(2) Boolean network models

Goal: Design a basic dynamic model that reflects its biological behaviour.

Bare minimum: lactose absent ⇒ operon off
lactose present, glucose absent ⇒ operon on.

Need
- Model variables: Represent dynamic elts. of the system
- Parameters: Outside elements (constant)

Lac operon:

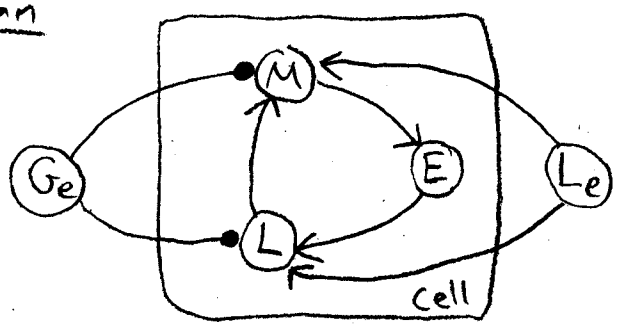
Model variables	Parameters
M: mRNA	L_e: external lactose
L: internal lactose	G_e: external glucose
From LacZ: E: LacZ polypeptide	
From LacZ: B: β-galactosidase	
From LacY: P: lac permease	
A: allolactose	

Simplifications:
- β-gal made up of 4 identical lacZ polypeptides ⇒ $B = E/4$
- LacY & lacZ translated at same rate ⇒ $P = E$
- Concentration of internal lactose & allolactose proportional ⇒ $A = kL$

Thus, we can ignore B, P, & A in the Boolean framework.

Note: This is just one, of many possible models!

* Wiring diagram



→ positive influence

—● negative influence

Boolean operations	logical	polynomial
AND	$z = x \wedge y$	$z = xy$
OR	$z = x \vee y$	$z = x + y + xy$
NOT	$z = \bar{y}$	$z = 1 + y$

Only 2 states allowed: 0, 1: on/off, present/absent, above/below certain threshold, etc.

Framework:

Wiring diagram consists of n nodes: $X_1, X_2, \ldots, X_n$

Each takes a value of 0 or 1

The set of global states is $V = \{0,1\}^n = \{(x_1, \ldots, x_n) : x_i \in \{0,1\}\}$.

Each $X_i(t)$ is a function $\mathbb{N} \longrightarrow \{0,1\}$.

$X_i(t+1) = f_{X_i}(X_1(t), X_2(t), \ldots, X_n(t))$ "transition functions"
"update rules" or "rules"

Use a synchronous update:

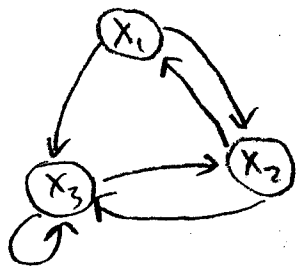
$X = (X_1, X_2, \ldots, X_n)$. $f(X) = (f_{X_1}(X), f_{X_2}(X), \ldots, f_{X_n}(X))$.

↑ recall: these are functions of t.

State space (or "phase space"): Directed graph (V, T),

where $T = \{(X, f(X)) : X \in V\}$.

Ex:



$X_1(t+1) = f_{X_1}(X_1(t), X_2(t), X_3(t)) = X_2(t)$

write as:
$$\begin{cases} X_1 = f(X_1, X_2, X_3) = X_2 \\ X_2 = f_{X_2}(X_1, X_2, X_3) = X_1 \vee X_3 \\ X_3 = f_{X_3}(X_1, X_2, X_3) = (X_1 \wedge X_2) \vee X_3 \end{cases}$$

Suppose the initial condition is $X(0) = (X_1, X_2, X_3) = (0, 0, 1)$.

$$\begin{cases} X_1(1) = f_{X_1}(0,0,1) = 0 \\ X_2(1) = f_{X_2}(0,0,1) = 0 \vee 1 = 1 \\ X_3(1) = f_{X_3}(0,0,1) = (0 \wedge 0) \vee 1 = 1 \end{cases} \Rightarrow X(1) = (0,1,1)$$

$$\begin{cases} X_1(2) = f_{X_1}(0,1,1) = 1 \\ X_2(2) = f_{X_2}(0,1,1) = 1 \\ X_3(2) = f_{X_3}(0,1,1) = 1 \end{cases} \Rightarrow X(2) = (1,1,1).$$

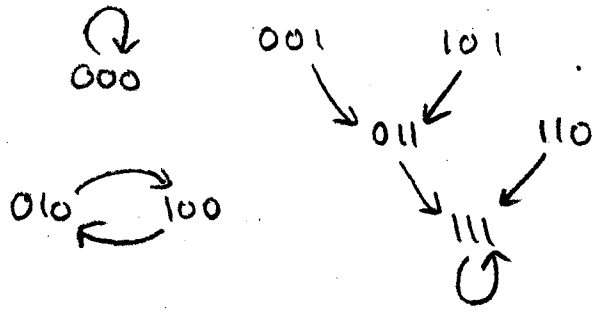
(4)

$$\begin{cases} X_1(3) = f_{X_1}(1,1,1) = 1 \\ X_2(3) = f_{X_2}(1,1,1) = 1 \\ X_3(3) = f_{X_3}(1,1,1) = 1 \end{cases} \Rightarrow X(3) = (1,1,1) \Rightarrow X(4) = X(5) = \dots = (1,1,1).$$

The trajectory of $(0,0,1)$ is $(0,0,1) \to (0,1,1) \to (1,1,1)$

The state $(1,1,1)$ is a fixed point.

The entire state space looks like:



(Use dvd.vbi.vt.edu to plot)

Sometimes we use capital letters instead:

Ex: lac operon $\quad X_1 = M, \quad X_2 = E, \quad X_3 = L$

$f_{X_1} = f_M, \quad f_{X_2} = f_E, \quad f_{X_3} = f_L$

Next step: Choose functions

Model assumptions "everything takes 1 time-step"

- Transcription & translation require 1 unit time.
- Degradation of mRNA & proteins occurs in 1 time step.
- If β-gal is present, lactose metabolism takes 1 time step:
  If lactose & β-gal available at t, but new lactose can't be brought in, then at $t+1$, all lactose converted to glucose & galactose.

Update functions

- **mRNA**: f_M:

  For mRNA to be present at time $t+1$ $(F_M(x) = 1)$

  - no external glucose present at time t: $(G_e(t) = 1)$

  and • either internal or external lactose should be present:

  Propose: $X_M(t+1) = f_M(t+1) = \overline{G_e} \wedge (L(t) \vee L_e)$.

  Ask: Does this make sense when: $G_e(t) = 1$? ✓

- **LacZ polypeptide**: f_E:

  IF mRNA is available at time t $(M(t) = 1)$, LacZ polypeptide is produced & available at $t+1$ $(M(t+1) = 1)$.

  Propose: $X_E(t+1) = f_E(t+1) = M(t)$

- **Lactose (internal)**: f_L

  * External glucose available $(G_e = 1) \Rightarrow$ no lactose brought into cell
    $\Rightarrow L(t+1) = 0$.

  * External glucose absent $(G_e = 0)$:

    Internal lactose will be available if either of these is satisfied:

    (i) External lactose and lac permease $(P = E)$ are present: $E(t) \wedge L_e = 1$

    (ii) Internal lactose is present but no β-gal $(B = E/4)$ to metabolize it
    $L(t) \wedge \overline{E(t)}$

  Propose: $X_L(t+1) = f_L(t+1) = \overline{G_e} \wedge [(E(t) \wedge L_e) \vee (L(t) \wedge \overline{E(t)})]$