Exercises (lectures 9 and 10)

Problem 17. Protein bursting. Carry out the steps in the analysis of protein bursting in an autoregulatory repressor network. The matrix equation for the covariance matrix is

\[ M\Sigma + \Sigma M^T = -D, \]

with

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

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

1. Write down the equations in component form. Since \( \Sigma_{12} = \Sigma_{21} \), there are three independent equations.

2. Solve for \( \Sigma_{11} \) and \( \Sigma_{22} \) in terms of \( x_2^* \) and \( \Sigma_{12} \) and substitute into the remaining equation. (Use the fixed point equations \( \kappa g(x_2^*) = \gamma x_1^* \) and \( \kappa_p x_1^* = \gamma_p x_2^* \).)

3. After some algebra, express \( \Sigma_{12} \) in terms of \( x_2^* \), and hence show that

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

where

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

Problem 18. Linear noise approximation for a population of cells. Consider a population of \( n_{\text{max}} \) identical cells each with a single copy of the same gene. Let \( n_1(t) \) denote the number of active genes and \( n_2(t) \) the number of mRNA. Setting \( x_j = \langle n_j \rangle / \Omega \), where \( \Omega \) is the system size, the various reactions and the corresponding rate equations based on mass-action (valid in the limit \( \Omega \to \infty \)) are as follows:

1. Gene activation and inactivation

\[
n_1 \xrightarrow{k_+(n_{\text{max}}-n_1)} n_1 + 1, \quad n_1 \xrightarrow{k_-n_1} n_1 - 1, \quad \frac{dx_1}{dt} = k_+(x_{\text{max}} - x_1) - k_-x_1
\]

2. mRNA production and degradation

\[
n_2 \xrightarrow{\kappa n_1} n_2 + 1, \quad n_2 \xrightarrow{\gamma n_2} n_2 - 1, \quad \frac{dx_2}{dt} = \kappa x_1 - \gamma x_2.
\]
a) Write down the full master equation for the joint probability distribution $P(n_1, n_2, t)$.

b) Determine the stoichiometric coefficients and the propensities for the four single-step reactions.

c) Using part (b), determine the resulting two-dimensional Fokker-Planck equation for $p(x_1, x_2, t)$, and write down the corresponding Langevin equation.

d) Verify that in the thermodynamic limit $\Omega \to \infty$, we obtain the deterministic rate equations. Hence show that there is a unique stable fixed point $(x^*_1, x^*_2)$.

e) Linearizing the FP equation about the fixed point by setting $X_i(t) = x^*_i + \Omega^{-1/2}Y_i(t)$, and taking the large time limit shows that the stationary covariance matrix $\Sigma$ satisfies the equation

$$M\Sigma + \Sigma M^T = -D,$$

with

$$M = \begin{pmatrix} -(k_+ + k_-) & 0 \\ \kappa & -\gamma \end{pmatrix}, \quad D = \begin{pmatrix} 2k_- x^*_1 & 0 \\ 0 & 2\kappa x^*_1 \end{pmatrix}.$$ 

By solving the matrix equation for the covariance, obtain the following Fano factors:

$$\frac{\text{var}[n_1]}{\langle n_1 \rangle} = \frac{k_-}{k_+ + k_-} = 1 - \frac{\langle n_1 \rangle}{n_{\text{max}}},$$

$$\frac{\text{var}[n_2]}{\langle n_2 \rangle} = 1 + \frac{\langle n_2 \rangle}{\langle n_1 \rangle} \frac{\gamma}{k_+ + k_- + \gamma} \frac{\text{var}[n_1]}{\langle n_1 \rangle^2}.$$

Note that $\langle n_j \rangle = \Omega x^*_j$ and $\text{var}[n_j] = \Omega \Sigma_{jj}$. We immediately see that the presence of a transcription factor increases the Fano factor of mRNA above one.

**Problem 19. Clock gene network.** Consider the kinetic equations of the following clock gene model

$$\frac{dm}{dt} = \kappa K^m - \gamma \frac{m}{K_m + m},$$

$$\frac{dx_C}{dt} = \kappa_p m - \gamma_p \frac{x_C}{K_p + x_C} - k_1 x_C + k_2 x_N,$$

$$\frac{dx_N}{dt} = k_1 x_C - k_2 x_N.$$

a) Rewrite these equations in the canonical form

$$\frac{dx_i}{dt} = \sum_{a=1}^{6} S_{ia} f_a(x), \quad i = 1, \ldots, 3,$$

by determining the stoichiometric coefficients $S_{ia}$ and the propensity functions $f_a(x)$ with $x = (m, x_c, x_N)^\top$. 
b) Given the stoichiometric coefficients and propensities, calculate the drift and diffusion terms $A_i(x)$ and $D_{ij}(x)$, respectively, in the FP approximation of the master equation,

$$\frac{\partial p}{\partial t} = -\sum_{i=1}^{3} \frac{\partial A_i(x)p(x,t)}{\partial x_i} + \frac{1}{2\Omega} \sum_{i,j=1}^{3} \frac{\partial^2 D_{ij}(x)p(x,t)}{\partial x_i \partial x_j},$$

**Problem 20. Computer simulations.** Use the SSA to numerically investigate the following systems.

(a) The model of regulated transcription considered in problem 18. There are two discrete variables (number of active genes $n_1$, and number of mRNA molecules $n_2$) and four reactions (gene activation and deactivation, mRNA production and degradation). Take the parameter values $k_+ = 0.03 \text{ min}^{-1}, k_- = 0.2 \text{ min}^{-1}, \kappa = 10 \text{ min}^{-1}, \gamma = 0.2 \text{ min}^{-1}$ and consider the two cases $n_{\text{max}} = 10, n_{\text{max}} = 100$. Run the simulations for sufficient time to reach steady-state. Plot a histogram of $n_1(T)$ and $n_2(T)$ based on 100 simulations, say, where $T$ is the final time. Determine the mean and variance, and compare the numerical Fano factor with the theoretical expressions based on the diffusion approximation. [In this problem all factors of the system size $\Omega$ cancel, that is, $\Omega f_a(n/\Omega) = f_a(n).$]

(b) Consider a toggle switch with promoters states in quasiequilibrium, whose deterministic kinetic equations are given by

$$\frac{dx_1}{dt} = -x_1 + \frac{\kappa_p}{1 + x_2^2}, \quad \frac{dx_2}{dt} = -x_2 + \frac{\kappa_p}{1 + x_1^2}. \quad (12.16)$$

The latter is bistable for any $\kappa_p > 1$. What is the origin of the quartic powers? Determine the stoichiometric coefficients and the propensities. Run simulations of a stochastic version of the model, in which fluctuations in the number of protein molecules are taken into account. (Set the system size $\Omega = 1$.) Consider the cases $\kappa_p = 5, 50, 500, 5000, \text{ (and at least } 10,000 \text{ reaction steps for each).}$ Verify that the system exhibits bistability for $\kappa_p = 5000$, whereas noise dominates at $\kappa_p$ so there is no bistability. What happens for $\kappa_p = 50, 500$?

(c) The circadian clock model with stoichiometry and propensities obtained in problem 19. Use the following parameter values: $\kappa = 0.5 \text{ nM h}^{-1}, \gamma = 0.3 \text{ nM h}^{-1}, K_m = 2.0 \text{ nM}, K'_m = 0.2 \text{ nM}, \kappa_p = 2.0 \text{ h}^{-1}, \gamma_p = 1.5 \text{ nM h}^{-1}, K_p = 0.1 \text{ nM}, k_1 = k_2 = 0.2 \text{ h}^{-1}$. Take the system size $\Omega = 100$. Plot a sample trajectory of the number of mRNA $M$ and the number of cytosolic clock proteins $X_C$ as a function of time, and check that the oscillation period is around 22 hours. Compare with solutions of the deterministic kinetic rate equations. Also plot several sample trajectories in the $(M, X_C)$-phase-plane superimposed on the deterministic limit-cycle.

**Problem 21. Stochastic Brusselator model**

The classical Brusselator model consists of two chemical species $X$ and $Y$ interacting through the
following reaction scheme:

\[ \emptyset \xrightarrow{a} X , \quad X \xrightarrow{b} Y , \quad 2X + Y \xrightarrow{c} 3X , \quad X \xrightarrow{d} \emptyset \]

a) Let \( n_1(t) \) and \( n_2(t) \) denote the number of \( X \) and \( Y \) molecules at time \( t \), respectively, and take \( \Omega \) to be cell volume. Determine the stoichiometric coefficients and propensities of the four single-step reactions, and use this to construct the Brusselator master equation.

b) Use Gillespie’s SSA to simulate the stochastic Brusselator. Take parameter values (in time\(^{-1}\)) \( a = 50, \; b = 50, \; c = 1 \) and \( d = 5 \). Set the system size \( \Omega = 100 \). Take the initial conditions \( n_1 = 1000, \; n_2 = 2000 \). Plot both the solutions \( n_1(t), n_2(t) \) in the time domain, and in the phase-plane.

c) Now suppose that \( \Omega \) is sufficiently large so that we can carry out a system-size expansion of the master equation. Set \( c = d = 1 \). Linearize the resulting FP equation about the fixed point \((u^*_1, u^*_2)\), with \( u^*_1 = a, \; u^*_2 = b/a \), to obtain the multivariate FP equation for an OU process with

\[
\mathbf{M} = \begin{pmatrix} b - 1 & a^2 \\ -a^2 & -b \end{pmatrix},
\]

and

\[
\mathbf{D} = \begin{pmatrix} 2(b + 1)a & -2ba \\ -2ba & 2ba \end{pmatrix}.
\]

d) Using the results of part c), write down the Langevin equation for the stochastic Brusselator under the linear noise approximation. Show that the components of the spectrum are given by

\[
S_1(\omega) = 2a((1 + b)\omega^2 + a^4)\Gamma(\omega)^{-1}, \quad S_2(\omega) = 2ab(\omega^2 + 1 + b)\Gamma(\omega)^{-1},
\]

where

\[
\Gamma(\omega) = (a^2 - \omega^2)^2 + (1 + a^2 - b)^2\omega^2.
\]

**Problem 22. Noise-induced oscillations.** Consider a stochastic relaxation oscillator involving an activator and repressor. The activator enhances expression of both proteins, whereas the repressor acts by binding to the activator to form an inert complex. Let \( N_A, \; N_R \) and \( N_C \) denote the number of activator \( A \), repressor \( R \) and complex \( C \) molecules, respectively. Denotes the corresponding concentrations by \( x_A = N_A/\Omega \) etc. There are four reactions involving production and degradation of proteins with burst sizes \( b_A \) and \( b_R \):

\[
N_A \xrightarrow{f_A} N_A + b_A, \quad N_R \xrightarrow{f_R} N_R + b_R \\
N_A \xrightarrow{g_A} N_A - 1, \quad N_A \xrightarrow{g_A} N_A - 1
\]
with propensities

\[ f_A = \kappa_A \frac{x_A}{1 + x_A/K_A}, \quad f_R = \kappa_R \frac{x_R}{1 + x_R/K_R}, \quad g_A = \gamma_A x_A, \quad g_R = \gamma_R x_R. \]

There are two more reactions involving the formation of the complex, and degradation of the complex to \( R \) due to degradation of \( A \) within the complex:

\[ A + R \rightarrow C, \quad C \rightarrow R, \]

with propensities \( k_C x_A x_R \) and \( \gamma_A x_C \), respectively. It follows that the kinetic equations are

\[
\begin{align*}
\frac{dx_A}{dt} &= b_A f_A(x_A) - k_C x_A x_R - k_A x_A, \\
\frac{dx_R}{dt} &= b_R f_R(x_R) - k_C x_A x_R + k_A x_C - \gamma_R x_R, \\
\frac{dx_A}{dt} &= k_C x_A x_R - k_A x_C.
\end{align*}
\]

(a) Numerically simulate the deterministic system for the following parameter values:

\[ \kappa_A = 50, b_A = 5, \gamma_R = 5, b_R = 10, K_A = 0.5, K_R = 1, \gamma_A = 1, \gamma_R = 0.1, \alpha_0 = 0.1, k_C = 200. \]

Show that the system is excitable by running two simulations, one from the initial conditions \((x_A, x_R, x_C) = (0, 10, 35)\), and another from initial conditions \((x_A, x_R, x_C) = (5, 10, 35)\). What changes about the behavior if \( \gamma_R = 0.2 \)?

(b) Set the system size \( \Omega = 1 \). For the same parameter values as (a) with \( \gamma_R = 0.1 \) use Gillespie’s SSA to numerically run simulations of the stochastic version of the model based on the chemical master equation. Explain the observed differences in behavior between the deterministic and stochastic versions of the model.