Read: Chapter 2.3–2.7: Bistability in the lactose operon on *Escherichia coli*: A comparison of differential equation and Boolean network models. By R. Robeva and N. Yildirim, pages 47–73.

1. Recall another model of the *lac* operon that we saw last time:

$$\begin{aligned} f_M &= A, \\ f_B &= M, \\ f_A &= (B \wedge L_m) \vee L \vee (A \wedge \overline{B}). \end{aligned}$$

   Does this model exhibit bistability? Why or why not?

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

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

   Since this model cannot distinguish between basal, medium, and high levels of lactose, it cannot exhibit bistability. Add a new parameter L_{em} that stands for "at least medium levels of extracellular lactose". Modify the Boolean functions so the new model exhibits bistable behavior for medium lactose concentrations.

Summary of relevant literature.

A review of bistability and a discussion of the necessarity of postive feedback loops can be found in [Fer02]. Bistable switches govern standard cell processes such as cell fate determination [FM98], cell cycle regulation [PSF03, SMC$^+$03], and maintenance of epigenetic traits [HBL03].

A study of bistability in the *lac* operon was published in a 2004 *Nature* paper [OTL$^+$04]. The ODE models of the *lac* operon that exhibit bistability were published in [YM03], in [YSHM04]. Bistability was observed in the original Boolean network model of the *lac* operon [VCS11]. The arabinose (*ara*) operon in *E. coli* was recently modeled with a Boolean network and was shown to exhibit bistability [JM17], which was observed experimentally in [SH97].

Another well-studied bistable switch governs the lytic and lysogenic cell cycles in the phage lambda virus. A logical model was published in 1976 [TGL76]. In 1995, a 4-node Boolean network model was proposed in [TT95]. A Boolean model was proposed in [HL11] where extra variables were used to model the time-delays, and this Boolean model exhibits bistability. This paper also contains a Boolean model of the *lac* operon that incorporates time-delays and exhibits bistability.

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