HW2

Thursday, September 19, 2024 2:00 PM

Exercise. Consider a Boolean model of the *lac* operon, based on five variables: mRNA (M), β-galactosidase (B), *lac* permease (P), allolactose (A), and intracellular lactose (L), and the following transition functions:

$$f_M = A$$
$$f_B = M$$
$$f_P = M$$
$$f_A = A \vee (L \wedge B)$$
$$f_L = P \vee (L \wedge \overline{B})$$

(a) What other assumptions are made in this model? (E.g., presence or absense of extracellular sugars, time-steps, degredation, etc.)

We are assuming that there is always lactose outside of the cell, but no glucose. We are also assuming that metabolism, translation, transcription, and degradation all take the same amount of time. Similarly, we are assuming that updating happens at the same time for each update function.

(b) As we saw in class, the dynamics do not accurately reflect the behavior of the biological system it is meant to model. Therefore, something is wrong. Four of these functions are reasonable; justify each one in a single well-written sentence.

1) If there is allolactose available, then mRNA will be translated.
2) If there is mRNA available, then β-Galactosidase will be transcribed.
3) If there is mRNA available, then permease will be transcribed.
4) Problem function.
5) If there is permease or if there is lactose that has not been cleaved by β-Galactosidase, then there is lactose inside of the cell.

(c) Explain why one of these functions does not accurately reflect the underlying biology and/or the model assumptions. Propose a modification, aimed at eliminating the biologically infeasible fixed point, $(0, 0, 0, 1, 0)$. Give a rationale for your modification and specify the biological mechanism or model assumptions that justify the change.

The problem function is for allolactose. The problem is that the model originally predicted that there would be lactose inside of the cell without any metabolization happening. This can be fixed in the model if we add the "leaky faucet" assumption into the model as we talked about in class. This can be implemented as follows:

$f_A = A \vee (L \wedge B) \vee (L \wedge \neg P)$

This function now says that there is allolactose in the cell if there was allolactose in the cell before, or if there is lactose that was cleaved by β-Galactosidase, or if there is any lactose inside of the cell that got inside through diffusion forces instead of through the permease protein. This adds the leaky faucet assumption into our model that corrects the problem with the fixed point.

(d) Use Macaulay2 to convert these Boolean functions into polynomials over $\mathbb{F}_2 = \{0, 1\}$. Then find the fixed points using a Gröbner basis of a particular polynomial ideal.

```
R = ZZ/2[x1,x2,x3,x4,x5];

J = ideal(x1^2-x1, x2^2-x2, x3^2-x3, x4^2-x4, x5^2-x5);
Q = R / J;

RingElement | RingElement :=(x,y)->x+y+x*y;
RingElement & RingElement :=(x,y)->x*y;

f1 = x4;
f2 = x1;
f3 = x1;
f4 = x4 | (x5 & x2) | (x5 & (1+x3));
f5 = x3 | (x5 & (1+x2));


I = ideal(f1+x1, f2+x2, f3+x3, f4+x4, f5+x5)

G = gens gb I
```

```
i1 : R = ZZ/2[x1,x2,x3,x4,x5];

i2 :
     J = ideal(x1^2-x1, x2^2-x2, x3^2-x3, x4^2-x4, x5^2-x5);

o2 : Ideal of R

i3 : Q = R / J;

i4 :
     RingElement | RingElement :=(x,y)->x+y+x*y;

i5 : RingElement & RingElement :=(x,y)->x*y;

i6 :
     f1 = x4;

i7 : f2 = x1;

i8 : f3 = x1;

i9 : f4 = x4 | (x5 & x2) | (x5 & (1+x3));

i10 : f5 = x3 | (x5 & (1+x2));

i11 :

      I = ideal(f1+x1, f2+x2, f3+x3, f4+x4, f5+x5)

o11 = ideal(x1 + x4, x1 + x2, x1 + x3, x2 x3 x4 x5 + x2 x3 x5 + x3 x4 x5 + x3 x5 + x4 x5 + x5, x2 x3 x5 + x2 x5 + x3 x5 + x3)

o11 : Ideal of Q

i12 :
      G = gens gb I

o12 = ( x4 + x5   x3 + x5   x2 + x5   x1 + x5 )
```

A=L=P=B=M or the operon is turned on

(e) Draw the wiring diagram of the old and new Boolean model.

old New

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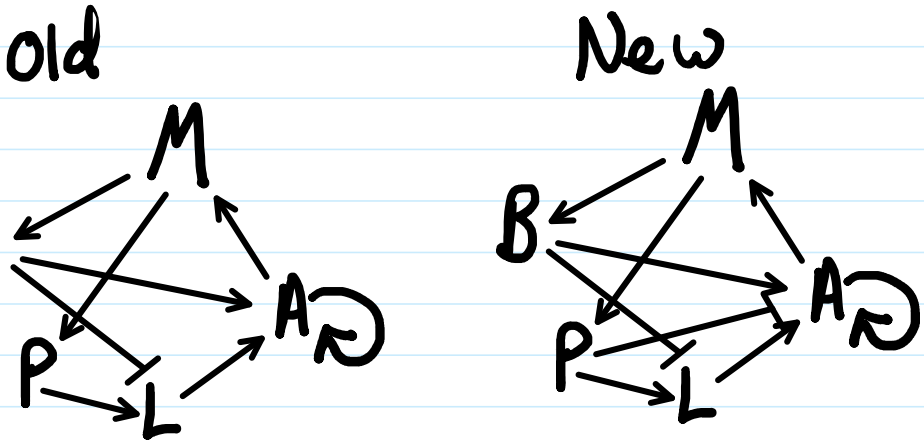
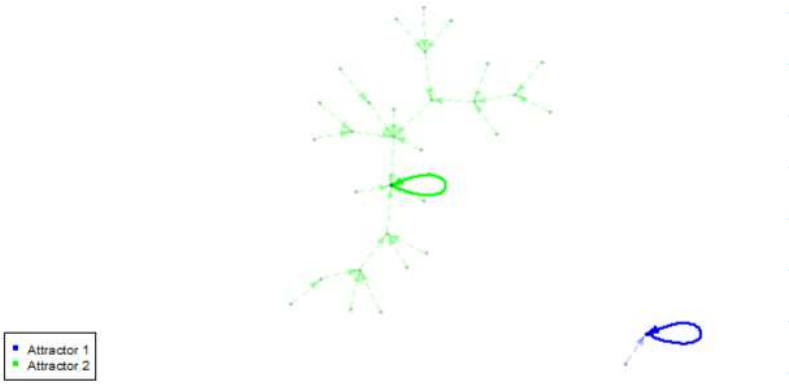


(f) Use the BoolNet package in RStudio to find the attractors and plot the state space. Include a print-out or screenshot.

lac-operon.txt

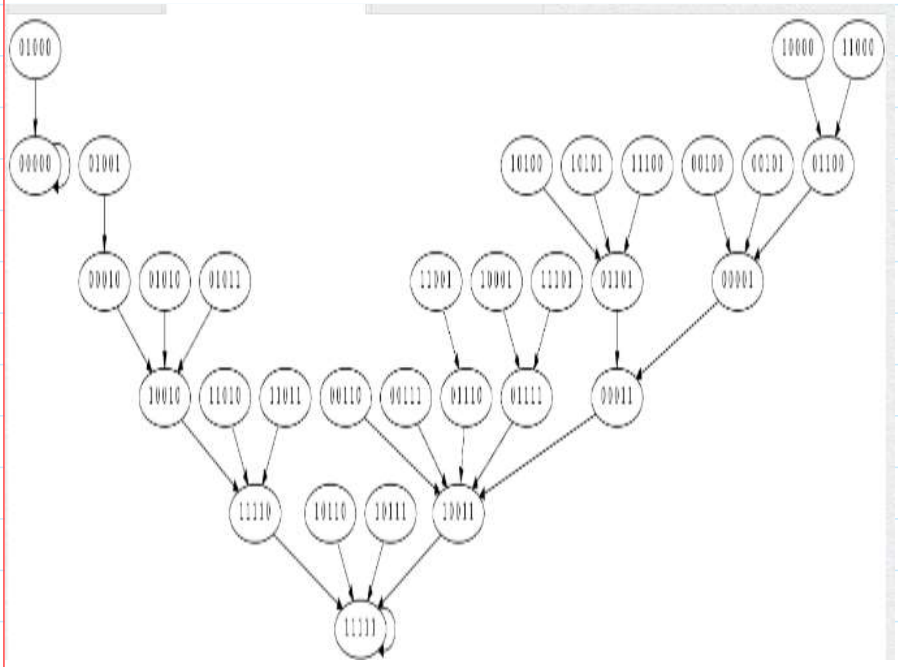
```
1  targets, factors
2  M, A
3  B, M
4  P, M
5  A, A | (L & B) | (L & !P)
6  L, P | (L & !B)
7
```

```
Attractor 1 is a simple attractor consisting of 1 state(s) and has a basin of 2 state(s):

 |--<----|
 V       |
 00000   |
 V       |
 |-->----|


Genes are encoded in the following order: M B P A L

Attractor 2 is a simple attractor consisting of 1 state(s) and has a basin of 30 state(s):

 |--<----|
 V       |
 11111   |
 V       |
 |-->----|


Genes are encoded in the following order: M B P A L
```



(g) Repeat the previous step, but with either Cyclone or GINsim.

```
# lac operon
NUMBER OF VARIABLES: 5
NUMBER OF STATES: 2
M = A
B = M
P = M
A = A | (L AND B) | (L AND NOT P)
L = P | (L AND NOT B)
```



(h) Justify why the long-term behavior of the system (fixed points) agrees with what we should expect biologically.

I think that this is what we should expect biologically, because once lactose enters the cell, then it will need to be processed until all of the lactose is metabolized. Since one of the assumptions that we are operating under is that there is always extracellular lactose, and no glucose, then the cell will have to continuously process the lactose. This means that the operon will have to stay on for the long-term behavior.