Read: Chapter 2 of *Mathematical Concepts and Methods in Modern Biology* (Robeva & Hodge, 2013). Bistability in the lactose operon of *Echerichia coli*: A comparison of differential equation and Boolean network models. By R. Robeva and N. Yildirim.

Chapter 6 of *Algebraic and Discrete Mathematical Methods for Modern Biology* (Robeva, 2015). Steady state analysis of Boolean models: a dimension reduction approach. By D. Murrugarra and A. Veliz-Cuba, pages 121–139.

Exercises.

1. In this exercise, you will construct the finite field of order 9.

   (a) Find an irreducible polynomial of degree 2 in $\mathbb{F}_3[x]$. Note that any such $f \in \mathbb{F}_3[x]$ for which $f(c) \neq 0$ for all $c \in \mathbb{F}_3 = \{0, 1, 2\}$ will work.

   (b) Write down all 9 elements of $\mathbb{F}_9 \cong \mathbb{F}_3[x]/I$, where $I = \langle f \rangle$ is the ideal generated by the polynomial you found in Part (a). All of the elements should be of the form $g + I$, for some $g \in \mathbb{F}_3[x]$.

   (c) Construct the addition table of $\mathbb{F}_9$ and the multiplication table of $\mathbb{F}_9^* := \mathbb{F}_9 \setminus \{0\}$, like what we did for $\mathbb{F}_4$ in class. You should omit the "$+I$" for clarity of notation.

2. Consider the reactions where two substrates S and T compete for binding to an enzyme E to produce two different products P and Q:

$$E + S \underset{p_2}{\overset{p_1}{\rightleftharpoons}} ES \xrightarrow{p_3} P + E$$

$$E + T \underset{q_2}{\overset{q_1}{\rightleftharpoons}} ET \xrightarrow{q_3} Q + E$$

   Assume that each reaction follows the Michaelis-Menten kinetics. Also, assume that that the initial enzyme concentration is $E_0 = [E] + [ES] + [ET]$.

   (a) Derive rate equations for P and Q in this system in terms of $[ES]$ and $[ET]$. That is, determine $d[P]/dt$ and $d[Q]/dt$.

   (b) Derive rate equations for ES and ET.

   (c) Assume that the enzyme-substrate complexes reach equilibrium quickly: $d[ES]/dt \approx 0$ and $d[ET]/dt \approx 0$. Solve for $[E]$ in each of these equations.

   (d) Equate the two expressions for $[E]$ from Part (c) and solve for $[ET]$.

   (e) Solve for $[ES]$ by plugging your answers to Parts (c) and (d) into $E_0 = [E] + [ES] + [ET]$. You should not have $[E]$ or $[ET]$ in your final answer.

   (f) Plug this into the original ODE for $d[P]/dt$.

   (g) Repeat the previous three steps but solve for $[ES]$ instead of $[ET]$.

   (h) Explain the effects of the competition occuring.

3. Recall our original 3-variable Boolean model of the *lac* operon:

$$\begin{aligned} f_M &= \overline{G_e} \wedge (L \vee L_e), \\ f_E &= M, \\ f_L &= \overline{G_e} \wedge ((E \wedge L_e) \vee (L \wedge \overline{E})). \end{aligned}$$

For each of the 4 possible initial conditions, $G_e, L_e \in \mathbb{F}_2^2$, the model had one connected component with the biologically correct fixed point. Compute the probability that this would have happened purely by chance. (Assume a uniform distribution.)

4. Recall the 3-variable ODE model of the *lac* operon proposed by Yildirim and Mackey in 2004, where $M(t) =$ mRNA, $B(t) = \beta$-galactosidase, and $A(t) =$ allolactose (concentrations), respectively.

$$\begin{aligned} \frac{dM}{dt} &= \alpha_M \frac{1 + K_1(e^{-\mu\tau_M} A_{\tau_M})^n}{K + K_1(e^{-\mu\tau_M} A_{\tau_M})^n} - \widetilde{\gamma_M} M \\ \frac{dB}{dt} &= \alpha_B e^{-\mu\tau_B} M_{\tau_B} - \widetilde{\gamma_B} B \\ \frac{dA}{dt} &= \alpha_A B \frac{L}{K_L + L} - \beta_A B \frac{A}{K_A + A} - \widetilde{\gamma_A} A \end{aligned}$$

Suppose the exponential decay constants are estimated from the literature to be $\widetilde{\gamma_M} = .441$, $\widetilde{\gamma_B} = .031$, and $\widetilde{\gamma_A} = .55$.

(a) Compute the half life for M, B, and A.

(b) Justify the following Boolean model by explaining the logical expression defining each transition function:

$$\begin{aligned} f_M &= A & \qquad f_{B_{\text{old}}} &= \overline{M} \wedge B \\ f_B &= M \vee \big(B \wedge \overline{B_{\text{old}}}\big) & \qquad f_A &= (B \wedge L_m) \vee L \end{aligned}$$

What approximate timestep is assumed by this model?

(c) Find the fixed points of this model using computational algebra. Use the variable order $(M, B, B_{\text{old}}, A) = (x_1, x_2, x_3, x_4)$, and include your code from Macaulay2, Singular, or Sage.

(d) Does this model exhibit bistability? Justify your answer.