

*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 the Boolean model of the *lac* operon that incorporated time-delays:

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

Does this model exhibit bistability? Justify your answer.

2. 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:

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

What approximate timestep is assumed by this model?

- (c) Assuming  $(M, B, B_{\text{old}}, A) = (x_1, x_2, x_3, x_4)$ , write the polynomial form of the Boolean model above. The easiest way to do this is to go into Sage and type the following commands (hit shift-enter after each one):

```
%default_mode macaulay2
R = ZZ/2[x1,x2,x3,x4] / ideal(x1^2-x1, x2^2-x2, x3^2-x3, x4^2-x4);
RingElement | RingElement :=(x,y)->x+y+x*y;
RingElement & RingElement :=(x,y)->x*y;
```

Now, if you want to store  $f = (x_1 \vee x_2) \wedge x_3$ , you can enter `f=(x1 | x2) & x3`. Typing `f` will give the polynomial form of  $f$ .

- (d) Open a new tab of Sage (so you aren't in the Macaulay2 environment), and find the fixed points of the Boolean network by solving  $\{f_1 + x_1 = 0, \dots, f_4 + x_4 = 0\}$ .

- (e) Does this model exhibit bistability? Justify your answer.
3. So far, we have used designated “old” variables to separate the time scales of dilution and degradation processes from those of synthesis. Alternately, this can be done implicitly through the logical assumptions built into the transition functions. For example, if we choose to work with  $\gamma_A = 1.8 \times 10^{-4}$ , then the degradation time for  $A$  will be slower than both  $M$  and  $B$ . Instead of introducing an  $A_{\text{old}}$  variable, we propose the following model, which builds this feature into the function:

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

- (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 ADAM software to sketch 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?

### Summary of relevant literature.

The ODE models of the *lac* operon are from the papers [YM03] and [YSHM04].

In [HL11], the authors showed how a Boolean network can capture features such as dilution, degradation, and time delays, and still exhibit bistability. They applied their ideas to Boolean network models of the *lac* operon and of the lambda phage virus.

### Other things to explore.

Read about the bistable switch between the lytic and lysogenic 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 network model exhibited bistability.

## References

- [HL11] F. Hinkelmann and R. Laubenbacher. Boolean models of bistable biological systems. *Discrete Cont. Dyn. Sys. Ser. S*, 4(6):1443–1456, 2011.
- [TGL76] R. Thomas, A.-M. Gathoye, and L. Lambert. A complex control circuit. Regulation of immunity in temperate bacteriophages. *Eur. J. Biochem.*, 71(1):211–227, 1976.

- [TT95] D. Thieffry and R. Thomas. Dynamical behaviour of biological regulatory networks—ii. immunity control in bacteriophage lambda. *Bull. Math. Biol.*, 57(2):277–297, 1995.
- [YM03] N. Yildirim and M.C. Mackey. Feedback regulation in the lactose operon: a mathematical modeling study and comparison with experimental data. *Biophysical J.*, 84(5):2841–2851, 2003.
- [YSHM04] N. Yildirim, M. Santillan, D. Horike, and M.C. Mackey. Dynamics and bistability in a reduced model of the lac operon. *Chaos*, 14(2):279–292, 2004.