure

$$\mu(x,\widehat{a},t) = \delta(x-X(t))\mathbf{1}_{A(t)<\widehat{a}}, \tag{A.29}$$

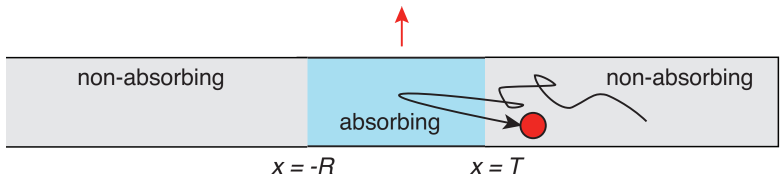

Fig. 6.2: One-dimensional diffusion with a partially absorbing trap in the interval $[-R,R]$.

and set $F(\widehat{a},t)=f(X(t))\mathbf{1}_{A(t)<\widehat{a}}$ for a test function $f(x)$ in $\mathbb{R}$. Using Itô's lemma and the definition of the occupation time, we have

$$\begin{aligned} dF(\widehat{a},t) &= \left[Df''(X(t))dt+\sqrt{2D}f'(X(t))dW(t)\right]\mathbf{1}_{A(t)<\widehat{a}} \\ &\quad -\delta(A(t)-\widehat{a})\int_{-R}^{R}\delta(X(t)-y)f(y)dy. \end{aligned} \tag{A.30}$$

It follows that

$$\begin{aligned} \int_{-\infty}^{\infty}f(x)\frac{\partial\mu(x,\widehat{a},t)}{\partial t}dx &= \int_{-\infty}^{\infty}\mu(x,\widehat{a},t)\left[Df''(x)dt+\sqrt{2D}f'(X(t))dW(t)\right]dx \\ &\quad -\delta(A(t)-\widehat{a})\int_{-R}^{R}\delta(X(t)-y)f(y)dy. \end{aligned} \tag{A.31}$$

Integrating by parts and using the arbitrariness of f yields an SPDE for μ:

$$\frac{\partial\mu(x,\widehat{a},t)}{\partial t}=D\frac{\partial^2\mu(x,\widehat{a},t)}{\partial x^2}+\sqrt{2D}\frac{\partial\mu(x,\widehat{a},t)}{\partial x}\xi(t)-\nu(x,\widehat{a},t), \tag{A.32a}$$

with

$$\nu(x,\widehat{a},t)=\delta(A(t)-\widehat{a})\delta(X(t)-x)\mathbf{1}_{(-R,R)}(x). \tag{A.32b}$$

Note that ν vanishes outside the trap. Finally, averaging with respect to the white noise process and the random occupation time threshold yields

$$\frac{\partial p^{\Psi}(x,t)}{\partial t}=D\frac{\partial^2 p^{\Psi}(x,t)}{\partial x^2}-\nu^{\Psi}(x,t)\mathbf{1}_{(-R,R)}(x), \tag{A.33}$$

with

$$p^{\Psi}(x,t)=\mathbb{E}[\langle\mu(x,\widehat{a},t)\rangle]=\langle\delta(x-X(t)\Psi(A(t))\rangle, \tag{A.34a}$$

$$\nu^{\Psi}(x,t)=\left\langle\delta(x-X(t))\delta(A(t)-\widehat{a})\right\rangle=\left\langle\psi(A(t))\delta(x-X(t)\right\rangle. \tag{A.34b}$$

The subsequent solution strategy is analogous to the case of an absorbing boundary [11, 13]. That is, for an exponential distribution $\Psi(a)=\mathrm{e}^{-\kappa_0 a}$ we recover the classical inhomogeneous diffusion equation

$$\frac{\partial p(x,t)}{\partial t} = D\frac{\partial^2 p(x,t)}{\partial x^2}, \quad x \in (-\infty,-R) \cup (R,\infty), \tag{A.35a}$$

$$\frac{\partial q(x,t)}{\partial t} = D\frac{\partial^2 q(x,t)}{\partial x^2} - \kappa_0 q(x,t), \quad x \in (-R,R), \tag{A.35b}$$

together with the matching conditions

$$p(\pm R,t) = q(\pm R,t), \quad \partial_x p(\pm R,t) = \partial_x q(\pm R,t). \tag{A.35c}$$

(We have denoted the solution within the trap by the function $q(x,t)$.) The final step is to identify the solution p and q as the Laplace transforms of the corresponding propagators

$$P(x,a,t) = \left\langle \delta(x - X(t)\delta(a - A(t) \right\rangle, \quad x \in (-\infty,-R) \cup (R,\infty), \tag{A.36a}$$

$$Q(x,a,t) = \langle \delta(x - X(t)\delta(a - A(t)\rangle, \quad x \in (-R,R). \tag{A.36b}$$

B. Sticky reflecting Brownian motion

The notion of sticky reflecting Brownian motion (BM) dates back to work by Feller in 1952, who considered various boundary conditions for the diffusion equation in $[0,\infty)$ that are consistent with stochastic processes behaving like standard Brownian motion in $(0,\infty)$ [34]. Ito and McKean [43] subsequently showed how to construct sample paths of sticky reflecting BM using a random time change that slowed down reflected paths so that the total time spent at the origin $x=0$ has positive Lebesgue measure. The latter is specified by the stickiness parameter. In this section we briefly describe the Ito and McKean construction and then consider the more recent formulation of sticky BM based on the inclusion of a strongly localized attractive potential close to the boundary at $x=0$ [9].

B.1 Slowed down reflecting BM in $[0,\infty)$

Let $Y(t)$ be a reflecting BM, that is, $Y(t)=\sqrt{2D}|W(t)|$, where $W(t)$ is a standard Wiener process and D is a constant diffusivity. That is,

$$\langle W(t)\rangle = 0, \quad \langle W(t)W(t')\rangle = \min(t,t'). \tag{B.1}$$

Following supplementary Sect. 6A, define the local time at the origin according to [43, 58, 57]

$$\ell(t;Y) = \lim_{\varepsilon\to 0}\frac{D}{\varepsilon}\int_0^t \mathbb{I}_{[0,\varepsilon]}(Y(\tau))d\tau, \tag{B.2}$$

where $\mathbb{I}_\Sigma(x)=1$ if $x\in\Sigma$ and is zero otherwise. (It is often convenient to include the factor of D in the definition of the local time, which means that $\ell(t)$ has units of length.) It can be proven that $\ell(t)$ exists and is a positive, non-decreasing function of t. The corresponding SDE for $Y(t)$ is the so-called Skorokhod equation

$$dY(t) = \sqrt{2D}dW(t) + d\ell(t;Y). \tag{B.3}$$

(Note that ε, $Y(t)$ and $\ell(t)$ have units of length.) Formally speaking $d\ell(t;Y) = \delta(Y(t))$, which means that each time the particle hits the boundary it is given an impulsive kick back into the domain $x>0$. Introduce the additive continuous increasing function

$$T(t) = t + \nu\ell(t;Y)/D, \tag{B.4}$$

where ν is a fixed positive constant with units of length. Note that $dT/dt = 1$ except at times where a trajectory contacts the origin. The reflected BM is slowed down at the origin by constructing the new stochastic process [43]

$$\widehat{Y}(t) = Y(T^{-1}(t)). \tag{B.5}$$

The amount of time spent at the boundary $x=0$ can now be characterized in terms of the occupation time at the origin, as outlined in Ref. [48]. The occupation time is defined as

$$A(t;\widehat{Y}) := \int_0^t \mathbb{I}_0(\widehat{Y}(s))ds = \int_0^t \mathbb{I}_0(Y(T^{-1}(s))ds. \tag{B.6}$$

Performing the change of variable for each sample path $s = T(\tau)$ gives

$$\begin{aligned} A(t;\widehat{Y}) &= \int_0^{T^{-1}(t)} \mathbb{I}_0(Y(\tau))dT(\tau) \qquad \text{(B.7)} \\ &= \int_0^{T^{-1}(t)} \mathbb{I}_0(Y(\tau))d\tau + \frac{\nu}{D}\int_0^{T^{-1}(t)} \mathbb{I}_0(Y(\tau))d\ell(\tau;Y). \end{aligned}$$

The first integral on the right-hand side is simply the occupation time of reflected BM at a single point $x=0$ over the time interval $[0,T^{-1}(t)]$ and is identically zero. On the other hand, the second integral concentrates the integral to all points at which $\mathbb{I}_0(Y(\tau)) = 1$ so that $A(t) = \nu\ell(T^{-1}(t);Y)/D$. We thus obtain the result

$$A(t;\widehat{Y}) = \frac{\nu}{D}\ell(t;\widehat{Y}). \tag{B.8}$$

Clearly the amount of time the Brownian particle is stuck at the origin depends on the stickiness parameter ν. Eqs. (B.3) and (B.8) correspond to the SDE for sticky reflecting BM $\widehat{Y}(t)$[1].

B.2 Reflecting BM with a strong localized potential near the origin

We now turn to a more recent formulation of sticky BM that is based on reflecting BM in $\mathbb{R}^+$ with a strongly localized attractive potential energy function in a neighborhood of the origin, as illustrated in Fig. 6.3. More specifically, let $U^\varepsilon(x) \in C^2(\mathbb{R}^+)$ represent a family of potentials parameterized by ε, $\varepsilon > 0$, with the following properties [9]:

(i) $U^\varepsilon(x) \approx 0$ for $x \geq \varepsilon$. In particular, $U^\varepsilon(x)$, $\partial_x U^{\varepsilon(x)}$, $\partial_{xx} U^\varepsilon(x) \leq O(\varepsilon)$ for $x \geq \varepsilon$. This assumption means that outside the boundary layer $(0,\varepsilon)$, the force acting on the particle is negligible and it simply diffuses.

(ii) Within the boundary layer $(0,\varepsilon)$ the function $U^\varepsilon(x)$ takes the form of an attractive potential well that becomes deeper and narrower as $\varepsilon \to 0$. The MFPT to escape from the boundary layer is approximately $\varepsilon \mathrm{e}^{\Delta U}$ where ΔU is the height of the potential barrier.

(iii) There exists a parameter ν such that

[1] One technical point is that there are no strong solutions for sticky BM $\widehat{Y}(t)$, meaning that not every realization of the Wiener process is mapped to a path of $\widehat{Y}(t)$. However, there does exist a weak solution in the sense that the probability density of sample paths (solution of the corresponding FP equation) is unique [**?**].

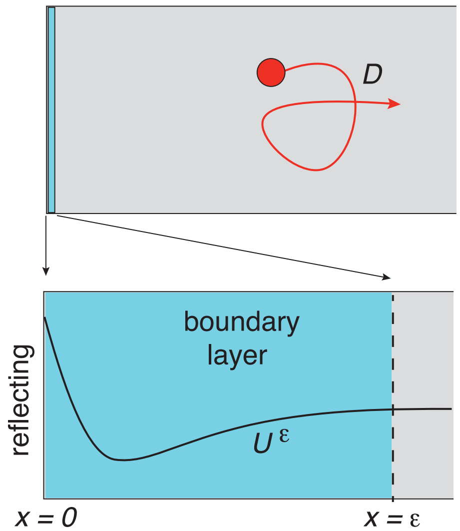

Fig. 6.3: Boundary layer construction near $x = 0$ for sticky BM. Within the boundary layer $(0,\varepsilon)$ there is a strongly attracting potential well, whereas the potential is approximately flat for $x \geq \varepsilon$.

$$\lim_{\varepsilon\to 0}\int_0^{\varepsilon} \mathrm{e}^{-U^{\varepsilon}(x)/k_BT}\,dx = \nu. \tag{B.9}$$

This condition is the source of stickiness at the origin with ν ultimately being identified with the stickiness parameter. Using steepest descents, it can be shown that

$$\sqrt{2\pi k_BT}\lim_{\varepsilon\to 0}\frac{\mathrm{e}^{-U^{\varepsilon}(x_0)/k_BT}}{\sqrt{\partial_{xx}U^{\varepsilon}(x_0)}} = \nu, \tag{B.10}$$

where x_0 is the location of the minimum of $U^{\varepsilon}(x)$ in $(0,\varepsilon)$. Assuming that $\partial_{xx}U^{\varepsilon}(x_0) \approx U^{\varepsilon}(x_0)/\varepsilon^2$, it follows that $|U^{\varepsilon}(x_0)| \sim |\log\varepsilon|$ and the left-hand side is $O(1)$. We also see that the MFPT is proportional to ν so that increasing ν makes the boundary more sticky.

An example of a family of potentials satisfying the above three properties is the Morse potential [9]

$$U^{\varepsilon}(x) = \overline{U}\left(1-\mathrm{e}^{-(x-x_0(\varepsilon))/\xi(\varepsilon)}\right)^2 - \overline{U}, \tag{B.11}$$

with $x_0 = O(\varepsilon^2)$, $\xi = O(\varepsilon^2)$ and $\overline{U}$ defined implicitly as the solution to the equation

$$\xi\mathrm{e}^{\overline{U}/k_BT}\sqrt{\pi k_BT/\overline{U}} = \nu. \tag{B.12}$$

The latter is chosen so that Eq. (B.9) holds.

For any $\varepsilon > 0$, the position $X(t)$ of the particle evolves according to the SDE

$$dX(t) = -\gamma^{-1}\partial_x U^{\varepsilon}(X(t))dt + \sqrt{2D}dW(t), \tag{B.13}$$

with a reflecting boundary at the origin. (More precisely, the stochastic variable should be written as $X_\varepsilon(t)$ since the solution will depend on ε. We drop the subscript for notational simplicity.) The friction coefficient γ satisfies the Einstein relation $\gamma D = k_B T$. Let $\rho(x,t)$ denote the probability density of the stochastic variable $X(t)$. The associated FP equation is given by

$$\frac{\partial \rho}{\partial t} = D\frac{\partial^2 \rho}{\partial x^2} + \gamma^{-1}\frac{\partial}{\partial x}[\partial_x U^{\varepsilon}(x)\rho], \tag{B.14}$$

with $D\partial\rho(0,t) + \gamma^{-1}\partial_x U^{(\varepsilon)}(0)\rho(0,t) = 0$.

As shown in Ref. [9], one can use matched asymptotics to derive an effective FP equation in the limit $\varepsilon \to 0$ that recovers the sticky boundary condition first introduced by Feller [34]. Let $p(x,t)$ denote the leading order term in an asymptotic expansion of the outer solution in the region $x \geq \varepsilon$, which evolves according to the standard diffusion equation

$$\frac{\partial p(x,t)}{\partial t} = D\frac{\partial^2 p(x,t)}{\partial x^2}, \quad x \geq \varepsilon. \tag{B.15}$$

Similarly let $q(x,t)$ denote the corresponding term of the inner solution with

$$\frac{\partial q(x,t)}{\partial t} = \gamma^{-1}\frac{\partial}{\partial x}\left[\partial_x U^{\varepsilon}(x)q(x,t)\right] + D\frac{\partial^2 q(x,t)}{\partial x^2}, \tag{B.16}$$

for $x \in (0,\varepsilon)$, together with the reflecting boundary condition

$$D\partial_x q(0,t) + \gamma^{-1}\partial_x U^{\varepsilon}(0)q(0,t) = 0. \tag{B.17}$$

Introducing the stretched coordinate $X = x/\varepsilon$ and keeping only the leading order terms gives

$$0 = \gamma^{-1}\frac{\partial}{\partial X}\left[\partial_X U^{\varepsilon}(\varepsilon X)q(\varepsilon X,t)\right] + D\frac{\partial^2 q(\varepsilon X,t)}{\partial X^2}, \tag{B.18}$$

for $X \in (0,1)$, with $D\partial_X q(0,t) + \gamma^{-1}\partial_X U^{\varepsilon}(0)q(0,t) = 0$. The solution for q is

$$q(\varepsilon X,t) = \mathscr{N}(t)\mathrm{e}^{-U^{\varepsilon}(\varepsilon X)/k_B T}, \quad X \leq 1, \tag{B.19}$$

with the time-dependent amplitude $\mathscr{N}(t)$ determined by matching the inner solution $q(\varepsilon X,t)$ with the outer solution $p(x,t)$ at $x = \varepsilon$ and $X = 1$.

Since the perturbation is not singular, matching can be performed at a single point, which is equivalent to imposing the continuity condition $p(\varepsilon,t) = q(\varepsilon,t)$. Using the fact that $\mathrm{e}^{-U^{\varepsilon}(\varepsilon)/k_B T} \sim 1$ and $p(\varepsilon,t) \sim p(0,t)$, we obtain the leading order condition $\mathscr{N}(t) = p(0,t)$. A second condition on $\mathscr{N}(t)$ is obtained from the requirement that the total probability is conserved,

$$\frac{d}{\partial t}\left(\int_0^{\varepsilon} q(x,t)dx + \int_{\varepsilon}^{\infty} p(x,t)dx\right) = 0. \tag{B.20}$$

Moving the time derivatives inside the integrals and using the diffusion equation for p yields

$$\begin{aligned} 0 &= \left(\int_0^{\varepsilon} \frac{d\mathscr{N}(t)}{dt} \mathrm{e}^{-U^{\varepsilon}(x)/k_BT} dx + D\int_{\varepsilon}^{\infty} \frac{\partial^2 p(x,t)}{\partial x^2} dx\right) \\ &= \frac{d\mathscr{N}(t)}{dt} \int_0^{\varepsilon} \mathrm{e}^{-U^{\varepsilon}(x)/k_BT} dx - D\partial_x p(\varepsilon,t). \end{aligned} \tag{B.21}$$

Finally, taking the limit $\varepsilon \to 0$ using Eq. (B.9) and setting $\mathscr{N}(t) = p(0,t)$ yields the boundary condition

$$\nu \frac{\partial p(0,t)}{\partial t} = D\frac{\partial p(0,t)}{\partial x}. \tag{B.22}$$

From the diffusion equation for p, we see that this is equivalent to the boundary condition first introduced by Feller [34], namely,

$$\nu \frac{\partial^2 p(0,t)}{\partial x^2} = \frac{\partial p(0,t)}{\partial x}. \tag{B.23}$$

Formally speaking, the full probability density $\rho(x,t)$ can then be written in the form

$$\rho(x,t) = \lim_{\varepsilon \to 0} p(x,t)\mathrm{e}^{-U^{\varepsilon}(x)/k_BT} = p(x,t)(1+\nu\delta(x)). \tag{B.24}$$

This follows from the assumed properties of $U^{\varepsilon}(x)$. It will be convenient for our subsequent analysis to rewrite the full FP equation for sticky BM in the form

$$\frac{\partial p(x,t)}{\partial t} = D\frac{\partial^2 p(x,t)}{\partial x^2}, \quad x \in (0,\infty), \tag{B.25a}$$

$$q(t) = \nu p(0,t), \quad \frac{dq(t)}{dt} = D\frac{\partial p(0,t)}{\partial x}. \tag{B.25b}$$

This makes explicit the notion that the probability of being at the origin has finite Lebesgue measure and consequently a nonzero occupation time. Note that if $\nu = 0$ then $q(t) = 0$ and we recover reflecting BM.

6.3 Numerical method for simulating sticky BM

The derivation of the FP equation for sticky BM, see Eqs. (B.25a) and (B.25b), was based on taking the limit $\varepsilon \to 0$ of reflecting BM in the presence of a local attractive potential well of width ε. However, as highlighted in Ref. [9], simulating the corresponding SDE (B.13) for small ε in order to generate sample paths of sticky BM is not particularly efficient, since a very small step size is needed in order

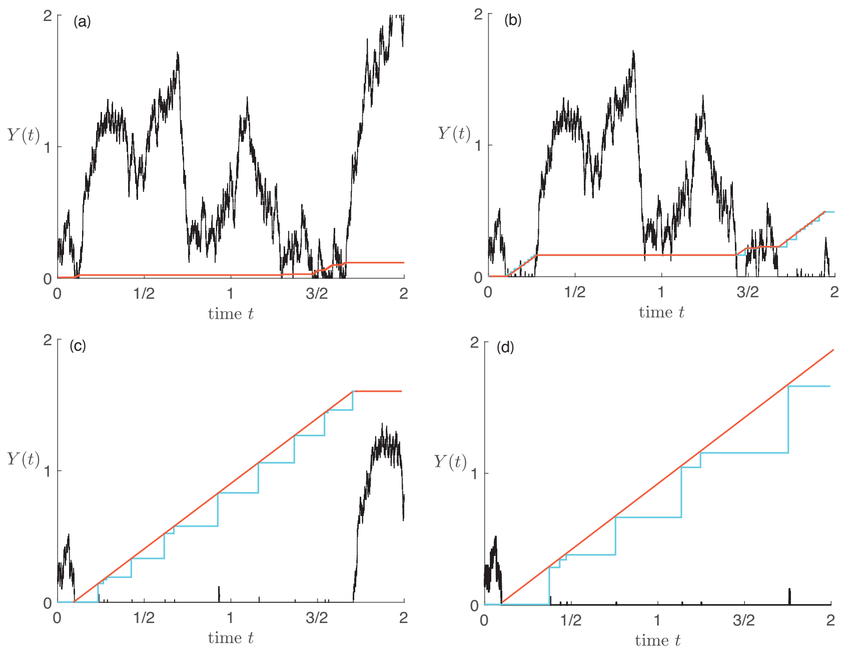

Fig. 6.4: Sample paths $Y(t)$ of the sticky random walk algorithm presented in Ref. [9] for different values of the stickiness parameter: (a) $\nu = 0.1$; (b) $\nu = 1$; (c) $\nu = 10$; (d) $\nu = 20$. Other parameter values are $x_0 = 0.2$ and $h = 0.01$. We also plot the accumulation time $A_0(t)$ at the origin, which is shown as a piecewise smooth (red) curve. Short-lived excursions away from the origin are smoothed out. However, the time intervals between such excursions are indicated by the (blue) staircase).

to achieve reasonable accuracy. Here we briefly describe a more effective numerical scheme for simulating sticky BM that was also introduced in Ref. [9]. This is based on constructing a continuous time Markov chain that represents a sticky random walk. We use this algorithm to illustrate the fact that the occupation time at the origin, see Eq. (B.8), has a non-zero Lebesgue measure.

Suppose that $\mathbb{R}^+$ is discretized by setting $x = nh$ for positive integers n with h the lattice spacing. The sticky random walk on the lattice can be simulated exactly using a simple Monte Carlo algorithm. Let $N(t)$ denote the lattice site occupied by the random walker at time t. The position is updated as follows [9]:

(I) If $N(t) \geq 1$ then the particle jumps to one of the neighboring lattice sites $N(t) \pm 1$ with equal probability. The waiting time for the jump is exponentially distributed with mean waiting time $h^2/2$.

(II) If $N(t) = 0$ then the particle jumps to the right with unit probability. The waiting time for the jump is again exponentially distributed but the mean waiting time is now $h^2/2 + \nu h$, where ν is the stickiness parameter.

Example realizations of the sticky random walk are shown in Fig. 6.4. The plots are generated using the MatLab code presented in appendix A of Ref. [9], which has been slightly modified in order to display the occupation time $A_0(t)$ at the origin. As expected the occupation time tends to increase with ν. Finally, note that the potential construction can be combined with the encounter-based method of supplementary Sect. 6A to develop a probabilistic formulation of partial absorption at a sticky boundary [22]

C. Semi-permeable membranes

Diffusion through semipermeable barriers or membranes has a number of applications in cell biology. One of the best-known examples is a lipid bilayer that regulates the flow of proteins and ions between different subcellular compartments and the exchange of molecules with the extracellular environment, see Sect. 6.1. Semipermeable barriers also occur at the multicellular level, as exemplified by electrical or chemical gap junctions, see Sect.6.7. At the macroscopic level, multi-particle diffusion across a semi-permeable membrane is modeled by taking the Fickian flux across the membrane to be continuous and to be proportional to the difference in concentrations on either side of the barrier; the constant of proportionality identified as the permeability. For example, suppose that $\mathcal{M}$ denotes a closed bounded domain $\mathcal{M} \subset \mathbb{R}^d$ with a smooth concave boundary $\partial\mathcal{M}$ separating the two open domains $\mathcal{M}$ and its complement $\mathcal{M}^c$, see Fig. 6.5. The boundary acts as a semipermeable interface with $\partial\mathcal{M}^+$ ($\partial\mathcal{M}^-$) denoting the side approached from outside (inside) $\mathcal{M}$, see Fig. 6.5. Let $u(\mathbf{x},t)$ be the concentration of particles at $\mathbf{x}$ at time t. Then $u(\mathbf{x},t)$ is the weak solution of the diffusion equation with a permeable or leather boundary condition on $\partial\mathcal{M}$

$$\frac{\partial u(\mathbf{x},t)}{\partial t} = D\nabla^2 u(\mathbf{x},t),\ \mathbf{x} \in \mathcal{M} \cup \mathcal{M}^c, \tag{C.1a}$$

$$J(\mathbf{y}^{\pm},t) = \kappa_0[u(\mathbf{y}^-,t) - u(\mathbf{y}^+,t)], \quad \mathbf{y}^{\pm} \in \partial\mathcal{M}^{\pm}, \tag{C.1b}$$

where $J(\mathbf{x},t) = -D\nabla u(\mathbf{x},t)\cdot\mathbf{n}$ is the particle flux, $\mathbf{n}$ is the unit normal directed out of $\mathcal{M}$, D is the diffusivity and κ_0 is the (constant) permeability. Eqs. (C.1) are a special case of the Kedem-Katchalsky (KK) equations [45, 46, 47], which also allow for discontinuities in the diffusivity and chemical potential across the interface. The macroscopic KK equations can be derived by considering a thin membrane and using statistical thermodynamics. More simply, Eqs. (C.1) arise from treating the interface as a thin layer of slow diffusion $D = O(h)$, where h is the width of the layer, and taking the limit $h \to 0$ [2]. Although the KK equations were originally developed within the context of the transport of non-electrolytes through biological membranes, they are now used to describe all types of membranes, both biological and artificial. (See the recent collection of articles in Ref. [63].) One application of artificial membranes is reverse osmosis for water purification and for extracting energy from variations in salinity [54, 74].

Advances in single-particle tracking and imaging methods are beginning to provide details of single particle trajectories that cannot be captured by macroscopic models. This has motivated a number of stochastic models at the single-particle level. One approach is to consider random walks on lattices in which semipermeable barriers are represented by local defects [71, 50, 64, 49]. An alternative approach is to use stochastic differential equations (SDEs). These generate sample paths of a Brownian particle that are distributed according to a probability density satisfying a corresponding FP equation. However, incorporating the microscopic analog of the permeable boundary condition (C.1b) is non-trivial. If $\partial\mathcal{M}$ were a totally reflecting

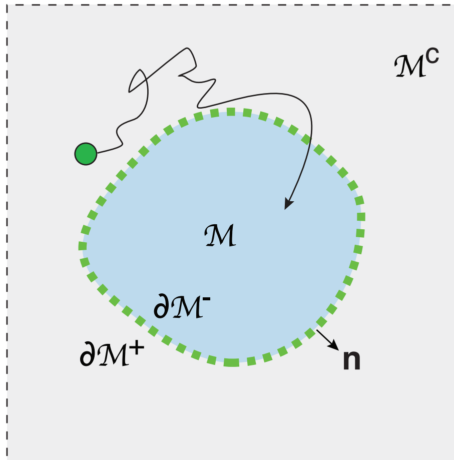

Fig. 6.5: Diffusion through a closed semipermeable membrane in $\mathbb{R}^d$.

(Neumann) or partially reflecting (Robin) boundary, then Brownian motion (BM) confined to $\mathcal{M}$ would need to be supplemented by an additional impulsive force each time the particle contacted the boundary (prior to possible absorption). Mathematically speaking, this can be implemented by introducing the boundary local time along the lines of Sect. 6A.The latter determines the amount of time that a Brownian particle spends in the neighborhood of points on the boundary. A rigorous probabilistic formulation of one-dimensional BM in the presence of a semipermeable barrier is much more recent, and is based on so-called snapping out BM [51, 52, 12, 21]. Snapping out BM sews together successive rounds of partially reflecting BM that are restricted to either $x < 0$ or $x > 0$ with a semipermeable barrier at $x = 0$. Suppose that the particle starts in the domain $x > 0$. It realizes positively reflected BM until its local time exceeds an exponential random variable with parameter κ_0. It then immediately resumes either negatively or positively reflected BM with equal probability, and so on. (Note that SDEs in the form of underdamped Langevin equations have been used to develop efficient computational schemes for finding solutions to the FP equation in the presence of one or more semipermeable interfaces [72, 33]. This is distinct from snapping out BM, which is an exact single-particle realization of diffusion through an interface in the overdamped limit.)

There are a number of reasons why it is advantageous to formulate diffusion through a semi-permeable barrier in terms of snapping out BM. First, it provides a method for simulating Brownian motion in the presence of such a barrier [76]. Second, rather than solving a Fokker-Planck of the form (C.2), we can express the (weak) solution for p in terms of the solution q of partially reflected BM. Third, it provides a probabilistic framework for developing more general probabilistic models of diffusion through semi-permeable membranes based on encounter-baed models of absorption, see supplementary material 6A.

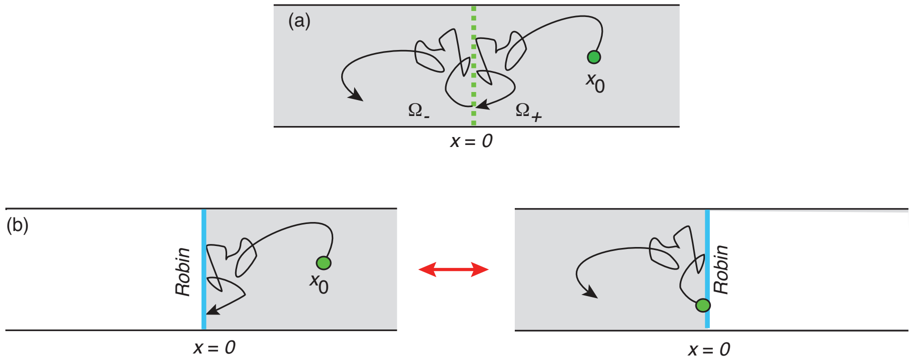

Fig. 6.6: Snapping out BM. (a) Single-particle diffusing across a semipermeable interface at $x=0$. (b) Decomposition of snapping out BM into the random switching between two partially reflected BMs in the domains $\Omega_\pm$.

B.1. Snapping out BM in $\mathbb{R}$

Consider an overdamped Brownian particle diffusing in a 1D domain with a semipermeable barrier or interface at $x=0$. Let $p(x,t)$ denote the probability density of the particle at position x at time t. The corresponding FP equation takes the form

$$\frac{\partial p(x,t)}{\partial t} = -\frac{\partial J(x,t)}{\partial x}, \quad J(x,t) = -D\frac{\partial p(x,t)}{\partial x}, \quad x \neq 0, \quad t > 0, \tag{C.2a}$$

with the following pair of boundary conditions at the interface:

$$J(0^\pm,t) = \mathcal{J}(t) := \frac{\kappa_0}{2}[p(0^-,t) - \sigma p(0^+,t)], \tag{C.2b}$$

where κ_0 is a constant permeability and σ, $0 \leq \sigma < 1$, represents a directional asymmetry that can be interpreted as a step discontinuity in a chemical potential [45, 46, 47, 33]. This asymmetry tends to enhance the concentration to the right of the interface. (If $\sigma > 1$ then we would have an interface with permeability $\kappa_0\sigma$ and bias $1/\sigma$ to the left. A symmetric interface corresponds to the case $\sigma = 1$.) The arbitrary factor of $1/2$ on the right-hand side of Eq. (C.2c) is motivated by the corresponding probabilistic interpretation of snapping out BM, see Sect. III. Finally, D is the diffusivity, γ is the friction coefficient, and the two quantities are related according to the Einstein relation $D\gamma = k_BT$. (In the following we set the Boltzmann constant $k_B = 1$.) For simplicity, we take the diffusive medium to be spatially homogeneous. However, the domains $(-\infty,0^-]$ and $[0^+,\infty)$ could have different diffusivities, for example. That is, $D = D_-$ for $x<0$ and $D=D_+$ for $x>0$ with $D_- \neq D_+$.

The dynamics of snapping out BM is formulated in terms of a sequence of killed reflected BMs in either $\Omega_- = (-\infty,0^-]$ or $\Omega_+ = [0^+,\infty)$ [51, 52, 12, 21], see Fig.

6.6 Let $\mathcal{T}_n$ denote the time of the n^{th} killing (with $\mathcal{T}_0 = 0$). Immediately after the killing event, the position of the particle is taken to be

$$X(\mathcal{T}_n^+) = \lim_{\varepsilon \to 0^+} \left[-Y_n \varepsilon + (1 - Y_n)\varepsilon \right], \tag{C.3}$$

where Y_n is an independent Bernoulli random variable with $\mathbb{P}[Y_n = 1] = \mathbb{P}[Y_n = 0] = 1/2$. Suppose that $X(t) \in \Omega_+$ for $t \in (\mathcal{T}_n, \mathcal{T}_{n+1})$, that is, $X(\mathcal{T}_n^+) = 0^+$, and introduce the boundary local time (see supplementary material 6A and Sect. 8.6)

$$L_n^+(t) = \lim_{\varepsilon \to 0^+} \frac{D}{\varepsilon} \int_0^t \Theta(\varepsilon - X(\tau + \mathcal{T}_n)) d\tau. \tag{C.4}$$

The boundary local time $L_n^+(t)$ tracks the amount of the time the particle is in contact with the right-hand side of the interface over the time interval $[\mathcal{T}_n, t]$. The SDE for $X(t)$, $t \in (\mathcal{T}_n, \mathcal{T}_{n+1})$, is given by the Skorokhod equation for reflected BM in the half-line Ω_+:

$$dX(t) = \sqrt{2D} dW(t) + dL_n(t) \tag{C.5}$$

for $t \in (\mathcal{T}_n, \mathcal{T}_{n+1})$, where $W(t)$ is a Wiener process with $W(0) = 0$. Formally speaking,

$$dL_n^+(t) = \lim_{\varepsilon \to 0^+} \delta(X(t + \mathcal{T}_n) - \varepsilon) dt, \tag{C.6}$$

so that each time the particle hits the interface it is given a positive impulsive kick back into the domain. The time of the next killing is then determined by the condition

$$\mathcal{T}_{n+1} = \mathcal{T}_n + \inf \left\{ t > 0,\ L_n^+(t) \geq \widehat{\ell} \right\}, \tag{C.7}$$

where $\widehat{\ell}$ is an independent randomly generated local time threshold with

$$\mathbb{P}[\widehat{\ell} > \ell] = \mathrm{e}^{-\kappa_0 \ell / D},\ \ell \geq 0. \tag{C.8}$$

On the other hand, if $X(\mathcal{T}_n^+) = 0^-$ then the next round of reflected BM takes place in the domain Ω_-. The corresponding SDE is

$$dX(t) = \sqrt{2D} dW(t) - dL_n^-(t), \tag{C.9}$$

with $t \in (\mathcal{T}_n, \mathcal{T}_{n+1})$, $X(t) \in \Omega_-$,

$$L_n^-(t) = \lim_{\varepsilon \to 0^+} \frac{D}{\varepsilon} \int_0^t \Theta(\varepsilon + X(\tau + \mathcal{T}_n)) d\tau, \tag{C.10}$$

and

$$\mathcal{T}_{n+1} = \mathcal{T}_n + \inf \left\{ t > \mathcal{T}_n : \quad L_n^-(t) \geq \widehat{\ell} \right\}. \tag{C.11}$$

We now use renewal theory to sketch a proof that the distribution of sample paths in 1D snapping out BM is given by the solution of the corresponding FP Eq. (C.2). For an alternative proof in 1D see Ref. [51] and for the generalization to higher spatial dimensions see Ref. [21]. Let $p(x,t)$ denote the probability density of snapping out BM for $p(x,0)=\delta(x-x_0)$ and $x_0>0$. Let $q(x,t|x_0)$ be the corresponding solution for partially reflected BM in Ω_+. (It is straightforward to generalize the analysis to the case of a general distribution of initial conditions $g(x_0)$ that spans both sides of the interface.) The densities p are related to q according to the last renewal equation [12, 21]

$$p(x,t)=q(x,t|x_0)+\frac{\kappa_0}{2}\int_0^t q(x,\tau|0)[p(0^+,t-\tau)+p(0^-,t-\tau)]d\tau, \quad x>0, \tag{C.12a}$$

$$p(x,t)=\frac{\kappa_0}{2}\int_0^t q(|x|,\tau|0)[p(0^+,t-\tau)+p(0^-,t-\tau)]d\tau, \quad x<0. \tag{C.12b}$$

The first term on the right-hand side of Eq. (C.12a) represents all sample trajectories that have never been absorbed by the barrier at $x=0^{\pm}$ up to time t. The corresponding integrand represents all trajectories that were last absorbed (stopped) at time $t-\tau$ in either the positively or negatively reflected BM state and then switched to the appropriate sign to reach x with probability 1/2. Since the particle is not absorbed over the interval $(t-\tau,t]$, the probability of reaching $x\in\Omega_+$ starting at $x=0^{\pm}$ is $q(x,\tau|0)$. The probability that the last stopping event occurred in the interval $(t-\tau,t-\tau+d\tau)$ irrespective of previous events is $\kappa_0 d\tau$. A similar argument holds for Eq. (C.12b).

The renewal Eqs. (C.12) can be used to express p in terms of q using Laplace transforms. First,

$$\widetilde{p}(x,s)=\widetilde{q}(x,s|x_0)+\frac{\kappa_0}{2}\widetilde{q}(x,s|0)[\widetilde{p}(0^+,s)+\widetilde{p}(0^-,s)], \quad x>0, \tag{C.13a}$$

$$\widetilde{p}(x,s)=\frac{\kappa_0}{2}\widetilde{q}(|x|,s|0)[\widetilde{p}(0^+,s)+\widetilde{p}(0^-,s)], \quad x<0. \tag{C.13b}$$

(Note that equation (C.13) is equivalent to the resolvent operator equation (8) of [51].) Setting $x=0^{\pm}$ in equation (C.13), summing the results and rearranging shows that

$$\widetilde{p}(0^+,s)+\widetilde{p}(0^-,s)=\frac{\widetilde{q}(0,s|x_0)}{1-\kappa_0\widetilde{q}(0,s|0)}. \tag{C.14}$$

Substituting back into equations (C.13) yields the explicit solution

$$\widetilde{p}(x,s)=\widetilde{q}(x,s|x_0)+\frac{\kappa_0\widetilde{q}(0,s|x_0)/2}{1-\kappa_0\widetilde{q}(0,s|0)}\widetilde{q}(x,s|0), \quad x>0, \tag{C.15a}$$

$$\widetilde{p}(x,s)=\frac{\kappa_0\widetilde{q}(0,s|x_0)/2}{1-\kappa_0\widetilde{q}(0,s|0)}\widetilde{q}(|x|,s|0), \quad x<0. \tag{C.15b}$$

Calculating the full solution $p(x,t)$ thus reduces to the problem of finding the corresponding solution $q(x,t|x_0)$ of partially reflected BM in Ω_+. As we have shown elsewhere, this then establishes that $p(x,t)$ satisfies the interfacial conditions (C.2c).

The next step is to evaluate $\widetilde{q}(|x|,s|x_0)$. Laplace transforming the FP equation for $q(x,t|x_0)$ for. $x>0$ yields the BVP

$$D\frac{\partial^2\widetilde{q}(x,s|x_0)}{\partial x^2}-s\widetilde{q}(x,s|x_0)=-\delta(x-x_0),\quad x>0, \tag{C.16a}$$

$$D\frac{\partial\widetilde{q}(0,s|x_0)}{\partial x}=\kappa_0\widetilde{q}(0,s|x_0). \tag{C.16b}$$

That is, we can identify $\widetilde{q}(x,s|x_0)$ with the Robin Green's function for the modified Helmholtz equation on $[0,\infty)$. Writing the general solution for $x<x_0$ as

$$\widetilde{q}(x,s|x_0)=A\mathrm{e}^{-\sqrt{s/D}x}+B\mathrm{e}^{\sqrt{s/D}x} \tag{C.17}$$

and substituting into the Robin boundary condition shows that

$$\widetilde{q}(x,s|x_0)=B\left(\mathrm{e}^{\sqrt{s/D}x}+\frac{\sqrt{sD}-\kappa_0}{\sqrt{sD}+\kappa_0}\mathrm{e}^{-\sqrt{s/D}x}\right). \tag{C.18}$$

Using the fact that the bounded solution for $x>x_0$ is proportional to $\mathrm{e}^{-\sqrt{s/D}x}$, imposing continuity of $\widetilde{q}(x,s|x_0)$ across x_0 and matching the discontinuity in the first derivative yields the solution

$$\widetilde{q}(x,s|x_0)=\frac{1}{2\sqrt{sD}}\left(\mathrm{e}^{-\sqrt{s/D}|x-x_0|}+\frac{\sqrt{sD}-\kappa_0}{\sqrt{sD}+\kappa_0}\mathrm{e}^{-\sqrt{s/D}(x+x_0)}\right). \tag{C.19}$$

Note, in particular, that

$$\widetilde{q}(|x|,s|0)=\frac{1}{\sqrt{sD}+\kappa_0}\mathrm{e}^{-\sqrt{s/D}|x|}, \tag{C.20}$$

and

$$D\partial_x\widetilde{q}(0,s|0)=\kappa_0\widetilde{q}(0,s|0)-1. \tag{C.21}$$

The form of the solution (and corresponding modification of the Robin boundary condition) when the particle starts at the barrier plays a significant tole in establishing the equivalence of snapping out BM.

Equation (C.15) now becomes

$$\widetilde{p}(x,s)=\widetilde{q}(x,s|x_0)\Theta(x)+\frac{\kappa_0\mathrm{e}^{-\sqrt{s/D}|x|}}{2\sqrt{sD}}\Gamma(s), \tag{C.22}$$

with $\Gamma(s)=\widetilde{q}(0,s|x_0)$. It follows from equation (C.22) that the density $\widetilde{p}(x,s)$ satisfies the Laplace transform of the semi-permeable membrane BVP (C.2). First, taking the second derivative of equations (C.22) for $x\neq 0^\pm$ and using equation (C.16a) shows that

$$D\frac{\partial^2 \widetilde{p}(x,s)}{\partial x^2} - s\widetilde{p}(x,s) = -\delta(x-x_0), \quad x \in \mathbb{G}. \tag{C.23}$$

Second, equation (C.22) implies that

$$\widetilde{p}(x,s) + \widetilde{p}(-x,s) = \widetilde{q}(x,s|x_0) + \frac{\kappa_0 \mathrm{e}^{-\sqrt{s/D}|x|}}{\sqrt{sD}}\Gamma(s), \tag{C.24a}$$

$$\widetilde{p}(x,s) - \widetilde{p}(-x,s) = \widetilde{q}(x,s|x_0) \tag{C.24b}$$

for $x > 0$. Differentiating equation (C.24a) with respect to x and taking $x = 0^+$ we have

$$\partial_x \widetilde{p}(0^+,s) - \partial_x \widetilde{p}(0^-,s) = \partial_x \widetilde{q}(0^+,s|x_0) - \frac{\kappa_0}{D}\Gamma(s) = 0 \tag{C.25}$$

We have used the Robin boundary condition (C.16b). Hence,

$$D\partial_x \widetilde{p}(0^+,s) = D\partial_x \widetilde{p}(0^-,s). \tag{C.26}$$

Similarly, differentiating equation (C.24b) with respect to x and taking $x = 0^+$ gives

$$\begin{aligned} D\partial_x \widetilde{p}(0^+,s) + D\partial_x \widetilde{p}(0^-,s) = D\partial_x \widetilde{q}(0^+,s|x_0) &= \kappa_0 \widetilde{q}(0,s|x_0) \\ . &= \kappa_0[\widetilde{p}(0^+,s) - \widetilde{p}(0^-,s)]. \end{aligned} \tag{C.27}$$

Finally, combining equations (C.26) and (C.27) yields the permeable boundary condition

$$D\partial_x \widetilde{\rho}(0^{\pm},s) = \frac{\kappa_0}{2}[\widetilde{\rho}(0^+,s) - \widetilde{\rho}(0^-,s)]. \tag{C.28}$$

This establishes that the snapping out BM is a single-particle realization of the stochastic process whose probability density evolves according to the diffusion equation with a semi-permeable membrane at $x = 0$.

Interfacial asymmetry ($\sigma < 1$) can be incorporated into snapping out BM by taking the independent Bernoulli random variable Y_n in Eq. (C.3) to have the biased probability distribution $\mathbb{P}[Y_n = 0] = \alpha$ and $\mathbb{P}[Y_n = 1] = 1-\alpha$ for $0 < \alpha < 1$ [21]. The 1D renewal Eq. (C.13) becomes

$$\widetilde{p}(x,s) = \widetilde{q}(x,s|x_0) + \frac{\kappa_0 \alpha}{2}\widetilde{q}(x,s|0)[\widetilde{p}(0^+,s) + \widetilde{p}(0^-,s)], \quad x > 0 \tag{C.29a}$$

$$\widetilde{p}(x,s) = \frac{\kappa_0[1-\alpha]}{2}\widetilde{q}(|x|,s|0)[\widetilde{p}(0^+,s) + \widetilde{p}(0^-,s)], \quad x < 0. \tag{C.29b}$$

Setting $x = 0^{\pm}$ in Eqs. (C.29), summing the results and rearranging recovers equation (C.14). It can then be shown that snapping out BM with biased switching and $\alpha > 1/2$ is equivalent to single-particle diffusion through a directed semipermeable barrier with an effective permeability $\kappa_0\alpha/2$ and bias $\sigma = (1-\alpha)/\alpha$.

C.2 Snapping out BM in $\mathbb{R}^d$

Let us return to the setup of Fig. 6.5. Single-particle diffusion now takes place on the space $\mathbb{G} = \overline{\mathcal{M}} \cup \overline{\mathcal{M}^c}$. Here $\overline{\mathcal{M}} = \mathcal{M} \cup \partial\mathcal{M}^-$ and $\overline{\mathcal{M}^c} = \mathcal{M}^c \cup \partial\mathcal{M}^+$ are disjoint sets so that $\mathbf{y} \in \partial\mathcal{M}$ corresponds to either $\mathbf{y}^+ \in \partial\mathcal{M}^+$ or $\mathbf{y}^- \in \partial\mathcal{M}^-$ treated as distinct points. Let $p(\mathbf{x},t|\mathbf{x}_0)$, $\mathbf{x},\mathbf{x}_0 \in \mathbb{G}$, denote the probability density of the particle with the initial condition $\mathbf{X}_0 = \mathbf{x}_0 \in \mathcal{M} \cup \mathcal{M}^c$ and set

$$p(\mathbf{x},t) = \int_{\mathbb{G}} p(\mathbf{x},t|\mathbf{x}_0)g(\mathbf{x}_0)d\mathbf{x}_0 \tag{C.30}$$

for any continuous function g on $\mathbb{G}$ with $\int_{\mathbb{G}} g(\mathbf{x}_0)d\mathbf{x}_0 = 1$. The density p satisfies the FP equation

$$\frac{\partial p(\mathbf{x},t)}{\partial t} = D\nabla^2 p(\mathbf{x},t),\ \mathbf{x} \in \mathcal{M} \cup \mathcal{M}^c, \tag{C.31a}$$

$$J(\mathbf{y}^{\pm},t) = \kappa_0[p(\mathbf{y}^-,t) - p(\mathbf{y}^+,t)], \quad \mathbf{y}^{\pm} \in \partial\mathcal{M}^{\pm}, \tag{C.31b}$$

together with the initial condition $\rho(\mathbf{x},0) = g(\mathbf{x})$. We wish to derive the higher-dimensional version of the renewal equations (C.12) by sewing together partially reflected BMs in the domains $\mathcal{M}$ and $\mathcal{M}^c$, see Fig. 6.7.

B.2.1 Partially reflected BMs in $\mathcal{M}$ and $\mathcal{M}^c$

Consider a Brownian particle diffusing in the bounded domain $\mathcal{M}$, see Fig. 6.7(a) with $\partial\mathcal{M}^-$ totally reflecting. Let $\mathbf{X}_t$ denote the position of the particle at time t. In order to write down a stochastic differential equation (SDE) for $\mathbf{X}(t)$, we introduce the boundary local time

$$L^-(t) = \lim_{\varepsilon \to 0} \frac{D}{\varepsilon} \int_0^t H(\varepsilon - \text{dist}(\mathbf{X}(\tau), \partial\mathcal{M}^-))d\tau, \tag{C.32}$$

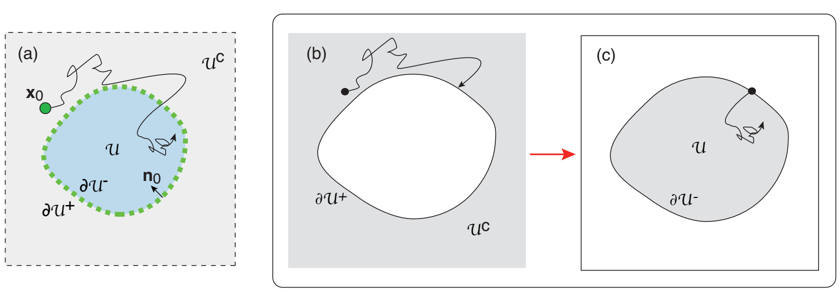

Fig. 6.7: Decomposition of (a) snapping out BM into two partially reflected BMs corresponding to (b) $\mathbf{X}_t \in \mathcal{U}^c$ and (c) $\mathbf{X}_t \in \mathcal{U}$, respectively.

with $\text{dist}(\mathbf{X}(\tau), \partial\mathcal{M}^-)$ denoting the shortest Euclidean distance of X_τ from the boundary $\partial\mathcal{M}^-$. The corresponding SDE then takes the form

$$d\mathbf{X}(t) = \sqrt{2D}d\mathbf{W}(t) - \mathbf{n}(\mathbf{X}(t))dL^-(t), \tag{C.33}$$

where $\mathbf{W}(t)$ is a d-dimensional Brownian motion and $\mathbf{n}(\mathbf{X}(t))$ is the outward unit normal at the point $\mathbf{X}(t) \in \partial\mathcal{M}$. The differential $dL^-(t)$ can be expressed in terms of a Dirac delta function:

$$dL^-(t) = Ddt\left(\int_{\partial\mathcal{M}^-} \delta(\mathbf{X}(t) - \mathbf{y})d\mathbf{y}\right). \tag{C.34}$$

Partially reflected BM in $\mathcal{M}$ is then obtained by stopping the stochastic process $\mathbf{X}(t)$ when the local time $\mathbb{L}^-(t)$ exceeds a random exponentially distributed threshold $\widehat{\ell}$ [39]. That is, the particle is absorbed somewhere on $\partial\mathcal{M}^-$ at the stopping time

$$\mathcal{T}^- = \inf\{t > 0 : \ L^-(t) > \widehat{\ell}\}, \quad \mathbb{P}[\widehat{\ell} > \ell] = \mathrm{e}^{-\kappa_0 \ell/D}. \tag{C.35}$$

The marginal density for particle position (prior to absorption),

$$q_-(\mathbf{x},t|\mathbf{x}_0)dx = \mathbb{P}[\mathbf{x} \leq \mathbf{X}(t) < \mathbf{x} + d\mathbf{x}, \ t < \mathcal{T}^-|\mathbf{X}_0 = \mathbf{x}_0],$$

satisfies the diffusion equation with a Robin boundary condition on $\partial\mathcal{M}^-$:

$$\frac{\partial q_-(\mathbf{x},t|\mathbf{x}_0)}{\partial t} = D\nabla^2 q_-(\mathbf{x},t|\mathbf{x}_0) \text{ for } \mathbf{x}, \mathbf{x}_0 \in \mathcal{M}, \tag{C.36a}$$

$$D\nabla q_-(\mathbf{x},t|\mathbf{x}_0) \cdot \mathbf{n} = -\kappa_0 q_-(\mathbf{x},t|\mathbf{x}_0) \text{ for } \mathbf{x} \in \partial\mathcal{M}^-, \tag{C.36b}$$

and $q_-(\mathbf{x},0|\mathbf{x}_0) = \delta(\mathbf{x} - \mathbf{x}_0)$.

An analogous construction holds for partially reflected BM in $\mathcal{M}^c$, see Fig. 6.7(b). Given the local time

$$L^+(t) = \lim_{\varepsilon \to 0} \frac{D}{\varepsilon} \int_0^t H(\varepsilon - \text{dist}(\mathbf{X}(\tau), \partial\mathcal{M}^+))d\tau, \tag{C.37}$$

and stopping time

$$\mathcal{T}^+ = \inf\{t > 0 : \ L^+(t) > \widehat{\ell}\}, \quad \mathbb{P}[\widehat{\ell} > \ell] = \mathrm{e}^{-\kappa_0 \ell/D}. \tag{C.38}$$

one finds that the marginal density

$$q_+(\mathbf{x},t|\mathbf{x}_0)dx = \mathbb{P}[\mathbf{x} \leq \mathbf{X}(t) < \mathbf{x} + d\mathbf{x}, \ t < \mathcal{T}^+|\mathbf{X}_0 = \mathbf{x}_0]$$

satisfies the Robin boundary value problem (BVP)

$$\frac{\partial q_+(\mathbf{x},t|\mathbf{x}_0)}{\partial t} = D\nabla^2 q_+(\mathbf{x},t|\mathbf{x}_0) \text{ for } \mathbf{x}, \mathbf{x}_0 \in \mathcal{M}^c, \tag{C.39a}$$

$$D\nabla q_+(\mathbf{x},t|\mathbf{x}_0) \cdot \mathbf{n} = \kappa_0 q_+(\mathbf{x},t|\mathbf{x}_0) \text{ for } \mathbf{x} \in \partial\mathcal{M}^+, \tag{C.39b}$$

and $p_+(\mathbf{x},0|\mathbf{x}_0)=\delta(\mathbf{x}-\mathbf{x}_0)$.

Modified boundary condition for $\mathbf{x}_0 \in \partial\mathcal{M}$

As in the 1D case, the boundary condition for partially reflected BM in $\mathcal{M}^c$ is modified when the particle actually starts on the boundary. In order to show this, we first Laplace transform Eqs. (C.39) with respect to time t:

$$D\nabla^2\widetilde{q}_+(\mathbf{x},s|\mathbf{x}_0)-s\widetilde{q}_+(\mathbf{x},s|\mathbf{x}_0)=-\delta(\mathbf{x}-\mathbf{x}_0),\ \mathbf{x},\mathbf{x}_0\in\mathcal{M}^c, \tag{C.40a}$$

$$D\nabla\widetilde{q}_+(\mathbf{x},s|\mathbf{x}_0)\cdot\mathbf{n}=\kappa_0\widetilde{q}_+(\mathbf{x},s|\mathbf{x}_0)\ \text{for}\ \mathbf{x}\in\partial\mathcal{M}^+. \tag{C.40b}$$

Consider a small cylinder $\mathcal{C}(\varepsilon,\sigma)$ of uniform cross-section σ and length 2ε with a point $\mathbf{y}\in\partial\mathcal{M}$ at its center of mass, see Fig. 6.8. Let $\mathcal{C}^+(\varepsilon,\sigma)=\mathcal{C}(\varepsilon,\sigma)\cap\overline{\mathcal{M}^c}$ For sufficiently small σ, we can treat $\Sigma_0\equiv\mathcal{C}^+(\varepsilon,\sigma)\cap\partial\mathcal{M}^+$ as a planar interface with outward normal $\mathbf{n}(\mathbf{y})$ such that the axis of $\mathcal{C}^+(\varepsilon,\sigma)$ is aligned along $\mathbf{n}(\mathbf{y})$. Given the above construction, we integrate Eq. (C.40a) with respect to all $\mathbf{x}\in\mathcal{C}^+(\varepsilon,\sigma)$ and use the divergence theorem:

$$\begin{aligned}&\int_{\Sigma_\varepsilon}\nabla\widetilde{q}_+(\mathbf{y}',s|\mathbf{x}_0)\cdot\mathbf{n}(\mathbf{y}')d\mathbf{y}'-\int_{\Sigma_0}\nabla\widetilde{q}_+(\mathbf{y}',s|\mathbf{x}_0)\cdot\mathbf{n}(\mathbf{y}')d\mathbf{y}'\\&\quad\sim\frac{1}{D}\int_{\mathcal{C}^+}[s\widetilde{q}_+(\mathbf{x},s|\mathbf{x}_0)-\delta(\mathbf{x}-\mathbf{x}_0)]d\mathbf{x},\end{aligned} \tag{C.41}$$

where Σ_ε denotes the flat end of the cylinder within $\mathcal{M}^c$. If $\mathbf{x}_0$ is in the bulk domain $\mathcal{M}^c$, then taking the limits $\varepsilon,\sigma\to 0$ shows that the flux is continuous as it approaches the boundary, since the right-hand side of Eq. (C.41) vanishes. On the other hand, if $\mathbf{x}_0=\mathbf{z}\in\partial\mathcal{M}^+$ then taking the limits $\varepsilon,\sigma\to 0$ gives

$$\lim_{\varepsilon\to 0^+}D\nabla\widetilde{q}_+(\mathbf{y}+\varepsilon\mathbf{n}(\mathbf{y}),s|\mathbf{z})\cdot\widetilde{q}_+(y)-D\nabla\widetilde{q}_+(\mathbf{y},s|\mathbf{z})\cdot\mathbf{n}(\mathbf{y})=-\overline{\delta}(\mathbf{y}-\mathbf{z}), \tag{C.42}$$

where $\overline{\delta}$ is the Dirac delta function for points on $\partial\mathcal{M}$ such that for any continuous function $f:\mathcal{M}\to\mathbb{R}$ we have $\int_{\partial\mathcal{M}}f(\mathbf{y})\overline{\delta}(\mathbf{y}-\mathbf{z})d\mathbf{y}=f(\mathbf{z})$. Finally, noting that the first flux term on the left-hand side satisfies the boundary condition (C.40b), we deduce that

$$D\nabla\widetilde{q}_+(\mathbf{y},s|\mathbf{z})\cdot\mathbf{n}(\mathbf{y})=\kappa_0\widetilde{q}_+(\mathbf{y},s|\mathbf{z})-\overline{\delta}(\mathbf{y}-\mathbf{z}). \tag{C.43}$$

Applying a similar argument to partially reflected BM in $\mathcal{M}$ we find that

$$D\nabla\widetilde{q}_-(\mathbf{y},s|\mathbf{z})\cdot\mathbf{n}(\mathbf{y})=-\kappa_0\widetilde{q}_-(\mathbf{y},s|\mathbf{z})+\overline{\delta}(\mathbf{y}-\mathbf{z}). \tag{C.44}$$

The extra terms on the right-hand side of Eqs. (C.43) and (C.44) play a crucial role in the subsequent analysis. They will also be confirmed by directly differentiating example explicit solutions.

The Green's function $\widetilde{q}_+(\mathbf{x}_0,s|\mathbf{z})$ with $\mathbf{z}\in\partial\mathcal{M}$ and $\mathbf{x}_0\in\mathcal{M}^c$ can be related to the corresponding inverse local time [44]

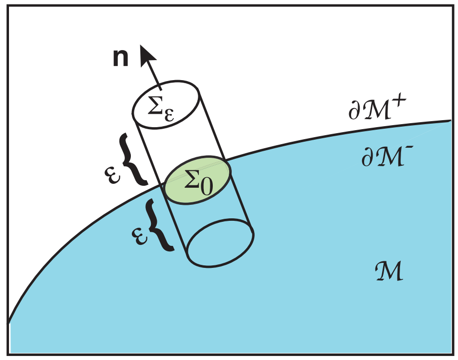

Fig. 6.8: Cylinder construction across the semipermeable membrane. See text for details.

$$\mathbb{E}[\mathrm{e}^{-s\mathcal{T}^+}|\mathbf{X}_0=\mathbf{x}_0]=\int_0^\infty f(\mathbf{x}_0,t)\mathrm{e}^{-st}dt, \tag{C.45}$$

where $f(\mathbf{x}_0,t)$ is the FPT density for being absorbed on $\partial\mathcal{M}$. In terms of the survival probability

$$Q(\mathbf{x}_0,t)=\int_{\mathcal{M}^c} q_+(\mathbf{x},t|\mathbf{x}_0)d\mathbf{x}, \tag{C.46}$$

we have

$$\begin{aligned} f(\mathbf{x}_0,t)&=-\frac{dQ(\mathbf{x}_0,t)}{dt}=-\int_{\mathcal{M}^c}\frac{\partial q_+(\mathbf{x},t|\mathbf{x}_0)}{\partial t}d\mathbf{x}=-D\int_{\mathcal{M}^c}\nabla^2 q_+(\mathbf{x},t|\mathbf{x}_0)d\mathbf{x}\\ &=D\int_{\partial\mathcal{M}}\nabla q_+(\mathbf{z},t|\mathbf{x}_0)\cdot\mathbf{n}d\mathbf{z}=\kappa_0\int_{\partial\mathcal{M}}p(\mathbf{z},t|\mathbf{x}_0)d\mathbf{z}. \end{aligned} \tag{C.47}$$

Hence,

$$\mathbb{E}[\mathrm{e}^{-s\mathcal{T}}|\mathbf{X}_0=\mathbf{x}_0]=\kappa_0\int_{\partial\mathcal{M}}\widetilde{q}_+(\mathbf{z},s|\mathbf{x}_0)d\mathbf{z}=\kappa_0\int_{\partial\mathcal{M}}\widetilde{q}_+(\mathbf{x}_0,s|\mathbf{z})d\mathbf{z} \tag{C.48}$$

by the standard symmetry property of Green's functions.

Renewal equation

We define the multidimensional version of snapping out BM as follows. Without loss of generality, suppose that the particle starts in the domain $\mathcal{M}^c$. It realizes reflected BM in $\mathcal{M}^c$ until it is killed when its local time $L^+(t)$, see Eq. (C.37), is greater than an independent exponential random variable $\widehat{\ell}$. Let $\mathbf{y}^+\in\partial\mathcal{M}^+$ denote the point on the boundary where killing occurs. The stochastic process immediately restarts as a new round of partially reflected BM, either from $\mathbf{y}^+$ into $\mathcal{M}^c$ or from $\mathbf{y}^-$ into $\mathcal{M}$. These two possibilities occur with equal probability. Subsequent rounds of partially reflected BM are generated in the same way. We thus have a stochastic process on the set $\mathbb{G}$. As in the one-dimensional case [51], it can be proven that snapping out BM is a strong Markov process. This means that we can consider a multi-dimensional version of the renewal equation introduced in [12]. First, let

$$q_+(\mathbf{x},t) = \int_{\overline{\mathcal{M}^c}} q_+(\mathbf{x},t|\mathbf{x}_0)g(\mathbf{x}_0)d\mathbf{x}_0, \tag{C.49a}$$

$$q_-(\mathbf{x},t) = \int_{\overline{\mathcal{M}}} q_-(\mathbf{x},t|\mathbf{x}_0)g(\mathbf{x}_0)d\mathbf{x}_0, \tag{C.49b}$$

where $q_+(\mathbf{x},t|\mathbf{x}_0)$ and $q_-(\mathbf{x},t|\mathbf{x}_0)$ are the solutions of the Robin BVPs (C.39) and (C.36), respectively. By construction, the probability density $p(\mathbf{x},t)$ satisfies the last renewal equations

$$p(\mathbf{x},t) = q_+(\mathbf{x},t) + \frac{\kappa_0}{2}\int_0^t \left\{\int_{\partial\mathcal{M}} q_+(\mathbf{x},\tau|\mathbf{z})[p(\mathbf{z}^+,t-\tau)+po(\mathbf{z}^-,t-\tau)]d\mathbf{z}\right\}d\tau,$$
$$\mathbf{x}\in\overline{\mathcal{M}^c}, \tag{C.50a}$$

$$p(\mathbf{x},t) = q_-(\mathbf{x},t) + \frac{\kappa_0}{2}\int_0^t \left\{\int_{\partial\mathcal{M}} q_-(\mathbf{x},\tau|\mathbf{z})p(\mathbf{z}^+,t-\tau)+p(\mathbf{z}^-,t-\tau)]d\mathbf{z}\right\}d\tau,$$
$$\mathbf{x}\in\overline{\mathcal{M}}. \tag{C.50b}$$

The first term on the right-hand side of Eqs. (C.50a) and (C.50b) represents all sample trajectories that have never been absorbed by the boundary $\partial\mathcal{M}^+$ and $\partial\mathcal{M}^-$, respectively. The corresponding integral term in equation (C.50a) represents all trajectories that were last absorbed (stopped) somewhere on $\partial\mathcal{M}^\pm$ at time $t-\tau$ and then switched to the domain $\overline{\mathcal{M}^c}$ with probability 1/2 in order to reach $\mathbf{x}\in\overline{\mathcal{M}^c}$ at time t. Since the particle is not absorbed over the interval $(t-\tau,t]$, the probability of reaching $\mathbf{x}\in\overline{\mathcal{M}^c}$ starting at a point $\mathbf{z}\in\partial\mathcal{M}^+$ is $q_+(\mathbf{x},\tau|\mathbf{z})$. We then have to integrate with respect to all starting positions $\mathbf{z}$ at time $t-\tau$. An analogous interpretation holds for the integral term on the right-hand side of Eq. (C.50b), with $q_+\to q_-$ and $\partial\mathcal{M}^+\to\partial\mathcal{M}^-$. Finally, the probability that the last stopping event occurred in the interval $(t-\tau,t-\tau+d\tau)$ irrespective of previous events is $\kappa_0 d\tau$.

We wish to establish that $p(\mathbf{x},t)$ is a (weak) solution of the FP Eq. (C.31) under the initial condition $p(\mathbf{x},0)=g(\mathbf{x})$. It is clear that $p(\mathbf{x},t)$ satisfies the diffusion equation in the bulk so, as in the 1D example, we focus on the boundary conditions. Laplace transforming the renewal equations(C.50a,b) with respect to time t gives

$$\widetilde{p}(\mathbf{x},s) = \widetilde{q}_+(\mathbf{x},s) + \frac{\kappa_0}{2}\int_{\partial\mathcal{M}} \widetilde{q}_+(\mathbf{x},s|\mathbf{z})\Sigma_p(\mathbf{z},s)d\mathbf{z} \tag{C.51a}$$

for $\mathbf{x}\in\overline{\mathcal{M}^c}$ and

$$\widetilde{p}(\mathbf{x},s) = \widetilde{q}_-(\mathbf{x},s) + \frac{\kappa_0}{2}\int_{\partial\mathcal{M}} \widetilde{q}_-(\mathbf{x},s|\mathbf{z})\Sigma_\rho(\mathbf{z},s)d\mathbf{z} \tag{C.51b}$$

for $\mathbf{x}\in\overline{\mathcal{M}}$. We have set

$$\Sigma_\rho(\mathbf{z},s)=\widetilde{p}(\mathbf{z}^+,s)+\widetilde{p}(\mathbf{z}^-,s). \tag{C.52}$$

Taking the normal derivative of Eqs. (C.51a,b) with $\partial_\mathbf{n}\equiv\mathbf{n}\cdot\nabla$ in the limit $\mathbf{x}\to\mathbf{y}\in\partial\mathcal{M}$ gives the pair of equations

$$\partial_\mathbf{n}\widetilde{p}(\mathbf{y}^+,s)=\partial_\mathbf{n}\widetilde{q}_+(\mathbf{y}^+,s)+\frac{\kappa_0}{2}\int_{\partial\mathcal{M}}\partial_\mathbf{n}\widetilde{q}_+(\mathbf{y},s|\mathbf{z})\Sigma_\rho(\mathbf{z},s)d\mathbf{z}, \tag{C.53a}$$

$$\partial_\mathbf{n}\widetilde{p}(\mathbf{y}^-,s)=\partial_\mathbf{n}\widetilde{q}_-(\mathbf{y}^-,s)+\frac{\kappa_0}{2}\int_{\partial\mathcal{M}}\partial_\mathbf{n}\widetilde{q}_-(\mathbf{y},s|\mathbf{z})\Sigma_\rho(\mathbf{z},s)d\mathbf{z}. \tag{C.53b}$$

Next, imposing the boundary conditions (C.40b) and (C.40b) for partially reflected BM and the modified boundary conditions (C.43) and (C.44) yields

$$D\partial_\mathbf{n}\widetilde{p}(\mathbf{y}^+,s)=\kappa_0\widetilde{q}_+(\mathbf{y}^+,s)+\frac{\kappa_0}{2}\int_{\partial\mathcal{M}}[\kappa_0\widetilde{q}_+(\mathbf{y},s|\mathbf{z})-\overline{\delta}(\mathbf{y}-\mathbf{z})]\Sigma_\rho(\mathbf{z},s)d\mathbf{z}, \tag{C.54a}$$

$$D\partial_\mathbf{n}\widetilde{p}(\mathbf{y}^-,s)=-\kappa_0\widetilde{q}_-(\mathbf{y}^-,s)-\frac{\kappa_0}{2}\int_{\partial\mathcal{M}}[\kappa_0\widetilde{q}_-(\mathbf{y},s|\mathbf{z})-\overline{\delta}(\mathbf{y}-\mathbf{z})]\Sigma_\rho(\mathbf{z},s)d\mathbf{z}. \tag{C.54b}$$

Subtracting this pair of equations, we find that

$$\begin{aligned}D\partial_\mathbf{n}\widetilde{p}(\mathbf{y}^+,s)-D\partial_\mathbf{n}\widetilde{p}(\mathbf{y}^-,s)&=\kappa_0[\widetilde{q}_+(\mathbf{y}^+,s)+\widetilde{q}_-(\mathbf{y}^-,s)]-\kappa_0\Sigma_\rho(\mathbf{y},s)\\&\quad+\frac{\kappa_0^2}{2}\int_{\partial\mathcal{M}}[\widetilde{q}_+(\mathbf{y},s|\mathbf{z})+\widetilde{q}_-(\mathbf{y},s|\mathbf{z})]\Sigma_\rho(\mathbf{z},s)d\mathbf{z}=0.\end{aligned} \tag{C.55}$$

The last line follows from setting $\mathbf{x}=\mathbf{y}^+$ and $\mathbf{x}=\mathbf{y}^-$ in equations (C.51a) and (C.51b), respectively, and adding the results. Finally adding equations. (C.54a,b) gives

$$\begin{aligned}&2D\partial_\mathbf{n}\widetilde{p}(\mathbf{y}^\pm,s)\\&=\kappa_0[\widetilde{q}_+(\mathbf{y}^+,s)-\widetilde{q}_-(\mathbf{y}^-,s)]+\frac{\kappa_0^2}{2}\int_{\partial\mathcal{M}}[\widetilde{q}_+(\mathbf{y},s|\mathbf{z})-\widetilde{q}_-(\mathbf{y},s|\mathbf{z})]\Sigma_\rho(\mathbf{z},s)d\mathbf{z}\\&=\kappa_0[\widetilde{p}(\mathbf{y}^+,s)-\widetilde{p}(\mathbf{y}^-,s)].\end{aligned} \tag{C.56}$$

Hence, we have established the equivalence of multidimensional snapping out BM with single-particle diffusion through a smooth semipermeable membrane of the form shown in Fig. 6.5.

D. Diffusion in an intermittent confining potential

Stochastic resetting is a mechanism whereby a system is returned to its initial state at a random sequence of times that is typically generated by a Poisson process with constant rate r, see Sect. 7.5. The simplest example is a Brownian particle that instantaneously resets to its initial position $\mathbf{x}_0 \in \mathbb{R}^d$ [28, 29, 30]. There have been a wide range of generalizations at the single particle level, see the review [32] and references therein. These include both modifications in the underlying stochastic dynamics in the absence of resetting and modifications in the resetting protocol itself. In order to develop physical implementations of resetting, it is necessary to relax the assumption of instantaneous resetting. This has motivated the inclusion of various sources of delays including finite return times [66, 67, 60, 7, 68, 10] and refractory periods [31, 59]. An alternative practical realization of non-instantaneous resetting is to use an external trapping or confining potential that is alternatively switched on and off [42, 82, 75, 83], see Fig. 6.9. During the ON phases, a diffusing particle tends to move toward the minimum of the potential, which thus plays an analogous role to the resetting position in perfect resetting. The return phase is clearly of finite duration. Moreover, once the particle reaches a neighborhood of the minimum, it tends to remain there until switching to an OFF state, which is analogous to a refractory phase. Diffusion in an intermittent potential is an example of a diffusion process in a randomly switching environment, see Sect. 6.5.

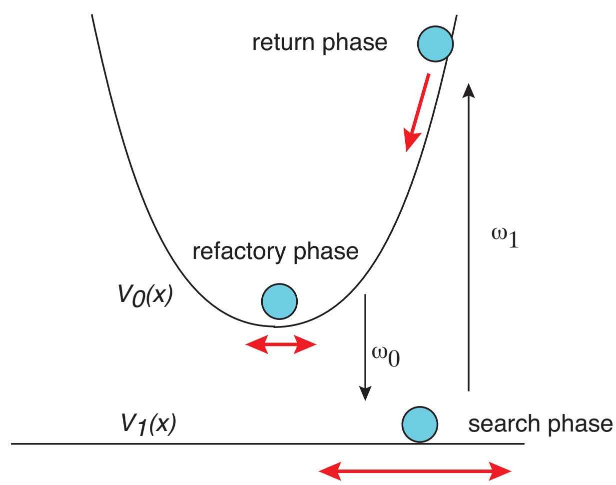

Fig. 6.9: Diffusion in an intermittent confining potential.

D.1 Diffusion in an intermittent potential as a switching-diffusion process

As recently shown in Ref. [24], one can develop a probabilistic representation of diffusion. in an intermittent potential by combining Itô stochastic calculus with a stochastic representation of continuous time Markov chains. For the sake of illustration consider 1D Brownian motion. We assume that there exists a finite set of potential energy functions $\{V_0, V_1 \ldots, V_{K-1}\}$ such that the potential at time t is $V_{N(t)}$ where $N(t) \in \{0, \cdots, K-1\}$ is a K-state continuous-time Markov chain (see Sect. 3.3). There are two distinct switching mechanisms, which are illustrated in Fig. 6.10 for a two-state process. The first mechanism consists of the particle switching between different internal conformational states $n \in \{0, \cdots, K-1\}$ that "see" different potentials V_n (particle switching scenario). For example, the particle could represent a protein that changes its shape in an external electric field, resulting in a redistribution of its ionic charges. In the second mechanism the particle has a fixed internal state while the external potential physically switches between different discrete states (potential switching scenario). At the single-particle level, the stochastic dynamics is the same whether $N(t)$ is interpreted as a discrete conformational state of the particle or an internal state of the potential. However, the two scenarios differ significantly at the population level, even if the particles are non-interacting, see also Sect. 6.5.

The stochastic dynamics of a single particle is expressed in terms of the pair of stochastic variables $(X(t), N(t)) \in \mathbb{R} \times \{0, \cdots, K-1\}$. In between jumps in the discrete state, the particle evolves according to the hybrid SDE (hSDE)

$$dX(t) = -\frac{1}{\gamma} V'_{N(t)}(X(t))dt + \sqrt{2D}dW(t), \tag{C.1}$$

The discrete stochastic process $N(t)$ is a K-state continuous-time Markov chain with a $K \times K$ matrix generator $\mathbf{A}$ that is related to the corresponding transition matrix $\mathcal{K}$ according to

$$A_{nm} = \mathcal{K}_{nm} - \delta_{n,m} \sum_{k=0}^{K-1} \mathcal{K}_{km}. \tag{C.2}$$

We also assume that the generator is irreducible so that there exists a stationary distribution $\boldsymbol{\sigma}$ for which $\sum_m A_{nm}\sigma_m = 0$. It is useful to decompose the transition matrix as $\mathcal{K}_{nm} = P_{nm}\lambda_m$, with $\sum_{n,n\neq m} P_{nm} = 1$. That is, the jump times from state m are exponentially distributed with rate λ_m and P_{nm} is the probability distribution that when a jump occurs the new state is n for some $n \neq m$. The hybrid evolution of the system with respect to $X(t)$ and $N(t)$ can then described as follows (see Sect. 5.3 and Box 5D). Suppose the system starts at time zero in the state (x_0, n_0). Call $X_0(t)$ the solution for $n = n_0$ such that $X_0(0) = x_0$. Let $\mathcal{T}_\ell$, $\ell \geq 1$, denote the sequence of jump times for a given realization of the stochastic process such that

$$N(t) = N_\ell, \quad \mathcal{T}_\ell \leq t < \mathcal{T}_{\ell+1}. \tag{C.3}$$

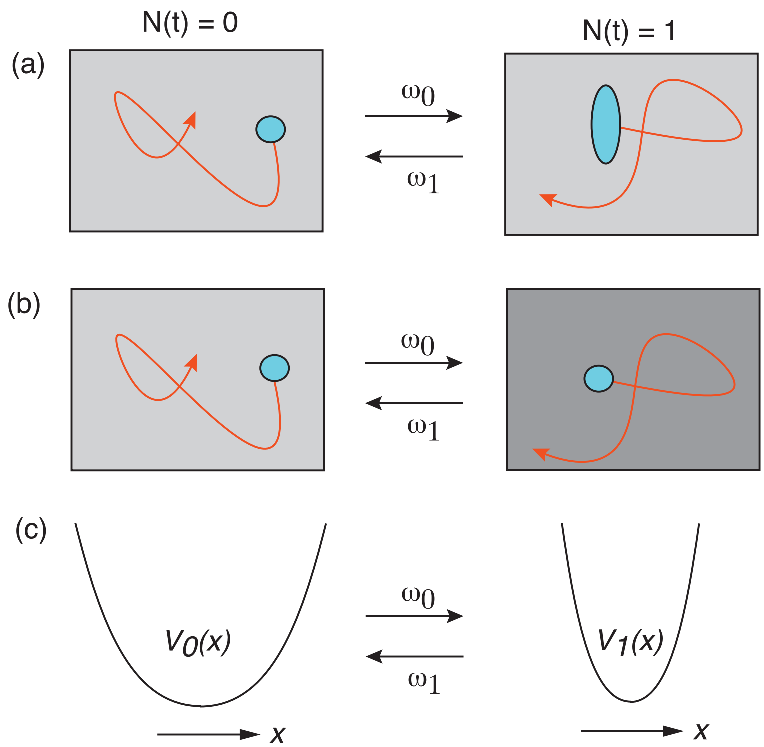

Fig. 6.10: Two alternative sources of switching for a two-state hSDE. (a) The particle switches between two different conformational states with internal energies ε_n, $n = 0, 1$ (indicated by the particle shape). (b) The subsystem generating the potential switches between two conformational states with internal energies ε_n, $n = 0, 1$ (indicated by the shade). (c) Both mechanisms result in the effective potential "seen" by the particle, $V_{N(t)}(x)$, depending on the discrete state $N(t)$.

In particular, $N(\mathcal{T}_\ell^-) = N_{\ell-1}$ and $N(\mathcal{T}_\ell) = N_\ell$. Note that we take $N(t)$ to be right-continuous, as illustrated in Fig. 6.11 for a 2-state Markov chain. Taking $\mathcal{T}_0 = 0$, the resulting piecewise continuous dynamics can be rewritten as

$$(X(t), N(t)) = (X_\ell(t), N_\ell) \quad \text{for } \mathcal{T}_\ell \leq t < \mathcal{T}_{\ell+1}, \tag{C.4a}$$

with

$$dX_\ell(t) = -\frac{1}{\gamma} V'_{N_\ell}(X(t))dt + \sqrt{2D}dW(t) \quad \text{for } \mathcal{T}_\ell \leq t < \mathcal{T}_{\ell+1}, \tag{C.4b}$$

$$X_\ell(\mathcal{T}_\ell) = X_{\ell-1}(\mathcal{T}_\ell^-). \tag{C.4c}$$

Equations (C.4a) -(C.4c) specify the hSDE.

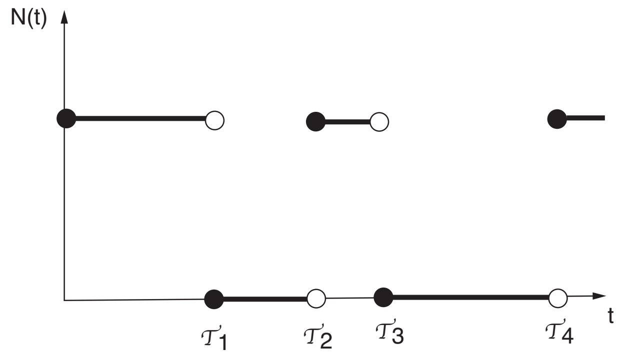

Fig. 6.11: One path of a 2-state Markov chain $N(t) \in \{0,1\}$, illustrating that it is right-continuous. Jumps occur at the times $\mathcal{T}_\ell$, $\ell \geq 1$.

Stochastic calculus of hSDEs

Since the finite state Markov chain $N(t) \in \{0,\ldots,K-1\}$ is independent of $X(t)$, we can combine the Itô formulas for SDEs and Markov chains. First, consider the latter. Let $h : \{0,\ldots,K-1\} \to \mathbb{R}$ denote an arbitrary, bounded function on the Markov chain. Using telescoping, we have

$$\begin{aligned} h(N(t)) - h(N(0)) &= \sum_{\ell=1}^{\ell_t} [h(N_\ell) - h(N_{\ell-1})] = \sum_{\ell=1}^{\ell_t} [h(N(\mathcal{T}_\ell)) - h(N(\mathcal{T}_{\ell-1}))] \\ &= \sum_n \sum_{\ell=1}^{\infty} \int_0^t [h(n) - h(N(s^-))]\delta(s-\mathcal{T}_\ell)\delta_{N(s),n} ds \\ &= \sum_{m,n} \int_0^t [h(n) - h(m)] d\mathcal{N}_{nm}(s), \end{aligned} \tag{C.5}$$

with

$$d\mathcal{N}_{nm}(t) = \sum_{\ell=1}^{\infty} \delta_{N(t^-),m}\delta_{N(t),n}\delta(t-\mathcal{T}_\ell)dt. \tag{C.6}$$

Note that

$$\mathcal{N}_{nm}(t) = \sum_{\ell=1}^{N(t)} \delta_{N(\mathcal{T}_\ell^-),m}\delta_{N(\mathcal{T}_\ell),n} \tag{C.7}$$

is the number of jumps $m \to n$ in the time interval $[0,t]$. The corresponding differential equation is

$$dh(N(t)) := h(N(t)) - h(N(t^-)) = \textstyle\sum_{m,n}[h(n) - h(m))]d\mathcal{N}_{nm}(t). \tag{C.8}$$

Taking expectations of both sides with respect to the jump process in the case $f(n) = n$ yields

$$\mathbb{E}[dN(t)] = \sum_{m,n}(n-m)\mathbb{E}[d\mathcal{N}_{nm}(t)]. \tag{C.9}$$

Using the definition of the transition rates $\mathcal{K}_{nm}$ we have

$$\mathbb{E}[d\mathcal{N}_{nm}(t)] = \mathcal{K}_{nm}\mathbb{E}[\delta_{m,N(t^-)}]dt. \tag{C.10}$$

Next we consider an indexed set of smooth, bounded functions $f_n : \mathbb{R} \to \mathbb{R}$, $n \in \{0,\ldots,K-1\}$. The extended Itô formula for $f(t) = f_{N(t)}(X(t))$ is then

$$df(t) = d_x f_{N(t)}(X(t)) + f_{N(t)}(X(t)) - f_{N(t^-)}(X(t)), \tag{C.11}$$

where $d_x f_{N(t)}(X(t)) = f_{N(t)}(X(t)+dX(t)) - f_{N(t)}(X(t))$ is the change due to a small displacement in the position and $f_{N(t)}(X(t)) - f_{N(t^-)}(X(t))$ represents a discrete jump, which only occurs at the discrete times $\mathcal{T}_\ell$. Combining Itô's formula for SDEs with equation (C.8) gives

$$\begin{aligned} df(t) = &\left(-\frac{1}{\gamma}V'_{N(t)}(X(t))f'_{N(t)}(X(t)) + Df''_{N(t)}(X(t))\right)dt \\ &+ \sqrt{2D}f'_{N(t)}(X(t))dW(t) + \sum_{m,n=0}^{K-1}[f_n(X(t)) - f_m(X(t))]d\mathcal{N}_{nm}(t). \end{aligned} \tag{C.12}$$

The extended Itô formula (C.12) can be used to derive the corresponding differential CK equation for the hSDE, which was simply written down in Sect. 6.5. Introducing the empirical measure

$$\rho_n(x,t) = \delta(x - X(t))\delta_{n,N(t)}, \tag{C.13}$$

we have the identity

$$f_{N(t)}(X(t)) = \sum_{n=0}^{K-1}\int_{\mathbb{R}}\rho_n(x,t)f_n(x)dx. \tag{C.14}$$

Taking differentials of both sides with respect to t yields

$$df(t) = \left[\sum_n\int_{\mathbb{R}} f_n(x)\frac{\partial\rho_n(x,t)}{\partial t}dx\right]dt \tag{C.15}$$

Substituting equation (C.12) into the left-hand side of equation (C.15) and using the definition of ρ_n gives

$$\begin{aligned} &\sum_n\int_{\mathbb{R}}\rho_n(x,t)\left[-\frac{1}{\gamma}\frac{\partial f_n(x)}{\partial x}V'_n(x) + D\frac{\partial^2 f_n(x)}{\partial x^2} + \sqrt{2D}\frac{\partial f_n(x)}{\partial x}\xi(t)\right]dx \\ &\quad + \sum_{n,m}\left[\int_{\mathbb{R}}\delta(x - X(t)))[f_n(x) - f_m(x)]dx\right]d\mathcal{N}_{nm}(t) = \sum_n\int_{\mathbb{R}} f_n(x)\frac{\partial\rho_n(x,t)}{\partial t}dx. \end{aligned}$$

Performing an integration by parts,

$$\sum_n \int_{\mathbb{R}} f_n(x) \left[\frac{1}{\gamma} \frac{\partial V_n'(x)\rho_n(x,t)}{\partial x} + D_n \frac{\partial^2 \rho_n(x,t)}{\partial x^2} - \sqrt{2D_n} \frac{\partial \rho_n(x,t)}{\partial x} \xi(t) \right.$$
$$\left. + \sum_m \delta(x - X(t))[d\mathcal{N}_{nm}(t) - d\mathcal{N}_{mn}(t)] \right] dx = \sum_n \int_{\mathbb{R}} f_n(x) \frac{\partial \rho_n(x,t)}{\partial t} dx.$$

Since the functions f_n are arbitrary, we obtain the hybrid stochastic partial differential equation (hSPDE)

$$\frac{\partial \rho_n}{\partial t} = D \frac{\partial^2 \rho_n}{\partial x^2} + \frac{1}{\gamma} \frac{\partial}{\partial x}[V_n'(x)\rho_n] + \sqrt{2D} \frac{\partial \rho_n(x,t)}{\partial x} \xi(t)$$
$$+ \sum_m \delta(x - X(t))[d\mathcal{N}_{nm}(t) - d\mathcal{N}_{mn}(t)]. \tag{C.16}$$

Finally, define the indexed set of probability densities

$$p_n(x,t) = \left\langle \mathbb{E}\left[\delta(x - X(t))\delta_{n,N(t)}\right] \right\rangle, \tag{C.17}$$

where $\mathbb{E}[\cdot]$ and $\langle \cdot \rangle$ denote taking expectations with respect to the white noise process and the Markov chain, respectively. The indexed densities p_n evolve according to a forward differential Chapman-Kolmogorov (CK) equation, see 6.5. This follows from taking expectations with respect to the white noise process and the Markov chain. In particular, noting that

$$\begin{aligned}
\mathscr{I}_n(x,t) &:= \left\langle \mathbb{E}\left[\sum_m \delta(x - X(t))[d\mathcal{N}_{nm}(t) - d\mathcal{N}_{mn}(t)] \right] \right\rangle \\
&= \sum_{m=0}^{K-1} \mathcal{K}_{nm} \left\langle \mathbb{E}\left[\delta(x - X(t))[\delta_{m,N(t)}\right] \right\rangle - \sum_{m=0}^{K-1} \mathcal{K}_{mn} \left\langle \mathbb{E}\left[\delta(x - X(t))[\delta_{n,N(t)}\right] \right\rangle \\
&= \sum_{m=0}^{K-1} [\mathcal{K}_{nm} p_m(x,t) - \mathcal{K}_{nm} p_n(x,t)] = \sum_{m=0}^{K-1} A_{nm} p_m(x,t),
\end{aligned} \tag{C.18}$$

we obtain the CK equation

$$\frac{\partial p_n}{\partial t} = -\frac{\partial J_n(x,t)}{\partial x} + \sum_{m=0}^{K-1} A_{nm} p_m(x,t), \tag{C.19}$$

with

$$J_n(x,t) = -\frac{1}{\gamma} V_n'(x) p_n(x,t) - D \frac{\partial p_n(x,t)}{\partial x}. \tag{C.20}$$

The first term on the right-hand side of equation (C.19) represents the probability flow associated with the SDE for a given n, whereas the second term represents jumps in the discrete state n.

D.2 Diffusion in a switching harmonic potential

Let us return to the two-state process shown In Fig. 6.9, in which a confining harmonic potential is randomly switched on and off in order to provide a physical realization of stochastic resetting [42, 82, 75, 83]. The corresponding hSDE takes the form

$$dX(t) = -\frac{1}{\gamma}\partial_x V(x,t)dt + \sqrt{2D}dW(t), \tag{C.21}$$

with

$$V(x,t) = N(t)V(x), \quad V(x) = \frac{\mu x^2}{2}, \tag{C.22}$$

and $N(t) \in \{0,1\}$. The two-state Markov chain $N(t)$ is sometimes called a dichotomous noise process..The corresponding CK equation is

$$\frac{\partial p_0(x,t)}{\partial t} = D\frac{\partial p_0(x,t)}{\partial x^2} - \omega p_0(x,t) + \omega p_1(x,t), \tag{C.23a}$$

$$\frac{\partial p_1(x,t)}{\partial t} = \mu\frac{\partial xp(_1(x,t)}{\partial x} + D\frac{\partial p_0(x,t)}{\partial x^2} + \omega p_0(x,t) - \omega p_1(x,t). \tag{C.23b}$$

For convenience, we have absorbed the drag coefficient into the amplitude μ of the harmonic potential, and taken $\mathcal{K}_{01} = \mathcal{K}_{10} = \omega$. Note that p_0 and p_1 correspond, respectively, to the potential being OFF and ON. It does not appear possible to derive a closed expression for the nonequilibrium stationary state (NESS) $p^*(x)$ of the corresponding time-independent CK equation. However, one can determine the Fourier transform $\widehat{P}_n(k) = \int_{\mathbb{R}} \mathrm{e}^{-ikx} p_n^*(x)dx$ and use this to derive various asymptotic approximations [75]. We summarize the basic results here.

Fourier transforming the steady-state version of equations (C.23a) and (C.23b) gives

$$-Dk^2\widehat{P}_0(k) - \omega\widehat{P}_0(k) + \omega\widehat{P}_1(k) = 0, \tag{C.24a}$$

$$-Dk^2\widehat{P}_1(k) - \mu\frac{d}{dk}\left[k\widehat{P}_1(k)\right] + (\mu-\omega)\widehat{P}_1(k) + \omega\widehat{P}_0(k) = 0. \tag{C.24b}$$

Expressing $\widehat{P}_0(k)$ in terms of $\widehat{P}_1(k)$ using equation (C.24b) and substituting the result into equation (C.24a), one finds that [75]

$$\widehat{P}_0(k) = \frac{\omega}{\omega+Dk^2}\widehat{P}_1(k), \tag{C.25a}$$

$$\widehat{P}_1(k) = \frac{C_0}{(\omega+Dk^2)^{\omega/(2\mu)}}\mathrm{e}^{-Dk^2/(2\mu)}. \tag{C.25b}$$

The normalization constant $C_0 = \omega^{\omega/(2\mu)}/2$. For general parameter values, it is not possible to invert these Fourier transforms. However, following Ref. [75], suppose that the system operates in the slow switching regime $\omega \ll \mu$. In that case, we have

$$\widehat{P}_0(k) \approx \frac{\omega}{2[\omega + Dk^2]} e^{-Dk^2/(2\mu)}, \quad \widehat{P}_1(k) \approx \frac{1}{2} e^{-Dk^2/(2\mu)}. \tag{C.26}$$

These can be inverted to give the following approximation of the NESS [75]:

$$p_0^*(x) = \frac{1}{2} \frac{\sqrt{\omega/D} e^{\omega/(2\mu)}}{4} e^{-\sqrt{\omega/D}|x|} \operatorname{erfc}\left(\frac{\sqrt{\omega/D}}{2\mu} - \sqrt{\frac{\mu}{2D}} |x| \right), \tag{C.27a}$$

$$p_1^*(x) = \frac{1}{2} \frac{e^{-\mu x^2/(2D)}}{\sqrt{2\pi D/\mu}}, \tag{C.27b}$$

where $\operatorname{erfc}(x) = (2/\sqrt{\pi}) \int_x^\infty e^{-z^2} dz$ is the complementary error function. Note that $p_1^*(x)$ dominates near the origin, which is consistent with the idea that in the ON state, the harmonic potential localizes the particle to a neighborhood of the origin, which is the minimum of the potential. On the other hand, $p_0^*(x)$ dictates the behavior in the tails of the NESS, since the particle is no longer trapped.

These results are illustrated in Fig. 6.12, where we plot $p_0^*(x)$ and $p_1^*(x)$ for different choices of μ and ω. From the asymptotic behavior of the Gaussian and the complementary error function, one finds that in the limit $\mu \to \infty$,

$$p_0^*(x) \approx \frac{1}{2} \frac{\sqrt{\omega/D}}{2} e^{-\sqrt{\omega/D}}, \quad p_1^*(x) \approx \frac{1}{2} \delta(x). \tag{C.28}$$

As noted in Ref. [75], this is precisely the NESS for pure diffusion with instantaneous resetting to the origin at a rate $r = \omega$ followed by a Poissonian refractory period whose mean waiting time is $\langle \tau \rangle = 1/\omega$ [31]. The observation that diffusion in an intermittent harmonic potential with a large amplitude μ behaves like diffu-

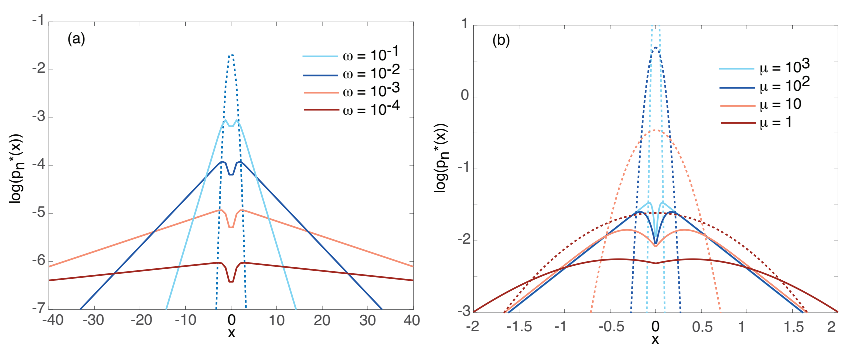

Fig. 6.12: Nonequilibrium stationary state (NESS) for an overdamped Brownian particle in an intermittent harmonic potential. The stationary densities $p_0^*(x)$ (solid curves) and $p_1^*(x)$ (dashed curves) are plotted for various values of (μ, ω) and $D = 1$. (a) Fixed $\mu = 1$ and different switching rates ω. The curves for $p_1^*(x)$ are indistinguishable for this case. (b) Fixed $\omega = 1$ and different potential amplitudes μ.

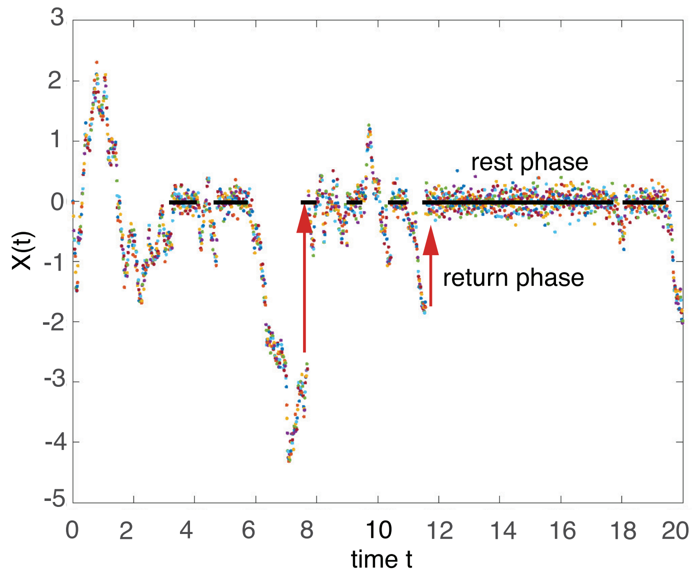

Fig. 6.13: Diffusion in an intermittent harmonic potential. Sample trajectory of the particle position $X(t)$. The horizontal bars indicate the time intervals during which $N(t) = 1$ (the ON state). Other parameters are $D = 1$, $\mu = 100$ and $\omega = 1$. The step size for the numerical simulation is $dt = 0.01$. Since μ is relatively large, transitions from OFF to ON result in a sharp return of the particle to the origin.

sion with instantaneous resetting and a refractory period is further confirmed in Fig. 6.13, where we plot $X(t)$ for a single long run.

Finally, note that in the fast switching limit, the hSDE (C.21) reduces to the Ornstein-Uhlenbeck process

$$dX(t) = -\partial_x \overline{V}(x)dt + \sqrt{2D}dW(t), \quad \overline{V}(x) = \frac{\mu}{4}x^2. \tag{C.29}$$

Again we have absorbed γ into μ, and we have used the fact that $\sigma_0 = \sigma_1 = 1/2$. It immediately follows that the system converges to an equilibrium stationary state with

$$p^*(x) = \frac{e^{-\mu x^2/4D}}{\sqrt{4\pi D/\mu}}. \tag{C.30}$$

This result also follows from equations (C.25a) and (C.25b) by noting that if $\omega \gg \mu$ then [75]

$$\widehat{P}(k) = \widehat{P}_0(k) + \widehat{P}_0(k) \approx e^{-Dk^2/\mu}, \tag{C.31}$$

which is the Fourier transform of the Gaussian in equation (C.30).

Chapter 7
Active transport

A. List of corrections

p. 551. Delete the insert "$F_j(t)$" at the end of the first para in Section 7.4.

p. 551. Delete the sentence *"It remains to determine the distribution $F_j(t)$ for a given target"* at the start of the second para of Section 7.4

p. 552. In the sentences above and below equation (7.4.2) replace *"inter-arrival time"* by *"first-arrival time"*. In the derivation of the renewal equation for the Binomial moments we condition on the first (or next) arrival time with distribution $\mathcal{F}_j(t)$. Suppose, instead, that $\mathcal{F}_j(t)$ denotes the inter-arrival time density of packets to the jth target The relationship between the conditional FPT density $f_j(t)$ of a single search-and-capture process and $\mathcal{F}_j(t)$ is more complicated than the single target case. This is due to the fact that the arrival event of the next packet to the j-th target could occur after an arbitrary number of deliveries to other targets. It follows that (ignoring refractory periods)

$$\begin{aligned}\mathcal{F}_j(t) &= \pi_j f_j(t) + \pi_j \sum_{k\neq j} \pi_k \int_0^t f_k(\tau) f_j(t-\tau)d\tau \\ &\quad + \pi_1 \sum_{k,k'\neq j} \pi_k \pi_{k'} \int_0^t \int_0^{t-\tau} f_k(\tau) f_{k'}(\tau') f_j(t-\tau-\tau')d\tau' d\tau + \ldots \end{aligned} \tag{A.1}$$

Laplace transforming both sides using the convolution theorem gives

$$\widetilde{\mathcal{F}}_j(s) = \pi_j \widetilde{f}_j(s) + \pi_j \sum_{k\neq j} \pi_k \widetilde{f}_j(s)\widetilde{f}_k(s) + \pi_j \sum_{k,k'\neq j} \pi_k \pi_{k'} \widetilde{f}_j(s)\widetilde{f}_k(s)\widetilde{f}_{k'}(s) + \ldots \tag{A.2}$$

Summing the geometric series leads to the closed expression

$$\widetilde{\mathcal{F}}_j(s) = \frac{\pi_j \widetilde{f}_j(s)}{1-\sum_{k\neq j}\pi_k \widetilde{f}_k(s)}. \tag{A.3}$$

Note, in particular, that

$$\int_0^\infty \mathcal{F}_j(t)dt = \widetilde{\mathcal{F}}_j(0) = \frac{\pi_j \widetilde{f}_j(0)}{1-\sum_{k\neq j}\pi_k \widetilde{f}_k(0)}. = \frac{\pi_j}{1-\sum_{k\neq j}\pi_k} = 1 \qquad \text{(A.4)}$$

as required. We have used the fact that $\widetilde{f}_j(0) = \int_0^\infty f_j(t)dt = 1$ for all $j = 1,\ldots,N$.

p. 556. Delete *"(We keep the symbol r as the resetting rate.)"* below equation (7.4.19a):

p. 557. Delete *"without resetting"* below equation (7.4.21)

p. 558: Caption of Fig. 7.21. Change *"as a function of resetting radius x_r for $d = 1,2,3$ and $r = 0.1,10$"* to *"as a function of x_0 for $d = 1,2,3$"*

B. Modeling stochastic search-and-capture as a G/M/1 queue

In Sect. 7.4 we showed how the accumulation of resources in a target due to a sequence of search-and-capture events can be mapped onto a queuing process. The particular queuing model that is most relevant to the target problem is the $G/M/n$ model. Here the symbol G denotes a general inter-arrival time distribution $F(t)$, which will depend on the first passage time distribution of the individual search-and-capture processes. The symbol M stands for a Markovian or exponential service-time distribution $H(t) = 1 - \mathrm{e}^{-\lambda t}$, and n denotes the number of servers. In the case of a first-in-first-out utilization policy we have $n = 1$ (a single server queue), whereas $n = \infty$ (infinite server queue) when the target resources packets are consumed independently, see Fig. 7.1. In Sect. 7.4 we modeled target resource accumulation in terms of a $G/M/\infty$ queue. Here we use classical results from the analysis of $G/M/1$ queues [27, 1] to develop the analogous theory for the first-in-first-out utilization policy. Such an analysis is warranted due to significant differences in the mathematics of single-server and infinite-server queues. For simplicity, we focus on the case of a single target or queue. A single-server queuing system is characterized by two sequences $\{T_n, n \geq 1\}$ and $\{S_n, n \geq 1\}$ of independent positive random variables. The first is the inter-arrival times of customers with common distribution function F and the second is the service times with common distribution function H. Each arriving customer joins the line of customers who are waiting to receive attention from the single server. When the n-th customer reaches the head of the line, it is served for a period S_n and then immediately leaves the system. Let $Q(t)$ denote the number of waiting customers at time t, including any customer currently receiving service (the queue length). Then $\{Q(t) : t \geq 0\}$ is itself a stochastic process whose statistics is determined by F and H. Although Q is not a Markov chain in the case of a $G/M/1$ queue there exists an imbedded discrete-time Markov chain that can be used to calculate quantities of interest such as the moment generating functions of the queue length when a new customer arrives and customer waiting times [27]. In contrast, although a $G/M/\infty$ queue is also non-Markovian, it can be analyzed in continuous time by using renewal theory to solve integral equations for various moment generating functions [80, 55], see Sect. 7.4.

B. 1 $G/M/1$ *queue as an imbedded Markov chain*

Consider the queue $G/M(\lambda)/1$ consisting of a single server, in which individual customers arrive according to a general (non-Markovian) distribution $F(t)$ and the waiting time to service a customer is exponentially distributed with intensity λ. Let A_n be the time of arrival of the nth customer and let $Q(A_n)$ be the number of customers waiting in line ahead of the customer at the time of arrival. We have the iterative equation

$$Q(A_{n+1}) = Q(A_n) + 1 - V_n, \tag{B.5}$$

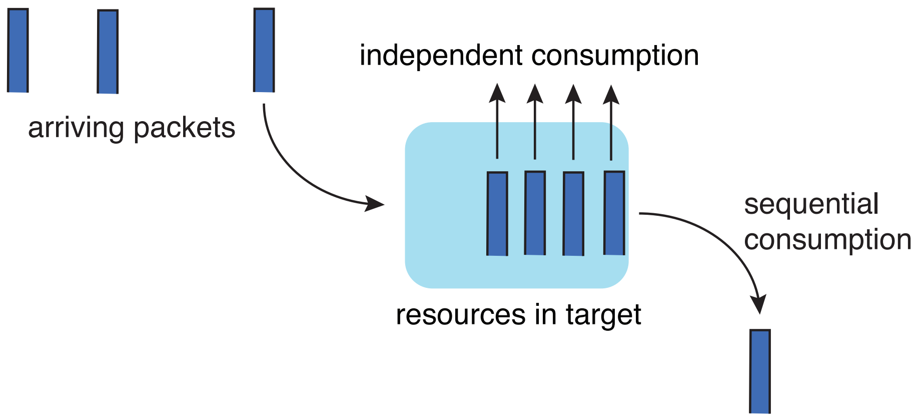

Fig. 7.1: Accumulation and consumption of resources in a target. The sequential delivery of packets of resources leads to an accumulation of resources in the target. In a sequential consumption model, resources are used in the order they are received (first-in-first-out policy). In an independent consumption model, each packet within a target is utilized independently of the others.

where V_n is the number of departures (customers served) in $[A_n, A_{n+1})$. Note that V_n depends on $Q(A_n)$ since not more than $Q(A_n)+1$ individuals can depart during this interval. However, given $Q(A_n)$ the random variable is independent of $Q(A_1), A(Q_2), \ldots Q(A_{n-1})$ so that equation (B.5) represents a discrete-time Markov chain. Hence, its dynamics is completely determined by the transition probabilities

$$K_{ij} = \mathbb{P}(Q(A_{n+1}) = j | Q(A_n) = i).$$

We calculate these transition probabilities by noting that

$$K_{ij} = \mathbb{E}_X \left[\mathbb{P}[V_n = 1 + i - j | Q(A_n) = i, X] \right], \tag{B.6}$$

where X is the stochastic inter-arrival time. The number of departures over a time interval of length X is given by an exponential distribution with intensity λ, that is,

$$\mathbb{P}[V_n = |Q(A_n) = q, X = x] = \begin{cases} \dfrac{(\lambda x)^k}{k!} \mathrm{e}^{-\lambda k}, & k \leq q \\ 1 - \displaystyle\sum_{k=0}^{q} \dfrac{(\lambda x)^k}{k!} \mathrm{e}^{-\lambda k}, & k = q+1 \end{cases}. \tag{B.7}$$

It follows that the transition matrix has the general form

$$\mathbf{K} = \begin{pmatrix} 1-\alpha_0 & \alpha_0 & 0 & \ldots & \ldots & \\ 1-\alpha_0-\alpha_1 & \alpha_1 & \alpha_0 & 0 & \ldots & \\ 1-\alpha_0-\alpha_1-\alpha_2 & \alpha_2 & \alpha_1 & \alpha_0 & 0 & \ldots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \end{pmatrix}, \tag{B.8}$$

where

$$\alpha_j = \mathbb{E}\left[\frac{(\lambda X)^j}{j!}\mathrm{e}^{-\lambda X}\right]. \tag{B.9}$$

B.2 Asymptotic queue length

Suppose there exists a unique stationary solution $p_j = \lim_{n\to\infty}\mathbb{P}[Q(A_n) = j]$, which satisfies the equation $\mathbf{p} = \mathbf{pK}$ with $\sum_{j=0}^{\infty} p_j = 1$. (We will determine when such a solution exists below.) The first component of the stationary equation is

$$\begin{aligned} p_0 &= (1-\alpha_0)p_0 + (1-\alpha_0-\alpha_1)p_1 + (1-\alpha_0-\alpha_1-\alpha_2)p_2 + \ldots \\ &= \left(\sum_{j=1}^{\infty}\alpha_j\right))p_0 + \left(\sum_{j=2}^{\infty}\alpha_j\right)p_1 + \ldots \\ &= \alpha_1 p_0 + \alpha_2(p_0+p_1) + \alpha_3(p_0+p_1+p_2) + \ldots \end{aligned} \tag{B.10}$$

We have used the normalization $\sum_{j=0}^{\infty}\alpha_j = 1$. Introducing the new variables

$$y_i = p_0 + p_1 + \ldots + p_{i-1}, \tag{B.11}$$

we can write

$$y_1 = \sum_{i=1}^{\infty}\alpha_i y_i. \tag{B.12a}$$

Similarly, the second component of the stationary equation is

$$p_1 = \alpha_0 p_0 + \alpha_1 p_1 + \alpha_2 p_2 + \alpha_3 p_3 + \ldots,$$

which combined with the first line of equation (B.10) implies that

$$\begin{aligned} p_0 + p_1 &= p_0 + (1-\alpha_0)p_1 + (1-\alpha_0-\alpha_1)p_2 + \ldots \\ &= (\alpha_0+\alpha_1+\alpha_2+\ldots)p_0 + (\alpha_1+\alpha_2+\alpha_3+\ldots)p_1 + (\alpha_2+\alpha_3+\ldots)p_2 \\ &= \alpha_0 p_0 + \alpha_1(p_0+p_1) + \alpha_2(p_0+p_1+p_2) + \ldots, \end{aligned}$$

that is, $y_2 = \sum_{i=0}^{\infty}\alpha_i y_{1+i}$. Generalizing this analysis shows that

$$y_j = \sum_{i=0}^{\infty}\alpha_i y_{j+i-1}, \quad j \geq 2. \tag{B.12b}$$

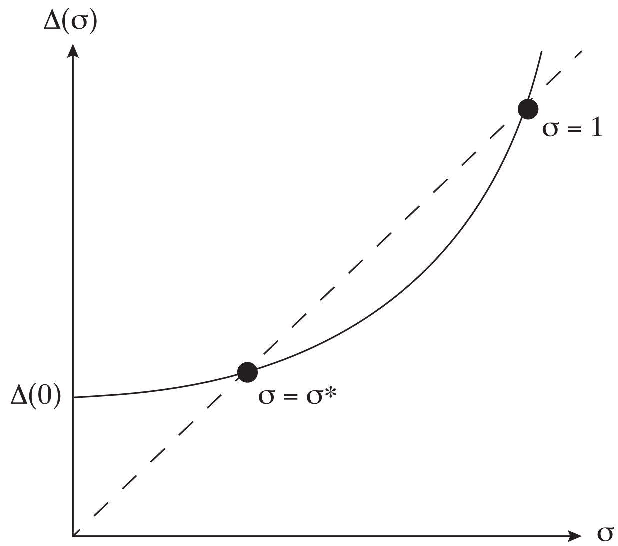

Fig. 7.2: Graphical construction of solutions to equation (B.17) for $\rho < 1$.

Consider the trial solution $y_j = 1 - \sigma^j$ for some σ, $0 < \sigma < 1$. Substituting into equation (B.12b) gives

$$1 - \sigma^j = \sum_{i=0}^{\infty} [1 - \sigma^{j+i-1}] = 1 - \sigma^{j-1} \Delta(\sigma), \quad \Delta(\sigma) \equiv \sum_{i=0}^{\infty} \alpha_i \sigma_i. \tag{B.13}$$

We thus obtain the following self-consistency condition for σ:

$$\Delta(\sigma) = \sigma. \tag{B.14}$$

One obvious solution of equation (B.14) is $\sigma = 1$ since $\Delta(1) = \sum_{i=0}^{\infty} \alpha_i = 1$. However, this does not result in a convergent series. In order to proceed further, we note that

$$\begin{aligned} \Delta(\sigma) &= \sum_{j=0}^{\infty} \alpha_i \sigma^j = \sum_{j=0}^{\infty} \left[\frac{(\lambda \sigma X)^j}{j!} \mathrm{e}^{-\lambda X} \right] \\ &= \mathbb{E}\left[\mathrm{e}^{-(1-\sigma)\lambda X} \right] \equiv G_X[\lambda(1-\sigma)], \end{aligned} \tag{B.15}$$

where G_X is the moment generating function of the stochastic process X. Given the inter-arrival time distribution $F(t)$, we have

$$G_X[s] = \widetilde{F}(s) := \int_0^{\infty} \mathrm{e}^{-st} dF(t). \tag{B.16}$$

Hence, the self-consistency condition (B.14) becomes

$$\sigma = \widetilde{F}(\lambda(1-\sigma)). \tag{B.17}$$

It is straightforward to show that $\Delta(0) = \alpha_0 > 0$,

$$\Delta'(\sigma) = \lambda \mathbb{E}\left[X \mathrm{e}^{-(1-\sigma)\lambda X}\right] > 0, \tag{B.18}$$

and

$$\Delta'(1) = \lambda \mathbb{E}[X] := \frac{1}{\rho}, \tag{B.19}$$

where ρ is known as the traffic intensity. Finally,

$$\Delta''(\sigma) = \lambda^2 \mathbb{E}\left[X^2 \mathrm{e}^{-(1-\sigma)\lambda X}\right] > 0. \tag{B.20}$$

In summary, $\Delta(\sigma)$ is a positive definite, convex, monotonically increasing function of σ for $\sigma \in [0,1]$. In addition, if $\Delta'(1) > 1$ then the graphical construction of Fig. 7.2 establishes the existence of unique solution $\sigma^* \in (0,1)$ that satisfies equation (B.17). Finally, the normalized stationary solution is

$$p_n = (1-\sigma^*)(\sigma^*)^n, \quad \widetilde{F}(\lambda(1-\sigma^*)) = \sigma^*. \tag{B.21}$$

B.3 Waiting times and busy periods

The n-th customer waits for a length of time

$$W_n = Z_1^* + Z_2 + \ldots + Z_{Q(A_n)}, \tag{B.22}$$

where Z_1^* is the excess service time of the current customer and Z_k, $k > 1$, are the service times of the other customers in the queue at time $t = A_n^+$. Since servicing is Markovian, the distribution of Z_1^* is the same as the distribution for Z_1. Hence, the waiting time generator is given by

$$\begin{aligned} G_W(s) :&= \mathbb{E}\left[\mathrm{e}^{-sW}\right] \\ &= \mathbb{E}\left[\mathbb{E}\left(\mathrm{e}^{-s(Z_1+\ldots+Z_Q)}|Q\right]\right] \\ &= \sum_{n=0}^{\infty} p_n \left(\mathbb{E}\left[\mathrm{e}^{-sZ}\right]\right)^n. \end{aligned} \tag{B.23}$$

Using equation (B.17) and the expectation

$$\mathbb{E}\left[\mathrm{e}^{-sZ}\right] = \lambda \int_0^\infty \mathrm{e}^{-sx}\mathrm{e}^{-\lambda x} dx = \frac{\lambda}{s+\lambda}, \tag{B.24}$$

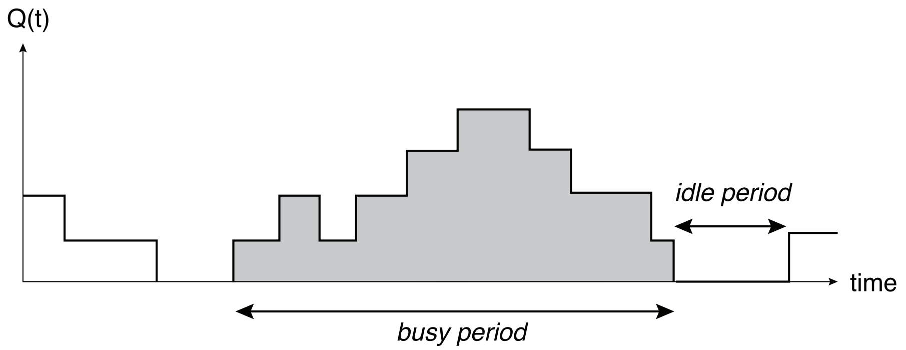

Fig. 7.3: Schematic illustration of the busy period and the idle period of a single queueing cycle. The total waiting time during the busy period is equal to the shaded area under the curve.

we find that

$$\begin{aligned} G_W(s) &= \sum_{n=0}^{\infty} p_n \left(\frac{\lambda}{s+\lambda} \right)^n \\ &= (1-\sigma^*) \sum_{n=0}^{\infty} p_n \left(\frac{\lambda \sigma^*}{s+\lambda} \right)^n \\ &= (1-\sigma) \frac{1}{1-\lambda\sigma^*/(s+\lambda)} = (1-\sigma^*) \frac{s+\lambda}{s+\lambda-\lambda\sigma^*}. \end{aligned} \tag{B.25}$$

Another important quantity in a queueing process is the time that elapses between two consecutive arrivals finding an empty system. This so-called cycle starts with a busy period BP during which the server is helping customers, followed by an idle period IP during which the system is empty. (Within the context of stochastic-search-and-capture process, the IP is a critical time interval during which the target cannot be utilized by downstream processes. A schematic illustration of a cycle is shown in Fig. 7.3. Let us introduce a set of random variables conditioned on the arrival of the first customer at $t = 0$, say:

$$\begin{aligned} Y = &\text{ the busy period } = \inf\{t > 0, Q(t) = 0\} \\ Z = &\text{ the cycle period } = \inf\{t > Y, Q(t) > 0\} \\ Q_B = &\text{ the number of customers served during the busy period} \end{aligned}$$

The following expression can be derived for the corresponding multi-variable generating function [26, 79]:

$$\mathbb{E}\left[e^{-sY} e^{-wZ} u^{Q_B} \right] = \frac{\lambda u [\widetilde{F}(w) - \sigma(s+w,u;\lambda)]}{s+\lambda-\lambda u \sigma(s+w,u;\lambda)}, \tag{B.26}$$

where $\widetilde{F}(s)$ is the Laplace transform of the inter-arrival distribution, see equation (B.16), and $\sigma(s+w,u;\lambda)$ is the smallest root of the implicit equation

$$\widetilde{F}(s+w+\lambda-\lambda u\sigma)=\sigma. \tag{B.27}$$

In particular, note that $\sigma(0,1:\lambda)=\sigma^*$, where σ^* is the smallest root of equation (B.17).

B.4 Target resource accumulation

We now incorporate a multiple search-and-capture process into a G/M/1 model of resource utilization. We assume that a single searcher returns to its initial position $\mathbf{x}_0$ after delivering its cargo, and then starts a new round of search-and-capture following a constant waiting time Δ_0. Let $\mathcal{T}_k$ denote the FPT for the kth round of search-and-capture, whose FPT density is given by $f(\mathbf{x}_0,t)$. Let τ_k be the corresponding time at which the kth packet of resources is delivered to the target. It follows that

$$\tau_1=\mathcal{T}_1,\quad \tau_k=\tau_{k-1}+\mathcal{T}_k+\Delta_0,\quad k\geq 2, \tag{B.28}$$

The inter-arrival time distribution $F(t)$ is then related to the FPT density $f(\mathbf{x}_0,t)$ of a single search-and-capture process according to

$$F(t)=f(\mathbf{x}_0,t-\Delta_0)\Theta(t-\Delta_0), \tag{B.29}$$

where $\Theta(t)$ is the Heaviside function. Laplace transforming this equation implies that

$$\widetilde{F}(s)=\widetilde{f}(\mathbf{x}_0,s)\mathrm{e}^{-\Delta_0 s}. \tag{B.30}$$

Finally, substituting for $\widetilde{F}$ into equation (B.17) leads to the self-consistency condition

$$\sigma=\widetilde{f}(\mathbf{x}_0,\lambda(1-\sigma))\mathrm{e}^{-\Delta_0\lambda(1-\sigma)} \tag{B.31}$$

Recall from Sect. 7.5.2 that in the case of a stochastic search process with resetting, the FPT density in Laplace space is related to the Laplace tranform of the survival probability without resetting according to

$$\widetilde{f}(\mathbf{x}_0,s)=\frac{1-(r+s)\widetilde{Q}_0(\mathbf{x}_0,r+s)}{1-r\widetilde{Q}_0(\mathbf{x}_0,r+s)}. \tag{B.32}$$

As a simple example, consider a diffusing particle on the interval $[0,L]$ with an absorbing target at $x=0$ and a reflecting boundary at $x=L$. Suppose that the particle resets to a point x_0 at a constant rate r (see Sect. 7.5). In the absence of resetting the Laplace transformed survival probability $\widetilde{Q}_0(x,s)$ satisfies the equation

$$D\frac{d^2\widetilde{Q}_0}{dx^2} - s\widetilde{Q}_0 = -1, \quad x \in (0,L), \tag{B.33a}$$

together with the boundary conditions

$$\widetilde{Q}_0(0,s) = 0,, \quad \partial_x \widetilde{Q}_0(L,s) = 0. \tag{B.33b}$$

The solution takes the form

$$\widetilde{Q}_0(x_0,s) = \frac{1}{s}\left(1 - \frac{\cosh(\sqrt{s/D}[L-x_0])}{\cosh(\sqrt{s/D}L)}\right). \tag{B.34}$$

In the limit $L \to \infty$, we obtain the corresponding survival probability on the semi-infinite interval:

$$Q_0(x_r,t) = \mathrm{erf}(x_0/2\sqrt{Dt}), \quad \widetilde{Q}_0(x_0,s) = \frac{1-\mathrm{e}^{-\sqrt{s/D}x_0}}{s}. \tag{B.35}$$

which is the Laplace transform of the survival probability on the half-line. It follows that the Laplace transform of the FPT density with resetting is

$$\widetilde{f}(x_0,s) = \frac{(r+s)\cosh(\sqrt{[r+s]/D}[L-x_0])}{s\cosh(\sqrt{[r+s]/DL}) + r\cosh(\sqrt{[r+s]/D}[L-x_0])}. \tag{B.36}$$

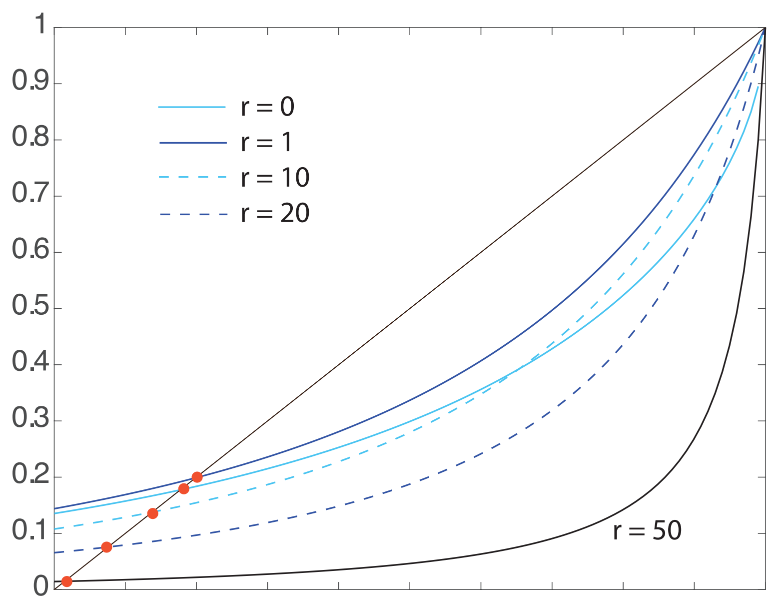

Fig. 7.4: Function $\Delta(\sigma)$ for diffusion with resetting on the half-line. $x_0 = D = 1$ $\lambda = 1 = \Delta_0$

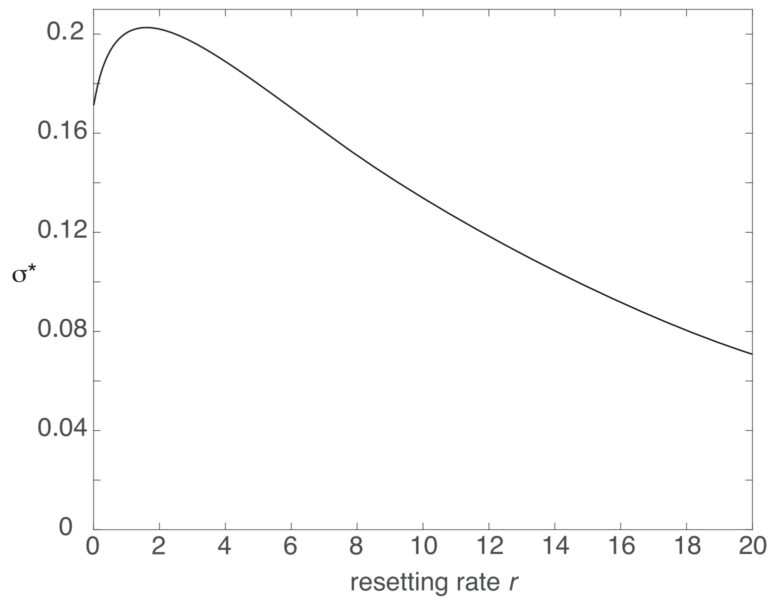

Fig. 7.5: Corresponding plot of σ^* vs r

In the limit $L \to \infty$ this simplifies as

$$\widetilde{f}(x_0, s) = \frac{(r+s)\mathrm{e}^{-\sqrt{[r+s]/D}x_0}}{s + r\mathrm{e}^{-\sqrt{[r+s]/D}x_0}} \tag{B.37}$$

C. Probabilistic formulation of stochastic resetting

Most studies of diffusion with instantaneous resetting focus on the distribution of sample paths expressed as the solution to a forward or backward Fokker-Planck (FP) equation with additional source and sink terms, see Sect. 7.5. However, there exists a complementary probabilistic approach in which individual sample paths are represented by solutions of a stochastic differential equation (SDE) for a jump-diffusion process [56, 24]. The latter probabilistic formulation has a number of useful features.

(i) There exists a generalised version of Itô's lemma for jump-diffusion processes that provides a direct link between sample paths and the underlying FP equation with resetting. This can be used to derive global density equations for populations of diffusing particles with local or global stochastic resetting [23].

(ii) The SDE for instantaneous resetting can be combined with a more general encounter-based formulation of diffusion-mediated surface absorption at a target boundary, see supplementary material 6A.

(iii) Stochastic calculus is playing an increasingly important role in stochastic thermodynamics [77, 78, 70, 73]. The latter extends classical ideas of entropy, heat and work to mesoscopic non-equilibrium systems. The generalised Itô's lemma for jump-diffusion processes has recently been used to determine the rate of stochastic entropy production along sample paths of diffusing particles with instantaneous resetting [24]. Averaging the stochastic entropy with respect to the ensemble of stochastic trajectories leads to a second law of thermodynamics that quantifies the degree of departure from thermodynamic equilibrium, The resulting analysis complements previous studies based on the Gibbs-Shannon entropy of the ensemble [37] or the ratio of the path probabilities of forward and time-reversed trajectories [65, 25, 62].

For simplicity, we focus on continuous one-dimensional (1D) diffusion processes. Let $X(t) \in \mathbb{R}$ denote the position of a single Brownian particle at time t that instantaneously resets to its initial position x_0 at the random times $\widehat{T}_n$ generated by a Poisson process $N(t)$ with rate r, see the appendix. The stochastic dynamics in the presence of resetting can be represented in terms of the jump-diffusion process [56, 24]

$$dX(t) = -\frac{V'(X(t))}{\gamma}dt + \sqrt{2D}dW(t) + (x_0 - X(t^-))dN(t), \tag{C.1}$$

where $W(t)$ is a Wiener process with

$$\langle W(t)\rangle = 0, \quad \langle W(t)W(s)\rangle = \min\{t,s\}. \tag{C.2}$$

The solution $X(t)$ is taken to be right-continuous so that

$$X(\widehat{T}_n) = \lim_{t\to\widehat{T}_n^-}(x_0 - X(t)) + \lim_{t\to\widehat{T}_n^-} X(t) = x_0, \tag{C.3}$$

which corresponds to perfect resetting. In standard formulations of stochastic resetting at the single-particle level [32], the SDE (C.1) is averaged over multiple realisations of the Poisson resetting process. Since $\mathbb{P}[\widehat{T}_n \in [t, t+dt]] = rdt$, equation (C.1) becomes

$$dX(t) = -\frac{V'(X)}{\gamma}dt + \sqrt{2D}dW \quad \text{with probability } 1 - rdt, \tag{C.4a}$$

$$dX(t) = x_0 - X(t) \text{ with probability } rdt. \tag{C.4b}$$

For a general introduction to jump-diffusion processes see Ref. [6].

C.1 Generalised Itô's lemma and the Fokker-Planck equation

Let $f(x)$ be an arbitrary smooth bounded test function on $\mathbb{R}$. The infinitesimal $df(X(t))$ can be decomposed as

$$\begin{aligned} df(X(t)) &= f'(X(t))[-V'(X(t))dt/\gamma - +\sqrt{2D}dW(t)] \\ &\quad + \frac{1}{2}f''(X(t)[-V'(X(t))dt/\gamma - \sqrt{2D}dW(t)]^2 \\ &\quad + \left[f(X(t)) - f(X(t^-))\right]dN(t) + o(dt). \end{aligned} \tag{C.5}$$

Using the identity $dW(t)^2 = dt$ and dropping all $o(dt)$ terms yields an extended version of Itô's lemma for the jump-diffusion process:

$$\begin{aligned} df(X(t)) &= [-f'(X(t))V'(X(t))/\gamma + Df''(X(t)]dt + \sqrt{2D}f'(X(t))dW(t) \\ &\quad + \left[f(X(t)) - f(X(t^-))\right]dN(t). \end{aligned} \tag{C.6}$$

The corresponding integral version of the extended Itô's lemma is

$$\begin{aligned} f(X(t) &= f(x_0) + \int_0^t \left[-f'(X(s))V'(X(s))/\gamma + Df''(X(s))\right]ds \\ &\quad + \sqrt{2D}\int_0^t f'(X(s))dW(s) + \int_0^t \left[f(X(s)) - f(X(s^-))\right]dN(s) \end{aligned} \tag{C.7}$$

Substituting for $dN(s)$ using (see the appendix)

$$dN(s) := h(s)ds = \sum_{n\geq 1} \delta(t - \widehat{T}_n)ds, \tag{C.8}$$

implies that the final integral can be rewritten as

$$\mathscr{I}(t) = \int_0^t \left[\sum_{n\geq 1}\left[f(X(s)) - f(X(s^-))\right]\delta(s-\widehat{T}_n)ds\right] \tag{C.9}$$
$$= \sum_{n\geq 1}\left[f(X(\widehat{T}_n)) - f(X(\widehat{T}_n^-))\right]\Theta(t-\widehat{T}_n) = \sum_{n\geq 1}\left[f(x_0) - f(X(\widehat{T}_n^-))\right]\Theta(t-\widehat{T}_n),$$

where Θ is a Heaviside function. We have used the fact that $X(T_n) = x_0$.

Let $p_r(x,t)$ be the probability density for the particle to be at position x at time t with

$$p_r(x,t) = \left\langle \mathbb{E}\left[\delta(x-X(t))\right]\right\rangle. \tag{C.10}$$

The subscript r means that p_r is the probability density in the presence of resetting at a rate r. Moreover, $\langle\cdot\rangle$ denotes expectation with respect to the white noise process and $\mathbb{E}$ denotes expectation with respect to the resetting process. We assume that the two sources of noise are uncorrelated. Consider the following equation for an arbitrary test function f:

$$\left[\int_{\mathbb{R}} f(x)\frac{\partial\rho(x,t)}{\partial t}dx\right]dt = df(X(t)), \tag{C.11}$$

where $\rho(x,t) = \delta(x-X(t))$. Applying Itô's lemma (C.6) and using equation (C.8) gives

$$\int_{\mathbb{R}} f(x)\frac{\partial\rho(x,t)}{\partial t}dx = \int_{\mathbb{R}}\rho(x,t)\left[-f'(x)V'(x)/\gamma + Df''(x) + \sqrt{2D}f'(x)\xi(t)\right]dx$$
$$+\sum_{n\geq 1}\delta(t-\widehat{T}_n)\int_{\mathbb{R}}[\delta(x-x_0)-\rho(x,t^-)]f(x)dx. \tag{C.12}$$

We have formally set $dW(t) = \xi(t)dt$ with $\xi(t)$ a white noise process such that

$$\langle\xi(t)\rangle = 0, \quad \langle\xi(t)\xi(t')\rangle = \delta(t-t'). \tag{C.13}$$

Integrating by parts and using the arbitrariness of f leads to the stochastic partial differential equation (SPDE)

$$\frac{\partial\rho}{\partial t} = D\frac{\partial^2\rho(x,t)}{\partial x^2} + \frac{1}{\gamma}\frac{\partial V'(x)\rho(x,t)}{\partial x} + \sqrt{2D}\frac{\partial\rho(x,t)}{\partial x}\xi(t)$$
$$+\sum_{n\geq 1}\delta(t-\widehat{T}_n)[\delta(x-x_0)-\rho(x,t^-)]. \tag{C.14}$$

Finally, taking expectations with respect to the white noise and resetting process recovers the standard FP equation for diffusion with resetting [32]:

$$\frac{\partial p_r(x,t)}{\partial t} = D\frac{\partial^2 p_r(x,t)}{\partial x^2} + \frac{1}{\gamma}\frac{\partial V'(x)p_r(x,t))}{\partial x} + r[\delta(x-x_0)-p_r(x,t)] \tag{C.15}$$

with $p_r(x,0)=\delta(x-x_0)$. We have used the identity

$$\mathbb{E}[\sum_{n\geq 1}\delta(t-\widehat{T}_n)dt]=\mathbb{E}[dN(t)]=rdt, \tag{C.16}$$

see the appendix.

The above SDE formulation of stochastic resetting can be extended to the case where the resetting point is distributed according to some density $\sigma_0(x)$ along the lines considered in Refs. [38, 81]. This means that at the n-th reset time $\widehat{T}_n$ we have $X(\widehat{T}_n)=X_n$ with $\mathbb{P}[X_n\in[x,x+dx]]=\sigma_0(x)dx$. Formally speaking, equation (C.1) becomes

$$dX(t) = -\frac{V'(X(t))}{\gamma}dt+\sqrt{2D}dW(t)+\sum_{n\geq 1}(X_n-X(t^-))\delta(t-\widehat{T}_n), \tag{C.17}$$

and equation (C.14) takes the form

$$\begin{aligned}\frac{\partial\rho(x,t)}{\partial t}&=D\frac{\partial^2\rho(x,t)}{\partial x^2}+\frac{1}{\gamma}\frac{\partial V'(x)\rho(x,t)}{\partial x}+\sqrt{2D}\frac{\partial\rho(x,t)}{\partial x}\xi(t)\\&\quad+\sum_{n\geq 1}[\delta(x-X_\ell)-\rho(x,t^-)]\delta(t-\widehat{T}_n).\end{aligned} \tag{C.18}$$

Finally, averaging Eq. (C.18) with respect to the white noise process and stochastic resetting gives

$$\frac{\partial p_r(x,t)}{\partial t}=D\frac{\partial^2 p_r(x,t)}{\partial x^2}+\frac{1}{\gamma}\frac{\partial V'(x)p_r(x,t)}{\partial x}+r[\sigma_0(x)-p_r(x,t)]. \tag{C.19}$$

C2. Poisson processes

In deriving the extended Itô's lemma, we combined stochastic Itô calculus with a stochastic representation of a Poisson processes. In this appendix we provide some mathematical background regarding the latter, see also Sect. 3.6.. Consider a sequence $\tau_1,\tau_2,\ldots$ of independent exponential random variables with the same mean $1/\lambda$:

$$\mathbb{P}[\tau_n\in[\tau,\tau+d\tau]]=\lambda \mathrm{e}^{-\lambda\tau}d\tau,\quad \ell\geq 1. \tag{C.20}$$

Introduce the jump times $\widehat{T}_n=\sum_{k=1}^n\tau_n$. The Poisson process $N(t)$ is a Markov process that counts the number of jumps occurring in the interval $[0,t]$. In other words,

$$N(t)=n,\quad \widehat{T}_n\leq t<\widehat{T}_{n+1}. \tag{C.21}$$

Note that $N(t)$ is defined to be right-continuous, $\lim_{\varepsilon\to 0^+}N(t+\varepsilon)=N(t)$. In particular, $N(\widehat{T}_n^-)=n-1$ whereas $N(\widehat{T}_n)=n$. This is illustrated in Fig. 7.6. The probability

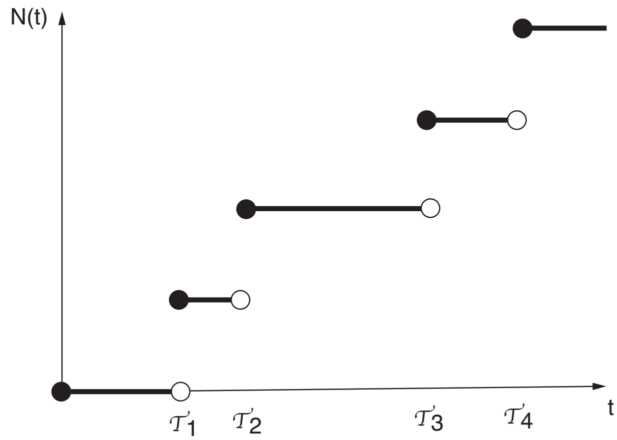

Fig. 7.6: One path of a Poisson process $N(t)$, illustrating that it is right-continuous. Jumps occur at the times $\widehat{T}_\ell$, $\ell \geq 1$.

distribution of the Poisson process is

$$\mathbb{P}[N(t)=n] = P_n(t) \equiv \frac{(\lambda t)^n \mathrm{e}^{-\lambda t}}{n!}. \tag{C.22}$$

Moreover, $N(t+s)-N(s)$, which is the number of jumps in the time interval $(s,t+s]$ has the same distribution as $N(t)$ so the Poisson process is time homogeneous. Introducing the moment generating function

$$G(z,t) = \sum_{n\geq 0} z^n P_n(t) = \mathrm{e}^{(z-1)\lambda t}, \tag{C.23}$$

we deduce that

$$\mathbb{E}[N(t)] = \left.\frac{\partial G(z,t)}{\partial z}\right|_{z=1} = \lambda t, \tag{C.24}$$

and

$$\mathbb{E}[N(t)(N(t)-1)] = \left.\frac{\partial^2 G(z,t)}{\partial z^2}\right|_{z=1} = (\lambda t)^2. \tag{C.25}$$

In particular, $\mathrm{Var}[N(t)] = \lambda t$. Moreover, defining the infinitesimal $dN(t) = N(t+dt)-N(t)$ and using the fact that the Poisson process is time homogeneous, we have

$$\mathbb{E}[dN(t)] = \lambda dt. \tag{C.26}$$

Let f be an arbitrary bounded function on $\mathbb{Z}$. Suppose that $N(t) = n$. Using telescoping we have

$$\begin{aligned} f(N(t)) - f(0) &= \sum_{k=1}^{n} [f(k) - f(k-1)] = \sum_{k=1}^{n} [f(N(\widehat{T}_k)) - f(N(\widehat{T}_{k-1}))] \\ &= \sum_{k=1}^{n} [f(N(\widehat{T}_{k-1}) + 1) - f(N(\widehat{T}_{k-1}))] \\ &= \sum_{k=1}^{\infty} \int_0^t [f(N(s-) + 1) - f(N(s-))] \delta(s - \widehat{T}_k) ds, \end{aligned} \tag{C.27}$$

which is independent of the particular value n. Using the fact that

$$\int_s^t \left(\sum_{k=1}^{\infty} \delta(\tau - \widehat{T}_k) \right) d\tau = N(t) - N(s), \tag{C.28}$$

we have

$$f(N(t)) = f(0) + \int_0^t [f(N(s-) + 1) - f(N(s-))] dN(s), \tag{C.29}$$

with

$$dN(\tau) = \sum_{k=1}^{\infty} \delta(\tau - \widehat{T}_k) d\tau. \tag{C.30}$$

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