Stochastic Processes in Cell Biology I: Supplementary material

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Chapter 2
Random walks and Brownian motion

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 $\kappa_0\to\infty$ 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 [1, 2, 12, 4, 13, 5]. The modified SDE is known as the Skorokhod equation. Probabilistic versions of the Robin boundary condition can also be constructed using the local time [17]. 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 [8, 9]. 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 has been developed using a so-called encounter-based approach [25, 26, 27, 28]. In this section we develop the encounter-based approach by considering the example of a single Brownian particle on the half-line $[0,\infty)$ with a partially absorbing boundary at $x=0$.

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

First suppose that there is a totally reflecting boundary at $x = 0$. 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 [2, 12]. 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 [25, 26, 27, 28]. 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

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

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:

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

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

(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 [25, 26, 27, 28]

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

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):

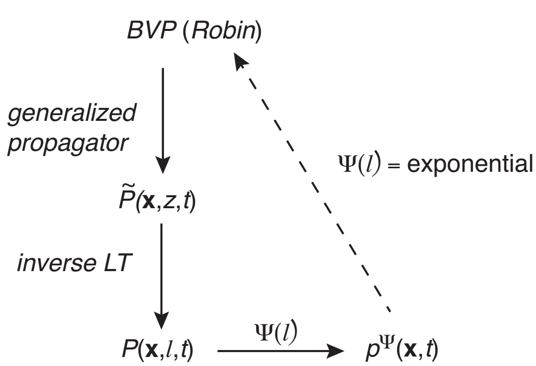

Fig. 2.1: Diagram illustrating the encounter-based framework for diffusion in a domain with a partially absorbing target. The solution of the BVP in the case of a constant absorption rate κ_0 generates the Laplace transform $\widetilde{P}(x,z,t)$ of the local time propagator $P(x,\ell,t)$. The inverse LT determines the marginal probability density $p^{\Psi}(x,t)$ according to equation (**??**).

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

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. 2.1. 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.

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Chapter 6
Diffusive transport

A. 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. 6.1. 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. 6.1. 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 $\partial\mathcal{M}$

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

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

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. (A.1) are a special case of the Kedem-Katchalsky (KK) equations [1, 2, 3], 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. (A.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 $h \to 0$ [4]. Although the KK equations were originally

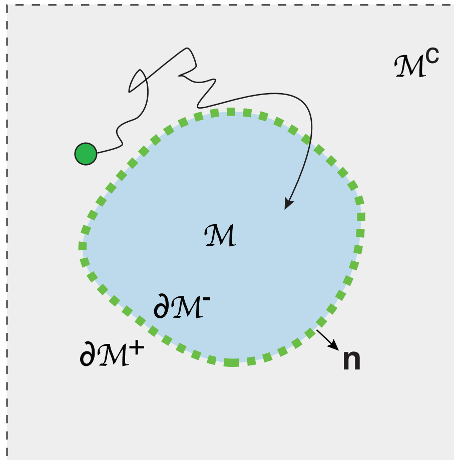

Fig. 6.1: Diffusion through a closed semipermeable membrane in $\mathbb{R}^d$.

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. [5].) One application of artificial membranes is reverse osmosis for water purification and for extracting energy from variations in salinity [6, 7].

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 [8, 9, 10, 11]. 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 (A.1b) is non-trivial. If $\partial\mathcal{M}$ were a totally reflecting (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. 2A.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, andi s based on so-called snapping out BM [18, 19, 27, 28]. 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 [20, 21]. This is distinct from snapping out BM, which is an exact single-particle realization of diffusion through an interface in the overdamped limit.)

A1. 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

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

with the following pair of boundary conditions at the interface:

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

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 [1, 2, 3, 21]. 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. (A.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 $\Omega_+ = [0^+,\infty)$ [18, 19, 27, 28], see Fig. 6.2 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

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

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 2A and Sect. 8.6)

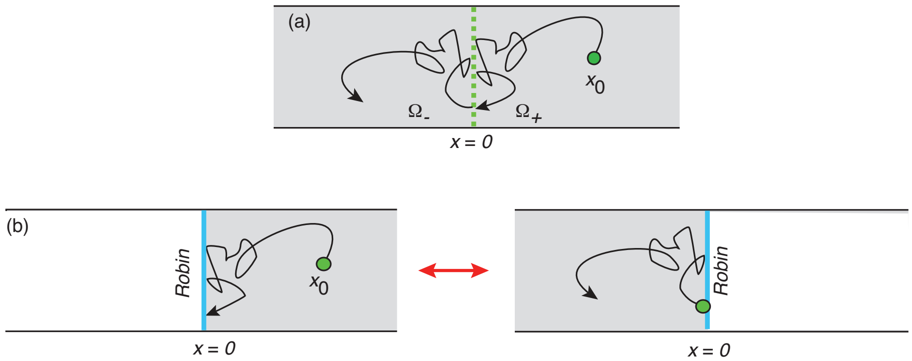

Fig. 6.2: Snapping out BM. (a) Single-particle diffusing across a semipermeable interface at $x = 0$. (b) Decomposition of snapping out BM into the random switching between two partially reflected BMs in the domains $\Omega_\pm$.

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

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_+:

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

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

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

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

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

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

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

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

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

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

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

and

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

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. (A.2). For an alternative proof in 1D see Ref. [18] and for the generalization to higher spatial dimensions see Ref. [23]. 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 [28, 23]

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

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

The first term on the right-hand side of Eq. (A.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. (A.12b).

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

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

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

(Note that equation (A.13) is equivalent to the resolvent operator equation (8) of [18].) Setting $x = 0^{\pm}$ in equation (A.13), summing the results and rearranging shows that

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

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

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

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

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 (A.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

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

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

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

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

and substituting into the Robin boundary condition shows that

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

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

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

Note, in particular, that

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

and

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

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 (A.15) now becomes

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

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

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

Second, equation (A.22) implies that

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

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

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

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

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

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

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

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

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

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

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 $x = 0$.

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 [18]. Second, rather than solving a Fokker-Planck of the form (A.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 2A.

Interfacial asymmetry ($\sigma < 1$) can be incorporated into snapping out BM by taking the independent Bernoulli random variable Y_n in Eq. (A.3) to have the biased probability distribution $\mathbb{P}[Y_n = 0] = \alpha$ and $\mathbb{P}[Y_n = 1] = 1 - \alpha$ for $0 < \alpha < 1$ [23]. The 1D renewal Eq. (A.13) becomes

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

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

Setting $x = 0^{\pm}$ in Eqs. (A.29), summing the results and rearranging recovers equation (A.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 $\sigma = (1-\alpha)/\alpha$.

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

Let us return to the setup of Fig. 6.1. 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

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

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

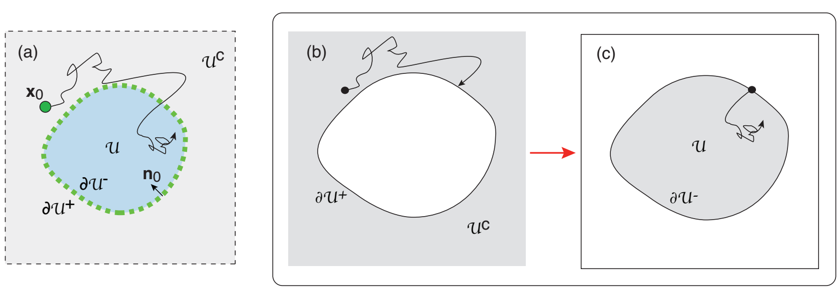

Fig. 6.3: Decomposition of (a) snapping out BM into two partially reflected BMs corresponding to (b) $\mathbf{X}_t \in \mathcal{U}^c$ and (c) $\mathbf{X}_t \in \mathcal{U}$, respectively.

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

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

together with the initial condition $\rho(\mathbf{x},0) = g(\mathbf{x})$. We wish to derive the higher-dimensional version of the renewal equations (A.12) by sewing together partially reflected BMs in the domains $\mathcal{M}$ and $\mathcal{M}^c$, see Fig. 6.3.

A.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. 6.3(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

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

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

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

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:

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

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 $\widehat{\ell}$ [17]. That is, the particle is absorbed somewhere on $\partial\mathcal{M}^-$ at the stopping time

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

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

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

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

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

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

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. 6.3(b). Given the local time

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

and stopping time

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

one finds that the marginal density

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

satisfies the Robin boundary value problem (BVP)

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

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

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

A.2.2 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. (A.39) with respect to time t:

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

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

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. 6.4. 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. (A.40a) with respect to all $\mathbf{x}\in\mathcal{C}^+(\varepsilon,\sigma)$ and use the divergence theorem:

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

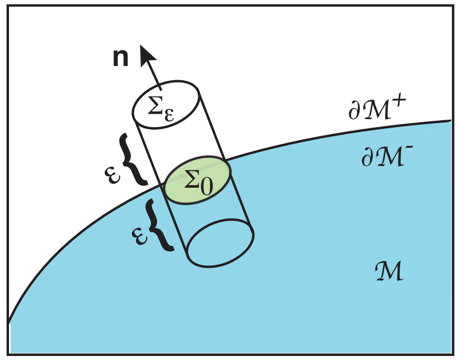

Fig. 6.4: Cylinder construction across the semipermeable membrane. See text for details.

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. (A.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

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

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 (A.40b), we deduce that

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

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

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

The extra terms on the right-hand side of Eqs. (A.43) and (A.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 [12]

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

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

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

we have

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

Hence,

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

by the standard symmetry property of Green's functions.

A.2.3 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. (A.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 [18], 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 [27]. First, let

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

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

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

The first term on the right-hand side of Eqs. (A.50a) and (A.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 (A.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. (A.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. (A.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(A.50a,b) with respect to time t gives

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

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

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

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

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

Taking the normal derivative of Eqs. (A.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

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

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

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

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

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

Subtracting this pair of equations, we find that

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

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

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

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. 6.1.

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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)

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

Laplace transforming both sides using the convolution theorem gives

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

Summing the geometric series leads to the closed expression

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

Note, in particular, that

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

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 [1, 2] 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 [1]. 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 [3, 4], 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

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

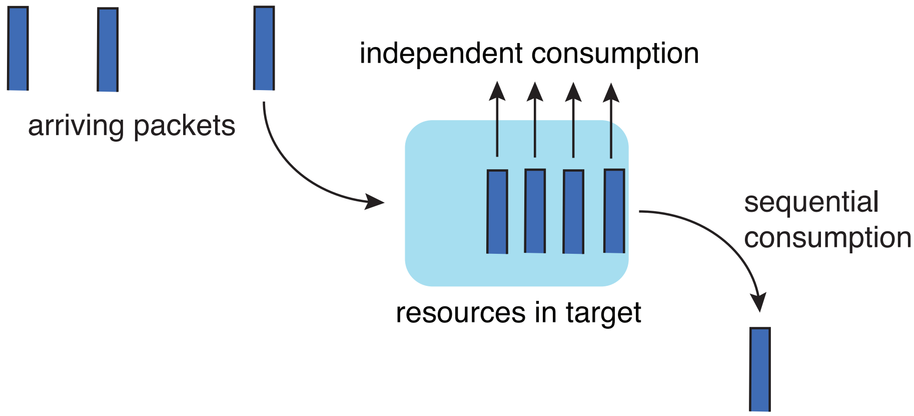

Fig. 7.1: Accumulation and consumption of resources in a target. The sequential delivery of packets of resources leads to an accumulation of resources in the target. In a sequential consumption model, resources are used in the order they are received (first-in-first-out policy). In an independent consumption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

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

where

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

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 $\mathbf{p} = \mathbf{p}\mathbf{K}$ 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

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

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

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

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

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

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

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

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

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

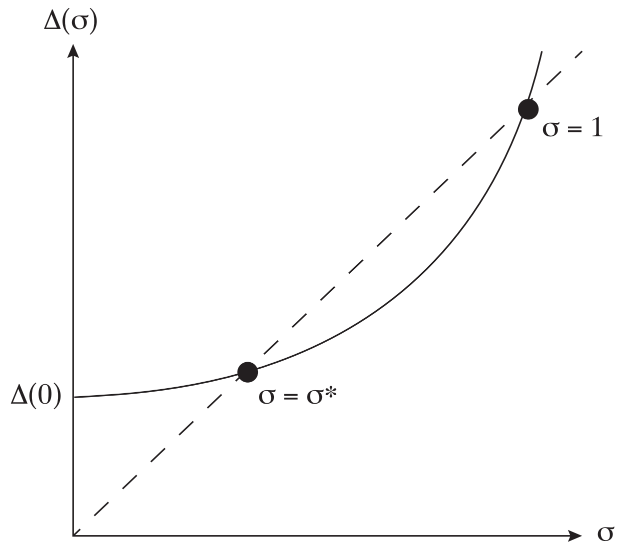

Fig. 7.2: Graphical construction of solutions to equation (B.17) for $\rho < 1$.

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. **??** 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

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

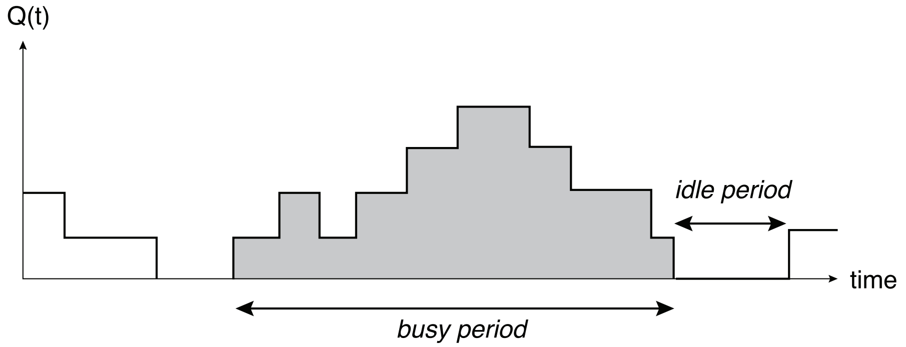

Fig. 7.3: Schematic illustration of the busy period and the idle period of a single queueing cycle. The total waiting time during the busy period is equal to the shaded area under the curve.

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 [**?**, **?**]:

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

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 resettingh 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

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

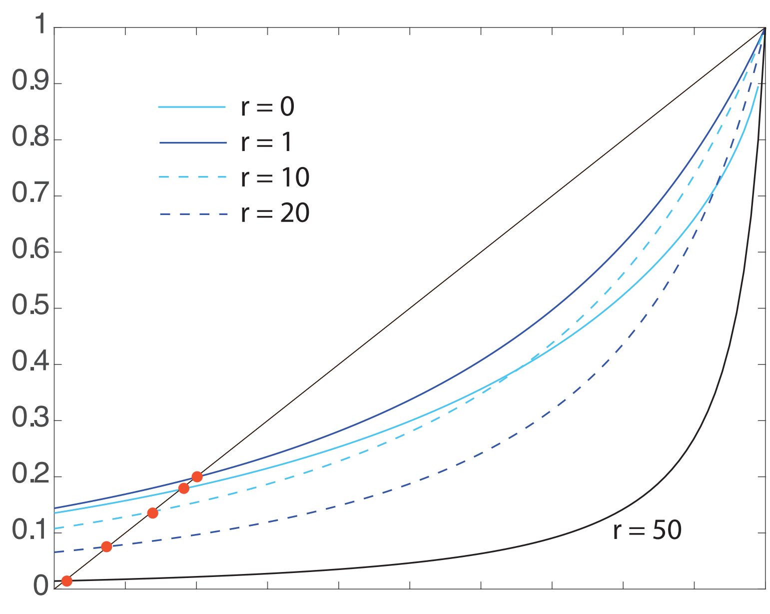

Fig. 7.4: Function $\Delta(\sigma)$ for diffusion with resetting on the half-line. $x_0 = D = 1$ $\lambda = 1 = \Delta_0$

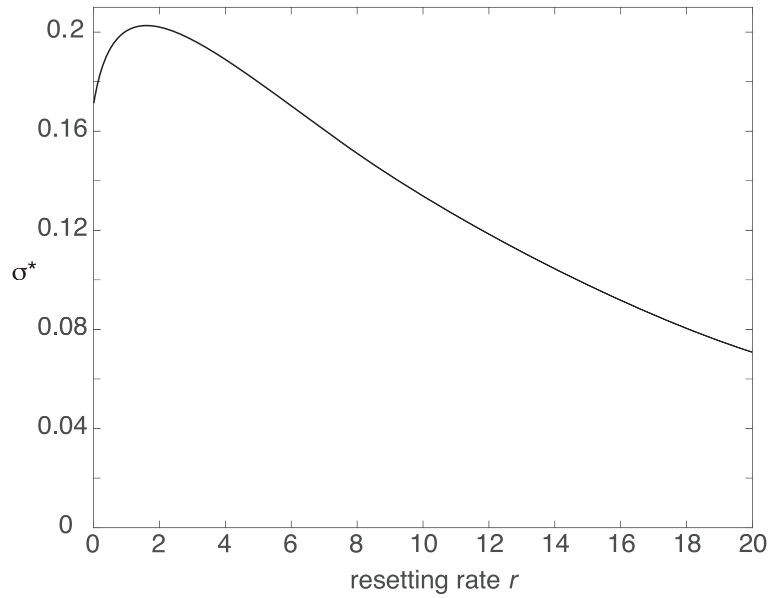

Fig. 7.5: Corresponding plot of σ^* vs r

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

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

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