Math 5110: Homework Assignment 12
Due on December 6, 2005

1. The Smolen et al model for a biological clock tracks three variables: P is amount of PER protein, C is the total amount of the protein dCLOCK, and F is amount of free dCLOCK. These proteins have the following interactions. F promotes the production of P, but represses the production of C. P binds to C and blocks both of the functions of F. Assuming that both the promotion and suppression act with time delays, they give the equations

$$\begin{aligned} \frac{dP}{dt} &= v_{sp}\frac{F(t-\tau_1)}{k_1+F(t-\tau_1)} - k_{dp}P \\ \frac{dC}{dt} &= v_{sc}\frac{k_2}{k_2+F(t-\tau_2)} - k_{dc}C. \end{aligned}$$

   To close the system, they assume that $F = C - P$ when positive, and $F = 0$ otherwise.

   a. Show that this system has an equilibrium with positive F.

   b. Assume that $\tau_1 = \tau_2 = 0$, so that there are no delays. Show that the equilibrium is stable.

   c. Instead of assuming that $F = C - P$, suppose that P and F bind with reaction constant k_3 and unbind with constant k_{-3}. Find the quasi-steady state value of F in terms of C and P.

   d. IF YOU HAVE EXTRA TIME ON YOUR HANDS, check whether the mechanism in part **c** can destabilize the equilibrium (if it exists) in the absence of a delay.

2. The Kurosawa et al model with a nuclear and cytoplasmic compartment tracks three variables: M represents that amount of mRNA that makes the PER protein, R represents the concentration of PER protein in the cytoplasm, and P represents the concentration of PER protein in the nucleus. These state variables have the following interactions. P represses the production of M (which occurs in the nucleus). New PER protein is produced as R in the cytoplasm, and diffuses back and forth from the nucleus, in addition to degrading while in the cytoplasm. They derive the equations

$$\begin{aligned} \frac{dM}{dt} &= \frac{1}{1+(\frac{P}{h})^n} - aM \\ \frac{dR}{dt} &= sM - (\delta+u)R + vP \\ \frac{dP}{dt} &= uR - vP. \end{aligned}$$

   a. Describe the meaning of each and every parameter.

   b. Creation of PER in the cytoplasm introduces a distributed delay of its entry into the nucleus. Suppose for simplicity that this is a fixed delay of length τ. In particular, suppose that P at time t is produced at a rate proportional to the amount of M at time $t-\tau$, but that it degrades at rate δ. Write a system of equations for M and P.

   c. Linearize this system around the equilibrium (M^*, P^*) by setting $M(t) = M^* + x(t)$ and $P(t) = P^* + y(t)$.

   d. Make the ansatz that $x(t) = x_0 e^{\lambda t}$ and $y(t) = y_0 e^{\lambda t}$. Substitute into your linearized system to find the characteristic equation for λ. HINT: Figure out how to use linear algebra to get rid of x_0 and y_0.

   e. IF YOU HAVE EXTRA TIME ON YOUR HANDS, check whether it is possible for this system to have pure imaginary roots.

   f. IF YOU HAVE MORE EXTRA TIME ON YOUR HANDS, find the exact form of the distributed delay under the assumptions of the differential equation model.