Chapter 9

Markov Jump Processes

In this chapter we consider a different kind of continuous time Markov process. A Markov jump process evolves through a sequence of exponentially distributed in time changes in its position, between which it is constant. We will give a precise definition of the Markov jump processes we consider including in the special case of chemical kinetics as well as consider certain the limiting behaviors of such models.

9.1 Poisson processes

We will build all of the processes considered in this section out of a single simple process that will play a role similar to the role played by Brownian motion in Chapter ??. That basic building block is the Poisson process, which is an example of a counting process, i.e. it is a *r.c.l.l.* integer valued process $N^{(t)}$ with $N^{(0)} = 0$ that is constant between (random) times $0 = S_0 < S_1 < S_2 \cdots$ at which $N^{(S_k^-)} = \lim_{t \to S_k^-} N^{(t)} = N^{(S_k)} - 1$. A Poisson process is a counting process with independent, stationary increments, i.e. if $s_1 < t_1 < s_2 < t_2$ then $\triangle_{s_1}^{t_1} N$ and $\triangle_{s_2}^{t_2} N$ are independent and the distribution of $\triangle_t^{t+s} N$ is independent of t.

Just as we saw that the requirement that a Brownian motion has independent increments and is continuous implied that those increments should be

Gaussian, the seemingly innocent properties defining a Poisson process, have somewhat severe implications. To see this fix an integer n and let $N_n^{(t)}$ be the number of time intervals $((k-1)/n, k/n]$ for $k \leq nt$ that contain at least one jump in the Poisson process $N^{(t)}$. Appealing to the independence and stationarity of the increments of $N^{(t)}$ we find that

$$\mathbf{P}\left[N^{(1)} = 0\right] = \mathbf{P}\left[N_n^{(1)} = 0\right] = (1 - p_n)^n$$

where $p_n = \mathbf{P}\left[N^{(1/n)} > 0\right]$. Therefore np_n converges to $\lambda = -\log \mathbf{P}\left[N^{(1)} = 0\right]$ (which also implies that $\lfloor nt \rfloor$ converges to λt). As a result we find that

$$\lim_{n\to\infty} \mathbf{P}\left[N_n^{(t)} > 0\right] = 1 - e^{-\lambda t}.$$

Now notice that $\mathbf{P}\left[S_1 \leq t\right] = \mathbf{P}\left[N^{(t)} > 0\right]$ and therefore that

$$\mathbf{P}\left[N_n^{(t)} > 0\right] \leq \mathbf{P}\left[S_1 \leq t\right] \leq \mathbf{P}\left[N_n^{(t+1/n)} > 0\right].$$

The bounds in the last display imply that

$$\mathbf{P}\left[S_1 \leq t\right] = 1 - e^{-\lambda t}.$$

In other words, the time of the first jump is exponentially distributed with parameter t. By the independence and stationarity of the increments of $N^{(t)}$, the times between jumps, $R_\ell = S_\ell - S_{\ell-1}$ are all independent $Exponential(\lambda)$ random variables. The fact that

$$\mathbf{P}\left[N^{(t)} = k\right] = \frac{(\lambda t)^k e^{-\lambda t}}{k!}$$

then follows after noticing that

$$\begin{aligned}\mathbf{P}\left[N^{(t)} \geq k\right] &= \mathbf{P}\left[\sum_{\ell=1}^{k} R_\ell \leq t\right] \\ &= \int_{\sum_{\ell=1}^{k} r_\ell \leq t} \lambda^k e^{-\lambda \sum_{\ell=1}^{k} r_\ell} dr_1 dr_2 \cdots dr_k.\end{aligned}$$

Before moving on, observe that the fact that $N^{(t)}$ is a $Poisson(\lambda t)$ random variable implies that $\mathbf{E}\left[N^{(t)}\right] = \lambda t$.

Notice that $N^{(t)}$ cannot be a martingale unless it is constant with probability 1 because it is non-decreasing. Nonetheless, martingales prove a useful concept in the context of Poisson processes. Assume that the Poisson process $N^{(t)}$ is adapted to the filtration $\mathcal{F}_t$ and that $\triangle_t^{t+s} N$ is independent of $\mathcal{F}_t$ for all $s, t > 0$. Consistent with our vocabulary from the chapter when these properties hold we say that $N^{(t)}$ is compatible with $\mathcal{F}_t$. Letting $M^{(t)} = N^{(t)} - \lambda t$ we find that for $s < t$,

$$\mathbf{E}\left[M^{(t)} \,|\, \mathcal{F}_s\right] = M^{(s)} + \mathbf{E}\left[M^{(t)} - M^{(s)} \,|\, \mathcal{F}_s\right] = M^{(s)} + \mathbf{E}\left[M^{(t)} - M^{(s)}\right]$$

where we have used the fact that $M^{(t)} - M^{(s)}$ is independent of $\mathcal{F}_s$. Using the fact that $\mathbf{E}\left[N^{(t)}\right] = \lambda t$, we conclude that $M^{(t)}$ is an $\mathcal{F}_t$-martingale. In fact, any counting process $N^{(t)}$ compatible with $\mathcal{F}_t$ that is also an $\mathcal{F}_t$-martingale must be a Poisson process with intensity λ.

We can use the martingale characterization of a Poisson process to generalize the definition. For a non-negative process $\lambda^{(t)}$ adapted to a filtration $\mathcal{F}_t$, we will refer to $N^{(t)}$ as the Poisson process with intensity $\lambda^{(t)}$ if $N^{(t)}$ is a counting process compatible with $\mathcal{F}_t$ and

$$M^{(t)} = N^{(t)} - \int_0^t \lambda^{(s)} ds$$

is an $\mathcal{F}_t$-martingale. It turns out that these more general Poisson processes can be expressed in terms of the simple unit intensity ($\lambda = 1$) Poisson processes we started with. Indeed, suppose that $Y^{(t)}$ is a unit rate Poisson process compatible with some filtration $\mathcal{G}_t$ and let

$$N^{(t)} = Y^{(\tau_t)}$$

where $\tau_t = \int_0^t \lambda^{(s)} ds$. Then $N^{(t)}$ is a counting process and is compatible with the filtration $\mathcal{F}_t = \mathcal{G}_{\tau_t}$. Moreover, for $s < t$,

$$\mathbf{E}\left[N^{(t)} - \tau_t \,|\, \mathcal{F}_s\right] = \mathbf{E}\left[M^{(\tau_t)} \,|\, \mathcal{G}_{\tau_s}\right]$$

where $M^{(t)} = Y^{(t)} - t$. Recalling that $M^{(t)}$ is a $\mathcal{G}_t$ martingale, we conclude that $N^{(t)}$ is a $\mathcal{F}_t$ martingale and therefore a Poisson process with intensity $\lambda^{(t)}$.

9.2 Markov jump processes

In this section we will use our general definition of a Poisson process to define a general set of continuous time Markov processes that evolve by occasional jumps through space. We will assume that our process evolves via a finite set of displacements, i.e. if $X^{(t)} \neq X^{(t^-)}$ then

$$X^{(t)} - X^{(t^-)} \in \{\zeta_\ell\}_{\ell=1}^{\infty}$$

for some set of vectors $\zeta_\ell \in \mathbb{R}^d$. The process $X^{(t)}$ will be *r.c.l.l.* and will satisfy

$$\mathbf{P}\left[\triangle_t^{t+h} X = \zeta_\ell \,|\, \mathcal{F}_t\right] = \lambda_\ell^{(t)}(X^{(t)})h + o(h) \tag{9.1}$$

where each $\lambda_\ell^{(t)}$ is continuous in time and space and satisfies $\sum_{\ell=1}^{\infty} \lambda_\ell(x) < \infty$.

Given a sequence of independent unit rate Poisson processes, Y_ℓ, we can define a process with these properties by setting

$$X^{(t)} = x + \sum_{\ell=1}^{\infty} N_\ell^{(t)} \zeta_\ell \tag{9.2}$$

where $N_\ell^{(t)} = Y_\ell^{(\tau_t^\ell)}$ with $\tau_t^\ell = \int_0^t \lambda_\ell^{(s)}(X^{(s)})ds$. Like a stochastic differential equation, (9.2) defines the process $X^{(t)}$ only implicitly because $X^{(t)}$ appears on both sides of the equation. Unlike for stochastic differential equations, we can solve (9.2) explicitly and thereby easily demonstrate the existence of $X^{(t)}$ solving the equation. We will introduce two representations of solutions to (9.2) in the next section.

Assuming that $X^{(t)}$ solves (9.2), observe that

$$\triangle_t^{t+h} X = \sum_{\ell=1}^{\infty} \triangle_{\tau_t^\ell}^{\tau_{t+h}^\ell} Y_\ell \, \zeta_\ell.$$

The probability that the ℓth Poisson process, $Y_\ell^{(\tau_t^\ell)}$, jumps in the interval $(t, t+h]$ is

$$\int_0^{\tau_{t+h}^\ell - \tau_t^\ell} e^{-s} ds = 1 - e^{-\int_t^{t+h} \lambda_\ell^{(s)}(X^{(s)})ds}$$

Taking the limit $h \to 0$, we find that this probability becomes $\lambda_\ell^{(t)}(X^{(t)})h + o(h)$. Moreover, when $Y_\ell^{(\tau_t^\ell)}$ jumps, $X^{(t)}$ changes by exactly ζ_ℓ. On the other

hand, the probability that any pair of processes, $Y_\ell^{(\tau_t^\ell)}$ and $Y_j^{(\tau_t^j)}$, jump in the interval $(t, t+h]$ is $\mathcal{O}(h^2)$. Consequently, (9.1) holds for any process satisfying (9.2).

Now suppose that $0 = S_0 < S_1 < S_2 < \cdots$ are the transition times of $X^{(t)}$ and let $k_t = \max\{k : S_k \le t\}$. Then, for any function f we can write

$$f(X^{(t)}) = f(x) + \sum_{k=1}^{k_t} \left(f(X^{(S_k)}) - f(X^{(S_{k-1})}) \right)$$

Note that this expression can be rewritten as

$$f(X^{(t)}) = f(x) + \sum_{\ell=1}^{\infty} \int_0^t \left(f(X^{(s^-)} + \zeta_\ell) - f(X^{(s^-)}) \right) dN_\ell^{(s)}$$

(recall that the differential of a step function is a Dirac delta function). Writing $M_\ell^{(t)} = N_\ell^{(t)} - \tau_t^\ell$, we find that

$$f(X^{(t)}) = f(x) + \sum_{\ell=1}^{\infty} \int_0^t \lambda_\ell^{(s)}(X^{(s)}) \left(f(X^{(s)} + \zeta_\ell) - f(X^{(s)}) \right) ds + \sum_{\ell=1}^{\infty} \int_0^t \left(f(X^{(s^-)} + \zeta_\ell) - f(X^{(s^-)}) \right) dM_\ell^{(s)}. \quad (9.3)$$

Since each $M_\ell^{(t)}$ is an $\mathcal{F}_t$-martingale, the term

$$\sum_{\ell=1}^{\infty} \int_0^t \left(f(X^{(s^-)} + \zeta_\ell) - f(X^{(s^-)}) \right) dM_\ell^{(s)}$$

is also an $\mathcal{F}_t$-martingale. Note the similarity between (9.3) and the integral form of Itô s formula for stochastic differential equations. There we found that the change in some function of a diffusion process $X^{(t)}$ could be expressed as a sum of a standard integral (ds) and an integral with respect to a martingale. Also as in the SDE setting, the integrand in the integral ds is the generator of the Markov process. For $X^{(t)}$ defined by (9.2), when the λ_ℓ depend only on position, the generator is defined by

$$\mathcal{L}f(x) = \sum_{\ell=1}^{\infty} \lambda_\ell(x) \left(f(x + \zeta_\ell) - f(x) \right).$$

Now fix a point y and consider the equation

$$\mathbf{E}\left[f(X^{(t)})\right] = f(x) + \int_0^t \mathbf{E}\left[\mathcal{L}f(X^{(s)})\right] ds$$

with $f(x) = \mathbf{1}_{\{y\}}(x)$. We find that if $p^{(t)}(y) = P_x\left[X^{(t)} = y\right]$ then

$$\begin{aligned} p_y^{(t)} &= p_y^{(0)} + \int_0^t \sum_{\ell=1}^{\infty} \mathbf{E}\left[\lambda_\ell(X^{(s)})\left(\mathbf{1}_{\{y-\zeta_\ell\}}(X^{(s)}) - \mathbf{1}_{\{y\}}(X^{(s)})\right)\right] ds \\ &= p_y^{(0)} + \int_0^t \sum_{\ell=1}^{\infty} \lambda_\ell(y-\zeta_\ell)p_{y-\zeta_\ell}^{(s)} - \lambda_\ell(y)p_y^{(s)} ds \end{aligned}$$

so that $p_y^{(t)}$ solves the so-called master equation

$$\frac{d}{dt}p_y^{(t)} = \sum_{\ell=1}^{\infty} \lambda_\ell(y-\zeta_\ell)p_{y-\zeta_\ell}^{(t)} - \lambda_\ell(y)p_y^{(t)}.$$

9.3 Simulating Markov jump processes

In this section we give several recipes to generate exact solutions to the equation

$$X^{(t)} = x + \sum_{\ell=1}^{\infty} N_\ell^{(t)}\zeta_\ell \tag{9.4}$$

where $N_\ell^{(t)} = Y_\ell^{(\tau_\ell^{(t)})}$ with $\tau_\ell^{(t)} = \int_0^t \lambda_\ell^{(s)}(X^{(s)})ds$ and the Y_ℓ are independent, unit intensity Poisson processes. We will assume that $\lambda_\ell^{(t)}(x) > 0$ for all t and x.

Because $X^{(t)}$, is constant between jumps, we can enumerate the discontinuities of $X^{(t)}$ as $0 = S^{(0)} < S^{(1)} < S^{(2)} < \cdots$. Suppose that we have already simulated up to time $S^{(j-1)}$ and let $T_\ell^{(j)}$ be the first time after time $\tau_\ell^{(S^{(j-1)})}$ that process $Y_\ell^{(t)}$ jumps. Note carefully that $S^{(j-1)}$ is a time measured from the perspective of $X^{(t)}$ while $T_\ell^{(j)}$ is a time measured from the perspective of $Y_\ell^{(t)}$ and while $S^{(j-1)}$ was a jump time for $X^{(t)}$, $\tau_\ell^{(S^{(j-1)})}$ may not have been a jump time for $Y_\ell^{(t)}$.

Suppose that ℓ_* is the index of the transition in $X^{(t)}$ occurring at time $S^{(j)}$, i.e.

$$X^{(S^{(j)})} - X^{(S^{(j)^-})} = \zeta_{\ell_*}.$$

Because the next jump time for $X^{(t)}$ corresponds (appropriately transformed) to the next jump time for $Y_{\ell_*}^{(t)}$, we can write

$$\int_{S^{(j-1)}}^{S^{(j)}} \lambda_{\ell_*}^{(s)}(X^{(s)})ds = T_{\ell_*}^{(j)} - \tau_{\ell_*}^{(S^{(j-1)})}.$$

Since $X^{(t)}$ is constant on the time interval $[S^{(j-1)}, S^{(j)})$ the last expression can be rewritten as

$$G_{\ell_*}(S^{(j)}) = T_{\ell_*}^{(j)} - \tau_{\ell_*}^{(S^{(j-1)})}. \tag{9.5}$$

where, for each ℓ we have defined the function

$$G_\ell(s) = \int_{S^{(j-1)}}^{s} \lambda_\ell^{(s)}(X^{(S^{(j-1)})})ds.$$

The important feature of Equation (9.5) is that the only unknown quantities appearing there is $S^{(j)}$ and ℓ_*. Because the $\lambda_\ell^{(t)}$ are positive, each G_ℓ is invertible and we can define the times

$$S_\ell^{(j)} = G_\ell^{-1}(T_\ell^{(j)} - \tau_\ell^{(S^{(j-1)})}).$$

Note that from (9.5), $S^{(j)} = G_{\ell_*}^{-1}(T_{\ell_*}^{(j)} - \tau_{\ell_*}^{(S^{(j-1)})})$. The times $S_\ell^{(j)}$ can be computed for each ℓ by either exact or numerical integration. Moreover, since $S^{(j)}$ is the time of the next jump in $X^{(t)}$, the unknown quantities $S^{(j)}$ and ℓ_* are identified by

$$S^{(j)} = \min_\ell S_\ell^{(j)} = S_{\ell_*}^{(j)}.$$

The preceding arguments suggest the following algorithm. Begin with a sequence of exponential random variables $R_\ell^{(1)}$ and set $S^{(0)} = 0$ and $X^{(0)} = x$. Assuming that we have generated $X^{(t)}$ up to the last jump time $S^{(j-1)}$ and that the next jump time $T_\ell^{(j)}$ after time $\tau_\ell^{(S^{(j-1)})}$ is known for each $Y_\ell^{(t)}$,

`1. For each` ℓ `compute`

$$S_\ell^{(j)} = G_\ell^{-1}(T_\ell^{(j)} - \tau_\ell^{(S^{(j-1)})}).$$

2. Set $\ell_* = \arg\min_\ell S_\ell^{(j)}$ and $S^{(j)} = S_{\ell_*}^{(j)}$.

3. Set $X^{(S^{(j)})} = X^{(S^{(j-1)})} + \zeta_{\ell_*}$.

4. Set $T_{\ell_*}^{(j+1)} = T_{\ell_*}^{(j)} - \ln(U)$ where U is a $Uniform(0,1)$ random variable.

5. For $\ell \neq \ell_*$ set $T_\ell^{(j+1)} = T_\ell^{(j)}$.

Before we move on to describing our second exact simulation scheme, observe that if $\lambda_\ell(x)$ happens to be independent of time, then

$$G_\ell(s) = (s - S^{(j-1)})\,\lambda_\ell(X^{(S^{(j-1)})})$$

so that

$$G_\ell^{-1}(r) = S^{(j-1)} + \frac{r}{\lambda_\ell(X^{(S^{(j-1)})})}$$

and

$$S_\ell^{(j)} = S^{(j-1)} + \frac{T_\ell^{(j)} - \tau_\ell^{(S^{(j-1)})}}{\lambda_\ell(X^{(S^{(j-1)})})}.$$

We now introduce an alternative scheme known alternatively as the Gillespie scheme, the stochastic simulation scheme, or kinetic Monte Carlo. The scheme is can be used to generate exact solutions to (9.4) when the λ_ℓ are independent of time. To derive the scheme we first have to consider some properties of the exponential distribution. Suppose that R_ℓ are independent random variables with R_ℓ drawn from the exponential distribution with rate λ_ℓ. Let ℓ_* be the index of the smallest of the R_ℓ. Then

$$\mathbf{P}\left[R_{\ell_*} > t\right] = \prod_\ell \mathbf{P}\left[R_\ell > t\right] = e^{-t\sum_\ell \lambda_\ell}.$$

Since the function $\mathbf{P}\left[R_{\ell_*} > t\right]$ completely defines the distribution of the random variable R_{ℓ_*} and since an exponential random variable R with rate λ satisfies $\mathbf{P}\left[R > t\right] = e^{-\lambda t}$, we can conclude that R_{ℓ_*} is an exponential random variable with rate $\sum_\ell \lambda_\ell$.

Now consider the distribution of the index ℓ_* of the minimum of the sequence of exponential random variables,

$$\mathbf{P}\left[\ell_* = j\right] = \mathbf{P}\left[R_j < \min_{\ell \neq j} R_\ell\right].$$

Using the independence of the R_ℓ to write the quantity on the right hand side of the last equation as an integral we find that

$$\begin{aligned}\mathbf{P}\left[\ell_* = j\right] &= \int_0^\infty \mathbf{P}\left[t < \min_{\ell \neq j} R_\ell\right] e^{-\lambda_j t} dt \\ &= \int_0^\infty e^{-t\sum_{\ell \neq j}\lambda_\ell} \lambda_j e^{-\lambda_j t} dt \\ &= \frac{\lambda_j}{\sum_\ell \lambda_\ell}.\end{aligned}$$

Returning to Equation (9.4), notice that when the $\lambda_\ell(x)$ do not depend on t, at any time the time to the next jump of $X^{(t)}$ is the minimum of a set of exponential random variables with rates $\lambda_\ell(X^{(t)})$, i.e. the minimum of the times to the next jumps of the $N_\ell^{(t)}$. Thus we can sample the next jump time by generating a random variable from $Exponential\left(\sum_\ell \lambda_\ell(X^{(t)})\right)$. We can then set $\ell_* = j$ with probability $\lambda_j(X^{(t)})/\sum_\ell \lambda_\ell(X^{(t)})$ and set the jump in $X^{(t)}$ equal to ζ_{ℓ_*}. Summarizing this simulation scheme, assume that we have generated $X^{(t)}$ up to (and including) the $(j-1)$st jump time $X^{(S^{(j-1)})}$. Then we can

1. Generate an exponential random variable R with rate $\sum_\ell \lambda_\ell(X^{(S^{(j-1)})})$.
2. Set $S^{(j)} = S^{(j-1)} + R$.
3. Select ℓ_* by setting $\ell_* = j$ with probability
$$\mathbf{P}\left[\ell_* = j\right] = \frac{\lambda_j}{\sum_\ell \lambda_\ell}.$$
4. Set $X^{(S^{(j)})} = X^{(S^{(j-1)})} + \zeta_{\ell_*}$.

When there are only a small number of possible values of the rates (though there may be many different ζ_ℓ), Gillespie's algorithm can be substantially more accurate than the next reaction method. The advantage stems from a rearrangement of the scheme so that, after grouping the set of possible jumps according to their rates (so that all ζ_ℓ in a single group correspond to the same rate), one can simply select the group corresponding to the next jump and then pick a ζ_ℓ uniformly from that group. Only rates that change groups

as a result of the jump need be updated, resulting in a dramatic decrease in computational effort between each jump for some problems.

Finally, we consider a scheme that generates an approximate solution to (9.4) but can be more efficient than the next reaction method or Gillespie's algorithm. Consider the equation

$$X_h^{(t)} = x + \int_0^t \sum_\ell Y_\ell^{(\tau_{h,\ell}^{(t)})}$$

where, for $t \in [kh, (k+1)h)$,

$$\tau_{h,\ell}^{(t)} = h \sum_{j=0}^{k-1} \lambda^{(jh)}(X_h^{(jh)}) + (t - kh)\lambda^{(kh)}(X_h^{(kh)}).$$

This scheme is called the τ-leap scheme. Notice its similarity with the Euler-Maruyama discretization for SDE. The τ-leap method only updates $X_h^{(t)}$ every h units of time and when $X_h^{(t)}$ changes its increments can involve multiple ζ_ℓ.

9.4 Stochastic chemical kinetics

We now consider some specific examples of the general jump Markov processes we have defined. These models describe the interaction of "species" (atoms, molecules, enzymes, viruses, bacteria etc.) which we will label using letters (e.g. A, B, C, etc.). The interactions are described via "reactions," of the general form

$$\sum_j \alpha_{\ell j} A_j \to \sum_j \alpha'_{\ell j} A_j, \tag{9.6}$$

where the $\alpha_{\ell j}$ and $\alpha'_{\ell j}$ are non-negative integers. The relationship in the last display describes the ℓth reaction, in which, $\alpha_{\ell j}$ units of species A_j are consumed for each j and $\alpha'_{\ell j}$ units of A_j are produced. The species appearing on the left hand side of (9.6) with positive α_{kj} are called reactants and the species appearing on the right hand side with positive α'_{kj} are called products. For example, the reaction

$$A + B \to C$$

says that a unit each of the reactant species A and B combine (and are consumed) in producing a unit of the product species C. The reactions

$$\{\} \to A \quad \text{or} \quad A \to \{\}$$

(i.e. $\alpha_{\ell j} = 0$ or $\alpha'_{\ell j} = 0$ for all j) says, respectively, that units of species A are introduced to or removed from the system. The symbol

$$A + B \rightleftharpoons C$$

is a shorthand signifying the presence of both reactions $A + B \to C$ and $C \to A + B$.

In this setting, equation (9.2) describes the evolution $X_j^{(t)}$ of the number of copies (the so called copy number) of species j present in the system. In terms of the notation we have just introduced, the possible jumps of $X^{(t)}$ are of the form

$$(\zeta_\ell)_j = \alpha'_{\ell j} - \alpha_{\ell j}$$

and the intensity of the ℓth Poisson process $Y_\ell^{(t)}$, $\lambda_\ell(X^{(t)})$, is the rate at which the ℓth reaction,

$$\sum_j \alpha_{\ell j} A_j \to \sum_j \alpha'_{\ell j} A_j,$$

occurs.

In many applications the intensities for each reaction are determined by so called "mass action kinetic," in which one assumes that the ℓth reaction is as likely to occur involving any possible distinct combination of copies of the reactant species involved in the reaction. In other words, one can imagine that each combination of copies of the reactant species involved in reaction ℓ carries its own independent exponential clock with a fixed rate κ_ℓ so that the total reaction rate is

$$\lambda_\ell(x) = \kappa_\ell \prod_j \alpha_{\ell j}! \begin{pmatrix} x_j \\ \alpha_{\ell j} \end{pmatrix}.$$

When mass action kinetics are assumed, the symbol

$$\sum_j \alpha_{\ell j} A_j \xrightarrow{\kappa_\ell} \sum_j \alpha'_{\ell j} A_j$$

completely describes the ℓth reaction, including its intensity. For example, the reaction $\{\} \xrightarrow{\kappa_\ell} A_1$ would have intensity $\lambda_\ell(x) = \kappa_\ell$, the reaction $A_1 \xrightarrow{\kappa_\ell} \{\}$ would have intensity $\lambda_\ell(x) = \kappa_\ell x_1$ the reaction $A_1 + A_2 \xrightarrow{\kappa_\ell} A_3$ would have intensity $\lambda_\ell(x) = \kappa_\ell x_1 x_2$, and the reaction $2A_1 \xrightarrow{\kappa_\ell} A_2$ would have intensity $\lambda_\ell(x) = \kappa_\ell x_1(x_1 - 1)$.

Example 27. *A model for enzyme kinetics involving a substrate S, an enzyme E, an enzyme-substrate complex SE, and a protein P,*

$$S + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} SE \xrightarrow{\kappa_3} P + E$$

represents the combination of substrate and enzyme into the enzyme-substrate complex, and the decomposition of that complex into a protein and and the enzyme. The model assumes mass-action kinetics so, if $X_1^{(t)}$ is the copy-number of the substrate, $X_2^{(t)}$ is the copy number of the enzyme, $X_3^{(t)}$ is the copy number of the enzyme-substrate complex, and $X_4^{(t)}$ is the copy number of the protein, then the rate of the $S + E \to SE$ reaction is $\kappa_1 x_1 x_2$, the rate of the $SE \to S + E$ reaction is $\kappa_2 x_3$, and the rate of the $SE \to P + E$ reaction $\kappa_3 x_3$.

The jumps for $X^{(t)}$ are

$$\zeta_1 = \begin{bmatrix} -1 \\ -1 \\ 1 \\ 0 \end{bmatrix}, \quad \zeta_2 = \begin{bmatrix} 1 \\ 1 \\ -1 \\ 0 \end{bmatrix}, \quad \textit{and} \quad \zeta_1 = \begin{bmatrix} 0 \\ 1 \\ -1 \\ 1 \end{bmatrix}.$$

Exercise 90. *Consider a set of species G, M, P, D, and B representing respectively, a gene, mRNA, a protein, a protein-dimer, and a gene bound to a protein-dimer, interacting via the reactions*

$$\begin{array}{ccc} G \xrightarrow{\kappa_1} G + M & M \xrightarrow{\kappa_2} M + P & M \xrightarrow{\kappa_3} \{\} \\ P \xrightarrow{\kappa_4} \{\} & 2P \xrightarrow{\kappa_5} D & D \xrightarrow{\kappa_6} \{\} \\ & G + D \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} B. & \end{array}$$

Assume that $X^{(t)}$ is the vector of copy numbers of G, M, P, D, and B and that $X^{(0)} = (1, 10, 50, 10, 0)$. Simulate one realization of $X^{(t)}$ up to time 10 using the next reaction method with rate constants $\kappa = (200, 10, 25, 1, 0.01, 1, 0, 0)$

and produce a single plot showing the trajectories of the mRNA, protein, and protein-dimer copy numbers. With this choice of reaction rates, reactions 7 and 8 do not occur. Reaction 7 in this system binds the gene and the protein-dimer. Since there is only 1 copy of the gene, once reaction 7 occurs (and before reaction 8 occurs), the copy number of G becomes 0 and therefore so does the rate of reaction 1. Without new mRNA being produced by reaction 1, reaction 3 slowly dissipates the mRNA in the system. As the amount of mRNA in the system dissipates, reaction 2 slows and the amount of the protein in the system also begins to dissipate (through reaction 4). Finally, as the amount of the protein decreases, the rate at which protein-dimers are created (by reaction 5) also slows and the protein-dimer also dispates (through reaction 6). Generate another similar figure using rate constants $\kappa = (200, 10, 25, 1, 0.01, 1, 2, 0.1)$ *and compare the two figures. Are the results what you would expect?*

9.5 Large copy number limits

For many chemical reaction networks it is reasonable to assume that the copy numbers of the various systems are very large. For example, Avogadro's number estimates the number of molecules in one mole of a substance as $N_A = 6.0221415 \times 10^{23}$. If the volume of the substance in question is V moles then the the number of molecules is $N_\nu = VN_A$. It common to keep track of the concentration $C^{(t)} = X^{(t)}/N_\nu$ of the various constituent species rather than their raw copy number $X^{(t)}$. In terms of $C^{(t)}$, Equation (9.2) becomes

$$C^{(t)} = C^{(0)} + \sum_{\ell=1}^{\infty} N_\nu^{-1} Y_\ell\left(\int_0^t \lambda_\ell^{(s)}(N_\nu C^{(s)})ds\right)\zeta_\ell \tag{9.7}$$

where, as usual, the Y_ℓ are independent, unit intensity Poisson processes.

It is also often reasonable to assume that the intensity functions $\lambda_\ell(x)$ are homogenous in the sense that

$$\lambda_\ell(N_\nu c) = N_\nu \lambda_\ell(c).$$

This happens, for example if the rate constant for the reaction $A_1 + A_2 \to A_3$ is proportional to N_ν^{-1} (i.e. it is inversely proportional to the volume of the

system) since, in this case,

$$\lambda_\ell(x) = \frac{\kappa}{N_\nu} x_1 x_2 = N_\nu \kappa c_1 c_2$$

when $c = x/N_\nu$. In this is the case the equation for $C^{(t)}$ becomes

$$C^{(t)} = C^{(0)} + \sum_{\ell=1}^{\infty} N_\nu^{-1} Y_\ell^{\left(N_\nu \int_0^t \lambda_\ell^{(s)}(C^{(s)})ds\right)} \zeta_\ell \tag{9.8}$$

We will assume that each intensity function is a smooth function. In particular this implies that for any $a > 0$,

$$|\lambda_\ell(x) - \lambda_\ell(y)| \leq K(a)\|x - y\|_2 \quad \text{for} \quad |x|, |y| \leq a$$

for some function $K(a)$. Note that this in turn implies that the function

$$F(x) = \sum_{\ell=1}^{\infty} \lambda_\ell(x)\zeta_\ell$$

satisfies the local Lipschitz condition

$$\|F(x) - F(y)\|_2 \leq \sum_{\ell} K(a)\|x - y\|_2 \|\zeta_\ell\|_2^2 \quad \text{for} \quad |x|, |y| \leq a.$$

We can rewrite (9.8) as

$$C^{(t)} = C^{(0)} + \int_0^t F(C^{(s)})ds + M^{(t)} \tag{9.9}$$

where

$$M^{(t)} = \sum_{\ell=1}^{\infty} N_\nu^{-1} M_\ell^{\left(N_\nu \int_0^t \lambda_\ell^{(s)}(C^{(s)})ds\right)} \zeta_\ell.$$

with

$$M_\ell^{(t)} = Y_\ell^{(t)} - t.$$

Recall that each of the $M_\ell^{(t)}$ are martingales, so $M^{(t)}$ is also a martingale.

Now define the ordinary differential equation

$$c^{(t)} = c^{(0)} + \int_0^t F(c^{(s)})ds \tag{9.10}$$

and note that (9.9) and the local Lipschitz property of F together imply that if

$$\tau_a = \inf\{t > 0 : \|C^{(t)}\|_2 \vee \|c^{(t)}\|_2 \geq a\}$$

then

$$\|C^{(t\wedge\tau_a)} - c^{(t\wedge\tau_a)}\|_2 \leq \|C^{(0)} - c^{(0)}\|_2 + K\int_0^{t\wedge\tau_a} \|C^{(s)} - c^{(s)}\|_2 ds + \|M^{(t\wedge\tau_a)}\|_2.$$

Now define the function $w^{(t)}$ by

$$w^{(t)} = \|C^{(0)} - c^{(0)}\|_2 + K\int_0^t \|C^{(s)} - c^{(s)}\|_2 ds.$$

Clearly $\|C^{(t)} - c^{(t)}\|_2 \leq w^{(t)} + \|M^{(t)}\|_2$. On the other hand

$$\frac{d}{dt}w^{(t)} \leq K\|C^{(t)} - c^{(t)}\|_2 \leq Kw^{(t)}$$

which in turn implies that

$$w^{(t)} \leq e^{Kt}\|C^{(0)} - c^{(0)}\|_2$$

so that

$$\|C^{(t\wedge\tau_a)} - c^{(t\wedge\tau_a)}\|_2 \leq e^{Kt}\|C^{(0)} - c^{(0)}\|_2 + \|M^{(t\wedge\tau_a)}\|_2.$$

Independence of the Y_ℓ implies that

$$\mathbf{E}\left[\|M^{(t\wedge\tau_a)}\|_2^2\right] = \sum_\ell N_\nu^{-2}\,\mathbf{E}\left[\left\|M_\ell^{\left(N_\nu\int_0^{t\wedge\tau_a}\lambda_\ell(C^{(s)})ds\right)}\zeta_\ell\right\|_2^2\right].$$

Using the fact that $\mathbf{E}\left[\left(M^{(t)}\right)^2\right]$ is the variance of $Y^{(t)}$ which (since $Y^{(t)}$ is $Poisson(t)$ distributed) is t, we find that

$$\begin{aligned}\mathbf{E}\left[\|M^{(t\wedge\tau_a)}\|_2^2\right] &= N_\nu^{-1}\sum_\ell \mathbf{E}\left[\int_0^{t\wedge\tau_a}\lambda_\ell(C^{(s)})ds\right]\|\zeta_\ell\|_2^2 \\ &\leq N_\nu^{-1}t\sup_{\substack{s\leq t\\ \|c\|_2\leq a}}\sum_\ell \lambda_\ell(c)\|\zeta_\ell\|_2^2.\end{aligned}$$

Noting then that

$$\mathbf{E}\left[\|C^{(t\wedge\tau_a)}-c^{(t\wedge\tau_a)}\|_2^2\right]\leq 2e^{Kt}\mathbf{E}\left[\|C^{(0)}-c^{(0)}\|_2^2\right]+2N_\nu^{-1}t\sup_{\substack{s\leq t\\ \|c\|_2\leq a}}\sum_\ell\lambda_\ell(c)\|\zeta_\ell\|_2^2$$

we find that, for any fixed t, $C^{(t\wedge\tau_a)}$ converges to $c^{(t\wedge\tau_a)}$ in the sense of mean squared error. By taking a large we can make τ_a arbitrarily large so that $C^{(t)}$ converges to $c^{(t)}$ for any finite time t. In other words, for N_ν large, the species concentrations, $C^{(t)}$, are governed by the ordinary differential equation (9.10).

We will now close this section with an analysis of the variations of the variations of $C^{(t)}$ around $c^{(t)}$. Define the process

$$V^{(t)}=\sqrt{N_\nu}\left(C^{(t)}-c^{(t)}\right).$$

Our analysis in the last section implies that if $\mathbf{E}\left[\|C^{(0)}-c^{(0)}\|_2^2\right]\sim N_\nu^{-1}$ (as one would expect), then

$$\mathbf{E}\left[\|V^{(t\wedge\tau_a)}\|_2^2\right]\leq Kt$$

for some constant K. In other words, we neither expect $V^{(t)}$ to vanish or explode in the large N_ν limit. The process $V^{(t)}$ satisfies the equation

$$V^{(t)}=V^{(0)}+\sqrt{N_\nu}\int_0^t\left(F(C^{(s)})-F(c^{(s)})\right)ds+\sqrt{N_\nu}M^{(t)}.$$

Because F is a smooth function, this last equation can be rewritten as

$$V^{(t)}=V^{(0)}+\int_0^t DF(c^{(s)})V^{(s)}ds+\sqrt{N_\nu}M^{(t)}+\mathcal{O}\left(N_\nu^{-1/2}\left(V^{(t)}\right)^2\right).$$

Since the bounds we have already established show that the last term is small when N_ν is large, it will be omitted from what follows. Without that term, the last equation describes $V^{(t)}$ as a continuous function of $M^{(s)}$ for $s\leq t$. On the other hand

$$\sqrt{N_\nu}M^{(t)}=\frac{1}{\sqrt{N_\nu}}\sum_{\ell=1}^\infty M_\ell^{\left(N_\nu\int_0^t\lambda_\ell^{(s)}(C^{(s)})ds\right)}\zeta_\ell$$

and the processes $N_\nu^{-1/2}M_\ell^{\left(\int_0^t\lambda_\ell(C^{(s)})ds\right)}$ are martingales with initial condition 0 and have discontinuities only of size $N_\nu^{-1/2}$. They have limiting quadratic

variation

$$\left[N_\nu^{-1/2} M_\ell^{\left(\int_0^\cdot \lambda_\ell(C^{(s)})ds\right)}, N_\nu^{-1/2} M_\ell^{\left(\int_0^\cdot \lambda_\ell(C^{(s)})ds\right)}\right]^{(t)} = \int_0^t \lambda_\ell(c^{(s)})ds.$$

In fact, using the general result on diffusion limits in Chapter ??, we find that

$$N_\nu^{-1/2} M_\ell^{\left(\int_0^t \lambda_\ell(C^{(s)})ds\right)} \to W_\ell^{\left(\int_0^t \lambda_\ell(C^{(s)})ds\right)}$$

in distribution where each W_ℓ is an independent Brownian motion.

Exercise 91. *Use the result in Section* **??** *to show that $N_\nu^{-1/2} M_\ell^{(t)}$ converges in distribution to a Brownian motion.*

So we conclude that, in the limit of large N_ν, $V^{(t)}$ converges in distribution to a solution of the linear stochastic differential equation

$$V^{(t)} = V^{(0)} + \int_0^t DF(c^{(s)})V^{(s)}ds + \sum_\ell \int_0^t \sqrt{\lambda_\ell(c^{(s)})}\, dW_\ell^{(s)} \zeta_\ell.$$

Exercise 92. *Solve the above SDE to obtain a formula for $V^{(t)}$ in the large N_ν limit. Evaluate* $\mathbf{E}\left[V^{(t)}\left(V^{(t)}\right)^T\right]$, *the asymptotic covariance of $C^{(t)}$.*

9.6 Bibliography