(5) Boolean modeling of biochemical reactions

Weaknesses of previous Boolean models:

* All processes take a single timestep.
* Only assume high & low levels in intracellular lactose. Medium levels are needed for bistability to exist.
* No delays incorporated.

We can add these type of features to the model:

(1) Dilution & degradation

Suppose Y regulates production of X.

Assume $Y(t)=1 \Rightarrow X(t+1)=1$ (activation takes 1 step).

Loss of X due to dilution & degradation takes several steps.

Introduce new variables $X_{old(1)}, X_{old(2)}, \ldots, X_{old(n)}$.

Properties:

(i) If $Y(t)=0$ and $X(t)=1$, then $X_{old(1)}(t+1)=1$.

(means amt of X reduced has been reduced once by dilution & degradation.)

[2]

(ii) IF $Y(t) = 0$ and $X_{old(i-1)}(t) = 1 \Rightarrow X_{old(i)}(t+1) = 1$.

Means X present at time t+1 has be reduced i times by dilution & degradation.

(iii) # "old" variables determined by # of timesteps required to reduce [X] below discretation threshold.

Thus, $X(t+1)$ when either $Y(t) = 1$ (new amount will be produced by t+1)

or, $X(t) \wedge \overline{X_{old(n)}(t)} = 1$ (previous amts of X still available).

$$\Rightarrow X(t+1) = Y(t) \vee (X(t) \wedge \overline{X_{old(n)}(t)})$$

(2) Medium levels of lactose

Introduce new variable L_{high} so that $L_{high} = 1 \Rightarrow L = 1$.

High lactose: $L = 1$, $L_{high} = 1$

Medium lactose: $L = 1$, $L_{high} = 0$

Low lactose: $L = 0$, $L_{high} = 0$.

(3) Time delays:

Say R regulates production of X, delayed by time τ (n steps)

Introduce new variables $R_1, R_2, \ldots, R_n$

Transition functions: $R_1(t+1) = R(t)$

$R_2(t+1) = R_1(t)$

$\vdots$

$R_n(t+1) = R_{n-1}(t)$

$X(t+1) = R_n(t)$

Boolean version of the Yildirim-Mackey model:

Recall:
$$\begin{cases} \dfrac{dM}{dt} = \alpha_M \dfrac{1 + K_1 \left(e^{-\mu \tau_M} A_{\tau_M}\right)^n}{K + K_1 \left(e^{-\mu \tau_M} A_{\tau_M}\right)^n} - \tilde{\gamma}_M M \\ \dfrac{dB}{dt} = \alpha_B e^{-\mu \tau_B} M_{\tau_B} - \tilde{\gamma}_B B \\ \dfrac{dA}{dt} = \alpha_A B \dfrac{L}{K_L + L} - \beta_A B \dfrac{A}{K_A + A} - \tilde{\gamma}_A A \end{cases}$$

where $A_{\tau_M} := A(t - \tau_M)$ $\quad \tau_M, \tau_B$ time delays

$\tilde{\gamma}_M = \gamma_M + \mu$

degradation rate ↑ dilution from cell growth

Need to estimate rate constants & time delays (from literature)

Estimated delays: $\tau_M = 0.10$ min, $\quad \tau_B = 2.00$ min.

Degradation rates are harder to determine experimentally.

Vary widely in literature:

Sample values:
$$\begin{cases} \gamma_A = .52 \text{ min}^{-1}, \ .0135 \text{ min}^{-1}, \ .00018 \text{ min}^{-1} \\ \gamma_B = .00083 \text{ min}^{-1}, \quad \gamma_M = .411 \\ \mu \in (.0045, .0347). \end{cases}$$

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Approach: Select middle of range estimates: $\mu = .03\ \text{min}^{-1}$

$\gamma_A = .0135\ \text{min}^{-1}, \Rightarrow \tilde{\gamma}_A = \gamma_A + \mu = .044$

$\gamma_B = .001\ \text{min}^{-1} \Rightarrow \tilde{\gamma}_B = \gamma_B + \mu = .031$

$\gamma_M = .411\ \text{min}^{-1} \Rightarrow \tilde{\gamma}_M = \gamma_M + \mu = .441$

Recall: Degradation is assumed to be exponential decay.

That is, $x' = -kx \Rightarrow x(t) = Ce^{-kt}$

Half-life: time t such that $x(t) = Ce^{-kt} = \frac{1}{2}C$

$\Rightarrow e^{-kt} = \frac{1}{2} \Rightarrow -kt = \ln\frac{1}{2}$

$\Rightarrow \boxed{t = \frac{\ln 2}{k}}$

Half-lives: $\tilde{h}_A = \frac{\ln 2}{\tilde{\gamma}_A} = 15.753$

$\tilde{h}_B = \frac{\ln 2}{\tilde{\gamma}_B} = 22.360$

$\tilde{h}_M = \frac{\ln 2}{\tilde{\gamma}_M} = 1.572$

Model: (1) Variables M, B, A

(2) Glucose absent, intracellular lactose present

2 parameters: L and L_{high}.

(3) Time-step $\approx$ 10 min. Ignore $\tau_M = .10$ min, $\tau_B = 2$ min

$\tilde{h}_M = 1.572$. All $\ll 10$.

(4) Introduce A_{old} (since $\tilde{h}_A \approx 1$ timestep)

B_{old}, $B_{old(2)}$ (since $\tilde{h}_B \approx 2$ timesteps).

Model:

$$f_M = A$$

$$f_B = M \vee (B \wedge \overline{B_{old(2)}})$$

$$f_{B_{old(1)}} = \bar{M} \wedge B$$

$$f_{B_{old(2)}} = \bar{M} \wedge B_{old(1)}$$

$$f_A = (B \wedge L) \vee L_{high} \vee (A \wedge \overline{A_{old}} \wedge \bar{B})$$

$$f_{A_{old}} = \left((\bar{B} \vee \bar{L}) \wedge \overline{L_{high}}\right) \wedge A.$$

Remarks: Most of these functions should be self-explanatory.

Justification for f_A: [Recall lac $\xrightarrow{\beta\text{-gal}}$ allo $\xrightarrow{\beta\text{-gal}}$ glucose & galactose]

3 ways for allolactose to be available at $t+1$

(i) β-gal & lactose are present

(ii) high levels of lactose (assume basal concentrations of β-gal)
($\Leftrightarrow$ enough molecular collisions)

(iii) Enough allolactose is present so that it's not degraded below threshold, and no β-gal present.

Results: DVD (dvd.vbi.vt.edu) is useful to analyze results.

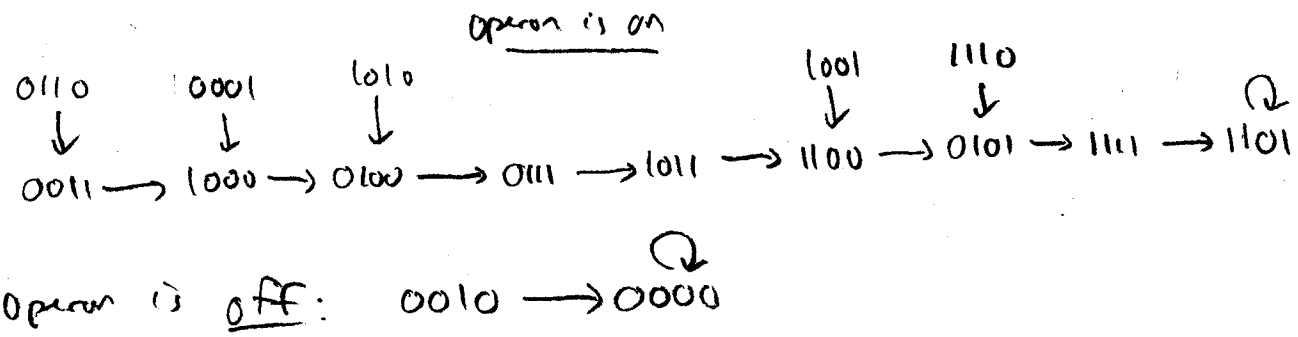
Consider 3 cases:

high lactose	$(L = L_{high} = 1)$	$\Rightarrow$ 1 fixed point
med. lactose	$(L = 1, L_{high} = 0)$	$\Rightarrow$ 2 fixed points
low lactose	$(L = 0, L_{high} = 0)$	$\Rightarrow$ 1 fixed point

Inducer level	L	L_{high}	M	B	$B_{old(1)}$	$B_{old(2)}$	A	A_{old}	on/off
low lactose	0	0	0	0	0	0	0	0	off
high lactose	1	1	1	1	0	0	1	1	on
med. lactose	1	0	0	0	0	0	0	0	off
med. lactose	1	0	1	1	0	0	1	0	on

fixed points

Bistable region, state space of points $(M, B, B_{old(1)}, A)$



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Summary:

- Boolean models can approximate delay diff. eqn models
- Necessary condition for bistability: distinguish ≥ 3 concentration levels.
- Bistability is independent of glucose in extracellular medium
  Lour model didn't catabolite repression mechanism
- Model ignores lac permease; considers only β-gal ⇒ of all feedback loops, only β-gal is responsible for bistability.
- Bistability appears to be robust. We approximated; ignored time delays.