1. 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 is a reasonble assumption of the approximate timestep assumed by this model? (There are multiple feasible solutions, but you need to justify your answer.)

   (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.

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

2. Draw the wiring diagram of the Boolean model

$$f = (f_1, f_2, f_3, f_4, f_5, f_6) = (x_6,\ x_1,\ x_2,\ \overline{x_3},\ x_4,\ \overline{x_5})$$

and then reduce it by eliminating the variables in the order $x_6, x_5, \dots$. Do each step by hand (i.e., show your work), an at each step along the way, write out the functions and draw the wiring diagram.

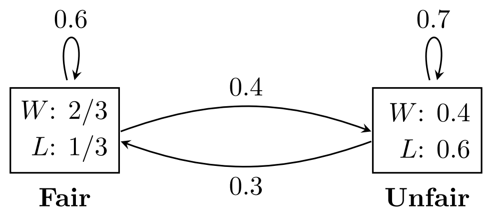
3. Consider the following Boolean network model of the *lac* operon:

$$\begin{aligned}
f_1 &= x_4 \wedge \overline{x_5} & \qquad f_7 &= x_6 \vee x_8 \vee x_9 \\
f_2 &= x_1 & \qquad f_8 &= x_2 \wedge x_{10} \wedge \overline{x_{11}} \\
f_3 &= x_1 & \qquad f_9 &= (x_8 \vee x_{10}) \wedge \overline{x_{11}} \\
f_4 &= \overline{x_{11}} & \qquad f_{10} &= x_{10} \\
f_5 &= \overline{x_6} \wedge \overline{x_7} & \qquad f_{11} &= x_{11} \\
f_6 &= x_3 \wedge x_8 & &
\end{aligned}$$

   (a) Use Macaulay2 to reduce this Boolean network, as much as possible, starting from the last variable.

   (b) Draw the wiring diagram of the reduced network. Find its fixed point(s) and use these to determine the fixed point(s) of the original network by back-substitution.

4. Consider the hidden Markov model of the *occassionally dishonest casino* that we saw in class, with the following probability parameters:



Suppose that upon playing this dice game four times, the result is $x = x_1x_2x_3x_4 = WLLW$. Assume there is an equal chance of starting at the fair vs. unfair state. In this problem, you will carry out the steps of the decoding and evaluation problems; see Chapter 9 of Robeva/Hodge. Please show your work, including intermediate steps, and include a state diagram with the W/L states and times, just like what was done in class.

(a) Use the *Viterbi algorithm* to compute the most likely hidden path $\pi = \pi_1\pi_2\pi_3\pi_4$ to emit x. That is, compute

$$\pi_{\max} = \arg\max_{\pi} P(\pi \mid x) = \arg\max_{\pi} P(x, \pi).$$

(b) Use the *forward algorithm* the compute the *probability* $P(x)$ of emitting x.

(c) Use the *backward algorithm* to compute the *posterior probabilities* $P(\pi_t = k \mid x)$.