Exercises (lectures 7 and 8)


a) Assuming that the concentration of mRNA is in quasiequilibrium, the unregulated and autoinhibitory models of lecture 10 become

\[
\frac{dx}{dt} = \alpha - \gamma p x, \quad \frac{dx}{dt} = \frac{\alpha}{1 + x/K} - \gamma p x,
\]

respectively, where \( \alpha = \kappa_p \kappa / \gamma \). Let \( x^* \) denote the fixed point protein concentration in either model, and define the network sensitivity by

\[
\Gamma = \frac{d \log x^*}{d \log \alpha} = \frac{\alpha}{x^* \, d\alpha}.
\]

Clearly \( \Gamma = 1 \) for the unregulated network. Determine \( x^* \) and \( \Gamma \) for the autoinhibitory network, and show that the latter has a smaller sensitivity.

b) Consider the kinetic equations for the autoregulatory repressor network:

\[
\frac{da}{dt} = \frac{\kappa K}{K + x^2} - \gamma a, \quad \frac{dx}{dt} = \kappa p a - \gamma p x.
\]

Let \( x^* \) be the unique fixed point of the network. By linearizing about the fixed point, determine the Jacobian matrix \( J \) and find the eigenvalues as functions of \( x^* \). Hence establish that \( x^* \) is linearly stable.

Problem 13. 3-state mutual repressor model. Consider a simplified mutual repressor model consisting of a single promoter with two operator sites \( OS_1 \) and \( OS_2 \) that bind to dimers of protein \( Y \) and protein \( X \), respectively (see Fig. 28 of lecture 11). If the dimer of one protein is bound to its site, then this represses the expression of the other protein. However, both sites cannot be occupied at the same time. Hence, the promoter can be in three states \( O_m, m = 0, 1, 2 \): no dimer is bound to the promoter \( (O_0) \); a dimer of protein \( Y \) is bound to the promoter \( (O_1) \); a dimer of protein \( X \) is bound to the promoter \( (O_2) \). Assuming that the number of proteins is sufficiently large, we have the transition scheme

\[
O_1 \xrightarrow{\beta K} O_0 \xrightarrow{\beta X^2} O_2,
\]

where \( \beta \) is a transition rate and \( K \) is a non-dimensional dissociation constant. Protein \( X \) (\( Y \)) is produced at a rate \( \kappa_p \) when the promoter is in the states \( O_{0,2} \) \((O_{0,1})\), and both proteins are degraded at a rate \( \gamma_p \) in all three states.

a) Write down the kinetic equations for the probability \( P_j(t) \) that the promoter is in state \( O_j \), \( j = 0, 1, 2 \) at time \( t \).

b) Assuming that the binding reactions are much faster than the rates of protein production and degradation, write down the quasi-steady-state solutions for \( P_j^* \).
c) Under the assumption of part b), show that the kinetic equations for the protein concentrations $x$ and $y$ are given by

$$\frac{dx}{dt} = -\gamma_p x + \kappa_p \frac{K + x^2}{x^2 + y^2 + K}$$
$$\frac{dy}{dt} = -\gamma_p y + \kappa_p \frac{K + y^2}{x^2 + y^2 + K}$$

d) Set $\gamma_p = \kappa_p = 1$. Show numerically that the deterministic system is bistable for $0 < K < K_c$ and monostable for $K > K_c$ for $K_c = 4/9$, by plotting the nullclines $\dot{x} = 0$ and $\dot{y} = 0$ in the $x - y$ plane.

**Problem 14. Hopf bifurcation.** Consider the planar model

$$\frac{dx}{dt} = \mu x + y - x(x^2 + y^2), \quad \frac{dy}{dt} = -x + \mu y - y(x^2 + y^2).$$

a) Determine the eigenvalues of the Jacobian at the origin $(0, 0)$ and show that the eigenvalues cross the imaginary axis as $\mu$ passes through zero.

b) Transforming to polar coordinates $x = r \cos \theta, y = r \sin \theta$ and using

$$\dot{r} = \frac{x\dot{x} + y\dot{y}}{r}, \quad \dot{\theta} = \frac{x\dot{y} - y\dot{x}}{r^2},$$

show that the equations can be rewritten as

$$\frac{dr}{dt} = r(\mu - r^2), \quad \frac{d\theta}{dt} = -1.$$  

Hence show that the system undergoes a Hopf bifurcation with respect to the parameter $\mu$.

**Problem 15. The Brusselator.** The Brusselator is an idealized model of an autocatalytic reaction, in which at least one of the reactants is also a product of the reaction. The model consists of two chemical species $X$ and $Y$ interacting through the following reaction scheme:

$$\phi \xrightarrow{a} X$$
$$X \xrightarrow{b} Y$$
$$2X + Y \xrightarrow{c} 3X$$
$$X \xrightarrow{d} \phi$$

These reactions describe the production and degradation of an $X$ molecule, an $X$ molecule spontaneously transforming into a $Y$ molecule, and two molecules of $X$ reacting with a single molecule of $Y$ to produce three molecules of $X$. The corresponding mass-action kinetic equations for $u_1 = [X], u_2 = [Y]$ are (after rescaling so that $c = d = 1$)

$$\frac{du_1}{dt} = a - (b + 1)u_1 + u_1^2 u_2,$$
$$\frac{du_2}{dt} = bu_1 - u_1^2 u_2.$$  

Determine the stability of the fixed point at $u_1^* = a, u_2^* = b/a$. Hence establish that the fixed point undergoes a Hopf bifurcation at the critical value $b = a^2 + 1$. 
Problem 16. Oscillations in NF-κB signaling.

There are a number of other cellular oscillators that are based on gene regulatory circuits, most of which have periods shorter than the circadian 24-hour cycle (ultradian oscillators). One well-known example is found in the nuclear localization of the NF-κB transcription factor, a key player in the response of mammalian cells to pathogens and stress.

In the absence of stimulation, NF-κB resides in the cytosol, since nuclear localization of NF-κB is inhibited by binding to IκB. On the other hand, following stimulation by cytokines, which are substances secreted by certain cells of the immune system, IκB kinase activity induces NF-κB to unbind, thus allowing it to enter the nucleus and initiate the expression of target genes, including its own inhibitor IκB. This generates a negative feedback loop that has a time delay between IκB transcription and translation. When this is combined with rapid IκB degradation, oscillations of NF-κB nuclear localization arise with a period in the range of 2–4 hours, depending on the cell type.

The NF-κB pathway exhibits a range of behaviors upon stimulation, including both damped and persistent oscillations, which can be understood in terms of the action of three distinct forms of the inhibitor (IκBα, IκBβ and IκBε), see Fig. 82. When all three of these forms are present in the cell, the pathway exhibits damped oscillations in response to stimulation (Figure 1.5A). However, when cells are modified so that certain IκB proteins are absent, the response changes. When IκBα is absent, cells show pathologically high activity, whereas when both IκBβ and IκBε are absent, cells respond to stimuli with sustained oscillations in NF-κB activity. This difference in behavior is a consequence of the fact that, of the three IκBα forms, only IκBα receives positive feedback from

Consider a model involving a single form of IκB. There are three state variables: $x$ (concentration of nuclear NF-κB), $y$ (concentration of cytosolic IκB), and $y_m$ (concentration of IκB mRNA). Conservation of NF-κB means that the cytosolic concentration of NF-κB is $1 - x_n$. The dimensionless
kinetic equations are

\[
\frac{dx}{dt} = A \frac{1 - x(t)}{\epsilon + y(t)} - B x(t) y(t) \frac{\delta + x(t)}{\delta + x(t)},
\]

\[
\frac{dy}{dt} = y_m(t) - I(t) \frac{(1 - x(t)) y(t)}{\epsilon + y(t)}
\]

\[
\frac{dy_m}{dt} = x(t)^2 - y_m(t),
\]

where \(I(t)\) represents an extracellular signal.

a) Numerically simulate the above system of ODES using the following parameter values: \(A = 0.007, B = 954.5, \delta = 0.029, \epsilon = 5 \times 10^{-5}\) and constant input \(I = 0.035\). Verify that \(x(t)\) exhibits spike-like oscillations. Given that the model is expressed in time units \(0.017^{-1}\) minutes (determined by degradation rate of NF-κB), what is the period of oscillations?

b) Show that the oscillations become smoother when \(I\) is tripled.

c) The pair of isoforms IκB\(\beta\) and IκB\(\epsilon\) that are not dependent on NF-κB for synthesis, can be incorporated into the model by including a constant background rate \(c_0\) of IκB production, that is,

\[
\frac{dy_m}{dt} = c_0 + x(t)^2 - y_m(t).
\]

Verify that when \(c_0 = 0.005\), the system still exhibits sustained oscillations but with diminished amplitude. What happens when \(c_0\) is increased to 0.02?