10.1 Diffusion approximation

The first step is to set \( f_a(n/\Omega)P(n,t) \rightarrow f_a(x)p(x,t) \) with \( x = n/\Omega \) treated as a continuous vector so that

\[
\prod_{i=1}^{K} e^{-S_{ia} h(x)} = h(x - S_{a}/\Omega)
\]

\[
= h(x) - \Omega^{-1} \sum_{i=1}^{K} S_{ia} \frac{\partial h}{\partial x_i} + \frac{1}{2\Omega^2} \sum_{i,j=1}^{K} S_{ia} S_{ja} \frac{\partial^2 h(x)}{\partial x_i \partial x_j} + O(\Omega^{-3})
\]

Carrying out a Taylor expansion of the master equation to second order in \( 1/\Omega \), along similar lines to the birth-death master equation of lecture 3, then yields a multivariate FP equation:

\[
\frac{\partial p}{\partial t} = -\sum_{i=1}^{K} M_{ij} \frac{\partial p(y)}{\partial y_j} + \frac{1}{2} \sum_{i,j=1}^{K} D_{ij} \frac{\partial^2 p(y)}{\partial y_i \partial y_j} ,
\]

(10.1)

where

\[
A_i(x) = \sum_{a=1}^{R} S_{ia} f_a(x), \quad D_{ij}(x) = \sum_{a=1}^{R} S_{ia} S_{ja} f_a(x).
\]

(10.2)

The system-size expansion works particularly well when the underlying deterministic system (9.10) has a unique stable fixed point since, after a transient phase, the dynamics consists of Gaussian-like fluctuations of order \( 1/\sqrt{\Omega} \) about the fixed point. Therefore, suppose that the deterministic system (9.10), written as

\[
\frac{dx_i}{dt} = A_i(x),
\]

has a unique stable fixed point \( x_* \) for which \( A_i(x_*) = 0 \), and introduce the Jacobian matrix \( M \) with

\[
M_{ij} = \left. \frac{\partial A_i}{\partial x_j} \right|_{x=x_*}
\]

(10.3)

Perform the change of variables

\[
x_i(t) = x_i^* + y_i(t)/\sqrt{\Omega},
\]

and substitute into the master equation (9.11). Under the approximations

\[
A_i(x) \approx A_i(x^*) + \frac{1}{\sqrt{\Omega}} \sum_{j=1}^{K} M_{ij} y_j, \quad D_{ij}(x) \approx D_{ij}(x^*) \equiv D_{ij},
\]

we obtain the following FP equation for \( \tilde{p}(y,t) = p(x^* + y/\sqrt{\Omega},t) \) (after dropping \( \tilde{\cdot} \) on \( \tilde{p} \)):

\[
\frac{\partial \tilde{p}}{\partial t} = -\sum_{i=1}^{K} M_{ij} \frac{\partial \tilde{p}(y,t)}{\partial y_j} + \frac{1}{2} \sum_{i,j=1}^{K} D_{ij} \frac{\partial^2 \tilde{p}(y,t)}{\partial y_i \partial y_j},
\]

(10.4)
Ornstein-Uhlenbeck (OU) process. Equation (10.4) is the FP equation for the multivariate form of the OU process with $D$ a constant diffusion matrix. A number of important results thus hold:

1. The solution of the FP equation is a Gaussian distribution for all times.

2. Define the mean and covariance according to

$$m_i(t) = \langle y_i(t) \rangle = \int_{-\infty}^{\infty} y_i p(y,t) dy_1 \ldots dy_K,$$

and

$$\Sigma_{ij}(t) = \langle [y_i(t) - \langle y_i(t) \rangle][y_j(t) - \langle y_j(t) \rangle] \rangle.$$

Since the coefficients in the FP equation are at most linear in $y$, one can derive explicit differential equations for the various moments by multiplying both sides by factors of $y$ and integrating by parts.

3. The first moment equation takes the form

$$\frac{dm_i}{dt} = \sum_{j=1}^{K} M_{ij} m_j(t), \quad (10.5)$$

which recovers the deterministic kinetic equation (9.10), after linearizing about the fixed point $x^*$. If we choose the initial condition $x = x^*$ then $m_i(t) = 0$ for all $t$, which we assume below.

4. The covariance matrix $\Sigma(t)$ with components $\Sigma_{ij}(t)$ evolves according to the matrix equation

$$\frac{d\Sigma(t)}{dt} = M\Sigma(t) + \Sigma(t)M^\top + D, \quad (10.6)$$

where $M^\top$ indicates the matrix transpose of $M$, that is, $M_{ij}^\top = M_{ji}$.

5. Since $x^*$ is a stable fixed point, the Jacobian $M$ has eigenvalues with negative real part, and $\Sigma(t) \to \Sigma_0$ where $\Sigma_0$ is the stationary covariance matrix satisfying the Ricatti equation

$$M\Sigma_0 + \Sigma_0 M^\top + D = 0 \quad (10.7)$$

This can be interpreted as an example of a fluctuation-dissipation relation. That is, the Jacobian $M$ characterizes the rate of approach to the steady state and thus represents the local damping or dissipation of fluctuations. On the other hand, the diffusion matrix $D$ characterizes the size of Gaussian fluctuations about trajectories approaching the steady-state, see Fig. 38.
10.2 Example: Translational bursting

As our first application of the system-size expansion, we consider a stochastic version of the autoregulatory network shown in Fig. 23. The corresponding kinetic equations are

\[ \frac{dx_1}{dt} = -\gamma x_1 + \kappa g(x_2), \quad \frac{dx_2}{dt} = \kappa_p x_1 - \gamma_p x_2, \]

where \( x_1(t) \) and \( x_2(t) \) denote the concentrations of mRNA and protein molecules at time \( t \), respectively. The parameters \( \gamma, \gamma_p \) represent the degradation rates, \( \kappa_p \) represents the translation rate of proteins, and \( \kappa g(x) \) represents the nonlinear feedback effect of the protein on the transcription of mRNA.

Suppose that there are \( N_1(t) = n_1 \) mRNA and \( N_2(t) = n_2 \) proteins at time \( t \). The corresponding master equation for the probability distribution \( P = P(n_1,n_2,t) \) takes the explicit form

\[ \frac{dP}{dt} = \kappa \Omega g(n_2/\Omega)P(n_1-1,n_2,t) + \gamma (n_1+1)P(n_1+1,n_2,t) + \kappa_p n_1 P(n_1,n_2-1,t) + \gamma_p (n_2+1)P(n_1,n_2+1,t) - [\Omega \kappa g(n_2/\Omega) + \gamma n_1 + \kappa_p n_1 + \gamma_p n_2] P(n_1,n_2,t). \]

(10.9)

Carrying out the system-size expansion yields the FP equation

\[ \frac{\partial p}{\partial t} = -\sum_{i=1,2} \frac{\partial A_i(x)p(x,t)}{\partial x_i} + \frac{1}{2\Omega} \sum_{i,j=1,2} \frac{\partial^2 D_{ij}(x)p(x,t)}{\partial x_i \partial x_j}, \]

(10.10)

with

\[ A_1(x) = \kappa g(x_2) - \gamma x_1, \quad A_2(x) = \kappa_p x_1 - \gamma_p x_2. \]

and a diagonal diffusion matrix \( D \) with non-zero components

\[ D_{11} = \kappa g(x_2) + \gamma x_1, \quad D_{22} = \kappa_p x_1 + \gamma_p x_2. \]

Linearizing the corresponding Langevin equation about the unique fixed point by setting \( X_i(t) = x_i^* + \Omega^{-1/2} Y_i(t) \), shows that \( Y_i(t) \) is an OU process, whose stationary covariance matrix \( \Sigma \) satisfies the matrix equation

\[ M \Sigma + \Sigma M^T = -BB^T \equiv -D, \]
Figure 5.5: Burstiness of protein synthesis. A) Stochastic simulation the minimal model of protein synthesis (Eq. 5.27). Both the red and the blue curve have the same mean ($\mu_p = 50$), but distinctly different variance. The difference is captured by the burstiness; ($\lambda_m; \lambda_p$) = (0.01; 0.2) [blue] and (0.01; 0.2) [red]. The degradation rates are the same for both: $\gamma_1 = 5$ mins and $\gamma_p^{-1} = 50$ mins. B) Burstiness can be observed experimentally. Trapping individual E. coli cells in a microfluidic chamber, it is possible to observe the step-wise increase of $\beta$-gal off the lacZ gene. [Cai L, Friedman N, Xie XS (2006) Stochastic protein expression in individual cells at the single molecule level. Nature 440:358-362].

with

$$M = \begin{pmatrix} -\gamma & \mu \\ \kappa_p & -\gamma_p \end{pmatrix}, \quad D = \begin{pmatrix} \kappa_p (x_2^*) + \gamma x_1^* & 0 \\ 0 & \kappa_p x_1^* + \gamma_p x_2^* \end{pmatrix}, \quad \mu = \kappa_p g'(x_2^*).$$

Note that $\mu > 0$ for an activator and $\mu < 0$ for a repressor.

The solution of the matrix equation yields

$$\Sigma_{22} = \left[ 1 + \frac{b}{1 + \eta} \right] x_2^*,$$

where

$$b = \frac{\kappa_p}{\gamma}, \quad \phi = -\frac{\mu}{\gamma_p}, \quad \eta = \frac{\gamma_p}{\gamma}.$$

Here $b$ is the burst size, $\eta$ is the ratio of degradation rates, and $\phi$ describes the strength and sign of the feedback. Finally, making the identifications $\text{var}[N_2] = \Omega \Sigma_{22}$ and $\langle N_2 \rangle = \Omega x_2^*$, the Fano factor for proteins is

$$\frac{\text{var}[N_2]}{\langle N_2 \rangle^2} = 1 + \frac{b}{1 + \eta} \frac{1 - \phi}{1 + b \phi},$$

Translational bursting has been observed experimentally, see Fig. 39.

**Effects of feedback.** The Fano factor of the autoregulatory feedback model is

$$\frac{\sigma_x^2}{x^*} = \frac{b + 1}{2} \frac{\gamma_p}{|b g'(x^*) - \gamma_p|}.$$
There are two distinct contributions to the deviation from Poisson-like statistics. First, the factor 
\((1 + b)/2 > 1\) for \(b > 1\) so that protein bursting tends to increase fluctuations. Second, the factor 
\(\Lambda = \gamma_p/|bg'(x^*) - \gamma_p|\) satisfies 
\(0 < \Lambda < 1\) for negative feedback \((g'(x^*) < 0)\), that is, negative feedback suppresses fluctuations.

What happens if there is positive feedback and the deterministic network exhibits bistability? We 
expect the noise to induce switching between the two stable fixed points. However, these will tend 
to be rare events since the noise is \(O(1/\sqrt{\Omega})\). This motivates the next example

### 10.3 The stochastic simulation algorithm (SSA)

The SSA, which was originally developed by Gillespie, is an efficient numerical scheme for generating 
effect sample paths of a discrete Markov process whose probability distribution evolves according 
to a chemical master equation. In the following we have to keep track of the system size \(\Omega\) and 
note that \(x = n/\Omega\).

The starting point for constructing the SSA is to define a new probability function \(p(\tau, a|n, t)\), which is the probability, given \(N(t) = n\), that the next reaction in the system will occur in the time interval \([t + \tau, t + \tau + \Delta \tau]\) and will be the reaction \(a\). From this perspective, both \(\tau\) and \(a\) are random variables conditioned on \(N(t) = n\). An analytical expression for \(p(\tau, a|n, t)\) can be obtained 
by introducing another probability function \(P_0(\tau|n, t)\), which is the probability, given \(N(t) = n\), that no reaction of any kind occurs in the time interval \([t, t + \tau]\). It follows from the definitions of \(P_0\) and the propensities \(f_a\) that \(P_0\) satisfies the equation

\[
P_0(\tau + d\tau|n, t) = P_0(\tau|n, t) \left[1 - \Omega \sum_{a=1}^{R} f_a(n/\Omega) d\tau \right],
\]

which is the product of the probability that no reaction occurs in \([t, \tau]\) and the probability that there are no transitions in the infinitesimal interval \([t + \tau, t + \tau + d\tau]\). Rearranging and taking the 
limit \(d\tau \to 0\) yields

\[
\frac{dP_0(\tau|n, t)}{d\tau} = -F(n)P_0(\tau|n, t), \quad F(n) = \Omega \sum_{a=1}^{R} f_a(n/\Omega).
\]

Under the initial condition \(P_0(0|n, t) = 1\), we have the solution

\[
P_0(\tau|n, t) = \exp(-F(n)\tau).
\]

We now note

\[
p(\tau, a|n, t)d\tau = P_0(\tau|n, t)\Omega f_a(n/\Omega)d\tau,
\]

which implies that \(p\) can be written in the form

\[
p(\tau, a|n, t) = F(n)\exp(-F(n)\tau) \frac{f_a(n/\Omega)}{\sum_b f_b(n/\Omega)}.
\]

Hence, \(\tau\) is an exponential random variable with mean and standard deviation \(1/F(n/\Omega)\), while \(a\) is 
a statistically independent integer random variable with \(x\)-dependent probability \(f_a(n/\Omega)/\sum_b f_b(n/\Omega)\).
Implementing the SSA. One exact Monte Carlo method for generating samples of the random variables \( \tau, a \) is to draw two random numbers \( r_1, r_2 \) from the uniform distribution on \([0, 1]\) with

\[
\tau = -\frac{1}{F(n)} \ln r_1 \quad (10.12a)
\]

\[
a = \text{the smallest integer for which } \Omega \sum_{a=1}^{a} f_a(n/\Omega) > r_2 F(n). \quad (10.12b)
\]

The direct method of implementing the SSA is as follows:

1. Initialize the time \( t = t_0 \) and the chemical state \( n = n_0 \)

2. Given the state \( n \) at time \( t \), determine the \( \Omega f_a(n/\Omega) \) for \( a = 1, \ldots, R \) and their sums \( F(n) \)

3. Generate values for \( \tau \) and \( a \) using equations (10.12a) and (10.12b)

4. Implement the next reaction by setting \( t \to t' = t + \tau \) and \( n_j \to n'_j = n_j + S_{ja} \).

5. Return to step 2 with \( (n, t) \) replaced by \( (n', t') \), or else stop.

There have been a variety of subsequent algorithms that differ in the implementation of step 2, including the next reaction method.

In many applications the mean time between reactions, \( 1/F(n) \), is very small so that simulating every reaction becomes computationally infeasible, irrespective of the version of the SSA is chosen. Gillespie introduced tau-leaping in order to address this problem by sacrificing some degree of exactness of the SSA in return for a gain in computational efficiency. The basic idea is to “leap” the system forward by a pre-selected time \( \tau \) (distinct from the \( \tau \) of the SSA), which may include several reaction events. Given \( N(t) = n, \tau \) is chosen to be large enough for efficient computation but small enough so that

\[
f_a(n/\Omega) \approx \text{constant in } [t, t + \tau) \text{ for all } a.
\]

Let \( \mathcal{N}(\lambda) \) denote a Poisson counting process with mean \( \lambda \). During the interval \([t, t + \tau)\) there will be approximately \( \mathcal{N}(\lambda_a) \) reactions of type \( a \) with \( \lambda_a = \Omega f_a(n/\Omega)\tau \). Since each of these reactions increases increases \( n_j \) by \( S_{ja} \), the state at time \( t + \tau \) will be

\[
N_j(t + \tau) = n + \sum_{a=1}^{R} \mathcal{N}_a(\Omega f_a(n/\Omega)\tau) S_{ja}, \quad (10.13)
\]

where the \( \mathcal{N}_a \) are independent Poisson processes. This equation is known as the tau-leaping formula.

However, there are two fundamental problems with the original formulation of tau-leaping. First, it is difficult to choose the appropriate value of \( \tau \) at each iteration of the algorithm - occasionally large changes in propensities occur that cause one or more components \( n_j \) to become negative. Second,
although tau-leaping becomes exact in the limit $\tau \to 0$, the inefficiency becomes prohibitive since the $R$ generated Poisson random numbers will be zero most of the time resulting in no change of state. These two issues have been addressed in various modifications in the tau-leaping procedure. Finally, note SSAs have also been developed for stochastic hybrid systems, which are defined in the next section.