So far we have focused on intrinsic noise associated with the production and degradation of mRNA and proteins. We neglected the effects of promoter noise by assuming that the binding/unbinding of transcription factor (TF) was much faster than these other processes. We now consider the former in more detail.

19.1 Feedforward gene network with promoter noise

Consider the simple gene regulatory network shown in Fig. 67, which consists of a gene that can be in one of two states, active or inactive. In the active state the gene produces protein \( X \) at a rate \( \kappa_p \), which subsequently degrades at a rate \( \gamma_p \), whereas no protein is produced in the inactive state.

Suppose that the switching rates \( k_\pm \) are finite but the expected number of proteins is sufficiently large (thermodynamic limit) so that we can represent the dynamics in terms of a continuous-valued protein concentration \( x \). Let \( M(t) \) denote the current state of the gene with \( M(t) = 1 \) (active) or \( M(t) = 0 \) (inactive). The concentration evolves according to the (piecewise) deterministic equation

\[
\frac{dx}{dt} = F_m(x) \equiv \kappa_p m - \gamma_p x, \tag{19.1}
\]

for \( M(t) = m \). (One could also have a nonzero protein production rate in both states.) The switching on and off of the gene is given by a two-state Markov process

\[
OFF \xrightleftharpoons[k_+]^{k_-} ON,
\]

with switching rates \( k_\pm \).

Let \( X(t) \) denote the stochastic protein concentration at time \( t \), and introduce the joint probability density

\[
p_m(x,t) \Delta x = \mathbb{P}[x < X(t) < x + \Delta x, M(t) = m].
\]

Figure 67: Simple example of a two-state gene regulatory network. The promoter transitions between an active state (bound by a transcription factor protein \( Y \)) and an inactive state with rates \( k_\pm \). The active state produces protein \( X \) at a rate \( \kappa_p \) and protein \( X \) degrades at a rate \( \gamma_p \).
It can be shown that $p_m(x,t)$ evolves according to a so-called Chapman-Kolmogorov (CK) equation

\[
\frac{\partial p_0}{\partial t} = -\frac{\partial}{\partial x}(-\gamma_p xp_0(x,t)) + k_-p_1(x,t) - k_+p_0(x,t) \tag{19.2a}
\]

\[
\frac{\partial p_1}{\partial t} = -\frac{\partial}{\partial x}([\kappa_p - \gamma_p x]p_1(x,t)) + k_+p_0(x,t) - k_-p_1(x,t), \tag{19.2b}
\]

with boundary conditions $p_1(0,t) = 0$ and $p_0(\kappa_p/\gamma_p,t) = 0$.

In the limit that the switching between active and inactive states is much faster than the protein dynamics, the probability that the gene is active rapidly converges to the steady-state $k_+/(k_+ + k_-)$ - the promoter is in quasiequilibrium ($\langle M(t) \rangle = \rho_1$) and we obtain the deterministic equation

\[
\frac{dx}{dt} = \kappa_p \rho_1 - \gamma_p x = \frac{\kappa_p k_+}{k_+ + k_-} - \gamma_p x. \tag{19.3}
\]

### 19.2 Steady-state solution and transcriptional bursting

We will characterize the long-time behavior of the system in terms of the steady-state solution, which satisfies

\[
\frac{d}{dx}(-\gamma_p xp_0(x)) = k_-p_1(x) - k_+p_0(x) \tag{19.4a}
\]

\[
\frac{d}{dx}([\kappa_p - \gamma_p x]p_1(x)) = k_+p_0(x) - k_-p_1(x). \tag{19.4b}
\]

The no-flux boundary conditions imply that $p_0(\kappa_p/\gamma_p) = 0$ and $p_1(0) = 0$. First, note that we can take $x \in [0, \kappa_p/\gamma_p]$ and impose the normalization condition

\[
\int_0^{\kappa_p/\gamma_p} [p_0(x) + p_1(x)]dx = 1.
\]

Integrating equations (19.4a) and (19.4b) with respect to $x$ then leads to the constraints

\[
\int_0^{\kappa_p/\gamma_p} p_0(x)dx = \frac{k_-}{k_- + k_+} = \rho_0, \quad \int_0^{\kappa_p/\gamma_p} p_1(x)dx = \frac{k_+}{k_- + k_+} = \rho_1. \tag{19.5}
\]

Here $\rho_n$ is the stationary distribution of the two-state Markov chain. Adding equations (19.4a) and (19.4b) we can solve for $p_0(x)$ in terms of $p_1(x)$ and then generate a closed differential equation for $p_1(x)$. Setting $\kappa_p/\gamma_p = 1$ for convenience, one finds that the total probability density $p(x) = p_0(x) + p_1(x)$ is given by

\[
p(x) = \frac{x^{k_+}/\gamma_p - 1(1-x)^{k_-}/\gamma_p - 1}{B(k_+/(k_p), k_-/\gamma_p)}, \tag{19.6}
\]

where $B(\alpha, \beta)$ is the Beta function:

\[
B(\alpha, \beta) = \int_0^1 t^{\alpha-1}(1-t)^{\beta-1}dt.
\]

In Fig. 68, we sketch $p(x)$, $0 < x < \kappa_p/\gamma_p$ for various values of $K_\pm = k_\pm/\gamma_p$. It can be seen that when the rates $k_\pm$ of switching between the active and inactive gene states are faster than the
rate of degradation $\gamma_p$ then the steady-state density is unimodal (graded), whereas if the rate of degradation is faster then the density tends to be concentrated around $x = 0$ or $x = 1$, consistent with a binary process. The latter scenario tends to occur in eukaryotic gene expression, for which the presence of nucleosomes and the packing of DNA-nucleosome complexes into chromatin generally make promoters inaccessible to the transcriptional machinery. Hence, transitions between open and closed chromatin structures, corresponding to active and repressed promoter states, can be quite slow.

The bimodal distribution corresponds to time-dependent fluctuations that exhibit translational bursting, as illustrated in Fig. 69.

Figure 68: Sketch of steady-state protein density $p(x)$ for a simple regulated network in which the promoter transitions between an active and inactive state at rates $k_{\pm}$. (a) Case $k_{\pm}/\gamma_p > 1$: there is a graded density that is biased towards $x = 0, 1$ depending on the ratio $k_{\pm}/k_-$. (b) Case $k_{\pm}/\gamma_p < 1$: there is a binary density that is concentrated around $x = 0, 1$ depending on the ratio $k_{\pm}/k_-$. 

Figure 69: (a) Unimodal distribution for relatively fast switching (1 minute). Bimodal distribution and translational bursting for slow switching (1 hour). [Adapted from Kaern et al. (2005).]
If we include both promoter and protein fluctuations, then we have to deal with the master equation

\[ \frac{dP}{dt} = \left[ k_+ m + k_- (1 - m) \right] P(1 - m, n, t) + \kappa_m P(m, n - 1, t) + \gamma_p (n + 1) P(m, n + 1, t) \\
- \left[ k_+ (1 - m) + k_- m + \kappa_m m + \gamma_p n \right] P(m, n, t). \] (19.7)

Since the transition rates are linear in \( n \) and \( m \), one could determine the means and variances by taking moments of equation (19.7). Here, we consider an alternative method, in which we treat the activation state \( M(t) \) of the gene as an upstream drive of gene expression (extrinsic noise), and use the theory of conditional expectations, whereby one first averages with respect to the intrinsic noise and then with respect to the extrinsic noise. The advantage of this method is that it can be applied to more general forms of time-dependent inputs. Furthermore, one is usually interested in the statistics of \( N(t) \) rather than \( M(t) \).

Suppose we condition on a particular realization of the stochastic process \( M(t) \), \( \sigma_t = \{ M(\tau), 0 \leq \tau \leq t \} \). First, define the conditional probability distribution \( \hat{P}_n(t) := \mathbb{P}[N(t) = n \cap N(0) = 0 | \sigma_t] \), which satisfies the master equation

\[ \frac{d\hat{P}_n(t)}{dt} = M(t)\kappa_p \hat{P}_{n-1}(t) + \gamma_p (n + 1) \hat{P}_{n+1}(t) - [M(t)\kappa_p + \gamma_p n] \hat{P}_n(t), \ n \geq 0. \] (19.8)

It follows that the mean and variance of \( N(t) \) condition on a particular realization \( \sigma_t \) are

\[ \mathbb{E}[N(t)|\sigma_t] = \chi(t), \quad \text{Var}[N(t)|\sigma_t] = \chi(t). \]

Given that \( \chi(t) \) is itself stochastic, the full system is an example of a doubly stochastic Poisson process. (There is also a Binomial component if \( N(0) > 0 \).)

From the tower property of expectation (see Handout I), we see that

\[ \mathbb{E}[N(t)] = \mathbb{E}[\mathbb{E}[N(t)|\sigma_t]] = \kappa_p \int_0^t \mathbb{E}[M(\tau)] e^{-\gamma_p (t-\tau)} d\tau. \] (19.10)

Suppose \( M(t) \) is a stationary process so that \( \mathbb{P}[M(t) = m] = \rho_m \) where \( \rho_m \) is the stationary distribution of the two-state Markov chain, see equation (19.5). Then

\[ \mathbb{E}[N(t)] = \frac{\kappa_p \rho_1}{\gamma_p} \left( 1 - e^{-\gamma_p t} \right) \xrightarrow{t \to \infty} \frac{\kappa_p \rho_1}{\gamma_p}. \] (19.11)

Similarly, from the law of total variance,

\[ \text{Var}[N(t)] = \mathbb{E}[\text{Var}[N(t)|\sigma_t]] + \text{Var}[\mathbb{E}[N(t)|\sigma_t]] \]
\[ = \mathbb{E}[N(t)] + \kappa_p^2 \int_0^t \int_0^t \mathbb{E}[(M(\tau') - \rho_1)(M(\tau'') - \rho_1)] e^{-\gamma_p (2t-\tau' - \tau'')} d\tau' d\tau. \]
From the analysis of a stationary dichotomous noise process,

\[ E[(M(\tau) - \rho_1)(M(\tau') - \rho_1)] = \rho_0 \rho_1 e^{-|\tau-\tau'|/\tau_c}, \quad \tau_c = \frac{1}{k_+ + k_-}. \]

so that, for \( \gamma_p \neq 1/\tau_c \),

\[
\int_0^t \int_0^t E[(M(\tau) - \rho_1)E[M(\tau') - \rho_1)]e^{-\gamma_p(2t-\tau-\tau')}d\tau'd\tau
= \rho_0 \rho_1 \int_0^t \int_0^t e^{-\gamma_p(2t-\tau-\tau')}e^{-|\tau-\tau'|/\tau_c}d\tau'd\tau
\]

\[
= 2\rho_0 \rho_1 \int_0^t -\gamma_p(2t-\tau-\tau')e^{-|\tau-\tau'|/\tau_c}d\tau'd\tau
= 2\rho_0 \rho_1 \frac{e^{-2\gamma_p t}}{\gamma_p + \tau_c} \left[ \frac{e^{2\gamma_p t} - 1}{2\gamma_p} + \frac{1 - e^{(\gamma_p-\gamma_c^{-1}) t}}{(\gamma_p-\gamma_c^{-1})} \right] \rightarrow_{t \rightarrow \infty} \frac{\rho_0 \rho_1}{\gamma_p(\gamma_p + \tau_c^{-1})}.
\]

We thus find that

\[
\lim_{t \rightarrow \infty} \text{Var}[N(t)] = \frac{\kappa_p \rho_1}{\gamma_p} + \frac{\rho_0 \rho_1}{\gamma_p(\gamma_p + k_+ + k_-)}.
\]

(19.13)

The first term on the right-hand side is the expected contribution from the Poisson process associated with protein fluctuations, whereas the second term is the contribution from promoter noise.

Now suppose we carry out a system-size expansion of the master equation for protein synthesis when the environment is in state \( n \). This leads to modified CK equations that describe the time evolution of the pdfs for the piecewise stochastic differential equation

\[
dX(t) = F_m(X)dt + \sqrt{\frac{D_m(X)}{\Omega}}dW(t)
\]

(19.14)

for \( M(t) = m \in \{0, 1\} \), \( \Omega \) the system size, and

\[
F_m(x) = \kappa_p m - \gamma_p x, \quad D_m(x) = \kappa_p m + \gamma_p x.
\]

(19.15)

We now have a combination of discrete environmental noise and continuous intrinsic molecular noise.

### 19.4 Noise-induced switching and Kramer’s formula

The above analysis can be generalized to the case of an autoregulatory network with positive feedback. The only difference is that the switching rate from the inactive to the active gene state becomes \( x \)-dependent: \( k_+ \rightarrow k_+(x) = k_+ x^2 \). It follows that

\[
\rho_1(x) = \frac{k_+(x)}{k_+(x) + k_-} = \frac{k_+ x^2}{k_+ x^2 + k_-} = \frac{x^2}{K + x^2}.
\]

In the deterministic limit \( \Omega \rightarrow \infty, k_\pm \rightarrow \infty \), we recover the rate equation

\[
\frac{dx}{dt} := A(x) = -\gamma_p x + \kappa_p \frac{x^2}{K + x^2}.
\]

(19.16)
Let us introduce the deterministic potential $U(x)$ by setting $A(x) = -dU/dx$. In the absence of noise, the dynamics can then be written as

$$\frac{dx}{dt} = -\frac{dU}{dx}, \quad (19.17)$$

The minima and maxima of the potential $U(x)$ correspond to stable and unstable fixed points of the deterministic dynamics, respectively. Hence the double well potential in Fig. 70(a) represents a bistable system with two stable fixed points $x_\pm$ separated by an unstable fixed point $x_0$. One can represent the dynamics in terms of a “ball rolling down the potential hill.” The final state depends on initial conditions.

If molecular noise is now included, then locally the system performs $O(1/\sqrt{\Omega})$ Gaussian-like fluctuations about one of the minima $x_\pm$. However, occasionally, a large fluctuation will push the system beyond the top of the hill at $x_0$ leading to a noise-induced transition to the other minimum. The effects of molecular noise can be captured by the FP equation

$$\frac{\partial p}{\partial t} = -\frac{\partial A(x)p(x,t)}{\partial x} + \frac{1}{2\Omega} \frac{\partial^2 D(x)p(x,t)}{\partial x^2}, \quad (19.18)$$

where

$$A(x) = bg(x) - \gamma p x, \quad D(x) = b^2 g(x) + \gamma p x, \quad g(x) = \frac{x^2}{K + x^2}.$$ 

This follows from applying the fast switching limit to the Langevin equation (19.14) with $D_m(x) \to D(x)$, $F_m(x) \to F(x)$ and $m \to \langle m \rangle = g(x)$.

Following the analysis of FPT problems, the effects of noise can then be visualized as stochastic trajectories moving along the associated potential $\Phi(x)$, see Fig. 70(b). Moreover, the mean rate of escape $\lambda_-$ from the metastable state $x_-$ to the metastable state $x_+$ is given by Kramer’s formula

$$\lambda_- = \frac{D(x_-)}{4\pi} \sqrt{|\Phi''(x_0)|} \Phi''(x_-) e^{-\Omega[\Phi(x_0) - \Phi(x_-)]} \quad (19.19)$$

Figure 70: (a) Deterministic double well potential $U(x)$ for autoregulatory network with positive feedback. Two stable fixed points $x_\pm$ are separated by an unstable fixed point $x_0$. (b) Effective potential (quasipotential) of the stochastic model, where noise can induce transitions between the two metastable states.
Figure 71: Stochastic trajectories moving along an energy landscape generated by the quasipotential of a two-dimensional bistable system such as the toggle switch.

Similarly, the mean rate of escape $\lambda_+$ from the metastable state $x_+$ to the metastable state $x_-$ is

$$\lambda_+ = \frac{D(x_+)}{4\pi} \sqrt{\frac{\Phi''(x_0)}{\Phi''(x_+)}} e^{-\Omega[\Phi(x_0) - \Phi(x_+)]}$$  \hfill (19.20)

A similar picture holds in higher-dimensional systems bistable systems such as the toggle switch, except now we have stochastic trajectories moving along an energy landscape as illustrated in Fig. 71. A major issue is how to extend the analysis to finite switching rates.