Read: Chapter 2: Bistability in the lactose operon of *Escherichia coli*: A comparison of differential equation and Boolean network models, by R. Robeva, and N. Yildirim. pages 57–73.

1. Recall our original Boolean network model for the *lac* operon:

$$f_M = \overline{G_e} \wedge (L \vee L_e)$$
$$f_E = M$$
$$f_L = \overline{G_e} \wedge ((E \wedge L_e) \vee (L \wedge \overline{E})).$$

Suppose now that L_e instead stands for external concentration of lactose that being at least medium. Introduce a new parameter $L_{e_{high}}$ to denote high levels of external lactose.

(a) Modify the transition functions above to get a model that exhibits bistable behavior for medium lactose concentrations.

(b) For the three possibile concentration levels of lactose; low: $(L_e, L_{e_{high}}) = (0, 0)$, medium: $(L_e, L_{e_{high}}) = (1, 0)$, and high: $(L_e, L_{e_{high}}) = (1, 1)$, sketch or print out the phase space of this model. Use the DVD software (`dvd.vbi.vt.edu`). Clearly show how this model exhibits bistability.

2. So far, we have used designated "old" variables to separate the time scales of dilution and degradation processes from those of synthesis. An alternate to introducing new variables this is to properly modify the transition functions.

Consider a model of the *lac* operon using variables M, B, and A, and parameters L and L_{high}. Suppose that the degradation time for A is much larger than that for M and B. In this case, choosing a proper timestep allows us to neglect the degradation times for M and B. Instead of introducing an A_{old} variable, we propose the following model:

$$f_M = A,$$
$$f_B = M,$$
$$f_A = (B \wedge L) \vee L_{high} \vee (A \wedge \overline{B}).$$

(a) Justify the three equations in this model, and why this captures the delay in the degradation of A. Your answer should be clear and convincing.

(b) Use the DVD software to sketch (or print) the phase space of this model for the three levels of lactose concentration: low, medium and high.

(c) Does this model exhibit bistability? Why or why not?